COLLAGEN FIBRIL NANOMECHANICS

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Background
Collagens are the result of millions of years of biological evolution and compose a unique family of proteins. The majority of collagens provide mechanical support for biological tissues. The most abundant collagen molecules expressed by cells, e.g., types I, II, III, self-assemble into larger structures, known as collagen fibrils (CFs). CFs display a complex structural architecture, and their properties are tuned by the cells expressing them by imposing forces. In turn, CF mechanics influence cell behavior and because of this are important for tissue homeostasis. In this context, CFs are mechanically exposed to varying loading environments throughout the body, yet they perform and maintain mechanical functionality. CFs show nonlinear, elasto-visco-plastic behaviour, and therefore, determination of their mechanical properties is non-trivial. Advances in nanotechnology instrumentation opened the door to investigate the mechanics of individual CFs, but the number of samples tested to date is small and many open questions remain.

Recent Advances
The mechanics of isolated and individual CFs is a multiparameter problem (Figure 1). From research to date, several mechanisms influencing CF mechanics have been identified. These are hydration, composition, chemical modification, and structure. Hydration levels greatly affect both the tensile and transverse apparent modulus [1, 2]. The mechanical stiffness of CFs can be increased up to 6-fold in tension by reducing hydration [1]. CFs undergo enzymatic and nonenzymatic chemical modifications, i.e., attachment of adducts and cross-linking. These modifications, influence the longitudinal and transverse mechanical properties of CFs. However, while the extremes, i.e., very small vs. very high amounts of cross-linking have been studied, a full mechanistic understanding of properties related to such modifications is missing. In addition, cross-linking type and amount are also related to collagen turnover and pathologies. In idiopathic pulmonary fibrosis (IPF), for example, collagen cross-linking has been identified as a driver of pathology influencing CF mechanics and mechanobiology [3]. Further, also nonenzymatic glycation (in vitro) has been related to nanomechanical stiffening of CFs [4]. Lastly, CFs are heterotypic [5], and relative amounts of type I and III also affect CF mechanics [6]. In tension, CFs show a complex behaviour with up to three different phases [7]. So far, five deformation mechanisms have been proposed but a mechanistic understanding is lacking. Yet, viscous properties have been associated to hydrogen bond (H-bond) rupture/reformation and molecular sliding.

Future directions
CFs are essential for human biomechanics and mechanobiology. Yet, our knowledge remains scarce, as the number of samples tested to date is on the order of a few hundred. To mechanistically understand CF mechanics and relate them to the complex multiparameter landscape (cf. Figure 1) significantly more studies of CF mechanics coupled with chemical analysis are required. Importantly, the full nonlinear elasto-visco-plastic behaviour needs to be assessed. This will not only deepen our understanding of CF mechanics in healthy tissues, but also the progression of connective-tissue pathologies.

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FROM MECHANOBIOLOGY OF AORTIC SMOOTH MUSCLE CELLS TO IMPROVED PROGNOSIS OF THORACIC AORTIC ANEURYSMS

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Background
The media of the aorta consists primarily of smooth muscle cells (SMCs) embedded in a highly structured matrix of collagen fibrils and elastin lamellae. Thanks to their phenotypic plasticity [1], SMCs normally maintain a certain mechanical homeostasis through variations of their active tone (contractile phenotype, short-term adaptation) and through synthesis and remodeling of the extracellular matrix (ECM) (synthetic phenotype, long-term adaptation). However, missingness of mechanical stimuli by SMCs (stress, strain, or stiffness) can alter the maintenance of mechanical homeostasis and induce impaired adaptations that are responsible for thoracic aortic aneurysm (TAA) [2]. Accordingly, there is a pressing need to investigate and model how SMC biomechanics participate in the development of TAA.

Recent Advances
Our recent contributions on this topic were both computational and experimental:
- using a finite-element model of growth and remodelling based on the constrained mixture theory, we showed that cell mechanosensitivity plays a critical role in TAA progression and remodelling [3].
- using traction force microscopy (TFM) on primary SMCs (Fig. 1), we recently found that SMCs of aneurysmal aortas apply larger traction forces than SMCs of healthy aortas [4]. We explained this result by the increased abundance of hypertrophic SMCs in aneurysmal aortas. Our experimental results also confirmed that SMCs modulate their traction forces according to the stiffness two regimes. We even found that SMCs apply optimal traction forces for a substrate stiffness of 12 kPa [5].

Future directions
It is now unanimously acknowledged that before catastrophic events such as rupture or dissections, TAAs enter a vicious circle combining phenotypic modulation/loss of SMCs and compromised biomechanical properties of the wall. Improvements in clinical care and prognosis will require that we are able to couple cell models informed by our recent experimental results with tissue level models of arterial mechanobiology [6]. About mechanoregulation, the motor–clutch-based model [7] may be the way to put forward, as it can also relate stiffness increase of the aortic wall to the increase of aortic failure.

Stéphane Avril is Professor at Mines Saint-Étienne (France) where he heads the research unit on vascular dysfunctions. His research group has made significant contributions in finite element modeling of cardiovascular applications, now transferred to a start-up named Predisurge. In 2015, Stéphane was awarded an ERC Consolidator Grant to investigate the mechanobiology of aortic aneurysms. Recently awarded an ERC Proof of Concept and after several visiting professorships at Yale University (USA), TU Vienna (Austria) and TU Graz (Austria), Stéphane has been investigating more and more the role of smooth muscle cells in aortic mechanobiology. He is an author of 180 publications in peer-reviewed journals and 4 patents.

Figure 1. a. Example of cultured SMC stained with fluorescent markers and observed with fluorescence microscopy; b. Strain field measured around a SMC cultured on 12 kPa substrate for TFM measurements.

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X-RAY CT ASSESSMENT OF LUNG FUNCTION AND BIOMECHANICS

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Background
The lung is a complex, over-engineered organ comprising airways, blood vessels and parenchymal tissue. To ensure its main function of gas exchange, the lung constantly undergoes structural deformation through breathing and pulsatile blood flow. The biomechanical properties of viscoelastic respiratory tissues play a crucial role in both normal physiology and in diseases. For example, mechanical ventilation of patients with acute respiratory failure can cause excessive stress and strain and energy dissipation within the parenchyma leading to injury, which significantly contributes to mortality, a condition referred to as Ventilator-Induced Lung Injury (VILI). The multiscale interaction of all the components that constitute the lung leads to a complex dynamic behaviour where lung function as a whole is not the sum of the behaviour of its individual components. Elucidating the lung microstructure and micromechanics in vivo in health and disease remains very challenging. X-ray CT is the state-of-the-art modality for imaging lung morphology. In the past decades, elastic image registration methods have been used to assess local lung biomechanics. However, clinical CT is limited in its spatial resolution. Synchrotron phase-contrast and K-edge subtraction CT offer unmatched capabilities in assessing local lung micromechanics and function, respectively. Although these techniques are not yet available in the clinical setting, they promise to further our understanding of lung biomechanics in experimental models.

Recent Advances
We previously introduced an energy-subtractive synchrotron CT technique that allows imaging regional lung function with unequalled spatial resolution in vivo in small animals. More recently, we have developed a synchrotron phase-contrast 4D-μCT technique that allows the in vivo assessment of local lung strain under mechanical ventilation in both the parenchyma and blood vessels (Figure 1). In the clinical setting, work is underway to assess local lung biomechanical biomarkers in mechanically-ventilated patients with acute respiratory distress syndrome (ARDS) due to Covid-19, using advanced CT image processing methods, and to study their association with clinical outcome.

Future directions
Synchrotron phase-contrast 4D-μCT is being used to assess lung micromechanics in disease models where it plays a critical role, such as VILI and fibrosis, where better understanding of the consequent lung extracellular matrix alterations and inflammation can offer new therapeutic and preventive opportunities. In the clinical arena, lung biomechanical parameters from patients with ARDS can be used to inform in silico lung models used to personalize mechanical ventilation settings for optimal lung protection, through “offline” simulation.

Figures

Figure 1: Quantitative mapping of lung tissue biomechanics in a live rat at 6 μm3 resolution. Sample X-ray phase-contrast CT image at 42 ms from start of inspiration (a); regional strain as a function of time computed within blood vessels (b) and airspaces (c). Modified from 3.

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Sam Bayat is currently Professor of Physiology at the University of Grenoble. He is an MD and obtained his PhD in Biomedical Instrumentation and Modelling at the University of Grenoble in 1998. He was a post-doctoral fellow and Visiting Scientist at the European Synchrotron Radiation Facility in 2003-2004 and invited professor at the University of Geneva in 2015-2017. He is chair of the Clinical Respiratory Physiology, Exercise and Functional Imaging group of the European Respiratory Society and member of the European Society of Molecular Imaging and the American and French Physiological Societies. His present research mainly focuses on lung functional imaging and biomechanics. He is an author of over 90 publications in peer-reviewed journals, 4 book chapters and more than 100 contributions to International and National Conferences.
STICKING TOGETHER: COMPUTATIONAL MODELLING OF CELL-CELL AND CELL-MATRIX INTERACTIONS

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Background
Within tissues, cells interact with each other (e.g., through cell–cell adhesion) and their matrix (e.g., through cell–matrix adhesion) at the same time, and these physical interfaces are integrated into biochemical signals that influence their behaviour. Although cell–cell and cell-matrix have been studied extensively in isolation, it is not completely understood 1) how cells sense the individual signals, 2) how cells integrate these, including potential regulating factors. Given the small size and dynamic nature (e.g., short lifetimes) of adhesions, the use of conventional microscopic and experimental techniques can be challenging and computational modelling can be a valuable resource to simulate and explore various “what if?” scenarios in silico and defining the key molecular components and mechanisms to be explored further.

Recent Advances
Many computational models of cell-matrix and cell-cell interactions, with the integrin and cadherin protein families as essential transmembrane links respectively, have been developed at different scales (tissue, cell, subcellular) to help understand the dynamical signalling and sensing mechanisms. At the subcellular scale, we and others have modelled cadherin binding and clustering [1], including the influence of the actin cytoskeleton and force [2-4] as well as signalling crosstalk [5-6]. Regarding integrin signalling, computational models have shown that the number of ligand-bound integrins increases with the number of ligands [7], which was extended to include ligand competition [8]. Simulations have also identified that ligand spacing exceeding 60 nm leads to a decrease in clustering [9-10]. To explain the mechanical aspects of cell-matrix interactions, molecular clutch models were developed [11-13] and extended to include for example Rho signalling [14]. We have developed a mechanochemical model to capture the biochemical and mechanical changes during the focal adhesion maturation process, including force-dependent talin unfolding and vinculin reinforcement and show that disassembly dynamics play a crucial role in stiffness sensing (work under review). In addition, we are developing a stochastic agent-based model to understand how YAP-based mechanosensing arises from the dynamics of integrin clustering, disassembly and nuclear translocation (unpublished data). Subcellular clutch models have been integrated to capture cell scale behaviour such as mechanical homeostasis [15] and cell motility [16-19], providing evidence for ‘negative durotaxis’ [20]. At the tissue scale, mechanical models including cadherin signalling have been, for example, used to understand the dynamic nature of gap formation in the endothelium [21].

Future directions
Considering that both integrin and cadherin families form bidirectional signaling linkages and transmit microenvironmental information across the cell membrane, including common effector molecules in the cascading signaling pathways, future work should focus on integrating cadherin and integrin computational models in order to elucidate the adhesive crosstalk. Moreover, further advances in experimental techniques will enable cell-specific calibration of the above models, allowing to elucidate cell-specific physiological and pathological mechanisms of adhesive crosstalk and ultimately contributing to improved biomaterial design and regenerative medicine strategies.

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Background
Large bone defects remain a clinical challenge, with a gold standard treatment – autologous bone graft transplantation – that presents many drawbacks. Design optimized scaffolds appear as a promising alternative however, bone scaffold design remains a trial and error approach where specific properties (e.g. porosity, pore size) are individually optimized, not taking into account interactions between scaffold design parameters and their influence on the dynamics of the regeneration process.

Recent Advances
Multiscale computer models of bone regeneration appear as a powerful tool towards scaffold design optimization however, it requires: 1) the validation of the models in terms of their ability to predict bone formation within the scaffold pores for different scaffold designs and 2) low computation time so that they can be integrated in an optimization framework. Several computer models of bone regeneration have been developed in the last decades (review [1]), however only few have compared model predictions with dedicated experimental data. In our group, we have combined in silico and pre-clinical studies to come to an understanding of the mechanisms behind uneventful (e.g. [2]) and compromised (e.g. [3]) bone healing. More recently, we have further developed these models to investigate the process of scaffold-supported bone regeneration [5,6] (Fig. 1), where we have tested the models against different experimental set-ups where different scaffolds designs have been used for bone regeneration in large defects. Using these validated models, we have then developed a computational framework, based on surrogate modelling techniques, that allows us to computationally optimize the design of scaffolds with the objective to achieve maximum bone regeneration [7].

Future directions
In the near future, we aim to test the potential of the models to predict bone healing outcome in patients and to use the developed tools to optimize patient treatment design, both in non-compromised and compromised conditions. In the long-term future, we would like to develop a computer tool that could help decision making in the clinic as well as contribute to the design on 3D printed support structures to promote the regeneration of bone.

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Sara Checa is currently Professor at the Julius Wolff Institute, Charite Medical University Berlin. She obtained her PhD in Biomechanics at the University of Southampton in 2007. She was a post-doctoral fellow at Trinity Centre for Bioengineering, in Dublin, between 2007-2009 and at Stanford University in 2013. She holds a Guest Professorship at the Technical University of Berlin. Her present research mainly focuses on the development of multiscale computer tools to investigate the mechanisms behind bone tissue regeneration and to support the design of novel treatment strategies. She is an author of more than 60 publications in peer-reviewed journals, 6 chapter books and more than 90 contributions to International and National Conferences.

Figure 1: Computer model predictions of bone regeneration within a strut-like PCL scaffold (A) implanted in a sheep tibia large bone defect [8], (B) Comparison of computer model predictions of bone regeneration with in vivo data. (C) Computer model predictions of the influence of scaffold design on the healing outcome.
Background

Vascular adaption is the ability of blood vessels to adapt throughout life depending on genetic programming and biochemical processes in response to multiple stimuli, including mechanical and hemodynamic forces [1]. Major cardiovascular diseases, such as atherosclerosis, are characterized by vascular adaptation processes. These processes are governed by multifactorial and multiscale networks of events involving feedback mechanisms, cause-effect relationships and mutual interactions of components across different spatial (i.e., from molecules to cells and tissues/organs) and time (i.e., from seconds to days and years) scales [2]. In the last decades, researchers have applied a wide variety of approaches to investigate adaptation events, conducting extensive in vitro, in vivo and in silico research. In this context, multiscale computational models inspired by systems biology principles are emerging as powerful tools to bridge in vitro models of single-scale phenomena to in vivo models of the whole system of interest.

Recent Advances

Both continuum and discrete modelling strategies are options for the investigation of vascular adaptation [2]. Recently, our research group has developed a multiscale agent-based modelling framework, integrating both continuum and discrete approaches, which is able to include components across different spatio-temporal scales and capture the dynamic interplay of the events characterizing vascular adaptation (Fig. 1). The framework is composed by three different modules simulating (i) hemodynamics and/or solid mechanics with a continuum approach, (ii) arterial wall remodeling in response to hemodynamic, mechanical, inflammatory stimuli through an agent-based model (ABM) of cellular dynamics and (iii) monocyte gene expression, providing an inflammatory stimulus to the ABM. The framework has been applied to study atherosclerosis [3], restenosis after balloon angioplasty [4] and in-stent restenosis [5]. While in [3,4] idealized models were built, in [5] a patient-specific model of stented superficial femoral artery, which integrates the effects of hemodynamics and monocyte gene expression on cellular dynamics, was developed. After proper calibration, the latter model was able to describe the 1-month arterial wall remodeling following stent deployment.

Future directions

Despite the multiscale agent-based modelling frameworks presented herein are promising tools for the study of vascular adaptation, major challenges regards

(i) the reduction of the computational costs, (ii) the process of model verification, calibration and validation against large patient-specific data sets, (iii) the inclusion of multi-omics data, defining patients’ molecular signature at the local level. Future research efforts are expected to address these challenges, thus advancing the multiscale computational solutions for a better understanding of the vascular diseases, and management of diagnosis, prognosis and treatment.

Figure 1: General representation of our multiscale framework of vascular adaption.

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3D BIOPRINTED SCAFFOLD WITH CONTROLLED RELEASE OF MESENCHYMAL STEM SECRETOME FOR BONE REGENERATION

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Background
Bone tissue engineering aims to repair bone defects through in vitro grafting of scaffolds manufactured by 3D printing, enabling a finer control of the scaffold porosity when compared to traditional methods [1-3]. Although this technique is promising, the results are not always satisfactory due to the poor ability of cells to deeply colonise the scaffold, both in vitro and in vivo, compromising the proper tissue regeneration [4, 5].

Recent Advances
Given such considerations, we have recently proposed a 3D-coprinted hybrid scaffold made by polycaprolactone (PCL) and alginate-based hydrogel containing lyosecretome [6], which is a freeze-dried formulation of mesenchymal stem cells secretome (pool of molecules composed by growth factors, cytokines, proteins, lipids, and oligonucleotides) that can promote cellular proliferation and differentiation aided to an effective scaffold colonisation. Thanks to the simultaneous presence of PCL, which provides mechanical resistance, and the hydrogel that releases the lyosecretome, the scaffold is designed to perform a double function: to stimulate its in vitro and in vivo bio-integration, thanks to lyosecretome action, and to bear loads. In this context, we demonstrated that the inclusion of the lyosecretome strongly improves the osteoinductive potency of the scaffold [7] and that its release kinetics can be controlled up to 10 days by tuning the parameters of scaffold manufacturing [6]. Moreover, the mechanical performance of the scaffold and its implications for the design of the device have been investigated by implementing a validated computational framework (structural Finite Element Analysis – FEA) to support the design of the hybrid scaffold. Results show an increase in mechanical properties by changing the scaffold infill pattern (145.38±28.90 vs 278.96±50.19, linear vs honeycomb, respectively), while alginate inclusion does not always impact the mechanical performance of the hybrid scaffold (stiffness: 145.38±28.90 vs 195.42±38.68 N/mm, with vs without hydrogel inclusion, respectively).

Future directions
A case study for repairing bone defect is proposed as future development. Starting from the patient-specific’s bone defect, the defect model is extracted from the instrumental images. Then, the model is modified in order to create the hybrid scaffold by adding the lyosecretome/alginate inclusion(s) and defining the structural parameters of PCL structure. Mechanical properties of hybrid scaffold is predicted for identifying the best configuration that satisfies the targets.

Michele Conti has been working in Biomechanics since studying for his master thesis about stent simulation (2007), continuing his research in computational biomechanics during the joint PhD in Biomedical Engineering (Pavia University, IT and Ghent University, BE). Afterwards he has contributed to promote the biomechanical activity of CompMech Group of Pavia University, where is actually Associate Professor in Industrial Bioengineering, fostering close collaboration with clinical partners. He has published over 70 papers in peer-reviewed international journals and organised several events about biomechanics and bioprinting, actively contributing to Italian chapter of ESB. He is currently member of the ESB council.

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Figures

Figure 1: 3D coprinting and characterization of hybrid scaffold.

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
WHAT MECHANICAL QUANTITY DO CELLS REGULATE IN SOFT TISSUES?

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Background

In soft biological tissues, cells seek to establish and maintain a preferred mechanical state, the so-called homeostatic state. This state is marked by a specific (non-zero) tensile stress. However, so far, it remains controversial whether cells directly regulate stress or whether they primarily control some other target quantity from which tensile stress results as a consequence [1]. Understanding what target quantity cells are primarily regulating in soft tissues and how they are doing this is one of the key questions of current soft tissue biomechanics and mechanobiology. Answering it will be an important step towards predictive computer simulations of growth and remodeling in soft tissues, which play key roles in various areas ranging from tissue engineering to clinical healthcare (e.g., aneurysms).

Figure 1: Combined experimental (left) and computational (right) framework to study interactions between cells and extra-cellular matrix (ECM)

Recent Advances

To identify the target quantity cells regulate in soft tissues we developed a combined experimental [2] and computational [3] framework (Fig. 1). Our experimental setup allows well-controlled biaxial stress and strain states in tissue equivalents. Our computational framework models soft tissues as networks of discrete fibers and cells. The interactions between both are represented by a detailed model of focal adhesions. We carefully validated our model and demonstrated that it can reproduce even complex phenomena such as the scaling relation between fiber density and homeostatic stress level. Subsequently, combining extensive experimental and computational studies, we were able to identify the key factors and processes in the homeostasis of soft tissues, in particular the target quantity that cells regulate on short time scales [4].

Figure 2: Microscopically informed continuum-scale model of growth and remodeling (left) and computer simulation of durotaxis (right)

Future directions

The insights provided by our combined experimental and computational framework open up several promising avenues of research. One relates to a new generation of microscopically informed continuum-scale simulation models of growth and remodeling (Fig. 2, left), another one to a detailed analysis of complex cell-ECM interaction patterns such as durotaxis (Fig. 2, right), which opens up ways to enhanced tissue engineering

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MODERN AI MEETS BIOMECHANICS: A NEW PARADIGM FOR IN SILICO MEDICINE

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Modern AI
Modern artificial intelligence (AI) has been intensively investigated in many fields ranging from computer vision to precision medicine. Different learning strategies such as deep learning, transfer learning or reinforcement learning have been developed to shift from applied artificial intelligence to the general artificial intelligence level. Advanced AI-driven models and tools have been developed to deal with multimodal biomedical data (scalar, text, image, signal, video).

Modern AI meets Biomechanics
In this new era, the Biomechanics field has been also metamorphosed with new AI-driven models and decision supports. AI technologies have been deployed with different perspectives such as computation speed augmentation, data interpolation/assimilation and physics/biology augmentation (synthetic data, in silico trials, hybrid modeling). Different methodologies to use AI have been also proposed such as single-AI approach, combination-AI approach or hybrid Physics-AI (Physics-Informed, Physics-Augmented, AI-embedded) approach.

Recent Advances
In this talk, we will present our recent discoveries in human locomotion learning [1-3] (Fig. 1), face/skull metamorphosis processes [4] (Fig. 2), and real-time soft tissue deformation [5-6] (Fig. 3) using different modern AI approaches (deep learning, transfer learning and reinforcement learning). Clinical applications related to ageing fall recovery and prevention, facial palsy rehabilitation and childbirth decision support will be presented and discussed.

Future directions
Modern AI brings new predictive and preventive capacities with emerging data and behaviors to study the human body systems and associated disorders. Before deploying in the clinical routine practice at a large scale, model explainability, user safety, ethical issues (error responsibility, data privacy) should be carefully addressed.

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Figure 1: Reinforcement learning and transfer learning for human falls learning and recovery.

Figure 2: Deep learning for face/skull metamorphosis.

Figure 3: Deep learning for real-time soft tissue deformation: physiological and forceps-assisted childbirths.
HOW BIOMECHANICS IS CHANGING WOUND CARE: CURRENT ACHIEVEMENTS AND FUTURE PROSPECTS

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Background
Difficult-to-heal wounds are currently considered among the most important, unsolved and expensive medical burdens. The major chronic wound types are pressure ulcers (PUs), also known as pressure injuries in the US, Canada and Australia), diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs). Each of these wound etiologies involves a considerable mortality risk, for example, PUs cause deaths of 5 per 100,000 people each year at the ages of 65-84, and of 24-30 per 100,000 annually among those older than 84 years [1]. Our research work - extending over twenty years - has explained why quantitative, absolute and generic injury thresholds to predict when PUs, DFUs or VLUs may occur in a certain individual will unfortunately forever remain intangible, despite the vast efforts and resources that have been invested in allegedly discovering such injury thresholds. This perspective talk will explain why seeking such injury thresholds is naive and will always remain the ‘search for the holy grail’; yet, it will also describe routes for constructive future bioengineering research work needed for better prevention and treatment of PUs, DFUs and VLUs even if currently, there are no simple or straight-forward injury thresholds to predict when a person may suffer a chronic wound.

Biomechanics in wound care research
The roles of biomechanics and mechanobiology in better understanding wound etiologies and improving wound care will be described, in both basic and applied research contexts [2,3]. Biophysical markers for early detection and for targeting prevention will be discussed, given the availability of mechanobiological approaches and methodologies to discover or test feasibility of such biophysical markers towards clinical use, including based on daily subepidermal moisture measurements, infrared thermography imaging, tissue oxygenation readings, high-resolution/contrast skin and wound image processing and hybrid modalities [4-7]. The emerging role of machine learning algorithms in processing the above sensory data will be demonstrated [8]. Some inherent complexities in the prevention and treatment of PUs, DFUs and VLUs will be elucidated, particularly that: (i) Susceptibility to hard-to-heal wounds depends on integrated body system functions which are extremely difficult to predict in individuals, especially in seriously ill patients. (ii) A continuum exists between prevention and treatment of wounds, and clinicians are often required to treat an existing wound while protecting adjacent (peri-wound) tissues from deteriorating at the same time. (iii) Bioengineering can

Amit Gefen is a Full Professor with the Department of Biomedical Engineering at Tel Aviv University and the Berman Chair in Vascular Bioengineering. The research interests of Prof. Gefen are in studying normal and pathological effects of biomechanical factors on the structure and function of cells, tissues and organs, with emphasis on applications in acute and chronic wound research. To date, Prof. Gefen published more than 300 articles in peer-reviewed international journals and multiple edited books on mechanobiology, cell and tissue biomechanics, with applications that are mostly in wound prevention and treatment. Prof. Gefen is listed among the top 50 most cited biomedical engineering scientists worldwide.

Future directions
Future bioengineering research in wound care is expected to rely heavily on robotics-aided experimental test systems, computational modeling and mechanobiological assays in cell cultures, which altogether facilitate better understanding of risk factors, injury cascades and (cost-)effective treatments.

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BUILDING AN ECOSYSTEM FOR DIGITAL TWINS IN HEALTHCARE

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Digital twins in healthcare
The use of digital twins in healthcare (DTH) is rapidly increasing. One application area is the personalisation of medical care, where DTH can take the shape of in silico models of organs and organ systems used to test various treatment options, to customise therapy or plan surgery. In the context of the development of medical therapies (drugs & devices), DTH can be used as a tool throughout the entire R&D process to identify knowledge gaps and flaws, obtain a holistic and better understanding of a patient's disease, design novel strategies, optimise therapies, optimise therapy production, increase safety (by providing additional scrutiny) and shorten the time to market. DTH can be used to improve healthcare organisations by driving efficiency, optimising operational performance and enhancing both patient and caregiver experience.

Towards a Virtual Human Twin
Current solutions labelled as DTH are mostly single-scale, single-organ, single disease systems simply because going beyond this is still too complicated and time-consuming, and hence prone to be neither realistic nor reliable. However, the human body is highly entangled: events occurring at one anatomical location at a given time may influence processes occurring at different locations and at different times. Therefore, the number of clinically relevant questions answerable with single-scale, single-organ, single disease models is relatively limited. Including several scales and levels of organisations - even in a question-driven approach - generates huge challenges to modelling, increasingly subject to bottlenecks. To accelerate the adoption of an integrated Virtual Human Twin, it must first become easier to develop them, even when they need to be multi-scale, multi-organ, and multi-disease.

An ecosystem approach
The challenges related to developing a Virtual Human Twin call are too substantial to be handled by any one research group or even research project. They call for an ecosystem approach. The European Commission’s Coordination and Support Action EDITH has as its objective to foster such an ecosystem and develop a roadmap towards the integrated Virtual Human Twin. The first step is an extensive mapping of relevant actors and initiatives, available resources (models, data sets, methods), infrastructures, DT-based solutions and services, as well as detecting technical and non-technical barriers to the uptake of DTH. This will allow to focus on the creation of a functional ecosystem bringing together all relevant stakeholders, including solution developers in academia and industry, technology/resource providers, end-users (particularly healthcare professionals and patients), regulatory agencies and HTA bodies. Leveraging the budding ecosystem, the consortium is working on a roadmap for accelerating the uptake of the DTH-based solutions and their further integration. They will develop a blueprint of the Virtual Human Twin and identify the required (technical) developments, including but not limited to interoperability, computability, and integration of health data. The previously identified stakeholder needs and implementation barriers will be addressed. Additionally, an analysis of areas of applicability will be conducted, targeting especially applications representing high unmet medical needs and/or high societal benefits or clinical values. Finally, instruments such as funding, policies, standards, and specific recommendations will be specified for short and mid-term, taking into account the current legal, ethical, social and regulatory framework and country-specificities.

Summary
In this perspective talk, I will present the first version of the aforementioned roadmap and discuss the vision of the Virtual Human Twin, as well as the identified research challenges, infrastructure needs and policy requirements.

Acknowledgements
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THROMBUS MECHANICS: FROM MICROSTRUCTURE TO IMAGING AND DEVICE DESIGN

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Background
Thrombi play a crucial role in two vascular diseases. If a thrombus gets lodged in an intracranial artery, this may lead to local reduction of blood flow to the brain, inducing an acute ischemic stroke (AIS). A thrombus can also form in the venous system, and if this happens in the legs, this leads to deep vein thrombosis (DVT). Although these diseases differ in etiology, they also have something in common: patients benefit hugely from fast and efficient thrombus removal from the arteries in the brain or the veins in the leg.

Clinical studies show that mechanical removal of thrombi — also called thrombectomy — greatly benefits the patients. The two main approaches to thrombectomy are (i) thrombus removal by aspiration, and (ii) thrombus removal using a stent retriever. It is still unclear what the optimal treatment strategy during an interventional procedure is and what the best device design is for thrombus removal.

Multiscale thrombus models
The mechanical properties of the thrombus play a crucial role in thrombectomy; the interaction with the vessel wall, the large deformation imposed on the thrombus by the device, and the thrombus fracture properties determine the success of the procedure. Recently developed mechanical models of the thrombus to describe these properties in a quantitative manner, and how they are related to the microstructure, are key elements in supporting the impact of thrombus biomechanics on clinical applications. The relationship between the 3D structure of the thrombus, the interaction between the (active) components in the thrombus, and how this is reflected in imaging characteristics and macroscopic properties (figure 1) are the key elements of this perspective talk.

Current and future applications
Once these models are validated, they can be applied in optimizing the design of new devices and treatment strategies through in silico approaches. To improve the treatment of AIS and DVT patients, these thrombus models can be used to develop in silico tools for virtual intervention planning and simulated clinical trials, and develop in vitro and in silico methods for the design and optimization of new devices. These topics will also be addressed in this talk.

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Figure 1: the relationship between microstructure and macroscopic behavior of thrombi

Dr. Frank Gijsen is currently associate professor at the department of Biomechanical Engineering at the TUDelft and the department of Cardiology at the ErasmusMC, and he is Editor in Chief of the Journal of Biomechanics. His present research focuses on image-based cardiovascular biomechanics, with an emphasis on application of multiscale models on the prediction of the growth, remodeling and failure of cardiovascular tissues.
Background
Over the past 20 years, the field of human movement biomechanics collected a huge amount of integrated 3D motion capture data in both healthy subjects and those with various musculoskeletal pathologies. This has resulted in a large data set of kinematics and kinetics describing locomotor function, during a range of activities of daily living in a large population. Further, with accelerated acquisition and increased quality of medical imaging, rich data sets on musculoskeletal geometry are also steadily becoming more available. While this data is often used to perform a case-by-case cross sectional analysis on specific individuals, they remain a sparse sample of specific populations. Therefore, we explored emerging techniques for population-based modelling approaches. Given the relevance of mechanical loading as driving factor and its high prevalence [1], the use, applicability, and relevance of these model-based approaches in knee OA will be discussed.

Recent Advances
Two specific population-based methods will be introduced, both based on data reduction and principal component analysis: The first is based on principle components derived from motion capture data – specifically joint angles or kinematics [2]. Using existing datasets from both healthy control subjects, and patient with knee OA, we determined and defined the average 3D kinematic gait pattern during walking gait along with the primary variations seen within a studied knee OA population. The second, relates to knee joint alignment – specifically femoral and tibial bone and cartilage geometry [3]. Using SSM modelling approach, the average geometry and primary variation in geometry are determined. In isolation, each of these approaches can determine specific kinematics and/or geometric variations which are unique to each population and may relate to disease onset or progression. Further, based on clustering methods, specific knee OA phenotypes can be defined, identifying subjects at risk of accelerated progression.

In combination with state-of-the-art musculoskeletal modelling, both these methods provide exciting opportunities to unravel the knee joint loading landscape of the knee OA joint. By using the statistical distributions of gait kinematics, and joint geometry – we can, at least in theory, clinically relevant parameters from MSK modelling such as joint contact forces and pressure. Using novel state-of-the-art methods, we can include different joint geometries in our musculoskeletal models to determine the effect of joint geometry on estimated joint contact parameters. Further, using reconstructions of gait patterns – the effect of different gait patterns on joint contact loading parameters can be determined.

Future directions
Population-informed models and simulations, if informed by rich enough data, will be used to develop machine learning based approaches to estimate joint loading parameters based on lower dimensional data (e.g., joint dimensions combined with 3D accelerometer data).

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Figure 1: Schematic representation of population-based joint loading landscape.

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TOWARDS PERSONALIZED SIMULATIONS AS
PRE-PLANNING TOOL FOR CARDIOVASCULAR PROCEDURES

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Background
Currently, computer modeling and simulation are increasingly mentioned as technology to represent and predict well-defined quantitative clinical endpoints. In cardiovascular applications, transcatheter aortic valve implantation (TAVI) and thoracic endovascular aortic repair (TEVAR) are examples of planned interventions to treat aortic valve and aorta disease respectively, while intra-arterial thrombectomy (IAT) is an emergency intervention to treat acute ischemic stroke. Despite their widespread clinical use, they still show some short- and long-term complications that require further investigation.

Recent Advances
Recently an inverse elastostatics method with exact linearization to obtain the zero-pressure configuration of the reconstructed-from-images vessels (Fig. 1a-2a) has been developed to obtain accurate results in terms of stress and strain field on the patient-specific domain. TAVI (Fig. 1b) – Starting from the developed patient-specific fluid-structure interaction (FSI) methodology [1], recent studies concern the inclusion of the coronary arteries, the fluid domain validation within MRI scans, the TAVI in patients with bicuspid aortic valve [2]. TEVAR (Fig. 1c) – The same verification and validation analysis we proposed in [3] has been recently applied to different stent grafts in order to have a library of the most used devices available to perform FSI simulations. The in silico TEVARs have been recently used prior to the real interventions to help clinicians in the pre-operative decisions.

IAT – The developed high-fidelity simulation to virtually reproduce the IAT has been validated with in vitro experiments [4-5] and used to model a patient-specific procedure [6]. Recently, we have investigated surrogate modeling techniques to have a real-time prediction of IAT outcomes [7].

Figure 1: (a) reconstructed aorta for FSI (b) TAVI and (c) TEVAR patient-specific simulations.

Figure 2: (a) angiography of a stroke patient and (b) simulated IAT to extract the thrombus.

Future directions
How these in silico technologies can be used, in which context, and at what point in time need to be always clarified when dealing with computational modeling. Personalized simulations as a pre-planning tool will be improved in the context of use of the single considered procedure: high-fidelity FSI models for the planned TAVI and TEVAR, surrogate models for the emergency IAT.

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CHEMO-MECHANICAL MODELS OF ACTIVE CELL FORCES IN GROWTH AND REMODELLING

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Background

Biological cells actively generate contractile and protrusive forces to probe their surrounding microenvironment, and mechanically communicate with other cells. In turn, cells continuously remodel their shape, size, and cytoskeleton in response to chemical and mechanical feedback which can stimulate active tissue growth and remodelling [1]. A growing field of research has evolved around theoretical mechanobiology and computational cell mechanics to provide fundamental insight into the biomechanisms that underlie dynamic cell activity and tissue reorganisation in disease.

Recent Advances

Remodelling of actomyosin, the force-generating machinery in cells, is stimulated by changes in cellular loading. Considering the chemical free energy of associated bound and unbound cytoskeletal proteins facilitates a natural coupling between stress/strain-rate dependent cytoskeletal remodelling and dynamic cellular contractility [2, 3]. We demonstrated that cell spreading and shape emerges from a competition between such chemical free energy and deformation of elastic cell constituents (Fig 1A), whereby cells assume low free energy states [4]. Extended to tissue-level, the model also provides a free-energy basis for heart failure [5] whereby increased cross-bridge cycling due to pathological loading can reduce the chemical potential of unbound proteins to drive muscle fibre assembly in hypertrophy. Active cell models can also provide insight into cancer progression and metastasis. We developed a theoretical model to uncover how gap junctions can amplify spatial variations in tumour cell volume by facilitating ion flow stimulated by growth-induced stress (Fig 1B), with implications for tumour invasion [6]. When tumour cells break away from a primary tumour, they may burrow through gaps in blood vessels which act as a superhighway to distant organs. In new work, we proposed a novel chemo-mechanical model to determine how the feedback between mechanosensitive signalling and active cell forces regulates endothelial gaps (Fig 1C). Combined with time-series imaging of junction remodelling, we determined that a critical balance between contractile and protrusive forces is required for stable adhesion [7]. Recently, we also developed a novel cell growth model to provide a biophysical explanation for stress-dependent growth in tumours and other tissue.

Future directions

An important future direction would be to explicitly couple active models for cytoskeletal contractility with size control for analysis of mechanosensitive feedback pathways in disease. Moving forward, such chemo-

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Figure 1: A) Simulated cell spreading as driven by free energy minimization [4]; B) Predicted spatial variance in tumour cell volume [6]; C) Endothelial gaps as regulated by competing active forces [7].

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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
Background

To form the patterns and behaviors that we observe in multicellular development, cells must carefully coordinate their behavior through biophysical and biochemical cues. Numerical modeling and theory are essential for analyzing the mechanism of such coordinated, collective cell behavior. To do so, single-cell models must be sufficiently detailed so they correctly capture essential aspects of individual cells and do not oversimplify. At the same time, single-cell models must be sufficiently simple and computationally efficient so they can be upscaled to multicellular systems. My team analyzes single cell behavior and multicellular development using a combination of mathematical, computational and experimental approaches. Our central tool is the cellular Potts model (CPM), a widely-used, lattice-based framework for modeling cell behavior. For most applications we couple the CPM with simulation models of the cellular microenvironment and relevant intracellular dynamics, a technique known as the hybrid CPM.

Recent Advances

I will present a series of our recent hybrid CPMs for modeling individual cell behavior, and show how these can be used to study the coordinated cell behavior that is seen in biological development. I will first discuss a series of models used to analyze observations such as anomalous cell migration patterns of immune cells [1], the effect of extracellular matrix stiffness on cell shape ([2] and Fig. 1A), cellular force transduction in fibrous ECMs ([3] and Fig. 1B), and models of anisotropic force generation [4]. I will then discuss how insights from single cell models translate to understanding of multicellular development [5,6] (Fig. 1C-D).

Future directions

In our ongoing work, we are developing strategies for experimental falsification and iterative correction of multicellular models of angiogenesis. Recent versions of our cell-ECM interaction models focus on how our descriptions of focal adhesions, the mechanosensitive ‘feet’ of cells by which they hold on the extracellular matrix, must be improved to analyze mechanical cell-ECM interactions. Also we invest in computational improvements to advance towards more detailed multicellular models. Altogether, I will resent the use of cell-based modeling in analyzing how local cell-microenvironment interactions coordinate cell behavior during multicellular patterning.

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MECHANOBIOLOGY OF CANCER PROGRESSION

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Context of the research
Female breast cancer is currently the most diagnosed cancer, with an estimated 2.3 million new cases per year. Breast cancer is known to be initiated by the mutation of specific oncogenes. It has been recently proven, however, that progression of the tumour is dictated by changes in the mechanical microenvironment of the mutated cells [1]. Breast cancer aggressiveness correlates specifically with fibrosis involving the deposition of a collagen matrix by stromal fibroblasts. Tumour-infiltrating immune cells like macrophages secrete signals that further increase collagen deposition and progressive tumour stiffening. This extracellular matrix acts as a progressive diffusive barrier. To overcome the progressive tumour resistance to anticancer treatments, it would be transformative for the field to understand and control how the tumour fibrotic environment evolves.

Background
The key mechanical/mass transport parameters of tumour stiffening are the fibrillar collagen matrix properties (e.g. stiffness, density, diffusion coefficient) and the microvascular network properties (e.g. geometry, permeability). These properties determine interstitial fluid pressure and blood flow velocity in the tumour, which modulate pH, diffusion (of endogenous molecules as soluble signals, nutrients, gases, metabolic products and of anticancer agents), cancer cell response (proliferation, motility, metabolism) and infiltration in the tumour of non-cancer cells (endothelial cells, macrophages, fibroblasts). Microfluidic-based platforms can recreate complex functional aspects of this mechanical environment in vitro. However, microvascular networks generated in vitro aren’t stable enough in terms of hierarchy and permeability, to reproduce physiological profiles of luminal flows.

Recent Advances
The embryonated avian egg experimental model allows to measure in vivo the effect of therapeutic agents injected in the embryonic circulation, on a structure called chorioallantoic membrane and/or on the embryo. This model has also been used to monitor in vivo the invasive features of human ovarian, thyroid, and skin cancer cells. My group has recently replicated the human microvascular niche and relevant druggability in vivo using this model [2].

Future directions
We will use human breast cancer cells adhering to 3D polymeric micro scaffolds to create arrays of tumour micro environments. We will implant the arrays in vivo in the chorioallantoic membrane of an embryonated avian egg, to elicit a foreign-body fibrotic reaction. We will vary the micro scaffolds geometry to condition tumour infiltration by the host’s vessels and cells. We will predict mass transport of solutes and anticancer agents by computational modelling. To validate the platform, we will quantify in vivo the dose-dependent efficacy and cancer specificity of therapeutic agents whose success is known to depend on the fibrotic stage of tumours.

Manuela T. Raimondi is currently Professor in bioengineering at the Department of Chemistry, Materials and Chemical Engineering “G. Natta”, Polytechnic University in Milano, where she obtained her PhD in Bioengineering in 2000 and was a post-doctoral fellow. In 2020, she was a visiting professor at the University of Pennsylvania in Philadelphia. She has pioneered the field of cell modelling, by contributing frontier tools such as synthetic stem cell niches and organs-on-chip, funded by 4 awards by the European Research Council. She is an author of 112 publications in peer-reviewed journals, 10 book chapters, 8 patents and more than 120 contributions to International and National Conferences.

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ACTIVE MATTER MEETS BIOENGINEERING: HOW MODELS OF ACTIVE TISSUE MECHANICS CAN IMPROVE BIOFABRICATION

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Background
Tissues are living materials that adapt their mechanical and rheological properties to the physical environment, which in turn alter the biological fate of its constituent cells. This needs to be taken into account in the development of new biofabrication processes, where engineers require quantitative material models that predict the rheological behavior of living cellular products and relate the physical micro-environment to cell fate. The last years have seen great improvements in active matter models of cell and tissue biophysics. Continuum approaches include active hydrodynamic models, which consider a tissue at long timescales as acontractile, active fluid with nematic and turbulent properties [1]. Prevailing cell-based mechanical models of tissues are the vertex model and its derivatives, which have been particularly successful in examining tissue rigidity transitions [2] and tissue rheology [3]. A recent development of vertex model is the active foam model [4], which considers tissues as foam-like structures, with individual cells behaving as active ‘bubbles’ or droplets, a paradigm that is also reflected in the active shell model for single cell mechanics [5]. However, despite their success in biological applications such as cancer and development, these models have not yet been widely adopted in the context of biofabrication.

Recent Advances
This perspective presents our latest developments in computational modelling of active tissues. We first revisit a theoretical hydrodynamic description of tissues as polar active fluids to explain the observation of collective contact guidance of epithelial cells following topological substrate cues, and demonstrate the close analogy between hydrodynamic theory and simulations of polar, self-propelled particles. Next, we introduce a novel active foam model of 3D tissues based on an active shell description of cells [6]. We demonstrate that the introduction of bond lifetime in this model through cell-cell friction qualitatively affects the jamming phase diagram. As such, this parameter represents a novel physical mechanism for tissue jamming with direct biological analogues in processes such as the epithelial-to-mesenchymal transition and tumor progression. Applied to the phenomenon of tissue spheroid fusion [7], this model predicts that a wide variety of micro-mechanical and material properties can be obtained by varying cell activity and cell-cell interfacial tension (contractility), including complete and arrested fusion and arrested versus fluidized tissue rheology, Fig. 1. Finally, we demonstrate how these structures can be harnessed in bioprinting different geometries of artificial tissue constructs.

Future directions
In the context of biofabrication, the active foam behavior of self-assembled tissues interacts with the encapsulating material, such as the bio-ink, to establish the biomechanical properties of engineered tissue constructs. Going forward, integrated multi-scale and multi-physics models that take into account this integration will be needed in order to become an integrative part of the engineering pipeline for biofabrication.

Figure 1. Phase diagram of spheroid fusion based on active foams

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Background
Bone is a naturally occurring composite material whose constituent phases are hierarchically organized to provide a structure that exhibits high stiffness and excellent resistance to fracture [1]. At the tissue-scale and above, there are now well-established structure-property relationships that provide good approximations of biomechanical performance through, most commonly, power-law relationships that relate tissue mineral density to elastic properties ($E \propto \rho^a$) However, below the tissue-level, the individual role of the constituents becomes prominent and more advanced theoretical and computational models are required to describe the mechanical response [2], [3]. While these models have provided excellent insight into sub-tissue biomechanics in the elastic regime, the prediction of damage and failure processes at this scale becomes extremely challenging. In particular, lamellar bone is composed of mineralised collagen fibrils that are embedded within an extra-fibrillar matrix comprised of hydroxyapatite minerals and non-collagenous proteins. Each of these constituent components exhibit drastically different mechanical behaviour and there remains some uncertainty on the precise arrangement of these constituents at lower length scales. This talk will provide a perspective on the structural roles of mineral, collagen and non-collagenous protein constituents by presenting our current understanding of bone biomechanics at small length scales, with quantitative insight provided by a range of recent multiscale models that we have developed in this area [3-9].

Recent Advances
Building on previous experimental observations, we have developed both finite element [3, 4, 7] and coarse-grained molecular dynamics [5, 6, 8, 9] models to investigate the roles of mineral, collagen and non-collagen proteins on the sub-tissue mechanical properties. These have investigated the relative roles of intra- and extra-fibrillar mineral on tissue biomechanics, demonstrating that the extra-fibrillar mineral is the phase that makes the primary contribution to tissue stiffness [4]. While the extra-fibrillar matrix is a key determinant of elastic properties, we provide evidence that intra-fibrillar mineralisation is essential in providing mineralised collagen fibrils both high strength and ductility [5]. Furthermore, these results show that mineralised collagen fibrils have fracture strains that are far higher than tissue-level fracture strains. These properties enable mineralised collagen fibrils to provide extrinsic toughening to crack propagation at this scale [6, 7], through mechanisms such as fibre bridging. Finally, we investigate the structural roles of non-collagenous proteins [7-8] and have predicted their significant potential to dissipate energy at mineral interfaces in the tissue. In agreement with experimental observations [10], these components likely play a critical role in the onset and evolution of damage at constituent interfaces at lower length scales. Together, these models show that subtle changes in constituent properties and/or arrangement can have a drastic impact on higher-level tissue performance.

Future directions
Our recent computational work has provided quantitative insight on the relative contributions of tissue constituents on bone biomechanics. However, significant challenges still remain. Such computational models are generally limited to an individual length scale, where it assumed that a characteristic representative volume element (RVE) can be defined. However, the definition of model parameters within these representations (both geometric and material) is extremely difficult, and computational models of this type remain “conceptual”, rather than being truly predictive. Future directions in this area require closer collaboration with the state-of-the-art experimental efforts in this area, to better define structural, compositional and mechanical properties of constituents at lower length scales.

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MODELING MECHANICS OF 3D PRINTED CERAMIC BONE SUBSTITUTE IMPLANTS TOWARDS PERSONALIZED DEVICES

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Background
3D printing is an emergent manufacturing technology recently being applied in the medical field for the development of custom bone prostheses and scaffolds. Among the several Additive Manufacturing technologies, 3D printing through vat PhotoPolymerization (VPP) is a lithography-based approach that may achieve the highest spatial resolution (less than 50 m) among currently known additive manufacturing strategies. Compared to metallic and polymeric biomaterials, calcium phosphate ceramics like hydroxyapatite (HA) tricalcium phosphate and biphasic calcium phosphate implants show strong osteogenic ability without adverse reaction. HA is of particular relevance since HA bone replacements have a similar initial mechanical characteristic to cancellous bone, although this can decline by 30-40% in situ after several months after implantation. Through VPP, HA can be used to create devices with sophisticated microarchitectural elements that have great resolution [1]. The ability to customize the device to match the patient’s individual needs makes 3D printing technology a game changer in the design process of such sophisticated biomedical equipment.

Recent Advances
The design of biomechanically reliable bone scaffolds necessitates a high-fidelity manufacturing process and a precise understanding of the mechanical properties of the constituent material. To this purpose, geometric fidelity analyses, mechanical characterization of miniaturized samples [2] and, eventually, micro computed tomography based finite element models are currently being generated [3,4]. Elastic modulus, fracture toughness and tensile strength are dependent not only on the manufacturing process parameters, but also on the sample size and consequently on average intrinsic defects occurring during the manufacturing process and thermal treatments.

Future directions
Developing characterisation methods for ceramic materials and microstructured bone scaffolds that take manufacturing parameters and characteristic size into consideration is a vital step in setting the groundwork for an innovative approach to more personalized devices. Indeed, a successful industry transition to this new design approach necessitates the integration of technology, concurrent multidisciplinary collaboration, and a robust quality management system. To bring innovation into the clinical practice of bone substitute devices, innovative multidisciplinary design optimization approaches integrating clinical image data analysis, high fidelity VPP printing process, patient-specific multiscale models, biomechanical and mechanobiological design, and immersive reality technologies for surgical planning must be implemented.

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Figure 1: Sketch of miniaturized sample and micro-CT based FEM mechanical analysis of VPP HAP scaffolds.
TO ASSESS THE RISK FOR A SURGICAL INTERVENTION: THROUGH FLOW BIOPHYSICAL MODELING OR MACHINE LEARNING?

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Background

Computational modelling based on physical equations of blood or air flow has significantly advanced over the past 20 years. After methods development to make simulations 1) patient-specific by building the geometry and boundary conditions based on patient-data [1], and 2) predictive by changing components of the model (geometry or parameter) while making the hypothesis the other ones are not changing [2].

Recent Advances

Typically however, patient-data are insufficient to estimate all the parameters of the model, i.e. to have a well-posed inverse problem. Different strategies can be adopted to tackle this issue [3]. In particular, machine-learning can offer prior information [4]. Reduced models offer cheaper to run simulations to predict or design the artificial device for an intervention, validated by 3D models and partial clinical data, for example in the context of pulmonary hypertension treated with a Potts’ shunt [5]. They allow patient-specific prediction of a surgical risk, such as the risk of portal hypertension in liver partial resection [6], although it requires a careful sensitivity analysis to understand how patient-data and model parameters are related [7].

Future directions

As machine-learning and deep-learning are making so much progress to predict for example the complexity of a surgery [8], what type of models will be more effective to assess surgical risks related to flow changes? Part of the answer is complementarity [9], especially when mechanobiological processes are not fully elucidated and thus not yet put in equations. In any case, a tight collaboration between scientists and clinicians is necessary to bring biophysical fluid models to the clinics, and to design model and data acquisition that are coherent with the surgery of interest.

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MECHANOBIOLOGY FOR CLINICAL CANCER PROGNOSIS:
CONTEMPORARY SCIENCE AND FUTURE, APPLICATIVE PROSPECTS

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Background

Cancer is currently the second cause of death worldwide, with 90% of mortality resulting from local or metastatic tumour-cell spreading. A critical step in metastasis formation is forceful invasion of tumour-detached cancer cells through dense tissue-microenvironments. To traverse their surroundings, invading cells must change morphology and apply forces. We and others have shown that invasive, metastatic cells are dynamically softer both internally [1,2] and externally as compared to non-invasive or benign cells, yet can also adapt and apply strong adhesive [3] and invasive [4,5] forces if advantageous. This perspective talk will be used to discuss the unique, highly dynamic and adaptable mechanobiology of cancer cells as well as the mechastructure and force application mechanisms that facilitate invasiveness. In addition, we will demonstrate how mechanobiology may innovatively be used to rapidly provide a clinically relevant cancer diagnosis and prognosis of metastasis likelihood, potentially also identifying target body-site.

Recent advances

The current, clinical gold-standard for tumour staging and treatment-choice is histopathological examination, which may take several weeks. Over the last decade we have shown that invasiveness of cancer and tumour cells may rapidly (2-3 hours) be evaluated in vitro via their forceful interactions [4,6]. Specifically, invasive cancer-cell subsets can forcefully push into and indent elastic, impenetrable, physiological-stiffness, synthetic gels [4,7], while non-invasive or benign cells do not significantly indent gels. The ensuing mechanical invasiveness measure, combining the number of indenting cells and their attained depths, provided accurate, early prediction of invasiveness in agreement with clinical prognosis [7,8]. Invasive subpopulations include, for example, cancer stem cells [9], associated with grim patient prognosis.

Invasive force application mechanisms require cells to adapt their mechastructure and interact with their microenvironment (cells & substrate). Cells reorganize their dynamic cytoskeleton [10,11] to facilitate force application. Via finite element models (FEM), we have shown that invasive-indentations must include a normal force element [12], and are not, e.g., a side-effect of strong, adhesive tractions. Solid-tumour cells typically invade via collective migration attached cell-cohorts that typically utilize strong cell-cell bonds. We have shown, however, that closely adjacent cells can indent more deeply than well-spaced cells, even without direct cell-cell interactions [5], likely resulting from substrate-mediated additive and synergistic force-interactions [13]. We have further observed that cell invasiveness is highly dependent on microenvironmet/gel mechanics [3,4], yet cell mechanics effects are minimal [13]. Mechanobiology can thereby be used to rapidly predict tumour invasiveness, nevertheless there is more to learn from the mechanical interactions of invasive cells.

Future directions

As organs vary in stiffness and the mechanical invasiveness is affected by gel mechanics, future developments include an approach to predict the likely metastatic body-site, within the same time-frame. We will discuss the ability to rapidly and quantitative predict the likelihood for metastasis and its effects on the clinic.

References


Acknowledgements

The support of the Israeli Ministry of Science and Technology is acknowledged (Medical Devices Program, Grant no. 3-17427, awarded to Professor Daphne Weihs in 2020).
NEWS FROM THE DEEP: MULTISCALE TISSUE MECHANICS OF COLD-WATER CORALS IN A CHANGING OCEAN

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Background

Ocean acidification is a threat to cold-water corals (CWCs) and could lead to dramatic and rapid loss of the reef framework habitat they build [1]. Weakening of structurally critical parts of the coral reef framework can lead to physical habitat collapse on an ecosystem scale [1,2], reducing the potential for biodiversity support. The mechanisms underpinning crumbling and collapse of CWCs can be described via a combination of laboratory-scale experiments and mathematical and computational models which I will illustrate in this talk.

Recent Advances

We sampled the main habitat forming CWC, Lophelia pertusa, from the Southern California Bight (SCB), a habitat representative of a future ocean. These CWCs are facing an aragonite concentration (Ωarag) ranging between 0.67-1.86; the lowest Ωarag condition that these corals have been recorded at to date [1]. We also sampled L. pertusa, from Scottish waters that are representative of a current ocean with Ωarag between 1.67-2.62 [3]. We obtained data from electron back-scatter diffraction and Raman spectroscopy (n=60), synchrotron radiation micro-computed tomography (SRµCT, n=75), nanoindentation (n=45), XRD (n=15), micropillar testing (n=144) (Figure 1) [3], and TEM (n=18). We developed a micromechanical model, supplemented by molecular dynamics simulations [3], to integrate our experimental data and to predict failure of CWC structures under climate change impacts.

Increasing porosity and dissolution from exposure to corrosive waters and bioerosion but on the structural length-scale are the main drivers for crumbling and collapse of reef habitat. Interestingly, CWC skeletal material reaches 462 MPa compressive strength and 45-67 GPa stiffness. This is 10 times stronger than concrete, twice as strong as ultrahigh performance fibre reinforced concrete, or nacre [4,5]. Contrary to what would be expected, CWCs retain the strength of their skeletal building material. They grow a strong and tuneable biomaterial which is interesting for a range of applications from novel adaptive materials to implants. The digital material is key to facilitate translation and data-driven material processing in these developments.

Future directions

Our results show how risk of crumbling of coral habitat can be assessed through evaluating increasing porosity and dissolution. We are currently generating a digital representation of the CWC material from crystal level to whole colonies (Figure 1). This will allow us to conduct data-driven analyses of habitat crumbling for entire reef systems. We complement our experiments and models with a database of >500 digitised CWCs from 1-30 cm (1 to >1000 branches). This information could help to determine tipping points of net reef habitat loss but also to develop assessment tools to quantify habitat provision of CWCs in present and projected future oceans [2]. Our results also point to mechanisms that allow CWCs to address some climate change impacts by adapting their skeletal building material. They grow a strong and tuneable biomaterial which is interesting for a range of applications from novel adaptive materials to implants.

Figure 1: Visualisation of a digital CWC material integrating computational and experimental entities in an entity relationship model.

References

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Acknowledgements

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CONTINUUM MECHANICS OF OPTIMAL TRABECULAR BONE

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Background
Trabecular bone contributes importantly to the various functions of the human skeleton and its heterogeneous architecture can be described by numerous parameters. Interestingly, bone volume fraction (BV/TV) and fabric (axes and extent of structural anisotropy) alone explain up to 98% of the variation in anisotropic elastic and yield properties independently of anatomical location. Accordingly, BV/TV and fabric are now widely used to estimate the apparent mechanical properties of trabecular bone in homogenized finite element models based on quantitative computed tomography images. In fact, Cowin and others integrated BV/TV and fabric in their continuum level remodeling algorithms. The principal fabric axes align with the principal stresses when free energy density is minimized for a given stress state [1], but the extent of the fabric orientation remains unknown. Moreover, no explicit results are available for optimality criteria other than free energy density.

Recent Advances
In the past year, the above optimization problem was formulated, and resolved analytically with three criteria for trabecular bone in the light of fabric-elasticity relationships, and their solutions were compared.

![Figure 1: Fabric eigenvalue ratios as a function of the principal stress ratios for the isotropic, asymmetric maximum principal strain criterion.](image)

For a given stress tensor, an optimal fabric was calculated that minimize volume fraction (BV/TV) under the constraint of a maximal biomechanical criterion. Three such criteria were selected: 1) the classical complementary free energy density, 2) an anisotropic measure of damage proposed in [2] and 3) an isotropic, but asymmetric measure of principal tensile and compressive strains. Fabric eigenvalue ratios were computed as a function of the principal stress ratios, while volume fraction was derived from the universal fabric-based material constants.

Analytical solutions were obtained for all criteria. For all criteria the minimum BV/TV was achieved for a fabric tensor that was aligned with the principal stresses. The extent of fabric anisotropy with respect to the stress anisotropy was derived for the first time and differed among the three criteria. The outcome of the principal strain-based criterion is shown in Fig. 1.

Future Directions
This recent work confirms the alignment of the fabric tensor with the principal stresses for the free energy criterion obtained in [1]. It also extends this result for two additional criteria and delivers the optimal volume fraction and fabric for a given stress tensor. The most realistic criterion needs to be confirmed on experimental grounds, but the principal strain hypothesis matches the poro-elastic mechano-transduction principle at the extracellular matrix level and accounts for a different threshold in tension and compression. The obtained results will allow to run and compare bone adaptation simulations at the continuum level for the three criteria. Most interestingly, the analytical resolution of the forward problem also provides the solution of the broader inverse problem that consists in finding the optimal stress tensor for an existing morphology. This last observation will contribute to the evaluation of musculoskeletal loading.

References

Acknowledgements
Grant no 200365 of the Swiss National Science Foundation is gratefully acknowledged.
POST-YIELD AND FAILURE IN SEMI-CRYSTALLINE PLLA: THE ROLE OF PLASTICITY IN THE AMORPHOUS PHASE

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Introduction
Poly (PLLA) initially showed promise as a load-bearing material for medical device applications such as biodegradable polymeric stents. However, poor performance in clinical trials has limited their use and providing sufficient stiffness and strength remains elusive. While many simulation approaches have been used to evaluate PLLA stents in silico, there is no consensus on the essential components of a material model for PLLA that captures both the initial response and that during degradation [1-2]. Here, a computational framework is presented that examines the post yield behaviour by considering a micromechanical model of a two-phase material. In particular, the role of plasticity in the amorphous phase in the post yield behaviour of the semi-crystalline polymer is explored.

Methods
A computational micromechanics model of semi-crystalline polymer using a representative volume element (RVE) approach is created (Fig 1A). Crystalline regions are anisotropic elastic, while amorphous regions are considered as isotropic elastic-plastic material and both are randomly assigned (Fig 1B). A remote strain is applied to the RVE, and periodic boundary conditions are enforced. In addition to the perfect plasticity of the amorphous phase, ductile damage (with element deletion) is introduced to prevent unrealistic local strains.

Results
Fig 1C shows the predicted remote stress-remote strain response for the RVE (without ductile damage) compared with experimental data [3] with the model parameters (crystalline volume fraction, etc.) based on the experimental study. While the yield point is in general agreement, the post-yield behaviour is not in agreement. The local stress and strain distributions in the RVE are examined and localisations in strain are used to estimate the point of failure. Other criteria are considered based on post yield softening and all predictions are compared to previously published experimental data [3-4]. When ductile damage is included in simulations, stress concentrations in the RVE lead to a cascading failure of elements and ultimately the formation of a large void in the RVE as shown in Fig 1D for $X_c = 53\%$.

Discussion
The present work shows the capability of a micromechanics model to explain experimentally observed changes in evolution of ductility as the polymer physical properties change. The results shown suggest that at a minimum, a two-phase micromechanical model which considers plasticity and ductile damage in the amorphous phase is necessary to elucidate the experimental phenomena. These simulations can provide the basis of a constitutive relation that can be used in device level simulations.

References

Acknowledgements
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DISSECTING THE ROLE OF ELASTIN BIOMECHANICS USING THE FINITE ELEMENT METHOD

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Introduction

Connective tissue diseases, such as Marfan Syndrome (MFS), can lead to cardiovascular failure due to changes in the microstructure and organization of soft tissues. It is characterized by aortic dilation and aneurysms, sometimes resulting in dissections, in addition to observable localized disruptions in the elastin lamellae—which play the primary load-bearing role in arteries at physiological pressures [1]. In previous ex vivo studies, we have assessed the straightening of elastin lamellae in mouse carotid arteries at different intraluminal quasi-static pressures using propagation-based synchrotron imaging [2]. This study outlines a computational approach with the goal of mirroring the biomechanical behavior of the imaged mouse arteries at their corresponding intraluminal pressures using the Finite Element Method (FEM). We report the Diameter-Pressure curve from 0-240 mmHg and compare to [2].

Methods

Segmented synchrotron images of the carotid artery are discretized into a mesh. Elastin lamellae are modelled as T2D2 truss elements (light green in Fig.1 b-c) with thickness corresponding to lamellae in [2] and the fiber-dependent matrix (dark green in Fig.1 b-c) is discretized and modelled as C2D3 plane-stress elements in 2D. A static analysis using Abaqus/Standard is used, and the elements of the lamellae and matrix meshes are coupled using cubic distributing continuum coupling [3]. The elastin lamellae are defined as neo-Hookean materials while the underlying matrix was defined as an anisotropic Gasser-Ogden-Holzapfel (GOH) material model [4]. With the goal of replicating the Diameter/Pressure curve, the material properties are adjusted iteratively while making three key assumptions:

1. Out-of-plane (axial) components of fibers are not accounted for, and the radial direction corresponds to the local coordinate component which was assumed to be distributed along a linear curvature gradient between lamellae, where the circumferential directions of the fibers are parallel to the closest lamella.
2. We assumed the neo-Hookean component of the GOH model to be zero or negligible. As such, we assume the artery’s isotropic response to arise from the interaction between lamellae and the underlying matrix.
3. Residual stresses are not taken into account in our model, and the compression of elastin, along with the tension in the adventitia is not accounted for.

Results and Discussion

The Diameter/Pressure curve, shown in Fig. 1 d shows that we can replicate the overall compliant characteristic of the artery using our method, with the dashed line representing data from our simulation falling between the variance of experimental diameters measured. We aim to integrate Residual Stress to our approach by applying loads that homogenize transmural circumferential stresses. Furthermore, added verification of this method will be done by comparing 3D segmented meshes to [2]. We hope to then use this method to gain a deeper understanding in the mechanical role of extent of elastin fragmentation/fenestration in aortic dissection.

References


![Diagram](image_url)

Figure 1 Illustration of our method in which we discretize segmentations of the arterial cross-sections, and apply the FEM on corresponding meshes.
POROUS TITANIUM/BRUSHITE SCAFFOLDS FOR THE TREATMENT OF LARGE BONE DEFECTS

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Introduction
The repair of large bone defects is one of the most critical clinical challenges in trauma surgery. Even though different types of materials and designs have been developed, most of these trials presented various deficiencies after the translation in the clinic. None of the proposed designs and materials could accurately mimic the mechanical and biological behaviour of natural bone. The “ideal” bone scaffold for treating large fractures must have collective properties to support healthy bone growth and avoid malunion or non-union [1]. This work aims to develop a porous composite scaffold that can imitate the natural bone by taking favourable characteristics of different materials to produce a bone scaffold that is biocompatible, appropriate for load-bearing applications, stimulates bone growth and promotes vascularisation at the defect site.

Methods
Porous titanium/brushite scaffolds (Ti/DCPD-Fe) were fabricated using powder metallurgy with a space holder process. Ti powder was mixed in different ratios with 10% iron-doped brushite. In order to create the porous structure, potassium chloride powder (0, 20, 40 vol%) was added as a space holder. Three temperatures were used for sintering in an inert atmosphere (800, 950, 1100 °C) with a sintering time constant of 2 h. The synthesised scaffolds were characterised in terms of phase constitution and porosity using XRD, helium pycnometer, SEM and micro-CT techniques. Based on the design of experiments principles (DOE), a parametric study was conducted to identify the appropriate fabrication conditions (mineral content, porosity and sintering temperature) that result in mechanical properties similar to those of natural cortical bone. Using ANSYS WORKBENCH, finite element analysis was done to investigate the stress and strain behaviour of the synthesised scaffolds. The CAD used was for femur bone with a 5 cm gap fulfilled with the synthesised scaffold (Figure 1a). In vitro cytotoxicity and proliferation assays were followed as well.

![Figure 1: The CAD of femur bone with a large bone defect (50 mm) replaced with the synthesised scaffold (a), the fabricated porous (Ti/DCPD-Fe) scaffold (b).](image)

Results & Discussion
XRD results confirmed that no oxidation of Ti was observed, even at high temperatures, while the heated iron-doped brushite was transformed into β-pyrophosphate known for its osteoconductive properties and controllable degradation rate. The powder metallurgy with space holder process was feasible in fabricating scaffolds with open, large enough and interconnected pores, which are supposed to allow vascularisation and ease penetration of cells. The synthesised scaffolds had open porosity ranging between 26 – 60% with a pore size was ~ 100 – 850 μm and interconnectivity of up to ~ 95%. The elastic modulus values for the porous composite scaffolds ranged between 3.30 – 20.50 GPa based on porosity value, mineral ratio and sintering temperature. Young’s modulus values for the porous composite scaffolds are comparable with that of the human femur bone (4 - 20 GPa) [2], which indicates they are supposed to minimise the stress-shielding effect. Also, they exhibited suitable compressive strength ~ 130 - 165 MPa at sintering temperature 1000°C or higher. These values are similar to the femoral cortical bone ~ 90 - 180 Mpa [2]. The numerical results showed that scaffolds with higher porosity and mineral content had lower stiffness values closer to that of natural bone and exhibited flexible biomechanical behaviour at the interface bone/scaffold. These findings suggest that the synthesised scaffolds have the potential to perform well for bone regeneration within large defects and could be biomechanically flexible in interaction with the surrounding tissue. In vitro outcomes displayed that all the synthesised scaffolds were non-toxic and biocompatible. Furthermore, cells presented excellent adhesion and growth, and their morphology showed a healthy attachment with a well-spread shape, which is indicative of high cellular interaction with all scaffolds’ surfaces.

References

Acknowledgements
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LARGE-SCALE PRODUCTION OF ACPC-DERIVED CARTILAGE ORGANOIDS

Florencia Abinzano (1), Jeske C.A. Feenstra (1), Rob P.A. Janssen (1,2,3), Keita Ito (1)


Introduction

Current treatments for articular cartilage defects often lead to fibrous repair tissue with insufficient mechanical properties. Furthermore, the supply of autologous chondrocytes is limited.[1] Spinner flask culture of chondrocytes supplemented with notochordal cell-derived matrix (NCM) can produce ECM-rich cartilage organoids.[2] However, the amount of organoids is still limited by the initial number of chondrocytes. A promising alternative is articular cartilage progenitor cells (ACPCs), which can be expanded up to 30 passages without dedifferentiating.[3] Therefore, the aim of this study was to develop a method to fabricate clinically relevant amounts of cartilage organoids using ACPCs, and to assess the quality of the mini tissues.

Methods

Human ACPCs were obtained from residual cartilage tissue from total knee replacement surgeries from the Maxima Medical Center (METC, number N16.148) following established protocols.[3] For pre-aggregated groups, 250,000 cells were seeded. Spinner flask culture followed the protocol by Crispim & Ito.[2] When mentioned, constructs were stimulated with one dose of 100 ng/ml of BMP-9 (day 1-3). After 14 days, GAGs (DMMB assay) and DNA (Qubit,ThermoFisher) were quantified. Alician blue staining was performed. A parallel (unconfined) compression test was performed (MicroTester G2, Cell Scale). Young’s modulus was calculated as the slope of stress/strain curve (0-20% strain). Statistical analysis was carried out using Prism (Graphpad). Multiple comparisons were assessed with a one-way ANOVA, followed by Bonferroni correction post-hoc t-test.

Results

BMP-9 stimulation synergized with spinner flask culture, leading to a significant increase in diameter (>200%, not shown) (p<0.0001) and GAG/DNA when compared to static culture and to using only NCM in the spinner flasks (Figure 1.a). NCM aggregated samples stimulated with BMP-9 presented more matrix than samples simply self-assembled in the stirrer flasks with BMP-9 alone (Figure 1.b), and were stiffer (Figure 1.c).

Discussion

In this study, BMP-9 stimulation improved cartilage matrix production, as shown by Morgan et al.[4] In contrast to Crispim and Ito, using only NCM with ACPCs in the spinner flasks did not stimulate proliferation and it was not fully incorporated into the organoids, resulting in smaller organoids.[3] Unlike chondrocytes, ACPCs may be less responsive to NCM, but also incorporated NCM could have interfered with cell-to-cell interaction necessary for ACPC maturation. However, when NCM was incorporated with cell proliferation, this lead to a more functional stiffer organoid. Therefore, upcoming experiments will focus on production of ACPC cartilage organoids by enabling self-assembly and stimulating ECM production by combining BMP-9 with other additives. This system has the potential to facilitate the fabrication of clinically relevant numbers of high quality organoids for cartilage repair.

References


Acknowledgements

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Figure 1: GAG/DNA was significantly higher for pre aggregated constructs stimulated with BMP-9 (a). More ECM in the organoids (b) translated to higher Young’s modulus (c).
THREE-DIMENSIONAL OSTEOCYTE LACUNO-CANALICULAR NETWORK AT THE BONE IMPLANT INTERFACE

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Introduction

Osteocytes are the most abundant cell type found in bones and play a key role in the regulation of bone metabolism. In woven bone, formed after implantation, osteocytes communicate with the implant surface via lacuno-canalicular network (LCN) and detect changes in mechanical loading by releasing numerous biochemical messengers that modulate bone metabolism [1,2]. It is not fully understood how the osteocyte extensive and intricate LCN adapts to the presence of an implant, to provide the mechanical stability, exchange of nutrients, and vascularization necessary for successful osseointegration [3]. The aim of this study is to investigate the LCN formed in peri-implant newly-formed bone tissue, to understand its structural complexity and differences compared to a mature bone tissue.

Methods

Sample. Cortical bone from a rabbit tibia was retrieved after the osseointegration of a standardized coin-shaped implant for 7 weeks (TiAl6V4, Ø5-H3mm). Samples were stored immediately following surgical removal, embedded in PMMA, sectioned to a baton of 2x5x2mm³ and polished to expose the mineralized tissue at the BII. Image acquisition. A FIB-SEM (FEI Helios NanoLab 660) was used in BSE mode to image a 20x30x30 µm³ region close to the implant. The 3D output images (stack of 1027 2D grayscale images) were obtained using a “Auto slice and view” software (Fig 1A), with an anisotropic pixel size of 16.78x16.78x20nm. Image processing was carried out using Fiji. Local excessive brightness was removed using a bandpass filter. A 3D Gaussian filter was then applied to reduce noise (std dev of 3pixels). Moreover, artifacts present in the image (eg saturation close to a cavity) were reduced by applying Kuwahava filter (sampling window width of 7 pixels). Finally, the lacunae canaliculi network was segmented from the mineralized bone (visual threshold).

Data analysis. Two preferential subvolumes with limited artefacts (9x9x16µm) were isolated around the osteocyte cavity, with visual differences in porosity. Canaliculi thickness maps were extracted using BoneJ plugin, and analyzed using a matlab routine.

Results and discussion

An ellipsoidal osteocyte lacuna was observed in the center of the imaged volume, connected to a dense meshwork of canaliculi (Fig 1B) and visually aligned parallel with the direction of the implant surface. The two isolated subvolumes presented different local porosity of 0.53% (fig 1.C1) and 2.34% (fig 1.D1), associated with relative maximum canaliculi thickness of 200±60 nm (fig 1.C2) and 240±80 nm (fig 1.D2). This difference of density may be due to the heterogeneity of the newly formed bone. Further analysis is ongoing (orientation, connectivity, etc) as well as comparison with data from a mature bone region, to highlight and understand differences in the bone tissue local micro and sub-nanostructure, close to an implant[4,5].

Figure 1: FIB-SEM “slice and view” (A); LCN network in the immature bone tissue (B), canaliculi connected to the same osteocyte (C1) and (D1), thickness distribution (C2) and (D2).

References


Acknowledgements

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COMPARISON OF FOOT-ANKLE MECHANICS AND MUSCULAR ACTIVATION BETWEEN RUNNING DRILLS AND RUNNING ACROSS DIFFERENT SPEEDS.

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Introduction
Running drills are frequently used on the field by athletic coaches to improve technique and strengthen the foot-ankle complex [1]. A previous study has shown that the form of the running drills can influence the plantarflexor musculotendon unit output [2]. However, this study has used a simplified rigid foot-model widely overestimating the ankle kinematics and energetics [3]. The aim of this study is to compare the foot-ankle joint mechanics in using a multi-segment foot model during running drills and running across different speeds. We hypothesise that the results could contribute to enhance the track and field coaches’ understanding of the mechanism underlying the running drills.

Methods
Thirteen long-distance runners performed five popular running drills (A-skip, B-skip, bounding, heel flicks, straight leg run (SL)) and run across three different speeds (2.75 m/s, 3.88 m/s, 5.00 m/s) on an indoor running track. Kinematics, kinetics and energetics values were calculated among the ankle, the midtarsal (MT) and the metatarsophalangeal (MP) joint according to the multi-segment foot model developed by Bruening [4]. Muscular activation was recorded for soleus, gastrocnemius medialis and lateralis and abductor hallucis in using surface electromyography. Repeated measures analysis of variances was used to compare variables between running drills and running across the three different speeds.

Results
Ankle and MP range of motion are lower during the running drills than running at 3.88 m/s and 5.00 m/s (p-value < 0.001, diff: ± 10°), except for bounding. The ankle joint moment, ankle positive and negative work are similar between running drills and running at 5.00 m/s, except for bounding inducing a larger positive (p-value < 0.001, diff: ± 0.35 J/kg) and negative work (p-value < 0.01, diff: ± 0.43 J/kg). MT and MP joint moments during the A-skip, heel flicks and SL are close to running at 3.88 m/s (MT ≈ 2.10 N.m/kg & MP ≈ 0.32 N.m/kg) whereas the MT and MP joint moments of the B-skip are close to running at 2.75 m/s (MT ≈ 1.80 N.m/kg & MP ≈ 0.23 N.m/kg). Contrariwise, the bounding induces a similar MT and MP joint moments compared with running at 5.00 m/s (MT ≈ 2.25 N.m/kg & MP ≈ 0.45 N.m/kg). Abductor hallucis, gastrocnemius medialis, gastrocnemius lateralis and soleus activation were statistically similar between running drills and running at 5.00 m/s. However, each percentage of muscular activation during the running drills were superior to running at 5.00 m/s (except for A-skip which was closer to running at 3.88 m/s).

Discussion
The most original aspect of this study is the exploration of the foot and ankle mechanism using a multi-segment foot model while performing the running drills. Compared to running at 5.00 m/s, running drills require stiffening the foot-ankle complex in reducing ankle and MP range of motion while also increasing activation of the plantarflexor and abductor hallucis. According to the foot-ankle moment estimated, the B-skip is the softest and the bounding is the hardest of the running drills. Track and field coaches should be aware that running drills induce similar or higher eccentric work on the ankle than running at 5.00 m/s.

References

Acknowledgements
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RECOVERY OF SHOULDER MOTION DURING GAIT AT 1-WEEK, 3-MONTHS AND 1-YEAR AFTER SPINAL FUSION SURGERY IN AIS

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Introduction

Adolescent Idiopathic Scoliosis (AIS) is a growth defect of the spine that primarily occurs in pre-pubertal children and is surgically treated when a curve exceeds 50° [1]. Presently, surgical outcomes are evaluated through 2D static radiographs, clinical examination and questionnaires. Although, the functional outcome (e.g. the gait performance) plays an important role in the patient’s evaluation of treatment success, no accurate, evidence-based predictions regarding the recovery of this functional outcome can be provided by the surgeon. Indeed, postoperative gait analysis of AIS patients has thus far only been documented 1-2 year postoperative at the earliest [1, 2]. Consequently, no information on the preceding recovery of gait in AIS patients exist, which prevents the understanding of early recovery or compensation mechanisms, e.g. in terms of shoulder motion, as well as its possible implications for enhanced rehabilitation. Therefore, the present study aimed to investigate the early gait recovery in terms of shoulder motion after spinal fusion surgery in AIS patients. It was hypothesized that AIS patients walked with a reduced range of motion (RoM) of the shoulder angle at 1-week postoperative and that the RoM gradually recovers to preoperative levels from 3 months to 1 year postoperative.

Methods

Seventeen AIS patients (Age: 17.3 ± 4.0; Gender: 15 Female and 2 Male) scheduled for spinal fusion surgery underwent an instrumented gait analysis protocol using a validated spinal deformity-specific marker protocol [3], both preoperatively (Pre-op) and postoperatively (Post-1Week, Post-3Months and Post-1Year). At all timepoints, patients walked on an instrumented, split-belt treadmill (Motek, Amsterdam, NL) at 0.75 m/s and 1.25 m/s walking speeds (not possible at Post-1Week) recorded using a 10-camera motion capture system (VICON Motion systems, Oxford, UK). Based hereon, range of motion (RoM) of the shoulder in the frontal and transverse plane was determined. A one-way ANOVA, followed by Bonferroni post-hoc testing (p<0.05), was performed to identify differences between timepoints.

Results

When walking at 0.75 m/s, the RoM of the shoulder angle decreased significantly (p<0.05) at Post-1W in the transverse plane compared to Pre-op and increased back to preoperative levels at Post-3M and Post-1Y, whereas no differences in the frontal plane were identified at this speed. In contrast, at 1.25 m/s the significant reduction in shoulder angle RoM persisted at Post-3M and Post-1Y (Table 1).

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Pre-Op</th>
<th>Post-1W</th>
<th>Post-3M</th>
<th>Post-1Y</th>
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</tr>
<tr>
<td>1.25 m/s</td>
<td>5.95 ± 2.42</td>
<td>4.62 ± 0.97</td>
<td>5.23 ± 1.20</td>
<td></td>
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<tr>
<td>15.34 ± 3.59</td>
<td>12.52 ± 2.93</td>
<td>11.91 ± 3.11</td>
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Table 1. Overview of the range of motion (RoM) of the shoulder angle in the transverse (T) and frontal (F) plane when walking (at 0.75 m/s and 1.25 m/s) at the different timepoints.

Discussion

The present study is the first study to investigate the early gait recovery in terms of shoulder motion after spinal fusion surgery in AIS patients. At 1 week postoperative, AIS patients walked with a reduced RoM of the shoulder, which increased back to preoperative levels at three months and one year after surgery. However, this recovery in shoulder angle was not present at three months and one year postoperatively when higher walking speeds were imposed which was assumed to be due to increased task demands. These findings suggest that early postoperative dynamic assessments could provide new insights in patient-specific and task-dependent recovery. This novel information could serve as a basis for patient-specific early rehabilitation protocols.

References

VERTEBRAL BODY TETHERING VS SPINAL FUSION: LOOKING BEYOND THE RADIOGRAPHICAL OUTCOME

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Introduction
Adolescent Idiopathic Scoliosis (AIS) is a growth defect of the spine that primarily occurs in pre-pubertal children and is surgically treated when a curve exceeds 50° [1]. Presently, spinal fusion (SF) surgery is established as the gold-standard treatment modality for patients with AIS [1]. Although, SF is associated with successful long-term outcomes in terms of deformity correction, it is also associated with a loss of spinal motion at the fused levels [1]. Therefore, fusionless treatments of progressive curves might be appealing, especially in the skeletally immature. Vertebral Body Tethering (VBT) is a fusionless growth-modulating technique for skeletally immature AIS patients with good curve control in selective indications [2]. Although the radiographic outcome, in the form of curve correction, is usually inferior to modern SF [2], potential advantages over spinal fusion have been reported in terms of function [1]. Nevertheless, comparative objective measurements of the degree of preservation of motion associated with both techniques are as of yet scarce. The aim of the present study is, therefore, to objectively measure and compare the postoperative trunk mobility, activity levels and functional outcome scores between VBT patients and SF patients.

Methods
From our prospective study sample, we matched 8 VBT patients based on curve type (Lenke classification), gender and follow-up duration with 8 SF patients. Preoperatively (Pre-OP), three months postoperatively (Post-3M) and one year postoperatively (Post-1Y) patients completed the following patient reported outcome measures (PROMs): SRS-22 (scored from 0-5), International Physical Activity Questionnaire (IPAQ) (scored from 0-5) and pain intensity scale (scored from 0-10). Furthermore, at both timepoints the patients performed a spinal deformity-specific motion analysis [3] that was captured using a 10-camera motion capture system (VICON Motion systems Oxford, UK) and consisted of a seated maximal trunk flexion. Maximal trunk flexion (°) was calculated using the markers placed on C7 and the pelvis. A one-way ANOVA (p<0.05) was performed to identify differences between groups.

Results
Radiographically, the main cobb angle correction from Pre-OP to Post-OP was significantly (p<0.05) greater for the SF group (Pre-OP = 55.1°; Post-1Y = 12.5°) compared to the VBT group (Pre-OP = 53.6°; Post-1Y = 27.9°). In terms of the PROMs, no significant differences were found between groups in both the overall SRS-22 score (SRS-22 score: Post-3M: VBT = 4.1 vs. SF = 4.0; and Post-1Y: VBT = 4.2 vs. SF = 4.3), as well as the subdomain ‘function’ (SRS-Function: Post-3M: VBT = 4.2 vs. SF = 3.9; and Post-1Y: VBT = 4.5 vs. SF = 4.5). Both groups had little to no pain Post-OP (VAS-score: VBT = 0.1 vs. SF = 0.2). In addition, no significant differences in Post-1Y physical activity levels were identified on the IPAQ (VBT = 2.2 vs. SF = 2.1). In terms of trunk flexion, the loss of forward flexion from Pre-OP to Post-3M was significantly (p<0.05) greater for the SF group (SF: 31% reduction vs. VBT: 15% reduction) compared to the VBT group, from which they partially recovered at Post-1Y (Figure 1).

Discussion
The present study aimed to integrate a radiographical comparison with an objective comparison of VBT and SF on the functional level. Even though SF patients have a superior radiographic outcome, this contrasts with improved spinal mobility during forward flexion in the VBT patients, which was not captured in the PROMs. These advantages of VBT should be further investigated in view of treatment selection in skeletally immature AIS patients whose curves progressed beyond the range of bracing.

References
A PLATFORM FOR IN-SILICO EXPERIMENT OF BONE REMODELING FOR UNDERSTANDING ROLES OF MECHANO-CHEMICAL COUPLINGS

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Introduction
Homeostasis of bone structure and function can be disrupted by an imbalance between osteoclastic resorption and osteoblastic formation of bone caused by disuse during prolonged bed rest and immobilization. Bone with a significant loss will be at high risk for developing osteoporosis and having a fracture [1]. To maintain bone health and to gain bone mass by drugs and weight-bearing exercise, effects of mechano-chemical couplings on bone remodeling needs to be understood. However, understanding and predicting the physiological or pathological processes of bone as a system remain difficult because of the complexity of relevant molecular and cellular behaviors. In this study, we propose a novel in-silico experimental platform that mathematically models bone remodeling by linking microscopic molecular and cellular interactions to macroscopic tissue/organ level behaviors.

Methods
In silico platform of bone remodeling, incorporating mechano-biochemical couplings (Fig. 1(a)), has been developed [2] by combining an image-based voxel finite element method (Fig. 1(b)) [3]. Important signaling molecules in bone remodeling such as sclerostin, RANK/RANKL/OPG, and semaphorin 3A (Sema 3A) were involved in the platform with mechanical stimulus. To investigate the roles of essential signaling molecules in bone remodeling, as is often conducted in vivo experiment, the molecule of interest was perturbed in silico on the proposed platform. A case study was conducted to investigate the effect of Sema 3A, known as a bone-protective factor [4], on bone remodeling, in which Sema3A-deficient mice were modeled in silico by down-regulating its production rate in the platform.

Results and Discussion
In silico perturbation experiment was performed for Sema 3A-deficient mice (Fig. 2). Trabecular surfaces under osteoclastic resorption/osteoblastic formation are indicated by red/blue colors, respectively. Comparing to the control model in Fig. 2(a), larger surface was occupied by osteoclasts resulting in osteoporotic bone with thin trabeculae and large pores, as shown in Fig. 2(b). Trabecular structure was qualitatively compared to in-vivo experiment (data not shown). Cancellous bone morphology in the Sema3A-deficient model was similar after 10 weeks of simulation to that obtained in vivo with BV/TV and trabecular number Tb.N significantly smaller than in the control model.

References

Acknowledgements
The authors thank Yuki Miya of Kyoto Univ. for developing the platform, and Tomoki Nakashima of Tokyo Medical & Dental Univ. for providing the experimental data of Sema 3A deficient mice and for their discussion. This work was partially supported by JST-CREST (JPMJCR22L5), Japan.
SINE-BASED ACTIVATION FUNCTION IS SUPERIOR IN PHYSICS-INFORMED NEURAL NETWORK FOR CARDIOVASCULAR FLOWS

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Introduction

Physics-Informed Neural Networks (PINNs) has emerged as a powerful approach to encode governing partial differential equations (PDEs) and training data to solve complex engineering problems. In cardiovascular applications, PINNs can be designed to encode Navier-Stokes equations and clinically-acquired hemodynamic data (e.g., from 4D Flow MRI) into the loss function to improve predictions. However, minimizing the loss function during the training process is challenging.

One strategy to improve the training operation is to use functions that maintain differentiability, non-linearity and minimize vanishing gradients; however, most popular activation functions lack these properties.

We propose to use a recently-introduced Fourier-based activation function that utilizes a periodic sine function [1]. The derivative of a sine function is a cosine, a phase-shifted sine, and thus, inherit the properties of the original function.

Methods

Test Case – 2D Stenosis: A 2D eccentric stenosis was created based on Varghese et al [2]. CFD simulations were performed using a higher-order finite-element solver, Oasis [3], at Re=5000 on a 240k triangle mesh.

PINNs Model: The solution $u(x, t)$ was approximated with a deep learning network $f(x; t; \theta)$, where $\theta$ represents the trainable parameters of the neural network. The loss function is defined as:

$$L_{\text{total}}(\theta) = L_{\text{PDE}} + \lambda_{BC}L_{BC} + \lambda_{\text{data}}L_{\text{data}} \quad (1)$$

where $L_{\text{PDE}}, L_{BC}$ and $L_{\text{data}}$ correspond to the loss term for the Navier-Stokes equation, boundary conditions, and known sensor data, respectively. The parameters $\lambda_{BC}$ and $\lambda_{\text{data}}$ aim to balance the interplay of the different terms in the loss function. The network consisted of 4 layers with 128 neurons/layer. The boundary conditions and velocity field at the mesh nodes were treated as unknown quantities. Sensitivity to sensor data (obtained from CFD) were tested by increasing sensor points from 25 to 400.

Activation Functions: We compared two standard activation functions, swish and tanh against a Fourier-based, periodic sine function (i.e., SIREN[1]). The formulation of the three activation functions are:

swish: $f(x) = x \cdot \text{sigmoid}(x)$ \quad (4)

tanh: $f(x) = \frac{e^x - e^{-x}}{e^x + e^{-x}}$ \quad (5)

Sinus: $f(x) = \sin(\omega x)$ \quad (6)

Sinus requires special initialization for the first layer and normalization of the input parameters from -1 to 1. We applied a strategy proposed by Pan et al. in our work [3].

Results

While PINNs model with sinus and swish activation functions converged, the tanh solution diverged due to diminishing gradients issues. Figure 2A shows presence of unsteady vortical structures due to the geometric perturbation (i.e., non-axisymmetric stenosis). Figure 2B shows a monotonic decrease in $L_2$ errors as the number of sensor data increases from 25 to 400. There is a rapid decrease in error norm from 25 to 100 points for sine function compared to swish function. Figure 2C shows the velocity field estimated by PINNs for 25 and 400 sensor points, marked with P1 and P4 respectively. Even with 25 sensor points, the sine-based velocity field shows the spatial dynamics that are not captured by swish activation function. At 400 sensor points swish and sine show similar $L_2$ norms; however, the qualitative velocity maps demonstrate that sine-based predictions better match the CFD results.

Discussion

We have demonstrated that sine activation function can substantially improve velocity field predictions compared to conventional activation functions. Second, sine activation function was able to reconstruct the gross velocity field even with 25 sensor points. The reduced requirements on sensor data are beneficial since clinically-acquired hemodynamic data is often scarce and sparse, for example, in 4D Flow MRI or dynamic perfusion CT imaging.

References

MEASUREMENT OF JOINT ANGLES IN A CANINE MUSCULOSKELETAL MODEL: DIRECT KINEMATICS VERSUS INVERSE KINEMATICS

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Introduction
Musculoskeletal modeling and simulations could provide insight into the physiologic and pathologic motion patterns of animals. Furthermore, it makes scientists capable of evaluating the effects of different orthopedic surgeries on gait patterns or investigating the effectiveness of different prostheses by using these models [1,2]. We generated a 3D canine musculoskeletal model to simulate normal gait in sound dogs. The aim of our study was to 1) develop a workflow for musculoskeletal modelling of dog movements and 2) compare the dog’s joint kinematics obtained by direct versus inverse kinematics to test the model's validity.

Methods
We used 3D motion capture data of a sound Labrador dog from our previous study. An anatomically valid 3D model of a canine skeleton, which was designed for educational purposes, was used as our base model. This model was imported to nmsBuilder software for 3D modeling. After the definition of the bodies, coordinates, required markers, joints, and muscles a 3D model was created and imported to OpenSim software to perform inverse kinematics based on the acquired motion capture data. The angles of the shoulder, elbow, carpal, hip, stifle, and tarsal joints were calculated via direct kinematics (DK) and inverse kinematics (IK) [3]. Calculation of the angles were based on three markers located proximal to the joint, near/on the center of the rotation of the joint and distal to the joint in the sagittal view (Figure 1). The obtained joint angles were finally smoothed by a Butterworth low-pass filter with a cutoff frequency of 6 Hz.

Results
Difference in joint range of motion between the DK and IK approach was 6.4° for the shoulder, 8.5° for the elbow, 18.4° for the carpal, 3.3° for the hip, 0.7° for the stifle and 2.4° for the tarsal joints. These results will be extended by including more dogs in our study and the final result will be statistically analyzed to present the differences in congress.

Discussion
Validation of the musculoskeletal models by comparing the DK and IK is an important step for the application of these models, which can give scientists insight into the model development and errors of DK such as skin displacement.

References
EFFECT OF VISION AND SURFACE SLOPE ON POSTURAL SWAY IN HEALTHY ADULTS

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Introduction
Postural control (PS) is achieved by a complex interaction between the central nervous system and three main systems including visual, somatosensory, and vestibular systems. The active collaboration of these systems ensures that the posture-stabilizing muscles of the legs and trunk respond almost instantaneously to balance disturbances. Various cognitive, sensory, or motor impairments can cause a patient to have difficulties maintaining, achieving, or restoring equilibrium. Previous studies underlined the relationship between PS and anthropometric parameters as well as neurologic disorders [1,2]. In this study we aimed to evaluate the postural balance of healthy young adults in flat and sloped standing positions with eyes open and closed, and compare recorded COP values with the standing position on flat ground with open eyes (standard condition).

Methods
Twenty-two healthy young adults (11 female and 11 male) aged between 24 and 34 years were recruited. The COP parameters of the participants were measured in standing on flat, uphill, and downhill positions (with a 20° slope) with eyes open and closed.

Results
Significant differences were recorded between our standard standing condition and standing uphill with closed eyes for all COP parameters (p<0.05). The difference between standard condition and standing downhill with eyes open and closed were limited to the length, average speed and anteroposterior displacement of the COP (p<0.05). There was a significant relationship between standing conditions and all COP parameters in this study (p≤0.004). The age of the participants had a significant effect on mediolateral and anteroposterior displacements of COP, support surface of COP, and support surface per length of the COP (p≤0.001). In addition, none of the COP parameters showed a relationship with the gender of the participants. With the exception of mediolateral displacement, body mass index also had a significant effect on all COP parameters (p≤0.043). The pairwise comparisons between the measurement conditions for each COP parameter are shown in Figure 1.

Conclusion
It can be deduced that in the studied population standing downhill leads to an impairment of balance and the loss of visual input increases this impairment. On the other hand, standing uphill only poses a challenge to balance in the absence of visual input in our study. The results of this study are currently being reviewed by the authors and will be presented in congress.

References

Acknowledgements
We are grateful to the participants of this project. This work was supported by grant number P34959-B from the Austrian Science Fund (FWF).
FRACTURE TOUGHNESS OF CANCELLOUS BONE TISSUES USED FOR THE MANUFACTURING OF HETEROLOGOUS BONE GRAFTS

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1. Department of Mechanical and Industrial Engineering, University of Brescia, Italy; 2. Biotech S.p.A., Italy; 3. CSMT Gestione S.c.a.r.l., Italy

Introduction and aim

As the number of bone defects caused by pathologies or traumas has constantly increased over time, medical devices (bone grafts) aimed at promoting tissue regeneration have been raising interest both in scientific and clinical literature. Whereas autologous bone is still regarded as the gold standard, the possibility to resort to perfectly compatible substitutes - among which heterologous bone (of mammalian origin) stands out - avoiding material harvest in patients and eventual surgical complications, is taken into high account in clinical practice. Several studies investigated the biological and medical features of the heterologous bone tissues used in grafts; however, literature about their mechanical behaviour is quite limited and a comprehensive research on their structural integrity is still lacking.

In this work, the fracture behaviour of trabecular bone tissues used for the manufacturing of commercial heterologous bone grafts was investigated, under the framework of fracture mechanics (FM). The applicability of the FM testing schemes proposed in the literature for the measurement of fracture toughness parameters was critically reviewed, and specific structure-property relationships researched.

Methods and results

The bone tissues examined were supplied by Biotech S.p.A., an Italian company that deals with the research and production of tissue substitutes for regenerative medicine. They were obtained from equine bones after a specific proprietary enzymatic-based treatment aimed at achieving perfect biocompatibility while preserving the collagenous part. Two different tissues, both obtained from the femur, were examined. One had the mineral content of the bone of origin (F), whereas the other was markedly demineralized (FF). Tissue microstructure and mechanical response under compression are presented in [1].

For the fracture characterization, Single-Edge notched in Bending, SE(B), tests were performed in quasi-static conditions and at room temperature. Specimens with two different sizes were tested. In consideration of the peculiar nature of these materials, special attention was paid to: (i) the specimen notching phase, necessary to introduce an artificial defect as sharp as possible replicating a natural crack, while preserving the region ahead of the crack tip from being damaged; (ii) the execution of correction tests necessary to take into account specimen indentation occurring during the fracture test, especially for FF tissue; (iii) the determination of a point that could be considered representative of fracture initiation in the fracture test. The fracture response turned out to be remarkably dependent on whether the tissue was demineralized or not (see Figure 1). The denser and stiffer F tissue showed a brittle behaviour, which was studied by resorting to the Linear Elastic FM model. On the contrary, the highly-compliant FF tissue showed a markedly ductile response, requiring the use of the Elastic Plastic FM model. Fracture toughness data from representative specimens of F and FF tissues, expressed as critical stress-intensity values (at fracture initiation), \( K_{IC} \) and \( K_{IC-J} \), respectively, are indicated in Figure 1, together with the corresponding apparent density values. \( K_{IC-J} \) is the equivalent stress-intensity value, back-calculated from \( J_K \) as reported in [2]. The relationship between fracture toughness and tissue density was researched and discussed also in the light of the micro-structural characteristics of the tissues specifically investigated.

![Figure 1: Loading curves from fracture tests on representative F and FF SE(B) specimens with nominal thickness of 10 mm, width (W) of 20 mm, and tested with span-to-W ratio of 4. The corresponding fracture toughness data are also indicated.](image)

References

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Acknowledgements

The authors are grateful to Fabbrica d’Armi Pietro Beretta S.p.A. (Gardone Val Trompia, Brescia, Italy) and to Industrie Polieco-M.P.B. S.r.l. (Cazzago San Martino, Brescia, Italy) for the financial support kindly provided.
THREE-DIMENSIONAL FLOW RECONSTRUCTION IN A DISSECTED AORTA FROM 4D-MRI DATA

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Introduction

Advances in flow reconstruction techniques allow predicting the evolution of the blood flow using sparse measurements. In this study, we investigate the potential of applying a linear dynamic estimator to reconstruct the unsteady three-dimensional blood flow in a dissected aorta from 4-Dimensional Flow Magnetic Resonance Imaging (4D-MRI) measurement data in one plane.

Methodology

The training data used to identify the dynamic estimator is generated using a simulated flow field in a rigid-wall patient-specific luminal geometry. This was reconstructed by manual segmentation of CTA data using Simpleware ScanIP and Autodesk Meshmixer and non-rigidly registered to the 4D-MRI domain. The flow field is simulated using Reynolds Average Navier Stokes (RANS) and the K-Omega SST turbulence model [1]. The simulation results match well with the 4D-MRI data, providing improved spatial and temporal resolution of the flow field.

Three-dimensional Proper Orthogonal Decomposition (POD) is used to obtain a reduced order model of the fluctuating flow. The flow field is approximated using the first four most energetic POD modes, which carry 96% of the total kinetic energy.

The training data used to design the dynamic estimator is obtained using the maximum and minimum streamwise velocity upstream of the aorta arch as input and the time coefficients of the POD modes as output. Figure 1 shows a schematic of the training and validation steps used to design the dynamic estimator.

Results

The estimator performance is validated using 4D-MRI velocity data (figure 2). The reconstructed flow field is then compared to the CFD (Computational Fluid Dynamics) and the 4D-MRI data at other planes. With reference to the training data from CFD, the average estimation accuracy is around 94%. This is the correlation coefficient between the fluctuating streamwise velocity at the different planes along the dissected aorta, part of which is shown in figure 2. When the reconstructed flow field is compared to the 4D-MRI data, the average estimation accuracy is around 90%, based on the maximum and minimum streamwise velocities on the planes.

The estimation accuracy looks very promising. Further investigations into improving it are currently being considered. To the best of the authors’ knowledge, this represents the first study to reconstruct the three-dimensional blood flow patterns using a linear dynamic estimator from planar 4D-MRI data.

![Figure 1: A schematic of the training and validation steps of the dynamic estimator](image1)

The dynamic estimator is identified using a subspace system identification algorithm, N4SID, with the fluctuated streamwise velocity upstream of the aorta.

![Figure 2: Dissected Aorta geometry with the input plane and selected validation planes (I, II and III) on the left and comparisons between the CFD, 4D-MRI and the reconstructed flow fields on the right.](image2)

References

BONE MATERIAL STRENGTH INDEX TO DIFFERENTIATE EARLY BONE STRUCTURE IN PATIENTS AFFECTED BY CRANIOSYNOSTOSIS

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Introduction
Craniosynostosis (CS) is a congenital craniofacial malformation, which involves premature cranial suture closure, leading to restricted brain growth and aesthetic problems [1]. Although surgical intervention reduce risk of raised intracranial pressure and normalise the head shape, unpredictable outcomes and incomplete correction of deformities have been reported. Furthermore, diagnosis of CS relies on physical and radiographic examination. Determining the material properties of the cranial bone in CS patients would provide an insight into bone response to surgical procedures [2]. However, the assessment of skull bone quality (SBQ) based only on the radiographs remains elusive and high radiation doses limit the number of patients receiving this examination. OsteoProbe (Active Life Scientific) is a portable handheld micro-indenter, specifically designed for clinical practice. OsteoProbe quantifies bone’s resistance to indentation as bone material strength index (BMSi). The aim of this study was to investigate if BMSi can be used as a biomarker to predict final head changes in craniofacial procedures.

Method
Following ethical approval, cranial bone samples were collected from 34 patients (age: 17 ± 34 months) surgically treated for CS correction at GOSH (London, UK).

![Figure 1: Osteoprobe microindenter (left); one- (top) and three-layered (bottom) bone samples](image)

Figure 1: Osteoprobe microindenter (left); one- (top) and three-layered (bottom) bone samples

Upon retrieval, samples were kept frozen at −20°C until examination. Specimens’ structures were characterized using micro-CT (μCT, Skyscan 1172), using a voxel size of 8.94 μm, a source voltage of 49 kV a source current of 200 μA and a 0.5mm aluminum filter. Bone thickness, bone volume fraction BV/TV, BMD and specific bone surface BS/BV were quantified using CTAn. Bone material quality was examined using OsteoProbe and BMSi was recorded for each bone sample. Surgical outcome was assessed by changes in cephalic index (CI, defined as cranial width over length) pre and post operation.

Results
Based on μCT appearance, bone structure was classified into one- (n=18) or three-layered (n=16). Our results revealed change in CI was significantly higher in one-layered sample (3.4 ± 2.8%) compared to three-layered (0.5 ± 4.2 %, p=.04). Using OsteoProbe differences in the structure of the bone samples were identified: a significantly higher BMSi was determined when three-layered and one-layered samples (57.5 ± 12.5 vs 38.9 ± 6.2, p<0.01) were compared. Significant higher BV/TV (p<0.01), bone thickness (p<0.01) and BMD (p<0.05) were found in trilaminar structure. BMSi was positively correlated with BV/TV (r = 0.72, p<0.01) and BMD (r = 0.35, p = 0.04) and negatively correlated with BS/BV (r = -0.83, p<0.01). In addition, lower BMSi values were associated with larger increase in CI (r=-0.4, p=.04). No correlations were found between patients age and CI.

Discussion
Microstructural and material differences between one- and three-layered bone structures were shown: OsteoProbe is a promising technique enabling physicians to evaluate in vivo tissue-level material properties of bone in a minimally invasive, simple and safe manner.

References
EXPLORATION OF HYDROGEL TISSUE SCAFFOLDS TO IMPROVE THE BIOMECHANICS OF OSTEOPOROTIC BONE

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Introduction

Osteoporosis is a skeletal disease characterised by low bone mineral density, loss in bone architecture, and reduced stiffness which results in high fracture risk [1]. Reports show that 8.9 million fractures occur annually due to fragility [2]. Risk of death is increased by 10% - 20% due hip fractures in women [3], therefore, total hip replacement (THR) is often used but it has some problems regarding aseptic loosening, periprosthetic fractures, and inflammations [4]. Figure 1 shows conventional and novel treatments highlighted in a recent review which shows that hydrogel tissue scaffolds impregnated with stem cells, drugs, and growth factors show promising biological impact on the osteoporotic bones [4]. However, the effect of hydrogels on the mechanical function of osteoporotic (OP) bone has not yet been investigated. This study aims to investigate feasibility of improving mechanical properties and biological regeneration using hydrogel tissue scaffolds.

Results

There is a significant increase in the structure’s stiffness when filled with hydrogel as illustrated by Figure 3. The increase in the stiffness is found to be dependent on the modulus of elasticity of the hydrogel. However, the failure loads are found to be comparable in all cases tested.

Discussion

This preliminarily work showed that hydrogels can immediately restore bone stiffness. It is likely that the use of hydrogels would also improve biological function as reported in the literature [4] This study uses a 2D structure, which has some limitations regarding fill, and contact assumptions but further work will be conducted to obtain results that are more robust by implementing 3D simulations and ex vivo experiments to understand the bone-hydrogel composite behaviour and validate the findings.

References

NUMERICAL INVESTIGATION ON THE PRIMARY AND SECONDARY STABILITY OF ROOT-ANALOGUE-IMPLANTS

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Introduction and Aim

The use of dental implants is a well-established approach for the restoration of chewing function after the loss of single or multiple teeth. Typically, threaded implants (TI) of different designs are used to anchor single tooth replacements or bridges in the mouth of the patient.

In cases where treatment requires the extraction of an existing, but severely damaged tooth, the shape the existing alveolus has to be considered. Such an existing alveolus might impede with the placement of a threaded implant. Either the cavity needs to be filled with bone substitute material, increasing the healing time until the implant can receive full function al loading, or diameter and/or length of the implant need to be chosen overly large to assure stability of the implant. This holds especially for multi-rooted teeth.

In such cases, custom root-analog implants (RAI) can offer an alternative, as they can be directly fitted to the geometry of the existing alveolus [1,2]. In this study, we compare a RAI with a TI in different bone blocks with respect to the the primary and secondary stability of using the finite elements method (FEM).

Materials and Methods

The geometry of tooth 47 (lower right 3rd molar) was extracted from an existing CBCT, and a RAI was designed based on this geometry. In a previous part of this study, two different RAIs (milled titanium, 3D printed titanium) were manufactured, and the surfaces were again scanned optically to determine manufacturing precision. In the current part of the study, the digital models of the RAIs were inserted into two different bone blocks (idealized rectangular sawbone block, and realistic bone segment taken from the same CBCT scan as the molar). FE models of a conventional TI inserted into the same bone configurations were used as reference. Material parameters are listed in Table 1.

<table>
<thead>
<tr>
<th>Material</th>
<th>Young’s Modulus</th>
<th>Poisson Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titanium</td>
<td>110 000 MPa</td>
<td>0.35</td>
</tr>
<tr>
<td>Cortical bone</td>
<td>13 700 MPa</td>
<td>0.30</td>
</tr>
<tr>
<td>Spongious bone</td>
<td>1 370 MPa</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 1: Material properties used in the simulations.

In a first simulation series, we assumed sliding contact at the bone/implant interface to simulate early loading condition. In a second series, we used glued contact instead at the bone/implant interface to simulate the osseointegrated state. We applied a force of up to 200 N to the top of the implant in all simulations.

Results

There were only minor differences between the two RAIs in the numerical investigations. In the FE simulations, the induced equivalent stresses on the TI were drastically higher than the stresses induced on the RAI. Furthermore, the healing status positively affected the RAI model, reducing the stresses from 23.7 MPa in the immediate loading to 13.2 MPa in complete osseointegration (see Figure 1).

Figure 1: Calculated stresses in the anatomical bone model for a RAI (top row) and the TI (bottom row) under immediate loading (left column) and after osseointegration (right column).

Conclusions

The investigated RAIs showed a promising biomechanical behavior in the numerical studies. Especially after osseointegration, the custom shape of the RAIs might offer might offer a suitable alternative for the TI.

References


Acknowledgements

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STATISTICAL MODELS INFORMED BY DXA IMAGES SLIGHTLY OUTPERFORM T-SCORE IN THE PREDICTION OF HIP FRACTURE

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Introduction

Frailty fractures due to osteoporosis represent a growing socio-economic burden as they cause a significant decrease in the quality of life, increase morbidity and mortality. As people live longer, the incidence of such fractures is increasing [1], which makes the need for an accurate fracture risk assessment tool urgent, in order to implement adequate preventive actions. In the clinical practice, osteoporosis severity is assessed based on T-score, derived from the areal Bone Mineral Density (aBMD) average measurement on DXA images. However, in spite of its correlation with fracture incidence, aBMD in not an accurate predictor of the risk of fracture [1]. Statistical models of femur shape and intensity built from CT scans have proved promising in improving hip fracture prediction [2]. Nevertheless, CT is not routinely performed for osteoporosis diagnosis, presenting a barrier to the adoption of such a methodology in clinical practice. In this context, this study aimed to assess the stratification accuracy of analogous shape and intensity statistical models developed from DXA images of the same cohort, which, instead, would be readily available.

Methods

DXA images of the proximal femur from a retrospective British postmenopausal women cohort [2] were employed to build Partial Least Square (PLS)-based statistical models. The cohort comprised 49 fracture and 49 control subjects, pair-matched for age, body weight and height. First, a Statistical Shape Model (SSM) was built through Deformetrica [3,4], which allowed to identify the main anatomical features of the population. Subsequently, the pixel-by-pixel BMD map was employed in order to build a Statistical Intensity Model (SIM). Eventually, the SSM and the SIM were merged into a unique Statistical Shape-Intensity Model (SSIM), gathering shape and density features together. PLS allowed identification of the space (PLS modes) of maximal covariance between the patients’ shape and density features and their known fracture status. By projecting the original features onto the PLS modes, the PLS components could be obtained for shape, intensity and the two taken together. Logistic regression models based on the statistical models built were then implemented taking the PLS components as predictors of the subject-specific hip fracture status. A 10-fold cross-validation procedure was adopted to train and test the stratification accuracy of the predictive models in comparison with T-score.

Results

All the shape modes taken together could not explain more than 24% of the variability in the fracture risk, while 7 intensity modes explained more than 90% of it. A total of 31 shape-intensity modes explained 90% of the shape-intensity variability, whereas 3 modes, shown in Fig.1, were sufficient to explain 90% of the variability in the fracture risk.

Discussion

The aim of this study was to investigate whether hip fracture risk prediction could be improved taking advantage of all the information contained in a DXA scan, i.e., the proximal femur shape and the BMD pixel-by-pixel map. As expected, the stratification accuracy of the SIM was superior to that of the SSM. The inclusion of the shape within the SSIM did not improve significantly the SIM accuracy. As a whole, despite smaller than the increase obtained with CT-informed statistical models [3], a significant 7% increase in stratification accuracy was achieved with respect to T-score.

References

Introduction
Bone is a natural biological composite material that demonstrates outstanding mechanical properties, which is mainly due to the intricate arrangement of its constituents across seven hierarchical levels [1]. At the macro-level, two types of bone can be identified: a dense cortical shell and spongy trabecular core, both of which comprise of lamellar bone at ultrastructural level. Much work has been done to understand structure-property relationships for the elastic behaviour of the tissue. For example, a power law equation ($E \propto \rho^\alpha$) can relate elastic modulus ($E$) to density ($\rho$) at the macrostructural level, but for the tissue level (mm scale), more complicated models are needed to account for structure and density [2], [3]. However, beyond the elastic regime (e.g., fracture behaviour), these relationships tend to break down and we need more involved models at each structural level to predict bone biomechanics. The objective of this study is to investigate the fracture behaviour of lamellar bone, focusing on the onset and evolution of microcracks in the bone ultrastructure.

Methods
Two-dimensional geometries of the bone ultrastructure were created in in finite element package ABAQUS comprising of cylindrical mineralised collagen fibrils (MCFs) embedded through an extra-fibrillar matrix (Figure 1). Between the minerals (transversely anisotropic elastic material [4]) and around the MCFs there are interphase regions filled with non-collagenous proteins (NCPs) that mediate bonding mineral-mineral and mineral-MCFs respectively. The MCFs were modelled as transversely anisotropic elastic-linear plastic material [5] through Hill48 plastic potential [6]. The interphases between the material components were considered to have the same material properties with an exception of fracture strength and were described through a phase-field damage model, which was implemented through a UMAT subroutine in the Abaqus finite element package. This method is capable of capturing the onset and propagation of microcracks and takes a non-local order parameter $\phi$ to describe the material condition with $\phi = 0$ for intact material and $\phi = 1$ describing fully broken material. The created model of tissue with and without a notch were then stretched to study the onset and evolution of microcracks, respectively. Meanwhile, a parametric study was carried out by varying the MCFs volume fraction as well as the interphase strength ratios to capture their role in bone biomechanics.

Results and Discussion
It was found that microcracks emerged from mineral rich area of the extra-fibrillar space under both transverse and axial loading, when the interphase strength of MCFs was higher than the interphase between minerals ($\sigma_{\text{interphaseMCF}} > \sigma_{\text{interphaseHA}}$). On the other hand, once $\sigma_{\text{interphaseMCF}} < \sigma_{\text{interphaseHA}}$, the microcracks showed no preference between the interphase regions under uniaxial loading. Simulating crack propagation in noted specimens demonstrated that MCFs do not affect the crack path at low MCF volume fractions. However, at the high volume fractions, it was found that MCFs could either facilitate cracking when $\sigma_{\text{interphaseMCF}} < \sigma_{\text{interphaseHA}}$ or act as a barrier to crack propagation when $\sigma_{\text{interphaseMCF}} > \sigma_{\text{interphaseHA}}$ (see Figure 1b). This implies that indeed the interphase region filled with NCPs dictates the failure behaviour of tissue under transverse loading at physiological $V_{\text{MCF}} = 50\%$. Under axial loading, we saw that their effect is less pronounced (Figure 1a).

Figure 1: (a) tissue effective properties under axial loading with different interphase strengths. (b) order parameter distribution for tissue under transverse loading when $\sigma_{\text{interphaseMCF}} > \sigma_{\text{interphaseHA}}$.

References

Acknowledgements
This work was supported by the European Research Council (ERC) under the grant agreement No. 804108.
**INTRA-OPERATOR COMPARISON OF TWO MODELS TO PREDICT VERTEBRAL FAILURE ON THE SAME EXPERIMENTAL DATASET**

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**Introduction**

Clinical use of finite element analysis requires a well-defined process and the evaluation of uncertainties. Literature models have rarely been compared on the same experimental dataset and the influence of operator have not been evaluated either. Therefore, this study compared two models of vertebral bodies including endplates, on the same experimental dataset, and evaluated the influence of the operator on the failure load.

**Material and methods**

The experiments were obtained in a previous study [1]. Twenty-eight vertebrae were extracted from eleven donors (5 males and 6 females, 61-87 y.o.). L1-L3 vertebral bodies with endplates were resected at the pedicles, loaded to failure on the anterior part with PMMA embedded supports. Samples were scanned with a QCT scanner ICT 256 (Philips Healthcare; 120 kV, 1489 mA/s), at 0.39 x 0.39 x 0.33 mm resolution with a calibration phantom (QRM-ESP, QRM GmbH, Germany).

Two FE models were considered in this study: ENSAM’s model [1]: linear hexahedron mesh was created by semi-automatic segmentation of the scan (1-1.5 mm). Each element was assigned an averaged density, which was then converted into Young’s modulus via the relationship from [3]. The mesh is constrained in Ansys with a linear resolution and the results are post-processed to find the failure load for which 1 cm³ of contiguous elements reach a 1.5% yield strain.

Lyon’s model developed by LYOS and LBMC [2]: A 1 mm³ quadratic tetrahedron mesh was created after manual segmentation. Specific densities for each element were assigned to each element and converted to Young’s modulus using the relationship from [3]. Specific yield stress was computed using a constant yield strain of 0.7%. Perfect plasticity was given to each element. Each resulting vertebral model was compressed to reach 1.9% of total strain. Non-linear analysis was performed with Ansys to acquire failure load.

The influence of the operator was assessed for each model by evaluating the model twice by the same operator, especially the segmentation which is the only semi-automatic step.

Intra-operator relative difference (%) = \[ \frac{|\text{Trial}_2 - \text{Trial}_1|}{(\text{Trial}_1 + \text{Trial}_2)/2} \times 100\]

**Results**

Experimental failure loads are 3120 ± 1595 N (m ± SD). Comparisons to the experiments (model) and between trials by the same operator (intra-operator) are given in (Table 1), in terms of accuracy (mean of the difference between the average of simulated trials and experimental failure load) precision (SD of this difference) and determination coefficient. Both models’ results are strongly correlated (R²=0.91). Each model’s results are close to the experiments (Table 1).

**Discussion and Conclusion**

Differences between models may be the consequence of differences in segmentation process, meshing and material attribution. Furthermore, differences due to the operator may also result from segmentation process and the sensitivity of the model to segmentation variation close to boundaries of the model. Comparison of models on the same dataset and operator influence are steps needed to assess the credibility of models.

**References**

INFLUENCE OF METASTATIC LESIONS ON TWO MODELS ASSESSING VERTEBRAL FAILURE

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Introduction

Literature contains various finite element models in terms of meshing parameters, mechanical behaviour, or failure criteria. However, models have not been applied on the same experimental datasets making comparison difficult [1]. Furthermore, the influence of metastatic lesions on failure load assessment has not been studied. Hence, this study aims at comparing two models on the same experimental dataset and evaluate the influence of the type of lesions on the models’ performances.

Material and Methods

Forty-five vertebrae with confirmed metastatic lesions were considered from eleven donors (8 males and 3 females, 49-71 y.o.). The vertebral bodies were resected at the pedicles and the endplates were removed resulting in parallel surfaces. Samples were scanned using a µCT (µCT100, Scanco Medical, Switzerland) at 24.5 µm isotropic voxel size. The samples were then tested to failure in compression using a servo-hydraulic testing machine [2].

Two FE models were considered in this study: Bern’s model developed by ARTORG [2]; A 0.98 mm linear hexahedron mesh was created from conversion of each voxel into elements. Computed mechanical properties gave to each element linear elasticity, yielding and plasticity with the accumulation of damage and irreversible strains. The non-linear FE model was run in Abaqus (V.6.13, Dassault Systems, France). Lyon’s model developed by LYOS and LBMC [3]; A 1 mm³-quadratic tetrahedron mesh was created. Average grey levels for each element were assigned to each element using a custom Python script. Then, the relationship from [4] was used to attribute Young’s modulus to each element. Specific yield stress was computed using a constant yield strain of 1.5%. Perfect plasticity was given to each element once they reached their yield stress. Each vertebral model was compressed to reach a total apparent strain of 1.9% [5]. Non-linear finite element analysis was performed with ANSYS (v21R1; Houston, USA).

Results

Bern’s and Lyon’s models show close results ($R^2=0.91$) with similar accuracy and precision (868 ± 1569 N for Bern and 656 ± 1683 N for Lyon). Accuracy and precision for both models show higher differences for blastic lesions compared to mixt and lytic lesions (Figure 1).

Discussion and conclusion

Models show similar performances even though their complexity are different: elasto-plastic perfect for Lyon and elasto-plastic with damage for Bern. However, when considering the type of lesions, blastic lesions show a significant overestimation compared to lytic/mixt lesions. This overestimation may be explained by the high density observed in blastic lesions [2]. A sensitivity study could be of interest to assess the impact of mineral density in metastatic lesions.

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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
NUMERICAL INVESTIGATION OF THE EFFECT OF SHAPE MODIFIED STRESS ENVIRONMENT ON OSTEOBLAST BONE REMODELLING.

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Introduction

Approximately 40 million bone fracture cases occur annually around the world and 5-15% of these fractures result in non-union or impaired healing [1]. Synthetic bone tissue engineering scaffolds are promising alternative treatments for critical-sized bone fractures [2]. Materials science has provided excellent progress in developing these scaffolds, leading to multiple innovative solutions such as 3D printed polymer-ceramic composite scaffold [3]. However, the function of shape in scaffold design has not been investigated to the same extent. Current tissue scaffolds mainly adapt regular architecture, which may limit their functionality, particularly for the regeneration of large defects. The aim of this study is to investigate the effects of the shape of scaffold fibres in a mechanically stressed environment on cell proliferation, migration, differentiation, and bone formation.

Methods

A numerical model adapted from Perier-Metz et al. [4] was used to create a mechano-biological simulation using Abaqus/CAE 6.18 (Simulia, Rhode Island) and C++ (ISO/IEC 14882:2020). The biological behaviour was modelled on three types of scaffold fibres: a regular 1 mm diameter cylinder, 1 mm diameter truncated cones with draft angles of -3° and -6°. Each fibre was designed as 3mm long and subjected to a constant compressive load of 15 Pa along their axis. 30% of the free positions of the distal ends of the fibre were initially seeded with mesenchymal stem cells, and the simulation was run over 180 iterations, representing a 6-month time-period, to model cell migration, differentiation, and proliferation.

A framework as presented in Figure 1, was used to calculate visual representations of new tissue formation using custom MATLAB code. The results of cell migration and bone volumes are shown in Figures 2A and 2B.

Figure 1: Computer framework of multiscale Mechano-biological model methodology illustration.

Results

Figure 2: A. Tissue formation (fibrous, cartilage and bone) at three and six month periods for the three fibre shapes. Axis in mm along length and width of fibre/callus. B. Percentage bone volume growth at two, four and six months normalised to fibre callus volume. R is a regular fibre shape, I1 is an irregular fibre shape with -3° draft angle, and I2 is an irregular fibre shape with -6° draft angle.

Discussion

The results from this study show that scaffold fibre shape has a significant impact on bone regeneration under mechanically stressed environments, as represented by over 100% volume change due to the shape change in terms of bone formation. Developed from a previous validated study [4], this mechano-biological relationship model has successfully predicted the bone regeneration, and future work will focus on extending this research to a full scale 3D printed bone tissue engineering scaffold, and validate the results in in vitro and in vivo environments.

References


28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
MODELING OF FLUID SHEAR STRESS ON SMOOTH MUSCLE CELLS IN COMMON CAROTID ARTERY MEDIA

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Introduction

Vascular smooth muscle cells (VSMCs) are exposed to interstitial fluid flow induced shear stress. The alterations in shear stress may result in abnormal VSMC phenotypic modulation which are associated with atherosclerotic plaque formation [1]. Understanding interstitial fluid flow and shear stress on VSMCs in common carotid artery (CCA) has a key role in preventive strategies for atherosclerosis.

To develop an appropriate model to describe the shear stress distribution on VSMCs, the components of the media tissue are taken into consideration since their deformational behavior directly affects the hydraulic permeability of the extracellular matrix around VSMCs. In this work, a lamellar unit (LU) of arterial media consisting of elastic lamellae (EL), VSMCs and interlamellar extracellular matrix (ECM) is developed and numerical methods are used to compute interstitial fluid flux through LU and flow induced shear stress on VSMCs in FEBio [2].

Methods

Figure 1 shows the representative volume element model of LU. Each different colored layer represents the components of LU. The geometry is constructed by considering the volume fraction of components.

A biphasic anisotropic fiber-reinforced constitutive model for ECM, biphasic neo-Hookean constitutive model for EL and solid neo-Hookean constitutive model for VSMC are employed. A pressure gradient in radial direction and a tensile stress in circumferential direction of LU are applied to have an appropriate circumferential stress-strain response of media layer.

The effect of age on shear stress on VSMCs is also investigated. Aging is represented by the change in the volume fractions of components and an increase in their elastic moduli.

Results

Figure 2 illustrates how LU deforms with increasing transmural pressure difference and tensile stress in physiological range.

Discussion

Both applied fluid pressure and tensile stress results in nonlinear deformation behaviour. While LU is stretched in circumferential direction, it is compressed in radial direction. The permeability through the radial thickness of the unit is changed depending on the radial compression. As a result, the interstitial fluid flow intensity and shear stress amount on VSMC are changed with pressure. Furthermore, it is observed that aging results in alterations in shear stress.

Figure 1: The meshed geometry of lamellar unit of human CCA media.

Figure 2: The deformation of LU in circumferential direction.

References

MECHANICAL CHARACTERIZATION OF A TRIPHASIC MEW PCL SCAFFOLD MIMICKING ARTICULAR CARTILAGE ARCHITECTURE

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Introduction
Due to its distinct structure and composition, articular cartilage is a soft tissue that offers a significant amount of dynamic load-bearing capacity while minimizing friction. Due to its avascular nature, however, cartilage is difficult to heal once damaged [1]. Several approaches have been investigated, but their homogeneous designs likely limit their viability. The absence of a native tissue-like structure and organization within such scaffolds may be the cause of regenerated tissue’s tendency towards poor mechanical characteristics [2]. Future treatment options depend on the creation of viable articular cartilage transplants with the necessary biochemical and biomechanical characteristics as well as zone-specific organization. Melt-electrowriting (MEW) allows the manufacturing of polymeric fibrous constructions in a precise manner with a high degree of flexibility in terms of fiber orientation, spacing, and dimension [3]. The aim of this study was to use MEW to fabricate multi-scale triphasic scaffolds by varying both fiber size and orientation to mimic articular cartilage’s zone-specific organization and properties.

Methods
Sample preparation. Medical grade poly (E-caprolactone) (PCL) (Mw = 70 kDa) was used to produce all structures on a custom-built MEW device, based on parameter sets established before [4]. Three groups were created for comparison. For the base-grid, a 0°-90° pattern was manufactured for 20 layers. For the mid-phase, a 0°-45°-90°-135° pattern was selected at a higher collector translation speed, to increase the mechanical stretch and thus decrease fibre diameter, for a total of 20 layers. For the triphasic constructs, both the base-grid and the mid-phase were combined and completed with a surface nanomesh, for which the feed rate was reduced by a factor of 10.

Structural analysis. All samples (n=3 per group) were imaged using a scanning electron microscope (SEM, SU5000, Hitachi, Japan). Fibre diameters were assessed using ImageJ (V. 1.51).

Mechanical properties. Scaffolds from all groups (n =3) were cut into rectangular shapes (4.0 cm x 1.5 cm) for testing, and a uniaxial tensile test was performed under quasi-static conditions (0.1 mm/s) until a strain of 150% was reached using an Instron E10000 testing machine (Instron, Massachusetts, USA).

Results
SEM imaging revealed fibre diameters of 19.8µm, 5.5µm and 640nm for the base-grid, mid-phase and the nanomesh respectively.

Discussion and Conclusion
In this study, multiscale triphasic constructs have been successfully manufactured, resembling the zonal architecture of cartilage. Tensile tests revealed Young’s moduli in the range reported for native articular cartilage, with the base grid providing critical mechanical support. Triphasic constructs therefore represent promising candidates for further evaluation by compressive testing, tribological assessments and in vitro cell studies.

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Acknowledgements
Funded by European Union’s Horizon 2020 Research and innovation programme under grant agreement No. 956004.

Figure 1: SEM image of the triphasic constructs with the nanomesh on top (red box), melt electrowritten on a fine microfibre mid-phase (blue arrow) and a microfibre grid (green arrow).

Young’s Moduli were found to be 4.5±0.72, 3.2±0.48 and 3.8±0.18 MPa for base-grid alone, mid-phase alone and the triphasic construct. The ultimate tensile strengths were found to be 0.38±0.03, 0.27±0.05 and 0.39±0.01 MPa, respectively.

Figure 2: E-Moduli (left) and Ultimate Tensile Strength (right) for the base-grid only, mid-phase only and the triphasic construct.
BIOMECHANICAL ALTERATIONS AFTER SPINAL FUSION TREATMENT AND THEIR RELATION TO CAGE SUBSIDENCE

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INTRODUCTION

Endplate fractures with cage subsidence after spinal fusion are a severe complication after discectomy and cage implantation which can lead to revision surgery (1). Cage subsidence may occur intraoperatively due to surgical damage of the endplate, but likewise occur postoperatively after an asymptomatic time interval (2). Accordingly, different underlying patho-mechanisms might be assumed. The aim of this study is to investigate the biomechanical changes that occur in the involved vertebral bodies after spinal fusion and to investigate their potential link to the risk for cage subsidence.

MATERIALS AND METHODS

A finite element model of an L1-L2 intact lumbar spine was developed from CT scans (Fig. 1a). The model includes the cortical shell, trabecular bone, intervertebral disc, cartilaginous endplates and 7 major ligaments. A lumbar fusion was simulated by removing the intervertebral disc and inserting an intervertebral cage (Fig. 1b). Linear elastic homogeneous properties were used for vertebral bodies, cartilaginous endplates, callus and intervertebral cage while hyper-elastic properties were used for annulus fibrosus and annulus pulposus. The contact between the facet joints was modelled as a frictional surface-surface contact. A compressive load of 500N was applied on the cranial face of the L1 segment, while the caudal face of the L2 segment was restrained of movement. A mechano-regulation algorithm simulating the spinal fusion process [3] was implemented to predict the bone tissue distribution after complete fusion.

RESULTS

Compressive strains in the adjacent vertebral bodies were different in the intact model compared to the fusion model post-surgery (Fig. 2). Lower strains in the adjacent vertebral body were predicted in the intact compared to the fusion model. In addition, compressive strains were different between the post-surgery situation and after the bone fusion had occurred. Lower strains were predicted after complete fusion (Fig. 2), however strains were still higher than in the intact case.

DISCUSSION AND CONCLUSION

Cage subsidence after spinal fusion remains a clinical challenge. Here, we developed a computer model to investigate the mechano-biological regulation during spinal fusion and its potential link to cage subsidence. Preliminary results show increased vertebral strains after spinal fusion and cage implantation, which may explain the risk of cage subsidence especially in the short term. In the future, we will investigate how these biomechanical alterations relate to tissue degeneration processes after fusion surgery.

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ACKNOWLEDGEMENTS

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The understanding of the organization and function of spinal motor systems is one major topic in animal locomotion. Although spinal sensorimotor systems were studied in detail, we still know little about the descending systems in the brainstem and how they interact with spinal circuits [1,2]. For example, how do these systems ensure stable locomotion across rough terrain? Or how do descending circuits from the brainstem interact with spinal sensorimotor systems to produce flexible motor function? Tackling such questions requires a multidisciplinary effort. In the international project Neuronex (https://c3ns.org), we combine behavioral, neurophysiological, computational, and robotic experiments to understand how mechanical scale and task demands determine the function of low-level control centers in the spinal cord and their interactions with high level control centers in the brainstem in small mammals.

The development of synthetic neuronal systems, which is one of the main goals of our project, will help to link all these scientific fields. We already have used simplified synthetic neuronal systems to test and develop cutting-edge hypotheses regarding motor control [3]. We expect that more advanced versions of them will be implemented as bio-inspired control system for robots and wearable devices (e.g., exoskeleton).

More sophisticated synthetic neuronal systems need to mimic the interactions between spinal-reflex control and higher locomotor centers. Small mammals like the rat are a good animal model to infer such interactions during posture and quadrupedal locomotion. Like for any dynamical system, their control strategies can be characterized by analyzing how they respond to external perturbations. We believe that active perturbations might be adequate to address the interplay between lower and higher locomotor centers. They can help to ask, for example, if there a threshold exists, at which spinal-reflex loop need to be helped by higher locomotion centers. Following this idea, a novel three-degrees of freedom platform, called “the shaker” was developed [4]. The shaker can generate single or combined horizontal, vertical, and tilting perturbations with a payload up to 1 kg. It can produce horizontal and vertical perturbations with amplitudes up to 1 cm at oscillation frequencies up to 10 Hz. The tilting motions were constrained to $15^\circ/s$. In addition, the shaker can measure single ground reaction forces (GRF) using up to four custom-build force plates mounted on the platform (see Fig. 1 A). In the conference, we will inform about the kinetic results of the world-wide first studies on rat actively perturbed locomotion. In those experiments, which were approved by the Committee for Animal Research of the State of Thuringia, Germany (registry number: 02-060/16), rats moved across a 2.3 m walking track, constructed around the shaker, at their preferred speeds. During active perturbations (horizontal and vertical), we recorded three-dimensional bones kinematics, single leg GRF, and electromyography of selected muscles of the hind limbs. We expect that by measuring motor responses to a range of perturbations, we can define the functional mapping between deviations in limb state, center of mass dynamics, and muscle activations.

Figure 1: Analyzing rat active perturbed locomotion. A) Experimental setup combining biplanar X-ray, and an active platform ("shaker") with force measure. B) ground reaction forces before (right forelimb) and during a horizontal perturbation (right hindlimb). The platform was shifted 10 mm in 0.05 s towards cranial. Grey lines represent the forces measured by the plates, blue lines the forces produced by the dynamics of the motion, and orange the forces exerted by the rat.

References

Acknowledgements
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THE EFFECTS OF PARTIAL WEIGHT BEARING ON THE HEALING PROCESS VIA BIOMECHANICAL SIMULATION

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Introduction
Interfragmentary movement (IFM) is a key quantity for fracture healing and determined by the gait cycle and the weight bearing of the patient. Partial weight bearing is part of postoperative treatment schemes and the orthopedic surgeon usually gives instructions, such as 10kg, 20kg or half body weight bearing. Only personalized simulations can identify the effect of different partial weight bearing regimes on the IFM of individual patients. To realize a high degree of individualization in the virtualization process, we aimed to define patient-specific boundary conditions via musculoskeletal simulations based on motion capturing data of patients with fractures of the lower extremity. We hypothesized that different levels of partial weight bearing can be tested virtually, and that the impact on the IFM can be individually quantified.

Methods
To cover a wide range of partial weight bearing scenarios, data were collected from healthy subjects (n=22) in various partial weight bearing tests. Both, healthy subjects and patients were monitored with the motion capturing system Xsens™. To guarantee compliance with the different partial weight bearing regimes during each exercise, sensor insoles (Moticon™) were used as a live feedback system. In addition, the sensor insoles allowed for a subsequent analysis of the ground reaction forces and the gait line of both healthy subjects and patients. The subjects completed the timed up and go tests with and without crutches under different partial weight bearing loads with respect to their body weight. The collected data were then biomechanically analyzed and the individual movements were passed to the musculoskeletal simulation system AnyBody™ (Figure 1 a)) to compute the corresponding joint and muscle forces and moments. These data now allowed to fit the patient data (n=5), collected in a similar way, to a wide variety of weight bearing regimes in order to investigate their influence on the IFM. Digital twins of the respective bone-implant-systems were generated based on post-operative clinical imaging and the corresponding joint forces were applied as boundary conditions in the simulations.

Results
The results revealed that a virtual analysis via a biomechanical simulation workflow of different partial weight bearing scenarios and their influence on the local mechanics in the fracture gap of the patients is possible (Figure 1, b)). Linking local stresses and strains in the fracture gap to the healing window (Figure 1, c)), cf. [1] and [2], offers the possibility to use the results in rehabilitation planning [3]. Furthermore, pathological processes resulting in non-union, or fractures displacement, especially in perarticular fractures, can be anticipated in the simulations and, therefore, can be avoid by personalized weight bearing recommendations.

Discussion
Since it is not possible to monitor a wide range of partial weight bearing regimes in one individual patient, a simulation-based workflow was chosen. This shows a clear correlation between fracture morphology, its treatment and the individual partial weight bearing. The effects on fracture healing are significant and have great potential for individualizing rehabilitation programs.

References

Acknowledgements
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Figure 1:
a) Musculoskeletal Simulation
b) Mechanical Situation of the Treatment
c) Fracture Gap with Claes Window

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
**BENDING RESPONSE OF A SOFT ACTUATOR FOR A WEARABLE HAPTIC DEVICE**

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**Introduction**

Human-machine technologies have faced exponential growth in recent years driven due to their enormous potential in revolutionizing our interactive experience with the world [1]. Wearable devices, for example, have transfigured the entire experience of how people communicate in the real world. This interaction would be employed in various applications ranging from entertainment to robotics and healthcare [2]. The receptor for wearable haptic devices is the skin, which is the largest exterior organ of the human body. It is the primary interface for several external stimuli, e.g. heat or cold, and configures a tactile interface, playing a crucial role in detecting mechanical stimuli [3]. Its ability in detecting the real-time touch-based information sent by the haptic device and the user’s perception defines the practicality of haptic technologies [1]. The wearable haptic devices need to be equipped with soft actuation mechanisms with broad stimulation modalities and quick action to communicate with the users. The present study aims to understand the actuation speed of the bending response of a piezoelectric material (PVDF ionic film) intended to be applied in a haptic device used for motor rehabilitation.

**Material and Methods**

A composite material (PVDF/Ionic Liquid-IL) was used to develop the actuation films. The IL (1-Methyl-3-propylimidazolium bis(trifluoromethylsulfonyl)imide) in the structure of this composite increases the content of the β phase, which is mainly responsible for the electroactive properties of PVDF [4]. The IL was mixed with DMSO in a 40/60% w/w (IL/PVDF) ratio. PVDF was then added to the solution in a proportion of 12/88% w/w (PVDF/DMSO). Once a homogeneous and transparent solution was achieved, it was cast into a glass substrate and heated up to 85°C for 1 hr in the oven to evaporate the solvent. Both faces of the films (30x6x0.1mm³) were then coated with thin layers of gold using a hot press. The displacement of the films, as well as their rising time, have been primarily studied. Here we define the rising time as 90% of their maximum bending response. The PVDF film strip has been actuated by a square pulse with a voltage of 20V.

**Results**

The average displacement of the three trials with the corresponding standard deviation measures 1.30 ± 0.27 mm, while the rising time measures 0.32 ± 0.06 s. Figure 1 represents the response of the PVDF strip when a voltage of 20V is applied.

![Figure 1: Rising response and the square pulse for 20V](image)

**Discussion and Conclusion**

When the PVDF strips are actuated by a 20V signal, they bend without a noticeable delay. The film moves by 30 mm in 0.32 s (i.e. rising time) which is comparable with the average human reaction time (200ms). The film, however, gradually relaxes just after the peak displacement while the input voltage is still ON. We attribute this to the dielectric loss constant, amplified by the presence of β-phase in the PVDF strips [5]. Unlike the actuation phase, when the input voltage is switched OFF, the film does not show quick relaxation. Ionic liquid crosslinks PVDF, causing memory-shape properties [6]. By the Joule effect, the temperature of the strip increases when there is current passing. Once that voltage is OFF, the temperature starts slowly decreasing, which prevents the samples from quickly returning to the initial position [7]. Reversing the polarity may lead to quicker relaxation. The dynamics of the PVDF strip under various stimuli will be investigated further in the design of the haptic device.

**References**

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**Acknowledgements**

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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
INFLUENCE OF THE TEAR PATTERN ON SHOULDER STABILITY AFTER ARTHROSCOPIC SUPERIOR CAPSULAR RECONSTRUCTION

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Introduction
Arthroscopic superior capsular reconstruction (ASCR) was introduced for the treatment of irreparable rotator cuff tears (RCTs) [1]. In ASCR a graft is fixed, in the supraspinatus (SSP) pathway, with the aim of restoring the stability of the shoulder. The four most common patterns of RCTs in ASCR include an irreparable full-thickness tear of the following tendons: SSP; SSP + Subscapularis (SC); SSP + Infraspinatus (ISP); and SSP+SC+ISP [2]. Concomitant procedures during ASCR may be considered to restore the action of the SC or ISP: pectoralis major transfer (PMT) or latissimus dorsi transfer (LDT) for the SC; and LDT or lower trapezius transfer (LTT) for the ISP [3]. However, biomechanical evidence regarding the role of the graft for tears extending beyond the SSP [4], and the necessity of concomitant procedures during ASCR, is lacking. The aim of this study was to evaluate the influence of the RCT pattern on the stability of the shoulder after ASCR, with or without concomitant procedures applied.

Methods
A 3D musculoskeletal model of the upper limb was modified to simulate the ASCR procedure and estimate the stability of the glenohumeral (GH) joint [5]. The four most common RCT patterns were modeled by removing the muscles, affected by the RCT, from the model. The muscular and joint reaction forces were estimated based on inverse dynamics, considering motion capture data collected from a biomechanics laboratory. The muscle force sharing problem was solved by minimizing muscle energy consumption, while ensuring the fulfilment of the equations of motion and the stability of the joints. The stability of the GH joint was estimated as the ratio between the GH reaction force components, augmented by a weighting factor that indicates the amount of additional muscular activity necessary to prevent dislocation of the shoulder. The insertion sites for the tendon transfer were defined with the guidance of experienced orthopedic surgeons. The comparison between the pre and postoperative conditions was based on ANOVA and Tukey’s test (p<0.05).

Results
For the isolated tear of the SSP, ASCR increased the stability of the shoulder (p<0.001), compared to the preoperative condition; for the SSP+SC pattern, it degraded stability (p<0.05); and for the SSP+ISP and SSP+SC+ISP patterns, although it increased stability, the improvement was not significant (Figure 1).

Discussion
The main finding of this study was that the isolated fixation of the graft in ASCR for RCTs extending beyond the SSP is not able to compensate for the loss of the SC and/or ISP. Our results provide biomechanical evidence to support the suggestion from orthopedic surgeons to not perform ASCR without repairing the SC tendon. Accordingly, the application of concomitant procedures that restore the transverse force couple is of great importance.

References

Acknowledgements
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Figure 1: Multiple comparison test of the four RCT patterns simulated: preoperative condition, mean and standard deviation, considering the analysed motion capture data, are shown; and postoperative condition, shoulder stability range, considering all shoulder positions for the fixation of the graft, is shown.
Computational Insights into Mechanical Changes in Bacterially Infected Cell Monolayers

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Introduction

Listeria monocytogenes (Lm) is a food-borne facultative intracellular bacterial pathogen that mainly affects individuals with a weakened immune system [1]. The gold standard for studying Lm infection is through in vitro models of infected epithelial or endothelial cell monolayers [2]. It has been observed that in these in vitro models, intracellular Lm infection alters the mechanical behavior of infected as opposed to neighboring uninfected cells. Lm infection affects not only the cellular mechanical properties through cytoskeletal reorganization but also their mechano-sensing mechanism [3]. Infected cells get less stiff while uninfected cells surrounding the infection domains become stiffer compared to cells never exposed to infection [1]. Moreover, Lm infection also alters the active behavior of cells which contract or protrude in a different manner. Our study develops a hybrid in silico model of Lm-infected cell monolayers to understand infection's impact on cell mechanics.

Materials and Methods

We implement a hybrid model of epithelial cell monolayers that combines an agent-based model (ABM) and a finite element model (FEM). The ABM simulates cells as discrete entities, accounting for example for cell-cell interaction forces and cell contraction, while the FEM retrieves the intracellular mechanical stimuli [4]. The ABM’s cell movement serves as input for the FEM, which considers the different mechanical properties of the cells. The FEM calculates intracellular stresses, which are thought to drive the cell’s new active response through its mechano-sensing mechanism [3]. This calculation results in the determination of new cell forces in the FEM, which then serve as input for the ABM.

Results

Our simulation results are validated using in vitro data. Cell movement in the ABM is compared with in vitro cell nucleus movement and additionally, the intracellular stress distribution in the FEM is compared with the stresses obtained through monolayer stress microscopy [5] (Figure 1).

Our results showed that varying levels of bacterial replication inside the monolayer affect its mechanical behavior, altering both the movement and dynamics of cells within the monolayer.

Discussion and Conclusions

The hybrid model developed in this work is a first step in understanding the mechanical alterations in cell monolayers during bacterial infections. By using our proposed model, we have been able to test different hypotheses regarding the altered mechanical behavior of infected cell monolayers, including changes in cellular contractility and in intercellular force transduction. Our results point that this hybrid model could be a valuable tool to unravel the mechanical alterations occurring in host cells during infection. It could assist us in the design of new experiments to test in the laboratory which can reveal novel virulence mechanisms employed by bacteria and lend key insight into basic host cell mechanobiology.

References


Acknowledgements

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METABOLIC ANALYSIS OF A WEARABLE UPPER LIMB EXOSKELETON FOR OVERHEAD WORK

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Introduction
Work related musculoskeletal injuries are a major cause of reduced productivity in the industrial sector. Long-term overhead work may lead to severe injury of the shoulders and has been recognized as a major cause of workdays lost [1]. As many modern production lines still require workers to perform long-term overhead tasks, wearable support devices were recently developed with the aim to mitigate the stress on the shoulders, preserve workers healthiness and ultimately increase productivity. The modern designs proposed are currently object of extensive research aimed to assess the impact on the worker, changes in posture, ergonomics and overall effectiveness [2]. The aim of this work was to test the effects on user’s metabolic expenditure of an upper limb exoskeleton recently designed by the authors for supporting overhead tasks.

Methods
The new exoskeleton (Fig. 1) was based on a previous design conceived for rehabilitation purposes and hand-to-mouth tasks [3]. The kinematics of the shoulder joint and the gravity support mechanism were specifically adapted to: (i) generate a suitable torque to support the arm in conditions of shoulder elevation larger than 90 deg. and (ii), extend the support to both arms. The gravity-support mechanism was designed to allow adjusting the level of compensation required for the task.

Figure 1: CAD design of exoskeleton

A healthy subject (male, 35 years, 196 cm, 96 kg) performed an overhead task consisting of slowly moving a weight of 1.5 kg with both hands, at shoulder elevation angle of about 120 deg., while standing still. This task simulated the use of a heavy power tool in overhead position. The task had a total duration of about 10 minutes, the subject had the opportunity to have a quick rest every minute. The task was repeated twice: with and without the exoskeleton. The user’s metabolic rate during the task was assessed via indirect calorimetry, using a COSMED K5 (www.cosmed.com). The readings were taken every 10 s in mix-chamber mode. Data from the first minute was discarded. The quantities measured were: respiratory frequency (Rf), respiratory exchange ratio (RER), metabolic equivalent (METS) and heart rate (HR).

Results
The comparison of the parameters is reported in table 1:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Free</th>
<th>With exo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rf (l/min)</td>
<td>20.2 (2.5)</td>
<td>14.5 (2.3)</td>
</tr>
<tr>
<td>RER (-)</td>
<td>1.003 (0.068)</td>
<td>0.950 (0.042)</td>
</tr>
<tr>
<td>METS (-)</td>
<td>2.1 (0.2)</td>
<td>2.0 (0.2)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>85.3 (3.6)</td>
<td>80.2 (2.2)</td>
</tr>
</tbody>
</table>

Table 1: Comparison of the metabolic parameters. Average and standard deviation over time.

All the differences were statistically significant (t-test, p-value < 0.05). All the parameters showed a reduced metabolic cost during the task with the exoskeleton.

Discussion and conclusion
Passive exoskeletons are designed to reduce the load on the targeted joints by redistributing it to other parts of the body. This leads to a different motor recruitment strategy needed to achieve the task. The metabolic cost of the task may be reduced. These preliminary results showed that the metabolic cost was reduced during an overhead task involving holding a heavy tool with both hands. Further work will require testing more subjects, extending the recording time and including different tasks. Moreover, the motor strategy should be further investigated by means of EMG and/or biomechanical modelling.

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TOMOGRAPHY IMAGING AND DIGITAL VOLUME CORRELATION OF THE LUNG DURING MECHANICAL VENTILATION

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Introduction
The study of lung mechanics to improve understanding of disease is important to futureproof resilience against potential novel threats to lung health. Medical imaging provides insight to lung health and function in a given instant. Dynamic imaging provides mechanical insight to enhance understanding of lung function. The use of digital volume correlation (DVC) in combination with high-resolution micro-CT imaging and in situ mechanics is gaining popularity for quantifying the mechanical behavior of various materials and structures. Techniques such as DVC have been used to characterize different biomaterials, including bone [1-3] and lung [4,5] among others.

Biomaterials, in particular soft tissues like the lung, exhibit time-dependent behavior. Therefore, the use of synchrotron radiation at SPring-8, Japan, was important to maximize imaging speed, and spatial resolution, to capture the lung architecture. This study aimed to use synchrotron radiation-based micro-CT and in situ mechanical ventilation to study the strain distributions in the lung in health and disease. Comparisons between lung groups in this mouse model were made. The results obtained from this experiment will be of fundamental significance for correlating relationships between microscale and macroscale measurements and the potential impact on patient management guidelines for mechanical ventilation.

Methods
Freshly culled mice had their lungs mechanically ventilated and imaged at various time points during the respiratory cycle. No live animals or human subjects were tested in this study. Alongside a control group, one group underwent alveolar lavage to remove surfactant from the airways. Pressure-Volume (P-V) characteristics were recorded to capture any differences in the initial mechanical state as well as potential changes during the experiment. A sequence of tomograms were collected from the lungs within the intact thoracic cavity. Digital volume correlation (DVC) was used to compute the three-dimensional strain field at the alveolar level from the time sequence of reconstructed tomograms.

Results
DVC analysis was performed using DaVis, LaVision. Images were downsized to 16bit *.raww images, with the background (such as the rib cage) segmented and removed. A sequence of images was collected for each sample and processed in DaVis. Full-field 3D strains of each lung sample were computed with sub-volume sizes screened to minimize errors in the computed strains. Figure 1 shows an example result computed for the lung images. It highlights global observations of inter-lobular slip as well as localized regions of poor ventilation (with the blue deformation contours).

Discussion
A methodology for in situ mechanical ventilation of rodent lungs with synchrotron radiation-based micro-CT was presented. Here whole lungs were imaged to highlight global as well as local trends in inflation behavior for diseased and healthy lungs. Comparisons of healthy and surfactant-free samples were performed. Architectural differences between groups were clearly observed. Their respective strain fields were quantified and compared in the context of their global lung compliance differences, measured via their P-V relationship. Methods and results shown here will inform on localized alveolar parameters for disease modelling, providing enhanced validation. Insight to local versus global strain and, therefore, loading/burden of the lung will also contribute towards structural health monitoring and management of diseased lungs.

References

Acknowledgements
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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
ENHANCING OSSEOINTEGRATION USING COMPLEX POROUS STRUCTURES

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Introduction

Cellular porous structures can potentially overcome the shortcomings of current solid orthopaedic implants [1]. In addition to their mechanical performance, their architectural properties may also play a critical role in the diffusion of nutrients and cell proliferation and differentiation [2]. To achieve an ideal balance of these properties, mechanobiology needs to be scrutinized as it is necessary to (1) consider the biological interaction of the structures with the surrounding tissue and (2) to study the relationship between mechanical loads on the structure and bone regeneration. The aim of this work is to investigate the design of complex porous structures and study their impact on bone mechanobiology based on an advanced computational patient-specific model.

Materials and methods

A uniaxial compression test at 10% strain and a mechano-driven regeneration model applied to a goat tibia [3] (Figure 1) were used to computationally study the behavior of six cylindrical porous scaffolds. Three triply periodic minimal surface geometries (skeletal based Gyroid SK-G, sheet based Gyroid G and Schwarz Primitive SP) with two porosities (70% and 90%) were considered. Bone material properties were inferred from a CT scan and the scaffold was made of titanium.

Results

The highest elastic modulus was found for the G70, which was 12 times higher than the value for the SK-G90. Furthermore, the structure with the highest bone ingrowth, SK-G90, reported a value 5 times higher than the one with the worst performance (SP70) (Figure 2). Figure 3 shows the regions of the granulation tissue that develop into bone for the two extreme cases.

Discussion

The mechanobiological properties of complex porous structures were successfully characterized. The results show that mechanobiological models provide additional insight about the response of the structures. Although the elastic modulus can be tuned by geometry and porosity, the same cannot be described for the bone ingrowth. This indicates that the geometry of each structure plays an important role in the bone regeneration process. As future lines of work, a validation of these results as well as a study with new designs to promote bone differentiation in the core of the structures will be investigated.

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Acknowledgements

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IDENTIFICATION OF TRANSVERSLY ISOTROPIC CONSTITUTIVE PARAMETERS USING IN-VIVO MACRO-INDENTATION METHODS

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INTRODUCTION

Many biomedical applications require the reliable identification of anisotropic soft tissue material properties for the use in numerical models, such as finite element analysis (FEA). Soft tissues exhibit large inter-subject and intra-subject variability in their material properties [1]. Therefore, a set of parameters must be identified for each individual person because there cannot exist applicable average properties in the literature. Further, standard mechanical tests are not suitable for in-vivo identification of material properties as extracting tissue samples is too invasive. Therefore, nowadays the identification is commonly achieved using a macro-indentation test. This test involves pressing on the tissue complex and measuring the force at varying indentation depths. Then, due to the absence of an analytical solution, the parameters are commonly identified using inverse FEA (iFEA), in which simulated results and experimental data are iteratively compared. Recently, it was shown that force-depth data is insufficient in determining the material properties for a two-parameter hyperelastic model, and that full-field surface deformation data (e.g., using digital image correlation) improves the identifiability [2]. Consequently, the aim of this study is to expand the identifiability analysis to anisotropic materials (with three and more parameters).

METHODS

First, we perform a numerical identifiability analysis for transversely isotropic hyperelastic models, which represent material that have a single preferred fiber direction by accounting for the stretch in the fiber direction. To evaluate the identifiability for a specific constitutive law, we consider the objective function (Eq. 1) that quantifies how the simulated results are affected by changes of the different parameters.

\[ F_{uf}(\mathbf{p}, \mathbf{p}^\ast) = \eta F_f(\mathbf{p}, \mathbf{p}^\ast) + (1 - \eta) F_s(\mathbf{p}, \mathbf{p}^\ast) \quad (1) \]

Where \( F_f \) is the reaction force error, \( F_s \) is the surface displacement error, \( \eta \) is a weight factor, \( \mathbf{p} \) is the parameter vector and \( \mathbf{p}^\ast \) is the target parameter vector. We then analyze the sensitivity of the objective function to changes in the parameters for different indentation depths and values of \( \eta \).

Finally, we use iFEA to minimize the objective function based on experimental results of an indentation test on transversely isotropic synthetic tissue phantoms. We validate these results by conducting biaxial stretch experiments to derive the parameters analytically.

Results

As shown in Figure 1, for a two-parameter constitutive law, the force-depth data creates an area where multiple parameter sets give similar simulated results. This structure exists in anisotropic material parametrizations as well, and we expanded these results into three (and more) parameter anisotropic material constitutive laws to identify the uniqueness of the gathered parameters in our experiments.

**Figure 1**: The 2D-space of possible two parameters solutions for a nearly incompressible 1\" order Ogden constitutive law (x axis – mechanical parameter c, y axis – mechanical parameter m), where each contour line represent a 5% increase in the error, and the white dot represents the "ground truth" parameter set.

Discussion

Analyzing the identifiability of anisotropic material properties is an important step before conducting iFEA using experimental results. The addition of surface displacement data to the force-depth data increases the certainty in the resulting parameters. Future work will employ indentations with an instrumented ultrasound, to obtain muscle fiber directions informing a transversely isotropic model.

References


Acknowledgements

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EVALUATION OF MARKERLESS MOTION CAPTURE USING MUSCULOSKELETAL MODELS

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Introduction

Motion capture is a valuable tool in biomechanical research and especially in musculoskeletal modelling for quite some time. It enables to recreate real human movements in models and consequently to calculate body-internal and external reaction forces. Marker-based motion capture (MMC) has long been the state of the art for this purpose [1]. Nevertheless, a good and reliable MMC setup is laborious in preparation and post-processing. Thus, there have also been innovations in recent years that have simplified kinematic recording. Inertial motion capture (IMC) is already widely used for musculoskeletal models and has been verified for its accuracy with them [2]. Recently, there are also systems based on simple optical video recordings (VMC) that often do not require instrumentation of the subjects. However, a broad database is lacking for these systems, especially in their use with musculoskeletal models. This work aims to compare MMC and VMC data for musculoskeletal models. Specifically, joint kinematics from range of motion (ROM) exercises are analyzed.

Materials and Methods

For this study, 18 subjects (12 male, 6 female) with a mean age of 23.8±2.7 y, mean weight of 71.3±11.7 kg and a mean height of 1.77±0.11 m were recruited. The kinematics 17 of motion (ROM) exercises, were simultaneously recorded with 12 MMC cameras (Vicon Vero v2.2, Oxford, UK) and 8 VMC cameras (CapturyLive, v. 250, Saarbrücken, DE) at 60 Hz. Every motion for each degree of freedom (DOF) was performed three times in a row by all subjects at a self-selected speed. The movements started in neutral joint position (0°) and were conducted in both directions to where the model (AMMR v. 2.3.4) had kinematic restrictions (e.g., knee abduction). The median root mean square error (RMSE) of the VMC driven coefficient 

Results

In total 612 calculations were performed and presented in Figure 1 combined for each investigated joint. The major joints’ median RMSE ranges from 2.8° for hip abduction over 4.1° for knee flexion, 6.5° for shoulder flexion and 6.7° for elbow flexion to 7.9° for shoulder abduction and hip flexion. The thorax-pelvis joint showed small errors for lateral bending (5.0°) but deviated more in flexion (15.8°) and rotation (13.4°). The highest RMSE are found for hand abduction (24.8°) and elbow pronation (36.1°).

Discussion

This investigation aimed to evaluate VMC against MMC using musculoskeletal models. The analysis of the 17 DOF showed that VMC grasps many joints well. Overall, the proximal extremity joints perform better than the distal ones except for elbow pronation. IMC driven models feature similar RMSE and r values for the lower extremities [3]. During hand flexion, tracking quality varied greatly, resulting in either relatively small or large deviation (median RMSE=14.8°). Otherwise, the lower tracking quality of the palm results in a high RMSE for elbow pronation and hand abduction. The differences in the thorax joints are caused because for VMC models, some motion is transferred to the pelvis and consequently the hip joint. Regarding the ankle, the flexion was tracked reliably (RMSE=6.3°) but inversion shows an error of 12.4°, probably due to VMC movement being transferred to the hip rotation. The rather larger deviations in the head are presumably due to the marker headband used for MMC, which was often worn differently by the test subjects and can thus lead to a joint offset in the musculoskeletal model. In summary, VMC driven models can represent human motion well. Even though some joints still need improvement, especially the lower extremities and the shoulder joint show a high accuracy with them [2].

References

Introduction

In-vivo mechanical characterization of soft tissues has emerged as a valuable diagnostic and therapeutic tool [1]. Techniques such as Magnetic Resonance Elastography (MRE) provide a platform for encoding motion-sensitive information with a phase-contrast pulse sequence, thereby providing an estimate of full-field displacement data. Using the measured data, an iterative inversion algorithm can then be used to extract the mechanical properties of soft tissue. Gradient-based optimization techniques are often employed to solve inverse problems. However, the inversion using the whole domain is computationally intensive and problematic. An alternative parallelized subzone-based approach [2] is implemented to expedite the inversion, in which the inverse problem is solved on each subzone independently. In addition, the superior convergence properties of the Levenberg-Marquardt algorithm have been utilized to accelerate the inversion algorithm.

Methods

The inverse problem is solved using synthetic data generated by modelling the physical system of MRE as a Boundary Value Problem (BVP) of elastodynamics. A linear viscoelastic and nearly incompressible material behaviour is assumed. The boundary conditions, along with the assumed distribution of storage ($G'$) and loss ($G''$) moduli, are given in Fig. 1. A FEM-based mixed formulation is used for solving the forward problem to obtain 3D harmonic displacement and pressure field solutions ($f = 60$ Hz). Next, the generated displacement field is used as measured data ($u_m$) for the objective function evaluation and enforcing boundary conditions. In iterative approaches, a forward problem is solved at every iteration, followed by sensitivity analysis utilizing the latest estimate of the unknown material parameters ($\mu$). In elastography, the forward problem is solved on the domain $\Omega \subset \mathbb{R}^2$ bounded by $\Gamma$ utilizing the following PDEs and boundary conditions:

$$\nabla \cdot (\mu \nabla u) - 2/3 \mu (\nabla \cdot u) I + p I = -\rho \ddot{u}$$

$$K(\nabla u) - p = 0 \quad \text{on } \Omega$$

$$\sigma = \lambda \text{tr}(\epsilon) I + 2\mu \epsilon \quad \text{on } \Omega$$

$$u = u_m \quad \text{on } \Gamma$$

where the scientific symbols have their usual meanings. In the subzone-based approach, rather than using the whole domain, the domain is divided into smaller overlapping spherical or cubic subzones. The inversion is then performed on each subzone in a parallel fashion.

Results

The subzone-based approach has been found to accelerate the inversion process. For a mesh grid of $32 \times 32 \times 32$, the parallelized algorithm converged in 50 minutes on an 8 Core Intel Xeon(R) W-2245 processor (see Fig. 2). In addition, it has been observed that the subzone size, overlap, and number of iterations per subzone influence the accuracy of the solution.

Discussion

A sensitivity analysis is being conducted to quantify the influence of each variable on reconstruction. Further, the developed algorithm is being tested on the publicly available in-vivo MRE dataset for the human brain [3].

References


Acknowledgements

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INVESTIGATING THE EFFECT OF REDUCED LOAD ON RAT ACHILLES TENDONS VISCOELASTIC PROPERTIES: A FINITE ELEMENT STUDY

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Introduction

The Achilles tendon (AT) is a mechanosensitive collagenous structure that adapts to its local mechanical environment [1]. For instance, changes in the loading cause alterations in the structural and compositional properties. However, the exact mechanisms remain unknown. Recently, in-vivo experiments were conducted to investigate the effect of reduced loading in AT properties by botox injection in combination with a metallic boot for 4 weeks [2].

In this study, we have developed finite element (FE) models based on data in [2] to understand the viscoelastic properties of the collagen network to investigate the adaptive mechanisms in AT due to reduced loading.

Methods

Two cylindrical FE models were generated in ABAQUS based on the average cross-sectional area (1.09±0.39 and 1.80±0.65 mm²) and length (11.2±1.08 and 11.9 ±2.10 mm) of control tendons (fully loaded, FL) and unloaded tendons (UL), respectively [2]. The first part of the experimental mechanical protocol was mimicked, which included cyclic loading (6% strain, displacement rate 0.1 mm/s), followed by one step of stress relaxation (8% strain, displacement rate 1 mm/s).

The tendons were modelled using a fiber-reinforced poro-visco-hyperelastic model [3] with a transversely isotropic matrix [4]. The FL and UL models were fitted to the experimental data (reaction force vs time) and the R² was calculated to determine the quality of the fit (MATLAB 2022a).

Results

The FE models were able to capture the experimental behaviour of the FL and UL tendons for both cyclic loading (CL) and stress-relaxation (SR) separately (Fig. 1, Table 1). Overall, the UL model showed larger elastic energy and higher energy dissipation than the FL model based on higher E₁ and lower damping η₀ (Table 1).

<table>
<thead>
<tr>
<th>Model</th>
<th>E₁ [MPa]</th>
<th>E₂ [MPa]</th>
<th>k₁</th>
<th>k₂</th>
<th>η₀ [MPa s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL FL</td>
<td>17.5</td>
<td>0.11</td>
<td>0.23</td>
<td>66.5</td>
<td>1053</td>
</tr>
<tr>
<td>CL UL</td>
<td>19.8</td>
<td>0.07</td>
<td>0.19</td>
<td>75.4</td>
<td>877</td>
</tr>
<tr>
<td>SR FL</td>
<td>45.0</td>
<td>0.18</td>
<td>0.83</td>
<td>37.5</td>
<td>2654</td>
</tr>
<tr>
<td>SR UL</td>
<td>53.1</td>
<td>0.19</td>
<td>0.67</td>
<td>34.8</td>
<td>2032</td>
</tr>
</tbody>
</table>

Table 1: Optimised parameters for cyclic loading (CL) and stress-relaxation (SR) for fully loaded (FL) and unloaded (UL) model respectively.

Discussion

The main differences between optimised parameters for cyclic loading and stress-relaxation were increased time dependence for both models, with higher elastic energy (increased stiffness) and viscoelasticity seen for the UL model. Both models showed a better fit to the cyclic loading (Fig.1ab) compared to the stress-relaxation (Fig.1cd). For the combined protocol the models were able to capture peak forces but not the overall relaxation times (Fig.1ef). In the near future, mechanobiological models will be developed to predict adaptive processes in AT under reduced loading.

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Acknowledgements

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A BIOMECHANICAL MODEL TO TEST THE EFFECTS OF A PASSIVE EXOSKELETON ON THE SHOULDER COMPLEX

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Introduction
In the last years, wearable passive exoskeletons grew in popularity. Modern devices rely on lightweight springs and cantilevers to exert torques reducing the load on human joints. Typical applications are in rehabilitation or in industry to assist workers during heavy tasks, e.g. overhead tasks. Several possible designs were proposed. Devices meant to be used in working environment need to be lightweight, minimally invasive, easy to use and not to causing discomfort to the user. The aim of this work was to introduce a new detailed model of the shoulder complex and to study the effects on shoulder kinematics of a modern exoskeleton i.e. the “Paexo”, by Ottobock (ottobockexoskeletons.com).

Methods
An OpenSim (opensim.stanford.edu) model of the bilateral shoulder complex was implemented. The novelty of this model is in the introduction of a detailed modeling of the scapulo-thoracic joint (Fig. 1). The model was based on a previous one [1].

Results
The measured kinematics in the free condition matched the findings of previous studies [1,2]. While wearing the exoskeleton, the scapular range of motion was larger in elevation and upward rotation, and smaller in abduction and winging. The scapulohumeral rhythm was also modified.

Discussion and Conclusion
This work represents a preliminary study on the effects on shoulder kinematics of wearable exoskeletons. The findings suggest a modified motion pattern of the shoulder complex while wearing the exoskeleton. The main limitation is the effect of the soft tissue artifact [4] on the shoulder markers that reduces the accuracy of scapula tracking. Another limitation is the use of a generic skeletal model that may not accurately match the anatomy of the subject. Further studies will require to refine scaling, a larger number of subjects and the analysis of kinetics (dynamics).

References

Acknowledgements
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QUANTITATIVE ASSESSMENT OF BONE MICROARCHITECTURE IN THE HUMAN KNEE USING PHOTON-COUNTING CT IS FEASIBLE

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Introduction
Visualization and quantification of bone microarchitecture are important in bone growth, aging, and disease studies. Bone microarchitecture can be non-invasively assessed using micro-computed tomography (µCT). While it is considered the gold standard for non-invasive imaging of bone, its applications have been limited due to its small field of view (FOV); more importantly, usage is limited to ex vivo analyses, hence, it cannot be used to evaluate bone and bone adaptive responses in a patient. High-resolution peripheral quantitative CT (HR-pQCT) is considered the gold standard for in vivo imaging of bone microstructure, but is limited in use because of the rather small FOV and a relatively long acquisition time [1]. Photon-counting CT (PCCT) is a promising alternative with a larger FOV and much shorter scanning time. It is unknown whether bone microstructure can be quantified using PCCT. Therefore, this study aimed to investigate the feasibility of using PCCT in quantifying bone microstructure and compare it to HR-pQCT.

Materials and methods
After obtaining ethical approval, one human cadaveric knee was scanned with PCCT (in-plane resolution: 0.14 mm; slice thickness: 0.10 mm), and HR-pQCT (0.06 mm voxel size). Anterior, central, and posterior volumes of interests (VOIs), each subdivided in three volumes of 2.5 mm height [2] (Figure 1) were defined in the load-bearing regions, resulting in 36 VOIs. Identical VOIs were mapped in PCCT and HR-pQCT images using image registration. Bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), trabecular number (Tb.N), and structural model index (SMI) were quantified.

Results
BV/TV, Tb.Th, and Tb.Sp were highly correlated; correlations were lower for Tb.N and SMI (Table 1, Figure 2).

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/TV</td>
<td>0.84</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tb.Th</td>
<td>0.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tb.Sp</td>
<td>0.81</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tb.N</td>
<td>0.59</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>SMI</td>
<td>0.58</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Table 1: Correlation between PCCT- and HR-pQCT-based parameters in 36 VOIs.

Figure 2: PCCT- and HR-pQCT-based BV/TV was highly correlated in 36 VOIs.

Conclusion
The good agreement between PCCT and HR-pQCT suggests that PCCT is a promising technique to visualize and quantify bone microstructure. The work will be extended to a larger number of knees. Moreover, µCT will be used for further evaluation of PCCT.

References
HOMOGENIZED FE MODELS CAN PREDICT HIP JOINT LOADING USING INVERSE BONE REMODELING AT THE FEMORAL HEAD

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Introduction
Physiological loading conditions are required for a multitude of problems, e.g., patient-specific finite element (FE) models can benefit from individualized and realistic loading conditions. Inverse bone remodeling (IBR) is a method to obtain such loading conditions by predicting the loading history directly from the bone microstructure. However, so far IBR required high-resolution CT images and micro-FE (µFE) models [1]. Thus, it was not applicable in vivo at most skeletal sites, time consuming, and the complexity of the models was limited given the constraints of specialized µFE solvers (e.g., no contact boundary conditions). To mitigate these shortcomings, we recently translated it to homogenized FE (hFE) [2], which works with clinical CT scans, reduces the computational effort and enables the use of standard FE solvers. The goal of this study was to replicate previous µFE-IBR hip joint loading predictions [3] using the new hFE-IBR method. Furthermore, our goal was to investigate how much material information is required in the hFE model for the loading history prediction.

Methods
In brief, IBR finds the loading history by using a finite set of unit-loads, that are combined and optimally scaled until a homogeneous tissue loading state is reached [1]. In this study, IBR was performed on a set of 19 femoral heads. Four unit-load cases were defined (Fig 1a), and µFE-IBR was applied, as described previously [3]. Additionally, hFE-IBR was performed on four model types with decreasing material information (Fig 1b): density- and fabric-dependent (ORTH0), density-dependent (INHOM), separate homogeneous cortical and trabecular material (HOM_HOM), and single homogeneous material (HOM). The new hFE-IBR algorithm was then used to predict the loading history, peak, and mean force. The root mean squared error (RMSE) of the loading history was calculated for each hFE model, using µFE-IBR as the baseline, and normalized by the µFE predicted peak force to get a relative RMSE.

Results
The average CPU-time for hFE-based predictions (50s) was considerably lower compared to µFE-based predictions (500th). The loading history converged towards the µFE model with increasing material information (Fig 1c). All hFE models except HOM were able to predict the same peak force direction as µFE (20°). The peak force magnitude decreased with decreasing material information. Mean force magnitude was relatively insensitive to the selected material model, but the angle tilted more and more towards the 60° load case with decreasing material information. The relative RMSE were: ORTH0 14.2±2.3%, INHOM 14.9±4.1%, HOM_HOM 32.3±4.4%, HOM 40.8±5.5%.

Figure 1: (a) Model region and unit-load cases. (b) Material mapping. (c) Predicted loading history.

Discussion
The loading history at the hip joint was successfully predicted using hFE-based IBR, with a mean relative RMSE of less than 15% compared to µFE-IBR and considerable reduction in computational effort. The usage of at least density-dependent material was essential for accurate predictions, whereas including fabric information improved the predictions only slightly. To summarize, hFE-IBR shows the ability for extremely fast loading history predictions at the price of a small error in the prediction. These results suggest that hFE-IBR can be used with clinically-available CT images and smooth meshes [4], which offer the application of realistic load cases (e.g., contact) in the future.

References

Acknowledgements
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Nanoscale Structural Changes in Bone Cartilage Unit Subjected to Compressive Loads

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Introduction
The bone cartilage unit (BCU) plays a crucial biomechanical role in enabling pain-free articulation and smooth transmission of compressive and shear stresses across diarthrodial joints [1]. Structural degradation and alterations in bone-cartilage cellular communication at the bone-cartilage interface has been proposed as a key early-stage marker for osteoarthritis [2]. Historically, there is a lack of studies investigating tissue graded hierarchical transition from the articular cartilage into the trabecular bone as a continuous unit. Here we analyze the changes in the fibrillar nanomechanical parameters under compression throughout the length of uncalcified and calcified regions within the BCU, using high brilliance small-angle X-ray scattering (SAXS).

Materials and Methods
BCU cores of (~5 mm L x 2 mm D) were extracted from a metacarpal-phalangeal joint adult bovine steer (16-24 months), using diamond drill bit, under constant irrigation (Fig. 1A) [3], SAXS scanning of the BCU were performed at beamline I22, Diamond Light Source, UK (beam-size ~20μm). A rectangular 2D area scan with the long side of the rectangle along the depth from the joint surface was performed on each sample before loading. A second SAXS scan was performed after samples were compressed to 30% strain and allowed to equilibrate, using a microcompression tester. Fibril-level ultrastructural parameters, fibrillar D-period (pre-strain), degree of variability associated with the D-period (ω), fibrillar orientation and degree of fibrillar orientation (ρ) were extracted from SAXS patterns (Fig. 1B).

Results and Discussion
The result shows the existence of a variation in fibrillar D-period (linked to fibril pre-strain), across the BCU, with higher values of D-period in calcified plate and a reduction of the D-period in the underlying trabecular bone to the values characteristic for Type I mineralized collagen in the pre-loaded state (Fig. 1C). Upon compression the changes in the D-period in each zone varies across the BCU, with significant reduction in deep zone and calcified plate (p<0.05). The result clearly shows that nanoscale ECM architectural parameters are inhomogeneous throughout the depths of BCU, and the deformation affects these nanoscale parameters differently. The findings may have biomechanical adaptive significance: higher in-built molecular level resilience/damage resistance to physiological compression, and disruption of the molecular-level pre-strains during remodelling of the bone-cartilage interface may be potential factors in osteoarthritis-based degeneration.

Figure 1: (A) BCU cores of 5mm length and 2mm dia. extracted from bovine metacarpophalangeal joints and placed in microcompression tester for SAXS scanning while kept hydrated (B) 2D SAXS patterns from articular cartilage, calcified plate and trabecular bone (C) Significant reduction in fibrillar pre-strain in deep zone of articular cartilage and underlying calcified plate upon loading.

References

Acknowledgements
We thank Diamond Light Source for beamtime (SM25602-2). This work is supported by EPSRC (EP/V011383/1). We thank Andy Smith and Olga Shebanova (DLS) for excellent technical support during the synchrotron beamtime.
CAN WE FIND SAFE HINGE LEVEL DURING OPENING WEDGE HIGH TIBIAL OSTEOTOMY USING HETEROGENEOUS TIBIAL MODELS?

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Introduction
Opening wedge high tibial osteotomy (OWHTO) is an established surgical procedure for treating patients with osteoarthritis (OA) of the medial knee with genu varum. Although the safety zone or wedge-cutting level, which can minimize the hinge fracture, have been introduced through previous studies, there is still controversy about the optimized safety zones. Therefore, the aim of this study was to analyze the stress distribution around the hinge levels at the lateral cortex of the tibia during OWHTO surgeries. It was hypothesized that if the hinge is located at the upper end of the articular cartilage of the proximal tibiofibular joint (PTFJ), stress at the lateral tibial cortex would be minimal, and fracture is least likely to occur because the hinge is at an anatomically independent position from the fibula.

Methods
Three-dimensional tibial models of a subject and three patients with medial compartment knee OA were reconstructed as heterogeneous finite models based on CT images using commercial software (Mimics 24.0 and 3-matic 16.0). To set heterogeneous material properties for each part of the model, Young’s moduli of them were converted from Hounsfield’s unit (HU) by applying empirical equation in existing studies. In each model, three different hinge levels (Proximal, 5 mm above the upper end of the PTFJ; Middle, upper end of the PTFJ; and Distal, 5 mm below the upper end of the PTFJ) were set. Between Middle and Distal level, we added three detailed hinge levels (1.25mm, 2.5mm, and 3.75mm distal from Middle level). The correction angles of each model were 5°, 10°, and 15° in the control subject and 6.9°, 7.7°, and 8.2° in the patients. Displacement at the posterior cut plane was applied referring to Hernigou’s table considering deformity angle. In addition, the displacement at the anterior cut plane was applied two-thirds of the displacement applied to the posterior cut plane with the help of the clinician. All computational analyses were performed by using commercial software (ABAQUS 14.0).

Results
For the control subject, as the correction angle increased, the maximum von Mises stress values in the lateral tibial cortex increased accordingly, regardless of hinge levels. In addition, the stress distribution area was smallest when the hinge was in the middle at each correction angle. For patients with a medial compartment knee OA, the trends of the maximum von Mises stress values were similar to those of the control subject. Although the maximum von Mises stress values of the distally located hinge were several times higher than the yield stress of the cortical bone, the values were relatively lower than those of the control subject.

Discussion
The results of this study confirmed the hypothesis that hinge at the point where the upper end of the articular cartilage of the PTFJ is located provides the least possibility of lateral tibial cortex fracture, as this is an anatomically independent position from the fibula. In addition, this study provides an opportunity to recall the meaning of safe hinge level and will be of great help in developing preoperative plans in clinical practice and reducing the occurrence of hinge fractures and related complications.

References

Acknowledgements
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TOWARDS A COMPUTER-AIDED PLANNING PROCEDURE FOR EPIPHYSIODESIS SURGERY

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1. Eindhoven University of Technology, The Netherlands; 2. Máxima Medical Center, The Netherlands

Introduction

Epiphysiodesis is a common treatment for growth arrest in adolescent patients. The goal is to surgically remove the growth plate (GP) with minimal removal of adjacent bone [1][2]. To this end, a surgical incision is made at the height of the GP where a surgical drill is inserted and as much as possible GP is removed. Presently, however, the surgical method used for the epiphysiodesis (e.g. location of incision / used instruments) is mostly based on experience of the surgeon and preference of the patient with respect to the scar location, and it is unclear if large differences would exist for different incision locations. The goal of this study therefore was to determine differences in GP and adjacent bone removal for different incision locations and drill diameters for a population of patients. It is expected that these results can help to decide if a patient-specific computer-aided planning would be useful.

Methods

MRI images of 23 patients (age: 12-14 years) were available from which the distal femur and proximal tibia GPs were manually segmented. A statistical shape model (SSM) of the GP was created to assess the variation in GP morphology in this population.

Then, a computational intersection algorithm was developed to simulate epiphysiodesis surgery for 2 drill diameters (4.5 or 9 mm), 3 locations (lateral L, medial M or bilateral BL) and 3 positions (at the GP level GPL, 10 mm superior S or 10 mm inferior I). With this algorithm, a cylindrical volume was generated (representing the drill) with its central axis starting at each voxel representing the GP running to the incision center, and the sum of the amount of bone within all cylindrical volumes was assessed. For the neighboring bone, 2 zones were defined: a danger zone that is <5 mm from the GP, and a forbidden zone that is >5 mm from the growth plate. The algorithm was applied to the mean SSM model as well as to the models representing the ±2SD of mode 1 and 2. The main outcome parameter was the amount of GP that could be ablated without touching the forbidden zone. In addition, it was determined how much of the danger zone needed to be removed to completely remove the GP.

Results

The SSM analysis revealed that most of the variation (80%) in GP shape related to the location of the curvature of the plate (mode 1) and the entire size of the plate (mode 2).

Discussion

The intersection algorithm showed that with a 4.5 mm drill both the distal femur and proximal tibia GP could be completely removed. For a 9 mm drill, however, small amounts of the forbidden zone would need to be removed and more damage to the danger zone was created. In both cases, on average, the amount of damage created to the danger zone was not very sensitive to the incision location and position. Nevertheless, considerable differences were found between geometry modes, suggesting that a computer-aided patient-specific planning could be useful.

References

PREDICTING BONE STRENGTH LOSS USING VOXEL BASED MORPHOMETRY AND FINITE ELEMENT MODELING

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Introduction
Fragility fractures at the hip can lead to significant adverse health outcomes and the lifetime risk of hip fracture is estimated to be 17% for women and 6% for men [1]. Finite element modeling (FEM) based on quantitative computed tomography (qCT) can be used to estimate bone strength, which can be used as a surrogate for estimated fracture risk.

Voxel Based Morphometry (VBM) is a technique used to compare similar but different images [2]. Using VBM, baseline and follow-up qCT scans can be registered to one another to create average bones across femurs of different shapes.

In this study, we used VBM to estimate average bone loss over an 18-month period, and then used the estimated average bone loss to predict the bone strength changes using FEM on a separate validation subset.

Methods
qCT scans from 107 subjects were selected from the UPLIFT weight loss clinical study (NCT03074643). Both baseline and 18-month follow-up qCT scans were available for each selected subject.

The femurs were segmented and registered (ANTsPy 0.3.1) to a template femur. The registered baseline scan was subtracted from the registered follow-up scan to create a map of the bone loss for each subject. For 99 of the 107 subjects, these differences were averaged at the voxel level to create an average amount of voxel-based density change.

Results
Predicted-18Mo simulations predicted a much smaller bone strength decrease (mean: -0.02kN; 95% CI: -0.13, 0.09kN) than the Actual-18Mo simulations (-0.24kN; -1.35, 0.87kN). Across all simulations, differences between the Predicted-18Mo vs. Actual-18Mo bone strengths averaged 0.22kN and ranged from -0.50kN to 1.36kN.

Discussion
In this study, we attempted to “age” baseline qCT scans to create models that simulated the bone loss over an 18-month period. Our predicted strengths substantially underestimated the amount of bone strength loss.

As we used an average bone change to “age” the qCT scans, differences between the Predicted-18Mo and Actual-18Mo were expected for individual subjects. However, we did not expect the mean strength loss to differ so greatly. Our “aging” process does not change the geometry; however, the geometric changes could play an important role in strength changes.

Future work should focus on investigating average and subject-specific longitudinal bone geometry changes in addition to bone density changes.

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Acknowledgements
This study was supported by the National Institute of Health (R01AG050656, K25AG058804, F31AG069414) and ETH focus area: Personalized Health and Related Technologies (Grant: PHRT 325).
CHARACTERIZATION OF HYDRATION EFFECT ON HAEMOSTATIC SPONGE STRUCTURE USING MULTIMODAL IMAGING

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Introduction

Haemostatic sponges are collagen or gelatin based elements used in surgeries such as the sinus lift [1]. Playing the role of a bone filler, the characterization of its mechanical and structural properties evolution during hydration are crucial to build predictive surgery simulations. For this reason, we addressed this study to determine the structural properties of collagen sponge during hydration using new non-invasive imaging protocol.

Methods

¼ of haemostatic sponges (Hemocollagene, Septodont) was immersed in physiological serum (NaCl 0.9%, B. Braun) at room temperature until it reached the hydrated state. We observed the haemostatic sponge microscopic structure before hydration using x-ray computational tomography (CT, EasyTom nano, RX Solutions) (Fig 1a) and during the hydration using magnetic resonance imaging (MRI) equipped with cryoprobe (Bruker Biospin) (Fig 1b). The same operator performed manual segmentation using 3D slicer software (www.slicer.org) to avoid discrepancies due to contour interpretation. The volume operations as well as mesh generation have been done with Pyvista and Tegten python libraries.

Results

The dry microstructure obtained was consistent with previous optical pictures and scanning electron microscopy [2].

Regarding the hydration evolution, we discriminated 3 sponge parts from MRI images: the global or effective volume ($Vol_{eff}$), the hydrated volume ($Vol_{hyd}$) and the air volume ($Vol_{air}$) (Fig 2). The decrease of $Vol_{air}$ was correlated with decrease of the $Vol_{air}$. The hydrated structure was consistent with subsequent biphotons microscopy imaging.

Discussion

Based on a new non-invasive protocol to explore collagen materials during hydration, we showed the decrease of the sponge volume is induced by the air removal. The collagen is preserved excluding the hypothesis of sponge dissolution in the fluid. The evolution of the $Vol_{air}$ was consistent with previous study [2] but delayed. Within the MRI the temperature was not imposed to 37°C neither during sample resting in between acquisitions. The impact of the experimental factor (e.g. solution, temperature environment) need to be investigated as well as the evolution the microscopic structure during the hydration. This new non-invasive tool could be adapted to explore the structure under mechanical essay.

References


Acknowledgements

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FREEZE DRIED WHARTON’S JELLY MECHANICAL RESPONSE CHANGE WITH HYDRATION

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Introduction

Perinatal tissues such as Wharton’s jelly (WJ) are investigated especially for regenerative medicine applications [1]. Assessing mechanical behavior as function of hydration is crucial to provide sound experimental characterization reducing discrepancies and to build predictive models fulfilling quality by design requirements. The hydration effect was already reported on mechanical strength and toughness [2]. It modifies the interaction between tropocollagen molecules such as direct electrostatic interactions, hydrogen bonds or water bridges. Molecular dynamics simulation of collagen microfibrils provides a complementary data to experiments to characterize tropocollagen molecules during the hydration process [4]. This work aims to propose a link in between both states, dry vs hydrated, at micro and macro scales.

Methods

WJ parts were isolated from human umbilical cords, washed in PBS and freeze dried. The tensile tests were carried out thanks to a Zwicky 0.5 equipped with a 10N load cell. To reproduce close physiological conditions ([NaCl]=9g/L, 37°C), a tank has been adapted to the machine. The hydration effect (d) has been characterized similarly to a damage parameter:

\[ d = 1 - \frac{E_h}{E_d} \]

where \( E_h \) and \( E_d \) are linear elastic moduli respectively for dry and hydrated conditions. Besides, all-atom molecular dynamics simulations of model collagen type I were performed using the microfibrillar X-ray crystallographic structure [4]. Up to 48,000 water molecules were added to reach 220% hydration using package NAMD on 160 CPUs.

Results

Engineering stress-strain curves are plotted in Fig. 1 in both conditions for a representative sample Elastic moduli strongly decreased from \( E_d=11.10 \pm 1.43 \text{MPa} \) to \( E_h=0.64 \pm 0.14 \text{MPa} \) leading, for a fully saturated sample, to a hydration effect parameter of \( d=0.94 \pm 0.02 \) (n=6). At lower scales, and for low hydration (57%, Fig 2), we observed two regimes with a transition around 30nm that decreased while hydration increased.

Discussion

The strong decrease of elastic modulus in between both states at macro-scale is consistent with the literature [2] and a single parameter allows predicting the hydration effect. On the other hands at micro-scale, increasing the hydration level reduces mechanical strength as water molecules act rather as a lubricant. Extending this work to larger strain is under progress [3] while linking micro and macro scale parameters.

References

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Figure 1: Stress-strain curves obtained for the same sample. The insert shows sample’s appearance at the beginning of the mechanical load with the same scale.

Figure 2: Variations of the self-diffusion coefficient with the position along the long z-coordinate of the crystal (c-axis) and with the hydration level (mass water/mass protein).
AN IMAGE-BASED METHODOLOGY TO QUANTIFY ULTRASONIC CELL DEFORMATION

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Background

Ultrasonic surgical cutting tools are an emerging technology which are becoming increasingly popular in the surgical arena and display several benefits over traditional devices. They utilise ultrasonic vibrations to cut biological tissues and have shown to have enhanced precision and improved healing times [1, 2]. The response to these tools at a cellular level, however, is largely unexplored. This is likely due to difficulties in studying the incision site and observing probe-tissue interactions, but also challenges around quantifying the strains cells experience during cutting and applying this to them in a controlled and clinically relevant manner. An insight into cell responses could lead to a deeper understanding of the tool-tissue interactions and help inform device design and implementation. Furthermore, ultrasonic vibrations are known to stimulate therapeutic biological effects via mechanobiological pathways in damaged tissues [3]. With further knowledge and understanding of the effects of ultrasound on cells, its regenerative capabilities could be applied to cutting devices to further facilitate tissue healing post-incision.

Recent Advances

In this work, we utilise an image-based ultrasonic shaking (IBUS) test to examine ultrasonic cell deformation and their resultant biological response [4]. Practically, this involves culturing cells on a PMMA strip attached to a 20 kHz sonotrode. The PMMA substrate was specifically tuned to create a standing wave during ultrasonic excitation resulting an area of large strain in the centre of the specimen. This enables pre-calibration prior to imaging, creating a test with scalable strain values and ensuring relevant stimulation. Cells are illuminated under a microscope with a phase contrast objective using a pulsed laser. They are then imaged using an ultra-high-speed camera whilst being ultrasonically vibrated, enabling real-time visualisation of cells while they are excited. An example of the images obtained can be seen in figure 1.

Results we have obtained thus far show images of cells deforming with the PMMA substrate with some visible internal cell components. We have shown that digital image correlation (DIC) analysis can be used to quantify the cell displacement and deformation as shown in fig 2.

Future directions

Future work involves imaging with fluorescent staining to highlight internal cell components and understand their role in cell deformation. Extraction of cells post-excitation will also be done to undertake biological assays and understand the biochemical implications of deformation. This will allow us to begin to understand the mechanobiological implications of ultrasound, and specifically ultrasonic surgical cutting tools, on cells. Finally, there is potential for this data to be compiled to inform a mechanical cell model that could be used to study cell mechanics.

References


Acknowledgements

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Introduction
Aortic valvular abnormalities, including aortic stenosis due to leaflet calcifications, are progressive diseases with increasing prevalence.[1] Calcification leads to malfunction of the valve which might block the heart to supply sufficient amount of oxygen-rich blood to the rest of the body. Although, surgical aortic valve replacement is the most efficient treatment option, due to invasiveness it is contraindicated for high-risk patients particularly above the age of 75. Therefore, transcatheter aortic valve implantation (TAVI) is the generally accepted standard care for aortic sclerosis.[2] TAVI is catheter-based minimally invasive procedure where the replacement valve is guided through a small incision in the femoral artery into the aortic annulus. Since the implanted valve changes the hemodynamics especially in the Sinus Valsava, an early diagnosis of blood flow abnormalities and disturbances is essential to avoid adverse outcomes. Computational fluid dynamics (CFD) and fluid-structure interaction (FSI) have emerged as approaches for assessment of aortic valve hemodynamics in idealised and personalised valve models. The present work aims at building a reliable and predictive computational (CFD and FSI) model through integration of the experimental data on the valve leaflet displacement acquired through a flow-loop in-vitro setup and 4D magnetic resonance imaging (MRI).

Methods
Fig. 1 illustrates the region of interest of the in-vitro setup (Fig. 1-A), experimental and MRI data (Fig.1-B,C), and computational model of the aortic valve (Fig.1-D, COMSOL Multiphysics 6.0). Through the experiments conducted with the in-vitro setup, transient pressure and velocity profiles were acquired and used as boundary conditions for both the semi-transient CFD and FSI models. The 2D axisymmetric geometric model was established by utilizing the 4D MRI scans, defining a linear deformation for the leaflets, initially assumed as rigid in the CFD model. The non-Newtonian characteristics of blood were neglected owing to the size of the artery. Given the transitional flow regime, the k-omega SST model was employed to address turbulence. Following mesh and inlet and outlet lengths analyses, CFD semi-transient simulations were performed to characterize local hemodynamic and flow disturbances in the sinus of Valsalva. These steady-state simulations considered the change of the velocity and pressure over time, as well as the valve changing geometry. After introducing mechanical properties of the leaflets, FSI analysis was performed in which the structure field is defined with mechanical properties of a healthy leaflet introduced in [3] and the aortic root handled as rigid.

Results
Despite the limited resolution (0.9 x 0.9 x 4.0 mm), the 4D MRI scans showed that the leaflet geometry was changing during the cardiac cycle. The tracked valve deformation and the hemodynamic conditions are used to validate the CFD and FSI models. Among the computational results, it is noteworthy that turbulence levels (turbulent kinetic energy, TKE) were relatively high from peak to late systole, but otherwise remained low. Moreover, high-velocity jet flow at the valve orifice during systole and recirculatory flows in the sinus during diastole were clearly observed, as shown by the velocity streamlines (Fig. 1-D). These findings agree with literature results.[4]

Discussion
The performed semi-transient CFD analysis based on an experimental-based deforming valve geometry is an effective alternative to the computationally intensive FSI simulations. Combining this method with flow-loop and 4D MRI data enables obtaining reliable results and strengthen the experimental-computational twin, allowing an extension to the analysis of in-vivo results.

References
MODELING AND SIMULATION OF AN OSTEOCYTE CELLULAR PROCESS INTERACTING WITH FLUID FLOW IN A CANALICULUS

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Introduction
An osteocyte is a bone cell situated inside hard bone matrix in an interstice (lacuna). It has many dendritic structures called processes that radiate outward in the bone matrix through cylindrical openings (canaliculi). Osteocytes can sense stress applied by the interstitial fluid flow and respond by releasing biochemical signals that regulate bone remodelling. Experiments have suggested that the stress and strain typically experienced at the macroscale tissue level have to be amplified 10X in order for osteocytes to have a significant response in vivo. The stress/strain amplification mechanism is not yet well understood [1-2]. Studies indicate that the process is the primary site for mechanosensation due to the tethering elements that attach the process membrane to the canalicular wall [3-5]. However, there are other potential factors which may also contribute to stress amplification such as canalicular wall geometry and osteocyte-associated proteins in the interstitial space called pericellular matrix (PCM) [6-7]. In this work, we perform computational studies on possible effects of canalicular wall roughness in stress/strain amplification.

Methods
The cellular process is modelled by a gradually tapered porous cylinder made from two families (longitudinal and circumferential) of orthogonal deformable fibers and a centered elastic spring connected to the cylinder surface by flexible fibers on cross sections. Canalicular wall roughness is modelled by randomly generated protrusions on the wall. The interstitial liquid is modelled by a viscous incompressible Newtonian fluid. The flow is modelled by the lattice Boltzmann equations (D3Q19 model). The fluid-structure-interaction is handled by the immersed boundary framework [8].

Results
Our preliminary results (Fig. 1) show a significant increase in deformation and shear stress on the cellular process when the canalicular wall is rough, compared to the smooth case. This suggests roughness may play a significant role in stress/strain amplification.

Discussion
Understanding the potential synergistic interplay between canalicular wall roughness and factors such as tethering elements and PCM may prove essential for better understanding of the stress amplification process.

Fig.1. Fluid shear stress by color on the process surface (the color cylinder) in a canalculus (the space bounded by the wall of the red solid (bone matrix) for the smooth case (upper) and rough case (lower). Re=0.001. One can see that the stress and stretching of the process is greater in the rough case.

References

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CELL PROLIFERATION STUDY: A NEW COMPUTATIONAL MODEL SOLVED BY THE SPH METHOD

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Introduction

When cell damage occurs cells tend to proliferate in order to replace the damaged ones [3, 4]. During this process, cells grow and divide into two new genetically identical cells [1, 2]. This is a well-organized process that is still not entirely understood due to its complexity. In the last years, computational models have started to be applied in the study of cell proliferation since they offer attractive advantages for biomedical research. Among them, less time and cost expenditure can be highlighted [5]. To solve these models, numerical methods are usually proposed and several examples can be found in the literature. The Smoothed Particle Hydrodynamics (SPH) method is a discrete meshless method and one of the most commonly used [6]. In this work, a new 3D non-linear algorithm to simulate cell proliferation was developed. The SPH and the Navier-Stokes equations were used and both the growth and division of single and multiple cells was considered. The viability of the algorithm was tested and further calibrated. Analyses of volume growth and evolution of the diameter, volume and form of the clusters were done.

Methods

The SPH discretizes the problem domain without pre-connected particles. Using these particles, an integral representation is obtained to find the approximation functions and to approximate the field function. With these functions and with the Navier-Stokes equations, particle approximation is done [6]. To initiate the algorithm, initial input data is needed. From this, particle discretization is done and three types of particles are created (cell, extracellular matrix and boundary). One cell is placed in the middle of the domain, and after that, for all particles, the initial velocity, internal pressure and acceleration are calculated. When all this is achieved, the cell starts to grow and divides when its initial volume doubles. The division creates a new particle/cell in the domain that also grows and divides, repeating the previous process. Throughout the iterations, the new positions of the particles are updated resorting to the kernel functions obtained in each one.

Results

For this work, 20 simulations were done in order to verify the reproducibility and viability of the algorithm. In all of them, 7 cell divisions were considered, as well as the evolution of the volume along the iterations, from the first individual cell to the last division. Also, as the number of cells increased, the total form, volume and diameter of the cluster of cells was considered and compared between all simulations since a random parameter was defined in the algorithm. When one cell was analysed, a linear volume growth was obtained until the cell doubled its initial volume. At this point, the division occurred. The simulations started with one cell and then an exponential growth in the number of cells along the division was visible. With the evolution of the number of cells, different clusters were formed but, in all simulations, the results were quite similar in terms of form, diameter and volume.

Discussion

In this work, the process of cell proliferation for a single cell and for groups of cells was simulated with the created algorithm. However, it is important to stress that the development of the algorithm is still in the beginning. Thus, several improvements can be done in future work in order to improve it and obtain more realistic simulations. In spite of that, even in the initial phase, the results were quite satisfactory. All simulations generated coherent results between them and followed what is described in the literature. This suggests that, in the future, this algorithm can be an efficient numerical tool to simulate the process of cell proliferation.

References


Acknowledgements

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SIMULATION OF ANGIOGENESIS DURING TUMOUR GROWTH PROLIFERATION

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Introduction
During tumour growth, when tumours achieve a critical size, their growth tends to stop due to poor blood supply, as it is dependent on a direct supply of nutrients [1, 2]. In these situations, tumour cells become capable of secreting tumour angiogenic growth factors that stimulate endothelial cells to initiate the process of angiogenesis [3]. During this process, endothelial cells proliferate and migrate towards the tumour cells, creating a new vessel network that will supply them and support their continued growth [1, 3]. The development of new mathematical and computational models to describe tumour-induced angiogenesis increased in the last years and currently, researchers seek to increase their accuracy by making them able to cover a growing number of biological phenomena [5]. As predictable tools of these phenomena, they have already proven their potential [6]. Different numerical methods have been used to solve these models. One popular example is the Smoothed Particle Hydrodynamics (SPH), a meshless discrete method [7]. The present work aimed to implement the process of angiogenesis in a previously developed 3D algorithm that simulates cell proliferation. This process was activated by VEGF concentration and different values and different locations for the focus of concentration were tested in order to see their influence on the growth of new vessels.

Methods
To discretize the domain, the SPH resorts to particles without a pre-established connection and uses them to obtain the approximation functions and to approximate the field function [7]. The algorithm combines four different types of particles: cell, extracellular matrix, boundary and blood vessel. The particle at the center of the domain was defined as cell and, after obtaining the initial velocity, internal pressure and acceleration of all particles, the cell was allowed to grow and divide, generating new cells in the domain, following an exponential growth. A VEGF gradient was also initially defined along the whole domain and the main concentration was defined in the area occupied by the cells. As the cell proliferates, and following the focus of VEGF concentration, a blood vessel was created.

Results
To verify the viability of the algorithm, different simulations were performed in order to verify if correct vessel growth was achieved along the iterations and following the growth of the cells. In all cases, the vessel grew towards the direction of the cells, which were defined as the source of concentration of VEGF. This growth was controlled by the growth of the cells so it did not occur in all iterations but only in specific ones. Different concentrations of VEGF and different positions of the focus of concentration were tested in order to verify their influence in the process of angiogenesis, namely, in the direction of the growth of the vessel. It tended to grow in the direction of areas where the concentration of VEGF was higher, which represented the location of the different focuses of concentration that were defined in each simulation.

Discussion
The process of angiogenesis was simulated in combination with the process of cell proliferation in a single algorithm. The new part of the algorithm, i.e. the angiogenesis process, was dependent on cell proliferation since the cells were the source of VEGF, which is the factor that stimulates vessel growth. Such is in accordance with what is defined in the literature. The direction of the growth was also coherent with the focus of concentration, as defined in the algorithm. The obtained results were satisfactory even if there is still room for improvement for the algorithm in future work.

References

Acknowledgements
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FSI COMPUTATIONAL MODEL OF A PATIENT SPECIFIC AAA
VALIDATED BY LED ILLUMINATED PIV

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Introduction
The development and the progression of abdominal aortic aneurysms (AAA) are greatly influenced by the blood flow behavior. Important hemodynamic variables, such as the wall shear stress and the oscillatory index can be used to better understand this phenomenon. However, current imaging approaches cannot accurately evaluate these indicators \textit{in-vivo}, numerical simulations are used instead. In order to trust the results of numerical simulation it is fundamental to properly validate them \textit{in-vitro}. The aim of this study is to validate a fluid structure interaction simulation of a patient specific AAA by means of 2D Particle Image Velocimetry.

Methods
A patient specific aortic aneurysm phantom was manufactured via 3D printing and material casting. Sylgard 184 was chosen due to its mechanical and optical properties. The model was inserted into a novel Hybrid Mock Circulatory Loop (HMCL) that reproduces physiological flow conditions \cite{1,2}. The outlets were connected to Hybrid-Units in order to replicate the Windkessel effect with pressure range of 0-40 mmHg.

A mixture of glycerol and water (61:39), matching the refractive index of the phantoms, was used as working fluid and the flow was seeded with 10 μm – diameter hollow spherical particles. A pulsed high-power LED (HardSOFT) and a line light were used to create a light sheet \cite{3}. The LED was operated with a pulse width of 10 μs and a pulse separation time of 200 μs. Two regions of interest proximal to the inlet were considered. The experimental setup is shown in Figure 1.

Results
The velocity fields obtained from FSI and PIV were compared for different instants of the cardiac cycle. In Figure 2 we show a good agreement between them at late systole. In particular, it can be seen that the recirculation appearing during the deceleration phase is properly captured in the FSI simulation.

Discussion
In this work a cost-effective LED illuminate PIV setup and a novel Hybrid Mock Circulatory Loop were used to validate \textit{in-vitro} the results of patient specific numerical simulation. Despite a slight underestimation of the velocity magnitude, the main complex flow features occurring in the aneurysmatic sac were correctly predicted. These results confirms that FSI simulations are a reliable tool to study the fluid dynamic of AAAs.

In future investigations we will assess the influence of the boundary conditions, varying the inlet flow rate waveform and the outlets Windkessel parameters.

References

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VIRTUAL TREATMENT PLANNING OF TRANSCATHETER EDGE-TO-EDGE MITRAL VALVE REPAIR

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Introduction

For patients with mitral valve regurgitation who are at high surgical risk, transcatheter edge-to-edge repair (TEER) can be a suitable treatment alternative to a surgical procedure [1]. The TEER device serves to reduce the backflow of blood through the mitral valve by reducing the regurgitant orifice area. At the same time, a sufficiently large diastolic orifice area should remain to prevent mitral stenosis after treatment. In this study, we investigate whether pre-interventional virtual planning based on echocardiographic data could support clinicians in finding the optimal device position for a patient. This could reduce the need for intra-operative planning and device placement attempts.

Methods

3D transesophageal echocardiography images of the left ventricle and mitral valve of a patient undergoing TEER treatment were acquired and segmented. A mechanical model of the pre-interventional mitral valve was built based on these segmentations. Virtual TEER interventions were performed by inserting different device types at various positions in the mitral valve model. Computational fluid dynamics simulations were performed to assess mitral valve hemodynamics both before and after the virtual intervention.

Results

Inserting the TEER device at different positions in the mitral valve model influences both the regurgitant and the diastolic orifice areas. The best device position determined with the model agrees well with the location the device was placed in the patient (Fig.1). The CFD simulations show an increased mitral valve pressure gradient in the post-interventional state, which is an expected trend due to the reduced diastolic orifice area.

Discussion

This work demonstrates a general workflow for virtual planning of TEER procedures based on routinely acquired echocardiographic images. Clinically relevant parameters including the mitral valve orifice areas and the mitral valve pressure gradient after the intervention can be computed with this approach. More patient cases need to be processed and evaluated to assess the applicability of the proposed workflow for making patient-specific outcome predictions.

References


Figure 1: Virtual mitral valve model with TEER devices inserted at different positions. Configuration B reduces the regurgitant orifice area the most (red area during systole), which agrees well with the central device positioning chosen in the actual intervention.
Introduction

Cementless stems are becoming more frequent in total hip arthroplasty surgeries. Despite recent progress, aseptic loosening due to incorrect osteointegration is still one of the main causes of failure [1]. With inadequate primary stability, physiological loading induces relative micromotion, and the bone tissue at the interface differentiates into fibrous, causing pain and the need for revision surgery. Long-term implant stability can be improved using an osteoinductive stem coating. The effect of induced micromotion on long-term osteointegration has been investigated in animal models [2]; nevertheless, these tests are invasive and painful and no longer approved by ethics committees. This study aims to develop a Finite Element (FE) model to predict implant osteointegration and partially replace animal experiments. To achieve this, a previous interface remodelling simulation [3] was extended and calibrated using data from animal tests without induced micromotion.

Materials and Methods

Cylindrical titanium alloy implants were inserted in four rabbits' tibiae, which were sacrificed 12 weeks after surgery. Bone-to-implant contact (BIC) percentages at the initial and final time were measured as well as the distances between bone and implant along the pin surface that was not in contact with bone (gap) at time zero. From micro-CT and Rx images, a FE model of the rabbit tibia (E=11 GPa, v=0.3) implanted with titanium pins (E=96 GPa, v=0.36) was generated (Figure 1A). The contact surface was modelled by assigning a different state to each contact element according to the initial configuration obtained from the animal experiment. Boundary conditions were applied to replicate physiological loads during rabbits’ running. Based on the results of the simulations, contact elements changed their states according to the finite state machine proposed in the previous study [3], updated with the introduction of a gap threshold value (Figure 1B) to consider that bone has a limited ability to bridge the distance from the implant. Simulations were run until convergence. In vivo data (final BIC=53% at 12 weeks) was used to calibrate the model and identify this threshold value. Following the calibration, the model was used to simulate a push-out test and predict the axial load that caused the macroscopic mobilisation of the pin.

Results

The maximum bone-implant gap the bone could bridge in 12 weeks was 80 μm, which reproduced the final experimentally measured BIC (53%). From the push-out test simulation, it was found that a force of 19 N (4.56 MPa) was needed for the macroscopic mobilisation of the pin.

Discussion

The push-out strength predicted was comparable to the one measured in a previous animal study (4 ± 1 MPa), performed with the same pin material coated or uncoated [4]. This modelling framework can be applied to predict improved long-term stability with osteoinductive coatings. Future work will apply this method for predicting the long-term stability of cementless hip stems, where data from animal models inform the human (femur-stem) model. This would represent an important tool for new stem design.

References


Acknowledgements

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Introduction
The characterization of biological tissues by means of constitutive models is a necessary task to carry out realistic and reliable finite element simulations. The arteries, in particular, present different mechanical properties, such as hyperelasticity and viscoelasticity, which are fundamental for their correct biological functioning. Although it is possible to describe these properties through constitutive models, this task involves the calibration of material parameters of such models in order to properly mimic the mechanical behavior of the studied material.
To determine these constants, optimization techniques that iteratively account for results computed via finite elements are often used, thus resulting in a very slow computational process. Therefore, it is proposed in this work to accelerate the process by creating a metamodel through a neural network trained with synthetic data obtained from finite element simulations. Adjustments of this type have been made with purely hyperelastic constitutive models [1], but have not yet been included. In this investigation, the non-linear viscoelastic component is included using a constitutive model recently proposed by Latorre et al. [2].

Method
A uniaxial relaxation test in the circumferential direction of a one-year-old guinea pig aorta artery is used to study the viscous effect described in these experimental results. To characterize the constitutive model, a fully connected neural network is trained, with 3 hidden layers formed by 6 neurons, using data from 5000 finite element simulations, changing only the parameters of the viscoelastic constitutive model and maintaining the hyperelastic parameters previously adjusted in a work already published by the authors [3]. The input of the network are 6 parameters that correspond to the viscous parameters of the viscoelastic constitutive model, while the corresponding output is made up of the data produced by the reduction of the dimensionality applied to 4001 time points by each simulation performed. This reduction of the dimensionality is done through the use of Principal Component Analysis (PCA) [4]. Therefore, with this network a metamodel is obtained, which receive the viscous parameters and deliver data that represent the applied stresses. Based on this metamodel, an optimizer is applied to determine the viscous parameters that deliver the best fit to the experimentally measured stress. With this last step, it is possible to adjust the parameters of the viscoelastic constitutive model that describe the data obtained from the uniaxial relaxation test of an artery.

Result
A metamodel with a Mean Squared Error (MSE) of 2.46% is obtained, which affects the accuracy of the parameters obtained after applying the optimizer. However, a set of parameters similar to that delivered by the classical method [3] is achieved. After plotting the curve delivered by the metamodel with the parameters obtained in [3] and contrasting it with the experimental data, some differences are observed in the beginning of the relaxation process (Figure 1) that are also attributed to the error of the metamodel. On the other hand, the time to obtain the optimal parameters is much lower compared to the methods that iterate with finite element simulations.

Figure 1: Comparison of the experimental response (black) and that of the metamodel (red) after evaluating the optimal viscous parameters obtained in [3].

References

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Introduction

Many diseases are driven by or have a direct effect on cell mechanical interactions with the extracellular matrix (ECM)\(^1,2\). Traction Force Microscopy (TFM) is the most common methodology to measure cell-matrix mechanical interactions within in vitro cultures. Collagen hydrogels are typically used to mimic the three-dimensional ECM. Classic 3D TFM considers the ECM as a continuum medium with homogeneous mechanical properties. However, local remodeling of the fibrillar network by cells leads to changes in the ECM mechanical properties near the cell that cannot be captured by continuum models and the length scale at which forces can be recovered is limited. In this work, we present a novel 3D data-driven TFM workflow based on a discrete fiber model that incorporates geometrical information from the imaged collagen network. Instead of solely relying on one constitutive model that describes the global behavior of the ECM, we accommodate the mechanical behavior of the collagen hydrogel to the geometric information of the fiber network extracted from a microscopy image. Moreover, we combined it with our previously presented nonlinear inverse method to accurately compute cellular forces\(^3,4\). As a result, we present a methodology that takes into account a more realistic representation of the cell’s mechanical microenvironment to further improve cell force recovery in collagen hydrogels.

Methods

Data-driven fibrous matrix generation. We developed a synthetic fibrous matrix generator, in which fibers of a given diameter and stiffness are discretized using nonlinear beam elements. The architecture of these synthetic matrices was defined by segmenting and skeletonizing fibers from second harmonic generation (SHG) images of real collagen hydrogels (Fig. 1A). Model parameters were obtained from fitting stress-strain curves obtained by means of shear rheology.

In silico ground truth simulations. First, we segmented a real confocal microscopy image of a cell that was embedded in a collagen hydrogel. Then, we embedded the relaxed state of the cell geometry in the synthetically generated matrix and we prescribed a 7 μm displacement at the closest point to the protrusion tip and obtained a ground truth matrix displacement field and a ground truth nodal force of around 3.5 pN (Fig. 1B). To analyze the performance of our traction recovery methods we added different levels of white Gaussian noise to the ground truth displacements. We tested the traction recovery accuracy of two different methods: a forward method, which computes forces directly from the measured (noisy) displacements, and our physics-based inverse method (PBIM)\(^5\), which imposes equilibrium of forces in the hydrogel domain.

Results

Fig.1C shows that the forward method leads to higher forces in other nodes of the cell surface that are not the tip node. This effect becomes more prominent with increasing noise, for which the magnitude of the forces is overestimated (~3 times higher force magnitude). PBIM is more robust against noise in this discrete-fiber framework since the node of maximum force corresponds to the cell’s tip for all the cases while preserving vector magnitudes and directions close to those of the GT. Moreover, it recovered forces more accurately than the forward method with errors below 20% versus errors of up to 80%, respectively.

Discussion

In this work, we presented a novel data-driven 3D TFM approach and validated its accuracy and viability by means of in silico ground truth simulations. These preliminary results lay the foundations of our future work, which will focus on applying this framework to real experiments with cells to obtain multiscale cell force information at length scales closer to the length scale of mechanotransduction.

References


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Figure 1: Summary of the work.
TOPOLOGY OPTIMISATION OF AN EXTERNAL CIRCULAR FIXATOR.

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Introduction

External fixation device systems are widely used to treat unstable fractures, limb lengthening, and the correction of pathological orthopaedic deformities, among other things. [1, 2]. This study aimed to perform biomechanical topography optimisation of a continuous dynamic compression system on the fracture surfaces to satisfy the demand by reducing materials and cost.

Methodology

The Ilizarov external frame, model was developed by Dassault Systems. The femur bone was attached via a four-pin connector to a cylinder in the design frame. The lower and upper part of the femur have been separated by 20m to mimic a real-life bone behaviour. In this study, the external cage, bone were 3 mm in mesh size and the pin 1mm. The experimental research has been conducted using Instron 5966 Series Dual Column Table Frames with 770N as the maximum load applied.

Results

Figure 1 shows the topology optimisation cycles results from the finite element analysis using tosca structure. The results shows that materials has been removed. Figure 2 shows the comparison of results from the von miss stress versus displacement for experimental analysis, and the finite element analysis before and after optimisation.

Discussion

During the Optimisation phase, the job task was configured to run for 25 cycles to obtain the high quality of the design shape after optimisation by reducing the weight by 40%. The results obtained from figure 1 and 2 shows that the cost of external fixator will be lower compare to the previous design due to less materials used.

References


Acknowledgements

The research was funded by the Tshwane University of Technology and the University of South Africa (Unisa). The experiments were conducted in biomechanics laboratory facilities at Unisa’s Science Campus in Johannesburg, Florida, South Africa.
DIRECT MEASUREMENT OF THE FORCES AND MOMENTS ACTING AT THE HINGE OF AN INSTRUMENTED HUMERAL COMPONENT FOR TOTAL ELBOW REPLACEMENT

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Introduction

In 2021, the number of primary and revision Total Elbow Arthroplasties (TEA) procedures performed has increased by 31.5% compared to 2020, reaching a total of 1,024 individual cases¹. Aseptic loosening radiographically remains the greatest problem encountered in TER procedures, with 17% of all patients experiencing the loosening of one or both components. To date, the in vivo forces in the elbow joint have yet to be quantified, representing a significant gap in our understanding of the mechanics of the elbow joint. This research aims to generate real-time in vivo force and moment data during activities of daily living (ADL) for the first time by internally instrumenting the custom humeral component of an unconstrained total elbow replacement to measure the 6 degrees of freedom (d.o.f) acting at the hinge axle.

Materials and Methods

i) Model Development & Finite Element Analysis (FEA). Using SolidWorks, a modified 3D model of a Discovery humeral component was developed with three cavities to house electronics and strain gauges. The mechanical loading of the model was evaluated in an FEA study carried out in COMSOL™ replicating the 6 d.o.f loads experienced by the joint in vivo. This study identified the optimum locations for strain gauges for sensitivity to all d.o.f and for selectivity.

ii) CNC Fabrication. A total of 10 titanium (Ti-6Al-4V) humeral implant prototypes were fabricated via CNC machining (fig.1). The cavities were sealed with lids welded via electron beam welding (EBW).

iii) Fatigue Testing. Four welded prototypes are being fatigue tested for durability, applying a sinusoidal waveform with a frequency of 5 Hz and a maximum joint reaction force (JRF) of 700N for 5 million cycles². The loading profile of this test simulates the cyclic flexion/extension motions that are associated with the elbow during normal ADL (fig.2).

iv) Instrumentation and Calibration

Axle loads are sensed by strain rosettes mounted in each fork cavity and in the main cavity. Stem tip loads are sensed by gauges enclosed in an annular cavity near the tip. The instrumentation is housed within the main cavity. Implants will be calibrated using custom fixtures and a loading machine.

v) Biomechanical Study

The implantation of pre-calibrated internally strain-gauged humeral implants in the humerus sawbone will validate the load measuring ability of the implant and enable stem loosening to be modelled. Physiological loading conditions will be applied by loads that mimic the JRF during the primary d.o.f of the elbow.

Results

The first cyclically loaded humeral component has successfully completed 5 million cycles at a peak load of 700N without failure. The load level at which 4 “runouts” are obtained with no fractures prior to 5 million cycles will be reported as the fatigue strength of the humeral stem. This demonstrates that the fatigue strength of the humeral component is greater than or equal to the runout load.

Discussion

Adding internal cavities to the humeral implant did not negatively impact its performance, as it was found to withstand the same loading conditions as previously tested humeral components³. After determining the fatigue strength of the 4 humeral components, it will be compared to that of Ti-6Al-4V, which has a known fatigue strength of 460 MPa⁴. The overall research project proposes to develop an instrumented humeral implant for TEA to measure hinge forces and moments.

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DEVELOPMENT OF A 2-SEGMENT FOOT MODEL FOR KINEMATIC MEASUREMENT OF MEDICAL GAIT ANALYSIS.

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Introduction
Instrumented gait analysis using optical motion capturing (OMC) represents an essential tool in the prevention, diagnosis, and therapy of a wide range of medical conditions. The ankle and foot are represented by a three segments analysis (Oxford Foot Model (OFM)). However, gait analysis with OMC and OFM is time consuming and requires a large setup. Inertial measurement units (IMU) could be a time efficient alternative with a good accuracy in the sagittal and moderate accuracy in the coronal and transversal planes [1, 2]. But the foot is only represented by one segment. This oversimplification of the foot does not allow a meaningful analysis for pathologies within the ankle and foot.

The aim of the study was therefore threefold:
1) Development of a 2-segment foot model
2) Assessing a norm data set
3) Evaluation of its reliability

Methods
The study was approved by the local ethics commission (#19-0177).
First, the existing model was amended by an additional IMU placed vertically onto the calcaneus (Fig. 1: 3). The position of the already existing IMUs (forefoot, shank, thigh, pelvis) remained unchanged (Fig. 1: 1, 2). This allowed the assessment of the three three major joint axis (Figure 1: A, B, C).

The positioning of the additional sensor has proven to be stable. Figure 2 shows the mean kinematic values for the reference population. The SPM showed no significant differences for inter-rater, intra-rater, test-retest reliability (p>0.05).

Discussion
The development of a 2-segment foot model seems a valuable extension to the current IMU setup. It allows to generate kinematic curves comparable to the OFM (with OMC) with a good intra-rater, inter-rater and test-retest reliability. A validation of the new model to the OMC is currently in progress. In the future, the IMU technology might proof a cost and time efficient method for a valid clinical gait analysis.

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HOW DO SINUSOIDAL SCAFFOLDS AFFECT FLUID FLOW-INDUCED WALL SHEAR STRESS AND MASS TRANSPORT?

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Introduction

Bone is one of the most transplanted tissues. About 1.6 million bone grafts are performed each year only in the United States [1]. This treatment has serious drawbacks, such as a higher risk of infections or even donor site morbidities. Therefore, an alternative is the use of scaffolds to create bone tissue. The role of scaffolds in bone tissue engineering is to mimic the native bone tissue and is used to provide a template that supports seeded cells to get an optimal environment for their proliferation [2] to re-build the damaged structure. Hence, an optimal scaffold design is important and must be found because even small changes in the geometry of the pore network of the scaffold influences the process of cell growth and mechanical properties [2,3]. Wall shear stress (WSS) has a significant role in the differentiation of cells, especially for bone. Even minor changes in the flow field, especially near the wall regions, can directly affect cell bioactivity. Therefore, in this work, we use computational fluid dynamics (CFD) simulations to investigate the WSS and the effect of the flow rate on mass transport rates in scaffolds. The numerical results were compared to µ-particle image velocimetry (PIV) experiments to evaluate the reliability of the CFD method.

Methods

Scaffolds, which have a sinusoidal channel featuring different frequencies, amplitudes, and characteristic lengths, are computationally created and meshed in SALOME®, while the simulations are carried out using the open-source CFD toolbox OpenFOAM®. An incompressible Newtonian fluid with a dynamic viscosity of 0.000001 m²/s is assumed. A diffusive-advection mass transport equation is solved on a laminar flow field using the solver scalarTransportFoam to evaluate the nutrient distribution on the scaffolds. The fluid flow is numerically solved by the three-dimensional Navier-Stokes equation. For the µ-PIV experiments, the simulated scaffolds are printed into a channel using the Two-Photon polymerization technique. The 3D printing process is based on cross-linking of photosensitive polymers induced by femtosecond pulsed lasers. A water suspension with 5% of 2 μm Polystyrene fluorescent tracer particles is used to investigate the flow field inside the sinusoidal channel.

Results

The CFD results show that increasing the frequency or amplitude of the sine waves of the channel above a threshold frequency or amplitude lead to a velocity decrease inside the sine cavities and a formation of secondary vortexes. The µ-PIV measurements confirm the numerical results. Furthermore, the CFD results indicate that the WSS changes with flow rate and geometry and decreases with increasing frequency. Fig. 1 shows that for an inlet flow rate of 5 mm/s the WSS is highest at the negative peaks of the sine waves where the channel is narrowest. Inside the sine cavities, the WSS is below 0.1 Pa due to the lower velocities.

![Figure 1: WSS for an inlet flow of 5 mm/s with a frequency of 3.5 mm⁻¹ and an amplitude of 0.1 mm.](image)

The mass transport of the nutrient inside the sinusoidal cavities is unevenly distributed and decreases, caused by lower concentration, over the length of the sinusoidal channel.

Discussion

As the results show, the sinusoidal texture decreases the WSS value below 0.1 Pa. This means that the sinusoidal geometry positively influences the WSS results and is compared to the channel wall at least 75% lower. For the differentiation of cells to osteoclasts, a WSS lower than 0.057 Pa is recommended [4]. Besides the scaffold design, the flow rate is another important factor that affects the WSS results and can be decreased in the next step.

References

OXYGEN DIFFUSION DYNAMICS WITHIN THE INTERVERTEBRAL DISC - A NANOSCALE AGENT-BASED MODEL

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Introduction

The intervertebral disc is the biggest avascular structure of the human body. In its central tissue, the Nucleus Pulposus (NP), a low amount of oxygen ($O_2$) molecules diffuses from the Cartilage Endplates, which separate the NP from the closest blood supply [1]. $O_2$ has a low solubility and travels through a tissue with only 4000 cells/mm$^3$. Hence, we hypothesize that $O_2$ molecules can travel through the extracellular matrix without being metabolized.

Methods

A 3D Agent-based (AB) model (Netlogo, v6.0.2) of a volume of ~1.1x10$^4$mm$^3$ with 2x10$^6$ patches was equipped with a corresponding amount of 4 NP cells and a physio-logical volume fraction of 21% of extracellular matrix, mainly Aggrecan (Agg) and Collagen (Col) (Fig. 1). A representative amount of 300 $O_2$ agents was distributed within the model, allowing to diffuse at 3 μm/s [2]. $O_2$ travelled through Agg with a 50% reduced speed, while Col was considered as obstacle.

To define the molecule dynamics, we assumed: (i) an axial directed diffusion (d.diff, blue arrows, Fig. 1) caused by the metabolism of $O_2$ by the cells in the center of the NP; (ii) a reactivity layer (r.layer) around each cell due to its metabolism. r.layer was either the cell radius (~8 μm) or the cell diameter (~16 μm). Within r.layer, $O_2$ was attracted towards the cell. d.diff varied between maximal (100%), i.e. straight downwards movement, and minimal (0%), i.e. total random movement. According to the r.layer and d.diff variations, six $O_2$ reactive transport cases of 1h (3600 timesteps) were simulated (Tab. 1). Each case was run three times.

Results and Discussion

Compared to 50% d.diff, 80% d.diff did not lead to higher average or maximal travel distance. However, $O_2$ metabolism decreased at higher d.diff. High r.layer and low d.diff (Case 4) led to only ~12% free $O_2$ and less than 2 mm average travel distance (Tab. 2).

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
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<tbody>
<tr>
<td>Avg td (mm)</td>
<td>1.96</td>
<td>4.34</td>
<td>3.57</td>
<td>1.88</td>
<td>4.34</td>
<td>3.33</td>
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<tr>
<td>Max td (mm)</td>
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<td>4.58</td>
<td>4.70</td>
<td>2.02</td>
<td>4.53</td>
<td>4.68</td>
</tr>
<tr>
<td>Met $O_2$ (%)</td>
<td>57.8</td>
<td>47.8</td>
<td>20.6</td>
<td>88.1</td>
<td>70.6</td>
<td>41.7</td>
</tr>
</tbody>
</table>

Table 2: Average (avg); maximal (max) travel distance (td) and metabolized (met) $O_2$ per condition

Less directionality is associated with reduced diffusion distances. Interestingly, case 5 (Tab. 2) coincides with results of an FE mechanotransport model, where at roughly 4 mm depth, the amount of metabolized $O_2$ was around 65%, according to Fick’s diffusion law [3]. Residual $O_2$ seems in case 5, however, high, considering that $O_2$ tension can be as low as 1% in large discs [4]. Hence, a prudent interpretation of transport models using partial differential equations in homogenized continua might be reasonable, since Fick diffusion possibly overestimates the probability of $O_2$ to reach cells in the center of the NP.

Beta-testing was performed to approximate experimental measurements in canine NP [1] that have a ~3 fold higher cell density. Using Case 1 (Tab. 1), the model predicted 2.9±0.7% residual $O_2$ after 1.95 mm, while experimentally measured $O_2$ tension was found to be as low as ~4% of initial tension after 2 mm travel distance. To our knowledge, this is the first nanoscale AB model that tackles molecular dynamics within the NP. On the one hand, the AB model simulates the probability of an $O_2$ molecule to reach a cell and can approximate measurements. On the other hand, in the AB model, the fact that $O_2$ travels over increased distances with d.diff higher than 50%, does not mean that the molecule reaches a NP cell along the way, in contrast to what continuum diffusion models with axial concentration gradients would calculate [3]. Hence, we might expect that NP cells see less $O_2$ than continuum models have described previously.

References


Acknowledgements

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NOVEL THERAPY SETTING BY USING VIRTUAL AND AUGMENTED REALITY– A COMPARATIVE FEASIBILITY STUDY

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Introduction
Immersive technologies such as Virtual or Augmented Reality (VR/AR) have gained substantial attention for therapeutic use. The virtual 3D-environment is already used for the treatment of pain or anxiety [1], but there is also potential for its use in physical rehabilitation. The VR lens provides a full virtual environment, whereas AR has the opportunity to place virtual obstacles on a transparent lens – where the background is still real. A combination of AR and VR technology (VAR) could be applied by using a so called “passthrough mode”. In this mode, the real background is captured by cameras of the lens and displayed virtually. This has the advantage of using the full spectrum of VR technology with a wide field of view.

The aim of the study was to perform a comparative usability study for the application of the three technologies VR, AR & VAR, with the background of suitability for a rehabilitation training with patients.

Methods
In a usability study with 20 healthy subjects, advantages, disadvantages and opportunities of the AR, VR and VAR technologies have been assessed. Participants were playing a grasping game on an AR and a VR headset. The game displayed moving apples in the 3D-environment at different distances/positions, which had to be captured by hand. The cameras of the AR/VR-lens were detecting the corresponding hand position therefore.

Parameters of interest were quality of the visual field of the lens, orientation in space, motivation, concentration, comfort and general usability of the devices. Feedback through an online survey has been performed (survey monkey). Rating has been done from 1= sceptical to 6=great. The game was played 3 minutes with each technology in standing position. Approval of the ethics commission of the Canton Zurich has been acquired.

Results
Participants were positively evaluating the use of virtual 3D-technologies with an average score of 5.4. Due to the extended visual field, VR and VAR technology were clearly preferred. For VAR, the real environment is virtually visible during the game, which improves orientation in space and provides an enhanced impression of balance & safety.

Discussion
The outcome suggests that VR and VAR technology were preferred compared to AR. In particular the large field of view and the good orientation in the room convinced the participants. With the VAR technology, not only the virtual hand was visible, but the entire arm compared to the VR technology. This can be beneficial for therapeutic purposes when proper execution of movement is a priority. With AR&VAR, a reference to the real environment all the time is provided. This can ensure a high level of safety for patients during the training. The advantage of VAR over AR is the significantly cheaper purchase price. This could make the use of VAR technologies accessible by more users.

Conclusions
All but two participants achieved higher motivation to grasp the fruits with the VR and VAR technology. This could be explained by the larger field of view and the condition that the fruits were found with smaller head movements.

A wider range of participants’ age needs to be considered get a deeper insight into the differences, advantages and disadvantages of AR, VR and VAR technologies in the field of rehabilitation. Performing a study with neurological patients will be of high interest.

References
A PIPELINE FOR MECHANOBIOLOGY-DRIVEN DESIGN OF SCAFFOLD
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Introduction
Porous scaffolds are used for providing favorable micromechanical environments for cellular activities (e.g., cell attachment, differentiation, proliferation, etc.) 1. To design the scaffold porous geometry for tuning micromechanical environment, the current available software (such as MSLattice and NTopology) has mainly focused on varying porosity. However, pore size, which is also an important parameter is largely ignored. In addition, numerous possibilities of scaffold geometries may cause high cost for trial-and-error scaffold design based on micromechanical environment. Therefore, in this study we aim to build a pipeline for mechanobiology-driven design of scaffold. This includes: (i) development of a software that allows precise and automatic generation of scaffold geometries for input variables of both pore size and porosity for different pore topologies; (ii) investigation of the porous geometry-influenced the fluidic properties – wall shear stress (WSS) and permeability for efficient mechanobiology-driven design of scaffold.

Methods
The triply periodic minimal surfaces (TPMS) topology has been commonly applied to scaffold design due to its advantages, such as high surface area to volume ratio, less stress concentration, and increased permeability. In our software development, different TPMS structure topologies (such as gyroid, FKS, etc.) were expressed using trigonometric equations combined with the level-set method as described in reference 2. So, altering the level constant for these trigonometric equations and varying the overall dimensions of a structure could allow for pore size and porosity to be specified. To apply this software for investigating the scaffold porous geometry-influenced WSS and permeability, the following scaffolds were created: (i) TPMS structures (gyroid and FKS topologies) with the porosity and pore size of 50% – 90% and 600 – 1000μm; (ii) non-TPMS structure (cylindrical-beam struts) with the same porosity range and pore sizes of 300 – 1000μm, as a comparison. For saving the computational cost, these geometries were then simulated using a previously developed multiscale computational fluid dynamics (CFD) model 3. An inlet fluid velocity of 1mm/s and an outlet pressure of 0Pa were applied to the macro model.

Results
Firstly, the scaffold design software that can accurately control the pore size, porosity for different TPMS pore topologies has been developed in this study (e.g., in Fig. 1). Secondly, from the CFD simulations, it was found that increasing pore size caused clear increases in permeability and decreases in WSS. Importantly, increasing porosity caused a slight increase in WSS and permeability, contrasting to pore size which had larger effects on both for all structures (TPMS and non-TPMS in Fig. 2). Furthermore, to allows fast estimation of WSS based on permeability, the empirical models were proposed to correlate these two parameters of the scaffolds (Fig. 2).

Discussion and Conclusion
The results indicate that pore size is an important variable for the fluidic properties. So, having a software, which comprehensively considers the porosity and pore size for TPMS structure generation is therefore necessary. For the application of this pipeline, the results of porous geometry-influenced WSS and permeability (Fig. 2) may help the users to determine the scaffold geometries according to their needs. Thereafter, the geometries will be generated in the design software. Moreover, the software allows the geometric data to be transferred to 3D printer for manufacturing. Furthermore, the empirical model will be useful for the circumstance that researchers need fast estimation of the WSS within scaffold based on the known permeability.

References

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A CLOT COMPOSITION DEPENDANT HYPERELASTIC MODEL IN THE SIMULATION OF DIRECT ASPIRATION THROMBECTOMY

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Introduction
Despite recent advancements in the treatment of acute ischemic stroke (AIS) by the use of stent retriever mechanical thrombectomy, complete recanalization of the occluded cerebral vessel is achieved in only 85% of cases, and 80% of AIS patients still suffer long-term disabilities [1]. Clot fragmentation and multiple clot removal attempts are associated with poorer clinical outcomes [2]. Fragmentation risk is associated with red blood cell (RBC) -rich clots rather than fibrin-rich clots [2,3]. Direct aspiration (DA) is an emerging alternative treatment for AIS. In DA procedures, a catheter contacts the distal face of the clot, and a negative suction pressure is applied in order to remove the clot from the vessel [1,2]. Currently, large-bore catheters are being developed with the goal to increase DA efficacy [2]. The influence of catheter design and blood clot composition on DA clinical outcomes has not been systematically investigated to date [4].

The current study outlines the first analysis of the effect of DA catheter diameter on clot deformation and fracture by the use of a finite element framework to simulate the aspiration of RBC- and fibrin-rich clots.

Methods
Considered is a cylindrical clot (3 mm in diameter) in direct contact with the distal end of a catheter with diameters of 1.2 mm, 1.62 mm, and 2.5 mm (Figure 1A). A negative suction pressure results in deformation of the clot into the catheter, characterised by the aspiration length $a$. In a fully successful DA procedure, the entire clot is ingested into the catheter when a critical pressure is reached. The clot material is modelled using a customized composition-dependent anisotropic hyperelastic constitutive law implemented as a user defined material subroutine (UMAT) in Abaqus [3,5]. This formulation incorporates non-linear volumetric and isochoric deformation of the RBC components of the clot, in addition to an anisotropic deformation of the fibrin network. Model parameters for RBC- and fibrin-rich clots were calibrated using experimental multi-axial test data [3].

Results
As shown in Figure 1B, RBC-rich clots aspirate further into the catheter than fibrin-rich clots at any sub-critical pressure. RBC-rich clots are also fully ingested at a lower critical pressure. Figure 3C shows that an increase in catheter diameter results in a lower critical pressure for full ingestion. The maximum principal stress in RBC-rich clots exceeds the measured fracture strength (0.01 MPa [2]), whereas stress levels computed in fibrin-rich clots do not exceed the measured fracture strength (0.045 MPa [2]) (Figure 1D). Finally, Figure 1E shows that clot compressibility is a key determinant of the success of DA.

Discussion
Our study presents the first FE analysis of DA thrombectomy. The obtained results support the clinical observation that fibrin-rich clots are more resistant to full ingestion into a DA catheter [6]. However, our results suggest that RBC-rich clots have a higher fragmentation risk, similar to clinical findings for stent retrievers [3]. Our findings also indicate that the use of large-bore catheters increases the probability of full ingestion and reduces the fracture risk.

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INTER AND INTRA MUSCULAR VARIABILITY OF RIGIDITY IN HEALTHY AND PARETIC MUSCLES: ULTRASOUND IMAGING

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Introduction
Through the estimation of shear wave velocity propagation in muscle tissue, shear wave ultrasound (SWE) assessments provide a reliable local quantification of rigidity during different positions and movements [1]. Several studies have investigated healthy and paretic muscle rigidity using SWE [2]. However, the assessments may not consider the most affected regions within the same muscle tissue nor the intramuscular variability of rigidity between muscles of the same muscle group, e.g., plantar flexors. This study aimed to explore the inter- and intramuscular variability of plantar flexors stiffness during prone and standing positions at different muscle lengths in healthy and paretic individuals.

Methods
A randomized controlled trial was set. Twenty-eight subjects were recruited and divided into two groups. The control group (CG) consisted of 14 healthy individuals with no history of neurological or muscular disorders (CG, n=14; age=43.9±9.6 years; BMI=24.5±2.5 kg/m²) and the stroke survivor group (SSG) consisted of 14 stroke survivors with spastic hemiparesis (SSG, n=14; age=43.9±9.6 years; BMI=24.5±2.5 kg/m²). Shear modulus (μ) of three plantar flexors (Gastrocnemii Medialis (GM) and Lateralis (GL), and Soleus (SOL)) was performed using shear wave elastography during two conditions: prone and standing position, at different muscle lengths (0°, 10°, 20°). Measurements were also performed in different proximo-distal regions of each muscle. During the two conditions, muscle activation of GM, GL, SOL and the tibialis anterior were evaluated.

Results
Our Results showed a high spatial stiffness variability between and within plantar flexors during dorsiflexion and the highest stiffness was observed in GM, especially in the distal region at 20°. In the prone position, the paretic muscle exhibits greater stiffness than in the healthy muscle (p<.05) and plantar flexor muscle activations were lower than 5% of maximum activation. However, in the standing position, an increase of stiffness in the healthy muscle compared to the paretic muscle was observed (p<.05). and plantar flexor muscle activations were higher than 5% of maximum activation.

Discussion
Active and passive states of ankle muscles could change differently the spatial distribution of stiffness in healthy and paretic muscles during ankle dorsiflexion. The contribution of the contractile component in the development of muscle stiffness in response to stretch should be taken into consideration in the quantification of the mechanical properties of paretic muscle.

Figure and Tables

Figure 1: Shear wave ultrasound images of the distal region of gastrocnemii medialis in prone position (left) and standing position (right) at different angle of dorsiflexion

Equations
Ultrafast ultrasound sequences are used to measure the shear wave velocity (Vs) using a time-of-flight algorithm in each pixel of the map [3]. Assuming a linear elastic behavior [4], a shear modulus is calculated using Vs as follows:

$$\mu = \rho V_s^2$$  \hspace{1cm} (1)

where $\rho$ the density of the tissue (1000 kg m$^{-3}$ for muscle)

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VALIDATION OF A KNEE FINITE ELEMENT MODEL FOR THE DEVELOPMENT OF SURGICAL TRAINING MODELS
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Introduction
Current knee surgical training models provide anatomically correct bony geometry but often lack functional biomechanical accuracy [1]. This inaccuracy has resulted in limited opportunities for surgeons to practice techniques like computer navigated total knee arthroplasty, which relies on measurements of joint mechanics. In this research, we aimed to develop a finite element model (FEM) which reproduces the mechanics of a healthy knee for developing biomechanically fidelic surgical training models, with validation through experimental assessment in a six-degree-of-freedom (6DOF) hexapod robot.

Methods
A knee FEM was developed with a reduced ligament set. Bones were modelled as rigid bodies, with deformable articular surfaces used for contact modelling. Kinematic axes were defined as open-chain cylindrical axes. Five ligaments – the lateral collateral ligament (LCL), the anterolateral ligament (ALL), the medial collateral ligament (MCL), the anterior cruciate ligament (ACL) and the posterior cruciate ligament (PCL) – were modelled as point-to-point linear springs. Latin hypercube sampling was used to adjust the reference strain (slack length) of each ligament to explore the range of manufacturing tolerances which may be produced.

Three knee models were manufactured, containing the distal femur, proximal tibia and fibula, and ligaments with different reference strains. The proximal femur and distal tibia were embedded into aluminum potting cups to match the orientation and alignment of the FEM. The potted knee models were mounted in a custom-built 6DOF hexapod robot with kinematic axes aligned with the robot’s axes.

In both the FEM and hexapod experiments, knee kinematics were measured at extension (15°), mid-flexion (45°), and full-flexion (90°). At each flexion angle: 1) all off-axis shear forces and moments were minimized using an adaptive load control algorithm. 2) 20 N of superoinferior (SI) tensile force was applied to ensure the ligaments were taught. 3) (a) ±10 Nm VV moment was applied with all other rotation and translation axes (except SI translation) constrained; (b) ±100 N AP load was applied with all three rotations axes, and mediolateral displacement constrained.

Results
The VV mechanics calculated using the FEM at extension were similar to the range of cadaveric knees (Figure 1). The VV mechanics of the manufactured knee models were similar to both the solution space of the FEM and the cadaveric results.

Discussion
The FEM reproduced the mechanics of healthy cadaveric knees. Experimental measurements of the knee models manufactured based on the FEM allowed for validation. Using knee models manufactured based on the FEM, surgeons can learn and practice surgical techniques which rely on measurements of joint mechanics in a low-risk environment.

References

Acknowledgements
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EXPERIMENTAL ASSESSMENT OF MECHANICAL CHANGES IN HUMAN OSTEOARTHRITIC CARTILAGE

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Introduction
Articular Cartilage (AC) is a complex connective tissue and plays a key role during load bearing, shock absorption, and lubrication in joints. However, traumatic events, aging and degenerative pathologies may affect its structural integrity, causing pain and long-term disability. Among these causes, osteoarthritis (OA) represents a health issue, which concerns 1 out of 4 people in Europe [1]. Moreover, it has been observed that OA affects also the mechanical behaviour of AC, with direct effects on both tribological and bearing activities [2], [3]. Within this scenario, this study aimed at quantifying the effects of OA on the viscoelastic properties of human cartilage through indentation and unconfined compression tests. Results may be exploited to Finite Element models, for a complete evaluation of the mechanical effects of OA on knee joints.

Methods
OA tibial plateaus were collected from six human subjects (M: 2 F: 4; 79±4 y/o) that underwent total knee replacement (at the Orthopedics and Orthopedic Oncology Unit, University Hospital of Padova CESC Code: AOP2649). Normal indentation (Fig. 1a) and unconfined compression tests (Fig. 1b) were carried out with Mach-1 Mechanical Tester (e-Biomomentum Inc.), to obtain instantaneous and equilibrium mechanical behaviour of AC. Normal indentation consisted in multiple measure points on the tibial surface, adopting a 0.3 mm of indentation amplitude with a velocity of 0.05 mm/s. Consequently, with a needle penetration procedure, the thickness of the cartilage layer was extracted. Stress-relaxation tests were realized in unconfined compression on cartilage disks (5 mm diameter). Four ramps (5% strain, 20% s⁻¹ strain rate) were imposed, the first with a relaxation time t = 600 s (preconditioning), while t = 1500 s for the others.

The Equilibrium Modulus and permeability were fitted with the Fibril-Network Reinforced Biphasic Model [5].

Results
The distributions of the Instantaneous Modulus (IM) (Fig. 2a) and the AC thickness (Fig. 2b) were obtained for the entire portion of the samples covered by AC [4]. Viscoelastic behaviour was analysed from stress-relaxation tests in unconfined compression (Fig. 2c-d).

Discussion
Significant variations have been observed even within the same sample for both instantaneous and long-term mechanical parameters, which can be directly correlated to local damage due to OA.

References

Acknowledgements
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AN INTEGRATED FRAMEWORK FOR EVALUATING MECHANICAL PROPERTIES AND STRUCTURE OF ARTICULAR CARTILAGE

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Introduction
Articular cartilage is a highly specialized connective tissue covering diarthrodial joints and, thus, playing a key role in supporting locomotion. Non-invasive approach, providing indirect information on the cartilage mechanical properties would be a potential method in early detecting tissue disorders, and evaluating new tissue engineering approaches and therapeutic treatments. Regarding cartilage mechanics, indentation represents an experimental method capable of reaching a high degree of accuracy through specifically designed testing protocols [1]. Concerning their biological structure, single-sided low-field nuclear magnetic resonance (NMR) method recently demonstrated its potential to study both soft and mineralized tissues [ref]. Accordingly, the study aimed at proposing an integrated, non-destructive framework capable of quantitatively evaluating cartilage mechanics and structure, following the main hypothesis that tissue characteristics change across its thickness.

Methods
Osteochondral specimens (N = 18) were cored from bovine knees. Cartilage thickness was estimated through a microCT apparatus (SkyScan 1072). Aiming to determine cartilage viscoelastic response, specimens were tested – five times each – by a multiaxial mechanical tester (Biomomentum), equipped with 6-mm spherical indenter. A specific testing protocol was developed [ref], inducing a nominal deformation of 15% of tissue thickness, equal to the averaged one developed during locomotion; after reaching the imposed deformation, a stress-relaxation of 300 s allowed to investigate tissue viscosity [2]. Hayes model [3] was used to fit the cartilage elastic response, determining tissue instantaneous (E0) and equilibrium (Eeq) modulus. The stretched exponential model [4] was selected for describing the stress-relaxation response, estimating tissue time constant (τ) and stretching parameter (β) starting from the measured maximum load (S0).
Specimens were then analyzed by a NMR single-sided device (MOUSE PM10, Magritek, NZ). CPMG, Saturation Recovery, Stimulated Spin Echo, and build-up Double-Quantum-like pulse sequences were performed in a unique procedure to determine T2, T1, D, and a parameter, α, related to 1H solid-liquid ratio. Data analysis – cartilage thickness, mechanical properties, and NMR parameters – was performed by custom-made codes (MATLAB 2022b, MathWorks).

Results and Discussion
The testing procedure enabled a sound measure of the cartilage viscoelastic parameters, i.e., mean percentage coefficient of variation (CoV%) of 6.1%, 7.8%, 4.3%, 3.5%, and 1.1%, for E0, Eeq, S0, τ, and β, respectively. NMR approach allowed to estimate the thickness of the cartilage (NMR vs microCT agreement: r = 0.97, Fig.1) and to distinguish its three sub-layers (superficial, middle, and deep). Significant discriminations (p < 0.05) among layers were highlighted by all NMR parameters supporting single-sided NMR as a sensitive method to detect cartilage structural changes – i.e., water confinement, proteoglycan and collagen organization.

Figure 1. Cartilage thickness evaluation: microCT versus single-sided NMR profiling.

Moreover, preliminary results suggest that cartilage mechanical stress-relaxation is related to NMR relaxation times (T2 and T1), diffusion coefficient D, and a parameter.

Conclusions
The results support the use of a combined indentation-NMR approach to investigate the main features of cartilage tissue. Future developments will deepen first the relation between tissue response and NMR-derived parameters. Moreover, the proposed pipeline will be applied to both healthy and pathological tissues, to prove the feasibility of the approach in detecting changes in cartilage homeostasis throughout degeneration stages.

References
THE ROLE OF STATISTICAL SHAPE MODELS IN THE DESIGN FRAMEWORK OF OSSEOINTEGRATED IMPLANTS FOR DISTAL FEMUR

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Introduction

The femoral morphology shows a high inter-subject variability. Thus, standardized prosthetic devices (e.g. osseointegrated stems for amputees or revision knees) may not sufficiently match with the anatomy of each individual \cite{1}. In recent years, Statistical Shape Models (SSMs) have been largely employed to represent the average form out of many three-dimensional objects, as well as their variation in shape \cite{2}. However, such statistical representations have not been used to solve the unmet needs associated to the design of prosthetic components yet. Therefore, the aim of this study was to evaluate the main modes of variation in the shape of the femoral canal, also considering different levels of osteotomy, which might support patient-matched implants design.

Methods

A total of 72 CT-scans of the lower limb were segmented to isolate the femoral canal region of interest (ROI), ranging from the tip of the lesser trochanter down to 75\% of the total length of the femur (Fig.1,a). The canals were then scaled, aligned, and 16 levels of resection were simulated, starting from a section corresponding to 25\% of the ROI up to the distal section (Fig.1,b). For each resection level, the main modes of variations were identified through Principal Component Analysis (PCA), extracting Principal Components (PCs) and defining the variability model \cite{3}. After obtaining the average shape \( \overline{M} \), the geometries corresponding to ± 2 standard deviations from \( \overline{M} \) where computed as:

\[
M_{1±2\sigma} = \overline{M} \pm \phi_i \cdot 2\sqrt{\lambda_i}
\]  

(1)

Where \( \phi_i \) are the eigenvectors representing the PCs, and \( \lambda_i \) are the associated eigenvalues, providing the respective variance. The shape of the canal for \( M_{1±2\sigma} \) was reconstructed every 10 mm and best fitted with an ellipse (Fig.1,c and d). The following parameters were then calculated: i) radius of curvature (\( R_c \)), by reconstructing the arc of circumference passing through the centroids of the canal; ii) ellipticity, as the ratio between the major and the minor axis of the ellipse at the distal-most section; iii) conicity, obtained as the square root of the ratio between the area in the distal segment and the minimum area; and iv) mean diameter. In order to identify which are the main variations in shape explained by the main modes, these parameters were compared, for each level of resection, between the two geometries of the main modes of variation (\( M_{1±2\sigma} \)), calculating their difference divided by the average of their values [\( \text{var}_v \)], thus reporting the range of values.

Results

The first three PCs explained more than the 87\% of the total variance, for each level of simulated osteotomy. By analysing \( M_{1±2\sigma} \) and \( M_{1±2\sigma} \) for a distal osteotomy (e.g. 70\% of the length of the canal), the first PC was associated to a combination of \( R_c \) (\( \text{var}_v=40\% \)) [625-855 mm], conicity (\( \text{var}_v=13\% \)) [1-5 mm], and ellipticity (\( \text{var}_v=9\% \)) [1-3 mm]. PC2 was still associated with the \( R_c \) (\( \text{var}_v=17\% \)) [806-850 mm], while PC3 with the diameter (\( \text{var}_v=67\% \)) [9-20 mm].

Discussion

The SSM presented in this study allowed to i) evaluate the variance in shape of the femoral canal, and ii) parametrize these variations according to the level of resection. For instance, the results for the segment corresponding to the 70\% of the length of the canal showed that, at that specified level, the parameters with the highest range variability for the first two PCs were the \( R_c \), conicity and ellipticity respectively, while the variations of the diameter were more prominent for the third PC. Therefore, this analysis proved able to provide information about the relevance of these parameters depending on the level of osteotomy suffered by the amputee. In this way, optimal solutions for the design and/or customization of osteo-integrated prostheses can be delivered, according to the patient’s residual limb.

References


Acknowledgements

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THE CONTRIBUTION OF LOWER-MINERALIZED TISSUE TO THE STRENGTH OF FRACTURED DISTAL RADII DURING HEALING

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Introduction
Distal radius fractures are common fractures in the elderly population [1]. Complications of these fractures are frequent [2]. A first step towards better outcomes is a thorough understanding of the healing process. High-resolution peripheral quantitative CT (HR-pQCT) enables in-vivo assessment of distal radius fracture healing at the microscale [3]. In previous studies using HR-pQCT, low-mineralized tissue was observed at the fracture region starting at three weeks post-fracture and tended to remodel into mature bone later [3]. This tissue was not included in quantitative assessments of the healing process as standard density thresholds were used for segmentation of the fractured radii from the scans. Resultingly, the contribution of this lower-mineralized tissue to the healing process is unknown. The aim of this study was to quantify the contribution of lower-mineralized tissue to the stiffness of the fracture region of distal radius fractures during healing using a dual-threshold approach.

Methods
HR-pQCT scans were available of a 20.4-mm region of the fractured distal radius of 48 postmenopausal women with a conservatively-treated fracture, acquired at 1-2, 3-4, 6-8, and 12 weeks post-fracture. Two series of micro-finite element (μFE-) models were created from the scans by voxel-to-element conversion: 1) a series based on a single density threshold of 320 mg HA/cm³ for segmentation; 2) a series based on a dual-threshold segmentation approach. In this approach, first the bone was segmented at a threshold of 200 mg HA/cm³, followed by erosion of one voxel to remove voxels included due to partial volume effects. The resulting model was then combined with the first series of models to obtain a series that differentiates between higher-mineralized (>320 mg HA/cm³) and lower-mineralized (200-320 mg HA/cm³) bone. A Young’s Modulus of 10 GPa and 5 GPa were assigned to the μFE-elements that represented the higher- and lower-mineralized tissue, respectively. An axial compression to 1% strain was simulated, from which stiffness of the single-threshold (S_single) and dual-threshold (S_dual) models were obtained. Linear mixed effects models were used to quantify the changes in S_single, S_dual, and their ratio during healing.

Results
S_dual gradually increased over time to a significant difference from the first visit at 6-8 and 12 weeks post-fracture (Fig. 1; top). The ratio S_dual/S_single - reflecting the contribution of lower-mineralized tissue to stiffness - was significantly higher at 3-4 weeks compared to the first visit and was no longer significantly different at 12 weeks (Fig. 1; bottom).

Discussion
Dual-threshold segmentation enables quantification of the contribution of lower-mineralized tissue to the healing of distal radius fractures. This tissue forms after the first weeks of healing and may help in the initial stabilization of the fracture. Its contribution to stiffness varied considerably among individuals and may indicate differences in fracture severity. Quantification of the contribution may help to improve our understanding of the healing of distal radius fractures.

References
CHARACTERIZATION OF VISCOELASTICITY AND DAMAGE ON ARTERIES FROM HYPOXIC GUINEA PIGS

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Introduction

Viscoelasticity and mechanical damage are two main sources of energy dissipation in arteries subjected to mechanical loading, that lead to a strain-rate and load-frequency dependent response, along with softening and hysteresis under cyclic loading. At high altitudes (above 2500 masl) animals are exposed to a condition induced by a low partial-pressure of oxygen, known as “hypobaric hypoxia”. Chronic hypoxia during development impairs the function and structure of several organs [1], however, few is known about the effects of high-altitude hypoxia on the biomechanical characteristics of arteries. The objective of this work is to characterise the passive viscoelastic and damage properties of arterial tissue exposed to hypoxia, aiming at improving the understanding of its mechanical response.

Methods

All procedures were approved by the Bioethics Committee of the Faculty of Medicine, Universidad de Chile. Guinea pigs were studied. Animals were randomly separated into two groups, “control” and “hypoxic”. Subjects assigned to the hypoxic group were subjected to hypoxia using a hypobaric chamber. Once euthanized, rectangular samples were cut from the thoracic aorta of each subject. Samples were assessed for in-vitro displacement-controlled uniaxial relaxation and biaxial tensile tests. The mechanical characterization of arteries is based upon the results of experimental tests. The constitutive model consists of a damage model [2] associated with the isochoric strain-energy component of an anisotropic hyperelastic model [3], and an orthotropic viscoelastic model using a multiplicative decomposition of the deformation gradient and a non-equilibrated strain-energy component in terms of inviscid Hencky strains [4], further assuming material incompressibility and isothermal conditions.

Results

The passive viscoelastic and damage mechanical behavior of the artery wall was group-wise characterized using a curve-fitting procedure applied to the experimental stress-stretch curves.

The material model parameters determined were associated to a finite-element simulation of a bulge pressurization test, in order to predict the pressure associated with the onset of damage. We analyzed a quarter-disk shaped structure, fixed along its curved perimeter and loaded by a deformation-dependent force per unit area always normal to the acting surface (see Figure 1).

![Figure 1: Schematic representation of the bulge test simulation. Undeformed (left) and deformed (right) configurations. Boundary conditions, transverse-isotropy direction ‘\( m_0 \)’ (characterized by an angle ‘\( \varphi \)’) and acting pressure ‘\( p \)’.](image)

Discussion

Finite-element simulations of the bulge pressurization test delivered pressures associated with the onset of damage that are compatible with a mixed hypertension condition. Therefore, the viscoelastic-damage characterization proposed is adequate to describe the passive mechanical response of arterial tissue from hypoxic guinea pigs, providing reliable parameters for its numerical simulation.

References


Acknowledgments

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COMPUTATIONAL OPTIMIZATION OF A SENSORIZED 3D-PRINTED SMART PATCH FOR CARDIORESPIRATORY MONITORING

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Introduction
The monitoring of cardiorespiratory activity offers crucial information for preventing critical health conditions, thus promoting the early diagnosis and treatment of cardiovascular and respiratory diseases (CVRDs) [1]. Wearables are valuable solutions for monitoring a variety of physiological parameters. A skin-interfaced biosensor based on fiber optics (i.e., the smart patch) is presented. The smart patch is capable of estimating heart rate and respiratory rate by detecting local ribcage strain caused by breathing and heart beating.

Methods
An in silico computational model was developed to prove the effectiveness of the patch design. The model geometry consists of the CAD structure matching the sensor design. Once patched to the skin surface, the sensor geometry was prescribed with bending and stretching boundary conditions. Deformations and vibrations were applied to the skin to model the simultaneous activity of the heart and lungs. The finite element mechanical analysis was carried out by employing the software COMSOL Multiphysics: the computational domain comprehends the patch, composed of silicone matrix and the fabric liners, attached to the human skin modeled as a layer with a constant thickness of 5 mm. A radial function is defined to model the shape of the chest and the cardiac activities. Model geometry and the boundary conditions are depicted in Figure 1.

![Figure 1: Schematic view of the computational model: on the left, the position of the sensor on the body; on the right, the boundary conditions in the numerical analysis.](image)

Results
The FEM based numerical analysis addresses the stretch and the bending of the skin during the breath, accounting for cardiac activities. Aiming to check the soundness of the patch design, the results are shown in terms of ε in the fiber direction (Figure 2).

![Figure 2: Summary of computational studies highlighting (a) the effects of breathing (blue line refers to inspiration and orange line to expiration) and (b) the effects of heart beating (blue line refers to systole and orange line to diastole) on the FBG sensor.](image)

Discussion
The model findings proved the effectiveness of the proposed design in concentrating ε along the longitudinal axis of the optical fiber. The smart patch presented in this study introduces a highly miniaturized and stretchable biosensor, which can be readily applied for cardiorespiratory monitoring in both clinical (such as on bedridden or wheeled patients and during MR examination) and real-life scenarios (e.g., while watching TV, reading a book, working at the desk, and sleeping).

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References
MACHINE LEARNING AND REDUCED ORDER MODELLING FOR THE SIMULATION OF BRAIDED STENT DEPLOYMENT

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Introduction

Flow diverters are self-expanding braided stents used in the endovascular treatment of intracranial aneurysms (IAs). Nowadays, surgeons choose the most suitable device based on their clinical experience and measurements taken on volumetric images acquired just before surgery. However, the configuration assumed by these devices once deployed within the parent vessel is not easily predictable. Given the tight timescale, there is a compelling need to develop computational models capable of simulating in real-time the deployment of flow diverters within patient-specific vessels to assist practitioners in the planning and interventional stages. Due to the large amount of degrees of freedom and the necessity to solve the contact with the wall, the computational time required by traditional techniques alone, such as finite element (FE) modelling, is excessively high. In this study, we propose a machine learning-based reduced order modelling (ROM) scheme for the prediction of the stent deployed configuration. The workflow is validated on an idealized IA model where geometrical and surgical parameters are considered.

Methods

High-fidelity simulations: The braided stent is modelled as a tubular net of interlaced wires, discretized using beam elements. Deployment simulations are performed using an efficient in-house, open-source FE solver [1]. The braided stent is first crimped by imposing a radial displacement to all its nodes, then bent along the artery centerline and finally released within the artery model, whose wall is assumed rigid [2,3]. We are interested in the final deployed configuration, hence quasi-static simulations are performed.

Idealized parametric model. The artery model is built as a tube with constant diameter $D_a$ around the vessel centerline, which is defined using a planar quadratic Bézier curve:

$$B(t) = (1 - t)^2P_0 + 2t(1 - t)P_1 + t^2P_2$$

where $P_0$ and $P_2$ are fixed and the 2D coordinates of the middle point $P_1$ are included in the parametrization. A spherical idealized aneurysm with center $C_a$ and diameter $D_a$ is then added to the artery model.

High-fidelity database. For the database, we considered as parameters $\mu = \{D_v, y_{P_1}, z_{P_1}, D_a, x_{C_a}, \eta\}$, where $\eta \in \{0, 1\}$ is the stent deployment site along the vessel centerline. A Latin hypercube sampling method is used to generate 150 combinations of $\mu$ and the corresponding stent deployment simulations are performed. We excluded 25 cases from the training database to test the model performance once trained.

ROM. As in [4], a non-intrusive reduced basis (RB) method is used: the RBs are extracted from the training database with the proper orthogonal decomposition and Gaussian process regression is used to predict the solution expressed in the RBs space for new parameters values. The reduced order model is validated by computing the nodal and average prediction error ($E_p$) between FE and approximated solutions among the testing cases. The imaging technique with the best spatial resolution, 3D rotational angiography (3DRA), is considered as evaluation criterion for the prediction.

Results

The average $E_p$ decreases as more RBs are considered and reaches a stable plateau equal to 0.02 mm with 15 RBs. This is 7 times lower than the spatial resolution of 3DRA (0.15 mm). As can be seen in Figure 1, the stent configuration adapts very well to the vessel curvature.

Discussion

With the proposed workflow, results are obtained in a few ms once the ROM is trained, compared to ~1h using traditional high-fidelity techniques, while retaining the mechanical realism and predictability of the deployed configuration. The limitations of this work are the use of a parametric model that only partially reproduces the complexity of IAs and the assumption of rigid arteries. Our current efforts focus on understanding the number of parameters needed to describe patient-specific geometries and introducing deformable-wall models.

References


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INFLUENCE OF NAOH TREATMENT AND FIBER ORIENTATION ON PCL ELECTROSPUN SCAFFOLD FRICITIONAL PROPERTIES

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Introduction
Solution Electrospinning (SES) with Poly(ε-caprolactone) (PCL) is an established method to fabricate nanofibrous polymeric constructs that are relevant for tissue engineering applications. This technique offers the advantage of controlling fiber orientation, which may provide morphological and biomechanical similarities to e.g. articular cartilage [1]. However, the use of PCL presents a challenge to de novo tissue growth, due to its hydrophobic nature [1]. NaOH treatment is a method to improve surface wettability that can be applied to electrospun PCL to overcome this. As the tribological function is an important mechanical property of articular cartilage, dependent on surface characteristics, the evaluation of frictional properties is crucial for articular cartilage regeneration constructs [3]. The aim of this study was to examine how NaOH treatment influences the frictional properties of electrospun samples with different fiber orientations.

Methods
Nanofibrous PCL-membranes were produced using conventional SES from a PCL/CH₃OH:CHCl₃ solution. A round collector was rotated at 200 RPM and 1500 RPM to form random and aligned fiber scaffolds. In addition, to obtain fiber alignment, conduction gaps (Kapton tape) were introduced on the collector surface. The obtained membranes were immersed in a NaOH solution (1M) for 1 hour. Frictional tests were performed on treated and untreated scaffolds (r_{radius} = 0.2 cm) with different fiber orientations using an Anton Paar MCR-301 rheometer. Scaffold specimens were tested at loads of 3N, 6N and 12N, corresponding to contact pressures of 0.24, 0.48 and 0.95 MPa, respectively. Specimens, immersed in PBS at room temperature, were tested with a pin rotating frequency of 2 Hz.

Results
No structural alterations, such as fiber morphology, were observed for NaOH treated scaffolds compared to untreated scaffolds. Additionally, NaOH residues on the fiber surfaces could be observed (Fig 1). The frictional response for each scaffold type was similar across all applied loads (Fig 2).
At an applied load of 12N, the frictional response (μ, coefficient of friction) for non-treated aligned samples was significantly (p < 0.05) higher than for unaligned fiber scaffolds (μ_{μA} = 0.269; μ_{μR} = 0.209). μ of treated aligned (μ_{μA} = 0.277) and treated random (μ_{μR} = 0.254) oriented fiber samples were not significantly different to non-treated membranes.

Discussion
An average contact pressure of 0.95Mpa is comparable to the physiological compressive pressure occurring in native articular cartilage during normal motion [4], therefore frictional behavior of the membranes was evaluated at an applied load of 12 N.
In all 4 conditions, the measured coefficient of friction remained in a physiologically acceptable range [5]. Indicating that, even if there is an effect of NaOH treatment or fiber alignment on frictional properties, this effect is negligible and clinically insignificant.
In conclusion, this study showed that the fiber alignment and NaOH treatment had minimal effects on the frictional properties of the scaffolds, and could therefore be considered for future improvements of construct performance in articular cartilage regeneration.

References

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CFD VIRTUAL ANGIOGRAM FOR AVM PRE-INTERVENTIONAL TREATMENT PLANNING

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Introduction
Congenital arteriovenous malformation (AVM) is a disorder in which arteries and veins are communicated directly without a normal capillary system. In AVMs, capillaries are bypassed by larger channels creating a low resistant shunt termed nidus, that causes a rise in the blood flow and pressure in the venous side [1]. The gold-standard technique to visualise the angioarchitecture of AVMs is intra-arterial digital subtraction angiography (DSA) [2], which is unfortunately, highly invasive. This work combines medical images and computational modelling to generate pre-intervention personalised CFD virtual angiograms with the aim to minimise invasive diagnostic procedures. An experimental campaign involving 3D printed phantoms and laser based diagnostics (Figure 2) is also employed to determine concentration and velocity fields for validation purposes.

Methods
A patient-specific geometry from an extracranial Yakes Type III AVM was extracted by segmenting head and neck CT scans from a 47yo male patient pre intervention (PreOp) obtained as part of an ethically approved protocol (NHS Health Research Authority, ref:19/SC/0090). The feeding artery (Ø ~3.7mm) was used as the inlet and the arterial outflow branch (Ø ~1.4mm), and two draining veins (Ø ~1.5-1.8mm) as the outlets. CFD simulations were performed considering an inlet periodic waveform obtained from the literature [4] and scaled based on DSA-based flow estimations. The nidus structure (vol: 1100mm$^3$) was modelled as a homogenous porous medium and the DSA contrast agent (CA) simulated as a passive scalar whose transport is described by a convection-diffusion equation as in [3].

Results
Figure 1 shows a qualitative and quantitative comparison between the in vivo DSA images and the in silico blood flow CA transport under steady and unsteady flow conditions. Quantitative comparison averages pixel intensity within vessel diameter bands located in selected region of interest (ROI) perpendicular to the flow direction.

Discussion
We present a computational approach that can generate patient-specific virtual angiograms in complex AVM geometries. Good qualitative agreement between patient DSA images and simulations is found. The quantitative analysis illustrates how the CFD results capture the trend of CA distribution for 4 of the 6 selected ROI of the geometry. An experimental platform has been developed to generate in vitro angiograms in the same patient geometry and quantify scalar transport using Laser Induced Fluorescence methods. We are also working towards implementing an heterogenous porous medium and an equivalent microfluidic network to better characterize the AVM nidus.

References

Acknowledgements
We acknowledge the support of The Butterfly AVM Charity and WEISS and Drs Gaia Franzetti and Mirko Bonfanti for laying the foundation for this research.

Figure 1: DSA and CFD CA distribution qualitative (top) and quantitative (bottom) comparison in selected ROI at critical points for the pre intervention (PreOp) scenario.

Figure 2: Experimental set up to acquire LIF measurements.
EFFECTS OF THE COLLAGEN COMPOSITION ON THE MECHANICAL MICROENVIRONMENT OF BREAST CANCER CELLS.

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Introduction

Mechanics plays a key role in cell function. In the literature, forces exerted by the cells in their extracellular matrix have been recently investigated to assess cell properties (focal adhesion, cell differentiation, and invasiveness) or to evaluate their potential metastatic and malignancy [1,2]. In particular, cancer cells have been shown to exert higher traction forces compared to healthy ones [2]. Thus, the analysis of the mechanical and structural microenvironment that favors the migration, proliferation and differentiation of metastatic cells is crucial to develop new cancer treatment strategies. The cancer developed from breast tissue is the most commonly diagnosed cancer type, accounting for 1 in 8 diagnoses worldwide. Therefore, this work aims to combine confocal imaging, and Focus Ion Beam with Scanning electron microscope (FIB-SEM) to evaluate the mechanical response of breast cancer cells in collagen hydrogels with different collagenous composition.

Materials and Methods

In this study, MDA-MB-231 cells were investigated as a common line to model late-stage breast cancer. They were initially cultured and stained using the commercial fluorescent dye CellTracker™. In the analysis of their mechanical behavior at different microenvironment, several extracellular matrices were mimicked by means of hydrogel substrates. They were prepared at different concentrations of only rat-tail collagen, only bovine-skin collagen or mixed 50/50 at 0.8, 1.5 and 2.3 mg/mL. The Traction Force microscopy (TFM) methodology was applied, which consisted of embedding 0.2 micron-sized fluorescent beads in the collagen gels and imaging their 3D spatial movements between the stressed and relaxed states of cells cultured on the gel [3]. This cell relaxation was achieved in situ by supplying Cyto-D, a cell-permeable inhibitor of actin polymerization. The particles’ displacement field and the traction force of cells were calculated computationally using the free Matlab™ toolbox TFMLab [3]. Confocal images of each analyzed cell were taken using a LEICA™ Stellaris 8 microscope and a 20x Glyc objective. Lastly, the microarchitecture of the different collagen hydrogels was characterized by the FIB-SEM ZEISS™ Crossbeam 550. After fixation, an osmium impregnation treatment (OTO) was applied to hydrogels samples to increase the back-scatter electron signal and the image contrast [4]. Images were taken at a voxel size of 9.5x9.5x19 nm and analyzed in the software AVIZO™.

Results

An example of a displacement field calculated via TFMLab is shown in Figure 1A. The results reported a significantly smaller displacement field as we increase the collagen concentration. A greater degradation of the collagen structure was also found in the hydrogels prepared exclusively with bovine collagen. In this composition, a weaker microarchitecture was also reported by FIB-SEM (example in figure 1B).

Discussion

In the concentrations analyzed in this study (up to 0.8 mg/ml of collagen), the cells seem to have greater migration in softer microenvironments with more bovine-skin proteins. This outcome could be related to their higher concentration of enzymatically degraded collagen fragments. While, the stiffer environment (2.3 mg/ml of collagen) prevent their expansion, mobility and cell survival, intermediate conditions (1.5 mg/ml of collagen) optimize their proliferation.

References


Acknowledgements

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Figure 1: A) Displacement field after cell relaxation calculated by TFM; B) example of a 3D reconstruction of the collagenous structure of the hydrogel from the FIB-SEM images.
FORCES AND TEMPERATURE MEASUREMENT DURING TEMPORAL BONE MILLING

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Introduction

Otologic surgery is performed using a hand-held milling tool to access anatomical areas of interest inside the temporal bone. This milling process generates heat, which diffuses in the living tissues and leads to potential thermal injuries. The facial nerve is especially at concern due to its location, near the standard surgical path for middle ear surgery. In fact, it has been shown that irreversible damages to nervous tissues occurred after one minute of exposition at a temperature of 41°C (1). However, monitoring the facial nerve temperature is difficult because of its complex anatomy and its difficulty of access inside the temporal bone. In the following study, we present a protocol allowing for simultaneous measurement of the facial nerve temperature and milling forces during an otologic surgery procedure on a cadaveric human temporal bone sample.

Methods

A cadaveric specimen of a left human temporal bone was obtained from a female donor aged approximately 80 years old and provided by the Laboratory of Anatomy of Nancy University Hospital, France. A thermocouple insertion protocol, previously validated on 3D printed synthetic samples (2) was applied, allowing for precise insertion of four 0.08 mm diameter, PFA-insulated thermocouples on the third portion of the facial nerve. The specimen was then manually milled by an expert surgeon with the use of irrigation (15cc/min flow rate) following middle ear surgery classical steps, with mastoidectomy and skeletonization of the facial nerve. Mastoidectomy was performed with a 4mm diameter tungsten carbide round burr, while skeletonization was performed using a 2mm diameter diamond burr. Surgical spindle rotation speed was manually controlled by the surgeon during the milling process and varied from 30,000 to 50,000 rotations per minute. Milling was performed under a Zeiss operating microscope using a Medtronic Indigo High-Speed Otologic Drill motor with a straight handpiece, an IPC console and an IPC System Multi-function Foot pedal. The measurement of milling forces was made using a Kistler™ 9119AA1 dynamometric platform. Forces were amplified through a Kistler™ 5167A charge amplifier, and both thermocouples and platform signals were acquired through a NI CompactDAC™ using a dedicated computer with NI Labiew™ 2020 software.

Results

As illustrated by figure 1, all four thermocouples signals followed the same trend, indicating good positioning repeatability. Temperature increased regularly in spikes, with a maximum recorded variation of 5.8°C. Forces signals showed extensive vibrations, characteristic of manual milling, with good repeatability between the milling sequences. A decrease in force signals values was observed between mastoidectomy and skeletonization phases. The values oscillated from -4.7N to 11.2 N, with the same order of magnitude for all components (X and Y axes corresponding to the milling plane and Z to the milling depth).

Discussion

We were able to measure the forces and temperatures generated during surgical milling of human temporal bones. Measured temperature variation did exceed the thermal damage threshold for nerves despite the use of irrigation, showing the importance of studying the process parameters to mitigate the heat generated and avoid complications. Additionally, force signals put in evidence the influence of surgical phases on the level of forces applied, and consequently the influence of the surgical tools and milling parameters. Further testing is required to assess the repeatability of those measurements, and determine good practices in otologic surgery milling.

References

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SAME OFFSET, DIFFERENT STABILITY: HOW HEAD LENGTH AFFECTS TAPER JUNCTION MICROMOTIONS IN TOTAL HIP ARTHROPLASTY

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Introduction

Modular neck systems allow intraoperative adjustment to adapt the implant length to patient’s anatomy or to replace only the damaged element of a hip prosthesis. Morse taper principle is frequently adopted to combine prosthetic components: after the application of the assembly force, the trunnion (male portion) locks the artificial joint through the compression of the taper (female portion) [1]. Nevertheless, modular prostheses present issues related to the establishment of relative micromotions between coupled elements, which can lead to implant failure due to cytotoxic metal debris onset. Micromotions can be influenced by surgeon-related factors including the selection of prosthetic components [2]. Although equal implant offsets can be achieved by assembling tapers and trunnions of different sizes, intraoperative adjustments are often limited to the head length. However, different studies reported that implant failure can be correlated with the head length variation due to presence of a lever arm between the head centre and the taper engagement area [2-3]. In this work, the head length impact on the head-neck junction stability was investigated through an in silico comparison between couplings with the same Offset.

Methods

Three head-neck junctions with different head lengths (S = 14.7 mm, M = 18.7 mm, and L = 22.7 mm) were designed compensating the lever arm introduction with a variation of the neck length (Fig. 1). The models consisted of a Ø 32 mm zirconia-toughened alumina (ZTA) head and a titanium alloy stem (Ti6Al4V), which was considered cylindrical for the whole neck. No angular mismatch between the two components was considered (perfect fit configuration).

A finite element (FE) model (Abaqus, Dassault Systèmes, France) of each configuration was implemented by simulating the insertion of the taper on the trunnion using a 4 kN applied force [3]. The head axial movement and the contact pressure were verified by analytical calculations proposed in [4]. Following the assembly phase, multibody (MB) derived loads (Adams View, MSC Software, USA) were imposed as boundary conditions in a FE simulation to estimate the taper junction micromotions as the relative slip (CSLIP) between the contacting surfaces during a normal walking cycle.

Results

The maximum micromotion was observed in the distal-medial area of the trunnion contact surface for all configurations. The L-size head model was the most critical case, showing a relative slip equal to 4.1 μm at 50% of the gait cycle (i.e., start of the swing phase). At the same time step, S-size model exhibited the lowest value of micromotions, reaching 1.7 μm (Fig. 2).

![Figure 2: (Left) Maximum CSLIP in S, M, and L configurations during a walking cycle. (Right) CSLIP distribution at 0.53 s in the L-size implant.](image)

Discussion

This study assessed the head-neck joint stability in implants with different head lengths. The proposed approach allows the simulation of specific geometry in different load conditions: this methodology can be useful to reduce the risk of implant failures, supporting clinical decision-making processes.

References


Acknowledgements

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THREE PHASES IN BONE TISSUE PROPERTIES FROM MICROMECHANICAL TESTING AT THE MATERIAL LEVEL

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Introduction

In ontogeny the properties and structure/composition of bone alter continuously according to demands placed upon it. Structural changes are concomitant to composition, architecture and physicochemical changes at the microscale which reflect at properties at the macroscale. We present here the pattern of properties at the osteon and interstitial lamellar level of a large collection of samples of human ribs [1] and clavicles [2] across a wide age range. Understanding of these patterns at the micro level may enable us to understand bone physiology in healthy ontogeny, in disease, as well as the developmental pressures placed upon it.

Methods

Sternal ends of the fourth and fifth ribs from 85 individuals (12-85 yrs) from the Forensic Institute in Tirana were employed in this study. The material was stored at -20°C and exposed to temperature variation for the least amount of time possible during testing. Experimental procedure involved nanomechanical tests on osteons and nearby interstitial lamellae by a CSM-NHT (CSM Switzerland) instrument, composition analysis (TGA) and physicochemistry (DSC, FTIR, XRD). Statistical analysis was carried out using the open-source software R 3.6.0.

Results & Discussion

The micromechanical data and most of the physicochemical data showed that there was a two-phase behaviour of bone tissue with age. A rise to a maximum value by the age of 35 and a decline thereafter. This behaviour, as expected, was related to the underlying chemistry and composition of the tissue [1]. However, the data has also raised some unanswered questions among which is the following conundrum: why do the interstitial lamellae decline after maturity? Do we really understand the osteon mediated remodelling of bone and its maturation in-situ? The prevailing wisdom [3] is that in the remodelling process old material is removed by newly laid down material and the older the material is the denser, harder and stiffer it becomes, by ageing in situ in ontogeny. We examined therefore, the relative magnitude (difference) of values of interstitial and osteonal lamellae across the full age range. There was no noticeable inflection at 35 and up to the age of 57yrs old and then it showed significant decline in the difference for both Hardness and Stiffness values. This means that in later life, the interstitial lamellae do not become even harder and stiffer than the osteonal ones; to the contrary the difference tends to decrease rather than increase!

![Figure 1: Difference in hardness of osteonal and interstitial lamellae across a wide age range.](image)

Conclusions

A combined examination of the material, compositional, and mechanical properties of bone tissue showed that it goes through 3 phases in ontogeny with cross over points at ~35 and ~57yrs old. The 1st phase is driven by modelling and maturing of the tissue up to age 35; the 2nd phase up to 57yrs is a phase for maintaining equilibrium with a very gradual deterioration of properties but equal weakening of both osteonal and interstitial lamellae, which nevertheless maintain their relative differences; the 3rd phase post-57yrs does not appear to be physicochemical in its make or origin, but simply a change in the relative ratios of bone resorption-vs-formation, removal-vs-addition of osteons.

References

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Acknowledgements

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EVOLUTION OF METABOLIC AND MECHANICAL COST OF WALKING WITH AN ABOVE KNEE PROSTHESIS SIMULATOR

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Introduction
At equivalent speed, a clear increase in metabolic cost is observed in lower limb amputees, particularly in above-knee amputees, compared to asymptomatic subjects during walking [1]. Previous articles have suggested that this extra cost may be associated with a lack of propulsion on the prosthetic side, and thus with the mechanical work that must be provided by the amputee to compensate [2]. The aim of this study was to verify this hypothesis by investigating the relationship between metabolic consumption and mechanical work in subjects equipped with a femoral prosthesis associated with feet with and without energy restitution.

Methods
Six asymptomatic subjects (4M/2F) walked in three conditions (Figure 1): 1. without a prosthesis (NA), 2. equipped with a knee prosthesis simulator associated with a foot with energy restitution (ERF) 3. equipped with the same simulator associated with a rigid foot (RF). Kinematic, kinetic and VO2 data were recorded. To obtain the metabolic cost of walking exclusively, oxygen consumption at rest while standing was subtracted from oxygen consumption measured during walking. The values were normalized to body mass. The mechanical power of each individual limb (ILM) was then calculated as the dot product of the body center of mass velocity and the resulting ground reaction forces on the lower limb under consideration [3]. Positive and negative work was calculated by numerically integrating the powers over time and normalizing them to body weight. To consider only the work done by the residual joints of the subject, and not that done by the prosthesis, the ILM work was replaced by the work of the hip on the prosthetic side. The total work was the sum of the absolute values of the positive and negative work.

Results
Metabolic rate was doubled between the condition without prosthesis and the two conditions with prosthesis (NA = 10.7 (1.0) mLO2.min⁻¹.kg⁻¹, ERF = 20.5 (2.0) mLO2.min⁻¹.kg⁻¹, RF = 20.5 (2.6) mLO2.min⁻¹.kg⁻¹). The ILM power for the three conditions and the hip powers for the two conditions with prosthesis are shown in Figure 2. The total mechanical work was equivalent in the three conditions (NA = 1.05 (0.21) W.kg⁻¹, ERF = 1.18 (0.28) W.kg⁻¹, RF = 1.03 (0.21) W.kg⁻¹) but the distribution was strongly asymmetrical for the condition with prosthesis simulator: the mechanical work on the contralateral side was 2.5 times greater than on the prosthetic side. This asymmetry was further exacerbated for the positive work (5.5-fold increase). The negative work was equivalent for the leg on the prosthetic side with both foot types and the condition without prosthesis (NA = -0.26 (0.05) W.kg⁻¹, ERF = -0.26 (0.07) W.kg⁻¹, RF = -0.21 (0.08) W.kg⁻¹). On the other hand, it was increased on the sound side for both types of foot (ERF = -0.34 (0.09) W.kg⁻¹, RF = -0.31 (0.07) W.kg⁻¹).

Discussion
Whether or not the foot returns energy has no real impact on the total mechanical work performed by the amputee or on his/her metabolic rate. The metabolic over-cost measured can probably be explained by the asymmetry in the distribution of mechanical work between the prosthetic and contralateral limbs observed as well as the overall increase in negative work that forces the muscles to function outside their optimal zone of use. This hypothesis could be verified experimentally via EMG or via the use of a musculoskeletal model.

References
LENGTH CHANGES OF THE MEDIAL PATELLOFEMORAL LIGAMENT DURING IN VIVO KNEE MOTION: A DYNAMIC EVALUATION

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Introduction
Medial patellofemoral ligament (MPFL) reconstruction is the primary surgical intervention for patients with recurrent patellofemoral instability.[1] Yet, the treatment is associated with high complication rates including pain, recurrent instability and restricted range of knee motion. [2] Two common causes are graft overloading and laxity, which are associated with surgical malpositioning. Clinical outcomes can be improved by a better understanding of MPFL elongation patterns and the effect of variations in graft placement. Therefore, this study aimed to assess length changes of the MPFL along the superomedial patellar edge throughout the range of knee motion.

Methods
A high resolution static and medium resolution dynamic CT scan of both knees were obtained in 115 knees of 63 healthy subjects (Figure 1). Static CT scans were obtained in full extension. Dynamic CT scans were obtained during an active flexion-extension-flexion movement in 11 seconds (full extension to 90° flexion).

Static and dynamic CT data were superimposed using image registration and transformations were interpolated to get 3D knee joint models per angle of flexion. Using the knee models, the MPFL length was measured from Schöttle’s point on the femur to three insertion points on the superomedial border of the patella (proximal, central, and distal; Figure 2). These locations corresponded with common attachment sites of the MPFL in anatomic studies. [4,5] The shortest wrapping path around the femoral condyle was selected as the MPFL length. Subsequently, MPFL length changes were assessed per flexion angle and expressed as percentual length changes relative to the length in full extension.

Results
The mean MPFL length in full extension was 58.4, 55.7 and 53.8 mm for the proximal, central and distal patellar insertion. During knee flexion, the median percentual MPFL length changes varied between -6 to 4 % relative to full extension (Figure 3). In the first 10° of flexion, the median MPFL length decreased by 2-3%. Beyond 10° of flexion, the elongation pattern depended on the patellar attachment site. The MPFL length of the central fibre restored to the length in full extension at 50° of flexion and subsequently decreased again to -2.7% (IQR, -6.2 to 1.1%) at 90° of flexion. The proximal fibre length decreased to -6.0% (-9.4 to -2.6%) and the distal fibre length increased to 1.9% (-1.5 to 7.7%) at 90° of flexion.

Discussion
The length changes of the MPFL depend on the patellar attachment site. The central MPFL bundle of the MPFL exhibited the most isometric behavior during knee flexion, whereas the MPFL slackened proximally and elongated distally. This suggests that reconstructing the MPFL at the central patellar insertion would result in the lowest complication rates when adhering to an isometric reconstruction. Surgeons should particularly avoid a too proximal patellar insertion, as that may increase the risk for complications due to overloading.

References
GENETIC ALGORITHM TO CALIBRATE A MULTISCALE COMPUTER MODEL OF BONE FRACTURE HEALING

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Introduction

In recent years the investigation of bone fracture healing progression with computational methods gained more and more interest[1]. The coupled dynamics of the (mechano)biological processes across different time- and length-scales makes experimental exploration challenging. This paved the way for in silico modeling to be used as a successful technique to unveil the hidden processes underlying bone regeneration. COMMBINI (COmputational Mechano-biological Model of Bone INjury ImmuNoresponse) has been created to investigate the inflammatory stage of bone healing. The parametric calibration of the model with experimental data needs an adequate methodology. Here, we present a machine learning approach for the parametric calibration of the computer model.

Material & methods

COMMBINI is a multiscale model of the immune response in bone healing. An agent-based model simulates the biological environment by representing the macrophage populations (cellular level) and cytokine concentrations (molecular level) within the healing region. The multiscale mechanisms and interactions are regulated by parameter-based algorithms, of which equations and values are collected from specialized literature[2,3]. The possibility to use a discrete agent-based model permits a direct comparison with immunofluorescent images of macrophage distribution collected from early healing stages in mice bone fracture[4]. Quantitative comparison between the experimental data and model cellular environment (in silico immunofluorescence) was used to calibrate the model. In detail, we employed Genetic Algorithm (GA) to calibrate the multiscale interactions simulated by the model. In the first instance, we evaluate the model sensitivity to the different parameters varying the values between two levels: 50% or 100% of the original literature-based value. Analysis of variance (ANOVA) evaluates the impact of each single variable on the model outputs as percentage of the total sum of squares (%TSS). The values of the most impactful parameters (%TSS > 1%) have been calibrated with GA. This method iteratively compares the model quantitative outputs with experimental data (e.g. macrophage count from immunofluorescent images[5]) and adapts the variables to reduce the in silico-in vivo differences. Each parameter is calibrated within a range of +/- 50% of the literature-based value. The calibration spans through multiple iterations ("generations") until below-threshold improvements are obtained.

Results

Model sensitivity analysis was run on the total number of macrophages predicted by the model at day 3 post-fracture. The most impactful parameters were “inactivated macrophages proliferation ratio” (k_p0, 77.2%), “pro-inflammatory macrophages doubling ratio” (k_p1, 11.0%) and “maximum macrophage recruitment ratio” (k_Rmax, 2.4%). GA analysis performed on the parameters required 7 generations to significantly reduce the quantitative difference with experimental images (yellow bars in Fig. 1). If compared with literature data, the GA converges to minor values for k_p0, while for the other parameters the tendency was to slightly increase the value (Fig. 1).

Discussion

The cellular level of the calibrated model showed a good agreement with experimental immunofluorescent data. Due to the efficiency of the presented calibration technique, its use will be extended to further calibrate the multiscale model when also mechano-biological modules will be included. The full calibration of the model with in vivo data, and its future validation for critical healing cases, will guarantee to COMMBINI a principal role in the preliminary planning of mechano-biological therapeutic strategies that supports bone fracture healing since the initial inflammatory response.

References

OPTIMIZATION AND INDUSTRIALIZATION OF A METABOLIC HOLTER DEVICE AND SOFTWARE DEVELOPMENT

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Introduction

The quantified-self of a person consists in the self-tracking of health and physiological parameters such as (but not limited to) heart rhythm, energy expenditure (EE), and sleep, using technology and devices such as smartwatches or wristbands, without the need of being supervised by clinicians. One of the first devices that came out on the market has been the BodyMedia Armband SenseWear® (SWA) (BodyMedia, Inc., Pittsburgh, PA), which has been proven to provide a valid measurement of EE during periods of physical activity in adults [1]. However, SWA company was acquired by Jawbone in 2013 and since January 2016 the company officially put SWA out of the market. Since then, there has not been a comparably easy-to-use, reliable and accurate way to routinely self-tracking the health and physiological parameters outside the laboratory in a free-living environment; therefore, this study aims to develop, optimize, and preliminarily validate a new metabolic holter device, based on SWA, aimed to analyze sleep tracking, activity level, and EE.

Materials and Methods

Following the SWA structure (enabling the analysis of activity level, sleep, and EE), the following input variables were considered for the device: movement, skin and environment temperature, galvanic skin response, heart flux, and user parameters (as height, weight, age, BMI). As gender and morphology have a direct impact on the subject’s metabolism [2] data will be classified by gender and by BMI considering three classes: Normal (BMI<25), Overweight (BMI between 25 and 30), Obese (BMI>30). From the previous data, the metabolic holter prototype uses a machine learning model to obtain EE, quality of sleep, and intensity of physical activity. An internal database of SWA data collected from 3706 patients was used to train each of these models. For each of the six groups, a randomly selected number of subjects (70% of the total) were chosen to train the machine learning, while the remaining 30% was chosen for the test set.

In order to optimize the software and check the measurement accuracy of the machine learning model in-vivo, a clinical study on 12 healthy volunteers has been performed. The aim of this was to compare the results (in terms of EE) measured during a standard clinical protocol by the new device with the ones obtained by the SWA sensor and by a metabolimeter, usually considered the gold standard.

Results

Figure 1 reports the energy expenditure against prediction. It is possible to highlight that the new holter, as the SWA, is able to properly detect the energy expenditure for each patient. The new device is characterized by a closer $R^2$ and a lower difference of the EE compared to the control (range of variability: 3.3-20.7%); for the 7 patients that have also the SWA measurement, instead, the range of percentile variability is from 6.5% to 36.9%.

![Figure 1: Energy expenditure in kJ against prediction; red dots correspond to the EE measured by the prediction, green squares correspond to the EE measured by the SWA, while blue triangles reported the values measured by the new device. The different lines represent the linear correlation, the $R^2$ values is also reported for the green and blue lines.](image-url)

Conclusion

In this study a prototype of a metabolic Holter device was developed and validated. Based on data from a previous commercial device, three machine-learning models were developed, tested and validated enabling the analysis of sleep, energy expenditure and physical activity. The clinical study allowed to check the reliability of the metabolic holter prototype for the energy expenditure evaluation. It has been highlighted that the new device prototype is able to correctly assess the energy expenditure, as shown by the high value of $R^2$ ($R^2=0.9106$), with an average accuracy of 3.6%.

References

BIOMECHANICAL ANALYSIS OF KNEE JOINT FLEXION IN HEALTHY, CRUCIATE DEFICIENT AND CRUCIATE SUBSTITUTE CONDITIONS

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Introduction
Cruciate ligament rupture is one of the most common knee injuries in sports, with 64% of athletic knee injuries in pivoting sports being due to ACL tears [1]. As cruciate ligaments cover an important role in joint kinematics and proprioception, injuries lead to functional alterations in joint stability and, in long term, to damages to adjacent structures. Reconstructive surgeries allow to restore functional stability to the deficient knee. This work aims to understand how much the knee joint function is influenced by the cruciate ligament damages and verify how the replacement strategies allow to restore the proper joint stability. Computational Models can predict the effects of traumatic events and surgical repair and replacement strategies. They provide information that would otherwise be difficult or impossible to obtain from experiments.

Materials and Methods
A 3D model of a knee was created to simulate knee movement and the impact of ACL and PCL injuries. The model was made using information from literature and CT images, and the materials were considered homogeneous and linear elastic isotropic [2]. The cruciate and collateral ligaments were modeled as different bundles and represented as one-dimensional elements: linear elastic isotropic beam elements for the collateral and non-linear springs for the cruciate [3]. The patellar tendon was divided into three bundles and represented as beam elements. The model was used to simulate the knee’s passive motion from 0° to 90° with a healthy knee, a knee with ACL injury, a knee with PCL injury and a knee with both ACL and PCL injury (injuries were represented by decreasing ligament stiffness by 25% and 50%). Finally, the model was used to simulate cruciate replacement firstly using the patellar tendon as a graft and then using a synthetic graft called LARS.

Results
The values of intra-extra rotation and the antero-posterior translation of the lateral and medial tibia were investigated. All cases examined follow the same trend, but the magnitude changed compared to the intact knee. After an initial extra-rotation between 0° and 10°, the tibia rotated internally and translated anteriorly with flexion. In amplitude, intra-rotation is larger as ACL stiffness decreases, as well as the anterior translation of the lateral compartment of the tibia. On the other hand, PCL-deficient reduced the anterior tibial translation both laterally and medially. When both the cruciate are injured, a significant increase in the internal tibial rotation and in the anterior translation occur (lower than the ACL deficient case). In case of cruciate reconstruction, the behavior is similar to the native. There are no significant differences in terms of antero-posterior translation and axial rotation of the tibia, both in the case of reconstruction with the patellar tend and with the synthetic graft.

Discussions & Conclusions
The results were consistent with experimental and literature data. The ACL and PCL play important roles in anterior-posterior constraint and joint stability, and injury to the ligaments affects joint kinematics. Cruciate reconstruction can effectively restore joint stability. The model developed in this study can be used for subject-specific predictions of joint kinematics and provide a basis for joint disease treatment.

Figure 1: A graph of the Tibial Rotation in case of Native Knee, ACL-deficient Knee and ACL-reconstructed Knee (with Patellar Tendon grafting). It is possible to see how the reconstructed knee behavior is closer to the native one, if compared to the ACL-deficient knee

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Introduction

Total Hip Arthroplasty (THA) is a highly successful surgical procedure. However, Periprosthetic Femoral Fractures (PFF) are a common cause of implant failure[1]. Cementless femoral components have a higher incidence of PFF compared to cemented implants, but the trend towards using cementless implants is increasing due to the advantages it offers. The contribution of different cementless stem designs to PFF risk is still a debated topic in the literature. This study compares the stress and strain distributions on physiological and osteoporotic femoral bones for different cementless hip stem designs under different loading conditions. The focus is on the perioperative period before osteointegration occurs. A biomechanical study using finite element analysis was performed to achieve the highest comparative value.

Methods

The study developed 4 finite element models and analyzed each one for healthy and osteoporotic bones; in detail 1 native control and 3 implanted femurs: one short anatomical stem with femoral neck preservation, one double-wedge press fit stem (Type 2) and one anatomical standard stem (Type 6). The bone geometry was reconstructed from CT images and three THA stem designs were implanted in the femoral bone. The material models used linear elasticity and different Young’s moduli and Poisson’s ratios were assigned to healthy and osteoporotic bones [2]. The stems were made of titanium alloy. The models were tested under 3 load conditions: gait, sideways falling, and four-point bending [2]. The gait test analyzed maximum force during daily activities, the sideways falling test simulated common clinical injuries, and the four-point bending test simulated the boundary conditions of the standard experimental test used to measure the resistance of the bone.

Results

Gait: Similar stress distribution found in anatomical stem (Type 6) and short anatomical stem with femoral neck preservation in native model. Type 2 stem reduced stress in proximal femoral area (Figure 1) and showed non-homogeneous stress with concentrations in small areas. In osteoporotic bone, increases of 5% in average von Mises stress were found in native, Type 6 and short anatomical stem; 10% increase was found in Type 2 stem.

Side-way falling: Native model had the highest stress in femoral neck, while prosthetic stems reduced stress, with higher stresses found in stem tip areas for Type 6 and short anatomical stems. Type 2 stem showed no remarkable stress concentrations. Stress overall increased in osteoporotic bone in all models, with the highest rise in Type 2 stem.

Four-Point Bending: All configurations in physiological bone models showed comparable stress distributions. Type 6 had higher stress in trochanteric area, Type 2 had high stress in distal part of stem. No significant difference in average stress in osteoporotic bone in any studied model.

Discussion

The critical phase of the press-fit THA is before stem osteointegration, as most fractures occur within the first six months after surgery: analyzing the prosthesis behavior can therefore be beneficial to understand the eventual consequences of a design over the other. The results of this study showed that anatomical stems with femoral neck preservation performed similarly to native models, while double wedge stems demonstrated a reduction in stress in the proximal femoral area and a theoretical higher risk of PFF. Type 6 stems confirmed the clinical evidence that the anatomic stem design represents a protective factor against stress-shielding. Therefore eventual resorption in anatomical stems, and mainly in neck preservation stems, could then be explained mainly by errors during surgical planning and surgical technique.

![Figure 1: A graph of the Average von Mises Stress in different regions of the femur (1=proximal, 9=distal) during the Gait test](image)

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**Objective**

Transcatheter heart valve thrombosis (THVT) is associated with reduced leaflet mobility, valve degeneration and possibly higher risk of stroke [1]. Data from the Bern Transcatheter Aortic Valve Implantation (TAVI) registry indicates that patients diagnosed with THVT might have a larger ascending aorta (AAo) compared to respective TAVI patients without THVT. This computational study aims to compare blood flow patterns in aortic root geometries with larger AAo as observed in THVT patients to those found in unaffected TAVI patients.

**Computational Method**

Two computational models of a parameterized aortic root with a biological tissue valve are created: (a) a model representing TAVI patients without THVT (control) and (b) a model with larger AAo as observed in THVT patients (THVT). The interaction of the motion of aortic wall and valve with the surrounding blood flow is implemented in a high-fidelity fluid-structure interaction solver. The coupling of a high-order Navier-Stokes solver [2] and the structural solver is achieved by an Immersed Boundary approach based on variational transfer [3]. Average systolic transvalvular pressure gradients are imposed according to patient data of Franzone et al. [4]. The resulting flow fields are analyzed and turbulent dissipation is quantified. To assess the washout efficiency of the sinus portions mass-less Lagrangian particles are seeded immediately upstream of the valve and traced over time periods of 0.1s. The traces are categorized into groups of particles that are advected into the ascending aorta, particles that contribute to the sinus washout, and particles that stagnate in the sinus portions.

**Results**

Although peak jet velocities during systole are comparable in both models, systolic backflow velocities towards the sinus portions are lower in the THVT model. Also, lower mean flow velocities and a lower turbulent dissipation rate can be observed in the sinus portions. However, the systolic turbulent dissipation rate in the AAo is higher in the THVT model compared to the control group. Lagrangian particle tracing reveals that most of the injected particles are advected directly through the ascending aorta (84% for control vs. 88% for THVT). However, more particles enter, but also leave the sinus and therefore contribute to the washout for the control model (+78%) compared to the THVT model.

**Conclusions**

A higher systolic turbulent dissipation rate in the larger ascending aorta of THVT patients might promote blood platelet activation. Lower systolic turbulent dissipation rate and lower velocities within the sinus indicate a lower washout rate. This is supported by the higher amount of washed-out particles for the control compared to the THVT model, suggesting a much lower washout efficiency of the sinus in THVT patients. The combination of the observed flow patterns could lead to thrombus formation and provide a possible explanation for the link between aortic root morphology and THVT.

**References**

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ASSESSING THE EFFECT OF FIXATION LENGTH IN LUMBAR SPINE COMBINING RIGID AND FLEXIBLE BODY MODELING

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Introduction
The growing incidence of degenerative spine diseases necessitating a segment fixation to solve spinal instability is dramatically increasing. At present, reducing the number of fixed vertebral levels is topic of heated clinical debate, but long fixations are still preferred as more stabilizing, and in case of pedicle screw failure, permit a more conservative revision treatment [1]. The study intends to explore this controversy, through a combined finite elements - rigid bodies approach, by investigating whether fixation length is a risk factor for the failure of the implant itself.

Methods
An experimental campaign was conducted recurring to a T12-S1 biomimetic phantom (Sawbones SKU3430) to characterize (i) a pathological condition of an osteolytic lesion in L3 combined with a posterior decompresion, and (ii) a long fixation (L) involving two levels above and below the lesion and (iii) a short fixation (S) connecting only the L3 adjacent levels in carbon-fiber reinforced PEEK (Fig. 1A). Concurrently, a T12-S1 rigid body spinal segment was designed recurring to the vertebral geometry of the phantom, consistent with an average human adult male anatomy. The intervertebral discs behaviour was characterized by eq. 1.2.

\[ \vec{F} = [K] \Delta \vec{s} + [C] \Delta \dot{\vec{s}} \] (1)
\[ \vec{M} = \sum_{p=0}^{k_p} [k_p] \Delta \vec{\omega}^p + [C_T] \Delta \dot{\vec{\omega}} \] (2)

With \( K, C, C_T \) respectively the translational stiffness, and translational and rotational damping diagonal matrices; \( \Delta \vec{s} \) and \( \Delta \dot{\vec{s}} \) describe the relative displacements and rotations of two adjacent vertebrae in the space. Ligaments were modelled as non-linear pre-stressed tension-only spring dampers and validated through backward stepwise reduction strategy [2]. Concerning the surgical outcomes, FEM was adopted to simulate the implant which were simulated fixed to the bones (Fig. 1B). The Young’s modulus was estimated through a four-point bending test on rods provided by CarboFix Orthopedics Ltd. The in vitro data permitted to validate the numerical surgical outcomes (Fig. 1C). From a mechanical perspective, the most severe internal loads occurring at the fixation joints are shear forces and bending moments [3]; hence, these loads, and the resulting Von Mises stresses along the rods, were compared between \( L \) and \( S \) outcomes in flexion-extension, lateral bending and axial rotation (Fig. 1D).

Discussion
Fixation length resulted strongly associated with implants internal loads in all the studied poses (consistent with patients’ post operative mobility). This calls the attention that the surgical practice of lengthening fixation should be reconsidered; indeed, the study demonstrated that the insertion of a larger number of pedicle screws don’t entail a more favorable load sharing, but, conversely, an hyperstatic construct with overloaded joints and shielded ones, making the \( L \) outcome more prone to failure.

Results
By simulating a hybrid protocol at 5Nm [4], a clear fixation-length dependence of the internal loads in the implants emerged, with \( L \) presenting up to 10 times higher moments in 2.5° axial rotation and in 10° extension, and generating more severe shear forces, like in 15° lateral bending where the most caudal fixation was subjected to ~1700N against ~300N. Reducing the fixed levels also permitted to contain Von Mises stresses (\( \sigma_{\text{max}}<40\% \)) at least) and to guarantee their uniform distribution: indeed, the central fixations of \( L \) always revealed shielded by the hence overloaded distal ones.

References
VALIDATION OF THE FORCELOSS FRAMEWORK FOR THE DIFFERENTIAL DIAGNOSIS OF DYNAPENIA

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Introduction
The loss of muscle force, or dynapenia, is a natural consequence of aging that may be accelerated or aggravated by ongoing pathological processes [1]. Dynapenia is typically associated with a reduced quality of life, and an early diagnosis is important. However, the identification of the primary cause of dynapenia, and the consequent clinical management of the patient, is challenging. Complementing current clinical measures with computer modelling and simulations (CM&S) techniques may facilitate this process. Personalized musculoskeletal (MSK) models and simulations, informed by experimental data, may be used as a falsification tool to test different clinical hypotheses, and – by exclusion – to identify the primary cause of dynapenia. To this purpose, we developed the ForceLoss framework, which we presented at the last ESB congress in Porto. In this abstract, we present the validation of the ForceLoss framework, which has so far been conducted using a public dataset [2].

Methods
Data from three editions of the Knee Grand Challenge competitions [2] were used to perform the study. Dynamometry and electromyography (EMG) data recorded while the subjects performed a knee extension task (maximal voluntary isometric contraction, MVIC) were processed to extract the maximal torques and the EMG linear envelopes. Image-based MSK models were then developed, following the INSIGNEO pipeline [3], using the available bony geometries. The models were placed in a sitting position (with hip and knee flexion angles set to 80° and 90° respectively) and simulations were run hypothesizing optimal muscle control (classical static optimization approach), in OpenSim. An external knee flexion torque was imposed, and iteratively increased till failure. To test different clinical scenarios, the level of personalization of the models was gradually increased, first by scaling the maximal isotonic force values of the quadriceps muscles with the physiological cross-sectional area extracted from medical images, then by setting the maximal activation level of the vastii and the rectus femoris muscles to the corresponding EMG linear envelopes (maximal value).

Results
For one subject, the first level of model personalization was sufficient to estimate maximal knee extension values within a 10% margin from corresponding experimental MVIC data (157 vs 146 Nm). For the other two cases, further limiting the maximal activation levels to those observed in vivo was necessary to achieve a good agreement between experimental and simulated data (substantial reduction from 126 to 69 Nm, comparable to the experimental values, 69 Nm).

Discussion
Based on these results we may conclude that all subjects were affected by a form of sarcopenia, which was accompanied by some neuromuscular problem in two cases. This suggests that the proposed framework may be suitable to conduct the differential diagnosis for dynapenia, through the combination of experimental measures and CM&S methods. To confirm these findings, we will test the ForceLoss framework on a dataset currently under construction. The dataset will be representative of a healthy adult population and of patients with osteoarthritis who will undergo a total knee arthroplasty.

References

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EVALUATION OF BIOMECHANICAL PROPERTIES OF SOFT TISSUES MIMICKING PHANTOMS BY IMPACT ANALYSES.

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Introduction

In oncology, the development of most pathological processes is accompanied by an alteration of the mechanical properties of the tissue and a change in its biomechanical properties [1]. Similarly, in dermatology, several skin diseases such as scleroderma or keloids scars alter the biomechanical characteristics of the skin [2]. Thus, the assessment of soft tissue properties is of great relevance for clinical diagnosis. The physicians often employ empirical techniques to assess the soft tissue stiffness and detect potential abnormalities. The objective of this work is to investigate the feasibility of using impact analysis to assess the biomechanical properties of soft tissue. This new approach is non-invasive, provides real-time information and is relatively inexpensive and ease-of-use compared to existing medical devices such as the Fibroscan© or the Cutometer©.

Methods

The experimental device consists of a 5 grams hammer equipped with a force sensor (8204, BK Connect, Brüel and Kjaer, Naerum, Denmark) that impacts a cylindrical beam in contact with the upper surface of the sample to be characterised. The assembly is integrated into a support that guides the punch and holds the sample during the measurement and ensures the reproducibility of the measurements (see Fig.1a).

Figure 1: Schematic description of the experimental device (a). Example of signal $s_i(t)$ corresponding to the variation of the impact force in function of the time (b).

A signal processing technique deriving from [3] was applied to the signal $s_i(t)$ corresponding to the variation of the force as a function of time during an impact of the hammer on the beam (Fig.1b). Thus, a time indicator, $Δt$, was obtained from the average of the difference, $Δt_i$, between the time of the first, $t_{i,1}$, and the second local maxima, $t_{i,2}$, of four signals $s_i(t)$.

$$Δt = \frac{1}{4} \sum_{i=1}^{4} Δt_i, \quad Δt_i = t_{i,2} - t_{i,1} \quad (1)$$

As a first step, the tests were carried out using agar-based phantoms which have been extensively employed to mimic biological soft tissues [4], with an agar concentration varying between 1g to 5g per 100 mL of deionized water. For specimens with different agar concentrations $c$, the indicator $Δt$ and its standard deviation, $σ_{Δt}$, were derived from the impact force signals $s_i(t)$.

Results

The time indicator $Δt$ decreases as a function of the agar concentration $c$ (Fig.2). According to an ANOVA analysis, for each agar concentration $c$, the values of $Δt$ are significantly different (p-value=4.10−10).

![Figure 2: Evolution of the time indicator $Δt$ in function of the agar concentration $c$ for one specimen.](image)

Discussion

The method can be used to distinguish the elastic properties of agar phantoms and has the advantage of being easy to use and inexpensive. Moreover, the behaviour of our indicator is consistent with others studies [5] and the sensitivity of the impact method is of the same order of magnitude as elastography or dynamic mechanical analysis.

References


Acknowledgements

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LIFTERS AND JUMPER CONTRIBUTIONS TO RUGBY LIFT PERFORMANCE – A PRELIMINARY STUDY ON ELITE PLAYERS

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Introduction

Rugby is played worldwide by both amateur and professional players. During a game, the ball reintroduction is critical for performance as during the 2015 rugby world cup, 50% of the tries were directly following it. To help the jumper to quickly catch the ball during its flight, two players can lift him. As the lift involves 3 players, its performance understanding is challenging, and trainers may also want to estimate each player contribution. Only one study [1] investigated it based on a 2D approach on videos. However, this approach was questioned [2] by highlighting the movement asymmetry between forward/backward lifters through vertical ground reaction forces measurement.

The aim of this study was to investigate the link between lift performance and ground reaction forces profiles of the three players during a rugby lift.

Methods

One elite threesome (one jumper and two lifters) volunteered for this study. They performed two series of ten lifts in a motion analysis room equipped with 15 optoelectronic cameras (Vicon, 100Hz) and 5 forceplates (AMTI, 1200Hz). A full markerset was used for each rugbyman but only the ones stuck on the jumper’s iliac crest were used in this preliminary study.

Between the two series, forward and backward lifters were switched defining two configurations (C1 and C2). The lift beginning was set as the lowest position of the jumper’s pelvis and its end as its highest position. The jumper speed was assessed by differentiating the position of one marker of the jumper’s pelvis. To characterize repartition between the three players, each of their impulse was computed as the integral of his vertical ground reaction force during the whole lift. Force data were divided by each player weight.

Results

According to the table 1, the average performances, considered as the average jumper velocity, between the two configurations were different (20%) even if the jumper impulses were the same. Ground reaction forces and impulses were higher for the backward lifter in C1 configuration and for the forward one in the C2 configuration.

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>J. speed (m/s)</th>
<th>VGRF max (N/N)</th>
<th>Impulse (s)</th>
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<tr>
<td></td>
<td>F</td>
<td>B</td>
<td>J</td>
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<tr>
<td>C1 N=10</td>
<td>2.0 (0.1)</td>
<td>1.9 (0.1)</td>
<td>1.7 (0.1)</td>
</tr>
<tr>
<td>C2 N=9</td>
<td>1.7 (0.1)</td>
<td>1.6 (0.1)</td>
<td>1.9 (0.1)</td>
</tr>
</tbody>
</table>

Table 1: mean and standard deviation of the jumper speed, vertical ground reaction forces and impulse for each player (J: jumper, B: backward lifter, F: forward lifter), over all lifts for each configuration (C1 and C2).

Discussion

Within a configuration the force and speed parameters were similar, but they changed when the lifters switched. Those players were trained enough to be repeatable but output varied with their position. The configuration with the best performance occurred when the backward lifter created the highest impulse value. This was not the case for the forward one, even when the total of the two lifters impulses was higher. This tendency is aligned with coach feelings. Impulse computing seems to give a help for separating each contribution but it is not the only parameter contributing to performance. However, it is only an example over one threesome which may have a specific technic and should be confirmed over various teams.

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Introduction

Transcatheter aortic valve replacement (TAVR) has emerged as an effective percutaneous treatment option for aortic stenosis, but the devices can be prone to early structural valve degeneration (SVD) due to mechanical damage or calcification.

Solid mechanics or fluid dynamics computational modelling approaches have been used to assess the performance of TAVR [1,2]. Fluid-structure interaction (FSI) approaches can investigate dynamic interactions between the device and adjacent blood flow. Such approaches have been applied in a limited fashion [3], but may be appropriate for analysis of pulsatile flow induced cyclical deflections of the valve leaflets and stent to understand the occurrence of SVD and overall device durability.

The objective of this study is to understand the impact of pulsatile flow induced leaflet and stent deformations on TAVR durability. To address this objective, we characterize the impact of pulsatile flow on the BHV and stent deflection using (a) a decoupled-Finite Element (FE) validated against experimental data and (b) a fully-coupled FSI model of a self-expanding TAVR device.

Methods

FE models of the ACURATE neo2 were developed using Abaqus/Explicit (Dassault Systemes), with representative material properties and pressure-based loading conditions. To account for the effects of the surrounding fluid in the FE model, a sensitivity analysis of the Rayleigh damping coefficient was conducted. Models were validated with in vitro test data of the ACURATE neo2 valve within a ViVitro Pulse Duplicator (ViVitro Labs). The impact of stent rigidity on the durability of the device was investigated using rigid boundary conditions, representative of first-generation, highly rigid Surgical Aortic Valve Replacement (SAVR) devices. These were compared to a model that incorporated a deformable TAVR stent (Fig. 1a). A fully-coupled FSI model of the TAVR device is in development, using the sub-grid geometry resolution (SGGR) method, which couples Abaqus CAE with FlowVision CFD (Capvidia, Leuven, Belgium).

Results

The FE model of the TAVR device showed good alignment with in vitro data, exhibiting a similar geometric orifice area, leaflet coaptation area and stent-commissure deflections. A high damping coefficient was required to capture the in vitro kinematics of the leaflets. For both rigid (SAVR) and deformable (TAVR) models, the peak maximum principal stress and strain occurred at the leaflet commissures (P1, Fig. 1b). Rigid boundary conditions greatly increased leaflet stresses.

Discussion

FE results predict that a rigid boundary condition, representative of a SAVR device, was associated with higher peak leaflet stresses in regions where failure has been reported in SAVR devices [4]. Thus, we propose that stent deflection may improve the durability of the BHV leaflets, reducing the risk of early SVD. Indeed, clinical trials reported a significantly lower rate of SVD in a self-expanding TAVR compared to SAVR devices [5]. However, it is important to note that models developed in this study do not account for device-specific variations in leaflet design. Additionally, the FE models cannot account for the effect of the surrounding flow, which induces complex pulsatile flow conditions on the device. A fully-coupled FSI model is in development to study pulsatile flow induced leaflet and stent deflections on TAVR device durability.


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BONE COLLAGEN TENSILE PROPERTIES OF THE AGEING HUMAN PROXIMAL FEMUR

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Introduction
Despite the dominant role of bone mass in osteoporotic fractures (OF), ageing bone tissue properties must be thoroughly understood to improve osteoporosis management [1]. In this context, collagen content and integrity are considered important factors, although limited research has been conducted [2]. Therefore, this study aims at investigating bone collagen tensile properties of the ageing human femur.

Methods
Bone sections of eighty fresh frozen cadaveric human proximal femora of 24 female and 19 male donors with a mean age of 81 (57 to 96) years were used in this study. Two cylindrical cortical bone samples were extracted from each section’s proximal, lateral side by manual drilling and cut to a length of 25 mm using a band saw. One sample of each section was glued into an aluminum sample holder while sample geometry (6 mm gauge length, 2 mm diameter) was machined on an engineering lathe. Then, samples were scanned by micro computed tomography (μCT) with a spatial resolution of 7.4 μm. Samples were mechanically tested in tension until a maximum engineering strain ε of 0.25 % on a multipurpose servohydraulic testing system while measuring displacement using a video extensometer. Subsequently, the same samples were demineralized in a buffered (pH 7.4) 0.5M EDTA solution at room temperature for 12 days before monotonically tested to failure on the same system. One sample of each section was used for compositional analyses. Gravimetric methods were used to determine mineral, organic, and water weight as well as bone tissue density.

Ultimate stress was defined on the apparent (σ_app), extracellular matrix (ECM) (σ_ECM) and collagen (σ_C) level as the division of ultimate force by apparent area (A_app), mean ECM area (A_ECM_mean), and minimum ECM area (A_ECM_min) respectively. Similarly, Young’s modulus of the mineralized (E_app,m) and demineralized (E_app,c) state at the different levels was defined as the ratio of the respective stress and strain. A coefficient of variation (CV) describing heterogeneity of the sample porosity was computed as the ratio of the standard error of A_F and A_F_mean.

Results
Samples exhibited mineral, organic, and water weight fractions of 58.7 ± 1.3 %, 35.0 ± 0.9 %, and 6.4 ± 1.6 %, and a bone volume fraction (BV/TV) of 0.93 ± 0.05 %. E_app,m (15.6 ± 1.8 GPa) correlated with BV/TV (p<0.001, r=0.55), and relative mineral weight (r=0.32). Interestingly, E_app,c does not depend on BV/TV but decreases with mineralization (p<0.001, r=-0.43) and correlates moderately with E_m (p<0.01, r=0.56). σ_app exhibits a correlation with BV/TV (p<0.05, r=0.27), and σ_C with CV (p<0.05, r=0.25). It was further observed, that σ_C is related to tissue mineral density (TMD) (p<0.001, r=0.39) (Figure 2).

Discussion
BV/TV, compositional and mechanical variables are in very good agreement with values reported in previous studies [3]. The negative correlations of both E_C and σ_C with TMD suggest that collagen-collagen bonds may be competing against collagen-mineral bonds. Further prospective work includes analysis of cement line density and collagen crosslink maturation by optical and Raman spectroscopy respectively.

References

Acknowledgements
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MODELING THE REACTION OF A LIVING CELL CYTOSKELETON TO MECHANICAL STRESS IN A FLOWING LIQUID

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Introduction
Studies on biomechanics of living cells are important in predicting their behavior in living tissue in response to naturally occurring mechanical stimuli. By recreating the types of stress [1,2] that a given type of cells experiences in the natural microenvironment and by examining their reactions, it is possible to model the behavior of both cells and entire tissues in the body. The mechanical properties of cells are primarily influenced by the cytoskeleton, which acts as a scaffolding on which the cell is based, and which reacts to changes in the physical environment in real time [3,4]. Assuming this, to adequately describe the behavior of a cell, it is necessary to describe the impact of mechanical loads on the architecture of the cytoskeleton and its influence on the changing properties of cells [1].

Particular attention should be paid to the cells of the bone tissue, which is subject to the constant influence of mechanical stresses [3,5]. By studying how cells respond to mechanical stress, one can predict what conditions will cause them to die and which conditions will increase their metabolic activity. This knowledge is extremely important in prosthetics and in the treatment of bone diseases.

Methods
The aim of the work is to develop an analytical model and to conduct numerical simulations using the finite element method in COMSOL, which describe the reactions of single, living connective tissue cells in response to mechanical loads. The secondary aim of the research is to develop a numerical model describing the transformation of the cytoskeleton architecture, especially actin filaments [6] under the influence of mechanical loads and to link the change in this structure with the mechanical and rheological properties of the cell. The dominant research hypothesis is the assumption that the changes in the architecture of the cytoskeleton can be described by optimizing equations, assuming that its reconstruction is aimed at maintaining unchanged internal conditions, homeostasis, at the lowest energy cost formulated as equation 1.

\[ W = \sum_i \sum_j ^2 \sigma_{ij} \epsilon_{ij} \]  

The proposed model considers the time-dependent and external loads dependent, and consequently also internal loads dependent, properties of the components of the cytoskeleton. This means that the constitutive equations depend on the current state, the coefficients adapt to the state at a given moment in time.

To make the developed model adequate to the actual cell behavior, it was necessary to constantly verify the calculations with the experimental reality and selecting the correct initial parameters for the models.

Results
The simulations and experiments confirmed that it is possible to approach the cytoskeleton modeling using the optimization method. The compaction lines determined by this method coincide with the cytoskeleton thread architecture under the influence of external loads changing over time, as shown on fig.1.

Discussion
The main goal of this work was to develop an analytical model based on optimization equations that adequately describes the cytoskeleton adaptation to the external loads. The presented numerical simulations confirmed that the formulated mathematical description makes it possible to determine changes in cytoskeleton architecture, taking into account the strain energy density. This makes it possible to compare the proposed model to the models already developed, first of all tensisegory model.

References
UPPER LIMB CRANKING ASYMMETRY DURING A WINGATE ANAEROBIC TEST IN WHEELCHAIR BASKETBALL PLAYERS.

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Introduction
Interlimb asymmetry of strength and/or motor coordination could limit the performance of wheelchair athletes or increase their risk of injury. Studies of the lower limbs have shown high between-subject variability in interlimb asymmetry that does not depend on the side of dominance and that does not change with fatigue [1]. Upper limb asymmetry is particularly large in highly classed manual wheelchair athletes [2]. The aim of this study was to evaluate the interlimb asymmetry of forces developed during a 30-s anaerobic Wingate arm test, the effects of fatigue on the force, and differences between high- and low-point players (HP versus LP). We hypothesized that asymmetry would not increase during the exercise and that asymmetry would be larger in HP than in LP players and larger in men than women players.

Methods
25 wheelchair basketball players (13 females and 12 males) performed a 30-s Wingate test on an arm ergometer. Participants were classified into two functional categories, high-point (n=12) and low-point (n=13), according to the International Wheelchair Basketball Federation classification. Data were collected with an arm ergometer (Lode Brachumera, Netherlands). Left and right arm forces were measured during the pushing and pulling phases at peak power (A_PP), at 10 sec of onset (A_10s), and at the end of the 30-s test (A_30s). We calculated total force asymmetry (SItot) using equation [1].

\[ SI_{tot} = \frac{|L_{tot} - R_{tot}|}{L_{tot} + R_{tot}} * 100 \]  

(1)

Results
Asymmetry changed during time exercise at each phase, significantly between A_PP and A_10s. In average, force asymmetry increases between A_PP and A_10s (12.5 ± 10.5% A_PP vs. 17.1 ± 14.8 A_10s; p=0.028) and tend to decrease after A_10s (14.5 ± 12.1 at A_30s; NS). No significant difference between functional categories was founded but tended to be greater in high-point players (13.7 ± 11% in HP vs. 10.8 ± 7.9% in LP; p=0.078) (Table 1). Asymmetry tended to be greater in the women, with significant differences between the men and women in the push phase (respectively, 9 ± 7% vs. 18.5 ± 10.1%; p=0.014).

Discussion
Inter-subject variability was high, but forces were asymmetric for most participants, especially women. It seems that differences in classification alone do not explain the tendency for higher force asymmetry in HP players. The bilateral asymmetry is higher at A_10s, which could show a link between the onset of fatigue and the peak of muscular imbalance. In literature, a commonly used threshold for studies on lower limbs is 10% [4]. A measurement above this threshold would be considered abnormal. However, when studying upper limbs, care should be taken when using this threshold, as upper limb asymmetries could be more prevalent due to the diverse range of tasks they can perform daily. The Wingate anaerobic test could reveal asymmetries that may affect sports performance or daily life.

Table 1: Comparison of mean symmetry index (SI %) all along the Wingate test (A_PP, A_10s, A_30s) of the total force, push force, and pull force between high points players (HP) and low points players (LP). M: mean, SD: Standard deviation, SI: Symmetry Index.

<table>
<thead>
<tr>
<th>SI (%)</th>
<th>HP M ± SD</th>
<th>LP M ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Force</td>
<td>13.7 ± 11</td>
<td>10.8 ± 7.9</td>
<td>.078</td>
</tr>
<tr>
<td>Push Force</td>
<td>14.3 ± 10.8</td>
<td>13.5 ± 9.3</td>
<td>.225</td>
</tr>
<tr>
<td>Pull Force</td>
<td>14.0 ± 12.3</td>
<td>12.5 ± 11.6</td>
<td>.060</td>
</tr>
</tbody>
</table>

References
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Acknowledgements
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BIOMECHANICAL STUDY ON ADDITIVELY MANUFACTURED NITINOL PATIENT-MATCHED DEVICE FOR UNICORONAL CRANIOSYNOSTOSIS

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Introduction

Unicoronal Craniosynostosis (UC) is the second most-common form of non-syndromic craniosynostosis and occurs when one of the coronal sutures ossifies prematurely in the newborn [1]. Reconstructive surgery is required to expand and remodel the skull. Spring Assisted Cranioplasty (SAC – consisting in using spring distractors to guide cranial remodelling) is a promising minimally invasive surgical treatment mainly adopted for the treatment of craniosynostosis of the sagittal suture [2]. It consists in positioning a spring-shaped steel distractor to guide cranial remodeling. A first objective of this project is to substitute steel with NITINOL, a NiTi alloy, to exploit its superelastic behaviour [3]. Superelasticity consists in a material’s ability to recover large deformations upon unloading: this is supposed to allow for constant force distraction and therefore improved cranial adaptation. The second aim of the work consists in designing a patient-matched spring-shaped distractor. Both the design complexity and device customization are addressed and overcome by means of Additive Manufacturing (AM) technology.

Method

A previous study established a UC population average skull shape by statistical shape modelling (fig.1a). Surgical cuts were simulated on a CAD model (fig.1b).

A novel device was designed, consisting in 3 pairs of unit spring cells (i.e. spring-shaped distractors) (fig.1b). The expansion of 3 spring unit cells, whose behaviour was based on existing distractors adopted in SAC, was simulated using FEA software (Ansys, 2020): surgical cut length and position, spring unit stiffness and spring notch location were optimized to minimize the model Cranial Vault Asymmetry Index (CVAI—a measurement of head asymmetry) by means of Design of Experiments (DoE). Spring expansion forces, spring opening distance and cranial remodeling were quantified. With this information, a number of optimized spring-shaped unit cell designs were created using SolidWorks, 2021 and the mechanical response was modelled in Ansys.

NiTi dogbone specimens were realized by laser powder bed fusion (LPBF) with optimized process parameters and mechanically tested to assess the material’s mechanical behaviour. Afterwards, a preliminary spring unit prototype was produced by means of LPBF process. Finally, the spring-shaped unit cells was mechanically tested in compression. The results were compared with the FEA model analysis for validation.

Results

DoE allowed to estimate and optimize surgical parameters and localized distraction forces (ranging from 24N to 32N), required to correct the UC model shape and minimize CVAI. NiTi tensile specimens confirmed the AMed material superelastic behaviour. Experimental NiTi parameters were implemented in the spring unit model to simulate its behaviour in compression. Experimental tests on the AMed spring validated the computational model (fig.2).

![Figure 2: experimental σ-ε curve for NiTi AMed specimens (a). Comparison between F-d curves of AMed device and simulated one (b).](image)

Discussion

In this work a design process for the development of a novel NiTi AMed spring-shape distractor for UC correction was proposed and validated. Next steps aim to finalize the spring unit design according to the required distraction forces. Upon design realization, the full AMed device will be prototyped tested in-vitro using a 3D printed skull replica.

References

A NOVEL APPROACH TO MEASURE TIBIOFEMORAL KINEMATICS IN HUMAN CADAVERIC KNEES WITH INTACT CAPSULE

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Introduction

Using the same definitions while describing and comparing kinematics is crucial since the choice of coordinate systems can lead to markable differences in the resulting curves and thus to different interpretations of normal kinematics [1, 2]. For this reason, landmark-based coordinate systems are recommended for measuring tibiofemoral kinematics [1]. However, accurate placement of landmark-based coordinate systems in native knees with intact capsule is challenging since the necessary landmarks cannot be directly accessed and are only estimated. Therefore, the aim of this study was to develop a workflow that allows accurate tracking of landmark-based femoral and tibial coordinate systems and their associated bone geometries in human cadaveric knees with intact knee capsule during dynamic testing.

Methods

This in vitro study used 15 fresh-frozen human cadaveric knees from hip center to malleoli with intact capsule and soft tissue approximately 10 cm superior and inferior to the knee joint space. Landmark-based femoral and tibial coordinate systems were generated by using segmented CT scans of the specimens. During preparation, the proximal and distal segments of the joint were skeletonized and measuring points were attached to the bones. 3D fittings of femur and tibia were then performed by aligning the segmented CT scans to previously acquired 3D point clouds of each bone (ARAMIS 12M, GOM Metrology GmbH, Braunschweig, Germany). To ensure accurate alignment, visual and quantitative inspections of the 3D fittings were conducted from different perspectives. Subsequently, 3D fitting information were saved and femur and tibia were transected and embedded to allow fixation in a six degrees of freedom joint motion simulator (Advanced Mechanical Technologies Inc., Watertown, USA). After mounting the specimen, the previously generated 3D fitting information of the segmented CT scans were again projected onto the residual bones using the measuring points. In this way, the 3D information of the complete femur and tibia was available even after the bones were cut. Based on this information, the relative position of the femoral and tibial coordinate systems was recorded and transferred to the joint motion simulator. Afterwards, the specimens were subjected to dynamic testing. During testing, the relative position of femoral and tibial coordinate systems was recorded by the joint motion simulator.

Results

Quantitative inspections of the 3D fittings using a tactile measuring instrument resulted in a mean deviation of 0.27 ± 0.21 mm between the real bone and the 3D fitted, segmented CT scan (Fig. 1).

Figure 1: Cadaveric femur with measuring points (green), 3D fitted, segmented CT scan (blue) and deviations between the real bone and the 3D fitted, segmented CT scan at specific points.

Discussion

The high accuracy of the 3D fitting demonstrates that this novel approach enables accurate measurement of tibiofemoral kinematics using landmark-based coordinate systems with intact knee capsule. Furthermore, knowledge of the relative positions of femoral and tibial bone geometries, rather than just their coordinate systems, also allows multiple analyses such as the projection of the flexion axis and flexion facet centers (FFC) onto the tibial plane. This enables the measurement of condylar motion [3] with intact knee capsule (Fig. 2). In addition, this novel approach allows subsequent transformation to kinematics of different landmark-based femoral and tibial coordinate systems, what is necessary when comparing data with different underlying definitions [2].

Figure 2: Projection of the femoral flexion axis and the FFCs onto the tibial plane (a) at different flexion angles (0°, 30°, 45°, 60°, 90°), showing condylar motion (b).

References

TIBIOFEMORAL GAPS OF HUMAN CADAVERIC KNEES BEFORE AND AFTER SACRIFICING BOTH CRUCIATE LIGAMENTS

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Introduction

Implant alignment and the resulting knee stability are crucial factors that affect short- and long-term outcomes of total knee arthroplasty (TKA) [1]. While the goal of gap balancing is to create equal and symmetric flexion and extension gaps to obtain correct soft tissue balance, it was shown that gaps in the native knee are neither equal nor symmetric through the arc of flexion [2]. However, tibiofemoral gaps of native knees are so far measured after tibial-cut and resection of the anterior cruciate ligament (ACL), while the “true” native gaps are mostly unknown. Therefore, the objective of this study was to quantify the tibiofemoral gaps of native knees at different flexion angles prior to tibia and ACL resection and to investigate changes after sacrificing both cruciate ligaments.

Methods

Eleven fresh-frozen human cadaveric knees were tested on a six degrees of freedom joint motion simulator (Advanced Mechanical Technologies Inc., Watertown, USA) by applying 100 N distraction force for 25 s at different flexion angles (0°, 30°, 45°, 60° and 90°) and different stages of resection (native knee and after resection of the cruciate ligaments) with all other forces/moments maintained at 0 N/Nm. Before testing, femur and tibia of each specimen underwent a complex 3D fitting process (ARAMIS 12M, GOM Metrology GmbH, Braunschweig, Germany) using segmented CT scans containing landmark based femoral and tibial coordinate systems. During testing, the relative position of femoral and tibial coordinate systems was tracked by the joint motion simulator. This allowed subsequent positioning of the segmented CT scans relative to each other to measure the tibiofemoral gaps medially and laterally along the mechanical axis of the tibia.

Measured gaps were normalized to the native medial gaps at 0° flexion to enable comparison of the specimens. Mean standardized gaps and standard deviations were calculated across the eleven specimens.

Results

Native medial and lateral gaps were tightest in extension, increased mostly until 30° flexion, then only showed a small increase until 60° and a slight decrease again at 90°. The lateral native gap was larger than the medial gap throughout the complete range of flexion. After resection of the cruciate ligaments, the gaps increased on both, the medial and lateral sides. In contrast to the native knees, the gaps continued increasing until 90° flexion.

Discussion

It was shown that the tibiofemoral gaps in native knees, prior to tibia-cut and ACL resection, are neither equal nor symmetric with a markable increase until 30° flexion. This may affect knee stability in mid-flexion after gap balanced TKA. Furthermore, sacrificing both cruciate ligaments resulted in a greater flexion-extension mismatch than in native knees.

References

PARACRINE EFFECTS OF MACROPHAGE PHENOTYPE ON TENDON TISSUE REMODELING

Hannah Brouwer1,2*, Amal Mansoor1,2*, Luuk Verberne1,2, Carlijn Bouten1,2, Anthal Smits1,2, Jasper Foolen1,2


Introduction
Tendinopathy is characterized by tissue degeneration and the transformation of the normally aligned extracellular matrix (ECM) towards a disorganized ECM. Simultaneously, polarized tenocytes change into randomly oriented tenocytes [3]. Restoration of the healthy tissue organization is an important challenge to restore its function. Macrophages are thought to be one of the key regulators during remodeling, and their polarization into a spectrum of phenotypes is hypothesized to play an important role in both tissue remodeling and fibrosis [2], being influenced by environmental cues such as cytokines and topographies [1]. The interplay between macrophages and tenocytes, and how this influences tendon remodeling remains unknown. In order to get a better understanding of the processes involved, we aim to elucidate the effect of paracrine signaling of distinct macrophage phenotypes on tendon-like tissue remodeling.

Methods
3D constrained microtissue platforms were used in vitro to create aligned tendon-like tissues consisting of tenocytes in a collagen type I gel (Figure 1). The microtissues were cultured in conditioned media (CM) from macrophages in three different biochemically induced polarization states, (IFN-γ+LPS stimulated M1, IL-4+IL-13 stimulated M2a, and IL-10 stimulated M2c). Microtissue contraction, tenocyte gene expression, cellular orientation, and collagen organization were analyzed to get more insight in the remodeling behavior.

Figure 1. 3D microtissue model using constraints [3]

Results
Macrophage-secreted factors showed to influence tenocyte tissue remodeling by differences in actin orientation (Figure 2A), collagen organization (Figure 2B), and gene expression (Figure 2C). Culturing in M1-CM resulted in less anisotropically orientated actin and collagen, and less expression of remodeling genes compared to M2a- and M2c-CM. Culturing in M2a- and M2c-CM resulted in a similar orientation of actin and collagen, while higher remodeling gene expression in M2c-conditioned samples, and higher collagen expression in M2a-conditioned samples was observed.

Discussion
Macrophage-secreted factors were shown to influence tenocyte tissue remodeling in terms of orientation and tenogenic marker genes. M1-CM resulted in less anisotropic tissue orientation and lower expression of tissue remodeling genes, indicating less tissue remodeling, compared to M2a- and M2c-CM samples. No clear differences between M2a- and M2c-CM samples could be found. Next, a transwell co-culture will be performed to further examine the paracrine interplay between macrophage phenotypes and tenocytes during remodeling, and to identify which paracrine factors (e.g. cytokines) are the main modulators. Further unraveling of the interplay between macrophages and tenocytes will provide us with new targets to steer functional tendon healing.

References
TRANSCATHETER MITRAL VALVE REPLACEMENT: ASSESSMENT OF LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

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Introduction
A majority of patients with severe mitral regurgitation (MR) is not eligible for surgical repair or replacement of the affected heart valve due to high surgical risk. Thus, interventional therapies such as transcatheter edge-to-edge replacement (TEER) or transcatheter mitral valve replacement (TMVR) are promising approaches to provide treatment for this patient group. However, the wide success of catheter-based replacement of the aortic valve could not yet been facilitated with TMVR, and this technique is still associated with high mortality [1]. Reasons for this are strong differences in treatment strategies, etiologies, as well as the anatomical challenges in aortic stenosis and MR. In this study we investigate whether in-silico modelling can be used to assess the patient-specific risk of left ventricular outflow tract obstruction (LVOTO) after TMVR, a condition that is associated with intra- and post-procedural mortality [2]. LVOTO can occur due to the TMVR device protruding into the left ventricle, already narrowing the LVOT. Furthermore, the device displaces the anterior mitral valve leaflet into the LVOT to which it can be entrained, worsening the obstruction.

Methods
The patient-specific anatomy of the left ventricle, the mitral valve, and the aorta was reconstructed from time-resolved computed tomography data in the systolic state. Subsequently, a virtual device is implanted using a finite element approach in which both device and anatomy are modelled as shell-elements. The tissue is modelled as linear elastic material, whereas the device is modelled as growing rigid body reaching its full deployment independent of the tissue properties. This device implantation is performed using the same device (model, size) as chosen in the real treatment. However, several positions varying in depth of the device into the ventricle, as well as tilting between the mitral valve and device axis are simulated. For each device configuration, a steady-state hemodynamic simulation is performed using a finite volume approach (STAR-CCM+, Siemens PLM). The steady state uses a peak-systolic volume flow rate measured from the pre-interventional stroke volume (SV) of the patient and accounting for the reduction of the SV due to treatment of the MR. Similar to the device position, the volume flow rate is varied, resulting in multiple simulations per patient. The following parameters are evaluated for each simulation: resulting minimal cross-sectional area in the neo-LVOT, the maximum velocity in the LVOT, the pressure gradient, and the force resulting from the pressure-distribution on the anterior mitral leaflet.

Results and Discussion
Computational modelling was shown to be a promising approach for identification of LVOTO risk assessment, as it provides not only detailed understanding of the anatomical configuration of the heart and the device but also provides functional information [3]. However, modelling of the anterior leaflet is usually omitted. This study includes the anterior mitral valve leaflet but opts for a strongly simplified numerical model at first. However, this model is evaluated on large variation of device positions as well as hemodynamic boundary conditions. The reason for this approach is, that necessary information for patient-specific modelling, such as information on the patient-specific tissue properties or the post-interventional SV will not be available from clinical routine data used for planning. Additionally, the implantation procedure itself is also affected by uncertainties, making it impossible to identify the exact configuration a-priori. Thus, we decided to simulate a set of different configurations to assess the entire physiological envelope of possible configurations of device position and hemodynamic boundary conditions. As this study is currently ongoing, only preliminary results are yet available. The methods will be applied to ten patients and results will be compared against post-interventional follow up data, to assess viability of individual LVOTO risk assessment.

References
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INTER-SPECIES DIFFERENCES IN PULMONARY ARTERY MORPHOMETRY AND HEMODYNAMICS

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2. Charité – Universitätsmedizin Berlin; Germany

Introduction

Large animal models, such as pigs or sheep, are commonly used in pre-clinical studies for evaluation of efficacy and safety of cardiovascular implantable devices such as heart valve prostheses. In-silico models for device evaluation, as for example finite element simulation of implantation procedures, might allow to omit animal experiments altogether in the future. However, these models might already provide valuable information regarding differences in mechanical and hemodynamic properties between human and animals, enhancing the information gathered from pre-clinical trials as well as the translation from animal models towards clinical application. In this study, the pulmonary artery of sheep, pigs, and humans were compared with respect to their anatomical and hemodynamic similarity focusing on parameters relevant for assessment of devices to be implanted in the pulmonary artery. The aim of this analysis was to understand whether these animal models adequately mimic the parameter ranges observed in human patients.

Methods

For this study, the subject-specific anatomy was reconstructed from CT image data, whereas the hemodynamic information was calculated using computational fluid dynamics.

The anatomy reconstruction was performed mostly manually using diastolic image data of 14 ovine, 41 porcine as well 48 human pulmonary arteries. For subsequent hemodynamic simulations, the reconstructed surface geometries had to be smoothed and truncated at all vessel in- and outlets. Anatomical parameters, such as the lengths of the main (MPA), left (LPA) and right pulmonary artery (RPA), their diameters, curvatures as well as the bifurcation angle between the LPA and RPA were calculated automatically, using a centerline-based approach.

To collect information on the subject-specific hemodynamics within the pulmonary artery, simulations were conducted using a finite volume solver STAR-CCM+ (v. 17.04, Siemens PLM). For some data sets also in-vivo measurements of the volume flow waveform in the MPA were available and were used as boundary condition. For subjects where this information was not available, average waveforms that were matched to the subject’s stroke volume and heart rate were used. Due to lack of information regarding the subject-specific pulmonary resistance, zero pressure boundary conditions were used for all outlets. The parameters to be evaluated were velocities, wall shear stresses and the oscillating shear index.

Results and Discussion

The anatomy of the pulmonary artery featured distinct differences between the three species. While lengths and diameters were roughly comparable, especially the diameter changes observed in humans were more rapid than that in both animals. This was most pronounced in the first bifurcation where the MPA splits into LPA and RPA. Furthermore, relevant differences in the curvatures of the LPA and RPA as well as the bifurcation angle between these two vessels were observed for the three species (see Figure 1).

Evaluation of the hemodynamic parameters is still ongoing. Especially due to the changes in curvatures and the bifurcation angle, inter-species differences in the hemodynamic parameter distributions are to be expected.

Quantification of those differences might allow to better understand the intricate differences between large animal models and human application and therefore lead to better designed animal experiments in the future. However, ideally computational simulations will provide an outright alternative to animal testing, if feasibility of assessing device effect and efficacy using these models can be demonstrated.

Figure 1: Box plots illustrating the differences in distributions of exemplary anatomic parameters between the three species.

Acknowledgements

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THE HARD REALITY OF SCATTERED DATA TO PREDICT HEART RHYTHM DISORDERS

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Introduction
Survivors of myocardial infarction (MI) have an increased risk to develop scar-related ventricular tachycardia (VT) years later. A VT is a heart rhythm disorder which may lead to sudden cardiac death. Guidelines, based solely on symptoms and left ventricular function, insufficiently identify high-risk patients. We envision digital twins (DTs) as a solution. A DT is a virtual copy of your patient which can consider multiple, time-evolving aspects of the underlying pathophysiology by integrating evidence-based medicine, data-driven models and mechanistic models into one hybrid VT prediction model (Fig 1)[1]. We postulate that including time-evolving aspects of the pathophysiology and using hybrid models, possibly leads to better VT predictions.

Figure 1: Schematic of a digital twin.

An interesting approach to develop such a DT can be the fast-scale-slow-scale model of Regazzoni et al. [2]. This model uses mechanistic models to simulate the current state of a patient (fast time scale, milliseconds to hours), whereas the change of parameters, i.e., the disease progression, was captured by a data-driven model (slow time scale, days to years) (Fig 2).

Figure 2: Schematic of the fast-scale-slow-scale model

To develop such a DT there is a need for time-evolving data that are representative for the patient’s state over time. However, although an abundance of clinical data is available, they are multimodal, heterogeneous, unstructured and contain missing values. Therefore, before a hybrid model can be created, understanding of the available data is essential. This is the primary aim of this study. Additionally, coupling different multimodal data and analyzing their time-evolving trends might already unravel new useful insights.

Methods
We gathered existing multimodal data (between 1995-2022) of 10 VT and 36 matched MI patients without VT. Dashboards are created to visualize the data and perform exploratory analyses providing the main characteristics and insights in the presence and heterogeneity of the data including clinical context. Subsequently, statistical analysis suggests which data could be of interest as input for the hybrid model.

Results
Lab, ECG, and vital functions measurements are studied. Additionally, diagnosis, medication, and admission data provide context to the results (Fig 3).

Figure 3: Example of a few dashboard figures.

Discussion
To optimize VT prediction, DTs are needed integrating patient-specific data in a hybrid way using data-driven and mechanistic models. Data is multimodal, heterogeneous, unstructured and contain missing values, making it important to critically select which data to include as model input. Dashboards and statistical analysis are of great usage for this.

References

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USING AN EQUIVALENT SURFACE TO QUANTIFY CONGRUENCE AND CONTACT VARIABILITY IN JOINTS

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Introduction
The level of congruence (or geometric conformity), between the articulating surfaces of a synovial joint can vary substantially between people. It has been hypothesised that a more incongruent instance of a joint could be more at risk of developing osteoarthritis [1]. However, previous methods of quantifying congruence have required detailed mathematical descriptions of the articulating surfaces and their relative position [2,3]. In this talk, we will: (1) share a recently published new method of measuring joint congruence [4], that works directly from the 3D segmented points clouds; and (2) show how the concept of an ‘equivalent surface’ (employed in our new method) has inspired application of statistical shape modelling to the variability of articular contact.

Materials and Methods
The first step of our new methodology is performing a finite element (FE) simulation of an elastic layer compressed between each set of segmented bones. The results of this are then interpreted using the elastic foundation model (Figure 1), enabling an equivalent, but simpler, contact geometry to be identified. From this, the equivalent radius (quantification of joint congruence) is found. This defines the radius of a sphere contacting plane (or “ball on flat”) that produces an equivalent contact to that in each joint. The minimal joint space width (in this joint position) can also be estimated from the FE simulations. The new method has been applied to ten healthy instances of the thumb metacarpophalangeal (MCP) joint.

Results
The ten thumb MCPs had similar levels and variability of congruence as other diarthrodial joints that have been characterised previously [5] and showed no relationship between congruence and joint space width (Figure 2).

Discussion
The new method can be used to perform efficient quantification of congruence directly from CT- or MRI-derived bone geometry in any relative orientation, lending itself to large data sets and coupling with kinematic models. However, we believe there is more that can be exploited from the concept of an equivalent surface, which is fundamental to this quantification of joint congruence.

Current work focusses on generating a Statistical Shape Model (SSM) to describe the dominant modes of variation of the equivalent surface generated in each of the ten healthy thumb MCP joints. Using a SSM methodology, it is possible to better understand joint contact variation rather than interrogate the whole bone geometry.

References

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A 3D MECHANOREGULATORY BONE HEALING MODEL COMBINING PATIENT-SPECIFIC GEOMETRY AND INDIVIDUAL LOAD DATA

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Introduction
The healing process of fractured long bones is a very complex process consisting of both biological and mechanical factors. In the last decades, simulation and modelling of bone healing have been used to understand the main mechanisms of the process, to develop implant designs and to explore specific clinical questions, cf. [3]. However, previous research on bone healing algorithms and strategies has been limited to 2D and simpler 3D geometries and has only used real patient geometry and image data prototypically, if at all. Therefore, we purposely chose real clinical data in both imaging and motion capturing as the basis in this study and combined them with currently available bone healing models.

Methods
The basis of the simulations is our established workflow consisting of model generation by segmentation of clinical imaging data combined with a musculoskeletal simulation based on the patient’s motion capturing data, cf. [1]. This process allows us to perform individualized biomechanical simulations of the patient’s bone-implant system, providing the macro-level information underpinning our mechanoregulatory bone healing model, cf. [2]. Based on the macroscopic mechanical stimulus, different processes can then be simulated at the cellular level (including migration, proliferation, differentiation of the different cell types) and then a new stiffness of the fracture as well as the callus area can be determined. With this new stiffness distribution, the macroscopic simulation can be performed again to get a new deformation state as new input for the mechanoregulatory healing model resulting in a loop describing a possible healing process. In our model, we have combined the different state of the art models from literature, cf. [3-6] for the inflammatory phase, the soft and hard callus phase, the biochemical signals and the blood perfusion. We then apply these models to data from a real patient and investigated the influence of different parameters and different numerical concepts on the results and their interpretation.

Results and Discussion
Figure 1 illustrates the overall framework, starting with a complex segmentation process which is manually controlled in order to get a correct callus and fracture gap. After motion capturing of the patient during a normal step forward, a musculoskeletal simulation is performed resulting in joint forces as patient-specific boundary conditions for the macroscopic simulations. The implemented healing models are currently being used to approximate the simulation results to the actual healing processes based on X-ray images through first parameter identifications. Since most models from the numerical point of view consist of coupled convection-diffusion-reaction equations and these are partially convection and/or reaction dominant, various discretization and stabilization concepts and their influence on the results must also be widely considered.

Figure 1: Illustration of our implemented workflow. Segmentation and model generation from CT data, musculoskeletal simulation based on patients’ motion capture data and simulation of the mechanical stimulus in the fracture gap as basis for the mechanoregulatory bone healing model.

References

Acknowledgements
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SIMILAR KNEE MECHANICS BUT DIFFERENT MUSCLE ACTIVITY: TIME FOR AUGMENTED ACL REPAIR AS ALTERNATIVE ACL SURGERY

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Introduction
InternalBrace™-augmented anterior cruciate ligament repair (ACL-IB; Arthrex Inc., USA) for proximal ACL ruptures is an alternative to ACL reconstruction (ACL-R). Preservation of the native ACL and no graft harvest in ACL repair is believed to maintain neuromuscular integrity and knee mechanics [1]. We compared knee biomechanics (kinematics, kinetics), ground reaction force (GRF), and m. semitendinosus activity within legs of ACL-IB and between ACL-IB, ACL-R and controls.

Methods
Twenty-nine patients 2 years after ACL-IB, 27 sex- and age-matched patients 2 years after ACL-R (hamstring tendon autograft) and 29 matched controls completed walking analysis. Knee kinematics (rotations, anterior translation) and kinetics were obtained using the Point Cluster Technique [2] and the Conventional Gait Model [3], GRF using force plates, and semitendinosus muscle activity using surface electromyography. Parameters were time-normalized to gait cycle (GC), muscle activity amplitude-normalized to activity during 30-45%GC (terminal stance), and compared within the legs of ACL-IB (paired t-test) and between ACL patients (involved legs) and controls (non-dominant leg, one-way analysis of variance (ANOVA) and posthoc Bonferroni tests) using statistical parametric mapping (P<0.05). Significant different intervals >2%GC were interpreted and mean of maximal differences in this interval calculated (mDiff).

Results
A small difference was observed within ACL-IB in posterior GRF (8-11%GC, mDiff -3%body weight (BW), P=0.043). Compared to controls, ACL-IB had significantly less anterior tibia position around heel strike (98-100%GC, P=0.016 and 0-3%GC, P=0.015, mDiff -8.9mm) and ACL-R significantly lower internal rotation moments (34-41%GC, mDiff -0.04Nm/kg, P<0.001). However, in these parameters a similar (non-significant) deviation was observed in the respective other ACL group compared to controls. While semitendinosus muscle activity did not differ between patients and controls, its activity was significantly higher in ACL-R than in ACL-IB prior heel strike (90-95%GC, mDiff 5*relative activity, P=0.003, Fig. 1).

Discussion
Observed mDiff in GRF within ACL-IB were within the

Figure 1: M. semitendinosus activity in ACL-IB (blue); ACL-R (red) and controls (green). ANOVA with posthoc results (grey area indicates significant different interval) 95% confidence interval of heathy subjects [4]. Hence, we did not observe relevant leg asymmetry in knee biomechanics, GRF, and muscle activity 2 years after ACL-IB. Comparison between patient groups suggest similar walking adaptations in knee biomechanics, while semitendinosus muscle function seems to differ. Hamstring muscles have been shown to influence the magnitude and timing of ACL loading [5] and may play a role in ACL-protection [6]. Therefore, the more similar activity after ACL-IB compared to controls may highlight the importance of preserving this muscle and its function as an agonist of the injured ACL. However, knee biomechanics still appear to be affected by the initial ACL rupture and may not return to normal. These results suggest no inferiority in ambulatory knee and semitendinosus function after ACL-IB, and strengthen the rationale for less invasive ACL-IB of proximal ruptures as alternative method to ACL-R. If these results are also present compared to patients using other grafts (e.g., patellar tendon) is still to be determined.

References

Acknowledgements
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ENGINEERING CURVED MEMBRANES FOR DRUG ABSORPTION TESTS IN THE PRESENCE OF ARTIFICIAL MUCUS

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Introduction

Investigating drug absorption is fundamental for assessing their efficacy. In the case of inhaled drugs, the ability to cross the alveolar barrier is also related to the presence of the mucosal lining. In healthy conditions airway mucus is a fundamental defense against toxins and pathogens, but diseases such as cystic fibrosis may alter mucus viscosity, hindering drug absorption [1]. Currently, standard in-vitro models are based on flat 2D semipermeable membranes at the air-liquid interface. Only recently have some studies attempted to replicate the spherical alveolar geometry [1, 2] or the presence of a diseased mucus layer [3]. However, they still lack lung properties known to modulate translocation such as stretchability and motion.

To this end, we developed transparent spherical membranes which replicate the alveolar architecture in a more accurate manner. They can be integrated in dynamic bioreactors [1] and coated with artificial mucus formulations to increase the relevance of the model for the study of drug absorption in pathophysiological conditions.

Methods

The membranes were fabricated by casting 1% w/v agarose – 5 % w/v gelatin solutions in custom moulds (Fig.1A). After agarose crosslinking (20 minutes at 4°C), the samples were incubated overnight at 37°C with 100 U/g microbial transglutaminase (mTG) enabling gelatin crosslinking. The gels were dried for 24h at 40°C and sterilized under UV for 30 minutes. Finally, the Agarose-Gelatin (AgGel) membranes were rehydrated in deionised water for 1h. Mechanical tensile tests to break were performed at a constant strain rate (0.2 s⁻¹) and the apparent elastic modulus (E_app) was derived as the slope of the stress strain curve in the linear region.

A549 cells were seeded on the membranes mounted in CellCrown inserts (100.000 cell/cm²) and in PET Transwells as control. Transepithelial electric resistance (TEER) measurement (EVOM – WPI) and bright field images (Olympus) were acquired to assess the presence of an intact monolayer. Then, transcellular and paracellular transport was respectively investigated with FITC-labelled dextran (0.5 mg/mL) and rhodamine (10 μM). Pg-p protein activity was calculated as the percentage of rhodamine passage from the basal to the apical compartment.

Results

The membranes are highly elastic in the range of pathophysiological strains (5-17%) [1] with E_app = 1.07 ± 0.35 MPa and failure stress = 0.13 ± 0.03 MPa.

As shown in Figure 1B, cells adhere and spread on AgGel membranes. Moreover, their performance was comparable with PET controls in terms of barrier tightness and transport features. The lower FITC passage indicated the formation of stronger tight junctions, while the higher Pg-p activity suggested that the membranes are able to promote cell polarization.

Conclusion

Spherical, transparent, and cytocompatible AgGel membranes were fabricated and characterised. Their properties in terms of shape, mechanical behaviour, cell compatibility, and permeability can be exploited for the development of more reliable and human relevant inhalation tests. Further tests are on-going to develop an artificial mucus gel able to replicate healthy and diseased mucus rheology and hence investigate drug adsorption in the presence of mucus and inflammatory cells.

References


Acknowledgements

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Introduction
During prolonged lying and sitting postures, the interaction between an individual and the underlying support surface can lead to damage of the skin and soft tissues, in the form of chronic wounds, such as pressure ulcers (PUs). Pressure monitoring systems have been used to evaluate this biomechanical interaction and determine the optimum postures and pressure relief strategies [1]. However, the short-term nature of this measure provides limited indicators of posture and mobility, which represent one of the primary interventions for PU prevention [2]. Our recent studies demonstrated the performance of selected biomechanical parameters derived from continuous pressure monitoring (CPM) [3,4] and an intelligent data processing involving convolutional neural network (CNN) was developed to detect both the frequency and type of postures. The aim of this study was to translate the CPM and algorithms to spinal cord injured (SCI) patients, deemed at risk of developing PUs [5,6].

Methods
Pressure data were acquired from twelve SCI patients, who were continuously monitored in phase 3 of their hospital rehabilitation. The study was approval by the Health Research Authority (IRAS-244580) and informed consent was provided from each patient. They were assessed on their allocated support surface, e.g., foam or air, using a CPM system (ForeSitePT, Xsensor, Canada) during prolonged periods of lying and sitting (48–72 h). Data was analyzed from pressure parameters and an intelligent algorithm was used to detect both the frequency and type of postures [5]. This involved a subject-specific threshold-based spatial derivative signal for detection of movements that offloaded vulnerable areas (MOVAs) and CNN for prediction of postures [4] (Figure 1). An independent clinical interpretation of movements and postures was retrospectively performed by a research nurse (SF). This information provided a subjective means to verify the events as predicted by the algorithm. The frequency of distribution of movement was correlated with spinal cord injury level and incidence of hospital acquired PU.

Results
The algorithm had an ~80% accuracy in detecting MOVAs when compared to clinical observations. Data revealed that higher SCI injury levels resulted in lower frequency of movement and larger gaps between MOVAs (Figure 2). These had a corresponding high rate of PU, when compared to low level injuries e.g., lumbar.

Discussion
Prediction of posture and mobility can be achieved by combining continuous pressure monitoring and intelligent algorithms. The study demonstrated the robustness of both the derivative and CNN in detecting MOVAs. This was successfully translated to a vulnerable cohort of individuals with SCI, revealing distinct trends in movement dependent on injury level with some tentative trends with PU incidence.

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Acknowledgements
Clinical data were acquired by the research nurse (SF) supported by Duke of Cornwall Spinal Treatment Centre, Salisbury, UK. This work was supported by a UK EPSRC award (EP/W031558/1).
**IMAGING AND MECHANICAL CHARACTERISATION OF HUMAN BLOOD CLOT ANALOGUES WITH DIFFERENT COMPOSITIONS AND DEGREES OF CONTRACTION**

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**Introduction**

Stroke is the 2nd leading cause of death worldwide. Endovascular thrombectomy is the current standard of care for patients with large vessel occlusions. However, these procedures are not effective in up to 40% of the cases [1]. Thrombi causing stroke are diverse in their composition and mechanical behaviour. In addition, clot composition and contraction are known to affect thrombus behaviour [2]. Computed tomography (CT) could be a suitable modality to assess thrombus properties prior to the thrombectomy [3]. The purpose of this study is to examine the imaging and mechanical properties of clot analogues with different RBC compositions and degrees of contraction.

**Methods**

Clot analogues were made from citrated whole blood of six healthy human donors. Clots were made with five different red blood cell (RBC) contents: 0, 25, 77, 94 and 99%, which span the range of compositions from ex vivo thrombi. Also, clots were made with three different platelet concentrations: 30*10³, 90*10³, and 270*10³ platelets/μL, which result in a low, medium, and high level of contraction, respectively. Clinical CT imaging was performed to measure the density. Perviousness, which reflects the clot’s permeability, was quantified by measuring the density after the administration of a contrast agent. Unconfined compression tests were performed and the high strain stiffness was obtained from the slope of the stress-strain curves at 75-80% strain.

**Results**

The compressive stiffness was significantly higher for the highly contracted clots compared to the low contracted clots (Fig. 1A). Within the high and medium contracted clot groups the stiffness tended to decrease with increasing RBC volume (Fig. 1B). Higher levels of contraction increased the CT density values (Fig. 2A). Also, the density values were higher for increasing RBC volume (Fig. 2B). Highly contracted clots tended to have higher perviousness values compared with medium and low contracted clots (Fig. 2C). There was only a significant difference in perviousness between the RBC volume groups within the highly contracted clot group (Fig. 2D).

**Discussion**

We demonstrated that clot compressive stiffness is dependent on both the degree of contraction and RBC content. As expected, the clot CT density increased with increasing RBC content. For the first time we showed that the density also increased with increasing degree of contraction. The perviousness appeared to increase with increasing level of contraction, but is only affected by RBC content in highly contracted clots. The implication is that the assessed CT imaging characteristics alone cannot directly characterize a clot’s RBC content and degree of contraction, and may therefore not be predictive of the mechanical behaviour.

**References**


**Acknowledgements**

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PARAMETRISATION OF THE CALCANEUS AND MEDIAL CUNEIFORM

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Introduction
Flatfoot is a condition commonly seen in children and sometimes adults, associated with foot arch flattening or lack of development of the foot arch and extreme foot malalignment. Surgical corrective surgery is one option for extreme cases; however, outcomes can be variable and the multiple factors that affect surgical outcomes are still not clearly understood [1]. Due to a general disagreement on the clinical or radiographic criteria to define this condition, it is still considered by most to be a poorly understood topic and consequently all associated definitions are still somewhat superficial [2]. This explains why it is important to determine the key parameters which define the condition.
This research aims to develop a parametric model to improve understanding of adolescent flatfoot surgery to recognise what influential factors are contributing to surgical outcomes. Differences between two specific bones - the calcaneus and the medial cuneiform, which will be altered in shape by Evans’ surgery – can then be compared between the pre- and post-operative shapes of these bones. The present paper outlines the methodology to achieve these goals within the context of this study.

Methods
The methodology applied here is based on the paper written by Pascoletti et al. (2021) [3] and applied using the MATLAB (v.17, The MathWorks, Inc., Natick, MA, USA) script written by Pascoletti. This method was used to analyse the morphological differences in two bones, the calcaneus and medial cuneiform, using five CT scans of feet acquired from cadavers.
In iso-topological meshes all nodes in the surface mesh are treated as landmarks. They are created implementing some transformations and the RBF (Radial Basis Function) method, where the information of each individual shape in the database related to location, scale and rotation are eliminated to make the shapes comparable. GPA (Generalised Procrustes Analysis) and PCA (Principal Component Analysis) are applied on the database to find the variability model \( \sum + \cdot \) that describes the dataset.

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Results
It was found that three Principal Components (PCs) were needed to explain 98% of the total variance of the dataset for the calcaneus and one PC for the medial cuneiform. A qualitative analysis using images was made comparing an average shape with the relevant PCs. A quantitative analysis was also made comparing the landmarks coordinates of the singular shapes with the average shape.

Discussion
This methodology has the potential to be effective regarding the shape analysis of the calcaneus and medial cuneiform, once applied on the actual pre- and post-operative shapes, being able to tell what these bones have in common and being able to highlight what change has been made to the post-operative bone. More importantly it will make it possible at a later stage to relate the pre- to post-surgery shapes to parametric shape changes and relate these to the surgical outcomes. This study establishes the PCA methodology for the clinical study that will accompany the flatfoot surgery. The implications are immediately obvious and very important, successful surgical outcomes can be related to certain shape changes and these through parametrisation are expressed in numerical form. The final objective then is, evidently, to start foot reconstruction for those predicted and optimum parametrised shape changes, which would lead to better surgical outcomes.

References

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MYOCARDIAL TRABECULAE IN ZEBRAFISH EMBRYOS IMPROVE TISSUE DEFORMABILITY AND REDUCE STRESSES

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Introduction
During the development of the ventricle, the myocardium differentiates into two layers, a compact zone and a trabeculated zone. Cardiac trabeculae are uneven ventricular muscular structures important for proper cardiac function, as malformations in these structures can lead to embryonic death. Trabecular formation, which occurs only on the outer curvature of the ventricle, is a mechanosensitive process, but the biomechanics involved in it is not completely understood. Further, it remains unclear whether these structures confer biomechanical advantages to the heart’s function, and how they might achieve this.

Methods
High-resolution, 4D imaging of zebrafish embryonic hearts at 2, 3, 4 and 5 days post fertilization (dpf) was performed with light-sheet microscopy using the Tg(cmlc2:GFP) line that expresses fluorescence in the myocardium. Motion tracking was performed with our validated algorithm [1], followed by image-based finite element (FE) simulations of tissue mechanics of zebrafish embryonic ventricles.

Results
At 3, 4, and 5 dpf, the trabeculated outer curvature (OC) region has higher contractile deformations compared to the non-trabeculated inner curvature (IC) (Fig 1A). This is likely due to trabeculations being standalone structures with reduced amount of surrounding tissue to constrain their deformations. However, before trabeculation occurs (2dpf) the opposite was true, suggesting that trabeculation has the function of conferring greater tissue deformability to the OC myocardium. We also discovered that between 2 and 3dpf, there is an increase in the curviness of the OC coupled with a reduction in thickness, which lead to higher tissue stresses. Comparing FE of normal trabeculated ventricles to FE of their artificially smoothed-out, non-trabeculated version (Fig 1B-C), trabeculations are found to be effective at reducing OC myocardial stresses, while retaining the same stroke volume and cardiac work. This is achieved by trabeculations providing bridging and bracing support at regions of high curviness and high stress. Results thus suggest that trabeculation also has the function of reducing overall stresses at the OC myocardium. The timing of trabeculation development also coincided with the time point when OC myocardium stresses increased due to geometric changes to the ventricle, corroborating this notion.

Discussion
Here, we discovered that embryonic ventricular trabeculations have two biomechanically beneficial roles: first of all, they improve myocardial deformability to aid contraction motions, and secondly, they reduce stresses in the OC myocardium. This specifically occurs at the developmental time point where stresses elevate due to ventricular curviness and thickness changes. As such, we speculate that trabeculation formation is mechanobiologically cued by high myocardial stresses at the OC. Future work to verify this is warranted.

References

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
CONTRAST-ENHANCED MRA WITH GRASP OUTPERFORMS THE CONVENTIONAL TWIST IN AORTIC DISEASES PATIENTS COHORT

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Introduction

Gadolinium based contrast-enhanced time-resolved magnetic resonance angiography (CE-MRA) techniques depict the anatomy and dynamics of complex vascular structures [1]. This is desirable to reduce the number of invasive procedures with their inherent radiation exposure on patients. TWIST (Time-resolved angiography With Interleaved Stochastic Trajectories) sequence is commonly used to perform a CE-MRA, it is based on Cartesian acquisition and sharing of k-space data between neighbouring time frames [2]. This trajectory is prone to motion-related image artefacts, which may result in spatial blurring of vessels. A recently introduced time-resolved 3D acquisition technique is GRASP (Golden-angle radial sparse parallel MRI) sequence, combining compressed sensing, parallel imaging, and golden-angle radial sampling and is less sensitive to motion compared to Cartesian acquisition types [3]. The use of GRASP for CE-MRA has not been reported yet. The aim of this patient study is the qualitative and quantitative comparison between TWIST and GRASP on a cohort of patients with aortic diseases.

Methods

N=30 patients (60.87±16.11 y.o., 7 females) with various chronic aortic diseases underwent a clinical examination on a 1.5T scanner (Magnetom SolaFit, Siemens) including a TWIST and a GRASP sequence. For the qualitative assessment, a radiologist assessed overall image quality, contrast, vessel sharpness and image artefacts on a 4-points Likert scale (1=excellent, 4=non-diagnostic). For the quantitative assessment, full width at half maximum (FWHM), temporal signal-to-noise ratio (tSNR) and signal to noise ratio (SNR) [4] were calculated from normalized signal intensity time courses in regions of interest (ROIs) at three aorta levels (see Figure 1). Vessel sharpness (vs) was calculated from intensity profiles at the same aorta levels [5].

Discussion

The GRASP sequence provided a superior overall image quality index, resulting from the qualitative scores of soft tissue contrast, sharpness and vascular contrast level – despite an increased artifact level compared to TWIST (Figure 2). The level of streaking artifacts increases with the level of undersampling. However, most streaking artifacts appeared in the periphery of the field-of-view (FOV) and the images remained of diagnostic value in the aortic regions. The improved vessel sharpness for all ROIs in GRASP is assumed to result from the higher in-plane resolution and from reduced sensitivity of the radial trajectory to respiratory motion. The higher levels of tSNR in GRASP data (also visible in smoother signal-time-courses in Figure 1) are likely linked to the smaller temporal footprint (temporal resolution). In TWIST, k-space lines are taken from a wider time range than TWIST resulting in the temporal footprint three times higher than temporal resolution (based on k-space center A=25% and sampling density of k-space periphery B=33%) [2]. Contrary, the FWHM was lower for TWIST in all locations indicating the weighting of the k-space center for the image contrast in TWIST (scan time for A~1s).

Conclusion

GRASP outperformed TWIST in temporal SNR, SNR, vessel sharpness and reduction in image blurring; streaking artefacts were clearly visible, but did not affect the diagnostic image quality. Including GRASP in the clinical protocols may improve diagnosis of aortic diseases patients.

References


Figure 1: Signal intensity over time for ascending aorta (AA, red) and descending aorta (DA_pulm, blue) at the level of pulmonary trunk and descending aorta at the level of infrarenal arteries (DA_renal, green) for TWIST and GRASP.

<table>
<thead>
<tr>
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<th>TWIST</th>
<th>GRASP</th>
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<tbody>
<tr>
<td>vascular contrast</td>
<td>2.6±0.51</td>
<td>1.46±0.52</td>
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<tr>
<td>vascular sharpness</td>
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<td>image artefacts</td>
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<td>overall image quality</td>
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<td>soft tissue contrast</td>
<td>1.5±0.50</td>
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Figure 2: (left) Qualitative assessment presented as mean ± standard deviation; (right) overall image quality comparison between GRASP (left) and TWIST (right).
MODELLING AORTIC FLOWS: IMPACT OF WALL DISPLACEMENTS ON LARGE-SCALE HEMODYNAMIC COHERENCE IN ASCENDING AORTA

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Introduction

The translation of Computational Fluid Dynamics (CFD) as supportive technology in clinics is hampered by the uncertainties affecting personalized blood flow simulations. The aorta is characterized by not negligible wall displacements [1], but the rigid-wall assumption is largely adopted. This represents a major source of uncertainty, as the real need for introducing aortic wall displacements in computational models is still debated. This study analyzes the impact of wall displacements on the large-scale flow structures in the healthy human ascending aorta (AAo). On three subject-specific models, two CFD simulations are performed: (1) assuming rigid walls, and (2) imposing personalized wall displacements through a moving-boundary method based on a radial basis functions (RBF) mesh morphing technique [2]. The impact of wall displacements on AAo large-scale hemodynamics is analyzed in terms of axial blood flow coherence (quantified applying a network approach [3]), secondary flows, and helical flow because of its physiological significance.

Methods

Aortic geometries were reconstructed at ten phases of the cardiac cycle from dynamic CT scans. On each analyzed subject two modelling strategies were adopted: (1) a rigid-wall CFD simulation performed on the baseline geometry at 0% (late diastole) phase of cardiac cycle; (2) a CFD simulation imparting subject-specific aortic wall displacements applying an RBF mesh morphing on the reconstructed transient geometries [2]. Simulations for the rigid- and moving-wall cases were performed using the finite volume method to solve the discretized Navier-Stokes equations on tetrahedral meshes, assuming blood as Newtonian. Further details on the simulation setup are reported elsewhere [2]. The effect of the aortic wall displacements on axial flow coherence was investigated building “one-to-all” networks [3,4] for the rigid- and moving-wall aorta, measuring the similarity of blood axial velocity waveforms $V_{ax}(t)$ (representing the generic network nodes) in the AAo with the subject-specific blood flow rate waveform $Q(t)$ (representing the network’s reference node) at the AAo inlet (Fig. 1). In each network, the link between the reference node and the $i$-th node was weighted by the correlation coefficient $R_{Q,i}$ between $Q(t)$ and $V_{ax,i}(t)$ at that node. The anatomical length of persistence of the $Q(t) - V_{ax}(t)$ correlation was quantified computing an ad-hoc network metric called Average Weighted Curvilinear Distance (AWCD) (Fig. 1) [4]. The impact of aortic wall displacements was also investigated in terms of secondary flow patterns and helical flow intensity and topology.

Results and Discussion

Results from the “one-to-all” analysis are reported in Fig.1 for one explanatory subject. Notably, $R_{Q,i}$ volume maps of the rigid- and moving-wall aortas are very similar. In general, $Q(t)$ waveform markedly shapes $V_{ax}(t)$ waveforms independent of wall displacements ($R_{Q,i}$ median values above 0.95). The anatomical length $AWCD$ of axial flow coherence with the driving proximal $Q(t)$ waveform (Fig. 1) varies from the 42% to 45% of the total AAo length for all subjects, with a 4.4% maximum difference between rigid- and moving-wall models. Contrarily, wall motion impacts more markedly secondary flow patterns and helical flow topology, whereas cycle-average helicity intensity remains almost insensitive to aortic wall displacements.

Conclusion

We conclude that the rigid-wall simplification can be a valid assumption in CFD simulations of the aortic large-scale fluid structures, providing a reasonable hemodynamic description in the context of potential clinical practicality. This is particularly true when helical flow, an indicator of physiological significance in arteries [5], is analyzed.

References

RUNNING IN CHILDREN WITH HEMIPLEGIA USING A NEW POSTERIOR LEAF ANKLE FOOT ORTHOSIS

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Introduction
Cerebral palsy involves muscle weakness and spasticity that cause alteration in gait and running cycle [1]. These difficulties are usually overcome by using orthoses, in particular ankle-foot orthoses (AFOs). However, the existing AFOs are unsuitable for sport or running practice both from a design point of view and for prescription of use. Therefore, the aim of this study was to compare the kinematics, kinetics, and spatiotemporal parameters during running with a new AFO specifically designed for sport activities versus barefoot condition.

Methods
Eighteen children with a diagnosis of hemiplegia (GMFCS I-II) were recruited at IRCCS Eugenio Medea and experiments were conducted with the approval of its Ethical Committee. Each participant was provided with a custom made AFO (an evolution of the Carbon Modular Orthosis [2]), specifically designed by ITOP Officine Ortopediche SpA to support motor activities. Running was evaluated in three conditions, at self-selected speed: (i) barefoot; (ii) upon delivery of the AFO (t0); (iii) after an adaptation period of approximately one month (t1).

Data acquisition was performed through eight-camera optoelectronic system (BTS Smart DX 700) and four coupled force platforms (BTS P-6000) using Davis protocol. For each participant only one valid trial for each lower limb for each condition was chosen. Kinematic and kinetic data were processed using an ad hoc script in Matlab®; SPM was used to detected statistical differences among the conditions. A non-parametric bivariate ANOVA (α = 0.05) was implemented (an independent factor, affected vs non-affected limb, plus a repeated-measures factor, barefoot vs with orthosis) followed by Mann-Whitney post hoc tests. The spatio-temporal parameters were instead analysed thanks to Minitab software, through which a 3x2 ANOVA (α = 0.05) with Tukey’s post hoc test was carried out.

Results
Figure 1 shows the affected ankle dorsi-plantarflexion in the running cycle in the three tested conditions (barefoot in black, with the new AFO at t0 in green and at t1 in blue).

Table 1 shows the effects of the new AFO on running spatio-temporal parameters: stride length, stride duration, speed, step length and cadence.

Discussion
During barefoot trials the recruited participants shown the equinus foot deviation, a prolonged plantarflexion during the entire cycle (Figure 1) and a power generation capacity at push-off 60% lower than physiological. The new AFO proved to be effective in correcting the foot position at initial contact (0-5%, p < 0.001) and to significantly reduce ankle plantarflexion throughout the running cycle (30-100%, p < 0.001); however was not able to decrease the deficit at push-off, but rather left it unchanged. The new AFO lead to an increase in stride length and duration, running speed, step length and to a decrease in cadence (Table 1). The elapse of an adaptation period did not seem to have significant effects on kinematics and kinetics; on the other hand, it contributed to increasing stride length, running speed and step length.

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INTRODUCTION

The study of microtubule (MT) mechanics and the pathways involved in the transfer of vibrations between tubulins is crucial to understand how MTs are stabilized within the cell. Indeed, the hierarchical organization of MTs is the basis of their stability, mechanics, and function. Modulation of MTs mechanics can alter cell equilibrium and be exploited in therapeutic approaches in cancer [1]; the MT stabilizer Taxol is a clear example. Therefore, this work aims at shedding light on the effect of atomic structure on MT mechanics, and how changes in tubulin induced by Taxol relate to MT properties, through a computational approach connecting different scales, from atom positions to macroscopic observables.

METHODS

We employed a multiscale approach to investigate the mechanics of MTs by integrating all-atom molecular dynamics (MD) simulations and Protein Structure Networks (PSN) with Normal Mode Analysis (NMA) on Elastic Network Models (ENM). All-atom structures of the dimers, in absence (MT\(^{\text{apo}}\)) and presence (MT\(^{\text{Tas}}\)) of Taxol, were optimized in systems representative of the MT wall in a total of 600ns of MD simulations. In PSN, tubulins were modeled as a graph where amino acids are nodes connected based on their interaction strength. This approach allowed us to obtain information about the propagation of vibrations within the MT, i.e. about mechanical communication between tubulins [2]. 300nm-long MTs were built by fitting tubulin rings onto an Electron Microscopy Density (EMD) map and replicating them axially (8.15 and 8.18 nm step for MT\(^{\text{apo}}\) and MT\(^{\text{Tas}}\)) [3,4] (Fig 1A). In ENM, residues are beads connected with springs if closer than 1.2 nm; we obtained MT vibrational frequencies and mechanical properties from NMA of ENM, assuming it as a hollow cylinder of homogeneous isotropic material [5].

RESULTS

The analysis at the molecular level revealed remarkable differences induced by Taxol. In MT\(^{\text{apo}}\), \(\alpha\)-tubulins mediate the mechanical communication between protofilaments (PFs) (Fig 1B), while the transfer of vibrations is driven mainly by \(\beta\)-tubulin in MT\(^{\text{Tas}}\) (Fig 1C). These results are interesting since Taxol interacts with residues in \(\beta\)-tubulin M-loop involved in MT\(^{\text{apo}}\) communication path. Moreover, Taxol induces loss of structure of the \(\beta\)-tubulin M-loop, known to mediate the interaction between adjacent PFs. At a higher scale, the persistence length (Lp), bending (Eb), shear (G), and Young’s (E) moduli of MT\(^{\text{apo}}\) and MT\(^{\text{Tas}}\) have been computed from NMA vibrational frequencies of 3 MTs, built from MD-derived tubulins. Results highlight that MT\(^{\text{Tas}}\) has increased mechanical properties (Fig 1D), in particular the shear modulus, reflecting the atomistic result that Taxol alters the inter-PFs interaction.

DISCUSSION

Our approach relates microscopic changes induced by Taxol and resulting changes in mechanics with MT stabilization. Taxol interaction with M-loop alters its structure and interferes with inter-PFs communication. This reverberates at a higher scale increasing MT mechanical properties, in particular the resistance to shear forces. Therefore, Taxol can stabilize 300nm-long MTs by strengthening inter-PFs interaction. It will be interesting to analyze the length dependance of this mechanism, providing insights for the design of drugs for cancer treatment and bioinspired nanomaterials.

REFERENCES

A Novel Approach for Examining Motion and Deformation of Left Ventricle: Finite Element Analysis of 3D Echocardiography Data

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Introduction
Stroke volume, ejection fraction, mass and size of the left ventricle (LV) are very important markers that are used by cardiologists in order to assess the global function and disease severity. For a more comprehensive evaluation, however, displacements, velocities, rotation, twist, torsion, strains, strain rates are investigated. For this purpose, data obtained from 2D/3D echocardiography (echo) devices are often analysed by a dedicated software. In the medical community, it is common practice to examine segmental (regional) values. For example, 3D echo data are analysed by dividing the LV endocardial surface into 16 or 17 areas (segments), which consist of several nodes (vortices) and the nodal values are averaged over the segments [1]. In this study, we aim to analyse LV motion and deformation from engineering perspective by using the finite element method (FEM).

Methods
As a first step, we export the tracked endocardial surfaces from 3D echo data by using the software 4D LV-Analysis from Tomtec Imaging Systems GmbH. The software discretizes the tracked surface over 862 nodes with 1720 triangular elements and enables to export the current coordinates of the nodes from the beginning of the systole to the ending of the diastole. Namely, the deformation state of LV endocardial surface is available at each time frame. From a computational perspective, the exported data is equivalent to obtaining the finite element (FE) solution of contracting LV [2]. Once having the deformation state of the LV at hand, one can calculate any deformation related quantity in a pointwise manner such as displacement along preferred directions, strains, rotation and surface curvature.

Results
A sample of echo data is processed into an FEM software and pointwise displacement distribution along z-direction is demonstrated in Figure 1. The preliminary results indicate that the deformation state of a point might not be necessarily in line with the deformation state of the averaged value over the segment in which the point exists. For instance, although the rotation of the apical segment has positive sign, various nodes on the apical segment might have negative sign.

Discussion
The new methodology enables to disclose local deformation behaviour rather than examining averaged segmental values. Although, the averaged segment values provide useful information and are widely used, looking at pointwise values might enable a more extensive LV assessment, which has not been attracted attention so far. For instance, averaging might be ruling out unusual localized deformations, particularly in pathological cases, which can be only detected through a point-wise distribution.

Figure 1: Exported acho data from 4D LV-Analysis Tomtec is processed into FEM framekwork. The LV endocardial surface and mitral valve plane are discretized with 1720 triangular elements over 862 nodes. The deformed shape and nodal displacement distribution along z-axis are illustrated during the entire cardiac cycle.

References

Acknowledgements
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MINERAL CONTENT AND MECHANICAL PROPERTIES OF CEMENT LINES IN HUMAN OSTEOAL Bone

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Introduction

Bone toughness is a complex property depending on the arrangement of the basic constituents (mineral and collagen), higher order structural motifs, and their numerous interfaces. Among these, cement lines (CLs) are thin layers separating secondary osteons from each other or from the interstitial bone. Based on the experimental evidence that microcracks are more frequently observed outside osteons than inside, CLs are believed to protect the osteons by deflecting cracks. However, CLs are still a poorly understood structure. Specifically, their composition, mineral properties, and biomechanical behavior are understudied. Here, we characterize CL mineral content and mechanical properties by combining high resolution backscattered electron imaging (hrBEI), including quantitative analysis (qBEI), with nanoindentation (nIND) on the same locations.

Methods

Cortical bone samples from two human femurs (male individuals, 40 and 81 years old) were harvested. Samples surface was smoothed with standard polishing using sandpaper, including a final step with ion polishing. A combination of qBEI (~0.5 μm pixel size) and hrBEI (~0.1 μm pixel size) was performed on selected osteons (~n = 62) to quantify mineral content and to highlight nanostructural features. Reduced modulus (Er) and hardness were measured across the CL in selected regions using nIND (Berkovich tip, 1–2.5 μm lateral spacing, 500–1000 μN load, 5500 total indent). For the evaluation, CLs were manually segmented from the corresponding osteons and the bone mineral density distributions (BMDs) of osteons and CLs were computed (Fig. 1). The correlation between mineral content and Er was obtained by superimposing nIND and qBEI measurements.

Results

CLs are tiny interphases with an average thickness of about 1–3 μm and a higher mineral content than the corresponding osteons (Fig. 1c). A spatial mapping of Er across two adjacent osteons exhibits a periodic alteration of stiffer and softer regions corresponding to bone lamellae, with a distinctive peak characterizing the CL (Fig. 2a and c). This increase in stiffness is spatially correlated with the mineral content (Fig. 2b and d). hrBEI allows to discriminate different osteonal features by their texture and the average Er could be computed inside the CL (29.34 ± 1.28 GPa), the stiffer lamellae (23.09 ± 1.36 GPa) and the more compliant lamellae (18.5 ± 0.69 GPa).

Discussion

We highlight a contrast in mineral content and elastic properties between the CL and corresponding osteon, which is higher than spatial variations of those properties within the osteon. This stiffness contrast may allow CLs to act as effective interfaces hampering crack propagation. Recent findings that CLs have reduced nanoscale porosity in comparison to adjacent lamellar bone explain the measured higher mineral content [1]. In contrast to previous literature [2,3], we report that CLs are stiffer than surrounding bone, which is in line with a reduced nanoporosity and higher mineral content. However, mineral properties of the CLs like crystal arrangement, dimensions and composition also contribute to the mechanical behavior, but these are unknown. Ongoing work aims at unraveling additional aspects of the mechanical behavior of CLs as well as the mineral properties using X-ray scattering.

References

EXTRALUMINAL AND INTRALUMINAL ARTIFICIAL URINARY SPHINCTERS: A COMPARISON OF BIOMECHANICAL FUNCTIONALITY

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Introduction

Artificial sphincters are implantable prosthetic devices that interact with tissues in order to replace the function of natural sphincters. Different mechanisms are employed to perform the occluding action, such as hydraulic, magnetic, shape memory. The optimal artificial sphincter should mimic the action of the natural one, avoiding degenerative phenomena of the surrounding tissues. Artificial Urinary Sphincters (AUSs) aim to resolve urinary incontinence, whose spread is extremely wide and socio-economical costs are enormous. Many different AUSs have been proposed, considering both extraluminal and intraluminal devices. Extraluminal AUSs are placed by invasive surgery. They frequently require revision, and further surgery is necessary. On the other side, the invasiveness of placing intraluminal device is minor, but its dimension and shape can determine patient bother. A further topic pertains to the mechanical stimulation of urethral tissues because of permanent occluding or positioning action. The mechanical stimulation may induce degenerative phenomena, as vasoconstriction, infection, atrophy and/or erosion, with consequent failure of the intervention. Despite the relevance of the phenomena, the design and validation of AUSs are performed by experimentations on cadavers and animal models, and clinical trials only. Such methodology is ethically and economically expensive, and does not provide quantitative information about tissues mechanical stimulation. This work aims to highlight the potentiality of computational biomechanics for investigating the reliability of the two principal extraluminal and intraluminal devices: AMS 800 and Relief, respectively.

Materials and Methods

A computational model of the urethra was developed, consisting of a 50 mm length and 5 mm radius cylinder with an elliptical lumen (8 and 5 mm major and minor axes). With regard to the investigation of Relief, the model also included the bladder. Hyperelastic formulations characterised the tissues mechanical behaviour. Concerning AMS 800, the model included the polymeric cuff and the fibre reinforced band (Fig. 1a). AUS and urethra devices were coupled. Contact strategies specified the interaction between model surfaces. The computational analysis included a preliminary step to simulate AUS wrapping around the urethra. During the next step, cuff pressure was progressively increased up to clinically applied values, such as 6 or 8 kPa [1]. The Relief model (Fig. 1b) accounted for all the external components interacting with urethral tissues. In detail, the structure for device positioning is manufactured with SME alloy [2]. A superelastic model characterised the mechanical behaviour of such components, while linear elastic models were adopted elsewhere. Contact strategies specified interactions between the different surfaces. The computational analysis accounted for two principal steps: positioning of the device at the bladder neck and opening of the positioning structure.

Results

The computational analyses made it possible to evaluate the mechanical stimulation of urethral tissues, such as stress and strain fields, with particular regard to the mostly loaded urethral sections (Fig. 2).

Conclusions

An in silico methodology has been proposed to investigate the mechanical functionality of different AUSs. The data provided are mandatory for the actual reliability assessment of AUS devices.

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Acknowledgements

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AGENT-BASED MODELING OF SPHEROID-ECM INTERACTION AND EVOLUTION UNDER FLUID FLOW

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Introduction

A spheroid is a group of cells, usually embedded in a hydrogel, with a quasi-spherical geometry. They are intended to mimic key cellular processes, such as communication, differentiation, migration and signaling, between others [1]. Given the 3D nature of spheroids, they are good in vitro models for the study of tumors, since they represent very well the proliferative dynamics present in cancer as well as their heterogeneity in terms of quiescence, hypoxic and necrotic regions found in spheroids [1-2]. In this work, we have developed a 3D agent-based model of spheroid evolution, based on the previous works developed in 2D [2], in which we have added the effect of the extracellular matrix (ECM) and laminar flow, in order to analyze the growth of the spheroid under different scenarios.

Methods

With respect to the mathematical model, nutrient diffusion from the medium to the spheroid nucleus and the dynamics of cell proliferation and death are considered. Depending on the concentration of nutrients, $\omega$ (eq. (1)), a cell can be in a proliferative state, if $\omega_q < \omega \leq 1$, quiescent, if $\omega_q < \omega \leq \omega_q$, hypoxic, if $\omega \leq \omega_h$ or necrotic. Different forces are considered in the model, namely, mechanical, between spheroid cells and between spheroid cells with ECM particles ($F_i^{m}$ and $F_i^{m,ECM}$, respectively); random ($F_i^{r}$); surface tension ($F_i^{f}$) and laminar flow ($F_i^{l}$), see eq. (2). $x_i$ is the cell position in eqs. (1)-(4). When a proliferative cell completes its cell cycle ($\hat{T}_i$, eq. (3)), it gives rise to a daughter cell and when a hypoxic cell remains in this state for a certain time ($\hat{T}_i$, eq. (4)), it becomes necrotic. In eqs. (1)-(4), $D_\omega$ is the coefficient for nutrient diffusion, $\kappa$ is the nutrient consumption rate, $v$ is the damping coefficient and $\mathcal{H}$ are the Delta and Heaviside functions, respectively. The parameter values are detailed in [2]:

$$\frac{\partial \omega}{\partial t} = D_\omega \nabla^2 \omega - \kappa \omega \sum_i \delta(x - x_i) \quad (1)$$

$$v \frac{dx_i}{dt} = F_i^{m} + F_i^{r} + F_i^{f} + F_i^{m,ECM} + F_i^{l} \quad (2)$$

$$\frac{d\hat{T}_i}{dt} = \mathcal{H}(\omega(x,t) - \omega_q) \quad (3)$$

$$\frac{d\hat{T}_i}{dt} = \mathcal{H}(\omega_h - \omega(x,t)) \quad (4)$$

Results

In this work, we have considered the following case studies: (i) the spheroid is partially immersed in the ECM in the absence of flow, and (ii) the spheroid has its upper (free) part subjected to a laminar flow, without considering the mechanical interaction with the matrix (Fig. 1):

![Figure 1: Left: initial conditions in which the spheroid is composed of 816 cells and the ECM of 10127 particles. Right: spheroid subjected to a laminar flow velocity of $1 \times 10^{-4}$ m/s in the upper region and null ECM interaction. The spheroid consists of 1679 cells, of which 77 form the necrotic core. The proliferative layer is magenta, the quiescent is blue, the hypoxic is green and the necrotic is black. The simulations are fully 3D and they correspond to 1000-time steps.](image)

Discussion

From the simulations performed, we have observed that the shape of the spheroid is conditioned by the mechanical environment. In this case, the matrix induces a stiffer microenvironment to cells, thus decreasing its compressed state and increasing proliferation, due to the translation and expansion of the spheroid towards the more rigid zone, increasing the thickness of the proliferative layer. In addition, the cells tend to move in the direction of flow, because of the tangential component (Fig. 1). These results are in agreement, qualitatively, with other in vitro studies in the literature [3-4]. These preliminary results will allow us to develop models of increasing complexity to recreate, in silico, the behavior and evolution of in vitro experiments of organoids [5].

References

REAL-TIME OPTIMIZATION OF UPPER LIMB JOINT KINEMATICS THROUGH A CONSTRAINED ISB-CONSISTENT MODEL

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Introduction
Real time robust upper limb joint kinematics description is a central point for several applications such as telerehabilitation and clinical evaluation. The use of wearable sensors (IMUs) together with state-of-the-art sensor fusion algorithms represents a convenient solution to unobtrusively monitor the subject performance in real-world environments. However, for long acquisitions (e.g., ~10 minutes), errors in joint angle estimates increase with time due to orientation drift thus affecting joint kinematics reliability. The aim of this work is two-fold: i) to propose a multi-segmental model of the upper limb compliant with the guidelines of the International Society of Biomechanics (ISB), ii) to propose a real-time optimization framework for the IMU-based joint kinematics estimation by setting ad-hoc model constraints based on both the physiological joint limits and the knowledge of the performed movement. The accuracy of the shoulder and elbow constrained kinematics was tested on one subject equipped with two IMUs during a 10-minute exercise.

Methods
A three-segment chain was designed following the Denavit-Hartenberg robotic convention to model the upper limb including the trunk, the upper arm (UA), and the forearm (FA). The shoulder and elbow joints were modeled as three (θ₁, θ₂, θ₃) and two (θ₄ and θ₅) degrees of freedom, respectively, following the sequence recommended by the ISB. The carrying angle θ₀ was modeled as a fixed and subject specific parameter. One healthy subject was equipped with two IMUs on the UA and FA and asked to grasp and slide a handle on a horizontal surface while seated. Four reflective markers were also placed on each IMU to provide the orientation reference. IMU and marker data were recorded for ten minutes at 100 Hz. Before this, the offset of each gyroscope was subtracted from angular velocity readings. For each time-step, the joint angles were obtained in an optimization framework by minimizing the difference between the orientation predicted using the upper limb model and the corresponding orientation computed using the sensor fusion algorithm [1] without magnetometer whose parameter was optimally tuned [2]. In addition, the optimal (θ₁, θ₂, θ₃, θ₄, and θ₅) solution had to satisfy two set of constraints. The first defined the extreme values for each θ based on the physiological joint limits. The second was determined exploiting the a priori task-specific knowledge. In fact, during the entire recording the elbow and wrist positions remained on a limited portion of space and the elbow was always higher than the wrist. Errors were computed as root mean square differences (RMSD) between the reference joint angles and those obtained through the optimization framework with and without applying the constraints, respectively.

Results
The RMSD (deg) for θ₁, θ₂, θ₃, θ₄, and θ₅ obtained with (without) the constraints amounted to 3.7 (3.5), 6.7 (6.8), 7.1 (7.7), 20.2 (23.0), 4.8 (6.2), respectively. The average execution time to perform ~60000 iterations amounted to 8.14 ms and 5.64 ms, with and without applying the constraints, respectively.

Discussion
By exploiting the knowledge of the performed movement, the proposed method allowed to reduce FA errors by around 15% (average RMSD equal to 12.5 deg vs 14.6 deg with and without applying the constraints, respectively) thus limiting the impact of the IMU orientation errors on the estimated joint angles. The execution time lower than the sampling period is suitable for a real-time joint kinematics computation.

References

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MODELLING TRANSCATHETER MITRAL VALVE REPLACEMENT USING THE LIVING HEART PROJECT

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Introduction

Transcatheter mitral valve replacement (TMVR) is an emerging alternative treatment for those patients not qualified for surgery. However, TMVR can determine an obstruction of the left ventricular outflow tract (namely, neo-LVOT) induced by the transcatheter heart valve (THV) displacing the native mitral valve leaflet towards the myocardial wall. This condition can lead to hemodynamic impairment and ultimately patient death.

Methods

The simulation study of TMVR in the failed annuloplasty band ring consisted of the following steps: 1. adapting the original living heart human model (LHHM) to account for a failed mitral valve by inhibiting the active contraction of the myocardial wall near the posterior papillary muscle; 2. modeling the suturing of the annuloplasty band ring into the mitral annulus using wire connections and contact conditions; 3. simulating the deployment of the S3 Ultra device by virtually inflating the balloon and then modeling the heartbeat of repaired mitral valve apparatus; 4. computational flow analysis of the left heart hemodynamics to quantify the sub-aortic flow and pressure gradient near the LVOT obstruction.

The LHHM developed by SIMULIA is an advanced cardiac tool in which the geometry is a realistic and accurate representation of an adult male anatomy [1]. The LHHM includes all ventricular and atrial chambers, heart valves and major vessels (i.e., the aorta, pulmonary artery and vena cava) and the biomechanical response is governed by an electrical potential activating the contraction of myocardial wall. The coupling with a 1-D lumped parameter model allows one to consider the interaction between the circulating blood and the deforming myocardium and thus obtain the pressure-volume loop. Anatomical parts are meshed with tetrahedral elements and linear truss elements (only for chordae tendineae) for a total of 443,564 mechanical degrees of freedom.

RESULTS AND DISCUSSION

A realistic and high-fidelity computational tool of cardiac biomechanics was used to virtually simulate the transcatheter mitral valve-in-ring replacement and then investigate the hemodynamic and structural mechanics of LVOT obstruction (Fig.1). The most striking finding is the assessment of the dynamic behavior of the neo-LVOT area over the cardiac cycle, suggesting that the risk stratification of patients undergoing TMVR should not only be based on pre-TMVR imaging criteria at end-systole. This finding improves our understanding of the impact that LVOT obstruction has on THV performance and offers a computational approach to better assess the anatomic suitability of patients undergoing TMVR. Ultimately, this knowledge has the potential to enhance procedural planning to yield better clinical outcomes and to inform the way we design the next-generation of transcatheter heart valves.

Figure 1: LVOT obstruction and estimation of neo-LVOT area using the LHHM.

References


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EFFECTS OF INTERVERTEBRAL DISC DEGENERATION ON THE SURFACE STRAIN DISTRIBUTION OF HUMAN VERTEBRAE

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Introduction
Intervertebral discs (IVDs) degeneration involves changes in biomechanics, structure of the extracellular matrix, genetics, and cellular activities and can turn into a painful pathological condition [1]. How these changes can affect the load transfer through the vertebrae, and consequently the local mechanical behaviour of the vertebrae is still unclear. In spine segments FE models, IVDs are frequently modelled with simplified mechanical properties [2], which may not be sufficient to describe the IVDs degeneration and apply realistic boundary conditions to the FE model of the vertebrae. The effects of the IVDs degeneration on the adjacent vertebrae can be evaluated experimentally by combining mechanical tests and Digital Image Correlation (DIC) to characterize the external strain field of both vertebrae and IVDs simultaneously. The aim of this study is to evaluate the strain distribution on the vertebral bodies.

Methods
Two T9-L1 spine segments were harvested from human donors (Ethical approval: Prot.n.113043) and imaged with a 3T Magnetic Resonance Imaging (MRI) and a Computed Tomography (CT) to establish the degeneration of the IVDs (IVDs degeneration level = 2) [1] and exclude critical bone pathology. All soft tissues and the anterior ligament were removed without damaging the IVDs. A high-contrast white speckle pattern was prepared on the surface of each specimen. A four-camera 3D-DIC system (Aramis Adjustable 12M, GOM) was used to measure the strains on the surface of the specimens, at 25 frames per second, with a measurement spatial resolution of 0.07 mm. The intact specimens were mechanically tested with a uniaxial testing machine (Instron 8500, 10kN load cell) to induce flexion loads, as defined by [3]. Each spine segment was loaded until the average minimum principal strain on the central vertebra reached approximately 3000µε (target to remain in elastic regime without damaging the bone). Ten preconditioning cycles up to half of the load corresponding to the target strain were applied. Then, each specimen was loaded monotonically to reach the target strain in 10s, 1s and 0.4s. To simulate a grade 5 degeneration [1] of the IVD, the nucleus of the T11-T12 IVD was entirely removed mechanically [4]. The specimens were tested again, following the same loading protocol. Random errors were evaluated in zero-strain condition as the standard deviation of the strain. The maximum and minimum principal strains were measured and compared before and after the IVD degeneration. Statistical analyses (Wilcoxon test, p=0.05) were performed in Prism.

Results
Random errors were smaller than 100µε. The maximum and minimum principal strains in the vertebrae close to degenerated IVD (T11 and T12), were significantly different before and after IVD degeneration (maximum principal strains: 1302µε vs 1885µε; minimum principal strains: -2711µε vs -3515µε; p=0.02).

Discussion
Results showed that IVD degeneration leads to an increase in the strains experienced by the adjacent vertebral bodies adjacent to the IVD degeneration with respect to the healthy condition (Fig1). Thus, the IVD degeneration causes an alteration in the transmission of loads through the vertebral body which reach larger strains close to failure strains [5]. Further analyses and mechanical tests on other specimens are still on going.

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Acknowledgements
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Figure 1: Minimum principal strains [%] evaluated in flexion on a T9-L1 spine segment, before (left) and after (right) T11-T12 IVD degeneration.
ROLE OF ANGIOTENSIN 1B RECEPTORS IN INDUCING REGIONAL DISPARITIES IN HYPERTENSIVE AORTIC REMODELING

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Introduction
Hypertensive arterial remodeling using angiotensin II (AngII) infusion in mice has been studied for over 20 years, uncovering the role of the renin-angiotensin system in blood pressure control. Although there are numerous studies on how AngII leads to hypertension development, central artery stiffening, and formation of abdominal aortic aneurysms (AAAs), many key questions remain unanswered, such as the role of AngII receptors on tissue-level consequences. Among the two primary AngII receptors, AT1R and AT2R, the former is expressed in two isoforms, AT1aR and AT1bR. Deletion of AT1aR suppresses AAA formation while deletion of AT1bR does not [1]. Interestingly, these effects are not mirrored by effects in vasoconstriction. AT1bR in smooth muscle cells mainly contributes to AngII-induced local vasoconstriction, whereas AT1aR has no clear effect thereon. AT1aR and AT1bR density has been shown to vary along the aorta, increasing from the proximal to the distal aorta, but it is still unclear how this affects the differential regional hypertensive remodeling response of the aorta. Our study aims to clarify this aspect by analyzing histo-mechanical metrics in multiple aortic regions in AT1bR gene-deficient mice, without or with AngII infusion.

Methods
We contrasted 14- and 28-day infusions of AngII at a rate of 1000 ng/kg/min in adult male and female wild-type (WT) and AT1bR null (Agtr1b−/−) mice by ex vivo histo-mechanical characterization in the ascending (ATA) and descending (DTA) thoracic aorta and the infrarenal abdominal aorta (IAA). Aortic segments were characterized functionally by biaxial extension-distention tests and isobaric vasoactive tests to obtain fundamental biaxial mechanical metrics [2]. Immunohistochemical stainings allowed layer-specific analysis of composition and infiltration of pan-inflammatory cells (macrophages, monocytes, and T-cells). Sample-specific analyses allowed identification of crosstalk between biomechanics and histology.

Results and Discussion
Mechanical and histological metrics revealed that baseline properties and AngII-induced remodeling were independent of sex in Agtr1b−/− mice. Focusing then on male mice, AngII-induced changes in aortic morphology and mechanics differed by region and genotype. A marked AngII-induced thickening of ATA but little thickening of IAA was seen in both genotypes. Despite no differences in the level of blood pressure elevation between AngII-infused WT and Agtr1b−/− mice, we observed marked thickening of the DTA in WT but not Agtr1b−/− mice. After AngII infusion, distensibility, elastic energy storage, energetically preferred axial stretch, and axial material stiffness decreased the most in ATA, less so in DTA, and little in IAA, independent of genotype. By contrast, biaxial wall stresses, circumferential material stiffness, and energy dissipation revealed marked variations within the DTA of AngII-infused WT but not Agtr1b−/− mice. Vasoactive tests revealed that the vasoconstriction to AngII was higher in IAA in WT mice, but this result was blunted in all regions in Agtr1b−/− mice. Histology showed that AngII-induced wall thickening was preferentially adventitial in the WT thoracic aorta, but more medial in Agtr1b−/− DTA. This distinctive behavior correlated with an increase in adventitial cell area. Immunohistochemistry revealed a marked increase in the pan-leukocyte markers in the ATA of all AngII-infused mice and in the DTA of WT mice, as well as a marked increase in the macrophage marker in all three segments of the aorta of AngII-infused WT mice. Conversely, DTAs of Agtr1b−/− mice showed only a moderate number of leukocytes after AngII infusion that was in line with the distinctive thickening and mechanical behavior, as also all aortic regions of Agtr1b−/− did not show increases in macrophages after AngII infusion. Therefore, in the context of aortic remodeling through AngII-induced hypertension in mice, AT1b receptor deletion surprisingly revealed to have differential effects along the aorta, particularly at the level of the DTA, where negative remodeling was significantly attenuated through modulation of the inflammatory response. It is thus necessary to continue to study the role of AngII in differentially influencing the multiple cell types that contribute to regional disparities in aortic remodeling.

References
288, 2022.

Acknowledgements
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INFLUENCE OF ANISOTROPIC CORTICAL BONE PROPERTIES IN PERIPROSTHETIC HIP FRACTURES

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Introduction

Periprosthetic femur fractures (PFFs) remain a major clinical challenge associated with increased mortality and morbidity [1]. Epidemiological studies show a relatively high number of PFFs during the early postoperative (EP) period, especially with cementless stems [2].

Recent experimental studies have reported crack propagations parallel to the femur axis under stance, and lateral fall loading conditions [3], which suggests a role of bone anisotropy on PFFs since the fracture direction aligns with osteon directions. However, the relative role of material anisotropy on early postoperative PFFs remains poorly understood.

Therefore, the main objective of this study was to investigate the influence of cortical bone anisotropy in periprosthetic hip fractures. To achieve this, finite element models (FEMs) of implanted femurs were developed and validated, considering anisotropic cortical bone material properties.

Methods

In this study, femur-specific FEMs were created, using Zweymueller stem design, based on the pre-and post-operative computer tomography scans provided by Saemann et al. [3].

Corresponding trabecular and cortical bone segments were modeled depending on the bone density using crushable foam and composite material models, respectively. Elasto-plastic and asymmetric cortical bone properties were defined in primary direction based on the experiments reported by Mirzalli et al. [4]. Material properties in the secondary direction were calculated by scaling the primary properties using the experimental findings of Reilly and Burstein [5].

The developed modeling strategy was tested under lateral fall loading conditions against the ex-vivo experiments documented by Saemann et al. [3]. Results were evaluated based on the force-displacement behavior alongside the fracture patterns for isotropic and anisotropic material models.

Results

Simulation results using the anisotropic material properties showed comparable force-displacement characteristics with the experiments. The ultimate force and displacement values before fracture resulted in respectively +13% and -10% differences compared with the experimental data. On the other hand, although following a similar force-displacement path initially, the simulation model with isotropic material properties clearly overpredicted the ultimate force and displacement values (Figure 1).

Regarding the fracture patterns, the simulation results using the anisotropic cortical bone properties showed similar fracture patterns as reported in the experiment.

Discussion

Periprosthetic bone fracture experiments have shown crack propagations parallel to the primary bone material direction, suggesting that the secondary material properties should play an important role. To test this hypothesis, we developed an anisotropic cortical bone modeling strategy and applied it to the FE models of ex-vivo PFF experiments.

Simulation results using anisotropic material properties predicted the ultimate force and displacement values compared to the experiments more accurately than the isotropic material properties. Additionally, the fracture patterns were also predicted realistically using the anisotropic material definition.

In the future, the modeling strategy presented in this study can help to predict PFFs more accurately and develop patient-specific strategies to mitigate such fractures.

References

### Introduction

The heart is an extremely complex organ at a structural level, and the orientation of cardiac muscle fibres determines cycles of healthy contraction-torsion and cardiomyocytes activation. In the event of ischemic heart disease, cardiac muscle alignment is disrupted, resulting in decreased pumping function. Current approaches for reproducing the biomechanical properties of cardiac muscle, in particular using fibre-based scaffolds, still fail to mimic the specific 3D geometry of cardiac muscle, and importantly, lack its complex elastic behaviour. Previous work shows that hexagonal structures can reversibly store more elastic strain energy and further promote cardiomyocyte (CM) maturation, compared to rectangular structures [1]. Thus, we hypothesised that the geometry of hexagonal lattice units in melt-electrowritten (MEW) scaffolds can be modified to tailor their anisotropic mechanics, thus allowing to produce tunable bioengineered myocardial constructs (BMC) that promote cardiac cell alignment and subsequent contraction in vitro.

### Methods

MEW scaffolds (0.5-mm thick) with hexagonal pores and internal half-angles of 30°, 45°, and 60° were designed using TrioBASIC-based software and printed from medical-grade poly(ε-caprolactone) using an in-house built device (Fig. 1A). Print fidelity and fibre diameter were quantified using brightfield (BF) and scanning electron microscopy (SEM) (Fig. 1B). The linear and nonlinear components of the elastic behaviour in each geometry were analysed by uniaxial monotonic and cyclical testing. An ad hoc MATLAB script was developed to isolate the linear elastic behaviour from the toe region (the nonlinear strain stiffening elastic regime at low strains) using mathematical modelling [2]. The elastic modulus, the transition point from the toe to linear elastic region, and the strain energy density in both regimes were quantified for each geometry.

### Results

Modified hexagonal MEW meshes showed an individual fibre diameter of ~9 µm for all geometries evaluated (Fig. 1C). 30° scaffolds showed a 32% decrease in print fidelity with respect to 45° and 60° scaffolds due to the small separation between adjacent rows and higher electrostatic interactions during printing. 30° scaffolds showed a 5-fold increase in tensile modulus compared to 60° scaffolds, whereas the strain range of the toe region in 60° meshes was up to 8 times greater than in 30° meshes (Fig. 1D). 60° scaffolds showed the widest nonlinear elastic (toe) region from 0 to 20% strain, which is ascribed to greater potential for fibre alignment under loading.

![Figure 1: A) Design of MEW hexagonal architectures with different internal half-angles and constant side length (0.4 mm). B) Fibre morphology and organization in MEW printed scaffolds. C) Fibre diameter and projected area as indicator of print quality. D) Representative tensile curves, definitions and quantification of mechanical parameters.](image)

### Discussion

The findings of this study shed light on the close connections among scaffold architecture and mechanics. This, together with the tunability that MEW provides as a microfabrication technique, can then be leveraged to probe cardiac cell function in response to scaffold geometry and mechanical microenvironment. Our approach allows for complex optimisation of anisotropic microarchitecture in order to tune BMC mechanical performance, which can guide CM alignment.

### References


### Acknowledgements

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LUMPED-PARAMETER MODEL TO ASSESS CORONARY BLOOD FLOW IN AAOCA: A FOCUS ON THE IMPACT OF BOUNDARY CONDITIONS

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Introduction

Anomalous aortic origin of the coronary artery (AAOCA) is a rare congenital disease that can cause sudden cardiac death (SCD). Starting from our encouraging result [1] we aim to develop a non-invasive patient-specific (PS) computational tool to simulate coronary blood flow (CBF) using multi-patient clinical data to understand how intramural coronary artery (CA) compression affects myocardial perfusion. In this paper we present the model setup and a sensitivity study focused on the impact of input data on the accuracy of the results. The final aim is to define an accurate tool with a limited use of invasive data.

Methods

Each arterial segment is described as an electrical circuit (Fig. 1A) whose components depend on the geometry of the vessel, its material, and blood properties [2]. A PS pressure waveform is used as inlet condition (Fig. 1B). The aorta’s outlet is modeled with a Windkessel circuit (Fig 1C), whereas the CAs’ outlet is defined by a 6-elements circuit (Fig. 1D) with an intramyocardial pressure source (Fig. 1E). The total resistance of each outlet is split among circuit resistive parameters [3].

Based on preliminary analysis we calibrate the model using geometrical data from CT images. To define a PS boundary conditions (BCs) we compute the total aortic resistance with the patient's cardiac output and mean arterial pressure [3]. The left ventricular pressure (LVP) waveform is rescaled based on the PS data, the right one is evaluated as 20% of LVP [3]. The definition of coronary resistance (Rc), allows us to differentiate two models: PS Model and Literature approach.

In PS Model we use Rc acquired in-vivo during catheterization exam under resting condition.

In Literature approach we estimated Rc using the analytical procedure proposed in the literature [3] to reduce the use of invasive data.

First, we run the model using PS in-vivo measured Rc. Then, we use Rc analytically computed with the aim to study the impact of BCs on accuracy of CBF assessment.

Results

Fig. 2 shows results considering the two ways of defining Rc. Simulated CBF are compared with in-vivo CBF. The mean square error (MSE) is evaluated and highlights a reduction in accuracy with the removal of Rc invasive information: 0.01 vs 0.57 and 0.02 vs 3.72 for RCA and LCA, respectively.

![Figure 2: 0D model vs in-vivo CBF. Blue circles: in-vivo PS Rc. Red triangles: literature approach.](image)

Discussion

Our results suggest that invasive Rc plays a key role in CBF assessment. The accuracy is dramatically reduced by using an analytical standard approach that does not consider the presence of AAOCA and the characteristics of the population. A future approach should consider specific population information in defining analytical Rc.

References


Acknowledgements

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TOWARDS THE DEVELOPMENT OF A ZEBRAFISH ACTION POTENTIAL MODEL

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Introduction

During the last 30 years, the use of zebrafish for studies of cardiac electrophysiology has exponentially increased. Of particular interest are the similarities in action potential (AP) characteristics, owing to the presence of ~69% human gene orthologues [1], which lead to functional similarities in cardiac ion channels [2]. Given the growing importance of this animal model, the development of an in-silico AP model is warranted, to help in understanding ionic mechanisms involved in the development of cardiac pathologies and the response to pharmacological therapies, while reducing the number of animals needed for experimentation. For this purpose, our goal was to develop a mathematical model of the zebrafish AP.

Methods

This work developed a detailed AP model for the adult zebrafish by including the main ionic currents involved. The TenTusscher and Panfilov AP model from 2006 (TP06) [3] was adapted to the zebrafish. A literature review was performed to identify individual ion channel experimental data (i.e., by patch-clamp) related to the principal currents responsible for the zebrafish AP. According to previous reports, the principal currents involved are the: i) fast Na⁺ current, I_{Na} responsible for the rapid depolarization of the AP; ii) T-type Ca²⁺ current, I_{CaT} (added to the TP06 model), which contributes to the initial AP upstroke; iii) L-type Ca²⁺ current, I_{Cal}, which maintains the AP plateau and provides the Ca²⁺ necessary for contraction; iv) rapid and slow delayed rectifier K⁺ currents, I_{Kr} and I_{Ks}, involved in repolarization; v) inward rectifier K⁺ current, I_{K1}, which contributes to late repolarization and maintains resting membrane potential; and vi) Na⁺/K⁺ pump and Na⁺/Ca²⁺ exchanger, important for restoring ionic balance during the resting phase. The transient outward K⁺ current, I_{to}, was removed from the TP06 model since it has been shown not to be present in zebrafish [2]. The newly developed AP model was parameterized by fitting to sharp electrode AP recordings from the ventricle of adult zebrafish isolated hearts maintained in 28°C HEPES-buffered saline solution and paced from the ventricular apex.

Results

After formulating the behavior for the different gating variables, the gates were integrated using the Rush-Larsen scheme, and simulations were run with a fixed time step of 0.02 ms. The Monte Carlo method was used to select which of the 11000 combinations of 34 parameters best fit the shape of the experimentally recorded AP while preserving model stability. Figure 1 shows the best numerical AP (black) compared to experimental AP recordings (blue), while the numerical and experimental AP features are reported in Table 1.

Discussion

This work represents the first attempt to develop an AP model for adult zebrafish. The model accounts for the main transmembrane currents that have been characterized in zebrafish and generally reproduce measured AP morphology. However, these results are considered preliminary, as the effect of heart rate (or stimulation frequency) on the AP (i.e., restitution) and the response to drugs must be examined to determine the validity and utility of the proposed model.

References

CORRECTING THE EJECTION FRACTION FOR BETTER HEART FUNCTION REPRESENTATION AND PROGNOSIS IN HEART FAILURE

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Introduction

Ejection fraction (EF), defined as the percentage of blood ejected per heartbeat, is widely used to evaluate heart function during heart failure (HF), but it is known that geometric changes to the heart during disease remodeling can cause it to become an inaccurate assessment of cardiac function [1, 2]. For example, during heart failure preserved ejection fraction (HFpEF), EF did not decrease in cases with failing hearts. Here, we evaluate the dependency of EF on cardiac geometry, and propose here a correction factor to EF to prevent this dependency, and show that the corrected EF (EFc) have improved prognosis capability.

Method

The proposed EFc is theoretically equivalent to obtaining EF from the mid-myocardial wall layer instead of the endocardial layer. It can easily be calculated from routine echo scan results, as:

\[ EFc = \frac{EDV}{EDV + 0.5 \times LV M / \rho} \times 1.9 \]

where EDV was the end-diastolic volume and \( \rho \) was the myocardial density. The ability of EF and EFc to indicate cardiac function was first evaluated with a simple cardiac numerical model translating strains to stroke volume and vice versa, and then with a porcine model of HFpEF induced by gradual inflation of the aortic cuff [3]. Finally, the prognosis ability of EF and EFc was evaluated on a retrospective clinical patient cohort admitted to Imperial College Healthcare NHS Trust, UK, composing of patients who were admitted with a troponin test request and echo scan.

Result and Discussion

Our numerical model showed that EF elevated with increasing left ventricular (LV) wall thickness and decreased with increasing chamber dilation, even without a change to mid-wall myocardial strains. This demonstrated that EF deviated from trends of cardiac function when geometric remodeling occurred. However, EFc was not affected by geometric changes, and was constant across various cardiac geometries if mid-wall strains were unchanged.

Our animal model investigations showed that EFc could distinguish between HFpEF animals from healthy controls, but EF could not (Fig 1).

Our clinical data confirmed that patients with HFpEF could be distinguished from those without heart failure with EFc, but not with EF (Fig 2). We used a multivariate Cox proportional hazards regression model to predict hospital readmissions due to heart failure in the cohort. We find that both EF and EFc predicted readmissions equally well in the group with low EF (EF<50%). However, in the group where EF≥50%, predictive models with EFc were significantly more accurate in predicting readmissions within 3 years: the leave one out cross-validation ROC analysis showed 18.6% reduction in errors, while the Net Classification Index (NRI) analysis showed that risk classification of true positive increased by 12.2%, and risk classification of false negative decreased by 16.6%. This demonstrates improved prognosis accuracy.

![Figure 1](image1.png)  
**Figure 1:** (A) EF and (B) EFc in a left ventricular hypertrophy (LVH) animal model and a coronary artery disease (CAD) animal model, compared to their appropriate controls. *p < 0.05 compared to control.

![Figure 2](image2.png)  
**Figure 2:** EF and EFc of all patients, stratified into HF (EF<40), HFmrEF (40≤EF<50) and HFpEF (EF≥50) and non-HF (not diagnosed with HF) based on ICD-10 codes. *p<0.05, NS: not significant, ANOVA.

Conclusion

We developed a corrected factor to the EF that could mitigate the skewing effects of cardiac geometric remodelling, enable distinguishing between normal and HFpEF hearts, and improve prognosis of hospital readmissions due to heart failure.

References


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Mandibular morphometry and TMJ ankylosis: from the perspective of Indian population

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Introduction

Long-standing ankylosis of the temporomandibular joint (TMJ) prevents the normal opening of the mouth causing reduced mandibular function. Alloplastic reconstruction has been a preferred treatment choice to restore the joint for many patients globally [1]. This study focuses on the evaluation of morphometric measurements of the mandibles of TMJ ankylosis (TMJA) patients in the Indian population.

Methods

The CT DICOM files of 51 TMJA patients (age range 10-56 years) were procured from AIIMS Delhi and reconstructed in Mimics (v25.0). Of these, 16 male and 15 female patients were having unilateral (13 right and 18 left) TMJA while 9 male and 11 female patients were having bilateral TMJA. The significant anatomical landmarks [2] are shown in Figure 1. The morphometric measurements evaluated were ramus length (Co-Go), minimum ramus width (MRW), gonial angle (∠CoGoMe), and mediolateral condylar width (Co.in-Co.out). The major focus of this study was on ramus length and its comparison with the different sizes of available stock TMJ prostheses. A maximum error of 2% can be considered in all measurements.

Results and Discussion

The measured landmarks of mandibles are shown in Figure 1. The ramus length was observed to have a minimum value of 23.77 mm (mean 48.31 mm) in Indian males unlike, 20.37 mm (mean 44.63 mm) in Indian females. The minimum size (45 mm) of a widely used standard commercial TMJ implant (Zimmer Biomet Microfixation™, Jacksonville, FL, USA) suffers length as well as medio-lateral fit discrepancy which might cause some long-term disabilities in ankylosis patients. To eliminate this size discrepancy, the size of presently available stock prostheses should be reduced according to the minimum possible size of the lower jaw of TMJA patients. A few other anomalies such as the inclination of the ramus with the sagittal plane, and the irregular gap between the mid-length of the TMJ implant and the ramus which might be assessed with normal mandibles in a future study.

Acknowledgement

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DATA-DRIVEN METHODS FOR PATIENT-SPECIFIC REDUCED ORDER MODELING OF COMPLEX AORTIC FLOWS

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Introduction

Data-driven approaches offer great potential to overcome the challenge of high computational cost associated with Computational Fluid Dynamics (CFD) in cardiovascular biomechanics [1]. The need for fast and accurate models has led to the exploration of Proper Orthogonal Decomposition (POD) to create Reduced Order Models (ROMs) that can provide efficient and accurate representations of flow field data, which may be obtained from in-vivo or in-vitro experiments [1, 2]. However, these flow field data are often noisy, and POD may not be effective in handling such noise. This study aims to investigate the use of Robust Proper Orthogonal Decomposition (RPOD) algorithm in cardiovascular biomechanics [3]. The effectiveness of the RPOD method is evaluated in comparison to the traditional POD method in reconstructing the flow dynamics inside a personalized human dissected aorta.

Methods

The flow data is obtained from an in-vitro Particle Image Velocimetry (PIV) experiment using a patient-specific phantom and boundary conditions. [4] This data has been used to validate CFD-derived flow fields with similar settings [5]. The measured flow field is decomposed into multiple POD and RPOD modes. Using these modes, Reduced Order Models (ROMs) are created for both POD and RPOD. The number of modes used for each ROM is 2, 10, and all available modes. The kinetic energy and reconstruction error of each ROM are then calculated.

Results

<table>
<thead>
<tr>
<th>Modes included</th>
<th>POD Energy (%)</th>
<th>POD Error (%)</th>
<th>RPOD Energy (%)</th>
<th>RPOD Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>86.33%</td>
<td>34.18%</td>
<td>98.15%</td>
<td>13.10%</td>
</tr>
<tr>
<td>1-10</td>
<td>91.72%</td>
<td>27.06%</td>
<td>99.78%</td>
<td>7.85%</td>
</tr>
<tr>
<td>all</td>
<td>~100%</td>
<td>~0%</td>
<td>~100%</td>
<td>~0%</td>
</tr>
</tbody>
</table>

Table 1: Percentage of energy captured in ROMs created from POD and RPOD

Table 1 shows that when using the same number of modes, ROMs based on RPOD capture a greater portion of kinetic energy and have a lower reconstruction error compared to ROMs based on traditional POD. The RPOD reconstructed flow field also appears to be spatially and temporally smoother compared to the original flow field.

However, the Full Order Model (FOM) calculated from RPOD method shows a significant difference compared to the traditional POD based FOM during diastole. (Figure 1) The velocity magnitude of the FOMs from RPOD ranges from 0 to 0.2237 m/s, while the original flow field from 0 to 0.3276 m/s at diastole.

Discussion

RPOD has been shown to outperform the traditional POD in reconstructing in vitro aortic flow dynamics due to its ability to filter out noise in the data. This shows the potential of RPOD in enhancing in-vivo velocity measurements obtained via medical imaging techniques. RPOD may over-filter certain parts of the flow field and further work on tuning of the filtering parameter might be worth exploring. Further work on coupling ROMs with machine learning algorithms to reconstruct aortic flows is currently underway.

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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
MODELLING MIDLINE SHIFT AND VENTRICLE COLLAPSE IN POST-STROKE CEREBRAL ODEMA

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Introduction
Intracranial pressure (ICP) is a crucial parameter for the evaluation of and clinical decision-making in post-stroke oedema. In recent decades, the midline shift of edematous brain has been used to estimate ICP non-invasively since it can be observed directly on brain imaging. Although previous studies have shown a linear relationship between ICP and MLS, this relationship lacks statistical significance [1]. Therefore, MLS is not sufficient for the estimation of ICP. In this study, we thus propose the first poroelastic model to study the relationship between ICP and MLS and explore the factors that can cause deviations from a linear relation.

Methods
A new mathematical model of brain ischaemic stroke and oedema is proposed as a predictive tool to estimate the relation between ICP and MLS in different types of post-stroke oedema in varying degrees of brain damage. The model consists of two components that simulate blood perfusion and oedema respectively. The cortical surface was subdivided into 8 perfusion territories (Fig. 1) according to vessel encoded arterial spin labelling magnetic resonance imaging and the brain modelled as a multi-compartment porous medium [2]. In this study, a population-averaged brain model is used.

Results
Different types of brain edema (resulting from ACA, MCA, PCA, hemispheric strokes) show significantly different MLS-ICP curves (Fig. 2). The permeability of the capillary network (which represents the severity of oedema) is also found to affect the relationship (Fig. 3). Note that only pathological parameters are varied while the physiologically-based parameters remain constant.

Discussion
The simulation results show that the type of post-stroke edema has a significant impact on the ICP-MLS relationship, with the ACA and PCA stroke oedema induce deformation from both the top and bottom. In contrast, MCA stroke oedema swells and compresses the brain from the side and thus contributes the most to MLS. Meanwhile, variations in capillary permeability indicates that the MLS is not only affected by the maximum pressure rise, but also the distribution of excessive water in the brain tissue. This suggests that patient-specific modelling of the ICP-MLS relationship is necessary to improve the accuracy of ICP estimation.

References
Introduction
Human balance is a complex combination of information, which mainly depends on the coordination of visual system, vestibular system and proprioceptive system to achieve its own stability. These inputs not only provide important information about body orientation and position, and they interact with each other.

Methods
6 elite and 10 national-standard freestyle ski aerials athletes and 14 healthy individuals participated in experiments, recorded AP(Anterior-posterior) and ML(Medialateral) direction center of pressure(COP) displacement of in four conditions, including stable surface eyes opening(T1), stable surface eyes closed(T2), unstable surface eyes opening(T3), unstable surface eyes closed(T4) for 30 seconds test, and calculated Sample Entropy(SE), Plantar Quotient(PQ) and Romberg Quotient(RQ), analysis different sensory function.

Results
Elite and national-standard athletes balance control have more effect of plantar stimulation than visual afferents, the opposite feature in healthy individuals. Interaction of visual afferents and plantar stimulation, athletes balance ability in AP and ML direction is better than healthy individuals, visual afferent condition shows opposite features.

Discussion
Elite and national-standard athletes are more sensitive to proprioception, visual sense do not affect athlete balance control. Meanwhile, the balance ability of ML direction is better than AP direction was common feature of athletes and healthy individuals, but visual afferents can cause a deviation in the direction of the ability of healthy individuals to control balance.

Figure and Tables
Figure1 and Figure2. Compare the effects of visual afferents and plantar stimulation on balance control ability. Feature of COP direction in elite athletes,

Table 1: Plantar Quotient and Romberg Quotient of different group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Direction</th>
<th>Elite</th>
<th>National-standard</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>ML</td>
<td>98.3±32.5</td>
<td>40.0±16.9</td>
<td>25.0±8.2</td>
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Equations
(1) Plantar Quotient calculation
\[ PQ = \frac{SE_{\text{foam}}}{SE_{\text{firm}}} \times 100 \]  
(2) Romberg Quotient calculation
\[ RQ = \frac{SE_{\text{eyes \ closed}}}{SE_{\text{eyes \ open}}} \times 100 \]  
The PQ provides information on the weight of plantar cutaneous afferents used in postural control. The PQ consists of the ratio between the COP sample entropy while the subjects stand on foam while they stand on firm surface. Likewise, this ratio betrays the influence of visual afferents in postural control. RQ is composed of the ratio of COP sample entropy when volunteer eyes are open and closed.

References
PREDICTING FEMORAL STRENGTH FROM 2D-3D DXA FINITE ELEMENT MODELS ACROSS AGE AND ETHNICITIES

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Introduction

Femur strength derived using quantitative computed tomography (QCT)-based finite element analysis (FEA) has been shown to be a better predictor of fracture risk than areal bone mineral density (aBMD) in a Caucasian cohort [1]. However, its adoption in clinical practice has been limited, as these models rely on the acquisition of 3D QCT images, which have higher costs and radiation exposure compared to 2D imaging methods such as dual-energy X-ray absorptiometry (DXA). Recent studies have utilised 2D-to-3D reconstruction of shape and BMD distribution (3D-DXA) to predict femoral strength [2, 3], but are limited in terms of sample size, or have been performed using ex vivo scans. This work validates and improves the prediction of femoral strength from 3D-DXA against QCT-based FE models, acquired from in vivo scans in a multi-centre study.

Methods

112 paired 3D-DXA and QCT images from five cohorts (age 20-88; absence of bone disease treatment) were included in this study. 3D-DXA images were estimated from 2D-DXA images using statistical shape and density modelling (3D-Shaper, Galgo Medical). A validated approach for sideways fall simulation was used [1, 2]. The bone anatomies were converted into smooth, continuum models with 10-node tetrahedral elements. Bone elastic moduli were mapped from Hounsfield units (K2HPO4 phantom, QCT Pro). Non-linear material properties (compression-tension asymmetry, strain-rate dependency) were assigned. Boundary and loading conditions used are indicated in Figure 1. Femur strength was calculated as the maximum force experienced in the femoral neck during loading.

Results

Bone volumes and femoral strength from 3D-DXA models were under-predicted (Figure 2A). Linear regression between 3D-DXA and CT volumetric BMD (vBMD) was $y = 0.88x + 24.8$ mg/cm$^3$, $R^2 = 0.72$. New geometries created by 1) binarising and eroding the 3D-DXA greystack volumes, and 2) calibrating vBMD within the modified 3D-DXA surfaces to obtain a 1:1 regression with CT vBMD, improved femoral strength prediction (slope: 0.97, offset: 0.68 kN; Figure 2B).

Discussion

The improvement in the coefficient of determination of vBMD from $R^2 = 0.72$ to $R^2 = 0.79$ was not reflected in the change in correlation for femoral strength. This suggests that optimisation of the bone distribution in the 2D-to-3D reconstructions of DXA scans may further improve the prediction of femoral strength.

References

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Acknowledgements

This work was supported by grants from the National Research Foundation Singapore (Future Health Technologies programme), the ETH focus area (PHRT #325, #430), the Korea Health Industry Development Institute (H122C0916), Hanmi Pharmaceutical Co. Ltd. (4-2018-0845) and the NIH (R01AG050656, K25AG058804, F31AG069414).
A NEW OPEN-SOURCE WORKFLOW FOR MULTISCALE MODELING OF HEPATIC PERFUSION

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Introduction

A failure of the blood micro-circulation in the liver is generally linked to the loss of cell functions and the development of hepatic diseases such as fibrosis. Therefore, studying liver perfusion allows us to better understand its degenerative and pathological behavior. The mechanism of hepatic perfusion is particular and involves several phenomena. The liver receives about 70% of the blood from the portal vein (PV) and 30% from the hepatic artery (HA) and drains it toward the hepatic vein (HV). These vessels bifurcate within the liver to form three vascular trees covering the entire organ tissue. Vessel bifurcation is accompanied by a size reduction resulting in a variation of diameter from $10^{-2}$m at the principal vessels to $10^{-5}$m at the final capillaries. The exchange between these vascular trees occurs at the final capillaries level. Given the strong dependency between macro- and micro-circulations, a multiscale model is essential to a better understanding of hepatic perfusion. The two main obstacles to a such model are the range of variation of the vessel diameters and the inability of current imaging techniques to capture small vessels. Recent studies have introduced a multi-compartment model that overcomes these limits in modeling highly perfused tissue [1] and it was applied to cervical, cardiac, and hepatic perfusion. This model uses optimization methods such as the CCO algorithm to generate low-level vessels in a way to mimic the anatomical vascular tree properties [2]. The current paper presents a patient-specific application of the multi-compartment model to liver perfusion using a fully open-source workflow that will be published in open access after its validation.

Methods

In this study, the HA supply is neglected, only the flows in PV and HV are considered. The geometry of the liver and the principal vessels of PV and HV are constructed based on CT-Scan sequences of a 62-years old male without a tumor (IRCAD database [3]). The flow in the vessels captured by CT is supposed unidirectional and is computed using mass conservation and Bernoulli equations. The results of the 1D flow at the terminal segments of the principal trees will be defined as boundary conditions for the flow in the parenchyma.

The smaller vessel trees, non-captured by CT are generated artificially using CCO. The artificial, but anatomically veracious, network is used to define a 3D flow in the parenchyma assimilated to a porous media. The main idea of the multi-compartment model is to divide each artificial vascular tree into N hierarchies based on vessel diameter. Let $C_{T,I}$ be a compartment defined by the hierarchy I (1 ≤ N) and the tree T (PV or HV). The blood exchange between HV and PV is only possible at the smallest capillary level defined by the compartment $C_0 = C_{W,0} \cup C_{HV,0}$. The flow in parenchyma is computed at each compartment $C_{T,I}$ according to the following Darcy system:

$$-k_{T,I} \nabla v(p_{T,I}) + \sum_{j=0}^{N} \chi_{T,I}(p_{T,I} - p_{T,I}) = 0$$

where $k_{T,I}$ is the permeability of $C_{T,I}$, $p_{T,I}$ its pressure, and $\chi_{T,I}$ is a coupling coefficient between $C_{T,I}$ and $C_{T,J}$. The permeability and the coupling coefficients are obtained by a parametrization process based on the architecture of the artificial tree [1]. Three compartments are defined in the current model. The parameterization process is carried out using a Python script and the FE simulations are performed using FreeFem++.

Results

The pressure distribution in the lower level is in the physiological range (Fig.1). The pressure value is maximal near to PV source points and minimal near to HV sink points. As expected, the velocity magnitude drops from higher to lower compartments since the pressure variation range decreases in the small vessels.

![Figure 1: Pressure in compartment $C_0$](image)

Discussion

The multi-compartment model permits to study the multiscale mechanism of liver perfusion. For lack of experimental data, the model can be validated by comparing the obtained results with a Poiseuille flow computed in the whole vascular tree. After validation, the presented workflow can be used to study the effect of pathological alterations on liver micro-circulation.

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MEASUREMENT OF PRESSURE DROP IN ARTERIAL STENOSIS WITH COLOR DOPPLER IMAGING

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Introduction
Vascular stenosis is a condition in which a vessel narrows, reducing blood flow to the tissues it supplies. Assessing the severity of vascular stenosis is critical to making therapeutic decisions. A standard method is to scan the narrowed area with ultrasound and measure geometric indices, providing limited information about the hemodynamic function. An alternative is to measure the pressure drop induced by the stenosis. It can be assessed by catheterization, an invasive medical procedure with some risk of complications, in which a pressure wire is inserted into the bloodstream. To limit cost and clinical side effects, non-invasive methods based on ultrasound imaging of blood flow would be more appropriate [1]. In this study, we present an original non-invasive method for estimating transtenotic pressure drop using clinical vascular color Doppler ultrasound.

Methods
Color flow imaging provides only the velocity projection along the ultrasound propagation axes. The innovative non-invasive method is based on 1) recovering the 2-D velocity vector field from this scalar Doppler velocity field by solving a zero-divergence optimization problem, and 2) deriving the relative pressures by integrating the Navier-Stokes equation. We validated our approach using multiphysics simulations and in vivo experiments covering different physiological conditions (mild and moderate severity, low to high flow).

Simulations – We performed computational fluid dynamics CFD simulations of axisymmetric transtenotic turbulent flows. After adding virtual seeding particles, we simulated color Doppler images generated by a linear ultrasound probe using the open-source simulator SIMUS [2, 3].

In vitro – Blood-mimicking fluid flowed into homemade carotid stenosis phantoms. Doppler velocities were acquired with a clinical ultrasound scanner (GE Vivid iq). Upstream and downstream pressures were measured with pressure guidewires (Philips ComboWire) to obtain the ground-truth pressure drops.

From color Doppler to pressure drops – To recover the velocity vector fields from the Doppler scalar fields, we minimized a regularized cost function that ensures the preservation of the Doppler velocities under the mass conservation constraint [4]. The pressure drops were then estimated by solving the Navier-Stokes equation using a finite difference method.

Results
Pressure drops estimated by color Doppler ranged from 0.5 to 28 mmHg for flow rates between 0.2 and 1 L/min. Considering both in silico and in vitro data (N = 26), we observed a very good agreement between Doppler-based and reference pressure drops (y = x - 0.04, r^2 = 0.97).

Discussion
In contrast to other studies [1], our results show that it is possible to estimate turbulent pressure losses in arterial stenoses using conventional color Doppler ultrasound. The next step will be to generalize our method to asymmetric stenoses. Once generalized, it will be tested in patients with carotid stenosis.

References

Acknowledgments
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A NUMERICAL AND EXPERIMENTAL APPROACH FOR EVALUATING THE RELIABILITY OF CERVICAL SURGICAL INSTRUMENTATION

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Introduction
Multi-use Surgical Instruments (SI) are composed of several instruments made of stainless steel, which can be reused and stored in the hospital for several surgeries after sterilization to avoid cross-infection among the patients. The sterilization process is generally performed internally at the hospital hosting the kit and it is an energy-intensive process (20kWh of electricity and 500l of water for medium-to-large-sized hospitals) [1]. These procedures lead also to complications in terms of (i) significant time loss in performing the safety and hygienic protocols; (ii) elaborated logistic management in the hospital [2]; (iii) fracture in the operating room due to difficulties in assessing the performances of the instruments after several usages (30 cases of intraoperative SI breakages of a total of 8132 surgeries [3, 4]). The introduction of the single-use SI can overcome the limitations reported above and also improve the economic and environmental impact that still occurs with standard instrumentation [1, 3–6].

This work aims to provide a workflow for the mechanical redesign of a multi-use SI into single-use SI (Figure 1), starting from the analysis of the current situation. The case study is an instrumentation kit for cervical cage implantation (Sharkage system, 2B1 s.r.l, Milan, Italy, Figure 1a).

Materials and Methods
The redesign of the instruments was based on two steps (i) Estimation of the mechanical strength through a validated approach. The ad-hoc simulation was performed on the most critical component of the kit using Abaqus 2022 (Dassault Systèmes, SIMULIA Corp., RI) assigning stainless steel material (E=210GPa; v=0.3) to the SI and imposing a displacement (7 mm) to an ad-hoc undeformable setup (Figure 1b1, a friction equal to 0.3 was defined). Three different experimental tests were performed to validate the model in terms of stiffness (K, slope of force-displacement curve) and local strains (εPron) measured using the strain-gauge rosette. (ii) Development of an in-vivo measurement system to identify the boundary conditions to which the instrumentation is subjected during surgery. An axial-torsional measuring system to be used during the surgical act was designed and tested (Figure 1b2).

Results
(i) Estimation of the mechanical strength through a validated approach. The numerical model demonstrated good agreement with the experimental test (with a percentage difference of less than 10% in terms of K and εPron). In the SI different zones resulted to be effected by von Mises stresses greater than the yielding stress (800 MPa) when the force is equal to 38 N (Figure 1b1).

Development of an in-vivo measurement system. To record the force and torque during the surgery, the design of the beat plug was modified to house the bi-axial load cell (Figure 1b2). Therefore, this information will be the basics in redesigning and assigning the new material to the single-use SI. A future step will be to perform the measurement activity during a real surgery or on cadaveric specimens.

Discussion
This work presents a path to redesign a SI starting from the knowledge of its mechanical behaviour. The final goal is reducing the life cycle assessment's economic and environmental impact of the instrument kit [2, 4].

References

Acknowledgments
The authors gratefully acknowledge Carlo Miglietta (2B1 Srl, Milan, Italy) and Davide Pizzamiglio (Leghe Leggere Lavorate Srl, Milan, Italy) for providing the CAD and the devices useful for the numerical and experimental activity.

Figure 1: The workflow for the mechanical evaluation of the current SI.
AN EXHAUSTIVE TEST PROTOCOL FOR THE MECHANICAL CHARACTERIZATION OF SURGICAL MESHES

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Introduction
The mechanical characteristics of surgical meshes, adopted for the strengthening of herniated abdominal wall and for the treatment of pelvic floor disorders, are often burdensome to determine and compare due to the absence of specific standards or harmonized test protocols [1], [2]. In this context, it is usual to adapt International Standards, available for different scopes, in terms of (1) reduction in specimens dimension and (2) adjustment of test parameters (e.g. strain rate) [3]. The computation of mechanical parameters is also affected by the lack of specific standards which define results to report as well as data post-processing methods. This study proposes an in vitro protocol for the mechanical characterization of surgical meshes. Its repeatability was tested on 14 polypropylene meshes, 3 composite meshes and 6 urogynecologic devices.

Methods
The test protocol was defined selecting three of the most performed test methods: ball burst test, uniaxial tensile test and suture retention test. All the tests are conducted under displacement-controlled conditions performing five replicates for each configuration. In uniaxial tensile test and in suture retention test, specimens are cut along the weak and strong knitting directions of each mesh. The test set up of ball burst test is adapted from ASTM D6797-15 using reduced dimensions of circular specimens and ball-burst attachment. Nonetheless, the ratio between the internal diameter of the ring clamp and the diameter of the spherical indenter, suggested by the standard, is not modified. The standardized testing rate of 300 mm/min is used for the penetration of the specimens by the indenter. The bursting strength (BS) and the corresponding membrane tension (MTmax) and dilatational strain (DSmax) are computed from the raw data. ISO 13934-1:2013 is used as reference standard for the uniaxial tensile test, although dogbone specimens are selected in order to reach a compromise between small dimensions and acceptable ruptures (beyond 5 mm from the gripped region). The test is performed at a rate of 20 mm/min. The displacement of the narrow zone is recorded through a Digital Image Correlation (DIC) system using two markers sewn on mesh locations that do not alter the motion of the yarns. Markers coordinates and raw data are used for the computation of specimens deformation and tension at rupture (SR and UTS). Moreover, from the slope of the initial portion of the strain vs tension curves the secant stiffness (k) is extracted. In suture retention test rectangular specimens (70 mm x 55 mm) are tested using a test configuration adapted from [3]. The specimens are clamped with the upper grip and a Assusteel® monofilament wire (0.350-0.399 mm diameter) is inserted 10 mm from the inferior edge of each specimen. The upper grip is moved vertically at a rate of 300 mm/min till rupture. The suture retention strength (SRS) is then computed from the peaks of the force-displacement raw curve according to ASTM D2261-13.

Results
The repeatability of the test methods was evaluated through a frequency analysis of the coefficient of variations (CVs) within the parameters computed on the 335 specimens tested. The CVs distributions for the different test methods (Figure 1) highlight a negligible variability among them. Median values between 0.05 and 0.14 are indeed found for the three test methods, with rare CV values over 0.25.

Discussion
The proposed protocol allows a comprehensive mechanical characterization of surgical meshes, providing (1) information complementary to the in vitro basic characteristic (e.g., uniaxial strain and tension) and (2) an estimation of mesh performance under physiologic-like loads. The proposed test protocol results easily replicable for all the 23 surgical meshes. We encourage its adoption in other laboratories in order to obtain an extended and comparable dataset, and to allow the determination of the inter-subject variability assessing its repeatability among different users.

References
A THERMODYNAMIC FRAMEWORK FOR SARCOMERE FORMATION IN CARDIOMYOCYTES SPREAD ON MICRO-PATTERNED SUBSTRATES

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Introduction
Identification of in-vitro protocols to develop mature cardiomyocytes (CMs) with ordered sarcomeric structures and aligned myofilaments is a challenge in cellular and tissue engineering [1]. An experimental study by Ribeiro et al. [2] reports human pluripotent stem cells (hPSCs) on high aspect ratio (AR) rectangular ligand patches develop aligned sarcomeres, however cells on square patches develop unaligned stress fibers (SFs). This mechanism of differentiation of hPSCs to mature CMs as a function of cell AR is not understood. We propose a novel thermodynamically based theoretical model for sarcomere and SF formation within a cell. We simulate the spreading of cells on square and rectangular adhesive patches and quantitatively compare our model predictions to experimentally measured levels of sarcomere formation.

Methods
We consider that cytoskeletal proteins can exist in three states within a CM: (i) bound as part of a SF ($\bar{N}_{SF}$), (ii) bound as part of a structured sarcomere ($\bar{N}_{BS}$), or (iii) unbound within the cytoplasm ($\bar{N}_{U}$). At steady-state conditions the chemical potentials of these three states are in equilibrium, which derives the areal density of sarcomeres at any point within the cell, given as

$$\bar{N}_{s} = \frac{1}{\tilde{\mu}_s} \frac{\bar{L}(1-\bar{N}_{SF})^2(\bar{N}_{U}+\bar{N}_{SF})\exp(\bar{L} \Delta \bar{U})}{\bar{L}_1 + (\bar{N}_{U}+\bar{N}_{SF})\exp(\bar{L} \Delta \bar{U})}.$$  (1)

We develop a statistical mechanics framework for CM spreading, analysing over two million cell spreads with MCMC walks [3]. The Gibbs free energy for a potential cell state is accepted if the energetic competition between sarcomere recruitment and elastic deformation reduces free energy relative to a reference state. Simulations are performed on micro-patterned ligand patches for comparison with in-vitro experiments [2].

Results
A sample of computed spread cells are shown in Fig. 1 for CMs on rectangular ligand patches. Highly aligned dense sarcomere structures are predicted for cells on 7:1 rectangular patches. In contrast, for a cell on a square patch our model predicts a low-density of sarcomeres. Computed sarcomere formation increases with AR, shown in Fig. 2B, in agreement with experimental measurements. Fig. 2C shows the computed distribution of sarcomere orientations as a function of patch AR. Again, strong agreement with experiments is observed, with elongated CMs exhibiting higher levels of alignment. Experimental images of Ribeiro et al. [2] for comparison, with similar trends to our model prediction. Our model uncovers the following mechanism: Gibbs free energy decreases with increased sarcomere density. Sarcomere areal density exponentially increases with in series units, driving an increase in sarcomere length. Such an increase in length is facilitated by elongated cells and opposed by isotropic cells of similar area.

Discussion
We present the first thermodynamically based theoretical model for sarcomere formation in CMs, and implement this model in a novel statistical mechanics framework to simulate cells spreading on micro-patterned ligand patches. Decreased Gibbs free energy is driven by sarcomere formation as cells spread into highly elongated states. Our model predictions are in strong agreement with the experimental observations of Ribeiro et al. [2]. The mechanism of sarcomere formation uncovered by our model may guide in-vitro strategies to generate mature contractile CMs. Optimal dynamic loading regimes promoting sarcomere formation can be identified using our model [4]. Our framework can be implemented into finite element models of a heart predicting the influence of a range of pathologies on remodelling of sarcomeres in-vivo [5].

References

Acknowledgements
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A THERMODYNAMIC FRAMEWORK FOR SARCOMERE EVOLUTION IN CARDIOMYOCYTES SUBJETED TO DYNAMIC LOADING

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Introduction

Development of in-vitro protocols to mature cardiomyocytes (CMs) with sarcomeric structures and aligned myofibrils is a key challenge in the field of cell and tissue engineering [1]. Physiologically sarcomeres consist of ordered actin-myosin (AM) bounded by Z-bands [2]. Similar to sarcomeres, stress fibres (SFs) actively generate tension through AM cross bridge cycling. However, SFs are unstructured and do not contain Z-bands or titin, and consequently generate lower levels of tension than sarcomeres [3,4]. The in-vitro study of Dou et al. [5] shows dynamic stretching increases sarcomere formation in comparison to static controls. The mechanism by which dynamic loading increases sarcomere formation and matures CMs is unknown. Understanding the role of mechanical loading in sarcomere formation would significantly contribute to the field of cardiac tissue engineering.

We propose a novel dynamic theoretical formulation for remodelling of sarcomeres and SFs. Our analyses uncover a thermodynamic basis for the relationship between dynamic loading and sarcomere formation, including the key energetic role of titin in this process.

Methods

In our thermodynamic framework, evolution and remodelling of sarcomeres and SF formation is driven by differences in chemical potential. Areal sarcomere evolution from unbound cytoskeletal proteins is derived:

\[
\frac{\partial \hat{n}_{SU}}{\partial t} = \omega_S P \exp \left( \frac{\hat{n}_{S} \mu_{U} - \mu_{S}}{k_B T} \right),
\]

where \( \hat{n}_{S} \) is sarcomere concentration in series, \( \mu_{U} \) is enthalpy of proteins in unbound states, and \( \mu_{S} \) is an activation barrier for sarcomere formation, \( P \) is a function of recruited bound AM proteins, where conservation of AM proteins is applied between unbound proteins \( \hat{n}_{U} \), SFs \( \hat{n}_{SF} \), and sarcomeres \( \hat{n}_{BS} \). Areal sarcomere generation from bound SFs, is:

\[
\frac{\partial \hat{n}_{SF}}{\partial t} = \omega_S P \left( \frac{\hat{n}_{SU} \hat{n}_{SF}}{\hat{n}_{U} \hat{n}_{BF}} \right)^{1/\nu_5} \exp \left( \frac{\hat{n}_{S} \mu_{BF} - \mu_{S}}{k_B T} \right),
\]

where \( \mu_{BF} \) is enthalpy of bound SF proteins. Sarcomere dissociation is controlled by the enthalpy of bound sarcomere proteins \( \mu_{BH} \), which is a function of strain and titin elasticity. Total remodelling of sarcomeres is:

\[
\frac{\partial \hat{n}_{S}}{\partial t} = \frac{\partial \hat{n}_{SU}}{\partial t} + \int_{C}^{D} \frac{\partial \hat{n}_{SF}}{\partial t} d\theta = 2 \omega_S \hat{n}_{S} \exp \left( \frac{\hat{n}_{S} \mu_{BF} - \mu_{S}}{k_B T} \right).
\]

Results

We simulate a CM spreading to a steady-state geometry over a two day period, which is then subjected to biaxial dynamic strain at 1Hz for a further eight day period. Evolution of SFs and sarcomeres in a cell subject to 20% loading, as well as static conditions shown in Fig. 1A. Dynamic loading leads to rearrangement of proteins in SFs, to form sarcomeres. Fig. 2B shows alignment and concentration of SFs and sarcomeres for static and dynamic cases. Fig. 2C shows model predictions of increased sarcomere concentration due to dynamic loading, in agreement with experimental values [5].

Fig 1: A) Dynamic evolution of protein concentration for static control (solid line) and biaxial dynamic loading (dashed line). B) SF and sarcomere orientation and concentrations following eight days of loading. C) Sarcomere concentration (normalised to static) following eight days of dynamic loading.

Discussion

The key finding that emerges from our novel thermodynamic framework is that titin stretch during applied dynamic loading of CMs results in a reduction in the standard enthalpy of sarcomeres, driving remodelling of cytoskeletal proteins from SFs to sarcomeres. Our model predicts that application of a dynamic biaxial stretch of 20% at 1 Hz results in a three-fold increase in sarcomere concentration, aligning with the in-vitro measurements of Dou et al. [5]. Our model suggests that titin knock-out experiments will lead to reduced sarcomere formation and increased SF formation under dynamic loading, as observed in-vitro [6]. The dynamic remodelling framework will also be extended to simulate hypertrophy due to altered mechanical loading of the myocardium [7].

References


Acknowledgements

Science Foundation Ireland (grant 18/ERCd/5481);
NUMERICAL DETERMINATION OF AN ANATOMICAL STRUCTURE’S UNLOADED STATE FROM IN VIVO MEDICAL IMAGING

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Introduction
Medical imaging allows bio-mechanician to obtain in vivo geometrical data, useful for patient-specific organic tissues mechanical modeling. However, geometrical data coming from medical imaging describe a strained state of anatomical structure under anatomical loading (such as weight, pressure, arterial tension etc). The non-linear mechanical behavior of the soft tissues constituting those structures prevents to easily find their unloaded geometry.
One who wants to study intravascular device positioning through mechanical computation would need a method to determine the unloaded state of an anatomical structure, assuming its mechanical behavior and its boundary conditions.
Numerical methods exist to find the unloaded geometry of a given loaded one, supposing the boundary conditions. Along those methods, some need from the user to write the variational formulation thus to have a control on the used solver [1]. Other methods can use enough of a structural solver as a black box [2], [3].
Most of those methods use volumic finite element modelling. Our work targets on applying such methods to shell and beam element and present limitations.

Methods
The fixed point algorithms found in the literature have been modified to work with shell or beam modeling, as presented in Figure 1. In particular, rotations must be taken into account.

Results
This algorithm was applied to simple cases and to anatomical ones. A case of cerebral aneurysm obtained from 3D rotational angiography is presented in Figure 2. It is supposed under homogeneous inner pressure, with nodes from its outlet totally blocked and hyperelastic mechanical behavior from literature [4].

Discussion
With the presented algorithm, we successfully approximated the solution of the inverse elastostatic problem of an anatomical structure’s inflation, through shell modeling.
We found that in addition to its dependence on material modeling and image analysis accuracy, this method is highly dependent on boundary conditions. Wrong agreement between those parameters would result in mechanical incompatibilities and prevent the algorithm to converge.
In particular, contact between the aneurysm wall and bone structures can lead to divergence of the algorithm.
Our work allows us to better identify and detect these cases of non-convergence.

References
CORONARY MICROVASCULAR DISEASE: HOW TO ASSESS THE LOCAL HEMODYNAMIC CHANGES

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Introduction

Between 50 and 65% of individuals presenting acute chest pain, but without occlusive pathologies of the epicardial coronary arteries, are affected by coronary microvascular disease (CMD) [1]. CMD is a responsible factor for cardiac perfusion impairment, with the endothelium subjected to an inadequate vasodilatory or pathological vasoconstrictive response. This pathology is characterized by a sensible alteration in the microvasculature local hemodynamics and represents a timely and unsolved clinical problem, due to the current diagnostic and treatment challenges. Due to the microscopic dimension, no current imaging or testing modalities consent in-vivo visualization of the vessel morphological and hemodynamic changes, delaying the diagnosis and the (limitedly) possible treatment. Aiming at assessing the perfusion impairment (i.e., the degree of the microvascular obstruction) through local hemodynamic descriptors, we develop an integrative platform based on additive manufacturing and computational fluid dynamics (CFD) providing the tool to analyse the hemodynamic alterations occurring in CMD.

Methods

This work is subdivided into an experimental, a computational, and a coupling phase. First, an idealized model of the coronary microvasculature is created. The bifurcating model (Fig. 1-A) is constructed by following the Murray’s branching model [2]. The model (1-mm inlet and 0.4-mm outlet diameter) is employed for both the experimental and the computational analyses. Second, on the experimental side, a hybrid fabrication protocol based on 3D printing and soft lithography (Fig. 1-B) is created. The substrate material is chosen based on surface reproducibility, cyto-compatibility and the similarity to vessel-like structures. Being the 3D printed material cytotoxic, polydimethylsiloxane (PDMS) and polytetrafluoroethylene (Teflon) were compared. To assess the reproducibility of the fluidic chips, surface profile measurements were conducted. Moreover, the cytotoxicity of the fabricated chips was preliminarily analyzed by culturing HEK cells. Third, the microvascular tree model is employed for conducting CFD simulations (steady-state, Ansys Fluent) at different perfusion conditions (Fig. 1-E). The boundary conditions for the in-silico model were derived from the in-vitro flow testing. Last, increasing levels of perfusion impairment were created (including the physiological ‘control’ case) by coupling the in-vitro and in-silico models (Fig. 1-F).

Results

The fabricated Teflon and PDMS chips resulted to be similar: significant differences (p-value < .03) were found in few regions of the PDMS chips due to manual fabrication. Following the HEK cell culture, no statistical differences were found between the PDMS and Teflon chips at harvesting days 3 and 7.

The experimental analysis of the obstructed scenarios provided the out-split boundary conditions for the CFD model, while an inlet flowrate of about 195 μl/min (set as flat inlet velocity of 0.012 m/s) was imposed. The wall shear stress (WSS) distribution was changing in function of the number and location of the occlusions, in agreement with the in-vitro measurements. A compensatory effect (different WSS gradients) was noticed in the upper portion of the microvascular tree as function of the obstructions’ localization.

Discussion

The reported integrated platform resulted suitable for the analysis of the hemodynamic changes occurring in the coronary microvasculature dysfunction and obstructions. Combining the potential of 3D printing and CFD analysis, this cost-effective platform can further the CMD biomechanical understanding and link to in-vivo measurements of coronary flow reserve.

References

COMPUTATIONAL OPTIMIZATION OF THE PRIMARY FIXATION
STABILITY OF PROXIMAL TIBIA FRACTURES

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Introduction

Bone fractures cause about two million hospitalizations per year just in the US. Some of them are highly complex with complication rates of up to 28% [1]. It is often unclear how the screws and plates shall be positioned for a specific fracture case and outcomes heavily depend on the surgeon’s experience.

An objective measure for the performance of clinically accomplished fracture reconstructions by means of finite element models (FEMs) under biomechanical loading was previously described [2]. The goal of this study was to use the same computational method for optimizing screw and implant placement of a clinically failed, multifragmentary tibia plateau fracture reconstruction (Schatzker VI).

Methods

Using the previously introduced method the clinical reconstruction was reverse engineered by means of a preop and postop CT scan for the segmentation of bone fragments and hardware materials (i.e. osteosynthesis screws and plates), respectively [2]. Hounsfield-Unit-derived bone material properties as well as joint and muscle forces from subject-specific musculoskeletal gait models were integrated in the FEM (Figure 1).

The case presented herein was clinically reconstructed with a posteromedial, lateral, and distal medial plate but required revision surgery one year postoperatively due to a non-union including failure of two medial screws. Thus, the reconstruction was optimized in two ways and compared to the clinical configuration:

- The medial plate was shifted more posteriorly to counteract the posterodistal fragment motion.
- A fully new configuration of screw placement with design freedom for patient-specific implants.

Results

By shifting the posteromedial plate more posteriorly, the maximum fragment motion in a gait cycle was reduced by 28% and the load on the screws was distributed more evenly. By using the full design freedom for the fracture fixation construct, the fragment motion could be reduced approx. tenfold, whereby the von Mises stresses on the screws also highly decreased (Figure 2).

Discussion

The case study presented herein illustrates the potential for biomechanical optimization of complex fracture fixation constructs, although absolute values need to be interpreted with caution as this method has not yet been validated experimentally. However, the clinically broken screws also showed the highest von Mises stresses in the FEM, providing a qualitative clinical proof-of-concept. After validation of the model, clinical outcomes of the fracture fixation could be predicted by means of fragment motion and screw loading.

References


Acknowledgements

Our gratitude to Alex Baker and Marco Drago from the Institute for Biomechanics for their support.
FUNDAMENTAL INSIGHTS INTO STENT-VESSLE INTERACTIONS THROUGH A NOVEL CONSTITUTIVE LAW AND IN-SILICO FRAMEWORK.

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This study presents a subject-specific in-silico framework in which we uncover the structure-function relationship between the spatially varying constituents of the aorta and the non-linear compliance of the vessel during the cardiac cycle uncovered through our MRI investigations. We then proceed to uncover a fundamental insight into stent-vessel interactions, and describe the mechanism by which Nitinol stents affect local vessel compliance. First, a microstructurally motivated constitutive model is developed, and simulations reveal that internal vessel contractility, due to pre-stretched elastin and actively generated smooth muscle cell stress, must be incorporated, along with collagen strain stiffening, in order to accurately predict the non-linear pressure-area relationship observed in-vivo. Simulations reveal that collagen and smooth muscle volume fractions increase distally, while elastin volume fraction decreases distally, consistent with reported histological data [1]. The study then presents a computational analysis of the influence of Nitinol-based devices on the biomechanical performance of a healthy patient-specific human aorta. Simulations reveal that Nitinol stent-grafts stretch the artery wall so that collagen is stretched to a straightened high-stiffness configuration. The high-compliance regime (HCR) associated with low diastolic lumen pressure is eliminated, and the artery operates in a low-compliance regime (LCR) throughout the entire cardiac cycle. The slope of the lumen pressure–area curve for the LCR post-implantation is almost identical to that of the native vessel during systole. This negligible change from the native LCR slope occurs because the stent-graft increases its diameter from the crimped configuration during deployment so that it reaches a low-stiffness unloading plateau. The effective radial stiffness of the implant along this unloading plateau is negligible compared to the stiffness of the artery wall. Provided the Nitinol device unloads sufficiently during deployment to the unloading plateau, the degree of oversizing has a negligible effect on the pressure–area response of the vessel, as each device exerts approximately the same radial force, the slope of which is negligible compared to the LCR slope of the native artery. We show that 10% oversizing based on the observed diastolic diameter in the mid descending thoracic aorta results in a complete loss of contact between the device and the wall during systole, which could lead to an endoleak and stent migration. 20% oversizing reaches the Dacron enforced area limit (DEAL) during the pulse pressure and results in an effective zero-compliance in the later portion of systole [2].

Figure 1: (a) Microstructurally based constitutive law; (b) Patient-specific FE model fit to MRI data, and predictions of wall constituent volume fractions; (c) simulations of the effect of ageing on Pressure-Area curves; (d) Stent deployment in patient specific model resulting in loss of high-compliance regime of aorta.

References
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Acknowledgements
This study was supported by the Irish Research Council (EPSPG_2016_194).
MINI INVASIVE IMAGING WINDOW TO GUIDE AND IMAGE FOREIGN BODY REACTIONS IN VIVO

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INTRODUCTION

The standardized assessment of the fibrotic reaction to the implantation of a biomaterial is based on ex vivo histopathological techniques that require a great number of sacrificed animals. Intravital microscopy allows instead to improve the resolution of microscopy images and to reduce the number of lab animals, but this procedure currently implies unethical and highly invasive imaging protocols. To advance the field, we developed a miniaturized imaging window, the Microatlas1, integrating a micro scaffold able to guide tissue regeneration in vivo. The Microatlas can be implanted subcutaneously in a living organism to allow tissue regeneration and time-lapse imaging at the interface with an implanted biomaterial. By using label-free two-photon microscopy within the Microatlas implanted in living chicken embryos and repopulated by the host cells and blood vessels, here we quantified the foreign-body reaction in the same tissue district, at subsequent time points during implantation (Figure1, a).

METHODS

We fabricated the scaffolds (of dimension 500x500x100μm3) on glass coverslips (Ø:12 mm) by two-photon polymerization of a polymer called SZ2080 (Figure1, a). We performed the chorioallantoic membrane (CAM) assay in living chick embryos at 3, 4 and 7 days after implantation. The imaging window was inspected in vivo by two-photon label-free and confocal microscopy. Collagen I was visualized in second harmonic generation (SHG). Embryos were sacrificed to perform ex vivo inspections. The CAM was labelled with DRAQ5 and imaged by confocal microscopy or stained by hematoxylin&eosin and paraffin-sectioned.

RESULTS

In chick embryos, confocal and two-photon inspections at implantation sites demonstrated growth of tissue inside the scaffolds (Figure1, b) and neo vascularization (Figure1, c) with presence of a capillary density six times greater than in unimplanted control tissue. SHG showed the presence of a preferentially oriented layer of collagen-I, with a density comparable with control regions. Confocal microscopy allowed for the quantification of cell density, that showed an infiltration rate two-fold greater than in untreated tissue. We identified and counted infiltrated cell populations, including granulocytes, fibroblasts and endothelial cells.

DISCUSSION&CONCLUSION

The Microatlas was able to guide the host foreign body reaction to the micro scaffolds, in terms of cell repopulation, collagen generation and capillary formation. This miniaturized device has the potential to be used as a reliable and ethical imaging window for intravital quantifications, potentially replacing the current highly invasive window chambers. Also, with the Microatlas we can reduce the number of animals employed in preclinical studies, refine, boost the analyses, and replace expensive and lengthy analyses of cellular density, blood vessels sprouting, collagen and fatty infiltrates based on traditional histopathology.

REFERENCES


Acknowledgements

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A SYNTHETIC EMBRYONATED AVIAN EGGSHELL COMPUTATIONAL MODELED TO PREDICT THE OXYGEN TRANSPORT

Claudio Conci (1), Leonardo Cherubin(1), Matteo Laganà(2), Emanuela Jacchetti(1), Manuela T. Raimondi(1)

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INTRODUCTION

The striking pandemic infection of Sars-Cov-2 highlighted the compelling need of experimental models aimed at speeding up the discovery and preclinical testing of new biological drugs, especially for drugs targeting the micro circulation (e.g. in diabetes, retinal disease, kidney disease, virology, etc.). Similarly, the vascular network is the key point in antiangiogenic, antibody-based and small molecule-based drug development for cancer research. The chicken embryo seems to be the perfect candidate to allow fast and versatile studies on a functional vascular network in response to injected targets. To this end, we computationally modeled an embryo at different developing time points (Figure 1, a) to identify a synthetic eggshell substitutive material providing physiological oxygenation.

METHODS

We performed computational simulations (COMSOL) to model a living chicken embryo at the 8th day of development and characterize its own protective shell. Thus, we modeled the egg as a prolate ellipsoid having radius of 1.4 and 1.7cm and a mesh having 195k tetrahedral elements. We assumed the eggshell as a porous material having a thickness of 300µm, porosity ~2% and tortuosity parameter equal to 1, juxtaposed to a thin film constituted by inner and outer shell layers having a total thickness of 65µm. We assumed the embryo localization in the central part of the egg having above an air sac of volume equal to 3 cm³ and an albumen layer of 18cm³ into the lower portion. For the chorioallantoic membrane, i.e. the embryo respiratory organ, we assumed a consuming surface of ~41cm² with a peak oxygen consumption, \( V_{\text{max}} \), equal to 5.14x10⁻⁶ mol/m²s and a kinetic governed by the Michaelis-Menten law (Figure1, b-c). Then, we assumed varying thickness of a membrane substitute material made of PDMS, with thicknesses of 100, 365, 800 µm.

RESULTS

Oxygen concentration decreased alongside the eggshell thickness with a concentration drop lower than 1% from the egg outer to inner boundaries. The air sac mean oxygen concentration resulted equal to 8.152mol/m³. Simulations performed on PDMS showed a decrease in air sac concentration ranging from 20% to 98% (Figure1, e) with respect to physiological values, considering the thinner and the thicker PDMS layer, respectively.

DISCUSSION

We developed a computational model able to predict oxygen concentration values in a chicken embryo at embryonic developing day 8. Our model agrees with experimental values found in literature with a mean error lower than 3% (Figure1, d). We are now performing measurements to validate boundary condition assumed in model, to calibrate the model and to extend its validity up to the 12th day of embryonic development. We are also experimentally testing our first synthetic eggshell substitute made of PDMS.

References

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Acknowledgements

Funded by the European Union (ERC, BEACONSANDEGG, G.A. 101053122). Views and opinions expressed are however those of the authors only and do not necessarily reflect those of the European Union or the European Research Council. Neither the European Union nor the granting authority can be held responsible for them.
A NEW SYNERGY-BASED FOOT MODEL: DESCRIPTION OF ARCHES MOBILITY IN HEALTHY AND FLAT FEET DURING GAIT

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Introduction

Internal mobility of the foot in gait analysis is usually addressed by multi-segment foot models (MFMs) [1]. These did prove clinical applicability, though cannot show measures of motion within the segments. Also, several markers are needed. Using Principal Component Analysis, we recently showed that the foot joint mobility can be represented with only four modes, or synergies [2]. Differently from the concept of degrees-of-freedom (DOF) in ideal joints such as revolute or spherical pairs, each synergy implies all bone motion components, thus establishing the coupling among them. The aim of this work is to test a synergy-based approach to reconstruct the foot joint motion during gait. In particular, the variation of foot arches in healthy and flat feet were compared, resorting only to three markers on the tibia and three on the foot.

Methods

Gait data were collected for 3 healthy and 3 flat foot volunteers during level walking, using a state-of-the-art experimental protocol [3]. Reference synergies and bones, featuring virtual markers and anatomical reference systems [4], were scaled on each subject based on foot length. Bone motion was reconstructed through synergy-based multi-body kinematic optimization, tracking the shank (6 DOF) and the foot posture as the linear combination of 4 bone synergies (4 DOF) at once, resorting to 3 markers on the shank and 3 markers on the foot, namely CA, FMH, VMH as in [3]. The angles characterizing the 3 arches of the foot (Fig.1) were also measured. T-test (p<0.05) identified differences between the two populations.

Results

Healthy feet showed considerable MLA and TA excursion, while arches were more open and less mobile in flat feet (Fig. 2). TA revealed almost the same capability to separate the two populations than the traditional MLA.

Discussion

The proposed synergy-based foot model worked successfully in the present initial clinical exploitation. With respect to standard MFMs, only three markers are needed on the foot, highly simplifying data collection and elaboration. Moreover, it allows the tracking of all bone motions, thus providing information about the complex foot behavior, such as the mobility of the longitudinal and transverse arches during walking.

References

EXPERIMENTAL IDENTIFICATION OF A CONTINUOUS, NON-LINEAR MAP OF THE KNEE COMPLIANCE

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Introduction
Understanding the knee response to loads is paramount to identify the causes of knee injuries and pathology [1]. Alternatively to explicit model of the joint, we present a present a continuous, non-linear map of the knee compliance: for any flexion angle and load, the map returns the relative position and orientation of the joint. In this work, we present how the map has been built and we will test it reliability versus experimental measure.

Methods
Three cadaveric legs were tested on a loading rig [2]. The femur reference system was set according to [3], while the tibia one was set as coincident with the femur one at leg full extension. Relative motion was expressed according to [4].

The rig is design to impose the knee flexion and a generic force and/or torque, leaving the remaining tibia-femoral motion components free to be determined by the joint equilibrium, while measuring the tibio-femoral motion with a stereophotogrammetric system.

First we measure the knee natural motion, i.e. without external loads.

To map the knee compliance, we then applied constant forces and torques along and about each axis of the tibia reference system, flexing the knee up to 140°.

For each loaded motion, knee compliance was defined according to [4].

To test the method, we compare the predicted knee compliance with experimental data obtained with four combined loading condition on each leg: a compressive load equal to 150 or 350 N in combination ± 10 Nm force and/or torque along and about each axis of the tibia reference system, flexing the knee up to 140°.

Results
Figure 1 shows the complie map in case of the drawer test, on the directly loaded AP components and on the IE. The complie is non linear: both anterior and posterior loads are associated with internital rotation of the knee. AP displacement varies non-monotonically with flexion. Table 2 report the Root Mean Squared error for the predicted vs measured knee displacement for the composed loading senario considered.

<table>
<thead>
<tr>
<th>Force</th>
<th>± [50,80,100]</th>
<th>+ [50,80,100, 150,200,250, 300,350]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torque</td>
<td>± [10,15,20]</td>
<td>± [5,8,10] ---</td>
</tr>
</tbody>
</table>

Table 1: Sign and magnitude of the applied load for the characterization of knee compliance: AA = abduction/adduction, IE = internal/external rotations; AP = antero/posterior, PD = proximo/distal, ML = medio/lateral translation.

<table>
<thead>
<tr>
<th>RMSe</th>
<th>AA</th>
<th>IE</th>
<th>AP</th>
<th>PD</th>
<th>ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.3°</td>
<td>4.1°</td>
<td>3.2 mm</td>
<td>2.0 mm</td>
<td>2.3 mm</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Root mean squared error between predicted and measure knee displacement under combined loads.

Discussion
Although other examples are available [5], to the authors knowledge this is the first continuous quantification of the knee compliance. This characterization of the knee could help in understanding ethology of knee pathology and in the design of better treatment and medical devices.

References
AUTOMATICALLY DESIGNED PATIENT-SPECIFIC INSTRUMENTATION FOR TOTAL ANKLE REPLACEMENT: AN IN-VITRO STUDY

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Introduction

Recent adoption of patient-specific instrumentation (PSI) in total ankle replacement (TAR) has enhanced positioning of the implant components, eliminating the need for complex external cutting jigs [1], with a significant decrease in operative time, reducing costs and risk for the patient [2]. We present an automatic procedure for the surgical pre-planning of TAR, also defining the cutting PSI for the tibia and talus. The accuracy of the proposed PSI is tested on one specimen.

Methods

The proposed procedure is based on the alignment of the BOX® Total Ankle Replacement – MatOrtho, but it is easily generalizable to different TAR. A pre-op CT scan (DICOM slicing 0.26mm) is acquired with neutral foot (Fig 1.A). To refer the implant, tibia and talus anatomical reference systems (ARS) are defined [3] and three points on the calcaneus, first, and fifth metatarsal bones are virtually palpated to identify the ground plane (Fig 1.B). If flexion angle in the pre-op scan is suboptimal for accurate surgical plan, flexion is adjusted using a patient specific ankle model reconstructing the individual joint motion based on articular morphology [4]. The implant is then aligned with the ground plane and ARS orientation. The surgeon can choose the implant size and between two axial alignments (Fig 1.C): the first based on the foot longitudinal axis, from the ankle center to the head of the second metatarsal; the second based on the mean orientation of the gutter planes. Once the prosthetic alignment has been confirmed, the bone models are virtually cut and the implant positioned (Fig. 1.D). PSI geometry is defined by intersecting a reference volume with patient’s bone model and TAR cuts (Fig. 1.E).

To test the procedure, we planned TAR for a specimen. The PSI were 3D printed (Fig. 1.F) and used to perform the cuts (Fig 1.G). After surgery, a post-op CT scan was performed and the position and orientation errors of post-op cuts with respect to the planned ones were quantified by model-to-model registration.

Results

Figure 1.H and 1.I shows the planned (blue) vs post-op (purple) cut bones. Table 1 reports the spatial orientation and position errors.

<table>
<thead>
<tr>
<th></th>
<th>FE</th>
<th>VV</th>
<th>IE</th>
<th>AP</th>
<th>PD</th>
<th>ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibia</td>
<td>0.4°</td>
<td>0.1°</td>
<td>0.1°</td>
<td>-0.1 mm</td>
<td>1.2 mm</td>
<td>0.5 mm</td>
</tr>
<tr>
<td>Talar</td>
<td>-1.3°</td>
<td>-1.1°</td>
<td>-0.7°</td>
<td>0.3 mm</td>
<td>0.3 mm</td>
<td>-0.6 mm</td>
</tr>
</tbody>
</table>

Table 1: Deviation of post-op cuts to pre-op planning: $FE =$ flexion/extension; $VV =$ varus/valgus, $IE =$ internal/external; $AP =$ antero/posterior, $PD =$ proximo/distal, $ML =$ medio/lateral.

Discussion

These preliminary findings support the efficacy of the adopted automatic methodology and the proposed PSI. Deviation of final cuts placement from the preoperative plan was less than 1.5 degrees in all orientations, providing greater accuracy than the ±3 degrees obtainable with traditional instrumentation and computer navigation [5].

References


Figure 1: Procedure for TAR planning and PSI design (top row), and experimental validation (bottom row).
IN-VIVO DETERMINATION OF PRE-STRESS AND TENSION LINES IN SKIN

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Introduction

Human skin is a difficult material to test and model, as its physical and geometrical properties depend on a host of parameters and conditions: thickness, location, age, health, ethnicity, hydration, etc. Destructive testing of skin samples only gives a partial picture, because harvesting skin dehydrates the sample and releases most of its residual stress, which is likely to alter its behaviour significantly.

In this study, we measure skin tension levels with the Reviscometer™ (CK electronic GmbH, Germany), a commercial device specially designed to test human skin in-vivo, non-destructively and non-invasively. We find that it is possible to determine, in-vivo, not only the orientation of patient-specific tension lines in real time, but also the amount of residual stress at a given location.

Methods

Experimental Protocol:
The Reviscometer™ has two needle sensors placed 2 mm apart: one emits an acoustic wave and the other acts as a receiver. The travel time gives the speed of the acoustic perturbation in all directions (360° in 10° increments). Experiments were carried out at room temperature on the volar forearm.

Analytical modelling:
We modelled the skin as an anisotropic, incompressible material under pre-stress, along a family of parallel fibres [1]. The strain energy density follows the Holzapfel-Gasser-Ogden (HGO) model with one family of fibres [2]. A detailed analysis reveals that the formula

\[ \sigma = \rho(v_{\text{max}}^2 - v_{\text{min}}^2), \]

(where \(v_{\text{max}}\) and \(v_{\text{min}}\) are the extreme values of the wave speed) is valid within an error of less than 9%.

Finite Element simulations:
We used a combination of Abaqus Standard and Explicit to simulate the wave propagating in human skin. The material parameters for the HGO model were as in human skin and taken from [3]. We employed symmetry conditions along both axes of symmetry, to reduce the computational cost. The mesh was refined in the impact region and had approx. 215000 elements. We replicated the in-vivo strains using an initial Static step in Abaqus Standard. We then used a Dynamic Explicit step and applied an instantaneous impulse, allowing the resulting wave to propagate. Finally, we measured the wave speed by tracking a specific identifiable feature of the wave at two points, 2 mm and 4 mm from the centre.

Results

We show that the Reviscometer™ can measure directly the in-vivo stress at a given site on human skin. The direction of skin tension can also be inferred from the Reviscometer™ data, as it corresponds to the fastest observed speed (Fig. 1). Additionally, we show that the wave created by the Reviscometer™ can be modelled as a surface wave propagating on a uniformly pre-stressed half-space, which we validate with Finite Element simulations.

Discussion

This study has clear applications in the identification of tension lines and the prediction of skin tension levels. These indicators are difficult to estimate in general, but they are most important factors in preoperative planning for surgeries, where incisions should be made along lines of maximum tension, to reduce scarring and the possibility for infection.

References


Acknowledgements

This work was supported by I-Form Advanced Manufacturing Research Centre, and by a Government of Ireland Postdoctoral Fellowship from the Irish Research Council (GOIPD/2022/367).
CAN EMG-DRIVEN MUSCULOSKELETAL MODELS ESTIMATE INDIVIDUAL MUSCLE DISPLACEMENTS?

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Introduction

Many movement disorders, including those caused by stroke and spinal cord injury, affect the neural control of muscle force and stiffness. To address this, neurorehabilitation seeks to restore healthy control patterns for each patient. In this context, electromyography (EMG)-driven musculoskeletal models are computational tools that enable studying relationships between muscle activation, muscle dynamics, and joint dynamics. EMG-driven models follow a bottom-up approach, i.e., they obtain joint level variables (such as joint torques and stiffness) from their constituting muscle-tendon units (MTUs), typically modelled as Hill-type muscle models. Several parameters of each constituting MTU are optimized to minimize the fitting error between reference and estimated joint torques, and a recent study proposed to minimize the fitting errors between reference and estimated joint torques and stiffness simultaneously [1]. Due to technical challenges, EMG-driven models are mostly validated at the joint level, and whether the neuromechanical states of the underlying MTUs are physiologically consistent remains an open question. This study presents the first attempts to validate EMG-driven model-based estimates of gastrocnemius medialis (GM) muscle displacements against experimental measurements via B-mode ultrasonography.

Methods

An experimental approach was used to obtain reference GM muscle displacements and joint torques and stiffness [2]. Four healthy young adults were seated with their right foot rigidly secured to a rotary motor, which was instrumented to measure ankle torque and displacement. Participants completed two different tasks: a torque-matched task and an EMG-matched task, where participants produced voluntary plantarflexion torque or average triceps surae EMG at 15% of their maximum, respectively, with the aid of real-time visual feedback. The motor moved the subject’s ankle through a 20-degree sinusoidal motion at 0.5 Hz. Small stochastic perturbations were superimposed on the large sinusoidal movement to quantify ankle impedance using time-varying system identification [3]. We evaluated the stiffness component of the estimated ankle impedance. B-mode ultrasound of the GM muscle-tendon junction was used to track muscle displacement. Experimentally recorded EMGs and joint angles were used to drive an EMG-driven model [1]. For each subject, reference joint torque and stiffness from the torque-matched task were used to calibrate the EMG-driven model, while the EMG-matched task was only used for validation purposes. Modeled muscle displacements were defined as changes in GM fiber length ($l_{GM}^f$) in the direction of the Achilles tendon, i.e., $l_{GM}^f \cos \varphi_{GM}$, where $\varphi_{GM}$ is the GM pennation angle.

Results

Preliminary results show that the EMG-driven model that was calibrated solely at the joint level accurately characterized a muscle-level variable, i.e., displacements of the GM muscle (Table 1). Fitting errors were greater in the task that was not used to calibrate the model.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Torque-matched task</th>
<th>EMG-matched task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>28</td>
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<td>3</td>
<td>31</td>
<td>41</td>
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<tr>
<td>4</td>
<td>13</td>
<td>111</td>
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</tbody>
</table>

Table 1: Normalized error between modeled and experimental GM muscle displacements. Results expressed as percentage of experimental RMS.

Discussion

While our results (Table 1) show the EMG-driven model that was calibrated solely at the joint level accurately characterized a muscle-level variable, i.e., displacements of the GM muscle, our results emphasize the need to validate complex musculoskeletal models across spatial scales. We envision that our novel approach combining expertise from different scientific communities will help us improve model parameter calibration, eventually leading to calibrated EMG-driven models that can simulate functional movements relevant to neurorehabilitation.

References


Acknowledgements

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MECHANICAL LOADING OF EX VIVO BOVINE TRABECULAR BONE IN 3D-PRINTED BIOREACTORS

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Introduction
In 2021, 18.3% of the world’s population was diagnosed with osteoporosis [1]. Bone biomechanical behaviour studies have shown that better understanding of bone tissue mechanics is key in the development of more effective strategies to prevent bone fracture, regenerate, and repair osteoporotic bone defects [2]. Although polycarbonate (PC) bioreactors have been successfully used to study tissue mechanics in bone cores ex vivo [3], they are difficult and expensive to fabricate, and the height-diameter ratio for bone cores is below the standard for mechanical compression tests [4]. A bioreactor system was developed using polyjet 3D printing and MED610™, which has been suggested as suitable for long-term culture [5]. This system had been validated in a previous study [6], however, leakage and other experiment limitations were observed. Thus, the objective of this study was to improve and continue the validation of the new bioreactor system in a long-term ex vivo bovine trabecular bone core experiment.

Methods
Twenty-two viable trabecular bone cores (10 mm height, 10 mm diameter) retrieved from a 3-year-old bovine sternum were individually cultured in custom-made 3D-printable MED610™ bioreactor chambers at 37°C and 5% CO₂, with constant culture medium perfusion (6.6 mL/hr), for 21-days (Figure 1a). Bone cores in bioreactors were ranked and sorted evenly based on their apparent elastic modulus (E_app) into control and loading groups (n = 11/group). The load group was stimulated mechanically (Figure 1b) five times per week with a “trapezoid” waveform that mimicked a physiological high-impact stimulus, with a Δ3000 με displacement and a strain rate of 3000 με/s for 120 cycles. Bone core E_app was assessed on days 0 and 21 in random order at room temperature with an initial 10 N pre-load, followed by a quasi-static -3000 με strain at -50 με/s. Data were analyzed in MATLAB 2020b (MathWorks) and E_app was calculated assuming linear elastic behavior with the last 50% of the linear force-displacement curve. A two-way ANOVA and a Tukey post-hoc tests (α = 0.05) were used to compare statistical differences between groups on days 0 and 21. A two-tailed t-test was used to compare between groups for percent differences in E_app after the 21-days (%ΔE_app). Shapiro-Wilk tests confirmed normality across all groups. All statistical analysis were performed in SPSS® Statistics 23 (IBM) and GraphPad Prism® 6.1 (Dotmatics).

Results
Bone cores tested on day 0 had a mean and a standard deviation E_app of 97.7 ± 30.3 MPa, with no significant difference between groups after sorting. After 21-days, the E_app decreased in all bone cores by 22.4% (± 20.6% SD) on average (Figure 1c). No significant differences in neither E_app nor %ΔE_app were observed between timepoints nor groups. Though not statistically different, there was a low % difference on day 0 between the E_app means of the load and control groups (0.1%), which increased to 7.3% after 21-days. Thus, the load group’s E_app decreased less, on average, than the control group (19.8% ± 19.6% decrease versus 25.0% ± 22.3%).

Discussion
The 21-days experiment was successful: no system leakage nor infections were observed. And although data analyses results do not follow the same trends in E_app changes as other ex vivo trabecular bone core studies using bioreactors [3,6], it is still relevant that the %ΔE_app decrease was higher in the control group. It is thought, then, that the mechanical stimulation might have helped in the overall bone health of the load group, to some extent. Stress-relaxation, culture medium, and histology analysis are being done for a deeper understanding of the unexpected bone behavior observed. More studies are required to address the small sample size limitations, as well as other possible sources of error, to confirm if this 3D-printed bioreactor system can be used (or not) for long-term ex vivo organ cultures.

References
A CORRELATIVE MULTIMODAL IMAGING APPROACH FOR SPATIAL TRANSCRIPTOMICS MECHANOREGULATION ANALYSIS

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Introduction
Bone is a hierarchical tissue with intricate metabolic processes spanning several spatial scales. Consequently, we have recently developed a correlative multimodal imaging (CMI) approach to correlate in vivo 3D micro-computed tomography (micro-CT) images with ex vivo 2D histological sections from the same bone sample [1], enabling a holistic analysis of this multiscale system. Likewise, spatial transcriptomics (ST) has enabled measuring high-resolution spatially resolved expression of thousands of genes from histological sections. However, a link between sub-cellular activity and organ- and tissue-level data is still missing. Therefore, in this work, we aimed to expand our CMI approach [1] to register ST data to the corresponding 3D micro-CT image. Through micro-finite element analysis (micro-FE) on the 3D image, the local mechanical environment can be correlated with the gene expression measured, enabling a unique association of organ-to-cell events.

Methods
The data used in this work consisted of time-lapsed in vivo micro-CT scans (10.5 μm, vivaCT 80) and formalin-fixed paraffin-embedded (FFPE) histological sections (5 μm thickness) from an adult female mouse femur. Micro-CT scans were Gauss-filtered (sigma 1.2) and binarized at 395 mgHA/cm³. A structurally intact FFPE section was prepared for the ST protocol [2] and transferred to a capture area of a ST slide (Visium, 10x Genomics). After probe hybridisation, ligation, library preparation and sequencing, the data was processed with Space Ranger (v.2.0.0). ST data was analysed with Scanpy and Squidpy, including Leiden clustering and uniform manifold approximation and projection (UMAP) algorithms. The 2D ST section was manually segmented based on the underlying tissues (bone, marrow, muscle, etc) and the mineralised bone matrix was 2D-3D registered to the corresponding in vivo micro-CT scan. Micro-FE analysis was performed to compute the mechanical signal as effective strain (EFF) using the 3D micro-CT image from the last time point. Spatially resolved gene expression data was correlated with the local mechanical environment (Spearman correlation coefficient, SCC).

Results
ST data yielded spatially resolved information for 19,112 genes (Q30 quality score above 93%, Figure 1A). Leiden clustering revealed anatomically credible clusters (Figure 1B) based on gene expression similarity, confirmed with UMAP. The ST data was successfully registered to the micro-CT scan (Figure 1C) and the mechanical environment was mapped to the gene counts obtained (Figure 1D), revealing genes both positively correlated with EFF, like Pick1 (SCC=0.26), and negatively correlated, such as Uqrc2 (SCC=-0.33).

Discussion
This work advances previous results [1], by establishing the computational tools required for a complete multiscale investigation of biological processes in bone. It can be applied to explore bone regeneration in defect models (shown here) or bone adaptation with other established models (like mouse vertebral loading), highlighting how organ- and tissue-level events influence (sub-) cellular activity. Indeed, we identified potential mechanosensitive genes, whose expression is associated with the perceived local strain (Figure 1D). With more comprehensive ST datasets, we hope to solidify the gene expression trends observed and isolate suitable targets for improving healing outcome or counter degenerative conditions such as osteoporosis.

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Acknowledgements
European Union (MechAGE ERC-2016- ADG-741883) and Functional Genomics Center Zurich (FGCZ).
VALIDATION OF A MULTIMODAL 2D-3D REGISTRATION ALGORITHM USING UNIMODAL SYNTHETIC EXPERIMENTS

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Introduction
Bone is a hierarchical tissue whose mechanobiological processes span several temporal and spatial scales. Recently, we have developed a correlative multimodal imaging (CMI) approach to correlate in vivo 3D micro-computed tomography (micro-CT) images with ex vivo 2D histological sections from the same bone sample [1], enabling a holistic analysis of this multiscale system. We analysed a mouse femur dataset of histological sections obtained along the samples’ longitudinal axis (LO), but it is not clear how cross-sectional (CS) images would perform. Further, an initial guess (IG) is required for the 2D-3D registration step, but its influence on the accuracy and convergence of the registration has not been quantified. Therefore, in this work, we developed a validation toolkit to perform synthetic experiments with known ground-truth (GT) transformations to evaluate the performance of our CMI approach. We compared the accuracy of 2D-3D registration for synthetic datasets containing CS and LO images of a mouse femur and quantified the convergence success of the registration depending on the IG considered.

Methods
The data used here was collected in a previous study [2], where 20-week-old C57BL/6J mice underwent femur defect surgery and were imaged weekly with in vivo micro-CT (10.5 μm, vivaCT 40) over seven weeks after surgery. Images were Gauss-filtered (sigma 1.2) and binarized at 395 mgHA/cm³. To mimic formalin-fixed paraffin-embedded LO and CS sections, three GT orientations were randomly sampled per condition and synthetic 2D datasets containing 25 parallel sections each were generated from 3D micro-CT at the last time-point (Figure 1A). Sections were 2D-3D registered iteratively based on binary image similarity. For each section, IG transforms were defined between 0-100% (step 25%) of their GT rotation and translation. Each registration ran for a maximum of 50 iterations, converging if the root sum squared error between GT and optimised parameters reached 1. The accuracy of the registration was assessed with mean dense registration error [3], normalised by the voxel size (in %).

Results
LO sections consistently achieved better performance than CS, with a convergence rate above 80% for sections initialised from 25% of the GT transform (Figure 1B). Additionally, successful registrations achieved sub-voxel accuracy, with mean DRE values below 3.5 % for all configurations (Figure 1C). At last, IG with deviations in translations were retrieved more successfully than rotations (Figure 1D).

Discussion
The validation of CMI approaches can be challenging due to limited multimodal GT datasets available. As our 2D-3D CMI approach relies on binary images, synthetic experiments using a single modality (micro-CT) are a viable alternative to assess its capabilities. Notably, our validation toolkit can reproduce realistic histological datasets, even image deformations that typically occur during sectioning (data not shown). Importantly, these findings are directly applicable to support the preparation of histological sections in future studies. Besides, its modular architecture provides a fast and versatile approach to benchmark new image similarity metrics and registration algorithms or repeat the analysis with datasets of other established preclinical models used in bone research, like the mouse caudal vertebra.

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Acknowledgements
European Union (MechAGE ERC-2016-ADG-741883).
NUMERICAL PREDICTION OF CALCIFIC REGIONS IN BIOPROSTHETIC HEART VALVES: CORRELATING IMAGING AND SIMULATION DATA

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Introduction
Calcification of bioprosthetic heart valves (BHV) represents a major concern since calcific aortic stenosis affects 12% of the population over age 75 and calcification limits BHV durability [1]. Calcification consists of the irregular deposition of mineralised crystals that change both the micro- and macro-scale architecture of the pre-treated biological tissues of BHV [2]. We thus intend to elucidate the mechanisms pertaining to the interaction of blood and valve motion that are correlated to calcification in BHV leaflets.

Methods
The study relies on both numerical simulations of the coupled blood and valve motion and on micro X-ray computed tomography (CT) measurements. The numerical simulation of a BHV model (Fig. 1B) is based upon (i) a finite-element formulation to solve the elastodynamics equation at a spatial resolution of about 500 µm [3], (ii) a high-order finite-difference formulation to solve the Navier-Stokes equations at a spatial resolution of about 100 µm [4], (iii) a variational approach for the transfer of information between the fluid and the structure [5]. The leaflets’ constitutive relation is the Holzapfel-Gasser-Ogden model fitted to match tensile test data on pre-treated bovine pericardium [6]. The simulation data are validated against in vitro measurements [7]. The microCT measurements use a cone-beam RX Solutions Easy Tom XL microCT system, with a flat panel Varian PaxScan detector operated at an accelerating voltage of 140 kV with a tube current of 180 µA. The voxel size of the microCT scans is around 20 µm.

Results
Four relevant metrics obtained from the displacement and velocity fields at the interface between the leaflets and the blood are calculated (Fig. 1D). These indicators are the oscillatory shear index (OSI), relative residence time (RRT), topological shear variation index (TSVI) and the scalar strain (SS). A minimisation problem is then formulated in order to correlate the insightfully chosen indicators to the distribution of large-sale calcific structures measured from microCT. The resolution of the least-square minimisation problem provides an equation convincingly correlating the observed calcification-prone intensity from microCT to the reconstructed one, the latter depending on the evaluated indicators (Fig 1E). Finally, a novel method based on the computation of finite-time Lyapunov exponents (FTLE) from the leaflets’ strain tensor (Fig. 1D) is devised to bring insights as to the leaflet motion at peak systole explaining the trustworthy observed correlation.

Discussion and Conclusion
The present study provides an equation to reliably predict from the four indicators calculated out of high-fidelity simulations of the coupled blood-valve system the regions on BHV leaflets where minerals tend to accumulate. We also observe that unstable motions of BHV leaflets at peak systole leading to high values of time-averaged FTLE are connected to calcification owing to the repeated strain exerted on the leaflets.

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A MULTISCALE MODEL OF IN-STENT RESTENOSIS IN CORONARY ARTERIES INTEGRATING DRUG KINETICS WITH CELL DYNAMICS

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Introduction

In-stent restenosis (ISR) is a major drawback affecting the outcome of percutaneous coronary intervention with drug-eluting stent (DES) implantation. ISR is the result of the impaired arterial healing response to the intervention-induced trauma, leading to excessive intimal growth due to the inflammatory-driven exacerbated vascular cell activities. The complete knowledge of the multiscale, multifactorial mechanobiological processes underlying ISR is still lacking. Multiscale agent-based modelling frameworks, integrating continuum- and agent-based approaches, have recently emerged as promising tools to capture the mechanobiological events driving ISR at different spatiotemporal scales [1]. However, the integration of drug kinetics within said frameworks has been under-investigated [2]. The present study proposes a novel multiscale agent-based modelling framework of ISR following DES implantation in coronary arteries.

Methods

The multiscale framework (Fig. 1) consists of the bi-directional coupling of two modules, namely (i) the drug transport (DT) module and (ii) the tissue remodelling (TR) module. The framework, applied to a 2D stented coronary artery cross-section, provides as output a 1-month follow-up artery geometry.

![Figure 1: Multiscale framework.](image)

The DT module performs transient simulations of drug transport by coupling Darcy’s law with advection-diffusion-reaction equations, in Comsol Multiphysics (Comsol, USA) [2]. The fraction of cell-specific receptor saturation (RS), computed within the DT module, has been considered as a measure of drug efficacy, and thus used to initialize the TR module. The TR module replicates vascular cell dynamics in response to the intervention-induced inflammation and to RS (accounting for the drug effect) through a 2D agent-based model (ABM) implemented in Matlab (MathWorks, USA) [3]. Different scenarios in terms of drug mass (DM), drug release profiles (RP), coupling schemes and idealized vs. patient-specific artery geometries were explored.

Results

Changes in the DM, RP and coupling schemes determined a variation in RS over time, in turn affecting the ABM response (Fig. 2, left). Moreover, by applying the framework to a patient-specific stented coronary artery cross-section, with an irregular and asymmetric geometry where the struts were not equally spaced, a heterogeneous RS map was obtained, in turn affecting the growth pattern (Fig. 2, right).

![Figure 2: Results of the multiscale framework of ISR.](image)

Conclusions

This work presents a novel multiscale agent-based modelling framework of ISR, integrating drug kinetics with an ABM of arterial wall remodelling. The analyses performed allowed exploring the sensitivity to different settings, coupling modalities and geometries. Moreover, the feasibility to be applied to patient-specific geometries was demonstrated. In future, the effect of different plaque composition on drug release will be assessed.

References


Acknowledgements

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KNEE JOINT PIVOT MOTION PATTERN DURING WALKING BEFORE AND AFTER UNICCOMPARTMENTAL ARTHROPLASTY

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Introduction
Knee osteoarthritis (OA) is a very common and disabling pathology. Symptoms are mostly pain, reduced joint function, and kinematic impairments [1,2]. One of the last treatments for advanced OA is total or unicompartmental knee arthroplasty (UKA). An UKA is preferred in young patients, because it needs less bone resection and allows for potential revision surgery at an older age [3]. While studies showed that UKA may preserve native knee kinematics (i.e., primarily guided by soft tissues) in cadaver knees [4], this has not been assessed in vivo yet. This study aims at assessing if the motion pattern of the knee center of rotation (i.e., joint pivot) is altered with UKA. The hypothesis was that the joint pivot motion remains unchanged after UKA.

Materials and Methods
Fifty-six (56) participants were included in this study. All patients received UKA at the orthopedic service of the Croix Rousse hospital (Lyon, France). Knee landmarks and kinematics were captured during gait using the KneeKG® system (Emovi Inc., Canada) before and 6 months after surgery. Joint pivot motion was determined during swing phase (from 60 to 100% of the gait cycle) by projecting consecutive transsepicondylar axis positions in the transverse plane (i.e., tibial plateau) during motion [5]. Joint pivot motion patterns were then divided into four categories, whether they displayed a shift of the transsepicondylar axis with I) no rotation (pure antero-posterior (AP) translation) or a rotation around II) a lateral pivot point, III) a medial pivot point or IV) a central pivot point (see Figure 1). Patients were classified based on their predominant pattern. All calculations were performed using MatLab (Mathworks, MA). Joint pivot motion patterns pre- and post-UKA were compared within each participant.

Results
Pre-operatively, 41 out of 56 (73%) patients presented a pure AP translation pattern during swing phase. Six months post-UKA, almost two thirds (60%) of the patients kept a similar pivot motion pattern (see “Non-changers” in Table 1). Interestingly, 97% of the patients who did not change their pivot motion pattern presented a pure AP translation pattern pre-operatively.

Table 1 - Distribution of joint pivot motion patterns pre- and post-UKA and proportion of non-changers for each pattern.

<table>
<thead>
<tr>
<th></th>
<th>Pre-UKA N (%)</th>
<th>Post-UKA N (%)</th>
<th>Non-changers</th>
</tr>
</thead>
<tbody>
<tr>
<td>I) Pure translation</td>
<td>41 (73)</td>
<td>45 (80)</td>
<td>80 %</td>
</tr>
<tr>
<td>II) Lateral pivot</td>
<td>5 (9)</td>
<td>2 (4)</td>
<td>20 %</td>
</tr>
<tr>
<td>III) Medial Pivot</td>
<td>4 (7)</td>
<td>5 (9)</td>
<td>0 %</td>
</tr>
<tr>
<td>IV) Central pivot</td>
<td>6 (11)</td>
<td>4 (7)</td>
<td>0 %</td>
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</table>

Discussion
The presented method extends the work done by Banks et al. [5] who determined the pivot point from fluoroscopic images. The proposed method which defines four different pivot motion patterns using gait analysis with the KneeKG system can be performed in a clinical setting [6]. Results show that after UKA, most patients kept the same joint pivot motion pattern they had before surgery. Interestingly, this was especially the case in patients who displayed pure AP translation pre-operatively. This suggests that while UKA can preserve native knee kinematics in terms of joint pivot motion, this may differ based on the pivot motion pattern pre-surgery. This innovative approach gives new insight on prosthetic knee motion in terms of rotation while walking and how to measure it. Further research is needed to explore associations between joint pivot motion and patients’ satisfaction in order to verify if preserving native kinematics could prevent residual pain post-surgery.

References
OSTEOGENIC POTENTIAL OF SUPRAMOLECULAR ALENDRONATE HYDROGELS: AN IN VITRO STUDY

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Introduction
Alendronate (ALN) is a bisphosphonate clinically used to treat skeletal disorders, including osteoporosis. Alendronate is incorporated in bone by the formation of noncovalent bonds with calcium present at the surface of hydroxyapatite [1]. Once osteoclasts resorb bone and take up alendronate it inhibits osteoclast activity and thereby reduces bone resorption. The binding affinity for calcium ions can also be utilized in the formation of hydrogels [2,3]. Through incorporation of alendronate endgroups gelation is achieved upon contact with calcium. Hydrogels with tunable configurations and physico-chemical properties can be used for cell or drug delivery to induce local bone repair. Promising candidates in regenerative medicine are supramolecular hydrogels based on ureido-pyrimidinone (UPy) moieties because they form dynamic non-covalent interactions [4]. This research aims to examine the ability of alendronate functionalized UPy hydrogels to support osteogenesis and osteoclastogenesis.

Methods
UPy solution containing 10 wt% UPy-ALN was mixed with cell suspension in calcium free PBS containing MSCs or PBMCs at concentrations of 10 x 10^6/ml and 100 x 10^6/ml respectively. 50 µl gel-cell suspension was extruded into calcium rich culture medium to achieve immediate gelation. Hydrogels with cells encapsulated were cultured for 4 weeks in medium supplemented with dexamethasone, ascorbic acid and β-glycerophosphate. On day 28, whole gel mounts (n=3) were stained with CNA, OsteoSense<sup>TM</sup> and Hoechst to analyze matrix formation (gel with MSCs) or stained with phalloidin and Dapi to visualize cell morphology (gel with PBMCs). To evaluate osteogenic differentiation gels (n=3) were cryo-embedded. Frozen sections were fixed, and immunohistochemistry was performed for markers RUNX-2 and Osteopontin (gel with MSCs).

Results
At the end of culture, differentiation of MSCs towards osteoblasts was achieved in UPy-ALN gels (Fig. 1A). Furthermore, matrix formation was observed with large quantities of collagen and hydroxyapatite (Fig. 1B). Regarding differentiation of PBMCs towards osteoclasts, cellular fusion was seen and multinucleated cells with an actin ring were detected (Fig. 1C). Remarkably, within certain multinucleated cells, nuclei were partly fragmented, indicating cellular apoptosis.

Discussion
UPy-ALN hydrogel demonstrated to support osteogenic differentiation and matrix formation. Interestingly, signs of apoptosis in osteoclast-like multinucleated cells were found. This might be a result of phagocytic osteoclasts internalizing UPy-ALN moieties causing ALN to inhibit the mevalonate pathway, which is necessary to function properly [5]. Thereby, UPy-ALN gel seems to allow bone formation while suppressing resorption. In combination with the ease of cell encapsulation and gelation upon injection in a calcium rich environment this gel has potential to be applied locally. This could be useful in for example early-stage OA when lesions occur in the subchondral bone. Although UPy-ALN gel has insufficient stiffness as substitute for large bone defects it might be used as osteoinductive material together with other materials, such as calcium phosphate. Different hydrogel formulations could be investigated to change its stiffness. As a next step, UPy-ALN gels will be injected in a bony environment to further explore its potential as biomaterial for bone regeneration strategies.

References

Figure 1 – (A) UPy-ALN gel section with MSCs encapsulated, showing cells positive for osteoblast markers OPN and RUNX-2. Whole gel mount (B) visualizing collagen (CNA), hydroxyapatite (OsteoSense<sup>TM</sup>) and nuclei (Dapi) in gel with MSCs and (C) showing an osteoclast-like multinucleated cell with an actin ring and nuclear fragmentation (white arrow) in gel seeded with PBMCs.
INVESTIGATING RUPTURE CHARACTERISTICS OF TISSUE-ENGINEERED Atherosclerotic Plaque Caps

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Introduction
Stroke can be initiated by rupture of the atherosclerotic plaque fibrous cap in a carotid artery. However, cap rupture mechanisms are not well understood yet. Understanding the impact of the structural components of the cap on its local mechanics may provide critical insights into plaque rupture. Various limitations within studying plaques in vivo and ex vivo highlight the need for additional methods to investigate rupture mechanics. Therefore, we created collagenous tissue-engineered plaque cap analogs [1]. In the current study, we obtain local collagen structural parameters, local mechanical properties, and rupture characteristics of these analogs to analyze the relationship between the local collagen architecture and local rupture mechanics of cap analogs.

Methods
Nine collagenous cap analogs with a soft inclusion (SI), mimicking the plaque lipid core, were created [1]. Afterwards, the analogs were imaged with multiphoton microscopy (MPM) with second harmonic generation (SHG) to visualize the collagen architecture. From the SHG images, the local fiber orientations were measured using a fiber orientation analysis tool (FOAtool, TU/e). After imaging, the analogs were exposed to uniaxial tensile tests until full rupture. Tissue deformation, the rupture initiation location, and the rupture propagation path of the tests were recorded with a high-speed camera (PL-D725, Pixelink). Local (Green-Lagrange) strains under tensile stretching were measured through DIC analysis using the software Ncorr [2].

Results
In three samples, the rupture initiated at a clamping site whereas in the other six samples, rupture initiated in the SI or at the SI-fibrous tissue interface. The DIC-derived local tensile strain (Ey) analysis at the timepoint of rupture initiation (Fig 1A) showed statistically significantly higher strain levels at the rupture initiation locations (Fig 1B). Qualitative analysis of rupture propagation paths showed inter-sample variation. In some samples, multiple ruptures were found which were connected by the rupture propagation (Fig. 1C). Moreover, the shape of the rupture propagation path differed between samples. The local predominant fiber angles and the rupture propagation path in a cap analog are shown in Fig 1C. The figure demonstrates that at most locations within the analog, the rupture propagated parallel to the local predominant fiber angle. Similar results were found in the other samples. Fig. 1D shows the rupture path versus the local predominant fiber orientation. The linear regression curve in figure 1D (R=0.60, β=1.04, p<0.001) shows that the rupture path angle approximates the fiber angle, again indicating that rupture in the analogs propagated parallel to the local fiber angle.

Discussion
We successfully visualized the collagen orientation and obtained local mechanical (strain) fingerprints in tissue-engineered cap analogs to study atherosclerotic plaque rupture. Local strain measurements showed that rupture in the analogs initiated at the elevated tensile strain regions. The strains found in the analog are similar to the local rupture strain found in a previous DIC-analysis of ex vivo human plaque tissue [3]. Despite the intersample variation in the rupture propagation path, it was found that the ruptures usually propagated parallel to the local predominant fiber angle. As a next step, we will investigate the rupture surfaces with scanning electron microscopy (SEM) to test our new hypothesis proposing that rupture propagation in the analogs is mostly parallel to the local predominant fiber direction. This data will help us to gain better understanding of the underlying failure mechanisms of plaques.

References

Acknowledgements
This research is funded by an NWO-Vidi grant (18360)
LOAD-INDUCED SCAPULA ROTATION AFTER ROTATOR CUFF TEARS DURING A 30° ARM ABDUCTION MOVEMENT

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Introduction

Rotator cuff tears are commonly associated with age and glenohumeral joint instability [1]. However, the mechanisms underlying glenohumeral motion are not fully understood. A superior glenohumeral translation is also likely to occur after a rotator cuff tear, however, scapula rotations might also be affected, and influence glenohumeral biomechanics and the measurement of the glenohumeral translation. This study aimed to explore scapula rotation after rotator cuff tears during an abduction movement with additional handheld weights.

Methods

Twenty-five patients with unilateral rotator cuff tears (64.3±10.2 years), 24 asymptomatic control subjects (55.5±8.2 years) and 25 healthy control subjects (26.1±2.3 years) participated in this study. Single plane fluoroscopy images were acquired for each shoulder during a 30° abduction and adduction movement in the scapular plane with and without additional handheld weights (0, 2 and 4 kg). Images were labelled with an automatic landmark detection algorithm [2] and scapula rotations were measured during the entire motion considering the rotation of the glenoid cavity. A linear mixed model (loads, shoulders) with random effects considering rotations were (26.1±2.3 years)

T

Methods

Figure 1 shows the upward scapula rotations for all shoulders during abduction. Analogous values but downward scapula rotations were observed during adduction. During abduction, we found a significant main effect for the asymptomatic side of patients (p=0.033) and a significant interaction effect of load for the symptomatic side of patients (p=0.002). Post-hoc tests showed significant differences for scapula rotations during abduction at 2 kg between the symptomatic side of patients and the non-dominant side of healthy subjects (p=0.007), at 4 kg between the symptomatic side of patients and both sides of healthy subjects (non-dominant p=0.005, dominant p=0.003), and for the symptomatic side of patients between 0–2 kg, and 0–4 kg (p<0.001).

During adduction, a significant main effect for load was observed in scapula rotation (p=0.046). Differences were found for scapula rotations during adduction for the non-dominant side of healthy subjects between 0–4 kg (p=0.049), for the dominant side of asymptomatic subjects between 0–2 kg (p=0.009) and 0–4 kg (p=0.043), and for the symptomatic side of patients between 0–2 kg (p<0.001) and 0–4 kg (p<0.001).

Discussion

The results presented herein show that the kinematics of the glenohumeral joint is load-dependent and load-induced scapula rotations are greater in asymptomatic rotator cuff tears and increase with increasing handheld weight. This implies that scapula rotation is involved in the compensation mechanisms of rotator cuff tears, particularly in more demanding tasks. Without accounting for scapula rotation, apparent glenohumeral translations might be measured and misinterpreted. Further investigations of load-dependent joint stability are necessary to gain a better understanding of glenohumeral motion and biomechanics during activities of daily living.

References


Acknowledgements

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COMPUTATIONAL SIMULATION OF PATIENT-SPECIFIC BLOOD COAGULATION IN STENT THROMBOSIS

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Introduction
The efficacy of stents to treat coronary artery stenosis is related to the hemodynamic environment. The struts of these devices disturb the local flow field and induce flow recirculation zones and endothelial damage [1]. The aim of this study is to improve understanding of the impact of injury induced blood coagulation on stent thrombosis and to identify risk factors that contribute to it, with the ultimate goal of improving stent designs. This will be studied analyzing local hemodynamics together with patient-specific clot formation using computational fluid dynamics (CFD).

Methods
A biophysical model of a fibrin-rich clot is developed based on the framework presented in Bouchnita et al. [2]. A system of coupled convection-diffusion-reaction (CDR) equations is used to solve the concentration of factor IX and X, prothrombin, thrombin, fibrinogen, fibrin, and fibrin polymer. The production or consumption of each of these agonists is incorporated into the source terms in the CDR equations. The computational domain consists of a 2D channel including a stent strut. A section of the bottom wall serves as a surface flux boundary condition representing a tissue factor (TF) coated surface. The clot is modeled as a porous medium with the porosity depending on the concentration of fibrin polymer. The model is implemented into FLUENT 2021 R1. A set of cases are studied with 3 different TF patch locations, with both average healthy and hypercoagulant coagulation parameters for a physical time of 30 minutes [3].

Results
When comparing the impact of the location of the TF patch, we observed that in the healthy case the clot was formed earlier and appeared to be smaller but denser proximal to the stent strut compared to the clot formed distal to the strut (Fig. 1A-D). When the TF patch was located after the recirculation zone no clot was formed (Fig. 3E-F), even in the case of hypercoagulant plasma (Fig. 3K-L). At the other TF locations, clot formation occurred at a significantly faster rate and resulted in a larger clot in the hypercoagulant case compared to the healthy case (Fig. 3G-J). Also in the hypercoagulant case the proximal clot (Fig. 3I-J) was denser than the distal clot in which the fibrin was completely spread downstream of the recirculation zone (Fig. 3G-H).

Discussion
Results demonstrated that the largest clots were formed when the wall was damaged right after the stent strut, probably due to the presence of the recirculation zone which allows for prolonged interactions between coagulation factors. More concentrated clots were formed proximal to the strut, likely due to the confinement of coagulation factors by the stent strut. The clot growth rate and size were increased in a hypercoagulant case compared to a healthy case, which highlights the importance of incorporating patient-specific parameters. We are currently working on investigating the effects of various stent designs and flow conditions on coagulation dynamics.

References

Acknowledgements
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EFFECT OF WEIGHT LOSS ON SUBCHONDRAL BONE CYST IN THE KNEE JOINT DURING GAIT: A 3D FINITE ELEMENT ANALYSIS

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Introduction

Obesity increases the risk of osteoarthritis (OA) by five times in men and four times in women when compared to non-obese men and women [1]. Subchondral bone cysts (SBC) appear in patients with knee OA causing pain and cartilage loss. However, the effect of weight loss and SBC on the biomechanical response of the cartilage-bone unit remains unknown. Here, we present a case study where we developed a patient-specific finite element (FE) knee joint model to investigate this effect in the knee during the stance phase of gait. We hypothesized that cartilage and bone stresses and strains would decrease as body weight is reduced while the inclusion of the SBC would lead to larger deformations.

Methods

The FE knee model was developed using magnetic resonance imaging (MRI) data of the left knee (age: 63 y/o, height: 1.55 m) from the CAROT trial [2]. MRI data at baseline was used to segment the knee joint tissues (3DSlicer). Segmented geometries of femoral and tibial cartilages, femoral and tibial bones, and menisci were imported into Abaqus (v.2021, Dassault Systèmes, Providence, USA) where meshes and boundary conditions were implemented (Fig. 1a). Tibia regions were differentiated in cortical, trabecular, and subchondral bone. In addition, another FE model was created including a spherical SBC (diameter: 6 mm), which was placed centrally in the medial tibial compartment ~1 mm below the subchondral bone plate. Bone, menisci, and the SBC were modeled as homogeneous, isotropic linear elastic materials, while cartilage was modeled as a neo-Hookean hyperelastic material (Fig. 1b).

The patient’s weight at baseline and 68-weeks of follow-up was 85 and 72 kg, respectively. Patient specific knee axial force and flexion-extension angle during the stance phase of gait were computed using motion analysis data at baseline with OpenSim [3] (Fig. 1c).

Results

At the first force peak of gait, FE models at baseline and 68-weeks showed a decrease in contact pressure, Von Mises stress, and maximum principal strain by 9.5%, 8.8%, and 7.7% respectively in the lateral cartilage. In the medial compartment, the same parameters decreased by 7.7%, 4.5%, and 2.3% respectively. Minimum principal stress and strain in the lateral cortical bone decreased by 10.4% and 11.0 %, respectively.

The inclusion of the SBC caused an increase in the minimum principal stress and strain by 8.5% and 9.1% respectively in the medial cortical bone (Fig. 1e-f).

Discussion

Based on the presented case study, weight loss reduces critical stresses and strains in articular cartilage and bone, which may lead to slowing down degenerative processes. On the other hand, while the inclusion of an SBC had a minimal impact on the cartilage biomechanics, medial cortical bone experienced large compressive stresses and strains. This case study will be extended to more subjects in the clinical trial to elucidate further pain and OA progression mechanisms.

References

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Acknowledgements

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NATURE-INSPIRED TOUGHENING MECHANISM OF 3D PRINTED HYDROXYAPATITE SCAFFOLDS FOR BONE TISSUE ENGINEERING

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1. Politecnico di Milano, Italy; 2. Massachusetts Institute of Technology, USA.

Introduction
The mechanical performances of Triply Periodic Minimal Surfaces (TPMS) have been extensively studied for Bone Tissue Engineering (BTE) applications [1]. Despite its biocompatibility and bioactivity, hydroxyapatite (HAP) usage in BTE applications is limited by its intrinsic brittleness. Furthermore, the strength and the toughness decrease drastically when porous structures (i.e. BTE scaffolds) are involved. Starfish ossicles exhibit a mineralized TPMS structure at a micron scale. The presence of dislocation-like defects in these structures makes the structure tougher [2]. 3D printing techniques can produce porous ceramic scaffolds with high fidelity. Finite Element Modeling (FEM) has been employed to assess both the elastic and fracture behavior of ceramic scaffolds [3]. The aim of this work is to determine the mechanical performances of a Schwartz-P TPMS and assess the role of an edge dislocation in the crack pattern evolution using a combined approach of FEM and experimental tests.

Materials and Methods
Bulk miniaturized HAP samples have 3D printed through vat-photopolymerization to assess the mechanical parameters to be used in FEM [4]. Morphological and mechanical characterization has been performed by means of synchrotron light radiation Computed micro-Tomography (µCT), micro-bendings and nanoindentations. The Schwartz-P TPMS have been designed in Matlab by using the following function:

\[ f = \cos\left(\frac{2\pi n x c_y}{n}\right) + \cos\left(\frac{2\pi n y c_x}{n}\right) + \cos\left(\frac{2\pi n z c_z}{n}\right) - b \]

where \(x, y,\) and \(z\) represent the Cartesian coordinates, \(b\) the known term, \(n\) the number of voxels used for the spatial discretization and \(c_x, c_y,\) and \(c_z\) the number of repetitive units in the space. The variable \(c_y\) has been properly tailored to provide a smooth transition between two adjacent integer values. Displacement-controlled elastic compressions have been performed in ABAQUS/Standard to assess the effective stiffness of the scaffold. The structure has been rotated from 0° to 90° with a step of 5° to assess the role of the angle between the load and the dislocation. Selected configurations, namely 0°, 45° and 90°, have been tested in compression to assess the fracture behavior by using ABAQUS/Explicit. The maximum principal stress criterion has been used for element deletion.

Results
\(\mu\)CT scans reveal an intrinsic porosity of 0.3% in the bulk samples. Micro bendings and nanoindentation reconstitute a stiffness of 100 GPa and a flexural strength of 100 MPa. The maximum effective stiffness of the TPMS is 22 GPa, corresponding to the 0° and 90° configuration, whereas the 45° configuration is the more compliant (15 GPa). The fracture behavior of the 0° dislocation configuration (Figure 1) exhibits the lower strength, while the higher is represented by the ideal structure in 0° and 90° configuration.

Discussion
The dimensions of the voids of intrinsic porosity can be represented as a bimodal distribution, where the largest pores are concentrated in the core of the beam. Due to the low value of intrinsic porosity, 3D printed HAP can be modeled as a continuum material in FEM. Concerning the TPMS, the effective stiffness in the 0° and 90° configuration is in accordance with a polynomial fitting of 3D printed porous scaffolds [5]. In each load condition, the presence of the dislocation does not affect the effective stiffness of the structure. Even if the ideal structure exhibits the highest strength, the failure is catastrophically brittle, whereas the 90° dislocation configuration is tougher since the dislocation introduces a local increase of stress at the tip of the dislocation, preserving other areas with load-bearing capability. Further fracture simulations are ongoing to corroborate the current results and a robust experimental campaign to validate the numerical results will be performed.

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Acknowledgments
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Introduction
Shoulder osteoarthritis (OA) is known to be associated with a wide range of bone erosion patterns and variable Humeral Head Migration (HHM) in the glenoid joint surface. This variability is known to importantly affects glenohumeral function and kinematics. The magnitude and direction of HHM based on static CT scan images are one the key assessments in surgical planning of anatomic Total Shoulder Arthroplasty (aTSA). However, these assessments in multiple functional arm positions could provide more functionally-relevant information for surgical planning. Therefore, the purposes of this study are (1) to assess the reliability of a methodology for measuring 3D in-vivo HHM in different quasi-static functional arm positions based on biplanar radiographs and (2) to assess the variability among patients with shoulder OA in this regard.

Method
Low-dose bi-planar radiographs (EOS imaging, Paris, France) were collected in 10 patients with shoulder OA, planned for an aTSA. Each patient was scanned at 8 different quasi-static arm positions: relaxed standing (RS), extension (EX-45°), flexion (F-45°, F-90° and F-120°), and abduction (AB-45°, AB-90° and AB-120°). The 2D scapula and humerus contours were segmented from the frontal and lateral images of the EOS images. Smoothed 3D bone shapes were manually segmented with Mimics (Materialise, Belgium) from standard-of-care CT scans. Custom MATLAB code was used to register the 3D bone shapes to the respective biplanar contours and quantify the humeral head position with respect to the glenoid (Fig. 1) [1]. Here, a sphere was automatically fitted to the humeral head and its corresponding center was determined. Similarly, the glenoid center was defined based on a best-fitted plane. Next, the HHM, evaluated as the translation of the humeral head center relative to the glenoid center, was measured in superior-inferior (SI) and anterior-posterior (AP) direction for all patients and positions and normalized to the humeral head diameter (Fig.1) [2]. Inter- and intra-observer reproducibility of the reconstructions were assessed by measuring surface-to-surface error (STSE) of the humerus and scapula and through intra-class correlation coefficients (ICCs).

Results
The ICC of posterior HHM in RS, AB-45, and F-45 showed good inter- and intra-rater reliability ranging from 0.8 to 0.9 (p<0.05). The STSE for the scapula and humerus in these three positions is reported in Table 1. The other positions demonstrated only moderate or poor (120AB) reliability (ICC<0.8 and P>0.05). The humerus center was located inferior-posteriorly in OA patients for CT, RS, 45F, and 45AB (Fig.2). Although paired t-test showed no significant differences between RS compared to CT-scan-based measurements (p>0.05), a trend towards more inferior-posterior HHM was observed in the upright RS compared to supine posture in the CT-scan (51.6±7.3 vs. 53.8±7.8% for SI and 58.2±8.9 vs. 57.0±8.1% for AP, respectively). 45AB and 45F were both associated with greater posterior HHM (63.2±13.7 and 62.7±9.9% of A-P HHM).

![Figure 1: Process of reconstructing the joint positioning](image1)

<table>
<thead>
<tr>
<th>Component</th>
<th>Intra-rater median (IQR)</th>
<th>Inter-rater median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scapula</td>
<td>4.7 (4.4)</td>
<td>6.6 (6.5)</td>
</tr>
<tr>
<td>Humerus</td>
<td>9.1 (4.0)</td>
<td>5.5 (3.4)</td>
</tr>
</tbody>
</table>

Table 1: STSE of the components in RS, 45AB and 45F

![Figure 2: Humerus center location in the glenoid plane](image2)

Discussion
The current methodology was shown to be reliable for three functional arm positions. Variability among patients in terms of posterior HHM in these positions has the potential for pre-operative clinical evaluation.

References
Introduction

Left Atrial Appendage Occlusion (LAAO), a percutaneous intervention with self-expandable devices (Fig. 1a), is a viable alternative to oral anticoagulants in preventing thromboembolism for about 30% of patients affected by atrial fibrillation. Indeed, it is estimated that over 90% of stroke-inducing clots are formed in the LAA. Despite its broad application, LAA morphological complexity hinders the procedure, leading to suboptimal implants and undesirable outcomes [1]. In this context, LAAO numerical simulations represent an effective tool in guiding clinical decisions, allowing the selection of the best implant strategy. Clearly, simulation reliability is strictly related to models accuracy (both for the device and the LAA) and correctness in mimicking the implant procedure, crucial issues impacting the outcome. The available limited literature [2] aims to simulate patient-specific implant scenarios for defining the optimal device positioning, but no attention is paid to the uncertainties of their models and how they affect the results. In this scenario, the present study aims to assess the usefulness of the numerical tool for preoperative planning as long as the simulations accuracy is assured.

Materials and Methods

A reliable LAAO numerical model was developed according to the following steps.

\textit{i}) A Finite Element (FE) model of the Watchman FLX device (Boston Scientific, Fig. 1a) was prepared following the pipeline in [3]. An accurate description of the Nitinol cage was adopted (material and geometry), while the covering fabric was disregarded, not affecting the device positioning.

\textit{ii}) 4 patient-specific anatomies (LAA and Left Atrium, LA) were reconstructed from CT images at the maximum LA volume. If on the one hand a correct description of the geometry is achievable exploiting the images, on the other hand wall thickness and mechanical properties cannot be estimated. Thus, uncertainty quantification was performed to evaluate their influence on the implant simulation. Finally, the CT images were segmented throughout the overall cardiac cycle to introduce realistic boundary conditions for Pulmonary Veins (PVs) and Mitral Valve (MV) (Fig. 1b).

\textit{iii}) Based on the real procedure [4], the steps to simulate the LAAO were: (a) \textit{positioning} of the device cramped into a catheter modeled as a rigid cylinder, (b) \textit{extraction} of the device from the catheter and \textit{deployment} into patient-specific anatomies without unscrewing (to allow the clinician to check and eventually reposition the device), (c) \textit{final release} of the device from the catheter (Fig. 1c). The outcomes of the analyses in terms of the device final configuration were discussed.

Results

The simulations proved to be a useful tool to evaluate the effectiveness of different device positionings, highlighting an interesting aspect. During the procedure, the surgeon injects a contrast medium under fluoroscopy after the \textit{deployment} but before the \textit{release} to assess the goodness of the device positioning. However, numerical results outlined how the deployed device configuration (what the clinician assesses under fluoroscopy) may differ from the released one (what is actually relevant for a successful implant) (Fig. 1c). Moreover, an influence of the uncertainties in describing the LAA on the final device configuration was found. The effect of boundary conditions was evident in the presence of certain LAA morphological features (e.g. small distance between MV plane and LAA implant zone), while mechanical properties affected the results in most cases.

Discussion and Conclusions

This study proved the need of a reliable numerical model to simulate the LAAO and the importance of correctly describing the phases involved in the procedure. The modeling features that impact the device final configuration and are deemed useful to accurately address clinical decisions were investigated, avoiding misleading interpretations of the outcomes.

Figure 1: a) LAAO overview; b) LAA model development; c) LAAO simulation steps and device configurations post-deployment and post-release.

References

EFFECT OF POLYMER CONCENTRATION ON MORPHOLOGY AND FUNCTION OF CHITOSAN AS DRUG-RELEASING SCAFFOLDS

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Introduction
Controlled polymeric drug delivery system is a field that has recently gained popularity. Polymers incorporated with drugs prove to be bioactive to provide their own therapeutic benefit and improve release kinetics, making the system more effective [1,2]. A scaffold is one such system that finds immense application in drug delivery and tissue engineering. There is a need for polymeric scaffolds to be engineered to meet the requirements of its application.

This study aims to develop chitosan scaffolds and test if parameters such as cross-linking, polymer concentration and freezing temperature can be exploited to change its design and function.

Methodology
Chitosan hydrogel containing diclofenac sodium was prepared and lyophilized to obtain porous dry scaffolds. Various combinations were produced in this manner by varying parameters such as cross-linking, polymer concentration (1% and 2%) and freezing temperature (-20°C and -80°C). Natural cross-linker Genipin was used for cross-linking. The scaffolds were subjected to characterizations such as swelling behavior, porosity test, FTIR, SEM, drug release and kinetics to analyze their properties.

Results and Discussions
Chitosan scaffolds in the presence of cross-linking showed decreased swelling, reduction in porosity and pore size, lesser release rate of drug when compared to un-cross-linked scaffolds.

Scaffolds produced with 2% polymer concentration exhibited lower swelling, reduction in pore size and porosity, and lower drug release rate than scaffold of 1% polymer concentration. Scaffolds produced using freezing temperature of -20°C showed increased swelling, higher pore size and porosity and faster release rate than scaffold produced at temperature of -80°C. Release of diclofenac sodium from all chitosan scaffolds (S1, S2, S3 and S4) found best fit in the Higuchi Model with Fickian Diffusion (for n<0.5) as the release mechanism.

The results showed that varying the parameters brought about some change in the design and function of the scaffold. Scaffolds S2 and S4 were able to regulate and sustain the release profile of diclofenac sodium drug from the scaffold making it an effective drug delivery device.

<table>
<thead>
<tr>
<th>Scaffold</th>
<th>Scaffold specifications</th>
<th>CDR (%) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>1% -80°C Uncross-linked</td>
<td>28.673 ± 2.40</td>
</tr>
<tr>
<td>S2</td>
<td>1% -80°C Cross-linked</td>
<td>26.377 ± 10.47</td>
</tr>
<tr>
<td>S3</td>
<td>1% -20°C Uncross-linked</td>
<td>30.575 ± 3.25</td>
</tr>
<tr>
<td>S4</td>
<td>2% -80°C Uncross-linked</td>
<td>18.410 ± 2.83</td>
</tr>
</tbody>
</table>

Table 1: Mean cumulative drug release (CDR) (%) ± standard deviation (SD) for 24 hours.

<table>
<thead>
<tr>
<th>Scaffold</th>
<th>Pore size (µm) ± SD</th>
<th>Max pores in the range (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>93.653 ± 24.41</td>
<td>70-80 and 110-120</td>
</tr>
<tr>
<td>S2</td>
<td>55.935 ± 23.12</td>
<td>80-90</td>
</tr>
<tr>
<td>S3</td>
<td>107.71 ± 32.35</td>
<td>90-110 and 150-160</td>
</tr>
<tr>
<td>S4</td>
<td>88.726 ± 16.87</td>
<td>70-80</td>
</tr>
</tbody>
</table>

Table 2: SEM analysis indicating average pore size ± SD of chitosan scaffolds.

Figure 1: Mean cumulative drug release (%) ± SD of Diclofenac Sodium.

References

Acknowledgements
We thank Mr. Shivanand. M. Shettigar for his assistance in the experiments. We also thank Dr. N.V. Anil Kumar for his guidance in the characterization studies.
VALIDATION OF A DIGITAL TWIN TO QUANTIFY THE LEVEL OF MOTOR CONTROL SUBOPTIMALITY IN PATIENTS

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Introduction
Neuro-musculoskeletal (NMSK) models, personalized and informed by experimental data, enable to predict internal biomechanical quantities which may have high informative value but that are difficult to measure in vivo. Motor control strategies that deviate from the so-called optimal control (e.g. a solution that minimizes the metabolic cost or energy expenditure) may further emerge, which may not be observed otherwise. Hence, we developed a Digital Twin in Healthcare (DTH), named JointForce, which we intend to position as a tool to quantify the level of suboptimality in a patient’s motor control. In first instance, JointForce models will be used to predict joint contact forces (JCF) using various approaches, i.e., classical static optimization (hypothesizing optimal muscle control) and EMG-assisted approach [1]. Before the JointForce DTH can be employed to assist clinical decision making, it requires to undergo proper validation. In this work we present a first validation of JointForce models, and their predictions, against the recording of instrumented knee implants from a public dataset [2].

Methods
Experimental data from the last four editions of the Knee Grand Challenge (KGC) [2] were employed in this study. Image-based MSK models were generated using an in-house pipeline that exploits the STAPLE toolbox [3] and nmsBuilder [4]. Muscle points extracted from a generic template [5] were mapped onto the reconstructed bony geometries and minimally adjusted in accordance with medical images. Muscle properties were scaled and tuned to ensure physiological muscle behaviour [6], or personalized with information from available experimental data (e.g., maximal isometric forces scaled with the physiological cross-sectional areas outlined on the images). Biomechanical simulations of level walking were performed in OpenSim (standard workflow, from inverse kinematics to static optimization) and CEINMS (EMG-assisted approach, following model calibration). Predicted knee JCFs were compared to the corresponding in vivo measurements in terms of RMSE and R². Statistical significance, between JCF profiles, was computed using Statistical Parametrical Mapping (a= 0.05).

Results
We hereby report the preliminary results on data from the 6th KGC (Figure 1). The static optimization approach produced estimates that more closely approximated the implant data (RMSE=0.42±0.1BW), compared to predictions resulting from the EMG-assisted approach (RMSE=0.88±0.06BW). However, the opposite was observed in terms of JCF profile similarity (R²=0.89±0.05 for static optimization, R²=0.91±0.03 for EMG-assisted approach).

Discussion
These first results are encouraging, although the overestimation associated to the use of the EMG-assisted approach requires further evaluation. The JointForce DTH is currently under validation using data from the other three editions of the KGC [2]. We expect to complete the validation in the next few weeks. Once the JointForce DTH is validated, we will identify a system (e.g., an index) to quantify the degree of neuromuscular suboptimality in a patient, based on the distance between the optimal solution (obtained via a static optimization) and the EMG-assisted solution.

References

Acknowledgments
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Figure 1: Knee joint contact forces predicted by the JointForce DTH, employing different approaches. Results are expressed in body weight (BW) and reported as mean and standard deviation across trials. In vivo recordings from an instrumented knee implant are reported for comparisons. Bars represent statistical significance (p<0.05).

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
Introduction
Articular cartilage defects in the knee affect a considerable proportion of the population and range from single focal defects to larger areas of diseased hyaline cartilage. Autologous and allogeneic osteochondral grafting have demonstrated positive outcomes by replacing the damaged region of cartilage with an auto- or allo-graft consisting of a cylinder of bone with a layer of cartilage [1]. However, the factors that affect the short-term stability of the grafts remain largely unknown with some evidence of graft subsidence and poor integration. The aim of this study was to understand the parameters that affect the immediate stability of osteochondral grafts within a tibiofemoral joint using finite element (FE) models. The objectives were to use previously derived and independently experimentally calibrated models to understand the effects of grafting parameters on contact mechanics and graft stability. The effects of graft site dilation, used to prevent damage to grafts upon implantation, was also investigated.

Methods
Previously [2], subject specific FE models of a human tibiofemoral joint were built and validated against experimental contact pressure data for 6 cases with different osteochondral graft conditions (Fig. 1, A). The models contained elementwise material properties of the bone derived from CT scan data with independent validation, and calibrated friction properties between the graft and host bone from an independent study of 12 osteochondral graft push-in tests. This tibiofemoral joint model was used as the foundation for parametric testing of graft properties. Parametric tests were performed to investigate the effect of changing the density-modulus relationship for the bone component of the graft and the effect of graft site dilation on graft stability. The latter was investigated in two ways, through experimentally validated push-in testing (two knees, 8 total sites, reported previously by McCall et al. [3]) with matching specimen specific FE models, using previously published methodology [4], and through implementing the dilation in the tibiofemoral joint FE model described above. The effect of the grafting parameters was examined by comparing the peak compressive stress, strain and contact pressure. Push-in force comparisons used the force at 1 mm of displacement below flush with surrounding cartilage.

Results
Good agreement was found (CCC=0.86, Fig. 1, B) between models and experimental data when testing the effect of graft site dilation on push-in force, despite no significant difference found between dilated and undilated sites experimentally. Graft bone density and dilation changes had little effect on the resultant tibial contact pressure in the knee joint model (<2% change in peak contact pressure). However, large changes were found internally when measuring peak stress, strain and internal contact pressure on the graft (Fig. 1, C).

Discussion
The agreement measured between experimental and computational models including dilation of the graft site continues to add confidence to the modelling approach. Large changes to the stress and strain of internal bone elements when varying properties and site preparation suggests that, clinically, increased care is required when picking autograft site or allograft properties in order to prevent damage to the bone and graft prior to bony integration. Further investigation into the tradeoffs between dilated and undiluted graft sites is required given the large changes to stress and strain despite non-significant changes to the push-in force.

References

Acknowledgements
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MECHANOBIOLOGICAL REGULATION OF LARGE BONE DEFECT REGENERATION WITHIN MEW AND FDM SCAFFOLDS

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Introduction

The treatment of large bone defects is an unmet clinical need. 3D printed scaffolds represent a promising strategy to support large bone defect regeneration. Scaffolds fabricated with melt electrowriting (MEW) were shown to perform better in terms of new bone formation in a critically sized rat femoral defect over fused deposition modelling (FDM) scaffolds [1]. However, how those specific scaffold microarchitectures influence the mechanical environment within the defect, the cellular behaviour within the scaffold pores and thus the bone formation pattern is not fully understood.

Here, we aim to investigate the influence of FDM and MEW scaffold microarchitecture on the bone healing process during scaffold-supported bone regeneration, using a computer modelling approach.

Methods

A multiscale in silico model for scaffold-guided bone regeneration [2] was adapted to replicate a previously published experimental set-up [1]: a large rat femoral osteotomy (5 mm) stabilized with an internal PEEK fixator and either (1) left empty or augmented with PCL scaffolds coated with hydroxyapatite (HA) fabricated by (2) FDM (Fig.1 A) or (3) MEW (Fig.1 B).

The computer model couples finite element analysis at the tissue level, to determine the mechanical environment within the scaffold, and agent-based models at the cell level describing the biological processes occurring throughout the healing.

Results

In the FDM scaffold, high mechanical stimuli favourable for fibrous tissue formation were determined within the scaffold pores, both after 6 and 12 weeks (Fig. 2A). In addition, a small amount of bone formation was predicted (Fig.2 A). In the MEW scaffold, mechanical stimuli more beneficial for bone formation were predicted close to the bone ends which, together with the higher specific surface available for tissue deposition, led to the observed enhanced newly formed bone, in agreement with experimental results (Fig.2 B). For the empty case, very limited bone formation was predicted, in agreement with the experimental data (Fig.2 C). Furthermore, the predicted shapes of the new bone ends resembled the ones observed experimentally, with spicules through the FDM scaffold pores and more rounded bone ends in the MEW scaffold.

Discussion

Our results show that not only the inherent scaffolds microarchitecture but also the induced mechanical environment can explain the experimentally observed enhanced bone formation within MEW as compared to FDM scaffolds.

In the future, we plan to include angiogenesis to better understand how micro-architectural features modulate vessel formation and the associated effects on the healing process.

References


Acknowledgements

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EXPERIMENTAL COMPARISON OF PRESSURE PERFORMANCES IN DIFFERENT CPAP DELIVERY TECHNIQUES.

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Introduction
CPAP (continuous positive airway pressure) therapy is widely used to treat patients with hypoxic respiratory failure to avoid the necessity of intensive care. The traditional CPAP therapy is delivered by an open configuration with some disadvantages such as high daily oxygen consumption, viral air contamination and high noise [1]. An alternative solution lies in an innovative system able to deliver CPAP therapy with a closed-loop breathing circuit [2]. The aim of this study is to evaluate the pressure performance of commercial devices able to deliver CPAP therapy, and to compare them with the innovative closed-loop concept performances, eventually aiming at an optimization of the pressure control in the closed-loop breathing circuit.

Methods
Three devices were tested: (1) a double flowmeter (DF, StarVent2, StarMed srl) that delivers a mixture of ambient air and oxygen used in combination with a positive end expiratory pressure (PEEP) valve to adjust CPAP level, (2) a device (iSleep, Breas Medical) for treating obstructive sleep apnoea (OSA) patients used in its standard open configuration and (3) in the novel closed-loop (CL) configuration. The CPAP devices were connected via a circuit to a lung simulator (TestChest V3, Organis Gmbh) and a flow analyser (FlowAnalyser Pro, IMT Analytics), and the therapy was delivered to a head phantom through the patient interface under normal operating conditions (DF and CL with a helmet – A and B3 respectively – and OSA with a full-face mask – B1). As a control, the OSA was also tested with the helmet interface (B2). All tests were performed using CPAP levels at 5 and 10 cmH₂O, simulating two pathological conditions normally treated with CPAP therapy: a post-surgery patient and an acute respiratory distress syndrome (ARDS) patient. Thirty-two tests were performed in total, measuring the pressure at the patient connection port.

Results
DF pressure oscillations (ΔP) result smaller than the OSA ones when used in all configurations (B1, B2 and B3) (Fig. 1). This could be caused by OSA pressure closed-loop control, which is based on a pressure measurement located inside the device itself. The distance from the interface may indeed induce a delay in pressure adaptations. The introduction of the helmet in the open configuration (B2) slightly reduces the oscillations with all the tested patients and CPAP levels (maximum reduction of 19%). On the contrary, closing the breathing circuit produces a ΔP increase since the exhaled gas is restrained to a large extent within the circuit.

Table 1 shows the PEEP values computed from the pressure trends. Compared to the set CPAP pressures, the DF imposes a higher PEEP, while the OSA device reaches PEEP values under the set ones, with worse performances when using a helmet due to greater leakage. When the post-surgery patient is treated with CL the PEEP value resulted very close to the set one.

![Figure 1: Comparison between pressure at the patient connection port in the four tested configurations during multiple breathing cycles.](image)

Table 1: ΔP and PEEP obtained in the four tested configurations. ΔP is the difference between expiratory and inspiratory peaks.

<table>
<thead>
<tr>
<th>CPAP level</th>
<th>Post-surgery</th>
<th>ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cmH₂O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>ΔP</td>
<td>4.9</td>
</tr>
<tr>
<td>10</td>
<td>ΔP</td>
<td>4.9</td>
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</table>

Discussion
Preliminary results highlight the importance of the pressure control, with particular reference to the pressure measurement location. Getting closer to the interface would indeed better compensate for the pressure oscillations and the leakage. The helmet use helps in stabilizing the ΔP, also thanks to its greater internal volume, but induces a higher leakage. Finally, closing the breathing circuit may solve open issues in viral load dispersion and oxygen consumption, but it complicates the pressure stabilization, which must be considered a crucial aspect for future optimizations.

References

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BLOOD FLOW MODELLING IN CORONARY ARTERIES: NEWTONIAN OR NON-NEWTONIAN?

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Introduction

The role of local hemodynamics in coronary atherosclerosis natural history is widely acknowledged [1]. In recent years, the combination of computational fluid dynamics (CFD) and medical imaging has allowed to profile wall shear stress (WSS) with high spatial and temporal accuracy [2]. However, the clinical use of CFD simulations is still hampered by the necessary assumptions related to the model-based strategy. This study is framed in the context of the evaluation of the budget of uncertainty associated with the adoption of blood rheology models in coronary angiography-based CFD simulations, with focus on WSS-based quantities linked to vascular diseases.

Methods

The geometry of 50 right coronary arteries (RCAs) of hemodynamically stable patients were reconstructed from angiography. Unsteady-state CFD simulations were performed with generalized Doppler-derived inflow waveform [3]. On each RCA model, two CFD simulations were performed: one adopting a Newtonian blood rheology model, the other adopting the shear thinning model proposed by Carreau (widely adopted in coronary hemodynamics simulations) [3]. The impact of blood rheology behaviour was evaluated in terms of the canonical WSS-based quantities TAWSS, OSI, and RRT. Additionally, the amount of variation in WSS contraction/expansion action on the endothelium along the cardiac cycle T was quantified by the Topological Shear Variation Index (TSVI) [4]:

$$\text{TSVI} = \left( \frac{1}{2} \int_0^T [\text{DIV}_{\text{WSS}} - \text{DIV}_{\text{WSS}'}]^2 dt \right)^{1/2}$$

where DIV\text{WSS} is the divergence of normalized WSS vector field. Luminal surface areas (SAs) exposed to disturbed hemodynamics (low shear area: LSA, oscillatory shear area: OSA, residence time area: RTA), and to high variation in WSS contraction/expansion action along the cardiac cycle (topological shear variation area: TSVA) were identified, based on objective thresholds on the patient-specific luminal distributions: the 20\textsuperscript{th} percentile of TAWSS; the 80\textsuperscript{th} percentile of OSI, RRT, and TSVI. The thresholds were obtained from Carreau model-based simulations, here considered as reference. The co-localization of Newtonian vs. Carreau-based SAs was quantified by the similarity index (SI) (0= no overlap; 1= total overlap) [3].

Results

Overall, the luminal distribution of the WSS-based quantities was remarkably similar, independent of the adopted blood rheology model (an explanatory case is presented in Fig.1). No remarkable differences emerged in the extension of disturbed SAs (Fig. 2), as confirmed by median [interquartile range] SI values close to one (SI\text{LSA}=0.92 [0.89, 0.95]; SI\text{OSA}=0.95 [0.94, 0.96]; SI\text{RSA}=0.92 [0.89, 0.95]; SI\text{TSVA}=0.95 [0.94, 0.96]).

![Figure 1](image1)

Figure 1: Luminal distribution and SAs for TAWSS, OSI, RRT, and TSVI in an explanatory case. C: Carreau; N: Newton.

![Figure 2](image2)

Figure 2: Scatter plots of disturbed hemodynamics SAs.

Discussion and conclusion

This study on 50 RCAs (which we are extending up to 144 models) suggests that assuming a Newtonian behaviour for blood in coronary hemodynamics simulations poorly impacts on WSS profiles.

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28\textsuperscript{th} Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
Motivation
The biomechanical function of the meniscus is of utmost importance to understand associated knee pathologies such as meniscal tears [1]. One of the most commonly performed mechanical tests to characterize the menisci in vitro is confined compression testing. Using this test configuration, biomechanical properties such as the tissue stiffness via its aggregate modulus (H_A) and its resistance to fluid flow, its hydraulic permeability (k) are assessed. However, variations in H_A and k have been reported between research groups [2,3,4,5]. Therefore, the objective of this study was to determine the effect of the test equipment, environmental conditions and sample preparation methods on the biomechanical properties at two laboratories.

Material and Methods
Both laboratories (Lab A: Miami, USA and Lab B: Ulm, Germany) performed confined compression tests of twenty porcine meniscal samples (n = 20). Lab A obtained the samples from a professional animal tissue provider (Animal Technologies Inc., TX, USA) and Lab B from a local slaughter. Both laboratories used a uniaxial mechanical tester (Univert, Cellscale in Lab A, Z10 Zwick GmbH & Co. KG in Lab B), each equipped with a porous indenter to allow for fluid exudation during compression. A total of three consecutive stress-relaxation tests were carried out at 10, 15 and 20% strain (loading rate 100% strain/min). Each strain level was held for 1800 s to allow complete load equilibrium. Ha and k were determined by solving a 1-D biphasic analytical model [6]. Wilcoxon testing was performed at all three strain levels to analyse differences in H_A and k between Lab A and Lab B. Friedman testing was used to analyse differences between the three strain levels. p < 0.05 was considered statistically significant.

Results
For all strain levels, H_A values in Lab A averaged about double of Lab B (p >0.05) (Figure 1, left). In Lab B, H_A was significantly higher at 10 % strain when comparing to the respective values at 15 and 20% strain. In Lab A, no significant differences for H_A between different strain levels were observed. k values were significantly higher in Lab B compared to Lab A (p < 0.001) (Figure 1, right). In Lab A, k decreased significantly with increasing strain level (p < 0.05). No differences were found for k between the strain levels in Lab B (p > 0.05).

Discussion
The assessed H_A values of Lab A are in the range of previous measurements on porcine meniscus [4,7]. In general, H_A was statistically higher in Lab A. This could have resulted from differences in porcine age (Lab A: 24 months vs. Lab B: 6 months). k was always significantly higher in Lab B than in Lab A. Lab A obtained k values in the range of those found in previous studies [2,3,7,8]. Moreover, k significantly decreased with increasing strain in Lab A, which was not evident in the tests of Lab B. An explanation for the differences in the k results between the two laboratories could be differences in the confined compression setup itself (indenter material, dimensional tolerances within the test chamber) and the age of pigs sampled. This study confirms that the specific test conditions can play a significant role for in vitro determined biomechanical properties of meniscus tissue. Hence, protocol standardization may be necessary to ensure comparability of results.

Acknowledgements
Study supported by NIH/NIAMS grant number 1R01AR073222

References
HYALURONIC ACID HAS NO TRIBOLOGICAL EFFECT ON DEGENERATED KNEE JOINT TISSUES – AN IN-VITRO STUDY

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Motivation
Therapeutic intraarticular injection of hyaluronic acid (HA) in knee osteoarthritis (OA) intends to maintain low-friction between the articulating cartilage and meniscus surfaces by restoring the comprised viscosity of the synovial fluid (SF) [5]. However, neither the friction properties of degenerated cartilage and meniscus nor the effect of HA injections on friction between these tissues have been sufficiently studied. Therefore, the aims of this tribological in-vitro study were (1) to quantify the coefficient of friction (CoF) of degenerated cartilage and meniscus tribosystems during simulated gait conditions [3] and (2) to investigate the impact of HA supplementation on the CoF.

Material and Methods
6 mild (49 ± 8 yrs) and 6 severe (80 ± 5 yrs) degenerated human knee joints were obtained from an official tissue bank (IRB 228/20). 6 mm cylindrical samples were extracted from the cartilage-to-cartilage contact area of the tibial plateau. Three cylindrical plugs were punched out from the anterior horn, posterior horn and pars intermedia of lateral menisci using a 5 mm biopsy punch. Flat cartilage plates (2 x 4 mm) were extracted from of the femur using a microtome blade. The following material pairings were tested: tibial against femoral cartilage (tribosystem cartilage) and femoral cartilage against the femoral-facing side of the meniscus (tribosystem meniscus). Synthetic synovial fluid (sSF) [2] and sSF with HA (Hylan G-F20; sSF + HA) were used as lubricants. Gait-like loading conditions were applied using a dynamic pin-on-plate device [3]. CoF of the simulated stance and swing phase were averaged from the last three cycles after 600 s. Differences in the CoF of mild and severe degenerated samples were analysed using Mann-Whitney testing, while Wilcoxon testing was used to compare the results when using different lubricants. p ≤ 0.05 was considered statistically significant.

Results
Neither, the CoF of the mild against the severely degenerated samples (Figure 1), nor the CoF between the groups using the two different lubricants (sSF against sSF + HA) indicated statistical differences (p > 0.05) for any of the tested conditions.

Discussion
Our results showed that (1) degenerated cartilage and meniscus still have sufficient functional friction properties under gait-like loading and (2) HA supplementation did not impact the CoF under these conditions. Overall, the CoF of degenerated, human samples were comparable to those of healthy bovine articular cartilage [2]. Although the surface and structure of the tissues changes with degeneration, the interstitial fluid pressurization lubrication seems to maintain its friction reducing effect [3,4]. Moreover, tribological studies have shown that HA is less effective under dynamic conditions [5]. It is known the intraarticular injection of HA reduces pain in-vivo. Based on our results we conclude that the mechanism of therapeutic effect of HA is rather due to biomechanical interactions than tribomechanics. Pin-on-plate friction tests require sample extraction out of the joint’s complex anatomy. Thus, future studies are necessary to better understand the role of friction in the progression of OA.

References

Figure 1: Coefficient of friction (CoF) of the stance phase (top) and swing phase (bottom). Mild and severe degenerated meniscus and cartilage samples were tested with synthetic synovial fluid (sSF) and with sSF and Hyaluronic Acid (sSF + HA). Non-parametric statistical analysis, *p<0.05; median with min/max

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
KNEE FLEXION ANGLE ESTIMATION BASED ON FUNCTIONALLY INSTEAD OF ANATOMICALLY DEFINED COORDINATE SYSTEMS

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Introduction

Knee angles are commonly presented in gait analysis reports. They are typically calculated as the relative angles between coordinate systems (CSs) rigidly attached to the femur and the tibia. To give these angles a consistent meaning, the CSs are defined with respect to anatomical landmarks. Defining accurate anatomical CSs is not an easy task, because it requires skills in marker placement, landmark identification and definition of a biomechanical model. Therefore we present a novel method to (i) functionally define two CSs attached to femur and tibia and (ii) functionally calculate the knee angle based on the relative differential kinematics between those CSs. The method has the advantage of being independent (i.e. invariant) of the choice of the original CSs of the femur and tibia, removing the need for accurate marker placement. Consequently, (i) the markers may be placed on optimal landmarks, for example, minimizing the soft tissue artifacts or improving subject’s comfort, and (ii) there is no need for anatomical calibration when technical marker clusters/triads are used.

Methods

The proposed method is based on representing the knee motion around an average screw (helical) axis (ASA), which is functionally determined across a gait cycle [1]. The method exploits the knee ASA to define a local CS relative to a body segment. The procedure is repeated twice, once for the femur and once for the tibia, in order to functionally obtain two CSs rigidly attached to the respective body segments. The relative pose of the two CSs can then be used to calculate features of the knee kinematics. In particular, when representing the orientation part of this relative pose in terms of Euler angles according to sequence XYZ, the angle about the X-axis represents the functional knee angle.

The method was tested on a gait analysis trial from the CAMS-Knee dataset [2] (trial 1 from subject “K8L”) recorded through fluoroscopy. See [3] for more details.

Results

Figures 1 and 2 show that the method produced consistent results for the invariant knee angles (green and blue) calculated according to the proposed procedure, even when the measured poses of the anatomically referenced CSs were randomly modified. Obviously, the anatomical angles (red and pink) lost their biomechanical meaning after such transformation.

Discussion

The invariant flexion angle is close to the anatomical one (figure 1). The method is useful when anatomical references are not available. As a limitation, it does not provide an absolute knee flexion angle, but an accurate estimation of the relative angular motion of the knee.

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Acknowledgements

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THE EFFECTS OF ANTI-OSTEOPOROTIC DRUGS ON A 3D DYNAMIC IN VITRO HUMAN BONE REMODELING MODEL

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Introduction
Osteoporosis is the most common bone remodeling disease causing a significant societal burden and an increased risk of mortality upon related fractures [1]. Novel drugs to prevent and treat osteoporosis are currently routinely tested in animal models with poor clinical translation [2]. In vitro bone remodeling models, employing osteoclast-osteoblast cocultures, could facilitate the investigation of human bone remodeling and thereby have the potential to improve preclinical testing while reducing the need for animal experiments. However, current osteoclast-osteoblast cocultures often lack physiological resemblance, including a 3D biomimetic environment and mechanical loading [3]. Here, we employed a coculture of human monocytes and mesenchymal stromal cells (MSCs) seeded on composite scaffolds and mechanically loaded with fluid shear stress to evaluate the effects of anti-osteoporotic drugs on human bone remodeling in vitro. As such, the capabilities and limitations of this in vitro model were studied.

Methods
Human MSCs and monocytes were seeded in a 1:5 ratio on mineralized silk fibroin scaffolds (N = 4-8 per group) [4] and cultured for 28 days in spinner flasks bioreactors, set at a rotation speed of 300 RPM, with coculture medium (α-MEM, 5% human platelet lysate, 1% antibiotic-antimycotic, 50 ng/ml RANKL and M-CSF, 10 nM dexamethasone and 50 µg/ml ascorbic acid) to stimulate osteoclastogenesis and osteogenesis. After 14 days, when cell differentiation was expected to be completed, anti-osteoporotic drugs alendronate and testosterone were added to the following groups: ALN: 2 µM alendronate, TEST: 75 nM testosterone, ALN+TEST: 2 µM alendronate and 75 nM testosterone. The control group remained untreated. To track remodeling and cytotoxicity, µCT scans were acquired and LDH activity was measured on medium samples taken weekly.

Results
On day 21, the treated groups all had a higher LDH activity than the control group (Figure 1A), indicating more cell death. Scaffold remodeling, tracked with µCT, revealed most mineral formation in constructs treated with only alendronate (Figure 1B+C). No clear treatment induced differences were found in mineral resorption (Figure 1B+C).

Discussion and Conclusion
Cell death was mainly expected in groups treated with alendronate, since alendronate is known for inducing osteoclast apoptosis [5]. The increased mineral formation in the alendronate group might be explained by binding of alendronate to the mineralized scaffold, the little resorption in this group, or a combination thereof. Surprisingly, this was not observed in the groups treated with both testosterone and alendronate. As only minimal differences in remodeling were observed between the treated groups and control group, future experiments require optimization of treatment timing and dosing. Nevertheless, this in vitro bone model shows the potential to track remodeling and cell viability in response to drugs.

References

Acknowledgements
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Figure 1: Medium LDH activity indicative for cytotoxicity (A). Formed mineralized volume (B) and resorbed mineralized volume (C) obtained with µCT. The dashed lines represent the addition of the anti-osteoporotic drugs.
ENDOSCOPIC STRIP CRANIECTOMY WITH HELMET THERAPY: A COMPUTATIONAL TOOL FOR PREDICTION OF HEAD RESHAPING
Lara Deliege (1), Alessandra Carriero (2), Silvia Schievano (1), Juling Ong (3), Greg James (3), Owase Jeelani (3), David Dunaway (3), Markus Bookland (4), Alessandro Borghi (5).


Introduction
Sagittal craniosynostosis (SC), occurring in 1 in 1,700 births [1], is caused by the premature closure of one or more cranial sutures, and results in abnormal skull development (long and narrow head shape). Endoscopic strip craniectomy followed by helmet therapy (ESCH) is a minimally invasive treatment recently adopted to correct SC. In this procedure, the fused suture is removed, and the skull shape normalized progressively by means of a patient-fitted helmet, designed to allow lateral growth while constricting the sagittal direction.

Methods
Six patients who presented with SC at Connecticut Children’s Division of Pediatric Neurosurgery were treated with ESCH (age at surgery: 11 weeks to 9 months) and recruited for this study. Day 1 postop 3D head scan imaging was used to produce the skin 3D models, and the respective skull and intracranial volume (ICV) models by means of surface offsetting (figure 1, right) in Meshmixer® followed by NURBS model creation in Simpleware ScanIP®. Cranial suture location was created on the skull using Solidworks along with the skull base, assumed to lie on the plane passing through nasion and auditore meati. A 15 mm-wide osteotomy from cranial bregma to lambda was modelled. Patient-specific helmet models (front and back) were created following postoperative planning as well as operating surgeon indications: areas of free space in each helmet model were left to allow for growth in targeted areas. All parts (skin, skull, ICV, helmet) were assembled, imported into Ansys Workbench and assigned tissue specific mechanical properties retrieved from literature. The model was meshed using linear tetrahedral elements (432,575 ± 86,043 elements). The simulation was divided into 3 loading steps: 1) and 2) helmet fitting (helmet front and back are separately displaced to fit around the head); 3) head growth, modelled using the thermal expansion model validated by Libby et al. [2]:

\[ \Delta V = V_1 \times \alpha \times \Delta T \]

Where \( \alpha \) is the coefficient of expansion, \( \Delta T \) is a temperature difference arbitrarily fixed at 100 °C, \( V_1 \) is the initial ICV, and \( \Delta V \) the ICV increase due to growth. The value of \( \alpha \) was fixed at 0.0061 °C for a 3 month-growth based on trial-and-error testing on one patient. The skull base was fixed in all directions to mimic skull base tethering. In 4 cases, the helmet model was updated (according to the growth) after 3 months of treatment and head growth was simulated for another period of 3-5 months according to the end of treatment date. Validation was carried out by comparing the simulated post-treatment surfaces with post-treatment clinical 3D scans.

Results
The treatment was simulated over 3 months (n=2) or 6 months (n=4). Comparison between the simulated post-treatment head shape and clinical 3D scans showed that 95.9% ± 2.8% of surface data points over the population are included in a [-3; 3] mm range. Figure 2 shows the surface difference pattern at the end of treatment: Accurate shape estimation was obtained over the population.

Discussion
Cranial vault remodeling following ESCH was modeled using a patient-specific 3D geometry where surgical osteotomies as well as helmet model were replicated based on surgeons’ indications. The results showed an accurate prediction of the therapy outcomes. Upcoming research will introduce patient-specific skull mechanical properties to further improve the model. This computational tool will help provide guidance and refine the current understanding on the necessary helmet treatment duration.

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Introduction
Fracture fractures in the hip are a growing risk for older adults [1] which potentially could be mitigated by better understanding local bone quality changes in the proximal femur. Current methods are often limited to regional analyses, such as volumetric (vBMD) or areal bone mineral density (aBMD) in the femoral neck or greater trochanter. Voxel-Based Morphometry (VBM) can be used to compare similar but different images at the voxel-level [2] and is a powerful tool for quantifying sub-regional bone quality changes in the femur. In this study, we demonstrate the use of VBM on quantitative computed tomography (QCT) scans of the proximal femur to investigate sex-related sub-regional bone quality changes over an 18-month period.

Methods
QCT scans from 67 females and 32 males (ages 65-85; BMI 27-45 kg/m²) were selected from the UPLIFT clinical trial [3]. All subjects underwent an aerobic exercise and caloric restriction intervention targeting 10% weight loss. No subjects were osteoporotic at study entry. Baseline scans and 18-month follow-up QCT scans were available for all selected subjects. A single template right femur was generated from 10 random baseline scans [4]. Every scan was manually segmented and, using the Advanced Normalization Tools (ANTS) Py 0.3.1, deformably registered to this template using a symmetric normalization transformation and cross-correlation as the optimization metric. The registered images were smoothed with a Gaussian filter (σ = 3mm) which renders the data more normally distributed [2]. Bone density differences for each subject were calculated by subtracting registered baseline scans from the registered 18-month follow-up scans, and an image of averaged bone density changes was created for males and females. These were compared using a two-sided t-test for each voxel, and a False Discovery Rate control of q<0.05 was used to address multiple comparisons [5].

Results
Local bone changes ranged from -0.011 to 0.023 g/cm³ for females and -0.005 to 0.022 g/cm³ for males. Both groups showed bone density increases on the anterior and posterior aspects of the cortical bone along with the posterior aspect of the femoral neck (Figure 1B and D). The average female showed a large density decrease in the greater trochanter (Figure 1A). The significantly different bone density changes between the males and females are mostly located in the femoral head and trochanter, and all have negative values, meaning the average female femur lost significantly more bone than the average male femur (Figure 1E).

Discussion
This is the first weight loss trial to quantify longitudinal sub-regional bone changes at the voxel level using VBM. While other longitudinal bone quality studies show regional bone loss, we found that there is also substantial local bone gain that may be overlooked in previous work. In many regions of the femur, females lost bone at a significantly higher rate than males. However, this is not uniform, and these areas may be a reason for the increased fragility fracture risk women have compared to males. Future studies should investigate if these regions are associated with increased fragility fracture risk (e.g., finite element analyses). VBM may be a useful tool for studying other effects (e.g., age or pharmaceutical treatment) on local bone changes and could be used to develop personalized bone change and fragility fracture risk models.

References

Acknowledgements
This study was supported by the National Institute of Health (R01AG050656, K25AG058804, F31AG069414).

Figure 1: (A) Female average bone loss; (B) Female average bone gain; (C) Male average bone loss; (D) Male average bone gain; (E) T-values of the difference between female and male bone changes. Non-significant bone changes are transparent.
A COMBINED CFD AND MESH MORPHING TECHNIQUE TO INVESTIGATE THORACIC AORTA HEMODYNAMICS

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Introduction

Thoracic aortic (TA) diseases are associated with high mortality rates [1] because of their silent nature, before acute events, and the lack of a screening program. Computational Fluid Dynamics (CFDs) represents a powerful tool for the study of blood flow and its relationship with pathophysiology of TA diseases [2, 3]. While standard CFD simulations affect the evaluation of hemodynamic parameters due to the rigid-wall assumption, Fluid-Structure Interaction (FSI) simulations have high computational times and need additional information on vessels wall that are difficult to be defined in-vivo. Recently, a strategy based on radial basis functions mesh morphing technique combined with transient simulations was presented [2, 4] to investigate TA hemodynamics. However, it was confined to the ascending aorta and it showed some intrinsic limitations. This work aims to overcome these limitations and to develop and implement a new procedure (CFD_morph) that integrates CFD simulations and mesh morphing techniques to study the hemodynamics of the entire aorta, following the geometrical variations of the vessel throughout cardiac cycle.

Methods

Starting from ECG-gated CT images, TA 3D models of five subjects were reconstructed through segmentation with a U-net deep neural network for ten phases of cardiac cycle [5]. An in-house algorithm for mesh morphing was applied to build the surface mesh from each 3D model, maintaining the same number of nodes and connectivity of the baseline mesh (0% phase). A mesh nodes mapping of TA wall at each phase was employed in a spline interpolation process to gain the wall displacement for the whole cardiac cycle. Motion of TA boundaries was included in the CFD simulation and used by the solver to handle volume mesh. Regarding the boundary conditions, patient-specific flow velocities were set at the inlet and blood pressure were imposed at the four outlets by implementing a lumped 3 element Windkessel model. In addition to the developed procedure, a standard CFD simulation (CFD0) for the 0% phase of TA has been performed to compare results in terms of fluid velocity and the main hemodynamic parameters. Ansys® Fluent® software was used for both the simulation strategies.

Results

The proposed approach allowed to cope with the TA patient-specific morphological variations and motion during the cardiac cycle, with no significant loss of mesh quality. Differences in terms of velocity distribution with respect to the CFD0 were found (Figure 1). For the CFD_morph a time lag equal to 0.072 s was detected between the descending aorta flow rate waveform and the inlet flow profile. Discrepancies between the two simulation strategies were also found in the main wall shear stress (WSS) based hemodynamic parameters. The CFD0 underestimated the surface areas with high oscillatory shear index and low time-averaged WSS.

![Figure 1: Velocity magnitude at different TA section and different times of cardiac cycle for the two simulation strategies (CFD0 and CFD_morph).](image)

Discussion

These findings show the impact of wall motion and aortic geometric variations during cardiac cycle on the assessment of TA hemodynamics. The combination of mesh morphing techniques and CFD simulations represents a powerful strategy to obtain motion-related patient-specific results, overcoming the main limitations of standard CFD and FSI approaches. A further analysis may also include pathological TA datasets.

References


Acknowledgements

MeDiTaTe Project has received funding from the EU’s Horizon 2020 research (No. 859836).
EFFECT OF GEOMETRY FEATURES ON KNEE JOINT MECHANICS: SUBJECT-SPECIFIC VS GENERIC MODELS BASED ON 39 PATIENTS

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Introduction

Finite element modelling is a useful alternative method for investigating stress distributions in knee joints since analytical solutions are not possible. Subject-specific knee joint modelling is well-established over decades. However, the geometry of knee tissues varies greatly among individuals, and these morphological differences may have substantial consequences for injury and disease risk [1]. To better improve patient outcomes, we must question whether a single-subject knee model is sufficient, e.g., for driving implant design decisions. Statistical shape modelling (SSM) is a well-established computational approach that uses compact descriptive values to capture the morphological diversity dispersed across a group of matching surfaces. SSM has not been applied to investigate the poromechanical behaviour [2] of the knees of a cohort. Our ongoing research uses a unified material and geometric modelling approach to isolate the effects of patient demographics, including sex and ethnic differences in tissue properties and knee anatomy, in a large population through modelling to discover generic and subject-specific biomechanical behaviours. The objective of the present study is to test the capacity of a SSM workflow to produce generic knee models for finite element contact analysis.

Methods

Two generic knee models have been created so far using a previously developed SSM workflow [3]: average-39 was generated from the right knees of 39 healthy subjects (45-69 years, white male), and average-8 from 8 knees randomly selected from the 39 subjects. Modal variations from average-39 will be examined. As an essential step for all subject-specific models, tissue geometries of each knee were reconstructed and meshed from MRIs obtained from the OAI [4], using an automated hexahedral meshing approach [5]. The SSM approach used the Coherent Point Drift algorithm to establish node correspondence between individuals’ point clouds for the bones, cartilages, and menisci. Following alignment of the point clouds, principal component analysis was applied to the registered knee joint data to extract the principal modes of geometric variation. Cartilages and menisci were modelled as fibril-reinforced fluid-saturated materials using a previously developed nonlinear constitutive model that is implemented in ABAQUS using the user-defined material option (UMAT) [2]. To model creep response associated with fluid pressure in cartilaginous tissues, we simulated a full extension joint load for each generic cohort and selected subject specific models. Joint loading consisted of a 600-N force ramped in 1s and remained constant for 6000s.

Results

Example results are shown in Figure 1. Statistical analysis on variations in joint contact mechanics will be performed once we have obtained all results in the coming months.

![Figure 1: Maximum contact pressure in the medial tibial cartilages with creep loading obtained from one subject-specific and two generic knee models.](image)

Discussion

The generic model built from randomly chosen 8 knees yielded quite different results from the model based on 39 knees, indicating a big number of joints is required for SSM modelling. Results have shown significant variance between subject and cohort averaged models. It is critical to capture inter-subject variability in subject-specific models as the results may be different from cohort averaged. Ongoing work includes reconstruction of multiple shape models and a complete comparison between the reconstructed shape models and subject-specific models.

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Acknowledgements

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RESIDUAL AORTIC DISSECTION NUMERICAL MODELLING

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Introduction
Thoracic aortic (TA) dissection (TAD) involves a tear in the aortic wall that propagates within it, resulting in the creation of a false lumen (FL) in which the blood flows. FL is separated from the true lumen (TL) by the neo-intimal flap (NIF). According to Stanford classification TAD type A concerns those with an initial tear on ascending TA whereas for type B it is located on descending TA. In most of the cases, type A is a surgical emergency requiring replacement of the ascending aorta with a prosthesis. Residual AD (RAD) may persist in the descending segment. It is managed, like other uncomplicated type B TAD, by drug treatment. However, in 45% of cases RAD badly evolves. The current clinical indicators to evaluate RAD evolution are unfortunately not discriminating enough to predict a risky evolution of RAD. TAD, and even more RAD, have been the subject of very rare numerical modelling. To our knowledge only two studies [1, 2] out of our group performed Fluid Structure Interaction (FSI) numerical simulations of RAD. They considered fluid behavior as Newtonian and none of these works has associated biomechanical markers with RAD adverse evolution through longitudinal follow up. The goal of the present work is to go further analyzing different configurations for structural domain to highlight which structure plays or not a major role and linking some biomechanical markers with adverse RAD evolution thanks to longitudinal follow up.

Methods
Fluid and mechanical solid solvers with system coupling of ANSYS (Inc, USA) were used to perform all the simulations. The RAD geometry derived from patient specific morphology (figure 1a). The unsteady and incompressible flow was assumed to be laminar and the fluid behaved as a shear thinning one using the Carreau model. Both the prothesis and aortic wall were modeled as linear elastic and isotropic materials. The Young modulus (E) of the aortic wall, \( E_{wall} \) was set to 1.2MPa, those of Dacron prothesis to 3.1GPa. The fluid and solid domains were discretized in 1,276,255 and 541,715 elements respectively. At the entrance, inlet Womersley velocity profiles were derived from an ascending aorta flow rate. At the outlets (3 aortic arch outlets and descending aortic outlet), a 3 elements WindKessel model was tuned for each of them, allowing pressure profiles to be defined [3]. 3 configurations were investigated. i) Rigid: all structural parts are assumed rigid, ii) NIF FSI: only NIF is deformable (\( E_{NIF} = 1.2 \) and 0.6MPa were tested), iii) Full FSI: all structural parts are deformable. For NIF FSI, element faces facing the aortic wall were embedding. For Full FSI, face prosthesis entrance and main descending outlet were embedding. Normal displacements of aortic branches outlet were not allowed. A initial pressure condition of 80mmHg was imposed at walls and resulted constraints were applied to start the simulation with zero displacements. The mean Reynolds value and Womersley number were 1279 and 27.6 respectively.

Results
Compared to rigid modelling, NIF FSI does not show any significant difference on the flow behavior and NIF displacements are negligible even for the most compliant NIF. In relation to Full FSI, Rigid modelling induces an overestimation of velocity values and flow rates in TL and FL whereas pressure overestimation is so small that it can be considered negligible. Rigid modelling underestimates the surfaces of low WSS and TAWSS. NIF and aortic wall maximum displacements exhibit the same curve shape with maximum value around 1.2mm for Full FSI (figure 1b).

Discussion
The results will be discussed according to the mechanical behavior of the different structures and more particularly on the difference between \( E_{wall} \) and \( E_{NIF} \). The relationship between NIF motion, whatever its amplitude, and the small pressure difference between FL and TL that never exceeds 5mmHg is not trivial. This point seems to be an essential key to understand mechanisms implicated in RAD main remodeling characteristics. Finally, it is important to underline that despite differences all models can predict thrombus formation at early stage though WSS cartographies and vortical structures evolution.

References

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Imaging Local Tissue Strain Using \textit{In Vivo} 4D Synchrotron X-ray µCT in Bleomycin-Induced Lung Injury in Rats

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Introduction
Pulmonary fibrosis is characterized by excessive and heterogeneous deposition of extracellular matrix (ECM) components, particularly collagen, altering the local lung tissue stiffness. There is evidence that changes in ECM micromechanics significantly impact cell function [1]. However, there are no techniques to assess the local ECM micromechanics in lungs, \textit{in vivo}. We applied a time-resolved synchrotron radiation phase contrast µCT technique (4D-µCT) to investigate local ECM deformation under controlled ventilation in bleomycin-induced lung injury [2], with an effective pixel size of 6 µm. Here, we computed and qualitatively compared images of local lung strain distribution within the lung tissue in normal and bleomycin-injured rat lungs.

Methods
The experiments were performed in 6 control and 7 bleomycin-injured anesthetized, muscle-relaxed and mechanically ventilated adult rats at 7 days post intratracheal instillation. X-rays from a synchrotron source were monochromatized at 38 keV. A free propagation phase-contrast setup was used with a sample to detector distance of 3.5 m. Images were reconstruction using the Paganin phase retrieval algorithm. Projection images were acquired at a constant frame rate using a fast camera (PCO Edge), coupled with optics determining a pixel size of 6 µm and 10 ms time resolution. The ECG signal was recorded and image reconstruction was retrospectively gated to both breathing and cardiac activity. Quantitative maps of local lung strain were computed using a previously described image-registration based processing pipeline [3].

Results
Figure 1 shows sample phase-contrast CT and composite strain maps in a representative control and bleomycin rat with lung injury. Further quantitative analysis of the local strain data is underway.

Conclusions
Here, we show a first comparison of quantitative images of local strain acquired in normal and bleomycin-injured \textit{in vivo} rat lungs, based on registration of dynamic 4D-µCT synchrotron phase-contrast images obtained at 6 µm voxel resolution. This approach will allow to investigate how the ECM micromechanical alterations influence fibrogenesis and vice-versa. Assessing the involved mechanisms will provide insight for developing new therapies.

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Introduction
Thanks to its excellent mechanical and biological properties, silk fibroin (SF) is a protein used in many applications of tissue engineering (TE), for example the ones involving controlled drug release. Despite this, the literature reports limited examples of SF in bioprinting as many problems still need to be addressed, including its time stability, low viscosity when in the form of solution, and, more importantly, the difficulty of 3D printing this material because of β-sheet formation in its structure during the printing process, leading to nozzle clogging [1]. In this work, we developed and optimized a blend of silk fibroin and sodium alginate (SA) for the release of lyossecretome, a freeze-dried formulation of mesenchymal stem cell secretome characterized by bioactive properties able to improve biological response [2].

Materials and Methods
Preparation SF solution was obtained starting from Bombyx mori cocoons. Three different degumming times in 0.02 M Na2CO3 were investigated: 30 min (standard protocol), 1, 2, and 4h. SF (5% w/v) degummed for 1,2, and 4h was blended with SA (10% w/v) obtaining three different formulations of SA-SF hydrogels. A hydrogel composed only by SA (10% w/v) was used as control.

Printing characterization Each formulation was evaluated in terms of printability and shape fidelity at two different time-points (7 and 14 days after SF preparation) to assess the time-dependent behaviour of SF. An extrusion-based 3D bioprinter was used for printing 3D structures, whose strand size, inter-filament distance and printability index were calculated to evaluate quantitively the printing performance.

Mechanical characterization Each formulation was evaluated with tensile and compressive mechanical tests at 7 and 14 days. Before testing, the samples were chemically crosslinked with solution formed by 2% w/v CaCl2 + 20% w/v KCl + 5% w/v protamine. Moreover, to understand the impact of the crosslinking method on the material structure, a comparison of this crosslinking solution with one composed only by 2% w/v CaCl2 was performed on SA hydrogel samples in terms of tensile test.

Release study: Lyossecretome was included in each formulation and its release over time was measured.

Results and Discussion
SF solution extraction was successfully optimized by increasing the standard degumming time from 30 min to 1, 2, or 4 h: reduced SF molecular weight allowed to achieve a printable protein solution, that remained capable of the conformational change from Silk I (random coil) to Silk II (β-sheet). This transition is fundamental to improve the scaffold’s mechanical properties and drug release. From a printing point of view, SA-SF hydrogels with a degumming time of 2 h and 4 h resulted to have a better performance in terms of shape fidelity and to be printable at both time-points. From a mechanical point of view, adding SF to SA hydrogel increased the compressive response, especially when degummed for 2 and 4 h, while it did not influence tensile performance (Figure 1b). However, the crosslinking method in the material was demonstrated to strongly influence the mechanical response. Indeed, the tensile modulus of SA hydrogel resulted to be three times higher when crosslinked with CaCl2 compared when treated with CaCl2+protamine+KCl solution (Figure 1c). Finally, degumming of SF for 2 and 4 h dramatically slowed the lyossecretome release and modified the kinetics and mechanism of release with respect to the SA hydrogel baseline.

Figure 1: Mechanical characterization: a) example of tensile sample and test; b) tensile and compressive modulus results; c) influence of crosslinking methods on tensile response

Conclusion
A 3D printable SA-SF hydrogel for TE applications was achieved. The results obtained from the different characterizations lay the foundation for future development of SA-SF bioinks with modulable mechanical and release properties, and their use in scaffold 3D printing.

References

Acknowledgements
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Introduction

The scaling procedure of a generic musculoskeletal model is a crucial operation that can lead to inaccuracies for all the subsequent stages of the musculoskeletal analysis [1]. Changing marker locations is a fundamental part of the scaling procedure since it allows to estimate the scale factors that best match experimental data. It’s a tricky operation manually executed so far, since it needs an iterative trial and error procedure. Thus, it is also time consuming and covers a large part of the whole musculoskeletal analysis. It may require from a half day to several weeks, according to the level of experience of the operator and to the desired level of accuracy. To diminish both time and efforts and to improve the accuracy of the scaled model, herein we present an innovative and automated procedure to scale generic MSK models in OpenSim environment.

Methods

This tool consists of a MATLAB script that exploits OpenSim API functionalities. The code takes in input three files: the generic unscaled model file containing the generic set of markers, the static experimental trial file and the scaling setup file containing the measurement sets and the marker weights defined by the user. This script consists of an iterative algorithm that performs several times the scaling procedure until a given condition (e.g. RMS marker error less than a threshold) is fulfilled: in every cycle, the highest marker error is detected and its coordinates on the generic model are modified of a quantity proportional to the such error. Additionally, the routine performs a check on the resulting scale factors: if they become too low or too high it means that the scaled geometry is not reliable and then the manual repositioning of the initial markers on the generic model is suggested.

The tool has been tested on two datasets: a) experimental MoCap data collected at the Biomechanics Laboratory of the “Sport and Anatomy Centre” of the University of Pisa (where a Vicon motion analysis system with eight infrared cameras @100 Hz is installed) and b) public domain data of the Grand Knee Challenge Competitions [2].

A generic Rajagopal model has been adopted even though in future other typologies of models will be considered.

Results

Preliminary results coming from the comparison of the scaled model of fifth edition of GKC subject with and without the tool show a net decrease of both RMS errors and max error than the manual procedure. As a result, these differences also reflect on markers errors locations over walking trial, where the API method seems to keep both RMS and max errors lower than the manual procedure (Table 1). According to the level of accuracy desired, this script employs certain amount of computational time: for an RMS error of marker trajectories < 0.003 m it may require up to 3 hours of simulation; instead for less strict criteria (RMS error <0.01 m), this script can lead the operation in less than half an hour.

<table>
<thead>
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<th>Scaling method</th>
<th>Static Error (m)</th>
<th>Gait Error (m)</th>
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<tr>
<td>Manual</td>
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Table 1: Markers mean error location (automated vs manual procedure) during static and walking trials of GKC 5th edition subject.

Discussion

The herein presented tool can represent a useful mean to improve the scaling procedure, by iteratively modifying marker locations of a generic musculoskeletal model to reduce markers position errors. This innovative tool has shown encouraging results, new tests in terms of experimental datasets and models adopted will be executed to further validate the algorithm, including the effect of marker weights.

![Diagram](image)

Figure 1: Tool operation flow. Inputs are: Unscaled model with markerset, scaling setup file and experimental static pose; The output is the scaled model.

References

1. Introduction
Osteoarthritis (OA) is the most common chronic joint disease. Current therapies for OA patients are limited to symptom relief and in advanced stages of the disease, joint replacement surgery. Altered joint loading is a critical and agreed risk factor for the onset and progression of OA. Therefore, ambulatory monitoring of joint loading-related parameters such as ground reaction forces and moments (GRFM) and tibiofemoral knee contact forces (KCF) have the potential to impact disease management of patients with knee osteoarthritis (PwKOA). However, OA knee joint loading in free-living situations is not well documented as so far inertial measurement units (IMUs) have rarely been combined with musculoskeletal modelling (MSK) workflows. Moreover, estimating KCF using IMUs is still lacking in literature to date. Establishment of such a workflow would impact the clinical management of OA based on objective joint loading measurements in an ecological context.

2. Materials and Methods
Twenty-eight PwKOA (18 females; age: 66.6 ± 7.3 y) walked on treadmill and overground at self-selected speed. A Vicon and an Xsens systems recorded the marker position and the body segment orientations. Using an enhanced MSK workflow - OpenSim Joint Articular Mechanics - with 12DOF knee, the motion capture (MoCap) data was used to calculate the KCF (gold standard). The IMU-based dataset was used as input for the inverse kinematics using a previously developed calibration method [1]. A customized probabilistic principal component analysis (PPCA) model that combines kinematic parameters (events, angles) was used to estimate GRFM based on a training dataset (18 PwKOA) [2]. The estimated GRFM were used as input in the zero moment point (ZMP) method to calculate the COP [3]. The inverse kinematics and external load (GRFM) were used to calculate the KCF that was then compared with the reference MoCap-based KCF.

3. Results
The KOA-based PPCA mean absolute error (MAE) was of <0.047 BW and <0.015 BWm for the estimated GRFM. The estimated COP revealed a moderate-strong correlation (R2: 0.60-0.96) in the anterior-posterior and medio-lateral direction with an average RMSE 1.5±0.4 and 1.0±0.3 cm, respectively. The KCF RMSE ranges between 0.22-0.55 BW with moderate-strong correlation (R2: 0.49-0.96). Compared to the MoCap-based KCF (Fig. 1), the IMU-based KCF average error was <0.5 BW at first and second peak as well as the impulse (<0.5 BW).

4. Discussion and Conclusions
The results show that the developed workflow accuracy would allow the detection of reported differences in KCF between healthy and PwKOA, which are in the order of 0.45-0.60 BW for the first KCF peak and 0.30-0.45 BW for the second KCF peak [4]. The customized probabilistic principal component analysis model, trained based on a PwOA showed an accuracy comparable to the previously developed model based on healthy adults. The developed workflow would eventually allow monitoring KCF in an ecological context and consequent impact of specific gait interventions on an individual patient’s locomotor function and joint loading. This is of high clinical importance to inform and help clinical practitioners to induce joint loading changes as part of the regular therapy sessions with the aim to reduce activity-related pain and disease progression.

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Acknowledgements
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INTRODUCTION
Many computational models have been developed for the lung at various spatial scales, while morphological studies combined with increased computing power have allowed for model expansion to smaller length scales. Yet, the wide range of experimental techniques and reported constitutive models for lung tissue at different length scales can lead to uncertainty when utilizing such material properties in computer modeling. Therefore, this study aims to use in silico modeling to compare, reconcile, and resolve the differences reported in lung tissue mechanics at different length scales. Specifically, this research aims to utilize computational modeling to study whether the emergent mechanical properties of lung tissue, based on microscale mechanical testing data, can be reconciled with the experimental data reported at the mesoscale.

METHODS
A finite element (FE) analysis was performed using COMSOL MultiPhysics at the mesoscale by assigning visco-hyperelastic microscale-based properties to alveolar septa based on previously reported in vitro and in situ experiments [1]. The 3D geometry comprised an array of approximately 10,000 alveoli represented by truncated octahedra and meshed using 2.2 million quadratic tetrahedral elements. The emergent properties from the FE analysis were then compared to mesoscale data from a study that utilized a comprehensive approach to determine the mechanical behavior of rat parenchyma [2]. The standard linear solid viscoelastic model was added to the microscale hyperelastic constitutive models to account for the effect of rate of loading [3]. The viscoelastic stress ($\sigma_q$) of the standard linear solid model was determined by the equation:

$$\sigma_q = 2n_1\dot{\gamma}_1$$  \hspace{1cm} (1)

Where $n_1$ is the viscosity and is related to the stiffness ($G_1$) and relaxation time ($\tau_1$) by $n_1 = G_1 \tau_1$. Also, $\dot{\gamma}_1$ is the strain rate.

RESULTS
The tensile test simulation results (Figure 1) showed reasonable agreement with the reported mesoscale data [2] at strains between 0.0-0.3. Specifically, the simulated curve based on the work of Perlman and Wu [1] showed slightly lower stiffness compared to the reported mesoscale behavior model below ~28% strain. Above 30% strain, the disagreement between the simulated microscale-based curve and the mesoscale dataset increased. The mean error was determined for each simulated case concerning the reported mesoscale data to quantify the difference in the resulting stress-strain curves.

DISCUSSION
In this study, we analyzed two of the most comprehensive and high-fidelity mechanical testing datasets published by other researchers for the purpose of this study: the microscale data reported by [1] and the mesoscale multimodal data of [2]. Overall, the comparative research successfully reconciled the mechanical properties of lung tissue across micro- and mesoscales. In addition, this research further confirmed the reasonable accuracy of the mechanical behavior reported for lung tissue in both experimental studies. Furthermore, this study showed that FE modeling could be used as an informative and guiding tool to investigate and potentially resolve the differences in reported lung tissue mechanical properties across spatial scales.

References

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AORTIC CALCIFICATIONS LOCALLY AFFECT DISSECTION BEHAVIOR

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Introduction
Acute aortic dissection (AAD) is a life-threatening condition in which a tear propagates through the wall of the aorta. Nearly 18% of AAD patients die before reaching the hospital, and 63% die within 30 days. Improving patient outcomes from these potentially lethal events is largely dependent on screening high-risk patients. Aortic calcification is one of the most prevalent comorbidities of AAD. A recent study found that the nearest calcification was on or slightly distal to the initiating intimal tear in over 60% of ADDs, suggesting a local effect on the aorta’s propensity for dissection. However, the local mechanics remain unknown. This study correlates calcification locations from micro-CTs (μCT) to local peel tensions to assess the hypothesis that calcifications have a local effect on delamination of the aorta.

Methods
Sample Preparation: Samples were cut from three human cadaveric aortas (73F, 75M, 86F) using *Anatomy Bequest Program, U of Minnesota*. Twenty-two (22) samples were identified as thoracic aorta samples with a μCT-detected calcification. **μCT Analysis:** Samples were scanned with an average resolution of 95.5 μm (NSI, Rogers, MN). Image analysis was performed using MATLAB (Fig. 1A). All calcified samples were computationally segmented into three regions: 1) >2mm before the calcification (control), 2) <2mm before the calcification, and 3) a calcification region starting at the calcification front and extending 2mm distal to the lesion. **Peel Testing:** Medial incisions were made to initiate peel propagation. Both “arms” of the incised sample were clamped, loaded onto a uniaxial testing machine (MTS, Eden Prairie, MN) equipped with 10N load cells, and pulled at 10 mm/s (Fig. 1B). Peel tension was defined as peel force divided by the sample width.

Results
Peel tension behavior varied across sample regions (Fig. 1C). Fig. 2 shows the average minima, maxima, means, standard deviation (σ, used as a measure of mechanical heterogeneity), and slopes (calculated by fitting a linear model to tension vs. displacement) for each region. The difference between the minima for region 2 and regions 1 and 3 were significant (p=0.0049 and p=0.0104, respectively), demonstrating a rise in the minimum peel tension approaching a calcification and a drop in tension adjacent to a calcification. The calcified regions were the most heterogeneous, significantly different from region 2 (p=0.0196). Slopes varied greatly, but tended to be positive before calcifications and negative in calcified regions with significant differences between regions 1 and 3 (p = 0.0089).

Discussion
The results demonstrate that aortic calcifications have a local effect on dissection. In general, the peel tension of samples with calcifications exhibited a “rise and fall” trend, captured by the rise and fall of the local minima, increase in the local heterogeneity, and the slopes turning from positive to negative when the peel front hits the calcified region (Fig. 2). This behavior suggests that calcifications might be initially protective against peel propagation but result in more brittle failure events when the local yield strength is exceeded. This study is, to our knowledge, the first to correlate media peel mechanics to CT imaging, a routine modality for clinical monitoring/diagnostics, and thus potentially valuable in assessing aortic wall failure risk.

References

Acknowledgements
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RISK ASSESSMENT OF ASCENDING AORTIC ANEURYSMS USING PROBABILISTIC MATERIAL PARAMETERS AND IN VIVO THICKNESS

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Introduction
Rupture and dissection are feared possible consequences of an ascending thoracic aortic aneurysm, associated with mechanical failure of the arterial wall. The failure risk of the aneurysm wall can be quantified as the difference between the in vivo wall stress and the wall strength. Estimating these values requires knowledge of material parameters, loading conditions and geometry of the aneurysm, all of which are affected by a high degree of uncertainty.

As a way to deal with this uncertainty, the concept of a probabilistic failure risk has been introduced, albeit for abdominal aortic aneurysms, by [1]. In this study, we have extended this approach by including the uncertainty related to the material parameters and in vivo thickness.

Materials & Methods
From 30 ATAA patients, 142 planar biaxial samples were tested to characterize the material behavior of the aneurysmatic tissue. Experimental stress-stretch curves were fitted according to [2], resulting in an estimation of a deterministic in vivo thickness at diastole $H_{\text{dias}}$ and five material parameters of the Gasser-Ogden-Holzapfel model ($C_{10}, k_1, k_2, \kappa, \alpha$) [3]. Based on all tested samples, probability density functions were generated for $H_{\text{dias}}, C_{10}$ and $k_1$. The value for $k_2$ is treated as a constant, physiological value for now.

To estimate a patient-specific peak wall stress (PWS), the aneurysm was modeled as an axisymmetric thick-walled cylinder with a known inner diameter at diastole $D_{\text{dias}}$, and was prestressed based on the condition of static equilibrium of the diastolic configuration with a known blood pressure $p_{\text{dias}}$. The transmural distribution of the collagen fibers ($\kappa, \alpha$) was determined according to [4]. The maximal stress was calculated by inflating the ATAA with a known systolic blood pressure $p_{\text{sys}}$ and axially stretching with $\lambda_{ax}$, while the material parameters and in vivo thickness were obtained through random sampling from the generated probability distributions.

A lognormal probability distribution was assumed for the wall strength ($Y$) which was derived from literature [1]. The probabilistic failure risk (PFI) is defined as [1]:

$$\text{PFI} = \int_0^{\omega_p} \left( \rho_{\text{PWS}}(p_{\text{PWS}}) \frac{\mu_{\text{PWS}}}{\rho_Y(y)} \right) dp_{\text{PWS}},$$

with $\rho_i$ the probability density function of the respective variable $i = \text{PWS}, Y$.

Results
$H_{\text{dias}}$ and $C_{10}$ were fitted with a lognormal distribution, $k_1$ was fitted with a Weibull distribution. Figure 1 shows the probability distribution of the wall strength $p_Y$ and the circumferential peak wall (Cauchy) stress $p_{\text{PWS}}$ ($\rho_{\text{PWS}}(p_{\text{dias}}) = 50\text{mm}; p_{\text{dias}} = 100\text{mmHg}; p_{\text{sys}} = 149\text{mmHg}, \lambda_{ax} = 1, k_2 = 3$), fitted over the histogram of PWS, resulting in a PFI of 12.48%.

Figure 1: Histogram of PWS (gray), with fitted $p_{\text{PWS}}$ (solid line) and $p_Y$ (dotted line). For this patient, the PFI is 12.48%.

Discussion & Conclusion
Material parameters and in vivo wall thickness are inaccessible in vivo and reported values from in vitro experiments are varying drastically. Therefore, a probabilistic view on material parameters and thickness is highly encouraged and will enhance the trustworthiness of biomechanical-motivated failure risk assessment methods. In this study, stochastic distributions were fitted to a large database of estimated material parameters and in vivo wall thicknesses. This led to a patient-specific probabilistic in vivo wall stress and failure risk assessment.

Until now, the loading conditions and diameters were determined in a deterministic way. As a next step, the presented framework needs to be generalized by including the stochastic nature of the blood pressure and the uncertainty related to the diameter measurements.

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Acknowledgements
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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
Introduction

1D haemodynamic partial differential equation (PDE) solvers present themselves as an excellent tool for modelling full body blood flows and pressures. In spite of their success, however, PDE solvers are still limited by a few key areas - namely on-the-fly uncertainty quantification, ill posed problems and (potentially) expensive computational cost. The field of haemodynamics is no exception to these limitations with a paramount need for solutions; to aid clinical judgement, account for inaccessible vessels and mitigate limited clinical resources. Thus there is a clear need for haemodynamic models that are able to predict clinical biomarkers with minimal input data whilst conveying model confidence in an intuitive manner.

Methods

We propose a novel Deep Residual Ambivalent Graph-convolutional Network (DRAGN) to provide accurate biometric predictions with uncertainty quantification. Bayesian inference is used as a proxy for uncertainty quantification via post-training dropout, with prediction stability obtained through multiple input perturbations - which is only possible due to the cheap evaluation of the trained neural networks. Additionally, ill-posed problems can be handled in a similar manner through sampling unknown parameters from a distribution, reducing the time taken to obtain patient measurements and subsequently reducing clinical workload. The network is trained on a synthetic patient database which is generated using in-house PDE haemodynamic solvers through sampling PDE input parameters from a uniform distribution and then rejecting any non-physical or non-physiological patients. The learning objective for the network is to predict the pressure and resistivity index for a pre-specified vessel (either the carotid or femoral artery) selected from a 77 vessel network. The network is then trained for up-to 100,000 epochs using a Latin hyper-cube sampling for parameter tuning with linear regression models to highlight areas for parameter sub-sampling.

Results

Once trained, DRAGN was able to evaluate 2000 patients per second with an inference time of 5e-4s. For pressure index metric prediction, DRAGN has a mean squared error of 9.4e-5 with the pressure index mean being 0.057. For resistivity index metric prediction, DRAGN has a mean squared error of 0.014 with the resistivity index mean of 1.2. DRAGN is still undergoing hyper-parameter tuning with daily performance increases.

Discussion

The residual graph convolutional neural network has showcased an ability for fast and accurate biomarker prediction allowing for on-the-fly uncertainty quantification and reducing clinical measurement acquisition time - removing current clinical barriers for haemodynamic solvers. The next steps, are to extend the neural network architecture such that it is capable of predicting transient responses (such as pressure waves) through utilising transient neural network architectures.

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EXPERIMENTAL INVESTIGATIONS AND CONSTITUTIVE MODELLING OF THE LAYER-DEPENDENT BEHAVIOUR OF THE HUMAN OESOPHAGUS

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The human oesophagus is a primarily mechanical organ, and its function depends on both the passive and active properties of its tissue wall. Knowledge of these properties can be used to investigate the effect of pathophysiology on the oesophagus’ function; to determine the tissue’s material parameters for finite element modelling of the organ for applications such as medical device design and surgical simulations; and to compare the mechanical properties of the tissue engineered oesophagus to that of the native organ. However, as of yet, outside of the authors’ own work [1,2], the passive properties of the human oesophagus have not been studied in regard its layer-dependent or viscoelastic behaviour [3,4]. The authors’ previous work involved mechanical testing of oesophagi retrieved from embalmed human cadavers, while the experimentation presented here is from oesophagi excised from fresh, recently deceased cadavers. Once excised, the three fresh oesophagi were separated into their two main composite layers: the mucosa-submucosa layer and the muscularis propria layer, as seen in Figure 1.

Samples were then cut in both the longitudinal and circumferential directions, and a series of uniaxial tensile tests in the form of increasing stretch-level cyclic tests and multi-step stress-relaxation tests were performed to study the anisotropic, viscoelastic behaviour of the oesophageal layers. The cyclic tests were conducted at 1% s⁻¹ and 10% s⁻¹ to investigate any strain rate-dependency. The experimental results showed the fresh oesophageal layers to have a greater stiffness in the longitudinal direction compared to the circumferential direction, and that the mucosa-submucosa layer is stiffer than the muscularis propria in both directions. Histological analysis was carried out to establish the fraction and orientation of collagen and elastin within the layers and to discuss how this relates to the layers’ macromechanical behaviour. The results of the histological analysis were used to inform a matrix-fibre constitutive model based on the internal variable method [5]. For the model, the identification of the material parameters was carried out in a modularised way: the hyperelastic parameters were first determined by comparing the equilibrium stress-stretch data obtained from the stress-relaxation experiments to the hyperelastic portion of the first Piola-Kirchhoff (PK) stress. Then, the viscous and damage parameters were established by comparing the full first PK stress to the 1% s⁻¹ cyclic data. Finally, the model was validated by predicting the response of the tissue at 10% s⁻¹ and comparing this to the 10% s⁻¹ cyclic experimental data. The model was able to successfully capture the anisotropy, visco-hyperelasticity, stress-softening and permanent set observed in the experimental results.

References

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**Introduction**

Patients with advanced cancer and femoral bone metastases can have an increased fracture risk. Patients with an expected low fracture risk are generally treated with radiotherapy to relieve pain, whereas patients with an expected high fracture risk are considered for prophylactic stabilizing surgery. However, fracture risk assessment is challenging when using the currently available methods. Therefore, we developed the BOne Strength (BOS) score, which aims to be an easy-to-use objective score for fracture risk assessment of patients with femoral bone metastases based on a patient-specific finite element (FE) model [1,2].

QCT scans are used as input to the FE models. Although only the proximal femur is included in the FE model, the complete femur must be scanned as the model is aligned based on the knee joint center (KJC). In some cases, the femur is not completely scanned, which makes it impossible to calculate the BOS score. In this study, we want to investigate whether a statistical shape model (SSM), which represents an average shape as well as its shape variations, can be used to estimate the KJC location. Therefore, our aim is to determine the accuracy of the KJC based on an SSM, and the effect of the SSM-fitted KJC on the BOS score.

**Methods**

We included 117 femurs from our BOS database [2], containing femurs of patients with femoral bone metastases who were treated with radiotherapy. The radiotherapy planning CT scan was used to generate a patient-specific non-linear isotropic FE model of the proximal femur, which was aligned to mimic stance by aligning the KJC with the femoral head center [1,2]. On the FE model, an axial load was simulated until failure and the failure load was normalized by body weight to calculate the BOS score.

To determine the KJC based on the SSM, we removed the distal half of the femoral mesh. We used an SSM that was previously created based on 79 CT scans of patients with vascular disease [3]. The number of points in the proximal part of the femoral mesh was downsampled by randomly selecting sample points on the surface of the mesh. An iterative closest point (ICP) algorithm was applied to fit the SSM to the proximal femur. Next, the KJC was determined from the fitted distal femur. A new FE model was created and aligned based on the SSM-fitted KJC.

We determined the difference between the location of the SSM-fitted KJC and the original KJC location, and tested this using a t-test. Additionally, we determined the correlation between the original and SSM-fitted BOS-score, and tested the difference between both BOS scores using a paired t-test.

**Results**

The average difference between the SSM-fitted KJC and the original KJC was 0.4 mm (SD 12.1, range [-37.8 28.9]), p=0.7) in mediolateral direction, 0.5 mm (SD 9.4, range [-23.8 17.4], p=0.6) in anteroposterior direction, and -2.6 mm (SD 24.5, range [-64.0 64.5], p=0.2) in distal-proximal direction.

The correlation between the original BOS score and the SSM-fitted BOS score was very high ($R^2=0.99$, $p<0.001$, Fig. 1A) and there was no significant difference between the original and SSM-fitted BOS scores ($p=0.3$, Fig. 1B).

**Discussion**

In this study, we determined whether the KJC can be accurately estimated using a SSM and we assessed the effect on the BOS score. In another preliminary study, we saw that KJC displacements in mediolateral and anteroposterior direction had the largest effect on the BOS scores, whereas the effect of changes in distal-proximal direction were small. Although the ranges of the differences between the original and SSM-fitted KJC location were large, the effect on the BOS score was limited. Hence, we conclude that it is possible to estimate the KJC and calculate the BOS score using a SSM in case the femur is not completely scanned. However, one should be careful, as also a small difference in BOS score could result in a different fracture risk assessment and a subsequent change in treatment plan.

**References**

CRITICAL SHOULDER ANGLE VARIABILITY ESTIMATED WITH A CAUSAL BAYESIAN NETWORK

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Introduction

The critical shoulder angle (CSA) is a morphological measure combining the glenoid inclination angle (GIA) and lateral extension of the acromion (LEA) [1]. High CSA has been associated to patients with cuff tear arthropathy (CTA), and low CSA to patients with osteoarthritis (OA) [2]. The CSA is increasing with age, without sex difference [3]. However, the effect of age on CSA has not been evaluated for CTA and OA separately, and more specifically the effect of age on GIA and LEA, which both influence the CSA. Hence, our objective was to evaluate the effects of age, sex, pathology, GIA, and LEA on CSA.

Methods

We included 65 CTA and 184 OA patients, and 174 normal subjects without any sign of pathology as controls (CTRL). The GIA and LEA were automatically measured from CT scans [4, 5]. GIA was defined as the angle between the scapular axis and the glenoid centerline projected onto the scapular plane. LEA was the projection of the most lateral point of the acromion on the scapular axis. CSA was the angle between the line connecting the inferior and superior borders of the glenoid, and the line connecting the inferior border of the glenoid with the most LEA. From these clinical data, we developed a causal Bayesian network to evaluate the effects of age, sex, and pathology on CSA as follows:

\[ CSA_i \sim \mathcal{N}(\mu_i, \sigma) \]

\[ \mu_i = \beta_{sex|pathology}[i] + \beta_{age|pathology}[i](age_i - \bar{age}) \]

In addition, to evaluate the effects of GIA and LEA as follows:

\[ CSA_i \sim \mathcal{N}(\mu_i, \sigma) \]

\[ \mu_i = \beta_{sex|pathology}[i] + \gamma_{sex|pathology}[i]GIA_i + \zeta_{sex|pathology}[i]LEA_i \]

We used the Hamiltonian Monte Carlo (HMC) method to estimate the posterior distribution. All variables were reported as z-score (except age), with CTRL standardizations, and 89% confidence intervals (CI). The Bayesian network analysis was performed with R (RSTAN package).

Results

For CTA, the CSA increased with age for both males and females (Fig. 1). For OA, age had a slightly negative effect on CSA for males and females. For CTRL, age and sex had no effect on CSA.

For the three groups, the CSA increased with the GIA and LEA. The effects of GIA and LEA on CSA were similar for CTRL and OA, but differed for CTA, with a higher GIA effect for CTA-males and a higher LEA effect for CTA-females (Fig. 2).

Discussion

Our results showed the relative importance of age, sex, GIA, and LEA on CSA, and most importantly the different effects in CTA, compared to OA and CTRL. These results may be helpful in the early detection of shoulder pathologies, and may improve the treatments of CTA and OA, based on simple radiological measurements of the GIA and LEA.

References


Acknowledgements

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ACOUSTIC MODAL ANALYSIS CAN QUANTIFY BONE SCREW STABILITY IN AN IN-VIVO ANIMAL STUDY

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Introduction

Primary and secondary stabilities are two key elements in achieving osseointegration. Conventional techniques such as pull-out test and insertion torque previously have been utilized to evaluate the screw stability [1,2]. However, they have been found to be non-repeatable and unfeasible for clinical applications. To assess the screw stability in an in-vivo testing condition, the aim of this study was to apply acoustic modal analysis and compare the results with the conventional destructive pull-out and conventional non-destructive Periotest tests. Periotest is a well-known modal analysis method in stability assessment of dental implants. To investigate the discernability of methods to slight changes, the tip design of screws was selected as a self-tapped and non-self-tapped types.

Methods

Two types of titanium self-tapped and non-self-tapped of 1.4 mm outer diameter embedded in right and left proximal tibia of 6 rabbits (Fig.1 a,b,c,d,e and f). The pull-out, Periotest and acoustic modal analysis (AMA) [3,4] methods were used to quantify the peak pull-out force (PPF), Periotest value and natural frequency (NF), respectively (Fig.1. i, g and h). To compare the primary and secondary stability, PPF, Periotest value and NF were compared within 3 durations: immediately after implantation (primary stability), euthanization after 4 and 8 weeks (secondary stability). In AMA, the tapping sound was recorded and transformed into the frequency domain using the fast Furrier transform (FFT) function; very similar to our previous studies [2,4] and first fundamental frequency results were compared to the other test methods.

Results

No significant differences were observed in primary stability in terms of the pull-out force (98±12 and 102±8 N), the Periotest value (22.6±3.6 and 24.2±4.1) and the NF (2434±67 and 2572±43 Hz) between the self-tapping and non-self-tapping screws (Fig1. 1, j and k). For the secondary stabilities (4-week and 8-week), the values were 228±32 vs. 268±26 N for the pull-out force -0.05±1.70 vs. -2.60±3.40 for Periotest, 3547±40 vs. 3751±35 Hz for the AMA natural frequency in the self-tapping and non-self-tapping groups respectively (Fig1. 1, j and k).

Discussion

Significant differences were observed between primary and both secondary stabilities which reveals the fact that the osteointegration was mainly achieved in the 4-week duration group. AMA could quantify the primary and secondary stability as the pull-out force did. Moreover, the AMA method is a non-destructive method with the potential of using in-vivo [1,2]. The Periotest values could quantify primary and secondary stabilities, but it is not accurate enough to discern between secondary stabilities. AMA and pull-out tests could quantify the secondary stability in both 4 and 8-week durations.

References

BIOMECHANICAL STABILITY OF LUMBAR SPINE INSTRUMENTED WITH INTERBODY FIXATION: WHICH CONSTRUCT PROVIDES BETTER STABILITY?

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Introduction

Low fusion rates and cage subsidence have been reported as the main drawbacks of lumbar fixation with static interbody cages [1]. Although several clinical and biomechanical studies have evaluated the efficacy of 360 interbody fixation constructs (Anterior cage plus posterior fixation) [2], no study has reported the biomechanical comparison between such constructs and more novel techniques which use standalone fixation implants. A cadaver validated computational model of lumbar spine was used to compare the biomechanics of spine instrumented with 360 fixations versus standalone cage with screw and cage with lateral plate systems. To compare the mechanical stability of different interbody fixation techniques in lumbar spinal segments with standalone interbody versus static cage with posterior fixation or lateral plate system.

Methods

An experimentally validated Finite element (FE) model of L1-Pelvic segment (Figure 1) was used to simulate ALIF and LIF lumbar fixation techniques including: ALIF cage at L5-S1 plus posterior screw-rod fixation (360 construct) versus ALIF standalone (screw through the cage). LIF cage at L4-L5 versus LIF cage with integrated two-hole lateral plate system. 4WEB Medical’s Truss ALIF (40mm x 28mm), Lateral Truss (26mm X 50mm) cages and 2-hole integrated plate systems were used for simulation of the surgical procedure. For 360 constructs, a generic posterior rod and screw system was used. All models were subjected to a 400N compressive pre-load followed by an 8 Nm moment to simulation Flexion-Extension, Left and Right Bending and Axial Rotation motions. The segmental kinematics and the load sharing at the inferior endplate were compared among the cases.

Results

The segmental motion in standalone ALIF construct was 1.3°(Flex-Ext), 1.4° (LB) and 1° (AR) versus 1°, 1° and 0.7° in 360 ALIF in the same planes of motion. When comparing lateral constructs, the motions were 1.5° (Flex-Ext), 1.1° (LB) and 0.9° (AR) in Lateral cage with plate versus 1.1°, 1.0° and 0.8° in the 360-lateral construct for the same loads. The peak stresses in extension for the LIF stand-alone cage were slightly higher than the posterior instrumented cases. When comparing the mechanical stress on the inferior endplate of the index segment, the Stand-alone ALIF had almost 20% higher peak stress compared to the 360 ALIF construct. In the lateral construct, the cage-plate segment experienced 15% lower stresses on the endplate compared to the 360-lateral construct.

Discussion

Our data suggest that the 360 construct were able to provide greater stability in the sagittal plane. The lateral cage with integrated plate had stability closed to the 360-lateral construct in axial rotation [1,2]. The standalone cage resulted in higher stresses at the endplate compared the 360 constructs. Standalone ALIF and LIF with lateral plate are biomechanically efficient alternatives to 360-fixation constructs at least under the controlled conditions analyzed in the present study. Clinical data are required to support the findings and defining the further role and application of stand-alone cages.

References

Introduction

The goal of kinematic alignment (KA) of total knee arthroplasty (TKA) is to precisely restore the individual knee anatomy, including ligament tension, by maintaining the patient-specific joint line [1]. Compared to conventional mechanical alignment (MA), this hypothesis has already been indirectly confirmed using functional knee scores since a faster recovery and improved outcomes were observed [2,3]. However, whether this improvement is directly associated with joint kinematics remains unanswered to date. Thus, conventional gait analysis considering only the rotatory components of joint kinematics (3-DOF) also comes to controversial results [4,5]. Therefore, the aim of the present randomized, observer-blinded, and prospective study was to analyze full knee joint kinematics (6-DOF) after KA TKA. Both a non-arthritic as well as a MA cohort served as references.

Methods

74 patients (34 KA, 40 MA) treated with the GMK Sphere TKA (Medacta), and 9 healthy controls were included. All patients had to complete a 3D gait analyses on a treadmill the day before surgery and one year later at maximum possible speed. Kinematic data was acquired with a motion capture system with 12 infrared cameras (200 Hz). For detailed 6-DOF knee kinematics a Helen Hayes marker set was modified by using additional markers resulting in an over-determination of leg segments, and a quasi-static (frame to frame calculation) optimization algorithm was used to calculate joint movements using an inverse kinematics approach. The Forgotten Joint Score (FJS) and the Knee Society Score (KSS) were collected. For statistics t-tests and Statistical Parametric Mapping were used.

Results

Post-OP, both groups show a significantly reduced knee extension in terminal stance (MA: p = 0.01, KA: p = 0.02) and significantly reduced posterior translations during swing phase (p < 0.01) (Fig. 1). The MA also shows a significantly reduced anterior translation during terminal stance (p < 0.01). In frontal plane rotations KA shows a tendency of a greater adduction during swing, in MA this difference is significant (p = 0.01, Fig. 1). In frontal plane translations, there are no differences between KA, MA, and Controls (Fig. 1). In transversal joint rotations and translations, there are no differences neither between TKA groups nor between TKA groups and controls in both conditions. Post-OP, the KA shows a significantly increased FJS score (KA = 63.7 vs. MA = 49.6, p = 0.01) whereas due to the KSS the groups do not differ (KA = 80.5 vs. MA = 74.5, p = 0.13).

Discussion

This study is the first to show 6 DOF knee kinematics one year after KA TKA. A significantly reduced anterior translation in terminal stance for MA appears to be associated with significantly reduced knee extension during this interval. For KA, this anterior translation is restored again, resulting into not as great reduced knee extension compared to controls. Contrary to expectations, MA shows a greater adduction post-OP in the swing phase, indicating that the static leg axis does not reflect the joint angles in motion. Considering all results, KA shows fewer significant differences compared to controls than MA, suggesting a more physiological gait pattern one year after TKA. This might be the reason why patients with KA are more likely to forget about their knee in everyday life.

References

POST-TRAUMATIC FIBRIL REORIENTATION IN CARTILAGE: ADAPTIVE IN SILICO MODEL VALIDATED AGAINST IN VITRO OA MODEL

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Introduction
Articular cartilage is a fibril-reinforced soft tissue, presenting a depth-dependent collagen fibril structure. Based on fibril orientation, cartilage can be divided into three zones in depth: superficial zone (parallel to the surface), middle zone (random orientation) and deep zone (perpendicular to the surface) [1]. Injurious mechanical loading and consequent cartilage defects in post-traumatic osteoarthritis (OA) are known to impair the mechanical environment of the tissue microstructure and consequently change the fibril orientation [2]. Recently, we introduced a finite element (FE)-based cartilage adaptive reorientation degeneration (CARED) model that includes a fibril reorientation algorithm (initially introduced for arterial wall tissue) to predict changes in cartilage fibril orientation upon altered mechanical environments [3]. In this study, we aim to validate the fibril reorientation predicted by CARED model with depth-dependent fibril reorientation upon longitudinal loading in a post-traumatic in vitro OA model.

Methods
Sixteen healthy human hip cartilage explants (8 mm diameter) were harvested from 80 yo female (fractured hip). Half-thickness focal defects were created on 8 samples using a scalpel. Both the intact and defect samples were loaded for 7 days using a dynamic loading bioreactor (10% unconfined compression at 1 Hz, 1 hr on - 1 hr off - 1 hr on). On days 1, 3, 5 and 7 of loading, one sample per group was fixed and sectioned. Depth-dependent fibril orientation was measured using polarized light microscopy (PLM) [4]. 3D FE models of both defect and intact samples were created in Abaqus, based on the geometry and depth-dependent fibril orientation information of the samples before loading obtained from PLM measurements. A fibril-reinforced poro-elastic material [5] was used, with model parameters characterized using experimental loading data and inverse FE analysis. One cycle of unconfined compression (10%, 1 Hz) was applied to the FE model. The fibril reorientation algorithm of CARED model [3] was used to run the FE simulations iteratively and estimate the fibril reorientation upon loading based on the principal strain directions.

Results
The depth-dependent collagen fibril orientation before loading in an intact sample (as control reference) is compared with intact and defect samples after 7 days of dynamic bioreactor loading in figure 1. For each sample, the PLM measurements across the sample depth, agreed qualitatively with the fibril orientation predicted by the adaptive FE model.

Discussion
The PLM results suggest that longitudinal loading of an intact explant increased the thickness of the superficial zone (red zone in figure 1) compared to the reference sample. In contrast, subjecting the defect sample to identical loading conditions, decreased the thickness of the superficial zone, by reorienting the fibrils perpendicular to the articular surface. This agrees with previous in vitro and in silico observations of decreased superficial zone thickness in post-traumatic OA [3, 4, 6]. Interestingly, the predicted depth-dependent fibril orientations after loading using the adaptive FE model for both intact and defect samples are in agreement with the PLM measurements. Therefore, FE-based principal strain directions are confirmed to be valid parameters to predict the collagen fibril reorientation in the adaptive FE models of intact and damaged cartilage upon mechanical loading.

References

Acknowledgements
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Introduction
Anterior cruciate ligament (ACL) injuries are among the most common sport injuries with an incidence of 1:3500. It is estimated that one million cruciate ligament tears occur worldwide each year. Tendons and ligaments have a limited self-healing capacity. Current treatment methods are based mainly on autologous implants, which are subject to limited availability, donor site morbidity and a second surgery site. As a result of its inability to sustain the mechanical load in the knee over the long term, synthetic cruciate ligaments are rarely used nowadays. Deficits exist in terms of biological compatibility, fatigue strength, and friction resistance. In order to regenerate a functional ligament, tissue engineering uses a three-dimensional scaffold that offers temporary mechanical stability and promotes cell ingrowth. Textile scaffolds are reproducible and scalable, and offer a three-dimensional structural design. Additionally, braided scaffolds can be produced with high strength, efficient loading, and sufficient porosity for cell ingrowth. The aim of this study is to investigate long-term degradable scaffolds based on poly-ε-caprolactone (PCL) for ACL replacement using the round braiding technique.

Methods
The scaffolds are based on melt-spun PCL monofilaments [1]. The round braiding technique was used for scaffold fabrication. Five different scaffolds based on different braiding parameter combinations are investigated. The influence of different braiding parameters regarding the maximum tensile load, elongation and stiffness (linear and toe region) are evaluated by tensile test. The tensile testing is performed in physiological length of the ACL (n=10). Furthermore, the critical morphological parameters for tissue engineering like porosity and pore size are characterized by μ-CT scans.

Results
The braided scaffolds reach tensile forces of approximately 4000 N. Thus, all scaffolds exceed the tensile forces of the native ACL (734-2160 N) [2]. Thereby, the implants do not exceed the diameter (9 mm) of the bone channel of the conventional surgical methods. The filament arrangement, the braid angle and braiding pattern significantly influence the stiffness as well as the maximum tensile force of the braids. The stiffness is a crucial mechanical value for physiological movement of the joint. The stiffness values of the linear region of the braids (131-236 N/mm) matches the native human cruciate ligament (180-242 N/mm) [2]. Porosity and pore size are crucial factors for cell ingrowth and tissue regeneration. Especially three-dimensional textiles provide an interconnected pore structure and possible guidance structure for cells.

Discussion
Overall, it can be concluded from the results of the testing that the requirements for ACL replacement can be achieved successfully. By adjusting the braiding parameters, further ligament applications such as medial and lateral knee ligaments or the rotator cuff can be addressed. Both the cell behavior on the scaffolds and the degradation behavior will be investigated in further research.

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UPPER AND LOWER EXTREMIT Y REACTION FORCES DURING VERTICAL ROCK WALL CLIMBING
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Introduction
Rock climbing has become increasingly popular as a recreational hobby and competitive sport. A great risk for injury exists for rock climbers including falling from heights, ligamentous injuries of the lower and upper extremities, and overuse of the forelimbs and hands [1]. The most common injuries in climbing are found in the upper extremity and include finger pulley rupture, physical wrist fractures, and chronic injuries such as chronic rotator cuff tear and brachialis tendonitis [2]. It can be predicted that substantial loading on the forelimbs predisposes even the most experienced rock climbers to injury. Despite such assumptions, there exists a gap in the literature exploring the force distribution on the limbs during vertical climbing and how this may explain the higher instance of forelimb injuries versus hindlimb injuries in human climbers.

Methods
In this study, we present isolated fore- and hindlimb substrate reaction forces of 45 participants, gathered using a triaxial force plate mounted to a treadmill climbing wall (Figure 1.). Each participant completed a total of 5 to 10 trials. From the data, the peak force and impulse were calculated.

Results
Both fore- and hindlimbs produced solely propulsive forces during climbing (Figure 2.). However, the magnitude of these forces was significantly greater in the hindlimb (~60% of body weight) versus the forelimbs (~15% of body weight). In the normal plane, we observed the forelimb contributing solely as a pulling force equal in magnitude to the pushing forces of the hindlimb. Both fore- and hindlimbs exert greater magnitudes of lateral force (~15% body weight) than medial (~5% body weight).

Discussion
Broadly, patterns of limb loading during climbing in humans closely match global expectations drawn from comparative animal data [3]. An unusual pattern was found concerning the relatively low magnitude of propulsive forces in the forelimbs. This may represent an active strategy for reducing overuse injuries in the highly mobile, but relatively weak forelimbs. By understanding the peak force and impulse as humans climb, injury prevention strategies can be developed to mitigate acute and chronic injuries in climbers. Adapting climbing techniques to off load high forces applied to the forelimbs and hands through shifting their COM closer to the wall in the tangential plane may be expressed in climbers with greater expertise to avoid such acute injuries as previously described. Future studies will aim to assess differences in limb loading patterns between novice and skilled climbers.

References

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EFFECT OF THE LUMBAR BELT ON TRUNK MOBILITY: A COMPARATIVE CLINICAL STUDY

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Introduction

Low back pain (LBP) is a highly prevalent health problem worldwide, with higher economic and social costs. Evidence suggests that lumbar belts may be beneficial in the treatment of LBP, as they reduce pain levels, limit extreme movements and significantly improve functional status and posture [1]. However, very few studies have reported on the biomechanical effects of wearing a lumbar belt during trunk movements.

In a clinical study, we aim to investigate several subjective and objective criteria in order to evaluate and understand the mechanisms of the benefit provided by the lumbar belt during different movements.

The effect of the lumbar belt on the spinal mobility using the fingertip to floor distance (FTF) and sternum to wall distance tests was assessed as a primary outcome. Secondary outcomes include kinematics of the spinal segments using a developed IMU-based system [2], and pressure applied by the belt on the trunk using piezoresistive sensors. Measurements will also include a numerical scale (NS) to assess pain levels, Oswestry Disability Index (ODI) to measure functional abilities related to LBP.

In this work, we present the first findings of this ongoing study, allowing us to draw some conclusion, especially about the mobility of the trunk.

Methods

A cohort of 16 LBP subjects and 16 matched controls were recruited for the study.

All measurements were performed during various movements such as anterior and posterior flexion, left and right lateral flexion, and the sit-to-stand movement. For assessing mobility, angular kinematics were measured with and without the belt, by means of 2-IMU sensors located at the L1, and L5 vertebrae. Outcome measures include lumbar lordosis, thoracic kyphosis, pelvic tilt and range of motion (ROM) of the lumbar and thoracic spine.

Clinical tests of spinal mobility using the FTF test in forward flexion, the FTF test in lateral flexion and the sternum to wall test in extension were also assessed.

Data were statistically analyzed using the Wilcoxon signed rank test to quantify the effect of wearing the belt on each variable.

Results

First findings were obtained for the lumbar spine kinematics using two sensors IMU located at L1 and L5 of 10 subjects (figure 1) and for spinal mobility tests in 5 subject (figure 2).

Table 1: Kinematics results of the lumbar spine

Table 2: Results of sternum to wall distance test during extension in 5 subjects.

Discussion

Obtained statistical results revealed a positive impact of wearing a lumbar belt on the majority of variables, with the exception of the maximum extension angle. By including all subjects and conducting all experiments, further insights into the clinical and biomechanical effects of lumbar belts during movements can be obtained.

References

OPTICAL COHERENCE TOMOGRAPHY (OCT) ASSOCIATED WITH CLEARING TECHNIQUE FOR MEASURING THE EVOLUTION AND DEGENERATION OF SKELETAL MUSCLE OPTICAL PARAMETERS

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Introduction
In 2002, diseases related to the osteo-articular system and muscles accounted for 7.1% of French social security expenditures, without taking into account neuromuscular diseases[1]. The aim of this research is to understand muscular degeneration whose physiopathology has not been precisely described (such as Duchenne's disease), to discover new therapeutic targets and to increase the chances of developing effective therapies. Duchenne Muscular Dystrophy (DMD) is the second most common monogenic disorder in Western countries. To date, no treatment exists to curb this disease [2, 3].

This work focuses on exploring the microstructure optical changes between physiological and DMD rat muscle. Several blind Image Quality metrics are used to estimate the degeneration of the muscle. Contrast per Pixel (CPP) and three different No Reference Image Quality (NR-IMQ) metrics were used to estimate the quality of OCT images: Perception base Image Quality Evaluator (PIQE), Naturalness Image Quality Evaluator (NIQE) and Blind/Reference less Image Spatial Quality Evaluator (BRISQUE). Histological measurements are compared to OCT image metrics.

Methods
Optical Coherence Tomography (OCT) imaging
To assess the three-dimensional microstructure architecture of the sample. An OCT system (Thorlabs OCT-TEL.220C1) with a wavelength of 1.300nm, a focal length of 18 mm and a maximum sensitivity range of 111dB was used. Before OCT imaging, samples were immersed in a PG in PBS for one hour, then fixed in a PG solution [5]. Finally, after finishing the imaging process, the sample is conserved again in PBS.

Muscle isolation
Wistar rats, were used in this study. The animals were housed in standard cages under controlled conditions of temperature and lighting. The protocol used in the present study complies with the principles of animal care and the French ethical rules of veterinary authorities, according with the “European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes” (Council of Europe No. 123, Strasbourg 1985). Contrast per Pixel (CPP) and three different No Reference Image Quality (NR-IMQ) metrics were used to estimate and compare the quality of OCT and histological images.

Results
Increase of homogeneous refractive index across the muscle and reduction of the scattering coefficient were induced by PG. This leads to an increasing transparency of tendons and muscle in visible light domain as shown in Figure 1 a, b. The transparency, also increased in the near infrared light spectrum, significantly improves OCT acquisition in terms of contrast and measurement depth. It can be seen in figure 1 that images obtain from OCT are similar to those obtain in a histology. Additionally, disintegration of muscle fibers and absence of muscle bundles unit is notable in pathological muscles.

Discussion
The application of new techniques like, OCT imaging enables to visualize and quantify the microscopic architecture of the muscle without destroying it, which gives the possibility to preserve the sample for further uses such as mechanical testing or molecular characterization. To assess the use of OCT imaging, with PG tissue clearance, morphological and mechanical analysis are going to be carried out. Using PG solution as a hyperosmotic solution exacerbated chemoelastic effects.

At this moment further analysis are being developed to characterize the image method. Also, to conclude more application that could be performed using the same method.

References
FLOW VISUALISATION AND SIMULATION IN REALISTIC ANEURYSMS GEOMETRIES TO DETERMINE THE RISK OF RUPTURE
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Introduction
Determining the risk of rupture of intracranial aneurysms is a great challenge. Geometrical parameters, such as sac volume and size, are commonly used to define a proper medical treatment. In recent years, hemodynamics parameters, such as shear stress and oscillatory shear index, have gained attention to predict the aneurysm rupture [1]. In the last few years, numerical flow simulations in complex biological structures have also gained considerable attention [2]. However, the primary challenge is the validation of the numerical procedures due to the complexity to measure velocity and shear stress and compare them to the computed results. The main goal of the present work is to classify geometrical and hemodynamic parameters to predict the possible rupture of the aneurysm using numerical simulations, tested with experimental values.

Methods
Numerical simulations were performed using realistic geometries. Aneurysms 3D models were reconstructed from the Aneurisk project [3]. The blood was modelled as a Newtonian fluid with constant properties. As a first approximation, the arterial walls were rigid, and no-slip boundary condition was considered. An oscillatory velocity profile was imposed at the inlet and the \( \kappa-\varepsilon \) turbulence model was employed. An experimental setup was designed to validate the numerical simulation. Dye injection technique and tracking particles technique were employed to visualise the flow distribution in the 3D printed aneurysms. A camera (Sony RX0 II F4.0) was used to capture videos, which later were processed to track particles and compute flow velocity and streamlines. The IR machine learning algorithm was used for classifying the geometrical and hemodynamic parameters.

Results
Using the dye injection and tracking particles techniques, the generated transparent model visualised the flow patterns with a regular camera. The obtained videos are clear enough to track particles and calculate velocities. The hemodynamics parameters were obtained through numerical simulation, using OpenFOAM. The IR analysis used the following hemodynamic parameters: wall pressure and wall shear stress, oscillatory shear index (OSI), residence time, gradient oscillatory number (GON), vorticity, Q criterion, stokes number for particles, and enstrophy to classify the aneurysm in combination with the traditional parameters. The algorithm inferred five rules for predicting the rupture of an aneurysm based on the variable \( O_{\text{MinSize}} \) (size ratio, sac diameter, sac height, parent vessel ratio) and a reliability of 82.8% was obtained.

Discussion
The proposed visualisation technique has shown promising results, as well as the IR algorithm as a prediction tool for aneurysm rupture. The performed numerical simulations showed good agreement with the experiments (qualitatively).

References

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TIME-DEPENDENT COMPUTATIONAL MODEL OF CARTILAGE MECHANOBIOLOGY DURING INJURIOUS AND CYCLIC LOADING

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Introduction
Computational models of osteoarthritis have been developed to estimate cartilage damage progression [1,2]. However, the models lack realistic time-dependent insights into the degradation, especially from a mechanobiology-based modeling standpoint. Understanding how rapidly the disease mechanisms act is crucially important for development of interventions.

Methods
Cartilage plugs (n = 75) from young calves (N = 9) were subjected to compressive injurious loading (50%, 100%/s) on day 0, followed by up to 12 days of physiological cyclic loading (15%, 1 Hz, haversine waveform, 40% duty cycle, four 1-h sessions per day). Optical density of Safranin-O-stained sections was measured to estimate aggrecan content [2]. Our time-dependent computational model of cartilage mechanobiology (Fig. 1) included a fibril-reinforced porohyperelastic material model and a lesion in high fibril strain region with the following mechanisms: 1) shear strain-based cell damage (proteolytic enzyme release), 2) fluid velocity-driven aggrecan depletion, and 3) increased aggrecan biosynthesis (function of hydrostatic pressure time derivative) [2,3]. Lesion formation was not explicitly modeled. Experimental and numerical aggrecan contents were compared near (within 50 μm from lesion edges) and away from lesions (absolute, relative near/away fractions; Fig. 2).

Results
The simulated injurious loading caused substantial decrease of aggrecan content throughout the plugs by day 12 (Fig. 2A). Injured and cyclically loaded model revealed markedly lower aggrecan content near compared to away from the lesion on day 12, similarly as in the experiments (p < 0.001, linear mixed effects model, Fig. 2B). Simulated cyclic loading resulted in rapid aggrecan depletion near the lesion over the first three days, ultimately reaching 41% of the away-from-lesion aggrecan content by day 12 (87% in the injury-only model; Fig. 2C).

Discussion
In our present state-of-the-art cartilage adaptation model, we combined realistic time, histologically observed lesion, physiological loading, and several mechanobiological mechanisms. The proteolytic enzymes from damaged cells decreased aggrecan content globally and fluid velocity locally near the lesion. Aggrecan biosynthesis was elevated away from the lesion and in the deeper tissues in the model with cyclic loading. The presented cell–tissue-level model improves understanding of time-dependent mechanisms behind cartilage damage progression and could be implemented into joint-level models to estimate how cartilage adapts to different loading scenarios.

References

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BIOMECHANICAL ASSESSMENT OF BONE GRAFT STABILITY USING A FEMORAL OVINE MODEL

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Introduction

Bone grafts are clinically used for a range of reconstructive orthopedic surgical applications such as bone repair, osteochondral grafting, and ligament reconstruction procedures [1]. Graft stability is vital to enable effective tissue regeneration between the host and graft bone [2]. Graft stability can be used to partly evaluate the risk of graft subsidence, measured by the force required to displace grafts below congruency, known as a push-out test [3]. The aim of this study was to assess the mechanical stability of various bone-only graft types at different stages after implantation compared to native bone.

Method

Push-out tests were performed on the bone-only portion of skeletally mature, distal ovine femurs. From 9 femurs, a total of 33 sites were tested. These had been implanted with either ex vivo porcine xenografts or ovine allografts (taken from an in vivo study 12 weeks after implantation) (N=6 and N=6 respectively), in vitro autografts (harvested from the medial side of the femur and implanted in the lateral side of the same specimen) (N=9), or nothing (native bone acting as a control) (N=12). The autografts were 10 mm long and 6.5 mm in diameter and implanted with an Acufex™ Mosaicplasty surgical toolkit (Smith and Nephew, MA, USA). The specimens were prepared for testing by segmenting the femurs at 10 mm from the test surface to expose the grafts from below. The grafts were uniaxially loaded at a rate of 1 mm/min, using a materials testing machine (3365 with a 5 kN load cell, Instron, UK) until a displacement of 10 mm below congruency or a maximum load of 2.5kN (Fig. 1).

Results

The maximum force was largest for the ex vivo grafts (mean value F = 1.50 ± 0.18 kN for the porcine xenografts; F = 2.11 ± 0.17 kN for the ovine allografts), then the native tissue (F = 1.19 ± 0.39 kN), and lastly the in vitro autografts (F = 0.34 ± 0.11 kN) (Fig. 2). The segment thickness and bone density, which had some experimental variability (10.91 ± 2.45 mm and 47.7 ± 10.2 %), did not appear to affect the maximum forces observed.

Discussion

The outcomes demonstrate that osseointegration in the ex vivo grafts result in an increase in the force required to displace bone-only femoral grafts, while immediately post-implantation (the autograft group), grafts are susceptible to subsidence at low loads. Future testing using osteochondral grafts will assess the contribution of bone and cartilage components to graft stability.

References

INTRODUCTION

The balance and corporal position of people with movement disorders improve when walkers or devices for the mobility aid are used [1]. The ability to walk and interact with the environment causes improvements in the gait, the muscle strength, the endurance, and the muscle innervation. In addition, the use of gait support systems promotes user participation and interaction, giving them greater autonomy and a better life quality. There are many works that offer solutions adapted to the patient’s condition and their pathology and allow doctors to personalize rehabilitation therapies based on patient’s evolution [2, 3]. However, many static training platforms, pediatric exoskeletons and smart walkers can be unfeasible for most rehabilitation centers. This project addresses the development of an affordable sensorised walker capable of detecting and storing parameters induced by the patient in a passive posterior walker prototype. The walker is designed for training the gait and monitoring of the patient’s progress. In this way, professionals in the rehabilitation field such as orthopedists, doctors and physiotherapists will be able to use the electronic instrumentation of the walker to complement the obtained information through observational assessment scales and personalize recovery therapies taking into account the data provided by each user in the performed tests.

METHODS

The proposed sensorised child walker (protected by the patent application: P202230983) is shown in Figure 1 and offers posterior support to patients between 3 and 8 years old with mobility problems. The wheeled U-shaped structure envelopes the user and allows the subject to move safely, avoiding any direct collisions between the child and the environment. In order to measure the exerted force by the patient, the walker integrates one load cell in the seat (SIWAREX® WL200 SP-S AA, Siemens Process Instrumentation, Germany), and two load cells in the upper front hand support (model 1042 Tedea Huntleigh, Vishay Precision Group, EU). In this way, the patient's interaction with the stand-up structure can be registered. Moreover, the back inclination is measured thanks to an inertial measurement unit (InvenSense® MPU6050, TDK Corporation, Japan) and the lower body muscular activity with the use of eight low cost electromyography sensors (MyoWare®, Advancer Technologies). All the signals mentioned are acquired by a controller (myRIO-1900 of National Instruments). An intuitive and easy application has been developed in LabView and allows the medical personnel to control the acquisition system, configure the patient’s session, view the data in real time during the session and save them once the test has finished. Three pediatric volunteers without mobility problems performed the first tests to evaluate the walker prototype during a simple trial. The patient had to follow a L-shaped path marked on the ground and return to the initial point with a normal gait without time limitation.

RESULTS AND DISCUSSION

The results obtained with healthy children show that the subjects exerted loads between 40% and 70% of their corporal weight on the seat, whereas the magnitude of the loads is around 7% of the corporal weight on the superior hands support. Besides, specialists have verified that the users walked with the back straightened during all the trial and the different leg muscular groups were activating as expected in each step during the gait.

REFERENCES


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Compression textiles and skin irritation: a clinical study

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Introduction

The working principle of many medical devices (e.g. lumbar belts, stockings) is based on their mechanical action on the body. Therefore, their contact with the skin must be considered carefully. Unfortunately, skin irritation is a common phenomenon that becomes a concern, because many patients do not tolerate their medical devices, leading to a poor therapeutic compliance. Exposure to a chemical agent or an allergic reaction are unlikely to occur here as these medical devices are designed to be hypoallergenic, and so we hypothesized that these cutaneous irritations are caused by the mechanical interaction of the skin with the device itself. Skin damage can be related to a prolonged pressure or shear [1, 2]. In addition, several researches have demonstrated how friction is involved in the process of skin abrasion [3].

In a recent survey on textile compression medical devices, users of the French market, we highlighted that, even though 85% were satisfied with medical device efficacy, 57% were not with the comfort and 44% declared skin problems (irritation, redness etc) in particular near the anti-slipping band.

Based on current data in the literature, it seems feasible to quantify the degree of skin damage by clinical criteria but also by certain biophysical measurements. Furthermore, the literature also demonstrates how the contact between the skin and an object is influenced by the mechanical properties of the skin, its roughness and the properties of the material in contact [1].

Thus, we propose a clinical study with the aim of identifying determining factors in the development of skin damage when wearing compression stockings. For this purpose, measurements of mechanical and biophysical parameters will be compared before and after use of two different models of textile compression device in relation to the severity of skin damage induced by the wearing of compression stockings. The aim of this communication is to present the mains results of this clinical study.

Materials and methods

25 patients were recruited at Saint-Etienne University hospital. All patients are compression devices users and have developed skin problems in the past. The study was performed according to the Declaration of Helsinki and was approved by the ethics committee (Comité de Protection des Personnes Sud Est V #21-THUA-01). Prior to participation in the study, all participants provided written informed consent.

The subjects were asked to wear two different brands of compression stockings (one on each leg) and to walk two times 15 min at 5km/h on a treadmill, with a 15 min rest on a chair in between. Immediately after removing the compression devices, the subjects’ skin was assessed by a clinician to evaluate the severity of the induced irritation.

Before putting on and after removing the compression stockings, mechanical and biophysical parameters (skin rigidity, skin layers thicknesses, skin temperature, and micro cutaneous blood flow) were acquired at 3 evaluated zones on each leg. Skin replicas of the six evaluated zones were also acquired before experiments to evaluate roughness.

Results

A Kolmogorov- Smirnov test was used to decide between parametric or non-parametric tests. Finally, the comparisons of the different variables according to the conditions before / after walking was performed using a repeated measures analysis of variance (ANOVA). Simple effects were analyzed by a Scheffé post-hoc test. Comparisons of the different variables were analyzed using the Wilcoxon test.

It was evidenced that irritation occurred mainly near the anti-sliding pads. Irritated skins were more compliant, hotter, with thicker epidermis, and a roughness with smaller periodicity in the longitudinal direction, higher in the circumferential one and more plateau than valley. These characteristics are specific of the thigh zone, the two other (popliteal fossa, calf) being significantly different. Results didn’t depend on the type of stocking used.

Last, the patient feeling (itching, heat, irritation, compression) did not correlate with irritation level as defined by medical practice.

This clinical study provides valuable insights for clinicians and manufacturers on the mechanical and biophysical factors that contribute to skin irritation when wearing compression stockings, particularly near the anti-sliding pads, and can inform the development of more comfortable and effective devices.

References


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TUNING THE MECHANICAL PROPERTIES OF ADA-GEL BIOINKS FOR BIOPRINTING APPROACHES BY VARYING THE OXIDATION DEGREE

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Introduction
Extrusion-based 3D bioprinting is one of the most promising and widely used technologies in tissue engineering. However, the development of 3D printable, biocompatible bioinks with tailored mechanical properties remains a major challenge in this field. Advanced alginate-based hydrogels, which include oxidized alginate in combination with proteins [1], are promising materials for bioprinting approaches and tissue engineering applications. The oxidation of alginate by sodium (meta)periodate resulting in alginate dialdehyde (ADA) enables to control and tune the degradation behavior. The combination of ADA with proteins, such as gelatin (GEL), improves the cell adhesion properties. However, to date the influence of the degree of oxidation of ADA on the complex mechanical properties of alginate-based hydrogels remains insufficiently understood.

Methods
We investigate the influence of the degree of oxidation on the mechanical properties of ADA-GEL samples through multi-modal mechanical analyses in compression, tension, and torsional shear under large strains [2]. Furthermore, we study the influence of the fabrication process by mechanically characterizing molded and 3D printed ADA-GEL samples.

Results
Figure 1 (left) shows an increase in stiffness and a more pronounced hysteresis with decreasing degree of oxidation (DO) from 25% to 6%. This observation can be explained by the controlled chemical oxidation of sodium alginate. Samples with a low DO consist of fewer aldehyde groups and more free G-residues available for crosslinking. Figure 1 (right) underlines the influence of the fabrication process on the mechanical properties. Molded ADA-GEL samples are (significantly) stiffer with more pronounced hysteresis compared to 3D printed ones. This can be attributed to the fact that molded ADA-GEL samples show a homogeneous structure and denser arrangement of the molecules.

Discussion
Our findings highlight that the degree of oxidation is an important parameter to tune alginate-based hydrogels for tissue engineering, e.g., to well match the properties of native tissues. In addition, our findings emphasize the importance of mechanically characterizing 3D bioprinted constructs for biofabricated functional tissue models. Based on the presented data, material model parameters for finite element simulations can be determined by using an inverse identification scheme, where the boundary conditions during testing are well captured. They thus form a valuable basis to further optimize materials and printing parameters in the future.

References

Acknowledgements
We gratefully acknowledge the support by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) grant BU 3728/1-1 and Projektnummer 326998133 – TRR 225 (subproject B03, B09).
A NUMERICAL WORKFLOW TO INVESTIGATE THE HEMODYNAMICS EFFECTS OF THE LEFT ATRIAL APPENDAGE OCCLUSION

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Introduction

The Left Atrial Appendage (LAA) is the main source of blood clots in patients with non-valvular Atrial Fibrillation (AF), accounting for over 90% of thrombi formation [1]. To lower the risk of cardioembolic events, LAA Occlusion (LAAO) has emerged as a key alternative treatment for patients with a contraindication to anti-coagulation therapy [2]. However, there is a risk of Device-Related Thrombosis (DRT) occurring in 2-16% of patients after LAAO [3]. In this context, numerical methods represent a powerful tool to both simulate the LAAO [4], using Finite Element (FE) analysis, and the LAA hemodynamics [5], by means of Computational Fluid Dynamics (CFD). In this work we present a patient-specific numerical workflow integrating the results of FE simulation of LAAO and CFD analysis to assess the effect of different LAAO configurations, in terms of device type and/or positioning, on the Left Atrium (LA) hemodynamics.

Methods

The workflow is composed by two consecutive numerical simulations: FE analysis of LAAO and post-LAAO CFD simulation. LA models were obtained from Computed Tomography (CT) images of patients who underwent LAAO. The models included Pulmonary Veins (PVs) and Mitral Valve (MV). For each model, different LAAO configurations were simulated. FE simulation of LAAO was run in Abaqus, using a validated device model [4]. The device was discretized with 1D elements. The LA was meshed with 2D shell elements. LA wall thickness and stiffness were assumed from literature. Edges of MV and PVs were fixed. The deformed LA model, as result of the device expansion within the LAA, was used to define the fluid domain for the CFD analysis (ANSYS Fluent). The CFD model was meshed with tetrahedral elements. AF boundary conditions were implemented [5], using an inflow pressure condition of 8 mmHg at PVs and an outflow velocity profile at MV. An example of the workflow is reported in Figure 1, showing, first, the FE model of LAAO and, second, the post-LAAO CFD simulation.

Results

Results of each post-LAAO CFD analysis analysed in terms of pressure, velocity, and main hemodynamic indices. Figure 2 shows the velocity field obtained from two CFD simulations of different LAAO configurations.

Discussion

In this study an integrated FE/CFD numerical workflow was presented, with the aim to investigate the effect of different LAAO configurations in a controlled in-silico environment. Given the importance of risk stratification in the follow-up of LAAO procedure, this tool could represent a key solution in the understanding of the DRT problem. The possibility to simulate any clinical scenario, by independently setting patient anatomy, device type and positioning, would allow to explore a potentially infinite LAAO configurations and highlight the most critical scenarios from CFD results.

References


Acknowledgements

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PATIENT-SPECIFIC OPTO-MECHANICAL MODELLING OF PHOTOREFRACTIVE KERATECTOMY

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Introduction
In the last two decades, corneal laser surgery has become a common procedure to correct medium-low refractive defects. It consists of reshaping the corneal surface by means of a laser in order to correct the present vision error. The action of the laser onto the eye causes a modification of the equilibrium among intra-ocular pressure (IOP) and the corneal tissue mechanics, that could cause a mismatch in the actual dioptic correction and, eventually, post-surgical complications, like ectasia. In this work, we propose an automatized finite element (FE) methodology to simulate Photorefractive Keratectomy (PRK) in order to obtain an opto-mechanical presurgical evaluation of the surgery outcome.

Methods
Our automatized methodology starts by receiving as input the point clouds of the anterior and posterior surfaces of the topographic acquisition. Due to the lack of peripheral surface data, corneal surface reconstruction $h(r, \theta)$ (Figure 1.a) is performed by means of Zernike’s polynomials: $h(r, \theta) = \sum_{n=0}^{c} \epsilon_n \cdot Z(p, \theta)$, where $\epsilon_n$ denotes the Zernike coefficients and $Z$ the polynomials [1]. Then, the reconstructed point clouds are directly meshed with the software ANSA pre-processor by BETA-CAE v22.0.1. A non-linear anisotropic Holzapfel-Gasser-Ogden constitutive model was chosen to model the behavior of corneal tissue, including in-plane and out-of-plane dispersion of the corneal collagen fibers [2]. Sliding boundary condition, where only radial displacements are allowed, were applied at the base of the cornea. A pre-stretch iterative algorithm [4] was used to compute the stress-free configuration and the patient’s IOP of 12 mmHg was applied to the posterior surface of the cornea. A PRK laser surgery was simulated by removing corneal tissue from the anterior surface (Figure 1.b). The ablation profile was calculated using wavefront calculation, as described by [3], aiming at correcting -4 D, as indicated by the topography of the patient. All mechanical simulations were calculated using ABAQUS. Corneal optics was calculated using an in-house algorithm.

Results
From the mechanical analysis (Figure 1.c), we can observe a concentration of stresses and strains in the optical zone ($R = 3$ mm), induced by the surgery, where the ablation is performed, due to the reduction of the thickness of the cornea. No geometrical abnormality arises from performing the PRK simulation on the FE model. From an optical point of view, if we look at the pre- and post-surgical maps of the mean curvatures, it can be noticed how the surgery performs a smoothing and a regularization of the surface refractive power.

Discussion
No post-surgical geometrical irregularities arose from performing the PRK surgery and a smoothed refractive correction was achieved. This methodology could become a useful tool for the clinicians to anticipate the surgery outcome, given that it allows to consider the optics and the mechanics of the cornea, both necessary to have a complete evaluation of the clinical state of the patient’s eyes. Clinical validation will follow on a larger patients’ database.

References

Acknowledgements
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Figure 1. a. Surface reconstruction of patient’s topography; b. FE model; c. Opto-mechanical analysis of the surgery.
A CONTRAST-ENHANCED X-RAY IMAGING APPROACH FOR CHARACTERIZING ARTICULAR CARTILAGE

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Introduction
Articular cartilage is a highly heterogeneous tissue mainly composed by water, proteoglycans and type II collagen. The onset of degenerative diseases (i.e., osteoarthritis) deregulates the homeostasis of this tissue since their early stages, requiring diagnostic techniques capable of detecting any subtle initial changes. Despite X-ray imaging is widely used for joint examination, low differentiation of soft tissues hinders the evaluation of cartilage tissue. The affinity of contrast agents (CAs) to specific components of cartilage tissue has been proposed to increase X-ray absorption of cartilage tissue. Nevertheless, the use of CAs should not impair the functionality of soft tissues. The aim of this study is to investigate the impact of a cationic, iodine-based CA (CA4+) on cartilage mechanical behaviour and radiopacity.

Methods
Osteochondral cores (Ø=10mm, h=10mm) were harvested from bovine stifte joints. Osteochondral cores underwent indentation test at a strain rate of 0.15s⁻¹ (Mach-I, Biomomentum). The maximum nominal deformation of 15%, applied by a 6-mm spherical indenter, was maintained for 300s [1]. Three test repetitions were performed at 40 min time intervals. Experimental curves were fitted to Hayes [2] and stretched exponential model [3] to estimate cartilage elastic (instantaneous modulus E₀) and viscous response (time constant τ and stretching parameter β), respectively. Afterwards, cores were subdivided into treated and control groups, exposing their cartilage tissue to CA4+ and PBS bath, respectively, for 22 h at room temperature [4]. Cores from both groups were then subjected to the previously described indentation protocol, (i) to investigate possible changes in cartilage mechanical properties induced by CA4+, and (ii) to assess any dependence of cartilage response on test repetition. Aiming to investigate the distribution of CA4+ in cartilage tissue, cores from treated group were then acquired with a clinical HR-pQCT (XtremeCT II, SCANCO Medical AG), at 60-µm isotropic voxel size. Data analysis – i.e., cartilage thickness, data fitting, CA4+ volumetric distribution – was performed with custom-made codes (MATLAB 2022b, MathWorks).

Results and Discussion
Contrast enhancement did not induce significant changes in E₀ values, although large data scattering was found in treated specimens. Conversely, both PBS preservation and contrast enhancement significantly decreased τ values, although the effect was higher in control group. Negligible effects were found in β values, regardless the core treatment or test repetition.

Volumetric analysis provided depth-wise distribution of the CA4+ across the entire cartilage thickness (Fig. 1), allowing to differentiate its main sub-layers. Overall attenuation significantly correlated to E₀ (R = 0.75, p < 0.05).

Conclusions
Preliminary results support the use of CA4+ for preclinical purposes. Proteoglycan content pointed out by contrast-enhanced HR-pQCT suggests correlation with cartilage instantaneous response to indentation. Due to overall effects, induced on tissue parameters by CA4+, correlation with cartilage properties measured prior to contrast enhancement should be considered. Further investigation on reversibility of CA4+ effects on cartilage properties, and CA4+ safety for eventual clinical applications, are required. Future activities will deal with correlations between cartilage mechanical properties and composition.

References
EFFECT OF THE LOADING DIRECTION ON THE PREDICTED MECHANICAL PROPERTIES OF THE MOUSE TIBIA

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Introduction
Understanding how bone responds to mechanical loading is fundamental for the development of new biomechanical treatments for musculoskeletal diseases [1,2]. The in vivo tibial loading model is used to investigate the effect of passive mechanical loading on the mouse tibia [1,3]. While a nominal axial load is applied to the tibia through the knee and the ankle joints, the real loading direction in the experimental setup may induce out-of-axis loads on the tibia. These loads may dramatically alter the local strain distributions which affect the bone remodeling [4]. The aim of this study was to evaluate the effect of the loading direction on the predicted local mechanical properties of the mouse tibia before and after passive mechanical loading.

Methods
Six female C57BL/6 mice were ovariectomized (OVX) at week 14 of age. At weeks 18 and 20, the right tibiae were scanned using in vivo micro-tomography (micro-CT; 10.4μm/voxel). The mice underwent mechanical loading (ML) treatment at week 19 (12N peak load, 40 cycles/day, 3 days/week on alternate days). This data was acquired from a previous study [1]. Micro-CT based finite element models were generated from the segmented images (hexahedral elements; isotropic linear elastic material properties) for the mice at weeks 18 and 20 [5]. Three independent unitary load cases were applied along the axial, medio-lateral or anterior-posterior directions for each mouse at each timepoint. The components of the strain and stress, principal strains, principal stresses and strain energy density (SED) were recorded at the Gauss points. Using scaling and the superimposition of the effects, the results were combined to calculate the local properties for different loading directions resulting from a 12N axial load (typical load controlled in the in vivo tibial loading model to induce osteogenic effects). Calculations were performed as a function of the angle from the inferior-superior axis (θ, 0-30° range, 5° steps) and the angle from the posterior-anterior axis (φ, 0°; anterior axis, positive anticlockwise, 0-355° range, 5° steps) (Figure 1). The SED distributions were calculated for each loading direction.

Results and Discussion
Results confirmed a higher sensitivity to a change in θ compared to a change in φ at both timepoints (results reported here only for SED, Figure 1). Lower SED values were found for different loading directions after mechanical loading, highlighting adaptation of the bone also for loading directions far from the nominal one. The difference in variability between week 18 and 20 may be due to the mice responding differently to OVX, and ML having higher effect on the cortical bone compared to OVX.

Conclusion
These results suggest that in studies which use the in vivo tibial loading model, repositioning of the tibia in the loading device may impact the distribution of local deformation and therefore of bone remodeling [3], and thus should be better controlled during the experiment.

References

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A BIOPHYSICALLY DETAILED COMPUTATIONAL MODEL OF THE FOUR CHAMBER HUMAN HEART ELECTROMECHANICS

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Introduction
Numerical simulations of the cardiac function are progressively becoming a powerful tool to better understand the heart function [1] and to support clinical decision-making [2]. Even though some area of heart modeling reached a certain level of maturity, whole heart models are emerging only in the last few years. Most of these works are focused on the ventricles almost neglecting the full atrial function. In this work we present a biophysically detailed fully coupled multiscale mathematical model of cardiac electromechanics (EM) of the whole human heart that accurately consider both atrial and ventricular contraction [3].

Models and Methods
Our whole heart model provides a 3D description of cardiac EM in all the four chambers and a 0D representation of the complete circulatory system. The 3D EM part includes: a novel anatomically-accurate rule-based method to properly represent the whole heart fiber architecture [4]; the cardiac electrophysiology, described by means of the monodomain equation with specific human ionic models; the mechanical activation, based on a sophisticated microscale active force generation model [5]; the myocardial tissue mechanic adopting an orthotropic active stress formulation with specific constitutive laws and model parameter for each cardiac region. The 3D EM is strongly coupled with a 0D closed-loop lampered parameters model of the entire cardiovascular network [6]. The coupling between the 0D-fluid and 3D-EM models is achieved by means of volume-consistency coupling conditions [6,7].

The numerical approximation of the whole heart model comprises: Finite Element (FE) Method and tetrahedral mesh, for the space discretization, and finite difference schemes, for the time discretization. The Segregated-Intergrid-Staggered numerical scheme is adopted: the models, contributing to both the cardiac EM and the blood circulation, are solved sequentially in a segregated manner using different resolutions in space and time [7]. Moreover, we employ recently developed stabilization terms, related to the circulation and the fibers-stretch-rate feedback, that are crucial to obtain a stable formulation in a four-chamber scenario [8]. All the mathematical models and numerical methods have been developed within life*, an in-house FE library focused on large-scale cardiac applications in a High Performance Computing framework [9].

Results
The validity of the whole heart model was demonstrated through EM physiological simulations in an anatomically accurate geometry of the entire heart which includes the initial tracts of the cardiac arteries (see Figure 1). Relevant mechanical biomarkers, obtained by numerical simulations, are successfully compared with those provided by the data reported in the literature. We show that our results fall within the physiological reference ranges for all the four chambers. Furthermore, we highlight the importance of considering the atrial contraction and the fibers-stretch-rate feedback terms, by comparing the results obtained with and without these features.

The proposed model provides an important contribution to the whole heart modeling and is a fundamental step towards the building block of physics based digital twin of the human heart.

References

Acknowledgements
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THICKNESS MEASUREMENT IN MECHANICAL SOFT TISSUE TESTING: VALIDATION AND UNCERTAINTY QUANTIFICATION

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Introduction
Due to the deformable nature of soft biological tissues, the measurement of the sample dimensions is challenging. In mechanical testing, these measurements are used to calculate the first Piola-Kirchhoff stress $P$ from the measured forces $f$:

$$P = f/(WH)$$

with $W$ and $H$ respectively the undeformed width and thickness of the cross sectional area on which the force is acting. Hence, an accurate measurement of the sample dimensions is crucial for a reliable stress estimation. Moreover, to truly assess the quality of a mechanical test result, uncertainties throughout the complete testing protocol need to be quantified and properly accounted for in the subsequent calculations. Literature is limited to a single study investigating different techniques for soft tissue dimension measurements [1]. In this study, we explore the use of laser technology to measure the sample thickness, quantify uncertainty and biological variability and their effect on the final test result.

Methods
Sample thickness was measured using different techniques: 1) a digital caliper, 2) a micrometer, 3) a tool developed within the framework of C4Bio, 4) an in-house developed Micro Laser Scanner (MLS) consisting of a Gocator 2120 line laser and a linear actuator, and 5) MLS combined with a scanning spray (MLSS) applied on the sample. All methodologies were applied on 2 synthetic samples made of different materials, with 10 repetitions in order to quantify uncertainty and to compare the different techniques. Additionally, we measured the thickness of porcine aortas using the MLS to quantify the biological intra- (regional variation within 1 sample) and inter-(average of 10 different samples) variability. The uncertainties and variabilities were then used in an uncertainty propagation framework to calculate the effect on the stress-strain response. To this end, virtual data of a uniaxial tensile test was created, assuming a typical fiber-reinforced hyperelastic material model.

Results
Table 1 gives an overview of the mean and standard deviation for two synthetic samples for each technique. Figure 1 shows the probability distributions for uncertainty (for MLSS and for the C4Bio tool), intra- and inter-sample variability and the effect of uncertainty on the stress-strain curve for 2 different sample thicknesses (H1 and H2).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mean ± Standard Deviation</th>
<th>Uncertainty MLSS</th>
<th>Uncertainty C4Bio</th>
<th>Inter-Sample Variability</th>
<th>Intra-Sample Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYN1</td>
<td>0.84 ± 0.006</td>
<td>0.03 ± 0.002</td>
<td>0.03 ± 0.005</td>
<td>0.03 ± 0.002</td>
<td></td>
</tr>
<tr>
<td>SYN2</td>
<td>1.02 ± 0.009</td>
<td>0.05 ± 0.004</td>
<td>0.05 ± 0.008</td>
<td>0.05 ± 0.002</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Mean ± standard deviation ($n=10$) of the thickness of 2 synthetic samples measured with different techniques.

Discussion
Table 1 shows a large variation between different methodologies, not only in magnitude of the standard deviation differs, but also the actual mean value. We expect an underestimation of the thickness when using contact methods (caliper, micrometer), but also with MLS: laser light penetrates transparent surfaces or the top layer of tissues. The use of a scanning spray will solve this, at the cost of a slight overestimation by adding a thin layer ($\pm 11$ $\mu m$) to the outer surface. A full validation of the different techniques is challenging due to the lack of a ground truth. The measurement uncertainties are relatively low compared to the intra and inter sample variability that was measured (Figure 1, left). The propagation of measurement uncertainties increases with increasing stretch and with decreasing sample thickness. Future work includes to investigate the effect of the scanning spray on the mechanical properties and the quantification and inclusion of other uncertainties throughout the testing protocol.

References

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Footnote:
1 The C4Bio tool is a cheap tool to measure sample thickness using image analysis on a calibrated side-view picture, developed within the framework of c4bio.eu
BEYOND GAIT SPEED

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Introduction
Measuring gait with inertial measurement units (IMUs) during clinical assessment results in new, objective information about the way people walk after stroke [1,2]. However, it is unclear if the way people walk after stroke is associated with walking ability in daily life. This study evaluated the additive value of IMU-based gait features over a simple gait speed measurement in the estimation of the walking ability.

Methods
Every fortnight, participants walked for two minutes on a fourteen-meter path with three IMUs. The dimensionality of the corresponding gait features was reduced with a principal component analysis. During the two days after the two-minute walk test, the walking ability was assessed by measuring the number of steps, and average and maximal gait speed in daily life. A gait-speed only linear mixed model was used as baseline model per daily life gait characteristic with the participant as the random effect. The principal components (PC) were added to the models via a forward selection procedure. Finally, the model fit of the combined models was compared to the baseline models.

Results
Eighty-one participants were measured during rehabilitation, resulting in 198 two minute walk test measurements and 135 corresponding daily life measurements (figure 1). The gait features were reduced to nine PCs with 85.1% explained variance. The linear mixed models demonstrated that gait speed measured with the 2 minute walk test was weakly associated with average and maximum gait speed and moderately associated with the number of steps per day (figure 2). The PCs did not considerably improve the outcomes in comparison to the gait speed only model.

Discussion
Measuring the way people walk after stroke with IMUs does not provide additive value in the estimation of walk ability in daily life. Future research should indicate if measuring gait with IMUs improves prediction of other relevant elements during rehabilitation.

References
1 Felius et al, Sensors, 22(3),2022.

Acknowledgements
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IN SILICO MODELLING OF ENDOVASCULAR DRUG DELIVERY FROM DRUG-COATED BALLOONS

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Introduction
The treatment of ischaemic artery disease has improved substantially in recent decades since the inclusion of local delivery of antirestenotic drug [1]. Drug-coated balloons (DCBs) are a promising temporary modality of drug delivery, serving as an alternative or complement to the implantation of permanent stents. The principle relies on the endovascular inflation of a balloon transferring part of its drug coating to the vessel on contact during a short time window. A greater understanding of the underlying mechanisms of DCB delivery and how the combination of procedural parameters, such as inflation time, inflation pressure, and drug loading, affect its performance is required. To this end, in silico modelling is explored.

Methods
We present a multiphysics computational model of endovascular drug delivery from a DCB. A finite element method framework is developed to represent 2D-axisymmetric idealised geometries of the device and multi-layered arterial wall, with the interdependent processes of balloon inflation, contact, artery deformation, transmural filtration, drug transport and retention simulated. To emphasize the early events of DCB delivery, all processes are simulated in a space and time-dependent fashion while accounting for the spatial frame deformation. Long-term retention of drug within the artery (up to 28 days) is observed.

Drug transport is governed by diffusion and advection, and drug retention follows two phases of non-linear, reversible, and saturable binding reactions.

Results
The main outputs of the simulation are the drug release profile from the DCB and the drug distribution across the arterial wall, in free and bound states. Drug content (DC) and specific receptor saturation (sRS) are common measures of safety and efficacy, respectively, and may be assessed while attempting variations in balloon inflation pressure, contact time, drug dose and delivery rate.

Discussion
The present work demonstrates the potential of in silico modelling as an assisting experimental tool alongside the traditional ways of preclinical and clinical testing. Medical device development greatly benefits from the reproduction and analysis of complex events, such as the endovascular delivery of drug, from the convenience of a computer. We suggest that sophisticated DCB delivery models accounting for time-dependent multiphysics phenomena may be more representative of clinically observed conditions. Moreover, beyond useful insights, they could provide a platform for hypothesis testing and optimization — tasks that may be impractical if restricted to in vivo and in vitro settings.

References
DESIGN OPTIMISATION OF NEXT-GENERATION SCAFFOLD-BASED BONE RECONSTRUCTION IMPLANTS: PHD THESIS PRESENTATION

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Introduction
This doctoral research demonstrates the latest advances in patient-specific design, biomechanical modelling, and optimisation of next-generation scaffold-based devices for reconstructing large jawbone defects. One outcome of this research is an innovative clinical planning tool used to inform and guide the decision-making process of a maxillofacial surgeon prior to undertaking a mandibular reconstruction procedure. This innovative research underpins the design and production of next-generation tissue scaffold implants. These new medical devices will be additively manufactured to be patient specific and, for the first time, enable the reconstruction of large segmental bone defects with the complete volume of the gap being filled with a porous 3D-printed tissue-engineered scaffold.

Research Project 1
Using computed tomographic (CT)-based finite element (FE) modelling combined with multiobjective optimisation, determine the optimal height \( h \) and angle \( \alpha \) to place a titanium fixation plate on a scaffold-based reconstructed human mandible (Fig. 1) so as to enhance tissue ingrowth, structural strength and structural stiffness of the scaffold-host bone construct [1].

Research Project 2
Develop a state-of-the-art CT-based FE sheep mandible reconstruction model by: (i) characterising the elastic mechanical properties of selective laser sintered (SLS) polyetheretherketone (PEEK) with a universal testing machine (Fig. 2a), (ii) inversely characterising the Young’s modulus of the intact sheep mandible cortical bone by in vitro mechanical testing with digital image correlation (DIC) and a digital twin CT-based FE model of the intact sheep mandible (Fig. 2b,c), and (iii) validating a digital twin CT-based FE model of the reconstructed sheep mandible with an additively manufactured SLS PEEK scaffold-based implant using in vitro mechanical testing with DIC.

Research Project 3
Using the CT-based FE model of the reconstructed sheep mandible and multiobjective optimisation, determine the optimal design of the scaffold microstructure (Schwarz P-surface unit cell) for a sheep mandible implant so as to promote tissue ingrowth through (i) enhancing mechanical stimulus of the scaffold, and (ii) enhancing permeability.

Research Project 4
Evaluate bone ingrowth conditions of a one-body tissue scaffold implant for reconstructing a segmental defect in a sheep mandible after 12 weeks in vivo (Fig. 4).

Conclusions
The impact of this research overcomes the limitation of current surgical practice of using grafted bone to bridge the defect. In addition, this research and methodology can be readily extended to include other orthopaedic surgical procedures such as spinal fusions or hip and knee reconstructions.

References
MODELLING HEMODYNAMICS WITH REAL PHYSIOLOGICAL CONDITIONS OF PATIENT-SPECIFIC CORONARIES

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Introduction

Modelling haemodynamics with real physiological conditions specific to each patient, using principles of physics, mathematics and engineering, is still a challenge [1-3]. Achieving a supporting tool which helps in clinical decision may help cardiologists and surgeons to better manage coronary artery diseases (CADs). Recent research works of the authors, with experience in hemodynamic modelling in patient-specific coronary arteries, have considered pulsatile flow, the viscoelastic property of blood [1,2], and arteries with rigid walls [3]. The well-known viscoelastic property of blood should be considered since it has a significant impact on hemodynamic results [1,2]. Blood flow is pulsatile and, thus, deformable walls of the arteries should be considered. However, hemodynamic results considering deformable walls or rigid walls are almost the same. Moreover, the computational time of assuming rigid walls is significantly lower [3], which is beneficial for hospital applications. In this way, the authors of the present study have used rigid walls. In the past, outlet pressure profiles defined in the literature, as typical boundary conditions of the arteries, were considered by the authors [1,3]. The imposition of pressure profiles as boundary conditions in the artery outlets means the creation of a pressure gradient along the artery, which is not physiologically correct and accurate when the distribution of flow and pressure is the desired solution, such the Fractional Flow Reserve (FFR) [4]. Lumped-parameter models (Windkessel) solve this issue. This model finds the accurate pressures in the coronary branches, based on the resistance of blood flow [4]. The main goal of the present research project (PTDC/EMD-EMD/0980/2020) is to obtain a non-invasive computed FFR and CT-derived coronary hemodynamic descriptors, on-site and minimizing costs for the hospital, through a software with the most accurate conditions as possible, assuming pressure profiles specific for each patient artery (Windkessel model) [4] and the viscoelastic property of blood (simplified Phan-Thien-Tanner model, sPTT) [1]. To our knowledge, no other authors have considered these two accurate properties simultaneously.

Methods

A patient-specific left coronary artery model with 40% stenosis was constructed through a semi-automatic method in Mimics®. The CT images were provided by the Vila Nova de Gaia/Espinho Hospital Centre, which also measured an invasive FFR of 0.93 for this patient, through a coronary angiography procedure. User-defined functions (UDFs) in ANSYS® software were created to define outlet pressures, specific for the patient, through a 3-element Windkessel model [4], and for the sPTT model [1]. The computed FFR and the descriptors - Oscillatory Shear Index (OSI), Relative Residence Time (RRT) and Time Averaged Wall Shear Stress (TAWSS) – were achieved.

Results

The computed FFR was equal to 0.910, having a 2.15% relative error when compared to the invasive measurement. Moreover, the descriptors OSI, RRT, and TAWSS, for a cardiac cycle, are presented in Figure 1.

Discussion

The obtained hemodynamic descriptors, for this patient, are accurate and physiologically correct for clinical observation since the relative error between the computed and invasive FFR is very small, meaning that the validation of the software is promising. However, this study is a proof of concept. The software will be completely validated with many patient-specific cases with different stenosis degrees and positions, and considering different Windkessel models (5 and 7 parameters). After validation, a software for clinical routine use in hospitals will be created. This tool would make it possible to assess CAD in a more accessible, quick, and non-invasive manner, improving the diagnostic efficiency and safety as well as cost savings.

References


Acknowledgements

Authors acknowledge the financial support of FCT Portugal regarding the R&D Project “PTDC/EMD-EMD/0980/2020”; and the institutions and researchers of FEUP, INEGI, FMUP and CHVNG/E that contributed for the promising results.
MODELING AEROSOL DELIVERY IN STENOSED AND STENTED TRACHEAS CONSIDERING DIFFERENT BREATHING CONDITIONS

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Introduction

Chronic obstructive lung diseases have a worldwide prevalence of about 10% and it is estimated that in 2030 will become the third cause of death in the world [1]. Aerosol therapy by inhalation is the main strategy for treating such disorders. Unfortunately, inhalers, nebulizers and other devices are not optimized to specific patients and lesions so that the drug delivered tends to deposit and reach different regions of the airways. The computational fluid dynamics has been widely used for assessing transport and deposition of aerosolized particles within healthy airways [2]. Fewer works focused on bronchial obstructions [3], stenosed and stented tracheas. The goal of this work is the analysis of the aerosol transport and deposition in such situations for improving delivering strategies.

Materials and Methods

The parametric geometries consist in two tracheal stenoses (symmetric and asymmetric), using 20, 30 and 50% lumen reduction (Fig. 1a) and two stented models, tracheal and carina Dumon prosthesis with a thickness of 1 and 1.5mm (Fig. 1b and 1c). Realistic forced breathing flows were obtained through a spirometry before and after prosthesis implantation. Light and normal activities were estimated in both cases. The airflow was considered as steady and turbulent using particle sizes of 1, 5, 10 and 15μm.

Results

Small particles (1 to 5μm) tend to reach the lower airways independently on the degree of stenosis. The deposition fraction (DF) ranges between 0 and 4% (Fig. 2). For the stented airways, the DF ranges between 0 and 6% (Fig. 3). For particles of 10 to 15μm, the DF in the upper airways tends to increase in both stenosed and stented situations. For the stenosed tracheas, the deposition increases especially at the carina due to the reduction of the lumen in both symmetric and asymmetric models at 12 and 18L/min. Higher flows (90L/min) promote a decrease of deposition.

Discussion

Stented airways show increased drug depositions in the regions where the device is located as these reduce the tracheal lumen. Tracheal endo-prostheses promote several disorders such as inflammation, tissue reaction among others. Side effects of local aerosol overdoses around stented areas are unknown and need further investigations.

References


Acknowledgements

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TUNING PATIENT-SPECIFIC CORONARY LUMPED PARAMETER MODELS IN PRESENCE OF SEVERE AORTIC STENOSIS

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Introduction

Fractional Flow Reserve derived from coronary computed tomography (FFR\(_{\text{CT}}\)) combines imaging acquisition techniques with computational fluid dynamics to serve as a non-invasive diagnostic tool in the assessment of coronary artery disease (CAD) [1]. Its use is currently limited to healthy-aortic valve patients as conventional coronary lumped parameter models may not predict the hemodynamic changes present in patients with severe aortic valve stenosis (AS) [2]. However, it is quite common to encounter patients with both diseases. This proof-of-concept study provides some guidelines for tuning patient-specific coronary lumped parameter models to predict FFR\(_{\text{CT}}\) in patients with CAD and AS.

Methods

Full-cycle hyperemic indices, such as FFR, may vary in patients with AS due to physiological changes, especially in the systolic phase of the cardiac cycle [2]. However, FFR\(_{\text{CT}}\) is blind to these perturbations unless the inlet and outlet boundary conditions are updated accordingly. Thus, there is a fundamental question, how to perform this update? To fill this gap, several anonymous patients with moderate coronary lesions were selected. CCTA images were collected and segmented to reconstruct the coronary tree and the myocardium. Two types of simulations were performed using ANSYS© software: (1) simulation of hyperemic flow in the presence of AS and (2) simulation of hyperemic flow without AS disease, both based on previous clinical works [2,3]. Patient-specific inlet aortic pressure and outlet open-loop 0D coronary lumped parameter networks were tuned and coupled to the 3D simulation via user-defined functions (UDF), making variations in the perfusion pressure (+10% in (2)), systolic phase of intramyocardial pressure (-14% in (2)), left ventricular mass regression (-23% in (2)), which estimates total coronary flow, and microvascular resistance (-12% in (2)). FFR\(_{\text{CT}}\) was analyzed in both scenarios.

Results

Figure 1 confirms that the perturbations imposed on the inlet and outlet boundary conditions led to the desired variation in the inlet systolic coronary flow (+20 % in (2)), concordant with those reported by clinicians. The diastolic coronary phase did not show significant differences.

Discussion

Tuning coronary lumped parameter models based on standard principles [4] may lead to an overestimation of coronary artery disease in patients with severe aortic stenosis [5]. Thus, it is crucial to introduce modifications to the inlet and outlet boundary conditions based on clinical outcomes. Here, we confirm that with this approach, FFR\(_{\text{CT}}\) may be a valid non-invasive procedure for evaluating coronary artery disease in patients with aortic stenosis, and even after surgical (SAVR) or transcatheter (TAVR) aortic valve replacement.

References


Acknowledgments

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IMPACT OF INTEROBSERVER LUMEN SEGMENTATION UNCERTAINTY IN FFR<sub>CT</sub>: THE LOCATION OF THE STENOSIS MATTERS

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Introduction

Coronary stenoses are the main cause of severe heart failure as they can reduce or even stop the blood supply to the myocardium. Fractional Flow Reserve derived from computed tomography (FFR<sub>CT</sub>) is a computational non-invasive procedure for evaluating the hemodynamic significance of those stenoses [1]. Quantitative assessment of the variability of FFR<sub>CT</sub> due to input uncertainties is essential for its integration into a clinical setting, especially when FFR is near the cutoff (FFR = 0.80) [2]. In this work, we present a hybrid invasive and in-silico study that aims to analyze the impact of interobserver segmentation uncertainty on a wide range of patient-specific coronary models.

Methods

Eight anonymous patients with moderate coronary lesions were enrolled (FFR = 0.815±0.03). The location of the patient’s stenosis varies among them: 60% located along one of the epicardial arteries, close to the ostium, and 40% in a 2<sup>nd</sup> or 3<sup>rd</sup> generation vessel, far from the ostium. 64-bit CCTA images were collected and segmented to reconstruct the coronary tree and the left ventricle (LV) using a threshold-based segmentation method [3], under the supervision of an experienced radiologist. The side branch truncation level was set at 1 mm. Interobserver variations (11±7%) [4] on the segmentation threshold were performed to obtain 2 variants of each patient’s anatomy, as shown in Figure 1. It is worth noting that these lumen variations are more pronounced as the vessel diameter decreases, i.e., at bifurcations and side branches.

Patient-specific coronary lumped parameter models were tuned and coupled to the 3D simulation to mimic the pulsatile and diastolic-predominant flow present in coronary arteries [5]. Simulations of the optimal segmented fluid domain and its variants were performed until the results matched those obtained by invasive catheterization, measured 2 cm distal to the stenosis.

Results

Mean contour plots show that along the larger vessel sections, there are no obvious variations in FFR<sub>CT</sub>. On the other hand, segmentation accuracy seems to be crucial on the smallest vessels to avoid a mismatch in FFR<sub>CT</sub>. Table 1 summarizes the mean FFR<sub>CT</sub> variation found as a function of stenosis location.

![Figure 2: FFR<sub>CT</sub> for each threshold. Left: 170 HU, center: 200 HU, right: 230 HU.](image)

<table>
<thead>
<tr>
<th>Location</th>
<th>Mean FFR&lt;sub&gt;CT&lt;/sub&gt; Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; gen branch</td>
<td>0.006</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; gen branch</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Table 1: Mean FFR<sub>CT</sub> variation.

Discussion

Pressure drops in coronary stenosis depend on both stenosis geometry and flow rate [6]. If the segmentation threshold is increased (smaller lumen), the inlet flow rate will be reduced. Thus, despite the smaller lumen diameter, the lower inlet flow rate will compensate pressure losses through the localized stenosis in larger vessels. This compensation is insufficient in smaller vessels, where the larger geometric variations dominate against the reduced flow rate. Therefore, we can conclude that the impact of interobserver segmentation uncertainty on FFR<sub>CT</sub> will be greater as the stenosis is located in smaller vessels.

References


Acknowledgments

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CARDIAC OUTPUT INFLUENCE ON THE FLOW IN A TRI-LEAFLET MECHANICAL HEART VALVE

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Introduction

Only little data is available on the hemodynamic performance of prosthetic heart valves at reduced and increased cardiac output (CO) as most studies were done for CO of 5L/min [1]. This study aims to close this gap by investigating the blood flow patterns for low CO (LCO) and elevated (ECO) in a tri-leaflet mechanical heart valve implanted in aortic position in comparison to blood flow patterns at normal CO (NCO).

Methods

A pulse duplicator with a multi-view imaging system (Tomo-PIV) [2] was employed to investigate the flow characteristics in the aortic root of a tri-leaflet MHV (TRIFLO 21mm, Novostia). The valve was tested at low (3 l/min), normal (5 l/min) and elevated CO (7 l/min) under hypotensive (60/40mmHg), normotensive (120/80mmHg) and hypertensive (110/180mmHg) pressure condition respectively [3]. The heart rate was set to 70 bpm. Flow topology, mean flow velocity, and turbulent kinetic energy (TKE) were extracted from the measured flow field throughout the cardiac cycle.

Results

All three haemodynamic configurations exhibited one central jet and three side jets at the sinus level. For increasing CO, jet impingement occurred further downstream the aortic root (Figure 1).

![Figure 1: Mean flow rate at peak systolic. From left to right: low CO (t=190 ms), normal CO (t=150 ms) and elevated CO (t=130 ms).](image)

The systolic jet took longer to fully develop in LCO resulting in delayed development of turbulence, such that peak TKE in the aortic root appeared later and lower (Figure 2). The opposite could be observed by comparing ECO with NCO.

Results at peak systole are summarized in Table 1.

![Figure 2: TKE calculated at different time instances through the cardiac cycle (left). TKE calculated along the central axis for peak systole.](image)

<table>
<thead>
<tr>
<th>u_max [m/s]</th>
<th>TKE [mJ]</th>
<th>Backflow [%]</th>
<th>Y_imp. [m]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCO</td>
<td>1.28</td>
<td>0.88</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>(-37%)</td>
<td>(-63%)</td>
<td>(-42%)</td>
</tr>
<tr>
<td>NCO</td>
<td>2.02</td>
<td>2.38</td>
<td>2.14</td>
</tr>
<tr>
<td></td>
<td>(+37%)</td>
<td>(+100%)</td>
<td>(+14%)</td>
</tr>
<tr>
<td>ECO</td>
<td>2.76</td>
<td>4.78</td>
<td>2.44</td>
</tr>
</tbody>
</table>

Table 1: Computed values at peak systole. Values are in comparison to NCO.

Discussion

Variations in CO do not translate to a simple rescaling of the haemodynamic parameters characterizing the aortic flow. Reducing the CO shows significant lower turbulent kinetic energy as well as a jet impingement further upstream resulting in a spatially reduced influence of the valve on the flow in the ascending aorta. In all three conditions, the TKE peak is reached in the downstream vicinity of the sinotubular junction. Independently of the flow rate, the flow in the sinus does not seem to show fully developed turbulence.

References

CORONARY ARTERY SEGMENTATION IN HYPEREMIA CONDITIONS FOR COMPUTED FFR ANALYSIS

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. It is caused by the deposition of lipid tissue on the artery wall, resulting in the constriction of circulatory channels (stenosis). High mortality rates and difficult diagnosis, increase the need of rapid and effective detection. One functional assessment of hemodynamic behavior is calculating the Fractional Flow Reserve (FFR). Authors of this work have used conventional coronary artery segmentation for FFR achievement. This type of segmentation relies on manual procedures being inherently linked with long execution times where human error is also probable. A commercial software was used [1]. Ma et al. (2020) [2] developed an effective semi-automatic segmentation method based on region growing and section area using coronary angiography examinations, an invasive procedure associated with rare but serious complications. Computed Tomography (CT) is a non-invasive alternative. Pan et al. (2021) [3] created an automatic technique based on machine learning. However, this method requires a great amount of data to create the training dataset. As far as we know, there are no works in the literature purposely focused on coronary artery segmentation for hemodynamic simulations and FFR analysis. Thus, the scope of this project is to develop an in-house Python software to obtain a rapid and precise segmentation of coronary arteries from CT scans. In hospital, FFR is obtained in hyperemia condition. Thus, the computed processing steps to obtain these conditions should be automated to have an instant response time and eliminate the need to rely on costly commercial software. Also, the advantage of Python code is to be made available as open source.

Methods

Python code is used to obtain the coronary artery model of a male patient with 40% stenosis. The process only requires a manual input of an aortic point and a coronary artery starting point. In first place, a smoothing operation is conducted to reduce image noise and minimize under or over segmentation issues. The software then separates the coronary artery and the aorta by identifying significant increases in section area and defining the boundary using a probabilistic random walks method [4]. Region-growing algorithm segments the artery and a 3D model, in resting conditions, is created. To create the hyperemia model for FFR achievement, the centerline of the coronary model is computed by removing pixels from the border and comparing adjacent layers, continuously. Then, to define the various branches, the points closest to each other are computed, and the tangent to each point is derived through interpolation. For each point and the corresponding tangent, a cutting plane is defined so that cross-sectional area of the artery can be obtained.

Results

Figure 1 shows the 3D model after segmentation and smoothing, also the respective centerline and the identification of the cross-section.

Discussion

This research is a proof of concept showing promising results in segmenting the 3D model and automatic computing both the centerline and cross-sections. These are tasks that were otherwise performed manually and are necessary to obtain the model in hyperemia conditions. In a near future, the model must undergo additional processing operations towards this end. Therefore, the inlet and the various outlet sections must be defined, and the cross-section area must be increased by a factor of 2.04 due to hyperemia conditions. The in-house code will be validated by computing many patients’ data, allowing rapid image processing and contributing to more efficient CVD detection.

References

3. Pan et al., Scientific Reports, 11: 14493, 2021

Acknowledgements

Authors acknowledge the financial support of FCT Portugal regarding the R&D Project “PTDC/EMD-EMD/0980/2020”; and the institutions and researchers of FEUP, INEGI, FMUP and CHVNG/E that contributed for the promising results.
**Introduction**

The fetal membrane is a complex biological structure that surrounds and protects the fetus during pregnancy [1]. It is a multilayered structure that comprises a mechanical dominant layer called the amnion, a compliant and extensible layer named the chorion, and part of the decidua [1]. It undergoes complex microstructural changes by the end of pregnancy [2], which will contribute to the weakening of the tissue in preparation for delivery [3]. Several factors associated with the mechanical response and the microstructure of the fetal membrane remain unknown and few studies were performed to define an accurate constitutive model able to characterize its mechanics and general behavior. Numerical methods might represent the key to access several information concerning the mechanical behavior of the fetal membrane. Therefore, this work aimed to analyze the biomechanics of the fetal membrane by resorting to the finite element method. The maximum principal stresses were analyzed for different intrauterine pressures. To do so, a finite element model of an inflation setup containing the multilayer fetal membrane was first calibrated using an experimental dataset.

**Methods**

The calibration of the multilayer fetal membrane model (Figure 1) was performed by adjusting the numerical apex displacement of our finite element numerical inflation setup to the experimental apex displacement reported by the Skala Lab – Morgridge Institute for Research. In terms of constitutive models, the amnion was characterized by the modified version of the Buerzle-Mazza constitutive model (Table 1):

<table>
<thead>
<tr>
<th>μ₀</th>
<th>q</th>
<th>m5</th>
<th>m2</th>
<th>m3</th>
<th>m4</th>
<th>N</th>
<th>v</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4</td>
<td>2.96</td>
<td>0.463</td>
<td>0.00228</td>
<td>41.12</td>
<td>1.27</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>MPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: parameters of the modified version of the Buerzle-Mazza constitutive model to characterize the amnion.

These parameters were retrieved from the literature, except for μ₀, which was obtained from inverse finite element analysis. The chorion (E=1MPa, ν=0.41) and the decidua (E=1MPa, ν=0.49) were characterized by elastic linear properties. The maximum principal stresses were analyzed in the amnion and the chorion layers for different intrauterine pressure.

**Results**

The maximum principal stress in the amnion layer increased over the gestational weeks and for abnormally higher intrauterine pressure, while the chorion only experienced a slight increase (Figure 2).

**Discussion**

These observations are aligned with the fact that the amnion is the dominant layer in the fetal membrane from a mechanical point of view, withstanding the majority of the forces associated with pregnancy and playing a more important role in the integrity of the fetal membrane as the intrauterine pressure increases [4].

**References**

Introduction
Constitutive models of aortic wall are important for its biomechanical analyses. Although structure based constitutive models are considered preferable, the lack of histological data on tissue structure is limiting and sometimes they are fitted to mechanical tests only [3]. This study compares the capability of different structure-based constitutive models to fit the mechanical tests with and without histological data. For this purpose, the most common models of arterial wall tissues were used, both postulating two fibre families, with (GOH [1]) and without (HGO [2]) dispersion of their directions. The differences between the investigated constitutive models are illustrated using finite element simulations of uniaxial and biaxial loading states of the arterial wall.

Methods
Samples of porcine aortas (size of 18×18 mm) were separated into two layers (adventitia and media) with similar thickness. Mechanical testing of the specimens was realized under equibiaxial extension in saline solution (37°C) with five cycles ensuring specimen preconditioning. Polarized light microscopy with automatic algorithm for evaluation of collagen fibre directions (in ~10⁶ points per histological slice) was used for analysis in 8 slices throughout the wall thickness and in both perpendicular planes. See [4] for more details. Histological parameters necessary for the constitutive model (mean angle and dispersion in each fibre family) were obtained by fitting the histograms with the von Mises probability density function. The fitting procedure was performed in Curve Fitting Toolbox in MATLAB. Then we used Hyperfit software (www.hyperfit.wz.cz) to fit the models to mechanical data either without or with consideration of histological parameters. The goodness of the fit was evaluated using coefficient of determination R². Finite Element simulations (using ANSYS software) simulated uniaxial and equibiaxial tension test and inflation of aorta.

Results
In agreement with [3], the mechanical tests showed anisotropic response with significant strain stiffening (higher in circumferential direction) for both aortic layers. When fitted with the chosen models without histological data (non-structural models), the HGO model resulted in two directions close to ±45°; while GOH model tended to isotropic fibre distribution. Both results contradict histological data. For both layers we obtained unimodal dominantly circumferential orientation of collagen fibres. However, the fit to biaxial tests with these fixed structural parameters was poor (R²<0.77) in all cases. Only if we replaced the Neo-Hookean model (used for isotropic matrix in both GOH and HGO models) with 3rd order Yeoh model to introduce isotropic strain stiffening, we obtained a perfect fit (R²>0.98). Results of FE simulations of uniaxial tension (with the same force) presented in Figure 1 show significant differences in stiffness between the investigated models. Their impact in equibiaxial tension and in the aortic wall inflation with all the details can be found in [4].

Conclusion
The presented simulations have shown the importance of histological analyses for structure based constitutive models. The structural parameters of the investigated models were in contradiction to histological information if estimated from mechanical tests only. In contrast, these models were not capable to reach a good fit to both mechanical and histological data. This shortcoming was overcome by the addition of isotropic strain stiffening to the original HGO and GOH models, i.e. by replacement of the Neo-Hookean description of the matrix with a 3rd order Yeoh model.

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Acknowledgements
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ANALYSIS OF BIOMECHANICAL RESPONSE AFTER CORNEAL CROSSLINKING WITH DIFFERENT FLUENCE LEVELS

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Introduction
To date corneal crosslinking (CXL) is the only treatment that halts the progression of keratoconus by increasing the stiffness to the weakened corneal stroma using Riboflavin and UV-A light to induce collagen crosslinks[1-3]. Modifications of the original CXL protocols have been introduced by adjusting one or both factors, trying to optimize the outcome of the procedure[4-6]. To determine the biomechanical response of CXL, uniaxial stress-strain measurements on porcine corneas are used by many authors[7, 8], which allows good comparability of results. The aim of this study is to analyze the biomechanical stiffening of porcine corneas after accelerated epi-off corneal crosslinking, with a fluence of 5.4 J/cm² up to 20 J/cm² in porcine corneas.

Methods
Ninety corneas from freshly enucleated porcine eyes were divided into five groups of 18 each. Group 1 to 4 underwent epi-off CXL using a dextran-based riboflavin solution and an irradiance of 18mW/cm², group 5 served as the control group. Groups 1 to 4 were treated with a total fluence of 20 J/cm², 15 J/cm², 10.8 J/cm² and 5.4 J/cm², respectively. Thereafter, biomechanical measurements were performed on 5 mm wide and 6 mm long strips using an uniaxial material tester. Pachymetry measurements were performed on each cornea.

Results
At 10% strain, the stress was 75%, 56%, 53% and 31% higher in groups 1 to 4 respectively compared to the control group. The Young’s modulus was 2.84MPa for group 1, 2.53 MPa for group 2, 2.47 MPa for group 3, 2.12MPa for group 4 and 1.62MPa for the control group. The difference between group 1 to 4 and the control group 5 were statistically significant (p=<0.001; p=<0.001; p=<0.001; p=0.021). In addition, group 1 showed significant more stiffening than group 4 (p=<0.001), no other significant differences were found.

Discussion
Additional mechanical stiffening can be achieved by increasing the fluence of the CXL. There was no threshold detected up to 20J/cm². A higher fluence could compensate the weaker effect of accelerated or epi-on CXL procedures.

References
WEARABLE SENSOR AND MACHINE LEARNING ESTIMATION OF KNEE MOMENTS FOR HEALTHY PARTICIPANTS

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Introduction
A major problem following a total knee arthroplasty (TKA) is adaptation of asymmetric gait patterns, which results in higher loads on the non-operated knee often leading to a second surgery [1]. Monitoring motion is crucial for recovery of the knee and helps improve alignment and load distribution. A major challenge is that gait kinetics cannot be accurately measured outside specialized laboratories [2], due to large estimation errors, altered natural gait [3,4] and the use of expensive cumbersome equipment. Thus, the need for a portable system to enable motion and force assessment in healthy and clinical subjects in natural environments. The purpose of this study is to develop a platform for kinetics estimation based on a fused inertial measurement unit (IMU) sensor network and machine-learning (ML) architecture.

Methods
Healthy participants were recruited for this study, with no history of musculoskeletal disorders or orthopedic surgeries or lower limb pain, and with the ability to walk without aids. Participants performed walking trials at a self-selected speed with eight fused IMU sensors (SageMotion, USA) strapped to them, and forty reflective markers placed on anatomical landmarks. Trajectories were tracked using an optical motion capture system (Qualisys, Sweden). Ground reaction force (GRF) was measured using synchronized embedded force plates (AMTI, USA). The inertial and optical motion capture were collected simultaneously and synced in time.

Knee biomechanical measures (knee flexion moment (KFM) and knee adduction moment (KAM, first and second peak) were calculated using gait analysis software (Visual3D, USA) via inverse dynamics. The ML model inputs were body parameters, GRF and distance from knee joint center to center of pressure, used to predict the KFM and KAM.

Results
Biomechanical measures were based on six healthy participants: four females and two males, age 29.00±2.37, mass 67.68±13.63 kg, height 1.68±0.09 m, BMI: 23.93±3.35 kg/m².

Results from the musculoskeletal modeling and direct cross product calculations (\(\overrightarrow{FXGRF}\)), that were then used as inputs for the ML modeling, are presented in table 1.

Data of more healthy participants and post-TKA patients (IRB approved, screening in process) is being collected and results will be presented at the conference.

Discussion
This study offers a wearable motion capture system for accurately assessing gait movement patterns and forces, based on a combined IMU-ML approach. This system has the potential to increase the efficacy, accessibility, and reliability of correcting pathologies post-surgery. In addition, the current IMU network has built-in modules for haptic feedback which can be used in future studies.

References
TIME VS. SPACE: COMPARING GAIT CYCLE NORMALIZATION METHODS AND THEIR EFFECT ON FOOT PLACEMENT CONTROL

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Introduction
Mediolateral (ML) foot placement (FP) is actively controlled to stabilize human walking. Studies agree that deviations in ML FP can be explained from the center of mass (CoM) state throughout the gait cycle [1,2]. The deviations are also explained increasingly better as the FP event is getting nearer. To do this analysis, the gait cycles must be normalized, but normalization methods differ between studies. In [1], strides are normalized based on the fore-aft distance between the CoM and the stance foot in every frame in percentage of the trial’s mean stride length. At phase 0, the CoM is directly above the stance foot in the sagittal plane and this moment is defined as midstance (MS). As the normalization is based on distance rather than time, we refer to this method as spatial normalization (SN). Other studies use temporal normalization (TN) [2], where the period of interest is resampled to a number of points with uniform temporal distance, instead of the uniform spatial distance used in SN. This difference means that different information is used in these approaches. In this study, we investigate the effect of this difference by comparing SN and TN and their ability to explain ML FP from the CoM state. We expect that differences will be small in normal walking but larger if the gait is clearly asymmetric, as can be the case in persons with neurological diseases or other impairments.

Methods
We used raw data of normal [3] and asymmetric [4] treadmill walking. An approximation of the CoM was available in both datasets. We filtered the data and detected gait events. We extracted individual gait cycles (from MS to MS) and normalized every cycle using SN and TN. Only unperturbed strides starting at right MS were considered. The CoM was expressed relative to the stance foot position at left MS. We thus calculated the position of the next FP as the relative ML position of the right foot at the right next MS, which marked the end of the cycle. For every person and speed, we demeaned the data and created multiple linear regression models based on the CoM state. We created a single model for each time point for TN and each distance point for SN according to [1,2]. The dependent and independent variables of each model were the position of the next ML FP and the three-dimensional position and velocity of the CoM. The coefficient of determination (R2 score) of every model indicates how well deviations in ML foot placement can be explained by the CoM state at phase i.

Results
As expected, we did not observe large differences between TN and SN in normal walking, except for a drop of the R2 score in SN for phases i < -0.5. At left MS, both models can explain more than 80% of the next ML FP variance. For asymmetric walking, we also did not find considerable differences between TN and SN. However, an increase of the R2 value can be seen at the beginning for SN (Figure 1). Further, the R2 values after the left heel strike are generally lower than in normal walking (R2 is 0.67 and 0.66 at left MS for TN and SN).

Discussion
Our results show that TN and SN can be used interchangeably for the development of phase dependent controllers, even for asymmetric walking. In SN, special care should be taken at the start of the stride though. In asymmetric gait, the R2 value at this phase (i < -0.51) stems from only one subject who had low R2 values for the complete first third of the stride. No other subject had strides starting at a spatial phase i < 0.48 though, so the low R2 score could not be compensated. The drop in SN for normal walking can also be traced back to this. The high variance in R2 score between subjects requires future investigation though. Future work should also compare both methods for faster motions like the swing foot movement or motions with changes of direction.

References
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4. Liu et al, OSF, Data, 2020

Acknowledgements
This work was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – SFB 1483 – Project-ID 442419336, EmpkinS.
SENSITIVITY STUDY OF THE HILL MUSCLE MODEL IN A MUSCULOSKELETAL SHOULDER MODEL

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Introduction
A significant part of the shoulder stability is provided by the rotator cuff (RC). A torn RC, often resulting in strong impairment during daily activity, can be treated with a RC repair, however, a re-tear occurs in 20-70% of the cases depending on its severity [1]. Tear size, shape, and retraction but also degree of muscle atrophy, fatty infiltration and tendon quality are decisive factors for a RC repair outcome. However, it is not yet well understood how they influence the repair outcome and why some patients show a poor functionality after repair. The effect of these risk factors on muscle physiology after RC repair can be assessed using musculoskeletal simulations with the Hill muscle model. However, before repair simulations can be performed, the sensitivity and interplay of the Hill model parameters need to be understood. Thus, the aim of this study is to evaluate the sensitivity of the Hill muscle model parameters on supraspinatus strength during shoulder abduction.

Methods
The modelling of the shoulder was performed in AnyBody Modeling System (ver 7.3.4, AnyBody Technology A/S, Aalborg, Denmark) [2]. The initial working range of the shoulder muscles was set by defining the optimal muscle fiber length and tendon slack length using a two-parameter calibration [3]. After calibration, ideal muscle strength (F₀), optimal fiber length (L₀f), tendon slack length (L₀t), tendon strain at F₀ (ε₀) and fraction of fast twitch fibers (F₇fast) were 70.2N, 4.8cm, 8.6cm, 5.3% and 40%, respectively. Subsequently, they were varied ±25%, ±50% and ±75% to assess their effect on the course of supraspinatus (SSP) strength from 0° to 120° of shoulder abduction.

Results
After calibration, SSP strength peaked with 280N at 20° abduction and subsequently continuously decreased with increasing abduction angle (Figure 1, Table1). F₀ varied overall muscle strength but not its course. When L₀f increased, the strength of the SSP increased and the peak shifted to a lower abduction angle. At 50% and 75% increase of L₀f, SSP strength peak shifted to a negative abduction angle and thus the SSP strength at 0° abduction decreased. Changing from an ε₀ of -75% to +75% decreased SSP strength by 28N or 10% of its initial strength and shifts the peak by 20° to higher abduction angles.

Discussion
We herein present a study of the effect of Hill parameters on muscle strength. The model was most sensitive to changes in muscle fiber (L₀f) and tendon length (L₀t), with peak strength varying and shifting strongly from 0° to 120° abduction. In contrast, variations in tendon stiffness had only a minor effect on the course of the supraspinatus strength. Sarcomere stretch and contraction explain these variations. These findings can be used to guide parameter selection for future RC repair simulations.

References

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F₀ [N]</th>
<th>L₀f [°]</th>
<th>L₀t [°]</th>
<th>ε₀</th>
<th>F₇fast [°]</th>
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<tr>
<td>Initial</td>
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<td>20°</td>
<td>100N</td>
<td>267N</td>
<td>30°</td>
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<tr>
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<td>150N</td>
<td>20°</td>
<td>100N</td>
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<tr>
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<td>220N</td>
<td>20°</td>
<td>100N</td>
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<tr>
<td>+25%</td>
<td>350N</td>
<td>20°</td>
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<td>267N</td>
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<td>490N</td>
<td>20°</td>
<td>100N</td>
<td>267N</td>
<td>30°</td>
</tr>
</tbody>
</table>

Table 1: Peak supraspinatus strength [N] at abduction height [°] initially and after ±25%, ±50% and ±75% variations of muscle strength (F₀), fiber length (L₀f), tendon length (L₀t), tendon strain at F₀ (ε₀) and fast twitch fibers fraction (F₇fast).

Figure 1: SSP strength during 120° arm abduction.
ULTRASOUND-BASED FSI MODELING OF ABDOMINAL AORTIC ANEURYSMS INCLUDING PATIENT-SPECIFIC VELOCITY PROFILES

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Introduction
Current abdominal aorta aneurysm (AAA) risk assessment is based on a ‘one size fits all’ approach. However, both wall mechanics and hemodynamics are highly dependent on the AAA geometry. Therefore, a patient-specific (PS) risk assessment is required, based on fluid-structure interaction (FSI) models [1]. Time-resolved 3-dimensional ultrasound (3D+t US) is the preferred image modality to extract the patient-specific geometry, since it is safe, fast and affordable. Furthermore, the hemodynamics may highly depend on the prescribed inlet velocity profile. Therefore, this study aims at obtaining PS inlet velocity profiles to employ in highly personalized FSI simulations.

Methods
Doppler acquisitions were executed proximal to the aneurysm region in 6 patients. Pulsed-wave Doppler was used to acquire the velocity profile over time and Color Doppler was used to obtain the velocity profile over the cross-section by extracting the color gradient (Fig 1). Furthermore, Doppler imaging enables the use of a PS heart rate, inlet radius and inlet length. FSI simulations employing generic and PS flow parameters were performed and the differences in hemodynamics and wall mechanics in the aneurysm region were evaluated. In an ongoing study, the US Doppler flow parameters are validated with the use of 2D Phase-Contrast MRI in healthy volunteers.

Results
Differences up to 500% in time-averaged wall shear stress (TAWSS, Fig. 2) were observed when the flow parameters were made PS, mainly explained by the differences in peak and mean flow. Furthermore, the spatial TAWSS patterns changed significantly. For the oscillatory shear index (OSI), large differences in spatial patterns were detected, caused by the skewness of the PS velocity profile over the radius. Finally, the wall stress values were significantly influenced by the PS flow parameters. Preliminary validation results are shown in Fig. 3, which shows good agreement of US- and MRI-derived velocity profiles over time.

Discussion
This study showed the large influence of inlet flow parameters on hemodynamics and wall mechanics of the AAA and therefore stresses the need for a personalized approach. The validation study will be extended to include patients. In future studies, the obtained framework will be further personalized using 3D+t US speckle tracking for wall motion, and validated with the use of 4D flow MRI. The envisioned framework for personalized 3D+t US-based FSI simulations paves the way for longitudinal studies on AAA development, growth, and rupture risk.

References

Acknowledgements
This work was supported by the Dutch Research Council (NWO) and received funding from the NWO talent program VIDI. This work was carried out on the Dutch national e-infrastructure with the support of SURF Cooperative.
THE IMPACT OF A LIMITED FIELD-OF-VIEW ON COMPUTED HEMODYNAMICS IN ABDOMINAL AORTIC ANEURYSMS

Judith Fonken (1,2), Esther Maas (1,2), Arjet Nievergeld (1,2), Marc van Sambeek (1,2), Frans van de Vosse (1), Richard Lopata (1)

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Introduction
To improve abdominal aortic aneurysm (AAA) rupture risk assessment, a large, longitudinal study on AAA hemodynamics and biomechanics is necessary, using patient-specific (PS) fluid-structure interaction (FSI) modeling [1]. 3-dimensional, time-resolved ultrasound (3D+t US) is the preferred image modality to obtain the PS AAA geometry for such a study, since it is safe, affordable and contains temporal information. However, the 3D+t US field-of-view (FOV) is limited compared to that of computed tomography (CT), and often fails to capture the inlet and aorto-iliac bifurcation geometry (Fig. 1). The limited FOV and the absence of the bifurcation does not significantly influence the numerical assessment of wall mechanics in the AAA region [2]. In this study, the impact of this limited FOV on the hemodynamics in the AAA was evaluated.

Methods
A framework was developed to add parametric inlet and bifurcation geometries to the aneurysm geometry by employing dataset statistics and parameters of the AAA geometry. The impact of replacing the PS inlet and bifurcation geometries, acquired by CT scans, by parametric geometries was evaluated by examining the differences in CFD-derived systolic and time-averaged wall shear stress (WSS$_{sys}$ and TAWSS, respectively) and oscillatory shear index (OSI) in the aneurysm region [3].

Results
Considerable differences in hemodynamics in the aneurysm region were observed when the PS inlet geometry was replaced by a parametric one (Fig. 2). Median 99th percentile differences up to 162% and median differences between 7.5-18.8% were observed (Fig. 3). For the bifurcation geometry, the largest differences were observed in the distal part of the AAA region (Fig. 2). In the remainder of the aneurysm, the differences were small. All medians of the 99th percentile difference values were below 20% (Fig. 3). For all hemodynamic quantities and all patients, the median absolute difference was below 1%.

Discussion
These results indicate that it is not feasible to replace the PS inlet geometry by a parametric one, since this causes significant differences in hemodynamics in the AAA region. Future studies should focus on extending the proximal FOV by registering multiple (3D+t) US acquisitions. For the bifurcation, the obtained results illustrate the feasibility of adding a parametric bifurcation geometry to the aneurysm geometry, with median differences all below 1%. After extending the proximal FOV, the obtained framework can be used to extract AAA geometries from 3D+t US for FSI simulations, despite the absence of the bifurcation geometry.

References

Acknowledgements
This work was supported by the Dutch Research Council (NWO) and received funding from the NWO talent program VIDI. This work was carried out on the Dutch national e-infrastructure with the support of SURF Cooperative.
CFD SIMULATIONS OF THE CO₂ REBREATHING IN DIFFERENT HELMET-LIKE INTERFACES FOR THE CPAP THERAPY DELIVERY

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Introduction

CPAP (continuous positive airway pressure) therapy, widely used during the COVID-19 pandemic, can be delivered to the patient through helmet-like interfaces, because of their tolerability. Under low flow rate conditions, especially for closed-loop ventilation circuit [1], the CO₂ could accumulate inside the helmet, and be rebreathed by the patient (with dangerous effects for concentration values over 1% [2]). In this work, a CFD approach was developed to study the CO₂ distribution under different inlet-outlet configurations, recurring to acceptable flow rate conditions (high flows cause waste of oxygen, noise and discomfort).

Methods

The CFD simulations were performed in Fluent (Ansys). A generic helmet and human head geometry were reproduced, with a dead space of approximately 20 L. One pipe was connected to the mouth to represent the airways (~ 0.15 L) and two pipes were connected to the helmet, as inlet and outlet flow extensions, in three different layouts (Figure 1): the standard layout (A), and two novel alternatives, the one attainable only with a customized helmet (B), the other possible with a commercial one (C). CPAP was set to 10 cmH₂O.

Results

In the standard layout (A), the CO₂ produced by the patient is confined in the mouth surrounding area (Figure 2), heavily impacting the CO₂ rebreathing (Table 1, A1). A higher flow didn’t improve the washout (A2), whereas the novel inlet-outlet layouts (B-C) helped in spreading the exhaled gas distribution, with consequent reduction of inhaled CO₂.

Discussion

Results highlight an unfavorable effect of the flow increase on the interface washout, but a relevant impact of the inlet-outlet layout on the CO₂ rebreathing. Indeed, by adopting a frontal outlet in commercial helmets, the CO₂ rebreathing reduces by 28%. This study sheds light on the washout issue in patient’s interfaces, providing novel insights in the design of optimized helmet layouts.

References


Acknowledgements

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A PROCEDURE FOR THE IN SILICO DESIGN OF ARTIFICIAL URINARY SPHINCTERS

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Introduction
Urinary incontinence represents a relevant healthcare problem worldwide, causing enormous socio-economic costs. With particular regard to male subjects, Artificial Urinary Sphincter (AUS) is the gold standard treatment. The principal component of the AUS is a cuff, which is wrapped around the bulbar urethra. The cuff is inflated with saline to occlude the urethral lumen. Cuff pressure is defined on the basis of clinical experience to ensure continence, up to high bladder pressure. Despite the continence efficacy, the physio-mechanical reliability of current AUSs is an open issue. AUS constantly applies occlusive actions that elicit non-physiological mechanical stimulations on tissues, leading to vasoconstriction, tissue infection, atrophy and/or erosion. Device revision is frequent, with relevant costs and patient bother. AUSs have been mostly designed on the basis of clinical experience, experimentations on cadavers or animal models and clinical trials. Such approach is extremely expensive and only a few configurations of the device can be analysed. Mostly, mechanical effects on urethral tissues are not investigated. In silico methods are expanding for the design of surgical devices. Biomechanical models allow to spread the investigation to many different configurations, providing also stress and strain fields within biological tissues, whose knowledge allows evaluating the physio-mechanical reliability [1]. The here proposed activities pertain to the definition of a procedure for the in silico design of AUS devices.

Materials and Methods
The procedure assumes a typical conformation of the AUS, as an inflatable cuff surrounded by a supporting band. The first step pertains to geometrical design, which investigates AUS wrapping uniformly around the urethra when the cuff is inflated. Parametric 3D CAD models and FEM computations allow evaluating different conformations. The design accounts for both overall geometry and details, such as the joint region.

A specific hyperelastic formulation is defined for the mechanical behaviour of the device rubber material. The assumption of different constitutive parameters allows analysing devices with different characteristics. The further step of the in silico procedure pertains to the analysis of interactions between AUS and urethra, which is defined as a cylinder with lumen. Tissues mechanical behaviour is defined by means of hyperelastic formulations, whose identification accounted for extensive experimental data [2]. The next step of the procedure couples AUS 3D CAD model and urethra. Contact strategies specify the interaction between the different surfaces. After FE discretization, the models are exploited to simulate lumen occlusion at different cuff pressures.

Results
A specific procedure, which couples 3D CAD and FEM tools, has been defined to design artificial sphincters accounting for the wrapping capability of the urethra (Figure 2) and the mechanical stimulation of urethral tissues. The approach provides information about stress and strain, which are responsible for tissue damage, and hydrostatic pressure, which entails vaso-constriction phenomena, as novel parameters for AUS optimization.

Conclusions
The investigations highlight the potentialities of in silico approach for design of AUS devices. The novelty of the proposed procedure is the evaluation of device reliability depending on mechanical stimulation of urethral tissues. The methodology further allows to specifically design the AUS depending on degenerative phenomena. In conclusion, the novel approach provides a design tool that amplifies the plethora of device configurations investigated, and minimizes the experimental and ethical efforts.

References

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FULLY CRYSTALIZED VERSUS PARTIALLY CRYSTALIZED LITHIUM DISILICATE CAD/CAM BLOCKS

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Introduction
Lithium disilicate is favored by most dentists over other esthetic materials due to its superb esthetic outcomes, satisfactory strength, and prolonged survival rates [1,2]. IPS EmaxCAD has served for years as the milestone for CAD/CAM esthetic restorative treatment. Due to its relatively high strength, lithium disilicate was always milled in a pre-sintered intermediate phase which necessitates a second firing procedure in a special furnace. Recently, new fully crystallized lithium disilicate blocks which require no additional firing step were introduced. However, the risk that hard milling would induce the formation of intrinsic flaws and negatively affects the long-term strength and abrasiveness of the final restoration is still questionable.

Methods
Rectangular shaped specimens were sectioned from LiSiCAD (n=20) and EmaxCAD blocks (n=10). The LiSiCAD were divided into: Polished; LiSiCAD-P (n=10) or Glazed; LiSiCAD-G (n=10). EmaxCAD specimens were subjected to combined firing/glazing cycle following the manufacturer’s recommendations. Specimens were subjected to 200,000 wear cycles at 20N force and 2mm sliding distance against natural premolars. Micro-CT was used to get pre and post scans for the teeth and volumetric enamel loss was calculated through scans overlapping (Figure 1). Ceramic wear was calculated based on weight loss. For fracture resistance test, full contour crowns of uniform thickness were milled from the tested blocks, then finished and sorted as previously described (n=20) then adhesively cemented to duplicated epoxy dies. Half of specimens (n=10) were aged in a chewing simulator, then both aged and non-aged specimens were subjected to static loading until fracture. Data were statistical analysed using One-way and Two-way ANOVAs and equivalent test for non-parametric results. The significance level was set at P≤0.05.

Results
LiSiCAD-P specimens had significantly lower mean ceramic wear values after 100,000 and 200,000 wear cycles (0.780±0.192 & 1.04±0.222 respectively) than EmaxCAD and LiSiCAD-G. No significant differences in volumetric enamel loss were seen between groups. Aging did not significantly affect the fracture resistance of any of the tested groups. EmaxCAD demonstrated the highest mean fracture load (1600±195). LiSiCAD-P and LiSiCAD-G were fractured at similar loads (990±222 & 915±262, respectively).

Figure 1: Overlapping of pre- and post wear test tooth models on 3-Matic software (Materialise, Belgium). Boolean subtraction is used to define the worn area.

Conclusion
EmaxCAD and LiSiCAD produce similar enamel wear rates which fall within the acceptable physiological wear rate. Polished LiSiCAD is more wear resistant than EmaxCAD or glazed LiSiCAD. LiSiCAD is less fracture resistant than EmaxCAD. Aging has no effect on the fracture resistance of any of the tested materials. Glazing did not improve the properties of LiSiCAD.

References
REDUCTION OF STRAIN CLUSTERS IN INJURED HEEL FINITE ELEMENT MODELS WITH A NEW PRESSURE ULCER DRESSING

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Introduction
Pressures Ulcers (PU) are soft tissue injuries that may occur when high and extended loads are applied to the tissues. The onset of PU has been mechanically explained by excessive shear strains [1]. When the unloading of the tissues is not possible, medical devices such as dressings can be applied to temporally relieve the tissues. However, there is little evidence showing the mechanical efficacy of these dressings to decrease the strains around PU. This study presents a Finite Element (FE) analysis of such efficacy on an asymptomatic heel and injured heels, with two different stages of PU.

Material and Methods
FE models were designed for one asymptomatic subject (Figure 1). Models were designed without PU, with stage-2 PU, and stage-3 PU, with and without the dressing. These models included skin, fat, muscle, and tendon tissues. Bones were supposed rigid. PU were simulated by removing tissues in a sphere portion 3.0 mm deep (stage-2 PU) or 5.0 mm deep (stage-3 PU). Tissues were supposed and defined as isotropic, homogeneous, and hyperelastic. The dressing was composed of two layers, the first one represented a compress modelled with an orthotropic linear elastic material, and the second one is a compressible honeycombed material with a hole under the bony prominence [2]. The dressing was tied to the skin after a prestress was applied. Bones were loaded with a vertical force equivalent to 6 % of the subject’s weight. A mattress, with a linear elastic material, was added to the model. Clusters of deformations were defined as groups of adjacent elements with Green-Lagrange maximal shear strains higher than 0.75 and compressive strains higher than 0.45 [3].

Results
The volume of the main cluster of deformation decreased in all models when the dressing was added (Table 1 and Figure 2).

<table>
<thead>
<tr>
<th>Cluster volumes (mm³)</th>
<th>Without dressing</th>
<th>With dressing</th>
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</thead>
<tbody>
<tr>
<td>no PU</td>
<td>3.277</td>
<td>1.898</td>
</tr>
<tr>
<td>stage-2 PU</td>
<td>2.187</td>
<td>1.280</td>
</tr>
<tr>
<td>stage-3 PU</td>
<td>1.891</td>
<td>1.227</td>
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</table>

Table 1: Volume of the main clusters of deformations.

Discussion
The dressing performed well to reduce the volume of tissues above potentially harmful strain thresholds. Strains levels remain high which means that additional care should be taken on top of the use of dressings. As a perspective, this analysis needs to be computed on more subjects.

References

Acknowledgements
We thank Alessio Trebbi for his help in the acquisition and segmentation processes.
MINIMAL DETECTABLE BONE FEATURES IN CT IMAGES AND DIGITAL 3D MODELS

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Introduction

Three-dimensional (3D) digital and additively manufactured models are increasingly used for pre-operative planning, and recently also for bone fracture treatment. However, the size minimum of detectable features in these models, including corresponding CT images, has not been determined yet. Hence, it remains unknown which features (e.g. fractures) might remain undetected. Therefore, this study aimed to investigate the minimal detectable bone features in CT images and corresponding digital 3D models.

Methods

Experimental

Figure 1: Experimental preparation of bone features (diaphyseal osteotomy, bone incisions, and bone lamellae)

Incisions in the diaphyseal radii with 200 and 400 µm width, and bone lamellae with 100, 200, 300, and 400 µm width were generated in twenty-paired forearm specimens (78 ± 8 years (5 male and female, each)). Additionally, an osteotomy was performed in the diaphysis, aiming to simulate a complete fracture, and was displaced by a 100 µm fracture gap using specimen-specific, additively manufactured guides (Figure 1). Specimens were then scanned with different CT scanners and corresponding digital 3D models were created. The effects of different CT scanners, specimen positioning, scan and segmentation protocols, and image post-processing settings on feature detectability were assessed. Furthermore, inter- and intra-operator variabilities were reported.

Results

In CT images, all 300 and 400 µm incisions and bone lamellae could be identified at a rate of 80 to 100%, respectively, independent of the investigated settings. In contrast, only 400 µm incisions and bone lamellae were visible in digital 3D models. Hereby, the detection rate was independent of the scan settings (Figure 2) but dependent on the selected image segmentation and post-processing algorithms.

Discussion

Clinical CT imaging allows for the detection of bone features in sub-voxel range [1], independently of imaging settings. Thus, the choice of voxel-size and corresponding radiation exposure for diagnostic purposes should conform to the suspected fracture, its typical gap size and dislocation. Corresponding digital 3D models introduce higher inaccuracies (voxel-size) and they should be verified with original CT images.

References


Acknowledgements

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FINITE ELEMENT STRAIN PREDICTION IN INTACT AND LESION-AFFECTED VERTEBRAL BODIES: A NEW VALIDATION EXPERIMENT

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Introduction

Accurate estimates of strain in human vertebrae would be important to quantify physiological deformations, and their modification by metastatic lesions, but a single study reported strain validation ($R^2 = 0.70$) [1]. To replicate damage mechanisms [2], vertebral endplate deformation should be permitted, while most existing studies either included endplates in endcaps [3] or removed them [4]. Only displacements could be accurately predicted when permitting endplate deformation by leaving in place intervertebral disks [5]. FE models of metastatic vertebral bodies could predict failure but using an endplate-removal setup [6]. This study aims to: (i) validate an experimental procedure that permits endplate deformation; (ii) test the procedure in intact and lesion-affected human vertebral bodies, measuring surface displacements and strain with Digital Image Correlation (DIC); (iii) determine the prediction accuracy of a FE model of the vertebral body.

Methods

Homogeneous distribution of the contact pressure was attempted by pressurizing a low viscosity gel acting on a thin deformable membrane covering the proximal endplate. Three human lumbar vertebrae (L3-L5, single donor) and three pseudo-vertebrae machined from bulk polyethylene underwent compressive testing in load control up to 2 kN, after removal of the distal endplate (flat caudal plane). Simulated lesions were obtained on human vertebrae by drilling hemispherical domes of increasing diameter (from 10 to 25 mm in steps of 5 mm) starting from the center of the flat caudal plane, with no involvement of the cortical wall. Displacement and strain fields were measured on three aspects (left/right anterolateral and posterior) by DIC, performing five repetitions per side. Endplate deflection was measured by an LVDT in specimens with lesions. CT-based FE models of intact and lesion-affected vertebrae, including cortical bone mapping [7] were built, and inhomogeneous [8] and transversely isotropic material properties [9] were assigned.

Load was distributed on the proximal endplate. Caudal plane was vertically fixed and circumferentially free to expand. FE and DIC were spatially registered (Figure 1).

Results

Accuracy vs. theoretical calculations in pseudovertebrae (3–8 % longitudinal strain underestimation) and precision in anterior aspects of human vertebrae ($\leq 0.2 \mu m$ for displacements and $\leq 30 \mu m$ for strains) support the validity of the loading scheme. Due to venous plexus, DIC data on posterior aspects were incomplete. Simulated lesions, even of 25 mm diameter, did not cause vertebral body collapse nor endplate failure. FE models accurately predicted: (i) longitudinal and circumferential displacements ($R^2 = 0.96$, slope = 1.15); (ii) longitudinal strains (median error 0.6%, 95% error within 27%). Circumferential strains were systematically overestimated (median error 39%).

Discussion

We developed and validated a new set-up to apply a uniform contact pressure upon the vertebral endplate. A CT-based FE model of vertebral bodies could accurately predict longitudinal and circumferential displacements, and longitudinal strains. There is initial evidence that simulated lytic lesions even of large diameter but not involving the cortex cannot induce collapse under physiological compressive loads.

References


Figure 1: Matching of DIC (top) and FE (bottom) data.

Figure 2: Maps of strain % accuracy of FE vs. DIC
MECHANICAL CHARACTERIZATION OF PORCINE CORNEAS THROUGH DIGITAL IMAGE CORRELATION ANALYSIS

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Introduction
Quantification of corneal mechanical properties is crucial for permanent refractive correction using laser ablation or corneal cross-linking (CXL) to accurately predict surgical outcomes. Uniaxial tensile tests have been used for material characterization, but these tests are not representative of the natural 3D loading by the intraocular pressure (IOP). Inflation tests better resemble the physiologic stress distribution, but tracking of the corneal surface displacement is difficult and has been previously limited to a single apical point [1]. In the present study we performed inflation tests under different corneal conditions exploiting digital image correlation (DIC) [2], a non-interferometric optical method for measuring the 3D displacement of the anterior corneal surface.

Methods
Fifteen freshly enucleated porcine eyes were divided into 3 groups and tested within 24 hours: 5 eyes (CXL group) were subjected to the Dresden CXL protocol (3 mW/cm² irradiance for 30min), 5 eyes (laser group) had the first 350µm of the anterior stroma removed with a femtosecond laser, and the remaining 5 eyes were de-epithelialized and served as the control group. The experimental setup is shown in Figure 1.A and consists of i) a pressure sensor inserted into the anterior chamber; ii) a pressure pump; iii) two cameras (Imager E-lite 2M, LaVision, Germany) with spatial resolution of 1280x1024 pixels; iv) the eye globe placed in a holder that allowed for corneal expansion. Saline solution was injected into the posterior chamber (0.0833 ml/min), and the IOP was recorded up to 80 mmHg. The 3D displacements of the central corneal region were tracked at a frame rate of 3 fps (Figure 1.B). The resulting point cloud was meshed and the principal in-plane strains were calculated using an in-house Matlab (The MathWorks Inc., Massachusetts) code, which exploits the membrane theory of the finite element method (FEM) [3].

Results
Maximum principal strains (MPS) values were compared for the three groups at ΔIOP values of 20 and 60 mmHg (Figure 2). At 60 mmHg, the laser group showed a statistically significant increase in MPS compared to the control group (7.5±1.2% vs 4.3±1.1%, p=0.008), and to the CXL group (2.7±0.3%, p=0.008). There was a trend (p=0.07) toward a reduction in MPS in the CXL group compared to the controls. Similar differences were observed at 20 mmHg.

Discussion
DIC cameras enabled a point-wise registration of the deformation of the central anterior corneal surface during inflation tests. CXL samples were stiffer than controls when subjected to the same IOP, while laser cut samples were significantly softer, possibly indicating a depth dependency of corneal mechanical properties [4]. This experimental data will be exploited to feed inverse FEM algorithms, to determine corneal mechanical properties, either in terms of depth dependence or to quantify the biomechanical alterations induced by CXL.

References

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Figure 1: A) experimental setup; B) displacement map

Figure 2: MPS at different IOPs in the three groups.
TENSILE TESTING OF SINGLE COLLAGEN FIBRILS FROM ACHILLES TENDONS FROM AN OSTEONECROSIS IMPERFECTA MOUSE MODEL

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Introduction
The homozygous oim mouse model of osteogenesis imperfecta forms homotrimeric collagen type I molecules, which assemble into fragile bone tissue [1]. Counterintuitively, it has been shown that individual collagen fibrils from oim/oim (severe OI type III) tail tendons have higher ultimate stress compared to wild-type (WT) fibrils [2]. However, collagen fibril mechanics are in part steered by the prevalence of enzymatic and non-enzymatic crosslinks between collagen molecules [3], and elevated non-enzymatic crosslinks have been reported in the bones of the oim mouse [1], compared to WT. So far, only fibrils from the positional tail tendons were investigated from oim/oim and littermate WT mice. No data exists on fibrils from energy-storing tendons. To fill this gap, here we report the mechanical properties of oim/oim and WT fibrils obtained from Achilles tendons.

Methods
Achilles tendons of two wild-type (B6C3Fe-a/aCol1a2/oim/oim) and two oim/oim (B6C3Fe-a/aCol1a2/oim/oim) mice were dissected and spread out on a glass slide to expose isolated collagen fibrils. Collagen fibrils (n=8 for oim/oim, n=5 for WT) of lengths of about 100 μm were tested to rupture at a strain rate of 5%/s. The tests were conducted in phosphate buffered saline (PBS, pH 7.4), at room temperature, using the NanoTens device [4]. In the NanoTens, fibrils are reversibly attached to a microgrigger mounted on an interferometric force probe, which is actuated to conduct the tensile tests. Fibril diameters were determined by means of atomic force microscopy (AFM) (NanoWizard Ultraspeed A, JPK, Germany) in Quantitative Imaging™ mode in PBS. Collagen fibrils are identified prior to tensile tests via their characteristic D-bandying by imaging in air in contact mode. Force-displacement data were transformed into engineering stress and strain data using the initial cross-section determined via AFM and length determined via optical microscopy. Tangent tensile modulus was calculated as the smoothed derivative of engineering stress vs. engineering strain. Stress-strain curves were classified as showing 3-phase behavior if, after the initial increase of tensile modulus and its consecutive post-yield decrease, another pronounced increase was observed before rupture. Fibril cross-sectional areas, ultimate stresses and strains, and tensile modulus values were not normally distributed. Hence, groups were compared by a Mann-Whitney-U-Test and reported as median and quartiles.

Results
Generally, samples of both groups, WT and oim/oim fibrils exhibited three-phase behavior, with a strain stiffening before rupture (see Fig.1). Geometrically, no significant differences were detected in dry fibril cross-sectional area, wet fibril cross-sectional area, or swelling ratio, between the tested oim/oim and WT fibrils. WT fibrils showed no significant difference in maximum tensile modulus before yield (oim/oim: 0.63 GPa (0.58-1.24 GPa), WT: 0.98 GPa (0.72-1.45 GPa)). Ultimate strength for WT fibrils (0.32 GPa (0.34-0.25 GPa)) was significantly higher than for oim/oim (0.14 GPa (0.08-0.26 GPa)). There was no significant difference in ultimate strains.

Discussion
Swelling ratios, tensile moduli and ultimate stresses measured in the present study were within the range of values previously reported for mouse tail tendons. The non-significant differences observed between the oim/oim and WT Achilles tendons in the swelling ratio and tensile modulus are in contrast with results previously found for tail tendon collagen fibrils [5]. This indicates that possibly different crosslink profiles exist in tendons according to their anatomical function, as well as in bone. This motivates further studies considering crosslink content analysis in oim/oim and WT tendons and demineralized bones in parallel to tensile testing of fibrils obtained from these tissues.

References
THE INFLUENCE OF TWISTED STRUCTURES OF THE ACHILLES TENDON ON STRAIN DISTRIBUTION – PATIENT-SPECIFIC FE STUDY

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Introduction
The Achilles tendon (AT) is a complex structure, consisting of three twisted sub-tendons [1], which influence the AT strain [2]. In Achilles tendinopathy, the tendon material properties and geometry are altered, in particular decreased Young’s modulus and tendon thickening [3]. The unilateral heel drop and heel rise exercises are commonly included in the rehabilitation protocols, but it remains unknown if these exercises provide an optimal strain [4] in Achilles tendinopathy patients. Finite element (FE) models of the AT facilitate the investigation of the effects of tendinopathic changes on local tendon strain [5]. The main aim of this study was to investigate the impact of two types of rehabilitation exercises on AT strain in patients with Achilles tendinopathy, including the effect of twist of the Achilles sub-tendons.

Methods
Ten participants with mid-portion Achilles tendinopathy (7 males, 3 females; age = 46 ± 16 years; weight = 75 ± 16 kg; height = 178 ± 10 cm; VISA-A score: 76 ± 17) participated in the study. The subject-specific geometries of the free AT were developed using 3D freehand ultrasound. Free form deformation method was used to develop subject-specific FE models of the AT for each type of twist, as in our previous study [6]. As a result, each subject had three different meshes, leading to total 30 subject-specific FE models used in our study. Material properties were defined as an incompressible, transversely isotropic hyperelastic material [7]. The subject-specific Young’s modulus was calculated as the slope of the line fitted to the stress-strain data between 30% and 60% of the peak force for each patient (Young’s modulus: 484.9 ± 125.7 MPa). Muscles forces of each patient were obtained by a combination of 3D motion capture and musculoskeletal modelling during a unilateral heel drop and a unilateral heel rise. The average of the muscle forces among patients was used as force boundary conditions for running subject-specific FE analysis. The average strain in the mid-portion and the location of the peak of the maximum Lagrange strain were calculated to compare the strain patterns between different exercises and twist types.

Results
Average strain in the mid-portion of the AT is larger during unilateral heel drop compared to heel rise (p < 0.05), for all the types of twist (Type I: 0.097 ± 0.028 and 0.084 ± 0.014, Type II: 0.097 ± 0.015 and 0.088 ± 0.013, Type III: 0.1 ± 0.017 and 0.09 ± 0.014, average ± standard deviation, for heel drop and heel rise, respectively). There was no significant effect of the twist for unilateral heel drop (p=0.846) nor for the heel rise (p=0.067). The peak strain is located in the mid-portion, where the thickened area is for the majority of the patients (n=6).

![Figure 1: A representative example of the distribution of the maximum Lagrange strain for the three types of twist and the two exercises.](image)

Discussion
The eccentric unilateral heel drop exercise resulted in significantly higher average strain compared to concentric unilateral heel rise, for all the three types of twist. The twist didn’t influence the average strain. However, it influenced the location and magnitude of the peak strain. None of the exercises induce an optimal strain [4]. The location of the peak strain showed large variation across patients but it didn’t change between exercises. The location of the peak strain is more related to the individual material properties and geometry rather than the muscle forces. Using these models, we will be able to further investigate the large variability in geometry and material properties amongst Achilles tendinopathy patients. This could allow to explore the potential of patient-specific rehabilitation programs, by including subject-specific material properties, geometry and muscle forces.

References
Using Biofidelic FEMS to Quantify the Efficacy of Invasive Prophylactic Treatments for Hip Fracture Prevention

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Introduction
Pharmacological treatments for the prevention of hip fractures in the elderly have limited cost-effectiveness [1], consequently a number of prophylactic augmentation methods have been proposed as alternatives. Trials using augmentation methods have been limited as the surgeries are controversial due to potential adverse effects. Therefore, it has not been possible to compare different methods on the same cohort. To compare the biomechanical efficacy of these methods in silico, finite element models (FEMs) of a sideways fall simulator have been developed [2], which consider the important role of impact loads to the femur as well as the load attenuation contributions from the soft tissue and pelvis. The purpose of this study was to use the FEMs to examine the fracture outcomes and changes to femoral loading capacity for several different femoral augmentation strategies.

Methods
Validated unaugmented FEMs of five specimens (age 68-94 years) which had fractured in ex vivo experiments [3] using a sideways fall simulator were used as controls. Three treatments (Figure 1) were applied to each of the specimens: the implantation of a fracture fixation nail [4], a bulk hydroxyapatite injection [5], and the same injection pattern for a novel bone-strengthening hydrogel currently in development. For the hydrogel augmentation, a local BMD increase of 20% was assumed for the affected elements. The impact velocity for all FEMs was 3.1 m/s.

Results
Figure 2 shows the number of fractured femurs for each augmentation method. As expected, all five unaugmented control specimens fractured. The HA injection was the most effective and prevented fractures in all five specimens. The bone-strengthening hydrogel prevented 4 fractures, and the implant prevented 2 fractures. Relative to the unaugmented controls, the peak force at the acetabulum increased by an average of 28.3% for the implant, 35.8% for the hydroxyapatite injection, and 33.7% for the hydrogel injection.

Discussion
This study compared the mechanical efficacy of several proposed prophylactic augmentation methods: the use of a fracture fixation nail, an injection of a ceramic-based hydroxyapatite cement, and an injection of a novel bone-strengthening hydrogel. The injections of the biomaterials prevented more fractures than the implant, possibly because the injections were able to strengthen the bone at the femoral neck cortex, which is typically where fractures initiate [6]. The percent force increase for the augmentation methods were higher than the estimated strength increases from pharmacological treatment, which is approximately 5.3% [7] for an aBMD increase of 3.3% [8]. An advantage of the FEMs is that they allow for the comparison of the effects of controversial interventions in the same subject models. The results and the FEMs could be used to further improve the placement of biomaterials in order to prevent hip fractures due to sideways falls.

References

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DESIGN OF A REVERSE SHOULDER IMPLANT TO MEASURE SHOULDER STIFFNESS DURING IMPLANT COMPONENT POSITIONING

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Introduction
Dislocation of the shoulder joint is one of the more common complications after reverse total shoulder arthroplasty [1], which is often associated with malposition of the prosthetic components [2]. Therefore, achieving sufficient shoulder stability should not be neglected when positioning the implant components. One parameter for assessing shoulder stability can be shoulder stiffness. The aim of this work is to develop a reverse shoulder implant prototype that allows intraoperative measurement of shoulder stiffness while varying the position of the implant components. The measured stiffness could provide a quantitative statement regarding the optimal positioning of the implant components, which can be adjusted accordingly in the final reverse shoulder prosthesis.

Methods
To measure the stiffness of the shoulder joint, it is necessary to record the joint angles and the torques generated during movement. The changes in the rotation angles were measured using 3D hall sensors and magnets. The magnets were placed under the humerosocket, and the hall sensors were integrated into the glenosphere. The strength of the magnetic field was used to determine the position of the humerosocket in relation to the glenosphere. The accuracies of the angle measurements were tested using a test bench (Figure 1).

![Figure 1: Test bench for 3-dimensional angular adjustment of the joint (alpha: abduction/adduction; beta: flexion/extension) Glenshphere with pyramidal arrangement of 4 hall sensors (A0-A3). Three magnets under the humerosocket.](image)

Three thin film pressure sensors were used to record forces at different points under the humerosocket. To obtain a force value from the sensor signal, the sensors were calibrated using a load cell. The variation of the implant components positions was integrated into the prototype implant through different constructive mechanisms to adjust the stiffness of the shoulder joint.

Results
In the range of ±45° flexion/extension combined with ±15° adduction/abduction, the joint position could be determined with sufficient accuracy (error e ≤ 5°). The areas near the combined maximum deflections of ±45° flexion/extension and ±45° adduction/abduction indicate the greatest deviation from the target angle (Figure 2). The force values of the thin film sensors enable the calculation of moments around two axes. As variable component position parameters, the tray offset, the neck-shaft angle and the humerus version were integrated into the implant prototype.

![Figure 2: Angle measurements with four hall sensors](image)

Discussion
Ideally, the accuracy of the angle measurements should only depend on the amount of deflection and not on the direction of deflection. The asymmetric behavior indicates a deviation from the correct positioning of the hall sensors. The application of a calibration matrix could compensate for the measurement errors and could demonstrate the potential of the new method for joint angle measurements. The accuracy of the torque measurements and the functionality of the mechanical arresting mechanisms must be investigated in further studies. Overall, the developed measurement method can help to avoid malpositioning of the implant components in reverse total shoulder arthroplasty.

References
DESIGN AND OPTIMIZATION OF A SIX-BAR LINKAGE TO ASSIST IN THE REHABILITATION OF THE PULP PINCH GRIP IN STROKE PATIENTS

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Introduction
Stroke usually results in neuromotor disabilities that can affect the movement of the fingers. As finger movement is essential for the most basic activities of daily living, there is a strong motivation to focus on finger rehabilitation after injury or stroke [1]. It is well established that repetitive flexion and extension movement of the fingers, even passively, can facilitate neuromuscular re-education, help prevent spasticity and even control pain associated with patients with hand paralysis due to acquired brain damage [2][3].

Figure 1 shows the 3D scanned hand of a stroke patient in two extreme positions of a pulp pinch grip movement. The initial position of the distal phalanx (DP) is defined by points $E_i$ (MIP joint) and $F_i$ (tip of the finger), and the final position is defined by points $E_e$ and $F_e$.

Figure 1: 3D scanned hand of the stroke patient: extended index (pink) and pulp pinch grip (green).

The goal of this work is to design a six-bar linkage intended for implementation in hand-held exoskeletons, which can move the DP from its initial to its final position, mirroring a pulp pinch grip movement.

Methods
Figure 2 shows the six-bar linkage selected for this application, in an arbitrary position defined by the input angle $\theta_2$. The set of parameters that define the geometry of the linkage is shown in Table 1. Some of these parameters are regarded as design variables, whereas others are regarded as derived parameters.

These derived parameters, plus the initial and final value for angle $\theta_2$, can be adjusted in such a way that segment $EF$ of the linkage matches the initial and the final positions of the DP of a 3D scanned finger of a stroke patient, by solving a two-position synthesis problem.

Figure 2: Six-bar linkage under consideration in an arbitrary position defined by input angle $\theta_2$.

Results
The variation of the ten design variables of the linkage using a genetic scheme, and the subsequent calculation of the derived parameters, allows us to achieve an optimum design for this six-bar linkage, which minimizes its dimensions and maximizes its mechanical advantage, so it can be powered by a small actuator.

Discussion
Concern for the quality of life in post-stroke patients and their ability to rehabilitate has gained prominence in recent years. Together, studies on exoskeletons with improved mechanical advantage and ergonomics still need revisions and refinements to adapt them to these special requests. The scanning process and mechanism optimization study shown are tools for the generation of personalized and optimal mechanisms for each patient.

References

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MIGRATION AND TRACTION FORCE CHARACTERIZATION OF PANCREATIC DUCTAL ADENOCARCINOMA CELLS ON STIFFNESS-TUNABLE SUBSTRATES

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Introduction
Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal malignancies [1]. In PDAC, the activation of stellate cells causes excessive production of extracellular matrix (ECM) with subsequent increase of tissue stiffness (Young’s modulus $E_\text{t}=1-4$ kPa in healthy pancreas, $E_\text{t}=4-43$ kPa in neoplastic tissue [2]), highly impacting tissue vascularization and limiting the effect of chemotherapy [3]. Solid stress and cancer-related stiffness are also associated with increased invasive potential. Understanding how PDAC cells respond to tissue stiffness and detecting the key players in the mechanotransduction processes could provide potential candidates for PDAC targeting. Here, we developed and used stiffness-tunable hydrogels and micropillar arrays to investigate in vitro the influence of substrate stiffness on PDAC collective and single cell behavior.

Methods
To mimic the stiffness of healthy pancreas and PDAC, two polyacrylamide (PAM) substrates (PAM low and PAM high, respectively) were fabricated as thin films bound to coverslips, following a published protocol [4]. The effective modulus $E_\text{s}$ of the PAM substrates, without and with a collagen coating, was characterized by nanoindentation tests (PIUMA, Optics11) performed in wet conditions (PBS) at 37°C. Human pancreatic cancer cell line (PANC-1) cells were then seeded on the collagen-coated PAM substrates ($n=3$ for each type), kept at 37°C and 5% CO₂, and imaged every 10 min for 6 h for random migration assays. MtrackJ plugin of ImageJ (NIH) was used to calculate the migration rate $v$ (μm/min) between two consecutive time points. Finally, for characterizing the traction forces exerted by the PANC-1 cells, two polydimethylsiloxane (PDMS) micropillar arrays with different bending stiffness ($k_\text{l}=72.3$ nN/μm and $k_\text{h}=217.2$ nN/μm) were designed (Solidworks) and fabricated by soft lithography. PANC-1 cells were then seeded on the fibronectin-coated micropillars, stained with rhodamine phalloidin after 24h, and after additional 24h fluorescence images were acquired and analysed (ImageJ, Matlab), measuring pillar deflections, and evaluating traction forces ($F$) as:

$$F = k \cdot x$$

(1)

where $k$ is the pillar bending stiffness (nN/μm) and $x$ is the measured pillar deflection (μm).

Results
The PAM low and PAM high substrates, without and with a collagen coating, exhibited effective modulus values in the range of pancreatic healthy and tumor tissue, respectively (Fig. 1A; PAM low: $E_\text{s}=0.56±0.36$ kPa and $E_\text{s}=1.05 ± 0.76$ kPa w/ collagen; PAM high: $E_\text{s}=18.79±5.29$ and $E_\text{s}=15.98 ± 5.08$ w/ collagen). PANC-1 cells seeded on PAM high substrates showed a higher migration rate ($v=0.34±0.004$ μm/min for PAM high; $v=0.18±0.003$ μm/min for PAM low, Fig. 1B). When seeded on micropillar arrays, PANC-1 cells exerted significantly higher mean traction forces on stiffer micropillars ($F=14.2±3.9$ nN for $k_\text{l}$, $F=32.5±9.7$ nN for $k_\text{h}$, Fig. 1C).

Discussion
Nanoindentation tests confirmed the suitability of PAM substrates in mimicking the stiffness of pancreatic healthy and tumor tissue. Biological tests showed that PANC-1 cells migrate faster on PAM high substrates and exert significantly higher mean traction forces on stiffer micropillars, confirming that the physical environment plays a critical role in cell behavior. Thus, the proposed approach could provide further insights into PDAC mechanotransduction processes. Tests on PANC-1 and fibroblasts co-cultures on PAM hydrogels and further micropillar array optimization are ongoing.

References

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MAXIMUM ARM ELEVATION INVOLVES DIFFERENT SPINOPELVIC MOBILISATION MECHANISMS IN THE ASYMPTOMATIC POPULATION

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Introduction

The physiological range of motion of the shoulder complex is limited to 150° [1,2]. Therefore, the possibility to elevate the arms over 150° involves the participation of other joints. Previous studies showed that arm elevation was associated with 3-D rotations of the thoraco-lumbar and cervical spine [1-4]. The kinematics patterns suggest compensation mechanisms between different sections of the spine. To date no studies assessed the spine analytically (vertebra by vertebra). A better knowledge of the 3-D kinematics of the spine during arm elevation should help to understand the biomechanics of arm elevation and better consider the stress on anatomical structures.

Material and methods

Nine right-handed asymptomatic volunteers were included (5 women, 4 men; mean [SD] age 24.9 [3.0] years; mean height 170 [11] cm; mean body mass index 23.5 [2.6] kg/m2). The study protocol was approved by a local institutional review board (CPP-IDFIII, no. 2013-A00660-45). Biplanar X-rays (sagittal and coronal) were acquired in 4 levels of humero-thoracic elevation: bilateral flexion 30° (E30), left arm flexion 140° (E140) and 180° (E180) and 180° elevation in the scapular plane (S180). Pelvis and spine were digitalized, with a template and a detailed 3D reconstruction respectively [3] enabling to compute postural parameters. Friedman’s ANOVA was performed followed by two-by-two Wilcoxon Signed-Rank tests when needed for comparing the mean parameters values in different positions. Variations in the position of the head, pelvis, and vertebrae (C3 to L5) were visualized using simplified geometric models.

Results

Mean sagittal curvatures T1T6 and L1S1 and frontal curvatures T7T12 and L1L5 were not significantly different between the four positions. Significant decrease in mean sagittal curvature C3C7 and T7T12 was observed between E30/E140 and maximal elevation positions E180/S180. All sagittal curvature parameters, regardless of position, had a standard deviation greater than 6° (max. 13°). The frontal curvatures and axial rotations did not exceed 10° in absolute value in 89% and 98% of the cases respectively.

Figure 1 illustrates two distinct examples of pelvis and spine kinematics The pelvis hardly moves for subject 1 while subject 2 leans forward. Subject 1 makes a left lateral bending at E140 and remains upright in the other positions while Subject 2 makes a progressive right lateral bending as the level of arm elevation increases.

Discussion and Conclusion

In this study, asymptomatic subjects were asked to adopt simple, standardized, position of arm elevation. Although a mean pattern of reduction in cervical lordosis and T7T12 sagittal curvature was identified at maximal arm elevation levels, a large variability in strategies was observed. 6/9 subjects move substantially their pelvis, on average forward (2cm from E30 to S180) and without axial rotation. The head was also mobilized but generally within a 5cm displacement limit in the transverse plane. However, 3/9 subjects adopted an unbalanced strategy by not keeping their head above the pelvis (distance between the centre of the acetabula and the odontoid in the transverse plane greater than 5cm). This study shows different pelvis and spine strategies to achieve the same arm position. Our results suggest that sophisticated personalized mechanisms are involved in such simple tasks as arm raising. Further work is needed, through investigations on a larger number of subjects, to identify the morphological, postural and biomechanical determinants of a strategy for this movement, including the upper cervical level.

References

CLASSIFYING PHYSICAL ACTIVITY LEVEL VIA KINEMATIC GAIT DATA

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Introduction
Objective analysis of gait abilities (Gait Analysis, GAn) in clinic is useful for motor assessment and physical activity level (PAL) monitoring in rehabilitation [1]. GAn represents a valuable tool for assessing gait disorders, levels of impairment, and gait parameters that are directly affected by PAL [2]. GAn is based on wearable motion sensors [3] or camera-based systems, generating an extensive set of data difficult to be managed, analysed, and interpreted. Machine Learning (ML) techniques can provide a viable solution to make GAn more manageable in clinic [4]. This study aims to correctly classify subjects’ PAL, via ML techniques driven by GAn data.

Methods
Kinematic gait data were collected from 37 healthy subjects (24 male and 13 female, 23 years old ± standard deviation (std_dev) of 3 years) while walking on a treadmill at natural speed. Motion data were acquired from wearable wireless Inertial Measurement Unit (IMU) sensors using as ground-truth a self-reported questionnaire (International Physical Activity Questionnaire - IPAQ). For each subject, consecutive windows of 6 gait cycles were considered for data augmentation. Statistical feature extraction was performed and reduced to the most significant ones via the Neighbourhood Component Analysis (NCA) [5] (20 features retained from lower limbs). Figure 1 shows the proposed data analysis process.

K-Nearest Neighbors (KNN), Random Forest (RF), Gradient Boosting (GBoost) and Support Vector Machine (SVM) models, have been trained and tested to validate the effectiveness of the approach.

Results
Applying systematic feature selection leads to increased classification performance for the considered models. A 4-Fold Cross Validation evaluated the models’ classification ability on unseen data. Table 1 shows the results in terms of means and std_dev of accuracy.

<table>
<thead>
<tr>
<th>Model</th>
<th>mean</th>
<th>std_dev</th>
</tr>
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<tbody>
<tr>
<td>KNN</td>
<td>0.82</td>
<td>0.06</td>
</tr>
<tr>
<td>RF</td>
<td>0.86</td>
<td>0.08</td>
</tr>
<tr>
<td>GBoost</td>
<td>0.82</td>
<td>0.03</td>
</tr>
<tr>
<td>SVM</td>
<td>0.87</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 1: 4-Fold Cross Validation models’ performances

Discussion
The retained features can be extracted using only seven lower body sensors (pelvis, thighs, shanks, and feet), proving sufficient to predict the PAL with good accuracy. The presented work served as a preliminary test on using ML techniques to extract clinically relevant information from kinematic data for future approaches to discriminate across levels of impairment.

References

Acknowledgements
Many thanks to the participants who contributed to this study, which was fully supported by the Luxembourg National Research Fund (FNR) under the project MEMENTO – Machine Learning-based Markerless gait analysis system for clinical assessment of human motiOn [16749075].
ASSESSMENT OF THE COMBINED EFFECTS OF VALVE PHENOTYPE AND ANEURYSM PROGRESSION ON ATAA HEMODYNAMICS

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Introduction
The presence of a bicuspid aortic valve (BAV), with consequent eccentricity of aortic inlet flow, gives rise to altered aortic hemodynamics. This seems to play a role in the highest prevalence of ascending thoracic aortic aneurysm (aTAA) in BAV patients, compared to subjects with tricuspid aortic valve (TAV) [1]. Characteristics of aortic hemodynamics in presence of eccentric inlet flow in both healthy and aneurysmatic aorta have been widely addressed, while perspective studies that investigate the evolution of hemodynamic patterns concurrently with aTAA progression are still limited. Therefore, the main goal of this study is to assess the role of both TAV and eccentric BAV inflow on hemodynamic results at different stages of aTAA.

Methods
Three geometries representing baseline healthy aorta (A00), intermediate aneurysm growth (A05), and fully developed aneurysm (A10), in a virtual patient from [2], are considered (Figure 1a). Transient computational fluid dynamics simulations are performed using Ansys Fluent (Ansys Inc.). The fluid domain is discretized with approximately 7e5 polyhedral elements. Blood is modeled as incompressible and Newtonian, with \( \rho = 1060 \text{ kg/m}^3 \) and \( \mu = 0.00345 \text{ Pa.s} \). The k-\omega SST model is employed to account for turbulence. A 3-elements WindKessel model is applied at each outlet to obtain a physiological pressure range of 120-80 mmHg [2,3]. A time-space-varying inlet velocity boundary model is implemented to reproduce TAV / BAV aortic inlet condition, resembling physiological data from [4]. A parametrized elliptic area is identified on the aortic valve plane, representing the valve orifice. A paraboloid velocity profile is imposed inside the ellipse, while everywhere else velocity is set equal to zero. An idealized inlet flow rate waveform is defined over a cardiac cycle and the maximum velocity for the elliptic paraboloid at each time step is assigned to achieve the correspondent instantaneous value of flow rate. Two different cases for the inlet conditions are considered: TAV (Figure 1b) and BAV (Figure 1c). Either TAV or BAV inlet conditions are applied at each stage of aneurysm growth to evaluate hemodynamic evolution.

Results and Discussion
In case of BAV phenotype, the inlet flow is concentrated in a small area of the aortic orifice and the maximum inlet velocity is higher.

Figure 1: Aorta segmentation with baseline, intermediate, and fully developed ATAA stages (a); TAV (b) and BAV (c) inlet velocity profiles at peak systole.

This causes the presence of a jet flow that impinges on the aortic wall in correspondence with an area of high wall shear stress (WSS), which is not present in TAV cases where the flow is more spread (Figure 2). At all stages of aneurysm growth, the time-averaged WSS in the ascending aorta are 2.5 times higher in presence of eccentric inflow, in agreement with previous findings [1]. The effects of aTAA bulge formation on hemodynamics results are minor, with variations of 5-7% between different stages for both BAV and TAV. These preliminary results highlight the necessity to account for the eccentric inlet flow when modeling aTAA hemodynamics.

Figure 2: Velocity streamlines (a-b) and WSS (c-d) at peak systole in the ATAA for the TAV (a,c) and BAV (b,d) cases at A05 aneurysm growth.

References

Acknowledgements
This project received funding from the Marie Skłodowska-Curie grant agreement MeDiTATe project no 859836.
AORTIC HEMODYNAMICS EVALUATION BASED ON REDUCED ORDER MODELS: EFFECT OF INLET CONDITIONS

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Introduction

Computational fluid dynamics (CFD) assessment of patient-specific hemodynamics using full order models is a viable tool to gain insights for pathology evaluation, treatment, and prevention [1]. However, its use in clinical practice is hindered by its high computational cost in terms of infrastructures and timing. Moreover, these limitations are reflected in the difficulties to be directly translated to clinicians. In this context, non-intrusive data-driven Reduced Order Models (ROMs) represent a promising tool for facing these limitations, allowing high-fidelity and fast hemodynamic evaluation in a user-friendly setup [2,3]. In this study, a workflow to create a ROM for the evaluation of aortic hemodynamics is presented, with the specific aim to investigate the effect of inlet conditions in case of both tricuspid (TAV) and bicuspid (BAV) aortic valve.

Methods

The geometrical model is obtained by segmenting a clinical CT dataset. The workflow to create and consume the ROM is entirely developed in the Ansys suite. A 3D parametric inlet velocity profile is defined by using a two-dimensional Gaussian function to model BAV and TAV configurations. The following five input parameters are defined and used in the ROM generation (Figure 1): inlet velocity peak ($v_{max} = 0 - 0.6$ m/s) for profile amplitude, standard deviations along major and minor axis ($\sigma_m = 8 - 15$ mm) for profile shape, rotation ($\theta = 0^\circ - 360^\circ$) and eccentricity ($\rho/\bar{\rho} = 0 - 1$) for profile position.

![Figure 1: Input parameters.](image)

Output parameters are velocity magnitude and direction, pressure, and wall shear stress in the whole domain. A set of 104 Design Points (DPs) is defined using an optimal space filling algorithm. For each DP, CFD results are computed, and output parameters are processed in form of snapshots. All the snapshots are then imported into the Twin Builder tool to create the ROM by compressing these data via singular value decomposition.

Results and Discussion

The results produce an interactive and high-fidelity estimation of the CFD solution. Figure 2 shows an example of the interface for ROM consumption provided by Ansys suite. ROM accuracy is evaluated by comparing the approximated solution given by the ROM and the full CFD solution calculated for the same input combination. Table 1 presents the average and maximum relative errors with respect to the full CFD for all the ROM output parameters. Errors remain below 8%, including the maximum values.

![Figure 2: Example of interface for ROM consumption stage: Ansys ROM viewer is used to set input parameters and analyze output parametric results.](image)

<table>
<thead>
<tr>
<th>Velocity</th>
<th>Pressure</th>
<th>WSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg relative error [%]</td>
<td>0.57</td>
<td>0.15</td>
</tr>
<tr>
<td>Max relative error [%]</td>
<td>2.69</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Table 1: Percentage of average and maximum relative errors for the ROM output parameters

The work demonstrates the potential to provide a user-friendly environment where clinicians can set up relevant valvular profile inputs to evaluate hemodynamic results on the aorta almost in real time.

References


Acknowledgements

This study has been partially supported by the Marie Sklodowska-Curie grant agreement No 859836.
INVESTIGATING THE TOOLPATH DESIGN OF 3D-PRINTED PVA CRYOGELS

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Introduction
It is widely reported that connective tissues, such as articular cartilage, have poor self-repair properties, and damage to such tissues has a significant negative impact on patient quality of life[1]. Soft tissues have complex structures and anisotropic mechanical properties that vary greatly depending on physiological function[2]. Owing to challenges with replicating natural tissues, soft tissue damage treatments are currently limited. Hence, there is great interest in researching soft tissue-mimicking materials. Polyvinyl alcohol (PVA) hydrogels have gained significant interest due to their biocompatibility and mechanical properties analogous to those of soft tissues. The mechanical properties of PVA hydrogels can be tailored for different applications[3]. However, challenges exist with constructing 3D tissue-like structures using hydrogels due to their soft and porous structure, and low viscosity[4]. Advances in additive manufacturing (AM) technologies have led to the development of printers with beds that can be chilled to sub-zero (°C) temperatures. These platforms enable the physical cross-linking of PVA hydrogels upon deposition, creating PVA cryogels (PVA-C). Research into toolpath variation and the effect of this on the mechanical properties is limited. In this study, the toolpath design and fabrication of PVA-C, and the subsequent impact on the mechanical properties, will be investigated.

Methods
The digital samples were designed (Autodesk Fusion 360, California, USA), sliced and converted into G-code (REGEMAT 3D designer, Granada, Spain), then customised by differencing the toolpaths, created using MATLAB (MathWorks Inc., Massachusetts, USA). A 11% w/w PVA solution was prepared by dissolving powdered PVA, with a hydrolysis of 99+% and molecular weight of 146-186 kDa, (Sigma Aldrich) in deionised water through autoclaving (one hour at 121°C), and continuously mechanically stirring the solution for two hours – one hour on a hotplate at 50°C, then one hour with the hotplate removed, allowing the solution to gradually return to room temperature). To fabricate the samples, a REGEMAT Bio V1 bioprinter (REGEMAT, Granada, Spain) fitted with a 0.58 mm nozzle was used. The bioprinter bed temperature was maintained at -8°C (+/- 0.5°C) during printing, to enable physical cross-linking of the PVA-C to occur upon deposition. By directly modifying the G-code, different toolpaths were used to fabricate the samples. After the completion of the printing, the samples were subjected to three 24 hour freeze-thaw cycles, undertaken at -20°C and room temperature. To assess the mechanical impact of the change in toolpath design, the samples were mechanically tested using a Bose Electroforce 3200 (TA Instruments, Delaware, USA).

Results
Preliminary results from this study are presented here. Figure 1 shows a CAM digital representation of a toolpath design, based on a sine-wave function. Figure 2 demonstrates a fabricated sample of PVA-C based on an alternating 0° to 90° toolpath.

Discussion
Toolpath design is an integral process parameter in AM. This study has investigated how different toolpaths can be designed and utilized for 3D printing PVA-C. The preliminary results show a sine-wave-based toolpath design, and a fabricated sample based on an alternating 0°-90° toolpath. The potential design options of the proposed technique present huge flexibility in terms of toolpath, material structure and hence the mechanical properties. The capability to add anisotropy into PVA structures, through toolpath variation, will enable the future fabrication of materials which more accurately mimic the mechanical behavior of natural tissue.

References
Introduzione

Gli arti artificiali ossee integrati per amputati transfemorali stabiliscono una diretta connessione tra l'esterno e il corpo del paziente, fornendo molti vantaggi rispetto alle protesi in materiale standard. Tuttavia, simili a protesi non cementate, il rischio di stress risulta minore. Per eseguire il studio, è stato indotto un movimento micrometrico permanente e mensile. Per ridurre i movimenti micrometrici e la migrazione permanente, è stata utilizzata una tecnica digital Image Correlation (DIC). Inoltre, la tecnica DIC è stata utilizzata per valutare la stabilità e la carico trasferito dell'OR 1 e OR 2.

Materiali e Metodi

Un femore umano cadavere è stato ottenuto attraverso un programma di donazione eticamente approvato. La osteotomia, dalle condille, è stata realizzata con un blocco di 200 mm. Il femore prossimale è stato inserito in una matrice. La dimensione della cavità femorale è stata misurata nel livello istmo (ellisse 17x14 mm) da immagini CT (slice thickness=0.6 mm, in-plane resolution=0.5 mm). Un impianto OTN di dimensioni 17 (Badal X, OTN) è stato inserito dopo aver riempito la cavità femorale per garantire il calibro ottimale press-fit. I test sono stati eseguiti con un macchinario di prova uniaxiale (Instron 8500, 10 kN load cell). Un centinaio di ciclo di carico (80-880 N) è stato realizzato a 30 Nm alla osteotomia, in corrispondenza con il calibro. I movimenti micrometrici e strutturali sono stati registrati e analizzati per la distanza e la variabilità. I ricercatori hanno realizzato una mappa per assicurare l'optimal press-fit. I test sono stati eseguiti con un macchinario di prova uniaxiale (Instron 8500, 10 kN load cell). Un centinaio di ciclo di carico (80-880 N) è stato realizzato a 30 Nm alla osteotomia, in corrispondenza con il calibro. I movimenti micrometrici e strutturali sono stati registrati e analizzati per la distanza e la variabilità. 

Risultati

Il campo di errore random era inferiore a 100 µε. Le deformazioni più piccole furono misurate vicino alla osteotomia (median±SD di ROI: ε 1=320±97 µε, Fig. 1b). Le deformazioni più grandi furono misurate distalmente (median±SD di ROI2: ε 1=1300±220 µε). Le deformazioni micrometriche lungo l'asse longitudinale erano superiori a 100 µm e stabili durante tutto l'esperimento. Le deformazioni permanenti lungo l'asse longitudinale erano 2 µm.

Discussione

La mappa DIC completa e gli strumenti utilizzati hanno mostrato che l'inserimento dell'impianto OTN porta a un alto carico di stress nella zona distale del femore e una concentrazione di carico strutturale (al livello del picco). Questa distribuzione strutturale è stata comparabile a quella reportata in un precedente studio sull'impianto transfemorale [1]. I movimenti micrometrici permanenti e i movimenti inducibili sono stati confrontati con i movimenti inducibili che inducono migrare fibrosa formazione [4]. Ciò suggerisce che l'esecuzione di un test in vitro sia stato portato a termine per aumentare il numero di specie.

Referenze


环科识别
AI-BASED GENERATION OF MULTIFARIOUS MEDICAL DATA FOR IN SILICO CLINICAL TRIALS

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1. Department of Biomedical Engineering, Eindhoven University of Technology, The Netherlands; 2. Department of Biomedical Engineering, CARIM School for Cardiovascular Diseases, Maastricht University, The Netherlands

Background
For universal acceptance of a medical product, In Silico Clinical Trials need to test it on a sample population which captures the heterogeneity in the population. Heterogeneity connotes different age groups, gender, and inclusion of pathological conditions. Sample population should preferably include equal number of patients in each of these groups to be statistically significant. However, it is difficult to procure sufficiently large and properly balanced sample sets fulfilling these requirements. Deep Generative Models (DGMs) act as a great solution to all these challenges as they can create well-balanced synthetic datasets. Architecture of DGMs is dependent on the kind of data to be generated. In this study, we therefore developed a new DGM strategy to capture the facets of medical data.

![Image](image1)

Figure 1: Challenges for ISCTs and their respective solutions

Method
Medical data can be classified into three classes: (a) Tabular Data (or One-Dimensional data) ; (b) Medical Images (or Two-Dimensional data) ; (c) Mesh geometries (or Three-Dimensional data). We identified the key requirements for each data type and the important patient-specific parameters for ISCTs. Each DGM framework has been designed based on these requirements to ensure that the generated data is clinically valid.

![Image](image2)

Figure 2: Overview of Deep Generative Models for different medical data

Results
Our observational and contextual assessment showed that class-based attribute learning in DGMs lead to creation of tenable synthetic samples.


Conclusion
Our results show that the DGMs such as Generative Adversarial Networks (GANs), Variational auto-encoders (VAEs) or a hybrid model should comprise facet-based learning potentiality for physiologically relevant sample generation. Further utilization of this surrogate dataset for AI models makes the models robust against privacy attacks.

References

Acknowledgements
This study was supported by the European Commission through the H2020 project “In Silico World: Lowering barriers to ubiquitous adoption of In Silico Trials” (topic SC1-DTH-06-2020, grant ID 101016503).
AUTOMATICALLY DETECTING FATIGUE GAIT BASED ON TIME SERIES BILATERAL PLANTAR FORCE DISTRIBUTION USING DEEP LEARNING ALGORITHMS.

Zixiang Gao¹²³, Yuqi He¹²³, Liangliang Xiang⁴, Gusztáv Fekete¹, András Kovács², Yaodong Gu³


Introduction:
Fatigue caused by long-distance running may induce alterations of distribution in foot mechanics, which can lead to structural overload. Therefore, the effect of running fatigue on plantar pressure has been more attractive. The risk of fatigue gait has been extensively demonstrated in past studies and is accompanied by changes in bilateral plantar pressure distribution. Early running fatigue detection would help training programs to adjust to prevent the increased risk of overuse injuries. The development of artificial intelligence and machine learning enables human activity recognition to be used effectively for action recognition, risk prediction and condition assessment. Although previous research has made great progress in human movement analysis and load prediction, it has not been sufficient the research in the field of automatic fatigue gait recognition. we decided to choose the Convolutional Long Short-Term Memory Network (ConvLSTM) model recently developed by Shi et al. [1] This model can improve the fully connected structure in the LSTM model into a convolutional structure while avoiding the loss of spatial and temporal information of plantar pressure. A aim was to perform automatic recognition of fatigue gait using the Convolutional neural network (CNN) and ConvLSTM deep learning models based on data from bilateral time series plantar forces.

Methods
Thirty healthy male amateur runners were recruited from the university and nearby community to participate in our study. This experiment requires the execution of a running-induced fatigue protocol developed by Koblbauer et al.[2] and 3 times successful tries of dynamic plantar force measurements before and after fatigue using a FootScan pressure plate. A heart rate monitoring band and 15-point Borg scale were applied to monitor and calculate the state of fatigue during the running-induced fatigue protocol. Specific details of the intervention have been described in previous study of Gao et al [3]. the ConvLSTM model improves the fully connected structure in the LSTM model into a convolutional structure (Figure 1). Where \( i_t \), \( f_t \), and \( o_t \) are the input gate, oblivion gate, and output gate of the model, respectively. \( x_t \) and \( h_t \) are the data input at the current moment and the output of the hidden layer at the previous moment, respectively. \( c_t \) is the cell state. The specific operation of ConvLSTM is represented by Equation (1-6).

\[
\begin{align*}
    i_t &= \sigma(W_{xi} * x_t + W_{hi} * h_{t-1} + b_i) \\
    f_t &= \sigma(W_{xf} * x_t + W_{hf} * h_{t-1} + b_f) \\
    o_t &= \sigma(W_{xo} * x_t + W_{ho} * h_{t-1} + b_o) \\
    c_t &= f_t * c_{t-1} + i_t * \tilde{c}_t \\
    h_t &= o_t * \tanh(c_t)
\end{align*}
\]

where \( \sigma \) represents the convolution operation and \( \circ \) represents the Hadamard product.

Results

<table>
<thead>
<tr>
<th>Model</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNN</td>
<td>0.800</td>
<td>0.874</td>
<td>0.718</td>
</tr>
<tr>
<td>ConvLSTM</td>
<td>0.867</td>
<td>0.874</td>
<td>0.859</td>
</tr>
</tbody>
</table>

Table 1: Classification results of total plantar pressure by different algorithms.

The average accuracy, sensitivity and specificity of the 5 test sets are shown in Table 3. The Accuracy of ConvLSTM is 86.7% greater than CNN (80%). Similarly, the Specificity of ConvLSTM is 85.9% greater than CNN (71.8%). However, sensitivity performed 87.4% in both deep learning models.

Discussion
These findings may provide evidence-based information for the assessment of risk factors for unilateral limb overuse injuries and for the early identification of fatigued gait.

References

Acknowledgements
This study was sponsored by the China Scholarship Council (CSC NO.202108330003).
VALIDATION OF HOMOGENIZED FINITE ELEMENT MODELS OF HUMAN METASTATIC VERTEBRAE USING DIGITAL VOLUME CORRELATION

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Introduction
Fragile vertebral fractures in patients with spinal metastases have an incidence of around 15% and significantly decrease patients’ quality of life [1]. Although prevention of these fractures would be of paramount importance, the currently adopted tools are not accurate (below 50% of specificity and sensitivity) enough [2]. Homogenized subject-specific finite elements (FE) models of the vertebrae, once properly validated, could be employed to predict fracture. Digital Volume Correlation (DVC) is a full-field technique that enables the measurement of the full 3D deformation within the bone [3]. These data can be used to evaluate FE models’ ability to predict local displacements and deformations into vertebral structure. Hence, the goal of this study is to present a validation framework where full-field numerical (from FE models) and experimental (from DVC) displacements are compared on multiple vertebrae, some of which with metastatic lesions.

Methods
Two thoracic four-vertebrae human spine segments with metastasis (one metastatic, one control and the two externally adjacent vertebrae) were obtained from an ethically approved donation program. Posterior arcs were removed, and external vertebrae were embedded in PMMA. Specimens were scanned in unloaded and loaded conditions inside a μCT system (Scanco VivaCT80, voxel size 39 μm) and were loaded in axial-compression up to physiological strains in the control (healthy) vertebra [4]. Displacements were measured by DVC with a nodal spacing equal to 50 voxels (DVC uncertainty was in the ranges 3-17 μm for displacements and 91-1030 με for strains). Homogenized linear elastic FE models of the middle vertebrae were generated from the unloaded scan. After computing tissue mineral density from voxels grey values, material properties of the bone were mapped on each element (Bonemat, Istituto Ortopedico Rizzoli) using a density-elasticity equation. The boundary conditions replicated the experimental test: displacements measured by the DVC were trilinearly interpolated and applied on the top and bottom nodes of the models. Numerical displacements predicted by FE model were compared to experimental displacements within a volume of interest selected in the middle third of the models. By differentiating the displacements using the same algorithm for experimental and computational values (Ansys APDL) also principal strain values were compared.

Results
FE- and DVC-derived displacements show a good agreement (Fig.1), especially in the cranio-caudal direction ($R^2 > 0.66, \text{RMSE} \leq 36 \mu m$), with lower accordance for the metastatic vertebrae than for the healthy ones. The FE strain fields instead, although of the same order of magnitude, were poorly correlated ($R^2 < 0.5$) with the experimental ones.

![Fig.1: Scatter plot (a) between experimental (b) and numerical (c) displacements in the cranio-caudal direction for one of the control vertebrae analysed.](image)

Discussion
The aim of this study was to assess the predictive accuracy of homogenized FE models of vertebrae with and without metastases taking advantage from experimental data. Loading the structure through the intervertebral disc allows to analyse larger displacements, keeping away from the uncertainty of the measurement data. The homogenized FE models could predict sufficiently well the experimental displacements, despite the presence of the lesions.

References
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Acknowledgements

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AORTIC SEGMENTATION VIA SYNTHETIC DATA AUGMENTATION STRATEGY FROM PC-MRI SMALL DATASET

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Introduction
Modern non-ionizing imaging methods such as three-directional phase contrast magnetic resonance imaging (3D PC-MRI) have the capability to provide three-directional velocity information throughout the cardiac cycle. The blood flow dynamics at any location in the acquired volume allows the quantification of hemodynamic parameters used in clinical setting for the assessment of cardiac and vascular diseases. Segmentation of 3D PC-MRI is a very demanding processing step due to the nature of the MRI datasets. In literature, several studies have proposed neural networks (NN) to perform segmentation [1] by using large image dataset. However, the availability of large patient data is limited making the training of the NN, a challenging process. The objective of this work is to develop and to evaluate the integration of real and synthetic PC-MRI images to enhance the segmentation of thoracic aorta using DL. The synthetic dataset is created by calculating velocity fields from computational fluid dynamic (CFD) simulations.

Materials and Methods
Synthetic high-resolution (HR) 4D velocity images (Fig. 1a) were obtained by analysing 250 CFD simulations from both healthy and pathological subjects. The CFD simulations are performed on synthetic aortic geometries generated using a Statistical shape model [3] able to cope with the complexity of the entire aorta and to include also the supra-aortic vessels. Transient CFD simulations were performed in OpenFOAM by adopting patient-specific boundary conditions: a 2D velocity profile was imposed at the inlet, while a 3-element Windkessel model was used to control the pressure at each outlet. Each CFD case was processed to obtain the corresponding low-resolution (LR) velocity maps following a four-step procedure [2]. Firstly, a fast Fourier transform (FFT) algorithm has been used to interpolate and filter-out high-frequency noise from the images in the Fourier domain, obtaining half-dimension data, and a zero-mean white gaussian noise was added (Fig.1b). Finally, an inverse FFT was applied to revert to the spatial domain (Fig.1 c-d). A specific 3DU-Net was set up and trained with the related 3D PC magnetic resonance angiography (PC-MRA) datasets combing both synthetics (250) and real (50) cases. A total of 10 real PC-MRA were used as test set. The effect on the DICE score (DS) was evaluated on four different combination of training data: only real data (No_Synth), and three combinations of synthetic and real data namely Synth40_50, Synth40_100, and Synth40_250.

![Figure 1: Workflow for the synthetic dataset](Image)

Results
The results obtained from the trained 3DU-Net, reported as DS score and standard deviation (SD) values, show an improvement in the segmentation performance in all the synthetic augmented cases compared to the only real one. Among all of them, the best accuracy improvement between augmented and only real training results was 28% and 20% for DS and SD respectively (Table 1).

<table>
<thead>
<tr>
<th>Method</th>
<th>Volume_R</th>
<th>Volume_S</th>
<th>DS</th>
<th>SD</th>
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</table>

Table 1: DICE scores. N.B: Volume_R = Real volumes, Volume_S = Synthetic volumes

Discussion and Conclusions
The findings show the benefits of using synthetic data augmentation for the 3DU-Net segmentation task. By expanding the synthetic dataset and utilizing novel synthetic data creation techniques.

References

Acknowledgements
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Deep Learning Thoracic Aorta Segmentation for Feature Extraction and Hemodynamic Analysis from 3D PC-MRI

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Introduction
The analysis of blood flow and of the morphological features plays an important role in the understanding, evaluation, and prevention of cardiovascular diseases. Currently, three-dimensional (3D) phase contrast (PC) magnetic resonance imaging (MRI) has seen broad clinical acceptance for the visualization and quantitative evaluation of blood flow in the heart, aorta and large vessels [1]. At the same time 3D PC-MRI allows the reconstruction of the anatomical structures. However, the associated segmentation process is high time consuming due to the image’s quality and their spatial resolution. Recently, to overcome this limitation, 3D PC-MRI-based segmentations of the aorta using deep learning neural network was proposed [1-2] by processing 1018 and 205 datasets, respectively. In this work, we propose a novel and optimised AI-based multidomain pipeline for the automatic segmentation of the thoracic aorta (TA) from 3D PC-MRI images and for the extraction of the patient-specific hemodynamic and morphological features.

Materials and methods
A collection of 50 3D PC-MRI volumes were acquired by two different clinical scanners: a 3 T Philips Ingenia scanner (Philips Healthcare) (N = 24), and a 1.5 Optim MR450w (GE Medical Systems) (N = 26). The acquired volumes cover the whole thoracic aorta. Magnetic Resonance Angiography (PC-MRA) images were generated for each patient and manually segmented to identify the thoracic aorta (TA). An automated segmentation system, using a 3D U-Net implemented with Tensorflow and Keras libraries, was trained to segment TA from the PC-MRA images. The system was tested using 10 PC-MRA images and generated patient-specific surfaces. A tool was developed using mainly the PyVista library to extract geometric and hemodynamic features from the patient-specific TA geometry and PC-MRI data respectively. Moreover, the tool accounts for a specific module that allows for the computation of MRI Wall Shear Stress (WSS) with different interpolation methods [3]. All the features were mapped for each phase of the cardiac cycle on the segmented volumetric mesh volume and on a customizable number of slices along the centerline of the geometry.

Results
The developed U-Net was tested on a test dataset. A mean DICE score (DSC) of 0.80 was measured. Fig.1d and Fig.1f show respectively the network segmentation and the characteristics that were retrieved for the given geometry. The results indicate how the general trend of the flow curves, flow value ranges and WSS correspond to the physiological examples presented in the literature for TA [4].

Discussion
In clinical practice, segmentation processes that are manual or semi-automatic take a lot of time and effort. Furthermore, specialized software that isn’t always user-friendly is needed for the examination of hemodynamic characteristics. The suggested pipeline was created as a small, efficient stream of connected, sequential processes that automate and customize the extraction of geometric and hemodynamic parameters as well as the automatic production of vascular surfaces that are patient specific. Segmentation accuracy of the 3D U-Net, even if on a smaller dataset, obtained comparable results to [1] (0.951 DSC) and [2] (0.91 DSC).

References

Acknowledgements
MediTaTe Project has received funding from the EU’s Horizon 2020 research (No. 859836)
ELUCIDATING THE MECHANICAL SIGNATURE OF DIFFERENT BRAIN LESIONS USING DYNAMIC NANOINDENTATION

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Introduction

The mechanism of human brain lesions, their growth, heterogeneity, and resistance to medications is driven by the dynamic interaction of mechanical cues between the diseased tissues and their surroundings. Elucidating the impact of these mechanical parameters on different brain lesions could lead to developing novel diagnostic techniques [1,2]. This study investigates the viscoelastic properties of healthy and diseased brain tissues, including epilepsy, glioma (malignant tumour) and meningioma (benign tumour), using dynamic nanoindentation in terms of storage and loss modulus.

Methods

The brain samples were obtained from two subjects diagnosed with glioma (5M and 48M) and two diagnosed with meningioma (27F and 52M). Two samples (healthy and diseased) were collected from the surgical excision of an epilepsy patient (19M). The Institute Ethics Committee (Ref. no. IEC-842/07.08.2020) approved this study; written consent was obtained from all subjects. We used iNano (KLA Inc. USA) nanoindenter equipped with a 100 µm diameter flat end indenter, 50 mN actuator and a temperature-specific liquid bath chamber. It utilises the continuous stiffness measurement method to calculate the viscoelastic parameters [3]. All the samples were tested within 3 hours post-operative surgery at physiological body temperature (37°C) submerged in normal saline solution. The Oliver-Pharr method was used to calculate the storage G’ and loss modulus G’’.

\[
K_s = \frac{F_0 \cos \phi}{x_0} \quad \text{in-contact} \quad \frac{F_0 \cos \phi}{x_0} \quad \text{out-of-contact}
\]

\[
D_s \omega = \frac{F_0 \sin \phi}{x_0} \quad \text{in-contact} \quad \frac{F_0 \sin \phi}{x_0} \quad \text{out-of-contact}
\]

\[
G' = \frac{K_s (1 + \nu)}{2d} \quad G'' = \frac{D_s \omega (1 + \nu)}{2d}
\]

where \(K_s\) is contact stiffness, \(D_s \omega\) is contact damping, \(F_0\) is applied oscillating force amplitude, \(x_0\) is the recorded oscillating displacement amplitude, \(\phi\) is the phase lag between force and displacement, \(\nu\) is Poisson’s ratio (considered 0.5), and \(d\) is the indenter diameter.

Results

We conducted dynamic nanoindentation on human brain samples, including those from patients with epilepsy, glioma, and meningioma. Our measure reported the diseased tissues to be stiffer than healthy tissue. The storage moduli of epilepsy, glioma and meningioma tissue were 300%, 64%, and 18% higher, whereas loss moduli were 354%, 46%, and 10% higher than healthy tissue, respectively.

![Figure 1: Viscoelastic parameters of healthy and diseased brain tissues.](image)

Discussion

This study evaluates the viscoelastic properties of healthy and diseased brain tissue and found significant differences in their stiffness. The primary cause of these differences is the microstructure alteration of diseased tissue. Overexpression of high molecular polysaccharide (hyaluronic acid) in glioma cells, procollagen molecules secreted to produce the fibrous structure in me, and abnormal arrangement of neurons in epilepsy make them stiffer than healthy brain tissues [1,4]. These findings will provide a deeper understanding of the mechanical behaviour of brain tumours and have the potential for developing improved diagnostic and treatment strategies based on mechanical signatures. However, further research with larger sample sizes is required to generalise these findings. Additionally, the use of in-vitro mechanical markers, combined with machine learning-based approaches, could potentially classify brain tumours with greater accuracy.

References


Acknowledgements

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Introduction

More than 10 % of the world population suffers from severe periodontitis with a high risk for teeth lost due to the periodontal supporting tissue damage. Currently, regenerating the periodontal ligament (PDL), connecting the bone to the tooth, remains a real technical and clinical challenge. In that context, periodontal tissue engineering appears as a relevant strategy. Providing and efficient in vitro engineered PDL relies on the suitable definition of the scaffolds and the applied cues. While periodontal cell stimulation in vitro is generally addressed through biomechanical signaling, biomechanical cues are known to play a determinant role in the PDL integrity1. In vivo, periodontal tissues are subjected to a complex masticatory cyclic biomechanical loading. Nevertheless, the few studies investigating the potential of human periodontal cells (PDLCs) mechanical stimulation in vitro were designed to better understand orthodontic tooth movement, hence involving a static loading. A study investigated the influence of a cyclic loading on PDLCs within a dynamic bioreactor2. But in this study, cells were seeded within a collagenous gel that may not be suitable regarding load transmission. While, many efforts are made in developing fibrous scaffolds, more representative of the fibrous PDL nature3. Regarding periodontal biomechanics, polycaprolactone (PCL) is known to have relevant properties4. In that context, the objective of the current study was to assess the potential of a 3D PCL fibrous scaffold to promote PDLCs mechanobiological behavior.

Materials and methods

Human PDLCs were seeded (10^4 cells.mL^{-1}) in a 3D PCL scaffold fabricated through electrospinning with a ring geometry to mimic the PDL geometry. (Figure 1). The loaded group (n = 3) was subjected to a static pre-load for 10 days followed by 11 days under a cyclic axial compressive loading, with a 100 µm displacement and 0.5 Hz frequency. A static group (n = 3) and a control group composed of scaffold without cells (n = 3), were let under static condition in the culture media during 21 days. The stiffness relative difference between day 0 and day 21 calculated. Parallelly, the relative difference of ALP activity and IL-6 protein amount were quantified at day 11 (starting day of the cyclic loading) and at day 21 (end of culture). The scaffolds were also observed using confocal microscopy. Three experimental series were performed, for a total of 9 (3x3) samples in each group.

Results and discussion

While the scaffold stiffness of the control group (without cell) only slightly decreased during the 21 days of incubation (-11 %), a significantly larger decrease, compared to the control group, was observed for the loaded and static groups (-37 % and -38 %, respectively, p-value ≤ 0.01, Mann-Whitney). The ALP activity and IL-6 concentrations decreased after the cyclic loading but increased in static conditions between day 10 and day 21. Confocal observations showed a layer of cells on the static scaffold surface (Figure 1, right). Only some isolated cell nuclei were observed on the loaded scaffold surface. Following this result, cells within scaffolds were counted after cells harvesting and detachment using trypsin-EDTA. In average, 15.10^4 and 6.10^4 cells.mL^{-1} were counted on the static and the loaded scaffolds after 21 days of culture, respectively, which confirms the presence of cells on both groups. Together, these results strongly suggest that the cyclic mechanical loading has an influence on PDLCs behavior. This validates the PCL fibrous scaffold capacity to transmit the mechanical loading to the cells. As a perspective, to evaluate the PDL in vitro engineering potential, a more physiological loading will be applied to a cell-seeded fibrous PCL scaffold with an architecture close to the PDL architecture.

Acknowledgements

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WINDSURFING BIOMECHANICS: FROM A SINGLE GOPRO TO MARKERLESS MOTION TRACKING AND PERFORMANCE ASSESSMENT

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Introduction

IQFoil windsurfing is a new type of Olympic windsurfing sport. Interestingly, there are limited publications that focus on the biomechanics of windsurfing in general and specifically in IQFoil windsurfing [1]. In this study, we will collect data in real-life conditions of windsurfing training sessions with the use of action cameras and wearables and develop an algorithmic flow to automatically synchronize, process, and analyze both sensor data and videos (markerless motion tracking). Thus, comparisons in speed, body, and board movement between multiple athletes will be possible. Therefore, the aim of this study is to quantify important data driven sports performance metrics for multiple athletes at the same time in real-life scenario trainings under the same surfing conditions.

Methods

Eight Olympic level athletes (4 M (male) and 4 F (female)) completed two windsurfing training sessions that lasted for about an hour each. The athletes performed various speed tests in a specific setup given by the coach and repeated the setup multiple times with a 4-minute break between each race. A GoPro camera was placed and mounted on the front of each IQfoil board, and the IMU data were extracted from the action camera videos using gpmf-parser [2].

An algorithmic flow was designed and implemented to synchronize, denoise, and analyze the data. Data analysis included estimation of wind direction, labeling of GPS segments as “upwind” or “downwind” accordingly, and calculating board rotation features such as roll and pitch per segment. Markerless motion tracking motion of the athletes on the segmented data was carried using an automatic pipeline, that merges all the training videos and extracts the body key-points using the OpenPose [3]. Subsequently, each type of motion (pumping, turning, high speed moments etc.) was tagged automatically in the video and used for post processing and visual purposes.

Results

Average downwind and upwind speeds of the male and female groups are shown in Figure 1 (A). Downwind presented higher speeds compared to the upwind condition (P=0.0009). Average knee flexion angles are presented in Figure 1 (B). The average KFA were significantly (P=0.036) higher (33.56 ± 5.75) under downwind compared to upwind (26.45 ± 6.47).

![Figure 1: (A) Average GPS speed (knots) from each sailing segment for two different sailing directions (upwind/downwind) for each athlete (M-Male, F-Female). (B) Right knee flexion (degrees) for the same configuration as the (A). (C) Snapshot frame from the video markerless tracking.](image)

Discussion

Action cameras and wearable sensors were used to collect data in real life environments, enabling us to leave from the laboratory to collect motion data. An algorithmic flow has been presented to synchronize all the data sources together and extract features related to the athlete’s and board movement. This is the first study, known to the authors, that collected and analyzed real life windsurfing (IQfoil) data from elite level athletes using wearable sensors. Future directions include further investigation of different kinds of motion movements (pumping, maneuvers etc.), heartbeat smartwatch data analysis and IMU sensor placement on the athletes for more accurate biomechanical and biomarker analysis.

References

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EFFICIENT COMPUTATIONAL METHOD FOR ADJUSTING THE STIFFNESS OF INDIVIDUAL 3D-PRINTED INSOLES

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2. Institute for Polymer and Production Technologies e.V., Germany

Introduction

Diabetes-adapted insoles are crucial for adequate and consistent distribution of plantar pressure. The International Working Group of Diabetic Foot recommends adjusting the stiffness of the insoles based on the plantar pressure distribution during gait [1]. Most Finite-Element (FE) models that simulate gait are too complex for clinical practice by implementing detailed geometries and muscle forces [2]. Therefore, the aim of our present study was to introduce an efficient computational method to adjust the stiffness of individual 3D-printed insoles during gait.

Methods

Medical image data of a subject (female, 27 years old) without diabetic foot syndrome was used to generate the individual left foot and a simplified skeleton geometry (one geometry). The shape of the sole was adapted to the subject’s foot by means of CAD, for which 3D scan data of the foot was used. The designed insoles were then additively manufactured from the thermoplastic copolyester with a gyroid filling structure and a filling of 20%. A 3D gait analysis including sole pressure measurement was carried out with the additively manufactured insole. The data from the pressure measurement was used to validate the FE model. Afterward, the ground reaction forces and marker trajectories obtained from the 3D gait analysis are imported into a musculoskeletal multibody (MMB) model (AnyBody Technology, Aalborg, Denmark) to calculate ankle joint reaction forces and moments during the gait. Subsequently, the FE model was created in Abaqus (Dassault Systèmes, Vélizy Villacoublay, France) from the geometries and boundary conditions obtained. Two time points were analyzed, the early and late mid-stance phases (Fig. 1).

The stiffness of the individual insole was adjusted in areas where high plantar pressures occurred by applying soft insole plugs (>100 kPa). Three different Young’s moduli were analysed in these areas (0.5 MPa, 1.0 MPa, 1.5 MPa) (Tab. 1).

Results

Validation shows a difference of 234 kPa between the experimental and simulated plantar peak pressure at the first high point and 30 kPa at the low point of the vertical ground reaction force. Adjustment in stiffness in areas with plantar pressure greater than 100 kPa resulted in a plantar reduction of approximately 16% to 26% by using a Young’s modulus of 0.5 MPa.

Discussion

Due to the observed deviation between the experimental and the numerically calculated peak pressure in the plantar, it is hardly possible to determine the quantitative reduction of plantar pressure by FE modeling. However, the areas of high plantar pressure can be identified, enabling the adjustment of the stiffness during gait by means of parameter analysis. By calculating joint reaction forces and moments using MMB modeling as boundary conditions, our presented method is time-efficient compared to FE models, where muscle forces are applied directly.

References


Acknowledgements

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Figure 1: Plantar pressure distribution [MPa] of the left insole (view from above) during the first peak (a) and low point (b) of vertical ground reaction forces and the partitioning of the insole.

<table>
<thead>
<tr>
<th>Area</th>
<th>1.5 MPa</th>
<th>1.0 MPa</th>
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<tbody>
<tr>
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<td>-13.01</td>
<td>-22.96</td>
</tr>
<tr>
<td>Lateral</td>
<td>-4.44</td>
<td>-8.15</td>
<td>-16.30</td>
</tr>
<tr>
<td>Midfoot</td>
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</tr>
<tr>
<td>Lateral</td>
<td>-6.78</td>
<td>-10.17</td>
<td>-16.95</td>
</tr>
<tr>
<td>Forefoot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toe</td>
<td>-11.30</td>
<td>-17.39</td>
<td>-26.09</td>
</tr>
</tbody>
</table>

Table 1: Percentage reduction of the peak plantar pressure depending on the Young’s moduli 0.5 MPa, 1.0 MPa and 1.5 MPa of the corresponding soft insole used compared to the peak plantar pressure.
Introduction
Instability in the glenohumeral joint (GHJ) can be caused by muscle imbalance and weakness related to rotator cuff tears (RCT), which can lead to abnormal movement of the joint and further pathologies [1]. The goal of this study was to understand the effect of RCT on the GHJ biomechanics in an ex vivo model, specifically during a 30° abduction test with additional weights simulating in vivo load-bearing situations. We investigated superior-inferior GHJ translations in shoulders with RCT and active muscle forces that occur during this motion.

Methods
In this ex vivo study, ten human shoulders were placed into an advanced muscular, force-controlled shoulder simulator. The rotator cuff (RC) – with two attachment points to the subscapularis (SSC) – and other glenohumeral tendons as the deltoid – with attachment points on the clavicula (DELTant), acromion (DELTmid) and latissimus dorsi were connected to a motorized pulley system. The shoulders were tested in a 30° scapular plane abduction-adduction cycle, simulating motion with an intact RC and different types of RCTs (supraspinatus (SSP), superior portion of SSC (SSCsup), infraspinatus (ISP), SSP&SSCsup, SSP&ISP and ISP&SSCsup&ISP) at four different weight levels (0 –3 kg additional weight). The position of the GHJ center (GHJC) was determined using the instantaneous helical axis method. Linear regression models for each type of RCT were used to determine the effect of weight on GHJC motion (log10(x + 1) transformed). The muscle forces during abduction were summarized in a boxplot at 30° abduction.

Results
During loaded abduction with additional weights, the average superior translation of the GHJC with an intact rotator cuff ranged from 3.3 to 6.8 mm. In shoulders with simulated SSP&SSCsup&SSP, the average superior translation ranged from 4.0 to 9.3 mm. The results also showed that the superior translation of the GHJC was significantly affected by the weight-induced load in both RC intact shoulders (p=0.024) and shoulders with SSP&SSCsup&SSP tear (p=0.004; Fig. 1). Generally, the median and variability of the muscle forces increased with increasing weight (Fig.2, DELTmid as an example). A decrease of the DELTmid, DELTant and SSC was observed in the SSP tear.

Discussion
In our laboratory setting, both the presence of RCT and additional weights increased GHJC superior translation during abduction and thus the instability of the joint. Most curiously, the SSP tear reduced the muscle activations, however, the GHJC translation was increased in this tear type compared with the intact RC. It seems that the muscle activations were reduced at the expense of the GHJC translations. Based on our results, the DELTmid is the main compensating muscle for RCT and for additional weight during abduction. This also agrees with Moroder et al. [2]. Shoulder biomechanics is compromised in RCTs and potential overload of compensating muscle should be monitored in affected patients.

References
ANATOMICAL RISK FACTORS INCREASING PATHOLOGICAL GROWTH IN CRANIOSYNOSTOSIS

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Introduction

Craniosynostosis (CS) are rare diseases caused by the premature fusion of cranial sutures and lead to cranial deformations. The surgical treatment avoids neurological and aesthetical problems. The main types are based on the 4 main sutures affected: sagittal, metopic, coronal or lambdoid. However, clinical subgroups were described depending on the timing of the suture fusion and the fusion of secondary sutures (fronto-parietal, squamous, lambdoid, parieto-mastoid and anterior base) [1-2]. The impact on the severity of the deformation is not known although it could have an impact on diagnosis and the surgical method applied [1]. Statistical methods are impossible due to the low number of patients and the high radiological readings. Many Finite Element Models (FEM) of pathological growth due to CS were developed [3-5]. However, input parameters in the models were very different as there is no consensus on pediatric material properties, bone thickness and growth mechanisms. The models are hard to compare. Furthermore, none try to analyze the sub-populations.

The aim of this study is thus to develop a parametric FEM capable of simulating multiple types of craniosynostosis and its sub-groups.

Methods

A parametric model was developed on MATLAB by simplifying the cranial vault geometry as a cut ellipsoid. 45 geometrical parameters were used to dimension the ellipsoid and model the bones, main and secondary sutures and fontanelles at each suture intersection. 18 mechanical parameters described the Young modulus of each part (fixed Poisson ratio of 0.28) and the applied pressure was calculated to obtain a logarithmic normal volume growth between 3 and 15 months. Two temporal parameters establish when the suture limits transform into bone (normal suture growth) and when an affected suture transforms into bone (craniosynostosis). The base of the skull was fixed at the center while the rest of the nodes could translate on the cut plane. The simulations were run on Radioss implicit solver. A convergence study was conducted on the mesh size and a sensitivity study analyzed the impact of parameter choices on growth results.

The normal growth model was evaluated using the final volume and shape comparison with a previously developed statistical growth model. The different cases were compared to the validated normal growth model in terms of deformation and strains at the sutures.

Results and Discussion

The geometrical parameters were chosen to fit a mean vault at 3 months. A model with 982 elements was chosen thanks to the convergence study. The sensitivity analysis lead to the choice of parameter values including a suture width of 0.5 mm, Young modulus of 200 and 3000 MPa for sutures and bones. The pressure P was applied such as P=1.28*log(time_step) + 5092, to obtain the clinically observed volume change during growth.

Figure 1: Normal volume comparison from clinical data (blue) and FEM results (black)(A). Initial FEM geometry (B). Deformation for partial (C), complete (D) fusions of the right coronal sutures with the right fronto-sphenoidal (E) and the right base sutures (F) compared to normal growth, antero-superior view.

The deformations for all CS cases were comparable to clinical observations, except for metopic synostosis. Compensatory growth were under-evaluated. The study showed that fusion of the secondary sutures had a significant difference on the deformations observed, with little differences on contralateral suture strains.

Conclusion

The present study shows how FEM can help clinical classification and the surgical procedure applied [1], especially when statistical methods are not applicable. The under-evaluations were similar to the ones found in previous FEM [3-5] and are in regions not affected by surgery. Yet they show that growth mechanisms are still misunderstood.

References

HEEL PAD COMPRESSION AND IMPACT DURING GAIT USING ULTRASONOGRAPHY AND IMU SENSORS: A PILOT STUDY

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Introduction

In-vivo measurements of heel pad compression during gait are scarcely described. Contrasting current methods [1,2], our custom-made walkway images the heel pad in-vivo and non-invasively during gait using a receded ultrasound transducer [3]. IMU sensors allow for concurrent measurement of lower extremity loading parameters [4]. We aimed to determine associations between heel pad compression and impact parameters during gait in a healthy population.

Methods

Sixteen healthy participants were positioned at the start of a 5.5m long walkway such that the left heel fully hit a receded ultrasound transducer (Philips Lumify) after 3.5m while walking barefoot at comfortable speed.

Ultrasound videos enabled measurements of heel pad thickness (HPT) as the shortest distance between skin and calcaneus (Fig.1) in 2 conditions: unloaded (HPTU) and maximally compressed during gait (HPTC). Heel pad compression (HPC) was calculated by subtracting HPTU from HPTC. HPC relative to HPTU was presented as HPC%

Results

All participants (age: 29.9±9.9 years, weight: 73.9±12.0 kg, height: 1.75±0.09 m, BMI: 24.2±2.9) completed the protocol. Outcomes (Table 1) were normally distributed. HPTC differed significantly from HPTU (p<0.001). Figure 2 and Table 2 show correlation outcomes.

Discussion

Heel pad compression and impact parameters correlated positively, indicating a complementary attenuation mechanism. As expected, compression also positively correlated with peak tibia acceleration.

To further investigate the relation between HPC% and PAR, we recommend to study the association between the change of these parameters at different gait speeds.

Limitations include two-dimensional assessment of heel pad compression, altered gait patterns due to aiming for the transducer, and barefoot assessment on hard surfaces might not generalize well to daily life situations.

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ASCENDING AORTIC ANEURYSM GROWTH PREDICTION BASED ON MACHINE LEARNING AND SHAPE FEATURES DERIVED FROM 3D SLICER

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Introduction
The ascending aortic aneurysm (AsAA) is a dilatation of a weakened part of the ascending aorta (AsA). The surgical decision for non-urgent cases is based on the maximum diameter assessment. The threshold is generally fixed at 55 mm [1]. Unfortunately, this does not seem to correctly reflect the AsAA patient’s risk of rupture [2]. In fact, patients with rapid growth of the aortic diameter (≥3 mm/year) should be considered for preventive surgical replacement [3]. In this regard, the research is now focused on determining new biomarkers able to predict the AsAA growth and developing user-friendly virtual environments for their detection. In this work, we present a machine learning (ML)-based method of predicting the AsAA risk of growth using as input 4 local shape features computed on the AsA geometry through a dedicated 3D Slicer extension.

Materials and Methods
A retrospective dataset including 50 patients with at least two pre-operative acquisitions (CT-Scans and/or 3D MRI) was used. An extension in the 3D Slicer environment based on Python, VTK and VMTK was developed to automatically pre-process the geometry and compute the following shape features (Figure 1):
• the maximum AsA diameter D;
• the ratio DCR between D and the length of the ascending aorta centerline C;
• the ratio EILR between the length of the external curvature line (ECL) and the internal curvature line (ICL);
• the tortuosity T defined as the ratio between the length of C and the length of the segment C₀ that connected the first and last points of C.

After, by exploiting the longitudinal acquisitions, a linear growth rate (GR) was calculated for each patient:

\[ GR = \frac{D'' - D'}{\Delta t} \]  

(1)

where \( \Delta t \) is the time interval between the first and second acquisition, \( D' \) is the diameter D related to the first exam and \( D'' \) to the second acquisition. The dataset was divided into two classes: the patients with \( GR \leq 3 \) mm/year composed the low-risk group (41 patients) while the others represented the class with rapid growth. Five different ML classifiers were trained with the shape features derived exclusively from the first exam as input and cross-validated to predict each patient’s belonging class. They were: decision tree (DT), logistic regression (LR), naive bayes (NB), support vector machine (SVM) and k-nearest neighbours (KNN). The classification performances were assessed reporting accuracy (ACC), sensitivity (SE) and specificity (SP).

Results
The classification performances are given in Table 1. SVM presented the best accuracy and specificity and together with LR and NB the best sensitivity.

<table>
<thead>
<tr>
<th></th>
<th>DT</th>
<th>LR</th>
<th>NB</th>
<th>SVM</th>
<th>KNN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC (%)</td>
<td>86</td>
<td>88</td>
<td>92</td>
<td>96</td>
<td>90</td>
</tr>
<tr>
<td>SE (%)</td>
<td>55.6</td>
<td>66.7</td>
<td>66.7</td>
<td>66.7</td>
<td>55.6</td>
</tr>
<tr>
<td>SP (%)</td>
<td>92.7</td>
<td>92.7</td>
<td>97.6</td>
<td>100</td>
<td>97.6</td>
</tr>
</tbody>
</table>

Table 1: Classification performances

Conclusions
The results show how the analysis of the AsA geometry could be crucial in predicting the aneurysm growth. Integrating more patient data and results from numerical simulations could help to identify aortic shapes potentially at risk of rupture.

References

Acknowledgements
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 859836.
Introduction

The approach of using in-silico models based on computer-aided engineering (CAE) to study diseases, suggest treatment strategies and predict surgical outcomes proved to be crucial in supporting the clinical staff [1]. However, the high numerical complexity and computational cost still represent a challenge with respect to the exploitation of such results. To overcome these limitations, new methods based on medical Digital Twins (DTs) are under development. DTs are virtual replicas of physical systems able to digitally replicate their behaviours providing a connection between the physical entities and the corresponding digital models [2]. In this work, we describe the techniques we use to build medical DTs and their application to two clinical cases: the drug-delivery simulation of the airway system and the determination of the effect of an exertion activity on the ascending aortic aneurysm.

Materials and Methods

The first step for building a medical DT based on simulation results involves data collection and image segmentation techniques to extract the geometry. A prerequisite is in fact having a high-fidelity model with accurate and calibrated boundary conditions able to represent the physics of interest, possibly validated with experimental data and medical images. A DT can be derived from both steady-state simulations generating static output fields (snapshots) and transient simulations providing time-varying results (scenarios). Physical parameters like pressures and flows but also geometric parameters altering the model shape can be identified. When implementing shape modifications, the mesh topology must be preserved and radial basis function (RBF) mesh morphing techniques [3] can be used. If real-time interaction with the system is required and a compromise in terms of minor loss of accuracy can be accepted, the adoption of reduced order models (ROMs) offers the possibility to save computational time [4]. They exploit data compression techniques such as Singular Value Decomposition (SVD) or Proper Orthogonal Decomposition (POD). Before the Digital Twin deployment, quality assessment and cross-validation of the ROM are necessary. Finally, dedicated visualization and consumption tools should be prepared to ensure the user’s interaction with the twin.

Results

Two demonstrators are proposed using these techniques. The first DT is developed to monitor the effects of drug inhalation. It is built using the commercial software Ansys Static Rom Builder by combining shape parameters related to the geometry of the airways and the drug particle size with physical parameters such as the inlet flow rate.

The second application is based on Ansys Dynamic ROM Builder and derives from fluid-structure interaction analyses. By combining an accurate patient-specific model and real-time retrievable data such as blood pressure and heart rate under conditions of physical exertion, it allows the observation of clinically relevant results at the aortic wall for the study of the aneurysm growth and rupture.

Conclusions

Results from DTs based on these techniques can be derived in almost real-time while high-fidelity simulations often require hours or days. The successful implementation of the proposed methodology suggests that it could be successfully exploited to assist the DTs generation and fruition in clinical applications.

References


Acknowledgements

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 859836.
DETERMINING STRESS RELAXATION OF TRABECULAR BONE TO SIMULATE PRESS-FIT CONDITIONS FOR CEMENTLESS IMPLANTS

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Introduction
Accurate modelling of bone-implant interfaces and the primary stability of implants depends on accurate material properties. The trabecular bone is generally modelled as a linear elastic material, while in reality the mechanical response of trabecular bone is time-dependent. Therefore, bone should be modelled as a viscoelastic material, with a response that varies with strain level. To our knowledge, nonlinear stress relaxation of trabecular bone has not yet been quantified in relation to bone mineral density (BMD), which may influence the primary fixation of orthopaedic implants. In this work, we present data of stress relaxation experiments of bovine bone.

Methods
34 Trabecular femoral bovine bone cylinders were harvested. Stress relaxation experiments on 16 samples were conducted by applying a uniaxial compressive strain (0.2 – 0.8%) for 24 hours to determine the test duration for the multiple stress relaxation experiments. The other samples were compressed with 0.2% strain for 30 minutes, after which they were stored to recover for 24 hours. This sequence was repeated on each sample for 0.4, 0.6, and 0.8% strain. Data of the 30 min experiments was extrapolated to 24 hours.

Results
After 24 hours, stress relaxation ranging from 41.0% to 68.7% was observed (Figure 1). Up to 52.9% of this stress relaxation occurred in the first 10 minutes. Extrapolating at different time points showed that accurate predictions could be made at 30 minutes, allowing for reduced experimental testing time.

No relevant relation was found between BMD (Φ) and time-dependent behaviour, which resulted in Equation 1, an adapted multiple superposition model (MSM).

\[ \sigma(\phi, \varepsilon, t) = (A \varepsilon + (B \Phi + D)) \times \varepsilon t^{E \Phi + G} \quad (1) \]

The parameters in Table 1 originate from the repeated stress relaxation data.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>A = 4.34 x 10^4</th>
<th>D = 669.6</th>
<th>G = -0.039</th>
</tr>
</thead>
<tbody>
<tr>
<td>B = -5.14 x 10^6</td>
<td>E = -3.63 x 10^6</td>
<td>F = -1.35</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Parameters for the stress function $\sigma(\phi, \varepsilon, t)$.

The use of Eq. 1 resulted in an average RMSE of 0.91 MPa and is displayed for one sample in Figure 2.

![Figure 2: Experimental stress relaxation in comparison with predictions of Eq 1. Sample has a density of 375.3 mg/cm3.](image)

Discussion
Most of the stress relaxation occurs within 10 minutes, which in clinical practice is still during surgery. However, stress relaxation continued even after 24 hours of testing. It is therefore important to model the viscoelastic behaviour up to 24 hours, which our newly developed viscoelastic model is capable of. The viscoelastic model is able to capture the nonlinear stress dependency and includes the influence of the BMD on the stiffness. BMD did not influence the time-dependent behaviour. Further testing will investigate the relation between BMD and the viscoelastic response for both bovine and human trabecular bone. Incorporating this viscoelastic behaviour in simulations of primary fixation in arthroplasty components will establish the influence of bone relaxation on primary fixation.

Acknowledgements
This collaboration project is co-funded by the PPP allowance made available by Health-Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships, and DePuy Synthes (Leeds, UK).
IN-VITRO AND IN-SILICO MODELING OF THE EFFECT OF GAG ON THE OPENING ANGLE OF THE ASCENDING PORCINE AORTA

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Introduction
Residual stresses (RS) play a vital role in vascular mechanics. RS contribute to the magnitude and intramural distribution of mechanical stresses in vivo, which in turn play an important role in dictating lethal ruptures. Circumferential RS, which can be assessed ex vivo using the opening angle method, remain poorly understood, and the proper implementation of RS in computational models remains an active area of research. Our previous efforts show that the opening angle is highest in the ascending region compared to other regions of the thoracic porcine aorta [1]. This suggests that circumferential RS exist in higher magnitudes in the ascending aorta, which is the focus of this work. Previous reports have also shown that circumferential RS are associated with the intramural extracellular matrix (ECM) constituents, such as collagen, elastin, and glycosaminoglycans (GAG) [1,2]. The purpose of this study was to decipher the extent of contribution of GAG to circumferential RS in the ascending aorta, and to gauge their effect in a computer model.

Methods
In-vitro experimentation involved excising sets of two adjacent aortic rings from the ascending region in 5 porcine aortas. One ring served as a control, while the second ring underwent enzymatic GAG depletion using 15U/mL hyaluronidase, 0.075U/mL chondroitinase ABC, 0.75U/mL heparinase for 48 hours at 37°C. The opening angle was then measured and the sulfated GAG content was quantified.

The in-silico study involved creating a finite element ascending aortic ring computer model using FEBio (https://febio.org/). The model combined an elastic porous solid matrix with the Donnan swelling induced by the presence of fixed charge densities (FCDs), simulating the presence of GAG [3]. The mechanical behavior of the solid matrix was modelled using a Holmes-Mow constitutive relationship, for which material parameters were estimated by curve fitting stress-strain curves obtained from experimental biaxial tests. The dimensions of the rings were acquired experimentally in a previous study [1], from 15 rings of 5 porcine aortas, from which the intramural FCDs distributions were also estimated using the quantified GAG content. The simulated opening angle was finally compared against experimental results.

Results
In-vitro investigations demonstrated that removal of GAG significantly reduced the opening angle in the ascending region by approximately 25.5% (paired sample t-test, p=0.009). In addition, the simulated aortic ring model with embedded FCDs in the solid matrix yielded an opening angle of 37 deg, accounting for 32.5% of the experimental opening angle of control rings in the ascending region, which was about 113.6±16.8 deg.

Discussion
Computer simulations have been found valuable in understanding the mechanics and the physiology of cardiovascular tissue and has the ability to predict ruptures, making it a promising technology for clinical applications. In this work, both in-vitro and in-silico studies demonstrated that GAG contribute to the opening angle of the ascending porcine aorta. The discrepancy between experimental and computational results was minor, as the contribution of GAG to the opening angle was 28.9±12.3 deg experimentally, vs. 37 deg computationally. These results suggest that a significant portion of RS is modulated by the amount of GAG present in the aortic wall, and that their effect on RS should not be ignored in future computer models. While eliciting new inquiries, these findings answer questions which not only contribute to basic science, but may also play an important role, in the longer run, in personalized medicine through computational modeling of vascular diseases.

References

Acknowledgements
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OPTIMIZATION OF TITANIUM SPINAL CAGES TO MAXIMIZE SYNTHETIC GRAFT CONTENT IN COMPOSITE IMPLANTS

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Introduction

Spinal fusion is the current gold standard for treating patients with degenerative disc disease [1]. Titanium alloys are commonly used to make cages for spinal fusion, which are used to keep the disc height stable while the vertebrae fuse together. Materials such as morselized bone may also be added to the cage to enhance its bioactivity. A monetite-based calcium phosphate (MCP) in combination with titanium has demonstrated potentially osteoinductive properties [2], and may be a synthetic alternative to bone graft. Maximizing the ratio of MCP to titanium could be desirable to maximize bone ingrowth and fusion. Further, the calcium phosphate can be incorporated into the cage and stored ahead of surgery. However, due to the brittle nature of MCPs, they cannot be incorporated in current implants effectively. The aim of this study was to topologically optimize titanium cervical spine implants to incorporate a bioactive but mechanically weak material such as MCP.

Methods

An outer geometry was established based on the shape of cervical vertebrae, with a height representing a typical distance between two cervical vertebrae in a healthy spine, as recommended by ASTM F2077. All quasi-static simulations were performed with Ansys (2020).

It was assumed that the Ti-6Al-4V material would exhibit isotropic behaviour and had a Poisson's ratio of $v = 0.3$. The elastic modulus was estimated from tensile testing of additively manufactured samples (power bed fusion with laser beam using Osprey titanium powder, Sandvik AB, Sweden, and an EOS 100, EOS GmbH, Germany), according to ASTM E8/E8M, as this would be the future method for producing the titanium cages. Samples were printed in both the vertical and horizontal direction, to test for isotropy in the printed material.

In the simulations, the bottom and top faces were bonded to stiff plates. Four different loading scenarios were investigated: flexion-extension, axial rotation, and a lateral bending with a compression preload [3]. Compression-shear was also included as part of the ASTM F2077.

To optimize global stiffness, an algorithm based on [4] was applied with an effective stress limit of 0.35 GPa (corresponding to the estimated fatigue life of Ti-6Al-4V [5]). Feature sizes were also limited to 1.5-2 mm to construct a semi-porous cage. The optimization problem was subjected to all the loading scenarios sequentially.

Results

The titanium tensile tests showed no significant difference between the different printing directions, with estimated elastic moduli of 112.5 ±4.9 GPa and yield stress of 1.17 ± 0.05 GPa. These values are comparable to the material property datasheet.

Discussion

Preliminary cage designs, were manufactured to investigate the structure’s mechanical behaviour under different load cases. The results imply that it is possible to produce a cage with a substantial volume for calcium phosphate incorporation. However, the cage requires a feature to allow bone growth from both endplates. Future work includes post-processing, experimental validation using ASTM F2077, and the addition of more complex geometrical features to enable clinical implementation.

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Acknowledgements

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MODELING OF ARTIFICIAL MUSCLE MADE OF A FIBER-REINFORCED CONDUCTING POLYMER FOR BIOMECHANICAL APPLICATIONS

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Introduction

Conducting polymer-based artificial muscle (CPAM) gained popularity in biomechanical applications, like an exoskeleton, drug delivery, cell biology and biomedicine due to their promising low voltage (< 5 V) driven input as well as due to high output force and work density compared to natural muscle [1,2]. The existing models of CPAM use linear stress-strain relations [3]. However, these polymers tend to show nonlinear behavior [4]. Additionally, fiber reinforcement can improve the electrical and mechanical properties of the CPAM [5]. This paper develops a coupled electro-chemo-mechanical model for a fiber-reinforced tubular conducting polymer-based artificial muscle (FTCPAM) using a continuum-mechanics approach. The model predicts the nonlinear response of the FTCAPM. Moreover, the change in fiber properties depicts a transition from swelling to deswelling of the actuator for the same applied voltage.

Methods

Consider the FTCAPM as a working electrode in a general electrochemical cell setup. FTCAPM shows an axial elongation or contraction due to ion diffusion through them with an application of voltage. A coupled electro-chemo-mechanical model for FTCAPM is developed. The model can be represented by three major sub-domains, i.e., electrochemical, coupling, and mechanical. The electrochemical-sub-domain represents the total charge stored in the actuator for an applied voltage. An electrical circuit analogy illustrates the redox reaction, which results in ion diffusion from the electrolyte to the FTCAPM. [3]. In this work, solving the diffusion equation in cylindrical coordinates derives the relation between the output current and input voltage in terms of modified Bessel function, electrical, and geometrical parameters [6]. The steady-state charge stored in the actuator per unit reference volume for a step voltage $V_0$ is given by Eq. (1).

$$Q = CV \left(1 + \frac{(R_0 \bar{R})}{(R \bar{R})^2} \right)$$  

(1)

The coupling domain represents the volume change due to the steady-state charge stored in the actuator, which is given by $\nu = 1 + \alpha Q$, where $\alpha$ is the coupling coefficient determined through experiments. Finally, the nonlinear axial actuation force is modeled following the invariant-based hyperelasticity approach. The actuator output force is given by Eq. (2).

$$F = 2\pi\left(\frac{4\mu_0 \sin^3 \phi}{\lambda_3} + \frac{\nu^2 \sin^2 \phi + \lambda_3^2 \cos^2 \phi - 1}{2} + \frac{\nu}{2} \ln \frac{r_2}{r_1} - \frac{\nu^2}{4} \right) + \frac{\nu^2}{2} \left(\frac{\nu^2}{2} + 4\xi \lambda_3^2 \cos^2 \phi \left(\nu^2 \sin^2 \phi + \lambda_3^2 \cos^2 \phi - 1\right)\right)$$  

(2)

Results

Fig. 1 shows the effect of fiber properties on the free strain ($F = 0$) of FTCAPM. The dimensions used in the simulation are similar to [5]. Fig. 2 shows a comparison between the existing experimental data and our model.

Discussion

Fig. 1 shows a transition in response of the actuator at a certain fiber angle and anisotropy factor. FTCAPM starts contracting instead of elongating for the same applied positive DC voltage. This axial deformation of the artificial muscle can be used to develop surgical tools for minimally invasive surgery, integrated with the exoskeleton by tuning the fiber properties.

References

MECHANICS OF CELL SPHEROIDS UNDER LARGE DEFORMATIONS

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Introduction
Fibrosis, the excessive accumulation of extracellular matrix (ECM) by activated fibroblasts, is a common feature of different pathological conditions. Fibroblasts are mechanosensitive cells and increased stiffness of the ECM can activate fibrotic pathways [1]. To study the mechanical properties of the ECM in vitro, fibroblasts are cultured in 3D spheroids. Mechanical assessment of cell spheroids can be accomplished via parallel plate compression. Mechanical properties of cell spheroids are determined from force vs displacement (F–δ) curves but available methods for extracting material properties are limited. Many approaches rely on applying (extended) Hertzian theory to the loading part of F–δ curves to fit for a compression modulus [2]. As spheroids exhibit low stiffness, they undergo large deformations at small external forces, and current contact mechanics models fail to describe such deformation behavior [3,4]. Here, we present a model including large deformation formulation, based on a hyperelastic material law to describe the deformation of cell spheroids subjected to parallel-plate compression.

Methods
Cell spheroids consisting of primary human fibroblasts cultured for four days were subjected to parallel-plate compression testing (MicroSquisher, CellScale) fitted with a round tungsten cantilever and accompanying SquisherJoy V5.23 software (CellScale, Ontario, Canada). The fluid bath test chamber was filled with sterile phosphate buffered saline (pH=7.4), and stage and optics were calibrated according to manufacturer’s instructions. Samples were compressed up to 50% apparent linear strain at different displacement rates. F–δ data was fitted using linear least squares regression on the Hertz and Tatara [3] models (custom MATLAB code) with fully constrained contact points (F=0, δ=0). Image analysis was performed to determine contact radius and lateral expansion of cell spheroids under compression.

Results
The dependence of compression modulus on the displacement rate is illustrated in Figure 1a. Furthermore, the hysteresis between the approach and retraction curves indicates viscous behavior of cell spheroids. Hertzian theory can be applied for compressive displacements up to 10-25% (depending on displacement rate). For larger deformations, where the force follows the third and fifth power of the displacement, Tatara analysis was used to extract the compression modulus (Figure 1b). The predicted contact radius and lateral expansion of cell spheroids were found to be in good agreement with the data obtained from image analysis. However, the error was significant in the case of larger deformations. Beyond 40% apparent linear strain, the volume of the cell spheroids decreased (compressible material) due to poroelasticity.

Discussion
The Hertzian theory and its modifications can be applied for small deformations while, for larger deformations, the Tatara numerical analysis is able to describe the deformation behavior of cell spheroids providing also their lateral profile. This indicates that linear elastic continuum mechanics with some important modifications can be applied to the case of large deformations. Nevertheless, spheroids exhibit at least also viscous behavior, which should be added in future models.

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Acknowledgements
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CLINICAL VALIDATION OF STATIC OPTIMIZATION DURING POST STROKE GAIT

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Introduction

Post stroke gait is characterized by muscle impairments leading to abnormal gait patterns and muscle function. Knowledge of individual muscle forces would facilitate rehabilitation and inform targeted exercise programs. However, they cannot be obtained, rather calculated from musculoskeletal modeling, based on motion capture and inverse dynamics approaches. Validation of different optimization algorithms has been limited on healthy populations, mostly because generic MSK models do not include patient-specific pathologies. Different methods have been proposed to address this, all of them being difficult to apply in a clinical setting [1]. Thus, the aim of this study is to, for the first time, validate muscle activations as calculated from less-demanding, easy-to-use and computationally cheap static optimization (SO) against synchronous electromyography (EMG) data during post stroke gait.

Methods

Three chronic stroke patients (1 male, mean (std) age: 57 (10) years), were recruited from a database of the General Hospital of Komotini, Thrace, Greece. Three-dimensional motion capture (10 cameras, Vicon) and two ground-embedded force plates (Kistler) were used to record position-time data during overground walking and ground reaction forces, sampling at 100 and 1000 Hz respectively. Five successful trials from each leg were used for further analysis. A generic full body musculoskeletal model [2] was linearly scaled to each patient based on a static trial and individual mass. Joint angles and muscle activations for both sides were calculated using the inverse kinematics Tool, and SO analyses in Opensim respectively, during stance phase. Bilateral surface EMG (Noraxon, USA) was collected at 2000 Hz on Tibialis Anterior (TA), Peroneus Longus (PL), Soleus (SOL), Gastrocnemius Lateralis (GL), Gluteus Maximus (GMAX), Gluteus Medius (GMED), Biceps Femoris Long Head (BFLH), Semiteninodius (SEM), Tensor fasciae latae (TFL), Vastus Lateralis (VL), Vastus Medialis (VM) and Rectus Femoris (RF) of both paretic and non-paretic side. EMG data were bandpass filtered at 30-300 hz, rectified and low-pass filtered at 6 Hz. To align order of magnitudes between SO and EMG, the latter was normalized to the peak of individual gait cycle and multiplied to peak of correspondent SO data. Similarity between SO and EMG was quantified with cosine similarity and root mean square error (RMSE) metrics. A COS closer to 1 indicates better agreement in activation timing between the two curves.

Results

For the paretic side, higher COS and lowest RMSE values were calculated for most muscles except TA, RF, TFL, with the exception of GMED (highest RMSE). For the non-paretic side, higher COS and lowest RMSE values were calculated for most muscles except TA, RF and VL, with the exception of GMED and SOL (highest RMSE).

![Figure 1: Mean COS and RMSE values for all muscles across subjects for both sides (blue: paretic, red: non-paretic).](image)

Discussion

The current study showcases the strength of Static Optimization to calculate main muscle activations of lower limb in an acceptable accuracy for post stroke patients with a hemiparetic side. Our results show comparable aggregate between EMG and SO to healthy data [3], with the exception of TA. The latter has showed activation throughout the stance phase, especially in the paretic side, which was not present in the calculated data from SO (activation only during early stance). In the case of RF and BFLH, low COS values for both sides are mainly due to different activation timings between EMG and SO, with the latter failing to estimate coactivation of both muscles as evident in EMG data. Future work will include more patients with different mobility profiles.

References


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GENERALIZATION OF MACHINE LEARNING MODEL PREDICTIONS OF KNEE JOINT FORCES TO POST STROKE GAIT

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Introduction

Post stroke symptoms, along with natural age-related sensorimotor decline, affect the lower limbs’ soft tissue homeostasis and/or skeletal integrity, resulting in pain, muscle loss and functional decline along with elevated fall and fracture risk. Forces acting on joints and resulting bone deformation (strain) can lead to degeneration of impact-absorbing cartilage or regulate fracture-protective bone mass and shape; hence, their exploration constitutes an urgent matter for prevention stroke-induced osteoarthritis (OA) and osteoporosis. Musculoskeletal (MSK) modelling can provide such subject-specific information, although its demand for high expertise and excessive computational cost has inhibited its widespread use. Alternatively, data-driven machine learning (ML) techniques are rapidly evolving to meet such healthcare needs. However, generalization to pathological populations of such models may be restricted, due to the scarcity of relevant training data. Hence, the aim of this study is to test the generalization of a ML model trained in healthy gait data to predict knee joint forces, to corresponding post stroke data which have been collected in different settings.

Methods

Participants consisted of fifty-four (54) healthy subjects, young and elderly, and three chronic stroke patients. Motion capture data of the healthy group were recorded at Movements and Postures Analysis Laboratory Leuven – KU Leuven, Belgium, whereas corresponding data of the stroke patients were recorded at the Biomechanics Lab – DUTH, Greece. All patients walked on a split-belt, instrumented treadmill. Healthy group walked on a range of speeds, from 3-7 km/h (~4700 gait cycles), whereas stroke group walked on preferred walking speed (10 gait cycles/each). Musculoskeletal (MSK) modelling included scaling a generic MSK model [1] to subject specific segmental dimensions, calculation of joint kinematics, muscle forces and knee contact forces (KCF) in OpenSim, during stance phase. Training dataset for the artificial neural network (ANN) consisted of lower limb joint angles of both legs as inputs and six components of KCF (three for medial and three for lateral compartment) from the healthy group. Once the optimal ANN architecture was found [2] through brute-force parameterization and 3-fold cross validation, the model was trained in all healthy data. To test its generalization, we computed R-squared and root mean square error between model-predicted and calculated KCFs during stance phase of gait of three stroke patients.

Results

We present the best results of medial KCF – as more relative to knee OA - from the stroke patient most similar to the healthy group in terms of mobility, age and sex.

Discussion

Our prediction results showed that a pre-trained ANN model on healthy data can moderately predict post stroke medial KCFs during stance phase of walking, based only on lower limb joint angles. This is comparable to results when the ANN was trained on the healthy data and all the trials of the testing subjects were excluded from the training dataset. However, generalization capability was heavily compromised when stroke patients deviated far from the training dataset (results not shown), in terms of mobility (one was hemiparetic) and sex (one was elderly male whereas the training dataset included only elderly female). Future work will research on optimal ML algorithm and architecture combined with best training scenarios that generalize sufficiently to stroke populations.

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Acknowledgements

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Figure 1: Mean ensemble curves of the three medial KCF components of 10 stance phases of one stroke patient. Table shown mean R-squared and RMSE values between predicted and calculated curves.
HAEMODYNAMIC ANALYSIS OF DIFFERENT SURGICAL STRATEGIES OF A TYPE-B AORTIC DISSECTION VIA VIRTUAL GRAFTING
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Introduction
Compliance mismatch between the aortic wall and Dacron grafts (DG) commonly employed in aortic surgery is a recognized clinical problem concerning aortic haemodynamics and morphology degeneration [1]. The rigidity induced by DGs can lead to an increased left ventricle (LV) afterload and extra aortic tearing. In this study, we quantify the impact of the compliance mismatch by virtually testing different surgical Type-B aortic dissection (TBAD) grafting strategies using patient-specific computational fluid dynamics (CFD) compliant simulations.

Methods
A TBAD patient was presented at St Bartholomew’s Hospital and treated with a 130 mm thoracic DG. Post-op CT scans were segmented and used as a baseline for analyzing different surgical strategies. After consultation with the clinical team, three virtual grafting strategies were explored in silico; these comprised different DGs lengths corresponding to mid, full descending aorta (MDA, FDA) and full aorta (FA) replacements. Two additional cases with compliant DGs were studied, one (G1) with a patient-specific aortic wall compliance and a second one (G2) with twice this value. The blood flow was modelled using a moving boundary method [2] to capture aortic wall displacement. Patient-specific 2D flow MR-driven inlet flow rate and dynamic outlet boundary conditions were employed. The aortic wall stiffness was calculated from cine-MRI. The energy loss (EL) and stroke work (SW) linked with LV afterload and wall shear stress (WSS) driven metrics, such as the endothelial cell activation potential (ECAP) related to atherosclerotic degeneration, were computed.

Results
A stiffer aorta and more extended grafting (MDA,FDA) were found to be associated with increased aortic pressure, EL and SW and a vertical shift in the pressure-volume loops (Table 1), with the exception of FA which lowered EL by 34%. Implementing a patient-specific compliant graft reduced the pulse pressure by 11% and the EL by 4% (see case G1, Table 1).

<table>
<thead>
<tr>
<th>Psys [mmHg]</th>
<th>Pdia [mmHg]</th>
<th>Stroke Work [W]</th>
<th>Energy Loss [W]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-op</td>
<td>97.5</td>
<td>68.4</td>
<td>0.65</td>
</tr>
<tr>
<td>MDA</td>
<td>100.1</td>
<td>68.9</td>
<td>0.71</td>
</tr>
<tr>
<td>FDA</td>
<td>101.5</td>
<td>70.9</td>
<td>0.73</td>
</tr>
<tr>
<td>FA</td>
<td>101.7</td>
<td>72.0</td>
<td>0.66</td>
</tr>
<tr>
<td>G1</td>
<td>96.2</td>
<td>69.9</td>
<td>0.64</td>
</tr>
<tr>
<td>G2</td>
<td>99.8</td>
<td>69.6</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Table 1: Aortic systolic and diastolic pressures, stroke work and energy loss for the six cases.

Discussion
The impact of compliance mismatch in TBAD was examined virtually. Our results indicate that lowering aortic compliance by increasing the rigid DGs’ length tends to augment the pressure, SW and EL. Exploring various graft intervention strategies can thus aid clinicians to optimise treatment in complex TBAD. The study also illustrates that benefits can be realised when grafts are made compliant implying that biomimetic grafts should be considered by manufacturers to lower patient risks of LV hypertrophy and heart failure [3].

References

Acknowledgements
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**CORNEA MECHANICAL MODEL OF KERATOCONUS EARLY CAUSES, USING PATIENT-SPECIFIC GEOMETRY AND MICROSTRUCTURAL DATA**

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**Introduction**

Cornea is a front part of the eye providing two thirds of its optical power through its lens shape. In keratoconus disease, the cornea shape is progressively altered to become conical, leading to optical aberration [1]. A late detection imposes a surgery, explaining the need of early diagnosis.

Keratoconus origin is not clearly determined [2]. While it is associated with a cornea thinning and a decrease of the mechanical properties, it is not clear which of these two effects is the driving one.

We propose a modeling approach in which we change independently the cornea geometry and mechanical properties from healthy to keratoconic ones.

**Methods**

We combined a multiscale model with a patient-geometry (see Fig.1) to simulate the mechanical response of corneas under pressure. The cornea behavior contains an isotropic contribution (matrix), and an anisotropic part (collagen lamellae). Orientations and fractions of each component come from experimental observations [3,4]. Mechanical parameters are then determined by fitting experimental inflation data from the literature [5]. This gives a reference set of parameters for healthy cornea. The keratoconus origin is studied by using first the geometry of keratoconic cornea with reference mechanical parameters, and second the geometry of healthy cornea with altered mechanical parameters. We compared the evolution with pressure of the SimK (a measure of cornea curvature) with the literature [6].

**Results**

Our simulations of healthy cornea show that the mechanical response comes mainly from the collagen, and in particular its prestretch. Keratoconic variations in SimK cannot be reproduced without changing the mechanical parameters, whatever the initial geometry. At the same time, changing the mechanical parameters is sufficient to recover the keratoconus response, even for a healthy geometry while. We can also compute the full elevation maps, showing a cornea similar to a keratoconus at a very early stage.

**Discussion**

Our work shows that the keratoconic response is primarily controlled by a weakening of the mechanical parameters [7]. More precisely, it is the collagen stiffness which seems the most critical parameter. This is consistent with the classical idea that collagen-rich tissues mechanical response is controlled by the collagen fibers. Our result show the interest of cross-linking treatments, which stiffen the collagen lamellae.

**References**


**Acknowledgements**

We thank A. Pandolfi for the 3D mesh code, K. M. Meek and S. Hayes for the X-ray experimental data, and J. Knoeri and V. Borderie for clinical maps.
CONSTITUENT-BASED QUASI-LINEAR VISCOELASTICITY: CAPTURING NON-LINEAR VISCOELASTICITY WITH QUASI-LINEAR MODELS

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Introduction
Arteries exhibit complex viscoelastic behaviours, which are highly non-linear both in terms of elasticity and viscosity [1]. Although previous works have proposed different solutions to model elastic non-linearity which capture well the arterial wall response to quasi-static deformations [1,2], in vivo the arterial wall is subjected to pulsatile loads for which viscoelastic phenomena cannot be neglected. Unlike for elasticity, effective solutions to model non-linear viscoelasticity are lacking. On the one hand, quasi-linear viscoelasticity (QLV) offers a practical solution to viscoelastic modelling [3], but its linear viscosity assumption is unsuitable to capture the viscoelastic behaviour of the arterial wall as a whole [1]. On the other hand, deformation-dependent parameters make fully non-linear viscoelastic models impractical. Indeed, their application to experimental data often leads to identifying specific solutions for each tested loading condition [1]. In the present study, we address this issue by applying QLV theory at the wall constituent rather than at the whole-wall level.

Methods
Five murine common carotid arteries were subjected to an experimental protocol of quasi-static and harmonic biaxial loading conditions for characterising their viscoelastic mechanical properties. In our constituent-based QLV (cbQLV) framework, the arterial wall was modelled as a constrained mixture of an isotropic elastin matrix and four families of collagen fibres in which collagen and elastin were assigned different stress relaxation functions [2,3]. Non-linearity in viscoelasticity was quantified in terms of dependency of the dynamic-to-quasi-static stiffness ratio on pressure, and the performance of our model was compared to that of standard QLV (sQLV).

Results
The experimentally measured dynamic-to-quasi-static stiffness ratio was negligible at low pressures (1.03±0.03 at a pressure range 40–80 mmHg; mean±standard deviation) and rose with increasing pressure (1.58±0.22 at 120–160 mmHg, Figure 1A). By assigning viscoelastic behaviour to collagen and almost purely elastic behaviour to elastin, cbQLV captured well the pressure dependency of this ratio (Figure 1B). Conversely, sQLV failed to capture this complex behaviour, yielding significant stiffening at low pressures and little increase at higher pressures (Figure 1C).

Discussion
Constituent-based QLV offers a practical solution to model complex non-linear viscoelastic behaviours using one set of deformation-independent viscous parameters. Its use in experimental studies on vascular disease will provide novel insights into how pathological changes in wall microstructure affect the mechanical behaviour of the arterial wall in vivo-like dynamic loading conditions.

References
FINITE ELEMENT ANALYSIS FOR BONE HEALTH ASSESSMENT IN CUSHING’S SYNDROME
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Introduction
Cushing’s Syndrome (CS) is a rare endocrine disease characterized by cortisol hyper-secretion. Since adequate diagnosis is often delayed 2–5 years, hypercortisolism exerts its harmful effect for a long time before it is diagnosed and treated [1]. Evidence from recent decades shows that, after effective treatment, usually obtained by the surgical removal of the tumor, the normalization of cortisol secretion is not constantly followed by the complete remission of the associated complications [2]. One among the several clinical manifestations in treated patients is persistent bone disease [1,2]. In an effort to uncover parameters that could be associated to eventual chronic deterioration, this study aims at evaluating femoral bone-related mechanical properties in female patients with long-term remission of CS.

Methods
Sixty-six female subjects were included in this study and stratified in two groups: (a) 34 long-term remission of Cushing’s syndrome cases, and (b) 32 healthy control patients. Images of the total hip were obtained using Dual X-ray Absorptiometry (DXA) and Quantitative Computed Tomography (QCT). QCT-images were used to derive patient-specific Finite Element (FE) models of the proximal femora. Bone was simulated as elastic and heterogeneous material, with stiffness distribution derived from QCT images. A sideways-fall impact was simulated for each subject and the resulting stress values were compare among the two different groups. Areal Bone Mineral Density (aBMD) and volumetric Bone Mineral Density (vBMD) were also studied. Statistical analyses were conducted in order to determine whether CS treated patients had similar femoral density and mechanical properties than control subjects.

Results
Figure 1 shows bone stiffness and Von Mises (VM) stresses for a patient’s model. Based on stiffness values, we can identify cortical/trabecular bone regions. As shown in Table 1, while aBMD measurements on the Total Hip (TH) and Femoral Neck (FN) of treated patients do not differ from those of control patients, vBMD and VM stress measurements show differences between the two different groups. Note that maximum stresses are higher in treated patients, indicating that these subjects may more easily reach the ultimate strength threshold under the same loading conditions and, as a result, they present a higher risk of fracture.

Discussion
CS female patients in remission have reduced vBMD, and impaired mechanical properties regardless of the menopausal status. These abnormalities may contribute to persistently elevate fracture risk even after long-term resolution of cortisol excess.

References

Acknowledgements
We thank Dr. Elena Valassi from the Endocrinology Department of the Hospital Germans Trias i Pujol, Spain for her assistance and access to clinical data. The authors acknowledge financial support from the Spanish Ministry of Economy and Competitiveness (CEX2018-000797-S), and also, from MCIN/ AEI /10.13039/501100011033/ and ‘FEDER Una manera de hacer Europa’ through the project PID2021-122518OB-I00. A.Giuliodori gratefully acknowledges the support of Generalitat de Catalunya i del Fons Social Europeu through the FI grant (09939/2020).
4D CT AS A TOOL TO MEASURE DYNAMIC SCAPHOLUNATE DISTANCE: A RELIABILITY STUDY

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Introduction
Scapholunate (SL) instability is the most common form of posttraumatic carpal instability. Despite its crucial role in guiding therapeutic options, early diagnosis and classification remain challenging (1). Four-dimensional computed tomography (4D CT) emerged as a novel imaging modality producing dynamic 3D image volumes over time, with a good temporal and spatial resolution. 4D CT has already been used to assess scapholunate (SL) instability (2), but no consensus on a gold-standard assessment for diagnosis has been reached. We present a technique to measure 3D scapholunate distance (SLD) based on 4D CT and its intra-observer reproducibility and interobserver reliability through a repeated-measures study in a representative patient cohort.

Methods
A 4D CT scan (Aquilion one, Canon, (voxel size: 0.468x0.468x0.5 mm)) of 7 patients suspected of SL lesion (positive Watson test and/or pain with palpation to the dorsal SL interval upon clinical examination and normal or inconclusive diagnosis based on plain radiographs) with video guidance was made after acquainting them with performing flexion-extension in the gantry. A 3D surface model of the wrist was created using Mimics (Materialise, Belgium). After identifying a dorsal, proximal and volar point on both the scaphoid and lunate (3), SLD was calculated at each interval. All 4D CT datasets were evaluated 3 times by 2 observers. Standard deviation (SD) of the differences between 2 measurements, Interclass Correlation Coefficient (ICC), Standard Error of Measurement (SEM) and Minimal Detectable Change (MDC) were calculated to evaluate intra- and interobserver variability.

Results
Results of the intra-observer evaluation for the first observer and second observer as well as inter-observer variability are given in Table 1.

<table>
<thead>
<tr>
<th>Reproducibility Observer 1</th>
<th>SLD Dorsal</th>
<th>SLD Proximal</th>
<th>SLD Volar</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD (mm)</td>
<td>0.37</td>
<td>0.64</td>
<td>0.58</td>
</tr>
<tr>
<td>ICC</td>
<td>0.98</td>
<td>0.97</td>
<td>0.95</td>
</tr>
<tr>
<td>SEM (mm)</td>
<td>0.052</td>
<td>0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>MDC (mm)</td>
<td>0.15</td>
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</table>

<table>
<thead>
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<th>Reproducibility Observer 2</th>
<th>SLD Dorsal</th>
<th>SLD Proximal</th>
<th>SLD Volar</th>
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</thead>
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<tr>
<td>SD (mm)</td>
<td>0.43</td>
<td>1.29</td>
<td>0.35</td>
</tr>
<tr>
<td>ICC</td>
<td>0.98</td>
<td>0.88</td>
<td>0.77</td>
</tr>
<tr>
<td>SEM (mm)</td>
<td>0.07</td>
<td>0.45</td>
<td>0.17</td>
</tr>
<tr>
<td>MDC (mm)</td>
<td>0.17</td>
<td>1.24</td>
<td>0.47</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Interobserver reliability</th>
<th>SLD Dorsal</th>
<th>SLD Proximal</th>
<th>SLD Volar</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD (mm)</td>
<td>1.44</td>
<td>1.19</td>
<td>0.99</td>
</tr>
<tr>
<td>ICC</td>
<td>0.86</td>
<td>0.94</td>
<td>0.85</td>
</tr>
<tr>
<td>SEM (mm)</td>
<td>0.54</td>
<td>0.29</td>
<td>0.38</td>
</tr>
<tr>
<td>MDC (mm)</td>
<td>1.51</td>
<td>0.81</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Discussion
Comparing MDC to the resolution of the scan and the minimal clinically important difference (an average dorsal SLD of 7.47mm was measured), MDC was low, indicates that 4D CT offers a sufficiently precise and clinically applicable measurement technique. Also ICC values were high for both intra- and interobserver variability, demonstrating a relatively small error variance. We conclude using the proposed points and 3D assessment to measure SLD based on 4D CT acquired images is a reproducible and reliable method.

We acknowledge the lack of correlation to wrist arthroscopy in this study, making it impossible to already conclude on the clinical relevance of these findings. Therefore, future work will focus on how the SLD changes during wrist motion, and correlate this to wrist arthroscopy.

References

Acknowledgements
We thank Arnout De Maré for the support in processing the data.
Introduction

The simulation of Intracranial Aneurysms (IAs) using Computational Fluid Dynamics (CFD) has been thoroughly studied over the past few years. The aim generally revolves around rupture risk assessment in order to aid physicians in their medical decisions. CFD patient-specific results should contribute to a better diagnosis and improve the relevance of a potential clinical intervention. While CFD has been widely applied for simulating IAs, the literature covering Fluid-Structure Interaction (FSI) remains scarce. Arterial tissue is commonly modelled as fully rigid, although publications have emphasized the wide range of mechanical properties and thickness profiles aneurysmal tissue can feature [1]. Among the few research works covering FSI in IAs, a large majority investigates complex patient-specific geometries [2]. This, along with different modelling hypotheses, impedes direct comparisons between studies, hampering the field's progress. Idealized aneurysm geometries are still missing for studying the FSI-related phenomena in a more controlled manner.

Figure 1: View of the simplified artery with various superimposed aneurysm shapes.

Methods

To bridge the gap between existing studies, we propose an idealized sidewall aneurysm geometry, composed of a toroidal artery intersected by a spherical aneurysm. The aneurysm membrane can be exchanged for more complex shapes, making the case extremely versatile (cf. Figure 1). It provides an adequate environment to assess the system's sensitivity with respect to a large span of physical parameters, such as the stiffness and thickness of the walls. We present our FSI simulation framework, which couples an Arbitrary Lagrangian-Eulerian (ALE) formulation for the fluid and an updated Lagrangian solid solver (described in [3]). The two solvers are strongly coupled, iterating between solving the incompressible Navier-Stokes equations and assessing the solid's hyperelastic response to fluid stresses. A non-Newtonian blood rheology model is applied for the fluid and haemodynamic metrics such as the Wall Shear Stress (WSS) and the Oscillatory Shear Index (OSI) are evaluated in the different simulated configurations.

Results

Using the introduced idealized aneurysm geometry, we study the impact of physical and geometrical parameters on the WSS and OSI. As these metrics are classically employed as risk indicators for IAs, we use them to quantify the discrepancies between different configurations. We also simulate a case with static arterial tissue as a reference in order to evaluate the limits of the rigid-wall assumption. Our findings demonstrate the relevance of FSI modelling depending on the prescribed physical parameters and aneurysm phenotypes.

Discussion

The few studies presenting FSI simulations of IAs explore intricate patient-specific structures and make use of a broad spectrum of physical parameters, whose impact on the obtained results remains largely unexplored. This research work paves the way towards a more unified view of FSI-related phenomena in IAs. Although the analysis of patient-specific geometries is our ultimate goal, we believe that simple trends must be highlighted in basic test cases like the one presented here.

References

THE EFFECT OF SUBSTRATE STIFFNESS ON ASTROCYTES AND LEPTOMENINGEAL CELLS

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INTRODUCTION
The meninges cover and protect the brain and spinal cord. The meninges are connected to brain tissue by the pia mater and arachnoid layers, also known as the leptomeninges. The cells that cover the leptomeninges and trabeculae of the subarachnoid space are known as leptomeningeal cells (LMC’s). The LMC’s interact with cortical astrocytes within the brain tissue – connecting the brain to the meninges on a cellular level.

As the structure and stiffness of the tissue’s extracellular matrix (ECM) regulates cellular function, changes in its stiffness with ageing and neuropathology can alter the mechanosensitivity of these resident cells. This may contribute to the progression of neuro-degenerative diseases [1]. From research it has been shown that as we age our cerebral ECM softens [2, 3, 4]. Moreover, research has found adult brain tissue to have a mean Young’s Modulus value of ~3kPa. Although, no research has been carried out in relation to the age dependency of leptomeningeal mechanics, the Youngs Modulus of the adult leptomeninges was found to be ~8MPa [5, 6]. This difference in stiffness between these two tissues in contact needs to be studied further to aid in understanding the neurological environment more in-depth to be able to diagnose disease and offer better treatments.

Therefore, the aim of this research is to investigate the effect of different substrates and substrate stiffnesses on cortical cells such as astrocytes and LMC’s.

MATERIALS AND METHODS
Immortalized DiTNC1 (rat cortical astrocytes) were seeded on substrates at different concentrations. The substrates chosen for this study were collagen, gelatin, and poly-L-lysine (PLL). Immunofluorescent staining and confocal microscopy were performed, as well as western blotting.

For immunofluorescence, three identical 12-well plates were incubated at 37°C, and one plate was fixed every day for three days. The three plates were then stained with primary antibody (GFAP 1:500, G3893) and secondary antibody (Anti-mouse 1:1500, Ab150113) as well as DAPI and phalloidin. Plates were then imaged using the confocal microscope at a magnification of 40X.

For western blotting, T75 flasks were coated with substrates, seeded with 5x10⁶ cells and incubated at 37°C for three days. Cells were then lysed, and electrophoresis and transfer was performed. The membrane was incubated in primary antibodies (GFAP 1:1000, G3893, GAPDH 1:5000, PA1987) at 4°C overnight, and then in secondary antibodies (Goat anti-

mouse 1:10,000, A11375, Donkey anti-rabbit 1:10,000, A32802) for ~2hrs at room temperature.

RESULTS
The main findings of the experiment will be cellular response and morphology (Figure C-F). Immunofluorescence and western blotting will be used to analyse and interpret the most prevalent biomarker identified in astrocytes, GFAP, in order to determine the frequency of expression. The data obtained will include quantitative protein expressions and qualitative descriptions of the morphology of the cells seeded on different substrates at various concentrations. The cells seeded on plastic culture ware will serve as the control.

Figure 1 (A) Bar chart of form factor (circularity) of cells at confluency on plastic and substrates at recommended concentrations. (B) Bar chart of solidity (density) of cells at confluency on plastic and substrates at recommended concentrations. (C-F) Immunofluorescent images of astrocytes seeded on Plastic, Collagen, Gelatin and PLL, respectively, staining for phalloidin (green) and DAPI (blue). Scale bar = 200μm.

DISCUSSION
For this study, by examining the morphological changes of astrocytes on different substrates and stiffnesses, the response of astrocytes varied across substrates. As the concentrations used for this experiment were that of the recommendations by the manufacturer, future experiments will aim to mimic the in vivo stiffnesses. Additionally, substrates which mimic the in vivo environment of the leptomeningeal and cerebral ECM’s will be examined. Moreover, future experiments will use LMC’s, as well as both cells in contact to establish a better understanding of their response to stiffness.

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BIOMECHANICAL PARAMETER PREDICTS SUCCESSFUL FETAL HEART INTERVENTION OUTCOME BETTER THAN CLINICAL SCANS

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1. Imperial College London, UK; 2. Children’s Heart Centre Linz, Austria

Introduction
Fetal heart interventions aim to resolve mid-gestational cardiac abnormalities, preventing the progression to malformations at birth. Fetal aortic valvuloplasty (FAV) is performed on fetal hearts with critical aortic stenosis and evolving hypoplastic left heart syndrome (CAS-eHLHS), to widen the aortic valve and promote healthier development in gestation, thus reducing the likelihood of a univentricular (UV) birth outcome from ~73% to ~32% [1]. However, a considerable number of cases develop to a UV birth outcome post-FAV, suggesting clinical scans alone lack satisfactory predictive capabilities, and patient selection from scans is not sufficiently accurate. Here, we performed image-based patient-specific cardiac finite element (FE) modelling, to investigate if biomechanical parameters have stronger predictive capabilities of birth outcomes, post-FAV, to improve patient selection.

Methods
Analysis of echocardiographic clinical data for pre-FAV CAS-eHLHS fetal hearts, such as valvular velocities, morphometrics and strains was conducted on 9 diseased fetal cases (4 with UV birth outcomes and 5 with biventricular (BV) birth outcomes). FE modelling was performed on 4D echocardiographic images of fetal left ventricles (LV), using previous methods [2] and was coupled to an age-scalable lumped parameter model. An optimisation algorithm ensured a patient-specific match between the FE models of these cases to clinical measurements. 5 healthy fetal LVs were also analysed and modelled for comparison.

Results
CAS-eHLHS results in reduced circumferential and longitudinal strains, stroke volume and the presence of mitral regurgitation. Pre-FAV echocardiographic parameters such as valvular velocities, morphometrics, and myocardial strain values and Z scores did not distinguish between cases that would go on to be BV or UV (sample plots in Figure 1A-B). However, cases that went on to be BV had significantly larger cardiac measurements compared to healthy cases (example of end diastolic volume (EDV) results in Figure 1B). With FE modelling of diseased LVs, cases with BV outcomes showed elevated peak LV pressure, work done, peak myofiber stress and back-computed myocardial contractility, compared to those with UV outcomes. Diseased biomechanical parameters were normalised by the regression curve of healthy data (Figure 1C-D), which showed peak myofiber stress to be significantly higher in cases with BV birth outcomes compared to UV, with no overlap in group parameters (Figure 1C).

Discussion
Our modelling results suggest that CAS-eHLHS cases that respond well to intervention (go on to be BV at birth, as opposed to UV) tend to be biomechanically “stronger” and larger, with generally larger myocardial contractility and LV size. Peak myofiber stress was able to significantly differentiate between models that would go on to be BV or UV post-FAV. Image-based analysis of the CAS-eHLHS cases, using clinical echocardiographic measurements, was generally unable to distinguish between cases that would go on to be UV or BV as clearly. An improved ability to predict outcomes will allow better patient selection and avoids patients going through procedural risks unnecessarily. Our findings thus demonstrate the benefits of incorporating in-depth computational models to the clinical assessment of CAS-eHLHS patients.

References

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Imperial College start-up funding.
REGION-DEPENDENT MATERIAL PARAMETERS FOR FULL-SCALE HUMAN BRAIN SIMULATIONS

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1. Institute of Applied Mechanics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Introduction
An accurate finite element (FE) model of the human brain reliably predicting its response under loading offers great possibilities for brain injury prevention, disease prediction, and surgical guidance. However, the brain is an extremely complex organ and shows high structural heterogeneity, both on a macroscopic and microscopic level. This also results in heterogeneous mechanical properties. Therefore, the identification of material parameters accurately describing the region-dependent mechanical behavior of human brain tissue is crucial. While the division of the human brain into different anatomical regions is well established, knowledge about regions with distinct mechanical properties remains limited and their importance for full-scale human brain simulations remains mostly unknown – not least due the lack of corresponding data.

Methods
We perform multi-modal mechanical testing on human brain tissue from 19 anatomical regions and use an inverse parameter identification scheme based on a hyperelastic Ogden model to identify mechanically distinct regions and provide the corresponding material parameters [1]. In a second step, we investigate the importance of using region-specific material parameters when modelling the full human brain [2]. To this end, we simulate an indentation of the brain occurring during surgical procedures, e.g., due to needle insertion. We compare parameter sets based on unconditioned and conditioned experimental data as well as different Poisson’s ratios.

Results
Our analyses show that we can assign the 19 anatomical regions to nine governing regions based on similar parameters and microstructures, as illustrated in Figure 1. Statistical tests confirm differences between the regions and indicate that at least the corpus callosum and the corona radiata should be assigned different material parameters in computational models of the human brain. The simulation results further highlight that accounting for region-dependent properties leads to significant differences in the predicted strain state compared to simulations assuming homogeneous material properties. Also, the Poisson’s ratio and using unconditioned or preconditioned data sets significantly affects the results of full-scale brain simulations, emphasizing the importance of carefully selecting the material parameters used.

Discussion
The presented analyses have important implications for choosing appropriate region-dependent material parameters for full-scale human brain finite element simulations in the future. The identified parameters will contribute to more precise computational models enabling spatially resolved predictions of the stress and strain states in human brains under complex mechanical loading conditions.

References

Acknowledgements
We gratefully acknowledge the financial support by the German Research Foundation (DFG) through the grant BU 3728/1-1 and by the FAU and the STAEDTLER Stiftung through the Emerging Talents Initiative.
MULTISCALE COMPUTATIONAL MODELS FOR PREDICTING HYDROGEL VISCOELASTIC PROPERTIES

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Introduction
Predicting hydrogel mechanical behaviour is essential to precisely control and guide cell behaviour [1]. Since hydrogel viscoelastic behaviour is strongly related to the interaction of liquid molecules with the solid network, different mathematical models have been proposed to simulate transport phenomena in gels. However, most of them present limitations such as the lack of correlation with gel viscoelastic properties or do not provide experimental validation [2]. We propose a versatile computational model to predict agarose hydrogel viscoelastic behaviour with tunable liquid phases thanks to the presence of soluble polysaccharides such as dextran, which is known to react mainly with water molecules [3], and hyaluronic acid (HA), a component of the extracellular matrix which also binds to polymeric network [4].

Methods
Agarose hydrogels were modelled as a homogeneous porous system, while the viscous phase (with dextran or HA) was considered as a spherical agglomerate linked to the water molecules and the agarose fibres in the case of HA. The liquid phase movement was described using the reaction-diffusion equation (eq.1), introducing an apparent diffusion coefficient $D_{app}$ (eq.2) which adapts the Einstein-Stokes coefficient $D_0$ through additional coefficients: $\beta$ considers the obstacle imposed by the porous matrix using the permeability ($\kappa$) and the hydrodynamic radius ($R_h$); $\delta$ includes the correlation between diffusive and mechanical properties through the average mesh size $\xi_{avg}$. They were derived by combining Brinkmann’s theory of hindered diffusion in porous media [5], Flory’s theory of rubber elasticity and the Amsden obstructing-scaling model [6].

\[
\frac{dc}{dt} = D_{app} \cdot \nabla^2 c - c \cdot \nabla v - v \cdot \nabla c - k_r c_{vm} \tag{1}
\]

\[
D_{app} = \beta(R_h, \kappa) \cdot \delta(\xi_{avg}) \cdot D_0 \tag{2}
\]

Modified Maxwell Standard Linear Solid (SLS, fig.1A-B) lumped parameter models were used to describe hydrogel mechanics reflecting dextran and HA interaction respectively with the viscous phase and with both solid and liquid phase. The model equations in the time domain were used to fit the experimental data obtained from the hydrogel mechanical characterisation using the epsilon dot method, deriving the instantaneous and equilibrium elastic modulus, and the relaxation time ($t_{rel}$) [3]. The dextran/HA-water reaction was expressed as a first-order equation as a function of the free polysaccharide concentration ($c_{vm}$). The model was implemented on Matlab 2022a and Simulink, and the results were optimised on the experimental data, using the least squares method.

![Figure 1. SLS models for A) dextran and B) HA-agarose hydrogels; C) $t_{rel}$ and D) $E_{eq}$ of dextran-agarose hydrogels; D) HA-agarose gel apparent elastic modulus.](image)

Results
The comparison of computational and experimental $E_{eq}$ and $t_{rel}$ data confirmed the model capability to predict the hydrogel mechanical behaviour in the presence of different $c_{vm}$ in the liquid phase. Despite the increase in dextran concentration and hence liquid phase viscosity, the mesh size $\xi_{avg}$ increases leading to the decrease of $t_{rel}$ (fig.1C), while the $E_{eq}$ constant trend (fig.1D) assesses the dextran effect only on the viscous properties’ modulation. Mechanical analyses are ongoing to validate the model in the case of HA; however, preliminary tests (fig.1E) suggested that the predicted values for $E_{app}$ are comparable with the experimental ones [5].

Conclusion
The presented computational framework resulted effective in predicting gel transport properties’ effect on viscoelastic features. In the future, the model will be adapted to other material combinations and coupled with in silico descriptions of cell response to the mechanical stimuli [1] to provide a useful tool for the design of hydrogels for regenerative medicine applications and advanced in-vitro models.

References
STRUCTURAL ANALYSIS OF METALLIC ORTHOPAEDIC IMPLANTS BASED ON ASTM STANDARDS: A SOFTWARE COMPARISON STUDY

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Graduate School of Biomedical Engineering, University of New South Wales, Australia

Introduction

The finite element (FE) method is a well-established method for performing in silico structural analysis of orthopaedic implants. In practice, this approach involves the generation of a volumetric mesh from a CAD object representing the implant, used to define the FE model (choosing element type and order, plus defining of material properties, boundary conditions and loads). The FE model is then solved by specialised software packages, producing estimations of material stresses and strains that can be further analysed. The FE analysis of orthopaedic implants is regulated by the American Society for Testing and Materials (ASTM) through multiple standards, e.g. [1-2].

In terms of tools available for performing these analyses, in recent years there has been a general trend towards the development of high-quality open-source computational packages aimed to the biomechanical community, including FEBio [3], a finite element solver integrated with pre- and post-processor utilities. Despite FEBio was verified in multiple test cases against Abaqus and NIKE3D [3], we are not aware of any comparison against commercial software packages for a realistic case like the analysis of an orthopaedic implant. Therefore, the aim of this work is to quantify the agreement between structural analyses performed with FEBio and ANSYS (https://www.ansys.com) following the ASTM standards.

Methods

We applied two workflows for the preparation of the FE model geometry from the CAD model of a femoral component of a knee implant provided with the [1] (retrieved from https://docs.conself.com/validation in STEP format). Our purpose was to compare the software packages considering the various modelling steps. We generated a first tetrahedral mesh (mean element size: 1 mm) directly from the CAD model using Ansys (MESH1). We created a second volumetric mesh (mean element size: 1 mm) transforming the STEP file in STL format with Gmsh [4], improving it using MeshLab [5] and finally using TetGen [6] in FEBio (MESH2). We then imported both meshes in both software packages, defined quadratic elements and applied to the model boundary conditions and loads as defined by ASTM F3161-16. The assigned material was CoCrMo (Young’s modulus: 230 GPa, Poisson’s coefficient: 0.29), modelled as linear elastic and isotropic. We performed convergence studies to ensure that our estimations of Von Mises stress at the ASTM points of interest (condyle region and notch regions, Figure 1) were reliable in all models and quantified the percent differences between the two software packages and between each software package and the results reported in the ASTM standard.

Results

Table 1 summarises the results from the FE simulations, while Figure 1(B) shows the results of a converged simulation performed in FEBio using MESH2.

![Figure 1: The implant geometry with highlighted points of interest (A) and Von Mises stresses computed by FEBio according to [1] using MESH2.](image)

<table>
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<tr>
<th>MESH1</th>
<th>MESH2</th>
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<tr>
<td>condyle</td>
<td>notch</td>
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<tr>
<td>FEBio vs ASTM</td>
<td>1.8%</td>
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<tr>
<td>ANSYS vs ASTM</td>
<td>0%</td>
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<tr>
<td>FEBio vs ANSYS</td>
<td>1.8%</td>
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Table 1: Percent differences of Von Mises stresses estimated at the points of interest by FEBio, ANSYS and reported in the ASTM standards.

Discussion

We found that FEBio and Ansys compute similar Von Mises stresses at the points of interest (~4% maximum difference). Ansys was computationally more efficient and could generate better geometrical models. In fact, we could not generate a usable volumetric mesh directly from the CAD file in FEBio. Pre-processing, however, is not a key FEBio development goal. We are currently performing similar analyses on a hip prosthesis [2] and tibial component to extend and confirm our findings.

References


Acknowledgements

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MIMU BASED POSTUROGRAPHY: COMPARISON OF METHODS

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Introduction
The application of Inertial Measurement Units (IMU) and Magneto IMU (MIMU) use is increasing in posturography, both in healthy and in pathological subjects, as demonstrated by the high number of papers focusing on this topic [1-2]. Posturography is considered the gold standard objective measure of standing postural control. The main measures of assessing balance are generally derived from the center of pressure (COP) (i.e. time-domain measures, frequency-domain measures), through force/balance plates [3-4] (COP approach, A-COP). Recently some attention has been paid to the possibility of extracting similar measures from the center of mass (COM) [4] or through MIMU [1], directly from the acceleration measured by sensors positioned close to the COM [2] (acceleration approach, A-ACC) or from the reconstructed position of the center of gravity (COG - projection of COM on the base of support, COG approach, A-COG) [5-6]. The aim of this study was to compare the posturographic parameters calculated with the above mentioned approaches: 1. from the COM trajectory measured through the trajectory of a marker positioned on the 5th lumbar vertebra [4] (A-L5), 2. A-ACC [2], 3. A-COG [5], 4. A-COP.

Methods
Instrumented posturography data were acquired on 13 healthy subjects (4M-9F, mean age 27.5±4.3 years, mean BMI 22.5±1.8 kg/m2, 41.4±1.8 shoe size), through a MIMU sensor (Muse, 221e srl, Italy, 100 Hz) positioned in correspondence of the 5th lumbar vertebra, fixed through an elastic band (A-ACC and A-COG), and simultaneously through a force plate (Bertec corp, FP6040, 200 Hz) as gold standard (A-COP) [3-4] and a stereophotogrammetric system (SMART-D, Bts srl, 200 Hz) (for A-L5). Subjects stood for 60 seconds with their eyes open and closed, in upright position with their arms along the body and their feet 30° apart (assured through a cardboard triangle), looking at a target, at eye level, 5 meters away. After a calibration refinement, MIMU data were processed as in [2] for A-ACC and by applying a Kalman extended filter for A-COG [5-6], and posturographic parameters extracted. A-COP and A-L5 parameters were calculated as in [2-3]. The measures obtained in A-L5 and A-COG were compared by computing the root mean square error (RMSE). Pearson’s correlation analysis was performed among the different posturographic measures.

Results
Results of the comparison between A-L5 and A-COG showed a RMSE of 22.1±2.1 and of 26.1±10.7 mm (mean±sd among all the subjects’ data) in the medio-lateral and anterior-posterior direction respectively. Results of the Pearson’s correlations coefficients showed excellent to good correlation in the ellipse area and sway area between A-COP/A-L5/A-COG, very good correlation in sway path between A-L5/A-COG, moderate correlation in the ellipse area between A-COP/A-L5/A-ACC (see Table 1).

Table 1: Results of the Pearson’s correlation in some parameters as example. Bold numbers indicate a statistically significant correlation.

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<tbody>
<tr>
<td>Ellipse area</td>
<td>0.84</td>
<td>0.71</td>
<td>0.75</td>
<td>0.69</td>
<td>0.73</td>
</tr>
<tr>
<td>Sway area</td>
<td>0.90</td>
<td>0.83</td>
<td>0.95</td>
<td>0.33</td>
<td>0.46</td>
</tr>
<tr>
<td>Sway path</td>
<td>0.35</td>
<td>0.48</td>
<td>0.83</td>
<td>-0.45</td>
<td>0.06</td>
</tr>
<tr>
<td>AP median frequency</td>
<td>0.13</td>
<td>-0.03</td>
<td>0.19</td>
<td>-0.05</td>
<td>0.00</td>
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</table>

Conclusions
Several methods to perform posturography were compared. Not all the parameters based on MIMU correlate significantly or well with the parameters from A-COP. A-ACC and A-COG showed encouraging results for future applications of balance assessment in daily living environments.

References

Figure 1. Scatterplot with regression line and Person’s correlation coefficient (R). * Statistically significant correlation.
AN ADVANCED MODELLING FRAMEWORK FOR ASSESSING KNEE ARTICULAR MECHANICS AND SOFT TISSUE LOADING AFTER TOTAL KNEE ARTHROPLASTY

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Introduction
Generic musculoskeletal models often present substantial errors in the prediction of joint function after total knee arthroplasty (TKA) [1]. Therefore, subject-specific modelling is necessary to understand mechanics of the knee and personalize revision surgeries. This study introduces an advanced modelling framework towards understanding the influence of different surgical parameters on the knee joint mechanics after TKA. The framework was verified using a detailed musculoskeletal model personalized to a subject measured within the CAMS-Knee project [2]. Loading and kinematics of the knee during level walking and squat were estimated and compared against data obtained from vivo measurements.

Methods
The subject-specific skeleton geometry was derived from CT images of a TKA patient K5R in the CAMS-Knee datasets (K5R, [2]). Bone segments were then linked to form a multibody model (Fig 1). Implant components were positioned within the subject-specific model based on their 3D pose within the CT images.

![Figure 1: Model development framework.](image1)

The ligament footprints were identified based on guidelines reported in previous anatomical literature. Ligaments were modelled as 1D nonlinear spring elements connecting the ligament attachment sites on the bones. Muscle attachment points and muscle parameters were scaled and adjusted from a previously developed model [3]

The knee was modelled as a 12 degree of freedom (DOFs) joint guided by elastic foundation contact. Skin-marker trajectories and ground reaction force data were inputs to the COMAK tool [4] to estimate knee kinematics and loading during five trials of simulated level walking and squat. The outcomes were validated against in vivo data collected from the same subject.

Results and Discussion
Overall, the model was able to accurately predict tibiofemoral kinematics and loading patterns measured in vivo (Fig 2). Results showed knee contact forces of up to 2.5 and 3.3 BW during walking and squatting, which indicate slight overestimation of the loads likely due to non-personalized parameters (e.g., muscle strength and ligament properties). Importantly, the framework also enables estimation of ligament and muscle forces as well as patellofemoral joint mechanics and thus allows further exploration towards understanding interrelationships between different joint structures.

![Figure 2: Forces and kinematics at knee during walking and squat.](image2)

Conclusions
Our modelling framework enables reliable estimation of the knee joint mechanics during dynamic and quasi-static activities, thus providing a predictive tool for future investigations into the influence of surgical parameters (e.g., ligament release and implant alignment) on the joint function after TKA.

References
ANISOTROPIC PROPERTY CHARACTERIZATION OF HUMAN CAROTID PLAQUES BY USING INVERSE FINITE ELEMENT MODELING

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Introduction
Plaque rupture occurs when the structural stresses are higher than the tissue strength [1]. Although plaques are highly heterogeneous in the structural organization and hence, in the mechanical properties, our current knowledge on plaque mechanical properties are limited to global, aggregate, isotropic behavior [2]. In this study, we obtained the local anisotropic elastic properties of human carotid plaques by using inverse finite element modeling (iFEM), and used these properties to obtain local failure measures at rupture.

Methods
Nine atherosclerotic human carotid endarterectomy (CEA) samples were collected. Then, the fibrous plaques were imaged by using second harmonic generation multiphoton microscopy to obtain local structural collagen information. Subsequently, uniaxial tensile testing was performed on the samples, combined with digital image correlation (DIC) to obtain local displacements. By using the acquired local collagen information, FE models of fibrous plaques were built as fiber-embedded, anisotropic, hyper-elastic, incompressible, Holzapfel-Gasser-Ogden (HGO) solids [3]. The FE models simulated the tensile tests. The iFEM framework [4,5] was used to predict \( C_1 \), \( k_1 \) and \( k_2 \) HGO constants by iteratively running FE models until the normalized mean square error (NMSE) between the computed and experimentally measured displacements is minimized by the Deep Partitioning based Bayesian Optimization (DPTBO) [6] (Fig.1).

Results
The iFEM approach was successfully applied, so far, on one representative strip. The associated error of the iFEM run was NMSE=4%, and the obtained material constant values were: \( C_1 =0.4 \) MPa, \( k_1 =0.4 \) MPa and \( k_2 =400 \). The trends were quite similar in both computational and experimental displacements with elevating levels of displacements from lower right to the top left regions (Fig.2).

![Figure 2: iFEM predicted computational (A) and experimental (B) displacement results.](image)

The FE model (Fig.3A) was then used, with the iFEM predicted HGO constants, to compute stress distribution on the sample. Eventhough not at the highest stress region, the rupture initiation was observed at a local high stress region (Fig.3B).

![Figure 3: Fiber embedded anisotropic FE model (A), FE model stress patterns for rupture region correlation showed within white dashed square (B).](image)

Discussion
In this study, we developed a pipeline for the characterization of local anisotropic elastic and failure properties of fibrous plaques. Preliminary assessment achieved a successful NMSE result. High stress patterns at the rupture initiation indicated that the local stress could be an important parameter for risk assessment. However, other structural metrics, i.e., collagen content or cross-linking, could be investigated as not all high stress regions ruptured. Next, the tested eight strips will be analyzed. To the best of our knowledge, this is the first study on the local assessment of anisotropic elastic properties and the failure properties of fibrous plaque tissue. Findings from this study hold the great potential in identification of stress fingerprints crucial for risk assessment tools.

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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
CONSIDERING MIXED EPISTEMIC AND ALEATORIC UNCERTAINTY IN THE STRUCTURAL VALIDATION OF A SAPIEN-3 TAVI FEM-MODEL

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Introduction
SimInSitu (EU-funded Project 101017523) is aiming to develop a patient-specific FSI-computer model, capable to predict the short- and long-term behavior of in-situ tissue engineered heart valve devices. Model credibility will be established based on a hierarchical development- and VVUQ-concept. The backbone of this platform is a Sapien-3 TAVI model, which is undergoing a tiered validation approach. Due to the limited availability of reliable Sapien-3 device specifications and in-vitro performance data, epistemic and aleatoric uncertainty play a crucial role during the model development and validation. Hence, a mixed UQ approach was implemented. We report here on the validation of the Sapien-3 FEM model considering structural in-vitro data.

Methods
A fully parametric FEM-model of the Sapien-3 TAVI device (Edwards Lifesciences) was developed in Abaqus Explicit for the sizes 23 & 26. All components, (stent-frame, leaflets, skirt, sutures, and balloon system) were considered. The VVUQ program was established in compliance with V&V-40. An exhaustive model verification was conducted, while the parametric approach allowed us to identify and select all relevant parameters for the uncertainty quantification. The structural model validation was conducted independently for the leaflet- and the stent-component, considering their principal mechanical functions. For the stent frame load-case, the expansion behavior (recoil diameter) using the balloon catheter was considered as the comparator [1], while for the leaflet load-case (Figure 1), the deformation in the closed state under quasistatic loading was chosen [2].

Figure 1: parametric Sapien-3 FEM model

Uncertainty propagation was conducted by means of a second order probability approach [3] and was implemented as a double-layer Monte-Carlo-Simulation (Figure 2). Individual metamodels were generated for both validation load-case models and both device sizes (Response-Surface-Models).

Figure 2: Nested Monte Carlo Simulation

Results
A small underestimation of the stent-frame expansion diameters was identified, while the leaflet-displacement was overestimated in general. The computed CDFs indicate for many output parameters a symmetric normal-like behavior while some stent-diameters show a very unsymmetric behavior, which could not be explained so far. The lower and upped bounds of the CDFs help to indicate the influence of the epistemic uncertainty.

Discussion
The implemented mixed UQ approach is very helpful assessing the individual impact of the epistemic and aleatoric uncertainty.

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MULTIMODAL MOLECULAR PROFILING TO PREDICT PATIENT OUTCOME AFTER CARTILAGE REPAIR SURGERY

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Prediction model for cartilage repair

Young adults with cartilage defects have a severely increased risk for the development of osteoarthritis later in life if not treated accordingly [1, 2, 3]. Adequate treatment of these defects and better phenotyping of these patients can contribute to the early detection of osteoarthritis and is critical for a delay in osteoarthritis development later in life. Which treatment applies to which patient is currently determined based on the surgeon’s experience, as well as MRI, the appearance and size of the defect, and the patient’s age and BMI. Nevertheless, some of these patients develop osteoarthritis or require a second surgery in the following years. Combining multiple analysis methods and patient outcome measures, this study aims to build a predictive model, using a multimodal methodology, for patients undergoing cartilage repair surgery. We combined data from fifty-three patients, including patient characteristics, pre and post-operative questionnaires, MRI, as well as a combination of in-tissue mass spectrometry analysis (lipids and proteins) of the infrapatellar fat pad (IPFP) with histology.

Multi-modal methodology

Fifty-three snap-frozen IPFP explants, collected during cartilage defect surgery were cut into two pieces. One was used for lipid analysis using Rapid Evaporative Ionization Mass Spectrometry (REIMS) and one for crossectioning and proteomics analysis using tandem Liquid Chromatography Mass Spectrometry (LC-MS/MS). Lipid analysis was performed at five different locations per explant with a diathermic knife linked to a REIMS ionization source coupled to a XEVO G2-XS qTOF to collect lipid spectral profiles in negative ion mode. REIMS has already been used as a method for drug detection, tissue identification, and classification. Therefore, this technique could function as possible prognostic or diagnostic tool in cartilage repair surgery. After analysis, the explants were embedded in paraffin for histological analysis.

Cryosections were made of the remaining part of the IPFP for protein analysis. Proteomic analysis in positive ion mode was performed on a Thermo Scientific Ultimate 3000 Rapid Separation UHPLC system, coupled to a Q-Exactive HF mass spectrometer, running in data-dependent acquisition mode.

Lipid and protein data were correlated to patient outcome (questionnaires, including pain scores), patient characteristics (e.g. age and BMI), MRI (hoffitis/synovitis), and histology (Hematoxylin and Eosin, fibrosis and inflammation) (Figure 1).

Figure 1. Schematic overview of the multimodal workflow. Created with BioRender.com.

To our knowledge, this is the first study using REIMS (lipids) and LC-MS/MS (proteins), together with additional patient outcome parameters on the IPFP to build a possible prediction model for cartilage repair surgery. Statistical analysis showed the importance of every data outcome parameter of patients after cartilage repair surgery. We were able to build a classification model that can help predict patient outcomes after cartilage repair surgery to help improve surgical decision-making and improve patient outcomes.

References
**Introduction**

Chemotherapy, either conventional or metronomic, targeted or adjuvant, is one of the major treatment modalities against cancer, with continuous efforts focusing to improve its efficacy. For instance, chemotherapy has been considered in combinatory protocols with anti-angiogenic (AA) drugs. AA treatments have shown significant potential in preclinical trials, through their direct effects – blocking new vessels and reducing the density of the existing vasculature. Moreover, in a process termed vascular normalization, AA drugs can improve blood perfusion and thus enhance the chemotherapeutic efficiency, by changing vessels’ pore and lumen size and by reducing interstitial fluid flow. Despite their promising potential, an improved understanding of AA drugs is necessary to enable their optimized administration.

In this contribution, we present an in silico multiscale cancer modelling framework, used to systematically investigate the role of individual mechanisms of action of AA drugs in tumour progression, with AA drugs considered as a monotherapy or in combination with chemotherapy.

**Methods**

The in silico modelling framework of cancerous growth spans across multiple scales by encompassing tissue and tumour biomechanics, angiogenesis, and blood flow through the vasculature and the interstitium [1,2]. It employs a partitioned finite element discretization approach to simulate the transport and balance of biochemical cues and the interaction among different cell populations (cancerous and healthy ones), and the delivery of cytotoxic agents. The model was used to interrogate several mechanisms of action of AA drugs and cytostatics. Initially, the importance of reducing the density of the existing vasculature was investigated, by employing four discrete vascular representations, corresponding to different levels of AA treatment. The vessels’ pore size and diameter were modified, to elucidate the effect of vascular normalisation. The main mechanisms of AA agents were considered with AA as a monotherapy or in combination with conventional and metronomic chemotherapy.

**Results**

The in silico framework was employed to simulate solid tumour development and was specified to in vivo data from a mammary carcinoma xenograft in immunodefinient mice. Computer simulations revealed that the higher the dose of AA drug which disrupts the vasculature, the more profound the effect on tumour volume regression (Fig. 1), with even a medium dose causing an 80% reduction in tumour volume. However, a very high dose of AA drugs caused severe damage on healthy cells too.

![Figure 1: (Top) Vascular network for the (a) control simulation, or corresponding to a (b) low, (c) medium, and (d) high dose of AA therapy respectively. (Bottom) Effect of AA drugs on tumour volume shown as grey outline.](image)

When combined with chemotherapeutics, a lower dose of AA drugs was able to shrink the tumour without causing such severe effects on healthy cells. Additionally, when chemotherapy was combined with vascular normalisation the effect on tumour regression was more pronounced (the final tumour volume is reduced from ~0.9 cm³ (chemotherapy) to ~0.1 cm³ (chemotherapy and vascular normalisation). Notably, metronomic chemotherapy demonstrated significant potential suppressing tumour growth with minimal toxicity to native tissue.

**Discussion**

Focusing on both the influence on tumour growth, tumour vasculature, and healthy tissue, our results indicated that combinatory treatments might be more beneficial than conventional chemotherapy alone [3]. Metronomic chemotherapy as a monotherapy can inhibit tumour growth with minimal toxicity, providing hope for a highly effective and well-tolerated therapy. Our findings underpin the potential of our in silico framework for non-invasive evaluation of therapeutic strategies for cancer regression and anti-angiogenic treatments.

**References**


**Acknowledgements**

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MECHANICAL PROPERTIES OF INDIVIDUAL OSTEOPOROTIC AND CONTROL TRABECULAE IN COMPRESSION

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2. Division Biomechanics, Karl Landsteiner University of Health Sciences, Krems, AT

Introduction

Osteoporosis, is characterized by increased bone fracture risk and remains a disease with high morbidity for the elderly. One known cause of increased fracture risk is the decrease of bone mass. In this context, the putative change of mechanical (material) properties of trabecular bone tissue remains to be fully elucidated and is complicated to assess, due to open porous structure of the tissue. Here, we excluded structural influence by performing compression tests on individual trabeculae excised from cadaveric and osteoporotic human donors.

Methods

12 cadaveric (control group: CTRL) and 15 osteoporotic (osteoporotic fracture: FRAC) human trabeculae were excised from human femoral heads and furnished with a speckle pattern for optical strain measurement. Samples were aligned and glued into custom-made 3D printed chambers with modified epoxy resin (Best-KL 6009). Compression tests were performed using a servo-electric load frame (SEL-mini, Thelkin), equipped with a 10 N load sensor (S2M-10, HBM), a video camera (Kitocam, Kitotec) and a water bath. Preparation and compression tests were done in Hank's Balanced Salt Solution (pH 7.4) to mimic physiological conditions. Sample geometry was obtained via micro-computed tomography (μCT100, SCANCO Medical) at a nominal resolution of 3.3 μm (voltage 70kVp, current 145 μA). Calculated stress is based on mean cross-sectional area, strain was calculated by tracking speckle positions at multiple points at the top and bottom of the samples as shown on the right in Figure 1. Statistical analysis was done in Python with using a two-tailed t-test (scipy.stats.ttest_ind).

Results

Determined mechanical parameters are (mean ± std) shown in Table 1.

<table>
<thead>
<tr>
<th>Properties</th>
<th>CTRL (12)</th>
<th>FRAC (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E [GPa]</td>
<td>11.2 ± 7.2</td>
<td>15.7 ± 7.7</td>
</tr>
<tr>
<td>σy [MPa]</td>
<td>35.1 ± 13.9</td>
<td>36.3 ± 18.3</td>
</tr>
<tr>
<td>εy [%]</td>
<td>0.5 ± 0.5</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>σu [MPa]</td>
<td>66.8 ± 24.7</td>
<td>79.5 ± 26.2</td>
</tr>
<tr>
<td>εu [%]</td>
<td>3.0 ± 3.0</td>
<td>2.0 ± 1.2</td>
</tr>
</tbody>
</table>

Table 1: Mechanical properties of individual trabeculae tested in compression. E tangent modulus, σy yield stress, εy yield strain, σu ultimate stress, εu ultimate strain.

Mechanical properties (CTRL vs. FRAC) are not significantly different from each other. The transition (yield) point is reached at nearly the same stress and strain values. Figure 1 illustrates a selected stress-strain curve under cyclic compressive load. Experiments were performed under displacement-control; therefore, the number of partial unloading cycles vary from three to seven per trabecula.

Discussion

Our compression test enables determination of mechanical properties of individual trabeculae under compression. Results can be compared to individual trabeculae of the same donor cohort loaded in tension with apparent moduli (8.5 ± 5.1) GPa for CTRL and (7.7 ± 4.4) GPa for FRAC [1]. In compression, trabeculae seem stiffer to tension, however, variation is large and more samples need to be tested for a clear statement. Nevertheless, this highlights the importance of the load case for determination of material properties of bone. The mechanical testing data (cf. Fig. 1) show that individual trabeculae do not behave linear elastically in compression, all partial loading-unloading and re-loading exhibit hysteresis. Similar to tensile tests we will apply a rheological model [2] to our data for identification of visco-elastic, visco-plastic properties. We expect our results to further clarify putative differences in tissue properties with osteoporosis and improve fracture risk estimation via computer models.

References

GAIT EVENTS DETECTION IN ABSENCE OF THE TOES' AND HEELS' POSITION

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2. Université Côte d’Azur, INRIA, Sophia Antipolis, France

Introduction

With the fast-paced technological developments, less expensive systems for gait analysis based on RGB-D cameras have emerged that are portable, markerless, and less intrusive in terms of occupied space, which facilitates their use for clinical applications [1,2]. However, their accuracy is usually lower than the gold-standard systems [3]. The state-of-the-art methods utilizing a single RGB-D camera in the frontal plane are inaccurate, unreliable, and gait events detection is still a challenging problem in this setting due to lack of heels position and inaccurate localization of the toes by most of the human pose estimation algorithms. Hence, we present a novel kinematic-geometric model for gait analysis, relying only upon distance-to-camera data (depth) of the ankles in the frontal plane [4].

Methods

This approach proceeds in three main steps: Identification of the gait pattern and modelling by parameterized curves (Fig. 1a, 1b), model fitting through optimization, and computation of spatiotemporal parameters. The proposed algorithm applies on both ankles’ depth data simultaneously, by minimizing through numerical optimization some geometric and biomechanical error functions. The utilized parametric curve is cubic Bézier curve (Fig. 1b) which its formulation is as follows:

\[ B(u) = (1-u)^3 P_1 + 3u(1-u)^2 P_2 + 3u^2(1-u)P_3 + u^3 P_4, \quad 0 \leq u \leq 1 \]

The model (Fig. 1b) consists of a straight line with a zero slope to model from the mid-flat foot to the beginning of the push-off phase, a cubic Bézier curve to model the push-off, swing, and heel-strike phases, and a straight line with a zero slope to model from the end of the heel-strike to the next mid-flat foot. This model applies in between two consecutive intersection points on ankles depth data, since these points are the only biomechanically deductible information from the raw data. These intersection points are the points where both ankles have the same depth and their curves intersect each other, showing the mid-flat foot for one leg and mid-swing for the other. In this model, gait events are the extremities of the curves relative to the interpolated line IL (Fig. 1d), obtained by fitting a line to the intersection points at the same time as fitting the model on data. To validate the model, 15 subjects were asked to walk inside the walkway of the OptoGait, while the OptoGait and an RGB-D camera (Microsoft Azure Kinect) were both recording.

Results & Discussion

Validation results (Table.1) show that the proposed model yields good to excellent absolute statistical agreement in spatiotemporal gait parameters (0.86 ≤ Rc ≤ 0.99). The first advantage of the proposed kinematic-geometric model is that it only uses the ankles’ depth data to extract gait events, without requiring other joints’ trajectories. Second, other types of RGB-D cameras or pose estimation algorithms can also be utilized. Third, utilization of the cubic Bézier curve enables obtaining different patterns based on its control points’ locations, opening the door to the applicability to various pathologies.

Table 1: Validation results for overall spatio-temporal parameters. PE% refers to percentage error and Rc is the Lins’ concordance correlation coefficient.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PE%</th>
<th>Rc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step Time (s)</td>
<td>2.3%</td>
<td>0.98 (0.97 to 0.99)</td>
</tr>
<tr>
<td>Step Length (m)</td>
<td>2.5%</td>
<td>0.98 (0.97 to 0.99)</td>
</tr>
<tr>
<td>Stride Time (s)</td>
<td>2.3%</td>
<td>0.98 (0.97 to 0.99)</td>
</tr>
<tr>
<td>Stride Length (m)</td>
<td>2.8%</td>
<td>0.98 (0.97 to 0.99)</td>
</tr>
<tr>
<td>Gait Speed (m/s)</td>
<td>2.2%</td>
<td>0.99 (0.98 0.99)</td>
</tr>
<tr>
<td>Cadence (steps/minute)</td>
<td>2.2%</td>
<td>0.98 (0.97 to 0.99)</td>
</tr>
<tr>
<td>Stance Phase (%)</td>
<td>1.5%</td>
<td>0.94 (0.90 to 0.98)</td>
</tr>
<tr>
<td>Swing Phase (%)</td>
<td>2.8%</td>
<td>0.90 (0.84 to 0.96)</td>
</tr>
</tbody>
</table>

References

BIORESORBABLE LATTICE WEDGE FOR PATIENT SPECIFIC TIME DEPENDANT STIFFNESS IN HIGH TIBIAL OSTEOTOMY FIXATION

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Introduction
A high tibial osteotomy (HTO) is an effective joint preserving surgery in cases of medial knee osteoarthritis, delaying the need for a total knee replacement by 10 years in 79% of cases [1]. Whilst effective, current HTO fixation methods come with some clinical problems: 41% of patients report discomfort due to large plate profile [2]; current fixation plates are too stiff, resulting in diminished bone healing capacity short term [3] and stress shielding long term; and up to a quarter of all HTOs are complicated by re-fracture at the lateral hinge [4]. It is argued these problems arise due to the one-size-fits-all approach of existing HTO fixation devices, recent efforts to address this limitation employ additive manufacture (AM) to create patient-specific devices [5]. To combat these problems the authors propose a novel concept: an additively manufactured bioresorbable lattice wedge, the design of which can be adjusted for patient-specificity, to stabilise the fracture from within the osteotomy. This allows for use of a smaller low-profile plate (Figure 1) and will reduce stress shielding as the lattice wedge is resorbed and replaced by the new bone.

Methods
A bioresorbable lattice allows for the overall stiffness of the fracture fixation device to reduce over time. Zinc was chosen for its favourable mechanical properties and degradation rate when compared to other metallic bioresorbable materials. The initial stiffness and rate of change of stiffness can be controlled through variation of the initial lattice design, for example body centred cubic (BCC) or face centred cubic (FCC), exemplified in Figure 2. Homogenisation was used to simplify the simulation of the lattice within ABAQUS.

Results

Figure 2: A graph showing a reduction in stiffness in zinc FCC and BCC lattices over a 78 week period (resorption rates taken from literature)

Figure 2 shows that lattice stiffness reduces over time as zinc material is resorbed by the body and that different lattice designs achieve different stiffness. Homogenised simplifications agree with standard lattice models.

Discussion
The bioresorbable lattice wedge allows for tailored stiffness variation during the fracture healing period. This provides stability short term but also reduces stress shielding long term when compared to the gold standard T-plate. In addition this allows for the use of a smaller fixation plate, which mitigates the problem of patient discomfort and helps to avoid revision surgeries.

References
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Acknowledgements
This work is funded in part by the UK EPSRC (grants EP/S02297X/1 and EP/S036717/1) and in part by the Manufacturing Technology Centre (MTC).
LOWER LIMB MUSCLE FORCES IN TABLE TENNIS FOOTWORK DURING TOPSPIN FOREHAND BASED ON MUSCULOSKELETAL

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Introduction
Obtaining biomechanical information about athletes’ bodies through modern technology and revealing the internal mechanisms of joints and muscles during movement is significant for athletes and coaches. Musculoskeletal models used in conjunction with non-invasive measurement methods allow the strength of individual muscles to be obtained for several motor tasks [1]. To gain a thorough understanding of the muscle activity information of the table tennis footwork technique and to further reveal its intrinsic mechanisms and functions, this study aimed to create a musculoskeletal model using OpenSim software to investigate the muscle forces, joint kinematic, and joint kinetic characteristics between the chasse step and one-step during topspin forehand stroke.

Methods
Six male table tennis athletes (height: 171.98 ± 4.97 cm; weight: 68.77 ± 7.86 kg; experience: 10.67 ± 1.86 years; age: 22.50 ± 1.64 years) performed chasse step and one-step footwork to return the ball from the coach by topspin forehand stroke. The kinematics, kinetics, and muscle activity of the lower limb were recorded by the motion capture, force platform, and Electromyography (EMG) system. Statistical parametric mapping (SPM) analysis was used to investigate any difference between the chasse step and one-step footwork during the stroke.

Results
As shown in Figure 1. The muscle force of the biceps femoris long head (p < 0.001), lateral gastrocnemius (p < 0.001), vastus lateralis (p < 0.001), vastus medialis (p < 0.001), rectus femoris (p < 0.001), and tibia anterior (p < 0.001) of the chasse step were significantly greater than the one-step footwork during the early stroke phase (stance). At the end of the stroke phase (push-off), the muscle force of the biceps femoris long head (p < 0.001), medial gastrocnemius (p < 0.001), lateral gastrocnemius (p < 0.001), rectus femoris (p < 0.001), and tibias anterior (p < 0.001) in the chasse step footwork was significantly greater than the one-step footwork. The muscle force of the ankle plantar flexor and valgus muscle groups in the one-step was significantly greater than in the chasse step. Besides, the moment and angle of hip flexion (p = 0.001) and angular rotation (p = 0.009) were significantly greater for the chasse step than the one-step footwork, as well as the ankle plantar flexion angle (p < 0.001) and moment (p < 0.001) of the one-step footwork were significantly higher than the chasse step footwork.

Discussion
The results of this study can be applied to movement control and injury prevention in table tennis footwork. Based on the results of this study, we recommend (1) strengthening the knee flexor and extensor muscle groups, such as the rectus femoris, biceps femoris, vastus lateralis, vastus medialis, medial gastrocnemius, and lateral gastrocnemius, to strengthen the chasse step footwork during landing to create a stable backward phase, (2) strengthen the hip flexor/extensor muscles, brings a gain to the racket’s maximum acceleration; (3) strengthen the plantar flexor muscle groups, such as the medial gastrocnemius and lateral gastrocnemius, thereby enhancing the power transfer of the one-step footwork at the end stroke phase during topspin forehand; (4) strengthen the muscle strength training of the non-dominant legs of table tennis players to reduce the risk of sports injuries.

References

Acknowledgements
This study was sponsored by the Major Program of the National Natural Science Foundation of China (19ZDA352).
NOVEL BIORESORBABLE PULMONARY VALVES: EXPERIMENTAL ASSESSMENT THROUGH AN ANIMAL TRIAL

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Introduction
Diseased heart valves are currently replaced by mechanical or biological substitutes. Both valve prostheses have their disadvantages. Mechanical prostheses require lifelong anticoagulant therapy while biological valves have a limited durability and reoperation is indicated [1]. In this unmet clinical need for novel artificial heart valves, there is a growing interest for tissue-engineered alternatives [1]. Specifically, a promising concept are bioresorbable valves. Here, a gradual decrease of the implanted synthetic scaffold material is accompanied with in vivo tissue formation, so called endogenous tissue restoration (ETR), ultimately leading to a new, natural and functional heart valve [2]. However, the involved processes are still unclear. We aim to better understand the influence of the scaffold characteristics such as wall thickness and fiber distribution on the scaffold degradation and ETR. The experimental data obtained in this study will be used to inform computational models that simulate the scaffold degradation and tissue growth processes. This can enable a simulation-based optimization of the scaffold characteristics.

Methods
The animal experiments were approved by the Animal Ethics Committee of KU Leuven and were conducted at the animal facility of KU Leuven. Eight sheep received a bioresorbable pulmonary valve. Two valve designs were tested, whereby four sheep received a thin-walled valve and four a thick-walled valve, with a six month follow-up. Baseline blood pressure was measured before surgery. Echocardiography and MRI were performed at regular timepoints during follow-up. Blood pressure was again measured at sacrifice. The pulmonary valve was explanted and samples were collected for histological and microstructural analysis, gel permeation chromatography (GPC), and mechanical analysis via uniaxial and planar biaxial mechanical testing.

Results
All eight sheep completed the six months follow-up time. Macroscopic evaluation showed functional valves with newly formed tissue and partially degraded scaffold material, as shown in figure 1. The first insights on follow-up ultrasound imaging indicate functional pulmonary valves with an expected effective orifice area, normal gradients and cardiac output and low regurgitation scores. Data analysis of MRI imaging, microstructural and mechanical testing is currently ongoing.

Figure 1: macroscopic image of a six months explanted pulmonary valve.

Discussion
The implanted pulmonary valves are not associated with complications or early deaths, analogous to previous studies [3]. No macroscopic differences can be observed between the thin- and thick-walled scaffolds. Ultrasound images also do not show differences between the two designs. The results on MRI imaging, histological and mechanical analysis will provide more information on the influence of scaffold microstructure and thickness on the scaffold degradation and ETR, and will be used in future work to inform computational models.

References

Acknowledgements
This work was funded by Horizon 2020 (SimInSitu project). We thank Mieke Ginckels, Hanne Van Dessel and David Célis for their support during the animal experiments and Kimberly Crevits for her help in the mechanical experiments.

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
COMPUTATIONAL SIMULATION OF THE ACTIVE BEHAVIOUR OF MOUSE ROTATOR CUFF MUSCLES

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1. Aragón Institute of Engineering Research (I3A), University of Zaragoza, Spain; 2. Regenerative Medicine Program, Foundation for Applied Medical Research (FIMA), University of Navarra (UNAV), Spain; 3. Instituto de Investigación Sanitaria de Navarra (IdiSNA), Spain; 4. Bioengineering, Biomaterials and Nanomedicine Networking Biomedical Research Centre (CIBER-BBN), Spain.

Introduction
The rotator cuff is the group of muscles and tendons that act to stabilize the shoulder and allow for its extensive range of motion. The set of these tissues surrounding the joint keeps the head of the upper arm bone firmly within the shallow socket of the scapula. Due to the frequent lesions among the tendons involved in this joint, there is still a challenge for orthopaedic surgeons to avoid muscle degeneration and chronicity [1].

In this work, a computational model for simulating the passive and active behavior of the infraspinatus and supraspinatus muscles of an animal model is presented. The model considers a detailed implementation of the muscle architecture based on photon confocal microscope images.

Material and Methods
The experimental study was conducted in accordance with the provisions of the European and Spanish legal normative (RD53/2013). Isolated supraspinatus and infraspinatus (n=3) mouse (wild-type (WT, C57BL/6J)) muscles and scapula were prepared to scan using the Zeiss LSM 880 NLO two photon confocal microscope. The computational model was developed in the Comsol Multiphysics finite element software considering the formulation proposed in [2] by means of a strain density energy function:

\[
\psi = \psi_{\text{vol}}(J) + \psi_{p}([\mathbf{C}, \mathbf{N}]) + \psi_{e}(\mathbf{C}_{e}, \lambda_{a}, \mathbf{N})
\]  

where \(J\) is the determinant of the strain deformation gradient \(\mathbf{F}\), \(\mathbf{C}\) is the isochoric part of the right Cauchy-Green deformation tensor, \(\mathbf{C}_{e}\) is the equivalent for the elastic component in the muscle fiber, \(\lambda_{a}\) is the active stretch of the fiber and \(\mathbf{N}\) is the fiber orientation.

Results
In Figure 1, the images obtained by the microscope are presented. Those images were used to determine the fiber orientation that allowed to define the anisotropy of the tissue. These orientations were obtained (Figure 2) for the infraspinatus muscle using a flow method analogy in the finite element program. Figure 3 also represents the active stretch along these fibers when muscle is activated isometrically.

Discussion
The computational model developed is able to reproduce the experimental behavior of the muscles from a previous work regarding the active force at both ends of the tissue. The complex contractile shortening and lengthening pattern of the pennated muscle fibers can be analyzed during different contractile conditions.

References

Acknowledgements
Project PID2020-113822RB financed by MCIN/AEI/10.13039/501100011033

Figure 1: Four cutting planes images using Epiplan-Neofluar 10x0.25 HD M27 obj. HeNe: 633 nm laser.

Figure 2: Fiber orientation for the infraspinatus muscle.

Figure 3: Active stretch plotted along the muscle fibers at the maximum developed force point.
INTRODUCTION

After myocardial infarction, cardiac fibroblasts adopt a myofibroblast phenotype that is characterized by elevated cell-generated contractile forces [1]. This increase in contractile forces contributes to activation of latent matrix-embedded TGF-β, increased wall stress, and fibroblast-to-myofibroblast transition, thereby promoting fibrosis, cardiac dysfunction, and heart failure [2-4].

Fibroblast contractility is regulated by the level of TGF-β1 and the degree of matrix stiffness, which are typically increased in the infarcted heart [5-6], yet it remains incompletely understood how these cues collectively influence cardiac fibroblast contractility. Here, we therefore investigated how TGF-β1 signaling and matrix stiffness collectively regulate cardiac fibroblast contractility.

METHODS

Cardiac fibroblasts were obtained by successfully differentiating human pluripotent stem cells (hPSCs), which was verified using qPCR and immunostainings. These hPSC-derived cardiac fibroblasts were seeded on polyacrylamide (PAA) gels of different stiffness, ranging from healthy (~15 kPa) to infarcted (~100 kPa) myocardium, and stimulated with TGF-β1 or a TGF-β inhibitor (SB431542). After 24 hours on gels, cell-generated contractile forces were measured using traction force microscopy.

RESULTS

Cardiac fibroblasts exerted contractile forces on the PAA gels which increased in magnitude with matrix stiffness (Figure 1). Additionally, we found that matrix stiffness regulated TGF-β1 responsiveness, resulting distinct mechanical behavior between TGF-β1 stimulated or inhibited cardiac fibroblasts in a specific range of matrix stiffness.

DISCUSSION

The mechanical environment of the heart is crucial for its function, which is reflected by the detrimental effects that increased fibroblast contractility has on cardiac function [2-4]. Understanding how cardiac fibroblast contractility is regulated is therefore a crucial step to develop novel therapies to treat cardiac fibrosis. While the individual roles of TGF-β1 and matrix stiffness in regulating fibroblast contractility have been recognized [5], our findings show that an interplay exists between these cues. Our current efforts are aimed at identifying the underlying mechanism that links matrix stiffness to the TGF-β pathway.

REFERENCES


ACKNOWLEDGEMENTS

We thank Robert Passier, University of Twente, for providing the human pluripotent stem cell line, and Marie-José Goumans, Leiden University, for insightful discussions.

Figure 1: Representative overlays of traction force vectors on phase contrast images of cardiac fibroblasts (TGF-β1 stimulated) on PAA gels of different stiffness.
EXAMINING THE EFFECT OF PARAMETERS ON MECHANOBIOLOGY AThEROMA PLAQUE GROWTH MODEL

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2. Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Spain

Introduction
Cardiovascular diseases, including atherosclerosis, are one of the main causes of mortality in developed countries nowadays. There is a huge quantity of substances and parameters involved in the process of formation of atheroma plaques, so it is important to understand how each substance and parameter influences the growth of plaques [1]. Therefore, the aim of this study is to analyse the influence of the parameters of a previous computational model of the formation of atheroma plaques in arteries [2], to determine the effect of these parameters in the growth and composition of atheroma plaques. The mathematical model used has a total of 52 parameters, which come from different studies and can be related to experimental or computational analysis. Among the experimental ones, there are some differences between the analysis conditions. Moreover, they come from studies of different species and from different arteries (coronary, carotid or aorta). Finally, some of them have been estimated based on computational results. Therefore, the values of the parameters can have a large variation, so it is relevant to perform a sensitivity analysis of the parameters of the model.

Methods
The geometry has been developed based on that of Olgac et al. [3] as it reproduces the mechanical stimuli that real patients are subjected to that lead to plaque apparition (TAWSS and OSI). The mathematical atheroma plaque model has been described and published by the same authors [2]. The software COMSOL Multiphysics (COMSOL AB, Burlington, MA, USA) has been used to computationally solve the model. All the 52 parameters have been increased and reduced by 10% in different simulations in a mono-variant sensitivity analysis. The percentage of change of volume of the plaque due to each one of the substances involved in its growth (foam cells that compose the lipidic core of the plaque, and synthetic smooth muscle cells and collagen fibers, that correspond to the fibrous layer of the plaque) has been analyzed, as well as the variation of the stenosis ratio.

Results
In figure 2, the variation of the volume of foam cells, synthetic smooth muscle cells and collagen fibers is represented in a graphic of parallel bars for the increase and reduction of the considered parameters of 10%.

Discussion
The variation of the selected parameters carries important variations of the results and, in some cases, the variation can be higher than 100%. In addition, it has been noticed that a variation of foam cells volume derives in more change of the stenosis ratio of the plaque than a change of synthetic smooth muscle cells or collagen volumes, due to their bigger volume. For all of this, it could be interesting to study the vulnerability of plaques by changing the analyzed parameters, knowing how each one of them affects to the volume of foam cells, synthetic smooth muscle cells and collagen fibers in the plaque.

References

Acknowledgements
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INFLUENCE OF FLUID-STRUCTURE INTERACTION IN A MODEL OFATHEROMA PLAQUE GROWTH

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3. Public University of Navarra (UPNA), Pamplona, Spain

Introduction

The consequences of atherosclerosis are one of the leading causes of mortality in developed countries today. Atherosclerosis can have serious outcomes, such as myocardial infarction, stroke or ischemia, depending on the affected artery. This disease causes a narrowing of the area available for blood circulation in blood vessels. This decrease in the lumen area is due to the formation of atheroma plaques in the arterial wall, caused by an increase in the endothelial permeability, which produces the flow of some substances from the bloodstream. The increase in the endothelial permeability may be due to several factors, including some mechanical stimuli caused by blood flow towards the arterial wall (such as Time Averaged Wall Shear Stress (TAWSS) or Oscillatory Shear Index (OSI), among others).

Methods

The formation of an atheroma plaque in an artery provokes changes in blood flow, and therefore in the mechanical stimuli that cause the aforementioned increase in the endothelial permeability. Therefore, we propose here a fluid-structure interaction analysis (FSI) based on a previously developed computational fluid dynamic model (CFD) of atheroma plaques development, to determine how these changes on the blood flow can affect the plaque growth.

There is a huge quantity of substances involved in atherosclerosis, but in the developed computational model we consider LDL, oxidised LDL, monocytes, macrophages, cytokines, foam cells, contractile and synthetic smooth muscle cells and collagen fibres. Due to the computational cost of a study in a three-dimensional model, we analyse the effect of FSI on a two-dimension axisymmetric model.

We model blood flow in transient mode with Navier-Stokes equations, considering three cardiac cycles [1]. We also use Darcy’s Law and Kedem-Katchalsky equations with the three-pore model [2] to calculate plasma and substance flows through the endothelium. Then, we use convection-diffusion-reaction equations to compute the inflammatory process in the arterial wall. The reactive terms of these equations are dependent on the considered substances. Finally, we model the arterial wall with a Yeoh hyperelastic constitutive law.

Due to big differences on the temporal scale of a cardiac cycle (ms) and the inflammatory process (several years), we have developed a semi-coupled model to address these different time scales.

Results

Our results compare atheroma plaques growth for the CFD and FSI models. Figure 1 shows the concentration of foam cells in the arterial wall, which are one of the substances that contribute most in the volume of the plaque. These results correspond to a calculation time of 10 years in both, the CFD and FSI models.

![Figure 1: Concentration of foam cells for the CFD and FSI models (A and B, respectively).](image)

As can be seen in Figure 1, the concentration of foam cells, as well as the growth of the plaque, are bigger for the case of CFD. In addition, it can be observed that, in the case of FSI, the arterial wall moves into the arterial lumen, whereas in the case of CFD this does not happen.

Discussion

A computational model of atheroma plaque formation has been developed, contrasting results for CFD and FSI. Results show that there is an important influence of the fluid-structure effect in the plaque formation.

References


Acknowledgements

This research was funded by the Spanish Ministry of Science and Technology through research project PID2019-107517RB-I00 and financial support to P. Hernández-López from the grant BES-2017-080239 and the regional Government of Aragón support for the funding of the research project T24-20R.
SENSOR-BASED CONTINUOUS ASSESSMENT OF POSTOPERATIVE SHOULDER ACTIVITY

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Introduction

Complex and unstable proximal humerus fractures require surgical treatment, with locked plating being a frequently used osteosynthesis option [1]. The outcomes of fracture treatment could be affected by the postoperative rehabilitation protocol [2], which however remains challenging to assess continuously over longer periods. This study aimed at continuously measuring postoperative shoulder activity over six weeks with sensors and comparing of two rehabilitation protocols.

Materials and Methods

Twenty-six elderly patients (19 f and 7 m, 62.5 ± 8.9 y) having complex proximal humerus fractures treated with locking plating were included at University Hospitals Leuven and Medical University Innsbruck. The two sites, randomized and encoded with H1 and H2, utilized different rehabilitation protocols with 3 weeks slings and immediate unrestricted mobilization, respectively. Shoulder activity was assessed continuously during the first 6 postoperative weeks in two consecutive periods via accelerometer-based sensor (AX3, Axivity) pairs attached on the upper arm of the treated side and on the chest as reference. Patients could follow normal daily activities. The raw data of the sensors was processed via calibration-based corrections, low-pass filtering and time synchronization. Shoulder angle including all directional components was evaluated as the rotation of the arm sensor with respect to the chest sensor. Experimental validation indicated 2° accuracy of this method. The evaluation was restricted to upright position of the chest (-30° - 30°) and excluded large accelerations (>1.5g). Shoulder elevation events were defined as peaks of the shoulder angle vs. time data. The daily average angle and total number of events were calculated, and their longitudinal evolution was evaluated in terms of absolute values as well as relative to the direct postoperative period. The effect of rehabilitation protocols was assessed by comparing the results of the two clinical sites.

Results

Total recording time was on average 31 ± 13.8 days, with 22 patients completing both 3-weeks measurement periods. Average shoulder angle of all patients ranged between 9.6° and 31.2°, exhibiting only mild evolution over time, with less than 5° increase over the observation period. The average number of daily shoulder elevation events were in the range of 547 – 6025, showing an increasing trend for most patients. The two clinical sites showed no characteristic differences in terms of the change in average shoulder angle (Fig 1, top). Results of H2 with immediate mobilization showed clearly increasing trend in the number of elevations vs. no apparent changes for H1 (Fig 1, bottom).

Discussion

Postoperative shoulder activity assessed with sensors over six weeks showed large differences between patients in terms of the average shoulder angle (3-fold) and number of elevation events (11-fold). The latter measure exhibited more characteristic longitudinal evolution and differences between rehabilitation protocols and thus may be a promising parameter of mobility monitoring. Future studies will investigate whether and how the assessed shoulder activity could affect the outcomes of fracture treatment.

References


Acknowledgements

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LIGAMENT PRE-TENSION DETERMINES OUTCOME IN SACROILIAC JOINT IN-SILICO MODELLING

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Introduction
Substantial preload in the sacrotuberous ligament (118N±74N; 65N in females; 172N in males [1]) or generally ligament pre-tension changes joint loading. The objective was to investigate the effect of ligament pre-tension on joint surface stress and relative motion using finite element (FE) models of the sacroiliac joints.

Methods
FE models were computed from CT scans of eight patients from a larger cohort (N=818, [2]) with known anatomical variants as well as a typical male (TMJ) and a typical female joint (TFJ). Models included information on isotropic, inhomogeneous bone elasticity (material mapping), (Fig. 1), and stiffness of ligaments/muscles (Fig. 3) from literature [3,4]. Different loading conditions and directions (Fig. 2), (singular, symmetric, and asymmetric) from in-vivo data were implemented (bipedal walking), the sacrum was pinned, and contacts were modelled as pressure-overclosure. A mesh convergence study was performed and yielded relative changes ≤9.0% in translations, ≤6.3% in rotations, ≤12.1% in von Mises stresses, for meshes with element (C3D4) numbers of 75,837, 215,058, and 609,142. Sensitivity analysis of modelling parameters was performed for TFJ with the most sensitive loading scenario (symmetric xyz).

Results
In all load scenarios, stresses were higher in TFJ than TMJ. A loading in anteroposterior direction (y) caused highest stresses and relative mobility. Ligament pre-tension was most sensitive with mean sensitivity factor (change in output / change in input) of 71.04 for translation, 43.09 for rotation, and 2.11 for mean stress.

Mean sensitivity factor of load intensity was 1.09 for translation, 0.91 for rotation, and 0.54 for mean stress. In general, relative motion was more sensitive to the parameter variations than resultant stress.

Discussion
Modelling results were highly sensitive to a variation of ligament pre-tension. That indicates that the individual preloading of ligaments is crucial. However, this must be validated, and the ligament pre-tensions need to be verified in situ.

References

Acknowledgements
We thank for the funding (research grant) from the Assessment of Spondyloarthritis international Society (ASAS) as well as the Rahel Hirsch programme of the Charité Universitätsmedizin Berlin during the conduct of this study.

Figure 1. Example of FE-model (TFJ) with density distribution. Please note that the model on the left shows a cut through the right ileum!

Figure 2: Example of FE-model (TFJ) with load application directions: medio-lateral (x), anteroposterior (y), and cranial-caudal (z).

Figure 3. Example of FE-model (TFJ) with ligaments and muscles (frontal plane). left=posterrior view; right=anterior view. Glut. Med.=gluteus medius muscle; Glut. Max.=gluteus maximus muscle; SS=sacrospinous ligament; PSL=posterior sacroiliac ligament; LPSL=long posterior sacroiliac ligament; ST=sacrotuberous ligament; ISL=interosseous sacroiliac ligament; ASL=anterior sacroiliac ligament; PS=pubic symphysis.

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Introduction
Within this descriptive case study, we aim to analyze the epidemiology of extra-articular femoral and tibial fractures in order to uncover patient-specific covariates that are associated to certain fracture locations and fracture types. We also aim to provide quantitative data of the well-known bimodal distribution of severe extra-articular lower-limb long bone fractures that appear to have maxima for young men and elderly women [1]. The main research questions are how combinations of age and sex are associated with extra-articular fracture(s) of the lower limb. What are risks of certain patient groups to suffer an extra-articular fracture of tibia or femur? What are biomechanical factors associated to the etiology of certain fracture locations?

Methods
The retrospective data evaluation was approved by the local ethics committee (EA4/099/22).

Inclusion criteria:
- Patient age of 18 years or more.
- Patients undergoing surgery for a fracture of a long bone of the lower extremity (femur or tibia) performed between 01.01.2005 and 30.04.2022.

Exclusion criteria:
- All critical clinical conditions at the time of the operation (e.g. unstable circulatory conditions, not fit for surgery and/or consent of treatment).
- Pregnant and lactating patients.
- Persons who are not legally competent.
- Proximal femur and femoral neck fractures.

Results
We identified 195 fractures from 169 unique patients of which had 155 one fracture, 12 had 2 fractures and 2 had 3 fractures.

<table>
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<th>Height (m)</th>
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<td>(15.8)</td>
<td>(0.09) femur</td>
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<td>0</td>
<td>94</td>
<td>94</td>
<td>0</td>
</tr>
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</table>

Table 1: Demographic fracture patient data.

Discussion
Extra-articular fractures of the lower limb seem to be associated to young or middle-aged patients with higher incidence for young males and tibial fractures. The second peak of the bimodal distribution for elderly women of 60 years and above as shown for all fractures [1], could not be observed here for extra-articular fractures of tibia and femur. We still see bimodal distributions, but between young and middle-aged patients and similar for men and women. Biomechanical factors associated to the etiology of extra-articular fractures of the lower limb remain to be elucidated, but high-speed trauma injuries might play the main role as seen in the high number of multiple fractures.

References

Acknowledgements
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EFFICIENT SENSITIVITY ANALYSIS FOR BIOMECHANICAL MODELS WITH CORRELATED INPUTS

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**Introduction**

Patient-specific biomechanical models are highly suited for outcome prediction of clinical interventions. Variance-based sensitivity analysis (SA) can be used for parameter-prioritization of these models based on their contribution to the total output uncertainty. Most variance-based SA approaches assume statistical input independence for the sake of computability while in many cases the inputs are correlated which may affect input importance ranking. Li et al. [1] proposed a new method to compute these correlated sensitivity indices. However, this method is computationally costly, especially for biomechanical models with large sets of inputs. Therefore, this study aimed to introduce an efficient SA methodology for biomechanical models while considering correlation.

**Methods**

The SA methodology is optimized concerning computational costs by using surrogate models. This methodology will be referred to as surrogate-based sensitivity analysis (SSA). A vectorial kernel orthogonal greedy algorithm [2] is used to create surrogate models of a 1D pulse wave propagation model (PWPM). This approach allows for the creation of a kernel-based surrogate model trained on a set of inputs and a specific output generated with the PWPM. The kernel-based surrogate model relates new input variables to an output of interest, thereby drastically speeding up the evaluation time. Afterward, a variance-based correlated SA, based on the work of Li et al. [1], was performed on the surrogate models. The trained surrogate models were verified using benchmark problems and an independent test set. To verify the two-step methodology whilst assuming input independence, SSA was compared to an established SA method for uncorrelated parameters based on adaptive generalized polynomial chaos expansion (agPCE) [3]. Later, the effects of considering correlations on the sensitivity indices (SIs) were investigated by changing the correlation coefficient $\rho$ between the aortic length and diameter from $\rho \in (-1,1)$.

**Results**

Verification with the benchmark problems and the independent test set showed that the surrogates were able to correctly mimic the PWPM. The largest normalized root mean square test error was 0.031 [-]. The agPCE and SSA methods were both used to compute the uncorrelated SIs of the systolic and diastolic aortic pressure. The biggest observed difference between the computed SIs of both methods was only 6.7 $\cdot$ 10$^{-4}$ [-].

![Figure 1: Computed SI for varying $\rho$ [-].](image)

Figure 1 shows the computed SIs for a subset of input parameters when considering correlations. Using a different value for the $\rho$ considerably affects the importance ranking of the correlated input parameters. Moreover, the SIs of non-correlated input parameters were also affected, but to a smaller degree.

**Discussion**

The low errors and small differences found during verification contribute to the robustness of our newly proposed methodology. The SSA allowed for a correlated SA at a low computational cost for a relatively complex cardiovascular model. By applying SSA on the pulse wave propagation model, a speed-up of a factor 27000 [-] was achieved. In the future, this method could be applied to more complex models. Taking into account the correlations had a large impact on computed SIs. Therefore, when performing SA, it is necessary to take correlations into account and to learn the dependency structure of the input space beforehand.

**References**


**Acknowledgements**

We acknowledge the EU’s Horizon 2020 research and innovation programme (No: 101016503 & 101017578) for funding.
VALIDATION OF OSTEOPOROTIC SYNTHETIC FEMORA – A MORE REALISTIC ALTERNATIVE TO EPOXY BONES?

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Introduction
The treatment of osteoporotic femoral fractures remains a challenging problem. Poor bone quality often leads to secondary loss of reduction and implant failure. Therefore, the development of new implants and their biomechanical testing is crucial (1). Besides human specimens, epoxy-based synthetic bones are considered the gold standard for mechanical testing of osteosyntheses, however, standard composite femurs provide unrealistically stable constructs and fail to realistically simulate bone-implant-interaction (2). As an epoxy alternative, we have developed polyurethane-based synthetic bone materials for open-cell cancellous bone (3) and cortical bone (4) in previous studies and validated them in compression and a screw-cut-out setting against human specimens. As a next step, the goal of this study was to merge the approved cancellous and cortical materials into osteoporotic femoral models and mechanically validate them against human specimens.

Methods
Silicone molds were casted from a 3D printed model of a femur. Synthetic femora (PuReBone) were then cast in these molds in a 2-step process. First, molds were filled with polyurethane mixtures for cancellous bone (3) and were then encased with cortical mixtures (4) (Fig. 1).

PuReBone (n=8) were tested in four-point bending (BEND, Fig. 1) in two planes (AP: anterior-posterior, ML: medial-lateral), and axial loading (AXIAL) as described in the studies by Heiner et al. and Gluek et al. to achieve comparability to their results with human healthy (5, n=6) and osteoporotic specimens (6, n=5). Corresponding stiffnesses were used as reference parameters. Analysis of variance followed by Tukey post-hoc test was used for statistical analysis to examine differences among groups (SPSS Statistics v.19, IBM, Amonk, USA).

Results
Bending stiffnesses of PuReBone were slightly, but not significantly higher than human osteoporotic bone (AP: p=0.91, ML: p=0.41). The same accounts for the axial stiffness, which do not show statistical differences between PureBone and human osteoporotic bone (p=0.85). Bending and axial stiffnesses of PureBone are statistically different to human healthy bone (p<0.005, Fig. 2).

Discussion
Osteoporotic polyurethane-based femurs showed mechanically similar behavior to human osteoporotic bones, but were significantly less stiff than healthy ones. However, by adapting the filler materials of the cancellous and cortical polurethane layers and using a 3D print negative created from a CT of a patient, the population variability of humans will be better addressed in biomechanical testing in the future.

References

Acknowledgements
We thank J. Libert for her help in conducting the experiments. MH and PA acknowledge the funding by the Austrian Science Fund (FWF): T1141-B and by PMU research fund – PMU FFF- A-2001/038-HOA.
FROM ANIMAL MODEL TO HUMAN STUDY: A MECHANICAL AND STRUCTURAL ANALYSIS OF THE STOMACH

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Introduction
Animal models are widely used in comparative medicine to substitute human studies. In gastroenterology, the pig is one of the most common models of the human digestive system due to its similar functionality [1,2]. Although this practice has been widely accepted, the question remains: Does porcine gastric tissue properly reflect the biomechanics of the human stomach? This study aims to answer this question through systematic mechanical testing and histology.

Methods
A region- and layer-specific comparative study between porcine and human gastric tissue was performed. While the porcine specimen was obtained from a local slaughterhouse, the human samples came from remnants after sleeve gastrectomy. To ensure the inactivation of smooth muscle cells, all samples were frozen at -20°C within 2 hours of procurement, thawed, and tested submerged in cardioplegic solution. Radial compression, shear, and planar biaxial extension tests with different loading protocols were conducted to analyze the dissimilarity of the directional, layer, and region-dependent material responses. The mechanical testing was complemented by a thorough microstructural analysis of the tissue through histology.

Results
The quasi-static tests revealed a clear region- and layer-dependent anisotropy for both species, which corresponds to the underlying tissue composition. The pronounced hysteresis formation implied strong viscoelastic properties of the gastric tissue, which were confirmed by stress-relaxation measurements. Although porcine and human tissue exhibited these properties, they were significantly dissimilar in other aspects. Human tissues not only differed in structure but also behaved drastically softer and showed differing regional trends and resilience to certain loading modes, see Figure 1.

Discussion
Since both wall composition and mechanical material properties of the stomach differed significantly between porcine and human gastric tissue, the present study highlights important open questions on the application of porcine animal models in the fields of gastroenterology and bariatric surgery. Although the digestive systems of both species may be comparable, animal models should be used with caution for biomedical studies. They can serve as useful preliminary studies to test study methodology, but should not be taken as a substitute for a human clinical study. The knowledge gained about the different biomechanical properties of porcine and human gastric tissue should be considered and used in the future evaluation of suitable constitutive models.

Figure 1: Stress vs stretch behavior obtained from radial compression tests of the porcine (solid line) and human (dashed line) stomach tissues. The intact wall (top) and its dissected layers, mucosa (middle), and muscularis (bottom) are shown compressed to stretches of 0.8 (blue), 0.6 (red), and 0.4 (green). The regional and layer-specific differences are especially pronounced within the intact wall and the muscularis.

References
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Acknowledgments
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Investigation of the bone density in an adolescent idiopathic scoliotic vertebra following a unilateral muscles paralysis

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Introduction
Asymmetric loading condition in an adolescent idiopathic scoliotic (AIS) spine alters bone-density, growth-pattern and deformity-progression[1]. Concave-sided paralysis of spinal-muscles in a scoliotic spine alters vertebral loads and decelerate deformity-progression[3]. However, the vertebral bone-density in a healthy and scoliotic spine with intact and unilaterally-debilitated muscles was not investigated. This study hypothesized that fluctuations in the muscular loading pattern change the bone-density in a scoliotic vertebra.

Methods
A L2 finite-element (FE) model was developed using one AIS 11.5-year-old adolescent data (Fig.1). The reaction loads, reported in [3], were applied to the model in three scenarios: normal-spine (N-S), AIS-spine-with-intact-muscles (AIS-In), and AIS-spine-with-unilaterally-weakened-muscles (AIS-UWM) (Fig. 1). Muscle-weakening was simulated [3] by reducing the physiological-cross-sectional-area of the concave-sided multifidus-lumborum and longissimus-thoracis-pars-thoracis muscles to reach 95% loss in their strength. A bone remodelling algorithm \(E \propto \rho^\alpha\) using a user-subroutine-program and FE-solver was used to calculate the bone-density in one year[4].

Results
The maximum values of the bone-density were found to be 0.3129, 0.3171, and 0.3121g/cm\(^3\) for the N-S, AIS-In and AIS-UWM models, respectively (Fig. 2). The lower surface of the cortical is constrained.

Conclusion
Results of this study propose that unilateral-weakening of muscles in an AIS spine can increase symmetric distribution of vertebral stresses and bone-density (Fig.2), and reduce the bone-density during growth[1].

References
Introduction

Myocardial fiber organization is one of the main contributors to the mechanical behavior of the heart. From a mechanical perspective, we can understand why this organization is essential for the heart’s functionality, but the underlying biological structuring mechanisms remain unclear. Here, we developed a computational model to test the hypothesis that, in combination with cell active forces, strain-mediated enzymic degradation can explain the healthy native myofiber/collagen organization.

Methods

An existing macroscale mechanics model of the left ventricle (LV) was used to extract the strain-time profiles at different transmural locations in healthy conditions [1]. The output of the macroscale model was given as input for a remodelling model which involves the interaction of cells, collagen fibers, and the remaining isotropic matrix [2] (Fig. 1). The multiscale framework was adopted to test which strain-dependent enzymic degradation profile can capture the remodelling response of the tissue at different transmural locations. Motivated by literature [3,4], two strain-dependent collagen degradation functions were chosen; namely, the V-shaped and monotonic functions, which characterize the directional strain-dependent degradation rate of collagen fibers (Fig. 2).

Results

The computational model was able to predict the emergence of the native myocardial fiber organization under the assumption of a V-shaped degradation function. The resulting predicted helix angle agreed well with experimental data of helix angle orientations from endo- to epicardium (Fig. 3A). The monotonic decreasing function displayed larger deviations from experimental data. The cell-mediated mechanisms (pre-stretch in Fig. 3B) did not have considerable influence on the results but provoked relatively larger variations at smaller deformations (mid-wall to epicardium).

Discussion

The results showed that the healthy myocardial fiber organization can be explained by strain-controlled enzymic degradation. The effect of cell-mediated mechanisms is smaller and primarily apparent at smaller deformations. In the future, our theory could be tested at additional transmural locations, as well as under pathological deformations.

References


Acknowledgements:

This work is supported by the partners of Regenerative Medicine Crossing Borders (www.regmedxb.com) and powered by Health–Holland, Top Sector Life Sciences & Health.
MECHANICAL PROPERTIES OF DIFFERENT TISSUES OF CAROTID 
ATHEROMA: EXPERIMENTAL APPROACH

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Introduction
Atherosclerosis is a life-threatening disease mainly occurring in carotid or coronary arteries. In case of carotid arteries, the rupture of fibrous cap encapsulating the cell debris, also known as lipid core, can induce a stroke. In clinics, the severity of the plaque is assessed only through the size of the stenosis. Computational modelling can help in the decision-making process and can bring deeper insight into the dilemma. The tissues both above the lipid core (referred to as fibrous cap) and beneath it are often not distinguished and specified as “fibrous tissue”. Although some publications suggested that both these tissues have similar mechanical properties [1], others recommend that plaque specific material properties are needed [2]. In this study, the potential difference in mechanical response between fibrous cap and original artery wall (media) is investigated combining histological and mechanical experiments.

Methods
Samples from carotid endarterectomy (Fig. 1A) were harvested at St. Anne’s University Hospital. From the plaque, rectangular specimens were dissected and tested under uniaxial tension (Fig. 1B). Note that all specimens were tested fresh, (less than 12 hours after extraction). Then, the specimens were fixed in formaldehyde solution and underwent histological analysis using H-E stain, Orcein stain and Masson-Goldner stain (M-G stain - Fig. 1C). From the histological images, the percentage of different tissue types (fibrous tissue, original media wall, cell debris = atherosclerotic mass and calcifications) were determined. Based on the amount of these tissues, the specimens were divided into 3 groups: prevailing fibrous tissue, media wall (mainly smooth muscle cells with elastic fibers) and specimens with majority of atheroma mass. Then, the stress-strain responses of the tissue types are compared to detect differences between the individual groups.

Results
The responses are shown in Fig. 2.

Discussion
The results suggest that the fibrous tissue (n=5) may have mechanical properties slightly different from the original artery wall (media, n=4). The stress-strain responses show high variability but the fibrous tissue seems to be stiffer and have slightly lower tensile strength compared to the media specimens, whereas strength of the atheroma specimen (n=1) is the lowest. The lower stiffness of media specimens might be due to difficulties in distinguishing between original media wall and the atheroma debris. Note that the media specimen with the lowest strength was influenced by a pre-existing defect in it.

Furthermore, the tissue located directly under LC was detected as (newly formed) fibrous tissue. This may suggest that the pathological changes occur both above and under the lipid core supporting thus the hypothesis of similar mechanical properties.

The collection of data continues to reach a data set sufficient for statistical analysis of differences between mechanical properties of the investigated tissue groups.

References

Acknowledgements
This work was supported by Czech Science Foundation project No. 21-21935S and Brno Ph.D. talent.

Figure 1: A: Carotid plaque, B: Uniaxial tensile specimen, C: Histological slice (M-G stain).

Figure 2: Stress-strain responses of n=10 different specimens (3 blue curves are almost identical).
HYPERELASTIC MATERIAL PROPERTIES OF PORCINE GROWTH PLATES VARY BY ANATOMICAL LOCATION

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Introduction
Simulation models of the knee can be used to investigate the local mechanical loading in the growth plate (GP) e.g. during gait. In order to obtain valid models, boundary conditions such as the material properties must be known. The cartilage of which the GP consists shows a typical viscoelastic behavior [1]. Since the fluid exchange of the growth plate with the surrounding tissue is slow, simplified material models, such as hyperelastic models, are also appropriate for various models [2]. The material behavior of the GP is highly inhomogeneous in relation to the depth [1] and anatomical location [3]. This study therefore aims to investigate the material properties of the different areas of the GP and to correlate them with histological examinations of the specimens.

Materials and Methods
Compression tests were conducted at cylindrical porcine bone-GP-bone samples (ø 8 mm), from different anatomical locations. The tests were carried out according to the termination point method, to separate equilibrium elasticity from the viscoelastic behaviour. Here, the sample was loaded and unloaded in 10 N steps up 50 N (= 4x body weight (BW)). At each step, the deformation was kept constant for 300 s. The termination points represent the stress-strain curve in equilibrium [4]. A hyperelastic material model after Yeoh was fitted to the loading path of each sample. Samples were processed for histology and safranin O/fast green and MOVAT’s pentachrome stainings. Histomorphometric analysis included determination of the height of the growth plate (GP) and of the resting (RZ), proliferative (PZ) and hypertrophic (HZ) zones, as well as chondrocyte area in the hypertrophic zone.

Results
The hyperelastic model after Yeoh is sufficient to describe the test data with a minimal $R^2$ of 0.941 (mean $R^2$ of 0.995) for all data sets. A statistical analysis showed a difference in medial and lateral samples, were for the same stress medial samples showed a higher strain. This was significant above stresses equivalent 76% BW (Figure 1).

The average growth plate height was slightly lower in the lateral region compared to the medial (733±47 and 973±227 μm, respectively), which seemed to be mostly impacted by a slightly lower resting zone (217±59 and 417±171 μm in the lateral and medial regions, respectively; Fig. 2 A, B). The resting zone represented about 29% of the total height of the growth plate in the lateral region, but about 41% in the medial region. The proliferative region represented about 43 and 35% and the hypertrophic 23 and 27% in the lateral and medial regions.

Discussion
It was shown, that the material behavior of the GP is non-linear in equilibrium state, which is particularly important for alternating loads, such as the gait. The height of the growth plate, particularly of the resting zone, was shown to be variable in the different regions. Differences in the tissue histomorphometry within the resting zones could explain their different mechanical behavior. Where the softer medial samples had a higher height of the GP and thus more deformable material compared to the lateral samples.

This study provides a testing protocol to investigate the GP material in its equilibrium state in physiological load conditions.

References
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Figure 1: Stress / Strain relation, clustered by the medial (blue) and lateral (red) side of the growth plate. The asterisk indicates the significance level, above medial and lateral samples are significant different

Figure 2: Histomorphometrical analyses of lateral and medial regions of porcine distal femoral growth plate. (B) MOVAT’s pentachrome staining with height of total growth plate (GP), resting (RZ), proliferation (PZ), and hypertrophic (HZ) zones.
PERFORMANCE OF TWO POSE ESTIMATION ALGORITHMS IN GAIT ANALYSIS AGAINST THE VICON REFERENCE SYSTEM

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Introduction

An affordable, easy-to-use, yet accurate gait analysis system is necessary for design of effective diagnostic and treatment programs (Yamamoto et al., 2022). Pose estimation is a low-cost alternative to the traditional optical and IMU-based motion capture systems. In this study, we examined the performance of two RGB-camera based human pose estimation methods, i.e., AlphaPose (Lv et al., 2022) and Google MediaPipe (Bazarevsky et al., 2020) for the lower limb joint kinematics extraction during self-selected walking against the Vicon motion capture system as the gold-standard reference tool.

Methodology

Five healthy male individuals (179.7±6.7 cm, 69.5±7.4 kg) walked through a four-meter path six times at self-selected normal walking speeds while their full-body movement was measured using two synced systems: 1- a ten-camera Vicon motion capture system at a sampling rate of 120 Hz and full-body plug-in gait markers (the reference system) and 2- a GoPro RGB camera capturing the motion in the sagittal plane. The anatomical angles of hip, knee, and ankle joints were subsequently calculated using the reference system coordinates and Cardan method with a YXZ sequence. The AlphaPose which gives seventeen 2D body landmarks and the Google MediaPipe that offers high-fidelity body pose tracking inferring thirty-three 3D body landmarks from RGB video frames were also used to estimate the coordinates of important landmarks. Body segment vectors were used to determine the sagittal plane angles for the left/right hip, knee, and ankle joints. The MediaPipe and AlphaPose predicted joint kinematics were compared to the Vicon reference system by calculating the normalized (divided to the range of data) root-mean-square-error (nRMSE) and performing one-way analyses of variance (ANOVA).

Results

One-way ANOVA reported significant differences (p<0.05) between Vicon and MediaPipe for both hips and left ankle as well as Vicon and AlphaPose for right hip and left knee (Table 1). Comparisons of mean±standard deviation (SD) of the right/left hip, knee and ankle kinematics parameters of the Vicon and pose estimation algorithms (MediaPipe and AlphaPose) indicated lower range of motion by MediaPipe as compared to AlphaPose and Vicon at the hip and knee joints (Figure 1a). As compared to Vicon, MediaPipe overestimated the ankle joint angles during dorsiflexion. AlphaPose reported lower nRMSE as compared to MediaPipe except for the left knee (Figure 1b).

<table>
<thead>
<tr>
<th>Joint Range of Motion</th>
<th>nRMSE</th>
<th>Vicon vs. MediaPipe</th>
<th>Vicon vs. AlphaPose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Hip</td>
<td></td>
<td>0.0000</td>
<td>0.0001</td>
</tr>
<tr>
<td>Left Hip</td>
<td></td>
<td>0.0000</td>
<td>0.1230</td>
</tr>
<tr>
<td>Right Knee</td>
<td>0.9796</td>
<td>0.0000</td>
<td>0.3170</td>
</tr>
<tr>
<td>Left Knee</td>
<td>0.8769</td>
<td>0.0000</td>
<td>0.0069</td>
</tr>
<tr>
<td>Right Ankle</td>
<td>0.1653</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Left Ankle</td>
<td>0.0000</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 1: (a) Joint range of motion in sagittal plane, (b) nRMSE of MediaPipe and AlphaPose predictions as compared to Vicon.

Discussion

Ankle kinematics cannot be reported by AlphaPose due to the absence of heel and toe detections thus limiting their joint angle measurements. MediaPipe is a cross-platform open-source framework, which can be used to design applications for gait analysis by providing real-time pose estimation. AlphaPose, with lower nRMSE, however, fails to predict ankle joint angles. Adoption of telerehabilitation is beneficial for reducing pain from low back pain, lumbar stenosis, neck pain, and osteoarthritis (Fiani et al., 2020). MediaPipe's ease-of-use, accessibility, and real-time analysis demonstrate its advantages for remote gait monitoring and its growing applications in future for crucial telerehabilitation purposes.

Reference


OBESITY’S IMPACT ON JOINT KINETICS AND KINEMATICS DURING GAIT
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Introduction
Obesity poses a significant burden on the musculoskeletal system, where individuals with higher waist circumference and body mass demonstrate difficulty in walking, balance, and maintaining strength and mobility while performing basic daily living activities. Quantifying the effect of obesity on the biomechanics (kinematics/kinetics) of gait remains inconsistent [1]. The study aims to quantify hip, knee and ankle joint kinematics and kinetics during gait in young participants with different BMI using subject-specific upper body mass distribution [2].

Methodology
Gait motion capture was performed for six healthy male subjects (normal weight BMI: 23.34±0.74, over-weight BMI: 27.05±0.43 and obese BMI: 31.15±0.18 kg/m3) using IMU sensors. IRB approval and informed consent were obtained prior to data collection. Fifteen anthropometric measurements, in addition to the subject’s height and weight, were recorded, and a full-body musculoskeletal model (AnyBody) was used to predict joint reaction forces and moments. The model was personalized using our subject-specific trunk segment mass (T1-S1) and CoM location prediction algorithms, which account for the subject’s body shape and internal tissue distribution, in addition to weight and height [2]. The algorithms utilized 15 anthropometric measurements of a male subject to predict the body shape, and a scalable cross-section template created based on the Visible Human Project (VHP) male subject images to compute the bone, fat, and lean tissues volumes [3]. The peak resultant joint reaction forces (JRF) and moments (JRM) at the hip, knee, and ankle were computed, normalized to the subject’s body weight and height, and averaged over four gait cycles for each subject. Joint range of motion (RoM) in sagittal plane was obtained at all three joints. One-way ANOVA was performed to compare the JRF, JRM, and RoM among normal, overweight, and obese subjects.

Results

\[\text{Figure 1 Sagittal Joint range of motion, peak joint reaction forces, and moments at hip, knee, and ankle averaged over four gait cycles.}\]

Discussion and Conclusion
Magnitudes of JRFs and JRM were higher in right joints of obese subjects [1]. However, comparison of their normalized values showed an overall decrease with BMI. Significant difference was observed in both hip JRF, left knee JRF, left hip and knee JRM. Increase in BMI had no significant effect on RoM. Ratio normalization of forces to mass is needed for comparing subjects of different masses [4].

Reference
RATIONAL DESIGN OF TUBULAR FIBER SCAFFOLDS FOR A SMALL DIAMETER VASCULAR GRAFT

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Introduction
Coronary artery and peripheral vascular damage are major contributors to cardiovascular disease, and prove particularly challenging to treat due to their relatively small vessel diameters (≤6 mm), their tortuosity, and their high hemodynamic demands. Synthetic grafts are a promising treatment, but in the longer term, they result in neointimal hyperplasia and reduced patency, largely due to mechanical mismatch and a lack of biologically adaptive properties. In this study, we rationally designed fiber scaffolds to provide mechanical properties that withstand hemodynamic pressure upon implantation while allow cellular infiltration and promote the formation of new tissue. In this preliminary investigation, we explored the different strategies of designing and fabricating tubular scaffolds with hexagonal microstructures using melt electrowriting (MEW) that could result in native-like stiffness and compliance.

Methods
Fiber tubular scaffolds (Ø2mm, length 3.5-5.1mm, thickness 0.2mm) were fabricated using an in-house built MEW setup. Scaffolds were manufactured from poly(ε-caprolactone) (PCL) [1], by extruding the molten PCL (88°C) by air pressure (2bars) through a 27G needle and depositing it on a computer-controlled cylindrical collector at high voltages (5.5-7.5kV). Four different strategies for designing tubular scaffolds hexagonal microstructure were explored (Fig. 1). The printed constructs were evaluated for their printing accuracy using optical microscopy and mechanical performance under the uniaxial ring test [2,3].

Results
The proposed strategies effectively produced high porosity scaffolds with a fiber diameter of ~10µm and pore sizes of ~350µm with minimal deviation from the programmed path (Fig. 1). All scaffolds in radial group and axial-diagonal design presented a 3 to 5 fold increase in modulus compared to the axial-basic scaffolds (Fig. 2). Additionally, the axial-basic and radial-diagonal scaffolds ruptured at strains between 0.5-1 while most of the axial-diagonal and radial-basic scaffold underwent plastic deformation within this strain region and only failed at strains greater than 2.

Discussion
Well-organized tubular constructs with native-like stiffness and high porosity were developed. The impact of printing direction demonstrated that aligning the fibers in the loading direction by using both design and fabrication strategies can improve the final scaffold’s modulus. Although $E_{ring}$ of all scaffolds were lower than the healthy HCA of young patient [4], the scaffolds from radial orientation design resulted in comparable strength of media and intima layer in HCA [5]. Based on these findings, the axial-diagonal and radial-basic designs were chosen for future in vitro cell studies under dynamic loading.

References
Introduction
Extracorporeal membrane oxygenation (ECMO) is a device that assists a patient's cardiopulmonary function by oxidizing the blood outside the body and supplying it back to the patient [1]. In the case of peripheral venaarterial (VA) ECMO (p-VA ECMO) that supplies blood back to the body through the femoral artery, a watershed region may be created in the aorta due to the flow of ECMO going against the natural blood flow. In this study, we undertake haemodynamics simulation using computational fluid dynamics (CFD) to assess the mixing of oxygen-rich blood from ECMO and oxygen-poor blood from the heart in a 3D patient-specific aorta at different ECMO flowrates. This allows us to understand the effects of the ECMO support levels on the treatment efficacy and the risk of complications.

Method
A 3D patient-specific geometry is reconstructed using a commercial segmentation package, Mimics. Three hybrid meshes composed of tetrahedral elements and prism layers at the walls is created with different total number of elements (approximately 2 to 4.7 million) in Ansys ICEM and the final mesh with a total of approximately 3 million is selected via mesh sensitivity study. Blood is an incompressible and non-Newtonian fluid whose viscosity is assumed to be governed by the Quemada viscosity model [3]. The continuity and momentum conservation equations are solved using Ansys CFX, with the three-element Windkessel model [4] coupled at each outlet and flow waveform imposed at the AA inlet [2] (scaled depending on the ECMO support level), as shown in Fig 1. On the other hand, a time-invariant ECMO flowrate is prescribed at the LIA. The level of ECMO support is defined by the ratio of total ECMO flow to the total cardiac output per cycle.

Results
Streamlines for 50% and 90% ECMO support levels at three time points are presented in Fig 2, where the native and ECMO flows are distinctly indicated by blue and red, respectively. In the case of a 50% ECMO support level, an ECMO flow does not reach IA and LCCA during the entire systole (T1 and T2). On the other hand, for a 90% support level, an ECMO flow passes through the IA and LCCA during the entire systole. The watershed region at the peak systole (T2) is located further down in the descending aorta at 50% support than 90%.

Figure 2: Streamlines over time. T1: mid-systolic acceleration (0.05s), T2: peak systole (0.15s), T3: mid-systolic deceleration (0.3s).

Discussion
At higher ECMO support ratios, the retrograde flowrate through the LIA becomes larger, creating low-velocity areas near the aortic arch adjacent to the heart. The formation of flow stagnation can cause thrombosis, which was also observed in the subject in this study; a thrombus was formed at the aortic root, which is shown as a dent in the reconstructed geometry in Fig 1 (a). Furthermore, if oxidized blood is not sufficiently supplied to the upper body for patients with heart and lung failure, e.g., 50% support in Fig 2, it can cause north-south syndrome.

References

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
CYCLIC LOADING OF HEALTHY AND DEGRADED CARTILAGE AND THE 3D COLLAGEN FIBRILLAR RESPONSE

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Introduction
The collagen fibrillar network in articular cartilage (AC) plays a crucial role in providing the tissue with its structural integrity alongside aiding the biomechanical response of the tissue and thus enabling normal joint function [1]. To date, there is limited knowledge into the structural response of the Type II collagen fibrils in response to repetitive cyclic loading. Here, we apply synchrotron small-angle X-ray scattering (SAXS) combined with in-situ cyclic loading of bovine articular cartilage explants [2,3]. With a focus on the deep zone fibrils, we investigate the changes to the network in terms of orientation, fibrillar strain and inter-fibrillar variability in cartilage with and without the treatment of the pro-inflammatory cytokine IL-1β [3]. We investigate the 3-dimensional orientation response inferred by a 3D reconstruction of X-ray scattering peak intensity distributions from the 2D patterns.

Materials and Methods
Full thickness cartilage explants from the metacarpal-phalangeal joint of bovine steers (18-24 months) were excised with 2 mm biopsy punches. The explants were incubated for 12 days in serum-free supplemented DMEM with and without IL-1β (5 ng/ml, Peprotech, UK). Following treatment, samples were tested at the SAXS beamline ID02 at The European Synchrotron Radiation Facility (ESRF, Grenoble, France). Using a custom-built micro-compression tester (Fig. 1A and [2,3]), samples were subjected to 150 cycles at 0.25Hz at 20% strain. SAXS patterns were acquired within the deep zone for every 5th cycle at both 0% and 20% strain levels. Resultant patterns were analyzed for change in total peak intensity (related to intrafibrillar order), fibril D-period (pre-strain) with associated inter-fibrillar pre-strain variability (w0), and fibril orientation.

Results and Discussion
We show that under cyclic loading there is a reversible increase in the fibrillar orientation distribution width whilst a largely constant direction of orientation is maintained. Through 3D reconstruction of the X-ray scattering peak intensity distributions, we show that the effect on the fibrillar network is a 3-dimensional conical orientation broadening along the normal to the joint surface. Further, at the intrafibrillar level, this effect is coupled with reversible reduction in fibrillar pre-strain under compression, alongside increase in the variability of fibrillar pre-strain. In IL-1β degraded cartilage, the collagen rearrangement under cyclic loading is disrupted and associated with reduced tissue stiffness. These findings have implications as to how changes in local collagen nanomechanics might drive disease progression and how these may link to ageing and osteoarthritis progression and thus, provides a pathway to a mechanistic understanding of such diseases.

Figure 1: (A) Experimental setup: microcompression tester in SAXS beamline (B) 3D SAXS model simulations of collagen fibrils in axially symmetric narrow (left) and broad (right) orientation distributions with the associated schematic 2D SAXS patterns represented below (C) model of the nano- and microstructural dynamics of cartilage collagen fibrils under cyclic compression indicating the reduction in fibril pre-strain (left) alongside a broadening of the fibril orientation distribution (right), with a reduced orientation change under IL-1β treatment.

References

Acknowledgements
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DOES 3D-REGISTRATION IMPROVE REPEATABILITY OF HR-PQCT-BASED HOMOGENIZED FINITE ELEMENT ANALYSIS?

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1. ARTORG Center for Biomedical Engineering Research, University of Bern, Switzerland; 2. Department of Osteoporosis, Inselspital, University of Bern, Switzerland

Introduction

High-resolution peripheral quantitative computed tomography (HR-pQCT) based finite element analysis may help to better detect the progression of bone disease in longitudinal studies. Recently, a unified homogenized finite element (hFE) methodology was developed, which uses the information of bone volume fraction (BV/TV) and fabric anisotropy ($M$) of the bone. This hFE methodology can predict stiffness and strength of experimentally tested distal radii and tibiae with a high level of accuracy [1]. Though, in longitudinal studies, scan misalignments may falsify the comparison of hFE results and must be corrected. Accordingly, the goal of this study is to develop and assess the benefit of a 3D registration method in comparison to the absence of registration.

Material and Methods

HR-pQCT scan misalignments can be adjusted using a preliminary 3d-rigid-body registration (fixed image= baseline, moving images= follow up scans). Using the resulting transformation matrices of the registration, the largest common region can be evaluated which is then used to create a patient specific hFE mesh (Abaqus elem. type= C3D8). The height of the common regions differs among patients; thus, the element size is different for each patient. After mesh generation, for each element, the BV/TV and $M$ were extracted in the original image (without image transformation) using the inverse of the transformation matrix and stored in the corresponding element. This approach enables to evaluate the same bone region of repeated scans without rotating and therefore interpolating the image. The previous hFE methodology was slightly modified. The post-yield behavior (simple softening) reported in [1] is element size dependent and was replaced by perfect plasticity. Consequently, strength is redefined using the 0.2% offset yield criterion. Resulting stiffness and strength of the modified hFE pipeline were validated on the same experimental data as reported in [1] with a minor adjustment of the material constants. The influence of 3d-registration was evaluated with a dataset of repeated distal radii and tibiae HR-pQCT examinations reported in [3]. Radii and tibiae were scanned with a double and triple stack scanning protocol, respectively. Scans were analyzed using the modified hFE methodology with and without 3d-registration. The coefficients of variation CV of the two options were calculated using the approach of [4]. Motion may occur during multiple stack scanning, resulting in a shift between the stacks. This shift limits the power of the 3d-registration and was detected by a dice coefficient (DC) of the mask below 99%. Complete and filtered (DC> 99%) dataset were analyzed.

Results

High correlation between modified hFE and experiments were observed in both stiffness ($R^2=94.1\%$, $p=2.7e-30$) and strength ($R^2=96.2\%$, $p=4.23e-33$). CV of repeated scans are becoming smaller by using preliminary registration (see table 1), especially for the intrinsic properties (apparent Young’s modulus ($E_{app}$) and yield strength ($\sigma_{yield}$)). Furthermore, the CV is higher in the radius compared to the tibia. By filtering the dataset (DC>99%), the CV is reduced.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radius double section; n=33, (n=26)</th>
<th>Tibia triple section; n=39 (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CV$_{noReg}$ %</td>
<td>CV$_{Reg}$ %</td>
</tr>
<tr>
<td>BV/TV</td>
<td>1.1 (1.1)</td>
<td>0.6 (0.4)</td>
</tr>
<tr>
<td>Stiffness</td>
<td>2.5 (1.9)</td>
<td>2.4 (1.5)</td>
</tr>
<tr>
<td>$F_{yield}$</td>
<td>4.0 (3.8)</td>
<td>3.3 (2.3)</td>
</tr>
<tr>
<td>$E_{app}$</td>
<td>3.7 (3.3)</td>
<td>2.4 (1.9)</td>
</tr>
<tr>
<td>$\sigma_{yield}$</td>
<td>6.4 (3.1)</td>
<td>3.5 (3.2)</td>
</tr>
</tbody>
</table>

Table 1: Coefficients of variation with (CV$_{Reg}$) and without (CV$_{noReg}$) 3d-registration and the p-values for complete and (filtered) dataset: double and triple stack protocol for radius and tibia, respectively.

Discussion

The implemented 3d-registration reduces the repeatability errors, and this reduction is statistically significant for BV/TV and the intrinsic mechanical variables. Higher CVs were observed in the radius compared to the tibia, that we attribute to the less reproducible scanning position but also to larger motion artefacts in the radius. Hence, the benefit of 3d registration is higher for the radius compared to the tibia.

References


Acknowledgements

We thank Andrea Mathis and Mathieu Simon for contributing to the HR-pQCT measurements.
EFFECT OF DESIGN PARAMETERS IN FB & MB UKA BIOMECHANICS

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Background

Unicompartmental Knee Arthroplasty (UKA) is a valid and less invasive alternative to Total Knee Arthroplasty for well-selected patients presenting single-compartment knee degeneration. Knee after UKA can reproduce the motion of the intact knee [1], with excellent results at 10 years of follow-up with modern designs [2]. Nowadays both Fixed Bearing (FB) and Mobile Bearing (MB) UKAs are available on the market, and different meta-analysis have demonstrated that both prostheses provided excellent clinical outcomes and survivorship in patients with UNI knee OA [3]. The aims of this study are (1) to identify the main design parameters used to develop and implant FB and MB UKA and (2) to analyze the effects induced by these different parameters in a FB and in a MB UKA, using a sensitivity analysis coupled with a validated finite element model [4,5].

Methods

For both MB and FB UKA, five design parameters were considered: polyethylene insert thickness, tibial component material, friction coefficient, anteroposterior slope, and tibial bone cut thickness. Two control models were defined based on the conventional features for MB and FB implants. The UKA configurations were then implanted in a knee joint model, following the surgical indications as reported by the manufacturer. A total of 216 configurations were analyzed, both at 0° and 90° of flexion, considering different parameter combinations, with a Finite Element Analysis based on previously validated models [4,5]. In detail, the distal extremity of the tibia was constrained and a vertical force was applied, equal to three times the average body weight, proportionally split between the medial and lateral compartments [4]. The results of the analysis were evaluated in terms of the change in average Von Mises stress in the tibial bone (considering four different regions of interest (medial and lateral, proximal and distal), contact area and average Von Mises Stress in the polyethylene insert.

Results

Results demonstrate that any design parameters alteration induces a variation from the control configuration both in terms of poly and bone stress. Among the analyzed parameters, bearing thickness, tibial bone cut, and slope angle are the most sensitive parameters for both implants. Figure 1 and 2 reported, for 0° of flexion, the percentage change from the control values in the different outputs, induced by the different parameters for a FB and an MB UKA.

Due to the different polyethylene insert design (flat for the FB and congruent for the MB UKA), the change in the polyethylene insert outputs are more sensitive in the fix-bearing designs. Due to the different materials used for the tibial baseplate, titanium for the FB and CoCr for the MB, the change in bone stress is more sensitive in the mobile designs.

Conclusions

Any change in the design parameters induced a variation (in terms of insert and bone stress) in comparison with the control configuration. FB designs led to lower bone stress variations, while MB design guaranteed more constant values for the insert.

References


Figure 1: Percentage change from the control values in the different outputs (listed in the first line) induced by the different parameters (reported in the first column) in a fixed bearing UKA at 0° of flexion.

Figure 2: Percentage change from the control values in the different outputs (listed in the first line) induced by the different parameters (reported in the first column) in a mobile bearing UKA at 0° of flexion.
CICLOPE: AN OPEN SOURCE PACKAGE TO BUILD FINITE ELEMENT MODELS FROM MICRO COMPUTED TOMOGRAPHY IMAGES

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Introduction

Micro Finite Element (microFE) models are often derived from volumetric stacks of micro Computed Tomography (microCT) images to non-destructively assess mechanical properties of bone specimens. Specifically, microFE models of bone specimens are used to quantify the effect of pathologies and treatments (also over time, thus including remodelling) on the mechanical response of bone at the tissue level. Different pipelines for the generation of microFE models of trabecular bone have been proposed in the past [1,2] and continue to appear [3,4]. However, as common in musculoskeletal imaging research, the general absence of reproducible image-to-model pipelines and the use of proprietary or non-open-source software strongly limit validation and comparison of results across studies.

The aim of this communication is to present and describe the code package Ciclope. Ciclope is a fully open-source pipeline, written in Python to maximise availability, that can be used to preprocess microCT data to obtain a corresponding microFE model (with two mesh type options), solve and postprocess it.

Methods

Ciclope implements a pretty standard pipeline to obtain microFE model results from microCT data, although several options are available in several pipeline steps.

Example Pipeline

1. Loading and inspecting microCT data, 
2. Image pre-processing 
   • Apply Gaussian smooth and/or Resample (optional)
   • Segment tissue (Fixed threshold or Otsu method)
   • Remove unconnected clusters of voxels
3. Mesh generation 
   • Create Unstructured Grid of voxels or tetrahedra
   • Generate FE model for simulation in CalculiX [5]
4. Analysis definition 
   • Material properties (from template file)
   • Definition of linear static uniaxial compression test
5. Launch simulation in CalculiX
6. Postprocessing 
   • Convert Calculix output to .VTK for visualization
   • Calculate apparent elastic modulus from reaction forces

Code design

Ciclope is composed of: (i) a core library of modules that generate the FE model; (ii) a library of utilities for pre- and postprocessing of images and FE models. The Python script generated during package installation can be used to launch analyses from the command line.

Code ecosystem

Ciclope relies on other open source tools
• Mesh exports are performed with meshio [6]
• Tetrahedra meshes are generated with pygalmesh [7]
• Ciclope models can be solved with CalculiX [5]
• Visualization (data, results) relies on itkwidgets and Paraview.

Results

The example in the Methods and in Figure 1 describes a linear static analysis of a trabecular bone specimens, which is being used by the authors to compare results between the voxel and tetra workflows, and to experimental Digital Image Correlation results. However, other use cases are already available in Ciclope, e.g. the analysis of a whole tooth or the elastoplastic analysis of a steel foam. Ciclope is available at https://github.com/gianthk/ciclope

Figure 1: microFE model and computed displacement field of a trabecular bone specimen from Ciclope

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Acknowledgements

We acknowledge support from the community for Open and Reproducible Musculoskeletal Imaging Research (ORMIR) and from Dr. Serena Bonaretti in particular.
EVALUATION OF VENTRICULAR STIFFNESS OF FROGS AND SNAKES

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Introduction
The vertebrate hearts have changed in structure and properties to adapt to different environments. Since the transition from aquatic to terrestrial environments was one of the most dramatic habitat changes during vertebrate evolution, terrestrialization may have prompted changes in the structure and properties of the heart. Previously, we showed that the ventricle of terrestrial toads was stiffer than that of aquatic frogs [1]. This result suggests that ventricles may have become stiff owing to terrestrialization. However, it is possible that the ventricles of the animals examined were not representative of their respective habitats because we examined only one type in each habitat. Here, to test further the hypothesis that terrestrialization caused ventricular stiffening, we measured ventricular stiffness in different animal species from those used in the previous study [1]. We compared the ventricular stiffness of frogs (aquatic) with that of snakes (terrestrial and arboreal) as a representative of reptiles that are less dependent on water than amphibians.

Methods
Three species of adult frogs and snakes with different habitats were used in the experiment: X. borealis (aquatic frog), E. quadrivirgata (terrestrial snake), and E. climacophora (arboreal snake).
To analyze the passive mechanical properties of the ventricles, we obtained the relationship between the ventricular pressure P and the ventricular volume V by introducing cardioplegic solution into diastolic-arrested ventricle. The ventricular volume was normalized to the ventricular weight in each animal to obtain a pressure P-normalized volume nV relationship. The P-nV relationship was fitted with

\[ P = a \cdot e^{b \cdot nV} + c \]  

(1)
to determine the stiffness constants \( a \), \( b \), and \( c \) [2, 3]. Constant \( b \) was used as the stiffness measure of the ventricle following a previous study [4].

Results
X. borealis (aquatic) had a smaller ventricle than other two species. The ventricles of E. quadrivirgata (terrestrial) and E. climacophora (arboreal) were more elongated than those of X. borealis (aquatic), indicating that the snake heart has a shape corresponding to their elongated bodies.
Figure 1 shows the stiffness constant \( b \) of ventricles. The stiffness constants \( b \) of E. quadrivirgata (terrestrial) and E. climacophora (arboreal) were significantly higher than that of X. borealis (aquatic). The stiffness constant

\[ b = 5 \pm 0.5 \text{ g/ml} \]

for E. quadrivirgata (terrestrial) was equivalent to that of E. climacophora (arboreal).

Discussion
In this study, we investigated the passive mechanical property of the ventricles of frogs and snakes in different habitats. The results suggested that the ventricles of terrestrial and arboreal species were stiffer than those of aquatic species. Compared to the previous studies [1], the ventricles of terrestrial and arboreal snakes were stiffer than those of aquatic frogs. Furthermore, the ventricular stiffness of terrestrial and arboreal snakes was comparable to that of terrestrial toads, even though their body shape differed significantly from terrestrial toads. After the terrestrialization of amphibians and the separation of reptiles from amphibians, amphibians and reptiles underwent their own unique evolution, for example, habitat diversification and loss of limbs. Our findings suggest that ventricular stiffness has been preserved even after amphibians and reptiles evolved independently. The combined results support the hypothesis that the transition from aquatic to terrestrial environments is key in evolutionary ventricular stiffening.

References
MECHANO-BIOLOGY OF TISSUE REGENERATION WITHIN SCAFFOLDS IN LARGE BONE DEFECTS COMORBID WITH TYPE 2 DIABETES

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Introduction

Bone has the ability to regenerate itself. However, the treatment of large bone defects remains a clinical challenge which gets even more challenging when comorbid with Type 2 Diabetes (T2D). T2D is a chronic metabolic disease known by the presence of elevated blood glucose levels that is associated with reduced bone regeneration, high fracture risk and non-union [1]. Scaffolds have a high potential in the treatment of large bone defects, acting as a guiding structure during bone regeneration [2]; however, their application in T2D is highly challenging. Moreover, the mechanobiological mechanisms behind bone regeneration within scaffolds in T2D remains largely unknown. This study aims to investigate the mechanobiological regulation of tissue regeneration within scaffolds in a large bone defect comorbid with T2D, using a combined in silico/in vivo approach.

Materials and Methods

An in silico approach [3] that combines finite element (FE) analysis, to determine the mechanical environment, and agent-based models (ABM), describing the biological processes, was used to investigate bone regeneration within scaffolds in healthy and T2D rats. Gyroid scaffolds were virtually inserted into a large bone defect in a rat femoral osteotomy model (Fig. 1), replicating an experimental setup. Scaffold pores were initially filled with granulation tissue, while PCL, PEEK and titanium material properties were assigned to the scaffold, plate and screws, respectively. Bone regeneration was simulated both in healthy and T2DM animals and compared with in vivo microCT after 6 weeks. In the FE models, differences in bone properties and animal body weight between healthy and T2D were taken into account. In the ABM, to simulate the effect of T2D on cellular behaviour, cellular activity rates (e.g. migration, proliferation) were adapted based on experimental values reported in the literature.

Results

Mechanical strains were higher in the T2D model compared with the healthy model, immediately post-surgery (Fig. 2). Specially, in the region close to the cortices, higher strains where predicted within the scaffold in the T2D animals. The predicted healing outcome was substantially different between the healthy and T2D. In the healthy case, the bone formed at the walls of the scaffold, similar to in vivo observations. The T2D model showed reduced bone formation, in agreement with in vivo data (Fig. 2).

Discussion and Conclusions

In this study, we developed a computational model to investigate the mechanobiological regulation of bone regeneration within scaffolds in large bone defects with T2D. The model was able to describe experimental observations of reduced healing potential in T2D defects. Future studies will focus on identifying the main cellular activities leading to this reduced healing outcome and the optimization of the scaffold design with the aim to enhance bone regeneration in T2D.

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Acknowledgements

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3D PHOTOPOLYMERIZED SCAFFOLD PORE SIZE REGULATES MESENCHYMAL STEM CELL PHENOTYPE

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Introduction

Mechanical stimuli from the environment affect mesenchymal stem cells (MSCs) morphology and functionality [1]. We observed an increased stemness maintenance for MSCs grown into a 3D custom-made scaffold [2]. We are now investigating the role of scaffold architecture in maximizing the cell stemness maintenance over the time, and the identification of molecular pathways most significantly involved in this process.

Methods

Custom made organic-inorganic polymeric scaffolds were produced by the two-photon polymerization technique with different dimension of cubic pores (15x15x15 μm³, 20x20x20 μm³) or graded pore (Named Nichoid), with a range between 10 and 30 μm transversely and 15 μm in the vertical direction.

Fig.1: Representative portion of the 3D investigated scaffolds (top view).

Finite element analyses (COMSOL Multiphysics®) were performed to evaluate the displacement (d) and bending and longitudinal stiffnesses (K=F/d) of each pores type. We built the model in stationary condition, and linear elastic and isotropic material properties (E=3.03GPa, υ=0.49, ρ=1200kg/m³) were imposed. We tested three load cases (|F|=70nN), one for each direction, placed at half-length of bars for representative pores (Fig.1).

Fig.2: a) Representation of truss displacement under the point load Fₓ=70nN. b) Pore stiffness along the three investigated directions; c) Analysis of MSCs capability to migrate.

10⁴MSCs were cultured for 24h and 7days, in 3D and 2D samples, using standard culture conditions. As pharmacological control, 1μm Cytochalasin-D for 1h was used to reduce internal cellular tension.

Fluorescence imaging was performed to investigate cell migration capability in situ and ex situ, nuclear morphology and nucleoskeletal organization. RNA-Seq and Bioinformatic Data Analysis were used to investigate the gene expression deregulation induced by the different scaffolds.

Results

RNA-Seq analyses indicate that culture conditions significantly affect gene expression. Among all the 3D conditions tested, cell stemness significantly increased only in Nichoid scaffolds. Computational analysis demonstrates that this condition induces increased gradients in the displacement and stiffness of the microscopic trusses that form the pore microgrid (Fig.2a,b). Fluorescence imaging shows that the 3D scaffold geometry does not affect the organization of several proteins primarily involved in the mechanotransduction pathway; on the contrary, it influences significantly the cell capability to migrate (Fig.2c).

Discussion

MSCs cultured in our 3D scaffolds do not show a significant cell reshaping and remodelling of the main structural proteins; however, it is appreciable a significative gene deregulation. Our hypothesis is that this phenomenon is guided by a modulation of the cell confinement and migration properties.

Our findings reveal novel aspects of the MSCs culture in 3D, representing a step forward in the control of stem cells via purely mechanical conditioning, thus paving the way to new strategies for MSCs translation to clinical applications.

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Acknowledgements

**PHENOMENOLOGICAL PREDICTION OF FALSE LUMEN THROMBOSIS IN TYPE B AORTIC DISSECTION**

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**Introduction**

Aortic dissection (AD) is a fatal condition caused by a tear in the aortic wall. This tear allows blood to flow between the layers of the aortic wall creating a secondary blood flow channel, known as the false lumen (FL). AD is classified into two types based on Stanford Classification System: type A, which originates in the ascending aorta, and type B, which occurs in the descending aorta. The level of thrombosis in the FL is a significant factor in determining the patient's chances of survival. Clinical studies have shown that the dilation and rupture of the FL are related to the absence of a thrombus in the FL. Complete thrombosis of the FL leads to improved outcomes for patients with type B AD, whereas partial thrombosis is a significant predictor of late dissection-related deaths. Therefore, understanding the conditions under which complete thrombosis of the FL occurs is important for assessing the risk of type B AD patients. In Type B AD, FL thrombosis is governed by local hemodynamic conditions, enhanced in low shear rate zones in the FL. This study presents a novel model for predicting FL thrombosis based on hemodynamic conditions in the FL. The new model is developed based on the findings of Menichini et al. [1] and Melito et al. [2].

**Methods**

The new model controls the thrombus growth only by considering the local shear rate and shear stress in the FL through a single equation known as the coagulant equation. The coagulant equation is a convection-diffusion-reaction equation that models the effect of all the biochemical reactions in the coagulation cascade. The degree of FL thrombosis is defined based on the coagulant concentration. Additionally, the effect of thrombus growth on blood flow is modeled through a fictitious force incorporated in the Navier-stokes equations. The blood is modeled as a non-Newtonian incompressible fluid.

**Results**

The new model was applied to a post-TEVAR Type B AD patient-specific case to compare the model prediction with the computer tomography (CT) scans. CT scans were taken one month and three years after TEVAR, shown in Figures 1A and B. The 1-month post-TEVAR geometry was considered a starting morphology to implement the thrombus model, and the computational fluid dynamics (CFD) simulation was run until the thrombus growth stopped. The final simulated FL thrombosis for this patient was compared with the 3-year follow-up scan (Figure 1B and C). The results show that the model can predict FL thrombosis in a patient-specific geometry and the predicted FL status is in excellent agreement with the 3-year follow-up scan.

![Figure 1: Reconstructed aorta from (A) 1-month post-TEVAR and (B) 3-year follow-up CT scan. (C) Predicted FL surface after thrombus growth over 20 cardiac cycles using the model in this study [3].](image)

**Discussion**

Understanding FL thrombosis is critical in monitoring and treating type B AD patients. Also, in a clinical setting, fast prediction of the extent and location of FL thrombosis is very beneficial. The computational cost of the new model is significantly lower than the previous thrombus model in [1], with an approximate 65% reduction in computational time. Such improvement means the new model is a significant step toward clinical applicability. The high computational efficiency of the model equips us with a tool to assist clinicians in prognosis and decision-making.

**References**


**Acknowledgments**

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*Alireza Jafarinia and Chlœe Harriet Armour contributed equally to this work

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SPATIAL MODELING OF YAP PHOSPHORYLATION THROUGH DIRECT INTERACTION WITH INTEGRIN ADHESIONS

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Introduction
Integrin-based mechanotransduction enables cells to sense and respond to changes in their environment. YAP is a crucial downstream player of integrin-based signaling whose function depends on translocation from the cytoplasm to the nucleus [1]. The phosphorylation of YAP regulates its ability to enter the nucleus. Recent findings suggest that YAP can be recruited to adhesions to be directly phosphorylated. However, it is not entirely clear how the characteristics of integrin adhesions such as variations in cluster size and distribution due to stiffness or the composition of the extracellular matrix, can influence this process.

Methods
We developed a spatial particle-based stochastic model to investigate the adhesion-mediated phosphorylation of YAP, and how this is regulated by integrin adhesion properties. The model is similar to one previously used to study FAK phosphorylation [2]. Integrin adhesions are randomly placed on a membrane at the bottom of the simulation box, and YAP molecules are initialized randomly in the simulation box. The model uses periodic boundary conditions in the X and Y directions and closed boundary conditions for the top and bottom surfaces. Each YAP molecule diffuses or engages in a reaction based on specific probabilities at each time step. The model takes into account the association and dissociation of YAP with adhesions, phosphorylation and dephosphorylation of YAP, and a lifetime and distribution size of adhesions, as they are known to dynamically turnover, see figure 1.

Results and discussion
With a fixed adhesion size and adhesion number, our simulation predicts a certain level of pYAP at equilibrium that does not depend on the random positions of the adhesions. Our simulations also show that the size of adhesions and the dephosphorylation rate have a significant effect on the accumulation of pYAP, see for example the effect of dephosphorylation rate in figure 2. Future work will focus on validating these results with dedicated experimental data. This work contributes towards gaining more knowledge on the mechanisms by which cells sense and adapt to their environments, which can aid in developing improved cancer and regenerative medicine treatments.

References

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IN SILICO HEMODYNAMICAL SIMULATIONS SHOW SECONDARY BENEFITS OF ANTIHYPERTENSIVE DRUGS

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Introduction

Although preventable, hypertension and hypertensive renal disease remain one of the major global risk factors for cardiovascular diseases, especially in the developed world [1]. Hypertension is defined as a chronically increased blood pressure (BP) above 140/90 mmHg and is related to an increase in peripheral resistance and decrease in arterial distensibility [2], similarly to an aging [1]. Available evidence confirms the ability of all five basic groups of antihypertensives to decrease arterial stiffness and consequently the BP in the long-term application [3]. Although proper treatment of hypertension attenuates its influence, the mechanisms by which hypertension accelerates atherosclerosis are poorly understood [4]. It is known that flow waveform for older subjects differs substantially from the young one mainly due to elevated arterial stiffness and consequently early wave reflection [5]. Moreover, the decreasing arterial stiffness via proper treatment of hypertension shifts the shape of the flow waveform to a young and healthy one [6]. Since arterial stiffness can be lowered through long-term application of antihypertensives, benefits of medical therapy could be not only in lowering the BP and peripheral resistance but also in improving the hemodynamic conditions.

Methods

Three finite volume models of patient-specific geometries of human carotid bifurcations were created based on CT-A scans. Laminar blood flow was modelled in Ansys® Fluent® using Carreau model of non-Newtonian incompressible liquid. To avoid an unrealistic piston profile at the inlet, a 3D parabolic velocity profile was computed from volumetric flow boundary condition. In total, two different (old [5] and young [7]) archetypal flow waveforms were used. Three element Windkessel was imposed at each outlet. Its parameters (three per each outlet) were estimated via nonlinear least-squares optimization method to fit the measured flow waveforms. The estimation methodology was inspired by [8]. The computational domain was discretized in time with a step size of 0.003 s. A time-averaged wall shear stress (TAWSS) together with a relative residence time (RRT) were used as hemodynamic indicators for the risk of atherosclerosis development. Regions are classified as atheroprone (from a merely fluid dynamic point of view) if TAWSS is < 0.48 Pa and RRT > 2.9 [9].

Results

Results were extracted from the 3rd cycle of transient 3D CFD simulations reaching a stabilized cyclic response. They show significant enlargement of the low TAWSS area (i.e., below the threshold value) for the older archetypal waveform (see Fig. 1) while the RRT remains almost constant for all geometries.

Discussion

Although low TAWSS is a necessary indicator of a plaque formation, it is not sufficient for reliable prediction of the future plaque location [10]. Since the low TAWSS region overlaps a region with oscillatory flow and high RRT, it seems that the significant decrease of the TAWSS caused by the old archetypal flow waveform may increase the risk of future atherosclerosis development, which is probably one of possible mechanisms how atherosclerosis is accelerated.

References


Acknowledgements

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SENSITIVITY OF KNEE JOINT FINITE ELEMENT SIMULATIONS TO UNCERTAINTIES IN MUSCULOSKELETAL MODELING INPUTS

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Introduction
Various simulation pipelines combining musculoskeletal and finite element (MS-FE) analyses have been developed to investigate mechanical responses of knee joint cartilage under different physical activities. However, it is not fully understood how the uncertainty in the MS modeling and simulation assumptions (optimization function for muscle activation patterns, marker position, cartilage stiffness, maximum isometric force of muscles) affect the predicted tissue-level mechanical responses of the FE models. Thus, we investigated sensitivity of the mechanical responses of the knee joint FE model to the MS modelling and simulation assumptions during gait.

Methods
One female participant was selected from a previously collected dataset (CAROT study) [1]. A previously developed atlas-based MS-FE modeling framework was utilized to generate the MS and FE knee joint models of the subject [2]. First, a MS knee model [3] with cartilage elastic modulus of 20 MPa, weighted optimization and knee markers in the location as per during the data collection was constructed. Then, some of the critical assumptions made during the MS modelling and simulation were varied resulting in five sets of MS simulation results [4] (Figure 1A). Five walking trials of the study subject were averaged to provide motion input for each FE model.

The FE model with knee ligaments modeled as spring bundles, fibril-reinforced poroviscoelastic cartilage and fibril-reinforced poroelastic menisci was simulated using the outputs (knee flexion angle, tibiofemoral joint contact forces, and joint moments) obtained from each of the aforementioned MS simulation (Figure 1A). Cartilage stresses and strains, estimated by the FE model, were compared between the models.

Results
The different assumptions in MS modeling and simulation moderately influenced the simulated stresses and strains of cartilage in the FE model (Figure 1B). In femoral cartilage, altered muscle activation optimization function and misplaced knee markers (anteriorly or posteriorly), with respect to the reference, resulted in highest maximum principal stresses and fibril strains in the FE model along the entire stance. Moreover, in tibial cartilage these higher stresses and strains were observed after midstance. However, reduced stiffness of soft tissues and altered maximum isometric force of muscles had negligible impact on the simulated cartilage stresses and strains.

Discussion
Marker placement and simulated neural solutions are important factors that affect the motion and muscle input parameters used in the FE model. However, the induced uncertainties in gait inputs to our FE model resulted in modest differences in tissue-level mechanical outcomes. These variations may become more significant when goal is to compare absolute mechanical responses.

References

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Figure 1: (A) Workflow of the study. (B) Simulated maximum principal stress and fibril strain in medial tibial and femoral cartilage for the FE model simulated with different MS model inputs.
IMPACT OF PATIENT MORPHOLOGY ON VALVE THROMBOSIS – COMBINING PATIENT DATA AND COMPUTATIONAL MODELING

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Introduction
Clinically apparent transcatheter heart valve thrombosis (THVT) is rare (<3% incidence), while subclinical THVT is more frequently found (7-35%). THVT may affect prosthetic valve function and lead to early valve degeneration [1-3]. The specific relevance of aortic root geometry on the occurrence of THVT and the etiology of THVT is largely unknown. Disturbed blood flow past prosthetic valves has been linked to thrombus formation [4]. Aortic morphology and dimensions and location of coronary ostia are known to influence the aortic flow field [5,6,7]. In this pilot study, our objective was to (1) investigate the aortic morphology of THVT patients compared to unaffected transcatheter aortic valve implanted (TAVI) patients, and (2) to investigate how the differences impact the aortic root flow using a dedicated computational model. We hypothesize that some aortic morphological features might promote THVT by affecting the wash-out efficiency of the sinus and the high shear stress regions downstream of the valve.

Methods
Aortic root morphology: 8 patients with THVT and 16 unaffected controls (2 controls per THVT patient with the same valve type and size) from the Bern-TAVI registry (clinicalTrials.gov Identifier: NCT01368250) were included. Aortic root dimensions were assessed from pre-TAVI multi-detector computed tomography scans and compared.
Computational model: The effect of the identified morphological differences on the flow field in the aortic root were investigated in a computational study. Two idealized aortic root geometries were used with sinotubular junction (STJ) and ascending aortic (AAo) diameters selected according to the observed patient dimensions (one THVT model and one control model). Typical pressure gradients seen in THVT patients, and the general TAVI patient population were imposed in the two models, respectively [1].

Results
The THVT patients were implanted with five different valve types and three different valve sizes. In THVT patients the right coronary artery height was significantly lower (-40%) and the STJ and AAo diameters tended to be larger (9% and 14%, respectively) compared to the controls.
In the computational study, the larger AAo and STJ diameters of the THVT model led to lower backflow velocities (-11%) at the STJ and lower velocity magnitudes (-5%) in the sinus compared to control. The systolic turbulent dissipation rate (Figure 1) was higher (8%) in the AAo and lower in the sinus (-9%) compared to control.

Discussion
This pilot study suggests that the individual aortic morphology might have a direct impact on clinically apparent THVT. In the computational study, the observed anatomical differences in THVT patients led to blood flow patterns potentially favoring thrombus formation by reducing wash-out efficacy in the sinus and promoting platelet activation in the turbulent jet distal to the valve. The observed anatomical parameters may be used to identify patients at risk for THVT but require validation in a larger clinical study.

References

Figure 1: The systolic turbulent dissipation rate in the control (left) and THVT patient model (right).
THE MODULATION OF MUSCULAR SYNERGIES AS A FUNCTION OF UNEXPECTEDLY PERTURBED GRASPING TASKS

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Introduction

Muscle synergies (MS) are central building blocks for motion production and offer the potential of a more intuitive control compared to conventional pattern recognition methods in upper limb prosthetics since they accompany grasping movements without delay [1]. However, it remains unclear until now to what extent a prosthetic pattern recognition control based on MS is affected by external perturbations. The aim of the study is to investigate the modulation of a MS model in the presence of external perturbations.

Methods

The activity of 12 arm muscles in 15 healthy volunteers was measured using EMG during object manipulation tasks with and without unexpected weight change. The movements of instrumented grasping objects were tracked using a Vicon optical system. MS were extracted with a non-negative matrix factorization (NNMF) during different grasping phases and grouped with a k-means cluster analysis. Their reconstruction was then performed once with temporal-fixed and once with spatial-fixed synergy components. A significant drop in reconstruction quality would indicate that activation changes cannot be modulated by the respective unfixed component. Wilcoxon signed-rank and rank-sum tests were applied for statistics.

Results

Independent of the motor correction due to external perturbations, the number of recruited MS remained unchanged for each grasping phase. While there was a significant reduction in the reconstruction quality of perturbation-induced muscle activation in temporal-fixed NNMF, this quality remained unchanged in spatial-fixed NNMF. The temporal modulation of subject-invariant MS significantly depended on the context of the perturbation, whereas the MS activation profiles showed a correlation with the object trajectories (Fig. 1).

Discussion

MS appear to be modulated by their temporal rather than their spatial components during perturbations. Thus, modulated MS do not affect the pattern recognition of a prosthetic control and the classification accuracy should not be changed. The context dependence of modulation may find introduction in prosthetics as a complementary control signal to detect the nature of perturbation. It could be used to automatically correct the prosthetic hand (e.g., a follow-up grasp in case of an unexpectedly heavy object).

References


Acknowledgements

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Figure 1: Relative centroids of spatial MS components from cluster analysis during the object manipulation phase (bar graphs, left) and corresponding temporal activations (line graphs, right) for expected (Block, gray), unexpectedly heavy (PertHeavy, purple), and unexpectedly light (PertLight, green) object weights. Spatial (DOT) and temporal ($\rho$) similarity values are next to the graph; $\rho_{50}$ is the similarity value for the first 50% of the manipulation phase and $\rho_{100}$ covers the entire grasping movement.
THE INFLUENCE OF THE POSITION ANGLE OF THE ARTIFICIAL BILEAFLET VALVE ON THE FLOW IN THE CORONARY ARTERIES

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Introduction
Ischemic heart disease (IHD) is one of the leading causes of mortality worldwide [1]. Some patients with IHD also have other diseases, including aortic stenosis and aortic valve dysfunction. The abnormal valve function causes disturbed blood flow. Often the only effective solution is artificial aortic valve implantation. This study aims to verify the influence of the position angle of the artificial bileaflet valve on the flow in the coronary arteries in patients with IHD since clinical studies do not report on the optimal orientation of the prosthesis [2,3].

Methods
The geometrical model of blood was generated in Mimics software from CT images of a patient with left coronary artery stenosis. The model consisted of the aortic root, Valsalva sinuses and coronary arteries. The bileaflet aortic valve was placed under the sinuses in four different angle positions: 0°, 90°, 120° and 240°.

The blood flow was determined using ANSYS 2020 R2 software. Flow velocity at maximum valve opening was determined on the basis of a Doppler ultrasound examination. The value of 0.97 [m/s] was set at the system’s inlet. The zero gauge pressure was set at the aortic and coronary arteries outlets. The blood flow was adopted as Newtonian.

Results
As a result of the simulations, we obtained blood flow in the aorta and coronary arteries. Figure 2 shows the flow velocity distribution in a stenosis cross-section in four different implantation angle positions of the bileaflet valve.

Discussion
The angle position of implantation of bileaflet aortic valve has a significant impact on the blood flow velocity in coronary artery stenosis. This means that in some cases, wrong implantation could lead to difficulties in blood transport through coronary arteries and to myocardial infarction. The angular position of the valve could also affect flow pattern, valve closure, and shear stress downstream of the valve. This requires further research. We expect that the conducted research will allow determine the methodology of assessing the optimal angle of valve implantation for a specific condition of a given patient.

References
MECHANICAL FUNCTION IN THE INFARCTED HEART SUPPORTED BY A REGENERATIVE ASSIST DEVICE: A COMPUTATIONAL STUDY

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Introduction
Adverse ventricular remodelling following acute myocardial infarction (MI) may induce ventricular dilation, fibrosis and loss of global contractile function, potentially resulting in heart failure. Cardiac patches, composed of living cardiac (https://projectbrave.eu/) may be able to restore cardiac function and reduce adverse ventricular remodelling post-MI. Computational modelling can aid in device design without the complex environment and intra-patient variability that make experimental techniques difficult and time-consuming. In this study, we employ computational modeling to assess the role of patch fiber orientation on functional improvement in cardiac pump function and local tissue mechanics.

Methods
We extended the finite element model of cardiac mechanics in [1] to model a cardiac patch, implanted over a chronically remodeled infarct area. The infarct had a circular shape, lacked active contraction and had a 10-fold increase in passive stiffness. A cardiac patch was modeled as a rectangular strip of material measuring 6 by 4 cm with a thickness of 2 mm. We assumed material properties of healthy myocardium within the cardiac patch. Fibers were aligned along the long side of the patch. In simulations P0, P45 and P90, the long side was oriented at an angle of 0, 45 and 90 degrees with respect to the LV circumferential direction. Cardiac function was assessed through global hemodynamics and local myofiber mechanics, computed in 3 points throughout the geometry. Local mechanics in the cardiac patch were averaged for a grid of 25 centrally positioned sites.

Results
The infarct, 15% in size, reduced stroke work by 30% compared to the healthy heart. Cardiac patch simulations showed minor increases in stroke volume and systolic pressure. Of the total loss in stroke work, 5.2%, 7.5% and 1.6% was recovered in simulations P0, P45 and P90 respectively. In the myocardium, stress-strain loops at locations UM, CI and LL (fig 1a.) were similar in the healthy case (REF); work density, represented by the surface area enclosed, was similar as well. In chronic MI (CMI), loops in healthy tissue at locations UM and LL skewed leftward, indicating reduced work density, and disappeared in CI. Loops in UM and LL recovered best in patch simulations P45. Stress-strain loops within the patch (P) generally showed reduced strain excursion, low fiber stress, and low work density. Furthermore, the stress-strain loop in simulation P90 was shifted to the left.

Discussion
The amount of pump function lost due to MI exceeded the loss in healthy tissue by about two-fold. This disproportional loss was attributed to unfavourable mechanical interactions between infarcted and healthy tissue, adjacent to the infarct area, resulting in a reduced ability to develop stress. The low patch-induced improvement of cardiac function is due both to the low patch volume (4ml) and to the limited strain excursion, resulting from tethering to the underlying stiff infarct. In varying the patch orientation, simulation P45 showed the largest amount of functional recovery. Work density in the patch was higher, but also work density in the native, infarcted and supported ventricle.

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**FOREARM MUSCULAR ACTIVITY DURING THE REAL VS VIRTUAL BOX & BLOCK TEST**

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**Introduction**

The use of virtual environments for rehabilitation in patients with neurological diseases is becoming increasingly common, such as the simulation of the Box and Block dexterity test (B&B). The use of virtual tests in rehabilitation has the advantage of being able to adjust the level of difficulty/demand to the patient’s condition. Although there are several works that have validated this test in virtual rehabilitation [1,2], these have focused on studying the correlation between the results of the real and virtual tests, and the kinematic requirements of the arm, but without checking if muscular demands of the hand and wrist are similar to the real ones, which is the proposal of this work.

**Material and Methods**

The experiment, approved by the ethics committee, consisted of recording the muscular activity of the right forearm of 9 healthy subjects by means of seven surface electromyography (EMG) sensors (Biometrics Ltd) placed in seven representative spots obtained in a previous work [3]. Both the real test and the virtual one, which uses the Leap Motion [2], were performed while the subjects were instrumented (Figure 1). EMG signals were properly filtered and normalized with 7 maximum voluntary contraction (MVC) actions according to [3] to obtain the muscle activity of all the spots.

![Figure 1: Subject instrumented with 7 EMG electrodes (left) while performing the real (centre) and virtual test (right).](image)

Five repetitions of each test were performed. In each repetition, subjects were asked to move 3 cubes from one container to another as fast as possible. The descriptive statistics (mean and range) of the 9 subjects for each record (real and virtual) were obtained. A repeated measures ANOVA was performed by spot with Bonferroni adjustment to check for significant differences (p ≤ 0.05) between repetitions, and an analogue ANOVA to check for differences (p<0.05) between the real and virtual test (considering only the last repetition of each).

**Results**

No significant difference in muscular mean and range was found between repetitions in both real and virtual test. Table 1 shows the statistics across subjects (mean values and standard deviation in brackets) of the mean and range EMG activity in last repetition for both tests, and cases with significant differences are in bold and underlined.

<table>
<thead>
<tr>
<th>Spot</th>
<th>REAL B&amp;B</th>
<th>VIRTUAL B&amp;B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>1</td>
<td>0.025(0.037)</td>
<td>0.084(0.016)</td>
</tr>
<tr>
<td>2</td>
<td>0.025(0.015)</td>
<td>0.041(0.023)</td>
</tr>
<tr>
<td>3</td>
<td>0.030(0.009)</td>
<td>0.058(0.024)</td>
</tr>
<tr>
<td>4</td>
<td>0.035(0.016)</td>
<td>0.073(0.041)</td>
</tr>
<tr>
<td>5</td>
<td>0.058(0.026)</td>
<td>0.081(0.031)</td>
</tr>
<tr>
<td>6</td>
<td>0.062(0.025)</td>
<td>0.088(0.033)</td>
</tr>
<tr>
<td>7</td>
<td>0.037(0.014)</td>
<td>0.059(0.041)</td>
</tr>
</tbody>
</table>

Table 1: Statistics across subjects (mean/SD) of mean and range EMG activity between real and virtual B&B. Significant differences in bold and underlined.

**Discussion**

Muscular ranges are not affected by the type of test, real or virtual, but there are muscular differences in the mean values in some spots. In general, all spots present greater mean values during the real test. In particular, in the real test there are significant greater mean muscular values of wrist and digit flexors, as well as in wrist extensors and radialis deviators. The results are in accordance with the hand kinematics observed in a previous work [4], where greater flexion of the proximal interphalangeal of the index, and the median posture of the interphalangeal of the fingers were found. These differences may be due to these hand posture differences but also to the fact that picking up a real cube require exerting enough pressure to avoid slipping. The wrist extensors in the real test requires a greater mean value, probably due to the difficulties of controlling virtual spatial limits. It is necessary to check if there are differences in the kinematic and muscular patterns in case of patients.

**Acknowledgements**

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WHICH ARE THE MINIMUM ACTIVITIES OF DAILY LIVING TO REPRESENT FOREARM MUSCLE ACTIVITY?

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Introduction

Assessing muscle activity of the forearm muscles during the performance of activities of daily living (ADLs) is important to understand muscle function, to identify muscle imbalances, in determining the effectiveness of rehabilitation interventions or the potential risk of injury, and to develop and evaluate assistive devices [1,2]. However, its applicability would benefit from reducing the number of tasks to be measured in a controlled environment and with a reduced cost of time. A recent work [3] identified a set of 10 tasks representative of the hand kinematics during ADLs. The aim of this work is identifying a small set of tasks representative of the forearm muscular activity during ADLs.

Material and Methods

We used the KIN-MUS UJI dataset [4] which contains recordings of muscle activities (7 channels) of 22 participants during the execution of 26 varied activities of daily living (Table 1). Muscle EMG was recorded using surface EMG bipolar electrodes and muscle activities were computed normalising EMG with the maximal values across all records for each subject. Their locations were chosen to maximize the extraction of information generated by the forearm muscles [4]. The recorded ADLs include 26 actions, most of them included in the Sollerman Hand Function Test (SHFT), commonly used to assess hand function in clinical settings and involve the interaction with objects of different sizes and weights. First, each record was rescaled to 1000 frames, and statistics (mean and range) were obtained from all data and each spot (\textsuperscript{26}STATS). Then, an iterative method was followed [3]: in each step, the data was reduced by removing each ADL data one-by-one, and the resulting N datasets were used to obtain N mean and range values for each spot (values obtained per each ADL; N = 26 – k, in the k-th step). In each step, the dataset explaining highest mean and range values was selected as input for the next step. This iteration was repeated until one ADL remained.

Results

Figure 1 shows the worst-case statistic (that statistic that least resembles the original) respect to the \textsuperscript{26}STATS, for each step of the iterative ADL removal. With only 3 ADL (#10, #11 and #14) the mean and range values of all the spots were equal or slightly higher than the statistics obtained from all the ADLs. Table 1 shows the statistics \textsuperscript{11}STATS) from this set of 3 ADLs and those obtained from \textsuperscript{26}STATS. Mean muscular activity values from \textsuperscript{11}STATS are slightly higher than \textsuperscript{26}STATS, and range values are very similar.

Discussion

The results suggest that a set with only 3 ADLs (Tying a shoelace, unscrewing two leads and cutting with a knife) could be enough to assess forearm muscle activity underlying ADL, with high level of similarity to those considering a wide set of varied ADL. Unscrewing two leads and cutting with a knife are already part of the activities included in the set of 10 activities representative of kinematics during ADL [3]. Therefore, adding the task of tying a shoelace could complete the set to be representative of both hand kinematics and muscle activity during ADL.

Acknowledgements

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References

INVESTIGATION OF HUMAN MITRAL VALVE MECHANICS USING AN IN-HOUSE HYBRID PHYSICAL-COMPUTATIONAL PLATFORM

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Introduction

The mitral valve (MV) is one of the most complex valves in human heart and prevents backflow of blood from the left ventricle (LV) to left atrium (LA). Given the increasingly high prevalence and significance of structural MV pathologies [1] and lack of diseased, large animal models to study them, it is imperative to develop a platform for modelling and testing of synthetic MVs with added advantages of anatomical consistency, reproducibility, and extended shelf life. In this work, a hybrid physical-computational platform is presented with anatomically informed MV geometry and controlled leaflet thickness capable of mimicking healthy human MV mechanics. The physical model was used to validate the finite element analysis (FEA) model. The validated FEA model can be used for fast parametric studies to investigate the effects of MV structural and/or material changes on its mechanics.

Methods

Physical Model: An idealized 3D MV geometry was created in SolidWorks using healthy human MV measurements [2] and further used to 3D print mould parts for elastomeric casting of silicone MV leaflets with Ecoflex 00-30 silicone and gauze. Chordae were embedded in the leaflets and glued at the other end to 3D printed papillary muscle posts. The fabricated MV annular section was embedded in Moldstar 15 (Fig 1A). A 3D left heart simulator flow rig was constructed for testing the synthetic MV. This rig was filled with blood mimicking mixture consisting of 40:60 water-glycerol volume ratio. To actuate the flow, a position-time curve was defined for the linear motor to create a reciprocal motion to mimic pulsatile physiological pressure associated with a cardiac output of 4.5 l/min and a forward stroke volume of 64 ml at 70 bpm (T=852 ms). Fluid pressures were measured in the LA and LV chambers and used to calculate the transvalvular MV pressure (Fig 1B).

FEA model: MV geometry was discretized into 18444 reduced integration hexahedral elements (C3D8R) with Abaqus (Dassault Systemes, USA - Fig 1C). An isotropic hyperelastic 5th order reduced polynomial material model was fit to Ecoflex 00-30 and gauze tensile test data and applied to each leaflet. Primary marginal chordae were defined in form of spring elements with a stiffness coefficient of 1.6 N/mm [3]. The mitral annulus and papillary muscle posts were fully fixed. Explicit general contact, including self-contact with an isotropic friction coefficient of 0.05 [3] was applied. A surface pressure ranging from -8 to 120 mmHg was applied to the ventricular side of the leaflets, representing a full cardiac cycle of 852 ms at 70 bpm.

Results

Qualitatively, the FEA and physical models showed good agreement in terms of valve closure and leaflet coaptation. However, a slight opening and regurgitant zone (shown in red) was visible in the physical model, which was further investigated quantitatively in ImageJ (NIH, USA) and was 4.22 mm² and was equivalent to 2.25% of the orifice area of an open MV in peak diastole. No bulging of the leaflets into the LA was detected in either of the models. The leaflet coaptation length was measured using the midsection cutview of the FEA model to be 6.55 mm, which is within the healthy range of 4.9 ± 3.8 mm [4].

Discussion

Preliminary results show good agreement between silicone FEA and physical model. This combined computational-physical platform is a powerful tool that allows for parametric sweep studies of MV non-pathological and pathological changes such as annular dilation, chordae rupture, papillary muscle position change, and calcification, which could provide insight on their clinical impact and assist with procedure planning and advance medical device development and testing.

References

SENSITIVITY OF INTRACRANIAL ANEURYSM HAEMODYNAMICS TOWARDS VARYING ARTERIAL TREE EXTENSIONS

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ERC-2021-COG CURE 101045042

Introduction
Blood flow simulations of the human arterial system present a promising tool to help answer open questions about the advancement of vascular diseases and their possible causes. Vessel malformations in the brain region, such as Intracranial Aneurysms (IA), pose a special challenge due to their delicate location and an overall heterogeneous arterial morphology between patients [1]. One key component required to obtain physiologically accurate flow profiles is adequately simulating the peripheral flow surrounding the region of interest. To further develop this topic, this study assesses the influence of different 3D domain extensions on IA haemodynamics.

Methods
Three patient geometries centered at the Circle of Willis are investigated, each harbouring an IA at the PCom-ICA junction (see Figure 1). The segmented geometries are varied progressively by reducing their spatial extension, resulting in three extension levels. The incompressible Navier-Stokes equations are solved numerically with generalized pulsative inflow conditions [2]. The intrinsically shear-thinning rheology of blood is described through the Carreau-Yasuda model. Outlet boundary conditions are derived from the Principle of Minimum Work and transformed into pressure conditions. The results are compared by inspecting the flow characteristics and common risk indicators, such as the Wall Shear Stress (WSS) and the oscillatory shear index [1].

Results
The obtained haemodynamic profiles show that locally constrained arterial trees can in some cases lead to considerable differences in flow structures, even in qualitative terms. The alterations of the flow are consistent with the changes of fluxes at the aneurysm's bifurcation and are therefore case-dependent. The WSS accordingly changes in magnitude and location following the change of the primary variables. Oscillatory shearing, caused predominantly by chaotic flow patterns, is found in regions of low shearing inside the dome.

Discussion
Different domain extensions can cause substantial changes in local haemodynamics. Their qualitative and quantitative measures however remain patient-dependent. IAs located at either of the posterior communicating arteries must be treated carefully since no general boundary condition model for this vessel type has been identified as optimal by the research community. The work affirms that simulation parameters, such as the domain size, can cause considerable inter-patient variability [3, 4] and should be treated following an elaborated unified strategy.

References

Figure 1: Maximum intensity projections of the flow velocity at diastole of two patients with ICA-PCom bifurcation aneurysms.
DXA-DRIVEN PIPELINE FOR BUILDING BIOFIDELIC FEMS FOR HIP FRACTURE RISK ASSESSMENT IN CLINICAL COHORTS

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Introduction

Osteoporosis is a chronic disease characterized by low bone mass and reduced structural integrity of bone [1]. Stratifying fracture risk based on aBMD alone lacks sensitivity for clearly identifying individuals at risk [2]. Femoral strength predicted using CT-based subject-specific biofidelic Finite Element Models (FEMs) is a promising alternative [3]. However, CT scans are associated with higher costs and radiation compared to DXA scans, which are currently used for diagnosing osteoporosis. In this project, we developed an automatic pipeline, for building biofidelic FEMs based on input from 3D optical- and DXA scanners, for quantifying fracture risk with and without preventive intervention in large clinical cohorts.

Methods

The automatic modeling pipeline was scripted in Python (vers. 3.9), utilizing different open-source and commercial software for solving various tasks. Inputs available for building the models are hip and whole body DXA scans (Hologic Horizon W), a database of 3D Shape scans using TC²® (vers. 19M) from subjects in a cohort of community-dwelling elderly Singaporean, and a database of pelvic FEMs.

![Figure 1](image1)

Figure 1: (1) DXA to a 3D-FEM, (2) Hip variables from whole body DXA scans, BMI matching pelvis and 3D shape scans, (3) Biofidelic model without intervention (4) Biofidelic model with cement augmentation and hip protector intervention.

The steps for building the biofidelic FEMs (Figure 1), demonstrated on a sample subject are: 1) 3D-FEM derived from the DXA scan of the proximal femur using 3D-Shaper® (vers. 2.11.1) and ANSA (vers. 22.0.1). Material properties are mapped to the FEMs as in [4]. 2) Descriptive variables for the hip are measured based on the whole body DXA scan, and a soft tissue and pelvis morphed to shape matching BMI matching of the subject. 3) The assembled model is subjected to a simulated sideways fall (LS Dyna 12.0) at an impact speed of 3 m/s [3]. 4) Preventive intervention module is called for modelling a selected risk mitigation strategy [5,6]. The femur is considered fractured if the 1st principal strain >2.8% as described in [7].

Results

The simulation results for a sideways fall of a female (age-62, height-146 cm weight-40kg, aBMD-0.689) with and without the use of interventions are shown in Figure 2. Augmenting the femur with cement injection increased the femur strength by 5%. Hip protector attenuated the femur force by 11%. Both interventions prevented fracture in the femur.

![Figure 2](image2)

Figure 2: (1) Force-time response for baseline (red), cement-augmentation (green), and hip protector (pink); (2) First principal strain response for baseline, cement-augmentation and hip protector model.

Discussion

A novel automatic pipeline has been developed for building biofidelic FEMs from DXA scans. The high level of automation will allow us to model large cohorts of elderly subjects for studying the efficacy of existing and emerging preventive treatments. The outcomes will be used to inform health-care economic models on expected risk reduction in the treatment arm vs. the placebo arm.

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Acknowledgements

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The Effects of Running Shoes on Ground Reaction Force in Male Recreational Runners

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Introduction

Running is an accessible type of cardiovascular exercise, among its numerous benefits. However, running-related injuries are prevalent among runners, with up to 79% of runners suffering from musculoskeletal ailments annually. The high incidence of running-related injuries has prompted healthcare professionals and researchers to investigate their causes and prevention strategies. Barefoot performance is an unstable condition, and barefoot running has recently gained popularity among runners who believe it may result in fewer running-related injuries. Bionic shoes combine the functions of barefoot running and foot protection and incorporate traditional unstable structures based on bionic science. The purpose of this study was to investigate how bionic shoes affect ground reaction force (GRF) before and after a 5 km run.

Methods

Sixteen male recreational runners participated in this study and finished two 5 km running sessions (a neutral shoe session and a bionic shoe session). Two-way repeated-measures ANOVAs were used to analysis the differences in GRFs.

Results

The results showed that compared to the neutral shoes, bionic shoes have significant decreases in vertical impulse, peak propulsive force, propulsive impulse, and contact time, while the braking impulse and vertical instantaneous loading rate (VILR) increased significantly. Main effects for a 5 km run were observed at vertical GRFs and anterior-posterior GRFs. Post-5 km running trials revealed an increase in peak vertical impact force, vertical average loading rate (VALR), vertical impact loading rate (VILR), peak braking force, and peak braking impulse, and a decrease in peak propulsive force and peak propulsive impulse. The interaction effects existed in VILR and contact time.

Discussion

The results suggest that bionic shoes may benefit runners with decreased injury risk during running. Based on the results of this study, bionic shoes and a 5 km run altered ground reaction forces during running, especially the vertical and anterior–posterior forces. These findings provide preliminary evidence suggesting that bionic shoes combined with the functions of barefoot running and protective elements, traditional unstable structures and bionic science may benefit runners in reducing injury risk during running.

Figure 1: Ground reaction forces (GRFs) waveforms of the mean (SD) over the stance period of four running tests. Significant main effects of the shoe conditions, 5 km run, and interaction effects (p < 0.05) are highlighted (grey horizontal bars at the bottom of the figure) during consistent periods from SPM1d analyses.

References

ESTIMATION OF INTERSEGMENTAL LOAD AT L5-S1 DURING LIFTING/LOWERING TASK WITH MARKERLESS MOTION CAPTURE

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2. Arts et Metiers Institute of Technology, Laboratoire de Conception Fabrication Commande, France

Introduction
In an industrial environment, workers are often required to repeat specific gestures in the workstation, which can cause musculoskeletal disorders (MSDs). Intersegmental load estimation plays an important role in MSDs risk evaluation [1, 2]. It can be calculated using marker-based motion capture and force platforms based on information such as human posture, external forces applied to the body, and anthropometric measurements. However, it is difficult to apply for evaluating the MSDs risk of workers in the factory without obstructing their activities. Therefore, in this study, we present a solution to estimate the intersegmental load at L5/S1 for the lifting/lowering task using a multiview markerless motion capture system.

Methods
Twelve individuals (24.2±2.3 years, 172.4±10.1cm, 65.9±14.7kg) took part in the study (CPP 06036, Paris VI). A surgeon attached 57 markers to each participant. The participants were instructed to lift a cardboard box onto a table and then move it back down. Two different systems were used to record the movement: a marker-based system (Vicon, UK) (synchronized with a force platform) and a markerless system with four digital cameras[3]. The dataset collected included over 180K multi-view face-blurred RGB frames and the corresponding 3D coordinates of 17 key points. A neural network [4] was trained for 3D human pose estimation (HPE) from multi-view RGB images. Three-fold cross-validation was performed during the training where the dataset was split into three parts with each being used as the test set in turn. Based on the HPE results, the human body was modeled as 10 body segments where the inertial properties of each were calculated through the method in [5]. The methods top-down and bottom-up [1] were applied to calculate L5/S1 loads. The top-down method was used for estimation with the RGB images, whereas the bottom-up reference was calculated with the data from Vicon and force platform. The RMSE was calculated between the load estimate and the reference value on the whole dataset.

Results
The load estimates were in good agreement with the reference (Figure 1). The RMSE for the force estimation in the three directions were approximately or less than 21N, regarding the moment, they were around or less than 11Nm (Table 1).

Discussion
The calculation of the load estimate with markerless system and with the reference adopted independent calculation strategies to compute body segments and the external forces. Therefore, the good agreement validated the consistency of the load estimation. Besides, the estimated load and the RMSE were in line with the results in the literature [1, 6]. In [6], the RMSE between the top-down and bottom-up with markerless method was below 28 Nm. However, in our study, the L5-S1 load based on markerless capture was evaluated against a more accurate bottom-up reference, based on marker-based capture and force platforms. While further validation in industrial setting should be performed, this study establishes the feasibility of estimating L5-S1 load thanks to a multiview markerless motion capture system.

References

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GUIDING CARDIAC FIBROBLAST ORGANIZATION BY STIFFNESS PATTERNS OF GELMA HYDROGELS

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Introduction
Cells are greatly influenced by the biomechanical signals of the extracellular matrix (ECM). In particular, ECM stiffness gradients and patterns are critical in cell migration (durotaxis) (1). On the other hand, cell and ECM organization is essential for the function of tissues like the myocardium. Several myocardial diseases, such as myocardial infarction (MI), are associated with a loss of cell organization and change ECM stiffness, with subsequential tissue malfunction. ECM mechanical cues are being used to guide cellular organization in engineered tissues and in vitro environments (2). However, little is known about how ECM stiffness guide cell organization. Therefore, a better understanding of this phenomenon will help to develop novel regenerative strategies. To the best of our knowledge, we report the first experimental evidence on how cardiac fibroblasts (cFb) align on ECM stiffness patterns on gelatin methacryloyl (GelMA) hydrogels.

Methods
10 µL of GelMA solution (10 % w/v) was placed in a bottom glass 6-wellplates well and allowed for physical gelation. Then, the gels were placed in a fluorescence microscope (Leica, DMi8) stage with a coupled PRIMO (Alvéole, France) device. PRIMO allows for UV-crosslinking of the gels with high-spatial resolution without using photomasks. Stiffness patterns of width 20, 50 and 200 µm separated 50 µm and length 500 µm were created with 10 s of UV illumination at 8.9 mW/cm². Nanoindentation (Optics11) was used to measure the stiffness patterns created. Primary cFb were seeded on top of the stiffness patterned gels and cultured for 24h in high-glucose DMEM medium (supplemented with 10% FBS and 1% P/S). Subsequently, samples were fixed and immunostained for the actin cytoskeleton and nuclei. cFb orientation was calculated using an open-source MatLab code (FOATool) (3).

Results
Stiffness patterns were created successfully with the stiffness of the UV-exposed area ~5-fold higher than the unexposed (Fig. 1A). cFb cultured on top of the gels aligned along the direction of the patterns (90°) for the 20 and 50 µm width patterns. In contrast, cFb seeded on 200 µm width patterns did not show any preferred aligned direction (Fig. 1B, C).

Discussion
We have applied a technique to locally crosslinking GelMA gels with UV light without needing photomasks. This technique can manipulate ECM stiffness in a high resolution in living cultures. Our results show that cFbs align in patterns below 200 µm in width, suggesting that stiffness-guided cell organization is effective at patterns sizes similar to cell dimensions. This phenomenon is similar to contact guidance generated by protein patterns (4). This evidence can serve to improve the understanding of how mechanical cues shape cell and tissue organization after MI.

References
PARAMETRIC ANALYSIS OF GEOMETRIC VARIANCE IN ARTICULAR CARTILAGE SAMPLE BIOMECHANICS USING FINITE ELEMENT

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Introduction
Osteoarthritis (OA) affects joint mechanics through e.g., degeneration of cartilage and subchondral bone. However, the mechanisms behind how the biomechanical properties change with OA are not fully understood. Experimentally, the variability in force response between different samples during mechanical testing is generally large, even when comparing multiple samples from the same knee. Such a high variability can hide key information during OA progression over time. Traditionally, the samples used in unconfined compression are assumed to be perfectly cylindrical. Ongoing work using in situ mechanical testing and synchrotron phase-contrast micro-tomography shows that the samples are not always perfectly cylindrical. In this study, we aim to quantify the influence of different geometric imperfections on cylindrical samples for the biomechanical properties of cartilage during unconfined compression using Finite Element (FE) modeling.

Methods
Based on experimental unconfined compression (2x15% strain, 1%/s), stress relaxation data from multiple bovine knee cartilage cylindrical samples from a single specimen was used to determine the fibril-reinforced poro-visco-hyperelastic (FRPVE) material parameters [1]. For this, a "geometrically ideal" average cartilage sample FE model was created in Abaqus. Based on the tomography images (n=34 samples), three geometric imperfections were identified: missing cartilage areas at the base, remnants of calcified cartilage at the base and an uneven top of the sample (Fig. 1A). The imperfections were assumed to behave like planes intersecting the ideal sample; the height and angle for each plane were measured (Fig. 1B). To quantify the influence of the imperfections, a 3-level Design of experiment (DOE) were designed with the levels based on the experimental mean +/- std. The DOE included 8 factors for creating the geometric imperfections that were simulated in 45 different combinations determined by the statistical software JMP. The outcome parameters were equilibrium forces, peak forces and relaxation times on each of the two stress-relaxation steps. The influence of the imperfections was calculated using 2-way ANOVA.

Results
The fitted FRPVE parameters were (E_m=0.27MPa, ν=0.22, E_s=4.3MPa, E_s=315MPa, k_0=0.01mm^4/NS) M_0=6.2). For the DOE results, the top angle contributed the most to the variation (25-50% of variability) in the equilibrium forces. The peak forces were affected almost equally by the top angle and the missing areas of cartilage (ca 25%) while relaxation times were most affected by the height of the remaining calcified cartilage (ca 30%).

Discussion
Based on our results, geometric variation of the samples due to small imperfections have an impact on the cartilage biomechanical response. This suggests that more rigorous sample preparation should be considered to minimize the imperfections. Also, this study can help to distinguish among the variability from sample preparation, uncertainties in mechanical testing and the inherent heterogeneity of cartilage tissue properties.

References

Acknowledgements
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CANCAN ALTERED MOTOR CONTROL DECREASE JOINT LOADS IN PEOPLE WITH TYPICAL AND INCREASED ANTEVERSION ANGLES?

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Introduction
Excessive loads at lower limb joints can lead to pain and degenerative diseases [1]. Increased femoral anteversion angle (AVA) can alter a person’s gait and lead to skeletal disorders [2]. Our previous work showed how large AVA increase muscle co-contraction during walking and lead to significantly increased hip and knee joint loads [3,4]. Real-time biofeedback training can be used to alter muscle recruitment strategies and therefore potentially decrease joint loads [5,6]. The aim of the current study was to investigate how different muscle recruitment strategies can alter joint loads in people with typical and increased femoral AVA.

Methods
Musculoskeletal simulations were performed to estimate muscle forces and joint contact forces (JCF) based on 3D motion capture data of one healthy, typical person (TYPper, AVA of 12°) and a patient with idiopathic increased femoral AVA (AVAPat), i.e. AVA of 39°. A musculoskeletal model was scaled to each participant’s anthropology. For the AVAPat, the model’s femoral AVA was modified to match the subject-specific values obtained from magnetic resonance images [7]. Both models and the corresponding motion capture data were used as input for Monte Carlo Analyses. A modified static optimization approach [5], which allowed to allocate different penalty weights to each muscle, was used to calculate muscle forces. The same random combination of muscle weights (n=10,000) was used for each model. OpenSim [8] was used to run 10,000 simulations for each model. Root-mean-square of muscle forces during the stance phase and peak JCF were compared between models. Pearson correlation coefficients (R) and regression slopes (S) between muscle forces and JCF were used to investigate each muscle’s impact on JCF. Furthermore, we compared our results to reference simulations based on static optimization with equal coefficients. For the AVAPat, the model’s femoral AVA was modified to match the subject-specific values obtained from magnetic resonance images [7]. Both models and the corresponding motion capture data were used as input for Monte Carlo Analyses. A modified static optimization approach [5], which allowed to allocate different penalty weights to each muscle, was used to calculate muscle forces. The same random combination of muscle weights (n=10,000) was used for each model. OpenSim [8] was used to run 10,000 simulations for each model. Root-mean-square of muscle forces during the stance phase and peak JCF were compared between models. 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Pearson correlation coefficients (R) and regression slopes (S) between muscle forces and JCF were used to investigate each muscle’s impact on JCF. Furthermore, we compared our results to reference simulations based on static optimization with equal weights for each muscle. To evaluate the practical implication of our simulation results, we conducted the following additional experiments. In six healthy participants real-time feedback of electromyography signals of important muscles (specified by our simulations) was used to evaluate if people can alter their muscle recruitment strategies during walking.

Results
TYPper walked faster (1.41m/s) than the AVAPat (1.15m/s). For most simulations, hip JCF were higher whereas patella and ankle JCF were lower in the AVAPat compared to the TYPper (Fig. 1). In both participants, soleus (R=-0.87/-0.89, S=-1.7/-2.2 for TYPper/AVAPat) and gastrocnemius medial forces (R=0.75/0.68, S=1.7/1.7) had a big impact on knee JCF, whereas peroneus longus (R=0.80/0.58, S=3.8/2.9) forces influenced ankle JCF. Hip JCF could be reduced by decreasing semimembranosus forces (R=0.41, S=1.9) in the TYPper. For the AVAPat, the rectus femoris (R=0.58, S=1.0) and gluteus maximus (R=0.43, S=2.1) forces had the biggest impact on hip JCF. In the TYPper hip, knee, patella and ankle JCF were reduced in 9%, 19%, 39% and 40% of all simulation compared to the reference simulation with maximum reduction in JCF by 8%, 11%, 33% and 4% respectively. In the AVAPat hip, knee, patella and ankle JCF were reduced in 41%, 31%, 20% and 37% with maximum reduction in JCF by 26%, 19%, 21% and 3% respectively. All participants of the biofeedback experiments could alter the muscle activity of the soleus. 83%, 33% and 50% of participants were able to alter gastrocnemius, rectus femoris, and semimembranosus activity, respectively.

Discussion
This is the first study that showed the potential to alter JCF with different muscle recruitment strategies. Our findings agree with experimental studies [5] and previous simulations based on different approaches [6,9]. Our healthy participants walked with very low rectus femoris activity, which might explain why a reduction in rectus activity was not feasible during the biofeedback training in 4 out of 6 participants. In summary, we showed that (i) altered muscle coordination can significantly reduce (up to 30%) hip, knee and patella JCF but not ankle JCF (less than 4%), (ii) the potential of reducing JCF with altered muscle coordination strategies is highly subject-specific and depends on the person’s musculoskeletal geometry and gait pattern, (iii) muscle recruitment re-training seems to have more potential in patients compared to healthy participants, and (iv) unfavorable muscle coordination can significantly increase JCF.

References
CHARACTERIZING PORO-VISCOELASTIC MATERIAL PROPERTIES OF BRAIN TISSUE-MIMICKING HYDROGELS

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Introduction
The biomechanical characterization of brain tissue provides important insights into the underlying mechanisms of brain injuries, cerebral pathologies and neurological disorders. In particular, the poro-viscoelastic nature of brain tissue, the interaction between fluid-induced and viscous relaxation, and the interpretation of such effects from experiments remain only partially understood. In this work, we exploited the controllable microstructure and reproducibility of a brain tissue-mimicking hydrogel to gain better insights into the poro-viscoelasticity of soft hydrated tissue.

Methods
We synthesized a composite hydrogel and compared the mechanical response to that of native brain tissue in indentation tests [1]. A model recently proposed by our groups to describe the poro-viscoelastic behavior of brain tissue was adapted to predict the behavior of the hydrogel [2,3]. We derived the water content of the mimicking material by dehydration and verified the porous microstructure by cryo-SEM imaging. An inverse parameter identification scheme was used to determine the material parameters applied [4]. Finally, we validated the model by finite element (FE) simulation of an additional experiment not used for parameter calibration.

Results
The hydrogel mimics the mechanical response of native brain tissue in the proposed indentation tests (Figure 1a). From the measured water content (>96%) we derived the solid volume fraction of the material. With this, we have fitted the first indentation cycle of the composite hydrogel (Figure 1b). In particular, the derived value for the permeability and the associated hydraulic conductivity \( k \) with \( k = 2.5 \times 10^{-3} \text{ m/s} \) in a similar range to that reported for brain tissue. We validated the model with a FE simulation of another experiment, which demonstrated excellent agreement with the viscoelastic relaxation behavior of the experimental data (see Figure 1c).

Discussion
In the future, sensitivity analysis of the material parameters will be used together with Darcy-like hydraulic conductivity measurements to better discriminate between porous and viscous effects in brain tissue and related mimicking materials.

References
Intervertebral disc impact on stresses in growthplates of an adolescent idiopathic scoliotic spine following unilateral muscle weakening

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Introduction
The purpose of this study was to look into the role of an intervertebral disc (IVD) in the stress distribution in an apical growthplate (GP) in an adolescent idiopathic scoliosis (AIS) trunk with intact and after a concave-sided debilitating of the multifidus-lumborum (MFL) and longissimus-thoracis-parsthoracis (LGPT) muscles. IVDs were not simulated in some studies for the sake of simplification. It was hypothesized that IVDs simulation could accurately predict the GP stresses which in turn leads to a better understanding of unilateral muscle weakness (UMW) effects on an AIS trunk stresses [1].

Methods
A motion segment finite element (FE) model of one scoliotic 11.5-year-old adolescent comprising the caudal GP of L2, each in two scenarios of including (FEI) and excluding (FEE) the IVD was developed (Fig. 1). The L2-L3 muscle and gravitational loads in the standing-posture [2], were applied to the GP (Fig. 1). The models were examined with intact and unilaterally-paralyzed muscles. Muscle-weakening was simulated [2,5] by reducing the physiological-cross-sectional-area of the concave-sided LGPT+MFL muscles to reach the 95% loss in the strength.

Results and Discussion
A similar intradiscal-pressure (0.19MPa) was found for FEI models with intact and unilaterally-debilitated muscles which agrees the in-vivo data[6].

Conclusions
Higher stresses on GPs in a FE model including than excluding an IVD was obtained which consequently indicates different vertebral bone-growth patterns according to Hueter-Volkmann’s law [1]. Accordingly, this study indicated the significance of simulating IVDs in the predicted pattern of vertebral growth and deformity-progression of an immature AIS spine.

References
MECHANICAL MODELING OF CEREBELLAR FOLIATION CAUSED BY MULTICELLULAR ACTIVITIES

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Introduction
The cerebellar cortex has a unique morphology characterized by accordion-like parallel folds called folia, which are closely associated with the cerebellar function. The folia are formed through inward migration of granule cells (GCs) proliferated in an external granular layer (EGL), and subsequent their accumulation to generate an internal granular layer (IGL). Although, in this foliation process, GC migration guided by Bergmann glia (BG) fibers is believed to play important roles in the folia lengthening [1], its mechanical mechanism is still unclear. To clarify how the fiber-guided GC migration contributes to the cerebellar foliation, in this study, we have developed a continuum mechanics model of tissue morphogenesis that links tissue growth and deformation to multicellular activities including proliferation and migration. By conducting computer simulations based on this mechanical model, we investigated the effects of fiber-guided GC migration on the folia lengthening [2].

Methods
The tissue growth and deformation during the cerebellar foliation were formulated based on the theory of continuum mechanics [3]. The cell proliferation and migration were modeled using a balance equation for the cell number density, and incorporated them into the above tissue model. By combining the proposed model with a finite element method, we simulated the folia lengthening in the cerebellar cortex caused by GC proliferation and migration. The cerebellar cortex at the initial state was simply modeled as a slightly curved two-dimensional strip with a length of 400 μm and a thickness of 50 μm, which is composed of three layers: EGL, molecular/Purkinje cell layer (ML&PCL), and IGL. The GCs proliferated in the EGL were assumed to migrate toward the IGL along the BG fiber orientation that depends on the tissue deformation.

Results and discussion
To investigate the effects of fiber-guided GC migration on the folia lengthening, we performed computer simulations under physiological condition, where the GCs strictly migrated along the BG fibers, and pathological condition, where the GC migration direction was disturbed by a random angle ranging from \(-\varphi_{\text{max}}/2\) to \(\varphi_{\text{max}}/2\) (Fig. 1). Under the physiological condition (Fig. 1a), the GCs spread radially toward the IGL around the fissure, while the GCs converged toward the IGL around the lobule. In contrast, under the pathological condition (Fig. 1b), impaired GC migration decreased the cell number density in the IGL and increased it in other layers. As a result, the folia lengthening was more promoted under physiological condition compare to pathological condition. These results showed that radial migration of GCs guided by Bergmann glial fibers, whose orientation depends on the surrounding tissue deformation, is a critical factor to produce elongated folia accompanied by the IGL with non-uniform thickness. Our mathematical model is a promising framework to explore the emergence of brain structure and function from mechanical and biochemical viewpoints, and potentially help clarify the mechanism of various neurological diseases.

Figure 1: Computer simulations on the lengthening of cerebellar folia caused by fiber-guided GC migration under (a) physiological and (b) pathological conditions.

References

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THE INFLUENCE OF CROSS-LINKING ON THE DEFORMATION MECHANISM OF COLLAGEN FIBRILS

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Introduction
Collagen type I is the main building component of various tissues. Its mechanical properties are directly derived from its structure of cross-linked tropocollagen (TC) molecules forming collagen fibrils. The cross-links are considered to be a key component of collagen fibrils as they can change the fibrillar behavior in various ways. While enzymatic cross-links (ECLs) are known for stabilizing the structure and improving the mechanical properties of the fibril and tissue, the accumulation of so-called Advanced-Glycation-Endproducts (AGEs) is associated with impaired material properties on the macroscale e.g. increased brittleness in bone. AGEs content in tissue has been observed to increase with aging and diabetes, some of the major concerns of western health systems, due to high glycation levels in the system. However, the mechanisms causing the deterioration in tissue behaviour remain unknown and the exact relationship between cross-link properties and fibrillar behavior is not well understood. Computational modelling can give insight into the nano-level structure of collagenous tissues, overcoming the limitations of imaging techniques in in-vitro studies, and providing a powerful tool for revealing the mechanical behavior of fibrils.

Methods
We use coarse-grained steered molecular models in order to evaluate the effect of AGE and ECL content on the mechanical behavior of the collagen fibril. Both types of cross-links are considered because AGEs mostly occur in aged or diabetic tissue where enzymatic cross-links are naturally present, since they have mostly been formed during growth and adult development. We build a 3D model of a representative part of the collagen fibril with 5 gap and overlap zones and a diameter of 20 nm, where the mechanical responses of TC molecules and cross-links are derived from reactive molecular dynamics simulations with atomistic resolution [1, 2]. We investigate the influence of cross-link density between TC molecules on stiffness, strength, and toughness (represented by work to failure) of collagen fibrils with a particular focus on AGEs increase on top of normal enzymatic cross-links.

Results
Our simulations show that the collagen fibrils stiffen at high strain levels beyond a certain strain limit when the AGEs content exceeds a critical value, while fibrils with lower AGEs density show softening mechanisms. In addition, the strength of the fibril increases with AGEs accumulation. We note that ECLs alone cannot cause the stiffened regime, but at low contents of AGEs cross-links may cause a stiffening of the collagen fibril that would not occur without them [2]. We analyze the force distribution within the TC molecules and the different types of cross-links (AGEs and ECLs) as well as their failure and demonstrate that a change of deformation mechanism is the origin of the stiffening and strengthening. A high AGEs content reinforces force transfer through AGEs cross-links rather than through friction between sliding tropocollagen molecules, which leads to failure by fracture of the tropocollagen molecules and sudden stress drops, causing a more abrupt failure of the collagen fibril [2].

Discussion
Our results provide a direct and causal link between increased AGEs content, inhibited intra-fibrillar sliding, increased stiffness, and abrupt fibril fracture. Still, it would be important to provide experimental confirmation to better calibrate models and address limitations.

References
BIOMECHANICAL EVALUATION OF GENERATIVELY DESIGNED PATIENT-SPECIFIC HIGH TIBIAL OSTEOTOMY PLATE FIXATIONS

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Introduction

High Tibial Osteotomy (HTO) is an effective joint preserving treatment for knee osteoarthritis (OA), offloading the affected area within the medial compartment to relieve pain and optimise joint movement [1]. The one-size-fits-all approach adopted in HTO results in major plate related complications such as delayed or incomplete healing, skin irritation, implant prominence, stress shielding, lateral hinge fractures, construct instability, eventually requiring a revision surgery, all of which diminish post-operative clinical outcomes and hinder the ultimate potential of HTO [2]. The authors have developed a novel design framework to produce patient-specific HTO plates from a CT scan using Generative Design (GD) [3]. Unlike conventionally designed HTO plates, the application of GD allows plate designs to simultaneously integrate patient factors, surgical planning, and patient specific biomechanics with the aim to reduce plate stiffness and profile on soft tissue.

Methods

A surrogate left tibia (Sawbones model 3401-1) with 10-degree varus deformity was used for virtual simulation of HTO. A biomechanical model of the HTO construct with the gold standard plate was developed and validated through finite element modelling, to attain plate design requirements. Subsequently, the clinical and biomechanical requirements were replicated within the GD domain to explore titanium (Ti-6Al-4V) fixation plates for HTO. The novel patient-specific plate designs (Figure 1) were comprehensively analysed through biomechanical assessment under physiologic loading, to attest their construct stability, healing efficacy, stress shielding effect, lateral hinge stability, and the risk of implant failure.

Results

Figure 1: HTO plate designs (a) Gold standard plate (b) GD plate A (c) GD plate B (d) GD plate C

Discussion

GD approach to HTO increases the patient-specificity of plate designs by creating personalized fixation conforming to both patient anatomy and biomechanics, minimising surface area, plate prominence and stiffness whilst maintaining construct stability, and thus improving mechanobiological performance and post-operative surgical outcomes.

References


Acknowledgements

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Background
In wound healing, tissue-resident fibroblasts get transiently activated by biochemical and mechanical cues and transition into myofibroblasts. Myofibroblasts are contractile cells with large focal adhesions and α-smooth muscle actin (αSMA) incorporated into stress fibers. They also deposit new extracellular matrix (ECM). After wound closure, myofibroblasts need to return to the quiescent fibroblast state, to prevent excess ECM deposition and eventual fibrosis.[1] At the center of this process is the reversible fibroblast-to-myofibroblast transition (FMT). In vitro experiments have shown that this reversible process is mainly controlled by changes in the tissue tension, i.e., Kollmannsberger et al. showed that high FN tension accompanied by an elevated αSMA expression and therefore myofibroblast phenotype occurs only at the growth front, while matured tissue returned to the quiescent fibroblast state in a microfabricated cleft system. Interestingly, even in absence of growth factors that initiate the FMT process, tensile forces were able to trigger the reversible FMT. [2] These results suggest FMT is regulated by mechanosensitive cellular signaling but the exact link with dynamic processes of ECM deposition has not been resolved. Here, we propose that a dynamic agent-based model is ideal to study the mechanisms of action of tensile forces in FMT.

Methods
We developed a tissue scale agent-based model using Python 3.8 to mimic the Kollmannsberger et al. 2018 setup in silico. Upper left corner of the 500 µm by 500 µm cleft was represented by a 100 by 100 grid. In this model, we accounted for the subcellular αSMA expression and YAP nuclear localization as well as active ECM protein (FN and collagen) production. The production and degradation of proteins were governed by discretized ordinary differential equations and the relationship between different variables have been determined using the in vitro data when available. We hypothesize that the change in tissue tension, due to dynamic ECM deposition, degradation and alignment, changes the mechanotransductive subcellular processes which in return change the ECM protein production, iteratively affecting the tissue tension and subcellular processes (Figure 1).

Results
We ran simulations until the in silico cleft was full of tissue agents and reported the tension, αSMA abundance as well as the abundance of YAP in the nuclei over the distance from the growth front (Figure 2). These results agreed well with the in vitro experiments. The results also suggest that FN is more abundant than collagen at the growth front where the alignment between the fibers and the cells is highest. As the tissue matures, more collagen is deposited alongside FN. Cells establish adhesions to collagen and can no longer pull on the FN fibers. Overall this is reflected in a decreased ECM-cell alignment and a decreased tension in the mature tissue. In summary our work establishes a first link between subcellular mechanosensitive processes involved in tension-mediated FMT. Future work will focus on confirming our predictions and extending the ABM with a mechanical model of the ECM tension. This multiscale framework will be an important step towards generating fundamental understanding of FMT.

Figure 1: The tissue scale ABM processes in the model.

Figure 2: Distribution of tension, abundances of αSMA, YAP, ECM proteins throughout the simulated tissue space (lines) compared to experimental data (points).

References

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NEW AUTOMATED ALGORITHM FOR MUSCLE ARCHITECTURE EXTRACTION FROM B-MODE ULTRASOUND IMAGES

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Introduction

Human muscle architecture has a critical impact on muscle contraction mechanics and is usually determined by ultrasound imaging of the connective tissues surrounding the fascicles [1]. Since manual measurements of fascicle length (FL), pennation angle (PA) and muscle thickness (MT) are time-consuming and technically demanding, especially during locomotor activities, several automatic tracking algorithms have been developed to extract FL, PA and MT from ultrasound images. However, due to the nature of the ultrasound data, which is characterized by low contrast, noise and speckle, there is much room for improvement both in terms of the accuracy of the results and the level of automation. The purpose of this study is to present preliminary validation results of a new algorithm developed to provide a robust estimation of muscle structure changes during movements.

Methods

Ultrasound images of the medial gastrocnemius during treadmill walking were recruited from ten gait cycles, each performed by a different young man [1]. Muscle architecture parameters were calculated on each 1% of each gait cycle by: a) manual digitization, b) the TimTrack algorithm [2] and c) the proposed algorithm. The proposed method involved three steps. First, the superficial and deep aponeuroses were detected by advanced image processing, getting and sorting objects according to their area or contour size, combining objects in pairs in order to automatically detect aponeuroses and processing the contours of the aponeuroses objects to return the corresponding curves. Secondly, the algorithm calculated orthogonal lines to the middle line of the muscle (in parallel to both aponeuroses) that intersected both aponeuroses into 5 points equally distributed along the muscle. MT was the average length of the line segments defined by their intersections with both aponeuroses. In the last step, fascicle orientation was estimated by an advanced image processing algorithm that included image decomposition, Laplacian pyramids and Gabor filters. For each fascicle object a line was fitted and FL was calculated between the fascicle’s intersections with the two aponeuroses. Finally, PA was calculated as the angle between the fascicle line and the tangent to the deep aponeurosis at the intersection points. Root mean squared error (RMSE) was calculated between manual and algorithmic measurements.

Results

The average (±SD) RMSE for the new algorithm was 3.2±1.1 mm for FL, 1.1±0.5 mm for MT and 1.5±0.4 deg for PA. The corresponding values for TimTrack were 6.25±1.8 mm for FL, 0.4±0.2 mm for MT and 4.4±1.7 deg for PA. Average waveforms of muscle architecture parameters across all gait cycles are shown in Fig 1.

Discussion

The new algorithm showed excellent performance in tracking FL and PA of gastrocnemius medialis during human walking when compared to manual procedures and TimTrack. Regarding MT, TimTrack was closer to manual measurement. However, due to its systematic nature, the larger error of the new algorithm may be due to differences in the assumptions made to calculate MT.

References


Acknowledgements

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THE EFFECT OF STRAIN ANISOTROPY ON THE INTERPLAY BETWEEN NOTCH SIGNALING AND VASCULAR SMOOTH MUSCLE CELLS

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Introduction
Vascular smooth muscle cells (VSMCs) are important regulators of arterial growth and remodeling. They have the ability to switch from a contractile quiescent phenotype to a more proliferative and migratory synthetic phenotype upon mechanical perturbations. Due to the pulsatile blood pressure, VSMCs are mainly exposed to cyclic circumferential strain in the vessel wall, which regulates their phenotypic switching. However, cyclic uniaxial strain has been reported to both up- and downregulate the expression of contractile phenotype markers compared to the static controls in vitro [1]. Furthermore, the underlying mechanobiological mechanisms by which strain regulates the phenotype of VSMCs are not fully understood. A better understanding of the interaction between strain and signaling pathways regulating VSMC fate is essential to understand and control the growth and remodeling in (pathological) vascular adaptation and regeneration. The Notch signaling pathway, increasingly recognized as mechanosensitive, may be the link between mechanical strain and VSMC behaviour [2], as the application of equibiaxial strain decreases Notch signaling, which in turn switches the contractile phenotype to a synthetic state in VSMCs [3]. Still, it is not clear if uniaxial strain, which better mimics the in vivo strain that VSMCs experience, would have a similar effect on Notch signaling, and to what extent this interplay determines the VSMC phenotype. Thus, the current study aims to explore the interplay between uniaxial strain and Notch signaling on VSMC phenotype, and compare the effects of equibiaxial and uniaxial strain in similar in vitro conditions.

Methods
Human coronary artery smooth muscle cells (Lonza) were cultured for 7 days in either smooth muscle cell growth medium (Cell Applications Inc.) to obtain synthetic VSMCs, or smooth muscle differentiation medium (Cell Applications Inc.) to obtain contractile VSMCs. Cells were stretched either equibiaxially or uniaxially with the Flexcell Tension System at 0.5 Hz for 48 hours. The displacement of membranes was analyzed, and the corresponding strains were calculated via digital image correlation. Immunofluorescence staining and quantitative polymerase chain reaction were conducted to characterize the changes in cell phenotype and Notch signaling upon the application of equibiaxial and uniaxial strain.

Results
Synthetic and contractile VSMCs showed their phenotypic characteristics in static conditions, with contractile VSMCs expressing more and fibrous alpha smooth muscle actin (αSMA) compared to synthetic VSMCs (Fig. 1A). The application of uniaxial and equibiaxial strain resulted in a similar decrease in contractility marker ACTA2 and Notch activating ligand JAG1 (Fig. 1B). However, in contrast to the equibiaxial strain condition, reduced gene expression was not translated in protein expression in the case of uniaxial strain, as the contractile VSMCs preserved their fibrous organization of αSMA (Fig. 1A).

Discussion
Our results indicate that Notch signaling in 2D in vitro cultured VSMCs responds similarly to uniaxial and equibiaxial strain. Therefore, we suggest that Notch signaling is responsive to the maximum principal strain, although there may be some post-translational modifications that affect the functional regulation of VSMC phenotype under uniaxial strain.

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Mechanical Evaluation of Bone Graft Enhanced Ovine Tibia Bone Defect Using Digital Volume Correlation

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Introduction
The mechanical behaviour of newly formed bone under compression has been examined using in situ X-ray computed tomography (XCT) and digital volume correlation (DVC) in femoral condyles [1]. Previously, four point bending has been employed in sheep models to assess the healing of fractures in long bones [2]. The aim of this study is to use ex situ XCT four-point bending to examine the 3D full-field residual strain distribution of newly formed bone treated with calcium sulphate based synthetic bone graft material in a tibia mid-shaft osteotomy, using DVC.

Methods
Sheep tibia bones with an osteotomy defect of 2 cm, were stabilised using an external titanium mono-fixator with half pins and retrieved 12 weeks post-operative. Three of the bone defects were packed with calcium sulphate pellets containing varying levels of parathyroid hormone (PTH) of 1, 2 and 5 ng/ml, and one was used as control. Two consecutive tomograms were acquired (Versa 520, Zeiss) for the calculation of the strain uncertainties (≤ 300 με) [3]. Ex situ four-point bending was used to measure the mechanical response of the regenerated tissue, within the apparent elastic region, max load 300 N (i.e. normal walking load). DVC analysis (DaVis10, LaVision, UK) was conducted using a single-step pass processing scheme (48 voxels) and 0% overlap to compute the strain distribution through the newly formed bone. Histology was also performed on the tissue using haematoxylin and eosin staining subsequent to the mechanical testing.

Results
All four specimens showed similar response to the load with the control specimen presenting the highest displacement (4.2 mm) (Fig1). DVC analysis shows higher compressive strain (ε33) at the inferior part of the osteotomy (approximately -2800 με). Similarly, the shear strain (γ) has a maximum value of 9000 με in the same region, whereas in the middle on the osteotomy is reaching a maximum value 4000 με (Fig.2). Histology shows callus formation and mineralisation of the regenerated tissue.

Discussion
This study explored the strain distribution in the newly formed bone treated with calcium sulphate pellets containing PTH. The XCT images showed that bone formation is uniform for all the different levels of PTH and therefore the strain distribution is dependent on both the growth and morphology of the tissue. Work is in progress to investigate the effect of PTH levels in the healing fracture, using energy dispersive X-ray spectroscopy (EDS).

References

Acknowledgements
This work was funded by Corthotec Ltd, and the Faculty of Technology at the University of Portsmouth.
Introduction
Ultrasound and microbubble technology has been used for various therapeutic applications, including the breakup of urinary stones, diagnostic imaging, and gene delivery. Recent advancement in ultrasound is using microbubble oscillation to enhance the effect of the drug in chemotherapy [1]. Since the compressibility of a bubble is large, the bubble oscillates with ultrasound. The oscillation of the intravascular microbubbles increases the permeability of endothelium, thus increasing the drug uptake to the tumor site. The dynamic of a bubble in a liquid confined within an elastic solid is investigated in this study to understand the microbubble behavior in a blood vessel. An external acoustic field is applied to the elastic confinement to obtain volume oscillations.

Methods
The physical system, shown in Figure 1, comprises a bubble in blood, modeled as a compressible non-Newtonian liquid confined in a blood vessel, an elastic solid. The motion of solid and liquid are described by the Navier and Equation of motion. For the constitutive model of non-Newtonian liquid, the power-law model is chosen. To increase the stability of the bubble, the bubble is encapsulated with an incompressible, Kelvin-Voigt shell [2-3]. It is assumed that the pressure inside the confinement has a linear relation with the volume change of the confinement. Finally, coupled differential equations are obtained and solved with explicit Runge-Kutta formulation in MATLAB.

Results
The effects of ultrasound frequency, shell rigidity ($G_s$), and the ratio of the initial shell radius to the bubble radius are investigated on the oscillation period and maximum value of bubble radius. The physical parameters are given in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shell viscosity</td>
<td>1 P</td>
</tr>
<tr>
<td>Liquid viscosity</td>
<td>0.01 P</td>
</tr>
<tr>
<td>Shell density</td>
<td>1100 kg/m³</td>
</tr>
<tr>
<td>Elastic modulus</td>
<td>2.2 GPa</td>
</tr>
<tr>
<td>Vapor pressure in bubble</td>
<td>2300 kPa</td>
</tr>
</tbody>
</table>

Table 1: Physical Properties.

Discussion
As observed from Figure 2, at higher rigidity of shell and frequency of external field, maximum bubble radius decreases which will cause bubble burst. Furthermore, the oscillation period of the bubble can be adjusted by the frequency of the external field.

Figure 1. Bubble encapsulated with shell in a blood vessel.

Figure 2. Effects of (a) ultrasound frequency on oscillation period of the bubble; (b) rigidity of shell and (c) initial shell radius value on the maximum value of bubble radius.

References

Acknowledgments
This work was financially supported by the Bogazici University Research Grant 19465. S.I. Kaykanat acknowledges TÜBİTAK-National PhD Scholarship Program in the Priority Fields in Science and Technology (2211-C).
CELL SPREADING ON FIBROUS MATRIX PREDICTED BY HYBRID CELLULAR POTTS MODEL WITH DYNAMIC ADHESIONS

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Focal adhesion dynamics

The interaction between cells and the microenvironment plays an important role in health and disease. A key component of the microenvironment is the extracellular matrix (ECM), which consists of many small and large proteins that give mechanical support to cells and offers a medium for cell-cell communication [1]. Relative to the cell the ECM consists of fibers of size comparable to the cell. They can be mechanically connected to each other by crosslinkers. Cells adhere to and sense the ECM via mechanosensitive contact points called focal adhesions (FAs). FAs are large protein complexes, which dynamically assemble and disassemble under the influence of mechanical tension [2].

Recently, our group has developed a hybrid Cellular Potts and Molecular Dynamics Model that describes the mechanics of ECM fibers in detail (presented elsewhere in this conference). [2] Here, we extend this model by introducing mechanosensitive FAs between cells and ECM. The FAs are modelled individually (following [4]): they attach to individual fibers and assemble and disassemble dynamically based on the tension between them and the cell. This ensures that focal adhesions can mature on stiffer substrates where they endure a larger tension than compared with a soft substrate on which they quickly disassemble. Making the cell-ECM interaction explicit in this way extends the scope of possible study with this model. It makes it possible to study the interplay between network architecture and cell behavior by changing the average connectedness of the network. Here, we consider the effect of the network connectedness on the spreading behavior of a single cell. Furthermore, we find that the cell can reorient and restructure parts of its local environment.

Fiber recruitment and cell spreading

Activating the hybrid CPM with dynamic adhesions enables massive restructuring and reorientation of the ECM. On stiffer parts of the ECM, the cell deforms the ECM slightly and can use it as an anchor for further migration. On soft ECMs, however, the contractile forces of the cell deform the ECM completely. This can be seen in Fig 1, where fibers are fully pulled towards the cell.

Apart of reorienting and restructuring of the matrix we recognize the known effect of cell spreading on stiff matrices in our model. [5] We see that cell spreading increases by increasing the average number of crosslinkers per fiber. This statistic is used as a proxy for ECM stiffness.

Figure 1: Recruitment of fibers by a simulated cell. From A-D a highlighted fiber is pulled inwards and place along the cells border.

Figure 2: Increasing the number of crosslinker increases the overall cell area. This only occurs after the network is properly connected (after the average number of crosslinker per fiber is greater than 1.0).

References
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MECHANOREGULATION OF BONE FORMATION DURING NON-UNIONS IN PREMATURELY AGEING MICE

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Introduction

Soft tissue mechanics plays a vital role in bone regeneration and yet, the local mechanical environment leading to compromised regeneration i.e., delayed- or non-union, remains to be elucidated. [1] Bone regeneration can be studied using time-lapse micro-computed tomography (micro-CT) enabling in vivo longitudinal experiments. Combined with micro-finite element (micro-FE) analysis, morphological changes of the bone architecture can be associated with strains at the tissue-level. [2] The PolgA mouse model of premature aging exhibits age-associated impaired bone regeneration in femur osteotomies studies. [3] Thus, we aim to study the mechanoregulation of bone formation during non-unions and compared to unions in PolgA mice by leveraging micro-FE analysis.

Methods

In vivo time-lapse micro-CT images of femur osteotomies in 12-week-old “young” (n=8) and 35-week-old “old” (n=8) female mice of a prematurely ageing PolgA mouse model were used. [3] The femur osteotomies were stabilised with a PEEK external fixator and mechanical stimulus was provided via ambulatory loading. At 3 week post-op, the young and old groups both presented 4 non-unions. Linear-elastic micro-FE models (Fig. 1a) were generated at each time point by converting mineral density values above 395 mg HA/cm³ linearly to Young’s modulus (4-12 GPa, ν=0.3) to compute the effective strain (EFF). [3] Volumes of formation were obtained by the overlay of registered binary time-lapped images. The modelling performance of EFF was determined via receiver operator characteristc (ROC) analysis. The computed area under the ROC curve (AUC) summarises the modelling performance of EFF as a predictor for bone formation during regeneration. The AUC ROC was computed within the osteotomy gap (OG) at increasing tissue mineral density thresholds, starting at 395 mg HA/cm³ and increased by steps of 25 mg HA/cm³ until the maximum threshold of 720 mg HA/cm³. Significance (p < 0.05) was determined via repeated-measures 3-way ANOVA with Bonferroni correction.

Results

The prediction of bone formation using EFF was significantly higher for both the union (p=0.014) and old (p=0.003) groups than for young and non-union groups (Fig. 1b). Significant differences in bone formation emerged (Fig. 1c) between union and non-union groups (p=0.010) within the osteotomy gap and also between young and old (p=0.043).

Discussion

Bone formation in soft tissue during regeneration is mechanically regulated, with old mice being more sensitive to EFF than young mice. Not only was bone formation in the non-union groups insufficient to bridge the OG, but also the deposition of bone was not mechanically regulated, especially in the young group. Whereas bone formation in both the old and young union groups could be predicted by the EFF in the soft tissue. However, it remains unclear whether the strains across the OG in vivo were too large to permit bone formation or if the femur was never effectively loaded by the mice of the non-union group. We conclude that bone formation during unions is mechanically regulated since it can be predicted by EFF whereas poor mechanoregulation in soft tissue in the OG is associated with non-unions.

References


Acknowledgements

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PERSONALISED COMPUTATIONAL MODELS TO STUDY THE IMPACT OF COVID-19 LUNGS UNDER MECHANICAL VENTILATION

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Introduction
COVID-19 has claimed millions of lives worldwide and the highly transmissible virus can cause devastating damage to organs, particularly affecting the lung. In some cases, COVID-19 pneumonia develops into acute respiratory distress syndrome (ARDS), a precursor to respiratory failure. If a patient fails to respond to non-invasive intervention, invasive mechanical ventilation (IMV) is required. IMV can save lives but can also lead to longer-term ventilator-induced lung damage.

This work proposes a modelling framework to analyse the lung function of mechanically ventilated COVID-19 patients to analyse flow and pressure distributions throughout the lung, using automated segmentation of patient pulmonary computed tomography (CT) scans to improve the practicality of modelling larger datasets.

Methods
From a selection of patient CTs, automated labelling of lung boundaries is carried out (Hofmanninger et al. [1]), along with the segmentation of airways, using existing trained machine learning models (Wang et al. [2]).

A volume-filling network generation algorithm, extended from Kitaoka et al, was used to fill the remaining lung volume with airways down to the 23rd generation. A reduced-order computational fluid dynamics simulation was then performed to study flow and pressure distributions throughout the lungs when under mechanical ventilation. This workflow is illustrated in figure 1.

References

Acknowledgements
The authors acknowledge financial support from Welsh Government, WG, (MA/KW/1457/20) and the Engineering and Physical Sciences Research Council, EPSRC (EP/V041789/1). The authors are also grateful for valuable discussions with healthcare professionals from Hywel Dda University Health Board, Swansea Bay University Health Board, and Cwm Taf Morgannwg University Health Board providing insight on their experiences with COVID-19 and data access.

Results
During the network generation process over 900,000 airways are created down to the 23rd generation, this network shows similar statistical properties to that seen in other works such as Weibel et al. [4]

Model resistances and compliances were adapted to investigate the global effects of these parameters, which had the expected effect on the pressure-volume loop. Two cases are compared, one with mild disease and another with severe disease. Results show the severe case displays a significant increase in lung distention when compared to the mild case.

The speed of segmentation and time efficiency is increased by using the automated framework as opposed to the semi-automated techniques previously utilised within 3D slicer (https://www.slicer.org/ - Fedorov et al).

Discussion
Covid-19-induced lung damage can produce fibrosis-like (reduced compliance and increased resistance to airflow) and emphysema-like (increased compliance and reduced resistance to airflow) effects in different regions of the lung. The distribution of these can cause significant changes to the flow and pressure distributions, thus directly influencing alveolar distension. This is particularly apparent when neighbouring regions have an opposing effect, i.e. one region has a lot of fibrosis and a nearby region has a lot of emphysema.

In addition to the improved time efficiency, utilising a ML based automated segmentation tool for labelling of CTPAs provides a consistent standard, avoiding intra-person differences that may arise if manually segmented.
EVALUATION OF 4D ULTRASOUND DATA TO DETERMINE THE RELATIONSHIP BETWEEN 3D AORTIC WALL DISPLACEMENT AND AGE

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Introduction
The cyclic deformation that blood vessels experience can be used to investigate the elastic and biomechanical properties of the vessels in vivo. Specifically, axial prestretch of the abdominal aorta is a phenomenon that impacts arterial physiology and pathology. Horny et al has shown that a decrease in axial prestretch is closely linked with age and abdominal aortic aneurysm (AAA) development [1, 2]. However, measuring axial prestretch in vivo is not possible, as it requires surgical resection of the aorta. Previous work has suggested that 3D displacement of the aortic wall, which can be measured via 4D ultrasound, could be used to estimate prestretch in living patients [3].

Methods
Ultrasounds were performed on human patients by Wojciech Derwich (MD) at Department of Vascular and Endovascular Surgery of the Goethe University Hospital Frankfurt (Main). All use of anonymized patient data was approved by local ethics committees. A commercial real-time 3D echocardiography system (Artida®, Toshiba Medical Systems, Otawara, Japan) equipped with a 3D transthoracic probe (Toshiba, PST-25SX, 1-4 MHz phased array matrix transducer) was used to acquire 4D ultrasound data. Ultrasound data was collected from a total of 154 patients (AAA = 81, diseased elderly = 31, young = 32, healthy elderly = 11). The data was segmented and masked using an in-house MATLAB code. The displacements with and without rigid body motion as well as the rigid body motion itself was evaluated in the longitudinal, radial, circumferential, and norm directions. The data was then compared using a Mann-Whitney U statistical test.

Results
Displacements without rigid body motion in the radial direction were found to decrease exponentially with increasing age, both in the evaluations containing AAA patients and excluding AAA patients. A power model

\[ y = ax^b \]  

where \( y \) is displacement and \( x \) is age, was fit to the data with fits of \( a = 64.70, b = -1.39, R^2 = 0.48 \) and \( a = 59.67, b = -1.36, R^2 = 0.46 \) for the group including the AAA patients and excluding the AAA patients, respectively. The rigid body motion in the longitudinal direction was found to increase significantly between patients under age 40 and patients over age 40 in the groups including and excluding AAA patients (Figure 1).

Discussion
Radial displacements of the aortic wall excluding rigid body motion – that are closely related to aortic distensibility – have been shown here to decrease exponentially with age, similar to the relationship between age and prestretch demonstrated in Horny et al [1, 2]. In the future, a model relating prestretch and 3D displacement will be investigated. The finding that rigid body motion in the longitudinal direction increases significantly with age when comparing both AAA patients and elderly patients without AAAs supports previous research and fits with the known negative correlation between prestretch and age and prestretch and AAA development [4]. The consistent norm of the displacements could explain the simultaneous increase in longitudinal rigid body motion and decrease in radial displacement. Further work is needed to confirm this finding.

References

Acknowledgements
We thank Achim Hegner for his help in the analysis. This work was supported by the Fulbright Program and the Hessian Ministry of Science and Art.
INFLUENCE OF BONE SCREW CONFIGURATIONS ON BONE HEALING BIOMECHANICS USING LOCKING COMPRESSION PLATE FIXATION

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Introduction

Locking compression plates (LCP) are increasingly being used as effective internal fixation devices of long bone fractures. It is agreed that the configuration of bone screws influences the support provided at the fracture site and can hence directly impact the bone healing process [1]. Previous studies have investigated the efficiency of LCP plates in limited cases of long bone fractures [2]. This study aimed to develop an algorithm based on a meta-model analysis of finite element (FE) modeling that estimates optimal screw configurations using biomechanics. The precision medicine approach provided by the algorithm promises to improve surgical outcomes and sheds light on the biomechanics of bone healing.

Materials and Methods

An FE model of the distal anatomical LCP plate attached to fractured bone was developed to analyze the biomechanics of an internal fixation system using ABAQUS (V6.12-1) (Fig. 1). The geometry of the FE model was extracted from a CT-Scan of the right tibia (Male, 65 yr.). To simulate a transverse fracture in the distal region of the tibia, a 3mm gap was created and filled with soft callus membrane mimicking the early healing stage. Upon model validation, the screw configurations were iteratively changed (Fig. 2), and the inter-fragmentary displacement, stress in the fixation plate, bone, and callus membrane were analyzed. Using a direct-search optimization code, the optimum solution was obtained. The repeatability of the algorithm was validated by changing the fracture region in 5 simulated models and repeating the calculations.

Results

The ranges of stress and strain in the fixation plate and bone were well comparable with results from literature [3] confirming the validity of the FE model. The maximum Von Mises stress, axial, and shear displacement in the callus for optimal screw configuration were 3.68 (±1.04) MPa, 6.38×10⁻⁷ (±3.87×10⁻⁷) mm, and 1.25×10⁻⁴ (±0.56×10⁻⁴) mm, respectively for the 5 different fracture models. In alignment with literature, the results confirmed that the screws should be positioned as close as possible to the fracture gap on either side for optimal healing [4].

Discussion

The optimization algorithm developed in this study can be used by clinicians as a biomechanically driven quantitative guideline during the critical surgical planning phase and by the biomedical orthopedic device industry to inform design and manufacturing decisions. Future work is needed to improve the optimization criteria based on observed clinical and biomechanical outcomes from post-op patient data.

References


Acknowledgements

The authors acknowledge the scientific funding support from the HEIC at Khalifa University.
GAIT PHASE IDENTIFICATION BASED ON IMU READOUTS USING THREE GRADIENT-BOOSTED MODELS

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Introduction
Inertial measurement units (IMU) have enabled quantitative gait analysis to characterize normal/altered gaits of young and elderly individuals and those with disabilities in the natural environment. Most current gait phase identification and temporal event detection methods using IMU readouts suffer from at least one of the following drawbacks [1]: (1) dependency on the morphology of the time series, making them dependent on the ground conditions; (2) lack of sensitivity and precision, making them impractical for real-time applications such as assistive and rehabilitative devices and active exoskeletons; and (3) lack of generalizability and reliability, making them unsuitable for unseen data. By combing and strengthening the implemented decision trees, gradient boosted methods (GBM) can be used in classification problems with high performance in real-time. Therefore, this study aimed to compare the performance of three GBMs in gait phase identification and interpret the feature importance produced by the models’ outputs.

Methods
The dataset used for this study contained IMU readouts obtained from seven able-bodied participants (26 ± 3 years old, 72 ± 13 kg, 177 ± 6 cm) during four gait modalities: oval-shaped walking over ground and walking, running, and inclined walking over the treadmill. Additionally, the readouts from two pressure insoles were used as references to identify gait phases. The dataset was split into training and test sets using the leave-one-out cross-validation approach. Seven-fold cross-validation was implemented with one participant’s readouts in the test set and the rest in training set in each fold. XGBoost [2], LightGBM [3], and CatBoost [4] models were fed with the raw IMU readouts labelled either stance or swing according to the reference pressure insole using the threshold of 10N.

Results
In total, 649,814 time-instants were labelled as swing (238,330 instants) or stance (411,484 instants) using the reference method. The average precision of 85%, 87%, and 83%, sensitivity of 91%, 92%, and 91%, accuracy of 85%, 87%, and 83%, and F1 Score of 88%, 90%, and 87% were obtained by XGBoost, LightGBM, and CatBoost models, respectively, to identify gait phases (Table 1).
It was observed that foot angular velocity in the sagittal plane had the highest contributions, among other kinematics time series, as an input to the models. In XGBoost and CatBoost models, foot vertical acceleration had the second highest contribution. Figure 1 shows the contribution of IMU readouts (acceleration and angular velocities presented in the anatomical frames) in the three models.

Discussion
Gait phases were predicted with high sensitivity (> 91%) and specificity (> 83%) as well as high accuracy (> 83%) using XGBoost, LightGBM, and CatBoost models. Among these models, LightGBM marginally outperformed the other two in identifying gait phases and spread the contributions over all the features (i.e., IMU readouts). Conversely, the contribution of the two most significant features in the XGBoost and CatBoost models was higher than the other features. This interpretation is concurrent with the other morphology-based temporal event detection methods using IMU readouts and distinguishes these GBMs from conventional neural networks. Finally, by increasing the number of participants, their sexual diversity, the gait patterns, and the activity type, gradient-boosted methods can be trained and employed in a comprehensive model for real-time gait analysis appropriate for diverse therapeutic applications.

References
MECHANICAL CHARACTERISATION OF FAT SUBSTITUTES FOR SUBCUTANEOUS DRUG DELIVERY EXPERIMENTAL MODEL

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Introduction

Subcutaneous tissue (also known as hypodermis or fat tissue) is a typical route for drug delivery. The primary advantage of subcutaneous drug delivery is it enables self-administration, which shifts the focus of patient care from hospital to the patient’s home. Despite the major benefits, it is difficult to accurately predict the dispersion and absorption of drug inside the subcutaneous tissue due to the complex interaction between not only the vasculature and lymphatics, but also with tissue deformation during injection. Hence, there is a need to develop an experimental model that can not only predict the mechanical behaviour of tissue, but also the drug delivery mechanics inside the tissue. With that as the ultimate goal, the present study has mechanically characterised commercial fat substitutes to provide a good understanding on the mechanical behaviour of potential materials in the market that can be used for developing the experimental model.

Methods

Commercial fat substitutes, namely Simulab, LifeLike and SynDaver were chosen for this study. Tests performed on the aforementioned fat substitutes include hardness, needle insertion, tension and compression. Hardness was measured using the durometer type OOO, while the remaining tests were performed with a universal mechanical testing machine (Lloyd LS1, AMETEK, Inc., USA). For the needle insertion test, a minimally (Ø20 mm) and highly (Ø1 mm) constrained boundary constraint condition was also investigated.

Results

Figure 1 shows the results obtained for the hardness, needle insertion, tensile and compression tests. Human data from literature was added into Figure 1c and d for comparison purposes [1-2].

Discussion

Results of the present study will serve as the baseline in developing an experimental model that can capture both tissue deformation and drug delivery mechanics for subcutaneous drug delivery. In addition, results of the present study will prove to be useful for any researcher considering the use of these commercial fat substitutes for their research.

References

DEVELOPMENT OF SCALABLE FINITE ELEMENT MODELS BASED ON KNEE LAXITY TESTS ON CADAVERS

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Introduction

The aim of the project was to use the results of laxity tests on cadaver knees to create scalable, subject-specific finite element (FE) models. The models should also be able to test different unicompartmental knee prostheses and compare them to the native knee.

Methods

For the experimental test with a robot, the alignment of the knee and the robot to each other must be known. This was solved by inserting carbon rods with metal beads in the middle of the femur and the middle of the tibia, where the attachment point for the robot was provided. This was then used to design a bone- and subject-specific 3D print that enclosed the bone and connected the two parts via the drilled channels of the rods. The 3D print could then be connected to an aluminum cylinder into which the bone was cemented, and which could be connected to the robot. The robot-knee alignment was hence defined and used to determine the position of the knee replacement using a 3D scanner (EinScan-Pro, Shining 3D).

In addition, the CT scan was used to determine the tibial and femoral knee coordinate system using the STAPLE MATLAB Toolbox [1]. Using the coordinate systems, it was possible to calculate the knee flexion angle during CT and correct the offset during the experiments. The femoral coordinate system was later assigned to the FE model as the knee coordinate system.

The experiments themselves were laxity tests consisting of anterior/posterior translations (134 N), varus/valgus rotations (10 Nm), and internal/external rotations (5 Nm). These were performed at different test angles covering the range from 5° extension to 120° flexion. The FE model was built using Ansys® Academic Research Mechanical (Release 21.1, ANSYS Inc.). The level of detail was chosen so that the model included the femur and tibia including their cartilages, both menisci, and the cruciate and collateral ligaments, modelled as 3D geometry. Therefore, the segmentation of an MRI scan using Mimics (Release 23.0, Materialise NV) was necessary.

A multilinear elastic material model was chosen as the material model for the ligaments with a uniaxial tensile test of a lateral collateral ligament as input. An initial area and length were assigned to calculate a stress-strain curve. In addition, a strain offset parameter was introduced to handle different initial strains. An additional internal/external stiffness was added to be able to calibrate their laxities.

An important feature of the FE model was to assign an initial strain to the ligaments, so that the ligaments were already assigned a notional strain. This maintains the actual geometry segmented from the MRI and helps that the ligament remains in tension.

With the level of detail chosen for the model, there is also only one principal component per laxity test, which prevents an over-constrained system.

Since the FE model is based on the MRI images and the experiments are based on the CT images, their positions are different. Therefore, the transformation matrix had to be known to correct the offset of the FE model. MeshLab [2] was used to align the bones, and the position offsets could then be calculated and accounted for.

Results

This scalable knee FE model build was applied to six knees that had a native geometry and three different unicompartmental knee joint replacement geometries. The difference in position between the experiments and the FE model could be offset. It was also possible to transfer the femoral coordinate system, defined by the entire femur to the FE model which only has the distal femur. With knowledge of the transformation matrix, the FE model could include the same implant position as implanted by the surgeon.

Discussion

A reliable framework for the development of knee FE models based on cadaver laxity testing was demonstrated. An improvement for future FE models would be to provide fixation so that the MRI and CT scans are taken at the same position. Otherwise, alignment between MRI and CT bones could also be improved by using fixed bone markers in each scan without compromising the integrity of the knee. In addition, the internal/external rotation during CT could not be accounted for because the STAPLE algorithm [1] was flawed. Initially, initial stretching could be fixed to a certain strain value; however, the challenge is whether this solution remains scalable.

References


Acknowledgement

We thank Innosuisse – Swiss Innovation Agency - for supporting this work.
INSOLE: AN IN-SILICO TOOL TO PREDICT INDIVIDUAL RESPONSE TO CORRECTIVE INSOLES DURING WALKING.

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Introduction

Corrective in-shoe insole are prescribed for a range of static and dynamics foot deformities including but not limited to clubfoot, excessive eversion as well as flexible flat foot [1]. These insoles aim to provide additional support, using a specific geometry and/or stiffness to either promote or limit a specific motion of the foot. They are typically designed and prescribed based on subjective assessment of gait as well as clinical experience. This often results in limited personalization and by extension the possibility of sub optimal results. This is further limited due the time-consuming testing and manufacturing processing making the testing of multiple insoles infeasible.

Along with many other medical and clinical problems, the addition of in-silico techniques may allow for an improvement in personalization and by extension, improvements in function following prescription. To do so, we aimed to develop an in-silico pipeline to first estimate individual subject’s response to an insole of known properties. Once developed such a model can be deployed in the prescription pathway to supplement the standard design pathways.

Methods

For this proof of concept, 8 subjects with a flatfoot deformity were taken from a historical dataset containing motion capture data while walking shod with and without a corrective insole, as well as insole manufacturer information. Motion capture data was used in combination with a state-of-the-art musculoskeletal model [2] to estimate joint kinematics during walking in both conditions.

A low-fidelity insole model representation was then defined whereby insoles were modelled as a set of spring elements which develop force/torque when a specific joint is moved. In this way, these springs can limit or resist specific motions.

The predictive model used a baseline condition (i.e., shod without insole) whereby measured motion was used to reduce the MSK model and outputs to a set of joint level torques which, when applied to the model in a forward simulation would result in the measure baseline condition. With the addition of the spring insole model – the response to an insole with specific stiffness can then be estimated.

For this proof of concept, we first used a calibration phase whereby insole model parameters were optimized until a minimum difference between measured (i.e., average of all shod with insole conditions) and estimated kinematics was achieved. Optimized insole parameters were then used in another set of forward simulations for trials which were not used in the calibration process. The root-mean squared error between measured and estimated kinematics were then used to assess the accuracy of our predictive model.

Results

Representative parameter optimization results can be found in Figure 1 whereby the reference (i.e., shod without insole), measured (i.e., shod with insole), and estimate insole response are shown.

Discussion

The developed predictive model shows a proof on concept for the implementation of a rapid low-fidelity spring-based insole model. The predictive ability of this model was tested on the same subjects who were used for calibration introducing bias toward better results. The ability to estimate insole model parameters from information available from the manufacturer would provide a more sound and robust approach and forms the basis of on-going work. Once validated, such a framework can assist the in-silico design of corrective insoles for correcting dynamic foot deformities.

References


Acknowledgements

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ACTIN FILAMENTS IN RESPONSE TO CHEMICAL OSTEOGENESIS SUPPLEMENTS ALTER THE MULTICELLULAR BEHAVIOR OF OSTEOCYTIC SPHEROIDS

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Introduction
Osteocytes are the most abundant cells in the bone to play an important role as control tower for bone remodeling. Our group has developed 3D osteocytic spheroids reconstructed by human mesenchymal stem cells (MSCs) [1, 2]. In this study, we investigated the multicellular behavior of the osteocytic spheroids in response to chemically induced osteogenic supplements (OS).

Method
We fabricated scaffold-free spheroids using human MSCs (Riken BRC, Japan). 2500 cells were subcultured in each well of U-bottom ultra-low attachment dish (Thermo Fisher, USA). As chemical OS, 50 μM ascorbic acid, 10 mM b-glycerophosphate, and 100 nM dexamethasone were added in high glucose DMEM (Gibco, USA). The spheroids were cultured for 2 or 7 days with or without the OS to measure their projected area. The samples were then collected and stained with Alexa Fluor 488 Phalloidin (Invitrogen, USA) and Hoechst 33342 (Invitrogen, USA).

Results and Discussion
As shown in Fig. 1(A) and (B), the sizes of the spheroids were decreased time-dependently and further shrunk by addition of the OS. We also conducted a fusion experiment of two spheroids as well as collagen embedding experiment of the spheroids in response to the OS. The results showed that the OS delayed the fusion speed of the two spheroids and dissociation speed of the spheroids embedded in the collagen matrix. To reveal the mechanism, we observed the actin filaments (F-actin) in the spheroid using the LSM880 (Carl Zeiss, Germany) with the Airyscan detector. From the super-resolution images of the F-actin in the spheroids in Fig. 1(C) – (H), we first found out that the F-actin on the surface of the spheroids was more tightly generated in the presence of the OS when compared to the one in the absence of the OS. The tight F-actin generated the greater tension to squeeze the spheroid, resulting in the smaller size. Furthermore, the tight F-actin played a role as a barrier in the fusion experiment and collagen embedding experiment, which delays the fusion speed and dissociation speed by capturing and disturbing the cells inside the spheroid to break up the barrier. In this study, we firstly reported the importance of the F-actin in the spheroids to modulate the multicellular behaviors of the spheroid model. Moreover, the three different experiments conducted in this study might become useful in vitro experiments to anticipate and measure the multicellular behaviors of the 3D culture model such as organoids.

Figure 1: (A) Spheroid reconstructed by human mesenchymal stem cells after 2-day culture in the presence of chemical osteogenic supplements (OS). A black bar indicates 200 μm. (B) Evaluation of projected area of the spheroids after 2- and 7-day incubation in the presence or absence of the OS. Fluorescence image of actin filaments (F-actin) and nuclei in the spheroid: (C), (F) F-actin, (D), (G) nuclei, and (E), (H) merge image of the spheroid without or with the OS, respectively. White bars indicate 20 μm.

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Acknowledgements
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IN SILICO EXPLORATION OF OSTEOPOROSIS DRUG EFFECTS ON BONE ADAPTATION BASED ON REMODELING AND MODELING

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Introduction
Bone-forming activity of osteoblasts is divided into remodeling-based and modeling-based bone formation depending on the presence or absence of coupling with bone resorption by osteoclasts. Osteoporosis drugs have been reported to have different effects on remodeling and modeling based on their specific mechanisms of action [1]. However, it is still unknown how the drug effects on remodeling and modeling contribute to the mechanical adaptation of the bone microarchitecture. In this study, we developed a mathematical model that enables to analyze drug effects on remodeling and modeling and explored effects of bone-forming drugs on the mechanical adaptation of the bone based on cellular dynamics and bone morphometry.

Methods
Bone metabolism was modeled by describing spatial and temporal evolution of cell activities regulated based on mechano-biochemical interactions where mechanical stimuli sensed by osteocytes trigger signaling cascades of the major molecules such as receptor activator of nuclear factor-κB ligand, osteoprotegerin, and sclerostin [2]. To explicitly describe remodeling and modeling, we modeled osteoclast–osteoblast coupling by a well-known matrix-derived coupling factor [3]. According to the concentration of these signaling molecules and mechanical stimuli sensed by osteocytes, probability of cell genesis and apoptosis of osteoclasts and osteoblasts were determined. By using a finite element cubic model of a cancellous bone obtained from a swine femoral head, drugs effects of romosozumab and teriparatide, major bone-forming drugs, on the mechanical adaption of the bone microarchitecture were explored through drug administration simulation.

Results
To validate the model, we investigated drug effects on bone volume fraction (BVF) and cell activities. While BVF decreased overtime without treatment, it increased with romosozumab and teriparatide administration (Fig. 1A). Romosozumab suppressed remodeling and promoted remodeling-based bone formation, whereas teriparatide promoted both remodeling and modeling (Fig. 1B). Because these results are consistent with known drug effects, the model was shown to be valid. To explore the drug effects on the mechanical adaptation of the bone, we further performed drug administration simulation under the condition that the principal stress directions were rotated 45 degrees. As a result, the adaptive change of the cancellous orientation was attenuated with romosozumab treatment but enhanced with teriparatide treatment, in comparison to that without treatment (Fig. 2).

Discussion
The above results suggests that differential drug effects on remodeling and modeling could lead to drug-specific effects on the mechanical adaptation of the cancellous orientation, which would bring a new perspective to osteoporosis treatment. Our in silico approach would pave the way for new pharmacological strategies for the patients with skeletal diseases.

References

Acknowledgements
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MICROSCELE COMPACT BONE PROPERTIES OF PATIENTS WHO UNDERWENT HIP ARTHROPLASTY: INFLUENCE OF AGE AND GENDER

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Introduction
In the nowadays aging society, fragility fractures pose a significant health and economic burden. Bone strength is primarily determined by mineral density, but also by tissue-level mechanical properties. The elastic properties of the bone extracellular matrix (ECM) have been extensively investigated over the past two decades. However, there is still limited knowledge on the yield properties and their relationship to composition and architecture. Thus, this work aims at the multimodal characterization of human femoral bone ECM in relationship to the patient's age, gender and hip fracture status. Here, we report the first collective micropillar compression data and its relationship to other ECM properties.

Materials and Methods
Femoral neck samples from 42 patients who underwent hip arthroplasty were collected together with anonymous clinical information about age, gender, and primary diagnosis (coxarthrosis or hip fracture). Cortical bone from the inferomedial region was analyzed in a site-matched manner using a combination of micromechanical testing (high-throughput micropillar compression [1], nanoindentation), with micro-CT and quantitative polarized Raman spectroscopy [2] for both morphological and compositional characterization (fig. 1).

Results and Discussion
All investigated bone properties were found to be independent of the patient's gender and diagnosis. Yield stress and elastic modulus demonstrated a positive correlation with the mineral fraction of bone (p<0.0001), yet all mechanical properties as well as the sample-level mineral density were nearly constant over age, in line with previous studies [3]. On the contrary, compositional properties demonstrate dependence on the patient's age (fig. 2): declining mineral to matrix ratio (p=0.02, R²=0.13, 2.6% per decade), surprisingly in contrast to tissue mineral density (TMD), and increasing collagen cross-link ratio (p=0.04, R²=0.11, 1.5% per decade). This suggests that an increase in bone collagen with age leads to decreasing mineral to matrix ratio.

Logistic regression classification was further applied to the final combined dataset of measured bone properties with the patient's clinical information to predict the presence of a fracture. The analysis showed that the patient’s age, bone micropillar yield stress, indentation hardness and TMD are the most relevant parameters for bone fracture risk prediction at 67% model accuracy. The output database is the first to integrate the experimentally assessed microscale yield properties, local tissue composition and morphology together with the available patient clinical information. It can be used for the future comparison of existing methods to assess bone quality as well as to form a better understanding of the mechanisms through which bone tissue is affected by aging.

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VARIABLE ROTATIONAL SPEED SUBSTANTIALLY REDUCE THE RATE OF HEMOLYSIS WITHIN IN-HOUSE ROLLER PUMP

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Introduction
In clinical practice, roller pumps (RPs) are mostly used in two medical methods – veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and cardio-pulmonary bypass (CPB). Currently, centrifugal pumps (CPs) stand the competition in the VA-ECMO, mainly due to the shorter lifespan of peristaltic tubing [1]. However, the hemolysis-related complications (e.g., hemolytic anemia, hyperbilirubinemia, and acute renal failure) are usually much more prominent in CPs [2][3]. Main difference between CP and RP is that the former provides continuous flow due to the inherent design of the pump while the latter produces pulsatile flow. The pulsatile flow has been attributed to several benefits such as shorter need of intensive care, better microcirculation, lower inflammatory events, and better perfusion to organs [4]. Moreover, the correct synchronization between pulsatile flow and ECG may support the heart performance during VA-ECMO session [5].

Even though the study [5] demonstrated the pulsatile feasibility of CPs (achieved by varying the rotational speed), it carries certain limitations (e.g., the pulsatile effect diminishes with higher flow rates and may increase hemolysis). On the other hand, RPs generate intrinsically pulsatile flow, and the pressure and flow waveforms can be widely modulated through varying rotational speed profile (RSP) [6]. Since hemolysis is a crucial factor in clinical practice, the paper focuses on its evaluation within an in-house developed two-roller pump with full occlusion using computational simulations with experimentally obtained boundary conditions.

Methods
A simplified 2D finite volume (FV) model of RP was created based on its real geometry. Laminar blood flow modelled as Newtonian incompressible liquid with viscosity 2.7 cP (35% of glycerine-water solution) was assumed. Atmospheric pressure and measured pressure waveform were used as boundary conditions at the inlet and at the outlet, respectively. The computational domain was discretized in time with a step size of 0.0005 s. The results were extracted from the 8th cycle which was sufficient to reach a stabilized cyclic response. Ansys® Fluent® was used as a solver which allow us to use in-house developed overset methodology for roller-tube interface. Variable RSP with different settings – constant (conventional) and variable RSP (rotational speed is decreased when the roller releases the tube). For both cases, the average value of RSP was maintained the same. The HI values were integrated to represent the total hemolysis value per period, where the variable RSP shows decrease by 35% compared to the constant revolution.

Results
Hemolysis index HI was collected at the outlet as mass weighted average and was compared for two different settings – constant (conventional) and variable RSP (rotational speed is decreased when the roller releases the tube). For both cases, the average value of RSP was maintained the same. The HI values were integrated to represent the total hemolysis value per period, where the variable RSP shows decrease by 35% compared to the constant revolution.

Discussion
The paper presents a new way of reducing the rate of hemolysis in RP by setting an appropriate RSP. It could be used together with a slight under-occlusion or lower occlusion angle to further lower the rate of hemolysis [8]. However, the benefits of these adjustments together still have to be evaluated. Moreover, variable RSP of the RP enables to generate a required flow waveform. Such a controlled system could bring an alternative approach (similarly to CP in [5]) of compensating the malfunctioning heart in VA-ECMO with respect to a patient’s ECG.

References

Acknowledgements
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AUTOMATIC SEGMENTATION OF THE SPINE FROM MR AND SYNTHETIC CT IMAGES

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Introduction

Subject-specific morphometric and finite element modelling studies of the spine often rely on CT scans, exposing subjects to harmful radiation. MR imaging does not expose the subject to radiation and is generally better suited for the visualization of soft tissues. With emerging deep-learning (DL) methods it is now possible to derive synthetic CT images from MR images to visualize bone [1]. Additionally, DL methods can be used for the automatic segmentation of various soft structures. The aim of this study was to train DL networks for the automatic segmentation of vertebrae, intervertebral discs (IVD), and nuclei pulposi (NP) based on MR images for the purpose of building biomechanical subject-specific spine models.

Materials and Methods

3D sagittal T1-weighted in-phase, out-of-phase, fat, water, and T2-weighted MR scans were taken from 13 adult volunteers (Fig. 1A; voxel size: 0.625x0.625x1 mm³; field of view: 420x420x100 mm³). For 4 volunteers additional T2-weighted scans were taken using compressed sensing, and a shortened sequence (Fig. 1C). Synthetic CT scans were generated from these images using a pretrained DL algorithm (Fig 1B; BoneMRI V1.5, MRIguidance). A DL network (nnUNet) was trained on the in-phase, out-of-phase, fat and water scans of 6 subjects for automatic segmentation of the IVD [2]. The same network was trained on the standard 3D T2-weighted scans of 6 subjects for the segmentation of the NP. For segmentation of the vertebrae, a pretrained DL network was selected [3,4].

Using the newly trained and pretrained networks, validation was performed on 2 of the remaining subjects. For the NP, validation was also performed on the additional T2-weighted sequences.

Results

Validating the networks for the segmentation of the IVDs and vertebrae on a scoliotic subject (cobb angle ~30°) resulted in Dice scores of 0.93 and 0.96, respectively (Fig. 1D). For the segmentation of the NP Dice scores range from 0.86 to 0.94 for 4 subjects, with similar results for validation against the additional sequences (Fig. 1D).

Discussion and Conclusions

Synthetic CT imaging enables a unique segmentation of discs and vertebrae without the need for registering CT and MR images and avoiding radiation exposure. Training a DL network on high-resolution T2-weighted images resulted in good automatic segmentations, even on accelerated sequences. These segmentations are accurate enough to create subject-specific models.

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Acknowledgements

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Figure 1: A) in-phase, out-of-phase, fat, and water MR images; B) Synthetic CT image; C) Various 3D sagittal T2-weighted images; D) Manual and automatic segmentations used for validation with the Dice score for each comparison.
A MECHANOBIOLOGICAL MODEL TO SIMULATE ANTIOXIDATIVE TREATMENT IN IMPACTED CARTILAGE

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4. Massachusetts Institute of Technology, USA

Introduction

Joint injuries can trigger cell-driven cartilage degeneration which may ultimately culminate into post-traumatic osteoarthritis (PTOA) [1]. When applied acutely after injury, antioxidants such as N-acetylcysteine (NAC) mitigate cell-driven proteoglycan (PG) degeneration [1,2]. Here, we aim to develop a computational mechanobiological model to assess how protection with NAC alters cell damage (oxidative stress) and subsequent PG loss in impacted cartilage over a two-week period after injury and acute treatment.

Methods

Our mechanobiological model relied on information from previous explant experiments involving drop-tower impacts (Fig. 1) [2]. We incorporated healthy, necrotic, apoptotic, and damaged cell states ($G_{d,e}$), post-impact damaged cell concentration as an initial condition [2], and enzymatic degeneration of PGs as in our previous 2-D mechanobiological model [3]. Apoptosis rate ($k_{\text{apoptosis}}$) and damaged cell-related enzymatic PG degeneration were estimated by matching simulated and experimental data post-impact [2]. An earlier report was used to estimate NAC transport properties in cartilage [4] and experimental 4-day NAC culture data [2] was used to calibrate the rate coefficient describing the extent to which NAC treatment reduces oxidative stress, interpreted as rate of cells switching their state from damaged to healthy ($k_{d\rightarrow h,e}$). Finally, we simulated PG content during 1-day NAC treatment followed by a 13-day period without NAC. The simulated relative PG content (bulk PG content in the 4-mm-wide impact vs. intact area) was evaluated from the model and compared to the experiments [2].

![Simulation of proteoglycan degeneration, cell viability and N-acetylcysteine treatment](image)

**Figure 1:** The NAC treatment model was constructed based on previous in vitro data of impacted cartilage.

Results

Without NAC treatment, we observed lower PG content at the superficial cartilage (Fig. 2A) and a relative PG content of 83% in the full-depth impact region when compared to the unloaded intact region at day 14 (Fig. 2B, red line). Simulated NAC treatment mitigated PG loss showing a similar temporal trend as observed in the experiments (93% relative PG content in the impact area at day 14, Fig. 2B, blue line).

![Proteoglycan distribution in the cartilage explant and B) comparison of the relative proteoglycan contents against earlier experimental data.](image)

**Figure 2:** A) Proteoglycan distribution in the cartilage explant and B) comparison of the relative proteoglycan contents against earlier experimental data.

Discussion

Our model successfully predicted mitigation of PG loss after NAC treatment due to reduction in the damaged cell concentration and oxidative stress. Interestingly, our simulation seemed to slightly overestimate the PG loss compared to the experimental NAC-treated group (Fig. 2B), suggesting that sublethal cell responses mitigated by NAC are not yet fully captured by the model. Next, we aim to expand our approach to consider possible biomechanical loading- and NAC-regulated alterations in PG biosynthesis. In the future, this model could be used to assess severity of an injury and to optimize treatment timing/dosage to mitigate oxidative stress and development of PTOA.

References


Acknowledgements

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ANATOMY BASED TEST MODEL OF THE SACROILIAC JOINT FOR BIOMECHANICAL TESTING OF IMPLANTS

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Introduction

Spino-pelvic fusion is a surgical intervention, which is frequently performed for fracture stabilization of the sacral bone or for caudal anchoring in spinal deformity correction. However, this surgical procedure is associated with a high failure rate like screw loosening or implant failure [1]. On the one hand, this is attributed to the high loads of the trunk weight combined with long lever arms of multisegmental spinal fusions. On the other hand, this is also caused by the complex loading situation in the sacro-iliac joint (SIJ) from bipedal walk with intermittent one footed stance phases resulting in phasic loading with nutation and counternutation as well as inflare and outflare movement of the SIJ [2]. However, these physiological loading conditions are not yet part of the pre-clinical evaluation of SIJ implants. Therefore, we aimed to create a test model for generating SIJ kinematics based on an anatomical mechanism as a basis for biomechanical implant testing close to the physiological situation.

Methods

An experimental model based on a mean CT scan of 98 patients was built, including L4 and L5 vertebrae, sacrum, ilium with pubic symphysis and proximal femur. The landmarks and basic dimensions of the bones were integrated and the SIJ surfaces were modelled as spherical segments with low distal congruency. The top border of L4 was placed horizontally, a sacral slope of 40° and a pelvic tilt of 12° were realized. All bones were produced out of 3D printed polyamide and the pubic symphysis was made of silicone. The anatomy and the identified landmarks were used to set up attachment points for seven ligaments and muscles. The ligaments were modeled with pretensioned wires whereas the muscles are passively activated using tension springs. Hip joints were emulated with hip cups and heads. The model is loaded by proximo-distal displacement of the L4 vertebra, leading to movement at the SIJ. With both femurs standing on the ground, a symmetrical two leg loading situation can be simulated. By changing the configuration of the ground support with a horizontal actuator, the model transfers from two leg stance into a right or left sided one leg loading situation by only supporting one femur. All movements are tracked using an optical measurement system (ARAMIS 12M, Carl Zeiss GOM Metrology GmbH, Braunschweig, Germany).

Results

An inflare-outflare movement of the two ilia, leading to an opening of the pubic symphysis, in combination with a nutation-counternutation movement, was generated. Symmetrical inflare and nutation movements were measured for two leg stance. When changing to left/right one leg loading situation, an asymmetric movement was generated (Tab. 1).

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<tr>
<th></th>
<th>Inflare in °</th>
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<tr>
<td>Two leg stance</td>
<td>Left 0.3</td>
<td>Right 0.3</td>
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<td></td>
<td>Left 0.2</td>
<td>Right 0.5</td>
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<tr>
<td>One leg stance right</td>
<td>0.4</td>
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<td></td>
<td>0.8</td>
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Table 1: Range of motion of the SIJ model during two leg stance and right/left one leg stance loading situation.

Discussion

The test-model creates a complex movement of the SIJ which is based on an anatomical mechanism and is well in line with reported values of biomechanical in vitro and in vivo studies [3]. In a next step, implant constructs for spino-pelvic fusion will be attached to the model to study and optimize implant failure mechanisms.

References

INFLUENCE OF BIOMECHANICAL LOADING ON THE PHYSICAL BEHAVIOR OF A HYDROGEL AFTER INJECTION INTO NATIVE HUMAN KNEES

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Introduction

The treatment of knee osteoarthritis ranges from non-operative, early interventional concepts up to operative joint replacement [1]. A new method under research is the injection of a gelatinous hydrogel, which can be loaded with agents like ibuprofen, other suitable NSAIDs or cartilage-protective ingredients [2]. As the hydrogel is injected into the knee joint capsule, there is potential risk of granulation and accumulation during knee articulation. The objective of this biomechanical in-vitro study is to investigate the physical behavior of the hydrogel after short-time physiological loading, when injected into native human cadaveric knees.

Methods

For this study, 15 fresh frozen, native human cadaveric knees with intact capsule, including all relevant tissues in the area of the knee joint, were used. The specimens were prepared, embedded and aligned with a six degrees of freedom joint motion simulator (Advanced Mechanical Technologies Inc., Watertown, MA) following a complex workflow. To restore joint fluid, 9 ml of human serum was injected into the capsule prior to testing. Native kinematics were recorded for level walking and stairs ascending activities (AVER75, [3], reduced to 25 % of the absolute load values [4]). 2.5 ml hydrogel, enriched with 0.03 % fluorescein, was injected retro patellar into the joint capsule (Fig. 1). To simulate short-term activities of the knee, the previously recorded kinematics were applied to the specimens in displacement control, leaving only axial load in force control. The specimens were exposed to 1800 cycles of level walking and 900 cycles of stairs ascending. After the loading, the capsule was opened using a medial parapatellar approach. For detection of the hydrogel, the articulating surfaces were visually inspected under ultraviolet light for fluorescein reaction. In addition to this, the articulating surfaces and the joint fluid were analyzed for a chemical polyethylene glycol reaction with Dragendorff reagent.

Results

The analysis of injected hydrogel was possible in 10 of 15 specimens, 5 specimens had to be excluded from the study because of leaking knee capsule or hydrogel injection into surrounding tissue as e.g. hoffa’s fat body. For all included specimens, except two, an even fluorescein distribution within the whole knee capsule was observed under ultraviolet light (Fig. 2). The Dragendorff reagent application to the articulating surfaces also showed no granulation nor accumulation of the hydrogel. For the extracted joint fluid, a reaction of the Dragendorff reagent was observed.

Discussion

The observed fluorescein detection and Dragendorff reagent reaction show, that no granulation or accumulation of the injected hydrogel occurs after short-term dynamic loading of the knee specimens. The hydrogel mostly dissolves in the joint fluid.

References

2. InGel-NxG, German BMBF funding code 13XP5086

Acknowledgements

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FRACTURE MANAGEMENT STRATEGIES INFLUENCE THE FRACTURE HEMATOMA PROTEOME AFTER MULTIPLE TRAUMA.

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Introduction

Multiple trauma can lead to impaired fracture healing [1]. The subsequent surgical intervention is important in stabilizing the patient and is considered the so-called ‘second hit’. However, invasive, prolonged surgery can cause excessive inflammation and may be detrimental to a patient’s condition [2]. This dilemma lies at the base of two main trauma-treatment strategies: Early-Total-Care (ETC) and Damage-Control-Orthopaedics (DCO). ETC aims at early, permanent fixation of all long bone fractures during primary surgery, whereas DCO focusses on temporary fixation, using e.g. external fixators for later definitive fracture fixation [3]. Both treatment methods have pros and cons, but exact cellular mechanisms that underlie their differential effects on fracture healing are not yet fully known. The fracture hemATOMA (fxH) has proven to be a key element in initiation and prolongation of the fracture healing cascade [4]. These cellular communication mechanisms depend in great part on proteins. Proteomics is increasingly applied in trauma research, but mainly on circulatory proteins. The aim of this study was to develop a protocol for the determination of proteins in fxH samples from a porcine multiple trauma model in which two surgical treatments were compared.

Methods

The porcine multiple trauma model consisted of bilateral femur fracture, blunt chest trauma, liver laceration, and controlled hemorrhagic shock. Animals were operatively and medically stabilized and monitored under ICU standards for 72 hours prior to sacrifice. Three experimental groups were defined: control (n=6), intramedullary nailing (ETC; n=7), and external fixation (DCO; n=7) (Figure 1). Intra-Hemorrhage samples were collected from the fracture site, snap-frozen and stored at -80°C to avoid molecular degradation. Samples were sectioned at 15µm at -20°C using a cryostat to facilitate protein extraction. Per sample, 10 sections were collected in Eppendorf tubes and dissolved in 100µL of 50mM ammonium bicarbonate buffer containing 5M urea, followed by 3 freeze–thaw cycles for protein isolation. A Bradford protein quantification assay was performed and 20µg protein were loaded on 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The SDS-PAGE ran for 10 min at 50V followed by 4 min at 180V. The gel was stained with Coomassie-blue for protein visualization. Protein bands were collected from the gel and digested using trypsin using a MassPREP robot. An HSA/immunoglobulin depletion was performed with 100 µg of the isolated protein. The digested samples were injected and separated on an Acclaim PepMap C18 analytical column (2µm, 75µm x 500mm, 100Å) coupled to a Thermo Fisher Scientific HPLC system. The HPLC system was coupled to an Orbitrap MS Q-Exactive instrument equipped with a nano electrospray Flex ion source. Raw data files were processed with proteome discoverer software for protein identification, and abundance and fold change calculations. The swiss-prot Sus scrofa database was used (TaxID 9823).

Results

Label-free proteomics analysis was performed to investigate the differences in protein expression between the ETC and DCO groups. For the first time in literature, the fxH proteome was described, finding a total of 2311 proteins. Protein interaction networks were generated using STRING software. The networks with the large enrichment effects were related to the cell cycle, electron transfer and hemoglobin complex go-term. Of these proteins, 30 proteins showed a statistical difference (adjusted p-value≤0.05; FC cutoff set at 1.5-fold) between the groups. Among those, 19 and 11 proteins showed higher abundance in the ETC and DCO groups respectively. These proteins are involved in cell cycle pathways and complement activation.

Discussion

This study shows that label free proteomics is a suitable analytical tool for protein analysis in fxH. The invasiveness of the surgical intervention had a clear effect on the fxH proteome at the injury site. Treatment-specific proteome changes were identified, linked to key processes in inflammation and fracture healing.

References

EMG-BASED JOINT TORQUE ESTIMATION USING PHYSICS-INFORMED NEURAL NETWORK IN HUMAN UPPER LIMB

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Introduction
When employing an exoskeleton or exosuit to augment strength and endurance, one must be able to calculate the joint torque of hand movements using surface electromyography signals. The calculated joint torque is sent to the actuator of the external device as a control signal. The musculoskeletal model can be used to estimate joint torque [1]. However, this paradigm has a slowdown problem, particularly in real-time applications. Due to the advantages of quick and easy implementation, data-driven approaches have recently become an attractive option; however, they suffer from accuracy during task variations [2]. In this study, a physics-informed neural network for joint torque estimation is proposed; first, we have predicted the joint angle, which was further used to compute joint torque using a derived equation of motion. Here, physics-based domain information is included in the data-driven model via the channel of the customized loss function. To illustrate the joint torque prediction in the suggested framework, we employed the surface ElectroMyoGram (sEMG) and time. The validation used self-reported data from a single healthy person for several elbow flexion trials. The outcome shows that the suggested framework is reliable and effective.

Methods
An sEMG input layer, an output neural layer, and four hidden layers make up the Artificial Neural Network (ANN) model utilized to estimate elbow joint angle (where the relation between sEMG and joint angle was facilitated). This model is further improved by the physics-based component entailing the underlying relationship between joint angle and joint torque, as shown in Fig. 1. In order to apply a physics-based constraint, a customized loss function is used.

The customized loss function in the proposed framework is defined as follows:
Total loss = Joint angle loss + Joint torque loss

\[ \text{Joint angle loss} = \frac{1}{N_u} \sum_{i=1}^{N_u} |\theta_i^p (\text{emg}_i^p, \tau_i^p) - \theta_i|^2 \]

\[ \text{Joint torque loss} = \frac{1}{N_f} \sum_{i=1}^{N_f} |\tau_i^p (\theta_i^p, \dot{\theta}_i^p, \ddot{\theta}_i^p) - \tau_i|^2 \]

where \(\theta_p\) and \(\theta\) are the predicted and actual joint angles, respectively. \(\tau_p\) and \(\tau\) are the torque from predicted and actual joint angles, respectively.

Results
The predicted torque from the physics-informed neural network agreed with the torque from inverse dynamics calculations for the elbow flexion motion, as shown in Fig. 2.

Discussion
Our model predicts elbow joint torque with reasonable accuracy, compared to the joint torque from an inverse dynamics model. The variation in the prediction may be due to overfitting and noise in experimental data for the given activity, indicating the need for the optimal architecture of ANN.

References
TRIAL-BY-TRIAL ERROR CORRECTION FOR ACCURATE BASEBALL PITCHING

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Introduction
In various motor skills in sports, such as throwing, kicking, and hitting, accurately controlling a ball to a target position in high-speed is one of the important skills. The final arrival position of the ball is approximately determined by its physical state at the release or impact. In high-speed baseball pitching, reducing the variability of the ball’s release angle is particularly necessary to reduce the variability of arrival position (Kusafuka et al., 2022). However, as there is always variability in human movements and it increases as the speed increases (Faisal et al., 2008; Fitts, 1954), how to decrease the variability is one issue. This study focused on one strategy; trial-by-trial error correction, which is to correct movements in the following trials facing an undesirable outcome. The intertrial change of ball’s release angle in baseball pitching was analyzed by autocorrelation analysis to clarify the error correction.

Methods
Two high-speed cameras (960 fps) were used to capture the baseball pitching of 14 skilled pitchers (sex: male; age: 20.7 ± 1.9 years; height: 177.0 ± 5.6 cm; weight: 76.5 ± 7.7 kg; 13 right-handed and 1 left-handed). The 3D positions of the ball during each pitching of 30 fast balls were obtained using an automatic image recognition technique based on deep learning (DeepLabCut). Therefore, no markers were placed on the ball. Pitchers were instructed to aim at the catcher’s mitt and throw as fast and accurately as possible. The release angle was defined as the elevation angle θ1 (−90° to 90°) and the azimuth angle θ2 (−90° to 90°) of velocity vector at the ball release in polar coordinates. The autocorrelation analysis was performed on the intertrial change of release angle and its coefficient in lag-1: ACF1 was calculated as an error correction index. The correlation between this index and the variability (standard deviation: SD) of release angle was examined.

Results
Figure 1 shows the intertrial change of θ1 and its ACF1 in typical pitchers. If no corrections are made, each value of release angle is close to the previous (ACF1>0). If over correction are made, values of release angle of consecutive trials tend to be on opposite sides of the mean (ACF1<0). For correction that lead to a small variability, each value of release angle is statistically independent of the previous, thus ACF1 is close to zero (van Beers et al., 2013). Figure 2a shows the correlation between ACF1 and SD in θ1, and Figure 2b shows that in θ2. ACF1 in the pitchers who have small SD of release angle were close to zero. On the other hand, ACF1 in the pitchers who have large SD of release angle tended to be negative in θ1, but be positive in θ2.

Discussion
The results suggest that the pitchers who have small variability of release angle made correction that lead to a small variability. On the other hand, it suggests that the pitchers who have large variability of release angle made over correction in θ1, but made no correction in θ2. These findings indicate that trial-by-trial error correction can be one strategy to decrease the variability, but there are different reasons that the correction goes wrong depending on the direction of errors.

References

Acknowledgements
The authors would like to thank Mr. Nishikawa and Mr. Tsukamoto for their cooperation in conducting the experiments. We would also like to thank members of Kudo lab and Nakazawa lab at the University of Tokyo for inspiring discussions. This work was in part supported by Japan Science and Technology Agency and JSPS KAKENHI 20H04069.
VALIDATION OF A MUSCULOSKELTAL HUMAN SHOULDER MODEL 
DURING A FORWARD FLEXION MOTION

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Introduction

Being an un-constrained joint, the shoulder can present numerous pathologies [1]. Shoulder biomechanics can be studied using non-invasive modelling tools, such as in-silico and in-vitro studies. These tools help to better understand shoulder biomechanics and the potential impact of pathologies or surgical techniques on the shoulder biomechanics. Computational shoulder modelling and in particular musculoskeletal modelling has been previously developed. One key element of these models is their validation; however, not all of them are using experimental data. Therefore, the goal of this study was to develop and validate a musculoskeletal shoulder model. The validation was performed using data from an experimental study.

Methods

OpenSim, an open-source software [2], was used to develop a musculoskeletal shoulder model. The model (Figure 1) is a subject-specific six degree of freedom (DoF) model based on previously published models [3,4]. The model includes eight Millard 2012 Equilibrium type muscles with a total of fourteen fibers (Anterior Deltoid (AD), Lateral Deltoid (LD), Posterior Deltoid (PD) (three fibers each); Supraspinatus (SSP), Infraspinatus (ISP), Subscapularis Superior (SBS) and Inferior (SBI), Teres Minor (TM) (one fiber each)). The model uses the International Society of Biomechanics coordinate system [5]. Forward flexion kinematics from our in-house cadaveric shoulder simulator (eight muscle-actuated, six DoF) were input into the musculoskeletal model. The forward flexion movement consisted of glenohumeral elevation from 0 to 45°, -30° external rotation and 50° anterior to the scapular plane. Muscle and joint reaction forces of the musculoskeletal model were calculated using Concurrent Optimization of Muscles Activation and Kinematics (COMAK) algorithm [6]. The forces calculated by COMAK were compared to the forces generated by the cadaveric shoulder simulator actuators to validate the model. The Pearson correlation coefficient, r, was used to represent the relationship between muscles forces from the musculoskeletal model and those measured by the shoulder simulator and thereby assess the validity of the in-silico approach.

Results

Muscle forces from the musculoskeletal model and the cadaveric shoulder simulator showed strong correlation during the simulated forward flexion (Pearson’s r>0.5, Figure 1) expect for SBI (Pearson’s r = -0.19).

![Figure 1: (A) Musculoskeletal model; (B) Pearson Correlation coefficients of muscle forces of the musculoskeletal model and the cadaveric shoulder simulator for the simulated forward flexion {Grey dashed line - Pearson’s r = 0.5}; (C) Cadaveric shoulder simulator](image)

Discussion

A good agreement was observed between the musculoskeletal model predictions and the muscle forces measured in-vitro for a forward flexion motion. The discrepancy between the model estimated and the experimental force for the SBI can be explained by the fact that the SBI is not a dominant muscle during forward flexion. The method described in this study will provide a non-invasive tool for assessing the impact of shoulder pathologies and surgical techniques on the shoulder biomechanics during different activities.

References


Acknowledgements

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DIMENSION MEASUREMENTS FROM PICTURES OF TENSILE TEST SAMPLES: GUIDELINES TO IMPROVE REPRODUCIBILITY

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Introduction

Studies characterizing experimentally biological tissues abound in the scientific literature, but with a large variability on outcomes [1]. C4Bio (https://c4bio.eu/) is an international community challenge founded in 2021, in which two testing campaigns were conducted to define and evaluate a consensus methodology for characterizing biological and synthetic samples from tensile tests. The observed inter-laboratory variability may be partially attributed to the measurement of the sample’s cross-section. Measuring dimensions on soft tissue samples with a caliper is still a challenge, and optical method may be a good alternative. This study aims to improve the reproducibility of sample dimension measurements from pictures, as plan during the C4bio challenge, and to estimate the effect of their uncertainty on the stress-strain curves through uncertainty propagation.

Methods

Image acquisition. Twelve synthetic samples were cut out from an industrial silicone plate using the C4Bio cutting tool (theoretical section area 4*2mm²). Samples’ pictures were taken with a high-resolution camera (COOLPIX P7100, ISO 100, 3648*2736 pixels) and calibrated using a millimeter (mm) paper. The samples were aligned with the mm grid. Dimensions were measured using Fiji (v1.53t, https://fiji.sc/) from a top picture (Figure 1) for the width, and from a side picture using a C4Bio holding device for the thickness.

Figure 1: Top and side pictures of a tensile sample

Initial procedure. Images were calibrated with a polyline of 4 points spaced by 10mm. Sample dimensions were the average length measured between 2 points at 5 locations in its reduced section. Extended procedure. Additional instructions were followed. Images were first filtered (local contrast enhancement, sharpen); the points should be pixel-accurate placed in a high contrast area, within the calibrated zone, and should be checked a posteriori.

Reproducibility. Three operators applied the two procedures. Scilab (v6.1.1 https://www.scilab.org/) was used for processing the dimensions and statistics (mean, standard deviation (SD), inter-quantile (IQ) range, Wilcoxon signed rank test…).

Effect on the stress-strain curves. The thickness and the width SD, plus a SD of 0.2N on the force, were propagated as independent variables on the force-strain curves from experimental tensile test of the samples.

Results

The picture mean scale was (mean ± 2SD) 18.1 ± 38 pixels/mm. The thickness and width distributions were non normal for the two procedures. The initial procedure led to the same variability for thickness and width (2.347 ± 0.147 and 4.027 ± 0.157mm respectively). Five out of 72 measures were identified as outliers. Two operators provided significant different sets of width measures (p<0.05). The extended procedure eliminated the risk of outlier and the significant difference between operators, and decreased the variability (2.293 ± 0.124 and 4.080 ± 0.108mm). It led to statistically different measures from the initial procedure (p < 0.0003), the mean and median being in the same order. The width IQ was reduced (from 0.087 to 0.055mm), not the thickness one. For both the initial and extended procedures, the stress SD along the mean stress-strain curve (3.7% and 2.9%) remains within the experimental corridor (5.2%), the extended procedure slightly reducing the stress range.

Discussion

Simple guidelines can help to reduce the uncertainty on dimensions. Filtering underlines the details of the picture and standardizes the image interpretation made by the operators; and a pixel-accurate location is closed to a 0.05mm uncertainty. But high-quality images are essential for the reliability [2]. On side pictures, due to the sample holding configuration, either the sample’s side or the mm grid were blurred, rendering the selection of points less accurate. In spite of this, the uncertainty on the dimensions of the section was coherent with the literature in percentage [3] and did not increase the variability observed experimentally on the stress-strain curves. Thus, it seems that, reducing the intra-operator variability can reduce the geometrical uncertainty, but this variability could not explain the inter-laboratory variability observed on the stress-strain curves [1].

References


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THE ROLE OF ANATOMICAL LOCATION IN SCAFFOLD-INDUCED HEALING OF CRANIOFACIAL BONE DEFECTS

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Introduction

When a bone fractures, successful healing is usually achieved within weeks. However, fracture severity and anatomical location can lead to delayed or non-healing. We developed a 3D in silico model of bone regeneration and used it to investigate the influence of a scaffold produced using melt electrowriting (MEW) and coated (or not) with cells or growth factors (GF) as treatment strategy in craniofacial bone defects, and to explore the role of the defect anatomical location (mandibular versus calvarial).

Methods

In silico model. We developed a 3D in silico model in FreeFEM [1], following an existing multiscale bioregulatory 2D model of bone fracture healing [2]. Our model captures biological processes across time and space scales, simulating osteogenesis and sprouting angiogenesis. At the tissue/cellular level, the spatiotemporal evolution of biochemical factors, cells and matrices is described using a non-linear system of taxis-diffusion-reaction partial differential equations. At the (intra)cellular level, the developing vasculature is simulated with discrete endothelial cells, regulated individually by one ordinary differential equation representing its intracellular module. Suitable initial and boundary conditions ensure the existence, uniqueness and non-negativity of the solution.

Domain. We investigated two types of craniofacial defects: calvarial and mandibular. The geometrical domains (Fig. 1) were deduced from critical-sized defects in rabbits and generated as finite element meshes. Due to symmetry, only one-fourth of each domain (blue region in Fig. 1) was simulated.

Implementation details. The healing progress of the two craniofacial defects was investigated with and without the application of the MEW scaffold. Migration of skeletal progenitor cells (SPCs) and vascular restoration were assumed from all domain surfaces (top, bottom and lateral) for the calvarial defect due to the presence of the periosteum and the dura mater. For the mandibular defect, SPCs migration was assumed only from the lateral surface. The MEW scaffold was simulated with initial and/or boundary conditions representing different burst-release profiles of cells and/or GF from the scaffold into the bone defect. We used Bayesian optimization to optimize the model parameters as pre-validation step.

Results

Our model adequately captured the biological processes of bone regeneration for the two types of craniofacial defects – in line with their developmental origin: intramembranous ossification for the calvarial defect due to a fast restoration of the vasculature, and intramembranous and endochondral ossification for the mandibular defect due to a more prolonged hypoxic injury site (results not shown). Our in silico predictions were compared with in vivo results [3] at 4 weeks post surgery to investigate the MEW scaffold as treatment. The in vivo mandibular defect showed no significant difference in bone volume (Fig. 2A), which led to non-healing. We used our model to explore adequate GF concentrations to load onto the MEW scaffold such that (delayed) healing was achieved (Fig. 2B).

Discussion

Our in silico model captured the biological reality of bone regeneration for different anatomical locations, allowing us to identify the most impactful conditions in vivo and to optimize tissue-engineered scaffolds.

References


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WHAT DO SURGEONS HEAR AND FEEL WHEN BREACHING CORTICAL WALLS AND HOW DO BREACHES AFFECT SCREW PURCHASE?

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Introduction
Freehand pedicle screw insertion is performed without intraoperative image guidance; thus, the procedure is reliant on intricate knowledge of vertebral landmarks and bone anatomy in conjunction with sense perception. Distinct audible vibration patterns created during pilot hole drilling are used to deduce whether the bit has perforated cortical walls. Tactile feedback during screw insertion, which is the feeling of torque in the hands, is used to determine if screws have breached cortical bone. The danger of screw breaching is iatrogenic injury and a potential increased risk of screw loosening and non-union. A large proportion of spine surgeons do not perform preoperative bone mineral density (BMD) scans routinely [1]. Thus, in a clinical setting, surgeons rely on these perceptions to identify breach as well as to judge the quality of bone under fixation and the extent of screw purchase. This study investigated breach diagnosis using acoustic emission (AE) and torsional (T) profiling. Furthermore, it aimed to determine how breached screws influence fixation stability, defined using maximum insertion torque (Tmax), pull-out force (Fmax), stiffness (S), energy (E) and displacement (d).

Methods
In vitro experimental testing was conducted on 58 ovine lumbar vertebrae. Specimens were prepared and all external soft tissues were resected. Samples were randomly subdivided into three trajectory groups: Normal Insertion, Ni (n = 26), Major Lateral Breach, BML (n = 16) and Major Medial Breach, BMM (n = 16). A novel rotation mechanism was used to induce breaches. Pilot holes were drilled at 1250 rpm into bones utilising an orthopedic drill and 2.5 mm surgical drill bit. AE was captured at a frequency of 48 kHz by a custom sound sensor module. Medical grade titanium, self-tapping pedicle screws (4.5 mm x 32 mm), having cylindrical shape and possessing singular thread, were inserted at 6.0 rpm following predrilled trajectories using a specialised mechanical system. Throughout insertion, screw depth and torque were digitally recorded. A universal electromechanical test machine with custom-made fixtures was used to destructively pull screws out of bones. Screws were evulsed at 5 mm/min, whilst force and displacement data were recorded at 50 Hz. Data was collated and stratified by insertion group. All factors were subjected to one-way ANOVA analyses, which revealed statistically significant decreases in fixation properties between breached and non-breached trajectories. Tukey Kramer tests assessed post-hoc significant differences between means.

Results
Separate, one-way ANOVAs revealed that the overall effect of insertion trajectory was not significant for Tmax (p = 0.10) nor AE (p = 0.40). The overall effect of insertion trajectory was significant for all pull-out test factors (p < 0.01), except for stiffness (p = 0.06). Post-hoc tests indicated there were significant reductions in pull-out factors relative to Ni as summarised in Figure 1.

Discussion
Means of AE and Tmax did not differ by trajectory, however, individual insertion curves revealed specific information about the tool path through bone and breach incidence. Each group had a unique insertion profile, which is valuable in delineating distinctive resistance patterns experienced by surgeons when drilling or screwing in vertebrae. High AE and T occur at the moment of cortical wall perforation; thus, these variables could be used to accurately identify breach. Strong signal variations provoked by changes in local tissue properties, such as density and microarchitecture, facilitate rapid detection of different material environments. Using AE and T for continuous monitoring of cortical walls may reduce the number of dangerous breaches that have been demonstrated to significantly decrease the mechanical integrity of the bone-screw construct.

References
SPINAL AXIAL TORQUE IN ADOLESCENT IDIOPATHIC SCOLIOSIS
BEFORE AND AFTER SURGICAL CORRECTION

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Introduction
The study of the distribution of mass in adolescent idiopathic scoliotic (AIS) patients has shown promising preliminary results. This method was initially developed by Duval-Beaupère and Robain [1], and it allows to evaluate the loads applied to the spine by the overhanging mass. Recent advances in low-dose x-ray imaging and 3D reconstruction methods opened the way to wider use in clinic, and to the definition of novel biomarkers of severity and risk of progression in AIS. For instance, recent works showed that the axial torque at the junctional vertebrae (Figure 1) could play a role in the progression of the deformity [2, 3].

The aim of this study was to analyze the spinal axial torque after surgical correction of severe scoliosis.

Methods
Twenty-nine AIS patients with an indication of surgery were included (54 ± 11° Cobb angle, 15 ± 2 years old at surgery). Patients underwent biplanar x-rays in free-standing position before and at last follow-up (between 10 and 48 months). Their spine and external envelope were reconstructed with validated methods, while distribution of mass was estimated assuming typical density distributions [4]. Spinal axial torque was calculated with a previously described method [2], which consists in calculating the load applied to each vertebra by the overhanging mass (Figure 1). With certain orientations and displacement of the vertebra, this results in an axial torque.

Data collection was approved by an ethical committee (CPP IDF IV: 14409). Results were reported as average ± standard deviation.

Results
The surgical procedure decreased the Cobb angle by 36° ± 11°. Table 1 reports spinal axial torque at specific vertebral levels.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Upper end</th>
<th>Apex</th>
<th>Lower end</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop [N/m]</td>
<td>4.6 ± 2</td>
<td>1.6 ± 1.2</td>
<td>3.0 ± 1.7</td>
</tr>
<tr>
<td>Postop [N/m]</td>
<td>2.8 ± 1.3</td>
<td>1.0 ± 1.0</td>
<td>0.7 ± 0.5</td>
</tr>
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</table>

Table 1: Axial torque pre- and post-operatively.

Postoperative decrease was significant at all vertebral levels (p < 0.01), and preoperative values were significantly different between levels (p < 0.05). Compared to 95th percentile of torque which was previously evaluated in asymptomatic subjects [3], more than 90% of patients had higher values at the upper and lower end vertebrae. Postoperatively, 62% of patients still had higher torque at the upper end vertebra than asymptomatic subjects, while only 38% patients showed abnormal values at the lower junction.

Discussion

Biplanar x-rays and 3D reconstruction are now well established to study skeletal morphology and alignment in weight bearing position. Only recently, methods have been developed to study mass distribution. Results of this study confirm that AIS patients show abnormally high spinal axial torque, especially at the end vertebrae, and that this parameter is normalized postoperatively for only a small number of patients. This further confirms that the axial plane plays an essential role in scoliosis. Further studies should focus on the relationship between this parameter and the development of postoperative mechanical complications.

References
Estimation of Knee Joint Contact Force Maxima During Gait Using a Video Camera and Demographic Data

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Introduction

Joint loading has a role in maintaining tissue homeostasis and contributes to the onset and development of joint conditions such as osteoarthritis [1]. Subject-specific load estimation could help in planning of treatment strategies, such as personalized rehabilitation, of such conditions [2]. Currently, subject-specific knee loading can be estimated with musculoskeletal modeling and simulation (MS) [3] but typically requires measurement in a motion laboratory, which involves time (participant preparation, analysis) and cost (large space, personnel, equipment). These limitations would be eliminated if knee joint contact forces (KJCFs) could be estimated from simple input predictors using artificial neural networks.

Methods

We trained feedforward artificial neural networks (ANNs) to estimate tibiofemoral KJCF maxima based on subjects’ mass, height, age, gender, walking speed, and peak knee flexion angle. First, the ANNs were trained with data from 5 existing motion capture datasets [4–8] and included 5000 trials from 296 subjects. Next, we measured the overground gait of 10 healthy volunteer participants, unrelated to the training data, using optical motion capture, while simultaneously recording their sagittal-plane motion with a video camera. Ten trials were recorded per participant. From each participant’s demographic data (mass, height, age, gender) and data extracted from video data using OpenPose [9] (walking speed, peak knee flexion), KJCF maxima in the medial and lateral compartments and the sum of the KJCF of both compartments were estimated with the trained ANNs. Reference KJCF maxima were MS-estimated from optical motion capture data using OpenSim. The estimation accuracy of the ANNs was quantified by the root mean square errors normalized to the mean of the MS-estimated maxima (NRMSE) and Pearson correlation coefficients (R) between the ANN-estimated and MS-estimated KJCF maxima.

Results

The NRMSE (normalized to the mean of MS-estimated maxima) and Pearson correlation coefficients between ANN-estimated and MS-estimated KJCF maxima across all subjects were 0.18 and 0.86 for loading of both compartments summed (Figure 1); 0.19 and 0.79 for the medial compartment; and 0.26 and 0.84 for the lateral compartment, respectively.

Discussion

We showed that ANNs can be used for approximating KJCF maxima during walking with demographic and video camera data. ANNs underestimated the loading maxima for all participants except those with very low loading, the reason for which will be examined in the future and the model refined accordingly. The use of ANNs eliminates the need for measurements in a laboratory setting and skips time-consuming MS analysis steps. Thus, the estimation of KJCF maxima could be done more portably, e.g., with a webcam during a physician’s appointment. Effortless estimation of KJCF maxima could support physical rehabilitation and gait retraining-based interventions.

References

BIOMECHANICAL DETERMINANTS OF CHONDROLABRAL COMPLEX LESIONS IN FEMOROACETABULAR IMPINGEMENT

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Introduction
The frequency of the chondrolabral complex lesions due to femoroacetabular impingement (FAI) in the study of cadaveric material is 93% [1,2]. As a biomechanically determined factor it can be subject to hip destruction and early osteoarthritis in Pincer-type impingement [3,4]. Work objective is to study the biomechanism and stress-strain behavior of the chondrolabral complex lesions in Pincer-type impingement during daily activity motions.

Methods
The SolidWorks package was used to build a 3D pelvis model with normal ratios in the femoroacetabular (FA) region and with Pincer-type impingement. Finite element analysis (FEA) of the stress-strain state (SSS) in ANSYS was performed to determine the von Mises stress, strain and total deformations for the isotropic pelvis model during 90° hip flexion and 15° internal rotation in daily motions.

Results
The maximum stress-strain values increased 2-3.4 times in the bone structure along the anterior upper acetabular rim, the femoral neck, and the acetabular labrum at the Pincer osteophyte contact area compared to the normal ratio in the FA model.

Discussion
The stress-strain increasing in contact area on the Pincer osteophyte and femoral neck can be a factor of the Cam-type osteophyte formation and the progression of acetabular rim ossification. Daily activity can lead to an increase in the maximum stress, as a factor of chondral delamination and destruction of the acetabular labrum. Early surgery is needed to avoid progression of the osteoarthritis in the Pincer-type impingement.

Figure and Tables

Figure 1: FEM of the femoroacetabular area with boundary conditions

Figure 2: Finite element mesh

Figure 3: Graphic representation of stress at the acetabulum in the model with pincer-type FAI

Figure 3: Graphic representation of stress at the chondrolabral complex in the model with pincer-type FAI

Table 1: Stress on the model elements

<table>
<thead>
<tr>
<th>Model Element</th>
<th>FE model with Pincer-type FAI</th>
<th>FE model with normal ratio in FA area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetabulum</td>
<td>11.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Labrum and cartilage</td>
<td>5.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>1.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

References
PARAMETRIC STUDY OF MECHANICAL BEHAVIOR OF AUXETIC GEOMETRIES FOR SKIN TISSUE ENGINEERING SCAFFOLDS

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Introduction
Skin is the biggest organ in human body. It is an anisotropic organ composed of three different thickness and composition layers which are not uniform across the body. This particular organ is also very susceptible to large wounds as a consequence of burns that can affect the high healing capacity of the skin, and often require some type of dressing structure that might enhance tissue regeneration. The aim of this work is to study different designs for tissue engineering scaffolds whose mechanical properties can be modified according to the patient’s wound needs, which could vary depending on the body location or the patient’s age or gender [1]. This property tuning can be achieved by using micro-scale auxetic designs. Auxetic structures are known to expand in multiple directions when stretched, so they could better conform to the wound shape and, in addition, could promote wound healing by providing enhanced mechanical support and facilitating cell migration and infiltration [2], which would improve the mechanical properties of the regenerated tissue.

Methods
A computational parametric study of the auxetic geometries has been conducted via numerical simulations of uniaxial tensile tests based on the finite element method (FEM) using the FEM software Abaqus. For this purpose, a versatile software tool based on Python scripts has been developed to automatize the process of generation, calculation, and subsequent results post-processing of the numerical models.

Results
After running the numerical simulations, mechanical properties of the scaffolds are obtained by taking the forces, displacements and sizes of the scaffolds and calculating their elastic modulus and stress-strain rates, which reveal a mechanical behavior similar to the characteristic ‘J-shape’ curve of the skin. This behavior consists of a low-mechanical stiffness at the beginning of the simulation, associated to the initial ‘unfolding’ of the structures, which is followed by a stiffening caused by the alignment of the fibers within the stretching direction that finally ends producing plastic deformation at high strain rates in some fibers, which is considered to be the use limit of the scaffold. With the aim of analyze these results for a possible clinic application, appropriate skin scaffold mechanical properties [4], along with Poisson’s ratio of the skin [5], are taken from literature and can be seen in Table 1, where they are compared with some representative results from the auxetic scaffold stretching simulations.

<table>
<thead>
<tr>
<th>Elastic Mod. [MPa]</th>
<th>Min. Poisson’s Ratio [-]</th>
</tr>
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<tbody>
<tr>
<td>Ref. Values</td>
<td>4.5 – 25 MPa</td>
</tr>
<tr>
<td>Num. Res.</td>
<td>5 – 60 MPa</td>
</tr>
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</table>

Table 1: Comparison of literature reference values [4][5] with some representative numerical results.

Both stiffness values are in a similar scale range and the ‘more auxetic’ Poisson’s ratio measured experimentally on skin [5] (-1.7) is among the values achievable by the auxetic designs.

Discussion
Auxetic design influence in the mechanical behavior of the scaffold has been numerically simulated and results show that auxetic scaffolds have tunable mechanical properties within skin-compatible value ranges, which opens the way for their use in custom-fit applications.

References

Acknowledgements
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Accrual of osteoclast precursors drives bone loss after denosumab discontinuation: A digital twin study

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Introduction

Incidence of osteoporosis (OP) is increasing with our aging population. Denosumab, a common treatment for OP, is a monoclonal antibody that binds to RANKL and thus reduces osteoclastogenesis, osteoclast-mediated bone resorption and remodeling rates. Upon cessation of treatment, however, resorption rises quickly to levels higher than baseline and rapid bone loss occurs [1]. This has been attributed to: blockaded differentiation and thus accumulation of (A) osteoclast precursors [2] or (B) osteomorphs, cells in the marrow originating from the fission of osteoclasts on the bone surface [3], (C) low osteoblast numbers leading to a higher RANKL/OPG ratio upon evacuation of denosumab than prior to treatment or (D) increased sclerostin production by osteocytes to return to the pre-treatment mechanostat setpoint. We quantify the relative contributions of these mechanisms to the withdrawal effect using an in-house micro-multiphysics agent-based (micro-MPA) model that generates digital twins of patient iliac crest biopsies.

Methods

For the micro-MPA model, bone and marrow cells are represented as agents on a voxel-based lattice and are motile and capable of producing or resorbing tissue and signaling molecules [4]. A micro-multiphysics solver is used to determine the diffusion, decay and reactions of signaling molecules (Fig. 1A). Concomitantly, the bone mechanical environment is simulated using micro-finite element analysis to determine the internal strains, which serve as stimulus for the osteocytes and osteoblasts. Starting from micro-computed tomography (micro-CT) scans of iliac crest biopsies (n=7) from postmenopausal women (age: 72±5 years) [4] simulation runs for 2 years of treatment followed by 2 years of discontinuation were executed based on four different versions of the model each isolating one of the mechanisms proposed in literature.

Results

All mechanisms lead to an increase in BMD during treatment followed by a drop during discontinuation (Fig. 1C). During treatment, the osteomorph and RANK/OPG ratio mechanisms best represented the clinical treatment data, with the other mechanisms overestimating the change in BMD. The sclerostin only mechanism failed to accurately represent the treatment phase of the clinical data and resulted in a premature drop in BMD. After treatment, the osteomorph mechanism best represented the initiation of denosumab withdrawal, but overestimated the total loss in BMD at two years post-discontinuation. In contrast, the simulations based on the accumulation of osteoclast precursors yielded a more conservative initiation of withdrawal, but better represented the long-term stabilization of the BMD in the clinical cohort.

Discussion

Our study suggests that both accumulation of preosteoclasts and osteomorphs play a key role in the cell-cytokine dynamics following denosumab discontinuation, with accumulation of preosteoclasts contributing approximately twice as many resurgent osteoclasts as osteomorphs but osteomorphs playing a role faster. Future work will include performing equivalence tests not only with the individual mechanisms but also with combinations of these to quantify contributions. This study demonstrates that micro-MPA models provide a fast and inexpensive tool to computationally test hypotheses relating to bone mechanobiology and may assist in formulating in silico trials to help reduce and refine human clinical trials targeting alternative strategies for OP treatment and sequencing of available pharmaceuticals.

References

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Acknowledgements

Support from the Swiss National Supercomputing Centre (project s1070) and the Euler compute cluster at ETH Zurich.

Fig. 1: (A) Diagram of cell-cytokine pathways included in micro-MPA model. (B) initial distribution of key cell types on 3-D biopsy and (C) bone mineral density trends

Announcements

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
MULTIBODY KINEMATIC OPTIMIZATION OF SCAPULAR KINEMATICS: 
THE EFFECT OF MARKER WEIGHTS

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Introduction
Scapular motion is essential for shoulder movement comprehension. To estimate scapular kinematics, skin marker-based method is generally used, but its accuracy suffers from soft tissue artefacts (STA) [1]. Experimental methods have been developed to improve scapular kinematic estimates, placing markers on the acromion or the scapula spine, but none of them fully annihilate scapular misorientation. Numerical methods have also been developed to further improve kinematics, such as multibody kinematic optimization (MKO), including point-on-ellipsoid scapulothoracic joint. Furthermore, weights applied to individual markers can be adjusted in MKO to counteract for STA local distribution. But the influence of individual marker weight on scapular kinematic accuracy has never been investigated. This study aimed to assess the influence of weights applied to the scapula markers on scapular kinematic estimates.

Methods
Fifteen healthy volunteers were equipped with 24 reflective-skin-markers and mimicked fourteen analytical, daily living and sport movements. The latter were equally decomposed in five static poses, to allow for the positioning of a scapula locator. Two kinematic models were implemented and scale using OpenSim. The reference model (REFmodel) was composed of the thorax and scapula segments with six degrees of freedom each, and anatomical landmarks from the scapula locator were used for inverse kinematics. The second model (M KOmodel) was adapted from Seth et al. [2] with a subject-specific point-on-ellipsoid scapulothoracic joint. Segment kinematics were estimated with MKO from skin markers. Especially for the scapula, six markers on the acromion and scapular spine were used. Weights of the scapula were optimized for each participant and each movement by minimizing the average scapular misorientation (θ) on the five poses (t) of each movement:

$$\theta = \frac{1}{T} \sum_{t=1}^{T} \cos^{-1} \left( \frac{\text{trace}(R_{MKO}^{-1}(t) \cdot R_{REF}(t)) - 1}{2} \right)$$

with $R_{MKO}$ and $R_{REF}$ the rotation matrices from scapula to thorax obtained from both the models. All optimized weighting sets were averaged and the three weighting procedures (homogenous vs optimized vs average) were compared using a linear mixed model.

Results
Mean weights from all optimized weighting sets for scapula markers ranged from 0.05±0.14 to 0.32±0.32 (Figure 1).

When weighting sets were individually optimized, significant smallest scapular misorientation was found (p<0.001; θ=14.6±3.7°), with a reduction of scapular misorientation ranging from -0.9±0.5° to -12.1±36.3°. By contrast no significant differences were observed between homogenous and mean optimized weighting set (p=0.547; θ=18.3±7.8° and θ=19.2±11.3°, respectively).

Discussion
Marker weight optimization resulted in improvements similar to those previously described with MKO methods [3]. Variability in the optimized weights highlighted the importance of marker redundancy for scapular kinematic estimates in MKO. In addition, weighting sets showed subject- and movement-specificity, which could be explained by subject- and movement-specific STA [1]. Nevertheless, for daily-based kinematic analyses, weights optimization appeared unsuitable.

This study presents some limitations. Using a scapula locator can be considered a “silver standard method” and optimization results were dependent on the kinematic model used.

To conclude, when estimating scapular kinematics in upper limb MKO, the use of homogenous weights applied on redundant markers located from acromion to scapular medial border spine are recommended.

References
INTRA AND INTER OPERATOR VARIABILITY IN A FINITE ELEMENT MODEL OF VERTEBRA FOR FAILURE LOAD PREDICTION

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Introduction

Vertebral fractures are frequent with the decrease of bone density due to age [1]. Finite element (FE) models of single vertebrae, based on QCT imaging, have been proposed to estimate failure load [2, 3, 5], but their reproducibility needs to be assessed before considering a clinical application [4]. Vertebra segmentation is a critical step for the model construction, because it is partially done manually and is potentially operator dependent. The aim of this study was to assess the intra- and inter-operator variability of a previously developed a finite element model of vertebra for failure load prediction [5]. It was hypothesized that the level of expertise of the operator, as well as scan resolution, would affect the reproducibility of the segmentation and, therefore, the predicted failure load.

Materials and methods

21 intact L3 vertebrae were scanned using a HRp-QCT device (XtremeCT, Scanco Medical AG, voxel size: 82 µm) with a calibration phantom (Mindway). To assess intra-operator variability, one experienced operator manually segmented vertebral bodies (3D slicer) twice from the scans resampled to 0.984 mm and 0.328 mm. To assess inter-operator variability, two additional operators with different levels of expertise (competent and beginner) performed segmentations from the aforementioned scans. FE analysis was then performed automatically as follows. Segmented vertebrae were meshed using 1 mm³ quadratic tetrahedron elements (Ansys 2019 R1). Each element was assigned a Young’s modulus, E, based on its density, ρQCT, using the relationship $E(MPa) = 3230\rho_{QCT}(g/cm^3) - 34.7$ [6], with a material step of 10 MPa. Perfect plasticity was given to each element once they reached 0.7% yield strain. Vertebras were compressed to reach a total strain of 1.9%, defined as the failure criteria [7]. For each vertebra and scan resolution, the relative difference between the failure loads obtained by the experienced operator after the first and second trials was calculated (intra-operator variability). The relative differences between the failure loads obtained by (i) the competent or beginner operator and (ii) the experienced operator (first trial) was calculated (inter-operator variability).

Results

Intra-operator variability was low at both voxel sizes, with an absolute relative difference on the failure load of 1.8±1.8% for 328 µm, and 3.6±2.7% for 984 µm (Figure 1). A finer scan resolution significantly (p=0.02) improved intra-operator reproducibility, which can be explained by an easier delineation of bone boundaries. Similar results were obtained for inter-operator variability in the failure load between competent and experienced operators. Inter-operator variability increased for a voxel size of 328 µm when the operator was a beginner compared to a competent operator, with an absolute relative difference on the failure load of 5.8±7.2% and some values above 15%. Notably, inter-operator variability was similar at both scan resolutions for the beginner operator.

Discussion and conclusion

Although intra- and inter-operator variability of failure load prediction due to segmentation is low, it should be considered when assessing the accuracy of FE models, especially for a clinical application where scan resolution is coarser (voxel size ≈ 1 mm). Moreover, a minimum experience with vertebra segmentation is required to get more reproducible results, motivating the development of automatic segmentation methods.

Acknowledgements

This project has received funding from Marie Sklodowska-Curie actions (895139), LabEx PRIMES (ANR-11-LABX-0063) and MSDAvenir.
A PROTOCOL FOR THE LOCAL MECHANICAL CHARACTERISATION OF METASTATIC BONE

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Introduction

Osteolytic bone metastases are responsible for long bone fracture leading to restricted mobility or surgery, which severely alter quality of life and have a huge socio-economic impact [1]. Patient-specific finite element (FE) models assessing the strength of tumoral bone segments can help predict bone fracture [2], but their accuracy is hampered by a limited knowledge of metastatic bone mechanical properties. Changing the constitutive law of metastatic and surrounding bone tissues in FE models can have an effect on both the predicted failure load and fracture location [3]. In this context, we proposed an experimental protocol to locally characterize the mechanical properties of metastatic and surrounding bone tissues, with the aim of incorporating them into FE models of metastatic bones.

Materials and methods

Six human bone specimens (femur or rib) containing metastatic and normal tissues were collected post-surgery. The primary cancer was breast (n=2), thyroid, rectal, myeloma or lymphoma. First, mechanical properties of the metastasis (soft tissue) were characterized on fresh frozen samples (Figure 1, left), following a previously published protocol on fresh tumor [4]. Briefly, AFM tests were performed on samples immersed in PBS using a Nanowizard3 AFM (JPK Instruments AG) equipped with an MLCT cantilever (Bruker) and a pyramidal tip. Elastic modulus and elastic fraction, defined as the ratio between equilibrium and instantaneous moduli (0: viscous; 1: elastic), were calculated using Hertz-Sneddon model [5] and standard linear solid model [6], respectively.

Second, samples were dehydrated, fixed and embedded, and mechanical properties of bone tissue were characterized (Figure 1, right). Non decalcified embedded bone samples were sectioned and metastatic, transition, and normal areas were identified from histological sections, using Masson-Goldner's trichrome staining. Force-displacement curves were obtained in each area on the remaining block using a TI950 nanoindenter (Hysitron – Bruker). The elastic modulus was identified using Oliver and Pharr model [7].

Results and discussion

Characterization of soft metastatic tissue revealed a variation in the elastic modulus over two orders of magnitude depending on the specimen (Figure 2). Preliminary tests on bone tissue were performed and results were consistent with the literature [8], with Young’s modulus values ranging between 15 and 20 GPa. The remaining specimens will be characterized and a sensitivity study will then be conducted to assess the influence of mechanical properties on the predicted failure load. This work has the potential to improve the accuracy of FE models and quantify uncertainties.

References


Acknowledgements

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Figure 1: Protocol for the mechanical characterization of metastatic bone from upper femoral extremity. Left: for soft tissue; right: for hard tissue

Figure 2: Elastic modulus of each fresh-frozen specimen in the (soft) metastatic area. The type of primary cancer is indicated. CLL: Chronic lymphocytic leukemia.
**THE FEASIBILITY OF BESPOKE REHABILITATION ROBOT HANDGRIPS TO MEET THE SPECIFIC NEEDS OF STROKE PATIENTS—PART 2**

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**Introduction**

Stroke globally is a common and serious healthcare problem, which usually causes disability and brings difficulties to people’s living [1]. Robotic-assisted therapy is considered one of the most effective methods to restore upper limb function in last few decades [2]. According to professionals’ recommendations in the UK National Clinical guidelines for stroke [3], bespoke rehabilitation devices are recommended to use. However, the majority of existing upper limb rehabilitation robots are limited in that they provide only a generic handgrip which cannot meet the needs of all stroke survivors due to the various movement patterns (e.g. spasticity) and upper limb weakness levels. This study investigates the technical and clinical feasibility of bespoke handgrips to meet stroke survivors’ needs through an online questionnaire with therapists and an estimation of manufacturing cost.

**Methods**

This study was conducted through two parts. The first part was the parametric design and manufacturing cost estimation of bespoke handgrips to identify the technical feasibility. The second part was an online questionnaire with 25 therapists to identify the clinical feasibility of bespoke handgrips.

**Results**

One wrist support and two different handgrips were designed, and their size (length and width of the handgrip) can be changed based on the individual anthropology data (Table 1). Additionally, by using additive manufacturing methods, the fabrication costs of bespoke handgrips reduced between 5%-15%.

![Image](image1)

**Table 1: Conceptual design of bespoke handgrip for rehabilitation robots developed by therapist**

Of the 25 therapists involved in this study, 76% had more than 5 years’ work experience. More than 90% of professionals (n=23) stated the positive impact of bespoke handgrips on rehabilitation outcomes and 72% (n=18) would like to use a bespoke handgrip with stroke survivors due to its high accessibility and variability (Figure 1).

![Image](image2)

**Figure 1: Sankey diagram of the benefit and concern of using bespoke upper limb rehabilitation robot handgrip based on questionnaire results.**

**Discussion**

The results indicate that a bespoke upper limb rehabilitation robot handgrip can improve stroke rehabilitation from both a technical and clinical perspective. The parametric design allows engineers to adapt the 3D design quickly (<1 minutes) according to stroke survivors’ data (e.g. palm width and length). By using the additive manufacturing method, users will be provided with more bespoke features such as the material, colour, and texture. Due to the variety of stroke survivors’ weakness levels, the standard handgrip is insufficient or uncomfortable to use. Professionals highlighted the potential of bespoke handgrips to increase the accessibility of upper limb rehabilitation robots and stroke survivors’ motivation. The safety and patient suitability (e.g. patients’ healthy condition) was reported as the main concern of using bespoke handgrip.

**References**

FABRICATION OF A PATIENT-SPECIFIC COMPLIANT AND TRANSPARENT PHANTOM FOR IN-VITRO AORTIC DISSECTION HAEMODYNAMICS

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Introduction
Aortic Dissection (AD) is a life-threatening and highly patient specific vascular condition in which the vessel wall splits creating a false lumen. In-vitro studies of AD are vital to understand its complex hemodynamics, provide reliable and quantitative data for numerical model validation and test intervention scenarios. The fabrication of patient-specific compliant and transparent phantoms of AD has been a main challenge for in-vitro haemodynamic studies using optical measurement techniques. A patient-specific compliant and transparent phantom of a type-B aortic dissection was fabricated for PIV measurements in our mock circulatory loop [1]. The overall vessel compliance was quantified and spatio-temporal measurements of wall displacement over the cardiac cycle were also obtained.

Methods
The geometry of the model was obtained from CT scans of a 77-year-old male subject to a chronic Type-B AD, which has been studied in [1] using a rigid phantom. In this study, we fabricated a patient-specific compliant and transparent phantom by a casting technique employing 3D printed PVA molds -dissolved in water and SylgardTM 184 Polydimethylsiloxane (PDMS) (Dow Chemical, USA) material for the vessel wall. The Young’s modulus was measured using a uniaxial testing rig (BT1-FR5.0TN, Zwick Roell Group, Ulm, Germany). The phantom was connected into a pulsatile circulatory loop described in [1] and its overall compliance -defined as C=ΔV/ΔP = (ΔV_in−ΔV_out)/ΔP-was determined. This was done by monitoring the volume change (ΔV) between the inlet and outlets for a given pressure change ΔP over the cardiac cycle. The flow rate was measured using an ultrasound flow meter (Sonotec, Germany) and the pressure by pressure transducers (Omega Engineering, UK). Fluorescent markers were placed on the vessel wall surface, illuminated using a laser light sheet (Diode-Pumped Solid-State Laser, Laserglow Technologies, Canada) and imaged by a high speed camera (Phantom VEO710, AMETEK, US) to enable wall displacement measurements. The latter were compared with values obtained by the moving boundary method in compliant CFD simulations of the same AD case [3].

Results
The Young’s modulus of the phantom material was 0.7±0.03 MPa, and lies within the range of reported Young’s modulus values for the aorta (0.2-0.8 MPa, [2]). The measured overall compliance was 0.33 ml/mmHg, comparable to the value reported in the simulations of Bonfanti et al. [3] for the same patient specific geometry.

Discussion
A patient-specific compliant and transparent AD phantom was fabricated enabling fluid structure interaction studies of AD by optical measurements such as PIV or PTV. This will allow highly resolved quantitative data to be obtained for the validation of numerical models. Further work is under way to fabricate phantoms with variable compliance to enable in-vitro testing of AD intervention scenarios.

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1. G. Franzetti et al, J. Biomech., 134, 110963, 2022

Acknowledgements
This work is supported by BHF Grant (VIRTUOSO) (NH/20/1/34705), the Wellcome/EPSRC Centre for Interventional and Surgical Sciences (WEISS) (203145/Z/16/Z), the PIONEER project EP/W00481X/1 and MEDICARE BB/X005062/1.
IN-VITRO HAEMODYNAMICS IN A PATIENT-SPECIFIC COMPLIANT DISSECTED AORTA

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Introduction
Aortic dissection (AD) is a vascular condition in which a tear forms on the aortic wall, which allows the blood to flow in and form a false lumen [1]. It is a complex, patient specific condition with high morbidity and mortality rate. Patient specific numerical modeling has shed light in the hemodynamics of the condition [2]; coupled with in-vitro studies can provide a powerful tool to personalize interventions for AD as was illustrated in our previous work [3]. Recent numerical studies of AD make use of compliant AD simulations to capture the wall motion (see [2] for example); these need to be rigorously validated in order to be translated to the clinic and such validation procedures are currently lacking. We report an in vitro, fluid structure interaction study of AD, aiming to aid understanding of the disease and the development of CFD approaches. A patient specific compliant phantom of a type-B dissected aorta is fabricated and the flow field and wall displacement are simultaneously resolved using a mock circulatory loop and high speed imaging and Particle Image Velocimetry (PIV).

Methods
A patient specific, compliant phantom of aortic dissection B was fabricated by Polydimethylsiloxane (PDMS) (Young’s modulus: 0.7MPa, refractive index (RI): 1.41); it is based on the patient/geometry studied previously using rigid phantoms [3]. The phantom was connected into a pulsatile flow mock circulatory loop described in [3] (see figure 1). A patient specific flow wave obtained from PC-MRI data was imposed at the inlet and dynamic boundary conditions at the outlets as described in [3]. The working liquid was water-glycerol-urea solution (45.64%:28.77%:25.58% by weight, RI=1.4118, viscosity:3.5 mPa·s, density:1130 kg/m³). The flow was seeded with Rhodamine B fluorescent polymer particles (20–50 μm, Dantec Dynamics, Denmark) and illuminated by a continuous wave laser light sheet (Diode-Pumped Solid-State Laser, Laserflog Technologies, Canada). A high-speed CMOS camera (Phantom VEO710, AMETEK, US) equipped with a 550 nm cutoff filter was employed to acquire images for time-resolved PIV (TR-PIV) measurements. The cross correlation algorithm was applied for successive PIV images to obtain the velocity vectors in selected planes. Pressure and flow data were acquired at inlets and outlets using pressure transducers (Omega, UK) and an ultrasound flowmeter (Sonotec, Germany) respectively. The wall displacement was simultaneously measured by means of fluorescent markers attached on the phantom wall.

Results
The outlet boundary conditions were tuned by adjusting parameters of the three element windkessel model to reproduce patient-specific systolic and diastolic pressure values and correct cardiac output flow rate distribution (see figure 2a for the flow rate measured at the outlets). Velocity fields and vessel wall displacement are obtained in different sections and planes of the vessel simultaneously (see figure 2b for a typical raw PIV image).

Discussion
This is the first attempt to characterize the hemodynamics of type-B aortic dissection in a patient-specific compliant phantom in vitro using high resolution TR-PIV measurements.

References
3. G. Franzetti et al, J. Biomech., 134, 110963, 2022

Acknowledgements
This work is supported by BHF Grant (VIRTUOSO) (NH/20/1/34705), the Wellcome/EPSRC Centre for Interventional and Surgical Sciences (WEISS) (203145Z/16/Z), the PIONEER project EP/W00481X/1 and MEDICARE BB/X005062/1.
INSTITABILITY ANALYSIS AFTER THORACIC SPINAL COMPRESSION AND FLEXION-COMPRESSION TRAUMA: AN IN VITRO STUDY

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Introduction
Spinal instability resulting from traumatic injury represents a constant matter of debate due to missing clear definitions. Detailed understanding of spinal instability might support surgical treatment as well as the optimization of fixing spinal implants. Numerous experimental studies have investigated the effects of spinal injuries on resulting instability patterns, primarily focusing on the cervical and lumbar spine and rarely using mechanical injury generation and detailed instability analysis [1]. The purpose of this in vitro study therefore was to determine the most relevant instability parameters after compression and flexion-compression trauma of the lower thoracic spine.

Methods
Twelve fresh frozen human thoracic spinal specimens (T9-T11; 4 f / 8 m; 40-60 years) including costovertebral and costotransverse joints were dynamically loaded with pure compression (n=6) or flexion-compression (i.e. compression + 10 Nm flexural preload, n=6). The impact was applied displacement-controlled with a velocity of 300 mm/s up to 20% of the T10 vertebral body height after applying a 400 N axial preload in a material testing machine. Traumatic injury was defined as load drop during controlled displacement of at least 10% and detectable injury in the lateral radiograph. Instability was measured in a universal spine tester before and after trauma by applying pure moments of 5 Nm in flexion/extension, lateral bending, and axial rotation to determine range of motion, neutral zone, coupled rotations, and coupled translations. Besides, translations under 100 N shear loads and height loss under 400 N axial compression were evaluated. Statistical analysis was performed using the Friedman test in SPSS with a significance level of 0.05.

Results
Traumatic injuries occurred at a median of 5 kN (2.4-9.2 kN) independent of the trauma type, resulting in AOSpine type A1 injuries [2] in all tested specimens. Pure compression mainly provoked isolated medial endplate fractures (n=5), whereas flexion-compression primarily led to combined anterior endplate fractures and upper vertebral body compression fractures (n=3, Fig. 1). Significant instability increases after trauma (p<0.05) were found for all parameters except coupled rotations (for both trauma types) and posterior shear translation (for pure compression trauma). Highest instability increases were detected for height loss (compr. +136% / flexion-compr. +200%) as well as for neutral zone values in flexion/extension (+177%/+188%) and lateral bending (+174%+/126%, Fig. 2). Range of motion and coupled translation increases were overall higher compared to shear translation increases.

Discussion
The present study focused on the effect of minor trauma on spinal instability in order to reveal the sensitivity of an instability analysis. With regard to clinical instability, the effects of major trauma, such as pincer-type or burst fractures, and other trauma types, such as flexion-distraction injuries, have to be investigated in future studies, as well as the protecting effect of the rib cage. In conclusion, height loss and neutral zone represent the most relevant instability parameters after (flexion-) compression trauma of the lower thoracic spine.

References

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AORTIC LOCAL BIOMECHANICAL PROPERTIES IN THE CASE OF ASCENDING AORTIC ANEURYSMS

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Introduction

Abstracts must comply with the format described below. The ascending aortic aneurysms (AsAA) is a high-risk cardiovascular disease with an increased incidence over years. The impact of the risk factors (age, gender, smoking, hypertension, obesity, aortic valve disorder, coronary artery disease, etc.) remains unclear (Erbel et al. 2015). In this study, we compare different risk factors based on the pre-failure behaviour (from a biomechanical point of view) obtained ex-vivo from an equi-biaxial tensile test.

Methods

A total of 100 patients (63 ± 12 years, 72 males) with AsAA replacement, were recruited. Equi-biaxial tensile testing of AsAA wall was performed on freshly sampled aortic wall tissue after ascending aorta replacement. The aneurysmal aortic walls are divided into four quadrants (medial, anterior, lateral, and posterior) and indicating two directions (longitudinal and circumferential). The stiffness and elasticity were represented by the maximum Young Modulus (MYM). In our study, the focus is on the relationship between MYM and the age, as well as ascending aortic diameter (Figure 1.)

Results and discussion

The mean thickness of the aneurysmal ascending aortic wall is 1.93 (± 0.41 mm). In general, when the aortic diameter increases, the aortic wall became thicker (p < 0.05, Figure 2.)

Figure 1. The distribution of the population according to the age and diameter.

Figure 2. The distribution of aortic thickness and AsAA diameter.

In terms of MYM, the longitudinal direction was significantly higher than that in the circumferential direction. Positive correlation was statistically significant between age and MYM (p < 0.05), as well as aortic diameter and MYM (p < 0.05).

Figure 3. Impact of age based on different quadrants. EM = maximum value of Young’s modulus; CIR = circumferential; LON = longitudinal; MED = medial; ANT = anterior; LAT = lateral; POST = posterior.

Figure 4. Impact of diameter based on different quadrants. EM = maximum value of Young’s modulus; CIR = circumferential; LON = longitudinal; MED = medial; ANT = anterior; LAT = lateral; POST = posterior.

Conclusions

The ascending aortic aneurysms’ pre-failure stiffness, related to the maximum value of Young Modulus, was positively correlated with the patient’s age and the diameter of the ascending aorta.

Acknowledgements

We thank the association of “Bourgogne Coeur” for the financial support in the experiments.

References

Introduction

Existing applications of cardiovascular field mainly focused on the shape of the aorta or any artery (Kim et al., 2019; Santoro et al., 2021), but not of the biomechanical properties. As far as we know, very few studies have explored the use of soft materials in printing arteries (Biglino et al., 2013; Kurenov et al., 2015; Vukicevic et al., 2016; Wang et al., 2016). These studies are about the pulmonary artery, mitral valve, and cerebral vessels. The reported stiffness value in these studies is lower than that of the human aorta (Sherifova and Holzapfel, 2019). The objective of our work was to look forward to printable materials that can represent the human aorta.

Methods

A fresh healthy human aorta was obtained from an autopsy from the department of pathology, University Hospital of Dijon, Dijon, France (Figure 1). The patient was 16 years old and died following pulmonary embolism with no underlying health condition.

Results and discussion

There was a difference between the expected printed thickness and the experimental measuring thickness, as well as MYM. The aortic wall had a thickness of 1.49 mm ± 0.34 mm. The mean failure stress and MYM were 0.48 ± 0.09 MPa and 0.91 ± 0.23 MPa respectively.

With the thickness increases, failure stress showed a rough increasing trend in the NinjaFlex material. The stiffness (ranging from 8.24 to 11.90 MPa) did not display a steady increasing trend depending on thickness. It can be caused by non-uniformity in the printing process. Failure stress and MYM of Filastic materials did not increase with the thickness. It displayed a highly heterogeneous behavior. For the material with 0.65 mm in thickness, failure stress and MYM reached the highest values simultaneously, 2.64 MPa and 23.16 MPa, respectively.

RTP was printed in different shore hardness (SH, Table 1) and two printed directions (direction A and direction B).

Table 1. Biomechanical properties of RTP materials according to the different thickness and SH.

![Image](https://via.placeholder.com/150)

**Discussion**

The aortic wall is normally considered as anisotropy and nonlinear. All of the three printed materials showed a nonlinear behavior. In the biomechanical properties of the human aorta study, the range of the failure stress is between 0.54 MPa and 2.18 MPa (Sherifova et al., 2019). In our study on the healthy aorta, the mean failure stress value was 0.48 MPa with MYM of 0.91 MPa. Among three printed materials, RTP had the closest biomechanical properties to the healthy aortic wall available for 3D printing equivalent (0.28 MPa in stress and 1.05 MPa in Young’s modulus), to create credible phantoms of the aorta.

**Acknowledgements**

We thank the association of “Bourgogne Coeur” for the financial support in the experiments. We also thank Dijon 3D company (Dijon, France) for providing the thermoplastic polyurethane material.

**References**

DEEP LEARNING-BASED AUTOMATIC SEGMENTATION OF SKELETAL MUSCLES

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3. INSIGNEO Institute for in silico Medicine, The University of Sheffield, UK;
4. Department of Mechanical Engineering, The University of Sheffield, UK

Introduction
Rapid and accurate muscle segmentation from Magnetic Resonance Imaging (MRI) is essential for the diagnosis and monitoring of many musculoskeletal diseases, and for creating personalized biomechanical models. Traditionally, muscle segmentation has relied on manual work by experts, which is very time-consuming and subject to inter-operator reproducibility errors [1]. The high labour cost becomes a bottleneck in muscle segmentation tasks of large cohorts of patients. With the development of deep learning technology in recent years, there has been a growing trend to apply deep neural network models for classification [3], segmentation [2], and recognition of targets in different scenarios. While a number of models have been already proposed, there is still room for improvement in the accuracy and efficiency of automatic multi-target segmentation of muscles. In this study, we aim to develop and test new deep-learning models for automatic muscle segmentation of human lower limbs.

Materials and Methods
The Unet [2], which is a widely used convolutional neural network (CNN) in medical image segmentation, will be used as a baseline for the purpose of comparison. Unet employs multiple convolution operations combined with up and down sampling to extract the feature information of different dimensions and levels of the image so as to segment and recognize the target image. In this study, two new CNNs (Model1 and Model2) are proposed by introducing attention mechanisms in Unet, to improve muscle segmentation. The data is composed of the full lower-limb MRI data of 25 muscles of the thigh part from eleven post-menopausal women (mean (standard deviation, SD): 69 (7) y. o., 66.9 (7.7) kg, 159 (3) cm) with no muscle disease, recruited by the Metabolic Bone Centre (Sheffield, UK) as part of larger studies. The study was approved by the East of England—Cambridgeshire and Hertfordshire Research Ethics Committee and the Health Research Authority (October 2000). Manual segmentations of each muscle were used as a gold standard [1]. The leave-one-out approach was used to evaluate the accuracy of the models in segmenting the muscles. In the evaluation phase, the mean values (11 trials; 16 muscles with high intra-operator reproducibility of the manual segmentations [1]) of three metrics were used to evaluate the accuracy of the models: Dice Score Coefficient (DSC) [4], Relative Volume Error (RVE), and Hausdorff Distance (HD).

Results
On the test set, both newly adjusted models performed better than the Unet (1.5% and 2% mean improvement in DSC and RVE, 20mm in HD, p<0.05). The percentage improvements over Unet for DSC, RVE, and HD were 2.2% (±1.54%), 3.2% (±3.1%), 38.1% (±18.1%) for Model1, and 2.0% (±1.4%), 2.6% (±2.2%), 31.7% (±20.1%) for Model2.

<table>
<thead>
<tr>
<th>Model</th>
<th>DSC</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unet</td>
<td>0.81</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>1-RVE</td>
<td>0.83</td>
<td>0.86</td>
<td>0.85</td>
</tr>
<tr>
<td>HD</td>
<td>49.9</td>
<td>29.9</td>
<td>32.4</td>
</tr>
</tbody>
</table>

Table 1: Testing results evaluation for Unet and two modified models. (* means p<0.05 in T-test)

Discussion
This deep learning approach provides the potential for automated segmentation, analysis of human muscles, and inputs for biomechanical models. There is a small average improvement in DSC and RVE but a good improvement in local errors (HD) of our modified models, which include attention mechanisms. In the future, it should be tested on a larger or different cohort to see whether the attention mechanism will improve the Unet output and evaluate the generalization ability of the model.

Acknowledgments
The study was partially funded by the EPSRC (EP/K03877X/1 and EP/S032940/1).

References
THE EFFECT OF PRE-STRESS IN TAVI PROCEDURE FINITE ELEMENT SIMULATIONS ON PATIENT SPECIFIC GEOMETRIES

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Politecnico di Milano, Italy

Introduction
In silico modelling of cardiovascular surgical procedures is an important tool used to assess and further analyse their outcome. A number of methods have been proposed to account for the stress state of vessels, which comes from internal blood pressure, reconstructed from diagnostic images. Not considering this pre-stress may result in inaccuracies when studying the interaction of the vessel with implantable devices [1,2]. However, it is important to demonstrate that its application leads to more reliable results. This can be achieved by highlighting the differences in the results between simulations in which the unloaded configuration is taken into account and simulations in which it isn’t, and comparing the results with real cases. This work studies the effect of the unloaded configuration on finite element simulations of Transcatheter Aortic Valve Implantation (TAVI) on patient specific geometries [3].

Methods
Patient specific geometries reconstructed from CT images in [3] were used. The unloaded configuration was obtained by means of inverse elastostatic (IE) methods [4] extended to work with anisotropic materials. The idea behind these algorithms is to predict the real stress-free configuration of the vessel, which is the shape it would assume if no blood pressure was applied on the internal wall, and is called zero-pressure configuration. The unloaded vessel is then pressurized up to diastolic condition obtaining a geometry deformed as in the original diagnostic image but with stressed walls (Figure 1). Results of simulations considering and not the unloaded configuration were compared in terms of possible complication detection, device positioning and vascular damage.

Results
The comparison of the simulations shows some important differences with results more similar to the in-vivo conditions when the unloaded configuration is accounted for. Accounting for the unloaded geometry modifies the deployment of the valve providing a better anchoring in the anulus region, but worsen the anchoring in distal positions. In addition, the stresses in the aortic wall result larger when the zero-pressure configuration is considered (Figure 2).

Discussion
The results highlight the importance of considering the zero-pressure configuration. Despite a more complex workflow, results of the simulations appear to be more reliable: a different patient who receives TAVI procedure may be subjected to a bad implantation of the device or to larger wall stress that could be correlated to complications post-implantation. If prestresses are not considered, then the simulation may not predict these bad outcomes of the procedure.

References

Acknowledgements
Work developed within the MUSA – Multilayered Urban Sustainability Action – project, funded by the European Union – NextGenerationEU, under the National Recovery and Resilience Plan (NRRP) Mission 4 Component 2 Investment Line 1.5: Strengthening of research structures and creation of R&D “innovation ecosystems”, set up of “territorial leaders in R&D”.

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
UNDERSTANDING THE BIOMECHANICAL SIGNIFICANCE OF EXTRACELLULAR MATRIX FOR FUNCTIONAL MUSCLE FORCE USING A BIO-INSPIRED ARTIFICIAL MUSCLE

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1. The University of Manchester, UK

Introduction
The extracellular matrix (ECM) in muscle fibres consists of three layers: the epimysium, the perimysium, and the endomysium. The ECM structurally maintains the morphology and limits the expansion of skeletal muscle, which affects the functional transmission of muscle force [1],[2]. The biological and biomechanical significance of ECM is not fully understood. This work aims to use a biomimetic approach through modelling an electro-hydraulic synthetic muscle, a Peano-HASEL actuator (PHA) [3], to understand the effect of the ECM on functional muscle force. Specifically identifying the ECM’s effect on damping, force-length relationship, and force-velocity relationship.

Methods
A validated 2D finite element model of Peano-HASEL artificial muscle fibre, built in COMSOL Multiphysics 6.1 (Cambridge, UK) [5], was used to evaluate the motion, force-length relationship, and force-velocity relationship. A biomimetic approach was used to design the artificial muscle that mimics the muscle and the constraint that mimics the ECM, which in turn may contribute to understanding the biomechanical significance of ECM. As shown in Figure 1a, muscle fibre is surrounded by the ECM. Similarly, in Figure 1b, a constraint like ECM was introduced into the artificial muscle fibre model. Loads from 0 to 21N (1.5N interval) were applied at point A in the arrow direction.

Results
Figure 2 shows the finite element results of artificial muscle fibre models with ECM. Specifically, Figure 2a shows the displacement-time curve under the no-load condition, which shows the damping response of the artificial muscular system to stimulus. As shown in Figure 2a, ECM models oscillate to rest faster than no constraint models, which means less vibration. Figure 2b & 2c show the force-length and force-velocity characteristics, respectively. The output strain and contraction velocity decrease with the tightening of the ECM because the ECM limits fibre expansion, while the output force is not affected.

Discussion
The ECM greatly affects damping characteristics, output strain and contraction velocity because the interaction between the artificial muscle fibre and ECM. Specifically, damping ratios of ECM models are 10 times lower; maximum output strains decrease by 4% to 6%; maximum contraction velocities are 1.5 to 5 times lower in comparison with the no constraint model. Aging causes reduced output force and contraction velocity in the force-velocity curve [4]. The results in this work show that as the extracellular tightens or stiffens, the contraction velocity of the muscle is reduced, indicating the shrink or tightening of the ECM may also lead to changes in force-velocity relationship in aging muscle.

References
5. Liu et al. TMECH (in review)
DYNAMIC STABILITY DURING VIRTUAL HEIGHT EXPOSURE IN CHILDREN WITH CEREBRAL PALSY – A CASE-CONTROL PILOT STUDY

Regine Lohss (1,2), Rebecca Winter (1), Beat Göpfert (1,2), Rosa Visscher (2,3), Reinald Brunner (1,2), Philippe Cattin (2), Carol-Clauudius Hasler (1), Elke Viehweger (1,2)

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Introduction

Cerebral palsy (CP) often affects dynamic stability and postural control [1], leading to walking impairments and a higher risk of falling [2]. Previous work has shown that the variability of spatiotemporal parameters can be used as a predictor of dynamic stability and fall risk [3]. Virtual reality (VR) is an increasingly used technology to induce such real-world postural challenges in a controlled environment [4]. The aim of this study was to investigate whether virtual height exposure can elicit changes in spatiotemporal parameters, self-perceived instability, and fear-of-falling (FoF) in children with CP or typical development (TD) and whether these parameters differ with virtual height between CP vs TD.

Methods

This case-control pilot study included 5 participants with CP. Main inclusion criteria were age 7-18 years, spastic CP, and gross motor function classification level 1 or 2. Excluded were children with orthopedic surgeries in the lower extremities (<1y) or botulinum toxin A (<6m). For comparison, 5 age-matched participants with TD were included. Participants were equipped with reflective markers and a head-mounted display. Following a short habituation time to adjust to the virtual environment, 6 walking trials were recorded barefoot (motion capture system) for each virtual plank height (Figure 1), applied in a randomized order.

![Figure 1: Virtual plank heights 0m, 3m, 5m (left to right).](image)

Dynamic stability was assessed by calculating the coefficient of variation of step time (CV-ST), stride width (CV-SW) and double support (CV-DS). A two-way ANOVA was performed to analyze the effect of the study group and virtual height on these parameters. Self-perceived instability and FoF were quantified for each height using a numeric rating scale (NRS, 0-10). Mann-Whitney U test with Bonferroni correction was used for between-group comparisons (CP vs TD).

Results

Participants with CP showed a steady increase of CV-ST and CV-DS from 0m to 5m, whereas participants with TD showed a decrease in both parameters from 0m to 3m and an increase from 3m to 5m. CV-SW in CP decreased from 0m to 3m and increased from 3m to 5m, whereas in TD it steadily decreased (Table 1). Simple main effects analyses revealed that the study group had a statistically significant effect on CV-ST (p=0.01) and CV-SW (p<0.01), and the virtual height on CV-SW (p=0.02).

<table>
<thead>
<tr>
<th>CV-ST</th>
<th>0m</th>
<th>3m</th>
<th>5m</th>
<th>0m</th>
<th>3m</th>
<th>5m</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>9.4</td>
<td>9.9</td>
<td>11.0</td>
<td>28.7</td>
<td>17.7</td>
<td>19.6</td>
</tr>
<tr>
<td>TD</td>
<td>5.5</td>
<td>4.7</td>
<td>7.1</td>
<td>35.0</td>
<td>25.9</td>
<td>15.4</td>
</tr>
</tbody>
</table>

*Table 1: Coefficient of variation (%) of step time (CV-ST), stride width (CV-SW), double support (CV-DS).*

Compared to TD, participants with CP showed significantly higher self-perceived instability at 3m and 5m (both p=0.02). FoF was not significantly different between both groups (Table 2).

<table>
<thead>
<tr>
<th>Instability (NRS)</th>
<th>0m</th>
<th>3m</th>
<th>5m</th>
<th>0m</th>
<th>3m</th>
<th>5m</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>0(0/0)</td>
<td>6(3/6)</td>
<td>5(4/7)</td>
<td>0(0/0)</td>
<td>4(3/7)</td>
<td>5(3/7)</td>
</tr>
<tr>
<td>TD</td>
<td>0(0/0)</td>
<td>0(0/0)</td>
<td>0(0/0)</td>
<td>0(0/0)</td>
<td>0(0/1)</td>
<td>1(0/1)</td>
</tr>
</tbody>
</table>

*Table 2: Numeric rating scale (NRS), median (Q1/Q3).*

Discussion

This study showed that virtual height exposure up to 5m can be used to elicit self-perceived instability and FoF, particularly in participants with CP. Both CP and TD respond to the virtual height by adapting their gait pattern variability. The results of this study underpin the potential of VR to analyze changes in dynamic stability in more challenging environments.

References


Acknowledgements

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PHYSICS-INFORMED NEURAL NETWORKS FOR PREDICTING FATIGUE DURING INTERMITTENT ISOMETRIC TASKS

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Introduction

The state-of-the-art in musculoskeletal dynamics estimation is Physics-Informed Neural Networks (PINNs), which are standard machine/deep learning models that exploit physics law equations by integrating them into the loss function in order to penalize the estimation of forces and/or kinematics of a virtual character [1]. Unlike finite element and conventional physics-based methods, PINNs do not require to explicitly model the complex underlying physics that govern the human body, and as showed in [1][2], they can be physically consistent while being more fast compared with neural network architectures such as CNNs and LSTMs.

In this work, we developed a PINN for predicting knee torques during intermittent isometric fatiguing tasks inspired by the Three-Compartment Controller Model (3CC) [3][4], which is a state machine that describes the transition of all muscle motor units of a human limb from one state (compartment) to another, namely active (MA), fatigued (MF), or resting (MR). Our model predicts the mean torque of the knee (in %MVC – maximum voluntary contractions) during active (MA) and fatigue state (MF) and can be used to both synthesize/simulate fatigue-driven motion for realistic 3D character animation as well as model temporally evolving ergonomic effects.

Methods

Our Physics-Informed Neural Network (Figure 1) consists of a three-layer Bidirectional Long Short-Term Memory (BiLSTM) network with 128 units, and a fully connected output layer. BiLSTM is an extension of LSTM that also has backward feedback connections along with forward ones, which aid the model to exploit both future and past data w.r.t. a specific time step, and as a result is more accurate than LSTM [5]. The model is fed with time steps (sec) and MA and MF (%MVC) of the current step (t) to produce knee mean torques of active and fatigue state of the next time frame (t+1). The loss of our model is defined as follows:

\[ L = MSE + \frac{1}{T} \sum_{t=0}^{T} (\frac{\partial MF}{\partial t} - F \cdot MA + R \cdot MF)^2 \]  

(1)

\[ \frac{\partial MF}{\partial t} = F \cdot MA - R \cdot MF \]  

(2)

where MSE is the mean square error of the prediction, F and R show at which rate the motor units fatigue or rest, respectively (for knee joint F = 0.01500 and R = 0.00149 [3]), and Eq.2 is the differential equation that describes fatigue state as presented in [3][4].

We implemented and trained our model using Python’s Tensorflow. The training dataset was obtained from [6] and consists of mean torques of the knee joint from 8 healthy (aged 29 ± 6 years old) subjects during intermittent isometric maximal voluntary contractions of the quadriceps while seated.

Figure 1: A general overview of our PINN.

Results

We compare the performance of our PINN with other architectures in terms of Normalized Root Mean Square Error (NRMSE) as shown in Table 1. Lower values indicate accuracy and good performance.

<table>
<thead>
<tr>
<th>Method/NRMSE</th>
<th>MA</th>
<th>MF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PINN (Ours)</td>
<td>3.01</td>
<td>3.95</td>
</tr>
<tr>
<td>LSTM</td>
<td>3.91</td>
<td>4.66</td>
</tr>
<tr>
<td>ANN</td>
<td>5.87</td>
<td>6.12</td>
</tr>
</tbody>
</table>

Table 1: The NRMSE values for mean torques during active and fatigue state (ANN – Artificial Neural Network).

Discussion

The primary goal of this work is to provide an automatic and fast solution of predicting fatigue without using physics-based methods. According to the results, our approach performs better than standard architectures, thus, indicating that our PINN models effectively the fatigue state of 3CC. As future work we would like to model all three states of the 3CC into one deep learning network and utilize/test our model to predict the fatigue of an animated virtual character in real-time.

References


28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
BIOMECHANICAL INTEGRITY OF THE CERVIX IN PATIENTS AT LOW- AND HIGH-RISK OF PRETERM BIRTH

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Introduction
Preterm birth (PTB) is birth before 37 weeks. Globally it occurs in 10% of pregnancies [1]. Despite its prevalence, PTB is difficult to predict and prevent [1,2]. Clinically, a short cervical length measured via transvaginal ultrasound and a history of PTB are predictors of PTB. Yet, cervical length screening sensitivity is only around 50%, and it is particularly poor at predicting PTB in low-risk populations and first-time pregnancies [3]. In this study, cervical aspiration stiffness is reported for pregnant patients at high- and low-risk for PTB. Additionally, patient-specific computational models are constructed from ultrasonic maternal anatomy and cervical stiffness to calculate overall cervical structural integrity. The biomechanical integrity of the cervix is compared between patients who deliver preterm and those that deliver to term.

Methods
Ultrasonic dimensions of the maternal uterus and cervix and in-vivo cervical aspiration stiffness (Pregnolia AG, Switzerland) were measured between 16-24 weeks gestation using an Institutional Review Board approved protocol at Columbia University Irving Medical Center. Measurements were taken in three clinical patient cohorts: 1. high-risk (sonographic short cervix and no history of PTB, n=17), 2. high-risk (history of PTB, n=26), and 3. low-risk for PTB (normal cervical length, n=50). Using our established parametric modeling methods [4], we built models of each patient’s uterus, cervix, fetal membrane, and supporting abdomen. We discretized models into elements (Hypermesh Altair, Troy, MI) and assigned all tissue material properties based on existing data, with a patient-specific cervical fiber stiffness determined through inverse finite element analysis (FEA) of the in-vivo aspiration procedure. Physiologically inspired loading, contact, and boundary conditions were applied, and FEA was run in FEBio Studio v1.3.0 for 16 patients from each cohort [5].

Results
The first principal stretch magnitude is generally larger in the high-risk group than the low-risk group (Fig. 1). The patients from the high-risk group who delivered extremely preterm (<28 weeks) have the largest 1st principal right stretches at the utero-cervical junction and the lowest of all cervical stiffnesses by aspiration.

Discussion
The computational results show a distinct stretch pattern in patients at high-risk for PTB, with excessively high radial stretches at the utero-cervical junction. The increased stretch at this junction in patients who delivered extremely prematurely shows that uterine wall tension is a driving factor in causing cervical funneling. Additionally, patients who delivered extremely preterm had the softest of cervices. A powered clinical study is needed to prove cervical stiffness and overall structural integrity are better predictors of PTB.

References

Acknowledgments
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MEASUREMENTS OF THE MECHANICAL PROPERTIES OF SKELETAL MUSCLE BY ULTRASONIC ELASTOGRAPHY AND SHEARING TESTS

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Introduction
Several experimental studies have investigated mechanical properties of skeletal muscle using in vitro or in vivo tests [1, 2]. Note that these experimental protocols lead disparate results often due to experimental protocols [3]. To our knowledge, there is few mechanical characterization studies comparing in vivo and in vitro approaches on the same skeletal muscles.

The objective of this study was to investigated the stiffness of rat flexor carpis ulnaris muscle from shear elastography wave (SWE) (in vivo) and pure shear tests (in vitro).

Methods
Seven male rats of Wistar strain aged 8 weeks were used in this study. SWE measurements were performed on flexor carpis ulnaris in vivo during three conditions: i) the left foreleg was placed 45° from the axis of the body, ii) the elbow was flexed at 90° and, iii) the probe was parallel to the myofibers. Then, mechanical tests were performed on muscle samples (taken from these same rat) based on pure shear tests. Myofibers were orientated parallel to the loading. The hyperelastic Ogden’s model was used to identify the mechanical behavior of skeletal muscle in vitro [2]:

\[ W(\lambda_1, \lambda_2, \lambda_3) = \sum_{p=1}^{N} \mu_p \left( \lambda_1^{a_p} + \lambda_2^{a_p} + \lambda_3^{a_p} - 3 \right) \]

The shear modulus obtained by mechanical tests in vitro is given by: \( \mu = \mu_1 \alpha_1 / 2 \)

Results
Ultrasound acquisition allows to visualize with more precision the different muscles of the rat’s forelimb and to obtain a cartography of shear modulus for the whole muscle (Figure 1). Regarding the mechanical test, pure shear responses of FCU muscles are shown in Figure 2 and obtained when muscles fibers were oriented in parallel to the loading. In the first order Ogden’s model case, the identification of mechanical parameters were obtained by an inverse method (Table 1). The ANOVA analysis shown that the difference is not significative (p=0.08).

<table>
<thead>
<tr>
<th>(n=7)</th>
<th>From SWE measurements</th>
<th>From mechanical shear tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu ) (kPa)</td>
<td>( 5.48 \pm 0.42 )</td>
<td>( 4.17 \pm 1.68 )</td>
</tr>
</tbody>
</table>

Table 1: Shear modulus obtained from SWE (in vivo), and mechanical tests (in vitro) by using first order Ogden’s model.

Discussion
The objective of this study was to compare the mechanical properties of skeletal muscle obtained by SWE and pure shear mechanical tests. The measurements shown a difference about 24% between in vivo and in vitro approaches. This result is probably due to the type of used muscles that doesn’t exhibit the lowest variability in measurements. Furthermore, the boundary conditions for pure shearing test should be improved. Thus, we argue that used methodology is important to optimize the mechanical properties measurements of skeletal muscle even isotropy assumption was made in this study.

References

Acknowledgements
This work was supported by Université Paris-Est Créteil.
Introduction
Poly-L-lactic acid (PLLA) is a polymer commonly employed for the manufacturing of bioresorbable stents since it offers a good balance between favourable mechanical properties and degradation time [1]. While different studies have characterized the behaviour of PLLA wire-braided stents prior degradation [2], the long-term properties have been poorly characterized, with a limited number of studies available. Most studies investigated the degradation behaviour of PLLA laser-cut stents in accelerated conditions [3,4] based on the hypothesis that there is a 4-fold factor between real-time and accelerated conditions [5]. However, this hypothesis has never been proved for PLLA wires and wire-braided stents. This study aims at giving a comprehensive description of the degradation properties (physical, thermal and mechanical) of bioresorbable PLLA wires and wire-braided stents. The investigation has been performed in both accelerated and real-time degradation conditions to compare the former methodology with realistic degradation times.

Methods
PLLA wires and in-house manufactured stents were degraded according to the ISO 13781. Samples were put in phosphate-buffered solution (PBS) and placed in the oven at T=37°C (real-time degradation, RD) and T=50°C (accelerated degradation, AD) for a total of 272 days and 114 days, respectively. At each observation point (Table 1), samples were removed from the oven and assessed in their physical, thermal and mechanical properties. Molecular weight, thermal properties and material spectra were evaluated with gel permeation chromatography (GPC), differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), respectively. Young’s modulus, tensile strength and ultimate strain were extracted from tensile tests on single wires, whereas radial force curves were obtained from crimping tests on stents. Optical microscopy and scanning electron microscopy (SEM) allowed for visual characterization at different time points. The outcomes from the two protocols (RD, AD) were compared to obtain the relation between the two conditions.

Results
The PLLA molecular weight sharply decreased between 36 and 50 days in AD while it showed a constant decrease in RD (Figure 1a). The mechanical properties of PLLA wires kept constant until day 50, then a sharp decrease was found until the wires were no more testable (day 114). In RD the wires showed constant mechanical properties as in AD until day 272 (Figure 1b). The visual inspection revealed a change in the colour of the stent upon degradation, turning from white to transparent (Figure 1c).

Discussion
This study provides a comprehensive investigation on the physical, thermal and mechanical behaviour of new PLLA wire-braided stents under two different degradation conditions that was never presented before. From the results it arises that an at least 6-fold factor should be introduced when performing accelerated degradation to match the properties obtained at realistic conditions (T=37°C), differently to what has been suggested in literature for PLLA dogbones.

References
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Acknowledgements
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 813869. This work reflects only the author’s view and the REA is not responsible for any use that may be made of the information it contains. The authors would like to thank Boston Scientific Ltd., Co. Galway, Ireland for their support and collaboration on this work. The authors would like to thank Dr. Olena Kudina for her support with GPC tests.
EXPERIMENTAL STUDY ON DENTAL CROWNS RETRIEVAL TOOLS: REMOVAL EFFICIENCY AND POTENTIAL PATIENTS’ DISCOMFORT

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Introduction

Advantages of cement-retained dental crowns over screw-retained ones have been highlighted in several studies, in terms of aesthetics, ease of fabrication and passive fit [1]. However, minor complications in implant-supported dental prostheses are frequent [2], and the retrievability of the crown is important to allow an accurate inspection of the implant site. Several tools might be used to retrieve a cemented crown, most of which apply impulsive loads to the prostheses. The influence of the luting agent and abutment shape on the number of impulses needed for the crown retrieval has been already investigated experimentally [3]. However, clinical studies show weak or no correlation between the impulses number and the patients’ discomfort, while the retentive force of the cement significantly affects their perceptions [4]. In this study, three impulse-generating tools were employed to retrieve cemented copings, measuring the force transmitted to the implants.

Materials and methods

Fourteen copings were welded at the extremities of 7 bars to create 7 noble-metal alloy dummies of a three-unit dental bridge. Each bridge had different copings height and taper angle, which are reported in Table 1.

<table>
<thead>
<tr>
<th>Bridge ID</th>
<th>Coping 1</th>
<th>Coping 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>5 mm, 0°</td>
<td>5 mm, 0°</td>
</tr>
<tr>
<td>B2</td>
<td>7 mm, 0°</td>
<td>7 mm, 0°</td>
</tr>
<tr>
<td>B3</td>
<td>5 mm, 2°</td>
<td>7 mm, 2°</td>
</tr>
<tr>
<td>B4</td>
<td>5 mm, 2°</td>
<td>5 mm, 4°</td>
</tr>
<tr>
<td>B5</td>
<td>5 mm, 0°</td>
<td>5 mm, 4°</td>
</tr>
<tr>
<td>B6</td>
<td>7 mm, 2°</td>
<td>7 mm, 4°</td>
</tr>
<tr>
<td>B7</td>
<td>7 mm, 0°</td>
<td>7 mm, 4°</td>
</tr>
</tbody>
</table>

Table 1: Three-unit bridge dummies used in the study.

The bridges were cemented with a temporary cement (Temp Bond NE) and removed with Sliding Hammer (SH) CORONA Flex (CF), and Magnetic Mallet (MM). Bridges not completely removed within 50 impulses were considered non-retrievable. An experimental setup comprising a piezoelectric load cell was designed to measure the forces generated during the procedure [5]. Each bridge was removed, cleaned, and cemented again 5 times for each tool. The three tools were compared in terms of percentage of successful retrieval and force transmitted to the implant; Kruskal-Wallis analyses and Bonferroni pairwise comparisons were performed to investigate the tools influence on the maximum force.

Results

The SH resulted the most efficient tool in terms of removal percentage (Figure 1), being able to retrieve all bridges in all tests, except for the ones with at least one 7 mm, 0° coping, which is the most retentive among the geometries used in the study. However, MM had a similar efficiency in this regard, while also achieving a significantly lower force (p<0.1) with most bridges (Figure 2).

Discussion and conclusions

MM can be considered a more suitable tool to retrieve cemented dental prostheses compared to CF. Moreover, since the force transmitted to the bone has a stronger influence on patients’ comfort compared to the number of impulses needed for the retrieval [4], MM could also be preferable compared to SH for most situations, in particular when only conical abutments are involved.

References

A BIOMECHANICAL MODEL-BASED SYSTEM FOR ASSISTING IN CLINICAL EXAMINATION OF PARKINSON’S DISEASE PATIENTS

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Introduction
Parkinson’s disease (PD) is a neurodegenerative disease that damages the human motor system. Various disease assessment scales are used in the diagnosis and severity assessment of neurodegenerative diseases. For PD, the most widely used rating tool is Unified Parkinson's Disease Assessment Scale (UPDRS) [1], which includes various motor tasks such as gait or hand movements, which physician visually evaluate and then a score of 0 to 5 is assigned based on the guidelines. However, specific aspects of movements are evaluated mainly qualitatively and subjectively [2-3]. Technological innovations make it possible to integrate wireless sensors into health monitoring systems and obtain not only quantitative, but also quantitative information on the movements performed by subjects with PD [4]. Kinematic data of movement alone provide only limited information about the performance of the movement but can be used as inputs of numerical musculoskeletal models. Modelling of the musculoskeletal system is a digital technology that is used to study muscle forces, tendon system forces and joint surface contact forces during movement that cannot be measured directly [5-7]. The main goal of this study is to present an application example of the biomechanical model-based system to assist in clinical examination of patients with PD. The current abstract presents an example of application to examine the gait of PD during clinical screening according to UPDRS Part III. The concept of the system is provided in Figure 1.

Methods
Kinematic data of the gait of the patient with PD were collected using 6 IMU sensors (Shimmer Sensing, Ireland), which were attached to the thigh, shank, and foot of both legs. Two groups of PD patients participated in the study: 15 PD subjects (mean age 61.1±11.2) and 12 healthy subjects (mean age 57.8±7.58) who were control subjects. The PD group was also divided according to the UPDRS score: UPDRS 0 \((n = 7)\) and UPDRS 1 \((n = 8)\), where 0 and 1 represent severity (1 being more severe than 0). Subjects performed movements with upper extremity and walking task of 5 meters. The study was approved by the local bioethics committee. IMU data (linear acceleration, angular velocity, and magnetic heading in 3D) was sampled at 51.2 Hz, stored onto PC, and processed via MATLAB. 10 degrees of freedom musculoskeletal model (MS model) of lower extremities with 18 Thelen muscle models [7] was developed in OpenSim. Inverse dynamic analysis was performed, and various kinetic parameters were calculated (joint torque, muscle forces, etc.) in each phase of the gait cycle. Statistical significance was evaluated using ANOVA.

Results
The torque values of the PD group during different gait cycles are higher than those of the CO group. Figure 2 shows joint torque of the knee joint during a gait cycle.

![Figure 2: Knee joint torque: blue – CO, red – PD, green – UPDRS0, black – UPDRS1, shaded areas represent standard deviation.](image)

Statistically significant differences were estimated between CO and PD groups in left knee flexion during early amortization (from 0 to 10%) phase of gait cycle.

Conclusions
Developed system can collect and evaluate data from the movements of the upper and lower extremities utilizing more accessible IMU sensors. Joint torque as kinetic parameter allows quantitative assessment during clinical examination of PD.

References
COMPUTATIONAL MODELING FOR EVALUATING THE EFFECTIVENESS OF PROTECTIVE PLATES IN NON-PENETRATING BALLISTIC IMPACTS

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(2) Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Introduction
A ballistic protective plate (BPP) is standard military equipment that reduces the risk of severe injuries in the torso area which are common in combat environments, being approximately 25-30% of all injuries [1]. Non-penetrating impacts of bullets or other ballistic threats such as blast explosions, shrapnel, or shrapnel shells with the BPP are accompanied by rapid and immediate deformations of the armour and underlying tissues. These are translated to mechanical energy absorbed in the tissues behind the armour, causing the injury known as ‘behind armour blunt trauma’ (BABT) [2].

That absorbed energy takes the form of pressure waves that propagate through the tissues, including deep tissues that are not in direct contact with the gear, resulting in rapid deformations, stretching and collapse of the tissues and associated cell and tissue death [3-4]. To date, there is no effective and cost-effective procedure for rapid testing of BPP designs. The objective of this study was to develop a novel, anatomically-accurate, finite element modelling framework as a decision-making tool to evaluate and rate the biomechanical efficacy of BPPs in protecting the torso from battlefield-acquired non-penetrating impacts.

Methods
To evaluate the biomechanical efficacy of BPPs designed for protecting the torso from a battlefield-acquired non-penetrating impact, a three-dimensional (3D), anatomically-accurate model of the torso was developed. The geometry of the upper-body model which we have developed is based on 267 transversal images of the torso from the Visible Human Project anatomical database [5]. To simulate a blunt impact with a BPP two plate types were modelled, representing generic designs of threat-level III and IV plates (according to NIJ Standard–0101.06). A 5.56 mm bullet was modelled as well as the projectile hitting the plates. We used the realistic dimensions, physical and mechanical characteristics of the plated and the bullet.

The constitutive laws and mechanical properties of all the tissue components were considered to represent homogenous-isotropic material behaviours, and specific parameter values were adopted from the literature. The material of the BPPs was Kevlar-29, assumed to be orthotropic elastic. The 5.56 mm bullet material was 4340 Steel.

Results
The results indicated that plate level-IV induces greater tissue strains and stresses post the ballistic impact; this is due to the fact that plate level-IV is larger, thicker and heavier than plate level-III, and therefore, its kinetic energy is higher and so is the shock wave which is transferred to the tissues behind plate level-IV.

Discussion
We have shown here, using a highly advanced FE modelling framework, that contrary to a false premise, a thicker and heavier BPP does not necessarily protect all underlying tissue structures better than a thinner, lighter plate.

Our modelling provides a versatile, powerful testing framework for both industry and clients of BPPs, at the stages of prototype design, prior to manufacturing and procurement processes, or for quantitative standardized evaluations of candidate products in purchasing decisions and bids.

References

Acknowledgements
The research is funded by Israel Ministry of Defence and the Israeli Defence Forces Medical Corps (number: 4440991484 awarded to Professors Amit Gefen and Yoram Epstein), and by the Israel Ministry of Innovation, Science & Technology (scholarship awarded to Maayan Lustig).

Keywords
Thoracic injury, Finite element modelling, Behind armour blunt trauma, Protective plate, Ballistic impact
PROTECTING THE SKIN OF PATIENTS WHO ARE POSITIONED SUPINE OR PRONE

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Introduction
Pressure ulcers (PUs), also known as pressure injuries, are soft-tissue damage associated with tissue exposure to sustained deformations and stress concentrations, typically in the vicinity of bony prominences or under a stiff, skin-contacting medical device due to unrelieved bodyweight forces [1-2]. In supine patients with impaired mobility or sensory functions (that are either permanent or temporary), the sacral region is a common site for PUs, including sacral DTIs [3].

Head-of-bed (HOB) elevation is a common clinical practice in hospitals causing the patient's body to slide down in bed because of gravity. This migration effect likely results in tissue shearing between the sacrum and the support surface, which increases the risk for PUs. However, migration-reduction technologies (MRT) incorporated in intensive care bedframes are aimed to aid in minimizing migration and stress levels.

Immersion and envelopment are also two critical benchmarks that determine the comfort and PU risk mitigation levels provided by medical support surfaces as they have a remarkable effect on the stress concentrations near bony prominences [4]. In the case of patients who are prone for ventilation or surgery, PUs may occur in the superficial chest tissues that are compressed between the rib cage and the support surface.

Our goal in this work is to present several methods of protecting the skin of patients who are positioned supine or prone and to evaluate their ability to lower the risk of PUs by means of finite element (FE) modeling.

Methods
We developed three-dimensional anatomically-realistic FE modeling frameworks of the human buttocks, as well as of the whole torso, both include the inner organs and tissues to simulate various scenarios of PU development in patients who are lying supine or prone, quantifying the effectiveness of each method in dispersing tissue stress concentrations near vulnerable tissue.

First, we modeled the effect of using MRT during HOB elevation, on the levels of shear stresses in the tissues. Second, we compared the risk of developing a sacral PU while lying supine on a regular foam mattress with respect to lying on a specialized, minimum tissue deformation mattress (MTDM) which closely conforms to the body contours. Third, we investigated the biomechanical efficacy of a dressing with a soft cellulose fluff core in protecting proned surgical patients from chest PUs occurring on the operating table.

Results
The modeling showed that the MRT system can reduce migration in bed, and therefore – minimize the risk for sacral PUs. In addition, we revealed that MTDM provides longer safe times for supine support in comparison to a regular flat mattress. For the prone position, we have shown that prophylactic dressings dispersed elevated soft-tissue stresses, protecting the skin from PUs.

Discussion
The quantitative methods presented here points to the strong prophylactic benefits in: (i) minimizing the migration in bed to reduce the biomechanical risk for PUs, (ii) alleviation of localized, sustained stress concentrations through good immersion and envelopment of the support surface (iii) using soft cellulose fluff core dressings for pressure ulcer prophylaxis, including during surgery for proned patients.

References

Keywords
Pressure ulcers, Soft Tissues, Supine, Prone, Finite Element,
PERSONALIZED FINITE ELEMENT ANALYSIS OF LARGE ABDOMINAL AORTIC ANEURYSMS USING MULTI-PERSPECTIVE 3D+T ULTRASOUND

Esther Maas (1,2), Tessa Timmer (1), Arjet Nievergeld (1,2), Judith Fonken (1,2), Marc van Sambeek (1,2), Richard Lopata (1).

1. Eindhoven University of Technology, Netherlands; 2. Catharina Hospital Eindhoven, Netherlands

Introduction

The need for rupture-preventing surgical repair of abdominal aortic aneurysms (AAAs) is currently based on the AAA diameter. However, a more patient-specific measure is required, as some AAAs rupture before the diameter threshold is reached, while other larger AAAs stay stable. With time-resolved 3D ultrasound (3D+t US) combined with finite element analysis (FEA), the mechanical properties and wall stress of the AAA can be obtained, providing additional rupture risk indicators.

Due to the limited field of view (FOV) of 3D+t US, larger AAAs cannot be captured in a single image. Previous research has focused on combining geometries from multiple US images for FEA [1], but model personalization with mechanical parameters derived from multi-perspective ultrasound has not yet been performed. The goal of this study is to perform mechanical characterization and wall stress analysis of large AAAs by temporally and spatially registering multiple 3D+t US images.

Methods

Sets of proximal and distal 3D+t US images of 7 AAA patients were automatically segmented with an in-house segmentation algorithm. Temporal registration was performed by tracking the aortic wall over different time frames [2], followed by reordering the frames in both the proximal and distal datasets into a single artificial cardiac cycle (Figure 1A-C). Diastolic and systolic time frames were selected for both images. The diastolic images were spatially registered using phase-only correlation [2-3] and the segmentations were combined (Figure 1D-F). The diastolic-to-systolic displacement was determined by performing speckle tracking on the individual images and combining the resulting displacements.

The combined diastolic geometry was converted to a prism mesh with 2 mm wall thickness. The shear modulus was estimated based on a FEA updating approach in Ansys, by adapting the shear modulus (G) until the displacements in the FEA matched the speckle tracking-derived displacements. For validation, this process was also performed on the proximal and distal images separately.

Results

Temporal and spatial registration of proximal and distal images was feasible for all 7 patients, leading to a 20-40% increase in FOV. Preliminary results comparing the shear moduli based on the separate and combined images (Figure 2) show that for some patients (2 and 3) these values are very similar, while for other patients differences up to 4MPa are found, indicating possible local variations in material properties.

Figure 1: Temporal (A-C) and spatial (D-F) registration of a proximal and distal 3D+t US images, with the segmentations marked in red.

Figure 2: Patient-wise shear moduli based on iterative FEA from proximal, distal, and combined images.

Discussion

This work shows the feasibility of patient-specific mechanical characterization and wall stress analysis of large abdominal aortic aneurysms based on 3D+t US. This is a step towards a more patient-specific non-invasive rupture risk indicator, which is suitable for large AAAs. Next steps are analysis of the local displacements, and application of the method in a longitudinal study, investigating the progression of the material properties and wall stresses with AAA growth.

References


Acknowledgements

This work is part of the MUSE project, which has received funding from the European Research Council (ERC).
ROLE OF VASCULAR SMOOTH MUSCLE CELL PHENOTYPE SWITCHING IN THE ROSS PROCEDURE: A COMPUTATIONAL STUDY

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Introduction

The Ross procedure is an excellent surgical solution to repair a diseased aortic valve. However, autograft failure is often observed due to excessive dilatation. We hypothesize that vascular smooth muscle cells (vSMCs) in the autograft adopt a degradative phenotype [1] and investigate whether the long-term outcomes of the Ross procedure would benefit from pharmacological treatment that reverts this phenotype switch.

Methods

The Ross procedure was performed on three sheep, who were euthanized after six months of autograft remodeling. Bulk RNA sequencing on the three extracted autograft samples was followed by differential analysis compared to four sheep pulmonary artery control samples. With this data, Gene Set Enrichment Analysis (GSEA, Bioconductor package fgsea) [2] was performed on selected curated gene sets from the GO Molecular Function and Biological Process ontologies [3], as well as from the Reactome pathway database [4], that are relevant to tissue growth and remodeling.

Our computational model for growth and remodeling of pulmonary autograft tissue [5] was adapted to account for the gene signature of vSMCs after phenotype switching obtained from GSEA. The simulation is also repeated assuming healthy vSMC behavior.

Results

<table>
<thead>
<tr>
<th>GO/Reactome term</th>
<th>NES</th>
<th>p</th>
<th>BH p</th>
</tr>
</thead>
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<tr>
<td>(1) GO:1904707</td>
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<td>0.04</td>
<td>0.10</td>
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<tr>
<td>(2) GO:0930020</td>
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<tr>
<td>(4) R-HSA-216083</td>
<td>2.01</td>
<td>&lt;&lt;0.01</td>
<td>&lt;&lt;0.01</td>
</tr>
</tbody>
</table>

Table 1: Results of GSEA, indicating normalized enrichment score (NES) and (BH adjusted) p-value (p, BH p).

Results of GSEA given in Tab. 1 show the gene expression profile of autograft vSMCs including upregulated cell proliferation (1), production of collagens (2), production of ECM degrading proteases (3), and integrin to cell surface interactions (4). No significant change in apoptosis, vSMC contraction and production of elastic matrix was observed.

Fig. 1 shows the outcomes of the model, either accounting for this vSMC behavior observed through GSEA or assuming a healthy phenotype, where in the latter case, the radius increases more slowly over time.

Discussion

A clear reduction of dilatation rate can be observed when vSMCs keep their healthy phenotype, proving the relevance of finding pharmacological solutions to avoid phenotype switching. However, due to the continuous turnover of collagen, gradual dilatation cannot be fully avoided, such that also (temporary) mechanical support of the autograft is recommended.

References

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Acknowledgements

Sequencing and differential gene expression analysis was performed by the VIB Nucleomics Core (www.nucleomics.be).
INVESTIGATING SKELETAL PERI- AND POST-MORTEM TRAUMA

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Introduction
The forensic anthropological analysis of trauma can provide evidence for foul play and contributes to the determination of cause and manner of death [1]. Bone mechanical and biological properties impact the way bone fractures due to the cross-sectional geometry and thickness of its cortical bone [2]. In the post-mortem (PM) interval bones will gradually lose some of their fresh characteristics and their mechanical and biological properties change which impacts their fracture pattern. The timing of skeletal trauma and the PM interval significantly impacts the reconstruction of the events leading up to death and the cause of death. However, there are no absolute time frames in which the characteristics of wet bone (perimortem) fractures transfer to dry (post-mortem) fractures. This study aims to identify any time-dependent trends that may highlight the time of transition within the early PM interval in which the characteristics of bone change from wet to dry bone properties. Furthermore, to support the hypothesis that the characteristics of bone fractures change significantly in the first ten weeks after death by investigating the mechanical, macroscopic, microscopic, and chemical changes in the first ten weeks post-mortem.

Methods
64 ribs of 4 rib cages of mature fallow and roe deer were used. 32 ribs were buried in 10 boxes with 10 litres of soil (pH 5.5-6.0) while the other 32 ribs were placed on trays with ~1cm of soil underneath them. The ribs were experimentally fractured through a three-point bending DARTEC Series HC25 hydraulic materials testing machine with a 25kN load cell at increasing weekly intervals. The fractures and bones were analysed using macroscopic analysis, SEM analysis, thermal analysis, biomechanical analysis, and ATR-FTIR analysis. These results were then considered to establish whether any time-dependent trends were present and if they were a reliable tool to identify when the fresh characteristics of bone were lost. Statistical analyses of variances (ANOVA) were also performed on the mechanical and chemical results.

Results & Discussion
In the exposed ribs of all the statistical analyses performed in this study only the normalised load values and the carbonate-to-phosphate ratios gave significant results. All remaining observations, including those that were not statistically assessed, proved inconclusive.

In the buried ribs, no significant difference was found in the macroscopic, microscopic, composition and biomechanical analysis (Figure 1), but only in the carbonate-to-phosphate ratio. The comparison of buried bones and exposed bones showed a significant difference in all the analytical techniques. The inconclusiveness of the results as far as PM interval determination is concerned was to be expected for the small PM period of 10wks. The alterations in these particular characteristics in the first 10wks PM may be too small or variable to detect.

Conclusions
The present study confirmed the flexible and environment-dependent nature of the peri-mortem interval. However, this study did not prove the hypothesis that characteristics of bone fractures change significantly between week 0 and week 10. Therefore, Forensic Anthropologists cannot identify and differentiate fractures with certainty within the first ten weeks of the PM interval from biomechanical characteristics alone.

References

Figure 1: ANOVA test results for the normalized energy to fracture, Collagen content, Crystallinity Index and Mineral to matrix ratio in the 10wks PM interval.
A COMPUTATIONAL INVESTIGATION OF THE TENDON-TO-BONE INSERTION: THE ROLE OF TISSUE ANISOTROPY

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Introduction
Understanding the mechanics of tendon-to-bone insertion is a challenging task, owing to the strong tissue dissimilarities occurring at this anatomical site: tendon is compliant and anisotropic, whereas bone is not only much stiffer but also much less anisotropic. At bimaterial attachments, differences in elastic properties can lead to peak stresses and failure. The insertion of the Achilles tendon (AT) into calcaneus bone (CB) occurs through a transitional tissue called fibrocartilage (FC). Some joints have two FC: enthesis FC anchoring tendon to bone and periosteal FC facilitating tendon sliding. Both FCs exhibit specific structure, composition and material properties, including a strong microstructural anisotropy at enthesis FC [1]. Little is known about the influence of FC properties on the force transmission from tendon to bone. Yet, such knowledge is of high clinical relevance as local stresses play a crucial role in enthesis pathologies and injuries such as enthesopathies and avulsion fractures. Here, we propose a two-dimensional (2D) finite element (FE) approach exploiting two idealized geometries of increasing complexity, to characterize the impact of enthesis FC on stresses at the tendon-bone interface.

Methods
Two FE models were developed and solved using Abaqus/CAE. The first model (Fig. 1) consisted in two regions with specific material properties, representing tendon and mineralized FC (mFC), with a load applied on the tendon extremity. In the second model (Fig. 2), we implemented a simplified geometry of AT attachment to CB, based on rat micro-computed tomography scans from a previous study [1]. The local stresses (extracted at the interface between AT and mFC) were investigated as a function of enthesis FC anisotropy and elastic properties. In both models, quadrilateral plane stress linear full integration elements were used. Bone and periosteal FC were considered isotropic, with an elastic modulus of 22 GPa and 17 GPa, respectively, based on previous nanoindentation measurements. Tendon and enthesis FC were considered transversally isotropic with a principal modulus ($E_t$) of 500 MPa and 17 GPa, respectively. Other parameters ($E_p, \nu_{tp}, \nu_p, G_t, G_p$) were computed through suitable relationships proportional to $E_t$ [2].

Results
Simulations based on the first model revealed strong variations in the stress level at the interface as a function of mFC anisotropy (Fig. 1). Such bi-material configuration is known to generate a stress concentration at the interface [3]. If both materials are isotropic, an interfacial stress 2.5 times higher than the applied boundary traction is generated. Here, we show that increasing the degree of anisotropy (expresses by the transversal component of the Poisson’s ratio $\nu_{tp}$) reduced stress concentration.

![Fig. 1: Spatial variations of Von Mises stress at the tendon-mFC interface, normalized by the applied boundary traction, as a function of the degree of anisotropy $\nu_{tp}$.
](image)

The same occurred in a more realistic setting (Fig. 2): using an anisotropic model for enthesis FC causes a reduction in interfaces stresses. Decreasing the elastic modulus mismatch between AT and FC also leads to a decrease in interfacial stresses but of a smaller extent than observed when changing the elastic anisotropy.

![Fig. 2: Normalized von Mises stress at the interface between AT and enthesis mFC (E-mFC) as a function of mFC elastic properties and anisotropy.
](image)

Discussion
Models accounting for tissue anisotropy resulted in lower interface stress compared to isotropic tissue models. Despite the idealized geometry, this result suggests the critical contribution of the mechanical anisotropy of FC, based on high aligned collagen fibers at the enthesis. Our findings should provide guidelines for bimaterial attachments and enthesis reattachment surgeries.

References
PREDICTING IMPACT RESPONSE OF HUMAN FEMUR USING MATERIAL MAPPING STRATEGY

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Introduction

Material property mapping is a crucial step in developing quantitative computed tomography (QCT) based patient-specific finite element (PSFE) heterogeneous model of bone. However, its accuracy is highly dependent on several factors, such as density–modulus relationships \((E-\rho)\) and the number of bone material sets. Significant moduli variation for both trabecular (80%) and cortical bone (40%) was observed using different \(E-\rho\) relationships previously reported in the literature [1]. This work aimed to investigate the influence of \(E-\rho\) relationships and the number of bone material sets on the prediction accuracy of the dynamic response of the human femur.

Methodology

A three-point bend test was performed from lateral to medial impact direction on the human femur (mid-diaphysis) at 1.42 m/s impact velocity, and its force-time response was recorded using a piezoelectric load cell. Before testing, the specimen was scanned using a QCT scanner (XtremeCT, Scanco, Inc., Switzerland). Heterogeneous PSFE models of bone were developed using Mimics (Materialise, Belgium) and Hypermesh (Altair Engineering, USA). Ten PSFE models with two types of \(E-\rho\) relationships i.e. linear (eq. 1) and power law (eq. 2) each with five different numbers of bone material sets (3, 10, 40, 100, and 300) were tested. The genetic algorithm-based inverse characterization method was used to optimize design variables \((a\) and \(b\)) for both trabecular and cortical bone. Optimization was run to minimize the root mean square error (RMSE) between the force-time response of the experiment and PSFE models. PSFE simulations were made to run corresponding to the time when the fracture was observed in our experiment and peak impact force was recorded at that instant. The performance of every model was evaluated in terms of the von Mises stress \((\sigma_{vom})\), maximum principal stress \((\sigma_{mps})\), and effective plastic strain \((\varepsilon_{eps})\) of elements at mid-diaphysis opposite to the impact (Fig. 1).

\[
E = a\rho + b \quad (1)
\]

\[
E = a\rho^b \quad (2)
\]

Results

Significant variation in peak force values was observed (Fig. 2 a) and power law (eq. 2) with 300 material sets best predicted the peak force (0.9% error). Predicted values of \(\sigma_{vom}, \sigma_{mps}\), and \(\varepsilon_{eps}\) of other models were compared to the most heterogeneous model i.e. model with 300 material sets as shown in Fig. 2 b, c, and d, respectively.

![Figure 1: Bottom elements used for the evaluation of PSFE models.](image1)

![Figure 2: (a) Variation in predicted peak force. Variation in RSME values of (b) \(\sigma_{vom}\) (c) \(\sigma_{mps}\) and (d) \(\varepsilon_{eps}\) at bottom elements.](image2)

Discussion

The prediction of the dynamic response of the human femur was dependent on both material mapping parameters [2]. Fig. 2a suggests that the \(E-\rho\) relationship significantly influences the prediction of peak force [3]. Fig. 2 b, c, and d indicate that the combination of material mapping parameters needs to be implemented for best prediction [1]. In this study force-times response was used from one experiment to obtain optimized PSFE models. Therefore, further validation is required with larger datasets to ensure reliable results.

References


Acknowledgments

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A PHYSICS INFORMED NEURAL NETWORK TO SIMULATE THE FREE BOUNDARY PROBLEM OF CELL MIGRATION

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Introduction

Single fish keratocYTE crawling in a two dimensional substrate is driven by actin polymerization forming protrusions at the leading edge and a dense actomyosin network known as lamellipodium; adhesion to substrate at the front; actomyosin retraction and finally detachment of the trailing edge. During this phenomenon, the centripetal flow of actin networks occur inside the cell powered by myosin motors. Here, a free boundary computational model has been developed considering momentum balance of actin flow, free and bound myosin dynamics, and actin dynamics. With an objective of quantitative understanding of complex dynamics during cell crawling and comparison with the experimental observations, we focus on the one dimensional “traveling-wave” solutions of the model. Later, these solutions are used to train a Physics-Informed-Neural Network (PINN) model in order to reproduce the solutions for any new one-dimensional domain with given specific boundary conditions.

Methods

The model developed is the viscoelastic flow model used in [1] with the incorporation of free boundary conditions. The governing equations are coupled nonlinear Partial Differential Equations (PDEs) which in general are difficult to solve analytically. To understand the spatial variation of actin velocity, actin density and myosin densities, we remove the complexity of time-dependence from the model and convert the system of PDEs to a set of Ordinary Differential Equations using a “traveling-wave” ansatz as discussed in [2]. The solution from this method is used to validate the prediction obtained by training a PINN model [3]. The free boundary model of cell crawling has four PDEs which are given below. Using Newton’s second law, the one-dimensional governing equation for the actin flow is of the form

\[ \frac{\partial u}{\partial t} + \tilde{\xi}u = \frac{\partial}{\partial x} \left( 2\eta \frac{\partial u}{\partial x} + \sigma m_1 \right) \]

The mass conservation equation for actin network, free myosin and bound myosin are of the form

\[ \frac{\partial p}{\partial t} + \frac{\partial (pu)}{\partial x} + \gamma p = 0; \]

\[ \frac{\partial m}{\partial t} = -k_1 m_1 + k_0 m_0 - \frac{\partial (um_1)}{\partial x}; \]

\[ \frac{\partial m_0}{\partial t} = k_1 m_1 - k_0 m_0 - \frac{\partial^2 m_0}{\partial x^2} \]

and the boundary conditions are given by

\[ 2\eta \frac{\partial u}{\partial x} + \sigma m_1 \bigg|_{A(t), B(t)} = 0; \]

\[ p \bigg|_{B(t)} = p_0; \]

\[ m_1 \bigg|_{B(t)} = m_0 \bigg|_{A(t)} = 0; \]

Free boundary conditions are given through boundary velocities

\[ V_{fA} = V_p + u \bigg|_{B(t)}; \]

\[ V_{fB} = u \bigg|_{A(t)} \]

Here, A(t) and B(t) are the positions of the rear and front boundaries of the one dimensional cell, respectively. \( V_p \) is the growth velocity at front, while all other variables and parameters have the same meaning as given in [1].

Results

By training a PINN we obtain a one dimensional “traveling-wave” solution for the actin flow velocity and the densities of F-Actin and myosin. They coincide well with the experimental observations as well as with the solution which was given in [1] and computed using classical methods of numerical analysis.

![Figure 1: Spatial variation of actin flow velocity inside the cell crawling with a constant velocity.](image)

Discussion

This project serves as a proof of concept which we intend to extended to two dimensions with temporal dynamics. Our goal is to combine data and physics to develop a deep learning-based simulation framework to analyze cell migration and validate the simulation results with experimental observations.

References

Modelling biofilm growth subject to local antibiotic delivery
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Introduction
Implant infection is a serious clinical problem, with treatment usually involving systemic delivery of antibiotics. However, due to the ability of bacteria within biofilms to survive antibiotic dosages that would ordinarily kill free-swimming proliferative bacteria, biofilm infections are extremely difficult to eradicate. Antibiotic resistance and tolerance confound the problem, often associated with nutrient insufficiency, hypoxia in the deeper layers of biofilm and antibiotic concentration at levels above the Minimum Inhibitory Concentration (MIC) [1]. An alternative approach is to deliver antibiotics locally in a sustained manner. In this study, we present a mathematical model of biofilm growth subject to antibiotic delivery, with the aim of understanding how the biofilm growth and composition depends on the drug dose and release rate.

Methods
We have formulated a 1D biofilm growth model in which we introduce controlled antibiotic release directly from the implant. If the release is inadequate to prevent bacterial growth, then infection can take hold, however if drug release is excessive then this may impair the recovery of healthy tissue around the implant. This represents a delicate balance, amenable to exploration and optimization through mathematical modelling.

The approach of modelling biofilm growth while optimizing antibiotic dose and release rate simultaneously may result in a more efficient biofilm prevention strategy. The model consists of different bacterial phenotypes, self-produced extra cellular polymeric substance (EPS), nutrient concentration, water volume fraction in the biofilm pores, growth of the biofilm and a porous implant filled with antibiotic (see Fig.1) [2]. We have simulated how different model parameters, including nutrient concentration, influence the growth of different bacterial phenotypes. We also simulated how different antibiotic-release strategies from a nano-porous implant impact on the time-course of biofilm growth and its constitution [3]. In this model, antibiotic-induced death of active bacteria along with natural death are considered.

Results
As expected, the density of proliferative bacteria increases moving away from the implant, where antibiotic is being delivered from and decreases with increasing antibiotic dose. However, the persisters bacteria, one of the main reasons for antibiotic resistance, increases with increasing antibiotic dose since the proliferative bacteria transforms into the persister phenotype in order to survive the antibiotic dosage.

Conclusions
Our model suggests that careful tailoring of antibiotic release could help prevent implant-associated infection as biofilm thickness and proliferative bacteria cells decrease with increasing antibiotic dosage. The model is able to capture experimentally observed resilience to antibiotic shown by persister cells. Our immediate next steps would be to find the optimal antibiotic delivery configuration such that the infection gets eradicated along with persister cells which will result in no further infections on the implant.

References

Acknowledgements
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DEVELOPMENT OF A 2-SEGMENT SPINAL FRACTURE FIXATION ROD TO MEASURE FORCES AND MOMENTS IN VIVO

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Introduction

Little information exists with regards to the loads acting on spinal rods during fracture stabilization and healing. Spinal trauma of the thoracolumbar junction represents 60–65% of thoracolumbar spine fractures [1]. Lumbar disc measurements were carried out first by Nachemson [2] and then by Wilke [3]. Forces carried by modified spinal fixators have been measured by Rohlmann et al [4]. Our current work is directed towards instrumenting a standard geometry spinal rod and stiffness used for fracture healing as seen in figure 1. Strain gauges housed internally measure the 6 dof of loading acting at the centre of the rod. This will enable the load sharing between rod and spine to be assessed and indicate the optimal time for removal of the rod [5].

Method

Grade 9 Ti-3Al-2.5V titanium tubes of 6.35mm outer diameter were instrumented internally with 9 strain gauges. The load bearing solid outer tube of wall thickness 0.7mm and a single inner sleeve of 160deg arc with a length of 60mm were manufactured. Strain gauges and electronics are pre mounted. Implant instrumentation is being evaluated for resolution, power, and speed. Strains will be amplified, digitized, telemetered, and powered using inductive coupling between an implanted coil contained at one end of the rod and an external coil [6]. The model was finite element analysed using COMSOL™ to validate the choice of strain measurement sites for efficacy of load sensitivity and selectivity. The construct both with electronics and without were then mechanically tested using a Wohler rod rotating machine, thus determining whether the instrument will be able to withstand cyclic fatigue loading conditions.

Results

The proposed construct was designed on COMSOL, appropriate boundary conditions and material settings were applied. 3 forces and 3 moments were applied separately. Machining grooves present in manufactured single sleeves dictated the 5 axial levels chosen, strains corresponding to the outer surface of tube and inner sleeve were tabulated out. Strains were analysed, sinusoidal profiles and their phase relationships were compared. Sensitivities and correlations were checked against various angle combinations and gauge locations were chosen as seen in figure 2.

Figure 2: Gauge locations and their positioning in the X, Y and Z axis within the grooves on the inner sleeve to be instrumented.

Errors and peak sensitivities varied with the angle of the rotated gauges. Gauges at 0 degrees gave the best ideal sensitivity for Fy,Mx,Mz and 45 degrees gave the best sensitivity for My,Fx,Fz. Correlation coefficients between the degrees of freedom were high but expected due to the regular structure of the implant. Ability of the combined chosen gauge sites to uniquely determine the 6 degrees of freedom applied were proven. 9 strain gauge channels were made available to allow room for errors during gauge placement. 5 levels were used for better discrimination and more selectivity, a combination of circumferential and rotational angles. To theoretically facilitate ‘infinite’ life, gauges will use a power coil to be inductively powered, and an antenna to transmit data. This aspect of electronics, powering and telemetering data out is subcontracted and currently on going. 8 outer tubes 150 mm length and 6 welded tubes of the same length encapsulating the inner sleeves were manufactured and polished to run further experimental tests. The fatigue test was set up in line with the titanium grade 9 used. Strain/bending moment of 627/ustr/Nm was calculated, corresponding to a fatigue failure bending moment of 4.5Nm. 1 million cycles corresponding to practical cyclic stresses of the implant are currently under going testing.

Future Work

Further testing in practice using calibration loading in a biomechanical study prior to use in vivo.

References

COMPUTATIONAL MODELING OF IN-STENT RESTENOSIS: PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION

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Introduction

Percutaneous coronary intervention (PCI) is a minimally invasive procedure wherein the plaque built up within the coronary arteries, as part of an inflammatory pathosis termed atherosclerosis, is pressed against the arterial walls using balloon angioplasty, and subsequently, a supporting scaffold called a stent is placed to restore normal blood flow within the artery. Endothelial denudation and overstretch injuries caused during the PCI procedure kick start a myriad of signaling cascades within the arterial wall resulting in uncontrolled tissue growth, eventually recreating obstructions to the blood flow. The condition is labeled in-stent restenosis and the mechanism associated is termed neointimal hyperplasia. An attempt is made herein to model restenosis by tracking the pathophysiology’s significant contributors including the platelet-derived growth factor (PDGF) and the transforming growth factor (TGF-β), which are released into the arterial wall post platelet aggregation and degranulation. Additionally, the evolutions of the extracellular matrix (ECM), the smooth muscle cells (SMCs) and the endothelial cells (EC) are tracked. A rapamycin based drug (e.g. sirolimus) is considered for evaluation of pharmacokinetics and pharmacodynamics and subsequent influence on the pathology of restenosis. A fully coupled multi-physical finite element system is hence set up that can provide insights with enough fidelity to adapt PCI parameters and alleviate the risks associated with restenosis.

Methodology

The cellular mediators of in-stent restenosis in the arterial wall (SMCs, ECs) are quantified in terms of cell densities, while the extracellular mediators (PDGF, TGF-β, ECM and the drug) are quantified in terms of their concentrations. The arterial wall is modeled as an open system allowing for transfer of cellular and extracellular species into and out of it. The Eulerian forms of the advection-reaction-diffusion equations that govern the evolution of the aforementioned species are established based on the biochemical interactions involved in the pathophysiology of restenosis. Patient-specific aspects of pathophysiology can be taken into account given the array of parameters defined for the equations setup.

The structural behavior of the arterial wall is assumed to be predominantly influenced by the medial and adventitial layers, and each layer is assumed to be composed of two families of collagen fibres embedded in an isotropic ground matrix. SMCs are considered to be the drivers of the growth process within the isotropic ground matrix, while collagen is assumed to modulate the compliance of the arterial wall.

Figure 1: growth observed around an idealized stent geometry due to endothelial denudation (Inset: explanted stented artery a few days (top left) and a few months (bottom right) after stent implantation [3])

References

3. Internal meeting, DFG project number 395712048, 2021.

Acknowledgements

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RESTORING DISORGANISED TENDINOPATHIC TISSUE USING MAGNETIC TOPOGRAPHICAL CUES

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Introduction

Tendons, which connect muscle to bone, are comprised of longitudinally-packed collagen type I fibres at length scales that range from the nano to the macroscale [1]. The main cell type, specialised fibroblasts called tenocytes, are arranged in between these collagen structures [2]. The strong anisotropy of the tendon’s collagen matrix results in a high cell aspect ratio, co-aligned with the collagen, ideal for proper tendon functioning [3]. However, in tendinopathy, i.e., tendon disease, cell and matrix anisotropy are lost, affecting tissue function and thus increasing rupture risk. As cells are known to be able to manipulate collagen organization [4], it is hypothesised that recovering the lost cell alignment promotes functional remodelling to an anisotropic and healthy tendon. The aim was thus to control cell aspect ratio and orientation, using injectable magnetic rods, in an isotropic collagen matrix, to promote functional tissue remodelling towards strong tissue anisotropy.

Methods

Super Paramagnetic iron-oxide nanoparticles in polymeric MicroRodS (SPµRs) [5] were used to provide topographical cues to the cells. Cells that encounter the rods can align their longitudinal axis to the rods’.

Figure 1: (a) in-vitro 3D isotropic tissue; (b-c) formation of isotropic microtissue; (d-f) formation of microtissues with SPµRs.

3D tendon microtissues (fig 1a) that mimic a tendinopathic isotropic tissue (fig 1b) were created in-vitro using a gel mixture of collagen type I and tendon like-cells. The isotropy was created in the tissue by restricting contraction of the collagen (orange) by the cells (green) in all directions using 12 black posts (fig 1c). In the same isotropy setup, SPµRs (black) were added to override the isotropy and promote anisotropy (fig 1d). Using a magnetic field, the SPµRs were aligned in the direction of the magnetic field (fig 1d) after which collagen was allowed to polymerise (fig 1e). Subsequently, the alignment response of the cells to the SPµRs was monitored (fig 1f).

Results

In the absence of SPµRs, an isotropic distribution of cellular actin stress fibres (green) developed in the microtissues (fig 2a). Whereas in the presence of magnetically aligned SPµRs (red), microtissues displayed preferential cellular co-alignment (fig 2b). It was shown that the cellular orientation can be manipulated to anisotropy using SPµRs in 3D microtissues, which would be isotropic without SPµRs.

Discussion

The cellular co-alignment was exhibited roughly throughout the tissue. A major variable at play was the concentration of rods to cells. The ratio of rods to cells has to be optimised to achieve complete and strong alignment throughout the tissue. The effect of the aligned cells on the existing collagen, the orientation of cell-secreted collagen and the effect of uniaxial cyclic load to investigate the strength of the topographical cues against strain avoidance, are also being assessed.

References


28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
DEVELOPMENT OF A MICRO TOMOGRAPHY PROTOCOL FOR PTA-CONTRASTED HUMAN MENISCUS

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Introduction

Contrast-enhanced micro tomography (CE-µCT) aims at enhancing X-ray contrast of low-density materials, mainly of soft tissues, allowing to investigate their 3D structure comprehensively. To promote CE-µCT as a standard technique complementary to immuno-histomorphometry, several aspects should be optimized: sample preparation and imaging; contrast agent diffusion together with minimizing tissue shrinkage; tissue preservation to ensure a not biased structural analysis and the complementarity with other assays [1]. In this study, a CE-µCT protocol on human knee meniscus with phosphotungstic acid (PTA) as contrast agent is under development by comparing it with chemical drying, a reference procedure to enhance contrast in biological samples, already experimented on human meniscus [2]. Indeed, PTA reveals preferentially collagenous structures [3], which are abundant in the meniscus, and it has been tested on animal models [4]. Nevertheless, replicating that protocol on human meniscal tissue highlighted only partial PTA diffusion, some tissue shrinkage and marked stiffening [5]. Therefore, an evolution of the protocol is under test.

Methods

Portions from human menisci (ethical approval 952/2021/Sper/IOR) underwent the following CE-µCT protocols. PTA concentration, originally at 1% (w/v) [4], was increased to 2% to improve diffusion; exposition to PTA lasted seven days. Water was compared to ethanol (EtOH) as solvent for PTA in terms of imaging. Samples were µCT scanned with source voltage 70 kV and current 250 µA, without metal filter (Skyscan 1172, Bruker, Belgium). As regards reference procedure – i.e. chemical drying – samples were dehydrated in ascending EtOH concentrations, treated with hexamethyldisilazane (HMDS), air-dried in a fume hood and then µCT scanned (40 kV, 250 µA; no filter) [2]. Sample dimensions before and after preparation for CE-µCT were measured by a caliper looking for shrinkage.

Results

Comparing sample contrasted by PTA in water respect to PTA in EtOH, meniscus radial section of reconstructed µCT images shows a major contrast, but a minor contrast agent diffusion; in both cases, signal appears highest on surface, corresponding to a major collagen density [2,4] (Fig. 1 A,B). HMDS drying resulted in minor image contrast (Fig. 1 C). Sample preparation caused tissue shrinkage in the case of chemical drying (~22% in volume change), not evident in the case of PTA contrast.

Discussion

CE-µCT can be particularly useful for investigating the physiopathology of the human meniscus, important in knee biomechanics, often degenerated and still difficult to repair. We are developing a meniscus CE-µCT protocol based on PTA as contrast agent, investigating if it is possible to characterize collagen distribution and make indirect interpretations on the alignment of the extracellular matrix as for cartilage [6]. Validation is an important phase, often poorly described in relative literature: with this aim, histological and mechanical, i.e. functional, characterizations are ongoing [5], also testing rehydration/PTA washing strategies to favour the complementarity between those (and other) assays and CE-µCT.

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Acknowledgements

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ULTRA-HIGH SPEED IMAGING FOR STUDYING ULTRASONIC CUTTING OF BONE & CARTILAGE

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Introduction

High-power ultrasonic surgery tools offer exciting opportunities for minimally invasive surgeries as their use requires low force while still providing high precision and preservation of critical biological structures such as nerves [1]. To understand the mechanics of ultrasonic cutting, a thorough understanding of blade-tissue interaction is necessary. This system is highly dynamic and depends on many factors such as properties of the tissue and the characteristics of the cutting device (type of blade, frequency, amplitude). In this study, we employ ultra-high speed imaging with imaging rates of over one million frames per second to temporally resolve deformation of bone and cartilage under ultrasonic cutting. We hypothesize that, by understanding the cutting process, it will be possible to optimize the cutting configuration leading to better outcomes for patients such as faster recovery and fewer complications.

Methods

In a preliminary study, a small cut was made in a piece of bovine cortical bone (from the femur) using a custom ultrasonic cutting device operating at 25 kHz and in chiseling configuration. The side surface of the specimen was prepared with a unique pattern, using a microcontact printing technique that is necessary to measure kinematics using Digital Image Correlation (DIC). The specimen was observed during the experiment with two high speed cameras (i-Speed 513, iX), capturing images at 75 kHz. The cameras were equipped with high magnification lenses (12x, Navitar), providing a field of view 8 × 4 mm² and the illumination was realized by means of a pulsed laser synchronized with camera acquisition. The gray scale images were processed with stereo DIC to measure relative motion of the bone specimen resulting from the interaction with the cutting tip.

Results

In this preliminary study displacements in bovine bone were measured resulting from the impingement of the ultrasonic tool vibrating with an amplitude of approximately 20 µm. The maximum displacement of the bone was measured as 2 µm (as seen in Figure 1), suggesting that the deformation is primarily concentrated close to the cutting site which cannot be resolved with the current state of high-speed camera technology.

Discussion

The proposed method of imaging ultrasonic cutting is capable of providing insight into tool-tissue interaction and measuring deformation resulting from the mechanical contact between the two. Due to the stiffness of bone, the majority of deformation is concentrated in the cutting region, therefore a following study was performed on human cartilage samples. In this study, even faster cameras will be employed (Shimadzu HPV-X, 5 MHz) resulting in temporally resolved motion of the tissue. The proposed method enables study of the effects of process parameters, such as operating frequency, amplitude or blade geometry. These mechanical parameters can affect the amount of cell death at the cutting edge and therefore the biological outcomes of the surgical procedure.

References


Acknowledgements

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IN SILICO MODELLING OF THE MULTISCALE AND CHEMO-MECHANO-BIOLOGICAL MECHANISMS BEHIND VASCULAR TONE ADAPTATION

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Introduction
The physiological behaviour of the cardiovascular system is highly affected by the mechanical response of arterial segments, that is in turn dependent from both tissue histological architecture and the contractile tone of smooth muscle cells. The former depends mainly on the different amount and arrangement of constituents (mainly, elastin and collagen fibers), while the latter on chemical drivers of vasoactivity, such as nitric oxide (NO) and reactive oxygen species (e.g., ROS and PN). Moreover, arterial segments undergo a continuous remodelling, that is changes in their structure (e.g., thickening, stiffening, or narrowing). Remodelling is driven by biochemical pathways (involving growth factors – GFs – and enzymes such as matrix metalloproteinases – MMPs) that are activated when the mechanical state (i.e., stresses and/or strains) is non-homeostatic, [1,2]. When remodelling is dysfunctional, pathologies develop. For instance, this occurs in chronic hypertension, where mechanical and biochemical drivers powerfully interact towards a dysfunctional response.

It is also noteworthy that the problem is highly multiscale since global hemodynamic conditions (e.g., heart rates, resistance of downstream vasculature) highly affect local flow conditions, and hence the local pressure field and the internal stresses affecting biochemical pathways and remodelling. Detailed high dimensional models (2D or 3D) can generally be used to simulate local hemodynamics of specific arterial sites, while the whole arterial tree is generally described through low dimensional descriptions (i.e., lumped 1D approaches).

Methods
This work presents a comprehensive multi-scale and multi-field computational framework that accounts for: i) a lumped 1D description of the macroscale arterial tree; ii) a continuum 3D model at the microscale of the local chemo-mechano-biological response of arterial tissues (accounting for passive and active tissue behavior); iii) biochemical-dependent vasoconstriction and vasodilation (the NO-ROS-PN biochemical chain), and biochemical-dependent tissue remodelling (the GFs-MMPs biochemical chain). Simulations from 3D chemo-mechano-biogical models drive how parameters of the lumped description vary as function of segment dilation, as well as tissue histology and vasoconstriction. An illustrative representation of the proposed methodology is reported in Fig. 1a.

Results
The applicative case study investigates the relationship between arterial vasodilatation and vasoconstriction with physical exercise. Figure 1b shows the short-term response of the arterial system during and after 1 hour exercise. The model predicts a release of vasodilators (NO), a decrease of vasoconstrictors (ROS), and a hemodynamic response leading to the maintenance of quasi-homeostatic shear stresses on endothelial cells in the intima. The obtained numerical results are consistent with available experimental data for normal and spontaneously hypertensive phenomena.

Figure 1: Multi-scale and chemo-mechano-biology rationale (a). Arterial short-term active response: vasodilation during 1h exercise and at rest.

Conclusions and Future studies
On-going studies are addressing the coupling of the framework with damage and healing mechanisms [3,4].

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A 3-Dimensional Multiphase Smooth Muscle Cell Model Exhibiting Anisotropy & Viscoelasticity

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Abstract
Smooth Muscle Cells (SMCs) constitute the major cells in the media layer of arteries and vessels. During biological processes, SMCs adapt their structure, dimension, and shape in response to mechanical and biochemical stimuli, thereby maintaining vascular tone to homeostatic levels [1]. The abnormal contractility of SMCs is associated with the development of many diseases such as hypertension and aneurysms. It is therefore essential to better understand the biomechanics of SMC dilation in health and disease.

In the present study, we examine the mechanical behavior of SMC when subjected to uniaxial tension tests, through Finite Element (FE) simulations. In general, vascular SMCs are spindle-shaped and have a single centrally located nucleus. The SMC intercellular space is a complex network comprising the actin and intermediate filaments that play a dominant role in the tensile properties of the cell [2]. Besides, it has also been reported that SCM exhibits hysteresis phenomena when subjected to stretch and release cycles [3]. Provided that, we present a 3-Dimensional multiphase SMC model, that encompasses the nucleus and cytoplasm surrounded by the cell membrane, as shown in Figure 1. The constitutive behavior of each phase is described through a strain energy function. The cell membrane and nucleus are treated as hyperelastic solids, whereas the cytoplasm is modelled as a transversally isotropic viscoelastic material incorporating one fiber family since. The model parameters are estimated by fitting the results of our simulations with previous experimental studies.

The cell is subjected to uniaxial tensile tests under different loading conditions including loading under constant velocity and loading/unloading process. In the latter case, large hysteresis phenomena are observed in the strain–stress curve obtained by our simulations, depicted in Figure 2. Those phenomena have been also reported experimentally [3]. In addition, we examine the dynamics of SMC for different fiber distributions and alignments. Our simulations indicate that the orientation and distribution of the filaments affect extensively the tensile properties of the cell.

Future directions
Many studies indicate that the intracellular calcium concentration determines the stiffness of SMC through an active contractile apparatus [4]. To this end, we want to introduce an active contribution to our current framework that will account for the calcium-activated response of SMCs.

References

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Figures

Figure 1: Geometry of the three-dimensional SMC model including the cell membrane, cytoplasm and nucleus depicted with yellow, blue, and purple color, respectively.

Figure 2: Comparison of the stress-strain curve obtained by our simulation with the experimental study [3] for a load/unload cycle tensile test.
DEVELOPMENT OF A COMPUTATIONAL/EXPERIMENTAL MODEL OF 3D VASCULARIZED TISSUES

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Introduction
Before undergoing clinical translation, it is essential evaluating the physiological reactions caused by biomaterials implantation. Integration of tridimensional (3D) cell culture systems and computational studies can help modelling the behavior of living tissues [1]. Computational fluid dynamics (CFD) analyses together with the application of a millifluidic optically accessible bioreactor (MOAB), suitable for dynamic culturing of cells in a 3D microscopic environment, have revealed to be a quick and reliable method for modelling vascularized tissue regeneration in vitro.

Methods

The cell culture platform consists of two rows of nine 3D microgrids, each of 500x500x40 µm, fabricated by 2-photon polymerization of the SZ2080 biocompatible photosensitive resin [2]. Each microgrid is characterized by pores of 50x50x20 µm³ (Figure 1). Cell proliferation was evaluated both on a flat substrate and inside the microgrids in static and perfused conditions (inside the MOAB). CFD analyses allowed to set up the optimal parameters and the shear stress values acting on 3D cells cultures. Co-cultures of endothelial cells and fibroblasts were performed and proliferation, together with tridimensional organization, were evaluated by confocal laser scanning microscopy (CLSM) (Figure 3). Specific growth factors (VEGF and TGF-β1) were administered for stimulating vessels formation.

Results

CFD analyses were performed for determining the optimal flow rate (10 µl/min) for achieving a maximum shear stress value of 0.1 mPa inside the microgrids (Figure 2). Co-cultures actively proliferated both in static and dynamic conditions and cell viability was not affected as shown by CLSM imaging. Upon administration of growth factors, co-cultures reorganized starting from day 4.

Discussion

CFD analyses allowed to evaluate optimal parameters for cell culture in dynamic conditions. The microscaffold and the bioreactor’s setup efficiently supported endothelial cells and fibroblasts growth. Experiments showed that this cell culture system is a quick and reliable tool for modelling vascularized tissue regeneration in vitro. Evaluation of vessels and connective tissue formation is ongoing in co-cultures. Administration of VEGF and TGF-β1 will be performed for estimating their cellular uptake/release kinetics.

Figures

Figure 1: a) Design of the bioreactor constituted by a chamber filled with micro-scaffolds (inset, b)).

Figure 2: Graphical representation of the estimated shear stress acting on the upper boundary surface of each micro-scaffold. The color map allows to identify the most stressed micro-scaffolds (in red).

Figure 3: Endothelial cells cultured in the 3D micro-scaffolds imaged by confocal laser scanning microscopy upon live (green)/dead (red) staining.

References


Acknowledgements

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AN UNSUPERVISED METHOD TO DETECT THE LEFT ATRIUM APPENDAGES AND CLASSIFY THEIR MORPHOLOGIES

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Introduction

The left atrial appendage (LAA) is the site where the left atrial thrombi are most likely (90%) to develop [1]. Despite the increasing interest that LAA has attracted over the last decade, the methods currently used to classify its morphology are mainly based on cardiologists’ judgment [2]. Given the remarkable improvement of imaging techniques, we propose an unsupervised quantitative method that can overcome the limits of the current classification systems. The resulting classification system is objective and reproducible.

Methods

 Routinely acquired clinical computerised tomography (CT) dataset from control and atrial fibrillation cases have been segmented to obtain the 3D shape of the left atrium (LA) and LAA. The 3D surfaces were meshed with triangular elements of side ~0.5 mm.

Our method consists of three steps: i) LAA detection, ii) features extraction, and iii) classification.

i) The detection of the appendage (Figure 1) is performed by analysing the skeleton-surface distances. We obtain the model’s skeleton by using the algorithm proposed by ref. [3]. Then we divide the 3D model into two groups using the distances threshold identified through the Otsu’s method [4], and we recognise the appendage by analysing the skeleton’s complexity. Finally, we cut the ostium of the appendage with a plane, consistently with the clinical imaging technique.

ii) The extracted features provide a quantitative characterization of the size and complexity of the LAA. We compute the appendage volume, and the ostium area and perimeter from the 3D models. The length of the main path of the appendage (representative of the main lobe), its complexity and the number of trabeculae are determined through a network analysis of the appendage’s skeleton (Figure 1).

iii) The new classification is obtained by performing a cluster analysis using the complete linkage method [5] based on the features correlation matrix (Figure 3). We cut the dendrogram in correspondence of correlation \( \rho = 0 \), forming groups of morphologies that are positively correlated.

Results

The developed code was able to correctly identify all the twenty-nine analysed LAAs and to extract all above mentioned features. Our method is based on quantitative measures that lead to an objective and reproducible classification system (Figure 3) that does not require one to specify the number of the classification groups in advance. Five groups were identified by cutting the dendrogram correspondingly with null correlation.

Discussion

Our approach is able to overcome the limitations of the current classification systems. It could be improved by increasing the sample size and the number of features, including the haemodynamic analysis and providing a probabilistic classification.

References

Introduction

Cells in living tissues such as the skin are constantly exposed to the “mechanoome” – a collection of stimuli of mechanical origin that can affect cell behavior and biological functions [1]. Ex vivo experiments and related computational models allowed us to quantify secondary chemomechanically coupled stimuli associated with skin stretch, such as local changes in fluid flow (Δµ), osmotic pressure (Δπ) and hydrostatic pressure (ΔP) [2]. Additionally, mechanical stimulation has been shown to improve the maturation of tissue engineered skin and to increase the proliferation of fibroblasts [3]. Tissue expansion – an existing mechanotherapy – stimulates skin growth using stretch, yet the mechanisms behind such profound effects of mechanical stimuli on skin remain unknown. It is likely that fibroblasts play a key role, since they are the main cell type in the dermis capable of remodeling the extracellular matrix, but the magnitude of stimulation needed to cause biological changes in these cells is unknown. We established in vitro systems to study the effects of osmolarity, hydrostatic pressure, and fluid flow on dermal fibroblasts in 2D and 3D cultures [4].

Methods

We developed dedicated bioreactors to expose primary adult human dermal fibroblasts cultured on tissue culture plastic (2D) or in collagen hydrogels (3D) to physiological increases in osmotic pressure (10 mOsm), hydrostatic pressure (20 kPa), and flow (10-20 um/sec). As an indicator of initial cell response, we measured intracellular calcium signaling using live-cell imaging. We further checked for downstream signaling pathway activation by western blotting. Lastly, we studied gene expression changes using bulk RNA sequencing.

Results

Live calcium imaging revealed distinct changes in intracellular calcium levels after changes in flow and hydrostatic pressure, but less so in response to osmolarity, suggesting that dermal fibroblasts feel chemomechanical stimuli even at these low levels. Furthermore, western blots revealed increased phosphorylation of AKT after exposure to 20 kPa pressure, suggesting that the initial calcium response to pressure is followed by intracellular signaling (Fig. 1a). Lastly, RNA sequencing showed that cells exposed to hydrostatic or osmotic pressure for 24 hours exhibit significantly altered gene expression in both 2D and 3D cultures, suggesting that the protein signaling cascade triggered by changes in chemical potential leads to transcriptional changes (Fig. 1b). Interestingly, cells in 3D cultures showed a stronger response than cells in 2D.

Figure 1: (A) Intracellular calcium levels, measured as pseudointensity, show distinct patterns when fibroblasts are exposed to chemomechanical stimuli. (B) Gene expression profiles of fibroblasts in 2D and 3D culture conditions after 20 kPa hydrostatic pressure for 24 hours compared to controls.

Discussion

Collectively, our results suggest that dermal fibroblasts not only feel, but also actively respond to mechanical stimuli in the physiological range. The response of cells in our 3D system underlines the importance of selecting an appropriate cell environment to study physiological stimuli in vitro. Further studies are needed to improve our understanding of human dermal fibroblast response to mechanical cues as this can aid in developing new mechanotherapies and understanding skin pathologies.

References


Acknowledgements

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OPTIMIZING BONE REGENERATION IN 3D SCAFFOLDS WITH COMPUTER-AIDED TECHNOLOGY

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Introduction
Bone regeneration is a crucial aspect of modern medicine, especially in cases of injury or disease that affect the skeleton, i.e., large bone defects. 3D scaffolds have emerged as a promising solution to support and guide the growth of new bone tissue. The integration of computer-aided technology has the potential to further optimize the bone regeneration process in these scaffolds by allowing for more precise and effective design and control. This combination of cutting-edge technology and medical application has exciting implications for the future of regenerative medicine. Recently, triply periodic minimal surfaces (TPMS) scaffolds have gained high interest in tissue engineering [1]. They are thought to resemble the bone microarchitecture due to their biomimetic geometry. Therefore, The goal of this study is to examine different TPMS structures and see how a mechano-driven bone regeneration model [2] can help design and optimize stabilization with various fixation systems. (Figure 1).

![Figure 1: Triply periodic minimal surfaces (TPMS) scaffolds considered for the large bone defect stabilized with 6 different fixation systems.](image)

Material and methods
A bone regeneration model [2], developed earlier, was used to forecast bone growth over time. The study focused on a large bone defect (3.6cm length, 3cm diameter). Four TPMS structures (diamond, gyroid, IWP, and primitive) with three different porosities (50%, 60%, 70%) were analyzed using PLA as the scaffold material. Six different fixation systems were evaluated (Figure 1), considering the weight of a 70kg patient for 16 weeks after implantation. This was implemented in a finite element code (Abaqus).

Results and discussion
First, bone ingrowth was analysed for the four different TPMS scaffolds and three different porosities, without fixation system. As a general rule, it was observed how bone ingrowth was concentric to the bone callus due to its geometric characteristics and the established boundary conditions. With higher porosity scaffolds more bone was formed compared to the ones with lower porosity scaffold.

Then, to simulate the effect of the fixation systems, the IWP with a 70% of porosity was chosen. Bone ingrowth was then estimated (Figure 2).

![Figure 2: Bone density distribution predicted for the different fixation times after 16 weeks from implantation.](image)

Bone ingrowth was heavily influenced by the chosen fixation system. A stiffer fixation (Figure 2f) reduces bone ingrowth, while a more flexible one (Figure 2d) promotes it.

In conclusion, we used computer aided technology based on a mechano-driven bone regeneration model and finite element simulations to optimize and predict bone regeneration within different scaffold designs and different fixation systems for long bone large defects. Computer model predictions suggest that higher porous scaffolds with less rigid fixations are more favorable. Future studies should focus on the experimental validation of these findings so that they can be used for the optimization of scaffold design to support bone regeneration in long bone large defects.

References

Acknowledgements
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EFFECT OF PEDALLING WORKLOAD ON KNEE JOINT FORCES

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Introduction

The study of the effect of pedalling power in cycling dynamic is a widespread study in the literature. These works are usually constrained to the sagittal plane and analyse scalar variables such as ranges or maximum values. This approach can lead to loss of relevant information, regarding the 3D dynamics of the cyclist. Hence, the objective of this work is to analyse the effect of pedalling power on the 3D joint forces along the pedalling cycle using statistical parametric mapping (SPM)3.

Methodology

The dynamic of the lower body during pedalling was analysed in 10 participants at 3 different pedalling powers (P1=170 W, P2=250 W and P3=310 W). All of them were male, had no underlying pathologies and used the bicycle as a means of transport. To solve the inverse dynamic problem, the kinematic data were obtained from the marker protocol developed by Martín-Sosa1. The pedal reaction force was obtained from the measurement equipment developed by the authors2. The tests were performed on a commercial bicycle provided by the laboratory anchored to a training roller. The dynamic problem was solved by the bottom-up method using vector dynamics and the d’Alembert principle. To analyse the effect of pedalling power on knee joint forces, a one-factor (pedalling power) statistical study with three levels (P1, P2 and P3) was carried out. The dependent variables in this study were the temporal evolution of knee joint forces. First, a MANOVA analysis was performed. If significant results were obtained (p<0.05), a one-way ANOVA analysis was performed for each variable. For those variables with significant results, a post-hoc study based on a two-tailed Student’s t-test was performed. Finally, the effect size (Cohen’s D) was calculated, defining a large effect size for a d value > 0.8, similar to that used by other authors4.

Results and Discussion

A MANOVA analysis was performed on the joint forces and significant differences were obtained. The subsequent ANOVA analysis for each force indicated that the forces in the Cranio-Caudal (CC) and Antero-Posterior (AP) directions of the 3 joints combined with the force in the Lateral-Medial (LM) direction of the knee showed significant differences due to the use of different pedalling powers. The paired study showed significant differences in all the above force components for all 3 comparisons except for the knee AP direction force (P1-P3 and P2-P3), figure 1. In this figure the intervals in which differences occur in the AP direction are contained in the recovery phase and close to the bottom dead centre (BDC). This component has its main source in the pedal movement. The differences may be related to the fact that as power increases, participants switch from exerting forces that were opposing the pedal movement to applying forces to favour the pedal movement. In the CC direction, once the BDC is passed, the joint force tends to be positive. This behaviour may be because in the first instants of the recovery phase the lower body tractions to pull the pedal. In this case, the increase in pedalling power causes the participants to exert a greater pull on the pedal to optimise the cycling effort. The LM force component of the knee joint force is mostly located at the top dead centre (TDC) and BDC. This behaviour may be caused by a lack of control of the lower body movement in this direction.

All intervals with significant differences between pedalling powers showed a Cohen’s D greater than 0.8. The use of the SPM can be a very useful tool to analyse different cases in the field of cycling biomechanics.

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Acknowledgements

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Introduction

In vivo, epithelial tissues are continuously in contact with the external environment [1]. For mimicking such condition in vitro, the air-liquid interface (ALI) approach is widely adopted [2]. Traditionally, ALI is obtained by using a transwell (with a semipermeable membrane) inserted in a well, in order to separate the liquid and the air compartments [3]. However, such static culture condition does not mimic the nutrient and gas transport provided by the native microvasculature and can lead to gradient formation. To overcome this limitation, culture medium recirculation can be adopted, knowing that it is crucial to avoid bubble formation and stagnation under the ALI, to prevent sample drying. Here, we developed a biomimetic bioreactor for ALI culture with recirculating culture medium, to be used for skin tissue engineering investigations.

Materials and methods

In detail, the bioreactor was designed for: 1) guaranteeing ALI culture; 2) allowing culture medium recirculation; 3) ensuring a continuous nutrient and oxygen transport across the ALI while avoiding air bubble stagnation under it; 4) being easy-to-use with conventional lab equipment. To fulfill these requirements, the bioreactor is composed of: 1) a culture chamber (CC) for housing a commercial transwell, used for separating the liquid and the air compartments; 2) a recirculation circuit for continuous culture medium flow. In detail, the CC (diameter = 37 mm, height = 24 mm) was designed (Solidworks) and manufactured by multijet printing (VisiJet M2S-HT250, ProJet MJP 2500 Plus, 3D Systems), and it consists of a lid and a cylindrical base with barbed inlet and outlet ports for tubing (inner diameter = 1 mm) connection (Fig.1A). The CC is part of a closed-loop recirculation circuit based on a multi-channel peristaltic pump (Ismatec), a medium reservoir, oxygen-permeable tubing (platinum-cured silicone tubing, Darwin microfluidics) and luer lock connectors (Fig. 1B). With the inlet and the outlet tubing both mounted on a pump cassette, the recirculation circuit ensures a constant volume of culture medium inside the CC with a controlled free liquid surface. Stationary computational fluid dynamic (CFD) simulations (COMSOL Multiphysics) were performed for supporting the optimization of the CC geometry. The CC was modeled with 3 domains (Fig. 1C) imposing inlet and outlet flow rates in the range 0.1-0.5 mL/min, for guaranteeing capillary-like flow velocity values within the CC [4]. Finally, performance tests were carried out in-house using demineralized water and testing different flow rates (0.1-0.5 mL/min) for 2 days for assessing the reliability of the bioreactor and possible air bubble stagnation.

Results

The CFD results showed that the flow streamlines follow the internal geometry of the culture chamber and flow tangential to the transwell membrane, avoiding recirculation regions (Fig. 1D). Preliminary in-house tests confirmed the bioreactor ease of assembling and use and its reliability. In particular, it was assessed that a constant volume of culture medium was maintained and, in case of air bubble presence, these were easily expelled within the CC at the free liquid surface before reaching the transwell membrane.

Conclusion

A biomimetic bioreactor providing ALI culture with recirculating culture medium was developed. Performance tests confirmed its ease of use, reliability, and the absence of air bubble stagnation under the transwell membrane. Biological tests with 3D models of skin, based on cell-seeded gelatin-methacryloyl (GelMA) hydrogels are ongoing. The constructs will be mechanically characterized by nanoindentation and compared with human skin tissue samples.

References

WEB.AM: WRIST EXPERIMENTAL AND BIOMECHANICAL ANALYTICAL MODEL

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Introduction

The stability and precision of wrist movement rely on mechanical interactions of the carpal bones [1], and damaged ligament(s) could alter their mechanical behaviour. However, although wrist injuries are common worldwide, there is still lack of 3-dimensional (3D) quantitative clinical tool to analyze these changes due to the wrist complex structure.

This research aims to develop a novel biomechanical wrist model, WEB.AM (Wrist Experimental & Biomechanical Analytical Model) for wrist kinematic analysis. We hypothesized that different wrist positions and conditions would display distinct web-like network patterns, which in turn, could address the complex challenges.

Methods

3D models from 5 cadaveric wrist were reconstructed using Mimics (Materialise NV, Belgium) from Computed Tomography (CT) images acquired at 11 different wrist positions: Neutral, 15°, 30° and 40° of Flexion and Extension, 5° and 10° of Radial Deviation, and 10° and 20° of Ulnar Deviation, using a custom-made jig (Figure 1).

The WEB.AM analysis program was developed using Matlab (Mathworks Inc, USA). An illustration of the network model is shown in Figure 2.

![Figure 1: Cadaveric wrist at 40° extension](image1)

The networks were compared and analyzed based on the changes between the network threads (e.g. Radius-Distal Scaphoid thread [DT1] and Distal Scaphoid – Capitate thread [DT2]).

Results

The networks between scaphoid, lunate and capitate at different wrist positions displayed distinct patterns. An example of the correlation between the networks of wrist neutral and flexion, with respect to R1 (length between distal radius and styloid process), has shown the following relations:

**With respect to R1**

Wrist at Neutral:
- DT1\_neu = 1.26 R1
- DT2\_neu = 1.70 DT1\_neu
- DT3\_neu = 0.4 DT1\_neu

**With respect to DT1\_neu and PT1\_neu**

Wrist at 30° Flexion:
- DT1\_flex = 1.11 DT1\_neu
- DT2\_flex = 1.11 DT2\_neu
- DT3\_flex = 1.31 DT3\_neu

References


Acknowledgements

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This work was supported by Singapore Ministry of Education (MOE) Academic Research Fund (AcRF) Tier 1 grant.
CFD-BASED SYNTHETIC DATA GENERATION FOR MACHINE LEARNING BASED PRESSURE DROP ASSESSMENT IN AORTIC STENOSIS

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Introduction

Aortic stenosis occurs when the aortic valve does not fully open during systole, which reduces and partially blocks blood flow to the systemic circulation. The type of treatment depends on the functional severity of the stenosis, which is assessed based on the trans-valvular peak pressure drop. Clinically, the pressure drop is routinely estimated analytically, which may lead to sub-optimal results since certain hemodynamic aspects are not fully captured (pressure recovery, turbulence) [1]. A promising solution is based on the use of a machine learning (ML) model to estimate the pressure drop based on patient-specific characteristics. Although an ML-based solution could provide the desired results in real-time, training an accurate model requires a large database of invasively measured pressure drops, which is difficult and costly to set up.

Methods

Our approach is to train the ML model with ground truth values computed using a high-fidelity computational fluid dynamics (CFD) model. The first step is to create a parameterizable anatomical model of the aortic valve. A large number of meshes is then generated based on this anatomical model. The difference between inlet and outlet pressure is calculated after performing simulations for various aorta and valve dimensions, and inlet flow values, all set based on population level characteristics. Thus, a dataset that maps valve and blood flow characteristics to pressure drop is obtained. The open-source CFD software OpenFOAM was employed for the dataset generation.

Results

A preliminary dataset of 105 cases was generated, with each sample containing different combinations for the adjustable parameters. These parameters are the vessel diameter (D), the average velocity of blood flow (U) and the percentage area reduction (Ar). A constraint was added to the sampling process to guarantee that the chosen combinations were realistic from a physiological standpoint: the blood flow at the inlet must be at least 50ml/s and not exceed 650ml/s [1]. For each case, a steady-state simulation corresponding to peak systole was run. The mean absolute difference between the predicted pressure drop and the analytically-derived value was computed to validate the results. The mean difference of 3.99 mmHg suggests that the blood flow characteristics are successfully captured during the simulations. As expected, the largest differences are obtained for cases with higher area reduction, when the circular area assumed in the formula does not apply to the actual geometry.

![Figure 1: Velocity ParaView visualization.](image)

Figure 1: Velocity ParaView visualization.

The correlation matrix computed for the dataset indicates that the blood velocity parameter appears to have the most significant impact on the pressure drop. This information is vital when optimizing the sampling process, leading to a synthetic dataset that closely matches the distribution of real-life data.

![Figure 2: Correlation matrix of the generated dataset.](image)

Figure 2: Correlation matrix of the generated dataset.

Discussion

Synthetic datasets are often used as an alternative to real-world data in machine learning applications. Medical data can be costly to obtain and sometimes require invasive procedures to be performed, making the generation of synthetic data an appealing alternative. By using the approach detailed herein, large datasets can be generated, enabling ML model training for pressure drop estimation in aortic stenosis.

References


Acknowledgements

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DETERMINING THE EFFECTS OF STRAIN RATE ON UNIAXIAL TENSILE BEHAVIOR OF SINGLE CURLY FIBER

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Mechanical Properties of single curly hair

The elastic modulus and the maximum strength of the single curly fiber is of the interest in cosmetic industry to study the integrity of the hair fiber. The challenge arises with the mechanical and geometric profile variations of these fibers collected from one donor. In this study, the tensile tests were conducted under different strain-rate at room temperature to study determine the variation in the elastic modulus and maximum stress of the single curly hair.

Background

Curly hair fibers are acknowledged to be fragile to mechanical stress compared to straight and wavy fibers[1]. This type of hair possesses the cross-sectional area with twists and bends with narrowed cross-sectional area along the fiber [2]. This can create the weak spots because when excessive force is applied [3] it can create high stress point over the small area of the fiber. These type of hair fibers are found amongst African population, and they received few attentions[4]. The studies across the cosmetic literature for hair fibers on the strength and elasticity are associated with the mechanical and chemical treatment[5]. The cosmetic industry may in turn look deeper in understating the behavior of curly hair to enable the market to perform specialized treatments for curly type hair only. This study focuses on the effect of strain-rate under dry condition at room temperature. Mechanical behavior of hair is critical in expanding knowledge that contributes cosmetic industry.

Recent Advances

Understanding the behaviour of curly hair to enable the market to perform specialized treatments for curly type hair only. The mathematical modelling of experimental data has been generated from the experimental results.

Future directions

The experimental results of this work will be used to estimate the material parameter of curly hair fiber which can then be used in 3D numerical modeling.

References


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Introduction
To visualize forces at the molecular level, several tension sensors have been developed using Förster resonance energy transfer (FRET) and applied in cultured cells [1-2]. However, it is very difficult to introduce these sensors in tissues. Recently, Tao et al. [3] developed transgenic mice expressing a tension sensor to visualize forces at the tissue level. Their used a high-cost FLIM (Fluorescence Lifetime Imaging) system to measure FRET and have not reported change in FRET in tissues with conventional CLSM (confocal laser scanning microscope). Furthermore, the fluorescent protein pair adopted in their sensor cannot be observed with widely-used 488 nm laser system. In a previous study, we developed a tension sensor by inserting a FRET cassette ssFRET-GR into actinin [4]. The FRET cassette is made of two fluorescent proteins EGFP and mCherry connected with spider silk protein. This sensor is bright enough and the tension applied to it can be evaluated with a FRET ratio that is the ratio of acceptor (mCherry) to donor (EGFP) fluorescence using a conventional 488 nm CLSM system. In this study, we introduced the gene of this sensor into the C57BL/6N mice to obtain mice expressing the tension sensor.

Methods
We introduced the gene of our actinin tension sensor engineered with the Cre/loxP system into the ROSA26 locus of the C57BL/6N mice, and crossbred them with Cre mice to obtain mice expressing the tension sensor. We excised various tissues, including the aorta and tendon, and isolated cells from each tissue with enzymes. The isolated tissues and cells were stretched with a tensile tester (STB 150W NK, Strex, Japan) under a conventional CLSM (LSM880, Carl Zeiss, Germany) with a 63× oil immersion objective at room temperature in phosphate buffered saline (PBS). The fluorescence of EGFP and mCherry was obtained under the excitation with a 488 nm wavelength laser at each stretch step to calculate the FRET ratio.

Results
The fluorescence was so bright that the change in the FRET ratio was observable with a general confocal microscope (Figure 1). We performed tensile tests of aortic tissues and confirmed that the FRET ratio decreased in response to stretch as expected (Figure 2). Interestingly, the decrease in the normalized FRET ratio was ~10% at 10% stretch for aortic tissues and tendons, while that of smooth muscle cells (SMCs) isolated from aortic tissue was ~20% at 10% stretch.

Discussion
It has been reported that strain in actin stress fibers in SMCs in the direction of the fiber axis was half of the strain in the smooth muscle layers in the circumferential direction of the aorta [5]. The relatively low FRET ratio change in aortic tissues than SMCs observed in this study may support this observation. The present FRET mice may become a powerful tool in the mechanobiology of cells and tissues.

References

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USE OF AGAR SAMPLES TO MIMIC THE ELECTROMECHANICAL PROPERTIES OF HUMAN BURN SKIN

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Introduction

Burn-related injuries account for 300000 deaths per year [1]. The complications related to burn injuries are hard to predict depending on the burn depth degree. The accuracy of a clinical assessment of a burn wound has been estimated between 50% and 80% [2]. Adequate identification of burn depth is essential to choose appropriate treatments. The electromechanical coupling within soft biological tissues appears to be a promising physical phenomenon for such discrimination [3]. Before clinical investigations, it is of major interest to find a substitute mimicking the electromechanical response of burn skin to validate this assumption. The aim of the present study is to test agar gel as a handy candidate especially for its easy tuning [4].

Methods

Standard compression tests have first been performed with a universal tensile machine (Zwicky0.5) equipped with a 10N load cell on 8mm diameters agar cylinders to assess its mechanical properties. Then indentation test has been conducted for the electromechanical experiments as it is a sound in-vivo technique [5]. Two contacts are required for electrical assessments, so a double spherical indenter has been developed to avoid stress concentration at contact edges. Electromechanical response has been measured in term of force and electrical resistance as function of displacement using the same tensile machine as for the mechanical tests. 6mm diameter spherical indenters were driven with a 0.01mm/s velocity to satisfy quasi-static conditions and reduce viscous effects.

Results

Mechanical response of Agar gel obtained through the standard compression was consistent with the literature [2, 4]. The electrical resistance R appeared to have an exponential shape with respect to the indentation depth x, as presented in Fig 1a over 9 tests. Its behavior has been fitted with the following equation:

$$ R = A e^{x/B} + C $$  \hspace{1cm} (1)

This equation led to an estimation of the average final resistance of $C = 14.93 \pm 2.71 k\Omega$ for a characteristic displacement of $B = 0.39 \pm 0.05 mm$ and a variation of resistance $A = 52.35 \pm 11.65 k\Omega$. The measurements were performed counter clockwise as it appears on Fig 1b. The value of $C$ increased as function of time translating a water loss.

Discussion

While presenting an asymptotic behavior, the electrical resistance was depth and time dependent, pointing out consistent values as well as dehydration effect. Then, the characteristic depth $B$ implies a 1.95mm displacement to reach a steady regime. Agar biphasic composition could allow reproducing the burn wound deprived of stratum corneum protection as this latter provides resistance up to $M\Omega$. Current investigations are aiming to explore on electrical properties tuning. Meanwhile, techniques are developed to measure in vivo the electrical response in burn wounds.

References

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Acknowledgements

This work was supported by the Lorraine University of Excellence interdisciplinary grant and the CHR grant respectively from the Lorraine University and the CHR Metz-Thionville.
MUSCLE FUNCTION AFTER MODIFIED SURGICAL TREATMENT OF COMPLETE HAMSTRING AVULSIONS IN AN ELDERLY POPULATION

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Introduction
The literature suggests an operative refixation of the ruptured tendons after complete hamstring avulsion onto the anatomical origin of the ischial tuberosity [1]. A modified surgical technique uses a refixation more proximally and laterally [2] to address an often reported postoperative complaint of pain in sitting [3]. The aim of this study was to determine hamstring muscle function after this modified surgical technique by assessing side-to-side differences in muscle strength and activation patterns during overground walking.

Methods
Thirteen patients (8 female, 5 males) with a median age of 64.2 (range, 52.1–80.4) years were followed up at a median of 46.2 (range, 11.2–75.0) months after surgery. Maximal isokinetic muscle strength of knee flexors (work [J/kg]) and the hamstrings to quadriceps (H:Q) ratio [4] was measured bilaterally using a dynamometer (60°/s, 240°/s). Muscle activation (Root Mean Square (RMS) [%MVC]) of vastus lateralis (VL) and medialis (VM), semitendinosus (ST) and biceps femoris (BF) as well as coactivation indices (CI) (VM-ST; VL-BF) [5] were analyzed for the stance phase. Statistical differences between the injured and non-injured leg were calculated using paired t-test (α<0.05).

Results
Total work for the knee flexors (0.92 vs. 1.00 J/kg (60°/s); 0.48 vs. 0.52 J/kg (240°/s)) were comparable between the injured and non-injured leg (p>0.05). H:Q did not differ between sides (p>0.05) (Fig. 1). There were no significant side-to-side differences in RMS and CI during walking in any of the muscles (Figs. 2 and 3).

Discussion
The comparable results between sides demonstrate that both muscle strength and muscle activity can be restored with this modified surgical technique. While the strength ratios of the thigh are within the normal range of a comparable healthy population [6], coactivation tends to be higher compared to healthy elderly [7]. The latter may represent a compensatory mechanism for improving stability. The promising functional results shown here represent evidence that the modified surgical technique appears to be a good alternative to conventional methods.

References
ON THE MECHANOME OF HUMAN SKIN

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Introduction
We aim at a mechanical characterization of human skin at tissue and cell length scales. Skin provides sufficient compliance to enable body movements but it also forms a mechanically stable barrier against external loads. At cell length scale, the mechanical properties of the extracellular matrix (ECM) determine its “mechanome” [1], influencing cells, e.g. during skin repair or growth.

Methods
Experimental characterization included ex-vivo multiaxial tensile tests, micro- and nano-indentation, in-vivo suction measurements and 3D tissue imaging. Observations were rationalized using a multi-layer poroelastic continuum model [2]. Each skin layer is represented as a bi-phasic material, with the solid part characterized by a fiber network and a compressible matrix, while interstitial fluid flows according to gradients of the chemical potential, as resulting from the fixed charge distribution in the tissue [3, 4].

In order to represent the transition between micro- and macroscale we used a hybrid discrete-continuum model representative of the heterogeneous microstructure of skin. Fibers are modeled as nonlinear elastic connectors. Multi-phasic continuum elements provide a representation of interstitial fluid, proteoglycans, anions, cations and other non-collagenous ECM components.

Results
The mechanical response in tensile tests indicates an average stiffness akin to a Young’s modulus of about 100 kPa, while local indentation leads to a stiffness of few kPa. Model parameters were selected to provide a reasonable fit for experimental data at macro- and micro-scales. The resulting multiscale model representation of skin allows investigating the relationship between tissue microstructure and its deformation and fracture properties.

Moreover, simulation of skin stretch in-vivo provides quantitative information on the associated changes in cues of the “mechanome”, which can affect biological processes. Specifically: (i) mean values of cell perceived forces at focal adhesions increase from 25 nN to more than 100 nN for an in-plane stretch of $\lambda = 1.1$; (ii) such physiologic deformations lead to significant displacement of the interstitial fluid, linked with gradients of its chemical potential. Corresponding average fluid velocities increase by several $\mu$m/sec; (iii) resident cells are also exposed to changes in hydrostatic pressure and osmotic pressure of more than 80 kPa and 10 kPa respectively (Figure 1).

Discussion
Mechanotransduction mainly considers changes of ECM stiffness as well as cell deformation as relevant cues associated with skin stretch. Our results demonstrated the existence of a rich set of physical signals that vary with in-plane tissue loading, constituting the mechanome of human skin. Future studies will focus on the direct measurement of these quantities, on the analysis of the biological processes that they activate, and on possible implications for improving our understanding of skin fibrosis and optimizing mechanotherapies.

References

Acknowledgements
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VORTICITY TRANSPORT-BASED ANALYSIS OF THE ABDOMINAL AORTIC ANEURISM HEMODYNAMICS

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Introduction

The Abdominal Aortic Aneurysm (AAA) is a vascular disease characterized by an unphysiological bulging of the abdominal aortic lumen. It has been recognized that local hemodynamics contribute to AAA progression because of its crucial role in transport of biochemicals and interaction with the wall [1]. In this context, a multitude of hemodynamic quantities has been proposed to provide biomechanical markers of disease evolution. However, these proposed quantities turned out to be only moderately associated with AAA progression, suggesting that a different perspective to decipher AAA flow complexity is needed. In this scenario, we propose a thorough characterization of the complex vortex structures produced and transported in the AAA, aiming at identifying vorticity-based quantities to be tested as potential markers and predictors of AAA evolution.

Methods

The geometry of eight AAAs was reconstructed from CT-scan data using PRAEVAorta (https://www.nurea-soft.com) [2]. The governing equations of fluid motion were numerically solved using the finite element open-source code SimVascular [3]. The AAA velocity data were used to compute the vorticity transport equation:

\[
\frac{D \omega}{Dt} = (\omega \cdot \nabla)u + \nu \Delta \omega
\]

where \(u\) is the velocity, \(\omega\) is the vorticity and \(\nu\) is the kinematic viscosity. The material derivative of the vorticity is given by the contribution of a stretching term (first term on the right side), quantifying the vortex lengthening due to velocity gradients, and of a term quantifying vorticity diffusion due to viscosity (second term on the right side). Moreover, the local swirling strength, quantified by the absolute value of the imaginary part of the complex eigenvalue of the velocity gradient tensor, was here analyzed to reconstruct the vortex dynamics.

Results

Volumetric maps at mid-deceleration point and time-histories of the volume-average value of the swirling strength and of the stretching term in eq. (1) are presented in Figure 1A, B for three explanatory models (AAAI presents a quasi-physiological blood flow canalization, AAAll is characterized by two consecutive expansions and AAAlll presents a marked expansion). A pressure-gradient mechanism induces the formation of a well-defined vortex ring in AAAll and AAAlll, as the inflow jet enters the AAA expansion region. Subsequently, it undergoes stretching and tilting, as confirmed by second peak of time-histories. The vortex ring dynamics along the systolic deceleration phase is analyzed in Figure 1C for AAAll and AAAlll by visualizing local swirling strength isosurfaces and vortex core lines. Contrarily to AAAll and AAAlll, the inflow jet does not roll up into a vortex ring in model AAAlll, because of its quasi-physiological geometry.

Discussion

Here a vorticity transport-based analysis is proposed on computational hemodynamics models of AAA, aiming at describing complex vortex structures hidden in the AAA hemodynamic richness. These structures are expected to be involved in intraluminal thrombus formation, inflammatory mechanisms, and platelets dynamics [4]. The presented approach might represent a useful tool for elucidating the link between intravascular blood flow patterns and clinical observations.

References

A MULTI SOURCE STATISTICAL SHAPE ANALYSIS FRAMEWORK FOR COMPLEX CARDIOVASCULAR STRUCTURES

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Introduction
Tomographic clinical datasets such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) provide fundamental information regarding diagnosis and treatment management. However, in clinical practice, anatomical analyses are carried out via simple morphometric parameters measured in 2D. Statistical shape modelling (SSM) provides a powerful tool for describing and analysing shape complexity. In the context of cardiovascular districts, several studies have been presented [1], mainly applied to the aorta. However, they present several limitations since they do not include the whole complexity of the thoracic aortic tract, excluding the supra-aortic vessels from analysis. In order to overcome this limitation, we developed a non-rigid registration algorithm. The purpose of this work was to demonstrate the power of this innovative algorithm by applying it to a different cardiac district, the pulmonary artery.

Methods
A total of 21 segmented pulmonary arteries and 28 aortas were considered, originated from MRI and CT images, respectively. All the pulmonary arteries were affected by Tetralogy of Fallot. The dataset of thoracic aortas included both healthy and aneurysmatic vessels. All the datasets were segmented in 3D-Slicer by using a region-growing algorithm. The segmented geometries were used to develop the SSM, where a template geometry has to be registered on all the other target geometries of the dataset. Starting from previous work [2], we developed an in-house algorithm for non-rigid registration based on (i) a modified gradient descent approach of the second order, (ii) a loss function based on the minimization of chamfer distance and (iii) four steps of remeshing. First of all, we carried out a rough preliminary non-rigid registration. Then, we built a new template as the mean shape of the registered meshes. This template was used to achieve a final, finer and more accurate non-rigid registration on all the target meshes, even on those where the initial registration was not correct. The second step was the use of PCA to achieve dimensionality reduction of the problem to few meaningful features that accurately represented individual characteristics in terms of size, curvature, orientation and so on. The results of our code were also compared with those obtained using the most widely used software in the literature for the non-rigid registration, such as Deformetrica and Gias2.

Results
It can be observed that, even though most of the target geometries presented very peculiar shapes, different from the one of the source mesh, excellent registration results were obtained by applying the proposed novel algorithm, as reported in Figure 1. The first 15 principal components (or modes), significant for more than 98% of the total variance, were used to reconstruct new geometries varying the first modes from -2 to +2 standard deviation. By varying the first mode, a progression in the shape from a short, straight and corrugated to a long and curved pulmonary artery was observed; meanwhile, for the thoracic aortas it was noticed a progression from healthy to completely aneurysmatic aorta. All these results were in perfect agreement with the composition of our initial datasets. Moreover, a significant improvement was detected with our code in comparison with the software available in literature through which most of the registrations failed.

Discussion
In this work we wanted to highlight the power and the versatility of our innovative algorithm. In fact, the presented algorithm was able to provide excellent non-rigid registration results not only over widely different geometries but also between different cardiovascular districts.

References
Introduction

Biomechanics and Robotics are synergistic disciplines. Soft Robotics is closing the gap between the two by using compliant materials and new technologies [1,4] and may provide avenues to explore biomechanical principles in relatively simpler engineering systems. Lateral deformation of the aponeurosis during muscular contraction has been shown to affect the stiffness response of the aponeurosis and possibly connected tendons, imbuing them with variable stiffness (VS)[2,3]. In Robotics, VS is a desired actuation feature allowing transient and controllable dynamics responses which can facilitate adaptivity to novel interactions [5]. Robotic VS mechanisms, while efficacious, can be complex and heavy, with large form factors [6,7]. We use silicone elements to mimic tendon/aponeurosis and provide static lateral displacement to mimic transverse loading to inform relatively minimalist VS mechanisms in robotic locomotion and provide insight into the biomechanical principles. We investigate the impact of varying lateral displacement and the length of the region laterally loaded on the force-displacement response of the element under tensile loads.

Methods

Silicone elements of shore hardness 40 (Cure on Mold Max 40) are molded with geometry: 100mm x 20mm x 4mm. L is the length of the tendon 100mm. Each element has tabs on either side of its width of length, l, that can be clamped and displaced using a continuous stretching mechanism. We vary lateral displacement, d, from 0 – 15mm in 5mm increments and load the element in longitudinal tension with a mechanical testing machine (Instron 3344) to 75% strain of the reference configuration, measuring longitudinal force production, F_{lo}.

Results

Our data shows decreasing force production observed for increasing d (Fig.1, Table.1). The low strain, “toe” region was largely unaffected by the lateral deformation, with changes seen at higher strains. The reference stiffness is increased with a larger l and the effect of lateral displacement on stiffness is also enhanced.

Discussion

In biological literature, the measurements are made on or very close to the aponeurosis and show a stiffness increase with d [4,5]. Future work will look to isolate the aponeurosis region to understand further our observations. In comparison to biological tendon/aponeurosis tissue, with high anisotropy and multi scale dynamics, silicone is isotropic and relatively simple. This may have a large effect on the impact of lateral loading. In conclusion, our data suggest that laterally loading silicone elements may be useful for variable stiffness in robotics, but indicate an inverse trend in this change when compared to biological analogs.

Figure and Tables

Figure 1: The maximum F_{lo} developed for each l/L tested. There is an overall increase in force, indicative of increasing stiffness and as d is increased this maximum force is lowered.

<table>
<thead>
<tr>
<th>l/L</th>
<th>F_{max}(d = 0mm)</th>
<th>F_{max}(d = 15mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>60.5464 N</td>
<td>55.8956 N</td>
</tr>
<tr>
<td>30%</td>
<td>57.9772 N</td>
<td>48.7578 N</td>
</tr>
<tr>
<td>20%</td>
<td>48.2521 N</td>
<td>45.2853 N</td>
</tr>
<tr>
<td>10%</td>
<td>48.8686 N</td>
<td>47.3551 N</td>
</tr>
</tbody>
</table>

Table 1: Variations in maximum force production (at 75% longitudinal strain) for tested l/L ratios at the two extremes of lateral displacement.

References

MECHANICAL CHARACTERISATION OF LOWER LIMB VASCULATURE IN DETERMINING AUTOGRAFT SUITABILITY FOR PERIPHERAL ARTERIAL DISEASE BYPASS SURGERIES

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Introduction

The estimated prevalence of peripheral arterial disease (PAD) is over 240 million people globally [1]. PAD is caused by atherosclerosis resulting in a narrowing of the arterial lumen. In advanced cases, this restricts blood flow, leading to a number of complications for the patient such as reduced or limited mobility, pain, tissue loss and ulceration, and possibly gangrene. A bypass graft may be required to restore blood flow [2, 3]. While other graft choices available, such as xenografts (bovine pericardium) and synthetic grafts (PTFE & Dacron), the use of autografts (venous conduit) remain the gold standard. However, depending on the extent of PAD, an arterial conduit may not be an option. Veins such as the great saphenous vein (GSV) are often used alternatively as optimal venous conduits. Unfortunately, approximately 40% of patients do not have the required length or lumen diameter of GSV available [4]. For example, if varicose veins are present within the vein it will not be used as a graft, despite a lack of studies determining the suitability of varicose veins as a graft option. This study aims to mechanically and structurally characterise lower limb vasculature to determine the suitability as a bypass graft option.

Methods

Human GSV and varicose veins (VV) and healthy margins (HM) were sourced from the University Hospital Limerick, Ireland. To prepare the tissue for microscale mechanical testing, transverse sections of the embedded fresh human tissue were sectioned to 400 μm thickness with liquid agarose and gelatin in a petri dish. The tissue was kept hydrated in 1X PBS at 4 °C before microscale testing to maintain tissue viability [5]. The Chiaro Nanoindenter was used to perform the microscale mechanical testing in this study (Figure 1). The displacement was detected by the optical fibre in the probe. The resulting load displacement graph is used to calculate the effective elastic modulus (Eeff) from the loading curve using the Hertz Contact Model. An automated 5x5 matrix scan, in 100 μm increments, was performed which provided a surface area heatmap of the Eeff (Figure 1).

Results

Preliminary results from this study are displayed in Figure 1. The data showed a significant difference between the Eeff of GSV 1.39[0.72-3.58] kPa and VV 0.09[0.04-0.27] kPa and between the Eeff of GSV 1.39[0.72-3.58] kPa and HM 0.42[0.22-1.18] kPa. No significance was observed between the VV 0.09[0.04-0.27] kPa and HM 0.42[0.22-1.18] kPa. Further, the Eeff heatmap generated during microscale testing demonstrates the heterogeneity of vascular at the microscale. This is an important observation to consider when determining the suitability of a vessel as a bypass graft.

Discussion

Initial results indicate that VV are not a suitable alternative for bypass grafts, although sparse, this is in keeping with current literature. However, biological heterogeneity within and between samples needs to be considered and further testing is required to develop bypass graft inclusion parameters for the optimal Eeff. Combining this micromechanical data with histological staining e.g. H&E would allow more robust tissue characterisation through visualisation of the microanatomy and tissue components like collagen and elastin which gives tissue its mechanical properties.

References

UTILISING A 3D FE MODEL TO ASSESS THE EFFECTS OF ANATOMY ON STRESS/STRAIN DISTRIBUTION IN OSSEOINTEGRATED IMPLANTS

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Introduction

Osseointegrated prostheses (OIP) for transfemoral amputees represent a solution to the array of complications caused by sockets. Bypassing the soft-tissues, loads are transferred directly through the musculoskeletal (MSK) system. Mechanical complications such as bone fracture, loosening, and implant failure represent a barrier to OIP success [1]; it is important to identify how the human anatomy affects the biomechanical profile of these OIPs so that clinicians can feel confident in their recommendations. The aim of the study is to assess the effects of gender and amputation length on stress/strain distribution across the bone-implant interface through utilisation of a 3D finite element (FE) model. The overarching goal is to improve patient outcomes by producing hypotheses on biomechanical failure to inform surgical intervention and implant design.

Methods

Four healthy adult CT scans (2 female) were used to generate 12 femur models of different lengths. Each bone was amputated at 30, 40 and 50% of the original lengths and the surgical procedure of implantation simulated to create bone-implant assemblies. The assemblies were meshed (minimum element size of 3mm) and material properties applied (using grey scale values for bone) forming 3D FE models. The femurs were subdivided into seven Gruen Zones (GZ) and fixed proximally. Representative loads [2] were applied to the distal face of the device in a static structural analysis with assumed full osseointegration contact. Data were cleaned and statistical analyses (p < 0.05) performed using non-parametric tests to understand the effects of anatomy on stress and strain distribution across the system.

Results

Median stresses and strains in the system were found to be similar amongst the different bone lengths (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Amputated Length</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Bone</td>
<td>EES</td>
<td>0.00306</td>
<td>0.00412</td>
</tr>
<tr>
<td></td>
<td>EVM</td>
<td>5.92</td>
<td>4.15</td>
</tr>
<tr>
<td>Implant</td>
<td>EES</td>
<td>0.00004</td>
<td>0.00005</td>
</tr>
<tr>
<td></td>
<td>EVM</td>
<td>4.72</td>
<td>5.67</td>
</tr>
<tr>
<td>Adapter</td>
<td>EES</td>
<td>0.00248</td>
<td>0.00179</td>
</tr>
<tr>
<td></td>
<td>EVM</td>
<td>2.70</td>
<td>2.63</td>
</tr>
</tbody>
</table>

Table 1: Summary data for median Equivalent Elastic Strain (EES) and Equivalent von Mises Stress (EVM) (MPa) for different amputation levels.

More detailed bone analysis, however, showed there were significantly different strains experienced in GZ3&5 (p = 0.022 and p = 0.029) and stresses in GZ4 (p = 0.018) (Figure 1). As femur length decreases, the implant is located higher up the medullary canal, closer to the increased proportion of trabecular bone that is less dense and more fragile than cortical bone. The results also showed a statistical difference (p = 0.004) between genders, with female bones experiencing higher strains (F:0.0068 and M:0.0002).

Discussion

This model facilitates quantification of stress and strain distribution, allowing predictions of mechanical complications associated with anatomical differences. Results indicate the importance of prescribed implant geometric specification in directing load transmission through the MSK system to optimise this stress/strain distribution and improve the probability of implant success.

References


Acknowledgements

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QCT-BASED COMPUTATIONAL BONE STRENGTH ASSESSMENT UPDATED WITH MRI-DERIVED ‘HIDDEN’ MICROPOROSITY

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Introduction
Microdamage accumulated by cyclic loading or single overloading events contributes to bone fragility through a reduction in stiffness and strength [1]. Quantitative computed tomography (QCT) based computational modelling fails to incorporate in vivo microdamage due to limited resolution. Magnetic resonance imaging (MRI) on the other hand, is sensitive to pathophysiological changes to adjacent bone marrow that is ‘hidden’ to clinical CT imaging. In the case of repetitive trauma, signal hyperintensity in fluid sensitive sequences is indicative of a stress response where edema, haemorrhage and hyperaemia are present alongside microdamage [2]. Here, we aim to quantify this signal hyperintensity and use it to derive a pre-existing damage variable that represents the underlying tissue damage prior to in silico overloading. This variable is incorporated into an existing nonlinear constitutive law to investigate its influence on material and whole bone stiffness and strength.

Methods
We use the equine athlete as a model for microdamage induced stress fracture where high-speed exercise induces subchondral microdamage. The distal metacarpals (MC3) from n=5 Thoroughbred racehorses were scanned by clinical QCT (0.3 mm voxel size), calibrated to bone mineral density (BMD) and converted to bone volume fraction (BV/TV). MR images (T1w, STIR) were acquired at 3T (0.3 mm voxel size) and registered to the QCT data. Regions of ‘dense’ or ‘sclerotic’ subchondral bone, where microdamage coalesces [3], were segmented from T1w images (Fig 1a). A patch-based similarity method [4] was used to generate pseudoCT (pCT) images from the STIR images away from the dense subchondral bone in healthy tissue (Fig 1a). A relative increase in STIR intensity in the dense bone region returned a lower pCT-derived BMD than the QCT (Fig 1a). Such signal reflects the presence of underlying porosities such as microdamage and increased vasculature [2]. We derived a damage variable (D\text{pex}) from the difference of pCT and QCT BMD distributions. Voxel based FE meshes were generated and equipped with an isotropic BV/TV-dependent elastic-viscoplastic material model (UMAT, Abaqus v6.16) [5,6]. We update the material model to incorporate D\text{pex} [7] and we performed in silico compression of the MC3 condyles before (D\text{pex} = 0) and after (D\text{pex} > 0) such update to investigate its influence on whole bone mechanical properties.

Results
pCT BMD was lower in all MC3 bones. Incorporating D\text{pex} resulted in a median reduction of material stiffness and strength of 20.3% and 20.9% respectively (Fig 1c).

Neither MC3 size nor volume of sclerotic bone correlated with QCT-only whole bone stiffness and strength. D\text{pex} correlated with a reduction in whole bone stiffness (R^2 = 0.74) and strength (R^2 = 0.89) (Fig 1d).

Discussion
We propose a methodology for incorporating MRI signal hyperintensity into a QCT-based FE models. The QCT-only modelling provided limited insights into mechanical properties of the MC3 whereas the detection and inclusion of D\text{pex}, if corroborated by experimental findings, could provide a means to detect when microdamage accumulation overwhelms protective increases in bone mass induced by prolonged exercise. The results illustrate the complimentary value of multimodal imaging to potentially capture existing microdamage in vivo. As we use clinically available imaging techniques, our results may aid research beyond the equine model on fracture risk assessment in human diseases such as osteoarthritis and bone cancers.

References

Acknowledgements
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MICROMECHANICAL CHARACTERISATION OF OSTEOARTHRITIC SUBCHONDRAL BONE BY MICROPILLAR COMPRESSION

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Introduction
Osteoarthritis (OA) is a multifaceted joint disease primarily characterised by the degeneration of articular cartilage. The clinical manifestation is one of pain and loss of mobility [1]. The heterogeneous pathophysiology of OA limits the efficacy of pharmacological and non-surgical interventions. To improve clinical outcomes, further insight into the complex pathogenesis of OA is required. Aside from cartilaginous changes, subchondral bone alterations are both a cause and effect of OA progression [2]. While the macrostructural alterations such as sclerosis and bone plate thickening are well documented, few studies have investigated the microscale mechanical properties of the underlying constituent tissue. Our aim was therefore to investigate whether microscale non-linear mechanical and compositional properties of OA subchondral bone differ from healthy bone.

Methods
Bone specimens from the distal tibia of 3 cadaveric donors (HC) and 2 arthroplasty patients (OA) were sectioned, embedded, and polished. A total of 227 micropillars were extracted via picosecond laser ablation by modifying our previous micromanufacturing protocol [3]. Micropillars (HC = 135; OA = 92) were extracted in arrays located in the subchondral bone plate (SCBP) and subjacent trabeculae (SCTB) (Figure 1a-b). Raman spectroscopy was performed following [4] and quantitative backscattered electron microscopy (FEI Quanta 650) were used to assess whether any relative differences in tissue composition could be explanatory of any differing mechanical properties [5]. Specimens were rehydrated for 24 h by submerging in Hank’s buffered saline solution and remained submerged throughout testing. Micropillars were compressed uniaxially to a depth of 15 µm with a cyclic profile of 1 µm loading followed by 0.25 µm unloading using a custom-made indenter (Alemnis AG). We used non-linear finite element analyses to back-calculate the elastic and strength properties from the load-displacement data of each micropillar as done previously [3].

Results
The micropillars exhibited average surface and base diameters of 32.2 µm and 93.3 µm, respectively. The average height was 143.1 µm and the average taper angle was 12.3°. Evaluation of the force-displacement curves shows that the pillar stiffness (K) and yield force (Fy) were significantly higher in the SCBP compared to the SCTB in the control sample, whereas the converse is realised in OA samples. The OA pillar stiffness and yield force is significantly higher than the HC in only the trabecular bone (Figure 2). Raman spectroscopy revealed no significant differences in the mineral to matrix ratio between pillar location or disease state (Figure 2).

Discussion
Results of our micropillar tests suggest that the morphological alterations to the subchondral bone that occur in progressive OA are accompanied by changes to the underlying tissue. This contrasts our Raman results which indicate no significant changes in the mineral to matrix ratio. Next steps focus on the analysis of other markers that may explain the increased strength observed in OA trabecular bone. The results we show here may help developing targeted therapies that prevent OA progression.

References
5. Kochetkova et al, JBMMB, 134:105405, 2022

Acknowledgements
This research is supported by EPSRC under Grant No. EP/P005756/1. The authors would like to thank the donors and their families.
Introduction

Mitravalve (MV) pathology is a growing cardiac epidemic, with mitral regurgitation alone leading to the degradation of physical function, quality of life and longevity for 24.5 million patients worldwide [1]. However, there is currently no large animal disease model of MV pathology that can test treatment devices, such as transcatheter MV replacement [2]. To address this, researchers use numerical predictive models, known as finite element analysis, to simulate a beating heart and predict cardiac deformation and fluid flow [3]. However, these models fail to account for morphological variation in the whole heart and MV due, in part, to a shortage of high-resolution 3D reconstructions of whole-aged human hearts. In this study, we present a methodology to use contrast-enhanced µCT to capture the geometry of aged cadaveric specimens ex-vivo and create a digital repository of aged human cardiac tissue. Using this repository, we can quantify the anatomic variation present in whole cardiac and MV of an aged cohort and in future, develop finite element models that can relate morphological variation to changes in cardiac biomechanics and fluid flow.

Methods

Using ex-vivo iodine-enhanced µCT, we determine how whole heart and MV gross morphology present in the geriatric heart (n=3). All samples originate from cadavers donated to the RCSI Anatomical Gift Program. Donors aged from 89-100 years at time of death (two male, one female). Whole cardiac tissue was harvested, immersed in 5% potassium triiodide (1:1) for 14 days [4], washed, then inflated with 4% w/w warm agar solution [4] to emulate end diastolic position. External agar was removed, and cardiac tissue was imaged in a µCT scanner (Nikon Metrology, USA) at 65-85µm (220kV, 130µA, 0.5mm copper filter, 1.42 fps). The µCT was then dissected, mounted with suture on a custom-made 3D-printed holder, and immersed in olive oil [5]. Explanted cardiac tissues were µCT imaged at 39-46µm (190kV, 130µA, 1 fps). All µCT data were then preprocessed using VG StudioMax (VolumeGraphics v3.0) and imported into 3D Slicer (v5.03, http://www.slicer.org). 3D reconstruction of whole ventricles and MV was completed using a combination of semi-automatic and manual segmentation. MVs were then anatomically registered against whole cardiac. All measurements were taken using 3D slicer digitally and no statistical analysis was conducted due to prohibitive sample sizes.

Results

Left ventricular (LV) segmentation (Figure 1) allowed for the measurement of LV volume and wall thickness (in triplicate) at both the apex and the lateral wall. LV wall thickness decreased relative to volume (volume D5<D9<D12), and apex ventricular wall thickness did not. µCT imaging of MV successfully facilitated high resolution (45-65µm) reconstruction of MV anatomy in end diastolic position (Figure 1). Morphological variation in MV annular area (area D5<D9<D12) was driven by variation in the anterior-posterior distance and was largest in specimen D12.

Discussion

Left ventricular wall thickness and MV annular diameters were within the values reported from in vivo echocardiographic measurements of elderly patients (11.1±3.3mm) [6] and healthy adults (annular area 70-120mm) [7], respectively. However, there are differences between individuals in all measurements taken. High-resolution MV models represent the most detailed human MV 3D reconstructions to date and display complex chordal attachment and varying valve leaflet thickness. Validation of intra-subject and covariate (LV and MV) morphological variation will necessitate imaging further samples. Using FE analysis, these 3D models will be used to study the mechanical implications of morphological variations to improve our understanding of MV mechanics in an aged cohort.

References

Introduction
The systematic review aims to identify and summarize the effects of foot orthoses on foot kinematics at the forefront, midfoot, and rearfoot.

Methods
Methods: The literature search was conducted following the inclusion criteria: (1) running or walking as the experience tasks, (2) three-dimensional kinematics were only included because the transverse alignment of the foot affects movement in the frontal plane in the two-dimensional analysis and exclusion criteria: (1) considering the foot to be a rigid part of the body, (2) those participants with neurological conditions, systemic diseases, or degenerative conditions were excluded from the study, (3) unpublished or non-peer reviewed articles was excluded, (4) studies on sensor insoles and vibration insoles were excluded. Three orthoses categories were categorized for data synthesis: (1) non-posted moulded, which customed or contouring the participants foot; (2) non-moulded posted, which flat orthoses without contouring, but with adding posting; (3) posted moulded that had customed-contouring and additional posting[1]. The Down and Black Quality Index in an adapted version to assess the methodological quality of each study.

Results
A total of 22 studies were included. Meta-analyses were not conducted due to comparisons were absence the same across orthosis design, foot posture, and gait. The significant differences that had a large effect size are described below. Forefoot: moulded posted orthoses effect the peak forefront eversion during walking (ES 1.14), posted orthoses decrease the dorsiflexion at heel contact at heel contact (ES 0.6) and effect the peak eversion during running (ES 0.58). Midfoot: In walking gait, moulded orthoses decrease the midfoot mean medial longitudinal arch (ES 0.43). Moulded orthoses and posted orthoses both increase the mean dorsiflexion (ES >0.4) and the mean abduction (ES >0.4). Rearfoot: In walking gait, moulded orthoses and posted orthoses both increase the mean rearfoot abduction (ES>0.04) and reduce the peak eversion (ES 0.63). Posted orthoses and moulded posted orthoses both increase the mean rearfoot plantarflexion (ES 0.47). In running gait, posted orthoses increase the rearfoot peak eversion (ES 0.4) and dorsiflexion at heel contact (ES 0.53).

Discussion
Molded posted orthoses are significantly effective in controlling forefront eversion. Forefoot kinematics in the frontal plane did not show significant results. Posted orthoses are more effective on the midfoot and rearfoot kinematics in all three planes. There are several limitations in data analysis of this study: as measurement of midfoot kinematics in the transverse plane is difficult, there was not sufficient data to analyze. Multi-segment running kinematics data are limited by the small number of studies included.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test gait</th>
<th>Intervention</th>
<th>Comparator</th>
<th>MD (95% CI)</th>
<th>ES</th>
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</thead>
<tbody>
<tr>
<td>Peak forefront eversion</td>
<td>W</td>
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<td>control</td>
<td>-1.4 (0.58 to 0.62)</td>
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</tr>
<tr>
<td>Postfoot DF at HC</td>
<td>R</td>
<td>arch posted (heel 6mm)</td>
<td>control</td>
<td>1.81 (1.24 to 5.98)</td>
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</tr>
<tr>
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<td>R</td>
<td>arch posted (heel 6mm)</td>
<td>control</td>
<td>1.86 (1.05 to 3.84)</td>
<td>0.85</td>
</tr>
<tr>
<td>Mean MLA</td>
<td>W</td>
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<td>control</td>
<td>1.55 (1.15 to 1.95)</td>
<td>0.42</td>
</tr>
<tr>
<td>Midfoot mean DF</td>
<td></td>
<td>moulded (medial)</td>
<td>control</td>
<td>1.02 (0.92 to 1.12)</td>
<td>0.85</td>
</tr>
<tr>
<td>Mean MLA</td>
<td></td>
<td>moulded (medial)</td>
<td>control</td>
<td>1.02 (0.92 to 1.12)</td>
<td>0.85</td>
</tr>
<tr>
<td>Mean abduction</td>
<td>R</td>
<td>moulded (medial)</td>
<td>control</td>
<td>1.02 (0.92 to 1.12)</td>
<td>0.85</td>
</tr>
<tr>
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<td>moulded (medial)</td>
<td>control</td>
<td>1.02 (0.92 to 1.12)</td>
<td>0.85</td>
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<tr>
<td>Mean rearfoot PF</td>
<td>W</td>
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<td>1.02 (0.92 to 1.12)</td>
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<tr>
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<td>arch posted (heel 6mm)</td>
<td>control</td>
<td>1.75 (1.29 to 4.08)</td>
<td>0.42</td>
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</tbody>
</table>

Table 1: The mean difference and effect size of the significant parameters.


References

Acknowledgements
We thank Ms Meng and her family for help in the study work and support.
EFFECT OF NEGLECTING PASSIVE SPINAL STRUCTURES ON ESTIMATED JOINT LOADS: A MUSCULOSKELETAL MODELLING STUDY
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Introduction

Accurate estimation of joint loading is of high significance to study the biomechanics of the spine. There are two musculoskeletal approaches typically used to determine these quantities: the forward-dynamics (FD) and the inverse-dynamics (ID) approach. While current ID models of the spine are becoming increasingly complex, they face the challenge of relying on accurate and comprehensive kinematic data, which most of the current motion capture technologies cannot provide for the spine. Furthermore, most ID spine models neglect the contribution of passive joint stiffness produced by ligaments and the intervertebral discs (IVDs). The major aim of this study was to quantitatively analyse the effect of individual passive structures (i.e., ligaments and IVDs) on the computed generalised net joint forces and torques in the spine using a combined FD and ID approach. A secondary aim of this study was to compare the model performance in two different musculoskeletal modelling environments (i.e., demoa and OpenSim).

Methods

The recently published generic baseline model [1], implemented in the demoa software environment [2,3], was used. The thoracolumbar spine model including six degrees of freedom intervertebral joints, a detailed musculature, intersegmental ligaments and IVDs, previously used in FD simulations of a forward flexion-extension movement [1], was transferred into the OpenSim modelling platform. Solutions for the equivalent modelling of individual structures (i.e., muscles, ligaments and IVDs) in OpenSim were found. Using the full kinematic description obtained from the FD simulations, systematic ID analysis was performed in a step-wise approach increasing the model complexity by adding individual biological structures to determine their individual impact on ID analysis results. Under consideration of identical geometry and soft tissue properties, the ID model kinematics and kinetics were cross-validated against FD simulation results using the in silico derived motion data.

Results

Inverse-kinematics and ID analysis was performed using the generic OpenSim spine model with and without the contribution of individual structures. The joint kinematics complied with the joint angles obtained in the FD simulation as a result of the prescribed motion.

Discussion

The novelty of this work comprises the capability to use a sophisticated generic spine model [1] across two different modelling environments exploiting the strength of each environment and musculoskeletal approach, e.g., the possibility to remove biological structures under the conservation of movement in the ID approach. Moreover, in a quantitative investigation, this study has shown that neglecting passive spinal structures leads to a significant overestimation of joint loading, and consequently muscle forces.

References

Introduction

As postoperative patellar complications are common, total knee arthroplasty aims to ensure proper patellar tracking. It depends on numerous parameters, as the size, the position and the orientation of the implants, and the balancing of ligaments. Computational simulations to estimate the kinematics and the knee contact forces after total knee replacement (TKR) have been extensively treated and numerous approaches can be found in the literature. However, experimental validations are often limited by the technological means available to the researchers and the need of compliance with ethical rules. For this reason, a knee testing rig offers an alternative solution for model validation. In this study, a leg workstation composed by 3D printed bones and real implants, and equipped with motion and force sensors, was adapted for experimental validation of the simulated patellar tracking with an in-house developed library.

Methods

A leg workstation for surgeon training (Mita®) with 3D printed tibia and femur was used in this work (Figure 1a). Bone geometries were reconstructed from preoperative CT scans, which allowed the virtual application of TKR implant geometries, so that the resulting cut bones were printed. Microport® tibia and femur implants were placed on the respective bones. A patellar prosthetic button was attached to a pressure sensor, linked to the tibia by a rope and to the femur by a spring in series with a strain gauge, so as to model the quadriceps tendon and to measure its tension. The movements of femur, tibia and patella were recorded by an optical motion capture system. The recorded motion of femur and tibia were used as inputs to the simulation. The recorded motion of the patella was used, on the one hand, to define its initial position in the simulation, and, on the other hand, in combination with the forces recorded by the pressure sensor and the strain gauge, to validate the results obtained from the simulation. Because this work was a preliminary study, cruciate ligaments were released and lateral ligaments were considered as rigid bodies (to avoid contact between femur and tibia implants), thus allowing a single degree of freedom at the knee, in addition to the three rotations at the hip. The sizes of these lateral rigid bodies and the initial spring (quadriceps tendon) tension were modified to simulate different gap and tension configurations. The multibody system and the rigid body contacts were simulated by an in-house developed library [1-2] (Figure 1b).

Results

The simulated motion consisted in manually flexing and extending the knee (motion typically exerted by the surgeon to ensure that the patella tracking is correct after TKR surgery). Histories of position, orientation and pressure of the patella during the motion were compared with experimental measurements, offering good correlations for all the configurations tested.

Discussion

This preliminary study yielded promising results and allowed to validate the simulation of patellar tracking made with the in-house library. The use of 3D printed models and sensors enabled to work with digital twins for low cost experimental validation. They can also offer physical realistic representation of bone pathologies and planned treatment for surgeon training. Future work will aim to increase the detail of the system, so that it reflects the anatomy with higher fidelity.

References


Acknowledgements

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A HOMOGENIZED CONSTRAINED MIXTURE MODEL FOR HEART VALVE GROWTH AND REMODELING

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Introduction

In situ heart valve tissue engineering (HVTE) may provide superior valve replacements compared to the currently available valve prostheses [1]. For in situ HVTE to be successful, a better understanding of the growth and remodeling (G&R) mechanisms is essential. G&R in engineered tissues is hypothesized to have similar mechano-regulated mechanisms as native G&R [2]. Due to limited experimental data on in situ tissue engineered valves, we have investigated native G&R in this study using computational models. Specifically, we investigated if heart valve mecanico-mediated G&R alone can explain the adaptation of pulmonary autografts after the Ross procedure. Since there is still uncertainty on the specific mechanisms of mechanically-regulated G&R, the potential consequences of both stress- and stretch-based mechanical homeostasis were evaluated.

Methods

To model heart valve G&R, a homogenized constrained mixture model [3] consisting of elastin, glycosaminoglycans (GAGs) and collagen was developed. In this model, turnover and production of collagen and GAGs were mediated by the stresses or strains experienced by these constituents. Changes in constituent mass due to deviations in either stress or strain could then result in changes in tissue composition, stiffness and/or volume. To simulate G&R after the Ross-procedure, the homeostatic collagen and GAG stretches (or stresses) were first determined by applying the diastolic pulmonary pressure to the outflow surface. Subsequently, this pressure was increased to its systemic diastolic level after which G&R was simulated until homeostasis was achieved.

Results

Both stretch- and stress homeostasis led to an increase in tissue mass and a change in morphology in our model (Fig 1a and b). This change is mainly characterized by a dilation of the leaflets, which was more extreme for stretch-homeostasis (Fig 1c and 1e). Despite this dilation, the average leaflet thickness increased by 27 and 43% in stretch- and stress-homeostasis, respectively. Upon achieving stretch-homeostasis, the leaflets contained more collagen and less GAGs compared to achieving stretch-homeostasis (Fig 2d).

Discussion

Leaflet thickening agreed well with the literature [4,5,6] for both stress- and strain homeostasis, and stress-homeostasis resulted in an increased collagen content as also observed in explants [4,5,6]. Altogether, this shows that mecanico-mediated G&R is able to describe the adaptation of pulmonary autografts due to changes in hemodynamic loading.

References


Acknowledgements

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A MULTI-SCALE PHYSICS-BASED COMPUTATIONAL MODEL OF MECHANICAL VENTILATION IN COVID-19 PATIENTS

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1. Duke University, USA; 2. East Carolina University, USA

INTRODUCTION
Coronavirus disease-2019 (COVID-19) is a severe respiratory illness that presents unprecedented challenges. COVID-19 acute respiratory distress syndrome (CARDS) differs significantly from typical ARDS, with increased mortality rate and occurrence of consolidation and ground glass opacities (GGOs). Mechanical ventilation (MV) is a common treatment to severe CARDS. MV has a high risk of ventilator-induced lung injury (VILI) and a consequently high mortality rate. Thus, this study aims to present a novel in silico coupled 3D/0D model capable of simulating patient-specific responses to MV based on clinically sourced CT images of four COVID-19-afflicted lungs, to improve the understanding of airflow dynamics in the lung during MV, and to provide new insights into risk factors of VILI.

METHODS
Four lung 4DCT scans obtained from patients hospitalized for COVID-19 are used. The geometry of the first airway generations, lung lobes, and COVID-19 damaged regions were segmented using Materialise Mimics 23.0 and the Chest Imaging Platform in 3D Slicer. The C++ simulation package CHASTE (Cardiac, Heart, and Soft Tissue Environment) was used to create conducting airways (Figure 1-top) and to establish multi-scale coupling of airways and a patient-specific sigmoidal acinar model [1]. Acini within segmented GGO and consolidated regions were modified with a surfactant loss to model damage. Airflow was presented with a modified Poiseuille flow profile with corrections to dynamic resistance and driven by a pressure-control ventilator waveform. Lung volume-based pleural pressure variation was modeled to simulate the weight of the chest cavity on a passive patient.

Results
Flow and volume over time from each simulation was analyzed in the full lung and within each lobe (Figure 1-bottom). Healthy and COVID-19 tidal volumes significantly differed in full lungs and between individual lobes. Lobar tidal volume was divided by total tidal volume to determine individual lobar share. Percent change in lobar share and relative COVID-19 damage, defined as the difference between lobar COVID-19 damage and average lung COVID-19 damage, had a strong negative correlation when all lobes are compared. Healthier lobes tended to increase their ventilation while more damaged lobes tended to decrease their share of ventilation in these simulations.

Discussion
There is a need for high-fidelity physics-based, patient-specific models of COVID-19 lungs to understand better and potentially improve MV outcomes. In this research, we developed multi-scale physics-based computational models of MV in COVID-19 patients and compared the results to a hypothetical healthy lung subjected to MV for comparison. This study is important as a basis for physics-based simulation of heterogeneous, patient-specific COVID-19-induced damage in mechanically ventilated circumstances. Results showed proportional redistribution of ventilation from heavily damaged lung lobes to less damaged lobes, which can place additional mechanical strain in those regions, offering further insight into the airflow mechanics of mechanically ventilated COVID-19 patients.

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Acknowledgements
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A MUSCLE MODEL FOR INJURY SIMULATION

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Introduction

Car accidents frequently cause neck injuries [1] that are painful, expensive, and difficult to simulate. The movements that lead to neck injury include phases in which the neck muscles are actively lengthened [2]. Actively lengthened muscle can develop large forces that greatly exceed the maximum isometric force (f_{ISO}) [3]. Although Hill-type models are often used to simulate human movement [4], this model has no mechanism to develop large tensions during active lengthening. When used to simulate neck injury, a Hill model will underestimate the risk of injury to the muscles but may overestimate the risk of injury to the structures that the muscles protect.

Methods

We have developed a musculotendon model that includes the viscoelasticity of attached crossbridges and has an active titin element (Figure 1). Titin is a giant elastic protein that spans the distance between the Z and M lines. When activated, our model viscously bonds a part of titin to the neighbouring actin filament, effectively halving the length of the segment of titin that is free to stretch. As a result, when the model is activated the stiffness of titin is effectively doubled: the titin-actin bond ensures that only the distal segment is free to lengthen.

To evaluate the model, we simulate the experiments of Leonard et al. [1] that feature extreme active lengthening. The experiment begins by maximally activating the contractile element (CE) at the optimal length. Next the CE is slowly lengthened until the observed force drops. For context, we repeat the simulations using a Hill-type muscle model [4].

Results

When the proposed model is activated and lengthened [3], it develops forces that greatly exceed f_{ISO}, similar to biological muscle (Figure 2). As in Leonard et al.’s experiments [5], the model can develop active forces beyond actin-myosin overlap, at least until the titin-actin bond slips off the actin filament. In contrast, the Hill-type model’s force is far lower.

Discussion

We next plan to evaluate the model by simulating active lengthening experiments that have been done on whole muscle [6] in rabbits. Following this, we will simulate the head and neck movements of a finite element model during an in-vivo whiplash experiment.

References


Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft under Germany’s Excellence Strategy – EXC 2075 390740016 (SimTech) – is gratefully acknowledged.
CERVICAL MUSCLE REFLEXES DURING LATERAL ACCELERATIONS

Matthew Millard1,2, Susanne Hunger1, Lisa Broß1, Jörg Fehr2, Christian Holzapfel3, Norman Stutzig1, and Tobias Siebert1

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Introduction

Autonomous vehicles will allow a variety of seating orientations that may change the risk of neck injury during an accident. Having a rotated head at the time of a rear-end collision in a conventional vehicle is associated with a higher risk of acute and chronic whiplash [1]. The change in posture affects both the movement of the head and the response of the muscles [2]. We are studying the reflexes of the muscles of the neck so that we can validate the responses of digital human body models that are used in crash simulations.

Methods

The neck movements and muscle activity of 21 participants (11 female) were recorded at the Stuttgart FKFS* mechanical driving simulator. The simulator executed driving maneuvers that generated lateral accelerations of up to 5m/s². Recordings were made in two conditions: one in which the participants looked ahead (0°, 6 trials), and another where they looked to the right (45°, 4 trials). The study was approved by the ethical committee of the University of Stuttgart (Az 22-001) and was conducted in accordance with the latest declaration of Helsinki.

During the maneuver we recorded the acceleration of the seat and electromyographic (EMG) signals from the sternocleidomastoid (STR) muscles using a Biopac MP 160 system (USA). EMG signals were high-pass filtered (500Hz), full wave rectified, low-pass filtered (10 Hz), and then normalized using data from a maximum voluntary contraction trial. EMG onset latency was evaluated between the onset of the acceleration of the seat and the onset of the normalized EMG of the STR muscles. The normalized EMG peak that occurred immediately following the onset was taken to be the strength of the reflex.

Results

The left and right STR muscles have reflexes that vary with the direction of the movement and the posture of the neck (Figure 1). As intuition would suggest, when moving to the right the activity of the right STR is earlier and stronger than the left STR (see the 3rd and 1st columns of Figure 1A and B for 0° and 45°). A similar but opposite pattern is observed when the seat moves to the left. The pattern of onset latency of the 0° and 45° trials are similar, but the reflex strengths differ.

Discussion

Similar to a smaller previous study [2] we found muscle activity of the neck is sensitive both to direction and posture. We plan to extend this work by examining how these responses differ across men and women, and also how these patterns compare with the other muscles we recorded (upper and lower trapezius).

References


Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft under Germany’s Excellence Strategy – EXC 2075 390740016 (SimTech) – is gratefully acknowledged.

*https://www.fkfs.de/en/test-facilities/driving-simulator/stuttgart-driving-simulator

Figure 1: The reflex latency and strength of the left (blue) and right (red) STR muscles is shown during lateral accelerations to the left and right (see purple movement annotation) in two conditions: looking straight ahead, and looking to the right by 45°. Plots include the 25th-75th percentile data and medians.
SCREW LENGTH IMPACT ON BONE STRAIN FOR A PROXIMAL HUMERAL PLATE VIA A NEURAL NETWORK MODEL

Daniela Mini, Karen Reynolds, Mark Taylor

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Introduction
Treatment of proximal humeral fractures is challenging and a high rate of failure has been reported when using locking plates [1]. For a given fracture, there are multiple options in terms of the number and length of screws needed to stabilise the fracture and hence it is difficult to capture the mechanics of all possible combinations. FE modelling were used in the past to understand the mechanics of fracture fixation, but due to its high computational cost is not possible to study all configurations. Therefore, the purpose of this study is to use a combination of FE analysis and surrogate modelling to analyse humeral bone strain as screws length are varied.

Methods
A CT image of a cadaver from the New Mexico Decedent Image Database (NMDID) was used to generate a FE model of a proximal humerus [2], in which a single fracture was simulated. A fracture plate with seven proximal screws and three distal screws was implanted. Non-homogeneous material properties were defined [3], tied conditions were set between the screws and the bone and an axial bending loading condition was simulated [4]. In order to vary the length of the seven proximal screws, four values of tip-to-joint distance (TJD) were introduced, defined as the distance between the tip of the screws and the bone surface [5], and training sets of 50, 100, 200, 500 and 1000 FE models were generated using the latin hypercube sampling method. A further set of 100 FE models was generated to test the network, once developed. All the models were run in Abaqus. The TJD of each screw and the strain in the humeral head were used as input and output for the generation of different Neural Networks (NN). The NN outputs were compared with the results from the FE analysis, showing $R^2$, slope and RMSE for the 100 unseen cases. Differences between single and multiple-output NN were shown, using the bone strain around each screw as output. To further test the quality of the NN, a set of 30 models was developed with additional intermediate values of TJD, and the output from the FE simulations was compared with the predictions of the NN. To understand the impact of the screws’ length in the humeral head, the best NNs were used to make a simulation of all 4$^7$ possible configurations.

Results
The NN predictions of principal strain around the proximal screws were compared with the FE results of the 100 unseen data, showing a good correlation and a low level of error ($R^2 = 0.99$, RMSE = 21.1-62.7 $\mu$strain). Single and multiple-output NNs gave comparable results, with the same $R^2$ and range of error ($R^2 = 0.96-0.99$, RMSE = 24.6-148.1 $\mu$strain). Once the NN was tested with intermediate values of TJD, a higher level of error was observed (RMSE = 28.7-1190.7 $\mu$strain). Predictions of all configurations made with NNs showed that the screw providing medial support is the most influential on the bone strain, and the safest configuration is the one with longer screws. (Figure 1)

Discussion
The aim of this study was to develop a Neural Network method to reproduce the bone strain varying the length of the screws of a fracture fixation plate implanted in the proximal humerus. The NN was able to give an accurate prediction of strain and compute the entire solution space, not feasible using FE alone. This technique can be used in the future to understand the influence of additional parameters.

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BIOMIMETIC 3D PRINTED INTERFACES

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Introduction
The design of interfaces between extremely soft and hard materials with dissimilar mechanical properties is challenging due to differences in load capacity, adhesive damage, and stress concentrations [1]. Natural architected structures, such as the tendon enthesis, offer high performance due to features such as morphological interdigitations and functional gradients [2]. Multi-material 3D printing techniques have made it possible to mimic these natural designs [3]. Here, we implemented some of these microarchitectural features (e.g., collagen-like helices, randomly distributed particles) using experiments and computational models to understand their impact on the mechanical performance of biomimetic soft-hard interfaces [4,5]. This study provides design guidelines for improving the mechanical performance of bioinspired soft-hard interfaces with potential applications in tissue engineering, soft robotics, and architectured materials.

Materials and Methods
Here, a 3D printer (ObjetJ735 Connex3) with voxel-level control was used to fabricate biomimetic soft-hard interfaces using two photopolymers (Agilus30™ Clear for the soft phase and VeroCyan™ for the hard phase). We considered the narrow section of a standard tensile test specimen and varied two interface parameters (i.e., width and geometrical design) using different values of width and different geometries (e.g., collagen-like helices and random particles). The specimens were 3D printed and tested for mechanical properties through quasi-static uniaxial tensile tests and digital image correlation (DIC). Stress-strain curves, elastic modulus, ultimate tensile strength, and strain energy density were obtained. The designs were modeled using finite element (FE) analysis in Abaqus 2017.

Results and discussion
We investigated the mechanical performance of soft-hard interfaces with different architectures, resulting in different patterns of contact surface area and total values. The best-performing designs had similar strengths and failure modes (failure within the soft region), while the control group (i.e., non-graded) underperformed. The cause of failure in the control group was due to shear strains at the interface edges. The results of the experiments were validated by numerical simulations, which showed strain concentrations at the edges of the interface in most of the specimens. The absence of sharp edges in the design and a smooth transition of material density can alleviate these strain concentrations and improve their mechanical performance. Maintaining connectivity of the hard material also ensured the integrity of the interfaces.

Figure 1: A) FE analysis of the soft-hard interfaces. B) DIC analysis of a knee-ligament system incorporating functional gradients.

Conclusion
Our study investigated the impact of design on the mechanical performance of soft-hard interfaces. Our findings highlight the significance of increased contact area, elastic modulus functions, and strain concentration mitigation in achieving high-performing interfaces. The application of these design features resulted in improved strength and toughness of the interfaces. Future research should use computational methods to optimize these interfaces, leading to the development of advanced materials with potential applications in medical devices, tissue engineering, and soft robotics.

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PREDICTION OF OVERLOADING FAILURE OF OSTEOSYNTHESIS PLATES USING VALIDATED FINITE ELEMENT SIMULATIONS

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Introduction
The role of osteosynthesis is to maintain fracture reduction until bone healing is achieved [1]. However, plastic plate bending via overloading is a common failure mode in midshaft fractures, ranging up to 17% and often requiring reoperation [2,3]. Plate bending was also observed in a recent ovine study [4] for six out of eight animals. The aims of this study were to replicate the in-vivo situation in a cadaveric experiment and to validate a finite element (FE) simulation to predict plastic plate bending.

Methods
An established ovine tibial osteotomy model fixed with locking plates [4] was replicated in-vitro in six cadaveric bones (Figure 1). Two implant materials (titanium or steel) and three fracture gap sizes (30, 60, 80 mm) were used to investigate the bending behaviour of the fixation construct biomechanically. Axial alignment of the proximal and distal ends of the bones was ensured using a laser-guided embedding station. Axial compression testing until plastic deformation of the plate was performed (Instron 5866). Construct displacement was measured with Aramis SRX (GOM) to eliminate potential slippage errors or test setup compliance (Figure 1b).

CT image-based specimen-specific FE models were created for each of the six constructs using Simpleware (Synopsis). Elastic and plastic implant material properties of titanium and steel were evaluated via uniaxial tensile testing of dog bone shaped samples extracted out of implant raw material profiles and incorporated into the models. The boundary and loading conditions were set to mimic the cadaveric experiment. The simulations were performed in Abaqus (SIMULIA). Stiffness, yield, and maximum loads were determined and compared between the experiment and FE models.

Results
Implant material properties determined for steel and titanium resulted in Young's moduli and yield stresses of 172.1 GPa and 887.7 MPa, and 104.3 GPa and 758.6 MPa, respectively. Yield and maximum loads of the constructs ranged between 469-491 N and 652-683 N, and between 759-995 N and 1252-1600 N for steel and titanium fixations, respectively. The FE models were able to predict the experimental results with high accuracy for stiffness (R²=0.96), yield (R²=0.97, Figure 2), and ultimate load (R²=0.97).

Discussion
This study demonstrated the ability of FE simulations to accurately predict plastic plate bending in osteosynthesis constructs. As the construct behavior was predominantly driven by the implant, knowing the underlying material properties was vital. In future, these validated FE models could be used to predict the subject-specific load bearing capacity of osteosyntheses in preclinical or clinical studies.

References

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3D STRAIN MEASUREMENT OF THE TENDON-BONE JUNCTION USING IN-SITU XCT MECHANICS AND DIGITAL VOLUME CORRELATION

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Introduction
Understanding the strain concentration and distribution at the tendon to bone junction or enthesis as a part of the musculoskeletal system is essential in development of implantable biomaterials and reconstructive surgeries [1]. Digital volume correlation (DVC) enables the 3D and internal mechanical deformation of complex structures. In-situ tensile testing micro X-ray computed tomography (micro-XCT) generates 3D scans of loaded and unloaded tissues [2]. Since soft tissue has a low X-ray attenuation coefficient, an appropriate contrast agent is usually used that enhances visualization enabling the 3D strain to be computed at the enthesis [3]. These contrast agents can potentially affect the mechanical properties of the tissues. The purpose of this study was to evaluate an optimal contrast agent whilst maintaining the tissue mechanical properties and to measure the full internal 3D strain at tendon to bone insertion by micro-XCT and DVC.

Methods
Samples were dissected from 8 months old male mice legs (Achilles tendon to calcaneus) under University of Portsmouth ethical approval (TETHIC-2022-104588). The force-displacement curves were acquired by uniaxial tensile testing until failure for samples stained with different contrast agents including phosphotungstic acid (PTA) in water, PTA in ethanol, and mercury II chloride (HgCl2) in water and compared to untreated samples. Data (n=3) was expressed as mean ± standard deviation (SD) and p value < 0.05 was considered as statistically significant. Samples with the optimal contrast agent was used for in-situ micro-XCT tensile testing with 4X optical magnification, 1.37 µm pixel size, and 1601 projection number. Samples were scanned once in unloaded condition and then at 1.5N load. Images were rigidly registered (Avizo, USA) and the 1st principle (Εp1), 3rd principle (Εp3), Von Mises (Εvm), and maximum shear (γ) strain were measured using local approach DVC with a multi-step processing scheme from 84 to 24 voxels/subvolume, 0% overlap, and removed body rigid movement (LaVision, UK).

Results
The ultimate load (mean ± SD) of samples treated with HgCl2, PTA EtOH, PTA H2O, and untreated sample were 9N, 4N, 3N, and 6N, respectively. As shown by the slope of the curves in the linear region, the sample stained with HgCl2 had substantially higher stiffness (12 N/mm) while the sample stained with PTA either in ethanol or distilled water had no significant difference compared to the untreated sample stiffness (4 N/mm). Subsequent experiments were conducted with PTA in ethanol. DVC results demonstrated Εp1, Εp3, Εvm, and γ strain throughout the sample. Although the load transmission is not homogenous, it was found that the load was localized mostly at the center of the enthesis where Εp1 reach the value of 16%, Εp3 -17.5%, Εvm 22.5%, and γ 12%. Von Mises strain was more intense in the center of the tendon and penetrated further into the bone than the 1st principle strain.

Figure 1: A) force elongation curve and B) stiffness for different contrast agents. C) unloaded 2D tomogram D) DVC 1st principle strain map on loaded 2D tomogram E) 3D 1st principle strain map.

Discussion
Compared to natural tissue, PTA in ethanol was the contrast agent that least affected the mechanical properties and can be used as contrast enhanced agent for in-situ micro-XCT tensile testing in elastic range. DVC results produced a full 3D internal strain map at tendon to bone insertion. This protocol can be used for 3D strain evaluation of soft tissues.

References

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Only in unloaded activities TKA design features dominate in the amount of rolling and sliding

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Introduction

Although total knee arthroplasty (TKA) is an established procedure with 95% survivorship, around 14-39% of patients report dissatisfaction with the outcome [1]. One of the reported causes is anterior knee pain due to paradoxical anterior sliding or insufficient femoral rollback during flexion [2]. Despite a wide number of available TKA designs, there is no clear consensus about how specific design geometrical features lead to either sliding or rolling of the femoral component and therefore to specific anterior knee kinematics during flexion. The aim of this study was to analyze whether TKA design features impact the in-vivo rolling/sliding ratio during loaded and unloaded activities and thus could help to minimize the dissatisfaction of patients.

Methods

Four cohorts (10 subjects each) of patients operated with TKA in diverse designs were analysed: 1) with a gradually changing radius posterior stabilized (G-Curve PS), 2) with a gradually changing radius cruciate retaining (G-Curve CR), 3) with an asymmetric bicruciate stabilized (A-BCS) and 4) with an asymmetric CR (A-CR). All patients underwent in-vivo fluoroscopic measurements in loaded lunge and unloaded flexion-extension knee movements to collect the 3D TKA motion from extension to maximal flexion [3]. To do so, 3D CAD Models of the TKA components were registered to the fluoroscopic images and movement data extracted. Medial and lateral distal points (Figure 1) were used to determine the anterior-posterior (AP) translation. Their path on the femoral condyles (Figure 1) were also determined. The Rolling/Sliding ratio was defined as the quotient of the tibia relative AP-translation and the femoral path length.

Results

During unloaded flexion-extension the G-Curve PS and G-Curve CR designs showed a behavior near a hinge joint from extension until mid-flexion followed by an increase in rolling towards posterior. Both asymmetric BCS and CR designs slid spontaneously towards anterior during early flexion but then continuously rolled posterior. During loaded lunge, both G-Curve cohorts behaved near to a hinge joint from extension until the maximal flexion was achieved (80°). Anterior sliding – however reduced – was found in early flexion with some rolling in the asymmetric cohorts, especially pronounced in the A-BCS.

Discussion

Both versions (PS and CR) of the gradually changing radius designs seem to limit paradoxical anterior sliding. On the other hand, the PS version achieved a mostly continuous translation (increased rolling) towards posterior. This may be due to a combination of radius changes and the post-cam mechanism. However, in both asymmetric designs (BCS and CR) an anterior sliding was observed but compensated by continuous translation (increased rolling) towards posterior. The kinematics of the TKA was substantially influenced by loading with unloaded settings allowing to identify kinematic differences between designs while under loading these vanished. However, these conclusions require further in-depth analysis in eventually larger cohorts.

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REAL-TIME FATIGUE TRACKING USING ELECTROMYOGRAPHY DRIVEN MUSCULOSKELETAL MODELS

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Abstract
Real-time Electromyography driven neuromusculoskeletal models can provide a robust approach to control wearable assistive devices over a wide repertoire of movements. However, the models are not designed to track changes in muscle activity due to fatigue, and would fail to provide a realistic estimate of joint torques in these situations. Here, we describe a fatigue model that can be appended to Hill-type neuromusculoskeletal models for real-time tracking of joint torques. This opens up a new type of human-machine interfaces that allow steering biomechanical parameters away from fatigue in addition to providing assistance during movement.

Introduction
Robust human-machine interfacing requires intuitive controllers that allow users to move in a wide repertoire of movements. This is crucial for wearable exoskeleton design. Real-time Electromyography driven neuromusculoskeletal models (uENMS-RT) have been shown to be robust controllers for providing assistance using ankle exoskeletons [1,2]. The ability of uENMS-RT to decode biological joint torques is enhanced by user specific calibration of musculoskeletal parameters. Once calibrated, the uENMS-RT requires only joint angles and muscle activity measurements which can be implemented in a minimal wearable approach [2].

However, the uENMS-RT does not account for changes in muscle activity due to fatigue. Thus, with continuous prolonged use or after fatiguing tasks, the user specific model may need to be revisited [3]. Fatigue models have been added to neuromusculoskeletal models for improving joint torque estimation during functional electrical stimulation [4] or modeling age related changes [5]. However, these models aim to accurately represent changes in biochemical compositions of fatigue, and are not suitable for user specific modeling of joint torques.

Thus, here, we describe a fatigue model that can be included to the uENMS-RT for real-time tracking of joint torques and control of human-machine interfaces. The proposed approach is aimed at user specific modeling of fatigue.

Design of user specific fatigue model

\[
\tau^j = \sum_{mt} (F^{mt} \cdot ma^{mt}) \tag{3}
\]

\[
F^{act} = F^{max} \cdot e^{(-Ka)}; \tilde{\tau}^{act} = \tilde{\tau}^{max} \cdot e^{(-K\alpha)} \tag{4}
\]

\[
\alpha = \frac{1}{t_p} \int EMG \cdot dt \tag{5}
\]

The uENMS-RT is based on Hill-type models [6,7] (Eqn 1, 2, 3). The muscle tendon force \(F^{mt}\) is the same as tendon force \(F^t\) and muscle force \(F^m\) scaled by cosine of the pennation angle \(\phi\) which depends on the optimal fibre length \((\tilde{l}^m)\). Eqn. 2 relates \(F^m\) and maximum isometric force \(F^{max}\), activation dynamics \(a(t)\), force-length and force-velocity relationship, and a damping factor \((d^m)\). The joint moments \((\tau^j)\) are derived from \(F^{mt}\) and moment arm \((ma^{mt})\) of the MTU across the joint (Eqn 3). Peripheral fatigue reduces the \(F^{max}\) and peak contraction velocity \((\tilde{\tau}^{max})\) exponentially [8]. Therefore, the actual \(F^{max}\) and \(\tilde{\tau}^{max}\) are modelled using Eqn (4). They are both scaled by a muscle specific fatigue index \(\alpha\) and a user specific fatigue index \(K\). \(\alpha\) is integrated EMG scaled by \(\frac{1}{t_p}\), where \(t_p\) is time passed since the activity in minutes. \(K\) is found in \([0, 1]\) by minimizing \(\tau_{model} - \tau_{tp}\).

Proposed Protocol and Discussion

Recruited participants will perform calibration, fatigue, and a real-time tracking protocols. During calibration, a user specific OpenSim model and uENMS-RT model will be setup from motion capture system, electromyography, and force plate data [2]. The fatigue protocol will be used to estimate the user specific fatigue parameters \(\alpha\) and \(K\). Finally, in the real-time phase, the users will perform walking tasks and the validity of the uENMS-RT to assess joint torques will be assessed. This will be a first study to track user specific joint torques accounting for user specific changes to muscle activity due to fatigue. Progress on this study will be shared at the conference.

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STUDY OF THE LOCATIONS AND MORPHOLOGY OF ISOLATED KNEE FOCAL CARTILAGE DEFECTS USING A STATISTICAL SHAPE MODELING APPROACH

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Introduction

Focal knee resurfacing implants (FKRIs) are an emerging alternative treatment for knee focal cartilage injuries. FKRIs are typically intended for the middle-aged population where biological cartilage procedures and total knee replacement are not proper options due to longevity concerns. The objective of a FKRI is to restore the articular cartilage surface to its native morphology in order to restore peak contact stress levels to healthy physiological levels. The design of an off-the-shelf FKRI thus requires detailed information about the most commonly occurring defect locations and the local morphology at these defect locations. The objectives of this work are threefold: (1) to develop a statistical shape model (SSM) of the distal femoral cartilage surface that captures morphology variation across the population, (2) to develop a heat map of cartilage defect locations to identify the areas where the local morphology needs to be characterized, and (3) to characterize the local articular cartilage surface morphology at the sites where cartilage defects commonly occur.

Methods

Magnetic Resonance Imaging (MRI) scans of 58 patients who were determined to be eligible for FKRI surgery were selected to be used for creating the SSM and heat map. The cartilage models were semi-automatically segmented from the MRI scans. Registration algorithms were used to find the point-to-point correspondence of the models. Models were translated and reoriented to a reference location to remove the relative differences in pose which are not related to the variation of the shapes. Principle component analysis was used to find the modes of variation within the population. The resulting statistical shape model was evaluated by investigating its compactness and accuracy [1]. To create the heat map, locally isolated cartilage defect models were manually segmented from MRI images. Segmented 3D mesh models were then aligned to the average shape of cartilage as created using SSM. This alignment step uses the same transformation matrices found during the alignment of the corresponding cartilage models while creating the SSM. The aligned overlap of the defect models shows the probability of damage occurrence at different locations on the average cartilage surface (Figure 1). To characterize the surface morphology of the healthy cartilage at defect locations, the local radius of curvatures are calculated by fitting a circle to the surface of the average SSM shape in anteroposterior and mediolateral directions at those defect locations (Figure 1).

Results

The compactness of the SSM model constructed from 58 patients shows that the first 10 modes cover 95 percent of the variation of the data. The accuracy of the SSM model is 0.37 mm which is below the input MRI data voxel size of 1.0 x 0.5 x 0.5 mm. The cartilage defect location heat map shows a concentration of defects on the medial condyle corresponding with the site of peak contact pressure during the stance phase of the gait cycle (Figure 1). The anteroposterior and mediolateral radius of curvatures of the cartilage surface measured from the average SSM shape on the observed hottest point were determined to be 23 and 38 mm respectively.

Discussion

This workflow proves to provide detailed information on the isolated focal knee cartilage defects with the required level of detail to enable FKRI design. A higher number of cases needs to be included to increase the heat map accuracy on lateral condyle and trochlea areas. To validate the use of the extracted implant design parameters, implant fit evaluation in a population sample set created using the SSM should be performed. This work may also be useful for guiding regenerative medicine or allografting approaches in cartilage repair.

References

NON-INVASIVE MRI-BASED CHARACTERIZATION OF CARTILAGE DEGRADATION USING VIRTUAL FIELDS METHOD

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Introduction

Articular cartilage degeneration is the hallmark of osteoarthritis (OA), the most common joint disease. Early stages of tissue degeneration are characterized by changes in the proteoglycan concentration and the collagen network. These changes alter the mechanical behavior, as the interaction between the constituents determine the mechanical properties of cartilage [1]. Although mechanical characteristics of cartilage were extensively studied in vitro [2], in vivo assessment lack behind, given the invasive nature of the experimental techniques. This study is a proof of concept that proposes a non-invasive MRI-based approach that uses the virtual fields material parameter identification method (VFM) to quantitively distinguish material parameters in a healthy and enzymatically degraded in vitro OA cartilage model, as the first step towards in vivo characterization.

Methods

2D displacement fields, determined from two bovine osteochondral plugs, one control and one enzymatically degraded (combination of collagenase inducing collagen degradation and chondroitinase inducing proteoglycan degradation) were collected [3]. Pixel-wise displacement data (shown in Figure 1) were extracted based on a unique MRI DENSE sequence performed during compressive loading at steady-state tissue response [4].

![Image](image_url)

**Figure 1:** Pixel-wise displacement maps in axial and transversal direction during cartilage-on-cartilage contact of A. control osteochondral plugs and B. enzymatically degraded osteochondral plugs

An inhouse code was developed based on an iterative approach of the VFM, presented in Figure 2 assuming a compressive Neo-Hookean constitutive model. Because the exact forces acting at the cartilage-on-cartilage interface are unknown, only Poisson’s ratio can be evaluated, as this material parameter is suggested in literature to be independent of boundary conditions [5]. The implementation of the VFM was validated using a finite element model with pre-determined material parameters.

![Image](image_url)

**Figure 2:** The VFM workflow: At initialization, an initial guess of the desired material parameters (c) is used to calculate the Cauchy stresses, which are a function of the experimentally determined deformation gradient tensors (F). This allows estimating the internal virtual work (IVW). The objective function defined as the difference between internal and external virtual works (EVW), is then minimized by iteratively altering the material parameters.

Results and discussion

The simulated Poisson’s ratios are 0.445 and 0.320 for the control and enzymatically degraded osteochondral plugs respectively. The results show a significant decrease in Poisson’s ratio of the degraded plug, which corresponds to an increase in tissue compressibility. This increase in compressibility can be a direct result of changes in tissue permeability, a characteristic of degraded tissue [6]. In conclusion, the developed non-invasive MRI-based approach allows us to not only distinguish between control and enzymatically degraded osteochondral plugs, but also gives quantitative insight into the changes in mechanical properties. Ultimately the proposed mechanical characterization approach could serve as a potential in vivo biomarker for early OA.

References


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MEASUREMENT OF HIGH STRAIN TENSILE FAILURE PROPERTIES OF CAROTID PLAQUE EMBOLUS ANALOGS

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Introduction
Acute ischemic stroke is a leading cause of death and morbidity [1]. Recent studies suggest that, in addition to embolus morphology, their mechanical properties contribute to complications in clot removal procedures [2,3]. In addition, thrombus low strain properties are well documented, and computational work has modelled the clot as a viscoelastic material [5,6]. High strain behaviour has yet to be characterized and is important to understand the high strain load profile of clots during mechanical thrombectomy. The goal of this project is to characterize the high strain tensile properties of carotid blood clot analogues and compare the results to a finite element, hyperelastic computational model.

Methods
Embolus analogues (EA) were created using human blood, following approved IRB protocols, with preliminary work done on bovine blood (IACUC approved). Briefly, extracted whole blood was anticoagulated with 0.32% wt. sodium citrate. Blood was separated via centrifugation and reconstituted to 214 x 10^6 platelets per mL and 40% vol. haematocrit. Blood was recalcified with 20 mM calcium chloride (CaCl₂) and 0.1 NIH Unit/mL thrombin from human plasma (BioPharm, Bluffdale, UT, USA). Carotid plaque samples were formed with an addition of 0.1 mg/mL human collagen Type 1. Recalcified blood was mixed and injected into “dog bone” tensile moulds with 16 mm length gauge section, following ATSM D638 standards, and allowed to coagulate at 37°C for 1 hour.

Once EAs were formed, the samples were attached to custom grips on a uniaxial load frame (Instron, Norwood, MA, USA) with a 5 N load cell. Once mounted, the specimen was loaded at a rate of 10% strain per second (based on sample gauge length) until sample fracture. From these data, a linear polynomial was fit to the curve prior to fracture to compute the modulus. The peak stress and strain were recorded. All samples were embedded in paraffin wax for histology and stained with a standard Carstairs protocol. All data analysis was performed using MATLAB’s statistics toolbox (Mathworks, Natick, MA, USA).

Results and Discussion
Nominal stress strain curves show strains of up to 250%, with highly linear behaviour. The measured mean elastic modulus was 5.43 ± 1.22 kPa, the maximum stresses were 10.2 ± 3.38 kPa, the maximum strains were 1.91 ± 0.29 with a linear R² value of 0.996. Bovine clots show a highly linear, elastic-like behaviour, similar to previous work (Figure 1). However, work by Boodt et al. [3] show a highly nonlinear compressive behaviour in clots, suggesting a compressive-tensile asymmetry. Work by Sugerman et al. shows similar tensile stiffnesses, however, reported strains at fracture were roughly 0.4 [7]. This method for loading clots in tension can be used to characterize the high strain properties of blood clots.

Figure 1: Nominal stress vs. strain curves for bovine tensile specimens, with cross-sectional area of 16 mm² in the gauge section.

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IN WATER AND ON LAND FORWARD AND BACKWARD SPATIOTEMPORAL GAIT CHARACTERISTICS

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Introduction

Forward and backward walking is a common exercise for rehabilitation due to the major role that locomotion plays in an individual’s quality of life [1]. Aquatic exercises are widely used alongside traditional land-based therapy because of the beneficial physical characteristics of water on various body systems [2]. Walking underwater, for instance, impacts the muscular-skeletal system, reducing fatigue and pain and improving the physical recovery rate as well as the joints’ range of motion [3]. A recent systematic review [4] pointed out that the use of wearable inertial measurement unit sensors (IMUs) in water for human biomechanical motion analysis is still limited. In particular, no previous studies investigated the kinematic differences between forward and backward walking in water using wearables. Therefore, the aim of this investigation is to explore gait analysis via customized IMUs estimating and comparing forward and backward spatiotemporal gait parameters and gait phases, in and outside water.

Methods

Five healthy female volunteers (24.5 ± 0.6 years old), with no previous history of injuries at the lower limbs, were included. They were asked to walk ten times at their preferred self-selected regular pace forward and backward in a straight line, inside and outside water (swimming pool: 1.20m depth, 33°C, Enjoy Sport center, Cernusco sul Naviglio, Milano, Italy). Two IMUs, developed by Tallinn University of Technology (Tallinn, Estonia) were placed on the instep of both feet using self-adhesive tape. The sensors are small (30x12x9mm) and lightweight (about 7g), causing as little discomfort as possible and not interfering with the subjects’ movements. The sensors include an absolute orientation sensor (BMX160, Bosch), sampling at 100Hz, a microcontroller and onboard memory. The devices have been specifically developed for underwater applications and therefore do not require any casing or specific precautions to be employed safely. The first two complete gait cycles of the left and right legs were investigated. Matlab (2022b) was used to define the gait events from the accelerometer data and to estimate the spatiotemporal gait parameters. The stride time is identified as the period between two subsequent homolateral foot strikes (respectively heel or toe strike during forward or backward gait) while the stance and swing components are identified respectively as the portions of the gait cycle in which the foot is in contact with the ground and in which it is undergoing motion.

Results

The results of stride time expressed in seconds and stance and swing components expressed as a percentage of the gait cycle are resumed in Figure 1, for both forward and backward gait on land (brown) and in water (blue). Right and left gait parameters are displayed together after checking the two populations with the two-sample Kolmogorov-Smirnov test to assess whether they come from the same distribution.

Discussion

The stride time underwater is more than doubled for both forward and backward gait, showing a much higher variability and uncertainty. In water, the stride time was observed to considerably decrease between forward and backward gait, with a difference of 0.5s (about 17% of the stride time during forward walking). These results might be related to the higher density of water with respect to air, which creates a safe environment that reduces the fear of falling during backward gait and simultaneously increases the difficulty of moving consistently, increasing the gait variability. Despite the differences in stride time, the partitioning of the gait cycle in stance (about 60%) and swing (about 40%) phases remains invariant for land and underwater environments and for forward and backward gait.

![Figure 1: Gait parameters (stride time, stance and swing components of the gait cycle) of forward and backward gait on land (brown) and in water (blue).](image)

References


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MULTI-OBJECTIVE OPTIMIZATION OF HOLLOW FIBER MEMBRANES ARRANGEMENT USING MODIFIED ENHANCED JAYA ALGORITHM

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Introduction

Recently extracorporeal membrane oxygenators (ECMO) have been widely used in critical care situations, especially for patients with dysfunctional hearts and lungs. Gas permeable membranes are this circuit's main component, and mass transfer generally has been done by increasing the fibers and module size. Thrombosis and hemolysis are the most critical complications during ECMO, which are associated with high patient mortality [1]. This study presents the optimization of the fiber membranes arrangement using a modified enhanced Jaya algorithm which is the combination of modified Jaya [2] and Enhanced Jaya algorithm [3].

Methods

In Lukitsch's study [4], the radial velocity fraction around the fibers is obtained at almost 1, indicating that the flow will be primarily radial around the fibers. So, 2D models with 24 fibers were investigated for fiber arrangement optimization. Three parameters have been considered in fiber arrangements: 1) Angle, 2) Diameter, and 3) distance-to-diameter ratio.

To completely understand each parameter's effect, 120 simulations have been done (100 for model identification and 20 for model verification). The 120 cases above were generated using a uniform random distribution function considering the angle of 30 to 60 degrees, the diameter of 300 to 700 μm, and the distance-to-diameter ratio of 1.25 to 2.25.

Three outputs and objectives have been considered in this study:

1) Membrane performance: The ratio of exchanged gas (CO2) flow rate to the fluid flow rate.
2) Dead zone area ratio: The ratio of the area with a velocity of less than 2% of the inlet velocity to the total area.
3) Wall shear stress average

Each objective has been modeled with a linear polynomial function. Inputs of the models were considered dimensionless, so the Reynolds number was used instead of the diameter. The models are considered as follows:

\[
\text{Objective} = f(\text{Angle}^a, \text{Re}^b, \text{L/D}^c) \quad (1)
\]

A modified enhanced Jaya algorithm has been employed to find the best values for powers a, b, c, and the polynomial model degree (a maximum degree of 6 has been considered for each input). Also, a single objective function with the summation of normalized mentioned objectives with weights that indicate their importance has been considered as follows:

\[
\text{Objective} = w_1 \text{Obj}_1 + w_2 \text{Obj}_2 + w_3 \text{Obj}_3 \quad (2)
\]

Results

Based on the obtained models, the maximum mass performance of 28% is calculated with an angle of 30 degrees, a diameter of 300 μm, and a distance-to-diameter ratio of 1.25. The maximum wall shear stress of 3.26 Pa and the minimum dead zone area ratio of 0.57% are obtained with the same parameters. Also, the minimum wall shear stress average of 0.1555 Pa is calculated with an angle of 40 degrees, a diameter of 700 μm, and a distance-to-diameter ratio of 2.25. For a better understanding and comparison of the objectives, the Pareto optimal solution, along with dominated points, is shown in Fig 1.

![Figure 1: Pareto optimal solution graph](image)

Discussion

As shown in Fig 1, increasing membrane performance results in decreasing the dead zone area ratio and increasing the wall shear stress average. So, based on the importance of each objective, the best arrangement will be obtained. For example, considering the equal weight result in membrane performance of 22.06%, dead zone area ratio of 0.64%, and wall shear stress average of 1.95 Pa with an angle of 30 degrees, a diameter of 300 μm, and a distance-to-diameter ratio of 1.35.

References

BIOMECHANICAL EFFECT OF LUMBAR SPINE DECOMPRESSION: COMPARISON OF TWO DIFFERENT SURGICAL TECHNIQUES

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Introduction
Lumbar spinal stenosis causes the compression of neurovascular structures. Surgical decompression seems to have better outcomes compared to conservative treatments. The different decompression techniques, such as hemilaminectomy and the full laminectomy, remove parts of the posterior spinal elements increasing the space in the spinal canal. Removal of these structures could aggravate or create spinal instability [1]. In addition, changes in anatomy and in the load distribution could also alter the disc strains.

The aim of this work was to assess the biomechanical effect of hemilaminectomy and laminectomy in the lumbar spine, in terms of mechanical stability and strains on the intervertebral discs.

Materials and methods
Twelve L2-S1 spine cadaver segments were prepared leaving intact the anterior and all the posterior ligaments, removing the soft tissues around the discs and the vertebral bodies. A white speckle pattern was sprayed to measure surface strains with Digital Image Correlation (DIC). The specimens were mechanically tested in flexion, extension, right and left lateral bending under 2.5 Nm. Each specimen was tested:

i) in the intact condition;
ii) after hemilaminectomy;
iii) after full laminectomy.

The surgical procedures were performed at the L4-L5 vertebrae by a neurosurgeon, randomly choosing the side for the hemilaminectomy.

Surface images were acquired by a 3D-DIC system with two sensors (GOM Aramis 12M). Image correlation and analysis were performed using optimized parameters [2]. The range of motion (RoM) and the tensile ($\varepsilon_1$) and compressive ($\varepsilon_2$) principal strains distribution were computed for each loading configuration.

Results and discussions
Correlations and measurements were successfully performed for all the loading configurations and all conditions. Data were analyzed at the stage where the maximum moment of 2.5 Nm was reached. The statistically significant ($p<0.05$, Wilcoxon test) large increase in range of motion after hemilaminectomy suggests a loss of stability in flexion; different trend in the other loading configurations did not show significant changes. Tensile and compressive strains over the specimens showed similar distributions in each loading configuration before and after the hemilaminectomy (Figure 1).

Lateral bending on the side where the hemilaminectomy was performed (ipsilateral) was the most challenging loading configuration due to the statistically significant increase in minimum compressive strain on L4-L5 disc surface ($p<0.05$, Wilcoxon test).

Tests on the full laminectomy are currently being completed.

Conclusion
This study aimed to evaluate the risk of instability and changes in the strain distribution after lumbar spinal decompression performed by hemilaminectomy or laminectomy.

These preliminary results showed that the increased RoM in flexion, after hemilaminectomy, did not seem to damage the L4-L5 disc. Indeed, no significant increases in $\varepsilon_1$ or $\varepsilon_2$ were observed. Conversely, in the ipsilateral bending, the minimum compressive strains increased despite the RoM did not change.

References

Acknowledgements
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Ethics
Bioethics Committee of UniBo (Prot. 113043 of 10 May 2021)
Introduction
Soft hydrogels play an important role in providing three-dimensional (3D) support for cell growth. Cell-seeded hydrogels are typically cultured under free-swelling unloaded condition. However, such culturing conditions do not always favour protein synthesis of mechanosensitive cells, such as those found in cartilage and tendon. Mechanical stimuli of various forms have been applied to stimulate cell growth. Fluid pressure is a key mechanical stimulus and has been shown to promote protein production and phenotype retention for cells [1].

Recently, melt-electrowritten (MEW) fibrous mesh was used to enhance mechanical stiffness of the gelatin methacryloyl (GelMA) hydrogels [2], but little is known if the MEW mesh can induce fluid pressurisation in the hydrogels during mechanical loading, which can serve as an additional form of stimulus. The purpose of this study was two-fold: (i) to determine the load-induced fluid pressurisation in two hydrogel systems, GelMA and agarose, using indentation tests coupled to an analytical biphasic material model, and (ii) to determine if MEW fibrous mesh can improve the load-induced fluid pressurisation in these hydrogels. We hypothesised that MEW mesh can elevate the fluid pressurisation in both GelMA and agarose hydrogels.

Methods
Poly-caprolactone (PCL) fibres of 20 µm diameter were MEW-printed in a grid structure on a layer-by-layer manner with 600 µm inter-fibrillar spacing to make a fibrous mesh of ~2mm thickness. 15% w/v GelMA and 4% w/v agarose mesh-free (non-fr) hydrogels of 2mm thickness were fabricated using custom-built Teflon mould. MEW mesh-hydrogel composite (fr-hydrogels) was fabricated by infusing the MEW mesh with hydrogel solution before cross-linking. The hydrogel constructs with and without MEW mesh went through mechanical indentation by a rigid, spherical indenter of 1 mm in diameter (Fig. 1A). The indentation protocol contained a combination of different indentation depths (50–250 µm, corresponding to 2.5–12.5% strain) applied at different loading rates (0.5–20 µm/s). The resulting force responses were curve-fitted to a biphasic Hertz material model to derive the biphasic mechanical properties of the hydrogels [3], which included the fluid load fraction representing the proportion of applied mechanical load carried by fluid pressure.

Results
The incorporation of MEW fibrous mesh into the hydrogels successfully improved the fluid load fraction for GelMA, but not for agarose (Fig. 1B). The negligible fluid pressure in nonfr-GelMA (~5 kPa) was elevated to as high as 64 kPa after being reinforced by the MEW mesh (Fig. 1C). However, the opposite was true for the agarose (Fig. 1C).

Discussion
GelMA was covalently cross-linked whereas agarose was physically cross-linked. Mechanical reinforcement by MEW mesh in terms of fluid pressurisation appears to depend on the cross-linking mechanism of the hydrogels. We show that MEW fibrous mesh can improve the load-induced pressurisation in GelMA, thereby suggesting additional advantages of using the MEW mesh to improve the cell growth through additional stimulus in the form of fluid pressure.

Acknowledgements
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References
PATIENT-SPECIFIC BONE PLATES: DESIGN STRATEGIES AND BIOMECHANICAL PERFORMANCE

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Introduction
Slipped capital femoral epiphysis (SCFE) is a prevalent hip disorder among adolescents. The possible causes include obesity, endocrine disorders, and heightened mechanical stress on the growth plate [1]. A corrective surgical procedure, Imhäuser osteotomy, comprising of realignment of the femoral head and shaft via femoral head-neck osteotomy, followed by stabilization using an orthopedic plate, is performed to restore hip motion and mechanics while limiting the incidence of avascular necrosis [2]. The present study endeavors to enhance the biomechanical performance of SCFE-patient-specific proximal femur fixation plates through the integration of computational modeling and topology optimization into the plate’s functionality under physiological loading conditions through experimentally validated finite element (FE) analysis. The objective is to support medical engineers in fabricating reliable and optimally sized patient-specific SCFE plates.

Methods
The aim of this study was to develop a patient-specific proximal femur fixation using computer-aided design (CAD) and topology optimization (TO) techniques. The case under consideration was a patient with SCFE (ethical approval no. WO20.057) who underwent Imhäuser osteotomy and fixation using patient-specific Ti-6Al-4V plating and screws. The design procedure commenced with imaging and clinical evaluation, followed by the creation of a 3D bone model. Virtual proximal femur osteotomy was executed, and the CAD plate was generated using SolidWorks by an instrumentmaker at the OLVG hospital. The TO plate was developed through the definition of an initial design domain and iterative TO process. The FE model was validated against experimental data obtained from the CAD plates using digital image correlation (DIC), and was extended to incorporate a musculoskeletal system to simulate more complex physiological loading conditions (i.e., two-leg stance and walking). Compression tests and cycling loading were performed to evaluate the long-term mechanical function of the plates (Figure 1a).

Results
The FE results (Figure 1b) indicate that the CAD plate experienced high levels of stress near its most lateral proximal screw during two-leg stance and walking scenarios. The maximum stress values recorded during these conditions were 233.0 MPa and 762.0 MPa, respectively. However, these levels of stress exceeded the designated safety margin while walking, thereby posing a risk of further plate fractures. On the other hand, the TO plate exhibited a more evenly distributed stress pattern that remained within the safety limit. Furthermore, the TO plate was 18.1% shorter and had a maximum thickness around the fracture gap that was doubled that of the CAD plate.

The results from the compression tests further revealed that all 3D-printed TO constructs failed at loads greater than walking loading condition. Meanwhile, three out of the four CAD constructs failed at lower loads compared to the maximum walking load. Additionally, the TO constructs demonstrated a 25.5% higher ultimate load value, 41.6% higher ultimate displacement, and 79.8% higher stored strain energy compared to the CAD constructs. The TO plate was also characterized by a reduced design area, a unique screw arrangement, and a 23.1% increase in weight as compared to the CAD plate.

Conclusion
These results highlight the biomechanical efficacy of patient-specific orthopedic plate design strategy using CAD and TO.

Figure 1: a) Experiment setup, b) FE results for CAD and TO plate under physiological loading conditions

References
MINERAL DENSITY AND MICROSTRUCTURAL MORPHOLOGY OF WOVEN BONE DURING DISTRACTION OSTEOGENESIS

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Introduction

Characterization of bone regeneration is being studied currently for several processes, such as fracture healing or distraction osteogenesis. In many of these situations, a disorganized type of bone, woven bone, is formed first, that will reorganize and densify over time [1]. Not much is known, however, about how this process evolves, and what the relationships are between changes in tissue properties and structural remodeling. Therefore, the purpose of this study was to investigate the evolution of woven bone tissue mineralization, tissue stiffness and microstructure in ex vivo samples from distraction osteogenesis experiments.

Methods

Samples of woven bone generated in a previous animal study were used [1]. In these experiments, 6 sheep underwent osteotomy followed by 15 mm distraction osteogenesis at their metatarsus to generate new bone. Samples of the callus region were harvested at days 35, 50, 79, 98, 161 and 525 after surgery (1 sample per timepoint) and scanned using microcomputed tomography (Scanco microCT100). This analysis provided the evolution of the mineral density at 4 specific interzones per sample that were used in the earlier nanoindentation studies. One of these analyzed areas is located in the original surrounding cortical bone (A in Fig 1) and the others in the newly formed woven bone (B3, B4 and B5 in Fig 1). In addition, the microarchitecture of the newly formed bone in the gap region was quantified by structural parameters such as connectivity density, trabecular number, thickness and separation.

Results and discussion

Results revealed that the mineral density of the woven bone tissue increased with time (from 600 to 1100 mgHa/cm³, mean values) during the regeneration process. These changes in mineralization correlated well with changes in tissue stiffness over time as measured at the same locations in a previous study [1] using nanoindentation (Fig. 2).

Over time, the bone microstructure also changed. The trabecular number decreased (3.1 to 2.2 per mm), while trabecular thickness and separation increased (0.10 to 0.38 mm and 0.35 to 0.49 mm respectively). A drastic reduction of connective density was found (125 to 7). All these results reflect the transition from a fine-grained disorganized structure to a courser grained organized trabecular structure.

These results provide more insight in the transformation of woven bone into mature lamellar bone during load adaptive bone remodeling.

![Figure 2. Elastic modulus measured versus mineral density in the same locations for all the samples](image)

References


Acknowledgements

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Figure 1. Mineral density distribution in one of the samples and locations of indentations in a previous study [1] in cortical bone (A) and new bone generated (B3, B4 and B5).
POTENTIAL OF USING SHELL ELEMENTS METHODS IN FSI SIMULATIONS OF PULMONARY ARTERIES

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Introduction

Using an in-silico model for cardiovascular hemodynamics simulations has grown significantly in recent years. The increased use of in silico models can be attributed to several useful properties like their accuracy in calculating vessel wall deformations, wall shear stress, velocity, and pressure fields. Moreover, their capability to evaluate multiple physiological scenarios within a wide range of patients can either improve the design of in vivo experiments, or even completely replace them. However, selecting the best model configuration for a specific cardiovascular application is a significant challenge, emanating from the required model accuracy, computational costs, the available data, and the type of analysis and study.

Three-dimensional (3D) fluid-structure interaction models provide the most detailed information regarding vessel wall deformation and hemodynamics, but these models are also hampered by large run-times and memory requirements. Using shell elements instead of solid elements is a promising way to reduce the computational cost while still considering wall movement, which is lost when using rigid tube computational fluid mechanics (CFD) approaches. In this study, we investigate the potential of using shell elements in an FSI simulation of pulmonary arteries.

Methods

A patient-specific geometry of the proximal pulmonary artery was generated, which includes the main pulmonary artery that bifurcates into the left and right pulmonary arteries. Blood was modeled as a Newtonian and incompressible fluid to simulate the hemodynamics. To impose the inlet condition, a physiologic time-averaged flow was used as the outflow of the right heart. A three-element Windkessel was applied at the outlets to mimic the physiological condition of the distal vasculature. To investigate the effect of the shell method on the local hemodynamics, FSI simulations with both solid and shell elements, and a rigid CFD simulation was done. For the FSI simulations, a hyperplastic model for the blood vessel wall was used.

To investigate the performance of each simulation and compare the difference in outcome, the wall shear stress (WSS) was analyzed using the COMSOL computing platform (https://www.comsol.com/). Being influenced both by wall motion and fluid flow, the WSS was considered an important hemodynamic parameter for this comparison.

Results

After a mesh convergence study, all simulations were run successfully. The globally distribution of WSS in all three case was similar, but locally have some different. In CFD case, the local WSS was different from FSI cases, while in FSI-Shell the pattern was close to FSI-Solid. The FSI-Shell simulations were two times faster than the FSI-Solid simulations.

![Figure 1: Comparison of wall shear stress in CFD, FSI-Shell, and FSI-solid simulation of the flow in a pulmonary artery bifurcation.](image)

Discussion

The result shows positive potential of using shell elements method in FSI simulation when considering hemodynamics. This method have the accuracy and computational cost between CFD and FSI-solid methods. In future work, the analysis will be repeated for transient inflow conditions.

Acknowledgements

We acknowledge the European Union’s Horizon 2020 research and innovation programme (grant agreement No 101017578) for their financial support.
3D STATISTICAL SHAPE MODELING FOR CLASSIFICATION OF TREATMENT EFFECTS ON OSTEOPOOROTIC MOUSE BONE GEOMETRY

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Introduction
In preclinical studies, murine bone models simulate osteoporosis and test different treatment strategies. Morphometric analysis using in vivo longitudinal micro-Computed tomography (μCT) scans typically measure the treatments effects on bone geometry. This method accounts for scalar changes such as cortical thickness [1], leading to unrepresentative measure of the treatment impact due to this geometric approximation. This study develops a Principal Component Analysis (PCA)-based model to enable: 1) localized quantification of the 3D geometric variations, given by the PCA modes, 2) classification of the most important treatment effects.

Methods
The examined population consisted of two groups, the treated after ovariectomy, “ML” (N = 6) and the untreated, “OVX” (N = 5). The “ML” group received mechanical stimulus at week 19 and 21. The right tibiae were scanned using in vivo μCT (10.4μm/voxel) every two weeks between week 14 and 24 [2]. Two time points, week 18 and 24, were included. Image slices from the midshaft were selected [3]. The proposed pipeline extracted surface meshes from images to represent the bone shapes. A bone structure at week 18 was used as reference. 3D image samples were rigidly registered, binarized and processed to enforce topological equivalence. The reference surface mesh was extracted from the surfaces in the reference image. This reference mesh was mapped to each bone sample by applying the displacement field found with elastic image registration (spatial resolution equal to 5 voxels) [4]. The mapped reference mesh on each bone composed the rows of the PCA-input matrix. The PCA temporal modes were primarily classified by score clustering and measuring the individual score changes (δα) over time. “α” denotes the scores and “δ” the differences. The scores were firstly normalized and clustered over the cohorts. Treatment-related modes were determined when the score changes are different in magnitude in the “ML” from those in the “OVX” group. Important treatment modes were identified by further performing paired two-sided Wilcoxon tests of the scores before and after treatment. For these modes, a pairwise analysis complemented the classification. The averaged Cohen’s effect sizes were also calculated.

Results and Discussion
The reference surface mesh was composed by tetrahedral elements with 8934 nodes. The first PCA 6 modes described 90% of the total variance. The first and sixth mode described significant treatment effects detected on the anterior crest and on very localized scattered features across the section, respectively (p<0.05) (Fig. 1a). Modes 1 and 6 captured 50% of the overall variance, and the effect sizes for their scores before and after the treatment were 1.9 and 2.4, respectively. Other treatment modes captured the endosteal resorption and periosteal apposition at the medial aspect (mode 2) and at the lateral aspect on the distal end (mode 4). Mode 5 captured the opposite change at the anterior crest on the distal end. The above changes (modes 2, 4 and 5) occur to a less extent as there is a noticeable trend of temporal score changes, but not statistically significant. The remaining modes described other minor sources of variation. Fig. 1b is the pairwise plot of the score changes for both cohorts and for the significant modes, highlighting the achieved clustering.

Figure 1: (a) Modes 1 and 6 illustrated as vectors on top of the mean shape. Contour colors show the vector magnitude. (b) Boxplots of score changes (δα) for mode 1 and 6 and scatter plot.

Conclusions
This study identified new 3D features that capture the main bone adaptation patterns to mechanical stimulus. The methodology has the potential for testing all treatment strategies in murine studies.

References

Acknowledgements
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VALIDATION OF A FRACTURE HEALING ALGORITHM ACROSS MULTIPLE FIXATION STABILITIES

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Introduction
Despite improvements in fracture treatment, non-union rates persist and best-practices to avoid them remain debated. Specifically, the optimal surgical fixation method for distal femoral fractures remains unknown due to constraints of in vivo and in vitro trials, such as limited patient and surgeon recruitment capacity [1] and limitations of in vitro callus development. In silico trials have previously addressed these gaps in other areas [2]. Fracture healing algorithms, such as the Ulm Fracture Healing Model [3], simulate the progression of fracture healing and have been used to compare fixation methods and configurations. Chondrogenesis and ossification are modelled based on mechanical strain in the callus. A finite-element (FE) model calculates strains due to expected loading. A healing algorithm calculates updated material properties of each callus finite element. The simulation is performed iteratively. Despite the progress of fracture healing algorithms, they have not been validated across different fracture geometries, healing metrics, and applied strains [3-4]. This study presents the validation of a fracture healing model against corresponding experimental data from literature [5] across 3 initial interfragmentary gap sizes and 2 initial interfragmentary strains (IFS).

Methods
An FE model was developed in MSC.Marc (v2021, MSC Software) of a simple transverse mid-diaphyseal metatarsal ovine osteotomy secured with an external fixator with a pre-defined callus domain. A 40 mm long section of the fracture region was modelled. The external fixator was represented as an axial spring according to design criteria of the original experiment [5]. An axial compressive load of 500 N was applied. A fracture healing algorithm was developed based on a modified version of the Ulm Fracture Healing Algorithm [3-4]. 6 initial fracture conditions were simulated, representing the experimental conditions of Claes et. al. (Table 1) [5]. Simulations were run for 56 iterations, representing 56 days.

<table>
<thead>
<tr>
<th>Group</th>
<th>Gap size (mm)</th>
<th>Strain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>E</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>F</td>
<td>6</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 1: Different combinations of gap size and allowed IFS simulated, matching published experiments [5].

Bending stiffness of the simulated facture region at the final iteration was assessed using an in silico four-point bending rig. The bone fragments were extended in length to match the experimental conditions [5].

Results
The simulated bending stiffness of the callus region at 8 weeks for groups A-F were 19.8, 19.7, 19.8, 1.8, 18.5, and 0.3 N mm⁻¹, respectively. These results are compared against experimental data in Figure 1 [5].

Discussion
The simulated callus bending stiffnesses at 8 weeks post-op fall within the corresponding published experimental values [5] for Groups A, B, C, and F. However, the negative effect of high strain is over-stated (Group D) and the negative effect of large initial gap size is under-stated (Group E). This study demonstrates an initial validation for four of the six simulated fracture configurations. Discrepancies between the presented model and experimental data will be addressed with a sensitivity study of the model.

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Acknowledgements
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Introdution
Aortic root connects the left ventricle to the ascending aorta and houses the aortic valve (AV) ensuring one-direction flow of blood during systole. The AV is normally composed of three leaflets, known as tricuspid aortic valve (TAV), but 1-2% of the population is born with only two leaflets, known as bicuspid aortic valve (BAV). The patients with BAV are considered at high risk of developing aneurysms and eventually dissection. The biomechanics of aortic root tissues are hypothesized to play an important role in the disease development. In this study, we use in-vivo echocardiographic images from TAV and BAV patients to analyze the differences in the biomechanics of aortic root tissues.

Methods
3D transesophageal echocardiographic (TEE) images of the aortic root were retrospectively acquired from 16 patients with the approval of the Institutional Review Board at the University of Pennsylvania. The images were segmented, registered, and converted into a medial model as presented in a previous study [1]. The medial models were remeshed with a quadrilateral elements.

Two methods were used for the biomechanical analysis: 1) patient-specific 3D inverse finite element (FE) modeling, and 2) population-level Bayesian inference based on radius variations. In the first approach, the frame just before AV opens was considered to be the reference, starting frame for the FE simulation, which was performed in FEBio [2]. Pressure waveform was determined using a Wind-Kessel model. Then, the displacement from other time frames was used to fit the biomechanical parameters of the finite element simulation using SciPy’s least square fitting algorithm.

In the second approach, radius and longitudinal stretch at the sinotubular junction (STJ) were extracted from the medial models. The root was modeled as a uniform cylinder with a closed-form solution of the governing equations, thus circumventing the need for finite element solver. A Fourier decomposition was performed to reduce the dimensionality and remove the effect of time-shift between images. A Bayesian approach previously developed [3] was used to infer the model parameters, including the reference radius and the stresses in the tissues, by matching the radius in the Fourier domain.

Results
The two approaches provided distinct advantages. The first, patient-specific approach preserves geometric details, but the effect of diastolic pressure and opening angle could not be accounted form. The second, Bayesian approach allowed us to calculate the population-level differences between TAVs and BAVs, but it discarded part of the information available from the images. The medial models of all TAVs and BAVs are shown in Fig. 1. The two groups are size matched, but still have some differences in their shapes [1].

Conclusion
The biomechanical differences we found in this work indicate that the aortic root tissue in BAV patients experience different intramural stresses that might be linked to the higher risk of aneurysm development. Future work will include implementation of growth and remodeling framework to further establish this link.

References
PREDICTING PELVIC FLOOR STRESSES DURING VAGINAL DELIVERY: A MACHINE LEARNING APPROACH

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1. INEGI, Portugal; 2. FEUP, Portugal

Introduction

The second stage of labor is associated with obstetric trauma, leading to long-term consequences such as incontinence or pelvic organ prolapse. These conditions greatly impact women’s quality of life [1]. Although a widely discussed topic, childbirth trauma remains unpredictable. As a tool to analyze the biomechanics of labor, computational models and the finite element method (FEM) are commonly used in problems that cannot be addressed in vivo. However, since the FEM can be computationally expensive, researchers in the biomechanical field have been resorting to machine learning (ML) algorithms to reduce the cost of simulations. FEM-based simulations are still costly to generate, but a well-trained ML algorithm can reduce the time required to predict the desired outcomes [2]. This work aims to use ML models to predict the stresses on key regions of the pelvic floor during vaginal delivery, using different input material parameters to characterize these muscles.

Methods

A dataset was generated using data retrieved from FEM simulations. Childbirth simulations were conducted with different material properties of the Martins constitutive model [3], to characterize the PFM (Equation 1).

\[ U = c e^{b(\frac{c}{T} - 3)} + A e^{a(\frac{d_T}{T} - 1)^2} - 1 \]  

(1)

The c, b and A material constants varied between [0.01, 0.03], [1.0, 2.0] and [0.01, 0.05], respectively, whereas a was kept constant. A total of 2189 simulations were successfully completed. A dataset was created in which each node of the pelvic floor corresponds to an observation. A total of 46 nodes of the PFM near the urogenital hiatus were selected, resulting in a total of 100694 observations. Features such as node number and position, initial coordinates, and material parameters were used for training. Five models, namely Decision Trees (DT), Random Forest (RF), Extreme Gradient Boosting (XGBT), Support Vector Regression (SVR), and Neural Networks (NN), were chosen for the study [2]. A training and test set were created with a 90/10 split, recurring to the stratified shuffle split method, to guarantee the same feature distribution in both sets. Subsequently, hyperparameter optimization with cross-validation was performed. The models’ performance was measured by the mean squared error (MSE) and the mean absolute error (MAE).

Results

In the FEM simulations, the stresses of the urogenital hiatus varied between 0 and 95 MPa, thus ML models must predict values within this range. Preliminary results of the tested algorithms are presented in Table 1. Performance assessment demonstrated that RF and NN algorithms provided the best results.

<table>
<thead>
<tr>
<th></th>
<th>DT</th>
<th>RF</th>
<th>XGBT</th>
<th>SVR</th>
<th>NN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSE</td>
<td>0.435</td>
<td>0.418</td>
<td>0.513</td>
<td>5.013</td>
<td>0.397</td>
</tr>
<tr>
<td>MAE</td>
<td>0.353</td>
<td>0.345</td>
<td>0.387</td>
<td>1.033</td>
<td>0.372</td>
</tr>
</tbody>
</table>

Table 1: MSE and MAE for the ML algorithms used.

Since the MAE represents a mean of all predicted values, this error can also be analyzed per node. Thus, Figure 1 presents the MAE measured at each of the 46 selected nodes near the PFM for the RF model.

![Figure 1: MAE per node for RF model.](image)

Discussion

This work represents a preliminary approach to predict the outcome of childbirth simulations with ML techniques. The results obtained are promising and can be further optimized by gathering additional data and use of alternative methods to increase the models’ performance. In a clinical setting, identifying stress levels or other relevant indicators in the pelvic floor can provide a patient-specific biomechanical analysis of potential delivery issues.

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Acknowledgements

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COMPARISON OF ZERO PRESSURE GEOMETRY AND PRESTRESS METHODOLOGIES IN CARDIOVASCULAR IN-SILICO ANALYSIS

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Introduction

Advanced computational frameworks have been used to recreate the biomechanical behaviour of Ascending Thoracic Aortic Aneurysms (ATAA), aiming to develop tools that assist clinicians in stratifying the risk of acute complications [1]. These frameworks are often assisted by in-vivo patient-specific data, obtained via medical imaging exams. This data is used, among other applications, to reconstruct patient-specific anatomical models. Computational Solid Mechanics (CSM) requires the reference configuration which is not directly assessable through imaging data as the blood vessel in physiological conditions (image configuration) is always loaded. This work compared the numerical results of CSM simulations of the ATAA wall obtained by two different prestressing approaches.

Methods

The ATAA wall was generated by extruding with uniform thickness (1.5 mm) the patient-specific lumen segmentation of Computed Tomography Angiography (CTA) data (Figure 1a)) and was modelled as a Neo-Hookean, isotropic and incompressible material. The wall prestressing was performed resorting to two methodologies: (i) implementation of a minimization algorithm that estimates the reference configuration [2]; (ii) calibration of a prestress tensor that balances a specific hemodynamic load and is included in the formulation of the Cauchy’s momentum equation [3].

Results

The results of the CSM simulations were obtained considering a Young Modulus of 1 MPa. Also, at the inner surface of the ATTA wall, a traction field obtained from 2-way Fluid-Structure Interaction simulations [4] was applied, and the domain extremities were fixed (Figure 1b)). In Figure 2, the average relative displacements and stresses for both methodologies at Slice 1 is presented. In both cases, the ATAA increases in diameter during systole in response to increased blood pressure. This diameter growth also induces an increase in the intramural stress field. During diastole, the blood pressure decreases as the blood injection stops, and the ATAA returns to its original shape. The zero pressure approach, however, overestimated the relative displacement magnitude and relative stress magnitude.

Discussion

The results evidenced that both methodologies produced similar evolutions (Figure 1b)) of the average relative displacement and stress. Nonetheless, these quantities were significantly overestimated by the zero pressure geometry. In future versions, it is intended to introduce the linearization of the material properties for the prestress methodology, which is expected to improve the agreement between the two approaches.

References


Acknowledgements

This research was funded by Portuguese Foundation for Science and Technology (FCT) under the project PTDC/EMD-EMD/1230/2021 and UNIDEMI UIDB/00667/2020. A. Mourato and R. Valente are also grateful to FCT for the PhD grants UI/BD/151212/2021 and 2022.12223.BD, respectively.
IMPACT OF DETAILED SKELETAL MODELS IN THE EFFICIENCY OF FORWARD DYNAMIC SIMULATION

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Introduction
For the simulation of some activities, detailed skeletal models are desirable. However, detailed models have a high number of degrees of freedom (DOF), and may include bodies with very different masses, making the simulation more difficult and less efficient, which can be a concern when real-time performance is required, as, for example, in predictive simulations. This work explores whether detailed models can be used for real-time simulations and seeks to quantify the penalty in efficiency they entail, by comparing the forward dynamic simulations of two multibody skeletal human models with different levels of detail in spine, shoulder and hand, for the same movement (squat and ball throw).

Models and methods
Two skeletal models of different levels of detail were tested for the same captured movement. The first model has 18 bodies linked by spherical joints, yielding 57 DOF [1]. The second model includes a more detailed modeling of spine, shoulders and right hand, leading to 29 bodies and 82 DOF (Figure 1).

The detailed spine model features three additional bodies (vertebrae L5-L3, L2-T12 and T11-T8) linked by spherical joints.

The detailed shoulder model includes, as separate bodies, the clavicle, linked to the thorax by a Cardan joint and to the scapula by a spherical joint, and the scapula, linked to the thorax by a tabulated macrojoint [2], introduced to benefit from the efficiency of the semi-recursive multibody formulation used for the forward dynamic simulation. The macrojoint look-up table has 3 DOF (three inputs), and was built in a preprocess by solving the kinematics of the thorax-clavicle-scapula closed-chain mechanism for any possible combination of the three inputs.

The detailed right-hand model features two additional bodies for modeling the thumb, linked by a spherical and a revolute joint, respectively, to the previous body in the chain, and two more bodies for the rest of the fingers, linked by revolute joints.

For the first model, 36 markers are needed in the motion capture, while, for the second model, 15 additional markers are necessary. The single motion capture was carried out with the 51-marker configuration, and then, it was processed separately for the two models. The Kalman-filter algorithm used to process the capture [3] is able to, once the chosen set of markers is selected in the first frame, track only that set of markers and ignore the rest. The forward dynamic simulation of the captured movement employed a CTC controller to track the captured trajectories [4], and used the trapezoidal rule as integrator.

Results and discussion
Table 1 shows the CPU-times required for the forward dynamic simulation of the 9.28-s capture using the two models, and the real-time ratios (real-time/CPU-time).

Table 1: Simulation times and real-time ratio.

<table>
<thead>
<tr>
<th>Model</th>
<th>CPU-time (s)</th>
<th>Real-time/CPU-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>57 dof</td>
<td>0.418</td>
<td>22.2</td>
</tr>
<tr>
<td>82 dof</td>
<td>1.048</td>
<td>8.85</td>
</tr>
</tbody>
</table>

It can be seen that the use of the detailed model entails a severe drop in efficiency. For a 44% increase in the number of DOF, the CPU-time increases in a 151%. However, for the tested detailed model, the implemented algorithm (macrojoint, semi-recursive formulation) allowed to still keeping the real-time ratio above 1 comfortably, which opens the door to use this kind of detailed models in predictive simulations.

References
ADJUSTMENT OF PROSTHETIC SOCKET USING FINITE ELEMENT ANALYSIS

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Introduction

Additive manufacturing techniques found a wide range of applications in the area of prosthetics. These technologies enabled the manufacturing of prostheses adapted individually to the patient’s anatomy. The prosthetic socket is the component of the prosthetic appliances which enable to attach residual limb to the prosthesis. The interface pressure between the residual limb and prosthetic socket has a significant effect on quality of users’ life. Due to the individual anatomical shape, it requires a high level of customization [1-2].

The finite element analysis delivered tools which enabled to evaluate the interface pressure between the residual limb and prosthetic socket and validate the socket shape. This will allow to speed-up the design process of prosthetic socket.

Methods

The finite element model consists of three components: residual limb, bone and prosthetic socket. Hyperelastic behaviour of residual limbs soft tissues were defined using generalized Mooney-Rivlin Solid strain energy function [3].

In this study, the donning procedure of press-fit sockets was simulated. During the first step of analysis, the value of the displacement vector applied to the socket ensures that this component is appropriately positioned.

In the second step of the analysis, following simulation of the donning procedure, the loads correspond to the loading conditions during selected activities and different gait phase were applied. Volume changes in the residual limb are considered as essential factor which significantly affects limb socket interface pressure. The analyses were conducted for two assumed level of changes: 5% and 10%.

Results

The obtained results allow for a detailed analysis of the interface between prosthetic socket and residual limb and evaluation of the durability of socket during various activities.

The highest values of the contact pressure after donning procedure were observed in the spots, specially designed in order to obtain the press fit socket. Nevertheless maximum value of contact pressure was lower than defined pain threshold.

The obtained results enable to indicate the area of residuum - socket interface which have to be corrected. For example, as shown in Figure 1, during the stance phase, the highest value of the contact pressure, 31.5 kPa, was observed at the distal tip of the residuum which is sensitive area.

Figure 1: Contact pressure during the stance phase (expressed in [Pa]) – residual limb

For the residual limbs after the increase in their volume, the highest values of contact pressure were observed for the upper edges of the socket sliding on the residuum surface. The observed changes have also a significant impact on the obtained value of contact pressure. Increase of 10% in the volume of residuum, results in increase in the value of maximum contact pressure equal to 80% (Fig. 2).

Figure 2: Contact pressure after donning procedure (expressed in [Pa]) for different value of relative volume change: a) 5%, b) 10%.

Discussion

The finite element analysis delivered tools which enabled to evaluate the interface pressure between the residual limb and prosthetic socket and validate the socket shape. This allows to speed-up the design process of prosthetic socket. Evaluation of prosthetic socket design using finite element analysis enable comparative assessment of wide range of socket design and their optimization.

References

INFLUENCE OF LOADING CONDITION ON THE ABILITY TO PREDICT HUMERAL STRESS SHIELDING

Christine Mueri(1), Adam Henderson (1), Ghislain Maquer (1), Jeffrey Bischoff (2), Hadi Seyed Hosseini (2), Philippe Favre (1)


Introduction
Stress shielding around the humeral stem is a potential complication after total shoulder arthroplasty. Clinical studies have highlighted that a large relative stem size (RSS) tended to increase bone resorption [1,2]. In silico clinical trials (ISCT) have been proposed to enrich clinical data for device performance assessment. The aim of this study was to evaluate the influence of loading conditions on humeral stress shielding predictions for ISCT when compared to existing clinical data.

Materials and Methods
A benchtop validation of a similar model was performed per the ASME V&V40 to ensure that the physics were captured accurately. For ISCT, we added a clinical validation aiming to reproduce clinically reported cortical thinning in the superior lateral cortex with a larger RSS [1].

A cohort of 34 virtual humeri was taken from an internal 3D bone database, and virtual surgery was performed with the same implant as the clinical study (Bio-Modular shoulder stem, Zimmer Biomet) (Fig. 1A-C). To study the influence of RSS, a stem size matching the size of the humeral canal as well as one size larger was implanted. The implanted bones were imported to a finite element (FE) software for meshing, contacts definitions and application of boundary conditions representative of daily usage (Fig. 1D-F). Bone material properties were assigned from the CT-based bone density information (Fig. 1E). The loading included two different conditions: 1.) the “JRF-only” included the humeral joint reaction forces (JRF) at three different abduction angles; 2) the “full loading” additionally included the major muscles forces (Fig. 1F) [3,4].

Figure 1: Steps for creation of FE models

Stress shielding was assessed by comparing the change in strain energy density (SED) between the intact and implanted bone in the same four regions of interest as in the clinical study [1] (i.e. lateral (L1 ($\theta_1$)), L2 ($\theta_2$)) and medial (M1, M2) aspect of the humeral stem, Fig 2.A). The models were then divided into two groups with (S+) and without (S-) stress-shielding as in [1].

Results
In the group of patients with severe stress shielding (S+), the most cortical thinning was observed in the proximal lateral aspect of the humeral stem (L1) followed by the proximal medial aspect (M1) [1] (Fig. 2A). With the “full loading” boundary condition, the same trend was replicated with the highest reduction in SED observed in the locations L1 followed by M1 (Fig. 2B & Fig. 3), whereas the “JRF only” condition could not replicate the clinical finding, with the largest change in SED observed in the location M1 (Fig. 2C). For both loading conditions, the S+ group had larger RSS compared to the S- group, which agreed with the clinical study.

Figure 2: Examples of cortical thinning [1] (A) and change in SED with full loading (B) and JRF only (C).

Figure 3: Change in SED in the stress shielding group (S+) with full loading and JRF only.

Discussion and Conclusions
The choice of loading conditions highly influenced the prediction of stress shielding. Applying “JRF-only” could not fully replicate the clinical findings. Including the muscle forces, the pattern of stress shielding around the humeral stem occurred in similar locations as observed clinically. Based on these findings, we consider our modelling approach appropriate for ISCT evaluations of stress shielding in the humerus.

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A MULTISCALE APPROACH TO STUDY CHONDROCYTE MECHANOBIOLOGY USING A CARTILAGE-ON-CHIP SETUP

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¹KU Leuven, Belgium; ²University of Liège, Belgium; ³University of Twente, the Netherlands

Introduction
Mechanical loading is an essential factor that regulate the health of chondrocytes. Understanding the mechanobiology of chondrocytes not only helps in unravelling factors that contribute to cartilage degeneration in osteoarthritis (OA), but also in devising mechanical cues to stimulate chondrocytes to regenerate cartilage in a tissue engineering scenario. Given that chondrocyte mechanobiology is a multiscale and multifactorial process, studying it in vivo is a daunting task. To circumvent this, we propose a multiscale in silico - in vitro approach using a combination of numerical modeling and a cartilage-on-chip microfluidic device [1] that mimics the mechanical environment of the chondrocyte in the knee joint. Using this approach, we investigate how mechanical loading might affect the synthesis of relevant matrix proteins by the chondrocyte that results in a change in the chondrocyte microenvironment.

Methods
Primary human chondrocytes (1.5 million cells/mL) were seeded in 2% w/v agarose hydrogel, together with fluorescent beads (3.17 microns, 5 millions/mL) and injected in the cartilage-on-chip device. The device was actuated for dynamic compression with a pressure of 300 mBar and a frequency of 1Hz. An in-house algorithm [2] was used to track the beads to obtain mechanical strains around the chondrocyte due to the mechanical loading imposed. Immunofluorescence staining was performed for Collagen 2 and 6, followed by confocal microscopy to obtain cell specific matrix deposition. Mechanical characterization of the agarose was executed separately and in-silico using unconfined stress relaxation experiments. Subsequently, a multiscale in-silico model of the setup was developed (Figure 1). The multiscale model consisted of 3 different length scales: i) Gel-level finite element (FE) model, containing the cell and bead laden hydrogel in the setup; ii) Cell-level FE model, containing individually segmented cells in hydrogel from the setup, and iii) Intracellular gene/protein regulatory network, which is an additive, semi-quantitative gene and protein regulatory network for chondrocyte mechanotransduction and inflammation developed using a combination of knowledge-based and inference-based approach [3].

Results
Mechanical characterization of the agarose hydrogel revealed that the stiffness of the hydrogel was reduced by 12% on addition of the chondrocytes. There was a further reduction of the stiffness by 10 % on addition of the beads. However, increasing the density of the beads from 1.5 million/mL to 10 million/mL did not cause significant change. By tracking the beads, the distribution of strain across the hydrogel in the cartilage-on-chip was obtained. Furthermore, on zooming in to individual cells, and obtaining brightfield and fluorescent microscopy images, we were able to calculate both cellular deformations as well as deformations of the cellular microenvironment (Figure 1). The gel level and cell level deformations obtained experimentally corresponded closely to the numerical predictions from the model. After a week of static culture of the cells in the setup, immunofluorescent staining revealed deposition of Coll2 and Coll6 by the cells in their near vicinity, thereby indicating the formation of a pericellular matrix by the cells (Figure 2).

Discussion
Using the cartilage-on-chip device together with in silico modeling, we were able to study chondrocyte mechanobiology in a multiscale manner from an external mechanical stimulus to a cellular response. The established workflow not only allowed measuring cell-specific deformations, but also measuring local deposition of matrix constituents by the cells that represent the pericellular matrix. The developed approach has huge potential to facilitate cartilage tissue engineering by unravelling suitable conditions to ensure gradual development of healthy cartilage.

References

Acknowledgements
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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
MECHANOBIOCHEMICAL BASED ORTHOTROPIC BONE REMODELING AROUND UNCEMENTED ACETABULAR COMPONENT

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Introduction

Aseptic loosening of acetabular component is often associated with the adverse effect of periprosthetic bone remodeling owing to stress/strain shielding. An earlier study proposed a thermodynamic-based model that could incorporate the coupling between the mechanical loading and biochemical reactions associated with bone adaptation [1]. Although mechanobiological (MBC) model was considered in a few studies, bone anisotropy was ignored in the algorithm [1, 2]. The objectives of the study were: (1) to develop a novel framework incorporating MBC model with the orthotropic bone remodeling algorithm, and (2) to further compare the predictions with those of orthotropic strain-based remodeling [3].

Methods

The patient-specific 3-D finite element (FE) models of intact and implanted hemipelves were developed following the procedure as reported in our previous study [4]. The implanted model comprised of pelvic bone and a component resembling Zimmer Trilogy™ acetabular cup having outer diameter of 54 mm with Ti-alloy metal-backing (5 mm thickness) and UHMWPE liner (6 mm thickness). The newly developed framework considered a thermodynamic-based bone adaptation along with the orthotropic material property determination based on the strains along the principal directions. The standard law of mass action was modified as Eqn. 1, to achieve the coupling between the concentrations of the constituents in the biochemical reactions (biochemical affinity of the reactions) and the mechanical stimulus [1].

\[ r_\alpha = k_+ \prod_{\alpha=1}^3 [N_\alpha]^{v_\alpha r} - k_- \prod_{\alpha=1}^3 [N_\alpha]^{v'_\alpha r} + l_{\alpha r} d_{\alpha r} \] (1)

Where \( r_\alpha \) and \( A_\alpha \) represents the rate and affinity of the \( \alpha^{th} \) biochemical reaction (\( \alpha = 1 \) to 5), \( l \) and \( k \) represents the phenomenological and reaction rate coefficients, respectively. \( d_{\alpha r} \) represents the rate of dilatation (rate of volume variation). \( v_\alpha r \) and \( v'_\alpha r \) are the stoichiometric coefficients of the mixture of \( N_\alpha \) entering and leaving the \( \alpha^{th} \) reaction, respectively [1].

Results

The changes in bone density distribution, after equilibrium in bone remodeling, corresponding to orthotropic strain-based model (Figure 1b) and orthotropic MBC model (Figure 1c) were compared. The orthotropic strain-based model predicted an appreciable bone resorption (~78%) in the region of interest (ROI) 1, whereas the orthotropic MBC model predicted a slightly lesser reduction in average bone density (~73%) in the ROI 1. The sectional plots of Figures 1b and 1c indicated similar trends of high bone resorption (70-80%) by the both models. However, more volume of bone elements (10-20%) were subjected to bone resorption in the orthotropic MBC model.

Discussion

Bone apposition was observed near the acetabular rim for orthotropic strain-based model and the orthotropic MBC model (Figure 1). However, bone resorption was more predominant in the orthotropic MBC model (Figure 1). Despite similarities, notable deviations in periprosthetic bone density distributions were observed (Figure 1). These results corroborated well with clinical studies. Hence this novel framework, combining biochemical and the mechanical stimuli along with bone anisotropy, adequately predicted bone adaptation around an un cemented acetabular component.

Figure 1: Changes in bone density distribution owing to implantation, sectional and lateral views: (a) immediate postoperative; (b) orthotropic strain-based model predictions; (c) orthotropic MBC predictions.

References

INFLUENCE OF POLAR GRADATION ON DESIGN OF FUNCTIONALLY GRADED POROUS ACETABULAR COMPONENT

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Introduction

The stiffness mismatch between an implant and host bone causes stress/strain-shielding in the periprosthetic bone, leading to bone resorption and eventual loosening. However, the adverse effect of stress shielding can be limited by reducing the overall stiffness of the implant. Alternatively, the implant’s stiffness could be reduced by introducing porosity, thereby varying the microstructure of the implant. Variation in stiffness across an implant can also be achieved by functionally grading the porosity of the implant material. This study is aimed at a novel design of functionally graded porous metal-backed (FGPMB) acetabular components.

Methods

The patient-specific three-dimensional finite element (FE) models of intact and implanted hemipelvises were developed following the procedure reported earlier [1]. The effective orthotropic mechanical properties of the porous structure were calculated using homogenization of a tetrahedron-based unit cell. The $V_1$, $V_2$ and $V_3$ denoted the volume fractions corresponding to porosity levels $p_1$, $p_2$ and $p_3$, respectively (Figure 1). The porosity levels $p_1$, $p_2$ and $p_3$ were taken as 50%, 0%, and 81%, respectively. A porosity of 50% was assumed at the inner radius ($\theta = 0^\circ$, $R = R_1$) of the component rim that corresponded to an elastic modulus of 30 GPa [2]. Since the cancellous bone around the dome experienced strain-shielding and eventual bone resorption [1], a porosity level of 81% was chosen at the dome ($\theta = 90^\circ$). A porosity level of 0% was chosen at the outer rim ($R = R_2$, $\theta = 0^\circ$), owing to bone apposition in the cancellous bone around the component rim [1]. The values of $V_1$, $V_2$ and $V_3$ were determined as follows:

$$V_1 = V_5 \left[ 1 - \left( \frac{R_1 - R_m}{R_1 - R} \right)^{m_R} \right]$$  \hspace{1cm} (1);

$$V_2 = V_5 \left( \frac{R_1 - R_m}{R_1 - R} \right)^{m_R}$$  \hspace{1cm} (2);

$$V_3 = 1 - \left( \frac{\theta_0}{\theta_0} \right)^{m_\theta}$$  \hspace{1cm} (3);

$$V_4 = \left( \frac{\theta_0}{\theta_0} \right)^{m_\theta}$$  \hspace{1cm} (4).

Here $\theta_0$ is equal to $90^\circ$, $m_\theta$ is the parameter that controls the gradation of porosity along the polar ($\theta$) direction. Moreover, $m_\theta$ was assigned with five different values, such as 0.1, 0.25, 0.5, 1.0 and 5.0. The parameter, $m_R$ controls the gradation of porosity along radial ($R$) direction and was taken as 1.0.

Results

Change in polar gradation exponent resulted in deviations in cancellous bone strains, average volumetric wear of polyethylene liner, implant-bone micromotion and changes in bone density distribution. Although $m_\theta = 0.1$ exhibited a 20% increase in the volume of elements with higher strains as compared to $m_\theta = 0.25$, a sudden change in the porosity was observed near the acetabular component rim ($\theta = 0^\circ$). As compared to $m_\theta = 0.25$, more volume of bone elements, ~75% and ~100% were subjected to bone resorption for $m_\theta = 0.5$ (section 1-1, Figure 2c) and $m_\theta = 5.0$, respectively. An increase of ~40% in the average bone density was noted for $m_\theta = 0.25$ in ROI 1. Only a minor increase of ~7% in average volumetric wear and implant-bone micromotion was observed with a reduction in polar gradation exponent from 5.0 to 0.25.

Discussion

A decrease in polar gradation exponent led to a reduction in bone resorption along with a slight increase in volumetric wear and micromotion. Bone resorption around the posterior-inferior region of the implanted acetabulum for different porous metal-backing was similar to that of solid backing [1]. It should however, be noted that as compared to the solid metal-backing, the bone apposition near the acetabular dome was higher for FGPMB. Hence, the FGPMB having polar gradation exponent of 0.25 appeared to be a viable alternative to the solid component.

References


Figure 1: 2-D representative metal backing.

Figure 2: Changes in bone density distribution owing to implantation: (a) immediate postoperative; (b) post remodeling, $m_\theta = 0.25$; (c) post remodeling, $m_\theta = 0.50$.
CHANGES IN SUBCHONDRAL BONE MICROSTRUCTURE AND SHAPE WITH AGE IN TIBIAL KNEE

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Introduction

Osteoarthritis (OA) is a degenerative joint disease, believed to be one of the leading causes of disability, with higher prevalence with aging [1]. The knee is a complex articular joint and one of the most commonly affected sites by OA. Subchondral bone, located just below the articular cartilage, is crucial to the functioning of the joint, helping to distribute forces and preventing stress concentrations. Despite the importance of subchondral bone in joint health, little is known about its microstructural, material and biomechanical changes with aging. This study aims to address this gap by characterizing the entire microstructure of subchondral bone in the tibial knee of adult and old rats, with a focus on both trabecular and cortical compartments. The ultimate goal of this study is to understand how changes in this region may contribute to the development of OA.

Methods

Proximal tibia specimens were harvested from adult and old (1 and 12 months old) Wistar rats (n=8), available as sample organ donation (approval: IACUC-22-2416) and scanned using X-ray micro-computed tomography (micro-CT, 10 µm voxel size, SkyScan1272). The subchondral trabecular compartment was separated from the cortical shell and trabecular bone morphology was quantified through bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), and degree of anisotropy (DA), comparing bone medial and lateral regions. The thickness of the cortical layer (subchondral plate) was computed in two selected regions of the medial and lateral plateaus (Fig.1a). The top cortical surface (featuring mineralized cartilage) was described by a polynomial function and the local Gaussian curvature was calculated [2].

Results

The global analysis of the subchondral trabecular bone revealed a higher DA in the medial region, which increased in both compartments with age, with higher DA in the lateral side. A decrease in BV/TV with age (up to 20%) was observed, mainly due to an increase in Tb.Sp. In contrast, an increase of up to 40% in cortical thickness was measured. These changes were present in both compartments (Fig. 1). Curvature was highly different between the two plateaus, with the lateral side characterized by a far less flat surface (Fig. 2). Aging seems not to affect local curvatures.

Fig. 1: (a) Illustration of the extracted regions for cortical analysis. (b) Percentage changes of trabecular and cortical bone parameters with age in the medial and lateral regions. * denotes a significant change with age.
Introduction

The shape of osteocytes and lacunae vary with age, bone mechanical stimuli and bone matrix quality. Specifically, osteocytes and lacunae are elongated in lamellar long bones [1, 2], and more spherical in immature long bone [3], aged long bone [4], flat bones [2], woven bone [5], long bones with osteopenia [6], osteoarthritis [6] and osteogenesis imperfecta [1]. Osteocyte-lacunar shape affects cellular and bone strains, and pericellular fluid velocity, when axial loads are applied [7]. To date, it is unknown the mechanical environment around osteocytes in response to physiological loading conditions. Thus, the aim of this study is to quantify the effect of osteocyte-lacunar morphology on the pericellular fluid velocity and on osteocyte and bone strain during walking and running. Altered osteocytes-lacunar shape may impair bone mechanics and mechanoadaptation.

Methods

We performed monolithic fluid-structure interaction (FSI) simulations (Abaqus) of two idealized osteocyte-lacunar models having same osteocyte volume (built in SolidWorks): a slightly elongated cell (minor and major axes ratio = 0.6) and a spherical cell (minor and major axes ratio = 1) [7]. Bone matrix around the osteocytes was modelled in a beam shape, with an interstitial fluid space of 0.75μm [7]. Ten dendrites (0.6 μm thick) were modeled for each cell. All bodies were meshed with tetrahedral elements. Cell and bone were linear elastic with bone having transversely isotropic properties (\( E_L = 16.61\text{GPa}, E_T = 9.55\text{GPa}, G_L = 4.74\text{GPa}, G_T = 3.28\text{GPa}, \nu_L = 0.37 \)) and cell being isotropic (\( E = 4.47\text{KPa}, \nu = 0.3 \)) [8]. The interstitial fluid were modeled as salted water (\( \rho = 1\text{E}^3\text{kg/m}^3 \) and \( \eta = 1\text{E}^9\text{MPa}^{-1} \)). The initial pore pressure was assigned to be zero. A multiaxial cyclic displacement was applied on the top, bottom, right and left surfaces of the bone block to simulate bone strain during 10 seconds of walking and running, accordingly to the values of human tibia strains reported in the literature [9]. Cell and bone maximum principal strains and the bone interstitial fluid velocities were calculated for each model. The monolithic FSI approach allowed for the mutual influence between solids and fluid.

Results

The maximum principal strains in the bone matrix were comparable in the more elongated cell vs. spherical one during walking. Controversially, the bone matrix principal strain for the spherical cell were twice as much as those for the more elongated cell during running. Cell strains and pericellular fluid velocities were higher in the spherical cell (Fig. 1) compared to the more elongated one during walking and running. The maximum principal strains were always higher in the spherical cell for both activities. Peak maximum strain and fluid velocity values were reported around the dendrites.

Discussion

This study shows that spherical osteocytes and surrounding ECM experience higher levels of strain, as well as higher interstitial fluid velocities, during intense physical activity such as running. Moreover, cases of bones that show spherical osteocytes have also been associated with reduced spacing between cells and smaller Young’s modulus [1, 10]. This could ultimately lead to an overall increase in bone and cell strains and pericellular fluid velocities, making bone fragile and cells more stimulated. Overall, these data may help us to better understand the implications of osteocyte shape in pathological cases of increased bone turnover and bone fragility such as osteogenesis imperfecta.

References


Acknowledgements

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OPEN HANDS: AN OPEN SOURCE STATISTICAL FINGER MODEL

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Introduction
Hand osteoarthritis (OA) affects joint movement and function, greatly impacting quality of life. Finger joint morphology is governed by the articulating bones and supporting ligaments, which differ between individuals and may be changed in disease. Population-based analysis of bone morphology using statistical shape modelling (SSM) can inform the design and testing of treatment devices and consumer products, as well as fundamental biomechanics studies. For example, statistical analysis of the thumb [1] has demonstrated morphological variation in the carpometacarpal joint. However, few researchers have access to the anatomic data required for such analysis, and there is cost, and risk associated with CT or MRI scanning volunteers. Therefore, this paper presents multi-body statistical shape models of the four fingers of the hand, providing models that can be published for open use whilst preserving the security of the underlying imaging data, for the purpose of supporting wider community efforts in hand biomechanical analysis.

Methods
A multi-body SSM pipeline was implemented in MATLAB (MathWorks, USA) on an exemplar training population of 10 right hands, imaged by CT at 0.3mm resolution, segmented, meshed and aligned [2]. Consentig participants (5F:5M, 27-37yrs) were free from disease or injury (ethics ref: IRAS 14/LO/1059 & ERGO 61718). Model generation included (1) non-rigid registration [3] for point correspondence between datasets, (2) estimation of interphalangeal joint axes and placing them into neutral flexion, to remove alignment variation during imaging, and (3) principal component analysis (PCA) for dimensionality reduction of size and shape variation. Nine principal components (PCs) of morphological variation were found for the distal, medial and proximal phalanx of the index, middle, ring and little finger. A Leave-One-Out cross-validation test was performed, calculating the mean vertex error in reconstructing the mean shape.

Results
The first PC represented phalanx size in all fingers and accounted for over 45% of the variation (Fig.1). Gross measures were extracted to illustrate this variation in scale (Table 1). Subsequent PCs showed variation in position along the palmar-dorsal axis and bone breadth. Repositioning successfully removed joint flexion variation from the PC results. The model has been shared as an open-source repository (https://github.com/abel-research/OpenHands).

Figure 1: Dorsal-Palmar and Radio-Ulnar plane views of four fingers; mean and extremes (+/- 2std) in PC1.

<table>
<thead>
<tr>
<th>Finger</th>
<th>DP</th>
<th>MP</th>
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<th>Total</th>
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<td>17.9</td>
<td>25.2</td>
<td>41.1</td>
<td>84.3</td>
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<tr>
<td>3</td>
<td>19.2</td>
<td>30.2</td>
<td>46.1</td>
<td>95.6</td>
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<tr>
<td>4</td>
<td>19.8</td>
<td>28.9</td>
<td>42.9</td>
<td>91.6</td>
</tr>
<tr>
<td>5</td>
<td>18.2</td>
<td>20.7</td>
<td>34.3</td>
<td>73.1</td>
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</table>

Table 1: Mean (standard deviation) bone lengths in mm from PC1.

Discussion
This study presents a pipeline for generating an anonymised finger SSM from healthy, living participants. The model describes a small, homogeneous population, and assumptions cannot be made about how it represents individuals outside the training dataset. However, it supplements gross anthropometric datasets with additional shape information, and if trained with additional CT images the model may be of use for investigating factors such as joint morphology, and for design of hand-interfacing devices and products. We encourage the community to use it, and to contribute.

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Acknowledgements
We thank Prof D Warwick, Dr L King, Dr A Darekar, and C Everitt for development of the imaging protocol and original data collection. This research was supported by funding from the European Union’s Horizon 2020 program (ref. 863183).
MODULAR CONTROLLER FOR PREDICTIVE SIMULATIONS OF HUMAN STANCE AND GAIT

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Introduction
Predictive musculoskeletal modelling is a useful tool for deriving biomechanical data in different scenarios. Gait models have been shown to be able to replicate physiological data [1, 2]. However, these models are specific to the gait task and their physiological plausibility is questioned. In the present work, a modular controller for predictive simulations is presented. In this controller, a hypothetical mesencephalic locomotor region (MLR) sends descending control signals to two different internal models, that organize five synergies to accomplish quite stance or gait.

Methods
The musculoskeletal model used in the simulations is based on that presented by Geyer and Herr [1]. The head, arms, torso, and the lower limbs are modelled as seven segments articulated by six pin joints, hips, knees, and hips. Seven actuators induce torques in these joints: hip flexors, gluteus, hamstrings, vastus, gastrocnemius, soleus, and tibialis anterior. Synergies, modeled as function-specific polysynaptic reflexes, send excitatory outputs to the actuators, based on synergy activation patterns modulated in amplitude and frequency, in a task-dependent way, by task-specific internal models (IMs). The IM for gait uses five synergies: compliant leg behaviour, leg propulsion, hip unloading, swing, and leg retraction, while the IM for stance only uses the compliant leg behaviour synergy. The output of the synergies is triggered and prolonged by different sensorial afferents, and is described as:

\[ u_i = \alpha (1 + \cos(2\pi \eta u_a + \pi + \phi)) \quad (1) \]

where \( u_i \) is the output of the synergy, \( u_a \) is the control signal from the MLR, \( \Phi \) is a phase coupling signal, \( \alpha \) are the modulation in frequency and amplitude of the internal model, and \( \eta \) is the sensorial modulation of the frequency. We developed simulations where the first 5 seconds were controlled by the stance IM and the following 25 seconds by the gait IM. The model was implemented in Simulink (MATLAB R2022a). The CMAES algorithm was used to optimize the synergy-specific parameters (13 for stance and 30 for gait) during 300 iterations [3].

Results
The model was able to keep balance at a physiological metabolic cost of 1.2 W kg\(^{-1}\) [4]. After 5 s, 10 s of steady walking was achieved at 0.8 and 1.3 m s\(^{-1}\) with physiological metabolic cost of 5.5 and 3.5 J kg\(^{-1}\) m\(^{-3}\), respectively [5]. Figure 1 shows the muscle activation and kinematics of the gait at 1.3 m s\(^{-1}\).

Discussion
We examined whether signals triggered by sensorial events but driven by tonic inputs can execute motor tasks. The resultant model is a hybrid of a central pattern generator (CPG) and a reflexive controller that can switch from stance to gait. Even though muscle activation do not fit physiological patterns, we expect those variables to be adjusted in further optimizations. Also, the model is intended to switch between different types of gaits while the stability is tested in a noisy environment.

References
A COHORT OF PATIENT-SPECIFIC AND VIRTUAL FINITE ELEMENT MODELS OF INTERVERTEBRAL DISCS AND MODEL VALIDATION

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Introduction

Finite element (FE) analyses have been used to study human tissues and organ biomechanics. However, automating patient-specific (PS) Intervertebral Disc (IVD) models can take time and effort to explore the poromechanical behavior of tissues under large deformations [1], and no cohorts have yet been generated to explore the particularities of morphology or whether the latter can be a factor in IVD degeneration (DD) [2]. This work aims to generate a FE mesh repository of PS models through a morphing process and extend it through a virtual cohort employing a statistical shape model (SSM). Simulations are performed to explore the effect of morphology and validate the modeling approach.

Materials and Methods

169 3D shapes of lumbar IVDs, from healthy to grade 4 degeneration states, generated during the European My Spine project (FP7-269909), were obtained from MRIs [3]. The segmentations included the annulus fibrosus (AF) and the nucleus pulposus (NP). The Bayesian Coherent Point Drift (BCPD) algorithm rigidly and non-rigidly aligned the meshes [4] to a previously validated structural mesh of the IVD to PS IVD segmentations [1]. Mesh morphing was carried out in seven stages to end with a mesh quality analysis and test the similarity between the morphed model and the segmentation through Hausdorff distance. Cartilage endplates (CEPs), not visible in the images, were created automatically, with a height between 0.7 and 1 mm. Synthetic IVDs were generated by SSM using the PS cohort. Mechanical simulations of physiological loads were performed, considering a swelling step, 8 hours of sleep, and 16 hours of daytime, applying 0.11 and 0.54 MPa of pressure on the upper CEP, respectively. The modeling approach was validated using the experimental data reported in [2]. FE-predicted displacements were obtained for a model morphed to the tested specimen, by imposing a compressive load of 500 N, which increased linearly from 0 to 10 s, then maintained for 3 h (creep).

Results

The first twelve modes of the SSM cover 90% variability, of which the first 3 represent coronal (46 to 52 mm), sagittal (34 to 40 mm), and height (7 to 17.5 mm) width, that cover healthy and DD models according to the Pfirrmann grading system [5] (Figure 1). There were no differences when comparing the mesh quality of the template model with the PS models, so BCPD maintains the proportions of the relative distances between the nodes. A 94% similarity was obtained between the AF and NP segmentations with their respective meshes. The mechanical variables, such as pore fluid velocity, show substantial variations in the transition zone (TZ) between AF and NP. Clinical imaging has shown DD onsets in the same TZ [6]. The relative error between the simulation of this validation and the experiment was 5.20% and presented a similar curve to the simulation of the previous work.

Impact

The cohort is a unique set of models to explore the effect of multiple geometric variations on the multiphysics and mechanobiology of IVD, including the full organ tissue structure [2]. The algorithm can create PS FE models from any segmented surface provided by third parties and generate thousands of representative synthetic models of healthy and DDs.

References


Acknowledgements

European Commission: Disc4All-MSCA-2020- ITN-ETN GA: 955735; O-Health-ERC-CoG-2021-101044828

Figure 1: Models generated with different heights.
CLOSED-FORM MODELING OF THE SOLEUS MUSCULOTENDON UNIT

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Introduction

Hill-type muscle-tendon unit (MTU) models, Fig. 1, are widely used in a variety of applications while maintaining an appropriate balance between model complexity and accuracy. Throughout the literature there are models of the MTU that use Splines and other conditional statements for modeling the hill-type muscle [1]. Finding a closed-form equation for this system enables to implement different controllers for controlling the MTU force in closed-loop fashion.

Two strategies were used to solve this issue. First, different \( \hat{L}^M \)s were tested using optimization and regression. Since in this strategy the optimization should be done for every muscle and gait separately, a second strategy was developed. In this strategy, equation (2) was simplified to a linear model, \( \hat{F}^m = a\hat{L}^m + b, \) and damping was added to the hill-type muscle model (Fig. 1). The linearized model assumption is valid while \( |\hat{L}^m| \leq 0.5 \) which is almost always the case for walking and running gaits [3].

Methods

There were some attempts in the literature to obtain the closed-form equation for the MTU [2]. The tendon force equation is derived by the following equation:

\[
\hat{F}^T = k^T (L^{MT} - \hat{L}^M \cos \alpha + \hat{L}^M \sin \alpha \dot{\alpha})
\]  

(1)

where, \( F^T \) and \( k^T \) are the tendon force and stiffness, respectively. The MTU length, \( L^{MT} \), and the pennation angle, \( \alpha \), are derived by the limb kinematics but the muscle fibre length, \( \hat{L}^M \), is derived by the integral of the following equation’s inverse:

\[
\hat{F}_v^M (\hat{L}^M) = \frac{\cos \alpha}{a(t)} \cdot \hat{F}_v^M = \hat{F}_v^M (\hat{L}^M)
\]

(2)

In this equation, \( \hat{F}_v^M \), \( \hat{F}_v^M \), \( \hat{F}_v^M \), and \( F^{PE} \) represent the optimal muscle force, muscle force-length, force-velocity, and the parallel element force, respectively. Since the muscle activation, \( a(t) \), is in the denominator of equation (2), the Clay Anderson’s muscle model with optimal parameters becomes unstable when \( a(t) \equiv 0 \):

![Figure 1: The pennate hill-type muscle model that is modified using a parallel damping element (in red)](image1)

![Figure 2: Tibialis Anterior tendon force during plantar/dorsiflexion using a dynamometer](image2)

![Figure 3: Comparison of the tendon forces obtained by the proposed MTU modeling technique with CEINMS toolbox for: a/b) Soleus and latGas using dynamometer, c/d) Soleus in gaits with various speeds](image3)

References

PREDICTIVE CONTROL OF PLANTARFLEXOR MUSCLE-TENDON FORCE DURING SIMULATED HUMAN HOPPING

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Abstract

Assistive devices (e.g., exoskeletons) could be used to steer a user’s musculotendon unit (MTU) loading in vivo. A challenge is to develop a control algorithm that is simple enough to enable fast computation and adaptable enough to handle different gait patterns. Here, we propose a nonlinear model predictive control (NMPC) approach to maintain a predefined threshold tendon force within the plantarflexor muscle-tendon complex during simulated human hopping.

Introduction

Human-in-the-loop (HIL) control of exoskeletons can identify the assistance strategy that minimizes a user-related cost function during gait [1]. A downside of this approach is that the computational time required for state-of-the-art HIL approach to identify the optimal assistance pattern is approximately half an hour [2]. Alternatively, we seek direct control of muscle-tendon (MT) force via estimation using available toolboxes [3] and a personalized closed-form model [4]. In this way, it should be possible to demonstrate direct control of a user’s tendon force – to say, target a given cyclic strain rate for tissue healing. Here, we use a modelling/simulation framework to demonstrate model-predictive control (MPC) that can predict future tendon dynamics and provide smooth exoskeleton assistance during simulated hopping.

Methods

Building on previous simple models of human hopping with passive-elastic exoskeletons [5] by adding a computationally-efficient closed-form equivalent model for MT force [4], a combined exoskeleton-MT model (Fig. 1a) can be obtained using the following equation:

\[ F^T = k^T (L^M - \dot{L}^M \cos \alpha + L^M \sin \alpha \dot{\alpha}) \]

where, \( F^T \) and \( k^T \) are the tendon force and stiffness, respectively. The MTU length, \( L^M \), and the pennation angle, \( \alpha \), are derived by the limb kinematics and the muscle fibre length, \( L^f \), is derived using the method discussed in [4]. Equation (1) is a state-space model of the combined exoskeleton-MT model:

\[ \dot{x} = Ax + Bu \ , \ x = \begin{bmatrix} F^T \\ L^M \\ L^f \end{bmatrix} \ , \ u = F_w . \]

Next, the derived nonlinear state-space representation is used as the inner model of an NMPC controller and the cost function of the controller is defined as:

\[ J = w_1 \Delta u^2 + w_2 (\Delta u)^2 + w_3 (F_w^*)^2 \]

where, \( w_i \) are constants and \( \Delta u \) is the exoskeleton actuator force increment. We extracted human-like specifications and activation dynamics from [5] (Fig. 1b) and the controller’s horizon and upper bound were set to 15 steps and 1000 N, respectively. To demonstrate feasibility in silico, we set the goal of the controller to keep tendon force under 1000 N. An interior-point method was used for solving the optimization problem.

Results and discussion

Over a range of simulated hopping intensities (Fig. 1b), our novel NMPC controller appropriately commanded exoskeleton actuator force (Fig. 1c) to maintain tendon force under the target threshold (Fig. 1d).

Figure 1: a) The simplified hopping and actuator model, b) activation dynamics for hopping, c) actuator assistive force, d) tendon force with and without assistance.

References

PATIENT SPECIFIC FINITE ELEMENT ANALYSIS OF HUMAN CORNEAL LENTICULES: AN EXPERIMENTAL AND NUMERICAL STUDY

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Introduction
In recent years, the prevalence of myopia has increased, and projections suggest that it will affect more than half of the world’s population by 2050 [1]. The number of elective refractive surgeries has also risen, estimated at a 30% yearly increase. The cornea’s curvature shape is the primary determinant of ocular refraction; therefore, evaluation and quantification of its biomechanical properties is necessary for accurate refractive procedures. Because it is difficult to obtain human samples, few studies have characterized young human corneal tissue [2]. Lenticule extraction surgeries provide a source of young cornea samples. The purpose of this study is to mechanically test and numerically model human corneal lenticules obtained from CLEAR surgery patients and to improve material modeling using a physiological description of its microstructure.

Methods
Five corneal lenticules from four patients (27 y- 30 y) were included in the study and uniaxially tested within 24 hours of surgery (KEK approval 2021-00145). (Fig 1a). Using preoperative data and surgical parameters a finite element mesh of the lenticule was created using GMSH 4.0 and ABAQUS 2020. The Holzapfel Gasser Ogden (HGO) material model was used to describe the cornea as a fiber-reinforced material [3]. Additionally, the angular integration approach was used to model the isotropic in-plane and aligned out-of-plane dispersion of the fibers, allowing for a more accurate representation of the microstructure and mechanics of the cornea. A Bayesian optimization algorithm was also used to obtain the best fit between the experimental and numerical results by adjusting the mechanical parameters of the model. The optimization was performed for each patient individually (patient-specific) and simultaneously for all patients (general model).

Results
The force-displacement response under uniaxial loading showed a typical non-linear behavior for all samples. From the finite element analysis, the von mises stress is uniform in the central region but increases near the attachments, where the experimental failures were also found (Fig 1b). Optimization of the mechanical parameters resulted in a good agreement with the experimental data for both the general and patient-specific fits (Fig. 2). The optimal parameters for the general model are $C_{10} = 24$ kPa, $k_1 = 4.98$ MPa and $k_2 = 40.34$.

Discussion
The study considers patient-specific geometry and physiologic fiber dispersion to estimate the hyperelastic behavior of human corneal stroma. The study demonstrates the small benefit of the patient-specific fitting over simultaneous parameter optimization. The results of the study can be used to improve the prediction of the mechanical behavior of the young cornea after refractive surgery. The stress-strain data obtained in this study are within the range of the literature [2]. One of the limitations of the study is that it includes only five lenticules from four patients with similar correction ranges, which does not represent the overall population.

References

Acknowledgements
This work was supported by the SNSF grant IZLIZ3_182975.
LIMB FLEXION INDUCED DEFORMATION OF FEMOROPOPLITEAL ARTERY STENTS IN THIEL EMBALMED CADAVERS

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Introduction
Nitinol stents placed in femoropopliteal arteries (FPA) are constantly exposed to variable mechanical loads during limb flexion often leading to their failure contributing to disease progression [1]. Thus, it is important to understand FPA behaviour and evaluate nitinol stent designs in this complex biomechanical environment to improve stent performance. Thiel embalmed cadavers present an excellent vascular test bed providing vascular patency and preserving tissue texture for a longer time [2]. Previous studies have used fresh/lightly embalmed cadavers resulting in loss of tissue texture altering FPA biomechanics [2, 3]. The objective of this study was to assess deformation encountered by self-expanding nitinol stents in FPA of Thiel embalmed cadavers due to limb flexion.

Methods
Cadaver specimens and perfusion: Three human Thiel embalmed cadaveric specimens were selected for the study. An arterial perfusion circuit was established to form entry and exit points and the arteries were perfused with Thiel solution at flow rate of 150-400 mL/min.

Clinical Imaging and Segmentation: Nitinol stents were deployed under fluoroscopic guidance. CT data was acquired, and 3D segmentations were performed for typical postures such as standing, walking, sitting, gardening and crossed leg in pre- and post-stented conditions shown in Figure 1. Limb-flexion induced deformation was quantified. Curvature Analysis: Quantified by fitting radius of the circumscribed circle to three centreline coordinates in the range of a window size at constant increments of arc lengths [4].

Results and Discussion
We report an average increase in curvature values from standing posture to all bent configurations in both pre- and post-stented FPA with distal end in the gardening posture showing maximum average curvature changes shown in Figure 2. A comparison of the pre- vs post-stented regions showed an average decrease in curvature in the stented region for all postures suggesting that the stent could impose restrictions on axial shortening ability of FPA resulting in distal kinking of the popliteal region. Clinical implication of this could be disruption in natural blood flow associated with restenosis and neointimal hyperplasia [5]. Thus, this study presents a novel test bed with arterial perfusion comparable to native FPA for stent placement and its deformation analysis.

Acknowledgement & Ethics Statement
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 813869. This publication reflects only the author’s view, and the REA is not responsible for any use that may be made of the information it contains. All cadaveric research is conducted in compliance with relevant anatomical legislation, with donors having given their consent in accordance with the Anatomy Act Scotland (1984) and the Human Tissue (Scotland) Act (2006)

References

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
Introduction

Coronary computer tomography angiography (CCTA) is an imaging technique which provides invaluable detailed anatomical information of coronary arteries, that are essential in the pre-procedural analysis and diagnostic process. To support and improve the diagnosis, accurate segmentation of the coronary arteries is a crucial step, for the purpose of stenosis detection and quantification of stenosis severity (e.g., with fractional flow reserve). Segmentation is typically manually performed by expert operators; however, this is a tedious and time-consuming work, that carries bias introduced by the radiologist [1]. Thus, an accurate, fast and fully automated segmentation pipeline is highly desirable, but challenging due to the relative complexity and high inter-subject variability of coronary anatomy [2, 3]. In this work, we describe the development and evaluation of a fully connected convolutional neural network (CNN) based pipeline for the automatic segmentation of the coronary lumen from CCTA images.

Methods

Overall, 168 CCTA scans of patient with at least one stenotic coronary were retrieved. The right and left coronary lumens were manually segmented, including the main branches, by expert operators. The original volumetric images and segmentations were sliced along the axial, coronal and sagittal direction (Figure 1a), in order to obtain 3 different datasets of 2D images with the corresponding segmentation mask. Each of the resulting dataset included ~40k couple of images and masks. The three dataset was randomly split into a training set and a test set (based on a typical 80/20 subdivision), then a CNN was implemented, based on the 2D U-Net architecture. Data augmentation was performed, including contrast and intensity adjustment and random affine transformations. Due to high class imbalance between the foreground (i.e., the coronary arteries) and the background, dice focal loss (DFL) was used to train the model, which is defined as a weighted sum between focal (FL) and dice (DL) loss: DFL = λFLDL + λFLD, λFL=0.3 and λDL=0.7 were used in this work. After the training phase, three models were obtained, for every slicing direction. To achieve coronary 3D reconstruction of a subject, the trained models were applied along each respective direction on one single CCTA acquisition. The final layer of the CNN for each of the three model was extracted and the three predictions were averaged. Finally, the activation function (i.e., softmax) was applied to obtain the 3D segmented volume.

Results

After the training, the CNN segmentation yielded a mean dice score (DS) of 0.754 along axial direction, 0.732 along the coronal direction and 0.745 along the sagittal direction, with respect to the manual ground truth segmentations. The main branches such as the left descending anterior artery, the left circumflex artery and the right coronary were generally precisely detected. Experimental results on different slices are shown in Figure 1b. The 3D reconstruction of the coronary arteries obtained combined the three models prediction is shown in Figure 1c.

Discussion

We developed a CNN-based automated pipeline for the automated segmentation of standard and stenotic coronary arteries from CCTA imaging. This tool has the potential to support stenting pre-procedural planning in a real clinical setting.

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TWO PHOTON POLYMERIZATION OF AN IMPLANTABLE MICROSCOPE OBJECTIVE FOR INTRAVITAL MICROSCOPY

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I. Introduction
Regulations for biomaterial testing rely on histopathological analyses of animal biopsies leading to ethical issues(1). In this context, intravital microscopy techniques allow to quantify in-vivo the foreign body reaction to the implant reducing the number of animals required to statistically validate the biomaterial(2,3). However, traditional windows chambers are invasive, lead to strong inflammatory reactions and fail in the reliability of long-term evaluations. Therefore, we developed a system of microlenses, coupled to a microscaffold, both incorporated in a miniaturised imaging window.

II. Materials and Methods
The device is microfabricated by two-photon polymerization (2PP) of a biocompatible photoresist called SZ2080(4). It is designed to act as an in-situ microscope objective with the aim to overcome the restrictions of in-vivo imaging related to tissue-induced spherical aberrations. The chip includes fluorescent beacons, allowing optical alignment for multiple observations. Firstly, we established the microlenses process of fabrication as 2PP of the outer shell followed by the UV bulk polymerization of SZ2080(5). We developed a dedicated protocol to fabricate both the microlenses and the 3D microscaffolds on the same chip. Then, we quantified the lenses dioptric power and magnification by coupling them to low numerical aperture objectives, to image stained cells cultured in-vitro both on flat substrates and inside the 3D microscaffolds.

III. Results
We proved the reliability of the microfabrication process and independently validated the microlenses morphological and optical quality and obtained a prototype of the integrated smart microstructured imaging window (Fig.1.A-C). Remarkably, the fabricated microlenses allow to efficiently excite the fluorescence of labelled cells (Fig.1.D-F) and collect high resolution, magnified images of them on a conventional two-photon scanning microscope (Fig.1.G-H). The chip enhanced the possibility to reduce optical aberrations related to intravital imaging.

IV. Discussion
Thanks to these encouraging results, the chip will now be used for in-vivo observations of the host inflammatory response to the implant of biomaterials, in the aim (a) to reduce the number of animals sacrificed in biomaterial testing procedures and (b) strengthening the validation protocols in both a qualitative and quantitative manner.

Acknowledgements
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 964481. Funded by the European Union (ERC, BEACONSANDEGG, G.A. 101053122). Views and opinions expressed are however those of the authors only and do not necessarily reflect those of the European Union or the European Research Council. Neither the European Union nor the granting authority can be held responsible for them.
CONSEQUENCES OF LIMITING ELECTROMYOGRAPHY AND GROUND REACTION FORCES ON MODELLED ANTERIOR CRUCIATE LIGAMENT FORCES

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1. Griffith University, Australia; 2. The University of Melbourne, Australia

Introduction
Modern computational models can accurately quantify anterior cruciate ligament (ACL) loads during dynamic tasks in the laboratory [1,2]. These models use body motion, ground reaction forces (GRF), and electromyograms (EMG). However, acquiring EMG and GRF outside the laboratory, i.e., sports fields or medical clinic, is challenging due to instrument costs, setup time, and skills to acquire and interpret data. Limiting EMG and GRF data, while maintaining model prediction accuracy, would be practically valuable for translation of ACL modelling technology outside the laboratory. We examined the consequences of limiting EMG and GRF on fidelity of model-predicted ACL loads.

Methods
Twenty-three healthy females (mean (±standard deviation) age, mass, and height of 19.7 (±4.0) years, 59.7 (±9.5) kg, and 1.65 (±0.06) m, respectively) performed a standardized drop-land-jump task, while body motion, GRF, and surface EMG were acquired. Data were used in four neuromuscular models: EMG-informed and static optimization, each with three dimensional (3D) and exclusively vertical GRF. For each model, external biomechanics, lower limb muscles, and knee contact forces were computed, and subsequently used to estimate ACL force [1,2]. The ACL force across stance and rank-order of participants based on their peak ACL force were compared across models using one-way repeated measures ANOVA and post hoc t-tests via statistical parametric mapping and Kendall's rank correlation, respectively.

Results
Compared to EMG-informed + 3D GRF, both EMG-informed and static optimization methods using only vertical GRF generated significantly higher ACL force (mean differences, 205.5 N and 253.8 N, respectively) for most of stance. When 3D GRF were used, differences between EMG-informed and static optimization were observed only within the final 20% of stance (mean differences, 116.4 N). Compared with static optimization + 3D GRF, both EMG-informed and static optimization combined with only vertical GRF generated significantly higher ACL force (mean differences, 89.1 N and 137.4 N, respectively) for most of stance (Figure 1). No statistically significant correlations in rank-order of participants were found between EMG-informed + 3D GRF and the other models (Table 1), meaning model configuration affects both absolute and relative magnitude of ACL forces. Although, vertical GRF is readily measured in-field using commercially available instruments, this study demonstrated using only vertical GRF substantially overestimated ACL loads. Simplifying the neural model to static optimization overestimated ACL loading even when modelling used 3D GRF.

Discussion
Simplifying requirement for experimental measures of muscle activation patterns via static optimization and/or reducing GRF from 3D to only vertical force resulted in spurious model estimates of ACL loading. Compared to modelling with 3D GRF, using only vertical GRF resulted in much larger ACL forces due to a lack of a posteriorly directed GRF during landing. The consequence of neglecting EMG in favour of static optimization was more complex. Individual responses were highly variable, but resulted in a small but significant increase in ACL loading for the cohort studied. Finally, rank order of participants based on their peak ACL loading could not be preserved under any simplified modelling approach used in this study. Findings indicate both EMG and 3D GRF should be included to model ACL loading during dynamic tasks.

Table 1: Kendall's rank correlation of peak ACL force between different modelling approaches during drop-land-jumping.

<table>
<thead>
<tr>
<th></th>
<th>SO + vGRF</th>
<th>SO + 3D GRF</th>
<th>EMG-inf + vGRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation</td>
<td>-0.028</td>
<td>-0.012</td>
<td>0.067</td>
</tr>
<tr>
<td>p-value</td>
<td>0.876</td>
<td>0.958</td>
<td>0.676</td>
</tr>
</tbody>
</table>

References
MODELLING THE INITIAL CALLUS PHASE IN BONE FRACTURES

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1. Introduction
Bone healing is the process of a fracture in which the reconstruction and continuity of the fractured bone occurs.[1] This process can be divided in the succession of six fracture healing phases: the acute inflammatory response, recruitment of mesenchymal stem cells (MSCs), generation of a cartilaginous and a periosteal bony callus, revascularization and neoangiogenesis at the fracture site, mineralization and resorption of the cartilaginous callus and bone remodelling. [2]
From these six processes, this paper focuses on the initial callus phase that happens during the third stage of the bone healing process. This phase is essential to obtain the initial geometry of the callus, that is needed for the development of subsequent consolidation phases. The proposed algorithm can be applied to 2D and 3D geometries, allowing the simulation of a finite element model to obtain information that otherwise is difficult to obtain. In this case, the information obtained is the volume of callus generated per day.

2. Materials and Methods
The growth algorithm for the initial callus phase depends on several interconnected phases. Each one of these phases has a different mission: calculation, topology, control and evolution [3].
The calculation phase consists of a finite element module that solves a diffusion problem for specific initial and boundary conditions.
For its part, in the topology phase, the algorithm: recognizes the surface, how it looks like and indicates how the callus will grow.
The growth rate check takes place during the control phase. In this phase, the growing speed can be modified according to the presence of different molecules in the blood.
Finally, in the evolution phase, the algorithm causes mesh growth where previously indicated.

3. Results
As a result of the application of this algorithm, different callus volume values have been obtained for different moments of callus closure for a transverse diaphyseal fracture of the femur. A transverse fracture is a horizontal fracture and the study case is made with a transverse six mm gap fracture:

<table>
<thead>
<tr>
<th>Day</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔVol (mm³)</td>
<td>0</td>
<td>3080</td>
<td>7008</td>
<td>9166</td>
<td>10279</td>
</tr>
</tbody>
</table>

Table 1: Callus volume increment for different days.

4. Conclusions
The algorithm for the initial callus phase allows the development of a tool that helps in the process to obtain information, generally difficult to access. This algorithm works with four well differentiated phases and it works for 2D and 3D.

5. References

6. Acknowledgements
This research was funded through the financial support of Department of Science, University and Knowledge Society of the Government of Aragon – Spain for the project “Biomechanical and clinical study of centromedullary nailing in the treatment of diaphyseal fractures of the femur” [project number LMP37_21, 2021]
Introduction

We here present the results of initial validation studies and proof-of-concept for the “TomoSAXS” multimodal X-ray analysis technique for characterization of collagenous tissues. Collagenous structures are key constituents in a range of biomechanically important soft tissues, and form a hierarchy in size from interlocking fibrils (nm), to collagen fibres (µm), and lamellae (10’s-100’s µm). A range of X-ray probing and imaging techniques exist to study the morphology and mechanics of these structures individually; Small Angle X-ray Scatter (SAXS) provides information on orientation and D-spacing between collagen fibrils [1], while microcomputed X-ray tomography (µCT) permits volumetric imaging of collagen fibres and lamellae [2]. TomoSAXS presents the first technique to correlative employ these modalities, providing information on nm-µm structures with a volumetric context.

Following development of the TomoSAXS algorithm using digital phantom data, validation has been performed on collagenous tissues at a range of resolutions, upon samples of varying complexity. Analysis of tendon collagen using varying probing resolutions from laboratory and synchrotron X-ray sources provides proof-of-concept for the quantitative analysis of nm-to-µm scale characterization of collagen structures using TomoSAXS.

Materials and Methods

Unlike other volumetric SAXS techniques (e.g. SAXS tensor tomography [3]), TomoSAXS uses complimentary µCT data to provide information on collagen fibril orientation. This information is subsampled and centred to mirror the (coarser) SAXS voxel map, and orientation values saved as separate matrices comprising azimuthal and lateral angles (respectively). These matrices are used to provide information for 3D collagen diffraction models [4] to simulate meridional SAXS peaks from interaction between X-ray beams and collagenous structures of discrete 3D orientations. These models are employed across a simulation of the TomoSAXS scan (SAXS maps sampled at differing angular orientations), providing estimates of per-voxel occupation of “χ-space” and overlap.

Voxel interactions are analysed in a cascading sequence, starting with those with the highest proportion of independent χ-space. The measured fibril D-period (Q position of respective peak in 1D azimuthal integration plots) and fibril morphology (fibril thickness inversely related to the ratio between χ-space/Q-space occupation) from 2D SAXS maps sampled at n angles are used to deconvolute signals from overlapping interactions until a 3D estimate is provided for every scanned voxel.

This methodology (developed in the Python [3.8] environment and validated upon digital phantoms of known per-voxel D-period and orientation) was first employed to study eight chicken foot tendon samples cured under differing tare loads and arranged in differing orientations, probed using DL-SAXS (Xenocs Xeuss 3.0; 450 µm³ voxel size) and µCT (Phoenix Tomo X; 14.5 µm³ voxel size) (Fig.). These same samples, alongside 12 additional samples, were further characterized at higher resolutions at the I22 (SAXS; 20 µm³ voxel size) and 113 (µCT; 1.63 µm³ voxel size) beamlines at Diamond Light Source.

Results and discussion

Validation of the TomoSAXS algorithm using digital phantoms suggests it estimates D-period and fibril morphology to >95% accuracy. Estimation of these properties in chicken foot tendon samples reflect differing tare loads and are comparable between scans of differing resolution. These results highlight the potential of the TomoSAXS method for characterizing the interplay between nm-scale and µm-scale collagenous structures. This provides a new opportunity for assessing a host of biomechanical enquiries including the effects of ageing and disease.

References


Acknowledgements

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LEARNING FACIAL MOTION USING DEEP REINFORCEMENT LEARNING AND FINITE ELEMENT MODELING

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2. Univ. Lille, CNRS, Centrale Lille, UMR 9013 - LaMcube - Laboratoire de Mécanique, Multiphysique, Multiéchelle, F-59000 Lille, France

Introduction

Due to altered facial muscle mechanism and nerve damage, patients with facial palsy or those who have undergone a facial transplant have an asymmetrical face and irregular facial movements [1]. A complex rehabilitation process is needed to restore a symmetrical face with balanced functionality. Thus, a better understanding of the facial motion mechanism plays an essential role in the recovery of symmetrical motions and typical facial expressions of the affected individuals. To provide feedbacks for decision support, computer-aided systems and physics-based models have been developed [2]. However, the predictive capacity of current solutions is still limited to explore the facial motion patterns with emerging properties. The objective of the present study is to develop a novel methodology using reinforcement learning and finite element modeling for the learning and prediction of face motion without a priori input motion patterns.

Materials and Methods

The developed methodology relates to a coupling between a reinforcement learning (RL) agent, a human finite element face model and associated simulation environments (Fig. 1).

Reinforcement Learning

Finite Element Modeling

Target Facial Motion

RL Agent

Action: muscle strain/force

State

reward

Multi-objective function

Figure 1: An overview of the innovative coupling process between FE modeling and RL.

Within the Artisynth modeling environment, a generic face FE model was used [3]. The soft tissue mesh consists of 6342 brick elements and 8720 nodes. Hypodermis layer was modeled using a Mooney-Rivlin hyperelastic law ($C_{10} = 0.4 \text{kPa}, C_{20} = 1.4 \text{kPa}, D = 50 \text{kPa}$). The Fung’s law was used for the epidermis and dermis layers ($c = 21.3 \text{kPa}, \mu_a = 5.9 \text{kPa}, \lambda_{ab} = 1 \text{kPa}, \kappa = 250 \text{kPa}$). Facial muscle was modeled as point-to-point Hill-type model ($\lambda = 1.4$, $\sigma_{\text{max}} = 100 \text{kPa}$, $P_1 = 0.05$, $P_2 = 6.6$). To perform the facial learning using deep RL, an information exchange protocol was developed to transfer action and state of the face between the PyTorch RL platform and the Artisynth FE platform. Deep deterministic policy gradient (DDPG) and Twin-delayed DDPG (TD3) algorithms were implemented to drive the simulations of symmetry-oriented and smile movements. Using the Euclidean distance and angle derived from 8 landmark sites around the mouth, different reward functions were developed. For evaluation and validation purposes, numerical results were also compared with experimental observations (Bosphorus database).

Results

As a result, the reinforcement learning agent encountered 100 episodes of random behavior in the environment before discovering the best course of action after more than 300 training episodes. When it comes to symmetry-oriented motion, the expected muscle excitations assist in raising the reward value from $R = -2.06$ to $R = -0.23$, which accounts for an 89% improvement in the face's symmetry value. Two spots at the mouth's edge move up 0.35 cm when the facial model smiles (Fig. 2), which is within the Bosphorus database's expected range of motions (0.4–0.32 cm).

Discussion and Conclusions

Reinforcement learning allows performing facial motion learning without a priori input motion data. The use of this approach leads to explore the facial muscle activation and contraction patterns for a specific movement. This opens new avenues for patients-specific face rehabilitation. As perspective, our novel methodology will be applied with image-based patient-specific model of the human face of the facial palsy and facial transplantation patients.

References


Acknowledgements

This work was financially supported by Sorbonne Center for Artificial Intelligence (SCAI).

Figure 2: The animation of the face for smile motion.
UNCERTAINTY QUANTIFICATION COUPLED WITH FINITE ELEMENT SIMULATION OF THE SECOND STAGE OF LABOR

Trieu-Nhat-Thanh Nguyen (1), Abbass Ballit (1), Jean-François Witz (1), Pauline Lecomte-Grosbras (1), Jean-Baptiste Colliat (1), Tien-Tuan Dao (1)
1. Univ. Lille, CNRS, Centrale Lille, UMR 9013-LaMcube-Laboratoire de Mécanique, Multiphysique, Multiéchelle, F-59000 Lille, France

Introduction

Finite element models of the pelvis system for labor and childbirth simulations have been commonly developed to analyze vaginal delivery mechanism leading to avoid potential complications (e.g. levator ani muscle injury) [1]. However, the reliability of the simulation outcomes remains a challenge due to complex pelvis system geometries and mechanical properties of the involved soft tissues. In particular, uncertainty quantification (UQ) of the input data and associated propagation effect is still not investigated. The objective of this work is to perform UQ of the material properties of the uterus soft tissues and to simulate its propagation during the second stage of labor simulation. In particular, dependent properties were modeled with specific uncertainty formulation.

Results

The displacement field of the uterus tissue along a specific path at the uterus neck during the UQ process is illustrated in Fig. 2.

![Figure 2 Displacement field of the uterus tissue along a specific path at the uterus neck under different simulation trials.](image)

Discussion and Conclusions

Uncertainty quantification is one of the best practices in biomechanical modeling to ensure the reliability of the outcomes [3]. This study showed that material properties of the uterus soft tissue are sensitive to the simulation outcomes and their uncertainties should be taken into consideration. In particular, the use of copula allows dependent properties to be taken into consideration. As perspective, the active uterus behavior will be integrated into a more realistic second-stage labor model and simulation. Then, uncertainty quantification will be conducted for more reliable decision support.

References


Acknowledgements

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EFFECT OF MECHANICAL AORTIC VALVES ON CORONARY ARTERY FLOW IN A PATIENT SUFFERING FROM ISCHEMIC HEART DISEASE

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Introduction
One of the most common diseases of the cardiac system is ischemic heart disease (IHD). It remains the leading cause of mortality worldwide [1]. To detect ischemia caused by artery stenosis and quantify its severity fractional flow reserve (FFR) method is commonly carried out.

In our study, we aim to assess the difference in FFR values in patients with a mechanical valve implanted. The study determines the effect of blood flow through artificial valves: trileaflet (TRI), bileaflet (BIL) and natural valves, on flow in stenosed coronary arteries and the value of the FFR index.

Methods

The geometrical model of blood was generated in Mimics software from CT images of a 50-year-old man with coronary artery stenosis. The model consisted of the aortic root with Valsalva sinuses and coronary arteries. We considered two types of mechanical valves, i.e. BIL and TRI valve and natural aortic valve (Figure 1). The design of the mechanical valve rings and BIL valve discs was modelled in our previous study [2].

The dynamics of blood circulation were determined using ANSYS 2020 R2 software. Flow velocity at maximum valve opening was determined from a Doppler ultrasound examination. The value of 0.97 [m/s] was determined at the inlet of the system. The zero gauge pressure was described at the aortic outlet and coronary arteries outlets.

Results

Using data from the results of pressure distribution, the FFR ratio was calculated and compared with the results of coronarography (Table 1). The FFR is defined as the ratio of mean pressure measured distally behind the stenosis location (Pd) to mean pressure measured proximally (Pa). The pressure (Pd and Pa) was calculated at a distance of five stenosis diameters from the maximum coronary artery stenosis as it is measured during the examination. Figure 2 shows the flow velocity change in the aortic root and ascending aorta.

<table>
<thead>
<tr>
<th>EOA Geometric flow area [cm²]</th>
<th>FFR [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>natural valve 2.85 3.74</td>
<td>83</td>
</tr>
<tr>
<td>BIL valve 1.53 2.88</td>
<td>78</td>
</tr>
<tr>
<td>TRI valve 0.73 1.61</td>
<td>77</td>
</tr>
</tbody>
</table>

Table 1: EOA geometric valves flow area and FFR ratio.

Discussion

The value of the FFR ratio for the natural valve (83%) is equal to the FFR value from coronarography (83%). The FFR values for BIL and TRI mechanical valves are 78% and 77%, respectively. The differences in the results may be due to the smaller EOA of the mechanical valves. Although the EOA for the TRI valve (0.73 [cm²]) is smaller than the BIL valve’s (1.53 [cm²]), the FFR value differs slightly. This is probably due to the shape of the TRI valve leaflets, which point toward the sinuses of Valsalva at the maximum opening and allow unobstructed blood flow into the coronary arteries.

Studies suggest that geometric parameters of the coronary artery are essential in the final hemodynamic results of the simulations. Defining distal boundary conditions is particularly challenging, as circulatory conditions in the coronary microcirculation are heterogeneous in health and disease. The values of pressure in a coronary artery, and consequently those of FFR, strongly depend on boundary conditions, especially those defined in the truncated ends of the arteries at the outlets [3].

Analysis of fluid behaviour indicates that implanting the valve before the aortic root does not cause vortices in the sinuses of Valsalva and reduces turbulent flow. However, this may have a negative effect on the closure of the valve leaflets.

References
ANALYZING ABDOMINAL AORTIC ANEURYSM VESSEL, LUMEN AND THROMBUS GROWTH USING 3D+T ULTRASOUND

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Introduction
An abdominal aortic aneurysm (AAA) is a localized dilatation of the aorta, which in case of rupture has a mortality rate of 80%. Current clinical guidelines of intervention are based on AAA diameter. However, biomechanical models can improve the prediction of rupture risk in a more patient-specific way, using e.g. CT, MRI or ultrasound (US) imaging [1, 2]. CT requires the use of X-ray and nephrotoxic contrast agents and MRI involves long scan times and high costs. US is safe, cheap, and adds temporal information for mechanical characterization of the AAA, therefore US is the preferred modality for clinical acceptance and longitudinal studies. However US has a low contrast, and limited field of view making it challenging to determine the entire geometry of the AAA. Intraluminal thrombus (ILT) is present in 75% of all aneurysms [3], and it is hypothesized that it reduces the wall stress, therefore decreasing the rupture risk [4]. However, on the other hand ILT reduces wall strength, affecting growth. The effect of ILT size on growth rate was analyzed in a CT-based study by Zhu et al., and they found that both cross-sectional aneurysm diameter and the presence of ILT are independent predictors of AAA growth [5]. However, no studies exist, analyzing ILT growth using 3D+t US. Therefore this study aims to use 3D+t US to analyze lumen, ILT, and vessel volume growth. To give more insights in the contradictory effects of ILT on AAA rupture risk.

Methods
Two patients were included with a clear thrombus on the US images, and having more than 3 follow-ups. To overcome the limited field of view, if available, multiple US acquisitions were registered using phase-only correlation, and fused using wavelet decomposition. A semi-automatic segmentation algorithm was used to determine the lumen, ILT and vessel geometry.

The geometries on multiple moments in time were matched using an iterative closest point (ICP) algorithm. The lumen, ILT, and vessel volume were determined in the overlapping region, and growth was analyzed.

Results
In Figure 1 an example of the aligned US images, and corresponding lumen/vessel segmentations are given. Figure 2 shows that the lumen volume is remaining more constant, compared to the thrombus/vessel volume. This figure also shows that Patient 1 has a lower growth rate (7 ml/year) compared to patient 2 (11 ml/year).

Discussion
In the proposed framework, the vessel, lumen and thrombus volume were analyzed over time. Those preliminary results show, that the lumen volume remains more constant, compared to the vessel volume, due to the increase in ILT size. Future work will focus on including more patients, to obtain a higher statistical power. Besides this framework could be used to analyze the effect of ILT on local vessel growth, and do wall stress-analysis including ILT, to give more insights in the contradictory effects of ILT on AAA rupture risk.

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Acknowledgements
This work was supported by e/MTIC, Medtech solutions for Earlier Detection of CArdiovascular Disease (MEDICAID) project.
PATIENT-SPECIFIC ANALYSIS OF THE HAEMODYNAMIC FACTORS CONTRIBUTING TO RESTENOSIS IN PERIPHERAL ARTERIAL DISEASE

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Introduction

Restenosis is the reoccurrence of stenosis, an abnormal narrowing (≥ 50% [1]) of blood vessels undergoing revascularisation procedures to treat atherosclerosis. Restenosis is linked with different demographic and clinical risk factors [2]. Altered haemodynamic indices also seem to play a role in restenosis progression [3]. Restenosis prediction models in the literature consider predictors in silos, sacrificing essential information contributing to what is, undoubtedly, a multivariable phenomenon. This results in models with limited predictive power. A more holistic approach integrating haemodynamic indices and routinely collected variables into data-driven models may lead to more accurate tools able to classify patients’ risk of developing restenosis in a defined time interval. For this, an in-depth understanding of the relevant haemodynamic factors to be included in the models and their contribution to disease progression is needed.

Methods

High-quality datasets of computed tomography (CT) scans and Doppler ultrasound images of six patients who underwent revascularisation procedures (i.e. stenting or bypass) having heterogeneous follow-up time points were considered. Data were obtained from VA Connecticut Healthcare Systems, West Haven, USA. The patients’ vessel geometries were reconstructed and patient-specific computational fluid dynamics (CFD) analyses were performed following the computational workflow developed by Colombo et al. [4]. An additional step accounting for neointimal hyperplasia (NIH) removal in the reconstruction phase was added to the algorithm. The most commonly reported haemodynamic indices linked to restenosis (i.e. Time-Averaged Wall Shear Stress (TAWSS), Oscillatory Shear Index (OSI), Relative Residence Time (RRT)) as well as the Topological Shear Variation Index (TSVI)) were computed. Their relationship with vessel lumen remodelling was investigated.

Results

Fig.1 shows TAWSS and RRT 3D haemodynamic maps and indices comparison within follow-ups for a patient of the cohort with an implanted bypass for whom no significant lumen remodelling was observed from baseline to 16-month follow-up. Despite this, the distributions of the haemodynamic indices were all statistically significantly different (Mann-Whitney U test, p-value ≤ 0.05) within the two considered time points.

![Figure 1: 3D haemodynamic maps and box plots of TAWSS and RRT distributions comparison at different follow-ups.](image)

Discussion

The relationship between vessel lumen remodelling and altered haemodynamic indices within follow-ups is critical to define their contribution towards disease progression. However, even small vessel changes might lead to statistically significantly different haemodynamic indices. This suggests that haemodynamic changes might not result in significant vessel lumen change immediately, but effects might appear in a longer time frame. Analyses performed on the whole dataset will help to better define the relationship between haemodynamics change and vascular remodelling, with the ultimate goal of developing accurate data-driven models for restenosis prediction.

References


Acknowledgements

We thank TIME project research group (Politecnico di Milano) for providing the reconstruction code. This work was supported by funding from UCL EPSRC CDT i4health [EPS/S021930/1]. The study was ethically approved with approval number AD0009 from VA Connecticut Healthcare Systems, West Haven, CT, USA.
PRE-CONDITIONING OF TRAINING DATA FOR GAUSSIAN PROCESS REGRESSION ENABLED OPTIMISATION OF THE NEOVAD

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2. Innovative Device & Engineering Applications (IDEA) Lab, Texas Heart Institute, TX USA

Introduction

The NeoVAD is a proposed axial Left Ventricular Assist Device (LVAD) specifically designed for use in paediatric patients between 5 and 20 kg. Paediatric patients often receive LVADs designed for adults that are operating externally and off-design due to the incompatible size of these devices [1,2]. The NeoVAD will be the first fully implantable LVAD for patients in this range, greatly increasing the quality of life by reducing the risk of infection and by ensuring device compatibility with small children.

To greatly reduce the computational expense of the blade design process, machine learning enabled surrogate models are created from a series of computational fluid dynamics (CFD) simulations that allow an optimisation routine to find the optimal design without the need for any additional simulations [3]. When creating the surrogate models from limited training data, care must be taken to ensure that the data is well conditioned to create reliable surrogate models.

Methods

The NeoVAD pump is an axial single-stage design consisting of a 2-blade rotor and a 3-blade stator. The blades are circular arc shaped, with constant thickness. The blades are parameterised using the following parameters: rotor inlet angle, \( \beta_1 \), rotor outlet angle, \( \beta_2 \), stator inlet angle, \( \alpha_2 \), rotor chord length, \( C_{\text{rot}} \), and stator chord length, \( C_{\text{stat}} \). A base set of 32 designs were created and were subsequently simulated using Ansys Academic Research CFX, Release 21.1 (Ansys Inc.). Optimising for either maximum efficiency or minimum dissipated energy at a chosen operating point should yield the same design as they are related by the equation

\[
e_{\text{loss}} = \Delta P \left( \frac{1}{\eta} - 1 \right)
\]

where, \( e_{\text{loss}} \) denotes dissipated energy, \( \Delta P \) pressure increase over the pump, and \( \eta \) efficiency. To examine the effect of the spread of data on surrogate model accuracy Gaussian Process Regression was used to fit to calculated efficiency, \( \eta \), dissipated energy, \( e_{\text{loss}} \), and by using a Box-Cox power transform of both efficiency and dissipated energy data.

Results

The spread of data is visualised in Figure 1. The Kolmogorov-Smirnov test was used to compare the normality of data and p-values were 0.82, 0.87, 0.94 and 0.91 for efficiency, dissipated energy, Box-Cox efficiency, and Box-Cox dissipated energy, respectively. The resulting optimal designs were compared between all four surrogate model creation methods and can be seen in Table 1.

![Efficiency and Dissipated Energy](image)

**Figure 1:** Normalised histograms of data over the 32 base designs for Efficiency, Dissipated Energy, Inverse Dissipated Energy and Box-Cox Transform Dissipated Energy.

![Table 1](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( \beta_1 ) (^{\circ})</th>
<th>( \beta_2 ) (^{\circ})</th>
<th>( \alpha_2 ) (^{\circ})</th>
<th>( C_{\text{rot}} ) [mm]</th>
<th>( C_{\text{stat}} ) [mm]</th>
<th>( \eta )</th>
<th>( e_{\text{loss}} ) [J/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \eta )</td>
<td>10.0</td>
<td>60.0</td>
<td>32.2</td>
<td>13.6</td>
<td>14.7</td>
<td>0.75</td>
<td>17.3</td>
</tr>
<tr>
<td>BC ( \eta )</td>
<td>10.0</td>
<td>60.0</td>
<td>29.6</td>
<td>16.3</td>
<td>10.5</td>
<td>0.50</td>
<td>9.3</td>
</tr>
<tr>
<td>BC ( e_{\text{loss}} )</td>
<td>10.0</td>
<td>60.0</td>
<td>31.9</td>
<td>16.4</td>
<td>13.4</td>
<td>0.40</td>
<td>13.8</td>
</tr>
<tr>
<td>Mean</td>
<td>10.0</td>
<td>60.0</td>
<td>31.3</td>
<td>16.1</td>
<td>13.2</td>
<td>0.44</td>
<td>14.0</td>
</tr>
</tbody>
</table>

**Table 1:** Design parameter results and surrogate predictions for each of the four surrogate models and the mean values across designs. Parameters in green indicates closest to mean and in red indicates furthest from mean.

Discussion

The resulting designs seen in Table 2 are sensitive to the spread of the training data. The rotor design is robust, in part to the constraints being set on allowable angles but also showing a maximum deviation of only 3% from the mean value. The stator design is much more sensitive showing a maximum deviation of 7% from mean in outlet angle and 20% deviation in chord length. Examining which designs deviate the most and least suggests that training data with a more Gaussian-like distribution results in more reliable surrogate models.

References

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Acknowledgements

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FALL RECOVERY LIMITATIONS FOR YOUNG ADULT AND ELDERLY MODELS THROUGH COUPLED DEEP REINFORCEMENT LEARNING SIMULATIONS

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Introduction

Human locomotion is a complex task relying on neural command to initiate biological processes regulating muscle activation and contraction mechanisms. The ability of these processes to adapt to unforeseen changes in the environment at any scale may be crucial in fall recovery. We have previously used deep reinforcement learning strategies to better understand human falls in both young adults [1] and by adapting muscle parameters for the elderly [2]. We have recently developed a coupled simulation solution to analyze the physical limits for fall recovery. In this present study, we investigate the sensitivity of learned fall recovery on displacement limits and age-parameters.

Methods

A 3D musculoskeletal model was developed using OpenSim-rl and a backwards falls-driven reward function on young adult muscle parameters. This model was then tested until the center of mass (COM) exceeded the right heel position by 7cm. The position and velocity of each body segment at this point was used to initiate a second simulation which rewarded for recovery (Figure 1). The second simulation learned the muscle activations required to recover from this particular fall. The sensitivity of this recovery behavior was then tested at different displacement values: 6,7,8 and 9 cm respectively; and by testing the sensitivity to ageing (elderly model), considering age-related changes in maximum isometric force, contractile velocity, hip range of motion in extension, passive elasticity and deactivation time, as described in our previous study [2].

Results

The young-model-learnt muscle activations to recover from 7cm of posterior COM displacement relative to the heel position for a backward fall, marked as left foot weight bearing, and showed fall recovery at 7 cm, 8 cm and 9 cm for young muscle parameter tests. No successful recovery was simulated in any of the 5 tests completed at each interval when this learnt behavior was simulated using the elderly muscle parameters. Table 1 shows a comparison of the maximum velocity values for four body segments amongst the completed simulations.

<table>
<thead>
<tr>
<th>Segment</th>
<th>Max Velocity (m/s)</th>
<th>P value (T-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>1.70 / 0.73</td>
<td>0.120</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0.54 / 0.20</td>
<td>0.062</td>
</tr>
<tr>
<td>Right foot</td>
<td>2.49 / 1.27</td>
<td>0.109</td>
</tr>
<tr>
<td>Left foot</td>
<td>3.94 / 2.38</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

Table 1: T-tests were completed on the mean maximum velocities (head, pelvis and each foot) over the 5 testing trials, comparing young (Y) and elderly (E) values across the 4 displacement limits.

Discussion

Simulations providing data for human falls can offer new insights into fall avoidance strategies however their limitations need to be thoroughly analysed. In this study, we investigated the sensitivity of learned behaviour to COM displacement during a fall as well as sensitivity to age-related muscle parameters. Our coupled simulation approach allows us to train models to recover from specific physical positions, such as this left-foot weight bearing backward fall example. This study also highlights a possible effect of age-related factors on the ability of the weight-bearing side to obtain a sufficient response to affect the outcome of the simulation.

References


Acknowledgements

The authors would like to thank the Région Hauts-de-France and Labex MS2T (Maîtrise des systèmes de systèmes technologiques) for the funding of this work.
USE OF AN INDUSTRIAL ROBOT TO RECORD HUMAN KNEE KINEMATICS IN VITRO - EVALUATION OF THE TEST METHOD

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2 Mathys a company of enovis

Introduction

In vitro experiments using 6-axis industrial robots are a common method for studying human knee kinematics, recording passive path (PP) during flexion, and measuring knee laxity at various angles. There is only limited research on the reliability of this test setup even if it has been used countless times for in vitro experiments [1-3]. To ensure reliability, the robot should have an automated determination of the force-and torque-free point at 0° flexion, high reproducibility, and sensitivity.

Method

Test specimens: An anonymized fresh-frozen human cadaveric right knee specimen with medial and lateral unicompartmental knee prosthesis was tested.

Robot set up: All tests were carried out with a 6-df robotic system (KUKA KR 150; KUKA Robotics) equipped with a 6-component force-torque sensor (Omega 160 IP60; ATI Industrial Automation, tolerances: force 2.5N, moment: 0.5Nm).

Finding the force and moment free state at 0° flexion: The goal was to develop a Matlab routine that automatically calculates the starting position, where no forces or torques are acting on the knee except for its own weight. The script determines the load on the robot arm and calculates the position where the knee is in a force-free and torque-free state, which will be used as the starting point of PP and the forces and moments will be set to zero. To test the accuracy of the tare program (TP), the tare point was determined 20 times. After each attempt, a manipulation was performed (e.g., internal rotation), and it was checked if the target values for forces and moments were within the measurement tolerances of the robot sensor.

Reproducibility of passive path (PP): The PP from 0° to 60° was repeated 21 times using the same starting point. The leg was unclamped and clamped again after each trial. Mean and standard deviation were determined for anterior-posterior displacement, internal and external rotation as well as varus and valgus moments.

Results

Validation of tare program: The TP works well and has a hit rate of 90% across all force and moment directions. The most inaccurate is the regulation of the varus and valgus moments where five measurements were outside the tolerance (see Table 1).

Discussion

TP can determine knee force- and moment-free state at desired knee angle reliably and is more accurate than a manual search. The reproducibility study of PP showed that many solutions exist for finding force and moment-free state for a knee flexion. This finding is particularly important for studies comparing cadaver knee prosthesis kinematics to the native state. Therefore, analyse absolute, not relative values when measuring laxity. Further, ligament tension and thus knee stiffness decreases with each pass of passive pathway due to both increased ligament stretching and temperature changes in the specimen and room. Conditioning of the leg according to the same protocol before the test is therefore recommended.

References


Acknowledgements

We thank Innosuisse for supporting this work.

Table 1: Count of trials within/outside tolerance range of sensor.
LOWER EXTREMITY GAIT BIOMECHANICS AND THEIR ASSOCIATION WITH TRUNK FLEXION IN PATIENTS WITH LUMBAR SPINAL STENOSIS

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Introduction

Patients with symptomatic lumbar spinal stenosis (sLSS) have a narrowing of the spinal canal causing nerve decompression which often leads to pain and weakness in the back and legs while walking. Patients with sLSS walk slower and their gait patterns differ from healthy controls, yet little is known about joint kinetics during walking [1]. It is believed that one strategy to relieve pain is that patients with sLSS increase trunk flexion during walking [1,2] and it has been shown that in patients with sLSS, the maximum trunk flexion angle is affected by the maximum hip extension angle, maximum hip flexion moment and step length [2]. Hence, the aims of this pilot study were i) to investigate whether lower extremity gait kinematics and kinetics differ between patients with sLSS, asymptomatic elderly controls and young healthy controls and ii) to assess whether these parameters are related to maximum forward trunk flexion during walking.

Methods

Joint kinematics and kinetics during walking were assessed in 10 patients with sLSS (5m/5f; age, 70±10 years; body mass index (BMI), 29±5 kg/m²), 10 asymptomatic elderly persons (5m/5f; 65±5 years; 25±6 kg/m²) and 10 young healthy persons (5m/5f; 26±2 years; 22±2 kg/m²) using a full body marker set and the Conventional Gait Model 2.3 (CGM 2.3) [3]. Data for four gait cycles per subject were extracted and time normalized to gait cycles (kinematics) or stance phases (kinetics). Differences in angle and external joint moment trajectories between groups were assessed using statistical parametric mapping (SPM, www.spm1d.org) with analysis of variance (ANOVA) with posthoc t tests with Bonferroni correction. The influence of maximum thorax flexion during gait on lower extremity biomechanics trajectories was assessed using scalar linear regression tests. The significance level was set a priori to 0.05 for all tests.

Results

Walking speed was slower in patients (0.97±0.15 m/s) than elderly (1.17±0.17 m/s, P=0.037) and young controls (1.31±0.18 m/s, P<0.001) and the maximum trunk flexion was greater in patients (3.5±9.0°, P=0.014) and elderly (8.2±6.4°, P=0.001) than in young controls (6.3±5.9°).

Figure 1 shows the kinematic and kinetic trajectories with significant differences between groups. At the hip, patients had lower flexion moments after heel strike than young controls (P=0.016) and lower adduction moments around 20% stance than elderly (P=0.003) and young controls (P=0.011). At the knee, patients and elderly had less extension in terminal stance than young controls (P=0.010 and P=0.013) and patients had lower extension moments after heel strike and in late stance than young controls (P=0.016 and P<0.002). At the ankle, patients had lower dorsiflexion moments during push-off than young controls (P=0.004).

Greater maximum trunk flexion during gait was significantly associated with lower hip flexion angles in swing phase (63–83% gait cycle, P=0.009), greater knee flexion angles during midstance (20–39% gait cycle, P=0.013) and lower hip extension moments in the second half of stance (72–80% stance, P=0.018).

Discussion

Although forward trunk flexion in patients was comparable to elderly controls, joint moments differed mainly between patients and young controls but not between elderly and young controls, while joint angles differed between elderly and young controls. Despite methodological differences (patients and controls vs. only patients, and trajectories vs. peak values) to Igawa et al. [2], we found that hip angles and moments were related to maximum trunk flexion. These results indicate that elderly controls might use different strategies than patients with sLSS to adapt their gait to a more forward flexed trunk.

References


Acknowledgements

This work was supported by the Department of Spine Surgery, University Hospital Basel and the Swiss National Science Foundation (SNSF #204461).
MULTI-MODAL NUMERICAL-EXPERIMENTAL SETUP TO IMPROVE THE IDENTIFIABILITY OF THE MATERIAL PARAMETERS OF SOFT TISSUES

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1. Faculty of Mechanical Engineering, Technion Institute of Technology, Haifa, Israel

Introduction

Finite Element Analysis (FEA) gains popularity in the biomedical field when it comes to study the interaction between soft tissues and medical devices. Yet, the modelling of the behaviour living tissues is challenging. Indentation tests, combined with inverse FEA, are among the preferred approaches for the in-vivo characterisation of tissues. However, the identifiability of the parameters may be insufficient when data come from only one experimental modality [1]. The difficulty to compute a unique set of material parameters for soft tissues may lead to critical errors in the prediction of their response to external loads. A method to evaluate the identifiability of soft tissue material parameters from simulated data using homogeneous isotropic hyperelastic materials has been proposed recently [1]. The current study aims to extend this work to heterogeneous (bi-layer) samples, and to validate it using indentations of silicone bi-layer samples with simultaneous measurements of the indentation forces and the surface deformations, using 3D Digital Image Correlation (3D-DIC).

Methods

Bi-layer silicone cylindrical samples, with radius and heights of 60 mm, were designed for this study. The top layer was composed of Ecoflex 00-20 and the bottom layer was Ecoflex 00-30 (Smooth-On, USA). A random speckle pattern was painted on the samples’ surfaces. Indentations were performed with a hemispherical indenter, radius 5 mm, with controlled displacement, δ, up to 10 mm. Stereo-cameras recorded the indentation sites deformation as shown in Figure 1.

![Figure 1: Indentation of a cylindrical silicone sample with displacement measurements using 3D-DIC.](image)

FEA was conducted to replicate the experimental procedure. The axisymmetric model of the cylindrical sample was assigned with isotropic, hyperelastic materials using the symmetrical Ogden-Moerman model with 2 parameters, c and m [2]. The objective function (Equation 1) was a combination of the indenter reaction force errors (F_r) and the surface displacement errors (F_u) and was computed for each δ. The weight factor, η, varied between 0 and 1 to modulate the influence of each measurement. The objective function was evaluated for multiple values of p1 = (c1, m1), for the bottom layer, and p2 = (c2, m2), for the top layer.

\[ F_{obj}(p1; p2; δ) = ηF_r(p1; p2; δ) + (1-η)F_u(p1; p2; δ) \]  \hspace{1cm} (1)

Results

The objective function grids were computed for all values of δ and η. An example for the bottom layer is shown in Figure 2. In this case, identifiability was optimal for η = 0.5, since the uncertainty area around is the smallest, and a unique set of parameters could not be obtained using only the force-depth data, as the uncertainty are spans nearly the entire parameter range.

![Figure 2: Identification of the bottom layer parameters at δ = 10 mm. The * accounts for parameters optimised according to experimental data.](image)

Discussion

The identifiability of material parameters is important for soft tissue modelling since these parameters are crucial for predicting the response to external loads [3]. Increasing the input data, e.g., by adding 3D-DIC measurements, could improve the identifiability, and thus, enhance the accuracy and precision of analyses. For more complex constitutive behaviours, including viscoelasticity or anisotropy, further data could be required. In the future, ultrasound indentations with various orientations will be performed to complete the input data set. An experimental campaign on the soft tissues of healthy subjects is also planned for evaluating the method with in-vivo data.

References

Introduction and Method
Ceramic on ceramic (CoC) total hip replacement clinical reports may on occasion note a noise or squeaking. There is much debate on whether this is an actual concern, but some medical centres want to avoid any possible negative impact on the patients’ wellbeing due to the noise generated [1]. The aim of this study is to determine factors influencing squeaking for CoC. Three different diameters CoC (BIOLOX Delta) hip replacements (28, 32 and 36mm, PINNACLE, n=3 each) were tested with a customised method to increase the severity of edge loading [2] in an electromechanical simulator. Loading and flexion were applied as Figure 1, whereas the abduction was maintained at -15 degrees and the internal and external rotation kept at 0 degrees. Edge loading was applied via a translational mismatch [3]. Deionised water was used as lubricant. Medial-lateral displacement was measured using a linear variable displacement transformer. Testing was carried out until a squeaking could be heard. The sound was recorded (Zoom H4n) with a RODE NTG-2 microphone placed inside the equipment. The audio signals were analysed with MATLAB (MathWorks, USA) through a Fast Fourier Transform (FFT) function (Figure 2). Surface roughness was measured on an undamaged area (pole) and the wear scar area of the head with a Talysurf CCI3000. The ceramic liner profile was measured by a coordinate measuring machine (ZEISS PRISMO) to determine the rim distance from the top surface.

Results
Squeaking frequencies averaged to 2.2kHz, whereas, the frequencies with the highest amplitude averaged to 1.7kHz for all samples. The squeaking frequency range was as follows; for the 28mm, 1.0-5.2kHz, for the 32mm, 1.6-1.8kHz, and for the 36mm 1.2-5.1kHz. The mean cycles tested until squeaking was heard were as follows; 440, 1650 and 520 cycles for the 28, 32 and 36mm respectively. After squeaking was heard the testing was stopped.

Discussion
The profile developed in this study was designed to increase the severity of edge loading, that is to say, the duration and magnitude of loading under rim contact. The severity increased for all samples as the test continued (example in Figure 3). Squeaking was defined when the frequency was 1kHz or higher [4]. The occurrence of squeaking varied between the bearing size, where the 32mm bearing size took the longest for squeaking to occur. An important relationship of the bearing size in this study is the rim geometry. The rim geometry varied for each bearing diameter group. The 32mm had the shortest rim distance. A second important relationship for squeaking in this study is the damage created to the head due to edge loading. Edge loading increased the surface roughness and this in turn may increase the friction when in contact with the bearing or the rim section. The increased surface roughness (mean increase of 0.183µm) may play a role in the occurrence of squeaking and increased severity of edge loading due to the higher friction.

A new methodology was developed to determine the occurrence of squeaking under lubricated conditions and determine the ceramic liner design factors which influence the results.

References
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BIOMECHANICAL IMPACT OF A SUBSEQUENT CHILDBIRTH ON THE FEMALE PELVIC FLOOR

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Introduction

More than one third of women throughout their lives will experience pelvic floor dysfunction (PFD) [1]. These disorders have been widely studied over the past few years, particularly about the effect of childbirth and pregnancy itself [2]. Model simulation of the pelvic cavity allows the study of PFD, as well as the analysis of the stresses and strains to which these structures are subjected when forces are involved, for example during childbirth [3]. Abaqus is one of the most used software for these simulations. The writing of scripts, which allow the parameterization of the models, makes it possible to perform simulations with different conditions, in a faster and more practical way.

The aim of this paper is to study the biomechanical impact of a first birth on the lesions that occur in the female pelvic floor in subsequent births. For this, in a first phase, the parameterization of the model was done. An algorithm was developed to parameterize the model in relation to the dimensions and constitutive parameters.

Methods

A simplified model of the fetal head (sphere) and pelvic floor muscles (cone) was created in Abaqus. This process was parameterized by creating a script, which allows the same simulation to be performed for different dimensions of the fetal head and pelvic floor muscles, as well as for different constitutive parameters or constitutive models (Figure 1).

Figure 1: Part of the algorithm where the assignment of dimensions to the model structures is done.

The fetal head was modeled with a linear elastic model (E=250 MPa and ν=0.22) and with shell elements (S3).

The pelvic floor muscles were modeled with the hyperelastic Neo-Hookean constitutive model (C10=0.19 MPa and D=1E-05) and with hexahedral elements (C3D8H). To simulate the descent of the fetal head, the upper face of the muscles was fixed, and head movements were restricted.

Results

Figure 2 shows the distribution of stresses along the base of the muscles, at the points of highest stress, for different fetal head diameters.

Discussion

Computational modeling allows better understanding of the influence of obstetric factors on the risk of pelvic floor muscle injury. The script developed allows the simulation of fetal descent, evaluating its impact on pelvic floor muscles, for different dimensions and mechanical properties. The next step will be to add damage to the constitutive model of the muscles, to study the biomechanical influence of a first vaginal delivery on the injuries that occur in subsequent deliveries.

References


Acknowledgements

The authors are grateful for the support of FCT under the Junior Researcher Contract CEECIND/01522/2020, and the funding from Project UIDB/50022/2020.
SUCTION CUP PLACEMENT IN INSTRUMENTED VAGINAL DELIVERY

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Introduction

Delivery is a very complex natural and physiological process, which depends on the morphology and configuration of the maternal pelvis as well as uterine contractility and fetal size [1]. When the course of labor is not favorable, it can be performed with the help of instruments, such as the suction cup, which allows minimizing trauma to the fetus. The correct placement of the suction cup is crucial to ensure the success of the suction cup extraction process. Currently, there is an established flexion point on the fetal head that is ideal for suction cup placement, but this may not be appropriate for fetal heads with unusual morphologies. The implications of the suction cup placement point on the fetal head and maternal muscles need to be evaluated. Computational models are valuable tools that allow the analysis of the mechanisms of childbirth in a non-invasive way.

Methods

The morphing of several fetal head morphologies was performed in order to simulate the impact of instrumented delivery on the maternal pelvis. For this purpose, MATLAB was used, and an algorithm was adapted that allowed morphing these structures, based on the finite element model of a standard fetal head, which is shown in Figure 1.

In addition to morphing for several percentiles, including prematurity and macrocephaly, morphing was also performed for situations that introduced asymmetries in the head (craniosynostosis). To ensure the success of the morphing, the ABAQUS software was used.

The methodology chosen for morphing the fetal head for different percentiles included defining the biparietal diameter (BPD) and occipitofrontal diameter (OFD) and establishing their relationship with the cephalic perimeter. In the case of craniosynostosis, it was necessary to establish other diameters and relationships between them, to cause the desired deformation.

Results

Figure 2 the morphing results for each of the craniosynostoses in study.

![Figure 2: FE mesh obtained after morphing for each of the craniosynostoses in study.](image)

Figure 2: a. plagiocephaly  b. scaphocephaly  c. brachycephaly

To understand how the morphing performed on the mesh changed its quality, a mesh quality analysis was performed (Figure 3).

![Figure 3: Quantification of the distortion of the elements, where in yellow are the warnings and the pink ones the errors.](image)

Figure 3: a. plagiocephaly  b. scaphocephaly  c. brachycephaly

Discussion

The developed algorithm achieved the proposed objectives, with relatively low percentage relative errors and with meshes with good quality. In the future, the goal will be to simulate the vaginal delivery of the different heads created by placing the suction cup in the position considered ideal and analyze if it is the appropriate position for fetal heads with unusual morphologies.

References


Acknowledgements

The authors are grateful for the support of FCT under the Junior Researcher Contract CEECIND/01522/2020, and the funding from Project UIDB/50022/2020.
IN SILICO CLINICAL TRIAL TO PREDICT THE EFFICACY OF HIP PROTECTORS FOR PREVENTING HIP FRACTURES

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Introduction

Osteoporosis (OP) is characterized by low bone mineral density (BMD) and bone architecture deterioration, associated with increased fracture risk. Hip fractures are of particular concern given their severe impact on the patient’s health. Therefore, reduction of hip fracture incidence is of major clinical importance. Hip protectors aim to reduce impact force at the hip upon falling, however different conclusions on their efficacy have been reported, which could be due to poor compliance [1]. In Silico trials, i.e. the use of computer modelling and simulation, with virtual patients, could improve the assessment of OP interventions. Finite element (FE) models of the femur based on Computed Tomography (CT) data have been validated for the prediction of the femur strength [2]. FE models have also been integrated in a multiscale approach to simulate side falls [3].

The aim of this work is to apply an In Silico trial framework to predict the efficacy of hip protectors in reducing hip fractures.

Materials and Methods

A cohort of 1044 virtual patients was generated based on a cohort of 94 postmenopausal women [4], for which CT scans of the proximal femur were available. A FE model was generated for each virtual patient [2]. Side falls were simulated using the fall model developed previously [3]. Under the assumption that elderly patients had long reaction times, the effect of muscle co-contraction on the impact was neglected. It was also assumed that patients were treated with antiresorptive drugs so that BMD did not decrease over time. A failure load map was obtained for each patient by simulating 28 impact directions [3]. The intervention group was simulated by assuming that 81% of the impact force was transmitted to the femur when patients wore the hip protector (attenuation of Hipsaver device of 19% [5]). For the placebo arm (no hip protector) attenuation provided by external devices was equal to zero.

A Markov chain workflow was implemented to predict fracture incidence in each arm. At each simulated follow up year, a Poisson distribution was randomly sampled to determine if each patient sustained one or more falls. Impact direction and force were randomly sampled from a range of possible scenarios [3]. A patient was considered fractured when impact force exceeded femur strength in the corresponding direction.

Compliance was implemented at each fall as an unbiased probability that the patient wore the device.

Results

Without hip protector, virtual patients experienced 66 proximal femur fractures in 10 years follow up, similar to the incidence reported in previous clinical studies [6]. Wearing the hip protector, fracture incidence was reduced to 35 (Fig 1). As expected, the efficacy of the device was dependent on compliance (RR=0.52-1.00).

Discussion

An In Silico trial technology was applied to predict the efficacy of hip protectors. Previous studies reported very different conclusions on their efficacy (RR=0.14-1.49) likely due to large differences in compliance among studies (30-80%) and in the design of devices [1]. The potential of this technology includes the possibility to test and compare different interventions or combination of treatments, to optimize treatment strategies, to improve clinical trial design and drug development. Models of OP progression and pharmacological treatments are currently being developed and integrated in the methodology.

References


Acknowledgements

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COMPARING THE STIFFNESS OF THE SKIN TO THAT OF COMMONLY USED SKIN-CONTACTING MEDICAL DEVICES IN CONTEXT OF MDRPUs

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Introduction
Medical device-related pressure ulcers (MDRPUs) are relatively common and account for a large and growing proportion of hospital-acquired pressure ulcers. Devices associated with MDRPUs are often used to perform essential, life-saving functions. They include continuous positive airway pressure masks, endotracheal tubes, nasogastric tubes (NT) and tube holders (THs), to mention a few. During the coronavirus pandemic, many forms of skin damage resulted from the prolonged use of respiration equipment [1].

Alleviation of the sustained mechanical loads in the skin at the skin-device contact sites is a key performance aspect in the prevention of MDRPUs. In particular, the risk of developing MDRPUs can be reduced by calculating the extents of matching between the material stiffness (i.e., the elastic modulus) of the skin-contacting materials in the given medical device and the stiffness of the native skin, which is a predictor of the skin and soft tissue stress concentrations that develop at and near the device interfaces [2]. The poorer the stiffness matching (i.e., the device stiffness over the skin stiffness ratio being farther than unity), the more intensified tissue stress concentrations are to be expected.

Methods
Using an integrated experimental-computational approach, we compared the biomechanical performance of commonly used skin-contacting medical devices and materials for pressure ulcer prevention with the corresponding properties of native skin [2].

We specifically measured the compressive stiffness properties of NTs and THs that are contacting the skin using a modified ASTM D3574-11 test standard. These empirical measurements were then compared to corresponding finite element simulations of the experiments to determine the mechanical properties via a ‘reverse engineering’ approach, in order to extract the elastic moduli of the skin-contacting material components per each tested medical device.

Results
The stiffness of hydrogel-based and foam-based dressing materials is within the 30-100 kPa range, which falls within the range of stiffness of adult skin, so in terms of modulus matching, there is a good fit [2][3][4]. In contrast, tubing devices demonstrated stiffness within the 30-400 MPa range, which is distant by two to three orders of magnitude from the stiffness of skin, i.e., all the tested tubes had poor modulus matching (Figure 1).

![Figure 1: Mapping of the stiffness properties of prophylactic dressings and skin-contacting materials in medical devices with respect to the stiffness of an adult skin (NT – nasogastric tube; TH – tube holder).](image)

Discussion
We report here a practical approach and metrics for quantitative evaluations and rating of materials for pressure ulcer prevention or for assessing the biomechanical risk involved in selection of certain skin-contacting materials for inclusion in the design of skin-interfacing medical devices, in the context of MDRPUs.

References

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MECHANICAL RESPONSE OF ENDOTHELIAL CELLS TO SHEAR FLOW AS POSSIBLE MARKER IN DEVELOPMENT OF ATHEROSCLEROSIS

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Introduction
Arterial endothelium lies right at the interface between blood flow and the aortic wall and its disruption has been hypothesized as one of the crucial players in atherosclerosis development and progression. To address the physiological conditions of arterial endothelium we conducted a study of endothelial cell behaviour under shear stress. By interconnecting tailored experiments of cells under shear flow with computational modelling, we gained further insights into the behaviour of individual cells under shear stress. The main aim of the study was to evaluate the viability and extend the capabilities of previously developed FEM structural models [1,2]. We hypothesize that excessive deformation may lead up to a disruption of the cell attachment to the underlying substrate and thus play a major role in lipid penetration through the endothelium.

Methods
Individual HUVEC cells (endothelial cells from an umbilical vein) were deformed using a microfluidic system Fluigent Flow EZ by a sequence of flow pulses, and phase images had been recorded (Fig. 1a) together with the flow measurement. The deformation has been evaluated by two image-processing methods: Centre of Mass (COM) shift [3] based on thresholding and more sophisticated Image Registration (IR) [4].

FEM calculations comprise several steps and utilize both structural and FSI analyses. Structural modelling includes determining the effective shear modulus of the complex cellular body (comprising of cytoskeleton, nucleus, membrane and cytoplasm, see Fig. 2a). FSI of the cell deformations under the previously measured flow serves as a bridge between experiments and structural modelling.

Figure 1. Cellular deformation due to shear flow in the direction indicated by a red arrow. (a) phase images of undeformed (green) and deformed (magenta) cell body and (b) non-structural Finite Element model under similar loading conditions.

Figure 2: (a) Inner structure of the hybrid FEM model [2]. Actin bundles (red), intermediate filaments (green), microtubules (blue) and nucleus (magenta), here shown without cytoplasm and membrane. (b) Deformation field using Image Registration at the top of the first cycle.

Results
The deformation of the cell in the experimentally-computational setup has been assessed while exploring the capabilities of image processing for the shear environment (Fig. 2b). Transitioning between the mechanical behaviour of the cell under physiological loading conditions into computational modelling (Fig. 1b) helps to validate the hybrid computational model. The time dependence of cell deformation in Fig. 3 shows viscoelastic behaviour, that needs to be incorporated for reflecting reality more precisely.

Figure 3: Cell deformation in the first cycle determined using Centre of Mass shift under shear flow.

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Acknowledgments
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Introduction
Cellular mechanics undergo complex changes during cancer progression in parallel with metabolic reprogramming due to altered demands on its motility. As the cytoskeleton forms a major part of cellular stiffness, this study focuses mainly on exploring cytoskeletal changes in cancer cells and evaluating their direct impact on cellular stiffness. However, the association between cellular stiffness and tumor cell aggressiveness is not straightforward and results vary depending on tumor type. The main aim of this study was to explore the relationship between the altered inner structural arrangement and cell aggressivity in prostate cancer cells using a combination of laboratory and computational methods.

Methods
The stiffness of prostate cancer cell line 22Rv1 and more aggressive PC-3 cells cultivated in an adherent state was evaluated using Atomic Force Microscopy (AFM) [1] with a spherical tip. Mechanical testing confirmed an increase in Young’s modulus for more aggressive prostate cancer cells. The amount of cytoskeletal proteins between cell types was determined using mass spectrometry-based proteomic analysis. To reflect on these changes and assess their individual impact on the cell’s mechanical response we used a previously-developed hybrid Finite Element Model of a cell body that comprises all three types of cytoskeletal fibers (actin bundles, intermediate filaments and microtubules) together with nucleus, membrane and cytoplasm (see Fig. 1) [2,3] under loading conditions mimicking the series of AFM measurements (example in Fig. 2).

Results
By determining the amount of tubulin, vimentin and actin in 22Rv1 and more aggressive PC-3 cell lines, we uncovered that whereas tubulin content stays almost unaltered, the stiffer PC-3 cells differ significantly in actin and vimentin content. The inner organization of the FE model is manipulated to correspond with these observations, which helps us to reveal the significance of individual cytoskeletal fibers in cancer cell mechanics. The simulations reflecting the observed changes in morphology and quantity of cytoskeletal components do not induce such stiffness differences as in the AFM experiments. This indicates that the stiffness alterations may be caused by cytoskeletal reorganization or the existence of another mechanically relevant cell component that has not been reflected yet in the computational modeling approach.

Future prospects
Even though the cytoskeleton has been given more attention in computational cellular mechanics than other organelles, it is not entirely ruled out that there are other contributing factors such as bonds between organelles. For instance, the reorganization in the cancer cell cytoplasm also includes changes in the architecture of mitochondria, which is responsible for generating energy for the cell. Thus, the attention will be directed toward the mitochondrial organization within the cytoskeleton together with their mutual interactions and how it impacts cancer cell mechanics.

References

Acknowledgments
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Introduction

Obesity increases the risk of osteoarthritis (OA) compared to non-obese subjects [1]. Strategies for early prediction to slow down OA progression are important to decrease societal and economical burdens. Numerical finite element (FE) modeling-based approaches have been developed to classify patients at high risk for OA [2]. However, these applications have not been used to estimate knee cartilage degeneration in larger cohorts.

In this study we aimed to predict the degeneration of knee cartilage in obese adults and investigate the importance of the level of patient-specific information. We hypothesized that patient-specific knee geometry is more important than patient-specific gait data for the prediction of cartilage degeneration, when compared to full patient-specific information.

Methods

115 subjects (95 females and 20 males, 63.8 ± 6.3 years, BMI: 37.0 ± 4.4 kg/m²) were selected from the CAROT trial at baseline [3]. Patient-specific knee axial force, varus-valgus moment, and flexion-extension angle during the stance phase of the gait were computed using motion analysis data (at baseline) in OpenSim. The FE knee models were created from MRI data using a validated template-based approach consisting of femoral and tibial cartilage, menisci, and cruciate and collateral ligaments [2]. The template was scaled according to the anatomical dimensions measured from each participant’s MRI. The computed gait data from each subject was used to drive the FE models in Abaqus. Cartilage and meniscus were modeled as fibril-reinforced poroviscoelastic (FRPVE) material [4]. A linear age-dependent function was implemented to estimate cartilage degeneration based on excessive and accumulated tensile stresses linked to collagen damage.

Cartilage degeneration volumes were predicted from 10 “years” (computational iterations) before baseline assuming that BMI was constant. The fully patient-specific predictions were compared to predictions where either gait data or knee geometry implemented represented the group average (“generic” approach) in which loading inputs were scaled according to body mass. Kellgren-Lawrence (KL) grades at baseline were utilized to evaluate the numerical predictions for each subject. Predictive accuracy was verified using receiving operating characteristics (ROC) and area under curve (AUC).

Results

Numerical predictions showed a better correlation in the medial compartment than lateral for both KL grades. Interestingly, predictions based on patient-specific geometry combined with generic knee gait showed a similar ability to predict cartilage degeneration grades as full patient-specific FE models. When attempting to separate predictions of KL0-KL1 vs. KL3-KL4, an adequate outcome was obtained for full patient-specific models (AUC = 0.71, p < 0.01) and for patient-specific geometry with generic gait data (AUC = 0.68, p < 0.01), but not for generic geometry and patient-specific gait data (AUC = 0.48, p = 0.73).

Discussion

Based on this study, our modeling approach was able to adequately categorize obese adults into normal and advanced OA groups. Results also suggest that patient-specific geometry has more impact than patient-specific gait data on the prediction of cartilage degeneration. This suggests that generic knee kinematics might be enough in prognostic tools to evaluate the risk of onset and OA progression.

References


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A UNIFYING APPROACH FOR THE STANDARDISATION OF KINEMATIC SIGNALS

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Introduction

In clinical movement biomechanics, kinematic data are processed into representative time-series signals that characterise the motion of body joints. Exacerbated by a lack of consensus around joint coordinate frame definitions, the influence of local segment frame alignment on the characteristics of these signals has proven to be a major limitation [1,2]. For consistent interpretation of joint motion to be possible, differences in frame definition must first be addressed. Building on a previously introduced Frame Orientation Optimisation Method (FOOM) [2], we present and assess a REFrame Alignment MEthod (REFRAME), exploring its ability to induce convergence towards a consistent set of knee kinematic signals in all six degrees-of-freedom.

Methods

REFRAME employs a self-contained optimisation approach to re-align local segment reference frames such that the resultant joint kinematics fulfil certain user-defined criteria. Here, an implementation of REFRAME based on the combined use of nonlinear and global optimisation algorithms is validated using in vivo knee kinematics captured using a moving videofluoroscope [3]. Different local femoral reference frames were defined based on three distinct methods of estimating the primary joint axis (cylindrical: CA, functional flexion: FFA, and transepicondylar: TEA) to derive flexion/extension, ab/adduction and int/external rotation, as well as anteroposterior, mediolateral and proximodistal translations over five stair descent trials [4]. The resulting kinematic signals associated with each of the approaches were optimised, using REFRAME to target minimum root-mean-square error (RMSE) vs. 0 for ab/adduction and int/external rotation, as well as minimum variance for anteroposterior (AP), mediolateral (ML) and proximodistal (PD) translation.

Results

Implementation of REFRAME realigned local segment frames to result in fundamental changes of the magnitude and characteristics of kinematic signals. This led to a reduction in peak RMSEs from 8.32 mm ± 0.05 mm (PD of FFA vs. TEA) and 6.15° ± 0.05° (int/ext. rot. of CA vs. TEA) to a maximum of 0.47 mm ± 0.08 mm (AP of FFA vs. TEA) and 0.20° ± 0.17° (flex/extension of CA vs. TEA), as well as evident convergence of most kinematic signals (Fig. 1).

Discussion

REFRAME demonstrated the ability to optimise the orientation and position of local segment frames, leading to sufficient changes to allow convergence of kinematic signals that were initially derived using different methods of primary axis definition. This standardisation protocol therefore holds the potential to enable consistent interpretation and comparison of joint kinematics derived using different approaches.

References

Introduction
In the field of movement biomechanics, validation of new motion analysis tools requires gauging accuracy against a gold standard. To achieve this, kinematic signals obtained from innovative systems are frequently compared to those stemming from previously validated setups. These comparisons often assume that, as long as the underlying movement is the same, the kinematics resulting from different sources or analysis techniques should lead to a consistent outcome. However, the exact orientation of local segment frames has demonstrated to substantially influence the magnitude and characteristics of the resulting kinematic signals [1-3], although this effect is often overlooked or misunderstood by validation studies. Here, we present a Frame Orientation Optimisation Method (FOOM) [3] that makes it possible to establish whether two datasets differ through frame alignment errors or whether the underlying joint kinematics are indeed fundamentally different.

Methods
Previously, the rotational knee kinematics of six subjects during level walking, stair descent and sit-to-stand-to-sit trials were assessed using inertial measurement units (IMUs), and subsequently compared to a reference simulator signal to determine accuracy [4]. To better understand the source of the observed differences between the IMU- and simulator-based signals, a Frame Orientation Optimisation Method was implemented. FOOM minimised cross-talk parameters in each dataset independently using least squares optimisation, allowing the standardisation of the kinematic signals ensuing from each measurement system by transforming local segment frames towards a common unspecified relative orientation.

Results
The presented FOOM framework led to an average 3.32° ± 1.24° rotation of local segment frames around the corresponding screw axis to achieve a decrease in root-mean-square error between IMU-based estimates and simulator reference signals from 0.79° ± 0.30° in out-of-sagittal-plane rotations to 0.29° ± 0.30°. Importantly, frame reorientation altered signal characteristics enough to allow for convergence on a consistent kinematic waveform around all three axes, while still retaining fundamental differences between individual subjects (Figure 1).

Discussion
Optimised kinematic signals point towards different interpretations of the evaluated movement patterns. While the converged signals differ from both original datasets, they become consistent with one another after reorientation of local segment frames. Results highlight the importance of accounting for differences in segment frame orientation when drawing conclusions from the comparison of kinematic data. Furthermore, the proposed FOOM protocol demonstrates the ability to independently realign segment frames to a common (even if initially unknown) optimal relative orientation that can allow the consistent interpretation of joint kinematics.

References
DESIGN OF UPPER LIMB EXOSKELETON ORTHOSIS FOR REHABILITATION PURPOSES

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Introduction
Automated rehabilitation orthosis typically focuses on lower limbs and the rehabilitation of lower limb conditions such as paraplegia and other Spinal cord injuries (SCIs). Rehabilitation upper limb exoskeletons (RULE) made for rehabilitation purposes are prohibitively expensive and are usually stationary apparatus. The aim of this work is to design and produce a RULE that is cheaper than the current existing options and portable to improve the quality of life of the user [1].

Methods
Five sections of 3D printed pieces were made and assembled to accommodate a human arm in a way that would provide motion assistance to the user, including shoulder movement, upper arm rotation and elbow extension. The exoskeleton was mounted into a standard backpack for mobility, where the user uses a remote control to move each joint. A control system was designed that uses servo motors for each degree of freedom. These motors work via an Arduino board that controls the motion range and speed for each joint. According to Plagenhoef et al, the average human arm requires a torque of 16.7 Nm to move at full extension [2]. To accommodate the variance in human arms and the mass of the exoskeleton, a servo motor was chosen for the shoulder that, when in 1:6.8 gear ratio, will produce 40 Nm of torque.

Results & Discussion
The first prototype of the exoskeleton allowed for five degrees of freedom, abduction/adduction from the shoulder, flexion, and extension of both the arm and elbow, internal and external rotation of the upper arm and lateral rotation of the shoulder. It is portable via a standard backpack with adjustable straps to allow simplified access and egress for the user. The user can integrate with the exoskeleton using 3 adjustable Velcro straps (see Fig 1).

The exoskeleton was made using a combination of machining and 3D printing. Most of the exoskeleton is printed with Polylactic Acid (PLA) which is a biocompatible material source from sugar cane.[3] Aluminum was used to make the backplate, mount and joint shafts. The full assembly, not including the machinery or 3D printer, costs under €400 to produce. Most of this comes from the cost of the aluminum stock and the servo motors used in the control system. The exoskeleton is relatively lightweight compared to the mass of an average human, weighing 4.6kg.

Figure 1 - The exoskeleton is seen here in isolation and with respect to a 183cm tall male.

Further testing is to be conducted on the exoskeleton, with additional improvements to be made such as a wireless remote control and an ABS 3D printed prototype.

Conclusion
The RULE can be used for its primary goal of patient rehabilitation. In addition, due to its low cost, it can be manufactured and used in developing countries where healthcare is more difficult to access.

References

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AUTOMATED SHOULDER MORPHING TO ASSESS SUBJECT SPECIFIC BIOMECHANICS OF ROTATOR CUFF TEAR AND OSTEOARTHRITIS

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Introduction
Clinical metrics pertaining to scapula morphology, such as the critical shoulder angle (CSA), have been observed to differ between osteoarthritis (OA) and rotator cuff tear (RCT) patients. RCTs are associated with a CSA > 35°, compared to OA patients who are more likely to have a CSA < 30° [4]. Experimental testing has shown that increased CSA leads to increased glenohumeral shear stresses [1]. It is thus hypothesized that the ratio of shear to compressive forces (instability ratio) is increased in RCT patients compared to OA patients in the glenohumeral joint, however patient-specific analysis has never been performed. To this end, we present an automated pipeline for creating and analyzing the glenohumeral joint reaction forces for patient-specific shoulders, along with validation through a comparative study of RCT and OA patients.

Methods
Patient specific glenohumeral joint forces were calculated for 10 patients with a RCT (mean CSA of 39.63°), and 10 patients with OA (mean CSA of 17.3°). The scapula and proximal humerus were manually segmented from CT by a clinical expert. The CSA was calculated using a true anterior-posterior projected plane from the CT scans. Computational modelling was performed with the AnyBody Modeling System (ver 7.3.4, AnyBody Technology A/S, Aalborg, Denmark) [2]. For personalization of the shoulder model, patient scapulae were registered to the original AnyBody scapula using the deterministic atlas algorithm from Deformetrica [3]. The Hausdorff distance (with 26'000 points per scapula) was used to measure the global accuracy of the morphing.

To achieve a patient-adapted joint configuration in the musculoskeletal model, the radius of each humerus was calculated using a simple sphere fit to the medial aspect of the segmented humeral head and used to define the glenohumeral joint center.

The glenohumeral compressive (medial-lateral), vertical shear (inferior-superior), and horizontal shear (anterior-posterior) joint forces were calculated for each patient over a 0°-90° abduction in the scapular plane. Forces were then normalized by body weight (%BW).

Results
The mean Hausdorff distances for the registration of all the OA and RCT patients to the AnyBody scapula were 2.37 mm and 2.40 mm, respectively. The joint reaction forces showed an increase in vertical and horizontal shear components in the RCT patient group, compared with the OA patients (Figure 1). The horizontal shear forces showed a difference of 6.5%BW, with a maximal force in the RCT group of 12.7%BW and 6.2%BW in the OA group. In the vertical plane, the difference was 3.8%BW with a maximal force of 23.9%BW in the RCT group, and 20.1%BW in the OA group. Compressive forces were similar between the groups, with a maximal compressive force of 42.5%BW in the RCT group, and 39.8%BW in the OA group, a 2.7%BW difference, mostly at higher humerus angles.

Discussion
Results of this study are consistent with previous research showing increased shear forces for patients with higher CSAs and increasing instability ratios for patients with increasing CSAs [1]. Within this work, we present an automated pipeline to import patient-specific scapula and glenohumeral morphological information, extracted from CT imaging, into the AnyBody modelling system. The pipeline demonstrated robustness to large morphological variation in the patient scapulae and requires little manual input. Preliminary results show good agreement of glenohumeral joint forces and muscle forces to previous studies, with the potential to efficiently analyze larger numbers of individual subjects.

References
DEVICE INDUCED DAMAGE OF ARTERIAL PORCINE TISSUE

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1. Introduction
An aspect of intravascular medical procedures is safe device navigation to optimally position the device, while minimizing tissue damage. If the conditions under which tissue damage occurs are known, this can be used to improve the device design and in guidance tools during medical procedures. A severe type of tissue damage is puncture, but prior to puncture collagen fibers in the vascular wall rupture. The vascular wall can be described using the model developed and characterized in [1]. This model includes a description of collagen fiber rupture in the vascular wall using an internal damage parameter. This damage mechanism that occurs during loading-unloading of tissue samples corresponds to the so-called Mullins effect. The purpose of this study is to quantify the fiber rupture mechanism by lumping this micromechanical phenomenon to a macroscopic damage parameter as a function of device geometry by loading-unloading indentation of arterial porcine tissue.

2. Materials and Methods
The experimental set-up consists of a displacement-controlled holder for the medical device-mimicking indentation tool. A porcine artery is pre-strained to physiological conditions. The force exerted by the device is measured. Fig. 1 shows a schematic of the experimental set-up.

![Figure 1: Schematic of the experimental test set-up.](image)

The arterial tissue damage model developed in [1] is an extension to the hyperelastic formulation in [2] and is implemented into the finite element package MSC.Marc through a user subroutine.

3. Results
As can be observed in Fig 2, the experimentally obtained indentation force, as a function of displacement up to puncture, is in qualitative agreement with results obtained in [1]. The energy dissipated during loading-unloading cycles is assumed to be fully attributed to internal fiber damage in the vessel wall, that can be measured and analyzed with a computational model (Fig. 3).

![Figure 2: Example of measured force-displacement behavior during loading-unloading indentation.](image)

![Figure 3: Calculated pseudo-elastic fiber damage variable [1] during indentation.](image)

An experimental-numerical approach is pursued to assess the evolution of the damage mechanism in the tissue, as shown in Fig 3.

4. Discussion and Conclusions
A combined experimental-numerical procedure has been developed to analyze device-induced tissue damage up to puncture. As a next step, device tip geometries, substrates and angles of approach will be varied. Results will be used to optimize device design for minimal vascular fiber damage and for the development of guidance tools for during medical procedures.

5. References

Acknowledgements
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A COMPUTATIONAL FRAMEWORK FOR MODELLING PATCH-AUGMENTED AORTIC ARCH RECONSTRUCTION

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Introduction

Hypoplastic left heart syndrome (HLHS) is a congenital heart defect characterized by an underdeveloped aortic arch and left ventricle. To survive these conditions, the underdeveloped aortic arch needs to be surgically enlarged and connected to the right ventricle. At the same time, a shunt is created to provide blood flow to the pulmonary arteries [1]. Given the highly non-linear mechanical behavior of native aortic tissue and available patch materials, it remains challenging for clinicians to predict the shape of the reconstructed aortic arch [2]. The shape of the aortic arch is vital for ventricular function and avoiding (long-term) complications [3].

To accurately predict the reconstructed aortic arch geometry, we present a flexible computational framework that allows us to study the effect of patch size, shape, and insertion location on the pressurized shape of the reconstructed neo-aorta.

Methods

We built a finite element framework replicating the surgical reconstruction of the hypoplastic aortic arch in HLHS patients. More specifically, we integrate the non-linear elastic behavior of the aorta and the patch, model surgical reconstruction, and simulate the pressurization of the reconstructed aorta.

Third-degree B-splines are used to describe the geometry of the aorta and the patch. This parametric description enables the geometries to be easily adapted and changed. Tetrahedral meshes are generated, and the model equations describing static equilibrium are solved using second-order Lagrange elements.

The geometry of the surgical cut of the aorta is described by level set functions. The resulting surfaces exposed by the surgical cut are used to model patch insertion. Insertion of the patch into the aorta is simulated by constraining the distance between the surface of the surgical cut and the patch to zero. We use a strain energy function that accounts for the anisotropic hyperelastic behavior of the mechanical behavior of the native aortic and patch tissues [4]. Finally, we simulate pressurization using a Neumann boundary condition on the internal surface of the aorta and on one side of the patch.

Results

Reconstruction of aortic arch is modeled here using an idealized geometry for the aorta and different patches. Figure 1 shows the aorta and the patches, before and after the reconstruction. The inserted patch enlarges the aorta but can lead to mechanical instability due to geometric or mechanical variation. The anisotropic hyperelastic behavior of the tissue plays an important role in the final shape.

Discussion

The framework presented here models the shape of the reconstructed aorta after pressurization. The final shape is highly dependent on the insertion location, the shape, and the material properties of the patch. These are important design variables to ensure adequate circulation, as well as to avoid complications, such as rupture or blockages. A large mismatch in mechanical properties between the patch and the aorta can lead to buckling and other mechanical failures [5].

Accurately predicting the final shape of the reconstructed aorta after pressurization is extremely complex. Using this framework, the shape of the reconstructed aorta during the cardiac cycle can be predicted. We aim to optimize the shape and insertion location of the patch with respect to post-surgical blood flow and oxygen delivery. The optimized patch can then be used to inform clinicians during this challenging surgery.

References

MIXED UNIFORM BOUNDARY CONDITIONS IMPROVE HOMOGENIZED FE MODELS OF BONE-SCREWS AND INVERSE REMODELLING

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Introduction
In the field of numerical bone biomechanics, either micro finite element model (μFE) or homogenized FE models (hFE) are used. The latter requires a material law that translates the information on the micro level into effective material behavior on the macro level. Different trabecular bone material models can be used, including orthotropic and isotropic material derived from homogenization based on kinematic uniform boundary conditions (KUBC) as well as periodicity-compatible mixed uniform boundary conditions (PMUBC) [1]. There are a number of studies that have described both [2] for stiffness or bone strength predictions. This work focuses on the question which kind of boundary condition is better suited in case of screw-bone construct and inverse bone remodeling algorithms. The gold standard are μFE models of the same construct or bone.

Material and Methods
Screw-bone construct stiffness: 15 cylindrical bone specimens with 18 mm diameter were extracted from micro CT scans of human distal radii and a screw was virtually inserted (Fig. 1, top). In the hFE models, isotropic and orthotropic trabecular bone material models either from KUBC or PMUBC-derived homogenized were assigned and the constructs were loaded in three load configurations. Structural stiffness and the error between μFE and hFE was evaluated.

Inverse bone remodeling (IBR) of proximal femora: bone stiffness and hFE were evaluated. Inverse bone remodeling (IBR) of proximal femora: micro FE and hFE models were created based on micro-CT scans of 19 femoral bones (Fig. 2, top). In analogy to the screw-bone samples, trabecular bone material was assigned using ortho- or isotropic material either from KUBC or PMUBC-derived homogenization. hFE-based IBR [3] was then applied to predict the loading history, which was discretized using four unit load cases. μFE and hFE model predictions were compared using the relative root mean square error (RMSE).

Results
Screw-bone constructs: Stiffness was predicted most accurately using PMUBC-derived orthotropic material (error: -0.7±8.0%) and least accurately using KUBC-derived isotropic material (error: 23.1±24.4 %) (Fig. 1, bottom).

IBR of proximal femora: The loading history was predicted most accurately using PMUBC orthotropic (RMSE: 14.2±2.4%) and least accurately using KUBC orthotropic material (RMSE: 20.5±3%) (Fig. 2, bottom).

Discussion
Both for screw-bone construct stiffness and hFE-based IBR, the results showed sensitivity towards the choice of boundary conditions used for homogenization. In both use cases, PMUBC-derived trabecular bone material properties showed better agreement with the μFE reference models, irrespective of material symmetry (iso-orthotropy). This agrees with a previous study suggesting closer agreement of PMUBC-derived material properties with effective material properties [4]. Including orthotropy only slightly improved the predictions in both use cases. However, these results are not generally transferable and should be checked once for other hFE studies and models.

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Acknowledgments
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INTRODUCTION

One of the main concerns in implant design is stress shielding minimization. As bone regeneration occurs due to a stress stimulus happening in the bone, a low stimulus caused by improper load transfer to the bone can lead to bone decay and further problems. Porous geometries are commonly used in scaffold design for promoting cell adhesion and proliferation. Additionally, with porous geometries it is possible to tune the mechanical properties through topological design. [1]

The aim of this work is to achieve an optimal design by training the neural network so that for any given constitutive matrix it has as the output the optimal unit cell topology (Figure 1). The network is therefore able to reverse the homogenization procedure [2].

![Figure 1 - Neural network scheme indicating the input and output data](image)

MATERIALS AND METHODS

For a set of several different geometries, homogenization with periodic boundary conditions (PBC) was performed. A uniform mesh of square 2D elements allows to directly impose the PBC. The original geometry is therefore simplified to fit the uniform mesh. The linear-elastic analysis is run using ABAQUS as the solver.

A feed-forward neural network was created and trained in MATLAB. Each neuron $i$ passes information forward in the network, according to (1)

$$ z = f(b + wx) = f(b + \sum_{i=1}^{n} w_i x_i) $$

where $f$ is the activation function, $b$ is the bias, $w_i$ is the weight from the neuron in the previous layer and $x_i$ is the value from the neuron in the previous layer. The training procedure adjusts the weights and bias by minimizing and error function for example the mean squared error (MSE).

The constitutive matrix was obtained by applying a unit strain in each of the three components (normal in the xx direction, normal in the yy direction and shear). Thus, the macro-stress tensor for each strain component provides a line of the constitutive matrix.

![Figure 2 – Examples of geometries from the lattice dataset](image)

Figure 2 – Examples of geometries from the lattice dataset

DISCUSSION

The NN allows for further optimization by taking as input the properties of bone, as shown in Figure 3. Therefore, it is possible to minimize the difference in mechanical properties between the scaffold and the bone in its surroundings, which leads to stress shielding.

![Figure 3 – Stress shielding minimization framework](image)

Figure 3 – Stress shielding minimization framework

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ACKNOWLEDGEMENTS

The authors truly acknowledge the funding provided by LAETA, under project UIDB/50022/2020 and the doctoral grant SFRH/BD/151362/2021 (FCT, MCTES, State Budget, ESF, Por_Norte) under the MIT Portugal Program.
Introduction

Differences in bone anatomy occur naturally in the population which result in different structural responses. To reduce the computational cost associated with the prediction of the remodelling process, machine learning techniques can be combined with the FEM. It is demonstrated in this work that neural networks achieve accurate solutions in a fraction of the time, with the main disadvantage being the need to collect large amounts of data.

Several approaches to bone remodelling taking advantage of neural networks can be found in the literature, with the work of [1] which predicts the trabecular arrangement from a known load case (direct problem), the work of [2] dealing with the inverse problem and predictive models to adjust the remodelling parameters, leading to more accurate predictions [3].

Materials and methods

In this work, a feed forward neural network (NN) was used. In these networks, each neuron or perceptron $i$ does a non-linear transformation, according to (1)

$$z = f(b + wx) = f(b + \sum_{i=1}^{m} w_i x_i)$$

where $f$ is the activation function, $b$ is the bias, $w_i$ is the weight from the neuron in the previous layer and $x_i$ is the value from the neuron in the previous layer. The training procedure allows to adjust the weights and the bias by minimizing an error function, for example the mean square error (MSE)

$$MSE = \frac{1}{n} \sum_{i=1}^{n} (y_i - \hat{y}_i)^2$$

The relevant variables for the problem are shown in Figure 1. The variables $\alpha$ and $\beta$ evaluate the angles of the two forces being applied, the variables $h, l$ and $\theta$ are geometry parameters to quantify anatomical differences.

Results and discussion

Figure 2 shows the output of the three layer network, which is the prediction of the density field for a new load case. The first column refers to the FEM result, the second column is the NN output and the third column quantifies the difference between the two.

Figure 2 – Neural network results

Qualitatively, the network was able to achieve accurate results in comparison to the FEM result. In order to provide a valid alternative to the FEM, the prediction time should be lower than the time necessary to run the analysis which can be extensive due to the iterative nature of the process.

Each remodelling analysis took 1020s while a prediction for the same number of points takes about 0.064s. The training procedure also took the equivalent time to run 3.4 FEM analyses.

The main disadvantage of the neural network framework is the amount of data which must be gathered in order to achieve accurate results.

Acknowledgements

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Strains and Failure Modes in Human Metastatic Vertebrae

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Introduction
Biomechanical studies [1, 2] have analysed the effects of bone metastases on the mechanical behaviour of the vertebrae, in order to improve our understanding of their risk of fracture. These studies provide remarkable insight about the overall mechanical properties of metastatic vertebrae, but how these lesions contribute to the failure process and failure pattern is still unclear. Micro-computed tomography (μCT) imaging and Digital Volume Correlation (DVC) provide unique quantitative assessments of the internal displacement and strain fields, and a clear identification of the failure mode and location of failure onset [3]. The aim of this study was to i) evaluate the local internal strain maps at failure in human metastatic and healthy vertebrae and ii) identify their different failure modes.

Methods
Fifteen four-vertebra spine segments, consisting of a metastatic (6x lytic, 6x mixed or 3x blastic) and a healthy vertebra in the middle, were obtained from an ethically approved donation program. The most cranial and most caudal vertebrae were partially embedded in bone cement to hold the specimen in a hand-operated jig equipped with a load cell (HBK, 10kN). Each specimen was loaded in uniaxial compression, inside a μCT scanner (Scanco VivaCT 80, isotropic voxel size = 39μm). Two scans of each specimen were acquired in zero-strain conditions to assess the DVC measurement uncertainty (standard deviation of the errors, SDER). Then, the specimens were loaded up to failure (first abrupt drop of the load) in order to measure the internal strains at failure. A global DVC approach (BoneDVC) [4], with a measurement spatial resolution of 1.95mm was used to measure the minimum principal strains (eps3). Percentage Strain Difference was computed as strain of the metastatic vertebra normalised with respect to the healthy vertebra. Scans in the unloaded condition and at failure were rigidly registered and overlapped to identify the location of failure onset and the failure mode of metastatic and control vertebrae.

Results
SDER for healthy and metastatic vertebrae were similar, and below 500με. Vertebrae with lytic metastases experienced the largest eps3 at failure (median ± standard deviation over the entire vertebral body: -8506 ± 4748 με), followed by vertebrae with mixed metastasis (-7035 ± 15605 με), healthy vertebrae (-5743 ± 5697 με) and with blastic metastases (-3150 ± 4641 με) (Fig. 1).

Discussion
Each type of lesion affected the strain of the internal tissue in a different way, making it essential to assess in detail the properties of the lesion, the bone microstructure, and the local tissue deformation in each case. Vertebrae with lytic and mixed lesions showed the largest deformations and high likelihood of fracture compared to the adjacent healthy control (Percentage Strain Differences, Fig. 1). Blastic metastasis can lead to failure of the affected vertebra or of the adjacent healthy one.

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Acknowledgements
The study was supported by the AOSpine (AOSDIA 2019 063 TUM Palanca, 2019), Marie Skłodowska-Curie (MSCA-IF-EF-ST, 832430/2018, 2018) and by the EPSRC (EP/K03877X/1 and EP/S032940/1, 2013 and 2019).

Fig. 1: strain over the vertebral body for each vertebra (median and SD) and percentage strain differences for each spine segment.
In the segments with lytic or mixed metastases, the vertebra with metastases failed first in 4/6 or 5/6 cases, respectively. In segments with blastic metastases the metastatic vertebra failed only in 1/3 cases. Onset failure location was near the endplates. In vertebrae with lytic metastases, the failure occurred between the endplate and the metastatic lesions, while in vertebrae with blastic metastases the failure occurred around the metastatic lesion (Fig. 2).

Fig. 2: failure pattern in vertebrae with lytic and blastic metastases. Vertebra before (red) and after (green) the failure. In yellow, overlapped regions

Lytic
Blastic
TRABECULAR TORSION CAN LOCALISE FRACTURE IN VITRO

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Introduction

Predicting the fracture in a trabecular bone sample is still a challenging task not for what is related to load magnitude but also for the “simple” localization of the fracture onset. Fracture appears as a chain of events where a local phenomenon triggers a sort of butterfly effect on an increasingly growing surrounding area. The fracture onset appears not related to strain/stress concentration as it emerges from linear models [1]; on the other hand, models embedding constitutive nonlinearities are not providing further insights. The complexity of those models, combined with their significant computational cost, makes the identification of a reliable, robust and accurate model still an open challenge.

Skeletonisation is an algorithm able to extract essential features about the topology of a 3D structure from its digital imaging. Using this approach, the intricated trabecular architecture can be described as a graph of truss/beam elements. In this study skeletonisation was applied to µCT images of trabecular bone samples; the resulting graph was used to initialise a FE model of beam elements to replicate the experimental uni-axial compression test conducted in vitro up to failure.

Materials and Methods

Datasets µCT of 14 bone samples (cylinders, D=10mm, h=20mm, BVTV 9.36+/-2.33%) from the LHDL dataset were binarised (fixed global threshold 143) and skeletonised (in-house Matlab script, homotopic thinning algorithm [2]). Trabeculae were identified between the nodes of the resulting graph; each trabecula was modeled as a beam element (homogeneous and isotropic linear material, E=19GPa, nI=0.3); circular cross sections were defined for each trabecula by computing the average distance between the skeleton and the bone surface on the binarized dataset. Nodal constrains were applied to replicate the uni-axial compression (nodes on the bottom region fully constrained; nodes at the top region imposed axial displacement and null transverse displacement). FE models were solved using Abaqus on a standard laptop. The map of the resulting nodal displacements and rotation were compared with the map of the fractured areas as identified by comparison between registered pre and post fracture µCTs [3]. For each model, the axial torsion (i.e. axial twist divided by the trabecular length) was calculate for all the trabeculae; the trabeculae having a torsion bigger than the 99th percentile were identified and for each one the minimum distance from the surface of the fractured volume was computed.

Results and Discussion

For all the models, the map of the magnitude of the nodal rotation showed an excellent match with fractured areas with damaged regions systematically overlapping the regions with highest values of nodal rotations. This information is not physically meaningful though, since it can embed rigid motions. Trabeculae over the 99th percentile of torsion appeared distributed at the average distance of 1.208 ±0.475mm from the fractured volume and the trabecula with highest value always appear within 0.01mm.

The results suggested that beam models based on the skeletonisation of the µCT datasets were able not only to capture the overall mechanical response of the trabecular structure but also to provide an indicator to localize the fracture onset. Trabecular torsion (an information not achievable from voxel-based µFEM) appeared spatially aligned with fractures for all the samples, being the trabecular with the highest value of torsion always close to the fractured volumes. This appear consistent with the laminar structure of the trabeculae for which torsion is likely to produce delamination of the lamellar pack.

The proposed modelling strategy based on beam elements is simple, and computationally light: this modelling approach makes it potentially feasible to embed the laminar structure of each trabeculae in the formulation of the beam elements; constitutive nonlinearities as well as large deformation would be also approachable for studying the post-delamination phase. Both these topics would be problematic and demanding with µFE approach.

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Introduction
Cardiovascular diseases are a leading cause of mortality globally, causing significant financial burden [1]. Coronary artery bypass surgery is the current standard treatment, but it can cause complications through the mismatch between the implant and host tissue [2]. The potential of the additive manufacturing (AM) of biomaterials has yet to be fully explored as potential solutions [3]. To date, the AM of PVA (polyvinyl alcohol, a versatile biomaterial that mimics arterial tissue [4]) and/or the resulting mechanical properties, have been limited by the manufacturing technique. In this study, the application of sub-zero, temperature-controlled, bioprinting enables fabrication of multi-layered samples. The effectiveness of this technique is evaluated against the tensile strength relative to the number of layers.

Methods
The design of 50x50x1.5 mm³ samples geometry was created using Fusion 360 (Autodesk, California, United States). The designed geometry was converted into G-Code through the slicing software REGEMAT 3D designer (REGEMAT 3D S.L., Granada, Spain), using an alternating 0-90 degree infill. A solution of 11% w/w PVA (146–186 kDa) and hydrolysis of 99 % (Sigma-Aldrich, Missouri, USA), was dissolved in deionised water by autoclaving for 1 h at 121°C, then mechanically stirred at 50°C for 1 h and further continuous stirring for 1 h until the solution reached room temperature (RT) (22.5 ± 1°C). A Regemat BIO V1 bioprinter (REGEMAT 3D S.L., Granada, Spain) was used to additively manufacture the samples. The samples were printed with a 0.58 mm nozzle in a multi-layer configuration, with each layer having a thickness of 0.25 mm (Figure 1). The printing temperature was maintained at -8°C throughout the printing process. After AM, all samples underwent 24 h freeze–thaw cycles (FTC) at −20°C and RT respectively. The samples were kept in deionised water for 4 days and then mechanically tested using a uniaxial tensile ramp test and a load cell of 2.5 N. The samples were clamped at both ends, preloaded and a displacement of 9.6 mm (+19.2% of initial sample length) was applied at a constant rate of 0.25 mm/sec. The load and displacement were recorded throughout the test, and the resulting load-displacement plot was used to evaluate the mechanical properties of the samples.

Results
The preliminary, raw load and displacement results are shown in Figure 2. The samples represent 6 alternating (parallel / perpendicular) layers after 2FTC and 3FTC. An increase in the tensile strength of the samples was observed with increasing layers and FTC.

Discussion
This study has presented a sub-zero bioprinting approach which shows potential towards fabrication of functional cardiovascular biomaterials. The method presented in this research, enables precise layering and homogeneity of PVA biomaterials, but results can vary depending on the number of layers, FTC, and printing parameters. This research provides a foundation for further studies to optimise conditions and investigate the materials potential for cardiovascular tissue engineering applications. The flexibility of AM could enable the fabrication of materials with variable mechanical properties, often described as functional graded materials via AM.

References

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Biomechanical Comparison of Reconstructive Techniques for Scapholunate Dissociation

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Introduction
Numerous reconstruction techniques have been introduced for the treatment of chronic scapholunate dissociation. The most widely used method is three-ligament tenodesis (3LT) [1], but there are many results that dorsal ligament reconstruction alone does not provide sufficient stability. To compensate for 3LT, the Mark-Henry technique (MHT) [2], which additionally performs volar ligament reconstruction, has been introduced, but it was too complicated. Recently, the SwiveLock technique (SWT) using autologous tendons and synthetic tapes has been introduced, but long-term clinical results are lacking [3]. We performed a biomechanical comparison of three different reconstructive techniques for scapholunate dissociation in a controlled laboratory cadaveric model (Fig. 1).

Methods
Eleven fresh-frozen upper extremity cadaveric specimens were prepared. A wrist simulator with a linear guide rail system and the motion capture system were used. The scapholunate distance, scaphoid rotation, and lunate rotation were measured with continuous flexion-extension and ulnar deviation–radial deviation movements. Results were compared in five conditions: (1) ligaments intact, (2) scapholunate dissociation, (3) SWT, (4) 3LT, and (5) MHT.

Results
Scapholunate dissociation resulted in a typical pattern of scapholunate instability. The scapholunate distance was restored similarly to the intact state after SWT and MHT, but over-tightening was observed after SWT. This means that SWT is over-tightened on the dorsal side and there is a risk of a hinge effect on the volar side. The lunate extension was restored similarly to the intact state after all reconstructions. However, the scaphoid flexion was restored only after SWT (Fig. 2). The SwiveLock technique is most effective in improving distraction intensity and rotational strength for the treatment of scapholunate dissociation.

Discussion
The SWT was most effective in improving distraction intensity and rotational strength. Given the complexity of the technique in 3LT and MHT, SWT may be a more efficient technique in terms of operating time and intraoperative damage to the volar side structures. However, the over-tightening effect occurs in the scapholunate distance, so it is considered that additional studies are necessary on the clinical effect.

References
STRUCTURE AND MECHANICS OF THE INTERVERTEBRAL DISC-ENDPLATE JUNCTION ANALYSED USING SYNCHROTRON CT AND DVC

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Introduction

The intervertebral disc (IVD)-endplate junction is mechanically vulnerable because material properties change abruptly, leading to stress concentrations. Failure of the endplates has been linked to spinal pathologies like disc degeneration, these conditions lead to back pain which is a major global health burden. Structural integration of the IVD and endplates involves the penetration of collagen fibres into the mineralised tissues of the endplates and underlying bone. High strains have been observed near the endplate junction in whole discs under axial compression, and failure of the IVD under axial compression usually occurs at the endplate. We have previously shown that it is possible to resolve the microstructure of both the hard and soft tissues of the disc endplate junction using synchrotron phase-contrast tomography, and that digital volume correlation (DVC) can be used to measure strains in the fibrous tissue of the annulus fibrosus [1]. We have also used DVC to measure nano-scale strains in bone and calcified cartilage [2]. This work combines these techniques to investigate load transfer across the soft-hard tissue boundary of the IVD.

Methods

Murine spine segments were imaged at beamline I13-2 at Diamond Light Source, UK with a voxel size of 1.6 μm. Samples were placed in a mechanical testing rig and imaged at multiple compressive load steps. DVC was used to measure displacement fields across the disc endplate boundary. Lagrangian strains were calculated from the displacement fields by polynomial fitting and differentiation. Tissue specific point clouds for DVC were created using Avizo 2021. Calcified tissue point clouds were generated from the nodes of a tetrahedral mesh of the microstructure. The uncalkified cartilage point cloud was created using manual segmentation, and fibre point clouds were generated using fibre tracing. DVC parameters were optimised for each tissue type individually, giving a displacement measurement accuracy of 17 nm in the calcified tissues and 327 nm in the fibrous tissue.

Results

Displacement fields and subsequent strains were measured for multiple regions of the disc-endplate boundary with sub-micron accuracy, see Figure 1. Optimal parameters for DVC depended on the tissue type analysed. Strain distribution varies regionally and with loading level, with calcified endplate strains initially significantly lower than strain in the soft tissues but becoming equivalent at higher loads, see Figure 2.

Discussion

These results improve our understanding of the 3D structure and mechanics of the IVD-endplate boundary. The methods used here provide an accurate way to investigate load transfer across soft-hard tissue boundaries at the microstructural scale and could be used to further our understanding of soft-hard tissue biomechanics in health, disease, and aging.

References


Acknowledgements

We gratefully acknowledge funding from EPSRC (EP/R513131/1 & EP/V011006/1), MRC (MR/R025673/1), Royal Academy of Engineering (CIET 1819/10), CZI (CZIF2021-006424), beamtime at Diamond Light Source (MT19322), and the EPSRC i4health CDT.
TUNABLE DESIGN AND STRUCTURE-PROPERTY CORRELATIONS OF CORE-SHELL COMPOSITE SCAFFOLDS OBTAINED BY 3D-PRINTING

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Abbreviations
PLA: poly(lactic acid); FDM: fused deposition modeling; SC: simple cubic; ST: simple tetragonal; BCC: body-centered cubic; FCC: face-centered cubic.

Introduction
Composite scaffolds combine the advantages of different biomaterials, thus better addressing the multiple needs of tissue engineering. In this work, we developed and characterized bioreabsorbable hybrid scaffolds composed of a 3D-printed PLA lattice core grafted with a bioactive hydrogel shell. While the core provides mechanical support, the hydrogel supports cell proliferation and osteogenic differentiation [1,2]. Moreover, the core-shell design and the use of additive manufacturing make this approach highly versatile, allowing to tailor the mechanical and functional properties of the scaffolds by varying the core/shell ratio and the lattice structure. The correlations between the mechanical properties of the scaffolds and their structure are here described according to Gibson-Ashby models for cellular solids [3].

Methods
Core specimens (10 x 10 x 10 mm³) were designed as lattice structures with fixed strut thickness but variable unit cell type (Table 1) and dimensions. They were 3D-printed by FDM of PLA, immersed at 40°C in a gelatin-chitosan hydrogel solution, freeze-dried and post-cured.

<table>
<thead>
<tr>
<th>Lattice type</th>
<th>n = 1.11</th>
<th>n = 1.83</th>
<th>n = 1</th>
<th>n = 1.39</th>
<th>n = 1.46</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>ST z</td>
<td>ST xy</td>
<td>BCC</td>
<td>FCC</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Lattice unit cells and corresponding values of the exponent n in power law fits (eq. 1) of relative modulus vs. relative density curves; for ST lattices different loading directions are considered (z and xy).

By changing the lattice cell type and dimensions, core void volume fractions between about 45% and 90% are obtained. These values correspond to a wide range of bioactive hydrogel content (5-50 wt% ca.) and water uptake. On the other hand, they also affect the stiffness and strength of the scaffolds, which resemble those of different types of spongy bone tissue. A proper balance between hydrogel content and mechanical properties should be found according to the specific target tissue. Looking for guidelines to exploit the scaffold property tunability, the hydrogel content can be estimated through theoretical predictions, showing good consistency with the experimental values.

Results and discussion
The appearance of a core and a core-shell specimen is displayed in Figure 1a. Noteworthily, the hydrogel fills all the void volume in the core and develops a highly interconnected porosity after freeze-drying, which is fundamental to ensure cell colonization.

![Figure 1](image_url)

Figure 1: (a) Photographs of a lattice core and a core-shell scaffold with SC lattice structure. (b) Relative modulus vs. relative density curves for different lattices; all curves are fitted with a power law model (eq. 1).

By changing the lattice cell type and dimensions, core void volume fractions between about 45% and 90% are obtained. These values correspond to a wide range of bioactive hydrogel content (5-50 wt% ca.) and water uptake. On the other hand, they also affect the stiffness and strength of the scaffolds, which resemble those of different types of spongy bone tissue. A proper balance between hydrogel content and mechanical properties should be found according to the specific target tissue. Looking for guidelines to exploit the scaffold property tunability, the hydrogel content can be estimated through theoretical predictions, showing good consistency with the experimental values. Moreover, it is possible to outline data-driven structure-property correlations like those in Figure 1b, showing the power law relationship between relative modulus and relative density for scaffolds with different lattice types. Interestingly, the slope of these curves also indicates whether the lattice deformation behavior is mainly dominated by stretching (n = 1) or by bending (n = 2).

References

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
YAP/TAZ AND MECHANICAL CUES AS TEMPORAL REGULATORS OF ANGIOGENESIS

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Introduction
Angiogenesis, i.e. the formation of new blood vessels, plays a crucial role in both health and disease. Better understanding and controlling this process could improve treatment strategies for associated diseases (e.g. cancer) and unlock the development of large tissue-engineered constructs.

Angiogenesis could be regulated by tuning the extracellular matrix (ECM), as suggested by experiments showing that ECM stiffness affects the process of tip cell formation [1]. This mechanoresponse might be explained by the crosstalk between the force-sensitive proteins YAP/TAZ and Notch [2], a key pathway for angiogenic EC fate selection. However, the underlying mechanisms are not fully clear yet.

Here, by coupling computational models of YAP/TAZ and Notch signaling, we investigated the effects that ECM stiffness, via the YAP/TAZ-Notch crosstalk, has on the temporal dynamics of endothelial cell (EC) fate selection, one of the key determinants of the density of the formed vascular networks.

Methods
An ordinary differential equation (ODE) model of the YAP/TAZ mechanoresponse [3] and an ODE model of Notch and VEGF signaling during angiogenesis [4] were coupled by assuming Dll4 inhibition by YAP/TAZ activation, as motivated by previous experiments [2] (see Fig. 1 for the model overview). These ODE models were extended to simulate rows of ten cells interacting via Notch. The YAP/TAZ-mediated Dll4 inhibition was fitted against in vitro qPCR data linking stiffness to Dll4 expression [5]. To simulate the temporal dynamics of EC fate selection at the onset of angiogenesis, in silico experiments were conducted; in particular, ECs were exposed to VEGF for 28 hours. EC fate selection times were determined based on their filopodia formation and stability, used to classify the EC phenotype.

Results
In agreement with previous experiments [5], DLL4 production decreased with increasing stiffness. This decrease was caused by a higher YAP/TAZ nuclear fraction. Additionally, we found that stiffer environments lead to increased average amounts of filopodia prior to patterning, but also slower EC patterning (Fig. 2). If DLL4 production decreases below critical levels, no patterning is observed anymore and hypersprouting occurs.

Figure 2: EC fate selection time (y-axis) for a row of ten cells (x-axis). The greener the color, the larger the filopodia content.

Discussion
Our study suggests the presence of a bi-phasic effect of stiffness on angiogenesis: a relatively small increase of the stiffness slows down EC fate selection, leading to sparser networks; whereas increasing the stiffness at higher values (e.g. 60 kPa and higher) leads to hypersprouting. While the latter has already been observed [1], the first trend could be validated in future experiments. Our study thus provides a first outlook on the YAP/TAZ-mediated influence of mechanics on the temporal dynamics of angiogenesis. In the future, the computational model will be further extended by including the effects of YAP/TAZ on other components of the VEGF-Notch crosstalk.

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Introduction
The periodontal ligament (PDL) binds the tooth to the alveolar crest. The orthodontic process involves exploiting the properties of this ligament to achieve the desired tooth displacement and orientation. Controlling the stress patterns can help optimize treatment in terms of speed and success of correction [1]. Previous studies ([1],[2]) have presented an analytical method for calculating the stiffness of the PDL in a single-rooted tooth. These models approximate the tooth as a paraboloid, where the strain distribution throughout the PDL for any given displacement is presented. The following research extends on the work by [1] and [2] by proposing a model which enables the use of patient data to determine the geometry of the root model, yet retaining the computational speed of the analytical models. This is useful where the root geometry for the patient can be obtained from CT imaging, allowing a closer approximation of the real root to be triangulated.

Methods
The PDL is assumed to be very thin, have uniform thickness, and have homogeneous, isotropic and linear elastic material properties. The boney socket and the tooth root are assumed to be rigid, and rotations of the PDL about each axis are assumed to be small. The surface is discretized into triangular elements. If the global displacements are applied to the crown, the strain in each element can be calculated since the geometric and material properties are defined in the literature ([1],[2]). Global stresses are calculated from summing the stiffness of all elements across the surface (Equation 1)

\[ F = \sum (AE/\delta) K u \]  

(1)

where \( K \) is the stiffness matrix, \( F \) is a vector of forces and moments, \( u \) is a vector of displacements and rotations, \( a \) is the surface area, \( E \) is the Young’s Modulus and \( \delta \) is the thickness of the PDL. Hydrostatic stress (\( \sigma_{\text{hyd}} \)), the average of the three normal stress components, can be obtained from the strains that were calculated for each element, as defined by Equation 2.

\[ \sigma_{\text{hyd}} = (E \varepsilon) / (3 (1 - 2v)) \]  

(2)

where \( \varepsilon \) is the normal strain on the element and \( v \) is the Poisson’s ratio. The semi-analytical model was written in MATLAB and a parabolic surface replicating the surface in [1] was imported as an STL file.

Results
The maximum hydrostatic pressure was compared to the model used in [1]. The analytical result for the maximum hydrostatic pressure was 9.200 kPa. The semi-analytical result was 9.183 kPa, a difference of 0.19%. The variation of the hydrostatic pressure across the surface can be seen in Figure 1.

Discussion
The analytical model for the stresses in the PDL under loading was derived using models from [1] and [2]. The semi-analytical model described in this paper improves on both papers by enabling the user to input image data of real teeth to determine the PDL stiffness. The results presented here closely matched the analytical solution; small discrepancies are expected due to discretization of surface.

References
FE ANALYSIS OF AN EXTERNAL STABILIZER APPLIED IN TREATMENT OF THE PROXIMAL PHALANX FRACTURE IN HORSES

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Introduction
Fractures of the proximal phalanx (P1) in horses belong to a wide group of fractures in those animals. Most of them are treated by means of surgical methods which give good results. However, treatment of multi-fragmental fractures of P1 is difficult and often gives unsatisfactory clinical outcome. In many cases, especially when the fracture is open and infected, they can be life-threatening problems.

We propose treatment of such complex fractures with application of an orthopaedic external stabilizer designed in Warsaw University of Life Sciences. The device is fixed into the third metacarpal bone (MC III) by five Apex screws. Its role is to unload the treated bone during getting up and standing after surgery. The aim of the present study is to verify strength of the stabilizer and influence of the device fixation on bone tissue behaviour.

Methods
The external stabilizer consists of two semi-circular arms oriented horizontally with respect to the third metacarpal bone axis and connected with each other by means of three vertical rods. In addition, two circular rods are fixed to the stabilizer to prevent the patient from standing on the hoof (Fig. 1).

We performed finite element (FE) analyses using Ansys 2021 package. The stabilizer was modelled as an isotropic elastic material (Young’s modulus 220 GPa, Poisson’s ratio 0.3) and bone as non-linear viscoelastic material by means of a constitutive equation formulated according to the method described in [1]. All degrees of freedom were fixed at the lower part of the circular rods. It is estimated that the force acting on the cannon bone during getting up is approx. 2743 N [2] for a horse weighing 500 kg. Therefore, we decided to apply force 3000 N on the upper surface of the MC III bone along its long axis.

Results
In Fig. 2 von Mises stress distribution in the stabilizer is presented. Also, the boundary conditions are shown. We can identify the most loaded regions of the stabilizer. The maximal value of stress in the orthopaedical device equals 1334 MPa.

![Figure 2: Stress distribution in the external stabilizer and the MC III bone.](image)

Discussion
The numerical results indicate that the construction of the external stabilizer is correct. However, closer analysis of bone behaviour in the vicinity of the screws is required. We observed stress and strain concentrations in those regions, which might lead to bone necrosis. This also suggests that strong bone remodelling might take place there. The phenomena can be minimised by optimising the angular orientation of the screws, which is also in the field of our interest.

References
SPATIALLY VARYING MULTI-COMPARTMENT MODEL OF BLOOD FLOW AND OXYGEN TRANSPORT IN THE HUMAN BRAIN

Stephen Payne
National Taiwan University, Taiwan

Introduction

The brain relies on a continuous supply of oxygen and other metabolic supplies since its storage capacity is very limited. Brain tissue is thus very highly perfused with every brain cell within a few tens of micrometers of a blood vessel. However, obtaining information about flow and metabolism is highly challenging and mathematical models play an important role in interpreting clinical data. Most models, however, are based on highly simplified compartmental models or highly detailed network models. A new multiple compartment model of blood flow and oxygen transport is thus proposed obtained via a porous medium model.

Theory

Three blood compartments (arterial, capillary, and venous) are assumed for simplicity, although additional compartments can be added as required. Conservation of mass in each compartment gives:

\[
\frac{\partial \phi_a}{\partial t} + \nabla \cdot (\phi_a \mathbf{u}_a) = -\phi_a \beta_{ac}(p_a - p_c)
\]

\[
\frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{u}_c) = \phi_a \beta_{ac}(p_a - p_c) - \phi_c \beta_{cv}(p_c - p_v)
\]

\[
\frac{\partial \phi_v}{\partial t} + \nabla \cdot (\phi_v \mathbf{u}_v) = \phi_c \beta_{cv}(p_c - p_v)
\]

where each compartment has volume fraction \( \phi_i \), pressure \( p_i \) and velocity field \( \mathbf{u}_i \) respectively. It is assumed that perfusion coupling between compartments is linearly proportional to the volume fraction and the driving pressure difference, with coefficient \( \beta_{ij} \). Darcy flow is assumed, following the homogenization procedure derived in [1]. Displacement of the solid phase is neglected, and a linear pressure-volume relationship assumed.

Continuity for oxygen transport is then applied, based on the same assumptions. These are re-written using the flow equations and conservation of volume. Further analysis of the relative magnitudes of the terms to simplify the equations then gives:

\[
\frac{\partial S_A}{\partial t} = \nabla \cdot (S_A (\mathbf{K} \nabla p_a)) - \frac{k_A S_A}{c_{ab}} (p_A - p_T)
\]

\[
\frac{\partial S_C}{\partial t} = \beta_{ac} \phi_a (p_a - p_c) (S_A - S_C) - \frac{k_C S_C}{c_{ch}} (p_c - p_T)
\]

\[
\frac{\partial p_T}{\partial t} = \frac{p_T}{\phi_T} \left[ \nabla \cdot (\phi_a \mathbf{K} \nabla p_a) + \nabla \cdot (\phi_c \mathbf{K} \nabla p_c) \right]
\]

\[
\frac{\partial S_C}{\partial t} = \frac{\phi_a}{\phi_T} \frac{S_A}{S_C} \left( \frac{k_C S_C}{c_{ch}} + \frac{k_C S_C}{c_{ch}} \right) (p_c - p_T)
\]

These are written in terms of the blood oxygen saturation and the tissue partial pressure of oxygen for convenience and a non-linear relationship for metabolism is assumed. Note that the venous compartment reduces to a constant oxygen concentration sink under the relevant assumptions, simplifying the governing equations significantly.

Values and boundary conditions are taken from [2]. The equations are then solved in a spherically symmetric annular shell, with properties scaled between grey and white matter as in [2].

Results

The radial variations in arterial and capillary blood oxygen saturation are shown in Figure 1. There is significant spatial variability with saturation values dropping towards the ventricles, although the tissue partial pressure remains high enough to ensure a sufficient metabolic rate throughout the tissue. Such variability is thus likely to be masked in imaging data.

![Figure 1: Arterial and capillary blood oxygen saturation against radial distance (both grey and white matter).](image)

Conclusions

A new multi-compartmental framework for spatially varying cerebral blood flow and oxygen concentration is presented. Future work will focus on the validation of these results against available experimental data and testing the model against medical imaging models of perfusion and oxygen extraction factor (OEF).

References


Acknowledgements

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ESTIMATING CEREBRAL MECHANICAL PROPERTIES NON-INVASIVELY THROUGH THE USE OF TISSUE PULSATIONS IN THE HUMAN BRAIN

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Introduction
The mechanical properties of in vivo brain tissue remain very poorly characterized. Ex vivo measurements often provide only a poor estimate of in vivo properties. These properties are, however, critical in understanding the brain’s behavior in both normal and pathological states. The use of ultrasound, via the Transcranial Tissue Doppler method (TCTD), has received new interest recently, as the measurements are well tolerated, even by patients, and are quick and cheap to acquire [1]. Brain tissue pulsations (BTP) are measured through the forehead and can be recorded simultaneously with many other physiological variables.

Theory
The brain is assumed to comprise a coupled solid-fluid system with a single fluid compartment. Hence:

\[ G \nabla^2 \mathbf{w} + \frac{G}{1 - 2\nu} \nabla(\nabla \cdot \mathbf{w}) - \alpha \nabla \cdot \mathbf{p} = \rho_s \frac{\partial^2 \mathbf{w}}{\partial t^2} \]

\[ \nabla \left( \frac{k}{\mu} \mathbf{p} \right) = \frac{\partial}{\partial t} \left( \alpha \nabla \cdot \mathbf{w} + \frac{p}{Q} \right) \]

where the solid is assumed to be a linear, isotropic material with density \( \rho_s \), shear modulus \( G \) and Poisson ratio \( \nu \). The fluid is taken to follow Darcy’s law with permeability \( k \) and viscosity \( \mu \), the Biot-Willis coefficient is denoted by \( \alpha \) and specific storage by \( Q \). The fluid has pressure \( p \) and the solid displacement \( \mathbf{w} \).

We assume a composite solution:

\[ w(r, t) = w_0(r) + \varphi_1(t) e^{i\omega t} \]

\[ p(r, t) = p_0(r) + \tilde{p}_1(t) e^{i\omega t} \]

Hence:

\[ \frac{d^2 \varphi_1}{dr^2} + \frac{2}{r} \frac{d \varphi_1}{dr} + \frac{\omega^2}{E} \varphi_1 = \frac{1}{E} \frac{1}{1 - \nu} \frac{1}{r^2} \]

\[ \frac{d^2 \tilde{p}_1}{dr^2} + \frac{2}{r} \frac{d \tilde{p}_1}{dr} - \frac{\omega^2}{E} \tilde{p}_1 = \frac{\omega^2}{E} \frac{1}{r^2} \frac{1}{1 - \nu} \frac{1}{r^2} \]

The solution requires four boundary conditions. At the brain surface, we assume zero displacement and unit non-dimensional amplitude pressure. At the inner (ventricle) surface, where \( r' = \delta \), we assume zero fluid flux and a mixed boundary condition for displacement.

Experimental data
BTP recordings were obtained from 20 volunteers at rest [1]. Recordings were obtained using a Brain Tissue Velocimetry (Brain TV) TCTD prototype (Nihon Kohden, Japan). This is equipped with a standard 2 MHz TCD probe, placed on the forehead approximately 1 cm above the orbit on the right side. Synchronous BP readings were obtained using a finger-cuff Finometer system. Velocity was integrated over time to obtain a BTP signal representing tissue displacement at 33 depths (22-86 mm). Good quality signals were recorded for the first 19 depths in all subjects. The data were converted to transfer function form to give an ensemble-averaged frequency response at the fundamental harmonic as a function of depth, Figure 1. There is significant variability between individual subjects, but a clear trend of increasing magnitude with depth.

Figure 1: Transfer function (top: gain; bottom: phase): individual subjects (black); population-averaged (red).

Results
Using a simple optimization method based on RMSE, we calculated the parameter values that yield the best fit to the population-averaged data (fitting only four key parameters). To ensure convergence, a wide range of the parameter space is explored. The parameter values (\( E = 17.6\) kPa; \( \kappa/\mu = 8.73 \times 10^{-7} \) m/s/kg; \( Q = 4.570 \) kg/m.s; \( \nu = 0.499 \)) are in line with existing literature.

Conclusions
A new methodology for estimating cerebral mechanical parameters is presented using BTP and preliminary results show promise. Future work will focus on more detailed analysis and the estimation of parameters under different conditions and for individual subjects.

References

Acknowledgements
SJP is supported by a Yushan Fellowship from the Ministry of Education, Taiwan (#111V1004-2).
A SPATIALLY VARYING MULTI-COMPARTMENT MODEL OF THE REGULATION OF CEREBRAL BLOOD FLOW AND VOLUME

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Introduction
The maintenance of adequate cerebral perfusion is a key aspect of healthy brain function. Dynamic cerebral autoregulation is the mechanism that acts to maintain cerebral blood flow constant in response to short-term changes in arterial blood pressure and is impaired in many cerebrovascular and neurodegenerative diseases. However, little is known about its spatial variability due to the difficulties in measurement of flow/perfusion in the human brain and no mathematical model yet exists of this. A new framework for considering the regulation of perfusion and blood volume in a simplified whole-brain geometry is thus presented and the different types of behaviour that are exhibited are highlighted.

Theory
Three blood compartments (arterial, capillary, and venous) are assumed for simplicity, although additional compartments can be added as required. Conservation of mass in each compartment gives:
\[
\frac{\partial \phi_a}{\partial t} + \nabla \cdot (\phi_a \mathbf{u}_a) = -\phi_a \beta_{ac} (p_a - p_c)
\]
\[
\frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c \mathbf{u}_c) = \phi_a \beta_{ac} (p_a - p_c) - \phi_c \beta_{cv} (p_c - p_v)
\]
\[
\frac{\partial \phi_v}{\partial t} + \nabla \cdot (\phi_v \mathbf{u}_v) = \phi_c \beta_{cv} (p_c - p_v)
\]
where each compartment has volume fraction \(\phi_i\), pressure \(p_i\) and velocity field \(\mathbf{u}_i\) respectively. It is assumed that perfusion coupling between compartments is linearly proportional to the volume fraction and the driving pressure difference, with coefficient \(\beta_{ij}\). Darcy flow is assumed, following the homogenization procedure derived in [1]. It is finally assumed that there is a linear relationship between changes in volume fraction and pressure in each compartment, i.e.:
\[
\frac{\phi_i - \bar{\phi}_i}{\bar{\phi}_i} = \frac{p_i - \bar{p}_i}{\bar{p}_i}
\]
This enables us to consider the responses of different compartments independently (since they are known to respond differently), providing a more general framework for the control of blood flow and volume. Three cases are considered: first, the pressure-volume relationship is purely passive; second, volume fractions remain constant; third, assuming typical/baseline values for each compartment.

The equations are converted into non-dimensional form, using a characteristic time, \(t_c\), length, \(L\), permeability, \(K_c\), and pressure, \(p_{ac}\). Analysis of the arterial compartment then yields \(t_c = 1/\beta_{ac} p_{ac}\), which has a value of around 60 seconds (values taken from [2]). Elimination of small terms then gives the final non-dimensional form in terms of the ‘corrected’ pressures and various non-dimensional groups:
\[
\frac{\partial p_a}{\partial t} = \left(\frac{K_c}{L^2 \beta_{ac}}\right) \nabla \cdot (p_a (K_a \nabla p_a)) - p_a (p_a - p_c)
\]
\[
\frac{\partial p_c}{\partial t} = \frac{Q_c g_a \alpha_a}{Q_a g_a \alpha_c} p_a (p_a - p_c) - \frac{\beta_{cv}}{\beta_{ac}} p_c (p_c - p_v)
\]
\[
\frac{\partial p_v}{\partial t} = \left(\frac{K_c}{L^2 \beta_{ac}}\right) \nabla \cdot (p_v (K_v \nabla p_v)) + \beta_{cv} \frac{Q_c g_a \alpha_c}{Q_a g_a \alpha_v} p_c (p_c - p_v)
\]
Values and boundary conditions are taken from [2]. The equations are solved in a spherically symmetric annular shell, with properties scaled between grey and white matter as in [2].

Results
A drop in inlet arterial pressure of 10% at time 0 is used to illustrate the model behaviour, as shown in Figure 1 for (spatially averaged) grey matter perfusion. The response times are very different, and a biphasic response is shown for two of the three conditions.

![Figure 1: Spatially averaged white matter perfusion in three cases: baseline, passive and isochoric.](image)

Conclusions
A new multi-compartmental framework for spatially varying regulation of cerebral blood flow and volume is presented. Future work will extend this to integrate more active mechanisms of control.

References

Acknowledgements
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TOWARDS PREDICTING THE DISCRETE GRADES FOR PROGRESSIVE CHANGES OF KNEE OSTEOARTHRITIS: A FINITE ELEMENT STUDY

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Introduction

Abnormal loading in the knee joint may lead to degenerative changes of articular cartilage [1]. Finite element models are used to simulate mechanical responses of joint tissues that can be utilized to predict tissues’ future condition [2]. However, the method we previously developed in [2] lacks evaluation of the relationship between the discrete Kellgren-Lawrence (KL) grading classifications, which is based on radiologic features of osteoarthritis (OA), and quantifiable continuous changes in OA, i.e., joint space narrowing (JSN). In this study, we tested if cartilage overexposure of healthy joints at the baseline can be used to predict knee osteoarthritis grades while correlating with JSN after an 8-year follow-up.

Methods

We obtained information from 103 subjects in the Osteoarthritis Initiative database. At baseline time, the subjects were less than 70 years of age with a BMI under 35 kg/m² and had both knees healthy. One knee per individual developed OA during the 8-year follow-up while the other remained healthy. All knees were grouped by the radiographic OA grade (KL) at the 8-year follow-up time; 29 stayed healthy (KL0); 1, 38 developed mild OA (KL2), and 36 developed severe OA (KL3). We created personalized knee finite element models for the medial and lateral tibiofemoral compartments using baseline information and simulated a simplified gait loading [2] (Fig. 1).

![Figure 1: a) Knee finite element models. b) Joint space measurement from X-rays at the baseline and 8-year follow-up. c) Median of simulated overexposure in joint compartments. d) Maximums of joint space narrowing vs overexposure. Whiskers show ranges. **p < 0.01.](image)

We used femoral medial-lateral and maximum anterior-posterior distances, and cartilage thickness from MRIs to scale the compartment template geometries; while sex, weight, age, height, walking speed, and joint alignment were used to estimate the peak joint contact forces by a neural network trained with musculoskeletal models’ results (r = 0.64) [3]. The overexposure corresponds to the sum of the overstress (with respect to age-dependent degeneration thresholds of tensile stress) times its duration in each model’s element over the stance phase of the gait. The JSN was defined as the percent change in joint space measured with the aid of an in-house MATLAB tool on frontal X-rays between baseline and follow-up times. Knee models used a biphasic fibril-reinforced cartilage formulation in FEBio software. For comparisons of overexposures to predict future KL grades and JSN, we used non-parametric statistical tests and Pearson correlations in MATLAB.

Results

Healthy and mildly affected joints differed from the severely affected joints (Fig. 1c), as determined either with the simulated over-exposure or the measured JSN. Medial compartment values were higher than lateral in the FE model (p < 0.001) in all KL groups, but only in KL2 for the JSN (p = 0.03). Over-exposure and JSN of matching knees did not linearly correlate either for the medial (r = 0.14, p = 0.15) or lateral (r = 0.18, p = 0.07) compartments, but only by taking the maximum values per knee compartment (r = 0.34, p < 0.001, Fig. 1d).

Discussion

The results suggest that articular cartilage overexposure may be used to predict the future radiographic OA grade of the whole joint, while one value per knee correlates with the maximum JSN experienced. Compartment-wise validations are needed since we used unique KL values per knee. The low correlations observed can be explained in part by the uncertainties in JSN calculations due to the variability in X-ray imaging alignment from baseline to follow-up. In addition, our method does not consider alterations in loading while OA progresses [4], which may increase cartilage overexposure in other regions, affecting the correlations observed. We foresee the need to incorporate tissue adaptation [5] into our pipeline to investigate mechanisms of cartilage thinning.

References

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DEVELOPMENT OF AN ADVANCED CULTURE SYSTEM TO INVESTIGATE VASCULAR TISSUE ENGINEERING BIOMECHANISMS

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Introduction

Vascular tissue engineering aims to regenerate vessels “at the target site” using cell-free scaffolds supporting endogenous regeneration. Ideally, the regenerated tissue is remodelled, guided by physiological hemodynamic loads, to resemble a vessel with native-like structural and functional properties [1]. Despite encouraging in vivo proof-of-concept studies [2], intimal hyperplasia and early stenosis remain prevalent complications in graft implantation. With the aim of investigating these phenomena, we succeeded in developing an advanced and versatile culture system able to perform cell seeding and mimic in vivo-like stimuli (pre-tensioning, wall shear stress (WSS) and cyclic pressure) for long-term experiments. Currently, experiments with different seeding and culture conditions and related biological analyses are ongoing to verify the suitability of the system to be used in a cell culture lab and its performances under different experimental protocols.

Methods

The system consists of a culture chamber, a rotating mixer for semi-automatic cell seeding, a pinch-valve to generate a pulsatile stress, and two fluid dynamic circuits (luminal and extraluminal compartments) each one composed by a roller pump, a reservoir and an air chamber (Figure 1). A custom graphic user interface allows to act on each peripheral device in manual control or to set an experiment by specifying the duration, the pumps’ flow rate, the pressure regime, and the culture chamber’s rotation speed for the seeding.

Human umbilical vein endothelial cells (HUVECs) [4] seeding was achieved using discrete rotations (4 angular position, each kept for 30 minutes). We evaluated flow-induced HUVECs morphology, cell adhesion to the substrate, cell orientation (SEM, immunofluorescence staining of e.g. F-actin, VE-Cadherin, pFAK, paxillin, ZO-1), and gene expression (e.g. KLF-2, vWF).

Results and discussion

The system was successfully subjected to bench tests to verify the no cytotoxicity, the compatibility with the assembly procedures under laminar flow hood, the hydraulic sealing (up to 400 mmHg), and the maintenance of sterility inside an incubator up to 21 days. We believe that the versatility and easiness of use are the features that most distinguishes the culture system here developed and presented from those commercially available or present in the state-of-the-art. Indeed, the system is robust and reliable in setting and exploit different seeding and stimuli protocols, allowing to perform a fine tuning of the experimental procedures. After cell seeding, we observed that HUVECs almost completely covered the graft and establish a complex cell-graft and cell-cell interaction network (Figure 2). All these observations endorse the possibility to obtain a functional cell-populated graft to subject to physio-pathological environments of fluid flow.

Figure 2: Immunostaining image.

The developed culture system and the drafting of ad hoc experimental protocols will allow to establish an accurate in vitro model to investigate complex biological interactions in vascular tissue engineering.

References


Figure 1: Culture system assembly.

Three-layered electrospun grafts (θ=θ=6 mm, l=60 mm), composed of a nanometric mesh of silk fibroin (SF) and polyurethane (PU) enclosed within SF layers, were manufactured and used for these tests [3].
COMPARISON BETWEEN TWO FACE MOBILITY INDEXES FOR HYPOMIMIA ASSESSMENT IN PARKINSON’S DISEASE

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Introduction

Parkinson’s Disease (PD) is a neurodegenerative disorder characterized by motor and non-motor symptoms. One of the clinical hallmarks of PD is hypomimia, i.e., a condition that leads to a reduction of face expressivity [1]. In order to provide an anatomic description of muscular movements during facial expressions and their subdivision depending on the displayed emotions, the Facial Action Coding System (FACS) was developed that describes facial expressions by means of action units [2]. One of the most used software embedding the FACS is OpenFace (OF) [3]. Recently the authors have developed a face mobility index (FMI), based on anatomical face landmarks, with the aim to provide a quantitative measure of hypomimia through an easy-to-interpret and intra-subject metric of face mobility normalized to the neutral expression. The aim of this study was to compare two indexes of face mobility in a cohort of PD and healthy subjects: a functional one (FMI) [4] whose metric is purposely devised to capture the physiological aspects of face mobility regardless emotions, since landmarks detection is driven by face muscle insertion points, with an OF based one (FMI_OF), which addresses emotions production from a cognitive point of view, being driven by action units. These different approaches could be combined in order to improve our understanding of PD hypomimia aetiology.

Methods

Videos of the basic emotions and the neutral expressions were acquired by means of a commercial camera (30 fps) on two cohorts of subjects: healthy controls (HC) (n = 17, age = 65.83±8.25 years) and PD (n = 29, age = 68.48±7.81 years). The frames corresponding to the peaks of emotions were extracted and two sets of facial landmarks were tracked. The FMI approach included 40 points determined as the points of insertion of facial muscles; landmarks were tracked with a self-developed software (TrackOnField). Whereas in the FMI_OF the 68 landmarks available in the software, commonly used in face recognition and emotion classification tasks were employed. From the tracked points, two sets of distances were defined as described in Figure 1 and the two indexes computed as in [4]. Finally, in order to compare the two approaches, Pearson correlation was employed at p<0.05 significance level.

Results

Results of the present study are reported in Table 1. Statistically significant correlations are found in the HC population for certain emotions. No statistically significant correlations were found in the PD cohort of subjects. Our results seem to indicate that the two indexes are capturing different aspects of face mobility that for some specific expressions (i.e., disgust, fear, sadness and surprise) are overlapping. However, when the results are translated to PD individuals this relationship is lacking.

<table>
<thead>
<tr>
<th>Emotion</th>
<th>ρ HC</th>
<th>p-value HC</th>
<th>ρ PD</th>
<th>p-value PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger</td>
<td>0.1335</td>
<td>0.6638</td>
<td>0.0821</td>
<td>0.6718</td>
</tr>
<tr>
<td>Disgust</td>
<td>0.6014</td>
<td>0.0297</td>
<td>0.0459</td>
<td>0.8132</td>
</tr>
<tr>
<td>Fear</td>
<td>0.6667</td>
<td>0.0128</td>
<td>0.3453</td>
<td>0.0665</td>
</tr>
<tr>
<td>Happiness</td>
<td>0.0287</td>
<td>0.9259</td>
<td>-0.1344</td>
<td>0.4868</td>
</tr>
<tr>
<td>Sadness</td>
<td>0.6279</td>
<td>0.0216</td>
<td>-0.0154</td>
<td>0.9367</td>
</tr>
<tr>
<td>Surprise</td>
<td>0.5967</td>
<td>0.0313</td>
<td>0.1146</td>
<td>0.5540</td>
</tr>
</tbody>
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Table 1: ρ and p-values of correlation between FMI and FMI_OF per emotion and cohort of subjects

Conclusions

It can be speculated that the two indexes measure different facets of hypomimia and might be complementary in PD. Future developments are needed to validate these measures through surface electromyography.

References

KNEE CARTILAGE MECHANICS IN FINITE ELEMENT ANALYSIS USING INPUTS FROM DIFFERENT MUSCULOSKELETAL SOFTWARE

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Introduction
Computational modeling has been widely used for estimating knee joint mechanics, predicting the progression of musculoskeletal (MS) diseases, and simulating the effects of rehabilitation exercises. Different MS-software have been used for these purposes, and some studies have already investigated the effects of using different MS software on estimations of e.g. muscle forces and joint contact forces (JCF) [1,2]. Although these studies have shown some differences in the body- and joint-level mechanics, no studies have yet investigated the effects on tissue-level mechanics. In this study, we utilized a musculoskeletal–finite element (MSFE) modeling workflow [3] to compare the tissue-level differences of the knee joint cartilage mechanics between the models driven by two widely used MS-modeling software, AnyBody and OpenSim.

Methods
Motion data and ground reaction forces from gait trials of one subject were utilized in the MSFE-workflow (Fig. 1, top). The two MS-modeling software used in the comparison were AnyBody (V.7.4.2, AnyBody Technology, Denmark) and OpenSim (V.4.4). The models used for the analysis were the Twente Lower Extremity Model v.2.1.1 [4] (AMMR 2.4.2) for AnyBody and the model by Rajagopal et al. [5] for OpenSim. Conventional pipelines were used in both MS-software to estimate knee joint angles, joint moments, knee JCF, and muscle forces. The knee flexion angle, Tibio- and patellofemoral JCF and moments were used as inputs in the FE analysis where the cartilages and menisci were modeled as fibril-reinforced poroviscoelastic material (Fig. 1, middle). The FE analysis was done with Abaqus (V.2020), and the geometry of the model was adapted from a study by Esrafilian et al. [6]. The inputs from both MS-software were used to estimate tissue-level knee mechanics (such as, the maximum principal stress) during the stance phase of the gait cycle.

Results
The values of the maximum principal stresses were similar on both medial and lateral tibial cartilage between the workflows with AnyBody and OpenSim, at the time of the maximum load during the stance phase (Fig. 1, bottom). The locations of the highest stresses were also similar in the medial cartilage but located more on the posterior side in the lateral cartilage with AnyBody workflow compared to OpenSim.

Discussion
This study showcases some similarities and differences between estimated knee cartilage mechanics in FE models using two widely used MS-software to obtain loading inputs. The small differences in the maximum principal stresses are most likely caused by the slightly higher vertical JCF and the smaller abduction moment estimated with AnyBody. The results suggest that acknowledging the characteristics of different MS-software in MSFE-workflows could be important, since they can affect the numerical predictions of tissue failure and knee osteoarthritis progression.

References

Acknowledgements
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IN SILICO – IN VITRO MECHANICAL CHARACTERIZATION OF Ti6Al4V GYROID SCAFFOLDS

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Introduction
As additive manufacturing processes have improved, so has interest in porous biomaterials increased. In the skeletal tissue engineering field, part of this interest has focused on Triply Periodic Minimal Surface (TPMS)-based scaffolds due to their ability to create biomorphic environments suitable for tissue growth [1]. Although this increase in interest has also led to an increasing amount of studies looking into the material properties of TPMS-based scaffolds, these studies use short samples, are limited to small ranges of volume fractions and usually consider volume fractions below 30% [2, 3]. In order to obtain a more complete picture of the material properties of titanium gyroid scaffolds, we are evaluating cylindrical samples of varying length for the entire range of volume fractions, both experimentally and in silico.

Methods
Cylindrical samples with gyroid unit cells of 1.5 mm and varying length to diameter ratios were created using ASLI [4] and manufactured in Ti6Al4V ELI (Grade 23) with a DMP Flex 350 (3D Systems, Leuven, Belgium) 3D printer, see Fig. 1.

Micro-CT images were taken of the printed samples with a TESCAN UniTOM XL Micro CT (TESCAN, Brno, Czech Republic) to characterize their morphology. Subsequently, quasi-static uni-axial compression tests were carried out using an Instron 5985 Universal Material Testing Machine (Instron, Norwood, MA, USA) equipped with a 250 kN load cell to determine the offset stress, quasi-elastic gradient and plateau stress of the samples. Samples were loaded in printing direction at a constant vertical strain rate of 10⁻³ s⁻¹ and displacements were tracked by means of digital image correlation. The experiments were then recreated with FE-simulations performed in Radioss (Altair Engineering Inc, Troy, MI, USA). To this end, the cylinders were placed between two rigid plates. The bottom plate was fixed while a displacement with an effective constant vertical strain rate of 10⁻³ s⁻¹ was applied to the top plate. Coulomb friction was assumed between the plates and the samples while the material behavior of the titanium scaffolds was described by means of a Johnson–Cook model [5].

Results and Discussion
Preliminary data showed offset stresses, quasi-elastic gradients and plateau stresses in line with values reported in literature for lower volume fractions. The initial experimental and in silico data, see Fig 2, also highlighted the limitations of using short samples to determine the material properties of porous structures under compression. As can be seen, the quasi-elastic gradients estimated in silico and experimentally increasingly deviate from each other as volume fraction increases. This is in line with expectations since the shown experimental data was acquired using short samples and length to diameters ratios are known to be critical for accurate measurement of material properties under compression. Currently, a set of experiments with long samples are being executed that we expect will yield results in line with our in silico findings, further highlighting the importance of appropriate sample sizes.

Figure 1: Short skeletal gyroid specimen of 20% volume fraction: a) STL model, b) printed specimen and c) FE-model.

Figure 2: Summary of initial in silico and experimental results.

References

Acknowledgements
This work was supported by the European Regional Development Fund – Interreg VA Flanders - The Netherlands (PRoSPERoS, CCI 2014TC16RFCH046) and the European Union’s Horizon 2020 Research and Innovation Programme via the European Research Council (ERC CoG INSITE 772418).
PATIENT-SPECIFIC FINITE ELEMENT MODEL FOR INTRAOPERATIVE FRACTURES PREDICTION WITH A COMMERCIAL DESIGN

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Introduction

Total hip arthroplasty (THA) is one of the most established surgical procedures. However, many are still causes of failure that a prosthesis implant could encounter, among which is the Intraoperative Femoral Fracture (IFF). Even if it does not represent one of the most frequent complications, one important aspect is that the failure incidence is strongly linked to the stem design. For this reason, investigating this failure scenario is essential for companies that want to put a new device on the market. In the last years, Finite Element (FE) models, and in general terms in silico trials, are increasingly becoming a tool to support experimental tests for the analysis of the performances of new devices. A new approach for predicting IFF using FE models capable of simulating crack propagation was recently proposed [1]. However, mock implant designs were used in this conceptual study. The present work aims to propose a real-world use of the workflow previously developed, by applying it to the Avenir Complete Hip System (Zimmer Biomet), identified from clinical register data managed by the Rizzoli Orthopaedic Institute in Italy as the one with the lowest IFF incidence.

Materials and Methods

A subject-specific FE model was developed starting from the CT scan of one patient: 3D femur geometry was obtained with a threshold-based segmentation, and a Boolean subtraction with the rasp of the nominal implant size was performed. The stem size and pose were obtained from pre-operative planning performed by an expert surgeon. The femur and stem components were meshed separately, and the material properties were then assigned: the bone was mapped element-wise using Bonemat software [2], while Titanium Alloy properties were assigned to the stem. A compressive load with a stepped curve from 1000 to 10 000 N was applied along the stem axis, and the femur was constrained 50 mm under the stem apex (Fig. 1a). A maximum principal strain criterion was used to identify local element failure. The elements that exceeded the tensile strain threshold value of 0.0073 [2] were deactivated, i.e., their elastic modulus was imposed as quasi-zero; after element deactivation, the load was kept constant to allow stress redistribution. From the outputs of the FE analysis performed in Ansys MAPDL, two main quantities were considered to identify and characterise the IFF: the volume ratio between the deactivated elements and the femur, and the area of the internal crack surface.

Results

Results obtained from the FE analysis in terms of crack propagation are shown in Fig. 1b. Two fracture paths, observed in the proximity of the lesser trochanter, reached the external femur surface under an applied load of 3000 N. The crack computed final volume ratio and area were 0.56% and 856.58 mm², respectively, showing an increasing trend as soon as the crack propagated.

Discussion and conclusions

This study demonstrated the possibility to apply the workflow recently developed to simulate IFF using a commercial stem design for which the clinical output and IFF incidence are known. The results obtained confirmed the validity of the metrics proposed to define the damage quantification criteria. In the next future, the primary stability of the commercial stem will be analysed, considering that, from the previous study with a non-commercial stem, the push-out stiffness rapidly decreased as soon as the crack started to propagate. Once the simulations will be applied to an augmented virtual cohort and the digital twin solution will evolve into an In Silico Trial, it will be possible to clinically validate the methodology. The present work represents a step forward towards the development a computational environment that estimates the IFF failure risk for THR.

References


Acknowledgements

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**EXPERIMENTAL ANALYSIS OF PLANTAR SKIN**

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**Introduction**

The plantar skin is a complex multi-layered structure of the foot. Its morphology and composition are related to its main functions, which are to protect the body against mechanical injuries and to adapt to external stresses during daily activities [1]. Its extra cellular matrix is mainly composed of elastic and collagen fibres, which are responsible for a non-linear, time-dependent and anisotropic behaviour [2]. Since skin plays a relevant role, it is important to maintain its integrity. Unfortunately, some diseases, e.g. diabetes, can cause skin damage [3]. Even if this topic is very crucial, there are very few studies reporting on skin mechanical properties [4] and none of them has analyzed or tested the plantar skin yet. In this context, this work aims to fully describe the mechanical behaviour of foot skin, in relation to tensile and compressive loads.

**Materials and Methods**

Experimental tests were performed on plantar skin collected from four male human donors, (56±18 years) undergoing amputation due to cancer, at the Orthopedics and Orthopedic Oncology Unit, University Hospital of Padova (CESC Code: AOP2649).

Samples were collected from the heel pad (HP), central (C) and metatarsal (Met) regions (Fig. 1a). Mechanical tests were performed with the Biomomentum testing machine (Model Mach-1 v500c, ©Biomomentum Inc.): uniaxial tensile tests were performed on 50 specimens cut according to posterior-anterior (PA), lateral-medial (LM) and diagonal (45° inclination D) directions; while compression tests were performed on 30 cylindrical samples (diameter 5 mm). For tensile samples (Fig. 1b), preconditioning was performed before two different protocols of failure (1%/s strain rate) and stress relaxation tests (5 ramps of 7% strain; 10%/s strain rate; 400s of resting). For compression samples (Fig. 1c), preconditioning was performed before two different protocols of loading-unloading (50% strain; 1%/s and 100%/s strain rates) and stress relaxation tests (5 ramps of 1% strain; 10%/s strain rate; 400s of resting).

**Results**

The ultimate tensile stress (6.10±2.9 MPa) and the failure strain (49.2±11.9 %), as well as the initial and final Young’s moduli, were obtained from failure tensile tests (Fig. 2a). These results demonstrate the plantar skin non-linear anisotropic behaviour, which was also confirmed by stress-strain curves obtained from compression tests. Stress-relaxation results, from both tensile and compression tests, highlighted the tissue’s time-dependent behaviour (Fig. 2b) (relaxation decay around 43%) and allow us to compute tissue viscoelastic parameters.

**Discussion**

Experimental results showed differences in the mechanical behaviour among different skin regions. Anisotropy has been observed in the heel pad and central regions and a higher stiffness was observed in the central one. These differences can be explained by observing the arrangement of skin Langer’s lines, which are concentric in the heel pad and metatarsal regions (giving high resistance to compression stress), while they are longitudinal in the central ones (conferring to the skin a high resistance to tensile stress). All the information obtained will be useful to develop in silico tools of the foot, for the evaluation of the influence of different pathologies, e.g., in diabetic patients, or to investigate the interactions between foot and footwear.

**References**

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**Acknowledgements**

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ON MODELLING THE MULTILAYER RESPONSE OF AORTA USING LAYER-SPECIFIC EXPERIMENTAL DATA

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Introduction

Healthy arteries are composed of three clearly defined layers: the intima consists of a single layer of endothelial cells, a thin basal membrane and a sub-endothelial layer; the media is composed of a 3D network of elastin, smooth muscle cells and collagen fibres; and the adventitia consists of fibroblasts, fibrocytes, ground matrix and thick bundles of collagen fibres.

To ideally describe the arterial wall from the mechanical point of view, three separate layers of this tissue are required for intima, media and adventitia layers. The reason for considering three separate layers also arose from histology of arteries because the composition of intima, media and adventitia layers (elastin, collagen and cell contents) is different. Since residual stresses have a strong influence in the final stress distribution within the arterial wall [1], including the residual stresses presented in a vessel is of paramount importance for the accurate modeling of their mechanical behavior under physiological conditions. It has been shown that the three individual aortic layers, undergo drastically different residual deformations upon separation.

Methods

To test the capability of the multilayer model, we used previously published layer-specific experimental data relating to the axial pre-stretch, the opening angle, the fiber distribution obtained by polarized light microscopy measurements, and the uniaxial and biaxial response of the porcine descending and abdominal aorta. We fitted the mechanical behavior of each arterial layer using a Gasser, Holzapfel and Ogden strain energy function using the dispersion parameter k from the experimental fiber distribution. A multilayer finite element model of the whole aorta with the dimensions of the circumferential and longitudinal strips was then built. This model was used to capture the whole aorta response under uniaxial and biaxial stress states. After validation of the multilayer model, a model of idealized descending thoracic aorta was built using the whole sample dimensions and thickness ratio between intima-media-adventitia previously obtained. The effect of the layer specific residual stresses under internal physiological and supra-physiological pressures were studied. A diastolic 9.33 kPa (70 mmHg), physiological systolic 16 kPa (120 mmHg) and supra-physiological systolic pressures 20 kPa (150 mmHg) were considered.

Results

The multilayer model provides a good approximation of the uniaxial and biaxial experimental data only when the residual stresses are included. Results for internal pressure application are shown in Figure 1. It can be clearly observed how the inclusion of residual stresses in the model strongly modifies circumferential stress maps. Maximal circumferential stress values appear in the inner radius when no residual stresses are considered whereas they appear in the outermost radius when residual stresses are accounted.

Discussion

Our results show that strong differences between multilayer models and experimental results can be observed, when residual stresses are neglected. The stress distribution obtained using the monolayer model evolve the discontinuous results obtained by the multilayer model. Accurate mechanical models of the artery are only obtained when a three-layer model with residual stresses are considered.

References


Acknowledgements

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FRACTURE MECHANICS OF CORTICAL BONE AT THE MICROSCALE BY SRμCT IMAGING AND DIGITAL VOLUME CORRELATION

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Introduction

The high resistance of bone to fracture originates from multiple toughening mechanisms that span several length scales [1]. Aging and disease lead to increased risk of bone fracture and it remains important to understand the mechanisms of crack growth in relation to these structural length scales to improve fracture prevention strategies. Here, we evaluate local fracture properties from full-field displacements in cortical bone tissue at the microscale. We combine in situ high-resolution synchrotron radiation micro-computed tomography (SRμCT) indentation and digital volume correlation (DVC) to quantify three-dimensional crack opening displacements and stress intensity factors along the crack front.

Materials and methods

Ovine cortical bone specimens (3 mm diameter, 4 mm length) were subjected to in situ step-wise indentation in beamline ID19 at ESRF using a custom-made microindenter equipped with a 30 μm high Berkovich tip. Specimens were loaded with three ~10 μm displacements steps and phase-contrast SRμCT images (0.67 μm voxel size) were acquired after mechanical relaxation. DVC was used to evaluate the full-field displacement distribution around indentation-induced cracks. Mode I, II and III crack opening displacements were obtained from the displacement difference on either side of the crack. We used a least-square regression to fit the crack opening displacement data to Williams [2] expansion of near crack-tip displacement from which we extracted the stress intensity factors in Mode I, II, and III (i.e., 𝐾_I, 𝐾_II, and 𝐾_III) along the crack front following [3], assuming an elastic modulus and Poisson’s ratio of 20 GPa and 0.3, respectively [4].

Results

3D crack opening displacements under the indenter tip were obtained (Figure 1). Median opening (Mode I) at the crack mouth amounted to 1.93 μm, while only 0.54 μm at the crack tip. Shear displacement (Mode II) remained below 1.5 μm at the crack mouth and 0.7 μm at the tip. Out of plane motion (Mode III) was less than 0.5 μm and 0.1 μm at the crack mouth and tip, respectively. Similarly, Mode I stress intensity factors were larger than Mode II and III in all analysed cracks and vary along the crack front. 𝐾_I ranged between 0.28 MPam² and 2.96 MPam², whilst 𝐾_II ranged between 0.01 MPam² and 0.50 MPam², and 𝐾_III between 𝐾_III 0.02 MPam² and 0.37 MPam².

Discussion

Crack opening displacements indicated a predominant Mode I fracture, as expected from the loading conditions. However, indentation loading with a Berkovich tip induced significant shear (Mode II). Variations of the stress intensity factors along the crack front emphasize the importance of a 3D characterization of the fracture toughness. 𝐾_I values were consistent with previous studies on a similar length scale, but lower than macroscale fracture testing [4]. Whilst we used here a linear-elastic fracture mechanics approach, future work will combine the experimental data with finite element analysis to account for the energy associated to plastic deformation [5]. Ultimately, this approach will allow us to explore bone failure in relation to microstructural changes due to aging or disease.

References


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TOWARDS MODELLING COLD-WATER CORAL REEF CRUMBLING

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Introduction

The structural complexity of cold-water corals (CWCs) is threatened by ocean acidification [1]. Increased porosity in the dead skeleton and weakening of structurally critical parts of the reef framework may lead to physical collapse on an ecosystem scale, reducing their potential for biodiversity support [1,2]. The implementation of computational models into an predictive tool that allows us to determine risk of reef collapse remains missing, partially due to the lack of 3D information of CWC skeletal structure. Here, we investigate the limitations of homogenized models for Lophelia pertusa CWCs based on the morphological variations of live and dead skeletal structure to advance suitable mechanical surrogate models of their complex architecture.

Materials and methods

We performed computed tomography (CT) of n=42 L. pertusa dead and live skeletal fragments. We segmented CWC skeletons and branches (Fig 1a) and quantified the morphology of (i) CWC colonies and (ii) skeletal branches to (i) explain how CWCs occupy the space and (ii) characterize the branching structure of L. pertusa. We used the FE method to determine the size of a representative volume element of CWC skeleton that allow us to use a mechanical homogenization approach. We created 64 FE models (edge lengths 11.5 to 3.4 cm) from two CWC specimens and 217 FE models from a mirrored (periodic) CWC structure (edge lengths 22.5 to 4.5 cm). We used isotropic hexahedral linear elements (E=65.7GPa, ν=0.29 [2]), kinematic boundary conditions, and six independent load cases to derive the stiffness tensor, $\mathbf{S}$, via the apparent stresses and strains [3]. Then, we analyzed the size dependency of the elastic symmetries and properties of the structure through an optimization procedure where the best orthotropic representation of $\mathbf{S}$, $\mathbf{S}^{\text{ORT}}$, was found [4]. The accuracy of the orthotropic assumption was quantified using Eqn. (1), where $\mathbf{S}^{\text{OPT}}$ is the orthotropic representation (i.e., off-axis terms $\to$ 0) of $\mathbf{S}^{\text{ORT}}$.

\[
\text{Err} = \frac{\sqrt{\text{det}(\mathbf{S}^{\text{OPT}}) \cdot \text{det}(\mathbf{S}^{\text{ORT}})}}{\text{det}(\mathbf{S}^{\text{OPT}}) \cdot \text{det}(\mathbf{S}^{\text{ORT}})}
\]

Results

Live CWC fragments showed greater surface area to volume ratio and a more compact structure compared to dead specimens. Skeletal branch morphology was highly variable, with dead CWC framework branches shorter and thicker than live specimens. The error of the orthotropic approximation of $\mathbf{S}$ decreased with increasing specimen size and converged to <3% at ~9 cm edge length (Fig 1b). Volume elements $>$13 cm showed Err$<1.5\%$ and reduced variability.

Discussion

We observed large morphological variations between dead and live L. pertusa colonies and branches. We determined a critical size of $\sim$13 cm from where homogenized models of L. pertusa skeletons at the structural level may be used, which corresponds to ~5 times the mean interbranch spacing. This is in line with other heterogeneous structures, such as trabecular bone [5]. We identified possible surrogate models to represent the branching structure of L. pertusa CWC (Fig 1c,d). For length scales $>$13 cm, a continuum finite element mechanical approach can be used to analyse mechanical competence whereas at smaller length scales, mechanical surrogate models need to explicitly account for the statistical differences in the structure. Current work is undergoing to implement these models for a CT database of $>$300 CWCs from 1 cm to 30 cm. This will allow us to scale up the analysis to entire reef systems to investigate reef crumbling due to the time CWCs are exposed to acidified waters.

References


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AGE INFLUENCE ON CUT-OUT RESISTANCE OF SUTURED MENISCUS: AN EXPERIMENTAL CADAVERIC STUDY

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Introduction
Surgical treatment of meniscal root detachment is changing from partial meniscectomy to root reinsertion with sutures [1] due to alterations in the knee joint contact biomechanics and early cartilage loss development [2]. Suture fixation techniques of meniscal roots can be grouped into transtibial [3] and in situ fixations [4], both techniques pierce the meniscal horn to pass a suture thread through the hole and reconnect meniscus to bone. Despite its importance for the survival of the repair, few works focus on determining the resistance of meniscal tissue cut-out by direct thread traction on the suture hole and, as far as we are aware, the influence of age on this resistance has not been yet studied.

Methods
This study tested 44 half human meniscal horns (resulting from splitting the meniscus perpendicularly to its transverse plane in two) of different age group: young ≤ 60; 60 < old. They were sutured with N°2 UHPW thread using a simple stitch. Two ink points at the suture hole area were marked on the meniscus surface aligned with the direction of the longitudinal meniscal root fibers. A displacement-controlled load-to-failure test was conducted using an universal testing machine. The meniscal horn was fixed with its longitudinal root fibers aligned with the suture thread and the traction direction (Figure 1). During testing, the marks were continuously recorded using a video camera synchronized with the testing bench. Using a custom videogrammetry software, evolution of the distances between marks was computed and used to determine the start of meniscal tissue cut-out at the suture hole.

Two-tailed independent measure t tests were conducted to evaluate differences between groups. P values ≤ 0.05 were regarded as significant.

Results
For tissue cut-out resistance, $S_c$, no significant differences between groups were found for lateral meniscus specimens. For medial meniscus, the young group needed a higher stress level to start tissue cut-out (Figure 2a). For each age group, average resistance was higher in medial specimens than in the lateral ones.

![Figure 1: Meniscal horn located in the testing machine.](image)

Meniscal horn tissue cut-out resistance, $S_c$, was:

$$S_c = \frac{F_c}{d \cdot t}$$

where $F_c$ is the traction at cutting time, $d \cdot t$, the projected suture-tissue contact area at the hole, where $d$ is the thread diameter, and $t$, horn thickness at the hole.

Regarding specimen resistance, $F_c$, for the lateral meniscus significant higher values were found for the old group, due to its higher thickness. No differences were found for the medial meniscus (Figure 2b). Medial meniscus showed higher average $F_c$ than lateral ones.

Discussion
Medial meniscal horn showed more tissue and specimen resistance for both groups. At the lateral horn, no differences were found for $S_c$ between age groups, but due to its age-thickening, $F_c$ was significantly higher for the older group. However, at the medial horn the opposite was found. The older tissue was less resistant, but due to a lower age-thickening, its $F_c$ did not result significantly different. Therefore, from a biomechanical point of view there is no reason to not repair detachments of older lateral meniscus roots using suture techniques, as currently done with younger menisci.

References

Acknowledgements
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CAN THE GEOMETRY OF THE ATEROMA PLAQUE INFLUENCE ON DRUG TRANSMURAL TRANSPORT ON DRUG ELUTING STENTS?
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Introduction
Coronary angioplasty with stenting is currently the most widely used treatment for advanced atherosclerotic lesions. The introduction of drug-eluting stents (DES), which deliver antiproliferative substances to the arterial wall, has contributed to the improvement of in-stent restenosis (ISR). Despite the improvement achieved with DES compared to bare metal stents, ISR remains a major clinical and technological challenge in the design of these intravascular devices. The development of computational models has led to great advances in the understanding of drug transport on DES, but they usually represent simplified healthy straight geometries or highly simplified plaques that do not reproduce the characteristic geometry and composition of them. However, there is growing evidence that plaque composition may well have an impact on drug distribution within diseased tissue.

Methods
In an attempt to address some of the limitations of the previously computational models, we perform a series of computational drug transport models to analyse and understand the effect of atheroma plaque composition and structure on spatio-temporal drug uptake within the tissue. To this end, a finite element model of an idealised coronary artery under conditions of atherosclerotic disease between DES and healthy tissue is performed, and the effect of plaque composition and structure on global drug distribution is investigated. Of all the geometric factors to be analysed, we focus on the thickness of the fibrous cap, the total length of the plaque and the length and thickness of the necrotic core and percentage stenosis.

Results and Discussion
The results clearly demonstrate that the spatio-temporal distribution of drug is highly dependent on the geometrical variables analysed. The composition of the core strongly influences the drug concentrations, due to the different density of binding sites in this region. The results suggest that lipid plaques give rise to higher drug concentrations than fibrotic plaques, while calcified plaques are drug-impenetrable, according to the assumptions assigned to the model. The impenetrability of calcified plaque has potentially important implications and, if large enough, may act as a significant barrier to drug from reaching arterial tissue where smooth muscle cells (SMCs) capable of proliferating and migrating to device-injured areas during implantation reside. The results also suggest that the presence of plaque, regardless of core composition, may slightly delay receptor saturation in the medial layer.

Figure 1. Spatial variation of sirolimus at five different time points (t=10 min, t= 1 h, t=4 h, t=24 h, t=48 h, t=7 days and t=30 days) for the baseline model.

Figure 2. Spatial variation of sirolimus at five different time points (t=10 min, t= 1 h, t=4 h, t=24 h, t=48 h, t=7 days and t=30 days) after stent implantation for the baseline model.

References

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A PRELIMINARY 3D FINITE ELEMENT STUDY OF CELL-SUBSTRATE INTERACTION IN MICROGRAVITY CONDITIONS

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Introduction
It is well stated that microgravity affects cell behavior. Cells critically depend on the mechanical properties of their environment. The substrate elasticity is recognized to play a significant role in cellular processes as adhesion and differentiation [1]. Several studies have investigated the cells response to substrate. However, these works were established in gravity conditions. Available studies in literature addressing the cell-substrate interactions in conditions of microgravity are extremely limited [2]. In this study, we propose a finite element (FE) model to analyze the mechanical response of a substrate due to cells presence, in conditions of microgravity.

Methods
A 3D FE model has been developed to predict the mechanical response of a substrate induced by a group of cells. The geometrical model simulates idealized cells, composed of nucleus, cytoskeleton and cortical shell, seeded on a gel substrate that is placed on a rigid glass. Dimensions of cells and substrate are in accordance with [1]. The geometry is then converted into a non-uniform tetrahedral mesh with roughly 350k elements and 1500k degrees of freedom. The cell components and the substrate gel are modelled with hyperelastic Neo-Hookean materials. Different values of Young’s modulus are considered for the cell (E_{cell}), i.e. 1 kPa, 12 kPa, 34 kPa mimicking mesenchymal stem cells (MSC), myoblasts and osteoblasts, respectively [1]. A Poisson’s ratio of 0.45 is set for cell components and substrate. For each value of E_{cell}, we performed FE simulations with different substrate stiffness spanning from 1 kPa to 40 kPa. A uniform prestress as in [1] is considered throughout the entire cytoplasm. We perform all simulations considering microgravity conditions equal to 10^{-6} g.

Results
We investigate the interaction between cells and substrate in terms of gel displacement and maximum principal logarithmic strain. Displacement (Figure 1) is maximum on cell edge and decreases inside and outside the cell. In this configuration, reduced gel displacement is observed between a cell and its neighbors, suggesting a weak crosstalk [1]. Figure 2 compares the behavior of different cell types in function of substrate stiffness. For MSC and myoblast, the strain decreases with increasing gel stiffness, while osteoblasts are insensitive to gel stiffness.

Discussion
The FE model predicts that also under microgravity, subtle changes in gel stiffness will significantly interact with MSC. The model may contribute to optimize the design of biomaterials for cell cultures during space flight. Tissue engineering in microgravity is a key research area that can be beneficial to understand crucial mechanisms in human health and disease.

References
MODELLING OF EYE LENS FUNCTION: OPTICAL AND MATERIAL PROPERTIES
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Introduction: The growth of research in computational models and data that these provide has added to understanding of lens function and ageing, notably the processes of accommodation and presbyopia. However, models are dependent on the parameters used in their construction and can give different data depending on material properties and how these are distributed, lens shape and zonular insertions. The parameters that affect shape change and stress distributions have been investigated as have software packages.

Methods: Finite Element models were developed from measurements of refractive index made on in vitro lenses (Figure 1). Modelling and simulated stretching was conducted using ANSYS based on biological lenses from four different ages: 16, 35, 40, 57 years old. Further models on a 35 year old lens were also constructed using ABAQUS software to compare to ANSYS modelling. Models considered varying distributions of elastic moduli based on refractive index profiles [1] and longitudinal modulus profiles taken from mechanical analysis [2] (Figure 2). Various combinations of zonular insertions were tested and simulated [3].

Results: The internal stress distributions depend on the modelling of elastic moduli in the cortex with a more even spread of internal stresses and fewer discontinuities in models that have a gradient of modulus than those with a uniform equivalent modulus. Greatest stresses are seen in the nucleus of the lens regardless of model type. There is no difference in optical power between models with gradient or uniform elastic modulus. Inclusion of equatorial zonule appears not to have an effect on lens shape change with simulated stretching but does affect stress distributions. Comparison of different software for the same lens indicate that shape change with simulated stretching are similar but there are variations in stress distributions.

Discussion: Modelling can provide data to complement experimental measurements on lens function and can relate optical and mechanical properties of the lens. Account needs to be taken of material property distributions, zonular insertions and different software packages.

References

Acknowledgements
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LONGITUDINAL SUBCHONDRAL BONE MICROSTRUCTURE AND JOINT LOADING IN RATS WITH POST-TRAUMATIC KNEE OSTEOARTHRITIS

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Introduction
Osteoarthritis is a disease of the whole joint with concurrent degeneration of cartilage and subchondral bone. Mechanical loading is believed to contribute to disease onset and progression [1]. Destabilization of the Medial Meniscus (DMM) is often used to trigger post-traumatic osteoarthritis in preclinical studies [2]. We longitudinally imaged subchondral bone and estimated joint loading using musculoskeletal modeling in rats with DMM. We hypothesized that DMM alters loading and subchondral bone microstructure in the medial tibia.

Materials and methods
Unilateral DMM or sham surgery was performed in male Sprague-Dawley rats (n=6 rats/group). Longitudinal in vivo micro-CT: The operated knee was imaged every other week for 6 weeks (Skyscan 1076, Bruker, 18μm, 65kV, 150μA, 2000ms, 0.8°, Al 1mm). After image reconstruction and filtering, subchondral bone microstructure was analyzed on the tibial medial plateau (BV/TV: bone volume fraction, BS/BV: specific bone surface, Tb.Th: trabecular thickness, Tb.Sp: trabecular separation, Tb.N: trabecular number, Sp.P.Th: subchondral bone plate thickness) [3]. Musculoskeletal model: 8 weeks after surgery, rat gait was recorded using biplanar fluoroscopy and ground reaction forces (several trials per rat) [4]. With these data, peak medial force and associated adduction angle were estimated with musculoskeletal modeling [5,6]. Histology and ex vivo micro-CT: Rats were sacrificed 8 weeks after surgery. All dissected knees were scanned as described above, and knee histology was performed (safranin-O staining) in half of the animals. Statistics: linear mixed-effects models were used for in vivo parameters and musculoskeletal outputs, and Wilcoxon rank-sum tests for ex vivo parameters.

Results
At 2 and 4 weeks, Sp.P.Th was higher in DMM versus sham. There was no interaction of time and surgery for other parameters (see Fig 1).

8 weeks after surgery, there were fewer and thicker trabeculae in DMM versus sham. Histology confirmed abnormal cartilage and bone structure (proteoglycan loss, bone cyst) (see Fig. 2).

Figure 2: LEFT: Subchondral bone parameters based on ex vivo scan (left) n=6 rats per group *p<0.05; **p<0.01; RIGHT: histological sections of the medial plateau in rat with sham surgery and DMM (right).

There was no difference in peak force on the medial compartment 8 weeks after surgery. Adduction angle was lower in DMM versus sham (see Fig. 3).

Figure 3: musculoskeletal outputs. N=6 rats, n=18 trials for sham; N=6, n=9 for DMM. BW=body weight; **p<0.01.

Discussion
DMM altered subchondral bone microstructure, resulting in fewer and thicker trabeculae. The musculoskeletal analysis showed no overloading of the medial compartment with DMM, but knee adduction angle was reduced. Although loading was not altered at joint level, it might be altered at tissue level. A finite element analysis of the knee joint could determine if local mechanical cues are associated with altered bone adaptation.

References

Acknowledgements
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Introduction

Simulating the hemodynamics with the real physiological conditions of each patient has been a challenge in order to help the treatment of cardiovascular diseases (CAD) in the hospital [1,2]. There are several metrics used to assess atherosusceptibility based on the pressure and the wall shear stress. The Fractional Flow Reserve (FFR) is considered to be a gold standard parameter to guide clinical decisions regarding revascularization procedures in coronary lesions. The procedure for its measurement consists of inserting a pressure wire into the stenosis coronary vessel and measuring the aortic pressure value ($p_a$) and the pressure distal to the stenosis ($p_d$), along the cardiac cycle. Thus, the FFR value is calculated by the ratio between $p_d$ and $p_a$ [3]. A FFR lower than 0.75 indicates a hemodynamically significant stenosis that induces ischemia and requires revascularization. Recent studies have proved that the Windkessel model is used to implement the outlet pressure boundary conditions specific of each patient [3], in order to obtain an accurate computed FFR instead of the invasive one. The 3-element Windkessel model has three parameters that need to be estimated: the proximal resistance ($R_p$), the distal resistance ($R_d$) and the compliance of the vessels ($C_v$) [4]. Recent studies of Deyranlou et al. (2020) [4] have shown that the distribution of resistances among the proximal ($R_p$) and the distal ($R_d$) resistances is 9 and 91%, respectively. However, other recent study of Jonášová et al. (2021) [3] indicates that this distribution of resistances is 3 and 97%, respectively. Thus, it is important to verify if these different distributions influence the hemodynamic results and, consequently, the FFR. Moreover, it is important to analyse the sensibility of the measured blood pressures, systolic pressure ($P_{systolic}$) and diastolic pressure ($P_{diastolic}$), provided by the hospital. As far as we know, no authors in the literature have analysed these two sensibilities in the calculated FFR.

Methods

A model of a patient-specific left coronary artery with 40% stenosis was constructed in Mimics® software to be imported in Ansys® software for hemodynamic simulations. CT images of the patient were provided by Vila Nova de Gaia/Espinho Hospital Centre. The invasive FFR measurement was 0.93. User-defined functions in Ansys® were created to define the outlet pressures of the patient, through the 3-element Windkessel model [3]. Moreover, blood was considered as viscoelastic and sPTT model was used [1].

Results

Table 1 presents the computed FFR considering 3 different scenarios. In Scenarios I and II, values for $P_{systolic}$ and $P_{diastolic}$ were taken as the average of the invasive pressure measurements made on the patient, at the hospital. In Scenario III, the pressure values were taken in the interval of what the American Heart Association® defines. Moreover, Scenarios I and III consider a resistance distribution different from II.

![Image](image_url)

**Figure 1:** Pressure waveforms, for the 3 different scenarios, for an outlet boundary condition.

Discussion

Although the computed FFR for the 3 scenarios is approximately 0.91, differences in the pressure waveforms can be observed when considering Scenario III. It means that the values of $P_{systolic}$ and $P_{diastolic}$ should be patient specific, measured at the hospital, to obtain an accurate computed FFR. No differences are observed between Scenario I and II. Moreover, the code implementation is valid for this patient case - error of 2.15% between comp. and inv. FFR. In the future, we want to validate the software with many patient cases.

References


Acknowledgements

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BI-LAYERED ELECTROSPUN AND MELT ELECTROWRITEN PCL CONSTRUCT AIMING TOWARDS A PROSTHETIC VASCULAR GRAFT

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Introduction

Blood vessels are the highway of the cardiovascular system, transporting blood and nutrients. Narrowing or total occlusions [1] are often a case cause, frequently necessitating a vascular graft. While large-diameter prosthetic vascular grafts have a relatively good outcome, the small-diameter grafts tend to fail as they largely remain without endothelium [2]. To improve the outcome when a vascular replacement is needed, new suitable artificial vascular grafts with favorable biological and biomechanical properties are vital. Melt-electrowriting (MEW) is a relatively new biofabrication technique that allows for the creation of micro-fibrous polymer scaffolds by precise layer-by-layer deposition. This enables a controlled structure which further leads to more case defined mechanical properties, tailored to vascular graft requirements. While MEW gives good control over the mechanical properties, it is typically too porous. In combination with solution-electrospinning (SES), lower porosity layers can be incorporated as SES produces denser membranes with thinner fibres. The aim of this study was to characterise the effect of an SES membrane either on the inside (imitating a tunica intima) or the outside (imitating a tunica externa) with a microfiber grid MEW layer as the main structural component.

Methods

Three combinations of tubular scaffolds were created by either an in-house developed MEW setup or in combination with solution-electrospinning (SES). Group1 was a MEW microfiber layered grid, Group2 was the same MEW grid with a thin electrospun layer outside while Group3 had a thin electrospun layer inside the MEW grid. A total of n = 3 specimens were tested for each group. Microscopy and optical profilometry were used to assess the fiber diameter and scaffold wall thickness. A quasi-static tensile test was performed in the longitudinal and circumferential directions of the tubular scaffold to evaluate the mechanical properties.

Results

The scaffold wall thickness for Group 1 was 188.3 μm (SD=21.8 μm), while for Groups 2 and 3 it was 208.0 μm (SD=21.8 μm). The stresses observed in the circumferential (yield) and longitudinal (at 1.7% strain) testing direction were 0.27 (SD=0.01) MPa, 0.30 (SD=0.01) MPa and 0.28 (SD=0.01) MPa for Group 1, Group 2 and Group 3, respectively.

Discussion & Conclusions

The addition of an inner or outer SES layer influences the behavior of the scaffold, especially below 100% strain. In the circumferential testing direction, we did not see a substantial increase in yield stress with the additions of an SES layer, however the toe region was shorter and the scaffold response was initially stiffer. Combining SES with MEW resulted in higher maximum stresses for both Group 2 and Group 3, but especially the combination of MEW on SES, where the maximum stress was almost doubled for the longitudinal direction compared to only MEW. While we have shown that adding an SES layer can increase mechanical properties and change the response in certain strain intervals, depending on the location of that layer, the mechanical properties are still considerably lower than values measured for native vascular tissue, therefore further development is required.

References


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EFFECT OF SCAFFOLD POROSITY AND LENGTH ON THE SURFACE CURVATURE OF TPMS STRUCTURES

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Introduction
When designing surfaces for cellular growth a factor that influences the cells behaviour is the curvature of the surface the cells are placed [1]. Taking this into account, the present work is focused on analysing the average surface mean curvature of Triply Periodic Minimum Surfaces (TPMS) scaffolds and how changing their design parameters influences their curvature.

Methodology
A TPMS is a zero mean curvature surface that divides a given space in two. The method used in previous works [2] adds an equal thickness to this surface on both sides, resulting in two volumes: the actual scaffold and the empty space. Furthermore, because of the nature of this method, the empty space is divided into two independent volumes, one on each side of the scaffold, which in turn results in two separate scaffold surfaces. To evaluate the average mean curvature of these surfaces, three different scaffold configurations were created: the original and two each possessing only one of the two possible structures (henceforth referred to as negative and positive side) (Figure 1). This was done for both the Schwartz Diamond and Gyroid designs with 1 mm sided scaffolds with porosities between 50% and 80%. Afterwards, Meshlab was used to smooth the interior surfaces [2] and measure the mean surface curvature and standard deviation of each structure.

Results
The results showed that the average mean curvature and standard deviation were very similar across all three configurations for each of the eight studied scaffolds (Table 1). Regarding the scaffold design parameters, two different factors were analysed, which were the length of the scaffold and its porosity. To test the influence of scaffold length, five different scaffolds lengths between 0.5 and 2.5 mm were analysed for both the SD and SG scaffolds (Table 2).

Discussion
Table 1 illustrates that the curvature on both surfaces of the TPMS scaffolds are almost identical. Furthermore, the results also showed a negative mean curvature across all eight scaffolds, meaning that adding volume to a TPMS surface will decrease its mean curvature on both sides. Finally, the relatively low standard deviation of the results showed that the interior surfaces of these TPMS designs possess a constant surface mean curvature. In terms of the influence of scaffold length Table 2 showed a decrease in the absolute value of the mean curvature average of the scaffolds with the increase in the scaffold length. In fact, the parameters are inversely proportional with a constant of proportionality of -0.913 for the SG70 scaffold and -1.189 for the SD70 scaffold. Regarding the effect of scaffold porosity on the mean curvature of the scaffolds, the results showed that for both the SD and SG scaffolds, the higher the porosity, the closer the average mean curvature is to zero. This is expected, seeing as the higher the porosity, the lower the wall thickness, meaning these scaffold surfaces are closer to the original TPMS surfaces which have a zero-mean curvature.

Table 1: Average Mean Curvature for different SG70 scaffold configurations.

<table>
<thead>
<tr>
<th>SG70</th>
<th>Original</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mm</td>
<td>-0.919</td>
<td>-0.913</td>
<td>-0.925</td>
</tr>
<tr>
<td>1.0 mm</td>
<td>-1.824</td>
<td>-0.610</td>
<td>-0.456</td>
</tr>
<tr>
<td>1.5 mm</td>
<td>-1.824</td>
<td>-0.610</td>
<td>-0.456</td>
</tr>
<tr>
<td>2.0 mm</td>
<td>-1.824</td>
<td>-0.610</td>
<td>-0.456</td>
</tr>
<tr>
<td>2.5 mm</td>
<td>-1.824</td>
<td>-0.610</td>
<td>-0.456</td>
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Table 2: Average Mean Curvature for SG70 scaffolds with varying scaffold lengths.

<table>
<thead>
<tr>
<th>SG70</th>
<th>Original</th>
<th>Negative</th>
<th>Positive</th>
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<tbody>
<tr>
<td>0.5 mm</td>
<td>-0.919</td>
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<tr>
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<td>-0.456</td>
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References

Acknowledgements
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NUMERICAL MODEL OF THE MECHANICAL BEHAVIOUR OF MEDICAL COMPRESSION STOCKINGS

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Introduction

One of the most frequent disorders affecting adults' lower extremities worldwide is chronic venous insufficiency (CVI). The cornerstone of CVI prevention and treatment is compression therapy, which seeks to reduce edema and enhance venous and lymphatic return from the lower limb. Thanks to their unique structures and fabrication techniques, compression fabrics can adapt to varied body shapes by delivering controlled compression, being highest at the ankle and gradually lowering up the garment [1].

The principle of pressure exertion is based on the circumference of the garment $C_1$ being smaller than the circumference of the body $C_2$, so that the threads of the inlay yarn are stretched and under tension when the product is in place [2]. The elongation ratio $\tau$ (%) can be defined by

$$\tau(\%) = \frac{C_2 - C_1}{C_1} ; C_2 > C_1$$

Precisely, the amount of compression is proportional to the degree of elongation, the elastic modulus of the material, and the contact surface between the product and the body [3].

The aim of this project is to represent, through a finite element model, the behaviour of a Medical Compression Stocking (MCS). By integrating a specific leg morphology, this model will allow to analyse the distribution of the pressures exerted, and thus adjust the characteristics of the MCS according to the needs of each patient.

Methods

To make the representation of the MCS by means of finite elements, the code is created in Python (Spyder), to be executed in Abaqus (Simulia, Dassault systems). According to the norm for the manufacture of medical compression products, for each course of the knitted structure, there must be an inlay yarn, which will be the main responsible for the compression.

To design the model, firstly, a geometrical characterisation of the MCS is carried out, taking into account the production parameters. Then, the MCS and its components are experimentally analysed to determine the behavioural laws that define them.

A first numerical model is created integrating the basic characteristics of the MSC, in which the two fundamental components are represented: the knitted structure and the inlay yarn. To represent the knitted structure, quadratic membrane elements are used to form a tube of similar dimensions to the MCS, and for the inlay yarn, connectors are used to create a helix along the length of the tube.

Results and discussion

This study constitutes the first steps towards the creation of a complete numerical model representative of the behaviour of Medical Compression Stockings. For this, it is necessary to continue with the characterisation of the different compression zones present in the MCS, both geometrically and mechanically. This will allow the properties of each part of the model to be correctly established for a realistic representation of the behaviour during use.

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Acknowledgements

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AN EXPLORATORY APPROACH TO MUSCULAR FATIGUE ASSESSMENT DURING EXOSKELETON-ASSISTED GAIT

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Introduction

Powered lower-limb exoskeletons are a new and emerging technology representing a promising solution for gait rehabilitation [1]. This technology has been studied and adopted mainly by spinal cord injury (SCI) and stroke patients [2]. During training with exoskeletons, evidence of muscular fatigue should be monitored because it can increase muscle spasticity, negatively impacting the recovery process [3]. Under fatigue conditions, the muscle’s contractile capacity changes, and shows modifications in the electromyographic (EMG) signal. This study aims at assessing the presence of muscular fatigue, during exoskeleton-assisted gait training, via surface EMG (sEMG) spectrum-based analysis.

Methods

Data were collected at the Sport and Movement Lab of LUNEX University (Luxembourg). Thirty healthy subjects (mean age ± std. dev: 23.2 ± 2.7 years) performed an exoskeleton-based gait training session of 60 minutes. 4 sEMG sensors were placed on the tibialis anterior (TA), soleus (SOL), vastus lateralis (VL), and biceps femoris (BF) (dominant side). sEMG envelope (raw data rectified and 9 Hz low pass filtered) thresholding was used to detect the muscle onset/offset. The median frequency (MF) of the Power Spectrum was evaluated inside a 250ms window centred around the envelope peak via the Fast Fourier Transform (MF-FFT) and the Short Time Fourier Transform (MF-STFT) [4].

Results

Figure 1 shows the decrease of VL MF-FFT data of a single subject during the training period. This decrease is directly linked with the onset of muscular fatigue [4]. Table 1 reports the average slopes (across all subjects) of the regression line that fits the MF-FFT values. TA, VL, and BF average slopes are negative with a smaller value for VL.

Discussion

Between the two used approaches for the assessment of muscular fatigue in exoskeleton-assisted gait training, the FFT algorithm applied to the MF was able to identify ongoing fatigue increase in three out of four muscles.

This preliminary investigation shows promising results on fatigue monitoring during exoskeleton-assisted gait training. In future works, the MF can feed machine-learning-based models to continuously supervise fatigue development in rehabilitation.

Figure 1: VL MF-FFT data of a single subject and regression line.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Average slope</th>
</tr>
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<tbody>
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<td>TA</td>
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</tr>
<tr>
<td>SOL</td>
<td>0.0470</td>
</tr>
<tr>
<td>VL</td>
<td>-0.2424</td>
</tr>
<tr>
<td>BF</td>
<td>-0.0041</td>
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Table 1: Average slopes (across all subjects) of the MF-FFT data regression line.

References

CAN TRANSIENT SIMULATIONS IMPROVE LOWER LIMB-PROSTHESIS INTERACTION ANALYSIS?

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Introduction

Human gait is a highly dynamic process; however, most numerical analyses to simulate a lower limb prosthetics wearer are still performed using an implicit static method [1]. To account for the dynamic effects, a transient numerical simulation was performed in this study, simulating a gait cycle of a lower limb-prosthetics system. Donning of the socket followed by heel strike and push-off conditions of the gait were analyzed using a recently developed generic transtibial limb model representing an average male amputee [2]. The static results previously obtained were compared with the transient simulation and the results in terms of contact pressure, stresses, strains, and the global deformation were evaluated. The numerical results show a significant difference between the transient and static numerical simulations due to the inertia effect incorporated in the dynamic analysis, indicating a more realistic gait simulation.

Methods

Well-established Finite Elements Method (FEM) was used to analyze the interaction between the below-knee amputated residual limb and the associated prosthetic socket and liner. In contrast to the previously commonly used implicit static method, a transient dynamic method was used to simulate the gait cycle, including the inertial effect of the residual limb-prosthetics system. The main difference between the static and dynamic analysis is that in the static analysis, only the stiffness matrix K is included in the calculation (1). Whereas in the dynamic case, the mass matrix M and the damping matrix C are taken into account, forming a second-order differential equation that can be solved by both implicit and explicit methods (2). This study used the implicit method to simulate donning of the socket (quasi-static) and the explicit method to simulate the gait cycle according to ISO 10328.

\[
[K][u] = f(t) \quad (1)
\]

\[
[M][\ddot{u}] + [C][\dot{u}] + [K][u] = f(t) \quad (2)
\]

Results

The results regarding the contact pressure at the limb-liner interface, as well as the stress-strain results of the socket, were analyzed with a dynamic FEM and compared to the static results to evaluate the applicability of the new transient approach. The relative comparison between the static and dynamic simulations shows that the former overestimates the results during the gait condition. Although the socket and the liner deform similarly, a significant difference in the magnitude of the results can be observed.

Figure 1: Left: Heel strike and push-off loading conditions according to the ISO 10328. Right: Numerical results in terms of contact pressure, stress-strain, and global deformation.

Discussion

This study took the novel approach of analyzing the socket donning and the gait of the transtibial amputee using a transient implicit and explicit method, hence creating more realistic loading conditions. Most researchers have used static simulations that exclude inertial and damping phenomena, which, as the analysis show, significantly affect the numerical results. The newly developed simulation can effectively incorporate dynamic effects and therefore allows for a more accurate assessment that supports the development of lower limb prostheses and the exploration of new manufacturing techniques, such as 3D printing of prosthetic sockets and liners.

References


Acknowledgements

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ON THE IMPACT OF ARTERIAL MODELLING IN CORONARY STENTING SIMULATIONS: A VALIDATED STUDY ON 5 PATIENT-SPECIFIC CASES

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Introduction
Recent studies highlighted the potential of patient-specific coronary stenting simulations to support clinical decisions for individual treatments [1,2]. A crucial point for a reliable stenting simulation is the modelling of the patient-specific artery. By exploiting invasive clinical imaging techniques, it is possible to have individual anatomical details in the reconstruction of the arterial geometry. Different aspects of the arterial mechanical modelling were considered in the literature, such as heterogeneous plaque description, modelling of different external layers (media and adventitia), and the effect on the mechanical properties of in vivo axial pre-stretching and pressurization [2]. However, it is still unclear which of these modelling aspects are essential for reliable outcomes in terms of clinical endpoints such as lumen gain and stent malappositions, and which can be considered excessive details given the uncertainties associated with clinical imaging data. To investigate this, five clinical cases were replicated through numerical methods involving the highlighted modelling aspects. The comparison with post-treatment clinical data allowed the impact of these aspects to be identified.

Methods
A phenomenological damage model capable of describing the deterioration of mechanical properties at high strain levels of media and adventitia layers was combined with the arterial model developed and validated in a previous work [2]. Damage model parameters were defined to best fit the arterial mechanical behavior in response to the replication of the stenting procedure of two clinical cases (cases A and B). The whole model was evaluated in its ability to predict the lumen area and stent malappositions by replicating three additional patient-specific cases (cases C, D and E). Once the model was validated, the five clinical cases were exploited to analyze the importance of each modelling aspect in representing the clinical outcomes.

Results
The developed damage model proved to be effective in comparison with post-stenting clinical data (Figure 1). Among the evaluated modelling aspects, interesting results were found in the role of damage modelling to predict the lumen gain and on a low impact of heterogeneous plaque modelling compared to the homogeneous one.

Discussion
The damage model proved to be essential for the development of a robust and validated arterial model. Patient-specific details of low impact on simulation outcomes can raise questions on the possibility of exploiting other imaging techniques for arterial reconstruction: techniques not able to capture the patient details such as plaque components but less invasive than catheter-based techniques might be a valid alternative for a future clinical application of stenting simulations.

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Acknowledgements
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Figure 1: The reconstructed arteries of the clinical cases replicated in this study (top) and a comparison between FEA results (with and without the damage model) and OCT data (pre- and post-stenting) (bottom).
EFFECT OF DENTURE CLEANERS ON SURFACE MICROROUGHNESS AND HARDNESS OF COBALT-CHROMIUM ALLOYS

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Introduction
Cobalt-Chromium alloys have been widely used for removable partial denture frameworks because of their satisfactory mechanical properties and relative low cost. Dental prostheses require hygiene to promote good oral and systemic health. Chemical cleaning solutions may be important alternatives/adjuvant methods to mechanical cleaning because they are accessible, easy to use, and cost-effective. Besides dedicated effervescent tablets, various chemical cleaning agents are used by patients. Changes in the physical and mechanical properties of Co-Cr alloys have been reported related to the contact with chemical sanitizers, having effects on the efficiency and longevity of the prostheses [1-3]. The aim of the study was to evaluate the effect of cleaning solutions on the surface of Co-Cr alloys in relation to the hardness and surface roughness.

Materials
Samples of non-precious alloys on cobalt-chromium basis: Wironit (Bego GmbH) [W], Heraenium CE (Kulzer GmbH) [H], Diadur (DFS - Diamon GmbH) [D], C alloy (Vaskut Dentál Kft) [C], Micronium Exclusiv (Schütz Dental GmbH) [M] were cast according to the alloy manufacturer’s instructions. They were finished, polished with 600-2000 grit sandpaper, and polishing paste, cleaned with alcohol. As cleaning solutions Corega Double Power (GSK Pharmaceuticals Ltd) [CT], Protefix Active Cleanser (Queisser Pharma) [PT], 9% acetic acid solution - vinegar [V], 3% hydrogen peroxide [O], 5.25% sodium hypochlorite [N] and distilled water [DW] as control were chosen. The specimens were divided in 6 groups and immersed in 50 ml of each solution, which was replenished every 1 hour. The immersion contact time was 900 minutes, simulating 6 months of a 5 minutes daily immersion. The surface roughness was measured with a profilometer Surftest SJ-201 (Mitutoyo, Kawasaki, Japan) with 0.8 mm reading length cut-off, for all groups. Arithmetic average roughness (Ra) and maximum absolute vertical roughness (Rz) measurements were performed. Leeb microhardness (HL) values were obtained by using a digital hardness tester Dyna Pocket (Zwick, Germany). Statistical analyses were performed.

Results
Surface roughness Ra, and HL hardness values are represented in Figures 1, 2.

Figure 1: Mean Ra values after immersion.

Figure 2: Mean HL values after immersion.

Relative to cleaning solutions, roughness was significant decreased for [V]. HL values increased significant for [V] (p=0.01), [N] (p=0.02) and [O] (p=0.01). As a result of roughness-hardness correlations records, a very strong negative correlation has been measured (r=-0.76 for Ra-HL and r=-0.84 for Rz-HL).

Discussions
Based on the obtained test results, it can be concluded that cleaning agents do not significantly affect the surface roughness of frameworks cast from Co-Cr alloys. Instead cleaning agents like acetic acid, hydrogen peroxide, and sodium hypochlorite increased surface hardness values, which would correspond to more brittle surfaces. Complementary studies are needed to evaluate this aspect over time on the longevity of the prostheses.

References
FE STUDY ON THE EFFECT OF PATIENT-RELATED VARIATIONS ON THE PRIMARY FIXATION OF A CEMENTLESS PEEK TIBIAL COMPONENT

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Introduction
The use of polyetheretherketone (PEEK- OPTIMA™) for the cementless tibial component is of interest because of its potential solution to avoid bone resorption due to peri-prosthetic stress-shielding. A new material for the cementless tibial component may have implications for the primary fixation, quantified by the micromotions between the tibial tray and bone. The micromotions may be dependent on patient-related factors. Therefore, the aim of this finite element (FE) study was to define the effect of patient-related variations, including sex, age and BMI, on the resulting micromotions of a cementless PEEK tibial component.

Methods
In this study, a CT database was used consisting of 74 healthy knees including the patient information on sex, weight, length and age. Consecutively, a workflow was created to generate FE models of these 74 tibiae including tibial tray and insert. The tibial tray was simulated with a Young’s modulus for either PEEK (3.7 GPa) or titanium (109 GPa). A musculoskeletal model was used to derive the implant-specific tibiofemoral contact forces including centers of pressure of a gait and squat activity. The contact forces were incrementally applied during four loading cycles. To quantify the primary fixation, the 95th percentile of the maximum resulting micromotions was defined.

Results
The largest resulting micromotions were generated at the anterior side and posterior lateral side of the tibial tray (Figure 1). The PEEK components generated significantly larger micromotions values than the titanium components (mean PEEK: 67.63 µm, mean titanium: 38.69 µm, p<0.001). No significant differences in micromotion values were seen between the sex and age groups (Figure 2). Higher BMI resulted in larger resulting micromotions (Figure 2). The difference between all three BMI groups was statistically significant (p<0.001).

Discussion
The current FE study demonstrates that a higher BMI results in larger micromotions, while variations in sex and age did not significantly influence the primary fixation. The current analysis provides some preliminary insights on primary fixation of cementless TKA components. We are currently performing a more in-depth multivariate analysis to identify the underlying mechanisms, such as interactions with bone quality. In addition, we plan on performing a more detailed analysis of outliers to investigate potential risk factors.

Figure 1: Resulting micromotion distribution (mm) at a left PEEK tibial tray interface after the 4th loading cycle of a squat activity.

Figure 2: 95th percentile of maximum resulting micromotions (µm) per sex and BMI groups for all PEEK tibial trays.

Acknowledgements
PEEK-OPTIMA™ is a trademark of Invibio Ltd. Implant geometry was supplied by Maxx Orthopaedics Inc.
NOVEL MULTI-LAYERED 3D BIOPRINTED CONSTRUCT AS ALTERNATIVE VASCULAR CONDUIT REPLACEMENT

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Introduction
Cardiovascular disease-related mortalities have risen from 12.1 million in 1990 to 18.6 million in 2019. In the last 5 decades, no viable alternative conduits have been found to alleviate the supply limitation of gold standards vascular graft.

Thanks to the explored 3D printing technology, the new challenge focuses on obtaining a 3D structure with several distinct layers to replicate the hierarchical organization of tissues. The ideal bioink would have mechanical, rheological, chemical, and biological characteristics according to the desired physicochemical properties, such as mechanical strength and robustness, and adjustable gelation and stabilization.

This work aims to reproduce blood vessel substitutes compliant with the shape, functionality, and integrity requirements of the original tissues, combining the advantages of the 3D bioprinting, decellularization process, and natural polymers and accounting for the presence of different cellular species simultaneously.

Methods
Enzymatic decellularization with of 6-month-pig aortas, was optimized. The decellularized powder was produced by cryomilling under N₂ the lyophilized product of the decellularization process and then solubilized with pepsin digestion. Decellularized ECM was included in gelatin/alginate bioinks. The composition (concentration of precursors and type of crosslinking) was optimized, and the printability was evaluated by rheological characterization. After a design of the 3 tunicae structures (SolidWorks), the G-Code was produced with CELLINK HeartWare software, and the construct was printed by Cellink Incredible+. The biocompatibility of the designed bioink was tested by encapsulating mouse fibroblast cells (L929) in the bioink, and the cell viability is assessed up to 28 days of culture.

Results
Decellularization. The optimized decellularization protocol produced a residual quantity of DNA lower than 50ng/mg of tissue, and the DNA fragment length lower than 200 bp (base pairs). Moreover, the DNA and RNA components were not visible in DAPI or hematoxylin and eosin staining.

3D Bioprinting. It was necessary to optimize the composition of a bioink able to withstand the printing of a segment of tubular construct up to 20 mm (40 layers) and to produce the hierarchical structure of different cell layers in the physiological aorta. Among the several compositions tested, the suspension resulting from 1.2% w/v gelatin, 6% w/v alginate, and 0.66% w/v dECM combined with a pre-printing crosslinking phase with internal gelation and a post-printing crosslinking with 1% CaCl₂ was able to produce tubular segments with a height up to 2 cm were produced. (Figure 1).

Biocompatibility evaluation. Live&Dead staining showed cells retained their printed position on day 1 after printing. After 5 days of culture, the cells started to extend and connect. These results indicate that the printing step, the post-printing process, and the novel-derived bioink are biocompatible and cytocompatible. After day 14 of static culture, cells proliferated and infiltrated. These results demonstrate that high cell viability can be achieved in the printed tubular constructs after printing.

Discussion
The bioink described in this study proved to be suitable for printing multi-layered constructs, capable of maintaining the three tunicae and avoiding the overlap of the different inks through the thickness, despite the increase in the number of layers up to 20 mm-segments. As predicted by the rheological results, we achieved printability and shape fidelity, considering that the geometrical structures and the dimensions of the printed structures were very close to those established in the design phase. By tailoring the printing parameters and the amount of dECM the desired mechanical properties can be met. The next step includes the use of three different cell lines simultaneously to replicate the native three-tunicae structure of large blood vessels.
Introduction

Both concussive and sub-concussive head accelerations have now been linked with numerous acute and chronic neurocognitive changes[1]. Instrumented mouthguards have been used to detect head accelerations, recording kinematic data from many sports[2]. However, coughs, bites, and sneezes can cause false positive impact recording. Thus, time consuming video verification of impact is often required. Recently, this burden has been alleviated via the development of machine learning algorithms that can isolate the true impacts [3]. However, since each contact sport has different impact characteristics, these algorithms must be specifically calibrated or validated. Despite the growth of female rugby union participation and an increasing number of professional players, no algorithms for female sport or rugby union have been developed. This study aims to develop the first algorithm to classify head acceleration data from exclusively female rugby union players.

Methods

Mouthguards instrumented with kinematic sensors were given to 25 participants for six competitive rugby union matches in an inter-university league. Video were recorded from the centre line of the pitch to enable the identification of genuine events. Data were collected using the previously validated boil-and-bite instrumented mouthguards. In total, 214 impacts were recorded from 460 match-minutes. Four machine learning algorithms were trained to predict genuine and spurious events using five matches, then tested using a sixth match. The classifiers were trained to determine key patterns in the descriptive features of the filtered six-axis kinematic data. Features were grouped into four categories, pulse parameters, positional derivatives, power spectral density, and wavelet transformations. The area under the receiver operator curve (AUROC) and area under the precision recall curve (AUPRC) were used as the performance measures of the models. Shapley additive explanation (SHAP) values were also found for the top performing models. The most important features for classification were predominantly pulse parameters and wavelet transformations at very low or high frequencies, shown in Figure 1.

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Test AUROC</th>
<th>Test AUPRC</th>
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<td>CatBoost</td>
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<tr>
<td>AdaBoost DT</td>
<td>0.89</td>
<td>0.81</td>
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</tbody>
</table>

Table 1: Performance of the classifiers on the test dataset, measured with AUROC and AUPRC.

Discussion

The classifiers in this study achieved state of the art performance in this classification task, illustrating that it is possible to create high performing head acceleration event classifiers for female rugby union. This will aid future researchers to more quickly and accurately identity head acceleration events within female rugby union. These findings represent an important development for head impact telemetry in female sport, contributing to the safer participation and improving the reliability of head impact data collection within female contact sport.

References


Acknowledgments

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BIONIC MUSCLE-INSPIRED DESIGN OF CABLE-DRIVEN LOWER LIMB REHABILITATION EXOSKELETON (C-LREX)

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Introduction
Cable-driven are preferred over traditional link-driven exoskeletons due to lighter weight, remote actuator provisions, and negligible inertial vibration. Nevertheless, the cable can be routed in multiple ways to mimic lower limb trajectory and remains an open challenge. In this study, for the first time, we employ bionic muscle-inspired cable routing to design Cable-driven Lower limb Rehabilitation Exoskeleton (C-LREX). Two cases were explored with and without intermediate hinges between the origin and insertion hinges. The performance of the model in terms of gait trajectory tracking, cable tension requirements, and induced joint forces was studied and quantified.

Methodology
The bi-planer lower limb model has three degrees of freedom (DOF); two at the hip (adduction/abduction and flexion/extension), and one at the knee joint (flexion/extension) [1]. 3D bionic muscle-inspired cable routing configurations are shown in Fig. 1.

Figure 1. Bionic muscle-inspired design of C-LREX: Major muscle group contributing during gait [2] (left). Sagittal and transverse planes view of bio-inspired cable routing configurations using long cables (I) and with intermediate hinges (II).

Case I employed two long cables joining the hip and the shank to simulate the Hamstrings (HA) and Rectus Femoris (RF), while in Case II, two intermediate hinges were added between the origin and the insertion hinges of the long cables to guide them closer to the limb without constraining their free movement. Bi-planar routing was used for the GL cable to mimic the GL muscle group which is primarily responsible for adduction motion. Similar bi-planar routing was used for the IL cable to avoid interference with the RF cable. Furthermore, other cables are modified accordingly to avoid interferences in each case as shown in the transverse plane view in Fig. 1. The foot muscle group was ignored as the foot was kept fixed perpendicularly to the shank. The model, with both routing configurations, was simulated for one gait cycle and the predicted trajectory was compared to data from the literature [3]. The allowed cable tension ranged between 7 and 100 N to ensure that the cables were always taut, and the maximum tension remained within the specified range.

Result and Discussion
The bio-inspired cable routings (with and without intermediate hinges) successfully tracked the desired bi-planar reference trajectory. Case II required a smaller peak cable tension (Fig. 2) and induced smaller joint force components (Fig. 3). These are the additional forces produced by the C-LREX on the user’s joints and should be minimized. The intermediate hinges provide restrictive support and guide the cable along a path that is closer to the lower limb, which makes the exoskeleton more compact and reduces the risk of cable instability and entanglement.

Comparison with other configurations of cable routings in C-LREX will be done in a future study.

Figure 2. Cable tension requirements

Figure 3. Cable-induced joint force components {CZ: compressive force. SX and SY: anterior-posterior and medio-lateral shear forces respectively}.

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STRATIFYING HIP FRACTURE RISK IN THE FULL AGES REYKJAVIK COHORT USING FINITE ELEMENT MODELLING

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Introduction

Areal bone mineral density (aBMD) derived from DXA-scans has moderate accuracy in identifying subjects at-risk of sustaining incident hip fractures. Attempts have been made to overcome the limitations of screening with aBMD, by using femoral strength predicted from quantitative computed tomography (qCT)-based finite element models (FEMs) [1]. However, the results have been inconclusive with the predictive power of FEMs matching that of aBMD at best (incident fractures). This may in part be due to the limited number and sample size of FE studies, whereas screening with aBMD has been validated against hundreds of thousands of datasets. One of the challenges, pertaining to building qCT-based FEMs, has been the manual labor associated with segmenting the qCT data. Recently, however, autonomous methods for segmentation have emerged. The aim of this work was to predict the femoral strength for left and right femurs for all subjects in the AGES cohort, and to compare the predictive power of femoral strength to aBMD in terms of stratifying fracture risk.

Methods

Available for this study were 4799 CT datasets acquired at baseline in the AGES study as well as demographic data. Left and right proximal femurs were segmented from the images using our deep neural network-based approach [2]. The resulting masks were used to build 9598 FEMs in accordance with our previous work [3]. The models were loaded in a sideways fall configuration simulating impact at 1 m/s (Fig. 1). Here we report the results from 4560 out of 4799 left femurs that were available for analysis. The most common reason for exclusion was the presence of motion artifacts in the CT data. The operators working on the FEMs were blinded to hip fracture status (at 5-7 year follow-up) throughout the study.

Figure 1: Boundary condition and loading conditions for the sideways fall simulations.

As DXA scans were not collected in AGES, CT-derived aBMD (aBMD_{DCT}) was used as a surrogate for DXA-derived aBMD (aBMD_{DXA}). Previous work [4] has established a relationship between the aBMDs as follows: \( aBMD_{DXA} = 0.924 \times aBMD_{DCT} + 0.137 \) (g/cm², \( R = 0.935 \)). Predictive performance of femoral strength and aBMD_{DCT} was evaluated using the area under the curves (AUCs) from Receiver Operating Characteristic (ROC) analysis. Boosting the predictive performance of aBMD_{DCT} and femoral strength was attempted by adding variables reflecting functional status to regression models (time to walk 6 m, self-reported fall-frequency, isometric leg and hand strengths, and time-up and go).

Results

Use of FEM-derived femoral strength resulted in higher AUC than achieved with aBMD_{DCT} after adjusting for age and sex (0.794 vs. 0.769). Most functional parameters boosted the predictive performance of both femoral strength and aBMD_{DCT} marginally. The largest boost was achieved with logistic models that incorporated age, sex, and time to walk 6 meters (0.801 for FEMs vs. 0.778 for aBMD_{DCT}).

Figure 2: Femoral strength vs. aBMD_{DXA} for 4560 subjects in the AGES cohort. Red circles indicate fracture cases and vertical line osteoporosis threshold.

Discussion

We found FEM-derived femoral strength to result in marginally higher AUC than aBMD_{DCT} did in the AGES cohort. Functional biomarkers provided a small boost in performance for both aBMD_{DCT} and femoral strength. We believe that this study demonstrates that image-based FEM technology has reached the stage where it is viable to carry out studies that are 1–2 orders of magnitude larger than current ones.

References


Acknowledgements

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EFFECT OF AORTIC VALVE GEOMETRY ON LEAFLET STRAIN WITHIN A PHANTOM SILICONE AORTIC HEART VALVE DURING CLOSING

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Introduction
This paper characterises the changes in strain profiles of the tricuspid aortic valve leaflets while closing in variable valve geometries, along with measuring free edge twist. The aim is to firstly demonstrate a workflow for assessing the mechanical behaviour of such valves to enable optimised designs and, secondly, to demonstrate the role of geometric parameters on valve performance.

Methods
Using a similar method to Van Loon [1], an stl file of the tricuspid aortic valve was produced with initial dimensions defined by De Hart [2] (Valve 1). The values of the commissure height and the leaflet tilt angle were then varied to produce a further two models (Valves 2 and 3 respectively). These stl models were converted to mould designs to cast the valves in silicone. Valves were mounted in a viewing tank incorporated into a flow system analogous to the human circulatory system. This was used to open and close the valve at a rate of 80 bpm with a pressure range of 80-120mmHg. Highspeed stereo-digital image correlation (6000fps) was performed on the upper valve leaflet during closing while simultaneous pressure readings were taken at the points shown in Figure 1. Readings for each valve were repeated four times.

Results
Displacement and mean maximum principle strain were recorded at 5 points on the top valve leaflet, then plotted against the mean transvalvar pressure drop. Figure 2 shows an example result. All valves showed discontinuous softening behaviour, which can be split into two stages. Stage 1 showed asymptotic softening to a critical value (Stage 2). Here it becomes much stiffer before softening again. The magnitude of displacement within Stage 1 varies significantly both between valves and between the locations on the leaflet. Stage 2 is more consistent between valves, with the magnitude and shape of the pressure drop curves being similar.

Discussion
Stage 1 behaviour is produced through the combination of geometry and material properties. The former causes significant differences in the profiles. Stage 2 is controlled predominantly by the latter, leading to similar looking Stage 2 curves across valve geometries. During Stage 1 the orifice of the valve has closed, and the leaflets fill under increasing downstream pressure. Here, twisting and locking of the free edge is observed. The critical value where Stage 1 ends and Stage 2 begins marks the end of the geometry defined displacement. Further deformation is caused by the sinking of the valve leaflets, the resistance to which, is determined by the material properties of the silicone. Within the leaflets themselves there is also significant differences in readings. Asymmetries lead to anticlockwise twisting regardless of valve geometry.

References

Acknowledgements
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Introduction
The response of soft tissues to an applied loading can be determined by strain measurement, which is a key parameter e.g. during experimental testing of joint kinematics using actively controlled motion test rigs. Typically, strain is measured using electrical resistance with strain gauges (SG), or optical sensors based on digital image correlation (DIC), among others [1-3]. These sensor systems are established in other areas of technology. However, these sensors have a limited range of applications in medical technology due to various challenges in handling human soft materials. The aim of this study was to compare directly attached foil-type SG and 3D-DIC to determine the strain of axially loaded human ligament structures.

Methods
Therefore, the medial (MCL) and lateral (LCL) collateral ligaments of 18 human knee joints underwent cyclic displacement-controlled loading at a rate of 20 mm/min in two test trials. In the first trial, strain was recorded with the 3D-DIC system and the reference strain of the testing machine (REF). In the second trial, strain was additionally measured with a directly attached SG.

Results
The most important finding of this study was that only the 3D-DIC provides results comparable to the reference. The SG demonstrate significantly lower strain values in comparison to the 3D-DIC and the reference (p < 0.0001).

Discussion
According to our results, both systems allow strain assessment within the range of elastic behavior of the ligament, however only the 3D-DIC provides results comparable to the reference. As described in the literature, the 3D-DIC method provides quantitative and qualitative results through full-field analysis of superficial ligaments. Nevertheless, SGs can be used to study the behavior of ligaments in joints, even if they are not superficial, and especially if they are optically inaccessible for 3D-DIC.

References
WEAR RATE COMPARISON BETWEEN ADDITIVE MANUFACTURED AND CASTED FEMORAL COMPONENTS

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Introduction
Additive manufacturing technology has shown important advances in recent years, which has helped increase its popularity in the orthopaedic field. The applications where this technology is currently being used include preoperative planning (1), patient specific cutting guides (2) and custom made implants (3).
Moreover, 3D printing has also been used for large scale manufacturing of some titanium implant components, such as cones (4), spinal cages (5) and cementless tibial components (6), from which there are even clinical results found on the literature.
Nevertheless, few literature covers 3D manufacturing of CoCrMo femoral components for total knee arthroplasty (TKA), and when it does, it is focused on custom made implants for patients with severe cases. These types of implants should also undergo pre-clinical testing in order to assure their mechanical properties. However, it is mainly focused on its fatigue testing (3), and not on its wear behaviour while articulating against an ultra-high-molecular weight polyethylene (UHMWPE) gliding surface.
Furthermore, as 3D printing is a faster and cost saving technology during the development phase of an implant, it could also be used to evaluate the wear behaviour of several femur designs without the need of investing in the expensive moulds and tools required to fabricate casted implants. However, there are no studies that confirm that 3D printed implants generate the same amount of wear as casted implants.
The purpose of this study is to compare the wear behaviour of an additive manufactured CoCrMo femoral component to the wear behaviour of a standard casted CoCrMo alloy femoral component.

Methods
Four medium size femoral components based on the Columbus® CR design (Aesculap AG, Tuttlingen, Germany) were additive manufactured out of CoCrMo (AM group). For the comparison group, four femurs from the clinically established casted CoCrMo alloy version of the femur implant (cast group) were selected. For both groups, the same UHMWPE gliding surfaces (Columbus® DD, size T3, high 10 mm) and tibial components were used.
Wear simulation according to ISO 14243-1 was performed on a load controlled 4 station knee wear simulator (EndoLab GmbH, Germany). The gliding surfaces were first be tested for 3 million cycles while articulating against the cast alloy femoral components. Afterwards, the same gliding surfaces were be tested for 3 million cycles while articulating against the additive manufactured femoral components.

Results
Before testing, the additive manufactured femoral components were analyzed in order to verify that they comply with the specifications of the drawing (specifically their roughness at the articulation surface and their geometry).
Wear rate of the UHMWPE gliding surface was calculated taking into account the 3 million cycles that each tested group underwent. An statistical analysis was performed in order to determine if there is a significant difference in the wear rate between both groups.
An analysis of the articulating surfaced (femoral components and gliding surfaces) was performed with a microscope in order to determine if both groups showed similar wear modes.

Discussion
Additive manufacturing is a versatile technology that helps to provide TKA implants for patients with severe cases as well as a tool during the development phase that can help save costs and time. However, it is important to assure that the wear behaviour of the UHMWPE gliding surfaces articulating against additive manufactured femoral components is not compromised.

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LOAD-INDUCED MICROSTRUCTURAL CHANGES OF COLLAGEN AND ELASTIN FIBERS IN THE HUMAN AORTIC WALL ARE LAYER-SPECIFIC

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Introduction
The mature human aortic wall evolved and developed into a three-layered structure, which on the one hand enables efficient blood flow and on the other hand provides strength to the aortic wall [1]. The health conditions in which the integrity of the aortic wall is at risk are therefore of great concern [2]. Effective treatment of such conditions could be strengthened by a predictive material model of the aortic wall, which could further support preoperative planning [3] and estimation of postoperative growth and remodeling [4]. A predictive material model of the aortic wall could only be developed based on experimental results that provide both the mechanical behavior and structural parameters of the aortic layers.

Methods
Medial and adventitial layers of human aortas were simultaneously subjected to equibiaxial loading and multi-photon microscopy (MPM). At several stretching steps, collagen and elastin were imaged based on their second-harmonic generation signal and two-photon excited fluorescence, respectively (Figure 1). The microstructural changes were quantified using the following parameters: number of fiber families, mean fiber direction, fiber orientation, fiber diameter, and fiber waviness, as in [5].

Results
The media and adventitia showed clearly distinct microstructural changes during equibiaxial loading (Table 1). In particular, the adventitial collagen, in contrast to the medial collagen, is divided into more fiber families. The medial elastin showed reduced waviness in contrast to the adventitial elastin. The medial collagen dispersion showed no change, while the adventitial collagen dispersion was substantially reduced. In addition, the waviness of elastin fibers showed a potential to serve as an indicator of tissue stiffness, while the waviness of collagen fibers served as an indicator of tissue strength.

<table>
<thead>
<tr>
<th>Structural parameter</th>
<th>Media</th>
<th>Collagen</th>
<th>Elastin</th>
<th>Adventitia</th>
<th>Collagen</th>
<th>Elastin</th>
</tr>
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<tr>
<td>FF</td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
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<tr>
<td>α</td>
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<td>κ</td>
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<td>W</td>
<td>↓</td>
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<td>↓</td>
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</table>

Table 1: Microstructural changes (‘↑’ corresponds to no change, ‘↑’ increase, and ‘↓’ decrease) in the parameters of the number of fiber families (FF), mean fiber direction (α), fiber dispersion (κ), fiber diameter (D), and fiber waviness (W) observed for collagen and elastin in the human aortic media and adventitia subjected to equibiaxial loading.

Discussion
The results reflect the latest knowledge on the load-induced changes in the microstructure of the human aortic layers. The quantified structural parameters could provide a direct input for multiscale material models [6] and further support the development of the material models from reproductive to predictive capabilities.

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Acknowledgements
This work was supported by grant no. P30260 of the Austrian Science Fund (FWF).
DESIGN, CHARACTERIZATION AND TESTING OF A PLATFORM FOR INVESTIGATING CELL RESPONSE TO CONTROLLED STRETCH

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Introduction

In vivo, mechanical cues are fundamental in promoting cell and tissue development and in maintaining homeostasis [1]. Thus, advanced investigation platforms able to replicate and combine native-like physical stimuli represent essential tools for investigating in vitro the biological response of cells under defined mechanical stimuli. In this study, we designed, characterized, and tested an investigation platform, based on a flexible substrate and a stretch bioreactor [2], for exposing adherent cells to controlled uniaxial stretch culture protocols in view of mechanotransduction studies, and we performed explanatory biological tests on human periodontal ligament stem cells (hPDLSCs).

Methods

The proposed investigation platform is composed of a flexible substrate combined with a previously developed stretch bioreactor [2]. The substrate presents two parallel rectangular wells (Fig. 1A) for enabling test parallelization and optimization of the culture medium volume. To guarantee a planar and uniform uniaxial strain, the substrate design was supported by finite element (FE) analyses (Abaqus, Dassault Systèmes). A uniaxial displacement of 3 mm (15% strain) was imposed at one side of the substrate while the opposite one was fixed, mimicking the bioreactor stretching. Once identified, the optimal substrate design was fabricated in polydimethylsiloxane (PDMS, Sylgard 184). Digital image correlation (DIC) method was adopted (VIC-2D system, isis-sys GmbH) to measure the substrate surface strain under uniaxial stretch (n=3). Explanatory biological tests were carried out on hPDLSCs from healthy donors. After coating with collagen I, the substrates were seeded with hPDLSCs, clamped in the bioreactor (Fig. 1B), and subjected to intermittent cyclic uniaxial stretch (8% constant pre-strain + 7% cyclic strain for 90 s (n=3) or 300 s (n=1) at 1 Hz every 6 h) for 3 days [3]. Cell-seeded substrates were cultured statically as control. Cell alignment was visually inspected by light microscopy and the expression of the osteogenic markers alkaline phosphatase (ALP), osteocalcin (OCN), and runt-related transcription factor 2 (RUNX2) was quantified by real-time PCR.

Results

FE and DIC analyses showed similar results (Fig. 1C), with a planar and mostly uniform strain distribution at the substrate well bottom with a mean strain value along the stretching direction ($\varepsilon_{xx}$) of 13.4% and 14.4±1.0%, respectively. Biological tests revealed cell alignment (Fig. 1D) and significant over-expressions of all considered genes with respect to the control when cells underwent the stimulation protocol with cyclic stretch lasting for 300 s.

Discussion

Providing controlled physical stimuli in vitro is fundamental for in-depth understanding the cause-effect relationship between the applied mechanical cues and the cellular response. Here, we developed and tested an investigation platform able to provide by stretching controlled planar and uniform strain to adherent cells. Also, the presented platform, allowing for various strain protocols, gives the possibility to separately unravel the effect of each stimulation parameter. Preliminary biological results showed that timing in stimulation can play a crucial role in promoting hPDLSCs alignment and differentiation. Further biological tests are ongoing to confirm the obtained results.

References

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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
SIMULATION OF LOWER LIMB MUSCLE ACTIVATION USING RUNNING SHOES WITH DIFFERENT HEEL-TO-TOE DROPS USING OPENSIM

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Introduction:
Although numerous studies have been conducted to investigate the acute effects of shoe drops on running kinematics and kinetic variables, the muscle force consequences remain unknown. Thus, the primary goal of this study was to compare the muscle force, kinematics, and kinetic variables of habitually rear-foot runners with the heel-to-toe drop of negative 8mm shoes (minimalist shoes) and the heel-to-toe drop of positive 9mm shoes (normal shoes) during the running stance phase using musculoskeletal modelling and simulation techniques.

Methods:
Experimental data of 16 healthy rearfoot strike pattern runners for a standard lower limb kinematic, ground reaction force and muscle activation were collected. The data were used OpenSim for musculoskeletal modeling simulation. In Matlab, the statistical parameter mapping paired t-test was used to compare the joint angle, moment, and muscle force waveform. Results: The results revealed differences in the sagittal ankle and hip angles and sagittal knee moments between the different heel-to-toe drops of running shoes.

Results:
The results found that with the negative 8mm running shoes, the ankle dorsiflexion angle, ankle eversion angle, knee flexion angle, hip flexion angle, hip internal rotation, and hip external rotation angle were significantly smaller than the positive 9mm running shoes. While the lateral gastrocnemius, Achilles tendon, and flexor hallucis longus muscles were significantly greater in the minimal shoe compared to normal shoes. The vastus medialis, vastus lateralis and extensor digitorum longus muscles force were smaller in the minimalist shoes.

Discussion:
Negative running shoes may cause runners to use a midfoot strike pattern. High muscle force in the gastrocnemius lateral, Achilles tendon, and flexor hallucis longus muscles demonstrated that increases the potential for Achilles tendonitis and ankle flexor injuries.

Reference:
EXPLORING THE MECHANISMS OF GROWTH PLATE DEVELOPMENT AND DISEASE PROGRESSION THROUGH A DYNAMIC TRABECULAR BONE MICROSTRUCTURE MODEL

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Introduction

Growth plate biomechanics is a growing field of research that examines the mechanisms that regulate bone growth and development. The growth plate, found at the end of long bones, is responsible for longitudinal growth and is crucial for proper musculoskeletal development, and depends on mechanical and biological factors. However, growth plate injuries and diseases can disrupt normal bone growth and lead to severe complications and diseases such as slipped capital femoral epiphysis (SCFE), Legg-Calvé-Perthes disease (LCPD), or Hip dysplasia (HD). This may alter the mechanical loading state in the region of the growth plate, affecting the process of endochondral growth. Advances in imaging and computational modeling provide valuable insights into the biomechanical forces and microstructural changes in the growth plate during normal growth (Moncayo-Donoso et al. 2019) and disease progression (Wilkinson and Zeggini 2021). This work presents a new model for endochondral growth that focuses on the role of trabecular groups in growth plate development. This model can aid in understanding the mechanisms of growth plate diseases and developing more effective treatments focusing on the mechanical factors involved in each developmental stage.

Methods

We developed a dynamic finite element model for growth plate development based on a bone remodeling approach that uses strain energy density as the main stimulus that controls the bone formation and resorption (Nackenhorst 1997). For the cartilaginous zones, the evolution law is based on the osteogenic index (OI) (Carter and Wong 2003) which will determine the strain ($\varepsilon$) related to proliferation ($d^p$) and hypertrophy ($d^h$) due to endochondral growth in the growth plate. Following the evolution law shown in Eq. 1.

$$\varepsilon = d^p + d^h = k_2OI$$

(1)

For the simulations, the domains are adopted from $\mu$CT scans and a linear isotropic model is implemented for its simplicity and under the assumption of small displacements due to the growing strains.

Results

Our model shows the evolution of the growth plate according to the mechanical action of the main trabecular groups. The evolution of the growth plate shown in mice $\mu$CT scans at different stages of development is used for validation of the dynamic model. Furthermore, the CT scans are used to test the proposed method in a 3D environment on a voxel-based domain.

Discussion

These findings have important implications for the understanding of diseases that affect the growth plate. For example, conditions such as congenital pseudarthrosis, which is characterized by a failure of the bone to heal properly, have been linked to abnormal trabecular patterns in the growth plate in addition to SCFE, LCPD or HD. By studying the trabecular patterns of the growth plate in a dynamic model, researchers may be able to identify early markers of these diseases and develop more effective treatments for patients. Furthermore, the understanding of the trabecular patterns of the growth plate in healthy development can provide insight into the optimal mechanical environment for bone growth. For instance, by investigating the optimal trabecular patterns in healthy growth plates, clinicians may be able to develop new surgical techniques or physical therapy protocols to promote bone growth and healing in patients with growth plate disorders. Further studies will provide valuable insights into the optimal mechanical environment for bone growth and healing.

References


Acknowledgements

This work was supported by the UTC Research Funding.
A REALISTIC ALVEOLAR DUCT MODEL FOR USE IN WHOLE-LUNG RESPIRATORY SIMULATIONS OF MECHANICAL VENTILATION

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1. Department of Biomedical Engineering, Eindhoven University of Technology, the Netherlands; 2. Department of Intensive Care, Maastricht University Medical Center+, the Netherlands

Background
Mechanical ventilation (MV) is often applied on the intensive care unit (ICU). While essential for patient survival, MV can induce local lung tissue damage due to the highly heterogeneous mechanical response of the lung to MV. This phenomena is better known as “ventilator induced lung injury” (VILI) and can potentially be life-threatening. Reduced order computer modelling of lung response to MV has the potential to locally assess metrics related to VILI development. As such, these models can serve as a valuable tool to study the mechanisms responsible for VILI. However, most respiratory models assume relatively simple alveolar behavior. These models can therefore not be easily adapted to account for pathologies that affect alveolar mechanics. This greatly limits the usability of these models for evaluating lung mechanics in ICU patients, as these patients often do suffer from respiratory conditions that impact alveolar mechanics.

In this study, a 3D finite element alveolar model was developed that can be adapted to represent the effect of pathologies. We use this model to study the impact of lung emphysema and lung fibrosis on the pressure-volume behavior of the alveoli. Finally, we generalize these pathological alveolar pressure-volume relations to assess the impact of MV on pathological lungs.

Methods
A 3D alveolar-duct model consisting of 32 alveoli based on the geometry introduced by (1) was created using shell elements in LS-Dyna. Material behavior was described using a 5-parameter Mooney-Rivlin hyper elastic material model. Elastic material properties of the healthy alveolar duct were derived using an efficient inverse modeling approach that aimed to recover the pressure-volume curves published in (1).

Next, the alveolar model was adapted to model two common respiratory diseases: emphysema was modelled by removing all internal walls of the alveolar duct, whereas fibrosis was modelled by increasing alveolar wall thickness by a factor 1.7 (2). Subsequently, 3D duct behavior was generalized and implemented in a previously developed reduced order respiratory model. Finally, the reduced order model was used to evaluate the effect of MV on lung mechanics in the case of fibrosis or emphysema in the right upper lobe, assuming a tidal volume of 560 mL.

Results
Using the inverse modelling approach a set of material parameters where found that allowed to accurately reconstruct the data presented in (1) (Figure 1A). Furthermore, by adjusting model geometry, a stiffening behavior was observed for the fibrotic alveolar model, whereas more compliant behavior was observed for the emphysematous case (Figure 1A). Note that not only the magnitude, but also the shape of the emphysematous and fibrotic curves are different compared to the healthy alveolar model.

In the case of the fibrotic lung it was observed that stretch in the diseased lobe was reduced considerably with respect to the healthy simulation, whereas stretch in all other lobes increased (Figure 1B & C). In the case of the emphysematous lung, stretch in the pathological lobe increased, whereas stretch in all other lobes decreased (Figure 1B & D).

Discussion
In this study we created a 3D finite element model that allowed to investigate the effect of various pathologies on alveolar mechanics. FEM model response was successfully generalized and implemented in whole lung simulations of healthy, emphysematous and fibrotic lungs. Future research should however be performed to verify the obtained pressure-volume curves for the studied pathologies. The developed alveolar duct model is promising for the evaluation of alveolar mechanics in the presence of pathologies in ICU patients.

References
A FULLY COUPLED COMPUTATIONAL FRAMEWORK FOR BONE FRACTURE REPAIR IN THE PRESENCE OF BIOABSORBABLE MAGNESIUM FIXATION DEVICES

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Biomechanics Research Centre (BioMEC), School of Engineering, University of Galway

Introduction
Magnesium (Mg) alloys have significant potential in orthopaedic applications as they avoid long-term complications associated within permanent metallic implants. Mg-based device reduce the need for implant removal surgeries as they are biodegradable, while also having osteoinductive properties and showing comparable mechanical properties to native bone tissue [1]. However, understanding the biomechanics of implanted Mg-based devices presents distinct challenges as they exhibit a non-uniform pitting corrosion process, which occurs simultaneously alongside the complex tissue repair process of the implanted region.

Materials and Methods
This study presents the coupling of a fracture repair and surface-based Mg corrosion algorithm developed by the author [2, 3] to predict the long-term viability of titanium and biodegradable Mg fixation plates for tibial fracture repair. A pre-processing step was implemented to calculate the random numbers for Mg corrosion, fracture callus generation and the homeostatic bone density. Bone fracture repair consisted of (i) bone fracture healing and (ii) bone remodeling. Bone fracture healing was implemented according to biphasic mechanoregulatory theory [4], whereby cells differentiated into different cell phenotypes based on the local biophysical stimulus. Bone remodeling was determined by local strain energy density (SED) and microdamage. Mg corrosion considered the role of β-phase components throughout the material volume to simulate non-uniform corrosion within the bone plates. All models were implemented through a series of user-defined field subroutines (USDFLD) within Abaqus Standard. The outlined algorithms were fully coupled allowing for bone ingrowth into regions once occupied by Mg components.

Results
Non-plated models underwent indirect fracture healing whereby the fracture gap was stabilised through soft callus formation, generation of a “bony bridge” and hard callus formation. The introduction of an internal plate stabilised the fracture region allowed for direct fracture healing to occur (Figure 1), whereby cells within the interfragmentary gap differentiated directly into mature bone cells, accelerating fracture healing outcomes and the reducing fracture callus volume. The introduction of an overly stiff titanium plate disrupted normal physiological loading, stress shielding cortical regions proximal to the plate. Mg implant strength decreased as Mg corrosion occurred allowing for restoration of normal loading, allowing for the tibia to remodel to pre-fractured morphology.

Discussion
This study presents the first fully coupled computational modelling framework to predict the long-term performance of biodegradable fixation devices. The model captured key aspects of the bone fracture repair process in the presence of plated fixators, showing good qualitative agreement with in vivo performance [5], highlighting the long-term potential of bioresorbable implants.

References

Acknowledgement and Ethics
This project has received funding from the Irish Research Council (IRC) Government of Ireland Postgraduate Scholarship (GOIPG/2017/2102).
Hierarchical Phase-Contrast Tomography (HiP-CT) is a recently developed technique to image intact human organs across length scales that combines propagation phase contrast X-ray imaging with hierarchical image acquisition [1&2]. The hierarchical approach allows for the analysis of acquired images at different levels of resolution, making it possible to reveal differences in structure at different scales [3]. This study assesses the application of HiP-CT by analysing structural differences in a whole human kidney across scales and different resolutions. Three image datasets including a whole human kidney scanned at 25 µm per voxel, and two local regions scanned at 6.5 and 2.6 µm per voxel, were analysed. Image registration is conducted across the three image datasets acquired from HiP-CT (Fig. 1). Image analysis and segmentation are then performed in Avizo version 2021 to segment arterial vessels from the Hip-CT images.

Results
Fig. 2 shows the segmented arterial vessels associated with the three datasets scanned at different resolutions.

Figure 1: 3D registered whole human kidney scanned at 25µm in red with two cylindrical regions scanned at 6.5µm in blue and 2.6µm in yellow. Regions inside the blue and yellow circles are associated with 6.5 and 2.6 µm image datasets.

Figure 2: Segmented arterial vessels associated with the three datasets scanned at different resolutions

The analysis of high resolution images revealed the presence of finer vessels and the complexity of the connections between them, which were not visible at the lower resolution setting. A total number of 76, 251, and 356 vessels were found for the three resolutions respectively.

Vessel networks analysis showed that one additional vessel generation was resolved at each step of resolution. The combination of multi-resolution data can be used to accurately calibrate the results obtained on larger organs with lower resolution data. This allows for the use of high resolution finest structures to more accurately pinpoint areas of interest or to provide more detailed analysis of the data. This can lead to more accurate diagnosis, treatment, or understanding of the underlying mechanisms of a given organ. Additionally, this combination of data can provide a more comprehensive view of the organ, allowing researchers to gain a deeper understanding of the anatomy, physiology, or pathology of the organ. Furthermore, this information can be used to better understand the structure and function of the vessels, as well as the associated diseases.

References

Acknowledgements
The authors acknowledge funding from the Chan Zuckerberg Initiative DAF (2020-225394), an advised fund of SVCF, the MRC (MR/R025673/1), Laboratoire d’Anatomie des Alpes Françaises (LADAF), and ESRF beamtime (md1252).
INVESTIGATION OF GENDER-SPECIFIC RISKS OF SKIN FOLDING AFTER BARIATRIC SURGERY: A COMPUTATIONAL APPROACH

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Introduction
Obese individuals who experience significant weight loss after bariatric surgery may have difficulty with excess skin that cannot adjust to their new body size [1]. Excess skin can lead to skin folding, which can be a source of dissatisfaction for many, with ~80% of women complaining about excess skin in the abdomen region and desiring body contouring surgery. About 20% of men also have problems with redundant skin, mainly in the abdomen [2]. The abdomen comprises organs and adipose tissue composed of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). The distribution of fat within these layers differs between men and women, with a relatively higher content of SAT in women and a higher content of VAT in men [3]. Using a computational model, we investigated if these differences in local fat distribution and reduction during weight loss can (partly) explain the differential risk of skin folding in women and men. We hypothesized that women are more likely to develop skin folding due to the relatively high reduction of SAT volume compared to men, while reducing VAT volume in men leads to less significant skin folding [4].

Methods
We developed a finite element model to simulate fat loss with a kinematic growth model implemented in Abaqus/Explicit via a user-defined subroutine (VUMAT). The fat loss starts at an initial state of extreme obesity with a Body Mass Index (BMI) of 60 kg/m², and we simulated a 75% fat reduction to reach a BMI of 30 kg/m². We mimicked the fat loss in a simplified 3D geometry, which consisted of four layers: organs in the core, VAT, SAT, and skin, all modeled as a compressible Neo-Hookean material. We based the fat distribution ratio h_{VAT}/h_{SAT} and the local fat loss ratio VAT_{loss}/SAT_{loss} for females and males on literature data (Table 1) [3], [4].

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>h_{VAT}/h_{SAT}</td>
<td>2.4</td>
<td>3</td>
</tr>
<tr>
<td>VAT_{loss}/SAT_{loss}</td>
<td>0.33-4</td>
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</table>

Table 1: VAT and SAT thickness ratio (h_{VAT}/h_{SAT}) based on ultrasound measurements of fat thickness [3], and local fat loss ratio (VAT_{loss}/SAT_{loss}) in women and men.

Discussion
Our simulations showed that the sex-specific fat distribution and local differences in fat reduction can affect the skinfold patterns in women and men, and support our hypothesis that women have an increased risk of skinfold formation after bariatric surgery. In future research, we aim to incorporate gravity and skin-rib connections to improve the accuracy of skinfold predictions. Such an improved model may help in identifying individuals with a high risk of skin folding prior to the weight loss.

References

Acknowledgements
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PATIENT-SPECIFIC COMBINED FEA-FSI METHODOLOGY TO MODEL THE TEVAR PROCEDURE

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Introduction
Thoracic Endovascular Aortic Repair (TEVAR) has been increasingly adopted to treat thoracic aorta pathologies since the first FDA stent-graft (SG) approval and it consists of placing a self-expandable SG into the pathological aortic region to recreate a more physiological condition [1]. Many SG-related complications are still to be investigated, and reliable computational models play a significant role in this context. This study aims at reproducing the TEVAR procedure in a patient-specific aorta using the finite element (FE) analysis [2]. Then, a novel Fluid-Structure Interaction (FSI) simulation is set up to address the post-TEVAR hemodynamics and investigate the SG behavior during the cardiac cycle.

Materials and methods
The deployment of a commercial Valiant Captivia thoracic SG (Medtronic Inc.) in a patient-specific aortic model was simulated in Ls-Dyna (ANSYS) using a previously validated explicit FE method. The SG model was meshed in ANSA (BETA CAE System): the stent was discretized with beam elements and the graft with triangular membrane elements. Nitinol and PET material parameters were calibrated with experimental tests [2]. The aortic model was segmented from pre-operative clinical CTA images using the software VMTK (Orobix Srl) and discretized with three layers of tetrahedral elements. An isotropic hyperelastic material following the Yeoh constitutive formulation was assigned to the aortic wall with literature parameters [2] and the arterial wall prestress was included as well. The stent deployed configuration resulting from the FE TEVAR simulation was compared with the stent segmented from post-operative CTA images as additional validation.

The FE simulation outcome was used as a starting point for the FSI modelling. In particular, a strongly coupled, two-way and boundary-fitted FSI simulation was carried out in Ls-Dyna (ANSYS). For the fluid domain, a physiological velocity waveform was imposed as inlet boundary condition (ascending aorta) and 3-elements Windkessel circuits were assigned to each outlet (three supra-aortic branches and descending aorta) to account for the downstream resistances [4]. The SG was modelled as an embedded body into the fluid mesh volume. For the structural domain, the SG and aorta meshes and stress/strain distributions at the end of deployment were imported from the FE simulation.

Results
In Fig.1(a), the CTA segmentation and the final stent-graft deployed configuration resulting from the FE simulation are depicted: a good agreement between the simulated and segmented stent reconstruction was obtained (difference below 11%). Fig.1(b) shows the FSI simulation results in terms of blood systolic velocity streamlines and contact/no-contact map between the SG and aorta at the systolic peak. The latter was evaluated as a measure of the SG dynamic sealing: during systole, 94.6% of proximal stent elements are in contact with the aortic wall.

Discussion
The proposed study combines a previously validated high-fidelity FE methodology with a novel FSI approach that includes both the aorta and SG model and considers their interaction in the cardiac cycle. This FEA-FSI methodology can be applied to patient-specific cases and it can be useful for investigating TEVAR complications, designing new devices or supporting clinical decisions before intervention.

References

Acknowledgements
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IN VITRO CHARACTERIZATION OF LOAD TRANSFER IN CERVICAL DISC REPLACEMENT ARTHROPLASTY

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Introduction
Degenerative cervical pathologies are growing, and the conventional treatment in cervical and lumbar is a fusion procedure. This kind of procedure involves a replacement of the disc using a static solution, such as cement, screws, or an implant. This replacement is associated with some potential complications such as, for example, a pathology of the adjacent segment or loss of mobility in the spine region [1, 2]. Cervical disc arthroplasties were developed as an alternative to fusion, and several prosthesis concepts are available in the market [3]. The present in vitro study analyzed the load transfer in adjacent vertebrae using the Mobi-C concept in the cervical region in comparison with the intact condition.

Materials and methods
An experimental model was created to mimic the cervical spine in a tensile tester machine to test the natural and prosthetic disc (figure 1). The C5 and C6 vertebrae were chosen for this study because they are located in the lower part of the cervical spine where loads applied are higher. Different materials are used in this system including the vertebrae, support pieces, the Mobi-C disc, a natural disc model, ligaments, and tri-axial strain gauges. The assembly can mimic the neutral, flexion of 10 degrees and extension of 10 degrees of the spine. Strain gauge sensors were used to evaluate the deformation in the anterior and posterior facets of the vertebral body of each vertebra.

Results
When comparing the natural and prosthetic models, it was concluded that the assembly with the natural discs distribute the load applied to the system less evenly across the vertebral body than the prosthetic disc. The difference between the highest strain value and the lowest is 517.53 £m/m for the natural disc model and 205.75 £m/m for the prosthetic disc model. The disparity between values in different sensors is noticeably higher in the natural disc than in the prosthetic disc (figure 2). The main conclusion was that the prosthetic disc distributes the load of the cervical spine on the vertebral body more than the natural disc model due mainly to its geometry and fixation region.

Conclusions
The strain analysis in the experimental assembly suggests that the Mobi-C implant transfers the load mainly around the vertebrae and can promote bone loss in the external cortical of adjacent vertebrae.

References

Acknowledgments
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Figure 1: Experimental apparatus to study the cervical disc arthroplasty (intact condition).

Figure 2: Comparison of natural joint and implanted cervical prosthesis.
CAN IN VITRO KNEE SIMULATORS REPLICATE KNEE BIOMECHANICS: A SYSTEMATIC REVIEW

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Introduction
In vitro knee simulators, which replicate kinematic and kinetic conditions in cadaveric specimens, have become increasingly prevalent in assessing medical implants or surgical reconstructions by facilitating invasive measurements and overcoming approximations due to tissue isolation. While these simulators are electromechanically designed to apply repeatable, controlled physiological loads and motions to cadaveric joints, alterations in biomechanical inputs question the biomechanical credibility of the simulator in replicating true joint physiology. Common examples include downscaling of ground reaction forces (GRF) to reduce applied muscle forces thereby preventing possible tendon rupture (1), or applying realistic loads but at much lower speeds while also discounting simultaneous control of multiple muscles owing to practical and computational difficulties encountered in real-time control (2).

This review article aims to summarize the parameters used in in vitro knee simulators, and compare it with in vivo biomechanical studies to understand the clinical relevance.

Methods
A systematic literature review using PRISMA guidelines was conducted on Google scholar, PubMed, and Web of Science using the keywords "knee simulator," "knee rig," "cadaver," "muscles," "biomechanics," and "in vitro." Cadaveric studies replicating human muscle loading were included in this review; computational simulations and wear-based simulators were excluded. 1036 studies were identified, and finally, 105 studies were filtered after removing duplicates and screening irrelevant abstracts. Trends in commonly altered biomechanical parameters, such as muscle forces, joint range of motion (ROM), and cycle time, were analysed and compared to those reported in vivo.

Results
Over the years, simulators evolved from single to multi-actuated devices to replicate in vivo physiology. Simulating closed chain activities, such as squatting, kneeling, and jump landing in vitro, the quadriceps force was downscaled to 12-66 % of the physiological values reported in vivo. For simulating open chain activities, downsizing was not found, probably due to lower muscle loads. Hamstring loads were often statically simulated to a load varying from 0 to 14% of its natural value. The simulator’s flexion speed ranges from 1°/s to 12°/s to accurately replicate GRF, which was substantially lower than its physiological value of 65°/s. These simulators' flexion ROM varies from 0° to 130°, limiting the posterior translation of femur and tibial rotation to 16 mm and 12°, respectively.

<table>
<thead>
<tr>
<th>Study</th>
<th>In vivo</th>
<th>In vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROM (deg)</td>
<td>30-160</td>
<td>15-20-20-10-70</td>
</tr>
<tr>
<td>Quad (BW, M)</td>
<td>5.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Ham (BW, S)</td>
<td>2.2</td>
<td>0.3</td>
</tr>
<tr>
<td>GRF (BW, M)</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Time (s)</td>
<td>2</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Table 1: Comparison of the biomechanical parameters during squatting in vivo and in vitro (M-Multiple actuator, S-Single actuator)

Discussion
In vitro simulators were found to avoid complete joint ROM due to the risk of tendon rupture and fixation shape. However, a more recent study by Schall et al. applied the true load within a limited flexion range (Table 1). Passive loading of hamstring was unable to replicate the physiology during ascent phase of closed chain activity. Unlike the in vivo studies after 30° flexion, the rotation speed is slowed due to reduced quadriceps and constant hamstring load. To replicate in vivo muscle loads and joint ROM on cadaveric specimens, it is important to strengthen the fixation of the actuator cable to the tendon. Individual muscles must be actuated separately to maintain a physiological line of action. Control strategies need to be simplified and improved, possibly even allowing direct feedback from the cadaver to reduce the latency. Finally, these simulator designs need to incorporate other activities of daily living and injuries requiring greater joint mobility. This study could valuable help surgeons and researchers in formulating physiologically meaningful interpretations of in vitro experiments.

References

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
A SELF-POWERED VENOUS BLOOD PUMP FOR SINGLE-VENTRICLE HEART DISEASE

Reza Rasooli (1), Knut Erik Teigen Giljarhus (1), Ingunn Westvik Jolma (1), Jan Ludvig Vinningland (2), Henrik Holmstrom (3), Aksel Hiorth (1)

1. University of Stavanger, Norway; 2. NORCE, Norway; 3. University of Oslo, Norway

Introduction

The Fontan procedure is the final stage of surgical palliation for single-ventricle heart malformations aimed at diverting the venous return directly to the pulmonary arteries. The lack of a subpulmonic ventricle leads to non-pulsatile pulmonary flow, systemic venous hypertension and eventually, failure. Although it is multifactorial, elevated IVC (inferior vena cava) pressure is accepted to be the primary cause of Fontan's high morbidity [1]. This study presents a novel self-powered venous ejector pump (VEP) to assist Fontan circulation. The proposed VEP exploits a fraction of aortic flow to generate a jet Venturi effect for the IVC flow and an atrial discharge to drain excess flow into the atrium (Figure 1). In vitro pulsatile experiments revealed the VEP’s potential to significantly lower IVC pressure while maintaining high levels of arterial oxygen concentration and improving flow pulsatility.

Methods

Computational fluid dynamics (CFD) simulations incorporating turbulent models and clinically relevant boundary conditions were conducted in OpenFOAM to identify the optimal geometrical parameters in both idealized and patient-specific total cavopulmonary connections (TCPC). The identified designs with optimal performance were then realized through 3D stereolithography printing for experimental examination. A pulsatile in vitro single-ventricle mock-up circulation loop (Figure 1) was developed to evaluate the VEP performance using physiological pressure waveforms simulating post-Fontan conditions. A non-Newtonian blood analog that closely matches the blood viscosity of Fontan patients [2] was prepared and utilized as the working fluid.

Results

Table 1 summarizes the in vitro key hemodynamic indices for different cardiac outputs and aortic pressures. The introduction of VEP into Fontan circulation resulted in reduced arterial pressure which was adjusted back to its TCPC state by increasing the CO through stroke volume. The VEP provided an IVC pressure drop of more than 2.6 mm Hg in all cases with an arterial oxygen saturation of greater than 86% and improved flow pulsatility.

<table>
<thead>
<tr>
<th>TCPC state</th>
<th>CO (L/min)</th>
<th>Q_{aoc} (L/min)</th>
<th>P_{IA} (mm Hg)</th>
<th>P_{IVC} (mm Hg)</th>
<th>C_{sa,O2} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCPC state</td>
<td>2.40</td>
<td>0</td>
<td>85.1 (40.1)</td>
<td>14.4 (0.4)</td>
<td>95</td>
</tr>
<tr>
<td>TCPC+VEP</td>
<td>3.42</td>
<td>1.09</td>
<td>84.9 (40.2)</td>
<td>11.6 (1.5)</td>
<td>89</td>
</tr>
<tr>
<td>TCPC state</td>
<td>2.40</td>
<td>1.23</td>
<td>99.9 (40.4)</td>
<td>14.4 (0.3)</td>
<td>95</td>
</tr>
<tr>
<td>TCPC+VEP</td>
<td>3.60</td>
<td>1.23</td>
<td>100.0 (40.7)</td>
<td>11.6 (1.9)</td>
<td>89</td>
</tr>
<tr>
<td>TCPC state</td>
<td>3.40</td>
<td>1.10</td>
<td>85.1 (40.6)</td>
<td>14.8 (0.6)</td>
<td>95</td>
</tr>
<tr>
<td>TCPC+VEP</td>
<td>4.51</td>
<td>1.10</td>
<td>84.8 (40.6)</td>
<td>12.2 (1.2)</td>
<td>86</td>
</tr>
<tr>
<td>TCPC state</td>
<td>3.40</td>
<td>1.20</td>
<td>100.1 (40.9)</td>
<td>14.8 (0.7)</td>
<td>95</td>
</tr>
<tr>
<td>TCPC+VEP</td>
<td>4.61</td>
<td>1.20</td>
<td>100.1 (40.5)</td>
<td>12.1 (1.4)</td>
<td>87</td>
</tr>
</tbody>
</table>

Table 1: In vitro mean and pulse pressure (in parenthesis) of the waveforms for both TCPC and VEP-assisted TCPC. CO: cardiac output, Q_{aoc}: aortic graft flow, P_{IA}: aortic pressure, A_P_{IVC}: IVC pressure, C_{sa,O2}: arterial blood oxygen concentration.

Discussion

Self-powered Fontan venous assist is an emerging concept that eliminates the need for external power and thus limits the driveline infection. Previously proposed solutions are either clinically unfeasible or have complex and moving elements [3,4]. Our proposed VEP is clinically feasible, has no moving parts, provides significant IVC support while maintaining high levels of arterial oxygen concentration, and more importantly improves pulmonary flow pulsatility.

References


Acknowledgements

Financial support from Dam foundation and Equinor Academia program is highly appreciated.
INVESTIGATION OF THE IMPACT OF NANOSCALE GEOMETRY ON THE MECHANICAL PROPERTIES OF HYDROXYAPATITE PLATELETS

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Introduction
The increase in bone fracture risk with age is generally explained by a loss of bone mass and an alteration in the skeletal architecture, but those effects contribute to only 75% of the increased risk of fracture. Recent studies have shown how changes in bone tissue mechanical properties could be a reasonable explanation for the remaining part of the age-related fracture risk increase [1]. Previous computational studies already associated properties of hydroxyapatite platelets with mechanical properties of bone nanocomposites. It has been observed, for example, that the size of hydroxyapatite crystals can influence the crack propagation at the nanoscale level [2], and that the nanosize confinement of HAP crystals controls the mechanical properties of the collagen-hydroxyapatite interface [3]. From an experimental point of view, whether and how the crystal platelets change with age is an open and still debated issue. Measurements of HAP platelets dimensions have been performed on mouse [4] and human [5][6] bone samples using X-ray diffraction, Fourier-transform infrared spectroscopy (FTIR) and electron microscopy, without establishing a unique correlation between their dimensions and age, both because of limitation of indirect measurement techniques (in which size changes could be a hypothesis, but not the only factor that plays a role) and because of the very small number of bone samples usually considered in each study. In our work we systematically investigate, through computer simulations, what is the effect of hydroxyapatite platelets’ size on their mechanical properties, to test the effect of aging on this crucial bone component.

Methods
We perform full atomistic molecular dynamics (MD) simulations of hydroxyapatite nanocrystals using the Interface Force Field (IFF) as an effective potential [7]. We study variations in hydroxyapatite platelets size in all the crystallographic directions a,b, and c. In particular we consider three different samples: ‘small’ (200Åx100Åx20Å), ‘medium’ (500Åx250Åx50Å), and ‘large’ (1500Åx800Åx100Å), based on experimental measurements in the literature. To assess hydroxyapatite single crystal mechanical properties, we perform uniaxial tension and compression tests along all three spatial directions, obtaining stress-strain curves and studying the maps of the per-atom stresses.

Results
In the following we show a preliminary result with the comparison of the stress-strain curves for platelets of different sizes (Fig. 1) and of the mechanical properties we computed for them (Tab. 1).

Discussion
Our preliminary results highlight a difference in term of mechanical response to loading due to the HAP size, both in term of ultimate strength and post fracture behavior. So far, extensive MD simulations are running on the HPC-Franklin facility at IIT, to obtain more systematic results for platelets of different size. Our comparison could clarify the issue of how HAP platelets change with age, on the basis of mechanical considerations. Our fundamental approach could advance the knowledge of age-related bone diseases and may open new routes for targeted intervention based on a deeper mechanical knowledge of the bone at a nanoscale level.

Table 1: Mechanical parameters of platelets of different sizes

<table>
<thead>
<tr>
<th>Platelet Size</th>
<th>Elastic Modulus [GPa]</th>
<th>Ultimate strength [GPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>200x100x20</td>
<td>137.809</td>
<td>6.792</td>
</tr>
<tr>
<td>500x250x50</td>
<td>128.724</td>
<td>7.573</td>
</tr>
</tbody>
</table>

References
4. O.Akkus et al., Bone, 34.3:443-453,2004
6. B. Foley et al., Crystals, 10.10:859, 2020

Acknowledgements
This work was supported by the Young Researcher Grant (2020-3615) from Fondazione Cariplo.
PATIENT SPECIFIC NUMERICAL STUDY OF AN INTRACRANIAL ANEURYSM MECHANICAL CHARACTERISATION DEVICE

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Introduction

Intracranial aneurysm is a life-threatening pathology related to the local weakening of the arterial wall. However, there is currently no method enabling to predict the breaking risk based on in vivo mechanical data. This work is part of a large-scale project that aims at providing clinicians with a non-invasive patient-specific decision support tool, based on both the in vivo mechanical characterisation of the aneurysm wall and machine learning analyses. The mechanical properties estimation of the unruptured intracranial aneurysm wall will be obtained from a deformation device coupled with a medical imaging system. The deformed anatomical image will be numerically treated to quantify the aneurysm wall stress state by finite element inverse analysis based on the luminal volume variation. This study aims at identifying and proving an observable aneurysm deformation induced by the device through patient specific numerical models. As the practitioner will never be able to precisely situate the device, several locations were considered. Prior to the inverse analysis procedure, increasing complexity artery models were studied (linear elastic, hyper elastic).

Methods

A patient specific Fluid-Structure Interaction (FSI) finite element model was developed on COMSOL Multiphysics. The device was designed as a guidance flux system. A single laminar flow included the pulsated flow (physiological liquid) and the artery blood flow: fluids were considered as miscible with respective inlet boundary conditions. A 1.5 s heart frequency pulsatile flow rate was applied at the artery inlet with the associated pulsatile pressure at the outlet [1]. A 0.8 s pulsatile flow was considered for the device to overlay the cardiac cycle systole. Flow rates of 150 mL/min (D1) and 190 mL/min (D2) were considered at the device inlet. A 10 mmHg intracranial pressure was applied on the artery outer wall [2].

For each device flow rate, a homogeneous model of the artery/aneurysm and a heterogeneous model depicting the local mechanical weakening of the aneurysm were considered. It was done with a linear elastic model (HOM1 and HET1) [3,4] and a Fung hyper elastic model (HOM2 and HET2) [2,3]. For each case, 5 device locations were studied: 60 artery models were built. The FSI was computed using the arbitrary Lagrangian-Eulerian technique (ALE). The wall displacement norm (µm) and the aneurysm luminal volume variation (mm³ and %) were analysed.

Results and discussion

Considering all the device locations and materials, the displacement induced by the device was between 300 µm and 1.2 mm in addition to the systole peak (figure 1). The luminal volume variation was between 1 % and 4.4 % compared to the initial systole volume (figure 2).

For further animal model studies, the Spectral Photon CT Counting has been chosen as clinical imaging technique, with a spatial associated resolution around 200 µm [5]. Based on this preliminary study, the displacements and associated volume variations (inverse analyses baseline), should be observable and exploitable during in vivo testing on small animals.

References


Acknowledgements

This work was supported by the Région Auvergne-Rhône-Alpes.
SUBJECT-SPECIFIC FEMOROACETABULAR IMPINGEMENT SEVERITY COMPUTATIONAL ASSESSMENT OVER VARIOUS ACTIVITIES

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Introduction
Femoroacetabular impingement (FAI) is associated with specific shape features of the hip joint and has been shown to increase the chances of developing osteoarthritis [1]. People with cam-type FAI are subject to repeated contact between excessive femoral bone and the acetabular rim, which can result in soft tissue damage in the acetabulum. This study aims to demonstrate the ability of a computational shape-motion model of cam-type FAI to differentiate impingement severity in a set of cam patients.

Methods
Patient-specific bony shape features were extracted for 20 clinically diagnosed cam-type hips (10 males and 10 females, age range 22-49 years) [2]. Points representing the acetabular rim and the femoral cam lesion were extracted from segmented three-dimensional CT images. These points were used as inputs to an existing computational impingement model [3], where 126 motion cases were applied. Motion cases included 14 hip activity motions, each completed by nine volunteers. The activities included variations of walking, sitting, squatting, lunging, cycling and a golf swing. The relative position of the acetabular and cam points was defined based on population average hip orientation from literature. The modelling assumption was that any overlap of the acetabular and cam points during a motion indicated that impingement had occurred. For each subject, the metrics recorded were: the total number of motion cases where impingement occurred (out of 126); and the maximum depth of impingement into the acetabular, averaged over all of the motion cases where impingement occurred. Depth was recorded in terms of the angle between the neck-cam and acetabular rim points. Mean depths for activities registering a singular impingement were not calculated.

Results
All subjects showed evidence of impingement, with the number of motion cases generating impingement varying from two (out of 126) to all 126 (Table 1). The mean maximum impingement depth for most subjects was within the range of 4°-10°. Just one subject had a much higher mean maximum depth of 22°. The hip that produced the highest depth possessed the largest cam alpha angle. Qualitatively, predicted impingement location varied with subject cam lesion location (Figure 1). Areas of predicted impingement displayed a greater proportion of anterior impingement from anterior cams, and a greater proportion posteriorly from superior cams.

<table>
<thead>
<tr>
<th>PC</th>
<th>IF (126)</th>
<th>Depth, mean ± stdev (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53L</td>
<td>126</td>
<td>22 ± 8</td>
</tr>
<tr>
<td>17L</td>
<td>119</td>
<td>6 ± 5</td>
</tr>
<tr>
<td>33L</td>
<td>86</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>75L</td>
<td>81</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>02R</td>
<td>75</td>
<td>6 ± 5</td>
</tr>
<tr>
<td>01R</td>
<td>60</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>11R</td>
<td>57</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>16R</td>
<td>49</td>
<td>5 ± 4</td>
</tr>
<tr>
<td>06R</td>
<td>45</td>
<td>4 ± 4</td>
</tr>
<tr>
<td>07R</td>
<td>28</td>
<td>4 ± 3</td>
</tr>
</tbody>
</table>

Table 1 – Patient-specific predicted impingement frequency and depth. (PC = patient code, IF = impingement frequency out of 126 possible cases).

Discussion
The results demonstrated the ability of the model to differentiate impingement severity in a set of cam patients. Impingement depth showed to be independent of cam location, congruent with a study using theoretical cams [3]. Whilst varying with cam location, it is unclear how impingement location mapping correlates to damage. The combination of higher impingement frequency and depth indicate greater impingement severity and potential for acetabular tissue damage.

References
COLLAGEN-MATRIX WRAP REDUCES CONTACT PRESSURE IN MENISCAL TEAR REPAIR: AN FEA STUDY.

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Introduction

Meniscal tears are one of the most common injuries to the human knee joint. To preserve the function of the knee joint and reduce the risk of degeneration due to meniscal injuries, meniscal tears need to be repaired. A meniscal suture is the most common repair method; however, suturing alone is ineffective in promoting healing in the more avascular white (zone 2-3) of the meniscus. To promote healing, suturing and wrapping with collagen-matrix techniques have been proposed to treat more complex meniscal tears, including radial tears crossing zones 0-3, defunctioning the meniscus [1]. However, there are still uncertainties about the ideal clinical management of meniscal tears, including suitable techniques for repairing menisci [2]. Therefore, the aim of this study is to evaluate the effect of meniscal repair of a radial tear using a rip-stop ‘H’ suture technique with or without the addition of a collagen membrane as a wrapping technique on the meniscus and contact surfaces using finite element analysis.

Methods

Two finite element (FE, Abaqus) models of a human knee joint lateral compartment were developed from previously published three-dimensional geometry [3]. The models comprised the femur, tibia, articular cartilage and lateral meniscus. The meniscus structure was generated to represent a radial tear (Fig 1a). FE models of the two techniques of meniscal tear repair: meniscal repair with (i) suture alone and (ii) suture and collagen-matrix wrap, were modelled (Fig 1b & c). The material properties of the components were a linear elastic for the bones, a hyperelastic Yeoh model for articular cartilage, and a linear elastic and transversely isotropic material model for the meniscus. The stiffness parameter for the suture was set as 46 N/mm [4]. The material property for the meniscus wrapped with ChondroGide collagen-matrix wrap (the green section in Fig 1c) was set as the meniscus material property with an added 30% strength. The boundary conditions allowed only one degree of freedom for 1000N load in the axial direction. Results from the repair techniques were compared by evaluating the effect of repairs on the contacting areas of the articulating surfaces, meniscus kinematics, and stress distribution around the repair.

Results

Meniscal repair with suture alone had higher local stresses and strains ($\sigma_{\text{max}} = 51\, \text{MPa}$ and $\epsilon_{\text{max}} = 25\%$) around the repair compared to the repair with suture and collagen-matrix wrap ($\sigma_{\text{max}} = 36.6\, \text{MPa}$ and $\epsilon_{\text{max}} = 15\%$) (Fig 2). Meniscus radial displacement was higher by ~2% in the suture alone meniscal repair model compared to meniscal suture with collagen-matrix wrapping. Pressure on the meniscus contact surface was higher by ~5% in the suture alone meniscal repair compared to the meniscal suture with wrap repair.

Discussion

We found that adding collagen-matrix wraps to the suture strengthens the repaired region, thus reducing the local peak stresses and strains around the suture. During high loadings and extreme kinematics conditions in the knee joint, peak stresses and strains will build up around the suture, which can result in the suture pulling out of the meniscus. The collagen-matrix wrap has a heterogenous material property reinforcing the meniscal repair region, increasing resistance to suture tear out. In our future study, we will investigate the combined joint kinematics and loading conditions in meniscal repair with wrapping techniques.

References

AN ENERGETIC ANALYSIS OF THE NON-CONTACT TONOMETRY: COMBINING NUMERICAL SIMULATIONS AND CLINICAL IMAGES

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2. Dept. of Chemistry, Materials and Chemical Engineering “Giulio Natta”, Politecnico di Milano, Italy.

Introduction

The cornea, the outermost layer of the eye, is responsible for transmitting and focusing light onto the retina. Any changes in its mechanical properties can result in visual impairment. Non-Contact Tonometry (NCT) is a clinical tool used to measure the intraocular pressure (IOP) and the mechanical properties of the tissue by deforming the cornea with an air jet and recording the deformation with a Scheimpflug camera [1][2]. The deformation is influenced by four factors: the eye’s geometry, the IOP, the pressure of the air jet, and the mechanical properties of the corneal tissue. In silico simulations of NCT can help to separate the effect of each factor. This work focuses on the system’s energy balance and the potential for combining numerical simulations with clinical images to diagnose and treat corneal diseases by characterizing the mechanical properties of the corneal tissue.

Methods

A patient-specific corneal model was created using data from the topographer Pentacam (collected at Antwerp University Hospital) and the method outlined in [3]. A Fluid Structure Interaction (FSI) simulation using the settings in [4] was conducted to replicate the action of the air jet of Corvis ST over the deformable patient-specific cornea. The energy balance of the system was analysed. The air pressure over the corneal surface (Fig. 1A) was taken out to calculate the total work of the air puff. The circumferential (Fig. 1B), radial and azimuthal stretch of the structural parts during the air puff were collected to calculate the strain energy of each component. The humors were modelled as incompressible fluids pressurized at 15 mmHg. For the same patient, the images derived from the tonometer were segmented (Fig. 2A). A Computational Fluid Dynamic (CFD) simulation was run to simulate the air jet against a moving boundary representing the dynamic deformation of the cornea as identified in the clinical images.

Results

During the NCT the work of the air puff is equal to the sum of the internal energy of the structural parts (Fig. 1C). The sclera, being the stiffest part, has the highest internal energy despite having the lowest deformation. As the humors are modelled as incompressible fluids, their pressure increases during the air puff [4] but their volume remains constant. As a result, the total work of the humors is zero.

Discussion

The energetic analysis of the NCT enables the isolation of the effect of the mechanical properties of the structural parts, independent of the influence of the IOP. The CFD analysis shown in Fig. 2B was used to calculate the work of the air puff. By measuring the work of the air puff, which is only supported by the structural parts, the proposed methodology can effectively characterize the mechanical properties of the eye tissues.

References

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Acknowledgements

This project has received funding from the European Union’s Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 956720.
REGULATORY MECHANISMS IN CARDIAC ACTIVE MECHANICS: FROM MICROSCALE MODELS TO MULTISCALE NUMERICAL SIMULATIONS

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2. Mathematics Institute, École Polytechnique Fédérale de Lausanne, Switzerland (Professor Emeritus)

Introduction
Cardiac muscle contraction is driven by subcellular processes that convert chemical energy into mechanical work. These processes are influenced by a complex network of regulatory and feedback mechanisms (e.g. calcium-driven regulation, length-dependent activation and force-velocity relationship), which play essential roles in the organ-level cardiac function (e.g. Frank-Starling mechanism). However, studying the fibers stretch-rate feedback (SRF) through numerical simulations poses numerous challenges, both at the modeling and methodological levels [1,2]. For this reason, the mathematical models proposed in the literature in the past have always - to the best of our knowledge - ignored this feedback. As a matter of fact, the effects of SRF on the overall cardiac function are still poorly understood.

Methods
We present a mathematical model of sarcomeres, based on a biophysically detailed description of troponin-tropomyosin complexes and cross-bridge dynamics. Remarkably, the model explicitly encodes the calcium-driven cooperative activation of the thin filament and the force-velocity relationship within a computationally tractable framework. We are thus able, for the first time, to simulate sarcomere contraction in a computational time that is suitable for multiscale simulations and with an explicit representation of the main proteins. Then, we propose two numerical schemes that allow to cure non-physical oscillations occurring in the numerical solution due to the presence of the SRF. These schemes address instabilities issues arising from the coupling of the microscale force generation model with the tissue mechanics and the blood circulation models, respectively.

Results
We are able to reproduce the healthy cardiac function for all the heart chambers, in terms of pressure-volume loops, time evolution of pressures, volumes and fluxes, and three-dimensional cardiac deformation, with excellent matching with cardiac physiology. Our results show that, when neglecting the SRF in the simulation, the fluxes across the semilunar valves largely exceed the physiological range. Moreover, we show that, thanks to the introduction of our stabilization terms, we are able to remove the non-physical oscillations that would otherwise affect the numerical solution.

Discussion
Our results allow to investigate the effects of the SRF on the cardiac organ-level function. This feedback, originating from the microscale force-velocity relationship of sarcomeres, reduces the active force in regions where fibers are rapidly shortening. The macroscopic effect is a homogenization of fibers shortening velocity that, from a hemodynamic perspective, results into a smoothing of the ejected blood flux. Hence, we postulate that the SRF, despite originating at the microscale, plays a crucial role in the macroscopic regulation of blood fluxes. However, if not properly managed at the numerical level, this feedback produces non-physical oscillations that may lead the numerical simulation to fail. Thus, the interplay between accurate mathematical models and efficient and stable numerical methods is of utmost importance to reproduce the heart physiology.

Figure 1: (a) Results of a four-chamber electromechanical simulations, highlighting the heterogeneous space distribution of the fibers elongation. (b) Blood fluxes across cardiac valves with and without fibers SRF.

References
BIOMECHANICAL EFFECTS OF LUMBAR MULTIFIDUS AND PSOAS MAJOR MUSCLE DYSFUNCTION ON THE LUMBOSACRAL SPINE

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Introduction

Low back pain (LBP) is a major health issue whose causes are manifold. Numerous problems are associated with a lack of core stability, altered segmental intervertebral motions, and a reduced range of motion [1,2]. Correlations with morphological and structural changes as well as weakness or contractures of the lumbar multifidus (MF) [2] or psoas major (PM) [1,3] muscles have been observed in vivo. However, methods for detecting muscle recruitment patterns and biomechanically relevant changes in the musculature in patients with LBP are limited. To improve understanding and treatment, this study aims to investigate whether changes in MF or PM in an active hybrid simulation model lead to pathological responses that are consistent with clinical observations of their role in the ethology of LBP.

Methods

We utilize a validated hybrid model of the healthy ligamentous lumbosacral spine [4] built in ArtiSynth [5]. Vertebrae L1-S1 are interconnected with hyper-elastic fibre-reinforced finite element discs, ligaments, and facet joints. The intra-abdominal pressure is considered as a force on the thorax via muscle forces acting on the abdomen. For the active model component, twelve sagittal symmetric muscle groups are implemented using 258 muscle fascicles with a Hill-type muscle model and a resting muscle tone of 0.1%. The muscle redundancy problem is solved using an inverse-dynamic tracking controller (TC) which provides a solution of the forward dynamic simulation. Values of the cost function are muscle activities squared as well as target poses of the thorax and the lumbar vertebrae. Thus, all bones cranial to the stationary sacrum are free to move. From an upright posture, the movements into different postures (-10° extension to +30° flexion) with loads of up to 20 kg held in both hands are simulated. Based on results of the healthy muscles in the respective postures, four sagittal symmetrical muscle variations are examined: Limitation of the force of PM (1) or MF (2) and increase of the resultant force of PM (3) or MF (4). For this, the upper or lower excitation limits of the TC are adjusted. All other muscles and settings are unchanged.

Results

Dysfunctions of MF and PM affect the biomechanical model results. With exception of (2), PM is not relevantly activated to a greater extent for the load cases considered. For (2) in 30° flexion, all other muscle sections of the erector spinae (ES) (Figure 1B), the lateral internal abdominal muscles, and PM are increasingly activated. This barely changes the intradiscal pressure (IDP). However, the stability of the model is reduced by extension of the settling phase when reaching the maximum deflection. The IDP increase is most pronounced in (3) (Figure 1C). The proportional increases in IDP and facet joint contact force is higher caudally. In upright standing lumbar lordosis remains almost constant, rotational compensation occurs inter-vertebrally. The intervertebral angles (IVA) increase for L2/3 to L4/5 and vice versa for L1/2 and L5/S1. Higher PM forces result in ES being more activated as well.

Figure 1: A) Active model with MF and PM highlighted in red. B) ES force change ΔF for (2) in 30° flexion C) Results for (3) in upright position without load in hands.

Discussion

The results of this study show that the simulation model used and solved with an inverse-dynamic TC provides consistent pathological model responses with PM and MF dysfunctions. These include a decrease in core stability, increased loading of lumbosacral structures, alteration of muscle activation patterns, and changes of IVA [6]. Overall, MF and PM are important stabilizers of the lumbar spine and have a low negative correlation. To further improve the validity and provide clinical relevance additional dysfunctions, personalized muscle parameters, and anatomies should be investigated in the future. One problem that remains to be solved is the consideration of the relation between pathophysiologic habits and the perception of LBP.

References

THE REASONS FOR DIFFERENCES BETWEEN 2D AND 3D ECHOCARDIOGRAPHY STRAIN MEASUREMENTS

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Introduction
Echocardiographic strain measurements can be performed in 2D or 3D. Specific patterns of discrepancy between 2D and 3D measurements are reported, but the exact mechanism for this is unclear [1]. Further, strain measurements in fetal hearts vary substantially in magnitude among different studies [2]. We aim to demonstrate possible reasons for these discrepancies.

Methods
4D echocardiography images (STIC mode) were obtained from 26 healthy fetuses at 22 and 32 weeks of gestation with IRB approval and consent. A validated cardiac motion estimation algorithm [3] was used to track the motion of fetal left and ventricles (LV & RV) and ventricular septum in 3D, and to calculate myocardial strains. 2D planar images were extracted from 3D images and quantifications were repeated in 2D for controlled comparison. Cardiac Finite Element (FE) simulations [4] were used to validate findings.

Results
2D versus 3D longitudinal strain (LS): 3D LS was found to be significantly lower than 2D LS in LV free wall (by 2% in strain magnitude) and septum (by 1.7%). This is due to LV twist, which causes out-of-plane and highly 3D motion in the longitudinal view, but in 2D, an inevitable projection to the 2D plane exaggerates myocardial longitudinal shortening (Fig 1a). FE modelling showed a significant correlation between twist magnitude and the 2D versus 3D LS error (R>0.87). The RV does not twist significant, and no 2D vs 3D LS difference was observed. This demonstrates the role of LV twist in causing this difference.

2D versus 3D circumferential strain (CS): 3D strain was found to be significantly higher than 2D circumferential strain (CS) by 3%, 3.6% and 2.5% in the LV free wall, RV free wall and septum, respectively. This can be explained by the systolic motion of heart towards the apex. This motion creates errors for 2D imaging as it introduces wider transverse cross-sections of the heart into the imaging plane, which negates contraction deformations (Figure 1b). FE results showed significant correlation between longitudinal displacement and 2D versus 3D CS error (R>0.98).

Timing Mismatch between CS and LS: Further, we observed a timing mismatch between when the longitudinal and circumferential lengths are at their peaks. The was thus no natural zero strain reference time point for 3D strain quantification, and favouring any one direction when specifying this reference will reduce strain magnitude of the other direction. For 2D quantification, strain in each direction is assigned its own zero-strain reference time point. This factor accounted for a further difference of strain 0.7-0.8% difference between 2D and 3D strains.

Discussion
2D strains have significant error, while 3D strains is more representative of cardiac physiology, and we advocate 3D strains. Our finding suggests that caution is necessary in interpreting strain results in the literature, due to several reasons for discrepancies, and that future standardization of strain measurements is necessary. Our findings in fetal echo is likely applicable to adult echo as well.

References

Acknowledgements
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Figure 1: Schematic explanation of differences between 2D and 3D LS (a) and CS (b)

Spatial variability of strains: Strains at epicardial versus endocardial locations differed substantially, accounting for 7% longitudinal and 8.9% circumferential strain magnitude differences. Since strain quantifications often require manual controls clinically, this can explain wide discrepancies between the different studies by reputable groups [2] (up to 6.3-7.1% strain magnitude difference). We further find that different smoothing extent during motion tracking can also substantially affect strain magnitudes.
DETERMINATION OF MATERIAL PARAMETERS OF SCAFFOLD-FREE CARTILAGE TRANSPLANTS IN DEPENDENCE OF THEIR CULTIVATION

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Introduction
Artificial cartilage can be investigated and characterized by biomechanical, biochemical, and histological analysis. The biomechanical properties contain a variety of relevant information for the functional characterization of cartilaginous tissue. Thus, the characterizations are usually carried out at the end of the cultivation time [1]. To better assess the maturity level of 3D scaffold-free cartilage transplants (SFCT), the article aims to identify and discuss correlations between biomechanical material parameters and cultivation conditions (time and mechanical stimulation). For this study, an optimized biphasic 3D Finite-Element (FE) modeling approach with tension-compression nonlinearity was implemented to determine the material parameters of SFCT [2].

Methods
The equine chondrocytes of the stifle joint were used for the production of SFCT. After cultivation and proliferation in monolayer cultures, cells were transferred into a three-dimensional structure without any artificial matrix, growth, or differentiation factors. In order to produce SFCT and the extracellular matrix, the samples were manually exposed to undifferentiated cyclic mechanical pressure (CMP). The duration, frequency, and intensity of pressure were determined under tactile and visual control [3]. The SFCT (n = 18) were analysed after 1 (0-fold CMP), 3 (5-fold CMP) and 6 (14-fold CMP) weeks of culturing. Chondrogenesis in SFCT was documented by macroscopic, biochemical, histological, and biomechanical analysis. For biomechanical investigations, Young's modulus E, fibre modulus $\xi$ and permeability k of samples were determined using uniaxial relaxation compression tests and a FE parameter identification routine [2]. The relaxation tests of the specimens were executed with a testing velocity of $v = 0.02 \text{ mm/s}$, an initial load of $F = 0.1 \text{ N}$, a relaxation time of $t = 3400 \text{ s}$ and a strain of 20 % [4]. For the computational approach, an optimised 3D FE-based method was developed to identify the biomechanical parameters (Figure 1a). The SFCTs were modelled with a compressible isotropic neo-Hooke's ground matrix reinforced with a spherical fibre distribution and constant permeability [2,4].

Results
For the parameter identification of SFCT, the 3D FE-model with an extended biphasic material model yields a $R^2 > 0.94$ (Figure 1b). The linear correlation results clearly demonstrate that the biomechanical parameters $E$ ($R^2 = 0.82, p < 0.05$), $\xi$ ($R^2 = 0.75, p < 0.05$) and $k$ ($R^2 = -0.74, p < 0.05$) correlate strongly with the cultivation conditions. The parameter $k$ indicates negative, the other parameters show positive correlations. Table 1 shows the calculated parameters. The Young's modulus and fibre modulus increase with increasing cultivation time and CMP, while permeability decreases.

Discussion
These results show that linear correlations between biomechanical parameters and cultivation conditions exist. Therefore, it is possible to characterize the maturity level of the SFCT. At the beginning of the cultivation time, the maturity level of the SFCT is very low. With increasing CMP and cultivation time, the stiffness of the SFCT increases and thus the maturity level. Future work will extend the correlations with parameters from the biochemical and histological analyses. Furthermore, the influence of mechanical stimulation will be analyzed in more depth. The optimized FE-model routine operated robustly. In addition, appropriate material models for SFCT will be developed and integrated in the FE-model.

References

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NUMERICAL STUDY OF MAGNETIC MICRO-BEADS STEER BY MAGNETIC RESONANCE NAVIGATION IN TUMOR EMBOLIZATION

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Introduction

Magnetic resonance navigation (MRN) of medicinal substances is gaining popularity in the treatment of liver cancer. This method relies on a cluster of particles formed by dipole-dipole interaction; the latter originates from the magnetic moments generated by the MRI scanner static magnetic field. These aggregates are then injected into the controlled blood flow where they are steered into the target branch by the combination of the magnetic gradient force and gravity.

The success of the MRN procedure depends on the aggregates shape, which determines their mobility and stability. To evaluate the latter we deploy a computational model. Prior research has only examined a few particle forces [1,3] or employed drag approximation models [1,2,3], both of which are unsuitable for clusters formed by the MRN approach. This study focuses on the issue of stability of the aggregates, which is determined by the interplay between the drag force applied on individual particles and dipole-dipole interaction.

Methods

Using the point-particle approach, a modified version of the Maxey-Riley equation [4] is used to model particle trajectories (p=particle, f=flow, m=mass, u=velocity, \(\xi\)=drag tensor):

\[
m_p \frac{du_p}{dt} = \xi(u_f - u_p) + m_f \frac{du_f}{dt} + m_f \left( \frac{D\mathbf{u}_f}{Dt} - \frac{D\mathbf{u}_p}{Dt} \right) - (m_p - m_f)g \quad (1)
\]

Where the terms on the right-hand side (RHS) represent in order drag, pressure gradient, virtual mass, gravity, and buoyancy forces. Additional forces such as gradient magnetic force, dipole-dipole interaction, and collision force also contribute to the RHS.

The dipole-dipole interaction force describes the interaction of magnetized particles and is responsible for their clustering. Dipole-dipole forces are opposed to shear forces generated by the non-uniform drag distribution across particles within the aggregate. To investigate the stability of the aggregates, the hydrodynamic forces on individual particles in the aggregate has to be thoroughly investigated, here by means of the immersed boundary method (IBM).

Results

The investigation starts with an a-priori simple case representing a chain of spherical particles oriented parallel or perpendicular to the flow direction. In fact, it represents an already challenging computational case for the IBM. The total drag is validated against experimental data and the bead-chain drag model (BDM) [5]. Fig.1(a) illustrates that even though the IBM results follow the trend of the experimental and BDM results, the IBM displays an error of ~10%. The distribution of the drag was then computed across individual particles (fig.1(b)), which demonstrates that the largest force is applied to the outermost particles, while the applied drag on other particles is much smaller. This indicates that the outermost particles of the aggregate are the loosest part of the chain.

Figure 1: (a) Comparison of experimental, BDM theoretical [5] and IBM drag coefficient values for bead-chains parallel to flow. (b) Distribution of drag force across a chain of 8 particles, parallel and perpendicular to flow.

Discussion

Preliminary results show that the immersed boundary method is suitable for determining the drag as its results are in a good agreement with the bead drag model and the experiments reported in the literature. However as the bead drag model is limited to a rigid chain of spherical particles, additional research is required to generalize the effect of the hydrodynamic force on aggregates of different shapes in a realistic arterial blood flow field.

References

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ASSESSMENT OF THROMBUS FORMATION IN ARTERIAL STENTS

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Introduction

After balloon angioplasty in arteries, stents are implanted to maintain the vessel’s dilation and ensure its patency. However, stent geometry, including the inter-strut spacing, length, and strut cross-section, affects stent-vessel interactions and alter blood flow patterns. In addition, poor stent design can increase particles residence time, create low wall shear stress and promote coagulation [1]. Furthermore, the struts could bring the risk of inflammation due to endothelial damage, intimal thickening, and thrombus formation. Assessing high risk geometrical features for thrombus formation and evaluating strategies for preventing thrombosis are essential in designing effective stents. Platelets play a crucial role in haemostasis and clot formation. They bind to the damaged endothelial cells through the processes of aggregation, activation, and adhesion. Additionally, in high shear flows von Willebrand factor (vWF), a protein that is sensitive to mechanical stress and hemodynamic forces, undergoes a conformational change to bind to collagen and platelets through A1 and A3 binding domains, respectively [2]. Thus, the combined effect of platelet activation due to collagen exposure and unfolding vWF due to hemodynamic alteration could start the thrombus formation. The aim of the current study is to quantify the mechanisms, underlie thrombus formation in stents in order to find means to prevent serious complications and maintain long-term patency.

Methods

The thrombus formation model can be described by the convection, diffusion, and reaction of biochemical agonists into a series of a coupled equations,

$$\frac{\partial [C_i]}{\partial t} + (V \cdot \nabla)C_i = D_i \Delta C_i + S_i(C_j).$$  \hspace{1cm} (1)

Where \([C_i]\) is the concentration of species \(i\), \(V\) is the velocity vector, \(D_i\) is the diffusivity of species, and \(S_i(C_j)\), are the source terms, production/consumption, for the \(i\) species. The current model of platelet-fibrin kinetics includes the features of our previously deposited bounded platelet model [3]. Concentration of un-activated platelets, activated platelets, ADP, thromboxane, prothrombin, thrombin, antithrombin, fibrinogen, fibrin, VWF folding/stretched and deposited bounded platelets are solved at each time step. Two different mechanisms for platelet activation, and adhesion are used. The gap between struts serve as a surface flux boundary condition representing a collagen surface to initiate thrombus formation. In addition, a combined effect of stretched vWF concentration and residence time on the struts are added to the model. The blood is considered as a Newtonian fluid, and thrombus considered as a porous medium. The model is implemented into FLUENT 2021 R1 (ANSYS Inc. PA) Computational Fluid Dynamics software. The computational domain consists of a 2D channel with a height of 3 mm and length of 250 mm. The simplified stent's architecture is denoted by eight unconnected squares in the model which represents cross sectional of the struts.

Results

The results of thrombus shape from our numerical 2D cartesian symmetric domain model with a parabolic velocity inlet profile, is shown in Figure 1.

![Figure 1: Visualization of velocity magnitude and the concentration of biomolecules. a) Velocity magnitude at 10 sec, b) vWF concentration at 10 sec, c) activated platelets at 10 sec, d) deposited thrombus at 200 sec.](image)

The results indicate a strong correlation between a high concentration of stretched vWF and thrombus formation at the first strut.

Conclusion

This computational model will enable identification of key factors associated with thrombus formation, resulting in new insights that are critical for guidelines to ensure patency of stents. This model accurately describes the interactions between the regulatory network of the coagulation cascade and dynamics of platelet deposition due to endothelial damage and hemodynamics.

References


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PREDICTIVE ERGONOMIC EVALUATION OF AUTOMOTIVE DIGITAL WORKSPACES

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**Introduction**

Modern-day industrial environment constantly evolves towards autonomous technological systems. Still, the human factor remains crucial. Human - machine interfaces (HMIs) are devices that enable and regulate smooth physical and cognitive interactions between humans and software or hardware systems. Therefore, a thorough evaluation of HMI designs adopting multiple criteria is imperative. In this work, we present a software framework that can be applied to perform ergonomic analysis of physical and digital prototypes using physiology-based digital twins in a simulation environment. The software was developed and tested for ergonomic evaluation of automotive HMI designs.

**Methods**

The framework is built upon OpenSim, a dedicated biomechanics software tool and is developed through Python scripting. It requires: (a) a digital twin of the assessed HMI design, (b) motion capture (MoCap) data of the user’s physical interactions with the HMI elements, and (c) a musculoskeletal OpenSim model. In cases where motion data is not available due to hardware limitations or experiment complexity, we have developed a separate module for predicting user – HMI interactions, based on the OpenSim MOCO software tool. The musculoskeletal model was scaled to represent different human body sizes based on anthropometric data acquired from the NHANES database [1]. There are two ergonomics analysis modes, namely the Static and Dynamic Posture Analysis. The former evaluates the user’s static posture at the time instant of interaction with individual elements of the HMI design and estimates three ergonomic indices depending on the task load, namely RULA, LUBA, and NERPA [2]. The latter can be applied to assess the overall user performance throughout the entire range of interactions within a given driving scenario. A collection of physics - based and anthropometric ergonomic indices is estimated, such as the Mean Torque Factor, Angular Impulse, Energy, RoM comfort factor, and RoM - torque comfort factor [3].

We assessed the capability of the predictive tool to yield similar ergonomic results compared to real MoCap data – based analysis. An appropriate scaled musculoskeletal model was selected, the HMI elements’ locations were defined, and the model’s joint angle trajectories were predicted by the tool. The real-world experiment was performed in a virtual reality (VR) setting at the VVR lab in University of Patras.

**Results**

The comparison results between the predicted and real MoCap data - based cases are presented in Figure 2 for the Static and Dynamic Analysis, respectively. These showcase minimal differences regarding Static Analysis scores and similar behaviour for the Dynamic Analysis indices.

**Discussion**

The developed system can be used to ergonomically assess digital HMI prototypes in virtual and physical environments regardless of MoCap hardware availability. Comparative analysis of multimodal HMI designs can be efficiently conducted in a simulation environment to assist manufacturers during product development phase, while reducing complexity and cost of experimental setups. The system can be further improved to be applied in an augmented reality (AR) digital twin simulation context.

**References**


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DEVELOPMENT OF AN IN VITRO PLATFORM TO DETECT TUMORIGENIC EVENTS IN HUMAN HAEMATOPOIETIC STEM CELLS (HHSCS)

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Introduction
Allogeneic haematopoietic stem cell transplant (HSCT) is a curative treatment for a number of diseases such as sickle cell anaemia, haemophilia, thalassemia and severe combined immunodeficiency. The treatments require patients to undergo lifelong pharmacological immunosuppression, and appropriate donors need to be identified to prevent adverse immune responses. In recent years, the use of gene-edited human haematopoietic stem cells (GE-hHSCs) has emerged as a solution [1]. However, gene editing can be accompanied by unwanted events that may lead to cancer [2]. For this reason, a system for efficiently detecting the generation of tumorigenic events is greatly needed.

Methods
A novel millifluidic optically-accessible bioreactor (MOAB S.r.l., Milano, Italy) [3] was functionalized with a silk fibroin scaffold resembling the physical bone marrow microenvironment and subsequently perfused with an appropriate culture medium. Human CD34+ HSCs or CD4+ lymphocytes were grown inside, alone, or in the presence of tumour cells. The expansion of specific populations was tested up to three months after culture start. In a follow-up, genetically modified CD34+ cells will be subsequently tested for the appearance of clonal expansion.

Results
Long term culture of primary, human, normal CD34+ or CD4+ cells was achieved at time-points up to three months. In these conditions, co-culture with tumour cells allowed us to detect the expansion of oncogenic events. Analytical assays, i.e. confocal microscopy and Fluorescence-Activated Cell Sorting (FACS) analyses, were optimized to efficiently detect the appearance of tumour cells. We defined a tumorigenic index of the system as the minimal number of tumour cells, loaded in the coculture system, that could be detected. As little as 100 tumour cells were clearly detected after three months of bioreactor culture. Current experiments are aiming at detecting as little as one tumour cell and/or the emergence of clonogenic CD34+ tumour cells.

Discussion
We validated an animal-free millifluidic platform, able to expand primary human cells and allow for the detection of rare tumorigenic events. The sensitivity of the system is currently being expanded by the use of state-of-the-art technologies, such as single-cell RNAseq. This model may allow the detection of rare tumorigenic events due to genetic editing in a reliable, cost-effective and animal-free setting.

References

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STRAIN RATIO DISTRIBUTIONS CAN ELEGANTLY DESCRIBE THE EFFECT OF LESION LOCATION AND SIZE IN FEMORAL METASTASES

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Introduction
The spread of primary cancer, in advanced disease, to distant organs such as bones, results in metastatic bone disease (MBD). Area effected by MBD transforms into abnormal tissue called lesion. These lesions in bones reduce overall load-bearing capacity and increase the risk of a fracture. The fracture risk is clinically undertaken using the Mirels’ score system [1]. Recently, CT-based finite element (FE) analyses have been used to evaluate risk. The process involves developing FE models from a patient’s CT scan and using the ratio of the absolute maximum principal strain in the diseased femur and the median strain in the same anatomical region of the disease-free femur [2]. These approaches do not provide a guide as to how location, size and growth of lesion, influence fracture risk. This study employs an automated process with the aim to provide a framework for holistic risk evaluation using strain ratio distribution over the entire diseased femur.

Methods
We have developed an automated process for conducting biomechanical analysis on computational models of a femur. Currently, the analyses are linear elastic and employ tetrahedral finite elements with four integration points. The nodes on the proximal condyles are linked to a single point representing Hip Joint Centre (HJC) while the nodes on the distal condyles are linked to a single point representing Knee Joint Centre (KJC). The model is subjected to varying physiological boundary conditions at HJC and KJC. Through an automated process, spherical cavities of different diameters and at different locations are created to represent a lesion. The analysis is undertaken for the disease-free femur repeated after the introduction of lesions. To reduce discretization error, identical meshes are used for both diseased and disease-free models (with the exception of the lesion). Thus the location of the integration points for both the models are identical. Equivalent strain at integration points is evaluated for both the diseased and disease-free femurs and the distribution of equivalent strain ratios (ESR) calculated at identical integration points across the femur used to describe the effect of the lesion.

Results
For the purpose of demonstration of the proposed automated process, standardized fourth generation Sawbones femur model is used with loads representing single legged stance [3]. Sample strain ratio distribution plots are shown in Figure 1 which describe their effect on femur as the location of lesion changes medial to lateral.

Figure 1: Strain Ratio distributions around 8mm diameter lesion with varying location, anterior view

We have also examined the effect of lesion size and cortical destruction using this automated process. We have also used the automated process to create animations of describing effects of lesion.

Discussion
The proposed automated process is capable of providing ESR distribution on the entire femur for lesion of any size and location. As strain ratios are scalar, their use appears to be more theoretically sound in comparison to recently publish work using principal strain ratios. By using this process sensitivity analysis can be conducted to evaluate the effect of lesions at different locations and of different sizes, with and without cortical destruction on entire femoral structure.

References

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VALIDATION OF A DATA GLOVE CALIBRATION PROTOCOL IN HAND OSTEOARTHRITIS PATIENTS

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Introduction

Data gloves are one of the most popular hand motion capture systems for manipulation tasks, providing accurate data when properly calibrated [1]. Although manufacturers specify that the glove has to be calibrated for each subject, an across-subject calibration protocol was developed in [1] to speed up the capture process. The protocol requires: (i) obtaining subject-specific (SS) gauge gains and cross-coupling correction factors to a set of subjects with varied hand size, and (ii) computing across-subject (AS) gains/correction factors as the average of the SS ones. Using the AS gains, motion capture for each new subject only needs recording a reference posture to compute anatomical angles. This protocol was validated for healthy participants by comparing results with a videogrammetric technique as a gold standard. Here, its validity for subjects with pathologies causing joint deformities, such as hand osteoarthritis (HOA), will be studied by means of comparing the joint angles obtained from using the AS gains obtained from healthy hands against those from using the SS gains of the HOA patients.

Methods

Two HOA patients volunteered to participate in the experiment, approved by the university ethics committee. The participants wore a CyberGlove data glove recording 16 degrees of freedom (DoFs) at 100Hz while following the glove calibration protocol [1], which consists in 44 recordings: static postures (to obtain gauge gains) and controlled movements (to apply kinematic cross coupling corrections). Furthermore, 5 additional static postures (Fig. 1) were recorded in order to study biases in joint angles.

Results

Mean biases and SD obtained for each DoF in HOA patients are presented in Fig. 2, along with biases obtained for healthy participants in [1]. Mean biases were higher for HOA patients in almost all DoFs, being all of them < 10º, except for CMC1_F (11.77º). Furthermore, patients reported difficulties for performing one of the calibration trials consisting of closed loop motions made between index finger and the thumb, repeatedly flexing and extending both digits while maintaining tip contact, used for thumb carpometacarpal calibration.

Discussion and conclusions

The obtained biases in HOA patients are acceptable despite the joint deformity and swelling. Moreover, the higher bias in CMC1_F is hypothesised to be due to patient difficulties in performing one of the calibration trials, which reinforces the suitability of the AS calibration in HOA patients, since it avoids the recording of difficult controlled movements whilst providing good accuracy.

References


Acknowledgements

DEVELOPMENT AND MECHANICAL EVALUATION OF AN INNOVATIVE DEVICE FOR SOFT TISSUE REPAIR

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Introduction
Tendon injuries represent one of the most widespread soft tissues lesions. Tendon injuries may arise due to acute sport activities, traumatic lesions or because, over the years, the tissue becomes more prone to degeneration [1]. Despite the high incidence rate of these lesions, current traditional solutions as sutures threads present several drawbacks and limitations, leading to suboptimal clinical outcomes. The main causes of failure are suture’s rupture, excessive scar tissue formation, and adhesions that lead to a reduction of the Range Of Motion (ROM) of the involved joints [2]. To overcome all the issues related to the use of traditional techniques, a new implantable device has been created. The innovative device concept involves a specific geometry that allows a uniform distribution of the stress field and a biocompatible and biodegradable material created ad hoc [3]. This work aims to demonstrate the correct mechanical response of the above-mentioned device.

Methods
For the mechanical evaluation of the device, numerical and experimental tests were performed on the assembly device plus tendon Figure (1). The numerical tests involved the simulation of a uniaxial tensile test, with the aim of analysing the mechanical response of the device, the distribution of the stresses on the tendon and on the surfaces of the device. The analysis was performed considering a nonlinear constitutive law for the tendon tissue and the device material.

Results
For the experimental evaluation some uniaxial tensile tests were performed employing samples of Achilles Swine tendons, by practicing a complete laceration of the cross-sectional area of the tendon and implanting the biodegradable device.

Discussion
The experimental and numerical tests showed promising results, allowing to demonstrate the correct functioning of the implantable device. Further steps will involve the validation of the technology in a relevant environment, testing the device on cadaveric models.

References

Acknowledgements
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FEASIBILITY OF BONE-LIKE PROSTHESES USING A PARAMETRIC TRABECULAR BONE MODEL AND DEM SIMULATIONS

Nicolas Rogalski (1), Ivan Iordanoff (2), Jérémie Girardot (2), Christophe Cluzel (3) & Sébastien Laporte (1)

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Introduction
To avoid stress shielding for titanium alloy prostheses, lattices can be used to reduce the apparent stiffness [1]. However, these lattices do not consider the physiological geometric anisotropy of the surrounding bone, which prevents optimal stress distribution. In this study, we numerically investigate the feasibility of biocompatible titanium alloy prostheses allowing osteointegration while respecting the geometric anisotropy of the bone, using a parametric model.

Materials and methods
Trabecular bone samples
From scanner images of 163 samples of bovine femoral trabecular bone, the preferred orientations of plates and rods were computed [2].

Parametric model
A parametric model was used to randomly generate cubic samples of synthetic bone, using a bone volume fraction (BV/TV) and the calculated preferred orientations as input data.

Discrete Element Method (DEM) simulation
The generated samples were used as computational domains in compression DEM simulations. The BV/TV was adjusted in the parametric model to maintain an apparent elastic modulus for bone and titanium alloys constitutive properties (Table 1), keeping the main orientations. The classical Ti-6Al-4V alloy was used, as well as a low modulus Ti-33Nb-4Sn alloy [3].

<table>
<thead>
<tr>
<th>Constitutive Material</th>
<th>Density (Kg. m⁻³)</th>
<th>Young’s modulus (Gpa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>1800</td>
<td>5</td>
</tr>
<tr>
<td>Ti-6Al-4V</td>
<td>4400</td>
<td>110</td>
</tr>
<tr>
<td>Ti-33Nb-4Sn</td>
<td>4400</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 1: Constitutive properties of bone and titanium alloys.

Feasibility area
The pore size obtained for the generated structures in alloys (Tb.Sp) was then plotted against the BV/TV of the bone sample (BV/TVbone). to estimate the range of physiological volume fraction required for a biocompatible material to be used while maintaining the elastic properties of the sample.

Results
The Tb.Sp as a function of the BV/TVbone for the 163 bone samples is shown in Figure 1 (A). Two synthetic structures are also illustrated in Figure 1 (B).

Discussion
A pore size limit of 1000 μm allows cell proliferation on the implant, its vascularization and the movement of waste and nutrients [1]. The large difference in elastic modulus between bone and Ti-6Al-4V makes it impossible to obtain samples with a pore size below 1000 μm. Recent research to propose low Young’s modulus titanium alloys allows however to generate samples of same modulus and required pore size. Figure 1 (A) can then be used to map the compatible bone areas according to their bone volume fraction to go from the generated samples to complete prostheses (between 0.3 and 0.5 approximately, which corresponds to dense areas in the femur). This study is limited to the elastic behavior, but the post-rupture and fatigue behavior of the samples should be analyzed. However, it illustrates the feasibility of structures maintaining physiological elastic properties and anisotropy directions, using a biocompatible alloy.

References
AN UNCERTAINTY QUANTIFICATION OF IN-SILICO TRIALS FOR THE USE CASE OF NON-UNION TREATMENT

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Introduction
Virtualization and in-silico trials in the clinical context offer numerous advantages and will be a useful addition to today’s established methods. Firstly, they are faster and more cost-effective. Secondly, they are safe and do not put human subjects or animals at risk. Additionally, in-silico trials allow for infinite variations in simulation conditions and parameters, enabling a comprehensive exploration of different scenarios especially if they are not feasible for ethical or legal reasons. Finally, in-silico trials are a valuable tool for data analysis and modeling, providing insights into the underlying mechanisms and processes. Nevertheless, simulations are subject to many factors that affect reliability and accuracy, and an understanding of these factors is necessary to evaluate results and to address their limitations.

Methods
The basis of the simulations for the in-silico trial and the uncertainty quantification is our established workflow consisting of model generation by segmentation of clinical imaging data combined with a musculoskeletal simulation based on the patient's motion capturing data, cf. [1]. Based on the collected patient data, new data sets are generated by varying the identified parameters and their influence on the results is analyzed. Thereby, the main outcome variables are local fracture gap mechanics, cf. [2] and implant stress. The varied parameters in the geometry and model generation, respectively, are the mesh fineness and the advantages of adaptive meshing to avoid local geometric singularities, as well as the mapping of the grayscale values from the CT data to local bone material properties. For the biomechanical simulations, a stochastic concept was chosen for the application of the boundary conditions in order to vary both the magnitude of the applied forces and their direction. This reflects different possibilities for performing individual movements and allows conclusions to be made about the probability of healing, cf. [3]. To generate new data sets, bones from a statistical bone model are augmented with fractures generated in a free-form software and virtually treated with CAD-based implant models. These virtually generated data sets are then also assigned with boundary conditions using the stochastic concept.

Results and Discussion
Within the framework of our concept for the generation of virtual data sets and associated boundary conditions, simple models of fractured bones with a corresponding treatment can be generated. These models are provided with stochastically applied boundary conditions and simulated. This allows to analyze the generated models under realistic motions and to make conclusions about possible healing potentials. The major advantage of this concept is the analysis of real and virtual patient data sets under motion sequences that could not be reflected in a clinical trial. For example, one can virtually test different partial weight-bearing recommendations for lower extremity injuries and get an indication of what this would mean for a patient. The same is applicable for different loading scenarios or rehabilitation exercises for the upper extremity. Figure 1 illustrates the overall framework, musculoskeletal simulations, stress-strain distribution of implant and fracture gap, material parameter identification via calibration phantoms and different meshing strategies.

Figure 1: Illustration of our implemented simulation workflow: musculoskeletal simulation based on patients’ motion capture data, finite element simulation of a treated fracture of the humerus, segmented bone from a CT scan with a six-rod calibration phantom and a adaptive meshing example representing a fracture in higher resolution.

References

Acknowledgements
This work was supported by the German Federal Ministry for Science and Education (BMBF) under the grant “VirtuS” (FKZ: 13GW0572).
Missing muscle excitations prediction during walking through a muscle-synergies based calibration method

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Introduction

Surface electromyography (sEMG)-driven models are a powerful tool for personalized rehabilitation protocols. However, their use outside of laboratory settings remains hampered due to the high number of required sEMG signals [1]. Muscle synergy analysis has been proposed to predict unmeasured muscles excitations from the measured signals [2]. Nevertheless, as best of authors’ knowledge, the reliability of a calibrated muscle-synergies approach to predict unmeasured muscles excitations, considering few sEMG recordings as muscle primitives, has not been previously investigated.

Methods

The sEMG data of 4 healthy individuals (age = 60.0±2.1 years, BMI = 26.7±4.1 kg/m²) have been recorded during walking. The electrical activity of the gluteus medius and maximus, adductor longus, tensor fasciae latae, sartorius, bicep femoris, semitendinosus, rectus femoris, vastus medialis and lateralis, gastrocnemius lateralis and medialis, soleus, peroneus longus and tibialis anterior was collected. Fifteen trials for each subject were divided into a calibration set (10 trials) and a test set (5 trials) after being filtered with standard procedures and normalized to the maximum value over all the trials [3]. Firstly, the calibration set was used to extract the muscle synergies primitives ($W_{k,c}$) and weights matrix ($H_{k,c}$) through non-negative matrix factorization methods, $k$ was the factorization number and varied between 2 and 6 and corresponded to the number of muscle synergies used. The root mean squared difference between the experimental excitations and $W_{k,c}$ was used as metric to determine which subset of $k$ sEMG better resembled $W_{k,c}$ ($\tilde{W}_k$), while a scale factor was defined as $S_{\tilde{W}} = \text{mean}(W_{k,c})/\tilde{W}_k$. The average of each $H_{k,c}$ for all the calibration trial was considered as subject-specific weights matrix ($\tilde{H}$). Then, for each trial of the test set, the same muscles defined in $\tilde{W}_k$ were selected as “measured” sEMG signals ($\tilde{W}_{k,T}$) while the others were treated as “unmeasured”. $\tilde{W}_{k,T}$ was then multiplied by $S_{\tilde{W}}$ and $\tilde{H}$ to reconstruct the complete set of muscle excitations ($\tilde{W}_{k,T}^{*}C^{*}\tilde{H}$). The actual trial-specific primitives ($W_{k,T}$) and vector of weights ($H_{k,T}$) have been extracted and used to predict the muscle excitations ($W_{k,T}^{*}H_{k,T}$) with the one obtained with the proposed method. The variance accounted for (VAF) was used as metric to compare the performance against the experimental excitations.

Results

In Figure 1 the experimental muscle excitations against the predicted ones using 5 muscle synergies are reported as example. High values of VAF are reported in Table 1 for both methods, suggesting an accurate prediction of the experimental measures.

![Figure 1: Muscle excitations of the 4 subjects (average of the test trials ± 1 standard deviation). In black the excitations reconstructed via muscle synergy analysis (5 primitives), in red the excitations reconstructed via the proposed method (5 muscles excitations as primitives).](image)

<table>
<thead>
<tr>
<th>Synergies</th>
<th>VAF t</th>
<th>VAF p</th>
<th>p-value</th>
</tr>
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<tr>
<td>2</td>
<td>.987 ± .005</td>
<td>.964 ± .011</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>3</td>
<td>.993 ± .003</td>
<td>.977 ± .008</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>4</td>
<td>.996 ± .003</td>
<td>.978 ± .008</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>5</td>
<td>.998 ± .001</td>
<td>.986 ± .004</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>6</td>
<td>.999 ± .001</td>
<td>.984 ± .005</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Table 1: Average VAF as total of each considered muscle for the two different methods (VAF t standard; VAF p proposed) to reconstruct the experimental muscle excitations.

Discussion

The reliability of the proposed method to track the “unmeasured” excitations was assessed. This could be pivotal in the creation of reliable iHealth sEMG-driven models considering a minimal experimental setup transferable in daily living conditions where the major requirements are a reduced number of sensors and the maintenance of a reliable characterization of the research subject’s neuromuscular status.

References

MUSCULOSKELETAL MULTIBODY SIMULATION OF PAEDIATRIC PATIENTS BEFORE AND AFTER FEMUR OSTEOTOMY

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Introduction
Severe rotational malalignment of the lower extremity of paediatric patients can lead to increased joint loads and non-physiological gait patterns and, therefore, to symptoms such as premature osteoarthritis [1]. One surgical treatment option is to perform derotational osteotomies [2]. The corrected bone position is expected to lead to an improvement of the gait pattern as well as a reduction of joint loading [3,4]. Experimentally capturing the joint loads of the lower extremities of children is complex and invasive. By means of software based musculoskeletal multibody simulations (MMBS) biomechanical data of joint dynamics based on gait analysis can be derived [5]. Because of the lack of data regarding joint loads of paediatric patients with rotational malalignment, the aim of our present study was to generate a MMBS model to simulate paediatric patients before and after osteotomy using 3D gait analyses as input to evaluate joint dynamics.

Methods
The pre-/postoperative gait of two patients of a similar age (patient1: 26/28 kg, 134/142 cm; patient2: 32/44 kg, 138/147 cm) treated with intertrochanteric osteotomy were simulated. Marker trajectories and ground reaction forces were captured with a motion capturing system collecting data from 21 skin markers and 3D force plates. A generic model of the lower limb [6] in AnyBody (Anybody Technology, Denmark) was used to calculate joint angles and loads. This model comprised six degrees of freedom per lower limb. On this basis, the model was adapted to the individual patients by integrating the marker data and scaling of segment dimensions based on that data. Precisely, scaling was performed according to the height and weight of each patient. Subsequently, inverse kinematic and inverse dynamic analyses were performed to calculate joint angles and forces during the gait.

Results
Within the generated MMBS model we simulated paediatric patients with rotational malalignment, before and after osteotomy, showing differences in joint angles up to 20° and resultant joint forces up to 2.5 times body weight (Figure 1).

Discussion and Outlook
The joint dynamics of paediatric patients with rotational malalignments have been insufficiently investigated so far [5]. For this reason, we adapted an existing MMBS model to simulate the gait of two paediatric patients before and after osteotomy, successfully calculating joint angles and loadings. In future studies, more patients and healthy subjects will be simulated to allow statistical comparison. The results of these simulations will also be used as boundary conditions for finite element analyses of the femoral bone.

References

Acknowledgements
This work was supported by the German federal ministry of education and research (BMBF), grant 13GW0293G.
ENZYMATIC DIGESTION OF TENDONOUS COLLAGEN SHOWS HIGH SPECIFICITY AT THE LEVEL OF THE INDIVIDUAL FIBRIL

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Introduction
Collagen fibrils (CFs) are the structural foundation of many tissues in the human body. Nevertheless, CFs are continually remodeled, through breakdown by enzymes, such as Matrix Metalloproteinases (MMP), and formation of new CFs, Supposed mechanisms by which MMPs break down CFs have up until now mostly been explored from the perspective of molecular simulations or whole tissue level experiments. Variability in CFs is consequently often ignored or assumed to be negligible. This study demonstrates how the breakdown of tendonous CFs can be observed at the level of the individual fibril via atomic force microscopy (AFM). Our findings reveal significant variations in the behavior of individual CFs during digestion that cannot be explained through existing molecular models of collagen structure [1] or MMP digestion [1,2].

Methods
Mouse tail tendon CFs (WT, female, 6 months) were prepared on rectangular cover slips that were equipped with dental silicon fluid cells. For digestion, CFs were incubated in a buffer solution (25 mM HEPES, 2mM CaCl2, 50 mM NaCl) containing 20 nM of activated MMP-1 at 37°C for 5 hours. Fibril topography data were collected with an AFM (Nanowizard 3, Bruker-JPK). Images were taken in dry state (tapping mode) in 20 μm x 20 μm regions of interest (ROI) with a resolution of 1024x1024 pixels using a rectangular cantilever (Nanosensors PPP-NCHR, f=330 kHz, k=42 N/m) before and after incubation in the digestion solution. For analysis, a custom Matlab script was used. First, AFM images were flattened followed by semi-automatic segmentation and classification of individual CFs (N = 414). Metrics like the CFs’ height at the apex, their aspect ratio and cross-sectional area were then retrieved from the segments and individually compared between the before and after images.

Results
Analyzing the digestion behavior of over 400 individual CFs reveals that neither damage, nor fibril size are reliable predictors of partial or full digestion, as can be seen in Figure 1. Though CFs that were classified as partially damaged had an overall higher chance of being digested, there were many that remained unchanged, despite visible damage. The only type of fibril that was consistently digested was the one described as fully ruptured, exposing a typical zig-zag pattern (see [3]).

Discussion
Previous research on collagen digestion has primarily focused on either large-scale examination of bulk materials or molecular-level analysis of low concentrations. This study, however, reveals that there are intriguing mechanisms to be uncovered by studying individual CFs at the scale of full digestion.

A core limitation of our approach is the fact that our ROIs do not cover the full lengths of individual CFs. While this will obscure the demarcation between the classes of intact/partially damaged CFs, the fact that we also observed many partially damaged CFs that were not digested despite offering many possible MMP-1 binding sites suggests that there must be a different mechanism at play.

References

Acknowledgements
The authors gratefully acknowledge funding of this work through the Vienna Science and Technology Fund (WWTF) – Project LS19-035: Combined optical single molecule and atomic force microscopy to elucidate enzyme-induced collagen degradation kinetics.
IN-SILICO APPROACH TO ELUCIDATE THE PATHWAYS LEADING TO PRIMARY OSTEOPOROSIS: AGE-RELATED VS. POSTMENOPAUSAL

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Introduction
Primary osteoporosis (OP) is the most common form of OP and includes gonadal insufficiency-related OP (type I), such as postmenopausal osteoporosis (PMO), and senile OP (type II), also called age-related OP (ARO). Understanding the etiology of the disease and in particular discerning which factors are intrinsic to ARO and which are intrinsic to PMO is key to treatment design, since both can concur in postmenopausal women but only some can be counteracted by medication. We have implemented a previously developed bone cell population model (BCPM) of bone remodeling [1] to analyze the effect of all those factors. The comparison between the clinical results of bone loss observed in men and women with age [2] and the in-silico results of the simulation of ARO (for men) and ARO+PMO (for women), was used to elucidate the importance of each factor independently or in conjunction with others.

Methods
The BCPM developed by Martin et al. [1] (see Fig.1), has been implemented and modified to consider the effects of ARO and ARO + PMO.

Fig. 1: Scheme of the bone cell population model.

Regarding ARO, the literature suggests: (1) a gradual increment of sclerostin production with age [3] and (2) a decrement of concentration of TGF-β (transforming growth factor beta) within bone matrix [4] as the cause of bone density loss (BDL). For PMO, three factors were discussed in the literature to produce BDL as a consequence of the drop of oestrogen after menopause: (3) increment of RANKL expression, (4) increased RANK responsiveness of osteoclasts, (5) decrease of OPG secretion by osteoblasts [5]. These effects have been modelled using a linear function of time in the case of sclerostin increase and bilinear functions of time in all other cases. The results of the BCPM were fitted to the clinical data of BDL corresponding to men (ARO) and women (ARO+PMO) [2] using a gradient-based optimization algorithm, so obtaining the temporal functions of the five factors that minimized the error between the clinical and the in-silico results.

Results
Fig.2 shows the best fit of the model to the clinical data.

Fig. 2: Comparison of in-silico and clinical results [2].

Discussion
The proposed BCPM was able to reproduce the clinical results of BDL for both men and women. Here, we hypothesized that BDL due to ARO is similar in men and women, since ARO is caused by a decrease in androgens and estrogens respectively, and both processes have a similar effect on sclerostin and TGF-β [6]. Moreover, the increase of sclerostin explained BDL in ARO better than the decrease of TGF-β. In PMO, the three effects suggested in the literature produced equivalent results in our BCPM model in terms of BDL, although it is likely that they affect other biological processes whose effects are not considered here.

References

Acknowledgements
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**Introduction**

Percutaneous approaches allow for minimally invasive treatment of structural heart diseases by implanting devices through a catheter that is inserted from a peripheral access into a blood vessel and driven to the intracardiac target structure. These approaches reduce convalescence time and surgery risks. However, these do not allow for direct vision of the catheter nor of the relevant anatomical structures, leading to the need for x-ray fluoroscopy to monitor the catheter. The use of x-ray fluoroscopy, and the associated risk for patients and operators, would be reduced if an alternative monitoring technology was available. To this aim, we propose the use of a sensorized catheter, the real-time simulation of its interaction with the relevant vessels as reconstructed from pre-operative imaging, and the rendering of real time results through mixed reality (MR) allowing for intuitive and ergonomic analysis of the model.

**Methods**

**Catheter sensorization** The distal tract of a catheter was equipped with fiber bragg grating (FBG) and electromagnetic (EM) sensors yielding the time-dependent (frequency=25 Hz) 3D position of 71 points homogeneously distributed (gap=8 mm) over the axis of the catheter [1].

**Vessel model** The 3D anatomy of the right femoral vein and the inferior vena cava of an adult male were reconstructed from CT scans. The anatomical model was embedded in a bounding box representing a linear elastic continuum (elastic modulus=1 MPa, Poisson ratio=0.3) mimicking the deformable constraint of the adjacent organs (Fig. 1).

**Numerical simulation** was developed in the open source *Sofa* framework [2]. Upon registration between the sensors reference frame (RF) and the vessel model RF, the virtual avatar of the catheter was defined as a series of 71 rigid spheres with 4 mm radius, equal to the cross-sectional radius of the catheter. These were displacement-driven based on the time-dependent data yielded by the sensors. To model catheter-vessel interaction, a collision model was implemented: the catheter was represented by a curvilinear cylinder fitting the 71 spheres. Contact between the cylinder lateral surface and the vessel wall was modeled by a Lagrangian Multiplier approach.

**MR interface** was implemented in Unity® and visualized through a Hololens™ 2 headset.

**Dataflow** from the sensors to computational model and to the MR interface was handled by ROS publisher/subscriber communication protocol, leveraging on ad hoc bindings and Unity® plugins.

**Preliminary in vitro benchmarking** was performed on a physical silicone replica of the vessel, included in a setup allowing for RF calibration and stereo-acquisition of markers on the wall of the vessel through high-speed cameras. The real sensorized catheter was inserted in the silicone phantom, and their physical interaction was simulated through the implemented modeling approach. The computed vessel wall displacements were compared vs. the 3D displacements of the real vessel wall reconstructed from stereo acquisitions.

![Figure 1: Vessel model and bounding box.](image)

**Results**

20 test simulations were run on a state-of-the-art laptop. All converged and were stable; their real-time performance depended on the number of contact interactions, resulting in an update frequency of the MR rendering ranging from 25 FPS to 7 FPS. In the in vitro benchmarking, vessel wall displacement was computed with an average error of 1 mm.

**Conclusions**

The proposed framework consists in a simulation that computes the deformed configuration of the vessel by updating in real-time the shape and position of the catheter as provided by the sensors. The 3D data are streamed to Hololens™ 2 which allows the holographic display. The frame rate is not high enough to define the simulation interactive so further efforts are required to optimize the computation of the contact response. Future studies will be focused on the GPU implementation of the strategies adopted in this work and on the validation in an experimental set-up.

**References**


**Acknowledgements**

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INVESTIGATING CERVICAL COLLAR DESIGN AND FIT: INTERFACE PRESSURE AND DISCOMFORT

Laurence Russell (1), Liudi Jiang (1), Davide Filingeri (1), Peter Worsley (1)

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Introduction

Cervical collars form part of the standard immobilization procedures for patients with a suspected cervical spine injury. However, several issues with their use have been identified [1]. Where the collars provide mechanical constraint to movement, there is a risk of soft tissue damage from prolonged pressure and shear loading. In addition, an altered microclimate can increase susceptibility to damage. The literature evaluating collar designs predominantly consists of observational studies and one-to-one comparisons between collars. Observational studies, reporting pressure ulcer incidence, have identified that time in a collar is a significant predictor of risk [1]. Some studies have compared the interface pressure and range of motion between collars, demonstrating significant difference between designs and materials [2]. The implications of poor design and fit of cervical collars on skin health have not been thoroughly investigated. This study aimed to evaluate four popular cervical collars against several bioengineering measures previously used for evaluating medical device interfaces and pressure ulcer risk.

Methods

A convenience sample of 25 participants was recruited for a randomized cross-over trial. Participants were randomized to two of four cervical collars commonly used in the emergency and rehabilitation settings (Miami J, Stiffneck, Philadelphia, Aspen Vista). Participants donned the collars in a supine position for 20 minutes. Interface pressure was measured at four locations (occiput, right/left mandible, chin). Microclimate was evaluated with combined temperature and humidity sensors at the device skin interface at three locations. Skin hydration and trans-epidermal water loss were measured under the chin before and after applying the collar. 3D scans were taken of each participant with and without the collars in situ, to estimate neck geometry measurements.

Results

Interface pressure was significantly higher at the occiput than at other locations for the Stiffneck, Philadelphia, and Aspen Vista collars (Figure 1). The Miami J collar showed little variation between measurement sights, indicating a more even interface pressure distribution. Interface pressure at the occiput was significantly higher for the Stiffneck collar compared to the other three (p < 0.05). This agrees with previous studies comparing the Stiffneck to the Aspen Vista [3].

Several participants experienced very low pressure at the chin (n = 4). Additionally, participants reported areas of concentrated pressure at different locations along the jaw and chin. This was observed to be due to differences in shape between the participant’s jaw and the collar chin rest. Indicating that variability in head geometry contributes to the distribution of interface pressure.

Participant-reported discomfort was significantly higher for the Stiffneck collar (p < 0.05). Although not statistically significant, higher discomfort was reported for the Philadelphia collar compared to the Miami J and Aspen Vista (p = 0.06 and p = 0.07 respectively).

Humidity was significantly higher for both Stiffneck and Philadelphia collars than Aspen and Miami J (p < 0.001). No significant difference was found between the Stiffneck and Philadelphia or Aspen and Miami J.

Discussion

This study identified significant variability in interface pressure distribution and evidence that this varies with head shape and size. Future analysis of this data set will evaluate the contribution of anthropometric differences to each experimental variable. This is a feature that has not been investigated in the current literature. Further investigation is warranted to fully understand the significance of anthropometric variability on collar fit and pressure ulcer risk.

References


Acknowledgements

This work was supported by the UK Engineering and Physical Sciences Research Council (EPSRC) grant EP/S02249X/1 for the Centre for Doctoral Training in Prosthetics and Orthotics.
PRESSURE DISTRIBUTION AT THE DEVICE SKIN INTERFACE OF A CERVICAL COLLAR: FINITE ELEMENT AND PHYSICAL MODELLING

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Introduction
Cervical collars form part of the standard immobilization procedures for patients with a suspected cervical spine injury. However, several issues with their use have been identified [1], including the risk of pressure ulcers from prolonged mechanical loads at the device-skin interface. Interface pressure is the standard for evaluating the mechanical conditions between devices and the skin. However, it is difficult to get a complete evaluation of interface pressure from in vivo studies. Measurement systems are mostly limited to discrete points or small regions of interest. To get a better understanding of the pressure ulcer risk, it is important to evaluate the distribution of pressure across the whole interface and to evaluate the internal stress and strain values in the skin and sub-dermal tissues. Several studies have successfully used finite element modelling to evaluate the device skin interactions [2]. However, to date cervical collars have not been thoroughly investigated. This study aimed to model a generic cervical collar design over an area of skin at risk of ulceration using a finite element model. The predicted mechanical conditions at the device interface were corroborated with physical model bench testing.

Methods
A physical model measured tension in the lateral straps and interface pressure at points across the collar back panel (Figure 1). The physical model consisted of a composite shell with a silicone skin layer matching the shape of a medium NIOSH head. The finite element model consisted of the back of a generic collar modelled as an 8 mm thick oval with second-order hexahedral elements (E = 0.5 MPa, ν = 0.4) (FEBio, USA). The head was modelled from surface scans of the physical model as a rigid surface. Displacements applied to the sides of the collar represented the applied strap tension.

Results
Table 1 compares the strap tension and interface pressures between the physical and finite element models.

<table>
<thead>
<tr>
<th>Test</th>
<th>Strap Tension [N]</th>
<th>Interface Pressure [mmHg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Test (Miami J)</td>
<td>9.9</td>
<td>36</td>
</tr>
<tr>
<td>Physical Test (Philadelphia)</td>
<td>9.9</td>
<td>88</td>
</tr>
<tr>
<td>FE Model</td>
<td>10.2</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 1: Physical and finite element model strap tension and maximum interface pressures.

Discussion
The finite element model corroborated with expected maximum interface pressures at a normal loading tension, measured with the physical model. Areas of high pressure observed in the finite element model match those identified as high risk in the literature [3], corresponding to the occiput. By using a combination of physical and finite element modelling a better understanding of the biomechanics at the device skin interface can be established. This work has demonstrated that pressure distribution can be evaluated for a generic collar design. Future work will develop finite element models specific to popular collar designs. In addition, population-based variations of head and neck shape will be included in parametric studies of collar design.

References

Acknowledgements
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THE EFFECT OF PROGRESSIVE HERNIATION ON LUMBAR INTERVERTEBRAL DISC SIX DEGREE OF FREEDOM MECHANICS

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Introduction
Irreversible changes in disc structure caused by compressive overload towards progressive herniation can alter six degree of freedom (6DOF) mechanics. These changes alter how the disc withstands loads and may leave the disc more susceptible to herniation or other injuries. Studies have shown that disc injuries can alter the disc’s mechanical response and may also be a predictor of herniation [1-2]. However, there are no studies on the progressive mechanical changes in the disc leading up to herniation. This study aimed to compare changes in disc mechanics leading up to and after herniation under combined flexion and axial rotation, followed by compressive overload.

Methods
Initial 6DOF mechanics from intact sheep lumbar segments (L2-L3, n=9) were measured in a hexapod robot using an established standardised testing protocol [3]. Specimens were then randomly assigned into one of three compressive overload displacement groups: 1, 2, or 3 mm. Prior to overload, specimens were postured at 13° flexion and 2° left axial rotation with no initial compressive displacement applied. After posturing, each group of specimens were loaded to their respective compressive displacements at 400 mm/min. Finally, the same 6DOF testing protocol was repeated. Differences in 6DOF stiffness and phase (a measure of energy absorption), before and after loading, within each group were assessed using repeated-measures ANOVA with a statistical significance of p<0.05, with marginal significance defined as 0.05<p<0.07. The presence of disc herniation was determined visually.

Results and Discussion
Disc failure occurred with increasing compressive displacement (Figure 1). Herniation was confirmed in two-thirds of specimens in the 2- and 3-mm groups. For the 1 mm group, stiffness in anterior shear and flexion significantly decreased and marginally decreased in left lateral shear and right axial rotation (Table 1). Phase for the 1 mm group increased in flexion, and right/left lateral bending. Specimens in the 2 mm group had decreased stiffness in flexion and right axial rotation, and increased phase in flexion, left lateral bending and right axial rotation. In the 3 mm group, stiffness decreased in posterior shear, flexion, left/right axial rotation. For the 3 mm group, phase increased in all DOFs except for anterior shear and right lateral bending, and marginally increased in posterior shear.

Figure 1: Failure curves of specimens loaded to 1 mm (red), 2 mm (blue), or 3 mm (green).

Table 1: Stiffness and phase p-values from before vs after loading data. Green: significant difference; yellow: marginal significance; red: no significance.

Compressive overload influenced disc mechanics in all groups where either stiffness or phase, or both, were significantly affected. It is possible that although observable macroscopic changes may not be present, particularly in the 1 mm group, microstructural changes altered the macro mechanics of the disc.

Conclusion
This research is ongoing, and although the present sample size was small and visible herniation did not occur in all specimens, significant disc mechanical changes occurred. These findings may be used as mechanical indicators of early-stage herniation in future studies.

References

Acknowledgements
Flinders Surgical Lab for providing resources and consumables.
THE EFFECT OF IMPLANT DESIGN ON SUPPORT MOMENT ASYMMETRY IN TOTAL KNEE ARTHROPLASTY PATIENTS DURING SIT/STAND TASKS

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Introduction

Side-to-side lower limb asymmetry is common among late-stage knee OA patients[1]. It is typically reduced, but not resolved to the level of healthy controls following total knee arthroplasty (TKA)[2]. Implant design can affect post-operative muscle activity during activities of daily living[3], which may subsequently result in differences in loading asymmetry too. It is not yet known whether such differences exist in post-op TKA patients. This study aimed to examine whether patients receiving a Medial Pivot (MP) implant differed significantly in their lower-limb loading asymmetry, compared to patients receiving a Posterior Stabilized (PS) implant and a group of healthy controls.

Methods

Twenty-six knee OA patients underwent TKA with either an MP (M=8, F=6; age=63.7± 5.7yrs) or a PS implant (M=6, F=6; age=66.3±8.2yrs) and were compared pre-operatively (<1 month) and post-operatively (12±1 months) to a group of age/sex-matched controls (CTRL) (M=6, F=8; age=64.4±5.6yrs). Participants were required to perform sit-to-stand (StS-Up) and stand-to-sit (StS-Down) tasks, while motion capture cameras tracked reflective markers placed according to a custom, full-body marker set. Force plates measured ground reaction forces for each limb, and the moment contact was made and lost with the chair. Inverse dynamics was used to calculate the sagittal support moment (summation of hip and knee extension and ankle plantar flexion) for each limb, during the raising and lowering phases of StS-Up and StS-Down, respectively. Data were time-normalized to the start and end of each phase, and normalized to participants’ body weight. Asymmetry was measured by calculating the difference (unaffected minus affected/non-dominant minus dominant for controls) in the area under the curve (ΔAUC) (0 = perfect symmetry)[4]. Both raw and absolute differences were calculated to provide insight into side-specific and overall asymmetry, respectively. Mann-Whitney U and Wilcoxon Signed Rank non-parametric tests (α=0.05) were used to compare between and within the groups.

Results

Pre-operatively, both patient groups favored their unaffected side significantly more than the CTRL group favored either side. The PS group was also significantly more asymmetric overall than the CTRL group for both tasks, whereas the MP group only differed significantly for StS-Up. The PS group favored their unaffected side significantly more than the MP group during both tasks and was significantly more asymmetric overall during StS-Down, but not StS-Up. Following surgery, both patient groups continued to favor their unaffected side during both tasks. However, the PS group displayed significantly less asymmetry post-operatively, whereas the MP group showed no significant improvement. Although both patient groups also continued to favor their unaffected side, overall limb asymmetry was similar to the CTRL group.

Discussion

The results concur with previous studies indicating that lower-limb asymmetry among knee OA patients improves, but is not resolved after TKA[2]. Although they displayed similar levels of asymmetry to healthy controls, the TKA groups favored their unaffected limb, whereas no pattern was detected in the CTRL group. Continuing to favor the unaffected side may be due to strength deficiencies or unresolved guarding strategies that persist after surgery. This may have implications for the development of OA in the contralateral limb. The PS group showed significantly greater improvements in joint loading asymmetry after TKA, compared to the MP group, but displayed significantly more asymmetry pre-operatively, making it difficult to determine the influence of implant design. Future studies must include groups with similar asymmetry pre-operatively, and will examine joint-specific contributions to asymmetry.

References

IMPACT OF SICKLE CELL DISEASE FOR OXYGEN TRANSPORT IN INTRACRANIAL ANEURYSMS

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Introduction

Neurological complications are more common in patients with sickle cell disease (SCD), with subarachnoid hemorrhage (SAH) of an intracranial aneurysm (ICA) among the most common. Due to the polymerization of sickle hemoglobin at low oxygen tension, the apparent viscosity of the blood increases in SCD. Increased viscosity affects blood flow resistance which could affect oxygen advection, further reducing oxygen levels and driving a cascade contributing to ICA formation and weakening.

Our aim in this study was to investigate how the geometry and blood rheology affect oxygen transport and consequently oxygen availability in an idealized ICA, testing the hypothesis that feedback between oxygen level, blood viscosity, and oxygen transport can aggravate the reduction in available oxygen in SCD.

Methods

Primitive geometries were used, in which an arched 4-mm diameter cylindrical tube represented the vessel, and an attached 9-mm diameter spherical bulge represented the aneurysm. Two parameters were studied: (1) the ratio between the aneurysm throat length and the aneurysm diameter (Lt/Da), and (2) the vessel curvature (κ).

The Carreau-Yasuda model with parameters dependent on the level of sickle hemoglobin (HbS) was used for the blood rheology. Oxygen transport in the blood and in the vessel wall was modeled using Fickian diffusion. A pulsatile velocity waveform and constant oxygen concentration were imposed at inlet. Outlet boundary conditions were fixed pressure and no axial oxygen gradient. A full factorial study was done on three factors: (1) HbS level, (2) aneurysm throat / aneurysm diameter ratio), and (3) vessel curvature, resulting in a total of 36 geometries and over 140 cases. Simulations were performed at the Minnesota Supercomputing Institute

Results

The average Peclet number in the aneurysm ranged from 30–4000, meaning that even for the extreme cases, oxygen transport was dominated by advection. Figure 1A and 1B compare the normalized oxygen distribution for the non-sickle and sickle cases, respectively for one geometric case. For smaller throat sizes, there is reduced oxygen transport, as quantified by Sherwood number through the aneurysm wall was lower in the sickle case as shown on Fig. 1C vs. Fig. 1D, even for large throat sizes.

Discussion

Oxygen availability is a potential issue in intracranial aneurysms. Aneurysm oxygen level was lower than the arterial level in all simulations, even those using healthy blood parameters, and the problem was more pronounced for SCD blood parameters. The higher viscosity of the sickle blood increases the effect of the narrow throat, and the poor oxygen transport can lead to even greater increase in blood viscosity. While this study can say nothing about the potential biological consequences of reduced oxygen availability in an aneurysm, it identifies oxygen availability as an important factor to consider.

References

GAIT BIOMECHANICS COMPARISON ANALYSIS USING VARIOUS ANKLE-FOOT OFFLOADING DEVICES

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Introduction
Currently, crutches are the standard care for patients who cannot load their ankle or foot due to conditions such as diabetic foot ulcers, fractures, sprains, surgeries, etc. Crutch gait, however, limits the use of the upper extremities, reduces walking speed, and is energetically inefficient. Consequently, alternative devices that remove loading from the foot and ankle while walking have been proposed. This study investigates the biomechanical outcomes of using crutches (CR) and two alternative devices: iWalk (IW) and ZeroG (ZG), as shown in Figure 1.

Figure 1: Devices for ankle-foot offloading. From left to right: forearm crutches, iWalk, and ZeroG.

Methods
The experiments comprised of 20 healthy participants (9 male, 11 female, ages 20.8-39.1). Each participant walked at a self-selected speed with each device, as well as normal unassisted gait. A 16-camera Vicon motion capture system at 120 Hz using the Plug-In Gait Body model [1], two AMTI force plates, and Cosmed K5 metabolic system were used to measure spatiotemporal parameters, ground reaction force (GRF), foot center of pressure (COP), center of mass (COM), joint kinematics and kinetics, as well as the metabolic cost. Moreover, the users rated their perceived exertion (RPE), stability, comfort, and preferences, using questionnaires. Repeated measures ANOVA was used to analyze the statistical significance of the differences between the different conditions, where the gait parameters of the weight-bearing leg were compared using each device relative to normal gait.

Results
All the devices changed the participants’ walking patterns in comparison to their normal gait. The hip and knee angles obtained using the ZG were the most similar to normal gait, whereas no significant differences were found for the ankle. The medial-lateral fluctuations of the COM were largest for IW and smallest for CR. The GRF peaks were most pronounced for CR, whereas for ZG and IW the magnitudes were comparable to normal gait, but delayed, as illustrated in Figure 2. The stance phase was most significantly elongated using CR and the stride length was most significantly shortened using IW. All the devices caused a reduction in the cadence and walking speed. The normalized metabolic cost, measured during a 6-minute walking test, is summarized in Table 1. The questionnaires revealed that CR were least preferred by the participants, whereas IW and ZG were similarly preferred.

Figure 2: GRF components in the sagittal plane.

<table>
<thead>
<tr>
<th>[ml/min]</th>
<th>CR</th>
<th>IW</th>
<th>ZG</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>[kg m/s]</td>
<td>11.56</td>
<td>8.51</td>
<td>5.35</td>
<td>3.19</td>
</tr>
<tr>
<td>STD</td>
<td>4.25</td>
<td>2.79</td>
<td>0.84</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Table 1: Metabolic cost of all devices and normal gait.

Discussions
Overall, the ZG led to gait parameters that were most similar to normal gait, which may be linked to the lowest metabolic cost and highest user preference, together with IW. This suggests that it may be preferable as a replacement for CR. The small mediolateral COM fluctuation using CR may indicate improved balance, however, the user rated them as the most unstable. This suggests that the instability feeling of the subjects stemmed from a different parameter. The lower GRF peaks obtained using ZG and IW may be beneficial to limit the risk of injury on the weight-bearing leg. These results could inform clinicians’ decisions regarding the prescription of such devices for patients with foot-ankle injuries and pathologies. Future research is planned to employ the results toward the design of new ambulatory devices that improve rehabilitation and patient care.

References
EFFECT OF COMBINING MUSCLE SUB-GROUPS IN THE MANDIBLE DURING MASTICATION: A FINITE ELEMENT STUDY

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Introduction

Defects in the mandible arising from infection, tumour or trauma need to be reconstructed for facial aesthetics and oral functions. Custom implants have recently gained popularity over stock implants owing to superior biomechanical outcomes. 3D printed custom implants need to go through standardised verification and validation protocols checking design efficacy [1]. Although finite element analysis is widely used for computational verification, it requires experimental validation for meaningful interpretation of results. Appropriate replication of the anatomy and functionality of the muscles of mastication is a challenge owing to the presence of multiple muscle sub-groups, resulting in complex lines of action. Mechanical testing of implant prototypes often simplify specimen loading during in vitro validation, overlooking the anatomical arrangement and physiological function of masticatory muscles [2]. In contrast, replicating all muscle sub-groups experimentally is often expensive and practically infeasible. This finite element study aimed to quantify the effects of combining sub-groups of mastication muscles on the stress distribution in the mandible during mastication, with the hypothesis that combining muscle sub-groups would not affect stress distribution.

Methods

A finite element analysis was conducted on an edentulous intact mandible model, assumed to be homogeneous and isotropic cortical bone, subjected to loading conditions experienced during mastication using Ansys Workbench 2020 R2 (Ansys Inc., USA). Jaw-closing muscles – masseter, temporalis and medial pterygoid – were simulated in four configurations varying in force magnitude, lines of action, and regions of muscle insertion. In the first configuration (M<sub>sep</sub>T<sub>sep</sub>), the masseter was simulated as two separate muscle sub-groups (superficial and deep), the temporalis as three sub-groups (anterior, middle and posterior), and the medial pterygoid as one [3]. In the second (M<sub>sep</sub>T<sub>com</sub>) and third (M<sub>com</sub>T<sub>sep</sub>) configurations, sub-groups of the temporalis and the masseter were individually combined, respectively. In the fourth configuration (M<sub>com</sub>T<sub>com</sub>), sub-groups of both the temporalis and the masseter were individually combined. Mastication was simulated on each of the four configurations using loads for six unilateral clenching tasks – intercusal (ICP), incisal (INC), canine (CAN), molar (MOL), left group (LGC) and left group with molar balancing (LGC+MB) – and one molar chewing task (MOL chew) [4]. The condyles of the mandible were rigidly fixed [3]. Magnitudes and regions of maximum stress were identified and compared across muscle configurations and mastication tasks.

Results

When configurations combining muscle sub-groups were compared to the baseline configuration M<sub>sep</sub>T<sub>sep</sub> across mastication tasks, the maximum stress increased the most during MOL chew, and decreased the most during ICP (Table 1). For all tasks in M<sub>sep</sub>T<sub>sep</sub>, regions of maximum stress were observed around their respective clenching points, except for LGC and LGC+MB, wherein these regions were found on the anterior aspect of ipsilateral coronoid process and balancing side, respectively. For all tasks in the remaining combinational configurations, the maximum stress was found in similar regions as those in M<sub>sep</sub>T<sub>sep</sub> but differed in magnitude.

<table>
<thead>
<tr>
<th>Tasks</th>
<th>M&lt;sub&gt;sep&lt;/sub&gt;T&lt;sub&gt;sep&lt;/sub&gt; (MPa)</th>
<th>M&lt;sub&gt;sep&lt;/sub&gt;T&lt;sub&gt;com&lt;/sub&gt; (MPa)</th>
<th>M&lt;sub&gt;com&lt;/sub&gt;T&lt;sub&gt;sep&lt;/sub&gt; (MPa)</th>
<th>M&lt;sub&gt;com&lt;/sub&gt;T&lt;sub&gt;com&lt;/sub&gt; (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOL</td>
<td>25.1</td>
<td>25.3</td>
<td>26.7</td>
<td>26.9</td>
</tr>
<tr>
<td>chew</td>
<td>–</td>
<td>+0.8%</td>
<td>+6.4%</td>
<td>+7.2%</td>
</tr>
<tr>
<td>ICP</td>
<td>48.4</td>
<td>47.8</td>
<td>45.1</td>
<td>44.5</td>
</tr>
</tbody>
</table>

Table 1: Maximum stress (MPa) in the mandible during select mastication tasks across muscle configurations.

Discussion

Regions of maximum stress found similar across muscle configurations could be attributed to the principle of vector addition, where combining muscle sub-groups produced a force comparable to their individual effects. Although the magnitude of maximum stress was hypothesized to remain unchanged across muscle configurations, computational approximations in the software could have potentially resulted in the observed variations; however, it must be noted that the maximum variations were <10% (Table 1). Results from this study vouch for a combination of muscle sub-groups for quasi-static computational testing of an intact mandible or mandibular implant designs. This could also result in potential simplification of experimental setups designed for quantification of native and/or altered mandibular biomechanics. However, the effect of combining muscle sub-groups should not be overlooked for dynamic simulations, wherein biomechanical parameters, such as kinematics and occlusion forces, need to be quantified.

References

TOPOLOGICALLY OPTIMIZED GRADED GYROID BONE SCAFFOLDS

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Abstract
Healing of large bone defects are still a challenge for clinicians and patients mainly due to limited availability of autologous bone grafts. Therefore, use of scaffolds as a carrier structure is current common practice. Among other functionalities, the scaffold should provide sufficient mechanical properties to endure the physiological loading while providing enough porosity and surface area for nutrition and oxygen delivery, waste disposal, cell attachments and bone growth. A proper design can be sought for by optimizing the geometry for sufficient strength, porosity, and the choice of material while ensuring manufacturability.

Topology optimization (TO) is an effective design method that iteratively distributes a given amount of material within a given design space under constraints. It is used to design scaffold topologies with optimal properties. However, very few TO studies exist that take into account fluid-flow based analysis and requirements while delivering a manufacturable graded gyroid structure. To address this need, here we propose an initial design framework (Figure 1) that integrates fluid flow-based FEA analysis in COMSOL software to a modified SIMP permeability model and reconstructs the final design in the form of a graded gyroid topology for bone scaffolds with enhanced regeneration properties.

Method

Figure 1: Topology optimization framework including physiological metrics.

Results

Figure 2: Optimal density distribution (top) and reconstructed graded gyroid structure (bottom).

The design results presented here aimed to design scaffolds under certain fluid velocity, shear rate and porosity requirements (Figure 2). Results show that the framework has potential to incorporate comprehensive metrics that are likely to result in further performance enhancements.

References

Acknowledgements
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DATA-DRIVEN GENERATION OF INLET VELOCITY PROFILES FOR CFD MODELLING IN THORACIC AORTIC ANEURYSMS

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Introduction
Computational fluid dynamics (CFD) has emerged as a powerful tool to investigate development and growth of aortic aneurysms. Previous works [1,2] showed that inlet boundary conditions (IBC) are crucial to accurately reproduce blood flow features in the ascending aorta. However, the availability of in vivo measurements to be used as IBC is limited. This hinders progress of research on ascending aortic disease. With this work, we aimed to address this issue by proposing a data-driven generative model of 4D aortic velocity profiles suitable for use in CFD modelling of the ascending aorta.

Methods
By exploiting principal component analysis (PCA), a statistical shape model (SSM) of 4D aortic inlet velocity profiles was developed starting from 4D flow magnetic resonance imaging scans of 30 subjects with ascending thoracic aortic aneurysm. Using the SSM, a dataset of 500 synthetic cases was generated. Velocity profiles from both the clinical and synthetic cohorts were characterized by computing flow morphology descriptors (e.g., flow jet angle – FJA, retrograde flow index, secondary flow index) of both spatial and temporal features. The synthetic dataset was then refined by excluding generated profiles which presented flow descriptors outside the physiological range observed in the clinical cohort. This selection resulted in the acceptance of 437 synthetic profiles with realistic properties.

Results
Statistically significant correlations were found between PCA principal modes of variation and flow descriptors in the synthetic cohort: mode 1 strongly correlated (p<0.0001) with positive peak velocity (PPV, r=0.94) and with the spatial heterogeneity of the velocity magnitude (quantified by the flow dispersion index, FDI [2], r=0.99), mode 2 strongly correlated with the FJA (r>0.99). The average velocity profile (Fig.1) obtained by the conducted PCA qualitatively resembled a parabolic-shaped profile but was quantitatively characterized by more complex features, such as 13° FJA at peak systole and non-null in-plane velocity. T-tests and Mann–Whitney U tests confirmed that no significant differences (p>0.05) existed between the clinical and synthetic cohorts (Fig.2), except for PPV (p = 0.040; clinical: 0.59±0.12 m/s, synthetic: 0.56±0.08 m/s).

Discussion
We investigated features of velocity profiles in the ascending aorta using SSM. Our results show significant inter-patient variability in eccentricity and orientation of these velocity profiles. This further supports the need for more realistic IBCs for CFD simulations of the ascending thoracic aorta. From the SSM we generated a cohort of 437 synthetic profiles with features overlapping the original cohort and that are suitable for use as IBC. We believe that the present work will contribute to the replacement of idealized IBCs in numerical simulations of blood flow with more realistic conditions. To this end, we have released all synthetic profiles [3].

References

Acknowledgements
This work was supported by NIHR Imperial College BRC (P69559) and Imperial College London BHF CoRE (RG/19/6/34387, RE/18/4/34215). The work has been released as a pre-print. All synthetic velocity profiles can be downloaded here. SSM and IBC codes can be found here.
A CT-BASED DEEP LEARNING SYSTEM FOR AUTOMATIC ASSESSMENT OF AORTIC ROOT MORPHOLOGY FOR TAVI PLANNING

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Introduction
Transcatheter aortic valve implantation (TAVI) is an alternative to traditional open-heart surgery for severe aortic stenosis [1]. Pre-TAVI planning is crucial for minimizing risk for complications and should include an accurate anatomic assessment of the aortic root (AR) apparatus [2]. Three-dimensional (3D) computed tomography (CT) angiography is the preferred imaging modality to evaluate both AR shape and structure prior to TAVI. However, there is currently no standardized method to evaluate AR morphology [3].

Methods
Two convolutional neural networks (CNNs) with 3D U-Net architectures (model 1 and model 2) were trained to perform automatic AR segmentation (model 1), and identification of aortic annulus and sinotubular junction (STJ) contours (model 2). The training set included 379 cases and validation was performed on 31 cases. Once trained, the CNNs were embedded in a fully automatic pipeline for AR analysis.

![Figure 1: schematic representation of the implemented automatic pipeline](image)

The devised system performs a series of steps to automatically quantify AR metrics. Briefly, AR region of interest (ROI) is detected through a template-matching approach and subsequent refinement of annulus and STJ planes is achieved through a min-cut algorithm. By computing the eigenvectors of the Laplace-Beltrami operator (LBO) [3], the plane of the Valsalva sinuses is automatically identified. Finally, minimum, maximum, and mean diameters, together with areas and perimeters are automatically computed for the detected planes. Automatic measurements were validated against a separate dataset of 178 CT scans of TAVI candidates for whom AR measurements were previously obtained using commercial software (3mensio, Pie Medical Imaging, Maastricht, Netherlands).

Results
The trained CNNs effectively segmented the aortic region, annulus and STJ, resulting in mean Dice scores of 0.93 for the AR, and mean surface distances of 1.16 mm and 1.30 mm for the annulus and STJ, respectively. Automatic measurements were in good agreement with manual annotations, yielding annulus diameters that differed by 0.52 [-2.96, 4.00] mm (bias and 95% limits of agreement for manual minus algorithm). Discrepancies in minimum diameters were 0.92 [-2.93, 4.78] mm. Significantly smaller discrepancies between the two techniques were obtained for the annulus area. Evaluating the area-derived diameter, bias and limits of agreement were 0.07 [-0.25, 0.39] mm. STJ and sinuses diameters computed by the automatic method slightly underestimated manual measurements, yielding differences of 0.16 [-2.03, 2.34] and 0.1 [-2.93, 3.13] mm, respectively.

Conclusions
We developed a fully automatic CT-based pipeline for the quantification of morphological biomarkers relevant for pre-TAVI planning, validating the analysis against ground-truth data from commercial software. Hence, the method proved to be quick and effective to assess AR anatomy, with potential for time and cost savings.

References

Acknowledgements
IRCCS Policlinico San Donato is a clinical research hospital partially funded by the Italian Ministry of Health.
INTRODUCTION

Cell migration is engaging in key physiological processes such as embryogenesis, wound healing, angiogenesis, and immune response. Unfortunately, it is also included in various pathologies, such as inflammation and cancer metastasis. In each of these physiological and pathological processes, cell migration involves the same basic mechanism of cell movement along or through tissue. This movement is driven by cellular forces, exerted through focal adhesions on the substrate or through cell-cell junctions with neighboring cells [1], and most importantly is also accompanied by extensive cell division events. It has been proposed that cell area [2] and cell-cell forces [3] impact various phases of the cell cycle during the expansion process of an epithelial layer. However, when it comes to cell cycle control during the more common physiological state of condensed epithelial tissues [4], the nature of size-based and force-based mechanisms and how they might be compiled to control the cell cycle transition and duration is still unclear. Here we map two-dimensional traction forces and intercellular stresses in highly dense epithelial tissue that still maintains unique dynamic patterns. We are now able to simultaneously track thousands of cells in a tissue, and track each cell; its morphology, progression in cell cycle state, and acting mechanical forces.

METHODS

As a model system for computing cellular forces [5], we prepared polyacrylamide gel as a substrate for a condensed colony of MDCK-Fucci cells (express Ctd1-red fluorescent protein during G1 and S phases and geminin green fluorescent protein during S-G2-M). We used traction force microscopy (TFM) to map traction force at the cell-substrate interface and monolayer stress microscopy (MSM) to map cell-cell stresses. We integrated our computational tools for stress measurement with image analysis tools, such as CellPose [6] and TrackMate [7].

RESULTS

We succeeded in accurately detecting the cell boundaries for highly dense epithelial tissue. We got an image analysis tool model that: 1. Skips gaps and extruded cells; 2. has an extremely high probability for successful segmentation; 3. Track cells in space and time, and relate spatiotemporal force patterns with individual cell morphology and cell cycle state.

CONCLUSION

The developed tool will become a cardinal pillar in our quest to decipher the complex relationship between the fundamental biological functionality of cell division, and physical properties such as force patterns, cell dynamics, and cellular morphology. But more so, our tool can be easily used for the study of mechanical effects on a variety of biological or molecular events such as differentiation, cell-cell communication via calcium signaling, and more.

REFERENCE


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MULTI MODALITY APPROACH FOR OPTIMIZING PROPHYLACTIC AUGMENTATION OF THE PROXIMAL FEMUR FOR HIP FRACTURE PREVENTION

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Introduction

Hip fractures in the elderly have severe consequences for the individual and are a major burden to the healthcare system. Hip fracture risk is affected by the load-bearing capacity of the femur which has been shown to decrease with low bone mineral density (BMD) [1]. The load that the femur is subjected to is multi-factorial, affected by biomechanical aspects of the fall, such as impact speed and impact direction [2]. The risk of fragility fractures can potentially be reduced by augmenting susceptible femora with injectable bone-strengthening hydrogel, which degrades and triggers new bone formation and a local BMD increase. The goal of the present study was (i) to estimate optimized augmentation patterns taking fall direction into account and (ii) to quantify the strength increase obtained by those patterns.

Methods

The Bi-directional Evolutionary Structural Optimization (BESO) [3] algorithm was coupled with a Finite Element (FE) model of a femur in a sideways fall loading configuration (Figure 1a) [4]. The initial volume to be optimized was 50mL, shown in Figure 1b, corresponding to the volume of the entire trabecular bone of the proximal femur. A BMD increase of 20% was assumed for bone elements infiltrated by the hydrogel. This initial volume selection allows the final optimized volume to be distributed in the proximal femur without restriction. The target volume after optimization was set to 5mL. Five different optimized patterns were calculated corresponding to five fall angles (-30°, -15°, 0°, 15°, 30°) as shown in Figure 1c, and fracture strength of the femurs with and without the optimized augmentation patterns predicted.

Results

Figure 2 shows a strength comparison before and after augmenting the optimized pattern for the different fall angles. As expected, the different fall angles resulted in five different optimized patterns. Relative to the unaugmented specimens, the strength increase was on average found to be 13.6% across fall angles.

Discussion

A topology optimization algorithm was developed that is capable of optimizing augmentation patterns of a bone-strengthening hydrogel that is assumed to increase the local BMD by 20%. Furthermore, the BESO algorithm was applied to FE simulations by examining different fall angles. The estimated patterns resulted in a strength increase for all examined fall angles compared to the unaugmented specimens. Overall, the outcome of this work could be used to design the injection strategy for the bone-strengthening hydrogel or other injectable biomaterials.

References


Acknowledgements

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EFFECT OF HUMERAL ROTATION ON ROTATOR CUFF STRAIN, 
LOADING AND KINEMATICS: AN IN-VITRO STUDY

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Introduction

Despite its main function as abductor, the role of the supraspinatus (SSP) as stabilizer and rotator cannot be neglected [1, 2]. A SSP tear may not only influence humeral head rotation during abduction but also the strength and loading of the acting (intact) rotator cuff (RC) muscles. The purpose of this study was, therefore, to investigate the effect of constrained humeral rotation on RC loading, strain and kinematics with intact and torn RC conditions.

Methods

Twelve fresh-frozen cadaveric shoulders were dissected to retain only the RC muscles and joint capsule. A speckled pattern was created in the bursal side of both SSP and infraspinatus (ISP) tendons for digital image correlation analysis (Figure 1). Optical tracking markers (GOM, Braunschweig, Germany) were fixed to the humerus and scapula, and anatomical landmarks were digitized to create bone fixed local coordinate systems [3].

Figure 1: 3D geometries of humerus and scapula, and surface generated from stochastic pattern. Strain (%) was analyzed in regions 1 (SSP) and 2 (ISP).

Glenohumeral abduction until 30° was simulated in the scapular plane by loading the SSP at 2 mm/s (EletroPuls E10000, Intron, MA, USA), with (1) free humeral rotation (+R) and (2) blocked humeral rotation (–R). A constant load was applied to the remaining RC. The loading protocol was applied to (a) the intact SSP, (b) after a 50% wide full-thickness tear was created in the SSP and (c) after the tear was further extended to 100% of the width of the tendon. Two SSP tears were investigated: a crescent-shaped (CS) tear (n = 6) and a reverse L-shaped (rLS) tear (n = 6) [4].

Results

Range of motion was significantly reduced in 7 of the 12 specimens due to blocked humeral rotation. The 100% CS tear led to an anterior translation in both test series (+R and –R). In the 100% wide rLS tear group, –R resulted in an anterior translation of the humeral head, in contrast to the posterior translation observed with +R. There were no significant differences in superior-inferior and anterior-posterior translations between +R and –R, for both CS and rLS tear groups. Translation in the medial-lateral direction was significantly different (p<0.05) between the +R and –R test series, for both tear shapes. Constrained rotation led to an increase in SSP loading force (Figure 2) and maximum SSP strain for both tear shapes. ISP strain exceeded SSP strain in the 50% CS and rLS tear groups with +R and –R.

Discussion

This study shows that blocking the rotational function of the SSP leads to an increase in SSP and ISP strains. As shown by Santos et al [4], the strain and load on the ISP (an external rotator of the shoulder) is higher than on the SSP at the beginning of abduction. However, since small RC tears do not biomechanically result in increased humeral rotation, it can be assumed that the load on the ISP is compensated by the subscapularis. These findings need further investigation.

References

PORE NETWORK MODELLING OF TPMS-BASED SCAFFOLDS FOR TISSUE ENGINEERING APPLICATIONS

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Introduction

The purpose of a Tissue Engineering (TE) scaffold is to provide support for cells adhesion, proliferation and differentiation into a specific phenotype. These cellular phenomena depend on the scaffold design and its structural properties (geometry, porosity, pore size, pore interconnectivity and surface area (SA)). Pore size has been reported to influence the differentiation of Mesenchymal Stem Cells (MSCs) [1], as well as the scaffold fluid dynamics, which in turn plays an important part in cellular activity regulation. Therefore, pore size control (and quantification) is crucial to design scaffolds for complex tissue regeneration as in the osteochondral interface.

The objective of this work is to implement Pore Network Modelling (PNM) approaches for extraction of porous phase topological information as pore size distribution; additionally, to perform phase simulations over TPMS-based scaffolds for TE applications. We will use the simulation outputs to validate the models by comparing Darcian permeability values with experimental and CFD outputs from previous works [2], [3].

Methodology

We used the SNOW algorithm [4] and an adaptation of the Maximum Ball Algorithm (MBA) to perform the segmentation of the porous phase of 3D TPMS binary images into pores and throats that we used to perform phase simulations. Then, we choose the Hagen-Poiseuille equation (1) as our pore-scale physics model to calculate the pressure drop along throats.

$$\Delta P = g_h^{-1} \times Q = \frac{8 \mu L_i}{\pi r_t^4} \times Q$$

Finally, a StokesFlow algorithm applies a flow rate over the network and calculates its pressure drop assuming outlet pressure = 0. The algorithm builds the coefficient matrix from the existing values of hydraulic conductance ($g_h$) and adjusts the matrix to solve for pressure in each pore, storing the results. The pressure field is, therefore, immediately calculated and the absolute permeability of the network can be calculated using Darcy’s law (Eq. 2):

$$Q = \frac{kA}{\mu L} \times \Delta P = \frac{kA}{\mu L} \times (P_i - 0)$$

Results

The implemented models allowed for permeability estimation in TPMS scaffolds with different porosities and basic designs (figure 1).

![Figure 1: Darcian permeability of TPMS scaffolds calculated with two alternative PMN algorithms in comparison with the analogous experimental results.](image)

Discussion

These algorithms still need some refining to completely resemble the transport of these (and other) TPMS scaffolds. In detail, improvements are necessary on the topological discrepancies of the methods used, and on fine-tuning the geometrical models implemented to the acquired network. However, the acquired permeability results are closer to the ones we estimated using the computationally more demanding CFD approach [3], still keeping the same hierarchy in terms of increasing permeability for increasing porosity.

Future work shall not only complete the refinement of the PMN approach, but also allow for the design of TPMS scaffolds for the osteochondral interface as a function of the pore size and transport properties.

References


Acknowledgements

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PREDICTING THE PREMORBID ANATOMY OF THE SCAPULA USING GENERATIVE MODELS

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Introduction
Total shoulder arthroplasty (TSA) is a surgical procedure to relieve pain and disability associated with glenohumeral osteoarthritis (OA). The goal of the procedure is to restore the anatomy and function by placing implants in the humeral head and the glenoid. The positioning of the implants plays a crucial role in the long-term success of the surgery. Due to the bone wear caused by OA, determining the proper implant position is challenging. In addition, since OA usually occurs bilaterally, preoperative planning based on the contralateral morphology is not possible. Therefore, we proposed an autoencoder-based approach to predict the premorbid scapular anatomy objectively.

Methods
Our dataset consisted of 60 healthy and 414 pathological segmented scapulae from CT scans. 12 healthy and 56 pathological cases were used for validation, and the rest were used to train our model. The model consisted of a common encoder trained with both healthy and pathological cases and two decoders that were trained separately with healthy and pathological cases. The goal of the encoder was to extract latent features from the entire dataset, and each decoder was used to reconstruct the healthy and pathological anatomy, respectively. To predict the premorbid anatomy, we used the encoder with the decoder that had been trained with healthy cases. This method allows objective prediction of the premorbid scapular anatomy based on the healthy cases in the dataset.

Results
The reconstruction accuracy of the autoencoders was found adequate, yielding a Dice overlap of 91% and 89% for healthy and pathological cases, respectively. Visual comparison of the pathological cases with their premorbid predictions showed that osteophytes present in pathological cases were reduced or completely removed in the premorbid reconstructions (Fig. 1a). In addition, biconcave glenoid cavities found in some pathological cases were corrected to a uni-concave surface after reconstruction (Fig. 1b). Finally, we investigated the difference between the glenoid version, an important parameter for surgical planning, of pathological cases and their premorbid prediction. Glenoid version of pathological cases was more posterior than healthy ones, with an average difference of 5.4°. However, the same comparison between pathological cases and their premorbid predictions revealed an average correction of only 1.9° (Fig. 2). Although the statistical analysis showed that there is a significant difference between the glenoid version of the pathological cases and their premorbid predictions (p = 0.001), this does not correspond fully to the healthy scapulae.

Discussion
In this study, we proposed an approach based on autoencoders to predict the premorbid anatomy of the scapula. Visual inspection showed that pathologies, such as osteophytes and biconcave glenoid cavities, were corrected and represented a healthier anatomy. However, the glenoid version of the premorbid reconstructions remains lower than in healthy control subjects. In the future, we will extend this work with generative adversarial networks to enforce more realistic glenoid version in the premorbid predictions.

Acknowledgements
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CHARACTERISATION OF THE PHANTOM TISSUE MODELS FOR MEDICAL DEVICE TESTING AND SURGICAL TRAINING

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Introduction

This research paper focuses on characterizing the mechanical properties of silicone rubbers used for the development of medical devices, medical training models and surgical procedural practice. High-fidelity phantoms provide test beds to improve all elements of healthcare. Silicones are commonly used material in tissue phantoms and are assessed here for use in skin and cardiovascular applications. Silicone rubber is a highly desirable tissue mimicking material for medical training equipment due to its longevity and hyper-elastic behavior. Experimental and analytical studies of commercially available, maxillofacial prosthetic silicone materials have focused on material tensile strength, tear strength, percentage elongation, material hardness and bond strength [1, 2]. This study investigates the mechanical behavior of silicone blends suited for a range of phantoms.

Methods

Hybrid silicone blends of theoretical Shore 00-40, 00-50 and 00-60 silicone rubber specimens were created using the method outlined in Figure 1. The tensile, compressive and tear behavior was characterized. The tensile load tolerated by a suture through the silicone rubber specimens was also measured, following an experimental method from ref. [3]. Experimental results may be used to determine optimal silicone materials for suture practice models used by medical professionals.

![Figure 1: Durometer hardness scales. (a) Highlights the unmixed materials; and (b) illustrates the mixing ratios.](image)

Digital Image Correlation (DIC) was used as a non-contact optical method for tracking and imaging the suture hold and tear through each sample. Platforms exploiting controlled silicone properties were then made to study applications where regional and individual soft tissue variations are important, such as the face.

Results

Figure 2 graphically displays the stress-strain results obtained from performing tensile tests on all the silicone specimens. Figure 2 also displays the DIC results obtained from the suture extrusion experiments as the sample began to tear.

![Figure 2: Sample stress-strain results and DIC image of the full-field strain observed during suture extrusion.](image)

Discussion

The silicone specimens exhibit typical, hyper-elastic stress-strain behaviour with a relatively steady increase in compliance as the samples range from Shore 00-70 to 00-10. Furthermore, the suture imaging results illustrate high strain concentrations around the suture, which may further influence the design of suture training equipment and protocols. This study demonstrated the ability to tune mechanical properties of silicones for any application across phantom types. Surgical training or medical device testing have different properties of interest from their phantoms and this paper provides a mechanical reference database to enable tailored solutions. The silicone materials characterised in this study were used in testing oxygen face mask fit on pressure-sensitive head models, testing mechanics of heart valves and development of a skin phantom for suture training devices (displayed in Figure 3).

![Figure 3: Medical applications of silicone rubber including for use in a high-fidelity head rig for assessing mask fit quality.](image)

References


Acknowledgements

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ISOLATED EFFECTS OF PATELLAR RESURFACING IN TOTAL KNEE ARTHROPLASTY AND THEIR RELATION TO NATIVE PATELLAR GEOMETRY

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Introduction
In total knee arthroplasty (TKA), the question of whether or not to resurface the patella remains controversial¹. There is evidence to indicate that patellar resurfacing can lead to both improved clinical outcomes and a reduced probability of revision surgery². The isolated effects of patellar resurfacing on patellar kinematics are rarely investigated. Nonetheless, knowing more about these effects could help to enhance present understanding of the emergence of kinematic improvements or deteriorations associated with patellar resurfacing. The aim of this study was to isolate the effects of patellar resurfacing from a multi-stage in vitro study, in which kinematics after total knee arthroplasty before and after patellar resurfacing were recorded. Additionally, the influence of the native patellar geometry on these effects was analyzed.

Methods
Eight fresh frozen specimens were tested successively with different implant configurations on an already established weight bearing knee rig³ (fig.1). Patello-femoral kinematics was thereby measured using an ultrasonic measurement system and its relation to the native patellar geometries was analyzed.

Results
After patellar resurfacing, the specimen showed a significantly medialized patellar shift. This medialization of the patellar tracking was significantly correlated to the lateral facet angle of the native patella. The patellar shift after patellar resurfacing was highly influenced by the position of the patellar button and the native lateral patellar facet angle (fig. 2). As a result, the ideal medio-lateral position of the patellar component was affected by the geometry of the native patella.

Discussion
Most important finding of the study was that the difference in the PS and PS+ tibial inlays did not change patello-femoral kinematics in a significant way, either in the native stage nor in the patellar resurfaced stage. Placing the patellar button significantly affected patellar tracking, which was medialized with the resurfaced patella. Patellofemoral rotations were not significantly affected by patellar resurfacing. Based on our results, it could be worth to consider the native patellar geometry to choose the medio-lateral position of the patellar implant, and thus minimize the deviation from patellar kinematics without patellar resurfacing. Further research is needed to analyze how to determine the medio-lateral implant position in everyday clinical workflows.

References
APPLICATION OF DIFFERENT OPTIMISATION CRITERIA TO STANDARDISE KINEMATIC SIGNALS

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Introduction

In motion analysis, kinematic signals are calculated from captured data points to allow the clinical interpretation of the underlying movement patterns of body joints. Although assessment of kinematic signals should inherently lead to a consistent interpretation of joint movement, regardless of the numerical approach used to derive them, this has proven not to be the case [1,2]. The recently presented Frame Orientation Optimisation Method (FOOM) [3] and REReference FRame Alignment MEthod (REFRAME) aim to realign local segment frames based on the numerical optimisation of specific criteria to allow convergence of different kinematic signals that represent the same underlying movement. Here, we validate and explore the use of distinct optimisation criteria on the characteristics of the resulting kinematic signals.

Methods

REFRAME reorientates and repositions femoral and tibial reference frames to optimise the values of user-selected criteria. Here, we assess the ability of REFRAME implementations based on different objective criteria to allow signal convergence and thus consistent interpretation of rotational knee kinematics. Previously captured in vivo, kinematic data from a moving videofluoroscope were processed by defining three different flexion/extension axes (cylindrical: CA, functional flexion: FFA, and transepicondylar: TEA), as well as the associated three-dimensional (3D) local femoral frames [4]. Flexion/extension, ab/adduction and int/external rotation according to these frames were determined during stair descent for a healthy subject. The resulting rotations were optimised by using REFRAME to target out-of-sagittal plane rotations based on one of five statistical parameters (root-mean-square error, sum of absolute values, variance, maximum absolute value, and range of motion over an activity cycle).

Results

The use of different methods to define a primary joint axis led to clearly distinct (raw) kinematic signals. Implementation of REFRAME repeatedly achieved signal convergence, regardless of the statistical parameter selected. However, the use of different parameters was shown to influence the characteristics of the resultant optimised signals to certain degree (Fig. 1).

Figure 1: Knee kinematics [°] (tibia relative to femur) for a sample subject stair descent trial before (raw) and after REFRAME implementations with different objective criteria. (CA and FFA covered by TEA in subplot 1 and rows 2-6).

Discussion

Five different REFRAME implementations (based on five different statistical parameters) successfully demonstrated their ability to allow convergence of kinematic signals derived using different methods but originating from a common movement. The choice of optimisation parameter(s) should be methodically selected to specifically address an underlying research question. REFRAME thus offers the flexibility to select from a variety of objective criteria, while consistently allowing a repeatable and valuable representation of joint kinematics.

References

SIMULATION OF MAXIMUM ELBOW FLEXION, EXTENSION, PRONATION AND SUPINATION ACTUATION TORQUES BASED ON ZONOTOPES

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Introduction

Maximum joint actuation torques that operators can perform are essential parameters for biomechanical risk assessment at the workplace. However, work equipment designers generally only have access to this data through the databases provided with digital mannequin software such as Delmia Human, Tecnomatix Jack or 3DSSPP. Moreover, these databases are often approximate [1–3] and sparse, leading to potential under-estimation of occupational risk exposure. In this study, a methodology was developed based on polytopes [4, 5] and musculoskeletal simulation to provide designers with more comprehensive and more reliable estimates of maximum actuation torques. As a partial validation process, this study compared max torques simulated with our tool to experimental measures described in the literature [6]. This experiment focuses on isometric actuation of the upper limb for different postures of the shoulder, elbow and fore-arm.

Method

The upper limb is described as a musculoskeletal system made of m muscles and p rigid bodies linked together by N degrees of freedom (DoF). Let $\mathbf{R} = [r_{ij}]$ be the matrix of the moment arms of muscle $j$ relative to the DoF $i$. $\mathbf{R}$ depends on the posture of the system. The vector $\mathbf{t}$ of actuation torques is linked to the vector of muscle tensions $\mathbf{f}$ by the equation

$$\mathbf{r} = \mathbf{R} \mathbf{f}$$

(1)

The set $\mathbf{T}$ of all achievable muscle tensions is a hypercube of dimension $m$. Its bounds can be computed thanks to a musculoskeletal engine (in this study, we used OpenSim [7]). According to equation (1), the set of achievable actuation torques is the image of $\mathbf{T}$ through the linear mapping defined by $\mathbf{R}$. Linear algebra states that it’s a special type of polytope called a zonotope, denoted $\mathbf{Z}$. The algorithm described in [8] was implemented to compute it efficiently. Any point on the external surface of $\mathbf{Z}$ is an extremum, where at least one joint torque is maximum. Hence, computing maximum joint actuation torques is equivalent to computing intersections or projections of $\mathbf{Z}$ with a line or a surface.

Results

The experiment described in [6] was simulated. The maximum isometric elbow flexion, extension, pronation and supination actuation torques were computed for various postures of the upper limb (shoulder, elbow and fore-arm). For instance, figure (1) shows the 3D-surface of maximum elbow flexion torques. Our simulations show similar trends as observed experimentally [6]. For example, maximum flexion torques show an ascending-descending curve with a peak at an elbow flexion angle about 90°; regarding max extension torques, no significant difference was found between neutral and pronated forearm postures.

Discussion

Considering these experimental and simulated isometric exertions, combining musculoskeletal simulation and zonotope formalism may lead to efficient computations and representations of the complex relations between coupled maximum joint actuations and postures. The validation process should be continued to confirm those encouraging results for non isometric tasks as well. This approach would be a convenient way to provide work equipment designers with more accurate and comprehensive estimations of maximum actuation performances of operators at the workplace.

References


Figure 1: simulated maximum elbow flexion torques for various position of the shoulder, elbow and fore-arm.
DEVELOPMENT OF A PIPELINE FOR 3D PRINTED CUSTOMIZED PLANTAR FOOT ORTHOSIS BASED ON FEM AND GAIT ANALYSIS

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Introduction
Plantar insoles (PI) are among the most commonly used external supports to treat musculoskeletal disorders. It has been reported that they provide therapeutic benefits via direct mechanical and neuromuscular effects on the lower extremities [1]. Even though recently computer aided technologies have been included in the design and production of PI, which were generally based on plaster casting and vacuum forming techniques, the subjective knowledge required by practitioners and lab technicians to develop PI has not been removed yet [2]. Among the current limitations we should consider the postural and pressure adjustments made through various deformation functions by the technicians and the impossibility for the patient to try the PI prior to purchasing it [2]. The aim of this study was the development of a methodology for planning and testing insoles through finite element modelling (FEM) combined with gait analysis and 3D printing.

Methods
A flatfoot geometry was acquired with a 3D scanner (Structure 3D). Plantar pressure data were acquired by pressure insoles (PedarX, Novel) during walking at self-selected speed at the manufacturer site. The foot-floor angle during stance was also measured through a markerless technique [3]. An stl surface was generated from pressure data and processed through Blender, Simplify 3D and PrusaSlicer: three insoles with different infills or inserts were designed and one was 3D printed (Bioflex, straight filling, 90% infill, 3D-Delta WASP-4070). The behavior of the designed insoles was tested in FEM (Abaqus): a previously developed foot model was scaled to match the subject-specific foot geometry, and both foot-floor angles and loads, acquired during gait, were used as boundary conditions [4]. Simulations with and without the three insoles were carried on and the results validated through the comparison with the experimental pressure recorded during gait. Simulated pressures and internal stresses in the plantar soft tissues were compared across the 3 insoles.

Results
Results are reported in Figure 1 and Table 1 in terms of pressure distribution and Von Mises stresses.

![Figure 1: Pressure and Von Mises stresses distribution on the foot with the 3 PIs.](image)

<table>
<thead>
<tr>
<th>PI</th>
<th>Peak Pressure</th>
<th>Peak Von Mises</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cad Cam solid infill</td>
<td>144 kPa</td>
<td>227 kPa</td>
</tr>
<tr>
<td>Straight infill with 2 inserts honeycomb</td>
<td>209 kPa</td>
<td>230 kPa</td>
</tr>
<tr>
<td>Infill 15% Full honeycomb</td>
<td>734 kPa</td>
<td>450 kPa</td>
</tr>
</tbody>
</table>

Table 1: Pressure and Von Mises stresses on the foot with the 3 PIs: peak values.

Conclusions
The simulated pressure and the internal stresses allowed to quantitatively assess the effects of the designed insoles, hence the proposed approach can be used to predict the effects of the designed PI prior to its production. This can aid in planning the insole without the need to perform the traditional long trial-and-error procedures as well as removing the subjectivity associated with the technician. Results showed still a better performance of the PI realized with CAD-CAM approach; therefore future developments will include trying different filling materials, slicing, inserts, and filling distribution.

References
INTEGRATED ASSESSMENT OF GLENOHUMERAL JOINT FUNCTION DURING DYNAMIC TASKS: A PRELIMINARY STUDY

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Introduction
The shoulder complex is characterized by distinctive biomechanics and its peculiar functions exploits the presence of different joints, including glenohumeral, scapulothoracic, sternoclavicular and acromioclavicular ones [1]. Indeed, its inherent structure allows for high mobility, but at the same time - in case of injuries, traumatic events, or pathologies – the shoulder is easily exposed to articular and periarticular problems. In literature, to evaluate the functional aspects of the shoulder complex, human movement analysis approaches [2] and surface electromyography (EMG) systems [3] are the most adopted. However, in the last years, ultrasonography has been reported to enable the quantitative assessment of glenohumeral joint by measuring the translation of the humeral head [4].

The aim of this study was to present a non-invasive in vivo testing procedure aiming at overall assessing the function of the shoulder complex, within a multi-dimensional approach, specifically focusing on the glenohumeral joint.

Materials and methods
The proposed setting included the integration of marker-based optoelectronic stereophotogrammetric system, surface electromyography, and ultrasonography. In this feasibility analysis the subjects were asked to execute two specific dynamic tasks, which characterize the glenohumeral joint function. The proposed protocol allowed an instrumental evaluation able to provide information about overall kinematics, muscular activations and synergies, and joint tissues constraining behavior in terms of humeral head displacement. From this feasibility study, we aim at obtaining simultaneous information about the complex kinematics in terms of multiple degrees of freedom characterizing the shoulder, the corresponding muscular activations – which define the active constraining behaviors of the involved periarticular structures - and, above all, the possibility of tracking the humeral head displacement – which reflects both the active and passive role of shoulder stabilizers; indeed, these data can be acquired during the realization of dynamic tasks and not only in static conditions.

The experimental setup and two examples of images of the glenohumeral joint acquired via ultrasonography are reported in Figure 1.

Conclusion and future works
This work represents a preliminary feasibility analysis of the protocol on a reduced number of subjects, but on-going studies are involving a cohort of subject affected by shoulder disorders in order to characterize their movement patterns in terms of shoulder joint kinematics, muscles activation, and humeral head displacement, and compare them with respect to a control group of healthy subjects.

Therefore, the main purpose of this work was to analyze in depth the complexity of shoulder joint and define reliable features and characteristics for the identification of altered patterns of function by exploiting non-invasive integrated approaches for in vivo assessment in inpatient settings.

References
DATA-DRIVEN FSI SIMULATION OF VENTRICLE AND AORTA INTEGRATING IN VIVO AND IN SILICO DATA

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Introduction
The integration of in silico and in vivo data is crucial to the development of high-fidelity digital twins of the cardiovascular (CV) system, but is a challenging task that requires specific imaging techniques and in silico setups. Advancements in imaging technologies are making it possible to gather a large amount of patient information. In parallel, in silico models are becoming a useful tool to simulate patient-specific conditions, treatments and therapies. However, the latter models require a large amount of physical parameters to be known, which are often very difficult to measure in vivo. In this study, we used data-assimilation techniques to merge high-resolution temporal CT scans with fluid structure interaction (FSI) simulations, resulting in the creation of a high-fidelity digital twin of the left ventricle (LV) and aorta system of a patient.

Material and methods
Gated CT scans of a patient are used to obtain segmentations of the aorta and the LV. Triangulated surfaces are generated for each of the 20 phases available of the cardiac cycle, and lagrangian markers are defined on these surfaces and tracked over time employing a gradient-based registration method [1] (Figure 1A). An in-house code based on the Immersed Boundary method [2] is developed to perform data-driven FSI simulations (Figure 1B), using a hybrid structural model that employs the nudging technique [3] to conform to in-vivo data. A spring-network model is adopted for describing the dynamics of soft tissues. The nudging technique is used simultaneously in a point-wise and integral way. For anatomical regions where in vivo data is accurate, point-wise nudging can be used to follow each individual lagrangian marker. For noisy regions, on the other hand, the nudging is used to follow integral variables such as the overall volume and area of the myocardium. At each outlet of the aorta, the Windkessel model is used to simulate the peripheral circulatory system.

Results
The methods used in this study allow for the accurate reproduction of the kinematics of the cardiovascular structures, which is crucial in order to capture the patient-specific hemodynamics. In addition, the method has the ability to switch from a pure FSI simulation to a pure kinematics-driven simulation in a continuous manner by adjusting the relative magnitude between the nudging technique and the structural model. This allows for greater flexibility in the simulation process, as different scenarios can be tested in order to achieve the most accurate results. The use of different nudging techniques, depending on the kind and quality of the in vivo data, further adds to the versatility and accuracy of the method. In the case of the aorta, point-wise nudging has been used (Figure 1C). For the LV, on the other hand, given the lower accuracy of in vivo data, nudging is used to follow integral variables: both the volume and area of the myocardium are used (Figure 1D).

Discussion
The combination of gated CT scans and FSI simulations has enabled the creation of an accurate CV model, representing a significant step towards the development of high-fidelity CV digital twins, despite limitations in available initial physiological parameters.

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Acknowledgments
This project has received funding from the Marie Skłodowska Curie grant agreement No 859836. FV acknowledges the ERC Stg-project CARDIOTRIALS number 101039657.
IMPLEMENTING DIGITAL TWINS OF THE CARDIOVASCULAR SYSTEM IN CLINICAL SETTINGS: AN AUTOMATED DEEP LEARNING PIPELINE

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Introduction
Cardiovascular diseases (CVDs) are a leading cause of death in Europe, accounting for 45% of all deaths [1]. The adoption of computational power and numerical tools has advanced the development of digital twins for CVDs, but their high computational cost and time have limited their implementation in clinical settings. In this work, we propose a workflow that combines deep learning, reduced order modelling (ROM) and computational fluid dynamics (CFD) to automatically build a digital twin of the patient’s thoracic aorta.

Material and methods
The framework starts with the segmentation of CT scans to create a 3D model of the patient's thoracic aorta, including supra-aortic vessels and the aortic root. To achieve this (Figure 1), a U-Net-based [2] neural network (NN) was trained using a dataset of 50 aortas that were manually segmented from patient-specific CT scans. Using this NN, a first step (raw) segmentation can be automatically obtained. Additionally, a statistical shape model (SSM) was created from the dataset to capture the morphological features of each aorta. The SSM can evaluate the similarity between the newly segmented aortas and the ones from the dataset. Moreover, it serves as a refinement step for the raw segmentation provided by the NN. The statistical information with the patient-specific information from the CT scan are integrated to obtain a high-fidelity segmentation. Finally, hemodynamic indices such as time averaged wall shear stress (TAWSS) can be estimated either performing a CFD simulation, or using a machine learning-based ROM trained on a large scale CFD dataset. The decision can be quantitatively taken based on the shape analysis. The large scale CFD dataset is created by performing transient CFD simulations on 400 synthetic aortic geometries generated using the SSM. The volumetric mesh for CFD simulations is automatically generated through an in-house python script based on ANSA. Each synthetic geometry has its own Windkessel parameters (optimised on the basis of inlet/outlet surface areas) in order to dynamically adjust the pressure at each outlet according to physiological values.

Results
Figure 1 shows the workflow applied to a test CT scan. The first-step automatic segmentation performed through the NN reaches a mean dice score of 0.93 compared to the manual one. Furthermore, the integration with the SSM can eliminate potential errors from the 3d model surface mesh. Regarding the DL-based ROM, a mean absolute error of 5% for the TAWSS, compared to CFD, is reached. Following the statistical shape analysis, if a new aorta is morphologically strongly different from the ones in the dataset, a full-order CFD simulation is performed in order to control the error on the estimated hemodynamic indices. This workflow allows to extract patient-specific information about the thoracic aorta from a CT scan of a patient almost real-time (~30 sec.).

Discussion
A completely automated workflow for the construction of a digital twin of the thoracic aorta has been developed with a significant speed improvement that enables the potential application in clinical environments, without significant loss of accuracy.

References

Acknowledgments
This project has received funding from the Marie Skłodowska Curie grant agreement No 859836.
VERIFICATION OF A PASSIVE ANKLE-FOOT ORTHOSIS DESIGN METHOD BY USING TRUSS MODELS

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Introduction

Passive ankle-foot orthoses (AFOs) are the most common treatment option for people suffering from foot drop. By holding the foot in a neutral position and thereby preventing its drop, a significant improvement of the patients’ gait pattern and comfortable gait speed can be realised [1]. However, the effect is limited and a discrepancy remains compared to the gait of healthy people [2]. Thus, active AFOs driven by motors and external power supply were developed, which allow for adjustability of the required ankle position. Their disadvantages, as high weight or difficult power supply, have inhibited their use in daily life so far [3]. Therefore, we develop a novel passive AFO that is equipped with supporting structures providing an adjustable assistance for patients. The main requirement for the new design is to provide an appropriate assistance for the patients’ needs, i.e. to match the support required by the patient and transfer this support through the product to the patient. A popular tool for investigating the effects of orthoses and similar devices (referred to as wearable assistive devices) are digital human models, allowing to study the biomechanical outcomes of the assistance [4]. In this way, a conceptual method was developed that enables the design of the passive AFO’s supporting structures in accordance with the pathological situation of the patients. This contribution aims to verify the method by using truss models of the passive AFO for different patients’ conditions.

Material and Methods

The elaborated method enables the integration of finite element models in musculoskeletal human models (MHMs) to design the passive AFO. To save computing time, the design of an AFO was discretized for each patient with beam elements and subsequently the number of beams was minimized by means of topology optimization (see Figure 1). The musculoskeletal human models are created from motion capture recordings of subjects in a gait laboratory. By biomechanical analysis of the gait records, the kinematics and externally applied loads at the truss models during the gait cycle are determined. The resulting stresses and deformations are calculated with these boundary conditions in the truss models and the resulting reaction forces are then applied as external forces to the MHM. Thereby, the biomechanical effects of the assistance with a truss model of the AFO can be simulated. By comparing the results, the verification of the method is realized. Therefore, the relation between the provided support to previously determined assistance-as-needed calculations [5] are examined.

Results

The results of the truss support show an activation of the plantarflexor muscles from 20 - 60 % of the gait cycle, referred to as the stance phase and no activation after 60 % of the gait cycle, the swing phase (see Figure 1). The supporting forces and torque depict the majority of provided assistance in the stance phase of the gait cycle and a minor part in the swing phase of gait cycle.

Discussion

The good agreement of resulting biomechanical effects of the truss AFO model simulations (muscle activations and provided support torque) compared to data from previous assistance-as-needed calculations (Figure 1) verify the developed passive AFO design method. Thus, the functionality of the method for providing design suggestions and the possibility to depict the interaction between MHM and AFO is proven. In the next validation step, model order reduced finite element models of the AFO will be used to incorporate a more realistic behaviour of the AFO design in the simulation.

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Acknowledgements

This work was (partly) supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Grants WA 2913/41-1, WA 2913/43-1 and MI 2608/2-1. This work was (partly) supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Grant SFB 1483–Project-ID 442419336.
A COMPREHENSIVE BIOMECHANICAL ANALYSIS OF HEMIPELVIC CUSTOM-MADE RECONSTRUCTIONS IN THE LONG-TERM FOLLOW-UP

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Introduction

The resection of primary bone tumors around the acetabulum and consequent bone reconstruction presents major challenges. Computer-aided design and 3D-printed technologies made it possible to realize anatomical custom-made prostheses that include a porous structure with good short-term results (e.g. [1]).

Aim of the present work is to investigate whether mechanical issues may arise in the long-term follow-up that would suggest considering subject-specific biomechanical factors in the prosthetic design, in addition to the anatomical ones. To this aim we performed a comprehensive biomechanical analysis, in the long-term follow-up, on six patients that received an anatomical 3D-printed custom hemipelvic reconstruction after bone tumour.

We quantitatively estimated:

1) The functional recovery through motion analysis tests that reported a general optimal recovery with kinematic patterns not significantly different between limbs [2];

2) The asymmetry coefficient of the internal loads through personalized musculoskeletal (MS) modelling that showed instead a residual significant asymmetry in the loads between limbs [3];

3) The load distributions in the prosthesis and in the host bone during the two selected motor tasks of walking (most frequent) and squat (bilateral and challenging for reversed asymmetry indices that indicated higher loads on the operated limb), to evaluate the strain/stress distribution in the reconstructed pelvic ring (reported here)

Material and Methods

Six patients (4 males/2 females, aged 31 ± 7 yrs, BMI 22.6 ± 2.9 kg/m2, follow-up time 32 ± 18 months) with an anatomical custom-made 3D-printed prosthesis after pelvic bone sarcoma were included [4]. At the time of the control, patients performed state-of-the-art motion analysis (walking, stair ascent, stair descent, squat and chair rise/sit), and a pelvic CT scan.

State of the art FE models of the reconstructed pelvic ring were generated from the CT data. Bones and prosthesis were modelled with 10-noded tetra, ligaments with tensile-only trusses. Material properties were derived from CT images for bone [5-8], and from literature for cartilage and ligaments [9-10].

Results and discussion

Results from MS models indicated that, despite the optimal kinematic recovery, the internal loads were significantly shifted towards the intact limb (asymmetry index between 5% and 25% on av.), with the notable exception of the squat (18% higher peaks in the operated limb on av.) [3].

FE preliminary results (5 patients): i) the custom prosthesis is generally not at risk of fracture. Peak of flexural stresses were however registered in the small flaps used to close the pelvic ring; ii) the intact bone always remains in safety conditions; ii) the residual bone does not show concerning strain concentrations, on the contrary it is generally shielded by the prosthesis that results to be too stiff, despite its trabecular structure. Values of strain energy density can be calculated to quantify the adverse bone remodeling probability.

In conclusion the preliminary results seem to indicate that there is room for improving the prosthetic design, in particular towards the development of a material structure that better resembles the mechanical bone properties and with particular attention on the small flap features that are used to close the pelvic ring, that seems to be the weakest prosthetic region in common activities.

References


Figure 1: The RX of patient #3 and a particular of the corresponding FE model derived from CT data

Hip and muscles’ forces (19 muscles per side, distributed over anatomical insertion area) were derived from the personalized MS models.
VARIABLE OXYGEN CONDITIONS AND CARDIOMYOCYTE STRUCTURE AND FUNCTION IN NOVEL IMMUNO-HEART CHIP

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Introduction
The immune system is known to play a multi-functional role in the recovery process after hypoxic cardiac injury. This process consists of an acute inflammatory response, followed by inflammation resolution, and then repair of the tissue [1]. Macrophages of certain functional phenotypes (M1: pro-inflammatory; M2: pro-healing) play different roles in each phase of this recovery process. Cardiac tissue is also populated by resident cardiac macrophages, which may also play a role in normal healthy function of the heart [2]. Shifts in macrophage functional phenotype may be required for healing (post-hypoxia remodeling of the heart) play different roles in each phase of this recovery process. As all previous in vitro cardiac experiments have been done without the presence of macrophages or their factors, this study is essential for the design of a novel platform that will establish a baseline of how macrophages and immunomodulatory factors influence cardiomyocyte morphology and function. Furthermore, the results will elucidate the synergistic effect of macrophages on cardiac function such as enhanced electrical connectivity—which may lead to stronger and more coherent force production.

Methods
Experiments involving the culture of both primary neonatal rat ventricular myocytes (NRVMs) and bone marrow derived macrophages (BMDMs) were carried out to examine the juxtacrine and paracrine effects they have on each other. Hypoxia was induced in the cardiomyocytes via a hypoxia chamber, at varying severities and durations. Cardiomyocyte structure was evaluated using custom ImageJ and Matlab codes that quantify architectural changes in cardiomyocyte cytoskeletons and tissue quality [4]. Different media compositions were used to induce M1 and M2 macrophage phenotypes. Macrophage functional activation was evaluated based on measurements of paracrine factor secretion via ELISA.

Results
Co-culture Common Media Formulation A common co-culture media was identified as having no significant effect on NRVM morphology (cell aspect ratio and area) and no significant effect on macrophage cytokine secretion. M1 and M2 stimulated media significantly reduced some cardiomyocyte architecture metrics.

Juxtacrine Co-culture When NRVMs and BMDMs were cultured together (Fig. 1), the presence of macrophages caused a significant reduction in NRVM architecture metrics (Z-line OOP, Actin OOP, mean continuous Z-line length (MCZL)) and tissue quality (Z-line fraction). Additionally, M1 and M2 media stimulations further exacerbated the decrease in Actin OOP and MCZL. In the presence of NRVMs, M1 and M2 macrophages significantly increased their secretion of TNF-α and IL-10 respectively.

Figure 1 (A) NRVM Monoculture and (B) NRVM-BMDM Co-culture. Stains: Nuclei (cyan), Z-lines (red), Actin (green). Triangles indicate macrophages and arrows indicate cardiomyocytes seeded in the same culture.

Paracrine Co-culture NRVMs and BMDMs were then cultured on separate coverslips where they could only communicate through paracrine factors. The same decreases in cardiac architecture and tissue quality observed previously were not observed under paracrine conditions, suggesting that physical contact is necessary to yield the structural changes. M1 macrophage secretion of TNF-α was no longer increased in paracrine co-culture, suggesting that cell-cell contact is required to induce the increased TNF-α secretion. M2 macrophages kept the increased secretion of IL-10, suggesting that NRVMs are secreting a paracrine factor that upregulates IL-10 secretion.

Discussion
Cardiomyocyte and macrophage responses to hypoxia have been studied separately, but the emergent properties that arise from the reciprocal interactions between these two cell types remain poorly understood due to challenges of such investigations in vivo. Moreover, these emergent properties are not necessarily the sum of the individual responses. The objective of this work was to develop a novel immuno-heart chip in order to elucidate the relationship between hypoxia, cardiomyocyte and biomechanics, and cardiomyocyte-macrophage interactions. The next step in this study is to evaluate the co-cultured tissue’s contractility (systolic, diastolic, and active stress) via our lab’s muscular thin film based “heart-on-a-chip” [5].

References
A KINEMATIC AND KINETIC COMPARISON OF THE COUNTER MOVEMENT JUMP AND STOP JUMP RECEPTIONS

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Introduction

Repetitive jumps, changes of direction and running may contribute to increase the risk of overuse injury in sports such as volleyball and basketball. Concerning tendinopathies, epidemiological studies have shown higher rates of patellar tendinopathies than Achilles tendinopathies [1]. Even if the practice of volleyball and basketball implies both vertical and horizontal jumps, no comparison between both jumps have been performed despite possible different implication on injury risk. The objective of this study was therefore to compare a vertical jump (counter movement jump – CMJ) and a horizontal jump (stop jump – SJ).

Methods

Thirty-four volleyball and basketball players (22.1±2.7 years old, 80.2±8.9 kg, 1.86±0.07m) were evaluated for CMJ and SJ receptions. After warm-up and familiarization, the volunteers performed 5 CMJs and 5 SJs. The SJ consists in a horizontal run-up followed by a one-foot horizontal impulsion and finally a bipodal vertical impulsion to perform a maximal vertical jump (Figure 1). In order to evaluate the reproducibility of the tests, the volunteers performed the same session again one week later.

Results

CMJ and SJ present poor to good reliability depending on the parameters studied (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle A (°)</td>
<td>0.62</td>
<td>0.86</td>
</tr>
<tr>
<td>Ankle M (N.m/kg)</td>
<td>0.51</td>
<td>0.11</td>
</tr>
<tr>
<td>Knee A (°)</td>
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<td>0.004</td>
</tr>
<tr>
<td>Knee M (N.m/kg)</td>
<td>0.21</td>
<td>0.71</td>
</tr>
<tr>
<td>Vert GRF (BW)</td>
<td>0.34</td>
<td>0.28</td>
</tr>
<tr>
<td>Ant GRF (BW)</td>
<td>0.58</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 1: Parameters' reproducibility. A stand for angle, M for moment and GRF for ground reaction forces.

The comparison of CMJ and SJ shows significantly different kinematics with less ankle dorsiflexion and increased knee flexion for the SJ. While the vertical ground reaction forces are similar for both jumps, antero-posterior forces are significantly increased during the SJ. The dorsiflexor moment is reduced for SJ but knee flexion moment in increased demonstrating that vertical and horizontal jumps will not solicit joints in a similar manner.

Discussion

The CMJ and SJ receptions only demonstrate relatively low reproducibility. Joint moment reproducibility was lower than previously reported in the literature [2]. It is worth mentioning that despite being a more complex gesture, SJ is not less reliable than CMJ.

Our results have shown significantly different kinematic and kinetic behaviors in the sagittal plane at the ankle and the knee joints demonstrating the complementarity of these evaluations for injury risk prevention.

References


Figure 1: Stop jump bipodal reception before vertical jump.

In this study the bipodal horizontal reception of the SJ was compared to the bipodal vertical reception of the CMJ. 3D markers were placed on the lower limbs (Codamotion, Charwood Dynamics) and receptions were performed on force plates (Kistler). Kinematic (ankle and knee angles in the sagittal plane) and kinetic (ankle and knee moments in the sagittal plane as well as the vertical and antero-posterior ground reaction forces) were computed using Visual3D software (C-motion). To evaluate the reproducibility of the evaluations, intra-class correlations – ICC (A, 1) – were computed as well as paired sample T-tests. To compare the receptions of the two types of jumps, paired sample T-tests were performed on the values measured during the 1st session.
DETERMINATION OF THE INTERNAL LOADS OF THE PROXIMAL PHALANX DURING REHABILITATION EXERCISES

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Introduction

In proximal phalanx fractures, plate fixation has grown in popularity due to their greater construct rigidity [1]. To effectively evaluate any novel osteosynthesis device in this growing application, the biomechanical environment in which it will function must first be understood. While some studies have investigated the loading on the bones in the hand [2, 3], to our knowledge, there has yet to be an investigation that measured the internal forces on the proximal phalanx during rehabilitation exercises. These values are crucial because an osteosynthesis device must be able to sustain these loads over the course of healing; however, they are not readily measured in non-load bearing activities. In this study we developed a method to determine the internal forces on the proximal phalanx during common rehabilitation exercises of fingertip to palm articulation.

Methods

The internal loads in the phalanx were estimated by measuring the displacement of a plastic plate with known material properties and calculating the resultant bending moments in finite element (FE) models. Three human cadaver arm specimens were used in this study. A pre-op high-resolution CT scan (XtremeCT, Scanco) was performed for each hand with a voxel size of 82 µm. The second, third, and fourth proximal phalanx of each specimen was osteotomized with a 3 mm gap at the mid diaphysis. A custom PEEK (Polyether ether ketone) plate was then used to fix the osteotomy with two 1.5 mm cortex screws (DePuy Synthes) on either side of the fracture. Next, the flexion tendons for each digit were isolated and securely fixed to steel cables with sutures. All surgical operations were performed by an orthopedic surgeon. A post-op CT scan was performed with the hardware in place for each phalanx with identical settings as above. After the surgical procedures, the hand was fixed to the base of an electrodynamic testing machine (MTS, Acumen) with the palm oriented upwards. Rehabilitation exercises were simulated by fully extending the hand and then individually flexing each digit until the fingertip touched the palm by pulling on the flexor tendons with the actuator of the testing machine. This test was repeated three times for each finger. The displacements of the bone fragments were measured using a stereographic camera system (Aramis SRX, GOM GmbH) over the course of flexion. FE models of each phalanx were created from the CT scans to achieve accurate bone geometry and hardware placement. The reaction moments at the center of the PEEK plate were calculated by imposing the displacement data measured by the camera tracking system on the FE models as boundary conditions. Descriptive statistics and One-Way ANOVA testing were performed in SPSS 27 (IBM Corp.).

Results

The maximum bending moment calculated in the second, third, and fourth phalanges were 7.24 ± 1.56, 8.02 ± 1.13, and 6.04 ± 1.12 Nmm respectively. The third and fourth phalanx groups were significantly different from each other (p = 0.009), while the other groups were not significantly different.

Discussion

This work demonstrated that the internal loads in the proximal phalanx can be calculated during non-load bearing rehabilitation exercises. These calculated loads are important for the evaluation of new osteosynthesis devices for the proximal phalanx. The non-contact methods developed here could be applied in a similar manner to other regions of the body to better understand the internal forces during non- and low-load bearing activities.

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Acknowledgements

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IN-SITU DETERMINATION OF SPATIAL STRAIN MAPS IN PORCINE GROWTH PLATES BASED ON MRI LOADING EXPERIMENTS

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Introduction

Mechanical loading is one of the regulating factors for longitudinal bone growth. Within physiological limits, compression of the growth plate (GP) has a stimulating effect, whereas exceeding a critical load is linked to the progression of deformities in the skeletally immature [1]. To implement growth modulating interventions, the relationship between mechanical loading and the resulting alteration in growth behavior must be understood. Because of the inhomogeneous morphology of the GP, knowledge of the continuous spatial distribution of strains throughout the GP thickness is of particular interest [2]. Therefore, the aim of this study was to assess the spatial strain distribution of porcine femoral GP under compressive loading.

Materials and Methods

Six fresh porcine knee joints (age: ~6 month) were dissected and mounted in an MRI compatible loading apparatus (Fig. 1), which allowed controlled axial compressive loading [3]. T1-weighted MR images were acquired using a 3T MRI scanner (Philips Medical Systems) for both unloaded and loaded (500 N, 1000 N) conditions [4]. Rigid and non-rigid image registration were performed to obtain the deformation of the femoral GP including the adjacent proximal and distal layers under the respective loads [3,4]. After segmentation of the GP, a distinct transition layer between the GP and the femoral metaphysis (GPmet), along with layers of the femoral metaphysis (Fmet) and epiphysis (Fep), a hexahedral finite element model was created using customized MATLAB routines. Finally, the obtained deformation field was applied to the finite element model to calculate strain maps using ABAQUS. Based on the median strain for each distinct layer, statistical analyses were performed using SPSS, while p ≤ 0.05 was considered statistically significant.

Results

The axial compressive strains in the GP and transition layer (GPmet) were significantly increased by up to 264% compared to the femoral epiphysis (Fep, p ≤ 0.022) for both loading conditions (Fig. 2). In addition, axial strains increased significantly after doubling the load from 500 N to 1000 N (p ≤ 0.028) for all layers. The maximum compressive strain of 7.9% occurred in the anterior region of the GP. Regarding the strains in lateral-medial direction, no significant differences were observed. In contrast, the strains in the anterior-posterior direction of the GP were significantly higher than in the proximal transition layer (GPmet, p ≤ 0.005) and femoral metaphysis (Fmet, p ≤ 0.005) for both load levels.

Discussion

To our knowledge, this was the first study reporting on continuous spatial strain maps of the femoral GP in situ under physiological compressive load conditions in a large animal model. The most important finding of the study indicates that the compressive strains within the cartilaginous GP were up to three times higher than in the adjacent bone tissue. Further, it was found that the strain distribution in the GP was highly inhomogeneous for all six specimens. This knowledge can contribute to a better understanding of the mechanobiology of the GP by identifying the strain patterns in different regions. Based on the determined spatial strain maps combined with the applied load during the experiments, region-dependent material properties can be identified using inverse FE analyses [5]. Moreover, the current approach can potentially be transferred to in vivo applications in human adolescents and thus may provide new insights for epiphysiodesis.

References

EVALUATION METHOD FOR HIGH FLEX LOOSENING OF POSTERIOR STABILIZED FEMORAL KNEE IMPLANTS UNDER DYNAMIC LOADING

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Introduction

Femoral loosening under high flexion is not covered by common biomechanical testing methods [1, 2]. Nevertheless, failures are reported and weight bearing in maximum flexion was associated with early loosening of the femoral component [3]. These failures can occur at two interfaces, bone-cement / implant or bone-cement / bone or as a mixture of these. This study focuses on the bone cement / implant interface.

Method

3 different posterior stabilized knee designs (prototypes and clinically established) were tested in a high flexion fatigue set-up with a minimum of n=3 specimens per test group. All specimens were cemented covering the anterior and distal surface using BonOs® R Genta (Osartis, Germany) on specially prepared aluminum blocks that simulated the prepared distal femur. The bone cement was prepared by vacuum mixing and used in a late stage of the application phase. The dorsal areas of the condyles were not covered to simulate osteolysis and / or insufficient cement application. Tests were conducted in 37 °C heated deionized water to respect the influence of environmental conditions regarding hydrolysis of the interface and mechanical properties of the bone-cement. A flexion angle of 160° was simulated during the test for all specimens. The load was applied with 5 Hz starting at a load level of 500 N, followed by incremental raising the load with steps of 250 N for 200 000 load cycles each until failure. Tests were evaluated regarding number of cycles, load level until failure and failure mode of the interface.

Results

Figure 1 shows the average numbers of cycles and the corresponding load level until failure for each design. Failure with remaining bone cement on both surfaces (implant and set-up) and failure without remaining bone cement on the implant were observed.

Discussion

This test method is appropriate to differentiate between designs of posterior stabilized femoral knee implants regarding the loosening under dynamic loading in high flexion. The number of cycles and load level at failure correspond to the failure mode respectively amount of remaining bone-cement on the implant.

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OSTEOARTHRITIS PATIENTS CLASSIFICATION BASED ON SUPPORT VECTOR MACHINES AND REGULATORY NETWORK MODELS

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Introduction
Knee osteoarthritis (OA) diagnosis is based on symptomatology, assessed through questionnaires such as the WOMAC [1]. But results can be biased by subjectivity, as ache is independent of radiological signs and is modulated by the patient’s psychological status, in addition to biological factors [2]. Finding mechanistic relations among data might reduce subjectivity in clinical decision-making for OA, while allowing the development of data-based prediction models. This study mines the relationships among clinical and molecular data in a cohort of women diagnosed with OA, through Support Vector Machine (SVM) and a mechanistic regulation network model (RNM).

Materials and Methodology
Women (n=51) with Kellgren-Lawrence grade 2-3 OA were classified using SVM [3] based on eight OA descriptors: catastrophe (CA), depression (DE), effusion (EF), functionality (FU), joint pain (JP), rigidity (RI), sensitization (SE), and synovitis (SY). Before the classification, a Youden’s test was performed for each classifier to determine the optimal threshold value for each descriptor. Three types of data were used as input for the SVM: (i) the most appropriate combination of OA descriptors; (ii) proteomic measurements of synovial fluid (SL) including IL-6, IL-8, IL-4, TNF-α, IL-18, INF-γ, IL-17, IL-1RA, and VEGF from 25 patients with effusion; (iii) patient-specific intracellular chondrocyte information (ICI) from transcription factors (i.e., AP1, CREB, FOXO, NF-κB, Sox9, CITED2 AND Runx2) obtained from the SL data out of an in silico RNM [4]. The most relevant input features per classifier were identified based on their relative weights (ω) in the SVM. The performance of each classifier was evaluated using receiver operating characteristic curve (AUC-ROC) analysis.

Results and Discussion
In each classifier in Fig. 1-3, the closest is ω to 1, the more relevant is the feature. Among the clinical data (Fig. 1), subjective inputs (CA, DE, SE) best classify (AUC ≥ 0.7) most of the WOMAC descriptors, pointing out potential bias in WOMAC-based diagnosis.

Acknowledgements

References

Figure 1: A) Normalized importance and B) ROC-AUC curves using OA descriptors inputs, omitted in white.
SIMULATION ENVIRONMENT FOR THE DEVELOPMENT OF NEUROMUSCULAR STIMULATION SYSTEMS

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Introduction
Stroke is one of the major causes of disability worldwide, which often leads to unilateral sensorimotor dysfunction. One possible form of therapy is functional electrical stimulation (FES). It has, however, some disadvantages, such as insufficient selective muscle activation for different grasps, early fatigue, and low force generation [1]. The high time consumption and poor availability as well as the rapid muscular fatigue of the patients limit the experimental studies. The low repeatability, for example due to misplacement of the electrodes and daily changing condition of the patients, further complicates the evaluation of the results. Computational simulations can be used as a fast and standardised alternative. Therefore, we developed a four-step simulation environment that allows us to evaluate selective forearm muscle activation and force estimation as a function of the different stimulation parameters stimulation current, pulse length, pulse shape, and frequency as well as electrode types, shapes, and orientation.

Methods
In the first step we build a finite element (FE) model based on personal MRI data. The model includes simplified geometric and anatomical features: electrodes, skin, fat, muscles, and bones. Stimulation near the terminal nerve branches of the muscles leads to muscle activation. We map this region of interest (ROI) by a defined volume in every muscle [2]. In the second step, we calculate the potential distribution in the tissue electrically transient. As the FE model is a linear time-invariant system, we can derive any stimulus from a short pulse (1 µs 1 mA) via linear combination of the system response using impulse response calculation [3]. If electrode arrays are considered, each element of the array can be assumed as an independent current source and the resulting potentials can then be superposed using Helmholtz superposition principle. For further calculations, only the potentials of the ROIs are used. In the third step, the nerve fibers within the ROIs are defined geometrically to determine points at which the extracellular potential is applied to the nodes of Ranvier of the nerves. Then, nerve activation is determined using either the activation function (AF) [4] or an adapted nonlinear nerve model (CRRSS) [5]. In the final step, muscle forces are determined using an adapted twitch model [6]. Since each activated nerve of the model innervates a motor unit, the forces resulting from the twitches can be superimposed to a total force depending on the stimulation frequency. Finally, we adjusted and tested the model parameters via force, movement, and EMG measurements on a person-specific basis.

Results
The lowest electrical stimulus strength (rheobase) for contraction of the extensor digitorum muscle (ED) is 2 mA (CRRSS) or 3 mA (AF) higher than the experimental measurement. The minimal time to double rheobase (chronaxy) differs from the experimental measurement by 44 µs (CRRSS) or 70 µs (AF) (Figure 1A). The normalised force of the ED shows the characteristic recruitment curve and a good overlap with a RMSE of 0.76% for the CRRSS nerve model (Figure 1B). The AF cannot reproduce that curve.

Discussion
With this simulation environment, we can map the selective activation behavior of the superficial musculature in accordance with experimental data using CRRSS. Thus, specific investigation of the influence of various stimulation and electrode parameters can be done. The environment can also be used to identify suitable stimulation sites by using optimisation algorithms or reinforcement learning without negative effects such as muscular fatigue.

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REMODELING OF 3D MATERIALS VIA A COMBINATION OF THE HOMOGENIZED CONSTRAINED MIXTURE THEORY WITH PLASTICITY

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Introduction

The Homogenized Constrained Mixture Theory (H-CMT) [1] is a cost-effective alternative to its classical counterpart [2]. Even though both frameworks predict remodeling of soft tissues, the former requires less memory storage than the latter. This advantage is achieved through a homogenization in time, which results in an expression involving a stress rate tensor $\dot{\sigma}$. The author [1] used this expression as the basis to formulate a ready-to-use equation that is applicable to 1D-like constituents only. However, if one wishes to predict the remodeling of 3D materials (e.g., dispersed & anisotropic fibers [3]), an equation in tensorial format should be developed instead. In this work, we propose a H-CMT framework, which can be applied to 3D materials. It is formulated by intersecting the founding tensorial expression of the H-CMT [1] with finite plasticity. By re-interpreting the remodeling variable as a plastic term, we were able to predict the remodeling of 3D-like materials based on standard “return mapping” algorithms.

Methods

We assume that the homeostatic stress only triggers remodeling isochorically, that remodeling is incompressible and that the strain energy density function can be split into a volumetric and a deviatoric component. By integrating the expression containing $\dot{\sigma}$ with the backward euler method and by choosing the deviatoric stress invariant $J_2$ as to reduce that resulting tensor expression to a scalar, we obtain

$$f = 0.5(\sigma' - \sigma_p') (\sigma' - \sigma_p') = 0,$$

where $\sigma$ is the current stress, $\sigma_p$ is a backstress variable that emerges from the aforementioned assumptions and the superscript “′” indicates that only the isochoric component should be considered. The scalar in Eq. 1 can be re-interpreted as a standard yield criterion for kinematic hardening, which is commonly used in finite plasticity.

Results

The intersection between the H-CMT and plasticity allowed us to adapt already existing “return mapping” algorithms and test them on anisotropic materials. We chose the strain energy function proposed by [3] to be our test case and we implemented it in our in-house Finite Element Method framework. Fig. 1 shows the evolution of stresses occurring in a completely constrained model. The stress components of the fiber develop such as to approach a homeostatic target.

Discussion

We proposed an extended version of the H-CMT, which is built upon the overlap between the work of [1] and plasticity. This can be achieved by modifying the original stress rate tensor expression in [1] and by using a deviatoric stress invariant as an equivalent yield criterion. The stresses in Fig. 1 converge towards homeostasis in the long term and their development is physically consistent. Due to these preliminary results, now the research community has access to a ready-to-use framework that predicts remodeling of 3D materials.

References


Acknowledgements

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3D STRAIN DISTRIBUTION VIA DVC IN ELECTROSPUN HIERARCHICAL SCAFFOLDS FOR TENDON/LIGAMENT REGENERATION

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Introduction

Tendons/ligaments (T/L) regeneration is complex since scaffolds must have a nanometric fibrous structure and ensure appropriate biomimetic mechanical properties [1]. Electrospinning can replicate T/L from the fibrillar-level up to the whole tissue [1,2]. Recently, Poly-L-lactic acid/Collagen (PLLA/Col) based, electrospun bundles and hierarchical scaffolds (EHS) have demonstrated to drive fibroblasts morphology and alignment both in static and dynamic cultures [3,4]. However, the full-field strain distribution, which drives the cellular fate, morphology and extracellular-matrix production on these structures at work, is totally unexplored so far. To achieve this goal, digital volume correlation (DVC) has proven to be a suitable technique [5]. This study aims at developing the first micro-CT in situ protocol in literature, to investigate the multiscale full-field strain distribution of electrospun scaffolds using DVC.

Methods

T/L fascicle-inspired electrospun bundles and T/L-inspired EHS of PLLA/Col 75/25 nanofibers were electrospun following a consolidated procedure [3,4]. The morphology of scaffolds was investigated via SEM and micro-CT. The mechanical properties of scaffolds were defined with a tensile test using a monotonic ramp to break in displacement control, with a strain-rate of 0.33 %/sec and dedicated capstan grips (n=5 bundles and EHS, hydrated for 2 minutes in saline before the test). The specimens (n=3 bundles and EHS) underwent a stepwise in situ micro-CT tensile tests. After two initial scans with specimen pre-loaded at the minimum strain allowed by the load cell sensitivity (bundles: 2%; EHS: 0%), they were progressively step-wise strained (bundles: 3%, 4%, 5%, 7%; EHS: 1.5%, 3%, 5%, 7%) and tomograms acquired (bundles: voxel size =13 μm; EHS: voxel size = 9 μm) after 15 minutes of waiting at each strain step, to allow for relaxation. To investigate the full-field strain distribution in scaffolds, a DVC analysis (SPAM software) [6] was carried out. For the analysis sub-volumes of 36 (bundles) and 40 (EHS) voxels were used with a 50% overlap (spatial resolution of respectively 468 and 360 μm). The uncertainty of the strain measurements (at the minimum strain step) was two orders of magnitude lower, compared to the in situ test values, for all samples.

Results & Discussion

Scaffolds resulted morphologically and mechanically similar to the T/L counterpart (whole tissue, fascicles and fibrils) [1]. Bundles and EHS showed a ductile behavior with large deformations. The micro-CT in situ workflow combined with DVC successfully allowed the study of the local mechanics of scaffolds. The DVC analysis on bundles and EHS revealed a progressive increment of the internal principal axial strains (εp1) during the test. Strains were mainly associated to the rearrangement of nanofibers and internal bundles during the initial loading regime and gradually distributed in the material with the progressive load. Strain peaks were also found close to clamps due to material constraint. The strain fields were consistent to those measured in natural tendon tissue [7]. These results will help to better understand the full-field mechanics of these electrospun scaffolds and their interaction with T/L cells.

Figure 1: In situ micro-CT image and DVC-computed strain distribution (εp1) from DVC for bundles and EHS at the different strain steps.

References


Acknowledgements

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INNOVATIVE ELECTROSPUN BIOMIMETIC MYOTENDINOUS-INSPIRED JUNCTIONS FOR SOFT ROBOTIC APPLICATIONS

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Introduction
The skeletal muscle can be considered the best actuator in nature. Aiming to reproduce its performances with artificial muscles, in the last years soft-robotics has received significant attention from the scientific community [1]. Among the several techniques to produce biomimetic fibrous muscle-inspired soft-actuators and scaffolds, electrospinning, working at the nanoscale, is one of the most promising [1, 2]. However, a problematic challenge is how to attach these fibrous actuators to the joints they will have to actuate, minimizing stress concentrations. Nature has developed sophisticated conical junctions to connect muscles to their tendons, called myotendinous junctions (MTJ) [3]. The aim of the study is to develop electrospun MTJ of Nylon 6.6 (tendon side) (NY) and polyurethane (muscle side) (PU) with different geometries, investigating their structure via SEM and micro-CT and evaluating their mechanical performances during tensile and fatigue tests.

Methods
Mats of aligned nanofibers were produced on a high-speed rotating drum collector [4] by firstly electrospinning NY, covering with paper masks (triangular for conical MTJ-like junctions and rectangular for flat ones [3]) the areas not to be further covered with electrospun nanofibers, then electrospinning PU. The mats were then rolled into bundles and removed from the collector, obtaining bi-material bundles with junctions of different geometries. In addition, to study the performances of the pure materials, bundles of pure NY or PU were produced and tested. Bundles morphology was investigated via SEM and micro-CT. Mechanical properties of the bi-material and pure bundles were investigated via a tensile test. For the bi-material bundles, the NY part was placed on dedicated capstan grips while the PU part was kept in the middle of the gauge length. Then a monotonic ramp in displacement control at 0.33 %/s of strain rate was applied till breakage for all the fabricated materials (n=5 for each category). Subsequently, for each bundle type (n=5 for each category), a fatigue test with a frequency of 1 Hz in displacement control was performed, cycling inside the linear region identified with the results of the tensile tests. Specifically, 10 packages of 10000 cycles were performed for a total of 100000 cycles. After each package, the specimens were fully unloaded at 0 N and reloaded.

Results & Discussion
The SEM investigation of NY and PU nanofibers showed a morphology similar to tendon collagen fibrils (NY) and muscle fibers (PU). The micro-CT investigation revealed an MTJ-like morphology for conical junctions, while the SEM showed progressive layers of overlap of NY and PU nanofibers along the junctions. As shown in Fig. 1, the mechanical properties of pure NY bundles showed an elastic-brittle behavior, while the pure PU a ductile one with an extensive nonlinear toe region. Both the bi-material bundles showed a ductile PU-like behavior: the one with conical junction showed an extended toe-region and a stiffer linear region, combining the most distinctive features of both materials. The fatigue tests showed a progressive stiffening of pure NY and a progressive decay of force of the pure PU as the cycles increase. The bi-material bundles showed intermediate values of between the two pure materials. Moreover, the bundles with the conical junctions showed a slower force decay compared to the flat ones. These results suggest the ability of the conical junctions to reduce the stress concentrations as the MTJ does.

Figure 1: Typical force-strain A), force-displacement B) and mean maximum peaks of force (and SD) for the cyclic tests C) of the different sample categories.

References

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NOVEL PATIENT-SPECIFIC BEATING HEART MODEL INCORPORATING ACTIVE CONTRACTILITY AND A PSEUDO-FLUID DOMAIN

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Introduction: In this study a framework to construct an efficient patient-specific finite element model of the left ventricle (LV) from tri-planar CINE echography scans is developed. A novel approach of implementing a pseudo-fluid domain inside the ventricle is proposed. Simulations are shown to be several orders of magnitude faster than conventional fluid-structure interaction models of the left ventricle and reveal that the framework is capable of correctly predicting complex pressure-volume (PV) loops for a range of physiological conditions.

Methods: As illustrated in Figure 1A, patient-specific geometries were created by generating splines based on tri-planar CINE echography scans of healthy human hearts using MATLAB. Meshes were generated using 3D continuum elements across two separate domains: a solid domain representing the myocardium, and a pseudo-fluid domain representing the blood in the LV. We develop novel user material subroutines (UMATs) to simulate the actively contractile myocardium in addition to the haemodynamic behaviour of the blood in the ventricle. During systole the pseudo-fluid domain behaviour is based on Windkessel formulation, where the total volume of all elements in the domain is tracked and used to determine the volumetric flow of blood from the LV to the aorta. The behaviour of this domain is governed by a biphasic aortic compliance and the peripheral resistance. Based on MRI and finite element analysis by Concannon and McGarry [1] aortic compliance is shown to be significantly lower at high pressures during systole than during low pressures during diastole [2]. Volume change of the LV is driven by active contractility of the myocardium. This material formulation for the myocardium incorporates sarcomere contractility and remodelling in addition anisotropic collagen structures.

Results: Figure 1B shows the computed distribution of myocardium active stress and fluid pressure during isovolumetric contraction and end-systole. Computed PV loops for the left ventricle are shown in Figure 1C for a case of Inferior Vena Cava Occlusion (IVCO). The model correctly predicts that stroke volume and ventricle pressure reduce over a series of cardiac cycles, as observed clinically. Additionally, in the first cycle a change in slope of the PV curve is computed during systole. However, in subsequent cycles the PV slope is constant during systole as reduced pressure results in a high aortic compliance throughout the cycle, as observed clinically. Computed changes in ventricle pressure as a function of time are also shown in Figure 1(b). Both systolic and diastolic pressure reduce with subsequent cycles. A plot of ventricle volume as a function of cycle time clearly illustrates the change of slope due to biphasic aortic compliance. Finally, computed active contractility as a function of cycle time is shown, demonstrating rapid rise in contractility during isovolumetric contraction, reduced rate of contractility increase during systole, and rapid reduction during ventricular relaxation phase. The authors are not aware of a previous finite element framework that has successfully simulated the complex patterns of ventricle pressure, volume and active contractility during IVCO. Importantly, our novel approach for simulation of active myocardium interaction with blood in the ventricle allows the simulation of a cardiac cycle in under five minutes, in contrast to several hours of simulation time for established fluid-structure-interaction models.

Figure 1: (A) Construction of FE model from tri-planar CINE echography scans; (B) distribution of myocardium active stress and fluid pressure during isovolumetric contraction and end-systole; (C) Computed pressure-volume, pressure-time, volume-time, active contractility-time relationships.

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Acknowledgements:
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AN INTEGRATED FINITE ELEMENT AND AGENT-BASED MODEL TO ANALYSE MECHANOSENSITIVE TUMOUR GROWTH

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Introduction
Tumour growth is a force-sensitive process, regulated in part by mechanical feedback from surrounding tissue [1]. Such mechano-responsiveness can govern tissue-specific risk and progression of cancer, ultimately impacting disease outcomes. However, the underlying biomechanisms by which mechanical loading influences cellular growth and proliferation have not yet been uncovered. In this study, we integrate custom finite element (FE) and agent-based (AB) models to determine how the feedback between single tumour cell growth and mechanical loading could restrict proliferation.

Methods
Model development: Cell size is regulated by an interplay between mechanosensitive ion channels, pumps, actomyosin tension, and cytosolic proteins that coordinate to manipulate cellular osmolarity and subsequently cell volume $V$ [2]. We propose that growth is induced by feedback between electro-osmotic ion fluxes $dc(\phi)/dt$ and biomass synthesis $dX/dt$, such that the osmotic pressure difference across the cell membrane is given by $\Delta P = RT(\sum \Delta c + X/V)$. Cell growth may then be written as $dV/dt = -L_{p,m}(\Delta P - \Delta \Pi)$, where the hydrostatic pressure $\Delta P$ depends on active cell stress and external mechanical loading.

Computational analysis: To consider chemomechanical cell-matrix interactions, a custom FE model was developed and integrated with AB modelling platform PhysiCell [3]. Cell migration and cycling are dependent on forces induced by adhesion, repulsion, and motility. Our framework also exhibits high performance owing to extensive GPU acceleration. Integrating our novel cell growth model, we aim to quantify the external pressure required to inhibit cell division by restricting growth below a critical mitotic volume $V_{\text{crit}}$ (Fig 1A).

Results
Our model predictions for osmotic control of division suggest that cell cycle synthesis drives growth, and that compressive loading can limit the potential for a cell to surpass the size checkpoint for division (Fig 1B). Our integrated FE-AB modelling framework can further characterize multicellular interactions and matrix loading. Simulations reveal that increasing matrix stiffness reduces the rate of cell proliferation in tumour spheroids (Fig 1C), due to the emergent stress-sensitivity of cell growth and division. Mean cell pressure is predicted to converge to a critical value, independent of matrix stiffness, at which proliferation is inhibited (Fig 1D). Cells at the tumour core are revealed to experience higher stress than peripheral cells, as supported by data from excised tumours [4]. Overall, simulations suggest that tumour spheroid size reduces with increasing matrix stiffness in a stress-dependent manner (Fig 1E), in agreement with recent findings [5].

Discussion
Our analyses suggest that stress-dependent tumour growth emerges from a constraint on osmotically-regulated cell growth, whereby cells cannot obtain a critical mitotic volume due to external loading. Simulation of multicellular proliferation using coupled finite element and agent-based models provides unique insight into the evolution of such macro-scale tissue behavior and mechanosensitive growth, with broad applications to patient-specific cancer diagnosis.

References

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KINEMATICS OF UPPER LIMB MOVEMENT IN RHINO:GRASSHOPPER

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Introduction

Every research on human motion is highly dependent on collected data. The accuracy and reliability of gathered data favourably impacts final result. Data processing, interpretation and proper analysis are also essential to retrieve useful joint health information from the system data [2]. The musculoskeletal systems of humans and animals are mechanically very complex and computational models must be highly simplified in order to be reasonably efficient [4]. To be able to gather and process biomechanical data compromises must be made to define boundary conditions. Even so, most of them are investigating gait and lower body activities. The scarcity of upper body models and calculation tools available limit the accessibility of resources for further researches to be made. Every additional software or model that calculates upper body kinematics or dynamics increases diversity. This gives a new approach on the solution and increases accessibility which might result in more research being done in a field. The aim of this paper is to develop and investigate Rhino Grasshopper software and kinematics computational model, which was done to introduce an additional tool that could be used for body motion analysis.

Methods

In this study, 6 BTS Smart DX-600 (BTS Bioengineering, Italy) cameras were used, together with Plug in Gait marker set. In order to study the movement characteristics of the upper body and limbs, a transfer movement was chosen. It is combination of 3 basic motions: lift, pivot, put down. Specifically, a health male subject (184 cm, 82 kg, 27 years old) transferred a patient weighing 57 kg from wheelchair to a bed in accordance with safe lifting guidelines. Total 5 measurements have been taken and 3 most consistent ones selected for further analysis. After initial data processing with BTS Bioengineering software, it was exported to .csv file that is easily accessible to most of the software. This serves as a baseline for further calculations that are being made by Rhino Grasshopper software. This software was chosen to bring low-cost solution to the field of bioengineering. It is based on 3D modelling and node element solutions that offers broad range of easy customisable tools. The extreme values of each joint movement were found and the range of motion (ROM) as the difference between these values was calculated. ROMs are calculated for the shoulder, elbow and wrist joints of the upper limb. To ensure that acquired and calculated data is correct, it has been compared with Biomechanics of bodies BoB software processed data of the same measurement. Finally, the difference (Δ) between the result mean values is calculated.

Results

Difference between results mean values are not exceeding 5% for upper body limbs. Right shoulder range of motion results can be seen in Figure 1. It has mean difference of 1.89° between native BoB and created Rhino Grasshopper models.

![Figure 1: Right shoulder range of motion (Flexion / Extension) calculation between kinematic BoB and Rhino:Grasshopper models](image)

The deviation can be explained in different reference usage. In Rhino Grasshopper model collarbone, together with C7 vertebra and shoulder marker creates main shoulder line plane, while reference of BoB model is unknown.

Discussion

Conceptual, physical and mathematical models have all proved useful in biomechanics [1]. Bringing more tools to the field encourages bigger array of researches and data by increasing availability and accessibility. Regardless of the use, confidence in computational simulations is only possible if the investigator has verified the mathematical foundation of the model [3]. Based on this statement, it is critical to check and evaluate data of every new model or modeling application prior to stating its usability.

References


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MULTI-SCALE CORONARY SIMULATION PIPELINE: VALIDATION AGAINST INTRAVASCULAR VELOCITY AND Pressures

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Introduction

Multi-scale computational fluid dynamics (CFD) simulations are a popular tool to obtain coronary pressures and velocities to make diagnostic assessments or study plaque remodelling. However, validation of these simulation tools, especially those based on non-invasive approaches are currently lacking. The goal of this study was to utilize a fully non-invasive approach to coronary CFD, based on computed tomography angiography (CTA) and evaluate predicted velocities and pressures against invasive measurements.

Methods

Patient Data: CTA, intravascular pressure and Doppler velocity were measured in 13 patients for 120 ± 55 cardiac cycles under resting conditions (see Figure 1A).

Multi-Scale CFD pipeline: Coronary anatomy was reconstructed for 13 patients. Fluid-structure interaction simulations were coupled to lumped parameter network (LPN) to model the heart and distal physiology (see Figure 2B) [1]. ~4% of the cardiac output was fed to the coronary arteries with 70-30 split to left vs. right side.

\[ Q_{\text{Doppler}} = \frac{\text{Area} \times \text{Average Peak Velocity}}{2} \]  \hspace{1cm} (1)

CFD velocity, flow rates and pressures were extracted at locations where intravascular data were measured.

Coronary Flow Rate Estimation: Doppler flow rate was estimated assuming a parabolic velocity profile, according to the following formula:

Statistical Analysis: A Shapiro-Wilks test was performed to check for normality. Since all anatomic and hemodynamic variables were found to be normally distributed, a two-sided paired Wilcoxon signed rank-sum test was used to compare CFD vs. intravascular data.

Results

Pressure: Figure 2 (top panel) shows a statistically significant correlation between CFD vs. intravascular pressures (p<0.01). Bland-Altman plot showed a positive bias of 26.5 [49 – 3.4] mmHg.

Velocity and Flow Rate: Figure 2 (bottom panel) shows no statistically significant correlation between CFD vs. intravascular Doppler velocity. The same was true for flow rates. Bland-Altman plot showed a negative bias of -3 [-16.3 – 10.4] cm/s for velocity (Figure 2, bottom panel), and a negative bias of -16.5 [-86 – 53] mL/min for flow rate.

Discussion:

Our findings demonstrate that multi-scale CFD simulations can predict invasive pressures but not velocities. The poor correlation for velocity data is attributed to boundary conditions that are derived from generic scaling laws and anatomical relations, an approach which is prevalent in the coronary CFD literature. Similar findings have been reported in a recent study that also highlights the deficiency of using such scaling-laws [2]. Improved approaches need to be developed if absolute velocity and flow rate are needed.

References

A METHODOLOGICAL APPROACH TO INTERPRET AND COMPARE THE VISCOELASTIC BEHAVIOR OF BIOLOGICAL TISSUES AND HYDROGELS

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Introduction

Cell behavior is strongly influenced by the physical properties of the microenvironment and complex mechanotransduction mechanisms are involved in cell and tissue development, homeostasis and even pathologies [1]. Thus, when developing materials mimicking the extracellular matrix of healthy or pathological tissues their mechanical features should be closely considered.

In this context, nanoindentation is a powerful technique for mechanically characterizing biomaterials and hydrogels at the cell-length scale, however, standardized experimental protocols and data analysis techniques are lacking. Here, we propose a methodological approach for quantitatively analyzing and comparing the time-dependent mechanical responses of different samples. As an explanatory study, stress-relaxation nanoindentation tests were performed on human and pig lung samples and on hydrogels in order to quantify and compare their viscoelastic properties.

Materials and Methods

Three different samples were mechanically characterized by nanoindentation: a human lung sample from a healthy donor, produced from research-consented organ donors in the framework of the prospective clinical study PROMol, a porcine lung sample from a slaughterhouse, and a gelatin-methacryloyl (GelMa) hydrogel sample, designed for in vitro 3D modelling lung tissue. Stress-relaxation tests were performed by using the Piuma nanoindenter (Optics11) in wet conditions at 37°C (probe stiffness = 0.024 N/m; probe radius R = 25.5 μm) and, setting the indentation mode (max indentation depth dmax = 1.5 μm). To perform stress-relaxation tests the set indentation depth was reached between 0.1 s and 0.2 s. The indentation depth was then held constant while recording the load, and after 5 s the tip was retracted. For each sample, 10 indentations were performed. The experimental curves were then fitted through a genetic algorithm, imposing 15 sets of initial random parameters and a value of the cost function equal to 10^-4 as stopping criteria, and using the Prony-series reported in Eq. 1, which describes the loading history during the holding phase [2]:

\[ P(t) = P(\infty) + \sum_{k=1}^{N} p_k \cdot e^{-t/\tau_k} N = 2 \]

Where \( p_k \) and \( \tau_k \) (the characteristic time constant) are the unknown parameters. The Eq. 2 (where \( \beta_k \) is a parameter used to take into account the non-ideality of the ramp time [3]), based on the \( p_K \) parameters obtained from the fitting procedure and defined as:

\[ g_k = \frac{p_K}{2\sqrt{\pi} \sqrt{\tau} \max p_k} \]

permits to define the relaxation modulus:

\[ G(t) = G(\infty) + \sum_{k=1}^{N} g_k \cdot e^{-t/\tau_k} \]

where \( G(t=0) \) is the instantaneous and \( G(t=\infty) \) is the equilibrium relaxation modulus. Then, for each sample, a set of mean \( p_k \)-parameters was obtained and consequently the mean instantaneous and equilibrium relaxation modulus were calculated, according to Eq. 3.

Results

Representative experimental and fitted curves for the human lung sample show the accuracy of the fitting method (Fig. 2A). Figure 2B shows the curves obtained using the set of mean parameters for all the samples. Average values of the instantaneous and equilibrium relaxation modulus are reported in Table 1.

![Figure 2: A) Representative experimental and fitted curves for human lung sample; B) Curves from mean parameters set for all samples.](image)

<table>
<thead>
<tr>
<th>Sample</th>
<th>G(0) (Pa)</th>
<th>G(\infty) (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUMAN LUNG</td>
<td>29.4 ± 23.8</td>
<td>22.2 ± 17.3</td>
</tr>
<tr>
<td>PIG LUNG</td>
<td>35.6 ± 32.1</td>
<td>23.0 ± 24.1</td>
</tr>
<tr>
<td>GELMA</td>
<td>117.0 ± 58.4</td>
<td>69.1 ± 39.7</td>
</tr>
</tbody>
</table>

Table 1: Average values of instantaneous and equilibrium relaxation modulus for all samples.

Discussion

The proposed approach allowed comparing the time-dependent behavior of the analyzed samples. In detail, nevertheless, the high variability of the results reported in Table 1 due to the heterogeneous nature of the tested samples, a quantitative measurement of the time dependent behavior of each sample was provided in terms of instantaneous and the equilibrium response, calculating the relaxation modulus at the onset and at the end of the holding phase.

References


28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
MODELING IN-VITRO MATURATION OF TISSUE-ENGINEERED BIOHYBRID HEART VALVE IMPLANTS

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Background

Biohybrid tissue-engineered implants offer promising possibilities to treat cardiovascular diseases. Tissue-engineered materials ability to grow and remodel can be utilized to produce implants that can adapt to changes within the human body. However, tissue-engineered materials lack enough mechanical strength to withstand physiological loading conditions. One approach to improve the mechanical properties is by using biocompatible reinforcement material. In our work, we focus on textile-based biohybrid heart valves. The embedment of a load-oriented textile scaffold in the implant acts as biomimetic reinforcement and guides the extracellular matrix (ECM) growth direction. Our main objective is to design biohybrid heart valves that can withstand physiological loading conditions within humans for decades. That makes it necessary to develop accurate and computationally efficient numerical models to support the implant design process.

Methods

We developed a macro-mechanical modeling approach for the maturation process of textile-reinforced biohybrid heart valves. Biohybrid heart valves can be modeled as a composite structure [1, 2]. The main valve constituents are (i) the biological tissue and (ii) the fiber-reinforced textile scaffold. The constitutive model defines the total Helmholtz free energy as the sum of energies of the individual valve constituents. The density of collagen is treated as an internal variable. We propose a new energy-based approach to model the densification of protein fibers during the implant maturation process. In this approach, we consider both static and dynamic cultivation processes. First, the model subdivides the densification rate into biologically driven and mechanically driven parts. In the next step, structural tensors introduce materials anisotropy into constitutive equations. Then, we embed the constitutive model into a solid-shell finite element formulation with reduced integration and hourglass stabilization [3]. By using several Gauss points through the thickness of each element, we can significantly reduce the computational costs of our simulations. Finally, we constructed a finite element simulation for an exemplary heart valve with a tubular design [4].

Results

To test the performance of our model, we constructed a shell structure with simple geometries under pressure loading. Then computed the collagen density evolution and the corresponding deformation and stresses. In the second example, we computed the maturation of exemplary heart valve with a tubular design. In the next step, we investigated the influence of scaffold design on the mechanical properties of the implant.

Figure 1: Cauchy stress contour along the longitudinal direction of tubular heart valve implant

Discussion

The model allows us to predict the evolution of collagen density during the maturation process. Collagen fibers distribution influences the stiffness and, consequently, the implant’s load-bearing capacity and stress distribution. Through this computational model, we can investigate the influence of the implant’s design parameters on the mechanical properties. This can help us to optimize the valve scaffold design and geometry.

References


Acknowledgements

Financial support provided by the German Research Foundation (DFG) for Project “Experimental investigations and modeling of biohybrid heart valves including tissue maturation – from in vitro to in situ tissue engineering” (RE1057/45-1 and RE 1057/45-2, Project number 403471716) of the DFG PAK-961 "Towards a model based control of biohybrid implant maturation" is gratefully acknowledged.
AI-BASED IDENTIFICATION OF ADULT SPINAL DEFORMITIES BASED ON MUSCLE ACTIVATIONS

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Introduction

Adult Spinal Deformity (ASD) is a three-dimensional condition affecting both skeletal and muscle structures. The impact of ASD on functional capacity has been recognized through increasing research on spinopelvic motion strategies during functional tasks, using marker-based motion capture. Despite the involvement of muscles, ASD research investigating muscle properties is scarce. Few studies reported physiological changes, such as increased fatty infiltration and decreased strength of spinopelvic muscles in static conditions. A recent study showed that muscle activity in ASD increased over time during walking. However, this study lacked a control group. The role of muscles during dynamic conditions thus remains understudied. Also, due to the overload of data in biomechanical research, including kinematics, kinetics and electromyography (EMG), and the associated challenge in discovering patterns, we recently started to explore the use of explainable artificial intelligence (AI) in pattern recognition. The goal of this pilot study was to explore the use of an AI algorithm to classify subjects with ASD from subjects with normal spinal alignment solely based on spinal muscle activation during overground walking.

Methods

In this pilot study, a sample of 43 subjects was included (33 ASD / 10 control). People walked at self-selected speed in our motion lab, during which muscle activity of 8 trunk and lower limb muscles around the pelvis was bilaterally measured using surface EMG. Pre-processing of the EMG study, bilateral muscle activation bilaterally measured using surface EMG. For this pilot study, bilateral muscle activation data of the iliocostal erector spinae was used. Pre-processing of the EMG signals included Butterworth bandpass filtering with cut-off frequencies at 20 and 450 Hz and full-wave rectification followed by lowpass Butterworth filtering with a cut-off frequency of 2.5 Hz. For each subject, the full strides of one step sequence were averaged into one left and one right stride. EMG signals were normalized by dividing by the max value per trial. Lastly, the EMG signal was reduced to 16 data points per side, resulting in 32 features per subject (Fig.1). A classifier was then applied on these 32 features using a supervised machine learning approach based on a random forest implementation trained with a 5-fold cross validation (WEKA v3.9). To explain the classifiers predictions, data was then reduced to two single features (a. baseline muscle activity; b. average left-right difference (Fig.1)), after which the classifier was retrained and reevaluated.

Results

Table 1 shows that the model was able to correctly classify 88% (F=0.88) of subjects based on 2x16 datapoints of iliocostal erector spinae activity during walking. Retraining and reevaluation of the model on two single features resulted in 72% correct classification for baseline muscle activity (F=0.72) and average left-right difference (F=0.66), showing these are two relevant biomarkers to discriminate ASD from controls.

Discussion

This pilot study indicated that an AI algorithm can discriminate deformed from healthy spines with almost 90% accuracy, based on EMG waveforms of one left and right spinal muscle. Secondary analysis showed that higher left-right asymmetry and increased baseline activity can partly explain the difference between ASD and controls. Future studies using AI, on larger datasets and other motor tasks, should further explore which other biomarkers can discriminate between ASD and controls, as well as between different ASD subtypes. Eventually, studying the contribution of muscle parameters during dynamic conditions to deformity progression and investigating the effects of interventions (e.g. fusion surgery or physiotherapy) on these muscle parameters will improve our understanding of ASD and lead to improved evaluation and treatment.

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5 Witten, I. H. et al. (Morgan Kaufmann Publishers Inc., 2016)
MECHANICS UNDERLIES IMPAIRED ANGIOGENESIS AND ENDOTHELIAL MOSAICISM IN CEREBRAL CAVERNOUS MALFORMATIONS

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Introduction
The underlying mechanics of pathogenic angiogenesis in the context of vascular disease progression remains poorly understood due to the challenges in force quantification in 3D multicellular systems. Cerebral Cavernous Malformation (CCM) is one such disease characterized by leaky, tumor-like vessels. ROCK1-dependent intracellular tension is one factor responsible for CCM lesions [1]. Further, CCM mutant endothelial cells (ECs) can form mosaic sprouts during invasion by attracting wild-type (WT) ECs [2]. This work combines 3D angiogenic assays, traction force microscopy (TFM), live confocal imaging, perturbation of mechanosignaling pathways, and scRNA sequencing to elucidate the role of impaired mechanics in this endothelial mosaicism for lesion formation.

Methods
We coupled a 3D in-vitro angiogenic invasion assay using extracellular matrix (ECM)-mimicking PEG with 3D TFM. PEG composition was modulated to mimic various stiffnesses, ligand binding, degradability and angiogenic cues. Hydrogels were mixed with either fluorescent beads or fluorescent gelatin for confocal image-based quantification of 3D ECM deformations or ECM degradation respectively. 3D tractions were inferred from ECM deformations around invading non-mosaic or mosaic (with WT-ECs) sprouts for control, CCM2-silenced, CCM2+ROCK1-silenced, and CCM2+ROCK2-silenced conditions. Live overnight imaging was used to visualize dynamics of non-mutant EC recruitment. Finally, immunostaining and scRNA sequencing were used to investigate the modified mechanotransductive machinery at the protein and gene expression levels.

Results
Mutant CCM2 ECs exert higher tractions, show increased ECM degradation, and invade further during both mosaic and non-mosaic 3D angiogenic sprouting. Non-mutant WT-ECs show increased invasion in CCM2-depleted mosaics where they are restricted to follower position by the hyper-angiogenic mutant ECs. These effects are rescued through further silencing of ROCK1 but not ROCK2, or upon treatment with blebbistatin (myosin inhibitor). Fascinatingly, WT-ECs in mosaic mutant sprouts display mutant-like morphologies with increased actin stress fibers, β1 integrin dependent focal adhesions, and nuclear invasion, but surprisingly not higher cell-ECM forces.

Dynamic live imaging revealed the capacity of WT cells to follow mechanically active mutant cells through cell contact, as well as to migrate in tunnels formed by mutant cells through ECM degradation. Force analysis of migrating mosaic cell pairs shows that the leading mutant EC uses pulling forces (on the ECM and on the WT EC) to lead the forward movement of the cell pair. Finally, scRNA sequencing of CCM ECs isolated from the 3D mosaic assay showed upregulation of signalling pathways previously identified in human lesions and mouse models confirming the biological relevance of our in-vitro findings.

Discussion
CCM2 loss leads to a ROCK1-dependent increase in force exertion and ECM degradation by mutant ECs which fuels the invasion of both mutant and WT-ECs. A mechanical continuum forms between the CCM2 mutant leader and the WT followers in which the mutant pulls strongly on the ECM while WT followers do not. Our novel 3D TFM workflows combined with multicellular in-vitro systems provide new tools for identifying disease mechanisms.

References
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DEEP LEARNING APPROACH FOR IN-STENT RESTENOSIS USING BIOLOGICALLY-INFORMED NEURAL NETWORKS

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1. Institute of Applied Mechanics, RWTH Aachen University, Germany

Introduction

Coronary artery disease (CAD) is one of the largest causes of death worldwide. Percutaneous coronary intervention (PCI) is one of the minimally invasive procedures used to overcome CAD by restoring blood flow in clogged coronary arteries. Unfortunately, PCI is associated with several risk factors including in-stent restenosis and stent thrombosis. Drug-eluting stents were developed to counteract the severe restenosis observed after bare-metal stent implantation. The risk of restenosis still prevailed due to the inhibitory effect of the drug on endothelial healing.

The current work focuses on developing a multiphysics-based model using a deep learning framework to include the effect of anti-inflammatory drugs embedded in the drug-eluting stents. An additional advection-reaction-diffusion equation governing the drug transport is introduced herein. Additionally, the effect of drugs, specifically rapamycin-based ones, on the proliferation of smooth muscle cells (SMC) is captured.

Methods

The highly resolved multiphysics model is based on a set of coupled partial differential equations (PDEs), which govern the mechanism of neointimal hyperplasia by capturing the effects of platelet aggregation, growth-factor release, cellular motility, endothelial barrier function and drug deposition [1]. This framework is intended to aid in individualizing the PCI parameters that include stent geometry, balloon overexpansion, and the level of drug embedment. Also, they assist in personalizing the post-operative therapeutic regimens.

Biologically-informed neural networks (BINNs), an extension of the physics-informed neural network (PINNs), are applied to solve the underlying dynamics of biological systems.

Results

Fig. 2 shows the normalized extracellular matrix (ECM) concentration and SMC density 100 days after PCI.

Discussion

The coupled PDEs have been successfully solved using BINNs, where the deep learning results are evaluated and verified by comparing the simulation results of classical finite element methods. Hence, deep learning based on BINNs can be regarded as a reliable methodology for modeling biological systems.

References


Acknowledgements

The German Research Foundation (DFG) for the SPP2311 subproject “In-stent restenosis in coronary arteries - in silico investigations based on patient-specific data and meta modeling” is gratefully acknowledged.
THE MOVEMENTS AND MORPHOLOGICAL CHARACTERISTICS OF THE SACROILIAC JOINT

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Introduction
Dysfunctional sacroiliac joint (SIJ) was considered as a source of the lower back pain [1]. Several researchers investigated anatomy and biomechanics of the SIJ to understand the relationship between the lower back pain and the SIJ. Many studies concluded the SIJ has little movement. However, some of the studies using spinopelvic parameters mentioned high pelvic incidence (PI) change [2]. Moreover, with the development of imaging techniques such as EOS system and vertical CT / MR, interest in sacroiliac joint movement and sagittal balance is increasing. Therefore, in this study, the movement of the sacroiliac joint were investigated by constructing an environment that could be measured and controlled more precisely than in past experiments. And we compared the morphological parameters of the sacroiliac joint between the small and the large movement groups.

Methods
We used 38 fresh cadavers (male 18, female 20). The mean age was 84.25 (81~92) years, and the mean height was 155.47 (142~161) cm. The changes in angle between the sacrum and hip bone were measured with sit and prone positions. Six optical markers were fixed on the surface of the bone directly, and five motion tracking cameras were used. After measuring the SIJ movement angle by weight bearing, the group with small movement and large movement were classified, and the difference in joint surface shape between the groups was analyzed (Fig. 1).

Results and discussions
Based on the SIJ movement angle of 2 degrees, they were classified into two groups (Fig. 2). In the group with small movement (group A), the ratio of males was high at 14 males and 5 females, and in the group with large movement, the ratio of females was remarkably high at 4 males and 15 females. There was no statistical difference in the articular surface shape of the SIJ between the two groups.

Figure 1: Measurement parameters for morphological characteristics of the SIJ.

Figure 2: Histogram of the movement of SIJ. Group A means small movement and group B means large movements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC [mm]</td>
<td>29.97</td>
<td>29.42</td>
<td>0.638</td>
</tr>
<tr>
<td>AB [mm]</td>
<td>57.80</td>
<td>56.88</td>
<td>0.473</td>
</tr>
<tr>
<td>ef [mm]</td>
<td>23.17</td>
<td>22.86</td>
<td>0.789</td>
</tr>
<tr>
<td>gh [mm]</td>
<td>26.76</td>
<td>28.06</td>
<td>0.238</td>
</tr>
<tr>
<td>gi [mm]</td>
<td>39.44</td>
<td>36.83</td>
<td>0.095</td>
</tr>
<tr>
<td>gh [mm]</td>
<td>27.14</td>
<td>28.63</td>
<td>0.177</td>
</tr>
<tr>
<td>gi [mm]</td>
<td>40.91</td>
<td>38.09</td>
<td>0.087</td>
</tr>
<tr>
<td>aeb [deg]</td>
<td>133.79</td>
<td>134.55</td>
<td>0.815</td>
</tr>
<tr>
<td>upper [mm²]</td>
<td>484.50</td>
<td>513.18</td>
<td>0.332</td>
</tr>
<tr>
<td>lower [mm²]</td>
<td>654.68</td>
<td>597.51</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Table 1: Measurements results for morphological parameters of the SIJ

References

Acknowledgements
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (No. NRF - 2019R1A2C1002609)
PARAMETER SENSITIVITY AND OPTIMIZATION OF THE MECHANO-IMMUNO-DRIVEN MODEL OF ENDOGENOUS TISSUE RESTORATION

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Introduction
Endogenous Tissue Restoration (ETR) is a promising regenerative biotechnology in which an implanted synthetic scaffold can transform into a fully remodeled and functional tissue. Computational modeling of this process can facilitate the optimization of the scaffold’s initial properties and degradation rate for a specific application. We describe a model of neo-tissue deposition and adaptation versus scaffold degradation, both driven by mechanical and inflammatory stimuli. We include a parameter sensitivity analysis and calibration to in vivo experimental data.

Methods
A theoretical framework for an ideal thick-walled cylinder was employed to model the growth and remodeling (G&R) of a tissue-engineered conduit graft using the homogenized constrained mixture theory (HCMT). According to the HCMT, the elastic deformation gradient of constituent \( j \) is

\[
F_{ij} = F(F_\rho)^{-1}(F^s_j)^{-1}
\]

where \( F \) is the deformation gradient of the mixture, \( F_\rho \) and \( F^s_j \) are the growth and remodeling deformation gradients, respectively. The densities of every constituent \( j \) also evolve as [1]

\[
\dot{\rho}_j = \dot{\rho}_j^\rho + \dot{\rho}_j^s
\]

Where subscripts + and – represent the production and removal rates. The mass turnover equations, including stress-induced (SI) and immuno-driven mechanisms, were adapted from [2]. The experimental data were collected in a sheep study in the framework of the H2020 SimInSitu project. Using material parameters from baseline scaffold experimental characterization and pressure levels measured during the animal trial, only a subset of 8 parameters - including the fiber material, basal mass turnover parameters, and the duration and shape of the inflammatory response - was selected for optimization. These unknown model parameters were calibrated through an optimization procedure using the animal trial output i.e. the inner radius \( r_i \) over time. Physically sound ranges of parameter values were determined for optimization. A Sobol analysis (SA) was also used to quantify the contribution of the uncertain model input, and their interactions, to the model’s output over time [3].

Results
Fig.1 shows the evolution of the vessel radius in time, for 1 case of the animal trial and the optimized model.

The optimization process was repeated for 50 initial informed guesses. Out of all converged parameter sets, 10 were retained, for which the normalized root-mean-square error (NRMSE) between the model and experimental output was < 0.05 (see fig. 1).

Discussion
As shown in Fig. 1, the model is nicely capable of reproducing the experimentally measured \( r_i \) over time during ETR. For the next phase of the work, we aim to decrease the model uncertainty using more experimental data and to use the model to predict ETR beyond the end point of the animal trials. Next, the model can be used to optimize the scaffold geometry (initial diameter and thickness) and its material properties toward optimal outcomes in terms of desired final radius and mechanical properties of the newly formed vessel.

References

Acknowledgments
The authors would like to thank the European Commission and its Horizon 2020 funding program (Grant ID: 101017523) for providing financial support to the SimInSitu project.
THE EFFECT OF OFFLOADING INSOLES ON GAIT KINEMATICS AND THE IMPLICATIONS FOR PLANTAR PRESSURE MANAGEMENT.

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Introduction
1.5 million deaths each year are directly attributed to diabetes and 422 million people currently suffer from diabetes around the world which is expected to rise to 643 million people by 2030 [1]. 25% of people with diabetes develop a diabetic foot ulceration (DFU) at some point in their lifetime [2] and about £650 million is spent by the NHS on DFU annually in England [3]. DFU prevention using early intervention of offloading footwear or insoles has been shown in the literature to be an effective strategy to reduce the risk of the formation of DFU [4]. This research aims to describe the effect of offloading insoles on gait kinematics and plantar pressure throughout the gait cycle.

Methods
Pilot data was collected on one 26-year-old male healthy subject (height: 176 cm, weight: 95 kg) walking at a self-selected speed on a treadmill. Three types of 10 mm thick insoles were used to offload high-risk foot regions: no offload (control), large calcaneal offload (LCO) and large first metatarsal head offload (LMHO). Measurements of gait kinematics, plantar pressure and ground reactions forces were taken with a 12-camera motion capture system (100 Hz, Miqus M3, Qualisys AB, Gothenburg, Sweden), an in-shoe plantar pressure measurement system (100Hz, F-Scan, Tekscan Inc., Norwood, MA, USA) and a split belt-instrumented treadmill (1000Hz, M-Gait, Motek Medical BV, Amsterdam, Netherlands).

Data was processed for presentation using custom MATLAB code and F-Scan Research 7.0 software.

Results

![Figure 1: The average peak plantar pressure (APPP) for the three insole conditions. The red dash circles indicate the offloading shape. The small square outlines indicate the location of peak plantar pressure.](image)

![Table 1: Plantar pressure and kinematic data for the three insole conditions.](table)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LCO</th>
<th>LMHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average peak plantar pressure (kPa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toes region</td>
<td>449</td>
<td>390</td>
<td>476</td>
</tr>
<tr>
<td>Metatarsal heads region</td>
<td>629</td>
<td>650</td>
<td>708</td>
</tr>
<tr>
<td>Calcaneus region</td>
<td>459</td>
<td>448</td>
<td>496</td>
</tr>
<tr>
<td>Pressure time integral (kPa·s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toes region</td>
<td>28.1</td>
<td>31.4</td>
<td>27.3</td>
</tr>
<tr>
<td>Metatarsal heads region</td>
<td>64.8</td>
<td>68.7</td>
<td>67.0</td>
</tr>
<tr>
<td>Calcaneus region</td>
<td>65.5</td>
<td>61.9</td>
<td>73.1</td>
</tr>
</tbody>
</table>

![Figure 2: Mean centre of force position (CoF) of 10 gait cycles when applying different insole conditions at self-selected walking speed. CoF is measured through an instrumented split belt treadmill with the origin normalized from optical camera measurements of sternum marker position (calculated using MATLAB).](image)

Discussion
This study shows that offloading insoles can decrease the calcaneal centre plantar pressure by 46% shown in Figure 1, which is also seen in other studies [4]. For the calcaneal and metatarsal head offloading condition we observe an 8% and 3% increase in heel strike velocity respectively. This kinematic change both increases plantar pressure and pressure-time integral in other regions as shown by increased peak pressure in metatarsal head region for in LCO condition and calcaneus in LMHO condition. Also for the first metatarsal head offloading condition, we observe a 20% narrower stance in gait, which may create stability problems. Whilst this study only presents results from one healthy subject it demonstrates offloading insoles work by both loading other areas of the foot and by changing gait kinematics. Further testing on diabetics and more participants is required for robust conclusions.

References
FACEMASKS’ PROTECTION EFFICIENCY IN ATTENUATED E. COLI BACTERIA FILTRATION

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Abstract

SARS-CoV-2 is a type of virus about 0.1 micrometer in diameter. The very small size makes it float in the air, and it can be easily breathed in with inspiratory air. In order to curb viral transmission, face covering has been recommended or mandated in indoor or outdoor settings during the past two and half years. Researchers studied the protection effectiveness of different facemasks through filtration testing, fluid flow visualizations, or computations simulations. Very few studies have evaluated the protection effectiveness through direct bacterial or viral reduction rate, which is one of the most straightforward indices for the protection that procedure can offer. The objective of this study was to evaluate the protection efficiency of varying facemasks via bacteria reduction. We designed a closed circulation filtration system where a certain amount of attenuated E. Coli was released into it and the facemask acted as the filter under different flow speeds. A petri dish was used to catch the filtered air to count the number of bacteria that passed through. Under the same flow rate and same amount of E. Coli release, the number of bacteria passing through different face coverings were compared between one-layer cloth, two-layer cloth, surgical, KF94, KN95, and N95, under the assumption of no leakage. The results showed that one or two layer cloth masks are not effective in filtrating out E.Coli bacteria. It indicates that they will not offer good protection in bacteria/virus intensive environment. The rest offers good protection from E.Coli under the situation of no leakage.

Figures

A close-circulation system was designed and built to check the filtration efficiency of different types of face covering from E. Coli (Fig. 1). An inhalation flow rate of 15 L/min was used to simulate the normal inhalation. During the test, the facemask was fixed between the buffer zone and flow conduit 2. Laminar flow regime was expected due to the low flow rate. The E-Coli containing solutions were sprayed into the system. The airflow transported the droplets toward the facemask, among which some would be filtered out by the facemask, while still others would escape the mask filtration and reached the petri dish. The petri dish was left 24 hours inside an incubator at a constant temperature of 25°C for 24 hours. Compare the number of E. Coli after 24 hours incubation are shown in Fig. 2 for one-layer bandana, two-layer cloth mask, surgical mask, and KN94 La Hautuer mask.

References

IMPACT OF VELOCITY ON MUSCLE FORCE GENERATION DURING LONG ECCENTRIC CONTRACTIONS

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Introduction
Eccentric muscle contractions are part of humans’ everyday living. For example, they are functionally relevant during jumping, running, or accidents associated with long muscle stretches. So far, the mechanisms of eccentric force generation need to be fully understood. Several studies reported a drop in force (defined as \(f_p\), Flitney and Hirst 1978) after an initial force peak (Figure 1, \(f_p\)). Interestingly, muscle \(f_p\) was followed by almost linear force redevelopment (Figure, slope2) during extensive stretches (Tomalka et al. 2017). However, how the stretch velocity affects \(f_p\) and force redevelopment remains largely unknown. This study examines the influence of stretch velocity on force generation in long (0.45 optimum fiber length (\(l_{opt}\))) stretches of skinned rat muscle fibers.

Methods
Extensor digitorum longus muscles were extracted from female Wistar rats (n=5). Muscle fiber preparation, permeabilization, and activation techniques were described in detail by Weidner et al. (2022). Skinned muscle fibers (n=39) were mounted in a fiber-test apparatus (600A, Aurora Scientific, Canada), which enabled measurement of fiber force and length. The sarcomere length was measured in the central segment of the fiber with an inverted microscope (Eclipse Ti-S, Nikon, Japan) and a high-speed video system (Aurora Scientific, 901B). Fibers were fully activated by calcium diffusion in the presence of ATP. After an isometric pre-contraction, the fibers were stretched from 0.85 to 1.3 \(l_{opt}\) at 1%, 10%, and 100% of the maximum shortening velocity (\(v_{max}\)).

Results
The force-length traces of the muscle fibers during isovelocity stretches did not reflect the changes in the slope of the underlying active isometric force-length relationship (Figure 1, dashed black line). Muscle fibers showed a steep initial increase in force (Figure 1, slope1). slope1 increased with stretch velocity by 85% \((p<0.001)\). \(f_p\) was absent (Figure 1, solid black line) in slow stretches (1% \(v_{max}\)). Moderate (10% \(v_{max}\)) and fast (100% \(v_{max}\)) stretches yielded a clear “\(f_p\)” (Figure 1, blue and red line). \(f_p\) tripled by increasing stretch velocity (10% to 100% \(v_{max}\), \(p<0.001\)). During the last half of the stretch (from 1.07 to 1.3 \(l_{opt}\), which is within the range of the expected descending limb of the force-length relationship), slope2 increased from 1% to 100% \(v_{max}\) by 180% \((p<0.001)\), from 10 to 100% \(v_{max}\) by 55% \((p<0.001)\), and from 1% to 100% \(v_{max}\) by more than 300% \((p<0.001)\).

Discussion
This study presents the first systematic in vitro investigation of the force response of mammalian muscle fibers subjected to long stretches (from 0.85 \(l_{opt}\) to 1.3 \(l_{opt}\)) at velocities across two orders of magnitude (1%, 10%, 100% \(v_{max}\)). Our results are compatible with forcible cross-bridge detachment, redevelopment of a cross-bridge distribution, and a viscoelastic titin contribution to fiber force during extensive stretches (Weidner et al. 2022). Results of this study regarding the velocity and length-dependency of \(f_p\) can improve muscle models and alter predictions of multi-body models. The observed linear force increase during long stretches might stimulate the interest of biologists, physiologists, and engineers alike as it may contribute to the reduction of necessary neuromuscular control in biological and mechanical locomotion systems.

References

Acknowledgements
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MINERAL MOBILIZATION NEAR THE LACUNAR AND CANAL NETWORK IN LACTATION

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Introduction
Bones constantly remodel to maintain their structural integrity. Additionally, the skeleton is a mineral source to satisfy metabolic demands, such as milk production during lactation. Calcium for the milk is mobilized by resorbing the skeleton. The bone must balance the competing mechanical and metabolic demands during this process. It must quickly supply sufficient minerals to milk while maintaining its structural integrity [1]. Osteocytes are responsible for directing this remodeling process.

Osteocytes are the most abundant bone cell. These cells coordinate remodeling within the bone and directly remodel their surrounding tissue through perilacunar/canalicular remodeling (PLR) [2-3]. PLR is an essential process that has been well-documented in lactation studies. However, the spatial preferences of PLR in the bone are still unclear. In this work, we use images from synchrotron X-ray radiation microtomography (SR\(\mu\)CT) to analyze changes in murine bone microstructure during lactation. Specifically, we analyze the spatial distribution of minerals and the distribution of osteocyte lacunae.

Methods
Tibia from age-matched virgin and lactating mice (n=5/group) were used for this study. Mice from both groups were sacrificed at 16 weeks of age.

The tibias were scanned at the Advanced Light Source (ALS) beamline 8.3.2 with an image voxel size was 1.3 um/voxel. The SR\(\mu\)CT scans were reconstructed using the Python package Tomopy. Paganin phase retrieval was applied during reconstruction to minimize interface intensity peaks and enable local mineralization analysis. SR\(\mu\)CT images were analyzed and visualized using a combination of Python and Dragonfly. Volumetric measurements confirmed that lactation had the expected effect on bone. Microstructural segmentation and distance maps were used to perform an in-depth analysis of bone’s spatial control of minerals.

Results
Lacunar volume measurements showed that the lactating group had significantly larger lacunae than the virgin group (p<0.05). This increase in lacunar volume is expected because lactation induces PLR to mobilize mineral [2]. We measured the spatial distribution of lacunae throughout the bone with respect to the bone’s vasculature and found that larger lacunae tend to be closer to the bone’s vasculature, especially in the lactating group (Figure 1).

Discussion
Our finding that larger lacunae tend to be closer to the vasculature, especially in the lactating group could suggest that PLR has a preference to occur near the bone’s transport system. This could be

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VERIFICATION WHETHER THE POROUS STRUCTURE MANUFACTURE WITH AM METHOD CAN BE SUITABLE FOR CELL CULTURE

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Introduction
The use of 3D additive manufacturing (AM) technology for the production of lab-on-a-chip systems is not a widespread technology [1] and is still under development. A growing number of publications has demonstrated the usefulness of 3D printing as a method for producing micro bioreactors [2, 3]. Currently, commercial 3D printing devices already offer printing resolution of 1-200 µm, and may use biocompatible materials.

Methods
We subjected a SLS printout to topographic and biological tests. Contrary to solid and liquid base methods, SLS does not require designing a porous structure in the CAD model [7], but it allows for obtaining a porous structure by properly setting the process parameters, that is the powder fragmentation. The designed 3D geometry is presented in Figure 1.

Figure 1: Culture disc: a) 3D model of a structure suggested for use in tissue engineering, b) dimensions of the culture disc

The PA2200 powder we used had a PSD of approx. 56 µm and is biocompatibility material. We used the WEHI 164 mouse Cell Line obtained from fibrosarcoma after 32 passages. Five culture discs were subjected to biocompatibility analysis. They were placed in wells A2 to A6, and the A1 well was designated as the reference well. We cultured cell in all wells. After 48 h and 96 h, the cell culture medium in the wells was replaced and microscopic observations were conducted after a week of the incubation.

Results
Based on our assumptions and previous results, the SLS increment technology allowed us to obtain the structure characterized by spatial and surface porosity which turned out to be suitable for cell culture of WEHI 164. The obtained disc structure was characterized by roughness (Sa) of 11.65 µm, a pore size of up to 100 µm, and an average pore size of 37.5 µm (Figure 2). The analysis was carried out on images captured at a 500× magnification using the software included with the Keyence VHX 750 microscope. Due to the preliminary nature of the research and the need to first determine the material properties and the process parameters, the assessment of whether the printed structure promotes the development of cells was only qualitative and based on the comparison of the culture medium colour in the course of the experiment. The colour of the culture medium changed evenly.

Figure 2: Analysis of the surface structure with marked size of sample pores.

It has not been possible, to detach all cells from the discs without destroying the material or damaging the cells, which may further indicate the positive effect of the structure on cell adhesion. Thus a viability test was performed by staining the cells.

Discussion
The SLS technology allowed us to achieve the desired porosity. Our previous experiences suggested a need for designing the disc with a frame; the idea was to help ease cell culture regardless of the used culture vessel type. To separate the cells from the structure, we performed trypsinization. We concluded that trypsinization did not reach all the pores of the structure, probably because the porous structure prevented the cells from leaving certain spaces during the incubation. The AM, which involves sintering PA2200 powder with a laser beam, offers new possibilities for producing convenient surfaces for tissue engineering. Based on micro- and macroscopic examination and observations, it can be concluded that the use of this additive printing technology and this specific printing material offers a wide range of possibilities for future applications in tissue engineering, both in the context of cell culture surfaces and culture platforms.

References
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Acknowledgements
The research of the first author was supported by the National Science Centre, Poland, under the scientific project 2017/27/N/ST7/01490 ("Novel bio-mechanical model of osteophyte development during osteoarthritis").

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
AN INVERSE FINITE ELEMENT ANALYSIS FOR THE DETERMINATION OF THE IN VIVO BIOMECHANICAL PROPERTIES OF THE BLADDER

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Introduction
Urinary incontinence (UI) has a prevalence of a up to 28%, with stress urinary incontinence (SUI) being the most common form [1,2], characterized by involuntary urinary leakage during physical strain, coughing or an increase in intra-abdominal pressure (IAP). SUI occurs when the intravesical pressure exceeds urethral resistance at which the urethra has the capacity to remain closed [2], and/or pelvic ligaments, are not stabilize the urethra. Assessment of bladder neck (BN) mobility in patients with SUI is essentially clinical, however, the imaging techniques such as ultrasound (US) and magnetic resonance imaging (MRI) are used as a method for evaluating this characteristic. The outcomes of radiographic images have been crucial and used as input for numerical methods.

The aim of the present study was to establish the IAP values and the in vivo biomechanical properties of the bladder tissue for two distinct groups (continent women and women with SUI). The numerical simulations of Valsalva maneuver were performed, applying the Ogden hyperelastic constitutive model to the bladder and also the inverse finite element analysis (FEA).

Methodology
To evaluate the presence and symptoms of UI, a sample of 11 women (n=6, Continent (control group) (CG) and n=5 with SUI (IG)) was recruited and submitted to scanning (MRI). In order to obtain the IAP and in vivo biomechanical properties of the bladder in the two distinct groups (CG and IG), it was adapted a 3D computational model (Fig. 1) of the female pelvic cavity [3], that corresponds a nulliparous 24 years old healthy female.

Results
Table 1 presents the material parameters for Ogden constitutive model, applied to the bladder tissue, obtained by inverse FEA for two groups. These parameters were obtained after adjusting the mechanical properties of support structures and IAP for the IG (5.0 MPa).

<table>
<thead>
<tr>
<th>variable</th>
<th>CG(n=6)</th>
<th>IG(n=5)</th>
<th>Variation(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$ [MPa]</td>
<td>0.180</td>
<td>0.202</td>
<td>10.89%</td>
</tr>
<tr>
<td>$\mu_1$ [MPa]</td>
<td>4.839</td>
<td>7.720</td>
<td>37.32%</td>
</tr>
</tbody>
</table>

Table 1. Material parameters of the bladder in women with and without SUI, and variation between the groups.

Figure 2 presents the results of the mechanical response of the uniaxial stress-stretch response for the 2 groups to compare the effect of material parameters (Table 1) obtained in this work, compared with the experimental curve.

Discussion
The biomechanical properties for the bladder of the Ogden constitutive model from the CG and IG have a difference of approximately 47% in stiffness, being greater for IG.

References

Acknowledgements
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Introduction
Recovery of the collagen structure after Achilles tendon ruptures are poor, resulting in high risk for re-ruptures [1]. The loading environment has an effect on mechanical properties of healing tendons but there is still limited knowledge regarding how it affects regeneration of the complex tendon structure. 3D organization of collagen fibers can be visualized at the microscale by phase-contrast microtomography (PhC-μCT) and collagen fibrils can be probed at the nanoscale using small-angle X-ray scattering (SAXS). Recently, SAXS tensor tomography (SASTT) was developed, enabling characterization of 3D structure at nanoscale [3]. This study aims to characterize the effect of in vivo loading in healing rat Achilles tendons by visualizing the regenerating structure at the micro- and nanoscale in 3D combining SASTT and PhC-μCT.

Methods
Achilles tendons from female Sprague-Dawley rats (10-12 weeks) were transected and allowed to heal while subjected to different in vivo loading scenarios [2]; full loading by free cage activity (FL) or unloading by Botox injections combined with steel-orthosis (UL). 3D measurements were performed on healing tendons (1 and 3 weeks, N = 1/group) fixed in formalin. The central part of the healing callus was analyzed by SASTT (cSAXS beamline PSI, 12.4keV, 150µm beam size, 30ms exposure, 6 tilt angles), and the reciprocal space map in each voxel was reconstructed [3] to obtain 3D fibril orientation and structural parameters [4]. PhC-μCT was performed (TOMCAT beamline PSI, 15keV, 4x magnification, 1.63µm pixel size, 33ms exposure) on the same samples and processed with a structure tensor analysis to quantify 3D fiber orientation [5]. 2D SAXS measurements were performed (cSAXS beamline PSI, 12.4keV, 50µm beam size, 30ms exposure) on unfixed, thawed healing tendons (1,2 and 3 weeks, N = 4/group).

Results
Unloading during tendon healing led to generally less material within the callus and a larger percentage of adipose tissue (Fig 1A). It also affected the regenerated fibrils and fibers, by being less packed, more disorganized, and less longitudinally oriented along the main axis of the tendon (Fig 1B). Regenerated fibrils in the unloaded tendon had almost a perpendicular orientation relative to the stumps (Fig 1B). As healing progressed from 1 to 3 weeks, fibers and fibrils within both groups became more homogenously organized and aligned, although UL tendons were not able to reach the same organizational structure as FL tendons. As opposed to FL tendons, stumps in UL tendons remained clearly distinguishable from the surrounding callus at the fibril level (Fig 1C). UL tendons also showed a delayed regeneration of fibril structure within the callus as d-spacing restoration was delayed (Fig 1D).

Discussion
Reduced in vivo loading resulted in a delayed and more disorganized regeneration of the collagen structure within the callus of healing tendons. Additionally, unloading seems to delay remodeling of the stumps during early healing, postponing the callus tissue to merge with the stumps as well as the maturation of the callus tissue. These structural effects due to unloading would strongly affect mechanical properties of the tendon tissue and could be one reason behind the impaired mechanical competence following immobilization during tendon healing [1].

References

Acknowledgements
Funding from the Knut and Alice Wallenberg Foundation and European Research Council (No 101002516). Paul Scherrer Institut, Switzerland for beamtimes at cSAXS and TOMCAT.

Fig 1. A) Microscale organization obtained by PhC-μCT (* = stump, arrowhead = adipose tissue) and B) nanoscale organization obtained by SASTT (number of glyphs = fibril amount, glyph direction = fibril orientation, glyph colour = degree of fibril orientation) in the centre of a 3-weeks fully loaded (FL) and unloaded (UL) healing tendon. C) Representative distribution of fibril d-spacing obtained by 2D SAXS around the stumps in 3 weeks. D) Evolution of average fibril d-spacing obtained by 2D SAXS in the centre of the callus and stumps across healing time.
DEVELOPMENT OF A FEMALE FINITE ELEMENT MODEL OF THE CERVICAL SPINE

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Introduction

The cervical spine a common site of injury in the vertebral column, with severe injuries resulting in permanent disabilities. However, most are minor with a low threat to life. One of the most common neck injuries is whiplash, and the plethora of clinical symptoms and sequelae have been classified as whiplash-associated disorders (WAD). The risk of sustaining WAD has been shown to be significantly influenced by gender. Females are at higher risk of developing symptoms [1]. Additionally, finite element human body models have proven to be fundamental tools for better understanding injury mechanics. As such, the aim of this work is to create a new finite element of the female cervical spine that will more accurately represent the group most affected by such injuries.

Methods

The initial geometry of the created model was obtained from the CT scans of a 49-year-old female subject and was generated using a hybrid methodology of combining medical images and parametric studies. Four different components were modelled: the vertebrae, the intervertebral discs, the facet joints, and the ligaments. Initially, all components were assumed to be isotropic materials with linear elastic properties to simplify the first simulations. Additionally, all ligaments were set to work only in tension. Due to the high element and node number of the complete model, a full simulation would take a significant amount of time. As seen in previous studies, it is possible to analyse and validate sections of the spine before simulating the entire model. As such, the model was divided into functional spinal units (FSU), consisting of pairs of vertebrae. The FSUs were subjected to six moments of pure moments of 1Nm working in flexion, extension, axial rotation, and lateral bending. Throughout the applications of the loads, the range of motion (ROM) was monitored.

Results

The accuracy of the developed model was validated by comparing output predictions with previously published experimental data. The results for flexion and extension were compared with the studies from Nightingale et al.[2] and Panjabi et al.[3]; the results for axial rotation and lateral bending were compared only with the study from Panjabi et al.[3]. As of the time of writing, only one FSU, the C6-C7 segment, has been completely validated. These first simulations show satisfactory outcomes, as seen in Figure 1. The only test that shows results outside of the experimental range is lateral bending. However, this stiffness has been found in previously validated FE models [4,5].

Discussion

The validation of the first FSU shows promising results for the complete validation of the developed cervical spine model. The deviation of the lateral bending results can be attributed to ligament positioning or misalignment between the applied moment and the vertebrae. The next step in this research, besides the conclusion of the validation process, is the addition of more realistic material behavior for most of the components.

References


Acknowledgements

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IMPACT OF SUPERCRITICAL CARBON DIOXIDE AS A DECELLULARIZATION AGENT FOR AORTIC TISSUE

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2 Department of Biomedicine, Biochemistry Unit, Faculdade de Medicina, Universidade do Porto, Portugal
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4 Seara, S.A., Vila Nova de Famalicão, Portugal

Introduction

Valvular heart disease is growing globally due to an increase in the aging population, leading to more valve replacement surgeries.[1] The use of both mechanical and biological prosthesis have reported risks (drawbacks) [2,3], thus new devices aimed at restoring normal tissue function through bioengineered matrices are essential. Scaffolds deriving from decellularized tissues have been used with varying degrees of success for human applications. However, most current protocols are long and use harsh chemicals with a negative impact on the extracellular matrix (ECM) mechanical performance and bioactivity [4]. This work aims to study the potential of supercritical carbon dioxide (scCO2) decellularization to preserve the original aortic tissue bifunctionality, in a faster and more efficient manner.

Methods

Experiments were performed on aortas of 6-months pigs, frozen after collection. The cellular materials were removed from tissues by scCO2 decellularization process. Samples were tested to evaluate the decellularized ECM via hematoxylin–eosin (H&E) staining and DNA quantification. The mechanical properties were analysed via uniaxial testing using a texturometer. The samples’ structure and morphology were characterized using SEM and histological analysis. Biocompatibility are ongoing by direct contact assays using Human Dermal Fibroblasts.

Results

The sc-CO2 decellularization protocol to produce a decellularized matrix was first optimized and validated through H&E staining and DNA quantification (Fig 1a, b, c). Among the several protocols tested, the tissue resulting from a combination of batch followed by semi-continues sc-CO2, was able to produce the desired structures, with increased ultimate tensile strength and young’s modulus of aortic valve while the elongation at break was inferior, when compared to untreated sample (Fig 1i).

Discussion

Supercritical fluid decellularization was able to completely remove cellular material that was embedded within the aorta matrix, with a more compact and rigid structure than untreated specimens and less degraded fibers than traditional treated aortas.

References


Acknowledgements

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LIMITATIONS OF HOMOGENIZED FINITE ELEMENTS ANALYSIS OF DISTAL TIBIA SECTIONS

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2. AO Research Institute Davos, Davos, Switzerland
3. Division of macroscopical and clinical Anatomy, Medical University of Graz, Graz, Austria

Introduction
High-resolution peripheral quantitative computed tomography (HR-pQCT) based homogenized finite element (hFE) analysis allows accurate prediction of stiffness and strength of the distal radius and tibia [1]. Despite the capacity of hFE to predict structural properties, it remains unclear if the homogenization scheme is able to capture high-strain localizations i.e. actual fracture zones [2]. Therefore, the objective of this study is to investigate the compressive post-yield behavior of the distal tibia and to compare hFE predictions with experimental tests by both qualitative and quantitative means.

Methods
Twenty-five fresh frozen anatomic specimens of human tibiae were used in this study. A 3 cm (3 stacks) distal section was scanned by HR-pQCT (XCT II, Scanco Medical, Switzerland). Then, sections were cut out as close as possible to the HR-pQCT triple stacks, lapped, and scanned in a μCT with a 24.5 μm voxel size. The sections were tested in compression up to failure and scanned again in μCT. The scans were then downsampled to 72.5 μm voxel size, similar to HR-pQCT resolution. hFE analysis was performed in order to reproduce the plastic deformation field resulting from the compressive experiment as closely as possible. On the other hand, registration between post- and pre-experiment scans was performed in two steps: 1) rigid registration, and 2) b-spline registration. Quantitative 3D registration assessment was performed using the Dice coefficient. The deformation gradient (F) was extracted in both hFE and registration. Then, volumetric deformation (detF) and the norm of isovolumic deformation (||F||) were obtained using the unimodular decomposition of F (eqn. 1). Finally, a qualitative assessment was performed by looking at the mid-slice of rigid and b-spline registration, and F resulting from both the registration and the hFE simulation.

\[ F = \text{det}(F)^{-1/3} \, \vec{F} \]  

(1)

Results
Structural parameters showed good agreement between the experiment and hFE both for stiffness (R²=0.89, slope=0.96 with 95% CI [0.82, 1.11]) and ultimate force (R²=0.97, slope=1.04 [0.95, 1.12]). The qualitative assessment showed a moderate increase of the mean Dice coefficient from 0.57 (rigid registration) to 0.62 (b-spline registration). The qualitative assessment of hFE sections allowed the classification of the samples into 3 categories: bad (14 sections), semi (6), and good agreement (5).

Discussion
The good correlations between hFE and experiment for structural parameters are similar to previous studies [1]. The qualitative assessment of the plastic deformation field is acceptable for registration but not for hFE. The failure zones determined by hFE correspond to registration only in 20% of the cases. We attribute these discrepancies to local elastic/plastic buckling effects that are not caught by our continuum-based FE approach exempt of strain softening. To conclude, the used hFE scheme captures reliably the elastic and yield response of the bone sections but not the subsequent failure process.

References

Acknowledgements
This work was funded by the ARTORG Center for Biomedical Engineering Research. The AO Research Institute Davos is gratefully acknowledged for the support in mechanical testing.
MECHANICAL PROPERTIES OF THE BICEPS BRACHII ALONG ITS PROXIMO-DISTAL LOCATION

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Introduction

The in vitro measurements of mechanical properties of passive skeletal muscle depend on several experimental factors as showed by Binder-Markey et al. [1]. On the other hand, some experimental parametric studies tackle the issue of the influence of several factors and their importance using healthy skeletal muscle [2-4]. Hereby, to better investigate the transverse anisotropy of skeletal muscle we propose to use an anisotropic hyperelastic model by using recent data obtained by Simon and Zidi [4].

Methods

Equibiaxial tests were performed with transversal slices of Wistar rats’ muscles. Each of the 48 samples was grouped with two factors, the zone (distal, medial or proximal) and the temperature testing (22°C or 37°C). From every sample, we got two experimental curves (along the axis 1 and 2), hence the third factor “Axis” to perform a three-way ANOVA. To take into account the hyperelastic and anisotropic properties of the skeletal muscle, we used an exponential strain energy function with the contribution of two families of orthogonal fibers aligned as:

\[ W = \frac{b_1}{2c_1} (e^{c_1(\lambda-1)^2} - 1) + \frac{b_2}{2c_2} (e^{c_2(\lambda-1)^2} - 1) \]  

Results


\[ I(\lambda) = S_1(\lambda)/S_2(\lambda) \]  

Figure 2: Mean values ± SEM grouped by specimen location for b (the stress-like parameter), c (the exponential parameter) and the maximal nominal stress.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>b (kPa)</th>
<th>c</th>
<th>Smax (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value Axis</td>
<td>0.857</td>
<td>4.55E-04</td>
<td>0.604</td>
</tr>
<tr>
<td>p-value Zone</td>
<td>1.40E-03</td>
<td>0.612</td>
<td>1.77E-04</td>
</tr>
<tr>
<td>p-value T(°C)</td>
<td>0.034</td>
<td>0.024</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Table 1: p-value of material parameters (b and c) and maximal nominal stress by factor (Axis, Zone and Temperature).

Discussion

From equibiaxial traction tests, the used anisotropic model permitted to identify the mechanical properties of skeletal muscle. The results obtained in different zones and for several temperature tests, showed that these experimental factors play a preponderant role in the mechanical behavior of the biological tissue. This is probably due to a greater proportion of connective tissue and a different pennation of the myofibers, as observed in the histological sections.

References


Acknowledgements

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A NOVEL APPROACH FOR QUANTITATIVE MUSCULOSKELETAL ASSESSMENT IN POST-STROKE REHABILITATION

Donatella Simoentti (1), Maartje Hendriks (2), Joost Herijgers (3), Carmen Cuerdo del Río (1), Bart Koopman (1), Noel Keijsers (2) and Massimo Sartori (1)

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Introduction
Assessing post-stroke gait recovery is a key goal in rehabilitation. Clinics typically use observational gait assessments [1] and 3D gait analysis to evaluate motor impairment. These methods have limitations, such as subjectivity and the need for expensive equipment and time-consuming setup. Additionally, current clinical assessments do not provide quantitative metrics on muscle strength and forces and how they affect gait over time. Neurromusculoskeletal (NMS) models [2] in equipped gait labs can provide objective evidence of a patient’s musculoskeletal function. However, the need for expensive equipment and manual sensor placement makes it not practical for clinical use. We developed a technology that includes a modular 64-textile-embedded EMG leg garment, an automated EMG clustering algorithm for quickly locating leg muscles, and an EMG-driven NMS model for estimating muscle-specific activation, ankle muscle-tendon forces, and torques during walking for post-stroke individuals.

Methods
For the study, seven individuals who had experienced hemiparetic strokes were recruited from the Sint Maartenskliniek in the Netherlands. The study involved recording EMG, kinetic, and kinematic data while the participants walked at a self-selected comfortable, and faster speed. A 64-channel EMG grid was embedded in a stretchable garment and applied to the affected leg. The 64 electrodes were then grouped into specific muscle clusters using a two-step non-negative matrix factorization (NNMF) algorithm. The average muscle activation was calculated for both speeds and input into an EMG-driven NMS model to estimate ankle torque. The estimated torque was then compared to experimental torque and torque estimated through manually selected EMG-driven NMS modeling.

Results and discussion
The study found that the NNMF-based EMG clustering method was effective in identifying the location of main leg muscles by analyzing 64-electrode activations during three gait cycles at a comfortable speed. The automatically derived muscle-specific clusters lead to consistent muscle-specific envelopes during both walking speeds. Additionally, the muscle-specific EMG envelopes had sufficient accuracy to drive the NMS model and estimate ankle torques during gait for post-stroke individuals. As a representative example, Figure 1 shows the results of EMG (Figure 1.A) and estimated torque (Figure 1.B) for comfortable walking.

Conclusion
The use of automatic NNMF-based EMG clustering and NMS models enables fast and quantitative assessment of musculoskeletal function in post-stroke individuals. It has the potential to be applied to other injured populations as well for efficient and accurate assessment of gait recovery in the clinical setting.

References

Acknowledgments
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Figure 1: A. Box plots displaying the distribution of R² (red) and NRMSE (blue) values computed between manually and automatically derived EMG envelopes of each muscle, across all subjects and gait cycles during comfortable walking. B. Distribution of R² and NRMSE values computed between experimental torque, and manually (blue) and automatically (red) derived EMG-driven ankle torque estimates, across all subjects and gait cycles at comfortable walking.
EXPERIMENTAL SELF DISINFECTING ALGINATE MODIFIED USING SILVER NITRATE, CHLOROHISSIDINE AND GREEN SYNTHESIS

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Introduction
Disinfection of alginate impression materials is a mandatory step to prevent cross-infection not only to the operator and patient but also to the laboratory technicians. However, post-setting disinfection could compromise the dimensional accuracy and properties of alginate. Thus, the aim of this study was to incorporate CHX, silver nitrate and green synthesized nano silver particles to dental alginate for pre and post setting self-disinfection.

Methods
Methods: Conventional alginate impression material was used in this study. 0.2 % silver nitrate (AgNO3 group) and 0.2 % chlorohexidine (CHX group) solutions were prepared using distilled water to be used for alginate preparation. Moreover, an aqueous plant extract solution was prepared from Boswellia sacra (BS) oleoresin and used to reduce silver nitrate to form nano silver particles that were used for preparation of a third modified group of dental alginate (BS+Ag group). Chemical analysis of the plant extract was performed by GC/MS analysis while characterization of the nanoparticles was carried out by SEM.

Agar disc diffusion assay was used to test the antimicrobial activity against Candida albicans, Streptococcus mutans, Escherichia coli, Staphylococcus aureus, and Micrococcus luteus [1]. Agar plates were incubated at 37 ± 1 °C for 48 h to allow the microorganisms to grow. Diameters of the circular inhibition zones formed around each specimen were measured digitally using AutoCad software. Elastic recovery of alginate was measured according to ISO 1563:1990 using a circular split mold of 12.5 mm diameter and 20 mm height. Specimens were gradually loaded up to 12 N, and then, the samples were gradually unloaded to allow for recovery from the deformation and elastic recovery was calculated [2]. Tear strength was evaluated using a Zwick testing machine until failure at a crosshead speed of 500 mm/min.

Results
GC/MS analysis of the plant extract revealed the presence of 42 volatile and semi volatile active compounds. The CHX, AgNO3 and the BS+Ag modified groups were effective and showed significantly higher inhibition zones compared to the control group against all tested strains (Fig. 1). One-way analysis of variance (ANOVA) showed statistically significant difference in the mean values of tear strength and elastic recovery between all the four tested groups with AgNO3 group reporting higher mean values compared to the others and the control. All the tested groups showed elastic recovery greater than 95 % and tear strength values within the acceptable documented ranges (Table 1).

Discussion
Silver nitrate, CHX and the green synthetized silver nano particles could be promising inexpensive potentials for preparation of a self-disinfecting alginate impression material without affecting its performance.

References
MULTIDIC AND DUODIC: OPEN-SOURCE SOFTWARE FOR 3D DIGITAL IMAGE CORRELATION AND THEIR APPLICATIONS IN BIOMECHANICS

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Introduction

Three-dimensional Digital Image Correlation (3D-DIC) is an optical-numerical technique for measuring the 3D shape and full-field displacement, deformation, and strain, from stereo images of the surface of an object, using digital images captured from multiple views. 3D-DIC is increasingly used in recent years for various biomechanical applications [1], e.g., for characterizing the mechanical behavior of hard and soft tissues, biomaterials, and biomedical devices. 3D-DIC is particularly valuable for identifying material parameters and validating the predictions of numerical simulations. However, the high cost of commercial 3D-DIC software that are typically also proprietary and closed-source, may pose a barrier and hinder the many qualities of 3D-DIC, especially for students and researchers. Recently, a few free open-source 3D-DIC software have been published (e.g., [2,3,4]). Specifically, MultiDIC [3] (github.com/MultiDIC) focuses on multi-view applications and enables the instantaneous calibration of numerous cameras using a dedicated 3D calibration object. DuoDIC [4] (github.com/SolavLab/DuoDIC), on the other hand, works only with two cameras, but offers a simpler calibration procedure that requires only a flat calibration target. Both toolboxes are written in MATLAB, providing the flexibility and simple implementation that meet the needs of the experimental biomechanics community.

Methods

The 3D-DIC procedure in MultiDIC and DuoDIC is organized in four main steps [3,4]:
1. stereo camera calibration: computing extrinsic and intrinsic parameters from a set of calibration images.
2. 2D-DIC (image correlation): analyzing speckled specimen images to identify grids of matching points using spatial and temporal cross-correlation.
3. 3D reconstruction: the results of step 1 and step 2 are combined to reconstruct image points in 3D space.
4. post-processing: the 3D point locations from step 3 are used to derive the full-field displacement, deformation, and strain maps.

We conducted several experiments for validating the displacement and strain results, and for demonstrating their efficacy in various biomechanical studies. Rigid translation and rotation experiments were used to evaluate the accuracy of displacement results and the strain errors (as any deviation from zero strain is considered a measurement error). Additionally, the ability of the 360-deg MultiDIC setup to reconstruct 3D surfaces from more than two cameras was examined by computing the merging errors between overlapping surfaces reconstructed by adjacent camera pairs.

Results

Using DuoDIC, with two cameras in a stereo setup, rigid body translations (15 increments of 0.2 mm) were accurate to within $(1.3\pm1.1)\times10^{-3}$ mm (mean±STD) and the strain errors were $(3.4\pm2.3)\times10^{-4}$. Using MultiDIC, with 12 cameras in a circular array, a full 360-deg 114 mm diameter cylinder was reconstructed with merging errors of 0.06±0.03 mm.

Discussions

We demonstrate the efficacy of open-source 3D-DIC software, such as MultiDIC and DuoDIC, in various biomechanical investigations. The software were successfully used in various biomechanical applications, such as imaging below-knee amputees’ residual limbs [5] for informing patient-specific prosthetic socket design [6], measuring human facial deformation for designing conformable wearable sensors [7], and for identifying unique sets of hyperelastic soft-tissue material parameters from indentation test results [8].

References

ULTRASTRUCTURAL STUDY OF INDUCED VASCULAR DAMAGE CAUSED BY IN VITRO STENTING

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Introduction
The number of coronary stent implantations (CSI) is rapidly increasing worldwide, with the most challenging complication after CSI being restenosis [1]. In addition to inflammatory processes, the degree of restenosis primarily correlates with the severity of vascular injuries [2], which are unavoidable during and after CSI interventions. To reduce the fatality rate of stents in CSI, scientists and manufacturers must develop safer stents by significantly reducing the risk of vascular injury. Therefore, in this study, we aimed to investigate coronary artery damage induced by in vitro stenting. This study of vascular damage is based on a biomechanical experiment simulating the loading conditions of stenting in vitro. After mechanical testing, damage to a coronary artery by in vitro CSI was investigated at the ultrastructural level using electron microscopy.

Methods
To simulate the in vitro loading condition during CSI, inside a custom-built test chamber, a square sample of a porcine coronary artery was stretched in two orthogonal directions while a stamp in shape of a stent-strut was indented into the sample with defined loads and orientations. To demonstrate the structural alterations under loading, coronary artery walls (unloaded vs. biaxially loaded and stamped) were chemically fixed with glutaraldehyde and prepared for electron microscopy investigations. On the one hand, the surface and the cross section of the vessel were examined using scanning electron microscopy (SEM), on the other hand, mechanically important constituents such as collagen, smooth muscle cells (SMCs), and proteoglycans (PGs) in the artery layers were made visible using electron tomography (3D-TEM).

Results and Discussion
The SEM results obtained in this study revealed that damage to the surface of the coronary artery after stenting was more pronounced when the stamp was oriented longitudinally than circumferentially. This could be explained by the structural composition of the media, where collagen fibers are preferentially oriented in the circumferential direction. Accordingly, it would be reasonable to design the stent network in such a way that the stent struts are primarily oriented in the circumferential direction. However, this is not the solution to avoid in-stent restenosis. The endothelial layer of the coronary artery was completely removed/injured under and around the area of the indented stent strut. Therefore, the development of restenosis will occur regardless of the orientation of the stent strut.

Regardless, the results showed that not only the intima of the coronary artery was damaged, but also the tunica media. The SMCs in the area of the stent strut were severely damaged, so that their functionality was questionable. It appears that the collagen fibrils were able to withstand the enormous mechanical stresses from the applied stent loads. Interestingly, PGs rearranged between the collagen fibrils. This behavior was detected by 2D TEM and could be confirmed with the help of 3D TEM and subsequent 3D reconstructions. Those revealed that PGs under the stented area were displaced by the dense structure of collagen fibrils, where PGs accumulated (see Fig. 1). This reorientation and clustering of PGs was more pronounced below the stamp mark than lateral to the stamp edges.

References

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MECHANICAL MODEL OF HUMAN STABILITY ON EXTERNAL FORCE-CAUSED FALL

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Introduction
Human movement analysis is an increasingly popular topic. However, there is still a need to develop knowledge about estimating the forces and moments of forces acting in the joints, since they cannot be measured unequivocally. The task gets even more difficult when the external force acting on the human body occurs. Thereto, the authors propose a model of human motion treated as a semi-closed chain, defined by the Euler-Newton equations [1]. This model was tested on the example of a force-caused fall, i.e. a fall that may occur during a sudden braking of a public transport vehicle. The input data were obtained with the use of an optoelectronic motion capture system BTS Smart, AMTI dynamometric plates and a dynamometer. The proposed model can be later on applied in devices for monitoring and assessing human movement.

Human body biomechanical model
The developed mechanical model can be described as a partially closed-chain two-dimensional model. Both legs are standing on separate dynamometric platforms so, the information on ground reaction forces (GRF) and centre of pressure (COP) of each of the lower limbs can be taken into calculation. Therefore, the values obtained from the platform on which the right leg is standing are treated as input data, while the analogous values obtained from the other platform are used to validate the model and the entire calculation procedure. This makes a closed chain from the right to the left lower limb. The part which makes the model partially closed chain is the upper part of the body – upper limbs and torso. To calculate the inertial and mass parameters, Demster’s model was applied [2].

Mathematical model
In the described model the human body was divided into 13 segments: 2 feet, 2 shanks, 2 thighs, a torso with a head as one segment, 2 arms, 2 forearms, and 2 hands. For each segment, the set of three equations was written, in agreement with the Newton-Euler method. In the end, the set of 39 equations and 39 unknowns is obtained. To calculate the necessary acceleration input data, Taylor’s series was used. This scheme was also applied for smoothing the data.

Results
The presented method allowed for the acquisition of a mechanical model of human motion in two-dimensional space. The vertical (Y) and horizontal (Z) forces obtained with the use of the model and measured by the force plates are shown in Figure 1. Additionally, the waveform of the external force applied to the participant is shown. One can notice, that the waveform representations of the GRF in time are less accurate when the system is perturbed by an external disturbance – while accelerations and inertial parameters have a more significant impact on the performance of the model. However, the vertical force calculation gives an accurate outcome.

![Obtained vertical and horizontal GRF and vertical GRF measured with the force plate for the external force-caused fall with a single pull.](image)

Conclusions
The proposed model can be considered sufficient for biomechanical studies. The inertial parameters of segments of the body have a crucial impact on the performance of the model, especially when studying fast-changing movements.

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COUPLED MODELING OF DRUG-COATED BALLOON TREATMENT OF PERIPHERAL ARTERY DISEASE

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Introduction
Peripheral artery disease (PAD) affects more than 200 million people in the world above 25 years of age [1]. The most common method of mitigating the effects of plaque buildup that causes PAD is balloon angioplasty which involves inserting a catheter into the narrowed part of the artery followed by balloon expansion and pushing the plaque on one side of the artery [2]. This sudden expansion damages the arterial wall and the body’s tissue repair mechanisms react, causing inflammation and restenosis by extensive tissue proliferation at the site of the procedure. Hence, drug-coated balloons were developed to deliver antiproliferative agents, such as paclitaxel, directly to the arterial tissue to prevent restenosis [2]. Computational models have provided insight into paclitaxel absorption and release with high precision; but the research was focused on drug-eluting stents [3]. Drug release and kinetics research on DCBs has been limited to extensively simplified 2D models which are intrinsically very constrained [1]. This abstract presents a 2D solid-fluid interaction model which is a novel method for solving the problem of drug absorption after the balloon has been deployed.

Methods
The computational procedure is implemented in PAK finite element (FE) solver [4]. The DCB is modeled as a linear elastic material with Young modulus of 920 MPa, Poisson’s ratio of 0.4, and material density of 1100 kg/m³. The flow of drug from the DCB is modeled using the Navier-Stokes equation while the artery is modeled using a hyperelastic Ogden model. Finally, the calcified arterial plaque is modeled using a modified Mooney-Rivlin model.

Results
The interface of the module designed in CAD Fields and Solid specifically for DCB treatment of PAD is shown in Figure 1. The model consists of a plate that mimics the expandable balloon and the pressure used for balloon inflation is approximated using prescribed displacements for each balloon. The balloon area is depicted by the marked zone of elliptical shape, and it is idealized with no fluid flow and no random drug diffusion. The mechanics described by the model are balloon inflation, plaque and arterial wall compression, and drug diffusion in steps depicted in Figure 2.

Discussion
The model can be used for the evaluation of the impact of DCB inflation time on angioplasty procedure, sequential application of multiple DCBs, inflation pressure on the timing of drug transport, and the amount of drug washed out of the system due to circulatory blood flow. This and prospective tissue-rupture and restenosis models are intended for in silico optimization of DCB angioplasty and maximization of drug effects.

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Introduction
The aortic valve is prone to dysfunction as it has to withstand a high-pressure gradient during diastole [1]. One of the most common aortic valve diseases is aortic valve stenosis, which is defined by the narrowing of the valve opening area caused by stiffening of the leaflets due to calcifications that restrict the valve movement. For high-risk patients, the disease is treated by Transcatheter Aortic Valve Implantation (TAVI), a minimal invasive technique in which an expandable prosthetic valve is inserted into the aortic root via cardiac catheterization. TAVI is still associated with a high risk of complications such as paravalvular leakage (PVL), where blood can flow back into the left ventricle [2]. In this contribution a computational framework to model the TAVI procedure is introduced which can be used to perform a fast, qualitative pre-operative risk assessment of paravalvular leakage.

Numerical method
An explicit finite element model is developed to simulate the TAVI procedure in patient specific, or synthetic, aortic root geometries. To verify the model, convergence tests on a periodic part of the initial device geometry, representing one loop of a CoreValve TAVI stent, are performed. To study the effect of the degree of calcification on the risk of paravalvular leakage, devices of different sizes are simulated for mildly and severely calcified valve leaflets. Finally, a postprocessing tool is developed to perform a pre-operative risk assessment of paravalvular leakage, using the deployed shape of the device and the patient specific aortic root anatomy. To this end, the Reynolds equation for a pressure driven, stationary, incompressible, viscous Poiseuille flow [3] is solved on the fluid volume between the aortic vessel and the device in the vicinity of the aortic annulus.

Results
Results show that the presence of calcifications on the valve leaflets lead to an increased risk for paravalvular leakage. Figure 1 shows the simulation result of a medium sized device deployed in a highly calcified synthetic aortic geometry for an average female. To estimate the leakage, the fluid flux is calculated and is indicated by the arrows. An estimation of the regurgitant flow rate of blood flowing past the device back into the left ventricle can be obtained using this method. Furthermore, the method allows for fast qualitative patient-specific profiling of PVL.

Discussion and conclusion
The developed computational model can be used to perform a pre-operative risk assessment of paravalvular leakage in patient specific aortic root anatomies. The method presented here allows for fast, qualitative patient-specific profiling of PVL for different aortic pressures. A first validation shows that the regurgitant flow rate is larger for a more severe degree of stenosis. Validation of the computational deployment framework will be performed by comparing numerical results of the deployed shape of the TAVI device to patient specific data.

References

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CAN OSTEOARTHRITIS AFTER ACL RECONSTRUCTION BE EXPLAINED BY (ALTERING) GRAFT MECHANICAL PROPERTIES?

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Introduction

Each year, 1% of active individuals rupture their Anterior Cruciate Ligament (ACL) [1]. Torn ACLs are often reconstructed using tendon autografts. However, in approximately half of the patients, ACL reconstruction (ACLR) leads to osteoarthritis (OA) within 5 to 15 years [2]. We hypothesize that OA results from a mismatch in mechanical properties between the native ACL and the used tendon grafts. Moreover, due to in vivo graft remodeling, graft stiffness decreases and knee laxity increases. It remains unknown however whether these changes contribute to the development of OA. Therefore, this study aims to assess the influence of altering graft mechanical properties on knee kinematics and cartilage loading, as a measure for the risk of developing OA.

Methods

The stance phase of the gait cycle was simulated in 4 subject-specific open-source available finite element models in the FEBio software [3,4]. The material properties of the ACL were adjusted to match currently used grafts, e.g. patellar (PT) and hamstring tendons (HT), at surgery. In addition, hypothetical, but clinically relevant, grafts with a range in decreasing stiffness, increasing transition strain (knee laxity), and a combination of both were implemented to mimic grafts during and after in vivo graft remodeling. The effect of these grafts on knee range of motion (anterior tibial translation (ATT) and internal tibial rotation (IR)) and tibial cartilage contact pressure were determined at the point of maximum posterior force on the femur.

Results

Reconstructing the ACL with a PT or HT graft resulted in a decrease in ATT and IR, and a minor relocation of tibial cartilage contact pressure. Moreover, both ATT and IR increased with decreasing graft stiffness and/or increasing knee laxity in 3 out of the 4 patients (Figure 1). A clear relocation in tibial cartilage contact pressure was found with a decreasing graft stiffness and/or an increasing knee laxity in those 3 patients (Figure 2).

Discussion

Currently, ruptured ACLs are mainly reconstructed using PT or HT grafts. Although initially those grafts do not substantially influence knee range of motion and tibial cartilage pressure patterns, a decreasing graft stiffness and increasing knee laxity, as clinically observed during graft remodeling, do. The increase in ATT and IR, both movements the native ACL restricts, indicates changed knee joint mechanics. Together with a relocation of the tibial cartilage contact pressure, this suggests abnormal loading of the knee which can lead to OA [5]. Interestingly, one of the patients did not show altered knee translations or tibial cartilage pressure patterns, indicating that not every patient might be at risk for the development of OA, which is in line with clinical outcomes. Altogether, this model paves the way towards the development of a patient-specific prediction model for ACL-reconstruction-induced OA. Besides, these results suggest the need for novel grafts with mechanical properties that match the native ACL and/or grafts that circumvent in vivo graft remodeling.

Figure 1: The ATT and IR are increased in grafts with a combination of decreased stiffness and increased knee laxity. With respect to the ACL, C1 has 59% stiffness and 132% laxity; C2 30% stiffness and 152% laxity; C3 19% stiffness and 163% laxity; C4 11% stiffness and 198% laxity; C5 7% stiffness and 290% laxity.

Figure 2: A relocation in tibial cartilage pressure is found with decreasing graft stiffness and increasing knee laxity.

References


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ARE KINEMATICS AND MUSCULAR FUNCTION ASSOCIATED WITH MOSAICISM TYPE IN MALES WITH FRAGILE X SYNDROME?

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Introduction

Fragile X Syndrome (FXS) is the leading form of inherited intellectual disability and autism spectrum disorder, caused by the transcriptional silencing of the gene Fragile X Messenger Ribonucleoprotein 1 (FMR1), which encodes an RNA binding protein that is implicated in a multitude of crucial neurodevelopmental processes, including early embryonic motor circuits [1]. There are two main categories of FMR1 mutations, “premutation” and “full mutation”, that are associated with different clinical phenotypes, and somatic mosaicism can represent a strong FXS phenotype modulator [2]. Mosaicism in FXS refers to two different FMR1 allele variations: size mosaicism (i.e. different numbers of CGG repeats between the two alleles), methylation mosaicism (i.e. full-mutation allele is fully or partially methylated) [3]. The present study explored the association between full mutation and/or mosaicism types, and musculoskeletal alterations in terms of gait analysis in a group of FXS children.

Methods

After appropriate informed consent by the parents, the gait of 36 FXS children ((FX) mean(±SD) age of 10 (±3.6) years, BMI of 19.4(±3.6) Kg/m2) and 10 controls ((CS), mean(±SD) age of 10 (±3.07) years, BMI of 20.4 (±4.5) Kg/m2) was assessed at the BiomovLab (CS) and at the Paediatric Department of the University of Padua. Within the FXS group 28 children with full mutation ((FX-FM), 3 children with methylation mosaicism (FX-MET) and 5 with size mosaicism (FX-DYM) were evaluated. Kinematics in terms of joint angles and surface electromyographic data (sEMG) were simultaneously acquired through four synchronized cameras (GoPro Hero3, 30fps) and an sEMG system (FreeEmg, BTS, 1000Hz) that collected the activity of Tibialis Anterior, Gastrocnemius Lateralis, Rectus Femoris and Biceps Femoris. At least three left and right gait trials per subject were processed. From sEMG parameters, envelope peak and its occurrence within the gait cycle were computed, sagittal plane kinematics was assessed from video recordings [2].

Results

In terms of sEMG, FX-FM and FX-DYM showed alterations on the sEMG signals in all muscles analysed with respect to CS during loading response, midstance, and midswing, FX-DYM also during push off. Even though FX-MET didn’t show any statistically significant differences neither with CS nor with FX-FM, their pattern differs from all the considered populations. In terms of joint angles FX-DYM and FX-MET showed significant reductions at the level of all the analysed joints when compared both with CS and FX-FM. An examples of the results is reported in Figure 1.

Discussion

Results, even though preliminary, seem to suggest that FX-DYM and FX-FM presented the same differences in the pattern in terms of sEMG when compared with CS, while FX-MET displayed a pattern more similar to CS, meanwhile in terms of kinematics the data showed similar alterations in FX-MET and FX-DYM.

References

DEVELOPMENT OF A HUMAN WHOLE-BODY MODEL TAKING INTO ACCOUNT THE CONNECTIVE TISSUE

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**Introduction**

Connective tissue is an essential component of multicellular animal life. Its main component collagen is one of the most important basic building blocks in our body. Connective tissue plays a significant role in spatial organization, stabilization and force transmission. Because almost all structures are interconnected by connective tissue, their stiffness is adapted depending on the requirements. Stiffness is determined by collagen types, proteoglycan content, and structure.

Computer simulations offer a way to analyze these complex structures in more detail. A frequently used method is the finite element method (FEM). Using FEM, the structures under investigation are decomposed into finite elements with specific properties. Geometries and spatial stiffness orientations are crucial for the accurate description of properties/materials. These geometries can be determined by imaging techniques and the stiffnesses can be determined by material samples in experimental setups. The determination of the stiffness orientation is challenging because it requires more resources (Sartori & Stark 2021).

The aim of this study is to build a human model considering the connective tissue to understand the interaction of elements/organs across a larger domain.

**Material & Methods**

We started from a FE model (trunk-model) that was created in a previous study and is based on the data from the Visible Human Project® (VHP) (Stark et al. 2016). That model contained the geometries for the bony elements, the intervertebral discs and the musculature, including their fiber architecture.

For the present study, we included data sets of a male and female body donor (♂:39 years, 90.26 kg, 1.88 m; ♀:59 years, 88 kg, 1.71 m) from the VHP. Digital image processing was used to select and reconstruct collagen-containing structures (Fig. 1). In each case, the data sets consisted of digitized RGB color images of cryosections with a resolution of ♂:0.144x0.144x1 mm and ♀:0.144x0.144x0.33 mm.

In a second step, a FE-model of the connective tissue with a resolution of 1x1x1 mm hexahedrons was created based on these reconstructions. The material descriptions were taken from the previous model and anisotropies were included. The connective-tissue FE-model was afterwards integrated into the trunk-model. For the simulation, the hip was fixed, and a load was applied to the cervical vertebrae (C1). The FEBio and the Postview software tools from the Musculoskeletal Research/Biomechanics Laboratories were used for the simulation and evaluation.

**Figure and Tables**

![Color-coded visualization (red:far, green:middle, blue:near) of the connective tissue for the male (Left) and female (Middle). As well as, the reconstruction of the fiber architecture (Right).](image)

**Results & Discussion**

The connective tissue could be reconstructed in detail across organs. Using methods from image processing we determined and analyzed the fiber directions. The data sets obtained in this way were used expand existent models. Simulation tests are ongoing research. We expect to use our mode to analyze e.g., the lateral force transmission between muscles and muscles to tissues. However, a detailed description is necessary for structures with a very high connective tissue content (e.g., knee).

Modelling connective tissue might be an important tool to understand cross-organ interactions.

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SIMPLIFIED SCREW-BONE INTERFACE MODELS FOR COMPUTATIONALLY EFFICIENT µFE SIMULATIONS

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Introduction
The realistic representation of the bone-screw interface is a challenging task and various approaches have been proposed. Computationally-intensive nonlinear µFE models [1] are able to model contact conditions including friction but are limited to small model sizes. Linear, computationally-efficient µFE models typically assume fully bonded screw-bone interfaces [2]. In order to realize contact in huge µFE models while maintaining computational efficiency, Steiner et al. [2] developed a simple technique which is based on the deletion of interface elements under tension. However, this technique may over-simplify the contact condition and has not been compared to general nonlinear contact µFE models. The goal of this study was to compare a well-known ABAQUS contact model to the Steiner model [2], a modified Steiner model, and a classical linear µFE model of a bone-screw.

Methods
Segmented µCT images of two human radius segments and a screw were used. The two specimens differed in their bone volume fraction (0.3 vs 0.17). Both specimens were cropped to a square cross section of ~9mm edge length and a height of ~15mm. The screw was digitally inserted with insertion depths of 50% and 100% of bone height (Fig. 1a). All images were resampled to 65.6µm resolution and voxel-based µFE models were generated. Three different loading scenarios were simulated (pull-out, compression and shear loading) by applying a displacement of 0.1mm to the top nodes of the screw (Fig. 1b). Linear-elastic, homogeneous material parameters were assigned to all materials. The reference model was a general contact model (hard contact with friction coeff. of 0.5, C) which was compared to fully bonded models (FB), tensionally-strained element deletion models (TED) from Steiner et al. [2] and a modification of TED (TED-M). The TED method involves deleting all bone-screw interface elements that experience positive volumetric strain in a single pre-simulation. TED-M allows for load redistribution of the interface elements by determining tensionally-strained interface elements in an iterative process prior to deletion. The forces at final displacement of FB, TED and TED-M were compared to those of C. All simulations were performed with ABAQUS Implicit (FB, TED, TED-M) and Explicit (C).

Results
For all load cases, all tested samples showed an overestimation of force when comparing FB to C (8% -36%). For TED and TED-M the force difference to C was reduced and reached values between -8% and 8%. The mean force difference was slightly lower for TED-M (1.9%) than for TED (2.1%) (Fig. 2).

Conclusion
The use of the FB interface led to a considerable overestimation of the resultant force, indicating that contact modeling is important for accurate µFE simulations of bone-screw constructs. In order to reduce computational effort, simple algorithms (TED & TED-M) applied to linear µFE models can efficiently replicate contact with much less error. The iterative algorithm (TED-M) could only marginally improve the accuracy compared to the even more efficient TED. However, further research using larger or higher-resolution samples is needed to fully demonstrate the efficiency and accuracy of these algorithms. It is important to note that the findings of this study are based solely on computer simulations and still require experimental validation.

References
AUTOMATIC REAL-TIME TOOL FOR THE PATIENT-SPECIFIC PERFORMANCE EVALUATION OF IMPLANT-SUPPORTED DENTAL REHABILITATION TREATMENT

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Introduction
Finite element models are used to assess short and long-term behavior of bone, implants and overall treatments [1] offering interesting information as stress and strain distributions and values. To ensure their clinical applicability, these methods must: 1) be semi or fully automatic, be real-time and return clinically relevant indicators. The objective of this study is to develop this tool and to assess its clinical relevance for a given clinical case.

Methods
From CBCT imaging and planned treatment information (implant reference and position), the MEDSCOPE software works in four steps. Firstly, the specific material properties were automatically computing around each implant from the CBCT imaging of the patient and the implant position coordinates. Secondly, based on the expected global occlusal force (force level and orientation), the resultant force and moment were computed for each implant using a 3D bar finite element model. Given this information (specific material properties and specific loads), detailed finite element models of bone-implant unit (including implant, surrounding bone and bone-implant interface) was automatically generated for each implant of the evaluated treatment, based on a previously validated FEM [2]. Stress and strain results are then used to compute three biomechanical criteria for each implant (Bone safety index, Osseointegration index and implant safety index). Given these criteria, specific weighting factors and considering the number of implant use for each treatment, a global score was computed.

![Figure 1: Workflow of the MEDSCOPE 1.0 software from inputs data to](image)

This method was applied to the evaluation of a patient-specific implant-supported prosthesis of eight artificial teeth supported by: 6 implants (6DI), five (5DI), four (4DI) and three implants (3DI). For each treatment, implants were positioned with the help of a surgeon.

Results
The entire process successfully operated from input data (CBCT data, implant reference and coordinates) without any user action requirement. The nominal time for the evaluation of a complete treatment is less than five minutes.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>1DI</th>
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<th>5DI</th>
<th>6DI</th>
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<tbody>
<tr>
<td>Mechanical results</td>
<td></td>
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<tr>
<td>Min BSI</td>
<td>28%</td>
<td>62%</td>
<td>61%</td>
<td>62%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Mean BOI</td>
<td>82%</td>
<td>62%</td>
<td>33%</td>
<td>28%</td>
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<tr>
<td>Min ISI</td>
<td>75%</td>
<td>72%</td>
<td>87%</td>
<td>77%</td>
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<tr>
<td>Global Score</td>
<td>65%</td>
<td>75%</td>
<td>72%</td>
<td>69%</td>
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The minimal ISI computed for all the implants of a given treatment is over 70% in all cases, indicated no significant risk of implant failure. The minimal BSI, indicated the higher risk of bone failure, is found for the 3DI treatment. Whereas, the difference is non clinically significant between four, five and six-implant treatments. The mean BOI decreased with the number of implants used indicated lower osseointegration potential for five and six-implant treatments compared to three and four-implant treatments. Finally, the maximal global score is computed for 4DI whereas the lower one is computed for the 3DI treatment.

Discussion
The developed tool enabled to automatically model and simulate In-use behavior of four complete patient-specific treatments, previously defined by an experimented surgeon, without any user action and within very short delay compared to usually expected in dental implantology. The global score, based on biomechanical criteria, suggest better global performance of the four-implant treatment compared to the other ones. This is explained by a higher osseointegration potential than five and six-implant treatment with similar bone and implant safety rate. experiment. This study showed the feasibility of the MEDSCOPE software to automatically compare treatment plan and help surgeons in analyzing the results. The next steps will consist in an extensive biomechanical criteria validation based on a retrospective study design.

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PREDICTING BRAIN STRAIN IN RUGBY HEAD IMPACT SIMULATIONS: IDENTIFYING KEY FEATURES

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Introduction
Head impact exposure in rugby has been implicated in a plethora of negative health outcomes. Despite extensive research on head impact metrics in American football and ice hockey, rugby's unique gameplay style and biomechanics demand separate investigation. Combining head impact data with brain strain simulation tools offers the potential to identify potentially injurious gameplay situations. This study aimed to use laboratory drop test data and a pre-trained convolutional neural network (CNN), in conjunction with machine learning feature importance algorithms, to understand the specific kinematic features most closely associated with regional brain strains resulting from a head impact.

Methods
A pre-trained CNN model [1] was used (Figure 1) to estimate voxel-wise maximal principal strains (MPS) from 1,806 laboratory drop test head impacts using a Hybrid III (50th percentile male) headform and neck. Peak MPS was extracted from the corpus callosum (CC), brainstem, cerebellum, and left and right cerebellar hemispheres for each impact. A dataset was generated from the linear and rotational acceleration and velocity data of each impact, comprising 73 features. Data were split into training (70%) and testing (30%) sets and fit with two non-linear regression algorithms, decision tree and random forest, both with a maximum depth of 5. These algorithms were chosen due to the presence of both high valued features and features with a high degree of collinearity in the dataset. Linear models were excluded as the relationship between each of the features and peak regional MPS was non-linear. Permutation feature importance was applied on each algorithm to identify the features most important in predicting peak regional MPS for each algorithm. The $R^2$ value between the predicted and actual testing data was used to determine the validity of the importance results and the optimal number of important features. Hyperparameters were not tuned as the purpose of the study was only to assess potentially dangerous gameplay kinematics.

Results
Both decision tree and random forest algorithms provided consistent feature importance results with high $R^2$ values using only 4 – 5 features (0.89 – 0.95 for random forest and 0.85 – 0.94 for decision tree). The x-direction change in rotational velocity and the y-direction peak linear acceleration were found to be the strongest predictors of peak MPS in the CC, followed by the peak resultant and x-direction rotational velocity. This suggests impacts to the side of the head may promote greater strains within this region of the brain. The resultant peak rotational velocity (PRV), followed by its log transform, and the x-direction rotational velocity were identified as the strongest predictors of peak MPS in the brainstem. Again implicating impacts to the side of the head as potentially more damaging. It should be noted, the x-direction rotational velocity held lower importance in predicting peak MPS in the brainstem than in the CC. Similarly, peak MPS in the cerebellum was best predicted by the PRV and its log transform, followed by the change in linear velocity and y-directional peak linear acceleration. On the other hand, the z-direction change in rotational velocity was deemed one of the most important features for predicting peak MPS in the cerebellar hemispheres, preceded only by the PRV and its log transform. This suggests that motion acting to rotate the head about the axis of the neck may influence the strain in this region of the brain. These results require further verification with data from on-field gameplay to draw more definitive conclusions.

Figures

Figure 1: Voxel-wise MPS predicted by the CNN from a forehead impact. Segments were separated along the sagittal plane with high strains seen above the CC in the cerebral hemispheres and the front of the brainstem.

References

Acknowledgements
None
THE IMPACT OF 4D-FLOW MRI-DERIVED INLET CONDITIONS IN FLOW SIMULATIONS OFANEURYSMAL TYPE-B AORTIC DISSECTION

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Introduction

The biological mechanisms driving the progression of Type-B Aortic Dissection (TBAD) are not yet well-understood. 87% of patients will experience aneurysmal dilatation of the false lumen (FL), for example, but current anatomical predictors of growth perform poorly. Better tools are needed to support clinicians in treatment planning and risk stratification. Haemodynamic analysis via 4D-Flow MRI (4DMR) and Computational Fluid Dynamics (CFD) may uncover quantities with greater predictive power than existing metrics, but such efforts are hindered by our limited understanding of the impact of modelling assumptions on simulation accuracy. The impact of inlet conditions in TBAD simulations have been examined in terms of pressure, velocity, and Time-Averaged Wall Shear Stress (TAWSS)\(^1,2\). However, disturbed shear and helical flow have been consistently linked with aneurysmal growth; their sensitivity to inlet conditions in TBAD remains unreported. In this study, we simulated flow in a TBAD case exhibiting widespread FL dilatation using various commonly applied, patient-specific inlet velocity conditions. Comparing the gold-standard patient-specific 3D inlet velocity profile (3D IVP) from 4DMR against equivalent uniform and axial profiles, we assess their impact on these potentially predictive quantities.

Methodology

Computed Tomography Angiography (CTA) data and 4D-Flow MRI (4DMR) data were acquired from a 56yo chronic TBAD patient under ethical approval from the local institutional review board (ID: 2019-00556). The fluid domain was manually segmented from baseline CTA data and elastically registered to the 4DMR domain. Follow-up 4DMR at two years was used to assess FL dilatation. Four commonly used inlet velocity profiles (IVP), as shown in Fig. 1, were derived from 4DMR data and applied at the inlet: a three-component, three-dimensional (3D) IVP, flow-matched flat (F) and through-plane (TP) IVPs and a modified 3D IVP with a 25% increase in each velocity component (+25%) to assess the impact of 4DMR velocity underestimation in the ascending aorta\(^3\). Three-element Windkessel outlet boundary conditions were calibrated using flow rate data from 4DMR and a brachial pressure measurement. Transient, rigid-wall simulations were performed using ANSYS CFX (ANSYS Inc, PA, USA).

Results

The inlet velocity profile affected the strength and directionality of helical flow and distributions of wall shear stress (WSS) throughout the FL, as shown in Fig. 1. At the point of greatest FL dilatation (β), weak helicity coincided with high OSI and RRT. Relative to the 3D IVP, the F and TP inlet conditions affected OSI and RRT to a greater extent than TAWSS (up to 167% vs 17%). The +25% IVP, had a greater mean impact on all flow metrics than flow-matched (F & TP) IVPs.

Conclusions

Our results demonstrate that the precise distribution of inlet velocity affects helicity and disturbed shear throughout the FL. By scaling the gold-standard 3D IVP within the reported error of 4DMR measurements, mean differences in all WSS metrics were affected to a greater extent than amongst the flow-matched conditions. Thus, even 3D IVPs may not provide sufficient accuracy for future clinical application due to 4DMR imaging errors. Further efforts may be needed to minimize these errors within acceptable bounds for the purpose of future large-scale clinical simulation studies and subsequent clinical application.

Acknowledgements

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HEMODYNAMIC COMPARISON OF BIOPROSTHETIC VALVES BASED ON IN VITRO 4D FLOW MRI

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Lorenzo Menicanti (1), Alberto Redaelli (2), Massimo Lombardi (1).

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Introduction

Bioprosthetic valves (BPVs) are largely employed for surgical aortic valve replacement [1]. In patients with small roots proper BPV selection is crucial to avoid risk of residual transvalvular gradients. To promote both comprehensive and consistent comparison among different BPVs, we herein combined 4D flow magnetic resonance imaging (MRI) with a standardized in vitro setting to map hemodynamic performances of BPVs.

Methods

4D Flow was acquired on a Magnetom Aera 1.5T (Siemens Healthcare, Erlangen, Germany) for the TrifectaTM, the Carpenter-Edwards PERIMOUNT Magna and the Crown PRT® pericardial BPVs [2], selecting the two smallest sizes. Each BPV was tested under steady flow conditions on an in vitro MRI-compatible system equipped with pressure transducers and including an aortic root phantom (Figure 1).

Hemodynamics was compared among BPVs in terms of 3D velocity field, peak of velocity (V_{MAX}), effective orifice area (EOA), transvalvular pressure drop (TPG), kinetic energy (KE) and viscous energy dissipation (\( \dot{E}_L \)). 4D Flow-based pressures were compared with ground-truth data from transducers.

Results

4D Flow effectively captured the 3D flow pattern of each BPV, its core jet isosurface and the actual EOA shape (Figure 2.A). Trifecta reported the lowest V_{MAX} for both the tested sizes (\( p < 0.001 \)), maximized EOA (\( p \leq 0.0002 \)) and minimized TPGs (\( p \leq 0.015 \)) if compared with Magna and Crown, these reporting minor EOA differences and comparable TPGs (\( p \geq 0.25 \)). Also, EOA shape was trilobal for Magna, triangular for Crown and circular for Trifecta, this also reporting the most proximal position for vena contracta (Figure 2.B). 4D Flow-derived TPGs strongly correlated (\( r^2 \geq 0.89 \)) against ground-truth data from the pressure transducers; \( \dot{E}_L \) proved to be inversely proportional to the fluid jet penetration.

Discussion

The proposed 4D Flow analysis pinpointed consistent hemodynamic differences among BPVs, highlighting that both design and size of pericardial BPVs directly impact on the downstream flow field pattern. To enable pulsatile flow conditions, inclusion of a pulsatile MR-compatible pump unit in the vitro system is on-going. The efficacy of non-invasive 4D Flow MRI could shed light on how standardize the comparison among BPVs in relation to their actual hemodynamic performances. If further extended, the protocol could also support pre-clinical assessment of prototypal cardiac valves and potentially reduce the need for animal testing.

References


Acknowledgements

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Identification of Immunomodulatory Topographies to Regulate Myofibroblast Differentiation and Influence Fibrous Encapsulation

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Introduction

Macrophages and fibroblasts are known to be key contributors of foreign body response. Macrophages can change their phenotype and secrete cytokines that trigger fibroblast differentiation⁴. Previous studies prove that the macrophages can be modulated using physical cues like topographies and can change their immune profile². In this study, we took a combinational approach to find topographies that can alter macrophage secretion profile as well as fibroblast differentiation to modulate FBR. This was tested in a condition called glaucoma which is treated using drainage devices to maintain IOP in the eye.

Methods

A poly (styrene-block-isobutylene-block- styrene) (SIBS) Topochip containing 2176 distinct topographies was fabricated using hot embossing. Three screens were performed, one with primary tenon fibroblasts where we quantified expression of the trans-differentiation marker alpha-smooth muscle actin (α-SMA) and a second where proliferation was quantified through EdU staining by automated image analysis. A third screen was done using primary macrophages for differential attachment. Surfaces were ranked and hits from the screen were chosen and validated for the same readouts and multiplex ELISA was done where macrophage’s secretion profile was quantified for pro- and anti-inflammatory cytokines.

Results and discussion

Topographies showed strong effect on tenon fibroblast morphology and stress fiber formation relative to flat control. α-SMA and EdU show a 4-fold differences between top and bottom hits. We opted to go for a dynamic three-pronged approach in selection of the hits for validation work that will be used for in vivo model, one for tissue integration, other for pro-encapsulation and lastly for anti-fouling. Chosen hits were fabricated and validated. Among them, three topographies were chosen, Topography 1153 was chosen for pro-encapsulation, topography 79 for tissue integration and topography 509 for anti-fouling. Chosen hits were correlated with cytokine analysis where we found topography 1153 with high levels of pro-inflammatory cytokines IL-6, IL-1β whereas topography 79 showed higher levels of arginase, IL-1Ra with low levels of IL-6, IL-1β compared to other hits.

Future Work

Based on the screening and validation results, we chose three topographies which were used to fabricate devices for the animal trials to test which can induce a better bleb survival and low encapsulation in in vivo rabbit model.

References

STRESS FIBERS IN AORTIC SMOOTH MUSCLE CELLS ALTER THEIR DIRECTION TO ELEVATED STRAIN DIRECTION UNDER HYPERTENSION

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Nagoya Institute of Technology, Japan

Introduction
Aortic walls become hypertrophy under hypertension [1]. The hypertrophy is believed to be caused by the homeostasis to keep circumferential (θ) stress constant [1], though its formation mechanism remains unknown. One possible process includes an increase in tension in stress fibers (SFs) in the vascular smooth muscle cells (VSMCs) as a result of elevated θ stress due to elevated intraluminal pressure. Since the SFs connect to the nucleus [2], the elevated tension in SFs transmits the force to the nucleus, which might change the gene expressions.

In our previous study [3], we found that SFs of VSMCs in aortas oriented at ~30° from the θ direction in radial (r-θ) plane, and normal strain in this direction due to the pulse pressure equals almost 0. This result indicates that SFs in VSMCs do not stretch due to the changes in blood pressure under a normal physiological state. We hypothesized that the strain increases at the initial phase of hypertension and returns to 0 after hypertrophy is completed since the cell responses are also completed. To evaluate the hypothesis, we measured the strain in the SF direction at the initial phase of hypertension and after completion of hypertrophy.

Methods
All animal experiments were approved by the Review Board of the Animal Committee of Nagoya Institute of Technology. Spontaneously Hypertensive Rats (SHR/Izm, 10-14 weeks, Japan SLC) and their control (Wistar Kyoto Rats, WKY/Izm, Japan SLC) were used as test models. The SHR was regarded as a model in which hypertrophy was completed.

After systolic and diastolic pressures were measured (BP-98A-L, Softron), a rat was sacrificed, and its thoracic aorta was excised. The pressure-diameter test was then performed to obtain the normal strains in the θ direction of the aorta, such as strain at the diastolic εdia and at the systolic pressures εsys from strain at the 0 mmHg ε0. For WKY rats, the strain at 179 mmHg intraluminal pressure εhyp was also measured as an initial phase of hypertension. The aortic specimens were sectioned into the 200-μm-thick ring specimen with a micro-slicer (DTK-1000, Dosaka-EM). The SFs in the sectioned specimen were stained in x200 diluted Alexa Fluor 647 Phalloidin (A22287, Thermo Fisher Scientific) for 2 h. The specimen was stretched under a confocal laser scanning microscope (FV3000, Olympus) with a custom-made tensile tester. At ε0, εdia, εsys, and εhyp of the tissue stretch, SFs and elastin autofluorescence images were captured. Local and normal strains in the θ ε00 and r direction εr and shear strain in the r-θ axes εrθ were measured from the strain markers created at the elastic laminas, as stated previously [4]. SF direction αSF from the θ direction in the r-θ plane was measured from the fluorescence images of SF, and its strain εSF was calculated from the ε00, εr, εθ, and εrθ.

Results and Discussion
Typical images of the SFs were shown in Fig. 1. SFs oriented in the αSF = 19 ± 2° at the εsys of WKY, αSF = 13 ± 1° at the εhyp of WKY, and αSF = 20 ± 2° at the εsys of SHR. These results indicate that SFs changed their alignment closer to the θ direction under hypertension and returned to their original direction after the completion of hypertrophy.

Strain in the SF direction was εSF = 0.01 ± 0.03 from εdia to εsys of WKY, εSF = 0.18 ± 0.04 from εdia to εhyp of WKY, and εSF = 0.03 ± 0.01 from εdia to εsys of SHR. In a physiological state of WKY, the strain in the SF direction was almost 0, as confirmed in a previous study [3]. At the initial hypertension condition, SF strain drastically increased, while the strain εSF again reached almost 0 levels after the completion of hypertrophy. These results indicate that the SF transmits the force applied to the aorta by changing its direction under hypertension and does not after the completion of hypertrophy.

![Figure 1: Superimposed images of SFs at different tissue strain levels. (a) Diastolic (green) and Systolic (red) strain levels. (b) Diastolic (green) and 179 mmHg intraluminal pressure strain levels. Bar = 20 μm.](image)

References

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This work in part was supported by KAKENHI 21H04955 from the JSPS, Tatematsu foundation, JP20gm0810005 from AMED.
THE GAPPING BEHAVIOUR OF THE MENISCUS VARIES ACCORDING TO THE TEAR TYPE

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Introduction
The main biomechanical function of the menisci is to homogenize the tibiofemoral load with the superior aim to prevent the knee joint from early degeneration. Tears of the menisci lead to an increased tibiofemoral contact pressure (CP), which can be mechanically explained by gapping of the torn meniscus tissue. Adequate suturing is able to restore the CP almost to the native state [1]. However, it is not known if different meniscus tears result in a different gapping behaviour, which is associated with an altered CP. Therefore, the aim of this study was to quantify both, the gapping of radial and longitudinal tears and their concomitant impact on CP.

Methods
Based on a statistical sample size calculation twelve fresh-frozen porcine knee joints were equally divided into a radial and a longitudinal tear group. Each knee underwent unicompartmental, convertible osteotomy for exact tear application and consecutive suturing [2]. A total of six 0.8 mm tantalum marker beads were positioned along the meniscus tears (Fig. 1 B, C). Peak CP was determined using calibrated pressure sensitive films (K-Scan 400, Tekscan Inc.) which were placed between the tibial plateau and the medial meniscus.

Fig. 1: Test setup (A) and representative images of a longitudinal (B) and a radial tear (C) (purple dashed lines) located at the posterior horn of the medial meniscus and the according RSA marker bead pairs for gapping analysis.

The joints were preloaded by 75 sinusoidal loading cycles ranging between 0-350 N using a customized loading rig (Fig. 1 A), which was integrated in a material testing machine. Then, the peak load (350 N) was hold constant and two synchronized x-ray images were acquired under Roentgen Stereophotogrammetric Analysis (RSA) conditions, visualizing the six markers. Gapping and peak CP were investigated in the native, torn and repaired state (longitudinal = vertical mattress suture; radial = inside-out suture). Gapping was evaluated by analyzing the change in distance of the marker bead pairs (RSAcore, Leiden University) (Fig. 2). Non-parametric statistical analysis was performed, while \( p < 0.05 \) was considered significant (Friedman).

Results
There was no change in gapping (\( p>0.43 \)) and peak CP (\( p=0.18 \)) in the longitudinal tear group (Fig. 2 A). In contrast, the radial tear led to a significant gapping (Fig. 2 B; \( p<0.02 \)) when comparing the native and the tear state, while the inside-out suture was able to restore gapping in the middle and outer zone of the meniscus. Accordingly, a trend towards an increase in CP after radial tear application was detected, which was again normalized after suture application.

Fig. 2: Comparison in distance change (median, min-max) of the three marker pairs during consecutive meniscal states and two tear types (A, B) and peak CP change (median, min-max) (C, D). Visualization of the CP change of the respective meniscal states (E, F); \( * = p < 0.05 \).

Discussion
The most important finding of the study is that not every meniscus tear type gap. Longitudinal tears do not gape under pure axial loading while radial tears tend to separate the tear interfaces. Accordingly, CP did not change after longitudinal tear simulation while untreated radial tears tended to increase the CP, especially in the inner zone next to the cartilage-cartilage contact. Concomitant, the suture for radial tear repair reduced gapping, thus, contributing to a reduced CP. However, the study is not free of limitations, which are mainly the lack of flexion/extension movements and the invasive osteotomy. To the best of the authors knowledge, this is the first in-vitro study, that combines RSA with pressure sensitive films for correlation between meniscal tear gapping and CP change. This study could provide a solid basis for in-vitro determination of rehabilitation knee loading regimes and possible negative influences on the gapping behaviour of injured/repaired menisci and respective reduced healing possibility.

References
Introduction
Physiological in silico models play a critical role in improving patient-specific kidney replacement therapies and making them available to help patients with reduced kidney function. Peritoneal dialysis (PD) is one such therapy [1], that is used to supplement kidney function in 15% of the kidney patients in the Netherlands [2]. Myself and others have improved the mathematical models of kidney physiology, including amongst others sex-specific differences [3], solutes, drug and toxin transport [4] and their interactions [5], influence of tubular architecture [6], alongside models of the device itself, marking all important discoveries but what lacks is a benchmarking of the different models on the same clinical dataset. In this work, we look at some of the historical models of PD and benchmark the efficiency of the models in predicting time-dependent evolution of six solute dialysate concentrations (urea, creatinine, sodium, potassium, phosphate, glucose and phosphate).

Methods
We chose two mechanistic models (Graff et al. [7], Öberg et al. [8]) and two analytical models used in clinical practice (Garred et al. [9], Waniekiewski et al. [10]). The four models, in combination, encompass various mechanisms that are essential to PD (diffusion, convection, lymphatics). We collected experimental data from multiple dwell studies in one or two sessions (n = 16) performed in pigs. We trained each of the models by fitting the dialysate solute concentrations (in some of the dwell studies) to predict the mass transfer area coefficients (MTAC) of each solute. Using the fitted MTAC, we predict the dialysate solute concentrations in the rest of the dwell studies. We assessed the root mean square error (RMSE) and the physiological plausibility of the fitted MTAC to find the best performing benchmark model (table 1, figure 1).

Results and Discussion
Table 1 shows that model 7 (Öberg et al.) is the optimal model in terms of low error in solute concentration predictions, applicability of the model to multiple datasets (with different initial dialysate concentration), physiological MTAC values and reasonable ultrafiltration values in pigs. This model is also modular and has been applied to automated PD and continuous flow PD. In the future, we aim to extend this model to mimic a novel PD device with an adsorption chamber to help with detoxification [9].

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<th>Model</th>
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Table 1: Is the model RMSE per solute (<±3%), is the model applicable to all the datasets, are the predicted MTAC physiological? Graff model (model 1-6) is a comparison of six models with the convection and lymphatics mechanisms turned on and off. Column 1-3 represent diffusion, convection and lymphatics parameter whether fixed or fitted (*). In the model, Column 4-6 represent the accuracy of predicting urea, creatinine, sodium, phosphate, glucose, potassium dialysate concentrations. Column 10 represents generalisability of the model to different datasets and 11 represent plausibility.

Figure 1: comparison of predicted data by Öberg model with pig data.

References
TOWARDS UNBIASED AND ACCURATE SIMULATIONS OF SCREW-BONE CONSTRUCTS WITH HOMOGENIZED FE MODELS

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Introduction

Homogenized finite element (hFE) models are increasingly used to investigate internal fixation of complex bone fractures with plates and screws. However, using hFE models for this purpose has also been criticized, especially if the screws are anchored in trabecular bone [1]. That is due to the many inherent simplifications, such as modelling trabecular bone as a continuum, and simplifying the screw thread geometry. Validating hFE models of screw-bone constructs based on experiments is challenging, as a lot of error sources are mixed and can hardly be separated (e.g. error due to homogenization, screw insertion damage, screw-bone contact). This might lead to biased models and could explain why some studies report good agreement with experimental results [2], while others do not [1]. In this study, we assessed hFE model accuracy using µFE models rather than experiments as a reference to delineate and control different error sources. As a first step, this study was limited to osseointegrated screws to exclude the effect of screw insertion damage and contact. hFE models were built based on “best evidence” without parameter tuning to avoid model bias.

Methods

15 cylindrical bone samples with 18 mm diameter were cut out of µCT scans (32.8 μm voxel size) of human distal radii (Fig. 1. [3]) and a screw was virtually inserted. Linear elastic µFE models were created including the screw thread geometry, bone microstructure and a fully bonded screw-bone interface. hFE models were created by separating cortical and trabecular bone and replacing the screw with a smooth cylinder. Linear elastic material properties were mapped to the screw, cortex (density-dependent), and trabecular bone (density- and fabric-dependent). Material constants for trabecular bone were obtained from a previous study using µFE-based homogenization [4]. A force of 100N was applied to the screw to simulate three load cases (pullout, shear in two directions) (Fig. 1).

1) µFE models with vs. without screw threads 2) µFE vs. hFE models with homogeneous material.

Results

The stiffness predicted by the hFE models was in good agreement with µFE models (error: -0.7±8.0%; CCC: 0.98) (Fig. 2). Slightly lower accuracy was achieved for peri-implant average SED (error: +8.6±16.3%; CCC: 0.96) and SED distributions did not always match between µFE and hFE models (Fig. 2). The delineation of error sources showed low overall errors both for neglecting screw threads (mean: 1.3%) and µFE vs. hFE models with homogeneous material (mean: 1.3%).

Discussion

This study showed that “best evidence” hFE models can provide reasonably accurate predictions of osseointegrated screw-bone construct stiffness relative to µFE models, even without parameter tuning. Averaged peri-implant SEDs were also captured with good accuracy, but the SED distribution could not be reproduced. Although this study has many limitations, the methodology could be extended step by step, e.g. by including material nonlinearity, contact and screw insertion damage separately into the models. Ultimately, this approach could provide a way towards unbiased and accurate hFE models of screw-bone constructs.

References

NUMERICAL EVALUATIONS OF FUNCTIONALLY GRADED POROUS INTERBODY CAGE FOR SPINAL FUSION

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Introduction

Functionally graded porous (FGP) interbody cages might offer a trade-off between porosity-based reduction of implant stiffness and mechanical properties. Although earlier studies have investigated the influence of graded porosity on the stress-strain related failure mechanisms, the effect of graded porosity on an interbody cage for spinal fusion has scarcely been investigated [1, 2]. A novel design of an FGP interbody cage is hypothesized to yield favourable bone remodelling owing to graded porosity and offer sufficient stiffness to restrict the Range of Motion (RoM), necessary for primary stability. The study aims to investigate the deviations in load transfer and associated potential failure of FGP interbody cages and to evaluate peri-prosthetic bone remodelling around various FGP interbody cages. A comparison with a cage model with 78% uniform porosity (P78 model) has also been undertaken.

Methods

The patient-specific FE models of the intact and implanted lumbar spine were developed following the procedure reported earlier [3]. The effective orthotropic mechanical properties of the porous structure were calculated using homogenization of a tetrahedron-based unit cell. The Porosity 1 (P1) and Porosity 2 (P2) of an interbody cage element are defined by volume fractions V1 and V2, which correspond to the porosity in the inferior/superior regions and the central region of the cage. Three different porosity levels of 48%, 65%, and 78% were considered for P1, which corresponds to FGP models A, B, and C, respectively. A P2 value of 0% was assumed, which corresponds to solid-Ti alloy in the central region of the cage. The gradation of porosity within the cage is governed by the following equations:

\[ V_1 = \left[ 1 - \left( \frac{h}{h/2} \right)^m \right] \quad (1); \quad V_2 = \left[ \left( \frac{h}{h/2} \right)^m \right] \quad (2) \]

Here, h is the cage height, m is the gradation exponent which controls the distribution of materials along the gradation direction (z). The applied loading conditions included a compressive follower load of 280 N, followed by a moment of 7.5 N-m to simulate flexion, extension, lateral bending, and torsion.

Results

The RoM of the implanted model was reduced by 81 – 88%, as compared to the intact model, for all physiological movements. Variations in stiffness affected strain distribution and bone remodelling around the cages. Peak strains of 0.5–1% were observed in less number of peri-prosthetic bone elements for the FGP cages as compared to the solid-Ti cage. For the FGP model C, bone apposition of 11–20% was predicted in the L4 and L5 regions of interest (ROIs) for the FGP model C. The deviations in bone density change between FGP Model C and P78 model were 3–8% for L4 and L5 ROIs (Figure 1). FGP resulted in a reduced average micromotion (~70–106 μm) as compared to solid-Ti (116 μm) for all physiologic movements.

Discussion

Implantation with cage led to an increase in peak strains and bone density around the interbody cage. However, the adverse effect of bone remodelling was less for the FGP cages as compared to solid-Ti cage. Although the P78 model offers almost similar mechanical behaviour and bone remodelling trends, the FGP Model C offers reduced RoM thereby improved primary stability. Compared to solid-Ti and uniformly porous cages, the FGP cage seems to be a viable alternative considering the conflicting nature of strength and porosity.

References

CLINICAL PERSPECTIVE OF DEVELOPING ROBOTIC SYSTEMS FOR ASSISTING PERCUTANEOUS TRACHEOSTOMY

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Introduction
Tracheostomy is frequently performed within the Intensive Care Unit (ICU) for patients who require prolonged mechanical ventilation [1]. Compared with traditional surgical tracheostomy (ST), percutaneous dilational tracheostomy (PDT) has demonstrated its superiority and potential regarding its lower complication rates and shorter operation time [2], [3]. However, complications associated with inappropriate PDT procedures still exist and sometimes cause severe consequences, including bleeding, tracheal perforation and pneumothorax. Robot-assisted approaches are widely adapted in minimally-invasive surgeries and regarded more efficient as well as safer over manually-performed ones [4], making developing surgical robots to perform PDT feasible. Currently there’s extremely limited research in robotic tracheostomy [5]. The purpose of the study is to collect clinical perspectives from stakeholders and build a design framework for robot-assisted PDT so future technologies can be developed that meet the clinical need.

Methods
An online survey with three sections was disseminated to intensivists through Qualtrics. First section of the survey collected clinical expertise and working experience related to PDT. The second section asked for evaluation of some design requirements identified from literature review. The third section clinical opinions were collected by asking for identification of challenges of the current procedure and specific objectives which robot-assisted PDT should achieve.

Results and Discussions
From Oct 2022 to Jan 2023, 15 clinicians participated in the survey. All participants had experience in directly performing PDT with average of 13.9 years. Results of clinical perspectives and their importance are illustrated in Figure 1.

Based on questionnaire results, current PDT procedure is associated with several challenges, including confined space and poor visualization of surgical site, perioperative bleeding, misposition of introducer needle, identification of puncture site and lengthy duration. Therefore if an assistive device is going to be developed, it should effectively address these issues and most significantly, demonstrate at least the equivalent level of overall safety comparing with manually-performed surgeries. Essential features tracheostomy robots should obtain were puncture and dilation so that maximum assistance can be provided with overall operation time significantly reduced. To complement drawbacks of the current procedure, perioperative image guidance and ventilation management should be adopted.

Conclusion
In this study, clinical perspectives and demands for developing tracheostomy robots were collected. By consulting professionals, a design framework was built based on safety and usability requirements. It will facilitate the development of robotic solutions which efficiently and effectively meet the clinical need. Rather than the finalised version, the design requirements will be amended continuously to capture clinical needs more specifically and comprehensively.

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MODELING THIN LAYER HYPERELASTIC SOFT BIOLOGICAL TISSUES THROUGH MACRO-SPHERICAL COMPRESSION TESTS

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Introduction

The study of the mechanical behavior of soft biological tissues associates the difficulty in obtaining adequate specimens with the need for repeatability validation on tests. It is of great value to obtain hyperelastic properties from different regions of the same tissue under physiological conditions [1] while preserving specimen integrity. The Hertz model allows the calculation of force-indentation depth curve by considering an elastic semi-infinite body submitted to spherical indentation. Subsequent developments, see for instance [2], generalized Hertz solution to the case of non-linear constitutive behavior of the body. The present study proposes a method of determining non-linear stress-strain relationship of finite thickness hyperelastic plates under non-destructive spherical compression tests. The model creation and validation were done by implementing optimization algorithms and finite elements analysis.

Methods

A 2D finite element axisymmetric model was created in Abaqus (Dassault Systèmes, France). The compressed homogeneous plate presented was characterized by a neo-Hookean hyperelastic constitutive relation and was compressed by a spherical rigid body. Plates of different thicknesses were loaded and the contact radius, generated by the compression, was evaluated as a function of sphere displacement for various geometrical configurations (ratio between plate thickness $H$ and sphere radius $R$). A fitting procedure was applied to the obtained curves enabling determination of the representative stress $\sigma^*$ vs representative strain $\epsilon^*$ response. The approach was then validated by being compared to other finite element simulation results with different material constitutive laws such as neo-Hookean, Mooney-Rivlin, Ogden and linear elastic.

Results

An example of simulation result is shown in Fig 1 for a plate twice thicker than the spherical tool. Obtained results are shown in Fig 2 comparing the constitutive laws used and $\sigma^*\epsilon^*$ curves deduced from the model. Two dimensionless sample thicknesses ($h=H/R$) are considered for two constitutive laws namely for neo-Hookean ($\sigma_{nh}^n$) and Ogden ($\sigma_{Ogden}^n$) materials. The results were satisfactory for all materials except linear elastic one (not presented here). Results confirmed that non-linearities did not influence the geometry of contact during simulations, as stated in [1].

Discussion

The presented method allowed setting up relations that take into consideration spherical compression tests in which the contact conditions between a physiologically relevant sized tool and the sample are non-linear, in the context of a non-uniaxial stress-strain state. Enhancing prior work [3], the model enables a precise evaluation of stress and strain relation for classical non-linear material laws. Currently, investigations are carried out to deal with limitations such as isotropy, homogeneity and quasi-incompressibility of the material. This model is applied to study the temporomandibular joint disc behavior which generally exhibits internal stresses [4]. Usually, sample harvests release these stresses. It can be avoided thanks to spherical compression tests on the whole disc.

References

BREATHING AS A MEDIATOR BETWEEN POSTURAL STABILITY AND STRESS IN STUDENTS

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Introduction
There is an increasing incidence of musculoskeletal conditions (58% increase from 1990 to 2017), especially among adolescents (up to 75% of the population) [1]. Psychological factors such as mismanaged stress, anxiety, and other emotions may be contributing factors [2]. Breathing affects motor control, postural stability, and plays several roles in physiological and psychological regulation [3]. Hence, breathing may be a mediator between posture and emotions. Yet, results from preliminary studies suggest that many cannot intentionally perform diaphragm breathing, impacting their posture, and affecting their emotional regulation abilities [4]. This study aims to identify a possible triangular link among posture, breathing, and stress.

Material and Methods
Twenty-nine healthy volunteers (20 male, 9 female) between 18 and 23 years of age, participated in the study. Breathing analysis was performed using optoelectronic plethysmography (OEP). Eight infrared cameras were used, and eighty-nine markers placed on the trunks of subjects [5]. Subjects were asked to stand on a force plate while their breathing (abdominal, pulmonary, and abdominal rib cage compartments) and displacement of the center of pressure (COP – 27 different variables among time, frequency hybrid domain measures) were recorded. Four recordings of three minutes each were made with subjects asked to keep their eyes closed or open and to breathe abnormally or naturally (i.e., without specific instructions). Subjects were classified as capable or not of abdominal breathing if the abdominal compartment was used more than the pulmonary one. Breathing and stability results were normalized based on the height of the subjects. Twenty volunteers also filled out dispositional measures of psychological health: State-Trait Anxiety Inventory (STAI-T) and Rosenberg Self-Esteem Scale (RSE). To evaluate possible relations among breathing, COP, and anxiety (STAI-T), all parameters were analyzed using a multifactorial ANOVA. Factors taken into consideration were gender, the requested modality of breathing, the position of eyes, and the actual capability to perform abdominal breathing. Multiple linear regression with stepwise variable selection was employed to identify possible relations among breathing, stability, and dispositional measures. Finally, binary logistic regression with forward feature selection was used to discriminate between subjects who could breathe abnormally or not.

Results
ANOVA analysis showed no significant difference between the requested modality of breathing nor positions of eyes, whereas significantly different behaviors were shown for gender and capability of abdominal breathing. Thus, the following analyses of the effect of breathing have been split by gender. One hundred thirteen acquisitions resulted valid for the breathing-stability analysis. Logistic regression was able to perfectly classify (100% accuracy) females (35 acquisitions) and males (78 acquisitions). Equations showed different behaviors for males and females. In males, abdominal breathers are more stable subjects while the opposite is suggested for females. Multiple regression identified linear dependency between abdominal rib cage volume and dispositional measures. In female subjects, RSE adjR² = 0.85, positive relation and STAI adjR² = 0.63, negative relation; in males STAI adjR² = 0.46, positive relation. Finally, dispositional measures were found to be related to the stability of the subjects in both males and females (male RSE vs COP adjR² = 0.91, female STAI vs COP adjR² = 0.83, RSE vs COP adjR² = 0.72).

Conclusions
The stability of volunteers was found to be linearly related to dispositional measures of psychological health. However, only 26% of female recordings presented abdominal breathing against 53% of male subjects. The imbalance of recordings and limited number of women present a clear limitation in the evaluation of female subjects. Nevertheless, strategies appear to be inverted between males and females. Breathing presents as a possible mediator showing relations to both stability and psychological health. However, in both cases, the relationship is inverted by gender. Such differences do not seem explicable by mere biology, and social canons should be taken into consideration.

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Acknowledgments
Funds from DTIC-UPF (BMYBOS-PLAWB00420) are acknowledged. A special thanks to all the volunteers who participated in the study.
RELIABILITY OF A NOVEL KNEE SIMULATOR AND ITS CONCURRENT VALIDITY AGAINST A VALIDATED DYNAMIC KNEE SIMULATOR

Orçun Taylan (1), Thomas Louwagie (1), Darshan Shah (1,2), Ilse Jonkers (3), Lennart Scheys (1,4)

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Introduction

In recent decades, a multitude of new ex-vivo knee simulators, frequently based on the Oxford Knee Rig (OKR) design and often limited to squatting motion, have been developed [1,2]. Such simulators are crucial to provide novel insights in knee biomechanics and evaluating the impact of surgical procedures and rehabilitation strategies [1,2]. Typically, new simulators are conceptually designed to allow more physiologic simulations by replicating more intricate and precisely controlled motions, and thus exhibit potential differences in comparison to their predecessors [1,2]. However, despite the advancements in current designs and control strategies, there remains a lack of quantitative data in literature that comprehensively evaluates the biomechanical behavior of the same knee across different simulators. Recently, we have developed a novel physiological knee simulator that allows the control of translations in three axes at the ankle as well as independent improved control of quadriceps and bilateral hamstring muscle groups to perform more complex motions beyond squatting. Therefore, the aim of this study is to assess the reliability of the novel knee simulator (NKS) and, for the first time, determine its concurrent validity with a previously validated OKR-based knee simulator (VKS) by repeating squatting motion in both simulators within a single cohort of cadaveric knees.

Methods

Seven fresh-frozen legs (82±8yrs) were subjected to squatting motions (30°-105°) on the NKS following previously described specimen preparation [2]. The quadriceps and bilateral hamstrings tendons were actively controlled using feedforward proportional-integral-derivative, while a constant vertical ankle force of 110 N was set as target, during the squatting motions. A cemented TKA (GMK Sphere, Medacta International, Switzerland) was then implanted in each knee. Subsequently, all postoperative knees were tested on the NKS and previously validated VKS [2], the latter only allowing squatting motion and with actively controlled quadriceps tendons and 50N force spring on each hamstring, using same flexion range, ankle load and time. All motion data were collected using a six-camera motion capture system (VERO-1.3X, Vicon, UK) with each knee tested in quintuplicate in both simulators. A pointwise intraclass correlation (ICC, 95% CI poor<0.4 and 0.74<excellent) and standard error of measurement (SEM) as a function of knee flexion angle were used to analyze the intra-simulator reliability of the resulting tibiofemoral kinematics, ankle and quadriceps loads within NKS as well as the inter-simulator reliability of tibiofemoral kinematics across the simulators [3].

Results

The mean intra-simulator reliability was excellent for valgus (ICC>0.99, SEM<0.09°) and tibial internal rotation (ICC>0.99, SEM<0.3°) during squatting (Fig.1). Moreover, the ankle (ICC>0.65, SEM<1.1N) and quadriceps (ICC>0.78, SEM<61.7N) showed good to excellent reliability. Additionally, the inter-simulator reliability was excellent for valgus (ICC>0.98, SEM<0.34°) and tibial internal rotation (ICC>0.82, SEM<1.5°) throughout the squatting motion.

Discussion

The novel knee simulator showed excellent kinematics and good force reliability, indicating the effectiveness of the implemented control strategy. Nevertheless, it is crucial to thoroughly assess the lower and upper CI of ICC and SEM to avoid misinterpretation. Besides, our findings exhibited that different OKR-based simulators have comparable kinematics during squatting despite potential hardware and software differences, suggesting they are primarily driven by the knee specimen itself.

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**KINEMATIC VS MECHANICAL ALIGNMENT IN MEDIALLY-STABILISED TKA: A MATCHED-PAIRS KINEMATIC ANALYSIS**

Orçun Taylan (1), Darshan Shah (1), Félix Dandois (1), Welfeng Han (2), Philippe Van Overschee (3), Lennart Scheys (1,4)

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**Introduction**

Mechanical alignment (MA) in total knee arthroplasty (TKA) is widely considered the gold standard, yet up to 25% of patients express dissatisfaction postoperatively [1]. Recently kinematic alignment (KA) emerged as an alternative technique in TKA, which endeavors to maintain the patient-specific knee alignment. Nevertheless, its efficacy in terms of improving biomechanical knee function and restoring the original soft tissue envelope remains uncertain [2]. Therefore, the aim of this study was to conduct a paired comparison of MA and KA using a physiological knee simulator.

**Methods**

Seven bilateral pairs of cadaveric lower limbs (86±5yrs) were subjected to passive knee flexion (10°-120°) and a squatting motion (35°-100°). The latter was performed with a 50N constant force spring on each hamstring and a quadriceps force actively controlled to maintain a constant vertical reaction force of 110 N at the ankle [3]. Subsequently, specimen-specific cutting jigs based on computed tomography (CT) scans were used to perform a medially-stabilised TKA (GMK Sphere, Medacta, Switzerland), with KA and MA being performed in the left and right specimens of each donor, respectively. Thereafter, all postoperative knees were retested with the same protocol. A six-camera motion capture system (Vicon, Oxford, UK) measured tibiofemoral kinematics using a pre-defined CT-based anatomical coordinate system while synchronized rosette strain gauges [3] affixed to the anteromedial (AM) and anterolateral (AL) regions of the tibia, 3cm below the joint line, measured bone strain. Tibial abduction and internal tibial rotation as well as AM and AL maximum principal strains were expressed in function of knee flexion angle. A generalized mixed model was used to compare tibiofemoral kinematics and bone strain between KA and MA TKA in relation to their respective native condition (p<0.05).

**Results**

Both MA (p>0.66) and KA (p>0.91) restored the native frontal plane kinematics during passive flexion (Fig.1). Only the tibial internal rotation demonstrated by MA knees was significantly different from native in early flexion (10°-43°, p<0.44). For squatting, internal rotation in KA (p<0.01) was significantly different from its native condition across the entire range flexion range. However, for ab-/adduction both alignment strategies resulted in kinematic behaviour similar to native (p>01) for abduction. In terms of bone strain, both KA and MA demonstrated similar AM strain. Nevertheless, for KA significant differences occurred from native between 79° and 100° (p<0.04). In terms of AL strain, none of the alignment strategies significantly differed from native (p>0.5).

![Figure 1: Average pre-to-post-operative changes in tibial abduction, tibial internal rotation, anteromedial strain and anterolateral strain for left knees (black) and right knees (red) during passive flexion (top) and squatting (middle and bottom).](image)

**Discussion**

Our findings, measured during passive flexion and squatting, indicated that there were no substantial biomechanical benefits that could be attributed to one of the two alignment techniques in terms of tibiofemoral kinematics. However, the results showed that the internal rotation of MA during squatting was more consistent with its native condition compared to KA. Additionally, analyzing bone strain revealed that although both MA and KA produced comparable magnitudes, MA had a tendency to decrease bone strain, whereas KA tended to increase strain during squatting.

**References**

WHAT COLLAGEN HYDROGEL FOR OPTIMAL MECHANOBIOLOGY OF 3D ENCAPSULATED SMOOTH MUSCLE CELLS?

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Introduction

Vascular smooth muscle cells (SMCs) normally regulate mechanobiological homeostasis in arteries when they express a contractile phenotype [1]. Traction Force Microscopy (TFM) is a technique to assess in vitro traction forces between the cell and the extracellular matrix [2]. Unlike previously performed SMC cultures on a hydrogel surface, 3D models of embedded SMCs offer a more realistic model of the in situ cell-matrix interactions [3], [4]. Because the matrix itself can induce SMCs phenotypic transitions, 3D TFM requires the use of in vitro hydrogels where SMCs keep their contractile phenotype. This study aims to assess the behaviour of SMCs embedded in hydrogels of varying composition and mechanical properties and then design a collagen hydrogel suitable for future TFM investigations.

Methods

Twelve chemically different hydrogels were derived from a 10 mg/ml Type I collagen solution (TeloCol-10, Advanced Biomatrix) varying the collagen solution dilution (from 2.5 to 10 mg/ml) and the pH (from 7.4 to 8 to allow cell viability). Hydrogels were prepared on ice to prevent early gelation. Each hydrogel solution was derived into both acellular and seeded hydrogels.

Primary aortic SMCs (AoSMC, Lonza) were cultured in growth medium (SmGM-2, Lonza) at 37°C with 5% CO2. Cells at passage P10 were gently mixed with the hydrogel solutions at three cellular densities (from 50 000 to 150 000 cells/ml) resulting in 16 different seeded hydrogels. Both acellular and seeded hydrogels were cured at 37°C for 1h before immersion in medium. Cell nuclei and actin fibres were imaged in fluorescence with confocal microscope (Axio Observer Z1 station, Zeiss) after a 5 days differentiation. Each cell population was quantified and characterized by cell shape (elongated/round) and length (> or <100µm).

The acellular hydrogel viscoelastic behaviour was characterized with a stress-controlled rheometer (Discovery HR 2, TA Instruments) with 15mm plate-plate geometry at 37°C in oscillatory uniaxial compression and shear at frequencies in the range 0.1-10.0 Hz.

Results and Discussion

High fractions of SMC contractile phenotype (Figure 1, (a)) were found in low collagen concentration hydrogels (p=0.001, ANOVA) and for sufficient initial cellular densities (p=0.008, ANOVA). Only the initial cell density seemed to significantly affect their average length (p=0.011, ANOVA). For TFM applications, an optimal initial cellular density maximizing the fractions of contractile SMCs while avoiding cell-cell contact phenotype (Figure 1, (b)) was obtained with a collagen hydrogel concentrated at 2.5 mg/ml at pH=8, and seeded with 100000 cells/ml.

![Figure 1: SMC populations in two different hydrogels. (a) Typical desired contractile phenotype. (b) A too high cell density limiting using TFM. Nuclei (blue) and actin fibers (red) were imaged by fluorescence.](image)

The acellular hydrogels exhibited different viscoelastic behaviours in shear and compression, with storage and loss moduli intersecting in compression. This could suggest that hydrogel microstructure present an anisotropy of organization or in cross-link point density along the axial axis. Because the SMC basal tone and contractibility adapt to the mechanical behaviour of the extracellular matrix [5], the SMCs traction force study requires 3D TFM on embedded cells in order to assess potential force heterogeneity.

Conclusion

A hydrogel was designed for studying in vitro embedded SMC mechanobiology. Future work will include the quantification of SMCs basal tone and assessment of their mechanobiological response to matrix loading.

References


Acknowledgements

This research was partially supported by the European Union’s Horizon 2020 research and innovation programme SimInSitu (Grant Agreement 101017523). We thank Claudie Petit for training us to AoSMC culture.
A METHODOLOGY TO STUDY THE MECHANICAL PROPERTIES OF NORMAL BREAST TISSUES

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Introduction

The breast is a heterogeneous organ composed of adipose, glandular, and fibrous tissues as well as the suspensory ligaments. It changes along the woman’s life and in a presence of a pathology [1]. It is known that the mechanical properties of such structures are affected by pathologies, i.e. tissues got stiffer in the presence of a disease [2]. Therefore, understanding the mechanical properties may improve current approaches either in diagnosis, treatment, or aesthetical procedures. It is important not only to understand the mechanical behavior of disease tissues but also the normal breast tissues. Thus, this short study aims to carry out a mechanical characterization of normal breast tissues.

Materials and Methods

In this study, the samples were harvested from a post-bariatric patient (after massive weight loss) who underwent a breast reduction shaping surgery. It was obtained one sample from each breast (right and left). The samples were cut in a cylindrical shape, with a diameter of 20 mm and a height of 10 mm. The mechanical characterization was achieved by performing indentation tests with a flat-ended indenter of diameter of 5mm, a 10N load cell, and a saline bath at 37°C (Figure 1).

The mechanical protocol was a two-step approach:

I. Preconditioning: 20 cycles with 10% strain at 30%/min

II. Stress-relaxation test: load up to 30% strain at 30%/min, hold for 360s at the final position and unload up to 0% at the same rate

Histology was also performed to evaluate the main tissue type presented in these samples.

Results

Following the mathematical approach of Delaine-Smith et al. [3], Young’s modulus was calculated in the two linear regions of the loading curve. The results are presented in the following table:

<table>
<thead>
<tr>
<th>Sample</th>
<th>1st linear region</th>
<th>2nd linear region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>2.69 – 7.35</td>
<td>6.01 – 16.42</td>
</tr>
<tr>
<td>Left</td>
<td>1.96 – 5.35</td>
<td>3.12 – 8.54</td>
</tr>
</tbody>
</table>

Table 1: Young’s modulus (kPa) for the two samples analyzed. Range of values obtained (minimum-maximum) depending on the mathematical approach.

Furthermore, the percentage of relaxation was approximately 36% for both samples.

Discussion

In literature, the results of stiffness of normal breast tissues (adipose and glandular) have a wide range of values. Not only do the intrinsic factors of a woman (e.g. age, menstrual cycle, pregnancy, menopause, and disease) contribute to this variability, but also the parameters of the mechanical tests have an impact on the results. The test speed, the strain amplitude, or the preconditioning are examples of parameters that might influence the stiffness. Therefore, the results obtained in this work can be compared and are in accordance with the values available in the literature [2,4,5].

Looking at the percentage of relaxation, we can observe that more time is needed to reach an equilibrium state. This study contributes to improve the knowledge concerning the mechanical behaviour of normal breast tissues and launches a foundation for future large scale studies.

References


Acknowledgments

The authors gratefully acknowledge funding from FCT, Portugal, under grant 2020.08718.BD, from research unit LAETA and from project MilmB1 - PTDC/EME-APL/29875/2017 financed through FEDER and FCT.

Figure 1: Mechanical apparatus for indentation of breast tissue samples.
DEVELOPMENT OF 3D PRINTED PATIENT-SPECIFIC SCAPHOID IMPLANT TO ACHIEVE CUSTOMISED SCAPHOID REPLACEMENT

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Introduction
Treatment of scaphoid bone fractures is always complex due to limited vascularization, difficult anatomic position for surgical access and unpredictable healing course due to patient movement. [1] Replacement of the scaphoid with an implant could be an alternative if the cartilage of the scaphoid fossa is still intact. In this study, a 3D printed patient-specific scaphoid was developed.

Methods
3D model of scaphoid was generated using CT scan of two cadaveric wrists. Special channels, 2mm in diameter, were created using Autodesk Meshmixer. Implant was 3D printed using titanium (Ti64ELI Grade 23) powders. 2mm suture anchors were used to suspend implant on trapezium and lunate separately.

Figure 1: Implantation of 3D-printed scaphoid in cadaveric wrist

Post-implant 3D CT scans were performed and bones segmented using Materialise Mimics. MATLAB software was used to calculate the translational and angular displacements of the scaphoid to evaluate its static stability during wrist flexion-extension and radioulnar deviation.

Results
Two 3D printed scaphoid implants based on the CT scan of the respective cadaveric wrist used in the study:

Table 1: SL angles for the two implanted wrists

<table>
<thead>
<tr>
<th>SL angle/°</th>
<th>Wrist positions</th>
<th>Neutral</th>
<th>RD</th>
<th>UD</th>
<th>Flex</th>
<th>Extend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist 1</td>
<td>57.2</td>
<td>46.1</td>
<td>46.3</td>
<td>49.3</td>
<td>49.3</td>
<td></td>
</tr>
<tr>
<td>Wrist 2</td>
<td>66.0</td>
<td>62.7</td>
<td>55.9</td>
<td>60.6</td>
<td>56.9</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: SL gaps for the two implanted wrists

<table>
<thead>
<tr>
<th>SL distance/mm</th>
<th>Wrist positions</th>
<th>Neutral</th>
<th>RD</th>
<th>UD</th>
<th>Flex</th>
<th>Extend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist 1</td>
<td>1.36</td>
<td>1.55</td>
<td>1.65</td>
<td>1.40</td>
<td>2.09</td>
<td></td>
</tr>
<tr>
<td>Wrist 2</td>
<td>2.25</td>
<td>1.98</td>
<td>2.27</td>
<td>1.36</td>
<td>2.61</td>
<td></td>
</tr>
</tbody>
</table>

Discussion
Static instability was observed for Wrist 2 as SL gap was more than 2mm and SL angle was more than 60°. Based on the CT scan images of Wrist 2, the screw position on the lunate bone was off-centered and slanted towards the dorsal end of the lunate. This could have caused the instability observed, where the scaphoid dissociates away from the lunate. In future work, computational simulation can be performed to determine the optimal suture anchor positions for stability of the scaphoid. Subsequently, a surgical guide can be developed for use by the surgeon during the surgical implantation.

References

Acknowledgements
This research was supported by AM Research Grant AM/SU009/2018, Temasek Polytechnic TPRF grant 2020TPRF2-9-IS-TRD-03 and Singapore Ministry of Health’s National Medical Research Council NMRC/CG1/007/2022-SGH.
SONIFICATION ANALYSIS OF MIDFOOT PLANTAR PRESSURE IN PRONATED AND NOT PRONATED RUNNERS

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Introduction
Runners are often concerned with how they step. Prone running is believed to cause the most overload (Mei et al, 2019). Therefore, ways of assessing foot posture, such as the Foot Posture Index (FPI), are used to obtain clinical information on the posture of an individual's foot. In addition to this information, it is necessary to understand how the foot behaves according to how the first contact occurs. In addition, how the load is transferred from the hindfoot to the forefoot as it passes through the midfoot. That said, it is necessary to observe how the overload in the midfoot region behaves in runners according to the type of step, as well as the relationship of this overload between the medial and lateral regions of the foot. This information is important so that it can be used for a running retraining process and visual and auditory forms of feedback can be used based on this information. Thus, this study aimed to identify sound markers for movement changes in runners with pronation or not pronation foot posture.

Methods
Data on peak plantar pressure from 40 recreational runners were collected using Flexinfit resistive insoles. Participants were categorized into two groups: pronate foot and not pronate foot with Foot Posture Index (FPI) (Redmond et al, 2006). All of them wore running shoes Run Falcon 1.0 (Adidas). Sonification data were collected using Twotone software. We used the C note in the first octave to transform numerical data into sounds according to the pressure magnitude. The sound file was decomposed using Audacity software into a spectrogram illustrating the main frequency components and their amplitudes.

Discussion
As there was no significant difference in the midfoot medial and lateral plantar pressure values, it was impossible to raise any sound marker that could identify these differences. These data corroborated the study by Chuckpaiwong (2008) when he compared the plantar pressure between normal feet and feet with low arch, being classified by the Navicular Drop. Perhaps because the foot pronation movement has a relatively small range of motion compared to other joints, this promotes few variations in plantar pressures in this region. Therefore, when the Sonification process occurred for each group, the sound produced did not provide differentiated harmonics or fundamental frequencies so that it could identify some sound marker.

Results

Figure 1: Spectrogram of the medial region of the right midfoot with the pronators in the FPI (above the black line) and the non-pronators (below the black line).

Figure 2: Spectrogram of the lateral region of the right midfoot with the pronators in the FPI (above the black line) and the non-pronators (below the black line).

<table>
<thead>
<tr>
<th>FPI</th>
<th>7.7%</th>
<th>15.4%</th>
<th>23.1%</th>
<th>30.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Pronated M right</td>
<td>41.5</td>
<td>79.11</td>
<td>90.51</td>
<td>98.82</td>
</tr>
<tr>
<td>Pronated M right</td>
<td>34.3</td>
<td>66.03</td>
<td>84.77</td>
<td>94.72</td>
</tr>
<tr>
<td>Not Pronated L right</td>
<td>32.47</td>
<td>67.29</td>
<td>84.8</td>
<td>93.55</td>
</tr>
<tr>
<td>Pronated L right</td>
<td>35.49</td>
<td>59.33</td>
<td>73.88</td>
<td>80.74</td>
</tr>
</tbody>
</table>

Table 1: Plantar pressure (kPa) of the first 31% midfoot contact time. (M-medial; L-lateral).

References

Acknowledgements
Thanks to the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the scholarship Ph.D. provided for the author.
COMBINING BIG DATA WITH CELL CULTURE ON THE 3D NICHOID TO DISCOVER NEW THERAPEUTIC STRATEGIES AGAINST CANCER

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Introduction

In recent years, the concept of synthetic lethality (SL) has gained increasing interest in the field of cancer therapeutics [1]. Here, we employed SL concept to discover new possible targets for the repurposing of so-called “migrastatics” drugs, agents which prevent cell spreading from the primary tumor site, to contrast the formation of metastases, and that can be used in combination with conventional “cytostatic” drugs that mainly target proliferation [2]. Moreover, in order to perform a drug repurposing operation, biological and medical big data could be exploited for computer-based approaches, which means to investigate new therapeutic possibilities for drugs that have already been approved for use in patients and are on the market [3]. After having computationally integrated these three concepts, we finally tested the resulting drugs in wet, treating cancer cells plated in the Nichoid, an innovative bioengineered micro-scaffold, able to mimic the structural niche of adhering cells in 3D culture [4].

Methods

Several types of data were retrieved from different databases (i.e. gene-disease associations from DisGeNET, SL couples from SynLethDB, drugs from DrugBank) and integrated. A specific scoring scheme allowed to extrapolate a set of genes associated with metastases, the SL couples in which they are contained and the drugs targeting SL partner genes. Then we selected two PARP-inhibitors (Olaparib and Veliparib) and two statins (Simvastatin and Lovastatin) for drug testing on BRCA1-mutated ovarian (OVPA8) and breast cancer (HCC1937) cell lines. Cells were expanded both on the Nichoid micro-scaffold fabricated by two-photon laser polymerization, and on conventional flat substrates, for viability comparison between the 2D and the 3D culture environment.

Results

We extrapolated a total of 63 genes associated to metastases, in turn contained in 168 SL couples and for which the partner genes turned out to be targets of 102 drugs. Among these drugs, our attention was drawn to statins, normally administered to lower lipid levels but, according to retrospective studies, with an unexplained connection to an improvement in the response to anticancer therapies [5]. In our preliminary experimental results from cell culture, the PARP-inhibitor Olaparib demonstrated a greater anti-proliferative effect on cells cultured on flat substrates, compared to those cultured on the Nichoid, as shown in Figure 1.

Discussion

The exploitation of SL strategies for assessing new drug targeting cell migration represents an important frontier in anti-metastatic cancer therapy, since it could help to overcome problems related to both drug resistance and side effects of chemotherapeutics. In our study, computer-based approaches have proven to possess the potential to accelerate the identification of the new therapeutic targets to be tested, which is a fundamental aspect in the field of anticancer research. Here, however, we also highlighted how equally important is to screen the new therapies in culture models in which cells can give a response as realistic as possible to the drug treatment.

References

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Acknowledgements

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ANALYSIS OF THE EFFECT OF COMBINED EXTRACORPOREAL LUNG AND KIDNEY SUPPORT USING A CARDIOVASCULAR MODEL

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Introduction

Extracorporeal membrane oxygenation (ECMO) is commonly used in intensive care to support cardiac and respiratory failure, yet up to 70% of these patients also suffer from acute kidney injury. The treatment for this complication, which involves connecting continuous renal replacement therapy (CRRT) to the ECMO circuit, lacks a gold standard and its connection configuration varies depending on the operator's practice and proficiency.

Aim of this study is to develop a cardiopulmonary model to investigate the effect of different CRRT connection schemes (see Figure 1 a-c)) on large ECMO cohorts. As a first step, this abstract focuses on the application to a veno-venous-ECMO (VV-ECMO) patient. A Global Sensitivity Analysis (GSA) using Sobol indices is conducted to identify most crucial model parameters for fitting, reducing the number of function evaluations (NFE) and thus its computational cost. Different solvers are compared with regard to performance and quality of the results.

Methods

A computational cardiovascular model has been extended by a pulmonary system and an ECMO system with an external pump, oxygenator, and additional cannulae. This model was fitted to an ARDS patient with Influenza A Pneumonia (f, 28y, sedated) using different state-of-the-art solvers. A GSA was conducted using the Sobol method to identify the model parameters most relevant for the fitting. The Saltelli extension of the Sobol sequence was used to generate 512 samples that served as inputs for the GSA.

Results

Left part of Figure 2 shows the Total Sensitivity Index, which measures the total effect of each model parameter on the output of the system, including interactions between them. Model fitting was performed using the intersection of the two most important parameters for each output. These parameters were the resistances $R_s$, arterial, $R_p$, arterial, $R_{cannula}$, inlet, $R_{cannula}$, outlet, $R_{oxygenator}$, the compliance $C_p$, arterial and the maximum elastance $E_{max}$, left ventricle.

Table 1 shows the results of different solvers for minimizing the root-mean-square error between simulated and clinical data, as well as the NFE required for convergence. The Sequential Least Squares Programming (SLSQP) algorithm was chosen for its low error value and computational cost. Its results are compared to clinical data on the right of Figure 2.

Discussion

A cardiovascular model including VV-ECMO was analyzed using GSA, which revealed that fitting the model using only a subset of important model parameters reduces computational cost while maintaining the quality of the fit. This framework will now be extended to a more comprehensive model that incorporates different CRRT strategies and phenotypes from larger patient cohorts.

Acknowledgements

This project is funded by the DFG SPP2014 “Towards the Artificial Lung” - PN: 447746988.
MERGING 4D ULTRASOUND AND MODIFIED VIRTUAL FIELDS METHOD TO REGIONALLY CHARACTERIZE ABDOMINAL AORTIC ANEURYSMS

Mirunalini Thirugnanasambandam (1,2), Esther J Maas (1,2), Arjet HM Nievergeld (1,2), Marc RHM van Sambeek (1,2), Stephane Avril (3), Richard Lopata (1)


Introduction
Clinical management of abdominal aortic aneurysms (AAA) has been solely based on the maximum diameter threshold. Attempts to replace this generalized parameter with more patient-specific scientific indices have led to the discovery of biomechanical markers of AAA progression and rupture risk. However, to ensure that these markers are truly patient-specific, it is crucial to identify the individualized material parameter values of each AAA. In this study, we present a novel method to extract this information on patient-specific material behavior from AAA wall motion using a combination of 4D ultrasound (US), speckle tracking, and a virtual field method (VFM)-based inverse method [1].

Methodology
Patients with AAA underwent 4D US acquisition at a frequency of 4-8 Hz over multiple heartbeats. Image volumes were segmented at the diastolic phase, and the inner- and outer walls were tracked using an in-house speckle-tracking algorithm [2]. The point clouds at systole and diastole were fitted to B-spline grids, which were then co-registered to minimize the distance between adjacent knots, thus generating the displacement fields of the inner wall and outer wall. Displacement vectors in the bulk of the AAA wall were generated by interpolating corresponding displacement vectors on the neighboring nodes in the inner wall and outer wall. An unsupervised and discretized spline smoother was used to smooth the final displacement field, which was used as the full-field deformation field in a modified virtual fields (mVFM) approach.

mVFM (illustrated in Figure 1) uses a virtual work-based cost function based on traditional VFM, which leads to fast convergence. It also adopts an iterative nature similar to that of the finite element updating method. An appropriate test function is automatically chosen, and serves to tactfully eliminate parameters that are difficult to estimate.

Results
An initial guess of $c_{10} = 1.2 \times 10^6$ Pa was used in an uncoupled Neo-Hookean material model. The optimized global and local material parameter values were predicted within 3 and 10 iterations, respectively.

Discussion
mVFM was successfully implemented using AAA deformation fields obtained from routine US images. The anterior AAA sac and the healthy abdominal aorta had the highest and lowest shear modulus respectively [3]. As a next step, the use of more sophisticated material models using better input data[4] within the mVFM framework will be evaluated.

References

Acknowledgements
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THE EFFECT OF ALVEOLAR BONE CREST SHAPE ON STRAIN DISTRIBUTION IN PERI-IMPLANT BONE TISSUE

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2 CEITEC – Central European Institute of Technology, Brno University of Technology, Czech Republic
3 Department of Anatomy, Faculty of Medicine, Masaryk University, Czech Republic

Introduction

With the increasing average life expectancy of the population, dental implants are used more often. In some cases, it is necessary to widen the alveolar crest area where the dental implant is inserted. This reduction should be from 1 to 3 mm and the alveolar bone's total height must be considered [1]. The aim of this study is to analyse the mechanical influence of the alveolar crest reduction and strain distribution in the peri-implant bone tissue during chewing.

Materials and methods

The mandibular bone segment (20 x 15 x 15 mm) was scanned by micro-computed tomography (GE phoenix vltome|x L240, GE Sensing & Inspection Technologies GmbH, Wunstorf, Germany) with voxel size of 30 μm. The sample of the human mandible was acquired from the Department of Anatomy, Faculty of Medicine, Masaryk University Brno, Czech Republic in full accordance with relevant institutional and legislative requirements. The geometry model of bone tissue with trabecular structure was created in the software RETOMO using thresholding (see Figure 1a)). The geometry model with alveolar crest reduction was created by cutting 1 mm of alveolar crest bone (see Figure 1b)). For analysis of peri-implant bone tissue, the cylinder with an 8 mm diameter around the dental implant was created. Geometry model of dental implant (Brånemark® System Mk III Groovy (NP Ø 3.3 mm, 11.5 mm)) was created in SolidWorks 2012 (Dassault Systèmes, France).

Material model of bone tissue and dental implant was assumed as homogeneous, linear and isotropic. Three variants of the material model of bone tissue (simulation of differently mineralized bones [2]) with different Young's modulus E= 5 GPa, 10 GPa and 15 GPa and Poisson's ratio μ=0.3 were created. The mechanical properties of the titanium alloy dental implants used in this study were E=110 GPa and μ=0.34. The dental implant was loaded with axial loading of magnitude 200 N and the segment was fixed. FE mesh was created by using SOLID 187 elements with around 9 million elements in all variants. The implant and bone were assumed as fully osseointegrated and for their interaction were elements CONTA174 and TARGE170 used. Contact was set as “always bonded”.

Results and discussion

The analysis of strain intensity values in peri-implant bone based on mechanostat hypothesis by Frost [3] was performed for all variants. The isolines of strain intensity are more consistent for the variant with alveolar crest reduction (see Figure 2). Also with the increasing Young's modulus, the strain intensity values in bone tissue are decreasing.

![Figure 2: Isolines of strain intensity for all variants](image)

Conclusion

This study shows changes of strain intensity distribution in the peri-implant bone with and without alveolar crest reduction.

References


Acknowledgements

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HOW WELL DOES A NEW DEVELOPED PIVOT TKA RESTORE THE NATIVE KINEMATICS: A CADAVERIC STUDY

Christoph Thorwaechter (1), Berna Richter (2), Brigitte Altermann (2), Arthur Bollinger (2), Henning Windhagen (3), Boris Holzapfel (1), Peter Mueller (1), Thomas Grupp (2), Matthias Woiczinski (1)

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Introduction

Ensuring a better outcome for the patients after total knee arthroplasty (TKA) is still a concern. With increasing number of procedures, further development is needed due to the dissatisfaction of 20% of patients after TKA [1, 2]. A cause for this dissatisfaction is seen in individual native kinematics, which is not supported with standard TKAs. One of the latest developments in TKA is the use of pivot implants, which are designed to support natural rotational and translational kinematics [1]. To date, its use as a cruciate retaining or cruciate sacrificing system is still subject of research and more companies want to include it in their product range [6]. The aim of this study was, therefore, to determine which newly developed TKA better restores the native translation and rotation.

Methods

Eight fresh frozen knee specimens (4 male, 4 female; Ø age: 80.1 ± 4 Years) were tested in a well-established, weight-bearing knee-rig (Fig.1) [3-5].

![Figure 1: Knee rig with native knee and optical markers for kinematics tracking.](image)

Femurotibial kinematics of the native knee was recorded with an optical tracing system (GOM, Braunschweig, Germany) while performing a squat of 30° - 130° of flexion (50N ground reaction force). Afterwards, a newly developed TKA (oneKNEE®, Aesculap, Tuttlingen) was implanted. The oneKNEE® TKA allows a simple change of inlays into the different unconstrained systems: cruciate retaining/cruciate sacrificing (CR/CS) and medial stabilized (MS). These systems were analyzed with and without PCL against the native kinematics.

Results

The femoral rollback until 90° flexion with the CR/CS (with and without PCL) and MS designs was not significantly different from the native situation (Fig.2 a). After 90° of flexion, the different TKA designs showed significantly different kinematics compared to the native. No differences were seen with and without PCL. The tibia rotation of the MS system (with and without PCL) was not significantly different from native rotation in flexion over 90° (Fig.2 b). The CR/CS implant allowed significantly different rotation over the whole flexion cycle with and without PCL.

![Figure 2: Mean values and 95 % confidence interval of a) femoral rollback, b) tibia rotation for native state, CR/CS and MS with (left) and without (right) PCL.](image)

Discussion

This study shows that the new TKA system restores native translation and rotation. The MS design seems to benefit in high flexion as seen in the tibial rotation results. The cruciate retaining option shows no significant influence in the pivot systems.

References


Acknowledgements

This study was supported by Aesculap AG.
A Data-Driven Constitutive Framework for Soft Biological Tissues

Computational biomechanics is a valuable tool to successfully model and understand physiological function. Constitutive material models for soft biological tissues lie in the center of these biomechanical simulations. However, different tissue types in living organisms have different mechanical characteristics that need to be reflected at the constitutive level which poses a challenge from modeling perspective. Constitutive models can be divided into two categories: classical analytical models, and data driven models. Classical constitutive models possess a fixed mathematical form that may be chosen with microstructural [1] or macroscopic [2] considerations in mind. These methods have the advantage of utilizing fewer material parameters than data driven models, and as a result it is straightforward to fit these material parameters to the mechanical test data. These models can also be constructed polyconvex a-priori, guaranteeing stability of the hyperelastic response. These models are often easy to implement and provide a good computational efficiency as they allow for closed form analytical calculations. On the other hand, complex structure of biological tissues makes it difficult to find the right mathematical form to represent strain energy functions such as exponential, polynomial, and power law forms that can be found in literature. A mathematical form chosen with a specific type of tissue in mind may not be successful in capturing the response of another type of soft tissue. This is especially a problem from the point of view of users, because choosing the right constitutive model may become a cumbersome process for an occasional user outside of mechanics community. We believe that biomechanics community needs an accurate yet flexible framework applicable to a wide range of soft tissues.

At this point, data driven models emerge as a novel approach to creating a unified model that is capable of predicting the mechanical response of various tissue classes [3]. In this study we propose a data driven constitutive framework based on B-Spline approximations. To this end, we start with the assumption of additive splitting of the strain energy function into volumetric, isotropic, and anisotropic components. We use B-Spline ansatz defined by the choice of control points and polynomial degree, in place of partial derivatives of the strain energy components. Our model allows the use of dispersion models from literature thanks to the employment of deformation invariants. Resulting framework communicates with the experimental data, adapts its control point values, therefore the B-Spline shape, by reducing the error between data and model prediction until a threshold value is reached. Thermodynamic consistency of the resulting free energy function is guaranteed with the use of simple optimization constraints imposed on the choice of B-spline control points [4]. We demonstrate the performance of our model on biological tissues of different characteristics: linea alba, myocardium, aneurismic aorta, and rectus sheath. Our model shows excellent fitting capabilities to the mentioned tissue data, utilizing a minimal number of control points. Finally, we compare the results of finite element simulations with our new model against the well-established Holzapfel-Ogden model [5]. The outcome of this work is a generic data-driven constitutive framework that can model any specific tissue given the data from uniaxial, biaxial, equibiaxial and shear experiments along with histological information from imaging techniques. We believe that this new method will bring the biomechanical simulations one step closer to everyday clinical use.

References:
BONE-FIBROCARTILAGE CROSSTALK AND OSTEOCYTE LACUNOCANALICULAR NETWORK AT THE TENDON-BONE INSERTION

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Introduction
Mechanobiological interactions between tissues are a crucial aspect of the musculoskeletal system. At joints, crosstalk between bone and cartilage cells may reach unhealthy levels in osteoarthritis [1]. The tendon-bone insertion often features fibrocartilage, a fibrous form of cartilage reinforced with minerals before anchoring to bone [2]. Tendons and bones contain cells (tenocytes and osteocytes) having communication abilities thanks to underlying networks of sub-micrometer channels. In bone, the latter is called the osteocyte lacuno-canicular network (OLCN) whereas in tendon it is referred to as nanotube network [3]. They serve multiple functions: in addition to communication, nanotubes in tendon are believed to provide biomechanical stability [3] while the OLCN is directly involved in bone mechanoresponsiveness [4] and mineralization [5]. Mineralized fibrocartilage (mFC) exhibits fibrochondrocytes (FCCs) occupying lacunae, often very close to each other. Here, we explore the possible crosstalk between osteocytes and FCCs as well as the behavior of the OLCN at the interface between the two tissues. We consider the Achilles tendon insertion into calcaneus bone, and we compare enthesis with periosteal fibrocartilage, two contiguous tissues sustaining different loading conditions: tension at enthesis and compression/shear at periosteal. We have previously shown microstructural [6] and material heterogeneity [7] of mFC. Here, we address additional mechanobiological aspects.

Methods
Rat samples (ULg IACUC-21-2340) were stained with rhodamine and then micro-computed tomography (micro-CT), quantitative backscattered electron imaging (qBEI), second harmonic generation (SHG) imaging and confocal laser scanning microscopy (CLSM) were combined on the same locations to highlight the functional porosity of bone and mFC at multiple length scales, as well as its link with mineral content and matrix organization.

Results
At the enthesis, some rows of FCC lacunae located entirely inside mFC, and therefore not directly exposed to rhodamine, got stained. Correlating micro-CT with CLSM revealed that the fluorescent molecule could reach the FCC rows through perforating channels, originating from the trabecular bone marrow space and reaching mFC. The OLCN seemed to stop or bend at the cement line separating bone from mFC, but exhibited a high connectivity with the perforating channels, providing an indirect path between osteocytes and FCCs (Fig. 1). Such connections were absent at the periosteal region. The previously highlighted enthesis anisotropy [6] was not reflected in osteocyte lacunae morphology.

Discussion
The illustrated communication paths between bone and mFC at the insertion, together with the striking absence of such connections at the periosteal region, suggests that different level of crosstalk between bone and fibrocartilage may be required to maintain healthy enthesis, also depending on fibrocartilage morphology (thickness) and biomechanical task. Crosstalk could be further explored by quantifying the permeability of the interface using fluid flow simulations [4].

References
7. Tits et al., ESB Conference 2022.
UNILATERAL TRANSFEMORAL AMPUTEES MIGHT BE AT RISK OF LATERAL COMPARTMENT DEGENERATION OF THE KNEE JOINT

Diana Toderita (1), Clement D. Favier (1), David P. Henson (1), Vasiliki Vardakastani (1), and Anthony M.J. Bull (1)

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Introduction

High-functioning unilateral transfemoral amputees (UTF) are susceptible to intact knee osteoarthritis (OA) [1], which is a mechanically-mediated condition. Unilateral transtibial amputees (UTT) are known to show medial intact knee compartment overload, which might explain the risk of OA for UTT [2], but little is known for UTF. This study aims to understand the mechanical indicators of the development and progression of knee OA in the UTF population.

Methods

Gait motion capture and force plate data were collected from seven UTF with no known secondary conditions. All participants were fitted with microprocessor-controlled prosthetic knees and dynamic response feet and have been prosthetic users for a minimum of two years. Seven able-bodied people (AB) were group matched to the UTF cohort by sex, age, height, and mass. The control dataset is a subgroup of a previous dataset [3]. Musculoskeletal modelling was performed using Freebody to compute joint contact forces [4].

Results

Figure 1 and Table 1 present the knee loading characteristics for UTF and AB. Whilst the UTF lateral compartment of the knee presented higher loading rates, peaks, and impulse (area under the force curve) than AB, there were no significant differences in the medial knee loading between UTF and AB. These findings show that the higher knee loading for UTF is localized to the lateral compartment.

Discussion

As high and repetitive loading might lead to joint degeneration [5], the higher knee loading rate, lateral knee contact forces and impulse observed in this study indicate that UTF might be more susceptible to lateral knee OA as opposed to medial knee OA, as is the case for UTT [2].

Conclusion

Unexpectedly, this study’s results indicate that the higher functional demand of the intact limb compared to AB may increase the risk of lateral knee OA in the UTF population, as opposed to UTF who might be more susceptible to medial knee OA [2]. Mitigation strategies could be explored through prosthesis adjustments, including alignment to shift the ground reaction force vector, or muscle strengthening to ensure optimal long-term musculoskeletal health.

Acknowledgements

The financial support from the Royal British Legion Centre for Blast Injury Studies is gratefully acknowledged.

References


Table 1. Intact knee joint loading rate, contact forces and impulse.

<table>
<thead>
<tr>
<th></th>
<th>UTF</th>
<th>AB</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee loading rate (Nm/kg)</td>
<td>4.8 ± 1.7</td>
<td>3.4 ± 0.5</td>
<td>p = 0.045</td>
</tr>
<tr>
<td>1st peak lateral knee force (BW)</td>
<td>2.1 ± 0.4</td>
<td>1.6 ± 0.5</td>
<td>p = 0.024</td>
</tr>
<tr>
<td>2nd peak lateral knee force (BW)</td>
<td>3.5 ± 0.9</td>
<td>2.8 ± 1.3</td>
<td>p = 0.322</td>
</tr>
<tr>
<td>Lateral knee impulse (BW s/m)</td>
<td>98.2 ± 17.0</td>
<td>77.1 ± 18.3</td>
<td>p = 0.029</td>
</tr>
<tr>
<td>1st peak medial knee force (BW)</td>
<td>1.0 ± 0.5</td>
<td>1.9 ± 0.4</td>
<td>p = 0.164</td>
</tr>
<tr>
<td>2nd peak medial knee force (BW)</td>
<td>2.0 ± 0.5</td>
<td>2.5 ± 0.7</td>
<td>p = 0.131</td>
</tr>
<tr>
<td>Medial knee impulse (BW s/m)</td>
<td>63.7 ± 13.8</td>
<td>72.8 ± 14.7</td>
<td>p = 0.108</td>
</tr>
</tbody>
</table>
Introduction

Articular cartilage (AC) defects are one of the most common symptoms of osteoarthritis, a degenerative disease affecting millions of people worldwide. Synthetic hydrogels, due to their high-water content and low friction coefficient, can mimic AC structural and mechanical properties and are therefore considered promising candidates for AC repair. In particular, Polyvinyl Alcohol (PVA) hydrogels have been investigated for the repair of chondral defects, due to their hydrophilic nature, good biocompatibility and suitable mechanical strength [1,2]. However, their tribological and compressive mechanical properties are not yet optimal for the substitution of AC and are still limiting their clinical application. This work is aimed at developing improved PVA hydrogels with tailored mechanical properties that mimic the ones of the articular cartilage of human knee.

Methods

Several scaffolds based on PVA hydrogels were prepared in different conditions, either varying hydrogel concentration (15%, 20%), either carrying out a partial oxidation treatment, or covering PVA with a superficial layer of decellularized human AC matrix. Details on the preparation of native and partially oxidized PVA hydrogels and composite PVA/AC scaffolds (Figure 1) characterized in this work can be found in previous publications [3,4]. Mechanical tests are carried out to compare the tribological and compressive mechanical properties with those of human AC. Indentation and consolidation test are developed according to a method recently proposed [5], while friction tests are carried out with a custom-made setup, based on a pin able to slide horizontally in contact with two flat surfaces, while a vertical compressive load is applied. Both the pin and the surfaces can be samples of PVA or AC, to evaluate the friction coefficient for different couplings. The applied load can be varied to simulate physiological joint compressive stress in the range of 0.5–5 MPa.

Results

The results of indentation tests (Figure 2) show that the almost-instantaneous compressive behavior of PVA varies with the hydrogel concentration. At maximum penetration depth, a lower concentration corresponds to an inferior indentation load. Moreover, partial oxidation treatment can affect the compressive mechanical behavior, reducing PVA stiffness. Therefore, it is possible to tune the compressive elastic modulus of PVA hydrogel scaffolds to match the one of AC.

Discussion

The compressive behavior of composite scaffold is expected to mostly depend on PVA hydrogel, due to its considerably higher stiffness, while the tribological properties can be affected by the surface coverage with decellularized human AC matrix. Moreover, the modification with AC layer will lead to the fabrication of a biohybrid scaffold which can benefit from the mechanical features of the hydrogel and the bioactive properties of the biological coating. The mechanical properties of PVA scaffolds will be compared with the ones of AC form cadaveric donors. In further developments of this study, the functional response of PVA hydrogel scaffolds in vivo, namely the interaction with the tissues of the knee joint, will be evaluated by numerical analyses considering different loading conditions, exploiting a finite element model of the knee joint in healthy or pathologic conditions.

References

3D MODELING OF CAROTID ARTERY AND PLAQUE PROGRESSION USING COUPLED AGENT BASED AND FINITE ELEMENT METHODS

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Introduction

It is well established that atherosclerotic plaque composition as well as its progression over time play a central role in determination of atherosclerotic plaque stability and vulnerability. This study includes an integrated approach for 3D reconstruction of patient-specific carotid bifurcation from US images and then the simulation of plaque progression using agent based modelling (ABM) and finite element modelling (FEM). The integration of different methodologies enables better understanding of atherosclerotic disease, as well as improved prediction of patients under increased risk of cardiovascular events.

Methodology

Deep learning techniques are used to segment the regions of interest including lumen and arterial wall areas, as well as plaque types. The U-Net, SegNet, and Pyramid Scene Parsing Network (PSPNet) architectures for multi-class image segmentation task have been applied. Afterwards, meshing techniques are applied to create the 3D geometry and hexagonal mesh of finite elements [1]. The characterization of carotid plaques in three dimensions could improve investigations of the changes of plaque morphology, geometry and its distribution and these can provide important information about the effects of anti-atherosclerotic therapies.

In addition, the ABM was coupled with shear stress and LDL initial distribution from the lumen. Iterative calculation inside the wall for lipid infiltration and accumulation using a random number generator for each time step has been used. The wall artery geometry has been changed which is modelled with FEM where agents from ABM are positioned inside these large finite elements. The ABM was coupled with an initial wall shear stress (WSS) profile, which triggers a pathologic vascular remodelling by perturbing the baseline cellular activity and favouring lipid infiltration and accumulation within the arterial wall. The ABM model takes shear stress and LDL initial distribution from the lumen and starts iterative calculation inside the wall for lipid infiltration and accumulation using a random number generator for each time step.

Results and Conclusions

For verification and validation of the proposed coupled methodology of ABM and FEM we used one specific patient for carotid artery model of plaque progression. The simulated model with ABM-FEM coupled model which has overall five chosen cross-sections is presented in Figure 1. The model on the left is coloured according to the distribution of total displacement of the nodes on the surface between lumen and intima. On the right, the change of the shape of the cross-sections of the arterial wall is shown in three specific moments in time (baseline, after 3 months and after 6 months).

First results show good agreement between proposed method and clinical measurements in the follow up for plaque progression. With the software presented in this study, it is possible to obtain additional information in three dimensions and perform the visualization of vascular structures in different planes from different angles [2].

Acknowledgements

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References

Introduction

High-fidelity mitral valve (MV) finite element (FE) models based on in vivo imaging have been increasingly developed [1,2]. To this aim, 4D echocardiography has been largely used since it provides well time- and space-resolved volumetric data, despite its inter-operator variability [1]. Cardiovascular magnetic resonance (CMR) can also be exploited [2]; it is operator-independent, it offers a better image contrast, but data consist in stacks of 2D images thus requiring a dedicated approach to reconstruct the 3D MV geometry. Also, regardless of imaging modality, chordae tendineae cannot be clearly identified, with uncertainty in their definition heavily hampering the reliability of computational results. Herein, we sought to advance CMR-based MV modelling by combining an improved method for MV 3D reconstruction with a dedicated approach for the calibration of chordae tendineae.

Methods

CMR images were acquired on a Philips Ingenia 1.5T scanner (Philips Medical System) on 18 evenly distributed radial planes [2], and on a stack of short-axis planes encompassing the entire MV. CMR planes were realigned by optimizing their normalized cross correlation, under the hypothesis of pixel-intensity similarity along their intersections [3]. Based on Fourier and NURBS fitting functions, the stress-free MV geometry was reproduced at late diastole (Fig. 1.a) from manual tracing of MV annulus, MV leaflets and papillary muscle (PMs) tips. The model was completed by a functionally equivalent model of chordae tendineae with insertions uniformly distributed over the leaflet surface (15 chordal insertions/cm² [4]). Chordae initial length was then calibrated [4]: the mid-systolic leaflet surface was reconstructed from CMR data (Ωₐₗ₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ₑ₉₅ empleado /E.

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Results

The method was preliminarily tested on a healthy MV. As compared to the initial setting at end-diastole, calibration made 95% of chordae longer, on average by 4.2 mm (+ 12.3%), and made 5% of chordae negligibly shorter, by 0.6 mm (-1.4%) on average. Chordae length calibration allowed for consistency between the simulated mid-systolic leaflet configuration and ground-truth CMR data (Fig. 1.b). At mid-systole, MV leaflets strain pattern (Fig. 1.c) well agreed with previous MV models [1, 4]. Force transferred to PMs reached 20.7 N, redistributed between the single antero-lateral PM (10.0 N) and the two heads of the postero-medial PM (8.5 N and 2.2 N, respectively).

Discussion

We effectively improved our CMR-based MV modeling strategy, which will allow achieving deeper insight into MV function and biomechanical implications involved in MV degenerative prolapse.

References

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Acknowledgements

IRCCS Policlinico San Donato is a clinical research hospital partially funded by the Italian Ministry of Health.
Introduction

Endoscopic Sleeve Gastrectomy (ESG) is an emerging surgical procedure of Bariatric Surgery (BS) that treats people with morbid obesity. ESG is safe, feasible, repeatable, and reversible. The volume of the stomach is reduced by approximately 70% through the plication of the greater curvature [1], [2]. ESG patients reported better results respect to other BS procedures in gastrointestinal symptoms, Quality-of-Life score and comorbidities remission [3], [4]. However, the current outcomes are limited due to the retrospective nature of the studies and short-term follow-up. The computational analysis was addressed to BS in the last years by means of a patient-specific approach [5]. The goal is to improve the precision, safety and outcomes of BS through a customized intervention planning and forecast of success. This study was aimed to develop in silico simulation of the ESG starting from a pre-surgical Magnetic Resonance (MR) of ten bariatric patients submitted to ESG. The results were compared to the actual ESG configuration obtained from a 6-months after ESG MR of the same patients.

Materials and Methods

From MRs performed on ten bariatric patients before and six-months after ESG (Fig. 1), the volume of empty stomach was processed to generate a virtual solid model composed by a double layer. The finite element discretisation was performed with hexahedral elements. The ESG sutures were created by means of wire features, to which a displacement connector was imposed. Each computational analysis was performed defining a fluid cavity and increasing the volume in a step time of 1 s by means of Abaqus 2020.

Results and Discussion

The post-ESG volumetric capacities obtained after the closure of the wires were compared to the actual post-ESG volumes segmented in MRIs, finding an average discrepancy of maximum 30ml (over 200ml). The elongation strain and pressure-volume behaviour of the pre- and post-ESG stomach of patient 1 (Fig. 2) after the ingestion of 400ml showed a different pattern distribution and mechanical response, revealing a higher pressurisation in post-ESG models.

Conclusions

The use of computational clinical tools could be a turning point in addressing the main issues related to BS. In fact, a patient-specific approach can improve the gastric solicitation of the stomach, which is crucial in weight loss and its maintenance because of the presence of chemo-mechanical receptors that perceive stimuli and send electric impulses to the brain, activating the brain regions of satiety. The final goal is the exploitation of a vast cohort of ESG-patients for the training and validation of an algorithm that will automatically detect the sutures’ location, starting from a pre-surgical MRI. This procedure could be used as a planning tool that will identify the optimal patient-specific surgery design by proposing different sutures patterns and forecasting the success rate of BS.

References


Acknowledgements

This work was supported by MIUR, FISR 2019, Project n°FISR2019_03221, titled CEComES: CEntrO di studi sperimentali e COnputazionali per la ModElliStica applicata alla chirurgia and by DICEA, BIRD 2022, titled Computational gastric biomechanics to improve bariatric surgery procedures with a patient-specific approach.
IN VIVO MECHANICAL CHARACTERIZATION OF THE OSTEOPOROTIC DISTRACTION CALLUS

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Introduction

Osteoporosis (OP) is a skeletal disorder characterized by a bone mineral density (BMD) decrease and a microarchitectural deterioration of the bone tissue, leading to an increase in bone fragility and risk of sudden fractures. Furthermore, one of the main problems of osteoporotic patients is their poor osteogenesis capability [1]. At present, quantitative knowledge reported about the influence of osteoporosis on bone regeneration is still limited. Bone transport (BT) through distraction osteogenesis (DO) is a recognized clinical bone regeneration process to repair large bone defects or traumas [2,3]. This work aims to mechanically characterize the evolution of osteoporotic BT distraction callus in vivo, quantifying the traction forces of the callus during the distraction phase.

Methods

In this study, BT in vivo experiments were carried out in 8 female merino sheep metatars, which were previously subjected to an OP induction protocol [1,4,5]. It has consisted of performing an ovariectomy, periodic injections of glucocorticoids, and low calcium and vitamin D diet until reaching a 20-30% reduction in BMD [6]. The OP progress was monitored by tracking the BMD by computed tomography images (CT), reporting a mean reduction of 25% at the beginning of the BT experiment (6 month after induction). Afterwards, the BT protocol consisted of a latency period of 7 days, followed by a distraction phase applying a daily of 1 mm bone fragment transport for 15 days, and a consolidation phase in which specimens were sacrificed at different time-points between 35 and 100 days after surgery. Distraction force records were monitored by using an instrumented fixator with load cells during the distraction stage [4,5].

Results

An example of OP distraction force measurement is shown in Figure 1. It may be seen the relaxation of the callus tissues post-distraction. Figure 2 shows the peak and post 8 minutes distraction forces recorded along the distraction phase in healthy [4] and OP sheep. It can be seen how the peak forces are significantly lower in OP animals, differentiating with healthy animals increasingly throughout the days. Furthermore, differences with control animals increase throughout the distraction days. However, the interdifference between groups is not as significant when comparing 8 minutes post-distraction force values.

![Figure 1: Distraction force measurement example.](image1)

![Figure 2: Peak (Left) and post 8 minutes (Right) distraction force in control [4] and OP group.](image2)

Discussion

This work reports quantitative results about the force applied to OP bone fragment being displaced along BT the gap. It shows how the recorded distraction force increases over the days, indicating a positive response of OP bone cells to the mechanical stimulus applied by distraction. However, the callus stiffening is generally slower than in healthy animals [4].

References


Acknowledgements

We thank the financial support from project PID2020-113790RB-I00 and FPI grant PRE2021-097629 by the Ministry of Science and Innovation (MCI) of the Spanish Government and the Spanish State Research Agency (AEI).

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
Introduction

Total knee arthroplasty (TKA) is the standard treatment for late stage knee osteoarthritis and considered one of the most successful surgical interventions in orthopaedics. However, patello-femoral (PF) complications like anterior knee pain frequently limit the functional performance of a reconstructed knee and reduce the quality of life for affected patients. While PF complications have been linked to PF contact loads, these are difficult to access in vivo. We therefore aimed to determine how the more accessible external knee flexion moment (EFM) is related to the PF contact force.

We did so by a combining in vivo measured tibio-femoral (TF) loading with fluoroscopically captured in vivo TF & PF kinematics in a musculoskeletal analysis of lower limb loading.

Methods

Six TKA patients (aged 65-80y) from the CAMS-Knee datasets [1] with instrumented tibial components performed 5-6 repetitions each of activities known to produce high PF forces: sit-stand-sit and squat. In vivo TF forces were measured by an instrumented tibial component, while a mobile video-fluoroscope synchronously captured the internal TF and PF kinematics. PF forces were computed by musculoskeletal modelling using the in vivo measured TF forces as a boundary condition to account for the unknown level of antagonistic muscle co-contraction [2]. The TF & PF kinematics reconstructed from fluoroscopy were used to determine the functional knee flexion axis, effective lever arm of the patellar tendon and the ratio of quadriceps force to patellar tendon force.

The forces were normalized to BW times body-height (BWHt). For the linear regression between the EFM and PF force, only time points with EFM > 0.001 BWHt were considered.

Results

For the sit-stand-sit and squat activities respectively, the peak in vivo measured TF forces were 2.81 ± 0.34 BW (mean ± SD) and 2.59 ± 0.51 BW, peak EFMs were 0.047 ± 0.007 BWHt and 0.042 ± 0.011 BWHt, while peak PF forces were 2.62 ± 0.45 BW and 2.38 ± 0.61 BW. With R² values of 0.94 and 0.84 the regressions between the EFM and PF force yielded slopes of 56 Ht⁻¹ and 54 Ht⁻¹ (Fig. 1). Given the small intercepts (0.014 and 0.023 BW) the slopes can be interpreted as fixed ratios between the two quantities.

Discussion

The novel combination of in vivo forces and internal patellar kinematics enabled us to provide a reliable prediction of PF contact forces. The fluoroscopic assessment minimized uncertainties related to patella location, while the in vivo TF force those related to antagonistic muscle co-contraction. The peak PF forces found in this study were in a similar range to the peak TF forces. The PF forces show a strong relationship with the external knee flexion moments, despite the low number of subjects and their variability in varus-valgus knee angles, age and BMI. Our results allow for a quick estimation of PF forces, as a possible source of anterior knee pain, based solely on the external knee flexion moments from quantitative gait analysis.

References


Acknowledgements

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MECHANICAL BEHAVIOR MODELLING FOR 3D-PRINTED RESORBABLE IMPLANTS OPTIMIZATION AND SOFT TISSUE RECONSTRUCTION

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Introduction

Breast cancer concerns 1 in 8 women in the world and is followed in 40% of cases by a mastectomy. Only 14% of women receive reconstructive surgery because of unfavorable clinical issues [1]. The need of innovative tissue engineering devices leads Lattice Medical company to bring a new 3D-printed device (see Fig.1), allowing the regeneration of soft tissue in order to replace the withdrawn breast. The implant, based on TEC (tissue engineering chamber) and fat-flat surgical technique, is constituted with bioresorbable thermosensitive materials to be fully absorbed by the body in several months, once the regeneration process is completed. In this industrial context, we need to assess some properties for predictive simulation: the TEC mechanical and biological properties over time, its sensitivity to implantation in the body temperature, its batch raw material variability and its structural 3D printed behavior. This would lead to a more enlightened numerical design and topological optimization work.

Methods

We use an experimental approach coupled with numerical validations. Characterization of mechanical properties and degradation kinetics of the polymer are estimated through monotonic and cyclic tensile tests with videoextensometry for local contact-less strain measurement controlled by CRAPPY software [2]. Testing were performed at room temperature (20°C) for standards requirement. Complementary testing is added at body temperature (37°C). To do so, a new experimental set-up is built, allowing to immerse tensile samples in heated water-filled closed environment regulated with a dual stream connection to a thermostatic bath. Samples were also characterized at different degradation levels and results show a strong influence of the temperature as well as batches of materials provided by the supplier. To account for these observations, a G’Sell type constitutive behavior law [3,4] is proposed (eq.1) with T the temperature, Tg the glass transition temperature of the batch, K(T) and p regulating the initial rigidity, w(T) for the plasticity, A(T) and B(T) for the threshold low, H(T) for the hardening, e才能 for the strain sensitivity, νm for the strain-rate sensitivity.

\[ \sigma = K(T) \cdot e^P \cdot \left(1 - e^{-w(T) \cdot e} \right) \cdot \left(1 + A(T) \cdot e^{-H(T) \cdot e^P} \cdot (e^{H(T)} \cdot e^P) \cdot e^{\gamma m} \right) \]  

with \( K(T) = K \cdot e^{-\frac{1}{T-T_g}} \)  

The mechanical behavior thus identified from the experimental data is then used to perform structural scale simulations. Finite element simulations (FE) of the MATTISSE breast implant were carried out using Abaqus software (see Fig.1).

Results

This experimental campaign made it possible to determine the properties of the material and its evolution using a modified G’Sell type law at the material scale. Using the previous behavior law, FE simulation of a compression on the MATTISSE implant were compared to the experimental results and show good agreement as shown in figure 1.

![Figure 1: Comparison of experimental curves of forces over displacement (orange) versus numerical (blue)](image)

Discussion

Complementary compression testing on MATTISSE implant with 3D full field displacement measurements using stereo-vision is currently investigated to have more relevant experimental-numerical comparison at room temperature and immerged at 37°C.

References


Acknowledgements

The authors would like to thank the Haut-de-France region, Centrale Lille Institut and Lattice Medical for providing financial support.
CODE VERIFICATION OF THE MICRO FINITE ELEMENT SOLVER PAROSOL USING THE METHOD OF MANUFACTURED SOLUTIONS

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Introduction

Despite the complexity and widespread use of micro-FE solvers in bone mechanics research, little attention has been paid to their code verification [1]. The present study uses the method of manufactured solutions (MMS) to verify the open-source micro-FE solver ParOSol [2] which is widely used in bone mechanics research.

Methods

MMS was originally developed for CFD codes [3], [4]. It has only recently been used to verify commercial FE solvers [1]. Here, one “manufactures” an analytical displacement vector field \( \mathbf{u}(\mathbf{x}) \), which need not be physically meaningful. This is used to derive strain and stress tensor \( \mathbf{\sigma} \) fields, the latter by applying a set of chosen constitutive laws. The stress divergence \( \nabla \cdot \mathbf{\sigma} \) is usually non-zero, and has to be balanced by “fictitious body forces” \( \mathbf{b} \) [1], the analytical expression for which can be determined easily using \( \nabla \cdot \mathbf{u} \), as the right hand side is already known. The computational problem is set up by defining the mesh, posing the manufactured displacement at all boundary nodes and the manufactured body forces at all nodes, and setting material properties for all elements.

The manufactured solution used in the present study is adapted from [1]. The domain is a unit cube (homogenous, isotropic linear elastic) with a grid spacing of \( h \) (Fig. 1). The displacement field is infinitely differentiable and sufficiently complex to exercise all terms in the governing equations. The analytical forms of strains, stresses and body forces based on this displacement field are obtained using the symbolic computing software Maple. HDF5 input files with this problem set-up were created corresponding to 5 different grid spacing values \( h = 0.2, 0.1, 0.05, 0.025, 0.0125 \). The original version of ParOSol was modified to be able to apply the distributed body force. The error at each node is defined as the magnitude of the difference between the numerical and analytical (i.e. manufactured) displacement vectors \( |\mathbf{u}_{\text{num}} - \mathbf{u}_{\text{MMS}}| \), normalised by the maximum value of the error across all nodes. The \( l_2 \) and \( l_\infty \) norms of these errors were analysed in dependence of grid spacing. At each refinement step, the observed order of convergence of the \( l_2 \) and \( l_\infty \) error norms were calculated as \( \text{OOC}_{\text{obs}} = \ln(l_2/l_2')/\ln(r) \). Here, \( l_2 \) and \( l_\infty \) correspond respectively to the error norms \( l_2 \) or \( l_\infty \) at the immediately coarser and finer meshes, and \( r \) is the ratio of grid spacings between the two meshes.

Results and Discussion

Fig. 2: Normalized error norms (left) and observed orders of convergence OOC_{obs} (right)

The observed convergence rates of \( l_2 \) and \( l_\infty \) error norms asymptotically approach the expected theoretical convergence rate (Fig. 2), evidencing a low likelihood of coding errors in the tested ParOSol version that can negatively influence the simulation results for linear elastostatic problems.

Conclusion

Expanding the suite of manufactured solutions will reduce this likelihood further. The methodology can be applied to newer versions of ParOSol that involve different constitutive models or require additional governing equations such as contact interactions.

References


Acknowledgements

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A MODEL TO EXPLORE INTERVERTEBRAL DISC CELL ACTIVITY IN ADVERSE BIOCHEMICAL ENVIRONMENTS

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Introduction
Intervertebral disc (IVD) degeneration (IDD) involves the imbalance between the anabolic and the catabolic processes that regulate the extracellular matrix of the disc. These processes are complex; redundant and feedback-looped, and improved integration of knowledge is needed. Accordingly, we present a nucleus pulposus cell (NPC) regulatory network model (RNM) that integrates critical biochemical interactions in IVD regulation and can replicate experimental results.

Methods
The RNM was built from a unique curated corpus of 130 journal articles in IVD research. Proteins were represented as nodes that interact among each other through activation and inhibition edges. Semi-quantitative steady states (SS) of the RNM (node activations) were calculated through a fuzzy interpolation of Boolean rules [1]. Simulation tests evidenced the limited literature knowledge to represent non-degenerate reference SS of NPC, and guided corpus enrichment through the STRING database (Fig.1).

![Figure 1: Topology of the enriched RNM.](image)

Then, a full factorial sensitivity analysis (SA) was performed to identify which out of the RNM 15 cytokines, and 4 growth factors affected most the structural proteins and degrading enzymes. The RNM was further evaluated against metabolic events measured in non-healthy human NP explant cultures, after 2 days of 1ng/ml IL-1B catabolic induction.

Results and Discussion
The enriched RNM represented successfully an anabolic basal SS, as we would expect in non-degenerate IVD (Fig.2, blue bars). IL-1B was able to increase catabolic markers and angiogenic factors and decrease matrix proteins (Fig.2). This shift of activity was confirmed by the explant culture measurements (Fig.3A-E).

![Figure 2: Baseline & IL1-1B Stimulated SS of the NPC RNM.](image)

![Figure 3: Relative gene expression of IVD anabolic (A, B, F) and catabolic (C-E) markers in human NP explants.](image)

![Figure 4: Sensitivity analysis with the A) cytokines and B) growth factors that most affected the RNM nodes.](image)

The present RNM was successfully confronted to independent in vitro measurements and stands for a unique model, to integrate soluble protein signaling at the tissue level and explore IDD onsets.

References
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Acknowledgements
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CROSSLINKING ENABLES LONG-RANGED CELL-MATRIX MECHANICS IN A HYBRID CELLULAR POTTS AND MOLECULAR DYNAMICS MODEL

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Hybrid model of cell-matrix mechanics

Mechanical interactions between cells and the extracellular matrix (ECM) are fundamental for tissue patterning and homeostasis. The major structural and load-bearing ECM components are fibrous proteins or proteoglycans such as collagen that assemble into complex networks, which cells realign and remodel. Cell traction forces can deform fibrous ECM over distances of multiple cell diameters [1–4], which has been implicated in long-ranged cell alignment and tissue morphogenesis [3–7].

Relating individual cell-level mechanics to tissue-scale behavior is an outstanding challenge which cell-based models such as the cellular Potts model (CPM) are well-positioned to address. These models are very good at representing realistic cell behavior, but generally coarse-grain the ECM as a uniform isotropic material (e.g. simulated with a finite element method). This type of ECM model fails to capture phenomena such as fiber accumulation near contractile cells and long-ranged force transmission. To address this limitation, we hybridized a CPM model of cells with a bead-spring model of fibrous ECM networks simulated with molecular dynamics methods (Figure 1).

Figure 1: We model cell and ECM using two different formalisms.

Model captures cell-ECM dynamics

We model a contractile cell pulling with discrete focal adhesion-like sites on the ECM fiber network, and demonstrate how network parameters affect cellular contractility (Figure 2). Our model shows agreement with experimentally measured dynamics of fiber densification and displacement [8]. Further, we show that contractile cell forces propagate over multiple cell radii scaling with power law exponent of -0.5 typical of viscoelastic ECM [1, 3]. Our model lays the foundation to investigate how local and long-ranged cell-ECM mechanobiology contributes to multicellular morphogenesis.

Figure 2: ECM crosslinking affects material properties and the extent of cell contractility.

References
ON THE ANISOTROPY OF THE MYOCARDIUM
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Introduction
Over the years, the description of the passive mechanics of the myocardium has become more and more complex, from an isotropic to an orthotropic material. This has been driven by experimental observations, as the one from Dokos et al. [1]. They subjected to shear tests cubic samples from porcine left ventricles, revealing an orthotropic behavior of the myocardium. This raises the important question of the microstructural origin of this anisotropy. At the cellular level, the cardiomyocytes are elongated cylinders, suggesting a transversely isotropic behavior. At least two microstructural features could explain the macroscopic anisotropy: The change of orientation of the cardiomyocytes, which varies by 120º over the heart wall thickness; At mesoscale, the cardiomyocytes are arranged into anisotropic bundles surrounded by thicker collagen layers [2].

In order to investigate which effect is required, we designed a multi-scale model of the myocardium, bridging the cell, sheetlet and tissue scales [3]. The model is then optimized to find the microscopic parameters that best match the macroscopic data. This enables us to test the contribution of different mesostructures.

Methods
We build different mesostructures combining a transverse isotropic myocardium with different collagen layers architecture. First, we didn’t put any collagen, to test the role in the change of cardiomyocytes orientation. Second, we use thin flat layer of collagen between thick layers of myocardium. Third, we use an elliptical shape for the collagen layer, surrounded by myocardium. These microstructures are numerically homogenized. Then, they are used to reproduce Dokos et al. experiments [1], by simulating the same shear tests. We included the variations of the myocardium orientation, as well as of the collagen layers, and the mechanical parameters are optimized.

Results
Results for the optimal models based on homogeneous and stratified mesostructures are shown on the figure (1). Elliptical mesostructure lead to results similar to stratified mesostructure. The model without collagen layer is not able to reproduce the experimental data, showing the importance of the layer arrangement and their rotation in the heart thickness.

Figure 1: Comparison of experimental (box plot with mean in green triangle, median in orange line) and theoretical (blue bar plot) shear stresses (normalized with respect to largest value) – figure from [3].

Conclusions
The variation of myofiber orientation through the myocardium, without mesostructure such as collagen planes, does not allow to describe the measured anisotropy at the macroscopic scale. Conversely, by taking into account the microstructural organization at the sheetlet scale, and the variation of the sheetlet orientation through the ventricle, it is possible to reproduce the macroscopic data. An additional finding is that some level of compressibility is required to fit the data. These findings call for a more thorough analysis of the mesostructural arrangement of the myocardium, and its role on the ventricular mechanics.

References
CANCER INVASIVENESS IS DETERMINED BY CELL ADAPTABILITY TO CHANGES IN MICROENVIRONMENT MECHANICS

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Introduction
Metastases are the leading cause of cancer-associated deaths. A key process in metastasis is cell invasiveness, which is driven and controlled by cancer cell interactions with their microenvironment. We have previously shown that invasive cancer cells forcefully push into and indent physiological-stiffness gels to cell-scale depths [1,2]. Notably, the percentage of indenting cells and their attained depths provide a clinically relevant prediction of invasiveness and the potential metastatic risk [2–4]. Cell-attained indentation depths are directly affected by changes in gel mechanics, which can in turn modulate the cells’ mechanics and force application capacity, inducing complex, coordinated mechanobiological responses. As experimentally isolating the different contributions is impossible, we use finite element modeling to evaluate the roles of cell and gel mechanics on cancer-cell invasiveness.

Methods
We extended our finite element model [5] to evaluate the roles of cell and gel mechanics on cancer-cell invasiveness. Cells were modelled as initially hemispherical, Neo-Hookean materials. The gel-substrate was modeled to match the elastic polyacrylamide gel used in experiments [2,6]. Cells apply forces at their perimeters and centers, respectively, pulling and pushing the gel surface; force balance (zero net force) is maintained.

Results
Under constant, literature based, cell cytoplasm and nucleus mechanics and cell-applied force levels, increasing gel stiffness 1-50 kPa significantly reduced the attained indentation depth by >200%. The gel’s Poisson ratio, however, reduced depths by up to 20% and only when the ratio was >0.4. In experiments, varying-invasiveness cancer cells, from lines of breast and pancreatic cancers, exhibited qualitatively different changes to indentation depth with gel-stiffness increase, e.g. large/small reduction or increase followed by reduction. We were able to accurately reproduce the experimental responses via coordinated changes in cell mechanics and applied force-levels, scaled based on published effects of gel-stiffness on cells.

Conclusions
Our work shows that different cancer invasiveness and metastatic risk-levels most likely result from the varying capacities of cells to adapt their mechanobiology in response to changing microenvironments.

References

Acknowledgements
The authors thank Yulia Merkher and Sally Kortam, supervised by DW, for obtaining the experimental results used to validate the model. The work was partially supported by the Israeli Ministry of Science and Technology (MOST) Medical Devices Program (Grant no. 3-17427, awarded to Prof. Daphne Weihs), by the Gerald O. Mann and the Frank and Dolores Corbett Charitable Foundations, and by the Applebaum Foundation.
Introduction

Structure-based constitutive models of arterial wall are important in biomechanical analyses. The most common models assume two symmetric fibre families, either perfectly aligned or dispersed [1, 2]. This assumption is seldom confirmed by histological analyses and the bimodal distribution of fibres may come from fibre waviness and from ignoring the differences between local and global orientations. This study applies automated polarized light microscopy for detecting the collagen fibre directions in porcine aorta under different types of biaxial extension eliminating the effect of waviness.

Methods

Porcine aortas were harvested in local slaughterhouse from 10 months old pigs. Specimens were cleaned and circumferential and axial directions were marked. Using a custom made biaxial tension device, they were fixed (under different biaxial stretches between 0.98 and 1.32) in 10 % formaldehyde solution at room temperature for 24 hours, then they were dehydrated and embedded in paraffin. Samples were sliced with micrometre (5 µm thick) in the circumferential–axial plane and every slice was stained with 0.1 % Picro Sirius Red. The local orientation of collagen fibres was investigated in the unloaded state and under different levels of biaxial extension. If both stretches differed by less than 0.02, the extension was considered as equibiaxial.

Polarized light microscopy with an automatic algorithm [3] was used for evaluation of collagen fibre directions in up to 8 histological slices throughout the wall thickness (in ~10³ points per slice). The resulting histograms were fitted with unimodal or bimodal von Mises distributions and grouped for inner (TM) and outer (TA) layers. The fitting procedure was performed in Curve Fitting Toolbox in MATLAB.

For statistical significance tests (α=0.05) one-way ANOVA was used. The data normality was verified by Kolmogorov–Smirnov test before performing ANOVA. Both analyses were performed in Minitab 15.

Results

For unimodal distributions the resulting mean angles \( \mu_m \) and concentration parameters \( b \) are presented in Table 1. While no impact of load on the mean angle was found, statistically significant differences in dispersion were found between the unloaded state and both circumferentially-dominated and equibiaxial loads, while only negligible differences occurred between these last two groups. A similar tendency of fibres aligned more circumferentially with increasing circumferential extension (including equibiaxial states) was found also for bimodal distributions.

<table>
<thead>
<tr>
<th>Load</th>
<th>TM</th>
<th>TA</th>
<th>TA+TM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \mu_m \pm SD )</td>
<td>( b_{av} \pm SD )</td>
<td>( \mu_m \pm SD )</td>
</tr>
<tr>
<td>Unloaded</td>
<td>0.4±21.4</td>
<td>1.2±0.97</td>
<td>-9.5±24.7</td>
</tr>
<tr>
<td>Circumf.-dominated</td>
<td>0.3±0.3</td>
<td>2.03±0.85</td>
<td>4.8±4.7</td>
</tr>
<tr>
<td>Axially-dominant</td>
<td>4.0±4.0</td>
<td>1.2±1.2</td>
<td>13.0±7.5</td>
</tr>
<tr>
<td>Equibiaxial</td>
<td>4.4±4.4</td>
<td>2.13±2.1</td>
<td>3.8±3.8</td>
</tr>
<tr>
<td></td>
<td>±10.8±0.71</td>
<td>±12.0±0.71</td>
<td>±0.51±0.51</td>
</tr>
</tbody>
</table>

Table 1: Mean angles \( \mu_m [\circ] \) (measured from the circumferential direction) and concentration parameters \( b [-] \) (with their standard deviations SD) in aortic wall and its layers under different types of biaxial load.

Conclusion

The presented histological analyses have shown dominantly circumferential collagen fibre orientation and an increasing alignment of their local orientations under circumferential extension of the specimen. The distribution was either unimodal of bimodal. It was shown that all of these distributions got closer to circumferential direction with increasing circumferential stretch. This suggests that the bi-modality of the analysed distributions may be related rather to fibre waviness than their dispersion. This hypothesis is further supported by the increase of fibre alignment even with equibiaxial deformation, that cannot induce any fibre rotation, as well as by nearly identical changes under equibiaxial and uniaxial extension. Structure-based constitutive models are defined by global fibre orientations and all our results show fibre alignment in circumferential direction with their increasing extension. Thus they dispute the existence of two fibre families as interpreted from bimodal distributions of local fibre orientations detected in some arteries; their bimodality is probably caused by fibre waviness.

References


Acknowledgements

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PATIENT-SPECIFIC BONE MODELING CAN BETTER PREDICT BIOMECHANICAL OUTCOMES OF SACRAL FRACTURE FIXATIONS

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Introduction
The sacrum is a biomechanical keystone as it transmits the load from the upper body to the lower extremities. High-energy traumas, such as car accidents or falls from height, can cause sacral fractures and an unstable pelvic ring [1]. Due to the more frequent use of pelvic CT scans, sacral fractures are more often recognized and treated surgically, although there is still controversy regarding the optimal management [2]. Previous finite element (FE) analyses were performed to assess fixation techniques used for sacral fracture treatment. However, all these investigations assumed identical bone quality at the S1 and S2 levels and employed averaged bone material properties, thus ignoring the biomechanical effect of local bone qualities [3,4]. Therefore, the current study aimed to evaluate the effect of the locally defined patient-specific bone quality by applying two different sets of bone material properties in six different fixation techniques used for treating Denis Type II unilateral sacral fractures.

Methods
Two FE models of the intact pelvis were constructed; the literature-based model (LBM) was developed with homogenous bone material properties taken from the literature, while the patient-specific model (PSM) was created with heterogenous bone material properties based on the quantitative CT scans. Unilateral transforaminal sacral fracture was modelled to assess six different fixation techniques: iliosacral screw (ISS) at S1 (ISS1), ISS at S2 (ISS2), ISS at S1 and S2 (ISS12), transverse iliosacral screw (TISS) at S1 (TISS1), TISS at S2 (TISS2), and TISS at S1 and S2 (TISS12) (Figure 1a-f). A 600 N vertical load with both acetabula fixed was applied to simulate a double leg stance. Vertical stiffness (VS) normalized with the intact condition, relative interfragmentary displacement (RID), and the von Mises stress values on the fracture interface were analyzed.

Results
The lowest and highest normalized VS was given by ISS1 and TISS12 techniques for LBM and PSM, 137% and 149%, and 375% and 472%, respectively. The maximum RID values were between 0.10 mm and 0.47 mm for all fixation techniques in both models. The von Mises stress results on the fracture interface show a substantial difference between the two bone modeling techniques, as PSM gave significantly lower stress values for all fixation techniques than LBM. Regarding the maximum stress values, the LBM gave higher values by 255.1, 20.3, 156.4, 286.9, 41.1 and 171.1 % compared to PSM. The boxplot figure including nodes that fell within the largest 1% of the stress values on the fracture surface are shown in Figure 2.

Discussion
Based on our results, all techniques can provide clinically sufficient stability. TISS12 was superior to all other fixations from a biomechanical point of view. Patient-specific bone modelling revealed that sacral fracture fixations should prioritize the S1 level over the S2, although long-term clinical trials are recommended to confirm the findings of the study.

References
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The project leading to the scientific results was prepared with the professional support of the Doctoral Student Scholarship Program of the Co-operative Doctoral Program (C1014064) of the Ministry of Innovation and Technology financed from the National Research, Development, and Innovation Fund.

Figure 1: The investigated fixation configurations: (a) ISS1, (b) ISS2, (c) ISS12, (d) TISS1, (e) TISS2, (f) TISS12.

Figure 2: Boxplot figure with nodes from LBM and PSM that fell within the largest 1% of the von Mises stress values on the fracture surface.
SEMIRIGID SPINAL FIXATION TECHNIQUES COULD HELP PREVENT PROXIMAL JUNCTIONAL KYPHOSIS – A FINITE ELEMENT STUDY

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Introduction
Proximal junctional kyphosis (PJK) is a relatively common mechanical complication following long instrumented posterior spinal fusions, with an incidence rate ranging from 17% to 39% within two years after the surgery [1]. Previous biomechanical studies suggest that one of the leading causes is the sudden mobility change between the instrumented and healthy spinal segments [2]. The current study investigates the biomechanical impact of two semirigid fixation techniques (SFTs) by comparing their effects on spinal mobility and pedicle screw loading with conventional rigid fixation.

Methods
Four T7-L5 finite element (FE) models were developed: 1) intact spine; 2) ø5.5mm titanium rods between T8 and L5 (TRF); 3) five ø1.9mm titanium rods between T8 and T9 connected with ø5.5mm titanium rods between T9 and L5 (MRF); 4) ø5.5mm PEEK rods between T8 and T9 connected with ø5.5mm titanium rods between T9 and L5 (PRF) (Fig. 1a-d). A modified multidirectional hybrid test protocol was employed with two successive loading steps [3]. First, a pure bending moment of 5 Nm was applied to simulate flexion, extension, lateral bending and axial rotation, and the intervertebral rotation (IVR) angles were recorded [4]. Second, the motion of the TRF technique was applied to the instrumented FE models to evaluate the von Mises stress values in the pedicle screws at the upper instrumented vertebra (UIV).

Results
In the load-controlled step, relative to TRF, at the uppermost instrumented segment, the IVR values increased by 46.8% and 99.2% for flexion, by 43.2% and 87.7% for extension, by 90.1% and 137% for lateral bending, and by 407.1% and 585.2% for axial rotation, in MRF and PRF, respectively. In the motion-controlled step, the maximum pedicle screw stress values at the UIV level were highest for TRF with 37.26 MPa, 42.13 MPa, 44.4 MPa, and 44.59 MPa for flexion, extension, lateral bending, and axial rotation, respectively. Compared to TRF, in the case of MRF and PRF, the screw stress values were reduced by 17.3% and 27.7% for flexion, by 26.6% and 36.7% for extension, by 6.8% and 34.3% for lateral bending, and by 49.1% and 59.8% for axial rotation (Fig. 2).

Discussion
FE analysis has shown that the semirigid fixations increase the mobility at the upper instrumented segment, providing a more gradual transition in motion between the instrumented and the healthy spinal segments. In addition, SFTs decrease the pedicle screw loads at the UIV level and hence could help reduce the risk for PJK. However, further investigations are recommended to evaluate the long-term clinical usefulness.

References

Acknowledgements
The project leading to the scientific results was prepared with the professional support of the Doctoral Student Scholarship Program of the Co-operative Doctoral Program (C1014064) of the Ministry of Innovation and Technology financed from the National Research, Development, and Innovation Fund.
PREDICTION OF KNEE OSTEOARTHRITIS USING MACHINE LEARNING ENHANCED FINITE ELEMENT MODELING APPROACH – DATA FROM OSTEOARTHRITIS INITIATIVE


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Introduction

Osteoarthritis (OA) is the most common degenerative joint disease, and its prevalence increases with aging population. Currently, there is no cure and only the symptoms, e.g., pain and inflammation, are treated. The problem with OA is its inevitable progression with time. The best option for reducing the number of OA patients would be disease prevention, which would, however, require identification of the patients with risk of OA. During recent years, artificial intelligence solutions based on, e.g., machine learning (ML) have developed rapidly and are used for various purposes, including prediction of diseases. Several ML based approaches on prediction of OA have also been suggested [1]. Finite element modeling (FEM) -based prediction of OA development has also been introduced [2]. There are no studies that compare these approaches equally or try to combine them. The aim of this study was to provide first insights into the classification accuracies between those two approaches (FEM vs. ML) to predict knee OA and future potential when merging these novel approaches.

Methods

Knee shape and cartilage thickness (dimensions) and angles (Fig. 1) were measured from anteroposterior radiographs of 1222 radiographically healthy knees (exclusion criteria in Fig. 2) taken at baseline from Osteoarthritis Initiative Database (OAI, http://nda.nih.gov/oai). The knees were divided into three groups based on their OA severity (KL grade [3]) at 8-year follow-up: KL01 (N=950): KL grades 0 and 1, KL2 (N=140): KL grade 2, KL34 (N=132): KL grades 3, 4, and total knee replacement. All measurements were done using an in-house Matlab (v. R2019b, MathWorks Inc.) graphical user interface.

The ML classification algorithm was trained utilizing two-fold balanced random forest classification ML approach with 5-fold cross-validation [4]. Subjects’ age, weight, height, and the baseline KL grade and measurements indicated at Fig. 2 were used as the predictor variables. The data was split 70% (N=856) and 30% (N=366) between training and validation data, respectively. This division was done separately for each KL group. FEM based knee OA predictions were performed by using the FE atlas-based modeling approach, where the FE geometry was based on the measured joint dimensions [2]. Due to limitation of x-ray, anterior-posterior dimensions of medial and lateral condyles of femur, required in generation of 3D FE model, were evaluated by the joint size. To combine the ML classification and FEM, based on the ML classification the FEM results were multiplied with factors 0.5, 1, and 1.5 for KL01, KL2, and KL34 groups, respectively. Finally, receiver operating characteristic (ROC) curve and area under curve (AUC) were calculated for ML, FEM, and FEM+ML based predictions for validation data.

Results

The accuracies of the trained ML model were 93% for the training data and 68% for the validation data. The AUC for FEM+ML was higher than the AUCs for ML and FEM for KL01 vs KL34 knees (Fig. 3).

Discussion

ML classification and FEM simulations for the cartilage degradation are suitable for prediction of knee OA development. Overall, FEM+ML is superior compared to approaches that utilize solely ML or FEM. In conclusion, a ML enhanced FEM approach is promising for prediction of OA development.

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Acknowledgements

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**INFLUENCE OF WALL SHEAR AND MECHANICAL STRESS ON Atherosclerotic Artery Disease in Human Coronaries**

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**Introduction**

Atherosclerosis in coronary arteries is the main cause of fatal and disabling coronary events [1]. It is well established that atherosclerotic plaque initiation and growth are affected by a local biomechanical factor; the blood flow induced wall shear stress (WSS) [2, 3]. However, the potential role of another biomechanical factor, the blood pressure induced wall mechanical stress (WMS) has been mainly overlooked. In this study, we investigated the individual and combined effects of WMS and WSS in atherosclerosis progression in coronary arteries.

**Methods**

Forty non-stented, non-culprit coronary arteries were imaged with near-infrared spectroscopy intravascular ultrasound (NIRS-IVUS) and optical coherence tomography (OCT) at the baseline and after 12 months (follow-up) [3]. The composition and geometry of the coronary plaques were reconstructed based on the co-registration of the segmented NIRS-IVUS and OCT data. WMS in the coronaries was computed with finite element models, using hyperelastic material models and incorporating initial stresses via the backward incremental method [4]. Max principal stress on the peri-luminal region at systolic pressure of 120 mmHg was reported. WSS was computed with Computational Fluid Dynamics and reported previously [3]. Vessel wall and plaque growth was quantified as plaque burden change (ΔPB) over time. For local analysis, the arteries were divided into sectors of 1.5 mm thickness and of 45° circumferential angle. The sectors were categorized as “diseased with lipid rich necrotic core (LRNC)”, “diseased w/o LRNC”, or “healthy”. The individual and combined effect of WSS and WMS on plaque progression was evaluated using Linear Mixed Model in SPSS by dividing the stress metrics in tertiles.

**Results**

There was an inverse correlation between the WSS and ΔPB for all three arterial sector types (Fig.1, top panel). The sectors exposed to lower WSS showed higher ΔPB. This correlation was strongest for the diseased sectors with LRNC. The correlation between WMS and ΔPB; however, depended on the sector type (Fig.1, bottom panel). The healthy sectors had a positive correlation whereas the diseased ones with LRNC showed a negative correlation. The analysis of the combined effect of WSS and WMS revealed that the highest ΔPB was associated with low WSS and high WMS for healthy sectors. For the diseased sectors with LRNC, both high and low WMS combined with low WSS were associated with higher ΔPB.

![Figure 1: Plaque burden change distribution based on WSS (top) and WMS (bottom)](image)

**Discussion**

Our findings suggest that the local atherosclerotic disease progression in coronary arteries is not only associated with the well-established WSS, but also with WMS, which has not received enough attention yet. Moreover, our results show that the association of the disease progression with WMS depends on the existing local structural composition. Our findings indicate the importance of biomechanical analysis and local plaque composition assessment for local atherosclerotic disease progression prediction. In the future, studies with larger cohort and multiple follow-up time points are warranted in order to fully understand the association between shear and structural stress with atherosclerosis development over time.

**References**

EXPERIMENT AND SIMULATION STUDY OF THE ENERGY ABSORPTION IN BIOMIMETIC SCAFFOLD LATTICES

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Introduction
Architected materials have been recently attracting attention due to their high stiffness-to-density ratio, tailored mechanical properties and high energy absorption, for multifunctional applications in aerospace, biomedicine such as implants and scaffolds, etc. To enhance energy absorption capacity of the conventional structures, new lattices are introduced and studied, some based on biological samples such as bone, to enable biomimetic architected materials [1]. In this study, we investigated two gyroid and dual-lattice [2] structures, in terms of their mechanical response under large strains and energy absorption capacity, through finite element analysis (FEA). Model predictions were validated through 3D printing and experimental compression testing.

Materials and Methods
Gyroid and dual-lattice models with 10% volume fractions were 3D printed using a FormLab3 elastic resin printer (SLA technology). Samples were testing under uniaxial quasi-static deformation-controlled compression loading of 85% strain, using a Zwick mechanical tester (Zwick Roell, GmbH & Co., Germany) as shown in Fig. 1. FE models generated to replicate uniaxial compression test, for the gyroid and dual-lattice structures, with 10% and 20% of volume fraction each. Models were meshed using tetrahedral (C3D10M) elements and the material properties was calibrated for the elastic resin shown in Table 1. The ABAQUS/Explicit solver was used analyze their mechanical response and energy absorption capacity for the four categories of lattices under 85% uniaxial compression deformation.

<table>
<thead>
<tr>
<th>Neo-Hookean Model</th>
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<tbody>
<tr>
<td>Resin</td>
<td>C10</td>
<td>D1</td>
</tr>
<tr>
<td>Elastic 50A</td>
<td>0.60 (Mpa)</td>
<td>0.25</td>
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</tbody>
</table>

Table 1: Physical and calibrated mechanical properties of elastic resin.

The energy absorption per unit volume, \( W \), for a lattice structure under compression with the strain up to \( \varepsilon \), is calculated by Eq. 1 [3].

\[
W = \int_0^1 \sigma(\varepsilon)d\varepsilon
\]

Results
The stress strain curve of the two experiments and the fitted finite element model for the 10% volume fraction of the dual-lattice structure is shown in Fig. 1.

Conclusions
We studied the mechanical response of two gyroid and dual-lattice lattices, as candidates for biomedical scaffolds. In the same volume fraction, dual-lattice shows higher stiffness, yield strength and energy absorption. As the volume fraction increases, the energy absorption capacity increases, the plateau region decreases, therefore, densification starts at lower strain.

References
CFD AND CSM MODELS OF THE ASCENDING THORACIC AORTA ANEURYSM WITH PATIENT SPECIFIC WALL DISPLACEMENT

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Introduction

The Ascending Aneurysmal Thoracic Aorta (ATAA) is a persistent enlargement of the aorta caused mainly by ageing or genetics. The European Society of Cardiology defines an ATAA as an aortic diameter increase of 50%. Surgery is advised if this diameter is higher than the 55mm cut-off. Nevertheless, 60% of individuals with aortic dissections before reaching the surgical limit experienced aortic failure. A new method is required to implement the geometric criterion, and it is believed that computational fluid dynamics (CFD) and computational solid mechanics (CSM) analyses can provide the solution. The application of these techniques frequently ignores the ATAA wall motion brought on by heartbeat and hemodynamics. Fluid-structure interaction (FSI) may be an option, but the time needed for each numerical solution is a limitation. In this study, SimVascular [2], an open-source program specialising in cardiovascular CFD, CSM, and FSI models, is utilised to examine the impacts.

Methods

The geometric model was developed in SimVascular using the SV MITK Segmentation for the first instance of Computed Tomography Angiography (CTA). This segmentation method is used for the wall deformation calculation for 20 equally spaced acquisitions throughout a cardiac cycle. After this first step, a Python script was implemented to translate all segmented geometric models into a wall displacement using the best centreline match. Both PyVista [3] and VMTK libraries were used. As boundary conditions, the wall deformation was used in CFD and CSM numerical models.

In the CFD model, the flow inlet condition was derived from the 4D-flow MRI and imposed downstream of the aortic valve. The outlet was defined as a three-element Windkessel model, also known as the RCR model, to simulate patient-specific arterial pressure. The blood was reduced to a Newtonian fluid with density of 1.06 g/cm³ and viscosity of 0.04 Pa.s. A laminar incompressible flow was taken into consideration for the Navier-Stokes equation solution.

In the CSM model, the Neo-Hookean hyperelastic model was used to describe the ATAA mechanical properties. The numerical parameters imposed are described in Valente et al. [4].

Results

The CFD model, complemented with the patient-specific wall deformation as a boundary condition, allows for a good agreement of patient-specific hemodynamics and wall shear stress compared to a 4D MRI. The CSM, on the other hand, can calculate the wall mechanical behaviour and translate the displacement measured as wall stress to characterize wall load.

Discussion

The CFD and FEA models and the patient-specific wall deformation ensure an excellent agreement compared with in-vivo data extracted from 4D MRI. Furthermore, these results of both models allow for replicating an FSI model result with significantly less computational time.

Acknowledgements

This research was funded by Portuguese Foundation for Science and Technology (FCT) under the project PTDC/EMD-EMD/1230/2021 “Fluid-structure interaction for functional assessment of ascending aortic aneurysms: a biomechanical-based approach toward clinical practice”, and UIDB/00667/2020 (UNIDEMI). R. Valente is grateful to the FCT for the PhD grant 2022.12223.BD. A. Mourato is also grateful to the FCT for the PhD grant UI/BD/151212/2021.
Introduction
The trapeziometacarpal (TMC) joint is the hand joint most affected by osteoarthritis (OA). Surgical treatments, such as arthroplasty, ligament reconstruction or trapezectomy, are sometimes required to treat pain or functional limitations induced by this pathology. Unfortunately, these surgical approaches sometimes lead to some complications like implant dislocation or thumb deformation [1]. Although multifactorial, these complications are associated to the intensity and nature of mechanical loads applied on the joints. Computational modelling is an alternative to understand these internal loadings and improve the surgical treatments. Nevertheless, current computational models of the TMC joint rarely include patient specificity, especially ligaments’ mechanical properties which differs importantly according to the patient [2]. Nonetheless, patient-specific modelling of the TMC joint ligaments is necessary to improve surgery benefits, given that the ligaments’ importance in the TMC joint stability. The objective of this study was thus to create patient-specific finite element models of the TMC joint ligaments, based on in vivo experimental data.

Methods
A finite element model of the TMC joint bones and ligaments was developed in FEBio [3]. The bones’ model was generated by segmentation from a patient’s CT scan. The three-dimensional ligaments’ geometry was created based on previous literature on ligaments’ length, width and thickness and attachment area measured on cadaveric specimens [4]. The ligaments modeled in this study were the five main ligaments identified on previous cadaveric studies, namely: the dorso radial ligament, the anterior oblique ligament, the posterior oblique ligament, the intermetacarpal ligament and the ulnar collateral ligament. The bones were modeled as rigid bodies and the ligaments were modeled with linear elastic isotropic material property. Ligaments’ extremities were tied to their attachment areas. TMC joint of 15 participants were tested with a test bench, to determine the individual force displacement data. Force-displacement of the participants’ TMC joint in flexion, extension, abduction and adduction were measured by force sensor and kinematic markers placed on the thumb. Patient-specific ligament Young modulus were calculated by matching computer predictions to force displacement data experimentally measured, by using the FEBio optimization module (Fig.1).

Results
Our computational model reveals important variations of the TMC joint ligament young modulus according to the patient. Important variations of ligament young modulus between the different tests (flexion, extension, abduction and adduction) were also observed within the same patient (more than 50 %).

Discussion
Our study proposes a new non-invasive method to individualize computational finite element models of the TMC joint ligaments. Even if some limitations could be considered, this study provides a non-invasive methodology to personalize computational models of the TMC joint with the aim of improving the patient treatments.

References
SKIN-TO-BONE INTERACTION: MECHANICAL CHARACTERIZATION BY PEELING TESTS ON PIG SCALPS

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Introduction
Fasciae are collagenic tissues permitting a large but finite sliding between organs, but also between skins and its underlying elements [1], [2]. Testing such materials remains a challenge due to high softness and hasty dehydration. Although the peeling test is currently used in the industry, it has seldomly been used to assess the adhesion strength between two living tissue until recently [3]. The objective of this study is to introduce the peeling test as a way to quantify the skin-to-bone interactions.

Materials and Methods
To this aim, peeling tests have been performed on porcine scalps (see Fig.1). The samples peeled were thin bands composed of three distinct layers excised from the scalp region of pig’s head: skin; collagenic tissues; and skull. The experimental setup was mounted on a Zwick / Roell tensile machine (load cell capacity of 500 N). The skull band was fixed at the bottom on a translatable tank while the skin was pulled upward by the machine cross head, hence measuring the needed force to separate both parts. To assess the reproducibility of such setup, two experimental campaigns were performed, varying the width and length of the specimen’s skin to skull interface.

Results
The separation of skin and bone induced progressive tear at the skin interface or within the collagenic layer (as seen on Figure 1). To compare the results from both campaigns, the measured peeling force have been normalized by the specimen width and the cross head displacement needed to complete the peeling have been normalized by the skin to bone interface length.

Discussion and conclusion
The extreme softness of the collagenic tissues inducing large sliding between skin and bone and occasional peeling within the collagenic layer resulted in a large observed variability of the obtained data. However, a clear tendency (i.e. plateau) have been observed. This will be exploited to fuel numerical models and would notably be useful to model the interaction between the scalp and skull. To the best of our knowledge, this study is the first attempt to quantify the skin-to-bone interaction using peeling test.

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Acknowledgements
The authors would like to thanks Maison Wagner from Marange-Zondrange, FRANCE for providing samples.
Introduction
Plagiocephaly, from the Greek word for “oblique skull”, is a deformation of the infant's skull during growth. The skull becomes oblique and strongly asymmetrical with a posterior flat spot. On the same side as this flat spot, a frontal hump develops, increasing the asymmetry. The purpose of the cranial orthosis is to guide the growth of the skull by creating expansion zones at the level of the posterior and anterior deformities. Like the recent works of Andikoetxea et al. [1], the development of a finite element model should allow us to improve the helmet treatment.

Methods
The measurements are taken digitally with a 3D scanner (Creaform). The digitized shape of the young patient’s head is modified with Rodin 4D Neo software to create a helmet adapted to his pathology. The objective of this rectification is to obtain a harmonious skull by increasing the volume in the flat areas. A cranial orthosis is modeled and printed in PA12 with HP MultiJet fusion technology, the orthosis is filled with foam. A digital twin of the child's head is developed. We determine three parts: the scalp, the skull, and the brain in this model. The head and the helmet are imported into Ansys Workbench®. Linear elastic properties are determined for the whole head model. PA 12 has linear elastic properties too unlike the Plastazote® foam of the helmet which is determined as hyperelastic [2]. The behavior law used is the modified Ogden model (Ansys Ogden foam) for compressible foams. In our case, a two term Ogden foam model is used. The simulation is performed for an infant wearing a helmet in supine position. The neck is modeled by a cylinder applied to the base of the cranial bone. Only the foam-scalp contact is defined with a relative movement between the two surfaces with a friction coefficient of 0.6 [3]. In order to achieve the finest possible simulation with a limited computation time we use the augmented Lagrangian method with an asymmetric behavior of the surfaces treatment.

Discussion
The treatment of the frictional contact as well as the implementation of hyperelastic mechanical characteristics for the helmet foam in our finite element analysis of the treatment of plagiocephaly with a cranial orthosis has allowed us to obtain convincing results. The comparison of the experimental and numerical results showed differences that could be explained by the uncontrolled movements of the young patient. After validation of the model, this calculation of pressures will allow to anticipate the hyper-pressures due to the shape of the orthosis and thus to be able to model the helmet in a more objective way before producing it. The multiplication of the number of patients and thus of analyses will allow us to refine our model.

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MULTISCALE COMPUTATIONAL MODELING OF NOTCH SIGNALING IN MECHANO-REGULATED GROWTH AND REMODELING

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Introduction
Arteries grow and remodel in response to mechanical cues. Hypertension, for example, is known to result in arterial thickening, but the underlying cellular mechanisms remain largely unclear. Notch signaling between vascular smooth muscle cells (VSMCs) plays important roles in arterial growth and remodeling (G&R) [1] and is affected by strain [2]. This suggests that Notch may be a key player in mechano-regulated G&R. Here, we investigated the role of Notch in hypertension using multiscale computational modeling.

Methods
A Notch signaling model [2] was adopted, simulating interactions between VSMC-bound Notch receptors and ligands, accounting for their sensitivity to strain. This model was coupled to a Finite Element (FE) model of arterial mechanics, including pre-stretches, to capture the influence of hypertension on VSMC phenotype, as modulated by Notch (Fig. 1A). In a subsequent study, the Notch model was coupled to a constrained mixture model [3], which considers the turnover and mechanics of arterial constituents, to capture in more detail the effects of Notch on VSMC behavior and associated tissue G&R in hypertension (Fig. 1B). This latter coupling was partly informed by in vitro data and also included a stress-driven stimulus for G&R to account for mechanisms other than Notch.

Results
The results from the FE analysis show that the hypertension-induced increase in stretch, especially on the luminal side (Fig. 2A), resulted in a decrease in Notch activity, and thereby a shift of the VSMCs towards a synthetic phenotype with higher G&R activity (Fig. 2B). These predictions are consistent with experimentally observed thickening in hypertension [4]. The coupling of the Notch model to a constrained mixture model revealed that Notch regulates the arterial thickening (Fig. 2C) in hypertension predominantly by increasing VSMC proliferation (Fig. 2D). The artery was predicted to rely on other mechanisms to achieve full remodeling in terms of VSMC and collagen density (Figs. 2D & 2E), as observed in vivo [5] (Fig. 2, crosses).

Discussion
Our simulations suggest that Notch mechanosensitivity may be a key mechanism in arterial G&R in response to hypertension. More knowledge on Notch may therefore be vital to increase our understanding of arterial adaptation. Notch may also play an important role in the search for novel therapies to steer G&R, for example in vascular disease or regeneration. Nevertheless, Notch alone cannot explain full remodeling, suggesting that it should be considered together with other pathways.

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Acknowledgements
Funding was provided by the European Research Council (Grant agreement No. 802967 and 771168) and the Marie-Sklodowska-Curie Global Fellowship (grant number 846617).
UNRAVELLING ADAPTATION STRATEGIES IN SIT-TO-WALK USING PREDICTIVE NEUROMUSCULAR SIMULATIONS

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Introduction
Standing up from a chair is a key daily life activity (>60x per day) that is sensitive to functional limitations as we age. Most stand-up movements transfer directly into walking (sit-to-walk). The aim of this study was to develop and validate a neuromusculoskeletal model with reflex-based muscle control to simulate the sit-to-walk movement, under various conditions (seat height, foot placement), reduced muscular capacity, reduced neural capacity, and altered movement objectives (pain). In this abstract we demonstrate how different seats and initial postures affect the sit-to-walk biomechanics and adaptation strategies from a lower seat (height = 35cm), and with asymmetrical foot placement (anterior-posterior position).

Methods
We developed a planar sit-to-walk musculoskeletal model (11 degrees-of-freedom, 20 muscles) and neuromuscular controller, whose parameters were optimized using a shooting-based optimization method [1]. The sit-to-walk controllers consist of a two-phase stand-up controller (P1, P2) and a reflex-based gait controller [2]. The stand-up controller uses delayed proprioceptive feedback from muscle length, force, velocity, and upper-body orientation. Both monosynaptic and antagonistic feedback paths are included in the controller. Control parameters were optimized to minimize the cubed muscle activation and gross cost of transport, at a prescribed minimum gait velocity, while avoiding falling, and excessive ligament stretch forces. We ran multiple parallel optimizations with the same initial guess and used the best set as start for the next set of optimizations. Final results were compared to a subset of recorded kinematics, ground reaction forces (GRF), and muscle activation (sEMG) from young (18-35 year) and older (>65 year) adults (n = 50), in which participants were asked to stand up and walk to a table at self-selected speed [2].

Results
When the height of the seat was reduced, the model showed a larger trunk angle in P1, which is in line with human motor control [3]. As expected, overall the lower seat requires higher muscle activations and results in higher joint loads: higher peak knee (+25%) and hip (+22%) loading in stance leg, and +10% in the stepping leg, and bilateral increase in peak load of the ankle (+12-16%). The biggest differences in muscle activation is bilateral less activation in the BFSH, and higher activation in the PSOAS and TA. For the stance leg, HAM and GMAX are more activated compared to a normal seat height.

In the asymmetric foot condition, the trunk was kept more upright. This posture results in a large reduction of hip load in the stepping leg compared to the normal condition (~48%). The bilateral knee loads are also slightly reduced (~5-7%), whereas the ankle load in the stepping leg is higher compared to the normal condition (~62%). There is less activation for HAM in the stepping leg, and RFEM and GAS have a longer activation on this side, and the peak VAS activation is higher.

Discussion
The predictive planar lower limb model was able to simulate sit-to-walk movements that match real-world kinematic and kinetic recordings. We demonstrated that the model can realistically simulate compensation strategies due to alteration in the neuromuscular system and alternative conditions such as seat height and foot positioning. Asymmetric foot positioning in which the stepping leg was placed backwards, leads to a large reduction of peak hip load in the stepping leg with the drawback of increased ipsilateral peak ankle load. This is relevant for clinic in for example hip arthroplasty rehabilitation to advice on the best sit-to-walk strategy during recovery.

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IN SEARCH OF CARDIOVASCULAR BIOMARKERS FOR PRE-ECLAMPSIA

Raoul van Loon(1), Claudia Popp(1), Dale Kernot(1), Jason Carson(1), Hari Arora(1), Jenny Myers(2), Edward Johnstone(2)

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Introduction

In pregnancy, modifications of the utero-ovarian arterial network cause a significant increase in blood volume distributed to the placenta and foetus. In pre-eclampsia, these modifications of the utero-ovarian arterial network is compromised, which results in a reduced perfusion of the placenta with corresponding negative implications for the foetus. An improved mechanistic understanding and the identification of new cardiovascular-based biomarkers would help stratify treatment of these patients.

Methods

The framework proposed here combines a range of maternal non-invasive measurements with cardiovascular pregnancy models [1]. The main measurements are displayed in Figure 1. Template models of pregnancy are personalised in a 2-step parameter optimisation approach, which tunes scaling parameters for the vascular compliance, blood volume, vascular resistance and vessel areas such that measurement outputs are mimicked [2].

Results

A range of dimensionless groups based on measured and model-predicted parameters was constructed in search of powerful new biomarkers for pre-eclampsia. These were compared with other proposed metrics such as pulsatility index and resistivity index. Results based on this patient dataset indicate that new biomarkers PPI and VI, based on blood pressure and velocity in the radial/arcuate arteries, respectively, outperform existing measures (Fig 2).

Discussion

Promising novel classifiers have been identified based on the predicted velocities and pressures in the placental vascular beds using our personalised cardiovascular models. These metrics seem to perform better than maternal brachial pressure as a biomarker for pre-eclampsia and should be explored further. Future work will therefore focus on larger datasets captured longitudinally throughout pregnancy to see their ability to classify earlier on in pregnancy.

References


Acknowledgements

R van Loon, D Kernot and E Johnstone would like to acknowledge the In-Utero project funded by Welcome Leap.
USING DIGITAL TWIN TECHNOLOGY TO REDUCE ANIMAL STUDIES FOR DEVELOPMENT OF PERINATAL LIFE SUPPORT SYSTEMS

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Introduction

To reduce the mortality and morbidity rate of extremely preterm infants (< 28 weeks of gestational age, GA), the Perinatal Life Support (PLS) consortium is developing a PLS system (https://perinatallifesupport.eu). The PLS system serves as a liquid-based incubator where the infant is submerged in fluid and the umbilical cord is connected to an artificial placenta [1]. This way, the organs of the preterm infant can mature similar as in the natural womb.

Several research groups [2–4] started animal experiments to define the optimal environment for fetal development. Besides the concern of ethics, animal studies require trained manpower, time, and money.

A digital twin of the experiment can overcome these drawbacks. Digital twin technology enables testing and tuning of the set-up before the actual experiment and allows for animal specific optimization of the experiment. Moreover, it provides support to operate the PLS system during the experiment. This study presents a mathematical model of a human fetus and how this model is translated to a digital twin that mimics the interaction between a PLS system and a fetal pig [3].

Methods

Based on [5,6], a human fetal cardiovascular mathematical model including gas-exchange and fetal growth is developed. This model is adapted to the fetal pig anatomy. Subsequently, the placenta is replaced by an artificial placenta and adapted to the experimental set-up of [3]. Figure 1 shows the development process of the mathematical models.

Results

Figure 2 shows the results of the mathematical model describing an average healthy human fetus in a natural womb. As verification, the mean flow through the foramen ovale, ductus arteriosus, the ascending aorta, and main pulmonary artery simulated by the model (green) is compared with literature data [7] (black).

Discussion

We developed a mathematical model that can describe the fetal hemodynamics. To develop a digital twin, the model should be dynamically paired with the experimental set-up data. Figure 3 shows the method proposal that will be carried out in April-June 2023 in collaboration with the research group of [3].

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MUSCLE OXYGEN SATURATION AS A BIOMARKER TO GUIDE RETURN TO PLAY AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Introduction

Return to play (RTP) protocols for anterior cruciate ligament (ACL) injuries involve full motion, strength, psychological readiness, GPS monitoring, isokinetic testing, and functional testing. However, current RTP criteria lack objective, internal, and continuous data necessary to complement current assessments. The ACL is crucial in stabilization, motion, and preventing internal rotation of the knee joint [1]. ACL ruptures cause increases up to 10-15° of anterior tibial translation at 30° of knee flexion [1]. Monitoring muscle oxygen saturation (SmO₂) levels utilizing wearable sensors enables the collection of continuous, internal, and objective data to monitor O₂ delivery and consumption in the surgical and contralateral limbs. Measurement and integration of digital biomarkers such as SmO₂ into electronic health records of athletes have the potential to compliment current rehabilitation exercises and therapies used during the RTP period [2], [3]. We hypothesize that muscle atrophy in the surgical leg post ACL reconstruction (ACLR) causes changes in SmO₂.

Methods

Currently ongoing is a multi-arm IRB approved study (20191389) assessing SmO₂ levels in the legs of healthy subjects (arm 1, n=50) and patients after ACLR (arm 2, n=50). Inclusion criteria involved participants being 14-22 years of age, have no history of prior ACLR, knee arthroscopic surgery, or hip arthroscopic surgery, and not pregnant. A standardized workout was created for testing at 6-, 9-, and 12-months post-ACLR. Sensors are placed on the vastus medialis (VMO) bilaterally using medical grade adhesives to record SmO₂. Healthy patients undergo testing once, while surgical patients undergo the testing at 6-, 9-, and 12-months postoperatively.

Results

Representative SmO₂ data recorded from a patient (21-year-old, female football athlete, outside-forward) after ACLR demonstrated a statistically significant difference in contralateral versus surgical limb average muscle oxygen saturation in the Tabata, leg press, and max-minute exercises at 6- and 9-month trials (Figure 1). There were no significant differences found between surgical and contralateral limbs during the leg press and max-minute exercises at the 12-month trial. The mean difference significantly decreased for the Tabata, leg press, and max-minute exercises between each visit from the 6 to 12-month period with r² values of 0.8656, 0.8163, and 0.8891, respectively. ACLR SmO₂ levels at the 12-month trials resembled the healthy cohort (not shown).

Discussion

The change in SmO₂ in ACLR patients is likely due to a combination of altered hemoglobin-oxygen unbinding, altered blood delivery, detraining, and muscle atrophy. These changes in SmO₂ in the ACLR subjects correlate with improvement in other RTP testing. SmO₂ data offers complementary, internal, and objective data in RTP criteria. Future work will enable the development of an integrative algorithm that physicians and physical therapists can employ to gauge athlete readiness following ACLR with broader implications to other musculoskeletal injuries.

References

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Acknowledgements

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MECHANICAL PROPERTIES OF THE HUMAN PIA-ARACHNOID COMPLEX

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Introduction
To study brain biomechanics during a head impact and better understand the mechanisms of traumatic brain injury (TBI), finite element (FE) models of the human head are frequently used. The cranial meninges are crucial structures to protect the brain against injury, showing the importance of including those structures into FE models. However, only little is known about the mechanical behavior of the human pia-arachnoid complex (PAC), forming the two innermost meningeal layers [1–3]. Therefore, in this study, bulge inflation experiments are performed on human PAC samples in order to determine their in-plane mechanical properties.

Materials & Methods
PAC tissue is carefully removed from fresh human brain tissue and cut into square samples with sides 30 mm. Sample thickness is measured prior to testing by means of two lasers, located on either side of the sample. During testing, samples are inflated at a constant volume rate until predefined pressure levels are reached as shown in Fig. 1. Full-field deformation of the samples is captured using 3D digital image correlation of the applied speckle pattern and pressure is measured. The mechanical response of PAC tissue is fitted to the first order Ogden constitutive model (equation 1) [4] using an inverse parameter identification framework based on the virtual fields method [5], including full-field displacement data and region-specific sample thickness.

\[
\psi = \frac{2\mu}{\alpha^2} (\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3) \tag{1}
\]

Results
The obtained material parameters of one PAC sample are \(\mu = 0.16\) MPa and \(\alpha = -37.46\) with normalized root mean square error NRMSE = 0.05. Fig. 2 shows a scatter plot of the experimental stretches in the sample along the main axes at the final loading step of 12.14 kPa.

Discussion
Preliminary results show a heterogeneous stress and stretch distribution in the PAC tissue during testing due to the inhomogeneous sample thickness. As seen in Fig. 2, the fitting is based on multiple stretch ratios \(\lambda_{11}\) and therefore contains more information than e.g. a typical planar biaxial experiment. The use of full-field deformation data makes it possible to address the sample heterogeneity and to eventually differentiate between the mechanical properties per sample region. More samples will be included in the future in order to obtain a representative set of material parameters for human PAC tissue, necessary for accurate computational predictions of stress and strain patterns in the brain during TBIs.

References
EFFECT OF BRUSHING ON THE SURFACE MICRO-ROUGHNESS OF DIFFERENT TYPES OF CAD/CAM CERAMICS

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Introduction

Some of the most commonly used CAD-CAM ceramic materials are leucite (feldspathic) ceramics, lithium silicate reinforced with zirconia and as well hybrid ceramics [2]. An important factor that contributes to the restorations roughness is the daily tooth-brushing [3]. Tooth-brushing combined with dentifrice, can lead to an increased surface roughness of dental restorations. Increased surface roughness more than 0.2 µm leads to an increased plaque accumulation, higher carries risks and antagonist wear [4].

Methods:

Twelve ceramic specimens (n=4) (Vita Mark II (M), Vita Suprinity (S) (Vita Zahnfabrick, Germany), Lava Ultimate (L) (3M, USA)), with dimensions of 10x10x1.5 mm were cut using a machine (Orthoflex PI Dental, Budapest, Hungary) that provides millimeter accuracy in milling.

The rectangular-shaped samples were polished using silicon carbide papers (600–2000 grit) and the final thickness of each specimen was checked with a caliper. The Z ceramic required an additional crystallization (25 minutes at 850 °Celsius) to achieve the final mechanical properties.

The samples were immersed in distilled water for one week at 37 °Celsius to simulate the oral environment. Afterwards the samples were brushed for 10,000 cycles using a electronic device  (Oral-B) and toothpaste (Colgate, Palmolive).

The surface roughness (Ra, Rz) was measured on each surface using a surface profilometer (Mitutoyo, Japan) during the immersion and after brushing. Five measurements were made on each sample for the micro-roughness assessment. As well the samples weight was registered using a five digits precision analytical balance to see in which degree the immersion affects their water absorption and their micro-roughness.

Results:

One-way ANOVA revealed that there were significant differences (p<.05) after the immersion for the micro-roughness values after 96 hours and after one week compared to the initial values, and especially for the S and M samples. Tooth-brushing influenced significantly the Rz values for the micro-roughness for all the materials, but significantly for the M samples.

Discussion:

Many studies investigated the effects of toothbrush abrasion and aging on the surface texture of CAD-CAM blocks, but there is little information in literature about this type of ceramics [1-4]. All the samples registered initial values under 0.2 µm for the micro-roughness and as well after the immersion and tooth brushing for 10,000 cycles.

References:

ACCURACY OF CAD- AND CT-BASED FE MODELLING TO PREDICT THE FATIGUE BEHAVIOR OF POROUS TITANIUM DENTAL IMPLANTS

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Introduction
Due to their improved osseointegration potential, 3D-printed porous dental implants are gaining growing interest [1]. While providing sufficient porosity for functionalization, such implants must exhibit appropriate fatigue strength to comply with the relevant standards. Finite element (FE) modeling has the potential to simulate time-consuming fatigue testing and thus shorten the design process [2]. The present work aimed at developing and calibrating a tool to predict fatigue behavior of porous implants by combining monotonic testing and FE simulation (Fig. 1) and compare accuracy of CAD-, or CT-based FE modeling.

Methods

Simplified test samples of 4.5 mm-diameter cylinders mimicking dental implants were designed based on the requirements of the ISO 14801. A fully porous section of 4.5 mm height was introduced around bone level (Fig. 2a). Two different unit cell geometries (Schwarz Primitive (SP) and Schwarz W (SW)) and three porosity levels (50%, 60% and 70%) were combined to generate six designs: 50SP, 60SP, 70SP, 50SW, 60SW and 70SW. 144 samples (24 per design) were manufactured by selective laser melting in Ti6Al4V (EOSINT M270). µCT imaging was performed to assess effective geometries of four samples per design (vivaCT, Scanco). Uniaxial tensile testing was performed on 3D-printed dog bone shaped samples to determine elastic modulus E and yield stress (σy). The porous samples were tested in vitro under bending compression at 30° off-axis load according to ISO 14801. Four samples per design were tested monotonically to determine ultimate load (F_{ult}^{exp}) (Instron 5866). Fatigue testing was performed at five load levels: 50%, 35%, 25%, 20%, and 15% of F_{ult}^{exp} (DYNA5dent, DYNA-MESS) with four samples at each level to measure the number of cycles to failure (N_F). Fatigue data was fitted with F = F_0 (2N)^b, assuming a constant h, to determine F_0, the specific fatigue force, for each design.

Linear elastic FE models (Fig. 2a) were built using two techniques, CAD-based and CT-based. The estimated monotonic failure F_{ult}^{FE} was defined as the load level for which the von Mises stress σ_{VM} > σ_y in a constant volume fraction %V of the porous region. %V was determined via best fit between F_{ult}^{FE} with F_{ult}^{exp} (Fig. 1). In a second step, fatigue life prediction was performed via linear regression of F_{ult}^{exp} and F_0 (Fig. 1). With α and β being the regression coefficients, the FE prediction of the fatigue resistance can be expressed as:

\[ F = (\alpha \cdot F_{ult}^{FE} + \beta)(2N)^b \]

Results
Fatigue behavior was accurately predicted for all designs except for the 60SP one that was overestimated by 34.1% (Fig. 2b). CT-based FE achieved stronger correlation between experimental and predicted specific fatigue force (R^2=0.87) and lower average prediction error (10.0%) than CAD-based FE (R^2=0.73 and 18.3%).

Discussion
The developed FE-based approach can accurately predict implant design's infinite fatigue life. This tool, requiring only simple monotonic testing for FE model calibration, can be an efficient surrogate for time consuming fatigue testing and therefore accelerate the development process of porous implants. By accounting for the differences between planned and printed geometries, CT-based models were more accurate than CAD-based models.

References

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A NEW HYPERELASTIC MODEL FOR HUMAN MYOCARDIUM

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Introduction

Human myocardium is formed by locally parallel muscle fibres which are arranged in layers, sometimes called sheets [1]. This structure determines the orthotropic mechanical response of myocardium, as evidenced by the results of biaxial extension tests and simple shear tests [2]. A suitable hyperelastic model for myocardium should reflect its structure and produce an orthotropic response with highest stiffness in the fibre direction, \( f \), intermediate in the sheet direction, \( s \), and lowest in the sheet-normal direction, \( n \) (\( f, s \) and \( n \) are mutually orthogonal). The most widely used model which satisfies these requirements is that proposed by Holzapfel and Ogden [3]. It introduces two orthogonal families of fibres, one in the \( f \) direction and the other in the \( s \) direction. The families are represented by two exponential terms in the strain-energy density function, formulated in terms of invariants \( I_{sf} = f \cdot C f \) and \( I_{ss} = s \cdot C s \) which equal the square of stretch in \( f \) and \( s \) directions, respectively (\( C \) is the right Cauchy-Green tensor). However, the family in the \( s \) direction is somewhat artificial since in myocardium there is no distinct family of fibres (collagen of others) arranged predominantly perpendicular to the muscle fibres; instead, the chains of myocytes are bundled by endomysial connective tissue with membraneous appearance [4]. For this reason, we present a modification of the model which reflects more accurately the laminar structure of myocardium and turns out to have better capability to reproduce experimental responses.

Methods

In our modification of the strain-energy density function the exponential term with the invariant \( I_{ss} \) was replaced by the term

\[
\Psi_{fs} = \frac{a_h}{2b_{fs}} \left( \exp(b_{fs}(K_1 - 1)^2 - 1) \right)
\]

which employs an uncommon invariant \( K_1 \) defined in terms of the cofactor of \( C \), \( \text{cof}(C) \), and the sheet-normal unit vector \( n \) (perpendicular to the sheets) as \( K_1 = n \cdot \text{cof}(C)n \) [5]. This invariant is essentially a 2-dimensional analogue of the invariant \( I_2 \) because it expresses the square of stretch of an infinitesimal area initially perpendicular to \( n \); more precisely it is the ratio of the area of the deformed infinitesimal sheet to its referential (initial) area. Thus, unlike the original model [3], our model explicitly includes a mathematical representation of the layered blocks of endomysial connective tissue (apparent in electron microscope [4]) that bind together the muscle fibres. The fibres and the isotropic matrix are modelled in the same way as in the original model [3] (i.e. by means of invariants \( I_{sf} \) and \( I_3 = \text{tr}(C) \)).

Results

The modified model was fitted to the results of 5 different biaxial tests and 6 different simple shear tests published in [2]. Although the proposed modification is quite subtle, it significantly improved the ability of the model to reproduce all the above-mentioned experimental data (\( R^2 \) increased from 0.90 to 0.98). As an example, Figure 1 shows the final fit to the data from equibiaxial extension test.

![Figure 1: Fit of the proposed hyperelastic model to the equibiaxial experimental data from [2].](image)

Discussion

The proposed model reflects more accurately the microstructure of ventricular myocardium and it has great capability to describe the mechanical response of myocardium in different biaxial and simple shear loading modes. However, derivation of the spatial elasticity tensor (necessary for implementation into commercial finite-element packages) is rather complicated due to the new term (1) of the strain-energy function.

References


Acknowledgements

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SCALABLE AGENT-BASED MODELLING OF CELL BIOMECHANICS AND THERAPY USING THE BIODYNAMO PLATFORM

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Introduction

*In silico* models in computational cell biomechanics are usually confronted with the fact that they need to capture processes across multiple spatial/temporal scales. These processes play out intracellularly, such as for instance gene regulatory dynamics, as well as extracellularly, such as their interactions with the extracellular matrix and parenchymal components. Moreover, intercellular processes often play a crucial role too, particularly during growth and developmental phases. Agent-based modelling (ABM) alone, or via hybrid multiscale procedures, is an attractive approach to explore complex biological processes. Here, we demonstrate ABM in biomedical applications using open-source simulation platform BioDynaMo [1]. We present a selection of examples to demonstrate the simulation of biological cell growth and development, therapy, and cell pathophysiology in chronic diseases.

Methods

ABM is a complex-system modelling method that assumes autonomous, interactive ‘agents’ that are denoted as a particles (cells) or segments (neurites, vessels), positioned in 2D/3D-space following an off-lattice approach, and ‘agent behavior’ is determined by rules as a Markov process. Our ABM platform, BioDynaMo, can encompass the interactions with other cells and response to external stimuli, their ability to secrete or/and uptake cytokines, enzymes, etc. The open-source project BioDynaMo, implements ABM and it has been designed to leverage modern software engineering techniques and enables high-performance computing using OpenMP, MPI and CUDA [1].

Results

The following figures illustrate the applicability of the ABM platform, BioDynaMo, through four simulation examples in cancer and wound healing/inflammation.

Discussion

We have demonstrated the BioDynaMo platform to simulate the development cancer by mimicking *in vitro* systems, to simulate the effect of cytostatics and other treatment modalities, and to simulate the pathophysiology of diseases such as pulmonary fibrosis. BioDynaMo is available at [www.biodynamo.org](http://www.biodynamo.org).

References


Acknowledgements

We are very grateful for the contributions of all BioDynaMo consortium members, the technical team, and the alumni.
STENT-GRAFTS DERIVED FROM AUXETIC UNIT CELLS: NUMERICAL SIMULATION OF DEPLOYMENT INTO A CURVED ARTERY

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Introduction
In tortuous aneurysms associated with abdominal aortic and iliac aneurysms, Endovascular aneurysm repair (EVAR) has faced severe complications which has been linked with diminished SG flexibility [1,2]. Stent design has been recorded to greatly influence SG mechanical behavior (flexibility and durability) [3,4]. Our team has investigated the potential of auxetic stents for EVAR applications [5] and the mechanical behavior of SG with novel stents derived from auxetic unit cells [6] when subjected to 180° angulation using finite element (FE) simulations respectively. In this work, we intend to expand on [6] by numerically simulating the deployment of novel SGs derived from auxetic unit cells in an idealized curved iliac aneurysm [7] using FE simulations and examine their in-vivo mechanical behavior in interaction with tortuous vessels.

Methods
Successful novel SG iliac limb candidates from our most recent work [6] CRE-DIA (chiral re-entrant - diamond) and CS-DIA (chiral star - diamond) that contain a combination of auxetic and positive Poisson’s ratio unit cells respectively are represented as FE models with Timoshenko beam elements B31 elements and 4-node quadrilateral S4 shell elements for the Nitinol based stent and PET graft respectively on Abaqus as depicted in figure 1 with similar stent diameter and graft length. The clinically relevant iliac aneurysm geometry and modelling of vessel wall properties can be found in previous study [7], where a frictional coefficient of 0.2 was utilized to model friction between SG and arterial vessel wall on Abaqus.

Results
In Figure 2, both CRE-DIA & CS-DIA SGs display no severe kinks when subjected to 180° bending and pressurization [6], which is an encouraging sign considering that commercial Z-stented SGs when deployed in curved arteries, displayed kinks & reductions in luminal cross-section analogous to its bending behaviour when subjected to 180° angulation [7]. On basis of preliminary results, CRE-DIA SG & CS-DIA SG demonstrate reduced CSARMAX and DSA values in comparison to the respective CSARMAX and DSA values of Z-stented SGs reported in [7]. However, the presence of a minor gap between the distal stents and vessel wall at the inner curvature of aneurysm is noted for both novel SGs similar to results reported for Z-stented SGs in a previous work [7].

Discussion
Perrin et al., [7] had demonstrated that all Z-stented commercial SGs faced kinks and reduced juxtaposition onto the inner vessel curvature of prior mentioned curved iliac aneurysm post-deployment. CRE-DIA & CS-DIA SGs show promising results in comparison to Z-stented SG, but further optimization of stent-design will be conducted on these candidates to improve their mechanical performance.

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THE EFFECT OF RESPIRATION ON THE IN-VIVO MECHANICAL EVALUATION OF LINEA ALBA BY SHEARWAVE ELASTOGRAPHY

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Introduction

In vivo characterization of abdominal wall mechanical properties is an important aspect for improving our understanding of the onset and treatment of abdominal hernias. Several methods have been developed to this end, such as the estimation of local tissue strain with optical or magnetic resonance imaging [1,2]. However, only a few studies focused on the mechanical characterization of linea alba. Shearwave Elastography (SWE) has provided promising results in assessing this tissue [3-4]. Biomechanical assessment of linea alba can be challenging because it has a nonlinear mechanical behavior, i.e., mechanical loading, such as breathing, can alter its tangent stiffness. The aim of this work was to determine the effect of breathing on the biomechanical assessment of linea alba using SWE during the normal breathing cycle.

Methods

Fifteen healthy adults (6 females, 9 men, 33 [26;40] years old, 24 [20;27] kg/m² body mass index, BMI) were included, after obtaining their informed consent (ethical committee CPP Ile-de-France VI 6001). SWE was performed with a Mach30 device (Supersonic Imagine, Aix-en-Provence, France) and a SL 18-5 probe. Subjects lied supine, and measurement were performed 1 cm below the navel; first the location of the linea alba was determined with a transversal scan, then transversal and longitudinal measurements were performed. Each measurement was a video of sufficient duration to span at least 4 breathing cycles (about 40 seconds). Measurements were repeated three times by one operator; a second operator repeated the protocol on a subcohort of 6 subjects. Breathing cycles were determined by tracking the movement of the abdominal wall in the video (25 Hz). SWE frames (~1 Hz) were postprocessed to extract Shearwave Speed (SWS) and relate it to the breathing cycle. Results were reported as median [1st;3rd quartile].

Results

The measurement was feasible in all subjects, irrespective of BMI. Average SWS was 2.4 [2.0;2.6] m/s in longitudinal direction and 2.2 [1.9;2.7] m/s in the transversal one. The difference was not significant (p>0.05).

Uncertainty was 0.2 m/s (8% coefficient of variation) in the longitudinal direction and 0.3 m/s (14%) in the transversal one, with not significant operator effect, which is consistent with previous studies [3].

Figure 1: Comparison between breathing phase (arbitrary units) and shear wave speed. Left panel shows an example where breathing cycles are observable in SWS, while in the right panel measurement uncertainty is higher than variations due to breathing.

Figure 1 shows examples of measurement during breathing cycle. SWS showed a clear cyclic pattern only in a small portion of the measurements. In general, variations due to uncertainty were higher than those due to the breathing cycle.

Discussion

Results confirm that SWE of the linea alba is sensitive to breathing. This could be considered as a confounding factor when assessing the tissue, but also as a mean to load the tissue and potentially detect pathological alterations which are not evident in the unloaded tissue. The main limitation of this work is that subjects were asked to breathe normally and were not specifically invited to use “abdominal breathing” rather than a “thoracic” one. It is possible that abdominal breathing (through the diaphragm) might have enhanced SWS variations during different breathing phases.

In conclusion, this study confirms that breathing can have a measurable effect on the SWS assessment of the linea alba, but further work is needed to refine the measurement protocol, to determine the effect of forced abdominal pressure and to ascertain the clinical relevance of such method.

References


Acknowledgements

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NEURAL RADIANCE FIELDS FOR VESSEL RECONSTRUCTION FROM 2D X-RAY CORONARY ANGIOGRAPHY PROJECTIONS

PROOF OF CONCEPT

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Introduction

X-ray coronary angiography (CAG) is the standard modality to assess the anatomy of coronary arteries and possible stenoses and to guide coronary interventions. An interventional-cardiologist uses these multiple consecutively acquired two-dimensional (2D) projections from different angles to obtain a mental perception of the complex coronary tree in three-dimensions (3D). A readily available 3D reconstruction of the coronary tree during this procedure facilitates e.g. properly chosen projections for optimal decision making.

A vast amount of traditional and machine learning methods have been proposed for the 3D reconstruction of vessels from CAG, yet the problem remains complex, as key challenges with automation, limited number of projection angles and cardiac and respiratory motion have not been completely solved. Neural Radiance Fields (NeRF) is an emerging deep learning technique for 3D reconstruction and could potentially tackle these challenges [1].

The aim of this work is to show the application of NeRF for vessel reconstruction from CAGs.

Methods

The development of NeRF for vessel reconstruction has been described elsewhere [1]. The feasibility of NeRF for coronary reconstruction will be demonstrated using image data from a single patient and will be assessed in two steps:

1. (more than) two projections from the CAG; and
2. using projections from a synthetic CAG constructed from a Coronary Computed Tomography Angiography (CCTA) using the same projections;

The 3D reconstruction from the CCTA is used as a reference.

X-ray CAG

For each angiogram an end-diastolic frame is selected, resulting in a single frame per projection angle as input for NeRF. The number of projections that is given to the model will be varied from one to the maximum number of selected frames, in order to study if NeRF can deal with limited number of projection angles. In all cases a 3D geometry of the coronary tree is outputted by the model.

Synthetic CAG

Segmentation of the coronary arteries, heart and ribs on CCTA provides a motion free situation, from which arbitrary X-ray projections can be created using volume rendering techniques. Identical angles are chosen for these synthetic angiograms.

Performance of NeRF will be assessed by comparing the centerlines of the coronary tree reconstructed from synthetic and real angiograms to the coronary centerlines from CCTA.

Results

Preliminary (eye-ballling) results show that NeRF can reconstruct the coronary tree from a limited number of projections. Quantitative assessment will follow.

Discussion

In this work it will be demonstrated if NeRF can deal with the challenges in reconstructing the coronary tree from (synthetic) coronary angiograms. A CCTA-derived coronary model will serve as ground truth for the reconstructions with NeRF. The minimum requirements needed for NeRF to obtain a proper 3D reconstruction, e.g. the number of clinically used projections, will be one of the results.

The use of synthetic angiograms is explored as a new approach to obtain motion free images from arbitrary projections and to validate CAG reconstruction techniques as the ground truth is already available.

Though it is considered that the general outline of the coronary tree from NeRF, described by centerlines, can be obtained, a validation of the complete 3D reconstruction requires more specific data such as intravascular imaging.

References

VIRTUAL COHORT GENERATION FOR IN SILICO TRIALS OF TRANSCATHETER AORTIC VALVE IMPLANTATION

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Introduction

After transcatheter aortic valve implantation (TAVI), patients can suffer from several procedural complications such as paravalvular leakage, and conduction problems. Two aortic valve morphologies that influence the occurrence of those complications are: (1) the shape of the left ventricular outflow tract (LVOT), either convergent or divergent, and (2) the angle between the LVOT and the ascending aorta (\(\angle \text{LVOT} - \text{AA}\)) (Fig. 1). TAVI manufacturers are still developing their devices to prevent these procedural complications in the future. In silico clinical trials are a promising method to increase the efficiency of the development of transcatheter aortic valve implantation (TAVI) devices. With an in silico trial, devices can be tested on virtual patients which are computer models that realistically mimic the physiological response induced by TAVI implantation. The domain of interest of each patient of the virtual cohort for TAVI evaluations is represented by a synthetic aortic valve geometry. The aim of this research is to develop a framework to generate synthetic aortic valve geometries, that (1) are anatomically plausible, and (2) allow for selection of the aforementioned morphologies.

Methods

Non-parametric statistical shape modeling (SSM) [1] was used to extract the mean shape and shape variance (shape modes) from a set of 97 stenotic aortic valve geometries. Each geometry within or outside this data set was approximated by adding a weighted combination of 24 shape modes to the mean shape. With the SSM 500 synthetic geometries were generated by sampling new weight combinations from an inferred distribution [2]. Logistic regression and linear regression models were used to filter synthetic geometries on LVOT morphology and \(\angle \text{LVOT} - \text{AA}\) respectively.

Results

Eight shape features, characteristic for aortic valve geometries, were compared between the real and synthetic geometries. The correlations between the eight features were similar for both groups (Fig. 2). A non-parametric multivariate ANOVA test revealed that the 8-dimensional distributions of both groups did not differ significantly (p = 0.47 > 0.05). Furthermore, the filters were able to successfully filter convergent or divergent geometries with a sensitivity of 98% and 99% respectively, and to filter small, medium and large angles with a sensitivity of 86%, 85%, and 97% respectively.

Discussion

These results demonstrate that the framework developed in this study, (1) succeeded in generating synthetic geometries that are anatomically plausible, and (2) makes it possible to select geometries with certain morphologies. Consequently, this framework has the potential to generate synthetic data sets for in silico TAVI trials. The next steps towards in silico TAVI trials is to integrate calcifications in synthetic geometries, and to simulate the hemodynamic and structural behavior of these valves before and after TAVI.

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Abstract

Introduction. A skeletal muscle fascicle length is a primary determinant for its functioning. Determining a muscle’s arrangement in a reliable way, requires a standardized imaging method. MRI-based diffusion tensor imaging of muscle (mDTI) gives three-dimensional and complex insights in a muscle structure. Within neurosciences DTI is an already accepted method and shows the arrangement of nerves by measuring the diffusion of water molecules along the nerve fibers\(^1\). Since muscles also contain a certain amount of water, mDTI also allows for a valid\(^2-4\), reliable and robust\(^5,6\) measurement of a muscle’s arrangement. Nevertheless, mDTI data processing seems time-consuming and dependent on consistency between operators and therefore less applicable for different purposes.

To turn mDTI into a tool of practical importance, the adjustment of the slice-by-slice muscle segmentation prior to fiber reconstruction provides most potential\(^7,8\). Therefore, it is of practical relevance to know how different muscle model shapes affect mDTI analysis. This study aims to analyze the influence of segmentation-based analysis (SBA) by two different operators on muscle fiber tractography. Furthermore, we want to compare these results to model-free analysis (MFA).

Methods. 15 healthy male subjects underwent a standard 3T MR diagnostics using a 16-channel shoulder coil (XL). A T1w and 2D echo planar DTI sequence were applied for the right shoulder. Total scan time was about twelve minutes. After acquisition, two different operators (SBA 1 and SBA 2) independently segmented each M. supraspinatus by using an individual routine. MFA did not contain a segmentation prior to tractography (Figure 1). Deterministic fiber tracking was performed using DSI Studio with the following stopping criteria: maximum angle between tract segments 10\(^\circ\), 40 mm ≤ tract length ≤ 130 mm; step size = 1.0 mm. Recommended DTI pre-processing steps were applied. For reliability analysis (ICC) we calculated values for the parameters fractional anisotropy, axial diffusivity, radial diffusivity, mean diffusivity, muscle volume and fascicle length.

Results. Overall methods ICC ranged between 0.615 (fascicle length) and 0.943 (fractional anisotropy). Interrater-reliability analysis for SBA 1 and SBA 2 showed an ICC between 0.872 and 0.991, with exception for muscle volume (0.711). In contrast, MFA revealed an ICC between 0.404 and 0.544. Without considering the results for the parameter fascicle length, ICC values for MFA varied between 0.726 and 0.933 (Table 1).

Discussion. mDTI allows a detailed and excellent reliable\(^9\) analysis of shoulder muscle structure independent of the segmentation. Since it is known that the human shoulder joint is challenging for any imaging technology, this study shows very promising results. Further, even the model-free, less time-consuming method (MFA) showed acceptable results. This makes mDTI suitable as a tool in prevention and rehabilitation. Therefore, mDTI claims practical relevance and may be considered as a standard sequence within a musculoskeletal MR application. Nevertheless, complex image processing and segmentation seems mandatory for an accurate measurement of fascicle length. It remains unclear whether MFA could be applied for any muscles with different fiber orientation.

References

FROM MUSCULOSKELETAL DIGITAL TWINS TO IN SILICO TRIALS OF NEW INTERVENTIONS: A JOURNEY

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Introduction

Digital Twins in Healthcare (DTH) are subject-specific quantitative predictive models used as clinical decision support systems in diagnosing, prognoses, and treating disease. The management of musculoskeletal pathologies is frequently informed by biomechanical quantities, but in many cases, measuring these quantities is difficult or impossible. DTH can provide accurate estimates of these quantities on a patient-specific basis, supporting the clinical decision process. Another important role of predictive models is their use in developing and de-risking new treatments, whether drugs, medical devices, tissue engineering solutions, physical therapies, surgical procedures, etc. These models, called In Silico Trials (IST), need to predict how specific quantities of interest represent the disease progression, how this progression changes because of the treatment, and whether the treatment may also cause adverse effects. But this prediction needs to be done not for a single patient but for cohorts of patients large enough to represent the whole target population.

There are many ways to develop IST solutions, but one particularly effective is using, at the core, a DTH model. However, transforming a DTH into a full-blown IST is a complex project. In this perspective talk, we use biomechanical DTHs as a guiding example to show the challenges of transforming a DTH into an IST pose.

Background

BBCT-Hip is a DTH to predict the risk of proximal femur fracture in osteopenic subjects. BBCT combines a stochastic model of falling with a CT-based finite element model of the femur to predict whether the femur will fracture for a given fall condition. ForceLoss is a DTH for the differential diagnosis of dynapenia. ForceLoss uses a patient-specific musculoskeletal dynamics model to test the various diagnostic hypotheses. DIIP is a DTH that predicts the risk of the most common failure modes for a patient treated with a joint replacement. DIIP currently test for aseptic loosening, dislocation, intra-operative fracture, and massive wear. We aim to transform these three DTHs into IST solutions: the first, to estimate in silico the efficacy of new anti-resorptive drugs; the second, to estimate the efficacy of anti-sarcopenia drugs; the third, to run in silico a complete risk analysis for new joint replacement designs.

Results

The transformation of BBCT-Hip into an in silico clinical trial required the generation of a virtual cohort, a disease progression model, and a treatment model. We summarise our recent work in cohort expansion, through which we transformed a collection of 94 patient-specific models in a cohort of 1000 virtual patients [1]. We also report on using a Markov-Chain Monte Carlo to reduce the computational costs of the In Silico Trial. Last, we report using the newly developed In Silico Trial to investigate the effect of compliance on the efficacy of a hip protector.

For ForceLoss, we discuss the challenges we faced in generating a virtual cohort and present tentative solutions.

For DIIP, we will discuss the challenge of automating the model’s generation and how to account for both patient and surgical variability. We will report some preliminary results on the risk of intraoperative fracture in a cementless hip stem and on the risk of massive wear in a knee replacement [2].

Discussion

Although limited, this experience helps explain the main challenges in transforming a digital twin in healthcare into a full-blown In Silico Trial. As part of the discussion, we also touch on IST’s regulatory challenges [3].

References

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Acknowledgements

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IMAGE-BASED IN VIVO ESTIMATION OF REGIONAL STRAIN AND STIFFNESS PROPERTIES OF THE WHOLE AORTIC VESSEL

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Introduction

The mechanical analysis of arterial tissues is a fundamental research topic in the field of cardiovascular pathologies [1]. It is well established that a plethora of cardiovascular diseases find their origin within the vessel biomechanics [2]. The current gold standard practice for tissue testing necessarily requires tissue harvesting. In order to avoid ex-vivo procedures, several image-based techniques for estimation of arterial mechanical properties were proposed [3]. The aim of the study is to present a workflow for semi-automatic estimation of strain and stiffness distributions on both ascending and descending aorta. The method is based on the segmentation and processing of ECG-gated CT datasets.

Methods

A total of 10 datasets of ECG-gated CT images was considered. All the datasets included the ascending and, where available, the descending portion of the aorta. The workflow included the following phases: segmentation (i), mapping (ii), strain (iii), stress (iv) and stiffness estimation (v). The automatic segmentation was carried out for each cardiac phase, according to an AI based algorithm (Figure 1 a). The aortic surface at baseline was then mapped with a structured mesh and then morphed to match the different cardiac phases with a morphing method. For strain estimation, the baseline centerline was calculated and the sectional length was evaluated for each point. The corresponding sectional length at each cardiac phase was recovered with the mapping from morphing. The circumferential strain ($\varepsilon_\theta$) at each section was calculated according to the sectional length ratio. For stress estimation, circumferential stress was calculated according by assuming the aorta as a pressurized membrane. For stiffness estimation, the circumferential Young’s modulus ($E_\theta$) was evaluated as the stress – strain ratio, assuming a linearized material response under physiological conditions.

Results

The resulting strain and stiffness distributions were correctly evaluated for each case. An example of two cases of whole aorta with the resulting $\varepsilon_\theta$ distribution at systolic peak (Figure 1 b) and the corresponding $E_\theta$ (Figure 1 c) are reported. In both cases a high strain area ($\varepsilon_\theta > 20\%$) exists at aortic valve level in the outer curvature. This demonstrates the workflow potential to cope the valvular plane movement caused by left ventricular kinematics. The reported $E_\theta$ values were contained in the 1 – 3 MPa range, in line with literature [4].

Discussion and Conclusion

In general, the workflow was correctly implemented and applied to a patient population. The results demonstrated the successful obtainment of a regional in vivo characterization of whole aortas in terms of strains and stiffness.

References


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AN APPLICATION FOR REMOTE RESPIRATORY PATTERNS DETECTION IN POST-SURGERY PATIENTS

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Introduction

Remote monitoring of clinical parameters plays a key role in different situations like pandemic health emergencies and post-surgery conditions, where the patient is impeded in his/her movements [1]. Currently several devices are available to fulfill this task, however in recent years, the huge development of smartphone technologies has opened the possibility to adopt phone-embedded sensors [2]. In this context, the current project proposes a new smartphone application dedicated to the respiratory and chest kinematic monitoring of patients who underwent cardiovascular/oncological chest surgery. The developed app uses embedded IMU signals to infer the chest kinematics. Additionally, the application is also able to integrate ecographic imaging from Point-of-Care Ultrasound probes (POCUS) devices and blood oxygenation data from bluetooth pulseoximeters. The collected data have been used for the training of an AI network in order to detect significant respiratory patterns.

Methods

Before developing the application, a first validation phase was carried out by comparing the measurements from the smartphone-embedded sensors with standalone IMUs. Five different positions were defined and tested, with two smartphone orientations for a total of ten configurations. The application was developed for the Android operative system. The application was programmed to be interfaced with a wearable pulse oximeter via bluetooth protocol. Additionally, the possibility to associate a set of POCUS ecographic acquisitions to each monitored case was given. The developed app was then distributed to a population of 100 healthy volunteers and 80 post-intervention patients who underwent cardiovascular/oncological chest surgery. A sample of population was also given a POCUS device. To evaluate its usability, the user was asked to give a score from 1 to 5 (best score). The signals were then stored in a database and fed as input to an AI neural network to determine differences between in terms of respiratory patterns.

Results

The validation revealed that both smartphone-embedded sensors and standalone IMUs have revealed the same performances in terms of measured range (Figure 1 a), except for vertically-oriented configurations, which produced artifacts. The application was successfully developed (Figure 1 b) and distributed to the users, producing a mean usability score of 4.25, to gather the data for the AI network.

Discussion and Conclusion

The current work demonstrates the successful validation and development of a smartphone application for respiratory dynamics recording. The workflow of monitoring was correctly validated to gather a significant population patient data.

References


Acknowledgements

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OSTEOINDUCITIVE SCAFFOLD DESIGN: DIGITAL OPTIMISATION AND PREVENTION OF OVER-SPECIALISATION

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Background

There is a compelling argument in favour of designing bone tissue engineering (BTE) scaffolds that can promote bone formation by carefully stimulating the mechanotransduction processes of osteogenic cells. However, current BTE techniques often fail to accurately predict, control and understand the local mechanical environment within the scaffold. Research has shown that scaffold design parameters, such as stiffness, pore size and pore shape are crucial for tissue growth [1], but most designs still neglect the considerable heterogeneity and inter-subject variability of native bone architecture. Furthermore, scaffold design typically relies on trial and error methods, which are costly and time-consuming. In this study we developed a digital parametric design tool that automatically generates heterogeneous scaffold structures with optimised local mechanical properties and porosity for user-specified objectives. We established a proof-of-concept for this novel tool via evaluation of the computational models and procedures, fabrication through a light-based 3D printing method, and characterisation of the 3D printed designs.

Methods

The design tool was implemented in C# as a plugin to the 3D modelling software Rhinoceros 3D and its algorithmic modelling platform Grasshopper. This plugin supports automatic cellular topology generation within arbitrary closed shapes and optimisation of individual strut thicknesses to meet both local strain and porosity targets under a specified load case, building on a heuristic strain-based optimisation algorithm derived by the authors [2]. The capabilities of this design framework were assessed in-silico and in-vitro for uniaxial compression by comparing the resulting optimized designs with controls, defined as homogeneous scaffolds with same outer shape and same mass as the optimized designs. Finite Element (FE) analyses were run in Abaqus to simulate material (stable stress) and structural (buckling) scaffold failure. Finally, designed models were manufactured in a photocurable acrylic resin using direct light processing, and mechanically tested under compression loading. The influence of added material or stochastic noise in geometry definition, onto structural failure was studied.

Results

All 3D printed scaffolds had good resolution. The optimised scaffolds presented higher stiffness and material failure loads under compression compared to controls. In contrast, the optimised scaffolds presented a lower structural failure load compared to controls. The FE models accurately predicted stiffness and failure load of the samples. Additionally, the models were able to accurately predict global buckling deformation under compression (Figure 1). The optimised scaffolds presented a substantially narrower strain range around the set target compared to controls.

![Figure 1: (a) In-silico and (b) in-vitro buckling of a cylindrical lattice scaffold under vertical compression. Colour scales refer to lateral displacement (mm).](image)

Addition of material in the transverse direction, as well as introduction of stochastic noise in the optimised scaffold geometry definition, increased the structural failure load while maintaining high porosity.

Conclusion

We developed and evaluated a scaffold design tool that automatically generates heterogeneous geometries tailored to user-defined deformation targets for stimulating bone cells. This tool is publicly available (link in Acknowledgements). The results showed that design optimisation based solely on stable material deformation analysis produces geometries that are more susceptible to structural failure than the non-specialized controls. However, the design optimisation framework presented here allows for the integration of mitigation features to prevent these risks of ‘over-specialisation’.

References


Acknowledgements

This work was partly supported by a postdoctoral fellowship grant from FWO. The tool discussed here is publicly available on the official Grasshopper website (https://www.food4rhino.com/en/app/digitalis3d).
Background and objectives
Bone metastases (BMs) are among the most debilitating complications for cancer patients. They are associated with poor prognosis and are often incurable. BMs develop through cancer-induced perturbation of the inherent bone remodelling process, which is responsible for healthy bone integrity through balanced resorption of old/damaged bone and formation of new tissue. Osteolytic BMs interfere with this balance in a vicious cycle whereby cancer cells favour bone resorption. Growth factors are released from the degraded matrix and enhance tumour growth, which in turn intensifies bone resorption. Mechanical loading naturally induces an opposite shift to the remodelling balance by stimulating bone apposition. Early in-vitro and in-vivo experiments suggest a therapeutic potential for mechanical stimulation against metastases in bone [1]. We developed a computational model of load-induced bone remodelling in the context of cancerous metastases, in order to screen for loading regimens with potential therapeutic benefits.

Methods
A hybrid cellular automaton (HCA) framework was implemented in FEniCSx. Cellular events (proliferation, differentiation, migration) were modelled using a cellular automaton on a regular 3D grid of 10 micrometer resolution. In parallel, a partial differential equation (PDE) problem was defined to solve for the local mechanical environment in response to external loading, based on a variational formulation of the equilibrium, constitutive, and stress-displacements equations. Another PDE problem was defined to represent the diffusion of osteoprotegerin (OPG), receptor activator of NF-κB ligand (RANKL), and parathyroid hormone-related protein (PTHrP) signals. The PDEs were solved using Finite Element solvers on linear elements with a mesh resolution of around 5 micrometers. Osteogenic cell secretion of OPG increased in response to increased strain, and decreased in response to PTHrP signals.

As a proof-of-concept, this model was tested for a sample of 20*20*20 cellular automaton grid, taken to represent an in-vitro experiment wherein cells would be seeded in a gel-type 3D carrier with no extra-cellar matrix (ECM) initially present. A 30% density of healthy cells was considered. Three scenarios were tested and compared: Healthy bone (only healthy cells were seeded), Metastatic bone (cancer cells were also seeded at a 20% density), and Loaded metastatic bone (cancer cells were seeded at 20% density and sideways loading was applied to the carrier).

Results
The concentration of osteogenic signal (relative concentration of OPG versus RANKL) dropped in the presence of cancer cells (Fig. 1). The signal was partially restored when loading was applied to the healthy + cancer cell co-culture. Mirroring these observations, the level of ECM deposition in the presence of cancer cells was lower than in a healthy culture. The level of ECM deposition in the metastatic culture was substantially increased when loading was applied. These qualitative predictions are consistent with the general observations reported in experimental BMs studies involving mechanical stimulation [1,2].

Discussion & Conclusions
We have developed an HCA framework to facilitate investigations into the development of bone metastases and the influence of mechanical stimulation. In-vitro protocols are being developed to validate it. The validated model will be used to identify potential therapeutic regimens of loading.

References

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This work was supported by a postdoctoral fellowship grant from FWO.
ASSISTING CLINICAL DECISION-MAKING BY PREDICTING TREATMENT RESPONSE FOR PAEDIATRIC MOVEMENT DISORDERS

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Introduction
Paediatric movement disorders, like cerebral palsy, often negatively impact walking behaviour. Although clinical gait analysis is usually performed to guide treatment decisions [1], not all respond positively to their assigned treatment [2]. Identifying these individuals based on their pre-treatment characteristics could alert clinicians and allow them to possibly adapt to a more personalized intervention. This study therefore presents an approach for identifying patients at risk of negative treatment outcomes. To automate this process, we applied a standard machine learning approach to standardly collected pre-treatment gait and anthropometric features.

Methods
Observational data of 119 patients with movement disorders were retrospectively extracted from a local clinical database, comprising sagittal joint angles and spatiotemporal parameters, derived from motion capture data pre- and post-treatment (physiotherapy, orthosis, botulin toxin injections, or surgery). Participants were labelled based on their change in gait profile score (GPS, worsened vs. maintained/improved ∆1.6°, [3]). Their pre-treatment features (sagittal joint angles, spatiotemporal parameters, anthropometrics) were used to train a linear support vector machine (SVM) classifier with 5-fold cross-validation and Bayesian optimization, within MATLAB Classification Learner App.

Results
28 out of 119 patients, worsened their GPS after receiving standard treatment, while 91 showed no change or improved. No significant differences in sex, age, height, weight, diagnosis, treatment, or pre-treatment GPS were present between those who worsened and those who maintained/improved their GPS (t or fisher exact test p>0.05). Those who worsened, increased their GPS from 10.7±3.1 to 13.0±3.5, while the others reduced their GPS from 12.4±5.0 to 10.8±3.3. An average accuracy of 88.2±0.5% was obtained, with a 96.0±0.9% true positive rate for identifying those at risk of worsening their gait and an area under the curve of 88.0±1.0% (Figure 1, Table 1).

Discussion
Overall, a classical machine learning model was able to identify patients at risk of worsening their gait after treatment, based on routinely collected gait features and anthropometrics. The output of such a model could function as a method for notifying clinicians that a certain individual might not respond well to the standard of care and a more personalized intervention might be needed.

References

Acknowledgements
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INFLUENCE OF CERVICAL TOTAL DISC REPLACEMENT ON MOTION IN THE TARGET SEGMENTS AND ADJACENT SEGMENTS

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Introduction

In contrast to cervical discectomy and fusion, total disc replacement (TDR) aims at preserving the motion at the treated vertebral level, thereby sparing the adjacent segments. Two-level TDR in particular is not sufficiently investigated yet. Therefore, the aim of this in-vitro study was to investigate the range of motion (ROM) of the cervical spine after one-level and two-level TDR in the target segments as well as the adjacent segments.

Methods

TDR was performed on seven fresh frozen human cervical spine specimens (C4-T1, mean age 40 ± 17 years) first one-level at C5-6 and then extended one level further caudal (C5-7). In the intact state and after each implantation the ROM of the specimens was evaluated. Each specimen was quasistatically loaded with pure moments up to 1.5 Nm in flexion/extension (FE), lateral bending (LB) and axial rotation (AR) in a universal spine tester for 3.5 cycles at 1 °/s. Motion tracking was performed for each vertebral body individually to determine the ROM of each spinal level. Statistical analysis was performed using a Friedman-test and post-hoc correction with Dunn-Bonferroni-tests (p < 0.05).

Results

In FE, one-level TDR (C5-6) moderately increased the ROM in all four segments, but only significantly at the cranially adjacent segment C4-5 (Fig. 1 A). Additional TDR at C6-7 further increased the ROM at the target segment (p = 0.054) but did not influence the other segments.

In LB, one-level TDR decreased the ROM at the target segment C5-6 significantly, without influencing the other segments (Fig. 1 B). Extending TDR to C6-7 decreased ROM in the target segment again but did not affect the adjacent segments.

In AR, one-level TDR at C5-6 decreased the ROM at the target segment (p > 0.05) while ROM at the caudally adjacent segment C6-7 was increased (Fig. 1 C). Additional TDR at C6-7 did not further affect the ROM. At both segments C4-5 and C7-T1, the ROM was not affected by TDR at all.

Discussion

The motion preservation capabilities in FE as well as the reduction of motion in LB and AR are in line with previous studies of the adjacent segments is not regularly reported. In FE, even one-level TDR results in increased motion not only in the target segment but also the adjacent segments. During the ventral approach and the decompression of the spinal canal the anterior longitudinal ligament, major parts of the ventral annulus and the posterior longitudinal ligament at the target level are dissected. This seems to have a motion increasing effect spanning several segments during FE loading but does not show a clear influence in LB and AR.

Figure 1: Median range of motion (ROM) and neutral zone of each motion segment during FE (A), LB (B) and AR (C). Errors bars represent range of ROM. Significant differences (p < 0.05) in ROM are denoted with an asterisk.

Acknowledgements

This work was funded by Centinel Spine LLC, West Chester, Pennsylvania, USA.
Introduction

Bone is well known for its ability to tolerate and repair damage. Damage propagation is hampered by several toughening mechanisms at different length scales, providing high strength and toughness. Damage repair is enabled by bone remodeling, which relies on an intricate multiscale porosity to house blood vessels and osteocytes with their processes. In cortical bone, blood vessels are accommodated in the central canals of osteons, and surrounded by several concentric layers of bone lamellae. Osteons are usually bordered by thin interphases called cement lines, which are believed to interact with damage by crack deflection. Because composition and mechanical properties of cement lines are not well known, the interplay between cement line properties and damage propagation is usually explored with computer models [1]. In our study, we use computational modeling combined with multimaterial 3D printing to investigate damage behavior of osteon-inspired systems, with the specific aim to understand how damage could be deflected or trapped inside the cement line (CL).

Methods

We designed 2D osteon inspired systems featuring a central hole (Haversian canal), a circular interlayer (cement line) and a homogenous matrix containing a notch, with scaled-up dimensions compatible with 3D printing (Fig. 1A). A damage-based finite element (FE) analysis, previously used to model damage in lamellar bone [2], was used. The model assumes that a critical equivalent plastic strain is needed to initiate damage and that damage evolution is controlled by a specific energy. Increasing damage decreases material stiffness and strength. We systematically varied the initial notch position with respect to the hole as well as CL material properties (stiffness and yield stress) keeping matrix properties constant. After finding the critical notch position that causes a crack to reach the hole, we introduced the CL around the hole and we investigated damage behaviour. Specifically, we determined the contrast in material properties (defined as material contrast) between matrix and CL, which was needed to influence damage pattern at different notch positions. For each scenario, small perturbations in the notch position were considered. We then used 3D polyjet printing to prototype selected models with interlayers printed using different materials than the matrix. The models were tested under mechanical conditions representable of the FE simulations.

Results

Different damage patterns were observed depending on CL properties and notch position (Fig. 1B): damage crossed the CL and either reached the hole or went straight, damage was trapped inside the CL or damage was deflected along the matrix-CL interface. In the two last cases, the hole was shielded. Decreasing CL stiffness and yield strength trapped damage inside the CL, whereas increasing both parameters led to damage deflection. The variation in material properties required to deflect damage was always higher than the one needed to capture damage (Fig 2). When damage met the CL at decreasing angles, the required material contrast decreased. The 3D printed samples had a qualitatively similar damaging behavior.

Discussion

Our results indicate that a thin interlayer can have a large influence on damage propagation. Trapping damage into the CL is less challenging than deflecting it. Cracks meeting the CL at high incidence angles may require a quite large increase in material property to be deflected (up to 3.5) which is probably challenging to be obtained in bone. This work also shows that 3D-printed synthetic materials can benefit from strategies used by bone to increase damage tolerance.

References

QUANTIFYING CELL FORCES EXERTED BY CHONDROCYTES IN THE CONTEXT OF OSTEOARTHRITIS

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Introduction

Osteoarthritis (OA) is the most common chronic joint disease. During disease progression, cartilage degeneration occurs, with associated changes in all other joint tissues. To date, OA is the leading cause of disability among elderly, and no known cure or proven strategy exists for reducing progression from early to end-stage OA. OA progression affects the function of integrins, focal adhesion proteins, which impairs the ability of cells to generate forces and interact with the extracellular matrix (ECM). Cellular forces are therefore an important indicator of disease progression. The Wnt signalling pathway is a key regulator and activator of cellular and molecular processes during the development of OA. During the course of OA, this pathway has been shown to be abnormally activated or suppressed [1], and the GSK3 inhibitor CHIR99021 (CHIR) may be used to promote its activation [2]. This study investigates the cellular forces generated in healthy and in CHIR-treated chondrocytes, as a chemical model of Wnt-hyperactivation, as previously reported in OA primary chondrocytes.

Methods

Traction Force Microscopy (TFM) is the most well-known method for calculating cellular forces in both 2D and 3D. In the past years, the Van Oosterwyck group has developed experimental procedures and computational algorithms for 3D time lapse TFM allowing the quantification of traction maps around cells embedded in an ECM-mimicking hydrogel [3, 4]. TFM infers cell-generated forces (tractions) from the measurement of hydrogel deformation combined with its mechanical (elastic) properties. In this work, TFM is applied to study force generation by chondrocytes in both 2D (using collagen-coated PAA substrate) and 3D (using RGD-functionalized PEG hydrogel) cases.

Results

To the best of our knowledge, for the first time the use of 3D TFM on chondrocytes has been shown. The 2D case is also being studied and compared with previously published data from the literature. Chondrocytes pull on the ECM in both 2D and 3D environments, as indicated by displacement vectors pointing towards the cell center. Preliminary results show a decrease in cell-generated tractions from 74±23 Pa to 61±10 Pa (n=3) in CHIR-treated chondrocytes. These results validate the use of these in vitro systems as platforms for further study of the OA impact on cellular force generation.

Discussion

The hypothesis that OA-chondrocytes generate lower tractions than healthy cells seems to be confirmed in our preliminary data based on the C28/I2 cell line. With the experimental and computational workflow here described, in follow-up experiments we will expand this analysis to primary human OA and non OA cells, where more profound PCM generation is expected.

References


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Optical Coherence Tomography Based Microelastography for Biomechanical Assessment of Natural and Artificial Cartilage

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Introduction

Osteoarthritis (OA) is the most common chronic joint disease. During disease progression, cartilage degeneration occurs, with associated changes in all other joint tissues. To date, OA is the leading cause of disability among elderly, and no known cure or proven strategy exists for reducing progression from early to end-stage OA. Mechanical loading plays a crucial role in cartilage homeostasis. By adjusting metabolic activity in response to joint loading changes, chondrocytes preserve the extracellular matrix (ECM) balance and maintain cartilage mechanical properties. However, early OA disrupts these processes and jeopardizes cartilage stability. The response of OA-impacted chondrocytes to loading remains an underexplored subject. This work describes the development of a technique for using Optical Coherence Tomography (OCT) in combination with controlled loading to extract spatially resolved information about the mechanical properties of a sample, namely cartilage and cell-seeded hydrogel.

Methods

OCT is based on the principle of low-coherence interferometry, using reflected or backscattered light reflected from a sample to study its optical structure. Having the central wavelength typically within near-infrared range, it achieves an imaging depth of several millimeters, which makes it convenient for cartilage explants. This non-invasive method can provide a spatial resolution in the 1-100 μm range and has various imaging advantages, including high-speed 3D imaging of optically turbid materials and in vivo capabilities. OCT is also highly sensitive to tissue motion: axial sample displacements less than 1 nm cause measurable changes in the phase of the complex OCT signal [1]. In this work, we have used phase-sensitive spectral domain OCT, as opposed to the common amplitude-based OCT application. First, raw phase information was obtained for every 2D OCT image. After moderate smoothing of the complex pixel values, phase difference values were converted into displacements, from which the axial strain map was then calculated by taking the spatial derivative in the depth direction. By simultaneously measuring the uniform force applied and the contact area, the elastic modulus map of the sample was obtained. The force value was derived from the deformation of a reference layer of known stiffness sandwiched together with the specimen of interest between an optical window and the movable piston that was used to impose deformations.

Results and discussion

The OCT based elastography approach was applied to natural cartilage as well as to hydrogel filled with cartilage cells, chondrocytes. These cells create a local pericellular matrix (PCM) area [2] that influences the global mechanical properties of the entire hydrogel system. With this preliminary results we were able to create elastic modulus maps with an uncertainty about ±20% for a spatial resolution of 50 μm. The approach was validated using finite element simulations in Abaqus as well as calculations based on singular value decomposition. The next step will be to combine the method with protein expression analysis to study both mechanical and metabolic changes in healthy and OA chondrocytes to understand their impact on the chondrocyte mechanical environment.

References


Acknowledgements

The authors gratefully acknowledge financial support from KU Leuven (IDN/20/019 project Rehab-4-earlyOA).
EFFECTS OF AN ACTIVE BACK-SUPPORTING EXOSKELETON ON KINEMATICS DURING LIFTING AND CARRYING LOADS

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Introduction
Exposure to ergonomic risk factors is one of the major occupational safety and health problems today. Repeated exposure to awkward postures and/or repetitive manual tasks can lead to work-related musculoskeletal disorders. Complaints in the neck and shoulder region and especially in the lower back are common among workers in manufacturing and logistics [1]. For several years, there has been growing interest in the use of active exoskeletons as a supportive ergonomic measure to control and reduce exposure to risk factors of work-related musculoskeletal disorders. There is evidence of the effects of back-supporting exoskeletons on kinematics and muscle activity during lifting and carrying external loads [2, 3]. However, there are few studies that explore the effect of active back-supporting exoskeletons on walking, as the most important secondary activity. The aim of this study was to analyze the effect of an active exoskeleton on kinematics for both lifting and carrying loads.

Methods
Ten healthy male volunteers (age: 41 years ± 12, height: 180 cm ± 6, weight: 81 kg ± 11) performed six gait cycles each with and without the use of an active exoskeleton (Cray X 5th generation, German Bionic Systems, Augsburg, Germany) for three different load scenarios (no additional weight, 5 kg, 15 kg). In addition, lifting tasks from the floor to pelvic height were performed (external load 5 kg, 15 kg). Kinematic parameters were determined using an eight camera marker-based Vicon system and an extended plug-in gait marker model (40 reflective markers). In addition to knee, hip joint and spinal angles, spatiotemporal parameters were determined for analysis of gait pattern and lifting times for more detailed study of lifting.

The paired t-test was used for statistical analysis.

Results
Overall, carrying tasks with exoskeleton showed significantly reduced gait velocity (Table 1). The joint angles studied tended to show a slightly lower range of motion during exoskeleton use in both the stance phase and swing phase (p > 0.05). Significantly lower range of motion were found for spinal rotation and lateral flexion (p < 0.01). The spine showed a slightly increased extension when using the exoskeleton.

Discussion
Use of the exoskeleton caused minor changes in lower limb kinematics during walking. Reduced gait speed may be attributed to the exoskeleton's own weight. During the lifting task, two different movement strategies could be observed. Grasping the weight on the ground occurred without exoskeleton primarily by flexion of the spine and with exoskeleton by means of flexion in the hip joint. In a next step, the influence of the exoskeleton on muscle activity during walking and lifting will be investigated which could be further applied for comparisons of muscle control.

References
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Acknowledgements
We thank German Bionic Systems for providing the exoskeleton.

<table>
<thead>
<tr>
<th>Gait velocity</th>
<th>No Exo</th>
<th>With Exo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.33 ± 0.13</td>
<td>1.12 ± 0.14</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>5 kg</td>
<td>1.38 ± 0.13</td>
<td>1.18 ± 0.14</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>15 kg</td>
<td>1.43 ± 0.13</td>
<td>1.24 ± 0.14</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Table 1: Gait velocity [m/s] with and without exoskeleton (Exo) in different weight conditions.

<table>
<thead>
<tr>
<th>Joint angle</th>
<th>No Exo</th>
<th>With Exo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip: 5 kg</td>
<td>85 ± 9</td>
<td>106 ± 11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Hip: 15 kg</td>
<td>89 ± 9</td>
<td>110 ± 10</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Spine: 5 kg</td>
<td>26 ± 10</td>
<td>-3 ± 11</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Spine 15 kg</td>
<td>25 ± 10</td>
<td>-3 ± 10</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Table 2: Joint angles [°] with and without exoskeleton (Exo) when grasping the weight under different weight conditions.
EFFECTS OF SHEAR STRESS-INDUCED THROMBUS BREAKDOWN ON THROMBOSIS IN AORTIC DISSECTION

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Introduction
False lumen (FL) thrombosis is a key factor in assessing prognosis in type B aortic dissection (TBAD) patients. Several computational models have been developed to predict thrombus formation and growth in TBAD [1,2]. Thrombosis is a complex and dynamic process involving both thrombus formation and breakdown which can occur simultaneously. While most existing models consider the role of low shear stress in the initiation and growth of thrombus, they often ignore the effect of thrombus breakdown induced by high shear stress. In this study, a new shear stress-induced thrombus breakdown function is proposed and implemented in our previous thrombosis model [1]. The performance of the refined model is assessed by comparing predicted thrombosis in a TBAD geometry with follow-up CT scans. The effect of thrombus breakdown on thrombus growth is also quantified.

Method
A new parameter τ is introduced into the thrombosis model to account for local shear stress experienced by each thrombus element, defined in Equation 1. Thrombosis is represented by the variable bound platelets (BP) and governed by Equation 2.

\[
\tau = \frac{1}{6} \sum (\sigma_{ii} - \sigma_{jj})^2 + \sigma_{ij}^2, i = x, y, z \quad (1)
\]

\[
\frac{\partial \text{BP}}{\partial t} = K_{\text{BP}} \phi_i \phi_H \phi_j \text{[AP]}
\]

\[
-K_{\text{breakdown}} \phi_{\text{BP}} \frac{\tau_{\text{local}}}{\tau_{\text{local}} + \tau_{\text{breakdown}}} \quad (2)
\]

Where τ is the total scalar shear stress calculated based on the stress tensor (σ), \(K_{\text{BP}}\) is a kinetic constant accounting for thrombus growth (12 s\(^{-1}\)), \(\phi_i\) is a switching function used to turn on and off thrombosis depending on the local concentration of each variable (coagulant, shear rate and residence time), \(K_{\text{breakdown}}\) is the rate of thrombus breakdown (300 s\(^{-1}\)), and \(\tau_{\text{breakdown}}\) is the shear stress threshold (0.3 Pa). Compared to our original model, the new model allows formed thrombus to detach when \(\tau_{\text{local}}\) exceeds \(\tau_{\text{breakdown}}\).

The refined thrombus model was applied to a patient-specific TBAD model (Figure 1A) – a computational mesh was generated in ICEM (v21.2). Simulations were performed using Ansys CFX (v21.2) and were run until thrombus volume plateaued. Blood was treated as a non-Newtonian fluid described by the Bird-Carreau model. A pulsatile waveform was applied at the inlet, with 3-element Windkessel models at each outlet [1].

Results
As shown in Figure 1, locations of thrombus formation predicted by the refined model matched the 3-year follow-up geometry better than the original model which did not account for thrombus breakdown. At location 1, the FL above the right renal artery was completely thrombosed, which was captured by the refined model. At location 2, partial thrombosis in the FL was captured by both models, but the original model overpredicted thrombus growth. Figure 2 shows change in thrombus volume as a function of simulation time. Improvements were achieved in both computational time and final predicted volume.

Discussion
This study shows the influence of shear stress-induced thrombus breakdown on predicted thrombus growth in a patient-specific TBAD. Comparisons with the follow-up CT scan and original model prediction demonstrated that accounting for thrombus breakdown not only improved the accuracy of predicted thrombus, but also reduced computational time by stabilising growth more quickly. The refined thrombosis model can replace our previous model for future patient-specific applications.

References
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INVESTIGATION OF SUBCLINICAL HEMOLYSIS IN AORTIC VALVE STENOSIS USING 4D FLOW MRI-BASED CFD SIMULATIONS

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Introduction
Subclinical hemolysis, release of hemoglobin without the destruction of the red blood cell (RBC) membrane, has been observed in patients with aortic stenosis (AS). Elevated cell-free hemoglobin levels impair nitric oxide bioavailability and promote endothelial dysfunction. Pathological post-valvular blood flow patterns are supposed to induce RBC damage. However, the location of the highest fluid stresses still remains unclear. In this study, we aimed to elucidate the origin of subclinical hemolysis based on in vivo flow measurements through 4D Magnetic Resonance Imaging (4D Flow MRI) and Computational Fluid Dynamics (CFD).

Methods
A computational model of an AS patient aortic geometry was created using medical imaging data. Temporally and spatially resolved boundary conditions taken from 4D Flow MRI measurements were implemented, see left side of Figure 1. A Non-Newtonian fluid model and two turbulent flow models (Reynolds-averaged k-ω SST and scale resolving SBES) were compared. A quantitative comparison between 4D Flow MRI and CFD was performed. Then, the CFD model was used to determine the location and time of highest flow-induced stresses and the role of turbulent flow characteristics.

Results
The overall feasibility of the 4D Flow MRI-based CFD simulation was proven with good agreement between the two velocity data sets and an R² of 0.79 (p<0.001) in a transversal plane of the ascending aorta, see Figure 1 right. Detailed Bland-Altman analysis revealed that the CFD results systematically underestimate the flow velocities when compared to MRI measurements with a bias of approximately 60 mm/s.

Discussion
In summary, a methodology to generate a 4D Flow MRI-based numerical fluid simulation model of AS flow within the aortic arch was developed and validated. Turbulent flow features within the free stream of the ascending aortic jet have been identified as the most prominent contributors towards RBC damage and the onset of subclinical hemolysis. Future work will validate the results in a higher number of patients and the load on the aortic valve caused by the deteriorated flow structures.

Acknowledgements
This study was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) TRR259.
VALIDATION OF A METHOD OF LOCATING THE PELVIS AND SPINAL JOINT POSITION IN A SEATED POSITION

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Introduction

To locate the pelvis and spinal joint position accurately in a seated posture is required for biomechanical investigation of seating comfort and safety. However, due to very limited number of the anatomical landmarks (ALs) than one can palpate in a seated position, existing methods based on ALs [1] are not applicable. In the present work, we propose a method consisting of two steps: 1) defining a personalized pelvis and spine kinematic model from a 3D surface body scan in a standing posture, 2) repositioning the kinematic model in a seated position with the ALs that can be easily obtained. The objective of this paper is to validate the proposed method using the MRI scans in four postures (including a standing and a seated one) for three females and six males obtained in [2].

Methods

The pelvis and spine are modeled as a kinematic chain, which is composed of 18 segments and articulated by a spherical joint. To define a personalized model, individual segment lengths are estimated using the PCA based method proposed in [3] from an external trunk shape. To estimate pelvis segment dimension, the statistical regression equations proposed in [4] are used with the anterior and posterior iliac spines (ASIS and PSIS) and pubic symphysis (PS) as inputs. The personalized kinematic model is then repositioned in a desired seated posture, characterized by \( N \) joint angles \( (q_j, j = 1, N) \), by minimizing the distance between \( M \) model-based \( (x_i, i = 1, M) \) and target palpable ALs \( (\bar{x}_i, i = 1, M) \) while keeping close to a reference posture \( (\bar{q}_j, j = 1, N) \):

\[
f = \sum_{i=1}^{M} w_i (x_i - \bar{x}_i)^2 + \sum_{j=1}^{N} v_j (q_j - \bar{q}_j)^2
\]

where \( w_i, v_j, \) and \( w_g \) are weighting coefficients.

In [2] the 3D external trunk shape and bone surfaces were reconstructed from the MRI scans, allowing the definition of the anatomical landmarks as well as intersegmental joint centers. For each subject, the external trunk shape and skin points closest to the target ALs in the standing posture were used to define the personalized kinematic model, and corresponding local coordinates of the ASIS and posterior iliac spines (PSIS) and pubic symphysis (PS) as inputs. The personalized kinematic model from a 3D surface body scan in a standing posture is required for biomechanical investigation of seating comfort and safety.

Results and Discussion

The prediction errors were on average 14.3, 17.5, and 14.2 mm respectively for the mean seating, standing and zero postures used as reference for optimization (Table 1). Better prediction was obtained with the seated posture as reference for the pelvis and lumbar joints as illustrated for one subject (Figure 1).

Acknowledgements

This study received funding from the SURCA French project.
ELUCIDATING THE LONGITUDINAL IMPACT OF SOLID MECHANICS ON Atherosclerotic Plaque in Real Coronary Arteries

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1) University of Texas at Dallas - Department of Bioengineering, United States

Introduction

In 2020 the CDC reported that 20% of deaths were attributed to cardiovascular disease (CVD) from 1999-2020 [1], [2]. In particular, coronary artery disease (CAD) accounted for roughly 55% of CVD-attributed deaths in 2020 alone, making it the leading cause of death across all CVD [2]. CAD is characterized by the formation of a fatty plaque within the walls of coronary arteries. It is known that flow-dependent low wall shear stress (WSS) contributes to plaque growth via increased inflammation [3], leukocyte infiltration [4], and low-density lipoprotein transport into the wall [5]. What is less known is how solid mechanics within the lesion impact plaque growth. Herein we investigated this relationship using longitudinal patient data and in-silico modeling to identify correlations between biomechanics and morphological features of plaque remodeling. The outcomes of this work will enhance our understanding of mechanics-driven plaque growth with implications in personalized treatment to minimize disease progression.

Methods

Currently, virtual histology intravascular ultrasound (VH-IVUS) is utilized to diagnose plaque severity and identify compositional features. We recently developed an automated meshing algorithm that uses VH-IVUS images to generate 3D volumetric meshes of coronary arteries for finite element analysis (FEA) [6]. We applied this meshing algorithm to a 16-patient dataset of paired baseline (BL) and 6-month follow-up (FU) VH-IVUS images. Quadratic tet10 elements with mean edge lengths of roughly 0.2mm were utilized with nonlinear Neo-Hookean material models. Material properties were literature derived and luminal surface pressure was patient specific. FEA was performed using FEBio and mean elemental effective stress and strain corresponding to each pair of BL and FU images was calculated. A separate script extracted image-derived features from each pair of BL and FU VH-IVUS images [Figure 1].

Results

Preliminary results using 13 of the 16 patient datasets (n = 842 images) suggest that larger changes in plaque area between BL and FU occur at low-mid eff. stresses whereas smaller changes in surface area occur at mid-high eff. stresses [Figure 2].

Discussion

Our preliminary results corroborate the work by Samady et al. who found that low WSS corresponded with increased plaque volume [7]. It is thought that endothelial cells lining the lumen must be in a constant state of motion to maintain healthy cell-cell connections between them and minimize transport of leukocytes or LDL into the wall. Smooth muscle cells (SMCs) inside the artery wall are similarly impacted by lower stresses, as seen during in-vivo experiments where SMCs in low stretch conditions (0-10%) proliferated less than those in large stretch conditions [8]. Further investigation is needed to quantify these relationships, but initial results point toward a mechanobiological remodeling paradigm driven by the mechanical forces felt at the cellular level.

Acknowledgments

This work was supported by funding from the AHA and the National Heart, Lung, And Blood Institute of the NIH. We thank Emory University (ClinicalTrials.gov; NCT00576576) for the data set used in this study.

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Figure 2. Mechanically mediated changes in plaque area. Results for the global dataset, y-axis: effective stress in kPa, x-axis: change in area in mm².
EFFECT OF FACET JOINT DEGENERATION ON SPINAL UNIT BIOMECHANICS

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Introduction

Facet joints contribute to the motion and stability of the spine. They are small cartilaginous synovial joints and with ageing, present with osteoarthritis [1]. While of importance in assessing the effect of spinal treatments, they are understudied and the mechanical effect of their degeneration is not well understood [2]. In this study, we used imaging and computational modelling data to assess the effect of different features of facet joint degeneration: cartilage thinning, joint calcification and changes in synovial fluid lubrication.

Method

First and following ethical approval, donated human posterior elements of the lumbar spine were imaged with HR-pQCT at an isotropic resolution of 44 microns. A total of 16 posterior elements from 5 spines (ages 42 to 83) were imaged. The images were segmented to isolate the cartilage by direct thresholding and semi-manual correction, computing the cartilage thickness, volume, and the volume of the calcified regions. Then, a generic finite element model of a L3-L4 functional spinal unit (FSU) was used to assess the effect of degeneration features on the FSU apparent stiffness in axial compression, on the ratio of load going through the facet joints, and on the mean facet joint contact pressure. The model consisted of one FSU, where the bone was simplified as homogenous and linearly elastic and the disc tissues as incompressible isotropic hyperelastic materials (annulus with a Yeoh model, and nucleus with a Mooney-Rivlin model) [3]. The cartilage and contact behavior of the joint were modelled using a soft contact interaction with bi-linear pressure-overclosure representing the cartilage thickness and its modulus followed by a contact penalty. Baseline values representing a “healthy” joint were a thickness of 0.5 mm, cartilage apparent modulus of 1.6 MPa and frictionless behavior [2]. These three parameters were systematically altered to generate 13 simulations with different degeneration features: thickness decreased to minimum 0 mm; modulus increased to maximum 2.4 MPa; and friction increased to maximum 0.9. A final model of fused facet joints was developed with a rough contact and no cartilage thickness. Models were completely fixed on one side and submitted to 1 mm axial compression (free rotations) centered posterior to the vertebral body.

Results

The image analysis demonstrated that all facet joints had some degeneration, with calcification present in all joints from 1% of the cartilage volume to 40% calcification. The computational study showed that biomechanical changes in cartilage thickness alone is different to changes due to a combination of degenerative features (Fig. 1). Including the increase in calcification (through an increased apparent tissue modulus) and in friction, the stiffness of the FSU increases more than with a decrease of thickness alone, and is accompanied by a decrease of the force going through the facet joints but a larger change in contact area, leading to an increase of mean contact pressure.

Discussion

Features of facet joint degeneration with osteoarthritis (cartilage thinning and calcification) were found to occur simultaneously. When incorporating into a computational model of a generic FSU, facet joint degeneration was found to have a significant effect on the FSU biomechanics. While this computational model was not validated for each of the degeneration cases, its baseline behavior was similar to that found in the literature [4]. Combined with previous studies analyzing the effect of joint-specific anatomy on the biomechanics [1], this work demonstrated the importance of including specimen- or patient- specific information of the facet joint when assessing FSU biomechanics.

References


Acknowledgements

Authors want to thank the donors and their families. Work funded by EPSRC grant EP/W015617/1.

Figure 1: Effect degenerative features (models A to C with decrease of thickness only, D to M with combined features; model N fused) on the FSU biomechanics. Changes w.r.t. baseline “healthy” model (FJF= facet joint force, FPRESS=mean contact pressure).

28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
LOWER LIMB AMPUTEES HAVE SIMILAR UPPER LIMB FUNCTION 8Y POST INJURY AS UNINJURED GROUP: THE ADVANCE COHORT STUDY

Fraj Watson (1), Angela E Kedgley (1), Alex Bennett (2), Anthony Bull (1)

1. Imperial College London, UK; 2. The Defence Medical Rehabilitation Centre, UK

Introduction

Increased biomechanical load on the upper limb (UL), and subsequent injury has been identified in wheelchair users [1]. We hypothesised that lower limb (LL) amputees make similar biomechanical compensations with their ULs through crutch use, balance and coordination needs, transfer activities and UL bodyweight loading.

ADVANCE is a 20yr prospective cohort study collecting medical and psychosocial data from 1145 military servicemen, half of whom sustain combat injury [2]. The aims of this study are to compare UL disability, at the initial assessment (a mean of 8yrs post-injury), in (1) LL amputees with the uninjured comparison group, and (2) the full cohort.

Methods

Disability of the Arm, Shoulder, and Hand (DASH) questionnaire data was collected from ADVANCE participants frequency matched for deployment, age, and rank. DASH scores range from 0-100, with a higher score denoting more UL disability.

DASH data was non-parametric, and appropriate statistical tests were used with an alpha level of 0.05.

Results

DASH data was available and valid for 1092 participants (mean age: 34yrs). DASH was higher for injured compared to uninjured participants (p<0.001). UL amputees, triple amputees and LL amputees with partial UL amputation had higher DASH scores than uninjured controls (p<0.002) (Table 1, Figure 1).

DASH was not significantly different between unilateral or bilateral LL amputees and uninjured controls. Similarly, DASH was not significantly different for triple amputees compared to unilateral major and partial UL amputees in isolation (Table 1, Figure 1).

<table>
<thead>
<tr>
<th>Injury type</th>
<th>n</th>
<th>DASH (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninjured</td>
<td>562</td>
<td>3.6 (8.3)</td>
</tr>
<tr>
<td>Injured</td>
<td>530</td>
<td>9.7 (14.2)</td>
</tr>
<tr>
<td>Non-amputee</td>
<td>363</td>
<td>9.8 (14.1)</td>
</tr>
<tr>
<td>Unilat LL amp</td>
<td>70</td>
<td>4.4 (7.0)</td>
</tr>
<tr>
<td>Bilat LL amp</td>
<td>38</td>
<td>5.9 (11.0)</td>
</tr>
<tr>
<td>UL amp (major + partial)</td>
<td>14</td>
<td>21.7 (19.5)</td>
</tr>
<tr>
<td>Triple amp (unilat major UL)</td>
<td>12</td>
<td>13.5 (13.7)</td>
</tr>
<tr>
<td>LL amp + partial UL amp</td>
<td>32</td>
<td>17.6 (20.3)</td>
</tr>
</tbody>
</table>

Table 1: DASH scores for ADVANCE participants

*p<0.002 per Bonferroni correction.

Figure 1: Violin plots for DASH scores of ADVANCE participants (LL=lower limb, UL=upper limb, uni=unilateral, bil=bilateral).

Discussion

Contrary to our hypothesis, unilateral and bilateral LL amputees had low DASH scores, similar to the uninjured population. This finding suggests minimal UL disability 8yrs post-injury that we hypothesised might result from high reliance on the ULs. Also, triple amputees and LL amputees with partial UL amputation were no more disabled than unilateral major UL amputees in isolation, further supporting the finding that LL amputation did not increase UL disability.

As expected, injured participants had more UL disability than uninjured participants. Equally, participants with major or partial UL amputations (in isolation or in combination with a LL amputation) had higher DASH scores than those that did not.

Overall, the ADVANCE cohort have lower DASH scores than equivalent military and civilian populations [3,4]. The ADVANCE cohort is currently young, so longitudinal study of their UL disability will be of great interest, particularly for the LL amputees.

References

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Acknowledgements

We thank the whole ADVANCE team and participants. This work is funded by the ADVANCE charity.
PRIMARY STABILITY OF CEMENTLESS TIBIAL TRAYS DURING STAIR DESCENT AND DEEP KNEE BEND: A MICRO-CT AND DVC ANALYSIS

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Introduction
Primary stability, the mechanical fixation between implant and underlying bone prior to osseointegration, is crucial for the long-term success of cementless tibial trays [1]. However, experimental studies on the initial internal strains between bone and implant are limited, due to previous experimental restrictions [2]. The aim of this study was to quantify, through micro-CT and digital volume correlation (DVC) analysis, the internal strain field across five cadaveric tibiae when subjected to two time-elapsed mechanical load sequences representing stair descent (SD) and deep knee bend (DKB), everyday activities known to expose the tray to posterior loading.

Methods
Five right human cadaveric tibiae were resected and impacted with a clinically employed titanium tibial tray (Attune, DePuy Synthes) by an experienced surgeon (ethics: HREC 186.20). The tibiae were potted distally, oriented with the resected surface flat. The time-elapsed loading spanned two days, the first for SD and the second for DKB. To replicate these activities, uniaxial loads were applied to the implanted tibiae through posteriorly offset prongs, the position of which matched the average position of the femoral medial and lateral condyles on the tibial tray during each load scenario [3]. The applied loads were scaled to the body weight (BW) of each donor for sequential load steps of 0.0 (preload), 0.5, 1.0, 1.5 and 2.5BW. For DKB, the peak load was extended to 3.5BW. After 20min relaxation, a micro-CT scan was acquired at each load step at 46µm/pixel (66min scan time), resulting in 45 loaded datasets. A repeated scan of the tibia in the unloaded condition (0.0BW) was taken for zero-strain error analysis (accuracy of the DVC analysis was 434µε, precision 177µε) [2,4]. Loaded scans were rigidly co-registered to the unloaded scan in each activity and DVC was performed (DaVis v8.3.1, algorithmic masking applied to remove air, 5-step progression with a final subvolume sidelength of 1.56mm (34pixels)) [2]. The minimum principal strain component ($P_{min}$) was calculated across the entire proximal tibia, before isolating subvolumes directly under the tibial tray (Fig1a).

Results
With progressive loading, increased compression of trabecular bone directly under the tibial tray was observed across all five tibiae for the two activities. There was large strain variation across tibiae and load steps (Fig 1b), with the 90th percentile ranging from -1,693µε to -94,942µε. For both activities, the posterior region consistently had the greatest compression across all tibiae, with peak compression concentrated in the posterior-medial region for four of the five tibiae, particularly during DKB (Fig 1a). Conversely, bone in the anterior region had the lowest compression across all tibiae. For DKB, the lowest compression occurred under the anterior-medial region of the tray (Fig 1a), whilst for SD across the whole anterior portion.

Fig. 1a) DKB $P_{min}$ distribution at 3.5BW via DVC; b) $P_{min}$ frequency distribution for the five tibiae during DKB.

Discussion and Conclusion
Progressive load corresponded to increased compressive strains, quantified via DVC, with variation of the strain distribution observed across the five tibiae and the two activities. Peak compression occurred in the cancellous bone under the posterior region of the tray for both activities, with reduced compression anteriorly, consistent with migration patterns of cementless tibial trays reported in clinical studies [1]. This study provides a means to experimentally quantify the internal strain distribution of human tibiae with cementless tibial trays, thereby increasing the fundamental understanding of the mechanical interaction between bone and implant and enabling to validate finite-element models.

References

Acknowledgements
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TOWARDS INDIVIDUALIZED BIOMECHANICAL MODELS IN MULTIPLE DOMAINS

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Introduction
Musculoskeletal simulations enable the non-invasive computation of biomechanical parameters like muscle forces or joint torques from experimental data, e.g., optical motion capture and force plate data [1]. Error sources like kinematic errors (e.g. soft-tissue artifacts), modelling assumptions or inaccurate model parameters lead to less accurate and reliable calculations. Model individualization methods may be applied to minimize the dynamic error caused by modeling errors, subsequently leading to more accurate calculations [2]. Commonly, musculoskeletal models are scaled using marker point clouds [3]. However, marker-based scaling methods cannot be applied when motion capture methods are used that are not based on optoelectronic marker-tracking (e.g. IMU- or depth camera-based). Therefore, our goal is to create a simple, holistic individualization process independent of the motion capture technique used. Our individualization method comprises multiple domains (muscle strength, mobility and anthropometry) in order to achieve a model that is as representative of the person as possible. This method minimizes the model-person inconsistency and its negative effect on computed biomechanical parameters.

Methods
We are investigating the individualization of musculoskeletal models in multiple domains using a combination of manual measurements and population data [4]. Individualization of the skeletal system (segment lengths) is achieved by measuring specific individual segment lengths using simple tools (e.g. tape or calliper). Individualization of muscle parameters (e.g. optimal fiber length, muscle activation/ deactivation times, force-length - or force-velocity properties) is to be achieved by extending the population data-based strength mapping algorithm (SMA) presented in [4]. The SMA adjusts isometric muscle strength of every muscle of a model based on metadata like biological sex, age, body height and a strength percentile. The model can also be individualized further by adjusting joint rotation axes and centers. This is accomplished by computing the instantaneous center or axis of rotation of a joint using multibody kinematics.

Results
We measured motion capture data and segment lengths for one participant. Both a segment length-based (a) and a marker-based approach (b) were used to scale a generic musculoskeletal model. Exemplarily, functional height measurement (reaching ranges to the front and upwards), the body height and the inseam height were used to compare the resulting models of the two scaling methods. Figure 1 depicts the scaled models and the investigated dimensions. The body and corresponding model dimension values are listed in table 1.

![Figure 1: Scaled models (left) and investigated body dimensions (right)](image)

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Person</th>
<th>Marker-based</th>
<th>Seg. Len-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body height (BH)</td>
<td>185</td>
<td>183</td>
<td>184</td>
</tr>
<tr>
<td>Inseam height (IH)</td>
<td>87</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>Range front (RF)</td>
<td>76</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Range up (RU)</td>
<td>212</td>
<td>213</td>
<td>214</td>
</tr>
</tbody>
</table>

Table 1: Excerpt of compared body and functional dimensions [cm]

Discussion
Our results indicate that segment-length based scaling provides similar results to conventional marker-based scaling results, while both correspond well to manually measured body and functional dimensions. We will further corroborate these indications by means of a laboratory movement study in conjunction with musculoskeletal simulations. Comparison of calculated results to real world data from the measurements should provide insights into the impact of joint axis individualization on the results. At a later stage we aim to investigate which musculoskeletal parameters need to be individualized in addition to the maximum isometric muscle forces.

References

Acknowledgements
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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
A sawbone based biomechanical study to compare compression force and osseous area of contact of two screws for foot and ankle joint arthrodesis

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Introduction:

Arthrodesis of the ankle joint is commonly performed in the operative treatment of symptomatic, end stage osteoarthritis and/or acquired flatfoot deformity. One frequent complication following ankle arthrodesis is the lack of bony joint fusion (non-union). In current literature, variable union rates in ankle arthrodesis following open or arthroscopic approaches with different fixation techniques have been reported [1]. When non-union occurs, it may be due to a number of factors, including failure to obtain and maintain compression across this joint during the healing process [2]. We compared headless compression screws (HCS, DePuy Synthes, Zuchwil, Switzerland) to the IOFix device (Extremity medical, Parsippany, NJ, USA) biomechanically in regard to fusion stability/force distribution (area of contact) that is created in a sawbone arthrodesis model.

Methods:

In an arthrodesis model consisting of two customized artificial bone blocks with a density of PCF 15 (solid foam; personalized blocks; Sawbones® Pacific Research Laboratories, Vashon, WA, USA), the IOFix screws and headless compression screws were inserted pairwise parallel to each other (after pre drilling K-wirers using a template for standardized drilling pattern) with a predefined torque of 0.5 Nm, while pressure transducers (K-Scan 4000, Tekscan, Inc., Boston, MA, USA) between the two sawbone blocks were compressed for the measurement of peak compressive force and the compression distribution (contact area).

Results:

IOFix screws distributed the compressive force over significantly larger areas compared to the area of contact created by headless compression screws, showing a more uniform contact area across the arthrodesis. Peak compression force showed no significant difference.

Discussion:

The IOFix fusion system distributes compressive forces across a significantly greater surface area than HCS screws do, making the compression at arthrodesis-site more uniform.

Ideally, there is moderate compression with uniform distribution across co-apted bone-surfaces in an arthrodesis, in order to minimize stress at areas of high peak contact, as well as neutralize shear and bending forces. By avoiding uneven compression across imperfectly co-apted surfaces, areas of high peak contact stress are minimized, reducing the risk of bone resorption by osteoclasis, failure of fixation and non-union.

In current literature, there is are several studies that investigate the clinical outcome and biomechanical properties of the IOFix device on the first metatarsophalangeal joint, however, there is only one biomechanical study performed on cadaveric ankle joints by Parker et al. [3,4,5], comparing the IOFix device to a single conventional lag screw.

Literature:

COMPUTATIONAL ANALYSIS OF VENTRICULAR EXPANDER TO TREAT DIASTOLIC DYSFUNCTION

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2. Department of Bioengineering, Imperial College London, United Kingdom

Introduction
Heart failure with preserved ejection fraction (HFpEF) is a major global health condition with an increasing prevalence. Although this condition is characterized by a normal ejection fraction (above 50%), elevated left ventricular filling pressures and diastolic impairment are common [1]. Due to limited pharmacological success, cardiac devices have been developed to restore diastolic function. The CORolla is a transapical, spring-like expander that transfers energy from systole to diastole. It was tested on animal models and on only a select few patients [4,5]. Here, we present finite element analyses (FEA) of an HFpEF-induced swine for modelling device implantation in different configurations. Cardiac performance was evaluated for each scenario and compared to the preimplantation and healthy (pre-induction) configurations to determine device effectiveness and potential use [6].

Methods
A generic spring-like expander device that resembles the CORolla was modelled with dimensions that fit the subject-specific anatomy. The device is comprised of six elastic wires with six coils between them that create three “arms”. A previously developed HFpEF-induced model was chosen for the implantation. Three configurations were considered: (1) basic implantation; (2) implantation after device rotation around the long axis; and (3) the second implantation orientation but with a less stiff device material. The results were compared to the corresponding untreated and preinduction healthy configurations (Figure 1) by plotting pressure–volume curves for each scenario.

Results
A pressure reduction of up to 12% was observed following implantation. All implantations resulted in increased end diastolic volumes. A maximal increase was observed in scenario 3, where the diastolic volume was similar to the preinduction configuration (~55 mL). EF remained above 60% for all scenarios. The end-systolic pressure-volume relationship (ESPVR) was reduced after device implantation and brought closer to healthy conditions (Figure 2).

The device has facilitated an increase in diastolic average stress while having limited influence on the systolic one. Changes occurred largely in the apex region, where the coils and the LV wall were in immediate contact.

Discussion
The device has successfully increased the EDV without hindering heart contraction. The ESPVR was also improved. The EF remained within preserved values for all scenarios, demonstrating the device’s safety profile. Arm rotation and device stiffness reduction have improved device performance without diminishing the compensatory high LV pressures. The device caused an increase in stress levels during diastole, with minor effects during systole. Stress distribution was mildly altered. An optimal deployment of the device and tailoring its dimensions are essential for reducing unnecessary elevations in LV stress and improving heart performance.

References
CONTACT AREA AND CONTACT PRESSURE IN KNEE IMPLANTS: COMPARISON OF DIFFERENT TESTING AND FE METHODS
Josef-B. Weiß (1), Hanna Bächle (1), Sven Krüger (1), Thomas M. Grupp (1,2)

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Introduction
The mechanical environment of articulating surfaces has a strong effect on the long-term survival of knee implants. Therefore, the analysis of the contact area and contact pressure between the articulating components is of particular interest. The FDA [1] and ASTM F2083-21 request an investigation of the contact area and stress in the tibiofemoral and patellofemoral articulating surfaces at different flexion angles. Finite element (FE) simulations are widely used to calculate these quantities. Their credibility requires assessment in accordance to ASME V&V40-2018. The Gold standard for in vitro measurements of these quantities are pressure sensitive films (e.g., FujiFilm®) or sensors (e.g., Tekscan®). However, the contact may be affected by these films, and therefore an optical measurement can be advantageous. The aim of this study is to evaluate the variability in both in silico and in vitro methods using a ball indentation test.

Methods
Mechanical problem:
MXE (0.1 % vitamin E blended polyethylene, 30 kGy gamma sterilized) plates are idented using a Ø 32 mm CoCr hip ball at a constant velocity of 5.0 mm/min until 1 000 N is reached at room temperature (see Figure 1). In vivo: 3 methods are used to measure the contact area and pressure: FujiFilm Prescale LLLW, FujiFilm Prescale MS and a digital-image-correlation system DIC (GOM Aramis (12M sensor configuration)) based on the assumption of rigid body displacement. Six measurements were made for each method.

In silico: The numerical code verification of ANSYS Mechanical 2022R1 was performed using the ASME V&V 40 framework. Sensitivity studies were performed for key model parameters, which were given contact formulation, friction coefficient μ and UHMWPE material model based on literature (Three Network Model (TNM) [2] and two Two-segment elastic-plastic material models (TS) (based on the data of GUR 1020 VE and GUR 1020 50kGy VE [3]).

Results
The measured and simulated contact areas and pressures are listed in Table 1. Mesh convergence of 1% was achieved with a final mesh density of 0.05 mm in the contact area.

<table>
<thead>
<tr>
<th>Method</th>
<th>Contact Area ± SD in mm²</th>
<th>Max. Contact Pressure ± SD in MPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescale LLLW</td>
<td>31.7 ± 5.4</td>
<td>N/A</td>
</tr>
<tr>
<td>Prescale MS</td>
<td>20.8 ± 0.3</td>
<td>N/A</td>
</tr>
<tr>
<td>DIC</td>
<td>27.7 ± 1.2</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 1: Result summary

Discussion
The measured contact areas are strongly influenced by the method used. The contact areas measured by DIC are in the same range as those measured with pressure sensitive films. The choice of material model used has little effect on the calculated contact areas generated by FE simulations. Although material models from the literature were used, a good agreement with the experimental data was found. The contact areas and pressures are not sensitive to variations in the coefficient of friction. FujiFilm Prescale LLLW tends to overestimate the contact area because small gaps are closed, as observed by Sarwar et al. 2017 [4]. To access the credibility of FE models, DIC-based methods should be considered as they do not interfere with the contact situation. Furthermore, they also allow continuous measurements during dynamic loading scenarios.

References
COUPLING EXPERIMENTAL & SIMULATION WORKFLOW OF TREATED HUMAN TIBIA CONCERNING INTERFRAGMENTARY MOVEMENT

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2. Saarland University Hospital – Clinic for Trauma, Hand and Reconstructive Surgery, Germany

Introduction
A personalized approach to fracture therapy necessitates the integration of knowledge and techniques from mechanics, orthopedic trauma surgery and computer science. Dealing with the topic of fracture healing, one aspect is always recurring: why do some fractures not heal and what happened in the fracture gap. To widen the knowledge of interfragmentary movement (IFM) we developed and built a testing device for force driven scenarios and evaluate the local fracture gap mechanic during gait cycle.

Methods
The experiments with human tibiae from body donations were executed on the self-designed testing device. The device replicates the loading scenarios of a treated human tibia during a gait cycle (see Figure 1). The experimental workflow starts with the removal of the soft tissue and the fracture generation. An orthopaedic trauma surgeon prepared the specimens with a fracture at the diaphyseal segment using a drilling machine. The fracture is then treated with a locking plate, locking head and nonlocking screws. A computer tomography (CT) scan including a six-rod calibration phantom for bone density are made from the treated tibiae for a subsequent simulation. In addition, the specimens were equipped with a speckle pattern to evaluate the upcoming surface strains by digital image correlation (DIC). The specimens are clamped into an individual mould clamping system. To generate individualized testing scenarios, we apply motion capturing data from our own database. Therefore, patients were measured with a motion capture system from Xsens (Xsens Technology B.V., Enschede, Netherlands). The motion data is then exported to the musculoskeletal simulation system AnyBody (AnyBody Technology A/S, Aalborg, Denmark) to compute realistic joint forces and internal joint forces [1]. These results serve as personalized input data for the testing device. The force is applied longitudinally and transversely to the bone axis by using multiple of linear modules. Two six-axis force sensors are measuring the forces during the entire experiment. Four cameras making pictures of the fracture gap to evaluate the IFM with DIC. For the finite element (FE) simulation (see Figure 2), the three-dimensional model is extracted from the segmented image stack of the CT, including the greyscale-based material properties. Furthermore, the measured force values of the sensors serve as personalized boundary conditions in the FE simulation.

Results
We are able to realistically reproduce the experiments in our simulations. By using various measuring techniques, we determine forces and momentums acting on the treated tibia during gait cycle. Furthermore, we are able to map the IFM from the experiment in our simulation, which is thereby validated.

Figures

Discussion
A limitation in this workflow is the transfer of the measured patient data to the bone of the donor. Nevertheless, we are able to describe the IFM in the best possible way under realistic circumstances. Widen the knowledge of the IFM and bone-implant behaviour is important as a base of understanding the healing process.

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Acknowledgements
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STATISTICAL MODELLING OF THE PLACENTAL VASCULATURE

Pascalle Wijnjes (1,2,3), Beatrijs van der Hout-van der Jagt (2,3,4), Wouter Huberts (1,3,5), Sjeng Quicken (1), Frans van de Vosse (1,3)


Introduction

Pregnancy is a beautiful but complex experience that affects both the mother and the developing fetus. Unfortunately, around 10% of all expectant mothers face pregnancy-induced hypertension, with 3% being diagnosed with the severe condition of pre-eclampsia [1]. The cause of these complications often stems from abnormal placentaion, leading to a malfunction in the crucial role the placenta plays in nourishing and sustaining the growing fetus [2]. Clearly, a closer examination of the placenta's vasculature, hemodynamics, and function is necessary. An accurate hemodynamic model of the placenta’s vasculature has the potential to unlock new physiological knowledge that can aid in the early detection and prediction of pre-eclampsia and other pregnancy complications. However, a detailed vascular model of the feto-placental placenta is difficult to obtain in practice. In this study, we aim to create an anatomical model of the feto-placental vasculature that ultimately will be used as a basis for a hemodynamics model.

Methods

For the model of the feto-placental vasculature, the placental geometry is defined on which a space-filling algorithm is applied [3,4]. This method allows the arterial system to grow within the placental boundaries and its functional units (cotyledons) according to rules that capture statistics of real vascular trees. For cardiovascular hemodynamical simulations, a combination of a 1D pulse wave propagation model – representing the feto-placental arterial system, and 0D windkessel models for the venous system will be applied to the simulated vasculature.

Results

The modelled term placenta (see Fig. 1) realistically mimics the placental vasculature: The central cord insertion leads to a somewhat symmetric vasculature with max 8 branches on the chorionic plate, space between villus trees is present to allow maternal blood to travel past the capillary’s membrane, the umbilical arteries have a diameter of 2 mm, and the smallest vessels are at capillary level (10 microns in diameter) and the number of cotyledons are all within the physiological ranges [5]. Also, the number of vessel segments within a diameter range shows good agreement with real placental vasculature data [6]. A simulated marginal cord insertion shows a monopodial structure on the chorionic plate, as is seen for real placentae. Also, abnormalities, such as velamentous cord insertions are modelled realistically. These umbilical arteries start bifurcating before they reach the placental chorion.

Discussion

The resulting arterial vasculature has shown to be realistic. The results are verified with literature and the missing information will be validated and tuned via a clinical study at the Máxima Medical Centre, Veldhoven, the Netherlands. The model shows great potential for clinical decision support regarding the treatment and prediction of pregnancy complications. Therefore, in the nearby future, this model will be used to simulate the hemodynamics through the vasculature and allows physicians to gain insight in the problematics of several pregnancy complications.

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Acknowledgements

We acknowledge the Eindhoven MedTech Innovation Center (eMTIC, Grant PICASSO) for funding.

Figure 1: Simulated feto-placental arterial vasculature with a central cord insertion. The color gradient shows the radius in millimeters throughout the modelled vasculature.
THE EFFECT OF VARIATION IN ANATOMICAL FEATURES ON KNEE JOINT LOADING: A POPULATION-BASED MODELLING APPROACH

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2. Materialise NV, Belgium
3. Laval University, Canada

1. Introduction
Excessive mechanical knee joint loading during activities of daily living has been hypothesized to play a crucial role in the development and progression of knee osteoarthritis [1]. One important key factor that is assumed to greatly contribute to variations in mechanical knee joint loading is the variation in joint geometry [2]. Recent developments in medical imaging processing techniques allow to accurately segment various anatomical geometries, that can be integrated in highly personalised in silico musculoskeletal models. Given that MRI images have now been collected in larger clinical cohorts, datasets have become available that allow us to describe the geometrical variation. In this study, we present how population-based modelling approaches, in particular statistical shape model (SSM)-based musculoskeletal modeling, can be exploited to understand the effect of variation in anatomical shape features on knee joint loading.

2. Materials and Methods
A workflow was developed to incorporate population-specific tibiofemoral joint geometry in a musculoskeletal model with a detailed 12 DOF knee joint [3]. Anatomical geometries were adopted from an existing SSM [4], built from MRI-images of 524 patients with knee osteoarthritis. We performed a dynamic gait pattern simulation for the extremes (+/- 3 standard deviation) of each of the first seven modes of variation using a healthy control gait pattern. The healthy control gait pattern was defined using the average of 2 minutes treadmill gait data of 23 healthy subjects (age = 36.69 +/- 4.16, BMI = 23.85 +/- 3.59). Variations in peak knee contact forces (KCF) were evaluated.

3. Results
The peak knee joint loading varied largely dependent on the individual SSM mode. Maximal variations up to 0.8 BW were found for mode 3 (tibial anterior/posterior position), whereas only limited variation in joint loading was observed for mode 2 (internal/external rotational alignment). Interestingly, the first mode of variation (frontal plane alignment/ ab-adduction alignment), that explained 21.7% of variation in the tibiofemoral population geometry, resulted only in a moderate change in knee contact forces of 0.15 BW.

Figure 1: 7 modes of SSM with +/- 3 deviations on the SSM mean. Mean KCF (green), first peak KCF (blue) and second peak KCF (red) are displayed and expressed in bodyweights (BW). Dotted lines are the opposite output to highlight variation in KCF.

4. Discussion and Conclusions
Population-based approaches, such as combining a SSM with a musculoskeletal simulation workflow, allow the identification of relevant tibiofemoral joint anatomical features that explain variability in knee joint loading. Our results highlight that relative anterior-posterior position of the tibia with respect to the distal part of the femur plays a key role in knee joint loading variability between patients with different anatomy.

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Acknowledgements: Authors acknowledge financial support through Research Fund Flanders G0E4521N, 1SC9922N.
ASYMMETRY OF MOVEMENTS AS A SIGNIFICANT INDICATOR OF WORKPLACE ERGONOMICS AND WELL-BEING

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2. Wrocław University of Economics and Business, Poland

Introduction

In recent years, methods for assessing the ergonomics of movements have become more critical with the emergence of new technical developments, such as inertial systems for motion analysis. Research has indicated that workplace ergonomics assessments often overlook movement asymmetry, even though symmetrical limb moving and loading are expected to reduce the energy expenditure associated with activities such as walking and standing [1]. Asymmetry of movements has been recognised as a potential risk factor in work-related musculoskeletal disorders. However, there is a lack of evidence regarding the effectiveness of observation techniques in assessing the asymmetry of movements in the workplace. Thus, the main objective of this research is to understand the risk factors associated with the asymmetry of movements and to develop an observational technique that can be used to assess the ergonomics of movements. Additionally, we investigate the relationship between asymmetrical movements of line workers and their well-being.

Methods

This observational, retrospective study investigated the standardised working tasks involved in the manufacturing process. In addition, a survey study was carried out to assess well-being at work.

The research included 42 machining workstation employees (MWE) (41.9±9.6y, 79.9±13.6kg, 1.76 ±0.07m) working on 12 devices and 44 assembly workstation employees (AWE) (35.5±9.5y, 69.2 ±13.3kg, 1.69±0.10m) working on nine devices. An MR3 myoMuscle full-body inertial system was used to record movements during a 30-minute observation. The mobility was characterised by measuring linear accelerations, angular displacements and velocity of the main body parts, separately for the left and right sides. In addition to detailed kinematics, a Movement Activity Index is proposed based on the selected variables [2,3].

Results

<table>
<thead>
<tr>
<th>MAI [%]</th>
<th>MWE group</th>
<th>AWE group</th>
<th>p1</th>
<th>p2</th>
<th>p3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAI LT side</td>
<td>31.9±5.1</td>
<td>19.6±2.6</td>
<td>0.010</td>
<td>0.043</td>
<td></td>
</tr>
<tr>
<td>MAI RT Side</td>
<td>35.0±5.4</td>
<td>22.1±3.4</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global MAI</td>
<td>36.6±6.8</td>
<td>25.5±2.7</td>
<td>0.019</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: The results of normalised motion activity indexes. Median +/- IQR of the MAI for the left (LT) or right (RT) side or a central segment is accompanied by the significant p-values of test statistics between groups (p1) or between sides within groups (p2, p3).

Discussion and Conclusions

The MWE group appeared to be more active in terms of all measured variables related to range of motion, maximum speed or maximum acceleration. Confirmation of this can be found in the Global MAI, which was significantly higher by approximately 11% for the MWE group. The right limb in both groups showed greater involvement in the work either of assembling or machining components. The AWE group, although on average showed less activity than the MWE group, proved to be significantly asymmetric. The right limb showed an 11% increase in activity. The result suggests that repetitive movements imposed by manufacturing processes and asymmetrical positions decrease physical well-being and produce fatigue and exhaustion. Additionally, almost 74% of workers from a study sample exceeded the mean value of the “healthy sample” which implies serious problems related to poor somatic well-being, such as regular exhaustion, weakness, tiredness and aches from different parts of the body.

Movement activity index proved to be a good indicator of movements and workplace ergonomics and proved to correlate with the assessed well-being.

References

PROPOSAL OF A NEW WRIST MODEL FOR SURGICAL PLANNING: THE ADDED BENEFITS OF 3D ANALYSIS

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Introduction

3D preoperative planning surgery is increasingly used with software already available for the shoulder, knee, and hip, but not yet for the wrist. Even though some manually constructed planning models for forearm surgery exist, they are time-consuming to build, making them unsuitable for clinical practice, and they have shown their limits in terms of measurements reproducibility [1,2]. The objective of this study is to propose a 3D measurement model at the distal radius considering geometric shapes (torus) that agrees within 5° with current models obtained with point landmarking.

Methods

Forty 3D forearm models (20 healthy and 20 pathological) were used in this study. For these 40 models, radial inclination in the frontal plane and volar tilt (or dorsal tilt) in the sagittal plane were measured using two different methods. On one hand, current methods consisting of landmarking anatomical points were used to obtain the two angles. On the other hand, angles were computed based on a new 3D developed model considering the main axis of the best-fitted torus on the radiocarpal surface (Figure 1). For both methods, the same longitudinal axis was automatically estimated analyzing cross sections of the radius shaft at various locations. The agreement between the two measurement methods was analyzed using Bland-Altman method.

Results

Results of the Bland-Altman method are summarized in Table 1. The 3D developed model considering torus main axes underestimated radial inclination and volar tilt by respectively 2° and 1.5° on average when compared to the handmade point landmarking model. Ninety-five percent of the deviations between the two measurement methods were within [-5°; 1°] for radial inclination and [-6°; 3°] for volar tilt.

Discussion

This study shows an acceptable agreement between the measurements made by the developed 3D model and current handmade methods. The agreement is very good for the radial inclination (coefficient of repeatability of 3°) and good for the volar tilt measurement (coefficient of repeatability of 4.5°). The definition of volar tilt is more controversial in the literature as to which points should be considered. A comparison of five different volar tilt measurement methods showed a difference of more than 6° between two measurement methods [3].

The 3D developed overcomes this problem since the measurements are generated from the entire radiocarpal surface, thus homogenizing, and improving the definition of the distal radius measurements. In addition, it contributes to an improvement of the reproducibility and a considerable saving of time since the anatomical landmarks are currently manually positioned.

Figure and Tables

Figure 1: (A) Radial inclination (RI) measurement based on landmarking of radial styloid and medium ulnar border point; (B) RI measurement based on the main axis of the self-intersecting spindle torus; (C) Volar Tilt (VT) measurement based on landmarking of dorsal and palmar ulnar border points; (D) VT measurement based on the main axis of the torus.

<table>
<thead>
<tr>
<th>Measurement method</th>
<th>Bias (°)</th>
<th>Limits of agreement (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RI (3D torus/points)</td>
<td>-2</td>
<td>[-2.5; -1.5]</td>
</tr>
<tr>
<td>VT (3D torus/points)</td>
<td>-1.5</td>
<td>[-2.2; -0.8]</td>
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<td>[1.8; 4.3]</td>
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<td></td>
<td></td>
<td>[-7.3; -4.8]</td>
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</table>

Table 1: Results from Bland-Altman method

References

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A TWO-PHASE HAEMODYNAMIC MODEL FOR ARTERIAL MICROVASCULAR BIFURCATIONS

Tchanon Wisitponchais, Junxi Wu, Asimina Kazakidi

Abstract

The mechanistic links between haemorheology and clinical diseases, such as ischemia and stroke, are poorly understood due to the small size of microvessels and their intrinsic variability [1]. Several studies of the microcirculation have suggested that formation of a cell-free layer (CFL) due to the core movement of red blood cells (RBCs) influences wall shear stress (WSS) and velocity profiles. A better understanding of the blood flow in microvascular arterial networks and of metrics not easily measured in vivo can be achieved with the use of computational fluid dynamics methods. This study investigated the three-dimensional (3D) hemodynamics in a bifurcation where both the CFL and RBCs phases were taken into account. Moreover, the effect of CFL width on wall shear stress and velocity distribution was examined.

Methods

The geometry of a symmetric 20-μm-vessel-diameter Y-junction was constructed and meshed with polyhedral elements in Star-ccm+. Using the volume of fluid (VOF) multiphase approach, blood was simulated as a two-phase flow model consisting of a Newtonian CFL phase and a Newtonian or non-Newtonian (Carreau-Yasuda model) RBCs phase. Rheological properties relating to the selected parent vessel diameter, a ~40% hematocrit in rats [2] and an in-vivo viscosity model were assigned. A wall distance of 1.7 and 2.6 μm was assumed as CFL width. For the bifurcations with different CFL width, a plasma viscosity of 1.3 mPa-s was assigned to the CFL phase, whereas RBC viscosity in the RBC phase was varied, such that a whole-blood viscosity of 3.68 mPa-s was achieved.

Results & Discussion

The two-phase haemodynamic model was able to capture blood movement and velocity profiles observed experimentally in animal arterioles [3, 4]. The maximum RBC velocity profile was at the center of the parent vessel (Fig. 1A&C), however in the daughter vessels, the RBC phase moved towards the inner wall of the bifurcation, even though the maximum velocity was detected near the outer wall (Fig. 1A&D). Moreover, the model demonstrated that CFL widths influenced the variation of wall shear stress (Fig. 1B) and velocity profiles (Fig. 1C&D). In comparison to Newtonian, assuming the non-Newtonian fluid at the RBC phase reduced wall shear stress at the Y-junction (Fig. 1B).

Figure 1: Two-phase haemodynamic model of a symmetric Y-junction with different CFL widths. A) CFL and RBC phases (blue and red, respectively) and velocity distribution. B) WSS at the Y-junction, compared to single phase (zero CFL width). C & D) Velocity profiles perpendicular to the axis of the parent (C) and the daughter vessel (D). Noted that, Pa, D1, RL, Newt., CY, OW, and IW stand for parent, daughter, referent line, Newtonian fluid, Carreau-Yasuda model, outer wall, and inner wall, respectively.

Acknowledgements

This work brings us a step closer to the understanding of blood rheology in microvessels.

References


Acknowledgements

Results were obtained using the ARCHIE-WeSt High Performance Computer (www.archie-west.ac.uk) based at the University of Strathclyde.
PRE-TRAINING VARIOUS VASCULAR GEOMETRIES WITH A DEEP LEARNING SIDE NETWORK IN PHYSICS-INFORMED NEURAL NETWORK SIMULATIONS OF VASCULAR FLUID DYNAMICS

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¹ Department of Bioengineering, Imperial College London, UK

Introduction
As universal function approximators, deep neural networks have the potential of being the surrogate solver of the Navier-Stokes (NS) equations. This was recently demonstrated via the Physics Informed Neural Network (PINN) on aneurysm flows [1]. However, PINNs are specific to the geometry of the flow domain and require slow training for each new geometric scenario encountered. To address this, Sun et al. [2] designed a simple parameterization of varied vascular geometries and pre-trained various geometric scenarios by adding the geometric parameter as an input to the PINN which allowed for the quick prediction of new geometric cases. Here, we present an alternative approach, where a deep learning (DL) side network is cascaded to a PINN domain network for the pre-training of varied geometric cases, which has the potential to enhance network robustness and decrease training complexity.

Method
The DL-PINN network architecture is shown in Fig 1. The network was tested on 2D stenosis flows, where the vascular geometry can be varied by a parameter to control stenosis severity. The DL-PINN was trained with 5 geometries with increasing stenosis levels and tested on 3 geometries with stenosis levels not yet seen by the network.

**Figure 1:** The architecture of the proposed DL-PINN network. A DL network (green) using case geometric parameters (f) is used to determine the weights of nodes in the PINN network (pink). A PINN pre-layer (yellow) increasing order of parameters, and a hard boundary constraint post-layer improved performance.

Result and Discussion
Importance of hard boundary post-layer: no-slip wall velocity and inlet/outlet boundary conditions were incorporated as hard constraints via polynomial profiles across vessel diameter, and tanh profiles along vessel length, which were imposed onto velocity outputs from PINN. This improved convergence of velocity from a 32.2% error to a 0.2% error in a test case.

**Importance of increased-order pre-layer:** PINN nodes are typically modelled as tanh functions, but such networks cannot model the second-order math functions (such as $x^2$ and $xy$) well. Our inclusion of the second-order pre-layer to calculate these functions improved convergence from 32.2% velocity error to 4.7%.

**Pre-training of varied geometric cases and predictions in unseen cases:** Using our case network pre-trained with 5 geometric cases of varied stenosis, prediction of flow and pressure fields for the 3 new cases unseens by the network had velocity and pressure errors around 0.2-0.8% and 3.5-4.5%, respectively, comparable to errors achieved in the training cases. Fig 2 shows the comparison with CFD results, showing a good match. Predictions of new cases were almost instantaneous, compared to the 2-4 minutes needed for CFD simulation of the same cases using COMSOL.

**Conclusion**
We demonstrated the feasibility of a DL-PINN network pre-trained to varied geometries and validated its ability to rapidly solve flow fields of geometric cases not yet seen by the network. In the future, this can be expanded to cover various vascular curvatures, cross-sectional size changes, and 3D flows. If successful, such an approach has important benefits. First, it can achieve ultra-fast, real-time fluid mechanics simulations to assist clinical evaluation. Second, it allows the network to evaluate various surgical options to find the optimal route, via parameterization of these options.

**References**

**Acknowledgements**
This work was supported by the Imperial college startup fund.
DEVELOPMENT OF NASAL SPRAY DELIVERY SYSTEM TARGETING AT THE POSTERIOR NOSE FOR MUCOSAL IMMUNIZATION

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2. Department of Mechanical Engineering, California Baptist University, Riverside, CA, U.S.A.

Abstract
Delivering vaccines to the posterior nose has been proposed to induce mucosal immunization. However, conventional nasal devices often fail to deliver sufficient doses to the posterior nose. This study aimed to develop a new delivery protocol that can effectively deliver sprays to the caudal turbinate and nasopharynx. High-speed imaging was used to characterize the nasal spray plumes. Three-dimensional-printed transparent nasal casts were used to visualize the spray deposition within the nasal airway, as well as the subsequent liquid film formation and translocation. Influencing variables considered included the device type, delivery mode, release angle, flow rate, head position, and dose number. Apparent liquid film translocation was observed in the nasal cavity. To deliver sprays to the posterior nose, the optimal release angle was found to be 40° for unidirectional delivery and 30° for bidirectional delivery. The flow shear was the key factor that mobilized the liquid film. Both the flow shear and the head position were important in determining the translocation distance. A supine position and dual-dose application significantly improved delivery to the nasopharynx, i.e., 31% vs. 0% with an upright position and one-dose application. It is feasible to effectively deliver medications to the posterior nose by leveraging liquid film translocation for mucosal immunization. Spray formulations of varying viscosities were also tested, and their posterior nose delivery efficiencies were quantified.

Figure
Liquid film translocation can significantly affect the nasal spray dosimetry in the nose [1]. High-speed imaging techniques were used to visualize the aerosol generation from soft mist and squeeze bottle sprays (Fig. 1). The soft mist spray bottle generated smaller aerosols could reduce the front nose deposition and increase spray dispensing beyond the nasal valve.

Considering that the liquid-holding capacity of the turbinate furrows is sensitive to the head orientation, two head positions were evaluated that tilted up and down from the flat supine position by 20°, respectively. As shown in Fig. 2a, when tilting the head up by 20° (equivalent to head on a pillow), most of the spray droplets were deposited in the inferior turbinate and nasal floor. This was because the vestibule was aligned with the inferior turbinate along the gravity in this case. Moreover, the liquid film traveled a shorter distance than the supine position, because tilting the head up by 20° changed the turbinate furrow from vertical to a 70° slope. Applying the second dose delivered significantly more doses to the caudal turbinate, but negligible dose was observed in the nasopharynx, as displayed in the middle panel of Fig. 7a. The posterior nose dose (i.e., caudal turbinate and nasopharynx) with one-dose and dual-dose applications was 2.9 mg and 34.0 mg, respectively (Fig. 2b). It was also noted that the same factors (gravity and flow shear) that helped mobilizing the liquid film could also reduce the maximal liquid film thickness, thus slightly decreasing the dose adhering to the same region.

Figure 2: Head orientation effects on nasal spray deposition distribution: (a) supine 20° tilted up (head on a pillow), and (b) supine 20° tilted back.

References
SCHLIEREN AND LASER FLOW VISUALIZATION OF FILTRATION AND LEAKAGE OF DIFFERENT FACEMASKS

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2. Department of Mechanical Engineering, California Baptist University, Riverside, CA, U.S.A.
3. Department of Biomedical Engineering, University of Massachusetts, Lowell, MA, U.S.A.

Abstract
Background and objective:
Due to the differing fibre densities and thicknesses of varying masks, some masks are more effective in blocking respiratory droplets than others. Mask protective efficiency depends not only on filtration efficiency, but also on the leakage fraction. To determine the effectiveness of different masks in preventing the transmission of COVID-19, Schlieren Optical Imaging (SOI) and laser sheet systems will be used to visualize the airflow during respiration. The objective of this study was to visualize the expiratory airflows from facemasks.

Methods:
(1) develop an optimal Schlieren system to visualize facemask flows.
(2) develop a laser system and visualize the facemask flows.
(3) use vapor to simulate aerosol transmission between two persons.

Summary of results:
(1) Surgical mask and KN95 reduce the exhaled flow velocity from 2~4 m/s (with no facemask) to around 0.1 m/s, thus decrease the transmission of virus-laden respiratory droplets. However, they have flow resistance.
(2) Bandana or n-gaiter has low filtration efficiency and high leakage fractions, thus provides low protection efficiency.
(3) Respiratory droplets mainly deposit around nose/mouth. Frequent touching these regions will increase transmission.
(4) Even KN95 and surgical mask can have 50% leakage from the gaps around the nose.

Figures
Considering the different physical properties of the respiratory airflow and droplets, four visualization methods have been developed. The Schlieren optical system will capture the in vivo expiration flows and is good at detecting facemask leakage (Fig. 1a). The laser optical system can vividly capture the details of the airflow patterns but has been only used for in vitro testing for safety reasons (Fig. 1b). The vapor-Sargel system mimicked the inter-personal transmission of respiratory droplets both qualitatively and quantitatively (Fig. 1c). The infrared thermal camera can capture the transient inhalation and exhalation, as well as the flow leakage, within breathing cycles (Fig. 1d).

References
A LSTM FRAMEWORK FOR ANKLE JOINT BIOMECHANICS PREDICTIONS FROM INERTIAL SENSORS DURING GAIT

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Introduction
The ankle joint plays a crucial role during gait, articulating the lower limb and foot-ground contact, keeping the body balanced, and transmitting the center of gravity. Evaluating the biomechanics of the ankle joint helps with gait function assessment, pathological gait analysis, and prosthesis and robot design. However, traditional data collection is limited to strict experimental settings and laboratory setups. With the advent of wearable technologies, inertial sensors have appeared as a reliable alternative due to their convenience, low cost, and data collection capability outside the laboratory [1]. This study aimed to implement recurrent neural networks (long-short term memory, LSTM) for predicting ankle joint angle, torque, and contact forces from the inertial sensors.

Methods
Twenty-five healthy participants were recruited for this study following ethical approval, with means and standard deviations of age 25.84±1.18 yrs, height 172.8±5.37 cm, and mass 71.4 ± 8.37 kg, respectively. Two inertial measurement unit (IMU) sensors were attached to the foot dorsum and the vertical axis of the distal anteromedial tibia in the right lower limb to record acceleration and angular velocity during running (Figure 1). Data processing was performed following a protocol established previously [2]. Inverse kinematics (IK), inverse dynamics (ID), and static optimization (SO) were performed to calculate ankle and subtalar joint angle and torque in the sagittal plane and contact forces. The architecture of our LSTM-MLP (multilayer perceptron) model was two layers of bidirectional LSTM with 256 neurons, followed by a three-layer MLP with 256 neurons for the first layer and 512 neurons for the second and third layers. The model was validated and tested in a custom nested K-fold cross-validation process.

Results
The average values of coefficient of determination (R2), mean absolute error (MAE), and mean squared error (MSE) for ankle dorsiflexion joint and moment, subtalar inversion joint and moment, and ankle joint contact forces were 0.89±0.04, 0.75±0.04, and 2.96±4.96 for walking and 0.87±0.07, 0.88±1.26, and 4.10±7.17 for running.

Table 1: Root mean squared error (RMSE) between measured values from the motion capture system and predicted values from the LSTM model for walking and running from nested k-fold cross-validation (mean± std).

<table>
<thead>
<tr>
<th></th>
<th>Walking</th>
<th>Running</th>
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<tr>
<td>Ankle dorsiflexion angle</td>
<td>2.97±0.47</td>
<td>3.21±0.74</td>
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<tr>
<td>Subtalar inversion angle</td>
<td>3.34±0.47</td>
<td>4.15±0.70</td>
</tr>
<tr>
<td>Ankle dorsiflexion moment</td>
<td>0.14±0.02</td>
<td>0.17±0.02</td>
</tr>
<tr>
<td>Subtalar inversion moment</td>
<td>0.05±0.01</td>
<td>0.04±0.01</td>
</tr>
<tr>
<td>Anterior/posterior reaction force</td>
<td>0.27±0.07</td>
<td>0.33±0.05</td>
</tr>
<tr>
<td>Vertical reaction force</td>
<td>0.52±0.09</td>
<td>0.43±0.03</td>
</tr>
<tr>
<td>Medical/lateral reaction force</td>
<td>0.10±0.01</td>
<td>0.11±0.01</td>
</tr>
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</table>

Discussion
Deep learning algorithms integrating with inertial sensors have emerged in recent years, as they are convenient and can capture biomechanics data outside the traditional gait laboratory. In this study, we found LSTM could predict ankle joint, moment, and contact forces with strong correlations (R2 > 0.8) and acceptable error during walking and running. Furthermore, nested K-fold cross-validation guaranteed good generalization by the multiple-validation, testing, and training models in a subject-independent manner [3]. This study proposed an LSTM framework for predicting the ankle joint, torque, and joint contact force from IMU sensors. It is a valuable tool for evaluating ankle biomechanics in lower limb pathological diagnosis and rehabilitation that is not limited to the experimental setting and is cost-effective.

References
NEW INSIGHTS FOR THE DESIGN OF BIONIC ROBOTS
Datao Xu 1,2,3, Xinyan Jiang 1,4, Wenjing Quan 1,2,3, Huiyu Zhou 1, Fekete, Gusztáv 2,3, Yaodong Gu 1
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Abstract
Introduction: Felines have significant advantages in terms of sports energy efficiency and sports flexibility compared with other animals, especially in terms of jumping and landing. The biomechanical characteristics of a feline (cat) landing from different heights can provide new insights into bionic robot design based on research results and the needs of bionic engineering. The purpose of this work was to investigate the adaptive motion adjustment strategy of the cat landing using a machine learning algorithm and finite element analysis.

Methods: This study combined the inverse kinetics model and the deep learning method to achieve the purpose of exploring the biomechanical characteristics of the whole landing phase of the cat, as well as the coordination strategy of each joint of the cat's forelimb when landing at different heights (Fig 1). Therefore, in order to more comprehensively explore the biomechanical characteristics of cat landing, the current study was mainly carried out from two aspects: 1) PCA and FEA (Fig 2); 2) inverse kinetics and deep learning method (DNN and LRP). Firstly, the GRF and joint kinematics (sagittal joint angle of wrist elbow shoulder) were collected when the cat landed from 4 different heights (60cm, 80cm, 100cm, 120cm). The landing phase was determined as the initial contact point to maximum elbow flexion. Then, the next steps are mainly divided into two steps.

Results and Conclusion: In the design of a bionic robot, there are considerations in the design of the mechanical legs: 1) The coordination mechanism of each joint should be adjusted intelligently according to the force at the bottom of each mechanical leg. Specifically, with the increase in force at the bottom of the mechanical leg, the main joint bearing the impact load gradually shifts from the distal joint to the proximal joint (Fig 3); 2) Strengthening the hardness of the materials located around the center of each joint of the bionic mechanical leg to increase service life (Fig 4); 3) Lower the center of gravity of the robot and keep the robot posture forward as far as possible to reduce machine wear and improve robot operational accuracy.

Figure 1: (A) Illustration of the position of two high-speed cameras and 3-D coordinates. (B) Illustration of cat landing procedure from the ready position to initial forelimbs contact the ground. (C) The complete free-body diagram of a single forelimb segment (D) Illustration of the position of red marker points on forelimbs of cats (E) Freebody diagrams of the three rigid links.

Figure 2. (A) Finite element 3D model of right forelimb at four landing heights. (B) Illustration of ligament and soft tissue of model. (C) Illustration of loading and boundary conditions. (D) Experimental verification of plantar pressure of cat right forelimbs. (E) Experimental verification results and finite element simulation results.

Figure 3. The classifier performance results of the DNN models.

Figure 4. (A) (B) (C) (D) are the stress distribution details of the wrist joint, elbow joint and shoulder joint of the cat's right forelimb landing from four heights of 0.6m, 0.8m, 1.0m and 1.2m respectively. (E) The maximum stress value of each joint at each landing height.
MODELLING BLOOD FLOW IN A MICRO-VESSEL BIFURCATION

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Introduction
Microvasculature accounts for most vessel length in the human body and plays a key role in oxygen transport and nutrients delivery. Currently, a widely used way to simulate microcirculation is the flow network model, where blood vessels are treated as rigid straight pipes and Poiseuille flow is assumed in each vessel. However, the network model oversimplifies the details of blood flow characteristics, especially near the vessel junctions, limiting its wider applications. In this work, we study the blood flow in 2D micro-vessel junctions of various geometries and boundary conditions using a recently developed lightning Stokes solver [1].

Methods
Blood flow in microvasculature is governed by Stokes equations (Reynolds number is much smaller than 1):
\[ \nabla p = \mu \nabla^2 \mathbf{u}, \]
\[ \nabla \cdot \mathbf{u} = 0. \]
Fully developed parabolic profile was imposed at both inlet and outlets of the junction and a no slip condition was assumed on the vessel walls.

Stokes flow was solved using a complex variable method, where the stream function was represented by two analytic complex functions (known as Goursat functions). Each analytic function was approximated using a rational function with poles exponentially clustered near each sharp corner of the flow domain [2]. Coefficients of the rational functions were found by imposing boundary conditions and solving a linear system.

A single vessel bifurcation consists of a parent branch and two child branches. We examined blood flow in bifurcations with different branching angle, diameter ratio and flow ratio between two child branches. The lightning Stokes solver allows for simulation of each case within one second on a standard laptop using Matlab.

Results
Figure 1 presents the solution of blood flow in a symmetric Y-junction with even flow partition and an angle of 90 degrees between two child branches. In this case, the maximum velocity was set as 1 and the streamlines were also plotted on top of the flow field. The smooth streamlines around the corners highlight the capability of the lightning Stokes solver to capture flow characteristics accurately around sharp edges. Note that this method is also capable of simulating blood flow in asymmetric geometries with asymmetric boundary conditions.

Discussion
One advantage of this new method for solving microcirculation is its great speed, accuracy and adaptability to different geometries and flow conditions. This mesh-free approach also makes it suitable for solving physiological fluid dynamics problems involving moving objects or boundaries.

A limitation of this work is that we neglect the effects of blood cells, especially red blood cells, on blood flow. In addition, our model geometry is 2D and purely passive. In future work, we will apply this method to simulate microthrombi transport in cerebral microcirculation. This will allow us to investigate the effects of cerebral microvascular geometry on microthrombi distribution, and thus their impact on blood flow and oxygen transport [3,4]. This will complement current in silico models of ischaemic stroke and its treatment [5].

References
INVESTIGATING THE GROWTH & REMODELING MODEL PARAMETERS INFLUENCE ON A HYPERELASTIC ARTERY

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Introduction
Predicting the evolution of an ascending thoracic aortic aneurysm (ATAA) is a challenge. Today the decision to perform surgery is based on the aneurysm diameter and more recently, on its evolution, measured on follow-up longitudinal images. However due to the complexity of both the aortic geometry, the tissue behavior and the blood flow, these criteria may over- or under-estimate the risk of rupture or dissection in some cases. Numerical simulation of aneurysm growth could provide additional information on the tissue state to identify the unstable cases requiring surgery. In this work we implemented an existing Growth and Remodeling (G&R) model based on the constrained mixture theory [1,3] and applied it to a generic tube geometry, to investigate the interaction between the model parameters.

Materials and Methods
The G&R model includes elastin, 4 collagen fiber families (axial, circumferential and two oblique) and Smooth Muscle Cells (SMCs) oriented in the circumferential direction. The strain energy density function of the tissue is written as:

\[ W = \rho^c (\frac{c_1}{2} (T_1 - 3) + K (J - 1)^2) + \rho^e c_1 c_2 (e^{c_2 (J_1 - 1)^2} - 1) + \rho^m \frac{m_1}{2m_2} (e^{m_2 (m_1 - 1)^2} - 1) \]

Where superscripts c, e and m stand for elastin, collagen and SMCs respectively, \( \rho \) is the constituent mass density and \( \mu, K, c_1, c_2, m_1, m_2 \) are material parameters. Following [2], elastin and collagen degrade due to ageing, but only collagen can be deposited. The deposition rate for collagen is:

\[ \rho^c_t = \rho^c_t \kappa \frac{\sigma_t^c - \sigma_t^h \kappa^c}{\sigma_t^h} \]

Where \( \rho^c_t \) is the deposition rate, \( \kappa \) is a gain parameter, \( \sigma_t^c \) is the current time stress and \( \sigma_t^h \) is the homeostatic stress. The model is formulated so that growth occurs when the tissue is out of the homeostatic state, defined by a homeostatic stretch \( \lambda \) for each constituent [1]. This G&R model was implemented as a user-subroutine in ANSYS APDL and applied to a single-layer tube (length = 180mm, inner radius = 10mm, thickness = 1.41mm). Growth is driven by a localized and progressive loss of elastin, and can only happen in the radial direction; therefore, the thickness and inner radius of the tube evolve with growth. G&R simulation could be computed over 8 years. The influence of several parameters, such as the deposition and degradation parameters for collagen and elastin, was investigated.

Results
Figure 1 illustrates the effect of the gain parameter \( \kappa \) on G&R for a given elastin degradation. We could observe that a larger \( \kappa \) corresponded to a higher compensation of the elastin loss, even far from the elastin defect; this is emphasized by a smaller average inner diameter and larger thickness. We could also observe that thickness does not have a monotonic evolution depending on the relative growth and degradation rates of both collagen and elastin. As shown in [2], parameters configurations can lead to stabilization or unstable growth of the vessel diameter.

Discussion and Conclusions
Our study aims to understand the relative influence of the different parameters on the structure evolution, as G&R models include a large number of parameters. This could help interpreting simulation results on more complex geometries such as patient-specific ones.

Acknowledgments
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References
PRIMARY FIXATION OF DENTAL IMPLANTS IN BONE SURROGATE - FINITE ELEMENT ANALYSIS CONSIDERING INSERTION DAMAGE

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Introduction

Primary fixation, mechanical engagement between implant and bone under functional loading, can be evaluated by implant motion (IM). To improve the understanding of primary fixation, computational models such as finite element analysis (FEA) have been developed; however, one common limitation in current FEAs is an assumption of intact bone properties without considering stress or damage generated from insertion [1]. Therefore, the objective of this study was to develop and validate an accurate FEA to investigate the primary fixation of threaded dental implants in a rigid polyurethane (PU) foam considering effects of the insertion process.

Method

Two implant designs: parallel-walled (Bränemark MkIII TiUnite NP 3.5×13 (P1) and Bränemark MkIII TiUnite WP 5.0×13 (P2), Nobel Biocare), and tapered implants (NobelActive® NP 3.5×13 (T1) and NobelActive RP 4.0×13 (T2), Nobel Biocare) were inserted into PU foam blocks (40×40×8 mm³, Ø 2.4/2.8 mm or Ø 3.2/3.6 mm, 20 PCF, Sawbones) in dry condition and room temperature (MACH-1 V500CST, Biomomentum). Fixation tests were conducted 2 days after insertion with 2 loading protocols: axial and 30-degree off-axis loading (Electroforce 5500, TA instruments) with 5 repeats for each implant design (Fig.1a). The IM was measured as vertical displacement (v) using a deflectometer (3540-001M-ST, Epsilon Technology Corp); and, as implant rotation angle (θ) analysed for off-axis loading using 2D tracking from video (Canon EOS Rebel SL2 DSLR, EF-S 18-55mm Lens, Canon. Inc., Digital Image Correlation Engine version 2.0 [2]).

A series of non-linear explicit FEAs were conducted including an insertion step and followed by a loading step (Abaqus 2017, Simulia). The insertion step was developed and validated against surface strains of the PU foam measured in the insertion tests [2]. After the insertion step, a v measured from the tests was applied on the implant reference point (RP) for the axial loading, while an off-axial force and a θ were applied on the implant RP for the off-axis loading (Fig.1b). The PU foam was modelled with a linear elastic (Young’s modulus of 123 MPa) and multilinear plastic material (8.06 MPa yield strength, and 30% fracture strain, from compression test data) with hexahedral elements with incompatible modes. The implant was modelled as a rigid body with bilinear rigid quadrilateral elements (Fig. 1b). An element-based surface contact algorithm was used with penalty formulation and friction coefficient, 0.61, between the implant and PU foam.

Results

The force-displacement curves predicted by the FEA were comparable to the experimental results (Fig.2). Differences in the PU foam-implant stiffness between FEA and experimental results ranged from 3.64% - 17.2% for axial loading, and for the off-axis loading 20.4%-20.7% for P1, P2 and T1 implants, and 45.0% for the T2 implant.

Discussion

The FEA model, which considers the foam deformation and damage near the implant due to insertion, achieved an overall good prediction of the stiffness in comparison to mechanical test results, particularly under vertical loading. Results were specific to the implant designs and PU foam properties used in the study.

References


Acknowledgements

We acknowledge funding from Nobel Biocare Services AG and the support of the Natural Sciences and Engineering Research Council of Canada, Canadian Foundation of Innovation, and Ontario Research Fund.
PRIMARY FIXATION OF DENTAL IMPLANTS IN BONE SURROGATE IN RELATION TO INSERTION TORQUE - BIOMECHANICAL EVALUATION

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Introduction
Primary fixation of dental implants, mechanical engagement between implant and bone, can be quantified by implant motion (IM) in preclinical assessment under external load to understand implant biomechanics [1]. A high insertion torque (IT) is believed to suggest firm anchorage. However, the relationship between the IT and primary fixation is not trivial. Therefore, the objective of this preclinical study was to investigate the primary fixation and its relationship to IT in rigid polyurethane (PU) foam for two implant designs.

Method
Two implant designs in two sizes [parallel-walled: Brånemark MkIII TiUnite NP 3.5×13 (P1) and WP 5.0×13 (P2), and tapered implants: NobelActive® NP 3.5×13 (T1) and RP 4.0×13 (T2), all from Nobel Biocare] were inserted into PU foam blocks (40×40×8 mm³, 20 PCF, Sawbones) with a pilot hole (Ø 2.4/2.8 mm for P1 and T1 or Ø 3.2/3.6 mm for P2 and T2) with a constant insertion speed (12 rpm, MACH-1 V500CST, Biomomentum), in dry conditions and room temperature. The fixation tests were conducted 2 days after insertion with 2 configurations: axial and 30º off-axis loading (Electroforce 5500, TA instruments) with 5 repeats (40 tests, Fig.1). Stepped-cyclic loading was applied: 5 cycles of preconditioning (∆v=6 N), followed by a 3-stepped cyclic loading of 35 N (mean) ±15 N (amplitude), 70±30 N, and 105±45 N (0.5 Hz and 20 cycles per step). For axial loading, IM was measured as vertical displacement (ν) (deflectometer, 3540-001MST, Epsilon Technology Corp.). For 30º off-axis loading, IM was measured as implant rotation angle (θ) analysed using 2D tracking (Canon EOS Rebel SL2 DSLR, EF-S 18-55mm Lens, Canon, Inc., spatial resolution 22.6-34.5 pixel/mm at 60 fps, Digital Image Correlation Engine version 2.0 [2]).

Results
P1 group had the lowest IT values, while T2 had the highest. Under axial loading, a moderate correlation between maximum ν and IT was found (R² = 0.59-0.69, Fig 2.) and no failures of the bone surrogate were observed. For 30º off-axis loading, similar coefficient of determinations were found between the maximum θ at the step 1 and IT, and the step 2 and IT (R² = 0.59 and 0.66, respectively); in contrast to step 3 (R² = 0.092, Fig.2). A few failures of the bone surrogate were observed during the last loading step.

Discussion
This preclinical study shows the complex relationship between implant IT and primary fixation. While low IT can result in more IM under loading, high IT does not necessarily guarantee better fixation, especially under high and/or complex loads as with off-axis loading. The moderate correlation for the non-failure cases suggested IT may predict primary fixation for stable interfaces over time; however, further studies are required to comprehensively understand interface biomechanics.

References

Acknowledgements
We acknowledge funding from Nobel Biocare Services AG and the support of the Natural Sciences and Engineering Research Council of Canada, Canadian Foundation of Innovation, and Ontario Research Fund.
**Introduction**

The bronchial rupture was generally associated with high-energy impacts such as automobile collisions. The main bronchus was mostly injured compared to the trachea and lobar bronchi. Generally, these injuries are life-threatening; around 70 to 80% of the patients may die before arriving at the hospital [1]. However, these injuries can be predicted by performing high-impact simulations on a human body model. Literature on experimental studies on the bronchi is limited to the quasi-static regime. Therefore, it is crucial to determine the material properties of the bronchi at high strain rates. The current study provides insight into the dynamic behavior of bronchi at strain rates from 25 to 80 s⁻¹.

**Methods**

In the current study, the bronchi samples were sectioned from the porcine lung tissue obtained from the local butcher shop. The bronchi samples were obtained by peeling away the soft parenchyma tissue on its surface using a scalpel. The uniaxial tensile tests were performed on the bronchi sample using a hydraulic based dynamic test setup at 0.5 (25 s⁻¹), 1 (45 s⁻¹), and 2 (80 s⁻¹) m/s velocities. The load responses of the sample were recorded at 20 kHz using piezo load cells of 1 kN capacity and data acquisition system (Dewesoft Corporation, Slovenia). Using a high-speed camera, the deformation of the sample was recorded at 20,000 fps. The load-displacement data was synchronized using a laser displacement sensor, which triggers the high-speed camera and data acquisition system at the same time.

**Results**

The experimental data set consists of 15 tests conducted along the axial direction on porcine bronchi as shown in Fig. 1. The stress-strain curve (see Fig. 2) reflects a nonlinear strain rate dependency behavior of porcine bronchi. The engineering stress-strain curve was segmented into a toe and elastic region using a MATLAB bilinear curve fit. The RMS error between the experimental and the bilinear model are minimized using the unconstrained multivariable optimization.

The bilinear material parameters shown in Table 1, reveal that the toe and elastic modulus values increase with strain rate. The toe modulus values increase from 0.32 to 0.42 MPa, and the elastic modulus value increases from 3.42 to 8.3 MPa. At the same time, the toe strain value decreases from 0.28 to 0.22.

**Discussion**

This study quantifies the variation of bilinear material properties of bronchi with strain rate. The nonlinear stress-strain behavior of bronchi is expected due to the presence of elastin and collagen. In the toe region, the elastin starts deforming, and the collagen uncrimp, whereas during the elastic region, the collagen fibers start deforming and tend to slide along the direction of loading. With the increase in strain rate, the total time available for the uncrimping and deformation of the tissue reduces, which results in the increase of modulus values and the decrease in toe strain. It should be noted that the current study was carried out only with the proximal bronchi. Studies by Sattari et al. [2] show that the modulus of the proximal and distal bronchi shows significant variation.

**References**


**Acknowledgements**

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PREMATURELY AGED POLGA MICE EXHIBIT DEGENERATED OSTEOCYTE NETWORK AND MECHANOSENSATION

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Introduction

Age-related osteoporosis is a major problem in human musculoskeletal health and has proven difficult to model in mice. Osteocytes, key mechanosensors of bone, have emerged as an important target for preventing age-related osteoporosis, characterized by decreased bone mass over time. This decrease results from the morphological changes in the osteocyte lacunocanalicular system (OCLN) and their diminished ability to sense mechanical stress [1]. PolgA D257A/D257A (PolgA) mice exhibit a naturally accelerated aging phenotype at 40 weeks with an early onset of clinically-relevant musculoskeletal aging characteristics, including frailty and osteosarcopenia [2]. However, the relevance of this model - as a model for age-related osteoporosis and to understand the responsible mechanism of age-associated changes in the OCLN - remains unclear. Here we demonstrate age-and sex-related bone changes and associated degeneration of the osteocyte network in both female and male PolgA mice.

Methods

Bone morphometric parameters were evaluated from the right femurs of homozygous female and male PolgA mice (n=9-11/group) and wild-type (WT) littermates (n=9-16/group) by micro-CT (voxel size: 10 µm). Changes in the bone structure were correlated with alterations in osteocyte density and dendriticity. Osteocytes and their dendrites were imaged with 3D confocal microscopy on Phalloidin-Hoechst-stained sections of PolgA mice (n=2-4/group), and the WT littermates (n=2-4/group) at 20 and 40 weeks. ImageJ and IMARIS software were used to quantify the osteocyte density and dendriticity from the confocal image stacks. Two-way ANOVA with Tukey corrections was used for statistical analysis.

Results

Micro-CT analysis revealed statistically significantly lower apparent volume density (AVD) in 40-week-old PolgA mice compared to age-matched WT (males: -25%, females: -15%) and 20-week-old PolgA mice (males: -24%, females: -19%) (Figure 1A). Quantifying confocal image stacks demonstrated a notable decrease in the number of dendrites per osteocyte in 40-week-old PolgA mice compared to aged-matched controls (males: -31%, females: -52%) and young PolgA (20-week-old males: -45%, females: -56%) (Figure 1B-C) indicating osteocyte network disruption in the PolgA mice at 40 weeks.

Discussion

Our results demonstrate age-related degeneration in bone architecture in PolgA mice. Furthermore, we found that the dendrite numbers per osteocyte decreased with age in both female and male PolgA mice, with greater reduction in females compared to males. Since similar age-related degeneration of the bone and osteocyte network has been observed in humans [3], our results suggest that the PolgA mouse could be a robust model for investigating molecular mechanisms responsible for age-related osteoporosis.

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Acknowledgments

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MODELING AND SIMULATION OF TISSUE GROWTH CAUSED BY CELL PROLIFERATION DURING MORPHOGENESIS

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Introduction

Biological tissues have a variety of characteristic shapes corresponding to their functions. The tissue shapes are formed through various cell behaviors during morphogenesis, such as hypertrophy and proliferation. In this process, multicellular dynamics is spatiotemporally regulated by the mechanical and biochemical environments [1]. However, the effect of changing environment on individual tissue shapes is difficult to investigate through in vivo experiments. In this study, to clarify the regulation mechanism of tissue shape by the stage-dependent mechanical environment, we developed a model that can simulate tissue growth caused by cell proliferation during morphogenesis.

Methods

To simulate tissue growth during morphogenesis, it is necessary to consider spatiotemporally heterogeneous cell activities regulated by the stage-dependent mechanical and biochemical environments. Therefore, we employed the material point method (MPM) [2], in which the physical domain is discretized by material points and the displacement field is calculated on background grid nodes based on continuum mechanics. To describe multicellular dynamics, we regarded a material point as a single cell. Tissues composed of numerous cells were modeled as a hyperelastic material following the compressible Neo-Hookean model. To express tissue growth caused by cell proliferation, we constructed a cell proliferation model by combining the unidirectional growth and split of material points (Fig. 1).

Results

Based on the cell proliferation model, we simulated the growth of spherical tissue with the surface of the lower half fixed. The tissue was composed of regularly distributed 6.6x10^4 cells. Young’s modulus and Poisson’s ratio of the tissue were set as E = 1.0 kPa and v = 0.4, respectively. The composing cells proliferated with random planes of division at random timings. Figure 2 shows the resulting volume of each cell in the growing tissue. The cell volume became spatially heterogeneous due to the randomness of proliferation. Because of the constraint, relatively large cells (red cells in Fig. 2) were observed in the upper half of the tissue. These results suggest that cellular mechanical behaviors depend on the constraint condition and their own activities.

Discussion

In this study, we developed the cell proliferation model that can simulate tissue growth caused by spatially heterogeneous cell activities during morphogenesis. By extending this model through the consideration of cell activities depending on the spatiotemporal mechanical and biochemical environment, it will be possible to simulate the formation of characteristic tissue shapes, such as femurs with femoral heads. Therefore, the proposed model will contribute to understanding the mechanism of tissue morphogenesis.

References


Acknowledgements

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QUADRICEPS AND HAMSTRINGS FORCE AND RATE-OF-FORCE DEVELOPMENT DEFICITS IN PEOPLE BEFORE ACL SURGERY

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Introduction

One of the most important aspects of return to sport assessments after an anterior cruciate ligament (ACL) reconstruction is the quadriceps and hamstrings strength [1]. The limb symmetry index (LSI) and the Hamstrings to Quadriceps ratio (H/Q ratio) are common metrics in return to sport evaluation, as achieving an LSI higher than 90% and a H/Q ratio of 50-80% decreases the chance of a second ACL injury [2].

A known problem with those metrics is that they overestimate the muscle force in the non-injured leg, as this measure decreases over the long period of rehabilitation after injury. Another important but less researched measure is the Rate-of-Force Development (RFD), assessing how fast one can recruit force. The gold standard for RFD assessment is an isokinetic chair, expensive and stationary equipment that limits its use mainly to research labs.

To address these issues, we used a handheld dynamometer in a public hospital environment and assessed the LSI and H/Q ratio of the force and RFD among people before an ACL surgery.

Methods

Sixteen recreational athletes, 14 males and two females, before an ACL reconstruction surgery (age 25.6 ± 7.1) and 23 healthy participants (age 28±5.7. 12 males and 11 females) signed informed consent and were recruited to this study.

Using a Microfet2 handheld dynamometer attached to a belt, the participants' quadriceps force, hamstrings force, and RFD were measured while sitting at the end of a treatment bed with their hip flat on the bed and their knee at 90 degrees. The dynamometer was placed 5cm above the lateral malleolus. After familiarization and a warm-up session, each participant was asked to push as hard and fast as possible for three repetitions with one-minute rest between reps, assessing the quadriceps.

The same routine was repeated for the hamstrings, with the assessor holding the dynamometer between his hand and a wall to stabilize it. Those methods are reliable, with an ICC of 0.83-0.93 [3,4]. Two RFD phases were measured, early and late (0-100ms and 0-200ms, respectively).

The LSI was calculated as the ratio between the injured leg value and the uninjured leg value and as the ratio between the left and right leg for the healthy participants.

Results

As shown in Table 1, the peak force LSI of the quadriceps is more affected than the hamstring's LSI. Further, the LSI of the RFD shows higher deficits in both muscle groups. All of the LSI values among non-injured participants are within the normal range [2].

<table>
<thead>
<tr>
<th>Quadriceps LSI (%)</th>
<th>Injured (n=14)</th>
<th>Non-Injured (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Force</td>
<td>80± 19.6</td>
<td>98.4±10.9</td>
</tr>
<tr>
<td>RFD100</td>
<td>69.6±29.1</td>
<td>91.3±17.1</td>
</tr>
<tr>
<td>RFD200</td>
<td>69.7±21.9</td>
<td>97.5±18.7</td>
</tr>
<tr>
<td>Hamstring LSI (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Force</td>
<td>92.1±29.1</td>
<td>102±16.4</td>
</tr>
<tr>
<td>RFD100</td>
<td>90.8±42.2</td>
<td>102±25.6</td>
</tr>
<tr>
<td>RFD200</td>
<td>83.4±39.6</td>
<td>107±27.7</td>
</tr>
</tbody>
</table>

Table 1: limb Symmetry Index of the quadriceps and hamstring muscles force and rate of force development among injured and non-injured participants

The H/Q ratio among the injured participants was 59.3%±17.7 for peak force, 48.9%±25.7 for early RFD, and 52%±28.2 for late RFD.

In comparison, the H/Q ratio among the non-injured participants was 58.2%±11.3 for peak force, 41.6%±15 for early RFD, and 48.9%±15 for late RFD.

Discussion

While the most common use of LSI in return to sport decision after an ACL injury is the peak force, we have found that early and late RFD are more affected among people before an ACL reconstruction. The H/Q ratio, on the other hand, presented as similar when comparing the injured and non-injured groups.

These findings show the importance of comparing not only to the injured leg but to a healthy cohort, as differences that might seem important could turn out to be less relevant.

As it is now possible to measure RFD with portable and inexpensive equipment, healthcare practitioners will be able to assess not only the peak force but also the LSI and H/Q ratio of the quadriceps and hamstring RFD.

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REAL WORLD GAIT ASSESSMENT IN PEOPLE BEFORE ACL SURGERY USING IMU AND STATISTICAL PARAMETRIC MAPPING

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Introduction
Anterior Cruciate Ligament (ACL) rupture is a common injury among young and active people that can lead to lower quality of life, strength, and movement asymmetries. These asymmetries expose individuals to reinjury risk and negatively impact the knee joint health in the long term [1]. While many have looked at asymmetries during demanding tasks such as jumping and stair ambulation, walking at a faster speed is a simple task suitable for assessment in the early phase after injury. Recently, Inertial Measurement Units (IMUs) have been used to evaluate movement in real-world conditions, not limiting assessment to a closed motion laboratory assessment [2].

The most common way to assess gait kinematics is by analyzing discrete points, such as local minima and maxima of the joint angles during the gait cycle. Another analysis method utilizes Statistical Parametric Mapping (SPM) over the full cycle, therefore not reducing the data to a single point in time [3]. Therefore, we aimed to use an IMU system to measure gait at three different speeds in real-world conditions and analyze the lower limb angles during the complete gait cycle.

Methods
A total of 24 recreational athletes before ACL reconstruction (ACLR) signed an informed consent and were recruited for this study. Using an XSENS IMU system lower limb model, comprised of 7 IMUs, each participant walked along 20 meters corridor in a hospital at three self-selected speeds: slow, comfortable, and fast. Each speed consisted of three trials (60 meters in total for each speed). Hip, knee, and ankle angles were averaged over the gait cycle for the injured and non-injured limbs. Next, SPM, a two-tailed, paired t-test comparison between the limbs was made. Discreet point analysis of local maxima and local minima was done using a two-tailed, paired t-test. All statistical tests were conducted using Python 3.7 with an alpha value of 0.05.

Results
The mean knee flexion angle of the injured leg during fast walking was higher than the angle of the non-injured at 32-47% and 92-94% percent of the gait cycle, as seen by a two supra-threshold cluster exceeding the critical threshold of t=3.1. The mean hip extension angle was lower than the angle of the non-injured at 32-47% of the gait cycle, as seen by a single supra-threshold cluster exceeding the critical threshold of t=3.1 (Figure 1).

Discrete point analysis found a statistically significant difference in the knee local minima angle at normal (2.4°, p<.05) and fast (2.8°, p<.05) walking speeds. Additionally, a statistically significant difference was found for the local hip minima angle at the fast speed only (2.1°, p<.05). No differences were found for the ankle joint (p>0.05).

Discussion
At fast walking speeds, people waiting for ACLR surgery presented with lower knee flexion and hip extension in their injured knee during terminal stance and lower knee flexion at terminal swing, compared to their contralateral knees. Analyzing only discreet points would miss these asymmetries and could lead to a less optimal rehabilitation plan. Therefore, this research supports assessment at different walking speeds and the use of SPM analysis to achieve more accurate information regarding gait asymmetries during gait.

References
FRACTURE ANGLES INFLUENCE HEALING IN FULLY REDUCED DISTAL FEMUR FRACTURES TREATED WITH LOCKING PLATES

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Introduction
There has been considerable research on the healing environment for fractures with inter-fragmentary gaps in which secondary healing (with callus) occurs due to inter-fragmentary strain. Fully reduced fractures treated with locking plates (device commonly selected for distal femur fractures) are considered to be stable permitting primary (osteonal) fracture healing. The possible subtle inter-fragmentary motions, which could inhibit osteonal repair at the early stage of healing in these reduced fractures due to weight bearing are not well understood. This study used finite element models to analyse the normal and shear inter-fragmentary motions between the bone fragments. The effect of fracture angles between bone fragments was compared.

Methods
Reduced fractures at the distal end of the femur fixed with a stainless steel locking plate were simulated in ABAQUS. The plate was placed on the lateral side of the femur. Both transverse fractures and oblique fractures with varying fracture angles were considered. The same screw configurations were applied to all the fractures. The coefficient of friction between the bone fragments was assumed to be 0.46 [1]. Cortical bone and the trabecular bone were assumed to be linear elastic. At the distal femur, condyles were supported by a layer of soft material, whose Young’s modulus was the same as meniscus [2]. Based on a previous study [3] the femoral head was partially restrained using a lateral spring. Load was applied from the centre of the femoral head to the centre of the condyles.

Results
Figure 1 shows the deformed position of the fractured fragments under 700N load (i.e fully weight bearing for a 71kg person) from the femoral head for three fracture angles. Normal and shear displacements were evaluated at the near and far cortices (close to and furthest from the plate). For the three fracture angles shown in Fig. 1 the results are shown in Fig. 2. It can be seen that fracture angles influence inter-fragmentary motion which has implications on healing.

Discussion
Inter-fragmentary motions are negligible for the transverse fracture. For oblique fractures, there are significant shear motions at both far and near cortex locations. At the far cortex position, the normal motion is restrained due to the compression between bone fragments. It is interesting to note that an increase in fracture angle does not always result in increased inter-fragmentary shear. The stability of the fully reduced fixation is related to the fracture angles. Inter-fragmentary motions are more likely to occur for oblique fractures. Such motions would have a major influence on the healing process and may prevent primary osteonal healing occurring. Alteration of the screw configuration or degree of weight bearing of the patient may be needed to facilitate primary healing.

References
ASSESSMENT OF KNEE PROPRIOCEPTION IN PATIENTS AFTER ACL RECONSTRUCTION OR ACL REPAIR

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Introduction
Anterior cruciate ligament (ACL) injury is one of the most common injuries of the knee [1]. This ligament is crucial for the stability of the joint. It is presumed that it also plays an important role in the proprioception, and its damage may affect its disturbance [2]. The basic method of ACL reconstruction is to replace the damaged ligament with a graft. Now, however, more and more often the new method named Internal Bracing is used, where the damaged ligament is not replaced, but is repaired and reinforced with synthetic tape, which allows for faster recovery [3]. Hence, the aim of this study was to determine the knee proprioception for patients after ACL surgery, depending on the method used (ACL repair using Internal Bracing or ACL reconstruction with hamstrings autograft), using Joint Position Sens (JPS) test.

Methods
Anterior cruciate ligament (ACL) The studies involved 48 participants who underwent ACL reconstruction using one of the two methods – with use of the Internal Bracing method (20 patients), as well as an autologous graft (28 patients) and the rehabilitation process has been completed. Patients were qualified for the project on the basis of clinical assessment made by an orthopaedist. The research was approved by the bioethics committee. The BIODEX System 4 Pro isokinetic dynamometer was used to test proprioception in the knee joint. First, the whole set of tests was performed for the healthy limb as a reference, and then for the operated limb. JPS test was defined as ability to reproduce the given angular position (30° and 60°) in the knee joint three times in two ways:

a. passively (muscles fully relaxed) - joint was moved to an appropriate angle and hold for 10 second (the patient was told to remember the position) and then returned to the starting position (90°). Next, the arm of dynamometer slowly moved participant’s shank. When the patient decided that the current position of the limb coincides with the memorized position, he/she stopped the machine with a button and the current angle was recorded
b. actively (moderately tense muscles) - in this variant, the muscles of the lower limb were maintain in moderate tension during learning and next, the participant reproduced appropriate angular position on his own.

Results
Table 1 presents the example results for JPS test for operated limbs for patients after ACL reconstruction (ACLR) and Internal Bracing method (IB).

<table>
<thead>
<tr>
<th></th>
<th>30°</th>
<th>60°</th>
</tr>
</thead>
<tbody>
<tr>
<td>passive</td>
<td>5.3</td>
<td>6.3</td>
</tr>
<tr>
<td>active</td>
<td>4.7</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Table 1: Mean JPS results [°] obtained for operated limbs for both group of patients.

Discussion
Analyzing the JPS results it can be seen that both group of patients generally obtained lower error values for 60° than 30°. Interestingly lower error values were noted for active variant for 30° and passive variant for 60° also for both group of patients. It is also hard to say which group obtained better results, as lower error values for ACLR were noted for 30° passive and 60° active, and in the other variants for IB, although here the differences were no longer as visible.

Summarizing, it can be concluded that there is a visible effect of ACL surgery type on knee proprioception. However, further studies is necessary in order to gain a deeper understanding of the discussed phenomena.

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Acknowledgements
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28th Congress of the European Society of Biomechanics, July 9-12, 2023, Maastricht, the Netherlands
WALL DISTENSIBILITY MODERATELY AFFECTS WALL SHEAR STRESS TOPOLOGICAL SKELETON AT THE CAROTID BIFURCATION

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Introduction

A link between wall shear stress (WSS) topological skeleton (TS) features and the onset of atherosclerosis in arteries has recently emerged [1,2]. The WSS TS, which is composed of WSS contraction/expansion regions linking fixed points (where WSS vanishes), can be investigated using computational hemodynamics. However, most of the studies on arterial WSS TS were performed adopting computational fluid dynamics (CFD) simulations under the rigid wall assumption. The unexplored effect of wall distensibility is here determined by carrying out fully coupled two-way fluid-structure interaction (FSI) simulations.

Methods

Subject-specific diastolic fluid domains of five healthy carotid bifurcations and their respective wall thicknesses were reconstructed from magnetic resonance (MR) angiography [3], including 15 radii of the proximal common carotid artery (CCA). Subject-specific flow rates from MR measurements [3] were used for the CCA inflow boundary condition (BC) and for tuning three-element Windkessel models at the external and internal carotid artery (ECA and ICA) outlets. Arbitrary Lagrangian-Eulerian formulation-based FSI simulations were carried out modelling the vessel wall as a fibre-reinforced anisotropic nonlinear material implementing the Holzapfel-Gasser-Ogden model [3]. The initial loading state and the collagen fibres orientations were obtained through prestress of the vessel wall [3]. Viscoelastic external support was accounted for by imposing a Robin-type BC [4]. Rigid wall CFD simulations were carried out adopting the same fluid mesh and simulation settings as FSI. All simulations were carried out in Simvascular [4]. In addition to the canonical WSS-based indicators time-average WSS (TAWSS) and oscillatory shear index (OSI), WSS TS was analysed according to a Eulerian-based method [1]. WSS contraction/expansion regions were identified by negative/positive values of the divergence of the WSS unit vector field \( \tau_s \). WSS fixed points were identified and classified by computing the Poincaré index and the eigenvalues of the Jacobian matrix [1]. The variability of the WSS contraction/expansion action was quantified by the topological shear variation index (TSVI) [1]. Pooled 20th percentile (TAWSS) and 80th percentile (OSI and TSVI) values were used to quantify the relative surface area (SA) exposed to TAWSS below (OSI, TSVI above) the corresponding threshold value.

Results

Fixed points type (saddle points, stable/unstable nodes, and foci), location, and the extent and strength of contraction/expansion regions were comparable between rigid and distensible cases (as exemplified in Fig. 1). TAWSS, OSI, and TSVI presented similar distributions as well (TSVI distributions are presented in Fig. 1 for one case). Absolute differences in SAs extension between rigid and distensible simulations were 2.3±1.9% (TAWSS), 1.0±0.8% (OSI), and 3.0±3.1% (TSVI, as detailed in the rank plot of Fig. 1).

Discussion

WSS TS features were only moderately affected by wall distensibility. Considering the increased complexity, cost, and inherent introduction of additional uncertainties to model wall distensibility, our findings suggest that rigid wall CFD simulations reasonably catch the WSS TS features of biomechanical interest. This is particularly relevant in view of a future clinical translation of CFD simulations [2], because of their reduced computational cost. However, the implemented FSI approach will allow the exploration of possible distinct or synergistic effects of hemodynamic and wall structural stimuli on atherosclerosis initiation.

References

DESIGN AND RAPID PROTOTYPING OF A NEW CRANIAL IMPLANT CONCEPT FOR CRANEOPLASTY

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Introduction
There is no standard procedure either for the design or the implantation of cranial implants. Also, there are no alloplastic cranial implants on the current market that are 100% biocompatible. The ideal material for all the heterologous cranioplasties has not been discovered yet [1]. Last, most of the state of the art is based on titanium screws fixation which has been associated with local inflammation, chronic infection and leaching of metal ions into local tissues after long-term skull implantation [2]. The aim of this work is to design and prototype a new concept that can be replicated in any area of the neurocranium, easy to attach without damage to the bones and has similar biomechanical properties to the bones that replace.

Methods
A comparison study of the models in the market was realized before the design. Later, an open source NRRD file [3] was used to segment the bone tissue in a patient missing a bone flap in the parietal-temporal area with 3D Slicer, then, the design of the components of implant were made using Blender, the rapid prototyping of the different parts fabricated by additive manufacturing and, ultimately, assembled for testing, surgical planning, and visualization purposes.

Results
A new cranial model was prototyped made of PEEK and assembled into a 3D printed bio-model of the patient’s neurocranium (Figure 1). This prototype contains different parts that sandwich together by anchors and a fixation system formed by self-locking zip ties placed on the meninges and washers that hold it together.

Discussion
This new concept presents the innovation of a geometry formed by different layers that simulate the cortical and trabecular bone (diploe) in a sandwich-based concept setting it apart from those currently lacking on the market. It also has a fixation system designed for easy attachment to the neurocranium without the need of titanium screws. The parts that are Patient-specific can be 3D printed in PEEK while the fixation system can be manufactured by traditional methods using plastic injection molding. In addition, since the fixation system contain non-metallic materials it reduces the possible complications post-surgery, and in case it needs to be removed, it can be detached from the neurocranium without damaging surrounding tissue.

References
REASONS FOR OSTEOPENIA IN ABOVE THE KNEE AMPUTEES: A BIOMECHANICAL EXPLANATION

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Introduction
Studies undertaken over the past 50 years have shown that above the knee amputees (AKAs) lose bone mass at rates of postmenopausal individuals. It has been established that load bearing physical activity is a major promoter of bone health. While therapeutic physical activities have helped improve bone health of returning space travellers [1], AKAs bone loss continues despite physical activity and disregarding significant differentiators such as age [2, 3]. This loss of bone mass results in a higher rate of femoral fractures in conjunction with the fact that AKAs are more likely to fall in comparison to able bodied individuals. It has been established that skeletal load bearing is a major promoter of bone health. Therefore, in this study we considered the mechanical environment furnished by prosthetic design and techniques, which permit AKAs high mobility levels and participation in sports.

We employ numerical simulation aimed to describe the mechanical environment and the interplay of prosthetics, skeletal and soft tissue system to explain osteopenia in above knee amputees.

Methods
A series of FE models were developed using skeletal geometries of the pelvis and the femur from a CT scan. Most previous studies on AKAs have limited their models to the femur. The hip joint was manipulated in frontal plane at 15° adduction with collated sagittal at 10° extension, 0° (neutral), 10° flexion and 20° flexion. A 3D scanned ischial containment socket (ICS) was fitted to the skeletal geometries, and body weight (BW) loading imposed from the total body centre of mass totalling 100% to 225% in 25% increments, as load bearing experienced by an individual weighting 100 kg representing loads experienced during walking or running. Finally, soft tissue compressibility between the ischium and the ICS was controlled allowing either: 5mm, 2.5mm and 0mm.
A second series of FE models for comparison were created following previous description substituting the socket design from ICS to SubIschial, the former is extensively prescribed while the latter is a novel and much more expensive technique.

Results
Proximal trabecular bone in a residual limb wearing an ICS, showed stunted levels of strain energy density (SED) in comparison to the SubIschial case (Fig 1a). For the ICS hip joint alignment at 20° of hip flexion consistently showed the highest levels in SED stimulation, trend amplified by higher amount of compressive soft tissue as mortar (Fig 1(b)).

Discussion
Our results show that intimate ischium capture, a technique employed for ischial containment sockets for comfort and as a mobility promoter, results significant reduction in the mechanical stimulation of the bone in comparison to the SubIschial socket. As this study is limited to numerical further research is needed to confirm our findings using in vivo data capture. To our knowledge, these models are the first ever that explain the mechanical effect of prosthetic techniques on bone loss in above the knee amputees.

References

Acknowledgements
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METAPHYSEAL VOIDS IN PLATED PROXIMAL HUMERUS FRACTURES TREATED WITH A NOVEL TECHNIQUE – A BIOMECHANICAL STUDY

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Introduction
The treatment of unstable proximal humerus fractures with metaphyseal defects – weakening the osteosynthesis construct – is challenging. A novel technique for cement augmentation of plated complex proximal humerus fractures with metaphyseal voids was recently developed.

The aim of this biomechanical study was to assess the stability of plated complex humerus fractures augmented according to the novel technique versus no augmentation.

Methods
Three-part unstable proximal humerus fractures with posttraumatic voids type AO/OTA 11-B1 were reproduced in 16 paired human cadaveric humeri with 76 years average age of donors (range 66–92), assigned pairwise to 2 groups for locked plating with identical screw configuration. In one of the groups, 6 mL PMMA-based partially cured bone cement of medium viscosity (7 min after mixing) was manually placed through the traumatic lateral window into the void of the humeral head prior to screw insertion. Biomechanical testing was performed in 20° adduction of the specimens under applied progressively increasing cyclic loading at 2 Hz until failure (Fig. 1). Interfragmentary and bone-implant movements were captured by means of motion tracking and triggered x-ray imaging.

Results
Initial stiffness was not significantly different between the groups, p = 0.47. Varus deformation (Fig.2a), fracture displacement at the medial aspect of the humeral head, cut-out (Fig.2b) and migration of the proximal plate screws were all significantly smaller in the augmented group after 2000, 4000, 6000, 8000 and 10000 cycles, p < 0.01. Number of cycles to 2 mm fracture displacement at the medial aspect of the humeral head was significantly higher in the augmented group, p = 0.02.

Discussion
From a biomechanical perspective, augmentation with PMMA-based bone cement placed in the posttraumatic void of the humeral head during locked plating of unstable proximal humerus fractures considerably increases fixation stability and can reduce the risk of postoperative biomechanically related complications.

Figure 1: Test setup with a specimen mounted for biomechanical testing.

Figure 2: Varus deformation (a) and cut-out of the proximal screws (b) shown over the first 10000 cycles in equidistant steps every 2000 cycles for augmented and non-augmented technique separately in terms of mean and standard deviation values.
BIOMECHANICAL COMPARISON OF TWO 2-MM HEADLESS CANNULATED SCREWS VERSUS A SINGLE 3-MM SCREW IN CAPITELLAR HUMERUS FRACTURE FIXATION

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Introduction
Dubberley Type IA fractures of the capitellum are the most common distal humerus fractures without condyle-epicondyle involvement. Their intraarticular pattern require mandatory operative treatment to achieve absolute stability. The aim of this study was to investigate the biomechanical performance of two methods for screw fixation of capitellum humeri fractures.

The aim of this study was to investigate the biomechanical performance of two methods for screw fixation of capitellum humeri fractures.

Methods
Capitellar fractures Dubberley IA (AO/OTA 13-B3) were reproduced in sixteen paired human cadaveric humeri with 76 years average age of the donors (range 66–92 years), pairwise assigned to two groups for fixation with either two 2-mm anteroposterior headless cannulated screws (group 1) or a single 3-mm anteroposterior headless cannulated screw (group 2). Biomechanical testing was performed in a setup simulating 20° elbow flexion (Fig.1). Progressively increasing cyclic loading was applied at 2 Hz until failure of the bone-implant constructs. Interfragmentary movements were captured by means of motion tracking.

Results
Initial stiffness was not significantly different between the groups, p = 0.33. Both axial displacement (Fig.2a) and flexion deformation (Fig.2b) at the fracture site after 500, 1000, 1500, 2000, 2500 and 3000 cycles were significantly smaller in group 1, p < 0.01. Number of cycles until 2 mm fracture displacement was significantly higher in group 1, p = 0.04.

Discussion
From a biomechanical perspective, fixation of Dubberley IA capitellar humerus fractures with two 2-mm anteroposterior headless cannulated screws is advantageous versus single 3-mm anteroposterior headless cannulated screw fixation and can favor early postoperative rehabilitation with reduced risk of biomechanically-related complications.
CONTACT-PRESSURE BASED, MULTI-SCALE KNEE MODEL TO PREDICT CARTILAGE DEGENERATION

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Introduction

Osteoarthritis (OA) is a whole joint disease, which most frequently affects the knee joint [1]. Cartilage degeneration is the hallmark of OA, however, the mechano-biological responses of cartilage during OA are not yet fully understood [2]. To increase understanding on cartilage degeneration, we recently developed a whole knee joint finite element (FE) models (including the femoral and tibial cartilages and menisci) that predicts cartilage degeneration based on loading conditions obtained from MSK modeling and integrated 3D motion capture data. However, the complexity and high computational costs prohibit these models to be used with adaptive algorithms, that requires to iteratively run the FE models to predict the time-dependent tissue degradation [3]. In this study, the validity of an FE model of the tibial medial compartment for prediction of cartilage degeneration based on contact-pressure estimation obtained from a MSK modeling workflow is verified for a healthy and progressive knee OA subjects against the whole joint FE models (gold standard). The reduced model efficiently predicts cartilage degeneration, which is promising to be used for adaptive modeling in the future.

Methods

Comparable to the original whole joint FE model, an FE model of the medial tibial compartment was built using fibril-reinforced poroviscoelastic material. The pressure distributions estimated by musculoskeletal models [4], based on 3D integrated gait data captured from a healthy (control) and a progressive knee OA subject were applied to the FE model. Fibral strain (FS) and maximum shear strain (MSS), were calculated in both models at the first peak of knee contact force. The normalized volumes of degraded elements and degrees of collagen and PG degradations were estimated with previously introduced degradation equations (Eqs. 1 and 2) [3].

\[
De_{\text{collagen}} = 1 - e^{-[FS-\text{threshold}]_{FS}} \quad (1)
\]

\[
De_{\text{PG}} = \frac{1}{3} \sqrt{|MSS-\text{threshold}_{MSS}|} \quad (2)
\]

Results

Computational cost estimated from the reduced model decreased by 8 times compared to the whole joint model (2h vs 16h). FS and MSS obtained from both models are visualized in Fig.1. The volume of degenerated elements and the average degrees of collagen degeneration (threshold: FS=10%) are given in Table 1. The degrees of PG degeneration are given for two thresholds (MSS=30% or 50%) [3,5].

Discussion

Larger areas of high FS and MSS are obtained for the OA compared to the control subject in both reduced and whole joint models (Fig. 1). The predicted locations of high FS and MSS are comparable between the two models, however, higher MSS are observed in the reduced model. This caused overestimating the degree and volume of PG degradation in the reduced model (Table 1), which can be due to excluding the role of the menisci, as an energy absorber tissue decreasing the pressure on cartilage. Therefore, the reduced model can correctly predict the location of degradation but may overestimate the degradation level. Additionally, the sensitivity of predicted PG depletion to the threshold suggests the needs for more accurate estimation of degradation thresholds in adaptive models.

Table 1: Percentages of volume (V) and degree (D) of collagen and PG degradation.

<table>
<thead>
<tr>
<th>Degradation Parameters</th>
<th>Control</th>
<th>OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>PG; threshold 30%</td>
<td>17.7</td>
<td>6.67</td>
</tr>
<tr>
<td>PG; threshold 50%</td>
<td>0.12</td>
<td>7.55</td>
</tr>
<tr>
<td>Whole Joint Model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td>0.03</td>
<td>0.92</td>
</tr>
<tr>
<td>PG; threshold 30%</td>
<td>4.37</td>
<td>4.66</td>
</tr>
<tr>
<td>PG; threshold 50%</td>
<td>0.02</td>
<td>7.77</td>
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References


Acknowledgements

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FIBRILLAR MECHANICS AND STRUCTURE OF FIBROTIC TISSUE USING IN SITU SYNCHROTRON X-RAY NANOMECHANICAL IMAGING

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Introduction
Keloids are an example of a fibrotic skin disorder linked to hypertrophic scarring [1], with abnormal extracellular matrix (ECM) composition in terms of collagen type and keloid-specific proteins. The biomechanics of the ECM is believed to be critical to progression of fibrotic disorders[2], but so far there is little known about the ultrastructure (fibrillar-level) biomechanics in keloid and scarring ECM. Here, we show how the combination of synchrotron small-angle X-ray scattering (SAXS), in-situ loading, and diffraction-based image correlation can quantify fibrillar strain, reorientation, and ordering in keloids under biomechanical loading [3].

Materials and Methods
Keloid samples were obtained from patients at the plastic surgery department at Barts NHS Health Trust with full ethical approval. Planar keloid sections were prepared (30-35×10-15×1mm³) with a double-scalpel setup and stored at -20°C till SAXS measurements. Samples were measured at the SAXS beamline I22 (Diamond Light Source, Harwell) using a Pilatus 2M detector (X-ray energy 14 keV; beam size 15 µm). Three types of experiments: scanning SAXS, in-situ tensile loading with scanning SAXS, and scanning SAXS with sample rotation (texture) were carried out on different samples. The 2D SAXS patterns were azimuthally- (I(q)) and radialy- (I(χ)) averaged using the software DAWN (www.dawnsci.org). I(q) and I(χ) profiles were analyzed [CITE] to extract ultrastructural parameters like fibrillar D-period (linked to fibril pre-strain), collagen peak intensity (fibrillar order), I(χ) peak position (fibrillar orientation).

Results and Discussion
SAXS images in Figure 1(A) shows peaks due to collagen fibrillar D-period and interfibrillar proteoglycan-rich phase. Under tensile loading, I(q) profiles show peak shift (increased D-period/fibril strain) and profile narrowing (reorientation and intrafibrillar ordering) in I(χ) (Fig 1(C)). Mapping these parameters across the tissue (Fig 1(D)) show i) clear internal pre-strain gradients in native state and ii) appearance of highly-stress fibrillar-level bands across the tissue. Our results demonstrate proof-of-concept in the use of synchrotron X-ray nanomechanical imaging to understand the mechanobiology of fibrotic disorders.

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AN ITERATIVE REGULARISATION ALGORITHM TO ESTIMATE PERMEABILITY IN MYOCARDIAL PERFUSION

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Introduction
Myocardial perfusion is the blood supply to heart muscle provided by the coronary arteries. The blood flow can be described by Darcy’s law as fluid flows through a porous media at the macro-scale. Additionally, contrast enhanced myocardial perfusion imaging uses an injected contrast agent (CA) as a proxy for blood flow in cardiac tissue. This imaging modality has previously been modelled as the advection-diffusion of the CA through a porous medium [1], which provided a computational framework enabling the direct mapping from permeability to local perfusion defect. In this work we propose a method to estimate permeability from observed contrast agent concentration.

Methods
An iterative algorithm was developed for inversely estimating the permeability by the observed CA concentration field, as a route to more accurate and detailed quantitative analysis. Several test cases of varying porous parameters, Peclet number (Pe) and boundary conditions were used to generate ‘observed’ data, on which to test the inverse estimation. The forward models of Darcy flow and CA advection-diffusion solved using the finite element method, implemented in FEniCS. The inverse problem was solved by Tikhonov regularisation approach: minimising an objective function containing two penalty terms: (1) the error between estimated concentration and observed concentration, and (2) the gradient of the permeability tensor. However, this inverse problem is ill-posed as the solution is not unique. Therefore, an iterative regularisation algorithm was developed, which iteratively adjusts the weighting of the penalty terms and updates the initial guess. This allows the optimiser to converge to a low overall error while preserving local inhomogeneities in permeability.

Results
The algorithm was tested for four types of permeability distribution: (a) homogeneous permeability, (b) homogeneous permeability with defect, (c) linearly inhomogeneous permeability, (d) linearly inhomogeneous permeability with defect. For (a), only one iteration of regularisation was required. For (b), the location, shape, defect and background permeability were successfully estimated within few iterations. For (c), the estimation was still acceptable with a L2 error norm about 0.12, although the permeability at the region where has no CA filled in are slightly mis-estimated. And for the most challenging case (d), the location and extent of the defect region was estimated with a same precision of error norm of (c), see Figure 1 for the contour plot of permeability estimation of (d). In addition, a parametric analysis was studied to find out the sensitivity to the parameter Peclet number (Pe) and observation frequency (Tm, the time scale of advection and observation). For test case (a), the error was very small and negligible. For (b)(c)(d), generally, both the error norm of estimated permeability (Error K) and concentration (Error c) increase when Pe increases, and the error remain stable when Tm is greater than 5 (See Figure 2).

Discussion
Generally, when Pe increases, diffusion takes less effect on CA’s movement, the estimation becomes harder due to not having enough concentration information. And Tm is noncritical for purely homogeneous permeability estimation. For inhomogeneous or defective permeability cases, when Tm is greater than a threshold, the performance of the estimation cannot be improved.

References
Introduction
With more than 80,000 deaths per year due to coronary heart disease in the UK and an associated cost of treatment estimated at £1.8 billion [1]. One promising technique for the early diagnosis of coronary disease is contrast enhanced magnetic resonance (MR) perfusion imaging. In this diagnostic approach a contrast agent (CA), typically gadolinium-based, is injected into the patient and MR images measure its progress through the coronary circulation. This CA transport distinguishes between the areas of myocardial tissue receiving blood and those which are not. In this study we introduce a novel computational model of MR coronary perfusion imaging to provide a platform for optimising this imaging technique across a range of imaging and physiological parameters.

Methods
Darcy’s law along with the continuity equation is derived to describe the blood flow in a poroelastic medium. And these equations are coupled with the poroelastic equation which characterising the deformation of myocardium. Its constitutive law is hyperelastic and taken into account three factors: the elastic behaviour of the skeleton, the change in free energy due to the incoming fluid and a barrier preventing the fluid porosity from becoming negative. Moreover, the transport of a freely diffusive CA is characterised through advection-diffusion equation. Finally, an Arbitrary Lagrangian Eulerian (ALE) formulation is applied to the resulting coupled system of reaction-advection-diffusion equations in this deforming poroelastic medium. The system of equations is solved by the Finite Element Method (FEM), implemented in FEniCS. An iterative approach is used to loop through the deformation of myocardium and blood flow rate until converged. Due to the large computational cost, HPC cluster is used.

Results
The schematic graph illustrates the configuration in Figure 1. A geometrically simplified cuboid model characterises coronary flow and cardiac mechanics. The coronary vessels are represented by three source terms of Gaussian functions. The middle source term can be removed to simulate the effect of a severe coronary stenosis. The drainage of blood fluid out of the capillaries and into the venous system is represented as a uniformly-distributed pressure-dependent sink term such that the term is only active when the pore pressure is greater than the venous pressure. Assuming the body force and acceleration of the solid is zero and the boundary condition on the left side is set to zero displacement in longitudinal x direction. A sample point near the middle source is chosen to illustrate the CA transport. When the middle term is switched on, the concentration goes up quickly and then it is washed out into venous sink term and gradually diffuses into tissue. While the middle term is off, the concentration increases slowly (See Figure 2).

Discussion
The results demonstrate that the transport of CA in myocardial perfusion can be modelled by using poromechanics theory coupled with advection-diffusion equation in Lagrangian frame. The effect of a severe coronary stenosis can be simulated. The model will be developed for application to realistic ventricular geometries in the future.

References

Acknowledgements
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VALIDATED, HIGH-RESOLUTION, NON-LINEAR, EXPLICIT FINITE ELEMENT MODELS FOR SIMULATING SCREW PUSH-IN STRENGTH

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Introduction

Bone screws are widely used in orthopaedic applications, but screw loosening is still a major concern [1]. Finite element (FE) models have been extensively used to predict the mechanical response of orthopaedic screws with the goal of improving screw design. However, studies in the past had to compromise between modelling the trabecular structure at a high resolution vs. sophistication in terms of mechanical properties and/or boundary conditions. This typically resulted in systematic differences being reported between experimental and FE model generated pull-out stiffness and strength results [2]. The aim of our work is to overcome the limitations of previous studies by utilizing explicit FE solvers that allow for modelling some of the complex mechanical interactions at play in bone-screw constructs at a micro level resolution. We validated our model against previously published experimental results from push-in tests [3].

Methods

The trabecular bone geometry of the samples was segmented from µCT images using Fiji (ImageJ 1.53t, NIH). The µCT images were resampled to a lower resolution (from 20 to 80 µm), followed by a direct voxel-to-8 node hexahedral element conversion, using an in-house MATLAB code. The screw geometries were digitally inserted into the FE model by removing bone voxels where bone and screw overlapped. The models were solved using Abaqus explicit solver (ABAQUS 2021, Dassault Systemes). FE models with different degree of sophistication were compared to experimental results: (i) bonded contact between bone and screw elements with linear elastic (LE) bone properties (E=8.4 GPa); (ii) same as (i) but with non-linear bone properties (CDP=concrete damage plasticity) and element deletion at 35% post-ultimate strain; (iii) sliding bone-screw contact (μ=0.3) and LE bone properties; (iv) and sliding bone-screw contact with CDP bone properties. The boundary conditions are shown in Figure 1 (a). The FE models were solved on a computer cluster with 128 GB ram and 64 CPUs.

Results

The FE models solved over 15h of wall-time on average. The maximum principal strain field of different models are shown in Figure 1, and the corresponding force-displacement curves are shown in Figure 2 (a). The fracture was found to be limited to near the threads in the case of friction contact, and for bonded contact only after trabecular fracture (CDP element deletion), similarly to previous experimental results [4], rather than the far field propagation found in previous linear models [2]. The frictional contact decreased the push-in stiffness from 8357 N/mm to 3947 N/mm, which better matches the 3876 N/mm found in the experimental result (Figure 2 (a)). The numerical model considering contact and material nonlinearity (model iv) matched the experimental results of different bone samples within 15% error in terms of stiffness, strength, and displacement at failure (Figure 2 (b)).

Conclusion

Non-linear friction contact and a CDP bone model can reduce the stiffness of numerical push-in simulations, and reproduce the experimental results within small error (15 %) for different bone samples. Friction contact and/or element deletion also limit the strain field to near the threads, which was observed experimentally [4].

References


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MODELLING OF CELL-SCALE HAEMODYNAMICS IN THE MATERNAL INTERVILLOUS SPACE OF HUMAN PLACENTA

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Introduction
The human placenta is a vital organ where the mother supplies oxygen and nutrients to her fetus. The solute transport process relies on robust maternal blood flow in the highly heterogeneous intervillous space (IVS) akin to random porous media [1,2]. Because the IVS contains flow channels which are comparable in size with red blood cells (RBCs), the particulate nature of blood can lead to rheological behavior beyond the description of existing continuum models [3]. In this work, we model cellular blood flow across realistic IVS as a suspension of deformable RBCs in plasma, to enable a mechanistic understanding of the structure-function relationship between the IVS’s architecture and haemodynamics.

Methods
3D IVS domains were reconstructed from synchrotron micro-CT image stacks of the human placenta tissue [4] (Fig. 1a). Cellular blood flow of designated feeding haematocrits (i.e. HF, volume fraction of RBCs) in the reconstructed flow domain was simulated with our high-performance parallel blood flow simulator HemeLB (open source: https://github.com/hemelb-codes/hemelb) using the lattice-Boltzmann and immersed-boundary methods [5]. For comparison, homogeneous Newtonian flow with physiological blood viscosity and pure plasma flow with liquid water viscosity were also simulated.

Results
Preliminary flow simulations in a large IVS domain, either for homogeneous blood (Fig. 1b) or for dilute RBC suspension (HF = 1%, Fig. 1c), recapitulate the exponential flow distribution reported for IVS flow [4]. Further simulations with homogeneous blood along three principal directions of a cropped cubic domain reveal a moderate degree of flow anisotropy (Fig. 1d). For semi-dilute RBC suspension (HF = 10%, Fig. 1e), the flow resistance in the three directions are indeed different (despite similar patterns for the RBC residence time, Fig. 1f), evaluated by the apparent viscosity of the suspension relative to plasma viscosity (Table 1). The RBC deformability is also found to have a notable effect, with elevated viscosity for hardened cells.

<table>
<thead>
<tr>
<th>RBC type</th>
<th>x-flow</th>
<th>y-flow</th>
<th>z-flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2.66</td>
<td>2.71</td>
<td>2.87</td>
</tr>
<tr>
<td>Hardened</td>
<td>2.95</td>
<td>2.96</td>
<td>3.13</td>
</tr>
</tbody>
</table>

Table 1: Relative apparent viscosity for HF = 10%.

Discussion
The cell-scale haemodynamics investigated here can help elucidate the elusive structure and function relationship in the IVS which may explain how impaired placenta architecture causes pregnancy pathologies.

References

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**INSTRUMENTED HARNESS TO IMPROVE THE WELFARE OF GUIDE DOGS**

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**Introduction**

Common assistive technologies for the visually impaired people (VIP) include white canes, electronic mobility aids and guide dogs. These aids enable VIP to navigate and detect obstacles in their path. The most commonly used tool is the white cane, but it has its limitations in detecting distant or moving objects as well as obstacles detached from the ground surface. To improve the perception of the environment and avoid obstacles, several assistive systems have been proposed [1]. These devices inform the VIP about hindrances and provide audible or tactile feedback. Although these aids offer some assistance, users must still navigate around obstacles themselves. Guide dogs, on the other hand, can detect objects from a distance and help VIP navigate around them. However, training guide dogs is time-consuming and expensive. Therefore, efforts are made to extend the working life of these dogs.

During the guidance, the VIP is connected to his dog companion via a harness and a handle. This handle links to the abdominal belt of the harness via two support points positioned approximately on the left and right side of the dog’s shoulder. An angle is created between the two support points when the handle is moved from its neutral position. Due to this introduced torsion and the tight linkage in the harness, excessive and permanent displacement of the handle can cause strains on the musculoskeletal system of dogs and thus lead to kinematic changes in their gait behaviour [2]. Hence, recent research suggests improving harness designs to reduce their impact on the dog’s biomechanics [3, 4]. In this context, we developed an instrumented guide dog harness. Our device is equipped with a millimeter wave radar technology which detects angular changes of the harness and returns biofeedback over an audio signal. We tested our system under laboratory conditions and demonstrated a measurement accuracy of our algorithm of 0.735° ± 1.877°.

**Methods**

*System:* Our portable prototype (Figure 1a) consists of a mm-wave radar (A111, Acconeer AB, Sweden) controlled by an RPi 4B (Raspberry Pi, UK) and powered by two Li-Ion batteries. Radar and controls are mounted to the bar near the grab handle. Two corner reflectors attached to the support points at about the height of the dog’s withers provide information about the prevailing geometry and the angle of handle position. The radar operates at 60 GHz and evaluates the energy in the reflected echoes from multiple transmitted pulses.

![Figure 1: (a) shows the mounting of the setup on the dog harness. (b) depicts the geometry of the harness during angular deviation (P1 and P2 – distance between radar and reflectors, D0 neutral distance, D* – actual distance, W – width of reflectors)](image)

According to the algorithm (Equation 1), the actual angle (β) of the harness handle is calculated from the analysis of the resulting peaks using the cosine theorem.

$$\beta = 90 - \cos^{-1}\left(\frac{D_0^2 + W^2 - P_2^2}{2D_0W}\right)$$  \hspace{1cm} (1)

**Biofeedback:** Our system allows biofeedback via a tone (750 Hz) with increasing pulse frequency at increasing angular deflection.

**Validation:** To test the accuracy of our system and ensure repeatability, we used a table prototype that mimics the movement of the harness. A motor with a rotation speed of 2° per second was used to rotate the two corner reflectors while the radar acquired data from the reflectors. The actual angle (controlled via the motor) was compared with the measured angle (captured with the radar).

**Results and Discussion**

Our system detected angular positions with an accuracy of 0.735° ± 1.877°. Hence, our prototype confirms the applicability of radar technology for the use in guide dog harnesses and provides the first biofeedback system solution for guide dog education.

**References**
