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This document collects the abstracts of the presentations hosted within the 2021 ESB-ITA annual meeting, held online on the MS Teams platform due to the health emergency from COVID-19 on September 23th and 24th, 2021.

The Meeting hosts:

- the presentation of three national or international projects, in which members of the ESB-ITA community are actively involved;
- the presentation of invited papers on three different topics in biomechanics (musculoskeletal biomechanics, cardiovascular biomechanics, tissue engineering);
- the presentation of a shortlist of three Master Theses for the selection of the ESB-ITA Master Thesis Award 2021.

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Computer science provides reliable support to surgeons by means of image processing tools, surgical simulators, pre-operative planning and surgical navigation systems. Such tools for *computer assisted surgery* are well established and their application is widespread in hospitals, providing for the visual interaction with a specific anatomical district. In this respect *in silico* medicine, i.e. the direct use of the methods of *computational mechanics and fluid dynamics* in the diagnosis, prevention or treatment of a disease, may provide suitable information for reliability assessment and optimal design of surgical procedures, instrumentations and prosthetic devices. The *in silico* models require *a priori* knowledge of the mechanical and rheological behavior of tissues and devices to be affordably applied. From cells to organs biomechanical investigations can be pursued by means of averaged or patient-specific models. An *averaged model* aims to characterize the typical behavior of the biological structure, by interpreting geometrical and mechanical features that are common to the widest segment of the population. Such models can be used in "*in silico* trials", which allow for example for the design and the assessment of novel procedures and devices. On the other side, a *patient specific model* is devised to interpret the mechanobiological behavior of the specific patient, thus allowing the design and/or the characterization of tailored surgical procedures, devices and prostheses. Real time applications can also provide unique aid to surgeons but require automated techniques for model's generation and management. Computational medicine can also be exploited for the *validation and the certification of biomedical devices*. Such *in silico* approach can have a remarkable societal impact in terms of costs reduction and ethical issues. The CECOMES project aims to create an Italian network able to promote the use of the *in silico* medicine and related technologies jointly with hospitals, research institutions and enterprises.

Emanuele Luigi Carniel is the Head of the Centre for Mechanics of Biological Materials of the University of Padova, and Associate Professor of Industrial Bioengineering. Research activities focus on the investigation of the mechanical functionality of biological tissues and structures and are carried out in cooperation with researchers from different fields, as engineering, biomedical science and surgery. The mission pertains to the optimization of surgical procedures and biomedical devices, especially concerning mechanical and mechano-biological aspects. A unique approach is followed, where in silico mathematical modelling, in vitro biomechanical experimentations on human and animal tissues and structures, and in vivo animal models are synergistically integrated to rationally design and validate novel procedures and devices. Research projects and activities are frequently developed y cooperation with industries, technological clusters and platforms. Novel products, processes and patents document the results of the cooperation.

SimInSitu

SimInSitu is aiming to develop a sophisticated in-silico method to predict the short- and long-term behaviour of in-situ tissue engineered heart valves by combing advanced tissue remodelling algorithms with a personalized virtual heart modelling approach. The method will be specifically developed to predict the complex transformation process of biodegradable heart valves from the initially synthetic scaffold into a fully remodelled & functional valve. This transformation process, named ETR for Endogenous Tissue Restoration, is the core technology for a new generation of very promising biodegradable vascular device currently developed by Xeltis. ETR makes the use of animal derived tissue, which is used in the majority of commercially available bioprosthetic heart valves, obsolete and avoids thereby durability related issues and potentially minimized the need for reoperations. Though, significant progress was made during the past years in developing ERT based devices, it remains very challenging, costly, time-consuming, and rich with obstacles. New knowledge can only be generated through a tedious trial & error process (requiring preclinical and clinical studies), since the restorative process cannot be replicated in an in-vitro environment.
Advanced Computer Modelling & Simulation technologies have the potential to overcome this limitation by allowing to test new designs, modified scaffold compositions, or other applications in a virtual patient-specific environment – in-silico.
SimInSitu will not only develop such a computer model but will also verify and validate it thoroughly by making use of the extensive in-vitro and in-vivo data available and where necessary will generate new data to support the credibility of this in-silico method. The availability of this computer model could contribute significantly to an acceleration of especially the ETR-device development and accelerate their translation into the clinic and market.

SimInSitu has received funding from the European Union's Horizon 2020 Research and Innovation Programme, under Grant Agreement n. 101017523.

Nils Götzen, holds a Dipl.-Ing in Aeronautical Engineering and MSc./Ph.D. in Biomedical Engineering. He has more than 25 years of experience in numerical methods with focus on biomechanics and medical devices. After completing his academic education, he started working as a stent development engineer & technical project manager for Biotronik and was responsible for the design development for the biodegradable magnesium stent/scaffold Magmaris, among other things. He then continued to work for Straumann AG as a Project/Program Manager for the Digital Dentistry program. Afterwards, he moved with his family to the Netherlands to work for Xeltis BV as the Senior Program Manager and was successfully bringing the Pulmonary Valve Project from the feasibility phase into clinical trial stage. Since 2017 he is working for 4RS as Senior FEA Consultant & Life-Science Expert.

Computer models informed by experimental data enable us to test hypotheses and make predictions, significantly streamlining the research and development cycle relative to trial and error. When it comes to medicine, experimentation relies on biological samples ranging from cultured cells to whole animals, so increased reliance on modelling has additional benefits. Harnessing Big Data and tremendous advances in computing power could pave the way to minimising and eventually eliminating the need for anything other than in silico 'experimentation' in medical research and development. The EU-funded ISW project will bring together a large European consortium and a multi-stakeholder advisory board to lay the groundwork to achieve this goal with attention to the models, regulation, standardisation and more.
The overall aim of the In Silico World project is to accelerate the uptake of modelling and simulation technologies for the development and regulatory assessment of all kind of medical products. This will be achieved by supporting the trajectory of a number of In Silico Trials solutions through development, validation, regulatory approval, optimisation, and commercial exploitation. These solutions, already developed to different stages, target different medical specialities (endocrinology, orthopaedics, infectiology, neurology, oncology, cardiology), different diseases (osteoporosis, dynapenia-sarcopenia, tuberculosis, multiple sclerosis, mammary carcinoma, arterial stenosis, etc.), and different types of medical products (medicinal products, medical devices, and Advanced Therapeutic Medicinal Products). In parallel the consortium will work with a large multi-stakeholder advisory board to form a community of Practice around In Silico Trials, where academics, industry experts, regulators, clinicians, and patients can develop consensus around Good modelling Practices. As the solutions under development move toward their commercial exploitation, the ISW consortium will make available to the Community of Practice a number of resources (technologies, validation data, first in kind regulatory decisions, technical standardisation plans, good modelling practices, scalability and efficiency-improving solutions, exploitation business models, etc.) that will permanently lower barriers to adoption for any future development.

In Silico World project has received funding from the European Union’s Horizon 2020 Research and Innovation Programme, under Grant Agreement n. 101016503.

Alfons Hoekstra currently holds a position as Associate Professor at the University of Amsterdam, The Netherlands and he is affiliated with the Computational Science Lab, which is part of the Informatics Institute of the Faculty of Science. He also holds a position as Professor in Computational Biomedicine at the ITMO University in Saint Petersburg, Russia.

Finite element assessment of diabetic foot insoles

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Background Diabetic subjects often develop an ulcer, caused by ischemic, neurological and biomechanical alterations [1]. One method for treating or preventing foot ulceration is to prescribe customized plantar insoles, usually designed and produced by manual techniques. Finite element modeling simulations have been recognized as a valid method for quantitatively estimate the effect of insoles with respect to its design [3].
Aim Verify if it is possible to apply a simplified methodology for insole efficacy testing, at the orthotic manufacturer site.
Material and Methods Foot geometries (3D scanner, Structure3D) and plantar pressures (PP - PedarX, Novel gmbh) data were registered on 9 diabetic neuropathic subjects (mean(SD) age 60.9(17.4) years and BMI 29.4(5.4) Kg/m2) while walking both overground and on a treadmill (2 km/h). Foot finite element models were developed [2] by meshing foot and insoles geometries from the scanned foot volume and the foot bones scaled based on each subject's foot morphology. Insole material properties were assigned according to the manufacturer's declared characteristics. Simulations were run with ground reaction forces and foot-ground angle during gait as boundary conditions. Four critical instants of the stance phase of gait were simulated [2]: with and without the insole. Models validity was assessed by the comparison between the experimental PP and the simulated ones. Simulated PP and Von Mises stresses in plantar soft tissues were compared across the different conditions.
Results and Discussion In the simulations run with the insole, high PPs were not completely redistributed, but Von Mises stresses, in the internal soft tissues, were reduced at the plantar aspect of the foot. The proposed methodology was successfully applied at the orthotic manufacturers. Future development will include the coupling between the shoe and the orthosis.

[1] Armstrong DG et al. SAGE 2017; 47(2):145-171
[2] Guiotto et al. J Biomech, 2014;47(12):3064-3071
[3] Telfer S. et al. J Biomech 2017;60:157–161

Anticipatory Postural Adjustments During Gait Initiation in People with Mild Chronic Low Back Pain

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Background Anticipatory Postural Adjustments (APA) and trunk flexion are fundamental mechanisms utilized prior to walking to produce optimal biomechanical condition [1]. However, individuals with mild Chronic Low Back Pain (mCLBP) showed an impaired neuro-mechanical control of the trunk during walking [2].
Aim To investigate the effects of mCLBP on APAs and trunk kinematics during gait initiation.
Material and Methods Eleven healthy adults and 11 adults with mCLBP performed 10 gait initiation trials. APA amplitude and duration, as well as the initial posterior peak force and the step initiation latency were obtained from force plate data. A motion capture system was used to assess the thorax forward leaning motion during step preparation and the first step spatiotemporal parameters. Group comparison was performed and a partial correlation analysis was used to evaluate the relationship between thorax motion and gait initiation parameters.
Results and Discussion Participants with mCLBP showed altered postural preparation, with comparable APA amplitude but longer duration compared to healthy controls. This was also associated with thorax motion during gait initiation, but tends to disappear during the first step execution.

[1] L. Laudani, *J Electr Kin*, 2006, vol. 16, pp. 603–610.
[2] L. Rum, in *Gait Posture*, 2021, vol. 84, pp

How the introduction of subject-specific musculoskeletal models affects the estimation of knee joint reaction forces

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Background Musculoskeletal modeling is a useful tool to predict the effect of interventions and to obtain information on human biomechanics in a non-invasive manner. Subject-specific models are assumed to have greater physiological reliability [1] but their realization requires a large amount of time, thus various generic models were made available over time to speed up the modelling process and address the most clinical necessities.
Aim The work aims to investigate the differences existing between a generic multibody model [2] and a personalized one, focusing on medial and lateral joint reaction forces.
Material and Methods One healthy woman performed 8 gait trials walking barefoot at self-selected speed and kinematics and kinetics were acquired. A subject-specific model was realized in nmsBuilder software [3] exploiting segmentation and information deriving from 3T MRI, and gait outputs were estimated via OpenSim [4] performing inverse kinematics, inverse dynamics, static optimization, and joint reaction analysis.
Results and Discussion Differences in the force peaks were observed in the knee joint; specifically, generic model overestimated the 1st peak and underestimated the 2nd peak for what concerns total joint reaction; subject-specific model also measured a two-fold higher 2nd peak looking at lateral joint reaction. These differences suggest that the utilization of different models may have an impact on the desired output. Nevertheless, since developing a personalized model is a data-greedy and time-consuming task and – in specific cases – differences may be not so high in absolute terms, the proper modelling choice is generally up to the particular necessities of studies.

[1] D. Saxby et al, Biomech Model Mechanobiol, 19:1169-1185, 2020.
[2] Z. Lerner et al, J Biomec, 48:644-650, 2015.
[3] G. Valente et al, Comput Methods Programs Biomed, 152:85-92, 2017
[4] S.L. Delp et al, IEEE Trans Biomed Eng, 54:1940-1950, 20

Numerical lubrication modeling of total hip replacements coupled with musculoskeletal multibody dynamics

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Background Nowadays a challenging topic in the framework of biomechanics is represented by the wear prediction of the human prostheses. Mainly due to the aging, the cartilage of a human synovial articulation deteriorates, then a total or partial replacement of the worn joint is often required. The implant composed by artificial surfaces has to guarantee long duration, mobility and stability, so an accurate tribological analysis is needed in order to design it.
Aim Regarding the human hip joint, the objective of this research was to develop an *in silico* tool able to compute, starting from his kinematics, the tribological quantities, such as lubricating synovial fluid pressure, contact pressure and wear, in order to analyse a particular implant from the biotribological point of view.
Material and Methods Since the load and the relative motion referred to a joint are completely dependent on the musculoskeletal kinematics of the full human body system, a multibody model able to solve the inverse dynamics of the human lower limb was presented and used to elaborate the tribological configuration of the hip during the gait. Then, a mixed elasto-hydrodynamic lubrication numerical model, based on the Reynolds equation was developed: the Reynolds equation's input of hip load and relative motion are represented by the output of the numerical musculoskeletal multibody model.
Results and Discussion While the validation of the multibody algorithm was conducted by comparing the hip load with the ones obtained *in vivo* by Bergmann [1], the results of the lubrication model were shown in terms of hip replacement wear prediction and synovial pressure fields.

[1] Bergmann G, et al, PLoS One 2016;11(5):e015561

Deep Learning to Support Endovascular Surgical Procedures

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Background In the last years, artificial intelligence technologies have been designed to address tasks related to the medical field [1].
Aim Deep learning (DL) can be used to solve specific problems related to different phases involved in endovascular procedures.
Material and Methods A DL pipeline is developed to automatically segment aortic lumen [2] and thrombus from preoperative images. For the intraoperative phase, a DL model is used as a surrogate of finite element analysis (FEA) to predict the aortic deformations induced by tools-tissue interactions. For the postoperative phase, an automatic method is used to extract the lumen and the stent from the postoperative images, allowing for follow-up evaluations.
Results and Discussion The preoperative segmentation provided a Dice Score Coefficient (DSC) of 0.93 ± 0.02 for the lumen, and a DSC of 0.89 ± 0.04 for the thrombus. The intraoperative model used as surrogate of FEA takes around 0.05 ± 0.04 s to predict the aortic deformation, and present a mean error of 1.69 ± 1.06mm. The postoperative model used to segment follow up presents a DSC of 0.93 ± 0.02. DL technologies have shown promising results in the endovascular field, allowing to automatize and standardize procedures.

[1] Shen D, Wu G, Suk HI. Annual review of biomedical engineering. 2017 Jun 21;19:221-48.
[2] Fantazzini A, et al, Cardiovascular engineering and technology. 2020 Oct;11(5):576-86.

A coupled isogeometric framework for the electromechanical activation of thin tissues

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Background Recent experimental studies have turned their attention to the electromechanics of thin tissues as objects of layer-wise tissue engineering [1]. In this scenario, a computational method for thin tissues' activation could be a valuable tool for preliminary design space exploration.
Aim The proposed computational model aims at reproducing the propagation of the action potential over a surface with the corresponding tissue contraction effects. To this end, two NURBS-based Isogeometric Analysis (IGA) tools have been coupled with a staggered procedure.
Material and Methods The electrophysiological stimulus is approximated by the monodomain model [2] over a surface in the three-dimensional space. Then, the stimulus pattern is converted into a mechanical load employing the well-established active strain approach [3].
Results and Discussion Exploiting the benefits of the high-order NURBS basis functions within a curvilinear framework, the method is found to reproduce complex excitation patterns with a limited number of degrees of freedom. Eventually, various numerical tests shows that the coupled electromechanical model can capture the excitation–contraction mechanism over thin tissues and reproduce complex curvature variations.

[1] Zimmermann W.-H. et al., Cardiovasc. Res. 71 (3) (2006) 419–429
[2] Colli-Franzone P. et al., Mod Physiol Flows, (2012), pp. 107-141
[3] Nobile F. et al., Int. J. Numer. Methods Biomed. Eng. 28 (1) (2012) 52–71

An automatic Deep Learning pipeline for real time digital twin of Aortic Aneurysm

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Background Cardiovascular diseases (CVDs) are accounted for 45% of all deaths in Europe [1]. Among these casualties, ascending Thoracic Aortic Aneurysm (aTAA) is the 19th common cause of human death [2]. Recently, the capacity to simulate in-silico patient-specific models, i.e., a medical digital twin, has pointed out the opportunity to give a structured, reproducible and predictive framework for developing personalized and preventive management strategies for CVDs. Despite this, the adoption of such techniques in a medical environment is limited by their high computational demand.
Aim In this work the feasibility of a real time medical digital twin was demonstrated. Two time-consuming and human-supervised operations are replaced with Deep Learning (DL) based algorithms.
Material and Methods The first operation is the segmentation of CT scan, from which the 3D model of the patient's aorta is obtained. The second one, is the Computational Fluid Dynamics Simulation needed to estimate the Wall Shear Stress (WSS) and the pressure distribution on the aortic wall. The DL algorithms used are both based on convolutional neural networks, the first acting on regular grids, while the second one on graph-based structures.
Results and Discussion Two Neural Networks (NN) were trained using in-house datasets. For the segmentation task a Dice coefficient of 0.96 was reached on the test dataset. Regarding the pressure and WSS prediction, the NN mean absolute error on the test set was of 4.1 Pa and 1.5 Pa respectively.

[1] Group, A.W. et al, Eur. Heart J. 39(7), 508–579 (2017)
[2] Chau, K.H. et al, Prog. Cardiovasc. Dis. 56: 74–80 (2013)

A Fully Automated Pipeline for Thoracic Aorta Geometric Analysis and TEVAR planning from Computed Tomography using Deep Learning

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Background Feasibility assessment and planning of thoracic endovascular aortic repair (TEVAR) require computed tomography (CT)-based analysis of geometric aortic features to identify adequate landing zones for endograft deployment. However, no consensus exists on how to take the necessary measurements from CT image data [1].
Aim We trained and applied a fully automated pipeline embedding a convolutional neural network (CNN), which feeds on 3D CT images to automatically segment the thoracic aorta, detects proximal landing zones (PLZs), and quantifies geometric features that are relevant for TEVAR planning.
Material and Methods For 465 CT scans, the thoracic aorta and pulmonary arteries were manually segmented; 395 scans were used to train a CNN, the remaining 70 scans were used for testing. The trained CNN was embedded within computational geometry processing pipeline which provides aortic metrics of interest for TEVAR planning.
Results and Discussion The trained CNN yielded a mean Dice score of 0.95 and was able to generalize to 9 pathological cases of thoracic aortic aneurysm, providing accurate segmentations. Arches with a common origin of the innominate and left carotid artery (CILCA) were characterized by significantly greater angulation ($p=0.015$) and tortuosity ($p=0.048$) in PLZ 3 vs. standard arches. Our tool allows clinicians to obtain objective and repeatable PLZs mapping, and a range of automatically derived complex aortic metrics.

[1] R. Erbel, et al., in *European Heart Journal 2014;35(41):2873-926*

Bioreactor platform combining perfusion and PEMF stimulation for *in vitro* bone research

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Background In bone tissue engineering, bioreactors represent powerful tools for developing functional substitutes to be used as *in vitro* models for bone research [1]. *In vitro*, flow-induced shear stress promotes bone cell proliferation, differentiation, and matrix mineralization [2]. In clinical practice, pulsatile electromagnetic field (PEMF) stimulation is empirically adopted to foster bone healing [3].
Aim Development of a bioreactor platform, combining tunable perfusion and PEMF stimulation, for studying the bone response to combined biophysical stimuli.
Material and Methods The 3D-printed bioreactor allows housing cylindrical scaffolds of different size. Uni-/bi-directional flow (0.006-24 ml/min) can be applied for cell seeding or perfusion culture. A commercial device provides PEMF stimulation (1.5 mT, 75 Hz). Fluid flow and magnetic field within the bioreactor were modelled (COMSOL). Human mesenchymal stem cells were seeded into commercial scaffolds and cultured for 15 days under unidirectional perfusion (0.3 ml/min).
Results and Discussion In-house tests and simulations confirmed that the bioreactor prevents air bubble entrapment and recirculation regions, with shear stress values (0.8-7.8 mPa) in the range known to promote calcium deposition [4]. Simulations showed that the construct is exposed to a homogeneous magnetic field of 1.5 mT. In biological tests, direct perfusion significantly increased alkaline phosphatase release compared to control. Tests under combined stimulations are ongoing.

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[2] Wittkowske et al, Front Bioeng Biotechnol, 15;4:87, 2016
[3] Massari et al, Int Orthop, 43(3):539-551, 2019
[4] A.B. Yeatts, J.P. Fisher, Bone, 48(2), (2011), 171-8

Magneto-responsive core-shell microbeads for engineering peristalsis and alveolar breathing in-vitro

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Background Physiologically relevant in-vitro models need to reproduce both structural and mechanical features of the in-vivo environment. However, despite the complexity of current systems, to date, the replication of three-dimensional stretching is a challenge [1, 2].
Aim For this reason, we developed a new bioprinting strategy to obtain core-shell structures, able to replicate the structure and motility of the intestinal and alveolar barrier thanks to magneto-responsive materials.
Material and Methods. A core-shell microbead (COSMIC) generator was designed and fabricated using commercial coaxial needles. The core-shell structures were characterised using 1 and 2% w/v alginate in the shell and i) air, ii) 0.1% liquid pluroinic or iii) 1 - 2 % w/v FITC-alginate (Creative PEGWorks, USA) in the core. A 0.1 M calcium chloride (CaCl2) solution was placed under the needle to allow alginate crosslinking. Spheres dimension was quantified in function of different extrusion velocities (10, 20, 40 μL/s) using brightfield and fluorescence images (Olympus, Japan) and the Image-j software. The deformation of 0.5 and 0.75% w/ agarose gels loaded with 5, 10 or 15% w/v magnetite nanoparticles was measured using image analysis [3]. Cell viability tests were performed using Caco-2 cells with an encapsulation density of 1 million/mL.
Results and Discussion Results show that our strategy is suitable to obtain cell-laden core-shell structures, which can be embedded in magneto-responsive gels to mimic physiological strain and deformation mechanisms. Thus, this study represents a step further towards the definition of physiologically relevant in-vitro models, which improve the translation between research and clinical applications and also have the potential to reduce animal *tests as required by EU directives.*

[1] Sakalem et al , J Coloproct, 38:90-93, 2018
[2] Hynes et al. POEU.2020
[3] Zhao et al. PNAS.2011

Towards retina biofabrication

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Background Age-related macular degeneration (AMD) is a leading cause of blindness in elderly people [1]. Currently, no effective therapies are able to restore tissue functionality. Retinal tissue engineering represents a promising alternative to repair the damaged tissue.
Aim The goal of this study was to develop a tissue engineered construct which includes the retinal structures affected by AMD.
Material and Methods The construct was fabricated layer-by-layer mimicking retinal hierarchical composition. Electrospinning technique was used to produce a prosthetic Bruch's membrane, whose properties were evaluated. A suitable biomaterial ink was then developed and optimized for the 3D bioprinting of the retinal cellular layers. To this end, the biomechanics of porcine retina was investigated carrying out uniaxial tensile tests.
Results and Discussion The prosthetic Bruch's membrane showed structural and mechanical similarities to native Bruch's membrane. Moreover, the scaffold was found to be biocompatible. Porcine retinal samples displayed a typical tensile stress-strain curve characterized by an initial linear elastic region followed by a plastic region. The average elastic modulus was 13.1 ± 6.16 kPa. A specific blend of sodium alginate and gelatin seems to be the most promising bioink for retinal tissue engineering. The printability of this bioink was demonstrated through rheological measurements and shape fidelity tests. Next, retinal cells will be incorporated in the bioink to reproduce retinal layers on the prosthetic Bruch's membrane. The successful outcome of this study will inform the treatment of an optimal biological substitute to be implanted in patients suffering from AMD.

[1] J. M. Colijn, et al., *Ophthalmology*,. 124(12), 2017, pp. 1753-1763

Enabling technologies for stiffness gradients in GelMAhydrogels obtained via microfluidic dynamic mixing

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Background Cells grow in a complex 3D microenvironment and their proliferation, migration and differentiation are strictly dependent on surrounding matrix properties. Gradients are the driving force of many physiological and pathological processes. Recreation of these gradients in *in-vitro* cultivation systems will help to fabricate functional tissue engineered constructs and physiologically relevant 3D disease model.
Aim This work presents enabling technologies for the optimization of the manufacturing of GelMA-based gradient hydrogels via microfluidic dynamic mixing [1].
Materials and Method A digital twin of the fabrication process has been developed, integrating theoretical and computational models, as well as experimental data, in order to predict and control the stiffness profile obtained within the constructs. The workflow for the development of the *in-silico* framework, based on rigorous verification, validation, and uncertainty quantification steps, is presented. The validation of the digital twin is based on reference settings of process variables, which result in constructs with an exponential stiffness profile.
Results and Discussion The developed digital twin has been employed for optimizing process variables in order to obtain a linear stiffness profile in the extruded construct without the need of expensive and time-consuming trial-and-error procedures. The presented knowledge is now a powerful tool for the creation of hydrogel constructs for desired tissue engineering applications, or for the screening of optimal 3D cell culture conditions.

[1] A. Lavrentieva, et al, M*acromolecular Bioscience* 20 (7) 2020

In vitro characterization of the three-dimensional strain pattern in human vertebrae affected by metastases

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Supervisor: Luca Cristofolini

Background Spinal metastases are malignant formations which alter the bone tissue microstructure and may reduce the load-bearing capacity of the vertebra and induce spinal failure. Clinicians face with the assessment of the risk of fracture, but most oncological patients remain with an indeterminate diagnosis. A comprehensive characterization of the mechanical behaviour of metastatic vertebrae, that may help clinicians in the decision making, is currently missing.

Aim The aim of the study was to identify the features of spinal metastases that are crucial for the assessment of the spinal instability, through the evaluation of the mechanical behaviour at fracture of metastatic vertebrae. This assessment was performed combining *in situ* mechanical testing, micro Computed Tomography (μCT) imaging and a global Digital Volume Correlation (DVC) approach (BoneDVC).

Material and Methods Eleven thoracic and/or lumbar spine segments consisting of two vertebrae, one with large lytic or mixed (including both lytic and blastic tissues) lesions and one adjacent control without lesions visible from clinical CT images, were prepared. Each specimen was scanned in step-wise axial compressive loading within a μCT at the University of Sheffield (UK). BoneDVC software was used to register the images of the undeformed and deformed specimens and measure the full-field displacements and strains. A preliminary methodological optimization of the DVC parameters was performed, identifying the best compromise between measurement uncertainties and measurement spatial resolution (zero-strain test). The internal full-field principal strains distributions at fracture in the control and metastatic vertebrae were measured and compared. Analysis of the strain distribution was performed to identify the regions with focalized strain concentrations. The association of the strain distribution with the metastatic features was explored.

Results and Discussion A measurement uncertainty of 564±197 με was obtained with a measurement spatial resolution of approximately 2 mm. The strain distributions of the control and the metastatic vertebrae revealed significantly different behaviours (Mann-Whitney test, $p<0.0001$). In particular, vertebrae with lytic metastases experienced higher compressive strains (-4957±2552 με) than the controls (-1864±1131 με). Strain concentrations were observed close to the lytic metastases. By contrast, vertebrae with mixed metastases, consisting of both lytic and blastic lesions, did not show a univocal trend (Fig. 1). The local strain analysis showed that in some cases the mixed-metastatic vertebra triggered high strains in the adjacent control vertebra. The investigation of the association between the strain field and the microstructure of the vertebrae showed that a few metastatic regions with denser trabecular patterns, which were expected to be stiffer, experienced larger strains than healthy tissue. This observation highlights the importance of assessing the quality of the metastatic tissue for the understanding of the mechanical stability of metastatic spine.

In conclusion, this study remarks the potential of a global DVC approach to measure the 3D strain field inside tissues with highly heterogenous microstructure, and the importance of the metastatic tissue properties and metastatic features, such as type, size, and position, for predicting the spinal instability. This evidence paves the way to new biomechanical-based criteria for assessing the spinal instability and fracture risk, and suggests further analysis at tissue level for modelling of metastatic vertebrae.

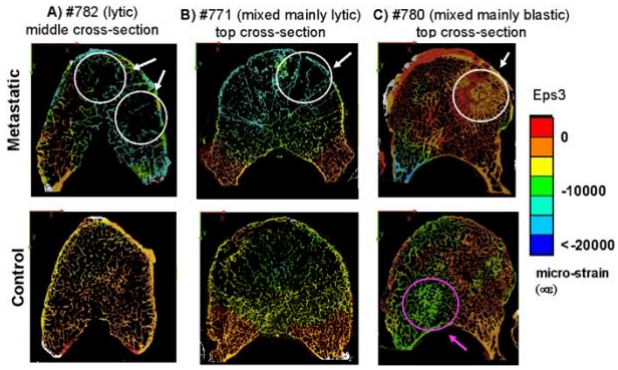

Figure 1: Comparison between the compressive strain field in a lytic (A), mixed with mainly lytic tissue (B) and mixed with mainly blastic tissue (C) metastatic vertebrae and their respective control vertebrae on μCT cross-section. White circles indicate lytic and blastic lesions, pink circle indicates a region with denser trabecular pattern with an unexpected behaviour.

Multi-Field Material Modeling and Computational Implementation of Cardiac Ablation

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Supervisor: Alessio Gizzi

Background Radiofrequency catheter ablation (RFCA) is an effective treatment for different types of cardiac arrhythmias. Computational modeling provides a viable option for predicting the outcome of cardiac ablation procedures.

Aim This work attempts to fill in some of the most important limitations found in numerical models available in the literature. We propose a novel coupled thermo–electro–mechanical model for myocardium response during RFA procedures. Within the framework of a realistic RF procedure, we enrich the constitutive model with additional key features which are neglected or poorly addressed in the literature: (i) anisotropy and, (ii) the nonlinear thermo–mechanical response. Our goal is to lay the foundations for a general computational framework capable of explaining the contribution of mechanical and induced thermal stress to the final tissue deformation at the end of the clinical procedure.

Material and Methods The RF source has been modeled with a quasistatic version of Maxwell's equations, augmented with a constant power constraint to simulate the power delivery protocol. The classical Fourier-based Pennes equation has been employed to model heat transfer, which includes the contribution of metabolic heat generation, blood perfusion, and electromagnetic heat generation due to the RF source. Blood and saline irrigation have been included via convective boundary conditions to reduce the computational complexity. The influence of mechanics on thermal conduction has been implemented via a pullback operation.
Temperature and damage dependency of biophysical parameters has been considered. Thermal isocontour at 50 °C has been used to assess the computed lesion; however, a more complex three-state cell death model has been employed to include thermally-induced damage in the mechanical framework. Major efforts have been dedicated to the mechanical model of the myocardium. A state-of-the-art hyperelastic constitutive model has been adopted for the passive response, which captures the main features of the tissue: (i) (nearly) incompressibility, (ii) anisotropy, and (iii) nonlinear response. Within a thermodynamically consistent framework, we enriched the formulation for nearly–incompressible passive mechanics, with well-established theories from thermo-mechanics and micro-mechanical damage to soft tissues.

Results and Discussion For the purely mechanical model, we employed a set of computational benchmark problems on simplified geometries (cube, cylinder). As a major finding, we observed that under uniaxial compression, the tissue undergoes a counterclockwise twist when the fiber reinforcement is included, while in the isotropic case expands equably under the same mechanical conditions. A preliminary analysis was performed to assess the effect of blood flow and saline irrigation. Our results show that, given the increasing contribution of convection, a lower temperature is observed, along with a spatial shift deeper in the tissue of the temperature peak. All the lesion characteristics decrease accordingly. Following a comparative analysis, we show the crucial role of anisotropy on the formation of the lesion. Higher temperatures and a more elliptical lesion are predicted for an increasing degree of anisotropy. Values of $\alpha=2$ and $\alpha=3$ give qualitatively more reliable results, compared to clinical evidence. Numerical analyses performed on the complete model showed a non-negligible effect of the thermo-mechanical coupling. During ablation, a clear upward shift of the tissue is observed, as a result of the isotropic matrix stiffening. After the ablation and load removal, a residual tensional state was observed, which emerged with a particular bilobed pattern in the stress and strain distributions. Based on the developed framework, we established that such an effect might be the result of the coexistence and interaction of the shrinking and expansion phenomena. Interestingly, it was noticed that the lesion calculated with the isotherm method can incorporate both effects, and thus, delimit the area in which the most mechanically relevant phenomena occur. In this study, we presented a multiphysics mathematical model of cardiac RFA, including the thermo-mechanical response of the ablated tissue. The novel approach has enabled us to have a deeper insight into the underlying thermo-mechanical phenomena involved in cardiac RFA, encompassing several aspects neglected in previous works.

Computational methods for the characterization of the mechanical behaviour of healthy and tumour cells

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Supervisor: Emanuele Luigi Carniel

Background Nowadays tumours are one of the principal causes of death in the world, more precisely the second one in Italy as in Europe. Tumour is caused by the uncontrolled growth and proliferation of mutated cells. Indeed, while healthy cells sense and respond to mechanical stimuli, by producing biochemical signals, in tumour cells these mechanisms are altered and biochemical signals are ignored. This results in an uncontrolled tumour cells proliferation and failure of the apoptosis process. Moreover, it has been seen that, when a healthy cell becomes a tumour one, a variation in its mechanical behaviour occurs, as well as in the mechanotransduction of signals that regulate cell's processes such as proliferation, migration and differentiation. Thence, biomechanical signals appear to play a key role in cells' life and behaviour.

Aim For the above-mentioned reasons, the main focuses of this Master thesis were: (i) to create a computational model and to characterize the mechanical behaviour of healthy and tumour cells in order to better understand the origin, the development and spread of cancer; (ii) to evaluate the contribution and the role of cell subcomponents in tumour mechanical processes; (iii) to pave the way for future computational models that will overcame the complexity of studying the neoplasms, in particular concerning the inter and intra tumour variability.

Material and Methods A three-dimensional finite element model of a cell was realized with the finite element software Abaqus Standard 2019 (Abaqus/CAE 2019, Dassault System). The model simulates a cell adherent to a substrate, composed of all those features that mainly contribute to the cell mechanics such as the cytoskeleton (composed of microfilaments and microtubules), cytoplasm, cell membrane and nucleus. The whole model was discretized by means of about 65000 hexahedral elements for cytoplasm and nucleus, about 23000 quadrilateral elements for cell membrane and 3000-line elements for the cytoskeleton, leading to about 330000 variables.
A continuum-tensegrity model was adopted to describe the behaviour of cells subcomponents. More precisely, cytoplasm, nucleus and cell membrane were defined as a homogeneous continuum material, while the cytoskeleton was modelled with a tensegrity structure, composed of compression and tension bearing elements that mimic the behaviour of microtubules and microfilaments, respectively. Viscoelastic properties were assigned to cell subcomponents, referring to values reported in the literature.
Two types of numerical simulations were realized: tensile tests and indentation tests. In tensile tests the cytoskeleton was firstly prestressed (first step), then tensile forces were applied at two opposite nodes of the plasma membrane (second step); in indentation tests (simulating Atomic Force Microscopy i.e., AFM indentation) an applied normal load phase (first step) was followed by a relaxation one (second step). In this latter, a hard sphere simulated the cantilever tip of the AFM, while approaching the cell.
Even if the model has the potential to hypothetically mimic all kinds of cells, this work primarily focused on chondrocytes (specialized cells present in the cartilage) and chondrosarcoma cells (malignant tumour cells that origin from chondrocytes), thanks to a larger availability of data in the literature with respect to other cells.

Results and Discussion The validity of the continuum-tensegrity choice for describing the cell was assessed by tensile tests. Consistently with data taken from literature, it was observed that at a linearly increase in stiffness (between 0% and 10%) corresponded to a non-linear increase in cell prestress. With indentation tests, it was realized a sensitivity analysis of the constitutive parameters of cell subcomponents, by comparing computational stress relaxation curves with Hertz model. These results showed the ability of the model to mimic the behaviour of an average human cell. It was also possible to observe the differences in mechanical behaviour between a healthy and a tumour cell. The outcomes suggested that the cytoskeleton plays a key role when a cell is tight from two opposite parts, while the cytoplasm mostly influences the cell response under compression. Furthermore, healthy cells appeared to be stiffer than tumour cells (Young's Modulus of chondrocytes were about two time higher than the chondrosarcoma cells'). This was assessed to be the effect of the increased cellular activity of tumour cells as reported in literature. These results could serve as a primarily step in the development of more accurate computational models for cell mechanics.

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