

# CELLULAR CONTRACTILITY AND SUBSTRATE ELASTICITY: SIMULATION OF THE ACTIN CYTOSKELETON

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## Introduction

Numerous experimental studies have established that cells can sense the stiffness of underlying substrates, and have quantified the effect of substrate stiffness on stress fibre (SF) formation, focal adhesion (FA) area, and also on the mechanical regulation of stem cell differentiation [Discher, 2005, Engler, 2006]. In order to investigate such behaviour, a mixed mode thermodynamic and mechanical framework that predicts FA formation [Deshpande, 2008] and growth is coupled with a material model that predicts SF formation, contractility and dissociation in a fully 3D implementation [Ronan, 2012]. This coupled SF-FA formulation is used to predict the response of cells seeded on different substrate stiffnesses.

## Methods

The contractile actin-myosin cytoskeleton is formed via assembly of phosphorylated myosin and polymerized actin filaments to form contractile SF bundles [Deshpande, 2007]. This is captured in our constitutive model by allowing SFs to assemble in any direction at any point located in the cell. SF formation is triggered by a calcium signal cascade which has been closely linked to cytoskeletal remodelling [Roberts, 2001]. The signal induced formation and tension dependent dissociation of the actin cytoskeleton is modelled using a first order kinetic equation. This equation gives the dimensionless activation level of a SF bundle,  $\eta$ , at any orientation, at any point in the cell:

$$\dot{\eta} = [1 - \eta] \frac{Ck_f}{\theta} - \left[ 1 - \frac{\sigma}{\sigma_0} \right] \eta \frac{k_b}{\theta}$$

The contractile behaviour of SFs due to the cross-bridge cycling of the actin-myosin pairs is described by a Hill like equation:

$$\frac{\sigma}{\sigma_0} = 1 + \frac{k_v}{\eta} \frac{\dot{\epsilon}}{\dot{\epsilon}_0} : -\frac{1}{k_v} \leq \frac{\dot{\epsilon}}{\dot{\epsilon}_0} \leq 0$$

where  $\sigma$  is the SF tension, and  $\sigma_0$  is the isometric tension, and  $\dot{\epsilon}$  is the strain rate. This SF formulation has been implemented in parallel with a Neo-Hookean material in a 3D finite element setting [Ronan, 2012].

## Results

Compliant substrates do not provide sufficient tension for SF persistence, causing dissociation of SFs and lower levels of FA formation (Fig1A). In contrast, cells on stiffer substrates are predicted to contain large amounts of dominant SFs. SF contractility leads to increased stress in the nucleus for stiffer substrates (Fig1B). Highly contractile smooth muscle cells are sensitive to stiff substrates (>10kPa); in contrast, chondrocytes are sensitive to compliant substrates (0.5-5kPa).

## Discussion

SF contractility plays a critical role in the substrate-dependent response of cells. Our prediction of increased actin SF formation on stiffer substrates is supported by the observations of Engler et al. [2006] and Solon et al. [2007] (Fig1C). These simulations offer insight into the mechanical regulation of SF formation and of stem cell differentiation.

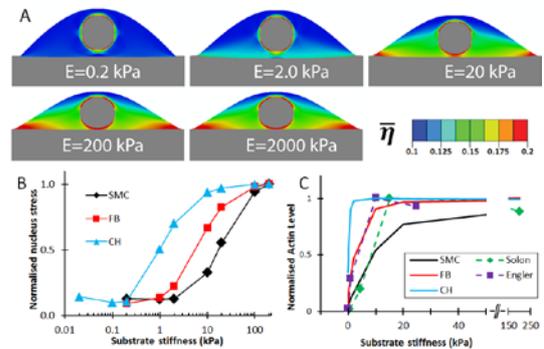


Figure 1: A – SF formation in cells adhered to different elastic substrates. B – Stress in the nucleus for smooth muscle cells (SMC), fibroblasts (FB), and chondrocytes (CH). C – comparison of actin activity in simulated (solid lines) and in-vitro (dashed lines) cells.

## References

- Discher *et al*, Science 310:1139-43,2005
- Engler *et al*, Cell 126:677-89, 2006
- Deshpande *et al*, PNAS, 103: 14015-20, 2006
- Deshpande *et al*, JMPS 56:1484-1510, 2008
- Roberts *et al*, J Appl Physiol, 90:1385-91, 2001
- Ronan *et al*, JMBSM 14:143-157, 2012
- Solon *et al*, Biophys J 93:4453-61, 2007

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