

## Computational investigation of the cytoskeleton response under static and fluid flow loading conditions

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### INTRODUCTION

Mechanical environment has key role in determining cell functions such as motility, division, differentiation and adhesion. Regulation of cellular function by mechanical forces is determined by the composition and structures of cells. While the cytoskeleton (CSK), a complex network of proteins, is known to be involved in force transmission inside the cell, the exact structural mechanisms involved in force sensing are not well understood. Using a computational cell model, this study aims to investigate how external forces generated by compression, stretching and fluid flow are sensed by the cell and transmitted internally through the CSK and how the Primary Cilia (PC) interacts with the CSK.

### MATERIALS AND METHODS

A 3D finite element (FE) cell model, including actin cortex, prestressed actin fibres and microtubules in a continuum elastic cytoplasm and nucleus<sup>1</sup> was used to investigate how the intracellular components affect cell response under compression, shearing and fluid flow.

Two sets of mechanical conditions were performed to study how each CSK component affects cell forces:

- *Static conditions:* a 4.5mm bead was modelled on the top of the cell and moved 0.5mm vertically towards the cell (compression) and 0.25mm horizontally along the cell (stretching) to investigate the role of each CSK component in force transmission.

- *Flow conditions:* the cell model was subjected to flow using a CFD model of a perfusion bioreactor chamber with an inlet fluid velocity of 1 mm/s. To further investigate cell mechanosensation, a PC was included in the cell model as a 5.2µm long cylinder and a diameter of 10 nm<sup>2</sup>.

### RESULTS

By isolation of the different cytoskeletal networks in this FE analysis, we demonstrated that the CSK components have different mechanical roles to respond to specific external perturbations: actin cortex and microtubules are the main components to resist compressive loads, whereas actin bundles and microtubules resist stretching, leading to tension in the action bundles and microtubules. Also, actin cortex does not have a mechanical role in resisting shearing loading conditions. Under static conditions, higher compressive forces were

observed in the cell model when more actin bundles are aligned with the direction of applied compression, whereas changes in the mechanical properties of microtubules did not affect internal forces. Simulations of cells with different PC mechanical characteristics, showed that the length and the stiffness of PC are responsible for the transmission of mechanical stimuli to the CSK. Fluid flow deflects the cilium, creating highest strains at the base of the PC and in the cytoplasm. The PC deflection created further tension in actin bundles but did not influence microtubules significantly. Our results indicate that cell mechanosensitivity can be altered by targeting PC length and rigidity.

## **DISCUSSION**

This study illustrates that considering a combination of cytoskeletal structures with their own elastic properties is necessary for a more complete description of cellular mechanical properties<sup>1</sup>. This study also shows how PC mechanics interacts with the cell and its cytoskeleton components when subjected to fluid flow. Our results further showed that the PC pulls on the actin bundles during deflection. The actin bundles are a highly mechanosensitive network of the CSK, responsible for CSK remodelling and formation of focal adhesion sites. It is a theoretical study that highlights many novel aspects of how CSK and PC influence cells' mechanosensitive response.

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