

Simulating the Role of Actin Cytoskeleton Remodeling in the Shearing of Chondrocytes

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INTRODUCTION

Actin filaments in chondrocytes dynamically adapt to mechanical loading through Rho-kinase mediated signaling mechanisms [1]. However, *in vitro* investigations of the response of cells to mechanical stimuli provide limited insight into these mechanisms due to the fact that cellular structure and function actively evolves in response to physical stimuli. Furthermore, a passive elastic computational model of cell behavior cannot be used to accurately compute stresses in a cell or the evolution of the actin cytoskeleton.

In this study, an active model that describes the assembly of the actin cytoskeleton in response to cell signaling, and the dissociation of the actin cytoskeleton in response to a reduction of intracellular tension is implemented. *In vitro* experiments of single chondrocytes undergoing shear deformation are simulated. Computations are compared to a passive hyperelastic model of the cell cytoplasm.

METHODS

The actin cytoskeleton is developed via the phosphorylation of myosin and polymerization of actin filaments which combine to form actin-myosin (AM) contractile units. In the present study the formation of AM contractile units is parameterized by the activation level η ($0 \leq \eta \leq 1$). The evolution of η , at any orientation, ϕ , is governed by a first order kinetic equation [2]:

$$\dot{\eta}(\phi) = [1 - \eta(\phi)] \frac{C \bar{k}_f}{\theta} - \left[1 - \frac{\sigma(\phi)}{\sigma_0(\phi)} \right] \eta(\phi) \frac{\bar{k}_b}{\theta}$$

The term in the first set of square brackets represents the assembly of AM contractile units in response to a signal of strength C ($0 \leq C \leq 1$). The second term represents the dissociation of contractile units in response to a reduction in tension to a value lower than the isometric tension, $\sigma_0(\phi)$, in the direction ϕ . k_f and k_b the dimensionless forward and backward reaction rate constants.

The AM contractility units are implemented as a user-defined material in ABAQUS. The 3D model of a single chondrocyte is based on *in vitro* cell geometries and testing parameters [3], with the cell adhered to a glass slide and a tungsten probe used to apply a shear load. A passive hyperelastic nucleus is included in the model with properties based on published studies [4].

RESULTS

As can be seen in Fig. 1(a), following $7.5 \mu\text{m}$ of probe indentation a reduction of tension at the front of the cell leads to a localized dissociation of AM contractile units. This gradual dissociation of AM contractile units at the base of the cell is illustrated in Fig. 1(b-d). A plot of computed probe force versus probe indentation is shown in Fig. 2 for a cell with an actively remodeling actin cytoskeleton. A curve is also shown for a passive cell, in which active contractility and remodeling are inhibited. The active cell provides significantly more resistance to shear deformation. It should also be noted that the maximum stress computed in the cell nucleus is 24% greater in the case of the passive model.

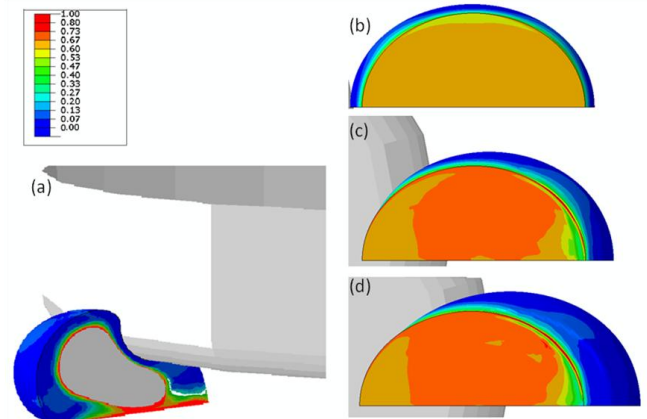


Figure 1 Contour plots of the density of AM contractile units as parameterized by the activation level η during shear.

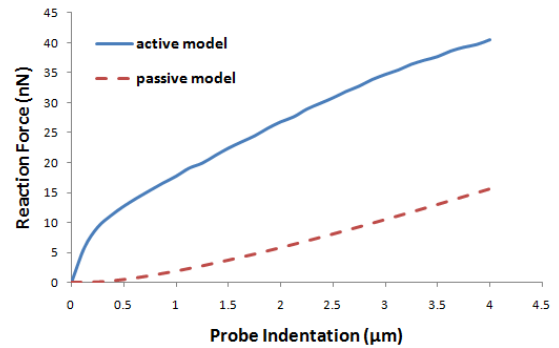


Figure 2 Computed probe force versus probe indentation curves for the active and passive models.

DISCUSSION

Results show a strong correlation with experimentally observed behavior in single chondrocytes experiencing shear. Confocal microscopy reveals an absence of actin at the front of chondrocytes following shearing [3]. Additionally, the disruption of AM contractile units using cytochalasin-D leads to a significant reduction in probe force required to shear adhered chondrocytes [5]. Clearly the active contraction and remodeling of the actin cytoskeleton plays a critical role in the deformation of chondrocytes. Recent *in vitro* studies have demonstrated the important role of nuclear deformation in gene expression [6]. We have demonstrated that the inclusion of active cytoskeletal evolution has a significant effect on computed nuclear stresses, and consequently on the development of a predictive framework for cell mechanotransduction.

REFERENCES

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