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Research paper

A constrained mixture approach to mechano-sensing and force generation in contractile cells

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ABSTRACT

Biological tissues are very particular types of materials that have the ability to change their structure, properties and chemistry in response to external cues. Contractile cells, i.e. fibroblasts, are key players of tissue adaptivity as they are capable of reorganizing their surrounding extra-cellular matrix (ECM) by contracting and generating mechanical forces. This contractile behavior is attributed to the development of a stress-fiber (SF) network within the cell's cytoskeleton, a process that is known to be highly dependent of the nature of the mechanical environment (such as ECM stiffness or the presence of stress and strain). To describe these processes in a consistent manner, the present paper introduces a mutiphasic formulation (fluid/solid/solute mixture) that accounts for four major elements of cell contraction: cytoskeleton, cytosol, SF and actin monomers, as well as their interactions. The model represents the cross-talks between mechanics and chemistry through various means: (a) a mechano-sensitive formation and dissociation of an anisotropic SF network described by mass exchange between actin monomer and polymers, (b) a bio-mechanical model for SF contraction that captures the well-known length–tension and velocity–tension relation for muscles cells and (c) a convection/diffusion description for the transport of fluid and monomers within the cell. Numerical investigations show that the multiphasic model is able to capture the dependency of cell contraction on the stiffness of the mechanical environment and accurately describes the development of an oriented SF network observed in contracting fibroblasts.

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1. Introduction

Biological tissues are very particular types of materials that have the ability to change their structure, properties and chemistry in response to external cues. This fast response capability can be attributed to the out-of-equilibrium nature of the tissue structure, resulting from a constant cross-talk between a population of cells and their surrounding extra-cellular matrix (ECM). These interactions allow cells to sense stimuli conveyed by the ECM (Lambert et al., 1998) (such as force, deformation or flow) and the ECM to restructure due to the action of cells (characterized by traction forces Tamariz and Grinnell, 2002; Dallon and Ehrlich, 2008 or enzyme degradation Vernerey et al., in press). In this context, a large number of studies have demonstrated that cell contraction and architecture were strongly dependent on substrate stiffness (Wang et al., 2000; Solon et al., 2007; Guo et al., 2006; Levental et al., 2006), giving mechanics

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a central role in cell-substrate interactions. Experimental studies on contractile cells (such as myofibroblasts) generally show that larger substrate stiffness results in higher cell stability that manifests itself by large spreading areas and generation of significant traction forces. In addition, actin staining procedures have shown that fibroblast contraction is associated with the formation of highly aligned stress-fibers (SF) within the cell's structure (cytoskeleton) that anchor at the point of cell-substrate adhesion and often span the entire length of the cell. The distribution and orientation of these fibers correlate very well with the presence of contractile forces applied by cells to their underlying substrate. These phenomena clearly illustrate the intricate interplay between mechano-sensing, force generation and cytoskeletal structure, which is essential to tissue remodeling.

Despite our more and more accurate understanding of the molecular mechanisms responsible for contraction, there are still many questions concerning the nature and mechanisms of mechano-sensing and force generation (Vernerey, 2010). To tackle these questions, it is necessary to develop mathematical models that are capable of describing the cross-talk between cellular mechanics and biochemistry in a quantitative fashion. From a modeling standpoint, cell contractility has often been considered in terms of prestress or prestrain, either within the context of fibrous networks (Mohrdieck et al., 2005) or continuum mechanics (Nelson et al., 2005; Vernerey and Farsad, 2011). While such simplified models capture well the mechanical aspects of cell contraction, they are unable to explain many features occurring from chemo-mechanical interaction at the molecular scale, such as dependency of contractility on substrate stiffness and ligand density. More recent studies by Deshpande et al. (2006, 2008) introduced a bio-mechanical model that is able to describe cytoskeleton contraction by considering molecular mechanisms associated with SF formation and focal adhesion assembly. This approach provides a promising means of capturing the chemo-mechanics of cell contraction but it neglects the multiphasic aspect of the cell's body in which monomer transport, interstitial fluid (cytosol) pressure and mass exchange can take place. The inclusion of the above physics is critical to respect fundamental physical principles such as mass conservation, but also in capturing key cellular phenomena such as osmotic loading and transport phenomena. In continuum mechanics, these types of phenomena have traditionally been described by the theory of porous media and mixtures Biot (1941, 1957); Truesdell and Noll (1965); Bowen (1980); Rajagopal and Tao (1995); Sun et al. (1999); Vernerey et al. (in press); these formulations were very successful in describing phenomena such as growth Humphrey and Rajagopal (2002); Garikipati et al. (2004), free swelling (Sun et al., 1999) and osmosis (Gu et al., 1999). Applications to the cell have thus far been limited to the flow-dependent mechanical response and swelling behavior of chondrocytes in response to their osmotic environment (Guilak et al., 2006).

The present paper proposes to extend the range of applications of mixture models to describe the coupled biochemical/mechanical processes responsible for cell contraction. The formulation is based on a description of cells that incorporate four key components of contractility: a passive solid cytoskeleton, an interstitial fluid representing the cytosol, an anisotropic network of SF and a pool of globular actin monomers that freely diffuse in the cytosol. To address the well known difficulties regarding stress partitioning and boundary conditions associated with classical theory of mixtures (Rajagopal and Wineman, 1990), we take the following approach. First, it is assumed that the two solid constituents (passive cytoskeleton and SF) undergo the same motion, which is consistent with the class of constrained mixture models introduced in Humphrey and Rajagopal (2002). Second, we adopt key concepts of poromechanics (Terzaghi, 1943) that consist of describing the motion of a fluid's constituents relative to solid constituent through diffusion-type relation (initially originated by Fick and Darcy). In this context, the mixture problem is well-posed and provides a flexible and robust theoretical framework to study the interactions between mechanics and chemistry (incorporating mass and energy exchange between constituents). The key features of the proposed model are as follows: (a) The SF network is described in statistical terms with a Von Mises distribution whose characteristics (mean, deviation) evolve in time. (b) The generation of contractile force by SF follows length–tension and velocity–tension curves that are known to accurately capture the behavior of sarcomeric structures. (c) The anisotropic formation and dissociation of the SF network depend on the level of contractile stress in existing SF and (d) SF formation is limited by the diffusion and quantity of globular actin monomers present in the cytoplasm. By capturing these important physics, we show that the formulation is capable to reproducing the mechano-sensitivity of cell contraction with respect to substrate stiffness as well as the general architecture of contractile cells.

The paper is organized as follows. In the next section, we provide the basis for the continuum description of the cell's body that contains both kinematics and structural components. Section 3 then concentrates on the conservation and exchange of mass occurring within the cell during contraction while mechanical equilibrium, SF contractility and cell elasticity are discussed in Section 4. Results and predictions of the proposed model are then described in Section 5 in which several problems are considered together with comparisons with experimental studies. A general discussion of the model, potential improvements and concluding remarks are finally provided in Section 6.

2. Constrained mixture description of cells

2.1. *Continuum assumptions and kinematics*

From a material's view point, a cell can be considered as a complex composite structure, composed of a large variety of interacting constituents, which may be solid (such as microtubules, actin filaments, intermediate filaments), fluid (the cytosol) or dissolved species (such as ions, monomers, diverse proteins). Under the assumptions that the characteristic length-scale associated with each constituent is small compared to its size, a cell can be viewed as a multiphasic continuum that can be very well described within the framework of mixture theory. Since the objective of