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Continuum modeling of forces in growing viscoelastic cytoskeletal networks

Jin Seob Kim [a], Sean X. Sun [a,b,*]

[a] Department of Mechanical Engineering, the Johns Hopkins University, Baltimore, MD 21218, USA
[b] Department of Chemical and Biomolecular Engineering and the Whitaker Institute of Biomedical Engineering, the Johns Hopkins University, Baltimore, MD 21218, USA

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ABSTRACT

Mechanical properties of the living cell are important in cell movement, cell division, cancer development and cell signaling. There is considerable interest in measuring local mechanical properties of living materials and the living cytoskeleton using micromechanical techniques. However, living materials are constantly undergoing internal dynamics such as growth and remodeling. A modeling framework that combines mechanical deformations with cytoskeletal growth dynamics is necessary to describe cellular shape changes. The present paper develops a general finite deformation modeling approach that can treat the viscoelastic cytoskeleton. Given the growth dynamics in the cytoskeletal network and the relationship between deformation and stress, the shape of the network is computed in an incremental fashion. The growth dynamics of the cytoskeleton can be modeled as stress dependent. The result is a consistent treatment of overall cell deformation. The framework is applied to a growing 1-d bundle of actin filaments against an elastic cantilever, and a 2-d cell undergoing wave-like protrusion dynamics. In the latter example, mechanical forces on the cell adhesion are examined as a function of the protrusion dynamics.

1. Introduction

Eukaryotic cells are constantly undergoing motion. In order to move, cells also exert significant traction forces on their underlying substrates (Discher et al., 2005; Dembo and Wang, 1999; Sniadecki et al., 2007), and protrusive forces on obstacles (Prass et al., 2006). At the molecular level, cell movements are driven by polymerization and depolymerization of cytoskeleton filaments and the action of molecular motors (Pollard and Borisy, 2003). What remains to be explained is the relationship between global cell shape and intracellular forces. Quantitation of intracellular forces is important in understanding how cells sense their mechanical environment, and how forces affect cell signaling. Toward this end, mechanical measurements on live cells using micromechanical techniques have emerged (Ziemann et al., 1994; Palmer et al., 1999; Yamada et al., 2000; Xu et al., 2000; Gardel et al., 2004; Deng et al., 2006; Bursac et al., 2005; Chaudhuri et al., 2007). These measurements show that the cytoskeletal network inside cells are relatively soft and viscoelastic. Slow relaxation of cellular stress is probably due to complex internal dynamics of the cytoskeleton. The present paper develops a general framework that can relate changes in the global shape of the cytoskeleton network with mechanical forces in the cell. The framework takes into account growth and shrinking of the cytoskeleton and its viscoelastic properties. We show that given the growth dynamics of the network, internal stress in the network can be computed. The growth dynamics is also coupled to the stress in the network. The framework is applied to 1- and 2-d proof-of-principle examples, including forces exerted on focal adhesions during wave-like growth of the cell leading edge.

At large enough length scales, the cytoskeletal network can be modeled as a continuum deformable body. A novel aspect of cytoskeletal networks, and indeed all living materials, is that their constitutive parts are not static but undergoing their own internal dynamics. Actin filaments are polymerizing and depolymerizing on time scales of seconds; branching proteins such as Arp2/3 and bundling proteins such as fascin change the network geometry dynamically (Pollard and Borisy, 2003). These remodeling activities can be classified into two types: Type one are changes that modify the local elastic properties of the cytoplasm, but do not change the shape of the cell. Activities such as polymer cross-linking and increases in filament density stiffen the network, but do not necessarily change the cell shape. Type two are changes that affect the material shape. Polymerization and depolymerization, which add and subtract material, fall into this category. In this paper, type one changes are equivalent with the term "remodeling" and type two changes are equivalent with the term "growth", although it is important to note that both types of

* Corresponding author at: Department of Chemical and Biomolecular Engineering and the Whitaker Institute of Biomedical Engineering, the Johns Hopkins University, Baltimore, MD 21218, USA.
E-mail address: ssun@jhu.edu (S.X. Sun).

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changes occur in the F-actin network in the living cell. There has been theoretical work on modeling the F-actin network constitutive law (Storm et al., 2005). This work analyzes the combined effects of mechanics and growth, which must be considered on an equal footing.

Dynamics of growing actin networks *in vitro* and *in vivo* have been studied extensively with experiments and modeling. In the context of a single filament, force generation by a growing stiff polymer was predicted theoretically (Peskin et al., 1993), and single filament measurements of microtubule force generation have been performed (Kerssemakers et al., 2006; Schek et al., 2007). Forces by growing actin filaments have been measured as well (Kovar and Pollard, 2004; Footer et al., 2007). In the context of a moving cell, F-actin network growth drives the motility of eukaryotic cells, including the fish keratocyte where experiments and mathematical modeling have been performed (Lee et al., 1993; Lacayo et al., 2007; Mogilner, 2006; Rubenstein et al., 2005). F-actin protrusions such as the lamellipodium and filopodium are also involved in changing the cell shape (Mejillano et al., 2004; Mogilner and Rubenstein, 2005; Atilgan et al., 2006, 2005). Mechanics, shape changes and force generation in endothelial cells and neutrophils have been examined (Herant et al., 2003; Reinhart-King et al., 2005). Mechanics and forces in a gel of cytoskeleton and motors have been studied (Joanny et al., 2003; Voituriez et al., 2006). For the bacterial cell *Listeria monocytogenes*, actin network growth occurs outside the cell body and propulsion of the F-actin comet tail has been described by continuum models and discrete filament simulations (Theriot et al., 1992; Giardini et al., 2003; Gerbal et al., 2000; Dickinson and Purich, 2006; Alberts and O'dell, 2004). Experiments on moving beads in a reconstituted F-actin network have also been performed (Loisel et al., 1999). Force measurements on a reconstituted growing network have been studied recently (Chaudhuri et al., 2007; Parekh et al., 2005). Finally, cytoskeletal networks also drive the motion eukaryotic sperm cells where instead of actin, the protein MSP is known to be a major contributor (Wolgemuth et al., 2005; Zajac et al., 2008).

A major conclusion from this body of work is that the cytoskeletal network has diverse morphologies in different contexts. The cytoskeleton network is the critical element controlling the shapes and forces in the cell. For example, in the filopodium, F-actin is organized in parallel bundles. In the lamellipodium of fish keratocyte, the F-actin network forms a dendritic branched structure. Within a single cell, the network in the cell cortex is different from the network in cytoplasm. Structures such as stress fibers and contractility from internal molecular motors further complicates the description. The mechanism of growth and remodeling is also different in different contexts. Thus, it is desirable to develop a general framework to quantify the process of cytoskeleton growth and remodeling where any mechanical properties of the network and any growth and remodeling mechanism can be incorporated. It is also desirable to incorporate experimentally measured network mechanical properties, spatial heterogeneity and anisotropic effects. A general framework such as this will connect growth remodeling mechanisms with macroscopic shape changes of the cell, predict internal forces and stress in the cell, and compute forces exerted by the cell on extracellular objects such as the substrate or obstructions.

The method in this paper starts with a continuum kinematic framework developed by Rodriguez et al. (1997) that decomposes the net deformation of a body into an elastic component and a growth component. This framework, in principle, is mathematically exact. When combined with a constitutive law for the body, a complete description of the internal forces and overall deformation is possible. The constitutive law can relate the molecular geometry of the cytoskeleton network with strains and/or strain velocities, and relate the strains and strain velocities to stress. And it is in the constitutive law where heterogeneous structures such as bundles and crosslinks can be incorporated. This paper applies this kinematic framework to viscoelastic materials which is more appropriate for cytoskeletal networks. We develop an incremental deformation approach to describe viscous stress, and analyze arbitrary growth dynamics and stress-dependent growth, and can model systems ranging from reconstituted networks to cells. The novel parts of our formulation are: (1) we incorporate small incremental growth and deformation, which converts an intrinsically nonlinear problem into a linear one with cumulative elastic quantities; (2) the deformation decomposition is developed for viscoelastic media which is applicable to the cytoskeletal network (Appendices) and (3) the development allows for coupling of any physically relevant phenomena such as the local stress in the material or local G-actin concentration with the growth tensor. The formulation is designed to be appropriate for biological systems. We apply the framework to several proof-of-principle 1- and 2-d examples. For the 1-d example, we show that stress-dependent growth can explain the force exerted by an F-actin bundle against a cantilever. For the 2-d case, we show that it is possible to compute forces on focal adhesions from cytoskeletal dynamics at the leading edge. The developed framework is therefore a versatile tool to analyze a range of problems in different contexts.

2. The model

In general, deformations must be described using tensor quantities. In the Appendices, we describe a general kinematic framework for examining incremental growth and deformation of a growing deformable body. We also develop a general relationship between the elastic and viscous stress with strain, strain velocity and a spatially varying growth rate. We show that the growth rate of the network affects the stress in the network and can be computed using a finite deformation formulation. The growth rate is also affected by the stress internal to the body, much like how a single bond reaction rate is affected by forces. We propose a phenomenological relationship between the growth rate and stress. For a single bond in the static limit, the model reduces to Bell's (1978) model of bond rapture rate.

For a 1-d situation, all the deformation and growth tensors are scalars. Equations in the Appendices simplify; the deformation from the $(k-1)$-th increment to the k-th increment in time is

$$F_k = A_k G_k = \frac{\partial x_k}{\partial x_{k-1}}, \tag{1}$$

where G_k is the growth at the k-th time increment and A_k is the mechanical deformation. Here $k=0$ is equivalent to $t=0$. Also we have $G_0 = A_0 = 1$. The net growth and net mechanical deformations are (Fig. 1)

$$\begin{aligned} G^{(k)} &= G_k G_{k-1} \cdots G_1 \equiv G, \\ A^{(k)} &= A_k A_{k-1} \cdots A_1 \equiv A. \end{aligned} \tag{2}$$

We note that growth of the cytoskeleton can be substantial, therefore the net deformation due to growth, G, can be substantially different from unity. To properly account for large deformations, we must use finite deformation models. The stress in the cytoskeletal network is due to mechanical deformation, A, only. The cytoskeleton is a viscoelastic material. The stress can be written as $\sigma = \sigma^e + \sigma^v$ where σ^e is the elastic part and σ^v is the viscous part. The Appendices describe a general constitutive