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Continuum mechanical model for cross-linked actin networks with contractile bundles

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ABSTRACT

In the context of a mechanical approach to cell biology, there is a close relationship between cellular function and mechanical properties. In recent years, an increasing amount of attention has been given to the coupling between biochemical and mechanical signals by means of constitutive models. In particular, on the active contractility of the actin cytoskeleton.

Given the importance of the actin contraction on the physiological functions, this study propose a constitutive model to describe how the filamentous network controls its mechanics actively. Embedded in a soft isotropic ground substance, the network behaves as a viscous mechanical continuum, comprised of isotropically distributed cross-linked actin filaments and actomyosin bundles.

Trough virtual rheometry experiments, the present model relates the dynamics of the myosin motors with the network stiffness, which is to a large extent governed by the timescale of the applied deformations/forces.

1. Introduction

Living cells actively sense and generate forces trough the cytoskeleton. Composed by filamentous and regulatory proteins, this composite material is an active material that can adapt its mechanics and perform mechanical tasks (Mizuno et al., 2007; Stricker et al., 2010).

Classified according to differences in architecture and function, there are three main types of cytoskeletal polymer networks: actin filaments, microtubules and a group of polymers known collectively as intermediate filaments. Their architecture is controlled by regulatory proteins: While the nucleation-promoting factors trigger the filament formation, the capping proteins stop the filament growth. In turn, polymerases tune the growth rate and the stability of the filaments whereas depolymerising factors and severing factors disassemble filaments. Lastly, crosslinkers and motor proteins are able to organise and reinforce higher-order network structures (Blanchoin et al., 2014; Fletcher and Mullins, 2010). The entropic and enthalpic elasticity of such networks (Wen et al., 2012) protects the cell against mechanical deformations and perturbations in their behaviour can result in marked pathologies.

In the context of cell mechanics, it is clear that trough active models is possible to replicate experiments and understand how the cytoskeleton activity is affected by the mechanical environment (Rodriguez et al., 2013). Studies in continuum

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theories propose stress fibers formation and contractility governed by cellular signalling and tension (Deshpande et al., 2007; Kaunas and Hsu, 2009; Kruse et al., 2003; López-Menéndez and Rodríguez, 2017; MacKintosh and Levine, 2008; Vernerey and Farsad, 2011). In particular, the idea behind the bio-chemo-model of Deshpande et al. (2007) has been successfully applied in simulations of cells on patterned substrates (McGarry et al., 2009; Pathak et al., 2008; 2011; Ronan et al., 2013), in studies of their resistance against shear (Dowling et al., 2012), compression (Ronan et al., 2012), and on the regulation of cell-cell junctions (Ronan et al., 2015).

By isolating biological molecules and reconstituting their activities, the *in vitro* studies assume an important role in the understating of cellular functions. *In vitro* biopolymer networks can be seen as a class of soft materials exhibiting pronounced nonlinearities while comprising only a few volume fractions of protein polymers (Koenderink et al., 2009; Köhler and Bausch, 2012). By using such *in vitro* reconstitutions in bulk rheology experiments, the researchers have been able to identify key conditions that trigger specific cytoskeletal processes and to quantify elastic and viscous properties (Fletcher and Mullins, 2010; Lieleg et al., 2010; 2009).

Indeed, the mechanical behaviour of biopolymer networks is largely determined at the microstructural level by the characteristics of individual filaments and the interactions between them. Despite the recent advances in rheological techniques, constitutive models remain an attractive option to gain a deeper insight of cell mechanics. By establishing correlations between microstructure and the mechanical behaviour, the constitutive models can work as an assisting tool to improve the experimental techniques and, therefore, the progress in biomedical researches (Unterberger and Holzapfel, 2014).

The purpose of this study relies on the development of a constitutive model involving the key components in cell contraction and motility, focusing on the modelling of the actin network. The actomyosin contractility allows adherent cells to operate in a nonlinear regime to control their mechanics actively, which drives these materials into nonequilibrium trough the internal conversion of chemical energy to mechanical energy. (Mizuno et al., 2007).

We consider *in vitro* conditions of a contractile actomyosin system consisting of a cross-linked actin network with embedded force-generating myosin II motors. The network behaves as a whole mechanical continuum and is comprised of (i) isotropically distributed cross-linked actin filaments, (ii) bundles of actomyosin contractile filaments with a preferred orientation, and (iii) a soft isotropic ground substance. Suitable constitutive relations in two different length scales are employed based on the idea of integrating the single filament response into a three-dimensional network (Lanir, 1983). The network is embedded in an isotropic soft ground substance and incorporate viscous effects (Holzapfel et al., 2014; Unterberger et al., 2013b).

In particular, at the lower scale, we use the relation between the tensile force and the end-to-end distance of a single and extensible worm-like actin filament (β-chain model), developed by Holzapfel and Ogden (2013). At the larger scale, these single filament relations are integrated within a full-network model (Göktepe and Miehe, 2005; Miehe, 2004; Miehe and Göktepe, 2005), without tube constraints. For the filaments not interacting with myosin, we assume enthalpic deformation of isotropic cross-linked network as the dominant contribution to elasticity, modelled using a non-affine microsphere model with rigid crosslinkers (Unterberger et al., 2013a; 2013b). Treated as entropic springs, the kinematics of the contractile bundles is integrated into a network under affine deformations assumptions, giving the capability to reproduce anisotropic responses (Wen et al., 2012).

Based on a continuum mechanical framework, our model provides quantitative predictions about the nonlinear elasticity of semiflexible biopolymer networks with molecular motors. The developed model is included into a finite element code to allow simulations with more complex geometries and boundary conditions.

2. Single filament models

The networks under study consist of single filaments cross-linked into a three-dimensional structure. Here we review the well-known worm-like chain model by exposing the relation between the tensile force and end-to-end distance of a single extensible filament. Following, we incorporate contractility capability in the bundles of actin-myosin filaments.

2.1. Holzapfel-Ogden β-model

Semi-flexible polymers are usually modelled by worm-like chains. Several publications present solutions to obtain the relationship between the tensile force actin at the ends of the filament f and the end-to-end distance r (Blundell and Terentjev, 2009; Holzapfel and Ogden, 2013; MacKintosh et al., 1995). The Holzapfel-Ogden β-model (Holzapfel and Ogden, 2013) deals with the extensibility of the filaments and considers curvature and local stretching for the kinematics. Fig. 1 contains the main features assumed for the constitutive relations, namely, the transversal deviation, geometry, and bending stiffness.

The thermal fluctuations are related with the bending stiffness through the persistence length, as follows

$$L_p = \frac{B_0}{k_B T} \tag{1}$$

where k_B is the Boltzmann constant and T is the absolute temperature. The stretch modulus μ_0 incorporates the extensibility of the filament. The arc-length s measure the coordinate along the filament backbone and the contour length L denotes the length of this backbone. The end-to-end distance r measures the distance between the end points.

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