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Constitutive modelling of composite biopolymer networks

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HIGHLIGHTS

- A new constitutive continuum model for composite biological networks.
- Model assessment by use of several sets of experimental data from the literature.

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ABSTRACT

The mechanical behaviour of biopolymer networks is to a large extent determined at a microstructural level where the characteristics of individual filaments and the interactions between them determine the response at a macroscopic level. Phenomena such as viscoelasticity and strain-hardening followed by strain-softening are observed experimentally in these networks, often due to microstructural changes (such as filament sliding, rupture and cross-link debonding). Further, composite structures can also be formed with vastly different mechanical properties as compared to the individual networks. In this present paper, we present a constitutive model presented in a continuum framework aimed at capturing these effects. Special care is taken to formulate thermodynamically consistent evolution laws for dissipative effects. This model, incorporating possible anisotropic network properties, is based on a strain energy function, split into an isochoric and a volumetric part. Generalisation to three dimensions is performed by numerical integration over the unit sphere. Model predictions indicate that the constitutive model is well able to predict the elastic and viscoelastic response of biological networks, and to an extent also composite structures.

1. Introduction

In the context of a mechanical approach to cell biology, there is a close relationship between cellular function and mechanical properties. Cells in a diseased state can exhibit a significantly altered mechanical response to external forces. This allows them to behave abnormally, promoting progression of the pathology. For example, in the case of cancer cells, it has been found that reduced adhesion strength (Rönnlund et al., 2013) promotes metastasis. However, the influence of cancer on the mechanical properties of cells is not unambiguous. Analysis of mechanical properties in pancreatic cancer cells revealed a distinctly more compliant behaviour (Suresh et al., 2004) while other studies have indicated an increased stiffness in response to mechanical probing, linked to an increased invasiveness (Rathje et al., 2014). In both cases, a rearrangement of the cytoskeleton was apparent. A comprehensive review of experimental results on various types of cancer cells with different techniques can be found in the literature (Suresh, 2007). Experiments performed on living cells revealed distinctly different functions of the respective types of cytoskeletal filament networks. The actin filament network fills the cytoplasm, and tears at high strain while being able to resist compression, thanks to being bundled into stress fibres. Intermediate filaments, on the other hand, are quite able to resist tension and strain harden, but are unable to bear compression. Together, they form a composite structure, which the microtubules stabilise in response to external tensile stresses (Maniotis et al., 1997). In support of this, a recent study (Rathje et al., 2014) showed that disruption of the microtubule network caused the intermediate filaments to collapse around the cell nucleus. The effect of the vimentin network on the cellular mechanical properties manifested itself as a significantly stiffer response linked to the vimentin network collapse. Further evidence in support of the influence in regulating cell stiffness has been presented (Guo et al., 2013), where knocking out the vimentin intermediate filament system in mouse embryonic fibroblasts was shown to affect the elastic shear modulus of the cytoplasm.

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This close connection between intracellular structure and cellular response has led to the development of numerous theoretical models of cytoskeletal networks. It is possible to use principles of continuum mechanics to characterise the cytoskeleton as a homogenised material. We have previously proposed a chemo-mechanical continuum model to evaluate the influence of cross-link dynamics on the viscoelastic response of cross-linked actin networks (Fallqvist and Kroon, 2012), and a well-known model for vulcanised rubber (Arruda and Boyce, 1993) was recently extended to predict the mechanical response of cross-linked actin networks by relating the chain stretch of the semiflexible filaments to the macroscopic deformation (Palmer and Boyce, 2008).

A disadvantage inherent to continuum models is the difficulty in interpreting model parameters in terms of structural or physical terms, for example the influence of network filament length. Models such as the lattice model (Satcher and Dewey, 1996) consider the microstructure of the actin cytoskeleton to theoretically estimate the shear modulus. To account for the semiflexible nature of many biological polymers such as the ones present in the cytoskeleton, attempts have been made to extend the Worm-Like Chain (WLC) model in describing the behaviour associated with networks of these polymers (Mackintosh et al., 1995; Storm et al., 2005). A conceptual model derived from experimental observations on a intracellular level is the tensegrity model (Ingber and Jamieson, 1985). The fundamental idea of this model is that the cytoskeletal actin network carries the prestress generated by the contractile machinery of the cell. This tension is then balanced by compression of the microtubules.

Common to the aforementioned models is the successful implementation of various theories to compute an adequate relation between an applied deformation and force (or stress and strain). However, lacking is the capability to predict the influence of a composite network structure. As previously mentioned, a composite structure of networks has been shown to affect the microstructural deformation in living cells (Maniotis et al., 1997). To quantify the effect, Wagner et al. subjected networks of actin filaments, neurofilaments and a composite structure of equivalent concentration to applied strain and measured the resulting stress (Wagner et al., 2009). The stiffer response with network rupture and subsequent strain softening of a composite structure emphasises the importance of properly accounting for the composite nature of the cytoskeletal network.

The influence of a composite structure as well as network rupture and softening behaviour is not accounted for in any of the aforementioned network models. We propose that the influence of heterogenity as well as irreversible effects (network damage and relaxation) on the mechanical behaviour can be modelled in an effective way by use of a micromechanically motivated continuum model. This general approach can then be specialised towards biological networks. We have previously proposed this model and shown that it qualitatively replicates the influence of filament length on the mechanical response of actin networks (Fallqvist et al., 2014). Here, we generalise it further and extend it to a formulation predicting the mechanical behaviour of not only homogenous biopolymer networks such as actin and intermediate filaments, but also a composite structure of them. This model aims to capture the passive response, i.e. effects from polymerisation and active responses due to mechanical signals (which might be present in a physiological context) are not taken into account.

To the authors' knowledge, the model is unique in that it incorporates a first attempt to quantify the interdependence of the different structures.

We begin by presenting the framework and model formulation in Section 2 and the numerical scheme in Section 3. The model is verified with respect to experimental results in Section 4, and parametric studies of the mechanical, viscous and damage parameters are performed to assess their influence on the mechanical behaviour and compare this to experimental observations of composite biopolymer networks. We conclude by discussing future possibilities and limitations of the model in Section 5.

2. Constitutive formulation

We start by deriving a one-dimensional model for filamentous networks, which is thereafter generalised to three dimensions, and finally anisotropy and viscoelastic behaviour are incorporated. Thereafter, a composite model for the intracellular cytoskeleton is presented.

2.1. One-dimensional description of a single network filament

To relate the micromechanics of filament–filament interaction to the macroscopic response, the behaviour of a single network filament is first established. The interaction can be considered in a general, phenomenological sense. This interaction can be governed by mechanisms such as binding of cross-links between filaments or friction. In this first formulation, we shall restrict ourselves to a phenomenological approach for simplicity. In this formulation, we split the one-dimensional deformation into bending and an effective stretch including all longitudinal filament deformation which may give rise to a mechanical response, not from only the aforementioned interfilament interactions, but also thermal effects from pulling out thermal undulations. In this way, more rigid biopolymers such as actin can be accounted for, as well as flexible ones, e.g. the intermediate filament vimentin.

An 'interaction' function f_s is introduced, which describes this effective interfilament interaction by a force-displacement relationship.

Consider two orthogonal filaments according to Fig. 1(a) in the reference configuration and Fig. 1(b) in the current, deformed configuration. For this unit, we define an initial length $L_f/2$, where L_f is the total filament length, and also introduce a reference length L_s. This can be seen as a model parameter defining a distance over which filament–filament interactions are active, e.g. initial cross-link length. In the deformed configuration, the total elongation of the unit u_e is given as

$$u_e = u_f + u_s, \tag{1}$$

where u_f is deformation due to bending of the filament, and u_s is interaction length deformation. From the definition of stretch, the total elastic stretch λ_e is then given as

$$\lambda_e = \lambda_f + 2\frac{L_s}{L_f}(\lambda_s - 1) \tag{2}$$

where λ_f and λ_s is the filament bending and aforementioned interaction stretch, respectively, related through the displacements as

$$u_f = \frac{L_f}{2}(\lambda_f - 1), \tag{3}$$

$$u_s = L_s(\lambda_s - 1), \tag{4}$$

$$u_e = \frac{L_f}{2}(\lambda_e - 1). \tag{5}$$

We can now define a strain energy function Ψ_{1D} for a one-dimensional unit as

$$\Psi_{1D} = \Psi_f + \Psi_s, \tag{6}$$

$$\Psi_f = \frac{\mu_f}{4}(\lambda_f - 1)^2, \quad \Psi_s = \frac{\mu_s}{2}\int_1^{\lambda_s} f_s(\lambda_s')\,\mathrm{d}\lambda_s' \tag{7}$$