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A model for compression-weakening materials and the elastic fields due to contractile cells

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ABSTRACT

We construct a homogeneous, nonlinear elastic constitutive law that models aspects of the mechanical behavior of inhomogeneous fibrin networks. Fibers in such networks buckle when in compression. We model this as a loss of stiffness in compression in the stress–strain relations of the homogeneous constitutive model. Problems that model a contracting biological cell in a finite matrix are solved. It is found that matrix displacements and stresses induced by cell contraction decay slower (with distance from the cell) in a compression weakening material than linear elasticity would predict. This points toward a mechanism for long-range cell mechanosensing. In contrast, an expanding cell would induce displacements that decay faster than in a linear elastic matrix.

1. Introduction

Biological cells can sense the mechanical state of the surrounding extracellular matrix, such as stiffness (Discher et al., 2005), deformations, forces, or stress (Lo et al., 2000; Reinhart-King et al., 2008; Winer et al., 2009; Shi et al., 2014; He et al., 2014). This is known as mechanosensing (Vogel and Sheetz, 2006). At the same time, cells actively contract, thereby applying tractions on the extracellular matrix and deforming it. The resulting displacement or stress fields can serve as signals to other cells (Reinhart-King et al., 2008; Winer et al., 2009; Shi et al., 2014), thus enabling neighboring cells to detect each other (Notbohm, 2013; Notbohm et al., 2015a).

Experiments using digital volume correlation with confocal microscopy (Franck et al., 2007) measured displacements in a 3D fibrin matrix caused by contractile fibroblasts seeded in it (Notbohm, 2013; Notbohm et al., 2015a). The fibrin matrix is not a homogeneous material, but rather a random network of slender fibers. The matrix displacements induced by cell contraction were found to decay much slower with distance from the cell than linear elasticity would predict. Thus, contractile cells embedded within a fibrin matrix can detect mechanical fields induced by each other at larger distances, compared to cells in a homogeneous gel matrix that behaves like a linear elastic material, or cells on a linear elastic substrate where displacements decay even faster (exponentially He et al., 2014). This observation of long-range cell–cell mechanical communication in 3D agrees with previous experiments that showed a similar effect for cells on a 2D fibrin substrate (Winer et al., 2009; Rudnicki et al., 2013). The mechanism for the long-range mechanosensing stems from the mechanical behavior of the fibrous network. It was shown (Notbohm, 2013; Notbohm et al., 2015a) that the displacements due to a contracting

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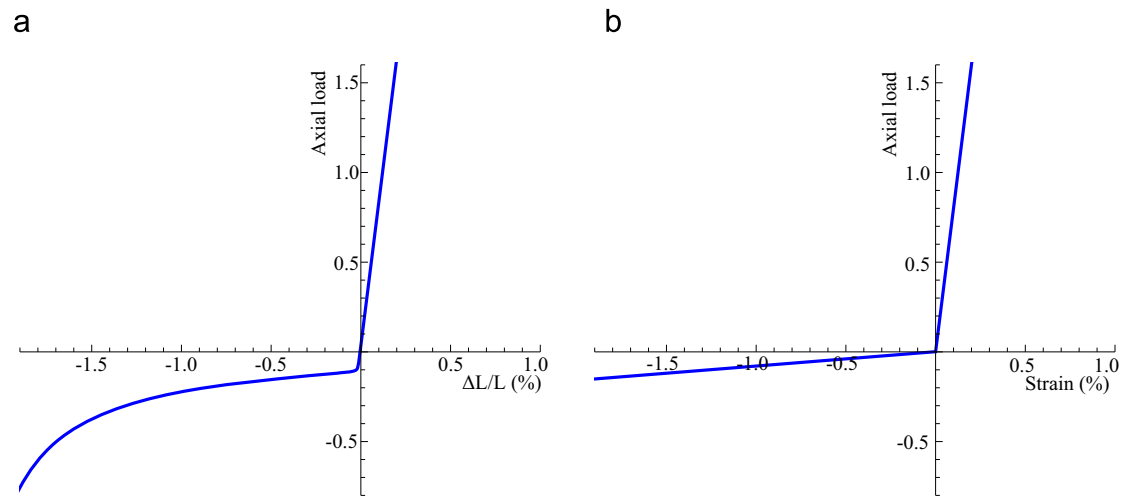

Fig. 1. (a) Typical relation between axial load (vertical axis, arbitrary units) and fractional change in the distance between endpoints (horizontal axis, percent) of an elastic beam that can buckle. (b) One-dimensional piecewise-linear stress–strain curve for a material that weakens in compression. Here $\rho = 0.1$. Horizontal axis: strain ε in percent. Vertical axis: normalized stress σ/α, where α is a one-dimensional elastic constant.

inclusion in a fiber network decay slower than in a homogeneous linear elastic material, because fibers lose stiffness in compression. The stiffness loss is due to *microbuckling*, namely buckling of individual fibers in the network that are in compression. See Lakes et al. (1993) and Kim et al. (2014, 2015) for various aspects of microbuckling.

We previously developed a finite element fiber network model (Notbohm, 2013; Notbohm et al., 2015a) that treated individual fibers as elements whose force-extension curve has smaller slope in compression than in tension, as in Fig. 1(b). This is an idealization of the typical relation between axial load and fractional change in the distance between endpoints of an elastic beam that can buckle, shown in Fig. 1(a). One notes the abrupt change of stiffness that occurs at a negative value of the load (the buckling load) in Fig. 1(a). The magnitude of the buckling load depends on the bending stiffness of fibers. For fibrin, the bending stiffness has been found to be nearly two orders of magnitude less than the value predicted by the pure bending model of linear elasticity (Piechocka et al., 2010). Accordingly, the buckling load is essentially taken to vanish in Fig. 1(b). Simulations of our finite element model in 2D (Notbohm, 2013; Notbohm et al., 2015a) with fiber elements obeying the compression weakening stress–strain law of Fig. 1(b) show that matrix displacements induced by a contracting spherical inclusion (representing the cell) decay according to a power law $u \sim r^{-n}$ with distance r from the inclusion center. Values of n depend on the connectivity of the network, but are always in the range 0.2–0.5, far below the value $n=1$ that 2D linear elasticity would predict. In 3D, values of n from simulations were in the range 0.6–0.9, and experiments yielded $n=0.52$, again much less than the linear elastic value $n=2$. Significantly, when the microbuckling elements were replaced by linear elastic ones that do not buckle (same stiffness in compression as in tension) the network simulations yielded values of n close to the linear elastic predictions (Notbohm et al., 2015a).

These finite element simulations of discrete network models provided strong evidence for the hypothesis formulated by Notbohm (2013) and coworkers Notbohm et al. (2015a): *microbuckling of fibrin enables long-range cell-induced displacements that facilitate mechanosensing*. The purpose of this paper is to provide theoretical support for this conclusion. So far, the evidence comes from experiments and numerical simulations of a discrete network (Notbohm, 2013; Notbohm et al., 2015a). Here we conjecture that a homogeneous solid with *lower stiffness in compression than in tension* will also exhibit slower decay of displacements/stresses due to a contracting inclusion than a linear elastic solid. In other words, the dominant factor responsible for the slow displacement decay is loss of stiffness in compression rather than the discrete character of the fiber network. We show this by first constructing a constitutive model with the requisite properties, then solving some relevant boundary value problems analytically.

Constitutive modelling is described in detail in Section 2. The analysis of relevant boundary value problems is spelled out in Sections 3 and 4. Sections 2–4 contain considerable technical details and may be omitted at first reading. We briefly present our main results in Section 5 (Results) and discuss their significance in Section 6 (Discussion).

2. Constitutive model

2.1. 2D constitutive law

We now describe a special elastic constitutive law, which loses stiffness in compression in a sense to be made precise. Such a constitutive law cannot be linear, even in the context of small deformations, if it is going to exhibit behavior analogous to that of Fig. 1(b) in more than one dimension. For simplicity we consider small deformations (linearized