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

1.1 Motivation

The purpose of this work is to provide theoretical evidence in support of a hypothesis formulated originally by Notbohm [1] and further studied recently by Notbohm et al. [2]: Microbuckling of fibrin enables long range cell mechanosensing.
Experiments [1, 2] measured displacements in a 3D fibrin matrix caused by contractile fibroblasts seeded in it, using a method developed in [3]. The matrix displacements induced by cell contraction were found to decay much slower with distance from the cell than linear elasticity would predict. It seems highly likely that this long range of cell-induced matrix deformations and stresses provides a mechanism for mechanosensing, or the detection of cells by their neighbors through sensing of cell-induced mechanical signals, at larger distances than in a linear elastic gel. It was asserted [1, 2] that the displacements and stresses due to a contracting inclusion in a fiber network, decay slower than in a homogeneous linear elastic material, because of loss of stiffness in compression. The stiffness loss is due to microbuckling, namely buckling of individual fibers in the network that are in compression. See [4, 5] for various consequences of microbuckling.

Finite element simulations of a fiber network model [1, 2] 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 [6]. Accordingly, the buckling load is essentially taken to vanish in Fig. 1(b). Simulations with 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 [2] for most network connectivities. This leads us to make the hypothesis that the dominant factor responsible for the slow displacement decay is loss of stiffness in compression, rather than the inhomogeneous, discrete character of the fiber network.

1.2 Summary and Results

To test the aforementioned hypothesis, we construct a homogeneous continuum model, but one with a nonlinear elastic constitutive law, in which the principal stresses depend on the principal strains in
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Figure 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 $\varepsilon$ in percent. Vertical axis: normalized stress $\sigma/\alpha$, where $\alpha$ is a one-dimensional elastic constant.

We call it the compression stiffness ratio. When $\rho = 1$ we are back to linear elasticity.

It is rather challenging to construct higher dimensional models that do this in an acceptable fashion. The stresses have to be continuous functions of the strains (though not necessarily differentiable), and they must be derivable from a strain energy density function, otherwise the elastic constitutive law is thermodynamically unsound. This task is the subject of Section 2 for the 2D case. The result is a strain energy density function that is a piecewise quadratic function of the principal strains. Its level curves in the principal strain plane are shown in Fig. 2(a), while those of the underlying linear elastic one are shown in Fig. 2(b).

The choice of a piecewise-linear stress-strain law neglects the gradual nonlinear strain stiffening typical of fibrin [6]. The findings of [1, 2] using elements that gradually stiffen in tension, but also [7], suggest that strain stiffening is not the primary factor causing the observed slow displacement decay. At the same time, choosing a piecewise linear constitutive law allows one to solve some important model problems analytically.

It should be noted that the model constructed here does not exhibit negative compressibility,
which is observed in many fibrin networks [8] and exhibited by the network model of [1, 2]. In particular, the Poisson ratio in the model is always between $-1$ and $1/2$. We infer that negative compressibility is not the primary factor in the long range mechanosensing mechanism (associated with the slow decay of elastic fields compared to predictions of linear elasticity). The model supports the conclusions of Notbohm et al. [2] that the primary cause is compression weakening. In the present homogeneous model, compression weakening is due to a constitutive nonlinearity, whereas in a fibrin network it is due to fiber microbuckling. It is possible that negative compressibility may play a secondary role in long range mechanosensing; this needs further investigation.

In Section 3 we consider a problem intended to model the shrinking cell in a fibrin matrix. The matrix may be finite but possibly large compared to the cell; we do account for external boundaries. We start with 2D. Our constitutive model is tractable in the radially symmetric case. In Section 3.1, the cell is modeled as a shrinking circle of radius $a$; the matrix as a disk of radius $A$, with the cell at its center. The case $A \gg a$ is typical. The matrix external boundary ($r = A$) is left free of applied forces (traction-free), while the cell boundary ($r = a$) suffers a prescribed negative radial displacement $-u_0$. This gives two boundary conditions. The matrix is assumed to be composed of the material with constitutive law developed in Section 2. This is characterized by two elastic constants and the stiffness ratio $\rho$.

There is a unique solution to this problem. The displacement field is radial, of the form

$$u(r) = c_1 r^{\xi_-} + c_2 r^{\xi_+}, \quad a < r < A, \quad (1.2)$$

where the exponents are given by

$$\xi_- = -\sqrt{\rho}, \quad \xi_+ = \sqrt{\rho}, \quad (1.3)$$

so that the first term in (1.2) decays, while the second grows, as the distance $r$ from the origin increases. The relevant stress components take the general form

$$\sigma(r) = c_3 r^{\xi_- - 1} + c_4 r^{\xi_+ - 1}, \quad a < r < A \quad (1.4)$$

The constants $c_1$ through $c_4$ are determined by the boundary conditions. For the complete closed-form solution see (3.10)–(3.12). When we set $\rho = 1$ we recover the linear elastic solution $u(r) = c_1/r + c_2 r$. For $0 < \rho < 1$, the decreasing term does decay slower than the corresponding linear elastic term, but the role of the growing terms seems unclear. We deal with this in sect. 3.2. We observe that the constants $c_2, c_4$ tend to zero in the limit as $A \to \infty$. This suggests that the growing terms may remain small. We find that this is indeed the case and deduce bounds for the displacement and the stress in the form

$$|u(r)| \leq u_0 M_1 \left( \frac{r}{a} \right)^{\xi_-}, \quad |\sigma(r)| \leq (u_0/a) M_2 \left( \frac{r}{a} \right)^{\xi_- - 1} \quad (1.5)$$
Observe that these inequalities involve only the negative exponent \( \xi_- \), although they bound the entire displacement and stress in (1.2), (1.4), including the growing terms. Also, they are universal, in the sense that the constants \( M_1 \) and \( M_2 \) are independent of \( A \) and \( a \) (the geometry). Rather, they only depend on the elastic constants and the stiffness ratio \( \rho \). Also the dependence of the bounds on \( r \) is through the ratio \( r/a \), that is, distance measured in cell radii. The bounds are completely independent of \( A \).

Since \(-1 < \xi_- < 0\), these bounds show that the displacement and stress fields exterior to a contracting spherical inclusion in a compression weakening material decay slower than the corresponding linear elastic ones; the latter would be bounded by

\[
|u(r)| \leq u_0 M_3 \left( \frac{r}{a} \right)^{-1}, \quad |\sigma(r)| \leq (u_0/a) M_4 \left( \frac{r}{a} \right)^{-2}
\]

The case of the infinite matrix is briefly dealt with in sect. 3.3. In sect. 3.4 we also consider the case \( \rho = 0 \), which is a singular limit. The general solution involves a \( \log r \) term; this raises certain mathematical and physical issues which are discussed in detail.

Radial displacement data from the 2D simulations of the fiber network model of Notbohm et al. [2] were fit to the form

\[
u(r) = C_1 r^{-n} + C_2 r^n,
\]

with fitting parameters \( C_1, C_2, n \). This form was chosen since it is consistent with (1.2), (1.3). The value \( \rho = 0.1 \) was used in these simulations. The resulting fit for \( n \) depends on the connectivity of the network simulated. The network of highest connectivity \( (C = 8) \) is likely to behave closest to the continuum model. In this case fits of the numerical data give \( n = 0.36 \), whereas choosing \( \rho = 0.1 \) in (1.2), (1.3) yields the continuum model prediction \( n = 0.32 \).

Why do cells contract instead of expanding to facilitate mechanosensing? Probably a good answer to this question is: because they can! That is, it may only be possible for the cell to exert tension on the matrix, because the mechanism is essentially winches pulling on ropes, i.e., actin motors pulling on actin filaments. These can sustain tension but not compression. So it may be physically impossible or difficult for the cell to push at the matrix.

This reason aside, we answer the following question in sect. 3.5: Suppose the cell has a choice between contracting and expanding. Which is more efficient for mechanosensing in a fibrin network matrix? Because of nonlinearity, reversing the sign of the applied boundary displacement \( u_0 \) does not simply multiply the solution by \(-1\), as would happen in linear elasticity. Instead, if the cell expands and pushes at the matrix (let \( u_0 < 0 \)) the solution is still of the form (1.2), (1.4) but with different exponents; the negative exponent is now \( \xi_- = -1/\sqrt{\rho} \). The bounds (1.5) still hold, but now the negative exponent \( \xi_- < -1 \) because of (1.1), moreover \( \xi_- \) approaches \(-\infty \) as \( \rho \to 0 \). As a result,
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the displacements and stresses due to an expanding cell in a compression weakening material decay faster than in a linear elastic material. Thus expanding cells would cloak themselves from other cells; this is counterproductive for mechanosensing. This result agrees with a numerical calculation in [1]: when a concentrated load is exerted in a finite element network model, the displacements decay faster (than linear elasticity predicts) in the direction towards which the force points, and slower in the opposite direction.

The 3D constitutive law is obtained by generalizing the 2D model in sect. 4.1. The 3D shrinking cell problem is formulated in sect. 4.2 as that of a sphere of radius \( a \), contracting with radial displacement \(-u_0\) at the center of a spherical matrix of radius \( A \), whose external boundary is traction free. The solution is more complicated than the 2D one, but qualitatively very similar. The displacements and stresses are still of the form (1.2), (1.4), but the exponents \( \xi_{\pm} \) now depend on the elastic moduli, in addition to the compression stiffness ratio \( \rho \). The complete solution is given in (4.8)–(4.10). The exponents \( \xi_{\pm} \) satisfy

\[-2 \leq \xi_- < -1, \quad 0 < \xi_+ \leq 1,\]

while universal bounds of the form (1.5) are still valid. Once again, in 3D the decay is slower than in a linear elastic matrix where the displacement would decay with \( \xi_- = -2 \). The conclusions of the 3D calculations are essentially the same as the the 2D ones.

2 Constitutive Law

To begin with, suppose the matrix plus the cell together occupy the whole 2D space \( \mathbb{R}^2 \) and is composed of linear elastic homogeneous isotropic material (undergoing small deformations, so that the linearized theory of elasticity is used). We thus have a displacement field \( u: \mathbb{R}^2 \rightarrow \mathbb{R}^3 \). The strain tensor (or \( 3 \times 3 \) matrix) is

\[ E = \frac{1}{2} (\nabla u + \nabla u^T), \quad E_{ij} = \frac{1}{2} \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) \]

In the matrix except the cell, the stress tensor is related to the displacement gradient by

\[ S = \lambda (\text{tr} E) 1 + 2\mu E \]

Here \( \lambda \) and \( \mu \) are the Lamé constants and \( 1 \) the identity tensor. In components, the above reads

\[ S_{ij} = \lambda E_{kk} \delta_{ij} + 2\mu E_{ij} \]

(the Einstein summation convention is used: summation over repeated indices is implied).
The principal stresses $\sigma_i$ (the eigenvalues of the stress tensor) are related to the principal strains $\varepsilon_i$ (the eigenvalues of the strain tensor) through

$$\sigma_i = C_{ij}\varepsilon_j$$

where

$$C = \begin{pmatrix} \alpha & \beta \\ \beta & \alpha \end{pmatrix}, \quad \alpha = 2\mu + \lambda, \quad \beta = \lambda$$

and $\lambda, \mu$ are the Lamé Moduli (elastic constants; $\mu$ is the shear modulus). In other words, the linear elastic principal stress-strain relations are

$$\sigma_1 = \alpha \varepsilon_1 + \beta \varepsilon_2, \quad \sigma_2 = \beta \varepsilon_1 + \alpha \varepsilon_2,$$  \hspace{1cm} (2.2)

Positive definiteness of $C$ is equivalent to

$$\alpha > |\beta|.$$  \hspace{1cm} (2.3)

Our first attempt toward constructing a constitutive law that weakens in compression is to consider piecewise-linear stress-strain relations. Consider the function

$$Z_\rho(x) = \begin{cases} x, & x \geq 0, \\ \rho x, & x < 0, \end{cases}$$  \hspace{1cm} (2.4)

where $0 \leq \rho \leq 1$ is the constant compression stiffness ratio. The graph of $Z_\rho$ is the curve in Fig. 1(b).

In 1D, one might replace the linear stress-strain relation $\sigma = \alpha \varepsilon$, where $\alpha$ is a modulus, by the piecewise linear stress-strain relation $\sigma = Z_\rho(\alpha \varepsilon)$; see Fig. 1.2. By analogy, we replace (2.2) with

$$\sigma_1 = Z_\rho(\alpha \varepsilon_1 + \beta \varepsilon_2),$$  \hspace{1cm} (2.5)

$$\sigma_2 = Z_\rho(\beta \varepsilon_1 + \alpha \varepsilon_2),$$  \hspace{1cm} (2.6)

In effect this multiplies stiffness by $\rho$ whenever the corresponding principal stress is negative (compressive). However, this turns out to be problematic. Suppose the argument of $Z_\rho$ in (2.5) is positive and the argument of $Z_\rho$ in (2.6) is negative. Then we have $\partial \sigma_1 / \partial \varepsilon_2 = \beta$ while $\partial \sigma_2 / \partial \varepsilon_1 = \rho \beta$, which means that if $\rho \neq 1$, there is no strain energy density function $W(\varepsilon_1, \varepsilon_2)$ such that $\sigma_i = \partial W / \partial \varepsilon_i$. Thus the stress-strain relations (2.5), (2.6) are not hyperelastic except in the trivial case of no weakening ($\rho = 1$) which coincides with linear elasticity. We therefore feel that this model is not satisfactory.

In order to overcome the lack of hyperelasticity just encountered, one might attempt to construct the strain energy function directly. However, since the change in stiffness is supposed to occur
when stresses, not strains, change sign, this is somewhat difficult. It is more natural to construct the complementary energy density function $U(\sigma_1, \sigma_2)$, with the property that

$$\frac{\partial U(\sigma_1, \sigma_2)}{\partial \sigma_i} = \varepsilon_i$$

Assuming that $W(\varepsilon_1, \varepsilon_2)$ is strictly convex and continuously differentiable, the stress-strain relations are invertible to the form $\varepsilon_i = \hat{\varepsilon}_i(\sigma_1, \sigma_2)$ and one has

$$U(\sigma_1, \sigma_2) = \sigma_i \varepsilon_i - W(\varepsilon_1, \varepsilon_2), \quad \varepsilon_i = \hat{\varepsilon}_i(\sigma_1, \sigma_2)$$

In 1D, one might adopt the stress-strain relation $\sigma = \alpha Z_\rho(\varepsilon)$, where $\alpha$ is a modulus. Then since $\sigma = W'(\varepsilon)$, we have

$$W(\varepsilon) = \frac{\alpha}{2} Z_\rho^2(\varepsilon)$$

Also since the strain-stress relation is $\varepsilon = \alpha^{-1} Z_{\rho^{-1}}(\sigma)$, the complementary energy is

$$U(\sigma) = \frac{\kappa}{2} Z_d^2(\sigma), \quad d = 1/\sqrt{\rho}, \quad \kappa = 1/\alpha$$

Thus the complementary energy is quadratic in $Z_d(\sigma)$ while for linear elasticity ($d = 1$) it would be $\kappa\sigma^2/2$. Now in 2D for linear elasticity, the complementary energy is

$$U_1(\sigma_1, \sigma_2) = \frac{1}{2} K_{ij} \sigma_i \sigma_j, \quad K = C^{-1}. \quad (2.7)$$

Thus one might be tempted to replace $\sigma_i$ by $Z_d(\sigma_1)$ above and to consider the complementary energy candidate

$$U_*(\sigma_1, \sigma_2) = K_{11} Z_d^2(\sigma_1)/2 + K_{22} Z_d^2(\sigma_2)/2 + K_{12} Z_d(\sigma_1) Z_d(\sigma_2)$$

The problem with this is that the resulting strain stress relations (partial derivatives of $U_*$) are not continuous functions of $\sigma_i$. While $Z_d^2(\sigma)$ is continuously differentiable in $\sigma$, $Z_d(\sigma)$ is not. So while the first two terms above are smooth, the trouble comes from the mixed term (third term involving $K_{12}$). This is easily fixed by modifying the third term (responsible for coupling between $\sigma_1$ and $\sigma_2$)

We let

$$U_\rho(\sigma_1, \sigma_2) = \frac{1}{2} K_{11} Z_d^2(\sigma_1) + \frac{1}{2} K_{22} Z_d^2(\sigma_2) + K_{12} \sigma_1 \sigma_2 \quad (2.8)$$

where $d = 1/\sqrt{\rho}$. This is once continuously differentiable (but only piecewise twice). Assuming $C$ and hence $K$ to be positive definite, it is also strictly convex. Thus the strain-stress relations are invertible and piecewise linear, and so are the stress-strain relations, while the associated strain energy is strictly convex, piecewise quadratic, and once continuously differentiable. Also, (2.8) coincides with the linear elastic complementary energy (2.7) whenever both $\sigma_i \geq 0$ (in the first quadrant of the principal stress plane). The stiffnesses change though whenever one or both of the
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\[ \sigma_i \text{ become negative. Thus } U_\rho \text{ coincides with a different quadratic function within each of the four quadrants of the principal stress plane. In particular, noting that} \]

\[ K = [K_{ij}] = \frac{1}{\alpha^2 - \beta^2} \begin{pmatrix} \alpha & -\beta \\ -\beta & \alpha \end{pmatrix} \]

one can write

\[ U_\rho(\sigma_1, \sigma_2) = \frac{1}{2} \hat{K}_{ij} \sigma_i \sigma_j, \quad (2.9) \]

where the matrix \( \hat{K} \), apart from \( \rho \), also depends on \( \sigma_i \) in a piecewise constant fashion. Specifically, it depends only on the signs of \( \sigma_i \), and takes the following four values in the corresponding four quadrants of the principal stress plane (numbered counterclockwise).

\[ \begin{pmatrix} K_{11} & K_{12} \\ K_{12} & K_{22} \end{pmatrix}, \quad \begin{pmatrix} K_{11}/\rho & K_{12} \\ K_{12} & K_{22}/\rho \end{pmatrix}, \quad \begin{pmatrix} K_{11}/\rho & K_{12} \\ K_{12} & K_{22}/\rho \end{pmatrix}, \quad \begin{pmatrix} K_{11} & K_{12} \\ K_{12} & K_{22}/\rho \end{pmatrix}. \quad (2.10) \]

It is possible to construct the strain energy density out of this. The result is

\[ W_\rho(\varepsilon_1, \varepsilon_2) = \frac{1}{2} \hat{C}_{ij} \varepsilon_i \varepsilon_j, \quad (2.11) \]

where \( \hat{C} = \hat{K}^{-1} \), is a piecewise constant matrix that takes four values, the inverses of (2.10), in four sectors of the principal strain plane that are the images of the four quadrants of the stress plane under the mapping \( (\sigma_1, \sigma_2) \mapsto (\varepsilon_1, \varepsilon_2) \) (given by the strain-stress relations due to (2.9)). See Fig. 2(a). Thus for example in the sector corresponding to \( \sigma_1 > 0, \sigma_2 < 0 \), the value of \( \hat{C} \) in (2.11) is

\[ \hat{C} = \frac{(\alpha^2 - \beta^2)\rho}{\alpha^2 - \beta^2 \rho} \begin{pmatrix} \alpha/\rho & \beta \\ \beta & \alpha \end{pmatrix}, \quad \text{provided } \alpha\varepsilon_1/\rho + \beta\varepsilon_2 > 0, \quad \beta\varepsilon_1 + \alpha\varepsilon_2 < 0. \]

The two inequalities above define the sector in the principal strain plane that corresponds to the quadrant \( \sigma_1 > 0, \sigma_2 < 0 \). Whenever these two inequalities hold, the stress-strain law is given by

\[ \sigma_1 = h(\rho)(\alpha\varepsilon_1/\rho + \beta\varepsilon_2), \quad \sigma_2 = h(\rho)(\beta\varepsilon_1 + \alpha\varepsilon_2), \quad \text{where } h(\rho) = \frac{(\alpha^2 - \beta^2)\rho}{\alpha^2 - \beta^2 \rho}. \quad (2.12) \]

3 The Shrinking Cell Problem in 2D

3.1 Formulation and Solution

We model the situation of a shrinking cell in a fibrin matrix. It turns out that radially symmetric solutions can be constructed analytically, so the cell is modeled as a disk of radius \( a \) (in 2D) centered at the origin, while the matrix is the annulus \( a < r < A \), where \( A \) is the outside radius and \( r = |x| \)
(a) Level curves of the strain energy density $W_\rho$ in the $(\varepsilon_1, \varepsilon_2)$ plane for $\rho = 1/9$. The blue and red straight lines separate the plane into four sectors. The strain energy density is equal to a different quadratic function in each sector. The blue line in the second quadrant and red line in the fourth quadrant correspond to uniaxial stress, $\sigma_1 = 0$. The blue line in the fourth quadrant and red line in the second quadrant correspond to uniaxial stress, $\sigma_2 = 0$. (b) For comparison, level curves of the corresponding linear elastic energy ($\rho = 1$). Blue lines correspond to uniaxial stress. (b) A single level curve of the strain energy density (thick curve). The four ellipses (blue, green, purple and brown) are the level curves of the four quadratic functions that equal the strain energy in different sectors.

Figure 2: (a) Level curves of the strain energy density $W_\rho$ in the $(\varepsilon_1, \varepsilon_2)$ plane for $\rho = 1/9$. The blue and red straight lines separate the plane into four sectors. The strain energy density is equal to a different quadratic function in each sector. The blue line in the second quadrant and red line in the fourth quadrant correspond to uniaxial stress, $\sigma_1 = 0$. The blue line in the fourth quadrant and red line in the second quadrant correspond to uniaxial stress, $\sigma_2 = 0$. (b) For comparison, level curves of the corresponding linear elastic energy ($\rho = 1$). Blue lines correspond to uniaxial stress. (b) A single level curve of the strain energy density (thick curve). The four ellipses (blue, green, purple and brown) are the level curves of the four quadratic functions that equal the strain energy in different sectors.
is radial distance from the center, while \( x \) is the position vector. Displacement fields with radial symmetry are of the form \( u(x) = u(r)x/r \) in terms of the radial displacement (scalar) function \( u(r) \). The principal strains and stresses are functions of \( r \):

\[
\varepsilon_1 = \varepsilon_r(r) = u'(r), \quad \varepsilon_2 = \varepsilon_\theta(r) = u(r)/r,
\]

where a prime indicates a derivative, while \( \varepsilon_1 \) is the radial strain and \( \varepsilon_2 \) is the circumferential strain. The equilibrium equations in terms of the radial stress \( \sigma_1 = \sigma_r(r) \) and hoop stress \( \sigma_2 = \sigma_\theta(r) \) reduce to

\[
(r\sigma_r(r))' = \sigma_\theta(r)
\]

(3.2)

We suppose that (i) the cell shrinks, and (ii) that the outside boundary of the matrix is traction free. We model (i) and (ii) by the boundary conditions

\[
u(a) = -u_0,
\]

(3.3)

where \( u_0 \) is a positive constant, and

\[
\sigma_r(A) = 0,
\]

(3.4)

respectively. The solution of the corresponding linear elastic problem (with \( \rho = 1 \)) has the property that \( \sigma_r(r) > 0, \sigma_\theta(r) < 0 \) for \( a < r < A \). Adopting these inequalities a priori as an ansatz in the case of the compression weakening material (\( 0 < \rho < 1 \)), the stress-strain relations are given by (2.12); hence the second boundary condition (3.4) becomes

\[
\alpha u'(A)/\rho + \beta u(A)/A = 0.
\]

(3.5)

Substituting (3.1) into (2.12), and the result into (3.2), yields a 2nd order linear ODE for \( u(r) \):

\[
r^2u''(r) + ru'(r) - \rho u = 0 \quad \text{for} \quad a < r < A;
\]

(3.6)

\( u(r) \) is also subject to the boundary conditions (3.3) and (3.5). The solution of this boundary value problem is admissible provided it can be verified a posteriori that it satisfies the ansatz

\[
\sigma_r(r) > 0, \quad \sigma_\theta(r) < 0 \quad \text{for} \quad a < r < A
\]

(3.7)

which ensures that (2.12) holds.

The general solution of the ODE (3.6) for \( u(r) \) is (letting \( \xi = \sqrt{\rho} \))

\[
u(r) = c_1 r^{-\xi} + c_2 r^\xi, \quad \xi = \sqrt{\rho}
\]

(3.8)
The radial displacement then takes the form
\[ u(r) = -u_0 \frac{(\alpha + \beta \xi) (\frac{r}{A})^{-\xi} + (\alpha - \beta \xi) (\frac{r}{A})^{\xi}}{c_1 (\alpha - \beta \xi) + A_{2\xi} (\alpha + \beta \xi)} \]  
(3.10)

The stresses are given by
\[ \sigma_r(r) = -(u_0/a) \frac{\xi(\alpha^2 - \beta^2) \left[ (\frac{r}{A})^{-\xi-1} - (\frac{r}{A})^{\xi-1} \right]}{c_1 (\alpha + \beta \xi) (\frac{r}{A})^{-\xi-1} + (\alpha - \beta \xi) (\frac{r}{A})^{\xi-1}}, \]
\[ \sigma_\theta(r) = -(u_0/a) \frac{\xi^2(\alpha^2 - \beta^2) \left[ (\frac{r}{A})^{-\xi-1} + (\frac{r}{A})^{\xi-1} \right]}{c_1 (\alpha + \beta \xi) (\frac{r}{A})^{-\xi-1} + (\alpha - \beta \xi) (\frac{r}{A})^{\xi-1}}, \]  
(3.11) (3.12)

In order to verify (3.7), we rewrite them as
\[ \sigma_r(r) = u_0 \frac{\xi a^2 (\alpha^2 - \beta^2) r^{-\xi-1} (A_{2\xi} - r^{2\xi})}{c_1 (\alpha - \beta \xi) + A_{2\xi} (\alpha + \beta \xi)}, \]
\[ \sigma_\theta(r) = -u_0 \frac{\xi^2 a^2 (\alpha^2 - \beta^2) r^{-\xi-1} (A_{2\xi} + r^{2\xi})}{c_1 (\alpha - \beta \xi) + A_{2\xi} (\alpha + \beta \xi)}, \]  
(3.13) (3.14)

In view of (2.3) and since \(0 < \rho \leq 1\ (0 < \xi \leq 1)\) we have \( \alpha \pm \beta \xi > 0 \). Also \( A_{2\xi} \pm r^{2\xi} \geq 0 \) and \( u_0 > 0 \). It follows from the above form that the inequalities (3.7) are satisfied. Therefore, with stresses (3.11), (3.12) provides the solution to the shrinking cell problem, for the constitutive law provided by the compression weakening model of Section 2.

The solution is proportional to the contractile displacement \( u_0 \) for \( u_0 > 0 \) (contraction). For \( u_0 < 0 \) (expanding cell) the ansatz (3.7) is violated. The solution in this case will be discussed in sect. 3.5.

In the special case \( \rho = 1 \ (\xi = 1) \) we recover the linear elastic solution. The displacement is of the form \( u(r) = c_1/r + c_2 r \), while stresses are of the form \( \sigma(r) = c_3/r^2 + c_4 \).

### 3.2 Universal Bounds

A glance at the general solution (3.8) shows that it contains a term that decays as \( r \) increases but also one that increases. That raises the question whether the second term would dominate for large \( r \). Recall that \( a \leq r \leq A \). Because of the boundary conditions, the constants \( c_1 \) and \( c_2 \) depend on \( A \); see (3.9). It turns out that \( c_2 \) decreases as \( A \) increases and actually vanishes in the limit of an infinite
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matrix (as \( A \to \infty \)). In contrast, \( c_1 \) does not vanish in this limit. In fact, using the inequalities (2.3), 0 < \( \xi \leq 1 \), we have \( \alpha \pm \beta \xi > 0 \) so that rewriting (3.10),

\[
\begin{align*}
    u(r) &= -u_0 \frac{A^{2\xi} (\alpha + \beta \xi) (r/a)^{-\xi} + a^{2\xi} (\alpha - \beta \xi) (r/a)^{\xi}}{a^{2\xi} (\alpha - \beta \xi) + A^{2\xi} (\alpha + \beta \xi)}, \quad a \leq r \leq A \\
    |u(r)| &\leq u_0 \frac{A^{2\xi} (\alpha + \beta \xi) (r/a)^{-\xi} + a^{2\xi} (\alpha - \beta \xi) (r/a)^{\xi}}{A^{2\xi} (\alpha + \beta \xi)} = u_0 (r/a)^{-\xi} + u_0 \frac{a^{2\xi} (\alpha - \beta \xi) (r/a)^{\xi}}{A^{2\xi} (\alpha + \beta \xi)}
\end{align*}
\]

But since 0 < \( r \leq A \) we have \( (a/A)^{2\xi} \leq (a/r)^{2\xi} \), so that the above gives the following bound for the displacements induced by a circular cell of radius \( a \) contracting radially with displacement \( u_0 \) in a circular matrix of arbitrary radius.

\[
|u(r)| \leq u_0 \frac{2\alpha}{(\alpha + \beta \xi)} (r/a)^{-\xi}
\]

(3.15)

The bound is universal in the sense that it is independent of the outside radius \( A \) and shows that the displacements decay with order \( O(r^{-\sqrt{\rho}}) \), despite the presence of the second (growing) term in (3.8). A similar calculation based on (3.13), (3.14) (noting for example that \( A^{2\xi} + r^{2\xi} \leq 2A^{2\xi} \)) gives universal bounds for the stresses in the form

\[
|\sigma(r)| \leq (u_0/a) M (r/a)^{-\xi-1}
\]

(3.16)

where \( \sigma \) stands for either \( \sigma_r \) or \( \sigma_\theta \), while the constant

\[
M = \frac{2\xi(\alpha^2 - \beta^2)}{\alpha + \beta \xi}
\]

depends only on material properties \( \alpha, \beta \) and \( \rho = \xi^2 \) but not on \( A \). We conclude that stresses and displacements induced by a contracting cell in a matrix composed of compression weakening material, decay slower than in a linear elastic matrix where \( u = O(r^{-1}) \) and \( \sigma = O(r^{-2}) \).

### 3.3 Infinite Matrix

Taking the limit as \( A \to \infty \) we obtain the displacement due to a shrinking cell in an infinite matrix (with the stress approaching zero at large distances)

\[
\begin{align*}
    u(r) &= -u_0 \left( \frac{r}{a} \right)^{-\xi}, \quad \xi = \sqrt{\rho}.
\end{align*}
\]

The stresses are

\[
\begin{align*}
    \sigma_r(r) &= (u_0/a) \frac{\xi(\alpha^2 - \beta^2)}{\alpha + \beta \xi} (r/a)^{-\xi-1}, \quad \sigma_\theta(r) = -\xi \sigma_r(r), \quad a \leq r < \infty
\end{align*}
\]

Thus for a compression weakening material with \( \rho < 1 \) (\( \xi < 1 \)) the displacements, \( u(r) = O(r^{-\xi}) \), and the stresses, \( \sigma(r) = O(r^{-\xi-1}) \) as \( r \to \infty \). Thus both decay slower than their linear elastic
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counterparts, which are $O(r^{-1})$ and $O(r^{-2})$, respectively. The lower the compression stiffness ratio $\rho = \xi^2$, the slower the decay. We conclude that regardless of whether cell mechanosensing is based on stresses or displacements, cells can sense each other over larger distances in fibrin networks than in materials that do not weaken in compression.

### 3.4 The Case of Zero Compression Strength

The case $\rho = 0$ is interesting but tricky; The limit as $\rho = 0$ in the solution (3.10), (3.11), (3.12) is

$$u(r) = -u_0, \quad \sigma_r(r) = \sigma_\theta(r) = 0, \quad a \leq r \leq A.$$  (3.17)

Taking the limit as $\rho = 0$ in the constitutive law (2.12), yields

$$\sigma_1 = \frac{\alpha^2 - \beta^2}{\alpha} \varepsilon_1, \quad \sigma_2 = 0$$

where $\sigma_1 = \sigma_r$, $\varepsilon_1 = u'(r)$ for the radially symmetric problem. Then the equilibrium equation (3.2) becomes $(r \sigma_r(r))' = 0$ or $(ru'(r))' = 0$. The general solution is

$$u(r) = c_1 \log r + c_2, \quad \sigma_r(r) = \frac{\alpha^2 - \beta^2}{\alpha} c_1/r$$

If we enforce the boundary conditions (3.3), (3.4), the second demands $c_1 = 0$ and the first that $c_2 = u_0$, thus for the bounded traction free matrix we recover (3.17). For the infinite matrix however, since the stress decays as $1/r$, we only have (3.3) to enforce and that leaves a one parameter family of solutions

$$u(r) = c_1 \log(r/a) - u_0$$

If we insist though that $u(r)$ remain bounded, then necessarily $c_1 = 0$ and the only solution is (3.17).

### 3.5 Expanding cells are short sighted

We ask the following question: Suppose the cell has a choice between contracting and expanding. What is more efficient for mechanosensing in a fibrin network matrix?

To answer this in the context of our model, suppose now that we change the sign in (3.3) and require $u_0 < 0$. Then the signs in (3.11) and (3.12) are reversed, and (3.7) is violated! The previous solution with a mere sign change does not apply here. One expects that changing the sign of $u_0$ will reverse the signs in (3.7), so that instead of (3.7), we will make the ansatz

$$\sigma_r(r) < 0, \quad \sigma_\theta(r) > 0$$  (3.18)
This will put the stresses in the second, as opposed to the fourth quadrant of the principal stress plane, involving a different quadratic branch of the energy function. Then \( \hat{C} \) in (2.11) will equal the inverse of the second, instead of the fourth matrix in (2.10). Accordingly (2.12) must be replaced by

\[
\sigma_1 = h(\rho)(\alpha \varepsilon_1 + \beta \varepsilon_2), \quad \sigma_2 = h(\rho)(\beta \varepsilon_1 + \alpha \varepsilon_2 \rho),
\]

with (3.1) still in force. This eventually results in a different ODE for \( u(r) \), namely

\[
r^2 u''(r) + ru'(r) - \rho^{-1} u(r) = 0 \quad \text{for} \quad a < r < A.
\]

The general solution is

\[
u(r) = c_1 r^{-d} + c_2 r^d, \quad d = 1/\sqrt{\rho}
\]

The main difference here is that always \( d > 1 \) and \( d \to \infty \) as \( \rho \to 0 \). For example the solution of the cell in the infinite matrix is

\[
u(r) = -u_0 \left( \frac{r}{a} \right)^{-d}, \quad d = 1/\sqrt{\rho}.
\]

while the stresses behave as \( \sigma(r) = O(r^{-d-1}) \). Thus, both displacements and stresses induced by an expanding cell decay faster than their linear elastic counterparts, which are \( O(r^{-1}) \) and \( O(r^{-2}) \), respectively. The lower the compression stiffness ratio \( \rho = 1/d^2 \), the faster the decay. Thus cell expansion is not a good mechanism for long range mechanosensing and makes the situation worse than in a linear elastic matrix. In a linear elastic matrix, cell expansion and contraction produce fields with the same decay rate.

### 4 Three Dimensions

#### 4.1 3D Constitutive Law

In 3D (letting Latin indices range over \( \{1, 2, 3\} \)), the linear elastic isotropic strain energy function in terms of principal strains is

\[
W(\varepsilon_1, \varepsilon_2, \varepsilon_3) = C_{ij} \varepsilon_i \varepsilon_j, \quad C = \begin{pmatrix}
\alpha & \beta & \beta \\
\beta & \alpha & \beta \\
\beta & \beta & \alpha
\end{pmatrix}
\]

where \( \alpha = 2\mu + \lambda, \beta = \lambda \) as before. Positive definiteness of \( C \) is equivalent to

\[
\alpha - \beta > 0, \quad \alpha + 2\beta > 0
\]

(equivalent to the usual \( \mu > 0, \ 3\lambda + 2\mu > 0 \)). The (principal) stress-strain relations are

\[
\sigma_i = C_{ij} \varepsilon_j
\]
For the compression-weakening material we construct the complementary energy in analogy to (2.8)

\[
U(\sigma_1, \sigma_2, \sigma_3) = \frac{1}{2} \sum_{i=1}^{3} K_{ii} Z_d^2(\sigma_i) + \frac{1}{2} \sum_{i=1}^{3} \sum_{j=1, j \neq i}^{3} K_{ij} \sigma_i \sigma_j
\]

In particular, this function is continuously differentiable and piecewise quadratic. The second derivatives are piecewise constant and suffer jump discontinuities across the planes \(\sigma_i = 0\) in principal stress space. Thus \(U\) equals a quadratic function in each octant. In particular, in the octant

\[
\sigma_1 > 0, \quad \sigma_2 < 0, \quad \sigma_3 < 0,
\]

we have that

\[
U(\sigma_1, \sigma_2, \sigma_3) = \hat{K}_{ij} \sigma_i \sigma_j, \quad \hat{K} = \frac{1}{(a-b)(a+2b)} \begin{pmatrix}
\alpha + \beta & -\beta & -\beta \\
-\beta & \frac{\alpha + \beta}{\rho} & -\beta \\
-\beta & -\beta & \frac{\alpha + \beta}{\rho}
\end{pmatrix}
\]

In this octant, the strain-stress relations read \(\varepsilon_i = \hat{K}_{ij} \sigma_j\). These are invertible for \(0 < \rho \leq 1\). The inverse can be found explicitly. The stress-strain relations \(\sigma_i = \hat{C}_{ij} \varepsilon_j\) with \(\hat{C} = \hat{K}^{-1}\) (\(\hat{K}\) as above) are valid in the sector of principal strain space which is the image of the octant (4.2).

### 4.2 The Shrinking Spherical Cell

In 3D the cell is modeled as a sphere of radius \(a\) centered at the origin, while the matrix is the region \(a < r < A\), or the portion of the sphere of radius \(A\) outside the cell. Again, \(r = |\mathbf{x}|\) is radial distance from the center, while \(\mathbf{x}\) is the position vector. Displacement fields with radial symmetry are of the form \(u(\mathbf{x}) = u(r) \mathbf{x}/r\) as in 2D. The principal strains and stresses are functions of \(r\):

\[
\varepsilon_1 = \varepsilon_r(r) = u'(r), \quad \varepsilon_2 = \varepsilon_3 = \varepsilon_\theta(r) = \varepsilon_\varphi(r) = u(r)/r.
\]

where \(r, \theta, \varphi\) are spherical polar coordinates. Since \(\sigma_\theta(r) = \sigma_\varphi(r)\), the equilibrium equations reduce to

\[
(r^2 \sigma_r(r))' = 2r \sigma_\theta(r),
\]

We impose the same boundary conditions (3.3), (3.4) as in 2D. The solution of the corresponding linear elastic problem (\(\rho = 1\)) has the property that \(\sigma_r(r) > 0\), \(\sigma_\theta(r) = \sigma_\varphi(r) < 0\) for \(a < r < A\). Once again we presuppose (3.7), to be verified later. Substituting (4.3) into the 3D stress-strain relations, and the result into (4.4), yields a 2nd order linear ODE for \(u(r)\):

\[
r^2 u''(r) + 2ru'(r) - \frac{2\alpha \rho}{\alpha + \beta(1 - \rho)} u(r) = 0 \quad \text{for} \quad a < r < A;
\]
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$u(r)$ is also subject to the boundary conditions (3.3) and (3.4). The solution of this boundary value problem is admissible provided it satisfies (3.7). Note that (4.5) involves the material constants $\alpha$ and $\beta$, in contrast to the ODE (3.6) for 2D. Letting

$$g(\rho) = \frac{\alpha \rho}{\alpha + \beta (1 - \rho)}$$

the general solution of (4.5) is

$$u(r) = c_1 r^{\xi_-} + c_2 r^{\xi_+}, \quad \xi_\pm = \frac{1}{2} \left( -1 \pm \sqrt{1 + 8g(\rho)} \right)$$

(4.6)

Observing that $g(0) = 0$, $g(1) = 1$ and that $g(\rho)$ is monotone increasing, we have that

$$-2 \leq \xi_- < -1, \quad 0 < \xi_+ \leq 1.$$  

(4.7)

Also, $\xi_- \to -1$ as $\rho \to 0$. Proceeding as in 2D we find the constants $c_1$ and $c_2$ in (4.6) from the boundary conditions (3.3) and (3.4). The solution can be written as follows. Define the constants

$$P_\pm = \pm \left( [\alpha + \beta (1 - \rho)] \xi_\pm + 2 \beta \rho \right), \quad Q_\pm = \alpha + \beta (1 + \xi_\pm), \quad R = \frac{(\alpha - \beta)(\alpha + 2\beta)}{(\alpha + \beta)^2 - \beta(\alpha + 3\beta)\rho}.$$  

The displacement is

$$u(r) = -u_0 \frac{P_+ \left( \frac{r}{A} \right)^{\xi_-} + P_- \left( \frac{r}{A} \right)^{\xi_+}}{P_+ \left( \frac{r}{A} \right)^{\xi_-} + P_- \left( \frac{r}{A} \right)^{\xi_+}}$$

(4.8)

The stresses are

$$\sigma_r(r) = \frac{R P_+ P_- \left[ \left( \frac{r}{A} \right)^{\xi_- - 1} - \left( \frac{r}{A} \right)^{\xi_+ - 1} \right]}{P_+ \left( \frac{r}{A} \right)^{\xi_- - 1} + P_- \left( \frac{r}{A} \right)^{\xi_+ - 1}}, \quad \sigma_\theta(r) = -\left( u_0 / a \right) \frac{\rho R \left[ Q_- P_+ \left( \frac{r}{A} \right)^{\xi_- - 1} + Q_+ P_- \left( \frac{r}{A} \right)^{\xi_+ - 1} \right]}{P_+ \left( \frac{r}{A} \right)^{\xi_- - 1} + P_- \left( \frac{r}{A} \right)^{\xi_+ - 1}},$$

$$a \leq r \leq A.$$  

(4.9)

Using (4.1), (4.6) and (4.7), one can show that

$$P_\pm > 0, \quad Q_\pm > 0, \quad R > 0.$$  

This implies that the inequalities (3.7) are satisfied and the solution is admissible. It is possible to derive global bounds (as for the 2D solution) of the form

$$|u(r)| \leq u_0 M_1 \left( \frac{r}{A} \right)^{\xi_-}, \quad |\sigma(r)| \leq (u_0 / a) M_2 \left( \frac{r}{A} \right)^{\xi_- - 1}$$

where $\xi_-$ is the negative root in (4.6), (4.7), while $M_1$ and $M_2$ are constants that depend only on $\alpha$, $\beta$ and $\rho$, that is, on material constants only, but not on the geometry (not on $A$, $a$). For $\rho < 1$, in view of (4.7) we have $\xi_- > -2$, hence these bounds imply that the decay is always slower than the linear elastic case $\rho = 1$ (for which $\xi_- = -2, \xi_+ = 1$).

In the limiting case $\rho = 0$ the solution for finite $A$ is given by (3.17) as in 2D.
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