Compression stiffening in biological tissues: On the possibility of classic elasticity origins

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Compression stiffening, or an increase in shear modulus with increasing compressive strain, has been observed in recent rheometry experiments on brain, liver, and fat tissues. Here we extend the known types of biomaterials exhibiting this phenomenon to include agarose gel and fruit flesh. The data reveal a linear relationship between shear storage modulus and uniaxial prestress, even up to 40% strain in some cases. We focus on this less-familiar linear relationship to show that two different results from classic elasticity theory can account for the phenomenon of linear compression stiffening. One result is due to Barron and Klein, extended here to the relevant geometry and prestresses; the other is due to Birch. For incompressible materials, there are no adjustable parameters in either theory. Which one applies to a given situation is a matter of reference state, suggesting that the reference state is determined by the tendency of the material to develop, or not develop, axial stress (in excess of the applied prestress) when subjected to torsion at constant axial strain. Our experiments and analysis also strengthen the notion that seemingly distinct animal treeTc[m6(eemingly)-9ng 1]. For vascularized tissue, an upper limit o homeostatic pressure is set by the ∼10-kPa blood pressure. *E i* shear stiffness of mammalian brain matter is ∼1 kPa for comparison [2,3]. One might naturally ask how, or whether, the latter value would be different in the case of living or otherwise prestressed tissue. Very recent results using magnetic resonance elastography indicate the shear modulus of living brain tissue increases linearly with intracranial (homeostatic) pressure [4].

A series of recent parallel-plate rheometry experiments have explored prestress effects in animal tissue and biopolymer network samples of characteristic size ∼1 cm by subjecting them to a combination of static axial compression and ∼1-Hz torsional oscillations [5–10]. To avoid slippage during torsion, and also to facilitate axial tension, adhesive contact is typically made between the rheometer plates and the ends of the cylindrical sample [11]. It has been pointed out that such adhesive boundary conditions effectively constrain the lateral dimensions of a sufficiently thin sample, resulting in a volume change when axial force is applied [8,9]. In this thin-film limit, one expects stresses within a fluid-containing tissue sample are redistributed into a state of near hydrostatic pressure. Thus, by adjusting the sample geometry and/or boundary conditions, parallel-plate rheometers provide a convenient way to measure the effect of various states of prestress on the shear storage and loss moduli of tissues.

These recent experiments have studied, in particular, the shear response of brain tissue (both normal and that isolated from human glioma tumors), as a function of prestress levels expected *i i* from homeostatic pressure considerations, as well as increased vascularization of the tumors [5]. Similar measurements were also carried out on liver tissue (both normal and that affected by fibrosis) [6]. In all four of these cases, shear storage modulus is reported to increase with applied uniaxial compression. The authors refer to this phenomenon as *c e i iffe i g*. Interestingly, when essentially the same experiment is done with the biopolymer network materials collagen and fibrin (major components of the extracellular matrix), the opposite effect is found: Shear storage modulus decreases with uniaxial compression, otherwise known as compression softening, but increases with extension [7

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one would consider to be well outside the regime of linear elasticity—on the order of 40% strain or more—the compression stiffening behavior also shows up in (and is qualitatively similar in) the small deformation regime where strains are less than ∼10%. This point is not addressed in prior theoretical work, which focuses on explaining compression stiffening from within the framework of hyperelastic models, such as Ogden models, presumably because such models are the most realistic ones available for capturing biomaterials undergoing physiologically relevant deformations [6,10]. However, such models contain multiple parameters that may be difficult to relate to any specific structure or signature.

Here we take the "minimal modeling" approach of trying to gain a theoretical understanding of compression stiffening at small strains and then test how well this linear approach does (or does not) reproduce experimental data at larger strains, fully aware that in doing so we are pushing the limits of the theory's validity. Nevertheless, our results suggest that the essential physics of compression stiffening is captured by linear elasticity theory; higher-order corrections are clearly needed at larger deformations. Thus, our interpretation of the leading-order compression stiffening mechanism is extremely simple and relies on no hyperelastic fitting parameters. We demonstrate the predictive power and universality of our approach by showing that it agrees with data from five different classes of biomaterials, including animal tissue (previously published in Refs. [5,6,10]), as well as some plant tissue and agarose gel samples, newly reported here.

That plant tissue should behave similarly to animal tissue in these prestressed rheometry experiments is not immediately obvious, given that plant cells contain cell walls, vacuoles, and chloroplasts, which animal cells do not. Plant cell walls allow the cells to withstand turgor pressures on the scale of megapascals [12] and presumably result in plant tissue typically having larger storage moduli than animal tissue at the many-cell scale. While plant tissue has long been modeled as an elastic solid [13

a solid under prestress [15]. Taylor expanding the energy density around the prestressed reference configuration yields

$$\frac{U}{V} = S_i \quad _i + \frac{1}{2} Q_i \quad _i \quad + \ldots , \tag{1}$$

where $_i$ is the combined deformation due to the prestress S_i and any other stresses subsequently applied to the reference state. In general, this deformation consists of a symmetric part e_i and an antisymmetric part w_i , i.e., $_i = e_i + w_i$. The key point (made 15 years prior to BK1) is that the presence of the linear term modifies the symmetry properties of the coefficients Q_i from those of the usual rank-four elastic modulus tensor [16]. In particular, invariance of the energy density under a rigid rotation requires that

$$Q_i \quad - Q \; _i \quad = S \quad \delta_i \quad - S_i \, \delta \quad , \tag{2}$$

$$Q_i \quad - Q_i$$

the BK1 formalism, we decompose the solid cylinder into small volume elements, each of which experiences a local, homogeneous strain and undergoes a rigid rotation. Consider the element located at (= , = 0,) and having volume and energy V and U , respectively. The only nonzero strain component is, switching to Voigt notation, $e_4 = 2e$ = $2e$ $= \gamma($). Equation (5) then says that

$$c_{44} = \frac{1}{V}\frac{\partial^2 U}{\partial[\gamma(\ )]^2} - \frac{P}{2}. \tag{8}$$

For an isotropic material with Lamé parameters $\lambda(= c_{12})$ and $\mu(= c_{44})$, this result extends to all volume elements, i.e., the shear modulus is given by

$$\mu = \frac{1}{V}\frac{\partial^2 U}{\partial \gamma^2} - \frac{P}{2}. \tag{9}$$

C. Torsion with uniaxial prestress

Next we consider the case S_i $= -\sigma\delta_i$ δ . This form is

One prior modeling effort to interpret the observed compressional stiffening has already been mentioned. Perepelyuk *et al.* propose a phenomenological model for simultaneous description of compression stiffening, tension softening, and shear softening [6]. This model involves two components: an incompressible cellular phase and a compressible filamentous (ECM) phase. Mechanical connections between the two components are allowed to break under load and re-connect when the load is removed. Compression is thought to expel fluid through the porous ECM phase, increasing the number of cell-cell contacts and resulting in greater resistance to shear. While reasonable agreement is obtained with their liver data [replotted here in Fig. 1(b)], this agreement might be due to the fact that there are at least five fitting parameters in the model (counting the power-law exponents.) Additionally, the reliance on two components is at odds with agarose gel and with brain and mango tissue, the former lacking a cellular component and the latter lacking a filamentous component, but nonetheless exhibiting compression stiffening qualitatively similar to that of liver tissue. Meanwhile, Mihai *et al.* address compression stiffening in homogeneous materials by showing that a subclass of Ogden hyperelastic models can account for compression stiffening in brain and fat tissue [10], but again, these models have a large number of fitting parameters. In contrast, the BK1 and Birch theories provide a simple, universal explanation for compression stiffening and reasonably agree with available data spanning five different material types, the sole fit parameters being a binary choice of reference state (i.e., whether to apply BK1 or Birch), and in the case of Birch, the Poisson's ratio. For nearly incompressible materials, the latter "fit parameter" is effectively eliminated. Again, which of the two reference states is appropriate to a given sample may to be related to the presence or absence of a fibrous ECM component.

To further test the ideas herein against the models of Perepelyuk *et al.* [6] and Mihai *et al.* [10], we suggest that additional high-precision rheometer measurement be carried out for a variety of living and nonliving soft materials, with simultaneous pressure measurement and supplementary Poisson's ratio measurement, if possible. Also, since in the BK1 theory it is c_{44}, not G'

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