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ABSTRACT

The mechanical properties of tissues play a critical role in their normal and pathophysiological functions such as tissue development, aging, injury, and disease. Understanding tissue mechanics is important not only for designing realistic biomimetic materials for tissue engineering and drug testing but also for developing novel diagnostic techniques and medical interventions. Tissues are heterogeneous materials consisting of cells confined within extracellular matrices (ECMs), both of which derive their structural integrity, at least in part, from networks of biopolymers. However, the rheology of purified reconstituted biopolymer networks fails to explain many key aspects of tissue mechanics. Notably, purified networks typically soften under applied compression, whereas many soft tissues like liver, fat, and brain instead stiffen when compressed. While continuum models can readily capture this compression-stiffening behavior, the underlying mechanism is not fully understood. In this perspective paper, we discuss several recently proposed microscopic mechanisms that may explain compression stiffening of soft tissues. These mechanisms include (I) interactions between the ECM and volume-preserving inclusions that promote extension-dominated stiffening of fibrous ECMs when subject to uniform compression, (II) ECM interactions with rigid inclusions under non-uniform compression, (III) other internal physical constraints that cause compression stiffening of cells and ECMs, and (IV) propagation of compressive forces through jammed, compression-stiffening cells. We further identify a few of the many open problems in understanding the structure–function relationship of soft-tissue mechanics.

I. INTRODUCTION

The mechanical properties of tissues are essential for their proper function,[1] and changes in these physical properties are the basis for numerous diagnostic techniques such as palpation, magnetic resonance elastography, and ultrasound imaging.[2,3] Changes in tissue mechanics are not only a sign of disease but also a normal aspect of tissue development, growth, and aging.[4,5] Defining how cells detect mechanical properties and how they adapt both acute responses and genetic programs to changes in physical signals is increasingly recognized as important for understanding cell biology.[6] Before the paradigm shift enabled by molecular biology, cell and tissue mechanical studies were a major aspect of research in biology and physiology; defining the physical properties of biological materials is re-emerging at the forefront of biological and biomedical research.

Developing a mechanistic understanding of the mechanical responses of biological tissues is important for designing new synthetic biomaterials or engineering constructs that can serve as replacements for injured tissue or as physiologically realistic environments for cell engineering, drug testing, and other applications.[7,8] Design of truly biomimetic materials is challenging because most soft tissues exhibit highly non-linear mechanical responses; theories developed to predict the responses of

superficially similar soft materials like elastomers (e.g., polydimethylsiloxane) or hydrogels (e.g., cross-linked polyethylene glycol) fail when applied to soft tissues. One example of non-linear response is in the dilation of large blood vessels during changes in blood pressure. Animals of different sizes and blood pressures have evolved aortas that display a complex relationship between diameter and the pressure caused by each beat of the heart, in order to optimize flow of blood down the vessel rather than distend the aorta and risk rupture.[9,10] A replacement vessel made from a linear elastomer would cause inefficient flow and increased risk of aneurysm.[11] A second example is the stiffening of soft tissues such as fat, brain, or liver, when subjected to uniaxial compression.[12–16] The shear modulus of these tissues—measured at small shear strains (~2%) applied in the plane perpendicular to the direction of uniaxial compression—increases several fold at even modest compression levels [Fig. 1(a)]. In contrast, when these tissues are stretched, they maintain a nearly constant shear modulus, indicating a strong tension–compression asymmetry [Fig. 1(a)]. Because cells are quite sensitive to the stiffness of their microenvironment,[17] these strain-driven changes in tissue rheology can have important biological consequences. These physical changes, even in the absence of any change in tissue architecture or chemistry, can lead to cellular changes that might for instance initiate or exacerbate fibrotic responses.[18]

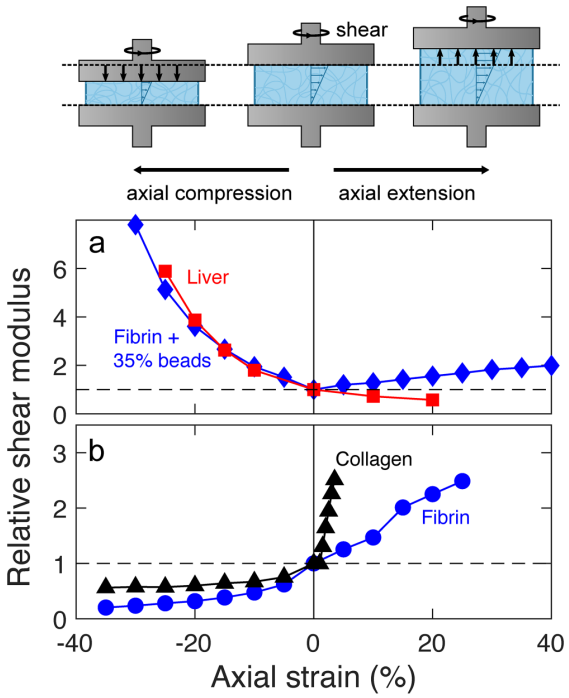

FIG. 1. Stiffening and softening in uniaxial strain. The shear modulus, measured within the linear regime (shear strain ~2%) is shown as a function of the applied axial strain for (a) liver and a composite of fibrin embedded with polysaccharide beads, and for (b) reconstituted networks of purified fibrin and collagen. Data adapted from Ref. 14.

A third level of complexity in tissue mechanics is that the apparent shear and Young's moduli, i.e., the resistances of a tissue to applied shear and uniaxial strain, respectively, are not simply related, even at the low levels of strain that typically occur *in vivo*. Furthermore, quantities such as Poisson's ratio are often ill-defined and depend sensitively on time scales and strain magnitudes, in a manner not seen in most synthetic materials.[19–23]

Tissues are composed of cells confined within extracellular matrices (ECMs), while cells contain a fibrous cytoskeleton embedded with ribosomes and other organelles (Fig. 2). As both the interior cytoskeleton and the ECM are formed by stiff or semiflexible biopolymer networks, one would naturally assume that these networks contribute to the mechanical response of tissues. In recent years, the mechanical response of purified biopolymer networks has been extensively characterized experimentally and largely understood theoretically. However, the properties of these purified systems alone are seemingly insufficient to explain tissue rheology.[14,28] Perhaps the most striking aspect of fibrous network mechanics is the large increase in shear modulus with increasing shear strains. Several theoretical models have been developed to account for shear strain stiffening,[29–31] enabling quantitative comparisons with experimentally measured rheology of purified biopolymer networks.[20,23,32–37] Although this strain stiffening may contribute strongly to the non-linear response of tissues that are rich in collagen or elastin, such as the aorta,[38] other soft tissues like liver and fat do not stiffen with increasing shear strain.[14] The response of purified fibrous networks to uniaxial strains also differs from that of soft tissues. Gels composed of purified, cross-linked fibrous networks typically soften in uniaxial compression and stiffen in extension [Fig. 1(b)], whereas tissues stiffen in compression but not in extension, as already discussed. The softening of fibrous networks in compression is largely a result of increased bending and buckling of a portion of the constituent filaments, whereas stiffening in extension correlates with an increasing contribution from the stiffer response of stretched filaments, in tandem with fiber alignment along the direction of extension. However, many examples of tissues, which generally contain an underlying fiber network, display qualitatively different responses to compression and extension. Nevertheless, recent work has shown that compression-softening purified networks can be functionally converted into compression stiffening materials by enmeshing within them a sufficient volume fraction of inert, volume-conserving particles[14] [Fig. 1(a)]; strikingly, the resulting composite materials acquire some of the structural and mechanical features of intact tissues.

To better understand the underlying mechanisms that govern tissue mechanics, and to design improved biomimetic materials, we need models that can faithfully predict the mechanical properties of tissues from the properties of their constituents and microstructures. Currently, most analyses of tissue mechanics rely on continuum theories that describe the macroscopic properties of tissues but do not explicitly consider the microstructure and diverse material constituents of tissues.[39–42] In such studies, the mechanical

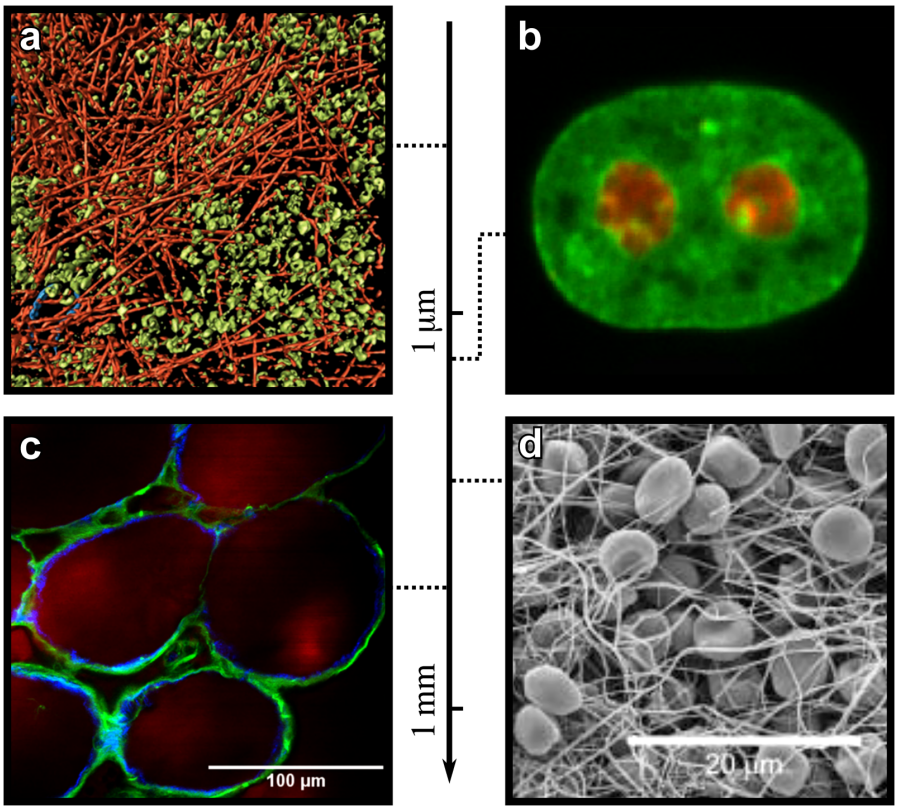

FIG. 2. Examples of naturally occurring network-inclusion composites. Location of the dashed lines along the vertical axis indicate an approximate inclusion length scale. (a) Actin (red) and ribosomes (green) within a *Dictyostelium discoideum* (slime mold) cell.[24] Image width ~800 nm. (b) HeLa cell nucleus with fluorescently labeled chromatin (green) with embedded liquid nucleoli (red).[25] Image width ~20 μm. (c) Human adipose (fat) tissue, consisting of lipid-containing adipocytes (red) embedded in an extracellular matrix rich in collagen (blue) and elastin (green).[26] Scale bar 100 μm. (d) Red blood cells enmeshed in fibrin within a blood clot.[27] Scale bar 20 μm.

response of tissues is first measured for certain loading conditions and then used to calibrate material parameters for suitably designed continuum models. Although such phenomenological continuum models quantitatively capture the non-linear behavior of tissues, they often contain fitting parameters that lack clear physical interpretations, thus providing limited insights into the underlying mechanisms responsible for tissue mechanics.

Motivated by the above considerations, in this Perspective, we discuss recently developed models that reveal microscopic mechanisms governing tissue mechanics. In particular, we focus on the origins of the compression-stiffening behavior of tissues, a key feature that differs from the typical compression-softening behavior of reconstituted fibrous networks. We first summarize physical mechanisms that can endow fibrous networks with compression-stiffening properties and then discuss the implications of these mechanisms for tissue mechanics. Finally, we discuss potential applications of these mechanisms and identify some open problems for future studies.

II. PHYSICAL MECHANISMS FOR COMPRESSION STIFFENING

As soft tissues are composite materials consisting of cells and fibrous extracellular matrices (ECMs), model systems comprising fibrous networks and cell-mimicking particles can provide useful insights into tissue mechanics. Recent studies suggest that embedding cells or similar volume-conserving particles in purified fibrous networks can convert intrinsically compression-softening networks into compression-stiffening, tissue-like materials.[14,28,43] In certain cases, similar effects can be achieved by introducing other physical constraints, such as local conservation of volume, even without cell-mimicking particles.[44] In this section, we summarize recently

discovered mechanisms for compression-driven stiffening of network-inclusion composites and discuss the implications of these mechanisms for tissue mechanics.

A. Mechanism I: Embedding soft but volume-conserving particles in fibrous networks

van Oosten *et al.* used continuum-mechanics based, finite element simulations to examine the mechanical properties of fibrous networks embedded with soft, incompressible spherical particles with a negligible shear stiffness.[14] Since the soft particles have negligible resistance to shear, the overall mechanical response of the composite is controlled by the properties of the interstitial network. When the composite is compressed uniformly (i.e., the centers of the soft particles move relative to each other according to a uniform compressive strain), the initially spherical deformable particles flatten along the loading axis and, to preserve their volume, expand along the perpendicular axes, exerting both tensile and compressive strains on regions of the surrounding fibrous network (sketched in 2D in Fig. 3(a)]. Because the interstitial network tends to stiffen when stretched and soften when compressed [Fig. 1(b)], the compression-induced biaxial expansion of the particles simultaneously induces stiffening and softening of the surrounding network in regions that are stretched and compressed, respectively. When the volume fraction of the particles is low, only a small portion of the interstitial network is subject to tension, and

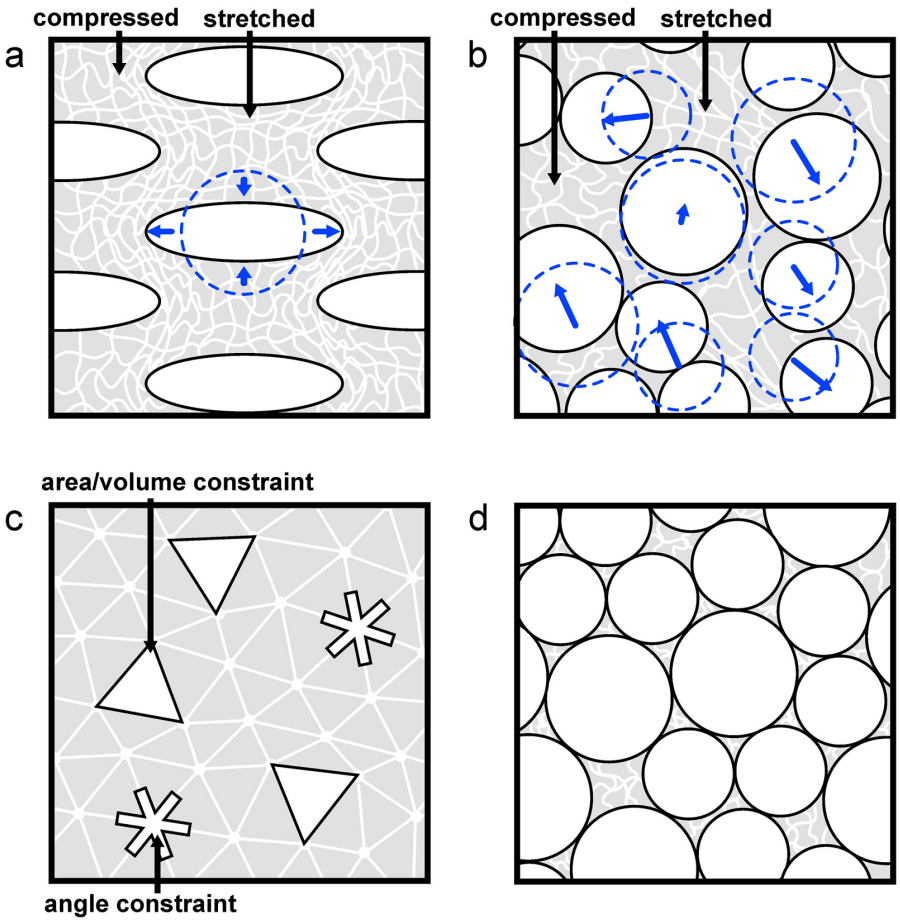

FIG. 3. Mechanisms for compression-driven stiffening of composites of networks and inclusions. (a) Network strain induced by inclusion deformation.[14] (b) Network strain induced by heterogeneous relative motion of inclusions.[28] (c) Stiffening of highly connected networks due to bending induced by angle-constraining cross-links or area (or volume) constraints.[44] (d) Propagation of inclusion–inclusion compressive forces throughout the sample, i.e., inclusion jamming.

the overall behavior of the composite is dominated by compression softening of the mostly unfilled fibrous network. Nevertheless, when the volume fraction of the particles is sufficiently high, but below the jamming threshold, the widespread tensile strains generated by the deforming particles affect a large portion of the interstitial network, driving the network into a tension-dominated stiffening regime, leading to a sharp increase in the measured stiffness of the composite. Thus, the mechanism responsible for this compression-driven stiffening phenomenon is the extension-stiffening tendency of the interstitial fibrous network, even though the macroscopic deformation applied to the composite is uniaxial compression.

In short, for a sufficiently large particle volume fraction, increasing the applied macroscopic compression leads to particle-induced stretching of the network, which out-competes local softening in compressed regions, yielding an overall compression-stiffening response for the composite. The cell-network model showed reasonable agreement with the rheology of collagen networks embedded with a sufficiently high (~30%) volume fraction of cells, and with the rheology of liver and other soft tissues.

B. Mechanism II: Embedding rigid particles in fibrous networks

More recently, Shivers *et al.*[28] employed discrete fiber network simulations to study the mechanical properties of disordered networks containing *randomly* distributed rigid particles. Simulations of networks without inclusions have been shown to reproduce the compression-softening and extension-stiffening behavior of purified reconstituted networks.[20,45] For rigid particles, particle-induced network strain is caused by relative translations or rotations of particles. In this way, tension is induced in the network by the non-uniform strain of the collection of inclusions, rather than by changes in particle shape. *A priori*, we can qualitatively predict the response of networks with very low or very high particle volume fractions. Specifically, for systems with a sufficiently small volume fraction of particles, the composite behaves similarly to unfilled purified networks and compression softens, due to an increased contribution of the soft, bending mode of fibers to the overall mechanical response. For systems with initial particle volume fractions exceeding the jamming threshold, there exists a system-spanning, mechanically stable network of particles in contact, and the elastic response of the composite is governed by the repulsive forces acting between particles, as we will discuss later.

The behavior of such composites with intermediate particle volume fractions is not obvious, and the situation is further complicated by the fact that the volume fraction of the particles *increases* as the system is macroscopically compressed. When composites with intermediate particle volume fractions are compressed, they exhibit an initial softening regime, in which the interstitial network undergoes relatively homogenous compression, yielding macroscopic softening. As the level of compression increases, however, the randomly dispersed rigid particles heterogeneously rearrange to accommodate their increasing volume fraction, exerting both compressive and tensile strains on the interstitial network [Fig. 3(b)], causing a macroscopic transition from a bending-dominated softening regime to a stretching-dominated stiffening regime. The compression level at which the crossover between compression softening and compression stiffening occurs decreases in magnitude as the initial volume fraction of particles increases. The predictions of the simulations agree qualitatively with the experimental data for the rheology of fibrin networks containing stiff dextran particles. Thus, embedding either soft (but volume-conserving) or rigid particles in fibrous networks can suppress the soft, buckling mode of the networks and instead promote the stiff, stretching mode of the networks (albeit by different mechanisms), leading to the overall compression-stiffening properties of the composite material.

C. Mechanism III: Introducing internal physical constraints in fibrous networks

Gandikota *et al.*[44] used a two-dimensional (2D) triangular lattice model to investigate the mechanical properties fibrous networks with internal physical constraints. Without any such constraints, these networks compression soften, because the fibers tend to realign along directions normal to the compression axis, leading to progressively fewer load-bearing elements along the loading direction. Moreover, fibers remain straight throughout the deformation without bending. To counteract this behavior, the authors considered two types of constraints: area-preserving fibrous loops and angle-constraining cross-links. When a sufficient density of area-preserving loops is added, external compression induces both stretching and bending of fibers (Fig. 3). The stretching mode promotes fiber realignment along the perpendicular axes, tending to soften the networks. At the same time, the bending mode resists fibers' bending around the area-preserving loops, tending to stiffen the networks. These two deformation modes compete to determine the overall behavior of the networks. When the bending mode has a stiffness much larger than that of the stretching mode, it is largely inhibited during compression; consequently, the stretching mode dominates networks' mechanics, leading to compression softening. When the opposite is true, the bending mode is too weak to combat the stretching mode, again yielding compression softening. When these two modes have comparable stiffness, the bending mode wins, causing compression stiffening.

When angle-constraining cross-links are present, however, external compression yields stretching of fibers as well as distortions of the angle-constraining cross-links. These cross-links resist changes in the angles between the attached fibers, offering a stiffening mechanism that competes with the softening mechanism induced by fiber realignment. When the angle constraints are sufficiently strong, the stiffening mechanism prevails and gives rise to compression stiffening.

One key difference between this mechanism and either mechanism I or II is that it applies to highly connected structures. The triangular lattice in 2D, with sixfold coordination, resists deformation primarily due to stretching of fibers.[46] Physiological collagen networks, for example, usually have much lower connectivity and resist deformation primarily by bending at small strains, as in the models used to study mechanisms I and II. At larger strains, stretching modes are activated by either deformation or rearrangement of the inclusions, causing overall compression stiffening. By

contrast, for networks such as the 2D triangular structures, other types of stiffening mechanisms, such as bending of fibers or angle-constraining cross-links, are required to give rise to compression stiffening.

D. Mechanism IV: Jamming

An important feature of mechanisms I and II is that stiffening in compression occurs while the volume fraction of particles remains below the so-called *jamming* point, at which particles begin to touch, and compressive forces acting between contacting particles can propagate through the entire sample [Fig. 3(d)]. The mechanical response of jammed systems is determined by the properties of the system-spanning network of forces between contacting particles. If the particle stiffness exceeds that of the interstitial network, or if the particles themselves compression stiffen, then the stiffness of a system driven to jamming by compression would be expected to exceed that of the same system prior to the applied compression. In this case, compression-driven jamming would yield compression stiffening. Since the onset of jamming is largely controlled by the volume fraction of particles (given that the network volume fraction is, typically, negligibly small), we can infer whether jamming-induced stiffening has occurred by considering whether the volume fraction of particles at a given level of macroscopic compression exceeds the corresponding jamming threshold. Finally, we note that the onset of jamming depends on the shape and size distribution of particles,[47] on the relevance of friction,[48] and on the tendency of the particles to deform.[49]

The various mechanisms discussed above have important implications for the compression-stiffening response of soft tissues. First, since tissues typically comprise a moderate to high volume fraction of cells embedded in a fibrous ECM, the interplay between the cells and ECMs can trigger the compression-driven, stretching mode of the fibrous ECM (mechanisms I and II), thereby leading to overall compression stiffening of tissues. This could be the case even if both the cytoskeleton and the ECM compression soften (similar to what has been observed for purified fibrous networks), provided that cells sufficiently resist volume changes. Second, both the cytoskeleton and the ECM may contain internal physical constraints—be they angle-constraining cross-links or volume-conserving vesicles and organelles—that can endow them with compression-stiffening properties in the first place (mechanism III). If this is true, then it is perhaps not too surprising that tissues also compression stiffen. Indeed, recent experimental data suggest that individual cells do compression stiffen,[44] although the underlying mechanisms for this behavior are not entirely clear. Finally, if the volume fraction of compression-stiffening cells exceeds the jamming threshold, the overall tissue behavior is then governed by the properties of the cells (mechanism IV), thereby exhibiting compression stiffening.

III. OUTLOOK AND PERSPECTIVES

While important progress has been made to reveal the microscopic mechanisms that regulate macroscopic tissue properties, much needs to be done to fully appreciate the structure–function relationship for soft tissues. This is a research area well suited to soft matter physics and engineering, which provide powerful techniques for characterizing material structures and for describing the mechanical properties of heterogeneous systems. In this section, we identify a few directions in which physicists and engineers can provide a greater understanding of the foundations of soft-tissue structures and functions.

A. Inelastic properties of soft tissues

Most studies focus on the static behavior of tissues, modeling tissues as (linear or non-linear) elastic solids, for simplicity. Nevertheless, most soft tissues, along with their components (i.e., cells and ECMs), exhibit inelastic properties like viscoelasticity, poroelasticity, and plasticity, which endow them with time-dependent, dissipative responses such as stress relaxation, creep, and hysteresis.[50] Hence, it is crucial to better understand the inelastic behavior of tissues and their components under various loading conditions, both theoretically and experimentally. Recent advances in this direction include studies on (i) the poroelasticity and plasticity of fibrous networks;[51–56] (ii) the poroelasticity, viscoelasticity, and viscoplasticity of cells;[17,57] and (iii) the viscoelasticity and poroelasticity of soft tissues like liver[39] and brain.[58] However, structurally informed models that can predict the inelastic properties of tissues directly from those of tissue components and from tissue structures remain largely unexplored. The need for such models is great, especially for designing improved biomimetic materials that can emulate tissue response over both short and long time scales, and for analyzing the dynamic response of tissues under shock loading in sports and accidents.

B. Cell mechanobiology

Tissues present unique modeling challenges not only because they are complex mixtures of fibrous ECM and adherent cells but also because cells are metabolically active, generating forces and remodeling the ECM. In particular, cells can alter the rheology of their microenvironment by directly applying forces to the surrounding ECM[59–62] and by chemically degrading or depositing ECM.[17,63] In turn, ECM rheology affects cellular stiffness and functions such as migration, differentiation, and growth.[64] Thus, to accurately model the rheology of living tissues over a wide range of length and time scales, we must better understand cell mechanobiology. Efforts toward this goal include advances in microscopy,[65,66] microrheology,[67–71] modeling,[35,72] and hybrid techniques like traction force microscopy. Recent developments in three-dimensional traction force microscopy enable the inference of forces exerted by single cells fully encapsulated in three-dimensional ECMs,[22,73,74] as well as the reconstruction of heterogeneous ECM stiffness induced by cell remodeling.[75,76] Clearly, there is a considerable need to combine these mechanobiological cues with physical principles to develop improved models that can capture both the active and passive response of living tissues. At the same time, we must design tractable experiments to validate the hypotheses and predictions of such models.

C. Clinical applications

Understanding the structure–function relationship for tissues also holds promise for clinical applications. Structurally informed

models, together with patient-specific data on tissue microanatomy (such as those obtained by hematoxylin and eosin staining),[77] can be used to guide the design of functional biological constructs that repair or replace diseased tissues,[78] to develop rehabilitation protocols (e.g., rest and loading procedures) that optimize tissue healing,[79] and to identify the possible transition of tissues from a healthy state to a diseased state.[80] For instance, such structural models could be used to determine the hot spots of stress concentration within tissues, hot spots that may cause elevated tissue stiffness and predispose cells to a malignant state. Such approaches could potentially open up new avenues not only for early diagnosis but also for novel medical intervention strategies, such as local tissue reconstruction to relieve mechanical stress and the associated negative mechanobiological effects, as opposed to invasive procedures that remove the entire section of tissues. Advancing our understanding tissue mechanics will improve health-care delivery and human conditions, and this effort can be guided by developments of theories and experiments.

IV. CONCLUSIONS

In this Perspective, we have discussed several physical mechanisms that may give rise to the widely observed compression-stiffening behavior of soft tissues, an important feature that seemingly defies the compression softening response one would expect based on the underlying fibrous network and our understanding of the compressive response of purified networks. These mechanisms include (i) cell–ECM interplay that triggers a compression-driven, tension-dominated stiffening mode of the fibrous ECM, (ii) physical constraints that endow individual tissue components (i.e., cells and ECM) with compression-stiffening properties, and (iii) propagation of compressive forces through contacting, compression-stiffening cells. Given the diversity and complexity of microstructures in soft tissues, which mechanism governs tissue mechanics is likely to depend on specific tissue characteristics, such as cell volume fraction, cellular stiffness, and intrinsic ECM structures. To better understand the origin of compression stiffening for soft tissues, we must design well-controlled experiments that can precisely manipulate the microscopic features of tissues and develop accurate structural models that relate the microstructure of tissues to their macroscopic response.

Our understanding of tissue mechanics is still quite limited, and much remains to be done before we can claim to understand the structure–function relationship of soft tissues. Toward this goal, we have identified a few of the many remaining open problems, such as deciphering the time-dependent, inelastic properties of tissues and predicting the influence of active, cell-induced forces and ECM remodeling. Research in tissue mechanics is challenging due to its highly interdisciplinary nature, requiring contributions from physics, mathematics, biology, chemistry, and engineering. Harnessing these fields, we must devise reliable experimental tools to probe the incredibly complex features of soft tissues and, at the same time, develop efficient theoretical models to incorporate the central mechanisms in play. These endeavors, while challenging, are highly rewarding due to their many important clinical applications, ranging from designing improved biomimetic materials that can replace impaired tissues to developing computer-aided, patient-specific interventions for various diseases. Such applications hold great promise for improving human health.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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