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Yifan Guo; Mohammad R. K. Mofrad ; Adrian Buganza Tepole  



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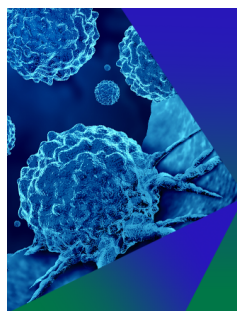
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ABSTRACT

Tissues grow and remodel in response to mechanical cues, extracellular and intracellular signals experienced through various biological events, from the developing embryo to disease and aging. The macroscale response of soft tissues is typically nonlinear, viscoelastic anisotropic, and often emerges from the hierarchical structure of tissues, primarily their biopolymer fiber networks at the microscale. The adaptation to mechanical cues is likewise a multiscale phenomenon. Cell mechanobiology, the ability of cells to transform mechanical inputs into chemical signaling inside the cell, and subsequent regulation of cellular behavior through intra- and inter-cellular signaling networks, is the key coupling at the microscale between the mechanical cues and the mechanical adaptation seen macroscopically. To fully understand mechanics of tissues in growth and remodeling as observed at the tissue level, multiscale models of tissue mechanobiology are essential. In this review, we summarize the state-of-the-art modeling tools of soft tissues at both scales, the tissue level response, and the cell scale mechanobiology models. To help the interested reader become more familiar with these modeling frameworks, we also show representative examples. Our aim here is to bring together scientists from different disciplines and enable the future leap in multiscale modeling of tissue mechanobiology.

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I. INTRODUCTION

Soft tissues often fulfill crucial mechanical functions in our bodies, from the skin protecting us from outside hazards, to the valves in the heart allowing for the correct flow of blood in our cardiovascular system. To produce physiological behavior, tissues have to be able to adapt to mechanical inputs. Soft tissues operate at the macroscale, on the order of centimeters (cm) to meters (m). At this scale, biomechanical adaptation takes the form of growth and remodeling, i.e., changes in mass and mechanical properties.^{1,2} However, even though we observe these macroscale changes and their biomechanical effects, growth and remodeling are emerging phenomena from the microscopic events driven by cellular activity. The process by which cells transform mechanical signals into intracellular signaling cascades and

cell–cell signaling networks is called mechanotransduction.^{3,4} In turn, cellular activity at the microscale, on the order of micrometers (μm)—such as cell proliferation and structural protein deposition—locally transforms the microstructure and, thus, the mechanical behavior of the tissue. These microscale changes, when coordinated over larger length scales, are what we measure as growth and remodeling at the tissue level.^{5,6} Therefore, to fundamentally understand the mechanical function of tissues, mechanistic models of the two-way coupling across scales are needed. This review explores first the tools at the two separate scales before diving into recent efforts to develop fully coupled multiscale mechanobiology models.

Soft tissues are inherently multiscale materials characterized by a complex structural hierarchy.⁷ Connective tissues show nonlinear and anisotropic strain-stiffening response at the macroscale.^{8,9} These properties can be explained by a fibrillar collagen microstructure described by metrics such as fiber orientation and crimp.^{10–12} Collagen is not the sole constituent. Elastin, fibrin, and other biopolymers also influence the mechanical behavior of connective tissue, particularly at small to moderate strains.^{13,14} From a computational point of view, modeling the mechanical behavior of connective tissue at the macroscale has been a focus of the biomechanics community for decades, and several constitutive models for different soft tissues have been developed, some of which are inspired by the fibrillar microstructure.^{15,16} However, to more accurately capture the hierarchical structure of these tissues, models at smaller scales have also been built. At the mesoscale, from micrometers (μm) to millimeters (mm), representative volume element (RVE) simulations with discrete fiber networks are an adequate modeling choice.^{17–20} Smaller scale models, for example, coarse grained or atomistic simulations, can capture the behavior of individual fibers or molecules.²¹ This review focuses on the meso- and macroscale description of tissue mechanics.

Models of growth and remodeling have been mostly described at the macroscale level using continuum mechanics. One approach relies on a geometric description of growth much like plasticity, it is often referred to as multiplicative volumetric growth.^{22–24} This description

is based on splitting the deformation into two parts, permanent volume changes due to addition or loss of mass, and deformations due to externally applied forces. Another approach is based on mixture theory.²⁵ In this approach, the key idea is to keep track of mass fractions of individual constituents. Both of these approaches will be reviewed in more detail later.

Models of mechanobiology have emerged by analyzing the cell and molecular scales. For soft tissues, the focus has been on mesenchymal cells, especially fibroblasts.^{26,27} For models of single cells, or even sub-cellular level, integrins and their aggregation into focal adhesions have been recognized as the key mechanical coupling between the extra-cellular matrix (ECM) and the cell.^{28,29} Models of mechanobiology at this scale, therefore, focus on how forces from the ECM can be transferred to the cell through these adhesions.²⁷ In turn, conformational changes at focal adhesions, together with cytoskeleton deformation linking cell–ECM interface all the way to the nucleus, trigger a myriad of intra-cellular cascades that we still do not fully understand.^{30,31} We review some of the mechanobiology models of the cell-scale, but focus particularly on the kinetics of focal adhesions.

Coupling the macroscale soft tissue mechanics, the mesoscale structure in terms of fiber networks, and the single cell interaction with the ECM at the microscale is an open challenge. Up-scaling from the lower spatial scales can be done by averaging quantities of interest to try to learn homogenized responses.³² Down-scaling has been traditionally been achieved by creating RVE models with boundary conditions in terms of quantities of interest from larger scales.^{17,19,20} We discuss emerging techniques to further integrate mechanics and mechanobiology across scales, see Fig. 1.

II. CONTINUUM MODELS OF TISSUE MECHANICS

At the macroscale, the mechanical behavior of tissues is naturally described within continuum mechanics. The basic variable needed to describe the local deformation and strain in the tissue is the deformation gradient tensor $\mathbf{F}$. To guarantee that the stress computed from the deformation, $\boldsymbol{\sigma}(\mathbf{F})$, is independent of change of coordinates or rigid

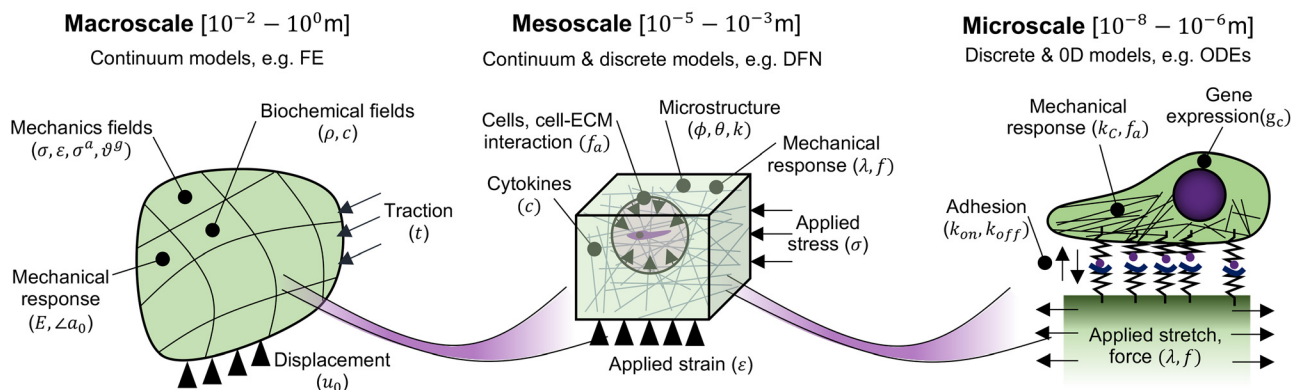


FIG. 1. Multiscale growth, remodeling, and mechanobiology modeling. At the macroscale, continuum variables such as stress, strain, chemical concentrations, and cell densities can be used to describe tissue mechanics and mechanobiology. These fields obey basic balance laws usually in the form of partial differential equations that can be solved with finite element analysis (FE). The evolution of the continuum fields requires constitutive models that should reflect the underlying mesoscale phenomena. At the mesoscale, tissues are characterized by fibrillar biopolymer networks constantly remodeled by cellular activity. Models at the mesoscale, thus, combine discrete and continuum models, e.g., discrete fiber networks (DFN), agent based models. Because it is the cellular activity that controls the growth and remodeling process, the mechanobiological response of cells to the properties and deformations of their immediate extra-cellular matrix (ECM) needs to be modeled at the microscale. At the microscale, discrete and 0D models (ordinary differential equations or ODEs) can be used to describe the cell–ECM interface as well as the intra-cellular signaling pathways triggered by mechanical cues.

body motion, stress is expressed as a function of the tensors $\mathbf{C} = \mathbf{F}^\top \mathbf{F}$ or $\mathbf{b} = \mathbf{F} \mathbf{F}^\top$. The tensors $\mathbf{C}$ and $\mathbf{b}$ are called the right and left Cauchy Green deformation tensors and are related to nonlinear strain measures. Since tissues have a nonlinear mechanical response, the basic building block to model soft tissue is usually the definition of a strain energy function Ψ . Even though linear elasticity descriptions are still popular,^{33,34} they are not adequate to model soft tissue. Tissues have been treated with simple models, such as the isotropic neo-Hookean strain energy or the Ogden strain energy.^{35–38} More nonlinear models that include anisotropy but are still largely phenomenological include Gasser–Ogden–Holzapfel, or May–Newman.^{10,39,40} The next level of sophistication are microstructure-driven models that ultimately depend on variables at the macroscale but encode details about fiber network orientation, diameter, and waviness distributions.^{9,41,42} Given a definition of the strain energy as a function of either $\mathbf{C}$ or $\mathbf{b}$, the stress is calculated from

$$\boldsymbol{\sigma} = J^{-1} 2\mathbf{b} \frac{\partial \Psi}{\partial \mathbf{b}}, \quad (1)$$

with $J = \det \mathbf{F}$.

Hyperelasticity is a good starting point, but it is still an approximation of soft tissue mechanical response, even when highly nonlinear and detailed strain energies are used. In reality, when mechanical work is done on tissue through applied forces, not all the energy gets stored as strain energy. There are several dissipative mechanisms that can be considered, such as viscoelasticity, damage, plasticity, and fracture.^{43,44} These phenomena can, however, be modeled by building on top of the hyperelastic assumption. For example, in the case of viscoelastic behavior, the energy can be decomposed into equilibrium and non-equilibrium components,^{18,45–47}

$$\begin{aligned} \Psi &= \Psi^{\text{eq}} + \Psi^{\text{neq}}, \\ \boldsymbol{\sigma} &= \mathbf{b} \frac{\partial \Psi^{\text{eq}}}{\partial \mathbf{b}} + \mathbf{b}^e \frac{\partial \Psi^{\text{neq}}}{\partial \mathbf{b}^e} = \boldsymbol{\sigma}^{\text{eq}} + \boldsymbol{\sigma}^{\text{neq}}, \\ \dot{\mathbf{b}}^e \mathbf{b}^{e-1} &= -\frac{J}{\eta_D} \text{dev}(\boldsymbol{\sigma}^{\text{neq}}) - \frac{2J}{9\eta_V} \text{tr}(\boldsymbol{\sigma}^{\text{neq}}) \mathbf{I}, \end{aligned} \quad (2)$$

where the split of the energy leads to two contributions for the stress, one coming from an equilibrium branch, and another from a Maxwell-type branch. The last component of the system in (2) denotes the evolution of the equation for the Maxwell branch. The rate of change $\mathbf{b}^e$ denotes the Lie time derivative of the elastic deformation, and it is proportional to the non-equilibrium stress. The model in (2) is just one of other possible descriptions of viscoelasticity,⁴⁷ introduced here because it builds naturally on top of a hyperelastic framework for nonlinear soft tissue. Section II A presents more detail regarding a particular example for nonlinear anisotropic materials.

A. Example: A nonlinear, anisotropic, microstructural, viscoelastic model

There are a wide variety of approaches to model the mechanical behavior of soft tissue, and this review only scratches the surface of this wide topic.¹⁶ To model multiscale mechanobiology, some notion of material response at the macroscale is needed. In the beginning of this section, we have introduced the basic framework of hyperelasticity. We then showed how this framework has been extended to account for viscoelasticity. Here, we show an example of a recently

developed microstructure-driven model for soft tissue. Consider the strain energy⁴⁸

$$\Psi(\mathbf{b}) = \Psi^{\text{m}}(\mathbf{b}) + \Psi^{\text{eq}}(\mathbf{b}, \theta) + \Psi^{\text{neq}}(\mathbf{b}, \theta) + p[J - 1], \quad (3)$$

with a hyperelastic neo-Hookean term $\Psi^{\text{m}}(\mathbf{b})$ to describe the isotropic ground substance of the ECM. The equilibrium anisotropic term is of the form

$$\Psi^{\text{eq}}(\mathbf{b}) = \frac{\mu^f}{2} \int \rho^{\lambda_w}(\lambda_w) \int \rho^\theta(\theta) \left[\bar{\lambda}^2 + \frac{2}{\bar{\lambda}} - 3 \right] d\theta d\lambda_w, \quad (4)$$

where μ^f is a shear modulus parameter for fibers, $\rho^{\lambda_w}(\lambda_w)$ is a probability distribution of fiber slack or waviness, $\rho^\theta(\theta)$ is a fiber orientation distribution, and the stretch $\bar{\lambda}$ is actually a function of the angle, the fiber slack, and the total deformation

$$\bar{\lambda}(\theta, \lambda_w) = \frac{\lambda(\theta)}{\lambda_w}, \quad \lambda(\theta) = \|\mathbf{F} \cdot [\cos(\theta), \sin(\theta), 0]\|. \quad (5)$$

The non-equilibrium part is of the same functional form as the equilibrium branch, but it is expressed in terms of the elastic portion of the non-equilibrium branch,

$$\Psi^{\text{neq}}(\mathbf{b}^e) = \frac{\beta \mu^f}{2} \int \rho^{\lambda_w}(\lambda_w) \int \rho^\theta(\theta) \left[\bar{\lambda}^e]^2 + \frac{2}{\bar{\lambda}^e} - 3 \right] d\theta d\lambda_w \quad (6)$$

with $\bar{\lambda}^e = \lambda/\lambda^v$ and λ^v being the viscous stretch of the viscoelastic branch. As before, the viscous branch evolves in time according to a relaxation equation. The rate of relaxation depends on the stress on the non-equilibrium branch,⁴⁴

$$J^\circ \boldsymbol{\tau}^{\text{neq}} = -\frac{1}{\eta} \boldsymbol{\sigma}^{\text{neq}}, \quad (7)$$

where $\boldsymbol{\tau} = J\boldsymbol{\sigma}$ is the Kirchhoff stress and η is a viscosity parameter associated with the time scale of relaxation. The basic behavior of this constitutive model is illustrated in Fig. 2.

The model presented here is a representative example,⁴⁸ but it builds upon a rich development of constitutive equations for biological materials. It considers viscoelasticity in a framework similar to Liu *et al.*⁴⁴ Other approaches for viscoelastic materials include fractional calculus^{49,50} and Prony series for different time scales of relaxation.^{51,52} The anisotropic component in terms of fiber orientation distribution is also a common theme in the literature.^{10,53} The waviness or slack distribution is not as widely used, although there are some other examples.^{54–56} As opposed to a waviness distribution, a common approach is to change from a simple model like neo-Hookean to an exponential fiber strain energy.¹⁶ The integration over the fiber waviness of a neo-Hookean model yields a nonlinear response similar to the exponential function for small to moderate stretches.⁴² The exponential function, however, has the potential limitation of unbounded stress increase for larger stretches, whereas the fiber waviness distribution, in the limit of large stretches, converges to a stiff neo-Hookean material. Thus, in terms of stability and sensitivity to parameters, the exponential potentials should be used with caution and only to predict deformations in the same range as the data used to calibrate the model.⁵⁷ A model based on fiber orientation and waviness distributions is more robust, but it comes with a higher computational cost.

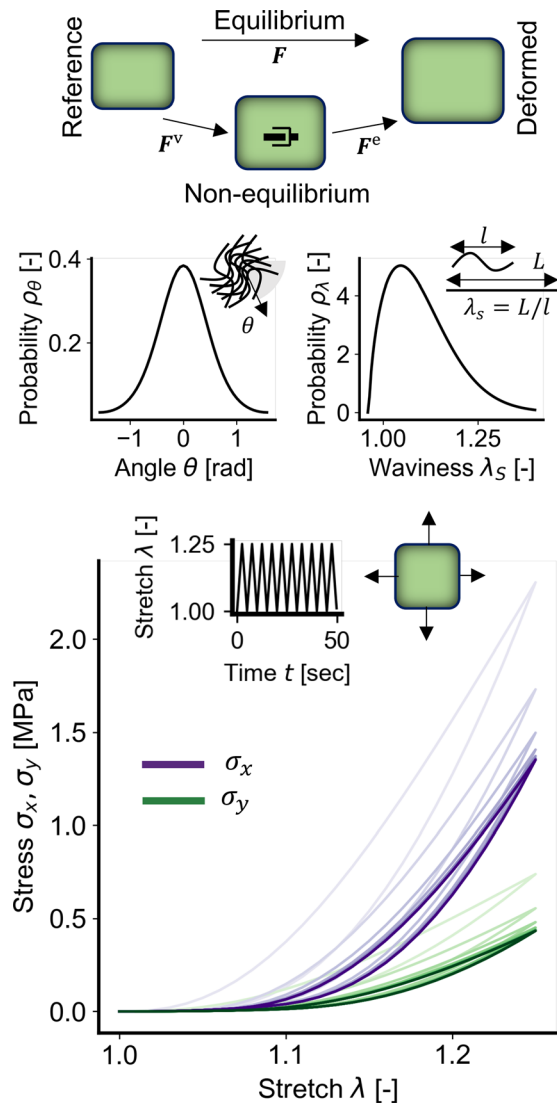


FIG. 2. Example: A nonlinear hyper-viscoelastic model based on microstructure features. The fiber network can be represented through probability distributions for fiber orientation and waviness. To account for viscoelasticity, the total deformation $\mathbf{F}$ is split into the equilibrium component—which depends on the total deformation—and a non-equilibrium branch. The non-equilibrium branch introduces the viscous deformation, $\mathbf{F}^v$, and the corresponding elastic deformation of the non-equilibrium branch, $\mathbf{F}^e$. When subjected to cyclic biaxial loading, this model can recreate the nonlinear, anisotropic, viscoelastic response of soft tissue.

Figure 2 shows a representative example with strain energy (3) showcasing the mechanical behavior of the tissue. The code to generate this figure is also available, see the Github link at the end of the article. The purpose of this example is to provide the reader not just with a synthesis of the state-of-the-art on soft tissue modeling but to further generate basic educational material that illustrates the key concepts covered in the review.

B. Growth and remodeling at the tissue level

Considering only the passive response, soft tissues already exhibit a rich mechanical behavior. It is even more fascinating to consider tissues' unique capacity to grow and remodel. There are two approaches to describe growth and remodeling at the macroscale that have become the most widely used. One is based on describing tissues as a mixture of the different constituents,²⁵ the second one is based on a geometric description.⁵⁸ In the constrained mixture model,^{25,41,59} the tissue is composed of mass fractions of constituents ρ_i and these satisfy the standard mass transport equation,

$$\dot{\rho}_i + \nabla \cdot (\mathbf{v}_i \rho_i) = m_i, \quad (8)$$

where $\mathbf{v}_i$ is the velocity of constituent i and m_i the mass production rate of each constituent.

The linear momentum balance of the mixture is the standard condition, $\nabla \cdot \boldsymbol{\sigma} = \mathbf{0}$, but with the stress being a sum of the stress from each constituent,

$$\boldsymbol{\sigma} = \sum \boldsymbol{\sigma}_i. \quad (9)$$

There is a constraint equation that relates the momentum exchange between different constituents,

$$\sum (\mathbf{p}_i + m_i \mathbf{v}_i) = \mathbf{0}, \quad (10)$$

where $\mathbf{p}_i$ is the momentum exchange between constituent i and all other constituents. Up to this point, the description is analogous to classical mixture theory approaches.⁶⁰ However, the connection to growth and remodeling is achieved in two ways. First, the mass source term for constituent i can be used to describe deposition and decay of structural proteins by cells. Second, the stress for a particular constituent can be calculated in a similar manner as (1), with one key change: the notion of evolving natural configurations.⁶¹ Equation (1) describes the stress in the material assuming that the left Cauchy–Green deformation tensor $\mathbf{b}$ captures deformation from a stress-free state. In the case that material is continuously deposited and destroyed, the stress for a constituent needs to be computed with respect to its own stress-free or *natural* configuration

$$\mathbf{F}_i^t = \mathbf{F} \mathbf{F}_i^{n-1} \mathbf{G}_i. \quad (11)$$

The deformation for constituent i that contributes to stress is $\mathbf{F}_i^t$, while the total deformation of the mixture with respect to the reference configuration is $\mathbf{F}$. Note that the reference configuration of the mixture is arbitrary and not necessarily stress-free, it is simply a configuration of the mixture from which one wishes to measure deformation. The tensor, $\mathbf{F}_i^n$ is the deformation from the stress-free or natural configuration of constituent i to the reference configuration of the mixture. To obtain $\mathbf{F}_i^n$, one would have to track the mixture over time and determine the instant at which constituent i was deposited. Consider the total deformation of the mixture as a parametric motion $\mathbf{F}(s)$, where s can represent time. If a constituent is deposited at some time $s = \tau$, then $\mathbf{F}_i^n = \mathbf{F}(\tau)$. Finally, the last tensor in (11), $\mathbf{G}_i$ captures pre-stress of constituent i as it is deposited in the mixture at the time $s = \tau$.

The mixture theory approach describes the tissue in extreme detail so as to account for individual constituents, the time at which they are deposited, the natural configuration of each constituent, and how they interact to produce the observed response of the mixture.

On the other hand, the detail comes at a price, specifically computational cost of keeping track of the time history of material deposition with respect to the motion of the mixture.²⁵

The alternative approach, multiplicative volumetric growth, follows the theory of large deformation plasticity,

$$\mathbf{F} = \mathbf{F}^s \mathbf{F}^g, \quad (12)$$

where $\mathbf{F}$ is the deformation of the tissue with respect to a single stress-free reference state. The growth tensor $\mathbf{F}^g$ is the permanent volume change due to mass addition or subtraction with respect to the initial stress-free state. The deformation $\mathbf{F}^s$ is the only one that contributes to the stress. In the case of a hyperelastic material,

$$\boldsymbol{\sigma} = J^{s-1} \mathbf{b}^s \frac{\partial \Psi}{\partial \mathbf{b}^s}, \quad \mathbf{b}^s = \mathbf{F}^s \mathbf{F}^{s\top} \quad (13)$$

with $J^s = \det \mathbf{F}^s$. The deformation that leads to stress in the material can be further decomposed into an equilibrium contribution and a non-equilibrium contributions when considering viscoelastic behavior, as shown in Sec. II A.

In the multiplicative decomposition, the growth tensor $\mathbf{F}^g$ captures the biological process. In particular, an evolution equation for the growth tensor is needed, i.e., an equation of the form $\dot{\mathbf{F}}^g$. This growth rate can be related back to mass deposition, similar to (8). In fact, it should also be noted the similarities between (12) and (11). Both approaches recognize the need to track the stress-free state and measure stress with respect to that configuration. The volumetric split, in contrast to the mixture model, distills the complex growth and remodeling process into a single tensor, without keeping track of the detailed history of deposition of individual constituents.⁶² Therefore, it has been more widely adopted in large scale computer simulations.^{22,63}

C. Example: A tissue growing in response to stretch

Consider the tissue with elastic response as illustrated in Fig. 2. Adopting the multiplicative growth framework,²² the total deformation is first split into the growth and stress-inducing deformations. The portion of the deformation that contributes to the mechanical response is further split into equilibrium and non-equilibrium branches, see Fig. 3. The mechanical response is thus analogous to before, but now with the additional growth deformation $\mathbf{F}^g$. To close the description, we introduce two more constitutive models. One is the specific form of the growth tensor. We assume that the tissue grows by adding material into each of the fiber directions,

$$\mathbf{F}^g = \int \rho^\theta \lambda^g(\theta) \mathbf{V}(\theta) \otimes \mathbf{V}(\theta) d\theta, \quad (14)$$

where $\mathbf{V}(\theta)$ is the direction vector for a particular orientation θ and $\lambda^g(\theta)$ is the growth in that direction. The other equation needed is the rate equation to determine how growth evolves over time. We assume that the growth rate is proportional to the elastic equilibrium stretch in the direction θ

$$\dot{\lambda}^g(\theta) = \frac{1}{\tau^g} [\lambda^s(\theta) - 1]. \quad (15)$$

This type of constitutive model has been successfully used to capture skin growth, axon growth, and muscle growth, among other applications.^{64,65} Alternative examples of constitutive rate equations

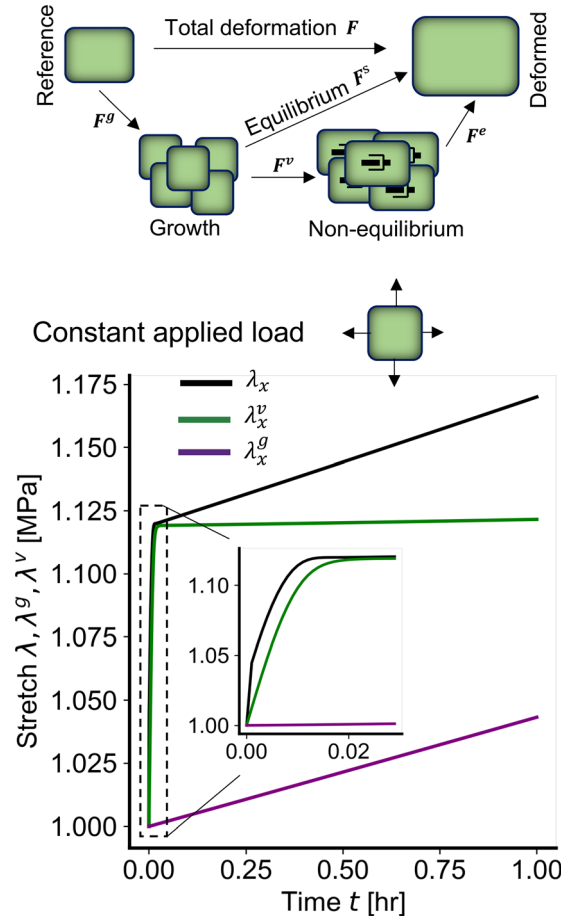


FIG. 3. Example: A tissue grows in response to stretch. This example follows the description of the elastic behavior shown above. The key addition is the split of the total deformation $\mathbf{F}$ into growth and stress-inducing deformations $\mathbf{F}^g$, $\mathbf{F}^s$. The component $\mathbf{F}^s$ is further split into equilibrium and non-equilibrium branches. The growth tensor is assembled by computing the growth in each of the fiber orientations $\lambda^g(\theta)$ with the rate of growth for a particular orientation being proportional to the elastic deformation in that direction. When subjected to a constant applied stress, the tissue initially creeps viscoelastically. Then, tissue grows by adding mass into each of the fiber directions. Because the tissue is subjected to constant stress, there is always some elastic deformation and, thus, growth will go on indefinitely in this example.

for growth are based on stress. In other words, stress away from a homeostatic state is the driver for growth. Stress-driven growth has been used to capture tumor and bacteria biofilm growth, for instance in Refs. 66 and 67.

Figure 3 shows a representative example to illustrate the main points of this theory. A biaxial state of stress is prescribed. This is analogous to a creep test. At the beginning, the material creeps due to the viscous, non-equilibrium branch of the deformation that carries the stress, $\mathbf{F}^v$. However, as time progresses, the viscous stretch equilibrates and it is the growth of the tissue that drives the total deformation. In this example, growth is proportional to the elastic deformation. Since the simulation is under constant stress, there is always some elastic deformation and thus growth would continue indefinitely in this

example. Note that the time scale of growth is assumed to be quite small in order to show representative changes in 1hr of simulated time. Yet, even with such a fast time scale for biological adaptation, it is still clear in Fig. 3 that there is a separation of time scales between the viscous response and the biological adaptation. Thus, the viscous response can be safely ignored for equilibrium problems over long periods of simulated time. If cyclic loading is present, then the viscoelastic response cannot be ignored. Similar to the previous example, the code to generate the figure is available in a public repository listed at the end of the review.

III. COUPLED BIOCHEMICAL AND MECHANOBIOLOGICAL FIELD EQUATIONS AT THE MACROSCALE

Even though in Sec. II, we already alluded to the fact that biological tissue can grow and remodel in response to mechanical cues, the biological processes driving growth and remodeling have not been discussed. Staying at the macroscale and aiming for a description almost entirely based on mechanics, the first approach is to consider growth and remodeling rates as a function of stress or deformation alone. This was, for instance, the approach in our example, Eq. (15), in which the growth rate was assumed proportional to the stretch along a fiber direction. A variety of these equations have been used in the literature.^{68–70} For example, growth as a function of fiber stretch⁶⁸ has been used to model heart adaptation, growth as a function of area stretch has been used to model skin growth.⁶⁹ This kind of coupling is not exclusive to the multiplicative growth theory but has also been used with the mixture model. For example, in Ref. 71, the deposition of constituents depends on the difference between the current stress and a target homeostatic stress.

Even though the direct coupling of the state of stress or deformation to the growth and remodeling rates is insightful, it completely ignores the underlying biology. One level of sophistication past the purely phenomenological models is to still consider the macroscale problem, but to expand the variables from being restricted to mechanics and instead incorporate cell and cytokine density and concentration fields.^{72,73} Cell populations and soluble chemical signals in the extracellular space satisfy partial differential equations for mass balance,

$$\begin{aligned}\dot{\rho} + \nabla \cdot \mathbf{q}_\rho &= s_\rho, \\ \dot{c} + D^c \nabla c &= s_c.\end{aligned}\quad (16)$$

The flux of the cells, $\mathbf{q}_\rho$, includes diffusion due to random walk of cells but can also account for advective terms for chemotaxis and haptotaxis.^{74,75} The flux of chemicals in (16) is typically Fickian diffusion. The source terms, s_ρ , s_c , are the key for coupling the biochemical fields to the growth and remodeling response of the tissue.

We focus on two main feedback loops between mechanics and biochemical fields. There is a clear role of connective tissue cells like fibroblasts to exert active stress on the ECM.^{76,77} For example,

$$\boldsymbol{\sigma}^a = \rho t^a \hat{\mathbf{v}} \otimes \hat{\mathbf{v}}, \quad (17)$$

which considers that the active stress is proportional to cell density with an average traction per cell t^a . The active stress is assumed in the direction of the fibers via the structural tensor $\hat{\mathbf{v}} \otimes \hat{\mathbf{v}}$ determined by the deformed fiber direction $\hat{\mathbf{v}}$. Cells also deposit ECM constituents and contribute to ECM degradation through the release of specific

proteins and enzymes. Thus, we can explicitly link cell and cytokine fields to changes in mass (growth), mechanical properties, and microstructure properties.^{41,54,55,78} For instance, we can propose a growth rate proportional to the cell density ρ in response to a signal c with a mass rate m ,

$$\dot{\lambda}^g = m c \rho. \quad (18)$$

Equations such as (18), together with the mass transport of cells and cytokines in Eq. (16), can, therefore, couple biochemical field equations to tissue growth and remodeling. This kind of approach has been used in models of wound healing,²² thrombus remodeling,⁴¹ and tumor growth,⁷⁹ to name some examples.

The converse feedback loop is the mechanobiological coupling from the stress and strain fields to the models of cellular activity. At the macroscale, this would require a way to relate strain and stress fields to cell behavior such as mass production terms or the active stress magnitude. This coupling is not straightforward because the process of transforming mechanical cues to cellular behavior is inherently restricted to the smaller spatial scales, as illustrated in Fig. 1. Often times, the mechanobiology coupling is bypassed in continuum models of tissue remodeling.^{80,81} However, there are some examples of models at the macroscale that consider a homogenized or average description of cell mechanobiology. The work by Moreo *et al.* for example, introduces macroscale quantities to capture a mechanobiology variable,⁸²

$$p_{\text{cell}} = \begin{cases} K_{\text{pass}} \theta, & \theta < \theta_1, \\ \frac{K_{\text{act}} p_{\text{max}}}{K_{\text{act}} \theta_1 - p_{\text{max}}} (\theta_1 - \theta) + K_{\text{pass}} \theta, & \theta_1 < \theta < \theta^*, \\ \frac{K_{\text{act}} p_{\text{max}}}{K_{\text{act}} \theta_2 - p_{\text{max}}} (\theta_2 - \theta) + K_{\text{pass}} \theta, & \theta^* < \theta < \theta_2, \\ K_{\text{pass}} \theta, & \theta > \theta_2, \end{cases} \quad (19)$$

where p_{cell} denotes a mechanobiology signal that regulates other biological processes such as mass production terms for collagen and cytokines. The model (19) is derived from a simplified model of cell-ECM mechanics. The variable θ in the model is a generalized strain of the ECM, $[\theta_1, \theta_2]$ is the range of strain in the cell over which the cell is capable of producing contractile force. The contractile force of the cell is assumed bi-linear, with an increasing slope starting from $p_{\text{act}} = 0$ at θ_1 , up to $p_{\text{act,max}}$ at θ^* , going back to zero contractile force at θ_2 . The parameters K_{pas} and K_{act} refer to the passive stiffness of the cell and the stiffness of the active contractile machinery of the cell, respectively. In summary, Eq. (19) is a good example of how macroscale strain quantities; in this case, the generalized strain θ can be used to compute a mechanobiology variable, in this case p_{cell} , to create coupled models of tissue mechanobiology at the continuum level.⁸² Other examples are Refs. 83 and 84. A different example is found in cardiac electrophysiology modeling, in which the macroscale stress/strain is related to the opening of ion channels.⁸⁵

Thus, there are strategies to couple tissue growth and remodeling equations to the underlying cellular mechanobiology. The coupling from cell density fields and cytokine concentrations to changes in tissue composition, mechanical properties, and active stress are intuitive even though they leave out many of the details of the underlying biological processes. The converse coupling, from the state of stress and

deformation to the cellular behavior, is more challenging because it is not naturally captured at the continuum level. While some attempts have been made to capture macroscale variables of mechanobiology, Sec. IV dives into the microscale models that capture in detail the way in which ECM deformation gets transmitted to cell deformation through the formation and remodeling of focal adhesions.

IV. MODELING MECHANOBIOLOGY AT THE CELL LEVEL

As reviewed so far, the mechanics of the tissue including growth and remodeling are well developed. Open problems persist when bridging between the macroscale biomechanics and the biophysics of the microscopic cell–ECM interaction. In this section, we focus on mesenchymal cells and connective soft tissues. For these tissues, the interface between the ECM and the cell is predominantly regulated through focal adhesions, and, in particular, binding between integrins and ligands on the substrate.^{86,87} At the scale of single cells, other mechanotransduction pathways are important in addition to focal adhesion dynamics. For example, ion-channels on the cell membrane can be activated as a function of strain.⁸⁸ Biophysics of cell–cell adhesion are also key for mechanotransduction and can regulate overall tissue growth and remodeling at the macroscale.⁸⁹ Mechanotransduction via cell–cell adhesions is particularly important for soft epithelial tissue. The epidermis, the top layer of the skin, is a cellular epithelial tissue that grows in response to stretch via α -catenin signaling activated by cell–cell cadherin junctions.⁹⁰ For hard tissue cells like osteocytes, interstitial fluid flow is a primary signal for mechanotransduction.⁹¹ Recent work has extended the relevance of fluid transport to other cells beyond those resident in bone.⁹² Finally, there are indirect paths for mechanotransduction through growth factors, either due to interacting between growth factors and the ECM in response to applied forces, or through secondary couplings between mechanotransduction pathways and growth factor production and cell membrane receptor activity.⁹³ Emphasis in this section will be placed on integrin signaling, since this is the primary mechanotransduction pathway for cells in soft connective tissue, where force transmission to single cells occurs via the fibrillar, load-bearing ECM. Toward the end of the section, however, we address some of the modeling tools applicable for a broader set of mechanosensing events.

A. Cell–ECM mechanotransduction through focal adhesions

Integrins are a family of transmembrane receptor proteins consisting of α and β subunits. There are 18 α subunits and 8 β subunits that combine to form 24 different integrins with finely tuned affinity to specific ligands and with different roles in cell mechanotransduction.⁹⁴ Binding of integrin to ECM ligands and subsequent force transmission from the ECM to the actin cytoskeleton triggers outside-in signaling that regulates cell behavior.³¹ Conversely, regulation of integrin activity depends on intracellular signaling pathways and forces from actin polymerization and molecular motors inside the cell in the process of inside-out signaling.⁹⁵ Integrins connect to the actin cytoskeleton through a number of cross linker proteins such as talin, vinculin and kindlin.^{96,97} Force sensitivity of the ECM–integrin–cytoskeleton complex has been studied in great detail with molecular dynamics simulations to understand the fundamental mechanisms of cell mechanotransduction through focal adhesions. Molecular dynamics of single integrin complexes are beyond the scope of this review but

can be modeled either with all-atom simulations or with coarse-grained models.⁹⁸ An efficient but still mechanistic way of describing integrin kinetics is through the model originally proposed by Bell more than half a century ago to describe cell–cell adhesion kinetics,⁹⁹ later extended to capture integrin binding kinetics in the presence of applied forces. According to this model, integrins can bind ligands in the substrate with certain probability P_{on} which depends on the relative concentration of integrins in the cell membrane and ligands on the substrate as well as the affinity between the two. The key insight of Bell's model of adhesion is the dependence of the dissociation rate on the energy stored at the adhesion. The bond dissociation probability follows a Boltzmann distribution. The energy stored at the adhesion, in turn, depends on the contractility of the cell and the stiffness of the substrate. The probability of forming a new bond between an integrin and a ligand can be expressed according to the Poisson process distribution,

$$P_{\text{on}} = 1 - e^{-\Delta t k_{\text{on}}}, \quad (20)$$

while the probability of bond dissociation is, likewise

$$P_{\text{off}} = 1 - e^{-\Delta t k_{\text{off}}}, \quad (21)$$

but with the dissociation rate in Eq. (21) depending on the energy at the adhesion through a Boltzmann distribution,

$$k_{\text{off}} = \hat{k}_{\text{off}} e^{\Delta E/k_B T}. \quad (22)$$

The energy at the adhesion, ΔE , depends on the stiffness of the substrate, a characteristic length scale, and the contractile force of the actomyosin motors in the cytoskeleton, which pull on the integrin–ligand bonds.¹⁰⁰ For the simplest case of linear elastic substrate, the energy at the adhesion is

$$\Delta E_{\text{le}} = f\gamma = \frac{f^2}{2k_{\text{ECM}}}, \quad (23)$$

where f is the contractile force, γ is the characteristic length scale, and k_{ECM} the substrate stiffness.

The initial model by Bell⁹⁹ has endured the test of time. It has gradually been improved, resulting on a rich history of model development and sophistication. For example, the model has been extended to capture the feedback between cell contractility and substrate stiffness,¹⁰¹ the role of integrin clustering,¹⁰² and the role of substrate viscoelasticity.²⁷ Local remodeling of the ECM has also been built upon this adhesion model.¹⁰³ Other variations of the model have incorporated a bimodal response of integrins to force such that the dissociation rate is not a decreasing function of the energy at the adhesion. Instead, a certain level of force increases the rate of integrin bond formation. This is called the catch-bond model and captures a positive feedback loop between force exerted by cells and growth of focal adhesions.¹⁰⁴ The model by Bell and the extensions to include the more sophisticated events—e.g., activation rates of different integrins, the catch bond response, integrin clustering—have been informed by atomistic models, but eventually condensed into rate parameters such as k_{on} and k_{off} used in Eq. (22).¹⁰⁵ Thus, even if the homogenized kinetics of integrin binding are much simpler compared to all-atom models, they are informed from molecular dynamics and coarse grained simulations to ensure that they still capture the same (homogenized) physics.

It should also be noted that Eqs. (20) and (21) are in terms of the discrete events, i.e., they describe the binding or dissociation of an individual bond. As a result, they need to be modeled with Monte Carlo sampling.¹⁰⁵ The homogenized version of this model assuming uniform distribution of integrins on the cell surface and ignoring saturation of ligand sites on the substrate is an ordinary differential equation (ODE)

$$\dot{\phi}_b = k_{\text{on}}(1 - \phi_b) - k_{\text{off}}\phi_b, \quad (24)$$

where ϕ_b is the fraction of integrin bonds with respect to the total number of integrins of a single cell. Equation (24) thus reduces the entire surface of the cell and the discrete adhesion events to a single scalar. Even though this simplification has been made often, spatial models accounting for integrin diffusion on the membrane and integrin clustering are also found in the literature.¹⁰⁶ For example, some of the most impressive work in this regard are the models of single cell migration on different substrates by Kim *et al.*^{107,108} These and other efforts that go from the single integrin kinetics to the modeling of whole cells increases the complexity by considering not only the mechanics at the adhesion, but also the complex mechanics of the actin cytoskeleton and of fiber networks nearby cells.^{109,110} Nonetheless, the cell–ECM adhesion components in these whole-cell models are still based on the fundamental Eqs. (22) and (24). When considering whole-cell simulations, the mechanics of the actin cytoskeleton mechanics can be captured with agent based models.¹¹⁰ For increased computational efficiency, homogenized models of actin cytoskeleton networks treated as a Maxwell solids have also been employed to model whole cells.¹¹¹

By modeling the adhesion of cells to the substrate accounting for biophysical phenomena, models such as (22) and (24) are a mechanistic tool to capture mechanosensing. Indeed, these models predict observed cell behavior such as increased contractility, stiffness, and adhesion in stiffer substrates compared to softer ones.¹¹² Models of cell migration based on (22) and (24) capture durotaxis, or the tendency of cells to migrate toward stiffer substrates.¹¹³ Therefore, simply by modeling the kinetics of the adhesion and how these depend on the biophysics of integrin bonds opens up a pathway to model how mechanical inputs such as stretch, stress, viscoelasticity, or stiffness of the substrate contribute to cellular activity.¹¹⁴

Even understanding the cell–ECM interface, there is still a lengthy and convoluted path to go from integrin–ligand bonds to the gene expression at the nucleus of the cells, which is what ultimately drives the long-term growth and remodeling of the tissue. The cascade of intra-cellular events taking place upon integrin binding and leading up to changes in gene expression is a topic for a review on its own and will not be covered in detail here.³¹ Briefly, integrin binding to ECM ligands—such as fibronectin or collagen—generates conformational changes in their cytoplasmatic domain and results in recruitment of proteins such as talin and vinculin that link integrins' cytoplasmic domain to the actin cytoskeleton in a force-dependent manner.^{97,98} Interaction among integrins and cross-linker proteins under force also drives clustering and maturation of the focal adhesions.¹⁰² One of the main pathways for signaling downstream of integrin activity is through focal adhesion kinase (FAK) phosphorylation.¹⁰⁵ FAK recruitment and phosphorylation at cell–ECM adhesions acts through Src tyrosine kinases to regulate downstream signaling cascades that affect cell behavior. For instance, the FAK–SRC complex regulates

GTPases signaling proteins including Rac1, Cdc42, and Rho, which have direct roles in actin cytoskeleton remodeling.¹¹⁵ Another end point of the integrin signaling pathway, that is, regulated through the FAK–SRC complex culminates in ERK activation, leading to the regulation of cell proliferation.¹¹⁶ Changes in the cytoskeleton also result in downstream gene regulation, for example, through the YAP/TAZ pathway.^{117,118} Forces transmitted from the ECM to the cell do not stop at the cytoskeleton but are transmitted to the nucleus through the LINC complex.¹¹⁹ Nuclear deformation itself offers another potential mechanism for mechanoregulation of gene expression, possibly through regulation of nuclear import of transcription factors and export of mRNA, both of which are enforced by the nuclear pore complex.¹²⁰ There are efforts on modeling the intra-cellular mechanobiology processes that take place beyond cell–ECM adhesion formation. In this front, some excellent work has been done to describe signaling networks for fibroblasts.^{121–123} For instance, in the work by Zeigler *et al.*,¹²⁴ the authors model how paracrine signaling in direct response to myocardial infarction can predict observed changes in heart tissue fibrosis through a cell-signaling model of fibroblast mechanobiology. The approach is similar in the work by Estrada and coauthors.¹²⁵ In general, a reasonable approximation of the problem is to rely on ordinary differential equations (usually Hill-type equations) and logic models linking mechanical cues to activity of intracellular signaling pathways to cell phenotype.^{126–128} These models can range in complexity, from considering only a couple of pathways with a small number of components¹¹⁸ to very detailed signaling cascades.¹²⁹

B. Models of cell mechanotransduction beyond cell–ECM adhesion

Even though most of this review is focused on mesenchymal cell mechanobiology for soft connective tissue growth and remodeling, it is worth devoting some attention at other modeling frameworks that are applicable to a broader range of tissues. Even for mesenchymal cells, other mechanotransduction pathways beyond cell–ECM adhesion are at play as discussed briefly at the beginning of the section. For epithelial tissues, which are highly cellular, a natural mathematical description of cell mechanics and mechanobiology is in terms of vertex models.¹³⁰ In this approach, the geometry of the epithelial tissue can be captured with polygons for each cell in 2D, or with prismatic polyhedra in 3D.^{131,132} Balance of momentum in vertex models usually follows from posing an energy minimization problem.¹³³ The energy functional allows the encoding of cell behavior—e.g., preferred cell area or volume—, as well as interaction energies between cells—e.g., cortical tension along faces or edges of the polyhedra shared by two or more cells. External forces can be also applied as boundary conditions. Minimization of the energy functional leads to force balance on the domain. Crucially, the energy potentials are used to encode the mechanobiological response via attractors toward a desired homeostatic state. Minimization of competing potentials can lead to emergent behavior as one potential is dominant over another. For instance, a well-established transition in epithelial tissue is whether they are more fluid-like or solid-like, which is a consequence of the competing energies for cell volume and surface tension.¹³⁴

Coupling of vertex models to the nonlinear tissue mechanics descriptions at the larger scales, such as the ones reviewed in Sec. II, have not been attempted and constitute an avenue for future research. On the other hand, homogenization of representative volume elements

from vertex models alone, without interaction with the fibrillar ECM, can be done to upscale mechanics of epithelial tissue to be used in continuum models of the larger scales.¹³⁵ More interestingly, vertex models pose the question of how to derive analogous mechanobiology potentials but for mesenchymal cells interacting with connective tissue ECM. In a fiber network, modeling cells as polyhedra could pose its own challenges. Alternative geometries for cells in epithelial tissue have been explored,¹³⁶ and could be used to model cells in fibrillar ECMs. Finite element models of single cells embedded in the ECM are also plausible but their use in multiscale modeling can be hindered by computational cost.¹¹¹

C. Example: A nonlinear model of cell adhesion and contractile stress

To illustrate the biophysics encoded in (20), (21), and (24), we show a representative example illustrated in Fig. 4. Compared to the literature, however, consider a nonlinear energy at the adhesion that builds upon the model we introduced in Eq. (3). This nonlinear model is in contrast with the more common linear models in the literature. For such a material, the energy at the adhesion becomes nonlinearly dependent on the contractile force and the stretch of the substrate, as opposed to the linear case in Eq. (23). For the nonlinear material model, the energy is $\Delta E = [\Psi(\bar{\lambda}) - \Psi(\lambda)]A_0 l_0$, with $\bar{\lambda}$ being the new stretch of the fiber or fiber network as it is pulled by the contractile force f at the site of adhesion and l_0, A are length scale and area parameters related to the column of substrate being deformed due to a single integrin-ligand bond. Because the model is nonlinear, it directly links stretch of the substrate to changes in binding probability, as seen in Fig. 4.

In addition to the nonlinear energy, the model includes one more level of sophistication: dynamic control of the contractile force according to the model by Cao *et al.*¹⁰⁶ In Fig. 4, the contractile force f is tightly regulated in a dynamic fashion. The model captures the reinforcement of the adhesion by modeling the coupling between the contractile force and the ECM stiffness,¹⁰⁶

$$f = \frac{f_0}{1 - \beta + \left(\frac{k_a}{k_{\text{eff}}} + \frac{k_a}{k_N} \right)}, \quad (25)$$

where f_0 is the pulling force on actin when there is no feedback, k_a is actin stiffness, k_N is nucleus stiffness, β is a feedback term, and k_{eff} is the effective stiffness of the substrate. In our example in Fig. 4, the stiffness of the substrate is the tangential stiffness since the model is nonlinear and the stiffness changes at different levels of stretch. Figure 4, thus, illustrates how the contractile force is regulated according to (25) to maintain an optimal level of adhesion as the tangential stiffness of the substrate changes.

To conclude the example, we recall the active stress mentioned briefly in Eq. (17). After solving for the adhesion probability of integrin-ligand pairs, estimating the total number of integrins per cell and solving for the contractile force as indicated in Eq. (25), the magnitude of the active stress becomes

$$||\sigma^a|| = t^a = f \phi_b \rho_i, \quad (26)$$

with t^a being the resulting traction magnitude and ρ_i the integrin density. The active stress is illustrated in Fig. 4. Due to the nonlinear

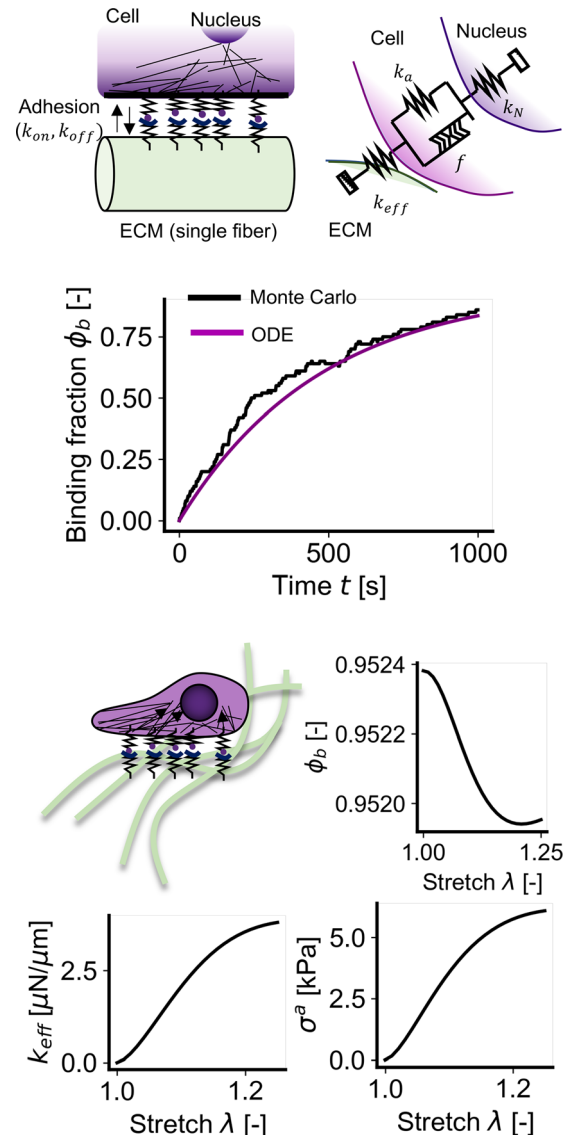


FIG. 4. Example: A nonlinear adhesion model. The interface cell–ECM results from the formation and dissociation of integrin–ligand bonds and focal adhesions. The kinetics at the adhesion are first-order with the dissociation rate dependent on the elastic energy at the adhesion. The elastic energy at the adhesion, in turn, depends on ECM deformation and the cell contractile machinery. Monte Carlo simulations of individual integrin–ligand pairs can be homogenized to obtain ordinary differential equations (ODEs). In the case in which the ECM is modeled as a nonlinear material, the apparent stiffness of the ECM k_{eff} is dependent on stretch. The integrin–ligand bond fraction remains largely unchanged with stretch; however, this is due to the dynamic regulation of the contractile force f based on Eq. (25). Even though the cell adhesion stabilizes to a similar value as stretch increases, the active stress exerted by the cell on the ECM changes in a nonlinear fashion to match the stiffness of the substrate.

tangential stiffness of the substrate with increasing stretch, k_{eff} , the cell active stress exhibits a corresponding regulation. Even though we have illustrated a rather essential description of cell adhesion, it illustrates the key concept that cells constantly form and dissociate

integrin-ligand bonds with the substrate, and the mechanobiology coupling occurs due to the biophysics at the adhesion, which depend on apparent stiffness (in turn a function of deformation) and the composition of the substrate. This type of model is intuitive when analyzing the cell scale, but in fact, most of the tissue level descriptions of growth and remodeling are coupled directly to the macroscopic elastic deformation or state of stress of the tissue, without considering the complex biophysics that link the ECM to the cell.⁷⁵

V. MULTISCALE GROWTH, REMODELING, AND MECHANOBIOLOGY

By this point, we hope to have convinced the reader that the macroscale mechanics of soft tissue, including growth and remodeling, are well established. Coupling between growth, remodeling and mechanobiology at the tissue level can be done by introducing continuum fields for cells and cytokines. These biological and biochemical fields can then be used in the reaction terms of the growth and remodeling equations, as well as in the active stress equation. On the other hand, as just reviewed, modeling the cell level biophysics, especially the integrin and focal adhesion kinetics, offers a necessary tool to capture the first link in the mechanobiology coupling: how forces are transmitted from the ECM to the cell. The purpose of this section is to review the existing approaches to go across these two scales in a unified framework.

A naive formulation for multiscale modeling is to simply nest models and build bottom-up approaches that capture all the details and mechanisms of the lower scales up to the macroscale response of the tissue. Multiscale coupling of this nature is feasible up to a certain extent.^{137–139} Yet, it becomes intractable for realistic biomedical applications. Some recent efforts in multiscale mechanobiology propose the use of an intermediate scale or mesoscale to gain a deeper understanding of how to couple cellular activity to tissue mechanics.¹⁴⁰ Other work aimed at gaining insight from the mesoscale are Refs. 17, 20, and 141. At the mesoscale, on the order of hundreds of μm , the ECM can be accurately modeled with discrete fiber networks.^{17,20,142,143} Cells can be considered with realistic geometries¹⁴⁴ or with more simple geometries such as ellipsoids.^{145,146} Mesoscale models allow for modeling of cell–cell and cell–ECM interactions.²⁹ Due to the manageable size of the domain, computational models from the single cell can be easily ported into mesoscale models by considering cells as agents.¹³⁷ Some information is inevitably lost in this scaling up, but enough detail can be maintained. Similarly, information from the larger, macroscale can be passed down to the mesoscale in the form of boundary conditions.³² Mesoscale models are perhaps the most natural playground to gain a deeper understanding of growth and remodeling across scales. Before diving into the open problems and opportunities, one last example is provided.

A. Example: A tissue remodels in response to cellular activity

To illustrate the concepts covered so far, Fig. 5 shows the integration of the cell adhesion model from Fig. 4 to the growing tissue model from Fig. 3. The ability to capture the coupling across scales in this case is achieved by considering a homogeneous solution. In other words, consider a tissue subjected to uniform boundary conditions (specified deformation) and populated by cells that all behave in exactly the same way. This greatly simplifies the coupling in terms of

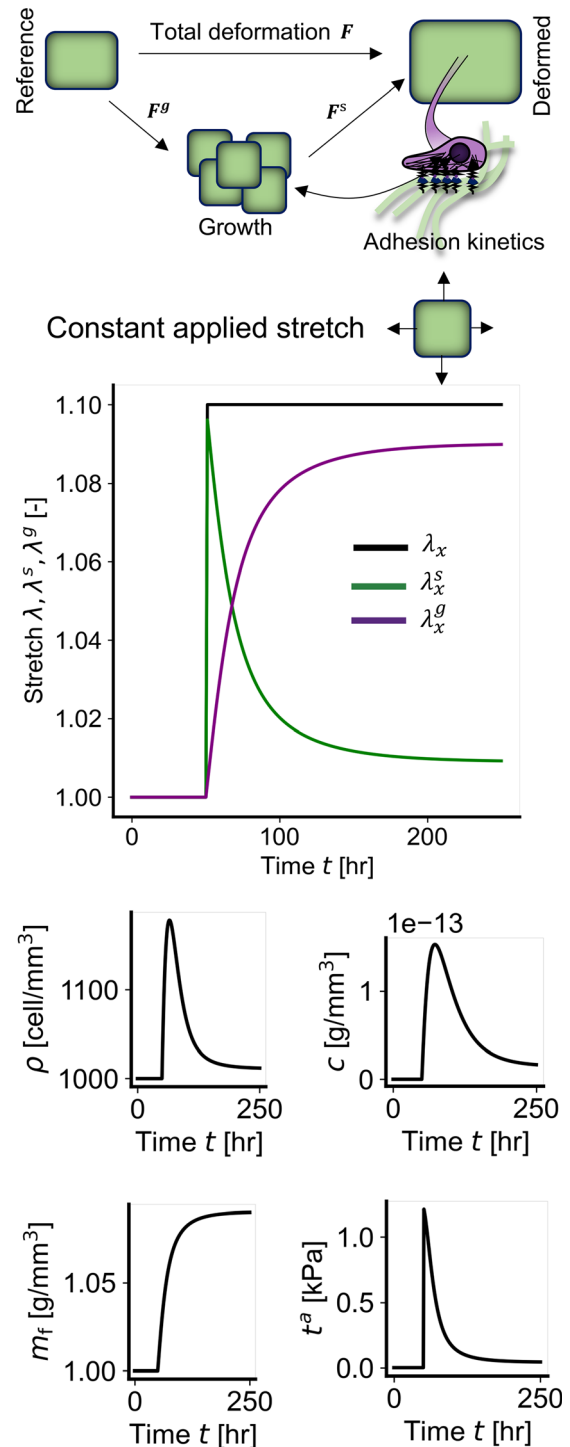


FIG. 5. Example: A fully coupled model of tissue growth. Following the tissue growth example, the total deformation of the tissue is split into growth and stress-inducing contributions. However, growth is now modeled based on collagen deposition m_f by cells ρ in response to $\text{TGF}\beta$ c and stretch. The link to stretch is based on the adhesion kinetics model described above, in particular the stress in the cell t^a . When subjected to a uniform applied deformation, tissue grows over time.

numerical simulation; yet, it still provides a window into the coupled behavior that can be observed when taking knowledge from different scales into account. In Fig. 5, the growth of the tissue is ultimately dictated by collagen deposition,

$$\dot{\lambda}^g = \dot{m}_f / \varrho_f, \quad (27)$$

where $\dot{m}_f$ denotes collagen mass production and ϱ_f is the density of collagen. Deposition of collagen is due to cells, denoted ρ . The process is further regulated by TGF β , denoted c , and a mechanobiology coupling, which, in this case, is taken to be the active stress magnitude t^a . The production of collagen is based on our previous work,⁷⁵

$$\dot{m}_f = \left(p_f + p_{f,c} \frac{c}{K_{f,c} + c} + p_{f,t^a} \right) \frac{\rho}{K_{f,\rho} + m_f} - (d_f + d_{f,\rho} \rho c) m_f, \quad (28)$$

with parameters as reported in Ref. 75. The cell and cytokine variables change in a similar manner. For the cell,

$$\dot{\rho} = \left(p_\rho + \frac{p_{\rho,c} c}{c + K_{\rho,c}} + p_{\rho,t^a} \right) \left(1 - \frac{\rho}{K_{\rho,\rho}} \right) \rho - d_\rho \rho + D_{\rho,\rho} (\rho_{\text{phys}} - \rho), \quad (29)$$

and for the cytokine,

$$\dot{c} = (p_{c,c} c + p_{c,t^a}) \frac{\rho}{K_{c,c} + c} - d_c c + D_{c,c} (c_{\text{phys}} - c). \quad (30)$$

Note that even though Eqs. (28)–(30) were originally developed for wound healing modeling⁷⁵ and follow a rich history of coupled wound healing model development,^{80,81,147} they can naturally capture the growth of tissues in response to stretch. One key idea is to couple the dynamic equations for cell and cytokine densities to the mechanical state of the wound through a mechanobiological variable, much in the spirit of the one introduced in Eq. (19).⁸² Here, however, the mechanobiology coupling is through the stress in the cell t^a , which is a product of solving the adhesion model illustrated in Fig. 4. The other key coupling is to link the collagen production by cells to the growth of the fibers, see Eq. (27). Together, this last example showcases the type of multiscale description needed to interrogate tissue growth and remodeling with a more detailed account of the mechanobiology processes at the cell level. Solving the coupled equations, it can be seen that the applied deformation stays constant over time, but the elastic deformation λ^s decays over time as growth, λ^g , increases. Growth of collagen fibers is facilitated by a dynamic response of cell density ρ , TGF β concentration c , collagen mass fraction m_f , and cell contractility t^a .

VI. OPEN PROBLEMS AND OPPORTUNITIES

The mesoscale models covered in Sec. V are able to bridge single cell biophysics to the nonlinear mechanics of the tissue. Yet, representative volume elements (RVE) of the mesoscale are still not readily usable in full field finite element simulations of tissues at the macroscale, where purely phenomenological approaches remain the default option.¹⁴⁸ The mesoscale models also might require simplifying assumptions for the single-cell biophysics models in order to be computationally manageable. A major roadblock in multiscale coupling is the complexity of intra-cellular biophysics regulating gene expression

and cell phenotype.^{129,149} Thus, despite our current understanding of cell mechanobiology at the microscale, and of the adaptation of tissues through growth and remodeling at the macroscale, fully coupled models spanning all scales remain an open challenge.

In recent years, machine learning (ML) and artificial intelligence (AI) have permeated into all fields of engineering and science. We argue that physics-informed ML methods can be used to couple models of cell mechanobiology at the microscale to models of ECM and tissue mechanics at the macroscale. The obvious route is to use ML for the acceleration of computationally intensive models. Physics-informed surrogate models, such as artificial neural networks (ANN) and Gaussian processes (GP), can be used to replace the computationally intensive models, essentially extracting input–output maps, which capture the underlying physics without the need for the computationally expensive physics solvers. This strategy has proven successful in several applications. For instance, we have shown how model order reduction and GPs can be used to replace computationally expensive finite element simulations to enable optimization of reconstructive surgery procedures under uncertainty.¹⁵⁰ We have also shown how ANNs can learn constitutive models of the mechanical response of biopolymer gels.¹⁹ Thus, ML and AI tools can speed up simulations by orders of magnitude while retaining accuracy, making fully coupled multiscale models of mechanobiology a reachable target in the near future. On the other hand, ML and AI are not magic bullets. Some of the possible pitfalls and challenges of trying to use black-box models in biomedical engineering and multiscale modeling have been outlined in a recent perspective article.¹⁹ One problem is to guarantee that the surrogate model is evaluated in regions over which there is sufficient confidence in the prediction. Alternatively, creating ML and AI models capable of transfer learning and extrapolation beyond the observed data while satisfying some essential physics constraints are needed. A second major challenge is how to deal with uncertainty. At the macroscale, the majority of models tend to assume deterministic behavior. Yet, even at the macroscale this is too simplistic. We have shown the role of uncertain material properties in biomedical applications such as skin growth in tissue expansion.¹⁵¹ Going down the spatial scales, reality becomes even more uncertain. Not only are the parameters specifying the models uncertain, but the process itself is stochastic, e.g., the adhesion kinetics at the single integrin level, or the intra-cellular events of mechanotransduction.¹⁵² Other challenges to integrate ML and AI into multiscale modeling frameworks are how to deal with sparsity of data, multi-fidelity and multi-modality data, and lack of interpretability of many ML, AI models.

In addition to overcoming the computational challenges of multiscale coupling, ML and AI can be particularly powerful to learn representations of the processes linking the mechanical signals at the cell membrane to the gene expression of single cells bypassing the complex intra-cellular signaling cascade dynamics.^{153,154} For example, in the very recent work by Bonnevill *et al.*,¹⁵⁵ the authors use artificial neural networks to predict the mechanobiological state of individual cells in terms of YAP/TAZ nuclear translocation based on biochemical inputs as well as cell and nuclear morphology. This is contrast with mechanistic approaches to model YAP/TAZ dynamics.¹¹⁸ Similar to the challenges outlined above for the physics-based ML frameworks, ML models that attempt to capture the biological processes inside the cell have to be posed in a Bayesian way in order to deal with the inherent variability and stochasticity of these processes.

Multiscale integration of current models at the nano-, micro-, and macroscales is needed. Yet, this does not mean that there are no outstanding challenges when considering these separate scales. For instance, for the microscale models, we have emphasized the modeling cell–ECM adhesions and their downstream signaling pathways, e.g., Ref. 121. Yet, these models ignore some important energetic considerations that can constrain the possible cellular response. The downstream effects of mechanotransduction pathways include remodeling of the cytoskeleton, proliferation, generation of active stress, etc., all of which depend on cell metabolism.^{156,157} Cell migration in different environments depends on the energy efficiency of different migration mechanisms.¹⁵⁸ The vertex models for epithelial tissues described in Secs. I–VI are based on energetic potentials. Thus, this kind of model could be extended to capture the explicit coupling between metabolism and mechanotransduction. Energy required for cellular activity could also be included as additional constraints in the ODE-based models of mechanotransduction such as Ref. 121.

At the tissue level, an active area of research is to build higher fidelity models that can account for detailed geometry, accurate boundary conditions, and tissue heterogeneities. For instance, recent work on tendon biomechanics has shown the importance of heterogeneous mechanical properties to correctly determine the *in vivo* state of stress of these tissues.¹⁵⁹ Work along similar lines of investigation has been done recently to determine the spatially varying properties of aortic tissues and the lamina cribrosa.^{160,161} Modeling interstitial fluid is commonplace in computational models of bone but has not received a similar level of attention in soft tissue.⁹¹

VII. CONCLUSION

In this review, a wide range of models spanning was covered, from a single integrin binding to the substrate to a tissue growing in response to stretch. The thread throughout has been the need to create fully coupled models of mechanobiology that can span all scales. These models are essential for a deeper understanding of how tissues form during development, how they physiologically adapt to mechanical cues, and how they maladapt in disease. We hope that this review will bring together scientists from different sub-fields and inspire them to tackle the outstanding challenges in multiscale modeling of mechanobiology.

SUPPLEMENTARY MATERIAL

See the supplementary material for the code to generate the figures in this article, which are available in the public repository <https://github.com/abuganza/MultiscaleMechanobiology>.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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