

Theory of Multiscale Epithelial Mechanics under Stretch: From Active Gels to Vertex Models

Adam Ouzeri^{1,*}, Sohan Kale^{1,†}, Nimesh Chahare^{2,‡}, Alejandro Torres-Sanchez^{1,2,§}, Daniel Santos-Olivan^{1,§},
Xavier Trepap^{2,3,4,||} and Marino Arroyo^{1,2,5,¶}

¹*Universitat Politècnica de Catalunya-BarcelonaTech, Barcelona, Spain*

²*Institute for Bioengineering of Catalonia (IBEC), The Barcelona Institute of Science and Technology, Barcelona, Spain*

³*Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain*

⁴*Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Barcelona, Spain*

⁵*Centre Internacional de Mètodes Numèrics en Enginyeria (CIMNE), Barcelona, Spain*



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Epithelial monolayers perform a variety of mechanical functions, which include maintaining a cohesive barrier or developing three-dimensional (3D) shapes, while undergoing stretches over a wide range of magnitudes and loading rates. To perform these functions, they rely on a hierarchical organization, which spans molecules, cytoskeletal networks, adhesion complexes, and junctional networks up to the tissue scale. While the molecular understanding and ability to manipulate cytoskeletal components within cells is rapidly increasing, how these components integrate to control tissue mechanics is far less understood, partly due to the disconnect between theoretical models of subcellular dynamics and those at a tissue scale. To fill this gap, here we propose a formalism bridging active-gel models of the actomyosin cortex and 3D vertex-like models at a tissue scale. We focus on relatively short timescales or jammed tissues, such that tissue deformation is controlled by cellular deformations rather than by topological transitions of the junctional network. We show that this unified framework recapitulates a number of seemingly disconnected epithelial time-dependent phenomenologies, including stress relaxation following stretch-unstretch maneuvers, active flattening after buckling, or nonreciprocal and nonaffine pulsatile contractions. We further analyze tissue dynamics probed by a novel experimental setup operating in a pressure-controlled ensemble. Overall, the proposed framework systematically connects subcellular cortical dynamics and tissue mechanics and ties a variety of epithelial phenomenologies to a common subcellular origin.

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I. INTRODUCTION

Many of the functions of epithelial monolayers are mechanical in nature. These tissues need to maintain barrier integrity during stretch, which occurs over a wide range of timescales and magnitudes during physiology and development. For instance, alveoli in the lungs undergo stretch cycles of more than 10% in areal strain at breathing frequency [1]. During blastocyst hatching in the early development of mammals, the trophectoderm can increase its area by several fold within a few hours, largely due to cellular stretch [2]. To

avoid excessive tension upon stretch, which may compromise cell-cell junctions and lead to mechanical failure, epithelial monolayers resort to sub- and supracellular tension buffering mechanisms at various timescales [3–6]. Tissue tension is required for tissue-scale pulsatile contractions during dorsal closure in *Drosophila*, when cells change their apical area by over 60% within a few minutes [7]. Besides stretching, epithelial monolayers undergo in-plane compression caused by externally applied or actively generated lateral confinement, which may lead to out-of-plane buckling and epithelial morphogenesis [8,9]. Tissue shaping in three dimensions (3D) can also be the result of apico-basal tensional asymmetries [10,11].

Despite significant progress [12], the quantitative characterization of the mechanics of epithelial sheets *in vivo* remains very challenging, and only a few *in vitro* techniques have been developed to measure the mechanical response of cell monolayers to stretch or compression. Free-standing cell monolayers have been tested in uniaxial creep or stress relaxation by suspending them between rods [13,14]. Tissue tension has also been measured using traction force microscopy (TFM) during stretch-unstretch maneuvers in cell monolayers adhered to deformable substrates [15]. Finally, tissue tension has been mapped using free-standing and pressurized epithelial sheets of controlled shape (epithelial domes), reaching areal strains of up to 300% [4,16]. These tests have identified a wealth of epithelial time-dependent phenomenologies, including reinforcement [15] and varying

*Present address: Sorbonne Université, CNRS, IBPS, Department of Computational, Quantitative and Synthetic Biology (CQSB), Paris, France.

†Present address: Department of Mechanical Engineering, Virginia Tech, Blacksburg, Virginia, USA.

‡Present address: Columbia University, New York, USA.

§Present address: European Molecular Biology Laboratory, Barcelona, Spain.

||Contact author: xtrepap@ibecbarcelona.eu

¶Contact author: marino.arroyo@upc.edu

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resting-length elasticity [3] under stretch, fluidization [15], and transient buckling [17] under compression, fluid or solid rheology under creep [13], tissue curling [18], and active superelasticity [4]. These approaches enable the mechanical characterization of a living tissue while performing live imaging of structural proteins as well as biochemical perturbations, and hence they provide an experimental method to connect subcellular dynamics and tissue mechanics. Focusing on timescales shorter than those required for topological transitions of the junctional network such as T1 transitions [6], which depending on the jamming state of the system can range from tens of minutes to hours, these studies have shown that many of these tissue behaviors are controlled by the dynamics of the actomyosin cortex [3,4], although at extreme deformations the intermediate filament cytoskeleton becomes mechanically active and plays an important role [4,19].

In contrast with these experimental advances, conventional vertex models used to study epithelial sheets theoretically are rooted in the capillary theory of foams and implement dynamics through generic drag forces [20–25]. However, it is increasingly recognized that theoretical and computational frameworks for time-dependent epithelial mechanics should be grounded in the physics of cytoskeletal and adhesive complexes at the subcellular scale [26,27]. Such frameworks could help clarify how intracellular mechanisms determine the time-dependent mechanics of tissues. In recent years, several enhanced two-dimensional (2D) vertex models have linked the active remodeling of cell-cell junctions to emergent tissue behaviors [28], including tissue deformations that excite isogonal modes [29], ratcheting junctional dynamics under pulsatile optogenetic stimulation [30,31], and the interplay between junctional mechanosensitivity and extended T1 transitions [32–34]. In these studies, junctional dynamics follow the logic of active gel theory, and by mapping epithelial tissues onto 2D junctional networks, the models achieve high computational efficiency. However, this comes at the expense of losing the ability to describe the 3D shape of cells and tissues. Furthermore, the drastic geometric simplification obscures the direct connection between effective junctional models and the underlying cytoskeletal dynamics. At the opposite end of the spectrum, recent approaches represent epithelial tissues with high geometric fidelity as interacting cellular surfaces in 3D but rely on simplistic descriptions of cortical rheology [25,35,36].

As a first step toward systematically linking subcellular processes to tissue-level mechanics in 3D, we develop a theoretical and computational framework that upscales actomyosin cortical dynamics within cells to the epithelial scale, under the assumption that the junctional network topology remains fixed. Although T1 transitions are essential for developmental processes involving epithelial flows, junctional remodeling typically occurs on slower timescales than cytoskeletal dynamics [3,31,37]. Thus, assuming a frozen junctional topology is appropriate for certain systems and within suitable observation windows. To describe the out-of-equilibrium dynamics of the actomyosin cytoskeleton, we resort to active gel theories [38], modeling active force generation, remodeling of the transient network, and molecular turnover. These models have been used to understand how the actin cytoskeleton controls the mechanics of single cells

[39–42], and have the potential to incorporate the coupled dynamics of multiple species, including signaling molecules [43,44] and order parameters describing the network architecture [39,45–47]. Here, we put forth a vertex model for epithelial tissues, whose time-dependent mechanics result from the net effect of an ensemble of active gel surfaces enclosing cellular volumes. In a steady state, this active-gel vertex model (agVM) recovers classical 3D vertex models [8,11,22]. Out of equilibrium, however, it differs from conventional dynamical vertex models in that tissue mechanics now result from cytoskeletal dynamics.

To formulate this model, we take advantage of Onsager’s variational formalism of irreversible thermodynamics [48,49]. We show that this formalism provides a natural framework to couple the collection of active gel surfaces making up the tissue, and to coarse-grain the exact theory into a hierarchy of computational models of varying spatial fidelity. After presenting this theoretical and computational framework, we show how this approach recapitulates, within a single framework, all the time-dependent phenomenologies discussed in the second paragraph, including some in which tissue behavior does not parallel single-cell behavior due to non-affinity. Furthermore, we apply the proposed computational model to study a novel experimental approach implementing a pressure-controlled mechanical ensemble representative of pressurized epithelia. Finally, we demonstrate how our multiscale modeling approach is able to predict nonreciprocal pulsatile modes similar to those observed *in vivo*, suggesting a built-in mechanism in epithelial tissues supporting the control of tissue tension and locomotion.

II. THEORETICAL AND COMPUTATIONAL MODEL

We place ourselves in a regime in which tissue deformation is accommodated by changes in cellular shape rather than topological changes in the junctional network, and assume that tissue mechanics is controlled by the mechanics of cellular surfaces. The negative tension caused by adhesion molecules in cell-cell junctions contributes to the total tension of these surfaces [50]. Here, we do not explicitly model this effect, implicitly assuming that it can be subsumed in the active gel model. However, our formalism can easily accommodate more detailed models of adhesion dynamics [26,51,52]. We further assume that cells keep their volume fixed in agreement with previous measurements in epithelial cells under stretch [13], but models of cell volume regulation could be included [53,54]. As a result of these assumptions, our model for epithelial sheets can be summarized as an ensemble of active gel surfaces enclosing 3D regions of constant volume, Fig. 1(a).

To formulate this theoretical model, we introduce first a specific instance of active gel theory for curved cortical surfaces, capturing the short-term elasticity of the cortex, the relaxation of elastic stresses by network remodeling, active contractility, and turnover dynamics (Sec. II A). We then cast this model into Onsager’s variational formalism of irreversible thermodynamics, which characterizes the active gel dynamics by minimizing a scalar Rayleighian functional with respect to generalized velocities (Sec. II B). This formalism provides a framework to couple the ensemble of the active gel surfaces

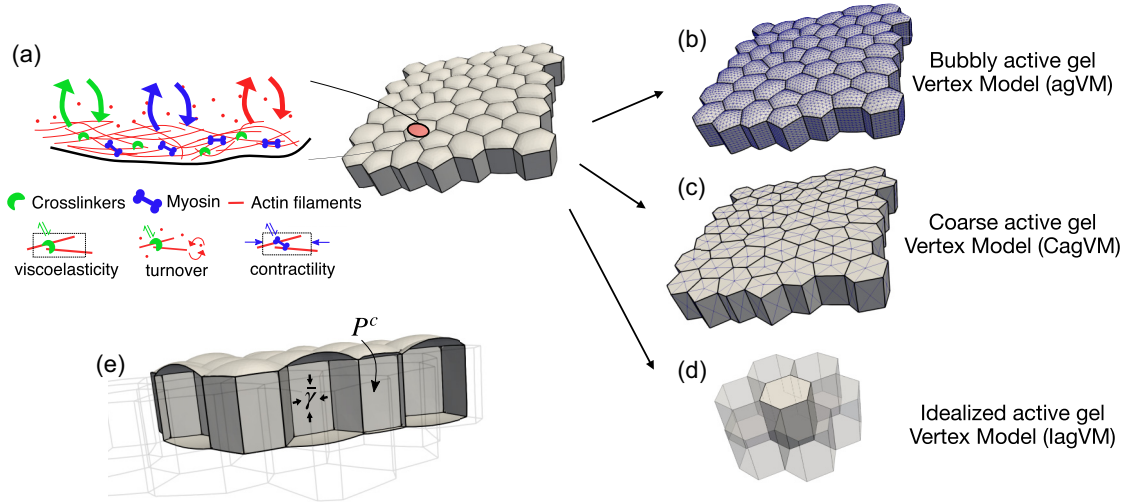


FIG. 1. The active gel Vertex Model (agVM). (a) The epithelial tissue is viewed as a collection of active gel surfaces enclosing cells of constant volume. The active gel describes cytoskeletal dynamics within each cell surface and accounts for turnover, short-term elasticity, viscoelastic remodeling, and active contractility. (b) This exact model is approximated using surface finite elements in the active gel Vertex Model (agVM). (c) The Coarse agVM (CagVM) considers a coarse mesh whose shape depends only on the vertices of polyhedral cells. (d) Further coarse-grained, the Idealized active gel vertex model (IagVM) assumes a crystalline tissue of identical cells undergoing affine in-plane deformation. (e) At steady state, agVM and CagVM are conventional vertex models with constant surface tensions on each apical, basal, and lateral face, and with cellular pressures enforcing constant cell volume constraints.

that make up a tissue, and also to discretize the exact theory into vertex models of varying resolution (Sec. II C).

A. Active gel model of the actin cortex

The actin cortex, a thin layer of contractile actomyosin gel adjacent to the plasma membrane [55–57], is composed of cross-linked actin filaments, and thus it can behave as an elastic network of semiflexible filaments. This behavior, however, is restricted to short timescales, between a few seconds and about a minute, because all components of the network undergo a continuous cycle of assembly and disassembly. Unbinding of a cross-linker or filament disassembly locally releases network elastic energy, which is dissipated in the frictional environment. In turn, the next cross-linker binds a partially relaxed network. Thus, at longer timescales, the cortex flows as a viscoelastic fluid [58]. Another key aspect of the cell cortex is the transduction of chemical energy into mechanical work through myosin motors or the out-of-equilibrium actin polymerization and binding of cross-linkers, effectively resulting in a contractile active tension dependent on network architecture [56].

Theoretical models of the actin cortex necessarily involve a drastic coarse-graining of the real system, in which over 100 proteins build and regulate the network [57] but still capture its fundamental physics at various scales. Below the cellular scale, microscopic models of individual filaments, cross-linkers, and motors can dissect the relation between network connectivity and contractility [59,60]. At cellular scales, active gel theories provide a mechanistic understanding of cell mechanics, morphogenesis, and motility using a continuum hydrodynamical description [39–42,61]. Here, we consider a relatively simple isotropic active gel model for an active viscoelastic medium undergoing turnover in the spirit of Ref. [62], but the upscaling framework presented here is

transparent to the specific choice of active gel model for the actin cortex and is thus compatible with further refinements of the theory.

We summarize next a specific active gel model for cortical surfaces used here, and refer to Appendix A for a detailed derivation and alternative active gel models. We view the cortex as a quasi-two-dimensional (quasi-2D) layer defining a surface. The shape of a cortical patch, i.e., a cellular face, is given by a time-dependent surface parametrization $\varphi : \Gamma_0 \times (0, T) \rightarrow \mathbb{R}^3$, which at each instant $t \in (0, T)$ maps an arbitrary planar reference configuration of the cortical surface Γ_0 to a deformed surface $\Gamma_t = \varphi(\Gamma_0, t)$. We describe Γ_0 and the ambient space with Cartesian coordinates, $\{X^1, X^2\}$ and $\{x^1, x^2, x^3\}$. The Lagrangian velocity field is given by $V(X, t) = \partial_t \varphi(X, t) = \dot{\varphi}(X, t)$, where here and elsewhere the dot denotes material time differentiation, that is, time differentiation at fixed X . The in-plane deformation of the cortical surface is characterized by the right Cauchy–Green deformation tensor $C_{IJ} = F_I^i F_J^i$, where $F_I^i = \partial \varphi^i / \partial X^I$ for $I = 1, 2$ and $i = 1, 2, 3$ is the deformation gradient. The Jacobian determinant of the transformation $J = \sqrt{\det C}$ measures local area changes.

We define on Γ_t a field of areal density of cortical material ρ . If the actomyosin gel has a constant volumetric density, then ρ is proportional to the cortex thickness. Likewise, we can define a field of nominal density per unit reference area in Γ_0 , denoted by $\varrho_0 = J\rho$. Mass balance of the cortical material undergoing turnover is expressed by

$$\dot{\rho} + \frac{J}{\rho} \dot{\rho} = r, \quad \text{or equivalently } \dot{\varrho}_0 = Jr, \quad (1)$$

where r is the turnover reaction rate. Noting that polymerization of cytosolic cortical materials with concentration c takes place at the plasma membrane, and that depolymerization takes place in the bulk of the cortical layer, we assume

that [4,39,41]

$$r = k_p c - k_d \rho, \quad (2)$$

where k_p and k_d are polymerization and depolymerization rates. At steady state, the left-hand side of Eq. (1) vanishes. Hence, assuming $c = c_0$ remains constant, at steady-state cortical density is $\bar{\rho} = k_p c_0 / k_d$.

At short times, the cortical network behaves like a nonlinearly elastic 2D material described by a hyperelastic energy density per unit mass $\Psi(\mathbf{C})$, which, if isotropic, should depend on two invariants of the tensor $\mathbf{C}$, i.e., $I_1 = \text{trace } \mathbf{C}$ and $I_3 = \det \mathbf{C}$ [63,64]. The calculation of these invariants implicitly involves the metric tensor of Γ_0 , which for our Cartesian coordinates is the identity. To represent network remodeling caused by the transient nature of cross-linkers and filaments, we introduce a material metric tensor, whose contravariant components are denoted by $G^{IJ}(\mathbf{X}, t)$, and view it as a dynamical variable describing the change in “resting strain” as the system undergoes dissipative internal relaxation [65–68]. We thus define the modified invariants relative to this material metric as

$$\tilde{I}_1 = C_{IJ} G^{IJ} \quad \text{and} \quad \tilde{I}_3 = \det C_{IJ} \det G^{IJ}. \quad (3)$$

This new dynamical field allows the system to reach an elastically relaxed state irrespective of the magnitude of the deformation. Indeed, when $G^{IJ} = C^{-1,IJ}$ we have $\tilde{I}_1 = 2$ and $\tilde{I}_3 = 1$, which naturally corresponds to the minimum of $\Psi(\mathbf{C}, \mathbf{G})$. This state can be physically interpreted as one in which the current configuration has become the reference configuration to measure elastic deformations. This approach can be interpreted as the multidimensional generalization of a one-dimensional (1D) spring element with variable resting length [3], which here is a second-order symmetric tensor field.

The total (2D) stress tensor of the cortical layer has an elastic component, that depends on the stored energy function per unit mass Ψ and that relaxes over time, and an active isotropic part, which we assume to be proportional to cortical density. The elastic part of the stress, expressed in the Lagrangian frame as the second Piola–Kirchhoff stress tensor, can be computed as $\mathbf{S}^e = 2\varrho_0 \partial \Psi / \partial \mathbf{C}$. We denote the Cauchy stress tensor of the cortical layer, the Eulerian counterpart of $\mathbf{S}^e$, with the symbol $\boldsymbol{\gamma}$ and reserve σ for the 2D stress (surface tension) of the tissue monolayer. Following conventional relations in continuum mechanics, the elastic Cauchy stress tensor is $\boldsymbol{\gamma}^e = (1/J) \mathbf{F} \mathbf{S}^e \mathbf{F}^T$. The total Cauchy stress tensor of the surface, accounting for active tension, then takes the form $\boldsymbol{\gamma} = \boldsymbol{\gamma}^e + \xi \rho \mathbf{g}$, where ξ is an activity parameter and $\mathbf{g}$ is the metric tensor of Γ_t . At steady state, $\boldsymbol{\gamma}^e$ fully relaxes to zero, and therefore $\boldsymbol{\gamma} = \bar{\gamma} \mathbf{g}$ where $\bar{\gamma} = \xi \bar{\rho}$ is the steady-state surface tension.

Force balance on the cortical surface in a low Reynold’s number regime can be expressed in terms of a tangential component

$$\nabla \cdot \boldsymbol{\gamma} + \mathbf{b} = \mathbf{0}, \quad (4)$$

where $\nabla \cdot$ is the surface divergence, and a normal component

$$\boldsymbol{\gamma} : \mathbf{k} + b_n = 0, \quad (5)$$

where $\mathbf{k}$ is the extrinsic curvature tensor of the surface. The tangential force density $\mathbf{b}$ and its normal counterpart b_n account for the tractions resulting from the interaction with the surrounding cytosolic or extracellular media.

The dissipative evolution law for the material metric is driven by the viscoelastic stress, tends to relax the stored elastic energy, and takes the form

$$\dot{G}^{IJ} = -\frac{\bar{\rho}}{2\varrho_0\eta} G^{IL} C_{LK} S^{e,KJ}, \quad (6)$$

where η is a viscosity parameter. This equation, along with mass balance and linear momentum balance in Eqs. (1), (4), and (5), govern the dynamics of shape and flow, given by $\dot{\varphi}$, of density ρ and of material metric $\mathbf{G}$ of the active viscoelastic gel. The resulting model corresponds to an active viscoelastic fluid, similar to classical ones [38] but with a hyperelastic response at short timescales and hence compatible with nonlinear models for networks of semiflexible filaments [69]. Furthermore, having a hyperelastic limit guarantees by construction thermodynamical consistency in the sense that elastic work is zero in closed deformation paths at fixed $\mathbf{G}$ and ρ , and hence elasticity does not contribute to power input or dissipation. This is not the case in general for models having hypoelastic limits [70]. For simplicity, here we take Ψ to be a 2D-compressible neo-Hookean hyperelastic model characterized by Lamé parameters λ and μ , which we consider as integrated through the cortex thickness, and hence have units of surface tension. In Appendix A, we develop an alternative model where active contractility drives the evolution of the material metric tensor $\mathbf{G}$ away from its thermodynamic equilibrium, imposing an active prestress rather than an additive active tension as in the model presented here. Figure 10 shows that both models lead to qualitatively similar results, albeit with noticeably different dynamics.

Several timescales emerge from this model, including the turnover time $\tau_{to} = 1/k_d$, the viscoelastic time $\tau_{ve} = \eta/\lambda$, and the viscoactive time $\tau_{va} = \eta/\bar{\gamma}$. The two last timescales are related through the dimensionless number $\bar{\lambda} = \lambda/\bar{\gamma}$, measuring the relative weight of cortical elastic modulus and active tension, which can therefore be interpreted as an elastocapillary number.

B. Variational characterization of the active gel dynamics

The active gel model introduced above admits a variational characterization. The state of an active gel surface is defined by the fields $\mathbf{X} = (\varphi, \varrho_0, \mathbf{G})$, all of which depend on position $\mathbf{X} \in \Gamma_0$ and time. The associated generalized velocities are $\mathbf{V} = (\dot{\varphi}, r, \dot{\mathbf{G}})$, where the reaction rate r is related to $\dot{\mathbf{X}}$ by Eq. (1). As developed in Appendix A, we can define the Rayleighian functional of the active gel surface as

$$\mathcal{R}(\mathbf{V}; \mathbf{X}) = \dot{\mathcal{F}}(\mathbf{V}; \mathbf{X}) + \mathcal{D}(\mathbf{V}; \mathbf{X}) + \mathcal{P}(\mathbf{V}; \mathbf{X}), \quad (7)$$

where $\mathcal{F}(\mathbf{X}) = \int_{\Gamma_0} \varrho_0 \Psi(\mathbf{C}, \mathbf{G}) dS_0$ is the free-energy functional accounting for the stored elastic energy in the gel, $\mathcal{D}(\mathbf{V}; \mathbf{X})$ is a dissipation functional accounting for the viscous remodeling of the material metric tensor and for the entropy production during turnover reactions, and $\mathcal{P}(\mathbf{V}; \mathbf{X})$ is an active power functional capturing the contractility of the gel and the out-of-equilibrium chemical potentials driving turnover.

Then, Onsager's variational formalism allows us to express the governing equations in Eqs. (2), (4), (5), and (6) simply as

$$V = \arg \min_W \mathcal{R}(W; X). \quad (8)$$

As compared with more general bracket and classical formalisms of irreversible thermodynamics [71–74], Onsager's approach is applicable in isothermal conditions to systems lacking underlying Poisson structures, which in the context of active gels is tantamount to low Re . These two assumptions are very reasonable in the context of cell and cytoskeletal mechanics, and consequently, this formalism is generally applicable to other active gel models, Appendix A and Refs. [47,75–77]. Thus, Onsager's formalism trades some generality for a variational structure, which is very useful to assemble complex models from different components and to coarse-grain such models, as discussed next.

C. Hierarchy of tissue models from subcellular active gels

With the variational characterization of the active gel dynamics, the formulation of a model for the epithelium, seen as an ensemble of active gel faces enclosing 3D regions of constant volume, becomes straightforward. Denoting the state variables of face f by X^f (its deformation map, density, and material metric fields), and the corresponding generalized velocities by V^f , we introduce the Rayleighian functional of this face, $\mathcal{R}^f(V^f; X^f)$, which may reflect heterogeneous material properties across the tissue. The tissue Rayleighian is then assembled as

$$\mathcal{R}^T(V^T; X^T) = \sum_{f=1}^{N_F} \mathcal{R}^f(V^f; X^f), \quad (9)$$

where N_F is the number of cellular surfaces in the tissue and where the tissue-wide state variables X^T and generalized velocities V^T collect those of each face, i.e., $X^T = (X^1, \dots, X^f, \dots, X^{N_F})$. The tissue dynamics, describing turnover dynamics, viscoelastic remodeling, and force balance, follow from the minimization of $\mathcal{R}^T(V^T; X^T)$ with respect to V^T subjected to constraints that keep cellular volumes constant and pairs of cellular surfaces meeting at an edge watertight (Appendix B).

With this formalism, the dynamical equations of the tissue are very easy to state, but remain very hard to solve exactly. Indeed, the minimization of $\mathcal{R}^T$ is performed over an infinite-dimensional space of functions representing the fields of velocity $\dot{\varphi}^f(X, t)$, reaction rate $r^f(X, t)$, and rate of material tensor $\dot{G}^f(X, t)$ over each face $f = 1, \dots, N_F$. However, the variational principle also provides a natural framework for numerical and analytical approximations by the direct application of the classical Rayleigh-Ritz method [47,75,76,78,79]. The idea is to seek approximate solutions by restricting the admissible functions to a finite-dimensional subspace and optimizing the functional within that subspace. For the tissue deformation φ^T , we consider a surface finite-element approximation based on a watertight triangulation of the cellular surfaces in the tissue. Because their spatial derivatives do not appear in the formulation, r^T , ϱ_0^T , and G^T can be approximated as triangle-wise constant fields over the triangulated surface. To reduce computational cost, and since we do

not aim at resolving spatial patterns of cytoskeletal dynamics within cellular surfaces, we further coarse-grain the approximation space for r^T , ϱ_0^T , and G^T to face-wise constant fields, while keeping a finer mesh to describe the curved geometry of cellular faces. We refer to this model as the active gel Vertex Model (agVM) in the remainder of the paper [Fig. 1(b)]. The agVM can be further coarse-grained to a degree in which each cell is a polyhedron whose configuration is given by the position of its vertices, Fig. 1(c), which we refer to as the coarse agVM, (CagVM). Finally, we can further coarse-grain the model by constraining the face deformations to conform to an affine (uniaxial or equibiaxial) planar deformation of a crystalline tissue made of identical polyhedral cells with hexagonal apical and basal faces [Fig. 1(d) and Appendix C]. We refer to this model as the idealized active gel vertex model (IagVM), which still accounts for turnover dynamics, viscoelastic remodeling dynamics, and tissue mechanics.

In summary, Onsager's variational formalism allows us to transparently formulate the dynamics of an ensemble to active gel surfaces enclosing constant cellular volumes. Furthermore, it enables the systematic coarse-graining of this model through the classical Rayleigh-Ritz approximation method, leading to a hierarchy of tissue models that range from high-fidelity finite element models to idealized models for crystalline tissues deforming affinely.

At steady state, our active gel model results in constant cortical densities, fully relaxed material metric tensors, and constant surface tensions at cell surfaces given by $\bar{\gamma} = \bar{\rho}\xi$, Appendix A (Sec. 7 a and 7 d), which are balanced by cellular pressures P^c keeping volume fixed [Fig. 1(e)]. Thus, at steady state, the agVM is a 3D vertex model with curved surfaces [11,25,80–82], sometimes called bubbly vertex models, whereas the CagVM results in a conventional 3D vertex model [22].

We allow for material parameters, and in particular cortical activity, to be different at apical, basal, and lateral faces, reflecting the effect of adhesions on surface tension [50] and possibly differences in cytoskeletal dynamics due to apico-basal polarization [18]. For this, we consider different apical, basal, and lateral activity parameters, ξ_a , ξ_b , and ξ_l . We define $\xi_{ab} = (\xi_a + \xi_b)/2$ and, in most calculations, unless otherwise stated, we assume that $\xi_a = \xi_b = \xi_{ab}$. We also define the corresponding steady-state active tensions $\bar{\gamma}_{ab} = \xi_{ab}\bar{\rho}$ and $\bar{\gamma}_l = \xi_l\bar{\rho}$.

D. Tension-strain relation of the tissue at steady state

As a background to understand the dynamical response of cell monolayers under stretch, we first consider the steady-state mechanical response of a tissue patch by tracking the effective surface tension of the tissue σ as a function of equibiaxial stretch. The tissue tension σ collects the net effect of all cellular surfaces on the mechanics of the tissue. It is the work-conjugate to the areal strain of the tissue, defined as $\varepsilon_A = (A - A_0)/A_0$, where A is the actual area of the tissue and A_0 is the area of the tissue in an arbitrary but fixed reference configuration. ε_A can be interpreted as a measure of the aspect ratio of cells relative to this reference.

In the idealized situation of a tissue with crystalline arrangement of identical prismatic cells with hexagonal apical

and basal surfaces, the relation between strain and tissue tension at steady state can be explicitly obtained as the following nonlinear relation [4]

$$\frac{\sigma}{\bar{\gamma}_{ab}} = 2 - \frac{\xi_l}{\xi_{ab}} \frac{k}{(1 + \varepsilon_A)^{3/2}}, \quad (10)$$

where k is a fixed dimensionless number, see Appendix C. Thus, even though at steady state all elastic stresses in the actin cortex have dissipated and hence the cortex behaves like an active fluid, the assembly of tense interfaces enclosing fixed volumes behaves like a nonlinear elastic solid. The first term accounts for the contribution of apical and basal tensions to tissue tension, is independent of strain, and determines the plateau at large areal strains. The second term in this equation captures the role of lateral surfaces on tissue mechanics, and depends on strain, i.e., on cell aspect ratio. Depending on the ratio ξ_l/ξ_{ab} , the tissue tension-strain relation has different shape with different tension-free aspect ratio [Fig. 2(a)]. In all cases, however, for sufficiently large lateral compression, i.e., for sufficiently columnar configurations, the net tissue tension becomes negative. This explicit equation for a crystalline tissue agrees very well with the response of the agVM and CagVM for a disordered tissue, from which we conclude that the details of tissue geometry are not important to predict this relation.

These results show that the maximum tissue tension at steady state in the agVM is $\sigma = 2\bar{\gamma}_{ab}$ and entirely due to tension in the actomyosin cortical surfaces. However, other structures can contribute to the mechanical response of cells, including other cytoskeletal fibers, the plasma membrane under tension, or the nucleus under compression. Imaging, laser ablations, and biochemical perturbations support the mechanical role of intermediate filaments (IF) under severe stretch [4,13,19]. To account for this effect contributing to the restiffening of stretched cells, we noted the much slower turnover time of IFs as compared with actin, as well as computational work pointing at the existence of an activation strain for IF engagement [83]. Accordingly, we introduce their effect as an elastic potential activated beyond a threshold strain, Appendix D, although the strain-stiffening response of IFs is itself time-dependent [19]. The strain-stiffening regime following the tensional plateau induced by this modeling of IFs is illustrated in Fig. 2(b). In the studies presented next, we introduce this effect when required as explicitly mentioned.

III. RESULTS

A. Tissue dynamics under stretch

1. Equibiaxial stress relaxation

To understand how the tissue dynamically reaches the mechanical steady state shown in Fig. 2(a) after a mechanical perturbation, we first turned to the experiments performed in Ref. [15] probing tissue rheology under stretch. In these experiments, Madin Darby Canine Kidney (MDCK) cells forming epithelial islands were seeded on a deformable substrate and subjected to equibiaxial stretch-unstretch maneuvers while tissue tension was quantified using monolayer stress microscopy. These experiments revealed that cell-substrate tractions were transmitted at the periphery of the

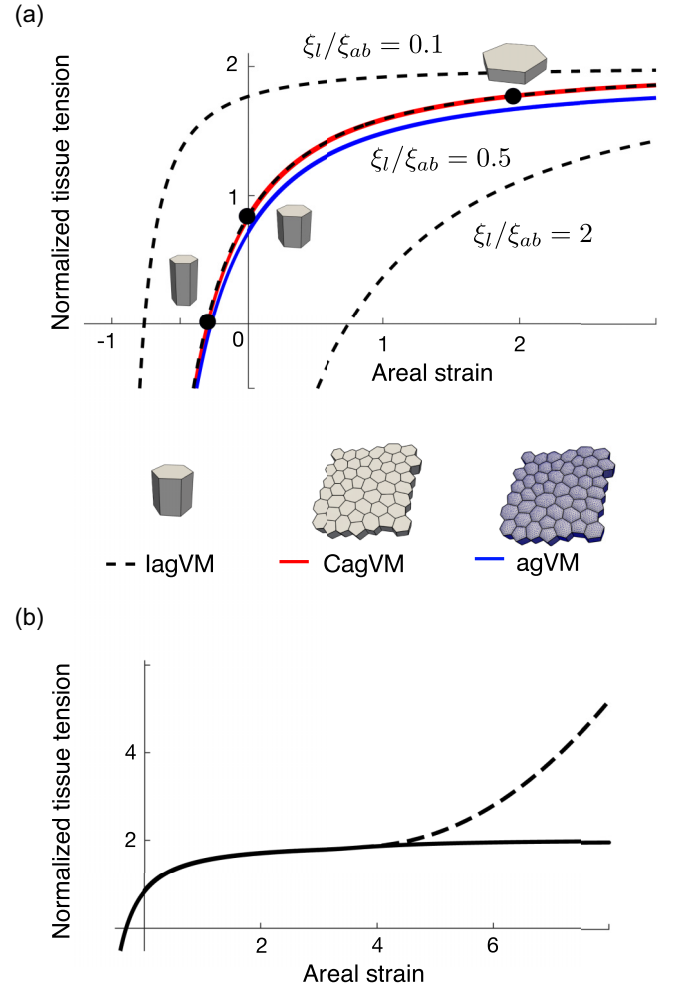


FIG. 2. Tension-strain relation at steady state. (a) Normalized tissue tension, $\sigma/\bar{\gamma}_{ab}$ as a function of areal strain predicted by the agVM, CagVM, and lagVM, for various ratios of lateral to apico-basal surface tensions. The reference configuration of the tissue is chosen such that cells are cuboidal with a height twice the average apico-basal edge length. (b) Illustration of the relation between tissue tension and strain when the strain-stiffening elastic potential modeling the engagement of intermediate filaments above a threshold is considered (dashed line). See Table I for material parameters.

cell island and that tension was nearly uniform in the central part of the tissue. Upon application of about 10% areal strain, tissue tension increased from a baseline tension to more than twice, and then partially relaxed over a few minutes to a value slightly higher than the baseline tension. Upon stretch cessation, tension decreased and then recovered the baseline over a few minutes [Fig. 3(b)].

To test whether our model is able to recapitulate this phenomenology, we focused on the central part of the island and subjected the CagVM and agVM models to equibiaxial stretch mimicking the experiments. We further considered a simplified lagVM model considering identical hexagonal cells with planar cortical patches [Fig. 3(a)]. This model results in five coupled ordinary differential-algebraic equations for the dynamics of turnover, viscoelastic relaxation, and strain, see Appendix C, and therefore is extremely efficient

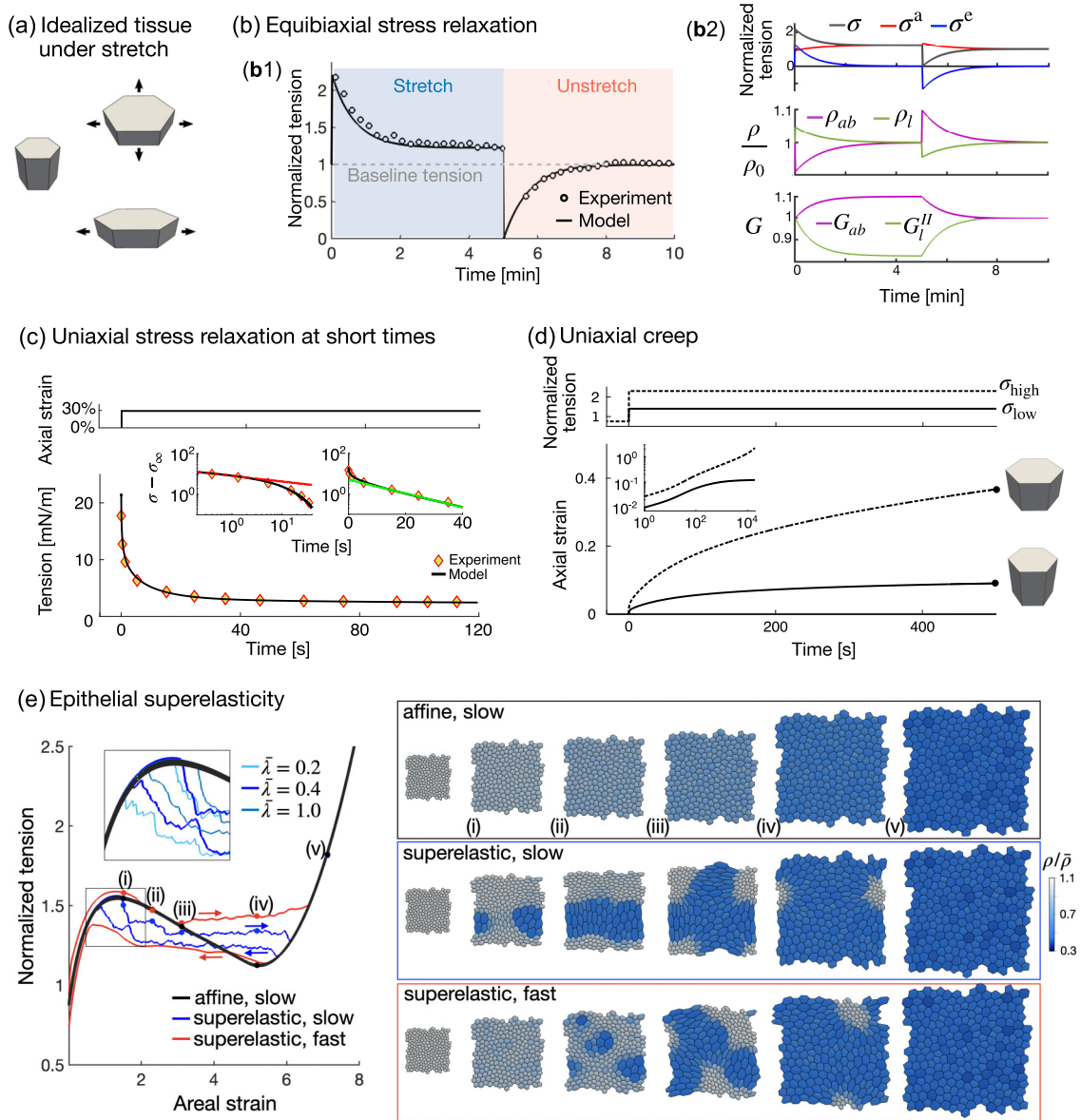


FIG. 3. Tissue dynamics under stretch. (a) Illustration of equibiaxial and uniaxial deformations of a cell in an idealized tissue (IagVM). (b1) Time evolution of tissue tension normalized by baseline tension during an equibiaxial stretch-unstretch maneuver with 10% areal strain amplitude, in quantitative agreement with the experiments in Ref. [15]. (b2) Top: dynamics of tissue tension (total, active, and elastic). Middle: dynamics of apico-basal (ab) and lateral (l) cortical densities. Bottom: dynamics of the apico-basal and lateral viscoelastic reference metric. G_{ab} is isotropic, for G_l we plot the component perpendicular to the tissue. (c) Stress relaxation following the sudden application of 30% uniaxial stretch in a model including the cortical active gel and a cytosolic power-law element, along with the data points from Ref. [3]. The log-log and semilog insets highlight the initial power-law relaxation with exponent $\alpha = -0.28$ (dashed red line is a power-law fit), followed by an exponential relaxation with timescale $\tau = 12.7 \text{ s} \approx \tau_{ve}$ (dashed green line is an exponential fit). (d) Creep dynamics for two magnitudes of applied tension, showing a solid-to-fluid transition when the applied tension exceeds $2\bar{\gamma}_{ab}$. Tension is normalized by $\bar{\gamma}_{ab}$. (e) Epithelial superelasticity, induced by softening due to exhaustion of cytoskeletal material and restiffening due to intermediate filaments, simulated with the agVM during a stretch-unstretch cycle, see also Movie 2 [84]. Fast ($\dot{\epsilon}\tau_{ve} = 2.8 \times 10^{-2}$) and slow ($\dot{\epsilon}\tau_{ve} = 2.8 \times 10^{-4}$) agVM simulations are compared with the simulation of a tissue deforming quasistatically and constrained to remain affine. The inset in the tension-strain plot shows the influence of the elastocapillary parameter $\bar{\lambda} = \lambda/\gamma_{ab}$ for slow agVM simulations (the reference value in the rest of the figure is $\bar{\lambda} = 0.4$). See Tables I and II for material parameters.

computationally. According to this model, tissue tension can be additively decomposed into active and elastic components, $\sigma = \sigma^a + \sigma^e$, with σ^e relaxing over time viscoelastically. For the CagVM and agVM models, tissue tension can be obtained using standard techniques of computational homogenization [85].

All three models provide indistinguishable results [Fig. 9(a)], and very accurately reproduce the experimental dynamics of tissue tension [Fig. 3(b1)]. According to our model, the phenomenologies qualified in Ref. [15] as “reinforcement” after stretch and “fluidization” after unstretch result from cytoskeletal dynamics within cells

involving changes in cortical density due to turnover and in the reference metric due to viscoelastic relaxation [Fig. 3(b2) and Movie 1 [84]]. In our simulations, fast stretch increases (decreases) the surface area of apico-basal (lateral) cell surfaces, instantaneously diluting (concentrating) the cortex before turnover reestablishes $\bar{\rho}$ over the timescale τ_{to} of about two minutes. This stretch-induced dilution and concentration of cortical material affects active tensions at cellular surfaces, resulting in a small decrease of the active component of tissue tension σ^a [Fig. 3(b2)]. The changes in shape of apical, basal, and lateral surfaces following fast stretch lead to elastic cortical tensions, which result in a sudden increase of the elastic component of tissue tension σ^e , which relaxes over a timescale of τ_{ve} as the viscoelastic metric tensors adapt to the current strain. These dynamics are reversed upon unstretch.

To select the material parameters, we chose an initial state with a cell aspect ratio comparable to the experiments ($h_0/s_0 = 2$ with h_0 the height and s_0 the length of an apical cell-cell contact) and selected the steady-state ratio of lateral and apico-basal surface tension $\bar{\gamma}_l/\bar{\gamma}_{ab} = 0.55$ to fit the steady-state tension after stretch application. Turning to dynamics, as discussed in the previous paragraph, the active and elastic components of tissue tension have opposite trends upon stretch-unstretch. Since tissue tension increases (decreases) upon stretch (unstretch), we conclude that changes in elastic tension dominate tension dynamics, and, consequently, reinforcement and fluidization phenomenologies of cell monolayers [15] result mostly from short-term elastic cortical tensions and their viscoelastic relaxation. We fit the viscoelastic parameters $\bar{\lambda} = \lambda/\bar{\gamma}_{ab} = 0.4$ and $\tau_{ve} = \eta/\lambda = 45$ s to reproduce the tension relaxation dynamics, finding a remarkable agreement with the experiments [Fig. 3(b)], with parameters consistent with previous estimations based on single cells (Appendix E). Although the equations controlling $\sigma(t)$ are highly nonlinear, the active and the elastic components of stress after stretch and compression closely follow exponential relaxations controlled by τ_{to} and τ_{ve} , respectively [Appendix C and Fig. 9(b)]. Because viscoelastic relaxation dominates tension dynamics, tissue tension is well approximated by a single exponential relaxation typical of a standard linear solid.

2. Uniaxial stress relaxation and creep

The ability of the setup in Ref. [15] to probe the timescales of stress dynamics below 10 or 20 s is limited by the need to refocus to acquire images of bead positions for traction force microscopy after stretch perturbation. The dynamics of stress relaxation at faster timescales can be tracked with a different setup in which a free-standing cell monolayer is suspended between two rods, enabling application and measurement of stress and strain [13]. Experiments probing the shorter timescales have revealed a biphasic stress relaxation, with an initial ATP-independent power-law relaxation, previously identified in single cells [86], followed by an exponential relaxation [3,87]. As shown by the previous example, our agVM describes the second of these behaviors. To examine the generality of the present modeling approach, we incorporated the power-law rheology into the tissue model. The physical origin of the required broad spectrum of relaxation

mechanisms is not clear and may involve distributions of filament lengths or of cross-linker timescales. In the absence of precise information, we introduced a spring-pot power-law element associated with bulk cytosolic or cytoskeletal shear rate (Appendix F) and examined the response of the tissue under uniaxial stretch [Figs. 3(c) and 3(d)]. This power-law element depends on two additional parameters, a power-law exponent α and a parameter controlling the strength of this element C_α .

The model predicts a biphasic power-law–exponential behavior in a stress relaxation test [Fig. 3(c)], which allowed us to easily fit the active gel and power-law element material coefficients to experiments reported in Refs. [3,87]. By fitting our model to these experiments on free-standing MDCK monolayers, we found faster turnover and remodeling rates as compared with MDCK monolayers attached to a matrix, suggesting that attachment to the matrix may slow cytoskeletal dynamics.

We then wondered if the model is able to describe the creep response as probed on free-standing monolayers under uniaxial stress. One striking experimental observation is that, while for low tensions MDCK monolayers behave like viscoelastic solids reaching a steady-state strain, for high tensions they flow like complex power-law fluids, at least within a range of deformations [13]. Our modeling framework provides a simple mechanism for this solid-fluid transition, since at steady state it predicts a maximum tissue tension [Fig. 2(a)]. Hence, if applied tension is above this threshold, the system cannot reach steady state and flows, at least before intermediate filaments become loaded. To test this idea computationally, we considered step tension increases above and below this threshold [Fig. 3(d)], recovering the solid-like response at low tensions and the fluid-like power-law behavior when applied tension exceeds $2\bar{\gamma}_{ab}$ (inset).

3. Epithelial superelasticity

We attribute the agreement between the IagVM, the agVM, and the CagVM in the situations examined so far to the affinity of deformations, according to which individual cells experience nearly the same deformation as the overall tissue. Nonaffinity is generally expected when the material is highly heterogeneous or contains unstable elements, which can result in the localization of deformation. Cell monolayers under stretch have been reported to develop strong nonaffinity during epithelial superelasticity [4], as a result of stretch-induced cortical dilution and mechanical softening, followed by restiffening due to intermediate filaments. To account for the limited amount of cytoskeletal material responsible for stretch-induced softening, we fixed the total mass of actomyosin in each cell, computed as the integral of ρ over all cellular surfaces plus the cell volume times the cytosolic concentration c , Eq. (1), see Appendix C4. To account for restiffening by intermediate filaments at very large stretches, we introduced an elastic potential that activates when areal strain becomes larger than a threshold, as described in Appendix D and Fig. 2(b). We performed simulations with the agVM, where a periodic tissue was stretched and unstretched at slow and fast loading rates, and compared these simulations with slow simulations where the tissue was constrained

to remain affine [Fig. 2(e) and Movie 2 [84]]. The affine simulations exhibited a nonmonotonic tension-strain relation reflecting the softening-stiffening behavior of individual cells. As previously shown with a much simpler model [4], the truly multicellular simulations exhibit a strong heterogeneity of cellular deformations as cells progressively transit between a low-strain and a high-strain state, resulting in a tension-strain relation for the tissue with a long plateau, reminiscent of the Maxwell construction during a phase change. Our simulations show that increased strain rate results in delayed emergence of the superelastic behavior and a larger hysteresis upon unloading. We interpret that cortical viscosity delays the switching of cells exceeding the unstable strain.

We observed that even in the slowest simulations, the system requires a higher tension than that predicted by the Maxwell construction to develop the superelastic behavior. A close look at our simulations showed that the system transitions collectively by switching a group of neighboring cells into the high-strain phase, which then grows largely by the propagation of the boundary of the high-strain region [Fig. 2(e) and Movie 2 [84]]. We can therefore understand the process in terms of nucleation and growth of the high-strain phase. Consistent with this view, faster loading results in multiple nucleation regions. This physical picture suggests that there exists an effective interfacial energy between the low- and the high-strain phases. We hypothesized that this interfacial energy should be related to the cortical elasticity, which couples nonlocally the deformation of neighboring cells. Accordingly, we found that lower (higher) normalized elastic modulus $\bar{\lambda}$ accelerates (delays) the transition and results in a narrower (broader) interface, Movie 2 [84]. Taken together, these results illustrate with epithelial superelasticity that non-affinity demands truly multicellular models and suggest that the development of the superelastic transition proceeds by first nucleating domains in the high-strain phase, and by then propagating the interface, whose width and effective energy depend on $\bar{\lambda}$.

In summary, we have shown that seemingly disparate phenomenologies in epithelial tissues, including reinforcement and fluidization under stretch or compression or superelasticity, can be explained by a theoretical model where tissue mechanics emerges from the behavior of an ensemble of active gel surfaces modeling subcellular cytoskeletal dynamics. Furthermore, if the tissue remains affine and isotropic and deformations nearly uniform, tissue rheology can be described with a computationally efficient model for an idealized tissue of identical prismatic cells.

B. Dynamics of epithelial domes under controlled pressure

1. The pressure-controlled mechanical ensemble with the monolayer inflator (MOLI)

Assays based on controlled in-plane stretch, such as those examined in the previous section, enable mechanical testing of living tissues under the canonical ensembles of imposed stress or strain. However, cell monolayers often operate in a pressure-controlled ensemble, particularly during development [88,89]. Epithelial domes with controlled size and shape provide a natural *in vitro* system to study cell sheets under pressure [4,16]. However, in previous imple-

mentations, pressure was self-generated by the active and polarized pumping of osmolytes. This process is transiently and stochastically disrupted by leaks, leading to uncontrolled fluctuations of pressure. To address this issue, a new microfluidic device was developed [Figs. 4(a) and 4(b)]. This device, termed a monolayer Inflator (MOLI), was fabricated from polydimethylsiloxane (Sylgard PDMS kit, Dow Corning) as described in Ref. [90]. Briefly, the device consists of two channels, one for epithelial cell culture and the other for the application of hydrostatic pressure, separated by a porous membrane. The epithelial cell side of the porous membrane was micropatterned with fibronectin using a photopatterning technique (PRIMO, Alveole Lab), creating circular regions of 80 μm diameter with low adhesion. MDCK strain II cells expressing CIBN-GFP-CAAX were used to visualize the cell membrane and tissue geometry. Upon application of hydrostatic pressure, cells in these regions detached and formed domes. The luminal pressure was controlled using a pressure channel connected to a reservoir of cell culture medium mounted on a motorized linear translation stage (Zaber), whose software enabled precise control of the fluid reservoir's position, allowing for accurate and controlled pressure conditions throughout the experiments.

To understand the mechanics underlying pressure-controlled assays using MOLI, we modeled the entire dome using the agVM. To simulate the experiments, we considered an initially planar tissue, constrained the basal nodes of the model to remain in the $z = 0$ plane outside of a circular region corresponding to the region of low adhesion in the experiments, and applied a pressure difference between the basal and apical sides of the tissue [Fig. 4(c)]. We introduced the potential restraining excessive stretch discussed earlier [Fig. 2(b)].

For circular footprints, the domes remained largely spherical, allowing us to simplify the analysis of tissue mechanics. Assuming a spherical cap geometry, and denoting the radius of the footprint by a and the height of the dome by h , the radius of the spherical cap can be computed as $R = (a^2 + h^2)/(2h)$ and the surface area of this spherical cap as $A = \pi(h^2 + a^2)$. Consequently, the areal strain of the dome relative to the initially planar state with area $A_0 = \pi a^2$ is

$$\varepsilon_A = \frac{A - A_0}{A_0} = \frac{h^2}{a^2}. \quad (11)$$

Furthermore, given the applied pressure difference ΔP , we can compute the tissue tension using Laplace's law as

$$\sigma = \frac{\Delta P R}{2} = \frac{\Delta P(a^2 + h^2)}{4h}. \quad (12)$$

ΔP and a are experimental inputs and h is easily accessible at high temporal resolution by imaging a single line of pixels across the midsection of the structure using the line scanning mode of the Zeiss LSM880 confocal microscope. Thus, these equations show that MOLI provides a method to characterize tissue rheology in a controlled pressure ensemble.

We started by applying a step pressure of $\Delta P = 200$ Pa, kept it constant, and tracked strain and tension over time as shown in Figs. 4(d) and 4(e). We observed that these quantities reached close to the steady state within a few minutes, consistent with the timescales of cytoskeletal dynamics and

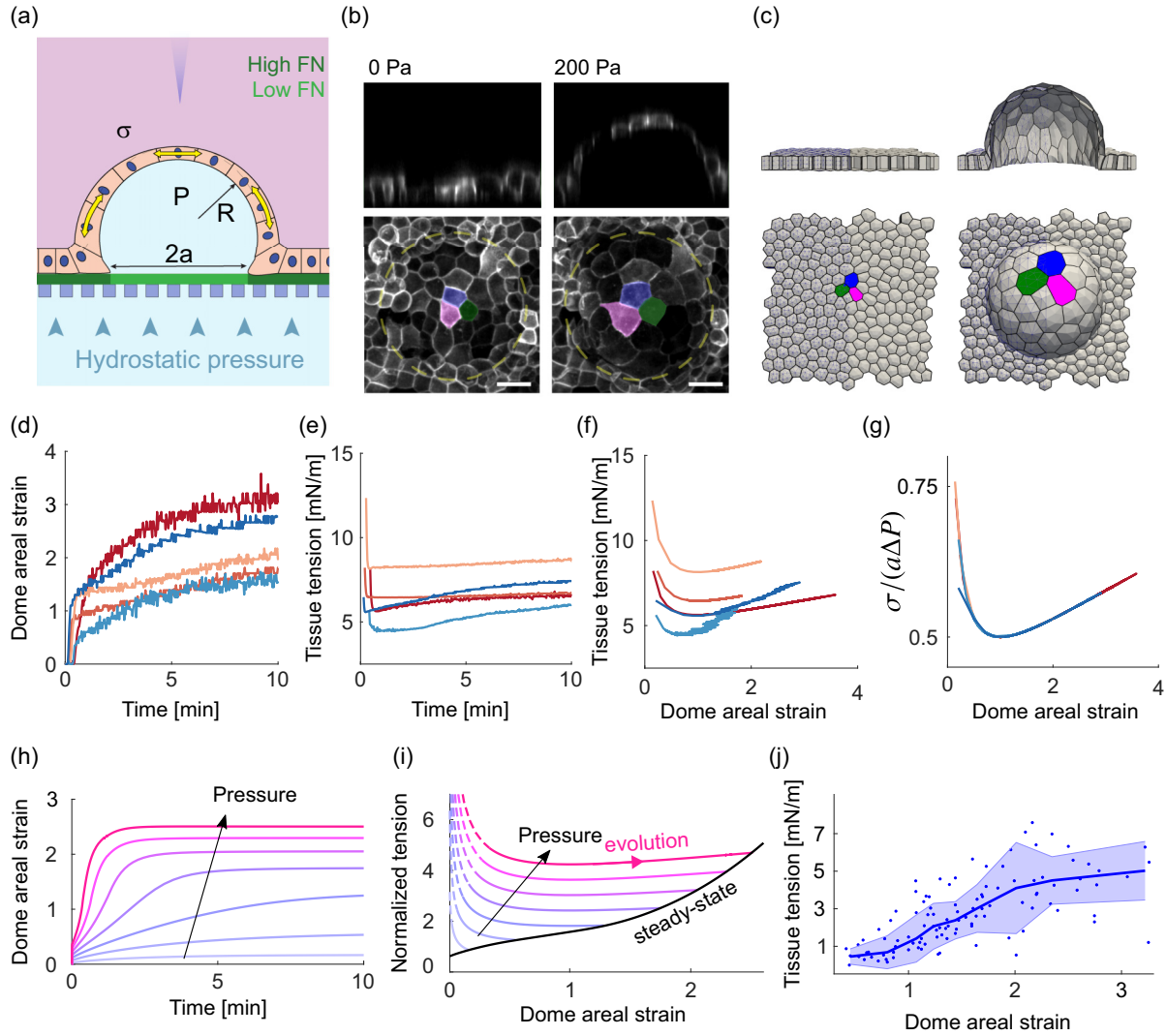


FIG. 4. Pressure-controlled mechanical ensemble with MOLI. (a) Illustration of the experimental setup. (b) Representative confocal sections of a dome at $\Delta P = 0$ and $\Delta P = 200$ Pa (scalebar: $20\ \mu\text{m}$) (c) agVM simulations of the experiment. Dynamic measurements of (d) strain and (e) tension following a step pressure application of $\Delta P = 200$ Pa for five representative domes with footprint radii a in the range 40 to $80\ \mu\text{m}$. (f) Tension-strain relation under these isobaric conditions, with data corresponding to panels (d) and (e), and (g) its normalization according to Eq. (13). (h) Strain as a function of time for different pressure levels, applied with a fast ramp and simulated with the agVM in panel (c), and (i) corresponding paths in tension-strain space, converging at long times to the steady-state constitutive relation of the tissue (shown in black). (j) Steady-state constitutive relation obtained experimentally by reducing pressure stepwise and waiting in each step for 5 minutes ($n = 12$, the line and shaded area represent the median and standard deviation, with 13 points in each bin). See Table III for material parameters.

as predicted computationally by the agVM [Fig. 4(h)]. During these experiments, we did not observe topological rearrangements of the network of cell-cell adhesions, divisions, or extrusions. To examine the constitutive response of the tissue, we plotted tension against areal strain [Fig. 4(f)]. Each dome exhibited a somewhat different response, but in all cases, tension was very high at low strains, reaching a minimum close to 100%, and then increasing again at large strains. This nonmonotonic response is very different to previously reported strain-tension relations for cell monolayers [4,13,16,19]. To interpret it, we can combine Eqs. (11) and (12) to obtain

$$\frac{\sigma}{a\Delta P} = \frac{1}{4} \left(\sqrt{\varepsilon_A} + \frac{1}{\sqrt{\varepsilon_A}} \right). \quad (13)$$

This equation shows that, given the footprint size a and the applied pressure ΔP , the dimensionless tension is proportional to $\sqrt{\varepsilon_A} + 1/\sqrt{\varepsilon_A}$ irrespective of the constitutive relation of the tissue, as this relation is a consequence of geometry and mechanical equilibrium alone. The nonmonotonic nature of this isobaric tension-strain curve, with a minimum at $\varepsilon_A = 1$, reflects the fact that the radius of curvature of the spherical cap with fixed footprint is minimum when the dome is a half sphere. We represented all the isobaric tension-strain curves according to Eq. (13), finding that they collapse onto a master relation reflecting the nature of our measurement [Fig. 4(g)]. This discussion shows that Eq. (13) alone does not provide any information about the mechanical response of the epithelial monolayer. Instead, it characterizes the locus of tension-strain

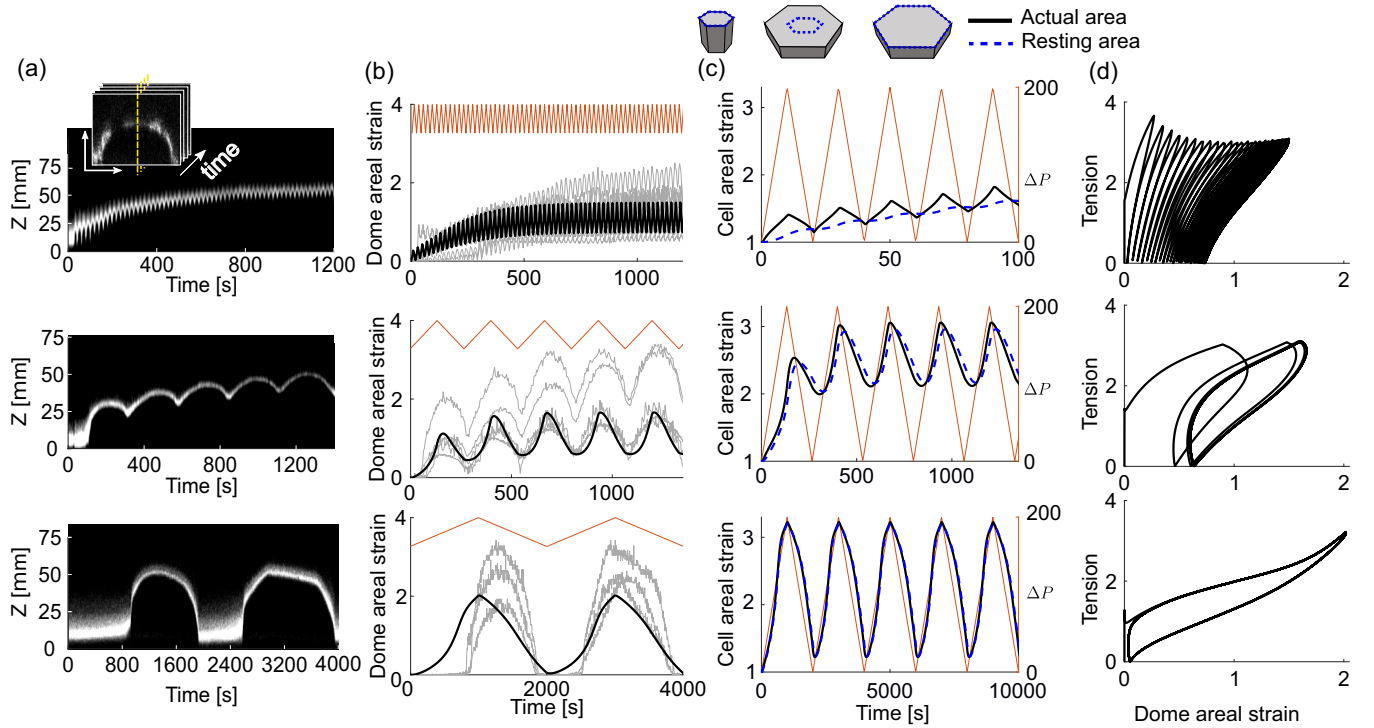


FIG. 5. Epithelial rheology under cyclic pressure. (a) Experimental kymographs of dome height for domes subjected to cyclic pressure between 0 and 200 Pa with periods of 20, 266, and 2000 s. (b) Experimentally measured areal strain as a function of time for selected domes (gray lines), and simulations with the agVM (black). The red curve indicates pressure as a function of time. (c) Dynamics of the actual area (black) and of the resting area (dashed blue) of the apical surface of a cell at the top of the dome during five cycles for the three different rates. The schematic at the top shows how, upon a sudden stretch, the resting area (computed in terms of the viscoelastic metric tensor as $A_{\text{resting}} = \int_{\Gamma_0} \sqrt{\det G} dS_0$) remains small and over time catches up with the actual area. (d) Dynamics of tissue tension in a dome as a function of dome areal strain according to the simulations, computed using Laplace's law as in the experiments. See Table IV for material parameters.

states of a spherical dome with fixed footprint abiding by the physical constraint of mechanical equilibrium. It also shows the nontrivial relation between strain and stress in the pressure-controlled mechanical ensemble of MOLI. Therefore, the curves in Figs. 4(d) and 4(e) cannot be interpreted as creep or stress-relaxation responses but rather as isobaric relaxation curves.

2. Quasistatic tension-strain relation

To connect our measurement with previous tension-strain data in quasistatic conditions [4,19], we reasoned that, for a given applied pressure and after a few minutes, the system should reach a steady state characterized by a pair $(\varepsilon_A^*, \sigma^*)_{\Delta P}$ lying on the putative steady-state constitutive relation of the tissue $\sigma^{\text{ss}}(\varepsilon_A)$. We should therefore be able to trace this constitutive relation by collecting the steady states as ΔP is swept. To test this approach, we first performed simulations, where, given the large strains attained experimentally, we accounted for IFs as previously described [Figs. 4(h) and 4(i)]. Experimentally, we chose to sweep ΔP by decreasing it, since a threshold pressure is required to initially delaminate the cell monolayer. We applied a pressure of $\Delta P = 200$ Pa, waited for 5 minutes, and then decreased the pressure in decrements of 20 Pa, allowing the system to relax in each step, until complete deflation. This process allowed us to collect the steady-state pairs $(\varepsilon_A^*, \sigma^*)_{\Delta P}$, Fig. 4(j), resulting in a quasistatic consti-

tutive relation $\sigma^{\text{ss}}(\varepsilon_A)$ that progressively increases toward a plateau of a few mN/m at high strains, in agreement with previous studies [4,16]. In summary, these results show that MOLI can be used to map the steady-state constitutive relation of cell monolayers. They also show that this technique allows us to measure the out-of-equilibrium responses of tissues to applied luminal pressures.

3. Dynamics of epithelial domes under cyclic pressure

To examine the ability of MOLI to probe epithelial rheology out of equilibrium, we subjected domes to triangular waves of pressure with amplitudes of 200 Pa and three timescales selected to be shorter, comparable, and longer than the characteristic relaxation timescale of the tissue. From confocal stacks of dome sections, we produced kymographs of dome height [Fig. 5(a)], which allowed us to compute the areal strain as a function of time [Fig. 5(b)].

For the fastest cycles, the dome strain increased during pressurization and decreased during depressurization, but without reaching complete strain recovery. Consequently, we observed a cumulative buildup of strain over time. After about 600 s (30 cycles), the maximum and minimum strains plateaued, and the system seemed to reach a limit cycle. A similar response was observed for the intermediate cycles, where the system took about four cycles to reach the limit cycle. For the slowest cycles, the system fully relaxed

upon depressurization to become planar and then required a threshold pressure to detach again, presumably due to the establishment of adhesive bonds. These experiments clearly demonstrated a rate-dependent response of the domes, consistent with the viscoelastic behavior of the active gel model underlying the agVM. To further examine the ability of our model to reproduce these results, we performed simulations of cyclic pressurization, finding that with similar material parameters as in previous examples, the agVM could quantitatively reproduce the most salient features of the experiments [Fig. 5(b)].

To physically interpret these results, we represented over a few cycles the actual area of the apical surface of a cell at the top of the dome, along with the resting area of that surface, computed in terms of the viscoelastic metric tensor as $A_{\text{resting}} = \int_{\Gamma_0} \sqrt{\det \mathbf{G}} dS_0$ where Γ_0 is the reference apical surface for that cell [Fig. 5(c)]. Under the largely equibiaxial stretch of this cell, the difference between these two areas controls the elastic part of apico-basal cortical tension, which dominates tissue tension in this stretched configuration. For the fastest cycle and during the loading phase, the simulations show that the resting area significantly lags behind the actual area, resulting in positive elastic tension that contributes to resisting the applied pressure and limiting deformation. During the unloading phase, even though the actual area decreases, it remains larger than the resting area for a while, resulting in positive elastic tension and further increase of the resting area, see Eq. (6), which slightly decreases at the end of the cycle. This results in a net increase of the resting area over the cycle. Consequently, in the next pressurization phase, the system can deform further. This process continues in subsequent cycles but, over time, the amount of increase and decrease of resting area in a given cycle balances, resulting in a limit cycle. The limit cycle is best appreciated in the tension-strain trajectory, Fig. 5(d), clearly showing that in our pressure-controlled mechanical ensemble neither tension nor strain is controlled. For cycles with intermediate rate, the behavior is similar, but the difference between actual and resting area is much smaller, leading to a faster convergence to the limit cycle. In the slowest cycling rate, the resting area nearly parallels the actual area, although the out-of-equilibrium tensions are still apparent in the tension-strain trajectory [Fig. 5(d)].

Taken together, our agVM simulations provide a clear mechanical interpretation of experiments on epithelial domes in a controlled pressure ensemble implemented with MOLI. They also show that the tissue rheology measured under cycling luminal pressurization can be explained by the viscoelasticity of the actomyosin cytoskeleton.

C. Loss of tissue planarity

To further examine how epithelial monolayers dynamically evolve toward the steady state upon mechanical perturbations, we focused on tissue dynamics under compression. As shown in Fig. 2(a), the steady-state tissue tension becomes negative for sufficiently large compression. Hence, being a slender thin film, a suspended monolayer buckles under compression, as reported in Ref. [17]. This reference further reports monolayers experiencing transient buckling, followed by a recovery of planarity within a few minutes. To test whether

this behavior can be explained by the CagVM, we considered an initially stretched strip of tissue clamped at its ends and rapidly brought the ends closer together by various magnitudes [Fig. 6(a)].

Based on the steady-state relation between tissue tension and uniaxial strain predicted by the idealized tissue model (IagVM), we chose two compression magnitudes that should result in a positive tension at long times and a larger compression that should lead to steady-state compressive tension. In all three cases, the tissue develops negative tension as a result of the short-term elasticity of the cortex, and buckles immediately after compression [Fig. 6(b) and Movie 3 [84]]. Over time, however, as viscoelastic relaxation and turnover take place over a timescale of a few minutes, the first two monolayers recover planarity and positive tissue tension, whereas the third monolayer remains buckled, albeit with a smaller out-of-plane amplitude. Thus, in agreement with experiments [17], our model predicts that monolayers may exhibit either transient or permanent buckling depending on the degree of compression.

Besides buckling, suspended monolayers have been used to understand how an apico-basal asymmetry of active tension results in loss of tissue planarity in the form of tissue curling at the edge of free-standing monolayers of MDCK cells [18]. To interrogate curling with our model, we considered tensed tissue strips clamped at opposite ends with larger basal than apical surface tension. This introduces an active spontaneous curvature in the tissue, which readily leads to curling at the free edges of the tissue strips, with a curl morphology very similar to that in experiments [Fig. 6(c)]. We tested the observation that the curling deflection increases linearly with tissue length [18]. We measured deflection in tissues of different lengths but equal clamped width for two different apico-basal tension ratios and recovered a linear relationship between deflection and tissue length, with the slope coefficient increasing with tensional asymmetry [Fig. 6(d)].

Since the agVM resolves not only tissue shape but also cellular shape, we noted that in our asymmetric monolayers, the apical surfaces of individual cells were much more curved than basal surfaces [Fig. 6(e)], in agreement with experimental observations in Ref. [18]. This fact can be easily understood from Laplace's law, since cellular pressure is uniform in our model within each cell, and hence the radius of curvature of apical and basal surfaces exhibits the same ratio as the corresponding surface tensions, irrespective of the applied stretch. Pressure being stretch-dependent, our model predicts an increase in radius of curvature of apical and basal surfaces as the tissue is stretched [Fig. 6(e)]. Thus, by connecting subcellular and monolayer scales, our model captures the consequences in cell and tissue shape of apico-basal polarization of active tension, enabling multiscale mechanical inference in cell monolayers [91].

D. Tissue pulsatility

Transient tissue stretch can also be the result of internal dynamics of cell monolayers in the form of tissue pulsations and traveling waves, which enable tissue morphogenesis [7,92,93] and multicellular migration [94,95], and are attributed to a combination of mechano-chemical interactions in

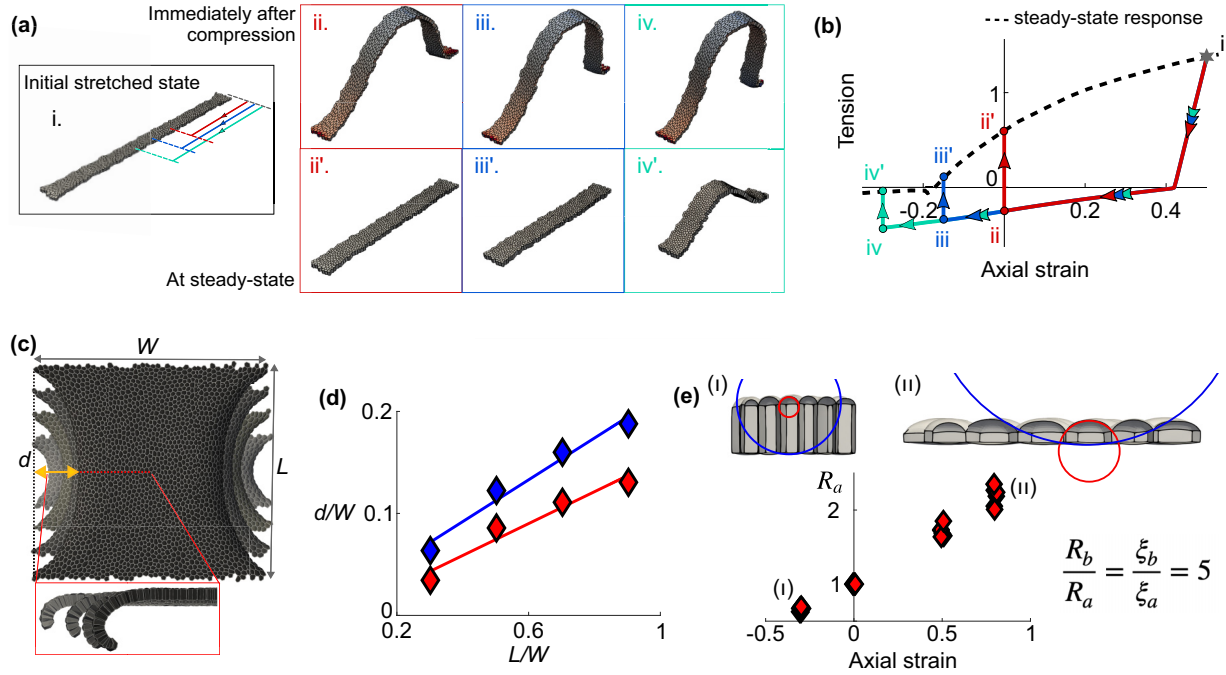


FIG. 6. Loss of tissue planarity. (a) Rectangular tissue strip with a 50% uniaxial prestretch from a reference state under tension rapidly compressed to 0% (red), -15% (blue), and -30% (cyan) uniaxial strain, Movie 3 [84]. The snapshots show the tissue shape immediately after compression ($t \approx 0$) and after relaxation ($t = 10 \tau_{10}$). (b) Corresponding trajectories in tension-strain space, where tension is normalized by $\bar{\gamma}_{ab}$. The quasistatic response of the CagVM is shown with a dashed black line, showing that the tissue strip is able to resist a small compressive tension at steady state following buckling. (c) Edge curling in a tissue patch with clamped ends in the presence of apicobasal asymmetry of active tension ($\xi_b/\xi_a = 2$) for four different tissue lengths L . (d) Curl deflection as a function of tissue length for $\xi_b/\xi_a = 1.5$ (red) and $\xi_b/\xi_a = 2$ (blue). (e) Effect of apicobasal asymmetry (here $\xi_b/\xi_a = 5$) on the curvature of apical and basal faces. The apical and basal radii of curvature increase with applied strain (we plot strain dependence of the apical radius normalized by its value at zero strain), but according to Laplace's law, their ratio remains constant following the relation $R_b/R_a = \xi_b/\xi_a$. See Table V for material parameters.

the cytoskeleton and biochemical signaling [44,62,96–100]. 2D vertex models have been used to study such pulsations, introducing phenomenological time delays [101,102]. Interestingly, a minimal model of the actin cytoskeleton including contractility, elasticity, and turnover is sufficient to develop spontaneous oscillations reminiscent of tissue pulsations [103]. Since these features are present in the agVM through the active gel model, along with an accurate geometrical representation of the tissue, we examined whether pulsations spontaneously develop in our model and the nature of such pulsations.

The tension-strain response given by Eq. (10), Fig. 2(a), collects steady states of a dynamical system, which need not necessarily be stable across parameter space. To analyze the stability of these fixed points, we performed linear stability analysis for the IagVM subjected to constant tension (Appendix C, Sec. C 2). For small tensions, we found that the eigenvalues of the system Jacobian matrix are real and negative, and hence the system is stable. At intermediate tensions, however, the system exhibits pairs of complex-conjugate eigenvalues, whose real part becomes positive above a tension threshold, indicative of linearly unstable behavior. For even larger tensions, eigenvalues become real, and the system is unstable. This picture is indicative of a Hopf bifurcation, with four regions depending on the stability of the steady states: (1) stable nodes characterized by exponential convergence from nearby states at low tension, (2) stable and (3) unstable

spirals at intermediate tensions, and (4) unstable nodes with exponential divergence at high tension [Fig. 7(a)].

To examine the nonlinear response of the system, we integrated in time the dynamical equations of the IagVM starting from a stable node and increasing suddenly the tension to values in each of these four regions. We first considered a system without the strain-stiffening mechanical barrier modeling the mechanical effect of IFs. Consistent with the linear stability analysis, the system reached stable steady states in regions (1) and (2), and diverged in regions (3) and (4) [Fig. 7(b)]. To better appreciate the dynamics of oscillatory states, we represented the orbits in the strain-apical cortical density plane [Fig. 7(c)], showing that the transition between regions (2) and (3) corresponds to a subcritical Hopf bifurcation diverging to infinity. By introducing the strain-stiffening behavior modeling IFs, however, we found that in region (3) the system reached limit cycles of sustained oscillations (supercritical Hopf bifurcation) [Fig. 7(c2)].

Pulsations emerging from our model can be understood by a positive feedback between contraction-induced densification of the cortex and enhanced contractility since $\gamma = \rho \xi$, slowed by viscoelasticity and the mechanical barrier, and eventually reversed by turnover, which dilutes the cortex and activates a complementary feedback loop involving cortical dilution during extension. Viscoelastic relaxation and turnover are thus built-in lag mechanisms of the actin cortex taming self-reinforcing active contraction or expansion.

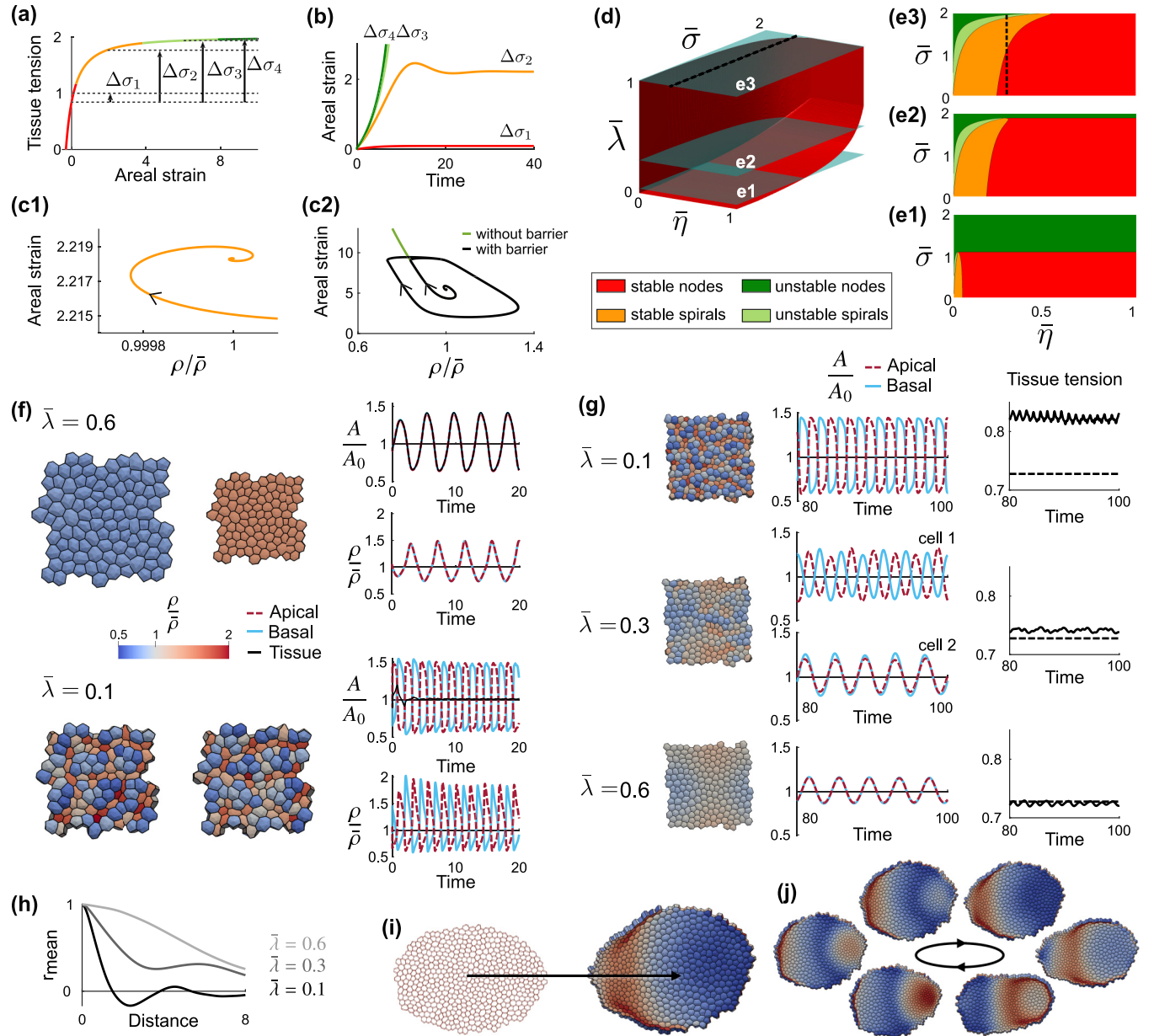


FIG. 7. Sustained pulsating patterns modulated by the physical properties of the actomyosin cortex. (a) Steady states in Fig. 2(a) color-coded depending on their dynamical stability. (b) Strain trajectories following tension increases of different magnitudes as predicted by the IagVM. (c) Orbits in the density-areal strain plane after a small tension perturbation around the steady state on either side of the stable-unstable boundary in panel (a). In panel (c2), we show the orbit of a system with a barrier limiting extreme cell deformations, leading to a stable limit cycle and sustained oscillations. (d) Stability diagram as a function of dimensionless tension, cortical elasticity, and viscosity, showing the surface separating stable and unstable regions. (e) Cross sections of the stability diagram in panel (d) along planes given by $\bar{\lambda} = 0.05, 0.3, 1$. The dashed line in panels (d) and (e3) corresponds to panel (a). (f) Pulsating modes in free-standing multicellular systems at constant tension described by the agVM for two values of $\bar{\lambda}$. Representative out-of-phase states, and time evolution of the normalized areas (tissue, apical, and basal), and of apical and basal densities. See also Movie 4 [84]. (g) Pulsating modes for a periodic tissue with constant area. Representative states, time evolution of apical and basal areas, and of average tissue tension (dashed lines are the tension of a nonpulsating steady state). See also Movie 5 [84]. (h) Spatial correlation averaged over time of apical density as a function of distance normalized by edge length s_0 for the three values of $\bar{\lambda}$ shown in panel (g). In all panels, time is normalized by τ_{to} and tension by $\bar{\gamma}_{ab}$. (i) Self-organized locomotion of a tissue interacting with a substrate through adhesion and friction. The arrow indicates the net displacement after 40 cycles (150 turnover times) of nonreciprocal collective pulsation. (j) Illustrative states along the nonreciprocal collective pulsation. See also Movie 6 [84]. See Table VI for material parameters.

In addition to tissue tension, the dynamical stability of the system should also depend on the viscoelastic parameters of the cortex. We thus systematically mapped the four regions of stability in a three-dimensional parameter space given by the key dimensionless parameters $\bar{\sigma} = \sigma / \bar{\gamma}_{ab}$ (normalized tissue tension), $\bar{\lambda} = \lambda / \bar{\gamma}_{ab}$ (normalized elastic modulus or elastocapillary number), and $\bar{\eta} = \eta / (\bar{\gamma}_{ab} \tau_{to}) = \tau_{va} / \tau_{to}$ (normalized remodeling viscosity) [Figs. 7(d) and 7(e)]. We note that the steady state of the system is independent of $\bar{\lambda}$ and $\bar{\eta}$. This map shows that unstable regions are associated with high tissue tension $\bar{\sigma}$ and low viscosity $\bar{\eta}$, as well as low normalized elastic modulus $\bar{\lambda}$. Thus, according to our model, pulsatile dynamics is favored by high tissue tension relative to cortical active tension, and by high cortical active tension relative to both cortex elasticity and viscous stress buildup in the timescale of turnover. Interestingly, high tissue tension has been shown to be required for pulsations during dorsal closure in *Drosophila* embryos [7], and a role for viscosity has also been suggested [93].

We then examined how these pulsations of a homogeneous idealized system manifest in a truly multicellular tissue. To study pulsatile behavior, we initially chose active gel parameters leading to a nonpulsatile steady state, and then reduced cortical elasticity to access different dynamical regimes. We first focused on a fixed tension ensemble. In agreement with the stability map above and for material parameters in the unstable spiral region, a biperiodic agVM subjected to constant tissue tension develops a breathing mode where all cells pulsate synchronously, leading to large changes of tissue area [Fig. 7(f) (top) and Movie 4 [84]]. However, as cortical elasticity is reduced, the breathing mode becomes unstable and the system self-organizes into nonaffine dynamical states not captured by the lagVM. These states are characterized by out-of-phase pulsations of neighboring cells and of apical and basal surfaces within cells. Compensation of different cell areas results in negligible macroscopic strain changes [Fig. 7(f) (bottom) and Movie 4 [84]]. Hence, this pulsation mode does not perform macroscopic power.

Since epithelial monolayers are generally laterally confined, we next considered a fixed strain ensemble with biperiodic boundary conditions. For low cortical elasticity ($\bar{\lambda}$), the system develops a similar dynamical mode as in the constant tension ensemble, with out-of-phase cell-to-cell and apico-basal pulsations [Fig. 7(g) (top) and Movie 5 [84]]. This figure compares the average tension in two tissues with identical steady state, but in one case this steady state is stable, and in the other case it is not, leading to pulsatile dynamics. The transition from nonpulsatile to pulsatile behavior at fixed $\bar{\lambda}$ can be triggered externally by stretch (leading to an increase in $\bar{\sigma}$) or internally by fluidizing the cortex or increasing the turnover time (both decreasing $\bar{\eta}$). Interestingly, the cell-to-cell pulsatile mode, reminiscent of that in the amnioserosa during dorsal closure in *Drosophila* embryos [7,93], results in a significant increase in average tissue tension compared with the steady-state tension in the absence of pulsations. By continuously driving the system out of equilibrium, pulsations prevent the relaxation of the elastic component of cortical tension in each cellular surface, contributing to an increase in the effective tension in the tissue. This result suggests that, by internally tuning cortical dynamics, epithelial cells may induce pulsations, which in turn provide a means to increase

tissue tension beyond a nominal value and pull on neighboring tissues.

At high cortical elasticity, the breathing mode of the fixed-tension ensemble is incompatible with the fixed-strain ensemble and, instead, the system develops coherent and propagating contraction waves involving tens of cells and in-phase apico-basal oscillations [Fig. 7(g) (bottom) and Movie 5 [84]]. This dynamical mode results in negligible perturbations of the steady-state tension. For intermediate $\bar{\lambda}$, the system develops a dynamical mode combining antiphase cell-to-cell and apico-basal pulsations with larger-scale propagating waves. These three regimes are clearly characterized by the spatial correlation of apical density capturing the lengthscale and the cell-to-cell correlation or anticorrelation of the different pulsation modes [Fig. 7(h)]. Additional simulations with the more constrained CagVM exhibited the same phenomenology but with delayed thresholds for pulsatility, attributed to the lower spatial resolution. Thus, our results show that cortical active gel parameters control not only the threshold but also the mode of pulsation, and in particular, that cortical elasticity increases mechanical coupling between cells, leading to collective pulsation modes. This role of cortical elasticity in regulating nonaffinity resonates with our previous results regarding epithelial superelasticity [Fig. 3(e)].

A close look at the collective pulsations for large values of $\bar{\lambda}$ [Fig. 7(g) (bottom) and Movie 5 [84]], shows that they are nonreciprocal and hence may provide a self-organized mode of locomotion. To further investigate this, we considered an elliptical tissue interacting with a substrate. We assumed that the basal plane remains attached to the plane of the substrate and modeled adhesion with an effective negative free energy proportional to the basal area. Furthermore, we considered the viscous drag of the basal plane with the substrate. Adhesion tends to expand the tissue, increasing $\bar{\sigma}$ and triggering the self-organized pulsation, which is collective by our choice of $\bar{\lambda}$. The system initially developed breathing pulsations, but after about 40 turnover times, these transitioned spontaneously to a polarized nonreciprocal limit cycle, which led to directed locomotion of the pulsating tissue [Figs. 7(i) and 7(j) and Movie 6 [84]]. These results are remarkably similar to the contractions during locomotion of *T. adhaerens* [94], albeit significantly slower, which we attribute to the absence of an explicit extension-induced contraction in our model [104].

In summary, we have shown that self-organized tissue pulsations can result from the intrinsic dynamics of the actomyosin cortex modeled as an active viscoelastic gel undergoing turnover. These pulsations are controlled by three dimensionless parameters and can be characterized by out-of-phase cell-to-cell pulsations, which enhance tissue tension, or by collective and nonreciprocal traveling contractions, which enable locomotion.

From a broader perspective, it has been previously shown that cell-to-cell pulsations enable directed remodeling of developing tissues by a ratcheting mechanism of cell-cell junctions, leading to collective T1 transitions [7,105]. In its present form, our work does not contemplate topological transitions of the junctional network. We note, however, that our analysis of the emergence of pulsations from a quiescent tissue is independent of such topological transitions. Furthermore, junctional rearrangements are slower than cytoskeletal dynamics owing to the slower turnover of relevant

structural proteins [3], which suggests that our approximation should be reasonable within a suitable observation window. For instance, Refs. [7,93] report tissue pulsations for tens of minutes without noticeable transitions. To capture ratcheting, our model could incorporate a mechanistic model for adhesion dynamics capturing the mechanosensitive endocytosis of adhesion molecules [31,37].

In our model, pulsations and the resulting nonaffine tissue deformations are the result of a dynamical instability of the collection of active gel surfaces. However, models that view the epithelium as a 2D tensional net of actively contracting edges have identified an alternative mechanism leading to similar nonaffine deformations based on isogonal soft modes of the network [29]. The existence of such modes is quite specific to the assumption that the tension in linear junctions dominates tissue mechanics, which may be particularly relevant to tissues displaying marked apical actomyosin junctional belts. Isogonal modes are easily excitable, i.e., by contraction pulses of medial actomyosin. An extension of our model, including dense actomyosin apical junctional belts, should capture the interaction of isogonal soft modes of the apical surface with the medial pulsations described here.

IV. SUMMARY AND OUTLOOK

We have examined theoretically and computationally a very simple premise, that the time-dependent mechanics of a cell monolayer devoid of topological transitions [3,4,6,7,17,18] depend on the cytoskeletal dynamics of a collection of curved cellular cortices. To this end, we have developed an out-of-equilibrium nonlinear framework that connects active gel models of the actomyosin cortex to a hierarchy of vertex-like models, ranging from high-fidelity finite-element simulations to idealized affinely deformed crystalline tissues. A variational formalism of irreversible thermodynamics is central to our theoretical framework, since it enables the dynamical coupling of the active gel surfaces making up the tissue and the systematic coarse-graining of the model. We have shown that a wide spectrum of epithelial phenomenologies is recapitulated by this model, including stress relaxation, creep, and superelasticity under stretch, transient buckling under compression, curling of tense tissues due to apico-basal tensional asymmetry, or self-organized pulsations with different dynamical modes and different functionality. While *ad hoc* models for each of these processes have been proposed, the single model presented here describes all of them with high fidelity regarding cellular and tissue shape, further providing information about the cortical state (density and reference elastic metric). We have shown that the required spatial refinement of the active gel vertex model (agVM) depends on the nature of cellular deformations, and, specifically, the affinity of the tissue. In fact, our results delineate the range of applicability of continuum theories for epithelial shells, including those homogenizing vertex models [27,106–112], which implicitly assume affinity of cellular deformations, and therefore cannot be directly applied to tissues undergoing superelastic transformations [Fig. 3(e)] or cell-to-cell pulsations [Figs. 7(f) and 7(g)].

We have assumed a very simple topology for the junctional network, but our model can be directly extended to account for scutoids [113] or other cellular arrangements. We have further

assumed that the junctional network does not change and have considered a relatively simple active gel model accounting for turnover, viscoelastic relaxation of the network, and active contractility. However, the framework can be adapted to tissue descriptions naturally accounting for cell rearrangements [35,36] and to richer multispecies models accounting for regulatory networks, and hence can provide a general background to integrate subcellular dynamics and emergent mechanical responses of cellular tissues. Besides the actin cytoskeleton, the framework can also accommodate other mechanical modules in epithelial tissues, such as adhesion complexes [51] or volume regulation [53,54]. As a proof of concept of this ability to combine various structural ingredients, here we have coupled the active gel description of cortical patches with a cytosolic power-law element and with an unspecific mechanical barrier limiting large strains. As opposed to minimalistic phenomenological models, our work suggests that this bottom-up modeling route has the potential to provide a mechanistic understanding of active nonlinear responses of tissues and integrate high-resolution observations, including 3D cell and tissue shape, tissue mechanics, and molecular localization and dynamics. We finally note that our modeling approach can be adapted to plant tissues by upscaling suitable models capturing yield and growth processes in the cell wall driven by turgor pressure [114,115].

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DATA AVAILABILITY

The data that support the findings of this article are openly available [116].

APPENDIX A: ACTIVE GEL VARIATIONAL FORMALISM FOR THE ACTOMYOSIN CORTEX

We provide next a detailed derivation of the active viscoelastic gel used to model the actomyosin cortex. This derivation is based on Onsager’s variational formalism for irreversible thermodynamics [48,49,75], applicable in isothermal and low *Re* conditions and complementary to classical irreversible thermodynamics [45,71] and bracket approaches such as GENERIC [72–74] or the single-generator bracket formalism [117,118]. According to Onsager’s variational formalism, the dynamics of the system minimize instantaneously a Rayleighian functional accounting for changes in free-energy, dissipation, and power input. Its main advantages are

the conceptual simplicity of minimizing a scalar functional when dealing with complex coupled and nonlinear models and the fact that the variational structure provides a natural framework for approximation and coarse-graining using the classical Rayleigh-Ritz method [47,75,76,78,79]. These advantages come at the cost of generality; Onsager's formalism can be derived from bracket formalisms by neglecting inertia and assuming isothermal conditions [119,120], two reasonable assumptions for epithelial sheets. It has been applied to model coupled problems in soft and active matter, coupling elasticity, viscous flows, diffusion, and chemical reactions.

Using this variational formalism, we develop next an active gel model for a generic cortical surface in the tissue. We first outline this formalism in Appendix A 1, describe the kinematics of a deforming surface in Appendix A 2, and state the equation of balance of mass for the cortical layer undergoing turnover in Appendix A 3. Appendixes A 4, A 5, and A 6 introduce the free-energy, dissipation, and active power functionals forming the Rayleighian functional of the system. Finally, the governing equations are derived using Onsager's formalism in Appendix A 7.

1. Onsager's variational formalism

We first provide an abstract and brief statement of Onsager's variational formalism. We assume that the system is characterized by a set of state variables $X(t)$ (i.e., shape, concentrations, densities) and a set of process variables V (i.e., hydrodynamic or diffusive velocities, reaction rates), which describe changes in the state of the system, either simply by $\dot{X} = V$, or more generally through a process operator $\dot{X} = P(X)V$, which often encodes mass balance principles.

Given the free-energy of the system $\mathcal{F}(X)$, the dissipation potential $\mathcal{D}(V; X)$ and the power supplied to the system $\mathcal{P}(V; X)$ (linear in V), we can form the Rayleighian functional, which establishes the competition between free-energy relaxation, dissipation, and power input as

$$\mathcal{R}(V; X) = \dot{\mathcal{F}}(V; X) + \mathcal{D}(V; X) + \mathcal{P}(V; X), \quad (\text{A1})$$

where, by the chain rule, the rate of change of free energy is linear in V and can be expressed as $\dot{\mathcal{F}}(V; X) = D_X \mathcal{F}(X) \cdot P(X)V$. Then, the dynamics of the system given by V instantaneously minimize $\mathcal{R}(V; X)$. The free-energy can be nonquadratic and nonconvex. The first-order optimality condition of this minimization principle provides the evolution equations and implies energy conservation, whereas the second-order optimality condition guarantees non-negative entropy production, as long as $\mathcal{D}(V; X)$ is non-negative, convex with respect to V , and $\mathcal{D}(0; X) = 0$.

Suppose the system is subjected to a constraint on the process variables given by $\mathbb{C}(X)V = 0$. Then, we can form the Lagrangian as $\mathcal{L}(V, \Lambda; X) = \mathcal{R}(V; X) + \Lambda \cdot \mathbb{C}(X)V$, where Λ are the Lagrangian multipliers, and the constrained dynamics follow from

$$\{V, \Lambda\} = \underset{V}{\operatorname{argmin}} \underset{\Lambda}{\operatorname{argmax}} [\mathcal{L}(V, \Lambda; X)]. \quad (\text{A2})$$

2. Kinematics

We model a cortical patch as a two-dimensional surface embedded in $\mathbb{R}^3$. We refer to Ref. [63] for a treatment of

continuum mechanics in general curvilinear coordinates, particularly useful to describe curved thin sheets like cortical layers. The motion of the cortical patch is described using a family of time-dependent mappings $\varphi : \Gamma_0 \times (0, T) \rightarrow \mathbb{R}^3$, where Γ_0 is an arbitrary planar reference configuration of the cortical patch. These mappings parametrize the shape of the cortical patch, the surface $\Gamma_t = \varphi(\Gamma_0, t)$, at each time instant t . We denote by $X = (X^1, X^2)$ points on $\Gamma_0 \subset \mathbb{R}^2$ and by $\mathbf{x} = (x^1, x^2, x^3)$ points on $\Gamma_t \subset \mathbb{R}^3$ described by Cartesian coordinates. In what follows, we drop the explicit dependence on time of the current surface, which we simply denote by Γ .

At each time instant, the parametrization φ induces natural basis vectors of the tangent plane of Γ given by $\mathbf{g}_I = \partial \varphi / \partial X^I$, where $I \in \{1, 2\}$. The inner product of these vectors defines the covariant components of the metric tensor $\mathbf{g}$ on Γ , $g_{IJ} = \mathbf{g}_I \cdot \mathbf{g}_J$, expressing the Euclidean metric of the ambient space in the surface coordinates. The contravariant components of the metric tensor g^{IJ} are defined by the relations $g_{IK} g^{KJ} = \delta_I^J$. We introduce the scalar field $g = \sqrt{\det g_{IJ}}$. Likewise, we can define the metric tensor $\mathbf{G}_0$ of the reference configuration Γ_0 and $G_0 = \sqrt{\det G_{0,IJ}}$. If $\{X^1, X^2\}$ are Cartesian coordinates, then the tensor $\mathbf{G}_0$ is just the identity matrix and $G_0 = 1$.

We introduce the unit normal vector field over Γ_0 as

$$\mathbf{n} = \frac{\mathbf{g}_1 \times \mathbf{g}_2}{|\mathbf{g}_1 \times \mathbf{g}_2|}. \quad (\text{A3})$$

Its variation over the surface characterizes its curvature. More specifically, the second fundamental form of Γ is a second-order symmetric tensor given by

$$k_{IJ} = -\frac{\partial n^i}{\partial X^I} \frac{\partial \varphi^i}{\partial X^J} = n^i \frac{\partial^2 \varphi^i}{\partial X^I \partial X^J}. \quad (\text{A4})$$

We describe next the local deformation of the continuum surface. At each time instant, the derivative of the deformation mapping, $D\varphi(\mathbf{X}, t)$, is a linear transformation that maps the tangent plane to Γ_0 (identified with $\mathbb{R}^2$) at point $\mathbf{X}$ onto the tangent plane to Γ at point $\varphi(\mathbf{X}, t)$, and is often referred to as the deformation gradient denoted by $\mathbf{F}(\mathbf{X}, t)$, or in components as $F^I_I = \partial \varphi^i / \partial X^I$. The deformation gradient contains information about local strain and about local rotations. To retain only information about local deformation, we introduce the right Cauchy–Green deformation tensor as [63]

$$\mathbf{C}(\mathbf{X}, t) = D\varphi^T(\mathbf{X}, t) D\varphi(\mathbf{X}, t). \quad (\text{A5})$$

The components of $\mathbf{C}$ in the basis associated with the coordinates $\{X^1, X^2\}$ of Γ_0 coincide with those of the metric tensor in the natural basis of the tangent plane to Γ given by $\{\mathbf{g}_1, \mathbf{g}_2\}$, that is $C_{IJ} = g_{IJ}$. The mixed components of the right Cauchy–Green deformation tensor are $C_I^J = g_{IK} G_0^{KJ}$, from which we can compute its trace $\operatorname{tr} \mathbf{C} = g_{IJ} G_0^{IJ}$ and its determinant $\det \mathbf{C} = g^2 / G_0^2$. The Jacobian of the mapping φ measures changes in area of the surface, allows us to change integrals between the reference and the deformed surface with $dS = J dS_0$, and is given by $J = \sqrt{\det \mathbf{C}} = g / G_0$.

Fixing $\mathbf{X}$, $\varphi(\mathbf{X}, t)$ describes the motion of a material particle. Therefore, the Lagrangian velocity of the surface takes values over Γ_0 and can be computed as

$$\mathbf{V}(\mathbf{X}, t) = \frac{\partial \varphi}{\partial t}(\mathbf{X}, t) = \dot{\varphi}(\mathbf{X}, t), \quad (\text{A6})$$

where the dot denotes the material time derivative (at fixed $\mathbf{X}$). The Eulerian velocity taking values over Γ is just the composition with the inverse deformation map $\mathbf{v}(\mathbf{x}, t) = \mathbf{V}(\varphi^{-1}(\mathbf{x}, t), t)$, or $\mathbf{v} = \mathbf{V} \circ \varphi^{-1}$ in short. The velocity field can be decomposed into a tangential component $\mathbf{v}_t$, and a normal component obtained as $v_n = \mathbf{v} \cdot \mathbf{n}$. The rate-of-deformation tensor is an Eulerian tensor characterizing strain rate and is given by [63,75]

$$\mathbf{d} = \frac{1}{2}(\nabla \mathbf{v}_t + \nabla \mathbf{v}_t^T) - v_n \mathbf{k}, \quad (\text{A7})$$

where $\nabla \mathbf{v}_t$ is the covariant derivative of $\mathbf{v}_t$ on Γ . The rate of deformation can also be expressed in Lagrangian terms using the relation $\mathbf{d} \circ \varphi = (1/2)\dot{\mathbf{g}}$. Consequently, we can express the rate of change of local area in Eulerian or Lagrangian terms as $\text{tr } \mathbf{d} \circ \varphi = \dot{J}/J$. In what follows, we implicitly imply the composition of Lagrangian or Eulerian fields by φ or its inverse depending on the context.

3. Cortical density and turnover

The actomyosin cortex is a very complex and dynamical cytoskeletal network composed of tens of structural and regulatory proteins maintained out of equilibrium. The main structural components are actin filaments, crosslinkers, and myosin minifilaments. The turnover of these components and the motor activity of myosins are actively driven using chemical energy supplied by ATP hydrolysis. The maintenance of the actin cytoskeleton accounts for a significant fraction of the metabolic budget of cells [121].

Here, we propose a minimal model of the cortex, similar to that in Refs. [39,41], where the local state of the actomyosin layer is given by a scalar coarse-grained density field of “cytoskeletal material.” The areal mass density of the active gel on Γ is denoted by $\rho(\mathbf{x}, t)$. If the gel is assumed to be 3D incompressible, then ρ can be interpreted as the thickness of the cortical layer. Because J represents a ratio between reference and deformed local areas, we can express the mass density per unit reference area as

$$\varrho_0(\mathbf{X}, t) = \rho(\mathbf{x}, t)J(\mathbf{X}, t), \quad (\text{A8})$$

where $\mathbf{x} = \varphi(\mathbf{X}, t)$.

Mass balance of the cortical material can be expressed by [39,41,75]

$$\dot{\rho} + \rho \text{tr } \mathbf{d} = r, \quad (\text{A9})$$

where the second term accounts for changes in cortical density due to the stretching or compression of the surface, whereas r reflects the net effect of assembly and disassembly of the cytoskeletal gel on cortical density. Alternatively, the mass balance equation can be expressed in terms of the reference density ϱ_0 . Indeed, time-differentiating Eq. (A8), we obtain $\dot{\varrho}_0 = \dot{\rho}J + \rho\dot{J} = J(\dot{\rho} + \rho \text{tr } \mathbf{d})$, and hence mass balance can also be expressed as

$$\dot{\varrho}_0 = rJ. \quad (\text{A10})$$

The chemical reactions underlying the turnover process encoded by r are driven by differences in chemical potentials between reagents and products. These chemical potentials may include thermodynamic components and out-of-equilibrium components that require an external power

supply. Given the active nature of actomyosin turnover, we assume here that the out-of-equilibrium component dominates the chemical potentials driving assembly and disassembly. Conventionally, it is assumed that turnover is the result of the treadmilling of actin filaments, polymerized near the membrane in a process dependent on the availability of actin monomers and depolymerized throughout the thickness of the gel. We incorporate these physical assumptions in our formalism and derive the form of r in Appendix A 7 b.

4. Elastic energy with respect to an evolving material metric

We model the short-term nonlinear elasticity of the network of semiflexible actin filaments using the thermodynamically consistent framework of hyperelasticity [63,64]. However, to account for the dynamical remodeling of the actin gel, where cross-linkers are transient, and filaments turn over, we introduce the notion of a time-evolving reference configuration as the material is being dynamically rebuilt. To capture this effect, we view the reference metric tensor as a dynamical variable, similar to previous models of nonlinear anelasticity, including viscoelasticity, growth, or plasticity [65–67]. This treatment of anelasticity and remodeling is equivalent to approaches based on the multiplicative decomposition of the deformation gradient [122] under the assumption of isotropy of the material [68,123]. In practice, we choose as dynamical variables the contravariant components of the material metric tensor, $G^{IJ}(\mathbf{X}, t)$, whose initial conditions are $G^{IJ}(\mathbf{X}, t = 0) = G_0^{IJ}(\mathbf{X})$. In analogy with actual metric tensors, the covariant and contravariant components of the material metric tensor are related by the relations $G_{IL}G^{LJ} = \delta_I^J$. Within this modeling framework, the reference configuration can be understood as a Riemannian manifold with a time-evolving metric $(\Gamma_0, \mathbf{G})$. Unlike $\mathbf{G}_0$, $\mathbf{G}$ is not Euclidean, and its incompatibility can result in residual stresses.

The introduction of a time-dependent material metric has a profound impact on the quantification of strain, which in essence is a comparison between the deformation-induced metric tensor $\mathbf{C}$ and the material metric tensor, and, for this reason, the free-energy density per unit mass of a nonlinearly elastic material is conventionally viewed as a function of both of these tensors, $\Psi(\mathbf{C}, \mathbf{G}_0)$. For an isotropic material, constitutive models are expressed in terms of the principal invariants of $\mathbf{C}$ relative to $\mathbf{G}_0$. For a quasi-2D material such as the cortical layer, only two principal invariants are sufficient, for instance, the trace ($I_1 = \text{tr } \mathbf{C} = C_{IJ}G_0^{IJ}$) and the determinant ($I_3 = \det \mathbf{C} = \det C_{IJ} \det G_0^{KL}$) [63], which when using Cartesian coordinates in Γ_0 simplify to $I_3 = C_{II}$ and $I_3 = \det C_{IJ}$. Often, the elastic potential $\Psi(I_1, I_3)$ is minimal when the deformation map is the identity map, i.e., when $I_1 = 2$ and $I_3 = 1$.

Here, we model the remodeling of the material by comparing $\mathbf{C}(\mathbf{X}, t)$ with the time-dependent material metric $\mathbf{G}(\mathbf{X}, t)$ in the elastic potential, $\Psi(\mathbf{C}, \mathbf{G})$. Accordingly, we introduce the invariants relative to the time-dependent material metric as

$$\tilde{I}_1 = C_{IJ}G^{IJ} \quad \text{and} \quad \tilde{I}_3 = \det C_{IJ} \det G^{KL}. \quad (\text{A11})$$

For an isotropic material, the elastic energy per unit mass is $\Psi(\tilde{I}_1, \tilde{I}_3)$. For a finite local deformation given by the symmetric and positive-definite tensor $\mathbf{C}$, now the system can relax

the elastic energy by adapting the material metric such that $G^{IJ} = C^{-1,IJ}$, since in this case we have $\tilde{I}_1 = 2$ and $\tilde{I}_3 = 1$. Hence, this formulation can be understood as a tensorial generalization of the notion of dynamical resting length for a 1D spring [3].

The total elastic energy stored in the network can be expressed as

$$\mathcal{F}[\varphi, \varrho_0, \mathbf{G}] = \int_{\Gamma_0} \varrho_0 \Psi(\mathbf{C}, \mathbf{G}) dS_0. \quad (\text{A12})$$

The dependence of this functional on φ can be understood from Eq. (A5).

Since the reference surface does not depend on time, we can compute the rate of change of the free energy as

$$\frac{d}{dt} \int_{\Gamma_0} \varrho_0 \Psi(\mathbf{C}, \mathbf{G}) dS_0 = \int_{\Gamma_0} [\dot{\varrho}_0 \Psi(\mathbf{C}, \mathbf{G}) + \varrho_0 \dot{\Psi}(\mathbf{C}, \mathbf{G})] dS_0, \quad (\text{A13})$$

which, when plugging in Eq. (A10) and using the chain rule, becomes

$$\begin{aligned} \dot{\mathcal{F}}[\dot{\varphi}, r, \dot{\mathbf{G}}; \varphi, \varrho_0, \mathbf{G}] &= \int_{\Gamma_0} [rJ\Psi(\mathbf{C}, \mathbf{G}) + \varrho_0 \dot{\Psi}(\mathbf{C}, \mathbf{G})] dS_0 \\ &= \int_{\Gamma_0} \left[rJ\Psi(\mathbf{C}, \mathbf{G}) + \varrho_0 \left(\frac{\partial \Psi}{\partial C_{IJ}} \dot{C}_{IJ} + \frac{\partial \Psi}{\partial G^{IJ}} \dot{G}^{IJ} \right) \right] dS_0. \end{aligned} \quad (\text{A14})$$

The first term in Eq. (A14) accounts for changes in free energy due to changes in mass as a result of turnover, whereas the second term captures changes in elastic energy density due to deformation, and the third term due to evolution of the material metric. The second term is the usual power of elastic stresses expressed in a fully Lagrangian way,

$$\int_{\Gamma_0} \frac{1}{2} \mathbf{S}^e : \dot{\mathbf{C}} dS_0, \quad (\text{A15})$$

where

$$\mathbf{S}^e = 2\varrho_0 \frac{\partial \Psi}{\partial \mathbf{C}} \quad (\text{A16})$$

is the elastic second Piola–Kirchhoff stress tensor. The integral in Eq. (A15) can be expressed in the spatial configuration following a standard calculation as

$$\int_{\Gamma} \boldsymbol{\gamma}^e : d\mathbf{d}S, \quad (\text{A17})$$

where $\boldsymbol{\gamma}^e$ is the elastic part of the Cauchy stress of the thin membrane given by [63]

$$\boldsymbol{\gamma}^e = \frac{1}{J} \mathbf{F} \mathbf{S}^e \mathbf{F}^T = 2\rho \mathbf{F} \frac{\partial \Psi}{\partial \mathbf{C}} \mathbf{F}^T. \quad (\text{A18})$$

In the last term, the power-conjugate tensor to the rate of change of metric, $\partial_{\mathbf{G}} \Psi$, is a thermodynamical stress-like quantity driving the evolution of the reference metric. For an isotropic material, because Ψ depends on the invariants in

Eq. (A11) only, an explicit calculation shows that

$$\frac{\partial \Psi}{\partial G^{IJ}} = C_{IL} \frac{\partial \Psi}{\partial C_{LK}} G_{KJ}, \quad (\text{A19})$$

and hence the last term can be rewritten in terms of $\mathbf{S}^e$ as

$$\int_{\Gamma_0} (C_{IL} S^{e,LK} G_{KJ}) \frac{1}{2} \dot{G}^{IJ} dS_0, \quad (\text{A20})$$

where the term between parentheses is stress-like tensor conjugate to changes in material metric. In summary, these expressions show that the elastic stress tensor drives both the deformation of the surface and the remodeling of the material.

This is a good moment to map our system to the abstract setting in Sec. A1. We identify the state variables as the deformation map of the surface, the density field, and the field of material metric tensors, $X(t) = (\varphi(\cdot, t), \varrho_0(\cdot, t), \mathbf{G}(\cdot, t))$. The process variables describing how the system changes are $V = (\dot{\varphi}, r, \dot{\mathbf{G}})$, where $\dot{\varphi} = \mathbf{V}$ is the velocity field. The process operator relating linearly the time-derivative of X and V is trivial for the first and third variables, and encoded by Eq. (A10) for the second. Equation (A14) shows that, as expressed in Eq. (A1), the rate of change of free energy can be expressed as a functional $\dot{\mathcal{F}}(V; X)$ linear in V .

A number of strain energy density functions Ψ have been proposed to describe the nonlinear elasticity networks of semiflexible filaments such as actin networks [69]. For the sake of simplicity, we chose an isotropic two-dimensional Neo-Hookean strain energy density. While the network may be 3D incompressible, it is 2D compressible [39], and, accordingly, we choose a compressible strain energy function of the form [64]

$$\bar{\rho} \Psi(\mathbf{C}, \mathbf{G}) = W(\mathbf{C}, \mathbf{G}) = \mu \left(\frac{\tilde{I}_1}{\sqrt{\tilde{I}_3}} - 2 \right) + \lambda (\sqrt{\tilde{I}_3} - 1)^2, \quad (\text{A21})$$

where $\bar{\rho}$ is a reference cortical density specified later, and λ and μ are 2D Lamé parameters (with units of surface tension) at the reference density $\rho = \bar{\rho}$. We assume that $\lambda = \mu$ [39].

5. Dissipation

The dissipation potential functional accounts for dissipation resulting from the motion of the surface, from turnover, and from cortical remodeling. We postulate a simple dissipation potential of the form

$$\begin{aligned} \mathcal{D}[\dot{\varphi}, r, \dot{\mathbf{G}}; \varphi, \varrho_0, \mathbf{G}] &= \int_{\Gamma} \frac{\eta_m}{2} |\mathbf{v}|^2 dS + \int_{\Gamma} \frac{1}{2\bar{k}} r^2 dS + \int_{\Gamma_0} \varrho_0 \Phi(\dot{\mathbf{G}}; \mathbf{G}) dS_0, \\ &= \int_{\Gamma_0} \frac{\eta_m}{2} |\dot{\varphi}|^2 J dS_0 + \int_{\Gamma_0} \frac{1}{2\bar{k}} r^2 J dS_0 + \int_{\Gamma_0} \varrho_0 \Phi(\dot{\mathbf{G}}; \mathbf{G}) dS_0, \end{aligned} \quad (\text{A22})$$

where the first integral is a local model for the viscous drag experienced by the cortical surface as it moves in a background dissipative medium with frictional parameter η_m , the parameter $\bar{k}$ controls the dissipation associated with reaction rates, and $\Phi(\dot{\mathbf{G}}; \mathbf{G})$ is a dissipation potential per unit mass due to remodeling of the cortical network. To be consistent with the

entropy production inequality, it should be non-negative, convex with respect to its first argument, and satisfy $\Phi(\mathbf{0}; \mathbf{G}) = 0$. For simplicity, we consider a quadratic potential of the form

$$\Phi(\dot{\mathbf{G}}; \mathbf{G}) = \frac{\eta}{2\bar{\rho}} \dot{\mathbf{G}}^{IJ} G_{IL} G_{JK} \dot{\mathbf{G}}^{LK}, \quad (\text{A23})$$

where η is a remodeling viscosity coefficient with units of surface viscosity [112].

6. Active power input

We specify next the distributed power input into the system rendering it an active continuous medium. We consider activity driving turnover as discussed in Appendix A3, and also the contractile activity resulting from the transduction of chemical power into mechanical power. There are different

conceptual approaches to modeling contractile activity [124]. One possibility is to consider that contractile units, such as myosin minifilaments, are active crosslinkers that bias the remodeling of the material described here using the material metric tensor $\mathbf{G}$. This assumption may be reasonable in situations where myosin minifilaments exhibit relatively strong processive behavior. Alternative to this material viewpoint, we may assume that myosin motors exert mechanical power on the spatial configuration of the cortical surface. This assumption may be pertinent if turnover of myosins is faster than that of other crosslinkers and filaments. We postulate a power input functional accounting for the turnover activity and, in principle, for both types of contractile activity, taking the form

$$\mathcal{P}[\dot{\varphi}, r, \dot{\mathbf{G}}; \varphi, \varrho_0, \mathbf{G}] = \int_{\Gamma} (-\Delta\mu^p + \Delta\mu^d) r dS - \int_{\Gamma_0} \mathbf{A}(\varrho_0, \mathbf{C}, \mathbf{G}) : \frac{1}{2} \dot{\mathbf{G}} dS_0 + \int_{\Gamma} \gamma^a(\varrho_0, \mathbf{C}, \mathbf{G}) : \mathbf{d} dS. \quad (\text{A24})$$

In the first integral, $\Delta\mu^p$ and $\Delta\mu^d$ are the out-of-equilibrium polymerization and depolymerization chemical potentials of the cortical gel. We account for the fact that polymerization is generally assumed to take place at the plasma membrane, and hence should be largely independent of ρ . We also note that polymerization should be limited by the availability of cytosolic cytoskeletal components described by concentration c (Appendix A3). Hence, consistent with the law of mass action, we assume that to linear order $\Delta\mu^p = \alpha^p c$ with α^p a constant parameter. Similarly, to model the fact that depolymerization takes place in the bulk of the thin cortical layer, and hence the net surface depolymerization rate should be proportional to the areal density of the cortex, we assume that $\Delta\mu^d = \alpha^d \rho$ with α^d a constant parameter.

In the second integral, the tensor $\mathbf{A}(\varrho_0, \mathbf{C}, \mathbf{G})$ is power-conjugate to the rate of change of material metric tensor and therefore can be understood as an active stress-like tensor analogous to the thermodynamic stress-like tensor in Eq. (A20). In principle, it can be a function of the state variables. The dependence on cortical density encodes the idea that active contraction should depend on the density of cortical material. The dependence on deformation and reference metric can encode mechanosensitive mechanisms by which active tension responds to strain or stress [see Eq. (A16)]. We come back later to the specific form of the active Lagrangian stress. Analogously, the third integral $\gamma^a(\varrho_0, \mathbf{C}, \mathbf{G})$ performs work against the rate-of-deformation tensor and hence can be viewed as an active Cauchy or spatial stress analogous to the elastic Cauchy stress in Eq. (A17). We follow the common assumption in active gel models that the active tension is isotropic and proportional to cortical thickness, $\gamma^a(\varrho_0, \mathbf{C}, \mathbf{G}) = \gamma^a(\rho) \mathbf{g} = \rho \xi \mathbf{g}$, where $\gamma^a(\rho) = \xi \rho$ is the scalar active tension and ξ is an activity parameter, although it is known that this relation is more complex and may depend on a more detailed description of network architecture [56,60]. With this assumption, the integrand of the third integral can be rewritten as $\gamma^a \mathbf{g} : \mathbf{d} = \gamma^a \text{tr } \mathbf{d} = \rho \xi \text{tr } \mathbf{d}$.

Using these constitutive assumptions and expressing all terms in the reference configuration, we can express the power input functional as

$$\mathcal{P}[\dot{\varphi}, r, \dot{\mathbf{G}}; \varphi, \varrho_0, \mathbf{G}] = \int_{\Gamma_0} (-\alpha^p c + \alpha^d \rho) r J dS_0 - \int_{\Gamma_0} \mathbf{A}(\varrho_0, \mathbf{C}, \mathbf{G}) : \frac{1}{2} \dot{\mathbf{G}} dS_0 + \int_{\Gamma_0} \gamma^a(\rho) J dS_0. \quad (\text{A25})$$

7. Governing equations of the active viscoelastic cortical behavior

Collecting the functionals introduced in the previous sections, we can form the Rayleighian functional of the system as

$$\mathcal{R}[V; X] = \dot{\mathcal{F}} + \mathcal{D} + \mathcal{P} + \mathcal{P}^{\text{ext}}, \quad (\text{A26})$$

where we recall that $V = (\dot{\varphi}, r, \dot{\mathbf{G}})$ and $X = (\varphi, \varrho_0, \mathbf{G})$, and, for completeness, we consider a functional $\mathcal{P}^{\text{ext}}$ accounting for the power supplied by external force densities acting tangentially ($\mathbf{f}$) and normally (f_n) to the surface,

$$\mathcal{P}^{\text{ext}} = - \int_{\Gamma} \mathbf{f} \cdot \mathbf{v}_t dS - \int_{\Gamma} f_n v_n dS. \quad (\text{A27})$$

The dynamics of the system according to Onsager's variational formalism result from minimizing $\mathcal{R}[V; X]$ with respect to V . Minimization with respect to $\dot{\varphi}$ leads to balance of linear momentum, with respect to r identifies the reaction rate, and with respect to $\dot{\mathbf{G}}$ supplies an evolution equation for the material metric.

a. Force balance

The variation of the Rayleighian with respect to $\dot{\varphi}$ results in

$$0 = \delta_{\dot{\varphi}} \mathcal{R} = \int_{\Gamma_0} \left[(S^{e,IJ} + \gamma^a J C^{-1,IJ}) \frac{1}{2} \delta \dot{C}_{IJ} + J(\eta_m \dot{\varphi} - \mathbf{f} - f_n \mathbf{n}) \cdot \delta \dot{\varphi} \right] dS_0, \quad (\text{A28})$$

for all admissible variations $\delta\dot{\phi}$, where $\delta\dot{C} = D\delta\dot{\phi}^T D\delta\dot{\phi} + D\delta\dot{\phi}^T D\delta\dot{\phi}$, see Eq. (A5). This expression allows us to identify the total stress tensor for the cortical layer (with units of surface tension) in its Lagrangian and Eulerian form as

$$\mathbf{S} = \mathbf{S}^e + \gamma^a \mathbf{J} \mathbf{C}^{-1} = \mathbf{S}^e + \xi \varrho_0 \mathbf{C}^{-1}, \quad \boldsymbol{\gamma} = \boldsymbol{\gamma}^e + \gamma^a \mathbf{g}, \quad (\text{A29})$$

see Eq. (A18). In this additive decomposition of the surface stress, we call the component $\mathbf{S}^e$ (or $\boldsymbol{\gamma}^e$) elastic because it derives from the elastic potential Ψ . However, we note that this component of stress is also controlled by the active prestress imposed by the stress-like tensor $\mathbf{A}$, as further discussed later.

The weak statement of balance of linear momentum in Eq. (A28) is the basis of the finite-element approximation of the theory, discussed later in Appendix B. For completeness, we provide next the more familiar spatial expression of the force-balance equations in the strong form. For this, we push forward all the functionals to the spatial configuration and perform variation of the Rayleighian functional with respect to the tangential and normal velocity fields, $\mathbf{v}_t$ and v_n . In the tangential direction, we obtain the following stationarity condition:

$$\int_{\Gamma} [\boldsymbol{\gamma} : \nabla \delta \mathbf{v}_t + (\eta_m \mathbf{v}_t - \mathbf{f}) \cdot \delta \mathbf{v}_t] dS = 0, \quad (\text{A30})$$

whereas in the normal direction we obtain

$$\int_{\Gamma} [-\boldsymbol{\gamma} : \mathbf{k} + \eta_m v_n - f_n] \delta v_n dS = 0. \quad (\text{A31})$$

Using the arbitrariness of the variations $\delta \mathbf{v}_t$ and δv_n and integration by parts, we obtain the strong form of momentum balance in the tangential and normal direction to the surface Γ

$$\nabla \cdot \boldsymbol{\gamma} + \mathbf{f} = \eta_m \mathbf{v}_t \quad \text{on } \Gamma, \quad (\text{A32a})$$

$$\boldsymbol{\gamma} : \mathbf{k} + f_n = \eta_m v_n \quad \text{on } \Gamma. \quad (\text{A32b})$$

The momentum balance equation in the normal direction is a generalized form of the Young-Laplace relation, relating the local curvature, surface tension, and pressure difference across the surface.

b. Turnover dynamics

Turnover dynamics follows from the variation of the Rayleighian with respect to r , leading to

$$0 = \delta_{\delta r} \mathcal{R} = \int_{\Gamma_0} \left[\Psi(\mathbf{C}, \mathbf{G}) + \frac{1}{\bar{k}} r - \alpha^p c + \alpha^d \rho \right] \delta r J dS_0, \quad (\text{A33})$$

for all variations δr , and hence

$$r = \underbrace{\bar{k} \alpha^p}_{k_p} c - \underbrace{\bar{k} \alpha^d}_{k_d} \rho - \bar{k} \Psi(\mathbf{C}, \mathbf{G}), \quad (\text{A34})$$

where we identify the polymerization and depolymerization rates discussed in Appendix A3 [39,41]. The last term in this equation is a thermodynamic driving force for turnover dynamics, according to which the active gel tends to disassemble to reduce its stored elastic energy. This term is ignored in the literature. To estimate whether this is a good approximation, we assume a metabolic rate for an epithelial cell of some tens of pW, and assume that 10% is spent sustaining turnover [121]. Consequently, the out-of-equilibrium chemical power

per unit area of cortex surface is of a few mW/m² for a cell with a surface area of 1000 μm^2 . We next estimate the mechanical power density associated with the first term in the integrand of Eq. (A33) to compare it with this estimation of the chemical power density driving turnover. The steady-state reaction rate can be estimated as $r = \bar{\rho}/\tau_{10}$, where τ_{10} is the turnover time, and hence the mechanical power per unit area of cortex surface can be estimated as $\bar{\rho} \Psi/\tau_{10} \approx \mu \epsilon/\tau_{10}$, where μ is the short-time shear modulus of the cortex, see Eq. (A21), and ϵ is the cortical strain. Considering a large strain of $\epsilon = 1$ to overestimate the mechanical component and assuming that μ is a few mN/m and τ_{10} a few tens of seconds (Appendix E), we estimate the mechanical power per unit area of cortical surface in the order of 0.1 mW/m². This rough estimation suggests that turnover is likely controlled by the out-of-equilibrium chemical potentials rather than by elastic driving forces. It also shows that mechanics and chemistry may both contribute to turnover dynamics and calls for a more detailed theoretical and experimental examination. For the sake of simplicity and to avoid introducing an additional parameter, we assume that this dimensionless number is small and ignore the mechanical contribution in Eq. (A34).

In summary, ignoring the mechanical coupling to turnover, we assume throughout the work that $r = k_p c - k_d \rho$. Except for the simulations in Fig. 3(e), we further assume a constant pool of cytosolic actin $c = c_0$. Under these conditions, the steady-state cortical thickness given by the condition $r = 0$ is

$$\bar{\rho} = k_p c_0 / k_d. \quad (\text{A35})$$

The characteristic timescale for turnover is $\tau_{10} = 1/k_d$.

c. Remodeling dynamics

Remodeling dynamics follows from the variation of the Rayleighian with respect to $\dot{\mathbf{G}}$, leading to

$$0 = \delta_{\dot{\mathbf{G}}} \mathcal{R} = \int_{\Gamma_0} \left[\varrho_0 \left(\frac{\partial \Psi}{\partial \dot{\mathbf{G}}^{IJ}} + \frac{\partial \Phi}{\partial \dot{\mathbf{G}}^{IJ}} \right) - \frac{1}{2} A_{IJ} \right] \delta \dot{\mathbf{G}}^{IJ} dS_0 \quad (\text{A36})$$

for all variations $\delta \dot{\mathbf{G}}^{IJ}$, and, hence, with our constitutive assumptions, we obtain

$$2\eta \frac{\varrho_0}{\bar{\rho}} \dot{\mathbf{G}}^{IJ} = -G^{IK} C_{KL} S^{e,LJ} + G^{IK} A_{KL} G^{LJ}. \quad (\text{A37})$$

This equation shows explicitly that the evolution of the material metric is driven by a thermodynamic contribution (the first term on the right-hand side), which tends to relax the elastic energy and is proportional to the elastic stress $\mathbf{S}^e$, and by an active term (the second term).

d. Summary of the governing equations and steady-state limit

In summary, the dynamics of the system are governed by the mass balance equation, expressed equivalently by Eq. (A9) or by Eq. (A10), the expression for the turnover reaction rate in Eq. (A34), the statement of mechanical force balance in Eq. (A28), and the evolution equation for the material metric in Eq. (A37). The main constitutive choices are the hyperelastic energy density function (Ψ), the dissipation potential for the material metric evolution (Φ), the forms of the spatial and

material active stresses ($\boldsymbol{\gamma}^a$ and $\mathbf{A}$), and the out-of-equilibrium chemical potentials driving turnover. These equations, independent of the choice of reference configuration, are a coupled system of partial differential equations for the shape, flow, and cortical density of the active gel surface, and of ordinary differential equations at each material point for the viscoelastic relaxation.

We examine now the steady state of this model, where $\dot{\varphi}$, $\dot{\varrho}_0$, and $\dot{\mathbf{G}}$ vanish. The mass balance equation shows that $r = 0$, which, ignoring the mechanical contribution to the turnover dynamics discussed above, leads to the steady-state cortical density $\rho = \bar{\rho} = k_p c_0 / k_d$. Equation (A37) shows that, at steady state,

$$\mathbf{S}^{e,II} = \mathbf{C}^{-1,IK} A_{KL} \mathbf{G}^{LJ}. \quad (\text{A38})$$

Let us consider two limiting scenarios for the mechanical active stresses. In Scenario 1, the material activity tensor $\mathbf{A}$ vanishes but $\xi \neq 0$. The equation above then shows that, in this scenario $\mathbf{S}^e = \mathbf{0}$, which for a reasonable elastic potential implies that $\mathbf{G}^{IJ} = \mathbf{C}^{-1,IJ}$, see the discussion following Eq. (A11). Thus, the elastic stresses dissipate completely by remodeling until the material metric has relaxed to the current deformation. Consequently, the stress tensor at steady state is uniform, isotropic, and exclusively of active origin, and can be expressed in the material frame as $\mathbf{S} = J\bar{\rho}\xi\mathbf{C}^{-1}$ and in the spatial frame as $\boldsymbol{\gamma} = \bar{\rho}\xi\mathbf{g}$. In Scenario 2, the spatial activity vanishes, $\xi = 0$ but $\mathbf{A}$ does not. In this case, only the elastic stress survives, but this stress cannot fully relax to zero because of the active power input driving the material metric away from its thermodynamic equilibrium $\mathbf{S} = \mathbf{S}^e = \mathbf{C}^{-1}\mathbf{A}\mathbf{G}$. This expression shows that it is possible to recover at steady state a uniform, isotropic stress tensor as in Scenario 1. Indeed, with the particular form of the material active stress

$$A_{IJ}(\varrho_0, \mathbf{C}, \mathbf{G}) = \varrho_0 \Xi G_{IJ}, \quad (\text{A39})$$

where Ξ is an activity parameter analogous to ξ , we recover at steady state $\mathbf{S} = J\bar{\rho}\Xi\mathbf{C}^{-1}$ and $\boldsymbol{\gamma} = \bar{\rho}\Xi\mathbf{g}$. In general, the material and spatial active stresses can act together to model different microscopic mechanisms of active contraction, leading to the steady state Cauchy stress $\boldsymbol{\gamma} = \bar{\rho}(\xi + \Xi)\mathbf{g}$. We note that, even if these two mechanisms of active contraction cannot be distinguished at steady state, they will, in general, lead to different dynamics (Fig. 10).

8. Comparison with junctional models in enhanced vertex models

As discussed in the introduction, our work is related to various enhanced vertex models that also try to understand the mechanics of epithelial tissues, starting from models of cellular junctions inspired by cytoskeletal dynamics [28–30,32–34]. These 2D vertex models assume that tissue mechanics is controlled by cell-cell linear junctions, which may be particularly appropriate for tissues with apical belts enriched with actomyosin, and propose various models to describe active contraction, remodeling, and mechanosensitivity of such junctions.

To establish a connection with such models, we particularize our active gel model to a 1D segment. In this case, the contravariant component of the material metric tensor

becomes $G = (L_0/L)^2$, where L_0 is the initial length and L the current resting length. A simple manipulation of Eq. (A37) then shows that $L^{-1}dL/dt$ is proportional to the difference between the elastic and active forces in the segment, $CS^e - AG$. Consequently, in the absence of elastic force, activity tends to shorten the segment, whereas when the active force is absent, the segment viscously elongates in response to the elastic force. It also shows that there is a stall elastic force for which the resting length does not change. The viscous part of these dynamics is considered in several enhanced vertex models [28,30,32,33], whereas the “walking-stall-slipping” phenomenology embodied in Eq. (A37) is postulated in Eq. (3) of Ref. [29]. In this reference, active contractility acts on the dynamics of the resting length, analogous to the action of the Lagrangian active stress $\mathbf{A}$ in Eq. (A37), whereas Ref. [32,33] consider an additive active contribution to junctional tension analogous to the role of the Eulerian active stress $\boldsymbol{\gamma}^a$ in our theory, Eq. (A29).

To describe various tissue processes driven by active T1 transitions, such as convergent extension, enhanced vertex models propose differential equations that control the mechanosensitive adaptation of active tension, i.e., accounting for myosin recruitment upon lengthening [29] or the catch-bond behavior of myosin [33]. Here, we do not account explicitly for such adaptive behaviors, which may require tracking explicitly the dynamics of myosins or other regulatory molecules. However, our turnover dynamics in Eqs. (1) and (2) together with the assumption that active stress is proportional to cortical density results in a stretch-induced reduction (and a compression-induced increase) of active tension, followed by the recovery to a baseline contractile tension, very much like Eq. (2) postulated in Ref. [32]. Taken together, this discussion suggests qualitative connections between the active gel model considered here and the active remodeling junctional dynamics of enhanced vertex models in the literature.

APPENDIX B: ASSEMBLING THE TISSUE MODEL, NUMERICAL DISCRETIZATION, AND COARSE-GRAINING

1. Tissue Rayleighian and governing equations

The previous section shows that the dynamics of an active gel surface with reference configuration Γ_0 , deformation map $\varphi(\mathbf{X}, t)$, Lagrangian cortical density $\varrho_0(\mathbf{X}, t)$, and material metric tensor field $\mathbf{G}(\mathbf{X}, t)$ can be obtained by minimizing the Rayleighian functional $\mathcal{R}[\dot{\varphi}, r, \dot{\mathbf{G}}; \varphi, \varrho_0, \mathbf{G}]$ with respect to the rates $\dot{\varphi}$, r , $\dot{\mathbf{G}}$ along with the statement of cortical mass balance in Eq. (A10).

As discussed in the main text, we view the epithelial tissue as an ensemble of active gel surfaces enclosing fixed cellular volumes. To formulate a mathematical model for such a system, we label cellular faces with index $f = 1, 2, \dots, N_F$, and introduce for each cell face f a reference configuration Γ_0^f (planar for convenience) and the fields φ^f , ϱ_0^f , $\mathbf{G}^f$, and r^f , allowing us to define the Rayleighian $\mathcal{R}^f$, which may contemplate different material parameters across the tissue. We also label cells with the index $c = 1, 2, \dots, N_C$, and edges where two faces meet with the index $e = 1, 2, \dots, N_E$. We

denote the set of cortical faces that delimit a given cell c by F_c , and the set of distinct pairs of faces that meet at edge e by F_e . For a pair of such faces, $(f, f') \in F_e$, their reference surfaces Γ_0^f and $\Gamma_0^{f'}$ are watertight along their common edge $E_0^e = \Gamma_0^f \cap \Gamma_0^{f'}$, and the condition that such faces remain watertight during deformation is expressed as $\varphi^f = \varphi^{f'}$ over E_0^e . If all cellular surfaces of cell c are watertight, then together they form a closed surface that delimits a 3D domain, whose volume can be computed using the divergence theorem as

$$V^c = \sum_{f \in F_c} \int_{\Gamma^f} \mathbf{n} \cdot \mathbf{F} dS = \sum_{f \in F_c} \int_{\Gamma_0^f} \mathbf{n} \cdot \mathbf{F} \circ \varphi^f J dS_0, \quad (\text{B1})$$

where $\mathbf{F}$ is a vector field with unit divergence such as $\mathbf{F} = (x, y, z)/3$.

Introducing the notation $\varphi^T = (\varphi^1, \dots, \varphi^{N_F})$, $\varrho_0^T = (\varrho_0^1, \dots, \varrho_0^{N_F})$, $\mathbf{G}^T = (\mathbf{G}^1, \dots, \mathbf{G}^{N_F})$, and $\mathbf{r}^T = (r^1, \dots, r^{N_F})$ for the deformation, cortical density, material metric, and reaction rate fields of the entire tissue, we can now form the tissue Rayleighian as

$$\begin{aligned} \mathcal{R}^T[\dot{\varphi}^T, \mathbf{r}^T, \dot{\mathbf{G}}^T; \varphi^T, \varrho_0^T, \mathbf{G}^T] \\ = \sum_{f=1}^{N_F} \mathcal{R}^f[\dot{\varphi}^f, r^f, \dot{\mathbf{G}}^f; \varphi^f, \varrho_0^f, \mathbf{G}^f], \end{aligned} \quad (\text{B2})$$

and the Lagrangian functional accounting for cell volume and edge constraints

$$\begin{aligned} \mathcal{L}^T[\dot{\varphi}^T, \mathbf{r}^T, \dot{\mathbf{G}}^T, P^T, \boldsymbol{\lambda}^T; \varphi^T, \varrho_0^T, \mathbf{G}^T] \\ = \mathcal{R}^T[\dot{\varphi}^T, \mathbf{r}^T, \dot{\mathbf{G}}^T; \varphi^T, \varrho_0^T, \mathbf{G}^T] - \sum_{c=1}^{N_C} P^c \dot{V}^c \\ + \sum_{e=1}^{N_E} \sum_{(f, f') \in F_e} \int_{E_0^e} \boldsymbol{\lambda}^{e, f, f'} \cdot (\dot{\varphi}^f - \dot{\varphi}^{f'}) d\ell_0, \end{aligned} \quad (\text{B3})$$

where P^c is the Lagrange multiplier enforcing the volume constraint of cell c (the cellular pressure), and $\boldsymbol{\lambda}^{e, f, f'}$ is the Lagrange multiplier enforcing watertightness of pairs of faces along edges (a traction field). Again, we introduce for convenience the tissue-wide variables P^T and $\boldsymbol{\lambda}^T$, collecting cellular pressures and edge tractions.

The constrained Onsager's variational formalism then stipulates that the dynamics of the tissue minimize $\mathcal{L}^T$ with respect to $\dot{\varphi}^T$, $\mathbf{r}^T$, and $\dot{\mathbf{G}}^T$, and maximize it with respect to P^T and $\boldsymbol{\lambda}^T$. The first-order optimality conditions

$$\begin{aligned} 0 = \delta_{\dot{\varphi}^T} \mathcal{L}^T, \quad 0 = \delta_{\mathbf{r}^T} \mathcal{L}^T, \quad 0 = \delta_{\dot{\mathbf{G}}^T} \mathcal{L}^T, \\ 0 = \delta_{P^T} \mathcal{L}^T, \quad 0 = \delta_{\boldsymbol{\lambda}^T} \mathcal{L}^T \end{aligned} \quad (\text{B4})$$

encode a coupled system of differential and algebraic equations to solve for the velocity $\dot{\varphi}^T$, the turnover rate $\mathbf{r}^T$, and the rate of change of material metric $\dot{\mathbf{G}}^T$ of all cortical surfaces in the tissue, for the pressure P^T of all cells in the tissue, and for the edge tractions $\boldsymbol{\lambda}^T$ keeping cellular faces together. Together with the cortical mass balance in Eq. (A10) for each cellular

surface, these fields allow us to evolve the state of the system given by $(\varphi^T, \varrho_0^T, \mathbf{G}^T)$.

2. Numerical discretization and coarse-graining using the Rayleigh-Ritz method

This optimization principle involves infinite-dimensional function spaces for all the unknown fields, and is analytically intractable in general. As discussed in the main text, a key benefit of the variational formalism is that it is ideally suited for analytical or numerical approximations using the classical Rayleigh-Ritz approximation method. In this method, an approximate solution is obtained by restricting the admissible functions to a finite-dimensional subspace and optimizing the functional within that subspace. In the main text, we discuss a hierarchy of increasingly coarse finite-dimensional approximation spaces, leading to tissue models ranging from high-fidelity finite element models to idealized vertex models for crystalline tissues undergoing affine deformations (Appendix C). In all cases, these models solve for the turnover and remodeling dynamics in the active gel surfaces of the tissue. In addition to enabling the numerical discretization of the problem in space, Onsager's formalism provides a variational framework for stable time-integration of the governing equations by discretizing in time the variational principle itself to define a time-incremental Rayleighian [47,75].

In summary, we have shown that Onsager's variational formalism allows us to transparently formulate the dynamics of an ensemble of active gel surfaces enclosing constant cellular volumes. Furthermore, the variational structure enables the systematic coarse-graining of this model through the classical Rayleigh-Ritz approximation method, leading to a hierarchy of tissue models of increasing simplicity.

APPENDIX C: IDEALIZED MODEL FOR A CRYSTALLINE TISSUE UNDER AFFINE STRETCH

We consider here an idealized epithelial tissue made of repeating units of polyhedral cells with flat regular hexagonal apico-basal faces and rectangular lateral faces in the reference state. We further consider two simple loading scenarios on such crystalline tissue: equibiaxial stretching where cells retain their regular hexagonal shape throughout the deformation, and uniaxial stretching along the hexagon's long axis keeping the width fixed (Fig. 8). In both cases, we assume affinity, i.e., that the deformation of each cell follows that of the tissue, and therefore each of the faces of the tissue remains planar with uniform density and material metric tensor. Thanks to the crystalline structure of the tissue and the uniformity of the allowed deformations, it is sufficient to study the dynamics of a single cell. Following the Rayleigh-Ritz method, we explicitly encode these assumptions into a constrained Rayleighian for the idealized tissue, and then minimize it with respect to the coarse-grained variable to obtain the governing equations of the Idealized active gel Vertex Model (IagVM). For concreteness, we develop the IagVM in the case of purely Eulerian active stress ($\mathbf{A} = \mathbf{0}$) and neglect the mechanical coupling to turnover reactions, the last term in Eq. (A34).

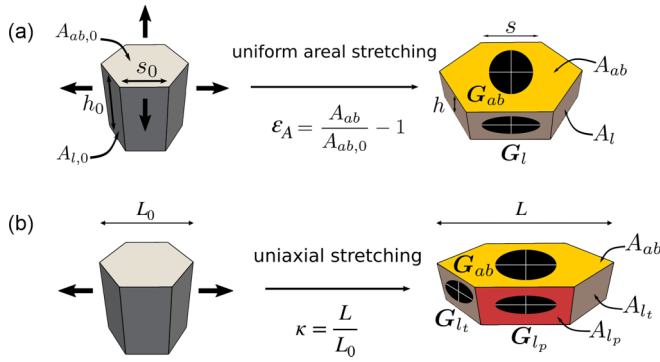


FIG. 8. (a) Illustration of the equibiaxial deformation of a cell in an idealized crystalline tissue. The ellipses represent the material metric tensor of apico-basal and of lateral surfaces after relaxation, when they adjust to the imposed deformation. (b) Analogous illustration for a uniaxial deformation.

1. Dynamics under equibiaxial deformation

For a regular hexagonal prism under equibiaxial deformation, all the lateral surfaces are mechanically equivalent. Apical and basal surfaces are also equivalent. We can express the current apico-basal area of the cell as $A_{ab} = (1 + \epsilon_A)A_{ab,0}$, where ϵ_A is the tissue areal strain and $A_{ab,0}$ is the initial apico-basal area of the cell, Fig. 8(a). Furthermore, volume conservation, $A_{ab,0}h_0 = A_{ab}h$, allows us to compute the cell height as a function of ϵ_A as $h = V_0/A_{ab} = h_0/(1 + \epsilon_A)$. The surface area of each of the six rectangular lateral faces after deformation, $A_l = sh$, can be computed by noting that the edge of the hexagon deforms according to $s = s_0\sqrt{1 + \epsilon_A}$, from which we conclude that $A_l = A_{l,0}/\sqrt{1 + \epsilon_A}$. The Jacobians of apico-basal and lateral surfaces are given by

$$J_{ab} = A_{ab}/A_{ab,0} = 1 + \epsilon_A, \quad (C1)$$

and

$$J_l = A_l/A_{l,0} = \frac{1}{\sqrt{1 + \epsilon_A}}. \quad (C2)$$

The right Cauchy–Green deformation tensor on the apico-basal faces is isotropic and given by

$$\mathbf{C}_{ab} = \begin{pmatrix} 1 + \epsilon_A & 0 \\ 0 & 1 + \epsilon_A \end{pmatrix}. \quad (C3)$$

For lateral faces, aligning the Cartesian coordinates with the sides of the rectangle [Fig. 8(a)], we obtain

$$\mathbf{C}_l = \begin{pmatrix} 1 + \epsilon_A & 0 \\ 0 & \frac{1}{(1 + \epsilon_A)^2} \end{pmatrix}. \quad (C4)$$

Thus, in such an idealized model, the areal strain of the tissue ϵ_A parametrizes all kinematic variables. Analogously, by the symmetry of our system, $\mathbf{G}_{ab}$ is an isotropic tensor, which depends on a single scalar that we denote as G_{ab} , and $\mathbf{G}_l$ is a diagonal tensor, whose diagonal elements are denoted by G_l^I and G_l^{II} . We can thus particularize the elastic potential $W(\mathbf{C}, \mathbf{G})$ to apico-basal and lateral surfaces and express it as functions of our reduced unknowns, that is, $W_{ab}(\epsilon_A, G_{ab})$ and $W_l(\epsilon_A, G_l^I, G_l^{II})$. This is clear by recalling Eq. (A21) and

noting that, on apico-basal faces

$$\tilde{I}_{1,ab} = 2G_{ab}(1 + \epsilon_A), \quad \tilde{I}_{3,ab} = G_{ab}^2(1 + \epsilon_A)^2, \quad (C5)$$

whereas on lateral faces

$$\begin{aligned} \tilde{I}_{1,l} &= G_l^I(1 + \epsilon_A) + G_l^{II}/(1 + \epsilon_A)^2, \\ \tilde{I}_{3,l} &= G_l^I G_l^{II}/(1 + \epsilon_A). \end{aligned} \quad (C6)$$

From Eqs. (C1) and (C2), we immediately obtain that

$$\frac{\dot{J}_{ab}}{J_{ab}} = \frac{\dot{\epsilon}_A}{1 + \epsilon_A} = -2\frac{\dot{J}_l}{J_l}. \quad (C7)$$

With these expressions and recalling Eq. (1), we obtain the evolution equations for the apico-basal and lateral densities as the ordinary differential equations

$$\dot{\rho}_{ab} + \rho_{ab} \frac{\dot{\epsilon}_A}{(1 + \epsilon_A)} = k_p c_0 - k_d \rho_{ab}, \quad (C8a)$$

$$\dot{\rho}_l - \rho_l \frac{\dot{\epsilon}_A}{2(1 + \epsilon_A)} = k_p c_0 - k_d \rho_l. \quad (C8b)$$

In the unit cell of the crystalline tissue, there are two apico-basal surfaces and six lateral surfaces. Therefore, the rate of change of free energy in the unit cell is

$$\dot{\mathcal{F}} = 2\dot{\mathcal{F}}_{ab} + 6\dot{\mathcal{F}}_l, \quad (C9)$$

where adapting Eq. (A14) to the present setting, we have

$$\begin{aligned} \dot{\mathcal{F}}_{ab} &= \frac{\rho_{ab}}{\bar{\rho}}(1 + \epsilon_A) \left(\frac{\partial W_{ab}}{\partial G_{ab}} \dot{G}_{ab} + \frac{\partial W_{ab}}{\partial \epsilon_A} \dot{\epsilon}_A \right) A_{ab,0}, \\ \dot{\mathcal{F}}_l &= \frac{\rho_l}{\bar{\rho}} \frac{1}{\sqrt{1 + \epsilon_A}} \left(\frac{\partial W_l}{\partial G_l^I} \dot{G}_l^I + \frac{\partial W_l}{\partial G_l^{II}} \dot{G}_l^{II} + \frac{\partial W_l}{\partial \epsilon_A} \dot{\epsilon}_A \right) A_{l,0}. \end{aligned} \quad (C10)$$

Analogously, we can write the dissipation potential in the unit cell as

$$\mathcal{D} = 2\mathcal{D}_{ab} + 6\mathcal{D}_l, \quad (C11)$$

where

$$\mathcal{D}_{ab} = \eta \frac{\rho_{ab}}{\bar{\rho}} (1 + \epsilon_A) \left(\frac{\dot{G}_{ab}}{G_{ab}} \right)^2 A_{ab,0}, \quad (C12a)$$

$$\mathcal{D}_l = \frac{\eta}{2} \frac{\rho_l}{\bar{\rho}} \frac{1}{\sqrt{1 + \epsilon_A}} \left[\left(\frac{\dot{G}_l^I}{G_l^I} \right)^2 + \left(\frac{\dot{G}_l^{II}}{G_l^{II}} \right)^2 \right] A_{l,0}. \quad (C12b)$$

Adapting to the present setting Eq. (A24) for the active power input, we obtain

$$\begin{aligned} \mathcal{P} &= 2\mathcal{P}_{ab} + 6\mathcal{P}_l = \left[2\gamma_{ab} - \frac{3A_{l,0}}{A_{ab,0}} \frac{\gamma_l}{(1 + \epsilon_A)^{3/2}} \right] \dot{\epsilon}_A A_{ab,0} \\ &= \sigma^a \dot{A}_{ab}, \end{aligned} \quad (C13)$$

where $\gamma_{ab} = \rho_{ab}\xi_{ab}$ and $\gamma_l = \rho_l\xi_l$ are the apico-basal and lateral active surface tensions. This expression allows us to identify the term between brackets as the active component of tissue tension

$$\sigma^a = 2\gamma_{ab} - k \frac{\gamma_l}{(1 + \epsilon_A)^{3/2}}, \quad (C14)$$

with $k = 3A_{l,0}/A_{ab,0}$ is a fixed geometric constant given by the reference state of the tissue.

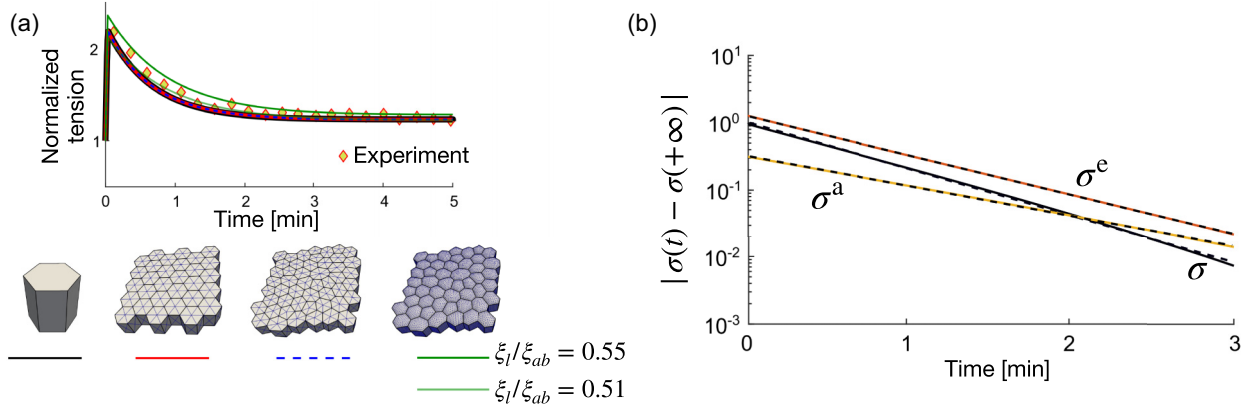


FIG. 9. (a) Quantitative agreement in a stress-relaxation scenario [that of Fig. 3(b)] between the idealized tissue model, a multicellular tissue made of hexagonal prismatic cells with the CagVM, and a disordered multicellular tissue with apical cell geometries taken from an experiment with the CagVM and the agVM models. In the agVM model, because of the curvature of cellular faces, a better agreement is found by adjusting the ratio between lateral and apicobasal active tensions. Experimental data are taken from Ref. [15]. (b) Total tissue tension (black) along with its elastic (orange) and active (yellow) components as a function of time in semilogarithmic scale to highlight exponential relaxation. Dashed lines show the exponential fit.

To include the power exerted by an externally applied tension σ on the tissue, we further include the external power input

$$\mathcal{P}^{\text{ext}} = -\sigma \dot{A}_{ab} = -\sigma \dot{\varepsilon}_A A_{ab,0}. \quad (\text{C15})$$

Gathering all the contributions, we write the Rayleighian for the unit cell of the tissue as

$$\mathcal{R}(X; V) = \dot{\mathcal{F}}(X; V) + \mathcal{D}(X; V) + \mathcal{P}(X; V) + \mathcal{P}^{\text{ext}}(X; V), \quad (\text{C16})$$

where $X = \{\varepsilon_A, G_{ab}, G_l^I, G_l^{II}\}$ collects all the state variables and V the corresponding time derivatives. Minimization of the Rayleighian with respect to the time derivatives of the material tensor components yields

$$\dot{G}_{ab} = -\frac{1}{2\eta} G_{ab}^2 \frac{\partial W_{ab}}{\partial G_{ab}}, \quad (\text{C17a})$$

$$\dot{G}_l^I = -\frac{1}{\eta} (G_l^I)^2 \frac{\partial W_l}{\partial G_l^I}, \quad (\text{C17b})$$

$$\dot{G}_l^{II} = -\frac{1}{\eta} (G_l^{II})^2 \frac{\partial W_l}{\partial G_l^{II}}. \quad (\text{C17c})$$

Then, minimizing the Rayleighian with respect to $\dot{\varepsilon}_A$, we obtain the expression for the total tissue tension as

$$\sigma = \sigma^a + \sigma^e = 2\gamma_{ab} - k \frac{\gamma_l}{(1 + \varepsilon_A)^{3/2}} + 2 \frac{\rho_{ab}}{\bar{\rho}} (1 + \varepsilon_A) \frac{\partial W_{ab}}{\partial \varepsilon_A} + 2k \frac{\rho_l}{\bar{\rho}} \frac{1}{\sqrt{1 + \varepsilon_A}} \frac{\partial W_l}{\partial \varepsilon_A}, \quad (\text{C18})$$

which clearly shows the additive decomposition of tissue tension into its active and its elastic components.

In a scenario where the total tension $\sigma(t)$ is given as a function of time, then Eqs. (C8), (C17), and (C18) provide a system of coupled and nonlinear ordinary differential-algebraic equations to solve for $\varepsilon_A(t)$, $G_{ab}(t)$, $G_l^I(t)$, $G_l^{II}(t)$, $\rho_{ab}(t)$, and $\rho_l(t)$. If instead $\varepsilon_A(t)$ is given, then Eq. (C18) can be interpreted as a constitutive equation for the tissue, whose

evaluation requires the time integration of Eqs. (C8) and (C17) to solve for the material metric tensor components and the densities.

For the stress-relaxation scenario studied in Fig. 3(b), we compared this idealized model, where we simply need to integrate a small system of differential-algebraic equations, with various tissue models of varying complexity, finding a remarkably good agreement [Fig. 9(a)]. In the reduced tissue model, following a step change in ε_A , the relaxation of the densities is exponential, and therefore the relaxation of the active tensions is also exponential. Instead, the relaxation of the material metric tensors, and hence that of tension, is not exponential and can be expressed in terms of Lambert W functions. However, the resulting dynamics for σ^e closely follow an exponential [Fig. 9(b)]. The combined effect of active and elastic relaxations also results in a nearly exponential relaxation of the total tissue tension.

2. Linear stability analysis

To analyze the stability of equibiaxial steady states of the system, we reformulate our problem by splitting the unknowns between those governed by ordinary differential equations (ODEs), $\mathbf{x} = \{G_{ab}, G_l^I, G_l^{II}, \rho_{ab}, \rho_l\}$, and that governed by an algebraic equation, $y = \varepsilon_A$. Then, the governing equations can be cast into a system of semi-explicit Differential-Algebraic equations (DAEs) of index 1 [125] of the form

$$\begin{aligned} \dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x}, y), \\ 0 &= g(\mathbf{x}, y), \end{aligned} \quad (\text{C19})$$

where the first equation encodes Eqs. (C8) and (C17) and the second equation encodes Eq. (C18). Since $g(\mathbf{x}, y) = 0$ and $\partial_y g$ is nonsingular, we can use the implicit function theorem to express y as a function of $\mathbf{x}$ and obtain a reduced system of ODEs given by [125]

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, y(\mathbf{x})) = \hat{\mathbf{f}}(\mathbf{x}). \quad (\text{C20})$$

The fixed points $\mathbf{x}^*$ of this system, characterized by $\hat{\mathbf{f}}(\mathbf{x}^*) = 0$, coincide with those of the original DAEs. Linearizing the reduced system about a fixed point $\mathbf{x}^*$ as $\mathbf{x}(t) = \mathbf{x}^* + \epsilon \mathbf{z}(t)$, we obtain the linear system of ODEs $\dot{\mathbf{z}}(t) = \mathbf{A} \mathbf{z}(t)$, where the matrix $\mathbf{A}$ is given by

$$\mathbf{A} = \frac{D\hat{\mathbf{f}}}{D\mathbf{x}}(\mathbf{x}^*) = \frac{D\mathbf{f}}{D\mathbf{x}}(\mathbf{x}^*, y(\mathbf{x}^*)) - \frac{D\mathbf{f}}{Dy}(\mathbf{x}^*, y(\mathbf{x}^*)) \left(\frac{Dg}{Dy}(\mathbf{x}^*, y(\mathbf{x}^*)) \right)^{-1} \frac{Dg}{D\mathbf{x}}(\mathbf{x}^*, y(\mathbf{x}^*)). \quad (\text{C21})$$

Because the solutions of the linearized system take the form $\mathbf{z}(t) = \exp(t\mathbf{A})\mathbf{z}_0$, the stability of the fixed point $\mathbf{x}^*$ is determined by the spectrum of $\mathbf{A}$, which depends on model parameters. The fixed point is stable (unstable) if all (any) of the eigenvalues have a negative (positive) real part. The imaginary part of an eigenvalue indicates whether the corresponding stable (unstable) mode evolves toward zero (infinity) with oscillations.

To identify the fixed points of the system, we note that at steady state $\sigma = \sigma^a$, and therefore we can obtain the steady-state strain as

$$\varepsilon_A^* = \left(\frac{k\gamma_l}{2\gamma_{ab} - \sigma} \right)^{2/3} - 1. \quad (\text{C22})$$

The condition that elastic tension has fully relaxed is met when $\tilde{l}_1 = 2$ and $\tilde{l}_3 = 1$ on apicobasal and on lateral surfaces, which using Eqs. (C5) and (C6) allows us to identify the steady-state components of the material metric as

$$G_{ab}^* = 1/(1 + \varepsilon_A), \quad G_l^{I,*} = 1/(1 + \varepsilon_A), \quad G_l^{II,*} = (1 + \varepsilon_A)^2. \quad (\text{C23})$$

Finally, the steady-state densities are simply $\rho_{ab}^* = \rho_l^* = \bar{\rho}$. We used Matlab's symbolic toolbox [126] to evaluate the Jacobian of the system $\mathbf{A}$ and its spectrum, allowing us to classify the stability of the system across the parameter space. We color-coded steady states with dark green for real positive eigenvalues, light green for complex eigenvalues with positive real part, orange for complex eigenvalues with negative real part, and red for real negative eigenvalues (see Fig. 7).

3. Dynamics under uniaxial deformation

Similarly to the equibiaxial case, we derive the kinematics for a cell under uniaxial deformation. We assume that the cell is stretched uniaxially along its long diagonal with a stretch ratio κ [Fig. 8(b)]. Under such assumption, the apico-basal surface area changes as $A_{ab} = \kappa A_{ab,0}$, with the Jacobian of the deformation on the apico-basal surfaces given by $J_{ab} = \kappa$ and the right Cauchy–Green deformation tensor given by

$$\mathbf{C}_{ab} = \begin{pmatrix} \kappa^2 & 0 \\ 0 & 1 \end{pmatrix}. \quad (\text{C24})$$

For the lateral surfaces, we need to distinguish the deformation of the two faces parallel to the direction of stretching, which we refer to as A_{lp} , and the deformation of the four other

transverse surfaces which we refer to as A_{lt} [Fig. 8(b)]. Using simple geometric arguments, we can compute the stretch ratios along each edge on a lateral face. Edges aligned in the direction of the applied deformation will be stretched by κ . Due to volume conservation of the cell, edges along the height of the cell will be stretched by a ratio of $1/\kappa$. Finally, edges in the transverse direction will be stretched by a ratio of $(\kappa^2 + 3)^{1/2}/2$. Therefore, the Jacobians of the deformation on the lateral surfaces are given as

$$J_{lp} = \frac{A_{lp}}{A_{lp,0}} = 1 \quad \text{and} \quad J_{lt} = \frac{A_{lt}}{A_{lt,0}} = \frac{\sqrt{\kappa^2 + 3}}{2\kappa}. \quad (\text{C25})$$

The corresponding Cauchy–Green deformation tensors are given by

$$\mathbf{C}_{lp} = \begin{pmatrix} \kappa^2 & 0 \\ 0 & \frac{1}{\kappa^2} \end{pmatrix} \quad \text{and} \quad \mathbf{C}_{lt} = \begin{pmatrix} \frac{3+\kappa^2}{4} & 0 \\ 0 & \frac{1}{\kappa^2} \end{pmatrix}. \quad (\text{C26})$$

Using the symmetries of the uniaxial setting, now $\mathbf{G}_{ab}$ is diagonal with two components, along and perpendicular to the stretch direction, which we denote by G_{ab}^I and G_{ab}^{II} . Analogously, the material metric tensor in parallel lateral and transverse lateral surfaces can be described by two scalars along the principal directions. Following an analogous procedure to the equibiaxial one, we can derive ordinary differential equations for the unknowns $\mathbf{x} = \{G_{ab}^I, G_{ab}^{II}, G_{lp}^I, G_{lp}^{II}, G_{lt}^I, G_{lt}^{II}, \rho_{ab}, \rho_{lp}, \rho_{lt}\}$, and an algebraic mechanical equation for the uniaxial stretch $y = \kappa$.

4. Modeling actin depletion under stretch

As discussed in Ref. [4], epithelial softening can take place as a result of the exhaustion of cytosolic material for polymerization of the actin cortex. To model this in our superelasticity simulations, we assume that the total mass of actin material M is constant in each cell, which can be expressed as

$$\int_{\Gamma_{\text{cell}}} \rho dS + cV_0 = M, \quad (\text{C27})$$

where Γ_{cell} is the surface of a cell and V_0 is its fixed volume. We denote by S the total area of the cell and S_0 its total area in a reference configuration. As a cell becomes stretched, S increases but V_0 remains constant. In the steady state, combining this equation with the turnover equation, we obtain

$$\bar{\rho} = \frac{M/S_0}{\frac{S}{S_0} + \frac{V_0 k_d}{S_0 k_p}}. \quad (\text{C28})$$

This expression shows that the dimensionless number $V_0 k_d / (S_0 k_p)$ controls the sensitivity to stretch-induced softening.

APPENDIX D: MECHANICAL BARRIER TO LARGE STRETCH OR COMPRESSION

As argued in the main text, at large stretches, the actomyosin cytoskeleton is thought to cease being the main cytoskeletal structure responsible for tissue tension because intermediate filaments become engaged. Besides intermediate filaments, the packing of adhesion molecules in shrinking cell-cell junctions or the nucleus trapped between tense apico-basal cortices can also result in strain-stiffening of the tissue.

TABLE I. Model parameters for Figs. 2 and 3(e).

Panel	$\bar{\lambda}$	λ/μ	τ_{ve}/τ_{to}	ξ_l/ξ_{ab}	K_{high}/λ	K_{low}/λ	J_{high}	J_{low}	$V_0 k_d/(S_0 k_p)$
Fig. 2(a)	1	1	0.5	0.5					
Fig. 2(b)	1	1	0.5	0.46	0.033	166.67	5	0.12	
Fig. 3(e)	0.2, 0.4, 1	1	0.5	0.46	0.033	166.67	6	0.12	10.07

Under compression, crowding at apico-basal surfaces or the nucleus can also result in strain-stiffening.

Even though the strain-stiffening response of intermediate filaments is rate-dependent [19], turnover and reorganizations of these and other structural elements of the cell are much slower than those of the actomyosin cortex and hence are viewed here as rate-independent components described by an effective free energy. To account for all these strain-stiffening mechanisms at large compression or stretch in a simplified manner, we consider a rather unspecific mechanical barrier limiting excessive stretching or lateral compression of cells. In our model, this barrier only becomes active at relatively large strains. We implemented a cubic energy functional on each surface that limits individual surface expansion after a certain threshold J_{high} :

$$\mathcal{F}_{high} = \int_{\Gamma_0} K_{high} \langle J - J_{high} \rangle^3 dS_0, \quad (D1)$$

where $\langle x \rangle = x$ if $x > 0$ and zero otherwise, and K_{high} modulates the strength of the resistance to deformations. We also implemented a cubic functional serving as a barrier to surface compression after a certain threshold J_{low} of the form

$$\mathcal{F}_{low} = \int_{\Gamma_0} K_{low} \langle J_{low} - J \rangle^3 dS_0. \quad (D2)$$

APPENDIX E: MATERIAL PARAMETERS

Parameter values were estimated from experimental data available in the literature. For instance, the monolayers under consideration have a thickness of about 10 to 15 μm [13]. Assuming a typical cell edge length s_0 to be around 5 μm [13], we chose the aspect ratio of cells at initial state to be $h_0/s_0 = 2$. Furthermore, we assumed that apical and basal tensions are contractile, and that contractility on the lateral faces dominates over adhesion so that ξ_a , ξ_b , and ξ_l are all positive quantities [127]. Due to adhesion energy at cell-cell contacts lowering the lateral surface tension [50], we reasoned that surface tension on lateral cell faces is lower than the average apico-basal surface tension. This ratio ξ_l/ξ_{ab} also determines the steady-state tension after stretch and the contact angle between faces, and was chosen in agreement with the observed geometry of cells, resulting in $\xi_l/\xi_{ab} \approx 0.1$ –1. Cortical viscoelastic remodeling due to cross-linker turnover is expected to be faster than the actin turnover such that $\tau_{ve}/\tau_{to} \approx 0.01$ –0.75 [3,55,128,129]. Following these references, we estimated cortical tensions in the mN/m range and turnover timescales of tens of seconds. For the ratio between cortical elasticity and active tension, $\bar{\lambda} = \lambda/\bar{\gamma}$, we turned to single-cell data in the low-frequency limit to estimate that this parameter should be close to one [129]. Finally, the spring-pot

material parameters $\{C_\alpha, \alpha\}$ were chosen to fit stress relaxation experiments in Ref. [3] and are compatible with physical estimates found in the literature [87,130]. Parameter values for each simulation are summarized in Tables I–VI.

Throughout the paper, we assume for concreteness that active tension is purely Eulerian, i.e., $\mathcal{P}^a$ is different from zero but $\mathbf{A}$ vanishes. We also implemented the case of nonzero $\mathbf{A}$, finding qualitatively similar results. To illustrate this, we use Eq. (A39) for $\mathbf{A}$ and compare our standard model with Eulerian activity parameters ξ_a , ξ_b , and ξ_l , and $\mathbf{A} = \mathbf{0}$ with one with the same Lagrangian activity parameters Ξ_a , Ξ_b and Ξ_l , and $\mathcal{P}^a = \mathbf{0}$, so that both models have the same steady state. All other parameters in the standard and alternative models are identical. Figure 10(a) shows a comparison of both models regarding the stretch-unstretch maneuver of Fig. 3(b) showing that both models agree in the steady states, in the qualitative dynamics, but predict different tensions out of equilibrium, as expected. Revisiting Fig. 7(c2), Fig. 10(b) shows the orbits of both models in the lagVM approximation for a parameter regime where the quiescent steady state is unstable, and pulsations are expected, showing a similar behavior with close limit cycles.

APPENDIX F: POWER-LAW RHEOLOGY: MATERIALS WITH MEMORY

For simplicity, we implemented the power-law rheology in a uniaxially stretched idealized tissue, see Appendix C 3. The key step for our modeling framework based on Onsager's variational formalism is to identify a meaningful rate of change of free energy and dissipation potential for the spring-pot element, which can then be added to the Rayleighian functional. Several works have investigated the formulation of thermodynamically consistent free energy and dissipation functionals for such fractional hereditary materials [131,132]. For a 1D spring-pot element, the free energy per unit volume is given by

$$\mathcal{F} = D_\alpha \int_{-\infty}^t \int_{-\infty}^t (2t - \tau_1 - \tau_2)^{-\alpha} \dot{\epsilon}(\tau_1) \dot{\epsilon}(\tau_2) d\tau_1 d\tau_2, \quad (F1)$$

where $D_\alpha = C_\alpha/[2\Gamma(1 - \alpha)]$ and Γ denotes the Gamma function [87]. C_α (with units of $\text{Pa} \cdot \text{s}^{-\alpha}$) and α are the material parameters characterizing the spring-pot element. The free energy in Eq. (F1) is fundamentally paired to a specific dissipation rate. By an argument involving the Clausius–Duhem inequality, the associated dissipation rate reads [132]

$$\mathcal{D} = 2\alpha D_\alpha \int_{-\infty}^t \int_{-\infty}^t (2t - \tau_1 - \tau_2)^{-\alpha-1} \dot{\epsilon}(\tau_1) \dot{\epsilon}(\tau_2) d\tau_1 d\tau_2. \quad (F2)$$

TABLE II. Model parameters for Fig. 3.

Panel	$\bar{\lambda}$	λ/μ	τ_{to}	τ_{ve}	τ_{ve}/τ_{to}	ξ_l/ξ_{ab}	α	C_α	$\bar{\gamma}_{ab}$	$C_\alpha h_0/(\bar{\gamma}_{ab} \tau_{ve}^\alpha)$
Fig. 3(b)	0.4	1	60 s	45 s	0.75	0.55				
Fig. 3(c)	0.6	1	30 s	10 s	0.33	0.4	0.4	2534 Pa s ^{α}	0.975 mNm ⁻¹	10.35
Fig. 3(d)	0.6	1			0.33	0.4	0.4			10.35

TABLE III. Model parameters for Fig. 4.

Panel	$\bar{\lambda}$	λ/μ	τ_{to}	τ_{ve}	τ_{ve}/τ_{to}	ξ_l/ξ_{ab}	K_{high}/λ	K_{low}/λ	J_{high}	J_{low}	$a\Delta P/\bar{\gamma}_{ab}$
Figs. 4(e) and 4(i)	1	1	38 s	19 s	0.5	0.7	0.333	166.67	2.3	0.12	1.211, 2.423, 3.6340, 4.845, 6.057, 7.268, 8.479

TABLE IV. Model parameters for Fig. 5.

Panel	$\bar{\lambda}$	λ/μ	τ_{to}	τ_{ve}	τ_{ve}/τ_{to}	ξ_l/ξ_{ab}	K_{high}/λ	K_{low}/λ	J_{high}	J_{low}	$a\Delta P/\bar{\gamma}_{ab}$
Figs. 5(b)–5(d)	1	1	38 s	19 s	0.5	0.7	0.333	166.67	2.3	0.12	6.057

TABLE V. Model parameters for Fig. 6.

Panel	$\bar{\lambda}$	λ/μ	τ_{ve}/τ_{to}	ξ_a	ξ_b	ξ_l/ξ_{ab}	K_{high}/λ	K_{low}/λ	J_{high}	J_{low}
Figs. 6(a) and 6(b)	1	1	0.25			0.5				
Figs. 6(c) and 6(d)	1	1	0.5	0.8, 0.6667	1.2, 1.3333	0.5	0.033	166.67	6	0.12
Figs. 6(e)	1	1	0.5	0.333	1.667	0.4				

TABLE VI. Model parameters for Fig. 7. In the last column, we report the viscous drag or friction of the monolayer with the substrate, ζ_m , in dimensionless terms as the ratio between the tissue size L and the hydrodynamic length $\sqrt{\eta/\zeta_m}$.

Panel	$\bar{\lambda}$	λ/μ	$\bar{\eta}$	ξ_l/ξ_{ab}	K_{high}/λ	K_{low}/λ	J_{high}	J_{low}	$L\sqrt{\frac{\eta_m}{\eta}}$
Figs. 7(a)–7(c)	1	1	0.3	0.5					
Fig. 7(c)	1	1	0.3	0.5	0.1667	0.1667	10	0.1	
Figs. 7(f)–7(h)	0.6, 0.3, 0.1	1	0.02	0.5	3.333	3.333	1.5	0.8	
Figs. 7(i) and 7(j)	0.6	1	0.01	0.5	3.333	3.333	1.5	0.8	28

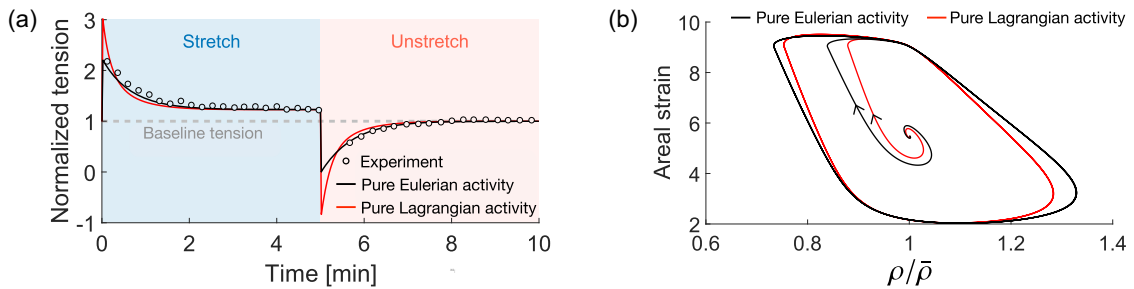


FIG. 10. Comparison of the standard model with purely Eulerian activity, $\gamma^a = \rho \xi \mathbf{g}$ and $\mathbf{A} = \mathbf{0}$, and an alternative model with purely Lagrangian activity, $\gamma^a = \mathbf{0}$ and $\mathbf{A} = \varrho_0 \xi \mathbf{G}$. (a) Tissue tension following a stretch-unstretch maneuver, Fig. 3(b), where the parameters of the alternative model with purely Lagrangian activity have not been changed to fit the experiments. (b) Density-area orbits reaching a limit cycle with both models, in a parameter regime where we expect tissue pulsations, Fig. 7(c2). In panels (a) and (b), we consider the IagVM.

Since the precise cellular structure responsible for the required broad spectrum of relaxation mechanisms is not clear, we associated the spring-pot power-law element to the bulk cytosolic or cytoskeletal shear rate. For a volume-preserving uniaxial deformation of the cytosol, the deformation gradient can be expressed as

$$\mathbf{F} = \begin{pmatrix} \kappa & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & \frac{1}{\kappa} \end{pmatrix}, \quad (\text{F3})$$

where κ is the uniaxial stretch ratio in the tissue, see Appendix C 3. The rate-of-deformation tensor can then be computed as

$$\mathbf{d} = \dot{\mathbf{F}}\mathbf{F}^{-1} = \begin{pmatrix} \frac{\dot{\kappa}}{\kappa} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & -\frac{\dot{\kappa}}{\kappa} \end{pmatrix}, \quad (\text{F4})$$

from which we can identify a scalar strain rate as $\dot{\epsilon} = \sqrt{2}\dot{\kappa}/\kappa$. Replacing this Expression in Eq. (F1) and multiplying by the cell volume, we obtain

$$\mathcal{F} = 2D_\alpha V_0 \int_{-\infty}^t \int_{-\infty}^t (2t - \tau_1 - \tau_2)^{-\alpha} \times \frac{\dot{\kappa}}{\kappa}(\tau_1) \frac{\dot{\kappa}}{\kappa}(\tau_2) d\tau_1 d\tau_2. \quad (\text{F5})$$

Using the Liebnitz integral rule, we can compute

$$\begin{aligned} \dot{\mathcal{F}} &= 4D_\alpha V_0 \frac{\dot{\kappa}}{\kappa}(t) \int_{-\infty}^t (t - \tau)^{-\alpha} \frac{\dot{\kappa}}{\kappa}(\tau) d\tau - 4\alpha D_\alpha V_0 \\ &\times \int_{-\infty}^t \int_{-\infty}^t (2t - \tau_1 - \tau_2)^{-\alpha-1} \frac{\dot{\kappa}}{\kappa}(\tau_1) \frac{\dot{\kappa}}{\kappa}(\tau_2) d\tau_1 d\tau_2. \end{aligned} \quad (\text{F6})$$

The corresponding dissipation potential is given by

$$\begin{aligned} \mathcal{D} &= 4\alpha D_\alpha V_0 \int_{-\infty}^t \int_{-\infty}^t (2t - \tau_1 - \tau_2)^{-\alpha-1} \\ &\times \frac{\dot{\kappa}}{\kappa}(\tau_1) \frac{\dot{\kappa}}{\kappa}(\tau_2) d\tau_1 d\tau_2, \end{aligned} \quad (\text{F7})$$

so that it cancels with the last term in Eq. (F6). The effective uniaxial tension due to this effect, σ_{cyt} , is obtained by taking the variation with respect to the uniaxial strain rate of the tissue $\dot{\kappa}(t)$,

$$\delta_{\dot{\kappa}}(\dot{\mathcal{F}} + \mathcal{D}) = \sigma_{\text{cyt}}(t) A_{ab,0} \delta \dot{\kappa}, \quad (\text{F8})$$

where

$$\sigma_{\text{cyt}}(t) = \frac{2h_0 C_\alpha}{\kappa(t) \Gamma(1 - \alpha)} \int_{-\infty}^t (t - \tau)^{-\alpha} \frac{\dot{\kappa}}{\kappa}(\tau) d\tau. \quad (\text{F9})$$

The hereditary integral in this expression for the power-law contribution to the tissue tension is numerically computed using the composite trapezoidal rule.

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