

Rigidity transitions in a three-dimensional active foam model of cell monolayers with frictional contact interactions

Jef Vangheel , Herman Ramon, and Bart Smeets ^{*}

Department of Biosystems, Division of MeBioS, *KU Leuven*, B-3001 Leuven, Belgium



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In morphogenesis and disease, biological tissues may exhibit diverse mechanical properties due to their capacity to switch between fluidlike and solidlike states. Here, we introduce a foam model to investigate how active mechanical properties and cellular interactions govern this fluid-to-solid transition in active cell monolayers. This model explicitly represents three-dimensional cell shapes and describes cell-cell interactions via discrete interacting surfaces. Simulations reveal that cell-cell adhesive tension promotes tissue fluidization in high-adhesive tissues, where it mainly promotes cell deformability, while it induces solidification in the low-adhesive regime, where it prevents cell-cell debonding. Moreover, we study the dynamic role of adhesive ligand turnover through an effective intercellular friction. Through simulated shear experiments, we find that intercellular friction strongly suppresses neighbor exchanges, but does not lead to solidlike tissue properties. We discuss the implications of our results for understanding the relationship between fluidization and the partial epithelial-mesenchymal transition, highlighting how differences in adhesion dynamics and intercellular friction may reconcile conflicting observations in tissue mechanics and cancer metastasis.

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I. INTRODUCTION

Biological tissues are active, living materials with mechanical properties that can vary dramatically depending on their context and functional requirements. Unlike inert materials, tissues are composed of active cells that generate forces and constantly remodel their connections with their neighbors. By tuning cell properties, tissues may undergo phase transitions, shifting from a fluidlike to a solidlike state, or vice versa [1–3]. These jamming and glass transitions play an important role in phenomena such as embryonic morphogenesis [4–10] and wound healing [11,12], and disease processes such as asthma [13] and cancer metastasis [14–18]. However, how single-cell properties affect global tissue behavior is not yet clear. For example, cell-cell adhesion has been found to solidify Madin-Darby canine kidney (MDCK) cell monolayers [19] and three-dimensional (3D) breast cancer cultures [18]. Furthermore, zebrafish tail elongation and zebrafish epiboly are driven by fluidization of the tissue regulated by the decrease of cell-cell adhesions [5,6]. In contrast, cell-cell adhesion was found to fluidize tissue in primary human bronchial epithelial cell (HBEC) monolayers [13].

Advances in understanding how single-cell properties govern tissue fluidity have been driven by computational models, which can be broadly classified into two limiting classes: colloidal-like models and vertex models. Colloidal-like models predict a fluid-to-solid transition at a critical density, as a function of cell activity and cell-cell adhesion, where adhesion

restricts cell movements and promotes jamming [19–21]. In contrast, vertex and Voronoi models represent deformable cells in confluent tissues [22] and have demonstrated how fluidity is governed by decreasing interfacial tension [23] and active cell motility [24]. In these models, a critical shape index—a geometric parameter that is a measure of cell elongation—predicts the fluid-to-solid transition. While initially limited to confluent tissues, later extensions of these models also accounted for the presence of intercellular pores [25,26]. For example, in their “active foam” model, Kim *et al.* demonstrated that cell-cell adhesion favors fluidization in confluent tissues, as predicted by vertex models, but promotes solidification in porous tissues [27]. Vertex models have also been extended to 3D, to explore the active properties of bulk 3D tissues [28–31] or to study the behavior of curved epithelial shells and sheets [32,33].

However, vertex family models treat tissues as collections of cell-cell interfaces rather than interacting surfaces. This makes it difficult to represent the dynamic properties of cell-cell contacts with adherent junctions, such as cadherins. These regulate contact expansion by locally inhibiting myosin contractility, thereby reducing the cell-cell interfacial tension [34–36]. Moreover, their bond strength and turnover rate also control the dynamics of cell-cell separation and relative cell sliding, producing an effective viscous cell-cell friction at long timescales [37–39]. Recent alternative modeling approaches represent cells as discrete interacting surfaces [40], offering a more detailed description of cell-cell interaction mechanics, albeit at the cost of increased computational complexity. Coupled with viscous active shell models [41,42], they enable parametrization using measurable mechanical properties of the actomyosin cortex. The cortex, approximated as viscous at long timescales [43–46], is then modeled as a curved, contractile, viscous shell encapsulating an incompressible cytoplasm [47,48].

^{*}Contact author: bart.smeets@kuleuven.be

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Here, we present a foam model of active cell monolayers that explicitly represents the 3D shape of individual cells and models cell-cell interactions through discrete, interacting surfaces [49,50]. This way, the active foam model intrinsically captures cell shape and tissue structure [51], including porosity, as determined by cell mechanical properties. In simulations of this model, we study cell dynamics, tissue structure, and viscoelastic properties. Furthermore, we explore fluid-to-solid transitions in an epithelial monolayer as a function of adhesive tension, cell motility, intercellular friction, and cell density. We characterize the fluid-to-solid transition by the onset of persistent caging and suppressed cell rearrangements, evidenced by reduced mean-squared relative displacements (MSRDs), decreased neighbor exchange rates, and slow relaxation dynamics, hallmarks of glassy behavior [5,15,24,52,53]. We show that increased cell-cell adhesive tension fluidizes at high adhesive tension, while promoting solidification at low adhesive tension. Moreover, we derive and validate theoretical scaling regimes that predict tissue fluidity based on cell-scale mechanical properties in both regimes. Finally, we examine the influence of intercellular friction on tissue-scale mechanical behavior. While intercellular friction strongly inhibits neighbor exchanges, it slows down tissue dynamics through a mechanism that is distinct from adhesive tension.

II. RESULTS

A. Computational model of foamlake cell mechanics with contact interactions

From a physical perspective, epithelial and embryonic cells are often described as soap bubbles and foams. The shape of each bubble inside the foam is determined by the surface tension that minimizes the overall surface area. Similarly, individual cell shapes can be considered as foam bubbles [56], with cortical tension from actomyosin contraction and intercellular surface tension from the opposing effects of cortical tension and intercellular adhesion [34]. Furthermore, actomyosin tension fluctuations, cell divisions, and cell migration affect tissue dynamics and structure [27,49,50]. Following previous work, we model a cell monolayer as an active foam [27,40,42,51,57]. In this model, we represent individual cells as pressurized bubbles with a resting radius R_0 when detached, cortex thickness t_c , tension γ , viscosity η_c , and a bulk pressure P^b required for maintaining cell volume Fig. 1(a) (see Appendixes A and B). Cell-cell (ω_{cc}) and cell-substrate (ω_{cs}) adhesion represent the combined effect of adhesive ligands and the reduction of myosin contractility at the interface [34]. In our model, these effects are incorporated through (1) a reduction of in-plane tension ($\gamma - \omega$), thereby determining the contact angle, and (2) a normal adhesive traction, governing the mechanics of cell pull-off, (see Appendix E). Adhesive ligand turnover further introduces cell-cell (ξ_{cc}) and cell-substrate (ξ_{cs}) friction.

We introduce a minimal model of cell activity based on an active pressure that acts along the outward surface normal of the cell. This pressure is modulated along the direction of cell polarization $\hat{\mathbf{p}}$, and includes both a polar component that drives net migration and a dipolar component that induces elongation. The resulting active pressure on the cell surface

is given by

$$P^a = \frac{2p_a}{L_c} \left(\underbrace{|\mathbf{r} \cdot \hat{\mathbf{p}}|}_{\text{migration}} + \underbrace{\lambda_a (\mathbf{r} \cdot \hat{\mathbf{p}})}_{\text{elongation}} \right) (\hat{\mathbf{n}} \cdot \hat{\mathbf{p}}), \quad (1)$$

where $\mathbf{r}$ is the vector pointing from the cell center to the cell surface, $\hat{\mathbf{n}}$ is the surface normal, L_c is the instantaneous length of the cell in the direction of cell polarization, p_a is the maximal active pressure, and λ_a is the relative strength of elongation compared to migration. Furthermore, we assume that the cell migrates by actin polymerization close to the substrate, so we limit the protrusive forces to a narrow region near the substrate [see Eq. (B2)]. In real cells, internal active forces are balanced by reaction forces transmitted to the substrate, which are typically oriented inward. As we do not explicitly model substrate traction, these reaction forces are implicitly assumed and not resolved in our framework. The cell polarity vector is given by $\hat{\mathbf{p}} = (\cos \phi, \sin \phi, 0)$, representing a minimal description of front-rear polarity confined to the substrate plane (xy). The angle ϕ undergoes rotational diffusion,

$$\frac{d\phi}{dt} = \sqrt{2D_r} \xi_n,$$

where ξ_n is Gaussian white noise and D_r is the rotational diffusion coefficient, corresponding to a persistence time $\tau_p = 1/D_r$. Motivated by observations from traction force microscopy [58], we assume that the static force dipole associated with cell elongation is stronger than the dynamically generated dipole that drives net migration and is balanced by substrate friction. We therefore set $\lambda_a = 4$, a representative value that prioritizes elongation over net propulsion. The cell active migration pressure p_a is then adimensionalized by balancing the migration pressure with the Young-Laplace pressure from free surface tension γ (see Appendix D), as

$$p_{\text{eff}} = \frac{\lambda_a p_a R_0}{2\gamma}.$$

The mechanical model is implemented by discretizing the cell surface as a triangulated mesh, where forces are computed for each node on the mesh [see Fig. 1(a)]. For node i , the equation of motion is

$$\begin{aligned} \mathbf{F}_i^\gamma + \mathbf{F}_i^b + \mathbf{F}_i^a + \sum_{(AB):i \in A} \mathbf{F}_{i,AB}^\omega \\ = -\mathbf{F}_i^{\eta_f} - \sum_j \mathbf{F}_{ij}^{\eta_c} - \sum_{(AB):i \in A} \mathbf{F}_{i,AB}^\xi, \end{aligned} \quad (2)$$

where the left-hand side includes forces from cortex tension $\mathbf{F}_i^\gamma$, bulk pressure $\mathbf{F}_i^b$, active cell migration $\mathbf{F}_i^a$, and adhesive contact $\mathbf{F}_{i,AB}^\omega$, where we sum over contacting triangles AB . The right-hand side of the equation includes forces linearly dependent on relative velocities from viscous drag with medium $\mathbf{F}_i^{\eta_f}$, cortex viscosity $\mathbf{F}_{ij}^{\eta_c}$ summed over connected nodes ij , and friction with substrate and neighboring cells $\mathbf{F}_{i,AB}^\xi$ summed over contacts AB . For the complete system, the governing equation takes the form $\mathbf{F} = \mathbf{C} \mathbf{v}$, where $\mathbf{F}$ is the combined vector of left-hand-side forces in Eq. (2), $\mathbf{v}$ are the nodal velocities, and $\mathbf{C}$ is a resistance matrix, which includes off-diagonal terms that capture hydrodynamic couplings arising from cortical viscosity and interfacial friction [59]. Solving

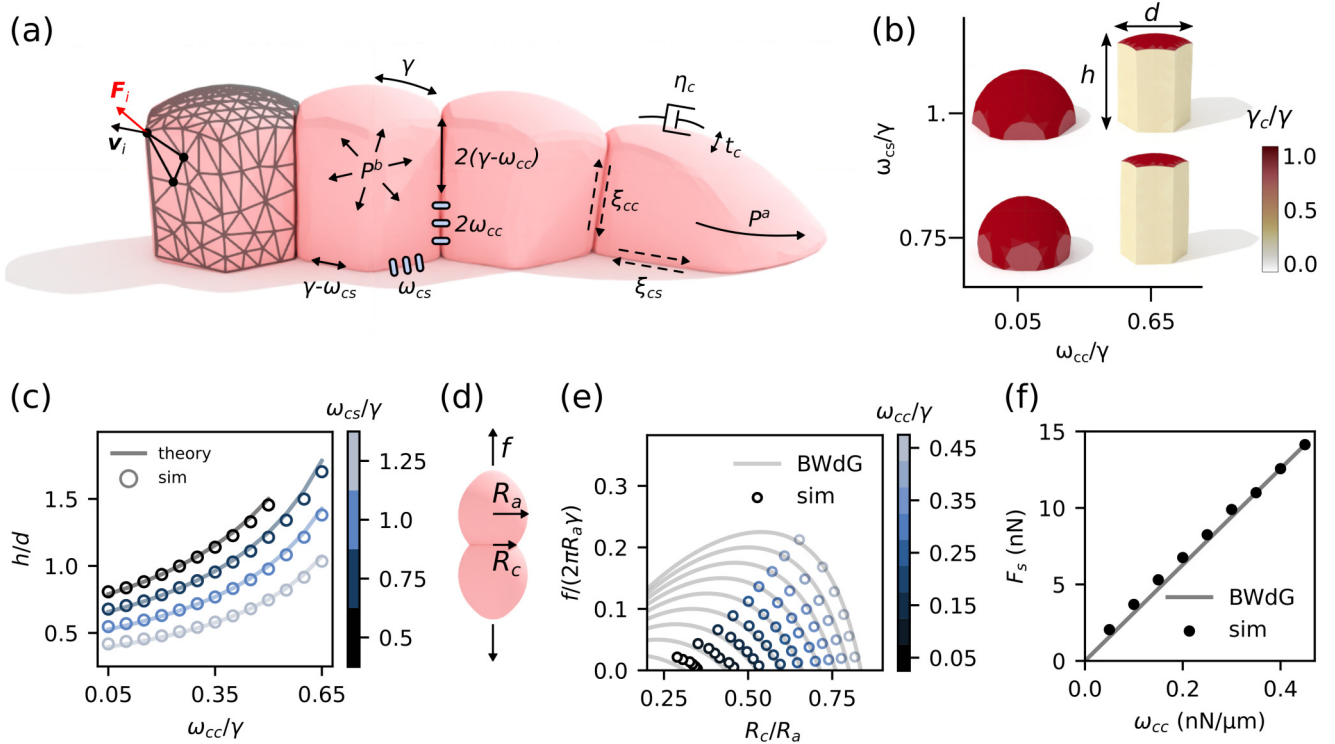


FIG. 1. Overview of the computational active foam model. (a) Active foam simulation of adhering cells on a substrate. Cell shape is outlined by a meshed surface (visualized on the left cell), which mechanically models the cell cortex with thickness t_c , surface tension, γ and viscosity η_c , and cell volume is maintained through the internal pressure P^b . Adhesive cell-cell (cc) and cell-substrate (cs) interactions are modeled by (1) an adhesive contact pressure ω mechanically coupling the cells, (2) reduction of surface tension at the interface ($\gamma - \omega$), and (3) an effective wet sliding friction ξ , accounting for dynamic bond turnover. Cell motility is modeled by an active pressure P^a [Eq. (1)]. At each time step, forces $\mathbf{F}_i$ are computed, and the overdamped equation of motion $\mathbf{C}\mathbf{v} = \mathbf{F}$ is solved to obtain the node velocities $\mathbf{v}$, where $\mathbf{C}$ is a grand resistance matrix containing the friction and viscous elements. (b) Simulated equilibrium cell shape ranges from squamous to columnar types by varying cell-cell (ω_{cc}/γ) and cell-substrate adhesive tension (ω_{cs}/γ). The color bar indicates local interfacial tension relative to cell-medium tension. (c) Aspect ratio (cell height h over diameter d) of a simulated hexagonal cell plotted as a function of ω_{cc}/γ and ω_{cs}/γ , and compared to the theoretical prediction $2h/d = (2\gamma - \omega_{cs})/(\gamma - \omega_{cc})$ [Eq. (C2)]. (d) Simulated dual micropipette aspiration of two adhering cells (Video S1 of the Supplemental Material [54]), and (e) comparison of simulated pull-off force as a function of normalized contact radius R_c/R_0 to Brochard-Wyart and de Gennes (BWdG) theory [55]. (f) Critical pull-off force in simulations follows the BWdG relation $F_s = \pi\omega_{cc}R_a \approx \pi\omega_{cc}R_0$ for adhesive vesicles.

this system yields the velocities $\mathbf{v}$, which are then integrated over time to obtain the nodal displacements. Details regarding the numerical discretization and computational implementation of the model are provided in Appendix B.

At equilibrium, the balance of interfacial tension dictates individual cell shapes and monolayer architecture: Cell-cell adhesive tension increases the contact area with neighboring cells, while cell-substrate adhesive tension promotes substrate spreading. The shape of adherent cells changes from squamous to columnar cells with increasing ω_{cc}/γ and decreasing ω_{cs}/γ [Fig. 1(b)]. In an ideal hexagonal configuration, the equilibrium shape attained in simulations reproduces the theoretical aspect ratio obtained from tension balance when varying ω_{cs} and ω_{cc} : $2h/d = (2\gamma - \omega_{cs})/(\gamma - \omega_{cc})$ [Eq. (C2)], with height h and cell-cell distance d [Fig. 1(c)].

Because our model explicitly captures interactions between distinct interfaces, it can accurately reproduce debonding and pull-off behavior during cell-cell separation—a key advantage that enables it to bridge the gap between classic adhesive sphere models and interface-based vertex models. By simulating a dual pipette aspiration experiment for cell-cell

separation, varying relative cell-cell adhesive tension ω_{cc}/γ , we show that our model replicates the theoretical prediction for adhesive vesicles as derived by Brochard-Wyart and de Gennes [55,60] [Fig. 1(e)]. Hence, our model reproduces the classical vesicle pull-off force $F_s = \pi\omega_{cc}R_0$ [Fig. 1(f)].

B. 3D structure and mechanical stress in static monolayers

We simulated cell monolayers by randomly initializing active cells on a substrate with periodic boundary conditions, followed by simulated annealing to achieve static configurations. We then characterized tissue structure and quantified the average hydrostatic tissue stress, σ_h , based on intercellular forces using the virial theorem. Our 3D foam model is able to represent both confluent and (micro- and macro)porous states by varying cell number density and adhesive tension ω_{cc} [Figs. 2(a) and 2(b)]. At high number density, the tissue remains confluent (area density ≈ 1), with tissue stress transitioning from compressive to tensile as cell-cell adhesive tension increases [Fig. 2(a)]. At low number density, increasing cell-cell adhesive tension results in the nucleation

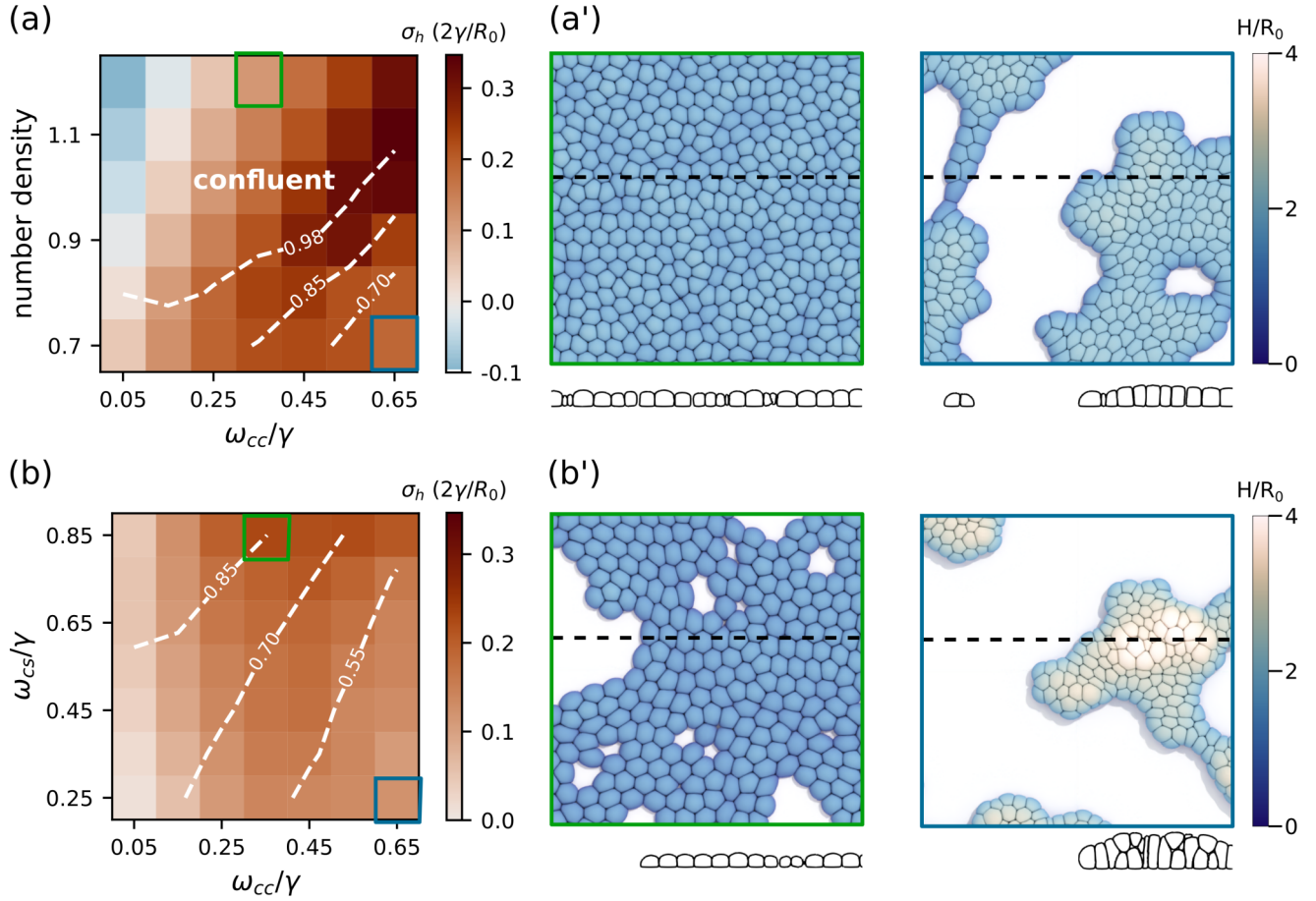


FIG. 2. Structure and mechanical stress in quasistatic monolayers of 400 cells. (a) Normalized hydrostatic tissue stress $\sigma_h R_0/2\gamma$ (positive values indicate tension and negative values indicate compression) for varying cell-cell adhesive tensions ω_{cc}/γ and number densities at constant cell-substrate adhesive tension $\omega_{cs}/\gamma = 0.825$. Dashed white lines show isocontours of two-dimensional (2D) cell density. (a') Visualizations of the apical and side views for parameters indicated by the blue and green boxes in panel (a). The dashed line indicates the position of the side view. The color bar shows the relative tissue height H/R_0 . (b) Hydrostatic tissue stress for varying cell-cell and cell-substrate adhesive tensions at constant number density 0.7. Dashed white lines show isocontours of 2D cell density. (b') Visualizations of the apical and side views. Tissue dewetting can be observed at low ω_{cs}/γ and high ω_{cc}/γ .

and growth of intercellular pores, ultimately leading to phase separation into a locally confluent, arrested gel phase. In the absence of active (outward) traction forces, cell clusters within macroporous tissue cannot sustain elevated tensile stress. Thus, tissue stress reaches its peak when the tissue is marginally confluent, coinciding with the onset of pore nucleation. Similarly, tissue stress increases with cell-substrate adhesive tension ω_{cs} [Fig. 2(b)], as area density increases with ω_{cs} . At low cell-substrate adhesion and high cell-cell adhesive tension, the cell monolayer becomes mechanically unstable, leading to cell extrusion and multilayering, reminiscent of liquid film dewetting [61,62]. It should be noted that, because our model restricts cell motility to the substrate, the tissue will not evolve toward mechanical equilibrium as described by the Young-Dupré equation. Rather, it stabilizes in an arrested gel-like state.

C. Cell deformation controls fluidity at high adhesive tension

Next, we quantified tissue fluidity in simulations of monolayers with actively migrating cells, undergoing rotational

diffusion with persistence time τ_p . To characterize tissue fluidity in simulations, we measured 2D mean-squared relative displacements between initially neighboring cell pairs [Fig. 3(a)]. By focusing solely on relative displacements, we eliminate the contribution of bulk tissue movements. These measures show that adhesive tension ω_{cc} can drive subdiffusive motion toward diffusive behavior [Fig. 3(a)]. We quantified the two-dimensional effective diffusivity as $D_{\text{eff}} = \text{MSRD}(\Delta t)/(4\Delta t)$ for lag times $\Delta t = 60\tau_p$ [Fig. 3(b)], which decreases by orders of magnitude by decreasing motile pressure. However, D_{eff} changes nonmonotonically with increasing ω_{cc} [Fig. 3(b)], indicating a gradual shift in tissue dynamics. This behavior is also reflected both in cell trajectories, which show caging at intermediate adhesive tensions [Fig. 3(c)], and in the rate of cellular rearrangements [Fig. 3(d) and Fig. S2 of the Supplemental Material [54]]. Therefore, we propose that the neighbor exchange rate serves as a robust order parameter to distinguish between solidlike and fluidlike tissue states [Fig. S2(d) of the Supplemental Material [54]]. We identify two distinct regimes: a low-adhesive regime where ω_{cc}/γ promotes solidification and a high-adhesive,

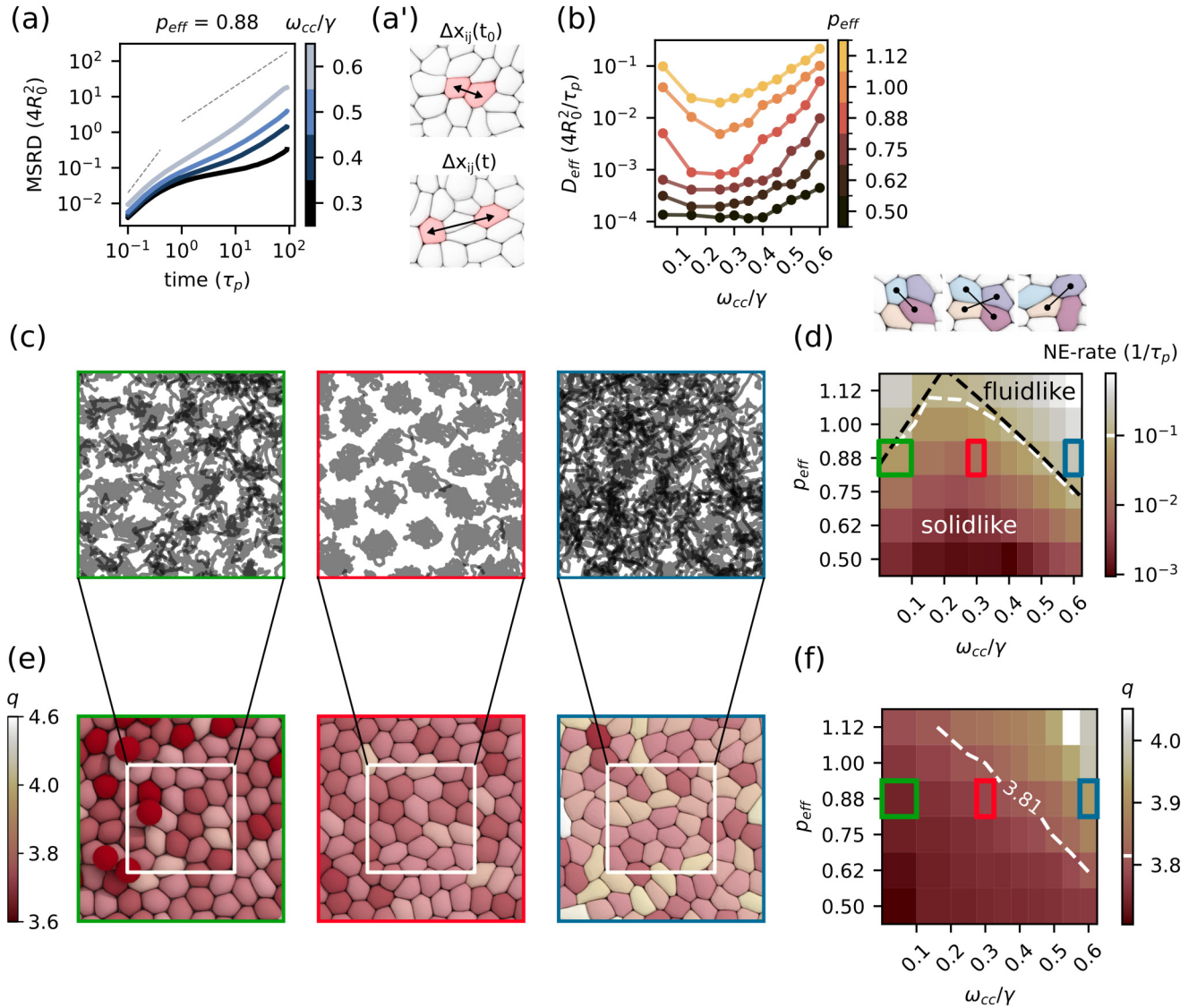


FIG. 3. Fluidity of confluent tissue at number density 1.1. (a) Mean-squared relative displacement between initially contacting cell pairs for varying ω_{cc}/γ , with (a') a visualization of the displacement between the cell pair ij . (b) Effective diffusion coefficient normalized by cell radius R_0 and persistence time τ_p . (c) Visualization of cell trajectories at $p_{\text{eff}} = 0.875$ and varying ω_{cc}/γ . (d) Neighbor exchange (NE) rate in the tissue as a measure for fluidity. The threshold that distinguishes solid from fluidlike tissue is set at NE rate = $10^{-1}/\tau_p$, indicated by the white dashed line. The black dashed lines indicate scaling $\Delta p_{\text{eff}}^* \propto \omega_{cc}$ for the low-adhesive regime and $p_{\text{eff}}^* \propto (1 - \omega_{cc}/\gamma)^{2/3}$ for the high-adhesive regime. The inset shows an example of T1 transition in confluent tissue. (e) Visualization of the apical cell shape. Cells become more elongated by increasing cell motility and adhesive tension. See Fig. S1 and Video S2 of the Supplemental Material for a visualization of the simulated tissues [54]. (f) Apical cell shape as a function of adhesive tension and cell motility for confluent tissue. The white line indicates the critical shape index $q^* = 3.81$ from vertex models [24].

confluent regime where ω_{cc}/γ promotes fluidization. This transition is smooth, where the contour shown in Fig. 3(d) indicates the onset of fluidlike behavior, rather than a sharp phase boundary.

At high adhesive tension, we hypothesized that the ability of cells to elongate modulates the probability of T1 transitions and thereby regulates tissue fluidity. This follows predictions of vertex models, where fluidization occurs as the shape index, a measure of cell elongation, increases beyond a critical value. In our foam model, cell elongation may arise from both external (interactions with neighbor cells) and internal (active cell elongation and migration) forces. In both cases, the

extent of elongation depends on the balance between (internally or externally generated) pressure and net cortex tension at the cell-cell interface, $\gamma_{\text{eff}} = \gamma - \omega_{cc}$. Restricting to internally generated active forces, we may estimate the 2D aspect ratio of a cell by equating the pressure difference over the surface at the long axis and the short axis (derivation provided in Appendix D). Assuming that the tissue fluidizes when a critical aspect ratio is reached, the critical motile pressure to fluidize is predicted to scale as $p_{\text{eff}}^* \propto (1 - \omega_{cc}/\gamma)^{2/3}$ [Eq. (D1)]. Here, the sublinear 2/3 scaling with the relative cell-cell tension $1 - \omega_{cc}/\gamma$ emerges from adhesive tension, also increasing the vertical aspect ratio of the cell [see

Fig. 1(b)], which reduces the elongation due to the migration pressure. Since this analysis neglects the contribution of rotational diffusion, it is only valid when the persistence time is sufficiently large compared to the mechanical relaxation time of the cell, which is the case in our simulations, where $\tau_p \gg \eta_{ct}/\gamma$ (see Fig. S3 of the Supplemental Material [54]).

The predicted scaling aligns well with observed neighbor exchange rates in simulations [Fig. 3(d)]. As expected, cells are more elongated when they behave fluidlike in confluent tissue [Fig. 3(e)]. Similar to vertex models, the apical cell shape appears to delineate solid from fluidlike tissues in the confluent regime, although the exact value of the critical shape index q^* could not be determined [Fig. 3(f)]. In our model, active cell elongation is driven by two potentially independent factors. First, the cell activity induces cell elongation along the cell's polarity, analogous to the preferred perimeter in self-propelled Voronoi models [24]. Second, the cell activity drives net migration, similar to the self-propulsion velocity in Voronoi models, while also elongating cells due to substrate friction and resistance from neighboring cells. Despite their distinct effects on single-cell dynamics, both parameters regulate the solid-to-fluid transition through the same critical shape index (see Figs. S4 and S5 of the Supplemental Material [54]).

D. Pull-off force controls tissue fluidity at low adhesive tension

At low adhesive tension, we observe that adhesive tension promotes tissue solidification, a behavior that was previously linked to the existence of intercellular pores [27] [Figs. 3(b) and 3(d)]. At high p_{eff} , intercellular pores emerge as cells delaminate in response to local crowding, effectively reducing the density of the bottom layer. However, we also observe fluidlike behavior in fully confluent tissue (see Fig. S6 of the Supplemental Material [54]). We propose that this behavior arises from the inclusion of normal adhesive forces and cell-cell debonding dynamics in our model. Here, adhesion energy acts as an energy barrier for T1 transitions. Hence, we expect the critical activity to scale as $\Delta p_{\text{eff}}^* \propto \omega_{cc}$ [Eq. (E1)], where Δp_{eff}^* denotes the shift in critical activity relative to the nonadhesive (density-dependent) glass transition. Notably, because this regime is dominated by debonding rather than cell elongation, it can give rise to fluidlike behavior even below the critical shape index, similar to subconfluent states [Fig. 3(f)].

At high number density, the density-dependent fluid-to-solid transition is a dominant mechanism at low adhesive tension. To better understand the role of adhesive tension in driving solidification in this regime, we simulated porous tissues at lower number density 0.6. Here, increasing adhesive tension ω_{cc}/γ drives cell movements from a diffusive to a subdiffusive regime [Fig. 4(a)]. Similarly, the diffusivity D_{eff} decreases by orders of magnitude by increasing cell-cell adhesive tension and by decreasing motile pressure [Fig. 4(b)], indicating caging by neighboring cells. Caging occurs when motility-driven agitation is too weak to overcome energy barriers to neighbor exchanges, which depend on cell density and adhesive tension [Fig. 4(c)]. Therefore, we simulated the minimal motile pressure $p_{\text{eff},S}$ that is needed for cell separation [Fig. 4(d)], which follows a similar trend to the BWdG relation, with the separation force increasing linearly with

adhesive tension ω_{cc} at low ω_{cc} . We find that this solid-to-fluid transition, measured by the rate of neighbor exchanges (see Fig. S8 of the Supplemental Material [54]), follows the scaling of the pull-off force [Fig. 4(e)]. This is consistent with a model in which tissue fluidity is governed by cell-cell separation, with adhesion promoting a jammed or glassy state, similar to attractive colloidal systems [20].

E. Cell-cell friction as a distinct solidification mechanism in cell monolayers

Finally, we investigate the effect of cell-cell friction ξ_{cc} on tissue dynamical properties. We simulate an active confluent tissue at $\omega_{cc} = 0.5$, a number density of 1.1, and vary ξ_{cc}/ξ_{cs} , the ratio of cell-cell to cell-substrate friction. Increasing intercellular friction drives tissue dynamics from diffusive to subdiffusive behavior [Fig. 5(a)] and greatly decreases neighbor exchange rates [Fig. 5(b)], effectively appearing to arrest the tissue (see Fig. S10 of the Supplemental Material [54]). This arrested behavior can be explained by the slowdown of T1-transition dynamics due to friction, where the tissue will become solidlike when the persistence time τ_p becomes smaller than the timescale of T1 transitions. This observation is in line with recent results from phase field model simulations [39] and experiments that observed solidlike states associated with maturing cell-cell adhesion proteins [19]. Remarkably, however, the critical cell shape index $q^* = 3.81$ does not align with the transition predicted by the NE rate [Fig. 5(c)], hinting at a distinct mechanism from shape-controlled jamming and glass transitions in the vertex model. To clarify this discrepancy, we examine the relaxation dynamics of the tissue through a simulated shear experiment, following Ref. [27], where an instantaneous shear strain ϵ_{xy} is applied to an active tissue, and the resulting shear stress σ_{xy} is tracked over time [Fig. 5(d)]. We observe a relaxation consisting of two phases: an initial fast decay driven by T1 transitions induced by the applied shear, followed by a slower relaxation phase due to glassy dynamics, where cell-scale migration forces may overcome remaining local energy barriers. The initial relaxation can be approximated by a stretched exponential function (see Fig. S11 of the Supplemental Material [54]). As expected from our previous results (Fig. 3 and Fig. S12 of the Supplemental Material [54]), the stress relaxes to zero at high active forces [Figs. 5(e) and 5(g)], consistent with fluidlike behavior. Due to the applied shear stress, the motile pressure p_{eff} required to fluidize the system is expected to be lower than that in the absence of shear [63,64]. At lower active force, however, the stress decays to a finite plateau within our accessible simulation timescales, which we refer to as a residual stress. Whether this plateau corresponds to a true yield stress in the infinite-time limit cannot be determined from our simulations due to timescale limitations. However, on longer timescales, we expect a further stress decay due to glassy relaxation dynamics [27,52]. On the other hand, the relaxation timescale τ_R extracted from this fit remains largely unaffected by cell activity, indicating that it primarily reflects short timescale passive relaxation. Interestingly, we find that intercellular friction affects only the relaxation timescale, but not the residual stress [Figs. 5(f)–5(h)], suggesting that only the viscous properties of the tissue change with

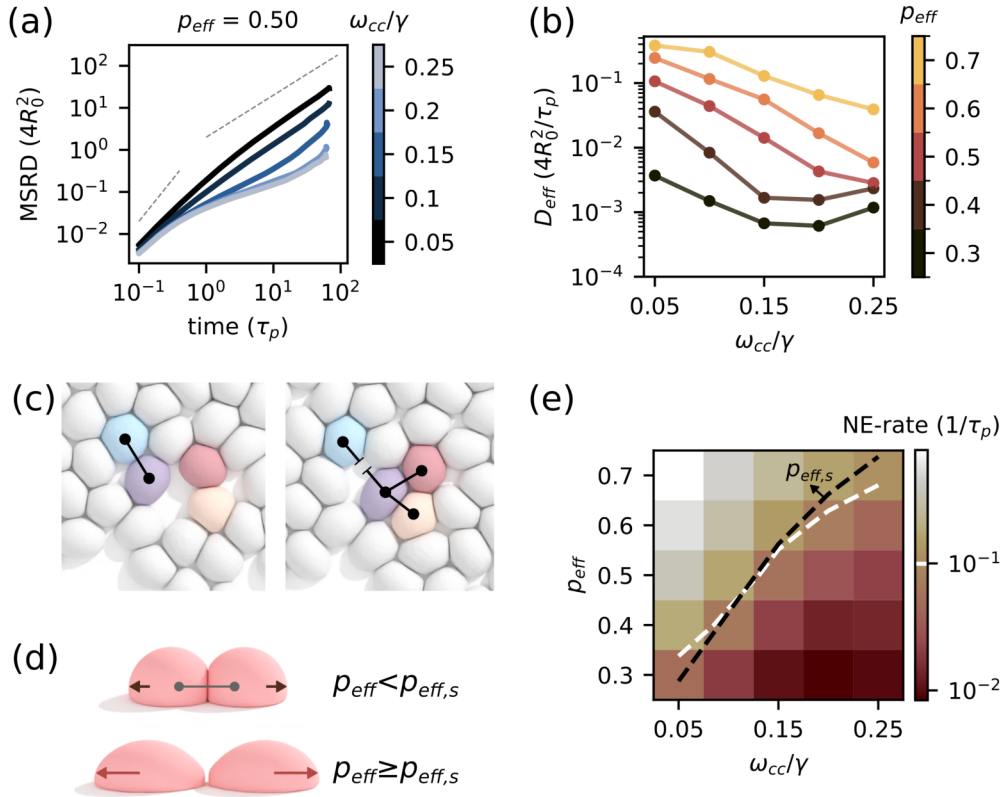


FIG. 4. Fluidity of porous tissue at number density 0.6. (a) Mean-squared relative displacement of simulated tissue as a function of cell-cell adhesive tension ω_{cc} . Dotted lines indicate superdiffusive and diffusive limits. (b) Normalized effective diffusion constant D_{eff} for changes in activity p_{eff} and adhesive tension ω_{cc} . (c) Example of cell-cell separation in porous tissue. (d) Minimal activity $p_{\text{eff},s}$ needed for separation of two cells migrating away from the cell-cell contact. (e) Measurement of neighbor exchange rate. We set a threshold NE rate = $10^{-1}(1/\tau_p)$, distinguishing fluidlike from solidlike tissue indicated by the white dashed line. The black dashed line indicates $p_{\text{eff},s}$. Note that this pull-off force is not linear with adhesive tension ω_{cc} . This is expected since in our cell motility model we assume cell migration enhances cell elongation (and decreases R_a), therefore decreasing the pull-off force as predicted by BWdG. See Fig. S7 and Video S2 of the Supplemental Material for a visualization of the simulated tissues [54].

cell-cell friction. Thus, tissues may appear solidlike based on cell dynamics alone, even though friction does not affect their static load-bearing capacity. Cell dynamics alone are therefore insufficient to distinguish between solidlike and liquidlike responses to external forces.

III. DISCUSSION

In this work, we presented a model of active cell monolayers based on deformable cells with explicit contact interactions, parametrized by physical properties of the actomyosin cortex. With this model, we examined the distinct mechanisms by which adhesive tension regulates cell dynamics and governs tissue mechanical properties [65].

On the one hand, adhesive bond strength governs the pull-off force between neighboring cells, reducing rearrangement rates and thereby decreasing tissue fluidity. This gives rise to a regime in which the critical activity required to fluidize the tissue increases linearly with adhesive tension (Fig. 6). Such behavior dominates in porous tissues, consistent with observations of mesodermal fluidization during embryogenesis [5,6,27]. However, this regime may also emerge in confluent tissues—despite the absence of intercellular pores—when activity is sufficient to overcome density-dependent jamming.

In this case, tissues may appear fluidlike even with a shape index below the critical value predicted by vertex models. On the other hand, adhesion proteins like E-cadherins are linked to the cytoskeleton, thereby downregulating cortex tension and effectively reducing interfacial tension [34]. This expands cell-cell contacts and promotes cell elongation through the reduction of the net tension at the cell-cell interface. Our results demonstrate that, in confluent tissue, decreased interfacial tension enhances tissue fluidity by facilitating cell deformation and elongation, in line with observations of primary human bronchial epithelial cells [13] and vertex model predictions [23,24] (Fig. 6). However, the mechanism underlying cell elongation is different compared to these models. In vertex models, the preferred cell shape q_0 itself is an input model parameter that depends on interfacial tension γ_c and actomyosin contractility with elasticity κ (as $q_0 = -\gamma_c/2\kappa$) [23]. In this approach, cell elongation can be achieved by negative interfacial tension. In contrast, we modeled cells with positive tension, consistent with force inference studies of epithelial tissue [66] and current understanding of interfacial cortex tension [34]. Rather, elongated shapes result from extracellular forces (cells pushing neighboring cells) and active intracellular (static and dynamic) force dipoles [67]. For these active mechanical properties, we were able to derive and

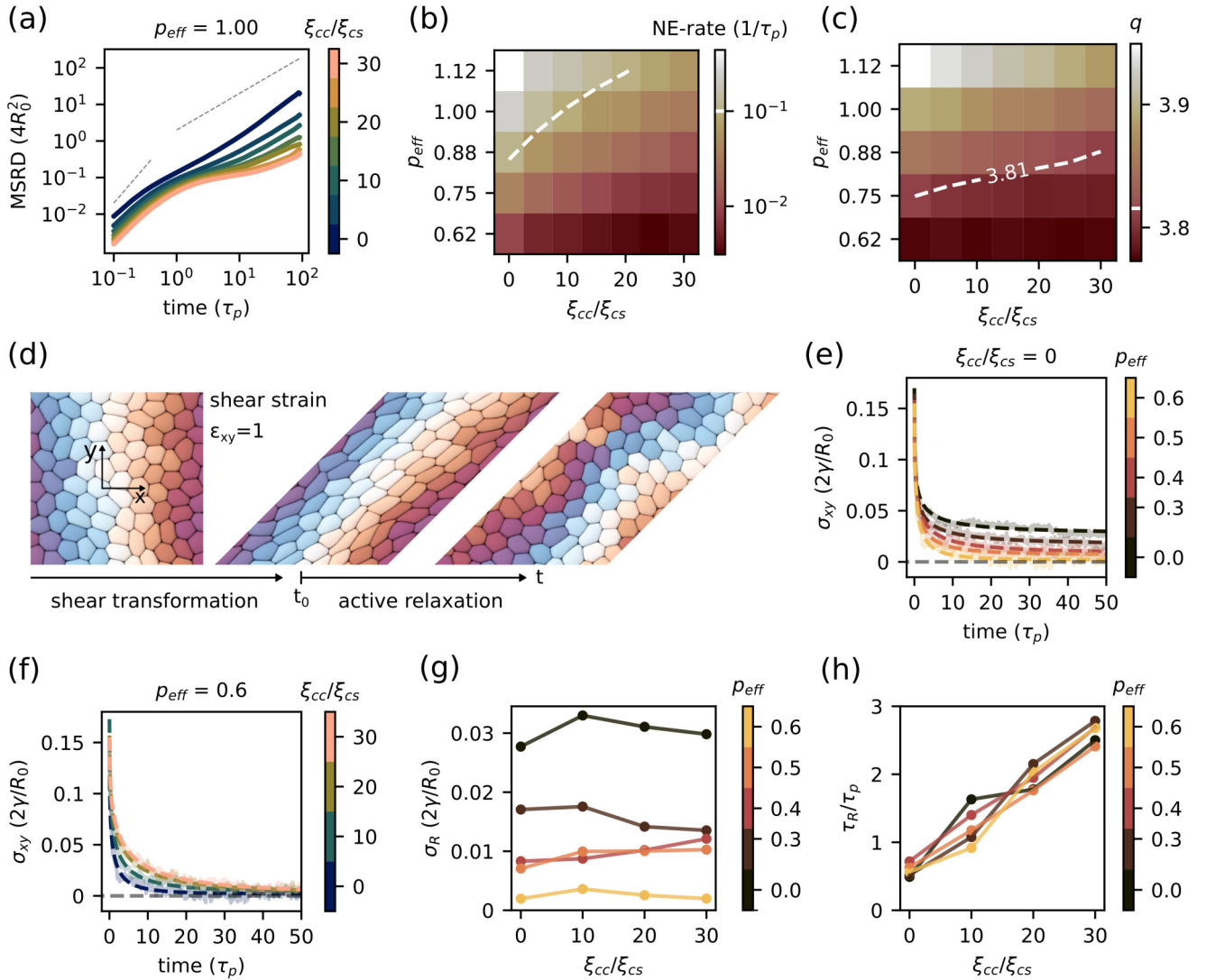


FIG. 5. The effect of cell-cell friction on tissue fluidity. (a) MSRD as a function of friction ratio ξ_{cc}/ξ_{cs} . (b) Neighbor exchange rate separating solidlike from fluidlike tissue at the threshold NE rate $= 10^{-1}(1/\tau_p)$. (c) Cell shape index q where the line indicates the critical shape index predicted by vertex models $q^* = 3.81$. See Fig. S9 and Video S4 of the Supplemental Material for visualization of the simulated tissues [54]. (d) Example of a tissue deformed by a shear strain $\epsilon_{xy} = 1$. After this instantaneous deformation, the tissue relaxes by T1 transitions. Individual cells are colored in distinct colors as a visual guide. Stretched exponential fit of shear stress σ_{xy} during relaxation as a function of (e) activity p_{eff} and (f) friction ratio. (g) Residual stress σ_R and (h) relaxation time τ_R as a function of friction ratio and cell activity.

verify explicit scaling laws for the fluid-to-solid transition, both for low and high adhesive tension. The interplay of these two regimes gives rise to a phase diagram that bridges between glass transitions in attractive colloidal systems and shape-dependent fluid-to-solid transitions at high-adhesive tension, as shown in Fig. 6.

Finally, with our model, we were able to investigate the role of cell-cell friction, which may emerge from adhesion turnover dynamics at long timescales [37,38]. These dynamics have been proposed to affect epithelial tissue mechanical properties during embryogenesis [65,68] and *in vitro* cell culture [19]. Our results show that intercellular friction slows tissue dynamics, yet the residual stress relaxes to zero within finite timescales, indicating that friction does not lead to true glassy or solidlike behavior. However, cell shape alone does not differentiate between diffusive and arrested dynamics due

to cell-cell friction: At high cell-cell friction, cells can deform beyond the critical shape while still displaying subdiffusive movements. Notably, this is mirrored in various observations in epithelial tissue, where the shape index remains above the critical value, yet cell dynamics exhibit solidlike behavior [13,69–71]. In other cases, however, vertex model predictions hold [72]. These discrepancies may stem, at least in part, from the omission of intercellular friction in vertex theory.

In addition, these results can help in understanding the role of (partial) epithelial-to-mesenchymal transition (pEMT) that has been associated with increased invasiveness and metastasis during tumor progression. Although it is not yet clear whether the unjamming transition (UJT) and pEMT are similar [73,74], both pEMT and UJT involve an initially solidlike epithelial tissue that fluidizes and remodels. The UJT in epithelial tissue is often characterized by sustained

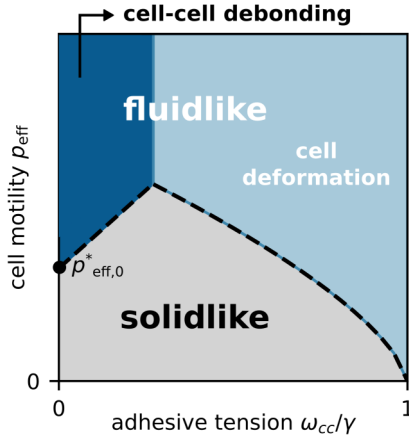


FIG. 6. Schematic representation of the rigidity diagram as a function of adhesive tension and cell motility based on Fig. 3(d). We consider two distinct mechanisms of tissue fluidization: cell-cell debonding (colloidal limit) or cell deformation (vertex limit). In the low-adhesive regime, fluidization is limited by cell-cell debonding, where adhesion induces solidification. In the high adhesive regime, fluidization is limited by cell deformation, where adhesive tension promotes fluidization. Here, $\rho_{\text{eff},0}^*$ indicates the density-dependent glass transition for nonadhesive particles. Note that at point J , the density to unjam at zero adhesive tension and activity, $\rho_{\text{eff},0}^*$, will move toward the origin.

E-cadherin expressions and increased adhesiveness, related to shape changes, maintaining epithelial barrier function. In contrast, during pEMT, cells lose E-cadherin-mediated adhesions and cell polarity and increase their migratory potential, whereas vertex models would predict solidification by decrease of adhesiveness. This model offers two possible explanations: In the low-adhesive regime, decrease of adhesion will fluidize the tissue, similar to colloidal-like systems [19–21], even at confluent density. An alternative explanation could lie in differences in bond kinetics, since N-cadherins and P-cadherins, associated with mesenchymal cell types, show faster turnover compared to E-cadherin [34,75]. This would effectively decrease intercellular friction and result in increased cell dynamics. However, the exact effects of E-cadherin on cell shape are still not well known. For example, both upregulation and downregulation of E-cadherin can lead to cell elongation and tissue fluidization [65,76]. Hence, the precise effects of intracellular mechanobiological factors such as adhesive ligands on cell mechanical properties—and consequently on tissue rheology—remain to be further elucidated.

This work highlights the importance of cell-cell contact interactions in understanding rigidity transitions in biological tissue. By explicitly accounting for intercellular tension, cell-cell debonding dynamics, and cell-cell friction, we bridge the gap between colloidal-like and vertex-based models of tissue mechanics. Moving forward, incorporating biased polarization mechanisms—such as cell-cell alignment or contact inhibition of locomotion—could shed light on their role in tissue dynamics and collective migration during embryogenesis and cancer metastasis [77]. This modeling framework also offers a platform to study how mechanical cell heterogeneity affects tissue rheology, providing insights into tumor

mechanics, where cell heterogeneity is one of the hallmarks of cancer [78]. Furthermore, cell populations during embryonic development are often heterogeneous, involving phenomena such as cell mixing and cell sorting. In these contexts, the role of tissue rigidity still remains an open question.

IV. METHODS

A. Mean-squared relative displacement

To exclude the effects of global tissue movements, we compute the relative 2D distances $\mathbf{x}_{ij} = \mathbf{x}_i - \mathbf{x}_j$ between cell pairs i, j . The mean-squared displacement of these relative distances is then computed for lag times Δt as

$$\text{MSRD}(\Delta t) = \langle (\mathbf{x}_{ij}(t_0 + \Delta t) - \mathbf{x}_{ij}(t_0))^2 \rangle,$$

where the cell pairs are in contact at time t_0 and $\langle \rangle$ denotes the average over both cell pairs and time. The MSRD is normalized by the cell diameter $\text{MSRD}(\Delta t)/(2R_0)^2$. An effective two-dimensional relative diffusivity D_{eff} is computed for lag times of $\Delta t = 60\tau_p$ as $D_{\text{eff}} = \text{MSRD}(\Delta t)/(4\Delta t)$.

B. Neighbor exchange rate

As a measure of T1 transitions, the NE rate is computed as the total number of new cell-cell contacts observed over the persistence time τ_p averaged over all cells visualized in Figs. 3(d) and 4(d).

C. Self-intermediate scattering function

We further measured the self-part of the relative self-intermediate scattering function

$$F_s(\mathbf{q}, \Delta t) = \langle \exp(\mathbf{q} \cdot \Delta \mathbf{x}_{ij}(\Delta t)) \rangle = \langle \cos(\mathbf{q} \cdot \Delta \mathbf{x}_{ij}(\Delta t)) \rangle,$$

where $\Delta \mathbf{x}_{ij}(\Delta t) = (\mathbf{x}_{ij}(t_0 + \Delta t) - \mathbf{x}_{ij}(t_0))$ gives the displacements between cell pairs i, j as defined for the MSRD to eliminate bulk drift and only reflect fluctuations around local cages. The average $\langle \rangle$ is taken over all time lags, cell pairs, and angles of $\mathbf{q}$. Glassy systems show long relaxation timescales, which can be seen by the plateau observed in F_s when it is analyzed at a length scale comparable to cell-cell distance $|\mathbf{q}| = \pi/R_0$.

D. Virial stress

The stress on tissue level is estimated by the virial stress theorem [79,80] as

$$\boldsymbol{\sigma} = \frac{1}{N} \sum_i \frac{1}{V_i} \int_{S_i} P^\omega(\mathbf{x}) \otimes (\mathbf{x} - \mathbf{x}_{0,i}) d\mathbf{S}_i,$$

where N is the number of cells, $P^\omega(\mathbf{x})$ is the contact pressure from neighboring cells on cell i , $\mathbf{x}$ is the contact point, $\mathbf{x}_{0,i}$ is the cell center, $\mathbf{S}_i$ is the directed cell surface pointing outward, and V_i is the cell volume. This stress is smoothed over time by a moving average with a window size of $\tau_p/10$, to limit the effect of fluctuating contact forces due to the discrete nature of the contacts. The hydrostatic tissue stress is then given by $\sigma_h = \text{tr}(\boldsymbol{\sigma})/3$.

E. Cell shape index

The apical cell shape is obtained by projecting the cell nodes onto the substrate and computing the convex hull of the projected points. From this, the perimeter P_i and area A_i are determined, and the shape index is defined as $q_i = P_i/\sqrt{A_i}$ for each cell i .

F. Tissue density

We measure 2D tissue density by projecting the cells on the substrate. The total area of this projected tissue is divided by the domain size A_{box} . This density differs from the number density, which is defined as $N\pi R_0^2/A_{\text{box}}$, where N is the total number of cells with cell volume $4/3\pi R_0^3$.

G. Simulation setup

N_0 cells with radius R_0 are seeded in a periodic boundary domain in a hexagonal pattern, where cell positions are displaced by a distance from a Gaussian distribution with standard deviation R_0 . Next, a fraction of $0.35N_0$ cells are removed using a Latin hypercube sampling method to ensure a uniform distribution of N cells in the periodic domain. In all simulations, the tissue consists of $N = 100$ cells, unless otherwise specified. Next, the size of the domain decreases linearly with time with velocity v_b until the desired number density $N\pi R_0^2/A_{\text{box}}$ is reached, with A_{box} the final size of the periodic domain, after a time $\tau_{\text{init}} = 360\eta_c t_c/\gamma$. Simultaneously, a centripetal force $\mathbf{F}_{cp} = v_b \xi_{cs} \pi R_0^2 \mathbf{e}_r$ is added to all cells during τ_{init} . Cells are allowed to relax for an additional time of $\tau_{\text{init}}/3$, without any active forces. These monolayers are then used to initialize the tissue simulations. For simulations shown in Fig. 2, the cell active migration pressure exponentially relaxes in time as $p_{\text{eff}}(t) = \exp(-2t/(3\tau_p))$. This effectively allows the system to cool down to an annealed state. For all other simulations, the cell activity p_{eff} is set fixed, and the tissue is allowed to reach steady state. Measurements of tissue dynamics only started after an additional simulation time of $2\tau_p$. For shear relaxation studies, we performed five independent simulation repeats; for all other studies, three repeats were conducted for each combination of cell properties shown. The model parameters that were used for the simulation can be found in Table I. All simulations were conducted in Python using the Mpacts particle-based simulation framework.

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J.V., H.R., and B.S. conceptualized the work; J.V. performed the simulations; J.V. performed the analysis; J.V. and B.S. wrote the manuscript; and all authors edited the manuscript.

DATA AVAILABILITY

The data that support the findings of this article are openly available [81].

APPENDIX A: RATIONALE OF THE ACTIVE FOAM MODEL

Following Refs. [40,42,48,82], we assume that cell shape is governed by the actomyosin cortex, which we assume to behave as a curved 2D liquid film at long timescales, with constant viscosity η_c . For simplicity, we assume equal shear viscosity, longitudinal viscosity, and bulk viscosity of the cortex. Hence, the total in-plane cortex tension is

$$\sigma_{2D} = \eta_c \nabla \mathbf{u} + \gamma_c \hat{\mathbf{I}}, \quad (\text{A1})$$

with in-plane velocity $\mathbf{u} = (u, v)$, and where surface tension $\gamma_c = \gamma$ at free surfaces and $\gamma_c = \gamma - \omega$ at contacts. This accounts for the reduction of actomyosin contractility at cell-cell (and cell-substrate) interfaces [34], producing an effective adhesive tension ω (see Appendix B 1). The in-plane tension balance then reads

$$\nabla \cdot \sigma_{2D} - \xi(\mathbf{u} - \mathbf{u}_j) - \xi_0 \mathbf{u} = 0, \quad (\text{A2})$$

where the second term includes cell-cell and cell-substrate friction with friction coefficient ξ [83] and cell-medium friction with damping constant ξ_0 . Since this stress acts on a curved surface, out-of-plane forces arise. Assuming a Kirchhoff-Love approximation of viscous bending, and with w the out-of-plane velocity, we write

$$\text{Tr}(\sigma_{2D})(\nabla \cdot \hat{\mathbf{n}}) + \Delta P - \eta_b \nabla^4 w - c_0 w = 0, \quad (\text{A3})$$

with $\hat{\mathbf{n}}$ the normal of the surface, $\eta_b = \eta_c t_c^3/3$ the viscous bending constant, and where $\Delta P = P^b + P^\omega + P^a$ is the pressure drop over the surface that is caused by the internal pressure P^b , contact pressure P^ω , and an active migration pressure P^a .

APPENDIX B: NUMERICAL IMPLEMENTATION OF ACTIVE FOAM MODEL

The governing equations of the cell cortex mechanics [Eqs. (A2) and (A3)] are discretized using a particle-based model, where the cell actomyosin complex is modeled as a triangulated surface mesh, and forces are computed for each node. In the following text, triangles are represented by A or B and nodes are represented by i, j , and k (see Fig. 7).

1. Cortex tension

Tension in the cortex arises from actomyosin contractility, modeled as an effective surface tension γ_c . At contact interfaces, cortex tension decreases by decrease of actomyosin activity [34], represented as an effective adhesive tension ω (see Fig. 7). The resulting surface tension in a triangle is given by

$$\gamma_c = \begin{cases} \gamma - \omega, & \text{for contacting surfaces,} \\ \gamma, & \text{for free surfaces.} \end{cases}$$

Therefore, the interfacial tension between two cells (the sum of the tension of the two contacting surfaces) is given by $2(\gamma - \omega_{cc})$, and the cell-medium interface tension is given by γ . At steady state, the contact angle 2θ between two contacting cells can be expressed as $2\gamma \cos(\theta) = 2(\gamma - \omega_{cc})$. The force on each node i of a triangle consisting out of nodes

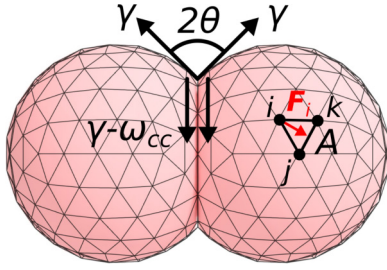


FIG. 7. Adhesive contact between two cells with surface tension γ and adhesive tension ω_{cc} . The cell is represented by a triangulated surface, representing the actomyosin cytoskeleton. The tension at the contacting surface of a cell is then given by $\gamma - \omega_{cc}$ and the cell-cell interfacial tension is the sum of the two contacting surfaces $2(\gamma - \omega_{cc})$. Assuming force balance, the contact angle 2θ between the two cells can be computed as $2\gamma \cos \theta = 2(\gamma - \omega_{cc})$. Tension in triangle $A = (i, j, k)$ is translated to forces $\mathbf{F}_i^\gamma$, $\mathbf{F}_j^\gamma$, and $\mathbf{F}_k^\gamma$ on nodes i , j , and k , respectively.

$A = (i, j, k)$ ordered counterclockwise in the direction of the triangle normal $\hat{\mathbf{n}}_A$ is then given by [84]

$$\mathbf{F}_i^\gamma = \frac{\gamma_c}{2} (\mathbf{x}_k - \mathbf{x}_j) \times \hat{\mathbf{n}}_A.$$

2. Cortex viscosity

Actomyosin remodeling is modeled as an effective cortex viscosity η_c . We distinguish between in-plane and out-of-plane bending viscosity. The in-plane viscous damping force between two nodes i, j with velocity $\mathbf{v}$ is given by

$$\mathbf{F}_i^{\eta_c} = \frac{\eta_c t_c}{\sqrt{3}} ((\hat{\mathbf{n}}_{ij} \cdot (\mathbf{v}_j - \mathbf{v}_i)) \hat{\mathbf{n}}_{ij} + (\hat{\mathbf{t}}_{ij} \cdot (\mathbf{v}_j - \mathbf{v}_i)) \hat{\mathbf{t}}_{ij}),$$

where the direction of viscous forces is given by the unit vectors

$$\begin{aligned} \hat{\mathbf{n}}_{ij} &= \frac{\mathbf{v}_j - \mathbf{x}_i}{\|\mathbf{v}_j - \mathbf{x}_i\|}, \\ \hat{\mathbf{t}}_{ij} &= \frac{\hat{\mathbf{n}}_A + \hat{\mathbf{n}}_B}{\|\hat{\mathbf{n}}_A + \hat{\mathbf{n}}_B\|} \times \hat{\mathbf{n}}_{ij}, \end{aligned}$$

with $\hat{\mathbf{n}}_A$ and $\hat{\mathbf{n}}_B$ the normals of the triangles making up the segment between nodes i and j . Note that we do not distinguish between bulk, extensional (η_e), and shear viscosity (η_c), effectively setting the Trouton ratio η_e/η_c to 1. In contrast, a Newtonian fluid typically has a Trouton ratio of 3.

The viscous bending moment between two adjacent triangles $A = (i, j, k)$, $B = (i, l, j)$ with small thickness t_c arises from the rate of angle deviation $\frac{d\phi}{dt}$ as

$$\|\mathbf{M}_{AB}^{\eta_c}\| = \frac{\eta_c t_c^3}{3} \frac{d\phi}{dt}.$$

From this bending moment, we derive the lever forces on the opposing nodes,

$$\begin{aligned} \mathbf{F}_k^{\eta_c} &= -\frac{\mathbf{M}_{AB}^{\eta_c} \times \hat{\mathbf{l}}_A}{l_A}, \\ \mathbf{F}_l^{\eta_c} &= +\frac{\mathbf{M}_{AB}^{\eta_c} \times \hat{\mathbf{l}}_B}{l_B}, \end{aligned}$$

with l and $\hat{\mathbf{l}}$ the length and unit vector from common axis (i, j) to lever point k or l . For lever A , this is

$$\begin{aligned} \mathbf{l}_A &= \hat{\mathbf{n}}_A \times (\mathbf{x}_j - \mathbf{x}_i), \\ l_A &= (\mathbf{x}_k - \mathbf{x}_i) \cdot \mathbf{l}_A. \end{aligned}$$

The forces on the common points (i, j) are weighted with the projected distance of the lever on the common axis,

$$\begin{aligned} y_{i,A} &= (\mathbf{x}_k - \mathbf{x}_i) \cdot (\mathbf{x}_j - \mathbf{x}_i), \\ y_{j,A} &= (\mathbf{x}_j - \mathbf{x}_k) \cdot (\mathbf{x}_j - \mathbf{x}_i), \\ y_{i,B} &= (\mathbf{x}_l - \mathbf{x}_i) \cdot (\mathbf{x}_j - \mathbf{x}_i), \\ y_{j,B} &= (\mathbf{x}_j - \mathbf{x}_l) \cdot (\mathbf{x}_j - \mathbf{x}_i), \end{aligned}$$

to obtain the forces on the common nodes for lever forces $\mathbf{F}_k^{\eta_c}$ and $\mathbf{F}_l^{\eta_c}$:

$$\begin{aligned} \mathbf{F}_i^{\eta_c} &= -\frac{y_{j,A}}{y_{i,A} + y_{j,A}} \mathbf{F}_k^{\eta_c} - \frac{y_{j,B}}{y_{i,B} + y_{j,B}} \mathbf{F}_l^{\eta_c}, \\ \mathbf{F}_j^{\eta_c} &= -\frac{y_{i,A}}{y_{j,A} + y_{i,A}} \mathbf{F}_k^{\eta_c} - \frac{y_{i,B}}{y_{j,B} + y_{i,B}} \mathbf{F}_l^{\eta_c}, \end{aligned}$$

which ensure force balance.

3. Internal pressure

We assume the cell cytoplasm to be incompressible. Therefore, we implement active volume control for each cell by a cytoplasmic pressure P^b using a PI volume controller

$$P^b = -K\epsilon_V(t) - K_i \int_0^t \epsilon_V(t) dt,$$

where $\epsilon_V(t) = (V(t) - V_0)/V_0$, with $V(t)$ the instantaneous volume and V_0 the equilibrium volume, K the proportional term and K_i integrative term. The force on a triangle A is given by

$$\mathbf{F}_A^b = S_A P^b(t),$$

with S_A the directed area of the triangle, which is simply distributed to nodes i as

$$\mathbf{F}_i^b = \frac{\mathbf{F}_A^b}{3}.$$

4. Active migration pressure

Cell activity is captured by two distinct but related effects: a net protrusive pressure and an elongation pressure [see Figs. 8(a) and 8(b)]. The net traction force of the cell is balanced by friction forces to drive cell movement at a constant velocity v_0 . Furthermore, the elongation pressure stretches the cell in the direction of polarization $\hat{\mathbf{p}} = (\cos \phi, \sin \phi, 0)$, where we assume that the cell polarity vector is a minimal representation of the cell front-to-rear polarity, restricted to the substrate plane xy that undergoes rotational diffusion:

$$\frac{d\phi}{dt} = \sqrt{2D_r} \xi_n,$$

where ξ_n is standard, Gaussian noise and D_r the rotational diffusion coefficient corresponding to persistence time

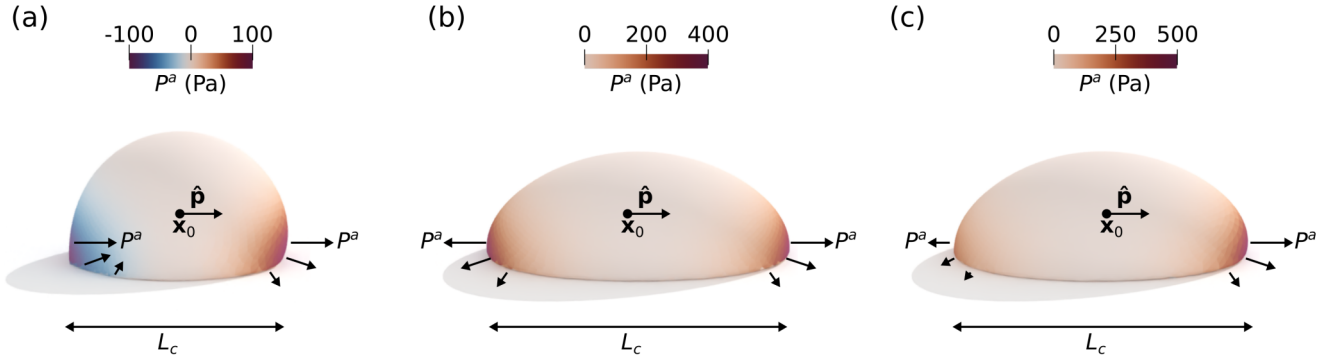


FIG. 8. Example of a single migrating cell for $p_a = 100$ Pa (a) with only the migration part, (b) with only the elongation part $\lambda_a = 4$, and (c) with both migratory forces and elongation forces as given in Eq. (B2).

$\tau_p = 1/D_r$. The pressure from cell migration on triangle A is

$$P_A^a = \frac{2p_a}{L_c} \left(\underbrace{|\mathbf{r}_A \cdot \hat{\mathbf{p}}|}_{\text{migration}} + \underbrace{\lambda_a(\mathbf{r}_A \cdot \hat{\mathbf{p}})}_{\text{elongation}} \right) (\hat{\mathbf{n}}_A \cdot \hat{\mathbf{p}}), \quad (\text{B1})$$

with $\mathbf{r}_A = \mathbf{x}_A - \mathbf{x}_0$ the vector pointing from $\mathbf{x}_0$ the center of the cell to the center of the triangle $\mathbf{x}_A$, L_c the instantaneous length of the cell in the direction of polarization, and λ_a the nondimensional scaling factor determining the strength of elongation relative to migration. In this minimal model of cell migration, we considered the migration part as a polar effect and the elongation part as a dipolar effect.

Furthermore, we assume that the cell migrates by actin polymerization close to the substrate, so we limit the protrusive forces to a narrow region near the substrate (located parallel to the xy plane) by multiplying P^a [Eq. (B1)] with a Gaussian kernel with a length scale λ_z similar to Ref. [85]. The total pressure on triangle A will be [see Fig. 8(c)]

$$P_A^{\text{eff}} = \frac{2p_a}{L_c} (|\mathbf{r}_A \cdot \hat{\mathbf{p}}| + \lambda_a(\mathbf{r}_A \cdot \hat{\mathbf{p}})) (\hat{\mathbf{n}}_A \cdot \hat{\mathbf{p}}) \exp \left[-\frac{1}{2} \left(\frac{\Delta z}{\lambda_z} \right)^2 \right], \quad (\text{B2})$$

with Δz the distance of the geometric center of the triangle relative to the substrate plane.

The triangle forces $\mathbf{F}_A^a = S_A P_A^{\text{eff}}$ are distributed to nodes i as

$$\mathbf{F}_i^a = \frac{\mathbf{F}_A^a}{3}.$$

5. Contact pressure

In our contact model, we assume a uniform adhesion over the interacting surfaces. Therefore, we define a linear contact pressure that includes both repulsive and adhesive interactions as a function of overlapping distance $\delta(\mathbf{x})$ between two surfaces, as

$$P_{AB}^\omega(\mathbf{x}) = P^0 - k\delta(\mathbf{x}). \quad (\text{B3})$$

Here, $P^0 = \omega_{\text{tot}}/h_0$ ensures attraction between the surfaces and $k = P^0/h_0$ ensures volume exclusion by repulsion, with h_0 the effective range of adhesion that is incorporated by translating the nodes over a distance $h_0/2$ in the direction of the node normals [see Fig. 9(a)]. Furthermore, ω_{tot} is the

total adhesion energy of the two surfaces: For two interacting cells $\omega_{\text{tot}} = 2\omega_{cc}$, where the factor 2 accounts for the two interacting surfaces, whereas for a cell adhering to a surface $\omega_{\text{tot}} = \omega_{cs}$. At equilibrium ($P_{AB}^\omega(\mathbf{x}) = 0$), the overlap of the translated surfaces is $\delta(\mathbf{x}) = h_0$.

Equivalently, we can derive the work of adhesion, defined as the energy to separate two cell surfaces, as

$$W = - \int_{h_0}^0 P_{AB}^\omega S_{AB} d\delta.$$

By inserting Eq. (B3) and assuming that the contact area S_{AB} is constant during separation, we retrieve the adhesion energy $W = \omega_{cc} S_{AB}$.

The overlap distance at a given test point $\mathbf{x}$ is computed with the translated triangles as

$$\delta(\mathbf{x}) = \max(0; 2(\mathbf{x} - s_{AB}) \cdot (\hat{\mathbf{n}}_{AB} \times \hat{\mathbf{l}}_{AB}) \tan(\alpha))$$

with $\hat{\mathbf{l}}_{AB}$ the intersection line between two triangles, s_{AB} an arbitrary point on the intersection line, $\hat{\mathbf{n}}_{AB}$ the normal of the common contact plane [see Figs. 9(b) and 9(c)] defined as

$$\hat{\mathbf{n}}_{AB} = \frac{\hat{\mathbf{n}}_A - \hat{\mathbf{n}}_B}{\|\hat{\mathbf{n}}_A - \hat{\mathbf{n}}_B\|},$$

and α the angle between the triangle and the contact plane $A \cap B$. The contact force and moment are obtained by integrating the total contact pressure over the oriented contact area S_{AB} on the common contact plane:

$$\begin{aligned} \mathbf{F}_{AB}^\omega &= \int_{\mathbf{x} \in A \cap B} P_{AB}^\omega(\mathbf{x}) dS_{AB}, \\ \mathbf{M}_{AB}^\omega &= \int_{\mathbf{x} \in A \cap B} P_{AB}^\omega(\mathbf{x}) dS_{AB} \times (\mathbf{x} - \mathbf{x}_{AB}), \end{aligned}$$

with $\mathbf{x}_{AB}$ the contact point defined as the geometric center of the intersection polygon. This force is distributed to nodes i ensuring conservation of momentum and force, assuming the forces are directed in $\hat{\mathbf{n}}_{AB}$. This results in a system of linear equations per contact pair:

$$\begin{aligned} \mathbf{M}_{AB}^\omega &= \sum_{i \in A} (\mathbf{x} - \mathbf{x}_{AB}) \times \mathbf{F}_{i,AB}^\omega, \\ \mathbf{F}_{AB}^\omega &= \sum_{i \in A} \mathbf{F}_{i,AB}^\omega. \end{aligned}$$

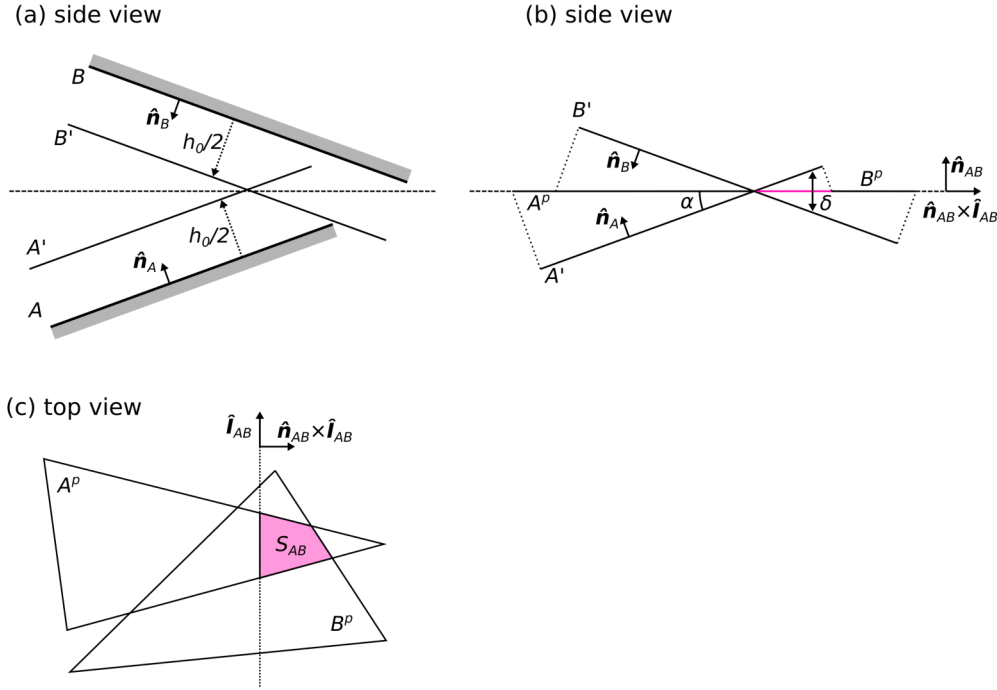


FIG. 9. Geometry of triangle-triangle contact. (a) Side view of two triangles A and B , which are virtually displaced over a distance h_0 along their node normals. Contact overlaps are computed based on these displaced triangles A' and B' . (b) Next, the triangles are projected on the contact plane (indicated by the dashed line) according to the triangle normals (indicated by the dotted lines), yielding A^p and B^p . The angle between the planes and the contact plane α is expressed as $\cos \alpha = \hat{n}_{AB} \cdot \hat{n}_A$. From α , the overlapping distance between the triangles can be obtained at a test point $\mathbf{x}$ as $\delta(\mathbf{x}) = 2(\mathbf{x} - \mathbf{s}_{AB}) \cdot (\hat{n}_{AB} \times \hat{\mathbf{i}}_{AB}) \tan(\alpha)$, with $\mathbf{s}_{AB}$ a point on the intersection line between the two triangles. The polygon where the projected triangles are overlapping and where $\delta > 0$ gives the contact polygon S_{AB} , indicated by the pink line. (c) Top view of the triangles, where the pink polygon indicates the contact polygon, and the dotted line the intersection line with normal $\hat{\mathbf{i}}_{AB}$.

The solution for this system is presented and discussed in the work of Smeets *et al.* [86].

6. Wet contact friction

A viscous contact force is included to account for drag between contacting surfaces with friction constant ξ_{ci} . The contact drag force acting on node i of triangle A of the contact pair (AB) is

$$\mathbf{F}_{i,AB}^\xi = \mathbf{C}_{AB}^\xi \cdot \sum_{k \in B} w_{ik}^{AB} (\mathbf{v}_k - \mathbf{v}_i),$$

determined by a friction tensor $\mathbf{C}_{AB}^\xi$ and weights w_{ik}^{AB} per node k of the B triangle. Weights w_{ik}^{AB} are assumed to scale with the relative contribution of the nodal contact forces to the overall contact force; thus,

$$w_{ik}^{AB} = \frac{(\mathbf{F}_{i,AB}^\omega + \mathbf{F}_{k,AB}^\omega) \cdot \hat{n}_{AB}}{6 \sum_{\forall k \in B} \mathbf{F}_{k,AB}^\omega \cdot \hat{n}_{AB}}$$

is used as an approximation. $\mathbf{C}_{AB}^\xi$ for a given contact area S_{AB} is estimated as

$$\mathbf{C}_{AB}^\xi = S_{AB} [\xi^\perp \hat{n}_{AB} \otimes \hat{n}_{AB} + \xi^\parallel (\mathbb{I} - \hat{n}_{AB} \otimes \hat{n}_{AB})],$$

with normal and tangential friction coefficients $\xi^\perp$ and $\xi^\parallel$ assumed equal in this study.

7. Medium damping

A general drag force on node i from liquid drag between cell and medium with viscosity η_f is given by

$$\mathbf{F}_i^{\eta_f} = -\mathbf{C}_i^{\eta_f} \cdot \mathbf{v}_i,$$

where we approximate the drag force from Stokes' law for spherical particles as

$$\mathbf{C}_i^{\eta_f} = 6\pi R_0 \eta_f \frac{S_i}{4\pi R_0^2} \mathbb{I} = \frac{3\eta_f}{2R_0} S_i \mathbb{I}.$$

$\mathbf{F}_i^{\eta_f}$ is small compared to other dissipative forces, but provides stability of the numerical integration scheme (conjugate gradient method) as it ensures that the resistance matrix is positive definite.

8. Equation of motion

For the overdamped environment, inertial forces can be neglected and the force balance for node i is given by

$$\begin{aligned} \mathbf{F}_i^\gamma + \mathbf{F}_i^b + \mathbf{F}_i^a + \sum_{(AB):i \in A} \mathbf{F}_{i,AB}^\omega \\ = -\mathbf{F}_i^{\eta_f} - \sum_j \mathbf{F}_i^{\eta_c} - \sum_{(AB):i \in A} \mathbf{F}_{i,AB}^\xi, \end{aligned}$$

where right-hand forces are viscous forces that linearly depend on relative velocities of the nodes as

$$\begin{aligned} \mathbf{F}_i^\gamma + \mathbf{F}_i^b + \mathbf{F}_i^a + \sum_{i \in A} \mathbf{F}_{i,AB}^\omega \\ = \mathbf{C}_i^{\eta_f} \cdot \mathbf{v}_i + \sum_j \mathbf{C}_{ij}^{\eta_c} \cdot (\mathbf{v}_i - \mathbf{v}_j) \\ + \sum_{(AB):i \in A} \mathbf{C}_{AB}^\xi \sum_{k \in B} w_{ik}^{AB} (\mathbf{v}_i - \mathbf{v}_k) \end{aligned}$$

with $\mathbf{C}_{ij}^{\eta_c}$ containing viscous elements from bending, shear, and elongation viscosity. For the total system of N nodes, this can be summarized as

$$\mathbf{F} = \mathbf{C} \mathbf{v}, \quad (\text{B4})$$

with $\mathbf{F}$ a $3N \times 1$ column matrix that represents all left-hand forces per node, $\mathbf{C}$ a $3N \times 3N$ sparse symmetric positive-definite friction matrix, and $\mathbf{v}$ a $3N \times 1$ column matrix representing the velocities of N nodes. The conjugate gradient method (CGM) is then used to solve for the node velocities every time step. Node positions $\mathbf{x}_i$ are updated every time step using a semi-implicit Euler integration scheme

$$\mathbf{x}_i(t + \Delta t) = \mathbf{x}_i(t) + \Delta t \mathbf{v}_i(t + \Delta t),$$

where $\mathbf{v}_i(t + \Delta t)$ are the projected new velocities obtained by solving Eq. (B4) at time $t + \Delta t$ via the CGM.

9. Remeshing

Because we model the cortex as a viscous fluid under surface tension, the discrete nodes tend to flow over the surface. To ensure the mesh quality, we remesh the triangulated surface. There are four remeshing stages based on Ref. [87]: split triangles, flip edges, split edges, and delete edges. In the first stage, triangles that are too big ($S_A > S_{\min}$) are split at the geometric center into three separate triangles. In the second stage, edges between triangles are flipped if the angles between two nodes opposing the edge add up to more than π . For a curved surface, this operation can result in area, volume, and shape changes. To limit this effect, flipping is only done for edges between neighboring triangles that make an angle $\theta < \pi/3$. Otherwise, the edge is split in the center where both triangles are subdivided into two triangles. In the last stage, edges between triangles that are too small ($S_A < S_{\max}$) are deleted, removing both triangles. This is repeated every $2\eta_{ct}/\sqrt{3}\gamma\Delta t$ time steps. With remeshing, we assume that the nodes do not carry local information, but are merely considered as discretization points to represent a continuous surface.

APPENDIX C: EQUILIBRIUM SHAPE OF CELLS IN A HEXAGONAL CONFLUENT TISSUE

Assume that a cell with cortex tension γ spreads out on a substrate with adhesive tension ω_{cs} and establishes a hexagonal confluent tissue with adhesive tension ω_{cc} between neighboring cells. Assuming volume conservation, the free

energy of the cell can be written as

$$\mathcal{F} = \gamma S_a + (\gamma - \omega_{cc}) S_l + (\gamma - \omega_{cs}) S_b,$$

where $S_a = S_b$ is the apical and basal cell surface area and S_l is the cell area in contact with neighboring cells. Let us define h as the cell height and d as the distance between the centroids of neighboring cells to rewrite the free energy as

$$\mathcal{F} = (2\gamma - \omega_{cs}) \frac{\sqrt{3}}{2} d^2 + (\gamma - \omega_{cc}) \frac{6}{\sqrt{3}} d h.$$

Given the cell is initially spherical with radius R_0 , and assuming volume conservation ($V_0 = 4/3\pi R_0^3$), we can write cell height h as a function of cell-cell distance d as

$$\begin{aligned} h &= \frac{8\pi R_0^3}{3\sqrt{3}d^2}, \\ d &= \sqrt{\frac{8\pi R_0^3}{3\sqrt{3}h}}. \end{aligned}$$

We use this relation to write the free energy as a function of cell-cell centroid distance:

$$\mathcal{F} = (2\gamma - \omega_{cs}) \frac{\sqrt{3}}{2} d^2 + (\gamma - \omega_{cc}) \frac{16\pi}{3} \frac{R_0^2}{d}$$

or as a function of cell height:

$$\mathcal{F} = (2\gamma - \omega_{cs}) \sqrt{V_0} h + (\gamma - \omega_{cc}) \sqrt{V_0} 8\sqrt{3} h.$$

By minimizing the free energy $\frac{d\mathcal{F}}{dd} = 0$, we can calculate the cell shape corresponding to minimal energy as a function of cortex tension and adhesive tensions. The derivative of free energy as a function of d is given by

$$\frac{d\mathcal{F}}{dd} = (2\gamma - \omega_{cs}) \sqrt{3} d - (\gamma - \omega_{cc}) \frac{16\pi R_0^2}{3d^2},$$

so we find the corresponding cell-cell distance

$$d/R_0 = \sqrt[3]{\frac{16\pi}{3\sqrt{3}} \left(\frac{\gamma - \omega_{cc}}{2\gamma - \omega_{cs}} \right)} \quad (\text{C1})$$

and cell height

$$h/R_0 = \left(\frac{2\pi}{3\sqrt{3}} \right)^{1/3} \left(\frac{\gamma - \omega_{cc}}{2\gamma - \omega_{cs}} \right)^{-2/3}.$$

From this, we calculate the ratio

$$h/d = \frac{1}{2} \left(\frac{2\gamma - \omega_{cs}}{\gamma - \omega_{cc}} \right). \quad (\text{C2})$$

As expected, this shows that cell-substrate adhesive tension ω_{cs} promotes squamous cell shapes, whereas cell-substrate adhesive tension ω_{cc} promotes columnar shapes. Finally, we may also find the apical area of the cell:

$$S_a = \frac{\sqrt{3}}{2} R_0^2 \left(\frac{16\pi}{3\sqrt{3}} \frac{\gamma - \omega_{cc}}{2\gamma - \omega_{cs}} \right)^{2/3}.$$

APPENDIX D: CELL ELONGATION FROM ACTIVE PRESSURE

The elongation pressure from cell migration $\lambda_a p_a$ works in a similar way as the preferred shape index q_0 in vertex

models. Let us observe the cell from the basal side in a 2D perspective and assume that the basal area deforms from a circular to an elliptical shape with semimajor axis a and semiminor axis b , from active elongation pressure $\lambda_a p_a$ in the direction of cell polarization $\hat{\mathbf{p}} = [1, 0]$. The cell periphery is given by $[a \cos(\phi), b \sin(\phi)]$, with ϕ the angle relative to the x axis, such that the radius of curvature of an ellipse can be written as

$$r(\phi) = \frac{(a^2 \sin^2(\phi) + b^2 \cos^2(\phi))^{3/2}}{ab},$$

which gives the curvature in the direction of elongation $r(\phi = 0) = b^2/a$ and orthogonal to $\hat{\mathbf{p}}$ $r(\phi = \pi/2) = a^2/b$. From the Young-Laplace law $\Delta P = 2\gamma_c/r$, we can calculate the expected curvature as a function of pressure exerted on the surface as

$$\Delta P = \begin{cases} \frac{2\gamma_c}{a^2/b}, & \phi = \pi/2, \\ \frac{2\gamma_c}{b^2/a} - \lambda_a p_a, & \phi = 0, \end{cases}$$

where $\lambda_a p_a$ is the pressure on the cell surface in the direction of the cell polarization $\hat{\mathbf{p}}$ from the migration pressure [see Eq. (1)]. This can be rewritten as

$$\lambda_a p_a = 2\gamma_c \left(\frac{a}{b^2} - \frac{b}{a^2} \right).$$

Assuming the basal area of the cell is conserved ($S_a = \pi ab = \pi R_{2D}^2$), we can find the relation between a and b . From this, we rewrite the balance as

$$\lambda_a p_a = 2\gamma_c \left(\frac{a^3}{R_{2D}^4} - \frac{R_{2D}^2}{a^3} \right)$$

or

$$\begin{aligned} \frac{\lambda_a p_a R_{2D}}{2\gamma_c} &= \frac{a^3}{R_{2D}^3} - \frac{R_{2D}}{a^3}, \\ \frac{\lambda_a p_a R_{2D}}{2\gamma_c} &= \frac{a^6 - R_{2D}^6}{a^3 R_{2D}^3}. \end{aligned}$$

We can solve a and b as a function of the nondimensionalized active pressure $p_{0,\text{eff}} = \frac{\lambda_a p_a R_{2D}}{2\gamma_c}$:

$$\begin{aligned} a &= R_{2D} \left(\frac{p_{0,\text{eff}} + \sqrt{p_{0,\text{eff}}^2 + 4}}{2} \right)^{1/3}, \\ b &= R_{2D} \left(\frac{p_{0,\text{eff}} + \sqrt{p_{0,\text{eff}}^2 + 4}}{2} \right)^{-1/3}. \end{aligned}$$

The aspect ratio $\mathcal{A} = a/b$ of the basal area of the cell becomes

$$\frac{a}{b} = \left(\frac{p_{0,\text{eff}}}{2} + \sqrt{\frac{p_{0,\text{eff}}^2}{4} + 1} \right)^{2/3}.$$

Solving $p_{0,\text{eff}}$ gives

$$p_{0,\text{eff}} = \frac{\mathcal{A}^3 - 1}{\mathcal{A}^{3/2}}.$$

According to vertex theory, the tissue should unjam when a critical perimeter-to-surface ratio or aspect ratio is reached, $\mathcal{A}^*$. Assuming confluent tissue, the effective tension γ_c is given by the cell-cell interfacial tension $\gamma_c = \gamma - \omega_{cc}$; we can calculate the critical active migration pressure p_0^* where $p_0 = \frac{\lambda_a p_a R_{2D}}{2\gamma}$ as

$$p_0^* = \frac{\mathcal{A}^{*3} - 1}{\mathcal{A}^{*3/2}} (1 - \omega_{cc}/\gamma).$$

Finally, we can use the calculations in Eq. (C1) to find a relation between R_{2D} and $\gamma_c = \gamma - \omega_{cc}$:

$$R_{2D} \propto d/2 \propto R_0 \left(\frac{\gamma - \omega_{cc}}{2\gamma - \omega_{cs}} \right)^{1/3},$$

so that the critical activity $p_{\text{eff}}^* = (\frac{\lambda_a p_a R_0}{2\gamma})^*$ is given by

$$p_{\text{eff}}^* \propto \frac{\mathcal{A}^{*3} - 1}{\mathcal{A}^{*3/2}} (1 - \omega_{cc}/\gamma)^{2/3} (2 - \omega_{cs}/\gamma)^{1/3}, \quad (\text{D1})$$

where we see that ω_{cc} and ω_{cs} will promote cell deformation and, according to vertex theory, tissue unjamming. Whereas ω_{cc} decreases cell interfacial tension that counteracts deformation, ω_{cs} promotes deformation by increasing the apical area πR_{2D}^2 of the cell, thereby reducing the pressure needed for cell deformation (from the Young-Laplace law $\Delta P = 2\gamma/r$).

APPENDIX E: CELL-CELL PULL-OFF

In the limit of porous tissue, cell-cell pull-off is the main driving factor of cell neighbor exchanges and thus tissue unjamming. The two opposing forces determining tissue cohesion are cell-cell rupture force and the active pulling force. The rupture force, previously derived by Brochart-Wyart and de Gennes [55], is approximated by

$$F_s \approx \pi R_0 \omega_{cc}.$$

The pulling force results from active migration of cells and is approximated by

$$F_a \approx p_a R_0 \lambda_z.$$

The tissue cohesion parameter p_a^* becomes

$$\pi R_0 \omega_{cc} = p_a^* R_0 \lambda_z$$

or

$$p_a^* \propto \frac{\pi \omega_{cc}}{\lambda_z}. \quad (\text{E1})$$

At low cell-cell adhesive tension and cell density, we expect the critical protrusive pressure p_a^* , where tissue changes from jammed to unjammed, to be proportional to ω_{cc} .

APPENDIX F: MODEL PARAMETERS

TABLE I. Model parameters.

Parameter	Symbol	Value	Unit
Cell radius	R_0	5	μm
Cell bulk modulus	K	2	kPa
Integrative term	K_i	2	kPa s^{-1}
Cortex active tension	γ	1	$\text{nN}\mu\text{m}^{-1}$
Cell-cell adhesive tension	ω_{cc}	0.05–0.6	$\text{nN}\mu\text{m}^{-1}$
Cell-substrate adhesive tension	ω_{cs}	0.825	$\text{nN}\mu\text{m}^{-1}$
Effective range of adhesion	h_0	0.1	μm
Cell-cell friction	ξ_{cc}	0.24	$\text{kPa s}\mu\text{m}^{-1}$
Cell-substrate friction	ξ_{cs}	0.96	$\text{kPa s}\mu\text{m}^{-1}$
Cortex thickness	t_c	0.15	μm
Cortex viscosity	η_c	10	kPa s
Active pressure	p_a	30–112.5	Pa
Active elongation scaling factor	λ_a	4	—
Activity height length scale	λ_z	2.5	μm
Cell polarity persistence time	τ_p	10	min
Medium viscosity	η_f	50	Pa s
Maximum triangle area	S_{max}	11.8	μm^2
Minimum triangle area	S_{min}	1.3	μm^2
Time step	Δt	0.1	s

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