Correlating cell shape and cellular stress in motile confluent tissues

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Collective cell migration is a highly regulated process involved in wound healing, cancer metastasis, and morphogenesis. Mechanical interactions among cells provide an important regulatory mechanism to coordinate such collective motion. Using a self-propelled Voronoi (SPV) model that links cell mechanics to cell shape and cell motility, we formulate a generalized mechanical inference method to obtain the spatiotemporal distribution of cellular stresses from measured traction forces in motile tissues and show that such traction-based stresses match those calculated from instantaneous cell shapes. We additionally use stress information to characterize the rheological properties of the tissue. We identify a motility-induced swim stress that adds to the interaction stress to determine the global contractility or extensibility of epithelia. We further show that the temporal correlation of the interaction shear stress determines an effective viscosity of the tissue that diverges at the liquid–solid transition, suggesting the possibility of extracting rheological information directly from traction data.

Significance

Using a self-propelled Voronoi model of epithelia known to predict a liquid–solid transition, we examine the interplay between cell motility and cell shape, tuned by cortex contractility and cell–cell adhesion, in controlling the mechanical properties of tissue. Our work provides a unifying framework for existing, seemingly distinct notions of stress in tissues and relates stresses to material properties. In particular, we show that the temporal correlation function of shear stresses can be used to define an effective tissue viscosity that diverges at the liquid–solid transition. This finding suggests a unique way of analyzing traction force microscopy data that may provide information on tissue rheology.

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So far, there is no unifying theory for these seemingly distinct notions of pressure and stress or their relationship to material properties. In this paper, we show that a recently proposed self-propelled Voronoi (SPV) model of epithelia (Fig. 1) \((15)\) provides a natural framework for unifying these ideas. One of the benefits of the SPV model is that it explicitly accounts for the forces that motile cells exert on the substrate. This allows us to develop a generalized mechanical inference method to infer cellular stresses from traction forces and to show that these match the stresses calculated from instantaneous cell shape, relating TFM data and mechanical inference techniques in motile tissues. Additionally, our method provides absolute values for junctional tensions and pressure differences. This is in contrast to equilibrium mechanical inference, which yields only relative forces \((21, 23)\).

There are two additive contributions to the mechanical stress that describe the forces transmitted in a material across a bulk plane. The first one represents the flux of propulsive forces through a bulk plane carried by particles that move across it. The second one describes the flux of interaction forces across a bulk plane. We demonstrate that the generalized mechanical inference measurements probe the latter, which we denote interaction stresses. The former, which we denote the tissue swim stress, approximates the contribution from cell motility to the osmotic pressure generated by cells immersed in a momentum-conserving solvent on a semi-permeable piston and hence to the tissue homeostatic pressure. The tensorial sum of the swim stress and the interaction stress is the total stress. The normal component of the total stress determines whether a tissue will tend to exert extensile or contractile forces on its environment, which is an important consideration in wound healing and cancer tumorigenesis.

An obvious open question, then, is how these stresses vary as a function of material properties. We find that the normal component of the interaction stress is contractile in both the solid and the liquid due to the contractility of the actomyosin cortex, although much more weakly so in the liquid state. In contrast, the normal component of the motility-induced swim stress is always extensile, corresponding to a positive swim pressure, although its magnitude depends on the phase: In a solid the swim pressure is negligible, while in the fluid it can be significant. This can result in a change in sign of the total mean stress: Indeed, we result in a change in sign of the total mean stress: Indeed, we find it is always contractile in the solid state but becomes extensile deep in the liquid state when cell motility exceeds actomyosin contractility. Because the transition from contractile to extensile does not coincide with the fluid to solid transition, it is natural to ask whether the stress displays any signatures of the fluid–solid transition. We develop a definition for the effective viscosity of the tissue that can be extracted from the temporal correlation of the interaction shear stress and find that it diverges as the tissue transitions from the solid state to the liquid state. Importantly, this theoretical prediction suggests that TFM combined with mechanical inference can provide rheological information about the tissue and could be tested by a new analysis of experimental data.

Results and Discussion

**SPV Model.** The SPV model describes an epithelium as a network of polygons. Each cell \(i\) is endowed with a position vector \(r_i\), and cell shape is defined by the Voronoi tessellation of all cell positions (Fig. 1), which has been shown to provide a good representation of some real epithelia, such as the blastoderm of the red flour beetle Tribolium castaneum and the fruit fly Drosophila melanogaster \((32)\). Like for vertex models, tissue forces are obtained from an effective energy functional \(E(\{r_i\})\) for \(N\) cells, given by \((7, 15, 26, 33, 34)\)

\[
E = \sum_{i=1}^{N} E_i = K_A (A_i - A_0)^2 + K_P (P_i - P_0)^2, \tag{1}
\]

with \(A_i\) and \(P_i\) the cross-sectional area and perimeter of the \(i\)th cell, respectively. The first term in Eq. 1 arises from incompressibility of the layer in three dimensions and its resistance to height fluctuations, with \(A_0\) a preferred cross-sectional area. The second term represents the competition between cortical tensions from the actomyosin network at the apical surface and cell–cell adhesions from adhesive complexes at intercellular junctions \((26)\), with \(P_0\) a preferred perimeter resulting from this competition. We simulate \(N\) cells in a square box of area \(A_T\), with \(A = A_T/N\) the average cell area and \(P_0\) the average cell perimeter with and period boundary conditions. The system is initialized with a set of \(N\) random cell positions, independently drawn from a uniform distribution. Throughout the simulations, we set \(A = A_0 = 1\) unless otherwise noted, and \(K_A = K_P = 1\).

Each Voronoi cell is additionally endowed with a constant self-propulsion speed \(v_0\) along the direction of polarization \(\hat{n}_i = (\cos \theta_i, \sin \theta_i)\) describing cell motility. The dynamics of each Voronoi cell are governed by

\[
\partial_t r_i = \mu F_i + v_0 \hat{n}_i, \quad \partial_t \theta_i = \sqrt{2D_\eta(t)}, \tag{2}
\]

where \(F_i = -\nabla_i E\) is the force on cell \(i\) and \(\mu\) is the mobility. The direction of cell polarization is randomized by orientational noise of rate \(D_\eta\), with \(\langle \eta(t) \rangle = 0\) and \(< \eta(t) \eta(t') > = \delta(t-t')\). The timescale \(\tau_\eta = 1/D_\eta\) controls the persistence of single-cell dynamics. As in self-propelled particle (SPP) models, an isolated cell performs a persistent random walk with a long-time translational diffusivity \(D_0 = v_0^2/(2D_\eta)\) \((29, 35, 36)\). After each time step, a new Voronoi tessellation is generated based on the updated cell positions. The cell shapes are determined in the process and the exchange of cell neighbors occurs naturally through topological transitions \((13)\).

We showed in ref. 15 that the SPV model exhibits a transition from a solid-like state to a fluid-like state upon increasing the single-cell motility \(v_0\), the persistence time \(\tau_\eta\), or the cell shape parameter \(P_0/\sqrt{A_0}\) that characterizes the competition between cell–cell adhesion and cortical tension. The phase diagram in the \((P_0, v_0)\) plane is reproduced in Fig. 1B. The transition is identified by setting the shape index \(q = (P_0/\sqrt{A_0})\) to the value \(q = 3.813\), where \(\langle \ldots \rangle\) denotes the average over all cells. It was shown in ref. 15 that the transition line located by \(q = 3.813\) coincides with the one based on the vanishing of the effective diffusivity obtained from the cellular mean-square displacement. Note that for fixed system size \(A_T\) and cell number \(N\), the preferred cell area \(A_0\) does not affect the interaction forces or cellular shapes. Hence the solid–fluid transition is insensitive to \(A_0\), as shown analytically in SI Text. The preferred area \(A_0\) only shifts the total pressure of the tissue by a constant.

**Developing and Validating Traction-Based Mechanical Inference.** It is well established that in a model tissue described by the energy Eq. 1, the mechanical state of cell \(i\) is characterized by a local stress tensor \(\sigma_{ij}^{(s)}\) given by \((21, 23, 37)\)
\[ \sigma_{\alpha\beta}^{(i)\text{int}} = -\Pi_i \delta_{\alpha\beta} + \frac{1}{2A_i} \sum_{ab \in E} T_{ab} \rho_{ab}^i, \]

\[ \Pi_i = \frac{\partial E}{\partial A_i}, \quad T_{ab} = \frac{\partial E}{\partial I_{ab}}, \]

where \( \Pi_i \) is the hydrostatic cellular pressure and \( T_{ab} = T_{a\beta} I_{ab} \) is the cell-edge tension, with \( I_{ab} = I_{ba}/|I_{ab}| \). Here we use Roman indexes \( i, j, k, \ldots \) to label cells and \( a, b, c, \ldots \) to label vertices, while Greek indexes denote Cartesian components. The summation in Eq. 3a runs over all edges of cell \( i \) and \( I_{ab} \) is the edge vector joining vertices \( a \) and \( b \) when the perimeter of cell \( i \) is traversed clockwise, as shown in Fig. S1A. The factor of 1/2 in the second term on the right-hand side of Eq. 3a is due to the fact that each edge is shared by two cells. We have used the convention that the cellular stress is positive when the cell is contractile and negative when the cell is extensile. Contractile stress means that if the cell is cut off from its neighbors, it tends to contract, consistent with the contractility of the actomyosin network within the cell.

Note that in a vertex model the interaction stress as defined in Eq. 3a is indeed the stress acting on the tissue boundary. This is, however, not the case for the Voronoi model because the Voronoi construction introduces constraints not present in the vertex model. We have verified that the differences are small (SI Text) and in the following use Eq. 3a as a good approximation for the Voronoi model.

Our goal is to obtain the distribution of cellular stresses in a layer of motile cells, where cellular configurations do not minimize the tissue energy, but are governed by the dynamics described by Eq. 2. In this case, as discussed in the Introduction, the local cellular stress can be written as the sum of contributions from interactions and propulsive forces as

\[ \sigma_{\alpha\beta} = \sigma_{\alpha\beta}^{(i)\text{int}} + \sigma_{\alpha\beta}^{\text{swim}}, \]

where, following recent work on active colloids (29, 30),

\[ \sigma_{\alpha\beta}^{\text{swim}} = -\frac{\nu_0}{\mu A_i} \sum_{\gamma} n_{\alpha\beta}^{\gamma}, \]

describes the flux of propulsive force \( \frac{\nu_0}{\mu A_i} \) across a boundary, calculated from a virial expression. The negative sign in Eq. 5 ensures that the swim stress follows the same convention as the interaction stress, i.e., is positive for contractile stress and negative for extensile stress. The swim stress is proportional to the cell motility \( \nu_0 \) and vanishes for nonmotile cells. The contribution \( \sigma_{\alpha\beta}^{(i)\text{int}} \) is still given by Eq. 3a, but depends implicitly on cell motility through the instantaneous values of \( \Pi_i \) and \( T_{ab} \) that are determined not by energy minimization, but by the system dynamics governed by Eq. 2. From the local stresses one can then obtain the total mean stress in the tissue as (SI Text) \( \sigma_{\alpha\beta} = \sigma_{\alpha\beta}^{\text{int}} + \sigma_{\alpha\beta}^{\text{swim}} \), with

\[ \sigma_{\alpha\beta}^{\text{int}} = \frac{1}{A_T} \sum_i A_i \sigma_{\alpha\beta}^{(i)\text{int}}, \quad \sigma_{\alpha\beta}^{\text{swim}} = \frac{1}{A_T} \sum_i A_i \sigma_{\alpha\beta}^{\text{swim}}. \]

In simulations where the energy functional is known, it is simple to directly extract the instantaneous pressures and tensions from cell shapes to calculate the interaction contribution \( \sigma_{\alpha\beta}^{(i)\text{int}} \). The definitions, Eq. 3b, give

\[ \Pi_i = -2K_A(A_i - A_0), \quad T_{ab} = 2K_P[(P_j - P_0) + (P_k - P_0)], \]

where \( ab \) is the cell–cell interface that separates cells \( j \) and \( k \). Both \( A_i \) and \( P_i \) are obtained at every time step of the simulation and implicitly depend on cell motility, parameterized by speed \( \nu_0 \) and persistence \( \tau \). This method directly infers the interaction stress from instantaneous cell shape fluctuations through Eq. 3a, yielding what we call shape-based stresses. While easily implemented numerically, this method is of limited use in experiments where the energy functional is not known and likely more complicated.

For this reason we develop a new mechanical inference method for motile monolayers that attempts to approximate the interaction stresses using only information that is accessible in experiments. Specifically, the proposed traction-based mechanical inference infers tensions and pressures from segmented images of cell boundaries and traction forces obtained by TFM. In the SPV model, we define the traction force at each vertex as the gradient of the tissue energy with respect to the vertex position \( t_{\alpha\beta} = -\nabla_\alpha E \), which balances the interaction force \( \Pi_i \). Equilibrium mechanical inference methods express the interaction force \( F_{\alpha\beta} = -\nabla_\alpha E \) at each vertex in terms of cellular pressures and edge tensions and the measured geometry of the cellular network (Eqs. S6–S8). Pressures and edge tensions are then obtained by inverting the equations \( \{\Pi_i, \{T_{ab}\}\} = 0 \). For a nonuniform epithelial layer of motile cells we invert the force balance equations

\[ F_{\alpha\beta} = \{\Pi_i, \{T_{ab}\}\} = t_{\alpha\beta}, \]

where the edge tensions \( T_{ab} \) have been written as the sum of cortical tensions \( T_i \) of adjacent cells (Eq. S7), reducing the number of independent unknowns. The interaction contribution to the local cellular stresses is then calculated using Eq. 3a. A constraint counting yields 4N force balance equations for 2N variables, rendering the system overdetermined, which requires the implementation of a least-squares minimization for the mechanical inference (SI Text).

The equations developed thus far require knowledge of the tractions at each vertex, which is again not realistic in experiments. Therefore, we have developed and implemented a coarse-grained version of this approach that uses experimentally accessible traction forces averaged over a square grid, with a grid spacing of the order of a cell diameter. Pressures and tensions \( (\Pi_i, T_{ab}) \) are then calculated by inverting the force balance equations at the center of each grid element,

\[ F_{\text{grid}} = \{\Pi_i, \{T_{ab}\}\} = t_{\text{grid}}. \]

An outline of the coarse-graining procedure is given in SI Text. We refer to stresses inferred from Eq. 9 as traction-based stresses. We emphasize that the traction-based stress from mechanical inference is generally different from the intercellular stress obtained with monolayer stress microscopy (MSM), which rests upon the assumption that the tissue is an isotropic, homogeneous, and linearly elastic material (18). The mechanical inference does not make such assumptions and is compatible with any epithelia whose cell–cell interactions can be decomposed into tensions at cell junctions and pressures within cell bodies. Examples include Drosophila ectoderm (9) and mesoderm (25), Drosophila wing disk (26), and Madin–Darby canine kidney (MDCK) epithelium (12).

Within the framework of the SPV model, we have validated the coarse-grained method by showing that the resulting traction-based stresses agree with the shape-based stresses computed exactly from the simulations (Fig. 2C and F).

### Stress Characterizes Rheological Properties of the Tissue.

To study the mechanical properties of motile confluent tissues, we simulate a confluent cell layer with periodic boundary conditions, using the SPV model. By examining the temporal correlations of the mean stress in the tissue, as defined in Eq. 6, we show that the tissue displays distinct mechanical properties in the liquid and the solid states. Thus, mechanical measurements such as those provided by TFM can be used to characterize the rheological properties of the tissue.

The stress tensor \( \sigma_{\alpha\beta} \) is symmetric and has three independent components in two dimensions. Both the mean and local stress components are most usefully expressed in terms of normal stress \( \sigma_n \), shear stress \( \sigma_s \), and normal stress difference \( \sigma_d \), with

\[ \sigma_{n,d} = \frac{1}{2} (\sigma_{xx} \pm \sigma_{yy}), \quad \sigma_s = \frac{1}{2} (\sigma_{xy} + \sigma_{yx}). \]

Each of the interaction and swim contributions can similarly be split in normal, shear, and normal difference components. Below
we focus on normal and shear stresses. TFM probes the forces exchanged between tissue and substrate, which by force balance are determined entirely by intercellular forces and hence by interaction stresses. In contrast, the swim components of stress and pressure cannot be probed in TFM, but contribute to the pressure $\Pi = -\sigma_n = \Pi_{\text{int}} + \Pi_{\text{swim}}$ that the tissue would exert laterally on a confining piston. As we show below, the swim contribution dominates the pressure in the liquid state.

Using the expression for the local stress obtained from cell shapes, the mean interaction normal stress of the tissue can be expressed entirely in terms of area and perimeter fluctuations in a virial-like form (SI Text)

$$\sigma^\text{int}_n = \frac{1}{A_T} \sum_i [2K_A A_i (A_i - A_0) + K_F P_i (P_i - P_0)]. \quad [11]$$

The first term represents the interaction contribution from the pressures within the cells. The second term is the contribution from the competition between actomyosin contractility and cell–cell adhesion that controls the cortical tensions. In our simulation, the cellular pressure is suppressed by setting $A = A_0$ and the normal stress comes mainly from the cortical tensions. Eq. 11 then provides a way for extracting mechanical information directly from cell shape based on snapshots of segmented cell images.

**Normal stresses are contractile in the solid phase and may become extensile deep in the liquid phase.** We show in Fig. 2 snapshots of the local interaction normal stress in the solid state (A–C) and in the liquid state (D–F). In both the solid and the liquid the interaction normal stress is on average contractile (red), with relatively weaker spatial fluctuations, but much larger mean value in the solid, where contractile cortical tension exceeds cell–cell adhesion.

Fig. 3 displays the total mean normal stress (the separate contributions from interaction and swim stress are shown in Fig. S2) across the solid–liquid transition. The color map shows that the total normal stress is contractile in the solid and across the transition line (Fig. 3A), black crosses, but changes sign and becomes extensile deep in the liquid. While the interaction stress is always positive due to cell contractility and consistent with experimental observations (1–3, 38), the change in sign of the total stress is due to the swim stress that is zero in the solid and always negative in the liquid (Fig. S2), indicating that motility induces extensile stresses, tending to stretch the tissue. The total normal stress is analogous to the stress on a wall confining an active Brownian colloidal fluid (29, 30). We speculate that its change in sign could lead to an expansion of the tissue if released from confinement due to substrate patterning or to surrounding tissue and may contribute to epithelia expansion in wound-healing assays. In our model confinement is provided by the periodic boundary conditions.

**The tissue effective shear viscosity diverges at the liquid–solid transition.** While the local shear stress averages to zero in both the liquid and the solid states, its temporal correlations provide a distinctive rheological metric for distinguishing the liquid from the solid and identifying the transition. The time autocorrelation function of the interaction shear stress,

$$C_{ss}(\tau) = \langle \sigma^\text{int}_s(t_0) \sigma^\text{int}_s(t_0 + \tau) \rangle_{t_0}, \quad [12]$$

Fig. 2. Comparison of shape-based and coarse-grained traction-based stress. (A–C) Solid state at $v_0 = 0.5$, $P_0 = 3.3$. (D–F) Liquid state at $v_0 = 0.5$, $P_0 = 3.8$. (A and D) Interaction normal stress $\sigma^\text{int}_n$ calculated from the instantaneous cell shapes obtained from Eqs. 3a and 7. Red denotes positive (contractile) stress and blue negative (extensile) stress. (B and E) interaction normal stress $\sigma^\text{int}_n$ calculated using the coarse-grained traction-based mechanical inference by inverting Eq. 9 and using Eq. 3a. The arrows denote the traction forces. (C and F) The coarse-grained traction-based mechanical inference is validated by plotting the traction-based stress against the shape-based stress in the solid (C) and in the liquid (F) state. The data are for 400 cells in a square box of side $L = 20$ with $D_t = 0.1$ and with periodic boundary condition.
where \(\langle \cdots \rangle_{t_0}\) denotes the average over the length \(t_0\) of the simulation, is shown in Fig. 4A for various \(v_0\) across the liquid–solid transition. Shear stress correlations decay in the liquid state and slow down as the transition is approached from the liquid side, becoming frozen in the solid. To quantify this we have defined the correlation time \(\tau_m\) as the time when the correlation has decreased below 1% of its initial value. This correlation time shown in Fig. 4B diverges at the liquid–solid phase transition, suggesting that shear stress autocorrelations can provide a robust metric for the transition. Our work therefore suggests that TFM combined with mechanical inference can provide a tool for the measurement of tissue rheology. Correlating such measurements with cell shape data will provide a stringent test for our theory. Finally, in the liquid state we define an effective viscosity \(\eta_{\text{eff}}\), using a Green–Kubo-type relation by integrating the correlation function over the duration of the correlation time \(\tau_m\),

\[
\eta_{\text{eff}} = \frac{A_T}{k_B T_{\text{eff}}} \int_0^{\tau_m} C_{ss}(\tau) d\tau,
\]

where we have used the ideal gas effective temperature \(k_B T_{\text{eff}} = v_0^2/(2\mu D_r)\) so that \(\eta_{\text{eff}}\) has dimensions of a shear viscosity in two dimensions. Of course the Green–Kubo relation is based on the existence of a fluctuation–dissipation theorem, which does not hold in active systems. For small values of the persistence time \(\tau_r\), however, the orientational noise in the SPV becomes uncorrelated in time and can be mapped onto thermal noise at an effective temperature \(T_{\text{eff}}\). In this limit we expect \(\eta_{\text{eff}}\) to indeed play the role of a shear viscosity. Remarkably, the effective viscosity shown in Fig. 4C and D grows as the tissue approaches the solid state from the liquid side and diverges at the transition. The effective viscosity quickly approaches zero deep in the liquid phase, suggesting that the system behaves as a gas of uncorrelated cells in this region.

Discussion and Conclusions

Using the SPV model we have formulated a unifying framework for quantifying the contributions from cell shape fluctuations and cell motility to mechanical stresses in an epithelial tissue. Cell shape fluctuations from actomyosin contractility and cell–cell adhesion control the interaction stress, while cell motility determines the swim stress that is generically present in all self-propelled systems (29, 30).

Unlike monolayer stress microscopy that computes interaction stress from traction forces by assuming the tissue to be a continuum linear elastic material (18), the traction-based mechanical inference method developed here incorporates spatial and temporal deformations of the tissue due to actomyosin contractility and cell shape fluctuations.
and cell-cell adhesion and can be generalized to account for cell division, apoptosis, and nematic/polar order of the tissue. In contrast to equilibrium mechanical inference techniques (21, 23), our approach does not require cells to be in or close to static mechanical balance, and it also provides the absolute scale of the junctional tensions and pressure differences. This can for instance be important for testing hypotheses involving mechanosensitive biomolecules. Experimentally, our method provides unique ways to extract intercellular interaction stresses from existing traction force data and segmented cell images.

The swim stress, on the other hand, cannot be measured using TFM as it represents the flow of propulsive forces across a bulk plane in the tissue. It contributes to the homeostatic pressure at the lateral boundary of the tissue. The sum of the swim stress and the interaction stress approximates the total stress at the tissue boundary, which is generally contractile but can become extensile when the tissue is deep in the liquid state and cell motility exceeds actomyosin contractility. The exact location of the transition from contractile to extensile depends on the average cellular pressure, which we fix by setting the average cell area to the preferred area, as discussed in SI Text. This change in sign may be observable in wound-healing assays where the transition from contractile to extensile behavior can result in tissue expansion upon removal of confinement by neighboring tissue.

We have extracted an effective tissue viscosity from the temporal correlation of the interaction shear stress. The correlation time and effective viscosity display a slowing down and arrest at the transition to the solid, thus serving as a direct probe of tissue rheology. Moreover, we observed a similar behavior for the temporal correlations of traction forces as demonstrated in SI Text. Therefore, our work suggests that TFM measurement (11) combined with mechanical inference could provide information on tissue rheology. To our knowledge, this has not been attempted yet on experimental data.

Our work sets the stage for examining the feedback between cell activity and tissue mechanics that is apparent in many tissue-level phenomena. Recent work has shown that mechanical stresses influence proliferation in tumor spheroids (28) and regulate cell growth in the developing Drosophila wing (43). Regulation of cell motility, as in contact inhibition of locomotion, has been proposed to explain stress patterns during collective cell migration (44). TFM has revealed the tendency of cells to move along the direction of minimal shear stress, a phenomenon termed “plithotaxis” (11). Our model provides a unifying framework for quantifying the relative roles of various cell properties, such as shape, motility, and growth, on the mechanics of the tissue.

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