

Proliferation symmetry breaking in growing tissues

Xinzhi Li¹, Aniruddha Datta¹, and Shiladitya Banerjee^{1*}*School of Physics, Georgia Institute of Technology, Atlanta, Georgia 30332, USA*

(Received 2 September 2024; accepted 21 October 2025; published 14 January 2026)

Morphogenesis of developing tissues results from anisotropic growth, typically driven by polarized patterns of gene expression. Here, we propose a self-organized model of anisotropic growth driven by feedback between cell polarity, mechanical pressure, and cell division rates. Specifically, cell polarity alignment can induce spontaneous symmetry breaking in proliferation, resulting from the anisotropic distribution of mechanical pressure in the tissue. We show that proliferation anisotropy can be controlled by cellular elasticity, motility, and contact inhibition, elucidating the fundamental design principles for anisotropic morphogenesis.

DOI: [10.1103/jgll-wsvt](https://doi.org/10.1103/jgll-wsvt)

Tissue morphogenesis is primarily driven by anisotropic growth [1–9], leading to the formation of directionally biased organ shapes. For instance, during *Drosophila* gastrulation, polarized intercalations, cell divisions, and motility work together to narrow the extending germband along the dorsal-ventral axis while elongating it more than twice its length along the anterior-posterior axis [2]. The development of *Drosophila* imaginal wing discs is another striking example of anisotropic morphogenesis, where polarized cell divisions shape the anisotropic organ [3–5,10,11]. Anisotropic growth is central to determining shapes in various organisms, including jaw-joint morphogenesis in zebrafish [12,13], limb bud development in vertebrates [14,15], and plant morphogenesis [16]. While anisotropic growth is widely observed in developing tissues, a fundamental question remains unanswered: How do cells collectively generate and sustain directional biases in growth?

One prevailing model is that tissue growth and morphogenesis are regulated by biochemical signaling, through patterned gene expression [17]. However, studies over the past decade have highlighted the significant role of mechanical forces in shaping tissue growth, size, and form [1,18–20]. Mechanical forces can influence local tissue growth rates [21–24], the rate and orientation of cell division [25–28], while cell growth and proliferation can, in turn, affect tissue mechanics through the generation and dissipation of active stresses [29,30]. This interplay between growth and mechanics suggests a complex crosstalk. However, the role of mechanical forces in self-organized anisotropic growth remains poorly understood.

Previous models of anisotropic tissue growth have either relied on predefined material anisotropy [9,31] or incorporated biochemical guidance [32,33] to set directional bias on

growth. In contrast, our work presents a fully self-organized mechanism for anisotropic growth that does not require imposed material anisotropies or external biochemical signals. We introduce the first physical model demonstrating how mechanical feedback between cell polarity and pressure can spontaneously generate anisotropic growth. Using a cell-based vertex model, we show that spontaneous cell polarization induces an anisotropic distribution of mechanical pressure, leading to biased division patterns: In areas with lower compression at the tissue rear, cell divisions occur more frequently, whereas in regions under greater compression at the front, cell divisions are less frequent. Using cell-based modeling and continuum theory, we show that the extent of division anisotropy can be tuned by modulating cell elasticity, motility, and contact inhibition, revealing fundamental design principles for anisotropic morphogenesis in growing tissues.

Discrete cell-based model. We constructed a cell-based model for a growing confluent cell monolayer using the framework of the vertex model [34–40], where the tissue is represented by network of cellular polygons that tessellate the plane. Tissue mechanics is governed by the energy function:

$$E = \frac{1}{2} \sum_{i=1}^N [K_A (A_i - A_0^i)^2 + K_P P_i^2] + 2 \sum_{\langle ij \rangle} \lambda_{ij} L_{ij}, \quad (1)$$

where the cell areas $\{A_i\}$ and perimeters $\{P_i\}$ are functions of the position of vertices $\{\mathbf{r}_i\}$ and the connectivity between cells, K_A and K_P are the area and perimeter elastic moduli, and $\sum_{\langle ij \rangle}$ represents the sum over all neighboring cells of cell i . The term quadratic in cell area A_i results from cell volume incompressibility [35,36,38], and $K_P P_i^2$ is the elastic energy associated with the actomyosin cortex. The third term describes the line tension, λ_{ij} , along the interface shared by cells i and j of length L_{ij} , which can be upregulated by increasing actomyosin contractility or by lowering cell-cell adhesion.

Cell growth is implemented by increasing the cell's target area A_0^i [41–43] as $dA_0^i/dt = G_0 e^{-k(A_i - A_0^i)^2}$, where the constant G_0 is the growth rate of individual cells in the absence of crowding and k is the cellular sensitivity to crowding. In

*Contact author: sbanerjee347@gatech.edu

crowded conditions, cells are under compression that causes deviations of cell area from its preferred value in isolation, leading to an increase in bulk cell pressure $\sim -K_A(A_i - A_0^i)$. This results in a decrease in cell area growth rate at a rate k , thereby lengthening cell cycle times. The parameter k thus models the effect of contact inhibition of proliferation [19], through mechanical feedback on growth. The number of cells in the tissue N increases through cell divisions, regulated by a G1 sizer model [44–46]. In this model, a cell grows in the G1 phase until its area is greater than a threshold value A_S , at which point it transitions to the S/G2/M phase where it resides for a fixed time period T (a timer) before dividing into two daughter cells. See the Supplemental Material [47] for a detailed discussion of the cell growth model and key assumptions.

In addition to growth and division, each cell can migrate actively. To model active cell migration, each cell is assigned a polarity vector $\mathbf{p}_i$ that defines the direction of migration. The overdamped equation of motion of cell vertex α is

$$\mu \frac{d\mathbf{r}_\alpha}{dt} = \mu v_0 \langle \mathbf{p}_i \rangle_\alpha - \frac{\partial E}{\partial \mathbf{r}_\alpha}, \quad (2)$$

where μ is the friction coefficient, v_0 is the cell crawling speed, and $\langle \mathbf{p}_i \rangle_\alpha$ is the average polarity vector of cells sharing the vertex α . The friction term μ represents both cell-substrate dissipation and internal cell-cell friction. With the given rules for polarity dynamics (discussed below), we simulated the vertex-based model of tissue growth, starting from a small colony of N_0 cells under free boundary conditions (Fig. S1 in the Supplemental Material [47]). See the Supplemental Material for details on simulation methods and parameter choices [47]. When a cell reaches the timer threshold, it divides by splitting perpendicular to its major axis, with the boundaries of the daughter cells passing through the centroid of the mother cell (Fig. S1 in the Supplemental Material [47]). The preferred areas of the daughter cells are determined by maintaining pressure homeostasis within cells before and after division. Following division, the ages of the daughter cells are reset to zero, and the directions of the polarity vectors are randomized. The network topology is updated using T1 transitions [38,40].

Isotropic growth. In the absence of any directional bias, the polarity vector of each cell undergoes rotational diffusion, resulting in isotropic growth [Fig. 1(a); Movie 1 in the Supplemental Material [47]]. Cell divisions occur mostly at the tissue boundary, recapitulating experimental observations [27,28]. This is due to crowding-induced suppression of growth at the bulk of the tissue, where the cells undergo cell cycle arrest (Fig. S1 in the Supplemental Material [47]). As a consequence, there is a buildup of cellular pressure at the center of the colony [Fig. 1(b); Movie 2 in the Supplemental Material [47]] and growth rate decreases from the boundary to the tissue center (Fig. S1 in the Supplemental Material [47]). Importantly, there is a negative correlation between cell pressure and the probability of cells being in the G2 phase, such that cell division is more likely in regions of low pressure near the tissue boundary [Fig. 1(c); Fig. S2 in the Supplemental Material [47]]. To quantify spatial variations in tissue mechanics, we computed the cell shape index $q = P/\sqrt{A}$ as a function of distance from the tissue center,

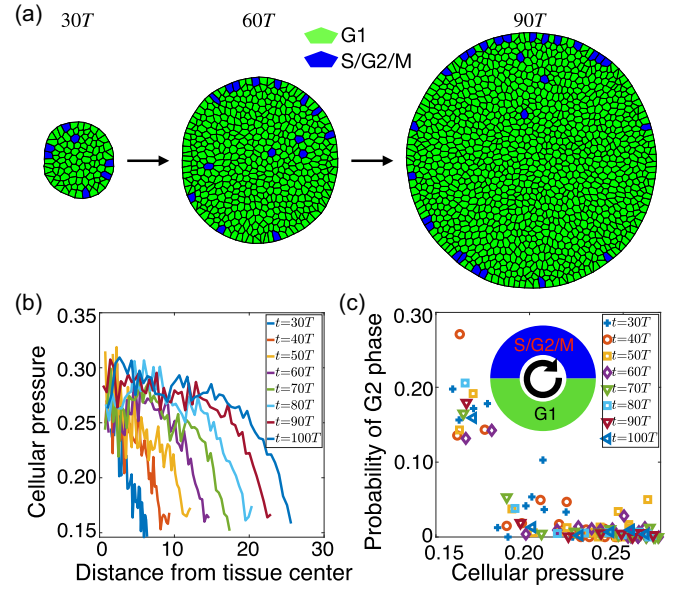


FIG. 1. Proliferation pattern in isotropic growth. (a) Time lapse of an isotropically growing tissue with random polarity. The colors represent cells in G1 (green) and G2 (blue) phases of the cell cycle. (b) Radial pressure distribution at various time steps. The crowded inner cells are under higher pressure from neighboring cells, which leads to lower growth rate. (c) Correlation between the probability of cells in G2 phase of the cell cycle with the cellular pressure. Inset: Schematic of cell cycle phases. See Table SI in the Supplemental Material for parameter values [47].

revealing a transition from a solidlike core ($q \approx 3.85$) to a more fluidlike periphery ($q \approx 4.1$), consistent with increased cell rearrangements and division activity near the boundary (Fig. S10 in the Supplemental Material [47]). The emergent patterns of proliferation can be controlled by modulating cell elasticity K_A and the contact inhibition parameter k (Fig. S2 in the Supplemental Material [47]).

Emergence of anisotropic growth. To more realistically model cell polarity dynamics, we incorporated two essential biological features: contact regulation of locomotion [48] and polarity alignment with neighbors [49,50]. Due to contact regulation of locomotion, cells on the boundary of the monolayer tend to migrate into free space, setting their initial polarity vectors normal to their free edges and pointing outward. Polarity dynamics of cells within the monolayer follow Eq. (3), where both the direction and magnitude of the polarity vectors evolve over time due to alignment interactions with neighboring cells.

$$\frac{d\mathbf{p}_i}{dt} = \kappa_p \sum_j \left(\frac{\mathbf{p}_j}{n_j} - \frac{\mathbf{p}_i}{n_i} \right). \quad (3)$$

Here, j labels the neighboring cells of the cell i , κ_p is the polarity alignment rate, n_i and n_j are the number of neighbors for cells i and j , respectively. Through these interactions, the growing tissue develops an anisotropic distribution of cell growth rate and polarity [Figs. 2(a) and 2(b)], anisotropy in division orientation [Fig. 2(c)], and an irregular shape due to differential growth (Movies 3 and 4 in the Supplemental Material [47]). Polarity sources and sinks naturally emerge

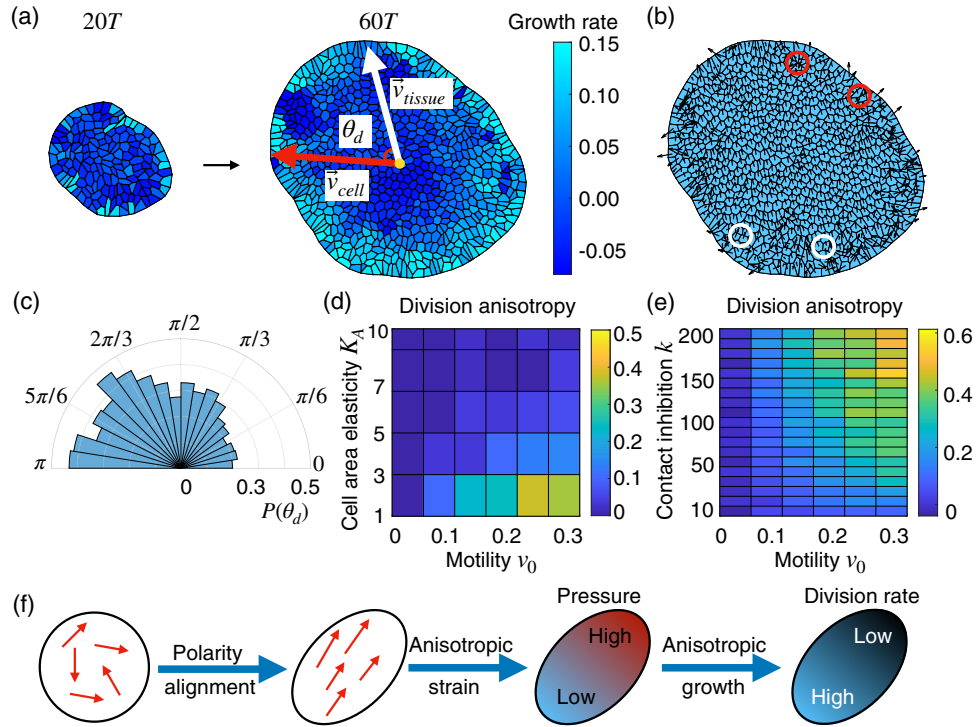


FIG. 2. Anisotropic division patterns in polarized tissues. (a) Time lapse of an anisotropically growing tissue. Colormap represents cell growth rate that shows anisotropic distribution within the tissue. On the right panel, we schematically depict the calculation of cell division angle θ_d . $\vec{v}_{\text{cell}}$ is the vector pointing from the tissue center to the center of the dividing cell and $\vec{v}_{\text{tissue}}$ represents the tissue axis defined as the average of all cellular polarity vectors within the tissue. (b) Cell polarity distribution. The white circles indicate local sources and the red circles mark local sinks. (c) Anisotropic angular distribution of cell divisions. Fewer cell divisions in the head part of the tissue with $\theta_d < \frac{\pi}{2}$ while more in the rear part with $\theta_d > \frac{\pi}{2}$. (d) Phase diagram of division anisotropy at various values of the contact inhibition of proliferation k and migration speed v_0 . (e) Phase diagram of division anisotropy at various values of the contact inhibition of proliferation k and migration speed v_0 . (f) Illustration of division symmetry breaking by polarity alignment. See Table SI in the Supplemental Material for a list of parameter values [47].

due to spatial variations in motility and mechanical constraints [Fig. 2(b)], leading to localized differences in stress accumulation. Consequently, mechanical stresses become anisotropic, giving rise to differential pressure distributions within the tissue. Since pressure is (negatively) correlated with the probability of cell division [Fig. 1(c)], differential pressure drives differential growth patterns [Fig. 2(f)].

To characterize the anisotropy of cell divisions, we calculated the angles of cell division θ_d , defined as the angle between the mean polarity vector and the vector joining the tissue center to the center of the dividing cell [Fig. 2(a), right]. $\theta_d < \frac{\pi}{2}$ indicates cell divisions in the head part of the tissue, while that in the rear part implies division angles $\theta_d > \frac{\pi}{2}$. The polar histogram in Fig. 2(c) shows the anisotropic distribution of cell divisions, with the head part exhibiting less divisions compared to the rear. We introduce the division anisotropy factor, $d_{\text{ans}} = 1 - N_h/N_r$, as a metric of anisotropic growth, where $N_h = N(\theta_d < \frac{\pi}{2})$ and $N_r = N(\theta_d > \frac{\pi}{2})$ are the numbers of division events in the head and rear parts, respectively. When cells divide isotropically, $d_{\text{ans}} = 0$, while $d_{\text{ans}} = 1$ indicates that all divisions occur in the tissue rear. Note that the number of cells in the head and the rear parts of the tissue remain approximately equal throughout growth (Fig. S5 in the Supplemental Material [47]).

We calculated d_{ans} at various cell area elasticity K_A and cell motility v_0 values. The phase diagram in Fig. 2(d)

shows that increasing v_0 increases d_{ans} , while increasing K_A decreases d_{ans} . This is understandable since directional motility (v_0) makes polarity alignment more efficient while K_A imposes stronger constraints on cell area and enhances uniformity. The contact inhibition parameter k also plays a key role in regulating division anisotropy, such that with the increasing k , cells become more sensitive to tissue crowding and thus the division anisotropy is enhanced [Fig. 2(e)]. In the absence of mechanical feedback on growth ($k = 0$), division anisotropy is lost (Fig. S6 in the Supplemental Material [47]). Overall, changing k , v_0 , and K_A modulates division anisotropy, and also influences tissue morphology (Figs. S7 and S8 in the Supplemental Material [47]). While it is expected that polarity alignment would induce a flocking transition to drive directional collective motion [51], the role of cell polarity in coordinating anisotropic divisions is unique, as discussed below.

Mechanical origin of proliferation symmetry breaking. Since polarity alignment promotes coordinated migration, cells at the tissue front accumulate in a directionally biased manner, generating a local compression zone. This results in a higher-pressure region at the tissue front, suppressing proliferation, whereas the rear of the tissue remains less compressed, allowing for increased cell division. This polarity-driven redistribution of mechanical stress is the key driver of the observed division anisotropy.

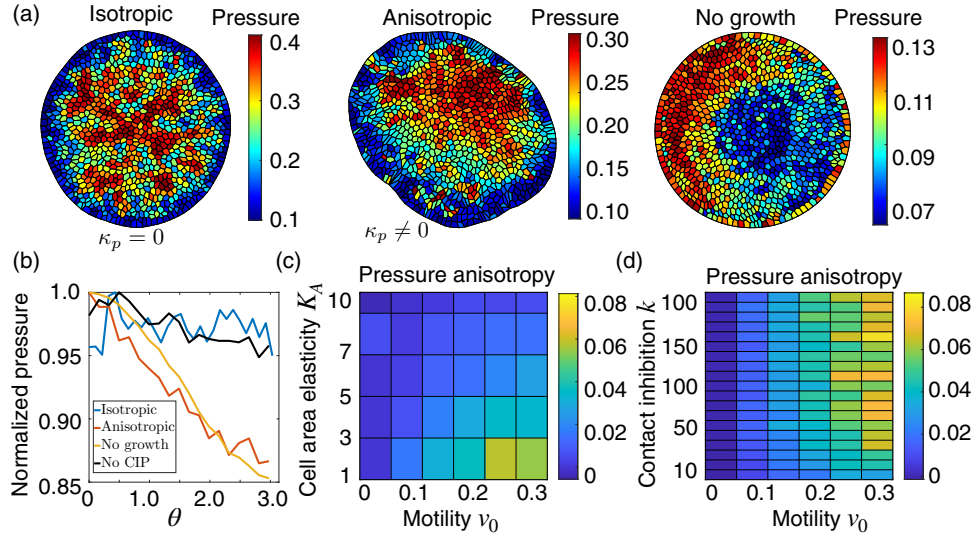


FIG. 3. Pressure anisotropy underlies proliferation symmetry breaking. (a) Snapshots of pressure distribution for an isotropically growing tissue (left), anisotropically growing tissue with polarity alignment (middle), and a tissue system without cell proliferation but under polarity alignment (right). The colors represent magnitudes of cell pressures. (b) Quantification of pressure anisotropy for the tissue configurations in panel (a) and the case without contact inhibition, $k = 0$. For each configuration, the pressure is normalized by its maximum value. (c) Phase diagram of pressure anisotropy at various values of cell area elasticity K_A and migration speed v_0 . (d) Phase diagram of pressure anisotropy at various values of contact inhibition k and v_0 .

We compared pressure distributions in a growing isotropic tissue, a growing anisotropic tissue, and a tissue without cell proliferation [Fig. 3(a)]. In the absence of polarity alignment [Fig. 3(a), left] or mechanical feedback on growth ($k = 0$; Fig. S6 in the Supplemental Material [47]), the tissue grows isotropically with an isotropic pressure distribution that decreases from the center to the boundary. When polarity alignment is present, the pressure distribution is anisotropic, corresponding to anisotropic growth [Fig. 3(a), middle; Movie 5 in the Supplemental Material [47]]. Here, cell divisions are less frequent in regions of high pressure and more frequent in low-pressure areas. Additionally, simulations of a nonproliferating tissue revealed that polarity alignment alone is sufficient to induce anisotropic pressure oriented along the polarity axis [Fig. 3(a), right], suggesting that pressure anisotropy is a precursor to division symmetry breaking. Quantification of angular pressure distribution [Fig. 3(b)] confirms that polarity alignment is indeed essential for anisotropic pressure.

Collectively, these results demonstrate that the symmetry breaking in proliferation is driven by the emergent anisotropy in pressure, which in turn is induced by a gradient in cell compression from the head to the rear of the tissue. This gradient results from tissue deformation induced by cell polarization, suggesting that cell elasticity can regulate the degree of pressure anisotropy. To quantify this, we calculated pressure anisotropy as $p_{\text{ans}} = 1 - p_r/p_h$, where p_r and p_h are, respectively, the average pressures in the rear ($\theta > \pi/2$) and the head ($\theta < \pi/2$) regions of the tissue, with θ representing the angle of each cell relative to the tissue center. We found that increasing cell area elasticity (K_A) suppresses pressure anisotropy [Fig. 3(c)], while increasing cell motility (v_0) and contact inhibition (k) enhances it [Fig. 3(d)]. Increasing contact inhibition strengthens pressure anisotropy by making cell proliferation more sensitive to mechanical constraints,

thereby further reducing growth in compressed regions while permitting greater expansion in uncompressed areas. This differential growth response enhances the pressure gradient across the tissue, reinforcing anisotropic proliferation. Furthermore, pressure anisotropy is negligible in the absence of contact inhibition of proliferation [Figs. 3(b) and 3(d); Fig. S6 in the Supplemental Material [47]]. These trends align with that of cell division anisotropy in Figs. 2(d) and 2(e), suggesting that pressure anisotropy underlies asymmetric proliferation patterns.

Continuum theory. To gain physical insights into the emergence of anisotropic growth, we formulated a minimal continuum model of a growing tissue. With the continuum model, we show that our proposed mechanism for proliferation symmetry breaking does not depend on the specific microscopic rules of the vertex model, but is a collective phenomenon resulting from the feedback between cell polarity, mechanical pressure, and proliferation. It suffices to illustrate the underlying physics using a one-dimensional model of a growing tissue, characterized by three time-varying fields, namely, density $\rho(x, t)$, velocity $v(x, t)$, and polarity $p(x, t)$, governed by the following set of equations:

$$\partial_t \rho + \partial_x(\rho v) = \kappa \rho (1 - \rho/\rho_0), \quad (4.1)$$

$$\mu v = \partial_x \sigma + \mu v_0 p, \quad (4.2)$$

$$\partial_t p = \kappa_p \partial_x^2 p + [a(\rho - \rho_c) - bp^2]p. \quad (4.3)$$

Mass balance implies that the density satisfies the continuity equation (4.1) with logistic growth, where κ is the growth rate constant and ρ_0 is the homeostatic density. The effective rate of exponential proliferation, $\kappa(1 - \rho/\rho_0)$, decreases with density, capturing the effect of contact inhibition of proliferation. Equation (4.2) represents force balance in the overdamped limit, where σ is the tissue stress field, μ is the friction with the substrate, and v_0 is the speed of active cell

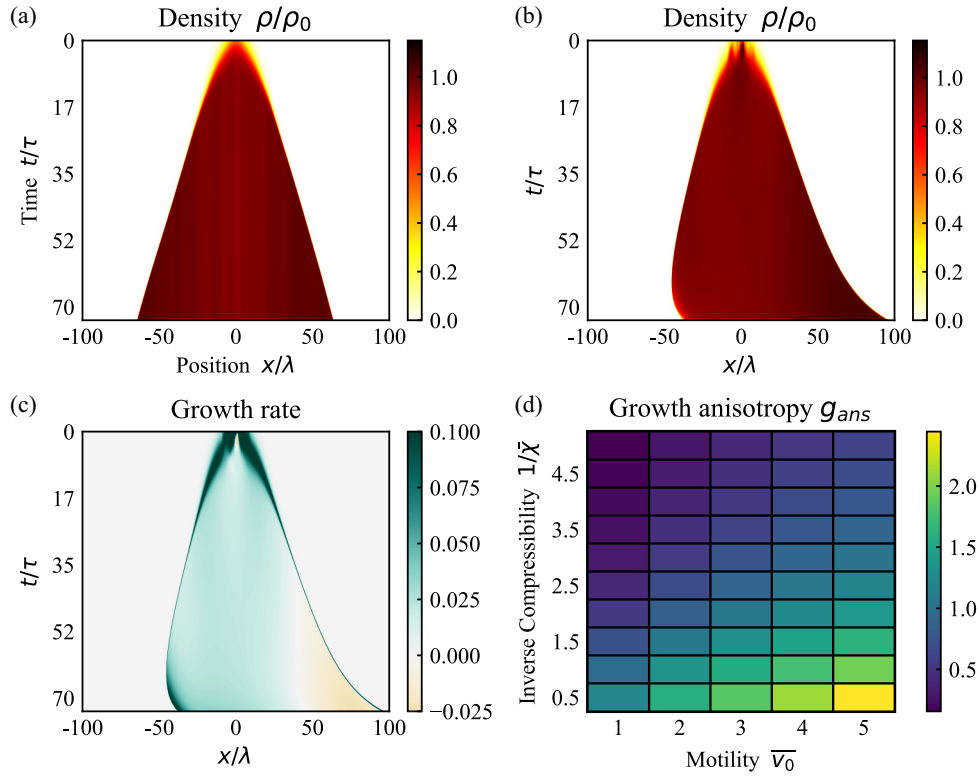


FIG. 4. Anisotropic tissue growth in the continuum model. (a) Kymograph of density of an isotropically growing tissue with $a = 0$ and $\kappa_p = 0$. (b) Kymograph of density for an anisotropically growing tissue with $a = 0.3$ and $\kappa_p = 1000$. The density is higher in $+x$ direction compared to $-x$ direction. (c) Kymograph of growth rate for the tissue in panel (b). The growth rate is higher in the negative x direction where the density is lower. (d) Phase diagram of growth anisotropy at various values of inverse compressibility $\bar{\chi}^{-1}$ and motility $\bar{v}_0$. Increasing $\bar{\chi}$ and $\bar{v}_0$ promotes growth anisotropy. See Table SII in the Supplemental Material for a list of parameter values [47].

crawling. We assume the constitutive equation of Maxwell viscoelasticity,

$$(1 + \tau \partial_t) \sigma = \eta \partial_x v - \Pi(\rho), \quad (5)$$

where η is the tissue viscosity, Π is the density-dependent pressure, and τ is the tissue fluidization timescale arising from intrinsic processes such as cell intercalations. The effective fluidization timescale is affected by cell proliferation and is inhomogeneous across the tissue (see the Supplemental Material [47]). We use a first-order expansion of the pressure around the homeostatic density ρ_0 , yielding $\Pi(\rho) = \Pi_0 + \chi^{-1}(\rho - \rho_0)$, where Π_0 is the homeostatic pressure and χ is the compressibility (inverse bulk modulus). Equation (4.3) describes cell polarity dynamics, with the first term describing polarity alignment at a rate κ_p and the second term drives symmetry breaking in the homogeneous steady state when the density is above a threshold ρ_c , given $a, b > 0$ (see the Supplemental Material [47]).

We analyzed Eqs. (4.1)–(4.3) both analytically and numerically in a domain with no-flux boundary conditions (see the Supplemental Material [47]). In the limit $v_0 = 0$ and $\eta = 0$, the model reduces to the porous-Fisher model [52], which would exhibit isotropic growth. In the absence of polarity symmetry breaking and polarity alignment ($a = 0$, $\kappa_p = 0$), we get isotropic growth with elevated proliferation rate at the tissue boundary [Fig. 4(a); Fig. S11 in the Supplemental Material [47]]. By contrast, a polarized tissue with nonzero κ_p exhibits anisotropic proliferation [Figs. 4(b) and 4(c)],

with an overall motion along the direction of polarity. The nonzero polarity field leads to an asymmetry in the velocity field (Fig. S12 in the Supplemental Material [47]), which in turn induces an anisotropic distribution of density [Fig. 4(b)]. Effective growth rate, $\kappa \rho(\rho - \rho_0)$, exhibits an anisotropic distribution [Fig. 4(c)] that captures the spatially varying rate of density change.

In order to quantify the anisotropy in growth, we defined the growth anisotropy index as $g_{ans} = 1 - G_+/G_-$, where G_+ is the sum of the growth rates in the head of the tissue (i.e., the half of the tissue in the direction of the average polarity) and G_- as the sum of the growth rates in the rear. For an isotropically growing tissue, growth rates are the same in the two halves of the tissue and $g_{ans} = 0$ (Fig. S13 in the Supplemental Material [47]). For anisotropically growing tissue, the growth rate is lower in the head than in the rear, so g_{ans} is nonzero. Thus, it is analogous to the division anisotropy index d_{ans} defined in the vertex model. In the continuum model, since the density ρ can be greater than ρ_0 locally, the growth rate can be negative and g_{ans} can exceed 1. We find that $g_{ans} \approx 0$ throughout the simulation for isotropic growth, but increases over time for the anisotropic case after some initial fluctuations (Fig. S13 in the Supplemental Material [47]). We calculated g_{ans} at a fixed tissue size for different values of normalized compressibility $\bar{\chi} = \eta \chi / \rho_0 \tau$ and motility $\bar{v}_0 = v_0 / \lambda \sqrt{b/\tau}$, where $\lambda = \sqrt{\eta/\mu}$. From Fig. 4(d), we see that increasing $\bar{\chi}$ and $\bar{v}_0$ increases the growth anisotropy, mirroring vertex model results [Fig. 3(d)].

To understand these results, it is instructive to examine the model behavior at long timescales and length scales, $t \gg \tau$ and $x \gg \lambda$, when the model reduces to the following nonlinear drift-diffusion equation:

$$\partial_t \rho + v_0 \partial_x (\rho p) \approx \partial_x (D(\rho) \partial_x \rho) + \kappa \rho (1 - \rho/\rho_0) \quad (6)$$

with an effective diffusivity $D(\rho) = \rho/(\chi\mu)$. For $v_0 = 0$, there is no net drift along cell polarity, and the system exhibits isotropic growth. Increasing v_0 amplifies the effect of drift compared to diffusion, driving polarized growth. If compressibility χ is high, diffusion is negligible relative to drift. As a result, the system maintains density gradients along the direction of cell polarity, thus amplifying growth anisotropy. Taken together, this minimal model establishes the critical role of cell polarity and growth-mechanics feedback in governing anisotropic proliferation.

Discussion. We identify an emergent, self-organized mechanism for anisotropic tissue growth arising from feedback between cell motility, mechanical pressure, and proliferation. Unlike previous models relying on predefined anisotropies or biochemical guidance [9,30–33], our model demonstrates how polarity-driven mechanical asymmetries can spontaneously break symmetry in cell divisions, leading to directional growth. These findings provide a mechanical framework for understanding anisotropic organ morphogenesis, particularly in contexts like early limb bud development [15,53,54] where migration and division patterns shape tissue architecture.

Acknowledgments. We thank Fernanda Perez-Verdugo for many useful discussions. We acknowledge support from the National Institute of General Medical Sciences, Grant No. NIH R35 GM143042).

Data availability. The data that support the findings of this article are not publicly available. The data are available from the authors upon reasonable request.

-
- [1] L. LeGoff and T. Lecuit, Mechanical forces and growth in animal tissues, *Cold Spring Harbor Perspect. Biol.* **8**, a019232 (2016).
 - [2] J. A. Zallen and E. Wieschaus, Patterned gene expression directs bipolar planar polarity in *drosophila*, *Dev. Cell* **6**, 343 (2004).
 - [3] L. A. Baena-López, A. Baonza, and A. García-Bellido, The orientation of cell divisions determines the shape of *drosophila* organs, *Curr. Biol.* **15**, 1640 (2005).
 - [4] L. Barrio and M. Milán, Regulation of anisotropic tissue growth by two orthogonal signaling centers, *Dev. Cell* **52**, 659 (2020).
 - [5] L. LeGoff, H. Rouault, and T. Lecuit, A global pattern of mechanical stress polarizes cell divisions and cell shape in the growing *drosophila* wing disc, *Development* **140**, 4051 (2013).
 - [6] E. Hannezo and C.-P. Heisenberg, Mechanochemical feedback loops in development and disease, *Cell* **178**, 12 (2019).
 - [7] H. Vignes, C. Vagena-Pantoula, and J. Vermot, Mechanical control of tissue shape: Cell-extrinsic and -intrinsic mechanisms join forces to regulate morphogenesis, *Semin. Cell Dev. Biol.* **130**, 45 (2022).
 - [8] H. J. Gustafson, N. Claussen, S. De Renzis, and S. J. Streichan, Patterned mechanical feedback establishes a global myosin gradient, *Nat. Commun.* **13**, 7050 (2022).
 - [9] S. Harmansa, A. Erlich, C. Eloy, G. Zurlo, and T. Lecuit, Growth anisotropy of the extracellular matrix shapes a developing organ, *Nat. Commun.* **14**, 1220 (2023).
 - [10] N. A. Dye, M. Popović, S. Spann, R. Etoiray, D. Kainmüller, S. Ghosh, E. W. Myers, F. Jülicher, and S. Eaton, Cell dynamics underlying oriented growth of the *drosophila* wing imaginal disc, *Development* **144**, 4406 (2017).
 - [11] T. Bittig, O. Wartlick, M. González-Gaitán, and F. Jülicher, Quantification of growth asymmetries in developing epithelia, *Eur. Phys. J. E* **30**, 93 (2009).
 - [12] J. Godivier, E. A. Lawrence, M. Wang, C. L. Hammond, and N. C. Nowlan, Growth orientations, rather than heterogeneous growth rates, dominate jaw joint morphogenesis in the larval zebrafish, *J. Anat.* **241**, 358 (2022).
 - [13] J. Godivier, E. A. Lawrence, M. Wang, C. L. Hammond, and N. C. Nowlan, Compressive stress gradients direct mechanoregulation of anisotropic growth in the zebrafish jaw joint, *PLoS Comput. Biol.* **20**, e1010940 (2024).
 - [14] R. Zeller, J. López-Ríos, and A. Zuniga, Vertebrate limb bud development: moving towards integrative analysis of organogenesis, *Nat. Rev. Genet.* **10**, 845 (2009).
 - [15] B. Boehm, H. Westerberg, G. Lesnicar-Pucko, S. Raja, M. Rautschka, J. Cotterell, J. Swoger, and J. Sharpe, The role of spatially controlled cell proliferation in limb bud morphogenesis, *PLoS Biol.* **8**, e1000420 (2010).
 - [16] E. Coen, A.-G. Rolland-Lagan, M. Matthews, J. A. Bangham, and P. Prusinkiewicz, The genetics of geometry, *Proc. Natl. Acad. Sci. USA* **101**, 4728 (2004).
 - [17] O. Wartlick, P. Mumcu, F. Jülicher, and M. Gonzalez-Gaitan, Understanding morphogenetic growth control—lessons from flies, *Nat. Rev. Mol. Cell Biol.* **12**, 594 (2011).
 - [18] C.-P. Heisenberg and Y. Bellaïche, Forces in tissue morphogenesis and patterning, *Cell* **153**, 948 (2013).
 - [19] K. D. Irvine and B. I. Shraiman, Mechanical control of growth: Ideas, facts and challenges, *Development* **144**, 4238 (2017).
 - [20] Y. Mao, A. L. Tournier, A. Hoppe, L. Kester, B. J. Thompson, and N. Tapon, Differential proliferation rates generate patterns of mechanical tension that orient tissue growth, *EMBO J.* **32**, 2790 (2013).
 - [21] M. Abercrombie, Contact inhibition and malignancy, *Nature (London)* **281**, 259 (1979).
 - [22] B. I. Shraiman, Mechanical feedback as a possible regulator of tissue growth, *Proc. Natl. Acad. Sci. USA* **102**, 3318 (2005).
 - [23] L. Hufnagel, A. A. Teleman, H. Rouault, S. M. Cohen, and B. I. Shraiman, On the mechanism of wing size determination in fly development, *Proc. Natl. Acad. Sci. USA* **104**, 3835 (2007).
 - [24] Y. Pan, I. Heemskerk, C. Ibar, B. I. Shraiman, and K. D. Irvine, Differential growth triggers mechanical feedback that elevates Hippo signaling, *Proc. Natl. Acad. Sci. USA* **113**, E6974 (2016).

- [25] M. Théry, V. Racine, A. Pépin, M. Piel, Y. Chen, J.-B. Sibarita, and M. Bornens, The extracellular matrix guides the orientation of the cell division axis, *Nat. Cell Biol.* **7**, 947 (2005).
- [26] P. Campinho, M. Behrndt, J. Ranft, T. Risler, N. Minc, and C.-P. Heisenberg, Tension-oriented cell divisions limit anisotropic tissue tension in epithelial spreading during zebrafish epiboly, *Nat. Cell Biol.* **15**, 1405 (2013).
- [27] A. Puliafito, L. Hufnagel, P. Neveu, S. Streichan, A. Sigal, D. K. Fygenson, and B. I. Shraiman, Collective and single cell behavior in epithelial contact inhibition, *Proc. Natl. Acad. Sci. USA* **109**, 739 (2012).
- [28] S. J. Streichan, C. R. Hoerner, T. Schneidt, D. Holzer, and L. Hufnagel, Spatial constraints control cell proliferation in tissues, *Proc. Natl. Acad. Sci. USA* **111**, 5586 (2014).
- [29] J. Ranft, M. Basan, J. Elgeti, J.-F. Joanny, J. Prost, and F. Jülicher, Fluidization of tissues by cell division and apoptosis, *Proc. Natl. Acad. Sci. USA* **107**, 20863 (2010).
- [30] T. Bittig, O. Wartlick, A. Kicheva, M. González-Gaitán, and F. Jülicher, Dynamics of anisotropic tissue growth, *New J. Phys.* **10**, 063001 (2008).
- [31] F. Bou Daher, Y. Chen, B. Bozorg, J. Clough, H. Jönsson, and S. A. Braybrook, Anisotropic growth is achieved through the additive mechanical effect of material anisotropy and elastic asymmetry, *eLife* **7**, e38161 (2018).
- [32] A. Erzberger, A. Jacobo, A. Dasgupta, and A. Hudspeth, Mechanochemical symmetry breaking during morphogenesis of lateral-line sensory organs, *Nat. Phys.* **16**, 949 (2020).
- [33] H. M. McNamara, S. C. Solley, B. Adamson, M. M. Chan, and J. E. Toettcher, Recording morphogen signals reveals mechanisms underlying gastruloid symmetry breaking, *Nat. Cell Biol.* **26**, 1832 (2024).
- [34] T. Nagai and H. Honda, A dynamic cell model for the formation of epithelial tissues, *Philos. Mag. B* **81**, 699 (2001).
- [35] R. Farhadifar, J.-C. Röper, B. Aigouy, S. Eaton, and F. Jülicher, The influence of cell mechanics, cell-cell interactions, and proliferation on epithelial packing, *Curr. Biol.* **17**, 2095 (2007).
- [36] D. B. Staple, R. Farhadifar, J. C. Röper, B. Aigouy, S. Eaton, and F. Jülicher, Mechanics and remodelling of cell packings in epithelia, *Eur. Phys. J. E* **33**, 117 (2010).
- [37] B. Li and S. X. Sun, Coherent motions in confluent cell monolayer sheets, *Biophys. J.* **107**, 1532 (2014).
- [38] A. G. Fletcher, M. Osterfield, R. E. Baker, and S. Y. Shvartsman, Vertex models of epithelial morphogenesis, *Biophys. J.* **106**, 2291 (2014).
- [39] S. Kim and S. Hilgenfeldt, Cell shapes and patterns as quantitative indicators of tissue stress in the plant epidermis, *Soft Matter* **11**, 7270 (2015).
- [40] D. Bi, J. H. Lopez, J. M. Schwarz, and M. L. Manning, A density-independent rigidity transition in biological tissues, *Nat. Phys.* **11**, 1074 (2015).
- [41] D. Gradeci, A. Bove, G. Vallardi, A. R. Lowe, S. Banerjee, and G. Charras, Cell-scale biophysical determinants of cell competition in epithelia, *eLife* **10**, e61011 (2021).
- [42] L. C. Carpenter, F. Pérez-Verdugo, and S. Banerjee, Mechanical control of cell proliferation patterns in growing epithelial monolayers, *Biophys. J.* **123**, 909 (2024).
- [43] L. C. Carpenter and S. Banerjee, Physical traits of supercompetitors in cell competition, *J. R. Soc. Interface* **22**, 20250638 (2025).
- [44] S. Xie and J. M. Skotheim, A G1 sizer coordinates growth and division in the mouse epidermis, *Curr. Biol.* **30**, 916 (2020).
- [45] F. Proulx-Giraldeau, J. M. Skotheim, and P. François, Evolution of cell size control is canalized towards adders or sizers by cell cycle structure and selective pressures, *eLife* **11**, e79919 (2022).
- [46] J. Devany, M. J. Falk, L. J. Holt, A. Murugan, and M. L. Gardel, Epithelial tissue confinement inhibits cell growth and leads to volume-reducing divisions, *Dev. Cell* **58**, 1462 (2023).
- [47] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/jgll-wsvt> for the details of simulation methods, parameter estimation, analysis of the continuum theory, and Figs. S1–S14.
- [48] B. Stramer and R. Mayor, Mechanisms and *in vivo* functions of contact inhibition of locomotion, *Nat. Rev. Mol. Cell Biol.* **18**, 43 (2017).
- [49] B. A. Camley, Y. Zhang, Y. Zhao, B. Li, E. Ben-Jacob, H. Levine, and W.-J. Rappel, Polarity mechanisms such as contact inhibition of locomotion regulate persistent rotational motion of mammalian cells on micropatterns, *Proc. Natl. Acad. Sci. USA* **111**, 14770 (2014).
- [50] E. Vercruysse, D. B. Brückner, M. Gómez-González, A. Remson, M. Luciano, Y. Kalukula, L. Rossetti, X. Trepas, E. Hannezo, and S. Gabriele, Geometry-driven migration efficiency of autonomous epithelial cell clusters, *Nat. Phys.* **20**, 1492 (2024).
- [51] F. Giavazzi, M. Paoluzzi, M. Macchi, D. Bi, G. Scita, M. L. Manning, R. Cerbino, and M. C. Marchetti, Flocking transitions in confluent tissues, *Soft Matter* **14**, 3471 (2018).
- [52] *Mathematical Biology: I. An Introduction*, Interdisciplinary Applied Mathematics, edited by J. D. Murray (Springer, New York, 2002), Vol. 17.
- [53] L. A. Wyngaarden, K. M. Vogeli, B. G. Ciruna, M. Wells, A.-K. Hadjantonakis, and S. Hopyan, Oriented cell motility and division underlie early limb bud morphogenesis, *Development* **137**, 2551 (2010).
- [54] A. Kicheva and J. Briscoe, Limbs made to measure, *PLoS Biol.* **8**, e1000421 (2010).