

Morphogen Patterning in Dynamic Tissues

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Embryogenesis integrates morphogenesis—coordinated cell movements—with morphogen patterning and cell differentiation. While largely studied independently, morphogenesis and patterning often unfold simultaneously in early embryos. Yet how cell movements affect morphogen transport and cells' exposure over time remains unclear, as most pattern formation models assume static tissues. Here we develop a theoretical framework for morphogen patterning in dynamic tissues, recasting advection-reaction-diffusion equations in the cells' moving reference frames. This framework (i) elucidates how morphogenesis mediates morphogen transport and compartmentalization: cell-cell diffusive transport is enhanced at multicellular flow attractors, while repellers act as barriers, affecting cell fate induction and bifurcations. (ii) It formalizes cell-cell signaling ranges in dynamic tissues, deconfounding morphogenetic movements to identify which cells could communicate via morphogens. (iii) It provides two new nondimensional numbers to assess when and where morphogenesis affects morphogen transport. We demonstrate this framework by analyzing classical patterning models with common morphogenetic motifs as well as experimental tissue flows. Our work rationalizes dynamic tissue patterning in development, constraining candidate patterning mechanisms and parameters using accessible cell motion data.

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I. INTRODUCTION

Embryogenesis requires the development of the embryo's form (morphogenesis) and the diversification of its cells' fates (differentiation) [1]. In morphogenesis, tissues grow, stretch, and flow, commonly guided by molecular patterns [2,3] through which cells communicate and coordinate fate decisions. While morphogenesis and patterning are mostly studied separately, they often unfold simultaneously, especially in early embryogenesis, when morphogenetic movements are substantial and key patterns are established [1]. Cells commonly produce or respond to morphogens, signaling molecules that can collectively elicit distinct cellular responses and spread between cells via diffusion or direct cell-cell transport. However, because morphogenetic movements rearrange tissue patches as signals travel through them, morphogenesis plays a confounding as well as generative role in patterning and these roles are hard to disentangle [4–9]. Recent progress has started to elucidate how the mechanics of morphogenesis can influence cell fates via mechanotransduction [10–14]. Yet the effects of motion itself—the kinematics of morphogenesis—on cell fate coordination remain unclear [5]. To this end, here we do not model the mechanical origins of cell movements—topics addressed by tissue mechanics [15–18]. Instead, we ask the following: given experimentally

measured tissue flows, how does morphogenesis shape morphogen transport through dynamic tissues?

The primary paradigms for morphogen patterning were developed for static tissues. Reaction-diffusion (RD) models [2,19] rely on nonlinear interactions and differential diffusion to generate morphogen patterns that break symmetries or amplify weak asymmetries [20–24]. Positional information (PI), instead, refers to morphogen gradients cues cells use to infer their relative positions and generate discrete fate patterns [25]. RD and PI provide complementary perspectives on morphogen pattern formation and interpretation [26], typically assuming static tissues. Pattern formation under advective transport remains comparatively unexplored, with recent studies focusing on protein patterns inside cells [27] and *in vitro* systems [28]. Tissue growth also affects RD dynamics [23,24,29,30] and PI [31–34]. However, embryogenesis involves complex tissue flows, and despite mounting experimental evidence [5,6,35–37], general frameworks to rationalize dynamic tissue patterning are missing.

Due to imaging advances, cell motion data (tissue velocities or cell trajectories) and patterning data (snapshots of gene expression, transcription factors, or signaling activity across tissues) are becoming increasingly available. An outstanding challenge is integrating noisy data on movement and molecules [37]. Morphogens can coordinate spatiotemporal patterns of gene expression—for example, Shh in the neural tube [38,39], FGF in the presomitic mesoderm [40], and Nodal and Lefty in left-right patterning [21]. In many systems, direct live imaging of morphogen ligands remains difficult, as does measuring their kinetic parameters, such as diffusivity, production, and removal rates [41], needed to validate patterning mechanisms. Even with adequate data, a core conceptual question of dynamic tissue patterning remains: How does morphogenesis affect the signals cells receive? Morphogens

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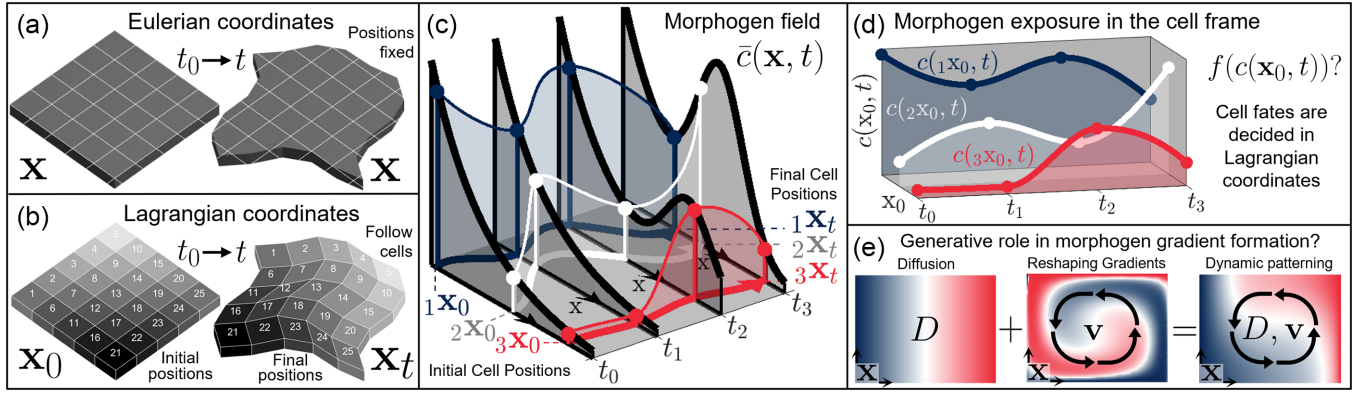


FIG. 1. Dynamic tissue patterning. (a) Eulerian coordinates represent fixed positions in space through which cells and morphogens move. (b) Lagrangian (cell) coordinates come with cells and are associated with labeled tissue patches over time. (c) Black curves depict snapshots of morphogen concentrations $\bar{c}(\mathbf{x}, t)$ at t_0, t_1, t_2, t_3 in the Eulerian coordinate $\mathbf{x}$. Red, white, and blue curves track morphogen exposure $c(\mathbf{x}_0, t)$ over time for three cells labeled by their Lagrangian coordinates $1\mathbf{x}_0, 2\mathbf{x}_0, 3\mathbf{x}_0$ as they move through $\bar{c}(\mathbf{x}, t)$ (Movie 1 [46]). (d) Gene expression dynamics and cell fate decisions depend on complicated functions $f(c(\mathbf{x}_0, t))$ of morphogen exposure over time. (e) Even in simple models where fates follow directly from morphogen patterns (e.g., the fixed gradient solution to the French Flag problem [25]), morphogenesis can affect fate patterns (in $\mathbf{x}$) by reshaping morphogen gradients. Left: Diffusion from a source on the left boundary of a two-dimensional epithelium forms a morphogen gradient colored with high (blue), medium (white), and low (red) morphogen concentrations. Middle: Tissue motion (morphogenesis, black arrows) rearranges the established pattern, without additional diffusion. Right: The combined effects of simultaneous diffusion and tissue motion generates a different pattern, distinct from mere rearrangement or static gradient formation.

activate intracellular processes based on cells' morphogen exposure over time [42–44] and the combination of motion and memory calls for theoretical frameworks to understand morphogen exposure along cell trajectories.

Theoretically, this requires a nonlinear reference frame change from standard fixed Eulerian coordinates ($\mathbf{x}$) [Fig. 1(a)] to Lagrangian coordinates—comoving with cells ($\mathbf{x}_0$ or $\mathbf{x}_t$) [Fig. 1(b)]. Throughout, we bold vectors and matrices but not scalars. Unlike Eulerian coordinates, Lagrangian coordinates are always associated with the same cells, even as they move. Figure 1(c) depicts a morphogen concentration $\bar{c}$ —the overbar indicates functions of Eulerian coordinates $\mathbf{x}$ —at different times (black curves). As cells (red, white, and blue) move through $\bar{c}(\mathbf{x}, t)$, they experience a dynamic morphogen exposure $c(\mathbf{x}_0, t)$. Confounding effects of morphogenesis on morphogen patterning arise because $c(\mathbf{x}_0, t) \neq \bar{c}(\mathbf{x}, t)$, and fate decisions happen in the cell's reference frame—i.e., in Lagrangian coordinates—taking $c(\mathbf{x}_0, t)$ as input [Fig. 1(d)]. In addition to affecting the positions sampled over time, morphogenesis may affect the morphogen concentrations at those positions by reshaping morphogen gradients. It is not obvious how the interplay of diffusion and deformation (the relative motion of different tissue patches) affects $c(\mathbf{x}_0, t)$ [Fig. 1(e)]. Here we develop a theoretical framework for analyzing the dynamics of $c(\mathbf{x}_0, t)$, revealing intimate connections on how morphogenesis mediates morphogen transport and exposure. This framework constrains morphogen patterning mechanisms—even when parameter measurements remain inaccessible—using accessible cell motion data.

II. RESULTS

In static morphogen patterning, $\bar{c}(\mathbf{x}, t)$ is described by the diffusion equation $\partial_t \bar{c} = \nabla \cdot (\bar{D} \nabla \bar{c})$ with isotropic diffusivity $\bar{D}(\mathbf{x}, t)$, typically complemented by source, degradation, and

reaction terms. When advective motion is present, $\bar{c}$ obeys the advection-diffusion equation

$$\partial_t \bar{c}(\mathbf{x}, t) = \overbrace{\nabla \cdot (\bar{D} \nabla \bar{c})}^{\text{Diffusion}} - \overbrace{\bar{\mathbf{v}} \cdot \nabla \bar{c}}^{\text{Advection}} + \dots, \quad (1)$$

where $\bar{\mathbf{v}}(\mathbf{x}, t)$ is an incompressible ($\nabla \cdot \bar{\mathbf{v}} = 0$, a simplifying assumption we relax later) velocity representing morphogenetic movements. Whenever possible, we omit the explicit $(\mathbf{x}, t)$ dependence. Throughout, we assume that morphogens comove with cells due, for example, to extracellular matrix (ECM) comovement, common in early amniotes [45]. Later, we incorporate the effects of cell divisions and deaths and relative tissue-ECM velocities [Supplemental Material (SM) Sec. 1] [46].

A. Morphogen exposure in the cell frame

We rewrite Eq. (1), changing coordinates from Eulerian $\mathbf{x}$ to Lagrangian $\mathbf{x}_0$, using the coordinate change $\mathbf{x}_t = \mathbf{F}_t'(\mathbf{x}_0)$ corresponding to cell trajectories [Figs. 1(a) and 1(b)]. Because Lagrangian coordinates map between cell initial positions $\mathbf{x}_0$ and later positions $\mathbf{x}_t$, one can visualize patterns on the initial (undeformed) or final (deformed) configurations. This resonates with “fate mapping” techniques in classical embryology in which initial embryonic regions are labeled according to where they go. Equation (1) for $\bar{c}(\mathbf{x}, t)$ transforms (SM Sec. 1 [46]) [47–49] into Eq. (2) for $c(\mathbf{x}_0, t)$, the time- t morphogen exposure of a moving tissue patch that started at $(\mathbf{x}_0, t_0)$:

$$\partial_t c(\mathbf{x}_0, t) = \overbrace{\nabla_{\mathbf{x}_0} \cdot (\mathbf{D}'_{t_0}(\mathbf{x}_0) \nabla_{\mathbf{x}_0} c(\mathbf{x}_0, t))}^{\text{Lagrangian diffusion}} + \dots, \quad (2)$$

where $\nabla_{\mathbf{x}_0}$ denotes derivatives with respect to $\mathbf{x}_0$. In Lagrangian coordinates, the Eulerian advection and diffusion terms reduce to a single term with an equivalent Lagrangian

diffusion tensor,

$$\mathbf{D}_{t_0}^t(\mathbf{x}_0) = \underbrace{D(\mathbf{x}_0, t)}_{\text{Diffusivity}} \underbrace{[\mathbf{C}_{t_0}^t(\mathbf{x}_0)]^{-1}}_{\text{Morphogenesis}}, \quad (3)$$

where $\mathbf{C}_{t_0}^t(\mathbf{x}_0) = [\nabla_{\mathbf{x}_0} \mathbf{F}_{t_0}^t(\mathbf{x}_0)]^\top [\nabla_{\mathbf{x}_0} \mathbf{F}_{t_0}^t(\mathbf{x}_0)]$ denotes the Cauchy-Green strain tensor, a symmetric positive definite (i.e., with real orthogonal eigenvectors and real positive eigenvalues) matrix and $\nabla_{\mathbf{x}_0} \mathbf{F}_{t_0}^t(\mathbf{x}_0)$ is the deformation gradient tensor. Therefore, in the cell frame, cell-cell morphogen transport blends the Eulerian diffusivity sampled along trajectories $[D(\mathbf{x}_0, t) = \bar{D}(\mathbf{F}_{t_0}^t(\mathbf{x}_0), t)]$ with the effect of their deforming environment, encoded in $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$. There is no advection term in the cell frame, absorbed in the material time derivative $d_t c(\mathbf{x}_0, t) = \partial_t c(\mathbf{x}_0, t)$. However, the spatial coordinate change $\mathbf{x} \rightarrow \mathbf{x}_0$ has a nontrivial effect on the non-cell-autonomous term $\nabla \cdot (\dots)$, representing spreading across cells [Eq. (1), SM Sec. 1 [46]]. Strikingly, Eq. (3) reveals that cell-cell transport in the cell frame inherits (i) the space dependence, (ii) anisotropy (direction dependence), and (iii) strength of deformation of its comoving environment. Without deformation, $\mathbf{C}_{t_0}^t(\mathbf{x}_0) = \mathbf{I}$, recovering isotropic Eulerian diffusion $[\mathbf{D}_{t_0}^t(\mathbf{x}_0) = D(\mathbf{x}_0, t)\mathbf{I}]$ or $\mathbf{D}_{t_0}^t(\mathbf{x}_0) = D\mathbf{I}$ if D is uniform in space. Note that in Eq. (1) and Eq. (2) the effective molecular diffusivity D may be locally regulated along trajectories by local factors such as cell number density [50] or ECM component concentrations [10]. Hereafter, we consider a fixed D without loss of generality and note that our framework applies to heterogeneous D .

B. Connection to the dynamic morphoskeleton

The relationship between $\mathbf{D}_{t_0}^t(\mathbf{x}_0)$ and $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$ provides an exact, profound connection between dynamic tissue pat-

$$\mathbf{F}_{t_0}^t(\mathbf{x}_0) = \begin{bmatrix} x_0 e^{-\alpha t} \\ y_0 e^{\alpha t} \end{bmatrix}, \quad \mathbf{C}_{t_0}^t(\mathbf{x}_0) = \begin{bmatrix} {}_1\lambda_{t_0}^t & 0 \\ 0 & \lambda_{t_0}^t \end{bmatrix}, \quad \mathbf{D}_{t_0}^t(\mathbf{x}_0) = D \begin{bmatrix} \lambda_{t_0}^t & 0 \\ 0 & {}_1\lambda_{t_0}^t \end{bmatrix}, \quad \lambda_{t_0}^t(\mathbf{x}_0) = e^{2\alpha t} \geq 1, \quad (4)$$

where ${}_1\lambda_{t_0}^t(\mathbf{x}_0) = 1/\lambda_{t_0}^t(\mathbf{x}_0) \leq 1$ due to incompressibility. It is instructive to compare the eigenvalues and (orthogonal) eigenvectors of $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$ and $\mathbf{D}_{t_0}^t(\mathbf{x}_0)$. The largest (smallest) eigenvector $\xi_{t_0}^t(\mathbf{x}_0)$ (${}_1\xi_{t_0}^t(\mathbf{x}_0)$) of $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$ coincides with the smallest (largest) eigenvector of $\mathbf{D}_{t_0}^t(\mathbf{x}_0)$, implying that the local contracting direction experiences enhanced cell-cell transport $D\lambda_{t_0}^t(\mathbf{x}_0) > D$, while the expanding direction experiences reduced cell-cell transport $D/{}_1\lambda_{t_0}^t(\mathbf{x}_0) < D$ [Fig. 2(c)]. These effects were recently experimentally realized, imprinting directionality on chemical waves [61]. The same conclusions hold for general nonlinear and time-dependent flows, where regions of high $\lambda_{t_0}^t(\mathbf{x}_0)$ define the DM [Fig. 2(a)], and the connection between $\mathbf{D}_{t_0}^t$ and $\mathbf{C}_{t_0}^t$ [Eq. (2)] reveals that repellers (attractors) identify barriers (enhancers) to morphogen transport from cell to cell [Fig. 2(d)]. These connections have been recognized in fluid mixing research [47–49] but not in the biological context.

It is key to recognize that (i) $\mathbf{D}_{t_0}^t(\mathbf{x}_0)$ parametrizes only non-cell-autonomous mechanisms, distinct from the advective transport of c : For $D = 0$, no morphogens are transported

tern and the dynamic morphoskeleton (DM) [51,52]—a frame-invariant, compressed representation of complex tissue flow defined from $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$ —that has been applied across model systems in developmental biology and active matter [16,51,53–59]. The DM reduces noisy cell trajectory data to a robust set of attracting and repelling coherent structures [60], hereafter just *attractors* and *repellers*. The largest eigenvalue $\lambda_{t_0}^t(\mathbf{x}_0)$ of $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$ quantifies the maximum separation of cells starting near $\mathbf{x}_0$ along the direction of its corresponding eigenvector $\xi_{t_0}^t(\mathbf{x}_0)$ by time t . High values of $\lambda_{t_0}^t(\mathbf{x}_0)$ locate repellers, i.e., initial ($\mathbf{x}_0$) tissue regions where nearby cells will maximally separate by time t [Fig. 2(a) and 2(b)]. Conversely, performing the analysis in backward time, high values of $\lambda_{t_0}^t(\mathbf{x}_t)$ mark attractors, i.e., final ($\mathbf{x}_t$) locations towards which initially separated cells will converge by time t [Figs. 2(a) and 2(b)] [51]. The DM can be extracted for tissue flows in one, two, or three dimensions. In one-dimensional (1D) flows, attractors and repellers are dynamic points [Fig. 2(b)]. In 2D flows, our focus here, attractors and repellers are dynamic 1D curves [Figs. 2(a) and 4]. Arising from the cumulative deformation along trajectories, the DM is undetectable from inspection of $\bar{\mathbf{v}}(\mathbf{x}, t)$, even in 1D [Fig. 2(b)]. See SM Fig. S3 [46] for a connection between Eulerian analysis and the DM using the experimental flow data from Fig. 4.

To interpret the connection between deformation ($\mathbf{C}_{t_0}^t$) and $\mathbf{D}_{t_0}^t$ [Eq. (3)], consider a linear, time-independent convergent extension velocity field $\bar{\mathbf{v}} = \alpha[-x, y]$, $\alpha > 0$. Near the origin, the x axis (y axis) represents a repeller (attractor) as trajectories on opposite sides will separate (converge) [Fig. 2(c)]. For this flow, $\mathbf{F}_{t_0}^t(\mathbf{x}_0)$, $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$, its eigenvalues $\lambda_{t_0}^t(\mathbf{x}_0)$ (largest) and ${}_1\lambda_{t_0}^t(\mathbf{x}_0)$ (smallest), and $\mathbf{D}_{t_0}^t(\mathbf{x}_0)$ are as follows:

between cells. (ii) The modulation of morphogen transport in the cell frame is due to tissue deformation, leaving the molecular diffusivity D unaltered. To visualize this effect, we solve Eq. (2) using the linear convergent-extension flow [Eq. (4)], an initial centered Gaussian $c(\mathbf{x}_0, t_0)$ [Fig. 2(e) (top)]. Without deformation, $\mathbf{D}_{t_0}^t = D\mathbf{I}$ and $c(\mathbf{x}_0, t)$ spreads isotropically [Fig. 2(e) (bottom)], reaching (i.e., $c > c_{\text{threshold}}$) four neighboring tissue patches (green) at time t . With deformation ($\alpha > 0$), $\mathbf{D}_{t_0}^t$ becomes anisotropic [Eq. (4)], enhancing (diminishing) morphogen transport across the attractor (repeller) [Fig. 2(f)]. In the cell frame at the initial time ($\mathbf{x}_0$), c reaches more cells along the direction of convergence than of extension [Fig. 2(f) (left)]. This non-cell-autonomous effect arises because tissue deformation sharpens and flattens morphogen gradients, modulating the diffusive fluxes between cells.

Visualizing morphogen exposure and transport in the cell frame ($\mathbf{x}_0$) [Fig. 2(f) (left)] deconfounds the effects of tissue flows, which become overwhelming for general flows (see Fig. 4 and Movie 4 [46]). Crucially, the effects

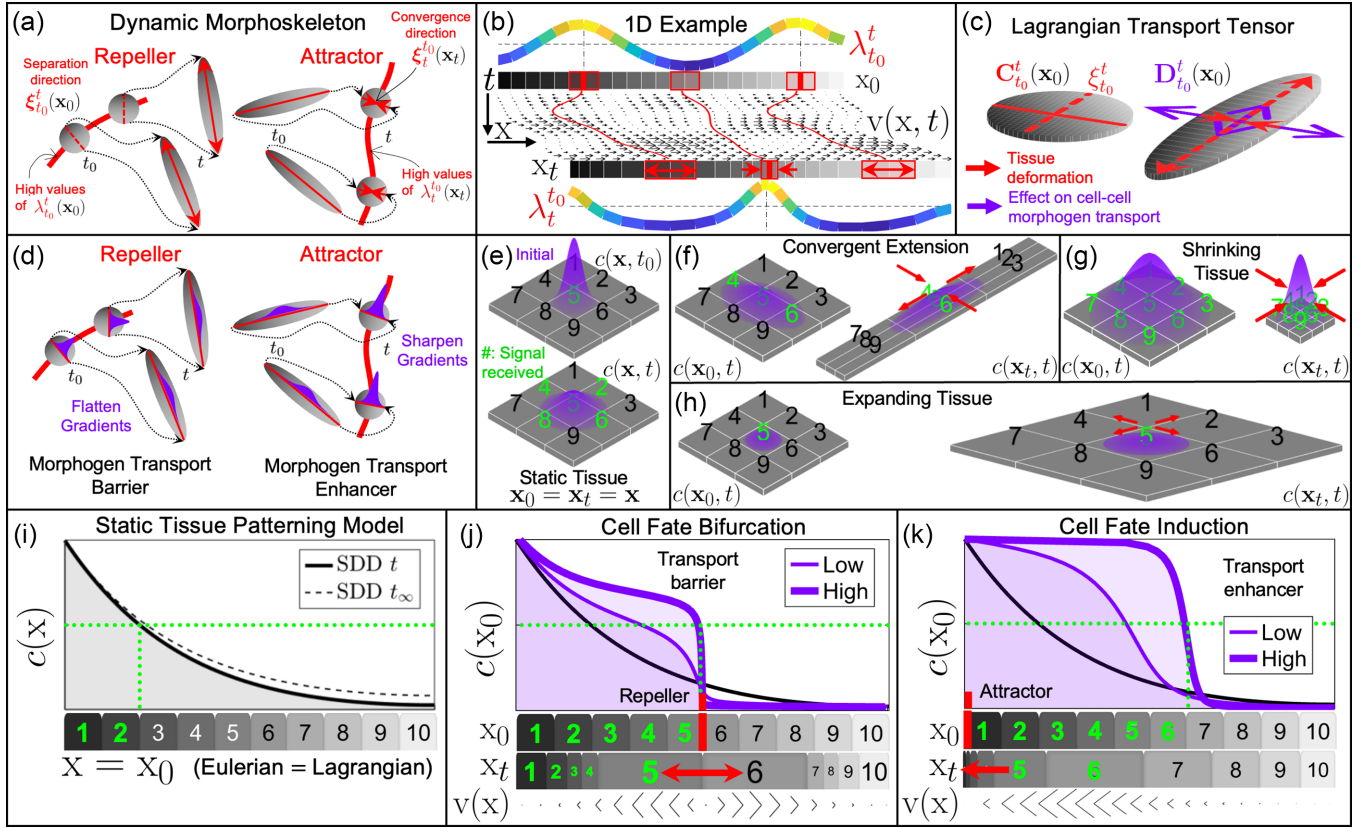


FIG. 2. The dynamic morphoskeleton mediates intercellular morphogen transport in the cell frame. (a) DM consists of attractors and repellers. High values (ridges) of $\lambda_t^0(\mathbf{x}_0)$ [$\lambda_t^0(\mathbf{x}_t)$] mark repellers (attractors) across which cells will maximally separate (converge) along the direction $\xi_t^0(\mathbf{x}_0)$ [$\xi_t^0(\mathbf{x}_t)$] during the time interval $[t_0, t]$. Repellers (attractors) are visualized at the initial $\mathbf{x}_0$ (final $\mathbf{x}_t$) tissue configurations. λ , ξ denote the largest eigenvalue and eigenvector of the Cauchy-Green strain tensor $\mathbf{C}$. (b) DM for simulated, 1D time-dependent velocity data consisting of two repellers and one attractor (red). (c) Visualization of $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$ and $\mathbf{D}_{t_0}^t(\mathbf{x}_0)$ [Eq. (3)] for the linear convergent extension flow [Eq. (4)]. In the Lagrangian frame, diffusive transport is enhanced (diminished) in the contracting (extending) direction. (d) Diffusive transport is maximally reduced (enhanced) across repellers (attractors). [(e)–(h)] Visualization of diffusive morphogen transport in the cell frame for static and uniformly deforming tissues. (e) An initial Gaussian of morphogen concentration $c(\mathbf{x}, t_0)$ with max concentration $c_{\max}$ and variance 0.01 diffuses ($D = 0.01$, no flux boundary conditions) above a static 2D epithelium (length 1), simulated from $t_0 = 0$ to $t = 1$ (all arbitrary units). Tissue patch labels turn green if average $c(\mathbf{x}_0, t) > c_{\max}/50$. (f) Simultaneous diffusion and convergent extension ($\mathbf{v} = [-x, y]$) with the same initial condition and parameters as (e). Final morphogen concentrations depicted in Lagrangian coordinates at initial positions [$c(\mathbf{x}_0, t)$, left] and final positions [$c(\mathbf{x}_t, t)$, right]. Tissue deformation reshapes morphogen gradients, mediating cell-cell diffusive fluxes in the cell frame. [(g) and (h)] Same as (f) for a uniformly shrinking ($\mathbf{v} = -[x, y]$) and expanding ($\mathbf{v} = [x, y]$) tissues. Movie 2 [46] shows the time evolution of panels (e)–(h). (i) Synthesis, diffusion, and degradation model $d_t \bar{c} = D \Delta \bar{c} - k \bar{c}$. Starting at t_0 , morphogens are secreted at the left boundary of a 1D domain with constant morphogen flux $Q = -D \frac{\partial \bar{c}}{\partial x}|_{x=0}$, and no flux at the right boundary. Within the domain, morphogens diffuse and degrade uniformly (rate k). The solid black curve shows concentrations at $t = k^{-1}$ with a fixed source at the left boundary and target tissue patches (1–10), colored green if concentrations exceed a morphogen threshold (green dotted line). The dashed curve is the steady-state solution $\bar{c}(x) = (Q/\sqrt{Dk})e^{x/\sqrt{D/k}}$. [(j) and (k)] Same as (i), with the addition of steady, nonuniform flows [$\mathbf{v}(x)$] with low ($\Omega_1 = 2$) or high ($\Omega_1 = 5$) deformation rates generating a strong repeller (j) and attractor (k), marked in red. Final deformed configurations $\mathbf{x}_t$ are shown below for high deformation rates. For the time evolution, see Movie 3 [46]. (j) The repeller limits diffusive morphogen transport across it. (k) Diffusive morphogen fluxes are enhanced away from the attractor. Parameters: [(i)–(k)] uniform $D = 0.001$, uniform $k = 0.01$, $t = 100$, $L = 1$. Fixed $c(0)$ on the left boundary (arbitrary units) and no flux on the right boundary. See SM Fig. S4(a) [46] for lower deformation rates and velocity fields used in (j) and (k).

of morphogenesis on cell-cell transport are not specific to this simple convergent-extension flow [Eq. (4)]. In general, time-dependent nonlinear flows with arbitrary morphogen distributions and additional cell-autonomous terms for sources, sinks, and reactions, these same insights about barriers and enhancers to diffusive cell-cell morphogen transport remain encoded in $\mathbf{C}_{t_0}^t(\mathbf{x}_0)$ [Eq. (3)], which quantifies morphogenesis and can be computed from experimental data [51,54,57].

C. Isotropic vs anisotropic deformation

In incompressible flows, deformation is purely anisotropic [Fig. 2(c)]. However, for compressible ($\nabla \cdot \bar{\mathbf{v}} \neq 0$) flows (e.g., due to cell division, death, and expansion), deformation has anisotropic and isotropic components encoded in $\mathbf{C}_{t_0}^t$, both affecting $\mathbf{D}_{t_0}^t$. We omit the dependence on $\mathbf{x}_0$ whenever possible. In general, $\mathbf{C}_{t_0}^t$ has two eigenvalues, $\lambda_t^0 \geq \lambda_t^1 > 0$. To isolate

isotropic and anisotropic effects, we use spectral decomposition and diagonalize $\mathbf{C}_{t_0}^t$ in its eigenbasis (SM Sec. 2) [46]

$$\mathbf{C}_{t_0}^t = \begin{bmatrix} \lambda_{t_0}^t & 0 \\ 0 & 1/\lambda_{t_0}^t \end{bmatrix} = J_{t_0}^t \begin{bmatrix} R_{t_0}^t & 0 \\ 0 & 1/R_{t_0}^t \end{bmatrix}, \quad (5)$$

where $J_{t_0}^t = \sqrt{\det \mathbf{C}_{t_0}^t} = \sqrt{\lambda_{t_0}^t \lambda_{t_0}^t}$ and $R_{t_0}^t = \sqrt{\lambda_{t_0}^t / \lambda_{t_0}^t}$. To first approximation, a small undeformed circular tissue patch is deformed by tissue flows into an ellipsoid [Fig. 2(c) and SM Fig. S2 [46]]. $J_{t_0}^t(\mathbf{x}_0)$ represents the ratio of final (t) to initial (t_0) area of the tissue patch started at $(\mathbf{x}_0, t_0)$, while $R_{t_0}^t(\mathbf{x}_0)$ denotes the ratio of ellipse major (along $\xi_{t_0}^t$) and minor axes (perpendicular to $\xi_{t_0}^t$), quantifying anisotropic deformation (SM Sec. 2). In incompressible flows [Eq. (4), Fig. 2(f)], $J_{t_0}^t = 1$. Conversely, in purely isotropic deformation $R_{t_0}^t(\mathbf{x}_0) = 1$: i.e., $\mathbf{C}_{t_0}^t$ does not have distinct eigenvalues and eigenvectors. General tissue flows produce both except at distinct locations where deformation is isotropic: $\mathbf{C}_{t_0}^t(\mathbf{x}_0) = J_{t_0}^t(\mathbf{x}_0)\mathbf{I}$ (SM Fig. S2) [46].

D. Patterning in compressible tissue flows

For compressible flows, Eq. (1) gains an additional term $-\bar{c}\nabla \cdot \bar{\mathbf{v}}$. In Lagrangian coordinates, Eq. (2) then becomes

$$\partial_t c(\mathbf{x}_0, t) = \frac{\nabla_{\mathbf{x}_0} \cdot (J_{t_0}^t \mathbf{D}_{t_0}^t \nabla_{\mathbf{x}_0} c)}{J_{t_0}^t} - c \nabla \cdot \mathbf{v}(\mathbf{x}_0, t) + \dots, \quad (6)$$

where $\nabla \cdot \mathbf{v}(\mathbf{x}_0, t) = \nabla \cdot \bar{\mathbf{v}}(\mathbf{F}_{t_0}^t(\mathbf{x}_0), t)$ indicates the velocity divergence sampled across trajectories. Equation (6) shows that also in compressible flows, the Lagrangian diffusion tensor inherits the anisotropy of its deforming environment, and $J_{t_0}^t$ provides an additional isotropic modulation of cell-cell transport magnitudes (SM Sec. 1) [46]. To gain intuition, consider the compressible linear convergent flow $\mathbf{v} = -\alpha[x, y]$, $\alpha > 0$, for which $\mathbf{C}_0^t = e^{-2\alpha t}\mathbf{I}$ and Eq. (6) gives $\partial_t c(\mathbf{x}_0, t) = \nabla_{\mathbf{x}_0} \cdot (De^{2\alpha t} \nabla_{\mathbf{x}_0} c) + 2\alpha c(\mathbf{x}_0, t)$. Isotropic shrinkage enhances diffusive fluxes, spreading signals to more cells [Fig. 2(g)]. Conversely, isotropic expansion ($\alpha < 0$) confines signals to fewer cells [Fig. 2(h)].

E. Dynamic cell fate bifurcations and fate induction

In development, morphogens are synthesized and degrade. In the classic synthesis, diffusion, and degradation (SDD) model, morphogens are locally produced at one boundary and diffuse and degrade (rate k) uniformly on a static domain [41,62]. In Fig. 2(i), the dashed black curve marks the steady-state solution $\bar{c} \propto e^{-x/\sqrt{D/k}}$, while the solid black curve shows a finite-time numerical solution $\bar{c}(x, t)$.

In dynamic tissue patterning, source and target cells may not maintain a fixed distance. However, even in the simplest case, when they do, deformation between them may affect their communication. To this end, consider an SDD model with a stationary compressible flow that generates a repeller between the source (left boundary) and target cells on the right [red segment in Fig. 2(j)] but zero velocity at the boundaries so that the spatial domain remains fixed. We display the solution $c(\mathbf{x}_0, t)$ [purple curve in Fig. 2(j)] for different strengths of the repeller (i.e., deformation rates). The repeller acts as a diffusion barrier, creating a steep gradient of $c(\mathbf{x}_0, t)$: At time

t , cells initially sitting on either side of the repeller will be exposed to markedly different morphogen concentrations. The black curve is as in Fig. 2(j). This simple example illustrates repellers' capacity to aid in morphogen compartment formation due to a non-cell-autonomous effect caused by tissue deformation, contrasted with mere advection. On the right of the repeller, for example, the velocity (advective transport) points to the right. Yet, cells on the right of the domain experience reduced exposure to morphogens from source cells. These findings resonate with recent experimental evidence associating repellers with cell-fate bifurcations during zebrafish body axis elongation at 12 hpf [54] and in chick embryogenesis at HH4-HH8 [56].

Another dynamic tissue patterning motif is the continual induction of cell fates as cells move through dynamically stable morphological structures. For example, in avian gastrulation, cells move towards and ingress through the primitive streak (PS), a sharp attractor [51]. As cells internalize, they complete epithelial-to-mesenchymal transitions that begin before they reach the attractor and involve non-cell-autonomous induction [63]. Morphogen patterning simultaneous with such a process could be described using the SDD model with advective terms and a morphogen source (mesoderm cells preinternalization) colocalized with a sharp attractor on the left boundary [Fig. 2(k)]. Figure 2(k) displays the solution $c(\mathbf{x}_0, t = k^{-1})$ for different deformation rates, showing enhanced transport of $c(\mathbf{x}_0, t)$ at the attractor, resulting in a steep rightward-expanding front. The left of the front, where c is high, labels induced cells. The advection is to the left (see $\mathbf{x}_t$), yet cell-cell diffusive fluxes are enhanced to the right.

F. Conditions for morphogenesis-mediated tissue patterning

Our framework relies on the following assumptions: First, morphogens diffuse through the ECM near cellular surfaces [64], limiting free diffusion away from the tissue. Second, the ECM moves with the underlying tissue, as observed in the gastrulating quail embryo [4] and in *Xenopus laevis* [65]. When cells and ECM are not comoving [66,67], our framework can be adapted by accounting for their relative velocity (SM Sec. 1) [46]. While we focus on extracellular diffusion, our framework applies to any transport mechanisms modeled by diffusive fluxes [Eq. (1)].

Next, we provide conditions to assess if tissue flows impact morphogen patterning during a time interval of interest $[t_0, t = t_0 + T]$, which is equivalent to answering: Has deformation affected diffusive fluxes $[\mathbf{D}_{t_0}^t(\mathbf{x}_0) \nabla_{\mathbf{x}_0} c(\mathbf{x}_0, t)]$ in the Lagrangian frame [Eq. (2)]? This transport question depends on $\mathbf{D}_{t_0}^t(\mathbf{x}_0)$ and $\nabla_{\mathbf{x}_0} c(\mathbf{x}_0, t)$, and there are two possible scenarios: (i) When there are mechanisms to maintain gradients, $\nabla_{\mathbf{x}_0} c(\mathbf{x}_0, t) \neq \mathbf{0}$, diffusive fluxes in the Lagrangian frame will be affected by deformations if $\mathbf{D}_{t_0}^t = D[\mathbf{C}_{t_0}^t]^{-1}$ deviates from $D\mathbf{I}$. (ii) When there are no mechanisms to sustain gradients $[\nabla_{\mathbf{x}_0} c(\mathbf{x}_0, t) \rightarrow \mathbf{0}]$, for deformation to be relevant, one also needs to ensure that $\nabla_{\mathbf{x}_0} c(\mathbf{x}_0, t)$ does not vanish before deformations become appreciable.

The first condition can be expressed as $\Lambda^{-1} < T$, where $\Lambda_{t_0}^t(\mathbf{x}_0) = \log(\sqrt{\lambda_{t_0}^t(\mathbf{x}_0)})/T$ is the finite-time Lyapunov exponent, evaluated where deformation is highest, i.e., at repellers or attractors (SM Sec. 3) [46]. Λ^{-1} is the Lyapunov time,

TABLE I. Nondimensional parameters and conditions to assess when tissue deformations affect patterning. If gradients are not sustained, and the fastest mechanism to eliminate gradients is not diffusion, L^2/D in Ω_2 should be replaced by the relevant timescale.

Parameters	Physical meaning	Conditions
$\Omega_1 = \Lambda T$	$\frac{\text{time scale of interest}}{\text{deformation time scale}}$	(i) With sustained gradients: $\Omega_1 > 1$
$\Omega_2 = \Lambda L^2/D$	$\frac{\text{time scale to eliminate gradients}}{\text{deformation time scale}}$	(ii) Without sustained gradients: $\Omega_1 > 1$ and $\Omega_2 > 1$

which indicates the time taken for a small initial undeformed tissue patch at $\mathbf{x}_0$ to undergo appreciable deformation—i.e., Λ^{-1} represents a deformation timescale (SM Sec. 3) [46]. In simple linear flows like Eq. (4), $\Lambda = \alpha$, and $\Lambda^{-1} < T \Rightarrow \alpha^{-1} < T$, meaning that for short T , deformation rates must be stronger (larger α) to achieve $\mathbf{D}'_{t_0} \neq \mathbf{D}\mathbf{I}$ [68,69]. For nonlinear stationary or nonstationary flows, Λ is the effective α and can be computed from experimental tissue velocities [51] or cell trajectories [52] for any time interval of interest. For scenario (ii)—when no mechanisms are known to sustain $\nabla c \neq \mathbf{0}$ —one needs to ensure that the deformation timescale Λ^{-1} is smaller than the diffusion timescale L^2/D [3], where L is the characteristic length of the region of interest for patterning (SM Sec. 3) [46]. We summarize these conditions in Table I.

If gradients are not sustained, and the fastest mechanism to eliminate gradients is not diffusion, then L^2/D in Ω_2 should be replaced by the relevant timescale, e.g., degradation k^{-1} . Alternatively, if a relay mechanism [70–72] drives morphogen spreading, then it should be replaced by L/w , where w is the effective front speed. Ω_1 and Ω_2 are frame invariant, nondimensional parameters, and the latter differs from the classic Péclet number ($\text{Pe} = |\mathbf{v}|L/D$), a ratio of advective and diffusive transport rates, which does not account for deformation. In the Lagrangian frame [Eq. (2)], advection is absent, and a uniform velocity ($\text{Pe} > 0$) generates no deformation ($\Omega_2 = 0$). Ω_2 can coincide with the alternative $\text{Pe} = \alpha L^2/D$ based on strain rates (α) but only in two specific cases: for linear stationary flows as in Eq. (4) or for general flows over infinitesimally short time intervals $[t_0, t = t_0 + \delta t]$ (SM Sec. 3) [46]. By contrast, Ω_2 applies to general, nonlinear mor-

phogenetic processes over finite times. Contrary to Eulerian advection-reaction-diffusion equations [Eq. (1)], morphogen dynamics in the moving cell frame depends on cumulative tissue deformation [Eq. (6)]—not contained in Eulerian quantities (Fig. S3 [46])—leading to new nondimensional parameters. For an algorithmic procedure to verify the conditions in Table I from experimental data, see SM Algorithm 1 [46]. See SM Figs. S4 and S5 [46] for calculation of these conditions in the SDD model and avian gastrulation data below.

G. Embryological light cones

The above results demonstrate how morphogenesis modulates diffusive fluxes [Figs. 2(c)–2(h)] and can thereby influence which cells communicate [Figs. 2(j)–2(k)]. To formalize this effect, we ask the following: If a cell ($\mathbf{x}_0^*$) sends signals via morphogen transport over $[t_0, t_0 + T]$, then which cells could receive them? Similarly, from which cells could $\mathbf{x}_0^*$ have received signals sent during a past time interval $[t_0 - T, t_0]$. We define these regions over increasing durations T as “embryological light cones” or $\text{ELC}_{t_0 \pm T}^*(\mathbf{x}_0^*)$. In cosmology, light cones bound domains of causal interaction and have been adapted in pattern formation in automata models [73,74]. Although classic light cones invoke a constant speed, the rate of molecular information propagation from cell to cell in dynamic tissues varies, modulated by morphogenetic movements ($\mathbf{C}_{t_0}^t$). Accordingly, ELCs can be curvilinear instead of conic but retain apices at $(\mathbf{x}_0^*, t_0)$ and expand into the past and future. Future cones can be estimated by evolving $c(\mathbf{x}_0, t)$, considering a source of c at $\mathbf{x}_0^*$ and subject to known

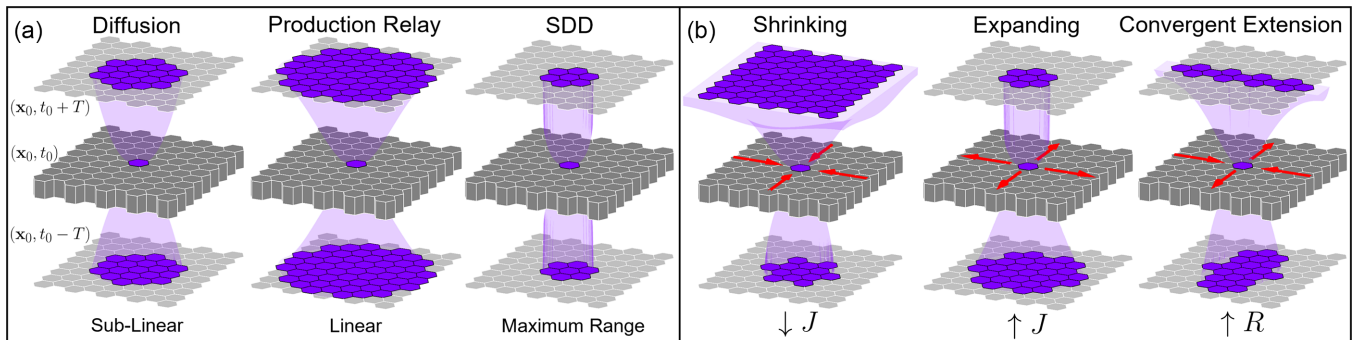


FIG. 3. Embryological light cones reveal cell-cell interaction ranges. All patches are depicted in Lagrangian coordinates (i.e., based on their positions at time t_0). Past and future cones for tissue patches at $\mathbf{x}_0^*, t_0$ depend on known or candidate signaling mechanisms and tissue deformation. A patch’s future $\text{ELC}_{t_0+T}^*(\mathbf{x}_0^*)$ (top) delimits cells $(\mathbf{x}_0)$ at $t = t_0 + T$ that can receive morphogen signals from cells at $\mathbf{x}_0^*$. A cell’s past cone $\text{ELC}_{t_0-T}^*(\mathbf{x}_0^*)$ (bottom) delimits cells that could have sent signals to $(\mathbf{x}_0^*, t_0)$ from $(\mathbf{x}_0, t_0 - T)$. ELCs simulated with a fixed source concentration $c = 1$ and threshold $c_{\min} = 0.1$ in different morphogen transport scenarios. (a) ELCs in static tissue patterning via diffusion (D), a production relay (front speed $w \approx 0.8$, SM Sec. 4) [46], and in the SDD model (degradation rate $k = 2$). (b) ELCs in dynamic tissue patterning via diffusion and stationary, isotropic negative ($\mathbf{v} = -0.8[\mathbf{x}, \mathbf{y}]$), positive ($\mathbf{v} = 0.8[\mathbf{x}, \mathbf{y}]$), and anisotropic $\mathbf{v} = 0.8[\mathbf{x}, -\mathbf{y}]$ deformation rates. All 2D simulations use parameters: $D = 0.2$, $t_0 = 0$, $T = 1$, and $L = 2$ (tissue size). For analytical predictions, see SM Secs. 4 and 5 [46].

or candidate signal propagation mechanisms over $[t_0, t]$. The ELC bounds the set of cells $(\mathbf{x}_0, t > t_0)$ exposed to morphogen concentrations above a threshold $c_{\min}$ (or threshold gradients etc.) based on thresholded cellular responses. Similarly, estimating past cones requires determining retrospectively the set of cells $(\mathbf{x}_0, t < t_0)$ for which $\mathbf{x}_0^*$ lies in their future cones at t_0 .

In static tissue patterning via simple diffusion, ELCs expand isotropically with time-dependent ELC radius r and are time-symmetric. Figure 3(a) shows ELCs for diffusion ($r \propto \sqrt{Dt}$); a production relay ($r \propto \sqrt{wT}$); and the SDD model, where the ELC expands to a fixed radius $r \propto \sqrt{D/k}$ (SM Sec. 4) [46], formalizing the classical notion of morphogen range [75,76]. In dynamic tissue patterning, morphogen signaling mechanisms rely on cell-autonomous sources, sinks and reactions, augmented by the non-cell-autonomous communication mechanisms in Eqs. (2) and (6), which affect ELCs. ELCs are no longer time-symmetric, even with constant deformation rates [Fig. 3(b), SM Sec. 4] [46], because continuous deformation introduces an explicit-time dependence to transport rates [consider for example Eq. (4)].

In an isotopically shrinking tissue ($J < 1$), future cones can grow superlinearly, enhancing cooperativity, while past cones are narrower. The opposite occurs in an isotropically growing tissue ($J > 1$), where past cones can expand super-linearly while future cone expansion slows. This reflects cells' waning global influence within a growing tissue and the efficiency of patterning before extensive growth [1]. When deformation is anisotropic ($R > 1$), past and future cones expand anisotropically, with enhanced and diminished ranges determined by the directions of convergence and extension [Figs. 2(c) and 2(f)]. Next, we consider the ELCs of example morphogen sources moving in measured avian gastrulation flows, which exhibit time-dependent, heterogeneous deformation.

H. Morphogen transport using avian gastrulation flows

Avian gastrulation involves fast, compressible, time-dependent tissue flows $\mathbf{v}(\mathbf{x}, t)$ over 12h [Fig. 4(a)] from $t_0 = 0h$ (developmental stage HH1) to $T = 12h$ (stage HH3), transforming the embryo's shape and forming the PS along the embryo's anterior-posterior (A-P) axis. The mechanisms generating these flows have been studied in mechanochemical models that generate the observed flows as output [16,78]. Simultaneous with this morphogenesis, gastrulation establishes the three germ layers, signaling through pathways activated by morphogens such as Nodal, Vg1, BMP, Wnt, and FGF [63,79]. The transport mechanisms and parameters of relevant morphogens remain largely unknown, though morphogens may be transported via diffusion through the subepiblastic ECM—comoving with cells [4]—and are likely limited to interaction ranges much shorter than the embryo diameter [80–82].

Here we take measured tissue flows as input to illustrate how our framework can be applied to experimental data to elucidate constraints on morphogen transport. We compute the DM from $\mathbf{v}(\mathbf{x}, t)$, consisting of two repellers [Fig. 4(b)] and one attractor [Fig. 4(c)], marking regions of highest deformation quantified by $\lambda_{0h}^{12h}(\mathbf{x}_{0h})$ and $\lambda_{12h}^{0h}(\mathbf{x}_{12h})$ [51]. Repeller 1 marks the initial position $(\mathbf{x}_{0h})$ of the embryonic-

extraembryonic boundary. The PS is marked by the attractor at the final embryo configuration $(\mathbf{x}_{12h})$. It is also informative to visualize its domain of attraction: i.e., the initial cells $(\mathbf{x}_{0h})$ that will eventually converge to the attractor [within red dotted curve in Figs. 4(b) and 4(d)]. Finally, Repeller 2 [Fig. 4(b)] splits the anterior-posterior domain of attraction that will converge to the anterior and posterior PS. Checking conditions in Table I on the DM, $\Lambda^{-1} \approx 4h$, hence $\Omega_1 \approx 3$ (Fig. S4 [46]), revealing $\mathbf{D}_{0h}^t \neq \mathbf{DI}$ after $t \approx 4h$ and where these deviations are strongest. Typical morphogen diffusivities are $D = 0.1\text{--}100 \mu\text{m}^2 \text{s}^{-1}$ [64]. Assuming diffusion-limited transport with $D = 1 \mu\text{m}^2 \text{s}^{-1}$ and $L \geq 200 \mu\text{m}$ (≈ 20 cell diameters), $\Omega_2 > 3$.

To elucidate the strength and anisotropy of deformation over $[0h, 12h]$, we use the eigenvalues and eigenvectors of $\mathbf{C}$ [Eq. (5)], displayed both on $\mathbf{x}_{0h}$ and on the deformed embryo configuration $\mathbf{x}_{12h}$ (to relate quantities at $\mathbf{x}_{0h}$ and $\mathbf{x}_{12h}$, see Fig. S2 [46]). Figure 4(b) shows $\log \lambda_{0h}^{12h}(\mathbf{x}_{0h})$, i.e., the strength of diffusion reduction (where >0) along the stretching direction (black bars), highlighting that diffusive fluxes reduce between separating cells (maximal across repellers). Figure 4(d) conversely reveals the directions (white bars) along which tissue patches shrink the most, showing that there is an enhanced diffusive flux [color bar as in Fig. 4(c), where >0] perpendicular to the A-P axis within the domain of attraction. It is instructive to visualize this information also at the final embryo configuration $\mathbf{x}_{12h}$. Figure 4(c) shows the strength of diffusion enhancement [where $\log \lambda_{12h}^{0h}(\mathbf{x}_{12h}) > 0$] and the direction (white bars), highlighting how diffusive fluxes are mostly enhanced laterally at the attractor, and mildly along the radial direction in the fountain-shaped region surrounding the anterior part of the PS and emanating from the Hensen's node. Because they exhibit the strongest modulation of cell-cell morphogen transport, repellers and attractors are the essential kinematic features that mediate this cell-cell communication, reshaping ELCs.

To visualize our predictions, we examined tissue patches [colored disks in Figs. 4(a)–4(d)] initialized (i) outside Repeller 1 (blue and magenta) and therefore in the extraembryonic tissue, (ii) in the anterior embryo (yellow), and (iii) anterior and posterior of Repeller 2 (green and cyan). We treat these five patches as morphogen point sources, secreting morphogens at a fixed rate during $[0h - 12h]$, using a typical morphogen diffusivity $D = 1 \mu\text{m}^2/\text{s}$ (see Fig. S5 [46] for alternative values). The source patches move with the tissue [Figs. 4(a) and 4(c)] but remain fixed in the cell frame [Figs. 4(b) and 4(d)]. In essence, our framework recasts morphogen transport dynamics, typically challenging to rationalize due to the complex flows, as an equivalent static tissue problem over the initial embryo configuration $\mathbf{x}_{0h}$, with the effects of cell motion on cell-cell signaling encoded in $\mathbf{D}_{0h}^{12h}(\mathbf{x}_{0h})$. Figure 4(e) shows the temporal evolution of the DM and $\mathbf{C}_{0h}^t$ for increasing t , decomposed as in Figs. 4(b) and 4(d). Overlaying the deformation fields, we plot a top-down view of each source's future ELC $_{0h}^t$, with colored contours marking the extents at each intermediate time. While initially expanding slowly in all directions ($\mathbf{D}_{0h}^t(\mathbf{x}_0) \approx \mathbf{DI}$), the effects of cumulative deformation manifest in the expansion of ELCs around 4h—when $\Lambda_{0h}^t > 1$ on the DM—and later become more dramatic. For example, before 4h, the green ELC ex-

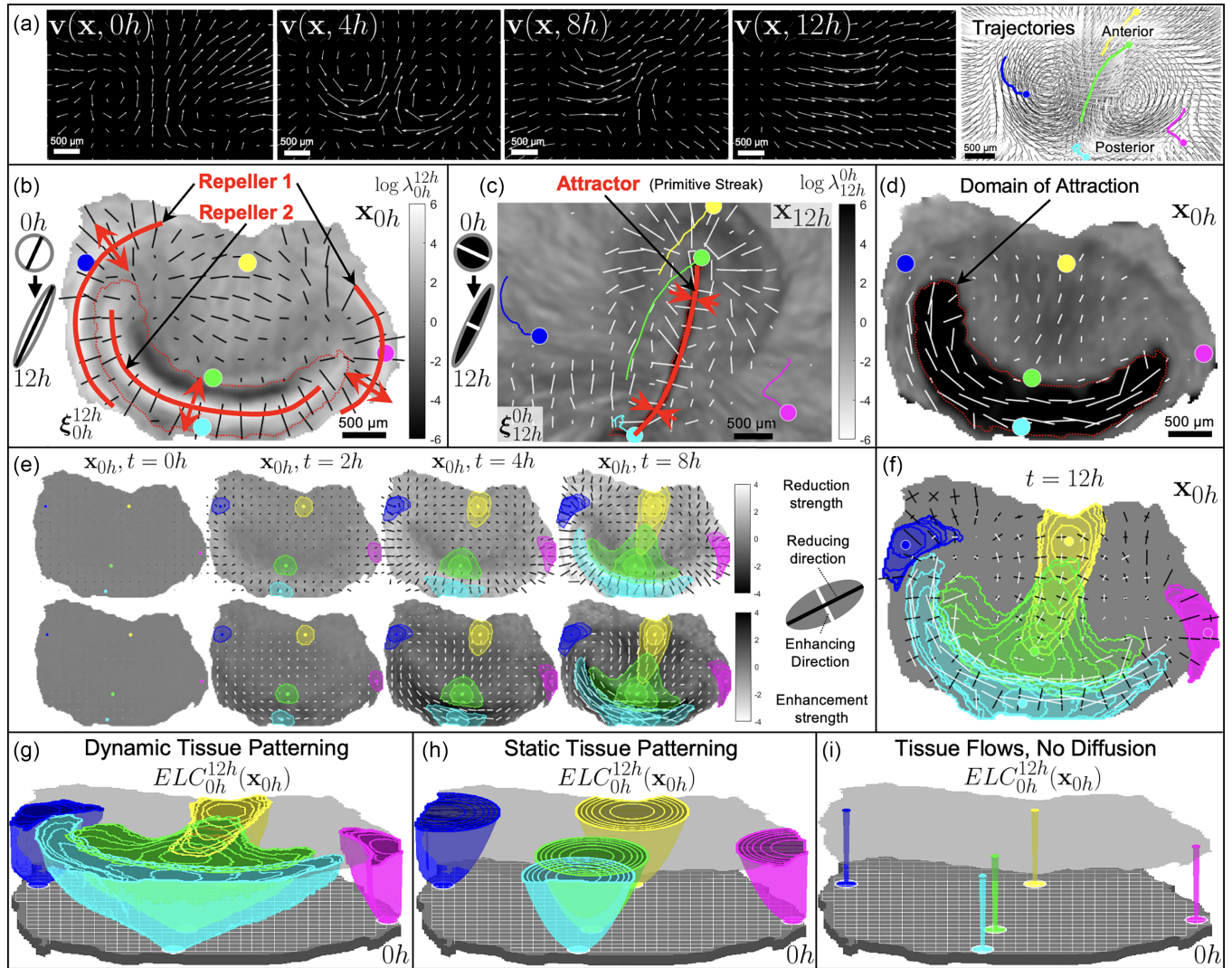


FIG. 4. Morphogenesis-mediated morphogen transport in avian gastrulation flows. (a) Tissue velocities during primitive streak formation in the chick embryo ($t_0 = 0h$ corresponds to developmental stage HH1 and $t = 12h$ to stage HH3), obtained via particle image velocimetry [77]. From $\mathbf{v}$, we compute cell trajectories (right) and tissue deformation encoded in $\mathbf{C}$ [51]. Source trajectories are depicted with markers at their final positions. [(b)–(d)] Analysis over the full 12h reveals two repellers and one attractor (the dynamic morphoskeleton [51]), along with directions ($\mathbf{C}$ eigenvectors) of convergence (white) and separation (black) with lengths proportional to their corresponding eigenvalues. (b) Two repellers (transport barriers) marked by high values of λ_{0h}^{12h} on $\mathbf{x}_{0h}$. Bars indicate the direction of maximum separation ξ_{0h}^{12h} with length proportional to $\log \lambda_{0h}^{12h} > 0$. (c) One attractor (transport enhancer) marked by high values of λ_{12h}^{0h} on $\mathbf{x}_{12h}$. Bars indicate the direction of maximum convergence ξ_{12h}^{0h} with length proportional to $\log \lambda_{12h}^{0h} > 0$. (d) Same as (c), displayed at the initial embryo configuration $\mathbf{x}_0$ [color bar as in (c)]. [(e) and (f)] Simulations with sources secreting morphogens at rate Q , which diffuse with $D = 1 \mu\text{m}^2/\text{s}$. Morphogens and cells move with $\mathbf{v}(\mathbf{x}, t)$ (a). (e) Top (bottom) row depicts the maximally stretching (shrinking) directions as in (b) and (d). Scalar fields on the top (bottom) depict the strength of cell-cell diffusion reduction (enhancement) on a log scale as in (b) and (d). Colored contours mark tissue patches at their $\mathbf{x}_{0h}$ positions raised above a threshold morphogen concentration $Q/100$ at $t = 0, 2, 4, \text{ and } 8h$. Note that these results do not depend on the value of $Q > 0$. (f) Contours from (e) along with the outermost contour and diffusive transport reduction (enhancement) directions corresponding to $t = 12h$. White (black) bars mark the direction of diffusion enhancement (reduction) proportional to their length. (g) Each source's future ELC_{0h}^t over increasing t . Nested contours correspond to ELCs at $(t = 2, 4, 6, 8, 10, \text{ and } 12h)$. Movie 5 [46] shows the time evolution of cell trajectories and dynamic tissue patterning associated with (b)–(g). (h) Same as G for static tissue patterning (no cell motion: $\mathbf{v} = \mathbf{0}$) using the same parameters as in (g). (i) Same as (g), where tissue flows are present but $D = 0$, highlighting that the role of morphogenesis in mediating non-cell-autonomous (or cell-cell) signaling is not due to cell-autonomous morphogen rearrangements.

pansion is mostly isotropic (expanding as a circle); after 4h, diffusive fluxes become enhanced across the posterior, especially perpendicular to the A-P axis [Fig. 4(f)].

Figure 4(f) depicts the ELCs as colored contours for 2h t intervals [as in Fig. 4(e)] and the final outermost contour

at 12h along with directions of maximum deformation ($\mathbf{C}_{0h}^{12h}$ eigenvectors). White (black) bars mark directions of enhanced (reduced) diffusion with bar lengths indicating the strength of this modulation. This panel also reveals the degree of isotropic [$J_{0h}^{12h}(\mathbf{x}_{0h})$] and anisotropic [$R_{0h}^{12h}(\mathbf{x}_{0h})$] deformation

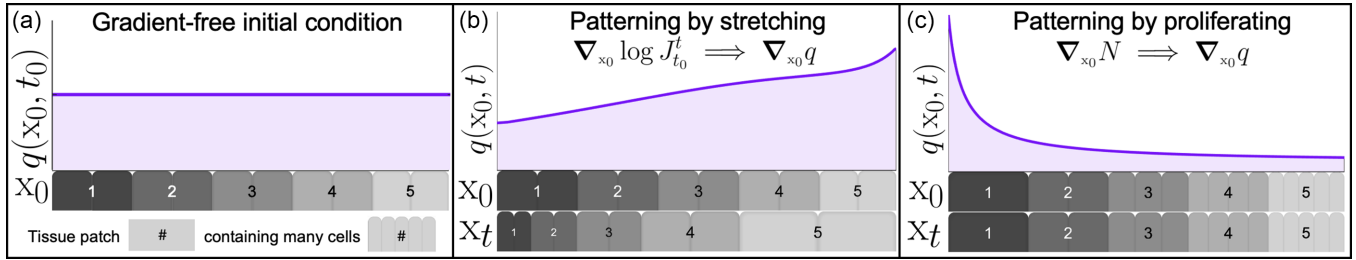


FIG. 5. Generative patterning role of tissue deformation and cell number dynamics. (a) Initially uniform $q(x_0, t_0)$ and $N(x_0, t_0)$ on an undeformed tissue with uniform patch areas $A(x_0, t_0)$. Equivalently, $n(x_0, t_0) = N(x_0, t_0)/A(x_0, t_0)$ and $c(x_0, t_0) = q(x_0, t_0)n(x_0, t_0)$ are uniform. Tissue patches are differently colored and contain multiple cells ($N(x_0, t)$ proportional to the number of elements in each patch). (b) A gradient in deformation ($\nabla_{x_0} J_{t_0}^t$, see $\mathbf{x}_t$ patch sizes) generates gradients in $q(x_0, t)$, while $N(x_0, t)$ remains uniform and constant as $k_d = k_e = 0$. Diffusion (with no-flux boundary conditions) lowers (raises) the per-cell morphogen exposure (q) of compressed (stretched) tissue patches. (c) The same initial condition as in A and no morphogenetic movements ($J_{t_0}^t = 1$), but with heterogeneous $k_d - k_e$ generates heterogeneous $N(x_0, t)$ [contrast cells per patch with panels (a) and (b)], lowering q in patches with more cells.

(SM Sec. 2) [46]. Entirely black (white) crosses indicate regions of isotropic expansion (shrinkage) with $J > 1$ ($J < 1$), where deformation is primarily isotropic. For example, tissue expansion outside Repeller 1 reduces fluxes in all directions, and a highly compressive region in front of Repeller 2 enhances diffusive fluxes in all directions. Interestingly, this region gives rise to Hensen's node. Regions where crossed bars differ in length or color indicate $R_{0h}^{12h} > 1$. Regions where both bars vanish remain undeformed ($J = R = \lambda = 1$).

Comparing Fig. 4(f) with Figs. 4(b) and 4(d) reveals the cumulative effects of morphogenesis on ELCs, as predicted from the DM. Repeller 1 effectively blocks communication between blue and magenta source patches and cells inside the embryo. The yellow patch experiences reduced lateral cell-cell communication and an enhanced one along the A-P axis, overlapping with the green ELC [Fig. 4(f)]. Green and cyan cells are both positioned near the domain of attraction, whose contraction expands their ELCs superlinearly to reach other cells brought near the PS. However, because Repeller 2 forms between them, green and cyan ELCs do not overlap [Fig. 4(f)]. This is due to reduced diffusive fluxes across repellers, which have compartmentalizing effects. Consistent with Figs. 2(j) and 2(k), the mediation of morphogen transport by attractors and repellers likely influences cell fate induction and bifurcation. It is key to notice that the modulation of ELCs by tissue deformations can be inferred from $\mathbf{C}$ —computable from experimental $\mathbf{v}$ —without solving any advection-reaction-diffusion equations.

ELCs in Fig. 4(g) [3D view of Fig. 4(f)] should be contrasted with ELCs for static tissue patterning with identical patterning parameters [Fig. 4(h)]. Without tissue flows ($\mathbf{v} = \mathbf{0}$), ELCs expand sublinearly and isotropically by simple diffusion. Instead, morphogenesis causes source cells' signals to reach a markedly different set of cells than in static tissues. Without morphogenetic movements, blue and magenta ELCs would penetrate into the embryo, yellow and green ELCs would not communicate, and instead green and cyan ELCs would overlap substantially. Crucially, morphogenesis alone does not carry any signals from cell to cell and setting $D = 0$ leads to nonexpanding ELCs [Fig. 4(i)]. We emphasize that our framework applies to the analysis of any non-cell-autonomous morphogen transport mechanisms that can be

modeled by an effective diffusion as in Eq. (1) (e.g., spreading via cytonemes, transcytosis). See SM Fig. S5 [46] for ELCs of these morphogen sources with other plausible patterning parameters.

I. Per-cell morphogen exposure

So far, we considered c (# molecules per unit area). However, when cell density (n , # cells per unit area) is heterogeneous, cell responses may depend on n [43,44,83,84]. To this end, we define $q = c/n$ —the average per-cell morphogen exposure (# molecules per cell) within a tissue patch. A confluent epithelium can be compressible due to cell divisions [rate $k_d(\mathbf{x}_0, t)$], extrusions [rate $k_e(\mathbf{x}_0, t)$], or tissue stretching. Using continuity equations (SM Sec. 5) [46], the dynamics of $n(\mathbf{x}_0, t)$ within a Lagrangian tissue patch obeys

$$\partial_t n(\mathbf{x}_0, t) = n(\mathbf{x}_0, t)[k_d(\mathbf{x}_0, t) - k_e(\mathbf{x}_0, t) - \nabla \cdot \mathbf{v}(\mathbf{x}_0, t)]. \quad (7)$$

In growth-dilution models of patterning [8,85,86], for example, $k_e = 0$ and $\nabla \cdot \mathbf{v} = k_d$ (tissue growth) so that $\partial_t n = 0$ (SM Sec. 5) [46]. In chick gastrulation (Fig. 4), instead, uniform division, localized extrusion, and heterogeneous tissue deformation cause n to nearly double in the constricting embryo [77] while n is halved in the extraembryonic tissue [87]. It is instructive to decompose changes in n into changes in (i) the patch's number of cells N and (ii) the patch's area A , as $n = N/A$. Cumulative changes in $A(\mathbf{x}_0, t) = A(\mathbf{x}_0, t_0)J_{t_0}^t(\mathbf{x}_0)$ are determined by the velocity while divisions and extrusions determine cumulative changes in $N(\mathbf{x}_0, t)$ along trajectories:

$$N(\mathbf{x}_0, t) = N(\mathbf{x}_0, t_0)e^{\int_{t_0}^t [k_d(\mathbf{x}_0, \tau) - k_e(\mathbf{x}_0, \tau)]d\tau}. \quad (8)$$

Combining Eqs. (7) and (8) with Eq. (6) yields Eq. (9), for $q(\mathbf{x}_0, t)$ (SM Sec. 5) [46], which explicitly accounts for division and extrusion and their role in morphogen dilution and redistribution of unbound morphogens. As in Eq. (6), non-cell-autonomous changes in q are still determined by $\mathbf{D}_{t_0}^t$ and $\nabla_{x_0} c$, which decomposes into gradients in q , N , and $J_{t_0}^t$. This further clarifies how morphogenesis contributes to

cell-cell morphogen transport: (i) by modulating $\mathbf{D}_{t_0}^t$ and (ii) via heterogeneous isotropic deformation $\nabla_{\mathbf{x}_0} J_{t_0}^t$.

To visualize each effect, consider an undeformed 1D tissue with uniform initial $A(\mathbf{x}_0, t_0)$, $q(\mathbf{x}_0, t_0)$, and $N(\mathbf{x}_0, t_0)$ and assume morphogens are conserved (no sources or sinks). Suppose that by a later time t tissue deformation ($J_{t_0}^t$) gradients develop due, for example, to heterogeneous active stresses or externally imposed forces. This deformation (morphogenesis) generates heterogeneous $q(\mathbf{x}_0, t)$ [Fig. 5(b)] from uniform initial q . Alternatively, suppose that heterogeneous $k_d - k_e$ develops [Eq. (8)]. Heterogeneous division and ex-

trusions likewise generate heterogeneous $q(\mathbf{x}_0, t)$ [Fig. 5(c)], also from uniform initial $q(\mathbf{x}_0, t_0)$ [Fig. 5(a)]. These simple examples highlight the additional generative role of morphogenesis in patterning enabled by explicitly accounting for cell density dynamics. Finally, $n(\mathbf{x}_0, t)$ may affect patterning parameters directly. For example, both patch-level production and removal may increase with n (SM Sec. 5) [46]. Similarly, cell-cell boundaries (with density proportional to n) may impede transport, thereby decreasing $D(\mathbf{x}_0, t)$ [50],

$$\partial_t q(\mathbf{x}_0, t) = \overbrace{N^{-1} \nabla_{\mathbf{x}_0} \cdot (\mathbf{D}_{t_0}^t [\underbrace{N \nabla_{\mathbf{x}_0} q}_{\text{per-cell morph. gradients}} + \underbrace{q \nabla_{\mathbf{x}_0} N}_{\text{cell-number gradients}} - \underbrace{q N \nabla_{\mathbf{x}_0} \log J_{t_0}^t}_{\text{isotr. deform. gradients}}])}_{\text{non-cell-autonomous}} - \underbrace{q(k_d - k_e)}_{\text{dilution \& redistribution}} + \dots \quad (9)$$

III. DISCUSSION

Morphogenesis can be thought of as a coordinate transformation—a view that dates back to D’Arcy Thompson’s seminal work [88]. This view, influential in studying how organismal form emerges and diverges, has not been adopted in the study of morphogen patterning. Yet patterning continues simultaneously with morphogenesis in early embryos, when cells process morphogen exposure and acquire fates in their moving frames (Fig. 1).

By recasting patterning equations (advection-reaction-diffusion) in the cell frame Eqs. (2) and (3), we uncovered elegant connections between morphogen patterning and morphogenetic movements: tissue deformation modulates intercellular (non-cell-autonomous) diffusive morphogen transport in remodeling tissues (Fig. 2). This modulation is highest on the dynamic morphoskeleton [51]: a set of robust multicellular attractors and repellers that reduce complex, noisy cell trajectories to their Lagrangian kinematic units [51,54,56,57]. Repellers (attractors) identify the strongest barriers (enhancers) to diffusive transport, affecting cell-cell interaction ranges across them (Figs. 2 and 4). These findings clarify how morphogenesis mediates morphogen exposure and cell-cell transport in dynamic tissues, with repellers aiding compartmentalization and fate bifurcations [Figs. 2(j) and 4]—consistent with recent experiments in zebrafish [54] and chick embryos [56]—and attractors supporting cell fate induction [Figs. 2(k) and 4]. Generating sharp repellers provides sensitivity [sharp $\nabla_{\mathbf{x}_0} c$; Fig. 2(j)] and robustness, as attractors and repellers are the most robust features in spatiotemporal flows [51], resolving a common static-tissue trade-off [89]. In the cell frame, steplike gradients generated by repellers may require less intracellular nonlinearity than smoother gradients to produce discrete fate domains.

To assess when morphogenesis affects morphogen patterning, we defined two nondimensional numbers (Table I), computable from the experimental tissue velocities and known or candidate signaling mechanisms. These numbers account for cumulative tissue deformations in remodeling tissues and are typically distinct from the classic Péclet number. Additionally, Lagrangian coordinates (Fig. 1) have another

key advantage: they disentangle the confounding effect of motion in morphogen patterning [5–7], providing an equivalent static (no advection) patterning problem that encodes cells’ deforming environments into an effective diffusion tensor Eqs. (2) and (3). Morphogenetic movements can dramatically reshape cell-cell interaction ranges compared to static tissue patterning and embryological light cones formalize these dynamic interaction ranges within highly remodeling tissues (Figs. 3 and 4). In the avian gastrulation example (Fig. 4), the strong cell-cell interaction range enhancement perpendicular to the PS might aid in continuous mesoderm induction [63,79,90]. Repeller 1’s compartmentalizing effects resonate with the extraembryonic region’s waning regulatory ability [91–93]. Repeller 2’s compartmentalizing effects resonate with the diverging gene expression of anterior and posterior sections of the PS [51], which ultimately give rise to different cell types [94]. Finally, we incorporated cell number density dynamics into our framework [Eq. (9) and SM Eq. 25] [46], formalizing key cellular mechanisms for morphogen dilution, redistribution, production, and removal [41]. This framework suggests additional generative roles of morphogenesis in patterning, forming stable morphogen gradients through heterogeneous tissue deformation [Fig. 5(b)] or proliferation [Fig. 5(c)] from an unpatterned initial condition.

Historically, embryologists have compared fate maps [$\mathbf{F}_{t_0}'(\mathbf{x}_0)$, where cells normally go and what they become] with specification maps (what cells $\mathbf{x}_0$ would become if isolated at t_0) to classify development as more “mosaic” (autonomous fates decisions) or “regulative” (cell-cell interactions required) [95,96]. Our framework helps rationalize regulative development in dynamic tissues, revealing on $\mathbf{x}_0$ what mechanisms would enable cells to interact amid morphogenetic movements. As next steps, we plan to examine 3D morphogenesis examples, where attractors and repellers are two-dimensional surfaces. Given the difficulty of relative motion between cells and the ECM, morphogenesis may strongly mediate morphogen patterning in 3D, where the confounding effect of motion is greater but resolved in Lagrangian coordinates. In addition to testing candidate morphogen patterning mechanisms given measured flow data, our framework can be

used to guide the development of mechanochemical models generating cell trajectories (e.g., vertex models [15]) or velocity fields (continuum models [16]), supporting integrated models of morphogenesis and cell differentiation. The latter will be particularly important when diffusing molecules feed back on tissue mechanics [9,97]. Future extensions include analysis of cell motion's random, mixing components [98,99] and explicitly accounting for dynamic neighbor exchanges at single-cell resolution (as opposed to the deterministic, continuum description of cell movements analyzed here).

Nonlinear dynamics offers the mathematical frameworks for describing spatiotemporal processes along trajectories. In cell-fate dynamics, cell trajectories live in high-dimensional gene expression space. Siggia, Rand, Briscoe, and coworkers [100–102], using advanced nonlinear dynamics concepts [103], devised a structurally stable compression (with minimal fitting parameters) of high-dimensional gene expression trajectories into low-dimensional cell fate dynamics among discrete attractors (stable cell states), saddle points, and repellers (unstable cell states). There, morphogen exposure serves as a control parameter, affecting the routes between discrete cell states via bifurcations (reviewed in [104]). Complementary to this perspective, the dynamic morphoskeleton [51] compresses tissue-space cell trajectories into minimal discrete units: positional attractors (where cells converge from their domains of attraction) and repellers (where cells separate). Both techniques provide geometrical insights that do not require detailed simulations or depend on molecular de-

tails [105]. While these dynamical systems are in different spaces (gene expression and position), they are intimately related because cell positions affect morphogen exposure, which instructs cell differentiation. Connecting attractors and repellers in position space and their dual objects in the fate decision space via morphogen exposures along cell trajectories (present work) requires new ideas. This connection will lead to quantitative frameworks for cell differentiation dynamics mediated by tissue-space information in dynamic tissues.

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The authors declare no competing interests.

DATA AVAILABILITY

No new data were created or analyzed in this study.

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