Active Nematic Defects and Epithelial Morphogenesis

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Active nematic defects and epithelial morphogenesis

Farzan Vafa\textsuperscript{1,2} and L. Mahadevan\textsuperscript{3,4}

\textsuperscript{1}Department of Physics, University of California Santa Barbara, Santa Barbara, CA 93106, USA
\textsuperscript{2}Center of Mathematical Sciences and Applications, Harvard University, Cambridge, MA 02138, USA
\textsuperscript{3}School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138, USA
\textsuperscript{4}Departments of Physics, and Organismic and Evolutionary Biology, Harvard University, Cambridge, MA 02138, USA

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Inspired by recent experiments that highlight the role of nematic defects in the morphogenesis of epithelial tissues, we develop a minimal framework to study the dynamics of an active curved surface driven by its nematic texture. Allowing the surface to evolve via relaxational dynamics leads to a theory linking nematic defect dynamics, cellular division rates, and Gaussian curvature. Regions of large positive (negative) curvature and positive (negative) growth are co-localized with the presence of positive (negative) defects. In an ex-vivo setting of cultured murine neural progenitor cells, we show that our framework is consistent with the observed cell accumulation at positive defects and depletion at negative defects. In an in-vivo setting, we show that the defect configuration consisting of a bound $+1$ defect state, which is stabilized by activity, surrounded by two $-1/2$ defects can create a stationary ring configuration of tentacles, consistent with observations of a basal marine invertebrate Hydra.

Figure 1: Schematic of our model. Epithelial activity driven by a nematic texture leads to a flow field that drives nematic defects. The defects then induce variations in the intrinsic metric and thence changes in the 3-d embedding of the epithelial surface. Image of Hydra in the center, adapted from [28].
\[ F_Q = \int d^2x \sqrt{\gamma} \tilde{K} g_{ab} \nabla_a Q^{ab} \nabla_c Q^{cd} - K'R \text{Tr}\left[Q^2\right] + \frac{1}{4} \epsilon^{-2}(1 - 2g_{ab}g_{cd}Q^{ab}Q^{cd})^2 \]

where \(g_{ab}\) is the metric, \(\nabla_a\) is the covariant derivative associated with it, and \(R\) is the scalar curvature. Here \(\tilde{K}\) is the Frank elasticity parameter in the single-constant approximation, \(K' > 0\) is a curvature elasticity that can be viewed as a geometric contribution to the potential: with \(R > 0\) (\(< 0\)), this term favors ordered (disordered) state, while last term governs the isotropic-nematic transition, with \(\epsilon\) controlling the microscopic nematic correlation length \([30]\).

We further assume that the surface relaxes via relaxational dynamics analogous to diffusion; a naturally invariant form is then given by Ricci flow \([31]\),

\[ \partial_t g_{ab} = -DR_{ab} + \lambda g_{ab} \]  

where \(R_{ab}\) is the Ricci tensor (which in 2D is given by \(R_{ab} = 2\epsilon^a_{cb}R_{bc} - \lambda g_{ab}\)), \(D > 0\) is the diffusivity, and \(\lambda(t) > 0\) controls the growth rate of the area. In general, \(\lambda = \lambda(x, t)\), but for simplicity we will take \(\lambda = \lambda(t)\). Eq. (2) follows from the gradient-flow of the free energy \(F_g = \int d^2x \sqrt{\gamma}k_{\phi}R_{ab} - \lambda\)

where \(\sqrt{\gamma} = \exp(\phi)\) \([32]\), \(k_{\phi}(x D)\) is an elastic constant penalizing changes in the Gaussian curvature \(R\).

Then the coupled dynamics of the nematic and metric fields associated with gradient descent and advection by a non-equilibrium flow \(\nu^\alpha\) \([33]\) yields

\[ \partial_t Q^a = -\nu^c \nabla_c Q^{ab} + [Q, Q]_{ab} - \gamma_Q 1/2 \gamma^{cd} \frac{1}{\sqrt{\gamma}} \frac{\delta F}{\delta Q^{cd}} \]

\[ \partial_t g_{ab} = - (\nabla_a \nu^c) g_{cb} - (\nabla_b \nu^c) g_{ca} - \gamma_{\phi} 1/2 \gamma^{cd} \frac{\delta F}{\delta g^{cd}} \]  

with \(\Omega_{ab} = (\nabla_a v_b - \nabla_b v_a)/2\) the vorticity, and \(\gamma_Q\) and \(\gamma_{\phi}\) are the viscous coefficients for the dynamics of \(Q^{ab}\) and \(g_{ab}\), respectively, with units of radians/\(\text{time}\).

Closure of the system (3)-(4) requires an equation for the active velocity field generated by the active stress \(\sigma^{ab}\).

We note that in Eq. (3) we have ignored the rate of strain alignment; in the biologically relevant, overdamped limit described by Eq. (5) this effect leads to a renormalization of the rigidity constant \([34, 35]\). In this context, \(\sigma^{ab} = \partial_t Q^{ab}\)

\([24, 36]\); i.e. we balance the active stresses with the substrate friction (neglecting elastic and non-local hydrodynamic effects \([37]\)), and therefore write \([33]\)

\[ \mu \nu^c = \partial_t \nabla_a Q^{ac} \]  

where \(\mu\) is the substrate friction, \(\partial_t\) is the active energy density with \(\partial_t > 0\) \((\partial_t < 0)\) corresponding to contractile (extensile) activity. We define the scaled activity coefficient \(\alpha = \partial_t / \mu\).

In terms of the problem parameters: \(\tilde{K}, K', \epsilon, \alpha, K_{\phi}, \gamma_Q, \gamma_{\phi}\), and the system size \(L\), we can define the nematic coherence length (or defect core radius) \(\xi = \sqrt{K_{\phi}}\), the geometrical coherence length \(\ell_{\phi} = \sqrt{K_{\phi} \epsilon}\), a “Gaussian curvature” length \(\ell_{R,\phi} = \sqrt{K'/\epsilon}\), and \(\ell_d = \sqrt{K' / |\epsilon'|}\), the defect separation length \([38]\); and the relaxation times \(\tau_Q = \gamma_Q \epsilon^2\) and \(\tau_{\phi} = \gamma_{\phi} L^2 / K_{\phi}\). This leads to the following dimensionless quantities: \(\xi / \ell_{\phi}, \tau_Q / \tau_{\phi}\), the ratio of coherence lengths for the nematic field and intrinsic geometry \((\alpha < 1\) because extrinsic geometry variations occur on scales large compared to the nematic defect core size); \(\tau_{\phi} / \tau_Q = (\gamma_{\phi} / \gamma_Q)(L/\xi_{\phi})^2\)

As a preliminary step before considering active defects, we discuss later is the ratio of the two different types of nematic elastic deformations. See the Supplemental Material \([27]\) for estimates of model parameters.

Eqs. (3) to (5) form a set of nonlinear partial differential equations that dictate the evolution of the nematic field \(Q^{ab}\) and the intrinsic geometry \(g_{ab}\) as a function of the activity \(\alpha\), when complemented by appropriate initial and boundary conditions. To make progress in a minimal setting for epithelial morphogenesis, we choose 2D isothermal (conformal) \([39]\) complex coordinates \(z, \bar{z}\) such that

\[ ds^2 = g_{zz}dz d\bar{z} + g_{z\bar{z}}d\bar{z} dz = 2g_{zz}|dz|^2 = e^\phi |dz|^2 \]  

and assume that the metric remains diagonal in these coordinates for all time. Furthermore, since the nematic tensor \(Q^{ab}\) is a traceless real bivector, we can write its components \(Q = Q^{zz}, \bar{Q} = Q^{z\bar{z}},\) with \(Q^{zz} = 0\), and \(Q = (\bar{Q})^*\).

Since the metric \(g_{zz}\) measures the area in the \(z\) coordinate system, assuming fixed cell size, this implies that we can interpret \(\varphi = \log g_{zz}\), i.e. the log of the cell density in these coordinates. In particular, the change in \(\varphi\) reflects cell division. In these coordinates, \(F_Q\) takes the form

\[ F_Q = \int d^2z \sqrt{g}[2Kg_{zz} \nabla z Q^{zz} \nabla_\bar{z} Q^{z\bar{z}} + 2K'g_{zz} \nabla z Q^{zz} \nabla_\bar{z} Q^{z\bar{z}} + 1/4 \epsilon^{-2}(1 - 2g_{ab}g_{cd}Q^{ab}Q^{cd})^2 \]

where \(K = K - K' > 0\) to guarantee positivity of the elastic energy, \(Q = Q^{zz}\) and \(\bar{Q} = Q^{z\bar{z}},\) and \(|\cdot|\) is defined in terms of the metric \([40]\). Here the covariant derivatives \(\nabla z Q^{zz} = DQ + 2(\partial_\varphi Q)\nabla z Q^{zz}\) and \(\nabla z Q^{z\bar{z}} = \bar{D} Q\), while the scalar curvature \(R = -4e^{-\varphi} \partial_\varphi \varphi\). The asymmetry in the appearance of \(\partial_\varphi\) in \(\nabla z Q\) and \(\nabla z Q\) is the underlying reason behind asymmetry in cell growth near defects: cells accumulate at positive defects and deplete at negative defects.

As a preliminary step before considering active defects, we consider the case of passive nematics with \(\alpha = 0\). Then the dynamics for \(Q\) and \(\varphi\) in isothermal conformal coordinates can be written as

\[ \partial_t Q_{\alpha} = 0 \]
The covariant derivative terms are
\( γ_{ϕ}∂_{t}ϕ = 4K[∂Q^+]^2 + 2K(Q^+∂Q^+ + Q^+∂Q^-) \)
\(- 4K'[∂Q^+]^2 - \frac{1}{4} ε^{-2}(1 - 4|Q|^2)(1 - 20|Q|^2) + λ \)
(10)
\[ γ_{ϕ}∂_{t}ϕ^- = 4K[∂Q^-]^2 + 2K(Q^-∂Q^- + Q^-∂Q^+) \]
\(- 4K'[∂Q^-]^2 - \frac{1}{4} ε^{-2}(1 - 4|Q|^2)(1 - 20|Q|^2) + λ \]
(11)

Now noting that \( Q^+ = (Q^-)^* \) and that in the vicinity of
the positive (negative) defect core \( ∂Q^+ (∂Q^-) = 0 \) leads to
\[ γ_{ϕ}∂_{t}ϕ^+ - γ_{ϕ}∂_{t}ϕ^- = 4K[∂Q^+]^2 + 4K'[∂Q^-] \]
\[ = 4K[∂Q^+]^2 > 0. \]
(12)

Interpreting \( ϕ \) as the logarithm of the cell density (since
the Gaussian curvature \( R = -4ε^{-ϕ}∂ϕϕ \)), in the absence
of net surface growth, this implies that \( ϕ \) will increase at
a +1/2 defect and decrease near a -1/2 defect (since the
two changes must balance each other), and the cell density
will increase (decrease) at plus (minus) defects, i.e., cells
accumulate (deplete) at the defects. This shows that in a
passive setting without activity, positive curvature growth
via a positive defect can still occur. The mechanism we
propose is a geometric alternative to previously-proposed
mechanisms for cell accumulation at topological defects due
to anisotropic friction [17, 18], and can operate either
independently or together with previously-proposed mecha-
nisms.

In the top panel of Fig. 2, we show the initial profile of
\( ϕ \) at \( t = 0 \) from our analysis, showing the dynamic asym-
bmetry between a plus and minus defect, consistent with the
experimental observations of cell density in the vicinity of
defects in murine neural progenitor epithelia [17]. In the
bottom panel of Fig. 2, we show that this asymmetry in
the shape in the neighborhood of ±1/2 defects is reflected
in the Gaussian curvature of the surface which is positive
(negative) near a plus (minus) defect, consistent with inde-
dependent observations in a different experiment [19].

Activity, i.e. \( α ≠ 0 \), leads to anisotropic flow because
of gradients in the nematic order parameter; this acts as
an additional source of geometric frustration, modifying the
Gaussian curvature of the sheet [27]. More generally, we
rewrote the coupled Eqs. (8) and (9) in complex coordinates
with \( ∂Q \rightarrow Q = ϕ + ε^2(ϕ)Q + ϕ^2Q^2 \) and
\( ϕ = ϕ^+ + ϕ^- \), where
\( ∂Q = ∂ϕ(ϕ + ϕ^2) \) and \( ∂ϕ = ∂ϕ^+ + ∂ϕ^- \),
\( ∂ϕ^+ = ∂ϕ^- + (ϕ^+ - ϕ^-) \)
\( θ = ϕ ϕ^2(ϕ)Q \) and \( ϕ = ϕ^+ + ϕ^- \) are the nematic field and the intrinsic geometry, we use a
finite-difference scheme with periodic boundary conditions
to simulate a ring-like structure seen in Hydra [27].

We find that an initially flat geometry with a single +1
defect in the center and two -1/2 defects on the edges, using
the ansatz from [41], settles into a stationary defect config-
uration of a ring of equally spaced +1 defects (bound state
of two +1/2 defects) separated by pairs of -1/2 defects in a
Fig. 2: Dynamics near defects. Following Eqs. (10) and
(11), where \( R = -4ε^{-ϕ}∂ϕϕ \), we show plots of (a) \( \frac{dx}{dt} \)
and (b) \( \frac{dy}{dt} \) for a single +1/2 (in red) and a single -1/2
defect (in blue), with the activity \( α = 0 \). Top inset: for
comparison, we show the experimental growth rate of nor-
malized cell density [17]. Middle and bottom insets: cor-
responding plots of active contribution for \( dϕ \) and \( dR \)
for \( φ = 0, α = 1 \). Parameters used are \( K = 1, K' = 1, ε = 1 \).

\[ γ_{ϕ}∂_{t}ϕ = 2Kg^{x,2}v_{x}^2Q + 2K'g^{x,2}v_{x}^2Q \]
\[ + 2ε^{-2}(1 - 4|Q|^2)Q \]
(8)
\[ γ_{ϕ}∂_{t}ϕ = -K_{ϕ}R + 4KQ(νQv_{x}^2 + Qv_{x}νQ) \]
\[ - 4K'[νQ]\]
\[ (1 - 4|Q|^2)(1 - 20|Q|^2) + λ \]
(9)

where the covariant derivative terms are \( νQv_{x}^2 = \bar{Q}∂Q + \)
\( 2(∂ϕQ)Q + 2Q∂ϕQ \) and \( ∂νQv_{x}^2 = ∂ϕQ + 2QQ\).

For a flat configuration with \( ϕ = 0 \), denoting \( ϕ^± \) and \( Q^± \)
as the local geometry and nematic field in the neighborhood
of ±1/2 defects, Eq. (9) in the neighborhood of a defect
simplifies to

\[ \frac{dx}{dt} = 0, \]
\[ \frac{dy}{dt} \]
\[ \frac{dϕ}{dt} \]
\[ \frac{dR}{dt} \]
Figure 3: **Defect texture and geometry.** We numerically integrate Eqs. (8) and (9) (with the substitution $\partial_t \rightarrow D_t$) to obtain steady state plots of (a) the magnitude of the nematic order parameter $|Q|$ and (b) the curvature density (given by $-4\partial\partial\varphi$). We note that the sign of the curvature correlates with the sign of the defect, and that the defect configuration is a lattice of $+1$ bound states separated by pairs of $-1/2$ defects. In the inset, we show the profile of the nematic order $|Q|$ (blue) and $\varphi$ (red) along the $x$-axis. The profile of $|Q|$, which is dictated by the nematic coherence length, is smaller than the width of the profile of $\varphi$ since $\ell_\varphi > \xi$. Parameters for simulations: $\alpha = -0.8$, $K = 1$, $K' = 0$, $\gamma_Q = \gamma_\varphi = 1$, $K_\varphi = 4$, and $\epsilon = 2$, in terms of which $\xi = 1$, $\ell_{R,Q} = 1$, and $\ell_\varphi = 2$. See text and the Supplemental Material [27] for details.

in [19]. Activity plays a key role in stabilizing this configuration, and in particular, the $+1$ bound state is a result of balance of Coulombic repulsion between the defects and active motility [27]. Indeed, the larger the activity parameter for the extensile case $\alpha < 0$, the tighter is the $+1$ bound defect. Moreover, the curvature is positive near a plus defect, and negative near a minus defect, as can be seen in Fig. 3(b).

20 Plotting the profiles of $|Q|$ and $\varphi$ along the vertical $x$-axis, we find that the peak in $\varphi$ near the origin indicates outward bulging of the geometry. Moreover, the profile of $|Q|$ which is dictated by the nematic coherence length is much narrower than the width of $\varphi$ along the $x$-axis, which is expected given that the geometric coherence length is larger than the nematic coherence length, i.e. $\ell_\varphi > \xi$ and similar to what was observed experimentally in [17] and in numerical simulations of phase field models e.g. [42]. (See [27] for a plot of the flow field at a late time).

To ground these results, we turn to observations of epithelial morphogenesis in *Hydra*, a small, fresh-water basal marine invertebrate that has been a model organism for studying the dynamics of body shaping [19, 43, 44]. The tubular body of the organism consists of a bilayer of epithelial cells which contains condensed supracellular actin fibers which align parallel to the body axis in the outer (ectoderm) layer and perpendicular to the body axis in the inner (endoderm) layer [45]. A variable number of tentacles form a ring around the body, near the head, and form when a single $+1$ defect is surrounded by a pair of $-1/2$ defects [19], with the sign of the curvature is correlated with the sign of the defect, consistent with our results summarized in Fig. 3. Indeed, a qualitative rendering of the shape associated with the presence of these bound defect states shown in Fig. 4(a) provides a simple projective view of the body plan in the neighborhood of the ring of tentacles.

Although knowing the intrinsic geometry does not always allow us to deduce the extrinsic geometry, it is possible to get a numerical approximation (see SI-Algorithm for finding embedding) of the local shape of the active surface as shown in Fig. 4(b),(c) near a $+1$ defect. Furthermore, we see that at early times the time evolution of the height follows the scaling law $h \propto \sqrt{t}$, which can be analytically derived by using Eq. (10) (see SI-Algorithm for finding embedding).

Our minimal framework coupling the dynamics of an active nematic field on a curved surface to the intrinsic geometry of the surface via relaxational dynamics has focused on the interplay between geometry and nematic defects and leads to three simple conclusions: (i) the sign of the curvature is correlated with the sign of the defect, (ii) cells accumulate and form mounds at positive defects and are depleted at negative defects, and (iii) a stationary ring configuration of equally spaced $+1$ defects separated by pairs of $-1/2$ defects can form. These results are consistent with experimental observations in different systems such as neural progenitor cells in-vitro and *Hydra* morphogenesis in-vivo. Moving forward, a more complete description must include a complete characterization of the dynamics of embedding and the possible time-dependence of isothermal coordinates, e.g. using phase field models for active deformable shells [42, 46] that account for both the induced and the intrinsic geometry of the manifolds, but now including feedback on activity of the form $\alpha = \alpha(Q^{ab}, g_{ab}, \ldots)$, potential directions for future work. Indeed, a recent preprint [47] submitted after the first version of the current paper was submitted has begun to address some closely-related questions.

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Figure 4: **Extrinsic geometry.** In (a), sketch of the geometry for the tentacle configuration from our simulation. The black dots represent +1 defects, the stars represent −1/2 defects, and black lines depict the nematic order. Three of the −1/2 defects are on the opposite side. In (b) and (c): snapshots from simulations of height u of tentacle in real space near a +1 defect for early and late times, where insets (adapted from [19]) are snapshots of tentacle formation near a +1 defect for early and late times. In (d), plot of the height h(t) at the center of the +1 defect as a function of time t. Red points are data from simulation and blue curve is the fit h(t) = h_0 [1 − exp(−t/τ)]^{1/2}, where we find that h_0 = 3.8L and τ = 0.01τ_ϕ. Initially, h(t) ∝ \frac{t}{\ell} \frac{L}{\tau} L \sqrt{\frac{t}{\tau_ϕ}} and τ ∝ τ_ϕ. See the Supplemental Material [27] for details. All plots use rescaled coordinates x' = x/L, y' = y/L, and t' = t/τ_ϕ.
In deriving this equation, we used the fact that up to a total derivative, $R \text{Tr}(Q^2) = 2(|\nabla_z Q|^2 - |\nabla_z Q|)^2$. So that the active stresses are balanced by the local substrate friction.

In the limit that $K/(\alpha \mu L^2), \gamma/(\mu L^2) \ll 1$, where $\gamma$ is the viscosity coefficient, we can neglect the elastic stress $\sigma_{ab}^{\text{el}} \sim [Q, \frac{\delta F}{\delta Q}]_{ab}$ and viscous stress $\sigma_{vis}^{\text{vis}} \sim \gamma(\nabla^i v^i + \nabla^i v^i)$, so that the active stresses are balanced by the local substrate friction.

In deriving this equation, we used the fact that up to a total derivative, $R \text{Tr}(Q^2) = 2(|\nabla_z Q|^2 - |\nabla_z Q|)^2$.