

Active patterns, geometry, and growth during morphogenesis

A Thesis

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by

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DECLARATION

This thesis is a presentation of my original research work. Wherever contributions of others are involved, every effort is made to indicate this clearly, with due reference to the literature, and acknowledgement of collaborative research and discussions.

The work was done under the guidance of Professor Vijay Krishnamurthy at the International Centre for Theoretical Sciences, Tata Institute of Fundamental Research, Bengaluru. Professor Vishal Vasan served as co-supervisor.



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In my capacity as supervisor of the candidate's thesis, I certify that the above statements are true to the best of my knowledge.



Vijaykumar Krishnamurthy

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List of Figures

1.1	Stages of development of a zebrafish	13
1.2	Mechanochemical models of pattern formation	16
2.1	Schematic: Actomyosin patterns in cells confined to micro-patterned substrates	19
2.2	Linear stability analysis of the equations on a disk-shaped domain . . .	27
2.3	Analytical results for a disk from the truncated model	29
2.4	Numerical results for a disk	30
2.5	Harmonic deformations of a disk	32
2.6	Patterns and phase diagram for higher mode deformations of a disk. . .	33
2.7	Patterns on a square	34
3.1	Schematic: Determinate, indeterminate growth, and schematic of a hydrodynamic model for a growing tissue	48
3.2	Model with imposed boundary stress: System size dynamics and long-time behavior of the displacement and velocity fields.	49
3.3	Fully autonomous model with activity: System size dynamics, long-time behavior of the displacement, velocity and density fields and contour plots of the final size and growth rates	56
3.4	Fully autonomous model with activity: Stresses in the homogeneous steady state and perennially growing phase	57
3.5	Fully autonomous model with activity: Oscillatory solutions	57
3.6	Fully autonomous model with activity: Long time limit of the fields for different boundary conditions on the cell density	60
3.7	Checks for implementation of moving boundary: Comparison of analytical and numerical solution for diffusion on a growing domain with prescribed velocity	66
4.1	Typical cellular processes that lead to large-scale anisotropies in tissue morphogenesis.	70
4.2	Schematic: Constructing a nematic tensor	70
4.3	Illustration of flow fields due to contractile and extensile nematic.	74

4.4	Simulation results for model with displacement, density, velocity fields for a few select parameter values.	75
4.5	From the experimental data, length of the long axis of the growing explant in time.	77
4.6	Quantification of cell shapes of the growing explant	77
4.7	Simulation results for the model with a displacement, velocity and nematic field and given morphogen forcing.	79
4.8	Long axis from model with different strengths of alignment terms. . . .	80

List of Tables

Table 2.G: Integrals in the Galerkin truncated equations	42
Table 4.1: Parameters in the simulation of the model with displacement, density, velocity and nematic field.	81
Table 4.2: Parameters in the simulation of the model with displacement, velocity and nematic fields, and a morphogen forcing	82

"If we wish to understand the nature of the universe, we have an inner hidden advantage: we are ourselves little portions of the universe, and so carry the answer within us."

– **Jacques Boivin**, The Heart Single Field Theory

Contents

Acknowledgements	3
List of figures	6
List of tables	7
Abstract	11
1 Introduction	12
1.1 Interplay of growth, geometry and patterning in development	12
1.2 Historical and conceptual context	15
1.3 Central questions	16
1.4 Thesis outline	17
2 Influence of boundary geometry on active patterns	18
2.1 Introduction	18
2.2 Model	20
2.3 Effective model for the patterns	21
2.4 Patterns on different shapes	26
2.5 Discussion	34
Appendices	36
2.A Deriving the thin-film limit of the cortex equations	36
2.B Cortical vs cytoplasmic flows	37
2.C Helmholtz theorem for a vector field on the plane	38
2.D Uniqueness of the boundary value problem for C and D	40
2.E Invertibility of the Dirichlet-Neumann operator	41
2.F Solving for C and D	41
2.G Integrals in the Galerkin truncated equations for a disk	42
2.H Finite element method for the model equations	42
3 A hydrodynamic model for determinate and indeterminate growth of tissues	45
3.1 Introduction	45

3.2	Model	46
3.3	Imposed boundary stress: Two special solutions	49
3.4	Fully autonomous model: Activity-controlled determinate and indeterminate growth phases	53
3.5	Discussion	58
	Appendices	59
3.A	Invertibility of the map from the moving domain to the fixed domain . .	59
3.B	Fully autonomous model: Sensitivity to diffusion, boundary conditions	61
3.C	Numerical method	61
3.D	Benchmarking the solution	62
3.E	The constitutive model is <i>not</i> Kelvin-Voigt at finite strain	67
4	Symmetry breaking in shape arising from tissue anisotropy	69
4.1	Introduction	69
4.2	A hydrodynamic model for an anisotropically deforming tissue	71
4.3	Growth dynamics of zebrafish explants and comparison to our model .	76
4.4	Summary	80
	Appendices	81
4.A	Parameters in the model with a nematic field	81
4.B	Parameters in the model with a nematic field and morphogen forcing .	82
5	Conclusions and perspectives	83
	List of publications	86
	Bibliography	86
	Index	97

Abstract

The emergence of shape and form in living systems remains one of the central open questions in developmental biology. In this thesis, we explore the interplay between pattern formation, change of form, and growth in development, using a continuum modeling framework.

First, we explore the couplings between the geometry of a fixed cellular confinement and patterns in the actomyosin cortex of cells. On an arbitrarily shaped two dimensional domain, we develop a framework for the Galerkin analysis of such patterns far from the linear stability regime. For a circular disk, our analytical results predict transitions from isotropic to anisotropic patterns as the Péclet and Damköhler number in the model are tuned. This is confirmed by an explicit numerical solution of the model. Extending our numerical analysis to harmonic deformations of the disk, we show that the emergent patterns are sensitive to the boundary curvature.

Next, we make the domain deformable and explore the interplay of patterns in cell number density, displacement, and velocity, in ensuring size control in growing tissues. We uncover two special solutions depending on the competition between tissue elasticity and strength of the active stress – a homogeneous steady state, and a perennially growing phase. We find explicit expressions for the final size and growth rates respectively, in these two special regimes. The model also shows oscillatory solutions at low birth-death rates of the tissue. In 2D, the phases persist but growth is isotropic unless heterogeneities in the initial conditions for the fields and/or shape are imposed.

Finally, we include the dynamics of an orientation field in the simple model above. The orientation field represents alignment of cell division axes and/or cell rearrangement directions and/or cell shape axes. Including this degree of freedom, we observe, in addition to states where the domain spontaneously changes shape from a circular to an elliptical shape, sustained time-dependent states. We then adapt the model to include observations from a real experimental system, viz explants of zebrafish embryos, and observe qualitative agreement between our simulations and the experimental system.

Chapter 1

Introduction

Living matter is maintained out of thermodynamic equilibrium by a continuous throughput of energy. This energy drives morphogenesis – the process by which tissues and organs acquire their shape and form. Morphogenesis underlies the broader program of development that transforms a single fertilized cell into a complex, functional organism, with robust size, shape, and organization.

The study of morphogenesis requires integrating physical principles with biological regulation. As tissues grow, their changing geometry both constrains and enables the emergence of spatial patterns, which, in turn, guide and regulate further growth during development. These coupled dynamics can be formalized through mechanochemical models, which capture how stresses, flows, diffusion, and reaction kinetics interact to produce organized structures. By situating development within a framework of nonequilibrium statistical mechanics, such models highlight how continuous energy flux sustains the emergence of order, linking microscopic interactions to macroscopic form.

1.1 Interplay of growth, geometry and patterning in development

Development involves a fascinating interplay between spatio-temporal organisation (patterns), increase in macroscopic size of the system (growth), and change of form (shape). While these processes typically unfold simultaneously, especially in early embryogenesis, they are often studied independently of each other. However, the interplay between growth and patterns is crucial for development. In this section, we illustrate this for two model organisms, viz the zebrafish *Danio rerio* and the fruit fly *Drosophila melanogaster*.

The underlying principles of development are primarily studied in a handful of model organisms, chosen for their experimental tractability. These organisms typically

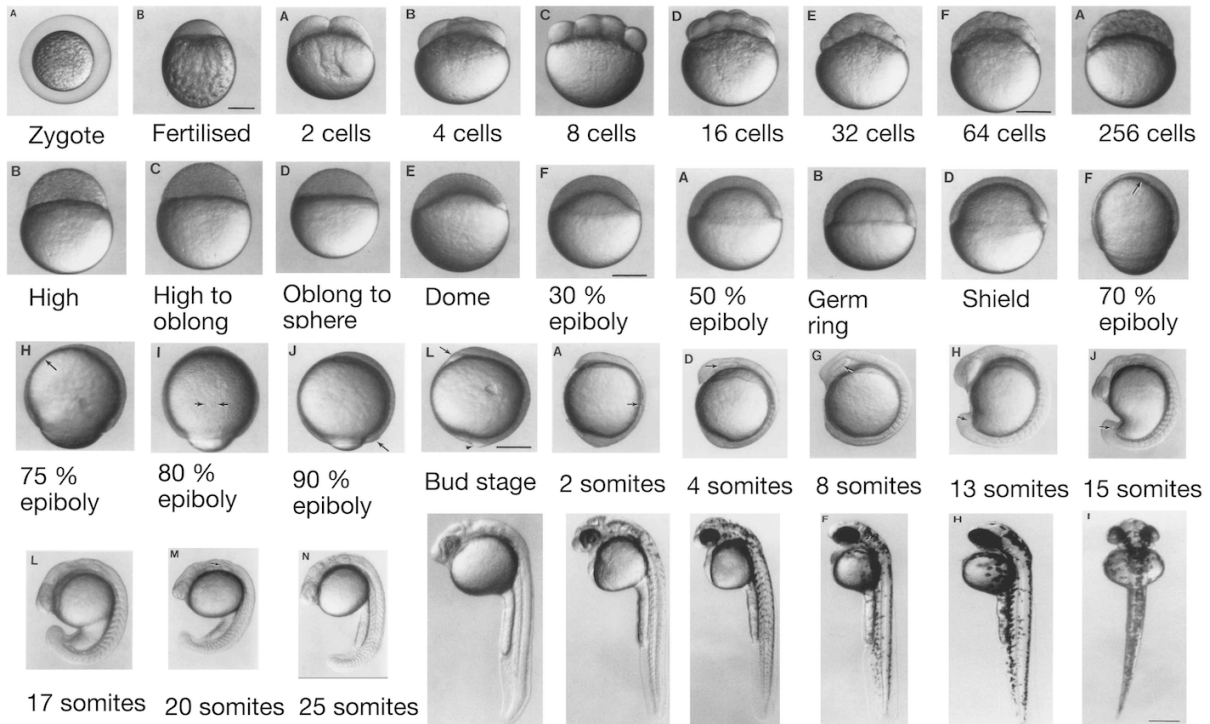


Figure 1.1: Stages of development of a zebrafish, as explained in [1]. After fertilization, the actin cytoskeleton – a thin meshwork of actin filaments, myosin motors and other proteins sitting below the plasma membrane of the cell – contracts and squeezes the non-yolky cytoplasm into the animal pole of the egg. This separates the cytoplasmic cap from the underlying yolk. The cap undergoes rapid cleavage. Cells that retain connection with the yolk form the yolk syncytial layer. Cleavage is followed by epiboly – where the cap cells cover the yolk. At 50% epiboly, when the cells have covered about half the yolk, a thickening – called the germ ring – occurs throughout the margin of the cells undergoing epiboly. This is followed by the shield stage – a localized thickening at the future dorsal (back) side of the embryo. As epiboly proceeds, convergence and extension movements take place, followed by formation of precursors of skeletal fragments called somites. Growth in the pre-somitic mesoderm happens in tandem with gene expression waves so that somites form at the right location, and are of the right size. This is the famous clock and wavefront model of somitogenesis. It is followed by organogenesis – optic vesicles and other cranial structures become more defined. By 48 hours, the embryo shows twitching and swimming like movements, and swims away. This figure is reproduced with permission from [1].

share several advantageous characteristics, such as fully sequenced genomes, rapid and well-characterized embryonic development, and short generation times.

Zebrafish are particularly valuable because their embryos are optically transparent, allowing direct visualization of internal organs and developmental processes. Zebrafish development proceeds through a sequence of distinct stages (see fig. 1.1): early rapid cell divisions post-fertilization (cleavage), the spreading of cells over the yolk (epiboly), coordinated cell movements establishing the three germ layers (gastrulation), followed by formation of somites (which are precursors of skeletal fragments). At various stages in its development, patterning processes, growth, and change of form, work in tandem to ensure the robustness of development. It has been shown, for instance, that during the cleavage stage, the geometry of the embryo guides asymmetric cell divisions [2,3]. These divisions are responsible for gradients in cell sizes and cell cycle progression, and therefore, patterns in cell fate. Further, at the epiboly and gastrulation stages, patterns in signaling morphogens (*Wnt*, *Nodal* and *BMP*) guide convergence-extension movements, and geometry dictates how germ layers are positioned. At the somite formation stage, coordination between the segmentation clock (a molecular oscillator that drives the formation of somites) and growth in the tissue anterior to the tip of its tail is important to ensure the right number, size and placement of somites [4]. Finally, at the post-embryonic stage, growth orients and scales striped pigmentation patterns, but sometimes qualitatively alters them [5].

The fruit fly *Drosophila melanogaster* has been a cornerstone of developmental biology for over a century, owing to its short generation time of about two weeks, small and well-annotated genome, and the availability of powerful genetic tools that allow precise manipulation of gene expression. In the early fly embryo, large-scale tissue flows are guided by the spatial distribution of myosin motors, with dorsal-ventral symmetry breaking providing the patterning cues that regulate deformation, while the embryo's geometry constrains how tissues move [6,7]. In imaginal discs – epithelial sacs of precursor cells found in larvae that develop into adult structures such as wings, legs, antennae, and eyes – morphogens such as *Dpp* and *Wingless* establish spatial patterns that guide cell fate and proliferation. The Hippo pathway integrates these biochemical signals with mechanical cues from tissue tension and cell-cell contacts, thereby regulating organ size and ensuring that discs achieve the correct geometry before metamorphosis [8,9].

This thesis explores three examples of minimal physical models coupling these aspects of morphogenesis, viz pattern formation, growth and change of form. In the next section, we survey some of the diverse ways in which such problems have been approached until now.

1.2 Historical and conceptual context

Patterns are ubiquitous in nature, and have inspired many a philosopher and artist. In his landmark 1952 paper [10], *The Chemical Basis of Morphogenesis*, Alan Turing proposed that diffusion and reaction of interacting chemicals can spontaneously generate patterns. This diffusion-driven instability has since been linked to phenomena such as the Belousov–Zhabotinsky reaction and pigmentation patterns in fish and animal coats. Yet Turing himself recognized that chemical interactions alone could not fully explain the emergence of biological form – "Well, the stripes are easy, but what about the horse part?", he is alleged to have said with regard to the zebra [11]. He advocated for a mechanical basis of morphogenesis, envisioning models that integrate chemical patterning with tissue growth, geometric transformations, and mechanical stresses – capturing the interplay between biochemical signals and the physical forces that shape living organisms.

Turing's 1952 paper, and extensions thereof, assumed fixed domains/quasi-statically changing domains. Real tissues, however, grow and deform simultaneously with pattern formation processes. D'Arcy Thompson's 1917 classic [12] *On Growth and Form* emphasized geometry, scaling and physical laws in shaping organisms, and used the theory of transformations to compare related morphologies. In the 1980s and 1990s, Murray and Maini systematically studied reaction–diffusion systems on growing domains, demonstrating how tissue expansion modifies pattern selection, directly linking mathematical biology to embryonic development [13]. Parallel advances in continuum mechanics came from Rodriguez, Hoger, and McCulloch [14], who introduced morpho-elasticity in the multiplicative decomposition of the deformation gradient into growth and elastic parts. This formalism provided a rigorous way to connect growth, geometry, and elasticity, and was later generalized by Goriely [15, 16] into a comprehensive mathematical framework for biological growth, emphasizing incompatibility, residual stresses, and mechanical instabilities.

Mechanochemical models also advanced during this period. These were mechanical analogues of Turing's activator/inhibitor system with different diffusivities. In avian feather bud patterns, for instance, mesenchymal cells migrate on an elastic substratum. The elastic resistance of the extra-cellular matrix (ECM) acts as an inhibitor and tunes the spacing between mesenchymal cell clusters [17, 18]. Oster and colleagues integrated extracellular matrix mechanics, cell density, and chemical signaling, highlighting how tissues couple biochemical and mechanical cues [19]. More recent active mechanochemical models [20, 21] showed how contractility of actomyosin drives flows, which feed back on myosin patterns via advection (see fig. 1.2). Friction inhibits flows and reduces the length scale between rings of actin in the trachea of *D. melanogaster* [21].

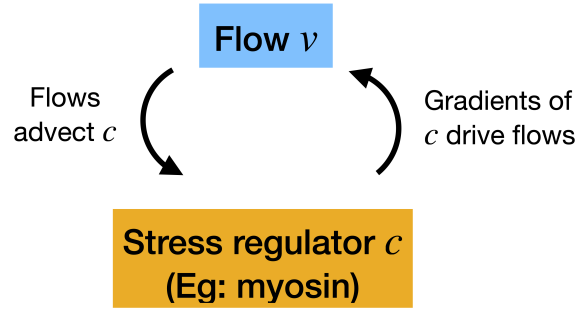


Figure 1.2: An example of a mechanochemical model, where gradients in the concentrations of stress regulators drive flows, and flows advect the concentration field of the stress regulator.

Recent work on growth has focused on scaling and size regulation in development [22, 23], distinguishing determinate and indeterminate growth phenotypes. In parallel, models with tissue anisotropy have introduced orientation fields into growth dynamics, offering new ways to capture directional patterning. Current models often treat growth and pattern formation separately rather than as a coupled dynamical system. It is not well-understood how mechano-chemical patterns are influenced by dynamically growing domains / domains with a non-trivial boundary shape, although this understanding is relatively better developed for Turing models [24–26]. Geometry defines boundary conditions and can provide long-range mechanical guidance for embryogenesis [27]. Geometry also distorts patterns: For instance, buckling of villi in chick embryos distorts the gradient of the morphogen Sonic Hedgehog (SHH) and restricts cell proliferation at the base of the villi [28]. Thus, geometry and pattern formation are co-dependent, in general. What about the couplings between growth and pattern formation? What are the emergent growth behaviors arising from patterns in scalar, vector and tensor fields? Current approaches [15, 16] need a prescription for the dynamics of the growth tensor, focusing on the consequences of growth (change of form), not the causes – What are the physical and biological mechanisms (advection, dilution, diffusion and reactions) that result in different kinds of macroscopic growth behaviors?

1.3 Central questions

The central questions this thesis tries to address include the following:

1. How do active mechano-chemical patterns "sense" boundary geometry? In a simple model for patterns in the actomyosin cortex of cells, how do the patterns change as the geometry of cellular confinement is changed?

2. How do biological tissues regulate their sizes? What sets the final size and growth rates? Does an asymptotic size always exist? If not, what is the mechanistic basis of determinate and indeterminate growth phenotypes [22,23]?
3. How do symmetry-breaking shapes emerge in growing tissues from local anisotropy? How do the results of such a model compare to experiments?

1.4 Thesis outline

The three chapters following the introduction of this thesis encompass three examples of the couplings between patterning, growth and change of form in morphogenesis.

In **Chapter 2**, we ask how boundary geometry affects active mechanochemical patterns. This is in context of a simple model for patterns in the actomyosin cortex of cells. It is well-known that the homogeneous steady state of this model is unstable to inhomogeneous perturbations at high activity. However, much of the analysis for the model is done for unbounded/periodic domains. The cell, nonetheless, is a bounded system, with a non-trivial shape. As micro-patterning experiments reveal with respect to patterns in concentration and orientation of cyto-skeletal structures, the geometry of cell confinement has a non-trivial impact on these patterns. Our aim in this work was to develop an analytical and numerical framework to solve for actomyosin patterns on arbitrarily-shaped flat geometries.

In **Chapter 3**, we explore the emergent growth dynamics in a continuum model for a growing tissue. We uncover determinate and indeterminate growth phases, depending on the competition between tissue elasticity and strength of the active stress at the tissue boundary. Remarkably, both these phenotypes appear in the same mechanochemical model, though they appear in evolutionarily divergent species. An extension of this model to tissues with inhomogeneous material parameters leads to the possibility of understanding proportionate growth in such systems.

In **Chapter 4**, we study how a nematic order parameter in the simple model for a growing tissue developed in chapter 3 leads to the emergence of non-isotropic shapes. This nematic field is representative of alignment of cell intercalation directions and/or cell shape axes and/or cell division axes. Exploring the parameter space for this model, we discover a plethora of possible shapes and orientation patterns, including sustained time-dependent states. We then adapt this model to study the elongation dynamics of explants from zebrafish embryos. Incorporating experimentally seen signaling profiles of Wnt, our model predictions agree qualitatively with experimental data.

Finally, in **Chapter 5**, we conclude with a summary, scope and limitations of our work, and discuss possible extensions and generalizations.

Chapter 2

Influence of boundary geometry on active patterns

2.1 Introduction

Pattern formation is a key driver of morphogenetic events at the cellular and tissue scales. The spatiotemporal variation of chemical concentration fields, flow fields, and filament orientation fields are implicated in many morphogenetic patterns. Many such patterns are mechanochemical in nature: chemical reactions and mechanical forces are fundamentally intertwined with each other. The origin of mechanical stresses can be traced to the forces generated by the energy consuming activity of molecular motors in the cellular cytoskeleton. Mechanochemical patterns in the actomyosin cytoskeleton are known to drive many cellular processes such as polarity establishment [29, 30], cell division [31], and cell motility [32–34]. Even large scale shape deformations of tissues, such as wound healing and convergence-extension movements, are influenced by actomyosin patterns [35–37].

The actomyosin cortex – a thin meshwork of actin filaments, myosin motors and associated cross-linking proteins located just beneath the plasma membrane – is an excellent candidate for mechanochemical pattern formation [38]. Myosin motors use the energy released in ATP hydrolysis to tug antiparallel actin filaments, generating contractile active stresses in the process [39]. Large scale gradients in these active stresses drive hydrodynamic flows [40]. At high activity, advective fluxes can overcome the homogenizing effects of diffusion and lead to spatiotemporal patterns [20, 41, 42].

Theoretical studies of pattern formation typically consider a fixed geometry – usually Cartesian domains with periodic or no-flux boundaries. On the other hand, morphogenetic patterns in cells and tissues display patterns on dynamical shape-shifting geometries. The dynamics of shape change is itself controlled by the mechanochemical stresses generated in the system. The resulting feedback between patterns and

shape leads to very non-trivial problems. An intermediate case is to consider the regime where the timescales for shape change are longer than the timescales associated with the formation of patterns. In this quasi-static regime, one can study the effect of boundary shape on pattern selection. For reaction-diffusion dynamics, such as Turing systems, the role of boundary geometry in selecting patterns (even on dynamical domains with prescribed deformations) has been studied [24,26,43]. The evolution of parr-mark patterns from stripes to spots during the growth of Amago trout is an example of such a system [24]. However, the role of boundary geometry in controlling mechanochemical patterns has not been explored extensively. Experimentally, such mechanochemical patterns are seen in cells plated on micropatterned substrates with controlled boundary shape. For instance, cells adapt their actomyosin cortical patterns in response to the geometry of their confinement [44–47] (see Figure 2.1).

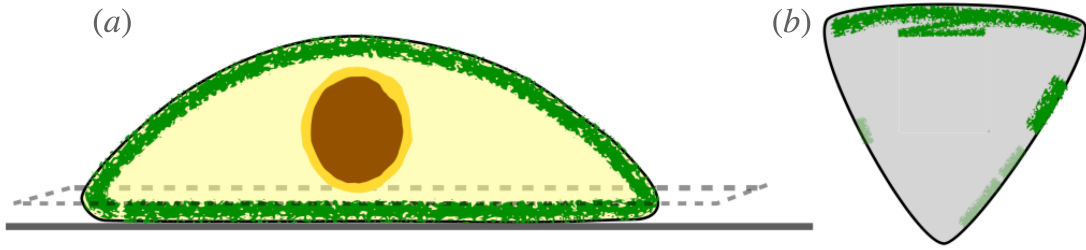


Figure 2.1: (a) The actomyosin cortex of cells (green) is a thin film of active matter. The plane shows a cross section for these cells. (b) Concentration patterns seen in nearly flat cells laterally confined in micro-patterned substrates are sensitive to the geometrical shape of the confinement. This schematic figure is motivated by the results in [44,45].

In this chapter, we consider a minimal mechanochemical model for the actomyosin cortex modeled as a thin film of an active material. The transport equation for the concentration field of an active stress regulator is coupled to the fluid flow resulting from active hydrodynamics. Considering finite-sized arbitrarily shaped two-dimensional domains with no-flux boundary conditions, we set up a general formalism to write an effective Galerkin truncated model for the dominant modes of the patterns. On a circular domain, our analytical predictions for the existence of anisotropically localized concentration patterns at the boundary, and their transition to isotropic patterns with change of activity and turnover rate, is in very good agreement with explicit numerical simulations of the model equations. For geometries that are perturbations of the circular disk, we find that the patterns can spontaneously localize at regions of high or low boundary curvature depending on parameters. Our results on triangular shaped domains show remarkable similarity with experimentally observed patterns. The transitions between various patterns predicted by our model with change in geometry can be tested experimentally.

2.2 Model

The actomyosin cortex is a viscoelastic gel. A very good description of this material is to consider it as an active viscoelastic fluid. We assume that we are operating at timescales greater than the Maxwell relaxation time for the cortex (~ 5 s) and develop an active fluid model. This thin-film model can be derived from the full 3D model [see Appendix 2.A] under the assumptions that the cortex thickness does not change in time, and hydrodynamic fields do not vary along the thickness of the cortex. Moreover, in the complete description, flows in the cortex, sourced by the contractility of the actomyosin system, are coupled to the cytoplasm via the passive stresses generated therein. It can be shown that these stresses are small compared to the stresses in the cortex [see Appendix 2.B]. Thus, we neglect cytoplasmic flows and their effects on cortical flows in our model.

Following [20], we consider the actomyosin system as a one-component fluid in which myosin motors are immersed. The concentration field changes due to diffusion, advection, dilution and turnover with the cytoplasm. Thus, we have,

$$\partial_t c + \nabla \cdot (vc) = \mathcal{D} \nabla^2 c - \kappa(c - c_0) \quad (2.1)$$

where c is the effective 2D concentration of actomyosin, v is the effective 2D flow field, $\mathcal{D}$ is the diffusion constant, κ is the turnover rate and c_0 is the base-level of the concentration field. The flow field v arises from force-balance: In the low-Reynolds number limit, the divergence of a total stress Σ balances friction against the membrane/cytoplasm. That is,

$$\gamma v = \nabla \cdot \Sigma \quad (2.2)$$

where γ is the friction coefficient and Σ is given by

$$\Sigma = (\eta_b - \eta)(\nabla \cdot v)\mathbb{I} + \eta[\nabla v + (\nabla v)^T] + \zeta \Delta \mu f(c)\mathbb{I}, \quad (2.3)$$

where η_b and η are the effective 2D bulk and shear viscosities, $\mathbb{I}$ is the identity tensor, $f(c)$ is the active stress regulation function, and $\zeta \Delta \mu$ is the active stress strength. We choose a Hill function response for the active stresses: $f(c) = c/(c + c_s)$, where c_s is a saturation concentration beyond which the active stresses asymptote to a constant. The active stress is isotropic in-plane. We have neglected degrees of freedom associated with the orientation of actin filaments.

Boundary conditions are no-flux for the concentration and zero velocities at the

boundaries:

$$v|_{\partial\Omega} = 0; \quad (\hat{n} \cdot \nabla c)|_{\partial\Omega} = 0, \quad (2.4)$$

where $\hat{n}$ is the outward unit normal in the domain. Since f is a function of c , this implies that $(\hat{n} \cdot \nabla f)|_{\partial\Omega} = 0$. On the boundary $\partial\Omega$, the unit normal $\hat{n}$ and the unit tangent $\hat{\tau}$ are such that $\hat{n} \cdot \hat{\tau} = 0$ and we assume $\hat{n} \times \hat{\tau} = \hat{z}$. We also define the normal derivative $\partial_n \equiv \hat{n} \cdot \nabla$ and the tangential derivative $\partial_\tau \equiv \hat{\tau} \cdot \nabla$ on the boundary. Scaling $x \rightarrow x \ell$, $t \rightarrow t \ell^2/D$, $c \rightarrow c c_0$, where $\ell = \sqrt{\eta/\gamma}$, the non-dimensional equations and boundary conditions are

$$\partial_t c = -\nabla \cdot (vc) + \nabla^2 c - R(c - 1), \quad (2.5)$$

$$\nabla^2 v + (\nu^2 - 1)\nabla(\nabla \cdot v) - v = -P \nabla \left(\frac{c}{c + c_*} \right), \quad (2.6)$$

where the Damköhler number $R = \kappa \ell^2/D$ compares the turnover timescale κ^{-1} with the timescale for diffusion on a length-scale ℓ , and the Péclet number $P = \zeta \Delta \mu / \gamma D$ is the ratio of activity to diffusion. The other non-dimensional parameters are $c_* = c_s/c_0$, the ratio $\nu^2 = 1 + \eta_b/\eta$, and those associated with the size and shape of the domain Ω , such as the ratio of the domain size to the hydrodynamic length, the aspect ratio for the domain, etc.

2.3 Effective model for the patterns

In this section, we first develop a formalism to solve (2.6) on any closed two-dimensional domain Ω of arbitrary shape. Using this framework, we setup a linear stability analysis calculation of the system (2.5) and (2.6) around the homogeneous state ($c = 1, v = 0$). Next, we will develop a Galerkin truncated system of equations for the expansion coefficients of the concentration field. These equations will provide an effective low-dimensional model that, as we will demonstrate in Section 2.4, predicts the phase-diagram of the concentration patterns even in the nonlinear regime.

Let ψ_j be the orthonormal Neumann eigenfunctions of the Laplace operator on Ω , i.e., $\nabla^2 \psi_j = -\lambda_j \psi_j$ with $\partial_n \psi_j|_{\partial\Omega} = 0$, $\lambda_j \geq 0$, and $\int_\Omega \psi_j^\dagger \psi_k = \delta_{jk}$ where $\dagger$ represents complex conjugation. The ψ_j form an orthonormal basis for expanding any function. Note that j is, in general, a multi-index. Furthermore, the eigenfunction corresponding to the zero eigenvalue is a constant on Ω and $\int_\Omega \psi_j = 0$ for $\lambda_j > 0$. In particular, we write

$$c(x, t) = 1 + \sum_k c_k(t) \psi_k(x), \quad (2.7)$$

where the summation is over the eigenfunctions ψ_k with eigenvalues $\lambda_k > 0$. We now multiply (2.5) by $\psi_j^\dagger(x)$ and integrate over Ω to obtain

$$\frac{dc_j}{dt} = -(\lambda_j + R) c_j + \int_{\Omega} \nabla \psi_j^\dagger \cdot (vc), \quad (2.8)$$

where we have performed an integration by parts and used the boundary condition $v|_{\partial\Omega} = 0$. If we can now express the flow v in terms of the concentration c , we will get a closed system of equations for the c_j . Note that this will lead to an infinite hierarchy of equations for the c_j . To obtain an effective reduced dynamical system, we shall truncate the expansion (2.7) by retaining only a few dominant eigenfunctions. A phase-space analysis of this dynamical system will then yield a phase-diagram of the possible patterns.

It may be important here to contrast finite arbitrary domains with periodic/infinite domains. On an unbounded or periodic domain, the Fourier modes are simultaneous eigenfunctions of the Laplacian, and of every operator in the linearised dynamics. The stability analysis then factorises: each wavevector contributes an independent block, and the spectrum follows from a dispersion relation. On a finite domain, this no longer holds. Expanding a perturbation in the Laplacian eigenbasis diagonalises only the diffusive part of the dynamics. The advective couplings are not functions of the Laplacian alone, so they do not share these eigenfunctions, and, instead, connect distinct modes.

For a given active stress function f (equivalently, given c), an explicit solution of the flow equation (2.6) is straightforward only in the case of simple rectangular domains. For more complicated boundary geometries, it is a non-trivial task to obtain a solution for v satisfying (2.6) with the boundary condition $v|_{\partial\Omega} = 0$. In the next subsection, we outline a procedure that, in principle, allows us to compute the vector field v given the Green's function for the Dirichlet boundary-value problem for a scalar field satisfying a modified Helmholtz equation. Subsequently, we use this procedure to compute the flow field and then develop the Galerkin truncation for a disk shaped domain.

Solving for the active flows

Defining $C \equiv \nabla \times v = C \hat{z}$ and $D \equiv \nabla \cdot v$, the flow equation (2.6) leads to

$$\nabla^2 C - C = 0, \quad \nu^2 \nabla^2 D - D = -P \nabla^2 f. \quad (2.9)$$

Using (2.6), we get v as

$$v = \nu^2 \nabla D + \nabla_{\perp} C + P \nabla f, \quad (2.10)$$

where $\nabla_{\perp} \equiv \hat{\mathbf{z}} \times \nabla$. Note that, owing to the linear term in $\mathbf{v}$ in the flow equation, we can directly write the above expression for $\mathbf{v}$. Else, flows must be obtained from the curl and divergence of the flow using the Helmholtz decomposition theorem [see Appendix 2.C].

Using (2.10), the flow boundary conditions $\hat{\mathbf{n}} \cdot \mathbf{v}|_{\partial\Omega} = 0 = \hat{\boldsymbol{\tau}} \cdot \mathbf{v}|_{\partial\Omega}$ translate to the following coupled equations

$$\nu^2 \partial_n D - \partial_{\tau} C = 0, \quad \nu^2 \partial_{\tau} D + \partial_n C = -P \partial_{\tau} f. \quad (2.11)$$

It is convenient to work with homogeneous equations. As such, we define

$$D = \mathcal{D} - P \sum_j \frac{\lambda_j f_j}{\nu^2 \lambda_j + 1} \psi_j, \quad \text{with} \quad f_j = \int_{\Omega} \psi_j^{\dagger} f. \quad (2.12)$$

Then C and D satisfy the following homogeneous equations on Ω

$$\nabla^2 C - C = 0, \quad \nu^2 \nabla^2 D - D = 0. \quad (2.13)$$

with the boundary conditions

$$\nu^2 \partial_n D - \partial_{\tau} C = 0, \quad \nu^2 \partial_{\tau} D + \partial_n C = F, \quad (2.14)$$

where

$$F = -P \sum_j \frac{f_j \partial_{\tau} \psi_j}{\nu^2 \lambda_j + 1}. \quad (2.15)$$

Note that in the above equation ∂_{τ} is the tangential derivative evaluated on the boundary $\partial\Omega$. These boundary conditions (2.14) are neither in the Dirichlet form nor in the Neumann form. Nevertheless we show in Appendix 2.D that the boundary-value problem defined by (2.13)-(2.14) has a unique solution.

To obtain a useful representation of the solution to (2.13)-(2.14), we relate the solution to the Dirichlet boundary-value problem associated with (2.13). To this end, suppose Ω is a subset of the plane such that $\partial\Omega$ is parameterized by a twice-continuously differentiable function. Then equations (2.13) possess a unique solution when their respective Dirichlet conditions, i.e., $C|_{\partial\Omega}$ and $D|_{\partial\Omega}$, are prescribed on $\partial\Omega$ [48]. In particular, there exists an operator $\mathbb{L}$ (the ‘Green’s function’ for the Dirichlet boundary-value problem) such that $C = \mathbb{L}(C|_{\partial\Omega})$. Similarly $D = \mathbb{L}_{\nu}(D|_{\partial\Omega})$ with $\mathbb{L}_{\nu=1} = \mathbb{L}$. Moreover, there is a unique Neumann condition corresponding to the solution of the Dirichlet boundary-value problem. Let $\mathbb{G}$ denote the operator which maps the Dirichlet condition $C|_{\partial\Omega}$ to the associated Neumann condition $\partial_n C$ when C satisfies $\nabla^2 C - C = 0$.

In other words, $\mathbb{G}(C|_{\partial\Omega}) = \partial_n C$. Likewise $\mathbb{G}_\nu(D|_{\partial\Omega}) = \partial_n D$ with $\mathbb{G}_{\nu=1} = \mathbb{G}$. The operators $\mathbb{G}$ and $\mathbb{G}_\nu$ are known as Dirichlet-Neumann operators. These operators are self-adjoint and positive, hence invertible (see Appendix 2.E). Further, we show in Appendix 2.F that for a large class of domains Ω , the solution to (2.13)-(2.14) can be expressed in the form

$$C = \mathbb{B}_\nu F, \quad D = \mathbb{A}_\nu F, \quad (2.16)$$

where $\mathbb{B}_\nu = \mathbb{L} \mathbb{K}_\nu^{-1} \mathbb{G}^{-1}$, $\mathbb{A}_\nu = \mathbb{L}_\nu \mathbb{G}_\nu^{-1} \partial_\tau \mathbb{K}_\nu^{-1} \mathbb{G}^{-1}$ and $\mathbb{K}_\nu = \mathbb{G}^{-1} \partial_\tau \mathbb{G}_\nu^{-1} \partial_\tau + \mathbb{I}$ with $\mathbb{I}$ the identity operator. Note that $\mathbb{L}$, $\mathbb{G}$, $\mathbb{L}_\nu$, and $\mathbb{G}_\nu$ can be computed explicitly only for a few domains $\Omega \subset \mathbb{R}^2$. Despite the rarity of explicit solutions to (2.13)-(2.14) due to the nontrivial dependence on the shape of the domain Ω , the cases where explicit solutions are available still provide valuable insight. The reason being that the flow v on a domain Ω is qualitatively similar to the flow on any domain Ω_ϵ that is diffeomorphic to Ω (see Appendix 2.F).

To summarize, using (2.12) and (2.16) we get the formal expressions for the curl and divergence of the flow

$$C = -P \sum_j \frac{\mathbb{B}_\nu \partial_\tau \psi_j}{1 + \nu^2 \lambda_j} f_j, \quad (2.17)$$

$$D = -P \sum_j \frac{\mathbb{A}_\nu \partial_\tau \psi_j + \lambda_j \psi_j}{1 + \nu^2 \lambda_j} f_j. \quad (2.18)$$

and the flow solution

$$v = -P \sum_j f_j \mathbf{u}_j(\mathbf{x}), \quad (2.19)$$

with

$$\mathbf{u}_j(\mathbf{x}) = \frac{\nu^2 \nabla (\mathbb{A}_\nu \partial_\tau \psi_j) + \nabla_\perp (\mathbb{B}_\nu \partial_\tau \psi_j) - \nabla \psi_j}{1 + \nu^2 \lambda_j}. \quad (2.20)$$

In the above expression, it should be noted that though $\partial_\tau \psi_j$ are evaluated at the boundary $\partial\Omega$ of the domain Ω , the result of the action of the operators $\mathbb{A}_\nu$ and $\mathbb{B}_\nu$ on $\partial_\tau \psi_j$ is a function defined on Ω . The gradients ∇ and $\nabla_\perp$ then act on this function leading to the vector field $\mathbf{u}_j(\mathbf{x})$ defined on Ω . The vector fields $\mathbf{u}_j(\mathbf{x})$ act as a basis for the expansion of the v with expansion coefficients f_j .

Linear stability analysis and Galerkin truncation

We now use the formal solution for the flow (2.19) in (2.8) to systematically analyze the resulting patterns in the concentration field $c(\mathbf{x}, t)$.

To analyze the stability of the homogeneous state ($c = 1, \mathbf{v} = 0$), we consider $c(\mathbf{x}, t) = 1 + \delta c(\mathbf{x}, t) \equiv 1 + \sum_j \delta c_j(t) \psi_j(\mathbf{x})$ with $\delta c_j \ll 1$. It is easy to see from (2.8) that only the divergence D of the flow contributes to the evolution of the δc_j at linear order. As such, the corresponding approximation for the expansion coefficient f_j of the active stress regulation function $f(c)$ is given by

$$f_j \approx \frac{c_*}{(1 + c_*)^2} \delta c_j. \quad (2.21)$$

Using this approximation in (2.18), the linearized equations of motion for the δc_j are

$$\begin{aligned} \frac{d\delta c_j}{dt} = & -(\lambda_j + R) \delta c_j + \frac{P c_*}{(1 + c_*)^2} \left[\frac{\lambda_j}{1 + \nu^2 \lambda_j} \delta c_j \right. \\ & \left. + \sum_k \frac{1}{1 + \nu^2 \lambda_k} \left(\int_{\Omega} \psi_j^\dagger \mathbb{A}_\nu \partial_\tau \psi_k \right) \delta c_k \right]. \end{aligned} \quad (2.22)$$

The integral involving $\mathbb{A}_\nu$ and the eigenfunctions ψ_j depends on the geometry of Ω via the Green's function $\mathbb{L}$ and the Dirichlet-Neumann operator $\mathbb{G}$. The evolution equations for the δc_j are coupled to each other. In other words, the linear stability matrix is non-diagonal in the ψ_j basis. This turns out to be a generic feature for most two-dimensional domains. Note that (2.22) holds for all δc_j under the assumption that they are small.

Next, we turn to develop a systematic Galerkin truncation of the modes in the expansion (2.7). We first consider $c_* \gg 1$ and approximate $f(c) \approx c(c_* - c)/c_*^2$. We then use the expansion (2.7) for c , multiply the approximate expression for f by an eigenfunction $\psi_j^\dagger$ and integrate over Ω to get

$$f_j \approx \frac{(c_* - 2)}{c_*^2} c_j - \frac{1}{c_*^2} \sum_l \sum_m c_l c_m \int_{\Omega} \psi_j^\dagger \psi_l \psi_m. \quad (2.23)$$

We now insert the above approximation for f_j in (2.19) and use the resulting expression

for v in the evolution equations (2.8) along with the expansion (2.7). This leads to

$$\begin{aligned} \frac{dc_j}{dt} = & -(\lambda_j + R) c_j - \frac{P}{c_*^2} \left[(c_* - 2) \sum_k \mathcal{E}_{jk} c_k \right. \\ & + \sum_{k,l} \left[(c_* - 2) \mathcal{F}_{jkl} - \sum_n \mathcal{E}_{jn} \mathcal{I}_{nkl} \right] c_k c_l \\ & \left. - \sum_{k,l,m} \left[\sum_n \mathcal{F}_{jkn} \mathcal{I}_{nlm} \right] c_k c_l c_m \right], \end{aligned} \quad (2.24)$$

where the expansion coefficients are

$$\mathcal{E}_{jk} = \int_{\Omega} \nabla \psi_j^\dagger \cdot \mathbf{u}_k, \quad (2.25a)$$

$$\mathcal{F}_{jkl} = \int_{\Omega} \psi_k (\nabla \psi_j^\dagger \cdot \mathbf{u}_l), \quad (2.25b)$$

$$\mathcal{I}_{lmn} = \int_{\Omega} \psi_l^\dagger \psi_m \psi_n, \quad (2.25c)$$

These integrals depend solely on the geometry of the domain Ω (the only material parameter is ν entering via the operators $\mathbb{A}_\nu$ and $\mathbb{B}_\nu$).

In principle, equations (2.24) provide an almost exact and closed set of equations for the time-evolution of the amplitudes c_j in (2.7) – the only approximation being (2.23). However, equations (2.24) are an infinite hierarchy of coupled nonlinear equations for the c_j . As such, to get an effective low-dimensional dynamical system, we will necessarily have to truncate the expansion by retaining only a few c_j . Further, even after this truncation, obtaining an analytically tractable system requires that we are able to evaluate the integrals in (2.25) on the domain Ω . This requires that we know the Neumann eigenfunctions ψ_j of the Laplacian operator, the Green's functions $\mathbb{L}$, $\mathbb{L}_\nu$ for the Dirichlet boundary value problem, as well as the Dirichlet-Neumann operators $\mathbb{G}$, $\mathbb{G}_\nu$. As remarked earlier, analytical expressions for these quantities are possible only in very few cases. However, they can always be computed numerically for any geometry.

2.4 Patterns on different shapes

We parametrize the domain Ω with a generalized set of orthogonal coordinates $\{\xi_1, \xi_2\}$ such that the boundary $\partial\Omega$ is defined as the level set $\xi_1 = a$, where a is a dimensionless number. Following [49], we will use $\eta_b/\eta = 3$ (and hence $\nu = 2$) unless stated otherwise. First, we shall illustrate the formalism developed in the previous section in the case when Ω is a disk of radius a . The phases resulting from both linear-stability analysis and the Galerkin truncation will be compared with numerical solutions of (2.5) and (2.6). Next, we will consider domains that are smooth deformations of the

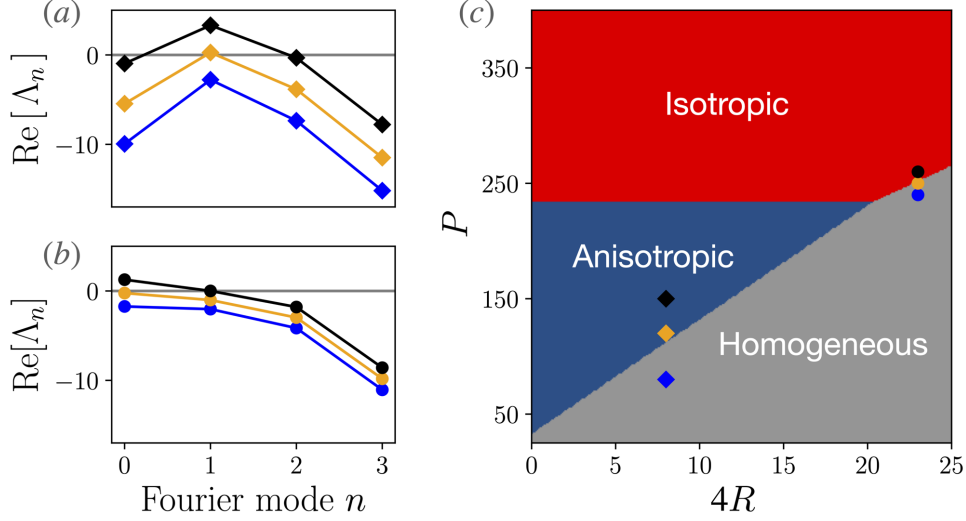


Figure 2.2: Linear stability analysis on a disk-shaped domain. Upon increasing P , the homogeneous state loses its stability with either (a) anisotropic modes having the largest growth rate at small R , or (b) isotropic modes having the largest growth rates at large R . The parameter values corresponding to the dispersion curves in (a) and (b) are marked in (c). The other parameters are fixed at $\mu \equiv a/\ell = 2, c_* = 4$. From the phase-diagram in the $P - R$ plane shown in (c), we conclude that linear stability predicts the pattern will always isotropize at large P .

disk and illustrate how boundary curvature controls the localization of concentration patterns.

Patterns on a disk

On any domain Ω , the Dirichlet values $C|_{\partial\Omega}$ and $D|_{\partial\Omega}$ can be expanded in a suitable orthonormal basis of functions $\{u_n\}$ defined on $\partial\Omega$. The choice of the orthonormal basis $\{u_n\}$ depends on the shape of the domain Ω . On the unit disc, a natural choice is $u_n = (2\pi)^{-1}e^{in\theta}$ for $\theta \in [0, 2\pi]$ and $n \in \mathbb{Z}$. Note the tangential-derivative operator equals ∂_θ in this basis and hence is a diagonal operator. The u_n form an orthonormal basis for the space of square integrable functions on the circle denoted by $L^2(\partial\Omega)$. For such a choice, we note that

$$\langle u_m, \partial_\tau u_n \rangle_{L^2(\partial\Omega)} = \int_0^{2\pi} \frac{d\theta}{2\pi} e^{-im\theta} \partial_\theta e^{in\theta} = in\delta_{mn}. \quad (2.26)$$

On a disk of radius a , the normalized Neumann eigenfunctions of the Laplacian are

$$\psi_{n,k} = \frac{1}{N_{n,k}} J_n \left(\alpha_{n,k} \frac{r}{a} \right) e^{in\theta} \quad (2.27)$$

where J_n is the n^{th} order Bessel function of the first kind, $n \in \mathbb{Z}$, the $\alpha_{n,k}$ satisfy $J'_n(\alpha_{n,k}) = 0$ where $'$ denotes differentiation, $k = 1, 2, 3, \dots$, and the constant $N_{n,k}$ is set

so that $\psi_{n,k}$ has unit L^2 -norm. The eigenvalue corresponding to $\psi_{n,k}$ is $\lambda_{n,k} = \alpha_{n,k}^2/a^2$. Further

$$\mathbb{A}_\nu e^{in\theta} = \frac{in}{\nu} \frac{I_n(a)I_n(r/\nu)}{d_n} e^{in\theta}, \quad (2.28a)$$

$$\mathbb{B}_\nu e^{in\theta} = \frac{I'_n(a/\nu)I_n(r)}{d_n} e^{in\theta}, \quad (2.28b)$$

where $d_n = I'_n(a)I'_n(a/\nu) - n^2 I_n(a)I_n(a/\nu)$ and I_n is the n^{th} order modified Bessel function of the first kind.

With this setup, we can now proceed towards the linear stability analysis of the patterns. We can explicitly evaluate the integral in (2.22) using (2.28a) above. As remarked earlier, the linear stability matrix in the case of the unit-disc also turns out to be non-diagonal in the $\psi_{n,k}$ basis. The equations for the perturbation amplitudes $\delta c_{n,k}$ remain coupled with respect to the index k . To proceed, we truncate to the first ten eigenfunctions in the k -index, and then for each n compute the largest eigenvalue Λ_n of the linear stability matrix. Figure 2.2(a-b) show the variation of Λ_n with n at several parameter values. The growth rates seen in Figure 2.2(a) show that the homogeneous state becomes unstable with increasing P and transitions into an anisotropic pattern ($n \neq 0$). On the other hand, Figure 2.2(b) shows that homogeneous state loses its stability and transitions into an isotropic pattern ($n = 0$). This allows us to construct the linear stability phase-diagram in the $P - R$ plane for patterns in the disk-shaped domain. We observe that the homogeneous state can lose its stability, upon increasing P , to either an anisotropic pattern or an isotropic pattern depending on the value of the turnover rate R . This linear stability analysis predicts that isotropic patterns can arise at large P even when $R = 0$.

Next, we proceed to develop an effective low-dimensional Galerkin model for the patterns. We truncate the concentration field as $c(r, \theta, t) = 1 + \rho_0 \psi_{0,1} + \rho_1 e^{i\varphi_1} \psi_{1,1} - \rho_1 e^{-i\varphi_1} \psi_{-1,1}$ where the amplitudes $\rho_i \in \mathbb{R}$ and the phase $\varphi_1 \in \mathbb{R}$. Using this trunca-

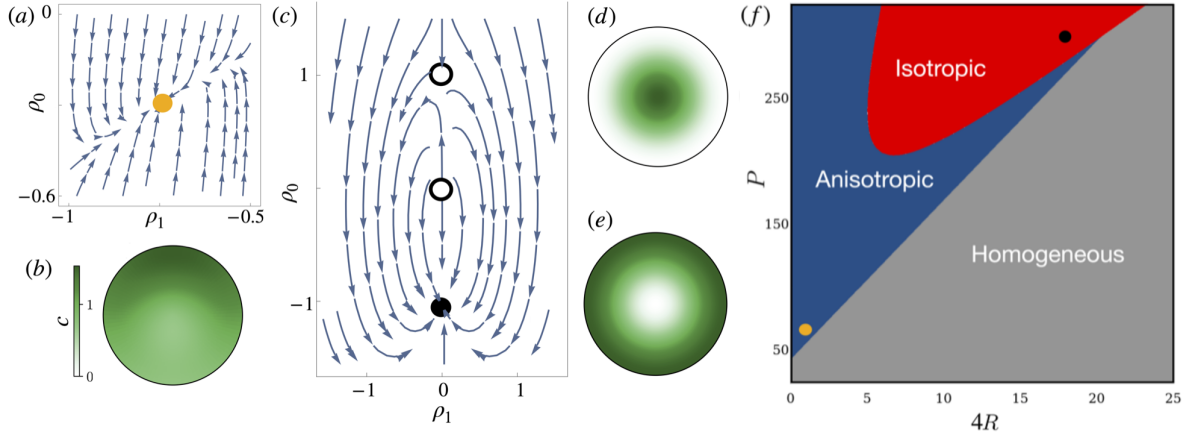


Figure 2.3: Results from the Galerkin truncated model. (a) Phase portrait of the system (2.29) where the stable fixed point leads to the anisotropic concentration pattern shown in (b). The phase is arbitrarily set to $\varphi_1 = \pi/2$. (c) Isotropic fixed points ($\rho_0 \neq 0$ and $\rho_1 = 0$) lead to concentration patterns shown in (d) or (e). The Galerkin truncated model (2.29) predicts that the fixed point corresponding to the pattern in (d) is unstable while that corresponding to (e) is stable. We also see in (c) that the homogeneous fixed point ($\rho_0 = 0 = \rho_1$) is unstable. (f) Phase diagram showing stability regions of the homogeneous, isotropic and anisotropic fixed points from the Galerkin model. Here $\mu \equiv a/\ell = 2$ and $c_* = 4$.

tion in (2.24) and evaluating the integrals (2.25), we get

$$\begin{aligned} \dot{\rho}_0 = & - \left(R + \frac{\alpha_{0,1}^2}{\mu^2} \right) \rho_0 - \frac{P}{c_*^2} \left[- (c_* - 2) a_{01} \rho_0 \right. \\ & - (c_* - 2) (a_{02} \rho_0^2 - a_{04} \rho_1^2) + a_{03} \rho_0^2 - a_{05} \rho_1^2 \\ & \left. + a_{06} \rho_0^3 + a_{07} \rho_0 \rho_1^2 \right], \end{aligned} \quad (2.29a)$$

$$\begin{aligned} \dot{\rho}_1 = & - \left(R + \frac{\alpha_{1,1}^2}{\mu^2} \right) \rho_1 + \frac{P}{c_*^2} \left[(c_* - 2) a_{11} \rho_1 \right. \\ & + [(c_* - 2) a_{12} + a_{13}] \rho_0 \rho_1 \\ & \left. + a_{14} \rho_1 \rho_0^2 - a_{15} \rho_1^3 \right], \end{aligned} \quad (2.29b)$$

and $\dot{\varphi}_1 = 0$. Here, $\mu \equiv a/\ell = 2$ and $a_{pq} > 0$ are related to the integrals in (2.25) and their values are listed in Appendix 2.G. We immediately see that the phase φ is decoupled from ρ_i and can be chosen arbitrarily with the choice fixing the direction corresponding to $\theta = 0$.

We summarize the results of the patterns arising from the Galerkin truncated model (2.29) in Figure 2.3. Analyzing (2.29), we find three kinds of fixed-points: (i) $\rho_0 = \rho_1 = 0$, (ii) $\rho_0 \neq 0, \rho_1 = 0$, (iii) $\rho_0 \neq 0$ and $\rho_1 \neq 0$. These respectively correspond to the homogeneous state, an isotropic pattern, and an anisotropic pattern. Within isotropic patterns ($\rho_1 = 0$), the concentration could be localized at the boundary ($\rho_0 < 0$) or

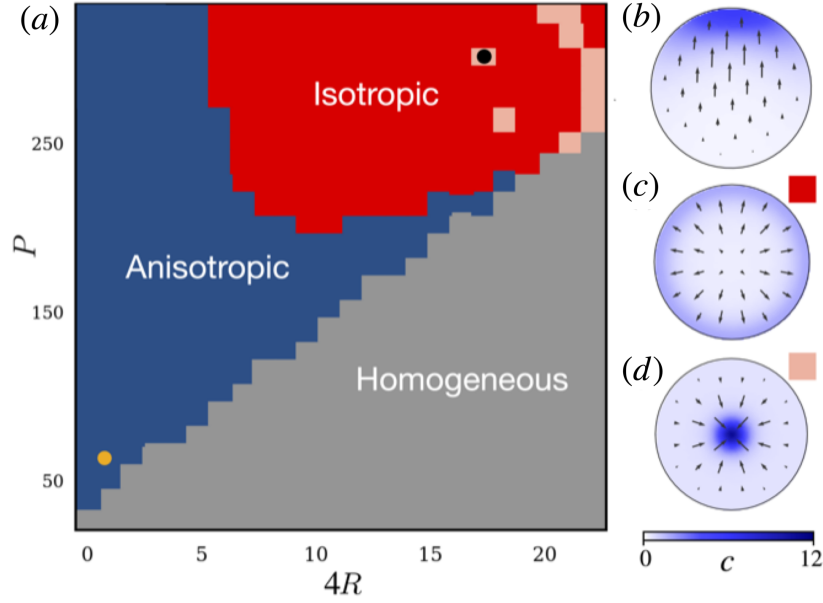


Figure 2.4: (a) Phase diagram resulting from the numerical integration of (2.5), (2.6). (b) Anisotropic concentration patterns corresponding to parameter values marked in the yellow dot in (a). (c-d) Bistable isotropic concentration patterns corresponding to parameter values marked in the black dot in (a). These center-localised and boundary-localised isotropic patterns arise by varying initial conditions in the high P and R region of parameter space. Here $\mu \equiv a/\ell = 2$ and $c_* = 4$.

localized at the center of the domain ($\rho_0 > 0$). Figure 2.3(a) shows the phase-portrait of the system around the fixed-point corresponding to the anisotropic pattern. We also plot, in Figure 2.3(b), the resulting concentration pattern arising from the fixed-point values for ρ_i . In Figure 2.3(c), we display the phase-portrait of the system around the fixed-points corresponding to the two isotropic patterns. We clearly see that the fixed-point corresponding to $\rho_0 > 0$ is unstable while that corresponding to $\rho_0 < 0$ is stable. Figure 2.3(d-e) show the respective concentration patterns at these fixed-points. We proceed to analyze the existence and the linear stability of the fixed points of (2.29) as a function of the parameters. In Figure 2.3(f), we construct the resulting phase-diagram of the patterns in the $P - R$ plane. The parameter values corresponding to the anisotropic and isotropic patterns shown in Figure 2.3(b,d,e) are indicated in the phase-diagram. We notice from this phase-diagram that the Galerkin truncated model predicts that isotropic patterns do not occur when $R = 0$, i.e., when there is no turnover of the concentration c . This should be contrasted with the prediction from the linear stability analysis of the homogeneous state shown in Figure 2.2.

To validate the predictions of the Galerkin truncated model, we numerically solve the full model (2.5)-(2.6) with the finite-element method (Appendix ??) using the FEniCS library [25, 50, 51]. For each parameter set, we start from the homogeneous state $c = 1$ and $v = 0$ with small random perturbations added to c and time-evolve the equations until a steady-state is reached. The results of this explicit numerical cal-

culatation are summarized in the phase-diagram Figure 2.4(a). The concentration and flow patterns corresponding to the parameter values indicated in the phase-diagram are shown in Figure 2.4(b-e). We observe the following points: (i) we find a very good agreement between the patterns predicted from the Galerkin model (2.29) (and Figure 2.3(f)) and those seen from the explicit numerical solution of the partial differential equations for c and v , (ii) the transition between the anisotropic and isotropic patterns (occurring in the highly nonlinear regime) predicted by the Galerkin model is captured quite well in the full numerics, (iii) consistent with the prediction of the Galerkin model, we do not get isotropic patterns when $R = 0$, (iv) in contrast to the prediction of the Galerkin model, we see a stable coexistence of two kinds of isotropic patterns (shown in Figure 2.4(c-d)) at high values of P and R , and finally (v) the phase diagram from the Galerkin model indicates that anisotropic patterns will remerge for large values of P when R is small; this is not seen in the full numerics. It is remarkable that a low-dimensional Galerkin model retaining only two modes can account for a large number of features seen in Figure 2.4(a)). Note also that the agreement of the reduced model with the full PDE model is demonstrated at $c_* = 4$, far beyond the validity of the approximation $c_* \gg 1$.

Deformations of the disk

The formalism that we developed in Section 2.3 applies to any (piecewise) smooth two-dimensional domain. However, analytical calculations are possible only on those domains for which the eigenfunctions of the Laplace operator, the Green's function for the Dirichlet problem and associated operators can be explicitly obtained. In the previous section, we showed that the concentration patterns, and the transitions between them, on a disk shaped domain can be accounted by a low-dimensional Galerkin model. To explore how the shape of the domain affects the resulting steady state concentration patterns, we consider smooth perturbations of the disk parametrized by

$$r(\theta) = a \left(1 + \sum_{l=2}^{\infty} r_l \cos(l\theta) \right), \quad (2.30)$$

where r_l is the amplitude of deformation corresponding to the l -th mode (see Figure 2.5). We don't consider $l = 1$, as it also involves a translation on top of a deformation. This can be seen by computing the centroid (x_l^c, y_l^c) for the l 'th deformation in $r(\theta) = a(1 + r_l \cos(l\theta))$:

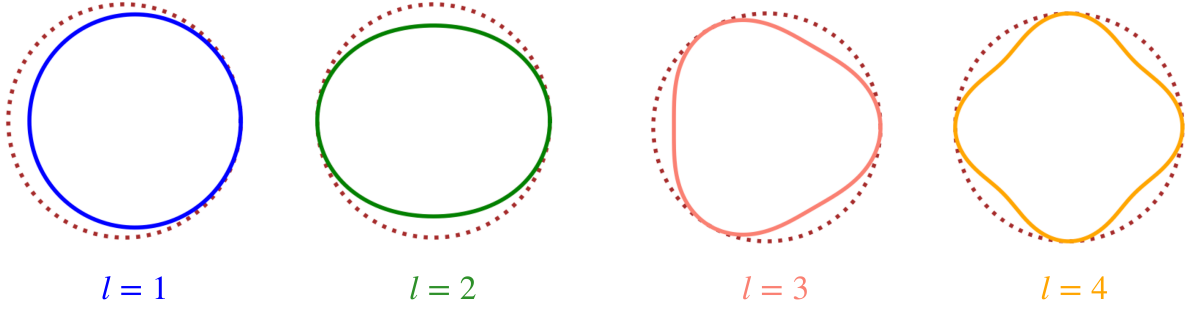


Figure 2.5: Harmonic deformations of a disk. For the l 'th mode, $r(\theta) = a[1 + r_l \cos(l\theta)]$. Here $r_l/a = 0.1$.

$$\begin{aligned}
 x_l^c &= \frac{\int x dA}{\int dA} = \frac{\int_0^{2\pi} \int_0^{r(\theta)} r^2 \cos \theta dr d\theta}{\int_0^{2\pi} \int_0^{r(\theta)} r dr d\theta} \\
 &= \frac{2}{3} \frac{\int_0^{2\pi} a^3 (1 + r_l \cos(l\theta))^3 \cos \theta d\theta}{\int_0^{2\pi} a^2 (1 + r_l \cos(l\theta))^2 d\theta} \\
 &= \begin{cases} 0 & \text{for } l = 0, 2, 3, 4, \dots \\ \frac{a l r_l (4 + r_l^2)}{4 \pi^2 (2 + r_l^2)} & \text{for } l = 1 \end{cases}
 \end{aligned} \tag{2.31}$$

$$\begin{aligned}
 y_l^c &= \frac{\int y dA}{\int dA} = \frac{\int_0^{2\pi} \int_0^{r(\theta)} r^2 \sin \theta dr d\theta}{\int_0^{2\pi} \int_0^{r(\theta)} r dr d\theta} \\
 &= \frac{2a}{3} \frac{\int_0^{2\pi} (1 + r_l \cos(l\theta))^3 \sin \theta d\theta}{\int_0^{2\pi} (1 + r_l \cos(l\theta))^2 d\theta} \\
 &= 0 \quad \forall l = 0, 1, 2, 3, \dots
 \end{aligned} \tag{2.32}$$

Thus, all higher-order deformations ($l \geq 2$) preserve the centroid at the origin and therefore represent purely geometric distortions of the boundary. This is not the case for $l = 1$.

We first consider deformations with $r_l = 0, \forall l > 2$. For small r_2 , Equation (2.30) results in a convex shape with a varying boundary curvature. To explore concentration patterns on such a domain, we numerically integrate (2.5)-(2.6) to find steady state solutions. The results of this calculation are summarized in the phase diagram in Figure 2.6(a).

We observe that the concentration patterns either localize nearly uniformly on the boundary or select regions of high/low boundary-curvature. For the case of the disk-shaped domain, the location of the peak of the anisotropic pattern was decided based on the random initial conditions. In contrast, on a domain deformed with an $l = 2$

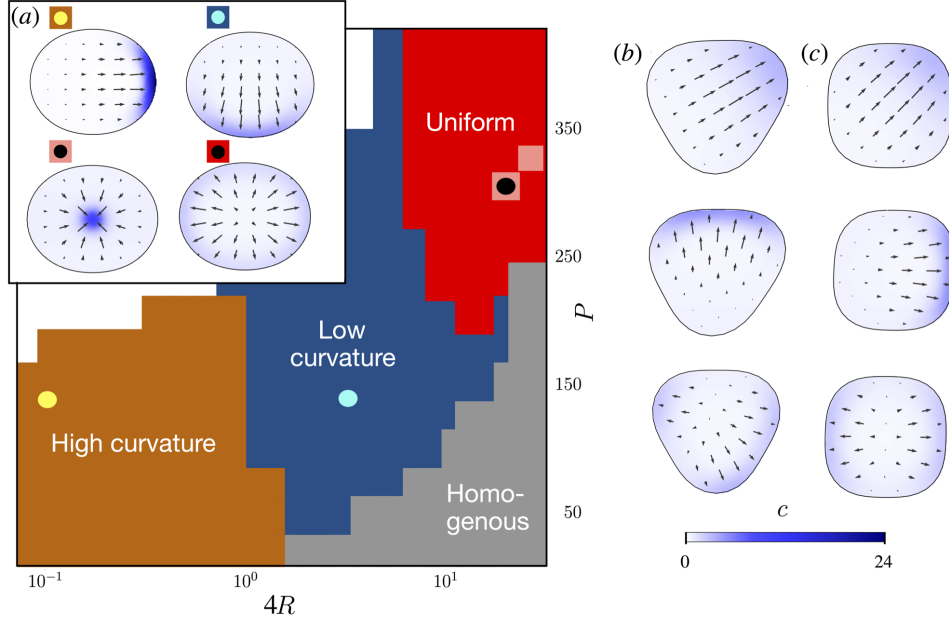


Figure 2.6: (a) Anisotropic patterns on an $l = 2$ deformation of the circle either select regions of high or low boundary curvature. At high values of P and R , the patterns localize either at the center of the domain or along the boundary depending on initial conditions. The phase-diagram in the $P - R$ plane is also shown. Patterns on (b) $l = 3$ and (c) $l = 4$ deformations can localize to vertices, edges, or both. In (b) and (c), the parameter values are $(P = 50, R = 1)$, $(P = 150, R = 5)$, and $(P = 200, R = 9)$ for each row. Here $\mu \equiv a/\ell = 2$ and $c_* = 4$.

mode, we find that the concentration patterns localize to regions of high boundary-curvature at low values of P and R . At intermediate values of P and R , the patterns transition to localize at regions of low boundary-curvature. Further, at large values of P and R , we find that there is a stable coexistence of concentration patterns that either spread nearly uniformly throughout the boundary, or are localized in the middle of the domain.

A shape closely related to the $l = 2$ deformation of the disk is an ellipse. However when Ω is an ellipse, in spite of the fact that separation of variables in elliptic coordinates provides explicit solutions to both the Laplace and Helmholtz equations, the Dirichlet-Neumann and tangential-derivative operators cannot be simultaneously diagonalized. As a consequence, one does not obtain explicit solutions to the boundary-value problem (2.13)-(2.14) for this choice of Ω . Nevertheless, we have numerically solved (2.13)-(2.14) on a ellipse-shaped domain and find that the resulting patterns is very similar to those shown in Figure 2.6(a).

For shapes with higher mode deformations of the disk, we expect a plethora of rich concentration patterns. For instance, on a convex domain with only an $l = 3$ deformation, the steady state patterns can either localize to a vertex, to an edge, or be localized at a vertex and the opposite edge, as shown in Figure 2.6(b). On a smooth square-shaped domain, concentration patterns can localize to single vertices, single

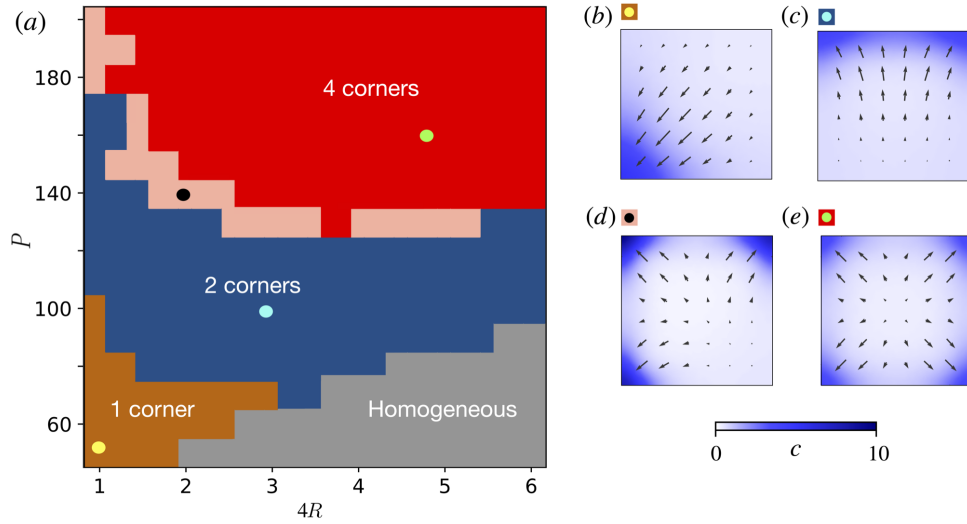


Figure 2.7: Patterns on a square localise at one, two, three or four corners (shown respectively in (b)-(e)). The parameter values for (b)-(e) are marked in the phase-diagram shown in (a). Here $\mu \equiv a/\ell = 2, c_* = 4$.

edges, or to opposite edges (Figure 2.6(c)).

The derivation of the truncated Galerkin equations may be carried out when Ω is a rectangular domain aligned with the coordinate axes in $\mathbb{R}^2$. Note, since the rectangular domain is *not* diffeomorphic to the circle (due to the presence of sharp corners in the rectangular domain), one does not expect the associated velocity fields to be qualitatively similar. Indeed, one expects the solutions to differ precisely at the corner points. Nevertheless there are some striking similarities between the concentration patterns obtained for the smooth square-shaped domain (Figure 2.6(c)) and the sharp-cornered square domain (Figure 2.7). In either case, solutions localize to the boundary regions. Further investigation is needed regarding the precise role the domain-geometry (and specifically the role of corners) plays in determining fixed-points of the truncated Galerkin equation and their stability properties.

2.5 Discussion

In this chapter, we studied pattern formation in a hydrodynamic model for the actomyosin cortex of cells. In addition to the physical parameters of the system, we have developed a systematic framework to investigate the influence of the boundary geometry in controlling the emergent patterns. For a disk-like geometry, our framework leads to explicit equations for the amplitudes of a Galerkin mode-truncated system. We demonstrated that the steady-state solutions of this reduced dynamical system captures the features of the patterns seen in the full partial differential equation system. The phase-diagram of patterns in the P - R plane predicted by the Galerkin model shows a remarkable agreement with that obtained from an explicit numerical

calculation of the full model. On the disk-shaped domain, our results predict that anisotropic patterns that break azimuthal symmetry can bifurcate into isotropic patterns with changing parameter values. On domains that are harmonic deformations of the disk, our numerical analysis shows that the emergent patterns can select regions of high or low boundary curvature depending on the parameter values.

We observe the following points. First, our model equations (2.5) and (2.6) contain a very minimal mechanochemical coupling between the concentration field c and the flows $\mathbf{v}$ resulting from the active stresses. What we have explored is the role of boundary geometry in controlling the resulting patterns. Our analytical framework for developing a Galerkin truncated low-dimensional model can be extended in a straightforward manner to include multiple interacting chemical species [20, 41]. Second, the sensitivity of the patterns to the boundary geometry arises from the independent manner in which advective and diffusive transports affect the dynamics of c . As we have shown, the solution of the flow equation (2.6) in an arbitrary domain with Dirichlet boundary conditions is given in terms of quantities involving Dirichlet-Neumann operators acting on velocity gradients. In other words, stresses developed at the boundaries can have a strong influence on the flow profiles, and hence on the concentration patterns. Third, the subtle differences between advective and diffusive transport is apparent even at the linear stability level. As mentioned in Sec 2.3, the linear stability matrix is not diagonal in the basis of the eigenfunctions ψ_j of the Laplace operator. The reason is that the Laplace and advection operators *do not* commute with each other in our case. This should be contrasted with the same problem in periodic and no-flux domains in one-dimension [20], or on the sphere [42]. Fourth, on domains with varying boundary curvature (such as the $l = 2$ deformation of the disk shown in Figure 2.6), the combined action of active advection and diffusion leads to patterns localizing at regions of the boundary with high or low curvature. In fact, we notice at a given high value of P , the boundary localization of patterns transitions from regions of high boundary curvature to regions of low boundary curvature as R is increased. Notice that R is itself the ratio of the length-scales associated with flow ($\ell = \sqrt{\eta/\gamma}$) and turnover ($\sqrt{D/\kappa}$). Varying boundary curvature introduces yet another length scale and the resulting competition leads to transitions in the localization of the pattern on the boundary.

Our study shows that a simple model for actomyosin patterns is sensitive to the geometry of the confining boundary. The predictions of our model can be tested in experiments where cells are plated on micropatterned substrates wherein the geometry of the confining region can be easily controlled. Further directions could explore including an orientational order parameter such as the nematic alignment of actin fibers and also explore domains that can deform in response to the boundary stresses.

Appendices

2.A Deriving the thin-film limit of the cortex equations

Here we attempt a heuristic derivation of the 2D equations for the cortex by thickness-averaging the 3D equations. Let c be the number per unit volume of actomyosin. This changes due to advection, dilution, diffusion, polymerization (primarily at the plasma membrane $z = 0$) and de-polymerization (everywhere in the bulk) [52]. Thus,

$$\frac{\partial c}{\partial t} + \nabla \cdot (\mathbf{v} c) = \mathcal{D} \nabla^2 c + v_P c_M \delta(z) - k_D c. \quad (2.33)$$

Here, $\mathbf{v}$ is the velocity of the active fluid in three dimensions, $\mathcal{D}$ is the diffusion constant, v_P is the polymerization rate, c_M is the actomyosin density at the membrane (located at $z = 0$) and k_D is the de-polymerization rate. Let us define the two-dimensional density and velocity fields as thickness-averaged quantities:

$$c_{2D} = \int_0^h c \, dz; \quad \mathbf{v}_{2D} = \frac{1}{c_{2D}} \int_0^h c \, \mathbf{v} \, dz, \quad (2.34)$$

where h is the thickness of the cortex. Integrating Equation (2.33) along z from 0 to h and using Equation (2.34),

$$\int_0^h \partial_t c \, dz + \nabla_{2D} \cdot (\mathbf{v}_{2D} c_{2D}) + j|_{z=h} - j|_{z=0} = \mathcal{D} \nabla^2 c_{2D} + v_P c_M - k_D c_{2D}. \quad (2.35)$$

where $\mathbf{v}_{2D} \equiv v_x \hat{\mathbf{x}} + v_y \hat{\mathbf{y}}$, $\nabla_{2D} \equiv \partial_x \hat{\mathbf{x}} + \partial_y \hat{\mathbf{y}}$ and $j = -\mathcal{D} \partial_z c + v_z c$ is the flux normal to the two-dimensional plane.

Assuming that the thickness of the cortex h does not change in time, the time derivative in the first term of Equation (2.35) can be taken outside the integral. Also assuming that there is no net normal flux of material into and out of the thin film, Equation (2.35) becomes

$$\partial_t c_{2D} + \nabla_{2D} \cdot (\mathbf{v}_{2D} c_{2D}) = \mathcal{D} \nabla^2 c_{2D} - k_D (c_{2D} - c_0) \quad (2.36)$$

where $c_0 \equiv \frac{v_P c_M}{k_D}$. Similarly, the thin-film limit of the full 3D force balance equation can be obtained as

$$\gamma \mathbf{v}_{2D} = \nabla_{2D} \cdot \boldsymbol{\sigma}_{2D} \quad (2.37)$$

where γ is the friction with the membrane/cytoplasm and $\boldsymbol{\sigma}_{2D} \equiv \int_0^h \boldsymbol{\sigma} \, dz$. Here, frictional drag emerges upon thickness-integrating the 3D momentum balance. In the

overdamped limit the 3D force balance is $\partial_j \sigma_{ij} = 0$. Integrating the in-plane components ($i \in \{x, y\}$) over the thickness and splitting the contracted index into in-plane and normal parts gives, for constant h , $\nabla_{2D} \cdot \sigma_{2D} + (\sigma_{iz}|_{z=h} - \sigma_{iz}|_{z=0}) = 0$, with $\sigma_{2D} \equiv \int_0^h \sigma dz$. Unlike the mass equation, where the normal fluxes at both faces vanish, the two faces are distinct here: the top is free ($\sigma_{iz}|_{z=h} = 0$) while the substrate transmits a tangential traction proportional to the sliding velocity, $\sigma_{iz}|_{z=0} = \gamma v_i$. The traction depends on the velocity at the substrate, $\mathbf{v}(z=0)$, which we have identified with the thickness-averaged velocity $\mathbf{v}_{2D}$. This is justified when the fields vary little across the film thickness. All viscosities in the model in the main text are 2D viscosities, $\eta_{2D} [M T^{-1}]$, related to the 3D viscosities $\eta [M L^{-1} T^{-1}]$ by $\eta_{2D} = \eta h$.

2.B Cortical vs cytoplasmic flows

In this section, we justify why we can ignore cytoplasmic flows, following [53].

The full model, with bulk cytoplasmic flows coupled to cortical flows [54], consists of a passive fluid in the bulk, with velocity $\mathbf{u}$, satisfying

$$\nabla \cdot \mathbf{u} = 0; \quad \nabla \cdot \sigma = 0; \quad (2.38)$$

where

$$\sigma = P\mathbb{I} + \eta_{\text{cyto}}[\nabla \mathbf{u} + (\nabla \mathbf{u})^T]. \quad (2.39)$$

Here, η_{cyto} is the viscosity of the cytoplasmic fluid, P is the pressure and $\mathbb{I}$ is the identity tensor in d dimensions.

The cortical flow velocity $\mathbf{v}$ satisfies

$$\nabla \cdot \left(\eta_{\text{cortex}}[\nabla \mathbf{v} + (\nabla \mathbf{v})^T] + \left(\eta_{\text{cortex}}^b - \eta_{\text{cortex}} \frac{2}{d} \right) \nabla \cdot \mathbf{v} \mathbb{I} \right) = -f_{\text{ext}} = -\sigma \cdot \hat{\mathbf{n}}, \quad (2.40)$$

where η_{cortex} and η_{cortex}^b are the shear and bulk viscosities of the cortex, and σ is the stress in the cytoplasmic fluid.

Boundary conditions ensure matching of the cortical and cytoplasmic velocities at the interface, i.e.,

$$\mathbf{e}_i \cdot \mathbf{u} \Big|_{\partial\Omega} = v_i; \quad \mathbf{n} \cdot \mathbf{u} \Big|_{\partial\Omega} = v_n \quad (2.41)$$

It can be shown [53] that the ratio of dissipation in the cortex $\mathcal{D}_{\text{cortex}}$ to that in the

cytoplasm $\mathcal{D}_{\text{cyto}}$ is

$$\frac{\mathcal{D}_{\text{cyto}}}{\mathcal{D}_{\text{cortex}}} = \frac{\eta_{\text{cyto}}}{\eta_{\text{cortex}}} \left(\frac{R}{\epsilon} \right) \quad (2.42)$$

where R is the mean curvature radius and ϵ is the thickness of the cortex. Typically, $R/\epsilon \sim 10^2$ [55–58], $\eta_{\text{cyto}} \sim 10^{-2} - 10^1$ Pa-s [59–61], and $\eta_{\text{cortex}} \sim 10^5 - 10^6$ Pa-s [53, 55, 56, 62]. Thus, dissipation in the cytoplasm is $10^{-5} - 10^{-3}$ times smaller than the dissipation in the cortex, and can be safely neglected for typical cell sizes. This means that the coupling of the cytoplasm to the cortex via σ in Equation (2.40) can be neglected, and the cortex can be treated as an isolated system.

2.C Helmholtz theorem for a vector field on the plane

Any well-behaved vector can be decomposed into a divergence-free (longitudinal) and a curl-free (transverse) part. We thus write

$$\mathbf{v} = \nabla \phi + \nabla \times \boldsymbol{\psi} \quad (2.43)$$

We define

$$\begin{aligned} D &\equiv \nabla \cdot \mathbf{v} = \nabla^2 \phi \\ \mathbf{C} &\equiv \nabla \times \mathbf{v} = \nabla \times \nabla \times \boldsymbol{\psi}. \end{aligned}$$

Since $\mathbf{v}$ is a vector on the plane, $\mathbf{C}$ must be a vector along $\hat{\mathbf{z}}$. Also, since $\nabla \cdot \mathbf{C} = 0$, $\mathbf{C}$ doesn't have an explicit z -dependence. Therefore, we write: $\mathbf{C} = C(r, \theta) \hat{\mathbf{z}}$. What follows can be considered as a proof of the Helmholtz theorem for 2-D vectors. Essentially, what we are doing is to write ϕ and $\boldsymbol{\psi}$ in Eq(2.43) explicitly.

$$\begin{aligned} \mathbf{v}(\mathbf{r}) &= \int dA' \delta^2(\mathbf{r} - \mathbf{r}') \mathbf{v}(\mathbf{r}') \\ &= \int dA' \nabla^2 \left(\frac{1}{2\pi} \ln |\mathbf{r} - \mathbf{r}'| \right) \mathbf{v}(\mathbf{r}') \\ &= \frac{1}{2\pi} \nabla^2 \left[\int dA' \mathbf{v}(\mathbf{r}') \ln |\mathbf{r} - \mathbf{r}'| \right] \\ &= \frac{1}{2\pi} \left[\nabla \left(\nabla \cdot \int dA' \mathbf{v}(\mathbf{r}') \ln |\mathbf{r} - \mathbf{r}'| \right) - \nabla \times \nabla \times \int dA' \mathbf{v}(\mathbf{r}') \ln |\mathbf{r} - \mathbf{r}'| \right] \\ &= \frac{1}{2\pi} \left[\nabla \left(\int dA' \nabla \cdot (\mathbf{v}(\mathbf{r}') \ln |\mathbf{r} - \mathbf{r}'|) \right) - \nabla \times \left(\int dA' \nabla \times (\mathbf{v}(\mathbf{r}') \ln |\mathbf{r} - \mathbf{r}'|) \right) \right] \\ &= \frac{1}{2\pi} \left[\nabla \left(\int dA' \nabla \ln |\mathbf{r} - \mathbf{r}'| \cdot \mathbf{v}(\mathbf{r}') \right) - \nabla \times \left(\int dA' \nabla \ln |\mathbf{r} - \mathbf{r}'| \times \mathbf{v}(\mathbf{r}') \right) \right] \end{aligned}$$

Now, since $\nabla = -\nabla'$,

$$\mathbf{v}(\mathbf{r}) = \frac{1}{2\pi} \left[\nabla \left(- \int dA' \nabla' \ln |\mathbf{r} - \mathbf{r}'| \cdot \mathbf{v}(\mathbf{r}') \right) + \nabla \times \left(\int dA' \nabla' \ln |\mathbf{r} - \mathbf{r}'| \times \mathbf{v}(\mathbf{r}') \right) \right]$$

Now,

$$\begin{aligned} \nabla' \ln |\mathbf{r} - \mathbf{r}'| \cdot \mathbf{v}(\mathbf{r}') &= \nabla' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) - \ln |\mathbf{r} - \mathbf{r}'| \nabla' \cdot \mathbf{v}(\mathbf{r}') \\ \nabla' \ln |\mathbf{r} - \mathbf{r}'| \times \mathbf{v}(\mathbf{r}') &= \nabla' \times (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) - \ln |\mathbf{r} - \mathbf{r}'| \nabla' \times \mathbf{v}(\mathbf{r}') \end{aligned}$$

And therefore,

$$\begin{aligned} \mathbf{v}(\mathbf{r}) &= \frac{1}{2\pi} \nabla \left(- \int dA' \nabla' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) + \int dA' \ln |\mathbf{r} - \mathbf{r}'| \nabla' \cdot \mathbf{v}(\mathbf{r}') \right) \\ &\quad + \frac{1}{2\pi} \nabla \times \left(\int dA' \nabla' \times (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) - \int dA' \ln |\mathbf{r} - \mathbf{r}'| \nabla' \times \mathbf{v}(\mathbf{r}') \right) \end{aligned} \quad (2.44)$$

According to the generalized Stokes theorem,

$$\begin{aligned} \int dA' \nabla' \times (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) &= \oint_C d\mathbf{l}' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) \hat{\mathbf{z}} \\ \int dA' \nabla' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) &= \oint_C \hat{\mathbf{r}}' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) d\mathbf{l}' \end{aligned}$$

So, finally, we have,

$$\begin{aligned} \mathbf{v}(\mathbf{r}) &= \frac{1}{2\pi} \nabla \left(- \oint_C \hat{\mathbf{r}}' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) d\mathbf{l}' + \int dA' \ln |\mathbf{r} - \mathbf{r}'| \nabla' \cdot \mathbf{v}(\mathbf{r}') \right) \\ &\quad + \frac{1}{2\pi} \nabla \times \left(\oint_C d\mathbf{l}' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) \hat{\mathbf{z}} - \int dA' \ln |\mathbf{r} - \mathbf{r}'| \nabla' \times \mathbf{v}(\mathbf{r}') \right) \\ &= \frac{1}{2\pi} [\nabla \phi + \nabla \times \psi] \end{aligned} \quad (2.45)$$

with

$$\phi = \int dA' \ln |\mathbf{r} - \mathbf{r}'| D(\mathbf{r}') - \oint_C \hat{\mathbf{r}}' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) d\mathbf{l}' \quad (2.46)$$

$$\psi = - \int dA' \ln |\mathbf{r} - \mathbf{r}'| C(\mathbf{r}') + \oint_C d\mathbf{l}' \cdot (\ln |\mathbf{r} - \mathbf{r}'| \mathbf{v}(\mathbf{r}')) \hat{\mathbf{z}} \quad (2.47)$$

In our problem, boundary terms go to zero since $\mathbf{v}|_{\partial\Omega} = 0$.

Thus,

$$\begin{aligned} \mathbf{v} &= \frac{1}{2\pi} \left[\nabla \int dA' \ln |\mathbf{r} - \mathbf{r}'| D(\mathbf{r}') - \nabla \times \int dA' \ln |\mathbf{r} - \mathbf{r}'| C(\mathbf{r}') \right] \\ &= \frac{1}{2\pi} \left[\nabla \int dA' \ln |\mathbf{r} - \mathbf{r}'| D(\mathbf{r}') - \nabla \times \int dA' \ln |\mathbf{r} - \mathbf{r}'| C(\mathbf{r}') \hat{\mathbf{z}} \right] \end{aligned} \quad (2.48)$$

Now,

$$\nabla \ln |\mathbf{r} - \mathbf{r}'| = \frac{1}{|\mathbf{r} - \mathbf{r}'|^2}(\mathbf{r} - \mathbf{r}') = \frac{1}{|\mathbf{r} - \mathbf{r}'|^2}[\hat{\mathbf{r}}(r - r' \cos(\theta - \theta')) + \hat{\boldsymbol{\theta}}r' \sin(\theta - \theta')] \quad (2.49)$$

$$\nabla \times \hat{\mathbf{z}} \ln |\mathbf{r} - \mathbf{r}'| = \frac{1}{|\mathbf{r} - \mathbf{r}'|^2}[\hat{\mathbf{r}}r' \sin(\theta - \theta') + \hat{\boldsymbol{\theta}}(r' \cos(\theta - \theta') - r)] \quad (2.50)$$

To conclude, if the divergence D and curl C are known, and the boundary condition for the velocity is $v|_{\partial\Omega} = 0$, the velocity can be written as:

$$\mathbf{v} = \frac{1}{2\pi} \int dA' \frac{1}{|\mathbf{r} - \mathbf{r}'|^2} \left[\hat{\mathbf{r}} \{ D(\mathbf{r}')(r - r' \cos(\theta - \theta')) - C(\mathbf{r}')r' \sin(\theta - \theta') \} \right. \\ \left. + \hat{\boldsymbol{\theta}} \{ D(\mathbf{r}')r' \sin(\theta - \theta') - C(\mathbf{r}')(r' \cos(\theta - \theta') - r) \} \right] \quad (2.51)$$

Note how complicated our problem would have gotten if we had to use the above expression to get $\mathbf{v}$ in terms of its divergence and curl! The friction term allowed an easier route via Equation (2.10), as in the main text.

2.D Uniqueness of the boundary value problem for C and D

As discussed in the main text, the curl C and the (modified) divergence D of the flow field $\mathbf{v}$ satisfy the following homogeneous equations on Ω

$$\nabla^2 C - C = 0, \quad \nu^2 \nabla^2 D - D = 0. \quad (2.52)$$

with the boundary conditions

$$4\partial_n D - \partial_\tau C = 0, \quad 4\partial_\tau D + \partial_n C = F. \quad (2.53)$$

To see that these equations have a unique solution, we first define a norm for a vector-field $\mathbf{v}$ defined on Ω in the following way

$$\|\mathbf{v}\|^2 = \int_{\Omega} \left[\text{tr}(\nabla \mathbf{v} \nabla \mathbf{v}^T) + (\nu^2 - 1)(\nabla \cdot \mathbf{v})^2 + \mathbf{v} \cdot \mathbf{v} \right]$$

Then the solution to (2.52)-(2.53) when $F = 0$, satisfies the following

$$\|\nu^2 \nabla D + \hat{\mathbf{z}} \times \nabla C\|^2 = 0.$$

Then from the definition of the norm, we conclude $D = 0, C = \text{constant}$ in Ω for such a solution. But the only constant solution to (2.52) is zero. Thus the only solution to (2.52)-(2.53) with zero boundary forcing, is the zero solution. Hence the boundary-value problem has a unique solution.

2.E Invertibility of the Dirichlet-Neumann operator

Using Green's identity, one can show that the Dirichlet-Neumann operator is a self-adjoint operator acting on square-integrable functions defined on $\partial\Omega$ [63]. Moreover, the Dirichlet-Neumann operator for modified Helmholtz is an invertible operator which can be seen from the following version of Green's identity obtained from the equation for C in (2.52)

$$\int_{\partial\Omega} C|_{\partial\Omega} \mathbb{G}(C|_{\partial\Omega}) = \int_{\Omega} (|\nabla C|^2 + C^2). \quad (2.54)$$

Indeed from the well-posedness of the Dirichlet boundary-value problem, the right-hand side above vanishes if and only if $C|_{\partial\Omega} = 0$. Hence $\mathbb{G}$ (and $\mathbb{G}_\nu$) is positive-definite and hence invertible.

2.F Solving for C and D

The boundary-conditions (2.53) may be re-expressed in the following matrix-operator equation

$$\begin{pmatrix} 4\mathbb{G}_\nu & -\partial_\tau \\ 4\partial_\tau & \mathbb{G} \end{pmatrix} \begin{pmatrix} D|_{\partial\Omega} \\ C|_{\partial\Omega} \end{pmatrix} = \begin{pmatrix} 0 \\ F \end{pmatrix} \quad (2.55)$$

As a consequence of the invertibility of $\mathbb{G}$ proved above, we can rewrite (2.55) in the following equivalent form

$$(\mathbb{G}^{-1}\partial_\tau\mathbb{G}_\nu^{-1}\partial_\tau + I)C|_{\partial\Omega} = \mathbb{G}^{-1}F \quad (2.56)$$

$$D|_{\partial\Omega} = \frac{1}{4}\mathbb{G}_\nu^{-1}\partial_\tau C|_{\partial\Omega} \quad (2.57)$$

Here, we have used $\nu^2 = 4$. Recall the boundary-value problem (2.52)-(2.53) has a unique solution. Thus the matrix-operator on the left-hand side of (2.55) and the scalar-operator on the left-hand side of (2.56) are both invertible. By expanding $C|_{\partial\Omega}$ and $D|_{\partial\Omega}$ in a suitable orthonormal basis of functions $\{u_j\}$ defined on $\partial\Omega$, (2.56) becomes a linear system of equations for the respective expansion coefficients. Owing to the uniqueness of solutions, the expansion coefficients in the u_j -basis are uniquely

determined from this system of equations. As a consequence, the Dirichlet conditions $C|_{\partial\Omega}$ and $D|_{\partial\Omega}$ are uniquely determined and moreover the solutions to (2.52) given by $\mathbb{L}(C|_{\partial\Omega}), \mathbb{L}_\nu(D|_{\partial\Omega})$ are also uniquely determined. Consequently, we obtain the velocity field v .

The above calculations can be carried out explicitly when Ω is the unit disc. For smooth deformations of the unit-disc given by

$$r(\theta) = 1 + \epsilon h(\theta) \quad \theta \in [0, 2\pi], \quad (2.58)$$

one can, in principle, exploit the analyticity of the Dirichlet-Neumann operator $\mathbb{G}$ to obtain solution to (2.56) perturbatively. For the above to be a diffeomorphism of the unit circle, it suffices to demand $|\epsilon h'| \leq \beta < 1$ for some real number β . It is well-known that the Dirichlet-Neumann operator depends smoothly (indeed analytically) on the shape of the domain. In particular this implies $\mathbb{G}, \mathbb{G}_\nu$ (and their inverses) depend analytically on ϵ , i.e., these operators can be written as a power-series in ϵ with coefficients as self-adjoint operators [63]. Though it is tedious to obtain explicit forms of the ϵ -expansions for $\mathbb{G}, \mathbb{G}_\nu$ (see [64, 65]) we can however conclude that the solution to (2.52)-(2.53) on the domain given by (2.58) is qualitatively close to the solution of the same boundary-value problem but posed on the unit disc.

2.G Integrals in the Galerkin truncated equations for a disk

We tabulate below the values of the coefficients in the Galerkin truncated model for patterns on the disk.

a_{01}	a_{02}	a_{03}	a_{04}	a_{05}	a_{06}	a_{07}
0.234	0.041	0.082	0.216	0.114	0.030	0.130

a_{11}	a_{12}	a_{13}	a_{14}	a_{15}
0.158	0.029	0.05	0.012	0.009

2.H Finite element method for the model equations

The finite element method does not discretize the equations directly. Instead, it solves an equivalent integral ("weak") statement, obtained by multiplying each equation by an arbitrary *test function*, integrating over Ω , and using integration by parts to transfer one derivative from the unknown onto the test function. This lowers the order of the highest derivative. We denote by tc a scalar test function, for the concentration,

unconstrained on $\partial\Omega$, and by $\mathbf{tv}$, a vector test function, for the velocity, required to vanish on $\partial\Omega$. The weak form for the velocity equation, $\nabla \cdot \Sigma = \gamma v$, is

$$\langle \gamma v, \mathbf{tv} \rangle + \langle \Sigma, \nabla \mathbf{tv} \rangle = (\Sigma \cdot \hat{n}) \mathbf{tv} \Big|_{\partial\Omega} \quad (2.59)$$

The weak form for the concentration equation, $\partial_t c + \nabla \cdot (vc) = \mathcal{D} \nabla^2 c - \kappa(c - c_0)$, is

$$\langle \partial_t c, tc \rangle + \langle \nabla \cdot (vc), tc \rangle = \mathcal{D} (\nabla c \cdot \hat{n}) tc \Big|_{\partial\Omega} - \mathcal{D} \langle \nabla c, \nabla tc \rangle - \kappa \langle c - c_0, tc \rangle \quad (2.60)$$

Here, $\langle \dots \rangle$ denotes $\int_{\Omega}(\dots)$.

Essential vs natural boundary conditions

The velocity condition $v|_{\partial\Omega} = 0$ is an *essential* (Dirichlet) condition. It must be built into the space of admissible functions by constraining the boundary nodal values of v to be zero. This is why $\mathbf{tv}|_{\partial\Omega} = 0$.

The no-flux condition $\hat{n} \cdot \nabla c = 0$ is a *natural* (Neumann) condition. It is imposed simply by dropping the term $\mathcal{D} (\nabla c \cdot \hat{n}) tc|_{\partial\Omega}$. It is never imposed explicitly on the discrete solution, and tc is unconstrained in $\partial\Omega$.

Mesh, elements, and the Galerkin choice

The domain is partitioned into a mesh $\mathcal{T}_h$ of non-overlapping triangles whose union approximates Ω and whose edges resolve $\partial\Omega$. On this mesh we build a finite-dimensional function space V_h spanned by nodal basis functions $\{\phi_i\}$. We take the ϕ_i to be continuous piecewise-linear (P1) Lagrange elements. Since a function in V_h is fixed once its nodal values are known, the unknown fields are represented by their values at the mesh nodes,

$$c(\mathbf{x}, t) \approx \sum_j c_j(t) \phi_j(\mathbf{x}), \quad v(\mathbf{x}, t) \approx \sum_j v_j(t) \phi_j(\mathbf{x}). \quad (2.61)$$

The *Galerkin* choice is to draw the test functions from the very same space, $tc, \mathbf{tv} \in V_h$, so that it suffices to enforce each weak form against every basis function ϕ_i in turn. Substituting the expansions then converts each integral statement into one algebraic equation per node – a finite linear system whose matrices are assembled element by element from integrals of the ϕ_i and their gradients.

Time integration

Only the concentration carries a time derivative; the velocity equation is quasi-static, fixing $\boldsymbol{v}$ instantaneously from the current state. Each step of the simulation therefore splits in two: first solve the steady velocity weak form for $\boldsymbol{v}$ given the present c , then advance c one step in time using that $\boldsymbol{v}$. Collecting the Galerkin equations for the concentration gives a system of ordinary differential equations in the nodal values $\boldsymbol{c}(t) = (c_1, c_2, \dots)$,

$$\boldsymbol{M}\dot{\boldsymbol{c}} = -\boldsymbol{A}(\boldsymbol{v})\boldsymbol{c} - \mathcal{D}\boldsymbol{K}\boldsymbol{c} - \kappa\boldsymbol{M}(\boldsymbol{c} - \boldsymbol{c}_0), \quad (2.62)$$

where $\boldsymbol{M}_{ij} = \langle \phi_i, \phi_j \rangle$ is the mass matrix, $\boldsymbol{K}_{ij} = \langle \nabla \phi_i, \nabla \phi_j \rangle$ the stiffness (diffusion) matrix, and $\boldsymbol{A}(\boldsymbol{v})$ the advection matrix. The diffusion term is stiff, so we treat it implicitly, while advection is handled explicitly. A simple and robust option is an implicit explicit (IMEX) scheme [66].

Chapter 3

A hydrodynamic model for determinate and indeterminate growth of tissues

3.1 Introduction

Understanding the physical principles that govern the regulation of size and shape in living systems is a fundamental problem. In this chapter, we study a minimal model for a growing tissue, and explore the physical mechanisms responsible for growth termination. We define growth as an increase in the macroscopic size of the system. In principle, growth could also mean an increase in cell numbers, cell mass, extra-cellular material, etc. However, at the coarse-grained level, these processes imply growth iff they contribute to increasing the appropriate measure of size for the system, viz length in 1D and area in 2D.

In many organisms, growth ceases after reaching a "target size", and growth curves asymptote to this target size. This is indeed true for birds and mammals, and most vertebrates [67]. Other organisms, however, do not have an upper size limit – growth likely occurs throughout the life of the organism. Growth curves could be attenuating (that is, growth rate decreases with age but no asymptote is reached within the lifetime of the organism), as in some crustaceans [68], or linear, as in planaria [69] and modular organisms like annelids [23]. These two distinct phenotypes – one in which growth ceases during the natural lifespan of the organism, and the other in which no notion of final size exists – are called *determinate* and *indeterminate* growth respectively [70].

The above definitions have since been expanded to include the effect of perturbations from the environment once an asymptotic size has been reached. Determinate systems show tight regulation in response to such a perturbation: At the tissue level, cell sizes and numbers coordinate to ensure final sizes are maintained, via what are known as compensation mechanisms [71–73]. At the organ level, catch-up growth/shrinkage in one organ after insults to other growing organs ensures body

proportions are maintained [74]. Indeterminate systems, however, change size with changing conditions throughout their life. Further sub-categories of determinate and indeterminate growth exist depending on size plasticity of species growing in different habitats. Sizes of crustaceans and insects do not vary much with habitat [22] but planaria lie on the opposite side of the spectrum: within a species, size of planarians varies between 0.5 – 25 mm and inter-species variations range from a few *mm* to about a meter-sized planarians [75]. In fact, planaria also exhibit what is known as *de-growth*, that is, shrinkage when starved [69, 76].

What is the mechanistic basis of these two phenotypes? Can they exist as two *phases* of the same growth model? In this work, we developed a minimal, coarse-grained model where determinate and indeterminate growth emerge as two special solutions, depending on the ratio of the strength of active stress and tissue elasticity.

Early physical models for growth control [77] implicated morphogens such as *Dpp* in *Drosophila*, over and under-expression of which resulted in drastically different wing sizes. However, such models do not incorporate the role of mechanics in halting growth. It is known, for instance, that skin cells grow in response to stretching [78]. Moreover, in *Drosophila*, the graded distribution of morphogens contrast with almost homogeneous growth [79]. On the other hand, models that couple mechanics and signaling dynamics [80–82] typically prescribe growth by hand. It is only recently that the role of mechanical fields in growth termination and kinetics is being explored [83].

In this chapter, we write a minimal coarse-grained mechanical model for a tissue where growth is implicit. We neglect the complexities associated with growth anisotropy and signaling morphogens and explore whether and how growth is controlled in this simplest setting.

3.2 Model

We model a growing tissue as a viscoelastic continuum of finite size with a boundary. Material points in the tissue are labeled by their position vectors $x(t)$, and the collection of all such points defines the time-dependent domain Ω_t and its boundary $\partial\Omega_t$. The tissue deforms due a velocity field $v(t, x)$ defined at each point $x \in \Omega_t$. Clearly,

$$\frac{dx}{dt} = v(t, x). \quad (3.1)$$

Say at $t = 0$, $x(0) = X$. The set of all X defines the initial configuration Ω_0 . We denote by $x(t, X)$ the solution to (3.1) starting from the initial condition X .

The *Lagrangian* displacement field is defined by $u(t, X) = x(t, X) - X$. To formulate the problem entirely in the current configuration, we need to write $u(t, x)$ corresponding to $u(t, X)$ by inverting the map $x(X)$. This is possible when divergence of

$\mathbf{v}$, computed in Ω_t , is bounded below [see Appendix 3.A]. The evolution equation for $\mathbf{u}(t, \mathbf{x})$, then, is:

$$D_t \mathbf{u}(t, \mathbf{x}) = \mathbf{v}(t, \mathbf{x}). \quad (3.2)$$

In the Eulerian sense, $D_t \equiv \left(\frac{\partial}{\partial t} + \mathbf{v}(t, \mathbf{x}) \cdot \nabla \right)$. However, on a Lagrangian mesh, $D_t \equiv \partial_t$. The convective term of the Eulerian material derivative is implemented in the numerics implicitly at the end of every timestep via Equation (3.1). Note that despite the fields being Lagrangian in the numerics, all derivatives and integrals are still computed on the current mesh. This is the updated Lagrangian formulation [84] – with fields carried on material nodes, but derivatives/integrals evaluated on the current mesh.

Equations (3.1) and (3.2) completely determine the time evolution of both the domain Ω_t and the displacement field $\mathbf{u}(t, \mathbf{x})$ defined on it, once the velocity field $\mathbf{v}(t, \mathbf{x})$ is specified. The description thus far is entirely kinematical. To obtain the velocity field, we need to invoke further dynamical considerations. For a closed system of equations, we presume that the velocity field will be defined in terms of the instantaneous domain Ω_t and the displacement field at that time. In other words, we neglect any history dependence of the material.

At the scale of tissues, dynamics is typically overdamped. As such, momentum conservation is encapsulated, at each instant of time, in a force-balance equation:

$$\nabla \cdot \boldsymbol{\sigma} + \mathbf{F}_{\text{ext}} = 0, \quad (3.3)$$

where $\boldsymbol{\sigma}$ is the total stress in the tissue and $\mathbf{F}_{\text{ext}}$ is any external force.

The total stress $\boldsymbol{\sigma}$ will have contributions from elastic ($\boldsymbol{\sigma}_{\text{elastic}}$), viscous ($\boldsymbol{\sigma}_{\text{viscous}}$), and active ($\boldsymbol{\sigma}_{\text{active}}$) components (see Figure 3.1c): The tissue is composed of cells that have junctional proteins in between them, and are continuously rearranging. This leads to elastic and viscous stresses in the tissue – they depend on the instantaneous gradients of the displacement and velocity fields respectively. A minimal description that captures this local behavior is to take $\boldsymbol{\sigma}_{\text{elastic}} = E [\nabla \mathbf{u} + (\nabla \mathbf{u})^T] + (E_b - 2E/d) (\nabla \cdot \mathbf{u}) \mathbf{I}$ and $\boldsymbol{\sigma}_{\text{viscous}} = \eta [\nabla \mathbf{v} + (\nabla \mathbf{v})^T] + (\eta_b - 2\eta/d) (\nabla \cdot \mathbf{v}) \mathbf{I}$, where E and E_b are shear and bulk elastic moduli, η and η_b are shear and bulk viscosities, and $\mathbf{I}$ is the identity tensor in d dimensions. Further, on tissue scales, cell division and death generate localized force distributions. The first moment of the force distribution is zero because all internal forces balance each other. Therefore, the dominant contribution from cell division and death is the second moment – a stress/force dipole. It can be shown that the magnitude of this stress depends on the force amplitude and separation distance between the point forces [85]. This stress, arising from cell division and

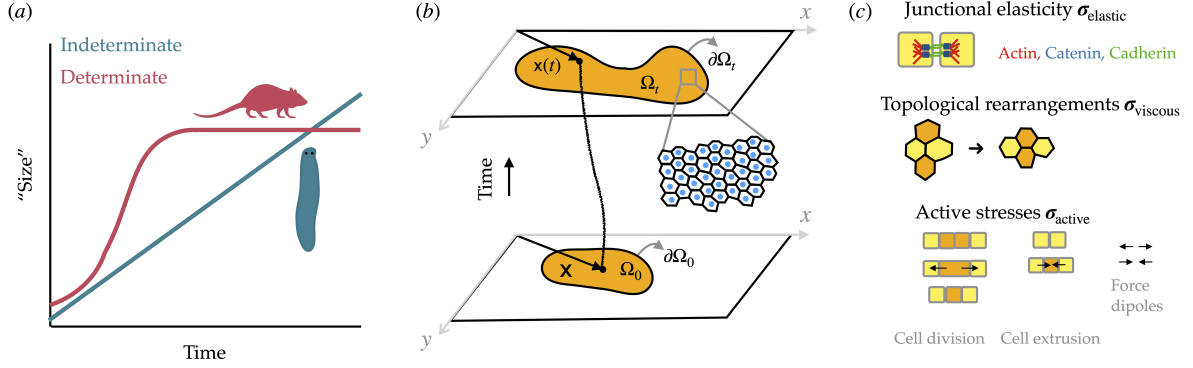


Figure 3.1: (a) Growth ceases during the natural lifespan of an organism in determinate growth, and no notion of final size exists for indeterminate growth. These growth curves for a mouse and planaria were adapted from [67] and [69] respectively. (b) Modeling a tissue as an active deformable material. Material points in the tissue are labeled by their position vectors $x(t)$, with $x(0) = X$. (c) The material is composed of cells that have junctional proteins in between them, and are continuously rearranging. This leads to viscoelastic stresses in the tissue. In addition, cells divide and die, giving rise to extensile and contractile active stresses respectively.

death, is an active stress (σ_{active}). It can be locally regulated by the cell number density ρ , local anisotropies in the tissue, as well as signaling fields. Specific choices for σ_{active} , and dynamical equations for the fields on which it depends, will be discussed later.

The external force F_{ext} can arise from constraints that restrict the motion of the tissue. For instance, a tissue may be confined in a region of space or its global motion could be constrained by the surrounding medium. A specific example of the latter scenario is the case of a quasi two-dimensional tissue growing on a substrate. In this case, the constraining medium restricts the growth to two dimensions and F_{ext} can be modeled as a frictional force $F_{\text{ext}} = -\gamma v$ exerted by the substrate on the tissue. This form of F_{ext} that we have chosen here is not crucial to the results of our work as long as it leads to unique solutions for the velocity in (3.3).

To complete the problem setup, we need to specify boundary conditions. On a deforming domain, the appropriate boundary condition will be to specify the total mechanical stress on the periphery of the domain. Thus, we will take

$$(n \cdot \sigma) |_{\partial\Omega_t} = \sigma_b(y), \quad y \in \partial\Omega_t, \quad (3.4)$$

where $\sigma_b(y)$ is a specified function and n is the unit outward normal to the boundary $\partial\Omega_t$. Given an initial condition $u(0, x)$ for the displacement field and the space-time dependence of the active stress, equations (3.1)-(3.4) completely specify the problem.

For an isolated tissue, it is natural to take $\sigma_b = 0$ on the boundary $\partial\Omega$. It is obvious that without any active stresses, i.e., $\sigma_{\text{active}} = 0$, the dynamics of an isolated tissue would be trivial. Before we turn to the autonomous dynamics of an isolated tissue

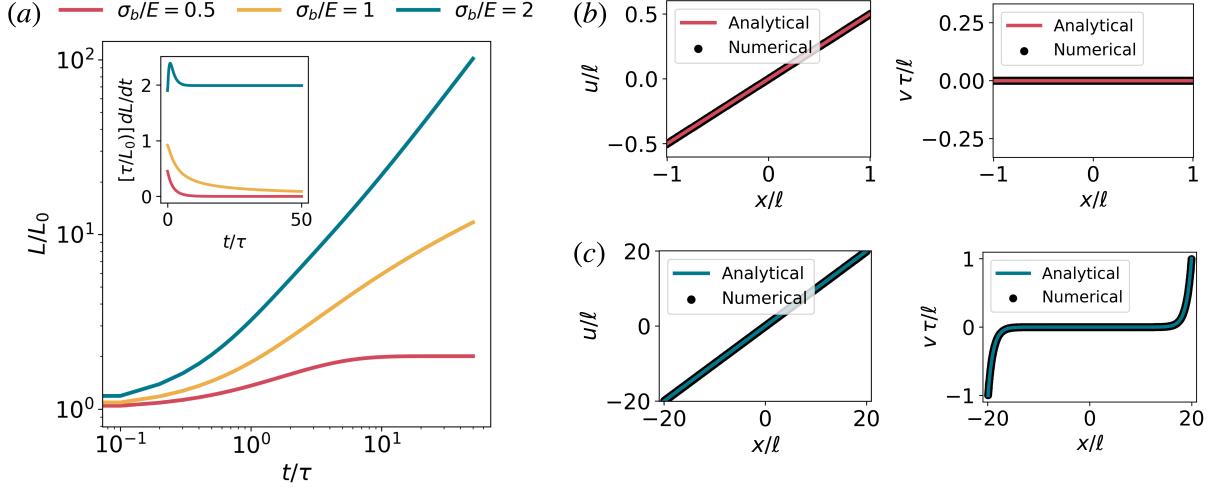


Figure 3.2: (a) Length of the domain in time for different values of the control parameter σ_b/E . (b) Displacement and velocity fields in the size-controlled phase when $\sigma_b/E < 1$. (c) Displacement and velocity fields in the perennially growing phase when $\sigma_b/E > 1$.

with active stresses, it is instructive to look at the case when $\sigma_{\text{active}} = 0$ and a specified stress σ_b is applied on the boundary.

3.3 Imposed boundary stress: Two special solutions

For simplicity, we will consider a one-dimensional tissue in which material points are labeled by their position vectors $x \in [-L(t)/2, L(t)/2]$. The governing equations are

$$\text{Kinematics} \quad \frac{dx}{dt} = v, \quad D_t u = v \quad (3.5)$$

$$\text{Force balance} \quad \gamma v = \partial_x \sigma \quad (3.6)$$

$$\text{Constitutive relation} \quad \sigma = E \partial_x u + \eta \partial_x v \quad (3.7)$$

$$\text{Boundary condition} \quad \sigma_{x=\pm L/2} = \sigma_b \quad (3.8)$$

Here, E is the elasticity and η is the viscosity of the tissue. For the boundary condition, we have taken into account the direction of the outward normal on the edges of the 1D domain.

We find that Equation (3.5) - Equation (3.8) possess two special solutions: a steady state corresponding to a tissue that is not growing and another state where the tissues grows perennially.

For the steady state i.e., $v = 0$, we find that the displacement field is

$$u^* = \frac{\sigma_b}{E} x. \quad (3.9)$$

Integrating the elastic strain obtained by the above over the domain at time t , one gets the change in length of the material upto time t . This gives

$$\frac{L^*}{L_0} = \left(1 - \frac{\sigma_b}{E}\right)^{-1}, \quad (3.10)$$

where L^* is the final length of the system at time t and L_0 is the initial size of the system. The expression on the right-hand side of the above equation can be interpreted as a growth-factor. Evidently this growth-factor diverges as $\sigma_b \rightarrow E$. Indeed, when $\sigma_b > E$, we obtain the perennially growing tissue. The same growth factor also determines the linear stability of the steady-state as shown below.

Scaling $x \rightarrow s = \frac{x+L/2}{L}$, $t \rightarrow \tau = t$, the derivatives transform as

$$\frac{\partial}{\partial x} = \frac{1}{L} \frac{\partial}{\partial s} \quad (3.11)$$

$$\frac{\partial}{\partial t} = \frac{\partial}{\partial \tau} + \left(\frac{v}{L} - \left(s - \frac{1}{2} \right) \frac{\dot{L}}{L} \right) \frac{\partial}{\partial s} \quad (3.12)$$

Then, the equations for the displacement and velocity transform to

$$\frac{\partial u}{\partial \tau} + \frac{\partial u}{\partial s} \frac{1}{L} \left(v - \dot{L} \left(s - \frac{1}{2} \right) \right) = v \quad (3.13)$$

$$\gamma v = \frac{E}{L^2} \frac{\partial^2 u}{\partial s^2} + \frac{\eta}{L^2} \frac{\partial^2 v}{\partial s^2} \quad (3.14)$$

with the boundary condition

$$\left. \frac{E}{L} \frac{\partial u}{\partial s} + \frac{\eta}{L} \frac{\partial v}{\partial s} \right|_{\{0,1\}} = \sigma_b. \quad (3.15)$$

Note that the equation for the movement of the domain also transforms as

$$\begin{aligned} \frac{d}{dt} \left(L \left(s - \frac{1}{2} \right) \right) = v &\implies \dot{L} \left(s - \frac{1}{2} \right) + L \frac{ds}{d\tau} = v \\ \text{Thus, } \frac{ds}{d\tau} &= \frac{1}{L} \left(v - \left(s - \frac{1}{2} \right) \dot{L} \right) \end{aligned} \quad (3.16)$$

By construction, the end points don't move in the new domain, which leads to

$$\frac{\dot{L}}{2} = v(1, t) = -v(0, t), \quad (3.17)$$

although points in the interior do move according to Equation (3.16).

Perturbing about the steady state $v^* = 0$, $u^* = \frac{\sigma_b L^* s}{E}$, $L^* = \frac{L_0}{1 - \frac{\sigma_b}{E}}$, and keeping

terms upto linear order in the perturbations, we have

$$\frac{\partial \delta u}{\partial \tau} + \left(\frac{\sigma_b}{E} - 1 \right) \delta v - \frac{\sigma_b}{E} \delta L \left(s - \frac{1}{2} \right) = 0 \quad (3.18)$$

$$\frac{E}{L^{*2}} \frac{\partial^2 \delta u}{\partial s^2} + \frac{\eta}{L^{*2}} \frac{\partial^2 \delta v}{\partial s^2} = \gamma \delta v \quad (3.19)$$

$$E \frac{\partial \delta u}{\partial s} + \eta \frac{\partial \delta v}{\partial s} \Big|_{s=0,1} = \sigma_b \delta L \quad (3.20)$$

$$\dot{\delta L} = \delta v(1, t) - \delta v(0, t) \quad (3.21)$$

For homogeneous boundary conditions, we write $\delta u = \tilde{\delta u}(s, \tau) + \frac{\sigma_b}{E} \left(s - \frac{1}{2} \right) \delta L(\tau)$. Expanding $\tilde{\delta u}, \delta v$ in a cosine basis, $\tilde{\delta u} = \frac{\delta u_0}{2} + \sum_{n=1}^N \delta u_n \cos(n\pi s)$, $\delta v = \frac{\delta v_0}{2} + \sum_{n=1}^N \delta v_n \cos(n\pi s)$, and writing δv_0 (δv_n) in terms of δu_0 (δu_n), we have

$$\delta u_m = \left(\frac{\sigma_b}{E} - 1 \right) \alpha_m^2 \delta u_m \quad (3.22)$$

$$\dot{\delta u}_0 = 0 \quad (3.23)$$

where $\alpha_m^2 = \frac{Em^2\pi^2}{\gamma L^{*2} + \eta m^2\pi^2}$.

That is,

$$\frac{d}{dt} \begin{pmatrix} \delta u_0 \\ \delta u_1 \\ \delta u_2 \\ \delta u_3 \\ \vdots \\ \delta u_N \end{pmatrix} = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdots \\ 0 & \left(\frac{\sigma_b}{E} - 1 \right) \alpha_1^2 & 0 & 0 & \cdots \\ 0 & 0 & \left(\frac{\sigma_b}{E} - 1 \right) \alpha_2^2 & 0 & \cdots \\ 0 & 0 & 0 & \left(\frac{\sigma_b}{E} - 1 \right) \alpha_3^2 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \\ 0 & 0 & 0 & \cdots & \left(\frac{\sigma_b}{E} - 1 \right) \alpha_N^2 \end{pmatrix} \begin{pmatrix} \delta u_0 \\ \delta u_1 \\ \delta u_2 \\ \delta u_3 \\ \vdots \\ \delta u_N \end{pmatrix} \quad (3.24)$$

This system is marginally stable (largest eigenvalue is zero) when $\sigma_b/E < 1$ and asymptotically unstable when $\sigma_b/E > 1$. Thus, even at the linear stability level, we can see that σ_b/E is a control parameter responsible for the stability of the homogeneous steady state (the determinate growth phase).

In the perennially growing phase, when $\sigma_b > E$, we find that the displacement field is

$$u^* = x, \quad (3.25)$$

where $x \in \left(-\frac{L^*(t)}{2}, \frac{L^*(t)}{2} \right)$ with $L^*(t)$ being the time-dependent domain length. The

velocity field is given by

$$v^*(x, t) = \frac{\ell}{\tau} \left(\frac{\sigma_b}{E} - 1 \right) \operatorname{sech} \left(\frac{L^*(t)}{2\ell} \right) \sinh \left(\frac{x}{\ell} \right), \quad (3.26)$$

where $\ell = \sqrt{\eta/\gamma}$ is a hydrodynamic length scale and $\tau = \eta/E$ is the Maxwell relaxation time for the material. Considering the motion of the end points of the tissue $\left(x = \pm \frac{L^*(t)}{2} \right.$ in Equation (3.26)), the domain length $L^*(t)$ satisfies:

$$\frac{dL^*}{dt} = \frac{2\ell}{\tau} \left(\frac{\sigma_b}{E} - 1 \right) \tanh \left(\frac{L^*}{2\ell} \right). \quad (3.27)$$

Since we assumed symmetric applied stresses on the two boundaries, equation (3.26) shows that v vanishes at the midpoint $x = 0$ of the tissue and v^* approaches its maximum magnitude at the boundaries, i.e., growth is predominantly at the boundary of the tissue. For a large tissue size, i.e., $L^* \rightarrow \infty$, the growth-rate approaches a constant

$$\left. \frac{dL^*}{dt} \right|_{L^* \rightarrow \infty} = \frac{2\ell}{\tau} \left(\frac{\sigma_b}{E} - 1 \right). \quad (3.28)$$

In other words, the entire domain grows linearly in time with the above growth rate, despite having a spatially nonuniform velocity.

We performed explicit numerical integrations of Equation (3.5) - Equation (3.8) to obtain time-dependent solutions. We use the finite element method via the FEniCS library [25, 50]. We find that these solutions approach either one of the two special solutions discussed above depending on the value of σ_b/E (see Figure 3.2(a)). The displacement and velocity fields from the numerics, and comparison with the analytical expressions above is shown in Figure 3.2(b)-(c).

To summarize, this simplified picture shows that the quantity σ_b/E determines the growth factor for the steady-state and controls the growth rate in the perennially growing state. Furthermore, in the latter state, the tissue velocity (and hence the growth) is localized at the boundaries, while the overall tissue size increases linearly with time.

The steady state is reminiscent of determinate growth, while the perennially growing state is similar to indeterminate growth seen across many species. In fact, the measured growth curves of larger mammals resembles the saturation of length with time seen in Figure 3.2(a). On the other hand, in organisms that show indeterminate growth, the length increases in an unbounded manner, as long as resources are available. For instance, planaria show continual growth (shrinkage) in the presence (absence) of nutrients. The length vs time curves shown in Figure 3.2(a) and the dependence of growth rate on applied stress Equation (3.28) resemble the case of indeterminate growth. It is remarkable to note that the steady state and perennially growing

state appear as two phases of the same continuum model of the tissue. The transition between these two phases is controlled by a balance between the applied boundary stress σ_b and the material parameter E .

For a tissue evolving autonomously, we expect that the applied stress σ_b should itself be determined self-consistently by other dynamical variables in the tissue. For instance, the tissue density, the concentration of signaling morphogens, and the anisotropic degrees of freedom of the tissue can influence the mechanical properties and hence control the emergence of the phases. Note that a prescribed boundary traction can mimic the kinematics of expansion, but the response rarefies the material – distinguishing it from true growth. In the next section, we consider a minimalistic description involving only the tissue density and show that determinate and indeterminate growth phases appear in an autonomous manner.

3.4 Fully autonomous model: Activity-controlled determinate and indeterminate growth phases

In this section, we make the system fully autonomous. The tissue is isolated, i.e.,

$$\hat{n} \cdot \sigma|_{\partial\Omega(t)} = \mathbf{0}. \quad (3.29)$$

Stresses now include an active component, arising from cell division and/or death events:

$$\begin{aligned} \sigma &= \sigma_{\text{elastic}} + \sigma_{\text{viscous}} + \sigma_{\text{active}} \\ &= E [\nabla \mathbf{u} + (\nabla \mathbf{u})^T] + (E_b - 2E/d) (\nabla \cdot \mathbf{u}) \mathbf{I} + \eta [\nabla \mathbf{v} + (\nabla \mathbf{v})^T] \\ &\quad + (\eta_b - 2\eta/d) (\nabla \cdot \mathbf{v}) \mathbf{I} - \zeta f(\rho) \mathbf{I} \end{aligned} \quad (3.30)$$

where $\mathbf{I}$ is the identity tensor in d dimensions, ζ is the active stress strength, and f is an active stress regulation function that depends on cell number density ρ . Here we assume that cell division axes are isotropic in the plane of the tissue. In general, they could be aligned, leading to another degree of freedom, $\mathbf{Q}$ – a tensorial quantity that needs its own evolution equation. This is addressed in the next chapter, where we make the active stress depend on $\mathbf{Q}$ and/or c , the concentration of a signaling morphogen implicated in growth control/initiation of convergence extension movements/oriented cell divisions, etc. For now, active stress arises from in-plane isotropic cell birth/death events. We choose $f(\rho) = \frac{\rho(\hat{\rho}-\rho)}{\rho^2+\rho_s^2}$, where ρ_s is the saturation density for the tissue and $\hat{\rho}$ is the setpoint of the active stress¹. This form assumes contractile

¹One can question why the setpoint of active stress is different from the homeostatic density for the tissue. This can be justified by treating $\hat{\rho}$ as a proxy for the steady state values of the nematic /

behavior (more cell deaths) at high cell densities ($\rho > \hat{\rho}$) and extensile behavior at low cell densities ($\rho < \hat{\rho}$). Our key result about the existence of two phases is, however, independent of this chosen form.

To close the model, we need an evolution equation for ρ . This is given by

$$D_t \rho = -(\nabla \cdot \mathbf{v}) \rho + \kappa \rho \left(1 - \frac{\rho}{\rho_0}\right), \quad (3.31)$$

where κ is the birth-death rate and ρ_0 is the homeostatic density of the tissue. Numerically, this equation too is solved in material form, retaining dilution/compression $-(\nabla \cdot \mathbf{v})\rho$, but not adding a separate $\mathbf{v} \cdot \nabla \rho$ term on the moving mesh. Note also that this equation requires no boundary condition when the problem is posed on an unbounded domain, and one boundary condition at the incoming boundary for a bounded domain. We added a small diffusion term to the equation for numerical stability. In the presence of diffusion, we need to impose boundary conditions at both ends. We choose $\rho_{\partial\Omega(t)} = \rho_0$. See Appendix 3.B for sensitivity analysis of our results to the magnitude of diffusion and boundary condition on ρ .

To summarise, Equation (3.1), Equation (3.2), Equation (3.3) and Equation (3.31) define the fully autonomous model for a growing tissue, with constitutive relation Equation (3.30) and boundary condition Equation (3.29). For simplicity, we analyse the system in 1D. The 1D equations for this fully autonomous model are

$$\text{Kinematics} \quad \frac{dx}{dt} = v, \quad D_t u = v \quad (3.32)$$

$$\text{Force balance} \quad \gamma v = \partial_x \sigma \quad (3.33)$$

$$\text{Constitutive relation} \quad \sigma = E \partial_x u + \eta \partial_x v - \zeta f(\rho) \quad (3.34)$$

$$\text{Cell number balance} \quad D_t \rho = -(\partial_x v) \rho + \kappa \rho \left(1 - \frac{\rho}{\rho_0}\right) \quad (3.35)$$

$$\text{Boundary condition} \quad \sigma_{x=\pm L/2} = 0 \quad (3.36)$$

Just like the model with imposed boundary stress and no activity, this model also has two special solutions: a homogeneous steady state, where the fields are given by

$$u^* = \zeta \frac{f(\rho_0)}{E} x; \quad v^* = 0; \quad \rho^* = \rho_0, \quad (3.37)$$

and the corresponding domain length is

$$\frac{L^*}{L_0} = \left(1 - \zeta \frac{f(\rho_0)}{E}\right)^{-1} \quad (3.38)$$

morphogen concentration, assumed to relax fast compared to the displacement, velocity and density fields, in this version of the model for a growing tissue.

Comparing Equation (3.38) and Equation (3.10), we see that $\zeta f(\rho_0)$ in this model plays the role of the imposed boundary stress of Section 3.3. This calculation can be extended to d -dimensions, assuming isotropy in $d - 1$ dimensions. In this case,

$$\frac{R^*}{R_0} = \left(1 - \zeta \frac{f(\rho_0)}{E}\right)^{-1/d} \quad (3.39)$$

Further, the velocity solution in the perennially growing phase is sourced by a non-uniform profile for ρ . The displacement and velocity fields are

$$u^* = x; \quad v^* = \frac{\ell}{\tau} \left(\frac{\zeta}{E} f(\rho_0) - 1 \right) \operatorname{sech} \left(\frac{L^*}{2\ell} \right) \sinh \left(\frac{x}{\ell} \right) - \zeta \int_{\frac{-L^*(t)}{2}}^{\frac{L^*(t)}{2}} \frac{\partial f}{\partial y} G(x, y) dy \quad (3.40)$$

where the Green's function G is given by

$$G(x, y) = \frac{1}{\gamma L(t)} + \frac{2}{\gamma L(t)} \sum_{n=1}^{\infty} \frac{\cos n\pi \left(\frac{x+L(t)/2}{L(t)} \right) \cos n\pi \left(\frac{y+L(t)/2}{L(t)} \right)}{1 + \frac{\eta}{\gamma} \left(\frac{n\pi}{L(t)} \right)^2} \quad (3.41)$$

The particular integral part of the velocity, $v_P^* = \zeta \int_{\frac{-L^*(t)}{2}}^{\frac{L^*(t)}{2}} \frac{\partial f}{\partial y} G(x, y) dy$ is bounded.

From the triangle inequality for integrals,

$$|v_P^*(x)| \leq \zeta \int_{-\frac{L}{2}}^{\frac{L}{2}} \left| \frac{\partial f}{\partial \rho} \frac{\partial \rho}{\partial y} G(x, y) \right| dy \leq c_0 \max_x \left| \frac{\partial \rho}{\partial x} \right| \quad (3.42)$$

Here we have used the fact that $\max_{\rho} |f'(\rho)|$ is finite, and that $G(x, y)$ is positive and evaluates to a constant when integrated over the domain. c_0 is a positive constant.

Then the growth rate of the domain can be computed by evaluating v^* at the end points. This leads to

$$\begin{aligned} \frac{dL}{dt} &= \frac{2\ell}{\tau} \left(\frac{\zeta}{E} f(\rho_0) - 1 \right) \tanh \left(\frac{L^*}{2\ell} \right) + v_P \left(\frac{L^*}{2} \right) - v_P \left(\frac{-L^*}{2} \right) \\ \Rightarrow \left| \frac{dL}{dt} \right| &\leq \frac{2\ell}{\tau} \left(\frac{\zeta}{E} f(\rho_0) - 1 \right) \tanh \left(\frac{L^*}{2\ell} \right) + \left| v_P \left(\frac{L^*}{2} \right) \right| + \left| v_P \left(\frac{-L^*}{2} \right) \right| \\ \Rightarrow \left| \frac{dL}{dt} \right| &\leq \frac{2\ell}{\tau} \left(\frac{\zeta}{E} f(\rho_0) - 1 \right) \tanh \left(\frac{L^*}{2\ell} \right) + 2c_0 \max_x \left| \frac{\partial \rho}{\partial x} \right| \end{aligned}$$

Taking the limit $L^* \rightarrow \infty$ leads to

$$\frac{dL^*}{dt} = \frac{2\ell}{\tau} \left(\frac{\zeta}{E} f(\rho_0) - 1 \right) + \mathcal{O} \left(\max_{t,x} \partial_x \rho \right). \quad (3.43)$$

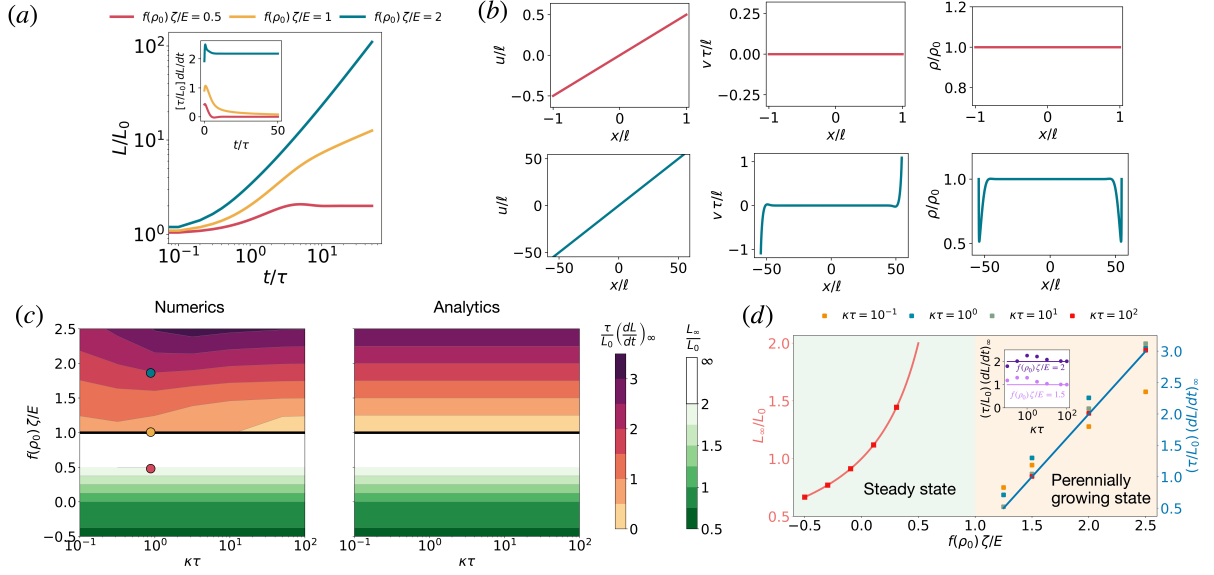


Figure 3.3: Fully autonomous model with activity. (a) Domain length in time for different values of the control parameter $f(\rho_0)\zeta/E$. (b) Displacement, velocity and density fields in the (top) size-controlled phase when $f(\rho_0)\zeta/E < 1$ and (bottom) rate-controlled phase when $f(\rho_0)\zeta/E > 1$. (c) Contour plots for steady-state lengths in the size-controlled phase (green) and growth rates in the perennially growing phase (yellow to violet) from the numerics and the analytical formulae Equation (3.38) and Equation (3.43) where the $\mathcal{O}(\nabla\rho)$ term is neglected in the formula for the growth rate. The black line denotes the boundary of the two phases. Points of a color correspond to lines of the same color in (a). (d) Dependencies extracted from the contour plot: Final size and growth rate as a function of the active stress for different values of $\kappa\tau$ in the homogeneous steady state (green) and perennially growing phase (red) respectively. Inset indicates the growth rate as a function of $\kappa\tau$ for two different values of the active stress.

The above equation implies that when gradients of the density field are suppressed (for instance at large κ), the first part of the RHS of Equation (3.43) is a good approximation for the growth rate of the domain, as seen in contours of the domain growth rate in Figure 3.3(c). In general, since forcing in the momentum balance equation in this model appears as $\partial_x f(\rho)$ in the bulk, as opposed to just an imposed stress in the model of Section 3.3, the velocity profile and domain growth rate of Section 3.3 now include an additional contribution from this bulk term.

The profile of the stresses in the two phases is shown in Figure 3.4. In the size-controlled regime, the active stress exactly balances the elastic stress (it is a negative constant in the extensile regime when $\rho_0 < \hat{\rho}$ while the elastic stress is the same positive constant (Figure 3.4a). The opposite is true in the contractile case when $\rho_0 > \hat{\rho}$ (Figure 3.4b)). This exact balancing of stresses does not happen in the perennially growing phase (see Figure 3.4c).

Note that in the formulation of the problem, we move the mesh at every timestep with the velocity computed from force balance at that timestep. For other details of

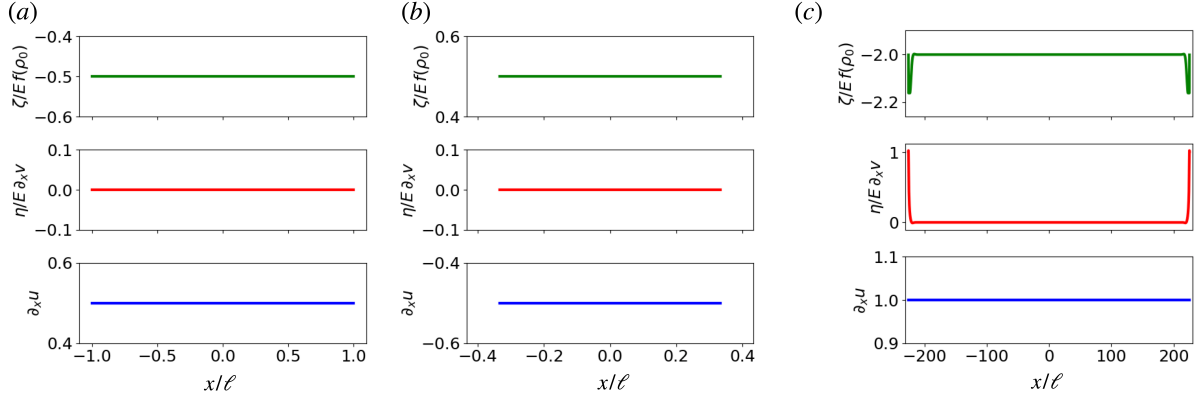


Figure 3.4: In the size-controlled phase, the active stress exactly balances the elastic stress, while the viscous stress decays to zero. In the perennially growing phase, there is a net non-zero total stress. Shown here is the long-term behavior of the three types of stresses (active: green, viscous: red, elastic: blue) (a) in the size controlled phase when the active stress is extensile, (b) in the size controlled phase when the active stress is contractile, (c) in the perennially growing phase.

the numerical method, see Appendix 3.C and 3.D.

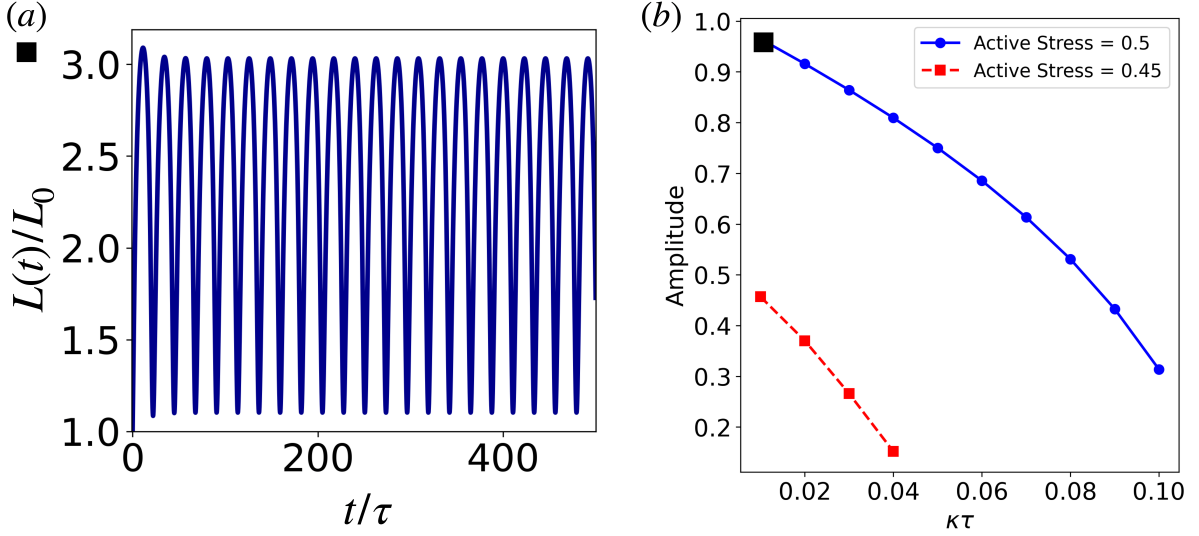


Figure 3.5: (a) Length of the domain in time for parameters $f(\rho_0) \zeta/E = 0.5$ and $\kappa\tau = 0.01$. (b) Variation of the amplitude of the oscillations of the domain length with $\kappa\tau$ for two fixed values of the active stress $f(\rho_0) \zeta/E$.

This model also shows oscillatory behaviour at low $\kappa\tau$, where domain length oscillates in time [Figure 3.5 (a)], with the amplitude of oscillation varying with $\kappa\tau$ as shown in Figure 3.5 (b). The mean length is that given by Equation (3.38). The oscillations can be understood as follows: As the cell number density tends to its homeostatic value ρ_0 , the tissue expands. Dilution leads to density being even lower than its homeostatic value. Since the birth-death rate is insufficient to compensate for the loss due to dilution, density keeps decreasing, going even below its homeostatic value, which leads to a local spurt in the number of cells (owing to the birth-death term). This flips

the sign of the active stress, making it contractile, and then extensile again. Note that the chosen form of active stress (which has both an extensile and a contractile part) and low $\kappa\tau$ are both crucial for oscillatory solutions.

3.5 Discussion

In this chapter, we modeled a visco-elastic tissue as a deformable continuum, specifying equations for the tissue displacement, velocity and density fields, and an equation for the movement of material points in the tissue. We uncovered bounded and unbounded growth phases, depending on the competition between active stress due to cell birth/death and the elasticity of the material. We saw these phases also for a reduced model with an applied boundary stress and no active stress in the bulk. These two special solutions are reminiscent of determinate and indeterminate growth, in terms of the shape of the growth curve in the two phenotypes. There is also an asymmetry in the model – extension allows bounded and unbounded growth, while compression only admits bounded de-growth, no unbounded de-growth. We also observed tissue-scale oscillations at low birth-death rate in the fully autonomous model, owing to the chosen contractile-extensile form of the active stress.

In problems relating to growth, while conservation laws are well-understood and agreed-upon, approaches to specifying the kinematics and constitutive laws in the problem have been diverse [86]. With regards to the kinematics of the problem, the bone of contention is the reference configuration to be used for specifying elastic strains. Taking a fixed reference configuration in a growth problem is questionable, because material points in the grown state may not exist in the past. However, the assumption of a fixed reference configuration can be justified if the grown state is dense, i.e., a control volume in the grown state always has points that existed in the past. Another option is to use evolving reference configurations for the displacement field, which needs specifying the ways in which relevant fields change the reference state. A third alternative involves the consideration that a growing body, is, in fact, a superposition of two bodies – one that deforms without mass increase and another that arose due to growth. The first body’s reference configuration does not change during deformation while that of the second body does. This is the basis of the multiplicative decomposition of the deformation gradient into a growth part and an elastic part [15, 16]. However, growth laws have to be prescribed in this framework. There is a fourth approach where the current body is endowed with a residual stress field or a new metric representing residual strains [87, 88]. In this approach, constitutive relations become implicit [89], and sometimes tied to the kinematics. Other approaches involve doing away with the notion of a reference configuration altogether. For instance, in [90], strains in the current configuration were written in terms of a directional number den-

sity in the current configuration, and constitutive laws depended only on this directional number density and its evolution.

Our approach in modeling the problem of growth assumes a fixed reference configuration for the elasticity field, which is justified in case of high number density in the grown state (to ensure mapping is possible, as stated above), and less birth-death events (which are known to relieve stresses and redefine the new stress-free state). Further, the kinematics of the problem is tied to the constitutive laws in our model, as the stresses involve derivatives computed on a moving domain. The material is not Kelvin-Voigt at finite strain (see Section 3.E). An exploration of a version of our model where the reference configuration of elasticity is reset (perhaps in a stress-dependent way by a delta function forcing in the displacement equation) and/or the constitutive relation is *nominally* long-time fluid is left for future work.

Finally, the model can be extended to study a composite tissue, with the two halves having different properties, such as different elastic moduli. In this case, it can be shown that, in the unbounded growth phase, the length fractions of the two halves with respect to the total length asymptote to a constant set by material parameters. That is, the tissue grows proportionately (relative sizes of different parts of the tissue with respect to the whole are maintained).

Appendices

3.A Invertibility of the map from the moving domain to the fixed domain

Taking the X derivative of Equation (3.1), and interchanging the t and X derivatives,

$$\frac{d}{dt} \frac{\partial x}{\partial X} = (\nabla_x v) \frac{\partial x}{\partial X} \quad (3.44)$$

By inverse function theorem, the map $x \rightarrow X$ is invertible at all times if the determinant of the jacobian matrix $\partial x / \partial X$ is non-zero at all times. Note, from the Jacobi formula,

$$\frac{d}{dt} \det \frac{\partial x}{\partial X} = \text{tr} \left(\text{adj} \frac{\partial x}{\partial X} \frac{d}{dt} \det \frac{\partial x}{\partial X} \right). \quad (3.45)$$

Then, using Equation (3.44) and cyclicity of the trace operator,

$$\frac{d}{dt} \det \frac{\partial x}{\partial X} = \text{tr} \left(\text{adj} \frac{\partial x}{\partial X} (\nabla_x v) \frac{\partial x}{\partial X} \right) \quad (3.46)$$

$$= \text{tr} \left(\det \frac{\partial x}{\partial X} (\nabla_x v) \right) = \det \frac{\partial x}{\partial X} \nabla \cdot v \quad (3.47)$$

Thus,

$$\det \frac{\partial x}{\partial X}(t) = \exp \left(\int_0^t (\nabla \cdot v)(x, s) ds \right) \quad (3.48)$$

That is, if $\nabla \cdot v$ is bounded below, the matrix $\partial x / \partial X$ has a non-vanishing determinant.

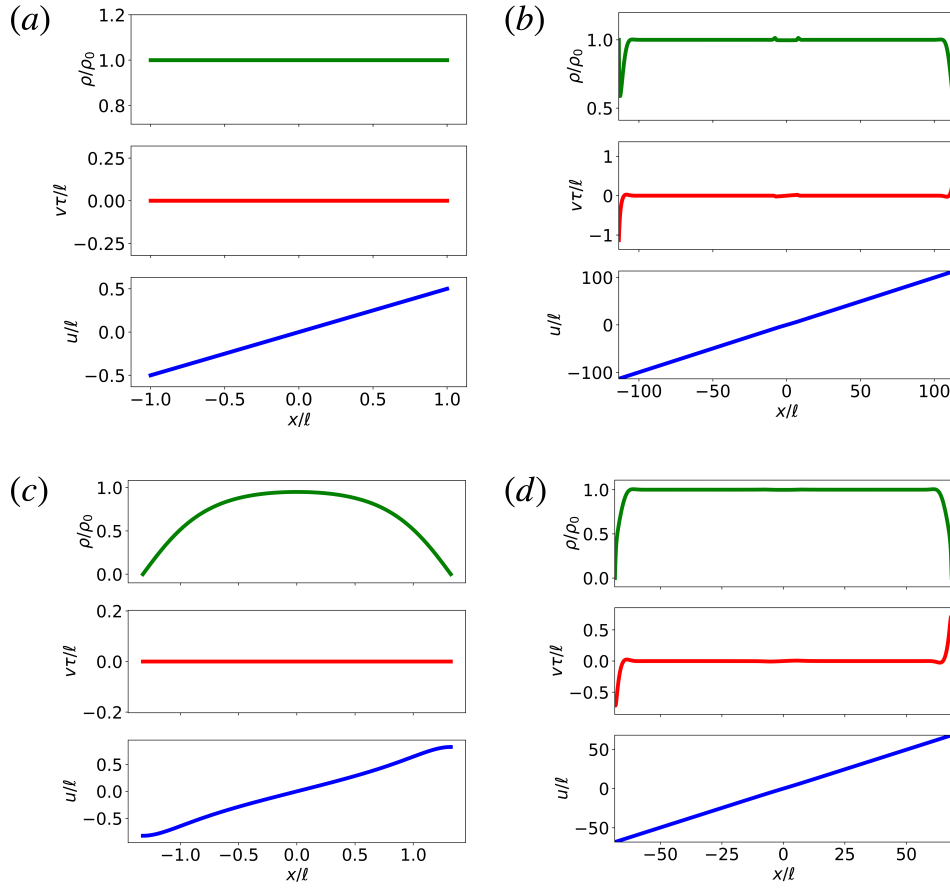


Figure 3.6: (a) Fields in the size-controlled phase for $\rho_{\partial\Omega(t)} = \rho_0$. (b) Fields in the perennially-growing phase for $\rho_{\partial\Omega(t)} = \rho_0$. (c) Fields in the size-controlled phase for $\rho_{\partial\Omega(t)} = 0$. (d) Fields in the perennially-growing phase for $\rho_{\partial\Omega(t)} = 0$.

3.B Fully autonomous model: Sensitivity to diffusion, boundary conditions

In this section, we discuss the sensitivity of our results to diffusion of, and boundary conditions on, the cell number density.

The key result about the existence of the two phases is true when $D\tau/\ell^2 \ll 1$, where D is the diffusion constant of the cell number density, ℓ is the hydrodynamic length of tissue and τ is its Maxwell relaxation time. We checked that the result holds for $0.01 \leq D\tau/\ell^2 \leq 0.1$, only the profiles of the fields and details about the contours changes. In this work, we fixed this parameter to $D\tau/\ell^2 = 0.1$.

As the boundary condition is changed from $\rho_{\partial\Omega(t)} = \rho_0$ to $\rho_{\partial\Omega(t)} = 0$, only the profile of the fields changes as in Figure 3.6. However the key result about the existence of a size controlled phase and a perennially growing phase still holds.

3.C Numerical method

We use the finite element method [91,92] to solve Equation (3.32)-Equation (3.36). Time integration is carried out by the forward Euler method, and weak solutions (solutions in the integrated sense) are sought by writing weak forms for the displacement, density and velocity equations. Discretized in time, these are

$$\begin{aligned} \left\langle \frac{\mathbf{u}^{n+1} - \mathbf{u}^n}{\Delta t}, t\mathbf{u} \right\rangle - \langle \mathbf{v}^n, t\mathbf{u} \rangle &= 0 \\ \langle \gamma \mathbf{v}^n, t\mathbf{v} \rangle + \langle \nabla t\mathbf{v}, \boldsymbol{\sigma}^n \rangle &= 0 \\ \left\langle \frac{\rho^{n+1} - \rho^n}{\Delta t}, t\rho \right\rangle + \langle (\nabla \cdot \mathbf{v}^n) \rho^n, t\rho \rangle + D \langle (\nabla \rho)^n, \nabla t\rho \rangle - \kappa \left\langle \rho^n \left(1 - \frac{\rho^n}{\rho_0} \right), t\rho \right\rangle &= 0. \end{aligned} \quad (3.49)$$

Here, $\mathbf{u}^n, \mathbf{v}^n$ and ρ^n are the displacement, velocity and density fields at the n 'th timestep respectively, and $t\mathbf{u}, t\mathbf{v}$ and $t\rho$ are their respective test functions. For each time n , a spatial field a (the displacement, velocity or density field) is represented in terms of interpolation functions N as $a^n = \sum_i a_i^n N_i$, where i denotes the space index and a_i^n are the weights associated with the interpolation functions. For a two-node element for instance, with the nodes at positions x_1 and x_2 , $a^n = a_1^n N_1 + a_2^n N_2$, where a_1, a_2 are the values of the field on the nodes, and $N_1 = \frac{x_2 - x}{x_2 - x_1}$, $N_2 = \frac{x - x_1}{x_2 - x_1}$ for a linear approximation of the function on said element. Then Equation (3.49) are solved to get the fields at the next timestep.

Further, the position of the nodes x_1 and x_2 is updated using the velocity field. The values of the fields at the nodes at time n (the a_i^n 's) are just carried to the new nodes at

time $n + 1$. It's the interpolating functions that get defined on the new mesh, to give the new field at time $n + 1$.

This is true without re-meshing, i.e, when no new nodes are added. However, with re-meshing, the idea is to redefine the elements and function space on the new mesh. The newly computed function on the old mesh is then L_2 projected on the new mesh. Minimizing the global integral error gives the corresponding new fields on the new mesh.

Our mesh is Lagrangian, i.e., the mesh nodes move with the material points, at the same speed as the material points. The label of the material points, however, is not the initial position X , but the current position x . Derivatives and integrals are computed on the current domain instead of the initial domain, and the stress measure used is the Cauchy stress, instead of the Piola Kirchhoff stress. This is the updated Lagrangian approach [84], which is often more robust when deformations are large.

3.D Benchmarking the solution

We can analytically solve diffusion on a moving domain (with prescribed velocity for the movement) by mapping the problem to a fixed domain. Here we compare the obtained analytical solution following [93] with our numerical solution to ensure our code correctly captures dynamics on a moving domain.

Note that diffusion on fixed boundaries becomes diffusion-advection-dilution on moving boundaries:

$$\frac{d}{dt} \int_{\Omega(t)} c(x, t) dV = - \int_{\Omega(t)} \mathbf{J} \cdot d\mathbf{S} = - \int_{\Omega(t)} \nabla \cdot \mathbf{J} dV \quad (3.50)$$

where $\mathbf{J} = -D\nabla c$ is the diffusive flux. In 1-D, this becomes,

$$\frac{d}{dt} \int_{\Omega(t)} c(x, t) dx = D \int_{\Omega(t)} \frac{\partial^2 c}{\partial x^2} dx \quad (3.51)$$

$$\implies \int_{\Omega(t)} \left[\frac{\partial c}{\partial t} + \frac{\partial(vc)}{\partial x} \right] dx = D \int_{\Omega(t)} \frac{\partial^2 c}{\partial x^2} dx \quad (3.52)$$

where the LHS follows from Reynolds Transport Theorem in 1-D and v is the velocity of the moving domain. Since the above is true for an arbitrary $\Omega(t)$,

$$\frac{\partial c}{\partial t} + \frac{\partial(vc)}{\partial x} = D \frac{\partial^2 c}{\partial x^2} \quad (3.53)$$

Exact solution for diffusion on growing domains when the velocity is supplied

We consider a linear reaction-diffusion process on a growing n -dimensional domain labeled by points $\mathbf{r} = (r, \mathbf{n})$ where $0 < r < R(t)$ with $R(t)$ is the increasing radius of the domain and $\mathbf{n}$ is a unit-vector indicating a direction ($\mathbf{n}$ only exists for $n \geq 2$). Domain growth is associated with a *radial* velocity field $\mathbf{v} = v(r, t) \mathbf{r}$ which causes points at a distance r from the origin to move to a distance $r + v(r, t) \Delta t$ in a short time Δt . Thus points at distances r and $r + \Delta r$, respectively, move to

$$r \rightarrow r' = r + v(r, t) \tau \quad (3.54)$$

$$r + \Delta r \rightarrow r' + \Delta r' = r + \Delta r + v(r + \Delta r, t) \Delta t. \quad (3.55)$$

Thus

$$\Delta r' = \Delta r + \Delta t [v(r + \Delta r, t) - v(r, t)] \approx \Delta r \left(1 + \Delta t \frac{\partial v}{\partial r} \right) \quad (3.56)$$

implying

$$R'(t) = R(t) + \Delta t \int_0^{R(t)} \frac{\partial v}{\partial r} dr \quad \implies \quad \frac{dR(t)}{dt} = \int_0^{R(t)} \frac{\partial v}{\partial r} dr \quad (3.57)$$

We consider uniform growth, i.e., $\partial_r v \equiv \sigma(t)$ is independent of r but could potentially depend on time t . Thus

$$\sigma(t) = \frac{1}{R(t)} \frac{dR(t)}{dt}. \quad (3.58)$$

We impose the boundary condition $v(0, t) = 0$ using which, on integrating (3.58), we find

$$v(r, t) = \frac{r}{R(t)} \frac{dR(t)}{dt} = \sigma(t) r. \quad (3.59)$$

We now consider the conservation of a mass density $C(\mathbf{r}, t)$, assuming that it evolves according to a linear reaction-diffusion mechanism. The associated conservation statement on the growing domain can be written as

$$\partial_t C = D \nabla^2 C - \nabla \cdot (\mathbf{v} C) + k C, \quad (3.60)$$

where $D > 0$ and k are the diffusion constant and reaction rate respectively. Assuming

a solution that only depends on the growth direction, i.e., $C(r, t) = C(r, t)$, we get

$$\frac{\partial C}{\partial t} = \frac{D}{r^{n-1}} \frac{\partial}{\partial r} \left(r^{n-1} \frac{\partial C}{\partial r} \right) - \frac{1}{r^{n-1}} \frac{\partial(r^{n-1} v C)}{\partial r} + k C, \quad (3.61)$$

$$= \frac{D}{r^{n-1}} \frac{\partial}{\partial r} \left(r^{n-1} \frac{\partial C}{\partial r} \right) - \frac{\sigma(t)}{r^{n-1}} \frac{\partial(r^n C)}{\partial r} + k C, \quad (3.62)$$

where n is the dimension. We impose zero diffusive flux conditions $\partial_r C = 0$ at $r = 0$ and at $r = R(t)$. With some given initial conditions $C(r, 0)$ our aim is to find the exact solution of (3.62). We first transform the spatial variable to a fixed domain: $r \rightarrow \xi = \frac{r}{R}$. This leads to

$$\frac{\partial}{\partial t} \rightarrow \frac{\partial}{\partial t} - \sigma \xi \frac{\partial}{\partial \xi}, \quad \frac{\partial}{\partial r} \rightarrow \frac{1}{R} \frac{\partial}{\partial \xi} \quad (3.63)$$

which implies

$$\frac{\partial C}{\partial t} = \frac{D}{\xi^{n-1} R^2} \frac{\partial}{\partial \xi} \left(\xi^{n-1} \frac{\partial C}{\partial \xi} \right) + (k - n \sigma) C. \quad (3.64)$$

Next, we transform the variable: $t \rightarrow \tau = \int_0^t ds \frac{D}{R^2(s)}$. Then

$$\frac{\partial C}{\partial \tau} = \frac{1}{\xi^{n-1}} \frac{\partial}{\partial \xi} \left(\xi^{n-1} \frac{\partial C}{\partial \xi} \right) + f(\tau) C \quad (3.65)$$

where

$$f(t(\tau)) = \frac{R(t(\tau))^2}{D} [k - n \sigma(t(\tau))]. \quad (3.66)$$

We use separation of variables to solve (3.65). Writing $C(\xi, \tau) = u(\xi) w(\tau)$,

$$\frac{1}{w} \frac{dw}{d\tau} - f(\tau) = \frac{1}{u \xi^{n-1}} \frac{d}{d\xi} \left(\xi^{n-1} \frac{du}{d\xi} \right). \quad (3.67)$$

With $-\omega^2$ as a separation constant, we get

$$\frac{dw}{d\tau} = [f(\tau) - \omega^2] w \quad \implies \quad w(\tau) = w(0) \exp \left[-\omega^2 \tau + \int_0^\tau ds f(s) \right], \quad (3.68)$$

and

$$\frac{d^2 u}{d\xi^2} + \frac{(n-1)}{\xi} \frac{du}{d\xi} + \omega^2 u = 0. \quad (3.69)$$

We need to find solutions of (3.69) with the boundary conditions that $u'(\xi) = 0$ at both $\xi = 0$ and $\xi = 1$.

- When $n = 1$, we get

$$u'' + \omega^2 u = 0, \quad (3.70)$$

and thus we need $\omega = m\pi$, $m \in \mathbb{Z}$ to satisfy the boundary conditions. The general solution is thus

$$u(\xi, \tau) = \sum_{m=0}^{\infty} a_m \cos(m\pi\xi) \exp \left[-m^2 \pi^2 \tau + \int_0^{\tau} ds f(s) \right]. \quad (3.71)$$

- When $n = 2$, we get

$$\xi u'' + u' + \omega^2 \xi u = 0, \quad (3.72)$$

the solutions of which are the zeroth-order Bessel functions $J_0(\omega\xi)$ and $Y_0(\omega\xi)$. Requiring u to be bounded at $\xi = 0$, we neglect the Y_0 solution. Imposing the boundary condition

$$\left. \frac{dJ_0(z)}{dz} \right|_{z=\omega} = 0 \quad \implies J_1(\omega) = 0, \quad (3.73)$$

determines the allowed values of ω as the zeroes of the 1st-order Bessel function. The general solution is thus

$$u(\xi, \tau) = \sum_{\omega} a_{\omega} J_0(\omega\xi) \exp \left[-\omega^2 \tau + \int_0^{\tau} ds f(s) \right], \quad (3.74)$$

where the summation is over those values of ω satisfying (3.73).

Three cases

1. Non-growing domain

With $R(t) = R_0$ in this case, we get

$$\sigma(t) = 0, \quad \tau = \frac{Dt}{R_0^2}, \quad f = \frac{R_0^2 k}{D}. \quad (3.75)$$

Hence $\tau \rightarrow \infty$ as $t \rightarrow \infty$. Thus

- $n = 1$

$$C(r, t) = \sum_{m=0}^{\infty} a_m \cos \left(\frac{m\pi r}{R_0} \right) \exp \left(-\frac{m^2 \pi^2 Dt}{R_0^2} + kt \right), \quad \text{with } m \in \mathbb{Z} \quad (3.76)$$

- $n = 2$

$$C(r, t) = \sum_{\omega} a_{\omega} J_0 \left(\frac{\omega r}{R_0} \right) \exp \left(-\frac{\omega^2 D t}{R_0^2} + k t \right), \quad \text{with } J_1(\omega) = 0. \quad (3.77)$$

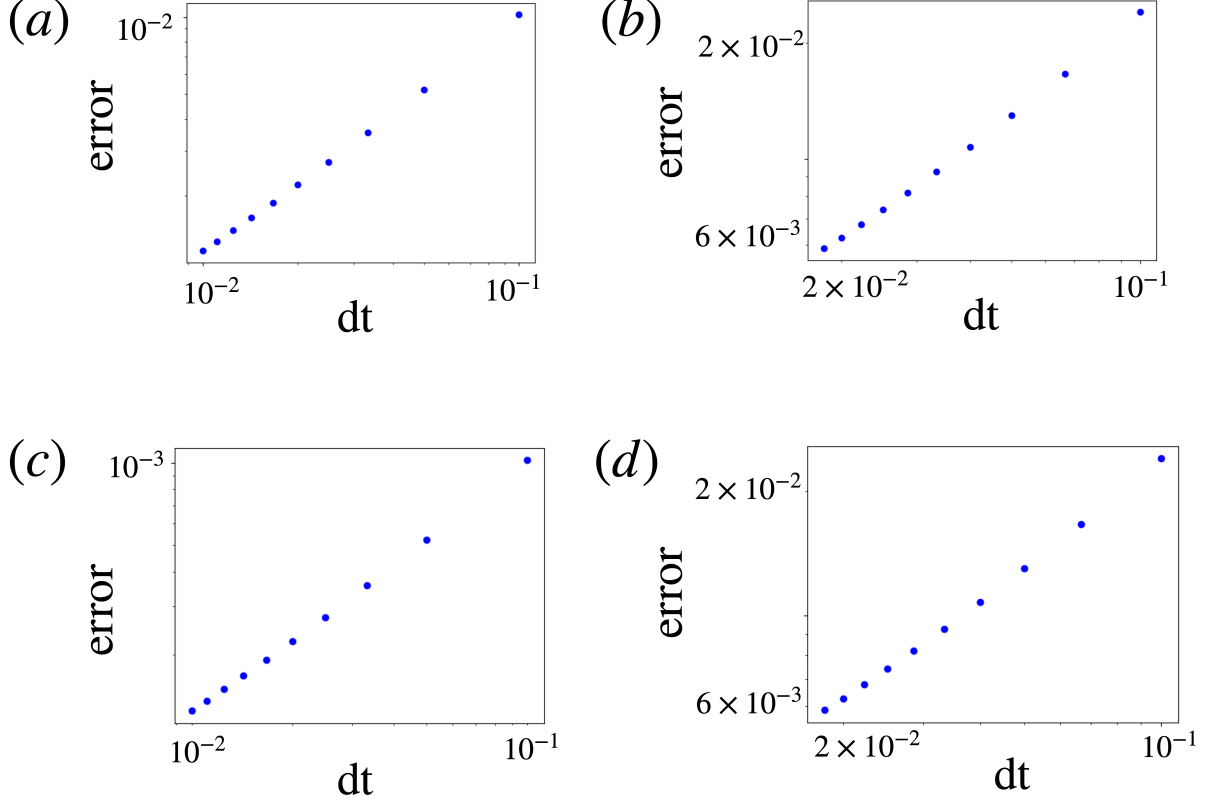


Figure 3.7: Errors from the numerical solution using the ALE method for movement and the analytical solutions computed above for (a) Linear growth in 1D, (b) Linear growth in 2D (c) Exponential growth in 1D (d) Exponential growth in 2D.

2. Exponential domain growth

With $R(t) = R_0 e^{\alpha t}$ in this case, we get,

$$\sigma(t) = \alpha, \quad \tau = \frac{D (1 - e^{-2\alpha t})}{2\alpha R_0^2}, \quad \int_0^\tau f(s) ds = \ln \left(\frac{D}{D - 2\alpha R_0^2 \tau} \right)^{(k-n\alpha)/2\alpha}. \quad (3.78)$$

Hence $\tau \rightarrow D/(2\alpha R_0^2)$ as $t \rightarrow \infty$. Thus

- $n = 1$

$$C(r, t) = \sum_{m=0}^{\infty} a_m \cos\left(\frac{m\pi r}{R(t)}\right) \exp\left[-\frac{m^2 \pi^2 D}{2\alpha R_0^2}(1 - e^{-2\alpha t}) + t(k - \alpha)\right], \quad (3.79)$$

with $m \in \mathbb{Z}$

- $n = 2$

$$C(r, t) = \sum_{\omega} a_{\omega} J_0\left(\frac{\omega r}{R(t)}\right) \exp\left[-\frac{\omega^2 D}{2\alpha R_0^2}(1 - e^{-2\alpha t}) + t(k - 2\alpha)\right], \quad (3.80)$$

with $J_1(\omega) = 0$.

3. Linear domain growth

With $R(t) = R_0 + \alpha t$ in this case, we get

$$\sigma(t) = \frac{\alpha}{R_0 + \alpha t}, \quad \tau = \frac{D t}{R_0(R_0 + \alpha t)}, \quad (3.81)$$

$$\int_0^{\tau} f(s) ds = \frac{R_0^2 k \tau}{(D - \alpha R_0 \tau)} + \ln\left(\frac{D - R_0 \alpha \tau}{D}\right)^n. \quad (3.82)$$

Hence $\tau \rightarrow D/(\alpha R_0)$ as $t \rightarrow \infty$. Thus

- $n = 1$

$$C(r, t) = \sum_{m=0}^{\infty} a_m \cos\left(\frac{m\pi r}{R(t)}\right) \exp\left[-\frac{m^2 \pi^2 D t}{R(t) R_0} + t k\right] \left(\frac{R_0}{R(t)}\right),$$

with $m \in \mathbb{Z}$ (3.83)

- $n = 2$

$$C(r, t) = \sum_{\omega} a_{\omega} J_0\left(\frac{\omega r}{R(t)}\right) \exp\left[-\frac{\omega^2 D t}{R(t) R_0} + t k\right] \left(\frac{R_0}{R(t)}\right)^2,$$

with $J_1(\omega) = 0$. (3.84)

3.E The constitutive model is *not* Kelvin-Voigt at finite strain

The constitutive law in our model cannot be understood as ordinary Kelvin-Voigt at finite strain because that uses the same strain measure for the spring and dashpot. However, our model does not. The elastic strain in our case is the $m = -1$ member of the Seth–Hill family of generalized strain tensors $E^{(m)} = \frac{\lambda^m - 1}{m}$ since $\partial_x u = 1 - \frac{1}{\lambda}$.

Here, $\lambda = \frac{\partial x}{\partial X}$ is the deformation gradient tensor. However, the strain measure used for the dashpot is the $m = 0$ member of this family. This can be seen as follows:

$$\dot{\lambda} = \frac{\partial}{\partial t} \left(\frac{\partial x}{\partial X} \right) = \frac{\partial}{\partial X} \left(\frac{\partial x}{\partial t} \Big|_X \right) \quad (3.85)$$

$$= \frac{\partial v}{\partial X} = \frac{\partial v}{\partial x} \frac{\partial x}{\partial X} = \lambda \frac{\partial v}{\partial x} \quad (3.86)$$

$$\implies \frac{\dot{\lambda}}{\lambda} = \frac{\partial v}{\partial x} \quad (3.87)$$

The $m = 0$ strain measure is

$$E^{(0)} = \ln \lambda \quad (3.88)$$

$$\implies \frac{dE^{(0)}}{dt} = \frac{\dot{\lambda}}{\lambda} \quad (3.89)$$

Thus, $\partial_x v = \frac{dE^{(0)}}{dt}$ and $\partial_x u = E^{(-1)}$. The strain measures for the spring and dashpot are different, which is not standard Kelvin-Voigt.

Chapter 4

Symmetry breaking in shape arising from tissue anisotropy

4.1 Introduction

Many biological systems show anisotropic growth. Zebrafish tissue at the 1000 cell stage (the cytoplasmic cap in Figure 1.1), when explanted onto a medium, breaks radial symmetry and grows preferentially along one direction. This is attributed to convergence extension movements [94, 95], where the tissue narrows along one direction and lengthens along the corresponding perpendicular direction. Such movements are also characteristic of germ-band extension in *Drosophila* [96], in which the germ-band doubles in length along the anterior-posterior axis, while subsequently narrowing along the dorsal-ventral axis. Similarly, cell aggregates, when taken out of their embryonic context, spontaneously organise to develop a body axis [97]. Shape change of these kinds implicates an interplay between mechanics, signaling, and local orientational order intrinsic to the tissue. The simple model in Chapter 3, with only a displacement, velocity and density field, and in-plane isotropic active stresses due to cell division and death (with cell division axes randomly oriented in the plane), does not produce shape change spontaneously, unless heterogeneities in the material parameters and/or initial condition for the density / domain shape are imposed.

How do we incorporate local anisotropy in the simple model of Chapter 3 to be able to explain anisotropic growth? What is the minimal coupling between such anisotropy and mechanical fields that suffices to produce spontaneous symmetry breaking?

The idea is to consider orientational degrees of freedom. These are representative of alignment of cell division axes and/or cell shape axes and/or cell intercalation directions in the tissue. It is characterized by the nematic order parameter, given by $Q = \frac{d}{d-1} \left\langle l^\chi \otimes l^\chi - \frac{1}{d} I \right\rangle_\chi$, where d is the spatial dimension, l^χ is the χ 'th cell's division axes/intercalation direction/shape axes, depending on the associated meso-

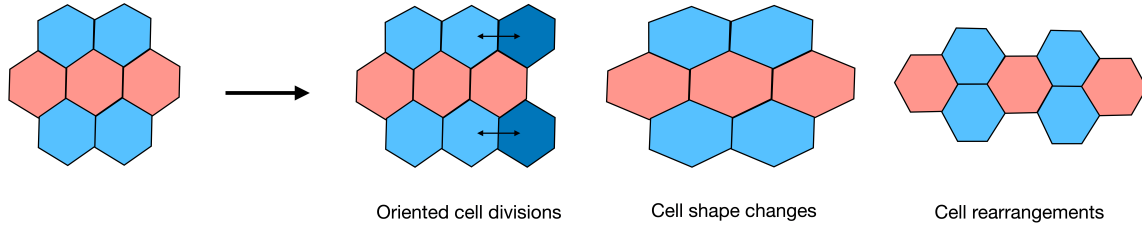


Figure 4.1: Typical cellular processes that lead to large-scale anisotropies in tissue morphogenesis.

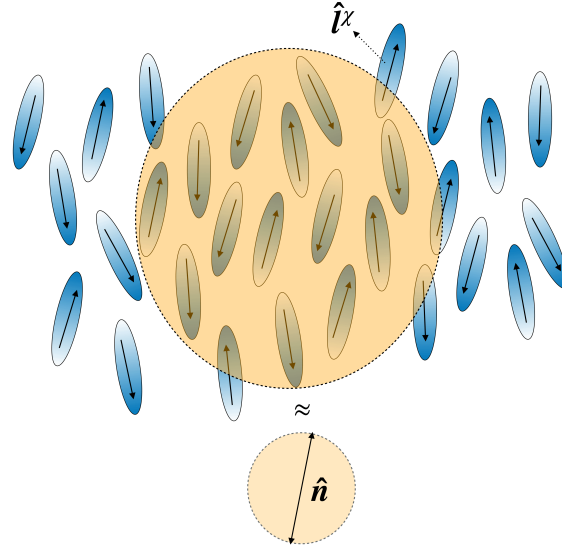


Figure 4.2: The nematic order parameter is obtained by coarse-graining over a control volume. Here, $\hat{l}^\chi$ is the χ 'th cell's shape axes and $\hat{n}$ is the mean direction of orientational order.

scopic phenomenon in consideration (cell division/rearrangements/stretching), $\mathbf{I}$ is the identity tensor in d dimensions, and $\langle \dots \rangle_\chi$ denotes spatial averaging over χ cells in a coarse-grained volume. Assuming the mean orientational order is along $\hat{n}$, this averaging can be performed explicitly, with $\mathbf{l} = (\cos \theta, \sin \theta)$ in 2D and $(\sin \theta \cos \phi, \sin \theta \sin \phi, \cos \theta)$ in 3D, leading to the following definition for a uniaxial nematic with orientational ordering along $\hat{n}$:

$$\mathbf{Q} = S \frac{d}{d-1} \left(\hat{n} \otimes \hat{n} - \frac{\mathbf{I}}{d} \right). \quad (4.1)$$

Here $S = \langle P_2(\cos \theta) \rangle$ is the magnitude of order and θ is the angle with respect to the direction of orientational order $\hat{n}$ (see Figure 4.2). Since the magnitude of order is related to the second order Legendre polynomial, $-1/2 < S < 1$, where $0 < S < 1$ denotes a positive nematic state, with molecular orientations $\mathbf{l}$ attracted towards $\hat{n}$, and $-1/2 < S < 0$ denotes a negative nematic state, with molecular orientations $\mathbf{l}$ repelled away from $\hat{n}$, thus picking an orientation perpendicular to it.

In this chapter, we consider an in-plane anisotropic active stress, now depending on the tensor $\mathbf{Q}$. To close this version of the model, we will write a dynamical equation for $\mathbf{Q}$, incorporating kinematic effects of flow on $\mathbf{Q}$, which also affects the flow via contributions to the passive and active stress. These equations, and how they fit into the overall model of Chapter 3, are discussed in detail in the next section.

4.2 A hydrodynamic model for an anisotropically deforming tissue

The dynamical equation for $\mathbf{Q}$ is given by [98–100],

$$D_t \mathbf{Q} + \mathbf{Q} \cdot \boldsymbol{\Omega} - \boldsymbol{\Omega} \cdot \mathbf{Q} - \alpha S \mathbf{E} = -\mu \mathbf{H}, \quad (4.2)$$

where $\boldsymbol{\Omega} = [\nabla \mathbf{v} - (\nabla \mathbf{v})^T]/2$ is the vorticity tensor, $\mathbf{E} = \frac{1}{2}[\nabla \mathbf{v} + (\nabla \mathbf{v})^T] - \nabla \cdot \mathbf{v} \mathbf{I}$ is the symmetric traceless part of the velocity gradient tensor, $\mathbf{H} = \frac{\delta F}{\delta \mathbf{Q}} - \frac{1}{d} \text{Tr} \left(\frac{\delta F}{\delta \mathbf{Q}} \right) \mathbf{I}$ is the molecular field corresponding to a free energy F , and α is the alignment/tumbling parameter that encodes the strength of the strain rate and vorticity in affecting alignment. Particles align if $|\alpha| > 1$ and tumble if $|\alpha| < 1$, and the sign of α encodes the shape of particles – rod-like particles have $\alpha > 0$ and plate-like particles have $\alpha < 0$.

Let us elaborate first on the kinematics of the problem: Flows affect $\mathbf{Q}$ by translating, rotating and stretching the director field. The infinitesimal change in the director field due to pure translation of the sample is given by

$$\begin{aligned} \delta \mathbf{Q} &= \mathbf{Q}(x + v_x \delta t, y + v_y \delta t, t + \delta t) - \mathbf{Q}(x, y, t) \approx \delta t \left(\frac{\partial \mathbf{Q}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{Q} \right) \\ \implies \left(\frac{\partial \mathbf{Q}}{\partial t} \right)_{\text{translation}} &= \frac{\partial \mathbf{Q}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{Q} \end{aligned} \quad (4.3)$$

The infinitesimal change in the $\mathbf{Q}$ field due to a rigid rotation of the sample is computed using the infinitesimal rotation matrix δR_{ij} . Clearly,

$$\begin{aligned} \delta Q_{ij} &\approx (\delta_{ik} + \delta R_{ik}) Q_{kl} (\delta_{lj} - \delta R_{lj}) - Q_{ij} \\ &\approx \delta R_{ik} Q_{kj} - Q_{ik} \delta R_{kj} \\ &= -\Omega_{ik} Q_{kj} + Q_{ik} \Omega_{kj} \end{aligned} \quad (4.4)$$

$$\implies \left(\frac{\partial \mathbf{Q}}{\partial t} \right)_{\text{rotation}} = \mathbf{Q} \cdot \boldsymbol{\Omega} - \boldsymbol{\Omega} \cdot \mathbf{Q} \quad (4.5)$$

Here, we have used $\delta R_{ij} = -\epsilon_{ijk} \omega_k = -\Omega_{ij}$, where $\boldsymbol{\omega} = \nabla \times \mathbf{v}$ is the vorticity of the flow, directed perpendicular to the plane, and $\boldsymbol{\Omega}$ is the vorticity tensor/antisymmetric velocity gradient. ϵ is the Levi-Civita tensor. Vorticity pseudovector and vorticity

tensor are related by $\omega_i = \frac{1}{2}\epsilon_{ijk}\Omega_{jk}$.

Finally, the $\mathbf{Q}$ field can also be stretched by the flow. The full derivation of the contribution from stretching requires a recourse to a microscopic approach [98, 100]. Up to lowest order in the fields $\mathbf{Q}$ and $\nabla \mathbf{v}$, the contribution is just

$$\left(\frac{\partial \mathbf{Q}}{\partial t}\right)_{\text{stretch}} = -\alpha S \mathbf{E}, \quad (4.6)$$

where α is the tumbling parameter that can be positive or negative as mentioned before, S is the magnitude of the $\mathbf{Q}$ tensor, and $\mathbf{E} = \frac{1}{2}[\nabla \mathbf{v} + (\nabla \mathbf{v})^T - \nabla \cdot \mathbf{v} \mathbf{I}]$ is the symmetric traceless gradient of the flow. The fact that S appears here and not in the other kinematic terms needs some explaining: Particles (rods/plates) stretch only if the magnitude of S at the position is non-zero. This is the statement that particles need to be present to be stretched. The fact that we neglected terms like $\mathbf{Q} \cdot \mathbf{E}$ in the equation necessitates the presence of S in this lowest order term. It does not appear in the translation and rotation terms because they are order one in $\mathbf{Q}$. In summary, these contributions specify fully how the kinematics of the flow affects $\mathbf{Q}$ – via translations, rotations and stretching.

The relaxational (non-conservative) contribution to change in $\mathbf{Q}$ is a dissipative flow down a free energy landscape, where free energy is the typical Landau-de Gennes energy:

$$F = \int d^d x [f_{\text{uniform}} + K_Q(\partial_\gamma Q_{\alpha\beta})(\partial_\gamma Q_{\alpha\beta})], \quad (4.7)$$

with $f_{\text{uniform}} = A Q_{\alpha\beta} Q_{\alpha\beta} + B Q_{\alpha\beta} Q_{\beta\gamma} Q_{\gamma\alpha} + C_1 (Q_{\alpha\beta} Q_{\alpha\beta})^2 + C_2 Q_{\alpha\beta} Q_{\beta\gamma} Q_{\gamma\delta} Q_{\delta\alpha}$ and K_Q is the nematic elasticity. The polynomial terms in F are responsible for the isotropic-to-nematic transition. This can be seen as follows: The coefficients of the quartics, $C_1, C_2 > 0$, stabilize the ordered phase and the coefficient of the cubic, B , renders the transition first order. What happens to the free energy landscape as the parameters A, B, C_1 , and C_2 are varied? To check this, we write the free energy as a function of the scalar order parameter S as $f_{\text{uniform}} = \frac{aS^2}{2} + \frac{bS^3}{3} + \frac{cS^4}{4}$, where $a = \frac{2Ad}{d-1}$, $b = \frac{3Bd(d-2)}{(d-1)^2}$, $c = \frac{4C_1d^2}{(d-1)^2} + \frac{4C_2(1+(d-1)^3)}{(d-1)^3}$. We fix $c > 0$ and $b < 0$, and vary a , which is a function of temperature for a thermotropic liquid crystal and a function of density for a lyotropic liquid crystal. As a is lowered, the free energy landscape goes from one with a single minimum at $S = 0$ (the isotropic phase) to one with two minima at $S = 0, -b/3c$ (at the isotropic-nematic coexistence) when $a = a_{\text{cr}} = 2b^2/9c$, to one with a single minimum again but now at $S = -b/3c$ (the nematic phase). As a is decreased further beyond a_{cr} , the order parameter continues to increase. If we had instead chosen $b > 0$, the order parameter at the N-I transition would be negative. This corresponds to the negative nematic state discussed before, which is theoretically possible but not seen

in experiments. For simplicity, we will assume $b = 0$, rendering it a second order transition, marked by change in the free energy landscape from one minimum to two as a is varied. Note that this is not an assumption in $d = 2$, given $b = \frac{3Bd(d-2)}{(d-1)^2}$.

In writing the elasticity term, we made a one-elastic-constant approximation. In general, a splay term like $\partial_\gamma Q_{\gamma\alpha} \partial_\beta Q_{\beta\alpha}$ is also possible at the lowest order, with a different cost (elasticity constant). Note that the role of the elasticity term is to introduce a correlation length $\sqrt{K_Q/|A|}$ over which $\mathbf{Q}$ can vary in the ordered phase when $A < A_{\text{cr}}$. Thus, change in nematic due to dissipative flow down the landscape of F is

$$\left(\frac{\partial \mathbf{Q}}{\partial t}\right)_{\text{dissipative}} = -\mu \mathbf{H}, \quad (4.8)$$

where $\mathbf{H} = \frac{\delta F}{\delta \mathbf{Q}} - \frac{1}{d} \text{Tr} \frac{\delta F}{\delta \mathbf{Q}}$ is the molecular field. Thus, we have

$$\begin{aligned} \left(\frac{\partial \mathbf{Q}}{\partial t}\right)_{\text{translation}} + \left(\frac{\partial \mathbf{Q}}{\partial t}\right)_{\text{rotation}} + \left(\frac{\partial \mathbf{Q}}{\partial t}\right)_{\text{alignment}} &= \left(\frac{\partial \mathbf{Q}}{\partial t}\right)_{\text{dissipative}} \\ \implies \frac{\partial \mathbf{Q}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{Q} + \mathbf{Q} \cdot \boldsymbol{\Omega} - \boldsymbol{\Omega} \cdot \mathbf{Q} - \alpha S \mathbf{E} &= -\mu \mathbf{H}, \end{aligned} \quad (4.9)$$

Moreover, the nematic order parameter also enters the passive and active stress in the flow equation. The passive nematic stress has a contribution from the free energy (the thermodynamically-adjusted Noether stress) and contributions from the rotation and alignment terms [100]. The lowest order contributions of $\mathbf{Q}$ to $\boldsymbol{\sigma}$ are:

$$\boldsymbol{\sigma}_{\mathbf{Q}, \text{passive}} = \mathbf{Q} \cdot \mathbf{H} - \mathbf{H} \cdot \mathbf{Q} - \alpha \mathbf{H}, \quad (4.10)$$

where α is the tumbling parameter. Here we have neglected many α dependent terms at the same order, because we wanted the lowest order effects of the alignment term at the lowest orders in $\mathbf{Q}$. Note that in the simulations reported throughout this chapter, we have neglected the passive orientational stress, since we were interested in the activity-dominated regime.

Finally, the nematic also enters the active stress. Intercalation movements, directed cell migration, oriented cell divisions, etc, generate point forces. The first moment of the force distribution is zero and therefore the dominant contribution from activity is a stress/force dipole (second moment of the force distribution). Without loss of generality, we choose the active stress to be

$$\boldsymbol{\sigma}_{\text{active}} = \zeta \frac{\rho}{\rho + \rho_s} \mathbf{Q}, \quad (4.11)$$

where ρ is the cell number density, ρ_s is the saturation density beyond which active stress asymptotes to a constant, and ζ is the active stress strength. When $\zeta < 0$, active-

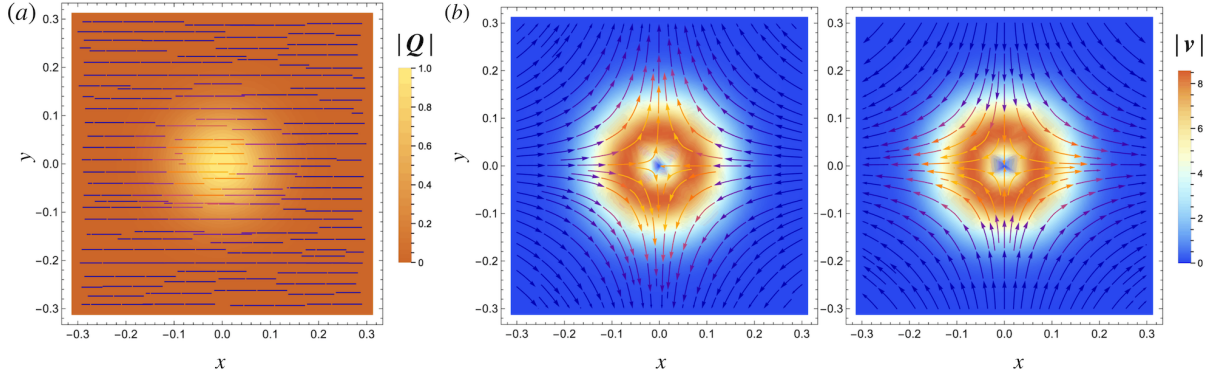


Figure 4.3: (a) Visualization of a nematic field $Q(x, y) = e^{-100(x^2+y^2)}((1, 0), (0, -1))$, centered at the origin. Color denotes magnitude in space, and lines denote the eigenvector corresponding to the largest eigenvalue. (b) Flow generated by the nematic in (a) for a contractile particle, i.e. $\zeta > 0$ in Equation (4.11). (c) Flow generated by the nematic in (a) for an extensile particle, i.e. $\zeta < 0$ in Equation (4.11). Flow was computed as divergence of the nematic field.

nematic particles are of the "pusher/extensile" type, i.e., flows align along the long axis of the nematic. On the other hand, when $\zeta > 0$, active-nematic particles are of the "puller/contractile" type, i.e., flows align along the short axis of the nematic [Figure 4.3].

The full model in presence of Q is now:

$$\text{Kinematics} \quad \frac{dx}{dt} = v, \quad D_t u = v \quad (4.12)$$

$$\text{Force balance} \quad \gamma v = \nabla \cdot \sigma \quad (4.13)$$

$$\begin{aligned} \text{Constitutive relation} \quad \sigma &= \sigma_{\text{elastic}} + \sigma_{\text{viscous}} + \sigma_{Q,\text{passive}} + \sigma_{\text{active}} \\ &= \sigma_{\text{elastic}} + \sigma_{\text{viscous}} + Q \cdot H - H \cdot Q - \alpha H + \zeta \frac{\rho}{\rho + \rho_s} Q \end{aligned} \quad (4.14)$$

$$\text{Cell number balance} \quad D_t \rho = -(\nabla \cdot v) \rho + \kappa \rho \left(1 - \frac{\rho}{\rho_0}\right) \quad (4.15)$$

$$\text{Dynamics of } Q \quad D_t Q + Q \cdot \Omega - \Omega \cdot Q - \alpha S E = -\mu H \quad (4.16)$$

$$\begin{aligned} H &= \frac{\delta F}{\delta Q} - \frac{1}{d} \text{Tr} \frac{\delta F}{\delta Q} \\ F &= \int d^d x \left[A \left(\frac{\rho_0}{2} - \rho \right) \text{tr} Q^2 + C_1 (\text{tr} Q^2)^2 \right. \\ &\quad \left. + C_2 \text{tr} Q^4 + K_Q (\partial_\gamma Q_{\alpha\beta}) (\partial_\gamma Q_{\alpha\beta}) \right] \end{aligned}$$

$$\text{Boundary conditions} \quad n \cdot \nabla Q|_{\partial\Omega(t)} = 0; \quad n \cdot \sigma|_{\partial\Omega(t)} = 0 \quad (4.17)$$

For an unbounded system, and no damping effects via viscosity/friction, an aligned extensile (contractile) active nematic is unstable to bend (splay) deformations for any

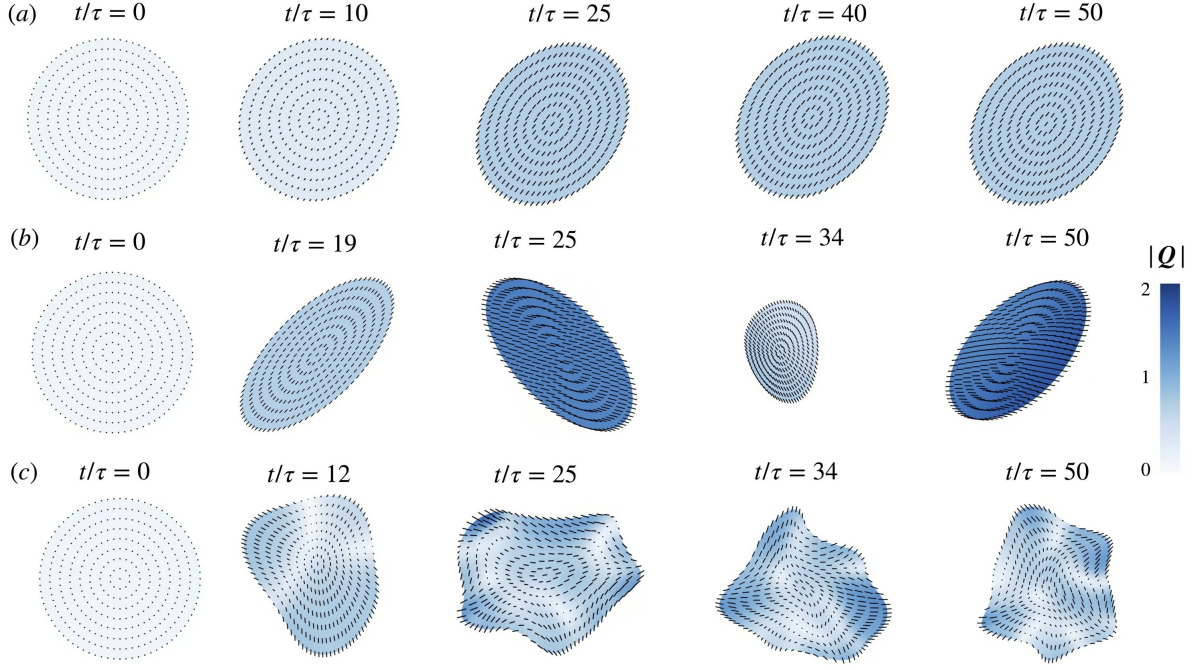


Figure 4.4: Numerical solutions of Equation (4.12) - Equation (4.16). Each row shows time evolution of the solution at different values of $K_Q \gamma / A \rho_0 \eta$, the ratio of the correlation length of the nematic and hydrodynamic length for the tissue, and different values of ζ / E , the ratio of the active stress stress strength and elasticity of the tissue. (a) $K_Q \gamma / A \eta \rho_0 = 1$, $\zeta / E = -1$. (b) $K_Q \gamma / A \eta \rho_0 = 10^{-4}$, $\zeta / E = -3$. (c) $K_Q \gamma / A \rho_0 \eta = 10^{-5}$, $\zeta / E = -3$. All other parameters were fixed as stated in Appendix 4.A. The passive orientational stress has been neglected in these simulations.

non-zero activity. This is the Simha-Ramaswamy instability [101], characterised by chaotic dynamics in which defects spontaneously appear and annihilate. For a finite system of size L , however, there is a critical activity K_Q / L^2 , beyond which chaotic states appear [99]. In addition to confinement, friction and viscosity are also known to suppress the Simha-Ramaswamy instability. In our simulations, we see a plethora of states — quiescent and chaotic — depending on the ratio of the correlation length of the nematic $\sqrt{K_Q / A \rho_0}$ and the hydrodynamic length $\sqrt{\eta / \gamma}$ of the tissue (see Figure 4.4).

The other non-dimensional numbers in the problem, and what they represent, is discussed in Section 4.A. Exploration of the parameter space with so many non-dimensional numbers is unfeasible. Instead, we wonder if the model can be adapted to a real experimental system. This is done in the next section, where we study the growth and shape kinetics in a real system, viz embryonic explants of zebrafish. We modify the general model above to exclude dispensable fields (like the number density of cells) and include more relevant fields like the signal of *Wnt*.

4.3 Growth dynamics of zebrafish explants and comparison to our model

In this section, we study the semi-autonomous growth of zebrafish explants, incorporating forcing by a signaling morphogen in the model detailed above. First, we quantify the growth dynamics, cell divisions, and cell shapes from experimental data, and use some of these observations to modify the model developed in the previous section. We then compare the predictions of the model with the experiments, and discuss some limitations.

At the 1000 cell stage (3 hours post fertilization (hpf)) during the development of zebrafish, our experimental collaborators separated the blastoderm from the yolk of the zebrafish embryo and incubated it for 4 hours, after which bright field microscopy was performed. The explant soon breaks radial symmetry, elongates preferentially along one direction and bends (see Figure 4.7b).

Quantification of growth dynamics, cell shapes, cell divisions, and the modified model

From the time lapse movies of the growing explant, the long axis of the convex hull of the time-dependent boundary shape was calculated. The time dynamics of this long axis showed that there was an initial lag phase, followed by an exponential phase [Figure 4.5 (a), (b)]. This analysis was repeated for explants treated with *hydroxyurea* (HUA), which blocks 80% cell divisions, and explants with knocked-down *Ecad*, which inhibits junctional elasticity. The former was done to explore the contribution of (oriented) cell divisions on elongation, and the latter to explore the role of cell-cell junctions in convergence extension. These perturbations have direct analogues for the model we develop.

The long axis dynamics for HUA-treated explants was indistinguishable from the wild-type [Figure 4.5(c)]. Further, there were only 40-60 cell division events per explant. However, 60% of them underwent oriented division, with their axes of division being within 30° of the elongation direction. This indicates that cell division, although correlated with elongation, is dispensable. Thus, for the model, we will ignore the dynamics of the cell number density field. Further, *Ecad*-knockdown mutants showed a time-lag in reaching the exponential phase, after which, elongation occurred at the same rate as the wild type [Figure 4.5 (c)]. The final size for *Ecad* mutants was, however, slightly smaller as compared to the WT.

Since cell division does not seem to be driver of shape change for the explant, we hypothesized that anisotropy in overall tissue shapes and flows may have its origins

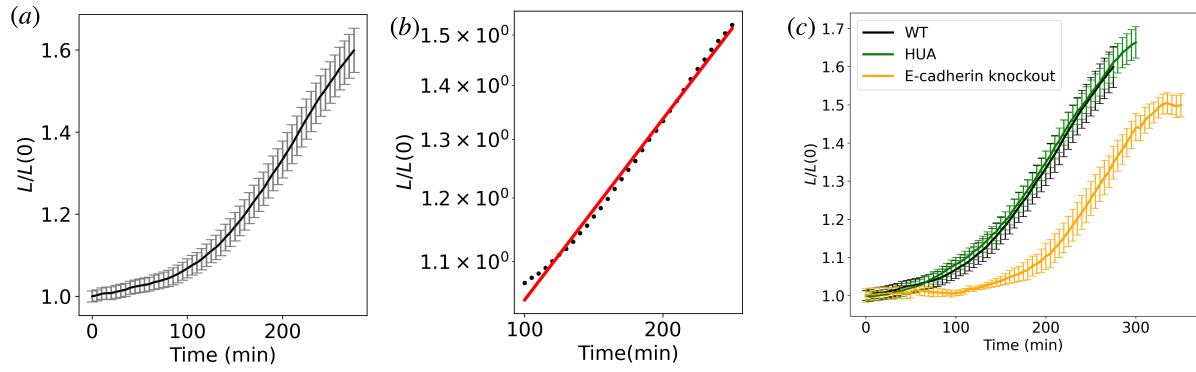


Figure 4.5: (a) Length of the long axis of the convex hull of the growing explant in time shows an initial lag phase followed by an exponential phase and saturation. (b) The same long axis as in (a) plotted on a log-linear scale for $t = 100$ to $t = 250$ min. Dots indicate experimental data and the best fit line to the experimental data is plotted in red. (c) Comparison of the long axis of the wild type (WT), a cell-division-inhibited mutant (HUA) and a junctional-elasticity-inhibited mutant (E-cadherin knockout).

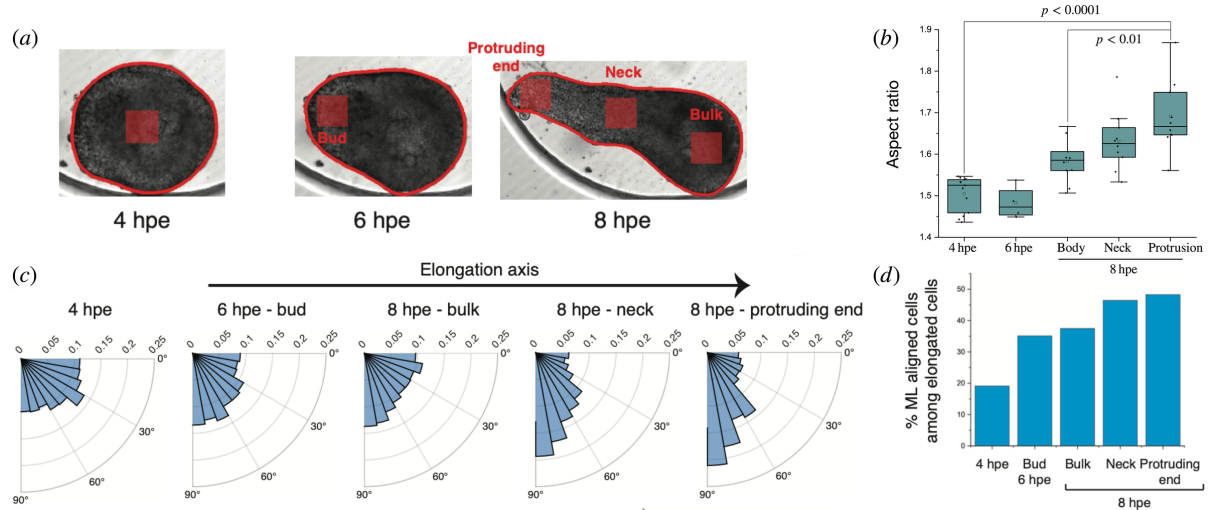


Figure 4.6: Quantification of cell shapes in the growing explant. (a) Representative images of the explants at the analyzed stages. Red boxes indicate region where high-resolution imaging was performed. (b) Aspect ratio of cells at specified time points. Individual data points are average aspect ratios of cells from respective explants. On each box, the solid line indicates the median and the bottom and top extents of the box represent the 25th and 75th percentiles respectively. (c) Cell orientation angle with respect to the axis of elongation (0°) at all stages except 4 hpe, where orientation was determined with respect to the horizontal axis. Constant bin width of 10° was used and the fraction of cells in each bin is indicated with blue bars. (d) Percentage of mediolaterally aligned cells ($\pm 20^\circ$ of axis of elongation) among elongated cells, which we define as cells with an aspect ratio of at least 1.7. Quantifications for this figure were performed by Arkajyoti Sanyal, Swarali Dighe and Sundar Naganathan. It has been included here with their permission.

in polarised cell shapes. To check this, explants were fixed at the round stage [4 hpe (hours post explant)], bud stage [6 hpe], and elongated stage [8 hpe]. These fixed ex-

plants were stained with phalloidin, which marks actin filaments (and thus, the cell membrane), and DAPI, which marks the nucleus. Cells were segmented using CellPose and then the aspect ratio of cells, and the orientation of their long axis w.r.t the elongation axis of the explant, was measured. This was done for the maximum intensity projection of 3-4 z-slices at $50 \mu m$ depth from the surface of the explant at the round, bud and elongated stages. Within the elongated stage, measurements were carried out separately in the bulk, neck and protruding end [Figure 4.6 (a)]. Aspect ratio showed a marked increase for the elongated stage, within which the protruding end had more elongated cells as compared to the bulk of the explant [Figure 4.6 (b)]. Further, the fraction of cells with their long axis perpendicular to the direction of elongation increased significantly with the stage of development, and spatially as one goes from the bulk to elongating region in the final stage [Figure 4.6 (c), (d)]. These observations indicate that we can think of the nematic field of our model as originating primarily from alignment of cell shape axes/cell intercalation directions, with the sign of active stress ensuring contractile/puller behavior. This analysis also shows that the correlation length of the nematic is smaller than the size of the tissue as a whole.

The most important modification to our current model is from signaling morphogens like *Wnt*, which are known to localise to one end of the explant before elongation begins [102]. We prescribe a forcing by *Wnt*, given by $c(x, t) = c_0 \left(1 + \tanh \left(\frac{x(t) - x_0(t)}{w} \right) \right)$, where $x(t)$ are the moving material points, $x_0(t)$ is the center of the hyperbolic tangent curve, prescribed to be within a fixed neighbourhood of $\partial\Omega(t)$, (experiments indicate that the signal scales with growth) and w is the width or steepness of the signal. This morphogen enters the active stress and the symmetry breaking terms of the free energy, since convergence extension movements are greater in the region where *Wnt* is present (the elongating region). Our modified model therefore becomes

$$\text{Kinematics} \quad \frac{dx}{dt} = v, \quad D_t u = v \quad (4.18)$$

$$\text{Force balance} \quad \gamma v = \nabla \cdot \sigma \quad (4.19)$$

$$\begin{aligned} \text{Constitutive relation} \quad \sigma &= \sigma_{\text{elastic}} + \sigma_{\text{viscous}} + \sigma_{Q, \text{passive}} + \sigma_{\text{active}} \\ &= \sigma_{\text{elastic}} + \sigma_{\text{viscous}} + Q \cdot H - H \cdot Q - \alpha H + \zeta \frac{c}{c + c_s} Q \end{aligned}$$

$$\text{Dynamics of } Q \quad D_t Q + Q \cdot \Omega - \Omega \cdot Q - \alpha S E = -\mu H \quad (4.20)$$

$$\begin{aligned} H &= \frac{\delta F}{\delta Q} - \frac{1}{d} \text{tr} \left(\frac{\delta F}{\delta Q} \right) \\ F &= \int d^d x \left[A \left(\frac{c_0}{2} - c \right) \text{tr} Q^2 + C_1 (\text{tr} Q^2)^2 \right. \\ &\quad \left. + C_2 \text{tr} Q^4 + K_Q (\partial_\gamma Q_{\alpha\beta}) (\partial_\gamma Q_{\alpha\beta}) \right] \\ \text{Signaling profile} \quad c &= c_0 \left(1 + \tanh \left(\frac{x(t) - x_0(t)}{w} \right) \right) \end{aligned} \quad (4.21)$$

$$\text{Boundary conditions} \quad \mathbf{n} \cdot \nabla \mathbf{Q}|_{\partial\Omega(t)} = 0; \quad \mathbf{n} \cdot \boldsymbol{\sigma}|_{\partial\Omega(t)} = 0 \quad (4.22)$$

Model predictions and limitations

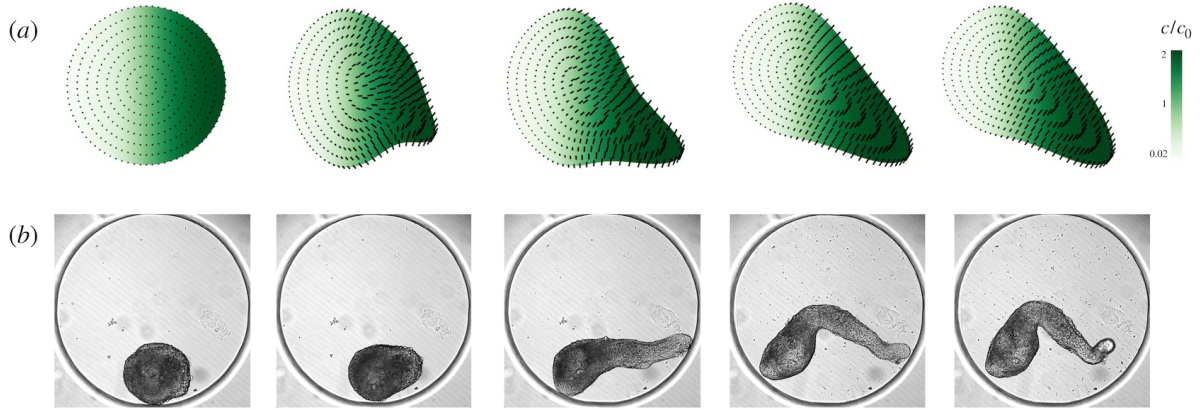


Figure 4.7: (a) Snapshots of simulation results for Equation (4.18)-Equation (4.21) with random initial conditions for $\mathbf{Q}$. The passive orientational stress has been neglected. Other parameters were fixed as in Section 4.B. Lines indicate the direction of the eigenvector associated with maximum eigenvalue of $\mathbf{Q}$. (b) Snapshots from the experimental movie.

The model above shows qualitatively the same growth behavior as the experiment (see Figure 4.7 for the simulation with parameters fixed as in Section 4.B). The explant can also bend, depending on either the direction $\mathbf{Q}$ picks up spontaneously with respect to the direction of ∇c , or due to the active nematic instability in contractile active nematics at low friction in the model. As in the simple model without nematic, here too, the competition between elasticity and magnitude of active stress at the boundary can result in determinate or indeterminate growth. Motivated by the difference in growth trends between the wild type and an Ecad-knockdown mutant as in Figure 4.5(c), we wondered if the model also shows this behaviour. What does a knock-down of Ecad translate to for the model? The way we understand it is that cells in Ecad knockdown mutants lose their ability to show directed cell rearrangements because of the inhibition of junctional contacts. In the model, this means reducing the alignment strength in the $\mathbf{Q}$ equation, which produces qualitatively similar dynamics as the experiment (Figure 4.8).

However, there are some marked differences between the experiment and the model: For one, in the experimental growth dynamics (Figure 4.5(c)), the ecad knockdown mutant shows a growth lag and then eventually picks up the same growth rate and final size as the wild type. While the final size can be tuned in the model via ζ/E , we

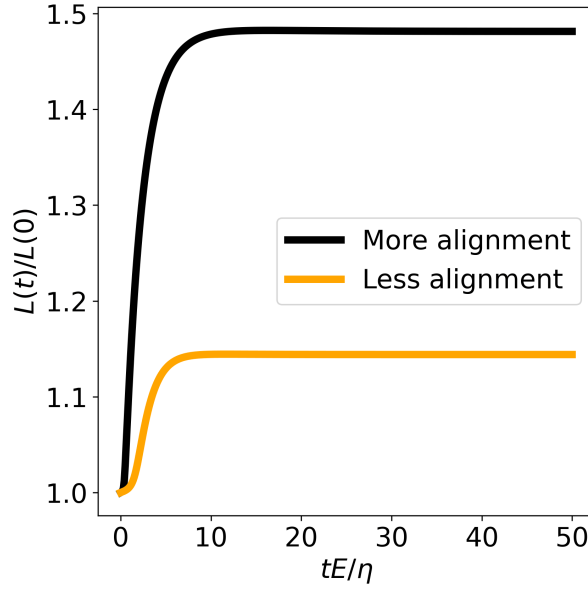


Figure 4.8: Long axis of the growing explant from solution of Equation (4.18) - Equation (4.21) for strong and weak alignment of the nematic. Parameters were fixed as in Section 4.B. Initial condition was set such that the long axis of $\mathbf{Q}$ is perpendicular to the direction set by ∇c . This plot from the model should be compared with the same analysis from the experiment as in Figure 4.5(c).

do not understand yet how to get the mutant (in the model) to reach the same growth rate. Perhaps in the real system, regulatory mechanisms come into play to ensure the growth rates and final sizes are not too affected by inhibiting junctional contacts.

4.4 Summary

In this chapter, we extended the growth model with a displacement, density and velocity field to now also include an orientational field representative of alignment of cell intercalation directions and/or cell division axes, etc. We saw quiescent and chaotic states reminiscent of active turbulence. We then adapted the model to explain growth behavior of zebrafish explants. Our model was modified to be devoid of the density field, since there were not many birth/death events during the convergence extension process, and, to include a morphogen field implicated in convergence extension movements. This morphogen was included as a prescribed forcing via a hyperbolic tangent profile as seen in experiments. With these additional fields, we were able to recover qualitatively some features of shape transitions seen in explanted tissue of zebrafish embryos.

It is worth placing this model in the context of other models for deformable tissues and/or cell aggregates that break symmetry to preferentially elongate along one direction. In [103], the authors obtain unidirectional elongation of zebrafish body axis from

an isotropic viscous fluid model, whose anisotropy comes from a prescribed viscosity gradient and a mass source localised at the tip. The symmetry breaking here is a material property, unlike ours, and there is no active stress. In [104], the authors model cell aggregates as deformable two-phase droplets with Cahn-Hilliard dynamics coupled to Stokes flow. Here too, the dynamics is passive, and an orientational field does not exist. Symmetry is broken via phase separation of the binary fluid system. Perhaps the model closest to ours is that of [105], which carries a nematic order parameter representing actomyosin cables. This model reproduces the transformation of the chick embryo proper from a disc to a pear shape. However, the model has no elastic stresses, and boundaries move with a prescribed velocity, in contrast with our model where the boundaries are free.

Clearly, elongation from a round initial condition is non-unique – a prescribed viscosity gradient, Cahn Hilliard dynamics, and an active nematic model can all produce it. This suggests that the model needs to be supported by quantitative, not just qualitative, agreements with experimental data. In this context, a careful inspection of what an Ecad knockdown means and what it can represent in the model is warranted. Particle Imaging Velocimetry (PIV) can be used to captures features of the flow that can be compared between the model and experiment. Further, one expects different profiles of Wnt to generate different shapes for the growing explant. Perhaps Wnt-soaked beads in the experimental system can create specific Wnt profiles, and the Wnt-profile-explant-shape dependence can be studied.

Appendices

4.A Parameters in the model with a nematic field

Parameter	E_b/E	η_b/η	ζ/E	ρ_s/ρ_0	$\mu A \tau \rho_0$	$\mu C_1 \tau$	$\mu C_2 \tau$	α	$\kappa \tau$	$K_Q \gamma / A \eta \rho_0$
Value in Figure 4.4	1	1	(a) -1 (b) -3 (c) -3	1	1	1	0	2	1	(a) 1 (b) 10^{-4} (c) 10^{-5}

The simulation assumes bulk and shear properties to be of the same order E_b/E , $\eta_b/\eta \sim 1$. Typically, bulk moduli are larger than shear moduli in 3D tissues. In a 2D cell monolayer, however, cells are not strictly confined to a volume – they can change their height or extrude out from the layer to relieve pressure. This "effective compressibility" in 2D means that the energy cost for tissue expansion/contraction (dilatation) is comparable to the cost of changing shape. $E_b \gg E$ also makes the equations stiff – small changes in density create massive pressure spikes. This requires incredibly small time steps to solve the system.

Further, the system is in a high-activity extensile regime, as indicated by $\zeta/E = -3$. This indicates that active forces are the dominant driver of morphology.

Moreover, $\rho_s/\rho_0 = 1$ indicates that the capacity for cells to generate collective stress starts to level off when the tissue reaches its equilibrium density ρ_0 . The observed behaviour in Figure 4.4 persists even when this ratio is modified.

The parameter $\mu A \tau \rho_0$ measures the competition between the mechanical relaxation time (τ) and the relaxation time set by the dynamics of the nematic ($\mu A \rho_0$). Setting it to one implies that if you perturb the cell alignment, it will return to its preferred state at roughly the same speed as the tissue relaxes its elastic stresses.

Finally, $\alpha = 2$ indicates a strong flow-aligning regime in a rod-like cell and $\kappa \tau = 1$ denotes that the cell proliferation rate (κ) is matched to the rate of relaxation of mechanical stresses (τ^{-1}).

4.B Parameters in the model with a nematic field and morphogen forcing

Parameter	E_b/E	η_b/η	ζ/E	c_s/c_0	x_0/ℓ	w/ℓ	$\mu A \tau c_0$	$\mu C_1 \tau$	$\mu C_2 \tau$	$K_Q/A c_0 \ell^2$	α
Value in Figure 4.7 and Figure 4.8 (More alignment)	1	1	2	1	0	5×10^{-2}	10	10	0	10^{-4}	2
Value in Figure 4.8 (Less alignment)	1	1	2	1	0	5×10^{-2}	2	10	0	10^{-4}	2

The physical meaning for parameters is same as in Section 4.A, except that the parameters corresponding to the density field are now replaced by those corresponding to the signaling morphogen. There are two new parameters – the origin of the tanh signaling profile x_0/ℓ and the width of the tanh, w/ℓ .

Chapter 5

Conclusions and perspectives

In this thesis, we explored three examples of the interplay between pattern, shape and growth in morphogenesis.

In Chapter 2, we ignored growth to explore the one-way coupling between the shape of a confining domain and patterns in the actomyosin cortex of cells. In the context of a hydrodynamic model for the cortex, we developed a framework to reduce the PDE system to a coupled ODE system for the modes of the concentration field, where geometry, encoded in eigenfunctions of the Laplacian on that domain, enters as a bifurcation parameter. This framework requires knowing these eigenfunctions, the Green's operator for the modified Helmholtz equation on said domain and Dirichlet-Neumann operators. For a disk, the phase diagram from stability analysis of the equations for the amplitudes of a mode-truncated system matches very well with the numerics, showing how anisotropic patterns give way to isotropic patterns as the Péclet and Damköhler number in the model are tuned. On harmonic deformations of the disk, patterns sit on low/high curvature regions depending on this Péclet and Damköhler number. For deformations of the disk, the operators in question can either be computed numerically, or as perturbative expansions of their forms on a circle. The geometry-dependent parameters in the ODE model can also be made time-dependent, lending insight on what happens to these patterns for imposed geometrical deformations in time. Finally, the model can be modified to include an orientational degree of freedom that is representative of the alignment of actin fibres. The dependence of these orientation patterns on domain shape has also been explored experimentally [44,45]. A preliminary study of the model with nematic on a disk reveals that there are regimes in parameter space where two ($+1/2$) defects sit at two opposing poles of the disk, and regimes where they chase each other in time. A detailed exploration of the geometry-dependence of such a model with nematic is left for future work.

In Chapter 3, we developed a minimal model for a growing tissue, where we uncovered bounded and unbounded growth regimes depending on the competition between elasticity and active stresses due to cell birth/death. These phases are remi-

niscent of determinate and indeterminate growth, atleast in terms of the shape of the growth curve in the two phenotypes. We obtained expressions for final size in the controlled (determinate) growth phase and growth rate in the perennially growing (indeterminate growth) phase in (a) a model with applied boundary stress and no activity in the bulk and (b) a model with zero stress at the boundary but a non-zero active stress in the bulk. We also saw oscillatory solutions in the low birth/death rate limit of the model, owing to the chosen contractile-extensile form of active stress. Proportionate growth of heterogeneous tissues, where length fractions of the different parts of the tissue become frozen in time, can be explored as an outcome for the model with and without activity. One can also incorporate a morphogen in the model, and explore conditions that could lead to a pattern of the morphogen that scales with growth. An interesting feature of our model for growth is that the constitutive laws in this framework are tied to the kinematics of the problem, since the model uses current-configuration strain, and the current configuration evolves in time. Our approach in modeling the problem of growth involves studying it as an emergent feature/consequence of the underlying processes. An exploration of a version of our model where the constitutive relation is *nominally* long-time fluid is left for future work. The work can also be extended to include non-autonomous influences by making the reference configuration with respect to which elastic strains are calculated, evolve in time. Finally, the problem can be extended to pose size regulation (in the context of the simple model we proposed) as a control problem. We can convert the PDE problem involving displacement and flow fields living on a deformable domain to an ODE problem for the final length of the tissue in one dimension, after which standard control-theoretic methods for ODEs apply. The control problem is to choose an active stress (residing by design only in the bulk or only near the boundary) such that the final length tends to a given value at a given time.

In Chapter 4, we studied how tissues break symmetry by including orientation fields that are representative of alignment of cell-rearrangement directions and/or cell division axes in our model. We observed quiescent and chaotic states reminiscent of active turbulence. With an imposed signaling profile and no density field, this model shows growth kinetics that resembles those seen in zebrafish explants. The model also predicts different shapes corresponding to different signaling profiles, in addition to variations in shapes produced by varying the parameters in the problem. For instance, reducing the width of the signaling profile (keeping other parameters and initial conditions fixed) leads to more pronounced bending in the explant. This can perhaps be tested in an experiment.

All in all, these three problems explored minimal models coupling geometry (via boundary conditions), pattern formation (in scalar, vector, tensor fields) and emergent growth behaviors resulting from these patterns, in a continuum mechanics framework.

The models are two-dimensional, deterministic, and continuum, and the biological systems they describe are sampled from a much broader landscape of morphogenetic phenomena. Much is left out — cell-level heterogeneity, noise, three-dimensional geometry, and the full complexity of the underlying biochemistry. Whether the qualitative conclusions survive these omissions is, in each case, an open empirical question. What the framework does offer is a language for posing such questions precisely.

Publications based on this thesis

1. **Jigyasa Watwani**, Sakshi Pahujani, Jemseena V., Vishal Vasani and K. Vijay Kumar. [Phys. Rev. E.](#), 2025. "Influence of boundary geometry on active patterns." This article was chosen as an Editor's suggestion.

In-preparation

1. **Jigyasa Watwani**, K. Vijay Kumar, Vishal Vasani. "A hydrodynamic model for determinate and indeterminate growth in model tissues."
2. **Jigyasa Watwani**, K. Vijay Kumar, Vishal Vasani. "Orientation dynamics in a growing tissue."
3. Arkajyoti Sanyal, Swarali Dighe, **Jigyasa Watwani**, Vishal Vasani, K. Vijay Kumar, Sundar Naganathan. "Elongation dynamics in zebrafish explants."

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Index

- active stress, 17–20, 22, 25, 35, 46, 48, 49, 53, 56–58, 69, 71, 73, 75, 78, 79, 83, 84
- actomyosin cortex, 16–20, 34, 83
- constitutive relation, 49, 54, 58, 59, 74, 84
- determinate growth, 16, 17, 45, 46, 48, 51–53, 58, 79, 84
- Dirichlet-Neumann operators, 24–26, 33, 35, 41, 42, 83
- Drosophila*, 12, 14, 46, 69
- explant, 17, 69, 75–80, 84
- finite element, 30, 42, 52, 61
- force dipole, 47, 73
- force-balance, 20, 36, 47, 49, 54, 56, 74, 78
- galerkin, 19, 21, 22, 25, 26, 28–31, 34, 35, 42
- growth, 12–17, 19, 45, 46, 48, 50, 52, 53, 56, 58, 59, 63, 64, 66, 67, 69, 75, 76, 78–80, 83, 84
- Helmholtz theorem, 23, 38
- indeterminate growth, 16, 17, 45, 46, 48, 52, 53, 58, 79, 84
- Landau-de Gennes free energy, 72
- mechanochemical patterns, 18
- morphoelasticity, 15, 58
- morphogenesis, 12, 14, 15, 17
- nematic, 17, 35, 53, 69, 70, 72–75, 78–83
- proportionate growth, 17
- signaling, 14, 15, 17, 46, 48, 53, 69, 76, 78, 82, 84
- Simha-Ramaswamy instability, 75
- Turing patterns, 15
- updated Lagrangian method, 47, 62
- viscoelastic, 20, 46, 48, 58
- zebrafish, 12–14, 17, 69, 76