Patterns Analysis in Coupled Parabolic-ODE Systems

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Abstract

This thesis builds upon previous work pioneered by Anna Marciniak-Czochra in using coupled reaction-diffusion equations to ODE to model pattern formation in Hydra, a freshwater polyp known for its regenerative abilities. Previous studies have shown that such models can successfully capture the emergence of spatial patterns of gene expression during regeneration, and have identified key signaling molecules such as Wnt and Notch as playing a critical role in this process. However, these models have largely ignored the physical properties of the tissues in which regeneration occurs. In this thesis, we come back to the model presented in [6] that integrates coupled reaction-diffusion to ODE models and see if we can reduce the amount of parameters, exhibit hysteresis and investigate the phenomenon occurring when we let one of the diffusion coefficients grow to infinity: shadow limits. Ultimately, this thesis aims to provide classical results on the topic and use these notions to further extend the analysis of the model.

Remark 1 (Color code for Editing). *Each color has a meaning:*

Pink text: A remark / Comment: `\com{ ...}`

Green text: Potential text to include but has the wrong formulation: `\incl{ ...}`

Blue text: A reference that is missing and has to be included in the bibliography : `\bref{ ...}`

Contents

> "In the 300 years since Newton, mankind has come to realize that the laws of physics are always expressed in the language of differential equations"
>
> — *Steven Strogatz*

1 Notations and Definitions

In the entirety of the thesis, we use the following naming conventions

- Δ: The Neumann Laplace operator defined by $\Delta f = \sum_{j=1}^{n} \frac{\partial^2 f}{\partial x_j^2}$ with domain

$$\mathcal{D}(\Delta) = \left\{ f \in \bigcap_{p \geqslant 1} W_{loc}^{2,p}(\Omega) : f, \Delta f \in \mathcal{C}(\Omega) \text{ and } \frac{\partial f}{\partial \nu} = 0 \text{ on } \partial\Omega \right\}$$

this notation is the one from [2], maybe it is unnecessarly developped for this thesis

Definition 1 (Sobolev spaces). *Let $\Omega \subset \mathbb{R}^n$ be a bounded domain with $\partial\Omega \in \mathcal{C}^1$. We denote by $W^{k,p}(\Omega)$ the Sobolev space defined by*

$$W^{k,p}(\Omega) := \left\{ u \in L^p(\Omega) : \forall \alpha \in \mathbb{N}^n, \varphi \in \mathcal{C}^\infty(\Omega), \exists v \in L^p(\Omega) : \int_\Omega v\varphi = (-1)^{|\alpha|} \int_\Omega u\partial^\alpha\varphi \right\}$$

Definition 2 (spectral bound). *Let $(L, \mathcal{D}(L))$ be a linear operator with spectrum $\sigma(L)$. We define the spectral bound $s(L)$ by*

$$s(L) = \sup\left\{ \mathfrak{Re}(\lambda) : \lambda \in \sigma(L) \right\}$$

Definition 3 (Growth Exponent). *We call the growth exponent of an exponentially bounded $\mathcal{C}^0$-semigroup $(T(t))_{t \geqslant 0}$ the real number w defined by*

$$w = \inf_{\mathbb{R}}\left\{ w : \exists M > 1, \forall t \geqslant 0, ||T(t)|| \leqslant Me^{wt} \right\}$$

2 Hydra Morphogenesis and regenerative properties

3 The importance of Wnt signaling

4 Emergence of Patterns and Diffusion-Driven Instability

How do patterns form? Pattern formation is the result of the collaboration of a large amount of biological processes ranging from the nanoscopic up to the microscopic scale. Together, they form motifs, which we define as the structural organization of cells in space and time, often leading to pretty shapes such as the fur coat in animals or that on the wings of a butterfly. In his pioneer paper published in 1952 [ref], Alan Turing proposes a

chemical model for pattern formation involving two chemical species: one Activator (u), one Inhibitor (v) (Probably inspired from the Lotka-Volterra prey-predator model introduced in 1910 which was itself applied to mathematical biology for the first time in 1926). The concentration of each specie is described with 2-morphogens reaction-diffusion equations with appropriate boundary conditions, *i.e.* equations of the form

$$\partial_t u = d_1 \Delta u + f(u,v) \qquad \text{on } \mathbb{R}^+ \times \Omega$$

$$\partial_t v = d_2 \Delta v + g(u,v) \qquad \text{on } \mathbb{R}^+ \times \Omega \qquad (4.1)$$

$$\partial_\nu u = 0; \quad \partial_\nu v = 0 \qquad \text{on } \partial\Omega$$

$$u(0,x) = u_0(x); \quad v(0,x) = v_0(x) \qquad u_0, v_0 \in X \qquad (4.2)$$

for a specific choice of f and g describing the chemical kinetics of the reaction. This choice is usually what determines the model type. To cite a few, we enumerate the Gray-Scott Model, Gierer-Meinhardt, Fitzhugh-Nagumo , Bard-Lauder , Schnakenberg, Belousov-Zhabotinskii, the list goes on... [B. Perthame]

5   General Theory

Consider positive integers $k, m, n \in \mathbb{N}$ such that $m + k = n$ and a bounded domain $\Omega \subset \mathbb{R}^n$. Let the $\mathcal{C}^2$-function $\boldsymbol{f} : \mathbb{R}^k \times \mathbb{R}^m \longrightarrow \mathbb{R}^{m+k}$ describe the reaction kinetics. We aim to investigate properties of the reaction-diffusion-ODE problem

$$\begin{aligned}
\partial_t \boldsymbol{u} &= \mathbf{D}\Delta\boldsymbol{u} + \boldsymbol{f}(\boldsymbol{u}) & &\text{on } \Omega \times \mathbb{R}^+ \\
\nabla u_i \cdot \nu &= 0 & &\text{on } \partial\Omega \times \mathbb{R}^+, \text{ for } i \in [\![m+1, k]\!] \qquad (5.1) \\
\boldsymbol{u}(\cdot, 0) &= \boldsymbol{u}_0(\cdot) & &\text{on } \Omega,
\end{aligned}$$

Theorem 1 (Spectral Mapping Theorem). *Consider a locally compact space X. Let A be the generator of a positive, bounded, compact, strongly continuous group on $\mathcal{C}_0(X)$, denoted by $(L(t))_{t\in\mathbb{R}}$. Then*

$$\sigma(L(t)) = \overline{\exp(t\sigma(A))}$$

Proof. see Theorem 1.1. from [1] $\qquad\qquad\square$

Definition 4 (Submatrices defined by a pair of indices). *Consider a matrix $A \in \mathcal{M}_n(\mathbb{R})$, for any couple of distinct indices (i,j) with $1 \leqslant i,j \leqslant n$, we introduce the notation A_{ij} to be the 2×2-matrix whose entries are formed by the entries of A on line and column i, j.*

Proposition 1 (Characteristic polynomial of a 3×3 matrix). *Consider a matrix $A \in \mathcal{M}_3(\mathbb{R})$ whose entries are the a_{ij} for $1 \leqslant i,j \leqslant 3$. Then*

$$\chi_A(\lambda) = -\lambda^3 + \operatorname{tr}(A)\lambda^2 - \left(\sum_{i<j} \det(A_{ij})\right)\lambda + \det(A)$$

Proof. It is a straightforward computation. The characteristic polynomial of A is given by

$$\det(A - \lambda) = \det \begin{pmatrix} a_{11} - \lambda & a_{12} & a_{13} \\ a_{21} & a_{22} - \lambda & a_{23} \\ a_{31} & a_{32} & a_{33} - \lambda \end{pmatrix}$$

By the rule of Sarrus, we get

$$\det(A - \lambda) = (a_{11} - \lambda)(a_{22} - \lambda)(a_{33} - \lambda) + a_{12}a_{23}a_{31} + a_{13}a_{21}a_{32}$$
$$- (a_{11} - \lambda)a_{23}a_{31} - (a_{33} - \lambda)a_{12}a_{21} - (a_{22} - \lambda)a_{13}a_{31} \quad (5.2)$$

$$= -\lambda^3 + (a_{11} + a_{22} + a_{33})\lambda^2$$
$$- (a_{11}a_{22} - a_{21}a_{12} + a_{11}a_{33} - a_{31}a_{13} + a_{22}a_{33} - a_{32}a_{23})\lambda + \det(A) \quad (5.3)$$

Hence the final result

$$\det(A - \lambda) = -\lambda^3 + \text{tr}(A)\lambda^2 - \left(\det(A_{12}) + \det(A_{13}) + \det(A_{23}) \right)\lambda + \det(A)$$

$\square$

- Linear / NonLinear decomposition

- Bound on the Nonlinear part $\mathcal{N}$

- Why is the spectrum so important here

- Define DDI

- Maybe include Finn's result on the d_1 d_2 ? (and add full acknowledgement to his work)

- linearization of a PDE system

- Solving for the eigenvalue problem

6   Reduction of the Model

In order to simplify the system, we use a two-step approach. First, by applying a quasi-steady-state approximation, and then by using a change of variable to further reduce the amount of parameters.

6.1 Quasi-steady-state approximation

The Quasi-steady-state (QSS) approximation is a technique inspired from the field of chemical kinetics or more generally biochemistry. When introduced, the purpose of such an approximation is to simplify the analysis by assuming that certain chemical species are reaching their steady-state concentrations quicker than other species in the system.

Previously used in an *ad hoc* fashion by biologists, QSS Approximation is now carefully described thanks to the framework provided by singular perturbation theory for equations emerging from chemistry. When performing QSS Approximation, the rate of change of concentrations of these slower species is assumed to be negligible compared to the rates of other reactions in the system. Therefore, the concentrations of these species can be approximated as constants during the time course of the reaction.

Remark 2. *Although the QSS Approximation can be proven to be physically relevant when applied to some systems (Reaction-Diffusion equations are a good example), the approximation may not always hold true under certain conditions.*

Coming back to our system, we perform a QSSA on the quantity r_b, *i.e.*, we assume $\frac{\partial r_b}{\partial t} \equiv 0$. and find that $(d + \mu_b)\boldsymbol{r_b} = b\boldsymbol{uv}$, therefore

$$\boldsymbol{r_b} = \frac{b}{d + \mu_b}\boldsymbol{uv}$$

For what follows, we define $\alpha = b/(d + \mu_b)$ and replace $\boldsymbol{r_b}$ in the system.

$$\frac{\partial}{\partial_t}\boldsymbol{u} = -\mu_f\boldsymbol{u} + m_1\frac{\alpha\boldsymbol{uv}}{1 + \alpha\boldsymbol{uv}} - b\boldsymbol{uv} + d\alpha\boldsymbol{uv}$$

$$\frac{\partial}{\partial_t}\boldsymbol{v} = \frac{1}{\gamma}\frac{\partial^2\boldsymbol{v}}{\partial x^2} - \mu_l\boldsymbol{v} + m_2\frac{\alpha\boldsymbol{uv}}{1 + \alpha\boldsymbol{uv}} - b\boldsymbol{uv} + d\alpha\boldsymbol{uv} - b_e\boldsymbol{vw} \qquad (6.1)$$

$$\frac{\partial}{\partial_t}\boldsymbol{w} = \frac{d_2}{\gamma}\frac{\partial^2\boldsymbol{w}}{\partial x^2} - \mu_e\boldsymbol{w} + m_3\frac{\alpha\boldsymbol{uv}}{1 + \alpha\boldsymbol{uv}}$$

6.2 Change of variable

Now that we have reduced the amount of variables from four to three, let us also operate surgery on the system to get rid of some parameters. First notice that $d\alpha - b = -\mu_b\alpha$, and then proceed to the change of variable

new variable / parameter	$\tilde{\boldsymbol{u}}$	$\tilde{\boldsymbol{v}}$	$\tilde{\boldsymbol{w}}$	$\tilde{m}_1$	$\tilde{m}_2$	$\tilde{m}_3$	$\tilde{\mu}_b$
value	$\sqrt{\alpha}\boldsymbol{u}$	$\sqrt{\alpha}\boldsymbol{v}$	$b_e\boldsymbol{w}$	$\sqrt{\alpha}m_1$	$\sqrt{\alpha}m_2$	$\sqrt{\alpha}m_3$	$\sqrt{\alpha}\mu_b$

the new system is then simpliying down to

$$\frac{\partial}{\partial_t}\tilde{\boldsymbol{u}} = -\mu_f\tilde{\boldsymbol{u}} + \tilde{m}_1\frac{\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}}{1+\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}} - \tilde{\mu}_b\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}$$

$$\frac{\partial}{\partial_t}\tilde{\boldsymbol{v}} = \frac{1}{\gamma}\frac{\partial^2\tilde{\boldsymbol{v}}}{\partial x^2} - \mu_l\tilde{\boldsymbol{v}} + \tilde{m}_2\frac{\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}}{1+\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}} - \tilde{\mu}_b\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}} - \tilde{\boldsymbol{v}}\tilde{\boldsymbol{w}} \qquad (6.2)$$

$$\frac{\partial}{\partial_t}\tilde{\boldsymbol{w}} = \frac{d_2}{\gamma}\frac{\partial^2\tilde{\boldsymbol{w}}}{\partial x^2} - \mu_e\tilde{\boldsymbol{w}} + \tilde{m}_3\frac{\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}}{1+\tilde{\boldsymbol{u}}\tilde{\boldsymbol{v}}}$$

For the sake of readability, we drop the $\sim$ notation in the future.

7   Behavior of the system

Looking at the kinetics system, the Jacobian matrix A is given by $A(\boldsymbol{u}, \boldsymbol{v}, \boldsymbol{w}) = (a_{ij})_{1\leqslant i,j,\leqslant n}$, with

$$A(\boldsymbol{u},\boldsymbol{v},\boldsymbol{w}) = \begin{pmatrix} -\mu_f + \dfrac{m_1\boldsymbol{v}}{(1+\boldsymbol{uv})^2} - \mu_b\boldsymbol{v} & \dfrac{m_1\boldsymbol{u}}{(1+\boldsymbol{uv})^2} - \mu_b\boldsymbol{u} & 0 \\[2ex] \dfrac{m_2\boldsymbol{v}}{(1+\boldsymbol{uv})^2} - \mu_b\boldsymbol{v} & -\mu_l + \dfrac{m_2\boldsymbol{u}}{(1+\boldsymbol{uv})^2} - \mu_b\boldsymbol{u} - \boldsymbol{w} & -\boldsymbol{v} \\[2ex] \dfrac{m_3\boldsymbol{v}}{(1+\boldsymbol{uv})^2} & \dfrac{m_3\boldsymbol{v}}{(1+\boldsymbol{uv})^2} & -\mu_e \end{pmatrix}$$

Lemma 1 (Routh-Hurwitz criterion). *The third order polynomial $P(z) = z^3 + a_2z^2 + a_1z + a_0$ has all its roots in the negative half-plane if and only if $a_0, a_1, a_2 > 0$ and $a_2a_1 > a_0$*

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