Analysis of pattern formation in reaction-diffusion models for cell polarization

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Abstract

Small GTPases are a family of signalling proteins that regulates cell shape through actin assembly. Actin filaments are a major component of the cellular cytoskeleton, a supporting structure of the cell. Patterns of GTPase activity are related to a variety of cell behaviors, including cell polarization, formation of protrusions such as filopodia, and actin waves. These phenomena are in turn related to cell migration, cancer metastasis and viral infection. We seek to investigate pattern formation in the context of GTPase activity through a variant of the reaction-diffusion partial differential equation model, known as the Wave Pinning Model. By determining the possible spatio-temporal patterns, as well as their required conditions, we can better understand the cellular behaviors corresponding to these patterns.

We first introduce and motivate the wave pinning model and its extensions involving F-actin feedback and source-sink terms. Next, we explore the behavior of the model with numerical simulations. We have identified patterns of localized spots, travelling waves, pulses, and others. We interpret some of these patterns as cell polarization, filopodia formation, and actin waves, as well as other complex behaviors that do not closely resemble common experimental observations.

Next, we delineate distinct parameter regimes with Turing analysis and local perturbation analysis (LPA). Turing analysis is a classical method for determining linear stability of homogeneous steady states. LPA is a recently developed technique that is able to detect instabilities to perturbations of finite size that cannot be detected by Turing analysis. LPA has the caveat that it describes only the limiting behavior of the system as the ratio of diffusion coefficient of the two forms of GTPase goes to zero.

We also study the effects stemming from the interaction of GTPase dynamics and the deforming cell boundary with a simplified wave pinning model coupled with cell size, and with Cellular Potts Model simulations coupling the full wave pinning model with the cell boundary. The results of the analysis allow us to comment on the impact of cell geometry, the various terms in our model and their interactions on pattern formation and cell behavior.
GTPases are a family of signalling proteins that controls cell shape. By changing shape, the cell can move and form protrusions such as filopodia. Cell movements are essential for embryonic development and cancer metastasis, while filopodia serve a variety of purposes. Therefore, studying the dynamics of GTPases helps us understand these biological phenomena.

This project focuses on pattern formation in a reaction-diffusion model describing the changes in levels of activity of GTPase across space and time. I ran numerical simulations to determine the possible patterns in this model. I found a pattern of spikes, which corresponds to filopodia formation, as well as a pattern of moving waves resembling wave-like cell activities observed in experiments. Next, I analyzed the model with both classical and recent mathematical techniques to find the conditions required by these patterns. Finally, I discussed the interactions between GTPase and cell shape.
Preface

This project is conducted by the author, Yue Liu, under the guidance of Professor Leah Edelstein–Keshet.

The models examined in this thesis are related to existing works by Mori et al [30], Holmes et al [16] and Verschueren & Champneys [43], and some of the results are reproduced as benchmarks for my analysis and numerical methods. The numerical simulations in Chapter 3 are produced with my own original code, and the text in this thesis is my own writing.

Figure 2.2 was produced by Leah Edelstein–Keshet, used with permission.

The simulations shown in Figure 6.3 were run by Elisabeth Rens, who together with Zachary Pellegrin developed the program used for the simulation. The figures are used here with their permission.

The code given in Appendix C are based on skeleton code provided by Dr. Timm Trekatis as a part of MATH 521 course material.

All other material is my original work, and has not yet been published. Some sections come from parts of my past course projects: parts of Sec. 3.1 and 3.8 from MATH 521, and parts of Ch. 5 from MATH 553.
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Dedication

To my parents
Chapter 1

Introduction

Cell polarization is a fascinating biological phenomenon where cells break their internal symmetry and form distinct internal regions in response to external signals. We are especially interested in the role of GTPase activity, a family of signalling proteins that regulate cell shape as well as cell polarity. Understanding the possible dynamics of GTPase activity has broad application areas including cell motility, cancer metastasis and viral infection.

There have been many recent developments in quantitative biology, specifically mathematical modelling. Most models are ODE, PDE, or agent-based, and some are stochastic. Their strengths and characteristics are discussed in [29], along with examples related to cell polarity.

The aim of this paper is to build and analyze a PDE model for GTPase dynamics, identify possible spatio-temporal patterns, as well as conditions under which these patterns are possible. This will contribute to understanding the essential mechanisms behind cell polarization and related phenomena.

In this chapter, we will provide a brief overview of the biological backgrounds, provide motivations for our model, discuss potential applications of our research, and review existing models of GTPase activity.

1.1 GTPase, the actin cytoskeleton and cell motility

Small GTPases are a family of signalling proteins that regulate the shape of the cell via polymerization of actin filaments [15]. Their main members are Rac, Rho and Cdc42. They all have a membrane-bound active form, which diffuse much slower than their inactive form.

The actin filaments, also known as F-actin, are assembled from monomers known as G-actin [24, Chapter 19.1] and form a major component in the cellular cytoskeleton. As a whole, the cytoskeleton supports and stabilizes the shape of the cell, anchors the cell to the extra-cellular matrix, as well as participates in a variety of cell functions such as movement, cell division,

By controlling cell shape, the interaction of GTPases and actin drives a form of cell motility. In the front of the cell, the GTPases Rac and Cdc42 up-regulate actin assembly, which extends the cell forward. At the same time, Rho GTPase activates acto-myosin contraction at the back of the cell, pulling the rear inward. Together this allows the entire cell to crawl forward.

Polarization is required for cell migration during embryo development (well known, see for example [13]). It also goes wrong in various stages of cancer metastasis [33]. Therefore, understanding the conditions under which cell polarization is possible is of great interest.

1.2  

Filopodia and virus invasion

Actin is also responsible for the formation of protruding structures such as lamellipodia and filopodia [1, Chapter 16]. Filopodia are thin, long, finger-like protrusions formed by tightly-packed bundles of actin filaments. Lamellipodia is a much larger structure containing an actin mesh, instead of bundles. Although filopodia serve many purposes, they are utilized by several types of virus during the infection process [3]. These viruses include dengue [48] and rabies [47], which use filopodia to enter the cell, and HIV-1 [32], which can trigger the formation of filopodia once inside a cell, and use it to facilitate transmission to another cell. Not all forms of GTPases are involved in this process. In [48] the authors showed that only Rac and Cdc42, but not RhoA, is relevant to virus infection.

Consequently, understanding GTPase activity and its implications to filopodia formation can suggest new ways of combating viral infections.

1.3  

Actin waves

In [44], the author observed wave-like F-actin activities in amoeba cells, and hypothesized that the wave pattern, in addition to cell polarization, plays a role in cell motility. A later study [46] experimentally observed wave fronts of the assembly of F-actin, and activities of Rac GTPase and a related protein (Hem-1) in human immune cells, and found that these wave fronts annihilate upon collision. In addition, the study found strong spatial correlation between Rac activity and actin waves, which is in turn strongly correlated with the advancement of cell edges, supporting the hypothesis that actin waves are related to cell motility.
1.4 Modelling motivation

In light of these discoveries, it would be interesting to incorporate actin assembly into our model in order to reproduce and explain the formation of actin waves.

The GTPase signalling network is highly complex. There are 40 proteins presented in [41], and it is still not a complete list. A mechanistically accurate model would contain too many variables and parameters for analysis. In order to obtain a mathematical model tractable for analysis, we will work toward a phenomenological, conceptual model that is simple yet still sufficient to produce the behaviors of interest.

Our work is mainly based on three previous studies: [30, 43, 16]. The most basic model, known as the wave pinning model, first proposed by [30], is a highly simplified and abstract model. This model considers only a single GTPase in isolation, and aims to describe cell polarization. The model uses a reaction-diffusion equation to describe the spatio-temporal dynamics of the active and inactive forms of a GTPase. The reaction term describes the rate of conversion of one form into the other, with an abstract nonlinear activation term and a linear deactivation term. As a whole, this model preserves the total amount of GTPase. One important biological fact to incorporate is the vastly different diffusion coefficient for these two forms, due to the fact that the active form is membrane-bound whereas the inactive form can move freely in the fluid cell interior. This turns out to be important for polarization and pattern formation. This will be shown in Ch. 4, 5.

There are two other papers proposed two separate extensions to the basic model, which we will analyze. The non-conservative extension proposed by [43] includes additional source and sink terms, which represents the production and decay of GTPase. This results in patterns that we will interpret as filopodia formation. The actin feedback extension proposed by [16] adds F-actin as another variable interacting with the GTPase, which produces patterns similar to actin waves.

Our main goal is for each model, to identify any possible spatio-temporal patterns in GTPase dynamics, and interpret their effect on cell shape. Then we determine the mathematical conditions for the existence of these patterns, which would correspond to the biological conditions for cell polarization, filopodia formation and actin waves.

This analysis will help us answer the following questions of interest:

Q1. How do the source and sink effects interact with the feedback effect
from actin assembly? GTPase source/sink terms lead to localized spots [43], whereas feedback from F-actin to GTPase results in travelling waves [16]. What kind of dynamic patterns arise when the two effects are combined in a single GTPase model?

Q2. Does locally elevated GTPase activation lead to localized pattern formation, or will the pattern spread farther away? Is the model consistent with viral infection through filopodia?

Q3. Do 1D and 2D geometries yield different patterns in GTPase activity? A top-down view of a cell can be approximated by a 2D domain (see Sec. 2.1), but cells can be forced into a 1D geometry using microfluidic channels or substrates with grooves.

Q4. What impact does cell size have on pattern formation? Cells differ significantly in size, even within the same species.

Q5. How do GTPase dynamics and a dynamic domain boundary interact? Given that GTPase regulates cell shape, a system with a dynamic boundary coupled with GTPase activity might yield a more complex behavior than with a static boundary.

Q6. Can the model account for the oscillating spots in GTPase activity observed in [39]? This was one of the motivations for combining the non-conservative terms, which results in spots, and actin feedback, which can potentially enable the spots to oscillate.

Q7. Does the presence of actin waves produce a qualitatively different movement pattern for the cell, compared to simple polarization? Cell movement can be modelled as the process of cell boundary deformation due to interaction with GTPase.

Q8. Can Turing analysis (introduced in Ch. 4) predict the wavelength of spatially periodic patterns, if such patterns exist?

Q9. How do the results of local perturbation analysis (LPA, introduced in Ch. 5) relate to the results of Turing analysis?

Q10. How does LPA and Turing analysis perform when there are more than two interacting species?
1.5 Related works

Beside our main references [30, 43, 16] which first proposed the wave pinning (WP) model and its extensions, there are other relevant papers. In [31], the authors used matched asymptotic analysis to explore the PDE bifurcations of the WP model, and obtained results on the speed and final pinned position of the wave front. In [27], the authors performed local perturbation analysis (LPA) on the actin feedback model and identified possible boundaries of pattern-forming parameter regimes.

There are many closely related models as well. In [17], the authors compared the WP model to a related model that involves both Rac and Rho GTPases (Rac enhances cell protrusion and expansion, whereas Rho activates cell contraction). Both have reaction terms similar to the WP model, but slightly modified to describe mutual inhibition. The paper found distinct regimes of the parameter space that correspond to different cell shapes and sizes, determined by equilibrium levels of Rac and Rho. The above model is further extended in [17] by incorporating Cdc42 and a few other proteins as well, with their own reaction-diffusion equations, resulting in a highly complex model. This model is able to recover wave pinning behavior. The authors also discussed how the presence of the other proteins influences LPA results.

There are models that consider the coupling between GTPase and the environment surrounding the cell. In [19], the authors consider a Rac-Rho model similar to [17], but with the additional coupling to the extracellular matrix, and investigated the formation of lamellipodia. In [49], the authors coupled GTPase dynamics to mechanical tension of the cell, and linked an array of cells together. This resulted in a variety of interesting collective cell behaviors, such as waves of oscillatory contraction and relaxation propagating through the group of cells. This model is related to our model in Sec. 6.1.1. In addition, this study also simulated groups of cells with dynamic shapes in 2D.

In [45], the authors derived a stochastic version of the WP model by tracking the number of GTPase molecules in discretized spatial compartments. This model reduces to the wave pinning PDE in the limit of very large number of molecules. It was found that the stochastic model preserves the wave pinning behavior when there is a large number of molecules and low randomness. The parameter regime for wave pinning shrinks as the number of molecules decreases or randomness increases.

All studies mentioned above are ultimately based on the WP model. There are other unrelated models for cell polarization as well. A broad
1.6 Thesis overview

Comparison between these models is given in [9, 20]. The Otsuji model [34] is another reaction-diffusion model for GTPase dynamics. It obeys mass conservation similar to the WP model, except with a very different reaction function. The authors focused on the behavior of the model under a time-dependent inhomogeneous stimulation. The usual behavior of this model is a single peak that follows the stimulation around, and persists after the stimulation is turned off.

Turing’s 1952 paper [42] is the earliest paper that studied diffusion-driven pattern formation. Rather than focusing on a specific model, the paper discussed reaction-diffusion systems in general. Some of its techniques are applied to our model in Ch. 4.

Another non-specific model of pattern formation is the Gierer–Meinhardt (GM) model [12], which is a well-studied model with many related papers. The GM model consists of a short-range activator and a long-range inhibitor diffusing at different rates. This model exhibits polarization, periodic static patterns as well as travelling waves, depending on parameters. All of these behaviors are present in the wave pinning model (with extensions), shown in Ch. 3. There is an extension to the GM model given in [28].

There are other very different approaches to modelling cell polarity. Some focus on proteins other than GTPases, some are more experimental and focus on fitting equations to observed data, and some use agent agent-based models. Many of these are reviewed in [29].

Some studies combine experimental observations with modelling. In [36], the authors proposed a model for GTPase dynamics similar to the WP model with different reaction and without mass conservation, and compares the simulations to indirectly measured GTPase activity in plant root hair cells. In [39], the authors measured GTPase and actin assembly in roundworm embryos, and fitted reaction functions to measurements.

Finally, there are many other directions used to study cell polarity both in experimental methods and mathematical modelling. Some of them are summarized in [37].

1.6 Thesis overview

Chapter 2 introduces the assumptions and formulations of the models in detail. We will also discuss how, in certain cases, the model obeys mass conservation, which simplifies the analysis.

Chapter 3 contains the numerical simulations of the models, under a variety of parameters and initial conditions, showing all known patterns. We
1.6. Thesis overview

also discuss the result of numerical experiments on determining conditions for existence of the patterns, which will guide the subsequent analysis.

Chapter 4 focuses on Turing analysis as a way to determine the linear stability of homogeneous steady state (HSS) solutions for our PDE models. This is of interest since a HSS unstable to spatially heterogeneous perturbation is a sufficient condition for pattern formation. We will also discuss how Turing analysis can help determine the wave length of the spatially periodic patterns, when these patterns exist.

Chapter 5 uses local perturbation analysis (LPA), a more recent technique, to detect another form of instability which requires a localized, sufficiently large perturbation. LPA is able to determine more distinct pattern-forming parameter regimes than Turing analysis, with the drawback that it only works in the limit that the ratio of the diffusion coefficients of the active and inactive forms goes to zero.

Chapter 6 discusses and analyzes two ways to couple the wave pinning model to a dynamic domain representing the effect of GTPase on the shape of the cell. The results allow us to more concretely comment on the consequence of GTPase dynamics on cell shape and the related biological phenomena.
Chapter 2

Mathematical models

In this chapter, we describe a few increasingly complex reaction-diffusion PDE models for describing the dynamics of GTPase activity in some domain representing a cell. The most basic one, known as wave pinning model, was proposed by [30], which focuses on explaining cell polarization. There are two separate extensions to this model, the first of which is the actin feedback model proposed by [16], which aims to describe a phenomenon known as actin waves. The second is the non-conservative model proposed by [43], which includes additional terms to be more realistic.

We will combine these two extensions into a single model, which has not been considered before. We will also discuss the choice of domain, and non-dimensionalization of the models.

2.1 Representing the cell with two- or one-dimensional domains

We will consider both 1D and 2D domains. Many kinds of cells of interest have a flat shape, which means that the vertical thickness would be too thin to support complex patterns. As such, a 3D model likely will not provide additional insight beyond a 2D model. For 2D, we consider square and circular domains. Although GTPase activity will affect the actin cytoskeleton, therefore deforming the shape of the domain over time, this effect will not be considered here. Instead, we assume the domain is static. We will return to this question in Chapter 6. The boundary conditions are no-flux, since GTPases cannot diffuse or be transported across the cell membrane.

For the ease of analysis and simulation, we also consider reducing the 2D models to 1D by considering some suitable subsets of the cell. The first way is to take a section across a diameter of the cell. This results in no-flux boundary conditions for the 1D PDEs at the two ends of the cell. The second way is to take the perimeter of the cell as our 1D domain. This give rise to periodic boundary conditions. Numerical experiments confirm that these two approaches give mostly analogous results. The subsequent sections will
2.2. Wave pinning model

This model was first proposed by [30] and involves only one GTPase in isolation. It is the basic model that the subsequent ones below built upon. It is intended to capture of polarization behavior necessary for cell motility.

Let \( u(x,t) \), \( v(x,t) \) represent the concentration of active and inactive form of a generic GTPases, respectively. Both quantities diffuse, but the inactive form diffuses much faster since GTPase can only be active when it is bound to the membrane, whereas the inactive form can move more freely inside the cytosol. Suppose that there is a basal activation rate, \( k \) for \( v \) to be converted to \( u \). Furthermore, \( u \) has a positive feedback effect on itself, which can be represented as a Hill-function activation term with height \( \gamma \) and Hill coefficient \( n \) (which controls its “sharpness”). The choice of the activation function is not important, as [31] showed. Any function with roughly the same shape will do. Since the activation is already nonlinear, we can assume deactivation is linear and still obtain interesting results. This yields the following equations:

\[
\begin{align*}
\frac{\partial u}{\partial t} &= D_u \nabla^2 u + f(u,v), \quad (2.1a) \\
\frac{\partial v}{\partial t} &= D_v \nabla^2 v - f(u,v), \quad (2.1b) \\
f(u,v) &= (k + \gamma \frac{u^n}{u_0^n + u^n}) v - \frac{\eta}{\text{A}(u), \text{activation rate}} u - \frac{\eta}{\text{inactivation rate}} u, \quad (2.1c)
\end{align*}
\]

Figure 2.1: Diagram illustrating the two ways to reduce the model to 2D. Left: horizontal slice across a diameter, with \( L \) being the length of the diameter. Right: the perimeter, with periodic parameterization \( s \).
2.2. Wave pinning model

where \( D_u \ll D_v, \ t > 0, x \in \Omega, \) where \( \Omega \) is a 1D interval \([0,L]\), or a 2D shape for example a square \([0,L] \times [0,L]\) or a circle. The no-flux boundary conditions are:

\[
\frac{\partial u}{\partial x} = \frac{\partial v}{\partial x} = 0 \ \forall \ x \in \partial \Omega. \tag{2.2}
\]

In 1D domain, this can be written as

\[
\frac{\partial u}{\partial x} \bigg|_{x=0} = \frac{\partial v}{\partial x} \bigg|_{x=0} = \frac{\partial u}{\partial x} \bigg|_{x=L} = \frac{\partial v}{\partial x} \bigg|_{x=L} = 0.
\]

The variables and the parameters have the following units:

\[
[u] = [v] = [u_0] = \frac{G}{l^m}, \quad [D_u] = [D_v] = \frac{l^2}{t},
\]

\[
[k] = [\gamma] = [\eta] = t^{-1}, \quad [L] = l, \quad [n] = 1, \tag{2.3}
\]

where \( m = 1 \) or \( 2 \) is the dimension of the domain, \( G \) refers to the concentration of GTPase, \( l \) is length and \( t \) is time. These are all strictly positive. Moreover, \( n \geq 2 \) is an integer.

2.2.1 Non-dimensionalization

This model can be scaled in order to reduce the number of parameters. Let

\[
\tilde{x} = \frac{x}{L}, \ \left( \tilde{y} = \frac{y}{L} \text{ if } 2D \right), \quad \tilde{u} = \frac{u}{u_0}, \ \tilde{v} = \frac{v}{u_0}, \quad \tilde{t} = \frac{t}{L^2/D_v}, \quad T = \frac{L^2}{D_v}.
\]

Applying this to the system (2.1) yields:

\[
\frac{\partial \tilde{u}}{\partial \tilde{t}} = \frac{D_u}{D_v} \tilde{\nabla}^2 \tilde{u} + \frac{T}{u_0} f, \quad \frac{\partial \tilde{v}}{\partial \tilde{t}} = \tilde{\nabla}^2 \tilde{v} - \frac{T}{u_0} f, \quad \frac{T}{u_0} f = \frac{T}{u_0} \left( k + \gamma \frac{\tilde{u}^2}{1 + \tilde{u}^2} \right) \tilde{v} u_0 - \frac{T}{u_0} \eta \tilde{u} \tilde{v},
\]

where \( \tilde{\nabla}^2 = \frac{\partial^2}{\partial \tilde{x}^2} + \frac{\partial^2}{\partial \tilde{y}^2}. \)

Now define

\[
\delta = \frac{D_u}{D_v}, \quad \tilde{f} = \frac{T}{u_0} f, \quad \tilde{k} = Tk, \quad \tilde{\gamma} = T \gamma, \quad \tilde{\eta} = T \eta,
\]

10
2.3. Actin feedback extension

and finally drop all tilde to obtain the scaled form of the system:

\[
\begin{align*}
\frac{\partial u}{\partial t} &= \delta \nabla^2 u + f(u, v), \quad \delta \ll 1 \quad (2.5a) \\
\frac{\partial v}{\partial t} &= \nabla^2 v - f(u, v), \quad (2.5b) \\
f(u, v) &= (k + \gamma \frac{u^n}{1 + u^n})v - \eta u. \quad (2.5c)
\end{align*}
\]

The remaining variables \((u, v)\), quantities \((x, t)\) and parameters \((\delta, k, \gamma, \eta)\) are all non-dimensional. The domain has been scaled to \([0,1]\) for 1D and \([0,1] \times [0,1]\) for 2D.

The characteristic behavior of this system when perturbed from a homogeneous equilibrium is the formation of a travelling wave-front that slows down and stalls before reaching the boundary, resulting in a polarized state, hence the name wave pinning. In the context of cells, this can be interpreted as cell motility, where one end of the cell expands and the other end contracts. For simulations of this model, see Sec. 3.3.

2.3 Actin feedback extension

This extension was proposed by [16] in order to capture the well-known actin wave effect observed in cells. Examples of such observations can be found in [44], for slime mold cells, and in [46], for human white blood cells. These experiments found trains of waves of actin activity propagating throughout the cells.

It is known that Rho GTPases such as Rac and Cdc42 up-regulate actin polymerization via a complex network of interacting proteins, including the WAVE complex, WASP and Arp2/3 [41], and in return, F-actin (the polymer form of actin) down-regulates Rho GTPase through RGA-3/4, for example[39]. This creates a negative feedback effect, making it natural to expect patterns periodic in time.

In the spirit of seeking simplicity, the entire network of interactions can be abstractly represented as follows: F-actin down-regulates GTPase activation while GTPase up-regulates F-actin. This leads to the actin wave model,
where $F$ represents F-actin:

\[
\begin{align*}
\frac{\partial u}{\partial t} &= \delta \nabla^2 u + f(u, v, F), \quad (2.6a) \\
\frac{\partial v}{\partial t} &= \nabla^2 v - f(u, v, F), \quad (2.6b) \\
\frac{\partial F}{\partial t} &= \epsilon (k_n u - k_s F), \quad (2.6c) \\
f(u, v, F) &= (k + \gamma \frac{u^n}{1 + u^n})v - (\eta + s \frac{F}{1 + F})u. \quad (2.6d)
\end{align*}
\]

The above is the scaled version of the system. The scaling procedure is similar to Sec. 2.2.1. Notice that if $s = 0$, then $F$ decouples from the dynamics of $u, v$ and the wave pinning system is recovered. $\epsilon$ is small, which represents the relatively slow response of actin to GTPase. This model can produce a variety of behaviors, shown in Sec. 3.5. These behaviors include wave pinning with oscillating front, reflecting pulses and travelling wave trains, the last of which can be interpreted to correspond to actin waves observed in experiments.

### 2.4 Non-conservative extension

In [43], the authors proposed to add source and sink terms to the GTPase dynamics. The source term represents the production of inactive GTPase. The sink term was originally intended to represent dilution effect due to GTPase causing the cell expanding locally, which is applicable only to Rac and Cdc42. Alternatively, it can be interpreted as the natural decay of active GTPase. The goal was to capture formation of localized active GTPase, and the idea to add source and sink terms comes from [36]. The scaled system is:

\[
\begin{align*}
\frac{\partial u}{\partial t} &= \delta \nabla^2 u + f(u, v) - c\theta u, \quad (2.7a) \\
\frac{\partial v}{\partial t} &= \nabla^2 v - f(u, v) + c\alpha, \quad (2.7b) \\
f(u, v, F) &= (k + \gamma \frac{u^n}{1 + u^n})v - \eta u. \quad (2.7c)
\end{align*}
\]

Notice that setting $c = 0$ recovers the wave pinning model. This model tends to produce a spatially periodic pattern consisting of a series of evenly-spaced, static spikes. Numerical results can be found in Sec. 3.6. These spikes, representing highly localized GTPase activity, can be interpreted as filopodia formation in the case where the GTPase causes the cell to expand.
2.5 Combining the models

It is straightforward to combine these two extensions to form a combined model:

\[
\frac{\partial u}{\partial t} = \delta \nabla^2 u + f(u, v, F) - c\theta u, \tag{2.8a}
\]

\[
\frac{\partial v}{\partial t} = \nabla^2 v - f(u, v, F) + ca, \tag{2.8b}
\]

\[
\frac{\partial F}{\partial t} = \epsilon (k_n u - k_s F), \tag{2.8c}
\]

\[
f(u, v, F) = (k + \gamma \frac{u^n}{1 + u^n})v - (\eta + s \frac{F}{1 + F})u. \tag{2.8d}
\]

As before, all parameters are strictly positive (except \(c, s \geq 0, \) and \(n \geq 2\)) and have unit dimension. \(c\) and \(s\) serve as switches to turn the two extensions on and off.

Notice that the Hill function in \(f\) is monotone increasing and bounded between 0 and 1, so

\[
0 < k < \partial_v f = k + \gamma \frac{u^n}{1 + u^n} < k + \gamma. \tag{2.9}
\]

This holds regardless of the other parameters, especially \(c\) and \(s\), which means it applies to all models. This observation will be useful later.

This model exhibits complex behaviors that can be seen as a mixture of the behaviors under the two extensions, unsurprisingly. Similar to the non-conservative extension, usually a series of spikes form. However, these spikes do not remain static. Instead, they move around with velocity depending on \(s\), and they can collide and interact in interesting ways. The simulation results can be found in Sec. 3.7.

2.6 Mass conservation and well-mixed models

An important feature to notice is that when \(c = 0\), the total mass of GTPase is conserved. This can be shown with the standard argument for no-flux
2.6. Mass conservation and well-mixed models

Figure 2.2: Graphical representation of the four models. Figure produced by Leah Edelstein-Keshet. (a) The wave pinning model. (b) The actin wave model. (c) The source & sink model. (d) The combined model. In these diagrams, \( u \) and \( v \) represents active/inactive GTPase as in the equations, F-actin corresponds to \( F \), the synthesis and decay arrows represents the \( c_\alpha \) and \( c_\theta u \) terms respectively, and the other arrows indicate feedback effects.

boundary conditions and the divergence theorem:

$$\frac{\partial}{\partial t} \int_{\Omega} (u + v)dx = \int_{\Omega} (\delta \nabla^2 u + f + \nabla^2 v - f) dx \quad \text{(substitute in the PDE)}$$

$$= \delta \int_{\Omega} \nabla^2 u dx + \int_{\Omega} \nabla^2 v dx$$

$$= \delta \left( \int_{\partial \Omega} \nabla u \cdot \hat{n} \ dS + \int_{\partial \Omega} \nabla v \cdot \hat{n} \ dS \right) = 0 \quad \text{(due to no-flux BC)}$$

(2.10)

Consider well-mixed systems, that is (2.8) with homogeneous initial condition. Then the diffusion terms drop out and we are left with a system of
2.6. Mass conservation and well-mixed models

ODEs:

\[ u_t = f(u, v, F) - \theta c u, \]  
\[ v_t = -f(u, v, F) + \alpha c, \]  
\[ F_t = \epsilon (k_n u - k_s F). \]

Equilibria of this system are called homogeneous steady states (HSS). If \( c = 0 \), by mass conservation \( w = u + v \), the mean concentration of GTPase across the domain, is constant. Therefore, we can reduce the system to

\[ u_t = f(u, w - u, F), \]  
\[ F_t = \epsilon (k_n u - k_s F). \]

Furthermore, if \( s = 0 \), then we are left with a single ODE:

\[ u_t = f(u, w - u) = g(u). \]

In this chapter, we introduced four models for GTPase dynamics and showed simplifications possible for the well-mixed models under mass conservation. In the next chapter we will demonstrate their behavior using numerical simulations.
Chapter 3

Numerical simulations

This chapter contains numerical solutions of the models introduced in Chapter 2. The numerical schemes used to produce these simulations are discussed in Sec. 3.1, and considerations for the parameters are given in Sec. 3.2. The simulations are run for long enough such that the system reaches an (apparent) steady state, or until the pattern is obvious.

The numerical simulation results of [30, 16, 43] are reproduced as a part of Sec. 3.3, 3.5, 3.6. These results are compared with simulations that uses different initial conditions and parameters that either better illustrate the model behaviors or lead to distinct behaviors not discussed by the earlier papers.

This chapter is closely related to the next two chapters. Much of the analysis is guided by the properties of the numerical solutions, while the analysis identifies possibly distinct parameter regimes and calls for more simulations.

3.1 Numerical methods

For the 1 spatial dimension case, we use a finite difference scheme in the spatial domain with 400 mesh points based on a modified version of Crank-Nicolson (CN) [4]. CN is an implicit scheme with 2nd order accuracy and reasonably efficient for linear systems (well known, see [22, Ch. 7.2]). However, the nonlinear reaction term $f$ can be computationally expensive for implicit treatment. The remedy is the IMEX (implicit-explicit) method proposed by [40]. The idea is to treat the nonlinear reaction term explicitly to save on complexity, while still treating the linear diffusion term implicitly, resulting in a linear system. It was found empirically that this adaptation mostly retains the stability of CN. Therefore, we use the IMEX-CN scheme as a compromise between stability and efficiency.

When actin feedback is present in the model, we use the simple explicit Euler scheme for $F$ since $F$ does not diffuse. This scheme can be summarized
3.2. Selection of simulation parameters

as follows:

\[(I - \frac{1}{2} h \delta \tilde{\Delta}) u_{n+1} = u_n + h[f(u_n, v_n, F_n) - c\theta u_n + \frac{1}{2} \delta \tilde{\Delta} u_n],\]

\[(I - \frac{1}{2} h \delta \tilde{\Delta}) v_{n+1} = v_n + h[-f(u_n, v_n, F_n) + c\alpha + \frac{1}{2} \delta \tilde{\Delta} v_n],\]

\[F_{n+1} = F_n + h\epsilon(k_n u_n - k_s F_n).\]

where \(h = \Delta t\) is the time step and \(\tilde{\Delta}\) is the discrete Laplacian. This is implemented in Matlab, and the program is provided in Appendix A.

For 2D simulations, we use a finite element method, with method of lines for spatial-temporal discretization and 1st degree polynomial interpolation for basis functions. The spatial domain is discretized with a regular mesh of 5000 triangles, and we use the same time stepping scheme (IMEX-CN) as in the 1D case. This is implemented with the FEniCS [2] package in Python, and the code is provided in Appendix C.

In both cases, we verified that the chosen step size \(h\) is sufficiently small by running the same simulation with time step \(h\) and \(h/2\), producing solutions \(u_h(x, t)\) and \(u_{h/2}(x, t)\) (and also for \(v\) and \(F\)), and checking that they do not differ by more than 0.01 at any \(x \in \Omega, t > 0\).

3.2 Selection of simulation parameters

For all simulations, we refer to the combined system of equations (2.8). The default parameters (which produce the most typical behavior for the systems) are summarized in Table 3.1.

Notice in the table that the unscaled domain length \(L\) is re-introduced as a parameter, whereas the non-dimensional domain remains \(0 \leq x \leq 1\). Explicitly varying \(L\) gives a convenient way to change multiple parameters. The selection of value for most of these parameters is based on [16], with \(\alpha, \theta\) coming from [43], and some modifications guided by Turing analysis (Ch. 4) and local perturbation analysis (Ch. 5).

Although these sets of parameters produce many known behaviors, it might not yield clean bifurcation diagrams for analysis. Therefore in other chapters, we use different parameter sets. Additionally, we will deviate from the default set in order to discuss the effect of certain parameters.

One consideration in choosing between parameter sets that produce the same qualitative behavior is their robustness, which means we desire to have the solution reproducible on a wide range of parameters. For example, the authors of [16] choose \(n = 3\) for the actin wave model because produces a
### 3.3. Simulations of wave pinning in 1D

#### Table 3.1: The parameters in the combined model, their meaning, and the values they take for different simulations. WP: wave pinning (Sec. 3.3); NC: non-conservative extension (Sec. 3.6); AF: actin feed back extension (Sec. 3.5); Combined 2: one of the parameter set used for the combined model (Sec. 3.7). All parameters (except $L$) are scaled to be non-dimensional, as in Sec. 2.2.1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>WP</th>
<th>NC</th>
<th>AF</th>
<th>Combined2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta$</td>
<td>Diffusion coef. ratio</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$L$</td>
<td>Domain length</td>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k$</td>
<td>Basal activation rate</td>
<td>$1.5L^2$</td>
<td>$1L^2 - 6L^2$</td>
<td>$1L^2$</td>
<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Nonlinear activation rate</td>
<td>$30L^2$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>Hill coefficient</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>$\eta$</td>
<td>Inactivation rate</td>
<td>$15L^2$</td>
<td>$5L^2$</td>
<td>$15L^2$</td>
<td>$5.2L^2$</td>
</tr>
<tr>
<td>$c$</td>
<td>NC terms on/off</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Source strength</td>
<td>$1.5L^2$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta$</td>
<td>Sink strength</td>
<td>$4.5L^2$</td>
<td></td>
<td></td>
<td>$5.5L^2$</td>
</tr>
<tr>
<td>$s$</td>
<td>Actin feedback strength</td>
<td>0</td>
<td></td>
<td></td>
<td>$0 - 50L^2$</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Actin reaction rate</td>
<td></td>
<td></td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>$k_n$</td>
<td>Actin activation rate</td>
<td>$24L^2$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_s$</td>
<td>Actin inactivation rate</td>
<td>$7.5L^2$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

considerably larger pattern-forming regime in the parameter plane compared to $n = 2$, which was used by [30, 43]. In Sec. 3.4, we show why a sharper non-linear function makes wave pinning more robust. For this reason, we choose $n = 3$ as the default parameter for most of simulations. However, in the LPA chapter (Ch. 5), we often use different parameters that result in bifurcation diagrams that are easier to read.

### 3.3 Simulations of wave pinning in 1D

For wave pinning, the parameters are taken from Table 3.1(WP). These parameters satisfy the condition that $\delta$ is small, and two stable homogeneous steady states exist when $v = 1$ as discussed in Sec. 3.4.

For initial conditions, the default is to start at $v = 1$ and $u \approx 0.102$, which corresponds to the lower homogeneous equilibrium. The higher equilibrium is at $u \approx 1.812$. Various perturbations will be applied to $u$ initially to trigger pattern formation. Another possibility is to start at $v = 1$, $u =$
0.834·ε(x), where u = 0.834 is the unstable equilibrium and ε(x) ∼ Unif[0, 2] is random noise.

Fig. 3.1 shows the simulation results in the form of kymographs, where the horizontal axis is time, the vertical axis is space, and color indicates the value of u, v. Observe that for the first two cases, the initial perturbation eventually smoothens out. However it does not cover the entire domain, resulting in polarization. The random initial condition also results in a polarized steady state. In these simulations, u can vary greatly across the domain while v is much closer to uniform, as expected given the difference in diffusion rate.

In Fig. 3.2, we use similar initial conditions except that the perturbation at one end is negative. The result is similar to the previous case except that the role of high/low u is flipped.

It is important to mention that if we start at the steady homogeneous equilibrium, and the perturbation is too narrow or too small, then the system will eventually be able to reach homogeneity again and polarization will not occur. With random initial conditions, polarization is also not guaranteed. The proportion of the domain with high/low active GTPase depends on the total amount of GTPase, and the polarity (i.e. whether u is high on the left or right side) is determined by the initial condition.

3.4 Simple analysis of wave pinning

In the wave pinning model, the steady state of the typical numerical solution (Fig. 3.3) is a partition of the domain into three regions, a high-u, a low-u and a relatively narrow transition zone, with u nearly constant in the first two. Due to the fast diffusion of v, its level is nearly constant throughout the domain. This suggests that in both the left and right regions, the solution is approximately a stable homogeneous steady state (HSS). This turns out to be the case for Fig. 3.3. However, note that the final v value is not necessarily close to its initial value. Numerical experiments show that this steady state is stable to small inhomogeneous perturbations. We call this final steady state the “wave pinning solution”.

These observations suggest the following necessary condition for wave pinning to occur: for some value of v∗, there are two HSS (u−, v∗), (u+, v∗) with u− < u+. Furthermore, they must be stable in two senses: (1) stable to any uniform perturbation in u (while v is held constant), and (2) stable to perturbation to both u and v, while conserving mass. These can be thought of as a common stable equilibrium to the following two ODEs, where u = u±
3.4. Simple analysis of wave pinning

Figure 3.1: Numerical simulation of the wave pinning model (2.5), with parameters from Table 3.1 (WP). Initial condition: \( v = 1, u = 0.102 \) on the whole domain except \( u = 6 \) for (a,b) \( 0 \leq x \leq 0.1 \); (c,d) \( 0.4 \leq x \leq 0.5 \); (e,f) random noise, \( u = 0.834 \cdot \epsilon(x) \). Note that not all initial conditions result in wave pinning: a small perturbation from the HSS will simply decay and no pattern forms. The behaviors shown in (a,b,e,f) reproduces the solutions shown in Fig. 2 of [30].
3.4. Simple analysis of wave pinning

Figure 3.2: Simulation of the wave pinning model (2.5) with parameters from Table 3.1(WP), except \( \gamma = 150 \), and initial condition \( v = 0.1866, u = 1.3134 \) except \( u = 0 \) on \( 0 \leq x \leq 0.1 \). In this case “negative wave pinning” occurs: the negative perturbation in \( u \) leads to formation of a low \( u \) region on the left of the domain.

satisfy:

\[
\frac{\partial u}{\partial t} = f(u, v^*), \quad \text{where } v^* \text{ is a constant parameter}, \tag{3.1}
\]

\[
\frac{\partial u}{\partial t} = f(u, w - u), \quad \text{where } w = u + v^* \text{ is a constant parameter}, \tag{3.2}
\]

This can be stated equivalently as a condition on \( f \) as follows: there exist \( v^*, u_- < u_+ \) such that

\[
f(u_-, v^*) = f(u_+, v^*) = 0, \tag{3.3}
\]

\[
\frac{\partial f(u_\pm, v^*)}{\partial u} < 0, \tag{3.4}
\]

\[
\frac{df(u, w - u)}{du} = \frac{\partial f(u_\pm, v^*)}{\partial u} - \frac{\partial f(u_\pm, v^*)}{\partial v} < 0. \tag{3.5}
\]

However, we know from (2.9) that \( \frac{\partial f}{\partial v} > 0 \). Therefore the condition (3.5) is redundant given (3.4). Related work in [31] considers a more general family of functions \( f \) of different forms, where both of these conditions are necessary. The authors found that these two conditions, together with the “Maxwell condition”, is sufficient for wave pinning to occur.

The equilibria \( (u_\pm, v^*) \) can be visualized by plotting \( f \), which is done
3.5 Simulations of actin feedback in 1D

We use the parameters from Table 3.1(AF) to simulate the actin feedback model (2.6). In the rest of this section, the $L^2$ factor is implied (e.g. $k = 6$ really means $k = 6L^2$).

The default initial conditions are $u = 0$ except $u = 4$ for $0 \leq x \leq 0.01$, $v = 2.5$, $F = 0$. We are not initializing near the stable HSS because doing so usually results in no patterning. The patterns observed are quite sensitive to initial conditions.

A variety of behaviors can be observed. Fig. 3.4 displays four qualitatively different behaviors: (1) wave pinning with oscillating boundary (WPO), where polarization occurs similar to wave pinning, but the front dividing the polarized regions oscillates back and forth; (2) reflecting pulse (RW), where a single pulse traverses the domain at constant velocity and gets reflected back whenever it reaches the boundary; (3) a single pulse (SP)

Figure 3.3: Final steady state of the wave pinning model showing three distinct regions: a high-$u$ region on the interval $0 \leq x \leq 0.2$ where $(u,v) \approx (1.7506,0.9801)$, a low-$u$ region on $0.5 \leq x \leq 1$ with $(u,v) \approx (0.1018,0.9664)$, and a transition zone in between. In all regions $v \approx 1$ is nearly constant, and the extremes are close to the high $(1.812,1)$ and low $(0.102,1)$ equilibria. Parameters and initial conditions same as in Fig. 3.1(a,b).

in Fig. 5.4, and this analysis is further expanded with LPA techniques in Sec. 5.2.
3.6 Simulations of non-conservative model in 1D

which is absorbed at the boundary, the system reaches an HSS afterward; (4) wave train (WT), a train of waves that originates either at a boundary or in the interior of the domain, and propagates with constant velocity until the waves are absorbed at boundaries. Additionally, with $k = 1.5, s = 5$, we can observe simple wave pinning (WP; not shown, visually similar to Fig. 3.1). Out of these, WT is the closest behavior to the actin waves observed in biological experiments [44, 46]. WPO appears to be related to simple wave pinning via a Hopf bifurcation for the location of the wave front. This is hard to verify since we do not have a closed-form equation that describes the movement of the wave front. The WPO behavior is qualitatively similar to the “tango waves” found in a very different reaction-diffusion model by [23]. The relation between these two behaviors is unknown.

In general, the spatial profile of $F$ lags behind $u$ as expected since it is a slowly reacting variable depending on $u$. The pattern in $v$ is usually in-phase with $u$ but with opposite sign, i.e., $v$ is high where $u$ is low, and vice versa. Moreover, the gradient of $v$ tends to be much shallower than $u$ due to its fast diffusion.

Additionally, there are some more complex patterns possible, shown in Fig. 3.5. These two share certain characteristics with the simpler patterns. The patterns shown in (a-c) are quite similar to WPO, except that the domain is divided into five polarized regions instead of two. The transient behavior near the beginning is also reminiscent of WT. The patterns in (d-f) can be seen as RW but with a group of four pulses rather than one.

Compared to the results in [16], these pictures show a richer range of patterns using mostly the same parameter set (with different scaling). The main difference is that here we used a longer domain size $L = 10$, providing more space for pattern to develop, whereas [16] used $L = 1$, which means the patterns are more confined and boundary effects are much more prominent.

3.6 Simulations of non-conservative model in 1D

For the non-conservative extension (2.7), we use the parameters from Table 3.1(NC). One noticeable difference with the parameter set (WP) is the much larger domain size $L = 10$. Since this model tends to produce periodic patterns, $L$ must be long enough to be able to support these patterns. The values for $\alpha, \theta$ are chosen so that $\delta = 0.01, \gamma = 30$ puts the system in the Turing regime (the pattern-forming regime where the HSS is linearly unstable, see Sec.4.2.2), yet is not too far from the regime’s boundary (see Fig. 4.2). Under this set of parameters, the unique equilibrium
3.7 Simulations of the combined model in 1D

$(u_*, v_*) \approx (0.3333, 1.2315)$ (see (4.13)).

Fig. 3.6 shows some simulation results. In (a,b), we initialize at the HSS and perturb $u$ on the left end of the domain. This perturbation quickly evolves into a narrow spike. The pattern then propagates throughout the domain, forming more spikes at regular intervals until running out of space. After that, the spikes shift slightly to be evenly spaced and eventually reach steady state shown in Fig. 3.7(a). This is the typical pattern formed under this model. Notice that the transition between the initial HSS and the final pattern happened very rapidly.

We can also start with small random noise superimposed on the HSS: $u = u_*(1 + \text{Unif}(-0.01, +0.01))$. In this case, after a brief transient phase, periodic patterns similar to Fig. 3.7(a) form. The exact number of peaks can vary depending on initial condition. We will discuss the wave length of the pattern in Sec. 4.2.3.

We have also experimented with slightly different parameter sets. In Fig. 3.6(c,d), we use a set of parameters where the HSS is linearly stable (as found in Sec. 4.2.2), so small perturbations to the HSS simply decays. However, this does not mean that the HSS is globally stable, since a strong, localized perturbation can lead to the formation of a single persistent spike, shown in Fig. 3.6(f). We call this the soliton solution. Its formation will be explained in Sec. 5.3.

Most other variations of the parameter set lead to patterns similar to Fig. 3.6(e), except for two interesting cases. If we use a smaller domain length, for example $L = 1$, we only get wave pinning, shown in Fig. 3.7(a). This is expected since the domain is likely too small to support a full period of the pattern. Using $\eta = 15$ leads to a periodic series of spikes with the top of the peak bifurcates into two, as shown in Fig. 3.7(b).

3.7 Simulations of the combined model in 1D

With both extensions “on”, the system displays much more complex behaviors. The first set of parameters we use are the same as Table 3.1(NC), but with $s$ varying. For initial conditions, we start at the unique HSS:

\[
    u_* = \frac{\alpha}{\theta}, \quad F_* = \frac{k_n}{k_s} u_*, \quad v_* = \frac{\epsilon_c \alpha + (\eta + s \frac{F_*}{1 + F_*}) u_*}{k + \gamma \frac{u_*^2}{1 + u_*}},
\]

and perturb it with some noise: $u = u_*(1 + \text{Unif}(-0.1, +0.1))$. The results are shown in Fig. 3.8. With $s$ low enough, the system behavior is similar to
the $s = 0$ case, where we get a static, spatially periodic pattern characteristic to the non-conservative extension (Fig. 3.8(a), compare to Fig. 3.6(a)). As we increase $s$, the peaks begin to move, reminiscent of the wave train behavior seen under the actin wave extension (Fig. 3.4(j)). These peaks move with constant velocity by themselves and appears to repel each other when the peaks get close. When $s$ is moderate, this repulsion is strong enough to make the peaks reverse their directions if they are on collision course (Fig. 3.8(b)). At higher $s$, they collide. With the parameter set from Table 3.1(NC), both pulses tends to survive when they collide and they simply pass through one another (Fig. 3.8(c)). However, for $L = 20$, we also observe the formation of a standing pulse that remains stationary for some time with a persistent oscillating amplitude (Fig. 3.8(d)).

We also use another parameter set from Table 3.1(Combined2). Under these parameters, the peaks sometimes annihilate upon collision (Fig. 3.9(c)), and sometimes only one survives (Fig. 3.9(b)). At even higher $s$, we observe a localized standing wave pattern that oscillates rapidly (Fig. 3.9(d)).

3.8 Simulations of wave pinning and non-conservative extension in 2D

We ran simulations in 2D for the wave pinning and non-conservative models using the same parameters as before. The initial conditions are $u = u_*$ except $u = 4u_*$ in the corner $[0,0.1] \times [0,0.1]$, and $v = v_*$, where $(u_*, v_*) = (0.3333, 1.1111)$ is the HSS for the non-conservative model. The results are shown in Fig. 3.10. The results for wave pinning are not surprising: $u$ initially spreads out from the corner as a 2D travelling wave, and that is eventually pinned along a front determined by the initial conditions.

The non-conservative model is more interesting. Based on 1D simulations, we expect evenly-spaced stripes to form around the corner as concentric rings, as happens initially. However, these rings quickly break up into spots. The spots shift around to become more evenly spaced, and then they settle as a steady state is reached. We have not found any parameter sets under which the ring pattern is stable.

These patterns are not sensitive to the shape of the domain. Simulations on circular, rectangular and other domains with simple shapes produced patterns with the same qualitative characteristics (not shown).
3.9 Simulations with spatially inhomogeneous parameters

In this section we consider cases where the parameters are dependent on space. The main motivation is that locally up-regulated GTPases are required for certain kinds of viruses to infect cells. Specifically, [48] shows that the formation of filopodia, which is regulated by GTPases, is essential for dengue virus to invade human endothelial cells. Other papers have shown that filopodia play a role in the infection of rabies [47] and HIV [32].

The main approach is to start with the combined model (2.8) in 1D and identify a parameter set that produces behaviors that we interpret as filopodia formation. We then allow one of the parameters to vary smoothly in space, such that there are regions where the parameter lies in the pattern-forming regime where the HSS is unstable, and others where it lies in the stable regime. The boundaries for the two regime can be estimated by running simulations with constant parameters, as in Sec.3.7. We expect to recover the familiar patterns in the unstable region. It would be interesting to see if the patterns can persist into the stable region, that is, whether we can get coexistence of the HSS and some stable pattern.

For this, we use the parameters from Table 3.1(Combined2), except with \( L = 20 \) so that the domain is long enough to support more peaks, which makes it easier to see the behavior in the interior of each region. There are two parameters we can change to represent local up-regulation of GTPase: the basal activation rate \( k \), and the feedback activation parameter \( \gamma \). We present the results using

\[
\gamma(x) = \left[ 15 + 15 \exp(- (x - 1/2)^2 / \sigma^2) \right] L^2, \tag{3.7}
\]

which is a Gaussian bump centered at the middle of the domain. Making \( k \) spatially dependent instead yields analogous results. From numerical experiments, with constant \( \gamma \), the boundary between the stable and unstable regime is near \( \gamma \approx 18.5 \). The unstable region where \( \gamma(x) > 18.5 \) is around half of the domain when \( \sigma = 0.2 \).

The results in Fig. 3.11 show that the pattern does not leak into the stable region. Furthermore, if \( \sigma \) is small enough, i.e. the unstable region is narrow enough, there will be a lone peak confined within it which oscillates in-place. In general, the system behaves as if there is a boundary near \( \gamma \approx 18.5 \) with Dirichlet boundary conditions. This suggests that local up-regulation does not impact the system behavior globally. Relating back to biology, this means that viral activity can create localized spots of high
3.9. Simulations with spatially inhomogeneous parameters

GTPase activity. For Rac GTPase, this will likely cause a protrusion that eventually evolves into a filopodia, facilitating viral entrance into the cell.
3.9. Simulations with spatially inhomogeneous parameters

(a) $u, k = 1.5, s = 18$
(b) $v, k = 1.5, s = 18$
(c) $F, k = 1.5, s = 18$
(d) $u, k = 1.5, s = 27$
(e) $v, k = 1.5, s = 27$
(f) $F, k = 1.5, s = 27$
(g) $u, k = 1.5, s = 36$
(h) $v, k = 1.5, s = 36$
(i) $F, k = 1.5, s = 36$
(j) $u, k = 6, s = 30$
(k) $v, k = 6, s = 30$
(l) $F, k = 6, s = 30$

Figure 3.4: Numerical simulations of the actin feedback model (2.6) with parameters from Table 3.1(AF), with $s, k$ as indicated by the labels, and default initial conditions. Each row corresponds to one parameters set, showing $u, v, F$ (left to right). We can observe the four behaviors discussed in the text as we vary $k$ and $s$: (a-c) Wave pinning with oscillating front (WPO); (d-f) Reflecting waves (RW); (g-i) Single pulse absorbed at boundary (SP); (j-l) Persistent wave trains (WT). These figures used a longer domain length compared to [16], which gives more room for the patterns to develop and lead to richer behaviors compared to Fig. 3 of [16].
3.9. Simulations with spatially inhomogeneous parameters

Figure 3.5: Some of the more exotic patterns observed under the actin feedback model (2.6) with parameters from Table 3.1(AF) and varying $k, s$. 
(a-c) $k = 5, s = 10$, default initial conditions. The pattern is similar to WPO but with more than two polarized regions; (d-f) $k = 5, s = 30$, default initial conditions except that the excitation region is $0 \leq x \leq 0.1$. The resulting pattern is similar to RW except that we have a group of four pulses traversing the domain together. These patterns were not discovered by [16], although the authors did find some “exotic” patterns not shown here.
3.9. Simulations with spatially inhomogeneous parameters

Figure 3.6: Numerical simulation of the non-conservative model (2.7) with (a,b) default parameters (Table 3.1(NC)); (c,d) $\gamma = 15L^2, \eta = 15L^2$. Initial condition: (a,b) $u = u_*$ except $u = 1$ on $0 \leq x \leq 0.1$, $v = v_*$. (c,d) $u = u_* = 0.33333$ except $u = 10u_*$ on $0.4 \leq x \leq 0.41$, $v = v_* = 3.19298$. In (a,b), the formation of a peak on the left side of the domain triggers the formation of new peaks some regular distance away, until space runs out. Once all peaks are formed, they shift slightly so that they are evenly spaced. In (c,d), the single initial peak persists, but it does not lead to formation of new peaks. We call this the soliton solution.
3.9. Simulations with spatially inhomogeneous parameters

(a) Default parameters

(b) $\gamma = 15L^2$

(c) $L = 1$

(d) $\eta = 15$

Figure 3.7: Final steady state pattern of the non-conservative model (2.7) with most parameters from Table 3.1(NC), except the parameters indicated on the labels. (a) and (b) correspond to the steady state of Fig. 3.6(a,b) and (c,d) respectively. In (c) the shortened domain results in wave pinning; (d) Higher deactivation rate $\eta = 15$ results in peaks with bifurcated tops. (a,b) reproduces Fig. 5 (a,d) of [43], respectively.
3.9. Simulations with spatially inhomogeneous parameters

(a) $L = 10, s = 3$

(b) $L = 10, s = 8$

(c) $L = 10, s = 18$

(d) $L = 20, s = 35$

Figure 3.8: Numerical simulations of the combined model (2.8) with default parameters from Table 3.1(NC) except with varying $L, s,$ and HSS+noise initial condition as described in the text. Here we only show the kymograph for $u,$ since both $v$ and $F$ are similar except that $F$ lags a little behind, and $v$ is out-of-phase. Their correspondence can be seen in earlier simulations. Notice the progression from static peaks, to moving but repelling peaks, to colliding peaks as $s$ increases.
3.9. Simulations with spatially inhomogeneous parameters

(a) $s = 5$

(b) $s = 8$

(c) $s = 18$

(d) $s = 35$

Figure 3.9: Numerical simulations of the combined model (2.8) with parameters from Table 3.1(Combined2) with varying $s$, and HSS+noise initial condition as described in text. Notice as we increase the actin feedback strength $s$, the behavior transitions from slowly moving, repelling peaks to colliding peaks, similar to Fig. 3.8. At higher $s$, we observe a rapidly oscillating standing wave pattern in some parts of the domain.
3.9. Simulations with spatially inhomogeneous parameters

(a) Wave pinning, $t = 1.25$

(b) Wave pinning, $t = 30$

(c) Non-conservative extension, $t = 0.145$

(d) Non-conservative extension, $t = 0.994$

Figure 3.10: 2D simulations of the wave pinning (a,b) and non-conservative (c,d) model, using the same parameters as in 1D (Table 3.1(WP) and (NC)), with $u$ shown on the left and $v$ on the right. For each model, two snap shots are shown: one when the pattern begin to take shape, and another after the system reached steady state.
3.9. Simulations with spatially inhomogeneous parameters

Figure 3.11: Simulations for the combined model (2.8) with $L = 20$, and spatially-dependent parameter $\gamma(x)$ as in (3.7), $s, \sigma$ as indicated in the labels, and all other parameters from Table 3.1(Combined2). The kymographs of $u$, and the snapshots at $t = 1$ are shown. Notice that the pattern forms in the middle of the domain where $\gamma$ is high enough to be in the unstable regime, and this pattern does not leak outside to the region where $\gamma$ is small. This reflects localized filopodia formation in response to viral activity.
Chapter 4

Turing analysis

In this chapter, we use Turing analysis to determine the stability of the homogeneous steady state (HSS) solutions under the wave pinning and non-conservative model. If a HSS is Turing-unstable, then even an infinitesimal perturbation can grow and lead to pattern formation. The results in this section will help to explain some of the patterns seen in Ch. 3, but not all of them. Other patterns, which require the initial perturbation to be sufficiently strong, will be explained by another technique (LPA) in Ch. 5.

In [43], the authors performed weakly nonlinear analysis on the non-conservative model, which is a more general method that contains Turing analysis as its leading order. We show the correspondence between our results and [43] in Sec. 4.2.2.

4.1 Overview of Turing analysis

Turing analysis is a technique for analyzing the stability of HSS solutions for reaction-diffusion systems. This was first done by Turing in [42], which was the earliest mathematical work to study diffusion-driven pattern formation. A more modern treatment of the theory can be found in [8, Chapter 11].

The main idea of Turing analysis is to linearize the system around a HSS. This HSS is required to be stable in the well-mixed model (WM), so that diffusion is necessary for instability. Then, use an ansatz for the solution to determine the stability of all possible spatially periodic modes. The HSS is linearly stable if and only if all modes decay in time.

We will focus on wave pinning and the non-conservative extension in one spatial dimension, which is within the scope of traditional analysis. The results show that Turing regimes exist for both of these cases. The simpler techniques no longer apply when actin feedback is added. Although the method can be generalized to those cases, the results will be harder to interpret.
4.2 Turing analysis of wave pinning model and non-conservative extension in 1D

For the wave pinning or non-conservative model in 1D, we start by linearizing the system (2.7) around a chosen HSS \((u_*, v_*)\). Define

\[(\tilde{u}, \tilde{v}) = (u, v) - (u_*, v_*)\]

the linearization can be written as

\[
\frac{\partial}{\partial t} \begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix} = D \frac{\partial^2}{\partial x^2} \begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix} + J \begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix},
\]

where \(D\) is a matrix containing the diffusion coefficients on the diagonal, and \(J\) is the Jacobian of the well-mixed (WM) system at \((u_*, v_*)\):

\[
D = \begin{bmatrix} \delta & 0 \\ 0 & 1 \end{bmatrix}, \quad J = \begin{bmatrix} \frac{\partial f}{\partial u} - c\theta & \frac{\partial f}{\partial v} \\ -\frac{\partial f}{\partial u} & -\frac{\partial f}{\partial v} \end{bmatrix} \quad \text{at} \quad (u, v) = (u_*, v_*)
\]

We are especially concerned with instabilities that occur only in the presence of diffusion. Since \(\partial_v f > 0\) (2.9), we have

\[
\text{det}(J) = -(\partial_u f - c\theta)\partial_v f + \partial_u f \partial_v f = c\theta \partial_v f \geq 0.
\]

For \(c > 0\), this means the HSS is stable in WM if and only if \(\text{Tr} J < 0\). In the case \(c = 0\), the system is degenerate. Using mass conservation, this degeneracy can be removed (as in (2.13)) and the Jacobian of the equivalent 1D system is exactly \(\text{Tr} J\), so the same condition applies.

Next, consider small perturbation from the equilibrium, i.e. \(|\tilde{u}|, |\tilde{v}| \ll 1\), therefore neglecting all non-linear terms. We are interested in whether this perturbation grows or not. The normal form ansatz is:

\[
\begin{bmatrix} \tilde{u} \\ \tilde{v} \end{bmatrix} = \begin{bmatrix} \alpha_u \\ \alpha_v \end{bmatrix} \cos(qx)e^{\sigma t}.
\]

Here \(q > 0\) is the wave number, which is the spatial frequency for the mode. Higher \(q\) represents a mode with more peaks in the domain. \(\sigma \in \mathbb{C}\) is the growth rate. A mode will grow if and only if its corresponding \(\Re(\sigma) > 0\). Only the cosine modes (and not the sine modes) are allowed due to the no-flux boundary conditions, which requires \(\partial_x(\tilde{u}, \tilde{v}) = 0\) at \(x = 0\).
4.2. Turing analysis of wave pinning model and non-conservative extension in 1D

Insert the ansatz into the PDE. Neglecting the non-linear terms, and dropping the tildes yields

\[
\sigma \begin{bmatrix} u \\ v \end{bmatrix} = -Dq^2 \begin{bmatrix} u \\ v \end{bmatrix} + J \begin{bmatrix} u \\ v \end{bmatrix} = (J - Dq^2) \begin{bmatrix} u \\ v \end{bmatrix} = M \begin{bmatrix} u \\ v \end{bmatrix},
\]

(4.4)

where \( M = J - Dq^2 \). Since this results from linearization at an equilibrium, \((u, v) \equiv (0, 0)\) is a trivial solution. For any non-trivial solutions to exist, (4.4) implies that \((M - \sigma I)\) must be singular, i.e. \( \sigma \) is an eigenvalue of \( M \).

For this 2-dimensional system, \( \sigma \) can be written as

\[
\sigma = \frac{1}{2} \left( \text{Tr} \, M \pm \sqrt{\text{Tr}(M)^2 - 4 \, \det M} \right).
\]

Since we require that the HSS \((u_*, v_*)\) be stable in the well-mixed model, we know that \( \text{Tr} \, J < 0 \). As a result, \( \text{Tr} \, M = \text{Tr} \, J - q^2(1 + \delta) \leq \text{Tr} \, J < 0 \), which means one of the eigenvalues will always have a negative real part. Therefore, the HSS is linearly unstable if and only if \( \det M < 0 \).

In general, \( \det M \) is a quadratic function in \( q^2 \) with a non-negative leading coefficient. For our system, it is

\[
\det M = q^4 \delta + q^2 \left( -\partial_u f + c \theta + \delta \partial_v f \right) + c \theta \partial_v f,
\]

(4.5)

where the partial derivatives are understood to be evaluated at \((u_*, v_*)\). The minimum with respect to \( q^2 \) occurs at \( q^2 = -A^2/4\delta \). However, when \( A > 0 \) the minimum really occurs at \( q^2 = 0 \), since \( q^2 \) cannot be negative. Therefore, the minimum value is

\[
H = \min_{q^2} \det M = \begin{cases} -\frac{A^2}{4\delta} + B & \text{if } A \leq 0 \\ B & \text{if } A > 0 \end{cases}.
\]

(4.6)

The problem is now is to determine whether \( H < 0 \), in which case the HSS is unstable, or \( H > 0 \), in which case the HSS is stable.

Since \( \partial_v f > 0 \) (2.9), we have \( B \geq 0 \) always, so if \( A > 0 \) then there is no instability. In summary, the conditions for Turing instability are precisely \( \text{Tr} \, J < 0, A < 0, B < A^2/4\delta \). The first two can be expanded as:

\[
\partial_u f - c \theta - \partial_v f < 0,
\]

\[
-\partial_u f + c \theta + \delta \partial_v f < 0.
\]
4.2. Turing analysis of wave pinning model and non-conservative extension in 1D

Therefore, the conditions can be rewritten as:

\[ \delta \partial_v f < \partial_u f - c \theta < \partial_v f, \]  
\[ 4 c \theta \delta \partial_v f < (-\partial_u f + c \theta + \delta \partial_v f)^2. \]  

(4.7a)

(4.7b)

Observe that (4.7a) implies \( \delta < 1 \), and it is easier to satisfy both inequalities if \( \delta \ll 1 \). This shows that pattern formation requires \( \delta < 1 \), which is a reasonable assumption based on biology (Sec. 2.2.1).

We will show that the conditions in (4.7) are in fact equivalent to the classical Turing analysis results from [8, Ch. 11.5], which states that the necessary and sufficient conditions for diffusive instability are

\[ J_{11} + J_{22} < 0, \]  
\[ J_{11} J_{22} - J_{12} J_{21} > 0, \]  
\[ J_{11} D_{22} + J_{22} D_{11} > 2 \sqrt{D_{11} D_{22} (J_{11} J_{22} - J_{12} J_{21})^{1/2}} > 0, \]  

(4.8a)

(4.8b)

(4.8c)

where \( J_{ij}, D_{ij}, i, j = 1, 2 \) are entries of the matrices \( J, D \) given in (4.2).

The first inequality (4.8a) is simply \( \text{Tr} J < 0 \), which reduces to the second half of (4.7a). The second inequality (4.8b) translates to \( \text{det} J > 0 \), which is always true for our model due to (4.3). Finally, squaring the last one (4.8c) and expanding the definitions yields exactly (4.7b). The signs are correct after squaring due to the first inequality of (4.7a).

4.2.1 Wave pinning

For the wave pinning model, \( c = 0 \), and (4.5) simplifies to

\[ \delta \partial_v f < \partial_u f < \partial_v f. \]  

(4.9)

There is always at least one equilibrium that satisfies the second inequality. Consider (2.13), and recall

\[ g(u) = f(u, w - u) = A(u)(w - u) - \eta u, \quad k < A(u) < k + \gamma. \]  

(4.10)

It is easy to see that \( g(0) > 0 \) and \( g(w) < 0 \), and \( g \) is continuous. Hence, there must be a point \( u_\ast \in (0, w) \) where \( g(0) = 0, g'(0) < 0 \). We can visualize this better by writing \( f(u, v) = A(u) v - \eta u \), then plot the two terms with respect to \( u \) while holding \( v \) constant, as Fig. 4.1. Note that this analysis does not require a specific form for \( A(u) \). Rather it applies to any sigmoid function with \( A(0) > 0 \). In this case, \( A'(u) \) is a bump-shaped function. For our choice of using a Hill function, as \( n \) increases \( A(u) \) becomes sharper.
4.2. Turing analysis of wave pinning model and non-conservative extension in 1D

Figure 4.1: Plot of $A(u)v$ (activation, red, with typical parameter values and $v$ constant), and $\eta u$ (inactivation, blue, for different values of $\eta$). Each intersection corresponds to a HSS. The HSS is stable in WM at the points where $\eta u$ crosses from below $A(u)$ to above. Note that generically, we either get a single stable HSS, or a triplet of two stable HSS and one unstable HSS in between.

and approaches a Heaviside step function $\mathcal{H}(u - 1)$ as $n \to \infty$, while $A'(u)$ becomes more concentrated and approaches a Dirac delta function $\delta(u - 1)$ as $n \to \infty$. The maximum of $A'(u)$ occurs at $u_{max} = \left(\frac{n - 1}{n + 1}\right)^{\frac{1}{n}} \approx \begin{cases} 0.5773 & \text{if } n = 2 \\ 0.7937 & \text{if } n = 3 \\ 1 & \text{as } n \to \infty \end{cases}$.

We can expand (4.9) and with a little manipulation, get

$$\delta A(u) + \eta < A'(u)v < A(u) + \eta. \quad (4.12)$$

Suppose $(u_*, v_*)$ is a stable HSS, that is, it satisfies the second inequality. Then in the case where $n$ is large, we must have $u_*$ close to $u_{max}$ for the first inequality to hold (at least for small $\delta$). This gives a rough method of predicting Turing instability based on the location of the HSS. Since HSS are not unique (in fact we have a one-parameter family of HSS given implicitly by $f(u_*, v_*) = 0$), and each HSS have different stability condition, it is hard to identify the stability boundary for all HSS.
4.2. Turing analysis of wave pinning model and non-conservative extension in 1D

4.2.2 Non-conservative extension

The non-conservative extension (2.7) has a unique HSS at

\[ u^* = \frac{\alpha}{\theta}, \quad v^* = \frac{c\alpha + \eta u^*}{A(u)} = \frac{c\alpha + \eta u^*}{k + \gamma \frac{u^*_n}{1 + u^*_n}}. \] (4.13)

This can be found by realizing that any HSS must satisfy

\[ 0 = f(u^*, v^*) - c\theta u^* = f(u^*, v^*) - c\alpha, \]

and \( u^* \) can be uniquely solved by cancelling the \( f \) term, and \( v^* \) solved by re-substituting \( u^* \).

This time, since the equilibrium is unique, we can simply evaluate \( H \) from (4.6) at the equilibrium to determine its stability given a set of parameters. We identify two main bifurcation parameters of interest: \( \delta \), the diffusion ratio, and \( \gamma \), the magnitude of the only non-linear term. Keeping the rest of the parameters the same as in Table 3.1(NC), we plot the level curve in \( \delta - \gamma \) plane where \( H = 0 \), which is the bifurcation boundary separating the linearly stable and unstable regimes, shown in Fig. 4.2. Compare this figure to Fig. 5 of [43], which is a similar diagram for a slightly different parameter set. Notice that the shape of the curves for \( \theta = 4, 4.5 \) in Fig. 4.2 and the boundary in Fig. 5 of [43] agree with each other.

In the unstable regime, as long as the initial condition is not spatially uniform, the system will produce the static, spatially periodic pattern as seen in Fig. 3.6(e). However the number of peaks vary depending on initial conditions and parameters. These patterns correspond to the solution identified in Fig. 5(a) of [43].

In the stable regime, any small perturbation to the HSS simply decays, the system returns to the HSS and no pattern forms. However, in some cases near the bifurcation boundary, a large, localized perturbation can lead to the formation of a single persistent spike. In contrast to the unstable regime, this does not lead to the formation of additional spikes. This corresponds to the soliton solution seen in Fig. 3.6(f), and the solution identified in Fig. 5(d) in [43]. Since the perturbation is not infinitesimal, this behavior cannot be predicted by the linear Turing analysis. Later in Sec. 5.3 we will explain the soliton solution using LPA theory.

4.2.3 Predicting the wave length of pattern formed under the non-conservative model

Given the periodic steady states seen in the non-conservative model (Fig. 3.6(e)), Turing analysis might be able to predict the period of the pattern. Leave \( \gamma \)
4.2. Turing analysis of wave pinning model and non-conservative extension in 1D

Figure 4.2: Boundary of the Turing-unstable regime in $\delta - \gamma$ plane, with $\alpha = 1.5$, $\theta$ varying and all other parameters from Table 3.1(NC). The unstable regime is on the upper-left, while the stable regime is on the lower-right.

as a bifurcation parameter, and fix all others as in Table 3.1(NC) (especially $\theta = 4.5, \delta = 0.01$ with regards to Fig. 4.2).

For this section, it is easier to think about the problem if we rescale $x$ so that the domain is $0 \leq x \leq L$, with $L = 10$ as given in Table 3.1(NC). With these parameters, the bifurcation boundary is at $\gamma = \gamma_0 \approx 24.706$.

Next, we plot $q$ versus the real part of $\sigma$ (denoted $\Re(\sigma)$), where $\sigma$ is the eigenvalue of $M$ with largest real part. This plot is known as the dispersion relation. When the HSS is unstable, there must be a range of $q$ such that the corresponding $\Re(\sigma) > 0$. Additionally, if we are not far from the bifurcation boundary, this range must be small. The plot is shown in Fig. 4.3.

Due to the boundary condition, the underlying Sturm-Liouville problem forces the wave number to be discrete, that is, we must have

$$q = q_n = \frac{n\pi}{L}, \quad n \in \mathbb{N}.$$  

The mode $q_n$ repeats its period $n/2$ times. With $L = 10$, we then expect the final pattern to repeat

$$N = \frac{n}{2} = \frac{qL}{2\pi}.$$
4.2. Turing analysis of wave pinning model and non-conservative extension in 1D

Figure 4.3: The dispersion relation for the non-conservative model with different values of $\gamma$, with other parameters from Table 3.1(NC). Notice that at bifurcation point $\gamma_0 = 24.706$, the curve is tangent to the x-axis at $q \approx 5.72$. For $\gamma = 25$, the range of unstable $q$ is $4.52 < q < 7.24$

periods, with $N$ restricted to (half-)integers. For $\gamma$ just at $\gamma_0$, the unstable modes are near $q = 5.72$ which corresponds to $N = 9.1037$. For $\gamma = 25$, the prediction is $7.5 \leq N \leq 11.5$.

We run numerical simulations with a random noise initial condition

$$u = (1 + \text{Unif}[-0.01, +0.01])u_*$$

to verify the prediction. Indeed, for $\gamma = 24.7 < \gamma_0$ (or smaller), the noise quickly decays and no pattern forms. The same happens for $\gamma$ just above $\gamma_0$, which is also expected since the unstable eigenvalue is vanishingly small, so patterns can form only after a very long time. With $\gamma = 25$, patterns readily form, but they usually repeats for 3 to 5 periods, contrary to the prediction.

However, upon a closer inspection, we found that there is an initial precursor pattern which forms gradually with the number of periods within expectation (usually $9 \leq N \leq 11$), with amplitude on the order of 0.1. Once a peak reaches a certain amplitude, it will very rapidly grow to the full size of the final pattern (amplitude $\approx 1.3$) while suppressing nearby peaks. Other precursor peaks farther away from the grown one might survive longer and eventually transition to full size, or be suppressed by another nearby peak
4.2. Turing analysis of wave pinning model and non-conservative extension in 1D

Figure 4.4: Simulations for the non-conservative model (2.7) with random initial conditions $u = u_*(1 + \text{Unif}(-0.01, +0.01))$, $v = v_*$ with default parameters from Table 3.1(NC) except $\gamma = 25$ in (a,b,c) and $\gamma = 24.75$ in (d). The color range is chosen so that the precursor pattern is more visible. The rapid transition from the shallower, higher frequency precursor pattern to the final pattern can be clearly seen.

which has transitioned sooner. Since the precursor pattern is very short-lived and shallow compared to the final pattern, it is easily overlooked.

Fig. 4.4 shows a few simulations focusing on the transition between the initial and final pattern. Here we see that the initial pattern has the expected number of peaks, while the final pattern has much less. The time of transition has some variability, and different regions can transition at different times. With $\gamma$ closer to the bifurcation boundary, it will take the initial pattern longer to form, but the transition is just as rapid. The effect of a growing peak suppressing nearby peaks is clearly visible. There is also some merging between adjacent peaks. Whether a peak survives or not depends on other nearby peaks, making this a non-linear interaction. Therefore the
system behavior after transition is beyond the scope of the linear Turing analysis.

As a result, Turing analysis cannot directly predict the number of peaks in the final pattern. In order to find out how many peaks are possible, we use periodic initial condition \( u = u_\ast (1 + 0.1 \cos(Nx/L)) \) to “force” a \( N \)-peaks solution. The result is that the final pattern can have anything between 3 and 11 peaks. Too few peaks leaves a large enough empty space between them for a new peak to form, while too many peaks leads to some peaks being suppressed after forming.

However, there is another way to use the Turing analysis results with the “minimum patch size” idea from [35]. The observation that there exist an upper bound on the number of peaks implies that there is a minimum patch size \( L_m \), which is the minimum domain length for \( L \) that can support a single peak. A solution with a single peak corresponds to the mode \( N = 1 \), so the \( L_m \) is the minimum \( L \), such that \( q = 2N\pi/L \) is within the unstable range. For our parameters, the unstable range is \( 4.52 < \gamma < 7.24 \), so \( L_m = 2\pi/7.24 \approx 0.8678 \). Our domain with length \( L = 10 \) can fit 11 sub-domains of length \( L_m \) inside, and each can support one peak. Therefore, this calculation predicts that the final pattern can have at most 11 peaks, exactly as observed. This method cannot predict the minimum number of peaks, however.
Chapter 5

Local perturbation analysis

Local perturbation analysis (LPA) is a method for examining the evolution of a localized perturbation to a homogeneous steady state (HSS) for a fast-slow diffusion-reaction system. It provides a way to systematically detect certain forms of nonlinear instabilities that are not detectable by Turing analysis. LPA was first developed by [14], and has been used in [9, 17, 16, 27] to analyze wave pinning and related models. We will compare our results to the results these earlier papers in the following sections. A comprehensive guide to LPA and other examples of application are given in [18].

In this section, we will compare the stability results from LPA with analysis of the well-mixed systems and Turing analysis. In particular, LPA provides a rough guide for parameter exploration and hints on possible regimes for the full PDE model.

5.1 Overview of LPA

The main idea behind LPA is to exploit the difference in the rates of diffusion, which allows us to go one step further than analyzing the well-mixed system (WM, (2.11)). Take the limit of the ratio diffusion coefficients (δ in our model) to 0 and consider the problem on an intermediate time-scale, i.e rescale time by $t = \sqrt{\delta} \tau$. In this case, as a leading order approximation, the fast diffusing quantities ($v$ in our model) diffuse infinitely fast, whereas the slowly diffusing quantities ($u, F$) do not diffuse at all. This can be understood as a sort of “zeroth order” asymptotic approximation in $\sqrt{\delta}$.

In this approximation, $v$ will always be spatially homogeneous since any inhomogeneity will be instantly smoothened out by the diffusion. We prescribe an initial condition where $u$ and $F$ are homogeneous across the entire domain with values $(u_*, F_*)$, except for a localized perturbation at some point $x_0$ in the interior of the domain. This perturbation is assumed to have
5.1. Overview of LPA

infinitesimal width but finitely positive height. That is,

\[ v(x, 0) = v_*, \]
\[ u(x, 0) = u_* + (\tilde{u} - u_*)\delta(x - x_0), \]
\[ F(x, 0) = F_* + (\tilde{F} - F_*)\delta(x - x_0), \]

(5.1)

where \( \delta(\cdot) \) denotes Dirac delta function. Note that this differs from Turing analysis, which assumes a global perturbation with infinitesimal height. For each of the slow variables, we can track the global level \((u, F)\) and the level at the local perturbation \((u_L, F_L)\) with two separate variables that depend solely on time, with initial conditions:

\[ u(t) = u(x,t), \quad x \neq x_0, \quad u(0) = u_*, \]
\[ v(t) = v(x,t), \quad v(0) = v_*, \]
\[ F(t) = F(x,t), \quad x \neq x_0, \quad F(0) = F_*, \]
\[ u_L(t) = u(x_0,t), \quad u_L(0) = \tilde{u}, \]
\[ F_L(t) = F(x_0,t), \quad F_L(0) = \tilde{F}. \]

(5.2)

Since the perturbation is interpreted to be very narrow, the local variables will have vanishing effect on the rest of the system, so only the global levels appear in the reaction term of \(v\), which in turn affects both local and global \(u, F\). Hence, in general, the LPA for the combined system (2.8) is:

\[ \frac{\partial u}{\partial t} = f(u, v, F) - c\theta u, \]
\[ \frac{\partial v}{\partial t} = -f(u, v, F) + c\alpha, \]
\[ \frac{\partial F}{\partial t} = \epsilon(k_n u - k_s F), \]
\[ \frac{\partial u_L}{\partial t} = f(u_L, v, F_L) - c\theta u_L, \]
\[ \frac{\partial F_L}{\partial t} = \epsilon(k_n u_L - k_s F_L). \]

(5.3)

The first three equations are exactly the same as the WM system (2.11). The resulting ODE system (5.3) is much easier to analyze than the full PDE system. For each set of interesting parameters, we produce a series of bifurcation diagrams with respect to different parameters with XPPAUT [10, 7] and Matcont [5]. These diagrams identify parameter regimes such that the ODE behavior is qualitatively different.
5.1. Overview of LPA

In this chapter, we follow AUTO’s convention on bifurcation diagrams. On one-parameter diagrams, red/black curves indicate positions of stable/unstable equilibria respectively, while green/blue indicate the range of stable/unstable limit cycles. On two-parameter diagrams, red/light blue/dark blue curves trace the position of limit points (fold points)/branch points (transcritical points)/Hopf points, respectively.

These results do not translate directly to the full PDE model for \( \delta > 0 \). In some cases distinct ODE regimes correspond to the same behavior for the PDE. In addition, LPA cannot help to detect any bifurcation with respect to \( \delta \), whereas Turing analysis (Ch. 4) can. In general, LPA results need to be verified with numerical PDE simulation with small \( \delta \).

![Figure 5.1: Illustration of the idea behind LPA, showing a localized perturbation to a HSS. The fast diffusing variable \( v \) is spatially homogeneous, while the slowly diffusing variable \( u \) can be decomposed into a global \( u_G \) and local \( u_L \) variables which do not depend on \( x \).](image)

There are some properties that LPA systems exhibit in general. First, for any solution

\[
    u = \phi(t), \quad v = \psi(t), \quad F = \varphi(t)
\]

of WM,

\[
    u = \phi(t), \quad v = \psi(t), \quad F = \varphi(t), \quad u_L = \phi(t), \quad F_L = \varphi(t)
\]

is always a solution of LPA. This means that any features (equilibria branches, limit cycles, bifurcation points) that appear on bifurcation diagrams of WM
must also appear on bifurcation diagrams of LPA. We call these “global branches”. LPA might (and usually does) have additional branches not present in WM, we call these “local branches”.

Note that the dynamics of the global variables are the same as the WM system. This means the eigenvalues of WM are a subset of the eigenvalues of LPA. In fact, it is easy to see that the Jacobian of LPA is block upper diagonal, with the top diagonal block being the Jacobian of WM. Consequently, if an equilibrium/limit cycle is unstable in WM, it must also be unstable in LPA. The converse is not true, however, as stability in WM does not imply stability in LPA.

The structure of the LPA system allows us to decompose the LPA dynamics into two steps, at least in the case where a stable equilibrium exists for WM. First, the global variables reach a stable equilibrium independent of the local variables, with \( v = v_\ast \). Next, consider the system with only the local variables, and set \( v = v_\ast \) as a constant parameter. If the global variables do not reach any stable equilibrium, they will enter the local equations as a non-autonomous forcing term. This will be helpful during some of the analysis.

For our models, notice that \( L \), the domain length, has no effect on the LPA dynamics. With the diffusion terms absent, \( L \) can be absorbed by rescaling of time, so this chapter assumes \( L = 1 \) for simplicity.

5.2 LPA for Wave pinning

The LPA system corresponding to the wave pinning model (2.5) is simply (5.3) with \( c = s = 0 \), and \( F, F_L \) equations removed. However, this can be simplified with mass conservation similar to Sec. 2.6. Introduce an additional constant parameter \( w = u + v \) for mean concentration of GTPases, and eliminate \( v \) from the equations. This results in a system of 2 ODEs:

\[
\frac{\partial u}{\partial t} = f(u, w - u), \\
\frac{\partial u_L}{\partial t} = f(u_L, w - u).
\]  

(5.4a)  

(5.4b)

For this model, we identify \( \gamma \) (the magnitude of the only nonlinear term) and \( w \) (total concentration) as primary parameters of interest.

In Fig. 5.2 and 5.3, there are seven regimes identified, which are summarized in Table. 5.1. The global branch can be easily distinguished, and its stability compared to WM agrees with earlier discussions. Compared to
5.2. LPA for Wave pinning

Figure 5.2: Bifurcation diagrams of the wave pinning WM and LPA systems (5.4) using bifurcation parameter \( \gamma \), and other parameters taking values from Table 3.1(WP) except \( w \). The purple lines are located at bifurcation points, separating the different parameter regimes. Notice that all curves in the WM diagrams (the global branches) also appear in LPA. Moreover, the global branch in LPA can be unstable in some intervals despite it being stable in WM, as discussed in Sec. 5.1.
5.2. LPA for Wave pinning

Figure 5.3: Two-parameter bifurcation diagrams of the wave pinning (a) WM and (b,c) LPA systems using bifurcation parameters \( w, \gamma \), and other parameters taking values from Table 3.1(WP). Each curve in these diagrams traces the location of a bifurcation point shown in Fig. 5.2, and forms the boundary of a parameter regime. The one-parameter bifurcation diagrams in Fig. 5.2 corresponds to vertical cross-sections of the diagrams here. The LPA regimes identified I to VII match with the regimes labelled in Fig. 5.2(b,d,f). These regimes and their meanings are summarized in Table 5.1. (c) A zoom into the region near the cusps in (b). We can compare (b) to Fig.3(a) of [17], which is a LPA diagram for the same model but different parameters. Observe that the two diagrams agree on the fold curves (red), but [17] omits the transcritical curve (light blue), which separates several distinct regimes.
5.2. LPA for Wave pinning

the earlier study [17], we have additionally traced a branch of transcritical bifurcation in two-parameter continuation in Fig. 5.3, which allows us to identify several new regimes.

<table>
<thead>
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<td>Stable</td>
<td>One stable GB, no LB</td>
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<td>Polarizable</td>
<td>One stable GB, one stable LB located above the GB</td>
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<td>Polarizable</td>
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<td>Two stable GBs, three stable LBs: one above both GBs, one in between, and one below both GBs</td>
</tr>
<tr>
<td>V</td>
<td>Polarizable</td>
<td>One stable GB, one stable LB located below the GB</td>
</tr>
<tr>
<td>VI</td>
<td>Unstable</td>
<td>The only GB is unstable, two stable LBs located on both sides of the GB</td>
</tr>
<tr>
<td>VII</td>
<td>Unstable</td>
<td>Three GBs, all unstable, four stable LBs located on both sides of the GB</td>
</tr>
</tbody>
</table>

Table 5.1: Summary of the wave pinning model regimes identified in Fig. 5.2 and 5.3. Abbreviations: GB: global branch; LB: local branch. Stable: all stable branches are global branches. Polarizable: there exist both stable global and local branches. Unstable: all global branches are unstable, in which case there must exist some stable local branches.

In Regime I, there is only one global branch, which is stable. In this regime wave pinning does not occur, and any perturbation to the HSS simply decays exponentially. We call this the stable regime.

In Regimes II/III/V, there is one stable branch of global solution, but stable local branches also exist. Their position in relation to the global branch differs by regime: in Regime II the local branch is above the global branch, whereas the opposite happens in Regime V. In Regime III there are local branches located on both sides of the global branch. The boundaries of the domains of attraction are given by the unstable branches between the stable branches. This means that a sufficiently large local perturbation in the right direction can lead to pattern formation. In Regime II, if the local initial perturbation is positive and above the threshold, then the LPA system will be attracted to an equilibrium with \( u_L > u \). The equivalent initial condition for the full PDE results in wave pinning, as verified by PDE simulations (Fig. 3.1). Regime V is similar except that the initial perturbation needs to
be sufficiently negative. In this regime, simulations for the full PDE model result in wave pinning only with a large negative perturbation, as observed in Fig. 3.2. In Regime III, wave pinning can occur for both large positive and negative perturbations. Regime IV is similar to III except that there are two stable global branches, which means that wave pinning can occur for two different global states. PDE simulations confirms that these predictions are correct. We call regimes with both stable global and local branches the polarizable regimes.

In Regime VI, the global branch is unstable, which means that any perturbation to the initial HSS can lead to pattern formation. Regime VII is the same, except that there are three global branches, all unstable. This regime behaves the same as VI for the full PDE. The HSS is also Turing-unstable for small $\delta$, following the analysis in Ch. 4. In fact, we can show that Regimes VI and VII corresponds exactly to the Turing regime as $\delta \to 0$.

First, since the global branch $\langle u_*, v_* \rangle$ is stable in WM, we know:

$$\left. \frac{df(u, w - u)}{du} \right|_{(u_*, v_*)} = \frac{\partial f(u_*, v_*)}{\partial u} - \frac{\partial f(u_*, v_*)}{\partial v} < 0. \quad (5.5)$$

Second, the global branch is unstable in LPA. The Jacobian for the LPA system is

$$\begin{bmatrix}
\frac{\partial f(u, w - u)}{\partial u} & \frac{\partial f(u, w - u)}{\partial v} \\
\frac{\partial f(u_L, w - u)}{\partial u} & \frac{\partial f(u_L, w - u)}{\partial v}
\end{bmatrix}
\left|_{(u = u_L = u_*, w = v_*)} \right. = \begin{bmatrix}
\frac{\partial f(u_*, v_*)}{\partial u} - \frac{\partial f(u_*, v_*)}{\partial v} & \frac{\partial f(u_*, v_*)}{\partial u} - \frac{\partial f(u_*, v_*)}{\partial v} \\
0 & \frac{\partial f(u_*, v_*)}{\partial u} - \frac{\partial f(u_*, v_*)}{\partial v}
\end{bmatrix}. \quad (5.6)
$$

We have already shown that the first eigenvalue $\partial_u f - \partial_v f$ is negative (5.5). So the global branch is unstable in LPA if and only if the second eigenvalue $\lambda = \partial_u f(u_*, v_*) > 0$. Hence this regime is characterized by

$$0 < \partial_u f(u_*, v_*) < \partial_v f(u_*, v_*),$$

which is exactly the condition for Turing (4.9) as $\delta \to 0$. This result can be similarly generalized to other models.

Bifurcation diagrams with respect to the other parameters (not shown) tell the same story: that there are Turing regimes, stable regimes, and polarizable regimes separated by fold and transcritical bifurcations. A few earlier studies have performed LPA analysis with different parameters: [9] used $k$ as bifurcation parameter, and [17] used $w$. Both have results and interpretations agreeing with ours.
5.3. LPA for non-conservative extension

5.2.1 More on Wave pinning

LPA allows us to further understand the wave pinning system. We can decompose of LPA dynamics into “global” and “local” steps as discussed in Sec. 5.1. For wave pinning, this is particular helpful since each step is a single ODE, allowing us to visualize the stability of the equilibria by plotting the right hand side of the ODE.

For the global dynamics, we plot $g(u) = f(u, w - u)$ against $u$. We know from Sec. 4.2.1 that, generically, $g(u)$ has one or two stable zeros. The special cases where $g(u)$ has a degenerate (i.e. double) root correspond to fold bifurcation points. The zeros corresponds to the global equilibria.

Next for the local dynamics, for each root $u^*$ of $g(u)$, we plot $f(u, w-u^*)$. One of its roots will be $u^*$, the others (if any) give locations of the local equilibria. The equilibria are stable if the derivative at the corresponding root is negative. The plots corresponding to each regime can be found in Fig. 5.4. This provide a way to enumerate all distinct regimes.

With a sharper Hill function (i.e. larger $n$), the “bumps” in Fig. 5.4(c-g) will be higher (e.g. the bump is higher in (d) than (c)). This means there will be a larger parameter range such that $f$ crosses the x-axis three times. This explains why larger $n$ makes pattern formation more robust, as claimed in Sec. 3.2.

5.3 LPA for non-conservative extension

The LPA system for the non-conservative extension is (5.3) with $c > 0, s = 0$ and $F, F_L$ removed. For this system, we identify $\gamma$ as the main bifurcation parameter of interest as before, as well as $c$, which controls the magnitude of the additional terms.

As before, we can decompose LPA dynamics into global and local dynamics. The global equilibrium $(u^*, v^*)$ (4.13) is unique. Then any local branches $u_L^*$ must satisfy $f(u_L^*, v^*) = 0$. Expanding this yields

$$A(u_L^*) \frac{c \alpha + \eta u^*}{A(u^*)} - \eta u_{L*} - c \theta u_{L*} = 0.$$

After some manipulations, we get

$$(c \theta + \eta) \left( u^* \frac{A(u_L^*)}{A(u^*)} - u_{L*} \right) = 0,$$

which simplifies to

$$\frac{A(u_L^*)}{A(u^*)} = \frac{u_{L*}}{u^*}. \quad (5.8)$$
5.3. LPA for non-conservative extension

Figure 5.4: Plots of the reaction term $f(u, w - u)$ (global) and $f(u, w - u_*)$ (local) (2.5c), with parameters from Table. 3.1(WP) illustrating each LPA regime identified for the wave pinning model. We do not plot the local curves corresponding to unstable global equilibria since they are irrelevant for determining dynamics in general. The roots of the global and local curves correspond to the position of global and local equilibria. Notice that the number and location of equilibria agrees with the bifurcation diagrams Fig. 5.2, 5.3.

Recall that

$$A(u) = k + \gamma \frac{u^n}{1 + u^n}, \quad u_* = \frac{\alpha}{\theta}.$$ 

Therefore (5.8) shows that the local branches are independent of both $c$ and $\eta$.

A few more things can be inferred from (5.8). First, for $\gamma \ll k$, the LHS $\approx 1$ so $u_{L*} = u_*$, which means that there is no local branch for small $\gamma$. We will show that for $\gamma \gg k$, there are always a high and low local branches. The low branch is $u_L \approx 0$, since with $\gamma \to \infty, u_L = 0$, both sides of (5.8) evaluate to 0. With a bit of further manipulation, we can get (in the limit $\gamma \to \infty$):

$$\frac{u_{L*}^{n-1}}{1 + u_{L*}^n} = \frac{u_*^{n-1}}{1 + u_*^n}.$$ 

(5.9)

The function

$$h(u) = \frac{u^{n-1}}{1 + u^n}$$
5.3. LPA for non-conservative extension

satisfies $h(0) = 0 = h(u \to \infty)$, and it has a single peak at $u_p \geq 1$ (provided $n \geq 2$). Following the discussion in Sec. 4.2.2 we will focus on parameters with $\alpha < \theta$, that is $u_\ast < 1$. Therefore there exist a point $u_{L\ast} > u_p > 1$ such that $h(u_{L\ast}) = h(u_\ast)$, which corresponds to the high local branch.

In the following bifurcation diagrams, we use parameters from Table 3.1 (Combined2) but with $\eta = 5$. These parameters yield bifurcation diagrams that are easy to view (the regimes are not too wide or too narrow). The same regimes are present for the parameters from Table 3.1(NC), which was used for simulations in Sec. 3.6, but the resulting diagram is hard to read.

Fig. 5.5 identifies four distinct regimes of the LPA system and they can be similarly interpreted as in the previous section. These regimes are summarized in Table 5.2.

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<tr>
<td>IV</td>
<td>Unstable</td>
<td>One GB, two LBs all unstable, each enclosed by a periodic orbit</td>
</tr>
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</table>

Table 5.2: Summary of the non-conservative model regimes identified in Fig. 5.5. For abbreviations see caption of Table. 5.1.

In Regime I, there are no local branches and the only global branch (the horizontal line in Fig. 5.5a) is stable. For the full PDE, all perturbation to the HSS decays and no pattern formation is observed. Regime II is a polarizable regime. Any perturbation with insufficient height decays. However, in the full PDE, if the perturbation is sufficiently tall and narrow, it will persist, leading to the soliton solution shown in Fig. 3.6(f).

Regimes III and IV has the global branch being unstable, so they both correspond to the Turing regime. In full PDE simulations, any perturbation leads to pattern formation, which tends to spread across the entire domain, as seen in Fig. 3.6(a,b,c). Regime IV is bounded by a pair of Hopf bifurcations. Here the global branch is unstable even in WM. The full PDE’s behavior in this regime is not qualitatively distinct from Regime III. This is a little surprising, since we might expect to see non-static patterns, such as oscillating spikes given the limit cycles.

Fig. 5.5(b) shows that $c$ has no effect on the location of the fold and
5.3. LPA for non-conservative extension

Figure 5.5: Bifurcation diagrams for the non-conservative extension, with other parameters from Table 3.1(Combined2) except $\eta = 5$. (a) WM, (b,c) LPA, using bifurcation parameters (a,b) $\gamma$, with $c = 1$, (c) $c$ and $\gamma$. Notice the thin polarizable regime II sandwiched between the stable I and Turing III regimes. The triplet of Hopf bifurcations, which is not present in wave pinning, turns out to be inconsequential.
5.4 LPA for actin feedback extension

For the actin feedback extension, we use mass conservation to eliminate $v$ from the LPA system as before, and identify $s$, the strength of actin feedback and $k$, the basal rate of activation as main parameters of interest. The result is a system of four ODEs:

\[
\begin{align*}
\frac{\partial u}{\partial t} &= f(u, w - u, F), \\
\frac{\partial F}{\partial t} &= \epsilon(k_n u - k_s F), \\
\frac{\partial u_L}{\partial t} &= f(u_L, w - u, F_L), \\
\frac{\partial F_L}{\partial t} &= \epsilon(k_n u_L - k_s F_L).
\end{align*}
\]

(5.10a) (5.10b) (5.10c) (5.10d)

It is rather hard to analyze the equilibria of this system by hand. So we will jump right to the bifurcation diagrams, shown in Fig. 5.6 and 5.7. We only distinguish between the regimes separated by fold and transcritical curves and omit the Hopf curves since it is unlikely that they will be significant, as explained below. We also ignore the very narrow regimes since they are likely inconsequential overall. The six regimes identified this way are summarized in Table 5.3.

One interesting characteristic of these diagrams is the unstable periodic orbits that exist for very narrow parameter ranges. They emerge as subcritical Hopf bifurcations. The unstable cycle enlarges until it collides with a saddle point, turning into a homoclinic orbit to the saddle, then it disappears beyond that. This is known as saddle-loop bifurcation, or homoclinic bifurcation (see [21, Ch.6.2]). Since the parameter regimes where the periodic solutions exist are very narrow, it is unlikely that a real cell would fall into one of these regimes, so we believe that the Hopf bifurcations are likely inconsequential to biology.

Compared to Fig. 5 of [16], which is a LPA diagram in $k - s$ plane containing only one of the Hopf curves (dark blue), our diagram (Fig. 5.7) additionally traces the fold (red) and transcritical (light blue) bifurcation points and identifies a larger number of distinct regimes. The authors of [16] identified the large Hopf bifurcation curve that forms a loop in Fig. 5.7,
5.4. LPA for actin feedback extension

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<tr>
<td>VI</td>
<td>Polarizable</td>
<td>One stable GB, three stable LBs located on both sides of the GB</td>
</tr>
</tbody>
</table>

Table 5.3: Summary of the actin feedback model regimes identified in Fig. 5.6. For abbreviations see caption of Table 5.1.

tracing the pair of Hopf points on the global branch in Fig. 5.6(d). However, since we now know that the periodic solutions exist only in a very narrow range of parameters, the Hopf curve is unlikely to form the only regime boundary as discussed by [16].

Fig. 6(b) of [16], which is a single parameter bifurcation diagram with respect to \( k \), tells a similar story to our Fig. 5.6(b,d) in the sense that it too identified subcritical Hopf bifurcations, as well as stable, polarizable and unstable regimes separated by fold and transcritical bifurcations.

The two parameter LPA diagram is investigated further in [27], which has computed eigenvalues of both the Turing and LPA systems and identified two Bogdanov-Takens (BT) and generalized Hopf (GH) bifurcations located on the main Hopf curve (the one that traces the pair of Hopf points on the global branch). The BT points are visible in Fig. 5.7; they are the end points of the Hopf curves, where they bifurcate off fold curves. The GH bifurcations are located on the Hopf curves, and not visible in our figures. At a GH point, there is another curve that branches off from the Hopf curve, which corresponds to a fold bifurcation for periodic solutions [21, Ch. 8.3]. This is a global bifurcation, which is hard to trace with AUTO. It is likely that there are codimension-2 bifurcation points lying on the other Hopf curves not discussed by [27].

The interpretations of the LPA diagrams are similar to the wave pinning model. Whenever we have a stable local branch, we expect some kind of pattern formation. Unlike the wave pinning model, there are multiple pos-
sible patterns in this model. In this case, LPA cannot accurately predict the type of pattern. Especially, the consequence of the subcritical Hopf bifurcations to the full PDE is not clear, but it might suggest some kind of (quasi-)periodic behavior.

We match the regimes shown in Fig. 5.6(e) with the numerical simulations in Fig. 3.4 in an attempt to identify distinct patterns with their corresponding regimes. Additionally, we use data from [16], which performed a parameter sweep in this plane and automatically classified the behavior into five categories: the four in Fig. 3.4, as well as no patterning.

Unsurprisingly, Regime I results in no patterning. Regime V roughly corresponds to usual wave pinning with static wave front. In Regime VI we get wave pinning with oscillating front (WPO, Fig. 3.4(a-c)). The correspondence is not exact, as expected since LPA is an approximation for $\delta \to 0$, while the full PDE uses a finite positive value for $\delta$.

However, Regimes II, III and IV cannot be conclusively identified with any one of the behaviors. The data from [16] suggests that II results in no patterning, while the regime corresponding to wave trains (WT, Fig. 3.4(j-l)) is contained within III. Regimes III and IV can both produce reflecting waves (RW, Fig. 3.4(d-f)) and single pulse (SP, Fig. 3.4(g-i)). It is possible that one of the Hopf curves omitted in Fig. 5.6 (e) (but shown in Fig. 5.7) forms the boundary of a distinguishable regime, but there are too many Hopf curves to be tractable and none seems to explain the transition between RW and SP.

Additionally, [16] observed exotic patterns near the boundary of the regimes. In Fig. 3.5, we showed some possible non-standard patterns (given suitable initial conditions) well within the interior of II. Moreover, in Regime II the system is polarizable (akin to Regime V of the wave pinning model in Fig. 5.3.5.2) so we expect for $s \to 0$ to recover wave pinning behavior, which is observed in full PDE simulations. This means that there must be another bifurcation boundary inside Regime II near $s = 0$, likely of non-linear nature, that indicates a transition from WP to more complex behaviors.

In summary, LPA worked well in identifying no-pattern and WP regimes. It is not very useful for predicting the more complex patterns. Many of those patterns involve interacting waves, which suggests that they are non-linear, non-local phenomena, explaining why LPA cannot account for them.
5.4. LPA for actin feedback extension

Figure 5.6: Bifurcation diagrams of the actin feedback extension. (a-d) Using bifurcation parameter $s$; (e) two-parameter continuation using $k, s$. In (e), the Hopf curves are omitted since they are too close to the other curves and clutter up the diagram. The regimes that are too narrow are not labelled since they are unlikely to be consequential. Notice the nearly vertical blue curves indicating unstable periodic orbits.
5.4. LPA for actin feedback extension

Figure 5.7: Same as Fig. 5.6(e) but with the Hopf curves included. A few Hopf curves lie very close to one of the other curves for most of their length, creating some very narrow regimes.
5.5 LPA for the combined Model

The LPA diagrams for the combined model are very complex, and mostly beyond the scope of interpretation. This is unsurprising given the complex behavior exhibited by the PDE. The bifurcation diagram shown in Fig. 5.8, which uses parameter values from Table 3.1(Combined2), contains many limit cycle bifurcations, such as torus and period-doubling. One thing the diagram can provide is the minimum value of $s$ required for any non-static patterns (corresponding to the first triplet of Hopf bifurcation in Fig. 5.8). With $s$ below this value, the system behaviour is the same as that of the $s = 0$ case, which reduces back to the non-conservative extension.

Figure 5.8: Bifurcation diagrams for the combined model using bifurcation parameter $s$, with other parameter values taken from Table 3.1(Combined2). Notice the many branches of periodic solutions and the bifurcations on them. In a parameter range around $s = 20$, there are no stable equilibria nor stable periodic solutions even though the system remains bounded, which suggests the presence of chaos.
Chapter 6

Interaction with changing domain

So far, the simulations and analysis assume a static domain for the PDE. However, given that the GTPases regulates cell shape and size, more realistically the domain should be dynamic as well. This chapter presents two approaches for adding the coupling between the changing domain and GTPase concentration to existing models.

6.1 Well-mixed wave pinning model in 1D with dynamic domain

The first approach is to consider the well-mixed wave pinning model, that is (2.13), repeated here:

\[ \frac{\partial u}{\partial t} = f(u, v) = g(u), \quad v = w - u. \]  \hspace{1cm} (6.1)

The goal is to couple this equation with the size of the domain, \( L \), which is no longer held constant. Here for convenience we interpret the domain to be one dimensional (so \( L \) is for length). The interpretation and analysis are identical for 2D domains (simply change \( L \) to \( A \) for area).

This approach is related to [49]. The authors considered the coupling between Rho GTPase and mechanical tension (which depends on cell size through \( L - L_0 \), where \( L_0 \) is the basal cell size) by adding a feedback term to the activation function. We will instead consider the dilution effects of changing cell size to GTPase dynamics. We will compare the results at the end of Sec.6.1.1. Another related study is [6], in which the authors also considered the dilution effects, but instead of GTPase dynamics they used a very different dynamics for force-producing molecules (i.e. actin, myosin).

The system (6.1) has been reduced to a single ODE using mass conservation. However, \( u \) and \( v \) are concentrations, but mass conservation is a statement about total mass, which is no longer equivalent should the size of the domain be dynamic.
We revise the equations as follows to obtain the correct conservation statement in this context. Let $T$ be the total mass of GTPase, which is constant. Define $U(t), V(t)$ to be the total amount of active/inactive GTPase, related to old variables via $w = T/L, u = U/L, v = V/L$. The original ODE should be restated in terms of $U$ and $V$. Remember $f(u, v)$ has unit of concentration/time, so the revised equation should be:

$$\frac{\partial U}{\partial t} = Lf(U/L, V/L), \quad V = T - U. \quad (6.2)$$

Rewrite in terms of the old variables, and expand the left hand side using the product rule of differentiation gives

$$\frac{\partial u}{\partial t} = f(u, v) - u \frac{\partial L}{\partial t} \frac{L}{L}, \quad v = T/L - u. \quad (6.3)$$

Notice that compared to (6.1), the only difference is the additional (*) term, which represents dilution effects. If the domain is expanding, i.e. $\frac{\partial L}{\partial t} > 0$, then the (*) term is negative since $u$ is diluted on an expanding domain, and vice versa: a contracting domain concentrates $u$, which corresponds to a positive (*) term.

We need an equation for $L$ to close the system. The simplest choice is to assume that the cell behaves like a Hookean spring, with rest length determined by $u$:

$$\frac{\partial L}{\partial t} = -\kappa(L - L_0(u)). \quad (6.4)$$

The rest length $L_0(u)$ should either be monotone decreasing if the GTPase causes contraction (Rho), or monotone increasing if the GTPase causes expansion (Rac/Cdc42). To be consistent with the non-linearity in the reaction term, which is a Hill function centered at $u_0$, we will also use a Hill function for $L_0$, centered at some $u_c$. For simplicity, we can assume all nonlinear
6.1. Well-mixed wave pinning model in 1D with dynamic domain

terms have the same Hill coefficient. Therefore, the full system is:

\[
\begin{align*}
\frac{\partial u}{\partial t} &= g(u) - \frac{u}{L} \frac{\partial L}{\partial t}, \\
\frac{\partial L}{\partial t} &= -\kappa(L - L_0(u)), \\
g(u) &= \left(k + \gamma \frac{u^n}{u_0^n + u^n}\right) \left(\frac{T}{L} - u\right) - \eta = f\left(u, \frac{T}{L} - u\right), \\
L_0(u) &= \begin{cases} 
L_b + (L_h - L_b) \left(1 - \frac{u^n}{u_c^n + u^n}\right) & \text{for Rho (contraction)}, \\
L_b + (L_h - L_b) \frac{u_c^n}{u_c^n + u^n} & \text{for Rac/Cdc42 (expansion)}.
\end{cases}
\end{align*}
\]

Here \(L_b\) means basal (minimum) rest length and \(L_h\) means heightened (maximum) rest length. We will refer to this system (6.5) as the dynamical cell size model, and its equilibria must satisfy:

\[
L = L_0(u), \quad u = \frac{k + \gamma \frac{u^n}{u_0^n + u^n}}{\eta + k + \gamma \frac{u^n}{u_0^n + u^n}} \frac{T}{L_0} = \frac{T}{L_0} \left(1 - \frac{\eta}{\eta + k + \gamma \frac{u^n}{u_0^n + u^n}}\right).
\]

Although we have scaled \(u_0\) away during non-dimensionalization in Sec. 2.2.1, here we put it back explicitly to remind us of the true dimensions of the terms. Nonetheless we will still take its value to be 1.

In the following analysis, we will make use of the sharp switch approximation. The idea is to let \(n \to \infty\) so that the Hill function terms approach Heaviside step function \(\mathcal{H}\), allowing us to make the following approximations:

\[
\frac{u^n}{u_0^n + u^n} \Rightarrow \mathcal{H}(u - u_0), \quad \frac{u^n}{u_c^n + u^n} \Rightarrow \mathcal{H}(u - u_c), \quad 1 - \frac{u^n}{u_c^n + u^n} \Rightarrow \mathcal{H}(u_c - u).
\]

These approximations make the system piecewise linear, so easier to analyze. It is still not fully linear, so we can still hope that the approximation will retain some of the interesting characteristics.

The parameter values we use are summarized in Table. 6.1. We will explain how to guide parameter selection with analysis based on the sharp switch approximations.

6.1.1 Contraction case (Rho)

First, consider the effect of Rho GTPase, which makes the cell contract. As before, we use \(\gamma\) as the bifurcation parameter, and \(T\) as a secondary
### 6.1. Well-mixed wave pinning model in 1D with dynamic domain

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dimension</th>
<th>Meaning</th>
<th>CC</th>
<th>EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$</td>
<td>$t^{-1}$</td>
<td>Basal activation rate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>$t^{-1}$</td>
<td>Nonlinear activation rate</td>
<td>0–25</td>
<td></td>
</tr>
<tr>
<td>$\eta$</td>
<td>$t^{-1}$</td>
<td>Inactivation rate</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>$L_b$</td>
<td>$l$</td>
<td>Basal rest length</td>
<td>1</td>
<td>5.5</td>
</tr>
<tr>
<td>$L_h$</td>
<td>$l$</td>
<td>Heightened rest length</td>
<td>3</td>
<td>16.5</td>
</tr>
<tr>
<td>$u_0$</td>
<td>$G$</td>
<td>Threshold for activation</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>$u_c$</td>
<td>$G$</td>
<td>Threshold for length</td>
<td>4</td>
<td>0.85</td>
</tr>
<tr>
<td>$T$</td>
<td>$G$</td>
<td>Total mass of GTPase</td>
<td>0–25</td>
<td>0–80</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>$t^{-1}$</td>
<td>Length reaction rate</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>1</td>
<td>Hill coefficient</td>
<td>0–\infty</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.1: Parameter values for the dynamical cell size model. CC and EC stand for contraction case (Sec. 6.1.1) and expansion case (Sec. 6.1.2), respectively. Abbreviation for dimensions: $t$: time; $l$: length; $G$: GTPase.

Under the sharp switch approximation, there are three possible branches of equilibria. Their locations and conditions of existence can be found with simple algebraic manipulations:

(a) $u < u_0$. Then $L = L_h$, and

$$u_1 = \frac{T}{L_h} \left( 1 - \frac{\eta}{\eta + k} \right).$$

The $u_1$ branch is independent of $\gamma$, and exists only if

$$T < L_h u_0 \frac{\eta + k}{k} = L_h u_0 (1 + \frac{\eta}{k}).$$

This means that the low GTPase activity equilibrium can only exist when there is not too much total GTPase.

(b) $u_0 < u < u_c$. Then $L = L_h$, and

$$u_2 = \frac{T}{L_h} \left( 1 - \frac{\eta}{\eta + k + \gamma} \right).$$

Notice that when $\gamma = 0$, we have $u_1 = u_2$, yet we should have $u_1 < u_2$. Therefore the $u_1$ and $u_2$ branches cannot both exist at low $\gamma$. The
existence condition for the \( u_2 \) branch simplifies to

\[
\frac{L_h u_0}{T - L_h u_0} \eta - k < \gamma < \frac{L_h u_c}{T - L_h u_c} \eta - k.
\]

Since \( u_0 < u_c \), this range is non-empty only if \( T > L_h u_c \). (Another possibility is \( T < L_h u_0 \), in which case the entire range lies below 0, so it is not biologically relevant). Hence the medium GTPase activity equilibrium requires that there is enough total GTPase, and the activation strength is at a moderate level.

(c) \( u > u_c \). Then \( L = L_b \), and

\[
u_3 = \frac{T}{L_b} \left(1 - \frac{\eta}{\eta + k + \gamma}\right),
\]

The existence condition is

\[
\gamma > \frac{L_h u_c}{T - L_b u_c} \eta - k.
\]

If the right hand side is non-positive, i.e. \( T < L_b u_c (1 + \eta/k) \), then the lower bound of \( \gamma \) is greater than zero. Otherwise the \( u_3 \) branch exists for all positive \( \gamma \). This means that the high GTPase activity equilibrium requires either high total GTPase or high activation, which makes sense.

We ask whether there are parameter settings that yield interesting behaviors, i.e. as many branches existing as possible, which means we want

\[
L_h u_c < T < \min \left( L_h u_0 \left(1 + \frac{\eta}{k}\right), L_b u_c \left(1 + \frac{\eta}{k}\right)\right) = \left(1 + \frac{\eta}{k}\right) \min(L_h u_0, L_b u_c). \quad (6.8)
\]

So we need

\[
\max \left( \frac{u_c}{u_0}, \frac{L_h}{L_b} \right) < \left(1 + \frac{\eta}{k}\right),
\]

and \( \kappa \) does not influence equilibrium behavior. The values in Table. 6.1(C) are reasonable choices that satisfy our condition (6.8).

Fix \( T = 15 \), which is within the interesting range where all three branches are possible. Then \( u_1 \) exists for all \( \gamma \), \( u_2 \) exists if \( 0.25 \leq \gamma \leq 19 \), and \( u_3 \) exists if \( \gamma \geq 0.8181 \). It turns out that all three branches are stable. Bifurcation diagrams are shown in Fig. 6.1, where we compare the sharp switch approximation \( (n \to \infty) \) for \( n = 20 \), where the nonlinearity is very sharp but still continuous.
6.1. Well-mixed wave pinning model in 1D with dynamic domain

Figure 6.1: Bifurcation diagrams for the dynamic cell size model (6.5) in the contraction case, (a,b) using bifurcation parameter $\gamma$; (c,d) two-parameter continuation using $T$ and $\gamma$, with other parameters from Table. 6.1(CC). (a,c) Using sharp switch approximation for the nonlinear terms (limiting case where $n \to \infty$) (b,d) Hill function nonlinearity with $n = 20$. The four fold points labelled A to D in (b) correspond to curves with the same labels in the two parameter continuation (d). In (d), the numbers indicate the stable branches that exist within each regime, e.g. 1,3 means $u_1$ and $u_3$ exist in this regime, but not $u_2$. The cusp is at $T = 16.16, \gamma = 0.2797$. The C curve crosses the x-axis just outside the frame.

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6.1. Well-mixed wave pinning model in 1D with dynamic domain

As the diagrams show, the sharp switch approximation retains most of the behaviors of the smooth nonlinearity. One major difference is that taking \( n \to \infty \) causes the fold points to become degenerate. The branches of unstable solutions are not shown, but conceptually, they should be horizontal lines at \( u = u_0, u = u_c \). The other main difference is that the curve labelled B in Fig. 6.1(d) becomes perfectly vertical in Fig. 6.1(c). As a consequence, whereas the \( u_1 \) branch exists for all \( \gamma \) for \( n \to \infty \), it only exists for a short range for \( n = 20 \).

Compare Fig. 6.1(d) to the earlier results in Fig. 5.3(a) for the same model (the well-mixed wave pinning model, (2.13)) but with \( L \) treated as a constant (albeit with slightly different parameters, though the general shape still holds). Observe that whereas Fig. 5.3(a) has one pair of fold points joined by a cusp point, Fig. 6.1(d) has two.

Notice that we did not find any periodic solution, as expected. Consider an increase in Rho activity, which makes the cell contract. This increase will further concentrate Rho, creating a positive feedback effect. This is in contrast to the results of [49], which considered the coupling between mechanical tension and Rho without the dilution effect. In this approach, the feedback from cell size to Rho is negative, which results in an oscillatory regime. The middle branch does not exist in this model, and there are two mono-stable regimes where only one stable branch exists. These two regimes are also present in our model.

6.1.2 Expansion case (Rac, Cdc42)

Next we consider the case where the GTPase makes the cell expand (Rac, Cdc42). In this case, a contracting cell concentrates the GTPase, driving its level up, and making it expand. This means that there is a negative feedback effect, which potentially leads to periodic solutions. We will consider the case \( u_c < u_0 \). As before, we have three branches of equilibria for \( n \to \infty \):

(a) \( u < u_c \). Then \( L = L_b \), and

\[
\begin{align*}
    u_1 &= \frac{T}{L_b} \left( 1 - \frac{\eta}{\eta + k_0} \right),
\end{align*}
\]

independent of \( \gamma \), exists only if

\[
    T < L_b u_c \left( 1 + \frac{\eta}{k_0} \right).
\]
6.2. PDE simulations with deforming boundary using the Cellular Potts Model

(b) \( u_c < u < u_0 \). Then \( L = L_b \), and

\[
    u_2 = \frac{T}{L_h} \left( 1 - \frac{\eta}{\eta + k_0} \right),
\]

again independent of \( \gamma \), exists only if

\[
    L_h u_c (1 + \frac{\eta}{k_0}) < T < L_h u_0 (1 + \frac{\eta}{k_0}).
\]

(c) \( u > u_0 \). Then \( L = L_h \), and

\[
    u_3 = \frac{T}{L_h} \left( 1 - \frac{\eta}{\eta + k_0 + \gamma} \right).
\]

The existence condition is

\[
    \gamma > \frac{L_h u_0}{T - L_h u_0} \eta - k_0, \quad T > L_h u_0.
\]

As before, the existence conditions are within expectation: the low GTPase activity equilibrium requires low total GTPase, and so on. We choose the set of parameters from Table. 6.1(EC), which are in line with the above requirement. For our choice of parameters, \( u_1 \) exists for \( T < 51.425 \), \( u_2 \) exists for \( 154.275 < T < 181.5 \), and with \( T = 40 \), \( u_3 \) exists for \( \gamma > 6.02128 \).

We fix \( T = 40 \) for the bifurcation diagrams. For the sharp switch approximation, all three branches are stable, and the bifurcation diagram is uninteresting: it looks the same as Fig. 6.1(a) except that the middle branch is missing. However, for \( n = 8 \), the system has a pair of Hopf bifurcation, see Fig. 6.2, and periodic solutions exist for an intermediate range of \( \gamma \), as expected.

6.2 PDE simulations with deforming boundary using the Cellular Potts Model

In this section, we discuss another approach where we couple the PDE for GTPase dynamics with the Cellular Potts Model (CPM) for the boundary of the cell in 2D. The results in this section are a collaboration with two other members of our group. The program we used for the simulation was developed by Zachary Pellegrin, and Elisabeth Rens who also adapted the code for our models and ran the simulation. I provided the equations and the parameter values.
6.2. PDE simulations with deforming boundary using the Cellular Potts Model

Figure 6.2: Bifurcation diagrams for the dynamic cell size model (6.5) in the expansion case, (a,b) using bifurcation parameter $\gamma$; (c,d) two-parameter continuation using $T$ and $\gamma$, with other parameters from Table 6.1(EC). (a) $T = 40$, which is left of both cusps in (c). Notice that AUTO had trouble keeping track of the periodic branch on the right side. The two blue curves likely form a closed loop. (b) $T = 65$, which is in between the two cusps. (c) shows that the pairs of fold and Hopf points are joined by a cusp in the $T - \gamma$ plane.
6.2. PDE simulations with deforming boundary using the Cellular Potts Model

An in-depth introduction to CPM can be found in [25]. The basic idea of CPM is to describe the cell and its surrounding environment on a regular square lattice, where each square can be in one of two states: occupied by the cell, or not. We then define an energy function of the following form for 2D simulations:

\[ E(p, A) = Jp + \alpha_p(p - p_0)^2 + \alpha_a(A - A_0)^2, \]  

(6.9)

where \( p \) and \( A \) are the perimeter and area of the cell, respectively, \( p_0 \) and \( A_0 \) are the “rest” perimeter and area (akin to the rest length of a spring), and \( J, \alpha_p, \alpha_a \) are constant parameters.

At each time step, we consider a local shape change at every point on the boundary of the cell, where the cell can either expand or contract by one square (a free square becomes occupied or vice versa). Whether this change takes place is decided randomly via a Monte Carlo algorithm, with its probability depending on the change in energy \( \Delta E \) if the change were to take place:

\[ p(\Delta E) = \min \left( 1, \exp \left( -\frac{\Delta E + Y}{T} \right) \right), \]  

(6.10)

where \( T \) is the “temperature” parameter describing how much randomness we allow. If the change decreases the energy by at least \( Y \), then it is always accepted. Otherwise the change is accepted with probability determined by a Boltzmann function, which decreases monotonically as \( \Delta E \) increases. A higher temperature means energetically disfavoured changes are more likely.

Next, we couple CPM with the combined PDE model (2.8) for GTPase dynamics. The details of the method can be found in [38]. We use the same lattice for both CPM and finite difference computation for the PDE. The energy function (6.9) is modified with an extra term depending on \( u \), such that GTPase activity makes either contractions (Rho) or expansions (Rac, Cdc42) more likely. At each iteration, we solve the PDE for 1000 time steps, with \( \Delta t = 10^{-5} \), then update the cell boundary according to CPM. The no-flux boundary conditions for the PDE are enforced by modifying the discrete Laplacian for each possible local boundary shapes. When the cell expands into a free square, the GTPase activity in the new square is set to be the same as the average of the adjacent squares. In order to enforce mass conservation, the GTPase activity in the local neighborhood is re-normalized to have the same total GTPase mass as before. In the case of contraction, the GTPase contained in the square to be freed is redistributed evenly to the neighboring squares.

In the simulations, we use parameters similar to the ones we used for numerical simulations in Ch. 3. The results are shown in Fig. 6.3, which
6.2. PDE simulations with deforming boundary using the Cellular Potts Model

focuses on the Rho (contraction) case. Notably, we obtained the three main patterns: wave pinning, spots and actin waves patterns in accordance with our expectations given the static boundary simulations from Ch. 3.

In Fig. 6.3(a,b), we obtain wave pinning. By comparing this figure to 1D simulations in Fig. 3.1 and 2D simulations with static boundary in Fig. 3.10(a,b), we notice the familiar defining characteristics of wave pinning: the cell is polarized into regions of high and low GTPase activity with the wave front stationary with respect to the cell. The cell as a whole slowly moves to the right as expected.

In Fig. 6.3(a,b), we obtain the spots pattern observed in 2D simulations corresponding to the non-conservative model in Fig. 3.10(c,d). Notice that even though we initialized the system at the unique HSS without any perturbation, the pattern still forms. The reason is that the HSS is unstable, which means the perturbation due to the random change in the boundary is sufficient to trigger pattern formation. The spots cause the boundary to cave in, which in turn pushes the spots away. In some cases we observed spots being split into two, or two spots being pushed together and merging due to boundary changes. It would be interesting to repeat the simulation for the expansion (Rac, Cdc42) case, where we expect the spots to cause formation of thin protrusions corresponding to filopodia.

In Fig. 6.3(e,f), we observe travelling waves that we interpret to represent the “actin waves” as described in Sec. 1.3. The dynamics of these waves are visually similar to videos of actual actin waves observed in experiments, for example the video supplements of [26]. We used the same parameters as in Fig. 3.4(j-l), where we obtained the persistent wave train behavior.
6.2. PDE simulations with deforming boundary using the Cellular Potts Model

(a) Wave pinning, \( t = 0.5 \)

(b) Wave pinning, \( t = 5 \)

(c) Spots, \( t = 0.06 \)

(d) Spots, \( t = 2 \)

(e) Actin wave, \( t = 0.1 \)

(f) Actin wave, \( t = 1 \)

Figure 6.3: Simulations of the coupled CPM-GTPase model. For each set of parameters, we show two snapshots of GTPase activity \( u \) in the cell, one just after the pattern has taken shape, and another one sometimes later to show how the pattern evolves and its effects on the shape and location of the cell. (a,b) Wave pinning, with \( c = s = 0, \delta = 0.04 \) and all other parameters from Table. 3.1(Combined2). Initial conditions: \( u = 0 \), except \( u = 3 \) on a region comprising 10% of the cell on the left edge, and \( v = 2 \). (c,d) Spots pattern, with \( c = 1, s = 0, \delta = 0.04 \) and all other parameters from Table. 3.1(Combined2). Initial conditions: \( u = 0.3333, v = 2.5278 \). (e,f) Actin waves, with \( s = 30L^2, k = 6L^2 \) and all other parameters from Table. 3.1(AF). Initial conditions: \( u = 0 \), except \( u = 5 \) on 10% of the cell on the left edge, and \( v = 2, F = 0 \).
Chapter 7

Discussion

We have shown a variety of possible behaviors in the wave pinning model and its extensions in Ch. 3. In Ch. 4 and 5, we analyzed the bifurcation properties of the model to determine the number and locations of distinct parameter regimes, and their correspondence with observed patterns. In Ch. 6, we investigated the interplay between GTPase dynamics and cell shape. In this chapter, we summarize the mathematical results and interpret their significance in answering the biological questions we posed in Sec. 1.4.

7.1 Summary of model behaviors

In one spatial dimension, we observed several patterns in the wave pinning model combined with the two extensions, some of which were reproduced in 2D. Here is a summary of their characteristics, along with the conditions for their existence and interpretations. For all patterns, a small diffusion ratio $\delta$ between active and inactive GTPase is required.

B1. Static wave pinning (Fig. 3.1, 3.2): the domain is partitioned into two or more alternating regions of high/low GTPase activity, with relatively narrow transition zones between them. We interpret this behavior as the most basic form of cell polarization. For this to happen, we need the feedback activation $\gamma$ to be strong enough, and total amount of GTPase $T$ at a moderate level to allow the existence of both low and high GTPase activity equilibria.

B2. Wave pinning with oscillating front (Fig. 3.4(a-c)): like (1) but the transition zone oscillates back and forth. This behavior has similar existence conditions as (1), but requires non-zero, weak actin feedback $s$. This might be a more realistic picture for cell polarization.

B3. Reflecting waves (Fig. 3.4(d-f)): a travelling pulse reflected back at boundaries. I am not aware of any corresponding experimental observations. Given a large enough $\gamma$ and moderate $T$, this behavior requires an intermediate range of $s$. 

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7.1. Summary of model behaviors

B4. Persistent wave trains (Fig. 3.4(j-k) in 1D, reproduced in 2D with moving boundary conditions in Fig. 6.3(e,f)): a train of travelling waves absorbed at the boundaries. We interpret this as representing actin waves. Beside the high $\gamma$ and moderate $T$, this behavior is observed only when both the basal activation $k$ and actin negative feedback $s$ are in an intermediate range, achieving a balance between them.

B5. Single pulse (Fig. 3.4(g-i)): perturbation to the HSS results in a single travelling pulse, which is eventually absorbed at the boundary and the system returns to HSS. The regime on which this occurs is next to the regimes for (3) and (4), and we could not identify a clear boundary separating these regimes.

B6. Static, spatially periodic spikes (Fig. 3.6 (a,b), Fig. 3.7(a)): A steady state consisting of a series of equally spaced thin spikes. In 2D, the corresponding pattern is a 2D lattice of spots. We interpret this to represent filopodia formation, since such a spike in Rac activity will likely cause a thin cellular protrusion. This behavior requires the source and sink terms, as well as a high enough $\gamma$ to put the system into the Turing regime.

B7. Lone static spike (soliton, Fig. 3.6 (c,d), Fig. 3.7(b)): a strong and highly localized perturbation leads to a single spike while the rest of the domain remains at the HSS. This too can correspond to filopodia formation. The corresponding parameter regime is a narrow range of $\gamma$ sandwiched between the stable regime and the Turing regime for (6).

B8. Repelling pulses (Fig. 3.8(a)): a series of spikes similar to (6), but the spikes are mobile and repel each other when they get too close. This behavior does not resemble any known observations. This happens when both the source and sink terms are present and the actin feedback $s$ is positive but weak.

B9. Colliding wave trains (Fig. 3.8(b)): travelling pulses that emerges either at the boundary or in the interior of the domain, and collide and interact in complex manner. The overall behavior is similar to (4), but much more unpredictable. The conditions are similar to (8) but require a high $s$.

B10. Localized rapidly oscillating standing waves (Fig. 3.9(d)): this is observed in a region of the domain occupied by a standing wave with a
short wave length and high oscillating frequency, and is usually transient. We are not aware of any corresponding experimental observations. The conditions are similar to (9) but require a very high $s$.

B11. Localized oscillating spikes (Fig. 3.11(e,f)): spikes that are confined locally but oscillate in amplitude. This occurs when the parameters are spatially inhomogeneous. Further, in a narrow region of the domain the parameters lie in a pattern-forming regime, and in the rest of the domain the parameters lie in the stable regime. This behavior is a caricature of filopodia formation in response to viral infection.

B12. Other “exotic” behaviors observed near the boundary of parameter regimes in the actin feedback model (Fig. 3.5). We have mostly ignored these as they are rather hard to characterize.

Note that there are a few behaviors that we could not identify with any known experimental observations. There are a few possible explanations. First, the parameter regime might be outside of the biologically relevant range. For example, (10) requires a very high $s$, which might not be possible to achieve. Second, the parameter regime might be too narrow, in which case a real cell would be unlikely to fall in this regime. Finally, the real system has greater complexity, heterogeneity and stochasticity, which is not captured by our simplified model. Some of the regimes, especially the narrow ones, might no longer exist after these factors are taken into consideration.

Altogether, we have identified behaviors that correspond to polarization, filopodia formation, and actin waves. These results will help us to explain such biological phenomena.

7.2 Biological and mathematical implications

We now return to the questions we posed at the end of Sec. 1.4.

Q1. The non-conservative terms result in multiple spikes of high GTPase activity (B6). Compared to simple polarization resulting from wave pinning (B1), the spots are much thinner than the polarized regions, but both patterns are static. Actin feedback turns static patterns to travelling pulses and waves. Together, this results in the spikes colliding with each other with various outcomes (B9), as well as the standing waves pattern (B10), both are quite distinct from static spikes and actin waves. The biological implication of these results are unclear.
Q2. Locally elevated GTPase activation leads to the localized formation of hot-spots of GTPase activity, which do not spread to other parts of the domain (B11). These hot-spots could be associated with filopodia formation. This suggests that if a virus can manipulate GTPase activation in its vicinity, either directly or through some upstream signalling proteins, then it can trigger the formation of a single filopodium which the virus then exploits to enter the cell.

Q3. The periodic spikes pattern in 1D (B6) becomes a lattice of spots in 2D, whereas we initially expected a stripe pattern given the 1D behavior. Waves trains (B4) in 2D can form curves and spirals, which cannot happen if the system is constrained to a 1D geometry. On the other hand, wave pinning (B1) behaves similarly in both 1D and 2D domains.

Q4. Formation of most patterns require the cell to be large enough. For example, the pattern of spikes (B6) requires the domain to be large enough to support at least one period of the pattern. The exact same parameters in a smaller cell can only result in wave pinning. If the cell is too small, then even wave pinning is not possible. This suggests that GTPase patterns are simpler in smaller cells.

Q5. In the dynamic cell size model, we showed that the coupling between GTPase and cell size can result in additional equilibria, which correspond to additional possible resting states for the cell. The Hopf bifurcation observed in the GTPase promoting cell expansion case shows that oscillations in both GTPase activity and cell size are possible. This behavior cannot be captured with a static domain. The CPM simulations in 2D showed that the wave pinning, spots, and wave train patterns retain their characteristics in a coupled model. However, the feedback from the deforming boundary can turn an otherwise static pattern into a dynamic one, such as the spots splitting and merging due to boundary movements. Altogether, the behavior is much more complex.

Q6. The models do not account for the experimentally observed oscillating spots without heterogeneity in the parameters. By allowing the parameters to vary in space in a very specific way, we can obtain spots that oscillate in-place (B11), but the oscillations are much smaller than observed in [39]. This suggests that our models lack certain ingredients that are essential to this behavior.
7.3 Future work

Q7. The CPM simulations (Fig. 6.3) indicate that both simple polarization and actin waves are consistent with cell motility. However, whereas simple polarization results in a regular movement at constant speed and direction, actin waves allow the cell to protrude in random directions, possibly allowing for local “exploration” and random motion.

Q8. Unlike LPA, Turing analysis can predict the wavelength of the initial precursor pattern. However, as the pattern evolves and the spikes interact, the system leaves the linear regime and the Turing results are no longer valid. We can use Turing analysis to indirectly predict the minimum wavelength of the final pattern.

Q9. The unstable regimes identified by LPA correspond to Turing-unstable regimes in the limit $\delta \to 0$. In the unstable regimes, any infinitesimal perturbation to the HSS leads to pattern formation. LPA additionally identifies the polarizable regimes, which are pattern-forming regimes that are Turing-stable. Pattern formation in these regimes require a sufficiently large perturbation to the HSS. On the other hand, Turing analysis can describe system behavior for $\delta > 0$, whereas LPA cannot. In Fig. 7.1, we illustrate the relation between LPA and Turing bifurcation diagrams.

Q10. The addition of feedback from actin assembly to the system results in many more bifurcations in LPA diagrams. We were forced to ignore some features, such as the Hopf curves, to keep the analysis tractable. In the presence of both actin and non-conservative GTPase terms in the model, the LPA diagrams become hopelessly complex to analyze. This limits the utility of LPA when there are many interacting species. LPA was also not very helpful for predicting the final pattern when multiple patterns are possible in the model.

7.3 Future work

There are a few directions for future work in this project.

We are interested in the properties of the soliton solution, which represents localized GTPase activity. The plan is to use asymptotic analysis to obtain a series expansion of the soliton solution in terms of the small parameter $\delta$. This would allow us to determine its stability, as well as width and height. LPA helped to determine the zone of attraction of a solitary peak in the limit $\delta \to 0$. In Fig. 5.5(b), Regime II, the black curve determines, in
7.3. Future work

Figure 7.1: Comparison of LPA and Turing bifurcation diagrams for the non-conservative model. (a) is a zoom of the LPA diagram from Fig. 5.5(b). (b) is the Turing bifurcation diagram similar to Fig. 4.2, except using the same parameters as (a). Observe that both the LPA-stable (I) and the LPA-polarizable (II) regimes in (a) located to the left of $\gamma_c = 16.765$ correspond to the Turing-stable regime below the blue curve in (b). The LPA-unstable regimes (III, IV) correspond to the Turing-unstable regime above the curve. The curve passes through $\delta = 0, \gamma = \gamma_c$. The bifurcation boundary between Regimes I and II, and between III and IV cannot be detected by Turing analysis. Given that numerical simulations have shown that the PDE produces the same behavior (Fig. 3.7(a)) in both Regimes III and IV, it is possible that these are not distinct regimes for the PDE. Overall, the LPA diagram (a) can be seen as a vertical slice of the Turing diagram (b) at $\delta = 0$, with additional bifurcation boundaries that separates the LPA-stable and LPA-polarizable regimes.

In this limit, the size of perturbation to the HSS needed to produce the soliton. Asymptotic analysis would provide correction terms to this estimation for a finitely small $\delta$.

There are also experimental results such as [39] that fitted the activation function of GTPase to observational data. We can use this function to replace the Hill function term in our model. This would arguably be more biologically relevant. It would be interesting to see how this replacement changes the bifurcation behaviors.

Another direction is to combine our work in Sec. 6.1 with the work of [49], by considering the dilution effect from cell size and the feedback from mechanical tension together. Since these two have opposite effects on GTPase
activity, their interaction would potentially be complex and interesting.

In Sec. 6.2, we only ran simulations for Rho (contraction case) so far. In the future, we plan to run simulations for the expansion case, as well as the parameter regimes that correspond to other behaviors.
Bibliography


BIBLIOGRAPHY


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Appendix A

Code for 1D simulations

The following program written in Matlab is used in Ch. 3 for running 1D simulations. The mathematical background is discussed in Sec. 3.1. Parts of the code for setting preferences and saving output has been removed for simplicity. A more complete version of the code will be published on Github: https://github.com/liuyue002/Wave-pinning-model.

Program A.1 Solver for the combined model(2.8) in 1D

```matlab
%% Numerics parameters
drawperframe=50; % update the animation once per 50 iterations
nx=400; % number of spatial discretization points
dx=1/nx;
T=1; % end time for the simulation
dt=0.0002; % time discretization
nt=T/dt +1;
nFrame=ceil((T/dt)/drawperframe);

%% Model parameters
LL=20^2; delta=0.01; k0=1.0*LL; gamma=18.5*LL; n=2; eta=5.2*LL;
c=1; theta=5.5*LL; alpha=1.5*LL;
s=40*LL; epsilon=0.1; kn=24*LL; ks=7.5*LL;

f = @(u,v,F) (k0+gamma.*u.^n./(1+u.^n)).*v - (eta+s*F./(1+F)).*u;

%% the unique equilibrium
u0=alpha/theta;
f0=u0*kn/ks;
v0=(c*alpha+(eta+s*f0/(1+f0))*u0)/(k0+gamma*u0.^n/(1+u0.^n));

x=linspace(0,1,nx)';
u=zeros(nx,1); v=zeros(nx,1); F=zeros(nx,1);
```

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Appendix A. Code for 1D simulations

\[ o = \text{ones}(nx, 1); \]
\[ A = \text{spdiags}([o -2*o o],[-1 0 1],nx,nx); \]
\[ A(1,1) = -1; \quad \% \text{for no-flux BC} \]
\[ A(nx,nx) = -1; \]
\[ A = A/(dx^2); \quad \% A \text{ is the discrete Laplacian} \]

\% initial conditions
\[ u = u0*(\text{rand(size(u))}*0.2+0.9); \]
\[ v(:) = v0; \]
\[ F(:) = f0; \]

\% Set up figure
\[ \text{fig}=\text{figure}(); \]
\[ \text{xlabel('x'); ylabel('u, v, F');} \]
\[ \text{axis([0 1 0 6]);} \]
\[ uu = \text{zeros(nFrame,nx);} \quad \% \text{for plotting kymographs} \]
\[ vv = \text{zeros(nFrame,nx);} \]
\[ ff = \text{zeros(nFrame,nx);} \]

\% Main solver
\[ \text{th} = 0.5; \quad \% 0: \text{forward Euler, 0.5: Crank-Nicolson, 1: backward Euler} \]
\[ Tu = \text{spye(nx) - th*dt*delta*A;} \]
\[ Tv = \text{spye(nx) - th*dt*A;} \]
\[ \text{for } ti = 1:1:nt \]
\[ \quad \text{if (mod(ti, drawperframe) == 1)} \]
\[ \quad \quad \text{cla;} \]
\[ \quad \quad \text{hold on;} \]
\[ \quad \quad \text{plot(x,u); plot(x,v); plot(x,F);} \]
\[ \quad \quad \text{legend('u', 'v', 'F);} \]
\[ \quad \quad \text{hold off;} \]
\[ \quad \quad \text{drawnow} \]
\[ \quad \quad uu(iFrame,:) = u; \]
\[ \quad \quad vv(iFrame,:) = v; \]
\[ \quad \quad ff(iFrame,:) = F; \]
\[ \quad \end \]
\[ \text{end} \]

\[ urhs = u + dt*(f(u,v,F) + (1-th)*delta*A*u - c*theta*u); \]
\[ unew = Tu\backslash urhs; \]
Appendix A. Code for 1D simulations

\[
\text{vrhs} = v + \text{dt} \ast (-f(u,v,F) + (1 - \text{th}) \ast A \ast v + c \ast \alpha); \\
v\text{new} = T \backslash \text{vrhs}; \\
F\text{new} = F + (\text{dt} \ast \epsilon \ast (kn \ast u - ks \ast F)); \\
F\text{=}F\text{new}; \\
u\text{=}u\text{new}; \\
v\text{=}v\text{new};
\]

end

figu = plot\_kymograph(uu, nFrame, nx, T);
figv = plot\_kymograph(vv, nFrame, nx, T);
figF = plot\_kymograph(ff, nFrame, nx, T);

The next program is for producing the kymographs.

Program A.2 plot\_kymograph.m

\[
\text{function } [\text{fig}] = \text{plot\_kymograph(uu, nFrame, nx, T)} \\
\text{tTick} = (0:0.2:1) \ast n\text{Frame}; \\
\text{tTickLabel} = \text{cellfun (@num2str, num2cell((0:0.2:1) \ast T), 'un', 0)}; \\
\text{xTick} = (0:0.2:1) \ast nx; \\
\text{xTickLabel} = \text{cellfun (@num2str, num2cell((0:0.2:1)), 'un', 0)};
\]

\[
\text{fig} = \text{figure}(); \\
\text{axis([0 nFrame 0 nx])}; \\
\text{% Ignore the initial transient conditions for calculating color range} \\
\text{umax} = \text{max(max(uu(10:end, :)))}; \\
\text{umax} = \text{ceil(umax*10)/10}; \\
\text{umin} = \text{min(min(uu(10:end, :)))}; \\
\text{umin} = \text{floor(umin*10)/10}; \\
\text{%umin = 0.32; umax = 0.35; \%tmp} \\
\text{ucolortick} = [\text{umin}\text{, umax}]; \\
\text{imagesc(uu', ucolortick)}; \\
\text{set(gca, 'YDir', 'normal')}; \\
\text{colorbar('FontSize', 40, 'TickLabels', ucolortick, 'Ticks', ucolortick)}; \\
\text{set(gca, 'XTick', tTick); \\
\text{set(gca, 'XTickLabel', tTickLabel)}; \\
\text{set(gca, 'YTick', xTick); \\
\text{set(gca, 'YTickLabel', xTickLabel)}; \\
\text{xlabel('t'); ylabel('x');}
\]

end

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Appendix B

XPPAUT programs for bifurcation analysis

The following XPPAUT [10] programs were used to produce some of the bifurcation diagrams in Ch. 5 and Sec. 6.1. Although the combined model covers all extensions of the wave pinning model, we should always use mass conservation to eliminate degeneracy whenever possible. Otherwise, we will obtain incorrect stability results due to the system’s degeneracy.

Matcont [5] was used for some of the other bifurcation diagrams. The Matcont scripts are fairly long so they are not included here, but they will be available on Github, along with our utility functions for plotting.

Program B.1 LPA for the wave pinning model (5.4), see Sec. 5.2

\[
\begin{align*}
\frac{du}{dt} &= F(u, w-u) \\
\frac{duL}{dt} &= F(uL, w-u) \\
F(G, GI) &= \left( k + \gamma G^n / (1 + G^n) \right) GI - \eta G \\
\text{par} \quad w &= 2, k = 1.5, \gamma = 0.01, n = 3, \eta = 15 \\
\text{init} \quad u &= 1, uL = 1.5
\end{align*}
\]

Program B.2 LPA for the actin feedback model (5.10), see Sec. 5.4

\[
\begin{align*}
\frac{duL}{dt} &= F(uL, w-u, FactinL) \\
\frac{du}{dt} &= F(u, w-u, Factin) \\
\frac{dFactin}{dt} &= \varepsilon(\kappa_n u - k_s Factin) \\
\frac{dFactinL}{dt} &= \varepsilon(\kappa_n uL - k_s FactinL) \\
F(a, b, c) &= (k_0 + \gamma a^n / (1 + a^n)) b - (\eta + s c / (1 + c)) a \\
\text{par} \quad w &= 2.5, \varepsilon = 0.1, \kappa_n = 24, k_s = 7.5, k_0 = 6, \gamma = 30, \eta = 15, s = 0.01, n = 3 \\
\text{init} \quad u &= 1, uL = 1, \text{Factin} = 5, \text{FactinL} = 5
\end{align*}
\]
Appendix B. XPPAUT programs for bifurcation analysis

Program B.3 LPA for the combined model, see Sec. 5.5. Set $c = 0$ for the non-conservative model.

\[
\begin{align*}
\frac{d\text{u}}{dt} &= f(u,v,\text{Factin}) - c*\theta*u \\
\frac{d\text{uL}}{dt} &= f(uL,v,\text{FactinL}) - c*\theta*uL \\
\frac{dv}{dt} &= -f(u,v,\text{Factin}) + c*\alpha \\
\frac{d\text{Factin}}{dt} &= \varepsilon*(k_n*u - k_s*\text{Factin}) \\
\frac{d\text{FactinL}}{dt} &= \varepsilon*(k_n*uL - k_s*\text{FactinL}) \\
f(G,G_I,\text{FACT}) &= (k_0 + \gamma*G^n/(1+G^n))*G_I - (\eta + s*\text{FACT}/(1+\text{FACT}))*G \\
\text{par} & \quad k_0=1, \gamma=30, \eta=5, n=3, \theta=5.5, \alpha=1.5, c=1 \\
\text{par} & \quad s=0.01, k_n=24, k_s=7.5, \varepsilon=0.1 \\
\text{init} & \quad u=1, uL=1, v=5, \text{Factin}=1, \text{FactinL}=1
\end{align*}
\]

Program B.4 The dynamic cell size model (6.5). Expansion case shown, contraction case is similar.

\[
\begin{align*}
\frac{du}{dt} &= (b+\gamma*(u^n/(1+u^n)))*(w/L-u) - \eta*u + u*k*(L-(Lb+Ldiff*(u^n/(uc^n+u^n))))/L \\
\frac{dL}{dt} &= -k*(L-(Lb+Ldiff*(u^n/(uc^n+u^n)))) \\
\text{par} & \quad n=8, k=5, w=40, \gamma=9, \eta=10, uc=0.85, Ldiff=11, b=1, Lb=5.5 \\
\text{init} & \quad u=1, L=1
\end{align*}
\]
Appendix C

Code for 2D simulations

The following program written in Python was used to run 2D simulations in Sec. 3.8. We make use of the FEniCS package [2], which is a well-known library for finite element methods. The output can be viewed with other softwares, such as Paraview.

This program is built upon the code provided by Dr. Timm Treskatis as a part of the teaching material for MATH 521: Numerical Analysis of Partial Differential Equations.

**Program C.1** 2D finite element code for the non-conservative model (2.7)

```python
from __future__ import print_function
from fenics import *
from mshr import *

p = 1  # order of interpolation
mesh = RectangleMesh(Point(0.0, 0.0), Point(1., 1.), 80, 80, "crossed")
V = FunctionSpace(mesh, "P", p)
# No-flux BC is automatically implemented by default

## Numerical methods parameters
theta = 0.5  # 1: Backward Euler, 0: Forward Euler, 0.5: C-R
T = 30.; t = 0.; dt = 1e-2; nt = int(T/dt)
drawPerIter = 5

## Model parameters
L = 1.; Du = 0.01; Dv = 1.; k=1.5*(L**2); gamma=30.*(L**2);
eta=15*(L**2); c=0.; thetalo=4.5*(L**2); alpha=1.5*(L**2);

## Unique equilibrium
ueq=alpha/thetalo;
veq=(c*alpha+eta*ueq)/(k+gamma*(ueq**2 / (1.+ueq**2 ));

## Initial conditions
v_old = interpolate(Constant(veq), V)
u_old = Expression(’x[0] < 0.1 ? 4.*ueq : ueq’, degree=p, ueq=ueq)
```

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Appendix C. Code for 2D simulations

\[ u_{old} = \text{interpolate}(u_{old}, V) \]

\[
\text{### Assemble the linear system}
\]
\[
\begin{align*}
\mathbf{u} &= \text{TrialFunction}(V) \\
\mathbf{v} &= \text{TrialFunction}(V) \\
\mathbf{z} &= \text{TestFunction}(V) \\
\mathbf{B}_1 &= (u \ast z + \theta \ast dt \ast Du \ast \dot{\text{grad}}(u), \text{grad}(z)) \ast dx \\
\mathbf{B}_2 &= (v \ast z + \theta \ast dt \ast Dv \ast \dot{\text{grad}}(v), \text{grad}(z)) \ast dx
\end{align*}
\]
\[
\mathbf{u} = \text{Function}(V, \text{name} = 'u'); \mathbf{u}.assign(u_{old}) \\
\mathbf{v} = \text{Function}(V, \text{name} = 'v'); \mathbf{v}.assign(v_{old})
\]

\[
\text{foldername} = 'OutputFolder' \\
\text{results}_\mathbf{u} = \text{File}(\text{foldername}+'/CN\mathbf{u}.pvd')
\]
\[
\text{results}_\mathbf{u} \ll (\mathbf{u}, t)
\]
\[
\text{results}_\mathbf{v} = \text{File}(\text{foldername}+'/CN\mathbf{v}.pvd')
\]
\[
\text{results}_\mathbf{v} \ll (\mathbf{v}, t)
\]

\[
\text{source}_\mathbf{term} = \text{interpolate}(\text{Constant}(c \ast \alpha), V)
\]

\[
\text{for } k \text{ in range}(nt):
\]
\[
\begin{align*}
\mathbf{f} &= (k+\gamma \ast (u_{old} \ast u_{old} \ast \ast 2)/(1. + u_{old} \ast u_{old} \ast \ast 2)) \ast \mathbf{v}_{old} - \epsilon_{\alpha} \ast u_{old} \\
\text{RHS} &= (u_{old} \ast \mathbf{z} - (1. - \theta) \ast Du \ast dt \ast \dot{\text{grad}}(u_{old}), \text{grad}(z)) + \mathbf{dt} \ast \mathbf{f} \ast \mathbf{z} - \mathbf{dt} \ast c \ast \text{thetaloss} \ast u_{old} \ast \mathbf{z} \ast dx \\
\text{solve}(&\text{B1} == \text{RHS}, \mathbf{u}) \\
\text{RHS} &= (v_{old} \ast \mathbf{z} - (1. - \theta) \ast \mathbf{Dv} \ast dt \ast \dot{\text{grad}}(v_{old}), \text{grad}(z)) - \mathbf{dt} \ast \mathbf{f} \ast \mathbf{z} + \mathbf{dt} \ast \text{source}\_\mathbf{term} \ast \mathbf{z} \ast dx \\
\text{solve}(&\text{B2} == \text{RHS}, \mathbf{v})
\end{align*}
\]
\[
\text{if } (k+1) \% \text{drawPerIter} == 0:
\]
\[
\begin{align*}
\text{results}_\mathbf{u} \ll (\mathbf{u}, t) \\
\text{results}_\mathbf{v} \ll (\mathbf{v}, t)
\end{align*}
\]
\[
\mathbf{u}_{old} . assign(\mathbf{u}) \\
\mathbf{v}_{old} . assign(\mathbf{v})
\]