SOLUTIONS OF EQUATIONS FOR THE REGULATION OF KINASE ACTIVITY IN A FINITE CYLINDRICAL CELL

A Dissertation

Presented to

the Faculty of the Department of Mathematics

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

By

Puchen Liu

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I dedicate the thesis to my parents who provide me permanent support in my pursuit of Ph.D program.

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Abstract

In this work, inspired by the reality in organisms and particularly the shape of axon of the neuron, new mathematical models of regulation of kinase activity are presented. In the view of mathematicians, those models are diffusion equations defined in finite cylinders but with mixed Robin boundary and Dirichlet boundary conditions. The first part of the thesis focuses mainly on the model with the linear mixed Robin boundary and Dirichlet boundary conditions. By use of variational principle and eigenvalue problem, the results are provided on the existence, uniqueness and boundedness of the weak solution (kinase concentration) of an abstract elliptical equation related to the kinase activity model. For the kinase activity model itself, the bound can be expressed as the function of relevant parameters. Furthermore, this work also obtains the existence of the time-dependent solution to the reaction diffusion equation generalized from this kinase activity model. Based on those results, the time-dependent solutions are presented in integral form. This work has shown the exponential convergence of the time-dependent solution to the solution of its corresponding steady state equation. The second part has demonstrated the existence and boundedness of the weak solution by use of variational principle for the kinase model with mixed nonlinear boundary conditions. Then the series representation of the nonzero solution is shown. Moreover, a critical equality in bifurcation analysis is obtained. By means of this equality, when a parameter varies, bifurcation analysis is demonstrated from the special case to the more general case. Particularly, the critical (bifurcation) value of this biological parameter has been determined mathematically as a function of other biological parameters.

By use of those theoretical results, some corresponding biological explanations are also provided. All of those have significance when considering biology signalling and biology control.

Contents

Chapter 1

Introduction

In this thesis, the goal is to provide the mathematical study of the regulation of kinase activity in a finite cylindrical cell. This work, in which the solution representation theory in Sobolev is employed and also the bifurcation analysis with corresponding computation is used, examines the solution properties and their biological implications. Those models are all formed in the three-dimensional space related to the mixed boundary conditions which are linear or nonlinear. The models and the biological principles, which in this thesis shall be referred to, were firstly introduced by Brown [1] and Kholodenko [2] and Kazmierczak and Lipniacki [3, 4]. The mathematical tools used here have just generalized the technique of series representation of solutions in Sobolev Space developed by Auchmuty [5-9], and also borrow some analytical tricks in bifurcation analysis to get the critical value of the parameter.

Some biological background, the model formulation and fundamental preliminaries are given in Chapter 2. In this chapter, the basic biological principles for presenting the mathematical model are mentioned. And the fundamental mathematical assumptions are provided.

In Chapter 3, by means of solution representation and analysis of eigenproblem, the goal is to develop the theoretical results on linear elliptical equation with nonhomogeneous mixed boundary conditions, which is generalized from our kinase activity model (2.4). Those theoretical results are the generalization of Auchmuty's work [5]. Then, based on the application of those results to the kinase activity model (2.4), concrete computations are also provided for the eigenvalue and eigenfunction related to the steady state biogical model (2.4) on the finite cylinder.

Chapter 4 aims to get the well-posedness of the reaction-diffusion model (2.5) generalized from the kinase activity model (2.3). By considering the existence and uniqueness of the solution to model (2.4) at first and using the result developed in Chapter 3, the well-posedness of (2.5) and the representation of its solution are obtained. Besides, the results have shown the exponential convergence of the solution of (2.3) to the solution of the corresponding steady state.

Chapter 5 provides the mathematical properties of the solutions and the biological significance with respect to the kinase activity models (2.3) and (2.4).

All above chapters are the first part of this thesis, in which the linear mixed boundary conditions are concerned. The second part of the thesis consists of Chapter 6 to Chapter 9, which are related to the nonlinear boundary conditions in the kinase activity model.

In Chapter 6, some properties of the solution related to (2.9) are directly analyzed. The result tells that the solution to (2.9) will be restricted into some bounded region near the solution of its steady state equation.

In Chapter 7, we present the theoretical results on the existence and boundedness of the weak solution for the steady state biological model (2.10), which can ensure the computation practicable in the next chapter. In this chapter, the convexity and the weak convergence on the Sobolev space are used.

In Chapter 8, the bifurcation problem related on the model (2.9) and (2.10) is considered. This part of work starts with considering the extreme case, i.e., the diffusion coefficient approaching infinity. In this extreme case, the biological model (2.1) (2.2) and (2.8), which is just the original model of (2.9), will change into an ordinary differential equation system. Then the critical value b_2^{crit} of the parameter b_2 is obtained in the case of axial symmetry for model (2.9) by investigating the solution of (2.10). An important equality is employed, which can be used to give bifurcation analysis about other biological parameters.

The conclusion shows that when $0 < b_2 < b_2^{crit}$ there exist the trivial solution and a positive stable solution of (2.10) and when $b_2 > b_2^{crit}$, there is only the stable trivial solution having the physical meaning.

In Chapter 9, the biological implications of the results related to (2.9) and (2.10) are demonstrated.

In Chapter 10, discussions and research directions are provided.

Chapter 2

Model Formulation and Preliminary

2.1 Kinase Activity and Cell-signalling Dynamics

Cells respond to external cues using a limited number of signalling pathways that are activated by plasma membrane receptors, such as G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs). Those pathways do not only transmit but they also process, encode and integrate internal and external signals [1]. Recent reports show that distinct spatio-temporal activation profiles of the same repertoire of signalling proteins result in different gene-expression patterns and diverse physiological responses [1-4, 10]. These observations indicate that pivotal cellular decisions, such as cytoskeletal reorganization, cell-cycle checkpoints and cell death (apoptosis), depend on the precise temporal control and relative spatial distribution of activated signal transducers [1]. And the mathematical models on those biological phenomena provide insights into the complex relationships between the stimuli and the cellular response, and reveal the mechanisms that are responsible for signal amplification, noise reduction and generation of many dynamical characteristics [1].

Activation of cell-surface receptors and their downstream targets leads to the spatial relocation of multiple proteins within the cell. During evolution, cells have developed not only means to control the temporal dynamics of signalling networks, but also mechanisms for *precise spatial sensing of the relative localization of signalling proteins*. The regulation of signalling within the cellular space is pivotal for several physiological process, such as cell division, motility and migration, which lead to cell self-organization during the evolution [1].

Among above signalling and activities, many cellular proteins undergo cycles of phosphorylation and dephosphorylation by protein kinases and phosphatases and this protein phosphorylation is one of the main ways by which protein activities are regulated in the cell [1]. Various protein kinases and phosphatases are localized to different components of the cell (e.g., the cell membrane, the cytosol, intracellular membranes, the nucleus) and may change their distribution in different conditions. The kinases and phosphatases of a particular protein are often located in different compartments. This kind of spatial segregation of opposing reactions is just the basic prerequisite for signalling gradients in universal protein-modification cycle.

Thus, the specificity of cellular responses to receptor stimulation is encoded by the spatial and temporal dynamics of downstream signalling networks. Those coupled spatial and temporal dynamics *guide pivotal intracellular processes* and

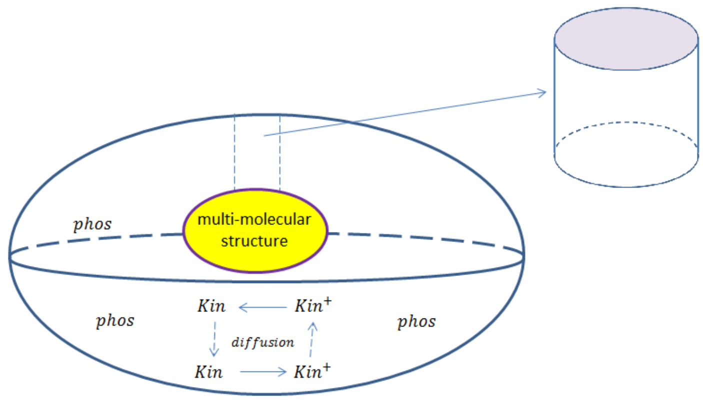

Figure 2.1: Multi-molecular Structure

tightly *regulate signal propagation* across a cell. It is apparent that the diffusion is unavoidable in the regulatory networks and when they process cellular signalling.

Kazmierczak and Lipniacki [3, 4] have provided some analysis of the kinase activity on the spherical cells mainly by means of numerical simulations. However, the spherical cell is factually only one of cases. In reality, there are many cells in the shapes of a finite cylinder, an ellipse and even a rugby ball. And the solutions to those models built on those cells probably show much difference with that to the model on spherical cells. New analysis becomes necessary and different conclusions probably arise. For example, there exists the difference between series forms of solutions in the spherical cell and in the finite cylindrical cell. Therefore, in order to obtain more universal conclusions, it is significant to investigate the kinase activity on different cells with the different shapes and to check what are the different or similar conclusions among those different situations.

What is more, research on the diffusion equation on the finite cylinder has played an important role in some topics of the geophysics and also in geochemistry (say, in geophysics, consider the change of fluid or Helium pressure on the cylinder) where the analytical solutions and concrete results are more interesting to geochemists and physical scientists.

Naturally, the question coming into the focus is that what are the boundary conditions when the kinase activity on the finite cylindrical cell is considered since the region that equations lie in is different ?

And once the new boundary conditions are presented, what are the corresponding changes about the solution and the method to obtain the solution of those new models? In this work, it is shown that although the shapes of cells are different the basic conclusions are similar. The more mathematical supports are demonstrated to the reasonable conjecture that under certain biological principles in cells, whatever the shapes are, kinase activity modes are similar.

Motivated by the aspects mentioned above and bacterial cell and the case of a kinase bound to a supra-molecular structure [1], several mathematical models of kinase activity are considered in this work (See next section). They model finite cylinders with mixed boundary conditions. In those models, the flux in the curvilinear boundary is assumed to be zero when considering cases of bacterial cells and the cylinders as part cut off from supra-molecular structure (See Figure 2.1).

Kholodenko [1] points out that signalling gradients can not be built solely by diffusion but requires the spatial segregation of opposing enzymes. Brown and Kholodenko [2] have analyzed and shown that in a simple system, in which kinase molecules are phosphorylated at the cell membrane and dephosphorylated by a phosphatase molecules located homogeneously in the cell cytosol, small diffusion implies high gradient and low kinase activity in the cell centor. Kazmierczak and Lipniacki [3,4] have studied mathematical models related to the kinase activity on the spherical cells and provided some analysis and treatment by numerical simulation with respect to the cases of spherical symmetry. Zhao *et al* [11] have also considered a reaction-diffusion model related to the kinase activity, restricted to one-dimensional spatial space, via numerical simulations.

All above authors mainly treated the problems from the view of a biologist or an engineer. They have not provided a strict mathemtical treatment. The thesis just describes some mathematical results about this kinase activity model.

The mathematical results are based on the technique of series representation of the solution, which is developed by Auchmuty [5-9] and related to representations of solutions using expansions in series of Steklov eigenfunctions. By those results, the properties of the solutions of main models can be obtained. Basic theorems on the bifurcation and tricks in bifurcation analysis are also used when the critical vaule of parameter is obtained.

2.2 Model Formulation

The cell will be modeled geometrically as a finite cylinder Ω with hight $2h$ and the center at the origin of the coordinate system (Refer to the notation following the model equations provided below). Here the biological quantities will be represented by the following functions:

$u = u(t, x)$ the concentration of the active kinase at time t and a point $x = (x_1, x_2, x_3)$ in the cell

$Q = const$ the total concentration of the kinase on the whole cell, which is assumed to be 1

$R = R(t)$ the surface concentration of the active receptors

$P = const$ the total surface concentration of the ligand bound receptors (active and inactive)

$\phi = \phi(t, x)$ the flux of the active kinase through the cell surface.

Generally the active kinase concentration satisfies the following reaction diffusion equation

$$\frac{\partial u}{\partial t} = d_1 \Delta u - b_1 u \tag{2.1}$$

where reaction coefficient $d_1 > 0$, and the parameter $b_1 > 0$ is the kinase dephosphorylation rate due to the action of uniformly distributed phosphatases. The flux ϕ of the active kinase results from its phosphorylation by receptors on the top disc implying the Robin type boundary condition

$$\phi = a_1 R(Q - u) = d_1 D_\nu u \tag{2.2}$$

where ν is the outward normal unit vector on the boundary, $D_\nu u$ denotes the dot product of ν and the gradient of u. And on the other parts of the boundary $\phi = 0$.

In the first part of this work, the basic biological preconditions consist of three aspects: The first, the membrane receptors bind extracellular ligand which leads to cascade of processes and receptor activation. The second, a steady state surface concentration of ligand-bound receptors on the top disc is uniform. The third, all ligand-bound receptors are active. In this case, $R = R(t) = const$. Then letting

$s = d_1 t,\ c = b_1/d_1,\ \alpha = a_1 R/d_1$ (but we still use t in stead of s to denote the time parameter), (2.1) and (2.2) can give the following reaction diffusion model on the finite cylinder (See Figure (2.2) in the next page)

$$\begin{cases} \dfrac{\partial u}{\partial t} = \Delta u - cu, & (t, x_1, x_2, x_3) \in [0, \infty) \times \Omega \\ D_\nu u + \alpha u = \alpha, & (t, x_1, x_2, x_3) \in [0, \infty) \times \Sigma^{top}, \\ D_\nu u = 0, & (t, x_1, x_2, x_3) \in [0, \infty) \times (\Sigma_{bot} \cup \Sigma_1), \\ u(0, x) = u(x), & (x_1, x_2, x_3) \in \Omega \end{cases} \tag{2.3}$$

where $c,\ \alpha$ are all strictly positive time-independent constants, ν is the outward normal unit vector on the boundary, $D_\nu u$ is the dot product of the normal vector ν and the gradient ∇u at the boundary, i.e., $D_\nu u = \nu \cdot (\nabla u)$, and Ω is the finite cylinder defined as

$$\Omega = \{(x_1, x_2, x_3) : x_1^2 + x_2^2 < 1, -h < x_3 < h\} \subset R^3$$

with its boundary $\partial\Omega = \Sigma^{top} \cup \Sigma_{bot} \cup \Sigma_1$. $\Sigma^{top} = \{(x_1, x_2, x_3) : x_1^2 + x_2^2 < 1, x_3 = h\}$ is the upper circular face, $\Sigma^{bot} = \{(x_1, x_2, x_3) : x_1^2 + x_2^2 < 1, x_3 = -h\}$ is the lower circular face and $\Sigma_1 = \{(x_1, x_2, x_3) : x_2^2 + x_2^2 = 1, -h < x_3 < h\}$ is the curvilinear boundary. Simply, part of the boundary is also denoted as $\Gamma =: \Sigma_{bot} \cup \Sigma_1$ later and $x = (x_1, x_2, x_3)$ or just (x, y, z) denote the points in Ω since they lie in three-dimensional space.

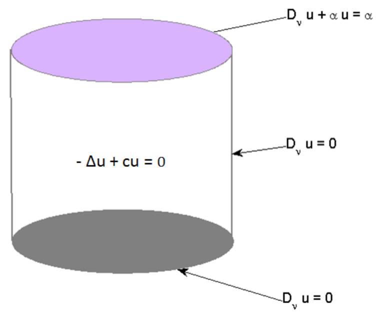

Figure 2.2: Kinase Activity Model in the Cell of Finite Cylinder

In chapter 4, it has been proved that solutions of above system (2.3) will converge exponentially to solutions of the steady state system

$$\begin{cases} -\Delta u + cu = 0, & x \in \Omega \\ \\ D_\nu u + \alpha u = \alpha, & x \in \Sigma^{top}, \\ \\ D_\nu u = 0, & x \in \Sigma_{bot} \cup \Sigma_1. \end{cases} \tag{2.4}$$

However, for the convenience and generality, the results on the abstract model generalized from (2.3) are firstly developed, which can be used directly to get the conclusions on (2.3). This abstract model is composed of a parabolic initial value problem with mixed Robin and Dirichlet boundary conditions

$$\begin{cases} \dfrac{\partial u}{\partial t} = \Delta u - cu + f, & (t,x) \in [0,\infty) \times \Omega \\ \\ D_\nu u + \bar{\alpha} u = \bar{g}, & (t,x) \in [0,\infty) \times \partial\Omega \\ \\ u(0,x) = u_0(x). \end{cases} \tag{2.5}$$

with Ω as that in model (2.3) &(2.4), $\bar{\alpha} = \alpha$ when $x \in \Sigma^{top}$, $\bar{\alpha} \equiv 0$ when $x \in \Gamma$ (Refer to (2.12)), and $\bar{g} = g = g(t,x)$ as $(t,x) \in [0,\infty) \times \Sigma^{top}$ while $\bar{g} \equiv 0$ as $(t,x) \in [0,\infty) \times \Gamma$, the initial value $u_0(x)$ belonging to the Sobolev space $H^1(\Omega)$.

In our investigation, above system (2.5) is considered as the sum of the following two systems (i.e the solution of (2.5) is regarded as the sum of solutions of the following two systems).

One is a parabolic equation with homogeneous boundary conditions

$$\begin{cases} \dfrac{\partial u}{\partial t} = \Delta u - cu + f, & (t,x) \in [0,\infty) \times \Omega \\ \\ D_\nu u + \bar{\alpha} u = 0, & (t,x) \in [0,\infty) \times \partial\Omega \\ \\ u(0,x) = u_0(x), & x \in \Omega. \end{cases} \tag{2.6}$$

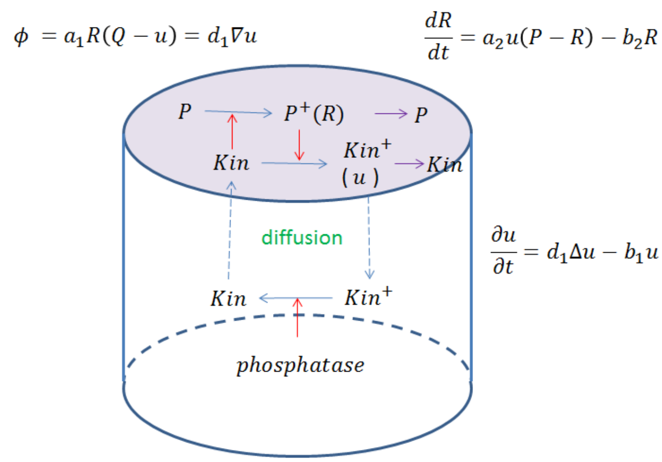

Figure 2.3: Kinase Activity with Feedback

and the other is the elliptic equation with non-homogeneous boundary conditions

$$\begin{cases} -\Delta u + cu = 0, & (t,x) \in [0,\infty) \times \Omega \\ D_\nu u + \bar{\alpha} u = \bar{g}, & (t,x) \in [0,\infty) \times \Sigma^{top} \\ D_\nu u|_{\partial\Omega} = 0, & (t,x) \in [0,\infty) \times \Gamma. \end{cases} \tag{2.7}$$

What is more, biological principles suggest that the limiting step during the formation of the active receptor complex is its phosphorylation by the kinase and in turn the active receptors may activate kinase molecules [3](Refer to Figure 2.3). In this case, the equation for their concentration $R(t)$ on Σ^{top} is

$$\frac{dR}{dt} = a_2 u(P-R) - b_2 R \tag{2.8}$$

where the reaction rate coefficients $a_2 > 0$ and $b_2 > 0$.

If d_1 is finite and strictly positive, by the transformation $s = d_1 t$ and the new notations (See (2.11) below), above equation (2.8), combining (2.1) and the flux equation (2.2), gives the following model with $u(0,x) = u_0(x) \in H^1(\Omega)$.

$$\begin{cases} \dfrac{\partial u}{\partial t} = \Delta u - cu, & (t,x) \in [0,\infty] \times \Omega \\ \\ \dfrac{dR}{dt} = -bR + qu(P - R), & (t,x) \in [0,\infty) \times \partial\Omega \\ \\ D_\nu u - \beta R(1-u) = 0, & (t,x) \in [0,\infty) \times \Sigma^{top}, \\ \\ D_\nu u = 0, & (t,x) \in [0,\infty) \times \Gamma. \end{cases} \tag{2.9}$$

The steady state of this system is

$$\begin{cases} -\Delta u + cu = 0, & x \in \Omega \\ \\ D_\nu u - \dfrac{\alpha u(1-u)}{\tau + u} = 0, & x \in \Sigma^{top}, \\ \\ D_\nu u = 0, & x \in \Gamma. \end{cases} \tag{2.10}$$

Here the parameters

$$c = \frac{b_1}{d_1}, \quad b = \frac{b_2}{d_1}, \quad q = \frac{a_2}{d_1}, \quad \beta = \frac{a_1}{d_1}, \qquad \alpha = \beta P = \frac{a_1 P}{d_1}, \quad \tau = \frac{b}{q} = \frac{b_2}{a_2} \tag{2.11}$$

are all finite strictly positive constants, and the region Ω and its boundary are the same to those in (2.3)& (2.4). This system will be studied in Chapter 6, Chapter

7, and Sections 8.2, 8.3, 8.4.

2.3 Notations and Mathematical Background

2.3.1 Notations

If X is a Banach space, a subset U of X is a **convex set** if $x, y \in U$ imply $(1-t)x + ty \in U, \forall t \in [0,1]$. When θ denotes any quantity and $\theta \geq 0$, it is called positive, if $\theta > 0$, it is called **strictly positive**.

Notations σ and $d\sigma$ will represent Hausdorff (N-1)-dimensional measure and integration with respect to this measure, respectively. This measure is called surface area. When the following condition (B1) holds, there is an outward unit normal ν defined at σ-almost everywhere (*a.e.*) point of $\partial\Omega$.

A function/functional $\psi : E \to (-\infty, \infty]$ is said to be **convex** if

$$\psi(tx + (1-t)y) \leq t\psi(x) + (1-t)\psi(y), \quad \forall x,\ y \in E, \quad \forall t \in (0,1),$$

it is said to be strictly convex if above inequality holds when " $\leq$ " changes into " $<$ " for any $x \neq y$ in E, $t \in (0,1)$. A functional ψ is (weakly) **lower semi-continuous** at x_0 if x_m converges to x_0 (weakly) implies $F(x_0) \leq \liminf_{m\to\infty} F(x_m)$.

Suppose that H is a linear space. A bilinear form $a : H \times H \to R$ is said to be **continuous bilinear form** if there exists a positive constant c such that $|a(u,v)| \leq c|u||v|$ for any $u, v \in H$, and it is said to be **coercive** if there is a constant $\alpha > 0$ such that $a(v,v) \geq \alpha|v|^2$ for any $v \in H$.

Assume that X and Y are Hilbert spaces, and X^* is the dual space of X. A sequence $f_n \in X^*$ **converges weakly-$*$** to f, written as $f_n \rightharpoonup^* f$, if $f_n(x) \to f(x)$ for every $x \in X$. An operator $K : X \to Y$ is **compact** if the image of any set N_0, which is bounded in X, has compact closure in Y i.e., $\overline{K(N_0)}$ is compact in Y for all bounded $N_0 \subset X$.

The **region** $\Omega \in R^N$ $(N \geq 2)$ is a non-empty, connected, open subset of R^N. $\overline{\Omega}$ denotes its closure and $\partial\Omega = \overline{\Omega}\backslash\Omega$ represents its boundary. A **Lipschitz domain/surface** is a domain in Euclidean space whose boundary is sufficiently regular in the sense that it can be thought of as locally being the graph of a Lipschitz continuous function. A point in Ω is denoted as $x = (x_1, x_2, \cdots, x_N)$(Sometimes (x, y, z)) in Cartesian coordinates. In our main model of this work, the region Ω as the finite cylinder will be represented using polar cylindrical coordinate in the form

$$\Omega = \{(\rho, \theta, z) : 0 \leq \rho < 1, 0 \leq \theta \leq 2\pi, -h < z < h\} \tag{2.12}$$

with boundary $\Sigma^{top} = \{(\rho, \theta, z) : 0 \leq \rho < 1, 0 \leq \theta \leq 2\pi, z = h\}$, $\Sigma_{bot} = \{(\rho, \theta, z) : 0 \leq \rho < 1, 0 \leq \theta \leq 2\pi, z = -h\}$ and curvilinear boundary $\Sigma_1 = \{(\rho, \theta, z) : \rho = 1, 0 \leq \theta \leq 2\pi, -h < z < h\}$, respectively.

$L^p(\Omega)$ and $L^p(\partial\Omega, d\sigma)$ $(1 \leq p \leq \infty)$ are the real Lebesgue spaces defined in the standard manner with the usual norm $||u||_p$ and $||u||_{p,\partial\Omega}$, respectively. The L^2-inner products are written as

$$[u, v] = (u, v) := \int_\Omega u(x)v(x)dx \ , \quad [u, v]_\partial = (u, v)_\partial := \int_{\partial\Omega} u(y)v(y)d\sigma \tag{2.13}$$

with the induced norms respectively as below

$$||u|| := ||u||_2 = (\int_\Omega u^2 dx)^{\frac{1}{2}}, \qquad ||u||_\partial = (\int_{\partial\Omega} u^2 dx)^{\frac{1}{2}}. \tag{2.14}$$

$H^1(\Omega)$ is the usual **Sobolev space** composed of all Lebesgue measurable functions f on Ω which has weak derivative $D_i f$ (the derivative to x_i, $i = 1, 2, \cdots, N$) satisfying $f, D_i f \in L^2(\Omega)$ and has the standard inner product and induced standard norm $||u||_{1,2}$,

$$[u, v]_1 = \int_\Omega [\nabla u \cdot \nabla v + u \cdot v] dx, \qquad ||u||_{1,2} = [u, u]_1^{\frac{1}{2}} \tag{2.15}$$

where ∇u stands for the gradient of u and $u \cdot v$ means the dot product of two vectors.

$H^1_R(\Omega) := \{w : w \in H^1(\Omega), D_\nu w + \bar{\alpha} w = 0,\ \forall x \in \partial\Omega\}$, where

$$\bar{\alpha} = \begin{cases} \alpha & \text{if } (x_1, x_2, x_3) \in \Sigma^{top} \\ 0, & \text{if } (x_1, x_2, x_3) \in \Gamma = \Sigma_{bot} \cup \Sigma_1 \ . \end{cases} \tag{2.16}$$

For any function g defined on Σ^{top}, $\bar{g}$ is defined as

$$\bar{g} = \begin{cases} g & \text{if } (t, x_1, x_2, x_3) \in [0, \infty) \times \Sigma^{top} \\ 0, & \text{if } (t, x_1, x_2, x_3) \in [0, \infty) \times \Gamma. \end{cases} \tag{2.17}$$

When considering the time-dependent equations, V may be simply used to represent $H^1(\Omega)$ itself or a linear subspace. The time-dependent solution $u = u(t, x)$ is regarded as functions $u(t)$ (or write as $u_t(\cdot)$) defined on Ω for *a.e.* each

$t \geq t_0$. I (usually $(0,T)$, $[0,T]$ or $[0,\infty)$) is an interval and X represents some Banach space, such as $L^2(\Omega)$ and $H^1(\Omega)$.

$C^0(I,X)$ consists of all the functions $u(t) : I \to X$ such that $u(t) \to u(t_0)$ as $t \to t_0$.

$L^p(I,X)$ $(1 \leq p \leq \infty)$ denotes the Lebesgue space consisting of all those functions $u(t)$ that take values in X for *a.e.* $t \in I$ such that the L^p norm of $||u(t)||_X$ is finite. This space can also be defined as the completion of $C^0(I,X)$ with respect to the norm

$$||u||_{L^p(I,X)} = (\int_\Omega ||u(t)||_X^p dt)^{1/p}.$$

Simply we write it as $L^p(0,T;X)$. We can also define the Sobolev spaces in this time-dependent setting , for example, we say $u \in H^1(0,T;L^2(\Omega))$ if u and Du are both in $L^2(0,T;L^2(\Omega))$.

2.3.2 Mathematical Assumptions

For the region Ω, there are the fundamental assumptions

(B1) Ω is a bounded region in R^N and its boundary $\partial\Omega$ is the union of a finite number of disjoint closed Lipschitz surface and each surface having the finite surface area.

(B2) The region Ω is said to satisfy **Rellich's theorem** if the imbedding of $H^1(\Omega)$ into $L^p(\Omega)$ is compact for $1 \leq p < P_s$ where $P_s(N) := 2N/(N-2)$ when $N \geq 3$, or $P_s(2) = \infty$ when $N = 2$.

(B3) The region Ω is said to satisfy a **compact trace theorem** if the trace mapping $\mathcal{T} : H^1(\Omega) \to L^2(\partial\Omega, d\sigma)$ is compact.

And for the reaction-diffusion equation (2.5), the following conditions are satisfied

(C1) When $N \geq 3$, $c \in L^p(\Omega)$ for some $p \geq N/2$ with $c \geq 0$ *a.e.* on Ω. When $N = 2$, $p > 1$ and $c \geq 0$ *a.e.* on Ω.

(C2) When $N \geq 3$, f and $f/\sqrt{c} \in L^2(0,\infty; L^p(\Omega))$ for some $p \geq 2N/(N+2)$ and $\bar{g} \in L^2(0,\infty; L^q(\partial\Omega, d\sigma))$ for some $q \geq 2(N-1)/N$. When $N = 2$, $p > 1$, $q > 1$.

Comments

The condition (C2) implies that the linear functional associated with integration against $f/\sqrt{c}$ is in the dual space of $L^2(0,\infty; H^1(\Omega))$ and with $\bar{g}$ is in the dual space of $L^2(0,\infty; H^1(\Omega))$. This is used in our proof of main results in Chapter 3 and Chapter 4. About f and $f/\sqrt{c}$, the condition can be relaxed as that they are in the space $L^\infty_{loc}(0,\infty; L^p(\Omega))$.

Particularly, in our models, c is strictly positive constant, $N = 3$, take $p = q = 2$. They satisfy both conditions (C1) and (C2) (Readers can refer to the section 2 of Ref. [8] for more comments on the condition similar to (C2)).

2.3.3 Definitions, Inner Products, and Norms

Definitions

1). `G-derivative`. When $\mathcal{F} : H^1(\Omega) \to (-\infty, \infty]$ is a functional, then $\mathcal{F}$ is said to be G-differentiable at a point $u \in H^1(\Omega)$ if there is a continuous linear functional $\mathcal{F}'(u)$ acting on $H^1(\Omega)$ such that

$$\lim_{t\to 0}\frac{\mathcal{F}(u+tv)-\mathcal{F}(u)}{t}=\mathcal{F}'(u)(v),\quad \forall v\in H^1(\Omega).$$

In this case, $\mathcal{F}'(u)$ is called the G-derivative of $\mathcal{F}$ at u.

2). `Exponential stability`. If a solution $u(t)$ of the Eq. (2.3), such that there are strictly positive constants ε and β obeying

$$||u(t)-u_{ss}||_{1,2}\le \beta e^{-\varepsilon t},$$

where u_{ss} is the solution of the steady state equation (2.4), then we say that the solution is exponential stable. If all solutions have this property, then system (2.3) is said to be exponentially stable.

3). `Inner Products, Norms and Functionals`.

For any $u, v\in H^1(\Omega)$, define the inner product $[u,v]_c$ by

$$[u,v]_c := (Au,v)=\int_\Omega \nabla u\cdot\nabla v dx+\int_\Omega cuvdx+\int_{\partial\Omega}\bar{\alpha}uvd\sigma, \tag{2.18}$$

with induced norm denoted as $||u||_c$, where c and $\bar{\alpha}$ are defined in (2.16) and (2.17) same as those in (2.5) and satisfies the mathematical assumptions in Section 2.3.2. In the biological models (2.3) and (2.9), c and $\bar{\alpha}$ are constants.

Define quadratic forms $\mathcal{D}_0$, $\mathcal{D}$ and Q on $H^1(\Omega)$as

$$\mathcal{D}_0(u)=\int_\Omega |\nabla u|^2dx+\int_\Omega cu^2dx+\int_{\partial\Omega}\bar{\alpha}u^2d\sigma, \tag{2.19}$$

$$\mathcal{D}(u) = \mathcal{D}_0(u) - 2\int_\Omega fudx - 2\int_{\partial\Omega} \bar{g}ud\sigma, \qquad Q(u) = q(u,u) = \int_\Omega u^2dx \tag{2.20}$$

Denote subset K of $H^1(\Omega)$ as

$$K = \{u \in H^1(\Omega) : \int_\Omega |\nabla u|^2dx + \int_\Omega cu^2dx + \int_{\partial\Omega} \bar{\alpha}u^2d\sigma \leq 1\} \tag{2.21}$$

Lemma 2.1. *Assume (B1)-(B3) and (C1)-(C2) hold, then the norm $||\cdot||_c$ induced by (2.18) is equivalent to the standard norm $||\cdot||_{1,2}$ in (2.15) on $H^1(\Omega)$. That is, there are strictly positive constants c_1, c_2 such that*

$$c_1||u||_{1,2} \leq ||u||_c \leq c_2||u||_{1,2}. \tag{2.22}$$

Proof. The method is very similar to that in Auchmuty's work, it is omitted here, please refer to the theorem 3.1 in Reference [8].

□

As for other basic definitions, notations, and terminology in time-dependent systems, this work will follow Auchmuty [8], Evans&Gariepy [12], and Temam [13].

Chapter 3

Linear Elliptical Equations on a Finite Cylinder and Related Eigencomputations

This chapter provides the important theoretical results on the more general linear elliptical model (3.1) generalized from (2.7) defined on the finite cylinder and also deals with the spectral representation of solutions and the relevant computation on the Steklov eigenproblem with mixed boundary conditions. Now consider the following model

$$\begin{cases} -\Delta u + cu = \tilde{f}, & (t, x) \in [0, \infty) \times \Omega \\ \\ D_\nu u + \bar{\alpha} u = \bar{g}, & (t, x) \in [0, \infty) \times \partial\Omega. \end{cases} \tag{3.1}$$

with the temporary assumption of $\tilde{f}, \bar{g}$ independent of the time in the following Sections 3.1 to 3.3.

3.1 Fundamental Theory on the General Elliptical Equation

At first, the following equation is investigated

$$\int_{\Omega}[\nabla u \nabla v dx + cuv]dx + \int_{\partial\Omega} \bar{\alpha} uv d\sigma = \int_{\Omega} \tilde{f} v dx + \int_{\partial\Omega} \bar{g} v d\sigma, \;\; v \in H^1(\Omega) \qquad (3.2)$$

which is the weak form of the elliptic partial differential equation (3.1).

Lemma 3.1. *Assume (B1)-(B3) and (C1)-(C2) hold for Eq.(3.1), then there is a unique minimizer $\tilde{u}$ of $\mathcal{D}(u)$ on $H^1(\Omega)$. Moreover this minimizer satisfies (3.2) and there are constants k_1, k_2 such that the following estimate holds*

$$||\tilde{u}||_{1,2} \leq k_1||\tilde{f}||_p + k_2||\bar{g}||_{q,\partial\Omega}. \qquad (3.3)$$

where $\mathcal{D}(u)$ is defined in (2.20), p, q are the same as those in (C2) and particularly in model (2.3) they can both equal 2.

Proof. Conditions (C1)implies that $\mathcal{D}_0$ defined in (2.19) is continuous, strictly convex and coercive on $H^1(\Omega)$ from the properties of the norm, the Sobolev imbedding theorem and inequality (2.22). When Rellich's theorem and the trace theorem hold, then the condition (C2) implies that the last two terms in the right-hand side of

(3.2) define two continuous linear functionals on $H^1(\Omega)$ when p, q are the same in (C2). Hence $\mathcal{D}$ is continuous and has a unique minimizer $\tilde{u}$ on $H^1(\Omega)$.

The functional $\mathcal{D}$ is G-differentiable and the derivative $\mathcal{D}'(u)$ is given by

$$\langle \mathcal{D}'(u),\ v\rangle = 2\int_\Omega [\nabla u \nabla v + (cu - \tilde{f})v]dx + 2\int_{\partial\Omega} (\bar{\alpha}u - \bar{g})v d\sigma.$$

A minimizer $\tilde{u}$ of $\mathcal{D}$ will satisfy $\langle \mathcal{D}'(\tilde{u}),\ v\rangle = 0$ for all $v \in H^1(\Omega)$, so $\tilde{u}$ satisfies (3.2).

Take $u = v = \tilde{u}$ in (3.2), then one has

$$\int_\Omega |\nabla \tilde{u}|^2 dx + \int_\Omega c\tilde{u}^2 dx + \int_{\partial\Omega} \bar{\alpha}\tilde{u}^2 d\sigma = \int_\Omega \tilde{f}\tilde{u} dx + \int_{\partial\Omega} \bar{g}\tilde{u} d\sigma$$

Thanks to condition (C1) and then apply Holder inequality to the right hand side,

$$||\tilde{u}||_c^2 \leq ||\tilde{f}||_p ||\tilde{u}||_{p'} + ||\bar{g}||_{q,\partial\Omega} ||\tilde{u}||_{q',\partial\Omega}$$

where p', q' are the conjugate indices to p, q respectively.

If the inequality (2.22) is used to the left-hand term and Rellich's theorem and compact trace theorem are applied to the right-hand terms, the inequality (3.3) is obtained. Thus, the proof is completed.

□

Lemma 3.2. *Assume (B1)-(B3) and (C1)-(C2) hold, then there is a unique solution $\tilde{u}$ of (3.2) in $H^1(\Omega)$ and there exist constants k_1, k_2 such that the inequality (3.3) holds.*

Proof. Lemma 3.1 shows that there is a solution $\tilde{u}$ of (3.2) and it is the unique minimizer of $\mathcal{D}$ on $H^1(\Omega)$. If there is another solution $\hat{u} \in H^1(\Omega)$ of (3.2), then $\hat{u}$ would be also a critical point of $\mathcal{D}$ on $H^1(\Omega)$. Since $\mathcal{D}_0$ is strictly convex, here it must hold $\hat{u} = \tilde{u}$.

□

Remark 3.3. *The inequality (3.3) provides an estimate for the continuous dependence of the solutions on the data $\tilde{f}$ and $\bar{g}$. This result implies that the problem of weak solutions of (3.2) in $H^1(\Omega)$ is well-posed provided that the source terms $\tilde{f}, \bar{g}$ satisfy the condition (C2), the boundary satisfies (B1)-(B3) and the equation satisfies (C1). Also the following conclusions are reached.*

Corollary 3.4. *Assume (B1)-(B3) and (C1)-(C2) hold, then there are continuous linear transformations $\mathcal{G}_{\mathcal{I}} : L^p(\Omega) \to H^1(\Omega)$ and $\mathcal{G}_{\mathcal{B}} : L^q(\partial\Omega, d\sigma) \to H^1(\Omega)$ such that the unique solution $\tilde{u}$ of (3.2) in $H^1(\Omega)$ has the following representation*

$$\tilde{u}(x) = (\mathcal{G}_{\mathcal{I}}\tilde{f})(x) + (\mathcal{G}_{\mathcal{B}}\bar{g})(x).$$

Furthermore, $\mathcal{G}_{\mathcal{I}}$ is a compact linear mapping when $p > 2N/(N+2)$ and $\mathcal{G}_{\mathcal{B}}$ is a compact linear mapping when $q > 2(1 - N^{-1})$. Particularly, in our kinase activity model, $N = 3$ and $p,\ q$ can both be 2.

Proof. The techniques of the proof are similar to those in the work of Auchmuty, please refer to [Corollary 4.3, 8]. □

What are the concrete representations of $\mathcal{G}_{\mathcal{I}}$ and $\mathcal{G}_{\mathcal{B}}$? They are given in the following sections after the related theoretical results are obtained.

3.2 Robin Eigenproblem and Spectral Representation of Solutions

Consider the corresponding Robin eigenproblem

$$\begin{cases} -\Delta u + cu = \lambda u, & x \in \Omega \\ \\ D_\nu u + \bar{\alpha} u = 0, & x \in \partial\Omega \end{cases}$$

with $\bar{\alpha}$ and c as those in (2.5) or (2.3). The weak form of this is to find non-trivial solutions of

$$\int_\Omega \nabla u \cdot \nabla v dx + \int_\Omega cuv dx + \int_{\partial\Omega} \bar{\alpha} uv d\sigma = \lambda \int_\Omega uv dx = 0, \quad \forall\ v \in H^1(\Omega). \tag{3.4}$$

Consider the variational principle (ζ_1) of maximizing Q on K and let

$$\mu_1 := \sup_{u \in K} Q(u)$$

where Q and K are defined in (2.20) and (2.21), respectively.

Theorem 3.5. *Assume (B1)-(B3) and (C1)-(C2) hold, then there are maximizers $\pm e_1$ of Q on K and μ_1 is finite. The maximizers satisfy (3.4) and $||e_1||_c = 1$. The corresponding eigenvalue λ_1 is the least strictly positive eigenvalue of (3.4) and $\mu_1 = \lambda_1^{-1}$. Here the norm $||\cdot||_c$ is induced by the inner product in (2.18).*

Proof. Since the norms $||.||_c$ and the standard norm in $H^1(\Omega)$ are equivalent (Lemma 2.1), K is weakly compact in $H^1(\Omega)$. Since $Q(\cdot)$ is weakly continuous on

$H^1(\Omega)$, it attains its supremum on K at a point e_1 and this supremum is finite.

If $||e_1|| < 1$, then there exists $\eta > 1$ such that $\eta e_1 \in K$ and then

$$Q(\eta e_1) = \eta^2 Q(e_1) > Q(e_1).$$

This contradicts the maximality of e_1 , one must have $||e_1||_c = 1$.

A Lagrangian functional for the problem $\mu_1 := \sup_{u \in K} Q(u)$ is $\mathcal{L} : H^1(\Omega) \times [0, \infty] \to R$ defined by

$$\mathcal{L}(u, \mu) := \mu[\int_\Omega |\nabla u|^2 dx + \int_\Omega cu^2 dx + \int_{\partial\Omega} \bar{\alpha} u^2 d\sigma - 1] - \int_\Omega u^2 dx$$

The problem of maximizing Q on K is equivalent to finding an inf-sup point of $\mathcal{L}$ on its domain because of

$$\sup_{\mu \geq 0} \mathcal{L}(u, \mu) = \begin{cases} -\displaystyle\int_\Omega u^2 dx, & \text{if } ||u||_c \leq 1 \\ \infty & \text{otherwise} \end{cases}$$

and

$$\inf_{u \in H^1(\Omega)} \sup_{\mu \geq 0} \mathcal{L}(u, \mu) = \inf_{||u||_c \leq 1} - \int_\Omega u^2 dx = - \sup_{||u||_c \leq 1} \int_\Omega u^2 dx.$$

Any such maximizer of Q will be a critical point of $\mathcal{L}(\cdot, \mu)$ on $H^1(\Omega)$, so it is a solution of

$$\mu[\int_\Omega \nabla u \cdot \nabla v dx + \int_\Omega cuv dx + \int_{\partial\Omega} \bar{\alpha} uv d\sigma] - \int_\Omega uv dx = 0, \qquad \forall v \in H^1(\Omega). \quad (3.5)$$

When $\mu > 0$, then above equation gives the form (3.4) with $\lambda = \mu^{-1}$.

When $\mu = 0$, then (3.5) implies $\sup_{u \in K} Q(u) = 0$. This is a contradiction since here u is the maximizer.

Thus, (3.4) holds at the maximizer.

If e_1 is such a maximizer, then the corresponding eigenvalue λ_1 in (3.4) satisfies: $||e_1||_c^2 = 1 = \lambda_1 Q(e_1)$.

Put $u = v = e_1$ in (3.5), then $\mu_1 = \lambda_1^{-1}$.

If λ_1 is not the least positive eigenvalue of (3.4), there will be a nonzero $\tilde{u}$ in $H^1(\Omega)$ satisfying (3.4) and the corresponding eigenvalue $\tilde{\lambda}$ such that $\tilde{\lambda} < \lambda_1$. Normalize $\tilde{u}$ to have c-norm 1, then (3.4) implies $1 = \tilde{\lambda} Q(\tilde{u}), \quad Q(\tilde{u}) = \tilde{\lambda}^{-1} > \lambda^{-1} = \mu_1$. This contradicts with that μ_1 is the supremum of $Q(\cdot)$. so λ_1 is minimal. The proof is finished.

□

Given the first J eigenvalues and corresponding c-orthonormal eigenfunctions, we now consider how to find the next eigenvalue λ_{J+1} and a corresponding normalized eigenfunctions. Assume the first J eigenvalues are $0 < \lambda_1 \leq \lambda_2 \leq \cdots \leq \lambda_J$ and $\{e_1, e_2, \cdots, e_J\}$ is the corresponding family of c-orthonormal eigenfunctions. This implies that

$$[e_j, e_k] = \lambda_j^{-1} \delta_{jk}, \quad \forall j, k \in \{1, 2, \cdots, J\},$$

here the Kronecker symbol $\delta_{jk} = 1$ when $k = j$ and $\delta_{jk} = 0$ when $k \neq j$.

For $J \geq 1$, define

$$K_J := \{ \quad u \in K : [u, e_j] = 0, \quad \forall j \in \{1, 2, \cdots, J\} \quad \}.$$

Consider the variational problem (ζ_{J+1}) of maximizing $Q(\cdot)$ on K_J and let

$$\mu_{J+1} := \sup_{u \in K_J} Q(u)$$

Theorem 3.6. *Assume (B1)-(B3) and (C1)-(C2) hold. Then K_J is a bounded closed convex set in $H^1(\Omega)$, μ_{J+1} is finite and there exist maximizers $\pm e_{J+1}$ of Q on K_J. These maximizers satisfy $||e_{J+1}||_c^2 = \lambda_{J+1}||e_{J+1}||_2^2 = 1$ with $\mu_{J+1} = \lambda_{J+1}^{-1}$ and $[e_{J+1}, e_j]_c = [e_{J+1}, e_j] = 0, \forall j \in \{1, 2, \cdots, J\}$. Moreover, λ_{J+1} is the smallest eigenvalue of this problem greater than or equal to λ_J.*

Proof. $\Phi_j(u) = [u, e_j]$, $j = 1, 2, \cdots, J$, are continuous on $H^1(\Omega)$ since (C2) and trace theorem hold.

Hence K_J is a bounded closed convex subset of $H^1(\Omega)$ similar to the set K. The next steps just follows the procedure described in the proof of Theorem 3.5. Readers can refer to Ref. [5] for remarks on more detailed steps of the proof, we omit them here. □

Remark 3.7. *Iterate the preceding process, one can obtain an increasing sequence $\{\lambda_j : j \geq 1\}$ of eigenvalues and a corresponding c-orthonormal sequence of eigenfunctions $\{e_j : j \geq 1\}$. Suppose $w_j(x) := \lambda_j^{1/2} e_j$ for each $j \geq 1$, then $\{w_j : j \geq 1\}$ will be an L^2-orthonormal subset of $H^1(\Omega)$ and $\mathcal{D}_0(w_j) = \lambda_j$ for each $j \geq 1$. Without confusion, we will still use $\{e_j : j \geq 1\}$ to denote this L^2-orthonormal subset* *in stead of* $\{w_j : j \geq 1\}$.

Theorem 3.8. *Assume (B1)-(B3) and (C1)-(C2) hold, then each eigenvalue* λ_j *of (3.4) has finite multiplicity and* $\lambda_j \to \infty$ *as* $j \to \infty$. *Moreover, the corresponding eigenfunction family* $\{e_1, e_2, \cdots, e_n, \cdots\}$ *is a maximal c-orthonormal subset of* $H^1(\Omega)$, *which is also a basis of the linear subspace* $H^1_R(\Omega)$ *defined over (2.16).*

Proof. Suppose the eigenvalue sequence is bounded above by a finite $\hat{\lambda}$, the corresponding sequence of eigenfunctions is a pairwise c-orthogonal set in $H^1(\Omega)$. So it converges weakly to zero. Then $Q(e_j) \to 0$, but

$$Q(e_j) \geq \hat{\lambda}^{-1} > 0, \quad \forall j \geq 1.$$

This is a contradiction. Therefore, no such $\hat{\lambda}$ exists and the first statement in theorem holds.

Now suppose $\{e_1, e_2, \cdots, e_n, \cdots\}$ is not maximal, then there is an eigenfunction w with $||w||_c = 1$ and $[e_j, w]_c = 0, \quad \forall j \geq 1$.

If $Q(w) > 0$, then there exists J such that

$$Q(w) > \mu_{J+1} = \lambda_{J+1}^{-1}$$

by the first statement. This is a contradiction.

If $Q(w) = 0$, then it contradicts with $||w||_c = 1$ since $||w||_c^2 = \lambda_0 ||w||_2^2$, where λ_0 is the corresponding eigenvalue to w. $\square$

Now it is the time to consider the weak solution of (3.1) with case of $\bar{g} \equiv 0$ on

$\partial\Omega$ and its weak form

$$\int_\Omega \nabla u \cdot \nabla v dx + \int_\Omega cuv dx + \int_{\Sigma^{top}} \alpha uv d\sigma = \int_\Omega \tilde{f} v dx, \;\; v \in H^1(\Omega) \tag{3.6}$$

By Remark 3.7 and Theorem 3.8, any solution u of (3.6) can be expressed by

$$u = \sum_{i=1}^{\infty} c_j e_j \tag{3.7}$$

where

$$c_j = [u, e_j], \qquad \forall\ j = 1, 2, 3, \cdots$$

and this inner product is defined in (2.13).

Put $v = e_j$ in (3.6), then the solution u satisfies

$$[u, e_j]_c = \int_\Omega \tilde{f} e_j dx := \hat{f}_j, \quad \forall j = 1, 2, 3, \cdots \ .$$

Substitute (3.7) into above equality, then (3.4) and the orthogonality yield

$$\lambda_j c_j = [u, e_j]_c = \hat{f}_j, \quad \forall j = 1, 2, 3, \cdots \ . \tag{3.8}$$

That is,

$$u(x) = \sum_{i=1}^{\infty} \lambda_j^{-1} \hat{f}_j e_j(x), \qquad \hat{f}_j := \int_\Omega \tilde{f} e_j dx,$$

and furthermore, it is rewritten as

$$u(x) = \int_\Omega G_I(x, y) \tilde{f}(y) dy, \qquad G_I(x, y) := \sum_{j=1}^{\infty} \lambda_j^{-1} e_j(x) e_j(y). \tag{3.9}$$

Equation (3.9) is called Robin eigen-expression of the solution to (3.6).

3.3 Steklov Eigenproblem and Spectral Representation of the Solution

In this section, we will consider the following Steklov eigenproblem

$$\int_\Omega \nabla u \cdot \nabla v dx + \int_\Omega cuv dx + \int_{\partial\Omega} \bar{\alpha} uv d\sigma = \delta \int_{\partial\Omega} \kappa uv d\sigma, \;\; \forall v \in H^1(\Omega) \tag{3.10}$$

which is the weak form of

$$\begin{cases} -\Delta u + cu = 0, & x \in \Omega \\ D_\nu u|_{\partial\Omega} + \bar{\alpha} u = \delta \kappa u, & x \in \partial\Omega. \end{cases}$$

where $\bar{\alpha}$ is defined in (2.16), α is the same as that in (2.3) (2.4) and

$$\kappa = \begin{cases} \frac{1}{\pi}, & \text{when } x \in \Sigma^{top} \\ 0, & \text{when } x \in \Gamma := \Sigma_{bot} \cup \Sigma_1 \;, \end{cases}$$

By means of the same procedure in [5], let

$$W = \{w \in H^1(\Omega) : [w, v]_c = 0, \;\; \forall \; v \in H_0^1(\Omega)\} \tag{3.11}$$

where the inner product $[\cdot,\cdot]_c$ defined in (2.18) is an equivalent inner product to the standard inner product on $H^1(\Omega)$. Then there holds

$$H^1(\Omega) = H_0^1(\Omega) \oplus_c W$$

where $\oplus_c$ indicates a c-orthogonal direct sum. Similar to [5], there is the following theorem.

Theorem 3.9. *Under the assumptions (B1)-(B3) and (C1)-(C2), for $N \geq 2$, the Steklov eigenproblem (3.10) has a sequence of real eigenvalues*

$$0 < \delta_1 \leq \delta_2 \leq \cdots \leq \delta_j \leq \cdots \to \infty, \quad j \to \infty,$$

each eigenvalue has a finite-dimensional eigenspace. The eigenfunctions $\tilde{e}_1, \tilde{e}_2, \cdots$ corresponding respectively to these eigenvalues form a maximal orthonormal (under the norm induced by inner product $[\cdot,\cdot]_c$) family in W, which is also orthogonal in $L^2(\partial\Omega)$.

The functions in W are weak solutions of

$$-\Delta u + cu = 0. \tag{3.12}$$

Consider the problem of finding weak solution of

$$\int_\Omega \nabla u \cdot \nabla v dx + \int_\Omega cuv dx + \int_{\partial\Omega} \bar{\alpha} uv d\sigma = \int_{\Sigma^{top}} gv d\sigma, \quad \forall v \in H^1(\Omega). \tag{3.13}$$

It means that the functions in W satisfying (3.13) are weak solution of (3.11) subject to

$$D_\nu u + \alpha u = g, \quad x \in \Sigma^{top}, \qquad D_\nu u = 0, \quad x \in \Gamma. \tag{3.14}$$

That is, (3.13) is the weak form of (3.12) and (3.14)

Therefore any solution w of (3.12) subject to (3.14) has the series representation

$$w = \sum_{i=1}^{\infty} w_j \tilde{e}_j \tag{3.15}$$

with $w_j = [w, \tilde{e}_j]_c$ for any $j = 1, 2, \cdots$. Plug this solution of series form into the weak form (3.13)

$$\int_\Omega [\nabla w \nabla v dx + cwv] dx + \int_{\Sigma^{top}} \alpha w v d\sigma = \int_{\Sigma^{top}} g v d\sigma, \qquad v \in H^1(\Omega)$$

and take $v = \tilde{e}_j$ successively, the following is obtained

$$w_j = [w, \tilde{e}_j]_c = \int_{\Sigma^{top}} g \tilde{e}_j d\sigma$$

Thus the solution w of (3.12) and (3.14) is expressed as

$$w = \int_{\Sigma^{top}} G_B(x, y) g(y) d\sigma(y),$$

where

$$G_B(x, y) := \sum_{j=1}^{\infty} \tilde{e}_j(x) \tilde{e}_j(y), \tag{3.16}$$

and w is just the solution of (2.7).

In summary, from the results in sections 3.1, 3.2 and this section, define

$$(\mathcal{G}_{\mathcal{I}}\tilde{f})(x) = \int_{\Omega} G_I(x,y)\tilde{f}(y)dy, \qquad (\mathcal{G}_{\mathcal{B}}\bar{g})(x) = \int_{\partial\Omega} G_B(x,y)\bar{g}(y)d\sigma(y),$$

then these operators are just those mentioned in Corollary 3.4, where the notation $\bar{g}$ is given by (2.17) and the kernels are defined in (3.9) and (3.16), respectively.

Remark 3.10. *The results and deductions in Section 3.1 to Section 3.3 still hold when $\tilde{f}$ and $\bar{g}$ are time-related in (3.1). In this situation, they can be denoted as $\tilde{f}_t$ and $\bar{g}_t$ and regarded as just another different functions from $\tilde{f}$ and $\bar{g}$ respectively. The coefficients in (3.7) and (3.15) will be time-related. And the related convergence for the series can be reached by use of the well-known Banach-Steihaus theorem under the standard norm $||\cdot||_{1,2}$ in (2.15).*

3.4 Computations on Steklov Eigenproblem of the Steady State Model

Assume in the cylindrical coordinate

$$s = \psi(\rho,\theta)Z(z), \tag{3.17}$$

is the eigenfunction where $\psi = \psi(\rho,\theta)$ is defined on the unit disc

$$B_1 = \{(\rho,\theta) : 0 \le \rho < 1, \quad 0 \le \theta \le 2\pi\}. \tag{3.18}$$

Put $\tilde{\delta} = \delta/\pi - \alpha$ and write (3.10) in cylindrical coordinates by

$$\int_\Omega (\nabla s \cdot \nabla v + csv)dxdydz = \delta \int_0^1 \int_0^{2\pi} sv\rho d\rho d\theta, \qquad \forall\ v \in H^1(\Omega). \tag{3.19}$$

But we will still denote the eigenvalue by use of δ in stead of $\tilde{\delta}$ in the following, then the classical form of (3.10) is explicitly expressed as below

$$\begin{cases} -\Delta s + cs = 0, & (\rho, \theta, z) \in \Omega \\ \dfrac{\partial s}{\partial z} = \delta s, & 0 \le \rho < 1, \quad z = h, \\ \dfrac{\partial s}{\partial z} = 0, & 0 \le \rho < 1, \quad z = -h, \\ \dfrac{\partial s}{\partial \rho} = 0, & \rho = 1, -h < z < h, \end{cases} \tag{3.20}$$

Plug (3.17) into the first equation in (3.20), the following are obtained

$$-[\Delta\psi(\rho,\theta)]Z(z) - \psi(\rho,\theta)\frac{\partial^2 Z(z)}{\partial z^2} + c\psi(\rho,\theta)Z(z) = 0.$$

Divide the two sides of above equation by $\psi(\rho,\theta)Z(z)$, and then

$$-\frac{\Delta\psi(\rho,\theta)}{\psi(\rho,\theta)} - \frac{Z''(z)}{Z(z)} + c = 0.$$

Put

$$\frac{Z''(z)}{Z(z)} - c = \lambda,$$

then there holds

$$Z''(z) - (\lambda + c)Z(z) = 0 \tag{3.21}$$

and

$$-\Delta\psi(\rho,\theta) = \lambda\psi(\rho,\theta), \qquad (\rho,\theta) \in B_1. \tag{3.22}$$

Checking the boundary conditions in (3.20), the following is reached

$$\frac{\partial\psi}{\partial\rho} = 0, \qquad \text{at} \quad \rho = 1. \tag{3.23}$$

The equations (3.22) or (3.23) just give the Neumann eigenproblem on the unit disc (3.18) in the two-dimensional space. And the weak form is

$$\int_{B_1} \nabla\psi\nabla w dxdy = \lambda \int_{B_1} \psi w dxdy$$

or in the cylindrical coordinate

$$\int_{B_1} \nabla\psi\nabla w\rho d\rho d\theta = \lambda \int_{B_1} \psi w\rho d\rho d\theta. \tag{3.24}$$

If $\lambda = 0$, then $\psi = 1$ is the corresponding eigenfunction of (3.22) with (3.23).

If $\lambda > 0$ (in fact, (3.24) can imply $\lambda \geq 0$), then let

$$\psi = \phi(\rho)L(\theta), \quad (\rho,\theta) \in B_1$$

where B_1 is the disc defined in (3.18).

Thanks to (3.22), the following is obtained

$$\phi''(\rho)L(\theta) + \frac{1}{\rho}\phi'(\rho)L(\theta) + \frac{1}{\rho^2}\phi(\rho)L''(\theta) = -\lambda\phi(\rho)L(\theta).$$

Divide the two sides of above equation by $\phi(\rho)L(\theta)$ respectively, there is

$$\frac{\phi''(\rho)}{\phi(\rho)} + \frac{1}{\rho}\frac{\phi'(\rho)}{\phi(\rho)} + \frac{1}{\rho^2}\frac{L''(\theta)}{L(\theta)} = -\lambda$$

i.e

$$\rho^2[\frac{\phi''(\rho)}{\phi(\rho)} + \frac{1}{\rho}\frac{\phi'(\rho)}{\phi(\rho)}] + \frac{L''(\theta)}{L(\theta)} = -\lambda\rho^2.$$

Put

$$\frac{L''(\theta)}{L(\theta)} = -\mu,$$

the following are obtaind

$$L''(\theta) + \mu L(\theta) = 0, \quad L(0) = L(2\pi), \quad L'(0) = L'(2\pi) \tag{3.25}$$

and

$$\phi''(\rho) + \frac{1}{\rho}\phi'(\rho) + (\lambda - \frac{\mu}{\rho^2})\phi(\rho) = 0, \quad \phi'(\rho)|_{\rho=1} = 0. \tag{3.26}$$

The following are just the solutions for (3.25)

$$L(\theta) = A_m\cos(m\theta) + B_m\sin(m\theta), \quad \mu = m^2, \quad m = 1, 2, \cdots$$

For the equation (3.26), notice that $\mu = m^2$ and by Ref. [p183, 14], the solutions are presented as

$$\phi(\rho) = J_m(\rho x_{m_n}), \quad \lambda = \lambda_{m_n} := (x_{m_n})^2 \tag{3.27}$$

where x_{m_n} is the nth nonnegative root of

$$J'_m(x) = 0 \tag{3.28}$$

provided that the order of roots is from the smaller to the larger, and $J_m(\cdot)$ and $J'_m(\cdot)$ are the standard Bessel function and the derivative function defined at [(3.2.10), 14].

So the Neumann eigenfuctions are

$$\psi(\rho,\theta) = J_m(\rho x_{m_n})(A_m \cos(m\theta) + B_m \sin(m\theta)), \quad m = 1, 2, \cdots \tag{3.29}$$

corresponding to the strictly positive eigenvalue

$$\lambda = (x_{m_n})^2, \quad n = 1, 2, \cdots$$

where x_{m_n} are those in (3.27).

Now it is the time to solve (3.21)

$$Z''(z) - (\lambda + c)Z(z) = 0$$

with boundary condition

$$Z'(z)|_{z=-h} = 0.$$

Since $\lambda + c = (x_{m_n})^2 + c \geq 0$, the solution can be obtained as

$$Z(z) = Ee^{\sqrt{\lambda+c}\ z} + Fe^{-\sqrt{\lambda+c}\ z}$$

and

$$Z'(z) = \sqrt{\lambda+c}(Ee^{\sqrt{\lambda+c}\ z} - Fe^{-\sqrt{\lambda+c}\ z}).$$

Plug above into the equation of boundary condition, it becomes

$$Z'(h) = \sqrt{\lambda+c}(Ee^{-h\sqrt{\lambda+c}} - Fe^{h\sqrt{\lambda+c}}) = 0$$

Solving it, the parameter relation is

$$E = Fe^{2h\sqrt{\lambda+c}}.$$

And so

$$Z(z) = F(e^{\sqrt{\lambda+c}(z+h)} + e^{-\sqrt{\lambda+c}(z+h)}) = \frac{F}{2}\cosh((z+h)\sqrt{(x_{m_n})^2+c}) \qquad (3.30)$$

Therefore, the solutions to the first equation in (3.20) under the boundary condition

$$\frac{\partial s}{\partial z} = 0, \qquad \frac{\partial s}{\partial \rho} = 0$$

show as

$$s(\rho,\theta,z) = J_m(\rho x_{m_n})[A_m\cos(m\theta) + B_m\sin(m\theta)]\cosh((z+h)\sqrt{(x_{m_n})^2+c})$$

with $m = 1, 2, \cdots$ and x_{m_n} is the nth positive zero of (3.28).

Then from the boundary equation i.e the second equation of (3.20)

$$\frac{\partial s}{\partial z} = \delta s, \qquad z = h \tag{3.31}$$

From (3.31), there holds the equality

$$\sinh((z+h)\sqrt{x_{m_n}^2 + c}) = \delta \cosh((z+h)\sqrt{x_{m_n}^2 + c}), \qquad \text{at } z = h$$

which gives

$$\delta_{m,n} = ((x_{m_n})^2 + c)^{\frac{1}{2}} \tanh(2h\sqrt{(x_{m_n})^2 + c})$$

with $x_{m_n} \geq 0$ and satisfying the equation (3.28).

In summary, from (3.29) and (3.31), the Steklov eigenvalue for (3.20) or (3.19) is

$$\delta_{m_n} = (x_{m_n}^2 + c)^{\frac{1}{2}} \tanh(2h(x_{m_n}^2 + c)^{\frac{1}{2}}) \tag{3.32}$$

and the corresponding Steklov eigenfunction is

$$s_{m_n} = J_m(\rho x_{m_n})(A_m \cos(m\theta) + B_m \sin(m\theta)) \cosh((z+h)(x_{m_n}^2 + c)^{\frac{1}{2}}) \tag{3.33}$$

where $m = 1, 2, \cdots$ and x_{m_n} is the nth strictly positive zero of (3.28) with zeros in order from the smaller to the bigger and J_m are the Bessel functions [(3.2.10), 14]. Here one can take $A_m = B_m = 1$ or other concrete constants. (Here n can also take the value of zero, in this case, $x_{m_0} = 0$).

In the case of $m = 0$, the solution is the axially symmetric case. Similar to (3.32) and (3.33), it has the simpler form

$$s_n = J_0(\rho x_n)\cosh((z+h)(x_n^2+c)^{\frac{1}{2}}) \tag{3.34}$$

with corresponding eigenvalue

$$\delta_n := \delta_{0_n} = (x_n^2+c)^{\frac{1}{2}}\tanh(2h(x_n^2+c)^{\frac{1}{2}}) \tag{3.35}$$

where $x_n := x_{0_n}$ is the n-th positive zero of

$$J_0'(x) = 0.$$

And more particularly, corresponding to $\lambda = 0$ and $x_0 = 0$, the first nonnegative Steklov eigenvalue and the Steklov eigenfunction are respectively

$$\delta_1 = \sqrt{c}\tanh(2h\sqrt{c}),\ \ s_1(\rho,z) = \cosh((z+h)\sqrt{c}),\ \ \rho\in[0,1],\ \ z\in[-h,h] \tag{3.36}$$

Here for convenience of the reader, the following are provided: the Bessel function $J_0(x)$ (respectively in series form and integral form)

$$J_0(x) = 1+\sum_{n=1}^{\infty}\frac{(-1)^n x^{2n}}{2^{2n}(n!)^2},\quad J_0(x) = \frac{1}{2\pi}\int_{-\pi}^{\pi}\cos(x\cos(\theta))d\theta \tag{3.37}$$

and $J_1(x)$ (Refer to [P185& P192, 14])

$$J_1(x) = \sum_{n=0}^{\infty} \frac{(-1)^n x^{2n+1}}{2^{2n+1}(n!)^2(n+1)}, \quad J_1(x) = \frac{1}{2\pi}\int_{-\pi}^{\pi} \sin(x\cos(\theta))\cos(\theta)d\theta \tag{3.38}$$

and the first six strictly positive zeros of $J_0'(x)$, i.e roots of (3.26) (more of them appear in Appendix C)

$$x_1 = 3.83170597020751231561\,4, \quad x_2 = 7.01558666981561875353\,9,$$
$$x_3 = 10.17346813506272207719, \quad x_4 = 13.32369193631422303239$$
$$x_5 = 16.47063005087763281255, \quad x_6 = 19.61585851046824202113$$

Chapter 4

Time-dependent Model on the Finite Cylinder

In this chapter the results in previous are needed.

Now in order to consider model (2.5), the time-dependent model (2.6) is firstly considered, which is copied as below (4.1)

$$\begin{cases} \dfrac{\partial u}{\partial t} = \Delta u - cu + f, & (t,x) \in [0,\infty) \times \Omega \\ \\ D_\nu u + \bar{\alpha} u = 0, & (t,x) \in [0,\infty) \times \partial\Omega \\ \\ u(0,x) = u_0(x). \end{cases} \tag{4.1}$$

This chapter just demonstrates the existence and uniqueness of the time-dependent solution for (4.1) under the weak sense.

Naturally, a solution $u(t,x)$ of (4.1) is considered as a trajectory in some infinite-dimensional phase space. In other word, $u(t, x)$ is regarded as a family of functions $u_t(\cdot)$ or denoted as $u(t)$, each member of which is defined on Ω.

Since the eigenfunctions $e_1, e_2, \cdots, e_n, \cdots$ (Refer to Theorem 3.6 and Remark 3.7) are L^2-orthogonal in $V = H^1(\Omega)$, the finite-dimensional subspace is denoted as

$$V_n := \text{span}\ \{e_1, e_2, \cdots, e_n\}.$$

Any $u \in L^2(\Omega)$ projects to space V_n as

$$P_n u = \sum_{j=1}^{n} u_{nj} e_j, \qquad u_{nj} = [u, e_j], \quad \forall\ j \geq 1$$

If $f \in V^*$, $\langle P_n f, v\rangle := \langle f, P_n v\rangle, \quad \forall v \in V$. This makes sense since $v \in V \subset L^2(\Omega)$.

Define $Q_n = I - P_n, \quad Q_n u = \sum_{j=n+1}^{\infty} u_{nj} e_j, \qquad u_{nj} = [u, e_j], \quad \forall j \geq n+1.$

Thus for the solution $u(t)$ of (4.1), the Galerkin approximation sequence $u_n(t)$ is employed, where

$$u_n(t) = \sum_{j=1}^{n} u_{nj}(t) e_j, \qquad u_{nj}(t) = [u(t), e_j], \quad 1 \leq j \leq n, \quad n \geq 2 \tag{4.2}$$

and each member $u_n(t)$ of the sequence solves

$$(\frac{du_n}{dt}, e_j) + (Au_n, e_j) = \langle f, e_j\rangle,$$

(See (2.18) for the linear operator A) with $(u_n(0), e_j) = (u_0, e_j)$, and $\langle f, e_j\rangle$ makes sense since $e_j \in V$ for any $j \geq 1$.

Note that the inner product $[u, v]$ in $L^2(\Omega)$ is defined by (2.13). And also there holds $u_{nj} = [u_n(t), e_j]$, $(\frac{du_n}{dt}, e_j) = \frac{du_{nj}}{dt}$ and $(Au_n, e_j) = \lambda_j u_{nj}$ (Refer to the definition of A in (2.18) and the equalities (3.4) and (3.8)).

Therefore a set of n ODEs is obtained for the components u_{nj}:

$$\frac{du_{nj}}{dt} + \lambda_j u_{nj} = \langle f(t), e_j \rangle. \tag{4.3}$$

It can be rewritten concisely as

$$\frac{du_n}{dt} + Au_n = P_n f, \tag{4.4}$$

where u_n is the one in (4.2).

The Theorem A1 and Theorem A2 in Appendix A guarantee that there is a unique solution of (4.4) for the u_{nj}, at least in some time interval $[0, T_n]$. Then the time interval can be extended to infinity if it is known that the u_{nj} are bounded. Note that if u_n is regarded as an n-component vector, it still needs to show that $\sum_{j=1}^{n} u_{nj}^2$ remains bounded. Using the idea of Robinson [15], the proofs on those conclusions are provided in Appendix A.

In brief, the general result can be attained which is presented in the following theorem.

Theorem 4.1. *(Well-posedness) Under the conditions (B1-B3) and (C1)(C2), the time-dependent weak solution of (4.1) is unique and continuously depends on initial data.*

Proof. Suppose that there are two solutions u and $\bar{u}$ of (4.1), then, by linearity of the equation, the difference of these two solutions, $y(t) = u - \bar{u}$ satisfies

$$\frac{dy}{dt} + Ay = 0.$$

Using Theorem A5, we can taking the appropriate inner product of this equation with y, it produces

$$\frac{1}{2}\frac{d}{dt}||y||^2 + ||y||_c^2 = 0,$$

whence

$$\frac{d}{dt}||y||^2 \leq 0.$$

It follows that

$$||y(t)|| \leq ||y(0)||,$$

which demonstrates continuous dependence on initial data, and in the case when $u(0) = \bar{u}(0)$ (i.e., $y(0) = 0$), uniqueness. $\square$

Combining the result in Chapter 3 related to (2.7), the well-posedness of (2.5) can be obtained

Note that the equations (4.3) can be solved in integral form

$$l_j^n = e^{-\lambda_j t} l_j^n(0) + \int_0^t e^{\lambda_j(s-t)} \langle f(s), e_j \rangle ds$$

(here we use l_j^n to denote u_{nj} instead).

Therefore any solution v of (4.1) can be written down in integral form as

$$v = \sum_{j=1}^{\infty} l_j^n e_j = \sum_{j=1}^{\infty} e^{-\lambda_j t} l_j^n(0) e_j + \int_0^t e^{\lambda_j(s-t)} \langle f(s), e_j \rangle e_j ds$$

Notice that

$$\langle f(t), e_j \rangle = \int_\Omega f(t,x) e_j(x) dx \qquad \forall f \in L^2([0,\infty) \times \Omega)$$

and the notation in the beginning of Subsection 3.2,

$$l_j^n(0) = [u(0), e_j] = \int_\Omega u(0,x) e_j(x) dx$$

Inspired by results in Chapter 3, define the kernel

$$G(\tau,x,y) = \sum_{j=1}^{\infty} e^{-\lambda_j \tau} e_j(x) e_j(y), \qquad (\tau,x,y) \in [0,\infty) \times \Omega \times \Omega \tag{4.5}$$

then the solution v of (4.1) reads

$$v(t,x) = \int_\Omega G(t,x,y) u(0,y) dy + \int_0^t \int_\Omega G(t-s,x,y) f(s,y) dy ds$$

Then the sum U of the solution w in section 3.3 (i.e., the solution of (2.7)) and the solution v of (4.1) (i.e., the solution of (2.6)) is the solution of (2.5) and equal to

$$\int_{\Sigma^{top}} G_B(x,y) g(y) d\sigma(y) + \int_\Omega G(t,x,y) u(0,y) dy + \int_0^t \int_\Omega G(t-s,x,y) f(s,y) dy ds$$

where the kernels are defined at (3.16) and (4.5), respectively.

Chapter 5

Solution Properties of the Kinase Activity Model on the Finite Cylinder

By the result in Chapter 3 and Chapter 4, the time-dependent solution (2.3) has the unique time-dependent solution which corresponds to the case of (2.5) with $f \equiv 0$ and $\bar{g} = \bar{\alpha}$.

Notice the following equality arising in Section 3.2

$$\lambda_j c_j = [u, e_j]_c, \quad i.e, \quad c_j = [u, e_j] = \lambda_j^{-1}[u, e_j]_c \tag{5.1}$$

then there is

$$\int_\Omega e_j^2 dx = \lambda_j^{-1}.$$

Thus for the solution of kinase model (2.3), it can read

$$U = \alpha \int_{\Sigma^{top}} G_B(x,y)d\sigma(y) + \int_{\Omega} G(t,x,y)u(0,y)dy$$

under the kernels given by (3.16) and (4.5). Therefore it is known that

$$|\int_{\Omega} G(t,x,y)u(0,y)dy| = |\int_{\Omega} \sum_{j=1}^{\infty} e^{-\lambda_j t} e_j(x)e_j(y)u(0,y)dy|$$

$$\leq \sum_{j=1}^{\infty} e^{-\lambda_1 t}|e_j(x)|\,|\int_{\Omega} e_j(y)u(0,y)dy| \leq \sum_{j=1}^{\infty} e^{-\lambda_1 t}|e_j(x)|\,||e_j||_2||u(0,y)||_2$$

$$\leq \sum_{j=1}^{\infty} \lambda_1^{-1} e^{-\lambda_1 t}|e_j(x)|\,||u(0,y)||_2 \quad \to 0 \ , \quad \text{when} \quad t \to \infty$$

under the $||\cdot||_2$ norm, where the second inequality is obtained by the Hölder inequality and the third inequality is obtained by (5.1).

So the time-dependent concentration of the kinase will exponentially converge to its steady state solution. Thus, investigation on the solution properties of steady state kinase activity model (2.4) is sufficient to know the solution properties of (2.3).

For the steady state model (2.4), the following conclusions are obtained

5.1 Solution Properties of the Kinase Activity Model on the Finite Cylinder

Existence and Uniqueness. *The solution of (2.4) exists and is unique.*

This is implied by results in Chapter 3 and above analysis.

Boundedness. *The solution of (2.4) is bounded under the* $||\cdot||_{1,2}$ *norm.*

Proof. Concretely, by the result in Section 3.3 and Ref. [5], it is known that for any $u \in H^1(\Omega)$, the trace inequality holds

$$\delta_1 \int_{\Sigma^{top}} u^2 d\sigma \leq \int_\Omega |\nabla u|^2 dx + \int_\Omega cu^2 dx$$

where δ_1 is the least strictly positive Steklov eigenvalue in (3.19) or (3.20), i.e., the one in (3.36).

Thus from the weak form of (2.4),

$$\int_\Omega [\nabla u \nabla v dx + cuv] dx + \int_{\Sigma^{top}} \alpha uv d\sigma = \int_{\Sigma^{top}} \alpha v d\sigma, \;\; v \in H^1(\Omega), \tag{5.2}$$

and by taking $v = u$ in above equation, the following is obtained

$$||u||_{1,2}^2 \leq \max\{1, c^{-1}\} \int_\Omega [|\nabla u|^2 + cu^2] dx \leq \max\{1, c^{-1}\} \int_{\partial\Omega} \alpha u d\sigma$$

Continuously, by Holder inequality,

$$||u||_{1,2}^2 \leq \max\{1, c^{-1}\} \delta_1^{-1/2} \alpha |\Sigma^{top}|^{1/2} \max\{1, c\}^{1/2} ||u||_{1,2}.$$

Thus, there holds

$$||u||_{1,2} \leq \max\{1, c^{-1}\} \delta_1^{-1/2} \alpha |\Sigma^{top}|^{1/2} \max\{1, c\}^{1/2} := B,$$

where

$$B = \begin{cases} \alpha(\pi\delta_1^{-1})^{\frac{1}{2}}c^{\frac{1}{2}}, & \text{if } c \geq 1 \\ \\ \alpha(\pi\delta_1^{-1})^{\frac{1}{2}}c^{-1}, & \text{if } 0 < c < 1 \ , \end{cases}$$

and δ_1 is the least strictly positive Steklov eigenvalue shown in (3.36). □

Positivity of the Solutions. *If the solution of (2.4) is continuous on $\overline{\Omega}$, then it is positive on Ω (the finite cylinder)*

Proof. For the solution u to (2.4), by its weak form (5.2), the following holds

$$\int_{\Omega}[|\nabla u|^2 + cu^2]dx + \int_{\Sigma^{top}} \alpha u^2 d\sigma = \int_{\Sigma^{top}} \alpha u d\sigma, \quad u \in H^1(\Omega). \tag{5.3}$$

Then there holds

$$u \geq 0, \qquad \text{for } x \in \overline{\Omega}, \tag{5.4}$$

since α and c are strictly positive.

If (5.4) is not true, then one can assume an open subset $\Theta_1 \subset \Omega$ such that $|\Theta_1| > 0$ and

$$u < 0, \quad x \in \Theta_1 \ .$$

Put $v = 0$ when $x \in \Omega \backslash \Theta_1$ and $v = u$ when $x \in \Theta_1$, then $v \in H^1(\Omega)$. Plug this v into the weak form (5.2), one can get

$$\int_{\Theta_1}[|\nabla u|^2 + cu^2]dx = 0$$

which implies that $u = 0$ for all $x \in \Theta_1$. This is a contradiction.

Note that u is continuous to the boundary, hence (5.4) is proved. □

On the other hand, when the solution of (2.4) is continuous, (5.3) can be also rewritten as

$$\int_\Omega [|\nabla u|^2 + cu^2]dx = \int_{\Sigma^{top}} \alpha u(1-u)d\sigma,$$

which, combining (5.4) and by the same procedure in proof of (5.4), implies

$$0 \le u \le 1, \qquad \text{for } x \in \partial\Omega.$$

Remark 5.1. *In (5.3) and (5.4), the strict positivity and boundedness of the solutions are obtained mathematically, but in the article [3], the authors have only acquired the boundedness and positivity through the physical background but not from mathematical perspective.*

Chapter 6

Time-dependent Kinase Activity Model with Nonlinear Boundary Conditions - Direct Analysis

In this chapter, the time-dependent model (2.9) is investigated by direct analysis on the solution with initial value $(u(t_0, x), R(t_0, x)) = (u(0, x), R(0, x)) = (u_0, R_0)$.

Let (u^*, R^*) represents the steady state solution, and in the second equation we use u^* to replace u. Then there holds

$$\frac{d}{dt}R + (b + qu^*)R = qPu^*, \qquad \text{so} \quad \frac{d}{dt}[e^{(b+qu^*)t}R] = qPu^* e^{(b+qu^*)t}R \quad .$$

This has the solution

$$R(t, x) = R_0 e^{-(b+qu^*)t} + \frac{qPu^*}{b + qu^*}(1 - e^{-(b+qu^*)t})$$

which means that in this case of substitution, the $R(t,x)$ will exponentially approach its steady state

$$R^* = \frac{qPu^*}{b+qu^*}. \tag{6.1}$$

Now substitute (6.1) into the third equation i.e., the boundary condition and then integrate the first equation by use of Gaussian theorem. Then there is

$$\frac{1}{2}\frac{d}{dt}\int_\Omega u^2 dx = \int_{\partial\Omega}(D_\nu u)u d\sigma - \int_\Omega |\nabla u|^2 dx - \int_\Omega c|u|^2 dx$$

with

$$D_\nu u = \beta[R_0 e^{-(b+qu^*)t} + \frac{qPu^*}{b+qu^*}(1-e^{-(b+qu^*)t})](1-u)$$

Note that $u(1-u) \leq 1/4$, then there holds the inequality

$$\frac{1}{2}\frac{d}{dt}\int_\Omega u^2 dx + \int_\Omega |\nabla u|^2 dx + \int_\Omega c|u|^2 dx \leq \frac{1}{4}\beta\int_{\Sigma^{top}}(R^* + (R_0 - R^*)e^{-\gamma t})d\sigma$$

where R^* shown in (6.1) and $\gamma := b + qu^*$. Above inequality further implies

$$\frac{d}{dt}\int_\Omega u^2 dx + 2\int_\Omega c|u|^2 dx \leq \frac{1}{2}\beta\int_{\Sigma^{top}} R^* d\sigma + \frac{1}{2}\beta e^{-\gamma t}\int_{\Sigma^{top}}(R_0 - R^*)d\sigma.$$

Multiply the two sides of above inequality by e^{2ct} and integrate the results from 0 to t respectively, then there holds

$$\int_\Omega |u|^2 dx \leq e^{-2ct}\int_\Omega |u_0|^2 dx + \int_{\Sigma^{top}}[\frac{\beta}{4c}(1-e^{-2ct})R^* + \frac{\beta}{2\gamma - 4c}(e^{-2ct} - e^{-\gamma t})(R_0 - R^*)]d\sigma$$

which means

$$\int_\Omega |u|^2 dx \leq \frac{\beta}{4c}\int_{\Sigma^{top}} R^* d\sigma + e^{-2ct}[\int_\Omega |u_0|^2 dx + \frac{\beta}{|4c-2\gamma|}\int_{\Sigma^{top}} (R_0 - R^*) d\sigma] \quad (6.2)$$

for any $t \geq 0$. From (6.2), take limits as $t \to \infty$, then

$$\int_\Omega |u^*|^2 dx \leq \frac{\beta}{4c}\int_{\Sigma^{top}} \frac{qPu^*}{b+qu^*} d\sigma, \qquad \text{when } c > 0$$

by notice of the equality (6.1).

That is, the spatial average of the active kinase concentration is bounded by the summation of some constants, i.e the spatial average of the concentration of initial active kinase, and certain weighted average of the initial active receptor concentration.

This result also implies that for the time-dependent model, the concentration will be restricted in some region near the steady state solutions.

Chapter 7

Weak Solution of the Steady State Model with Nonlinear Boundary Conditions

7.1 Existence of the Weak Solution

Consider the steady state equation below which is modified a little from (2.10)

$$\begin{cases} -\Delta u + cu = 0, & x \in \Omega \\ D_\nu u - g^+(u) = 0, & x \in \Sigma^{top}. \\ D_\nu u = 0, & x \in \Gamma \end{cases} \tag{7.1}$$

and define the functional

$$\mathcal{E}(u) = \frac{1}{2}\int_\Omega [|\nabla u|^2 + cu^2]dx - \int_{\Sigma^{top}} G(u)d\sigma, \quad u \in H^1(\Omega) \tag{7.2}$$

with the general case $\dfrac{\partial G(u)}{\partial u} = g^+(u)$, and in our model, for the convenience in proof, the function $g^+(u)$ is redenoted from g by

$$g^+(u) = \begin{cases} g(u), & \text{when } u \geq 0 \\ \\ 0, & \text{when } u < 0\ . \end{cases} \qquad \text{and} \quad g(u) = \frac{\alpha u(1-u)}{\tau + u} \tag{7.3}$$

since the physical meaning of kinase concentration requires $u \geq 0$.

The variational principle (ζ_{Nonl}) for the equation with mixed boundary condition is to minimize $\mathcal{E}(u)$ on $H^1(\Omega)$.

The G-derivative of $\mathcal{E}(u)$ is the linear operator $\nabla\mathcal{E}(u)$ with

$$(\nabla\mathcal{E}(u), v) = \int_\Omega [\nabla u \nabla v + cuv]dx - \int_{\Sigma^{top}} g^+(u)vd\sigma, \qquad \forall v \in H^1(\Omega).$$

The critical point of $\mathcal{E}(u)$ satisfies

$$(\nabla\mathcal{E}(u), v) = 0, \qquad \forall v \in H^1(\Omega)$$

which is equivalent to

$$\int_\Omega [\nabla u \nabla v + cuv]dx - \int_{\Sigma^{top}} g^+(u)vd\sigma = 0, \qquad \forall v \in H^1(\Omega). \tag{7.4}$$

We are interested in finding solutions of Eq.(7.4) which is the weak form of the system (7.1). This is proved using variational methods. Consider the functional $\mathcal{E}(u) : H^1(\Omega) \to R$ defined by (7.2).

Theorem 7.1. *When g^+ is given in (7.3) , then there are minimizers of $\mathcal{E}$ on $H^1(\Omega)$. These minimizers satisfy (7.4) (which are just the weak solutions of (2.10))*

Proof. From (7.3), we can obtain

$$g^+(u) = -\alpha u + \alpha(\tau+1) - \frac{\alpha\tau(\tau+1)}{u+\tau}.$$

And it has anti-derivative denoted as $G(u)$, then when $u \geq 0$, $G(u)$ has the form

$$G(u) = -\alpha\tau(\tau+1)\ln\tau - \frac{1}{2}\alpha u^2 + \alpha(\tau+1)u - \alpha\tau(\tau+1)\ln(1+\frac{u}{\tau})$$

which can be rewritten as

$$G(u) = -\frac{1}{2}\alpha u^2 + \alpha(\tau+1)u - \alpha\tau(\tau+1)\ln(1+\frac{u}{\tau})$$

since the constant term does not play an important role in the derivative. When $u < 0$, $G(u)$ is a constant which case is easy to treat. In the following, the case of $u \geq 0$ is treated exclusively.

Then, corresponding to model (2.10), the $\mathcal{E}(u)$ is rewritten as

$$\begin{aligned} \mathcal{E}(u) &= \frac{1}{2}\int_\Omega [|\nabla u|^2 + cu^2]dx + \frac{1}{2}\int_{\Sigma^{top}} \alpha u^2 d\sigma - \int_{\Sigma^{top}} G(u)d\sigma, \\ &= \frac{1}{2}\int_\Omega [|\nabla u|^2 + cu^2]dx + \frac{1}{2}\int_{\Sigma^{top}} \alpha u^2 d\sigma \\ &\qquad + \int_{\Sigma^{top}} \alpha(\tau+1)[\tau\ln(1+\frac{u}{\tau}) - u]d\sigma \end{aligned}$$

and the weak form (7.4) becomes

$$\int_{\Omega}[\nabla u\nabla v+cuv]dx+\int_{\Sigma^{top}}\alpha uvd\sigma-\int_{\Sigma^{top}}\alpha(\tau+1)(1-\frac{\tau}{u+\tau})vd\sigma=0, \qquad (7.5)$$

for any $v\in H^1(\Omega)$.

In the next, our goal is to prove that $\mathcal{E}(u)$ can attain its minimum value on $H^1(\Omega)$

On the one hand, the following can be obtained

$$\mathcal{E}(u)\geq\frac{1}{2}\int_{\Omega}[|\nabla u|^2+cu^2]dx+\frac{1}{2}\int_{\Sigma^{top}}\alpha u^2d\sigma-\int_{\Sigma^{top}}\alpha(\tau+1)ud\sigma.$$

And for any $\epsilon>0$, there holds

$$\alpha(\tau+1)u\leq\frac{\epsilon}{2}u^2+\frac{(\alpha\tau+\alpha)^2}{2\epsilon}$$

Thus, the following holds

$$\mathcal{E}(u)\geq\frac{1}{2}\int_{\Omega}[|\nabla u|^2+cu^2]dx+\frac{1}{2}\int_{\Sigma^{top}}(\alpha-\epsilon)u^2d\sigma-\int_{\Sigma^{top}}\frac{(\alpha\tau+\alpha)^2}{2\epsilon}d\sigma$$

Take one ϵ small enough such that $\alpha-\epsilon>0$, the functional

$$\mathcal{F}(u):=\mathcal{E}(u)+\int_{\Sigma^{top}}\frac{(\alpha\tau+\alpha)^2}{2\epsilon}d\sigma$$

defined on $H^1(\Omega)$ is coercive. And when $u<0$, by definition in (7.2) the conclusion also holds .

On the other hand, for sequence $u_m\to u$ (weakly) in $H^1(\Omega)$, it implies that

$\mathcal{T}(u_m) \to \mathcal{T}(u)$ (weakly) (Refer to Section 2.3.2) in $L^2(\partial\Omega, d\sigma)$ by the compact trace theorem.

Those imply that the functional

$$\int_{\Sigma^{top}} \alpha(\tau+1)[\tau \ln(1+\frac{u}{\tau}) - u] d\sigma$$

is (weakly) continuous in $L^2(\partial\Omega, d\sigma)$ (therefore on $H^1(\Omega)$) since the function $\ln(1+u)$ is continous for $u > 0$. Thus $\mathcal{E}(u)$ and therefore $\mathcal{F}(u)$ are weakly lower semi-continuous on $H^1(\Omega)$.

By theorems in [p511-513, 16], $\mathcal{F}(u)$ can attain its minimum, say, at u^1 in $H^1(\Omega)$. This also implies that $\mathcal{E}(u)$ attains its minimum at u^1 since the difference between $\mathcal{E}(u)$ and $\mathcal{F}(u)$ is only the constant

$$\int_{\partial\Omega} \frac{(\alpha\tau+\tau)^2}{2\epsilon} d\sigma \quad .$$

Therefore, therefore existence of weak solution of (7.5) (i.e., the solution of (2.10)) is proved .

□

Proposition 7.2. *Under certain ranges of the parameters α, τ, there is at least one nonzero positive minimizer of $\mathcal{E}(u)$.*

In fact, the trivial function $u = 0$ is certainly a solution of (7.1) and $\mathcal{E}(0) = 0$. By a counterexample, one can show that under certain value of parameters, there exists at least one positive minimizer of $\mathcal{E}(u)$. For example, if $\alpha = 3,\ \tau = \frac{2}{3}$, one can take $u_1 = \frac{1}{4}$ in $H^1(\Omega)$, there holds

$$\mathcal{E}(u_1) < \pi[\frac{1}{16} - \frac{\alpha}{32\tau} + \frac{\alpha(\tau+1)}{3 \cdot 64\tau^2}] = \pi[\frac{1}{16} - \frac{9}{64} + \frac{3.75}{64}] < 0$$

which means that there must exist one nonzero positive minimizer of $\mathcal{E}(u)$. Furthermore, this tells that under some ranges of parameters α and τ,there exists at least one nonzero positive solution of (7.1), where

$$\alpha = \frac{a_1 P}{d_1}, \qquad \tau = \frac{b_2}{a_2}$$

provided in (2.11).

Comments

Here theorem 7.1 and proposition 7.2 do not provide the concrete ranges of α and τ to ensure the nonzero positive minimizer of $\mathcal{E}(u)$. So it is necessary to give some bifurcation analysis to this model in the following Chapter 8 under classical sense since any classical solution to (2.10) is just one of its weak solutions.

7.2 Boundedness of the Weak Solution

Theorem 7.3. *If the weak solutions of (2.10) are also continuous on $\overline{\Omega}$, then they are bounded under the norm $||\cdot||_{1,2}$. This bound depends on α and τ.*

Proof. Assume that u is a solution of (2.10). In the weak form of (2.10),

$$\int_\Omega [\nabla u \nabla v + cuv]dx - \int_{\Sigma^{top}} \frac{\alpha u(1-u)}{\tau + u} v d\sigma = 0, \qquad \forall v \in H^1(\Omega),$$

taking $v = u$, the following is obtained

$$\int_{\Omega} [|\nabla u|^2 + cu^2] dx = \int_{\Sigma^{top}} \frac{\alpha u^2 (1-u)}{\tau + u} d\sigma \geq 0,$$

which, by the same procedure in the last proposition of Section 5.1, implies that

$$(1-u)(\tau + u) \geq 0, \qquad x \in \Sigma^{top}.$$

Thus

$$-\tau < u \leq 1, \qquad x \in \Sigma^{top}.$$

In the physical meaning, u is the concentration of the kinase, so it is nonnegative. Then if $u \neq 0$, the following inequality holds

$$\int_{\Omega} [|\nabla u|^2 + cu^2] dx < \frac{\alpha}{\tau} \int_{\Sigma^{top}} u^2 d\sigma < \frac{\alpha}{\tau} \pi,$$

which gives

$$||u||_{1,2} < (\frac{\alpha}{\min\{1, c\}\tau})^{\frac{1}{2}} ||u||_{2,\Sigma^{top}} < (\frac{\alpha}{\min\{1, c\}\tau})^{\frac{1}{2}}.$$

where the norms are defined in that over (2.13) and in (2.15), respectively.

$\square$

Chapter 8

Bifurcation Analysis and Series Representation of Solutions of the Kinase Activity Model

In this Chapter 8, the focus is on the model (2.9) with its steady state equation (2.10), but we start the work just from the original biological model.

8.1 Bifurcation on the Kinase Activity Model with Infinite Diffusion - Extreme Case

By use of the substitution $s = b_1 t$ and notations

$$d = \frac{d_1}{b_1}, \quad a = \frac{a_1}{b_1}, \quad b = \frac{b_2}{b_1}, \quad q = \frac{a_2}{b_1}, \tag{8.1}$$

the reaction-diffusion equation (2.1), flux equation (2.2) and receptor-kinase activation equation (2.8) together give the following model (here again use t in stead of s to denote the time parameter)

$$\begin{cases} \dfrac{\partial u}{\partial t} = d\Delta u - u, & (t,x) \in [0,\infty) \times \Omega \\ \\ \dfrac{dR}{dt} = qu(P-R) - bR, & (t,x) \in [0,\infty) \times \partial\Omega \\ \\ dD_\nu u - aR(1-u) = 0, & (t,x) \in [0,\infty) \times \Sigma^{top} \end{cases} \tag{8.2}$$

with $D_\nu u = 0$, as $(t,x) \in [0,\infty) \times \Gamma$ and the initial value $u(0) = u_0,\ x \in \bar{\Omega}$, where a, b, d, q, P are all positive constants, Ω is the finite cylinder defined in (2.12).

In (8.2), noticing (8.1), let

$$d \to \infty, \qquad \text{i.e.,} \quad \text{in (2.1)} \quad d_1 \to \infty,$$

then the active kinase concentration is uniform and the model becomes an ordinary differential system instead.

Integrating the first equation of (8.2) on the finite cylinder Ω, there holds the equation

$$\int_\Omega \frac{\partial u}{\partial t} dx = \int_\Omega d\Delta u dx - \int_\Omega u dx.$$

Then by Gaussian theorem and boundary conditions, the following equalities are obtained

$$(2h\pi)\frac{du}{dt} = \int_{\Sigma^{top}} dD_\nu u d\sigma - (2h\pi)u = \int_{\Sigma^{top}} (aR(1-u))d\sigma - (2h\pi)u,$$

where $d\sigma$ is the integration with respect to the boundary measure, i.e., $dxdy$ or $d\rho d\theta$ on the unit disc. In further,

$$(2h\pi)\frac{du}{dt} = \pi(aR(1-u)) - (2h\pi)u,$$

and it can be simplified as

$$\frac{du}{dt} = \frac{aR}{2h} - (1 + \frac{aR}{2h})u.$$

Thus in the case of infinite diffusion, the model degenerates to an ordinary differential system

$$\begin{cases} \dfrac{du}{dt} = \dfrac{aR}{2h} - (1 + \dfrac{aR}{2h})u, & t \in [0, \infty) \\ \\ \dfrac{dR}{dt} = qu(P-R) - bR, & t \in [0, \infty) \\ \\ u(0) = u_0, \quad R(0) = R_0 \end{cases} \tag{8.3}$$

Now consider the steady state solution. Let

$$qu(P-R) - bR = 0$$

and combine it with

$$\pi(aR(1-u)) - (2h\pi)u = 0.$$

Then, two steady state solutions are obtained

$$u_1^s = 0, \quad R_1^s = 0, \quad \text{and} \quad u_2^s = \frac{qaP - 2hb}{q(aP + 2h)}, \quad R_2^s = \frac{qaP - 2hb}{aq + ab}. \tag{8.4}$$

There exists a strictly positive steady state if and only if $qaP > 2hb$ which implies

$$b_1 b_2 < \frac{a_1 a_2 P}{2h} , \qquad \text{i.e.,} \qquad 2b_1 b_2 h < a_1 a_2 P . \tag{8.5}$$

Theorem 8.1. *Under the case of infinite diffusion, if (8.5) is satisfied, there exist a strictly positive solution (u_2^s, R_2^s) and the trivial solution (u_1^s, R_1^s) of (8.2), which are shown in (8.4), the solution (u_2^s, R_2^s) is asymptotically (exponentially) stable while the trivial solution is unstable. If the inequality in (8.5) holds in the opposite direction, then there is only trivial solution and no positive solution.*

Proof. Denote

$$F(u, R) = \frac{aR(1-u)}{2h} - u$$

and

$$G(u, R) = qu(P - R) - bR,$$

then the Jacobian matrix is computed as

$$J = \frac{\partial(F, G)}{\partial u \partial R}\Big|_{(u_2^s, R_2^s)} = \left\{ \begin{array}{cc} -\dfrac{aR}{2h} - 1 & \dfrac{a}{2h}(1-u) \\ & \\ q(P-R) & -qu - b \end{array} \right\}_{(u_2^s, R_2^s)}$$

That is,

$$J = \left\{ \begin{array}{cc} \dfrac{-q(aP+2h)}{2h(q+b)} & \dfrac{a(q+b)}{q(aP+2h)} \\ \\ \dfrac{q(aP+2h)b}{a(q+b)} & \dfrac{-aP(q+b)}{aP+2h} \end{array} \right\}.$$

Compute the eigenvalue of J, that is, put $|\lambda I - J| = 0$, where I is the identity matrix, and solve the values of λ.

From $|\lambda I - J| = 0$, the following is obtained

$$\lambda^2 + [\frac{q(aP+2h)}{2h(q+b)} + \frac{aP(q+b)}{aP+2h}]\lambda + \frac{aPq(aP+2h)(q+b)}{2h(q+b)(aP+2h)} - b = 0 \tag{8.6}$$

Consider

$$\begin{aligned} \Lambda = & \ [\frac{q(aP+2h)}{2h(q+b)} + \frac{aP(q+b)}{aP+2h}]^2 - 4[\frac{qaP}{2h} - b] \\ \leq & \ [\frac{q(aP+2h)}{2h(q+b)} + \frac{aP(q+b)}{aP+2h}]^2, \qquad \text{since } 2hb < qaP \end{aligned}$$

and on the other hand it can be also rewritten as

$$\Lambda = [\frac{q(aP+2h)}{2h(q+b)} - \frac{aP(q+b)}{aP+2h}]^2 + 4b > 0,$$

which implies that

$$\sqrt{\Lambda} > |\frac{q(aP+2h)}{2h(q+b)} - \frac{aP(q+b)}{aP+2h}|.$$

Thus, by above two inequality results, the roots of (8.6) are

$$\lambda_1 = -\frac{1}{2}\frac{q(aP+2h)}{2h(q+b)} - \frac{1}{2}\frac{aP(q+b)}{aP+2h} + \frac{1}{2}\sqrt{\Lambda} < 0,$$

and

$$\lambda_2 = -\frac{1}{2}\frac{q(aP+2h)}{2h(q+b)} - \frac{1}{2}\frac{aP(q+b)}{aP+2h} - \frac{1}{2}\sqrt{\Lambda} < 0,$$

Therefore, according to fundamental theorems in ODE, the positive steady state (u_2^s, R_2^s) is asymptotically stable when (8.5) is satisfied.

But for the Jacobian matrix in $(u, R) = (0, 0)$, the following form is obtained

$$J = \frac{\partial(F,G)}{\partial u \partial R}|_{(u_1^s, R_1^s)} = \left\{ \begin{array}{cc} -1 & \frac{a}{2h} \\ \\ qP & -b \end{array} \right\}$$

which has two eigenvalues

$$\bar{\lambda}_1 = -\frac{b+1}{2} - \sqrt{\frac{qaP}{2h} - b + (\frac{b+1}{2})^2}, \quad \bar{\lambda}_2 = -\frac{b+1}{2} + \sqrt{\frac{qaP}{2h} - b + (\frac{b+1}{2})^2}.$$

Obviously when (8.5) is satisfied, $\bar{\lambda}_1 < 0$ and $\bar{\lambda}_2 > 0$, then the steady state $(0, 0)$ is unstable. □

Remark 8.2. *If the inequality (8.5) becomes the equality* $2b_1b_2h = a_1a_2P$*, then it will give the critical value for related parameters. For example, take the parameter* b_2 *as the varying parameter, then the critical value* b_2^{crit} *will be given by*

$$b_2^{crit} = \frac{a_1a_2P}{2b_1h} \tag{8.7}$$

which is a transcritical bifurcation point when a_1, a_2, b_1, *and* h *are finite and strictly positive constants.*

8.2 Bifurcation on the Kinase Activity Model with Finite Diffusion - Case of Center Symmetry

In the case of finite diffusion, (8.2) can transform into (2.9). Then the steady state equation (2.10) is considered again but under the classical sense so as to give more detailed analysis.

In this case, we mean that the kinase concentration is only related to the argument z but not to ρ and θ. Then with the notation

$$u'' = \frac{d^2u}{dz^2},$$

the equation becomes

$$u'' - cu = 0.$$

By the result [Equation 130, 17], the solution is

$$u = c_1 e^{\alpha_0 z} + c_2 e^{-\alpha_0 z}, \qquad \alpha_0 = \sqrt{c}. \tag{8.8}$$

Then, the boundary conditions are rewritten as

$$D_\nu u - \frac{\alpha}{u+\tau} u(1-u) = 0, \quad z = h, \qquad D_\nu u = 0, \quad z = -h.$$

And from the later one, i.e.,

$$u'(-h) = 0.$$

the following can be reached

$$\alpha_0 c_1 e^{-\alpha_0 h} - \alpha_0 c_2 e^{\alpha_0 h} = 0, \qquad \text{i.e} \quad c_1 = c_2 e^{2\alpha_0 h}.$$

Plug the result into u, there holds

$$u = c_2 e^{\alpha_0 h}[e^{\alpha_0(z+h)} + e^{-\alpha_0(z+h)}]$$

Then by use of the boundary condition

$$D_\nu u - \frac{\alpha}{u+\tau} u(1-u) = 0, \quad z = h.$$

there is

$$c_2 = \frac{(\alpha - \tau\alpha_0)e^{2\alpha_0 h} + (\alpha + \tau\alpha_0)e^{-2\alpha_0 h}}{(e^{3\alpha_0 h} + e^{-\alpha_0 h})[(\alpha + \alpha_0)e^{2\alpha_0 h} + (\alpha - \alpha_0)e^{-2\alpha_0 h})]}$$

Thus the solution is obtained

$$u(z) = \frac{(\alpha - \tau\alpha_0)e^{2\alpha_0 h} + (\alpha + \tau\alpha_0)e^{-2\alpha_0 h}}{[(\alpha + \alpha_0)e^{2\alpha_0 h} + (\alpha - \alpha_0)e^{-2\alpha_0 h}]\cosh(2\alpha_0 h)} \cosh(\alpha_0(z+h))$$

From above expression, put

$$(\alpha - \tau\alpha_0)e^{2\alpha_0 h} + (\alpha + \tau\alpha_0)e^{-2\alpha_0 h} = 0$$

which gives

$$\frac{\alpha}{\tau} = \frac{\alpha_0(e^{2\alpha_0 h} - e^{-2\alpha_0 h})}{e^{2\alpha_0 h} + e^{-2\alpha_0 h}} = \frac{\alpha_0(e^{4\alpha_0 h} - 1)}{e^{4\alpha_0 h} + 1}.$$

And referring to (2.11) and (8.8) for the notations, we get the following equality

$$d_1 b_2 = \frac{a_1 a_2 P}{\sqrt{\frac{b_1}{d_1}}} \left(1 + \frac{2}{-1 + e^{4h\sqrt{\frac{b_1}{d_1}}}}\right). \tag{8.9}$$

Denote

$$b_2^{crit} = \frac{a_1 a_2 P}{d_1 \sqrt{\frac{b_1}{d_1}}} \left(1 + \frac{2}{-1 + e^{4h\sqrt{\frac{b_1}{d_1}}}}\right). \tag{8.10}$$

Theorem 8.3. *When other parameters are finite and strictly positive, there exists a critical value b_2^{crit} for parameter b_2 defined in (8.10). For model (2.10), when $b_2 < b_2^{crit}$, there exist the trivial solution which is unstable and a strictly positive solution which is stable, and when $b_2 > b_2^{crit}$, mathematically there exist the trivial solution which is stable and a strictly negative solution (no biological meaning) which is unstable.*

This is a special case of the result in next section 8.4.

8.3 Series Representation of the Solution on the Kinase Activity Model with Finite Diffusion - Case of Axial Symmetry

Since the boundary conditions in model (2.10) are independent of the argument θ in cylindrical coordinates, then it is enough to consider only the axially symmetric solution. That is, the solution of (2.10) is only the function of cylindrical coordinate arguments ρ and z but not that of θ.

Consider the model (2.10) copied below

$$\begin{cases} -\Delta u + cu = 0, & x \in \Omega \\ \\ D_\nu u - \dfrac{\alpha u(1-u)}{\tau + u} = 0, & x \in \Sigma^{top}, \\ \\ D_\nu u = 0, & x \in \Gamma. \end{cases} \tag{8.11}$$

Obviously, the trivial function $u \equiv 0$ is a solution.

If $u \neq 0$ almost everywhere, then by the definition of space W in (3.11), this solution will lies in W. And by Theorem 3.9, it can be represented in series form of Steklov eigenfunctions. That is, by (3.16) and (3.34), the solution of (8.11) has the following expression

$$u(\rho, z) = \sum_{n=1}^{\infty} C_n J_0(x_n \rho) \cosh[\sqrt{x_n^2 + c}(z + h)] \tag{8.12}$$

where x_n is the nth nonnegative root of $J'(x) = 0$ (Refer to (3.28)) and if let $C_n^* = J_0(x_n)^2 \sqrt{x_n^2 + c}\sinh[2h\sqrt{x_n^2 + c}\ ]$, the coefficient C_n in (8.12) has the form

$$C_n = 2(C_n^*)^{-1} \int_0^1 \frac{\alpha u(\rho, h)(1 - u(\rho, h))}{\tau + u(\rho, h)} J_0(x_n \rho) \rho d\rho \tag{8.13}$$

which in fact can be approximately computed in classical form by employing the nonlinear boundary conditions in (8.11).

Next step is to consider and determine the relation among coefficients in (8.12) by use of relevant tricks and the boundary conditions in the second equation of

(8.11).

The boundary equation in (8.11) can be rewritten as

$$\tau D_\nu u - \alpha u + (D_\nu u)u + \alpha u^2 = 0$$

and after rearrangement of the terms, it reads

$$(D_\nu u)u + \alpha u^2 = \alpha u - \tau D_\nu u. \tag{8.14}$$

Notice that

$$\frac{d}{dx}\cosh(x) = \sinh(x); \qquad \frac{d}{dx}\sinh(x) = \cosh(x).$$

And plug (8.13) into (8.14), the following is obtained

$$\begin{aligned}(\sum_{n=1}^{\infty} J_0(x_n\rho)\tilde{x}_n C_n \sinh(2\tilde{x}_n h))(\sum_{n=1}^{\infty} J_0(x_n\rho) C_n \cosh(2h\tilde{x}_n))\\ + \alpha(\sum_{n=1}^{\infty} C_n J_0(x_n\rho)\cosh(2\tilde{x}_n h))^2\\ = \sum_{n=1}^{\infty} J_0(x_n\rho) C_n[\alpha\cosh(2h\tilde{x}_n) - \tau\tilde{x}_n \sinh(2h\tilde{x}_n)].\end{aligned} \tag{8.15}$$

here conveniently $\tilde{x}_n = \sqrt{x_n^2 + c}$ for any $n = 0, 1, 2, \cdots$

Note the following properties of Bessel functions [Proposition 3.2.6, 15]

$$\int_0^1 J_m(\rho x_{n_1}) J_m(\rho x_{n_2})\rho d\rho = 0, \quad \text{for } n_1 \neq n_2,$$

$$\int_0^1 J_m(\rho x_n)^2 \rho d\rho = \frac{1}{2} J_{m+1}(x_n)^2, \quad \text{for } \beta = 0$$

and

$$\int_0^1 J_m(\rho x_n)^2 \rho d\rho = \frac{[x_n^2 - m^2 + \cot^2(\beta)] J_m(x_n)^2}{2x_n^2}, \qquad \text{for } 0 < \beta \leq \frac{\pi}{2}$$

In our case, $\beta = \pi/2, \quad m = 0$, thus the following holds

$$\int_0^1 J_0(\rho x_{n_1}) J_0(\rho x_{n_2}) \rho d\rho = 0, \quad \text{for } n_1 \neq n_2, \tag{8.16}$$

and

$$\int_0^1 J_0(\rho x_n)^2 \rho d\rho = \frac{1}{2} J_0(x_n)^2. \tag{8.17}$$

Multiplying the two sides of (8.15) by ρ respectively and then integrating about argument ρ from 0 to 1, by use of (8.16) and (8.17), the following is obtained

$$\begin{aligned} \sum_{n=1}^{\infty} \frac{1}{2} J_0(x_n)^2 [\tilde{x}_n \sinh(2h\tilde{x}_n) \cosh(2h\tilde{x}_n) + \alpha \cosh^2(2h\tilde{x}_n)] C_n^2 \\ = \sum_{n=1}^{\infty} (\int_0^1 J_0(x_n \rho) \rho d\rho) [\alpha \cosh(2h\tilde{x}_n) - \tau \tilde{x}_n \sinh(2h\tilde{x}_n)] C_n \quad . \end{aligned} \tag{8.18}$$

Then above equation (8.18) on infinite series just determines the values of coefficients $\{C_n\}$ of the solution (8.12).

It is almost impossible to get the accurate value of those coefficients.

However, in practice, the method of Galerkin approximation by Steklov expansion can be used to get the approximate value, which needs to solve some system related to n-parameters $C_1, C_2, \cdots, C_n$ directly.

That is, the expression

$$u_M(\rho, z) = \sum_{j=1}^{M} C_j s_j(\rho, z) \tag{8.19}$$

approximates and replaces the true solution u in the model. Then there holds

$$\begin{cases} -\Delta u_M + u_M = 0, & x \in \Omega \\ D_\nu u_M - \dfrac{\alpha u_M(1-u_M)}{\tau + u_M} = 0, & x \in \Sigma^{top}, \\ D_\nu u = 0, & x \in \Gamma. \end{cases} \tag{8.20}$$

Multiplying two sides of the first equation by s_i in above system and then integrating each terms on Ω, the following is obtained

$$\int_\Omega -\sum_{j=1}^{M} C_j \Delta s_j s_i dx + \int_\Omega \sum_{j=1}^{M} C_j s_j s_i dx = 0.$$

By Gaussian theorem, in further, there holds

$$\int_\Omega -D_\nu u_M s_i dx + \int_\Omega \sum_{j=1}^{M} C_j \nabla s_j \nabla s_i dx + \int_\Omega \sum_{j=1}^{M} C_j s_j s_i dx = 0.$$

Then thanks to the boundary condition and the c-norm orthogonality of $\{s_j\}_{j=1}^{\infty}$

the equality becomes

$$C_i\delta_i \int_{\Sigma^{top}} \rho s_i(\rho,h)^2 d\rho d\theta = \int_{\Sigma^{top}} \frac{\alpha u_M(\rho,h)(1-u_M(\rho,h))}{\tau + u_M(\rho,h)} s_i(\rho,h)\rho d\rho d\theta$$

It is simplified again as

$$C_i\delta_i \int_0^1 \rho s_i(\rho,h)^2 d\rho = \int_0^1 \frac{\alpha u_M(\rho,h)(1-u_M(\rho,h))}{\tau + u_M(\rho,h)} s_i(\rho,h)\rho d\rho \tag{8.21}$$

By the property (8.17) and results in (3.34) (3.35) (3.36)

$$s_n = J_0(\rho x_n)\cosh((z+h)(x_n^2+c)^{\frac{1}{2}}), \qquad \delta_n = \tilde{x}_n \tanh(2h\tilde{x}_n),$$

the previous equations (8.21) become

$$C_i = \frac{2}{J_0(x_i)^2\cosh(2\tilde{x}_i h)^2\delta_i} \int_0^1 \frac{\alpha u_M(\rho,h)(1-u_M(\rho,h))}{\tau + u_M(\rho,h)} s_i(\rho,h)\rho d\rho \tag{8.22}$$

with $\tilde{x}_i = (x_i^2+c)^{\frac{1}{2}}$ and $\{\delta_i\}_{i=1,2,\cdots,M}$ computed in (3.35). Above equations consist of M equations with M unknown variables $\{C_j\}_{j=1}^{M}$. To solve above equations further, the numerical method can be used to compute the integral in the right-hand side of (8.22) since the Bessel functions are developed in the software *Mathematica*.

Another way is to use the finite series form to replace the integrand approximately if the parameter $\tau^{-1} < 1$, i.e., $q/b < 1$.

The first linear approximation to the integrand is $\alpha u_M/\tau$. When $q/b << 1$, this approximation will have certain accuracy. And the equations (8.22) will become the linear algebra equations about M unknown parameters $C_1, C_2, \cdots, C_M$.

The second approximation is replacing the integrand by

$$\frac{\alpha}{\tau}u_M - \frac{\alpha(1+\tau)}{\tau^2}u_M^2,$$

since

$$\frac{\alpha u(1-u)}{\tau+u} = \frac{\alpha}{\tau}u - \frac{\alpha(1+\tau)}{\tau^2}u^2 + \sum_{n=3}^{\infty}\alpha(1+\tau)\tau^{-n}(-1)^{n-1}u^n$$

In this case, there will appear the quadratic terms of C_i, i.e., C_i^2.

8.4 Bifurcation on the Kinase Activity Model with Finite Diffusion - Case of Axial Symmetry

As the results in previous sections show, there probably exists a positive nontrivial solution represented in series for the equation with nonlinear boundary conditions. In this section, the investigation is put on the critical value of the biology parameters in (2.10). It is enough to analyze the linearized steady state equation to give the critical value b_2^{crit} of b_2, which is pointed out by Kazmierczak & Lipniacki [4]. That is, the following linearized equation of (2.10) in general case (axially symmetric case) is considered so as to obtain the critical values related to biological parameters,

$$\begin{cases} -\Delta u + cu = 0, & (x,y,z) \in \Omega \\ D_\nu u - \dfrac{\alpha}{\tau} u = 0, & (x,y,z) \in \Sigma^{top}, \\ D_\nu u = 0, & (x,y,z) \in \Gamma, \end{cases} \tag{8.23}$$

where the parameters satisfy (Refer to (2.11))

$$\frac{\alpha}{\tau} = \frac{a_1 a_2 P}{d_1 b_2}, \qquad c = \frac{b_1}{d_1} \tag{8.24}$$

Definition

The value b_2^{crit} is called the critical value of b_2 when it is the smallest value for which the steady-state solution of (8.23) is unstable.

If the relevant linear operator has all positive eigenvalues, then the solution of (8.23) is stable, which tells that by considering the smallest eigenvalue of the operator in (8.23) the critical value can be obtained.

Consider the eigenvalue problem under the classical sense

$$\begin{cases} -\Delta u + cu = \delta u, & (x,y,z) \in \Omega, \\ D_\nu u - \dfrac{\alpha}{\tau} u = 0, & (x,y,z) \in \Sigma^{top}, \\ D_\nu u = 0, & (x,y,z) \in \Gamma. \end{cases} \tag{8.25}$$

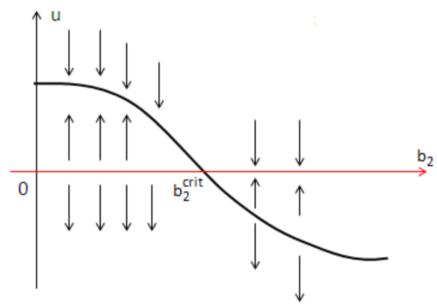

Figure 8.1: Diagram on Parameter b_2

the following theorem in term of original biological parameters is obtained.

Theorem 8.4. *There exists a critical bifurcation value b_2^{crit} defined in (8.26) for parameter b_2. When $b > b_2^{crit}$, then the zero solution to (2.10) is the asymptotically stable state for the corresponding evolutionary equation (2.9). When $0 < b_2 < b_2^{crit}$, the zero solution of (2.10) has lost the stability and there exists at least one strictly positive solution u^+ which can have the series form as shown in (8.12).*

$$b_2^{crit} = \frac{a_1 a_2 P(1 + e^{4h\sqrt{\frac{b_1}{d_1}}})}{d_1\sqrt{\frac{b_1}{d_1}}(-1 + e^{4h\sqrt{\frac{b_1}{d_1}}})} \tag{8.26}$$

Proof. As usual, suppose there is the nonzero solution of separable variable as $u(\rho, z) = \Phi(\rho)Z(z)$. Plug into first equation and separate the variables, and use the transformation of rectangular coordinate into cylindrical coordinate

$$x = \rho\cos(\theta), \quad y = \rho\sin(\theta), \quad z = z$$

with the domain

$$0 \le \rho \le 1, \qquad 0 \le \theta \le 2\pi, \qquad -h \le z \le h.$$

Then the first equation in (8.25) can be written as

$$\Phi''(\rho)Z(z) + \frac{1}{\rho}\Phi'(\rho)Z(z) + \Phi(\rho)Z''(z) - c\Phi(\rho)Z(z) - \delta\Phi(\rho)Z(z) = 0,$$

that is,

$$\frac{\Phi''(\rho)}{\Phi(\rho)} + \frac{1}{\rho}\frac{\Phi'(\rho)}{\Phi(\rho)} + \frac{Z''(z)}{Z(z)} - c - \delta = 0. \tag{8.27}$$

By separating of variables, the following two equations are obtained

$$\frac{Z''(z)}{Z(z)} = -v,$$

which is equivalent to

$$Z''(z) + vZ(z) = 0. \tag{8.28}$$

and

$$\Phi''(\rho) + \frac{1}{\rho}\Phi'(\rho) + (\delta - v - c + \frac{0}{\rho^2})\Phi(\rho) = 0. \tag{8.29}$$

Comparing (8.29) with Eq.(3.2.1) of [14], the parameters corresponding to those in [14] can be listed as

$$d = 2, \quad \lambda = \delta - c - v, \quad m = \sqrt{\mu} = 0, \quad \gamma = m = 0.$$

If $\lambda = \delta - c - v > 0$, according to the result in [14], the solution is

$$R(\rho) = J_0(\sqrt{\lambda}\rho) = a_0(1 + \sum_{n=1}^{\infty} \frac{(-1)^n(\sqrt{\lambda}\rho)^{2n}}{2^{2n}(n!)^2})$$

Denote $x_n = \sqrt{\lambda}$ and by the second boundary condition $D_\nu u = 0$ when $(x, y, z) \in \Sigma_1$, x_n should be the nonnegative zeros of

$$\cos(\beta)J_0(x_n) + \sin(\beta)x_n J_0'(x_n) = 0, \quad \beta = \frac{\pi}{2}. \tag{8.30}$$

(Refer to Proposition 3.2.6 of [14]). And $\{J_0(x_n)\}$ forms a basis in the space $C(0, 1)$ composed of continuous or piecewise continuous functions defined in $[0, 1]$.

For other boundary conditions, they are on $Z(z)$ of (8.28). The equations become

$$\begin{cases} Z''(z) + vZ(z) = 0, & \\ Z'(z) = 0, & z = -h, \\ Z'(z) - \dfrac{\alpha}{\tau}Z(z) = 0, & z = h \end{cases} \tag{8.31}$$

where $v = \delta - x_n^2 - c$.

Then it can be separated into three cases. Case 1, if $v = 0$, easily known from the boundary condition, it can not happen. Case 2, if $v > 0$, then it can be known that $\delta > 0$ always holds. In this case, it is impossible to say anything about the critical value. Thus, it is only needed to consider the case of $v < 0$. In this case, with boundary condition in the second equation of (8.31), the solution to the first equation of (8.31) has the form as

$$Z(z) = c_2 e^{\tilde{x}_n h}(e^{\tilde{x}_n(z+h)} + e^{-\tilde{x}_n(z+h)}) = D\cosh(\tilde{x}_n(z+h)), \tag{8.32}$$

where $\tilde{x}_n = \sqrt{x_n^2 + c - \delta}$.

Then now the boundary condition in the third equation is employed to determine the relation of parameters.

Plug (8.32) into the third equation of (8.31), the equation is obtained

$$(\tilde{x}_n - \eta)e^{2h\tilde{x}_n} = (\tilde{x}_n + \eta)e^{-2h\tilde{x}_n} \tag{8.33}$$

or its another form

$$e^{4h\tilde{x}_n} = 1 + \frac{2\eta}{\tilde{x}_n - \eta} \tag{8.34}$$

where

$$c = \frac{b_1}{d_1}\ , \qquad \eta = \frac{\alpha}{\tau} = \frac{a_1 a_2 P}{d_1 b_2} \tag{8.35}$$

(Refer to (2.11)) and $\tilde{x}_n = \sqrt{x_n^2 + c - \delta}$. In fact, the equation (8.34) should be written as

$$e^{4h\sqrt{x_n^2+c-\delta_n}} = 1 + \frac{2\eta}{\sqrt{x_n^2 + c - \delta_n} - \eta} \tag{8.36}$$

to show the correspondence of δ_n to x_n. More explicitly, (8.36) becomes

$$e^{4h\sqrt{x_n^2+\frac{b_1}{d_1}-\delta_n}} = 1 + \frac{2a_1a_2P}{d_1b_2\sqrt{x_n^2 + \frac{b_1}{d_1} - \delta_n} - a_1a_2P} \tag{8.37}$$

In the following deductions, only the least nonnegative value x_1 and $\delta_{min} = 0$ play the critical role.

Note that from (8.34) and the Implicit Function Theorem it is known that there is a unique strictly positive solution of $\tilde{x}_n$ which is a function of η. And by the formula of differentiation in the implicit function, the following is obtained

$$\text{if } \eta = 0 \ \text{ then } \tilde{x}_n = 0, \text{ and } \frac{d\tilde{x}_n}{d\eta} = [e^{4h\tilde{x}_n} + \frac{2\eta}{(\tilde{x}_n - \eta)^2}]^{-1} \frac{2\tilde{x}_n}{(\tilde{x}_n - \eta)^2} > 0 \text{ as } \tilde{x}_n > 0,$$

which means that $\tilde{x}_n$ is a strictly increasing function of η. In the following, $\tilde{x}_n$ is explicitly expressed as $\tilde{x}_n(\eta)$.

On the other hand, once $\tilde{x}_n$ is determined, the equality holds

$$\delta = x_n^2 + 1 - \tilde{x}_n^2(\eta).$$

The focus is the smallest eigenvalue δ which of course corresponds to the least strictly positive root denoted as x_0 of $J_0'(x) = 0$. That is,

$$\delta_{\min} = x_1^2 + c - \tilde{x}_1^2(\eta). \tag{8.38}$$

If $\delta_{\min} > 0$, then the solution is stable. So the critical value happens at $\delta_{\min} = 0$ and a critical value of η can be obtained and denoted as η_{crit}.

Plug $\delta_{\min} = 0$ and parameters in (8.35) into (8.34), by the known Implicit Function Theorem, the following is reached

$$e^{4h\sqrt{x_1^2+c}} = 1 + \frac{2aPq}{b\sqrt{d}\sqrt{x_1^2+c} - aPq}$$

which gives the critical value of b_2 as

$$b_2^{crit} = \frac{a_1 a_2 P(1 + e^{4h\sqrt{x_1^2+c}})}{d_1\sqrt{x_1^2+c}(-1 + e^{4h\sqrt{x_1^2+c}})} = \frac{a_1 a_2 P(1 + e^{4h\sqrt{c}})}{d_1\sqrt{c}(-1 + e^{4h\sqrt{c}})} \tag{8.39}$$

which is just similar to the formula (8.10) since the least root of (8.30) is $x_1 = 0$.

And it should be noted that $\delta_{\min} > 0$ in (8.38) implies

$$\tilde{x}_1^2(\eta) < x_1^2 + 1$$

which further implies $\eta < \eta_{crit}$ since $\tilde{x}_1(\eta)$ is the increasing function of η and $b_2 > b_2^{crit}$ by noting (8.35).

Thus the conclusions in the theorem are attained. □

Remark 8.5. *Furthermore, if denote $\varepsilon = d_1^{-1}$ and consider δ_{min} as the function of ε by Implicit Function Theorem. From (8.37), one can obtain*

(1) when $\varepsilon \to 0$, $\delta_{min} \to 0$, this is, $\delta_{min}(0) = 0$

(2) when $\varepsilon \to 0$,

$$\frac{\delta_{min}(\varepsilon)}{\varepsilon} \to b_1 - \frac{a_1 a_2 P}{2b_2 h}$$

which implies that

$$\delta'_{min}(\varepsilon)|_{\varepsilon=0} = b_1 - \frac{a_1 a_2 P}{2b_2 h}.$$

(3) this fact shown by (1) and (2) tells that

$$b_1 - \frac{a_1 a_2 P}{2b_2 h} = 0$$

is the critical equation under the condition that d_1 is infinite.

When

$$b_1 - \frac{a_1 a_2 P}{2b_2 h} < 0, \qquad i.e \quad b_2 < \frac{a_1 a_2 P}{2b_1 h},$$

δ_{min} *is a decreasing function of* ε*. That is, when* $0 < d_1 < \infty$*,* $\delta_{min} < 0$ *and the trivial solution is unstable and there must exist a strictly positive solution. And when*

$$b_1 - \frac{a_1 a_2 P}{2b_2 h} > 0, \qquad i.e \quad b_2 > \frac{a_1 a_2 P}{2b_1 h},$$

δ_{min} *is an increasing of* ε*. That is, when* $0 < d_1 < \infty$*,* $\delta_{min} > 0$*, the trivial solution is stable.*

In other words, when $b_2 < a_1 a_2 P/(2b_1 h)$ *and* d_1 *large enough, the equation (2.9) has the trivial solution which is unstable and a strictly positive solution* u^+ *which is stable. When* $d_1 \to \infty$*, the equation (2.9) degenerates to an ordinary differential system and it also has the unstable trivial solution and a positive stable solution.*

when $b_2 > a_1 a_2 P/(2b_1 h)$ *and* d_1 *large enough, the equation (2.9) has only one sensible trivial solution which is stable and there is no strictly positive solution. When* $d_1 \to \infty$*, the equation (2.9) degenerates to an ordinary differential system and it also has only one sensible trivial solution which is stable.*

Those results just conform to the conclusions in Theorem 8.1 and Remark 8.2.

Remark 8.6. *Note that* b_2 *is the receptor dephosphorylation coefficient which controls the receptor inactivation and is referred to as phosphatase activity. Intuitively, the higher is the phosphatase activity the lower is cell activity, and for sufficiently high* b_2 *(and other parameters fixed) cell may not be activated [3-4]. Our results in Theorem 8.4 have just mathematically verified this intuition.*

Remark 8.7. *The equation (8.37) plays a crucial role in the bifurcation analysis* *near the trivial solution, from which one can employ the bifurcation about any one of other parameters and even the combined bifurcation about two parameters. One can give the bifurcation results when varying the parameter h (which measures the size of the cell) based on the equation (8.37). In this respect, Auchmuty has provided treatment in detail, please refer to his article [18].*

Remark 8.8. *In Theorem 8.1, Theorem 8.3 and Theorem 8.4, the explicit critical values b_2^{crit} have been provided mathematically as a function of other parameters. However in article [4], the authors have only provided the critical value in the spherically symmetric solution of the kinase activity model with only single type of boundary conditions.*

Remark 8.9. *The results above show that the bifurcation direction is similar to those in [4] even though the shapes of the cells are different and the boundary conditions are different. Thus our results together with the existing work in [3] and [4] can give the partial support of the conjecture that for any shape of cells, say even the cell in shape of an ellipse or a rugby ball, the kinase activity modes should be similar. That is, they will have the same properties of the kinase diffusion and share similar bifurcation diagram on the solution of the models.*

Chapter 9

Parameter Analysis and Biological Implications

In this chapter, the parameter analysis is provided based on the results of Theorems 8.1, 8.3 and 8.4 in previous chapters.

Proposition 9.1. *For the finite diffusion case, by (8.10) and (8.39), b_2^{crit} is a decreasing function on the diffusion parameter d_1 and $b_2^{crit} \to \infty$ when $d_1 \to 0$.*

This means that as the diffusion becomes weaker, if the initial concentration is strictly positive, then the active kinase has a higher probability to converge to a strictly positive steady state on the whole cell (i.e all the chemical reaction will enter an equilibrium state for this kind of active kinases) and has a lower probability to go to the trivial steady state (i.e., zero concentration). This observation also means that if one wants to weaken or stop some biochemical reaction related to this active kinase, one just makes the diffusion stronger.

Proposition 9.2. *In the axially symmetric case, the critical value of b_2 is a decreasing function of the cylinder height $2h$.*

Proof. It is easy to get

$$\frac{db_2^{crit}}{dh} < 0.$$

$\square$

In biology, this observation in our model implies that when the cell length is short, the active kinase concentration can keep a higher probability to converge to a strictly positive steady state.

Proposition 9.3. *b_2^{crit} is the growing function of the polarity coefficient i if the receptor has the distribution in the top plate as below*

$$P = P_i(\rho) = \begin{cases} (1+i)(1-\rho)^i, \ 0 \le \rho \le 1 & \text{if } z = h \\ 0, & \text{if } -h \le z < h. \end{cases}$$

(This kind of distribution gives the total amount of receptors, which is fixed and equals to π and more receptors lie in the center of the plate.)

Proof. From (8.30), it can be found that

$$b_2^{crit} = \frac{a_1 a_2 P_i(\rho)(1 + e^{4h\sqrt{c}})}{d_1\sqrt{c}(-1 + e^{4h\sqrt{c}})}$$

Take the maximum of $P_i = 1 + i$, we have

$$b_2^{crit} = \frac{a_1 a_2 (i+1)(1 + e^{4h\sqrt{c}})}{d_1\sqrt{c}(-1 + e^{4h\sqrt{c}})}$$

As $i \to \infty$, b_2^{crit} will increase to infinity. $\square$

This implies that as the polarity increases there is more possibility of the active kinase to diffuse, particularly in the neighbourhood of top plate center and it attains a strictly steady state when it goes to the other endpoint or the cell center.

Chapter 10

Discussions and Future Directions

In this thesis, the representation of the solution to the kinase activity model in the cell of finite cylinder is considered . This kind of series representation can give a thorough treatment of the properties on the concentration of the active kinase with mixed boundary conditions. And also certain bifurcation analysis is provided with the critical value. By knowing this value, the kinase concentration in the cell can be controlled by adjusting the environment of the cell.

Because the models in this work are related to three dimensions, the qualitative analysis to them has certain challenge. Currently, there is a little work to give the direct bifurcation analysis in mathematics when the boundary conditions are mixed and nonlinear. Most of them are applying the numerical methods to consider the bifurcation. The work in this thesis just has given an attempt to present the strict mathematical investigation of this kind of models. The results have shown the similar bifurcation diagram but the solution has more complicated form than those in the spherical cell.

In the future, the strict bifurcation analysis is needed to consider when other parameters vary. And also it will be very interesting to consider the model when the cell has the shape of the ellipse and even the rugby ball.

Appendix

APPENDIX A

Theorem A1 Assume that $f(x)$ satisfies the Lipschitz condition, i.e

$$|f(x) - f(y)| \leq L(B)|x - y|, \forall x, y \in B,$$

where B is a bounded set . Then there exists a $T = T(x_0)$ such that the equation

$$\frac{dx}{dt} = f(x), \qquad x(0) = x_0$$

has a unique solution on $[0, T]$.

Theorem A2 Let $f(x)$ be a continuous function. Then there exists a $T > 0$ such that the equation

$$\frac{dx}{dt} = f(x), \qquad x(0) = x_0$$

has at least one solution on $[0, T]$.

The proof of this lemma can be obtained if the solution is approximated by a sequence of solutions of uniformly Lipschitzian equations, for which the Theorem A1 guarantees a solution (Refer to [13]).

Theorem A3 (Alaoglu weak-$*$ compactness). Let X be a Banach space and let f_n be a bounded sequence in X^*. Then f_n has a weakly-$*$ convergent subsequence . Particularly, if X is a reflexive Banach space and x_n is a bounded sequence in X, then x_n has a subsequence that convergent weakly in X (Refer to Yosida [14]).

Theorem A4 ([6, 14]) Let V be a Hilbert space and V^* its dual. If $g \in L^p(0,T;V^*), (1 \le p < \infty)$, then the following two statements are equivalent:
(i) $g = 0$ in $L^p(0,T;V^*)$
(ii) For $\forall\ v \in V$, $\langle g(t), v\rangle = 0$ for almost every $t \in [0,T]$.

Theorem A5 Suppose that $u \in L^2(0,T;V)$, and $\dfrac{du}{dt} \in L^2(0,T;V^*)$, then u is continuous (or except a set of zero measure) from [0, T] into $L^2(\Omega)$, with

$$\sup_{t\in[0,T]} |u(t)| \le C(||u||_{L^2(0,T;V)} + ||\frac{du}{dt}||_{L^2(0,T;V^*)}),$$

and

$$\frac{d}{dt}|u|^2 = 2\langle \frac{du}{dt}, u\rangle$$

for almost every $t \in [0,T]$, that is,

$$|u(t)|^2 = |u_0|^2 + 2\int_0^t \langle \frac{du}{dt}(s), u(s)\rangle ds.$$

About this theorem, please refer to Temam [6, 15].

Theorem A6 (Riesz Representation Theorem) For any Hilbert space H, the dual space $H^* \simeq H$ can be obtaind. Particularly, for every $x \in H$, $l_x(y) = (x,y)$ is bounded and has norm $||l_x||_{H^*} = ||x||$. Furthermore, for every bounded linear functional $l \in H^*$, there exists a unique $x_l \in H$ such that for all $y \in H$ $l(y) = (x_l, y)$, and $||x_l|| = ||l||_{H^*}$. It follows that $l \mapsto x_l$ is continuous. Please refer to [16] or [17].

Proofs on the existence of the solution of (4.1) related to the steps from (4.2) to (4.4)

UNIFORM BOUNDS ON $\{u_n\}$

Take the inner product of (4.4) with u_n to get

$$(\frac{du_n}{dt}, u_n) + (Au_n, u_n) = \langle P_n f, u_n \rangle.$$

Then note that $(Au_n, u_n) = a(u_n, u_n) = ||u_n||_c^2$ and

$$\langle P_n f, u_n \rangle = \langle P_n f/\sqrt{c}, \sqrt{c}u_n \rangle \leq ||P_n f/\sqrt{c}||_* ||\sqrt{c}u_n||.$$

Those can give

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}|u_n|^2 + ||u_n||_c^2 &\leq ||P_n f/\sqrt{c}||_* ||\sqrt{c}u_n|| \\ &\leq \frac{1}{2}(||P_n f/\sqrt{c}||_*^2 + ||/\sqrt{c}u_n||^2) \leq \frac{1}{2}(||P_n f/\sqrt{c}||_*^2 + ||u_n||_c^2). \end{aligned} \tag{A.1}$$

Thus (A.1) further implies that

$$\frac{d}{dt}|u_n|^2 + ||u_n||_c^2 \leq ||P_n f/\sqrt{c}||_*^2 \tag{A.2}$$

Integrate (A.2), the following holds

$$|u_n(T)|^2 + \int_0^T ||u_n(t)||_c^2 dt \le |u_n(0)|^2 + \int_0^T ||P_n f(t)/\sqrt{c}||_*^2 dt$$

By the assumptions, $f/\sqrt{c} \in L^2_{loc}(0,\infty;V^*)$(i.e., $f \in L^2(0,T;V^*), \quad \forall T < \infty$) (Refer to the Comments under condition (C2)) and (by Lemma B1 in Appendix B)

$$|u_n(0)| = |P_n u_0| \le u_0, \quad ||P_n f/\sqrt{c}||_* \le ||f/\sqrt{c}||_* \quad . \tag{A.3}$$

The inequality holds as

$$|u_n(T)|^2 + \int_0^T ||u_n(t)||_c^2 dt \le |u(0)|^2 + \int_0^T ||f(t)/\sqrt{c}||_*^2 dt, \tag{A.4}$$

a bound that is uniform in n.

Those two bounds contained in (A.4) tell that $\{u_n\}$ is uniformly bounded respectively in the two space

$$L^\infty(0,T;L^2(\Omega)) \quad \text{and} \quad L^\infty(0,T;V), \qquad \forall T > 0$$

To show that u is continuous into $L^2(\Omega)$, using Theorem A5, it is needed to obtain a bound on $\dfrac{du}{dt}$ in $L^2(0,T;V^*)$. Therefore the work with $\dfrac{du_n}{dt}$ is needed to show that a uniform bound can be found for this sequence. In fact,

$$\frac{du_n}{dt} = -Au_n + P_n f.$$

It is known that $P_n f \in L^2(0,T;V^*)$ and $Au_n \in L^2(0,T;V^*)$ too, since $u_n \in$

$L^2(0,T;V)$ and A is a bounded linear map from V into V^*. Thus, the following is obtained

$$\frac{du_n}{dt} \quad \text{is uniformly bounded in} \quad L^2(0,T;V^*)$$

EXTRACTION OF AN APPROPRIATE SUBSEQUENCE

In next steps, the Alaoglu compactness theorem and its corollary (Theorem A3) are used to extract a subsequence (which will be relabeled u_n that converges in various different sense).

A). First, u_n is uniformly bounded in $L^2(0,T;V)$, so by extracting a sequence, it can be ensured that

$$u_n \rightharpoonup u \quad \text{in} \quad L^2(0,T;V).$$

B). Also, a uniform bound on $\frac{du_n}{dt}$ in $L^2(0,T;V^*)$ is obtained, so by extracting a second subsequence it can be guaranteed that

$$\frac{du_n}{dt} \rightharpoonup^* \dot{u} \quad \text{in} \quad L^2(0,T;V^*)$$

It is written as $\dot{u}$ because it is not immediately obvious that in fact $\dot{u} = \frac{du}{dt}$ (the weak time derivative).

However, thanks to the definition of the weak-* convergence of $\frac{du_n}{dt}$ to $\dot{u}$, the following limit is obtained

$$\int_0^T \frac{du_n}{dt}(t)\psi(t)dt \to \int_0^T \dot{u}(t)\psi(t)dt, \qquad \forall \psi \in L^2(0,T;V).$$

Now, if $\psi(t) \in C_c^\infty(0,T;V)$, then the left-hand side can be integrated by parts to get

$$\int_0^T \frac{du_n}{dt}(t)\psi(t)dt = -\int_0^T u_n(t)\frac{d\psi}{dt}(t)dt \to -\int_0^T u(t)\frac{d\psi}{dt}(t)dt$$

by use of the weak convergence of u_n to u, since $\frac{d\psi}{dt} \in C_c^\infty(0,T;V) \subset L^2(0,T;V)$.

Then the following holds

$$\int_0^T \dot{u}(t)\psi(t)dt = -\int_0^T u(t)\frac{d\psi}{dt}(t)dt, \quad \forall \psi \in C_c^\infty(0,T;V)$$

and so $\dot{u} = \frac{du}{dt}$ as required. It is known that

$$\frac{du_n}{dt}(t) \rightharpoonup^* \frac{du}{dt}, \quad \text{in} \quad L^2(0,T;V^*).$$

C). To draw the same convergence of Au_n, A as a bounded linear operator from V into V^* is employed, so the weak convergence of u_n to u in $L^2(0,T;V)$ implies weak-* convergence of Au_n to Au in $L^2(0,T;V^*)$:

$$\int_0^T \langle Au_n, \psi\rangle dt = \int_0^T \langle u_n, A\psi\rangle dt \to \int_0^T \langle u, A\psi\rangle dt = \int_0^T \langle Au, \psi\rangle dt, \ \forall \psi \in L^2(0,T;V).$$

D) Finally, to show that $P_n f \rightharpoonup^* f$ in $L^2(0,T;V^*)$, it would be noted that functions of the form

$$\psi = \sum_{j=1}^k \psi_j\theta_j, \quad \psi_j \in V, \ \ \theta_j \in L^2(0,T;R)$$

are dense in $L^2(0,T;V)$. For such ψ

$$\int_0^T \langle P_n f(t), \psi(t)\rangle dt = \int_0^T \langle f(t), P_n\psi\rangle dt = \int_0^T \sum_{j=1}^k \langle f(t), P_n\psi_j\rangle \theta_j(t) dt \quad .$$

Now because $P_n\psi_j \to \psi_j$ in V for each j (see Lemma B1 in Appendix), the last term in above equality converges to

$$\int_0^T \sum_{j=1}^k \langle f(t), \psi_j\rangle \theta_j(t) dt = \int_0^T \sum_{j=1}^k \langle f(t), \psi\rangle dt.$$

This gives weak-* convergence of $P_n f$ to f in $L^2(0,T;V^*)$, and so weak-* convergence holds in $L^2(0,T;V^*)$ of all the terms in (4.5).

MORE PROPERTIES OF THE WEAK SOLUTION

It has been obtaind that

$$\frac{du}{dt} + Au = f \tag{A.5}$$

as an equality in $L^2(0,T;V^*)$, and Theorem A4 shows that this is equivalent to

$$\langle \frac{du}{dt}, v\rangle + a(u,v) = \langle f, v\rangle, \quad \text{for every } v \in V \text{ and almost every } t \in [0,T]$$

Since the limit value u has

$$u \in L^2(0,T;V) \quad \text{and} \quad \frac{du}{dt} \in L^2(0,T;V^*).$$

thanks to Theorem A5, u is actually continuous into $L^2(\Omega):\ u \in C([0,T]; L^2(\Omega))$.

Now, it is still needed to show that $u(0) = u_0$.

By choosing a function $\phi \in C^1([0,T]; V)$ with $\phi(T) = 0$, in the limit equation (A.5), and integrating from 0 to T and then the first integral by parts is done to obtain

$$\int_0^T -(u, \phi') + a(u, \phi) ds = \int_0^T \langle f, \phi \rangle ds + (u(0), \phi(0)) \qquad (A.6)$$

Then it can be done the same in the Galerkin equation (4.4) to obtain

$$\int_0^T -(u_n, \phi') + a(u_n, \phi) ds = \int_0^T \langle P_n f, \phi \rangle ds + (u_n(0), \phi(0)).$$

Then taking the limits in all the terms in above equation, the following equality holds

$$\int_0^T -(u, \phi') + a(u, \phi) ds = \int_0^T \langle f, \phi \rangle ds + (u_0, \phi(0)). \qquad (A.7)$$

since $u_n(0) \to u_0$. Noting that $\phi(0)$ is arbitrary and compare (A.6) and (A.7), $u(0) = u_0$ is obtained as required.

APPENDIX B

Lemma B1 If $X = H^1(\Omega) = V, H^1_R(\Omega)\ L^2(\Omega)$, $X = V^*$, or $(H^1_R(\Omega))^*$, then

$$||P_n u||_X \leq ||u||_X \quad \text{and} \quad P_n u \to u \quad \text{in } X$$

Proof. It only needs to prove the case that $X = V^*$ since other cases are easily drawn from the definition of the projection operator.

In V^*, the norm bound is expressed as

$$||P_n f||_{V^*} = \sup_{||v|| \le 1} |\langle P_n f, v \rangle| = \sup_{||v|| \le 1} |\langle f, P_n v \rangle| \le \sup_{||\omega|| \le 1} |\langle f, \omega \rangle = ||f||_{V^*}$$

Notice that each linear functional $f \in V^*$ corresponds to an element $\varphi \in V$ by use of the Riesz representation theorem (Theorem A6), so that $\langle f, v \rangle = ((\varphi, v)), \ \ \forall v \in V$, here $((\cdot))$ is the inner product defined on V. Now,

$$\langle P_n f, v \rangle - \langle f, v \rangle = \langle f, P_n v - v \rangle = ((\varphi, Q_n v)) = ((Q_n \varphi, v))$$

Thus,

$$|\langle P_n f, v \rangle - \langle f, v \rangle| \le ||Q_n \varphi|| ||v||.$$

Therefore,

$$\sup_{||v||=1} |\langle P_n f - f, v \rangle| \le ||Q_n \varphi||$$

and so tends to zero as $n \to \infty$ since the left-hand side term does. □

This lemma is used in (A.3) and other steps in Chapter 4.

APPENDIX C List of zeros for $J_0'(x) = 0$ from x_7 to x_{80} in precision of 29 digits :

$$
\begin{array}{ll}
22.7600843805927718980530051561, & 25.9036720876183826254958554469 \\
29.0468285349168550666478198838, & 32.1896799109744036266229841045 \\
35.3323075500838651026344790226, & 38.4747662347716151120521975577 \\
41.6170942128144508858635168051, & 44.7593189976528217327793527132 \\
47.9014608871854471212740087225, & 51.0435351835715094687330346332 \\
54.1855536410613205320999662145, & 57.3275254379010107450905042438 \\
60.4694578453474915593987498084, & 63.6113566984812326310397624179 \\
66.7532267340984934153052597500, & 69.8950718374957739697305364355 \\
73.0368952255738348265061175691, & 76.1786995846414575728526146235 \\
79.3204871754762993911844848725, & 82.4622599143735564539866106488 \\
85.6040194363502309659494254934, & 88.7457671449263069037359164349 \\
91.8875042516949852805536222145, & 95.0292318080446952680509981872 \\
98.1709507307907819735377591609, & 101.312661823038730137141056389 \\
104.454365791282760071363428140, & 107.596063259509172182670364278 \\
110.737754780899215108608652888, & 113.879440847594998134884174928 \\
117.021121898892425027576494601, & 120.162798328149003758119407829 \\
123.304470488635718016760032069, & 126.446138698516595697794480496 \\
129.587803245103996753741417841, & 132.729464388509615886774597352 \\
135.871122364789000591801568219, & 139.012777388659704178433546136 \\
142.154429655859029032700908100, & 145.296079345195907232422150855 \\
148.437726620342230395939277026, & 151.579371631401427992783504222
\end{array}
$$

$$
\begin{array}{ll}
154.72101451628595352476655565 2, & 157.86265540193029780509466960 9 \\
161.00429440536199346389341540 9, & 164.14593163464963540213252678 0 \\
167.28756718974408380356484785 8, & 170.42920116322663234774549742 0 \\
173.57083364097592863036704086 3, & 176.71246470276375745529773734 1 \\
179.85409442278838484508490290 6, & 182.99572287015296608408437309 5 \\
186.13735010929550802023984809 5, & 189.27897620037601409322580067 9 \\
192.42060119962570542177113155 5, & 195.56222515966258243078293560 4 \\
198.70384812977705212611810657 9, & 201.84547015619088230499981743 5 \\
204.98709128229234414435873423 0, & 208.12871154885005908148724652 2 \\
211.27033099420776661446279141 0, & 214.41194965446196982870027085 0 \\
217.55356756362418940178479051 0, & 220.69518475376935974481291028 3 \\
223.83680125517172874029155351 0, & 226.97841709642947178848018795 5 \\
230.12003230457909864762476955 7, & 233.26164690520061535434630624 1 \\
236.40326092251430120867342295 1, & 239.54487437946987058125885716 4 \\
242.68648729782870958512982035 6, & 245.82809969823980710755206208 5 \\
248.96971160030993716235251663 3, & 252.11132302266859400103494537 9
\end{array}
$$

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