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Model of the Interaction between Ligand and Receptor in the Brain

Master Thesis

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Abstract

This thesis studies the ligand-receptor interactions from a mathematical viewpoint and shows the change of ligand concentration due to the reciprocal actions between the ligand and the receptors. Adding the diffusion term to the existing model, we come up with our own general model. The dissertation studies the model in one-dimensional and two-dimensional spaces, respectively. We solve four one-dimensional cases with analytical and numerical methods. Those four cases are obtained on the possible permutation of two locations for the receptor compartment and two initial conditions. Three special cases in the two-dimensional space are provided—the first two are radially symmetric and the third one without symmetry. Numerical solutions for all the cases are provided and all the numerical methods are implemented in MATLAB. The numerical simulations, supplemented by the approximation of the real solution, are used to show how the ligand and the receptors interact with each other. All the findings in this thesis describe a quantitative interrelationship between the ligand and the receptors.

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Chapter 1

Introduction

In our brain, there are large quantities of receptors, or proteins, which can trigger a series of physiological reactions when they receive stimuli. These stimuli come from special molecules which have an effect when they form certain compounds with receptors. These small molecules, or ligand, attach to the receptors and send out certain signals, which lead the receptors into triggering a series of biochemical processes. Ligand comes from inside the body or outside. No matter where the ligand comes from, their interactions with the receptors are similar. The receptor-ligand interrelations are critical to numerous biological processes, such as neurotransmission, hormone synthesis and regulation of blood circulation. A clear understanding of those mutual actions can also help us figure out an efficient way to trigger or block specific physiological reactions. Hence, studying these ligand-receptor interactions can be very meaningful.

A number of quantitative methods have been developed to describe the ligand-receptor interaction in the past decade. And a lot of relating researches have been done, such as kinetic and thermodynamic analysis of ligand-receptor mutual actions [8] and protein-ligand complex [9]. A drug is also a kind of ligand and most therapeutic drugs have their effect by interacting with receptors, see [7]. The studying of reciprocal actions between small molecules and proteins has become the basis for an efficient drug-design scheme. Therefore, by having a clear view about these ligand-receptor binding processes, we can discover the most effective way to activate receptors or block them from ligand and consequently improve the efficiency of the medicine.

1.1 Background

The receptors have the potential to trigger physiological processes, but they need to bind with certain ligand to have this effect. The responses of the receptors can be distinct when they are bound to different ligand. To describe this mechanism in a metaphorical manner, imagine a jigsaw puzzle with a piece missing, but that missing piece is so crucial that we could not understand the whole puzzle without it. When the piece with the right shape and size (certain ligand) arrives, the puzzle is solved. A lot of related researches have been done to find the suitable piece, such as Pharmacokinetic-Pharmacodynamic (PK-PD) modeling [6] and receptor-based methods [9]. There are also many protein-based molecular designs focusing on the existing ligand [5]. Furthermore, Pilar et al [1] have shown that receptors binding to specific ligand is the key factor to control and

trigger the signaling transmission.

However, more and more evidence [1, 3, 8] is found which supports the idea that finding the certain ligand for the receptors is not adequate anymore. In addition, there is increasing awareness that the amount of drugs reside at their target also affects their clinical performance [4]. As a result, the importance of ligand-receptor interaction affected by ligand density comes to our attention, and we believe it will guide the search for new pharmaceuticals. This thesis aims to understand the mechanism of receptor-ligand interaction when ligand binding to receptor and forming a compound. Mathematical models of how the ligand concentration has effect on the ligand-receptor response have been thoroughly studied in two papers [3, 4]. These models have revealed interesting features involved in these processes, including the properties of ligand-receptor reciprocal actions and how receptor density affects the ligand concentration when the binding happens. They were only focused on the mechanism between the ligand and the receptors but the diffusion of ligand hadn't been taken into consideration. And these models were based on solving a system of ordinary differential equations (ODEs).

1.2 Model

This dissertation will analyze the ligand-receptor interactions from a quantitative view, and focus on the changes of the ligand and the receptor concentrations due to their reciprocal actions. To begin the study, it is better to have a clear idea about the ligand, the receptor, and how they interact with one another. Ligand is the small molecule which can attach to the receptor and give a certain signal, for example a drug. The receptor can receive the stimuli in the brain and trigger a series of biochemical processes, for instance, being in a good mood, getting rid of exhaustion, or relieving headaches. Based on the physiological experiments [2, 7], several biological behaviors of the ligand and the receptor are known, such as the diffusion of the ligand and the basic binding mechanism between the ligand and the receptor. In our model, we will not only consider the basic mechanism but also the dissemination of the ligand. Therefore, this thesis uses a system of partial differential equations (PDEs) to describe the interaction between the ligand and the receptor, because the ligand concentration depends on time as well as the corresponding distance to the receptor compartment. The general model that will be analysed throughout this thesis is

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d\Delta L - k_{\text{on}} f L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B. \end{cases} \quad (1.1)$$

Here L denotes the concentration of the ligand and B is the bound product of L and R , where R is the concentration of free receptors. The dissemination of the ligand is described as $d\Delta L$ and d is the diffusion coefficient. When d is zero the model is the general model without diffusion, otherwise it is a model with dissemination term. k_c is the rate of the ligand being washed out of the brain. The interaction between the ligand and the receptor consists of two parts: binding and unbinding. k_{on} and k_{off} are the rates of binding and unbinding, respectively. And f is defined as $f = R + B$, which describes the total concentration of the receptors. Based on some extra assumptions, we will solve several special cases. This paper will start from the simplest case, one-dimensional model, and then go to two-dimensional cases.

1.3 Methods

Inner region is defined as the receptor compartment, where receptors are located, and outer region is used to denote the region without a receptor. The two regions will be considered separately. For the inner region, we will only provide approximate solution and the method of matched asymptotic expansions [13, 14] is going to be used. To study the two-dimensional cases with radial symmetry, we will focus on their cross sections. In this way, we transfer two two-dimensional case into one in one-dimensional space, and consequently it simplifies the analysis of 2-d model. To implement the numerical simulations, forward-difference schemes [15] are used to approximate the derivatives and all the codes are based on MATLAB.

1.4 Structure

In Chapter 2 we will provide two general models. Chapter 3 focuses on solving the model in one-dimensional space, and four special cases will be shown in this chapter. We use the matched asymptotic expansions and numerical method to solve the first case. The numerical solutions of the other three cases will be provided. Chapter 4 considers the general model in two-dimensional space. Three cases will be presented in this chapter, first two are radially symmetric and the last one is nonsymmetric. All the results and summary will be presented in Chapter 5.

Chapter 2

General Models

In this chapter, we concentrate on giving a description of ligand-receptor interaction from a qualitative and quantitative view. Mathematical models will be used to simulate the biological activities of the ligand and the receptor, which have been monitored by a series physiological experiments [2, 7]. This part first presents the general model we already know. Then adding the diffusion term, we come up with our own model, which is the basis for the upcoming models. The general assumptions, the steps how to build our models, and the definitions of all the variables will be given. The values of all the constants used in the numerical simulations will be provided at the end of this chapter.

2.1 Assumptions

To build a consistent model, we need to begin with a few assumptions. Let $L(\mathbf{x}, t)$ be the concentration of the ligand, where $t \geq 0$ is time and \mathbf{x} defines the position in the region we are studying (in high-dimensional spaces \mathbf{x} can be a vector). Usually $\mathbf{x} \in \mathbb{R}^k$ and k can be 1, 2 or 3 for the models in different spaces. We usually rescale \mathbf{x} so that its size becomes 1. To further simplify our model, the receptors are only located in a tiny region. Based on the physiological effects, there are three factors affecting the concentration of ligand, which are: 1) a few of ligand are washed out of the brain; 2) the diffusion of the initial ligand in the region; 3) the binding and unbinding with the receptors.

- 1) Define k_c as the elimination rate, at which rate the ligand is being washed out of the brain.
- 2) We assume the diffusion coefficient is a constant, define it as d . Then, the diffusion can be described as $d\Delta L$.
- 3) Define B as the bound product of L and R when the ligand binds to the receptors, where $R(\mathbf{x}, t)$ is the concentration of the free receptors.

2.2 General Models

According to binding model [8], the interaction among the ligand and the receptor consists of two parts:

- i) Binding: the ligand binds to the receptors. Define k_{on} as the binding rate, which is the rate at which ligand binds to receptors.

ii) Unbinding: we assume the rate of unbinding is k_{off} .

The changing rate of B is just the difference between the binding and unbinding.

According to [8, 9] and the assumptions in the last section, when only considering the ligand being washed out of the brain and the basic mechanism with receptors we find a general model, that is

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L - k_{\text{on}} LR + k_{\text{off}} B \\ \frac{\partial B}{\partial t} = k_{\text{on}} LR - k_{\text{off}} B, \end{cases} \quad (2.1)$$

with no-flux boundary conditions. Here, we use these boundary conditions, because we assume there is no ligand leaving from the boundary. These boundary conditions will be used throughout this thesis.

The previous system only considers two factors affecting the concentration of the ligand, which are 1) being washed out of brain and 2) attaching to the receptor. As the diffusion also has an important role affecting the concentration of ligand and we want to study its influence, so we take the diffusion of the ligand into consideration as well. Adding the diffusion term, the model (2.1) becomes

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d\Delta L - k_{\text{on}} LR + k_{\text{off}} B \\ \frac{\partial B}{\partial t} = k_{\text{on}} LR - k_{\text{off}} B, \end{cases} \quad (2.2)$$

with no-flux boundary conditions. Moreover, we know B is the bound product of the ligand and the receptor. Let $f(\mathbf{x}, t)$ describe the total concentration of the receptors, free and bound, at position \mathbf{x} at time t . So we have following relations among R , B and f :

$$f = R + B \quad \text{or} \quad R = f - B. \quad (2.3)$$

Then, using (2.3), we can substitute R with $f - B$ and get the general model,

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d\Delta L - k_{\text{on}} f L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B. \end{cases} \quad (2.4)$$

This system also uses the no-flux boundary conditions, which make sure that no ligand leaving at the boundary. When trying to solve the system, the initial conditions should also be taken into account. The initial condition of B is always zero everywhere. For different cases, we have different initial conditions for L . We suppose the initial concentration of the ligand is not higher than L_C , and the initial concentration of ligand can be a function relating to L_C . The models in the following chapters usually assume f is a step function and that function doesn't depend on time. It means f is assumed to be a constant, defined as f_C , in the receptor compartment, while outside the compartment it is equal to zero. We have this assumption because it simplifies the system and makes it solvable.

2.3 Assumptions for Numerical Method

Numerical technique will be used to solve the problem. Using numerical method, we need to determine several constants, which will be given in this section. We suppose the volume of the brain is 1 liter (= 1000 cm³). The radius of a sphere with 1 liter volume is $r \approx 6.2$ cm. Assume the volume of the receptor compartment is 10 nanoliter (= 10⁻⁸ liter = 10⁻⁵ cm³). So compared with the whole brain, the receptor compartment is really tiny, and the radius of this tiny sphere is approximately 1.337×10^{-2} cm $\approx 2.16 \times 10^{-3} \times r$. All the constants and their selected values are listed in the following table:

Variables	Selected Values
k_{on}	10 ⁹ / (molar·h)
k_{off}	0.003 ~ 3.0 /h
k_c	1/h
d	10 ⁻⁶ cm ² /s
L_C	0.1 nanomolar
f_C	286.43 nanomolar

Here "molar" is a measure of the concentration of a solute in a solution. and it is denoted as "mol/L", i.e. 1 molar = 1 mol/L. The term "nanomolar" refers to 1 nanomolar = 10⁻⁹ molar = 10⁻⁹ mol/L.

2.3.1 One-dimensional Model

In one-dimensional space, we assume the whole region is a line segment and the receptor compartment is a small part of the segment, which is located at one end of the whole region. Comparing the size of the brain and that of the receptor compartment, we suppose the length of the line segment is 1, and the size of the tiny interval is $\varepsilon \sim \mathcal{O}(10^{-3})$. Thus, for the model in one-dimensional space, the region under study is $[0, 1]$, while the receptor compartment is $[0, \varepsilon]$ or $(1 - \varepsilon, 1]$.

Using those experimental values for the constants, both sides of our equation have the same measurement scale. With the requirement to preserve dimensional equality, the manipulation of complete equations is limited to certain operational rules when we try to get the solutions. This has already been discussed thoroughly by both Bridgman [10] and by Gibbings [11]. Addition and multiplication are permissible but other advanced mathematical operations, such as taking exponents and forming binomial expansions, are only acceptable when all the variables are non-dimensional. Thus, we need to non-dimensionalize our system of equations. Non-dimensionalization or scaling is the procedure to remove units or dimensions from a system of equations. We follow the steps shown in Chapter 1.5 of [13] to scale the variables. To scale the variables t and x , we assume there are two intrinsic units of measurement t_c and x_c with the same units as t and x respectively, such that

$$t = t_c \tilde{t} \quad \text{and} \quad x = x_c \tilde{x}. \quad (2.5)$$

t_c and x_c are called characteristic scales, which are constants with certain dimensions and represent characteristic values of the variables. As most of the variables are measured within one hour, so we choose $t_c = 1\text{h} = 3600\text{s}$. As we want the length of our studying region to be 1, we choose $x_c = 6.2\text{cm}$. We then make the change of variables $\tilde{t} = \frac{t}{t_c}$ and

$\tilde{x} = \frac{x}{x_c}$ to achieve dimensionless time and length. The change of the variables is based on the chain rule, for example,

$$\frac{\partial}{\partial t} = \frac{\partial \tilde{t}}{\partial t} \frac{\partial}{\partial \tilde{t}} = \frac{1}{t_c} \frac{\partial}{\partial \tilde{t}}.$$

Following the same steps to non-dimensionalize L , B and R , that is

$$L = L_c \tilde{L}, \quad B = B_c \tilde{B} \quad \text{and} \quad R = R_c \tilde{R}, \quad (2.6)$$

where L_c , B_c and R_c are the characteristic scales. As a result, \tilde{L} , \tilde{B} and \tilde{R} are the non-dimensionalized terms. The one-dimensional model uses $\frac{\partial^2 L}{\partial x^2}$ as the diffusion term and we substitute the variables with (2.5) and (2.6), then the general model (2.2) becomes

$$\begin{cases} \frac{L_c}{t_c} \frac{\partial \tilde{L}}{\partial \tilde{t}} = -k_c L_c \tilde{L} + \frac{d L_c}{x_c^2} \frac{\partial^2 \tilde{L}}{\partial \tilde{x}^2} - k_{\text{on}} L_c R_c \tilde{L} \tilde{R} + k_{\text{off}} B_c \tilde{B} \\ \frac{B_c}{t_c} \frac{\partial \tilde{B}}{\partial \tilde{t}} = k_{\text{on}} L_c R_c \tilde{L} \tilde{R} - k_{\text{off}} B_c \tilde{B}. \end{cases} \quad (2.7)$$

Multiplying $\frac{t_c}{L_c}$ on both sides of the first equation and $\frac{t_c}{B_c}$ on both sides of the second one, we obtain

$$\begin{cases} \frac{\partial \tilde{L}}{\partial \tilde{t}} = -k_c t_c \tilde{L} + \frac{d t_c}{x_c^2} \frac{\partial^2 \tilde{L}}{\partial \tilde{x}^2} - k_{\text{on}} R_c t_c \tilde{L} \tilde{R} + \frac{k_{\text{off}} B_c t_c}{L_c} \tilde{B} \\ \frac{\partial \tilde{B}}{\partial \tilde{t}} = \frac{k_{\text{on}} L_c R_c t_c}{B_c} \tilde{L} \tilde{R} - k_{\text{off}} t_c \tilde{B}. \end{cases} \quad (2.8)$$

Changing the variables has resulted in six new parameters appearing in the transformed system. They are

$$k_c t_c, \quad \frac{d t_c}{x_c^2}, \quad k_{\text{on}} R_c t_c, \quad \frac{k_{\text{off}} B_c t_c}{L_c}, \quad \frac{k_{\text{on}} L_c R_c t_c}{B_c} \quad \text{and} \quad k_{\text{off}} t_c.$$

If we let

$$L_c = R_c = B_c,$$

then there are only four parameters left. Define them as

$$\tilde{k}_c = k_c t_c, \quad \tilde{d} = \frac{d t_c}{x_c^2}, \quad \tilde{k}_{\text{on}} = k_{\text{on}} R_c t_c \quad \text{and} \quad \tilde{k}_{\text{off}} = k_{\text{off}} t_c.$$

So we get a new dimensionless system, which is

$$\begin{cases} \frac{\partial \tilde{L}}{\partial \tilde{t}} = -\tilde{k}_c \tilde{L} + \tilde{d} \frac{\partial^2 \tilde{L}}{\partial \tilde{x}^2} - \tilde{k}_{\text{on}} \tilde{L} \tilde{R} + \tilde{k}_{\text{off}} \tilde{B} \\ \frac{\partial \tilde{B}}{\partial \tilde{t}} = \tilde{k}_{\text{on}} \tilde{L} \tilde{R} - \tilde{k}_{\text{off}} \tilde{B}. \end{cases} \quad (2.9)$$

To determine the values of all the new parameters, we choose

$$L_c = R_c = B_c = 1 \text{ nanomolar} = 10^{-9} \text{ molar}.$$

Together with $t_c = 1\text{h} = 3600\text{s}$ and $x_c = 6.2\text{cm}$, the values of new constants are

$$\begin{aligned}\tilde{k}_{\text{on}} &= k_{\text{on}} R_c t_c = \frac{10^9}{\text{molar} \cdot \text{h}} \cdot 10^{-9} \text{ molar} \cdot 1 \text{ h} = 1, \\ \tilde{k}_{\text{off}} &= k_{\text{off}} t_c = \frac{0.003 \sim 3.0}{\text{h}} \cdot 1 \text{ h} = 0.003 \sim 3.0, \\ \tilde{k}_c &= k_c t_c = \frac{1}{\text{h}} \cdot 1 \text{ h} = 1,\end{aligned}$$

and

$$\begin{aligned}\tilde{d} &= \frac{dt_c}{x_c^2} = \frac{\frac{10^{-6} \text{cm}^2}{\text{s}} \cdot 1 \text{ h}}{(6.2 \text{ cm})^2} \\ &= 10^{-6} \cdot 3600 / 6.2^2 \approx 0.9365 \cdot 10^{-4} \approx 10^{-4}.\end{aligned}$$

Similarly, we also have to non-dimensionalize the terms of initial conditions. Assuming \tilde{L}_C and \tilde{f}_C are non-dimensionalized terms of L_C and f_C , respectively, so we have

$$L_C = \tilde{L}_C L_c \quad \text{and} \quad f_C = \tilde{f}_C f_c.$$

By the definition of f , we know

$$f = R + B.$$

Hence, we can calculate the non-dimensionalized term \tilde{L}_C and \tilde{f}_C , which are

$$\begin{aligned}\tilde{L}_C &= \frac{L_C}{L_c} = 0.1 \text{ nanomolar} / (1 \text{ nanomolar}) = 0.1 \\ \text{and } \tilde{f}_C &= \frac{f_C}{f_c} = 286.43 \text{ nanomolar} / (1 \text{ nanomolar}) = 286.43.\end{aligned}$$

Different notations will not affect the whole system and we also want a simpler notation, so substituting all the variables in (2.9) with the original variables without tilde and using the property (2.3), we obtain

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \frac{\partial^2 L}{\partial x^2} - k_{\text{on}} f L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B. \end{cases} \quad (2.10)$$

This rescaled dimensionless system will be used throughout this thesis. Although this system is exactly the same as general model (2.4), it's important to notice that all the parameters and variables here are dimensionless, and the values of new parameters are listed in the following table:

Variables	Dimensionless Values
k_{on}	1
k_{off}	0.003 \sim 3.0
k_c	1
d	10^{-4}
L_C	0.1
f_C	286.43

2.3.2 Two-dimensional Model

In two-dimensional space, the area under study is assumed to be a round disk with radius 1 and the receptor compartment has a relatively tiny size. For the model in two-dimensional space, we use the following

$$\Delta L = \frac{\partial^2 L}{\partial r^2} + \frac{1}{r^2} \frac{\partial^2 L}{\partial \theta^2} + \frac{1}{r} \frac{\partial L}{\partial r}$$

as the diffusion term. Following the steps to get the 1-d dimensionless system, we obtain the dimensionless system in two-dimensional space, which is

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \left(\frac{\partial^2 L}{\partial r^2} + \frac{1}{r^2} \frac{\partial^2 L}{\partial \theta^2} + \frac{1}{r} \frac{\partial L}{\partial r} \right) - k_{\text{on}} f L \\ \quad + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B. \end{cases} \quad (2.11)$$

The values of new dimensionless parameters are given in the following table, and we note that the new constants for two-dimensional model are the same as those for 1-d model.

Variables	Dimensionless Values
k_{on}	1
k_{off}	0.003 ~ 3.0
k_c	1
d	10^{-4}
L_C	0.1
f_C	286.43

Chapter 3

One-dimensional Model

This chapter focuses on one-dimensional model, which is the general model in one-dimensional space. Analysing the one-dimensional cases gives the intuition to solve the general model and it is also the basis for the analysis of the model in two-dimensional space. Some extra assumptions are given at the beginning, then we solve several cases with certain initial conditions. We will solve the system in inner and outer regions separately. Inner region is defined as the receptor compartment, where the receptors are located, and outer region is used to denote the region without receptor. Solving the system, we use matched asymptotic analysis [13] and Duhamel's principle [16] to get the inner and outer solutions. The numerical solution is also given. At the end of this chapter, the numerical simulations for three other cases are provided as well, which is followed by the comparison of those results.

3.1 Modeling

According to the discussion in Chapter 2, the whole region in this model is a line segment with length 1. The position on the line segment is defined by x , so it has the range from 0 to 1.

$$\Delta L = \frac{\partial^2 L}{\partial x^2}$$

is used as the diffusion term in system (2.4). And we assume, at time $t = 0$, $L(x, 0) = L_{\text{ini}}(x)$ and $B(x, 0) \equiv 0$, which are the initial conditions. We use the no-flux boundary conditions. To further simplify the question, we need some extra assumptions. There are two situations will be taken into consideration: 1) the receptors lie at one end of the line segment and 2) the receptors lie in the middle of the line segment. Within each scenario, there are two cases with different initial conditions. We assume at the beginning no ligand is bound to receptors, so $B(x, 0) \equiv 0$ for any $0 \leq x \leq 1$ is used as the initial condition for all four cases. But the initial conditions of L are slightly different:

1. $L_{\text{ini}}(x)$ is constant for all $0 \leq x \leq 1$, see Figure 3.1(a), which means at the beginning the ligand is evenly distributed in the brain;
2. $L_{\text{ini}}(x)$ is constant for $x_1 < x < x_2$ and otherwise zero, with $0 < x_1 < x_2 < 1$ where x_1 and x_2 are some constants, see Figure 3.1(b). In this case, at time $t = 0$, the ligand only exists in part of the region.

We only provide the detailed procedure to solve the first case, in which the receptors lie on the boundary, $L_{ini}(x)$ is a constant for all $0 \leq x \leq 1$, and $B(x, 0) \equiv 0$ for any $0 \leq x \leq 1$. For this case, both analytical solution and numerical solution will be provided, and we only give the numerical results for the other three cases.

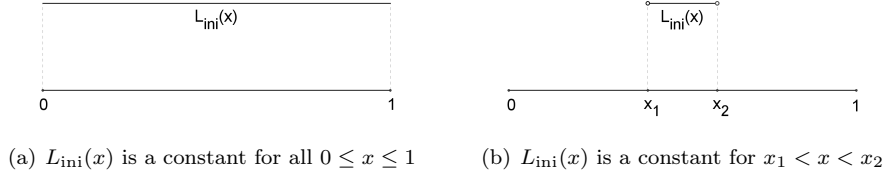


Figure 3.1: *Two Different Initial Conditions: (a) $L_{ini}(x)$ is constant on $(0, 1)$; (b) $L_{ini}(x)$ is a nonzero constant on (x_1, x_2) and otherwise zero.*

3.2 Receptors on the Boundary

We assume the receptors are located at the right end of the segment, i.e. near $x = 1$. The size of the receptor region is $\varepsilon \ll 1$, and the function $f(x, t)$, the concentration of receptors, is a step function and doesn't change with respect to t , that is

$$f(x, t) \equiv \begin{cases} 0 & \text{for } x \in [0, 1 - \varepsilon] \\ f_C & \text{for } x \in (1 - \varepsilon, 1] \end{cases} \quad \text{where } f_C \text{ is a constant.} \quad (3.1)$$

3.2.1 $L_{ini}(x)$ is constant and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$

First, we consider the initial conditions that the concentration of ligand is constant in the region at time $t = 0$.

Approximate Solution

Outer Region The outer region is defined as $[0, 1 - \varepsilon]$. In this region there is no receptor, which means $f(x, t) \equiv 0$ for $x \in [0, 1 - \varepsilon]$ and $B \equiv 0$, hence the general one-dimensional model becomes

$$\frac{\partial L}{\partial t} = -k_c L + d \frac{\partial^2 L}{\partial x^2} \quad \text{for } x \in [0, 1 - \varepsilon], \quad (3.2)$$

with boundary condition $\frac{\partial L}{\partial x}|_{x=0} = 0$ and initial condition $L(x, 0) = L_C$.

Setting $L(x, t) = e^{-k_c t} \tilde{L}(\xi, t)$ where $\xi = x/\sqrt{d}$, system (3.2) becomes

$$\frac{\partial \tilde{L}}{\partial t} = \frac{\partial^2 \tilde{L}}{\partial \xi^2} \quad \text{for } \xi \in \left[0, \frac{1 - \varepsilon}{\sqrt{d}}\right], \quad (3.3)$$

with boundary condition $\frac{\partial \tilde{L}}{\partial \xi}|_{\xi=0} = 0$ and initial condition $\tilde{L}(\xi, 0) = L_C$.

According to Duhamel's principle [16], the solution to the previous equation is

$$\tilde{L}(\xi, t) = \frac{L_C}{2\sqrt{\pi t}} \int_0^{\frac{1-\varepsilon}{\sqrt{d}}} \left[\exp\left(-\frac{(\xi-s)^2}{4t}\right) + \exp\left(-\frac{(\xi+s)^2}{4t}\right) \right] ds.$$

Since $\xi = x/\sqrt{d}$, we can switch back to the original variable x , that is,

$$\begin{aligned} L(x, t) &= e^{-k_c t} \frac{L_C}{2\sqrt{\pi t}} \int_0^{\frac{1-\varepsilon}{\sqrt{d}}} \left[\exp\left(-\frac{\left(\frac{x}{\sqrt{d}}-s\right)^2}{4t}\right) + \exp\left(-\frac{\left(\frac{x}{\sqrt{d}}+s\right)^2}{4t}\right) \right] ds \\ &= e^{-k_c t} \frac{L_C}{2\sqrt{\pi t}} \int_0^{\frac{1-\varepsilon}{\sqrt{d}}} \left[\exp\left(-\frac{(x-\sqrt{d}s)^2}{4dt}\right) + \exp\left(-\frac{(x+\sqrt{d}s)^2}{4dt}\right) \right] ds. \end{aligned}$$

We change the integration variable by letting $r = \sqrt{d}s$, so we get the outer solution

$$L(x, t) = e^{-k_c t} \frac{L_C}{2\sqrt{d\pi t}} \int_0^{1-\varepsilon} \left[\exp\left(-\frac{(x-r)^2}{4dt}\right) + \exp\left(-\frac{(x+r)^2}{4dt}\right) \right] dr,$$

which can be written as (for detailed procedure, see Appendix A.1.1)

$$L(x, t) = e^{-k_c t} \frac{L_C}{2} \left(\operatorname{erf}\left(\frac{x+1-\varepsilon}{2\sqrt{dt}}\right) - \operatorname{erf}\left(\frac{x-1+\varepsilon}{2\sqrt{dt}}\right) \right), \quad (3.4)$$

where

$$\operatorname{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-w^2} dw.$$

Hence we have

$$L(x, t) = e^{-k_c t} \frac{L_C}{2} \left(\operatorname{erf}\left(\frac{x+1-\varepsilon}{2\sqrt{dt}}\right) - \operatorname{erf}\left(\frac{x-1+\varepsilon}{2\sqrt{dt}}\right) \right). \quad (3.5)$$

By Taylor expansions, we have

$$\operatorname{erf}\left(\frac{x+1-\varepsilon}{2\sqrt{dt}}\right) = \operatorname{erf}\left(\frac{x+1}{2\sqrt{dt}}\right) + \frac{-\varepsilon}{2d\sqrt{\pi t}} e^{-\frac{(x+1)^2}{4dt}} + \dots$$

and

$$\operatorname{erf}\left(\frac{x-1+\varepsilon}{2\sqrt{dt}}\right) = \operatorname{erf}\left(\frac{x-1}{2\sqrt{dt}}\right) + \frac{\varepsilon}{2d\sqrt{\pi t}} e^{-\frac{(x-1)^2}{4dt}} + \dots$$

Thus, the approximation of the outer solution (3.4) can be written as

$$\begin{aligned} L_{\text{outer}}(x, t) &\sim e^{-k_c t} \frac{L_C}{2} \left(\operatorname{erf}\left(\frac{x+1}{2\sqrt{dt}}\right) - \operatorname{erf}\left(\frac{x-1}{2\sqrt{dt}}\right) \right. \\ &\quad \left. - \frac{\varepsilon}{2d\sqrt{\pi t}} e^{-\frac{(x+1)^2}{4dt}} - \frac{\varepsilon}{2d\sqrt{\pi t}} e^{-\frac{(x-1)^2}{4dt}} \right) + \dots \end{aligned} \quad (3.6)$$

Inner Region Now, we study the receptor compartment, where $x \in (1 - \varepsilon, 1]$. According to assumption (3.1), $f(x)$ is a constant f_C in this region, hence the system becomes

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \frac{\partial^2 L}{\partial x^2} - k_{\text{on}} f_C L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f_C L - (k_{\text{off}} + k_{\text{on}} L) B, \end{cases} \quad (3.7)$$

along with boundary condition $\frac{\partial L}{\partial x}|_{x=1} = 0$ and initial conditions:

$$L(x, 0) \equiv L_C \quad \text{and} \quad B(x, 0) \equiv 0 \quad \text{for } x \in (1 - \varepsilon, 1].$$

It's better to zoom in on the tiny interval $(1 - \varepsilon, 1]$, so we introduce

$$\bar{x} = \frac{x - 1}{\varepsilon^\delta} \quad \text{where } \delta > 0, \quad (3.8)$$

and how to choose δ will be given later. We can write system (3.7) with variable \bar{x} instead of x , that is

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + \frac{d}{\varepsilon^{2\delta}} \frac{\partial^2 L}{\partial \bar{x}^2} - k_{\text{on}} f_C L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f_C L - (k_{\text{off}} + k_{\text{on}} L) B. \end{cases}$$

This system can be rewritten as

$$\begin{cases} \frac{\partial^2 L}{\partial \bar{x}^2} = \frac{\varepsilon^{2\delta}}{d} \left(\frac{\partial L}{\partial t} + k_c L + k_{\text{on}} f_C L - (k_{\text{off}} + k_{\text{on}} L) B \right) \\ \frac{\partial B}{\partial t} = k_{\text{on}} f_C L - (k_{\text{off}} + k_{\text{on}} L) B. \end{cases} \quad (3.9)$$

We assume

$$L(\bar{x}, t) = L_0(\bar{x}, t) + \varepsilon^\alpha L_1(\bar{x}, t) + \dots$$

and

$$B(\bar{x}, t) = B_0(\bar{x}, t) + \varepsilon^\beta B_1(\bar{x}, t) + \dots,$$

where $\alpha, \beta > 0$ and they will be determined by the balancing technique. Then, the system (3.9) becomes

$$\begin{aligned} & \frac{\partial^2 L_0}{\partial \bar{x}^2} + \varepsilon^\alpha \frac{\partial^2 L_1}{\partial \bar{x}^2} + \dots \\ & \quad \textcircled{1} \qquad \qquad \textcircled{2} \\ & = \frac{\varepsilon^{2\delta}}{d} \left(\frac{\partial L_0}{\partial t} + k_c L_0 + k_{\text{on}} f_C L_0 - (k_{\text{off}} + k_{\text{on}} L_0) B_0 \right) \\ & \quad \textcircled{3} \\ & + \frac{\varepsilon^{2\delta+\alpha}}{d} \left(\frac{\partial L_1}{\partial t} + k_c L_1 + k_{\text{on}} f_C L_1 - k_{\text{on}} L_1 B_0 \right) + \dots \\ & \quad \textcircled{4} \end{aligned} \quad (3.10)$$

and

$$\begin{aligned} \frac{\partial B_0}{\partial t} + \varepsilon^\beta \frac{\partial B_1}{\partial t} + \dots & = k_{\text{on}} f_C L_0 - (k_{\text{off}} + k_{\text{on}} L_0) B_0 \\ & - \varepsilon^\beta k_{\text{on}} L_0 B_1 + \varepsilon^\alpha (f_C L_1 - k_{\text{on}} L_1 B_0). \end{aligned} \quad (3.11)$$

As $\alpha > 0$ and $\delta > 0$, the leading-order term of equation (3.10) is $\frac{\partial^2 L_0}{\partial \bar{x}^2}$ and the rest are higher-order terms, so we have

$$\begin{cases} \frac{\partial^2 L_0(\bar{x}, t)}{\partial \bar{x}^2} = 0 \\ L_0(\bar{x}, 0) \equiv L_C. \end{cases} \quad (3.12)$$

Integrating equation (3.12) twice, we obtain

$$L_0(\bar{x}, t) = L_{00}(t) + \bar{x}L_{01}(t), \quad (3.13)$$

where $L_{00}(t)$ and $L_{01}(t)$ are two functions only depending on t . Because $L_0(\bar{x}, 0) \equiv L_C$, so we have $L_{00}(0) = L_C$ and $L_{01}(0) = 0$. As the leading term of outer solution doesn't depend on x , so we let $L_{01}(t) = 0$. Thus, the leading-order term of the solution $L(\bar{x}, t)$ is

$$L_0(\bar{x}, t) = L_{00}(t), \quad (3.14)$$

where $L_{00}(0) = L_C$.

Then we try to get the expression of B_0 . From the leading term of equation (3.11), we get

$$\frac{\partial B_0}{\partial t} = k_{\text{on}} f_C L_0 - (k_{\text{off}} + k_{\text{on}} L_0) B_0. \quad (3.15)$$

To simplify the equation, letting $A_1(t) = k_{\text{on}} f_C L_0$ and $A_2(t) = -(k_{\text{off}} + k_{\text{on}} L_0)$, we get a nicer equation for B_0 , which is

$$\frac{\partial B_0(\bar{x}, t)}{\partial t} = A_1(t) + A_2(t) B_0(\bar{x}, t). \quad (3.16)$$

The general solution to equation (3.16) is

$$B_0(\bar{x}, t) = e^{\int_0^t A_2(\xi) d\xi} \int_0^t A_1(\eta) e^{-\int_0^\eta A_2(\xi) d\xi} d\eta + C_1(\bar{x}) e^{\int_0^t A_2(\xi) d\xi}, \quad (3.17)$$

where $C_1(\bar{x})$ is a function only depending on \bar{x} . Thus, the general solution to equation (3.15) is

$$\begin{aligned} B_0(\bar{x}, t) = & e^{\int_0^t -(k_{\text{off}} + k_{\text{on}} L_0(\bar{x}, \xi)) d\xi} \int_0^t k_{\text{on}} f_C L_0(\bar{x}, \eta) e^{\int_0^\eta k_{\text{off}} + k_{\text{on}} L_0(\bar{x}, \xi) d\xi} d\eta \\ & + C_1(\bar{x}) e^{\int_0^t -(k_{\text{off}} + k_{\text{on}} L_0(\bar{x}, \xi)) d\xi}. \end{aligned} \quad (3.18)$$

Because of the initial condition $B(\bar{x}, 0) \equiv 0$, we can get

$$C_1(\bar{x}) = 0.$$

Hence, the expression of $B_0(\bar{x}, t)$ is

$$B_0(\bar{x}, t) = e^{\int_0^t -(k_{\text{off}} + k_{\text{on}} L_0(\bar{x}, \xi)) d\xi} \int_0^t k_{\text{on}} f_C L_0(\bar{x}, \eta) e^{\int_0^\eta k_{\text{off}} + k_{\text{on}} L_0(\bar{x}, \xi) d\xi} d\eta.$$

Using the result (3.14), we can rewrite the expression of $B_0(\bar{x}, t)$, i.e.,

$$B_0(\bar{x}, t) = e^{\int_0^t -(k_{\text{off}} + k_{\text{on}} L_{00}(\xi)) d\xi} \int_0^t k_{\text{on}} f_C L_{00}(\eta) e^{\int_0^\eta k_{\text{off}} + k_{\text{on}} L_{00}(\xi) d\xi} d\eta. \quad (3.19)$$

Based on this expression, B_0 doesn't depend on \bar{x} anymore, although we still use the notation $B_0(\bar{x}, t)$.

Now, we already got the expressions of $L_0(\bar{x}, t)$ and $B_0(\bar{x}, t)$. As it is only the first term of inner solution and we want to get a more precise solution, so we are still interested in the expression of $L_1(\bar{x}, t)$. To get the solution of $L_1(\bar{x}, t)$, we need to balance both sides of equation (3.10). Based on $\alpha > 0$ and $\delta > 0$, we know the leading-order term is ①, while ④ has the highest order among the four terms in the equation. It remains to determine the balance between ② and ③. We choose ② as the second leading-order term and assume ③ has higher order, the reason is given in Appendix A.1.2. With this balancing, we have the following problem to solve:

$$\begin{cases} \frac{\partial^2 L_1(\bar{x}, t)}{\partial \bar{x}^2} = 0 \\ L_1(\bar{x}, 0) \equiv 0. \end{cases} \quad (3.20)$$

Integrating equation (3.20) twice, we obtain

$$L_1(\bar{x}, t) = L_{10}(t) + \bar{x}L_{11}(t),$$

with $L_{10}(0) = L_{11}(0) \equiv 0$. While the second term of outer solution only depends on t , so $L_{11}(t)$ should be zero. Then we can conclude that the approximate inner solution is

$$L_{\text{inner}}(\bar{x}, t) = L_{00}(t) + \varepsilon^\alpha L_{10}(t) + \dots \quad (3.21)$$

Matching There are two undetermined functions in the inner solution, which are $L_{00}(t)$ and $L_{10}(t)$. This paragraph uses the matching technique [14] to determine those unknowns.

In previous parts we already got the inner and outer solutions, but we don't want our solutions to have a dramatic change in the transition area between the inner and outer regions. To accomplish this, the two solutions should be close enough within the transition region. So letting \bar{x} go to minus infinity and x approach 1, we expect the outer and inner outer solutions to have same value. In other words, we require that

$$\lim_{x \rightarrow 1} L_{\text{outer}}(x, t) = \lim_{\bar{x} \rightarrow -\infty} L_{\text{inner}}(\bar{x}, t).$$

Based on the expression (3.6), we have

$$\lim_{x \rightarrow 1} L_{\text{outer}}(x, t) = e^{-k_c t} \frac{L_C}{2} \left(\operatorname{erf} \left(\frac{1}{\sqrt{dt}} \right) - \frac{\varepsilon}{2d\sqrt{\pi t}} e^{-\frac{1}{dt}} - \frac{\varepsilon}{2d\sqrt{\pi t}} \right) + \dots \quad (3.22)$$

According to (3.21), we know that

$$\lim_{\bar{x} \rightarrow -\infty} L_{\text{inner}}(\bar{x}, t) = L_{00}(t) + \varepsilon^\alpha L_{10}(t).$$

Thus, we can conclude that $\alpha = 1$,

$$L_{00}(t) = e^{-k_c t} \frac{L_C}{2} \operatorname{erf} \left(\frac{1}{\sqrt{dt}} \right)$$

and

$$L_{10}(t) = -e^{-k_c t} \frac{L_C}{2} \left(\frac{1}{2d\sqrt{\pi t}} e^{-\frac{1}{dt}} + \frac{1}{2d\sqrt{\pi t}} \right).$$

Hence, the inner solution can be approximated by

$$L_{\text{inner}}(x, t) = e^{-k_c t} \frac{L_C}{2} \left(\operatorname{erf} \left(\frac{1}{\sqrt{dt}} \right) - \frac{\varepsilon}{2d\sqrt{\pi t}} e^{-\frac{1}{4t}} - \frac{\varepsilon}{2d\sqrt{\pi t}} \right) + \dots \quad (3.23)$$

Numerical Results

In this part, we use numerical method to solve the following system

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \frac{\partial^2 L}{\partial x^2} - k_{\text{on}} f L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B, \end{cases} \quad (3.24)$$

along with the no-flux boundary conditions and initial conditions:

$$L(x, 0) \equiv L_C \quad \text{and} \quad B(x, 0) \equiv 0 \quad \text{for } 0 \leq x \leq 1.$$

Here the function $f(x, t)$, the concentration of receptors, is assumed to be a step function and doesn't change with respect to t , that is

$$f(x, t) \equiv \begin{cases} 0 & \text{for } x \in [0, 1 - \varepsilon] \\ f_C & \text{for } x \in (1 - \varepsilon, 1] \end{cases} \quad \text{where } f_C \text{ is a constant.}$$

We use the forward-difference formula [15] to approximate all the derivatives. Before programming, we have to write our system into the extrapolation formula (given in Appendix A.2.1). However, the formulas for boundary points are a little different from those for interior points, so we have to think about them separately. As soon as we get all the extrapolation formulas, we can implement them in MATLAB.

Boundary Conditions If using the extrapolation formula on the boundary points, there is a problem: two imaginary nodes $L_{N_x+1}^{(n)}$ and $L_{-1}^{(n)}$ appear in the formula. In this part, we will figure out how to deal with these points. The system uses the no-flux boundary conditions, which mean there is no ligand leaving on the boundaries, i.e.

$$\frac{\partial L}{\partial x} \Big|_{x=0} = \frac{\partial L}{\partial x} \Big|_{x=1} = 0.$$

Using forward-difference formulas to approximate the derivatives, we have

$$\frac{\partial L}{\partial x} \Big|_{x=0} \approx \frac{L_1^{(n)} - L_0^{(n)}}{\Delta x} \quad \text{and} \quad \frac{\partial L}{\partial x} \Big|_{x=1} \approx \frac{L_{N_x+1}^{(n)} - L_{N_x}^{(n)}}{\Delta x}.$$

Thus, the no-flux boundary conditions are enforced by explicitly requiring that $L_{N_x+1}^{(n)} = L_{N_x}^{(n)}$ and $L_0^{(n)} = L_1^{(n)}$. Using these results, we get the extrapolation formulas for the boundary points, which are given in Appendix A.2.2.

Numerical Simulations Using the extrapolation formulas given in last paragraph, we design the program to solve the general one-dimensional system (3.24). According to the discussion in Section 2.3, the values of parameters are $k_{\text{on}} = 1$, $k_{\text{off}} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

Our simulation starts at time $t = 0$ and ends at $t = 60$. We record all the values at each node and present the results at different times. Figure 3.2 and Figure 3.3 compare the analytical and numerical solutions. Figure 3.2 shows the real analytical solution and numerical solution in outer region. Figure 3.3 presents the approximation of inner solution and its numerical counterpart. The ligand concentration for the whole region at time $t = 1.0$, $t = 1.5$ and $t = 3.0$ are shown in Figure 3.4. While Figure 3.5 shows the enlarged plots around the receptor region. The solutions at time $t = 5.0$, $t = 6.0$ and $t = 10.0$ are given in Figure 3.6 and Figure 3.7. The solutions for the whole region are shown in Figure 3.6 and those near receptor compartment are given in Figure 3.7.

The comparison of the analytical and numerical solutions of the outer region at time $t = 30.0$ and $t = 60.0$ are given in Figure 3.2(a) and Figure 3.2(b), respectively. According to the plots, the analytical and numerical solutions perfectly match in the outer region, except the part near the receptor compartment. Based on this, we can say the analytical outer solution we got is pretty good. The inner region also having an impact on the outer solution is the reason why the analytical solution deviates from the numerical counterpart when approaching the receptor region.

Figure 3.3(a) and Figure 3.3(b) compare the approximate inner solution and numerical solution at time $t = 30.0$ and $t = 60.0$, respectively. From these plots we can see that the expansion of the inner solution couldn't approximate the numerical one very well. That's because we only expand the inner solution to the second term, which is a $\mathcal{O}(\varepsilon)$ term. The ε is assumed to be 5×10^{-3} , while the numerical solution of the inner region is around $\mathcal{O}(10^{-4})$, so the approximate inner solution with two terms is not accurate enough. To achieve a better approximation, we need to consider even higher-order terms.

Based on the numerical results given by Figure 3.4 and Figure 3.6, we can see the ligand concentration decreases during the whole procedure. That's because the ligand is constantly being washed out of the brain. At the beginning, the concentration of the ligand in the receptor compartment decreases much faster than the region outside the compartment. This phenomenon corresponds with what we expect. In the receptor area, the ligand was not only washed out of the brain but also bound to the receptors. However, when t getting large most of the ligand gathered in the receptor compartment, that's because in that region the ligand was bound to the receptors, while the majority of the ligand outside that area was washed out of the brain.

Figure 3.4-3.7 all show the information about ligand. In our system, some of the ligand bind to the receptor and form the bound product, so we are also curious about the change of its concentration. Figure 3.8 and Figure 3.9 present the numerical solutions of B , the bound product of L and R . Figure 3.8 shows the solutions of B at time $t = 1.0$, $t = 1.5$ and $t = 3.0$. While the other one shows those at time $t = 5.0$, $t = 6.0$ and $t = 10.0$. From both plots, we can see the concentration of bound product decreases throughout the whole period, although the speed is quite slow. When the procedure starts the bound product has highest concentration on the side near outer region, and it gradually changes to the other way round.

We are also interested in the change of the ligand concentration at certain positions. So we tracked the change of ligand concentration at the positions $x = 0.25$ and $x = 0.5$, see Figure 3.10. According to the numerical results, we can see the ligand concentration decreases quickly and approaches zero no matter at position $x = 0.25$ or $x = 0.5$. And

the decreasing rate also diminishes with respect to time t .

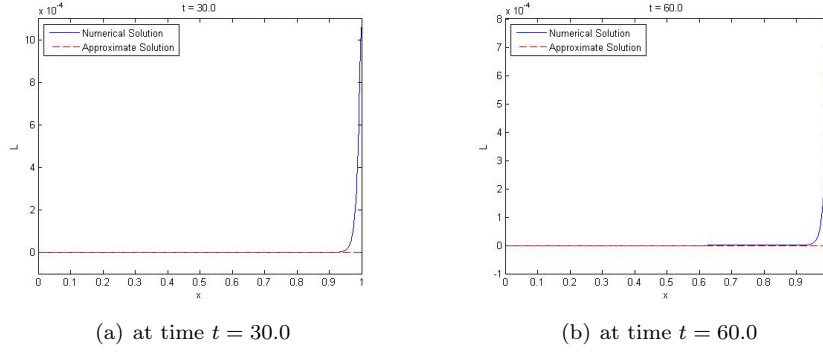


Figure 3.2: Comparison of the analytical outer solution and the numerical solution to system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x,0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , i.e. $f(x) \equiv f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red dashed lines are analytical solution of the outer region and blue lines are the numerical solution of that region. Figure 3.2(a) compares the solutions at time $t = 30.0$, while Figure 3.2(b) present the comparison at time $t = 60.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

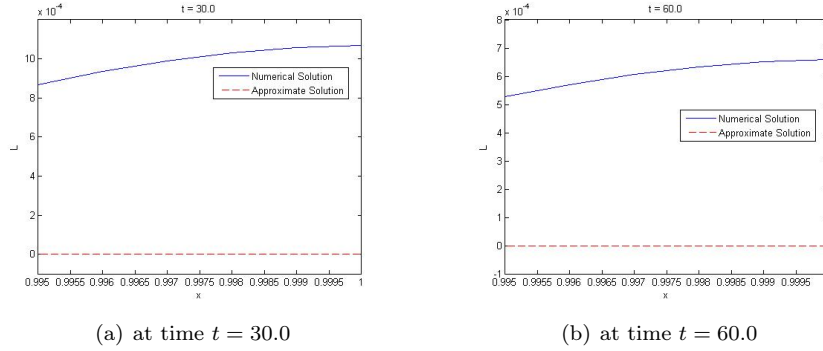


Figure 3.3: Comparison of the approximate inner solution and the numerical solution to system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , i.e. $f(x) \equiv f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red dashed lines are the approximations of the inner solutions and blue lines are the numerical solutions to the inner region. Figure 3.3(a) compares the solutions at time $t = 30.0$, while Figure 3.3(b) presents the comparison at time $t = 60.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

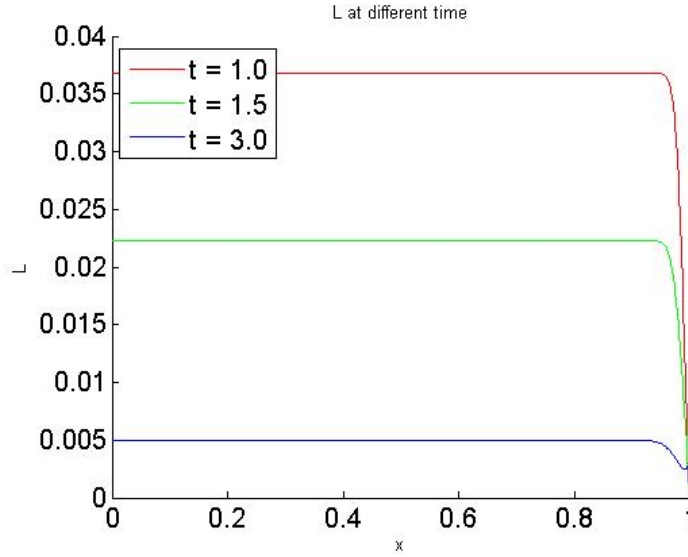


Figure 3.4: Numerical simulations of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , i.e. $f \equiv f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 1.5$, and blue one represents that at time $t = 3.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

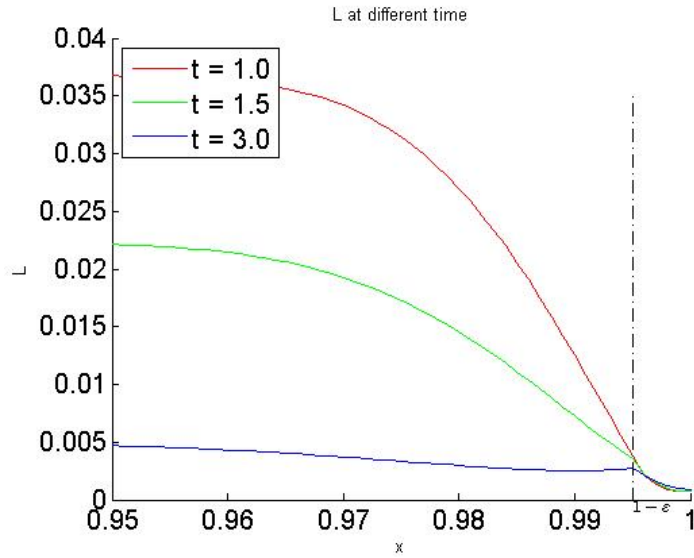


Figure 3.5: Numerical simulations of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x,0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , i.e. $f(x) \equiv f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Plots show the solutions with $x \in [0.95, 1]$, which is a region around receptor compartment. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 1.5$, and blue one represents that at time $t = 3.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

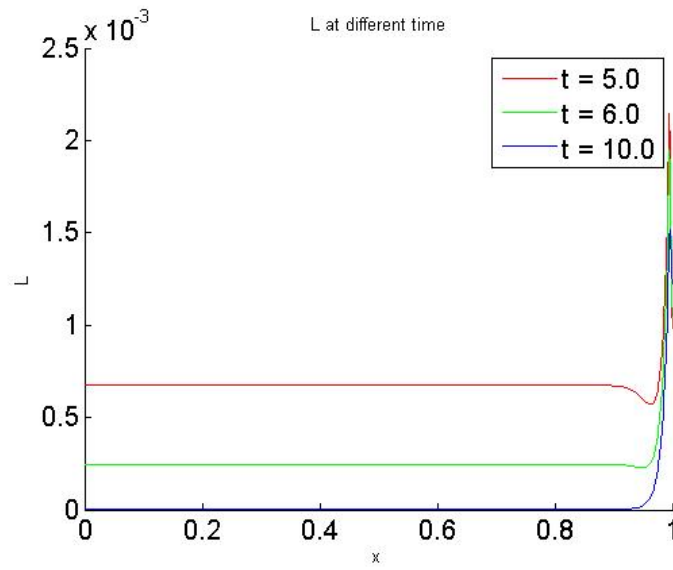


Figure 3.6: Numerical simulations of L of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x,0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , i.e. $f(x) \equiv f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red line shows the ligand concentration at time $t = 5.0$, green line shows that at time $t = 6.0$, and blue one represents that at time $t = 10.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

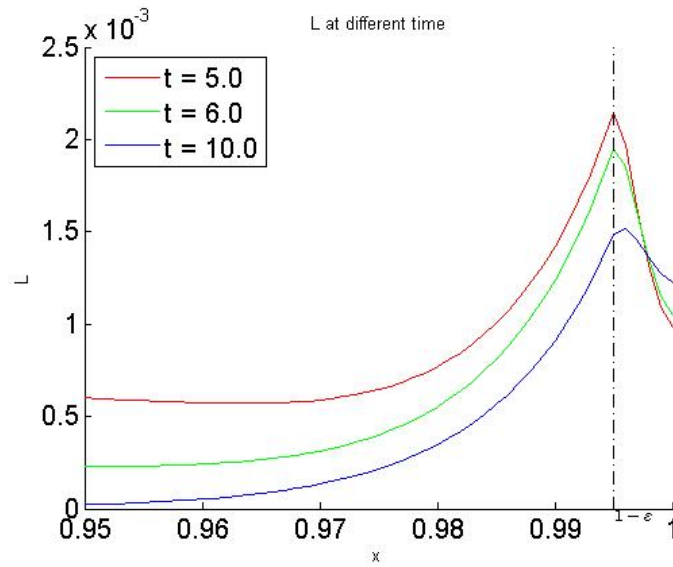


Figure 3.7: Numerical solutions around the receptor region of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , i.e. $f(x) \equiv f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Plots show the solutions around the receptor compartment with $x \in [0.95, 1]$. Red line shows the ligand concentration at time $t = 5.0$, green line shows that at time $t = 6.0$, and blue one represents that at time $t = 10.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

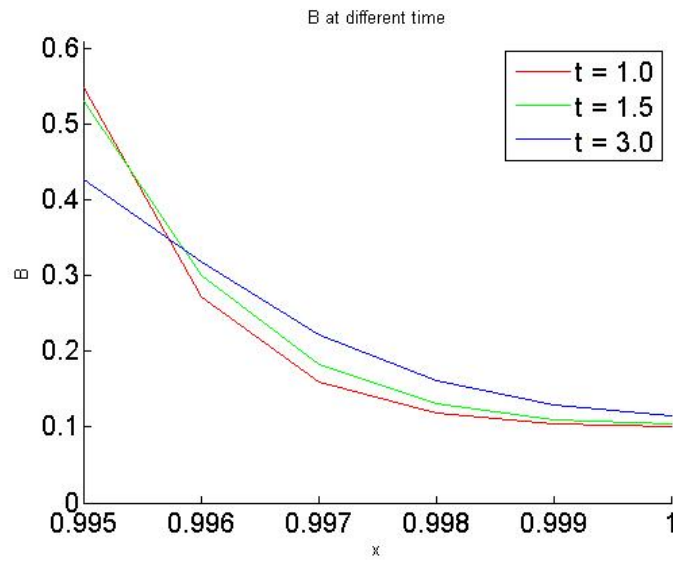


Figure 3.8: Numerical solutions of $B(x,t)$ of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x,0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , i.e. $f(x) \equiv f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. B denotes the concentration of the bound product of L and R , while x is the spatial position. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 1.5$, and blue one represents that at time $t = 3.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

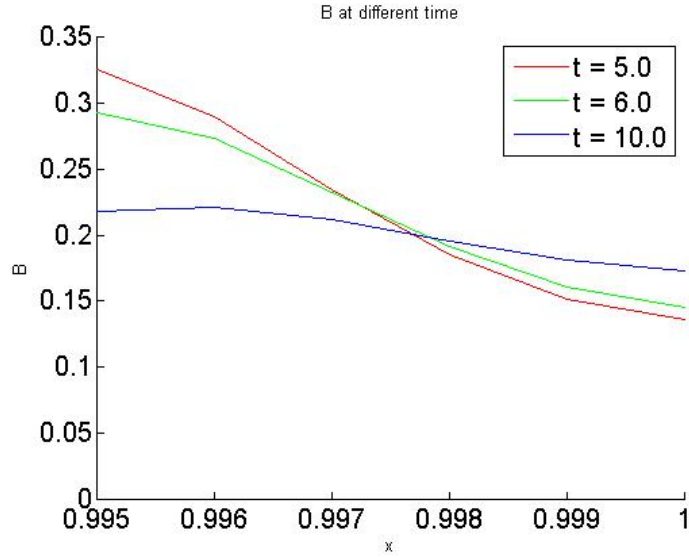


Figure 3.9: Numerical solutions of $B(x,t)$ of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x,0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , i.e. $f(x) \equiv f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. B denotes the concentration of bound product and x the spatial position. Red line shows the ligand concentration at time $t = 5.0$, green line shows that at time $t = 6.0$, and blue one represents that at time $t = 10.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

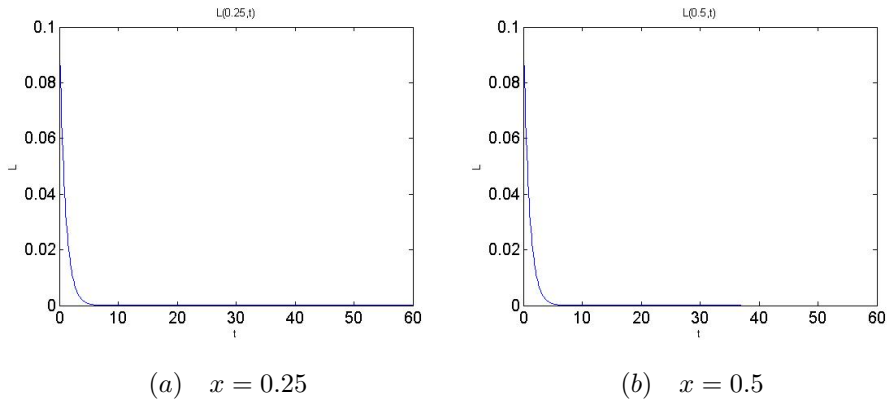


Figure 3.10: Sketches of the changes of ligand concentrations according to time at two different positions. In each plot, the vertical axis is the ligand concentration and horizontal axis is time. The time starts at 0 and ends at 60. The plot (a) shows the ligand concentration at $x = 0.25$ and plot (b) shows that at $x = 0.5$.

3.2.2 $L_{\text{ini}}(x)$ is constant for $x_1 < x < x_2$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$

In this part, we continue using numerical technique to solve system (3.24) along with the no-flux boundary conditions and initial conditions:

$$L_{\text{ini}}(x) = \begin{cases} L_C & \text{for } x \in (x_1, x_2) \\ 0 & \text{for } x \in [0, x_1] \cup [x_2, 1] \end{cases} \quad \text{and} \quad B(x, 0) \equiv 0 \quad \text{for } 0 \leq x \leq 1.$$

Moreover, the assumption (3.1) about $f(x, t)$ are still used. The values of all the parameters are going to be used are based on Section 2.3, they are $k_{\text{on}} = 1$, $k_{\text{off}} = 2$, $k_c = 1$, $d = 10^{-4}$. In addition, we choose $\varepsilon = 5 \times 10^{-3}$, $x_1 = 0.375$ and $x_2 = 0.625$.

We modified the code from the previous case and ran the simulation again. The concentrations of the ligand at time $t = 4.0$, $t = 5.0$ and $t = 10.0$ are shown in Figure 3.11. Based on the graph, we can know the ligand has been quickly washed out and it seems that the receptors have no effect on the concentration of ligand. The graph just looks like the diffusion of the initial ligand. Actually that is because the rate of the ligand being washed out is much faster than its diffusion, so the ligand has no time to reach the receptors before being washed out. In other words, the receptor compartment is too far away from the ligand, and only a few of the ligand can reach the receptor region before being washed out. Because of the tiny amount of the ligand arriving at that region, it's hard to see the change of the ligand concentration on the graph.

Similar to the previous case, we detect the changes of the ligand concentration at positions $x = 0.25$ and $x = 0.5$, see Figure 3.12. Comparing Figure 3.10 and Figure 3.12, we can see there is not too much difference between the two cases at position $x = 0.5$, while the difference at $x = 0.25$ is quite big. In previous case, the ligand concentration directly went to zero, because the ligand was consistently washed out of the brain. However, in this case, the ligand concentration increases until time $t \approx 7$ and decreases afterwards. The reason for this is that the ligand reaches this area due to the ligand diffusion, but the amount is really tiny, so it was quickly washed out.

If we slow down the rate of ligand being washed out or accelerate the diffusion, then we would expect the receptors have bigger effect on the change of the ligand concentration. First, we want to see how the result changes if less ligand has been washed out. Hence, we carry out another experiment, following all the assumptions and using same parameters, except k_c . Now, we set $k_c = 0.1$ instead 1. The results are given in Figure 3.13. We do see less ligand has been washed out during the same amount of time, but the change of ligand concentration caused by ligand-receptor interactions is still hard to see. Then we further decrease k_c and amplify the diffusion effect, i.e. letting $k_c = 0.01$ and $d = 10^{-3}$. Remaining the other parameters the same, we run the simulation again and present the new results at time $t = 5.0$, $t = 10.0$ and $t = 20.0$ in Figure 3.14. The effect of the receptor can be clearly seen, the left half of the interval has less ligand than the other half.

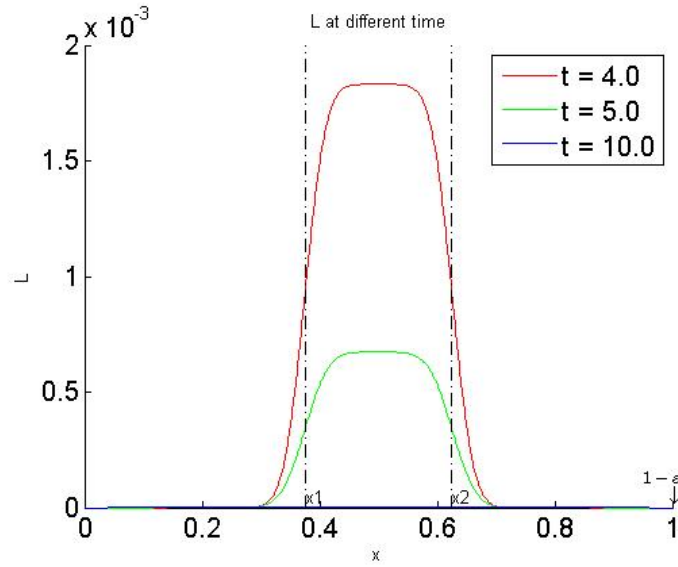


Figure 3.11: Numerical simulations of system (3.24) with the no-flux boundary conditions and the initial conditions: $L_{ini}(x) = L_C$ for $x_1 < x < x_2$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , and it is defined as $f(x) = f_C$ for $1 - \epsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red line shows the ligand concentration at time $t = 4.0$, green line shows that at time $t = 5.0$, and blue one represents that at time $t = 10.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $L_C = 0.1$, $f_C = 286.43$, $\epsilon = 5 \times 10^{-3}$, $x_1 = 0.375$ and $x_2 = 0.625$.

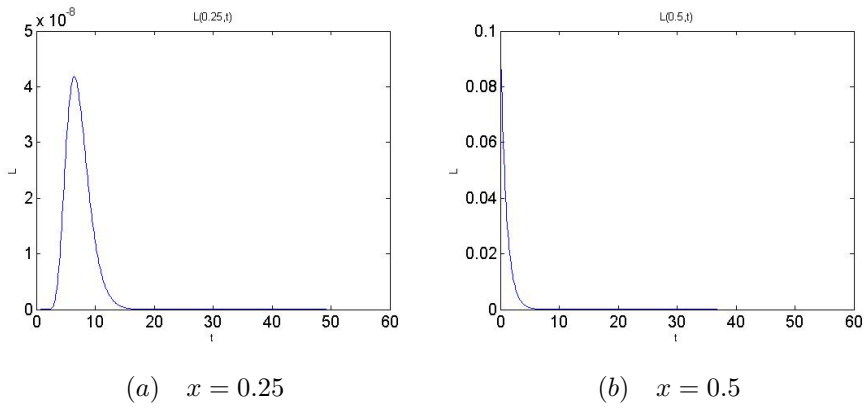


Figure 3.12: Sketches of the changes of ligand concentrations according to time at two different positions. The vertical axis is the ligand concentration and horizontal axis is time. The time starts from 0 to 60. The plot (a) shows the ligand concentration at $x = 0.25$ and the plot (b) shows that at $x = 0.5$.

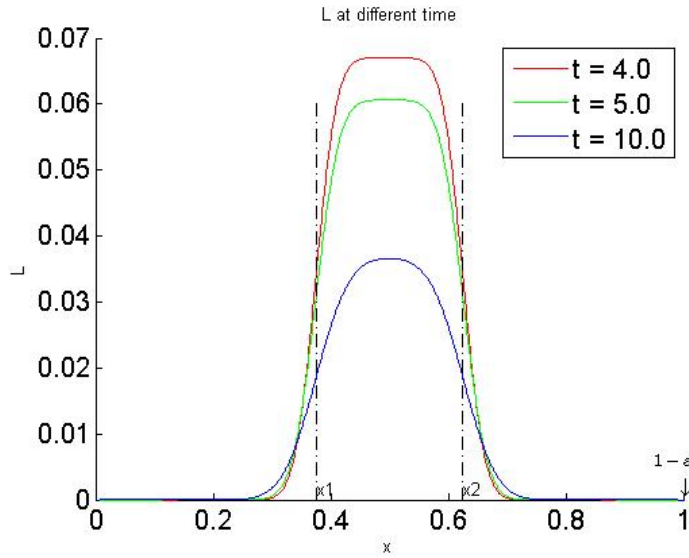


Figure 3.13: Numerical simulations of system (3.24) with the no-flux boundary conditions and the initial conditions: $L_{ini}(x) = L_C$ for $x_1 < x < x_2$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , and it is defined as $f(x) = f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red line shows the ligand concentration at time $t = 4.0$, green line shows that at time $t = 5.0$, and blue one represents that at time $t = 10.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 0.1$, $d = 10^{-4}$, $L_C = 0.1$, $f_C = 286.43$, $\varepsilon = 5 \times 10^{-3}$, $x_1 = 0.375$ and $x_2 = 0.625$.

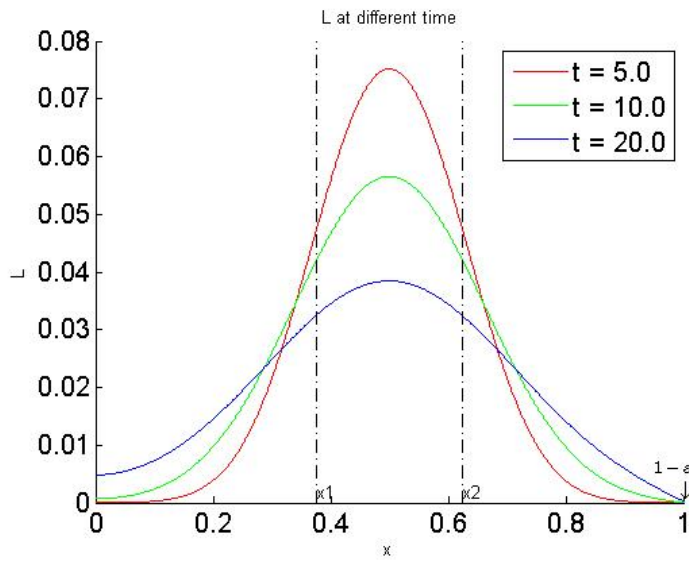


Figure 3.14: Numerical simulations of system (3.24) with the no-flux boundary conditions and the initial conditions: $L_{ini}(x) = L_C$ for $x_1 < x < x_2$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , $f(x) = f_C$ for $1 - \varepsilon < x \leq 1$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red line shows the ligand concentration at time $t = 5.0$, green line shows that at time $t = 10.0$, and blue one represents that at time $t = 20.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 0.01$, $d = 10^{-3}$, $L_C = 0.1$, $f_C = 286.43$, $\varepsilon = 5 \times 10^{-3}$, $x_1 = 0.375$ and $x_2 = 0.625$.

3.3 Receptors in the Middle

In this section, we consider another scenario with the receptors lying in the middle of the line segment, say near x^* , and the receptor compartment is $(x^* - \frac{\varepsilon}{2}, x^* + \frac{\varepsilon}{2}) \subset (0, 1)$. Just keep in mind, we say the receptor is lying in the middle, but it doesn't mean the receptor compartment should be located exactly at the center of the line segment. So x^* can be any number in the interval $(0, 1)$, but not close to 0 or 1. The size of the receptor compartment is $\varepsilon \ll 1$. We still suppose the function $f(x, t)$, the concentration of receptors, is a step function and it doesn't change with respect to t , that is

$$f(x, t) = \begin{cases} f_C & x \in (x^* - \frac{\varepsilon}{2}, x^* + \frac{\varepsilon}{2}) \\ 0 & x \in [0, x^* - \frac{\varepsilon}{2}] \cup [x^* + \frac{\varepsilon}{2}, 1], \end{cases} \quad (3.25)$$

where f_C is a constant. In the following, we will use numerical method to solve two cases with different initial conditions. $B(x, 0) \equiv 0$ for any $x \in (0, 1)$ is used as the initial condition of B for both cases, while the initial conditions of $L(x, t)$ are slightly different. Same as previous section, we assume $L(x, 0)$ is constant for $0 \leq x \leq 1$ for the first case, and for the second one $L(x, 0)$ is constant on the interval $x_1 < x < x_2$. Here we choose $x^* = 0.5$, $\varepsilon = 5 \times 10^{-3}$, $x_1 = 0.375$ and $x_2 = 0.625$ for the numerical simulation. According to Section 2.3, the values of other parameters are $k_{\text{on}} = 1$, $k_{\text{off}} = 2$, $k_c = 1$ and $d = 10^{-4}$.

3.3.1 $L_{\text{ini}}(x)$ is constant and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$

This part continues to solve system (3.24) with numerical method, but now the concentration of receptors, is defined as (3.25).

Following the previous routine, we plot the ligand concentration at time $t = 1.0$, $t = 1.5$ and $t = 2.0$, see Figure 3.15 and Figure 3.16. The ligand concentrations for the whole region at different times are presented in Figure 3.15, while the solutions on a tiny interval around the receptor region are shown in Figure 3.16. When the procedure starts, the concentration of the ligand dramatically decreases at the center of the region, where the receptor compartment lies. This can be attributed to the presence of the receptors. In the receptor compartment, ligand also binds to the receptors besides being washed out, so the ligand concentration plummeted at the center of the region. Based on the plots, we can also see the binding rate was higher than the rate of ligand being washed out.

Figure 3.17 shows the ligand change with respect to time at positions $x = 0.25$ and $x = 0.5$. The simulation starts at time $t = 0$ and ends at $t = 60$. But we only show the ligand concentration change at $x = 0.25$ from $t = 0$ to $t = 10$ and at $x = 0.5$ from $t = 0$ to $t = 1$, because the concentration only has dramatic change at the beginning and afterwards it is almost zero. Based on the plots, we can see the ligand concentration decreases faster at position $x = 0.5$ than that at $x = 0.25$. At position $x = 0.5$ the ligand concentration went to zero much faster than that at $x = 0.25$. It is because at position $x = 0.5$ the ligand is not only washed out of the brain but also bound to the receptors, and the binding rate is quite high.

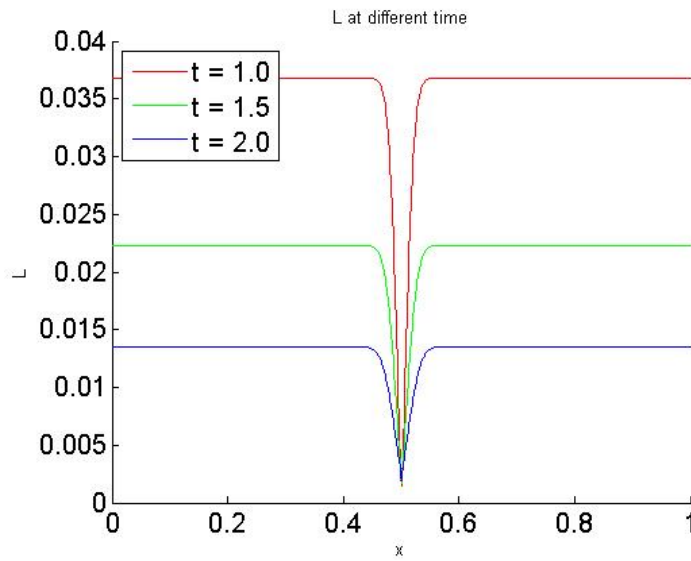


Figure 3.15: Numerical simulations of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , that is $f(x) \equiv f_C$ for $x^* - \frac{\varepsilon}{2} < x < x^* + \frac{\varepsilon}{2}$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 1.5$, and blue one represents that at time $t = 2.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $x^* = 0.5$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

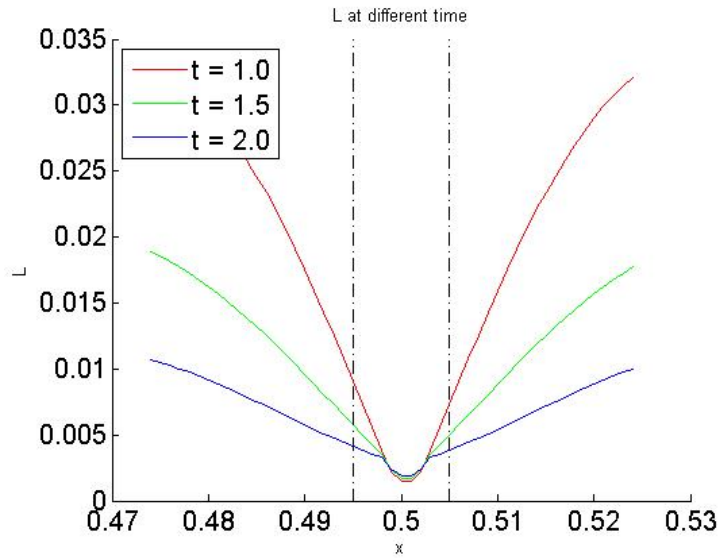


Figure 3.16: Numerical simulations of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , that is $f(x) \equiv f_C$ for $x^* - \frac{\varepsilon}{2} < x < x^* + \frac{\varepsilon}{2}$, otherwise zero. L denotes the ligand concentration and x the spatial position. Plots show the solutions around the receptor compartment with $x \in [0.474, 0.524]$. The area between the dashed lines is the receptor region. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 1.5$, and blue one represents that at time $t = 2.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $x^* = 0.5$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

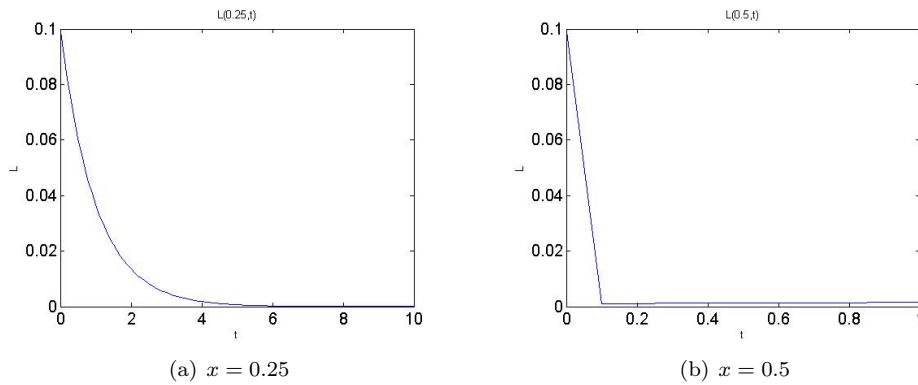


Figure 3.17: Sketches of the changes of ligand concentrations according to time at two different positions. The vertical axis is the ligand concentration and horizontal axis is time. The plot (a) shows the ligand concentration at $x = 0.25$ from $t = 0$ to $t = 10$ and the plot (b) shows that at $x = 0.5$ from $t = 0$ to $t = 1$.

3.3.2 $L_{\text{ini}}(x)$ is constant for $x_1 < x < x_2$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$

This part will continue to solve system (3.24) with numerical method. The no-flux boundary conditions and the assumption (3.25) about $f(x, t)$ will still be used. But the initial conditions become:

$$L_{\text{ini}}(x) = \begin{cases} L_C & \text{for } x \in (x_1, x_2) \\ 0 & \text{for } x \in [0, x_1] \cup [x_2, 1] \end{cases} \quad \text{and} \quad B(x, 0) \equiv 0 \quad \text{for } 0 \leq x \leq 1.$$

We changed the initial conditions and ran our code again. Figure 3.18 and Figure 3.19 present the ligand concentrations at time $t = 1.0$, $t = 1.5$ and $t = 2.0$. The ligand concentrations for the whole region at different times are shown in Figure 3.18, while the solutions on a tiny interval around the receptor region are given in Figure 3.19. From the plots, we can see the ligand concentration descends quickly, especially at the center of the receptor compartment. That is because in that region, the ligand is washed out of the brain and at the same time bound to the receptors. We also notice that Figure 3.16 and Figure 3.19 look almost the same. Although the initial conditions for this case are different from those for the previous one, the initial values at the receptor region are exactly the same. Hence, the plots around the receptor compartment are almost the same.

We also plot the changes of ligand concentration with respect to time at positions $x = 0.25$ and $x = 0.5$, see Figure 3.20. Compared with the case having the same initial conditions but the receptors lying at one end of the region, the ligand concentration at $x = 0.25$ has a similar pattern, which increases at the beginning and then approaches zero, see Figure 3.12 and Figure 3.20. The diffusion of the ligand first reaches the region and then it was washed out of the brain. Comparing Figure 3.20 and Figure 3.17, we can see at position $x = 0.5$ the changes of the ligand concentrations are quite similar, i.e. in both cases the amounts of the ligand drop to around zero just when the procedure starts. That is also because in both cases the receptor compartments have the same initial values.

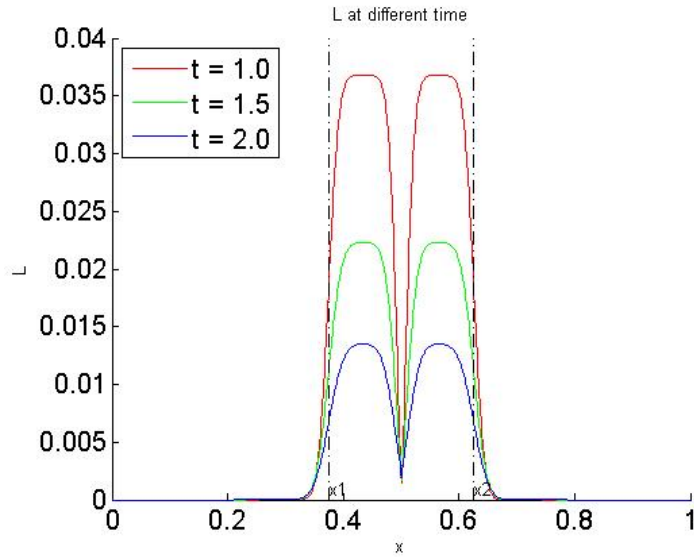


Figure 3.18: Numerical simulations of system (3.24) with the no-flux boundary conditions and the initial conditions: $L_{ini}(x) = L_C$ for $x_1 < x < x_2$, otherwise zero, and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , that is $f(x) = f_C$ for $x^* - \frac{\varepsilon}{2} < x < x^* + \frac{\varepsilon}{2}$, otherwise zero. L denotes the ligand concentration and x the spatial position. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 1.5$, and blue one represents that at time $t = 2.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $L_C = 0.1$, $f_C = 286.43$, $x^* = 0.5$, $\varepsilon = 5 \times 10^{-3}$, $x_1 = 0.375$ and $x_2 = 0.625$.

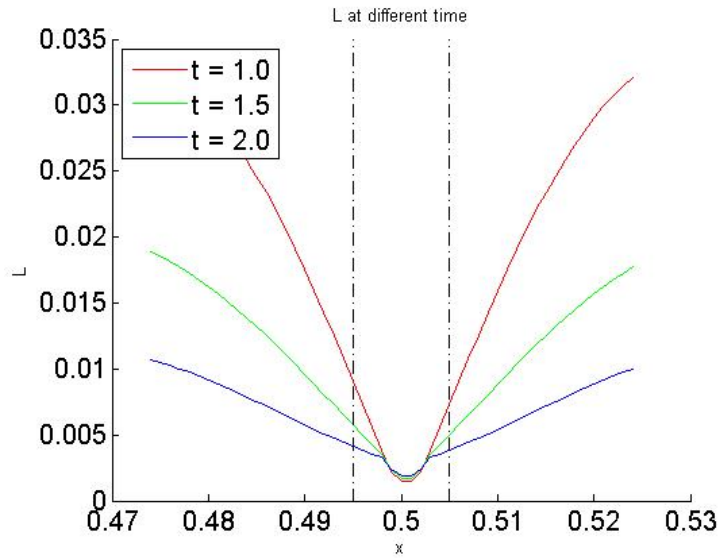


Figure 3.19: Numerical simulations of system (3.24) with the no-flux boundary conditions and initial conditions: $L_{ini}(x) = L_C$ for $x_1 < x < x_2$, otherwise zero, and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. f is a step function only depending on x , that is $f(x) \equiv f_C$ for $x^* - \frac{\varepsilon}{2} < x < x^* + \frac{\varepsilon}{2}$, otherwise zero. L denotes the ligand concentration and x the spatial position. Plots show the solutions around the receptor compartment with $x \in [0.474, 0.524]$. The area between the dashed lines is the receptor region. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 1.5$, and blue one represents that at time $t = 2.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $x^* = 0.5$, $\varepsilon = 5 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

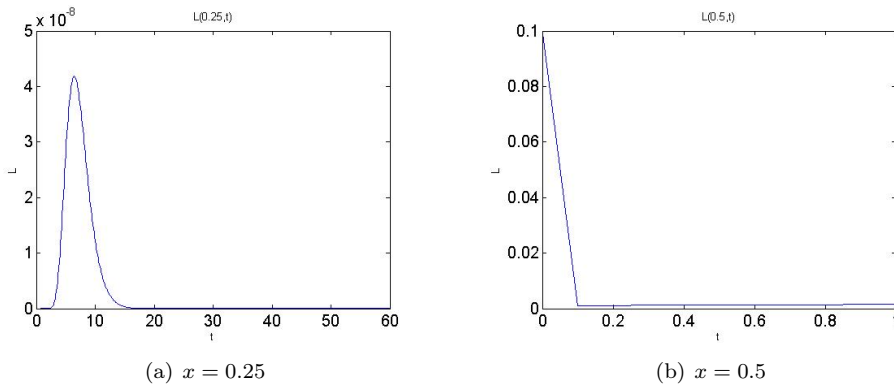


Figure 3.20: Sketches of the changes of the ligand concentrations according to time at two different positions. The vertical axis is the ligand concentration and horizontal axis is time. The plot (a) shows the ligand concentration at $x = 0.25$ from $t = 0$ to $t = 60$ and the plot (b) shows that at $x = 0.5$ from $t = 0$ to $t = 1$.

Chapter 4

Two-dimensional Model

In Chapter 3 we studied the model in one-dimensional space. In this chapter, we plan to go further, using a two-dimensional model to simulate the procedure involving the ligand and the receptors. As we assume the brain is a round disk in two-dimensional space, the model will be given in polar coordinates. This chapter provides three cases, the first two are radially symmetric and the last one without symmetry.

This section starts with a general model, system (2.4) with a diffusion term in polar coordinates. Section 4.1 provides the general assumptions for this chapter and the initial conditions that are going to be used. The initial condition of B is still assumed to be zero everywhere, while the initial condition for L is based on Gaussian function. The initial conditions for different cases are slightly different, which will also be discussed in Section 4.1.

In Section 4.2 and Section 4.3 we focus on the radially symmetric models. In Section 4.2, we assume the receptors lie on the circular boundary of the region under study, while in Section 4.3 the receptor compartment is at the center. Analytical and numerical solutions for the case with receptors on the boundary are provided, while we only give the numerical solution for the other radially symmetric case. Because of radial symmetry, the analysis can be simplified by analyzing the cross section. The analytical solution to the first radially symmetric case is based on matched asymptotic technique [13, 14]. And the outer solution is derived from Gaussian function.

Finally, Section 4.4 turns our attention to the nonsymmetric case. The initial conditions for this case are same as those for the radially symmetric case with the receptors at the center. But the receptor compartment is located neither at the center nor on the boundary. Numerical simulations are provided to give a clear view about the trend of the ligand concentration.

4.1 Modeling

Similar to the one-dimensional cases, the general assumptions for this chapter are based on Chapter 2. Here the region under study is assumed to be a round disk, so it's better

to write the model in polar coordinates. We use

$$\frac{\partial^2 L}{\partial r^2} + \frac{1}{r^2} \frac{\partial^2 L}{\partial \theta^2} + \frac{1}{r} \frac{\partial L}{\partial r} \quad (4.1)$$

as the diffusion term in system (2.4), where $r \in [0, 1]$ is the radial coordinate and $\theta \in [0, 2\pi)$ is the angular coordinate. As is standard, we assume a positive angular coordinate means that the angle θ is measured counterclockwise from positive x -axis.

According to Section 2.2, we need to make sure that there is no flux at the boundary. Actually, no flux at the circular boundary $r = 1$ is enough to preserve all the ligand in the whole region. However, we impose another boundary condition at the center for the radially symmetric cases. That is because we want to make sure the solution is smooth at the origin. Moreover, we will analyse the outer and the inner regions separately, and the systems in both regions need boundary conditions.

For all the cases, the initial value of B is zero everywhere, i.e.

$$B(r, \theta, 0) \equiv 0 \quad \text{for any } r \in [0, 1] \text{ and } \theta \in [0, 2\pi). \quad (4.2)$$

While the initial conditions of $L(r, \theta, t)$ are different. And the assumptions for $f(r, \theta, t)$, the concentration of the receptors, depend on the location of the receptor compartment.

For the radially symmetric case with receptors on the boundary, we assume the concentration of ligand is highest at the center and it is constant outside the receptor compartment, that is, for any $\theta \in [0, 2\pi)$

$$L(r, \theta, 0) = \begin{cases} L_C \exp\left(-\frac{r^2}{2\sigma_0^2}\right) & \text{for } r \in [0, 1 - \varepsilon] \\ L_C \exp\left(-\frac{1}{2\sigma_0^2}\right) & \text{for } r \in (1 - \varepsilon, 1]. \end{cases}$$

Here we suppose there is no receptor in the region with $r \in [0, 1 - \varepsilon]$, and we call that part outer region. The receptor compartment or inner region is the part with $r \in (1 - \varepsilon, 1]$.

For the radially symmetric case with receptors at the center and the nonsymmetric case, the initial ligand concentration is assumed to be spread out from the center, so the initial condition of L is defined as

$$L(r, \theta, 0) = L_C \exp\left(-\frac{r^2}{2\sigma_0^2}\right) \quad \text{for } r \in [0, 1] \text{ and any } \theta \in [0, 2\pi). \quad (4.3)$$

For this case, the outer region is the area with $r \in [\varepsilon, 1]$, while the inner region is $r \in [0, \varepsilon)$.

The both initial conditions of the ligand concentration we mentioned above are all defined with σ_0 , where σ_0 is a constant and we choose $\sigma_0 = 0.1$ for the numerical simulations.

4.2 Radially Symmetric Case with Receptors on the Boundary

In this section, we consider a radially symmetric case in two-dimensional space. Because of radial symmetry, all the variables don't depend on θ in this section. Hence we focus

on the study of its cross section, which is the intersection of the real solution with a plane through the center. For both radially symmetric cases, we still use the previous notations, although L , f and B don't depend on θ anymore. Thus, the general two-dimensional system becomes

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \left(\frac{\partial^2 L}{\partial r^2} + \frac{1}{r} \frac{\partial L}{\partial r} \right) - k_{\text{on}} f L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B, \end{cases} \quad (4.4)$$

along with the boundary conditions

$$\frac{\partial L(r, t)}{\partial r} \Big|_{r=0} = 0 \quad \text{and} \quad \frac{\partial L(r, t)}{\partial r} \Big|_{r=1} = 0. \quad (4.5)$$

We assume all the receptors lie on the circular boundary of the round disk, so here the receptor compartment is located at $r = 1$ with size ε . Hence the initial conditions become

$$L(r, 0) = \begin{cases} L_C \exp\left(-\frac{r^2}{2\sigma_0^2}\right) & \text{for } r \in [0, 1 - \varepsilon] \\ L_C \exp\left(-\frac{1}{2\sigma_0^2}\right) & \text{for } r \in (1 - \varepsilon, 1] \end{cases} \quad (4.6)$$

and

$$B(r, 0) \equiv 0 \quad \text{for any } r \in [0, 1]. \quad (4.7)$$

Again assuming $f(r, t)$, the concentration of receptors, is a step function, that is

$$f(r, t) \equiv \begin{cases} 0 & \text{for } r \in [0, 1 - \varepsilon], \\ f_C & \text{for } r \in (1 - \varepsilon, 1]. \end{cases} \quad (4.8)$$

In the following parts, we will provide the analytical solution and numerical simulations for the system mentioned above.

4.2.1 Analytical Solution

This part gives an approximate solution to the radially symmetric case with receptors on the boundary. As this case is radially symmetric, the analysis is focusing on the cross section, which is the intersection of the whole area with a vertical plane through the center. The exact solution for the outer region is provided. Following the method of matched asymptotic expansions, we get an approximation for inner solution.

Outer Region

Based on definition, the outer region is the region with $r \in [0, 1 - \varepsilon]$. As $f(r, t) \equiv 0$ for $r \in [0, 1 - \varepsilon]$ and there is no receptor in this region, hence we don't need to consider the bound product of the ligand and the receptor. As a result, the equation (4.4) becomes

$$\frac{\partial L}{\partial t} = -k_c L + d \left(\frac{\partial^2 L}{\partial r^2} + \frac{1}{r} \frac{\partial L}{\partial r} \right) \quad \text{for } r \in [0, 1 - \varepsilon], \quad (4.9)$$

with boundary condition

$$\frac{\partial L(r, t)}{\partial r} \Big|_{r=0} = 0 \quad (4.10)$$

and initial condition

$$L(r, 0) = L_C \exp\left(-\frac{r^2}{2\sigma_0^2}\right) \quad \text{for } r \in [0, 1 - \varepsilon]. \quad (4.11)$$

To solve equation (4.9), we assume

$$L(r, t) = e^{-k_c t} \tilde{L}(\xi, t) \quad \text{where } \xi = \frac{r}{\sqrt{d}}.$$

Based on this assumption, we have

$$\frac{\partial L}{\partial t} = \frac{\partial}{\partial t} \left(e^{-k_c t} \tilde{L}(\xi, t) \right) \quad \text{and} \quad -k_c L = -k_c e^{-k_c t} \tilde{L}(\xi, t).$$

Then we can rewrite the equation (4.9) in terms of $\tilde{L}(\xi, t)$, that is

$$-k_c e^{-k_c t} \tilde{L}(\xi, t) + e^{-k_c t} \frac{\partial \tilde{L}}{\partial t} = -k_c e^{-k_c t} \tilde{L}(\xi, t) + e^{-k_c t} \frac{\partial^2 \tilde{L}}{\partial \xi^2} + \frac{e^{-k_c t}}{\xi} \frac{\partial \tilde{L}}{\partial \xi}.$$

Cancelling the term $-k_c e^{-k_c t} \tilde{L}(\xi, t)$ and multiplying $e^{k_c t}$ on both sides, we get a system depending on ξ , that is

$$\frac{\partial \tilde{L}}{\partial t} = \frac{\partial^2 \tilde{L}}{\partial \xi^2} + \frac{1}{\xi} \frac{\partial \tilde{L}}{\partial \xi} \quad \text{for } \xi \in \left[0, \frac{1 - \varepsilon}{\sqrt{d}}\right], \quad (4.12)$$

along with boundary condition

$$\left. \frac{\partial \tilde{L}(\xi, t)}{\partial \xi} \right|_{\xi=0} = 0 \quad (4.13)$$

and initial condition

$$\tilde{L}(\xi, 0) = L_C \exp\left(-\frac{d\xi^2}{2\sigma_0^2}\right). \quad (4.14)$$

The general solution to equation (4.12) is

$$\tilde{L}(\xi, t) = \frac{A_0}{4t + C_0} \exp\left(-\frac{\xi^2}{4t + C_0}\right),$$

where A_0 and C_0 are two undetermined constants. According to initial condition (4.14), we obtain

$$C_0 = \frac{2\sigma_0^2}{d} \quad \text{and} \quad A_0 = \frac{2\sigma_0^2 L_C}{d}.$$

Hence the final solution to (4.12) is

$$\tilde{L}(\xi, t) = \frac{L_C \sigma_0^2}{2dt + \sigma_0^2} \exp\left(-\frac{d\xi^2}{4dt + 2\sigma_0^2}\right).$$

Writing the solution back into the original notation and substituting ξ with r/\sqrt{d} , we get the solution for system (4.9), which is

$$L(r, t) = \frac{L_C \sigma_0^2}{2dt + \sigma_0^2} \exp\left(-\frac{r^2}{4dt + 2\sigma_0^2} - k_c t\right). \quad (4.15)$$

Inner Region

Now, we study the receptor region, i.e. $r \in (1 - \varepsilon, 1]$. In this region, we have $f(x) \equiv f_C$, hence the system becomes

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \left(\frac{\partial^2 L}{\partial r^2} + \frac{1}{r} \frac{\partial L}{\partial r} \right) - k_{\text{on}} f_C L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f_C L - (k_{\text{off}} + k_{\text{on}} L) B, \end{cases} \quad (4.16)$$

with boundary condition

$$\left. \frac{\partial L(r, t)}{\partial r} \right|_{r=1} = 0 \quad (4.17)$$

and initial conditions

$$L(r, 0) = L_C \exp\left(-\frac{1}{2\sigma_0^2}\right) \quad \text{and} \quad B(r, 0) = 0 \quad \text{for } r \in (1 - \varepsilon, 1]. \quad (4.18)$$

As the size of this region is ε , so we want to introduce a new variable, which is

$$\bar{r} = \frac{1 - r}{\varepsilon^{\bar{\delta}}} \quad \text{with } \bar{\delta} > 0, \quad (4.19)$$

where $\bar{\delta}$ will be determined in the following part. Writing system (4.16) with respect to variable \bar{r} , it becomes

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \left(\frac{d}{\varepsilon^{2\bar{\delta}}} \frac{\partial^2 L}{\partial \bar{r}^2} - \frac{1}{\varepsilon^{\bar{\delta}}} \frac{1}{1 - \varepsilon^{\bar{\delta}} \bar{r}} \frac{\partial L}{\partial \bar{r}} \right) - k_{\text{on}} f_C L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f_C L - (k_{\text{off}} + k_{\text{on}} L) B. \end{cases}$$

As $1 - \varepsilon^{\bar{\delta}} \bar{r} \approx 1$, so substituting $1 - \varepsilon^{\bar{\delta}} \bar{r}$ with 1 in previous equation and rearranging all the terms, then we have

$$\begin{cases} \frac{\partial^2 L}{\partial \bar{r}^2} - \varepsilon^{\bar{\delta}} \frac{\partial L}{\partial \bar{r}} = \frac{\varepsilon^{2\bar{\delta}}}{d} \left(\frac{\partial L}{\partial t} + k_c L + k_{\text{on}} f_C L - (k_{\text{off}} + k_{\text{on}} L) B \right) \\ \frac{\partial B}{\partial t} = k_{\text{on}} f_C L - (k_{\text{off}} + k_{\text{on}} L) B. \end{cases} \quad (4.20)$$

We suppose the expansions for the solutions are

$$L(\bar{r}, t) = L_0(\bar{r}, t) + \varepsilon^{\bar{\alpha}} L_1(\bar{r}, t) + \dots \quad (4.21)$$

and

$$B(\bar{r}, t) = B_0(\bar{r}, t) + \varepsilon^{\bar{\beta}} B_1(\bar{r}, t) + \dots, \quad (4.22)$$

where $\bar{\alpha}, \bar{\beta} > 0$. Substituting the expansions (4.21) and (4.22) into (4.20), we can rewrite the system as

$$\begin{aligned}
& \frac{\partial^2 L_0}{\partial \bar{r}^2} + \varepsilon^{\bar{\alpha}} \frac{\partial^2 L_1}{\partial \bar{r}^2} + \varepsilon^{\bar{\delta}} \frac{\partial L_0}{\partial \bar{r}} + \varepsilon^{\bar{\delta} + \bar{\alpha}} \frac{\partial L_1}{\partial \bar{r}} + \dots \\
& \quad \textcircled{1} \quad \quad \quad \textcircled{2} \quad \quad \quad \textcircled{3} \quad \quad \quad \textcircled{4} \\
& = \frac{\varepsilon^{2\bar{\delta}}}{d} \left(\frac{\partial L_0}{\partial t} + k_c L_0 + k_{\text{on}} L_0 f_C - (k_{\text{off}} + k_{\text{on}} L_0) B_0 \right) \\
& \quad \quad \quad \textcircled{5} \\
& + \frac{\varepsilon^{2\bar{\delta} + \bar{\alpha}}}{d} \left(\frac{\partial L_1}{\partial t} + k_c L_1 + k_{\text{on}} L_1 f_C - k_{\text{on}} L_1 B_0 \right) + \dots, \\
& \quad \quad \quad \textcircled{6}
\end{aligned} \tag{4.23}$$

and

$$\begin{aligned}
\frac{\partial B_0}{\partial t} + \varepsilon^{\bar{\beta}} \frac{\partial B_1}{\partial t} + \dots = & k_{\text{on}} f_C L_0 - (k_{\text{off}} + k_{\text{on}} L_0) B_0 \\
& - \varepsilon^{\bar{\beta}} k_{\text{on}} L_0 B_1 + \varepsilon^{\bar{\alpha}} (f_C L_1 - k_{\text{on}} L_1 B_0).
\end{aligned} \tag{4.24}$$

According to the assumptions $\bar{\delta} > 0$ and $\bar{\alpha} > 0$, the leading term is $\frac{\partial^2 L_0}{\partial \bar{r}^2}$ and the other terms all have higher orders, so we have

$$\begin{cases} \frac{\partial^2 L_0(\bar{r}, t)}{\partial \bar{r}^2} = 0 \\ L_0(\bar{r}, 0) = L_C. \end{cases} \tag{4.25}$$

The general solution to previous system is

$$L_0(\bar{r}, t) = L_{00}(t) + L_{01}(t)\bar{r}, \tag{4.26}$$

where $L_{00}(t)$ and $L_{01}(t)$ are two functions only depending on time t . According to the initial condition, we get $L_{00}(0) = L_C$ and $L_{01}(0) = 0$. Hence the first term of inner solution is

$$L_0(\bar{r}, t) = L_{00}(t) + L_{01}(t)\bar{r}, \quad \text{with } L_{00}(0) = L_C \text{ and } L_{01}(0) = 0. \tag{4.27}$$

Then consider the first term of B , which should satisfy the following equation

$$\frac{\partial B_0(\bar{r}, t)}{\partial t} = k_{\text{on}} f_C L_0(\bar{r}, t) - (k_{\text{off}} + k_{\text{on}} L_0(\bar{r}, t)) B_0(\bar{r}, t).$$

This equation is almost the same as equation (3.15) in Section 3.2.1, only with different variable, so we still use previous result, that is

$$B_0(\bar{r}, t) = e^{\int_0^t -(k_{\text{off}} + k_{\text{on}} L_0(\bar{r}, \xi)) d\xi} \int_0^t k_{\text{on}} f_C L_0(\bar{r}, \eta) e^{\int_0^\eta k_{\text{off}} + k_{\text{on}} L_0(\bar{r}, \xi) d\xi} d\eta.$$

Now, we already got the expressions of $L_0(\bar{r}, t)$ and $B_0(\bar{r}, t)$. To let the solution be more precise, we are also interested in the expression of $L_1(\bar{r}, t)$. To get the solution of $L_1(\bar{r}, t)$, we need to balance the other terms of equation (4.23). As we already knew the leading-order term is $\textcircled{1}$, and based on $\bar{\alpha} > 0$ and $\bar{\delta} > 0$, we can conclude that $\textcircled{4}$, $\textcircled{5}$

and ⑥ are the higher-order terms in the equation. It remains to determine the balance between ② and ③. Letting ③ balance itself and ② be higher-order term, we have $\bar{\alpha} > \bar{\delta}$. The reason to choose this balance is given in Appendix B.1.1. Based on our choice, we get an extra requirement for $L_0(\bar{r}, t)$, that is

$$\frac{\partial L_0(\bar{r}, t)}{\partial \bar{r}} = 0.$$

According to expression (4.26), we get $L_{01}(t) = 0$. Considering the next term of inner solution, we need to solve the following system:

$$\frac{\partial^2 L_1}{\partial \bar{r}^2} = 0 \quad \text{with } L_1(\bar{r}, 0) = 0.$$

The solution to previous equation is

$$L_1(\bar{r}, t) = L_{10}(t) + L_{11}(t)\bar{r} \quad \text{with } L_{10}(0) = L_{11}(0) = 0.$$

Thus, the approximation of the inner solution is

$$L_{\text{inner}}(\bar{r}, t) = L_{00}(t) + \varepsilon^\alpha (L_{10}(t) + L_{11}(t)\bar{r}) + \dots \quad (4.28)$$

Matching It remains to determine the function $L_{00}(t)$, $L_{10}(t)$ and $L_{11}(t)$, we will use the matching technique again to determine the unknowns. The fundamental idea of matching technique concerns the tiny transition region around $r = 1 - \varepsilon$. To connect the expansions on either side of this region, we introduce an intermediate variable $r_{\bar{\eta}}$, defined as

$$r_{\bar{\eta}} = \frac{r - 1 + \varepsilon}{\varepsilon^{\bar{\eta}}}, \quad (4.29)$$

with $\bar{\eta} > 1$. This interval for $\bar{\eta}$ comes from the requirement that the intermediate variable is valid in a tiny neighborhood around $1 - \varepsilon$. So r can be written as

$$r = 1 - \varepsilon + \varepsilon^{\bar{\eta}} r_{\bar{\eta}}, \quad (4.30)$$

which is followed by

$$\bar{r} = \frac{1 - r}{\varepsilon^{\bar{\delta}}} = \varepsilon^{1-\bar{\delta}} - \varepsilon^{\bar{\eta}-\bar{\delta}} r_{\bar{\eta}}. \quad (4.31)$$

Then the outer and inner solutions will be rewritten in terms of intermediate variable $r_{\bar{\eta}}$. Using (4.30) in (4.15), we get

$$L_{\text{outer}}(r, t) = \frac{L_C \sigma_0^2 e^{-k_c t}}{2dt + \sigma_0^2} \exp\left(-\frac{(1 - \varepsilon + \varepsilon^{\bar{\eta}} r_{\bar{\eta}})^2}{4dt + 2\sigma_0^2}\right). \quad (4.32)$$

Based on Taylor series, we have

$$\exp\left(-\frac{(1 - \varepsilon + \varepsilon^{\bar{\eta}} r_{\bar{\eta}})^2}{4dt + 2\sigma_0^2}\right) = \exp\left(-\frac{1}{4dt + 2\sigma_0^2}\right) + \exp\left(-\frac{1}{4dt + 2\sigma_0^2}\right) \frac{\varepsilon}{2dt + \sigma_0^2} + \dots$$

Hence, the outer solution (4.32) can be written as

$$L_{\text{outer}}(r, t) \sim \frac{L_C \sigma_0^2 e^{-k_c t}}{2dt + \sigma_0^2} \exp\left(-\frac{1}{4dt + 2\sigma_0^2}\right) \left(1 + \frac{\varepsilon}{2dt + \sigma_0^2} + \dots\right). \quad (4.33)$$

Similarly, we do the same procedure for the inner solution (4.28), and it becomes

$$L_{\text{inner}}(\bar{r}, t) = L_{00}(t) + \varepsilon^{\bar{\alpha}} L_{10}(t) + \left(\varepsilon^{\bar{\alpha}+1-\bar{\delta}} - \varepsilon^{\bar{\alpha}+\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} \right) L_{11}(t) + \dots \quad (4.34)$$

After getting the inner and outer solutions in terms of intermediate variable, we have to match them. Because $\bar{\delta} > 0$, $\bar{\alpha} > \bar{\delta}$ and $\bar{\eta} > 1$, $L_{00}(t)$ is the leading term in the inner solution. With this, we can match (4.33) with (4.34). To match those two expansions, the inner and outer approximations must give the same result when they are expressed in this transition layer variable, which implies $\bar{\alpha} = 1$. Then we get

$$L_{00}(t) = \frac{L_C \sigma_0^2 e^{-k_c t}}{2dt + \sigma_0^2} \exp\left(-\frac{1}{4dt + 2\sigma_0^2}\right)$$

and

$$L_{10}(t) = \frac{L_C \sigma_0^2 e^{-k_c t}}{(2dt + \sigma_0^2)^2} \exp\left(-\frac{1}{4dt + 2\sigma_0^2}\right).$$

The next term in inner solution is $\varepsilon^{\bar{\alpha}+1-\bar{\delta}} L_{11}(t)$. Since we only have $\bar{\eta} > 1$ and don't know $\bar{\eta}$ is larger or less than 2, so the next term in outer solution is either

$$\frac{L_C \sigma_0^2 e^{-k_c t}}{2dt + \sigma_0^2} \exp\left(-\frac{1}{4dt + 2\sigma_0^2}\right) \left(-\frac{\varepsilon^{\bar{\eta}} r_{\bar{\eta}}}{2dt + \sigma_0^2}\right)$$

or

$$\frac{L_C \sigma_0^2 e^{-k_c t}}{2dt + \sigma_0^2} \exp\left(-\frac{1}{4dt + 2\sigma_0^2}\right) \left(-\frac{\varepsilon^2}{4dt + 2\sigma_0^2}\right).$$

As $L_{11}(t)$ doesn't depend on $r_{\bar{\eta}}$ and $\bar{\alpha} + 1 - \bar{\delta} < 2$, so $\varepsilon^{\bar{\alpha}+1-\bar{\delta}} L_{11}(t)$ can balance with neither of the terms above, which means $L_{11}(t) = 0$. Therefore, the approximate inner solution is

$$L_{\text{inner}}(r, t) \sim \frac{L_C \sigma_0^2 e^{-k_c t}}{2dt + \sigma_0^2} \exp\left(-\frac{1}{4dt + 2\sigma_0^2}\right) \left(1 + \frac{\varepsilon}{2dt + \sigma_0^2} + \dots\right). \quad (4.35)$$

4.2.2 Numerical Results

This part provides the numerical simulations for the radially symmetric case (4.4), with boundary conditions (4.5) and initial conditions (4.6) and (4.7). Moreover, $f(r, t)$ is assumed to be a step function, which is defined by (4.8).

To get the numerical solution, we need to write the system into an extrapolation formula to approximate the system of equations. The detailed steps to get the finite difference expression and the general formula are given in Appendix B.1.2. We use the notation $L_{i,j}^{(n)}$ to represent the value of L at the position (r_i, θ_j) and at time t_n . $B_{i,j}^{(n)}$ uses the same notation. Forward-difference formulas [15] are used to approximate all the derivatives. As we mentioned before, this is a radially symmetric case, so we only need to study its cross sections. Just to notice that we keep the index j in notations $L_{i,j}^{(n)}$ and $B_{i,j}^{(n)}$, even though the system doesn't depend on θ . That is because we want to keep the notation inconsistency and the formulas with this notation can be easily extended to more general cases.

However, the general expression is not valid for boundary points, because there are two

imaginary points $L_{N_r+1,j}^{(n)}$ and $L_{-1,j}^{(n)}$ when using the extrapolation formula to estimate the boundary points. So we have to determine the values for those points separately. In the following parts, we will discuss the boundary points and present the numerical results.

Boundary Conditions

For the boundary points, the time derivatives remain the same, while the partial derivative of L with respect to r needs to be modified, hence we have to reconsider the formulas for L at positions $r = r_0$ and $r = r_{N_r}$. As the formula for B only depends on time derivative, so we still can use that general extrapolation formula. When using the general extrapolation formula to compute $L_{0,j}^{(n+1)}$ and $L_{N_r,j}^{(n+1)}$, there are two imaginary points $L_{-1,j}^{(n)}$ and $L_{N_r+1,j}^{(n)}$, respectively. We choose $L_{N_r+1,j}^{(n)} = L_{N_r,j}^{(n)}$ and $L_{-1,j}^{(n)} = L_{1,j}^{(n)}$. Then we can get the extrapolation formulas for the boundary points. The reason to choose those values for imaginary points and all the extrapolation formulas for boundary points are given in Appendix B.1.3.

Numerical Simulations

As we already got the extrapolation formulas for all the points, then we can implement the numerical simulation for the radially symmetric case with the receptors on the boundary. We choose $\varepsilon = 2 \times 10^{-3}$ and the choices for other constants are based on the discussion in Section 2.3.

Figure 4.1 plots the ligand concentration at time $t = 1.0$, $t = 2.0$ and $t = 3.0$. The solutions at different times are plotted with different colors: black line is the initial ligand concentration, and the solutions at $t = 1.0$, $t = 2.0$ and $t = 3.0$ are colored with red, green and blue, respectively. We also plot its reflection next to the solution on the interval $[-1, 0]$, even though a solution for $r \in [0, 1]$ is enough to show the results. That is because the cross section of the real solution consists of two symmetric parts: the solution on interval $[0, 1]$ and its reflection.

Based on these plots, we can see the ligand concentration is invariably highest at the center of the studying region. The plots mainly show the diffusion of the ligand and it seems that the receptors have no effect on the ligand concentration. This is because the diffusion of the ligand is much slower than the rate of ligand being washed out, so the ligand can hardly reach the receptor compartment before being washed out. From another perspective, the phenomenon is caused by the fact that the receptor region is too far away from the initial ligand and it's quite difficult for the ligand to reach that region by diffusion.

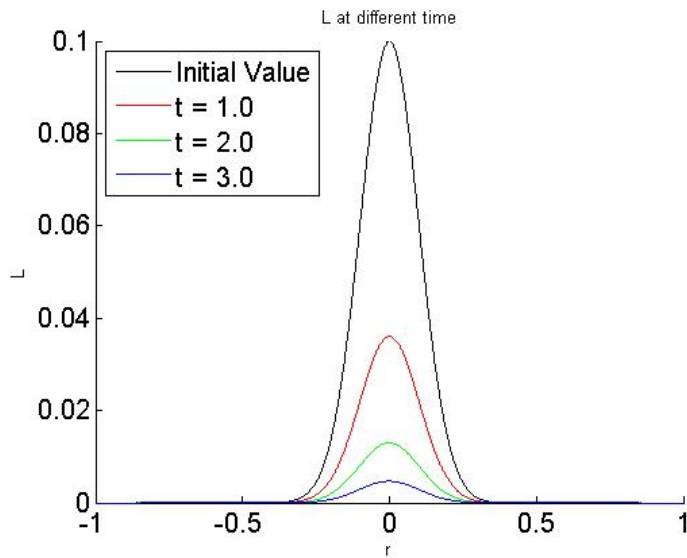


Figure 4.1: Numerical simulations of the radially symmetric case (4.4), with boundary conditions (4.5) and initial conditions (4.6) and (4.7). Here $f(r, t)$ is assumed to be a step function, which is defined by (4.8). L denotes the ligand concentration and r the spatial position. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 2.0$, and blue one represents that at time $t = 3.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 2 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

4.3 Radially Symmetric Case with Receptors at the Center

In this section, we consider another radially symmetric case with the receptors at the center. All the receptors are assumed to lie in a round disk with radius $\varepsilon \ll 1$. The initial condition of B is still zero everywhere. While the initial condition of L is defined by Gaussian equation, because we assume at the beginning the ligand concentration is highest at the center and it's getting lower when it's far away from the center. Thanks to radial symmetry, the analysis only needs to be focused on its cross section and all the variables don't depend on θ anymore. Thus, the general two-dimensional system becomes

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \left(\frac{\partial^2 L}{\partial r^2} + \frac{1}{r} \frac{\partial L}{\partial r} \right) - k_{\text{on}} f L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B, \end{cases} \quad (4.36)$$

along with boundary conditions:

$$\left. \frac{\partial L(r, t)}{\partial r} \right|_{r=0} = 0 \quad \text{and} \quad \left. \frac{\partial L(r, t)}{\partial r} \right|_{r=1} = 0, \quad (4.37)$$

and the initial conditions:

$$L(r, 0) = L_C \exp\left(-\frac{r^2}{2\sigma_0^2}\right) \quad \text{for } r \in [0, 1] \quad (4.38)$$

and

$$B(r, 0) \equiv 0 \quad \text{for any } r \in [0, 1]. \quad (4.39)$$

Again assuming $f(r, t)$, the concentration of receptors, is a step function, that is

$$f(r, t) \equiv \begin{cases} f_C & \text{for } r \in [0, \varepsilon), \\ 0 & \text{for } r \in [\varepsilon, 1]. \end{cases} \quad (4.40)$$

In the following part, we will give the numerical solution to this system.

4.3.1 Numerical Results

In this part, we use numerical method to solve system (4.36), along with boundary conditions (4.37) and initial conditions (4.38) and (4.39). Moreover, $f(r, t)$, the concentration of receptors, is defined by (4.40). We follow the notations from the previous section. The detailed steps to get the extrapolation formula and the general formula are given in Appendix B.1.2. The formulas for boundary points are shown in Appendix B.1.3. Note that the initial conditions and the assumption for f are different from the previous case. In the following part, we will present the numerical results.

Numerical Simulations

After getting the extrapolation formulas for all the points, we implement the numerical simulation for the radially symmetric system (4.36). We choose $\varepsilon = 2 \times 10^{-3}$ and the choices for other constants are based on the discussion in Section 2.3. Figure 4.2 plots the ligand concentrations at time $t = 1.0$, $t = 2.0$ and $t = 3.0$. The solutions at different

times are plotted with different colors: black line is the initial condition, and the solutions at $t = 1.0$, $t = 2.0$ and $t = 3.0$ are colored with red, green and blue, respectively. Same as previous case, we plot not only the solution on $r \in [0, 1]$ but also its reflection on the interval $[-1, 0]$.

Based on these plots, we can see when the procedure started the concentration of the ligand descended at the center of the region, where the receptor compartment is located. This is because most of the ligand in that area was bound to the receptors. However, in the end the ligand concentration is highest at the receptor compartment, which is also caused by the presences of the receptors. In the receptor compartment the ligand combined with the receptor and formed the ligand-receptor compound, while in other area most of the ligand was washed out. According to Figure 4.2, the ligand concentration had dramatic change in the receptor compartment. In order to have a clear view of that, we zoom in on the receptor region, see Figure 4.3. The receptor compartment has the lowest ligand concentration, because of the existence of the receptors.

Figure 4.2 and Figure 4.3 provide a lot of information about the ligand and present the change of ligand concentration due to the interactions between the ligand and the receptor. In the model, the ligand also binds to the receptor and forms the bound product. So we are also really interested in seeing the change of bound product density. Figure 4.4 presents the numerical solutions of B , the bound product of L and R . We can see the bound product has the highest concentration on the side near outer region when the procedure starts, but in the end the concentration is higher on the other side of the region.

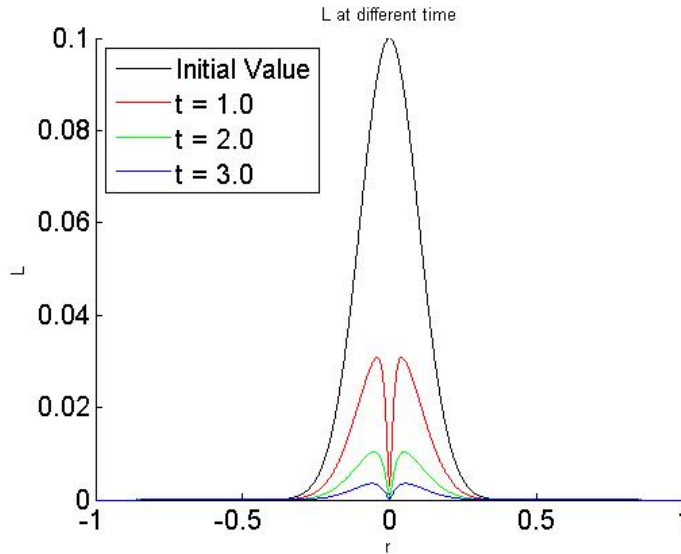


Figure 4.2: Numerical simulations of the radially symmetric case (4.36), with boundary conditions (4.37) and initial conditions (4.38) and (4.39). Here $f(r, t)$ is assumed to be a step function, which is defined by (4.40). L denotes the ligand concentration and r the spatial position. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 2.0$, and blue one represents that at time $t = 3.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 2 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

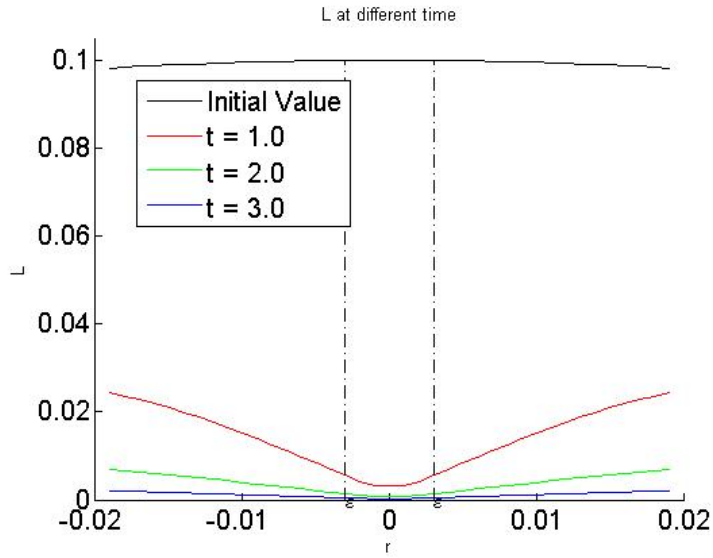


Figure 4.3: Numerical simulations of the radially symmetric case (4.36), with boundary conditions (4.37) and initial conditions (4.38) and (4.39). Here $f(r, t)$ is assumed to be a step function, which is defined by (4.40). L denotes the ligand concentration and r the spatial position. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 2.0$, and blue one represents that at time $t = 3.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 2 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

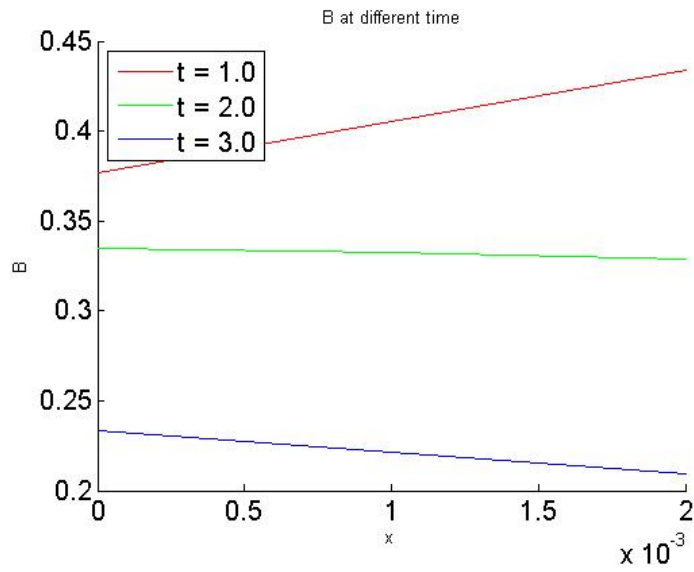


Figure 4.4: Numerical simulations of B of the radially symmetric case (4.36), with boundary conditions (4.37) and initial conditions (4.38) and (4.39). Here $f(r, t)$ is assumed to be a step function, which is defined by (4.40). B denotes the concentration of bound product and r the spatial position. Red line shows the ligand concentration at time $t = 1.0$, green line shows that at time $t = 2.0$, and blue one represents that at time $t = 3.0$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 10^{-4}$, $\varepsilon = 2 \times 10^{-3}$, $L_C = 0.1$ and $f_C = 286.43$.

4.4 Nonsymmetric Case

In this section, we consider a case without radial symmetry. Using (4.1) as the diffusion term in system (2.4), we get the following system,

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d \left(\frac{\partial^2 L}{\partial r^2} + \frac{1}{r^2} \frac{\partial^2 L}{\partial \theta^2} + \frac{1}{r} \frac{\partial L}{\partial r} \right) \\ \quad - k_{\text{on}} f L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B, \end{cases} \quad (4.41)$$

with boundary condition

$$\left. \frac{\partial L(r, \theta, t)}{\partial r} \right|_{r=1} = 0, \quad (4.42)$$

and initial conditions

$$L(r, \theta, 0) = L_C \exp\left(-\frac{r^2}{2\sigma_0^2}\right) \quad \text{and} \quad B(r, \theta, 0) \equiv 0, \quad (4.43)$$

for $r \in [0, 1]$ and any $\theta \in [0, 2\pi)$. This system will be our model throughout this section. The receptor compartment is assumed to be $(r_1, r_2) \times (\theta_1, \theta_2)$ and located neither at the center nor on the boundary of the entire region. Based on the assumptions in Chapter 2, the receptor region should be tiny enough compared to the whole region, which requires $(r_2 - r_1) \cdot (\theta_2 - \theta_1) \ll 1$. Moreover, assuming $f(r, \theta, t)$, the concentration of receptors, is a step function and it doesn't depend on time, so $f(r, \theta, t)$ is defined as

$$f(r, \theta, t) \equiv \begin{cases} f_C & \text{for } r \in (r_1, r_2) \text{ and } \theta \in (\theta_1, \theta_2), \\ 0 & \text{otherwise,} \end{cases} \quad \text{for any } t, \quad (4.44)$$

where f_C is a constant.

4.4.1 Numerical Results

To have a clear view about the ligand-receptor interactions, we will run the numerical simulation to solve the nonsymmetric case (4.41) along with boundary conditions (4.42) and initial conditions (4.43). Following the steps for the radially symmetric cases in previous sections, we first get the general extrapolation formula to approximate the system, then consider the boundary conditions, and in the end present the result of 3D simulation. The notations are inherited from the previous cases, and again forward-difference formulas are used to approximate all the derivatives. Appendix B.2.1 provides the detailed calculations to get the general extrapolation formula. In the following, we will discuss the boundary points separately and provide the numerical solution to this model. We use 3D plot to present our solution. The xy -plane denotes the region under study and z -axis represents the concentration of ligand, so we can clearly see which area has the highest density of ligand.

Boundary Points

As we know, the general extrapolation formula is only valid for the interior points. We have to deal with boundary points separately. Here the problem can be even more

complicated. There are boundaries at $r = 0$, $r = 1$, $\theta = 0$, and $\theta = 2\pi$, so it's necessary to determine several imaginary points, such as $L_{-1,j}^{(n)}$, $L_{N_r+1,j}^{(n)}$, $L_{i,-1}^{(n)}$ and $L_{i,N_\theta+1}^{(n)}$ for $0 \leq i \leq N_r$ and $0 \leq j \leq N_\theta$. As there is no definition for these points, we have to choose certain values for them. We divide those boundary points into several groups and discuss them separately. Following what we have done for the radially symmetric cases, we leave the detailed steps and the results in Appendix B.2.2.

Numerical Simulations This part presents the numerical results of the system (4.41) with boundary conditions (4.42) and initial conditions (4.43). Moreover, $f(x, t)$, the concentration of receptors, is defined by (4.44). As is standard, we assume a positive angular coordinate means that the angle θ is measured counterclockwise from positive x -axis. We use 3D simulation to present our results, x and y coordinates define the positions of the region under study, while z -axis shows the concentration of ligand, which clearly shows how the ligand concentration changes at different times.

Here we choose $r_1 = 0.45$, $r_2 = 0.5$, $\theta_1 = \frac{2\pi}{5}$, and $\theta_2 = \frac{\pi}{2}$. The choices for other constants are based on the discussion in Section 2.3. We first ran the simulation with following constants: $k_{\text{on}} = 1$, $k_{\text{off}} = 2$, $k_c = 1$, $d = 10^{-4}$, $L_C = 0.1$ and $f_C = 286.43$. But the results we get are not exactly what we want. It seems that almost no ligand can reach the receptor region. The reason is that the diffusion coefficient is too small, so the ligand could hardly reach the receptor compartment before being washed out. We want to see how the interactions between the ligand and the receptor affect the concentration of the ligand. Hence, we increase the diffusion coefficient, letting $d = 6$, and run the simulation again, we get better results, which are given in Figure 4.5. The plots show the 3D simulations of system (4.41) from time $t = 0$ to $t = 12.50$. The vertical axis in each figure is the concentration of the ligand, and the colors denote the concentration of the ligand, on a scale from blue (low) to red (high). We can see the ligand started from the center and gradually spread out by diffusion. Although the total amount of ligand was decreasing, more and more ligand gathered at the receptor compartment. That is because in the receptor compartment the ligand was bound to the receptors, while in the rest of the area most of the ligand was washed out of the brain.

In Figure 4.6, we plot the cross sections of the numerical solutions at different times. Each cross section is the intersection of the solution with a vertical plane passing through the center of the receptor compartment and the origin. Although our system is in polar coordinates, when plotting the curves we still use the Cartesian coordinates. That is why in the graph the horizontal axis is x -coordinate instead of radial coordinate. The vertical axis is the ligand concentration. We marked the cross sections of the solutions at different times with different colors. From the plots, we can see the total amount of ligand decreased all the time and more and more gathered around the receptor compartment.

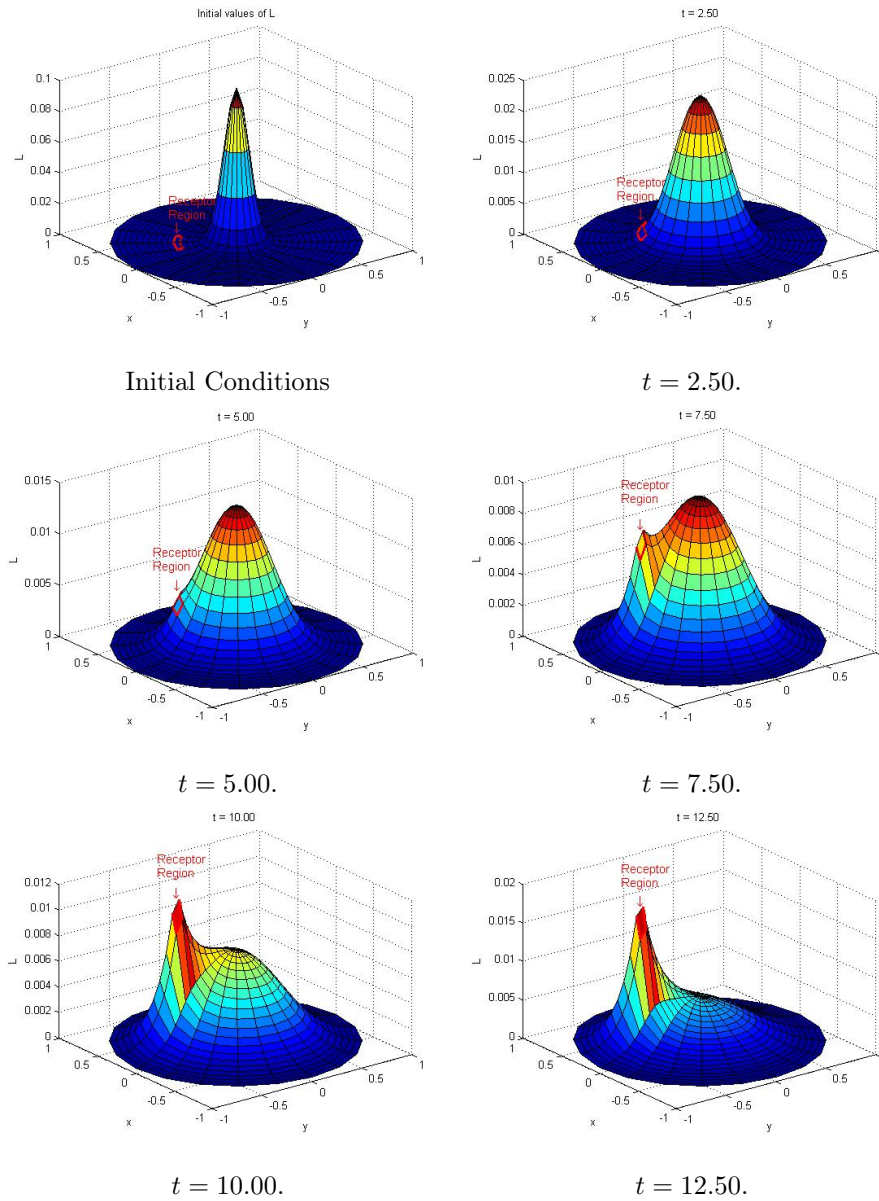


Figure 4.5: Numerical solutions of system (4.41) along with boundary conditions (4.42) and initial conditions (4.43). $f(r, \theta, t)$ is defined by (4.44). First subfigure shows the initial values of the ligand. The other five show the ligand concentrations at time $t = 2.50$, $t = 5.00$, $t = 7.50$, $t = 10.00$ and $t = 12.50$, respectively. The vertical axis is the concentration of ligand. The blue disk is the area under study. The receptor region is the area marked in red. The colors denote the concentration of the ligand, on a scale from blue (low) to red (high). Each subfigure has different scale of the vertical axis: the vertical axis range of the first subfigure is $[0, 0.1]$, that of the second subfigure is $[0, 0.03]$, the vertical axes of the the subfigures at time $t = 5.00$ and $t = 12.50$ range from 0 to 0.02, and at time $t = 7.50$ and $t = 10.00$ the scale of vertical axis is $[0, 0.012]$. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 6$, $L_C = 0.1$, $f_C = 286.43$, $r_1 = 0.45$, $r_2 = 0.5$, $\theta_1 = \frac{2\pi}{5}$ and $\theta_2 = \frac{\pi}{2}$.

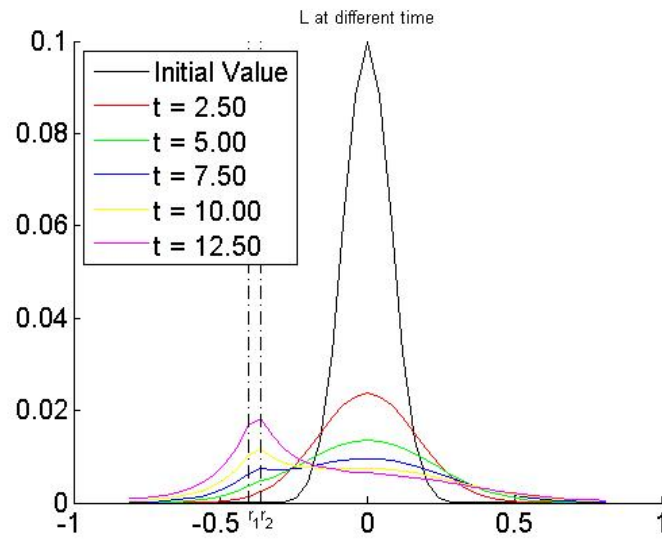


Figure 4.6: Cross sections of the numerical solutions of the system (4.41), with boundary conditions (4.42) and initial conditions (4.43). Here $f(r,t)$ is assumed to be a step function, which is defined by (4.44). L denotes the ligand concentration and r the spatial position. Plot shows the cross sections of the solution through the receptor compartment at time $t = 0$, $t = 2.50$, $t = 5.00$, $t = 7.50$, $t = 10.00$ and $t = 12.50$. The solutions at different times are marked by different colors. Parameter values: $k_{on} = 1$, $k_{off} = 2$, $k_c = 1$, $d = 6$, $L_C = 0.1$, $f_C = 286.43$, $r_1 = 0.45$, $r_2 = 0.5$, $\theta_1 = \frac{2\pi}{5}$ and $\theta_2 = \frac{\pi}{2}$.

Chapter 5

Summary

This thesis was performed to gain further insight in understanding the interaction between the ligand and the receptor. Adding diffusion term to the existing model, we built a general model to simulate the process, which is

$$\begin{cases} \frac{\partial L}{\partial t} = -k_c L + d\Delta L - k_{\text{on}} f L + (k_{\text{off}} + k_{\text{on}} L) B \\ \frac{\partial B}{\partial t} = k_{\text{on}} f L - (k_{\text{off}} + k_{\text{on}} L) B, \end{cases} \quad (5.1)$$

where L denotes the concentration of the ligand and B is the concentration of ligand-receptor bound product. This model considered three factors, which are the ligand being washed out of brain, the basic binding mechanism with the receptors, and the diffusion of the ligand. We assumed there was no flux at the boundary.

Firstly, the general model was considered in one-dimensional space. Four cases were given, the first two had the same location of the receptor compartment, which was located at one end of the region under study, while the last two assumed the receptors were located at the center of the whole region. The ligand concentration decreased during the whole procedure, because the ligand was constantly being washed out of the brain. At the beginning of the procedure, the concentration of the ligand in the receptor compartment decreased much faster than that in the outer region, but in the end more and more ligand gathered in the receptor compartment. This phenomenon corresponded with what we expected. In the receptor region, the ligand was not only washed out of the brain but also bound to the receptors when the process just started. However, when t enlarging the ligand was still bound to the receptors in the inner region, while the majority of the ligand outside that compartment was washed out. Compared to the change of ligand concentration, the density of the bound product didn't have dramatic change throughout the whole process. When the experiment started the bound product of the ligand and the receptor had the highest concentration on the side near the outer region, but it gradually changed to the other way round.

The detailed steps to solve the first one-dimensional case were given. The case assumed the receptor compartment was located on the boundary and had the following initial conditions: $L_{\text{ini}}(x)$ was a constant and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. The analytical solution was based on the method of matched asymptotic expansions. Getting the outer solution, we used Duhamel's principle. The numerical solution was given, and we also

compared it with the analytical solution. According to the comparison, the analytical outer solution can perfectly match the numerical solution. However, the expansion of the inner solution was not accurate enough. That is because the expansion only had two terms and the second term was around $\mathcal{O}(10^{-3})$, but the numerical solution was about $\mathcal{O}(10^{-4})$. The solution was too small to be approximated by a two-term expansion. Considering higher-order terms would achieve a better approximation. Based on the numerical simulations, the ligand concentration decreased very quickly, because most of the ligand was washed out of the brain. Since the ligand was bound to the receptors in the receptor compartment, in the end the ligand concentration in this region was higher than the rest of the area.

The numerical simulations for other three one-dimensional cases were given as well. One of the cases also assumed the receptor region was located at one end of the region, but with different initial conditions, $L_{\text{ini}}(x)$ was constant for $x_1 < x < x_2$ and $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$. Based on the first simulation, the ligand was washed out quickly and the ligand was difficult to reach the receptor compartment via diffusion. In order to see the effect of the receptors on ligand concentration, we decreased the elimination rate k_c and increased the diffusion coefficient d , and then ran the simulation again. It turns out that the ligand on the side with receptors had less density than the other side. That is because in the receptor compartment the ligand needed to be bound to the receptors.

The other two cases assumed the receptor compartment was located at the center of the region. The initial condition of B for these two cases is $B(x, 0) \equiv 0$ for $0 \leq x \leq 1$, but they had different initial conditions for L : one assumed $L_{\text{ini}}(x)$ was a constant for $0 \leq x \leq 1$; the other supposed $L_{\text{ini}}(x)$ was constant for $x_1 < x < x_2$. In both cases, the ligand concentration plummeted at the center of the receptor compartment, because the ligand was also bound to the receptors besides being washed out of that region. Moreover, the both cases had the same initial values at the receptor compartment, so in the two scenarios the ligand at the center got very close to zero once the procedure started.

The second part of this dissertation analysed the model in two-dimensional space. Based on all the numerical results, we can see when the procedure started the concentration of the ligand plunged at the inner region, where the receptors were located. However, at the end of the simulation the ligand concentration was highest in that region. Both phenomena were caused by the presences of the receptors. At the beginning, the ligand in the receptor compartment was bound to the receptors besides being washed out. At the end of the procedure the ligand combined with the receptors and formed the ligand-receptor compounds, while in the outer region most of the ligand was washed out. The change of the concentration of the bound product is similar to that in the one-dimensional model. The bound product had highest concentration on the side near outer region when the procedure started, but in the end the concentration was higher on the other side of the inner region.

Three two-dimensional cases were provided, the first two with radial symmetry and the last one without symmetry. In the first case, we supposed the receptors were located on the circular boundary of the whole region. Based on these plots, we can see the ligand concentration is invariably highest at the center of the region under study. It looks like the plots just showed the diffusion of the ligand and the receptors had no

effect on the ligand concentration. That is because the diffusion of the ligand was much slower than the rate of ligand being washed out, so the ligand didn't have enough time to reach the receptor compartment before being washed out. From another perspective, the receptor region was too far away from the initial ligand and it's quite difficult for the ligand to reach that region by diffusion.

The other radially symmetric case assumed the receptor compartment was located at the center of the region and was solved with numerical method. The numerical solutions of ligand concentration and the density of ligand-receptor bound product are presented. The concentrations of the ligand around the receptor region at different times were provided to give a clear view of what happened around the receptor compartment. The results of the bound product were given at the end of that section. According to the plots we got, the concentration of the ligand dived at the center of the region, where the receptor compartment was located, just when the procedure started. However, the ligand concentration was eventually highest in the inner region. The change of the concentration of the ligand-receptor compound went through a gradual procedure, within which the original peak of the density became the nadir, and vice versa.

For the two-dimensional case without symmetry, we gave the numerical solution and presented the change of ligand concentration with 3D plots. We first ran the simulation with the constants from Section 2.3. Because of a small diffusion coefficient the ligand could hardly reach the receptor compartment, consequently we didn't see the interactions between the ligand and the receptors. Hence, we accelerated the diffusion and ran the simulation again. We clearly see the ligand gradually diffused from the center and eventually gathered at the receptor compartment. The reason is that in the receptor compartment the ligand was bound to the receptors, while most of the ligand outside had already been washed out of the brain.

Chapter 6

Acknowledgments

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Appendix A

One-dimensional Model

A.1 Analytical Solution

A.1.1 Writing $L_{\text{outer}}(x, t)$ as a combination of error functions.

The outer solution

$$L(x, t) = e^{-k_c t} \frac{L_C}{2\sqrt{d\pi t}} \int_0^{1-\varepsilon} \left[\exp\left(-\frac{(x-r)^2}{4dt}\right) + \exp\left(-\frac{(x+r)^2}{4dt}\right) \right] dr$$

can be written as

$$L_{\text{outer}}(x, t) = e^{-k_c t} \frac{L_C}{2\sqrt{d\pi t}} \int_0^{1-\varepsilon} \left[\exp\left(-\left(\frac{x}{2\sqrt{dt}} - \frac{r}{2\sqrt{dt}}\right)^2\right) + \exp\left(-\left(\frac{x}{2\sqrt{dt}} + \frac{r}{2\sqrt{dt}}\right)^2\right) \right] dr.$$

Letting $u = \frac{r}{2\sqrt{dt}}$, we get

$$L_{\text{outer}}(x, t) = e^{-k_c t} \frac{L_C}{\sqrt{\pi}} \int_0^{\frac{1-\varepsilon}{2\sqrt{dt}}} \left[\exp\left(-\left(\frac{x}{2\sqrt{dt}} - u\right)^2\right) + \exp\left(-\left(\frac{x}{2\sqrt{dt}} + u\right)^2\right) \right] du.$$

Then splitting the integral into two integrals, we have

$$\begin{aligned} L_{\text{outer}}(x, t) &= e^{-k_c t} \frac{L_C}{\sqrt{\pi}} \int_0^{\frac{1-\varepsilon}{2\sqrt{dt}}} \left[\exp\left(-\left(\frac{x}{2\sqrt{dt}} - u\right)^2\right) + \exp\left(-\left(\frac{x}{2\sqrt{dt}} + u\right)^2\right) \right] du \\ &= e^{-k_c t} \frac{L_C}{\sqrt{\pi}} \left[\int_0^{\frac{1-\varepsilon}{2\sqrt{dt}}} \exp\left(-\left(\frac{x}{2\sqrt{dt}} - u\right)^2\right) du \right. \\ &\quad \left. + \int_0^{\frac{1-\varepsilon}{2\sqrt{dt}}} \exp\left(-\left(\frac{x}{2\sqrt{dt}} + u\right)^2\right) du \right]. \end{aligned}$$

Defining $w_1 = \frac{x}{2\sqrt{dt}} - u$ for the first integral, we have

$$\begin{aligned} & \int_0^{\frac{1-\varepsilon}{2\sqrt{dt}}} \exp\left(-\left(\frac{x}{2\sqrt{dt}} - u\right)^2\right) du \\ &= -\int_{\frac{x}{2\sqrt{dt}}}^{\frac{x-1+\varepsilon}{2\sqrt{dt}}} e^{-w_1^2} dw_1 = \int_{\frac{x-1+\varepsilon}{2\sqrt{dt}}}^{\frac{x}{2\sqrt{dt}}} e^{-w_1^2} dw_1. \end{aligned}$$

For the second one, we define $w_2 = \frac{x}{2\sqrt{td}} + u$ and get

$$\int_0^{\frac{1-\varepsilon}{2\sqrt{dt}}} \exp\left(-\left(\frac{x}{2\sqrt{dt}} + u\right)^2\right) du = \int_{\frac{x}{2\sqrt{dt}}}^{\frac{x+1-\varepsilon}{2\sqrt{dt}}} e^{-w_2^2} dw_2.$$

Using the previous results in the outer solution, we obtain

$$\begin{aligned} L(x, t) &= e^{-k_c t} \frac{LC}{\sqrt{\pi}} \left[\int_0^{\frac{1-\varepsilon}{2\sqrt{dt}}} \exp\left(-\left(\frac{x}{2\sqrt{dt}} - u\right)^2\right) du \right. \\ &\quad \left. + \int_0^{\frac{1-\varepsilon}{2\sqrt{dt}}} \exp\left(-\left(\frac{x}{2\sqrt{dt}} + u\right)^2\right) du \right] \\ &= e^{-k_c t} \frac{LC}{\sqrt{\pi}} \left[\int_{\frac{x-1+\varepsilon}{2\sqrt{td}}}^{\frac{x}{2\sqrt{td}}} e^{-w_1^2} dw_1 + \int_{\frac{x}{2\sqrt{td}}}^{\frac{x+1-\varepsilon}{2\sqrt{td}}} e^{-w_2^2} dw_2 \right] \\ &= e^{-k_c t} \frac{LC}{2} \left(\operatorname{erf}\left(\frac{x+1-\varepsilon}{2\sqrt{dt}}\right) - \operatorname{erf}\left(\frac{x-1+\varepsilon}{2\sqrt{dt}}\right) \right), \end{aligned}$$

where

$$\operatorname{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-w^2} dw.$$

A.1.2 Determining the Balance in the Inner Solution

Using asymptotic expansion to approximate the inner solution, we get following system:

$$\begin{aligned} & \frac{\partial^2 L_0}{\partial \bar{x}^2} + \varepsilon^\alpha \frac{\partial^2 L_1}{\partial \bar{x}^2} + \dots \\ & \quad \textcircled{1} \qquad \qquad \textcircled{2} \\ &= \frac{\varepsilon^{2\delta}}{d} \left(\frac{\partial L_0}{\partial t} + k_c L_0 + k_{\text{on}} f_C L_0 - (k_{\text{off}} + k_{\text{on}} L_0) B_0 \right) \\ & \quad \textcircled{3} \\ &+ \frac{\varepsilon^{2\delta+\alpha}}{d} \left(\frac{\partial L_1}{\partial t} + k_c L_1 + k_{\text{on}} f_C L_1 - k_{\text{on}} L_1 B_0 \right) + \dots \\ & \quad \textcircled{4} \end{aligned} \tag{A.1}$$

As we know $\alpha > 0$ and $\delta > 0$, so we can conclude that $\textcircled{1}$ is the leading-order term and $\textcircled{4}$ has the highest order among the four terms in equation (A.1). It remains to determine the balance between $\textcircled{2}$ and $\textcircled{3}$. There are following possibilities:

(i) ②~③.

The condition ②~③ requires that $\alpha = 2\delta$. With this, $L_1(\bar{x}, t)$ should satisfy

$$\frac{\partial^2 L_1}{\partial \bar{x}^2} = \frac{1}{d} \left(\frac{\partial L_0}{\partial t} + k_c L_0 + k_{\text{on}} L_0 f_C - (k_{\text{off}} + k_{\text{on}} L_0) B_0 \right),$$

at the same time $L_1(\bar{x}, 0) = 0$. According to (3.14) and (3.19), L_0 and B_0 only depend on t . Simplifying the equation, we have

$$\frac{\partial^2 L_1}{\partial \bar{x}^2} = \frac{1}{d} \tilde{L}_{10}(t), \quad (\text{A.2})$$

where

$$\tilde{L}_{10}(t) = \frac{\partial L_0}{\partial t} + k_c L_0 + k_{\text{on}} L_0 f_C - (k_{\text{off}} + k_{\text{on}} L_0) B_0. \quad (\text{A.3})$$

As $\tilde{L}_{10}(t)$ is a function only depending on t , so the solution to equation (A.2) is

$$L_1(\bar{x}, t) = C_2(t) + C_3(t)\bar{x} + \frac{1}{2d}\bar{x}^2\tilde{L}_{10}(t),$$

where $C_1(t)$ and $C_2(t)$ are two unknown functions depending on t . Based on $L_0(\bar{x}, 0) = L_C$, $B_0(\bar{x}, 0) = 0$ and expression (A.3), we have $\tilde{L}_{10}(0) \neq 0$, which implies $L_1(\bar{x}, 0) \neq 0$. So the previous expression doesn't satisfy the initial condition. Hence, this case is not possible.

(ii) ③ balances itself and ② is higher order.

We need $2\delta < \alpha$ to fulfill this condition. Then we get an extra requirement for $L_0(\bar{x}, t)$, that is

$$\frac{\partial L_0}{\partial t} + k_c L_0 + k_{\text{on}} f_C L_0 - (k_{\text{off}} + k_{\text{on}} L_0) B_0 = 0.$$

Based on results (3.13) and (3.18), $L_0(\bar{x}, t)$ and $B_0(\bar{x}, t)$ cannot satisfy this extra condition, so this case is also not the one we want.

(iii) ② \gg ③.

This condition requires $\alpha > 2\delta$, so ① and ② are the first two leading-order terms. In this case, the conclusion is consistent with the original assumptions, and so this is the balancing we are looking for.

A.2 Numerical Solution

A.2.1 Extrapolation Formula

To implement the numerical method, we need to write our system into the extrapolation formula. We first specify each of the independent variables on a grid as

$$\begin{cases} x_i = x_0 + i\Delta x, & \text{for } i = 0, \dots, N_x \\ t_n = t_0 + n\Delta t, & \text{for } n = 0, \dots, N_t, \end{cases}$$

where x_0, t_0 are the starting points and $\Delta x, \Delta t$ are the step sizes for each variable. Designate $L_i^{(n)}$ as the solution to the differential equation at the position x_i and at time

t_n . We use forward difference expressions [15] to approximate the partial derivatives of L . At time t_n , the derivative of L with respect to t can be approximated by

$$\left. \frac{\partial L}{\partial t} \right|_{x_i} \approx \frac{L_i^{(n+1)} - L_i^{(n)}}{\Delta t} + \mathcal{O}(\Delta t). \quad (\text{A.4})$$

The other partial derivatives of L are approximated by

$$\begin{aligned} \left. \frac{\partial L}{\partial x} \right|_{x_i} &\approx \frac{L_{i+1}^{(n)} - L_i^{(n)}}{\Delta x} + \mathcal{O}(\Delta x) \\ \text{and } \left. \frac{\partial^2 L}{\partial x^2} \right|_{x_i} &\approx \frac{\frac{L_{i+1}^{(n)} - L_i^{(n)}}{\Delta x} - \frac{L_i^{(n)} - L_{i-1}^{(n)}}{\Delta x}}{\Delta x} + \mathcal{O}(\Delta x) \\ &\approx \frac{L_{i+1}^{(n)} - 2L_i^{(n)} + L_{i-1}^{(n)}}{(\Delta x)^2} + \mathcal{O}(\Delta x). \end{aligned}$$

Using previous estimations, the general one-dimensional system can be written as extrapolation formula, i.e.

$$\left\{ \begin{aligned} \frac{L_i^{(n+1)} - L_i^{(n)}}{\Delta t} &= -k_c L_i^{(n)} + d \cdot \frac{L_{i+1}^{(n)} - 2L_i^{(n)} + L_{i-1}^{(n)}}{(\Delta x)^2} - k_{\text{on}} f L_i^{(n)} \\ &\quad + (k_{\text{off}} + k_{\text{on}} L_i^{(n)}) B_i^{(n)} \\ \frac{B_i^{(n+1)} - B_i^{(n)}}{\Delta t} &= k_{\text{on}} L_i^{(n)} f - (k_{\text{off}} + k_{\text{on}} L_i^{(n)}) B_i^{(n)}. \end{aligned} \right.$$

We put all the terms relating to t_{n+1} on the left side and the terms with t_n on the right, then we have

$$\left\{ \begin{aligned} L_i^{(n+1)} &= \left(1 - k_c \Delta t - \frac{2d\Delta t}{(\Delta x)^2} - k_{\text{on}} \Delta t f \right) L_i^{(n)} + \frac{d\Delta t}{(\Delta x)^2} L_{i+1}^{(n)} \\ &\quad + \frac{d\Delta t}{(\Delta x)^2} L_{i-1}^{(n)} + \Delta t k_{\text{off}} B_i^{(n)} + \Delta t k_{\text{on}} L_i^{(n)} B_i^{(n)} \\ B_i^{(n+1)} &= \Delta t k_{\text{on}} f L_i^{(n)} + (1 - \Delta t k_{\text{off}}) B_i^{(n)} - \Delta t k_{\text{on}} L_i^{(n)} B_i^{(n)}. \end{aligned} \right. \quad (\text{A.5})$$

A.2.2 Boundary Conditions

In this part, we will study the boundary points. At the boundary points, the time derivatives remain the same, hence the approximations (A.4) still hold true. While the partial derivative of L with respect to x will change a little bit. Based on no-flux boundary conditions, we choose $L_{N_x+1}^{(n)} = L_{N_x}^{(n)}$ and $L_0^{(n)} = L_1^{(n)}$. So at the boundary $x = 1$, the extrapolation formula becomes

$$\left\{ \begin{aligned} L_{N_x}^{(n+1)} &= \left(1 - k_c \Delta t - \frac{d\Delta t}{(\Delta x)^2} - k_{\text{on}} \Delta t f \right) L_{N_x}^{(n)} + \frac{d\Delta t}{(\Delta x)^2} L_{N_x-1}^{(n)} \\ &\quad + \Delta t k_{\text{off}} B_{N_x}^{(n)} + \Delta t k_{\text{on}} L_{N_x}^{(n)} B_{N_x}^{(n)} \\ B_{N_x}^{(n+1)} &= \Delta t k_{\text{on}} f L_{N_x}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{N_x}^{(n)} - \Delta t k_{\text{on}} L_{N_x}^{(n)} B_{N_x}^{(n)}. \end{aligned} \right. \quad (\text{A.6})$$

Appendix B

Two-dimensional Model

B.1 Radially Symmetric Cases

B.1.1 Balancing of the Inner Solution

We already got the expressions of $L_0(\bar{r}, t)$ and $B_0(\bar{r}, t)$, but we are still interested in the expression of $L_1(\bar{r}, t)$, since we want a more precise solution. To get the solution of $L_1(\bar{r}, t)$, we need to balance the other terms of equation (4.23). As we already knew the leading-order term is ①, and based on $\bar{\alpha} > 0$ and $\bar{\delta} > 0$, we can conclude that ④, ⑤ and ⑥ are the higher-order terms in the equation. It remains to determine the balance between ② and ③. There are following possibilities:

(i) ②~③.

The condition ②~③ requires that $\bar{\alpha} = \bar{\delta}$, then we have

$$\frac{\partial^2 L_1}{\partial \bar{r}^2} + \frac{\partial L_0}{\partial \bar{r}} = 0 \quad \text{with } L_1(\bar{r}, 0) = 0. \quad (\text{B.1})$$

Using the result (4.27), we have

$$\frac{\partial^2 L_1}{\partial \bar{r}^2} + L_{01}(t) = 0,$$

which can be solved by

$$L_1(\bar{r}, t) = C_1(t) + C_2(t)\bar{r} - \frac{1}{2}\bar{r}^2 L_{01}(t),$$

where $C_1(t)$ and $C_2(t)$ are also two undetermined functions depending on t . According to the initial condition, we have $C_1(0) = C_2(0) = L_{01}(0) = 0$, the inner solution is approximated by

$$L_{\text{inner}}(\bar{r}, t) = L_{00}(t) + L_{01}(t)\bar{r} + \varepsilon^{\bar{\alpha}} \left(C_1(t) + C_2(t)\bar{r} - \frac{1}{2}\bar{r}^2 L_{01}(t) \right).$$

Writing the inner solution in terms of intermediate variable $r_{\bar{\eta}} = \frac{r-1+\varepsilon}{\varepsilon^{\bar{\eta}}}$, we have

$$\begin{aligned} L_{\text{inner}}(\bar{r}, t) = & L_{00}(t) + \left(\varepsilon^{1-\bar{\delta}} - \varepsilon^{\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} \right) L_{01}(t) \\ & + \varepsilon^{\bar{\alpha}} C_1(t) + \left(\varepsilon^{\bar{\alpha}+1-\bar{\delta}} - \varepsilon^{\bar{\alpha}+\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} \right) C_2(t) \\ & - \frac{\varepsilon^{\bar{\alpha}}}{2} \left(\varepsilon^{1-\bar{\delta}} - \varepsilon^{\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} \right)^2 L_{01}(t). \end{aligned}$$

As $\bar{\alpha} = \bar{\delta}$, so we can simplify the previous equation, which becomes

$$\begin{aligned} L_{\text{inner}}(\bar{r}, t) = & L_{00}(t) + \left(\varepsilon^{1-\bar{\delta}} - \varepsilon^{\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} \right) L_{01}(t) + \varepsilon^{\bar{\delta}} C_1(t) \\ & + \left(\varepsilon - \varepsilon^{\bar{\eta}} r_{\bar{\eta}} \right) C_2(t) - \frac{\varepsilon^{\bar{\delta}}}{2} \left(\varepsilon^{1-\bar{\delta}} - \varepsilon^{\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} \right)^2 L_{01}(t). \end{aligned}$$

Several terms need to be determined, while there are only two terms in the outer expansion. We cannot determine all the unknowns with those two terms, so we need higher-order terms of outer solution, which we don't want to consider. Hence this case is not what we are looking for.

(ii) ② balances itself and ③ is higher-order term.

This condition requires $\bar{\alpha} < \bar{\delta}$. Under this condition, we have to solve the following equation:

$$\frac{\partial^2 L_1}{\partial \bar{r}^2} = 0 \quad \text{with } L_1(\bar{r}, 0) = 0.$$

The solution to this equation is

$$L_1(\bar{r}, t) = L_{10}(t) + L_{11}(t)\bar{r} \quad \text{with } L_{10}(0) = L_{11}(0) = 0.$$

So the approximation of inner solution is

$$L_{\text{inner}}(\bar{r}, t) = L_{00}(t) + L_{01}(t)\bar{r} + \varepsilon^\alpha (L_{10}(t) + L_{11}(t)\bar{r}).$$

Substituting \bar{r} with intermediate variable $r_{\bar{\eta}}$, we have

$$\begin{aligned} L_{\text{inner}}(\bar{r}, t) = & L_{00}(t) + \left(\varepsilon^{1-\bar{\delta}} - \varepsilon^{\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} \right) L_{01}(t) \\ & + \varepsilon^{\bar{\alpha}} L_{10}(t) + \left(\varepsilon^{\bar{\alpha}+1-\bar{\delta}} - \varepsilon^{\bar{\alpha}+\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} \right) L_{11}(t). \end{aligned}$$

To match inner and outer solutions, we have to determine the values of $\bar{\alpha}$, $\bar{\delta}$ and $\bar{\eta}$, or at least their relations. We start with determining the dominating term and there are following possibilities:

(a) $L_{00}(t) \sim \varepsilon^{1-\bar{\delta}} L_{01}(t)$.

This condition requires $1 - \bar{\delta} = 0$, which means $\bar{\delta} = 1$. Then the inner solution becomes

$$\begin{aligned} L_{\text{inner}}(\bar{r}, t) = & (L_{00}(t) + L_{01}(t)) - \varepsilon^{\bar{\eta}-1} r_{\bar{\eta}} L_{01}(t) \\ & + \varepsilon^{\bar{\alpha}} (L_{10}(t) + L_{11}(t)) - \varepsilon^{\bar{\alpha}+\bar{\eta}-1} r_{\bar{\eta}} L_{11}(t). \end{aligned}$$

To determine all the terms we need higher-order terms in the outer solution, which is not what we want. So we will not consider this case.

(b) $\varepsilon^{1-\bar{\delta}} L_{01}(t)$ is the leading term.

To fulfill this condition, we need $1 - \bar{\delta} < 0$, that is $\bar{\delta} > 1$. And we can get $L_{01}(t) = 0$. Then we can balance $L_{00}(t)$ with the first term of outer solution. Because $1 - \bar{\delta} < 0$ and $\bar{\alpha} < \bar{\delta}$, we have $\bar{\alpha} + 1 - \bar{\delta} < \bar{\alpha}$ and $\bar{\alpha} + 1 - \bar{\delta} < 1$, which means we can only balance $-\varepsilon^{\bar{\alpha}+\bar{\eta}-\bar{\delta}} r_{\bar{\eta}} L_{11}(t)$ with the second term of outer solution. But there doesn't exist $r_{\bar{\eta}}$ in the second term of the outer solution, so it's still not possible to balance the terms.

(c) $L_{00}(t)$ is the leading term.

This condition requires $1 - \bar{\delta} > 0$, i.e. $\bar{\delta} < 1$. As $\bar{\delta} > 0$ and $\bar{\alpha} < \bar{\delta}$, so we have $1 - \bar{\delta} < 1$, $\bar{\alpha} < 1$ and $\bar{\alpha} + 1 - \bar{\delta} < 1$. While the second term of outer solution has order $O(\varepsilon)$, hence $L_{01}(t) = L_{10}(t) = L_{11}(t) = 0$, which is not what we are looking for.

No matter how we choose $\bar{\delta}$, there is no suitable balancing for the second term of the inner solution. Hence, this case is not possible either.

(iii) ③ balances itself and ② is higher order.

We need $\bar{\delta} < \bar{\alpha}$ to fulfill this condition. With this, ① and ② are the first two terms in equation (4.23). In this case, the conclusion is consistent with the original assumptions and this is the balancing we are looking for.

B.1.2 Extrapolation Formula

To use an extrapolation formula to approximate the system, we first specify each of the independent variables on a grid as

$$\begin{cases} r_i = r_0 + i\Delta r & i = 0, \dots, N_r \\ \theta_j = \theta_0 + j\Delta\theta & j = 0, \dots, N_\theta \\ t_n = t_0 + n\Delta t & n = 0, \dots, N_t \end{cases}$$

where r_0 , θ_0 and t_0 are the starting points and Δr , $\Delta\theta$ and Δt are the step sizes for corresponding variables. Let the solution to the differential equation be designated as $L_{i,j}^{(n)}$, which represents the value of L at the position (r_i, θ_j) and at time t_n . Similarly, $B_{i,j}^{(n)}$ means the value of B at the position (r_i, θ_j) and at time t_n . For the radially symmetric cases, as we only focus on their cross sections, so L and B don't depend on θ at all. The notations $L_{i,j}^{(n)}$ and $B_{i,j}^{(n)}$ are still used, even though the index j has no meaning. Because in this way, we can remain the inconsistency in the notations and the formulas can be easily extended to more general cases, for instance, the nonsymmetric case. We use forward difference expressions [15] to approximate the partial derivatives of L . At time t_n , the derivative of L with respect to t can be approximated by

$$\left. \frac{\partial L}{\partial t} \right|_{(r_i, \theta_j)} \approx \frac{L_{i,j}^{(n+1)} - L_{i,j}^{(n)}}{\Delta t} + \mathcal{O}(\Delta t). \quad (\text{B.2})$$

The other partial derivatives of L are approximated by

$$\begin{aligned} \left. \frac{\partial L}{\partial r} \right|_{(r_i, \theta_j)} &\approx \frac{L_{i+1,j}^{(n)} - L_{i,j}^{(n)}}{\Delta r} + \mathcal{O}(\Delta r) \\ \text{and } \left. \frac{\partial^2 L}{\partial r^2} \right|_{(r_i, \theta_j)} &\approx \frac{\frac{L_{i+1,j}^{(n)} - L_{i,j}^{(n)}}{\Delta r} - \frac{L_{i,j}^{(n)} - L_{i-1,j}^{(n)}}{\Delta r}}{\Delta r} + \mathcal{O}(\Delta r) \\ &\approx \frac{L_{i+1,j}^{(n)} - 2L_{i,j}^{(n)} + L_{i-1,j}^{(n)}}{(\Delta r)^2} + \mathcal{O}(\Delta r). \end{aligned} \quad (\text{B.3})$$

The derivative of B with respect to t can be approximated by

$$\left. \frac{\partial B}{\partial t} \right|_{(r_i, \theta_j)} \approx \frac{B_{i,j}^{(n+1)} - B_{i,j}^{(n)}}{\Delta t} + \mathcal{O}(\Delta t). \quad (\text{B.4})$$

Using the formulas (B.2), (B.3) and (B.4), the system (4.4) can be written as extrapolation formula, which is

$$\begin{cases} \frac{L_{i,j}^{(n+1)} - L_{i,j}^{(n)}}{\Delta t} = d \left(\frac{L_{i+1,j}^{(n)} - 2L_{i,j}^{(n)} + L_{i-1,j}^{(n)}}{(\Delta r)^2} + \frac{L_{i+1,j}^{(n)} - L_{i,j}^{(n)}}{r_i \Delta r} \right) \\ \quad - (k_c + k_{\text{on}f})L_{i,j}^{(n)} + k_{\text{off}}B_{i,j}^{(n)} + k_{\text{on}}L_{i,j}^{(n)}B_{i,j}^{(n)} \\ \frac{B_{i,j}^{(n+1)} - B_{i,j}^{(n)}}{\Delta t} = k_{\text{on}f}L_{i,j}^{(n)} - k_{\text{off}}B_{i,j}^{(n)} - k_{\text{on}}L_{i,j}^{(n)}B_{i,j}^{(n)}. \end{cases}$$

Rearranging all the terms, we get the final extrapolation formula for system (4.4), that is

$$\begin{cases} L_{i,j}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}f} - \frac{2d\Delta t}{(\Delta r)^2} - \frac{d\Delta t}{r_i \Delta r} \right) L_{i,j}^{(n)} \\ \quad + d\Delta t \left(\frac{1}{(\Delta r)^2} + \frac{1}{r_i \Delta r} \right) L_{i+1,j}^{(n)} + \frac{d\Delta t}{(\Delta r)^2} L_{i-1,j}^{(n)} \\ \quad + \Delta t k_{\text{off}}B_{i,j}^{(n)} + \Delta t k_{\text{on}}L_{i,j}^{(n)}B_{i,j}^{(n)} \\ B_{i,j}^{(n+1)} = \Delta t k_{\text{on}f}L_{i,j}^{(n)} + (1 - \Delta t k_{\text{off}})B_{i,j}^{(n)} - \Delta t k_{\text{on}}L_{i,j}^{(n)}B_{i,j}^{(n)}. \end{cases} \quad (\text{B.5})$$

B.1.3 Boundary Conditions

As the extrapolation formula we got in previous section is not valid for boundary points, so this part takes those points into consideration. For the boundary points, the time derivatives remain the same, hence the approximations for $B_{i,j}^{(n+1)}$ still hold true. While using the extrapolation formula (B.5) to compute $L_{0,j}^{(n+1)}$ and $L_{N_r,j}^{(n+1)}$, there are two imaginary points $L_{-1,j}^{(n)}$ and $L_{N_r+1,j}^{(n)}$, respectively. So we have to choose the values for these two points. The boundary condition assumes there is no flux leaving the whole region, i.e.

$$\frac{\partial L(r,t)}{\partial r} \Big|_{r=0} = 0 \quad \text{and} \quad \frac{\partial L(r,t)}{\partial r} \Big|_{r=1} = 0.$$

Using the forward difference formula to approximate this boundary condition, we have

$$\frac{\partial L}{\partial r} \Big|_{r=0} \approx \frac{L_{1,j}^{(n)} - L_{0,j}^{(n)}}{\Delta r} + \mathcal{O}(\Delta r),$$

and

$$\frac{\partial L}{\partial r} \Big|_{r=1} \approx \frac{L_{N_r+1,j}^{(n)} - L_{N_r,j}^{(n)}}{\Delta r} + \mathcal{O}(\Delta r).$$

To satisfy the boundary condition, we need to impose $L_{1,j}^{(n)} = L_{0,j}^{(n)}$ and $L_{N_r+1,j}^{(n)} = L_{N_r,j}^{(n)}$. For the other imaginary points $L_{-1,j}^{(n)}$, as the system is radially symmetrical, $L_{-1,j}^{(n)}$ has the same value with $L_{1,j}^{(n)}$. So we define $L_{-1,j}^{(n)} = L_{1,j}^{(n)} = L_{0,j}^{(n)}$.

The following part will present the extrapolation formulas for the boundary points. According to our assumption, the receptor compartment is located on the boundary of our studying area. There is no receptor on the side with $r = r_0$, so the extrapolation formula for the boundary point at $r = r_0$ can be simplified to a formula without B . But here we still include B in the extrapolation formula, because in this way the

formula can also be valid for the other radial symmetric case. Keep in mind that the initial conditions and the assumption for f are not the same for both cases. Hence, the extrapolation formulas for the boundary points are:

a). The points with $r = r_{N_r}$.

Based on the general formula (B.5) and using $L_{N_r,j}^{(n)}$ to substitute $L_{N_r+1,j}^{(n)}$, we get following extrapolation formula

$$\begin{cases} L_{N_r,j}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}f} - \frac{d\Delta t}{(\Delta r)^2}\right) L_{N_r,j}^{(n)} + \frac{d\Delta t}{(\Delta r)^2} L_{N_r-1,j}^{(n)} \\ \quad + \Delta t k_{\text{off}} B_{N_r,j}^{(n)} + \Delta t k_{\text{on}} L_{N_r,j}^{(n)} B_{N_r,j}^{(n)} \\ B_{N_r,j}^{(n+1)} = \Delta t k_{\text{on}f} L_{N_r,j}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{N_r,j}^{(n)} - \Delta t k_{\text{on}} L_{N_r,j}^{(n)} B_{N_r,j}^{(n)} \end{cases} \quad (\text{B.6})$$

b). The points with $r = r_0$.

Using $L_{0,j}^{(n)}$ to substitute terms $L_{-1,j}^{(n)}$ and $L_{1,j}^{(n)}$ in the general extrapolation formula, we get

$$\begin{cases} L_{0,j}^{(n+1)} = (1 - \Delta t k_c - \Delta t k_{\text{on}f}) L_{0,j}^{(n)} + \Delta t k_{\text{off}} B_{0,j}^{(n)} + \Delta t k_{\text{on}} L_{0,j}^{(n)} B_{0,j}^{(n)} \\ B_{0,j}^{(n+1)} = \Delta t k_{\text{on}f} L_{0,j}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{0,j}^{(n)} - \Delta t k_{\text{on}} L_{0,j}^{(n)} B_{0,j}^{(n)} \end{cases} \quad (\text{B.7})$$

B.2 Nonsymmetric Case

B.2.1 Extrapolation Formula

Following the notations from previous radially symmetric cases, (B.2) and (B.3) are used to approximate the derivatives with respect to time and the derivatives of L with respect to r . To write the system into extrapolation formula, we also need the approximations of the derivatives of L with respect to θ , which are

$$\begin{aligned} \frac{\partial L}{\partial \theta} \Big|_{(r_i, \theta_j)} &\approx \frac{L_{i,j+1}^{(n)} - L_{i,j}^{(n)}}{\Delta \theta} + \mathcal{O}(\Delta \theta) \\ \text{and } \frac{\partial^2 L}{\partial \theta^2} \Big|_{(r_i, \theta_j)} &\approx \frac{\frac{L_{i,j+1}^{(n)} - L_{i,j}^{(n)}}{\Delta \theta} - \frac{L_{i,j}^{(n)} - L_{i,j-1}^{(n)}}{\Delta \theta}}{\Delta \theta} + \mathcal{O}(\Delta \theta) \\ &\approx \frac{L_{i,j+1}^{(n)} - 2L_{i,j}^{(n)} + L_{i,j-1}^{(n)}}{(\Delta \theta)^2} + \mathcal{O}(\Delta \theta). \end{aligned}$$

Using these approximations together with (B.4), we can write the general two-dimensional system into an extrapolation formula, that is

$$\left\{ \begin{array}{l} \frac{L_{i,j}^{(n+1)} - L_{i,j}^{(n)}}{\Delta t} = d \left(\frac{L_{i+1,j}^{(n)} - 2L_{i,j}^{(n)} + L_{i-1,j}^{(n)}}{(\Delta r)^2} + \frac{L_{i+1,j}^{(n)} - L_{i,j}^{(n)}}{r_i \Delta r} \right. \\ \quad \left. + \frac{L_{i,j+1}^{(n)} - 2L_{i,j}^{(n)} + L_{i,j-1}^{(n)}}{r_i^2 (\Delta \theta)^2} \right) \\ \quad - (k_c + k_{\text{on}f})L_{i,j}^{(n)} + k_{\text{off}}B_{i,j}^{(n)} + k_{\text{on}}L_{i,j}^{(n)}B_{i,j}^{(n)} \\ \frac{B_{i,j}^{(n+1)} - B_{i,j}^{(n)}}{\Delta t} = k_{\text{on}f}L_{i,j}^{(n)} - k_{\text{off}}B_{i,j}^{(n)} - k_{\text{on}}L_{i,j}^{(n)}B_{i,j}^{(n)}. \end{array} \right.$$

Rearranging all the terms in previous formula, the general extrapolation formula is the following:

$$\left\{ \begin{array}{l} L_{i,j}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}f} - \frac{2d\Delta t}{(\Delta r)^2} - \frac{2d\Delta t}{r_i^2 (\Delta \theta)^2} - \frac{d\Delta t}{r_i \Delta r} \right) L_{i,j}^{(n)} \\ \quad + \frac{d\Delta t}{r_i^2 (\Delta \theta)^2} L_{i,j+1}^{(n)} + \frac{d\Delta t}{r_i^2 (\Delta \theta)^2} L_{i,j-1}^{(n)} + \frac{d\Delta t}{(\Delta r)^2} L_{i-1,j}^{(n)} \\ \quad + d\Delta t \left(\frac{1}{(\Delta r)^2} + \frac{1}{r_i \Delta r} \right) L_{i+1,j}^{(n)} + \Delta t k_{\text{off}} B_{i,j}^{(n)} \\ \quad + \Delta t k_{\text{on}} L_{i,j}^{(n)} B_{i,j}^{(n)} \\ B_{i,j}^{(n+1)} = \Delta t k_{\text{on}f} L_{i,j}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{i,j}^{(n)} - \Delta t k_{\text{on}} L_{i,j}^{(n)} B_{i,j}^{(n)}, \end{array} \right. \quad (\text{B.8})$$

for $0 \leq i \leq N_r$ and $0 \leq j \leq N_\theta$. N_r and N_θ have the same meanings as those in the radially symmetrical cases. But here we need one more extra assumption, N_θ is even, which will provide convenience to us when we try to handle the boundary points.

B.2.2 Boundary Conditions

The general extrapolation formula (B.8) is only valid for the interior points. Because using the general formula on the boundary points, the extrapolation formula contains imaginary points such as $L_{-1,j}^{(n)}$, $L_{N_r+1,j}^{(n)}$, $L_{i,-1}^{(n)}$ and $L_{i,N_\theta+1}^{(n)}$ for $0 \leq i \leq N_r$ and $0 \leq j \leq N_\theta$. So we have to figure out a way to deal with those imaginary points. Here there are boundaries at $r = 0$, $r = 1$, $\theta = 0$, and $\theta = 2\pi$, so it's necessary to determine several imaginary points. We will divide those boundary points into five groups and discuss them separately.

1. The points at positions (r_i, θ_0) and (r_i, θ_{N_θ}) with $0 < i < N_r$.

For each i , the points at (r_i, θ_0) and (r_i, θ_{N_θ}) are actually the same point, so we let $L_{i,-1}^{(n)} = L_{i,N_\theta-1}^{(n)}$ and $L_{i,N_\theta+1}^{(n)} = L_{i,1}^{(n)}$. Then, the extrapolation formulas for these points

are

$$\left\{ \begin{array}{l} L_{i,0}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}} f - \frac{2d\Delta t}{(\Delta r)^2} - \frac{2d\Delta t}{r_i^2 (\Delta \theta)^2} - \frac{d\Delta t}{r_i \Delta r} \right) L_{i,0}^{(n)} \\ \quad + \frac{d\Delta t}{r_i^2 (\Delta \theta)^2} L_{i,1}^{(n)} + \frac{d\Delta t}{r_i^2 (\Delta \theta)^2} L_{i,N_\theta-1}^{(n)} + \frac{d\Delta t}{(\Delta r)^2} L_{i-1,0}^{(n)} \\ \quad + d\Delta t \left(\frac{1}{(\Delta r)^2} + \frac{1}{r_i \Delta r} \right) L_{i+1,0}^{(n)} + \Delta t k_{\text{off}} B_{i,0}^{(n)} \\ \quad + \Delta t k_{\text{on}} L_{i,0}^{(n)} B_{i,0}^{(n)} \\ B_{i,0}^{(n+1)} = \Delta t k_{\text{on}} f L_{i,0}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{i,0}^{(n)} - \Delta t k_{\text{on}} L_{i,0}^{(n)} B_{i,0}^{(n)}, \end{array} \right.$$

and

$$\left\{ \begin{array}{l} L_{i,N_\theta}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}} f - \frac{2d\Delta t}{(\Delta r)^2} - \frac{2d\Delta t}{r_i^2 (\Delta \theta)^2} - \frac{d\Delta t}{r_i \Delta r} \right) L_{i,N_\theta}^{(n)} \\ \quad + \frac{d\Delta t}{r_i^2 (\Delta \theta)^2} L_{i,1}^{(n)} + \frac{d\Delta t}{r_i^2 (\Delta \theta)^2} L_{i,N_\theta-1}^{(n)} + \frac{d\Delta t}{(\Delta r)^2} L_{i-1,N_\theta}^{(n)} \\ \quad + d\Delta t \left(\frac{1}{(\Delta r)^2} + \frac{1}{r_i \Delta r} \right) L_{i+1,N_\theta}^{(n)} + \Delta t k_{\text{off}} B_{i,N_\theta}^{(n)} \\ \quad + \Delta t k_{\text{on}} L_{i,N_\theta}^{(n)} B_{i,N_\theta}^{(n)} \\ B_{i,N_\theta}^{(n+1)} = \Delta t k_{\text{on}} f L_{i,N_\theta}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{i,N_\theta}^{(n)} - \Delta t k_{\text{on}} L_{i,j}^{(n)} B_{i,N_\theta}^{(n)}. \end{array} \right.$$

2. The points at positions (r_0, θ_j) with $0 \leq j \leq N_\theta$.

At the origin, the Laplacian is approximated by the following expression,

$$\Delta L|_{r=0} \approx \frac{4(\tilde{L} - L_{0,j})}{(\Delta r)^2}. \quad (\text{B.9})$$

Here \tilde{L} is the nearest-neighbor mean value of L at the origin, in other words,

$$\tilde{L} = \frac{\sum_{j=0}^{N_\theta} L_{1,j}}{N_\theta + 1}.$$

Using previous expression to substitute the Laplacian, the system at the origin can be approximated by

$$\left\{ \begin{array}{l} \frac{L_{0,j}^{(n+1)} - L_{0,j}^{(n)}}{\Delta t} = \frac{4d(\tilde{L} - L_{0,j})}{(\Delta r)^2} - (k_c + k_{\text{on}} f) L_{0,j}^{(n)} \\ \quad + k_{\text{off}} B_{0,j}^{(n)} + k_{\text{on}} L_{0,j}^{(n)} B_{0,j}^{(n)} \\ \frac{B_{0,j}^{(n+1)} - B_{0,j}^{(n)}}{\Delta t} = k_{\text{on}} f L_{0,j}^{(n)} - k_{\text{off}} B_{0,j}^{(n)} - k_{\text{on}} L_{0,j}^{(n)} B_{0,j}^{(n)}. \end{array} \right.$$

Putting all the terms relating to time t_{n+1} on the left side of the equation the rest on the right side, we have

$$\left\{ \begin{array}{l} L_{0,j}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}} f - \frac{4d\Delta t}{(\Delta r)^2} \right) L_{0,j}^{(n)} + \frac{4d}{(\Delta r)^2} \tilde{L} \\ \quad + \Delta t k_{\text{off}} B_{0,j}^{(n)} + \Delta t k_{\text{on}} L_{0,j}^{(n)} B_{0,j}^{(n)} \\ B_{0,j}^{(n+1)} = \Delta t k_{\text{on}} f L_{0,j}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{0,j}^{(n)} - \Delta t k_{\text{on}} L_{0,j}^{(n)} B_{0,j}^{(n)}. \end{array} \right.$$

3. The points at positions (r_{N_r}, θ_j) with $0 < j < N_\theta$.

When getting the extrapolation formulas for the points at positions (r_{N_r}, θ_j) with $0 < j < N_\theta$, there exist several imaginary points $L_{N_r+1,j}^{(n)}$ with $0 < j < N_\theta$. Again using the result from previous case, i.e. $L_{N_r+1,j}^{(n)} = L_{N_r,j}^{(n)}$, the extrapolation formulas for those points become

$$\left\{ \begin{array}{l} L_{N_r,j}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}f} - \frac{d\Delta t}{(\Delta r)^2} - \frac{2d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} \right) L_{N_r,j}^{(n)} \\ \quad + \frac{d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} L_{N_r,j+1}^{(n)} + \frac{d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} L_{N_r,j-1}^{(n)} + \frac{d\Delta t}{(\Delta r)^2} L_{N_r-1,j}^{(n)} \\ \quad + \Delta t k_{\text{off}} B_{N_r,j}^{(n)} + \Delta t k_{\text{on}} L_{N_r,j}^{(n)} B_{N_r,j}^{(n)} \\ B_{N_r,j}^{(n+1)} = \Delta t k_{\text{on}f} L_{N_r,j}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{N_r,j}^{(n)} - \Delta t k_{\text{on}} L_{N_r,j}^{(n)} B_{N_r,j}^{(n)}. \end{array} \right.$$

4. The points at positions (r_{N_r}, θ_0) and $(r_{N_r}, \theta_{N_\theta})$.

For the point (r_{N_r}, θ_0) , substituting $L_{N_r+1,0}^{(n)}$ with $L_{N_r,0}^{(n)}$ and letting $L_{0,-1}^{(n)} = L_{0,N_\theta-1}^{(n)}$, we have

$$\left\{ \begin{array}{l} L_{N_r,0}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}f} - \frac{d\Delta t}{(\Delta r)^2} - \frac{2d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} \right) L_{N_r,0}^{(n)} \\ \quad + \frac{d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} L_{N_r,1}^{(n)} + \frac{d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} L_{N_r,N_\theta-1}^{(n)} + \frac{d\Delta t}{(\Delta r)^2} L_{N_r-1,0}^{(n)} \\ \quad + \Delta t k_{\text{off}} B_{N_r,0}^{(n)} + \Delta t k_{\text{on}} L_{N_r,0}^{(n)} B_{N_r,0}^{(n)} \\ B_{N_r,0}^{(n+1)} = \Delta t k_{\text{on}f} L_{N_r,0}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{N_r,0}^{(n)} - \Delta t k_{\text{on}} L_{N_r,0}^{(n)} B_{N_r,0}^{(n)}. \end{array} \right.$$

For the other point $(r_{N_r}, \theta_{N_\theta})$, using $L_{N_r,N_\theta}^{(n)}$ to substitute the imaginary point $L_{N_r+1,N_\theta}^{(n)}$ and choose $L_{N_r,N_\theta+1}^{(n)} = L_{N_r,1}^{(n)}$, so we obtain

$$\left\{ \begin{array}{l} L_{N_r,N_\theta}^{(n+1)} = \left(1 - \Delta t k_c - \Delta t k_{\text{on}f} - \frac{d\Delta t}{(\Delta r)^2} - \frac{2d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} \right) L_{N_r,N_\theta}^{(n)} \\ \quad + \frac{d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} L_{N_r,1}^{(n)} + \frac{d\Delta t}{r_{N_r}^2 (\Delta\theta)^2} L_{N_r,N_\theta-1}^{(n)} + \frac{d\Delta t}{(\Delta r)^2} L_{N_r-1,N_\theta}^{(n)} \\ \quad + \Delta t k_{\text{off}} B_{N_r,N_\theta}^{(n)} + \Delta t k_{\text{on}} L_{N_r,N_\theta}^{(n)} B_{N_r,N_\theta}^{(n)} \\ B_{N_r,N_\theta}^{(n+1)} = \Delta t k_{\text{on}f} L_{N_r,N_\theta}^{(n)} + (1 - \Delta t k_{\text{off}}) B_{N_r,N_\theta}^{(n)} - \Delta t k_{\text{on}} L_{N_r,N_\theta}^{(n)} B_{N_r,N_\theta}^{(n)}. \end{array} \right.$$

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