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Mathematical Modeling of Potassium Modulated Viral Infection

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MATHEMATICAL MODELING OF POTASSIUM MODULATED VIRAL INFECTION

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by

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THESIS

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Abstract

In recent years, there is a growing interest in the investigation of using potassium to treat virus infections. In the region of infection, there is a biological observation of extracellular potassium level being typically very low whereas the intracellular potassium levels are much higher. There are numerous biological studies showing that elevated potassium levels in the extracellular membrane tends to block virus infections. A recent effort in this direction is a collaborative research conducted by mathematicians and biologists from the University of Texas at El Paso, New Mexico State University, and the University of New Mexico, where we develop a mathematical model that demonstrates the blocking effect extracellular potassium has on the Myxoma virus in rabbits. In this thesis, we will conduct preliminary analysis of the mathematical model proposed in this project, with an emphasis on answering the question whether this model is capable of predicting the potassium blocking effect on virus infections at all. More specifically, this model is composed of a system of parameterized ordinary differential equations for various cell number densities and reaction-diffusion equations for virus and potassium concentrations. Particularly for the latter, we establish lower and upper bounds for the virus and potassium concentrations using a comparison principle, and show that the model admits positive and thus biological relevant solutions. Furthermore, the upper bounds are given in closed-form expression of model parameters and they help us provide an affirmative answer to the fundamental question raised before. Such a positive answer motivates the implementation of a computational method for the numerical simulation of the model, and we present some simulation results confirming our prediction in the last part of the thesis.

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Chapter 1

Introduction

Potassium ion denoted as K^+ is necessary for the function of all living cells, and is present in all plant and animal tissues. Potassium ions are critical ions used by the body to maintain cellular membrane potential [7].

There is research supporting the impact high levels of extracellular potassium has on T cells and tumors, where T cells are cells that help make up the immune system. They found that elevated extracellular potassium characteristic of the extracellular space within tumors reduced the uptake and consumption of local nutrients by anti-tumor T cells inducing a state of functional caloric restriction. The treatment of anti-tumor T cells with elevated extracellular potassium enabled the enhanced destruction of large, established tumors [26]. In this research, we will be studying the affects elevated extracellular K^+ has on a particular virus.

Myxoma virus denoted as MYXV was introduced into the European rabbit population of Australia in 1950. Myxoma virus causes a topical lesion on the skin. In European rabbits, however, myxoma virus causes the fulminant disease, myxomatosis. When the virus was introduced into the wild rabbit population in Australia, Europe and Great Britain, the virus was extremely deadly, killing 99 percent of infected rabbits [5]. Today, the virus is used in laboratory research in various ways.

In this research, we will be studying the lesions created by the virus to model the impact potassium has on the viral replication. In lesions caused by MYXV, it shows they contain high levels of cell death. The research shows that extracellular K^+ levels are extremely low ($\sim 3\text{--}5\text{ mM}$) and intracellular K^+ levels are extremely high ($\sim 50\text{--}150\text{ mM}$) [23]. When there are high levels of localized necrosis (the death of the cells due to disease or injury),

there is an increase of potassium in the extracellular membrane [3]. This increase may inhibit viral spread.

Motivated by these experimental observations, Dr. Bartee from the University of New Mexico initiated a collaborative research project in which biologists and mathematicians from his institution, the University of Texas at El Paso, and New Mexico State University are involved to construct a mathematical model aiming at explaining the observed blocking of virus infection by high potassium concentration levels. The overall project contains several stages and components. First, we proposed a mathematical model based on differential equations to describe the interaction between various types of cells, viruses, and the potassium. Next, preliminary analysis is conducted trying to answer the important question whether this model is capable of predicting any blocking effect at all, with the model parameters being assigned biologically meaningful values. Once we obtain an affirmative answer to this fundamental question, effort is devoted in the development of a computational tool for numerical simulation of the model, which allow us to compute approximations to the solutions that are not analytically obtainable. The main contribution of this thesis is in the preliminary analysis, where theoretical bounds on the virus and potassium concentrations are obtained from a comparison principle, which allow us to show that on the one hand the solutions to the model are always biologically meaningful, and on the other hand the largest achievable potassium level is far above the observed blocking threshold, which indicates that it is certainly possible for the model to predict virus blockage by high potassium concentrations.

More specifically, we will be using reaction-diffusion equations as our basic modeling method [6]. Experimental results demonstrate that in the early stage of infection, the lesion occupies a small circular region on the top of the skin and its radius changes with time. In this model, however, instead of worrying about a free boundary [8], we will consider a stationary but much larger circular domain so that the boundary of the lesion does not reach the domain boundary during the period of interest. To model the abrupt blocking effect of viral infection by large potassium concentration, the infection rate of normal cells by virus

is controlled by a smoothed Heaviside function [28] in potassium concentration, so that the rate reduction is turned on and off depending on whether the potassium passes a certain threshold. In this work, we will estimate solutions to our model by applying a comparison principle for reaction-diffusion equations. Particularly, lower and upper bounds of the virus and potassium concentrations will be derived, so that we can gain deeper understanding of whether the potassium can play a significant role in the viral infection process.

To this end, the rest of the thesis is organized as follows. The mathematical model itself described in detail in Chapter 2 and in Chapter 3 we briefly address the existence and uniqueness of the solutions to this model, whereas the details are left for a separate publication. The main contribution of the thesis is provided in Chapter 4 and Chapter 5. In particular, in Chapter 4 we first review a comparison principle of model reaction-diffusion equations of interest and then use it to construct lower and upper bounds for the virus and potassium concentrations. Next in Chapter 5, as a demonstration of the application of the model, these bounds are utilized to answer the question whether it is possible for the model to produce enough potassium that reaches the blockage threshold using model parameters estimated by independent experiments. Such affirmative answer has encouraged the development of a computational tool in a separate effort of the collaborative project, whose typical simulation results are also presented at the end of Chapter 5 for completeness. Finally, we go over some concluding remarks in Chapter 6.

Chapter 2

The Mathematical Model

To model the modulation of virus infection by potassium on the skin, we distinguish among three different types of cells: the normal cell, the infected cell, and the dead cell, whose densities will be denoted by B_1 , B_2 , and B_3 , respectively. Since it is well known that cells are nearly incompressible, it is expected that:

$$B_1(\mathbf{x}, t) + B_2(\mathbf{x}, t) + B_3(\mathbf{x}, t) = c_0 , \quad (2.1)$$

where $\mathbf{x} = (x, y)$ is the spatial coordinate, t is the time abscissa, and c_0 is a constant denoting the number of cells per unit area. While the dynamics of the cell number densities are described by classical population growth models [21], the growth, conversion, and lysis rate (life cycle of the virus) are dependent on the concentration of the virus and potassium, denoted by $V(\mathbf{x}, t)$ and $P(\mathbf{x}, t)$, respectively.

As both virus and potassium diffuses throughout the skin region [27], we model their dynamics by reaction-diffusion equations, where the reaction terms describe the release of virus or potassium particles upon the death of infected cells and the consumption of virus in the infection of normal cells, etc.

In the rest of this chapter, we first describe the differential equations governing the dynamics of cells, virus, and potassium, and then complete the system with appropriate initial and boundary conditions. Then, due to the observation that lesions are usually circular in their early stages [4], we shall concentrate on the radially symmetric [30] case and cast the problem in polar coordinates.

2.1 Governing Equations

By collaboration within the research group, we propose the following simplified equations in (2.2) and the smoothed version of the Heaviside function (2.3) to be a part of the mathematical model. Let $\Omega \subset \mathbb{R}^2$ be a closed and bounded Lipschitz domain [12] that contains the origin point, the cell number densities B_1 , B_2 , and B_3 are governed by the following ODEs that are parameterized by $\mathbf{x} \in \bar{\Omega}$:

$$\frac{\partial B_1}{\partial t} = -\theta F(P)B_1V, \quad (2.2a)$$

$$\frac{\partial B_2}{\partial t} = \theta F(P)B_1V - \beta B_2, \quad (2.2b)$$

$$\frac{\partial B_3}{\partial t} = \beta B_2, \quad (2.2c)$$

where $\theta > 0$ is a constant designating the infection rate of normal cells by virus and $\beta > 0$ is a constant designating the death rate of infected cells. The scaling coefficient $F(P) \in [0, 1]$ is introduced to model the blockage of virus infection by high concentration of potassium:

$$F(P) = 1 - \frac{1}{1 + e^{-2k(P-P_s)}}. \quad (2.3)$$

Here P_s is a constant representing the potassium concentration threshold that is observed in experiments for the activation of virus blockage effect. The second term on the right hand side of (2.3) is a smoothed Heaviside function with $k \gg 0$ being a constant describing the fast transition. Note that if $P \approx 0$, we have $F(P) \approx 1$ thus virus infects the normal cells at its full strength; whereas if P is very large, we have $F(P) \approx 0$ and the infection is completely blocked.

Since both virus and potassium diffuse in the region of interest, their dynamics are modeled by the following equations:

$$\frac{\partial V}{\partial t} = F(P)b\beta B_2 - (\theta F(P)B_1 + \gamma)V + D_V \nabla^2 V, \quad (2.4)$$

$$\frac{\partial P}{\partial t} = a\beta B_2 - \tau P + D_P \nabla^2 P. \quad (2.5)$$

Here $b > 0$ and $a > 0$ are constants designating the amounts of V and P released when infected cells die, respectively, $\gamma > 0$ describes the lysis rate of viruses that are not consumed

in the infection of normal cells, $\tau > 0$ is the absorption rate of potassium into the cells, and D_V and D_P are the diffusion coefficients of the virus and potassium, respectively. In these equations, the Laplace operator [18] is given by $\nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2}$.

2.2 Initial and Boundary Conditions

The system of differential equations are accompanied by initial and boundary conditions given next. We assume v_0 units of virus is injected into the cell located at $\mathbf{x} = 0$ at time $t = 0$, [1] thus the initial data for virus is given by:

$$V(\mathbf{x}, 0) = v_0 \delta_0(\mathbf{x}) , \quad (2.6)$$

where $\delta_0(\mathbf{x})$ is the Dirac measure such that for all smooth and compactly supported function f on \mathbb{R}^2 there is $\iint_{\mathbb{R}^2} f(\mathbf{x}) \delta_0(\mathbf{x}) d\mathbf{x} = f(0)$. [11]

Since virus takes time to infect normal cells, the initial condition for cell number densities are given simply by:

$$B_1(\mathbf{x}, 0) = c_0 , \quad B_2(\mathbf{x}, 0) = 0 , \quad B_3(\mathbf{x}, 0) = 0 . \quad (2.7)$$

Similarly, because potassium only enters the extracellular space when infected cells dies, the initial condition for P is:

$$P(\mathbf{x}, 0) = 0 . \quad (2.8)$$

We assume that the infection center (the origin point) is far away from the domain boundary $\partial\Omega$ and thus specify the no-flux boundary conditions [14] for both virus and potassium concentrations:

$$\mathbf{n} \cdot \nabla V(\mathbf{x}, t) = 0 , \quad \mathbf{n} \cdot \nabla P(\mathbf{x}, t) = 0 , \quad \forall \mathbf{x} \in \partial\Omega , t \geq 0 , \quad (2.9)$$

where \mathbf{n} is the unit outer normal vector on $\partial\Omega$ and ∇ is the gradient operator. Note that no boundary condition is needed for the cell number densities B_i , $i = 1, 2, 3$, as no spatial derivatives are involved in (2.2).

2.2.1 Radial Symmetric Case

In the early stage after the virus injection, the infection usually exhibit radially symmetric pattern; thus in this thesis we assume the domain Ω is a disk with fixed radius $R \gg 0$ and to this end rewrite the problem in radial coordinate $r = (\mathbf{x} \cdot \mathbf{x})^{\frac{1}{2}}$:

$$\frac{\partial B_1}{\partial t} = -\theta F(P)B_1V, \quad (2.10a)$$

$$\frac{\partial B_2}{\partial t} = \theta F(P)B_1V - \beta B_2, \quad (2.10b)$$

$$\frac{\partial B_3}{\partial t} = \beta B_3, \quad (2.10c)$$

$$\frac{\partial V}{\partial t} = F(P)b\beta B_2 - (\theta F(P)B_1 + \gamma)V + D_V \frac{\partial}{\partial r} \left(r \frac{\partial V}{\partial r} \right), \quad (2.10d)$$

$$\frac{\partial P}{\partial t} = a\beta B_2 - \tau P + D_P \frac{\partial}{\partial r} \left(r \frac{\partial P}{\partial r} \right), \quad (2.10e)$$

where $B_1 = B_1(r, t)$, $B_2 = B_2(r, t)$, $B_3 = B_3(r, t)$, $V = V(r, t)$, and $P = P(r, t)$. Correspondingly, the initial condition is given by:

$$B_1(r, 0) = c_0, \quad B_2(r, 0) = 0, \quad B_3(r, 0) = 0, \quad (2.11a)$$

$$V(r, 0) = v_0 \bar{\delta}_0(r), \quad P(r, 0) = 0, \quad (2.11b)$$

for all $0 \leq r \leq R$ and $\bar{\delta}_0(r)$ is the Dirac measure such that for all smooth and compactly supported function f on $[0, +\infty)$ there is $\int_0^\infty 2\pi r f(r) \bar{\delta}_0(r) dr = f(0)$. Lastly, the boundary conditions for V and P are:

$$\frac{\partial V}{\partial r}(0, t) = \frac{\partial V}{\partial r}(R, t) = 0, \quad \frac{\partial P}{\partial r}(0, t) = \frac{\partial P}{\partial r}(R, t) = 0, \quad t \geq 0. \quad (2.12)$$

Note that the homogeneous Neumann condition (2.12) at $r = 0$ is due to the symmetry of the solutions [2].

Remark: Strictly speaking, we need to show that the solutions to the problem in Sections 2.1–2.2 are radially symmetric when Ω is a disk; this, however, follows from the existence and uniqueness to the problem that will be addressed in the next two chapters.

Chapter 3

Well-posedness of the Problem

While the main result will be derived in the next chapter, we shall briefly address the well-posedness [10] of the problem in Chapter 2 herein. In particular, we shall review a well-posedness theorem for a class of reaction-diffusion equations by Martin and Smith [17] and tailor it to our context. To this end, let us focus on a general scalar reaction-diffusion equation:

$$\begin{cases} \partial_t \varphi = D \nabla^2 \varphi + f(\mathbf{x}, t, \varphi), & t > 0, \mathbf{x} \in \Omega, \\ \mathbf{n} \cdot \nabla \varphi(\mathbf{x}, t) = 0, & t > 0, \mathbf{x} \in \partial \Omega, \\ \varphi(\mathbf{x}, 0) = \varphi_0(\mathbf{x}), & \mathbf{x} \in \bar{\Omega}, \end{cases} \quad (3.1)$$

where $\Omega \subset \mathbb{R}^2$ is given the same as before, and f and φ_0 are prescribed functions with sufficient regularity to be specified later.

3.1 A Well-posedness Theorem by Martin and Smith

In their original work [17], Martin and Smith developed a general well-posedness theory for the reaction-diffusion system of abstract functional-differential equations; and we adopt it here and restate it for the particular case of the problem given in (3.1).

Theorem 1. *Suppose $D > 0$ is a constant, Λ is a closed convex subset of \mathbb{R} , and f satisfies the following conditions:*

(1a) *f is a continuous function from $\bar{\Omega} \times [0, T_f) \times \Lambda$ to \mathbb{R} , where $0 < T_f \leq \infty$.*

(1b) *For each $R > 0$, there exist $\nu = \nu(R) \in (0, 1]$ and $L = L(R) \in (0, \infty)$ such that:*

$$|f(\mathbf{x}, t, \varphi) - f(\mathbf{x}, s, \psi)| \leq L (|t - s|^\nu + |\varphi - \psi|)$$

for all $t, s \in [0, R] \cap [0, T_f)$, $\mathbf{x} \in \bar{\Omega}$, $\varphi, \psi \in \Lambda$, and $|\varphi|, |\psi| \leq R$.

(1c) The subtangential condition: for all $(\mathbf{x}, t, \varphi) \in \bar{\Omega} \times [0, T_f) \times \Lambda$:

$$\lim_{h \rightarrow 0^+} \frac{1}{h} d(\varphi + hf(\mathbf{x}, t, \varphi), \Lambda) = 0 ,$$

where $d(\cdot, \cdot)$ is the standard distance between an element and a set.

In addition, suppose the family of linear operators associated with (3.1) when $f \equiv 0$ is invariant (does not change when a transformation is applied) in Λ for all $t > 0$ and $\varphi_0 \in C(\bar{\Omega}, \Lambda)$. Then (3.1) has a unique non-continuable classical solution φ defined on $\Omega \times [0, T)$ where $T = T(\varphi_0) \in (0, \infty]$ and $T \leq T_f$, and $\varphi(\mathbf{x}, t) \in \Lambda$ for all $(\mathbf{x}, t) \in \bar{\Omega} \times [0, T)$.

Note that in Theorem 1, φ and ψ are numbers and not functions and we also see that if $f \equiv 0$, (3.1) is just a linear diffusion equation and the invariance of its solution in the convex domain Λ is a direct consequence of the maximum principle [20]. Hence the main component of the theorem to verify in our context is the subtangential condition (1c), which essentially states that when the flow of the solution reaches the boundary of Λ from inside, it must be pushed back and thus ensures that the solution to (3.1) stays inside the invariance domain Λ . This concept is used in many research papers like the research done by Martin and Smith [17] and the research done by Zizi Wang, Zhiming Guo, and Huaqin Peng [31]. Throughout the rest of this thesis, Λ is assumed to be the positive real line $[0, +\infty)$; but we shall remain using the notation Λ for simplicity.

In the remaining sections of this chapter, we shall verify the conditions in Theorem 1 for V and P , whereas deriving bounds for these variables using a comparison theorem will be the topic of the next chapter. In particular, denoting the source terms for V and P (the function f in (3.1)) by f_V and f_P , respectively, from (2.4) and (2.5) we obtain:

$$f_V(\mathbf{x}, t, \varphi) = F(P(\mathbf{x}, t))b\beta B_2(\mathbf{x}, t) - (\theta F(P(\mathbf{x}, t))B_1(\mathbf{x}, t) + \gamma)\varphi , \quad (3.2)$$

$$f_P(\mathbf{x}, t, \varphi) = a\beta B_2(\mathbf{x}, t) - \tau\varphi . \quad (3.3)$$

Thus to make use of Theorem 1 to establish the existence and uniqueness of the solutions

to V and P , especially the regularity of f_V and f_P , we shall first look at the cell number density solutions.

3.2 Cell Number Density Solutions

The cell number densities B_1 , B_2 , and B_3 are governed by the equations (2.2) with initial condition (2.7), which can be integrated in time to obtain:

$$B_1(\mathbf{x}, t) = c_0 \exp\left(-\int_0^t \theta F(P(\mathbf{x}, s))V(\mathbf{x}, s)ds\right), \quad (3.4)$$

$$B_2(\mathbf{x}, t) = e^{-\beta t} \int_0^t e^{\beta s} \theta F(P(\mathbf{x}, s))B_1(\mathbf{x}, s)V(\mathbf{x}, s)ds, \quad (3.5)$$

$$B_3(\mathbf{x}, t) = \int_0^t \beta B_2(\mathbf{x}, s)ds. \quad (3.6)$$

On the one hand, it is not difficult to see that as long as P and V exist, there is $B_1 \geq 0$, which then indicates $B_2 \geq 0$, and thus $B_3 \geq 0$. On the other hand, seeing that

$$\frac{\partial(B_1 + B_2 + B_3)}{\partial t} = 0$$

by summing up (2.2) we immediately obtain:

$$B_1(\mathbf{x}, t) + B_2(\mathbf{x}, t) + B_3(\mathbf{x}, t) = c_0$$

for all $\mathbf{x} \in \Omega$ and $t \geq 0$ as long as P and V exist.

Hence we conclude that for all $T > 0$ such that $P(\mathbf{x}, t)$ and $V(\mathbf{x}, t)$ is C^1 on $\Omega \times [0, T]$, the cell number solutions are C^1 on $\Omega \times [0, T]$ and they satisfy:

$$0 \leq B_1(\mathbf{x}, t), B_2(\mathbf{x}, t), B_3(\mathbf{x}, t) \leq c_0, \quad \forall \mathbf{x} \in \Omega, 0 \leq t \leq T. \quad (3.7)$$

Note that to establish a local and then global existence of all solutions, we shall follow a standard fix-point strategy [22]:

1. Let $m = 0$ and define $P^{(m)} = 0$ and $V^{(m)} = 0$.
2. Given $P^{(m)}$ and $V^{(m)}$, one obtains C^1 solutions $B_1^{(m)}$, $B_2^{(m)}$, and $B_3^{(m)}$ using (3.4–3.6) and they satisfy (3.7).

3. Using $B_2^{(m)}$ one verifies that f_P in (3.3) is Lipschitz continuous hence obtains an updated solution $P^{(m+1)}$ that is continuously differentiable by Theorem 1.
4. Using $B_1^{(m)}$, $B_2^{(m)}$, and $P^{(m+1)}$, one verifies that f_V in (3.2) is Lipschitz continuous and thus obtains an updated solution $V^{(m+1)}$ that is continuously differentiable, again, by Theorem 1.
5. Increase the counter: $m \leftarrow m + 1$, and repeat Steps 2–5.

The details of the fix-point iteration as well as estimates that ensure convergence will be addressed in a separate paper, as the focus for this thesis is to provide bounds on V and P and investigate the possibility of potassium to reach the threshold value.

Note that an alternative approach to show the well-posedness for B_1 , B_2 , B_3 , V , and P altogether is to use a more general result in the same reference [17, Theorem 1] for system of time-delayed integral and differential equations; this approach, however, technically boils down to the same iterative argument outlined earlier.

From this point on, we shall thus **assume** that the cell number solutions are continuously differentiable for all $t \geq 0$ and they satisfy the bounds given by (3.7).

3.3 Existence and Uniqueness of V and P

Let T_f be any fixed positive number, then by the assumption at the end of previous section, f_P given by (3.3) is Lipschitz continuous in both t and φ on $\bar{\Omega} \times [0, T_f] \times \Lambda$, hence verifying (1a) and (1b) in Theorem 1 for f_P . To show the subtangential condition (1c), let $\varphi \in \Lambda = [0, \infty)$ be arbitrary, we have:

$$\varphi + hf_P(\mathbf{x}, t, \varphi) = \varphi + h(a\beta B_2(\mathbf{x}, t) - \tau\varphi) = (1 - h\tau)\varphi + ha\beta B_2(\mathbf{x}, t) .$$

Because $B_2 \geq 0$, we have $\varphi + hf_P(\mathbf{x}, t, \varphi) \geq 0$ for all $h < 1/\tau$; that is, $d(\varphi + hf(\mathbf{x}, t, \varphi), \Lambda) = 0$ for all $h < 1/\tau$, which verifies (1c).

As the initial condition for P is zero, we obtain immediately by Theorem 1 that $P(\mathbf{x}, t)$ exists, is unique, non-negative, C^2 in \mathbf{x} , and C^1 in t for all $(\mathbf{x}, t) \in \bar{\Omega} \times [0, T_f]$.

Now we are ready to switch the attention to V and notice that f_V in (3.2) is Lipschitz continuous in both t and φ on $\bar{\Omega} \times [0, T_f] \times \Lambda$. As for the subtangential condition, we again assume $\varphi \in \Lambda$ is arbitrary and compute:

$$\varphi + hf_V(\mathbf{x}, t, \varphi) = [1 - h(\theta F(P(\mathbf{x}, t))B_1(\mathbf{x}, t) + \gamma)]\varphi + F(P(\mathbf{x}, t))b\beta B_2(\mathbf{x}, t) .$$

Because $0 \leq B_1 \leq c_0$ and $0 \leq F(P) \leq 1$, we have:

$$\theta F(P(\mathbf{x}, t))B_1(\mathbf{x}, t) + \gamma \leq \theta c_0 + \gamma$$

and thus $\varphi + hf_V(\mathbf{x}, t, \varphi) \geq 0$ for all $h < 1/(\theta c_0 + \gamma)$, which verifies (1c) similarly as f_P as discussed earlier.

To show the existence and uniqueness of a solution V using Theorem 1, there remains an obstacle that the initial condition given by (2.6) is not a classical function. Nevertheless, this can be circumvented by first replacing the Dirac delta function by a standard mollifier [25] and then using a density argument. To this end, we conclude that $V(\mathbf{x}, t)$ exists, and it is unique, non-negative, C^2 in \mathbf{x} , and C^1 in t for all $(\mathbf{x}, t) \in \bar{\Omega} \times (0, T_f)$.

Lastly, since $T_f > 0$ is arbitrary, we can extend the result to the time interval $t \in [0, \infty)$.

Chapter 4

Bounds for Virus and Potassium

Focusing again on the general reaction-diffusion equation (3.1), we shall adopt a comparison theorem by the same authors [17] as given below.

Theorem 2. *Given all conditions in Theorem 1, suppose in addition that $\varphi^\pm(\mathbf{x}, t)$ and $f^\pm(\mathbf{x}, t, \varphi)$ satisfy:*

(2a) φ^\pm are C^2 in \mathbf{x} and C^1 in t functions from $\bar{\Omega} \times [0, T']$ into Λ , where $0 < T' \leq \infty$.

And for all $(\mathbf{x}, t) \in \bar{\Omega} \times [0, T']$:

$$\varphi^-(\mathbf{x}, t) \leq \varphi^+(\mathbf{x}, t) \quad \text{and} \quad [\varphi^-(\mathbf{x}, t), \varphi^+(\mathbf{x}, t)] \subseteq \Lambda .$$

(2b) f^\pm are continuous functions from $\bar{\Omega} \times [0, T'] \times \Lambda$ to \mathbb{R} such that they satisfy the following differential inequalities:

$$\begin{cases} \partial_t \varphi^+ \geq D\nabla^2 \varphi^+ + f^+(\mathbf{x}, t, \varphi^+) , & 0 < t < T' , \mathbf{x} \in \Omega , \\ \mathbf{n} \cdot \nabla \varphi^+(\mathbf{x}, t) \geq 0 , & 0 < t < T' , \mathbf{x} \in \partial\Omega , \\ \varphi^+(\mathbf{x}, 0) \geq \varphi_0(\mathbf{x}) , & \mathbf{x} \in \Omega , \end{cases} \quad (4.1)$$

and similarly:

$$\begin{cases} \partial_t \varphi^- \leq D\nabla^2 \varphi^- + f^-(\mathbf{x}, t, \varphi^-) , & 0 < t < T' , \mathbf{x} \in \Omega , \\ \mathbf{n} \cdot \nabla \varphi^-(\mathbf{x}, t) \leq 0 , & 0 < t < T' , \mathbf{x} \in \partial\Omega , \\ \varphi^-(\mathbf{x}, 0) \leq \varphi_0(\mathbf{x}) , & \mathbf{x} \in \Omega . \end{cases} \quad (4.2)$$

(2c) $f(\mathbf{x}, t, \varphi^+(\mathbf{x}, t)) \leq f^+(\mathbf{x}, t, \varphi^+(\mathbf{x}, t))$ for all $(\mathbf{x}, t) \in \bar{\Omega} \times [0, \min(T', T_f))$.

(2d) $f(\mathbf{x}, t, \varphi^-(\mathbf{x}, t)) \geq f^-(\mathbf{x}, t, \varphi^-(\mathbf{x}, t))$ for all $(\mathbf{x}, t) \in \bar{\Omega} \times [0, \min(T', T_f))$.

Then one has $T \geq \min(T', T_f)$, where T is the time of existence for $\varphi(\mathbf{x}, t)$ in Theorem 1, and for all $(\mathbf{x}, t) \in \bar{\Omega} \times [0, \min(T', T_f))$ there is:

$$\varphi^-(\mathbf{x}, t) \leq \varphi(\mathbf{x}, t) \leq \varphi^+(\mathbf{x}, t). \quad (4.3)$$

Our strategy to derive bounds for V and P using this comparison principle is to first derive bounds for the source terms f_V and f_P , respectively, and then compute the bounds V^\pm and P^\pm that satisfy the inequalities of (4.1) and (4.2). To this end, following (3.3) and using the fact that $0 \leq B_2 \leq c_0$, we have:

$$\begin{aligned} f_P(\mathbf{x}, t, \varphi) &= a\beta B_2(\mathbf{x}, t) - \tau\varphi \geq -\tau\varphi, \\ f_P(\mathbf{x}, t, \varphi) &\leq a\beta c_0 - \tau\varphi. \end{aligned}$$

Thus bounds on the source term f_P can be defined as:

$$f_P^-(\mathbf{x}, t, \varphi) = -\tau\varphi, \quad f_P^+(\mathbf{x}, t, \varphi) = a\beta c_0 - \tau\varphi, \quad (4.4)$$

and there is $f_P^- \leq f_P \leq f_P^+$ for all $(\mathbf{x}, t, \varphi) \in \bar{\Omega} \times [0, +\infty) \times \Lambda$.

Similarly for f_V given in (3.2), we have:

$$\begin{aligned} f_V(\mathbf{x}, t, \varphi) &= F(P(\mathbf{x}, t))b\beta B_2(\mathbf{x}, t) - (\theta F(P(\mathbf{x}, t))B_1(\mathbf{x}, t) + \gamma)\varphi \\ &\geq -(\theta c_0 + \gamma)\varphi, \\ f_V(\mathbf{x}, t, \varphi) &\leq b\beta c_0 - \gamma\varphi. \end{aligned}$$

Hence $f_V^- \leq f_V \leq f_V^+$ where:

$$f_V^-(\mathbf{x}, t, \varphi) = -(\theta c_0 + \gamma)\varphi, \quad f_V^+(\mathbf{x}, t, \varphi) = b\beta c_0 - \gamma\varphi. \quad (4.5)$$

Noticing that all of f_P^\pm and f_V^\pm are linear functions in φ , we shall thus define P^\pm and V^\pm as solutions to the diffusion equations given by (4.1) or (4.2) with the inequalities replaced by equalities. To this end, we shall first derive the solution to the reaction-diffusion equation with linear source term on a circular domain as given in the next section.

4.1 Solution to Reaction-Diffusion Equations with Linear Sources on a Circular Domain

Let the domain Ω be a disk with radius $R > 0$ and assume the source term is $f(\mathbf{x}, t, \varphi) = C_0 - C_1\varphi$ where C_0 and C_1 are constants, we solve following the reaction-diffusion problem in this section [19]:

$$\begin{cases} \frac{\partial \varphi}{\partial t} = D \frac{\partial}{\partial r} \left(r \frac{\partial \varphi}{\partial r} \right) + C_0 - C_1 \varphi, & t > 0, 0 \leq r \leq R, \\ \frac{\partial \varphi}{\partial r}(0, t) = \frac{\partial \varphi}{\partial r}(R, t) = 0, & t > 0, \\ \varphi(r, 0) = \varphi_0(r). & 0 \leq r \leq R. \end{cases} \quad (4.6)$$

To begin with, noticing that $Q(r, t) = \frac{C_0}{C_1} + C_0 e^{-C_1 t}$ satisfies the following PDE:

$$\begin{aligned} \frac{\partial Q}{\partial t} &= -C_0 C_1 e^{-C_1 t} = C_0 - C_1 Q(r, t), \\ \frac{\partial Q}{\partial r}(0, t) &= \frac{\partial Q}{\partial r}(R, t) = 0, \end{aligned}$$

we see that finding a solution φ to (4.6) is equivalent to finding a solution $Z(r, t) = \varphi(r, t) - Q(r, t)$ to the problem:

$$\begin{cases} \frac{\partial Z}{\partial t} = D \frac{\partial}{\partial r} \left(r \frac{\partial Z}{\partial r} \right) - C_1 Z, & t > 0, 0 \leq r \leq R, \\ \frac{\partial Z}{\partial r}(0, t) = \frac{\partial Z}{\partial r}(R, t) = 0, & t > 0, \\ Z(r, 0) = \varphi_0(r) - \frac{C_0}{C_1} - C_0. & 0 \leq r \leq R. \end{cases} \quad (4.7)$$

The method of separating variables will be utilized for this purpose.

First, let us look for a non-trivial solution in the form $Z(r, t) = F(r)G(t)$ that satisfies the PDE and the boundary conditions, then one has:

$$\begin{aligned} F(r)G'(t) &= DG(t) [F'(r) + rF''(r)] - C_1 F(r)G(t) \\ \implies \frac{G'(t) + C_1 G(t)}{DG(t)} &= \frac{F'(r) + rF''(r)}{F(r)} = k \end{aligned}$$

for some constant k , and on the boundaries $F'(0) = F'(R) = 0$.

Thus $F(r)$ is the solution to the Sturm-Liouville problem [16]:

$$\begin{aligned} (rF'(r))' - kF(r) &= 0, \quad 0 \leq r \leq R, \\ F'(0) = F'(R) &= 0, \end{aligned}$$

and following a standard Fourier-Bessel analysis [9] we have $k = -\lambda^2$ for some $\lambda \geq 0$, such that $F(r) = J_0(\lambda r)$ satisfies the boundary conditions, where J_m , $m \in \mathbb{Z}$ is the Bessel function of the first kind with the index m . Using the fact that $J'_0(r) = -J_1(r)$, we see:

$$F'(0) = F'(R) = 0 \quad \Leftrightarrow \quad J_1(0) = J_1(\lambda R) = 0.$$

Note that the first equality is automatically satisfied and for the second one we need λR to be a root of J_1 . Thus, we let the zeros of J_1 be denoted by $0 = \alpha_0 < \alpha_1 < \alpha_2 < \dots$, one thus obtains $\lambda_n = \alpha_n/R$, $k_n = -\lambda_n^2$, and the eigenfunction $F_n(r) = J_0(\alpha_n r/R)$, $n = 0, 1, 2, \dots$.

For each n , the corresponding function $G_n(t)$ solves the ODE:

$$G'_n(t) + (C_1 - Dk_n)G_n(t) = 0,$$

and thus one may choose $G_n(t) = e^{-(C_1 + D\lambda_n^2)t}$ and any solution $Z(r, t)$ can be written as:

$$Z(r, t) = \sum_{n=0}^{\infty} A_n e^{-(C_1 + D\frac{\alpha_n^2}{R^2})t} J_0\left(\frac{\alpha_n r}{R}\right) \quad (4.8)$$

for some constants A_n , $n = 0, 1, \dots$.

To determine A_n , we set $t = 0$ in (4.8) and compare it to the initial condition in (4.7) to obtain:

$$\varphi_0(r) - \frac{C_0}{C_1} - C_0 = \sum_{n=0}^{\infty} A_n J_0\left(\frac{\alpha_n r}{R}\right).$$

Using the orthogonality of eigenfunctions in the Sturm-Liouville theorem [24], namely:

$$\int_0^R r J_0\left(\frac{\alpha_n r}{R}\right) J_0\left(\frac{\alpha_m r}{R}\right) dr = 0, \quad \forall m, n \geq 0, \quad m \neq n,$$

the coefficients are thus computed by:

$$A_n = \frac{\int_0^R r \left(\varphi_0(r) - \frac{C_0}{C_1} - C_0\right) J_0\left(\frac{\alpha_n r}{R}\right) dr}{\int_0^R r J_0\left(\frac{\alpha_n r}{R}\right)^2 dr}. \quad (4.9)$$

To simplify the numerator, we use the facts that $J_0(0) = 1$ and $rJ_0(r) = (rJ_1(r))'$ to compute:

$$\int_0^R rJ_0\left(\frac{\alpha_n r}{R}\right) dr = \begin{cases} \frac{1}{2}R^2, & n = 0, \\ J_1(\alpha_n) - J_1(0) = 0, & n \geq 1; \end{cases}$$

whereas for the denominator the Lommel's integral [15]:

$$\int rJ_m(\lambda r)^2 dr = \frac{1}{2}r^2 [J_m(\lambda r)^2 - J_{m-1}(\lambda r)J_{m+1}(\lambda r)], \quad \forall m \geq 0, \lambda \geq 0$$

is used to obtain:

$$\int_0^R rJ_0\left(\frac{\alpha_n r}{R}\right)^2 dr = \frac{1}{2}R^2 J_0(\alpha_n)^2.$$

Putting everything together, the solution to (4.6) is:

$$\varphi(r, t) = \frac{C_0}{C_1}(1 - e^{-C_1 t}) + \sum_{n=0}^{\infty} \frac{\int_0^R r\varphi_0(r)J_0\left(\frac{\alpha_n r}{R}\right) dr}{\frac{1}{2}R^2 J_0(\alpha_n)^2} e^{-(C_1 + D\frac{\alpha_n^2}{R^2})t} J_0\left(\frac{\alpha_n r}{R}\right). \quad (4.10)$$

This formula is used to derive bounds for both P and V in the next two sections.

4.2 Bounds for Potassium Concentration

In the case of potassium, the initial conditions for both P^- and P^+ are given by the zero function. Setting $\varphi_0 \equiv 0$ in (4.10), one obtains $\varphi(r, t) = (C_0/C_1)(1 - e^{-C_1 t})$. Hence in the case of f_P^- , there is $C_0 = 0$ and $C_1 = \tau$ and thus $P^- = 0$; whereas for f_P^+ , there is $C_0 = a\beta c_0$ and $C_1 = \tau$, which leads to $P^+ = \frac{a\beta c_0}{\tau}(1 - e^{-\tau t})$. By the comparison theorem, we obtain the following bounds for P :

$$0 \leq P(r, t) \leq \frac{a\beta c_0(1 - e^{-\tau t})}{\tau}. \quad (4.11)$$

Note that the lower bound is also established by the well-posedness theorem in the previous chapter, where P stays in the invariance domain $\Lambda = [0, +\infty)$; and the upper bound will provide crucial information regarding whether it is possible for potassium to reach the threshold value at all.

4.3 Bounds for Virus Concentration

In the case of the virus, the initial conditions for both V^- and V^+ are set to the same one as V , i.e., $v_0\bar{\delta}(r)$, see (2.11b). Hence in (4.10) one sets $\varphi_0(r) = v_0\bar{\delta}(r)$ and obtains:

$$\int_0^R r\varphi_0(r)J_0\left(\frac{\alpha_n r}{R}\right)dr = \frac{1}{2\pi}v_0J_0(0) = \frac{v_0}{2\pi}.$$

To this end in the case of f_V^- , $C_0 = 0$ and $C_1 = \theta c_0 + \gamma$, hence there is:

$$V^-(r, t) = \frac{v_0}{\pi R^2} \sum_{n=0}^{\infty} \frac{e^{-(\theta c_0 + \gamma + D_V \frac{\alpha_n^2}{R^2})t} J_0\left(\frac{\alpha_n r}{R}\right)}{J_0(\alpha_n)^2};$$

and in the case of f_V^+ , $C_0 = b\beta c_0$ and $C_1 = \gamma$, thus:

$$V^+(r, t) = \frac{b\beta c_0(1 - e^{-\gamma t})}{\gamma} + \frac{v_0}{\pi R^2} \sum_{n=0}^{\infty} \frac{e^{-(\gamma + D_V \frac{\alpha_n^2}{R^2})t} J_0\left(\frac{\alpha_n r}{R}\right)}{J_0(\alpha_n)^2}.$$

By the comparison theorem, an lower and an upper bounds for V are given by:

$$V^-(r, t) \leq V(r, t) \leq V^+(r, t). \tag{4.12}$$

Chapter 5

Application of the Analysis

In this chapter, we will utilize the analysis result to derive bounds on both the virus concentration and potassium concentration by substituting the model parameters with estimated values from various independent studies.

5.1 Coefficient Values

In Table 5.1 we summarize values and units for the model parameters that are used in our model. Since these parameters are estimated from independent biological studies with generally different experiment environment, they do not necessarily reflect the actual values in the rabbit skin infection experiment conducted by the collaborating team from University of New Mexico. Nevertheless, we hypothesize that these estimations provide reasonable orders of magnitude for the actual values and thus the conclusion thereafter is still meaningful. And we briefly explain their biological meanings below:

- The total number of cells c_0 per square millimeter (mm) is derived from the usual assumption that there are 10^6 cells per cubic millimeter and the thickness of rabbit skin cells is 3×10^{-2} millimeter.
- The baseline infection rate θ designates the portion of normal cells infected by each virus per hour (h).
- The death rate of infected cells given by β equals the reciprocal of mean survival time of these cells.
- The absorption rate of extracellular potassium τ equals the reciprocal of the average

Table 5.1: Parameter Estimations

c_0	$3 \times 10^4 \text{ cell} \cdot \text{mm}^{-2}$
θ	$1.5 \times 10^{-8} \text{ h}^{-1} \cdot \text{virus}^{-1}$
β	0.15 h^{-1}
τ	$3 \times 10^{-4} \text{ h}^{-1}$
D_P	$0.1 \text{ mm}^2 \cdot \text{h}^{-1}$
k	$10^{-4} \text{ millimole} \cdot \text{mm}^{-2}$
P_s	$10^{-6} \text{ millimole} \cdot \text{mm}^{-2}$
a	$10^{-10} \text{ millimole} \cdot \text{cell}^{-1}$
D_V	$0.01 \text{ mm}^2 \cdot \text{h}^{-1}$
b	$300 \text{ virus} \cdot \text{cell}^{-1}$
v_0	$10^4 \text{ virus} \cdot \text{mm}^{-2}$

time that extracellular potassium is absorbed into the normal cells.

- D_P and D_V are the diffusion coefficient for the potassium particles and viruses, respectively.
- k is a parameter in the smoothed Heaviside function to model the abrupt blocking effect when the potassium reaches a certain threshold.
- The threshold in the previous item P_s is measured in number of potassium particles (millimole) per square millimeter, and it is obtained from experimental observations.
- a describes the number of potassium particles released when an infected cell dies.
- b describes the non-consumed virus that is released when an infected cell dies.
- And lastly, v_0 is the amount of viruses injected to the center of the lesion at the beginning of the experiments.

5.2 Estimates for Potassium Concentration

From (4.11), we see that the largest possible value for the potassium concentration is $a\beta c_0/\tau$, hence our expectation is that if this value is larger than P_s , then the model has the potential of predicting the blocking of virus infection by high potassium concentration levels. To this end, since among all parameters involved in this comparison the absorption rate τ is the least reliable, we thus obtain a bound on τ such that $a\beta c_0/\tau > P_s$:

$$\frac{a\beta c_0}{\tau} > P_s \Leftrightarrow \tau < \frac{a\beta c_0}{P_s} = 0.45 \text{ h}^{-1};$$

and we see that the estimated value in Table 5.1 is far below this critical value. Hence it is reasonable for us to believe that the model can effectively predict the blocking effect, as seen in the simulation results given next.

5.3 Verification by Numerical Simulation

Motivated by earlier results, we can provide a set of simulation results that are obtained by solving the problem numerically by a finite volume method [29]. In particular, we consider two tests, denoted by Test A and Test B, respectively:

- In Test A, the blocking factor is completely turned off no matter how large P is; that is, we replace $F(P)$ by the constant 1 in Eqns. (2.10) whereas all other parameters are provided in Table 5.1.
- In Test B, the blocking factor $F(P)$ is computed using the parameters k and P_s , also given in Table 5.1.

The simulated virus concentrations at different times (36, 60, 120, 240, 360, and 600 hours since injection) are plotted and compared for the two tests in Figure 5.1. In particular, the horizontal axis represents the distance of a spatial point from the center of the lesion, and the dashed curves and solid curves correspond to the virus concentration plots for Test A and Test B, respectively. On the one hand, we can observe the growth of the lesion in the

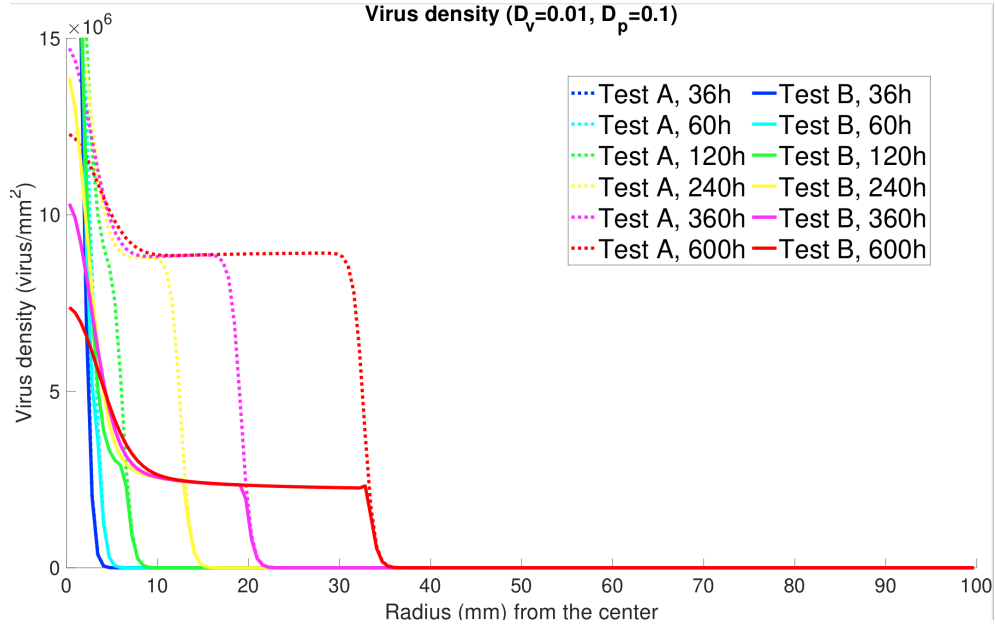


Figure 5.1: Comparing simulated virus concentration at various times without potassium blocking scaling factor (Test A) and with potassium blocking scaling factor (Test B)

sense that the boundary of high virus concentration region moves towards right as time increases, which is consistent with lab observations. On the other hand, we also observe significant reduction in the virus concentration level throughout the simulation time when the blocking effect is turned on, which agrees well with the prediction in previous section.

Chapter 6

Conclusion

It is clear from this work's analysis that potassium does reach the provided threshold value within a stationary circular domain. After we defined the model type and the governing equations in Chapter 2, we were able to express the relationship between the different concentrations V and P with respect to the cell number densities B_1, B_2 , and B_3 . In Chapters 3 and 4, we adopted the well-posedness and comparison theorems by Martin and Smith [17] that allowed us to evaluate the lower and upper bounds of potassium and virus concentration to estimate solutions to the model. For this, it was necessary to show that there exists unique solutions for V and P with mild regularity. Finally, we used estimated parameters and a given P_s obtained from collaborating experimental studies, which allowed us to conclude the potassium build up in fact reaches the designated threshold value. And this prediction is confirmed by simulation results of the model without and with the potassium blocking factor term.

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Curriculum Vitae

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