REACTION-DIFFUSION MODELS OF CANCER DISPERSION

by

Kim Yvette Ward
B.S. 1990, Virginia Commonwealth University
M.S. 1992, Virginia Commonwealth University

A Dissertation Submitted to the Faculty of Old Dominion University in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY

COMPUTATIONAL AND APPLIED MATHEMATICS

OLD DOMINION UNIVERSITY
May 1998

Approved by:

John A. Adam (Director)
Mark Dorrepaal (Member)
Richard D. Noren (Member)
Roger Pullin (Member)
John Tweed (Member)
The phenomenological modeling of the spatial distribution and temporal evolution of one-dimensional models of cancer dispersion are studied. The models discussed pertain primarily to the transition of a tumor from an initial neoplasm to the dormant avascular state, i.e. just prior to the vascular state, whenever that may occur. Initiating the study is the mathematical analysis of a reaction-diffusion model describing the interaction between cancer cells, normal cells and growth inhibitor. The model leads to several predictions, some of which are supported by experimental data and clinical observations [25]. We will examine the effects of additional terms on these characteristics. First, we study the model after incorporating the effects of the immune system at a rate proportional to the existing tumor population. Secondly, we assume that the immune system harvests the tumor population at a constant rate independent of the tumor population followed by inclusion of logistic growth of the cancer cells into the behavior of the growth inhibitor.
Next, we consider a model which consists of only two interacting populations, cancer cells and enzyme. We study this system of equations via two existing approaches.

We conclude with a nonlinear problem of cancer dispersion in which an integral equation governing the propagation of the cancer front is obtained. A primary difference between this model and the previous models is the inclusion of another major transport process called convection. For a special case we find an approximate solution to this equation.
ACKNOWLEDGMENTS

I have been blessed with a strong family bound together by love, patience, faith and trust. My parents, Emma Lee Snow Ward and Frank Ward Sr., have empowered their children with the qualities consistent with the definition of family. For never setting limitations on the abilities and dreams of their children, I thank them. I am grateful to my siblings Carmen, Frank Jr., Alison and Sheila for their support and friendship. A special thank you is extended to Alison for all the advice given to me of which has proven to be as valuable as gold. May God continue to bless you all!

Since my family made me aware of humane qualities, I was able to recognize them in my best friend and now husband, Dr. Joseph Manthey. Thank you for your loyal friendship, moral support, computer assistance and the rambunctious two-year old we call Adrian. May God continue to bless you all!

Thank you Dr. John Adam for maintaining confidence in me. The encouragement, support and guidance you have provided me since the first day we met has gone a long way and will always be with me. The enthusiasm and vigour you exhibit for life is inspirational.

I would like to express my gratitude to the members of my committee, Dr. Dorrepaal, Dr. Noren, Dr. Perry and Dr. Tweed for providing me with much useful feedback.

A special thank you is extended to Dr. E. T. Gawlinski and Dr. S. S. Shen for
taking time from their busy schedules to answer all my inquiries and provide me with materials.

Thank you Barbara Jeffrey and Gayle Tarkelsen for always listening to me despite how busy you were. I value that time, our new friendship and the many much needed lunches the two of you have provided.

Never fear Randy, Randolph and Tom, you are not forgotten. It was the three of you who got me off to a new start with a positive attitude towards mathematics. Thanks guys. May God continue to smile on us all!
TABLE OF CONTENTS

Page

LIST OF FIGURES ................................................................. vii

Chapter

I. INTRODUCTION ................................................................. 1

II. INVASIVE TUMOR GROWTH RESULTING FROM
TRANSFORMATION-INDUCED GLYCOLYSIS .................. 5
   MODEL ................................................................................. 7
   STABILITY ANALYSIS ..................................................... 11
   APPROXIMATE ANALYTICAL SOLUTIONS .................... 15
   WAVEFRONT PROFILES .................................................. 19
   CONSTANT DECAY RATE ............................................... 22
   CONSTANT HARVEST RATE .......................................... 27
   LOGISTIC GROWTH IN CANCER TISSUE ...................... 34

III. WAVES OF PURSUIT AND EVASION ......................... 40
    GOVERNING EQUATIONS ............................................. 41
    WEAKLY NONLINEAR APPROACH ................................. 43
    PHASE PLANE ANALYSIS .......................................... 50
    WAVEFRONT PROFILES .............................................. 56

IV. AN EXAMPLE OF NONLINEAR CANCER DISPERSION .... 58
    GOVERNING EQUATIONS ............................................. 60
    STEADY STATE SOLUTIONS .......................................... 62
    BIFURCATION EQUATION EXAMPLE ............................. 67
    SLOPE-STABILITY THEOREM .................................... 71
    PROPAGATION OF CANCER FRONT ............................... 78
    EXAMPLES ........................................................................ 80

V. CONCLUSIONS ................................................................. 86

BIBLIOGRAPHY ................................................................. 90

APPENDIXES

I. DERIVATION OF PROFILE ............................................. 94
II. INTERFACIAL WIDTHS OF ACID AND TUMOR .............. 98
III. DERIVATION OF PROFILE FOR MODIFIED MODEL .... 100
IV. INTERFACIAL WIDTH OF ACID FOR MODIFIED MODEL .. 102

VITA .................................................................................... 103
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Case I. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $p_2 = 1$, $\delta_1 = 12.5$, $\delta_3 = 70$ with speed $c = 0.0128$ (0.03mm/day). The wavefronts are propagating from left to right. Note the sharp tumor profile and the formation of a tumor-host hypocellular interstitial gap.</td>
</tr>
<tr>
<td>2.2</td>
<td>Case II. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $p_2 = 1$, $\delta_1 = 0.5$, $\delta_3 = 70$ with speed $c = 0.0064$ (0.01mm/day). The wavefronts are propagating from left to right. Note the sharp tumor profile and the formation of a tumor-host hypocellular interstitial gap.</td>
</tr>
<tr>
<td>2.3</td>
<td>Constant Decay Rate Case I. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $p_2 = 0.05$, $\delta_1 = 12.5$, $\delta_3 = 70$ with speed $c = 0.0128$. The wavefronts are propagating from left to right. Note $\eta_2$ is less steep.</td>
</tr>
<tr>
<td>2.4</td>
<td>Constant Decay Rate Case II. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $p_2 = 0.05$, $\delta_1 = 0.5$, $\delta_3 = 70$ with speed $c = 0.0064$. The wavefronts are propagating from left to right. Note the tumor profile is less steep.</td>
</tr>
<tr>
<td>2.5</td>
<td>Extinction time. Plot of $t_e$ against $\bar{H}$ for fixed $\bar{H}_L$. As $\frac{\bar{H}}{\bar{H}_L}$ increases, $t_e$ decreases. Note $t_e = 1$ corresponds to 1.65 weeks.</td>
</tr>
<tr>
<td>2.6</td>
<td>Constant Harvest Rate Case I. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $p_2 = 0.0894427$, $\delta_1 = 12.5$, $\delta_3 = 70$ with speed $c = 0.00378297$. Observe that the invading front is less steep with harvesting.</td>
</tr>
<tr>
<td>2.7</td>
<td>Constant Harvest Rate Case II. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $p_2 = 0.0894427$, $\delta_1 = 0.5$, $\delta_3 = 70$ with speed $c = 0.00378297$. Observe that the invading front is less steep with harvesting.</td>
</tr>
<tr>
<td>2.8</td>
<td>Logistic Growth in Cancer Tissue. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $p_2 = 1$, $\delta_1 = 12.5$, $\delta_3 = 70$ with speed $c = 0.0128$.</td>
</tr>
<tr>
<td>3.1</td>
<td>The characteristic polynomial $p(\lambda)$ from (3.76) as a function of $\lambda$ as $\rho$ varies. There is a critical value $\rho^<em>$ such that for $\rho &gt; \rho^</em>$ there is only one real positive root and two complex ones with negative real parts.</td>
</tr>
</tbody>
</table>
3.2 Waves of Pursuit and Evasion. Enzyme $L$ (dash) and cancer $N$ (solid). The travelling waves of pursuit evasion via approximate analytical solution. The cancer population wave is the forerunner after which the enzyme population follows. ................................. 57

4.1 Case I operating curve for the steady state problem where $x_e$ is the position of the interface and $R$ is the reproduction rate. The parameter values are: $\alpha = 4.7$, $\gamma_1 = 10$, $\delta_1 = 5$, $\gamma_2 = -10$, $\delta_2 = 5$, $u_1 = 5.5$, and $I_c = 15$. ................................................................. 69

4.2 Case II operating curve for the steady state problem where $x_e$ is the position of the interface and $R$ is the reproduction rate. The parameter values are: $\alpha = 2.5$, $\gamma_1 = -5$, $\delta_1 = 10$, $\gamma_2 = 0$, $\delta_2 = 3$, $u_1 = 1.46$, and $I_c = 15$. ................................................................. 70

4.3 Sketch of the function $\Gamma(\lambda)$ defined by (4.59). ......................... 77

4.4 Example I. Propagation of the cancer front without convection. An approximate solution $x_c$ vs. $t$ where $u_1 = 0.22$ (solid), $u_1 = 0.24$ (long dash) and $u_1 = 0.45$ (short dash). .................................................. 83

4.5 Example II. Propagation of the cancer front with convection. An approximate solution $x_c$ vs. $t$ where $u_1 = 0.22$ (solid) and $u_1 = 0.45$ (short dash). .................................................. 85
CHAPTER 1
INTRODUCTION

A tumor is a new growth of tissue in which the normal balance between cell proliferation and cell death is disturbed. When a tumor is in the avascular stage of growth it lacks its own network of blood vessels to supply oxygen, nutrients and remove waste. The tumor depends solely on diffusion processes for oxygen, nutrients and waste transport. Therefore, tumors in the avascular stage cannot grow beyond a few millimeters in diameter (1-2 mm), remain in situ (localized) and do not metastasize (spread). Aggregations (clumps) of cells which invade their surrounding environment are referred to as malignant tumors or cancer cells. Cancer cells have the ability to develop in any tissue of the body that contains cells capable of division. Cancer cells metastasize through the lymphatic system or blood stream to lymph nodes and other tissues in the body, subsequently destroying adjacent normal or healthy tissue.

The transition from in situ carcinoma (epithelial in origin) to invasive cancer involves vascularization of the tumor. More specifically, growing tumors produce and secrete diffusable chemical substances that stimulate new capillary growth from the host’s vasculature, a process known as angiogenesis. The new capillary sprouts grow toward and ultimately penetrate the tumor. The vascularized tumor is now provided with additional means of oxygen, nutrients and waste transport. As the vascularized tumor grows it exerts pressure on surrounding tissue consequently forcing tumor cells between intercellular (between cells) spaces. Thus, the confinement to a dormant avascular state has been lifted and rapid growth ensues.

One of the mechanisms for invasion of cancer cells through tissue membrane and into blood and lymphatic vessels involves enzymatic processes. It is known
that tumors contain and secrete a variety of proteolytic enzymes. The release of these enzymes by growing tumors may break down the cell membrane of normal cells, allowing the cancer cells to invade and move further into the host. This process is known as basement membrane degradation.

Cancer is a very aggressive disease and there are numerous approaches one can take mathematically to try and describe its characteristics. Many mathematical models studied thus far have been one-dimensional models [3], [60]. The solutions have provided insight into the nature of the growth processes in more realistic geometries. From a mathematical modeling point of view, there are at least three components to the system that will play a role in the underlying theoretical problems. They are

- cancer cells, sometimes referred to as cancer tissue since we are dealing with continuum models;
- normal cells, sometimes referred to as normal tissue;
- the presence of at least one type of enzyme.

In addition, we need to recognize the fact that healthy people possess a defense mechanism against cancer cells. This mechanism is the immune system which will attempt to suppress the growth of cancer cells. It is therefore desirable to develop mathematical models that will describe the interaction between normal cells, cancer cells and whatever type of enzyme (growth factors or growth inhibitors) they will produce. Inhibitory mechanisms, often in the form of killer cells, are produced by the immune system. Thus, host organisms are capable of hindering cell invasion by sending these specialized killer cells to fight malignant cells. The outcome of this struggle determines whether the cancer is rejected or becomes dominant.
Now, in an attempt to elude this attack by the immune system, the cancer cells may lose cell surface molecules needed for recognition by some immune cells or form aggregates with platelets, lymphocytes and neutrophils which results in an environment favorable to the survival of the cancer cells. Even if these evasive actions are successful, growth of all the cancer cells arriving at a possible new organ site is not guaranteed. The response may be associated with growth factors produced by the cancer cell's microenvironment. Thus, even in a simplified model very complex interactions may occur which pose highly relevant biological questions which have to be considered in any more realistic and intricate model.

This dissertation provides a combination of mathematical modeling and phenomenology of cancer dispersion, allowing for qualitative predictions. The spatial-temporal dynamics of the one-dimensional models discussed pertain primarily to the transition of the tumor from an initial neoplasm to the dormant avascular state, i.e. just prior to the vascular state, whenever that may occur.

In a recent paper by Gatenby and Gawlinski [25] the authors hypothesized that changes caused by the tumor to the environment at the microscopic or cellular level may provide a simple yet complete foundation for understanding invasive cancer. They developed a continuum model of tumor invasion in an attempt to understand how cancer, both primary and metastatic, invades and destroys normal tissue. They consider a system of three coupled reaction-diffusion equations in order to investigate travelling wave solutions for normal cells, cancer cells and excess hydrogen ion concentration, $H^+$, an acid produced by the cancer cells which is essentially responsible for breaking down the cell membrane of normal cells. As will be displayed in Chapter 2, their work is very complicated; however their model does not take into account the effects of the immune system. Therefore, we will
incorporate in a simplistic manner, the effects of the immune system into that model in order to observe the consequences and compare them with the results of Gatenby and Gawlinski. These characteristics will be incorporated via two approaches. In our first approach we assume that the immune system harvests the tumor population at a rate proportional to the existing tumor population and secondly at a constant rate independent of the tumor population. We also study the model by including logistic growth of the cancer cells into the behavior of the growth inhibitor.

In Chapter 3 we will study a simplified version of the Gatenby and Gawlinski model. We will employ the techniques of earlier work by Chow and Tam (in an ecological context) [10] in studying the interaction between cancer cells and normal cells.

A nonlinear problem of cancer dispersion is studied in Chapter 4. The primary difference between this model and the models contained in the previous chapters is the addition of a convection term as another possible major transport process. We find multiple steady state solutions and investigate their stability and instability. For the time-dependent case, we will derive an integral equation which determines the propagation of the cancer front. We conclude this chapter with a specific example.
CHAPTER 2

INVASIVE TUMOR GROWTH RESULTING
FROM TRANSFORMATION-INDUCED
GLYCOLYSIS

In this chapter I will introduce the basic model by Gatenby and Gawlinski which will be adapted and extended. In particular, in section 2.2 the stability analysis is discussed in detail, supplementing the brief discussion provided in Gatenby and Gawlinski. The model describes, at the cellular level the interaction between a growing tumor and surrounding normal tissue in the region where the tumor and normal tissue meet, commonly referred to as the tumor-host interface. No assumptions were made about the origin of the growing tumor.

Useful models of cancer growth must include characteristics common to many tumors [6], [7], [12], [15] and [20]. One such characteristic is the evolution of the tumor towards a more undifferentiated state [32], [46], [47], [56] and [57]. This evolution is accompanied by an increased rate of glycolysis in tumor cells, leading to substantial production of lactic acid from glucose. This change results in increased acid production, and the diffusion of the acid into adjacent healthy tissue creates an environment surrounding the tumor in which the tumor cell population can increase, and normal cells are no longer viable [25].

There are two key elements of this tumor invasion mechanism. First, due to primitive metabolism, spaces between the tumor tissue have a low pH. This element is supported by clinical data showing that tumors in situ use approximately one order of magnitude more glucose than normal tissue [5], [45], [59] and that tumor interstitial pH is about 0.5 units lower than normal tissue [2], [4], [18], [28]
and [29]. The second element is that a pH environment advantageous to tumor tissue will diminish the viability of normal tissue. Studies by [1], [27], [31], [36], [49] and [55] show that normals cells are most viable at an extracellular (outside of cells) pH of 7.4 and a sharp decline in viability when the extracellular pH is below 7.1.

In this mathematical model the evolution of normal cells, cancer cells and increased acid production is modeled as a system of reaction-diffusion equations. The solutions to these equations yield quantitative information about the structure and evolution of the tumor-host interface. Some of the main results, which are also supported by experimental data and clinical observations [26], [37], [38], include

- the existence of an acidic pH gradient extending from the tumor-host interface;
- critical parameters controlling the transition from benign to malignant growth;
- tumor wavefront velocities consistent with in vivo tumor growth rates;
- recognition of a hypocellular interstitial gap at the tumor-host interface;
- demonstration of a strong correlation between the interfacial morphology and tumor wavefront velocity.

The hypothesis by Gatenby and Gawlinski results in complex interactions consistent with various features of cancer biology.
2.1 Model

The full model, which determines the spatial-temporal variations of the three fields $N_1$, $N_2$ and $L$ is governed by the following system of coupled reaction-diffusion equations:

\[
\frac{\partial N_1}{\partial t} = r_1 N_1 (1 - \frac{N_1}{K_1} - \alpha_{12} \frac{N_2}{K_2}) - d_1 L N_1 + \nabla \cdot (D_{N_1} [N_2] \nabla N_1)
\]

\[
\frac{\partial N_2}{\partial t} = r_2 N_2 (1 - \frac{N_2}{K_2} - \alpha_{21} \frac{N_1}{K_1}) + \nabla \cdot (D_{N_2} [N_1] \nabla N_2)
\]

\[
\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + D_3 \frac{\partial^2 L}{\partial x^2}.
\]

The variables and parameters are:

$x$: position with units cm.

$t$: time with units sec.

$N_1(x,t)$: density of normal tissue with units cells/cm$^3$.

$N_2(x,t)$: density of neoplastic tissue with units cells/cm$^3$.

$L(x,t)$: excess $H^+$ ions concentration with units M = moles/liter.

$r_1, r_2$: growth rates of normal and neoplastic tissue with units sec$^{-1}$.

$K_1, K_2$: carrying capacities or saturation levels of normal and neoplastic tissue with units cells/cm$^3$.

$\alpha_{12}, \alpha_{21}$: competitive effects of $N_2$ on $N_1$ and $N_1$ on $N_2$ (units dimensionless).

$D_2, D_3$: Diffusion constants for neoplastic tissue and $H^+$ ions with units cm$^2$/sec.

$d_1$: mortality rate of normal tissue with units 1/M · sec.
$r_3$: production rate of $H^+$ ions with units $Mcmand^3/sec\cdot cell$.

d_3$: absorption rate of $H^+$ ions with units $1/sec$.

We begin with studying the significance of the terms in the equations. The behavior of the normal tissue is determined by

(i) the logistic growth of $N_1$ with growth rate $r_1$ and carrying capacity $K_1$,

(ii) the Lotka-Volterra competition strength parameter $\alpha_{12}$ characterizing the normal tissue growth reduction due to competition with the tumor tissue for space and other resources,

(iii) the interaction of $N_1$ with excess $H^+$ ions leading to a death rate proportional to $L$, and

(iv) cellular diffusion with an $N_2$-dependent diffusion coefficient, $D_{N_1}[N_2]$, since normal tissue is only able to diffuse into regions where $N_2$ is small due to a volume exclusion effect.

Similarly, the neoplastic tissue growth is determined by

(i) the logistic growth of $N_2$ with growth rate $r_2$ and carrying capacity $K_2$,

(ii) $\alpha_{21}$ characterizing the tumor tissue growth reduction due to competition with the normal tissue for space and other resources,

(iii) cellular diffusion with an $N_1$-dependent diffusion coefficient, $D_{N_2}[N_1]$, since tumor tissue can spread only into regions where healthy tissue number density is low.
We recognize the fact that healthy tissue, which successfully performs a particular function and assumed to be at its carrying capacity, \( N_1 = K_1 \), will occupy all available space within the volume of tissue adjacent to the tumor. Therefore, since healthy tissue will not be diffusing in space, the following simplifying assumption is made:

\[
D_{N_1}[N_2] = 0. 
\]  \hspace{1cm} (2.2)

Gatenby and Gawlinski conducted ten duplicate experiments for the duration of three days at pH 6.9 versus 7.5 in which no reduction occurred in the rate of growth of the tumor cells. Thus, since no decline in the growth rate of the tumor cells has been observed at the pH levels examined, there is no acid concentration dependent death rate. Hence, we make the next simplifying assumption, namely that

\[
D_{N_2}[N_1] = D_2(1 - N_1/K_1). 
\]  \hspace{1cm} (2.3)

The rate of change of the excess \( H^+ \) ions is determined by

(i) exponential growth of \( N_2 \) with production rate of \( H^+ \) ions \( r_3 \),

(ii) absorption of \( H^+ \) ions to take account of the mechanisms for increasing local pH and

(iii) chemical diffusion.

In this analysis competition for space and resources between the two populations occurs for a certain range of parameters, which implies the importance of the Lotka-Volterra parameters for a quantitative description of the tumor-host interface. However, following Gatenby and Gawlinski we limit ourselves to the
case where $\alpha_{12} = \alpha_{21} = 0$. Also shown in this analysis, for aggressively invasive cancers, coexistence between the tumor tissue and the normal tissue is not possible and therefore the Lotka-Volterra competition will not effect the structure and dynamics of the tumor-host interface. Thus, the restriction $\alpha_{12} = \alpha_{21} = 0$ will not affect the qualitative behavior of the model but will make it more analytically tractable.

Incorporating the stated assumptions (2.2)-(2.3) and our restriction on the Lotka-Volterra parameters into the system (2.2) reduces it to

$$
\frac{\partial N_1}{\partial t} = r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - d_1 L N_1 \\
\frac{\partial N_2}{\partial t} = r_2 N_2 \left(1 - \frac{N_2}{K_2}\right) + D_2 \frac{\partial^2 N_2}{\partial x^2} \\
\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + D_3 \frac{\partial^2 L}{\partial x^2}.
$$

(2.4)

Before analyzing this model we express it in non-dimensional terms by introducing the quantities

$$
\eta_1 = \frac{N_1}{K_1}, \quad \eta_2 = \frac{N_2}{K_2}, \quad \Lambda = \frac{L}{L_0}, \quad \tau = r_1 t, \quad \xi = \sqrt{\frac{r_1}{D_3}} x
$$

(2.5)

where

$$
L_0 = r_3 K_2 / d_3
$$

(2.6)

which on substituting into (2.4) yields the following dimensionless form of the governing equations

$$
\frac{\partial \eta_1}{\partial \tau} = \eta_1 (1 - \eta_1) - \delta_1 \Lambda \eta_1 \\
\frac{\partial \eta_2}{\partial \tau} = \rho_2 \eta_2 (1 - \eta_2) + \Delta_2 (1 - \eta_1) \frac{\partial^2 \eta_2}{\partial \xi^2} \\
\frac{\partial \Lambda}{\partial \tau} = \delta_3 (\eta_2 - \Lambda) + \frac{\partial^2 \Lambda}{\partial \xi^2}.
$$

(2.7)
where

\[ \Delta_2 = \frac{D_2}{D_3}, \quad \delta_3 = \frac{d_3}{r_1}. \tag{2.8} \]

and

\[ \delta_1 = \frac{d_1 r_3 K_2}{d_3 r_1}, \quad \rho_2 = \frac{r_2}{r_1}. \tag{2.9} \]

\[ \tag{2.10} \]

2.2 Stability Analysis

The procedure here is to determine the fixed points of the governing equations (2.7) and investigate the stability and determine the conditions for instability.

In the spatially homogeneous situation we find four fixed points \( F_i, i = 1, 2, 3, 4 \) which are:

- \( F_1 : \eta_1 = 0, \quad \eta_2 = 0, \quad \Lambda = 0 \)
- \( F_2 : \eta_1 = 1, \quad \eta_2 = 0, \quad \Lambda = 0 \)
- \( F_3 : \eta_1 = 1 - \delta_1, \quad \eta_2 = 1, \quad \Lambda = 1 \)
- \( F_4 : \eta_1 = 0, \quad \eta_2 = 1, \quad \Lambda = 1. \)

We observed that \( F_1 \) represents the absence of all tissue and acid; \( F_2 \) represents the absence of tumor tissue and acid, but the healthy tissue existing at its carrying capacity; \( F_3 \) represents the coexistence of tumor tissue at its carrying capacity and healthy tissue at a reduced level and \( F_4 \) represents the tumor tissue existing at its carrying capacity having killed off all the healthy tissue.

In a linearized stability analysis one assumes that close to the fixed point, the original nonlinear problem can be approximated by a linear one. This linearization
is accomplished by the Taylor series for functions of several variables and results in a matrix of the form

\[
A = \begin{bmatrix}
\frac{\partial f_1}{\partial \eta_1} & \frac{\partial f_1}{\partial \eta_2} & \frac{\partial f_1}{\partial \lambda} \\
\frac{\partial f_2}{\partial \eta_1} & \frac{\partial f_2}{\partial \eta_2} & \frac{\partial f_2}{\partial \lambda} \\
\frac{\partial f_3}{\partial \eta_1} & \frac{\partial f_3}{\partial \eta_2} & \frac{\partial f_3}{\partial \lambda}
\end{bmatrix}
\]

(2.11)

and is often referred to as the community matrix. The stability of the fixed point is then determined by evaluating the matrix at the fixed point and investigating eigenvalues \( \lambda \), which are solutions of \( |A - \lambda I| = 0 \), where \( I \) is the identity matrix. In particular, the fixed point is stable if \( Re(\lambda) < 0 \) for all of the eigenvalues. For our model where

\[
\begin{align*}
f_1(\eta_1, \eta_2, \Lambda) &= \eta_1(1 - \eta_1) - \delta_1 \Lambda \eta_1, \\
f_2(\eta_1, \eta_2, \Lambda) &= \rho_2 \eta_2(1 - \eta_2), \\
f_3(\eta_1, \eta_2, \Lambda) &= \delta_3(\eta_2 - \Lambda),
\end{align*}
\]

(2.12)

we obtain the community matrix

\[
A = \begin{bmatrix}
1 - 2\eta_1 - \delta_1 \Lambda & 0 & -\delta_1 \eta_1 \\
0 & \rho_2 - 2\rho_2 \eta_2 & 0 \\
0 & \delta_3 & -\delta_3
\end{bmatrix}
\]

(2.13)

For \( F_1 \), namely \((0,0,0)\), (2.13) gives

\[
|A - \lambda I| = \begin{vmatrix}
1 - \lambda & 0 & 0 \\
0 & \rho_2 - \lambda & 0 \\
0 & \delta_3 & -\delta_3 - \lambda
\end{vmatrix} = 0
\]

(2.14)
where $I$ is the identity matrix. From (2.14) we find the eigenvalues $\lambda$ are

$$\lambda_1 = 1, \lambda_2 = \rho_2, \lambda_3 = -\delta_3. \quad (2.15)$$

For $F_2$, namely $(1,0,0)$, (2.13) gives

$$|A - \lambda I| = \begin{vmatrix} -1 - \lambda & 0 & -\delta_1 \\ 0 & \rho_2 - \lambda & 0 \\ 0 & \delta_3 & -\delta_3 - \lambda \end{vmatrix} = 0 \quad (2.16)$$

from which we find the eigenvalues $\lambda$ are

$$\lambda_1 = -1, \lambda_2 = \rho_2, \lambda_3 = -\delta_3. \quad (2.17)$$

Therefore, $F_1$ and $F_2$ are unstable, which implies that the slightest disturbance in $\eta_1$ and $\eta_2$ for $F_1$, and the slightest disturbance in $\eta_2$ for $F_2$ will continue to grow towards one of the other two stable fixed points (which will be verified below).

Similarly, for our third fixed point $F_3$, that is, $(1 - \delta_1, 1, 1)$, (2.13) gives

$$|A - \lambda I| = \begin{vmatrix} (\delta_1 - 1) - \lambda & 0 & -\delta_1(1 - \delta_1) \\ 0 & -\rho_2 - \lambda & 0 \\ 0 & \delta_3 & -\delta_3 - \lambda \end{vmatrix} = 0 \quad (2.18)$$

and thus the eigenvalues are

$$\lambda_1 = \delta_1 - 1, \lambda_2 = -\rho_2, \lambda_3 = -\delta_3. \quad (2.19)$$

Thus, $F_3$ is stable when $\delta_1 < 1$ and unstable when $\delta_1 > 1$. Finally for the last fixed point $F_4$ which is $(0,1,1)$, (2.13) gives

$$|A - \lambda I| = \begin{vmatrix} (1 - \delta_1) - \lambda & 0 & 0 \\ 0 & -\rho_2 - \lambda & 0 \\ 0 & \delta_3 & -\delta_3 - \lambda \end{vmatrix} = 0 \quad (2.20)$$
which has eigenvalues

\[ \lambda_1 = 1 - \delta_1, \quad \lambda_2 = -\rho_2, \quad \lambda_3 = -\delta_3 \]  

(2.21)

and we observe that \( F_4 \) is stable when \( \delta_1 > 1 \) and unstable when \( \delta_1 < 1 \).

Two important situations arise from this analysis. First, if a spatial region occupied by the system in one of the stable fixed points is adjacent to one at an unstable fixed points, then the stable region will grow into the unstable region in the form of a travelling wavefront [3]. Secondly, if a tumor evolves such that \( \delta_1 \) increases through unity, the dynamics and structure of that tumor will shift from benign to malignant growth (crossover) from \( F_3 \) to \( F_4 \).

As a result of this analysis, we find that tumors have a small fraction of normal cells. There is supporting data showing that benign tumors are polyclonal (derive from different cells) and contains sections with the histology of benign tissues [19], [35], [48].

Another biologically significant prediction is that of a crossover from \( F_3 \) to \( F_4 \) as \( \delta_1 \) increases through unity. We see that for the dimensionless biological parameter

\[ \delta_1 = \frac{d_1 r_3 K_2}{d_3 r_1} \]  

(2.22)

the malignant transformation of cells will not effect \( r_1 \) or \( d_1 \) since they characterize only the healthy tissue. Changes to the remaining parameters, which characterize the tumor tissue, which cause \( \delta_1 \) to increase through unity are consistent with clinical observations. The changes and clinical observations were:

1. \( \delta_1 \) increases linearly with the carrying capacity of the tumor population, \( K_2 \).

   Initial tumor growth is avascular (not supplied with blood vessels) [21], [30] resulting in limited nutrient supply which reduces \( K_2 \). Thus, as predicted by
the model tumor growth is limited. However, as the tumor transitions from avascular to vascular $K_2$ is increased resulting in greater tumor growth.

(2) $\delta_1$ increases linearly with the production rate of acid by the tumor, $\gamma_3$. Thus, the tumor growth is predicted to be more aggressive as the tumor becomes more glycolytic, consistent with studies [5], [45], [59] that show malignant tumors take up more glucose than benign tumors and that among malignant tumors increased uptake of glucose strongly correlates with poorer patient prognosis.

(3) $\delta_1$ increases as the reabsorption rate of acid, $d_3$ decreases predicting that tissue environments in which acid washout is diminished are permissive for malignant growth. Although this prediction has not been explicitly tested, [48] found that states of vascular disruptions tend to be sites predisposed to cancers.

Based on the clinical correlations, Gatenby and Gawlinski identify the crossover at $\delta_1 = 1$ with the transformation of noninvasive tumors, ($\delta_1 < 1$), into invasive malignant tumors ($\delta_1 > 1$).

2.3 Approximate Analytical Solutions

By use of the analytical results it is possible to make specific biological predictions concerning the dependence of the structure and dynamics of the tumor-host interface upon the basic system parameters.

We now seek travelling wave solutions to our dimensionless form of the governing equations (2.7). First, we seek solutions of the form

$$\eta_1(\xi, \tau) = \eta_1(\zeta)$$
\begin{equation}
\eta_2(\xi, \tau) = \eta_2(\zeta)
\end{equation}
\begin{equation}
\Lambda(\xi, \tau) = \Lambda(\zeta)
\end{equation}

where

\[ \zeta = \xi - cr \]

and \( \eta_1(\xi, \tau), \eta_2(\xi, \tau) \) and \( \Lambda(\xi, \tau) \) is a travelling wave propagating at a constant speed \( c \) in the positive \( \xi \)-direction. Hence, substitution into (2.7) yields

\begin{align*}
-c \frac{d\eta_1}{d\zeta} &= \eta_1(1 - \eta_1) - \delta_1 \Lambda \eta_1 \tag{2.24} \\
-c \frac{d\eta_2}{d\zeta} &= \rho_2 \eta_2(1 - \eta_2) + \Delta_2(1 - \eta_1) \frac{d^2 \eta_2}{d\zeta^2} \tag{2.25} \\
-c \frac{d\Lambda}{d\zeta} &= \delta_3(\eta_2 - \Lambda) + \frac{d^2 \Lambda}{d\zeta^2}. \tag{2.26}
\end{align*}

Based on the parameter values obtained from [34], [43] and [44], \( \Delta_2 \ll \rho_2 \) is always the case since \( \rho_2 \approx O(1) \) and \( \Delta_2 \approx O(10^{-5}) \). Hence, equation (2.25) is approximated by a logistic equation with solution

\begin{equation}
\eta_2(\zeta) = \frac{\eta_0}{(1 - \eta_0) \exp(\frac{\rho_2 \zeta}{c}) + \eta_0}
\end{equation}

where \( \eta_0 \) is \( \eta_2(0) \), that is, at the center of the front. Noting that \( \eta_2 \in [0, 1] \), if \( \eta_0 = \frac{1}{2} \) we obtain

\begin{equation}
\eta_2(\zeta) = \frac{1}{1 + \exp(\frac{\rho_2 \zeta}{c})}. \tag{2.28}
\end{equation}

If \( c \) is so small that \( -c \frac{d\Lambda}{d\zeta} \) is negligible (though \( |\frac{d\Lambda}{d\zeta}| \) is not necessarily small at the front) then from (2.26) we find

\begin{equation}
\frac{d^2 \Lambda}{d\zeta^2} - \delta_3 \Lambda = -\delta_3 \eta_2. \tag{2.29}
\end{equation}
The method of variation of parameters yields integrals that cannot be solved analytically in closed form. Thus requiring the extremes \( \lim_{\zeta \to -\infty} A = 1 \) and \( \lim_{\zeta \to \infty} A = 0 \) allows us to solve for \( A(\zeta) \) in which we obtain

\[
A(\zeta) = \begin{cases} 
1 - \frac{1}{2} \exp(\sqrt{3} \zeta) & \zeta < 0 \\
\frac{1}{2} \exp(-\sqrt{3} \zeta) & \zeta \geq 0.
\end{cases}
\] (2.30)

To solve equation (2.24) we use standard algebra to rewrite as a Bernoulli equation of order 2 (See Appendix I). Then solving on each interval and making use of the appropriate \( A(\zeta) \) we obtain

\[
\eta_1(\zeta) = \begin{cases} 
\frac{c \exp[-p e^{s\zeta} + s\zeta] p^{s/q}}{\gamma(r/q, p) p^{(s-r)/q} + \gamma(s/q, p) - \gamma(s/q, pe^{s\zeta})} & \zeta < 0 \\
\frac{c \exp[-p e^{-q\zeta} - r\zeta] p^{r/q}}{\gamma(r/q, pe^{-q\zeta})} & \zeta \geq 0,
\end{cases}
\] (2.31)

where

\[
p = \frac{\delta_1}{2c\sqrt{3}},
q = \sqrt{3},
r = \frac{1}{c},
s = \frac{c}{\delta_1 - 1},
\gamma(a, x) = \int_0^x e^{-t^{a-1}} dt.
\] (2.32)

Due to the fact that the spatial gradients of the wavefront profiles are sharply peaked functions, we follow Gatenby and Gawlinski by defining the edge position \( E(\tau) \) and the width \( W(\tau) \) of a profile by:

\[
E_j(\tau) = \frac{\int_{-\epsilon}^{\epsilon} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}{\int_{-\epsilon}^{\epsilon} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}
\] (2.33)
and

$$W^2_1(\tau) = \int_{-\epsilon}^{\epsilon} \left[ \xi - E_f(\tau) \right]^2 \frac{\partial}{\partial \xi} f(\xi, \tau) \, d\xi$$

where $f$ is either the $\eta_1$, $\eta_2$ or $\Lambda$ profile. By use of our analytic results the integrals obtained in closed form yields (See Appendix II)

$$W_{\Lambda} = \sqrt{\frac{2}{\delta_3}}$$

(2.35)

and

$$W_{\eta_2} = \frac{\pi c}{\sqrt{3} \rho_2}.$$  

(2.36)

Due to the complexity of the analytical solution in equation (2.31), a simple result was not obtainable for the widths of the normal tissue profile, $W_{\eta_1}$.

From the wavefront profiles we observe that an abnormal decrease in the number of cells present (hypocellular interstitial gap) between the advancing tumor edge and the retreating healthy tissue develops when $\delta_1$ increases beyond unity. When $\delta_1 >> 1$, Gatenby and Gawlinski found the dependence of this gap, $\xi_0$ to be

$$\xi_0 = \frac{\log \left( \frac{\delta_1}{2} \right)}{\sqrt{\delta_3}} + \sqrt{\frac{c}{\sqrt{\delta_3}}} \quad \delta_1 >> 1.$$  

(2.37)

Gatenby and Gawlinski numerically obtain their wavefront profiles. From the numerical solutions a value of $c$ was determined and then used to obtain the wavefront profiles analytically. In order to completely solve the model equations they would have to find an analytical expression for $c$ in terms of the basic system parameter. Thus, Gatenby and Gawlinski solved numerically for $c$ by using Newton's method.
as well as analytically via marginal stability analysis [13], [14], [51] and [52]. The analytical result for $c$ is a transcendental equation, namely,

$$c = \Delta_2 \eta'_{1}(\zeta = 0; c) + 2\sqrt{1 - \eta_1(\zeta = 0; c)} \rho_2 \Delta_2$$  \hspace{1cm} (2.38)

where $\eta_1$ and $\eta'_1$ are evaluated at $\zeta = 0$, but still depends on $c$ (2.31).

### 2.4 Wavefront Profiles

In figures 2.1 and 2.2 we plot the wavefront profiles for two cases. One case is malignant ($F_4$), $\delta_1 = 12.5 > 1$ and the other benign ($F_3$) $\delta_1 = 0.5 < 1$. Investigating the wave profiles for two different combinations of parameter values we find when $\delta_1 > 1$, figure 2.1, the normal tissue is completely destroyed behind the advancing wavefront. Also, note that the interstitial gap depends on the value of $\delta_1$ and increases as $\delta_1$ increases. When $\delta_1 < 1$, figure 2.2, we have cancer cells and normal cells coexisting behind the wavefront. The wavefronts are propagating from left to right.
Figure 2.1: Case I. \( \eta_1 \) (solid), \( \eta_2 \) (short dash) and \( \gamma \) (long dash). \( \rho_2 = 1, \delta_1 = 12.5, \delta_3 = 70 \) with speed \( c = 0.0128 \) (0.03mm/day). The wavefronts are propagating from left to right. Note the sharp tumor profile and the formation of a tumor-host hypocellular interstitial gap.
Figure 2.2: Case II. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $\rho_2 = 1$, $\delta_1 = 0.5$, $\delta_3 = 70$ with speed $c = 0.0064$ (0.01mm/day). The wavefronts are propagating from left to right. Note the sharp tumor profile and the coexistence of tumor and healthy tissue behind the wavefront.
2.5 Constant Decay Rate

A modified version of Gatenby and Gawlinski equation for the behavior of the tumor tissue is presented. The equation is modified by assuming that the tumor population is harvested by the immune system via a constant decay rate, $\alpha$. By harvesting the tumor population we affect its mortality rate and, if it is not excessive, the tumor population will conform to a new equilibrium state [11].

The behavior of the tumor tissue consist of logistic growth of the tumor tissue in which the mortality rate is enhanced due to harvesting, by a term linearly proportional to $N_2$. The governing equations for this model are

\begin{align*}
\frac{\partial N_1}{\partial t} &= r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - d_1 LN_1 \\
\frac{\partial N_2}{\partial t} &= r_2 N_2 \left(1 - \frac{N_2}{K_2}\right) - \alpha N_2 \\
\frac{\partial L}{\partial t} &= r_3 N_2 - d_3 L + D_3 \frac{\partial^2 L}{\partial x^2}
\end{align*}

(2.39) \hspace{1cm} (2.40) \hspace{1cm} (2.41)

where the simplifying assumptions $D N_1 [N_2] = 0$ and $\alpha_{12} = \alpha_{21} = 0$ have been used. Algebraic manipulation of equation (2.40) allows it to be written as

\begin{equation}
\frac{\partial N_2}{\partial t} = \bar{r}_2 N_2 \left(1 - \frac{N_2}{K_2}\right)
\end{equation}

(2.42)

where $\bar{r}_2 = r_2 - \alpha$, $\bar{K}_2 = K_2 \left(1 - \frac{\alpha}{r_2}\right)$ and $r_2 > \alpha$. If $\alpha > 0$, this corresponds to reduction in the growth rate and carrying capacity. If $\alpha < 0$, where $-r_2 < \alpha < 0$, we have increased the growth rate and carrying capacity. These changes will induce directly proportional changes in $\delta_1$ and $\rho_2$, namely

\begin{equation}
\bar{\delta}_1 = \frac{d_1 r_3 \bar{K}_2}{d_3 r_1} \quad \text{and} \quad \rho_2 = \frac{\bar{r}_2}{r_1}.
\end{equation}

(2.43)

We observe that the parameter values have changed, that is $r_2$ and $K_2$ are replaced by $\bar{r}_2$ and $\bar{K}_2$ respectively. Thus, the analysis follows through as in
section 2.3. Hence, our solutions are

\[ \eta_2(\zeta) = \frac{1}{1 + \exp\left(\frac{\rho \zeta}{c}\right)}, \quad (2.44) \]

\[ \Lambda(\zeta) = \begin{cases} 
1 - \frac{1}{2} \exp(\sqrt{\delta_3} \zeta) & \zeta < 0 \\
\frac{1}{2} \exp(-\sqrt{\delta_3} \zeta) & \zeta \geq 0,
\end{cases} \quad (2.45) \]

and

\[ \eta_1(\zeta) = \begin{cases} 
\frac{c \exp[-pe^{-q} + s\zeta] p^{s/q} q}{\gamma(r/q, p) p^{(s-r)/q} + \gamma(s/q, p) - \gamma(s/q, pe^{q\zeta})} & \zeta < 0 \\
\frac{c \exp[-pe^{-q} - r\zeta] p^{r/q} q}{\gamma(r/q, pe^{-q\zeta})} & \zeta \geq 0,
\end{cases} \quad (2.46) \]

where

\[ p = \frac{\delta_1}{2c\sqrt{\delta_3}}, \]
\[ q = \sqrt{\delta_3}, \]
\[ r = \frac{1}{c}, \quad (2.47) \]
\[ s = \frac{(\delta_1 - 1)}{c}, \]
\[ \gamma(a, x) = \int_0^x e^{-t^{a-1}} dt. \]

The interfacial widths of the acid and tumor tissue are

\[ W_\Lambda = \sqrt{\frac{2}{\delta_3}} \quad (2.48) \]

and

\[ W_{\eta_2} = \frac{\pi c}{\sqrt{3} \rho_2}. \quad (2.49) \]

When the constant decay rate \( \alpha \) exceeds the maximum proportional growth rate, the population will be driven towards extinction. In figures 2.3 and 2.4 the wavefront profiles are illustrated for \( \delta_1 = 12.5 \) and \( \delta_1 = 0.5 \), respectively. The growth
rate of the tumor tissue relative to the normal tissue, $\rho_2$, has been reduced when $\alpha > 0$. 

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Figure 2.3: Constant Decay Rate Case I. \( \eta_1 \) (solid), \( \eta_2 \) (short dash) and \( \gamma \) (long dash). \( \rho_2 = 0.05, \delta_1 = 12.5, \delta_3 = 70 \) with speed \( c = 0.0128 \). The wavefronts are propagating from left to right. Note \( \eta_2 \) is less steep.
Figure 2.4: Constant Decay Rate Case II. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $\rho_2 = 0.05$, $\delta_1 = 0.5$, $\delta_3 = 70$ with speed $c = 0.0064$. The wavefronts are propagating from left to right. Note the tumor profile is less steep.
2.6 Constant Harvest Rate

We discuss in this section an alternative harvesting strategy for a modified version of Gatenby and Gawlinski's model. Suppose we incorporate the effects of the immune system by introducing a constant harvesting term, \( H \) in the \( N_2 \) equation.

Subjecting the tumor population described by the logistic equation to harvesting at a rate \( H > 0 \) yields the following governing equations

\[
\begin{align*}
\frac{\partial N_1}{\partial t} &= r_1 N_1 (1 - \frac{N_1}{K_1}) - d_1 L N_1 \\
\frac{\partial N_2}{\partial t} &= r_2 N_2 (1 - \frac{N_2}{K_2}) - H \\
\frac{\partial L}{\partial t} &= r_3 N_2 - d_3 L + D_3 \frac{\partial^2 L}{\partial x^2}
\end{align*}
\]

where we have made use of the simplifying assumptions \( D_{N_1} [N_2] = 0 \) and \( \alpha_{12} = \alpha_{21} = 0 \). Focusing our attention on (2.51)

\[
\frac{\partial N_2}{\partial t} = r_2 N_2 (1 - \frac{N_2}{K_2}) - H = \rho_H(N_2)
\]

it can be written as

\[
\rho_H(N_2) = -\frac{r_2}{K_2} \left[ \left( N_2 - \frac{K_2}{2} \right)^2 - \left( \frac{K_2^2}{4} - \frac{HK_2}{r_2} \right) \right].
\]

We see for \( \rho_H(N_2) = 0 \) the equilibrium values are the zeros of a quadratic, namely

\[
N^*_2 = \frac{K_2}{2} \left( 1 \pm \left[ 1 - \frac{4H}{r_2 K_2} \right]^{\frac{1}{2}} \right), \quad (2.55)
\]

that is, \( \rho_H(N_2) > 0 \) when \( N^-_2 < N_2 < N^+_2 \) where

\[
N^-_2 = \frac{K_2}{2} \left( 1 - \left[ 1 - \frac{4H}{r_2 K_2} \right]^{\frac{1}{2}} \right) \quad (2.56)
\]

\[
N^+_2 = \frac{K_2}{2} \left( 1 + \left[ 1 - \frac{4H}{r_2 K_2} \right]^{\frac{1}{2}} \right). \quad (2.57)
\]
From (2.55) we see real positive roots exists if and only if

\[ H < \frac{r_2 K_2}{4} = H_L. \]  

(2.58)

For \( H < H_L \) the larger of the two roots is \( N_2^+ \). If \( 0 < H < H_L = H_M \), the maximum possible growth rate of the tumor population with the property that any larger harvest rate will lead to the depletion of the population (eventually to zero), there are two positive steady states one unstable, \( N_2^- \), and the other stable, \( N_2^+ > N_2^- \).

If \( H > H_L \) we can calculate the extinction time \( t_e \) from (2.54) by separation of variables. In particular if the initial population in (2.51) is \( N_2(0) = K_2 \) then we find

\[ t_e = \frac{4}{r_2} \left( \frac{H}{H_L} - 1 \right)^{-\frac{1}{2}} \arctan \left( \frac{H}{H_L} - 1 \right)^{-\frac{1}{2}} \]  

(2.59)

Plotting \( t_e \) as a function of \( H \) we see as the immune system increases the cancer population decreases. We can write (2.54) as

\[ \frac{\partial N_2}{\partial t} = \rho_H(N_2) = -\frac{r_2}{K_2} (N_2 - N_2^-)(N_2 - N_2^+) \]  

(2.60)

\[ = \frac{r_2}{K_2} (N_2 - N_2^-)(N_2^+ - N_2). \]  

(2.61)

Let \( N = N_2 - N_2^- \) and \( m = N_2^+ - N_2^- = [1 - \frac{4H}{r_2 K_2}]^{\frac{1}{2}} \). Then

\[ \frac{\partial N_2}{\partial t} = \frac{r_2}{K_2} (N_2^+ - N_2^- - N) \]

\[ = \frac{r_2}{K_2} N (m - N) \]

\[ = \frac{r_2}{K_2} m N (1 - \frac{N}{m}) \]

\[ = r_2 \left[ 1 - \frac{4H}{r_2 K_2} \right]^{\frac{1}{2}} N (1 - \frac{N}{m}) \]

\[ = r_2 N \left( 1 - \frac{N}{K_2} \right) \]  

(2.62)
where $K_2 = m$. Equation (2.62) is the logistic equation with growth rate $r_2$ and saturation level $K_2$ (carrying capacity) both reduced by the factor $\sqrt{1 - \frac{4H}{r_2K_2}}$. Again, this effects $\delta_1$ and $\rho_2$. At this point everything carries over from Gatenby and Gawlinski's analysis. Hence, the solutions

$$\eta_2(\zeta) = \frac{1}{1 + \exp(\frac{\bar{\rho}_2\zeta}{c})},$$

(2.63)

$$\Lambda(\zeta) = \begin{cases} 
1 - \frac{1}{2} \exp(\sqrt{\delta_3}\zeta) & \zeta < 0 \\
\frac{1}{2} \exp(-\sqrt{\delta_3}\zeta) & \zeta \geq 0,
\end{cases}$$

(2.64)

and

$$\eta_1(\zeta) = \begin{cases} 
\frac{c \exp[-pe^{\zeta} + s\zeta]r^{s/q}q}{\gamma(r/q,p)r^{s-r}/q + \gamma(s/q,p) - \gamma(s/q,pe^{\zeta})} & \zeta < 0 \\
\frac{c \exp[-pe^{-\zeta} - r\zeta]p^{r/q}q}{\gamma(r/q,pe^{-\zeta})} & \zeta \geq 0,
\end{cases}$$

(2.65)

where

$$p = \frac{\delta_1}{2c\sqrt{\delta_3}},$$

$$q = \sqrt{\delta_3},$$

$$r = \frac{1}{c},$$

$$s = \frac{(\delta_1 - 1)}{c},$$

$$\gamma(a,x) = \int_0^x e^{-it}a^{-1}dt,$$

(2.66)

and

$$\bar{\rho}_2 = \frac{r_2}{r_1},$$

$$= \rho_2 \left[1 - \frac{4H}{r_2K_2}\right]^{\frac{1}{2}}.$$

(2.67)
By use of our analytic results the integrals obtained in closed form yields

\[ W_\lambda = \sqrt{\frac{2}{\delta_3}} \]  

(2.68)

and

\[ W_{n_2} = \frac{\pi c}{\sqrt{3\hat{\rho}_2}}. \]  

(2.69)

Therefore if \( c \neq c(\hat{\rho}_2) \), then \( W_{n_2} \) for the inclusion of harvesting is greater than \( W_n \) independent of harvesting and thus the invading front is less steep with harvesting.

The effect of reduced \( \delta_1 \) from (2.27) in Gatenby and Gawlinski is to reduce \( \xi_0 \), marginally. Thus, in (2.27), if \( \overline{\alpha} = \sqrt{1 - \frac{4H}{r_2 K_2}} \) then when \( \delta_1 >> 1 \) we still have

\[ \xi_0 = \frac{\log\left(\frac{\overline{\alpha}\delta_1}{2}\right)}{\sqrt{\delta_3}} + \sqrt{\frac{\overline{\alpha}c}{\sqrt{\delta_3}}} \quad \delta_1 >> 1. \]  

(2.70)

According to (2.38)

\[ c = \Delta_2 \eta_1(\zeta = 0; c) + 2\sqrt{1 - \eta_1(\zeta = 0; c)} \hat{\rho}_2 \Delta_2. \]  

(2.71)

For large \( \delta_1 \), \( c \rightarrow 2\sqrt{\rho_2 \Delta_2} \). Thus, \( W_{n_2} \rightarrow \frac{2\pi\sqrt{\Delta_2}}{\sqrt{3\hat{\rho}_2}} \) is still larger than when \( H = 0 \). The wave profiles using the same parameter values as Gatenby and Gawlinski are presented in this section. The invading front is less steep by a factor of \( (1 - \frac{4H}{r_2 K_2})^{\frac{1}{2}} \).
Figure 2.5: Extinction time. Plot of $t_e$ against $H$ for fixed $H_L$. As $\frac{H}{H_L}$ increases, $t_e$ decreases. Note $t_e = 1$ corresponds to 1.65 weeks.
Figure 2.6: Constant Harvest Rate Case I. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $\rho_2 = 0.0894427$, $\delta_1 = 12.5$, $\delta_3 = 70$ with speed $c = 0.00378297$. Observe that the invading front is less steep with harvesting.
Figure 2.7: Constant Harvest Rate Case II. $\eta_1$ (solid), $\eta_2$ (short dash) and $\gamma$ (long dash). $\rho_2 = 0.0894427$, $\delta_1 = 0.5$, $\delta_3 = 70$ with speed $c = 0.00378297$. Observe that the invading front is less steep with harvesting.
2.7 LOGISTIC GROWTH IN CANCER TISSUE

In this section we extend Gatenby and Gawlinski’s model by incorporating the effects of logistic growth of the cancer cells into the equation for the rate of change of the excess $H^+$ ions.

The governing equations for this model are now

\[
\begin{align*}
\frac{\partial N_1}{\partial t} &= r_1 N_1(1 - \frac{N_1}{K_1}) - d_1 LN_1 \\
\frac{\partial N_2}{\partial t} &= r_2 N_2(1 - \frac{N_2}{K_2}) + D_2(1 - \frac{N_1}{K_1}) \frac{\partial^2 L}{\partial x^2} \\
\frac{\partial L}{\partial t} &= r_3 N_2(1 - \frac{N_2}{K_L}) - d_3 L + D_3 \frac{\partial^2 L}{\partial x^2}
\end{align*}
\]

where $K_L$ is the saturation level of the enzyme. Making the simplifying assumptions

\[
D_{N_1}[N_2] = 0 , \quad D_{N_2}[N_1] = D_2(1 - \frac{N_1}{K_1}) , \quad \alpha_{12} = \alpha_{21} = 0,
\]

and applying the transformation of variables

\[
\begin{align*}
\eta_1 &= \frac{N_1}{K_1}, \quad \eta_2 = \frac{N_2}{K_2}, \quad \Lambda = \frac{L}{L_0}, \quad \tau = r_1 t, \quad \xi = \sqrt{\frac{r_1}{D_3}} x
\end{align*}
\]

where $L_0 = r_3 K_2 / d_3$ yields the following dimensionless form of the governing equations

\[
\begin{align*}
\frac{\partial \eta_1}{\partial \tau} &= \eta_1(1 - \eta_1) - \delta_1 \Lambda \eta_1, \\
\frac{\partial \eta_2}{\partial \tau} &= \rho_2 \eta_2(1 - \eta_2) + \Delta_2(1 - \eta_1) \frac{\partial^2 \eta_2}{\partial \xi^2} \\
\frac{\partial \Lambda}{\partial \tau} &= \delta_3(\eta_2 - \eta_2^2 K - \Lambda) + \frac{\partial^2 \Lambda}{\partial \xi^2}
\end{align*}
\]

where

\[
\begin{align*}
\delta_1 &= \frac{d_1 r_3 K_2}{d_3 r_1}, \quad \rho_2 = \frac{r_2}{r_1}, \quad \Delta_2 = \frac{D_2}{D_3}, \quad \delta_3 = \frac{d_3}{r_1}, \quad K = \frac{K_2}{K_L}.
\end{align*}
\]
2.7.1 Stability Analysis

In this section we determine the fixed points of the governing equations and analyze their stability using a linearized stability analysis.

The fixed points $F_i$, $i = 1, 2, 3, 4$ are:

$F_1 : \eta_1 = 0, \eta_2 = 0, \Lambda = 0$

$F_2 : \eta_1 = 1, \eta_2 = 0, \Lambda = 0$ \hspace{1cm} (2.81)

$F_3 : \eta_1 = 1 - \delta_1(1 - K), \eta_2 = 1, \Lambda = 1 - K$

$F_4 : \eta_1 = 0, \eta_2 = 1, \Lambda = 1 - K$.

$F_1$ represents the absence of all tissue and acid; $F_2$ represents the absence of tumor tissue and acid with the healthy tissue existing at its carrying capacity; $F_3$ represents coexistence of tumor tissue and healthy tissue and $F_4$ represents the tumor tissue existing at its carrying capacity having killed off all the healthy tissue. The community matrix for our model where

\[
\begin{align*}
 f_1(\eta_1, \eta_2, \Lambda) &= \eta_1(1 - \eta_1) - \delta_1 \Lambda \eta_1, \\
 f_2(\eta_1, \eta_2, \Lambda) &= \rho_2 \eta_2(1 - \eta_2), \\
 f_3(\eta_1, \eta_2, \Lambda) &= \delta_3(\eta_2 - \eta_2^2 K - \Lambda)
\end{align*}
\]

is

\[
A = \begin{bmatrix}
1 - 2\eta_1 - \delta_1 \Lambda & 0 & -\delta_1 \eta_1 \\
0 & \rho_2 - 2\rho_2 \eta_2 & 0 \\
0 & \delta_3 - 2\delta_3 \eta_2 K & -\delta_3
\end{bmatrix} . \hspace{1cm} (2.83)
\]

As seen in Gatenby and Gawlinski's model evaluating the matrix at $F_1$ yields the eigenvalues $\lambda$

\[
\lambda_1 = 1, \lambda_2 = \rho_2, \lambda_3 = -\delta_3 \hspace{1cm} (2.84)
\]
and evaluating the matrix at $F_2$ we obtain the following eigenvalues
\[ \lambda_1 = -1, \lambda_2 = \rho_2, \lambda_3 = -\delta_3. \] (2.85)
Thus, $F_1$ and $F_2$ are unstable and will grow towards a fixed point. For $F_3$ which is $(1 - \delta_1(1 - K), 1, 1 - K)$, the community matrix gives
\[
|A - \lambda I| = \begin{vmatrix}
-1 + \delta_1(1 - K) - \lambda & -\delta_1(1 - \delta_1(1 - K)) \\
0 & -\rho_2 - \lambda \\
0 & \delta_3 - 2\delta_3K - \delta_3 - \lambda
\end{vmatrix} = 0. \tag{2.86}
\]
The eigenvalues are $\lambda_1 = -1 + \delta_1(1 - K), \lambda_2 = -\rho_2, \lambda_3 = -\delta_3$, from which we deduce $F_3$ is stable when $\delta_1 < \frac{1}{1-K}$ and unstable when $\delta_1 > \frac{1}{1-K}$. Our last fixed point $F_4$, namely $(0, 1, 1 - K)$ gives
\[
|A - \lambda I| = \begin{vmatrix}
1 - \delta_1(1 - K) - \lambda & 0 & 0 \\
0 & -\rho_2 - \lambda & 0 \\
0 & \delta_3 - 2\delta_3K & -\delta_3 - \lambda
\end{vmatrix} = 0 \tag{2.87}
\]
where we determine the eigenvalues are
\[ \lambda_1 = 1 - \delta_1(1 - K), \lambda_2 = -\rho_2, \lambda_3 = -\delta_3. \] (2.88)
Thus, $F_4$ is stable when $\delta_1 > \frac{1}{1-K}$ and unstable when $\delta_1 < \frac{1}{1-K}$.

2.7.2 Approximate Analytical Solutions

Looking for travelling wave solutions to our dimensionless form of the governing equations we assume the solutions of the form
\[
-c \frac{d\eta_1}{d\zeta} = \eta_1(1 - \eta_1) - \delta_1\Lambda\eta_1 \tag{2.89}
\]
\[
-c \frac{d\eta_2}{d\zeta} = \rho_2\eta_2(1 - \eta_2) + \Delta_2(1 - \eta_1)\frac{d^2\eta_2}{d\zeta^2} \tag{2.90}
\]
\[
-c \frac{d\Lambda}{d\zeta} = \delta_3(\eta_2 - \eta_2^2K - \Lambda) + \frac{d^2\Lambda}{d\zeta^2}. \tag{2.91}
\]
The solution for $\eta_2$ is unaffected by the inclusion of logistic growth hence

$$\eta_2(\zeta) = \frac{1}{1 + \exp(\frac{\rho_2}{\zeta})}. \quad (2.92)$$

However, we obtain a new solution for $\Lambda(\zeta)$, $\zeta < 0$ which is

$$\Lambda(\zeta) = \left\{ \begin{array}{ll}
(1 - K) + (-\frac{1}{2} + K) \exp(\sqrt{\delta_3 \zeta}) & \zeta < 0 \\
\frac{1}{2} \exp(-\sqrt{\delta_3 \zeta}) & \zeta \geq 0.
\end{array} \right. \quad (2.93)$$

For our $\eta_1$ for $\zeta \geq 0$ the solution is unchanged but we have a new solution for $\eta_1$ when $\zeta < 0$ which is

$$\eta_1(\zeta) = \left\{ \begin{array}{ll}
c q \exp((s - r_1 K) \zeta + ((r_1(K - 1/2)) / q) e^{\pi \zeta}) \\
\{((s - r_1 K) / q)^{-\pi q / (s - r_1 K)} \times \\
(\gamma((s - r_1 K) / q, (-r_1 K - 1/2) / q)) \\
- \gamma((s - r_1 K) / q, (-r_1 K - 1/2) / q) e^{\pi \zeta}) \\
+ p^{-r/q} \exp[p + (r_1(K - 1/2)) / q] \gamma(r/q, p) \} & \zeta < 0 \\
\frac{c \exp[-pe^{-\pi q} - r\zeta] p^{r/q} q}{\gamma(r/q, pe^{-\pi q})} & \zeta \geq 0.
\end{array} \right. \quad (2.94)$$

The formulas used to calculate the interfacial widths of acid and tumor tissue profiles

$$E_j(\tau) = \frac{\int_{-\epsilon}^{\epsilon} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}{\int_{-\epsilon}^{\epsilon} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi} \quad (2.95)$$

and

$$W_j^2(\tau) = \frac{\int_{-\epsilon}^{\epsilon} \frac{[\xi - E_j(\tau)]^2 \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}{\int_{-\epsilon}^{\epsilon} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}} \quad (2.96)$$

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
yields

$$W_\Lambda = \frac{2 - 4K + k^2}{q^2(K - 1)^2}$$  \hspace{1cm} (2.97)

and

$$W_{\eta_2} = \frac{\pi c}{\sqrt{3}\rho_2}.$$  \hspace{1cm} (2.98)

2.7.3 Wavefront Profiles

The curves are the approximate analytical results for one case. In figure 2.8, $\delta = 12.5$ and $c = 0.0128$. 

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Figure 2.8: Logistic Growth in Cancer Tissue. \( \eta_1 \) (solid), \( \eta_2 \) (short dash) and \( \gamma \) (long dash). \( \rho_2 = 1, \delta_1 = 12.5, \delta_3 = 70 \) with speed \( c = 0.0128 \).
CHAPTER 3
WAVES OF PURSUIT AND EVASION

In this chapter I will discuss and develop in a rather different manner than the Gatenby and Gawlinski model, a substantially simplified and modified version of their equations. The mathematical model studied is a modified Lotka-Volterra system of coupled reaction-diffusion equations in an attempt to understand some of the basic features. The model simply describes the interaction between cancer cells and growth inhibitor dispersed by means of an immune response mechanism. This is a phenomenological or "toy model" in the sense that it does not attempt to explain the whole phenomenon of cancer but provide us with insight into one of its many fundamental processes. We search for travelling wave solutions of the model via two existing but different approaches.
3.1 Governing Equations

The continuum model we consider is a system of two coupled reaction-diffusion equations. The system which determines the spatial distribution and temporal evolution of the two fields $\tilde{N}$ and $\tilde{L}$ is governed by

$$\frac{\partial \tilde{N}}{\partial \tau} = r_N \tilde{N} \left( 1 - \frac{d}{r_N} \tilde{L} \right)$$  \hspace{1cm} (3.1)

$$\frac{\partial \tilde{L}}{\partial \tau} = -r_L \tilde{L} + \alpha \tilde{L} \tilde{N} + D_L \frac{\partial^2 \tilde{L}}{\partial \tilde{x}^2}. \hspace{1cm} (3.2)$$

The variables and parameters are:

- $\tilde{x}$: position with units cm.
- $\tau$: time with units sec.
- $\tilde{N}(\tilde{x}, \tau)$: the number density of cancer cells with units cells/cm$^3$.
- $\tilde{L}(\tilde{x}, \tau)$: the enzyme produced by the immune system with units $M = \text{moles/liter}$.
- $r_N$: the growth rate of the cancer cells with units sec$^{-1}$.
- $r_L$: a reduction term with units 1/sec.
- $D_L$: diffusion coefficient for the enzyme with units cm$^2$/sec.
- $d$: the mortality rate of cancer cells with units $1/M \cdot \text{sec}$.
- $\alpha$: production rate of the enzyme with units $M \text{cm}^3/\text{sec} \cdot \text{cell}$.

The behavior of the cancer cells is determined by

(i) a linear growth term,

(ii) the reduction in the growth rate of cancer cells, $r_N$, represented by the quadratic term $\tilde{N} \tilde{L}$, and
(iii) $d$ the mortality rate.

Obviously, we could have also included a logistic term, but for the most part we are interested in the reduction in the growth rate of cancer cells due to effect of the immune system which seeks to reduce the rate at which these cells proliferate. Although cancer cells do invade the host environment as seen in chapter two, we do not here include a diffusion term. At this point, we are more interested in the effect of the diffusion of $\bar{L}(\bar{x}, \tau)$, which is the enzyme produced by the immune system to counteract the destructive effects of the cancer cells. Hence, the rate of change of the growth inhibitor enzyme is determined by

(i) a reduction term, $r_L$, because the enzyme may well be depleted by the normal evacuation systems in the body, such as blood circulation and may also decay to other products,

(ii) the production rate, $\alpha > 0$, which models the response of the immune system to the presence of cancer cells so the coupling term $\alpha \bar{L}N$ essentially indicates that, the more cancer cells there are, the more a healthy immune system will produce the enzyme to counteract the effects of the cancer at least up to some maximum level, and

(iii) the diffusion coefficient, $D_L$, which accounts for the chemical diffusion of the enzyme.

So, bear in mind these are very generic terms but together they represent a simple model describing some of the features that are occurring in a real host/tumor system. As it turns out this system of equations is very similar to a predator-prey model with diffusion that was developed some years ago by Chow and Tam [10],
and not surprisingly we are able to derive solutions that are analogous in form to theirs.

We nondimensionalize the system by setting

$$N = \frac{\alpha \tilde{N}}{r_L}, \quad L = \frac{\tilde{L}}{r_N},$$
$$t = r_N \tau, \quad x = \frac{x}{\alpha}. \quad (3.3)$$

We consider here only the one-dimensional problem, so the equations (3.1)-(3.2) become,

$$\frac{\partial N}{\partial t} = N(1 - L) \quad (3.5)$$
$$\frac{\partial L}{\partial t} = \rho L(N - 1) + D \frac{\partial^2 L}{\partial x^2} \quad (3.6)$$

where

$$\rho = \frac{r_L}{r_N}, \quad D = \frac{D^3_L}{r_N r_L^2}. \quad (3.7)$$

and we are only interested in positive solutions.

### 3.2 Weakly Nonlinear Approach

Our first method for seeking travelling wave solutions is a weakly nonlinear approach. In an unbounded domain it is reasonable to search for travelling wave solutions to Lotka-Volterra systems. Since (3.5) involves only the time derivative, it can be integrated to give

$$N(t, x) = f_1(x) \exp \left\{ t - \int_0^t L(t', x) dt' \right\} \quad (3.8)$$

where $f_1(x)$ is the initial distribution in space. Substitution of (3.8) into (3.6) yields

$$\frac{\partial L}{\partial t} = D \frac{\partial^2 L}{\partial x^2} - \rho L \left[ 1 - f_1(x) \exp \left\{ t - \int_0^t L(t', x) dt' \right\} \right]. \quad (3.9)$$
The choice of the initial distribution is not entirely arbitrary since we are going to look for travelling wave solutions which means biologically the cancer can be thought of as a moving wavefront. Even though tumors do not necessarily have well define boundaries neither do these wavefronts and therefore they represent useful models for the process that is occurring. Thus, to obtain asymptotic travelling waves, we take the initial distribution $f_1(x)$ to be

$$f_1(x) = a \exp(-b|x|), \quad a, b > 0$$  \hspace{1cm} (3.10)

which essentially corresponds to a spike with the greatest concentration at the origin falling off exponentially at a rate $b$. This is motivated biologically by the fact that the cancer cells are concentrated near the center of the tumor and mathematically by the fact that it makes computing the wave speed relatively easy. Since $f_1(x)$ is an even function the solutions must be even in $x$, therefore, it suffices to restrict them to $x \geq 0$. Define the dependent variable

$$\xi = x - ct$$  \hspace{1cm} (3.11)

which depicts a wave travelling from left to right where $c$ is a positive number known as the speed of propagation. Our aim is to determine $c$ and the waveforms $N(\xi)$ and $L(\xi)$ such that

$$N(x, t) = N(\xi)$$  \hspace{1cm} (3.12)

$$L(x, t) = L(\xi)$$  \hspace{1cm} (3.13)

as $t \to \infty$, $x \to \infty$ with $\xi$ kept fixed. Putting $\xi' = x - ct'$ and noting (3.10)-(3.11), (3.8) and (3.9) can be rewritten for $x \geq 0$, as

$$N(t, x) = a \exp \left\{-b \left( x - \frac{1}{b} t \right) + \frac{1}{c} \int_{\xi}^{x} L \left( \frac{x - \xi'}{c}, x \right) d\xi' \right\}$$  \hspace{1cm} (3.14)
From equations (3.14)-(3.15), we observe that we must choose the speed of propagation as

\[ c = \frac{1}{b}. \quad (3.16) \]

If we let \( x \to \infty \) in (3.14)-(3.15) and make use of (3.11)-(3.13), and (3.16) we obtain the following equations for the waveforms

\[ N(\xi) = a \exp \left\{ -b\xi + b \int_\xi^\infty L(\xi') \, d\xi' \right\} \quad (3.17) \]

\[ DL''(\xi) + cL'(\xi) - \rho L(\xi) \left[ 1 - a \exp \left\{ -b\xi + b \int_\xi^\infty L(\xi') \, d\xi' \right\} \right] = 0. \quad (3.18) \]

To determine the waveforms \( N(\xi) \) and \( L(\xi) \) we need to solve the nonlinear integro-differential equation (3.18) on which we impose the boundary conditions

\[ L(\xi_0) = \beta_1 \quad (3.19) \]

\[ L(\infty) = 0. \quad (3.20) \]

For large values of \( \xi \) (3.17) and (3.18) yield

\[ N(\xi) = a \exp(-b\xi) \quad (3.21) \]

\[ DL''(\xi) + cL'(\xi) - \rho L(\xi) [1 - a \exp(-b\xi)] = 0. \quad (3.22) \]

Introducing a new independent variable

\[ \eta = \frac{2}{b} \sqrt{\frac{\alpha p}{D}} \exp \left( \frac{-b\xi}{2} \right) \quad (3.23) \]

and the constants

\[ \nu = \frac{2}{b} \sqrt{\frac{\rho}{D}}, \quad m = 1 - \frac{2c}{Db} \quad (3.24) \]
allows the linear equation (3.22) to be transformed into the form

\[ \eta^2 \frac{d^2 L}{d\eta^2} + m\eta \frac{dL}{d\eta} + L(\eta^2 - \nu^2) = 0 \]  
(3.25)

which becomes the well known Bessel equation when \( m = 1 \). Noting (3.16) and (3.24) we have

\[ b^2 = \frac{2\pi n}{D} > 0. \]  
(3.26)

Since \( \eta \to 0 \) as \( \xi \to \infty \) (3.20) implies \( L(\eta = 0) = 0 \). The appropriate solution to (3.25) when \( m = 1 \) is

\[ L(\eta) = k J_\nu(\eta) \]  
(3.27)

where \( k \) is a constant and \( J_\nu \) denotes the \( \nu \)'th order Bessel function of the first kind. For small \( \eta \) (or large \( \xi \)), we use the asymptotic expression for \( J_\nu \) in (3.27) to obtain

\[ L(\xi) = k \left( \frac{\eta}{2} \right)^\nu \Gamma(\nu + 1) \left( \frac{\rho}{b^2 D} \right)^\frac{1}{2} \exp \left( -\sqrt{\frac{\rho}{D}} \xi \right) \]  
(3.28)

where \( \Gamma \) designates the gamma function and use has been made of (3.23) and (3.24). The equations show that the wavefronts are sharp because the waveforms descend with exponential rates \( b \) and \( \sqrt{\rho/D} \) respectively in the direction of propagation.

3.2.1 Solution by Frobenius Method

For \( m \neq 1 \) (3.25) with a regular singular point at \( \eta = 0 \) can be solved using the Frobenius method. We will obtain the coefficients of the power series solution to (3.25) when \( m \neq 1 \). Writing (3.25) in normalized form, we have

\[ \frac{d^2 L}{d\eta^2} + \frac{m}{\eta} \frac{dL}{d\eta} + \frac{(\eta^2 - \nu^2)}{\eta^2} L = 0. \]  
(3.29)
Since,

\[ P_1(x) = \frac{m}{\eta} \quad (3.30) \]
\[ P_2(x) = \frac{(\eta^2 - \nu^2)}{\eta^2} \quad (3.31) \]

both fail to be analytic at \( \eta = 0 \), we conclude that \( \eta = 0 \) is a singular point of (3.25). Now, consider the functions defined by the products \( \eta P_1(x) = m \) and \( \eta^2 P_2(x) = \eta^2 - \nu^2 \). Both of these product functions are analytic at \( \eta = 0 \) and so \( \eta = 0 \) is a regular singular point. Since \( \eta = 0 \) is a regular singular point, we seek solutions for \( 0 < \eta < r \), we assume a solution of the form

\[ L = \sum_{s=0}^{\infty} c_s \eta^{s+r} \quad (3.32) \]

where \( c_0 \neq 0 \). Then

\[ \frac{dL}{d\eta} = \sum_{s=0}^{\infty} (s + r)c_s \eta^{s+r-1} \quad (3.33) \]

and

\[ \frac{d^2L}{d\eta^2} = \sum_{s=0}^{\infty} (s + r)(s + r - 1)c_s \eta^{s+r-2} \quad (3.34) \]

substituted into the given equation (3.29) yields

\[
\begin{align*}
[r(r-1)+mr-\nu^2]c_0 \eta^r + [r(r+1)+m(r+1)-\nu^2]c_1 \eta^{r+1} + \\
\sum_{s=2}^{\infty} \left[(s+r)(s+r-1)+m(s+r)-\nu^2\right]c_s + c_{s-2} \eta^{s+r} = 0.
\end{align*}
\] (3.35)

Equating to zero the coefficient of the lowest powers of \( \eta \), we obtain the indicial equation

\[ r(r-1) + mr - \nu^2 = 0 \quad (3.36) \]

which has the following roots

\[ r_{1,2} = \frac{(1 - m) \pm \sqrt{(m - 1)^2 + 4\nu}}{2}. \quad (3.37) \]
Equating to zero the coefficient of the higher powers of \( \eta_1 \), we obtain the condition

\[
\left[ r^2 + r(m + 1) + m - \nu^2 \right] c_1 = 0 \quad (3.38)
\]

where setting \( r = r_1 \) yields \( c_1 = 0 \). Also, we obtain the recurrence formula, for \( s \geq 2 \)

\[
\left[ (s + r)(s + r - 1) + m(s + r) - \nu^2 \right] c_s + c_{s-2} = 0 \quad (3.39)
\]

where again setting \( r = r_1 \) gives

\[
c_s = -\frac{c_{s-2}}{(s + r_1)(s + r_1 - 1) + m(s + r_1) - \nu^2}. \quad (3.40)
\]

We note that all odd coefficients are zero, since \( c_1 = 0 \). The general even coefficient may be written as

\[
c_{2s} = \frac{(-1)^s c_0}{\prod_{i=1}^{s} D_i} \quad (3.41)
\]

where

\[
D_i = (2i + r_i)(2i + r_i + m - 1) - \nu^2. \quad (3.42)
\]

Expanding \( D_i \) and rewriting as

\[
D_i = 4i^2 + ib + c \quad (3.43)
\]

where

\[
b = 4r_i + 2m - 2 \quad (3.44)
\]

\[
c = r_i^2 + r_i m - r_i - \nu^2 \quad (3.45)
\]

we solve for \( i \) finding the solutions

\[
i = \frac{-b \pm \sqrt{b^2 - 16c}}{8} \quad (3.46)
\]
where substitution of equations \( b \) and \( c \) clearly yields

\[
i_{1,2} = \frac{(2r + m - 1) \pm \sqrt{(m + 1)^2 + (2\nu)^2}}{4}. \tag{3.47}
\]

Now, defining

\[
\alpha_1 = 1 - i_1 \tag{3.48}
\]

\[
\alpha_2 = 1 - i_2 \tag{3.49}
\]

and rewriting \( D_i \) in terms of \( \alpha_1 \) and \( \alpha_2 \) we have

\[
D_i = 4(\alpha_1 - 1 + i)(\alpha_2 - 1 + i). \tag{3.50}
\]

Thus by

\[
\prod_{i=1}^{s} D_i = 4^s \prod_{i=1}^{s} (\alpha_1 - 1 + i) \prod_{i=1}^{s} (\alpha_2 - 1 + i) \tag{3.51}
\]

\[
= \frac{4^s \Gamma(\alpha_1 + n) \Gamma(\alpha_2 + n)}{\Gamma(\alpha_1) \Gamma(\alpha_2)} \tag{3.52}
\]

we can write (3.41)

\[
c_{2s} = \frac{(-1)^s c_0 \Gamma(\alpha_1) \Gamma(\alpha_2)}{4^s \Gamma(\alpha_1 + n) \Gamma(\alpha_2 + n)}. \tag{3.53}
\]

### 3.2.2 Features of the Waveforms

In this section we demonstrate how to obtain the travelling waves numerically. To obtain the general features of the waveforms, we rewrite the non-linear equation (3.18) as

\[
\frac{\rho L - cL' - DL''}{\rho L} = a \exp\left\{-b\xi + b \int_\xi^\infty L(\xi') \, d\xi'\right\}. \tag{3.54}
\]

By logarithmic differentiation of (3.54) and simplification, we deduce a third-order differential equation, namely

\[
DLL''' + L'' [cL - DL' + DbL(1 + L)] +
\]

\[
L' [cbL(1 + L) - cL'] - bpL^2 (1 + L) = 0. \tag{3.55}
\]
Introducing two new parameters $\beta_1$ and $\beta_2$ as the initial values of $L$ instead of (3.19) and (3.20) we have

$$L(\xi_0) = \beta_1, \quad L'(\xi_0) = \beta_2,$$  \hspace{1cm} (3.56)

and by way of (3.18) we derive a third condition

$$L''(\xi_0) = \frac{\rho L}{D} \left[1 - a \exp(-b \xi_0)\right] - \frac{c \beta_2}{D}$$  \hspace{1cm} (3.57)

where

$$\gamma = \int_{\xi_0}^{\infty} L(\xi') \, d\xi'.$$  \hspace{1cm} (3.58)

We may adapt numerical methods of initial-value problems to (3.56)-(3.57). We begin by setting $\gamma = 0$ in (3.57) which would then allow us to use an iteration procedure for the problem.

### 3.3 Phase Plane Analysis

The second technique is that of a phase plane analysis. In order to determine the fixed points of the governing equations and analyze their stability using a linearized stability analysis, we begin by setting the spatial and temporal derivatives to zero and solve for the fields. The fixed points $F_i, \; i = 1, 2$ of equations (3.5)-(3.6) are

$$F_1 : \; N = 0, \; L = 0$$  \hspace{1cm} (3.59)

$$F_2 : \; N = 1, \; L = 1.$$  

Hence, $F_1$ represents the trivial absence of all cancer tissue and enzyme and $F_2$ represents the coexistence of cancer tissue and enzyme. The linearized stability analysis is completed by computing the eigenvalues of the community matrix

$$A = \begin{bmatrix}
1 - L & -N \\
\rho L & \rho(N - 1)
\end{bmatrix}$$  \hspace{1cm} (3.60)
at each of the fixed points given. $F_1$ gives

$$|A - \lambda I| = \begin{vmatrix} 1 - \lambda & 0 \\ 0 & -\rho - \lambda \end{vmatrix} = 0$$

(3.61)

where $I$ is the identity matrix. The eigenvalues of $F_1$ are found to be

$$\lambda_1 = 1, \quad \lambda_2 = -\rho$$

(3.62)

and thus $F_1$ is a saddle point and hence unstable. The eigenvalues of $F_2$ are found by computing the matrix

$$|A - \lambda I| = \begin{vmatrix} -\lambda & 1 \\ \rho & -\lambda \end{vmatrix} = 0$$

(3.63)

which yields

$$\lambda_1 = i\sqrt{\rho}, \quad \lambda_2 = -i\sqrt{\rho}$$

(3.64)

where $i = \sqrt{-1}$. Therefore $F_2$ is a centre and thus is neutrally stable. If a travelling wave solution exists it may be written in the form

$$N(x,t) = N(\xi)$$

$$L(x,t) = L(\xi)$$

(3.65)

where

$$\xi = x - ct$$

(3.66)

and where $c$ is the positive wave speed which has to be determined. If solutions of this type exist, they represent travelling waves moving to the right in the $\xi$-plane. Substitution of (3.65)-(3.66) into the governing equations (3.5)-(3.6) gives
the ordinary differential equations
\[ -c \frac{dN}{d\xi} = N - LN \quad (3.67) \]
\[ -c \frac{dL}{d\xi} = -\rho L + \rho LN + D \frac{d^2 L}{d\xi^2}. \]

By making the substitution
\[ W = \frac{dL}{d\xi} \quad (3.68) \]
we obtain a system of first order ordinary differential equations given by
\[ \frac{dN}{d\xi} = -\frac{N}{c} (1 - L) \]
\[ \frac{dL}{d\xi} = W \]
\[ \frac{dW}{d\xi} = \frac{\rho L}{D} (1 - N) - \frac{cW}{D}. \quad (3.69) \]

Since this nonlinear system is not necessarily analytically solvable, we investigate
the qualitative behavior by phase plane methods. In the \((N, L, W)\) phase space
there are two fixed points of which one, \((0, 0, 0)\) is unstable and the other, \((1, 1, 0)\) stable. A trajectory that connects two fixed points is said to be heteroclinic.
From previous analysis of Fisher's equation, [16], [40], only the heteroclinic tra­
jectory depicts a bounded positive wave with biological meaning. Thus, for our
model there is the possibility of a travelling wave solution from \((0, 0, 0)\) to \((1, 1, 0)\).
Therefore, we should look for solutions \((N(\zeta), L(\zeta))\) of (3.69) with the boundary
conditions
\[ N(-\infty) = 0, \quad L(-\infty) = 0, \quad N(\infty) = 1, \quad L(\infty) = 1. \quad (3.70) \]

The stability of the fixed points is determined by the community matrix which,
for (3.69) is

$$A = \begin{bmatrix}
\frac{1-c}{c}(1-L) & \frac{N}{c} & 0 \\
0 & 0 & 1 \\
-\frac{\rho D}{c} & \frac{\phi}{c}(1-N) & -\frac{\phi}{c}
\end{bmatrix} \quad (3.71)
$$

$F_1$ in (3.69), that is $(0,0,0)$, is unstable since the eigenvalues $\lambda$ of its community matrix, given from (3.71) by

$$|A - \lambda I| = \begin{vmatrix}
\frac{-1}{c} - \lambda & 0 & 0 \\
0 & -\lambda & 1 \\
0 & \frac{\phi}{D} & -\frac{\phi}{D} - \lambda
\end{vmatrix} = 0 \quad (3.72)
$$

from which we find

$$\lambda_1 = -\frac{1}{c} \quad (3.73)$$

$$\lambda_{2,3} = \frac{-c \pm \sqrt{c^2 + 4D\rho}}{2D} \quad (3.74)$$

and has at least one eigenvalue that has a positive real part. Linearizing (3.69) about $F_2 (1,1,0)$ the eigenvalues $\lambda$ are given by

$$|A - \lambda I| = \begin{vmatrix}
-\lambda & \frac{1-c}{c} & 0 \\
0 & -\lambda & 1 \\
-\frac{\phi}{D} & 0 & -\frac{\phi}{D} - \lambda
\end{vmatrix} = 0 \quad (3.75)
$$

and so are the roots of the characteristic polynomial

$$p(\lambda) \equiv \lambda^3 + \frac{c}{D}\lambda^2 + \frac{\rho}{cD} = 0. \quad (3.76)$$

For $\rho \neq 0$, by the Routh-Hurwitz criteria for this cubic equation where

$$a_1 = \frac{c}{D}, \quad a_2 = 0, \quad a_3 = \frac{\rho}{cD} \quad (3.77)$$
the conditions for $\text{Re}\lambda < 0$ are

$$a_1 > 0, \quad a_3 > 0, \quad a_1a_2 > a_3.$$  \hspace{1cm} (3.78)

Clearly, the three conditions are not satisfied, thus $(1, 1, 0)$ is linearly unstable. To observe how the solutions of this polynomial behave as the parameters vary we consider the plot of $p(\lambda)$ for real $\lambda$ and see where it crosses $p(\lambda) \equiv 0$. Differentiating $p(\lambda)$, the local maximum and minimum are at

$$\lambda_M = -\frac{2c}{3D} \quad \text{and} \quad \lambda_m = 0,$$  \hspace{1cm} (3.79)

respectively and are independent of $\rho$. For $\rho = 0$, which corresponds to increased levels of the enzyme, we find the roots of the characteristic polynomial are

$$\lambda_{1,2} = 0 \hspace{2cm} \lambda_3 = -\frac{c}{D}.$$  \hspace{1cm} (3.80)

Hence, the second fixed point $(1, 1, 0)$ is stable under suitable parameter restrictions. Since one of the fixed points is stable there is the possibility of a travelling wave solution towards the steady state. Since the local extrema are independent of $\rho$, we have the situation portrayed in figure 3.1. Thus, there is a critical value $\rho^*$ such that for $\rho > \rho^*$ there is only one real positive root and two complex roots with negative real parts. The existence of a critical $\rho^*$ means that, for $\rho > \rho^*$, the wavefront solutions $(N, L)$ of (3.69) with boundary conditions (3.70) approach the steady state $(1, 1, 0)$ in an oscillatory manner while for $\rho < \rho^*$ they are monotonic.
Figure 3.1: The characteristic polynomial \( p(\lambda) \) from (3.76) as a function of \( \lambda \) as \( \rho \) varies. There is a critical value \( \rho^* \) such that for \( \rho > \rho^* \) there is only one real positive root and two complex one with negative real parts.
3.4 Wavefront Profiles

The phase plots for the model are presented in this section. We see from the figure that the cancer population, $N$ propagates ahead of the enzyme, $L$. These waves are referred to as "waves of pursuit and evasion".

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Figure 3.2: Waves of Pursuit and Evasion. Enzyme $L$ (dash) and cancer $N$ (solid).

The travelling waves of pursuit evasion via approximate analytical solution. The cancer population wave is the forerunner after which the enzyme population follows.
CHAPTER 4
AN EXAMPLE OF NONLINEAR CANCER DISPERSION

In this chapter we derive a one-dimensional model of cancer dispersion based on a continuum approach. The primary difference between this model and the models presented in the previous chapters is the addition of another possible major transport process called convection. A similar model without the convection term has been developed by Shen and Perry in [54]. We make the following assumptions:

(i) The number of cancer cells depend on diffusion. Diffusion involves the spreading of the cancer from a region of higher concentration to a region of lower concentration.

(ii) The number of cancer cells may also depend on convection. This is biologically plausible since cancer cells metastasize through the blood or lymphatic vessels to distant parts of the body.

(iii) The cancer metastasizes if the total cancer cell number is higher than a critical number. This is biologically plausible since the diameter of avascular tumors is about 1-2 mm ($\approx 10^6$ cells) whereas the diameter of a vascularized tumor may be approximately 1cm ($\approx 10^9$ cells) [50].

(iv) The problem is spatially one-dimensional.

Assumption (iii) implies a metastatic rate that depends on the distribution of the cancer cells and when the number of cancer cells reaches a critical number metastasis occurs. As the number of cancer cells increase the metastatic rate
increases, which yields positive feedback. Although this is an assumption for the mathematical analysis it should be noted that this is probably not true of most cancers. Biology, i.e. aggressiveness, is more important then the cancer cell number. Assumption (iv) models the case of unidirectional diffusion.

This study focuses on the mathematical analysis of the stability of the steady state solutions and the propagation of the cancer front and leads to qualitative conclusions. From assumptions (i) and (iii), conservation of the mass yields a reaction-diffusion equation with positive feedback. As a consequence of this feedback our model is nonlinear, exhibits multiple steady state solutions and has a jump discontinuity, commonly referred to as a saddle-node bifurcation.

Let

\[ \hat{I} = \hat{I}(\hat{x}, \hat{t}), \quad 0 \leq \hat{x} \leq \hat{L}, \quad 0 \leq \hat{t} < \infty \]  

be the distribution of the cancer cell number. We assume without loss of generality, the cancer spreads from left to right, thus the function \( \hat{I}(\hat{x}, \hat{t}) \) is monotonically decreasing in \( \hat{x} \) for all \( \hat{t} \). Hence, when \( \hat{I}(\hat{x}, \hat{t}) > \hat{I}_c \), the critical distribution, the reaction which promotes metastasis is accelerated and when \( \hat{I}(\hat{x}, \hat{t}) < \hat{I}_c \), that reaction rate is significantly reduced. Therefore, the equation \( \hat{I}(\hat{x}_c, \hat{t}) = \hat{I}_c \) determines the position of the cancer front, \( \hat{x}_c \), which separates the cancerous region from the metastatic (or possibly noncancerous) region. Thus, \( \hat{x}_c(\hat{t}) \) represents the propagation of the cancer front. In the case of steady state, the cancer front is fixed at \( \hat{x}_c \equiv \hat{x}_e = \text{constant} \).
4.1 Governing Equations

The model mechanism we consider is

\[
\frac{\partial \hat{I}}{\partial \hat{t}} = \frac{\partial}{\partial \hat{x}} \left( \hat{k}(\hat{x}) \frac{\partial \hat{I}}{\partial \hat{x}} \right) - \hat{u}_0 - \hat{u}_1 \hat{I} - \hat{\nu}(\hat{x}) \frac{\partial \hat{I}}{\partial \hat{x}} + \hat{R} S(\hat{x}) f(\hat{x}; \hat{x}_c),
\]

\[0 < \hat{x} < \hat{L}, \ 0 < \hat{t} < \infty.\]

The variables and parameters are:

\(\hat{x}\): position with units cm.

\(\hat{t}\): time with units sec.

\(\hat{I}(\hat{x}, \hat{t})\): distribution of the cancer cell number with units gm/cm\(^3\).

\(\hat{k}(\hat{x})\): diffusion coefficient with units cm\(^2\)/sec.

\(\hat{u}_0\): apoptosis (programmed cell death) with units gm/cm\(^3\)/sec.

\(\hat{u}_1\): exponential decay rate of cancer cells with units sec\(^{-1}\).

\(\hat{\nu}(\hat{x})\): the flow speed of the blood or lymphatic vessels with units cm/sec.

\(\hat{R}\): reproduction rate of cancer cells with units gm/cm\(^3\)/sec.

\(S(\hat{x})\): represents the tissue structure and is positive.

\(f(\hat{x}; \hat{x}_c)\): a growth factor for the reproduction of cancer cells.

Non-dimensionalizing the system, we introduce the quantities

\[
k = \frac{\hat{k}}{k_0}, \ x = \frac{\hat{x}}{L_0}, \ t = \frac{k_0 \hat{t}}{L_0^2}, \ I = \frac{\hat{I}}{I_0},
\]

\[
u_0 = \frac{\hat{u}_0 L_0^2}{I_0 k_0}, \ u_1 = \frac{\hat{u}_1 L_0^2}{k_0}, \ \nu = \frac{\hat{\nu} L_0}{k_0}, \ R = \frac{\hat{R} L_0^2}{I_0 k_0},
\]

(4.3)

(4.4)
which on substituting into (4.2) yields the following dimensionless form of the governing equations

\[
\frac{\partial I}{\partial t} = \frac{\partial}{\partial x} \left( k(x) \frac{\partial I}{\partial x} \right) - u_0 - u_1 I - v(x) \frac{\partial I}{\partial x} + R S(x)f(x; x_c),
\]

\(0 < x < L, \ 0 < t < \infty.

where \(L = \hat{L}/L_0\). Thus, the rate of change of the distribution of the cancer cell number is determined by

(i) the diffusion effect \(\frac{\partial}{\partial x} \left( k(x) \frac{\partial I}{\partial x} \right)\)

(ii) the mass loss from the primary cancer due to metastasis \(u_0 + u_1 I \ (u_0 > 0, u_1 > 0)\),

(iii) the convection term,

(iv) the reproduction of the cancer due to chemical or biochemical reaction,

\(R S(x)f(x; x_c)\).

The growth factor \(f(x; x_c)\) has a discontinuity of the first kind at \(x = x_c\) since the self-enhancement is reduced in the non-continuum cancer region. We choose a growth factor representative of the fact that most of the action is occurring inside the tumor itself. Thus, growth factor is taken to be

\[
f(x; x_c) = \begin{cases} 
    f_s(x) > 0, & \text{if } 0 \leq x \leq x_c, \\
    f_w(x) \geq 0, & \text{if } x_c \leq x \leq L
\end{cases}
\]  

(4.6)

where \(f_s(x)\) is a continuous function, \(f_w(x)\) is a continuous nonincreasing function and \(f_s(x_c) > f_w(x_c)\) when \(0 < x_c < L\). It is the discontinuity at \(x = x_c\) that introduces nonlinearity and positive feedback to our problem. The assumption
implies that the reproduction rate is much stronger when $I > I_c$ than when $I < I_c$. The position $x_c$ of the cancer front is determined by the cancer front condition

$$I(x_c, t) = I_c.$$ \hfill (4.7)

We have the zero flux boundary conditions

$$\frac{\partial I}{\partial x}igg|_{x=0,L} = 0$$ \hfill (4.8)

which implies no movement outside the tumor. Therefore the governing equations for our problem are (4.5), (4.7) and (4.8). The objective is to solve the following two problems. First, what choices of constants $u_0$, $u_1$ and $R$ will force $x_c$ to be fixed at a desired point between 0 and $L$. In order to answer this question requires finding steady state solutions of the problem (4.5), (4.7) and (4.8). Secondly, how does the cancer front $x_c(t)$ propagate? By solving the initial boundary value problem (4.5), (4.7),(4.8) and

$$I(x, 0) = g(x), \quad 0 < x < L$$ \hfill (4.9)

we can in principle answer this question.

### 4.2 Steady State Solutions

For the steady state problem $x_c(t)$ is a constant which is denoted as $x_e$. We need to solve the nonhomogeneous spatial differential equation

$$\frac{d}{dx} \left( k(x) \frac{dI}{dx} \right) - v(x) \frac{dI}{dx} - u_1 I = -R S(x)f(x; x_c) + u_0, \quad 0 < x < L, \hfill (4.10)$$

subject to the homogeneous boundary conditions

$$\frac{dI}{dx}igg|_{x=0,L} = 0,$$ \hfill (4.11)
and

$$I(x_e) = I_e.$$  \hspace{1cm} (4.12)

In order to employ the Sturm-Liouville theory of differential equations we must place the differential equation (4.10) in self-adjoint form, namely

$$\frac{d}{dx} \left[ p(x) \frac{dy}{dx} \right] + [q(x) + \lambda s(x)]y = 0, \quad x_1 < x < x_2, \hspace{1cm} (4.13)$$

where \(p(x) > 0\) and \(s(x) > 0\) in \((x_1, x_2)\), and \(p'(x), q(x)\) and \(s(x)\) are all continuous functions in the interval \([x_1, x_2]\). We can transform (4.10) into self-adjoint form by multiplying through by the function \(\mu(x) = p(x)/k(x)\), producing

$$p(x) \frac{d^2I}{dx^2} + \mu(x)[k'(x) - v(x)] \frac{dI}{dx} - \mu(x)u_1 I = \mu(x)[-RS(x)f(x; x_e) + u_0]. \hspace{1cm} (4.14)$$

Equation (4.14) is now in self-adjoint form provided we choose \(p(x)\) such that

$$p'(x) = \mu(x)[k'(x) - v(x)] = \frac{p(x)[k'(x) - v(x)]}{k(x)}. \hspace{1cm} (4.15)$$

By solving this first order differential equation for \(p(x)\), we find

$$p(x) = k(x) \exp \left( - \int^x \frac{v(u)}{k(u)} du \right). \hspace{1cm} (4.16)$$

Thus, our differential equation (4.10) in self-adjoint form yields

$$\frac{d}{dx} \left[ p(x) \frac{dI}{dx} \right] - u_1 r(x) I = (-RS(x)f(x; x_e) + u_0) r(x) \hspace{1cm} (4.17)$$

where

$$r(x) = \exp \left( - \int^x \frac{v(u)}{k(u)} du \right). \hspace{1cm} (4.18)$$

When solving (4.17) we will make use of the eigenfunctions of the corresponding associated homogeneous problem consisting of the differential equation

$$\frac{d}{dx} \left[ p(x) \frac{dI}{dx} \right] = -\lambda_n r(x) I(x) \quad 0 < x < L \hspace{1cm} (4.19)$$
and the boundary conditions
\[ \frac{dI}{dx} \bigg|_{x=0,L} = 0, \quad (4.20) \]
where \( \{\lambda_n\}_{n=0}^{\infty} \) are the eigenvalues with corresponding normalized eigenfunctions \( \{\varphi_n\}_{n=0}^{\infty} \).

We now assume that the solution \( I = I_e(x) \) of the nonhomogeneous problem (4.17) can be expressed as a series of the following form
\[ I_e(x) = \sum_{n=0}^{\infty} I_n \varphi_n(x) \quad (4.21) \]
where the \( I_n \) are simply the Fourier coefficients of \( I_e(x) \) to be determined. We know by the orthogonality of the eigenfunctions, namely
\[ \int_0^L r(x) \varphi_m(x) \varphi_n(x) \, dx = \delta_{mn}, \quad (4.22) \]
where \( \delta_{mn} \) is the Kronecker delta, that the Fourier coefficients can be obtained via the calculation
\[ I_n = \int_0^L r(x) I(x) \varphi_n(x) \, dx, \quad n = 1, 2, \ldots \quad (4.23) \]
However, we cannot use (4.23) to calculate \( I_n \) since we do not know \( I(x) \). Thus, we will try to determine \( I_n \) so that the problem (4.17) is satisfied, and then use (4.23) to find \( \varphi_n(x) \). Observe that \( I_e \) as given by equation (4.21) always satisfies the boundary conditions (4.20) since each \( \varphi_n(x) \) does.

Now consider the differential equation that \( I_e \) must satisfy. This is just (4.17) with \( I \) replaced by \( I_e \), that is
\[ \frac{d}{dx} \left[ p(x) \frac{dI_e}{dx} \right] - u_1 r(x) I_e = (-R S(x) f(x; x_e) + u_0) r(x) \quad (4.24) \]
with the boundary conditions
\[ \frac{dI_e}{dx} \bigg|_{x=0,L} = 0, \quad (4.25) \]
and

\[ I_e(x_e) = I_e. \tag{4.26} \]

Substitution of the eigenfunction expansion (4.21) into the differential equation (4.24) yields

\[- \sum_{n=0}^{\infty} I_n r(x) \varphi_n(x) (\lambda_n + u_1) = r(x) (-RS(x)f(x; x_e) + u_0) \tag{4.27} \]

where we have made use of the associated homogeneous eigenvalue problem

\[- \frac{d}{dx} \left[ p(x) \frac{d\varphi_n}{dx} \right] = -\lambda_n r(x) \varphi_n(x), \quad 0 < x < L \tag{4.28} \]

with boundary conditions

\[ \frac{d\varphi_n}{dx} \bigg|_{x=0,L} = 0. \tag{4.29} \]

Therefore, multiplying both sides of (4.27) by \( \varphi_n(x) \) and integrating from 0 to \( L \) we obtain the following Fourier coefficients

\[ I_n(x_e) = \frac{1}{\lambda_n + u_1} \left[ -u_0 \delta_n \left( \int_0^L r(x) \, dx \right)^{-1/2} + R \int_0^L S(x)f(x; x_e)r(x) \varphi_n(x) \, dx \right] \tag{4.30} \]

where \( n = 0, 1, 2... \) and we have assumed that we can interchange the operations of summation and differentiation. Thus, substitution of (4.30) into (4.21) yields a particular solution to the nonhomogeneous problem (4.24). Since \( \varphi_n(x) \) are the eigenfunctions of (4.28- 4.29), \( I_e(x) \) expanded in the form of (4.21) satisfies (4.25). To satisfy the cancer front condition (4.26) we need to properly choose \( x_e \). By (4.21-4.27), (4.26) becomes

\[ \sum_{n=0}^{\infty} \frac{1}{\lambda_n + u_1} \left[ -u_0 \delta_n \left( \int_0^L r(x) \, dx \right)^{-1/2} + R \int_0^L S(x)f(x; x_e)r(x) \varphi_n(x) \, dx \right] \varphi_n(x_e) \]

\[ = I_e \tag{4.31} \]
for simplicity after subtraction of $I_c$ from both sides, (4.31) can be denoted as

$$G(x_e, R) = 0.$$  \hspace{1cm} (4.32)

This is the nonlinear equation for the $x_e$ and is called the \emph{bifurcation equation}. It usually has multiple solutions for given $u_0$, $u_1$ and $R$. But physically meaningful solutions are those with $0 \leq x_e \leq L$. 

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
4.3 Bifurcation Equation Example

We can determine analytically an approximate functional dependence of the position of the cancer front \( x_e \) on the parameters \( R, u_0 \) and \( u_1 \). In the steady state problem (4.5), (4.7) and (4.8) we make the following assumptions for the functions and parameters: \( k(x) = 1, S(x) = 1, u_0 = 0, f_s(x) = \gamma_1 x + \delta_1, f_u(x) = \gamma_2 x + \delta_2 \) and \( L = 1 \). Also \( v(x) \equiv \text{constant} = \alpha, \alpha \geq 0 \). Upon substitution we obtain the bifurcation equations

\[
\begin{align*}
-\frac{d^2 f_s}{dx^2} + \alpha \frac{df_u}{dx} + u_1 I_1 &= R(\gamma_1 x + \delta_1), \quad 0 < x < x_e \\
-\frac{d^2 f_u}{dx^2} + \alpha \frac{df_u}{dx} + u_1 I_2 &= R(\gamma_2 x + \delta_2), \quad x_e < x < L
\end{align*}
\] (4.33)

which have the general solutions

\[
I_1(x) = e^{\frac{\alpha x}{2}}[C_1 \cosh(\mu x) + C_2 \sinh(\mu x)] + \frac{R}{u_1^2}[(\gamma_1 u_1 x + \delta_1 u_1 - \alpha \gamma_1)]
\] (4.34)

\[
I_2(x) = e^{\frac{\alpha x}{2}}[D_1 \cosh(\mu x) + D_2 \sinh(\mu x)] + \frac{R}{u_1^2}[(\gamma_2 u_1 x + \delta_2 u_1 - \alpha \gamma_2)]
\] (4.35)

where

\[
\mu = \frac{\sqrt{\alpha^2 + 4u_1}}{2}.
\] (4.36)

Applying the boundary conditions \( I'_1(0) = 0 \) and \( I'_2(1) = 0 \) yields, respectively, the equations

\[
C_1 \frac{\alpha}{2} + C_2 \mu = -\frac{R \gamma_1}{u_1}
\] (4.37)

and

\[
D_1 \left[ \frac{\alpha}{2} \cosh(\mu) + \mu \sinh(\mu) \right] + D_2 \left[ \frac{\alpha}{2} \sinh(\mu) + \mu \cosh(\mu) \right] = -\frac{R \gamma_2 e^{-\alpha/2}}{u_1}. \] (4.38)
When we apply the matching procedure, $I_1(x_e) = I_2(x_e)$ and $I'_1(x_e) = I'_2(x_e)$ at the cancer front which is fixed at $x_e = x_e = \text{constant}$, we obtain

$$\begin{align*}
C_1 \cosh(\mu x_e) + C_2 \sinh(\mu x_e) - D_1 \cosh(\mu x_e) - D_2 \sinh(\mu x_e) = & \ \frac{Re^{-\alpha x_e/2}}{u_1^2} [(\gamma_2 - \gamma_1)u_1 x_e + (\delta_2 - \delta_1)u_1 - (\gamma_2 - \gamma_1)\alpha] \\
\text{and}

C_1 \left[ \frac{\alpha}{2} \cosh(\mu x_e) + \mu \sinh(\mu x_e) \right] + C_2 \left[ \frac{\alpha}{2} \sinh(\mu x_e) + \mu \cosh(\mu x_e) \right] - \\
D_1 \left[ \frac{\alpha}{2} \cosh(\mu x_e) + \mu \sinh(\mu x_e) \right] - D_2 \left[ \frac{\alpha}{2} \sinh(\mu x_e) + \mu \cosh(\mu x_e) \right] = & \ \frac{Re^{-\alpha x_e/2}}{u_1} (\gamma_2 - \gamma_1).
\end{align*}$$

Algebraically solving the four equations (4.37)-(4.40) for the four unknown yields lengthy expressions for the constants $C_1$, $C_2$, $D_1$ and $D_2$. Therefore, we use the cancer front condition (4.26) to obtain a relationship between $R$ and $x_e$. Numerically, for the following two groups of parameters:

(i) $\alpha = 4.7$, $\gamma_1 = 10$, $\delta_1 = 5$, $\gamma_2 = -10$, $\delta_2 = 5$, $u_1 = 5.5$, and $I_c = 15$;

(ii) $\alpha = 2.5$, $\gamma_1 = -5$, $\delta_1 = 10$, $\gamma_2 = 0$, $\delta_2 = 3$, $u_1 = 1.46$, and $I_c = 15$;

we obtain corresponding curves of the functions $x_e = x_e(R)$ in the $R$, $x_e$ plane, referred to as the operating curves. In figure 4.1, note the existence of multiple steady states. For a given reproduction rate there are two possible positions for the interface.
Figure 4.1: Case I operating curve for the steady state problem where $x_e$ is the position of the interface and $R$ is the reproduction rate. The parameter values are: $\alpha = 4.7$, $\gamma_1 = 10$, $\delta_1 = 5$, $\gamma_2 = -10$, $\delta_2 = 5$, $u_1 = 5.5$, and $I_c = 15$. 

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Figure 4.2: Case II operating curve for the steady state problem where $x_e$ is the position of the interface and $R$ is the reproduction rate. The parameter values are: $\alpha = 2.5$, $\gamma_1 = -5$, $\delta_1 = 10$, $\gamma_2 = 0$, $\delta_2 = 3$, $u_1 = 1.46$, and $I_c = 15$. 

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
4.4 Slope-Stability Theorem

The following theorem will be used to determine which portions of the operating curves correspond to stable steady states and which portions correspond to unstable steady states.

**Theorem 1 (Slope-Stability)** The steady state solution of

\[
\frac{d}{dx} \left( k(x) \frac{dI_e}{dx} \right) - v(x) \frac{dI_e}{dx} u_1 I_e - R S(x) f(x; x_e) + u_0, \quad (4.41)
\]

\[0 < x < L,
\]

with the cancer front condition

\[I_e(x_e) = I_c, \quad (4.42)
\]

and boundary conditions

\[\frac{dI_e}{dx} \bigg|_{x=0,L} = 0, \quad (4.43)
\]

is linearly stable if \((\frac{dR}{dx_e}) > 0\) and unstable if \((\frac{dR}{dx_e}) < 0\) and is neutrally stable if \((\frac{dR}{dx_e}) = 0\).

To prove the Slope-Stability Theorem we perturb the steady state solution and the equilibrium cancer front position according to the following equations

\[I(x, t) = I_e(x) + \eta(x, t), \quad (4.44)
\]

\[x_e(t) = x_e + \zeta(t). \quad (4.45)
\]

Substituting (4.44), (4.45) into (4.5) and making use of (4.10) we obtain the following

\[\frac{\partial \eta}{\partial t} - \frac{\partial}{\partial x} \left( k(x) \frac{\partial \eta}{\partial x} \right) + u_1 \eta + v(x) \frac{\partial \eta}{\partial x} = R S(x) (f(x; x_e + \zeta) - f(x; x_e)). \quad (4.46)
\]
The perturbations, which are small, are taken to be
\[ \eta(x, t) = \eta_1(x)e^{-\lambda t}, \tag{4.47} \]
and
\[ \zeta(t) = \zeta_1 e^{-\lambda t}. \tag{4.48} \]
Notice we have stability when \( \lambda > 0 \) and instability when \( \lambda < 0 \). Substitution of (4.47) and (4.48) into (4.46) yields
\[
-\lambda \eta_1 - \frac{d}{dx} \left( k(x) \frac{d\eta_1}{dx} \right) + u_1 \eta_1(x) + v(x) \frac{d\eta_1}{dx} = \]
\[
R S(x)(f(x; x_e + \zeta) - f(x; x_e))e^{\lambda t}. \tag{4.49}
\]
In solving for \( \eta_1 \), we must put (4.49) in self-adjoint form via the detailed technique presented in section 4.2. Hence, we have
\[
\frac{d}{dx} \left[ p(x) \frac{d\eta_1}{dx} \right] - [u_1 - \lambda] r(x) \eta_1 = \]
\[
-R S(x)(f(x; x_e + \zeta) - f(x; x_e))r(x)e^{\lambda t} \tag{4.50}
\]
where \( p(x) \) and \( r(x) \) remain unchanged from section 4.2, see (4.16) and (4.18).

Now expressing \( \eta_1(x) \) as an eigenfunction expansion yields
\[
\eta_1(x) = \sum_{n=0}^{\infty} H_n \varphi_n(x). \tag{4.51}
\]
Thus, substituting the expansion into (4.50) and making use of its associated eigenvalue problem
\[
\frac{d}{dx} \left[ p(x) \frac{d\varphi_n}{dx} \right] = -\lambda_n r(x) \varphi_n(x), \tag{4.52}
\]
we multiply both sides of the resulting equation by \( \varphi_m(x) \) and integrate with respect to \( x \) from 0 to \( L \) obtaining,
\[
\lambda_n H_n + H_n(u_1 - \lambda) = Re^{\lambda t} \int_0^L r(x) S(x)(f(x; x_e + \zeta) - f(x; x_e))\varphi_n(x) \, dx. \tag{4.53}
\]
Linearizing the right hand side of (4.53) with respect to $\zeta$ about $x = x_e$ keeping only terms of order $\zeta$, we obtain

\[
H_n = \frac{RS(x_e)R(x_e)\zeta_1 \Delta f \varphi_n(x_e)}{\lambda_n + u_1 - \lambda},
\]

where

\[
\Delta f = f_s(x_e) - f_w(x_e) > 0, \text{ when } 0 < x_e < L, \tag{4.55}
\]

\[
r(x_e) = \exp \left( - \int x \frac{v(x)}{k(x)} \, dx \right). \tag{4.56}
\]

Thus, from (4.51) we find

\[
\begin{align*}
\eta_1(x) &= \sum_{n=0}^{\infty} H_n \varphi_n(x) \\
&= RS(x_e)R(x_e)\zeta_1 \Delta f \sum_{n=0}^{\infty} \frac{\varphi_n(x_e)\varphi_n(x)}{\lambda_n + u_1 - \lambda}.
\end{align*}
\]

Substitution (4.44) and (4.45) into the cancer front condition (4.9) we have

\[
I_c = I_c(x_e)
\]

\[
= I_e(x_e + \zeta) + \eta(x_e + \zeta, t)
\]

\[
= I_e(x_e) + I'_e(x_e)\zeta + \eta(x_e, t) + \text{higher order terms}
\]

\[
= I_c + I'_e(x_e)\zeta + \eta(x_e, t) + \text{higher order terms}
\]

(4.58)

where $I'_e(x_e)$ is short notation for $(dI_e/dx)|_{x=x_e}$. Omitting higher order terms and solving (4.58) for $\zeta$ yields

\[
\zeta(t) = \frac{-\eta(x_e, t)}{I'_e(x_e)}. \tag{4.59}
\]

Hence, by (4.47) and (4.48) we find

\[
\zeta_1 = \frac{-\eta_1(x_e)}{I'_e(x_e)}. \tag{4.60}
\]
Next we compute the slope of the operating curve. If $x_e = \bar{x}_e$ is not a critical point of $G(x_e, R)$ in (4.30) then the implicit function theorem implies that $x_e$ is a differentiable function of $R$ in the neighborhood of $\bar{x}_e$ by (4.31). By (4.30- 4.31),

$$\frac{\partial G}{\partial R} = \sum_{n=0}^{\infty} \left( \frac{1}{\lambda_n + u_1} \int_{0}^{L} S(x)f(x; x_e) r(x) \phi_n(x) \, dx \right) \phi_n(x_e)$$

$$= \frac{1}{R} \left( I_e + \frac{\mu_0 \phi_0(x_e)}{u_1} \right).$$

(4.61)

where $\phi_0(x_e) = (\int_{0}^{L} r(x) \, dx)^{-1/2}$. Also by (4.30) and (4.31), we find

$$\frac{\partial G}{\partial x_e} = RS(x_e) \Delta f \sum_{n=0}^{\infty} \frac{\phi_n^2(x_e)}{\lambda_n + u_1} + I_e'(x_e).$$

(4.62)

Computing $I_e'(x_e)$ on the right hand side of the above equation from (4.57-4.60) yields

$$I_e'(x_e) = -RS(x_e) \Delta f \sum_{n=0}^{\infty} \frac{\phi_n^2(x_e)}{\lambda_n + u_1 - \lambda}.$$  

(4.63)

Hence, (4.60) becomes

$$\frac{\partial G}{\partial x_e} = -RS(x_e) \Delta f \sum_{n=0}^{\infty} \frac{\lambda \phi_n^2(x_e)}{(\lambda_n + u_1)(\lambda_n + u_1 - \lambda)}.$$  

(4.64)

By (4.57 and (4.65), in a neighborhood of $\bar{x}_e$ we have

$$\frac{dR}{dx_e} = \frac{-\partial G}{\partial x_e} \frac{\partial G}{\partial R}$$

$$= \frac{R^2 u_1 S(x_e) \Delta f}{u_1 I_c + u_0 \phi_0(x_e)} \sum_{n=0}^{\infty} \frac{\lambda \phi_n^2(x_e)}{(\lambda_n + u_1)(\lambda_n + u_1 - \lambda)}$$

$$\equiv \Gamma(\lambda), \text{ say.}$$

(4.65)

From Sturm-Liouville theory,

$$\lambda_n = O(n^2) \text{ as } n \to \infty,$$

(4.66)
and $\{ |\varphi_n(x)| \}_{n=0}^{\infty}$ is uniformly bounded. Hence,

$$
\sum_{n=0}^{\infty} \frac{\varphi_n^2(x_e)}{\lambda_n + u_1} \quad \text{and} \quad \sum_{n=0}^{\infty} \frac{\varphi_n^2(x_e)}{\lambda_n + u_1 - \lambda}
$$

(4.67)

are both convergent. A sketch of $\Gamma(\lambda)$ is shown in figure 4.3. From (4.65) we can see that $\Gamma(\lambda)$ passes through the origin and has vertical asymptotes at

$$
\lambda = \lambda_n + u_1
$$

(4.68)

and a horizontal asymptote at

$$
\Gamma(\lambda) = \frac{R^2 u_1 S(x_e) r(x_e) \Delta f}{u_1 I_c + u_0 \varphi_0(x_e)} \sum_{n=0}^{\infty} \left( \frac{\varphi_n^2(x_e)}{\lambda_n + u_1} + \frac{\varphi_n^2(x_e)}{\lambda_n + u_1 - \lambda} \right)
$$

$$
\rightarrow - \frac{R^2 u_1 S(x_e) r(x_e) \Delta f}{u_1 I_c + u_0 \varphi_0(x_e)} \sum_{n=0}^{\infty} \frac{\varphi_n^2(x_e)}{\lambda_n + u_1} \equiv \gamma \quad \text{as} \quad \lambda \to -\infty. \quad (4.69)
$$

From figure 4.3 we can see that (4.65) has only positive (nonnegative) roots if

$$
\left( \frac{dR}{dx_e} \right) > 0.
$$

To complete the proof of the Slope-Stability Theorem requires showing that

$$
\left( \frac{dR}{dx_e} \right) \text{ never dips below } \gamma. \quad \text{Since } I_e(x) \text{ is a strictly decreasing function, we have } I'_e(x_e) < 0. \quad \text{Hence (4.62) implies}
$$

$$
\frac{\partial G}{\partial x_e} < R S(x_e) \Delta f \sum_{n=0}^{\infty} \frac{\varphi_n^2(x_e)}{\lambda_n + u_1}. \quad (4.70)
$$

By (4.61), $\left( \frac{dG}{dR} \right) > 0$ as long as $I_c + \frac{u_0 \varphi_0(x_e)}{u_1} > 0$. Therefore,

$$
\frac{dR}{dx_e} = - \frac{\frac{\partial G}{\partial x_e}}{\frac{\partial G}{\partial R}} \quad > \quad - \frac{R S(x_e) r(x_e) \Delta f \sum_{n=0}^{\infty} \frac{\varphi_n^2(x_e)}{\lambda_n + u_1}}{\frac{1}{R} \left( I_c + \frac{u_0 \varphi_0(x_e)}{u_1} \right)} \quad = \quad \gamma. \quad (4.71)
$$

Hence, the steady-state solution is linearly stable if $\left( \frac{dR}{dx_e} \right) > 0$ since (4.65) has only positive roots and linearly unstable if $\gamma < \frac{dR}{dx_e} < 0$ since (4.65) has a negative root.
This completes the proof of the slope stability theorem.
Figure 4.3: Sketch of the function \( \Gamma(\lambda) \) defined by (4.59).
4.5 Propagation of Cancer Front

In this section our aim is to describe the propagation of the interface between the cancerous region and metastatic region, that is \( x_c = x_c(t) \). In order to accomplish this goal we need to solve the initial boundary value problem (4.5) and (4.7-4.9). In section 4.2 we observed that when the spatial differential equation was put into self-adjoint form, equation (4.17) the function \( r(x) \) appeared as a multiplier of each term. This suggests that we write equation (4.5) as

\[
\frac{r(x)}{\partial I}{\partial t} - \frac{\partial}{\partial x} \left[ p(x) \frac{\partial I}{\partial x} \right] + u_1 r(x) I = (RS(x)f(x;x_c) + u_0) r(x). \quad (4.72)
\]

We will solve this nonhomogeneous initial boundary value problem by assuming the solution \( I(x,t) \) can be written in the form

\[
I(x,t) = \sum_{n=0}^{\infty} i_n(t) \varphi_n(x), \quad (4.73)
\]

where \( \{\varphi_n(x)\}_{n=0}^{\infty} \) are orthonormal eigenfunctions of (4.19) and (4.20), and then showing how to determine the coefficients \( i_n(t) \). Substituting (4.73) into (4.72), multiplying by \( \varphi_m \) and integrating with respect to \( x \) from 0 to \( L \) yields

\[
\frac{d}{dt} i_n + \lambda_n i_n(t) + u_0 \delta_{0n}(\int_0^L r(x) dx)^{-1/2} + u_1 i_n(t) \]

\[= \int_0^L RS(x)r(x)f(x;x_c)\varphi_n(x) dx. \quad (4.74)\]

To solve for \( i_n(t) \) we obtain an integrating factor which allows this first order ordinary differential equation to be written as

\[
\frac{d}{dt} \left[ e^{(\lambda_n + u_1)t} i_n \right] = \int_0^t e^{(\lambda_n + u_1)\tau} \times \left[ \int_0^L RS(x)r(x)f(x;x_c)\varphi_n(x) dx - u_0 \delta_{0n}(\int_0^L r(x) dx)^{-1/2} \right] d\tau. \quad (4.75)\]

We see from (4.9), the initial condition

\[
I(x,0) = \sum_{n=0}^{\infty} i_n(0) \varphi_n(x) = g(x). \quad (4.76)
\]
Hence, multiplying (4.76) by $\varphi_n(x)$ and integrating from 0 to $L$ yields

$$i_n(0) = \int_0^L g(x)\varphi_n(x) \, dx. \quad (4.77)$$

Therefore, $i_n(t)$ is obtained by integrating equation (4.75) and applying (4.77) yielding

$$i_n(t) = i_n(0) + \int_0^t \exp\left((\lambda_n + u_1)(\tau - t)\right) \times$$

$$\left[\int_0^L R S(x) r(x) f(x; x_c(\tau)) \varphi_n(x) \, dx - u_0 \delta \int_0^L r(x) \, dx \right]^{1/2} \, d\tau, \quad (4.78)$$

where $n = 0, 1, 2, 3, \ldots$. By the cancer front condition (4.7),

$$I(x_c, t) = I_c = \sum_{n=0}^{\infty} i_n(t) \varphi_n(x_c) \quad (4.79)$$

we obtain the following nonlinear integral equation

$$I_c = \sum_{n=0}^{\infty} \left\{i_n(0) + \int_0^t \exp\left((\lambda_n + u_1)(\tau - t)\right) \times$$

$$\left[\int_0^L R S(x) r(x) f(x; x_c(\tau)) \varphi_n(x) \, dx - u_0 \delta \int_0^L r(x) \, dx \right]^{1/2} \, d\tau\right\} \varphi_n(x_c(t)) \quad (4.80)$$

which determines $x_c(t)$. Unfortunately, solving this integral equation in general is extremely complicated. Nonetheless, we will find numerical solutions of $x_c(t)$ for different parameters in the succeeding section.
4.6 Examples

4.6.1 Example I

In order to illustrate the solution procedure, we will consider the following example where \( k(x) = 1, \ v(x) = 0, \ S(x) = 1, \ f_s(x) = 1, \ f_w(x) = \beta, \ L = 1, \ g(x) = H(1 - x), \) where \( H \) is a positive constant.

From (4.28-4.29) we find the eigenvalues

\[
\lambda_0 = 0, \ \lambda_1 = \pi, \ \lambda_2 = 2\pi, \ldots.
\]  

(4.81)

with the corresponding eigenfunctions

\[
\phi_0(x) = 1, \ \phi_1(x) = \sqrt{2}\cos(\pi x), \ \phi_2(x) = \sqrt{2}\cos(2\pi x), \ldots
\]  

(4.82)

Taking a two mode approximation, from (4.73) we have

\[
I(x, t) = i_0(t) + i_1(t)\sqrt{2}\cos(\pi x).
\]  

(4.83)

By (4.28) and (4.74) we find the following equations for \( i_0(t), \ i_1(t) \) and \( x_c(t) \) which are

\[
i_0(t) + i_1(t)\sqrt{2}\cos(\pi x_c) = I_c,
\]  

(4.84)

\[
\frac{d i_0}{d t} + u_1 i_0 = -u_0 + R[\beta + (1 - \beta)x_c],
\]  

(4.85)

\[
\frac{d i_1}{d t} + (\pi^2 + u_1)i_1 = \frac{\sqrt{2}R}{\pi}(1 - \beta)\sin(\pi x_c).
\]  

(4.86)

From (4.77) computing the initial conditions for \( i_0(t) \) and \( i_1(t) \) yields

\[
i_0(0) = \int_0^1 g(x)\phi_0(x) \, dx = \frac{H}{2}
\]  

(4.87)
and

\[
i_1(0) = \int_0^1 g(x)\varphi_1(x) \, dx = \frac{2\sqrt{2}H}{\pi^2}.
\]

(4.88)

The numerical solution for \( x_c(t) \) for the given parameters

\[
u_0 = 0.35, \quad I_e = 1.0, \quad R = 0.64, \quad H = 2.1 \quad \beta = 0.5
\]

(4.89)

and for the three different values of \( u_1 \), namely

\[
u_1 = 0.22, \quad u_1 = 0.24, \quad u_1 = 0.45
\]

(4.90)

are shown in figure 4.4. The solid line corresponds to \( u_1 = 0.22 \), the long dash line corresponds to \( u_1 = 0.24 \) and the short dash line corresponds to \( u_1 = 0.45 \). When \( u_1 = 0.22 \), the rate at which metastasis occurs is not high enough to balance the reproduction rate of cancer cells. The cancer front advances due to diffusion. When \( u_1 = 0.24 \), the metastatic rate is high enough to overcome the effects of the reproduction rate of cancer cells. Thus, the cancer front advances initially, but eventually the cancer front retreats. The time it takes for this change to occur, is called the waiting time. The waiting time corresponds to the time interval which passes before the cancer front retreats. When \( u_1 = 0.24 \) the waiting time is finite and is approximately 0.37. When \( u_1 = 0.22 \) the waiting time is defined as infinity and is zero when \( u_1 = 0.45 \). Therefore, we conclude that the larger the metastatic rate, the shorter the waiting time, as seen by comparison of \( u_1 = 0.24 \) and \( u_1 = 0.45 \).
Figure 4.4: Example I. Propagation of the cancer front without convection. An approximate solution $x_c$ vs. $t$ where $u_1 = 0.22$ (solid), $u_1 = 0.24$ (long dash) and $u_1 = 0.45$ (short dash).
4.6.2 Example II

In this example we take \( k(x) = 1, \ v(x) = 1, \ S(x) = 1, \ f_s(x) = 1, \ f_w(x) = \beta, \)
\( L = 1, \ g(x) = H(1 - x), \) where \( H \) is a positive constant.

We find the eigenvalues

\[
\lambda_0 = 0, \quad \lambda_1 = \frac{1 + 4\pi^2}{4}, \quad \lambda_2 = \frac{1 + 16\pi^2}{4}, \ldots
\]  

(4.91)

with the corresponding eigenfunctions

\[
\phi_0(x) = \frac{1}{\sqrt{1 - e^{-1}}}, \quad \phi_1(x) = \sqrt{\frac{2}{1 + 4\pi^2}} e^{\pi/2}[-2\pi \cos(\pi x) + \sin(\pi x)], \ldots
\]  

(4.92)

Taking a two mode approximation, we have

\[
I(x, t) = \frac{i_0(t)}{\sqrt{1 - e^{-1}}} + i_1(t) \sqrt{\frac{2}{1 + 4\pi^2}} e^{\pi/2}[-2\pi \cos(\pi x) + \sin(\pi x)].
\]  

(4.93)

By (4.28) and (4.74) we find the following equations for \( i_0(t), \ i_1(t) \) and \( x_c(t) \) which are

\[
\frac{d}{dt} \frac{i_0(t)}{\sqrt{1 - e^{-1}}} + i_1(t) \sqrt{\frac{2}{1 + 4\pi^2}} e^{\pi/2}[-2\pi \cos(\pi x_c) + \sin(\pi x_c)] = I_e,
\]  

(4.94)

\[
\frac{d}{dt} \frac{i_1}{\frac{1 + 4\pi^2}{4} + u_1} = \frac{-u_0}{\sqrt{1 - e^{-1}}} + R \left[ \int_0^{x_c} \frac{e^{-x}}{\sqrt{1 - e^{-1}}} \, dx + \int_{x_c}^1 \frac{\beta e^{-x}}{\sqrt{1 - e^{-1}}} \, dx \right],
\]  

(4.95)

\[
\frac{d}{dt} \frac{i_1}{\frac{1 + 4\pi^2}{4} + u_1} \left[ \frac{1 + 4\pi^2}{4} + u_1 \right] i_1 = R \left[ \int_0^{x_c} e^{-x/2}[-2\pi \cos(\pi x) + \sin(\pi x)] \, dx + \int_{x_c}^1 \beta e^{-x/2}[-2\pi \cos(\pi x) + \sin(\pi x)] \, dx \right]
\]  

(4.96)

with the initial conditions for \( i_0(t) \) and \( i_1(t) \) which are computed as follows

\[
i_0(0) = \int_0^1 g(x) \varphi_0(x) \, dx
\]  

\[
= \int_0^1 H(1 - x)(1 - e^{-1})^{-1/2} \, dx
\]  

\[
= \frac{H}{2\sqrt{1 - e^{-1}}}
\]  

(4.97)
and

\[ i_1(0) = \int_0^1 g(x)\varphi_1(x) \, dx \]
\[ = \int_0^1 H(1-x)\sqrt{\frac{2}{1+4\pi^2}} e^{-\pi^2/2}\left[-2\pi \cos(\pi x) + \sin(\pi x)\right] \, dx. \tag{4.98} \]

For the parameters

\[ u_0 = 0.35, \quad I_c = 1.0, \quad R = 0.7, \quad H = 2.1 \quad \beta = 0.5 \tag{4.99} \]

and for the two different values of \( u_1 \), namely

\[ u_1 = 0.22, \quad u_1 = 0.45 \tag{4.100} \]

where have the following curves illustrated in figure 4.5. In this case where \( v(x) = 1 \) there is no tumor reduction. Thus, we conclude that the metastatic rate is not high enough to balance the reproduction rate of the cancer cells and the cancer front advances due to diffusion and convection.
Figure 4.5: Example II. Propagation of the cancer front with convection. An approximate solution $x_c$ vs. $t$ where $u_1 = 0.22$ (solid) and $u_1 = 0.45$ (short dash).
CHAPTER 5
CONCLUSIONS

The phenomenological modeling approach we have presented examines the dynamic behavior of one-dimensional models incorporating salient features of cancer. Obviously, the continuum models do not include all possible factors contributing to cancer maturation or diffusion, but these models do incorporate several major components as simply as possible. Since a less intricate system contains characteristics present in a more complex system, a one-dimensional model can provide insight for more realistic three-dimensional models. Invading cells can behave like a front of cells moving as a wave. Therefore, our analytical focus was on understanding the nature of this wave of translation and the changes which arise at the interface between the invading tumor and noncancerous or metastatic region.

The mathematical model by Gatenby and Gawlinski provides a mechanism for invasive tumor growth [25]. This mechanism, which involves changes of the microenvironmental pH caused by the tumor, yields interactions consistent with various aspects of cancer biology.

Gatenby and Gawlinski's model made several predictions which were confirmed by experimental data and clinical observations. The first prediction was that of an acidic pH gradient extending from the tumor-host interface. Demonstrated was the fact that normal cells were no longer viable in an acidic interstitial pH below 7.1. The model also predicts the critical parameters, which are consistent with experimental and clinical observations, controlling the transition from benign to malignant growth. Finally, the model predicts, at the tumor-host interface, a hypocellular interstitial gap. We are interested in the effects of additional terms on
these characteristics. To this end, we studied modifications of the model developed by Gatenby and Gawlinski. First, we assumed that the immune system harvests the tumor population at a rate proportional to the existing tumor population. This assumption yields a decline in the tumor population when this rate $\alpha$ exceeds the natural rate of growth. This assumption also induced directly proportional changes to the dimensionless biological parameter $\delta_1$ which allowed us to investigate the tumor growth as we vary parameters which characterize the tumor tissue and $\rho_2$ which is the ratio of the growth rate of the tumor tissue to that of the normal tissue. For $\alpha > 0$, we observed that the growth rate and carrying capacity of the tumor population were reduced.

Secondly, we incorporated the effects of the immune system by means of a constant harvesting term. This allowed us to conclude that the critical harvest rate is the maximum possible growth rate of the tumor population, which is a biologically plausible result. When the harvest rate exceeds the maximum growth rate we were able to calculate the biological extinction time of the tumor population as a function of the harvesting rate.

In Chapter 3 we developed a simplified model based on the model by Gatenby and Gawlinski. The study of this system of two coupled equations is an attempt to make a transition between two existing but different approaches to travelling wave solutions. First, this model was examined via techniques of earlier work by Chow and Tam [10]. We began by solving the spatially independent equation and substituting into the remaining or secondary equation. This led to integro-differential equations for the waveforms in which we are able to calculate by appropriately choosing the speed of propagation. Solving these equations yields sharp wavefronts.
The second technique was a phase-plane analysis. This involved first reducing the system of two coupled reaction-diffusion equations to a system of first-order ordinary differential equations and completing a linearized stability analysis. The waves obtained were called waves of pursuit and evasion, since one of the waves was the forerunner, cancer population, after which the other wave, enzyme population, followed.

In Chapter 4, we studied a one-dimensional model of cancer dispersion. This model incorporated convection as an addition transport process. We used the condition \( I(x,t) = I_c \) to determine the cancer front position \( x_c(t) \) which separates the cancerous and metastatic region. We found the possible existence of multiple steady-state fronts, of which some are stable. On the operating curves, figures 4.4 and 4.5, the solutions corresponding to the negative slope are unstable and all other solutions are neutrally stable. This result is referred to as the slope stability theorem. Due to the instability there exist turning points around which the solutions do not continuously depend on all parameters. At these turning points an infinitesimal change in the reproduction rate may cause a large jump of the position of the cancer front.

For the unsteady state we derived an integral equation for the cancer front \( x_c(t) \). Due to the level of complexity in solving for \( x_c(t) \) in general, we obtain a numerical solution for \( x_c(t) \) for various parameter values. In section 6 of Chapter 4, our examples I and II involved taking a two and one mode approximation, respectively. Future work includes a two or three mode approximation involving various other choices of \( v(x) \). In addition, we will choose functions for \( v(x) \) motivated by biological considerations. Future work involves also examining possible bistability of the model after introducing a periodic "forcing" term, such as chemotherapy,
into the system.
BIBLIOGRAPHY


APPENDIX I

Derivation of Profile

Recall from Chapter 2 section 3 the equation

\[-c\eta'_1 = \eta_1(1 - \eta_1) - \delta_1 A \eta_1. \tag{A.1}\]

Rearranging (A.1) into the proper form for a Bernoulli differential equation yields

\[\eta'_1 + \frac{1}{c}(1 - \delta_1 A) \eta_1 = \frac{1}{c} \eta_1^2. \tag{A.2}\]

The Bernoulli equation may be reduced to the linear, first-order differential equation

\[v'(\zeta) - \frac{1}{c}(1 - \delta_1 A)v(\zeta) = -\frac{1}{c} \tag{A.3}\]

via the substitution

\[v(\zeta) = \frac{1}{\eta_1(\zeta)}. \tag{A.4}\]

Since \(A\) has the piecewise definition

\[A(\zeta) = \begin{cases} 
1 - \frac{1}{2}\exp(\sqrt{3} \zeta) & \zeta < 0 \\
\frac{1}{2}\exp(-\sqrt{3} \zeta) & \zeta \geq 0
\end{cases} \tag{A.5}\]

two calculations are necessary after this point.

In this paragraph, we complete the calculations for the case \(\zeta \geq 0\). Equation (A.3) becomes

\[v'(\zeta) - \frac{1}{c}(1 - \frac{1}{2}\delta_1 e^{-q\zeta})v(\zeta) = -\frac{1}{c}. \tag{A.6}\]
Using an integrating factor we obtain

\[ v(\zeta) = \exp \left( r\zeta + pe^{-\zeta} \right) \left[ -r \int_0^\zeta \exp \left( -r\zeta' - pe^{-\zeta'} \right) d\zeta' + k \right] \]  \hspace{1cm} (A.7)

where

\[ r = \frac{1}{c} \quad \text{and} \quad p = \frac{\delta_1}{2cq}. \]  \hspace{1cm} (A.8)

Using the substitution

\[ u = pe^{-\zeta'} \]  \hspace{1cm} (A.9)

we rewrite the integral

\[ I(\zeta) = \int_0^\zeta \exp \left( -r\zeta' - pe^{-\zeta'} \right) d\zeta' \]

\[ = -\frac{1}{pr/qq} \int_p^{pe^{-\zeta}} u^{r/q-1} e^{-u} du \]

\[ = -\frac{1}{pr/qq} \left[ \gamma(r/q, pe^{-\zeta}) - \gamma(r/q, p) \right] \]

where

\[ \gamma(a, x) = \int_0^x e^{-u} u^{a-1} du \]  \hspace{1cm} (A.10)

is the incomplete gamma function. Substituting this integration result into (A.7) yields

\[ v(\zeta) = \exp \left( r\zeta + pe^{-\zeta} \right) \left[ \frac{r}{pr/qq} \left( \gamma(r/q, pe^{-\zeta}) - \gamma(r/q, p) \right) + k \right]. \]  \hspace{1cm} (A.11)

To solve for the unknown constant \( k \) we note that there is all normal tissue ahead of the cancer front and hence that we must have \( v(\infty) = \frac{1}{v(\infty)} = 1 \). Since the exponential function becomes unbounded, it is necessary that

\[ \frac{r}{pr/qq} \left( \gamma(r/q, 0) - \gamma(r/q, p) \right) + k = 0 \]  \hspace{1cm} (A.12)
from which
\[ k = \frac{r}{p^{r/q}} \gamma(r/q, p). \]  
\hspace{1cm} (A.13)

Hence, we obtain
\[ v(\zeta) = \exp \left( r\zeta + pe^{-\zeta} \right) \left( \frac{r}{p^{r/q}} \right) \gamma(r/q, pe^{-\zeta}). \]  
\hspace{1cm} (A.14)

Since (A.12) is not a sufficient condition we have confirmed that \( v(\infty) = 1 \) using L'Hôpital's rule.

Next, we complete the calculations for the case \( \zeta < 0 \). Equation (A.3) becomes
\[ v'(\zeta) + (s - \frac{\delta_1}{2c}e^{\zeta})v(\zeta) = -\frac{1}{c}. \]  
\hspace{1cm} (A.15)

Using an integrating factor we obtain
\[ v(\zeta) = \exp \left( -s\zeta + pe^{\zeta} \right) \left[ \int_{0}^{\zeta} \exp \left( s\zeta' - pe^{\zeta'} \right) d\zeta' + k \right] \]  
\hspace{1cm} (A.16)

where
\[ s = \frac{\delta_1 - 1}{c}. \]  
\hspace{1cm} (A.17)

Using the substitution
\[ u = pe^{\zeta'} \]  
\hspace{1cm} (A.18)

we rewrite the integral in terms of the incomplete gamma function
\[ I(\zeta) = \int_{0}^{\zeta} \exp \left( s\zeta' - pe^{-\zeta'} \right) d\zeta' = \frac{1}{p^{s/q}} \int_{p}^{pe^\zeta} u^{s/q-1}e^{-u} du = \frac{1}{p^{s/q}} \left[ \gamma(s/q, pe^{\zeta}) - \gamma(s/q, p) \right]. \]
Substitution of this integration result into (A.16) yields

$$u(\zeta) = \exp \left( -s\zeta + pe^{a\zeta} \right) \left[ \frac{-r}{p^{s/q}q} \left( \gamma(s/q, pe^{a\zeta}) - \gamma(s/q, p) \right) + k \right].$$  \hfill (A.19)

Continuity at $\zeta = 0$ requires

$$k = \frac{r}{p^{s/q}q}$$  \hfill (A.20)

thus we obtain

$$u(\zeta) = \exp \left( -s\zeta + pe^{a\zeta} \right) \times \left[ \frac{r}{p^{s/q}q} \left( \gamma(s/q, p) + \gamma(r/q, p)p^{(s-r)/q} - \gamma(s/q, pe^{a\zeta}) \right) \right].$$  \hfill (A.21)

Using the fact that $\eta_1(\zeta) = \frac{1}{u(\zeta)}$ and piecing together the solutions for $\zeta \geq 0$ and $\zeta < 0$ leads to the following piecewise solution for $\eta_1$, namely

$$\eta_1(\zeta) = \begin{cases} 
\frac{c \exp[-pe^{a\zeta} + s\zeta]p^{s/q}q}{\gamma(r/q, p)p^{(s-r)/q} + \gamma(s/q, p) - \gamma(s/q, pe^{a\zeta})} & \zeta < 0 \\
\frac{c \exp[-pe^{-a\zeta} - r\zeta]p^{r/q}q}{\gamma(r/q, pe^{-a\zeta})} & \zeta \geq 0.
\end{cases}$$  \hfill (A.22)
APPENDIX II
Interfacial Widths of Acid and Tumor

We first derive the analytical result for the interfacial width of the tumor tissue profile. From

\[ \eta_2(\zeta) = \frac{1}{1 + \exp\left(\frac{\rho_2 \zeta}{c}\right)} \quad (A.1) \]

we find

\[ \eta_2'(\zeta) = -\frac{\rho_2}{c} \left[ \frac{\exp\left(\frac{\rho_2 \zeta}{c}\right)}{(1 + \exp\left(\frac{\rho_2 \zeta}{c}\right))^2} \right] \quad (A.2) \]

By definition of the edge position \( E(\tau) \) of a profile, namely

\[ E_f(\tau) = \frac{\int_{-\infty}^{\infty} \xi \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}{\int_{-\infty}^{\infty} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi} = \frac{N_1}{D_1} \quad (A.3) \]

we calculate

\[ N_1 = -\frac{\rho_2}{c} \int_{-\infty}^{\infty} \left[ \frac{\zeta \exp\left(\frac{\rho_2 \zeta}{c}\right)}{(1 + \exp\left(\frac{\rho_2 \zeta}{c}\right))^2} \right] d\zeta = 0 \quad (A.4) \]

and

\[ D_1 = -\frac{\rho_2}{c} \int_{-\infty}^{\infty} \left[ \frac{\exp\left(\frac{\rho_2 \zeta}{c}\right)}{(1 + \exp\left(\frac{\rho_2 \zeta}{c}\right))^2} \right] d\zeta = 1. \quad (A.5) \]

Thus, after integration by parts we observe that

\[ E_{\eta_2} = \frac{N_1}{D_1} = 0. \quad (A.6) \]

Now, by use of the definition for the width \( W(\tau) \)

\[ W_f^2(\tau) = \frac{\int_{-\infty}^{\infty} \left[ \xi - E_f(\tau) \right]^2 \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}{\int_{-\infty}^{\infty} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi} = \frac{N_2}{D_2} \quad (A.7) \]
we find that $D_2 = D_1 = 1$ and

$$N_2 = -\frac{\rho_2}{c} \int_{-\infty}^{\infty} \left[ \frac{\zeta^2 \exp\left(\frac{\rho_2 \zeta}{c}\right)}{(1 + \exp\left(\frac{\rho_2 \zeta}{c}\right))^2} \right] d\zeta = \frac{c^2 \pi^2}{3 \rho_2^2}. \quad (A.8)$$

Hence, we find the following interfacial width of the tumor tissue profile

$$W_{\tau_2} = \frac{\pi c}{\sqrt{3} \rho_2}. \quad (A.9)$$

By use of the same definitions for the edge position $E(\tau)$ and width $W(\tau)$ of a profile we calculate the interfacial width of the acid. From

$$\Lambda(\zeta) = \begin{cases} 
1 - \frac{1}{2} \exp(\sqrt{\delta_3} \zeta) & \zeta < 0 \\
\frac{1}{2} \exp(-\sqrt{\delta_3} \zeta) & \zeta \geq 0
\end{cases} \quad (A.10)$$

we find

$$\Lambda'(\zeta) = \begin{cases} 
-\frac{\sqrt{\delta_3}}{2} \exp(\sqrt{\delta_3} \zeta) & \zeta < 0 \\
-\frac{\sqrt{\delta_3}}{2} \exp(-\sqrt{\delta_3} \zeta) & \zeta \geq 0.
\end{cases} \quad (A.11)$$

Thus,

$$D_1 = -\frac{\sqrt{\delta_3}}{2} \left[ \int_{-\infty}^{0} \exp(\sqrt{\delta_3} \zeta') d\zeta' + \int_{0}^{\infty} \exp(-\sqrt{\delta_3} \zeta) d\zeta \right] = -1 \quad (A.12)$$

and

$$N_1 = -\frac{\sqrt{\delta_3}}{2} \left[ \int_{-\infty}^{0} \zeta' \exp(\sqrt{\delta_3} \zeta') d\zeta' + \int_{0}^{\infty} \zeta \exp(-\sqrt{\delta_3} \zeta) d\zeta \right] = 0 \quad (A.13)$$

therefore,

$$E_{\lambda} = \frac{0}{-1} = 0. \quad (A.14)$$

Again we calculating the width $W(\tau)$ we find that $D_2 = D_1 = -1$ and

$$N_1 = -\frac{\sqrt{\delta_3}}{2} \left[ \int_{-\infty}^{0} \zeta'^2 \exp(\sqrt{\delta_3} \zeta') d\zeta' + \int_{0}^{\infty} \zeta \exp(-\sqrt{\delta_3} \zeta) d\zeta \right] = 0. \quad (A.15)$$

Hence, the interfacial width of the acid profile is

$$W_{\Lambda} = \sqrt{\frac{2}{\delta_3}}. \quad (A.16)$$
APPENDIX III

Derivation of Profile For Modified Model

For the case \( \zeta < 0 \) we obtain the following new solution for \( \Lambda(\zeta) \) which is

\[
\Lambda(\zeta) = (1 - K) + \left(-\frac{1}{2} + K\right)e^{\sqrt{\delta_3} \zeta}
\]  

(A.1)

from which we find

\[
\Lambda'(\zeta) = \sqrt{\delta_3}(\frac{1}{2} + K)e^{\sqrt{\delta_3} \zeta}.
\]  

(A.2)

Thus the solution for \( \eta_1(\zeta) \) when \( \zeta < 0 \) has also changed and will now be derived. Again, substitution into

\[
u'(\zeta) - \frac{1}{c}(1 - \delta_1 \Lambda)u(\zeta) = \frac{1}{c}
\]  

(A.3)

yields

\[
u'(\zeta) - \frac{1}{c}(1 - \delta_1 (1 - K) - \delta_1 (K - \frac{1}{2})e^{\delta_3 \zeta})u(\zeta) = \frac{1}{c}.
\]  

(A.4)

For simplicity, if we let

\[
\alpha = s - r\delta_1 K \quad \text{and} \quad \beta = \frac{-r\delta_1(K - 1/2)}{q}
\]  

(A.5)

where

\[
r = \frac{1}{c} \quad \text{and} \quad s = \frac{\delta_1 - 1}{c}
\]  

(A.6)

then (A.4) can be written as

\[
u'(\zeta) + (\alpha - \beta e^{\delta_3 \zeta})u(\zeta) = \frac{1}{c}.
\]  

(A.7)
By comparison with previous calculations in Appendix I yields

\[ v(\zeta) = \exp\left(-\alpha\zeta + \beta e^{\sigma\zeta}\right) \left[-\frac{1}{c q \beta^{\alpha/q}} \left(\gamma(\alpha/q, \beta e^{\sigma\zeta}) - \gamma(\alpha/q, \beta)\right) + k\right]. \tag{A.8} \]

Continuity at \( \zeta = 0 \) requires

\[ k = \frac{1}{cq^p/q} \gamma(\tau/q, p) e^{p-\beta}. \tag{A.9} \]

Hence, we obtain

\[ v(\zeta) = \exp\left(-\alpha\zeta + \beta e^{\sigma\zeta}\right) \times \left[-\frac{1}{c q \beta^{\alpha/q}} \left(\gamma(\alpha/q, \beta e^{\sigma\zeta}) - \gamma(\alpha/q, \beta)\right) + \frac{1}{cq^p/q} \gamma(\tau/q, p) e^{p-\beta}\right]. \tag{A.10} \]

Therefore our solution is

\[ \eta_1(\zeta) = \frac{cq \exp[\alpha\zeta - \beta e^{\sigma\zeta}]}{\beta^{-\alpha/q} (\gamma(\alpha/q, \beta) - \gamma(\alpha/q, \beta e^{\sigma\zeta}) + p^{-\tau/q} e^{p-\beta} \gamma(\tau/q, p))} \tag{A.11} \]

in which substitution for \( \alpha \) and \( \beta \) from (A.5) yields the following solution for \( \eta_1 \), where \( \zeta < 0 \) as

\[ \eta_1(\zeta) = \left\{ \begin{array}{l}
\frac{cq \exp\left[\left(s - r\delta_1 K\right)\zeta + \left((r\delta_1(K - 1/2))/q\right) e^{\sigma\zeta}\right]}{\left\{(-r\delta_1(K - 1/2))/q\right\}^{-\left(s - r\delta_1 K\right)/q} \times \\
\left(\gamma((s - r\delta_1 K)/q, (-r\delta_1(K - 1/2))/q)\right) - \gamma((s - r\delta_1 K)/q, (-r\delta_1(K - 1/2))/q) e^{\sigma\zeta}) + p^{-\tau/q} \exp[p + (r\delta_1(K - 1/2))/q] \gamma(\tau/q, p)\right. \end{array} \right\}. \tag{A.12} \]
APPENDIX IV

Interfacial Width of Acid For Modified Model

It is necessary to only show the calculations for the interfacial width of the acid.

From

\[ \Lambda(\zeta) = \begin{cases} (1 - K) + (-\frac{1}{2} + K) \exp(\sqrt{\sigma_3} \zeta) & \zeta < 0 \\ \frac{1}{2} \exp(-\sqrt{\sigma_3} \zeta) & \zeta \geq 0 \end{cases} \]  

we find

\[ \Lambda'(\zeta) = \begin{cases} \sqrt{\sigma_3}(-\frac{1}{2} + K) \exp(\sqrt{\sigma_3} \zeta) & \zeta < 0 \\ -\frac{\sqrt{\sigma_3}}{2} \exp(-\sqrt{\sigma_3} \zeta) & \zeta \geq 0. \end{cases} \]  

Thus, by the formula

\[ E_f(\tau) = \frac{\int_{-\epsilon}^{\epsilon} \xi \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}{\int_{-\epsilon}^{\epsilon} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi} = \frac{N_1}{D_1} \]  

we find

\[ E_m = \frac{N_1}{D_1} = \frac{K}{q - Kq} \]  

By use of the definition for the width \( W_f(\tau) \)

\[ W_f^2(\tau) = \frac{\int_{-\epsilon}^{\epsilon} [\xi - E_f(\tau)]^2 \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi}{\int_{-\epsilon}^{\epsilon} \frac{\partial}{\partial \xi} f(\xi, \tau) d\xi} = \frac{N_2}{D_2} \]  

the interfacial width of the acid profile is found to be

\[ W = \frac{2 - 4K + k}{q^2(K - 1)^2}. \]
VITA

Kim Yvette Ward was born in Richmond, Virginia. She received the Bachelor of Science degree in Mathematics from Virginia Commonwealth University in August of 1990 and remained until the completion of the Master of Science degree in Mathematics in August of 1992.

In the fall of 1992, Ms. Ward enrolled in the Ph.D program in Computational and Applied Mathematics at Old Dominion University. She was awarded a Black American Doctoral Research Assistantship from 1992 to 1993 followed by receiving a State Graduate Deans’ Fellowship from 1993 to 1997. Currently, she is on the staff of The Department of Mathematics and Statistics at Old Dominion University.
