A CONTROL THEORETICAL ANALYSIS OF TUMOR INVASION

A Project Report

submitted by

SOHINI SARKAR

in partial fulfilment of the requirements

for the award of the degree of

BACHELOR OF TECHNOLOGY

DEPARTMENT OF ELECTRICAL ENGINEERING

INDIAN INSTITUTE OF TECHNOLOGY MADRAS.

May 2013

THESIS CERTIFICATE

This is to certify that the thesis titled **A Control Theoretical Analysis of Tumor Invasion**, submitted by **Sohini Sarkar**, to the Indian Institute of Technology, Madras, for the award of the degree of **Bachelor of Technology**, is a bona fide record of the research work done by her under our supervision. The contents of this thesis, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma.

Dr. Ramkrishna Pasumarthy
Research Guide
Assistant Professor
Dept. of Electrical Engineering
IIT-Madras, 600 036

Place: Chennai
Date: 20 May 2013

ACKNOWLEDGEMENTS

Acknowledgements are redundant as no amount of words could ever express your love and gratitude towards those who made you what you are today. But since an exclusive section has been provided to me in my thesis for the same, I will try my best to do justice to the act of thanking. First and foremost, a heartfelt thanks to my guide and an ultra cool professor, Dr Ramakrishna Pasumarthy for his unfailing guidance and involvement throughout my final year, be it my project or my MBA interviews. I would also like to thank Kruttika, Sai Krishna and Vijay for putting up with my untimely lab visits.

Now comes the list of those without whom my stay at IIT Madras would have just been like the ones which the beautiful deers in our campus live: eat, sleep and run for your life when danger (quizzes/end semester exams/deadlines in my case!) is chasing you at a neck breaking speed. I would like to thank Chandan Sruthi for being much more than just a ex-roommate; Meghana, Himaja, Pranitha and Sabah for being the best girlfriends I could ever ask for; Girish for the coffee table discussions on anything and everything under the sun except academics; Sarthak for being my go-to buddy; Rohan for the rudimentary philosophies on life; Vignesh for being the ideal awe inspiring senior, one which everyone wishes to have during their college days; Syed and Evelyn for being such sweet and doting juniors; Abraham, Ankit and Jobin for unassumingly helping me out with my CR responsibilities; Chitra, Meghana and Prakruthi for sharing my craze for DJ nights; and Abhinav, Anuja, Archith, Divya, Karthik, Madhavi, Nandita, Nitish, Saptarshi, Sidharth, Sireesha, Sivaramakrishnan, Soumya, Snigdha, Sujan, Sunaina among others for being there whenever I needed them. Add to this a bunch of IIT alunmi, namely, Josheph, Arjun and Surbhi for being such super amazing super seniors! I would also like to extend my gratitude towards Professor Mohan for showering me with so much love and care throughout my stay.

Last but not the least, I would like to thank my family for being the most wonderful insti-

tution of my life; Maa for being my unofficial teacher ever since I have started recoginising alphabets and numbers; Baba for being the inconspicous backbone in everything I do and Rishi for being such an awesome and irritating brother. As of now, there is no special person in my life. That probably has to wait till I find someone and write another acknowledgement during my postgraduate studies.

ABSTRACT

We analyse tumor invasion as a travelling wave solution to the set of state equations that govern the interaction of transformed and the normal cells. At first, we survey some mathematical models for the initial stages of tumour progression, mainly the phenomenological models for prevascular growth. After that, we present a detailed description of the simplest kind of reaction diffusion equations. Based on that, we finally look into the stability of the travelling wave solution and its implications on the key biological quantities appearing as key parameters in the model equations.

KEYWORDS: Mathematical Modeling, Lotka Volterra equations, Tumor host interaction

TABLE OF CONTENTS

CERTIFICATE i

ACKNOWLEDGEMENTS ii

ABSTRACT iv

TABLE OF CONTENTS v

LIST OF FIGURES vi

1 INTRODUCTION 1

1.1 Introduction to Tumor Modeling 1

1.2 Phenomenological Models 1

1.3 Lotka Volterra Equations 2

2 REACTION DIFFUSION EQUATIONS 5

2.1 Introduction 5

2.2 Fisher–Kolmogoroff Equation and Propagating Wave Solutions 5

2.3 Asymptotic Solution of the Fisher–Kolmogoroff Equation 9

3 ANALYSIS OF TUMOR INVASION 13

3.1 Introduction 13

3.2 Methods 13

3.3 Results and Discussion 15

LIST OF FIGURES

1.2.1 Comparison of the logistic, von bertalanyffy (with $\lambda = 2/3$ and $\mu = 1$) and Gompertz functions for tumour growth 3

1.3.1 Prey/Predator v/s Time and Phase plane plots of a conservative system . . . 4

1.3.2 Prey/Predator v/s Time and Phase plane plots of a dissipative system 4

2.2.1 Phase plane trajectories of the travelling wave solution 7

CHAPTER 1

INTRODUCTION

1.1 Introduction to Tumor Modeling

Cancer is a leading cause of cause of death worldwide, accounting for nearly 8 million deaths per year. Experts predict that deaths globally will continue rising, with an estimated 9 million people dying from cancer in 2015 and 11.4 million succumbing in 2030. Thus, cancer poses major public health questions. Cancer is a generic term for a large class of diseases that can affect any part of the body; malignant tumors and neoplasms are often used as synonyms. A characteristic feature of cancer is the rapid creation of abnormal cells growing beyond their usual boundaries and often invading adjoining parts of the body, spreading to other organs. In this chapter, I will investigate several mathematical models of tumor growth. I will also present a brief introduction to Lotka Volterra equations.

1.2 Phenomenological Models

An ideal model of tumor growth for a real world situation should satisfy several criteria:

1. The model should have a physiological basis;
2. The model should improve general understanding at microscopic as well as macroscopic level of tumor growth.
3. The model should have breadth, in the sense that it should be applicable to different patients or animals with the same type of tumor.

A tumour, at least in its early stages, has a sigmoid growth curve, first accelerating and then decelerating to an apparent limit. The logistic equation

$$\frac{dN}{dt} = rN(1 - \frac{N}{K}) \tag{1.2.1}$$

has been used a model for tumour growth. Here, N is the size of the tumour, usually measured as a number of cells or as a volume. $N(t) \to K$ in this model. Generalising this model, von Bertalanffy used the equation

$$\frac{dN}{dt} = f(N) = \alpha N^{\lambda} - \beta N^{\mu} \tag{1.2.2}$$

to represent tumour growth, where α, β, λ and μ are positive parameters with $\mu > \lambda$.

A particular case of von Bertalanffy equation is the surface rule model, which states that growth is proportional to surface area (since nutrients have to enter through the surface) and decay is proportional to size. Then for a tumor of constant shape we recover 1.2.2 with λ = $2/3$ and μ = 1.

Now define $a = \alpha - \beta$, $b = \beta(\mu - \lambda) = \beta(1 - \lambda)$. Then von Bertalanffy equation 1.2.2 becomes

$$\frac{dN}{dt} = aN^{\lambda} - bN^{\lambda}(\frac{N^{1-\lambda} - 1}{1 - \lambda}) \tag{1.2.3}$$

Now taking limit as $\lambda \to -1$, we obtain

$$\frac{dN}{dt} = aN - bNlogN = -bNlog\frac{N}{K} \tag{1.2.4}$$

where $K = exp(a/b)$. This is known as Gompertz equation.

1.3 Lotka Volterra Equations

The Lotka Volterra equations are first introduced by Volterra in 1931. Assuming that there is only one quadratic interaction between the different species, a general syatem that gives the population of n different species is given by the following set of n differential equations:

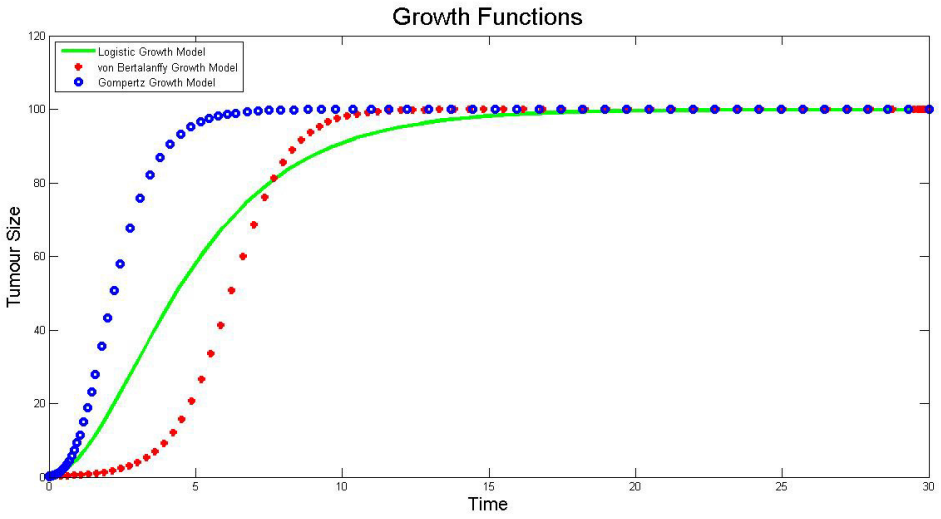

Figure 1.2.1: Comparison of the logistic, von bertalanyffy (with λ= $2/3$ and μ = 1) and Gompertz functions for tumour growth

$$\frac{x_j}{t} = \varepsilon_j x_j + \sum_{k=1}^{n} a_{jk} x_j x_k \text{ , } (j = 1, ...n). \tag{1.3.1}$$

In this mode, x_j is the number of individuals of species j, the ε_j's are the growth rates and the a_{jk}'s are the interaction coefficients of the species. We introduce the interaction matrix $A = (a_{jk})$, of which the elements are the interaction coefficients.

When we take as initial data for system 1.3.1 that all x_j's except for one (say for $j = 1$) are zero, we get the single species logistic growth model:

$$\frac{dx}{dt} = \varepsilon x - ax^2. \tag{1.3.2}$$

The dynamics of this model (for both ε and a positive) are well understood. For small x, the quadratic term is negligible and the population grows almost exponentially. However as it gets larger, the quadratic term becomes significant, limiting the growth and providing an upper bound $x = \frac{\varepsilon}{a}$.

The Lotka Voterra equations allow for interactions between several coexisting species and are much more realistic then the single-species logistic model. We can classify the various

systems by its interaction matrix A.

The main classes are

1. **cooperative** (resp. **competitive**) if $a_{jk} \geq 0$ (resp. $a \leq 0$) for all $j \neq k$,
2. **conservative** if there exists a diagonal matrix $D > 0$ such that AD is skew-symmetric,

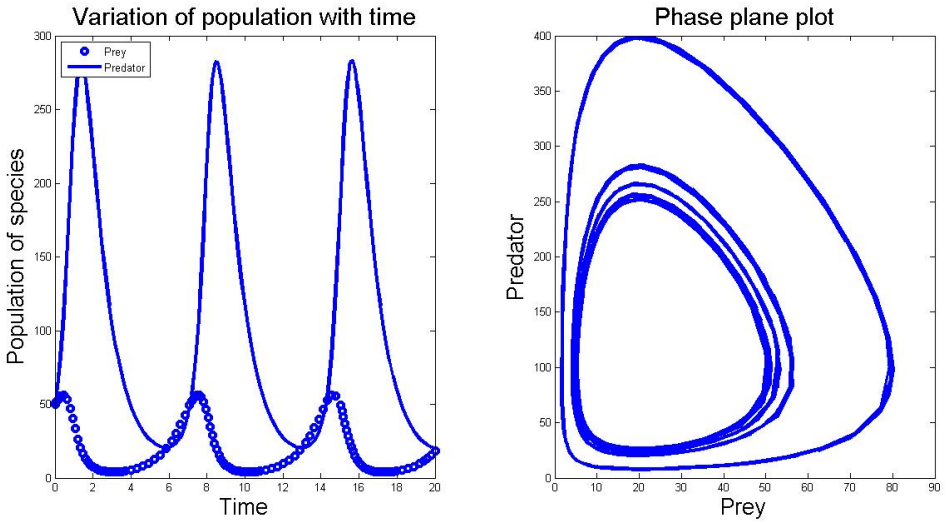

Figure 1.3.1: Prey/Predator v/s Time and Phase plane plots of a conservative system

3. **dissipative** if there exists a diagonal matrix $D > 0$ such that $AD \leq 0$.

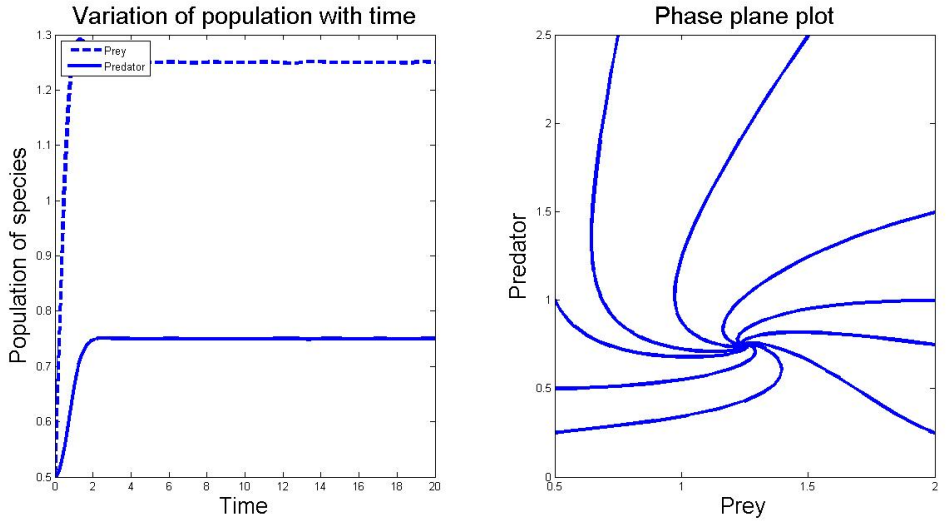

Figure 1.3.2: Prey/Predator v/s Time and Phase plane plots of a dissipative system

CHAPTER 2

REACTION DIFFUSION EQUATIONS

2.1 Introduction

The logistics equation is a first-order differential equation that is widely used to model the growth of a population as described above. The heat equation, a second order differential equation is used to describe the diffusion of heat over time. The combination of these two equations, logistics and diffusion, describes a reaction-diffusion which accounts for diffusion and growth. The Fisher Kolmogoroff equation has been analysed in detail in this chapter.

2.2 Fisher–Kolmogoroff Equation and Propagating Wave Solutions

The classic simplest case of a nonlinear reaction diffusion equation is

$$\frac{\partial n}{\partial t} = kn(1-n) + D\frac{\partial^2 n}{\partial x^2} \tag{2.2.1}$$

where $k$is a positive parameter and can be physically interpreted as the natural growth rate as well as the carrying capacity of n in the absence of t. Rescaling the variables,

$$t^* = kt \text{ , } x^* = x(\frac{k}{D})^{1/2} \tag{2.2.2}$$

we get the equation in the following form:

$$\frac{\partial n}{\partial t} = n(1-n) + \frac{\partial^2 n}{\partial x^2} \tag{2.2.3}$$

In the spatially homogeneous situation, the steady states are $n = 0$ and $n = 1$, which are respectively unstable and stable. This suggests that we should look for travelling wavefront solutions for which $0 \leq n \leq 1$; negative n has no physical meaning. If a travelling wave solution exists it can be written in the form

$$n(x,t) = N(z)\ ,\ z = x - ct \tag{2.2.4}$$

where c is the wavespeed.

Substituting this travelling waveform, $N(z)$ satisfies

$$N^{''} + cN^{'} + N(1\text{-}N) = 0, \tag{2.2.5}$$

where primes denote differentiation with respect to z. A typical wavefront solution is where N at one end, say, as $z \to -\infty$, is at one steady state and as $z \to \infty$ it is at the other. So here we have an eigenvalue problem to determine the value, or values, of c such that a nonnegative solution N exists which satisfies

$$lim_{z\to\infty} N(z) = 0\ ,\ lim_{z\to-\infty} N(z) = 1$$

Studying the above euqation for N in the (N, M) phase plane where

$$N^{'} = M\ ,\ M^{'} = -cM - N(1-N) \tag{2.2.6}$$

which gives the phase plane trajectories as solutions of

$$\frac{dM}{dN} = \frac{-cM - N(1-N)}{M} \tag{2.2.7}$$

This has two singular points for (N, M), namely, (0, 0) and (1,0). A linear stability analysis shows that the eigenvalues λ for the singular points are

$$(0,0) : \lambda\pm \;=\; \frac{1}{2}[-c \pm (c^2 - 4)^{\frac{1}{2}}] \;\Rightarrow\; \text{stable node if} c^2 > 4, \text{ stable spiral if } c^2 < 4$$

$$(1,0) : \lambda\pm \qquad = \qquad \frac{1}{2}[-c \quad \pm \quad (c^2 \quad + \quad 4)^{\frac{1}{2}}] \qquad \Rightarrow \qquad \text{saddlepoint.}$$

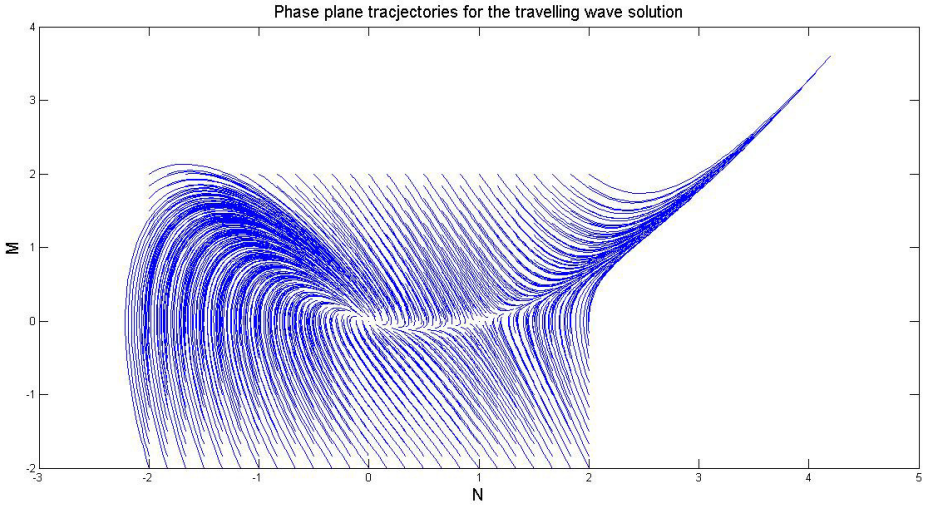

Figure 2.2.1: Phase plane trajectories of the travelling wave solution

In terms of the original dimensional equation, the range of wavespeeds satisfies

$$c \geq c_{min} = 2(kD)^{1/2}. \tag{2.2.8}$$

A key question at this stage is what kind of initial conditions $n(x, 0)$ for the original Fisher–Kolmogoroff equation will evolve to a travelling wave solution and, if such a solution exists, what is its wavespeed c.

If

$$n(x,0) = n_0(x) \geq 0 \text{ , } n_0(x) = 1 \text{ if } x \leq x_1 \text{ ; } n_0(x) = 0 \text{ if } x \geq x_2 \tag{2.2.9}$$

where $x_1 < x_2$ and $n_0(x)$ is continuous in $x_1 < x < x_2$, then the solution $n(x,t)$ evolves to a travelling wavefront solution $N(z)$ with $z = x - 2t$. That is, it evolves to the wave solution with minimum speed $c_{min} = 2$.

The dependence of the wavespeed c on the initial conditions at infinity can be seen easily from the following simple analysis. Consider first the leading edge of the evolving wave where, since$n$ is small, we can neglect n^2 in comparison with n. The above equation is linearised to

$$\frac{\partial n}{\partial t} = n + \frac{\partial^2 n}{\partial x^2} \tag{2.2.10}$$

Consider now

$$n(x,0) \sim Ae^{-ax} \text{ as } x \to \infty \tag{2.2.11}$$

where $a > 0$ and $A > 0$ is arbitrary and travelling wave solutions in the form

$$n(x,t) = Ae^{-a(x-ct)} \tag{2.2.12}$$

Substitution of the last expression into the linear equation gives the dispersion relation, that is, a relationship between c and a,

$$ca = 1 + a^2 \Rightarrow c = a + \frac{1}{a} \tag{2.2.13}$$

We see that $c_{min} = 2$ the value at $a = 1$. For all other values of $a(> 0)$ the wavespeed $c > 2$. For all other values of $a(> 0)$ the wavespeed $c > 2$.

Now consider min[e^{-ax}, e^{-x}] for x large and positive (since we are only dealing with the

range where $n^2 \ll n$). If

$$a < 1 \Rightarrow e^{-ax} > e^{-x}, \tag{2.2.14}$$

and so the velocity of propagation with asymptotic initial condition behaviour like 2.2.11 will depend on the leading edge of the wave, and the wavespeed c is given by 2.2.13. On the other hand, if $a > 1$ then e^{-ax} is bounded above by e^{-x} and the front with wavespeed $c = 2$. We are thus saying that if the initial conditions satisfy 2.2.11, then the asymptotic wavespeed of the travelling wave solution of is

$$c = a + \frac{1}{a}\ , 0 < a \leq 1\ , c = 2\ , a \geq 1. \tag{2.2.15}$$

The Fisher–Kolmogoroff equation is invariant under a change of sign of x, as mentioned before, so there is a wave solution of the form $n(x,t) = N(x + ct)\ , c > 0$, where now $N(-\infty) = 0\ , N(\infty) = 1$.

2.3 Asymptotic Solution of the Fisher–Kolmogoroff Equation

Travelling wavefront solutions $N(z)$ for satisfy the following equation:

$$N^{''} + cN^{'} + N(1 - N) = 0 \tag{2.3.1}$$

and monotonic solutions exist, with $N(-\infty) = 1$ and $N(\infty) = 0$, for all wavespeeds $c > 2$. The phase plane trajectories are the solutions of the following equation:

$$\frac{dM}{dN} = \frac{\text{-}cM\text{-}N(1\text{-}N)}{M} \tag{2.3.2}$$

There is a small parameter in the equations, namely, $\varepsilon = 1/c^2 \leqslant 0.25$, which suggests we look for asymptotic solutions for $0 < \varepsilon < 1$. Since the wave solutions are invariant to any shift in the origin of the coordinate system (the equation is unchanged if $z \rightarrow z$ + constant), let us take $z = 0$ to be the point where $N = 1/2$. We now use a standard singular perturbation technique. We use the following transformation in order to find the solution as a Taylor expansion in the small parameter ε:

$$N(z) = g(\xi)\ ,\ \xi = \frac{z}{c} = \varepsilon^{1/2} z. \tag{2.3.3}$$

With the above equation and the equation satisfying the solutions of $N(z)$, together with the boundary conditions on N, becomes

$$\varepsilon \frac{d^2 g}{d\xi^2} + \frac{dg}{d\xi} + g(1-g) = 0$$

$$g(\text{-}\infty) = 1\ ,\ g(\infty) = 0\ ,\ 0 < \varepsilon \leq \frac{1}{c_{min}^2} = 0.25, \tag{2.3.4}$$

and we further require $g(0) = 1/2$.

The equation for g as it stands looks like the standard singular perturbation problem since ε multiplies the highest derivative; that is, setting $\varepsilon = 0$ reduces the order of the equation and usually causes difficulties with the boundary conditions. Now, we look for solutions of the above equation as a regular perturbation series in ε; that is, let

$$g(\xi;\varepsilon) = g_0(\xi) + \varepsilon g_1(\xi) + ... \tag{2.3.5}$$

The boundary conditions at $\pm\infty$ and the choice of $N(0) = 1/2$, which requires $g(0;\varepsilon) = 1/2$ for all ε, gives the conditions on the $g_i(\xi)$ for $i = 0, 1, 2, ...$ as

$$g_0(-\infty) = 1\ ,\ g_0(\infty) = 0\ ,\ g_0(0) = 1/2\ ,\ g_i(\pm\infty) = 0\ ,\ g_i(0) = 0 \text{ for } i = 1, 2, .. \qquad (2.3.6)$$

On substituting 2.3.5 into 2.3.4 and equating powers of ε we get

$$O(1) : \frac{dg_0}{d\xi} = -g_0(1\text{-}g_0) \Rightarrow g_0(\xi) = \frac{1}{1+\varepsilon^{\xi}} \qquad (2.3.7)$$

$$O(\varepsilon) : \frac{dg_1}{d\xi} + (1 - 2g_0)g_1 = -\frac{d^2 g_0}{d\xi^2}$$

and so on, for higher orders in ε. The constant of integration in the g_0-equation was chosen so that $g_0(0) = 1/2$ as required by 2.3.6. Using the first of 2.3.7, the g_1-equation becomes

$$\frac{dg_1}{d\xi} - (\frac{g_0^{''}}{g_0^{'}})g_1 = -g_0^{''}, \qquad (2.3.8)$$

which on integration and using the conditions 2.3.6 gives

$$g_1 = -g_0^{'} ln\{4|g_0^{'}|] = \epsilon^{\xi}\frac{1}{(1+\varepsilon^{\xi})^2} ln[\frac{4\epsilon^{\xi}}{(1+\varepsilon^{\xi})^2}] \qquad (2.3.9)$$

In terms of the original variables N and z 2.3.3, the uniformly valid asymptotic solution for all z is given by 2.3.5- 2.3.9 as

$$N(z;\varepsilon) = (1+e^{z/c})^{-1} + \frac{1}{c^2}e^{z/c}(1+e^{z/c})^{-2} ln[\frac{4e^{z/c}}{(1+e^{z/c})^2}] + O(\frac{1}{c^4}), \qquad (2.3.10)$$

$$c \geq c_{min} = 2.$$

Let us now use the asymptotic solution 2.3.10 to investigate the relationship between the

steepness or slope of the wavefront solution and its speed of propagation. Since the gradient of the wavefront is everywhere negative a measure of the steepness, s say, of the wave is the magnitude of the maximum of the gradient $N^{'}(z)$, that is, the point where $N^{''} = 0$, namely, the point of inflexion of the wavefront solution. From 2.3.3 and 2.3.5, that is, where

$$g_0^{''}(\xi) + \varepsilon g_1^{''}(\xi) + O(\varepsilon^2) = 0 \tag{2.3.11}$$

which, from 2.3.7 and 2.3.9, gives $\xi = 0$;that is, $z = 0$. The gradient at $z = 0$, using 2.3.10, gives

$$-N^{'}(0) = s = \frac{1}{4c} + O(\frac{1}{c^5}) \,, \tag{2.3.12}$$

which only holds for $c \geqslant 2$. This results implies that the faster the wave moves, that is the larger the c, the less steep is the wavefront. The above result can be generalised to single-species population models where logistic growth is replaced by an appropriate $f(u)$, so that we get

$$\frac{\partial u}{\partial t} = f(u) + \frac{\partial^2 u}{\partial x^2} \tag{2.3.13}$$

where$f(u)$ has only two zeros, say u_1 and $u_2 > u_1$. If $f^{'}(u_1) > 0$ and $f^{'}(u_2) < 0$ then by a similar analysis to the above, wavefront solutions evolve with u going monotonically from u_1 to u_2 with wavespeeds

$$c \geq c_{min} = 2[f^{'}(u_1)]^{\frac{1}{2}} \tag{2.3.14}$$

CHAPTER 3

ANALYSIS OF TUMOR INVASION

3.1 Introduction

The tumor host interface of an invasive cancer is morphologically a traveling wave in which the tumor edge represents the wave front propagating into and replacing the surrounding normal tissue. Since observable, untreated cancers propagate into normal tissue, this mathematical system must also yield solutions in which the tumor state and the normal tissue state are stable in isolation but the latter is unstable in the presence of tumor and will therefore inevitably be invaded by tumor. In this chapter, I have attempted to develop a simple mathematical framework which focuses on the certain behavourial aspects of the tumor host interface, namely, the advance of the tumor tissue into the the surrounding host tissues, and the key biological parameters controlling this behaviour.

3.2 Methods

If we denote by $N(x,t)$ and $T(x,t)$ normal and tumor cell density, respectively, at time t and spatial position x, then the existence of a constant speed traveling wave indicates that the solution of the state equations must be written in the general form

$$N(x,t) = N(x \pm ct)\,, T(x,t) = T(x \pm ct), \tag{3.2.1}$$

where c is the wave speed. Such a solution is a constant profile traveling wave moving in the positive (with $-c$) or negative (with $+c$) x direction. The wave boundary is a transition region

from normal tissue to malignant tissue with the tumor front propagating into normal tissue at speed c.

In a mixture of populations competing for space and substrate, the governing system that will give rise to a traveling wave solution typically takes the form

$$\frac{\partial n}{\partial t} = f[n] + D\frac{\partial^2 n}{\partial x^2} \tag{3.2.2}$$

where n is the vector whose components represent the population densities, f is the non-linear population kinetics function, and D is a diagonal matrix of diffusion coefficients presumed to be greater than zero. The simplest conceptualization of the tumor-host interface is that derived from a population ecology picture in which populations of tumor cells and normal cells compete for the same spatial volume and nutritive substrate and interact with one another through a variety of potentially complex mechanisms. Each population initially grows according to a Malthusian growth law but is limited to some maximum carrying capacity, with the growth rates and carrying capacities possibly being different for each population.

It is reasonable to assume that a variety of interactions between the cellular populations have adverse effects on each population and can be included in lumped, phenomenological competition terms. The simplest and most widely used of these models is of the Lotka-Volterra type. For simplicity, we write the Lotka-Volterra with one dominant tumor population, T, interacting with one dominant native (normal) cell population, N:

$$\frac{\partial N}{\partial t} = r_N N(1 - \frac{N}{K_N} - \frac{b_{NT}T}{K_N}) + D_N\frac{\partial^2 N}{\partial x^2} \tag{3.2.3}$$

$$\frac{\partial T}{\partial t} = r_T T(1 - \frac{T}{K_T} - \frac{b_{TN}N}{K_T}) + D_T\frac{\partial^2 T}{\partial x^2} \tag{3.2.4}$$

where r_N and r_T are maximum growth rates of normal cells and tumor cells K_N and K_T denote the maximal normal and tumor cell densities; b_{NT} and b_{TN} are the lumped competition

terms; b_{TN} is a lumped, phenomenological term which includes a variety of host defenses including the immune response, and b_{NT} is the negative effects of tumor on normal tissue such as tumor-induced extracellular matrix breakdown and microenvironmental changes. D_N and D_T are cellular diffusion (i.e., migration or invasion) coefficients.

This system in equations 3.2.3 and 3.2.4 can exhibit solutions of the form in equation 3.2.1 in which one population can invade the other. The equilibrium fixed poitns for the system are

$$(0,0)\ ,\ (K_N,0)\ ,\ (0,K_T)\ ,\ (\frac{K_N - b_{NT}K_T}{1 - b_{NT}b_{TN}}, \frac{K_T - b_{TN}K_N}{1 - b_{NT}b_{TN}})$$

Linearinzing the system, we get

$$\begin{pmatrix} \frac{dN}{dt} \\ \frac{dT}{dt} \end{pmatrix} = \begin{pmatrix} r_N - \frac{2r_N N}{K_N} - \frac{r_N b_{NT} T}{K_N} & \frac{-r_N b_{NT} N}{K_N} \\ \frac{-r_T b_{TN} T}{K_T} & r_T - \frac{2r_T T}{K_T} - \frac{r_T b_{TN} N}{K_T} \end{pmatrix} \begin{pmatrix} N \\ T \end{pmatrix} \tag{3.2.5}$$

3.3 Results and Discussion

Specifically, the model yields the following final steady states:

1. $N = 0\ , T = 0$: The Jacobian is given by

$$A = \begin{pmatrix} r_N & 0 \\ 0 & r_T \end{pmatrix}$$

   Given that both r_N and r_T are maximum growth rates are mentioned earlier and are hence positive, since the eigenvalues are positive, this trivial solution is an unconditionally unstable state and hence is biologically irrelevant.

2. $N = K_N\ , T = 0$: this corresponds to normal, healthy tissue with no tumor cells present.

$$A = \begin{pmatrix} -r_N & -r_N b_{NT} \\ 0 & r_T - \frac{r_T b_{TN} K_N}{K_T} \end{pmatrix}$$

Regardless of the starting point, the system always evolves to this state if both $b_{TN}K_N/K_T >$ 1and $b_{NT}K_T/K_N < 1$. If the starting point is sufficiently close to $N = K_N$, $T = 0$ (as would occur in early tumor development), only the former condition need be satisfied.

3. $N = 0$, $T = K_T$: this corresponds to complete tumor invasion with total destruction of adjacent normal tissue.

$$A = \begin{pmatrix} r_N - \frac{r_N b_{NT} K_T}{K_N} & 0 \\ -r_T b_{TN} & -r_T \end{pmatrix}$$

Regardless of the starting point, the system always evolves to this state if both $b_{TN}K_N/K_T <$ 1 and $b_{NT}K_T/K_N > 1$. If the starting point is sufficiently close to $N = 0$, $T = KT$ (as would occur when tumor treatment is initiated), only the former condition need be satisfied.

4. $N = (K_N - b_{NT}K_T)/(1 - b_{NT}b_{TN})$, $T = (K_T - b_{TN}K_N)/(1 - b_{NT}b_{TN})$: this corresponds to tissue composed of tumor and normal cells, for example, desmoplastic tumor.

$$A = \begin{pmatrix} -r_N(\frac{-2K_N - K_T - b_{NT}K_T + b_{TN}K_N + b_{TN}b_{NT}K_N}{K_N(1-b_{NT}b_{TN})}) & \frac{-r_N b_{NT}(K_N - b_{NT}K_T)}{K_N(1-b_{NT}b_{TN})} \\ \frac{-r_T b_{TN}(K_T - b_{TN}K_N)}{K_T(1-b_{NT}b_{TN})} & -r_T(\frac{-2K_T - K_N - b_{TN}K_N + b_{NT}K_T + b_{TN}b_{NT}K_T}{K_T(1-b_{NT}b_{TN})}) \end{pmatrix}$$

The system evolves to this state if both $b_{NT}K_T/K_N < 1$ and $b_{TN}K_N/K_T < 1$. One limitation of this model is that if the carrying capacities K_N and K_T are limited only by available space, this state of coexistence is biologically unphysicai because it violates the spatial constraint sum-rule that $N/K_N + T/K_T \leq 1$.

(5.4) is the euqation governing the tumor edge advancing as a propagating wave into normal tissue and its speed is given by

$$c_{T\to N} \geq 2\sqrt{r_T D_T(1 - \frac{b_{TN}K_N}{K_T})} \tag{3.3.1}$$

Furthermore, making the biologically plausible assumption that carrying capacities for nor-

mal and tumor cells are not substantially different,the inequalities required for state 3 stability will hold only if b_{NT} is large, and b_{TN} is small, i.e., the presence of tumor has a significantly adverse effect on the normal cell population but not vice versa. The most obvious contribution to b_{NT} comes from the fact that tumor cells consume much more resources than do normal cells. Equation 3.3.1 is in the form of an inequality because the actual velocity is dynamically selected by the system based on the width of the tumor interface at the initial time, i.e., $T(x,t = 0)$.

Fully successful tumor therapy requires the system parameters be changed to yield steady state 2 instead of 3 or 4. This will essentially reverse the traveling wave so that normal tissue (which in this case becomes the stable steady state) will propagate into tumor (now the unstable steady state) causing the latter to completely regress. Assuming that tumor has already developed as a traveling wave, successful therapy will at minimum, require that

$$\frac{b_{TN}K_N}{K_T} > 1 \tag{3.3.2}$$

Ensuring the complete eradication of the tumor will require that the state $N = K_N, T = 0$ be globally stable so that, in addition to 3.3.2, the condition for state 2 global stability must be met as well

$$\frac{b_{TN}K_N}{K_T} < 1 \tag{3.3.3}$$

If conditions 3.3.2 and 3.3.3 are met, the normal tissue would recover at a speed given by

$$c_{N\to T} \geq 2\sqrt{r_N D_N(1 - \frac{b_{NT}K_T}{K_N})} \tag{3.3.4}$$

In considering successful therapeutic strategies, the above mathematical model of tumor-host interaction focuses attention on four critical parameters: b_{TN} and K_T, the competition term and carrying capacity of tumor, andb_{NT} and K_N, the competition term and carrying capacity of the normal tissue surrounding the tumor. The model explicitly demonstrates that any ther-

apy must be viewed in a context that includes measurements of effects on tumor and adjacent normal cells. Therapeutic strategies, therefore, should include the following:

1. Reduce K_T: A clear method for reducing the carrying capacity for the tumor population is decreasing vascularity which explains the recent interest in anti-angiogenic drugs. Two caveats, however, must be added. First, if the reduction in angiogenesis also affects normal tissue, then the therapy may also reduce K_N and the inequalities in equation 3.3.2 or 3.3.3 may not be satisfied. Second, if $b_{NT} \ll 1$, then a several-fold reduction in K_T may be insufficient to suitably alter the stability of the steady states.

2. Reduce b_{NT} and increase b_{TN}: This demonstrates the need for experimental data that quantifies the relative contribution of various mechanisms to the lumped competition term b_{NT}. Similar quantification of components of b_{TN} (e.g., immunological response) is also required. If we can estimate the value of b_{NT}, both the identification of potential therapeutic approaches and quantifications of their expected effect on the propagating wave of tumor invasion can be obtained.

3. Increase K_N: This is tumor therapy directed explicitly towards normal cells. The maximum density of normal cells is ordinarily dependent on cell-cell interactions rather than substrate limitation. The mathematical model predicts that therapy that decreases contact inhibition in normal cells by increasing K_N could reverse the inequality in 3.3.1, possibly resulting in tumor regression.

References

1. Robert A. Gatenby and Edward T. Gawlinski, A Reaction-Diffusion Model of Cancer Invasion, *Cancer Res* **56**, 5745-5753 (1996).

2. A. Reardon and A. Novikov, Front propagation in reaction- diffusion equations.

3. Xu-Yan Chen, Dynamics of interfaces in reaction diffusion system, *Hiroshima Math. J.* **21** 47-83 (1991).

4. W. van Saarloos, Front propagation into unstable states: Marginal stability as a dynamical mechanism for velocity selection, *Physical Review Letters* **A37**, 211-229 (1988).

5. Nicholas F. Britton, Essential Mathematical Biology, First Edition, Springer, Berlin, (2003).