

ANALYSIS OF SOLID TUMOR GROWTH MODELS:
MECHANISMS OF VOLUME LOSS AND SLOWED
GROWTH RATE

by

Lacey Huebel

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Approved by:

Co-Major Professor
Dr. Ivan Blank

Co-Major Professor
Dr. Marianne Kortzen

Abstract

Studies on the mathematical modeling of solid, avascular tumor growth have been prevalent since the 1960s, with pioneers such as Greenspan and Hill. As experimental studies have improved, the mathematical models have evolved in order to remain relevant. One important issue in modeling tumor growth is the assumed method of volume loss within the tumor. McElwain and Morris constructed one of the first models considering apoptosis as a mechanism of volume loss, and an analysis of their work is presented. Another important issue in modeling tumor growth is the cause behind slowed growth rates of tumors as they develop. John Adam proposes that the cause is chalone production, and an analysis of this work is also presented.

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Chapter 1

Introduction

Attempts to extend an individual's life beyond the onset of tumors is nothing new; in fact, surgeries to remove tumors were described in a work by physician Aetius of Amida (593 A.D.) [2]. There is now a great body of work dedicated towards understanding the development and growth of tumors. As with most studies of population dynamics, mathematical modeling can provide great insight into the dynamics of tumor growth.

The models that form the focus of this paper are tumor-level analyses (as opposed to cellular-level analyses) of avascular tumors. An avascular tumor is one that does not yet have blood vessels, and so the only method for the transportation of nutrients throughout the tumor is diffusion. As a result, at some point the cells in the center of the tumor will not have enough nutrient to survive and will die off.

The different models of tumor growth consider between 1 and 4 phases of development. In phase I the tumor is small enough that the process of diffusion can provide enough nutrient throughout the entire tumor. Thus, all of the cells within the tumor are proliferating at their normal rate. Some models focus their attention on tumors at this stage of development alone. If the tumor grows larger, then the cells in the center begin to experience a reduced rate of mitosis, or cell division. A tumor with two regions is said to be in phase II. Again, there are some models that only consider tumors in phase I and II, or even just phase II [1] [5]. Finally, the tumor grows so large that the cells in the center do not have enough nutrient to survive. These cells then die off by necrosis - a type of cell death that is caused by stressors in the environment. The result is the development of a necrotic core inside of the previously discussed region of cells experiencing slowed growth. The necrotic core consists of dead-cell material. This tumor with three regions is said to be in phase III. Some models go on to describe a fourth phase, in which another middle region of slowed growth develops.

One interesting issue that presents itself is the cause of slowed growth in phase II. The cells are otherwise healthy, but they do not reproduce at their normal rates. Some attribute this fact to a byproduct of necrosis, while others assume that the cause has to do with nutrient levels. Still others believe that tissue-specific mitotic inhibitors, or "chalcones," cause this drop in mitosis. Chalcones are produced by the tissue, and they control the growth of the tissue by slowing mitosis.

Another interesting issue is that tumors are able to reach steady states while proliferation continues, implying that some mechanism of volume loss must occur if the model does not consider chalone production. Some authors assume that the cause of volume loss is the disintegration of necrotic debris that is then able to "flow" out of the tumor. Others attribute the volume loss to a different method of cell death: apoptosis. Apoptosis is a method of cell death in which a cell is "tasked to die" in a productive manner for the greater good of its environment.

Two of the pioneers of mathematically modeling the growth of tumors are Hill and Greenspan, who began this work in the 1960s and 1970s. Both authors, especially Greenspan, are still frequently cited today. Greenspan assumed that the cause of volume loss and slowed growth rates amongst otherwise healthy cells was a byproduct of necrosis [7]. Following Greenspan's work, but citing experimental evidence that tumors can reach steady-states before the onset of necrosis, McElwain and Morris proposed a model that assumes that apoptosis is the cause of volume loss within the tumor [8]. Chapter 2 is an analysis of this model. Focusing on the cause of slowed rates of mitosis in otherwise healthy cells, Adam (following Glass' lead) proposed that chalone production within the tumor caused these depressed mitosis rates [1]. Chapter 3 is an analysis of this model.

Chapter 2

Apoptosis and Tumor Growth; McElwain and Morris

McElwain and Morris derived mathematical models describing tumor growth for three phases of tumor development. The feature that distinguishes this model from its predecessors (including Greenspan's model) is the assumption that volume loss is due to the process of apoptosis. Apoptosis, or "programmed cell death," is a method of cell death in which a healthy cell is made to die in a manner that benefits the cell's environment. The alternative method of cell death is necrosis, which occurs due to some type of stress. A brief description of apoptosis and necrosis appears in section 2.1. In McElwain and Morris' model, the rate of volume loss due to apoptosis is considered to be uniform throughout the tumor. Also, for simplicity the authors assume radial symmetry.

In phase I, all cells within the tumor are able to receive the amount of nutrient requisite for normal proliferation and nutrient consumption, and the tumor grows at an exponential rate. At some point, the nutrient level at the center of the tumor drops to the level $\hat{\sigma}$ and the cells are no longer able to continue at their normal pace. The tumor is now in phase II, with the cells in the outer region enjoying enough nutrients to continue mitosis as usual, and the cells in the inner region undergoing slowed rates of growth and consumption. In this stage, of course, the tumor itself experiences a decreased growth rate due to the slower level of mitosis within its interior. Finally, the center of the tumor finds nutrient levels dropping to the level σ_i , which induces necrosis and the tumor is now in phase III. At this point, the tumor develops a region of dead cells at its center.

McElwain and Morris found that a steady state can be obtained in either phase II or phase III using their model. This result is in line with empirical evidence. In this steady state, volume gained through cell proliferation is offset by volume lost due to apoptosis. Another point made by McElwain and Morris is that cells tend to move toward the center of the tumor [8]. One likely cause of this motion is competition for nutrient amongst the cells [2]. The main impetus behind this competition is that the regions of the tumor have sizes that are fixed by the amount of nutrient that is present. The outer regions of the tumor also have higher proliferation rates, and therefore have more cells competing for space in a fixed region.

Mathematically, the preceding points can be expressed as follows: nutrient consumption and cell proliferation rates are constant multiples of the function

$$f(\sigma) = \begin{cases} 1 & \hat{\sigma} \leq \sigma \\ \frac{\sigma}{\hat{\sigma}} & \sigma_i < \sigma \leq \hat{\sigma} , \\ 0 & \sigma \leq \sigma_i \end{cases} \quad (2.1)$$

giving the requisite normal growth preceding depressed growth, which in turn precedes cell death. Let $Af(\sigma)$ represent the nutrient consumption and let $sf(\sigma)$ represent the proliferation rate.

What follows in this chapter are the derivations of the equations and solutions of these equations that are presented in McElwain and Morris' article. Section 2.1 gives a brief overview of apoptosis. In section 2.2 we solve the ordinary differential equations that underly the work of McElwain and Morris. Sections 2.3, 2.4, and 2.5 present derivations of the explicit solutions describing the radial growth of the tumor and the boundaries of the relevant regions in phases I, II, and III respectively. Section (2.6) is a presentation of a steady state analysis of the tumor in phases II and III. Note that all terms are dimensionless and the systems are expressed using spherical coordinates. The notation used by McElwain and Morris is listed in the appendix.

2.1 Overview of Apoptosis and Tumor Growth

In order to effectively model tumor growth, it is important to consider the mechanism of volume loss. Empirically, It is possible for a tumor containing proliferating cells to reach a steady state, and there are different explanations for the implied volume loss. The different methods of volume loss necessarily accompany different governing equations behind the models of tumor growth.

There are two different ways for cells to die: necrosis and apoptosis. Patton and Wilson [9] provide a good description of the differences between the two types of cell deaths. Necrosis, or "cell murder," is a process that is initiated through some sort of stress on the cell and typically effects a large group of cells at once. Each cell within the group disintegrates randomly and leaks cellular material. Patton and Wilson go on to explain that apoptosis is more like "cell suicide." It effects individual cells and can be initiated by the cell itself, other cells, or the surrounding tissue. When a cell dies by apoptosis, the cell shrinks and the cytoplasmic organelles condense. This produces a higher proportion of membrane to cellular matter and as a result, the cell breaks apart into membrane-bound apoptic bodies. These bodies are then consumed through the process of phagocytosis - in which the apoptic bodies are taken into the cell membrane, melded with compartments called phagosomes, and then this duo is broken down and released. According to Patton and Wilson, there are three different situations in which a cell might die by apoptosis. The first of these situations, initiated by surrounding cells or tissue, is when a perfectly healthy cell dies for the greater good

of the surrounding environment. One example of this situation is that a fetus initially has webbed fingers and toes, but at some point the cells forming the webbing die off by apoptosis. The second situation is that apoptosis might be initiated because a cell is old and worn out, and in this case it is currently unclear who initiates apoptosis. The third cause behind apoptosis, likely initiated by the cell itself, is due to a cell being defective. In this way, a defective cell has a way to help its environment by ridding its surroundings of itself in an orderly fashion.

The programmed death of defective cells brings up an important issue, in that cancerous cells are still able to persist with apoptosis, a control mechanism, in place. The hypothesized explanation, given in Sluyser's article, is that the process by which cells change into cancerous cells involves gene mutation, and this gene mutation blocks the normal process of apoptosis [11]. This allows the cancerous cells to form a tumor that is not subject to apoptosis from the surrounding cells and tissue. Of course, the tumor is now a microenvironment for its cells. Thus, apoptosis is believed to be initiated from within the tumor for its own cells [10]. In other words, apoptosis now occurs for the greater good of the tumor instead of the greater good of the surrounding body. It is actually still difficult to determine with certainty a cell's particular method of death during experiments, but some of the aforementioned distinguishing traits of apoptosis are observable [9].

The two different methods of cell death accompany two different models of tumor growth. If necrosis is assumed to be the cause of volume loss within the tumor, volume loss only occurs within the necrotic region (once it is formed) and actually occurs as a byproduct of cell death. If apoptosis is assumed to be the cause of volume loss, the volume loss will occur throughout the entire tumor, and the loss accompanies the death of the cell. Some models attribute a tumor's volume loss to a byproduct of necrosis and others assume that apoptosis is the cause. It is likely that the actual cause of volume loss is a combination of several methods, including the two aforementioned methods. For simplicity, most models only consider one method of volume loss. In his model, Greenspan assumes that volume loss is due to the disintegration of necrotic materials [7]. This assumption, however, is not necessarily in line with experimental observations. According to Araujo and McElwain's article "A History of the Study of Solid Tumor Growth..." [2], experiments conducted by Sutherland and Durand in 1973 revealed that a tumor can reach a steady state in phase II - before the onset of a necrotic core. This could not happen under the assumption that a tumor's sole method of volume loss occurs as a byproduct of necrosis.

With this experiment in mind, McElwain and Morris provided one of the first mathematical models that assume that apoptosis is the mechanism of volume loss (2). With this assumption that the cause of volume loss is apoptosis (as opposed to necrosis), the model "include[s] a constant cell loss rate in the entire viable region" [2]. In this model, both necrosis and apoptosis are still assumed to occur.

2.2 Solutions for the Main Differential Equations

In this section we tackle the strictly mathematical task of deriving the solutions to the differential equations $\frac{k}{r^2} \frac{d}{dr} \left[r^2 \frac{d\sigma}{dr} \right] = A$ and $\frac{k}{r^2} \frac{d}{dr} \left[r^2 \frac{d\sigma}{dr} \right] = \frac{A\sigma}{\hat{\sigma}}$. These solutions will be essential to us in sections 2.4 and 2.5.

We now solve the first differential equation,

$$\frac{k}{r^2} \frac{d}{dr} \left[r^2 \frac{d\sigma}{dr} \right] = A. \quad (2.2)$$

Notice that in order to get the constant on the right-hand side of the equation (as desired), $\sigma(r)$ must have the form

$$c_1 + c_2 r^{-1} + c_3 r^2.$$

The inhomogenous term can be determined as follows:

$$\begin{aligned} A &= \frac{k}{r^2} \frac{d}{dr} \left[r^2 \frac{d}{dr} (c_1 + c_2 r^{-1} + c_3 r^2) \right] \\ &= \frac{k}{r^2} \frac{d}{dr} [2r^3 c_3 - c_2] \\ &= 6k c_3. \end{aligned}$$

Therefore, $c_3 = \frac{A}{6k}$. Hence, the solution for (2.2) has the general form

$$\Upsilon = c_1 + c_2 r^{-1} + \frac{Ar^2}{6k}. \quad (2.3)$$

Now we turn to the second differential equation, which can be re-written as follows:

$$\begin{aligned} \frac{A\sigma}{\hat{\sigma}} &= \frac{k}{r^2} \frac{d}{dr} \left[r^2 \frac{d\sigma}{dr} \right] = \frac{k}{r^2} \left[2r \frac{d\sigma}{dr} + r^2 \frac{d^2\sigma}{dr^2} \right] \\ 0 &= \frac{d^2\sigma}{dr^2} + \frac{2}{r} \frac{d\sigma}{dr} - \frac{A}{k\hat{\sigma}} \sigma. \end{aligned}$$

Note that $r = 0$ is a regular singular point. Thus, the Method of Frobenius can be used to solve

$$\frac{d^2\sigma}{dr^2} + \frac{2}{r} \frac{d\sigma}{dr} - \frac{A}{k\hat{\sigma}} \sigma = 0 \quad (2.4)$$

near $r=0$.

The indicial equation is $s(s-1) + 2s + 0 = 0$, or $s^2 + s = 0$, which has roots $s = 0$ and $s = -1$. These roots differ by an integer and they need to be considered independently.

Case 1: $s = 0$

In this case, let $\sigma_1(r) := r^0 \sum_{n=0}^{\infty} a_n r^n = \sum_{n=0}^{\infty} a_n r^n$.

Then $\frac{d\sigma_1}{dr} = \sum_{n=0}^{\infty} n a_n r^{n-1}$ and $\frac{d^2\sigma_1}{dr^2} = \sum_{n=0}^{\infty} n(n-1) a_n r^{n-2}$.

These can be substituted into the differential equation (2.4) for the first first step in the following derivation:

$$\begin{aligned}
0 &= \sum_{n=0}^{\infty} n(n-1) a_n r^n + 2 \sum_{n=0}^{\infty} n a_n r^n + \left(\frac{-A}{k\hat{\sigma}} \right) \sum_{n=0}^{\infty} a_n r^{n+2} \\
&= \sum_{n=0}^{\infty} n(n+1) a_n r^n + \left(\frac{-A}{k\hat{\sigma}} \right) \sum_{n=0}^{\infty} a_n r^{n+2} \\
&= \sum_{j=-2}^{\infty} (j+2)(j+3) a_{j+2} r^{j+2} + \left(\frac{-A}{k\hat{\sigma}} \right) \sum_{j=0}^{\infty} a_j r^{j+2} \\
&= 0a_0 r^0 + 2a_1 r^1 + \sum_{j=0}^{\infty} \left[(j+2)(j+3) a_{j+2} + \left(\frac{-A}{k\hat{\sigma}} \right) a_j \right] r^{j+2}.
\end{aligned}$$

Thus, a_0 is arbitrary, $a_1 = 0$, and for all $j \geq 0$, $a_{j+2} = \frac{A}{\hat{\sigma}k} \frac{a_j}{(j+2)(j+3)}$. This recursive definition and the fact that $a_1 = 0$, lead to the fact that all odd terms in the series will be zero. Now to find the solution σ_1 using the remaining (even) terms. Since a_0 can be any real number, suppose $a_0 = 1$. The indexed constants can now be expressed as follows:

$$\begin{aligned}
a_0 &= 1 \\
a_2 &= \frac{A}{\hat{\sigma}k \cdot 3 \cdot 2} \\
a_4 &= \frac{A}{\hat{\sigma}k \cdot 3 \cdot 2} \cdot \frac{A}{\hat{\sigma}k \cdot 4 \cdot 5} \\
&\vdots \\
a_{2j} &= \left(\frac{A}{\hat{\sigma}k} \right)^j \left(\frac{1}{(2j+1)!} \right).
\end{aligned}$$

These constants can be substituted into the definition $\sigma_1(r) = \sum_{n=0}^{\infty} a_n r^n$ to get

$$\begin{aligned}
\sigma_1(r) &= \sum_{j=0}^{\infty} \frac{\left(\frac{A}{\hat{\sigma}k}\right)^j}{(2j+1)!} r^{2j} \\
&= \sqrt{\frac{k\hat{\sigma}}{A}} \frac{1}{r} \sum_{j=0}^{\infty} \frac{\left(r\sqrt{\frac{A}{k\hat{\sigma}}}\right)^{2j+1}}{(2j+1)!} \\
&= \frac{\sinh\left(r\sqrt{\frac{A}{k\hat{\sigma}}}\right)}{r\sqrt{\frac{A}{k\hat{\sigma}}}} \\
&= \frac{\sinh(Br)}{Br},
\end{aligned}$$

with $B := \sqrt{\frac{A}{k\hat{\sigma}}}$.

Case 2: $s = -1$

In this case, let $\sigma_2(r) := r^{-1} \sum_{n=0}^{\infty} a_n r^n = \sum_{n=0}^{\infty} a_n r^{n-1}$.

Then $\frac{d\sigma_1}{dr} = \sum_{n=0}^{\infty} (n-1)a_n r^{n-2}$ and $\frac{d^2\sigma_1}{dr^2} = \sum_{n=0}^{\infty} (n-1)(n-2)a_n r^{n-3}$.

Once these are substituted into the differential equation, we get the first equality in the following derivation:

$$\begin{aligned}
0 &= \sum_{n=0}^{\infty} (n-1)(n-2)a_n r^{n-1} + 2 \sum_{n=0}^{\infty} (n-1)a_n r^{n-1} + \left(\frac{-A}{k\hat{\sigma}}\right) \sum_{n=0}^{\infty} a_n r^{n+1} \\
&= \sum_{n=0}^{\infty} n(n-1)a_n r^{n-1} + \left(\frac{-A}{k\hat{\sigma}}\right) \sum_{n=0}^{\infty} a_n r^{n+1} \\
&= \sum_{j=-2}^{\infty} (j+2)(j+1)a_{j+2} r^{j+1} + \left(\frac{-A}{k\hat{\sigma}}\right) \sum_{j=0}^{\infty} a_j r^{j+1} \\
&= 0a_0r^0 + 0a_1r^1 + \sum_{j=0}^{\infty} \left[(j+2)(j+1)a_{j+2} + \left(\frac{-A}{k\hat{\sigma}}\right) a_j \right] r^{j+1}.
\end{aligned}$$

Thus, a_0 and a_1 are arbitrary and for all $j \geq 0$, $a_{j+2} = \frac{A}{\hat{\sigma}k} \frac{a_j}{(j+2)(j+1)}$. First, if a_0 is taken to be zero and a_1 is taken to be 1, the result is the same sum from Case 1 and thus the result is $\sigma_1(r) = \frac{c_1 \sinh(Br)}{r}$. On the other hand, if a_1 is taken to be

zero and a_0 is taken to be 1, the result is $\sigma_2(r) = \frac{c_2 \cosh(Br)}{r}$.

Hence, the two linearly independent solutions to (2.4) are

$$\sigma_1(r) = \frac{\sinh(Br)}{r}$$

and

$$\sigma_2(r) = \frac{\cosh(Br)}{r},$$

and hence the general solution of the differential equation (2.4) is

$$\Theta(r) = c_1 \sigma_1(r) + c_2 \sigma_2(r). \quad (2.5)$$

Note that $\sigma_2(r)$ is unbounded at $r = 0$. Now the stage has been set for the derivations of the equations governing tumor growth in the three different phases from ([8]).

2.3 Phase I

In this phase, the tumor is completely comprised of living, proliferating cells. Some cells do die off due to apoptosis, and the rate of volume loss per unit volume is denoted by λ . The cellular proliferation rate is called s .

Using (2.1), the model for the diffusion in Phase I is

$$\frac{k}{r^2} \frac{d}{dr} \left(r^2 \frac{d\sigma}{dr} \right) = A, \quad 0 \leq r \leq R_0. \quad (2.6)$$

Figure 2.1 provides a diagram of the tumor in phase I.

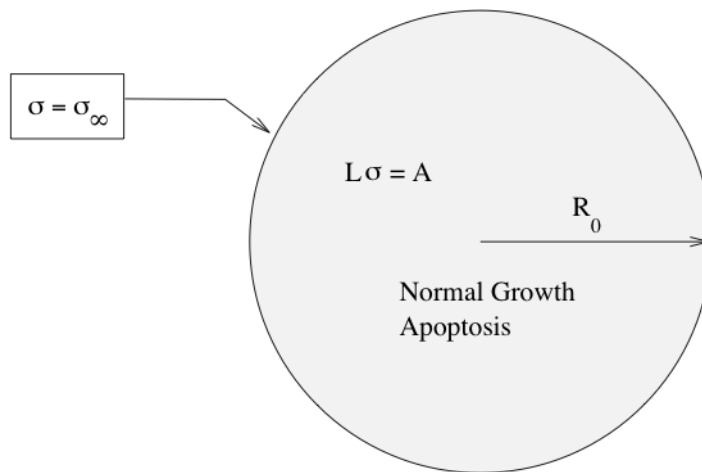


Figure 2.1: Diagram of tumor in phase I, where $L\sigma := \frac{k}{r^2} \frac{d}{dr} \left(r^2 \frac{d\sigma}{dr} \right)$

The differential equation (2.6) was solved in section 2.2 as equation (2.3), where it was determined that the general solution has the form

$$\Upsilon = c_1 + c_2 r^{-1} + \frac{Ar^2}{6k}.$$

Since $r = 0$ is part of the current purview and $\sigma(r)$ must be bounded at $r = 0$, we find $c_2 = 0$.

Now, let R_0 represent the outer radius of the tumor. Also, assume a constant nutrient concentration σ_∞ on the boundary of the tumor. Then it follows that $c_1 = \sigma_\infty - \frac{A}{6k}R_0^2$. The net result is the following equation for $\sigma(r)$ during phase I (equation (3) from McElwain and Morris' work):

$$\sigma(r) = \sigma_\infty - \frac{A}{6k}(R_0^2 - r^2). \quad (2.7)$$

Next we formulate an equation for the radius of the tumor during phase I. From the definitions of s and λ (the growth rate and death rate per unit volume respectively), it is clear that $\frac{dV}{dt} = (s - \lambda)V$. This can also be expressed as

$$\frac{4\pi}{3} \frac{dR_0^3}{dt} = s \frac{4\pi}{3} R_0^3 - \lambda \frac{4\pi}{3} R_0^3. \quad (2.8)$$

Using the equation $\frac{dV}{dt} = (s - \lambda)V$, we must have $V = ce^{s-\lambda t}$, and therefore

$$\frac{4\pi}{3} R_0^3 = ce^{s-\lambda t}.$$

Hence,

$$\begin{aligned} R_0 &= \tilde{C} e^{\frac{1}{3}(s-\lambda)t} \\ &= \tilde{C} e^{\frac{1}{3}(1-\gamma)\tau}, \end{aligned}$$

where $\tilde{C} = R_0(0)$, $\gamma := \frac{\lambda}{s}$, and $\tau := st$. Thus, for $\xi := BR_0$,

$$\xi(\tau) = \xi(0) e^{\frac{1}{3}(1-\gamma)\tau}, \quad (2.9)$$

which gives us the equation for the outer radius of the tumor.

It is now possible to determine the radius at which the tumor will proceed into phase II. By definition, the tumor will make the switch once the nutrient level in the center of the tumor drops to $\sigma = \hat{\sigma}$ and a region of slow growth necessarily develops. Mathematically speaking, the tumor will remain in phase I until $\sigma(0) = \hat{\sigma}$. McElwain and Morris label the scaled radius at this point as ξ_s , and use equation (2.7) to determine:

$$\begin{aligned}\hat{\sigma} &= \sigma_\infty - \frac{A}{6k} (R_0^2 - 0^2) \\ \frac{A}{6k} R_0^2 &= 6(\sigma_\infty - \hat{\sigma}) \\ (BR_0)^2 &= 6\left(\frac{\sigma_\infty}{\hat{\sigma}} - 1\right).\end{aligned}$$

This leads to equation (5) from McElwain and Morris' article; that at the point when a tumor moves from phase I into phase II the scaled outer radius of the tumor is

$$\xi_s = \sqrt{6\left(\frac{\sigma_\infty}{\hat{\sigma}} - 1\right)}. \quad (2.10)$$

This completes the analysis of Phase I. Equation (2.7) represents the nutrient concentration at a given radius within the tumor and equation (2.9) describes the evolution of the scaled outer radius of the tumor with respect to time. Equation (2.10) gives the critical outer radius of the tumor; i.e., the radius at which the tumor transitions into Phase II.

2.4 Phase II

In this phase, the tumor has now developed a region of slow growth in its core due to lack of nutrient. From equation (2.1), the nutrient diffusion can be expressed as

$$\frac{k}{r^2} \frac{d}{dr} \left[r^2 \frac{d\sigma}{dr} \right] = \begin{cases} \frac{A\sigma}{\hat{\sigma}}, & 0 \leq r \leq \hat{R} \\ A, & \hat{R} \leq r \leq R_0 \end{cases}. \quad (2.11)$$

Figure 2.2 is a diagram of a tumor in phase II.

Note that both differential equations in equation 2.11 were solved in section 2.2. Using the results in equations (2.5) and (2.3), we have the following general form for $\sigma(r)$:

$$\sigma(r) = \begin{cases} c_1 \frac{\sinh(Br)}{r} + c_2 \frac{\cosh(Br)}{r}, & 0 \leq r \leq \hat{R} \\ c_3 r^{-1} + c_4 + \frac{A}{6k} r^2, & \hat{R} \leq r \leq R_0. \end{cases}. \quad (2.12)$$

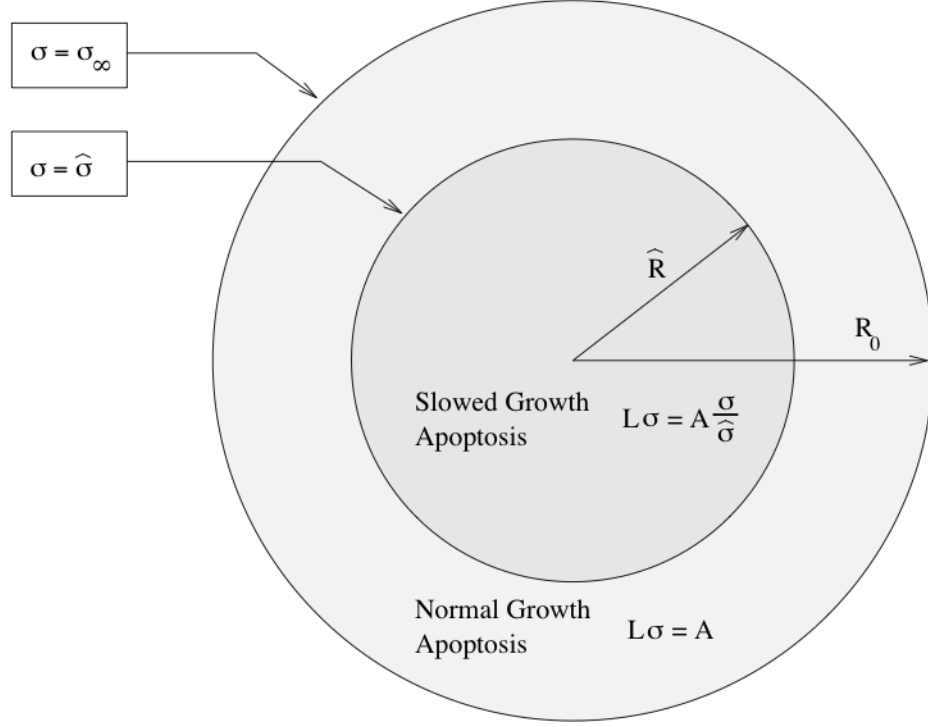


Figure 2.2: Diagram of tumor in phase II, where $L\sigma := \frac{k}{r^2} \frac{d}{dr} \left(r^2 \frac{d\sigma}{dr} \right)$

2.4.1 Nutrient Level on Region of Slowed Growth

First, suppose $0 \leq r \leq \hat{R}$. From equation (2.12), we have the general form of the solution

$$\Theta = \frac{c_1 \sinh(Br)}{r} + \frac{c_2 \cosh(Br)}{r}.$$

In this case, the domain of interest includes $r = 0$. As $\frac{\cosh(Br)}{r}$ is unbounded at this point, in the current situation it must be true that $c_2 = 0$. Thus,

$$\Theta(r) = \frac{c_1 \sinh(Br)}{r}.$$

The constant c_1 can be determined using the boundary condition $\sigma(\hat{R}) = \hat{\sigma}$, and it is clear by inspection that $c_1 = \frac{\hat{\sigma} \hat{R}}{\sinh(B\hat{R})}$. Thus, sigma can be expressed as

$$\sigma(r) = \hat{\sigma} \frac{\hat{R} \sinh(Br)}{r \sinh(B\hat{R})}, \quad 0 \leq r \leq \hat{R} \quad (2.13)$$

in the region of decreased growth.

2.4.2 Nutrient Level on Region of Normal Growth

Now we turn to the formula for σ in the region of normal growth. Namely, we suppose $\hat{R} \leq r \leq R_0$, and the boundary conditions for $\sigma(r)$ (by definition) are $\sigma(R_0) = \sigma_\infty$ and $\sigma(\hat{R}) = \hat{\sigma}$. From equation (2.12), we see that $\sigma(r)$ has the form $c_3 r^{-1} + c_4 + \frac{A}{6k} r^2$. Now, using $\sigma(\hat{R}) = \hat{\sigma}$ along with this general solution for σ yields

$$\hat{\sigma} = \sigma(\hat{R}) = \frac{A}{6k} \hat{R}^2 + \frac{c_3}{\hat{R}} + c_4.$$

This implies that

$$c_4 = \hat{\sigma} - \frac{A}{6k} \hat{R}^2 - \frac{c_3}{\hat{R}}.$$

Next, using $\sigma(R_0) = \sigma_\infty$, we see that

$$\sigma_\infty = \sigma(R_0) = \frac{A}{6k} R_0^2 + \frac{c_3}{R_0} + c_4,$$

and therefore

$$c_4 = \sigma_\infty - \frac{A}{6k} R_0^2 - \frac{c_3}{R_0}.$$

Setting the two different equations for c_4 equal to one another provides

$$\begin{aligned} \sigma_\infty &= \hat{\sigma} - \frac{A}{6k} \hat{R}^2 - \frac{c_3}{\hat{R}} + \frac{A}{6k} R_0^2 + \frac{c_3}{R_0} \\ \Rightarrow c_3 &= \left(\frac{R_0 \hat{R}}{\hat{R} - R_0} \right) \left(\sigma_\infty - \hat{\sigma} + \frac{A}{6k} (\hat{R}^2 - R_0^2) \right), \end{aligned}$$

and hence, σ can now be expressed as

$$\sigma(r) = \frac{A}{6k} r^2 + \frac{1}{r} \left(\frac{R_0 \hat{R}}{\hat{R} - R_0} \right) \left(\sigma_\infty - \hat{\sigma} + \frac{A}{6k} (\hat{R}^2 - R_0^2) \right) + c_4.$$

Therefore, using $\sigma(R_0) = \sigma_\infty$, it is now clear that

$$c_4 = \sigma_\infty - \frac{A}{6k} R_0^2 - \frac{R_0}{\hat{R} - R_0} \left(\sigma_\infty - \hat{\sigma} + \frac{A}{6k} (\hat{R}^2 - R_0^2) \right).$$

Hence,

$$\begin{aligned}
\sigma(r) &= \sigma_\infty + \frac{A}{6k} (r^2 - R_0^2) - \frac{\hat{R}}{\hat{R} - R_0} \left(\sigma_\infty - \hat{\sigma} + \frac{A}{6k} (\hat{R}^2 - R_0^2) \right) \\
&\quad + \frac{1}{r} \left(\frac{R_0 \hat{R}}{\hat{R} - R_0} \right) \left(\sigma_\infty - \hat{\sigma} + \frac{A}{6k} (\hat{R}^2 - R_0^2) \right) \\
&= \sigma_\infty + \frac{A}{6k} (r^2 - R_0^2) + \left(\hat{\sigma} - \sigma_\infty - \frac{A}{6k} (\hat{R}^2 - R_0^2) \right) \left(\frac{\hat{R} r - R_0}{r \hat{R} - R_0} \right).
\end{aligned}$$

Thus, on the interval $\hat{R} \leq r \leq R_0$,

$$\sigma(r) = \sigma_\infty + \frac{A}{6k} (r^2 - R_0^2) + \left(\hat{\sigma} - \sigma_\infty - \frac{A}{6k} (\hat{R}^2 - R_0^2) \right) \left(\frac{\hat{R} r - R_0}{r \hat{R} - R_0} \right). \quad (2.14)$$

Note that this is equation (8) from McElwain and Morris' paper.

2.4.3 Derivative of Nutrient Concentration

At this point, we have one expression for σ in the inner region $0 \leq r \leq \hat{R}$ (namely equation (2.13)), and another expression for σ in the outer region $\hat{R} \leq r \leq R_0$ (namely equation (2.14)). We now need to turn to the question of the regularity of σ across \hat{R} . To this end we examine the free boundary problem satisfied by σ and the corresponding boundary conditions imposed upon $\sigma(r)$ at $r = \hat{R}$.

The equation for $\sigma(r)$ has the form $L\sigma = f$, where L is second order, linear, and elliptic and $f \in L^\infty \subset L^p$ for all p . Thus (by Calderon-Zygmund theory), for any chosen p , $\sigma \in W^{2,p}$, and so it follows that $\nabla\sigma \in W^{1,p}$. Now by the Sobolev embedding theorem, $\nabla\sigma \in W^{1,p} \subset C^\alpha$ for $\alpha = 1 - \frac{n}{p}$, $n < p$, which means $\sigma \in C^{1,\alpha}$. (See Gilbarg and Trudinger [6] chapters 7 and 9 for the relevant mathematical background.) This inclusion implies that the derivatives of σ must be continuous. Hence, the two expressions for σ must agree at $r = \hat{R}$, and their derivatives must also agree at $r = \hat{R}$ (see equations (2.13) and (2.14)).

Now, recall that on $0 \leq r \leq \hat{R}$, the differential equation involving σ was solved and it involved 2 constants. Of course, as one boundary of the domain was 0 and one of our linearly independent solutions was unbounded at zero, one of the constants became zero. The other constant was determined using the second boundary condition $\sigma(\hat{R}) = \hat{\sigma}$. Similarly, the solution for σ on $\hat{R} \leq r \leq R_0$ involved 2 constants, that were determined using the 2 boundary conditions $\sigma(\hat{R}) = \hat{\sigma}$ and $\sigma(R_0) = \sigma_\infty$. In summary, on each of the two domains, we came across an equation with two unknown constants that were determined using two boundary conditions.

However, we now have the "extra" boundary condition that the derivatives of the expressions in (2.13) and (2.14) must agree at $r = \hat{R}$. Ordinarily, this would lead to an over-determined boundary-value problem (i.e. a boundary value problem in which

we don't expect a solution to exist since there are too many boundary conditions to satisfy). The reason it works here is that in this case \hat{R} is unknown, and the additional boundary condition is thus not only not a problem, but in fact necessary. This is the basic characteristic of free boundary problems. The discontinuity of the second derivative is necessitated - or built in - to the problem. Along this discontinuity, the "extra" boundary condition appears and one is then (hopefully) able to describe the free boundary.

Hence, we must now evaluate the derivatives of σ from equations (2.13) and (2.14) at \hat{R} , and set the two resulting equations equal to one another. From equation (2.13),

$$\begin{aligned} \left. \frac{d\sigma}{dr} \right|_{r=\hat{R}} &= \left. \frac{-\hat{\sigma}\hat{R} \sinh(Br)}{r^2 \sinh(B\hat{R})} + \frac{\hat{\sigma}\hat{R}B \cosh(Br)}{r \sinh(B\hat{R})} \right|_{r=\hat{R}} \\ &= \frac{-\hat{\sigma}}{\hat{R}} + \hat{\sigma}B \left(\frac{\cosh(B\hat{R})}{\sinh(B\hat{R})} \right), \end{aligned}$$

and from (2.14),

$$\begin{aligned} \left. \frac{d\sigma}{dr} \right|_{r=\hat{R}} &= \left. \frac{Ar}{3k} + \left(\hat{\sigma} - \sigma_\infty - \frac{A}{6k}(\hat{R}^2 - R_0^2) \right) \left(\frac{\hat{R}}{\hat{R} - R_0} \right) \left(\frac{R_0}{r^2} \right) \right|_{r=\hat{R}} \\ &= \frac{Ar}{3k} + \left(\hat{\sigma} - \sigma_\infty - \frac{A}{6k}(\hat{R}^2 - R_0^2) \right) \left(\frac{R_0}{\hat{R}(\hat{R} - R_0)} \right). \end{aligned}$$

These equations can be set equal to one another for the following

(Note $B := \sqrt{\frac{A}{k\hat{\sigma}}}$, $\rho := B\hat{R}$, $\xi := BR_0$):

$$\frac{-\hat{\sigma}}{\hat{R}} + \hat{\sigma}B \left(\frac{\cosh(B\hat{R})}{\sinh(B\hat{R})} \right) = \frac{A\hat{R}}{3k} + \left(\hat{\sigma} - \sigma_\infty - \frac{A}{6k}(\hat{R}^2 - R_0^2) \right) \left(\frac{R_0}{\hat{R}(\hat{R} - R_0)} \right).$$

First, multiply both sides by $\frac{\hat{R}(\hat{R} - R_0)}{\hat{\sigma}}$ to get

$$\begin{aligned} R_0 - \hat{R} + B\hat{R}(\hat{R} - R_0) \left(\frac{\cosh(B\hat{R})}{\sinh(B\hat{R})} \right) &= \frac{A\hat{R}^2(\hat{R} - R_0)}{3k\hat{\sigma}} + R_0 - R_0 \frac{\sigma_\infty}{\hat{\sigma}} \\ &\quad - \frac{A(\hat{R}^2 - R_0^2)R_0}{6k\hat{\sigma}}. \end{aligned}$$

Now canceling the R_0 's and use the definition of B results in

$$-\hat{R} + (B\hat{R}^2 - B\hat{R}R_0) \left(\frac{\cosh(B\hat{R})}{\sinh(B\hat{R})} \right) = \frac{B^2\hat{R}^2(\hat{R} - R_0)}{3} - R_0 \frac{\sigma_\infty}{\hat{\sigma}}$$

$$-\frac{R_0 B^2 (\hat{R}^2 - R_0^2)}{6}.$$

Solving for $R_0 \frac{\sigma_\infty}{\hat{\sigma}}$ and dividing by R_0 yields

$$\frac{\sigma_\infty}{\hat{\sigma}} - 1 = -1 + \frac{\hat{R}}{R_0} - \left(\frac{B\hat{R}^2}{R_0} + B\hat{R} \right) \left(\frac{\cosh(\rho)}{\sinh(\rho)} \right) + \frac{B^2\hat{R}^3}{3R_0} - \frac{B^2\hat{R}^2}{3}$$

$$-\frac{B^2(\hat{R}^2 - R_0^2)}{6}$$

$$= -1 + \frac{\rho}{\xi} - \left(\frac{\rho^2}{\xi} - \rho \right) \left(\frac{\cosh(\rho)}{\sinh(\rho)} \right) + \frac{\rho^3}{3\xi} - \frac{\rho^2}{3} - \frac{\rho^2 - \xi^2}{6},$$

or

$$\frac{\sigma_\infty}{\hat{\sigma}} - 1 = \frac{1}{6}(\xi^2 - \rho^2) + \left[\rho \left(\frac{\cosh(\rho)}{\sinh(\rho)} - 1 \right) - \frac{\rho^3}{3} \right] \left[\frac{1}{\rho} - \frac{1}{\xi} \right]. \quad (2.15)$$

The preceding equation provides a way to find \hat{R} in terms of the outer radius R_0 . The particular format of equation (2.15) will be useful later on, as it will become necessary to solve this equation for $\rho \left(\frac{\rho \cosh(\rho)}{\sinh(\rho)} - 1 \right)$.

2.4.4 Radial Growth of Tumor in Phase II

The growth equation in Phase II given in McElwain and Morris' equation(10) is

$$\frac{4\pi}{3} \frac{dR_0^3}{dt} = s \frac{4\pi}{3} (R_0^3 - \hat{R}^3) - \lambda \frac{4\pi}{3} R_0^3 + 4\pi s \int_0^{\hat{R}} \frac{\sigma(r)}{\hat{\sigma}} r^2 dr. \quad (2.16)$$

Substituting (2.13) into the integral in (2.16) (since (2.13) describes σ on $(0, \hat{R})$) yields

$$\frac{4\pi}{3} \frac{dR_0^3}{dt} = s \frac{4\pi}{3} (R_0^3 - \hat{R}^3) - \lambda \frac{4\pi}{3} R_0^3 + 4\pi s \int_0^{\hat{R}} \frac{\hat{R} r \sinh(Br)}{\sinh(B\hat{R})} dr.$$

Using $\xi = BR_0$, $\gamma = \frac{\lambda}{s}$, and $\tau = st$, and integrating by parts gives us

$$\begin{aligned}
\frac{4\pi}{3} \frac{dR_0^3}{dt} &= s \frac{4\pi}{3} (R_0^3 - \hat{R}^3) - \lambda \frac{4\pi}{3} R_0^3 + \frac{4\pi s \hat{R}}{\sinh(B\hat{R})} \left(\frac{\hat{R}}{B} \cosh(B\hat{R}) - \frac{1}{B^2} \sinh(B\hat{R}) \right) \\
\frac{1}{3} \frac{dR_0^3}{dt} &= \frac{s}{3} R_0^3 - \frac{s}{3} \hat{R}^3 - \frac{\lambda R_0^3}{3} + \frac{s \hat{R}^2 \cosh(\rho)}{B \sinh(\rho)} - \frac{s \hat{R}}{B^2} \\
\frac{B^3}{3s} \frac{dR_0^3}{dt} &= \frac{B^3 R_0^3}{3} - \frac{B^3 \hat{R}^3}{3} - \frac{\lambda B^3 R_0^3}{3s} + \frac{\hat{R}^2 B^2 \cosh(\rho)}{\sinh(\rho)} - B \hat{R} \\
\xi^2 \frac{d\xi}{d\tau} &= \frac{1}{3} (\xi^3 - \xi^3 \gamma - \rho^3) + \rho^2 \frac{\cosh(\rho)}{\sinh(\rho)} - B \hat{R}.
\end{aligned}$$

Hence, the result is equation (11) from McElwain and Morris,

$$\xi^2 \frac{d\xi}{d\tau} = \frac{1}{3} ((1 - \gamma)\xi^3 - \rho^3) + \rho \left(\frac{\rho \cosh(\rho)}{\sinh(\rho)} - 1 \right). \quad (2.17)$$

Now we solve for $\rho \left(\frac{\rho \cosh(\rho)}{\sinh(\rho)} - 1 \right)$ in equation (2.15) and substitute the result into equation (2.17). We obtain

$$\begin{aligned}
\xi^2 \frac{d\xi}{d\tau} &= \frac{1}{3} ((1 - \gamma)\xi^3 - \rho^3) + \left(\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6}(\xi^2 - \rho^2) + \frac{\rho^3}{3} \left[\frac{1}{\rho} - \frac{1}{\xi} \right] \right) \frac{\rho \xi}{\xi - \rho} \\
&= \frac{1}{3} ((1 - \gamma)\xi^3 - \rho^3) + \left(\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6}(\xi^2 - \rho^2) \right) \frac{\rho \xi}{\xi - \rho} + \frac{\rho^3}{3} \\
&= \frac{1}{3} (1 - \gamma)\xi^3 + \left(\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6}(\xi^2 - \rho^2) \right) \frac{\rho \xi}{\xi - \rho},
\end{aligned}$$

which is equation (12) from McElwain and Morris:

$$\xi^2 \frac{d\xi}{d\tau} = \frac{1}{3} (1 - \gamma)\xi^3 + \left(\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6}(\xi^2 - \rho^2) \right) \frac{\rho \xi}{\xi - \rho}. \quad (2.18)$$

This equation governs the motion of the outer radius of the tumor. We can use this equation in conjunction with equation (2.15) in order to describe both the radius of the inner region of the tumor and the outer radius of the tumor. This equation also completes the analysis of the growth of the tumor in phase II. An analysis of the results of this growth equation can be found following the analysis of phase III, in section (2.6).

2.5 Phase III

Once again using (2.1), the diffusion in Phase III is

$$\frac{k}{r^2} \frac{d}{dr} \left(r^2 \frac{d\sigma}{dr} \right) = \begin{cases} 0, & 0 \leq r \leq R_i \\ \frac{A\sigma}{\hat{\sigma}}, & R_i \leq r \leq \hat{R} \\ A, & \hat{R} \leq r \leq R_0. \end{cases} \quad (2.19)$$

Figure 2.3 provides a diagram of the tumor from this phase.

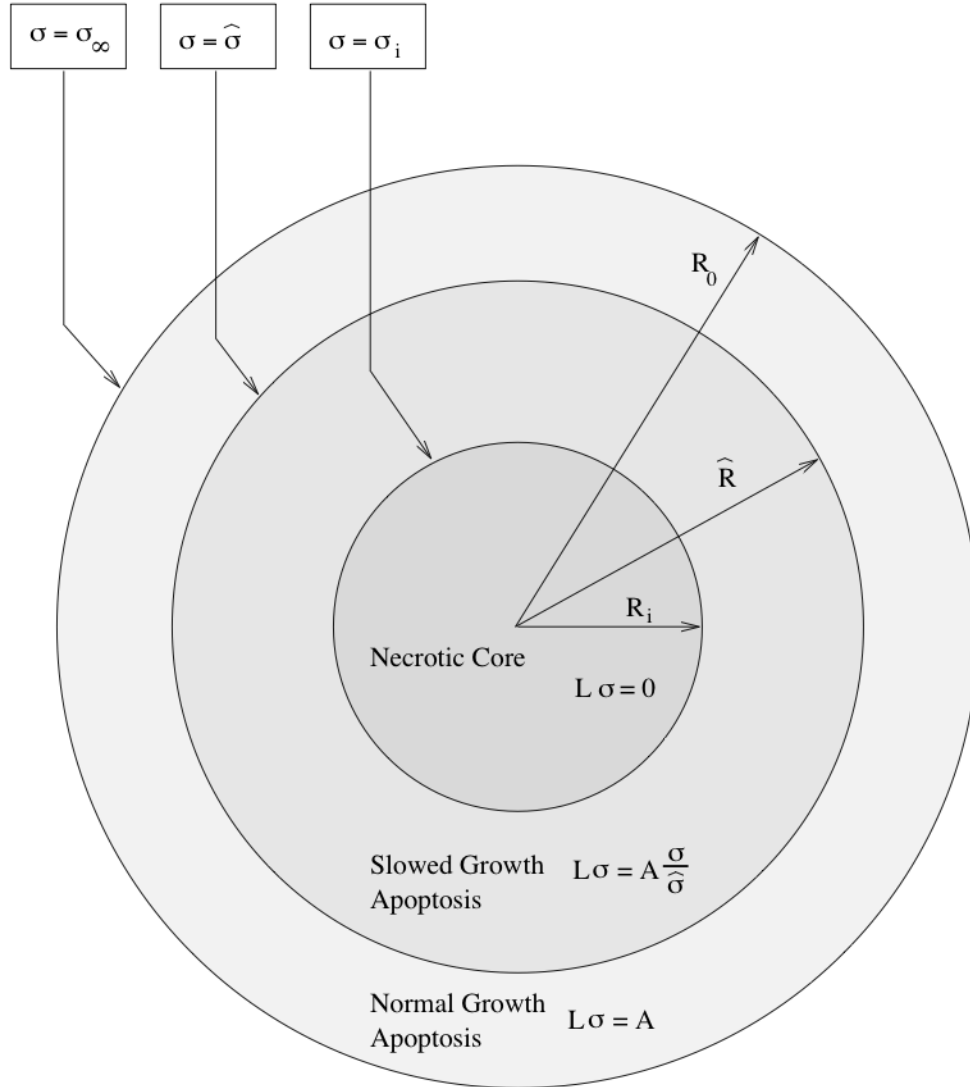


Figure 2.3: Diagram of tumor in phase III, where $L\sigma := \frac{k}{r^2} \frac{d}{dr} \left(r^2 \frac{d\sigma}{dr} \right)$

The differential equation from (2.19) on the interval $0 \leq r \leq R_i$ has a general solution of the form $\Phi(r) = c_1 r^{-1} + c_2$, for some constants c_1 and c_2 . The differential

equations on the intervals $R_i \leq r \leq \hat{R}$ and $\hat{R} \leq r \leq R_0$ were solved in section (2.2) as equations (2.3) and (2.5) respectively. The result is the following general solution:

$$\sigma(r) = \begin{cases} c_1 r^{-1} + c_2, & 0 \leq r \leq R_i \\ c_3 \frac{\sinh(Br)}{r} + c_4 \frac{\cosh(Br)}{r}, & R_i \leq r \leq \hat{R} \\ c_5 r^{-1} + c_6 + \frac{A}{6k} r^2, & \hat{R} \leq r \leq R_0. \end{cases} \quad (2.20)$$

This equation for $\sigma(r)$ in phase III presents nine unknown quantities:

$$c_1, c_2, c_3, c_4, c_5, c_6, R_i, \hat{R}, \text{ and } R_0.$$

Fortunately, we also have 9 boundary conditions. Some of these conditions arise from biology, some are due to the continuity of σ , and some are due to the elliptic regularity of σ [6]. The conditions, along with the subjects from whence they appear, are given in table 2.1.

Condition	Background of Condition
1. $\sigma(0)$ is bounded	Biology
2. $\sigma(R_i^-) = \sigma_i$	Biology
3. $\sigma(R_i^+) = \sigma_i$	Continuity of σ
4. $\sigma'(R_i^-) = \sigma'(R_i^+)$	Elliptic Regularity
5. $\sigma(\hat{R}^-) = \hat{\sigma}$	Biology
6. $\sigma(\hat{R}^+) = \hat{\sigma}$	Continuity of σ
7. $\sigma'(\hat{R}^-) = \sigma'(\hat{R}^+)$	Elliptic Regularity
8. $\sigma(R_0) = \sigma_\infty$	Biology
9. Growth Equation for R_0 (2.28)	Biology

Table 2.1: *Boundary Conditions in Phase III*

Using the numbering presented in the table, condition 1 will allow us to determine c_1 and condition 2 will lead us to c_2 . We will then simultaneously use conditions 3 and 4 in order to determine c_3 and c_4 . Next, we will use conditions 6 and 8 in order to determine the values of c_5 and c_6 respectively. Finally, we will use equations 5 and 7 in order to describe the free boundaries R_i and \hat{R} respectively, and condition 9 will lead us to a formula for R_0 . Note that we will derive an explicit formula for R_0 (equation (2.29)), \hat{R} will be defined in terms of R_0 (equation (2.27)), and R_i will be defined in terms of \hat{R} (equation (2.25)).

2.5.1 Nutrient Level Inside Necrotic Core

First we examine the case $0 \leq r \leq R_i$, which describes the necrotic core. As given in equation (2.20), on this region $\sigma(r) = c_1 r^{-1} + c_2$. Since σ is bounded at $r = 0$, it

must be true that $c_1 = 0$, and hence $\sigma = c_2$. Furthermore, as $\sigma(R_i) = \sigma_i$, c_2 must equal σ_i and thus $\sigma(r) = \sigma_i$ on $0 \leq r \leq R_i$.

2.5.2 Nutrient Level on Region of Slowed Growth

The second case is the interval $R_i \leq r \leq \hat{R}$, on which $\frac{k}{r^2} \frac{d}{dr} \left(r^2 \frac{d\sigma}{dr} \right) = \frac{A\sigma}{\hat{\sigma}}$. The solution, presented in equation (2.20), has the general form

$$\sigma(r) = \frac{c_3 \sinh(Br)}{r} + \frac{c_4 \cosh(Br)}{r}.$$

Finding the constants c_3 and c_4 will take some work.

To determine the values of the two constants it is necessary to employ two of the boundary conditions, namely that $\sigma(R_i) = \sigma_i$ and that $\frac{d\sigma}{dr}$ is continuous over the boundary value $r = R_i$. These conditions, along with the definitions of $\sigma(r)$ on the intervals $[0, R_i]$ and $[R_i, \hat{R}]$, give us

$$\left. \frac{d}{dr} \left(\frac{c_3 \sinh(Br)}{r} + \frac{c_4 \cosh(Br)}{r} \right) \right|_{r=R_i} = \left. \frac{d}{dr} (\sigma_i) \right|_{r=R_i} = 0.$$

Hence, the two boundary conditions result in the equations

$$\frac{c_3 \sinh(BR_i)}{R_i} + \frac{c_4 \cosh(BR_i)}{R_i} = \sigma_i$$

and

$$\frac{Bc_3 \cosh(BR_i)}{R_i} - \frac{c_3 \sinh(BR_i)}{R_i^2} + \frac{Bc_4 \sinh(BR_i)}{R_i} - \frac{c_4 \cosh(BR_i)}{R_i^2} = 0.$$

In order to make these equations easier to manipulate, they should be rewritten using the definitions of hyperbolic trigonometric functions. The resulting equations are

$$\sigma_i = \frac{c_3}{2R_i} (e^{BR_i} - e^{-BR_i}) + \frac{c_4}{2R_i} (e^{BR_i} + e^{-BR_i})$$

and

$$0 = \frac{Bc_3}{2R_i} (e^{BR_i} + e^{-BR_i}) - \frac{c_3}{2R_i^2} (e^{BR_i} - e^{-BR_i}) + \frac{Bc_4}{2R_i} (e^{BR_i} - e^{-BR_i}) - \frac{c_4}{2R_i^2} (e^{BR_i} + e^{-BR_i}).$$

The first equation yields

$$2R_i \sigma_i = (c_3 + c_4) e^{BR_i} + (c_4 - c_3) e^{-BR_i}. \quad (2.21)$$

In the second equation, we multiply both sides by $2R_i^2$ for

$$0 = R_i B c_3 e^{BR_i} + R_i B c_3 e^{-BR_i} - c_3 e^{BR_i} + c_3 e^{-BR_i} + BR_i c_4 e^{BR_i} - BR_i c_4 e^{-BR_i} - c_4 e^{BR_i} - c_4 e^{-BR_i}.$$

After some grouping and rearranging terms we have

$$BR_i(c_3 + c_4)e^{BR_i} - (c_3 + c_4)e^{BR_i} = (c_4 - c_3)e^{-BR_i} + BR_i(c_4 - c_3)e^{-BR_i},$$

or

$$(BR_i - 1)(c_3 + c_4)e^{BR_i} = (BR_i + 1)(c_4 - c_3)e^{-BR_i}. \quad (2.22)$$

Combining equations (2.21) and (2.22) will provide expressions for $(c_3 + c_4)$ and $(c_4 - c_3)$. First, we solve equation (2.22) for $(c_4 - c_3)$ and put this into equation (2.21) to get

$$2R_i\sigma_i = \frac{1 + BR_i}{BR_i - 1}(c_4 - c_3)e^{-BR_i} + (c_4 - c_3)e^{-BR_i}.$$

The two terms on the right hand side can combine to get

$$2R_i\sigma_i = \frac{1 + BR_i + BR_i - 1}{BR_i - 1}(c_4 - c_3)e^{-BR_i},$$

or

$$2R_i\sigma_i = \frac{2BR_i}{BR_i - 1}(c_4 - c_3)e^{-BR_i}.$$

Thus, solving for $(c_4 - c_3)$, we have

$$\begin{aligned} c_4 - c_3 &= 2R_i\sigma_i e^{BR_i} \left(\frac{BR_i - 1}{2BR_i} \right) \\ &= e^{BR_i} \left[\sigma_i R_i - \frac{\sigma_i}{B} \right]. \end{aligned}$$

Now we return to equations (2.21) and (2.22). This time, we solve equation (2.22) for $(c_3 + c_4)$ and plug this result into equation (2.21). This gives us the following equation:

$$2R_i\sigma_i = \frac{BR_i - 1}{BR_i + 1}(c_3 + c_4)e^{BR_i} + (c_3 + c_4)e^{BR_i}.$$

After grouping terms and rearranging, this equation becomes

$$2R_i\sigma_i = \frac{2BR_i}{BR_i + 1}(c_3 + c_4)e^{BR_i}.$$

Now we solve for $(c_3 + c_4)$:

$$\begin{aligned} c_3 + c_4 &= \frac{1 + BR_i}{2BR_i} [2R_i\sigma_i e^{-BR_i}] \\ &= e^{-BR_i} \left[\frac{\sigma_i}{B} + \sigma_i R_i \right]. \end{aligned}$$

Hence, we have determined that

$$c_4 - c_3 = e^{BR_i} \left[\sigma_i R_i - \frac{\sigma_i}{B} \right]$$

and

$$c_3 + c_4 = e^{-BR_i} \left[\frac{\sigma_i}{B} + \sigma_i R_i \right].$$

Now, finally, we perform the following derivation:

$$\begin{aligned} \sigma(r) &= \frac{c_3}{r} \sinh(Br) + \frac{c_4}{r} \cosh(Br) \\ &= \frac{c_3}{2r} (e^{Br} - e^{-Br}) + \frac{c_4}{2r} (e^{Br} + e^{-Br}) \\ &= \frac{c_3 + c_4}{2r} e^{Br} + \frac{c_4 - c_3}{2r} e^{-Br} \\ &= \frac{e^{-BR_i} \left[\frac{\sigma_i}{B} + \sigma_i R_i \right]}{2r} e^{Br} + \frac{e^{BR_i} \left[\sigma_i R_i - \frac{\sigma_i}{B} \right]}{2r} e^{-Br} \\ &= \frac{\sigma_i}{Br} \left[\frac{e^{Br-BR_i} - e^{-(Br-BR_i)} + BR_i e^{Br-BR_i} + BR_i e^{-(Br-BR_i)}}{2} \right] \\ &= \frac{\sigma_i}{Br} [\sinh(B(r - R_i)) + BR_i \cosh(B(r - R_i))]. \end{aligned}$$

This gives us the form of $\sigma(r)$ on $[R_i, \hat{R}]$, which is equation (16) in McElwain and Morris' article:

$$\sigma(r) = \frac{\sigma_i}{Br} [\sinh(B(r - R_i)) + BR_i \cosh(B(r - R_i))], \quad R_i \leq r \leq \hat{R}. \quad (2.23)$$

We do note that R_i still needs to be determined.

2.5.3 Nutrient Level on Region of Normal Growth

Finally, the remaining case is the interval $\hat{R} \leq r \leq R_0$, where $\frac{k}{r^2} \frac{d}{dr} \left(r^2 \frac{d\sigma}{dr} \right) = A$. From equation(2.20), the general solution to this differential equation is

$$\sigma(r) = c_5 r^{-1} + c_6 + \frac{A}{6k} r^2.$$

The boundary conditions that we use in order to determine the values of c_5 and c_6 are $\sigma(\hat{R}) = \hat{\sigma}$ and $\sigma(R_0) = \sigma_\infty$ respectively. The final solution is

$$\sigma(r) = \sigma_\infty + \frac{A}{6k} (r^2 - R_0^2) + F \left(\frac{1}{R_0} - \frac{1}{r} \right)$$

on $\hat{R} \leq r \leq R_0$, for some constant F that causes σ to satisfy $\sigma(\hat{R}) = \hat{\sigma}$. The computation for this equation is quite similar to that carried out in the analysis of phase II, and is thus omitted.

2.5.4 Analysis of Free Boundaries

In summation, the results of the preceding sections become equation (16) from McElwain and Morris:

$$\sigma(r) = \begin{cases} \sigma_i, & 0 \leq r \leq R_i \\ \frac{\sigma_i}{Br} [\sinh(B(r - R_i)) + BR_i \cosh(B(r - R_i))], & R_i \leq r \leq \hat{R} \\ \sigma_\infty + \frac{A}{6k} (r^2 - R_0^2) + F \left(\frac{1}{R_0} - \frac{1}{r} \right), & \hat{R} \leq r \leq R_0. \end{cases} \quad (2.24)$$

Now we use the boundary condition $\sigma(\hat{R}) = \hat{\sigma}$ and the middle equation from (2.24) to get equation (17a) from McElwain and Morris, namely that

$$\frac{\hat{\sigma}}{\sigma_i} = \frac{1}{\rho} (\sinh(\rho - \eta) + \eta \cosh(\rho - \eta)). \quad (2.25)$$

This equation gives us a description of R_i in terms of \hat{R} .

Now, we introduce the constants

$$\eta := BR_i \text{ and } G := \frac{\sigma_i}{\hat{\sigma}} (\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)).$$

We proceed to eliminate the constant F from the third equation in (2.24) and derive an equation for R_i . Using the condition that σ' is continuous over \hat{R} , we have the following:

$$\begin{aligned} \frac{A}{3k} \hat{R} + \frac{F}{\hat{R}^2} &= \frac{B\sigma_i}{B\hat{R}} \left[\cosh \left(B \left(\hat{R} - R_i \right) \right) + \eta \sinh \left(B \left(\hat{R} - R_i \right) \right) \right] \\ &\quad - \frac{\sigma_i}{B\hat{R}^2} \left[\sinh \left(B \left(\hat{R} - R_i \right) \right) + \eta \cosh \left(B \left(\hat{R} - R_i \right) \right) \right] \\ &= \frac{\sigma_i}{\hat{R}} [\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)] - \frac{\sigma_i}{B\hat{R}^2} \frac{\rho \hat{\sigma}}{\sigma_i} \quad \text{by equation (2.25)} \\ &= \frac{\sigma_i}{\hat{R}} [\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)] - \frac{\hat{\sigma}}{\hat{R}}. \end{aligned}$$

Therefore,

$$F = \hat{R} \sigma_i [\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)] - \hat{\sigma} \hat{R} - \frac{A}{3k} \hat{R}^3. \quad (2.26)$$

Substituting this into the second equation from (2.24) and evaluating at \hat{R} yields

$$\begin{aligned}\hat{\sigma} &= \hat{R} \left(\frac{1}{R_0} - \frac{1}{\hat{R}} \right) \left(\sigma_i [\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)] - \hat{\sigma} - \frac{A}{3k} \hat{R}^2 \right) \\ &\quad + \sigma_\infty + \frac{A}{6k} (\hat{R}^2 - R_0^2),\end{aligned}$$

or

$$\begin{aligned}\frac{\sigma_\infty}{\hat{\sigma}} - 1 &= \frac{\hat{R}}{\hat{\sigma}} \left(\frac{1}{\hat{R}} - \frac{1}{R_0} \right) \left(\sigma_i [\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)] - \hat{\sigma} - \frac{A}{3k} \hat{R}^2 \right) \\ &\quad + \frac{1}{6} (\xi^2 - \rho^2) \\ &= \left(1 - \frac{\rho}{\xi} \right) \left(\frac{\sigma_i}{\hat{\sigma}} [\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)] - 1 - \frac{1}{3} \rho^2 \right) \\ &\quad + \frac{1}{6} (\xi^2 - \rho^2) \\ &= \left(1 - \frac{\rho}{\xi} \right) \left(\frac{\sigma_i}{\hat{\sigma}} [\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)] - 1 \right) - \frac{1}{3} \rho^2 + \frac{1}{3} \frac{\rho^3}{\xi} \\ &\quad + \frac{1}{6} (\xi^2 - \rho^2) \\ &= \left(1 - \frac{\rho}{\xi} \right) G - \frac{1}{3} \rho^2 + \frac{1}{3} \frac{\rho^3}{\xi} + \frac{1}{6} (\xi^2 - \rho^2).\end{aligned}$$

The final line of this derivation is equation (17b) from McElwain and Morris' article; namely

$$\frac{\sigma_\infty}{\hat{\sigma}} - 1 = \frac{1}{6} (\xi^2 - \rho^2) + \left(G\rho - \frac{\rho^3}{3} \right) \left(\frac{1}{\rho} - \frac{1}{\xi} \right). \quad (2.27)$$

This equation describes \hat{R} in terms of R_0 .

2.5.5 Radial Growth of Tumor in Phase III

The growth equation in this late phase is expressed in McElwain and Morris' article as equation (18):

$$\frac{4\pi}{3} \frac{dR_0^3}{dt} = s \frac{4\pi}{3} (R_0^3 - \hat{R}^3) - \lambda \frac{4\pi}{3} (R_0^3 - R_i^3) + 4\pi s \int_{R_i}^{\hat{R}} \frac{\sigma(r)}{\hat{\sigma}} r^2 dr. \quad (2.28)$$

This equation will be used to give us a formula for R_0 . First we examine the integral term at the end of the preceding equation. Since the integral is being taken over the interval $[R_i, \hat{R}]$, the middle definition of $\sigma(r)$ from equation (2.24) is appropriate. Now the integral in question can be expressed as

$$\frac{4\pi s\sigma_i}{B\hat{\sigma}} \int_{R_i}^{\hat{R}} r [\sinh(Br - BR_i) + BR_i \cosh(Br - BR_i)] dr.$$

This integral can be evaluated using integration by parts to get the following:

$$\begin{aligned} \frac{4\pi s\sigma_i}{B\hat{\sigma}} \left(r \left[\frac{1}{B} \cosh(Br - \eta) + R_i \sinh(Br - \eta) \right] \Big|_{R_i}^{\hat{R}} \right. \\ \left. - \int_{R_i}^{\hat{R}} \frac{1}{B} \cosh(Br - \eta) + R_i \sinh(Br - \eta) dr \right). \end{aligned}$$

After carrying out the remaining integration and plugging in the bounds, we have

$$\frac{4\pi s\sigma_i}{B\hat{\sigma}} \left(\frac{\hat{R} - R_i}{B} \cosh(B\hat{R} - \eta) + \left(\hat{R}R_i - \frac{1}{B^2} \right) \sinh(B\hat{R} - \eta) \right).$$

Now factoring out $\frac{1}{B^2}$ and using $\rho = B\hat{R}$ and $\eta = BR_i$ provides

$$\begin{aligned} & \frac{4\pi s\sigma_i}{B^3\hat{\sigma}} ((\rho - \eta)\cosh(\rho - \eta) + (\rho\eta - 1)\sinh(\rho - \eta)) \\ &= \frac{4\pi s\sigma_i\rho}{B^3\hat{\sigma}} (\cosh(\rho - \eta) + \eta\sinh(\rho - \eta)) - \frac{4\pi s\sigma_i}{B^3\hat{\sigma}} (\eta\cosh(\rho - \eta) + \sinh(\rho - \eta)) \\ &= \frac{4\pi s}{B^3} \rho \left[\frac{\sigma_i}{\hat{\sigma}} (\cosh(\rho - \eta) + \eta\sinh(\rho - \eta)) - 1 \right] \quad \text{by (2.25)} \\ &= \frac{4\pi s}{B^3} \rho G. \end{aligned}$$

Using this (and that $\gamma := \frac{\lambda}{s}$, $\xi := BR_0$) the growth equation (2.28) can now be

rewritten as

$$\begin{aligned}
\frac{4\pi}{3} \frac{dR_0^3}{dt} &= s \frac{4\pi}{3} (R_0^3 - \hat{R}^3) - \lambda \frac{4\pi}{3} (R_0^3 - R_i^3) + \frac{4\pi s}{B^3} G\rho \\
\frac{1}{3s} \frac{dR_0^3}{dt} &= \frac{1}{3} (R_0^3 - \hat{R}^3) - \frac{1}{3} \frac{\lambda}{s} (R_0^3 - R_i^3) + \frac{1}{B^3} G\rho \\
\frac{1}{3s} \frac{dR_0^3}{dt} &= \frac{1}{3B^3} \left(B^3 R_0^3 - B^3 \hat{R}^3 - \gamma B^3 R_0^3 + \gamma B^3 R_i^3 \right) + \frac{1}{B^3} G\rho \\
\frac{B^3}{3s} \frac{dR_0^3}{dt} &= \frac{1}{3} (\xi^3 - \rho^3 - \gamma \xi^3 + \gamma \eta^3) + G\rho \\
\xi^3 \frac{d\xi}{d\tau} &= \frac{1}{3} (1 - \gamma) \xi^3 + \frac{1}{3} \gamma \eta^3 - \frac{1}{3} \rho^3 + G\rho \\
&= \frac{1}{3} (1 - \gamma) \xi^3 + \frac{1}{3} \gamma \eta^3 + \left[\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6} (\xi^2 - \rho^2) \right] \frac{\rho \xi}{\xi - \rho} \quad \text{by (2.27)}.
\end{aligned}$$

This completes the derivation of equation (19) from McElwain and Morris' article, namely that

$$\xi^3 \frac{d\xi}{d\tau} = \frac{1}{3} (1 - \gamma) \xi^3 + \frac{1}{3} \gamma \eta^3 + \left[\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6} (\xi^2 - \rho^2) \right] \frac{\rho \xi}{\xi - \rho}. \quad (2.29)$$

This equation models the change in the scaled outer radius of the tumor with respect to time during phase III.

2.6 Steady State Analysis

2.6.1 Phase II

As mentioned in section 2.1, the assumption that apoptosis is the method of volume loss within the tumor is aligned with experimental evidence that a tumor can reach a steady state without the onset of a necrotic core. McElwain and Morris' model has that quality: from phase II, a tumor either obtains a steady state and remains in phase II or develops a necrotic core and proceeds into phase III.

Firstly, as in phase I, the tumor in phase II could move ahead into phase III. This occurs, by definition, when the nutrient concentration in the center of the tumor drops to $\sigma = \sigma_i$, causing the cells there to die off by necrosis. As with a tumor in phase I, the radius of the tumor at the moment it moves into phase III can be described. McElwain and Morris call the scaled radius at this point ξ_c , and they call the value of $\rho := B\hat{R}$ at this point ρ_c . The transition occurs when $\sigma(r=0) = \sigma_i$.

Recall equations (2.15) and (2.18) from section (2.4):

$$\frac{\sigma_\infty}{\hat{\sigma}} - 1 = \frac{1}{6}(\xi^2 - \rho^2) + \left[\rho \left(\frac{\sinh(\rho)}{\cosh(\rho)} - 1 \right) - \frac{\rho^3}{3} \right] \left[\frac{1}{\rho} - \frac{1}{\xi} \right]$$

and

$$\xi^2 \frac{d\xi}{d\tau} = \frac{1}{3}(1 - \gamma)\xi^3 + \left(\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6}(\xi^2 - \rho^2) \right) \frac{\rho\xi}{\xi - \rho}.$$

Plugging $r = 0$ into equation (2.13) gives the following:

$$\begin{aligned} \sigma_i &= \sigma(r = 0) \\ &= \lim_{r \rightarrow 0} \left[\hat{\sigma} \frac{\hat{R} \sinh(Br)}{r \sinh(B\hat{R})} \right] \\ &= \frac{\hat{\sigma} \hat{R}}{\sinh(B\hat{R})} \lim_{r \rightarrow 0} \left[\frac{\sinh(Br)}{r} \right] \\ &= \frac{\hat{\sigma} \hat{R}}{\sinh(B\hat{R})} \lim_{r \rightarrow 0} [B \cosh(Br)] \\ &= \frac{\hat{\sigma} \hat{R}}{\sinh(B\hat{R})} B \\ &= \frac{\hat{\sigma} \rho_c}{\sinh(\rho_c)}. \end{aligned}$$

The resulting equation involving ρ_c in terms of constants (equation (14) in McElwain and Morris' article) is

$$\frac{\sigma_i}{\hat{\sigma}} = \frac{\rho_c}{\sinh(\rho_c)}. \quad (2.30)$$

This implicit equation for ρ_c along with equation (2.15) could be used in order to solve for ξ_c .

Another possibility for a tumor in phase II is that it never enters phase III; the tumor might reach a steady state and never develop a necrotic core. To study the radius ξ_* of this dormant tumor, we first set $\frac{d\xi}{d\tau}$ equal to zero in equation (2.18). If it is possible for the tumor to remain in a dormant state, that is, if ξ_* and ρ_* exist, ξ_* and ρ_* must satisfy both equation (2.15) and this refined version of equation (2.18). Therefore,

$$0 = \frac{1}{3}(1 - \gamma)\xi_*^3 + \left(\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6}(\xi_*^2 - \rho_*^2) \right) \frac{\rho_* \xi_*}{\xi_* - \rho_*} \quad (2.31)$$

and

$$\frac{\sigma_\infty}{\hat{\sigma}} - 1 = \frac{1}{6}(\xi_*^2 - \rho_*^2) + \left[\rho \left(\frac{\sinh(\rho_*)}{\cosh(\rho_*)} - 1 \right) - \frac{\rho_*^3}{3} \right] \left[\frac{1}{\rho_*} - \frac{1}{\xi_*} \right]. \quad (2.32)$$

Now the values of the scaled radius of the tumor itself and the scaled radius of the region of slowed growth within the tumor have been described for a both tumor that reaches a steady state and a tumor that moves into phase III. It is now important to verify that a tumor can in fact reach a steady state in phase II. In the Appendix of McElwain and Morris' article, this issue is examined.

At first, the situation is examined under the assumption that $\sigma_\infty = \hat{\sigma}$. The interpretation of this assumption is that the nutrient level at the surface of the tumor is at the level that induces slowed proliferation rates on the cells. An implication of this assumption is that $\xi := BR_0 = B\hat{R} =: \rho$. Thus, equation (2.17) in terms of ξ becomes

$$\begin{aligned} \xi^2 \frac{d\xi}{d\tau} &= \frac{1}{3} [(1 - \gamma)\xi^3 - \xi^3] + \xi \left(\xi \frac{\cosh(\xi)}{\sinh(\xi)} - 1 \right) \\ &= -\frac{1}{3}\gamma\xi^3 + \xi \left(\xi \frac{\cosh(\xi)}{\sinh(\xi)} - 1 \right). \end{aligned}$$

We then set $\frac{d\xi}{d\tau} = 0$ in the preceding equation and find that the solution $\xi = \xi_*$ must satisfy

$$\frac{1}{3}\gamma\xi^2 = \xi \frac{\cosh(\xi)}{\sinh(\xi)} - 1. \quad (2.33)$$

Since $\xi > 0$, this equation will have a solution for any $\gamma > 0$.

Now that the situation in which $\sigma_\infty = \hat{\sigma}$ has been considered, the remaining case is $\sigma_\infty > \hat{\sigma}$. In this more general case, McElwain and Morris note, a dormant state will be reached in phase II as long as "the value of ρ_c which satisfies (2.30) [is] larger than ρ_* " [8]. This will be satisfied for small enough $\frac{\sigma_i}{\hat{\sigma}}$.

2.6.2 Phase III

Now we analyze a tumor that has progressed into phase III. This is more simple than the other phases, as the tumor will never leave phase III. Either a dormant state will be reached or the tumor will continue to grow. Of these two situations, the only one worthy of discussion is the case in which the tumor reaches a dormant state in phase III. If this is to be true, $\frac{d\xi}{d\tau}$ would need to equal zero in equation (2.29). Thus, if values of ξ_f, η_f , and ρ_f exist such that a dormant state is reached in phase III, then they must satisfy

$$\frac{1}{3}(\gamma - 1)\xi_f^3 - \frac{1}{3}\gamma\eta_f^3 = \left[\frac{\sigma_\infty}{\hat{\sigma}} - 1 - \frac{1}{6}(\xi_f^2 - \rho_f^2) \right] \frac{\rho_f \xi_f}{\xi_f - \rho_f}, \quad (2.34)$$

along with equations (2.25) and (2.27).

Chapter 3

Slowed Growth rate and Chalone Production; Adam

Empirically, it is known that a tumor develops a region of cells that experience a slowed proliferation rate. The preceding model by McElwain and Morris is one example of a model that attributes this drop to an insufficient level of nutrient in the middle region. Others, such as Greenspan, attribute the drop to a byproduct of necrosis [7]. Glass, however, was one of the first to attribute the slowed growth rates to mitotic inhibitors [4].

In general, mitotic inhibitors regulate tissue growth. Currently, synthetic mitotic inhibitors are frequently used in order to treat cancer. Also, it has been empirically observed that there are tissue-specific mitotic inhibitors that are actually produced by the tissue itself. Bullough is one of the pioneers in the subject matter, and he labeled these inhibitors "chalones". As Bullough states, "...not only the functional state of the tissue but the whole structure of an adult mammal may need at all times to be actively maintained against the possibility of collapse into mitotic anarchy" [3]. In other words, the tissue produces chalone in order to prevent itself from growing limitlessly. Many believe that in certain types of cancer, a lack of chalone production (or an immunity to chalones) is partially to blame for the unchecked growth of the cancer [5]. Now we are presented with a case similar to that in Chapter 2 with apoptosis. Here, the tumor appears to be unaffected by mitotic inhibitors from the surrounding tissue, but the tumor itself might be producing its own chalone in order to control its own growth in such a way that benefits itself [5].

One of the first models to focus on the role of mitotic inhibitors was that of Glass [4]. This model was expounded upon by Shymko and Glass [5] to consider varying geometries of the tumor in three-dimensions. The production of chalones is assumed by Glass to be controlled by a "switch function": at any point close enough to the center of the tumor chalones are being produced at some constant production level, and elsewhere chalones are not being produced [2].

Adam [1] also considered a one-dimensional model of chalone production within the tumor, and he also assumed radial symmetry. Unlike Glass, however, Adam considered a chalone production rate that decreases linearly with respect to distance from the center of the tumor. Thus, the source term in Adam's model is defined to

be

$$S(x) = \begin{cases} 1 - \frac{2}{L}|x|, & |x| \leq \frac{L}{2} \\ 0, & |x| \geq \frac{L}{2} \end{cases} . \quad (3.1)$$

Figure 3.1 is a diagram of a tumor from Adam's model, and figure 3.2 is a graph of the production rate of chalone across a cross-section of the tumor.

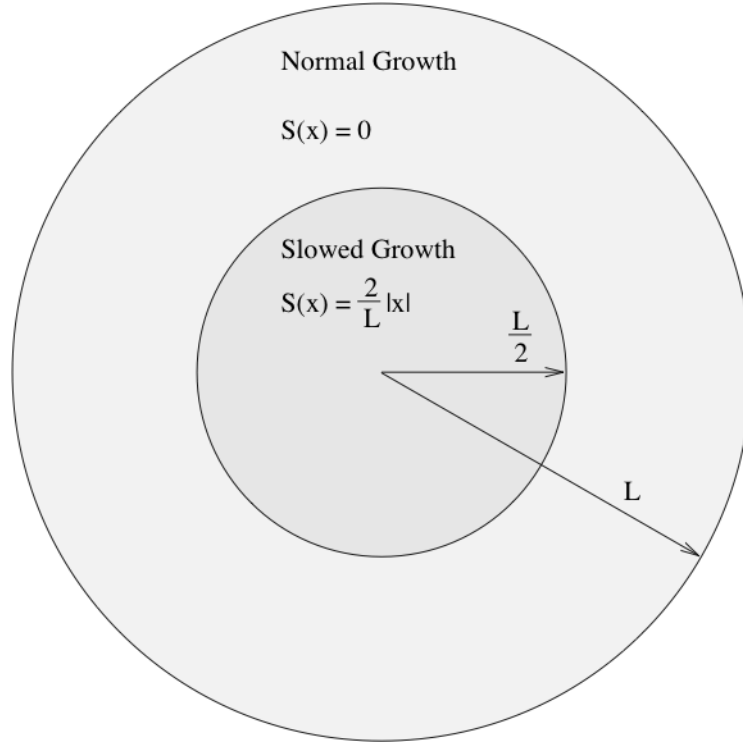


Figure 3.1: *Diagram of tumor from Adam's model*

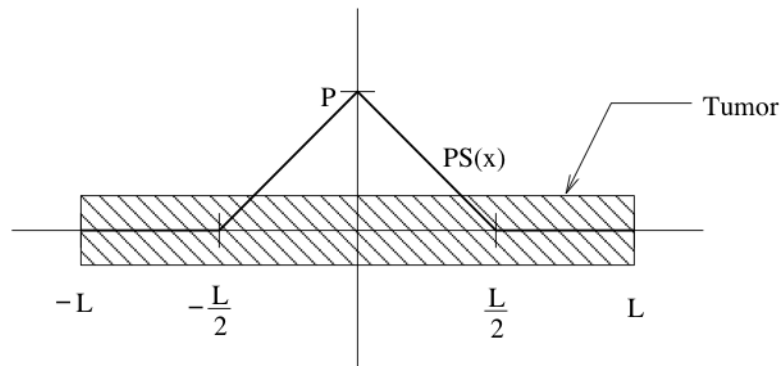


Figure 3.2: *Cross-section of tumor with chalone production rate $PS(x)$*

In Adam's model, the tumor is in Phase II so there is no necrotic core. This is just an implicit fact as Adam does not refer to different phases of tumor growth in his article. Also, Adam does not consider a mechanism of volume loss in this model.

Adam's article is an analysis of a partial differential equation representing chalone concentration, $C(x)$, with respect to distance from the center of the tumor. Directly from Adam's article, the coefficients involved in the PDE are defined as follows:

"Chalone is produced at a rate P per unit length, diffuses with diffusion coefficient D , and decays at a rate λ , proportional to its concentration $C(x, t)$ (the time dependence may be ignored...)" [1].

This leads to the PDE

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} - \lambda C + PS(x) \quad (3.2)$$

describing the diffusion of chalones in the tumor. Due to the differences between the timescale for diffusion of inhibitor versus the timescale of the growth of the tumor, for the purposes of this model the function C is considered to be independent of time. Furthermore, Adam assumes that there is a zero growth rate of the concentration of the chalone with respect to time. Using this hypothesis, along with the new definitions $\alpha = \sqrt{\frac{\lambda}{D}}$ and $\varphi = -\frac{P}{D}S(x)$, equation (3.2) can be rewritten as

$$\frac{d^2 C}{dx^2} - \alpha^2 C = \varphi(x). \quad (3.3)$$

3.1 Solution of the PDE for $C(x)$ on Region of Slowed Growth

We first solve (3.3) on the region of slowed growth, where the source term $S(x)$ is non-zero. This equation can be solved explicitly using Green's function techniques. To this end, we need to find a function $G(x, \xi)$ such that

$$C(x) = \int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi) [\varphi(\xi)] d\xi.$$

$G(x, \xi)$ is necessarily unique, and in equation (7) of his article, Adam states that the function is

$$G(x, \xi) = \begin{cases} G_1(x, \xi) := \frac{-1}{2\alpha} e^{\alpha(x-\xi)}, & -\frac{L}{2} \leq x \leq \xi \\ G_2(x, \xi) := \frac{-1}{2\alpha} e^{\alpha(\xi-x)}, & \xi \leq x \leq \frac{L}{2}. \end{cases} \quad (3.4)$$

This definition must be checked against the aforementioned criteria. Note that by using (3.3) we have

$$\begin{aligned}
\int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi)[\varphi(\xi)]d\xi &= \int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi)[C''(\xi) - \alpha^2 C(\xi)]d\xi \\
&= \int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi)C''(\xi)d\xi - \alpha^2 \int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi)C(\xi)d\xi \\
&=: A - \alpha^2 B.
\end{aligned}$$

First, we examine A .

$$\begin{aligned}
A &= \int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi)C''(\xi)d\xi \\
&= -\frac{1}{2\alpha} \int_{-\frac{L}{2}}^x e^{\alpha(\xi-x)} C''(\xi)d\xi - \frac{1}{2\alpha} \int_x^{\frac{L}{2}} e^{\alpha(x-\xi)} C''(\xi)d\xi \\
&=: -\frac{1}{2\alpha} I_- - \frac{1}{2\alpha} I_+.
\end{aligned}$$

By the definitions presented thus far, in order for $G(x)$ as defined in equation (3.4) to satisfy the requirements of the Green's function, it is necessary that

$$\begin{aligned}
C(x) &= A - \alpha^2 B \\
&= \frac{-1}{2\alpha} (I_- + I_+) - \alpha^2 B.
\end{aligned} \tag{3.5}$$

Note that

$$\begin{aligned}
I_- &:= \int_{-\frac{L}{2}}^x e^{\alpha(\xi-x)} C''(\xi)d\xi \\
&= e^{\alpha(\xi-x)} C'(\xi) \Big|_{\xi=-\frac{L}{2}}^{\xi=x} - \alpha e^{\alpha(\xi-x)} C(\xi) \Big|_{\xi=-\frac{L}{2}}^{\xi=x} + \alpha^2 \int_{-\frac{L}{2}}^x e^{\alpha(\xi-x)} C(\xi)d\xi,
\end{aligned}$$

using integration by parts twice. Evaluating at the bounds yields

$$\begin{aligned}
I_- &= C'(x) - e^{\alpha(\frac{-L}{2}-x)} C' \left(\frac{-L}{2} \right) - \alpha C(x) + \alpha e^{\alpha(\frac{-L}{2}-x)} C \left(\frac{-L}{2} \right) \\
&\quad + \alpha^2 \int_{-\frac{L}{2}}^x e^{\alpha(\xi-x)} C(\xi)d\xi.
\end{aligned} \tag{3.6}$$

I_+ can be approached in a similar fashion, and after integrating by parts twice and evaluating at the bounds we get

$$\begin{aligned}
I_+ &= -C'(x) + e^{\alpha(x-\frac{L}{2})}C' \left(\frac{L}{2} \right) - \alpha C(x) + \alpha e^{\alpha(x-\frac{L}{2})}C \left(\frac{L}{2} \right) \\
&\quad + \alpha^2 \int_x^{\frac{L}{2}} e^{\alpha(x-\xi)}C(\xi)d\xi.
\end{aligned} \tag{3.7}$$

Thus, using equations (3.6) and (3.7), we have the following:

$$\begin{aligned}
A &= \frac{-1}{2\alpha} (I_- + I_+) \\
&= \frac{-1}{2\alpha} \left(\alpha^2 \int_{-\frac{L}{2}}^{\frac{L}{2}} (-2\alpha)G(x, \xi)C(\xi)d\xi + e^{\alpha(x-\frac{L}{2})} \left[C' \left(\frac{L}{2} \right) + \alpha C \left(\frac{L}{2} \right) \right] \right. \\
&\quad \left. - 2\alpha C(x) + e^{\alpha(\frac{-L}{2}-x)} \left[-C' \left(\frac{-L}{2} \right) + \alpha C \left(\frac{-L}{2} \right) \right] \right) \\
&= \alpha^2 B + C(x) - \frac{1}{2\alpha} e^{\alpha(x-\frac{L}{2})} \left[C' \left(\frac{L}{2} \right) + \alpha C \left(\frac{L}{2} \right) \right] \\
&\quad - \frac{1}{2\alpha} e^{\alpha(\frac{-L}{2}-x)} \left[-C' \left(\frac{-L}{2} \right) + \alpha C \left(\frac{-L}{2} \right) \right].
\end{aligned}$$

Hence, we need

$$C(x) = A - \alpha^2 B,$$

where we now know that

$$\begin{aligned}
A - \alpha^2 B &= \frac{-1}{2\alpha} (I_- + I_+) - \alpha^2 B \\
&= -\alpha^2 B + \alpha^2 B + C(x) - \frac{1}{2\alpha} e^{\alpha(x-\frac{L}{2})} \left[C' \left(\frac{L}{2} \right) + \alpha C \left(\frac{L}{2} \right) \right] \\
&\quad - \frac{1}{2\alpha} e^{\alpha(\frac{-L}{2}-x)} \left[-C' \left(\frac{-L}{2} \right) + \alpha C \left(\frac{-L}{2} \right) \right] \\
&= C(x) - \frac{1}{2\alpha} e^{\alpha(x-\frac{L}{2})} \left[C' \left(\frac{L}{2} \right) + \alpha C \left(\frac{L}{2} \right) \right] \\
&\quad - \frac{1}{2\alpha} e^{\alpha(\frac{-L}{2}-x)} \left[-C' \left(\frac{-L}{2} \right) + \alpha C \left(\frac{-L}{2} \right) \right].
\end{aligned}$$

In order for this equation to hold, it is necessary that

$$0 = -\frac{1}{2\alpha}e^{\alpha(x-\frac{L}{2})} \left[C' \left(\frac{L}{2} \right) + \alpha C \left(\frac{L}{2} \right) \right] - \frac{1}{2\alpha}e^{\alpha(\frac{-L}{2}-x)} \left[-C' \left(\frac{-L}{2} \right) + \alpha C \left(\frac{-L}{2} \right) \right].$$

Thus, it must be true that

$$0 = \left[C' \left(\frac{L}{2} \right) + \alpha C \left(\frac{L}{2} \right) \right] \quad (3.8)$$

and that

$$0 = \left[-C' \left(\frac{-L}{2} \right) + \alpha C \left(\frac{-L}{2} \right) \right]. \quad (3.9)$$

Since this model is acting under the assumption of radial symmetry,

$$C \left(\frac{L}{2} \right) = C \left(\frac{-L}{2} \right)$$

and

$$C' \left(\frac{L}{2} \right) = -C' \left(\frac{-L}{2} \right).$$

Thus, the two requirements in equations (3.8) and (3.9) are actually equivalent. Therefore, the only criteria needing to be satisfied is

$$C' \left(\frac{L}{2} \right) = -\alpha C \left(\frac{-L}{2} \right). \quad (3.10)$$

In Adam's article this criteria is never explicitly stated, yet clearly it must hold in order to validate his Green's function solution. Adam's work is modeled after the work of Glass, and Glass' article [5] does articulate a *similar* boundary condition. In equation (4), Glass asserts that

$$D \frac{\partial C}{\partial r} \Big|_{r=R} = -\beta C(R), \quad (3.11)$$

where β is defined to be the ratio of the permeability of the tissue surface over the diffusion coefficient of the chalone. This equation results from the assumption that the chalone will become diluted upon passing through the boundary of the tumor, and that the flux on the boundary of the tumor is equal to the "leakage flux" [5]. Using Adam's notation (and Glass' notation as well) we call the diffusion coefficient D , and we introduce the notation that the permeability of the tissue is M . Thus, $\beta = \frac{M}{D}$.

This condition (3.11) validates the Green's function in Adams article if and only if

$$\begin{aligned} \frac{M}{D} &=: \beta \\ &= \alpha \\ &:= \sqrt{\frac{\lambda}{D}}, \end{aligned}$$

where λ is the rate of decay of the chalone [1]. Equivalently, it must be true that

$$M = \sqrt{D\lambda}. \quad (3.12)$$

This relationship between the permeability of the tissue surface, the diffusion coefficient of the chalone, and the decay rate of the chalone seems like somewhat of a stretch and is not mentioned in Adam's article. However, it will be assumed here in order to continue an analysis of Adam's model.

Under the assumption (3.12), it has now been verified that $C(x)$ is given explicitly by:

$$C(x) = \int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi) [\varphi(\xi)] d\xi,$$

where $G(x, \xi)$ is defined according to (3.4). Observe that this representation holds for fairly general source terms φ .

3.2 Evaluation of $C(x)$ on the Region of Slowed Growth

Now we turn to the evaluation of $C(x)$ when the source function φ is taken to be $-\frac{P}{D}S(x)$ as in Adam's article [1]. Adam gives the formula

$$\frac{DC(x)}{P} = \frac{2}{\alpha^3 L} \left[e^{-\alpha \frac{L}{2}} \cosh(\alpha|x|) + \alpha \left(\frac{L}{2} - |x| \right) - e^{-\alpha|x|} \right]$$

in equation (11) of his article, and we look to verify this equation.

The definition of G in equation (3.4) and the definition $\varphi = -\frac{P}{D}S(x)$ give us

$$\begin{aligned}
C(x) &= \int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi) \varphi(\xi) d\xi \\
&= \frac{-P}{D} \int_{-\frac{L}{2}}^{\frac{L}{2}} G(x, \xi) S(\xi) d\xi \\
&= \begin{cases} \frac{-P}{D} \left[\int_{-\frac{L}{2}}^x G_2(x, \xi) S(\xi) d\xi + \int_x^{\frac{L}{2}} G_1(x, \xi) S(\xi) d\xi \right], & x < 0 \\ \frac{-P}{D} \left[\int_{-\frac{L}{2}}^0 G_2(x, \xi) S(\xi) d\xi + \int_{-\frac{L}{2}}^x G_2(x, \xi) S(\xi) d\xi \right], & x \geq 0 \end{cases}
\end{aligned}$$

These integrals can now be evaluated. First, consider $x < 0$. We have:

$$\begin{aligned}
\frac{-DC(x)}{P} &= \int_{-\frac{L}{2}}^x G_2(x, \xi) S(\xi) d\xi + \int_x^0 G_1(x, \xi) S(\xi) d\xi + \int_0^{\frac{L}{2}} G_1(x, \xi) S(\xi) d\xi \\
&:= I + II + III.
\end{aligned}$$

$$\begin{aligned}
I &= \frac{-1}{2\alpha} \int_{-\frac{L}{2}}^x e^{\alpha(\xi-x)} \left(1 + \frac{2}{L}\xi \right) d\xi \\
&= \frac{-1}{2\alpha} \int_{-\frac{L}{2}}^x e^{\alpha(\xi-x)} d\xi - \frac{1}{L\alpha} \int_{-\frac{L}{2}}^x \xi e^{\alpha(\xi-x)} d\xi \\
&= \frac{-1}{2\alpha^2} \left[e^{\alpha(\xi-x)} \right]_{-\frac{L}{2}}^x - \frac{1}{L\alpha} \left[\frac{\xi}{\alpha} e^{\alpha(\xi-x)} \right]_{-\frac{L}{2}}^x - \int_{-\frac{L}{2}}^x \frac{1}{\alpha} e^{\alpha(\xi-x)} d\xi \\
&= \frac{-1}{2\alpha^2} + \frac{1}{2\alpha^2} e^{\alpha(\frac{-L}{2}-x)} - \frac{x}{L\alpha^2} - \frac{1}{2\alpha^2} e^{\alpha(\frac{-L}{2}-x)} + \frac{1}{L\alpha^3} - \frac{1}{L\alpha^3} e^{\alpha(\frac{-L}{2}-x)} \\
&= \frac{-1}{2\alpha^2} - \frac{x}{L\alpha^2} + \frac{1}{L\alpha^3} - \frac{1}{L\alpha^3} e^{\alpha(\frac{-L}{2}-x)}.
\end{aligned}$$

Also,

$$\begin{aligned}
II &= \frac{-1}{2\alpha} \int_x^0 e^{\alpha(x-\xi)} \left(1 + \frac{2}{L}\xi\right) d\xi \\
&= \frac{-1}{2\alpha} \int_x^0 e^{\alpha(x-\xi)} d\xi - \frac{1}{L\alpha} \int_x^0 \xi e^{\alpha(x-\xi)} d\xi \\
&= \frac{1}{2\alpha^2} \left[e^{\alpha(x-\xi)} \right]_x^0 - \frac{1}{L\alpha} \left[\frac{-\xi}{\alpha} e^{\alpha(x-\xi)} \right]_x^0 + \int_x^0 \frac{1}{\alpha} e^{\alpha(x-\xi)} d\xi \\
&= \frac{1}{2\alpha^2} e^{\alpha x} - \frac{1}{2\alpha^2} - \frac{x}{L\alpha^2} + \frac{1}{L\alpha^3} e^{\alpha x} - \frac{1}{L\alpha^3}.
\end{aligned}$$

Finally, we have

$$\begin{aligned}
III &= \frac{-1}{2\alpha} \int_0^{\frac{L}{2}} e^{\alpha(x-\xi)} \left(1 - \frac{2}{L}\xi\right) d\xi \\
&= \frac{-1}{2\alpha} \int_0^{\frac{L}{2}} e^{\alpha(x-\xi)} d\xi + \frac{1}{L\alpha} \int_0^{\frac{L}{2}} \xi e^{\alpha(x-\xi)} d\xi \\
&= \frac{1}{2\alpha^2} \left[e^{\alpha(x-\xi)} \right]_0^{\frac{L}{2}} + \frac{1}{L\alpha} \left[\frac{-\xi}{\alpha} e^{\alpha(x-\xi)} \right]_0^{\frac{L}{2}} + \int_0^{\frac{L}{2}} \frac{1}{\alpha} e^{\alpha(x-\xi)} d\xi \\
&= \frac{1}{2\alpha^2} e^{\alpha(x-\frac{L}{2})} - \frac{1}{2\alpha^2} e^{\alpha x} - \frac{1}{2\alpha^2} e^{\alpha(x-\frac{L}{2})} - \frac{1}{L\alpha^3} e^{\alpha(x-\frac{L}{2})} + \frac{1}{L\alpha^3} e^{\alpha x} \\
&= -\frac{1}{2\alpha^2} e^{\alpha x} - \frac{1}{L\alpha^3} e^{\alpha(x-\frac{L}{2})} + \frac{1}{L\alpha^3} e^{\alpha x}.
\end{aligned}$$

Hence,

$$\begin{aligned}
\frac{-DC(x)}{P} &= I + II + III \\
&= \frac{-1}{2\alpha^2} - \frac{x}{L\alpha^2} + \frac{1}{L\alpha^3} - \frac{1}{L\alpha^3} e^{\alpha(\frac{-L}{2}-x)} + \frac{1}{2\alpha^2} e^{\alpha x} - \frac{1}{2\alpha^2} \\
&\quad - \frac{x}{L\alpha^2} + \frac{1}{L\alpha^3} e^{\alpha x} - \frac{1}{L\alpha^3} - \frac{1}{2\alpha^2} e^{\alpha x} - \frac{1}{L\alpha^3} e^{\alpha(x-\frac{L}{2})} + \frac{1}{L\alpha^3} e^{\alpha x} \\
&= \frac{-1}{\alpha^2} - \frac{2x}{L\alpha^2} - \frac{e^{-\alpha\frac{L}{2}}}{L\alpha^3} (e^{-\alpha x} + e^{\alpha x}) + \frac{2}{L\alpha^3} e^{\alpha x} \\
&= \frac{-2}{L\alpha^3} \left[\frac{L\alpha}{2} + x\alpha + e^{-\alpha\frac{L}{2}} \left(\frac{e^{-\alpha x} + e^{\alpha x}}{2} \right) + e^{-\alpha|x|} \right] \\
&= \frac{-2}{L\alpha^3} \left[\frac{L\alpha}{2} - |x|\alpha + e^{-\alpha\frac{L}{2}} \left(\frac{e^{\alpha|x|} + e^{-\alpha|x|}}{2} \right) + e^{-\alpha|x|} \right] \\
&= \frac{-2}{L\alpha^3} \left[\alpha \left(\frac{L}{2} - |x| \right) + e^{-\alpha\frac{L}{2}} \cosh(\alpha|x|) - e^{-\alpha|x|} \right].
\end{aligned}$$

This completes the derivation for $C(x)$ when $x < 0$. The derivation for $C(x)$ when $x \geq 0$ is similar and is not included here. In the case $x \geq 0$, $C(x)$ again works out to provide the same answer as in the case $x \leq 0$, which is in line with the assumption of radial symmetry. This completes the derivation of equation (11) from Adam's article:

$$\frac{DC(x)}{P} = \frac{2}{\alpha^3 L} \left[e^{-\alpha\frac{L}{2}} \cosh(\alpha|x|) + \alpha \left(\frac{L}{2} - |x| \right) - e^{-\alpha|x|} \right]. \quad (3.13)$$

3.3 Solution for C(x) on Region of Normal Growth

Now we have found an explicit formula for $C(x)$ when $|x| \leq \frac{L}{2}$. This can be extended by finding a formula for $C(x)$ on $|x| > \frac{L}{2}$. Because of the elliptic regularity results that we used in Chapter 2, it is necessary that both $C(x)$ and $C'(x)$ be continuous on $|x| = \frac{L}{2}$. Thus, any formula for $C(x)$ on $|x| > \frac{L}{2}$ must match up with equation (3.13) for $|x| = \frac{L}{2}$. Due to the assumption of radial symmetry, it is sufficient to analyze the case $x \geq 0$. Therefore, we evaluate $C(x)$ from equation (3.13) at the boundary of the tumor ($x = \frac{L}{2}$):

$$\begin{aligned}
C\left(x = \frac{L}{2}\right) &= \frac{2P}{D\alpha^3 L} \left[e^{-\alpha \frac{L}{2}} \cosh\left(\alpha \frac{L}{2}\right) - e^{-\alpha \frac{L}{2}} \right] \\
&= \frac{2P}{\alpha L \lambda} \left[\frac{1}{2} + \frac{1}{2} \left(e^{\frac{-\alpha L}{2}} \right)^2 - e^{-\alpha \frac{L}{2}} \right] \\
&= \frac{P}{\alpha L \lambda} \left[1 + \left(e^{\frac{-\alpha L}{2}} \right)^2 - 2e^{-\alpha \frac{L}{2}} \right],
\end{aligned}$$

and so

$$C\left(|x| = \frac{L}{2}\right) = \frac{P}{\alpha L \lambda} \left[1 - e^{\frac{-\alpha L}{2}} \right]^2. \quad (3.14)$$

Note that this is equation (13) from Adam's article. Also, notice that

$$C'\left(x = \frac{L}{2}\right) = \frac{P}{\alpha L \lambda} \left[-\alpha - \alpha \left(e^{\frac{-\alpha L}{2}} \right)^2 + 2\alpha e^{\frac{-\alpha L}{2}} \right]. \quad (3.15)$$

Now, on $|x| > \frac{L}{2}$, $S(x) = 0$. Thus, the partial differential equation for $C(x)$ becomes

$$C''(x) - \alpha^2 C(x) = 0. \quad (3.16)$$

The solution to this differential equation has the form

$$C(x) = c_1 e^{\alpha x} + c_2 e^{-\alpha x}. \quad (3.17)$$

The constants in this equation can be determined using equations (3.14) and (3.15).

Notice from those two equations that $C'\left(\frac{L}{2}\right) = -\alpha C\left(\frac{L}{2}\right)$. Thus,

$$\begin{aligned}
-\alpha c_1 e^{\alpha x} - \alpha c_2 e^{-\alpha x} &= \alpha c_1 e^{\alpha x} - \alpha c_2 e^{-\alpha x} \\
2\alpha c_1 e^{\alpha x} &= 0 \\
c_1 &= 0.
\end{aligned}$$

Hence, equation (3.17) becomes

$$C(x) = c_2 e^{-\alpha x}. \quad (3.18)$$

This definition of $C(x)$ along with equation (3.14) combine to yield

$$\begin{aligned}
c_2 e^{-\frac{\alpha L}{2}} &= \frac{P}{\alpha L \lambda} \left[1 + \left(e^{-\frac{\alpha L}{2}} \right)^2 - 2e^{-\frac{\alpha L}{2}} \right] \\
c_2 &= \frac{P}{\alpha L \lambda} \left[e^{\frac{\alpha L}{2}} + e^{-\frac{\alpha L}{2}} - 2 \right] \\
&= \frac{4P}{\alpha L \lambda} \left[\frac{e^{\frac{\alpha L}{4}} - e^{-\frac{\alpha L}{4}}}{2} \right]^2 \\
&= \frac{4P}{\alpha L \lambda} \left[\sinh \left(\frac{\alpha L}{4} \right) \right]^2.
\end{aligned}$$

The resulting equation for $C(x)$ for $x > \frac{L}{2}$ is equation (14) from Adam's article:

$$C(x) = \frac{4P}{\alpha L \lambda} \left[\sinh \left(\frac{\alpha L}{4} \right) \right]^2 e^{-\alpha x}. \quad (3.19)$$

3.4 Behavior of $C(x)$

Adam uses the definition of $C(x)$ found in equation (3.13) to study some particular values of chalone concentration within the tumor. First, note that by the definition of chalone production found in (3.1), the production of chalone is at its highest level when $x = 0$ (at the center of the tumor). Also, using equation (3.13), the concentration of chalone at this point is

$$\begin{aligned}
C(x=0) &= \frac{2P}{D\alpha^3 L} \left[e^{-\alpha \frac{L}{2}} + \alpha \left(\frac{L}{2} \right) - 1 \right] \\
&= \frac{2P}{\alpha L \lambda} \left[e^{-\alpha \frac{L}{2}} + \alpha \frac{L}{2} - 1 \right].
\end{aligned} \quad (3.20)$$

Furthermore, it is clear by inspection that $C'(0) = 0$, as

$$C'(x) = \frac{2P}{\alpha \lambda L} \left[\alpha e^{-\alpha \frac{L}{2}} \sinh(\alpha|x|) - \alpha + \alpha e^{-\alpha|x|} \right],$$

which agrees with what is required by elliptic regularity theory. Therefore, 0 is a critical value of $C(x)$. Note that

$$x_1 := \frac{1}{\alpha} \ln \left(2e^{\frac{\alpha L}{2}} - 1 \right)$$

is also a critical value of $C(x)$:

$$\begin{aligned}
C' \left(\frac{1}{\alpha} \ln \left(2e^{\frac{\alpha L}{2}} - 1 \right) \right) &= \frac{2P}{\alpha \lambda L} \left[\frac{\alpha}{2} e^{-\alpha \frac{L}{2}} \left(2e^{\frac{\alpha L}{2}} - 1 - \frac{1}{2e^{\frac{\alpha L}{2}} - 1} \right) - \alpha \right. \\
&\quad \left. + \alpha \frac{1}{2e^{\frac{\alpha L}{2}} - 1} \right] \\
&= \frac{2P}{\alpha \lambda L} \left[-\frac{\alpha}{2} e^{-\frac{\alpha L}{2}} - \frac{\frac{1}{2} \alpha e^{-\frac{\alpha L}{2}}}{2e^{\frac{\alpha L}{2}} - 1} + \frac{\alpha}{2e^{\frac{\alpha L}{2}} - 1} \right] \\
&= 0.
\end{aligned}$$

However, as $e^{\frac{\alpha L}{2}} > 1$, we see that $2e^{\frac{\alpha L}{2}} > 1 + e^{\frac{\alpha L}{2}}$, which leads us to $x_1 > \frac{L}{2}$. It also can be shown numerically that for all $x = x^*$ such that $0 < x^* < x_1$, $C'(x^*) \neq 0$.

To examine the nature of the critical point 0, we first notice that

$$C''(x) = \frac{2P}{\alpha \lambda L} \left[\alpha^2 e^{-\alpha \frac{L}{2}} \cosh(\alpha|x|) - \alpha^2 e^{-\alpha|x|} \right],$$

or

$$C''(x) = \frac{2P\alpha}{\lambda L} \left[e^{-\alpha \frac{L}{2}} \cosh(\alpha|x|) - e^{-\alpha|x|} \right].$$

Therefore,

$$\begin{aligned}
C''(0) &= \frac{2P\alpha}{\lambda L} \left[e^{-\frac{\alpha L}{2}} - 1 \right] \\
&< 0.
\end{aligned}$$

Hence, $C(x)$ is maximized locally when $x = 0$. Since $C(x)$ is continuous and $C'(x) \neq 0$ for x such that $0 < x < x_1$ where $x_1 > \frac{L}{2}$, we know that $C(x)$ on $[0, \frac{L}{2}]$ is in fact maximized when $x = 0$. We also now know that $C(x)$ is monotonically decreasing from $C(0)$ to $C(\frac{L}{2})$ (recall that the values of $C(0)$ and $C(\frac{L}{2})$ are given in equations (3.14) and (3.20)). Since we are assuming radial symmetry, $C(x)$ has the same behavior on $[-\frac{L}{2}, 0]$.

3.5 C(x) and Tumor Growth

Now we can examine the effects that the chalone has on the growth of the tumor. Adam works under the assumption that chalone slows the cells' mitosis rates until a certain critical value of the concentration of chalone, $C(x) = \theta$, is reached and mitosis ceases. Under this assumption, the tumor will reach a steady state when $\theta = C(x)$ throughout the tumor. Note that in the model of McElwain and Morris, when a tumor was in a steady state the cells still experienced mitosis. This mitosis was just offset by the volume lost. Here in Adam's model, no mechanism of volume loss is

under consideration. Therefore, it is necessary that in order for the tumor to reach a steady state, there can be no mitosis. Due to this fact, we restrict our consideration to a tumor with chalcones being produced throughout the tumor. In order to keep the notation consistent, we will define the cross-section of this tumor to be the region $\left[-\frac{L}{2}, \frac{L}{2}\right]$.

We will now turn to an examination of the value of the radius of this dormant tumor, L_s . First, we introduce the notation

$$n := \frac{P}{2\lambda\theta} \quad \text{and} \quad l := \frac{\alpha L_s}{2} = \frac{1}{2} \sqrt{\frac{\lambda}{D}} L_s.$$

Note that the terms are dimensionless. Now, in order for no cells in the tumor to undergo mitosis, it is necessary that $C(x) \geq \theta$ for all x such that $-\frac{L}{2} \leq x \leq \frac{L}{2}$. Thus, as we determined in section (3.4) that $C(x)$ decreases monotonically from $x = 0$ to $x = \left|\frac{L}{2}\right|$, in order for mitosis to cease on the entire region $\left[-\frac{L}{2}, \frac{L}{2}\right]$, it is sufficient to have $C\left(\left|\frac{L}{2}\right|\right) \geq \theta$. This leads to the critical value $C\left(\left|\frac{L}{2}\right|\right) = \theta$ at which mitosis will not occur throughout the tumor. As we have labeled the limiting radius of the tumor L_s , we now have

$$C\left(\frac{L_s}{2}\right) = \theta. \tag{3.21}$$

This equation can be used to find an explicit formula for L_s , and hence l . From equations (3.14) and (3.21) we have

$$\frac{P}{\alpha L_s \lambda} \left[1 - e^{-\frac{\alpha L_s}{2}}\right]^2 = \theta, \tag{3.22}$$

or

$$\left[1 - e^{-l}\right]^2 = \frac{2\theta\lambda\alpha L_s}{P} = \frac{l}{n}. \tag{3.23}$$

Clearly, for all $n > 0$, this equation has the trivial solution $l = 0$. There are also nontrivial solutions for a large enough value of n . Note that by taking derivatives on equation (3.22) (and using elliptic regularity results) we have the additional equation

$$\frac{1}{n} = 2e^{-l} (1 - e^{-l}). \tag{3.24}$$

We can eliminate n by solving for $\frac{l}{n}$ in equations (3.23) and (3.24) to get

$$2l = e^l - 1. \tag{3.25}$$

This equation was solved numerically in Adam's article, where it was determined that $l = 1.2573$, corresponding to $n = 2.4554$. Adam was also able to conclude that "two non-trivial solutions to (3.23) exist for n greater than this value, while there are no nontrivial solutions for n less than this value." Finally, Adam concluded that

"for all those values of L satisfying

$$(1 - e^{-l}) \geq \frac{1}{n}$$

the growth is stable and that a limiting size of tissue exists" [1].

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Appendix A

Notation for Apoptosis as a Volume Loss Mechanism..., McElwain and Morris

$\sigma(r)$	nutrient concentration in tumor at radius r
σ_∞	nutrient concentration on boundary of tumor
$\hat{\sigma}$	nutrient deficiency phenomena below this nutrient concentration
σ_i	critical level of nutrient concentration, below which cells die
R_0	outer radius of the tumor
\hat{R}	Radius in tumor such that $\sigma(\hat{R}) = \hat{\sigma}$
R_i	Radius in tumor such that $\sigma(R_i) = \sigma_i$
s	growth rate per unit volume
λ	death rate per unit volume
A	value such that $Af(\sigma)$ represents nutrient consumption
k	coefficient of diffusion of the nutrient in the tumor
τ	st , where t represents time
B	$\sqrt{\frac{A}{k\hat{\sigma}}}$
ξ	BR_0
γ	$\frac{\lambda}{s}$
ρ	$B\hat{R}$
η	BR_i
G	$\frac{\hat{\sigma}}{\sigma_i}(\cosh(\rho - \eta) + \eta \sinh(\rho - \eta)) - 1$