A Two Strain Spatiotemporal Mathematical Model of Cancer

With Free Boundary Condition

by

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ABSTRACT

In a 2004 paper, John Nagy raised the possibility of the existence of a hypertumor i.e., a focus of aggressively reproducing parenchyma cells that invade part or all of a tumor. His model used a system of nonlinear ordinary differential equations to find a suitable set of conditions for which these hypertumors exist. Here that model is expanded by transforming it into a system of nonlinear partial differential equations with diffusion, advection, and a free boundary condition to represent a radially symmetric tumor growth. Two strains of parenchymal cells are incorporated; one forming almost the entirety of the tumor while the much more aggressive strain appears in a smaller region inside of the tumor. Simulations show that if the aggressive strain focuses its efforts on proliferating and does not contribute to angiogenesis signaling when in a hypoxic state, a hypertumor will form. More importantly, this resultant aggressive tumor is paradoxically prone to extinction and hypothesize is the cause of necrosis in many vascularized tumors.
DEDICATION

For my siblings, Pascual M. and Ana Alvarez
And my parents, Pascual R. and Margarita Alvarez
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Chapter 1

INTRODUCTION

Douglas Hanahan and Robert Weinberg first presented their theory about conditions for tumor growth in 2000 (and expanded it in 2011). The theory suggests tumorigenesis occurs when (and only when) a single cell acquires the following six characteristics: (1) self-sustaining proliferative signaling, (2) evading external sources of growth suppression, (3) resisting apoptotic signals, (4) promoting tumor angiogenesis, (5) enabling replicative immortality, and (6) ability to invade surrounding tissue and metastasize [26]. While these traits are usually sufficient, they are not necessary but it demonstrates cancer is an evolutionary process; any mutations that redirect more of the body’s resources to cancer cells will be selected [32].

Malignant tumors arise from previously healthy and genomically intact cells and are made up of various cell phenotypes, both cancerous (parenchyma) and healthy (stroma). They affect almost all classes of vertebrates but appear to be most common in mammals [20, 21]. Tumors evolve by clonal selection of cell populations that proliferate in an unconstrained manner, accumulate mutations, and compete for nutrients or space [2]. These tumors tend to share similar characteristic behaviors of, uncontrolled growth, lack of tissue integration, invasion of surrounding tissue, and metastasis [37]. Natural selection always favors more aggressive parenchyma cell phenotypes [31].

Nagy tried to answer the following two questions in 2004 [36]. First, what allows for parenchyma diversity and the tissue-like organization among parenchymal and stromal subpopulations? Secondly, how will the parenchyma population evolve over time? He argued if tumors act like ecological communities, then cell types should segregate into distinct niches and live off of different sets of resources because of competitive exclusion [36]. However, if tumors are more like integrated tissues, natural selection should favor diverse but cooperative cell types. His results showed that if a mutant cell type becomes established within a tumor, and that cell type applies more resources to proliferation than residents do, then the mutant type will tend to invade, eventually become established within and often dominate the tumor [36]. Paradoxically, his model also showed selection can favor phenotypes that eventually destroy part or perhaps all of the tumor - a situation he refers to as a hypertumor. The hypertumor mechanism may be a cause of the necrosis
observed in many vascularized tumors [36].

The work published since the appearance of Nagy’s article has consisted mainly of biological/evolutionary reviews on cancer growth (see [15, 25, 23, 31, 33, 13, 4, 34]). The mathematical models since then have addressed a variety of topics. In Thalhauser et al’s paper [47], the authors model a tumor cord - growing tumor tissue surrounding pre-existing blood microvessels - but allow the two phenotypes to carry out one process each, either cell growth or motility. Their results were that overly aggressive growers would have a greater chance of causing microvessel collapse, ischemia, and eventual starvation and death to all cells in the local area and, conversely, aggressive movers would be less likely to cause ischemia. They hypothesize that prevention of ischemia is a selective force in favor of the aggressively motile cells, even before a tumor becomes metastatic. Their version of the hypertumor is analogous to the aggressive grower class and they hypothesize that evolution of the grower class is selected against by the instability it can cause in the local vascular network. The main differences between our model and Thalhauser et al’s model are that both of our parenchyma phenotypes are able to carry out both processes, motility and growth, compete for resources, and also that our domain has a free boundary.

In the work done by Nagy and Armbruster [39], the authors return to the model in [36] and add energy management via ATP to the model to investigate if ATP can lead to an evolutionary description of the angiogenic switch. The results in their paper [39] are in line with those of [36] and additionally show that the strategy leading to extreme vascular hyperplasia may explain the vascular hyperplasia evident in certain tumor types. This model [39] is described by a system of ODEs, thus not taking into account any of the spatial effects of the system. Other models address the question of whether hypertumors can be caused by tumor phosphorous demand [38], which we do not explore in our model.

There has been plenty of work done using free-boundary value problems to resolve questions stemming from mathematical oncology (for a review, please see [3, 35, 42]). Tumorigenesis is an ideal candidate for free-boundary problems because we are interested the way tumors advance in time and in space, and, since tumors are living tissue, they should be able to move around, grow, and spread. The mathematical modeling of tumor growth via free-boundary problems can be split into two categories, those that model avascular tumors and those that model vascular tumors. The bulk
of the published material falls into the former group (see [16, 8, 6, 18, 42, 43] and references therein) because they are modeling tumors in vitro. The few vascular tumor models either do not include necrosis [19] or fail to capture the competition between competing phenotypes [14]. Those that do contain both competition and necrosis are primarily concerned with the effect of drug treatment to reduce the overall size of the tumor [28, 27].

In our model, we modify the definition of a hypertumor to incorporate spatial effects as well. Hypertumors arise, in our model, when a mutant cell type applies more resources locally to reproduction than the residents do and causes the growth in that region to become negative. If the density of the resident strain decreases in that region only, or in the whole tumor region in the case that the resident strain gets wiped out, we call this a hypertumor. Our findings back Nagy’s results indicating that heterogeneous tumors behave more like ecological systems than like integrated tissues when taking into consideration spatial effects of the system.

Our study seeks to answer three questions about the hypertumor phenomenon through mathematical modeling and simulation. Can the mechanism account for necrosis in vascularized tumors? Dr. Nagy [36] hypothesized that it could, and if our spatial model can show the appearance of necrosis in simulated situations similar to those in which they are observed in vivo, this will help to support the concept that necrosis can be caused by hypertumors.

Additionally, we would like show that hypertumors can cause tumors to shrink in size. If hypertumors can cause resource instability along the boundary of the tumor, this would cause the tumor to reduce in size since the cells in that region would necrose and then wash away via the advective flow.

Lastly, there are different kinds of tumors in which there is a separation between different parenchymal cells, e.g. squamous cell carcinoma. If we show that the hypertumor mechanism can also describe this process of separation, it would illuminate how prominent this mechanism may be in nature.

We address these questions by formulating a mathematical model that describes three aspects of a single solid tumor: change in mass over time and space; change in tumor vascularization over time and space; and competition between two different parenchyma cell types. Furthermore,
we assume the tumor occupies a well-defined region in space and the boundary of this region is held together by the forces of cell-to-cell adhesion [16].

1.1 Biological Model Assumptions

The main assumptions used in the present work are listed below:

1. Throughout the tumor, just two components occupy volume: parenchyma cells (of both phenotypes) and necrotic cells. We assume that the contribution to the volume from VECs is negligible.

2. The tumor is partitioned into a viable region and, possibly, a necrotic core (if one forms). The interface is identified as the surface where the limiting nutrient supply rate ($\Phi(v)$) takes a given critical value (here, $\Phi(v) < 0$).

3. Tumor cells die only if the local density of nutrient is not sufficient to feed them, or as a result of inter-phenotype competition for space.

4. Dead tumor cells may naturally disintegrate into waste products, mainly water.

5. Dead tumor cells do not actively move, but are subject to passive displacement via advection.

6. Dead tumor cells outside the tumor are phagocyted by macrophages.

7. Chemical factors naturally degrade.

8. Nutrients are mainly carried by the capillary network.

9. The density of all cell types are assumed to be the same.

10. Nutrient is absorbed by living tumor cells.

1.2 Model Formulation

Tumors are formed from the cell-to-cell adhesion of parenchymal cells and grow by cell mitosis [50]. Initially, when tumors are forming, they get all of their nutrients from the surrounding stroma [50]. As this tumor grows, having the nutrients diffuse into the tumor from the surrounding stroma is no longer enough to support the growing mass and the tumor must grow its own vasculature to support itself.
We consider a tumor growing in $B(0, R(t))$, the ball of radius $R(t)$ in $\mathbb{R}^n$, where $n = \{1, 2, 3\}$. We choose this geometry because when tumors are forming they clump into spheroids, as seen in Figure 1.1 [50]. Thus, using spherical symmetry for our model is a reasonable assumption. Furthermore, we assume that the region is only occupied by parenchymal cells, i.e. no stroma is found within the tumor. Tumors develop their own vasculature when they reach the critical radius of approximately 1 mm [50]. This vasculature is formed when vascular endothelial cells (VECs) combine with existing microvessels from the surrounding stroma and form new blood vessels in the tumor [50]. The microvessels and VECs have a mass that is insignificant when compared to that of the parenchymal cells, so in our model we track the total vasculature to measure the availability of nutrients but do not take it into account when determining the mass of the tumor.

Tumors grow at a rate proportional to the net amount of mass created or lost through the competing biological processes of mitosis and apoptosis giving them a changing boundary as they evolve. Thus, tumors are natural candidates for mathematical problems described by a free boundary. This boundary will change in time as the mass it surrounds evolves and thus our spatial domain is time-dependent.

Figure 1.1: Picture of a tumor spheroid taken using an electron microscope [41]
We assume there is no background tissue in competition with the tumor cells for space or nutrient. While this is a very strong assumption, it allows us to focus solely on the interplay between these two competing processes in a regime where a nascent tumor has already displaced some small amount of healthy tissue.

In his 2004 paper [36], Nagy developed a system of nonlinear ordinary differential equations to model a heterogeneous primary neoplasm by tracking the mass of two different parenchyma cell types, the mass of the vascular endothelial cells and the total length of microvessels. We begin the formulation of our model by modifying Nagy’s ODE system [36] to incorporate spatial diffusion for the two different cancerous phenotypes and the endothelial cells, with densities denoted respectively by $u_1, u_2$, and $y$; the local microvessel length density will be denoted by $z$ and the resource availability will be summarized in the single variable $v$. The time-dependent radius of the tumor will be denoted by $R(t)$. We modify the growth functions of $u_1$ and $u_2$ to incorporate competition between the two types of parenchyma cells.

Table 1.1: Table of System Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Meaning</th>
<th>Units</th>
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</thead>
<tbody>
<tr>
<td>$u_i$</td>
<td>Parenchymal cells of type $i$</td>
<td>mass/volume</td>
</tr>
<tr>
<td>$u_N$</td>
<td>Necrotic cells</td>
<td>mass/volume</td>
</tr>
<tr>
<td>$y$</td>
<td>Vascular endothelial cells</td>
<td>mass/volume</td>
</tr>
<tr>
<td>$z$</td>
<td>Local microvessel length density</td>
<td>length/volume</td>
</tr>
<tr>
<td>$v$</td>
<td>Local resource concentration</td>
<td>moles/mass</td>
</tr>
<tr>
<td>$w$</td>
<td>Advective Velocity</td>
<td>length/time</td>
</tr>
<tr>
<td>$R$</td>
<td>Radius of tumor spheroid</td>
<td>length</td>
</tr>
</tbody>
</table>

Figure 1.2 describes the dynamics of the model and Table 1.1 define the variables used in the system. The necrotic cells have a washout rate $\mu_N$ and are formed from the interspecies
competition at rate $b$ and/or from the limiting nutrient supply rate, $\Phi_i$, becoming negative. The parenchymal cells $u_i$ grow when the limiting nutrient supply rate, $\Phi_i$, is positive. The local resource concentration proxy variable, $v$, is affected directly by the mean microvessel length density, $z$, and inversely by the local parenchymal cell density, $u_i$. This dependence is given by (1.2). If $v$ gets high enough it also contributes to the growth of the VECs, $y$, which also washout at a rate $\beta$. The mean microvessel length density, $z$, is directly affected by the concentration of VECs and by the washout with the rate given in (1.9).

Let $u_1(s,t)$ and $u_2(s,t)$ be the mass density of parenchymal cells at time $t$ and position $s$ with phenotypes 1 and 2, respectively. Define $u(s,t) := u_1(s,t) + u_2(s,t)$, which is the total mass density of the non-necrotic tumor cells. Then $u_i(s,t)$ and therefore $u(s,t)$ take units mass/volume. Nevertheless, these densities have no clear biological meaning, but their integrals do. For example,

$$\int_{\mathcal{A}} u(s,t) \, ds, \quad \mathcal{A} \subset \Omega$$

is the total mass of living tumor cells in a region $\mathcal{A}$.

Furthermore, let $y(s,t)$ be the mass density of immature vascular endothelial cells from which mature blood vessels arise. Again, $y(s,t)$ takes units mass/volume, and

$$\int_{\mathcal{A}} y(s,t) \, ds, \quad \mathcal{A} \subset \Omega$$

is the mass of VECs in region $\mathcal{A}$.

Let $z(s,t)$ be local microvessel length density at $s$ and $t$. In the original model [36], this quantity was denoted as $v$ and was derived from the main dependent variables; here it arises naturally as one of the modeled variables. Its unit is length/volume, and

$$\int_{\mathcal{A}} z(s,t) \, ds, \quad \mathcal{A} \subset \Omega$$

is the total length of microvessels in $\mathcal{A}$. We scale $z(s,t)$ such that normal tissue has $z = 1$.

We assume that blood vessels supply critical resources. The local resource concentration $C(s,t)$, is further assumed to be in quasi-equilibrium set by local vascular density, $z(s,t)$. Let $C_m > 0$ be the fixed concentration of resources in arterial blood with units mol/volume. Then we assume

$$C(s,t) = \frac{C_m z(s,t)}{k + z(s,t)}$$

(1.1)
with $k > 0$ constant with the same units as $z(s, t)$, namely length/volume. Therefore, $C(s, t)$ has the same units as $C_m$ and we may write it as $C(z)$.

Cancers cells also compete for resources locally. Therefore, we measure the mean resource availability at point $s \in \Omega$ as the ratio

$$v(s, t) := \frac{C(z)}{u(s, t) + \varepsilon} = \frac{C_m z(s, t)}{(u_1(s, t) + u_2(s, t) + \varepsilon)(k + z(s, t))},$$

where $\varepsilon > 0$ is incorporated so that the ratio does not become infinite when $u(s, t)$ approaches 0.

We thus write $v(u_1, u_2, z)$. Note that the meaning of $v(u_1, u_2, z)$ is different than the meaning in Nagy’s model [36]. In that model $v$ stood for the local resource concentration. In our model, $v$ stands for the local resource concentration per unit mass.

Local per capita tumor growth rates depend in part on local resource availability, $v(u_1, u_2, z)$. Let this dependency be represented by the function $\Phi(v)$, where we will suppress the arguments of $v$ for brevity. In general, we assume that $\Phi'(v)$ is everywhere positive for $v \in [0, \infty)$, saturating (that is, $\Phi \to \Phi_{\text{max}}$ as $v \to \infty$, with $\Phi_{\text{max}}$ a constant) and $\Phi(0) \in (-\infty, 0)$ since in general more resources means more proliferation and less death [36]. Units of $\Phi$ are 1/time. In our implementation we use the Gammack et al. model [22], which was also applied in the 2004 ODE model to govern the dynamics of the $i$th phenotype:

$$\Phi_i(v) = \frac{A_i v^2}{c_{i1}^2 + v^2} - B_i \left(1 - \frac{v^2}{c_{i2}^2 + v^2}\right).$$

(1.3)

Values for parameters $A_i, B_i, c_{i1}, c_{i2}$ can be obtained empirically and are found in [22] and [48].

Local per capita growth rate also depends on crowding, measured directly by local cell density, $u(s, t)$. In other words, space is also a resource (c.f. Assumption 3 in 1.1). Biologically, this assumption is justified by observations in vitro and in vivo [50]. Although it is well-known that transformed cells often lack the contact inhibition characteristic of "healthy" cells, as bulk pressure inside regions of cell culture and tumors increases due to cell proliferation in a confined space, mortality of transformed cells also increases. In addition, tumor cells are known to acidify their local environment. Local acidification also increases mortality rate. Experiment and clinical observation also shows that phenotypes within the tumor vary in their acidification ability and in their tolerance to the acid environment. Therefore, phenotypes affect the local "carrying capacity"
of other phenotypes around them, and different phenotypes may not experience the same social growth retardation in the same location.

Cancer cells move. They move seemingly randomly, in response to chemical gradients, both soluble and fixed in the matrix, and due to advection. We also assume tumor tissue to be homogeneous with respect to diffusion, i.e., the diffusion coefficient is constant (c.f. Assumptions 1, 3, 9, and 10 in 1.1).

Necrotic cells do not move, but are subject to passive displacement via advection. They can either naturally disintegrate into waste products or be phagocytosed by macrophages if they are on the boundary of the tumor mass (c.f. Assumptions 1, 3, 4, 5, 6, 9, and 10 in 1.1). We combine all of these rates into a single constant, $\mu_N$, with units given in Table 1.3.

All these considerations lead to the following growth equations for the tumor mass:

\[
\frac{\partial u_i}{\partial t} = (\Phi_i(v) - bu_j)u_i - \nabla \cdot (wu_i) + d_i\Delta u_i, \quad i, j \in \{1, 2\}, i \neq j
\]

\[
\frac{\partial u_N}{\partial t} + \nabla \cdot (wu_N) = \sum_i (bu_iu_j + \Phi_i^- u_i) - \mu_N u_N \quad i, j \in \{1, 2\}, i \neq j,
\]

where $b$ and $d_i$ are nonnegative constants representing between-phenotype competition and the diffusion constant, respectively. The vector $w$ represents the advective radial velocity as a function of time and position satisfying $w(0) = 0$. The function $\Phi_i - bu_j$ is the overall "growth" term for $u_i$, thus $u_i$ will either increase in density or necrose depending on the sign. Parameter $b$ has units per mass per time, and $d_i$ have units length$^2$/time whose values have an upper limit determined in [46], the units for $\Phi_i$ are given in Table 1.2.

Cancer cells activate angiogenesis by secreting a signal that either directly or indirectly stimulates endothelial cells to migrate to the site of origin to the signal, differentiate, and organize into functional microvessels [50]. The strength of this signal depends on local resource availability, $v(s, t)$. We assume that the different phenotypes vary in their ability to generate this signal. Let $h_i(v)$ be the signal strength of the $i$th phenotype experiencing an environment with local resource availability $v(s, t)$. For now we assume the following form for $h(v)$ because it matches the qualitative picture obtained from experiments in [30, 45]:

\[
h_i(v) = \zeta_i ve^{-\xi v}.
\]
The nonnegative constant $\zeta_i$ is the $i$th phenotype’s general angiogenic effectiveness, and the positive constant $\xi_i$ determines the resource availability at which the $i$th phenotype maximizes its angiogenic signal. Specifically, $h_i(v)$ is maximized at $v = 1/\xi_i$. Biologically, $h'_i(v) < 0$ for all $v > 1/\xi$ because cells "turn the signal down" as resources become increasingly available. On the other hand, $h'_i(v) > 0$ for $v \in [0, 1/\xi)$ because at such low resource availability, cells become physiologically stressed to the point where their ability to generate the signal becomes impaired [30, 50]. Genes for certain important angiogenic signaling molecules, including vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (bFGF), and platelet-derived growth factor (PDGF-β), appear to have a mechanism which allows expression even when hypoxia becomes severe [45].

Because of the complexity of the angiogenic signal, the units of the signal strength $h(v)$ are arbitrary. Therefore, the units of $\zeta$ are "signal units" × mass × volume/mol, and those of $\xi$ are mass × volume/mol.

Signal strength at location $s$ and time $t$ is assumed to be a weighted average of the signals produced by cells at that location. Therefore, the signal strength at point $s$ and time $t$, which we denote $H(u_1, u_2, v)$, is
\[
H(u_1, u_2, v) = \frac{u_1(s, t)h_1(v) + u_2(s, t)h_2(v)}{u_1(s, t) + u_2(s, t)}.
\]  
(1.7)
Local signal strength $H(u_1, u_2, v)$ therefore has the same units as the $h_i(v)$.

This angiogenic signal stimulates VEC proliferation. We assume that the signal initiates proliferation at basic rate $\alpha$, which has units per "unit signal" per time. Immature vascular endothelial cells both mature and die at constant per capita rates [30, 50], which we combine into a single rate parameter $\beta$, with units per time (c.f. Assumption 7 in 1.1). VECs disappear by either dying or incorporating themselves into a growing blood vessel [50]. These, and the assumptions of the angiogenesis signal proliferation and homogeneous random diffusion of VECs leads to the following model of VEC dynamics:
\[
\frac{\partial y}{\partial t} = (\alpha H(u_1, u_2, v) - \beta) y(s, t) + d\Delta y(s, t).
\]  
(1.8)
We assume that microvessels arise from the VEC population. They do so at per capita rate $\gamma$, with units length per mass per time. Since $\beta$ represents the maturation rate of VECs and also
their death rate, we must have $\gamma \geq \beta$. Existing microvessels are also remodeled, as described in [36]. In addition, we can also add a mortality rate associated with cell density, since we know that vessels collapse under pressure, which causes their resorption [9, 10, 5, 29]. As a first approximation we assume that this pressure-induced mortality is proportional to tumor size, say $\eta \sqrt{R(t)} + \epsilon$, where $\eta$ is a nonnegative constant with units volume per mass $\times$ time and $\epsilon$ is a fixed small positive constant. Estimates for $\eta$ are derived from the work of Jain et al. [5, 10, 29] since research has shown that microvessels deteriorate due to intratumor pressure [49]. Microvessels cannot move. These assumptions yield the following model:

$$\frac{\partial z}{\partial t} = \gamma \frac{y(s,t)}{1 + R^2(t)} - \frac{\delta z^2(s,t)}{u(s,t)} - \eta \sqrt{R(t)} + \epsilon z(s,t),$$

where $\delta$ is a positive constant with units mass per length $\times$ time. The coefficients $\gamma \frac{y}{1 + R^2(t)}$ and $\eta \sqrt{R(t)} + \epsilon$ are chosen based on reasonable assumptions about cancer growth. There is very literature describing the decrease in vascularization as we move from the boundary towards the center of the tumor stemming from the increased pressure in the interior of the tumor. These particular functions were chosen so that the tumor does not die out immediately in our simulations.

Necrosis occurs when there is not sufficient vascular supply to a region of a tumor. It is a common feature in certain kinds of tumors that have grown to a significant size [30]. Because of this, it has been a feature of many mathematical models of cancer [7, 19, 14, 28, 27]. In our model, the lower $y$ is the more likely there is to be necrosis in that region (c.f. Assumption 8 in Section 1.1). We numerically define necrosis to occur for $u_i$ in the region where $\Phi_i < 0$. This is because cells have a stronger growth dependence on blood supply than they do from any spatial constraints [22]. Choosing $\Phi_i < 0$ means that cells are dying and this is what we define as necrosing (c.f. Assumption 2 in 1.1).

<table>
<thead>
<tr>
<th>Function</th>
<th>Meaning</th>
<th>Units</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Phi_i$</td>
<td>Local per capita growth rate of cell type $i$</td>
<td>$1/\text{time}$</td>
<td>[22]</td>
</tr>
<tr>
<td>$h_i$</td>
<td>Angiogenesis signal strength of cell type $i$</td>
<td>Signal strength units*</td>
<td>[1]</td>
</tr>
<tr>
<td>$H$</td>
<td>Mean angiogenic signal strength</td>
<td>Signal strength units*</td>
<td>[1]</td>
</tr>
<tr>
<td>$\gamma \frac{y}{1 + R^2(t)}$</td>
<td>VEC recruitment rate</td>
<td>$1/\text{gm/day}$</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\eta \sqrt{R(t)} + \epsilon$</td>
<td>Pressure-induced microvessel decay rate</td>
<td>$\text{ml} \cdot \text{length/gm-day}$</td>
<td>Assumption</td>
</tr>
<tr>
<td>$B(0, R(t))$</td>
<td>Ball of radius $R(t)$ in $\mathbb{R}^n$</td>
<td>length</td>
<td>Assumption</td>
</tr>
</tbody>
</table>
1.3 Advection Speed

To calculate the advection velocity \( \mathbf{w} \), we make the assumption that \( u_1 + u_2 + u_N \equiv u^* \), where \( u^* \) is a constant we later choose to be 1 so \( u_N \) is the volumetric fraction of necrotic cells permanently or temporarily in the tumor. We shall assume that necrotic cells only move via advective flow, do not diffuse, and that their degradation rate \( \mu_N \) is independent of the density of parenchymal cells (when \( \mu_N = 0 \) the dead cells remain permanently). Then,

\[
\begin{align*}
\frac{\partial u_1}{\partial t} + \nabla \cdot (\mathbf{w} u_1) - d_1 \Delta u_1 &= \Phi^+_1 u_1 - \Phi^-_1 u_1 - bu_2 u_1, \\
\frac{\partial u_2}{\partial t} + \nabla \cdot (\mathbf{w} u_2) - d_2 \Delta u_2 &= \Phi^+_2 u_2 - \Phi^-_2 u_2 - bu_1 u_2, \\
\frac{\partial u_N}{\partial t} + \nabla \cdot (\mathbf{w} u_N) &= \sum_i (bu_i u_j + \Phi^+_i u_i) - \mu_N u_N \quad i, j \in \{1, 2\}, i \neq j,
\end{align*}
\]

(1.10)

where \( \Phi^+_i \) and \( \Phi^-_i \) are the positive and negative parts of \( \Phi_i \), respectively. To calculate \( \mathbf{w} \) we exploit \( u_1 + u_2 + u_N \equiv u^* \), sum the three equations in (1.10), and use \( \nabla \cdot (\mathbf{w} u_i) = \mathbf{w} \cdot \mathbf{u}_i + u_i \nabla \cdot \mathbf{w} \) to obtain

\[ u^* \nabla \cdot \mathbf{w} - d_1 \Delta u_1 - d_2 \Delta u_2 = \left( \sum_i \Phi^+_i u_i \right) - \mu_N u_N, \]

which can be rewritten as

\[ u^* \nabla \cdot \mathbf{w} = d_1 \Delta u_1 + d_2 \Delta u_2 + \left( \sum_i \Phi^+_i u_i \right) - \mu_N u_N, \]

and, integrating over \( B(0, r) \) on the left-hand side,

\[ u^* \int_{B(0,r)} \nabla \cdot \mathbf{w} \, dr = u^* \int_{\partial B(0,r)} \mathbf{w} \cdot d\mathbf{S} = u^* w(r,t)|S^n(r)|. \]

Here we have used the radial symmetry to replace the vector \( \mathbf{w}(r,t) \) by its constant magnitude \( w(r,t) \) on the boundary of the ball multiplying the outward unit normal vector \( \mathbf{n} \). As for the right-hand side, we have

\[
\begin{align*}
d_1 \int_{B(0,r)} \Delta u_1 \, dr + d_2 \int_{B(0,r)} \Delta u_2 \, dr + \int_{B(0,r)} \left( \sum_i \Phi^+_i u_i \right) - \mu_N u_N \, dr \\
= d_1 \int_{\partial B(0,r)} \nabla u_1 \cdot \mathbf{n} \, dS + d_2 \int_{\partial B(0,r)} \nabla u_2 \cdot \mathbf{n} \, dS + \int_{B(0,r)} \left( \sum_i \Phi^+_i u_i \right) - \mu_N u_N \, dr,
\end{align*}
\]

where \( \nabla u_1 \cdot \mathbf{n} \) is the outward unit normal derivative of \( u_1 \).
Hence,
\[ w(r, t) = \sum_{i=1}^{2} \frac{d_i}{u^*} \int_{\partial B(0, r)} \nabla u_i \cdot n \, dS + \int_{B(0, r)} \left( \sum \Phi_i^+ u_i \right) - \mu_N u_N \, dr. \]  
(1.11)

The boundary at \( R(t) \) moves just like the cells, so that \( \dot{R}(t) = w(R, t) \):
\[ \dot{R} = \sum_{i=1}^{2} \frac{d_i}{u^*} \int_{\partial B(0, R(t))} \nabla u_i \cdot n \, dS + \int_{B(0, R(t))} \left( \sum \Phi_i^+ u_i \right) - \mu_N u_N \, dr. \]
which, after applying the boundary conditions at \( r = R(t) \), gives
\[ \dot{R} = \frac{1}{|S^n(r)|} \int_{B(0, R(t))} \left( \sum \Phi_i^+ u_i \right) - \mu_N u_N \, dr. \]  
(1.12)

Now the integral on the right hand side represents the net new volume created/lost and, therefore, upon division by the surface area of the \( n \)-ball of radius \( R \) must equal the rate of change of \( R \).

To summarize, by combining the equations (1.4), (1.8), (1.9), (1.10), and the functions (1.2), (1.3), (1.6), (1.7), (1.11) lead to the following system we wish to consider:

\[
\begin{aligned}
\frac{\partial u_i}{\partial t} &= (\Phi_i(v) - b_i u_j) u_i(s, t) - \nabla \cdot (wu_i(s, t)) + d_i \Delta u_i(s, t), \quad i, j \in \{1, 2\}, \ i \neq j, \\
\frac{\partial y}{\partial t} &= (\alpha H(u_1, u_2, v) - \beta) y(s, t) + d_y \Delta y(s, t), \\
\frac{\partial z}{\partial t} &= \frac{\gamma}{1 + R^2(t)} y(s, t) - \frac{\delta z^2(s, t)}{u(s, t)} - \frac{\eta R(t) + \epsilon z(s, t)}{} , \\
u_N &= u^* - u_1 - u_2, \\
w(r, t) &= \sum_{i=1}^{2} \frac{d_i}{u^*} \int_{\partial B(0, r)} \nabla u_i \cdot n \, dS + \int_{B(0, r)} \left( \sum \Phi_i^+ u_i - \mu_N u_N \right) \, dr \\
\dot{R} &= \frac{1}{|S^n(r)|} \int_{B(0, R(t))} \left( \sum \Phi_i^+ u_i \right) - \mu_N u_N \, dr \\
\Phi_i(v) &= \frac{A_i v^2}{c_i^2 + v^2} - B_i \left( 1 - \frac{v^2}{c_i^2 + v^2} \right), \\
H(u_1, u_2, v) &= \frac{u_1(s, t) h_1(v) + u_2(s, t) h_2(v)}{u_1(s, t) + u_2(s, t)}, \quad h_i(v) = \zeta_i v e^{-\xi v}, \\
u(s, t) &= u_1(s, t) + u_2(s, t), \quad v(s, t) = \frac{C_m z(s, t)}{u(s, t)(k + z(s, t))}
\end{aligned}
\]

(1.13)
with initial and boundary condition

\[
\begin{align*}
Q(s, 0) &= Q_0(s), \quad s \in \Omega(t) \\
\frac{\partial Q(s, t)}{\partial n} &= 0, \quad s \in \partial \Omega(t)
\end{align*}
\]

(1.14)

where \(\Omega(t) = B(0, R(t))\) is the ball in \(\mathbb{R}^n\), \(n = \{1, 2, 3\}\), and \(\frac{\partial}{\partial n}\) is the unit normal derivative. For simplicity, in (1.14) we mean \(Q = (u_1, u_2, y, z)\) and \(Q_0\) is the initial condition for \((u_1, u_2, y, z)\).

When we derived the equation for \(w\) (1.11), we did it in spherical coordinates in order to have a general formula for any coordinate system with radial symmetry. While this allows for a more complete model, this complicates the numerics because of the \(1/r^2\) terms in the equation. To simplify the numerics, we consider the one-dimensional version, thus we solve the system on the line \([0, R(t)]\) instead of on the sphere. Rewriting the Laplacian on the line and modifying the initial and boundary conditions (1.14) reduces our model to the following system:

\[
\begin{align*}
\frac{\partial u_i}{\partial t} &= (\Phi_i(v) - b u_j) u_i - \frac{\partial}{\partial r}(w u_i) + d_i \frac{\partial^2 u_i}{\partial r^2}, \quad i, j \in \{1, 2\}, i \neq j \\
\frac{\partial y}{\partial t} &= (\alpha H(u_1, u_2, v) - \beta) y + d_y \frac{\partial^2 y}{\partial r^2} \\
\frac{\partial z}{\partial t} &= \frac{\gamma}{1 + R^2(t)} y - \frac{\delta z^2}{u + \varepsilon} - \eta \sqrt{R(t)} + \epsilon z \\
v(r, t) &= \frac{C_m z(r, t)}{(u(r, t) + \varepsilon)(k + z(r, t))}
\end{align*}
\]

(1.15)

with initial and boundary conditions

\[
\begin{align*}
Q(r, 0) &= q_0(r), r \in [0, R) \\
\frac{\partial Q(R, t)}{\partial r} &= 0 \\
\frac{\partial Q(0, t)}{\partial r} &= 0
\end{align*}
\]

(1.16)

where, for simplicity, by \(Q\) in (1.16) we mean \(Q = (u_1, u_2, y, z)\) and \(Q_0\) is the initial condition for \((u_1, u_2, y, z)\). The homogeneous Neumann boundary condition is required by the assumption that the domain contains all the parenchyma and vascular endothelial cells and nothing else.

We take as natural units millimeters for length, days for time, centigrams for mass, and milliliters for volume. Cancer cells have a density approximately equal to that of water (1gm/mL) [50]. The values for the parameters used in the system are found in Table 1.3
We use a similar initial condition as in [36] but assume instead that $u_2$ is nonzero in a small spherical region compared to $u_1$, which is positive on the whole domain. The vascularization of a tumor should be higher as it gets closer to the outer edge of the tumor [44], thus the variable $y$ should have a higher initial value near the core of the tumor and decrease its value since less microvessels means more angiogenesis signaling [50].

In order to solve the problem (1.15), (1.16), and (1.12) first we make a change of variable to fix the domain $\Omega(t)$ to be the unit ball for all time, and thus get rid of the free boundary problem and replace it with a fixed boundary problem [17]. Using the new variable $\tilde{r} = r/R(t)$ and the chain rule to calculate the partial derivatives in (1.15) and (1.16) we arrive at the new model (after dropping the tildes) for the case of one spatial dimension, which we explore in more detail in Chapter 2, we have

\[
\begin{align*}
\frac{\partial u_1}{\partial t} &= (\Phi(v) - bu_j)u_1 - \frac{1}{L(t)} \frac{\partial}{\partial r} (\frac{d_i}{L^2(t)} u_i - \frac{\partial^2 u_i}{\partial r^2}) + \frac{r \dot{L}(t)}{L(t)} \frac{\partial u_i}{\partial r} \\
\frac{\partial y}{\partial t} &= (\alpha H(u_1, u_2, v) - \beta) y + \frac{d_y}{L^2(t)} \left( \frac{\partial^2 y}{\partial r^2} \right) + \frac{r \dot{L}(t)}{L(t)} \frac{\partial y}{\partial r} \\
\frac{\partial z}{\partial t} &= \frac{\gamma}{1 + L^2(t)} y - \frac{\delta z^2}{u + \varepsilon} - \eta \sqrt{L(t)} + \epsilon z + \frac{r \dot{L}(t)}{L(t)} \frac{\partial z}{\partial r} \\
v(r, t) &= \frac{C^*_m z(r, t)}{(u(r, t) + \varepsilon)(k + z(r, t))} \\
w(r, t) &= \frac{d_1}{u^* L(t)} \frac{\partial u_1}{\partial r} + \frac{d_2}{u^* L(t)} \frac{\partial u_2}{\partial r} + \frac{L(t)}{u^*} \int_0^r \left( \sum_i \Phi_i^+ u_i - \mu_N u_N \right) d\tilde{r} \\
\dot{L}(t) &= L(t) \int_0^1 \left( \sum_i \Phi_i^+ u_i - \mu_N u_N \right) d\tilde{r}
\end{align*}
\]
### Table 1.3: Parameters and their default values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Meaning</th>
<th>Value</th>
<th>Units</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_i$</td>
<td>Max Proliferation rate of phenotype $i$</td>
<td>.06</td>
<td>day$^{-1}$</td>
<td>[22, 48]</td>
</tr>
<tr>
<td>$B_i$</td>
<td>Basic Mortality of phenotype $i$</td>
<td>.06</td>
<td>day$^{-1}$</td>
<td>[22, 48]</td>
</tr>
<tr>
<td>$\hat{c}_{1i}$</td>
<td>Resource sensitivity (proliferation)</td>
<td>0.8</td>
<td>mol/µL/gm</td>
<td>[22, 48]</td>
</tr>
<tr>
<td>$\hat{c}_{2i}$</td>
<td>Resource sensitivity (mortality)</td>
<td>0.4</td>
<td>mol/µL/gm</td>
<td>[22, 48]</td>
</tr>
<tr>
<td>$b$</td>
<td>Cell packing constraint</td>
<td>.0004</td>
<td>gm$^{-1}$ day$^{-1}$</td>
<td>Assumption</td>
</tr>
<tr>
<td>$d_i$</td>
<td>Cell diffusion constants</td>
<td>$1 \times 10^{-5}$ cm$^2$/day</td>
<td>[46]</td>
<td></td>
</tr>
<tr>
<td>$C_m$</td>
<td>Serum resource concentration</td>
<td>95</td>
<td>mmHg</td>
<td>[22]</td>
</tr>
<tr>
<td>$k$</td>
<td>Resource delivery parameter</td>
<td>1.375</td>
<td>length*/µL</td>
<td>[22]</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>Angiogenesis signal parameter</td>
<td>0.4</td>
<td>(U·gm·mL/mmHg)$^{**}$</td>
<td>[30]</td>
</tr>
<tr>
<td>$\xi$</td>
<td>Angiogenesis peak parameter</td>
<td>0.06</td>
<td>gm·mL/mmHg</td>
<td>[30]</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>VEC proliferation response</td>
<td>0.06</td>
<td>(U$^{-1}$)$^{**}$ day$^{-1}$</td>
<td>[36]</td>
</tr>
<tr>
<td>$\beta$</td>
<td>VEC disappearance rate</td>
<td>0.04</td>
<td>day$^{-1}$</td>
<td>[36]</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>VEC maturation rate</td>
<td>4</td>
<td>length*/gm/day</td>
<td>[36]</td>
</tr>
<tr>
<td>$\mu_N$</td>
<td>Necrotic wash-out rate</td>
<td>0.0005</td>
<td>/gm/day</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Microvessel remodeling rate</td>
<td>0.004</td>
<td>cgm/length*·day</td>
<td>[30]</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Microvessel collapse rate</td>
<td>.006</td>
<td>ml/gm·day</td>
<td>[5, 10, 29]</td>
</tr>
</tbody>
</table>

*Scaled in microvessel length units such that for normal tissue, $z = 1$.

**U stands for angiogenesis signaling units.
Chapter 2

NUMERICAL METHODS

In Chapter 1 we derived our model of cancer. In this chapter we cover the numerical methods used to solve the system (1.17), (1.12), and (1.16) as well as provide numerical results about stability. The main tool for simulating this model is MATLAB, but we have written our own numerical scheme using finite difference methods to solve the system. We use a "divide and conquer" method seen in the work done in the field operator splitting to separate the growth of the radius (1.12) from the system of PDEs (1.17) and combine their solutions before the end of the time-step [24]. In other words, at time $t_{n+1}$, we first solve for the radial growth using the values at $u^n$ then use the length, $L(t_{n+1})$, to solve for the solution of the system $u^{n+1}$.

The inter-species competition coefficient, $b$, is generated randomly for each simulation. The inter-species competition should be the same for each phenotype since there should not be a difference with how phenotype 1 interacts with phenotype 2 versus how phenotype 2 interacts with phenotype 1. The $b$'s are generated randomly on the interval $[0.0002, 0.0004]$ in each simulation. The rest of the parameter values are all fixed at the values given in Table 1.3.

2.1 Finite Difference Scheme

To solve the system (1.17), we use an implicit method numerical scheme to get the solution at the following time step. We approximate the time derivative using a first-order forward difference scheme and the spatial derivatives using second-order central differences. In other words, we have

$$u_t \approx \frac{u_k^{n+1} - u_k^n}{\Delta t}$$

and

$$u_r \approx \frac{u_{k+1}^{n+1} - u_{k-1}^{n+1}}{2\Delta r}, \quad u_{rr} \approx \frac{u_{k+1}^{n+1} - 2u_k^{n+1} + u_{k-1}^{n+1}}{\Delta r^2}$$
Thus, the system, (1.17), when written using these difference schemes becomes

\[
\begin{array}{l}
\left\{ \begin{array}{l}
\frac{u_{i,k}^{n+1} - u_{i,k}^n}{\Delta t} = (\Phi_i - bu_{j,k}^n)u_{i,k}^{n+1} - \frac{\partial w_k^n}{L_{n+1}} w_{i,k}^{n+1} - \frac{1}{L_{n+1}} \left[ \frac{u_{i,k+1}^n - u_{i,k-1}^n}{2\Delta r_n} \right] \\
\quad + \frac{1}{L_{n+1}^2} \left[ \frac{u_{i,k+1}^{n+1} - 2u_{i,k}^{n+1} + u_{i,k-1}^{n+1}}{\Delta r_n^2} \right] \\
\quad + \frac{r\dot{L}_{n+1}}{L_{n+1}} \left[ \frac{u_{i,k+1}^{n+1} - u_{i,k-1}^{n+1}}{2\Delta r_n} \right], \quad i,j \in \{1, 2\}, i \neq j \\
\end{array} \right.
\end{array}
\]

(2.1)

where \( L_n := L(t_n) \), the length of the interval at time \( t_n \), and the \( \partial w_k^n \) term is calculated with a similar forward difference formula as above applied to (1.11) but instead of using a finite difference for the integral in the equation, we evaluate the integrand using the known solution at time \( t_n \) by the fundamental theorem of calculus. \( \Delta r_n \) is the mesh at time \( t_n \) and is, initially, equally spaced with 101 points on the interval \([0, 1]\). To solve equation (1.12) for \( L(t) \), we use a first-order forward difference formula and calculate the integral using a trapezoidal rule with the functions in the integrand being evaluated at time \( t_n \). To add additional points to the mesh we track a subset of the \( \{t_k\} \) starting with \( t_0 \). Whenever the difference between \( L(t_j) - L(t_k) > 0.01 \), \( j > k \), we add an additional point on the mesh and then use the size of the radius at \( t_j \) as our reference for future iterations. We do not delete points from the mesh if the radius shrinks.

Solving the system (2.1) for all of the terms with \( t_{n+1} \) yields a matrix equation of the form

\[
A U^{n+1} = U^n,
\]

(2.2)

where \( A \) is a tridiagonal matrix of size \( 4M \times 4M \), \( M \) representing the number of mesh points, the vector \( U^n \) is the solution at time \( t_n \), and \( U^{n+1} \) is the unknown solution at time \( t_{n+1} \). The subdiagonal, diagonal, and superdiagonal entries for each variable of \( A \) are, respectively,
\[
\begin{align*}
\frac{r \dot{L}_{n+1} \Delta t}{2L_{n+1} Dr_n} & - \frac{d_i \Delta t}{(L_{n+1} \Delta r_n)^2} - \frac{\Delta t w^n_k}{2L_{n+1} \Delta r_n} \\
1 - (\Phi_i - bu_j) \Delta t & + \frac{2d_i \Delta t}{(L_{n+1} \Delta r_n)^2} + \frac{\Delta t}{L_{n+1}} \partial w^n_k, \quad i, j \in \{1, 2\}, i \neq j, \\
\frac{-r \dot{L}_{n+1} \Delta t}{2L_{n+1} Dr_n} & - \frac{d_i \Delta t}{(L_{n+1} \Delta r_n)^2} + \frac{\Delta t w^n_k}{2L_{n+1} \Delta r_n} \\
\frac{r \dot{L}_{n+1} \Delta t}{2L_{n+1} Dr_n} & - \frac{d_y \Delta t}{(L_{n+1} \Delta r_n)^2} \\
1 - (\alpha H - \beta) \Delta t & + \frac{2d_y \Delta t}{(L_{n+1} \Delta r_n)^2} \\
\frac{-r \dot{L}_{n+1} \Delta t}{2L_{n+1} Dr_n} & - \frac{d_y \Delta t}{(L_{n+1} \Delta r_n)^2}, \quad (2.3)
\end{align*}
\]

Applying the boundary conditions (1.16) to (2.3) is done by modifying the first and last entry of A.
for each variable. The right hand side of (2.2) is

$$
\begin{bmatrix}
0 \\
u_{i,2} \\
\vdots \\
u_{i,M-1} \\
0
\end{bmatrix}, \quad i, j \in \{1, 2\}, i \neq j,
$$

$$
\begin{bmatrix}
0 \\
y_{2} \\
\vdots \\
y_{M-1} \\
0
\end{bmatrix},
$$

so we have $U^n = (u^n_1, u^n_2, y^n, z^n)^T$ for (2.2) and each zero in (2.4) represents the Neumann boundary condition for each variable.

2.2 Convergence of Numerical Scheme in The Case of a Prescribed Solution

In order to demonstrate the convergence of the numerical scheme, we rewrite the differential equations in our model (1.13) in the form $Lu = 0$ for the appropriate differential operator $L$, and then add on the right-hand side the "load" term given by $Lu^e$, where $u^e$ is the prescribed solution we want to approximate. Thus, we replace the original homogeneous system by a non-homogeneous one whose analytical solution is the prescribed $u^e$. Then we use the numerical scheme (modified to include the obvious terms corresponding to the nonzero right-hand side) to find an approximate solution $u_{\text{approx}}$ and compute the error in the approximation by taking the difference between $u^e$ and $u_{\text{approx}}$ at all the time-space grid points. For ease of notation in this section, we shall call
\{u^e_1, u^e_2, y^e, z^e\} = u^e. If we want the system (1.17) to have solution

\[ u^e_i = L^{i+1}(t)(1 - r)^{i+1}, \]  

(2.5)

(where for \( i = 3, 4 \) we mean \( y^e, z^e \), respectively) then we make appropriate changes to the right hand side of (1.17) so that the system converges to the solution \( u^e \).

By modifying (2.1) slightly, the system (2.6) will have solution \( u^e \). To do this, we add a few terms to the right-hand side of (2.1), which yields the following system of equations

\[
\frac{v^{n+1}_{i,k} - v^n_{i,k}}{\Delta t} = (\Phi_i - bu^n_{j,k})u^{n+1}_{i,k} - \frac{\partial w^n_{i,k}}{L_{n+1}} u^{n+1}_{i,k} - \frac{1}{L_{n+1}} w^n_{i,k} \left[ \frac{u^{n+1}_{i,k} - u^{n+1}_{i,k-1}}{2 \Delta r_n} \right] \\
+ \frac{1}{L_{n+1}^2} \left[ \frac{u^{n+1}_{i,k+1} - 2 u^{n+1}_{i,k} + u^{n+1}_{i,k-1}}{\Delta r_n^2} \right] \\
+ \frac{r \hat{L}_{n+1}}{L_{n+1}} \left[ \frac{u^{n+1}_{i,k+1} - u^{n+1}_{i,k-1}}{2 \Delta r_n} \right] + (i + 1)L^{i+1}_{n+1}\hat{L}_{n+1}(1 - r)^i \\
- (\Phi_i - bu^n_{j,k})u^e_i + \partial w^e u^e_i - w^e(i + 1)L^{i+1}_{n+1} \\
- d_{i}(i + 1)L^{i+1}_{n+1}(1 - r)^{i-1}, \quad i, j \in \{1, 2\}, i \neq j
\]

\[
\frac{y^{n+1}_k - y^n_k}{\Delta t} = (\alpha H - \beta) y^{n+1}_k + \frac{1}{L_{n+1}^2} \left[ \frac{y^{n+1}_{k+1} - 2 y^{n+1}_k + y^{n+1}_{k-1}}{\Delta r_n^2} \right] \\
+ \frac{r \hat{L}_{n+1}}{L_{n+1}} \left[ \frac{y^{n+1}_{k+1} - y^{n+1}_{k-1}}{2 \Delta r_n} \right] \\
+ 4L^{3}_{n+1}\hat{L}_{n+1}(1 - r)^3 - (\alpha H - \beta) y^e - 12d_{3}\hat{L}_{n+1}(1 - r)^2
\]

\[
\frac{z^{n+1}_k - z^n_k}{\Delta t} = \frac{\gamma}{1 + L_{n+1}^2} y^n_k - \frac{\delta z^n_k}{L_{n+1}^2} + u^{n+1}_{1,k+1} u^{n+1}_{2,k} + \varepsilon z^{n+1}_k - \sqrt{L_{n+1}} \eta z^{n+1}_k \\
+ \frac{r \hat{L}_{n+1}}{L_{n+1}} \left[ \frac{z^{n+1}_{k+1} - z^{n+1}_{k-1}}{2 \Delta r_n} \right] \\
+ 5L^{4}_{n+1}\hat{L}_{n+1}(1 - r)^4 - \frac{\gamma}{1 + L_{n+1}^2} y^e - \frac{\delta(z^e)^2}{u^e_1 + u^e_2 + \varepsilon} - \sqrt{L_{n+1}} \eta z^e,
\]

with new initial and boundary conditions

\[
\begin{align*}
  u_i(r, 0) &= (1 - r)^{i+1}, \quad r \in [0, 1) \\
  \frac{\partial u(0,t)}{\partial r} &= -(i + 1)(1 - r)^i \\
  \frac{\partial u(1,t)}{\partial r} &= 0.
\end{align*}
\]

(2.7)

Now, it remains to find the order with which the numerical method (2.6) converges to (2.5).

To do so, we find a constant, \( p \), such that

\[ ||u_h - u^e|| = Ch^p \]

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where $h = \Delta r = \frac{\Delta t}{\Delta t + 2}$ and $C > 0$ is a constant. Another way to calculate $p$ is by finding the ratio of $||u_h - u^e||$ to $||u_{h/2} - u^e||$ which yields

$$\frac{||u_h - u^e||}{||u_{h/2} - u^e||} = 2^p,$$

and thus

$$\log_2 \left( \frac{||u_h - u^e||}{||u_{h/2} - u^e||} \right) = p.$$

The table below gives the values used and the average $p$ for $u_e$.

<table>
<thead>
<tr>
<th>$\Delta t$</th>
<th>$\Delta r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.0476</td>
<td>0.72</td>
</tr>
<tr>
<td>0.05</td>
<td>0.02439</td>
<td>0.80</td>
</tr>
<tr>
<td>0.025</td>
<td>0.01235</td>
<td>0.88</td>
</tr>
<tr>
<td>0.0125</td>
<td>0.00621</td>
<td>0.93</td>
</tr>
<tr>
<td>0.00625</td>
<td>0.00311</td>
<td>0.96</td>
</tr>
<tr>
<td>0.003125</td>
<td>0.00155</td>
<td>0.99</td>
</tr>
<tr>
<td>0.001562</td>
<td>0.000775</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.1: Comparison of $p$ values for different step sizes.

The end time for all of the simulations in Table 2.1 is 1000 days (\sim 3 years), thus we are confident any simulation up to 1000 days is numerically stable. We suspect simulations past 1000 days should be stable as well, but, to minimize computing time, we ended all of the simulations in Chapter 3 after this time period. We also added mesh points as needed according to the scheme we used in Section 2.1, so the convergence result using operator splitting is for the system with a moving boundary, not just a fixed domain.

Additionally, we investigate the changes in the solution with decreasing values of $\Delta t$ to determine what effects, if any, increasing the number time steps has on the solution. Table 2.2 has the values of $\Delta t$ on the left and in between the values of $\Delta t$, on the right, are the values of the $\ell^\infty$-norm of the differences. For example, the first value of column $u_1$ is the value of $||u_{1,\Delta t_1} - u_{1,\Delta t_2}||_\infty$, evaluated on the larger mesh since $u_{1,\Delta t_1}$ and $u_{1,\Delta t_2}$ coincide on those mesh points. It can be seen that as $\Delta t$ decreases, there is no significant change in the error to the solution. Thus, we feel that using $\Delta t = 0.1$ is reasonable and reduces the computation time.
<table>
<thead>
<tr>
<th>$\Delta t$</th>
<th>$u_1$</th>
<th>$u_2$</th>
<th>$w$</th>
<th>$y$</th>
<th>$z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>4.397e-4</td>
<td>4.295e-4</td>
<td>4.611e-6</td>
<td>5.580e-5</td>
<td>1.001e-3</td>
</tr>
<tr>
<td>0.05</td>
<td>1.980e-4</td>
<td>1.957e-4</td>
<td>4.105e-6</td>
<td>2.935e-5</td>
<td>4.855e-4</td>
</tr>
<tr>
<td>0.025</td>
<td>7.512e-5</td>
<td>6.941e-5</td>
<td>3.849e-6</td>
<td>1.247e-5</td>
<td>2.954e-4</td>
</tr>
<tr>
<td>0.0125</td>
<td>3.950e-5</td>
<td>4.038e-5</td>
<td>2.352e-6</td>
<td>8.191e-6</td>
<td>9.339e-5</td>
</tr>
<tr>
<td>0.00625</td>
<td>3.850e-5</td>
<td>3.957e-5</td>
<td>2.352e-6</td>
<td>8.191e-6</td>
<td>9.339e-5</td>
</tr>
</tbody>
</table>

Table 2.2: Comparison of solution norms for different values of $\Delta t$.

In conclusion, because of the results in both tables 2.1 and 2.2 we are confident that the differential system with the given load (2.6) and prescribed known solution (2.5), the numerical method converges with first order accuracy. This leads us to believe that the numerical method (2.1) without the load, $Lu^e$, for the differential system (1.17) will also converge with first order accuracy.
In 2004 Nagy hypothesized, but did not explore, that heterogeneous tumors would behave more like ecological systems than integrated tissues when taking into consideration the dynamics of spatial movement on the system [36]. Additionally, the hypertumor mechanism has been hypothesized to be a cause of the necrosis observed in many vascularized tumors [36, 40]. In our attempt to answer these questions using simulations, we find both necrotic tissue forming, as well as polymorphic tumors with both niche segregation, albeit incomplete - though indicative of the behavior of the tumor for longer time-scales, as well as tissue integration. We are primarily interested in three different cases for the growth functions $\Phi_i$; the $\Phi_i$’s cross each other and either the mutant or resident strain has a higher growth rate in the hypoxic region while the other strain is a better grower in the normoxic region, and when $\Phi_2(v) > \Phi_1(v)$ for all $v$. The subcases are related to the angiogenesis signaling for each strain ($h_i$). (Note to reader: The density graphs - green and gray color scheme - are plotted so that the the sum of $u_1$ and $u_2$ are shown and any whitespace is the local density of necrosing cells. For example, if for some point, $\tilde{r}$, the top of the gray curve reaches 0.3, the green curve plotted on top reaches 0.8, and the whitespace covers the rest up, then the mutant strain has 30% of the local density, the resident strain has 50% of the local density, and the necrosing cells cover the remaining 20% of the density at that point.)

In Figure 3.1 the mutant strain has a higher proliferation rate than the resident strain when below $v \approx 42$, lower proliferation rate when $v > 42$, and has a lower angiogenic signaling rate than the resident strain for all $v$. The tissues segregate, albeit incompletely, into distinct niches as was hypothesized by Nagy [36]. Furthermore, the mutant strain is unable to successfully invade the tumor tissue (in our 1000 day time scale) towards the center because the vascularization is higher in that region - the mutant strain is favored in normoxic regions - and the advective flow moves the mass away from the center. A similar pattern is observed when the mutant strain forms on the outer edge of the tumor; c.f. Figure 3.2.

The mass of the tumor taken up by the resident strain varies depending on where the mutant strains form. The closer the mutant strain is to the core, the more likely the mutant strain is to
Figure 3.1: The mutant strain is able to invade but not completely. Parameters different than Table 1.3 are \( A_1 = 0.02, A_2 = 0.04, d_2 = 2 \times 10^{-5}, \xi_1 = 0.04, \xi_2 = 0.01 \)

...
Figure 3.2: The mutant strain forms on the edge and invades slower. Parameters different than Table 1.3 are $A_1 = 0.02$, $A_2 = 0.04$, $\xi_1 = 0.04$, $\xi_2 = 0.01$.

On the other hand, if the mutant strain has a slower growth rate than the resident strain when the tumor is in a hypoxic state, has a higher angiogenic signaling rate than the resident strain, then the tumor behaves locally like integrated tissue; c.f. Figure 3.4 and 3.5. We hypothesize that the tissue integration of parenchymal cells occurs because the resident strain forms a parasitic relationship on the mutant strain by piggy-backing off the mutant strain’s increased angiogenic signaling capabilities. In this scenario, neither strain will drive the other to extinction nor will they separate into distinct niches since the mutant strain is unable to out-compete the resident strain and the resident strain benefits from its parasitic relationship with the mutant strain. Additionally, for the tumor size, this parasitic relationship leads to larger tumors than if the resident alone were...
Figure 3.3: Comparison of invasion based on location of mutant. Parameters different than Table 1.3 are $A_1 = 0.02$, $A_2 = 0.04$, $\xi_1 = 0.04$, $\xi_2 = 0.01$

present because of the added vascularization, and thus mass, that is formed in the tumor. There is no appreciable difference in size with regards to where the mutant strain forms.

If, under the same conditions as Figure 3.5 and 3.4, the mutant strain forms on the edge, the mutant strain goes extinct but there is no change in tumor size versus a tumor with only the resident strain. The extinction is due to the added intratumoral pressure from the tumor size that decreases vascularization.

The hypertumor mechanism described in [36] has the most noticeable effect on tumorigenesis whenever the following conditions are met: the mutant strain has a more aggressive growth rate than the resident regardless of the local resource density available, the mutant focuses almost all of its resources to proliferating and very little to angiogenic signaling, and is formed near the core (c.f. Figure 3.6). When these three conditions happen, the mutant invades, becomes necrotic, and eventually dies since it is unable to sustain itself due to its reduced ability to form new vasculature. There is evidence to suggest that in the region of necrosing tissue a palisading effect occurs, but further investigation is needed to fully understand this phenomena [50]. We caution that in Figure
Figure 3.4: The resident strain benefits from increased angiogenic signaling by the mutant strain; the mutant strain forms in the middle of the tumor. Parameters different than Table 1.3 are $A_1 = .04$, $A_2 = .02$, $\xi_1 = 0.01$, $\xi_2 = 0.04$
Figure 3.5: The resident strain benefits from increased angiogenic signaling by the mutant strain; the mutant forms at the core. Parameters different than Table 1.3 are $A_1 = .02$, $A_2 = .04$, $\xi_1 = 0.04$, $\xi_2 = 0.01$
Figure 3.6: The mutant strain invades, forms a hypertumor, and eventually will die if it cannot produce enough new vasculature.

3.6 the mutant strain can provide enough vasculature for itself in the time-scale used in simulation, so this is not a true hypertumor. Running simulations on a longer time scale or completely shutting off the mutant strain’s angiogenic signaling capabilities will definitively answer this question.

When the mutant forms in the middle, the tumor reduces drastically in size after the death of the mutant, but does not go extinct. The tumor segregates into a regions with the resident strain and mutant residing in distinct niches. Our model predicts that the hypertumor forms a necrotic ring around the resident strain, essentially cutting it off, but not eliminating, the tumor; c.f. Figure 3.8. In this scenario it is possible that the resulting tumor is no longer a threat to
Figure 3.7: The formation of a necrotic core. Once a necrotic core is formed it will permanently be there.

the host depending on the size of the resident strain. The total vascularization is increasing in the region with the resident strain but decreasing, and thus eventually wiping out the mutant cancer cells, in the region with the mutant strain; c.f. Figure 3.8.

If the resident strain has a higher proliferation rate with respect to the nutrient availability, i.e. the growth functions, $\Phi_i$, do not cross, then the resident strain will always wipe out the mutant regardless of how much angiogenic signaling is provided by the mutant. This is because our initial assumptions about the resident strain is that it will provide enough vasculature for itself in absence of the mutant strain; i.e., it will out-compete the mutant and drive it to extinction.
Figure 3.8: The mutant strain invades, forms a hypertumor, and reduces the final tumor size.

The simulations above all had an initial concentration of 0.2 cg/mL for the mutant parenchymal strain. Since this may be seen as an already established strain, we show simulations that start with an initial concentration of 0.02 cg/mL do not go extinct. Thus, the simulations previously shown are all viable and are shown instead of the simulations with the smaller initial concentration due to the time it takes for the simulation to end. Figure 3.11 shows the simulations for the decreased initial value for the mutant strain.

Biological studies show that if a large enough tumor cannot maintain its vasculature the tumor will necrose [50]. Thus, we investigate numerically to find the constant initial values of $u_1, u_2, y, z$ that will drive the tumor to extinction. We note that by extinction of the tumor, we are
Figure 3.9: The formation of a necrotic ring around the resident strain. The hypertumor encloses the resident strain but does not eliminate it from the tumor, possibly reducing the tumor size after the necrotic cells are phagocyted.
Figure 3.10: The invasion of the mutant strain in the hypertumor. It closes off the resident strain but does not eliminate it. The yellow line between the blue and red is the barrier formed by necrosing cells.
Figure 3.11: Simulations showing the final size of the tumor when $u_2 = 0.02$.

referring to the equilibrium of the system corresponding to $(\bar{u}_1, \bar{u}_2, \bar{u}_N, \bar{y}, \bar{z}, \bar{R}) = (0, 0, 1, 0, 0, 0) := E^0$, since in order to satisfy the assumption $u_1 + u_2 + u_N = 1$, we must have $u_N = 1$. Even though we do not have a rigorous proof that $E^0$ is locally asymptotically stable, our simulations suggest that if $\frac{y}{z} \leq \frac{n}{2\gamma}$ the tumor is unable to recover from its hypoxic state by the time the simulation is over, and seems to eventually become completely necrotic. Figure 3.12 shows the end result for one such scenario and taking note of the $y$-axis scaling, the tumor is almost entirely composed of necrotic cells. We find it reasonable to assume that any tumor that reaches this level of density will eventually be driven to extinction and it is only a matter of time until the tumor shrinks to zero if we ran the simulations longer.
Figure 3.12: A necrotic tumor after 1000 days
CONCLUSION AND FUTURE WORK

In Chapter 2 we implemented a numerical method to solve our system of equations; showed that the numerical scheme used converges to a known special solution and is valid for the time-scales used in Chapter 3; and numerically explored the stability of the equilibrium. We still feel that this area can be improved upon, in particular in showing that the numerical scheme is valid for longer time scales. We are interested in investigating longer time scales because Nagy conjectures that the hypertumor mechanism can lead to much longer lived tumors that are self-limiting or die out on a longer time scale [36]. If his conjecture is correct, we should see a change in inflection in the tumor growth. In the 1000 day time scale we used we had varied sizes of tumors, but it is important to note that all of these tumors were continuing to grow when we ended the simulation. In particular, we would like to see what are the eventual fates of the tumors in figures 3.6 and 3.8.

Analysis of the spatially heterogeneous steady state may provide some insight into self-limiting tumors. With our current model this was particularly difficult since the system of ODEs that results is implicit in the the highest-order derivative \(y'' = f(t, y, y', y'')\). Although MATLAB can handle such a system - in particular its \texttt{ode15i} solver comes to mind - the solver can only do so for initial value problems, not boundary value problems, which we have because of the no flux conditions at the endpoints. Thus, investigating this would require either programming our own numerical scheme or looking at different software that can handle such problems. Additionally, finding upper limits on the values for the numerical exploration of the basin of attraction can also be done, though it is not immediately clear if this will give any new biological insight into tumor growth.

Furthermore, we could modify the equation for the microvessel length density, \(z\), to include location dependent intratumoral pressure and a reduction VEC recruitment rate as the tumor grows. We believe this change in the dynamics would lead to, possibly, more realistic models of spheroid tumors.

In Chapter 3 we have shown that there is sufficient evidence that the ecological ecosystem versus integrated tissue question can be answered by the angiogenic signaling and proliferation rates
of each parenchymal lineages in the tumor. To find conclusive biological evidence, we would look at relevant biological data - in particular mouse xenographs - to determine whether the same patterns arise \textit{in vivo}. Further research is warranted for investigating the effects parenchymal motility has on tumor growth. Our work shows that varying cell motility rates can change the local density and have a dramatic effect on the vascular network that forms. Mark Chaplain’s work in modeling vascular tumor networks suggests this as well [11]. Figures 3.6 and 3.8 hint at palisading regions found in tumors to arise from the hypertumor mechanism. Scouring the oncological data for tumors that have two distinct lineages separated by a region of necrosis would be a first step to resolve this question.

In Chapter 1 we set to answer three questions. First, can the hypertumor mechanism account for necrosis in vascularized tumors. Simulations suggest that this is a good hypothesis for biologists to explore. In particular, the scenario depicted in Figure 3.6 shows a necrotic region appearing at the core which is the area where necrosis occurs in spheroid tumors seen in patients [50].

Secondly, can the hypertumor mechanism account for a decrease in the size of a tumor. The scenario pictured by Figures 3.8 and 3.9 shows a reduction in the size of the tumor after the hypertumor forms and is established, thus the hypertumor also resolves this question affirmatively.

Lastly, can the hypertumor mechanism separate the two competing parenchymal cells into different regions where they reside independently of the other strain, \textit{i.e.}, niche segregation. Figures 3.8 and 3.9 describe this separation. The region on the right of Figure 3.8 is only has the mutant parenchymal cells while the region on the left has the original resident parenchymal cells. This is the separation into distinct ecosystems that Nagy alluded to in [36].

The hypertumor presence, if observed \textit{in vitro} or \textit{in vivo}, would be a very powerful biological force governing the dynamics of tumor cells. As an extension of this project, it would be worthwhile to collaborate with biologists and oncologists to see if there is any evidence of hypertumors in either animal or human studies. This could be a valuable post-doctoral position, possibly at a medical school or interdisciplinary computational biology program.
BIBLIOGRAPHY


