Growth of Necrotic Tumors in the Presence and Absence of Inhibitors

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ABSTRACT

A mathematical model is presented for the growth of a multicellular spheroid that comprises a central core of necrotic cells surrounded by an outer annulus of proliferating cells. The model distinguishes two mechanisms for cell loss: apoptosis and necrosis. Cell loss due to apoptosis is defined to be programmed cell death, occurring, for example, when a cell exceeds its natural lifespan, whereas cell death due to necrosis is induced by changes in the cell’s microenvironment, occurring, for example, in nutrient-depleted regions. Mathematically, the problem involves tracking two free boundaries, one for the outer tumor radius, the other for the inner necrotic radius. Numerical simulations of the model are presented in an inhibitor-free setting and an inhibitor-present setting for various parameter values. The effects of nutrients and inhibitors on the existence and stability of the time-independent solutions of the model are studied using a combination of numerical and asymptotic techniques.

I. INTRODUCTION

In vivo cancer growth is a complicated phenomenon involving many interrelated processes, and correspondingly the mathematical modeling of such problems is very difficult. However, over the past 20 years an increasing number of mathematical models describing solid tumor growth (or multicellular spheroid growth) have appeared in the literature [1–8]. Typically, such models regard the tumor as a growing spherical mass of cells whose internal architecture consists of a layer of proliferating cells surrounding a necrotic core. A third, intermediate, region of quiescent cells is also sometimes included. Analysis of such models enables the relative importance of the different mechanisms involved in the growth process to be examined and may also assist in assessing the relative merits of different courses of drug treatment or
chemotherapy [9–15]. Many of the existing deterministic tumor models consist of an ordinary differential equation coupled to one or more reaction–diffusion equations. The ordinary differential equation derives from mass conservation applied to the tumor and describes the evolution of the tumor boundary, whereas the reaction–diffusion equations describe the distribution, within the tissue, of nutrients such as oxygen and glucose and growth inhibitory factors (GIFs) such as chalones [16–18].

In an earlier paper [19] we considered the evolution of a single tumor prior to the onset of necrosis and examined the effects of externally supplied nutrients and inhibitors on the existence and stability of radially symmetric, time-independent (nonnecrotic) solutions. Here this work is extended to include the simplest heterogeneous tumor configuration, which comprises a central necrotic core and an outer layer of proliferating cells. Both models provide insight into the action of a number of different inhibitory mechanisms. In particular the inhibitor can be regarded as either an anticancer drug or a naturally occurring inhibitor stimulated by the immune system in response to the foreign body. In [19] we showed that with no inhibitor present, nontrivial solutions exist, and are stable, for a range of the system parameters that corresponds to a balance between cell proliferation and natural cell death, or apoptosis [20–22]. In addition, where no nontrivial solutions exist, the trivial, tumor-free solution is stable. By permitting the existence of tumors that possess a central necrotic core, in this paper we are able to extend the range of parameters for which nontrivial solutions exist and also to distinguish apoptosis and necrosis as distinct cell loss mechanisms. As mentioned above, apoptosis describes natural, or programmed, cell death caused, for example, by aging of the tumor cells. By contrast, necrosis describes cell death that is triggered by the microenvironment when, for example, the local nutrient concentration is insufficient to sustain an individual cell.

In the following sections we use a combination of numerical and analytical techniques to investigate how the growth of a radially symmetric tumor can be influenced by different types of nutrients and inhibitors. Several results are derived that could be validated with experimental data. For example, we show that when no inhibitor is present and the necrotic core is small, changes in the necrotic radius occur much more rapidly and on a larger scale than changes in the outer tumor radius, the balance between the rate of apoptosis and the nutrient concentration at which necrosis commences determining whether growth or regression of the tumor ensues; the rate of cell degradation due to necrosis does not affect this result. Necessary conditions for the existence of tumors that possess the thin proliferating
rim frequently observed in vitro are also derived. Modifications to a tumor's growth characteristics brought about by the action of different types of inhibitors are also investigated and shown to have a significant effect in certain cases. The implications of these results for the development and treatment of cancer are also discussed.

2. THE MATHEMATICAL MODEL

The mathematical model studied here describes the evolution of a spherically symmetric, multicellular spheroid. The center, or necrotic core, of the tumor contains only dead cells and has radius \( r_{in}(t) \), while the outer, proliferating rim contains rapidly dividing cells and has radius \( R(t) \). The model focuses on a single externally supplied nutrient such as glucose or oxygen and also on a growth-inhibitory species. The inhibitor may be regarded as either an anticancer drug or a chemical produced in vivo as part of the host's immune response to the foreign body. We examine the effect that these chemicals have on the subsequent development of the tumor.

The model comprises two reaction–diffusion equations, describing the evolution of the nutrient and inhibitor species, denoted \( \sigma \) and \( \beta \), respectively, and an integrodifferential equation, governing the evolution of \( R(t) \). The necrotic radius \( r_{in}(t) \) is defined implicitly, occurring where \( \sigma \) attains a specified value \( (\sigma_{\text{neq}}) \) and such that cell proliferation is possible only when \( \sigma > \sigma_{\text{neq}} \) and necrosis occurs when \( \sigma < \sigma_{\text{neq}} \).

Fuller derivations of the mathematical model can be found in [1,3,19,23]. Here, for brevity, the governing equations are presented in spherically symmetric polar coordinates and in dimensionless form.

\[
0 = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \sigma}{\partial r} \right) - [\Gamma \sigma + \gamma_1 \beta] H(r - r_{in}),
\]

\[
0 = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial \beta}{\partial r} \right) - \gamma_2 \beta H(r - r_{in}),
\]

\[
R^2 \frac{dR}{dt} = \int_0^R \{ S(\sigma, \beta) H(r - r_{in}) - N(\sigma, \beta) H(r_{in} - r) \} r^2 \, dr,
\]

subject to

\[
\frac{\partial \sigma}{\partial r} = 0 = \frac{\partial \beta}{\partial r} \text{ on } r = 0,
\]

\[
\sigma = \sigma_x, \beta = \beta_x, \text{ on } r = R(t),
\]

\[
\sigma, \frac{\partial \sigma}{\partial r}, \beta, \frac{\partial \beta}{\partial r} \text{ continuous across } r = r_{in}(r),
\]

\[
\sigma = \sigma_{\text{neq}} \text{ on } r = r_{in}(r),
\]

\[
R(0) = 1.
\]
Following [1,3,19], by scaling time with the longer tumor growth timescale ($\sim 0.5$ mm/day) rather than a typical nutrient/inhibitor diffusion timescale ($\sim 1$ min), we have adopted once again a quasi-steady approach, with $\partial / \partial t = 0$ in (1) and (2). Denoting by $H(\cdot)$ the Heaviside step function [$H(x) = 1$ if $x > 0$, $H(x) = 0$ if $x \leq 0$], we assume that since the necrotic core contains only dead cells, any nutrient/inhibitor reaction terms in (1) and (2) are identically zero there. Thus the term $\Gamma_0 H(r - r_{in})$ describes the consumption by the proliferating cells of the nutrient, and $\gamma_1 \beta H(r - r_{in})$ describes their destruction by the inhibitor.

In (2) we assume that inside the proliferating region the inhibitor decays at the constant rate $\gamma_2$.

In (3) we distinguish between cell proliferation, denoted by the term $S(\sigma, \beta)$, which is confined to the annulus $r_{in} < r < R$, and cell loss due to necrosis, denoted by the term $N(\sigma, \beta)$, which is restricted to nutrient-depleted regions of the tumor, where $\sigma < \sigma_{tec}$. We assume that the proliferation rate is a balance between cell birth and apoptosis or programmed cell death (see [9,20,21,24,25] for a description of the structural changes involved in apoptosis). Although there is ambiguity regarding the differences between apoptosis and necrosis as cell loss mechanisms, here we define the key difference as follows: necrosis is induced by the external microenvironment whereas apoptosis is an intrinsic property of a cell. Insufficient nutrient levels may trigger cell death due to necrosis, whereas if a cell lives beyond its natural lifespan then cell death due to apoptosis may result. The model thus explicitly contains two different cell loss terms: in Equation (3) cell loss due to apoptosis is incorporated into $S(\sigma, \beta)$ while $N(\sigma, \beta)$ describes cell loss due to necrosis. To date only McElwain and Morris [23] and Byrne and Chaplain [19] have incorporated apoptosis into a mathematical model of tumor growth. Following [19], to simplify the analysis, throughout this paper attention is focused on a proliferation rate that is linear with respect to both $\sigma$ and $\beta$. Thus we consider

$$S(\sigma, \beta) = s(\sigma - \tilde{\sigma})(1 - \beta / \tilde{\beta}),$$

(9)

where $s, \tilde{\sigma}, \tilde{\beta}$ are constants. In (9), with $\beta = 0$, we interpret $s\tilde{\sigma}$ as the local birth rate and $s\tilde{\sigma}$ as the local death rate due to apoptosis (i.e., we assume that the volume fraction loss due to apoptosis is constant). The factor $(1 - \beta / \tilde{\beta})$ is interpreted as the reduction in the proliferation rate due to the inhibitor. [Although other, more physically realistic, choices for $S(\sigma, \beta)$ could be studied, the resulting models generally require numerical solution and are therefore not considered here.]
Assuming further that necrosis manifests itself as a constant volume loss term at all points inside the necrotic core, we fix \( N(\sigma, \beta) = 3\lambda \). Substituting with \( S(\sigma, \beta) \) and \( N(\sigma, \beta) \), Equation (3) can be rewritten as

\[
R^2 \frac{dR}{dt} = \int_{r_n}^R s(\sigma - \bar{\sigma}) \left(1 - \frac{\beta}{\beta_0}\right) r^2 dr - \lambda r_n^3. \tag{3'}
\]

Equations (4)–(8) close equations (1)–(3'). Equation (4) reflects the assumed symmetry of the tumor. In (5), \( \sigma_0 \), and \( \beta_0 \) are the constant nutrient and inhibitor concentrations on the outer tumor boundary. Equation (7) ensures continuity of the dependent variables and their first derivatives, whereas Equation (6) defines \( r_n \) implicitly. Finally, Equation (8) defines the initial, scaled tumor radius.

Before continuing with our analysis, we remark that the manner in which \( \beta \) is coupled into the model equations enables us to investigate how two different inhibitory mechanisms effect tumor growth. The inhibitor either acts directly on the cells, reducing their proliferation rate in (3'), or it acts indirectly in (1) by reducing the nutrient levels available to the tumor cells.

3. NUMERICAL SIMULATIONS

Numerical solution of the mathematical model defined by Equations (1)–(8) necessitates solving the two free boundaries \( R(t) \) and \( r_n(t) \). Since \( R(t) \) satisfies an integrodifferential equation, tracking the outer tumor radius is relatively straightforward. By contrast, the necrotic core radius is defined implicitly by (6) and evolves on different timescales, depending on the tumor’s size. For example, the asymptotic analysis contained in Section 4 and the Appendix demonstrates how immediately after the onset of necrosis \( r_n \) evolves on a rapid timescale during which \( R \) remains approximately constant. For these reasons, in this paper we restrict attention to simple nutrient/inhibitor consumption terms for which solution of the mathematical model can be viewed as a two-stage process. First, solution of the reaction–diffusion equations yields \( \sigma \) and \( \beta \) in terms of \( R(t) \) and \( r_n(t) \). Second, expressions governing \( R \) and \( r_n \) are obtained by imposing (7) and substituting with \( \sigma \) and \( \beta \) in (3').

3.1. INHIBITOR-FREE SOLUTIONS

With \( \beta = 0 \) so that \( S(\sigma, \beta) = s(\sigma - \bar{\sigma}) \) (i.e., cell birth rate = \( s\sigma \), and cell loss rate due to apoptosis = \( s\bar{\sigma} \)), solution of Equation (1), subject to
(4)–(6), yields the following expression for the nutrient concentration \( \sigma \):

\[
\sigma = \begin{cases} \\
\sqrt{\Gamma} A & \text{for } \rho \in (0, r_{in}), \\
\frac{A}{r} \left[ \sinh \sqrt{\Gamma} (r - r_{in}) + \sqrt{\Gamma} r_{in} \cosh \sqrt{\Gamma} (r - r_{in}) \right] & \text{for } \rho \in (r_{in}, 1),
\end{cases}
\]

(10)

where

\[
A = \frac{\sigma_x}{\sigma_{nec}} \frac{R}{\left[ \sinh \sqrt{\Gamma} (R - r_{in}) + \sqrt{\Gamma} r_{in} \cosh \sqrt{\Gamma} (R - r_{in}) \right]}.
\]

Imposing Equation (7), we deduce that \( r_{in} \) is related to \( R \) by the equation

\[
\left( \frac{\sigma_x}{\sigma_{nec}} \right) \sqrt{\Gamma} R = \sinh \sqrt{\Gamma} (R - r_{in}) + \sqrt{\Gamma} r_{in} \cosh \sqrt{\Gamma} (R - r_{in}).
\]

(11)

Substitution with \( \sigma \) in (3') yields the following differential equation for \( R(t) \):

\[
R^2 \frac{dR}{dt} = s \frac{\sigma_{nec}}{\Gamma^{3/2}} \left[ \sqrt{\Gamma} (R - r_{in}) \cosh \sqrt{\Gamma} (R - r_{in}) \right]
\]

\[
+ \left( \Gamma R r_{in} - 1 \right) \sinh \sqrt{\Gamma} (R - r_{in})
\]

\[
- s \left( \frac{\tilde{\sigma}}{3} (R^3 - r_{in}^3) + \lambda r_{in}^3 \right).
\]

(12)

Equations (11) and (12) can be solved simultaneously, subject to \( R(0) = 1 \), to determine \( R(t) \) and \( r_{in}(t) \). To simplify the following analysis, it is convenient to introduce the scaled radii

\[
\eta(t) = \sqrt{\Gamma} R(t) \quad \text{and} \quad \zeta(t) = \sqrt{\Gamma} r_{in}(t),
\]

so that, with \( \eta(0) = \sqrt{\Gamma} \), Equations (11) and (12) transform to give

\[
\left( \frac{\sigma_x}{\sigma_{nec}} \right) \eta = \sinh(\eta - \zeta) + \zeta \cosh(\eta - \zeta),
\]

(13)

\[
\eta^2 \frac{d\eta}{dt} = s \frac{\sigma_{nec}}{\Gamma^{3/2}} \left[ (\eta - \zeta) \cosh(\eta - \zeta) + (\eta \zeta - 1) \sinh(\eta - \zeta) \right]
\]

\[
- s \left( \frac{\tilde{\sigma}}{3} (\eta^3 - \zeta^3) + \lambda \zeta^3 \right).
\]

(14)
Before presenting numerical results, we mention how (13) and (14) are modified for nonnecrotic tumors. Referring to [19], we remark that if \( \sigma(\tau) > \sigma_{\text{nec}} \quad \forall \tau \in [0, R] \), then \( \zeta = 0 \). In this case \( \sigma \) attains its minimum at the origin, the analog of (13) defines \( \sigma(0) = \sigma_{\text{nec}} \eta / \sinh \eta \), and (14) becomes

\[
\eta^2 \frac{d\eta}{dt} = s \sigma_{\text{nec}} \eta \left( \frac{\eta}{\tanh \eta} - 1 \right) - \frac{s \sigma \eta^3}{3}.
\]

Figures 1a–c summarize the range of qualitative behavior obtained when there is no inhibitor present, i.e., \( \beta = 0 \). Three possible outcomes are observed. In the first case, both \( \eta \) and \( \zeta \) increase, or decrease, monotonically toward equilibrium values \( \eta_e \) and \( \zeta_e \), say, which are independent of \( \eta(0) \) and \( \zeta(0) \); that is, the tumor evolves to a final configuration with an interior necrotic core. In the second case, all initial data evolve monotonically to a nonnecrotic tumor configuration for which \( \eta > \zeta_e = 0 \); that is, the tumor evolves to a final configuration with no necrotic core. In the third case, \( \eta \) and \( \zeta \) decay monotonically to zero, so that the tumor eventually disappears. Typical examples of each mode of behavior are reproduced in Figures 1a–c. From the simulations we observe that the type of behavior that is realized is strongly related to the relative importance of cell loss due to apoptosis, cell proliferation, and cell loss due to necrosis, as embodied in the parameters \( \tilde{\sigma}, \sigma_e, \) and \( \sigma_{\text{nec}} \). As \( \tilde{\sigma} \) decreases, decay of the tumor to zero is superseded first by evolution of the tumor to a steady, nonnecrotic configuration for moderate values of \( \tilde{\sigma} \) and to a steady necrotic configuration for even smaller values of \( \tilde{\sigma} \). (The discussion in Section 4 of the existence of steady-state tumor configurations renders this result more explicit.)

The effect that the choice of \( S(\sigma, \beta) \) has on the tumor’s growth characteristics becomes apparent when the linear proliferation rate is replaced by a logistic term and we fix

\[
S(\sigma, \beta) = s \sigma \left( 1 - \frac{\sigma}{\tilde{\sigma}} \right)
\]

in Equation (3). In this case, with \( \tilde{\sigma} \) constant, we interpret \( s \sigma^2 / \tilde{\sigma} \) as the 

**cell loss term due to apoptosis.**

This modification leaves (13) unchanged whereas (14) is superseded by the following equation for \( \eta \):

\[
\eta^2 \frac{d\eta}{dt} = s \sigma_{\text{nec}} \left[ (\eta - \zeta) \cosh(\eta - \zeta) + (\eta \zeta - 1) \sinh(\eta - \zeta) \right] - s \lambda \zeta^3 \\
- \frac{s \sigma_{\text{nec}}^2}{2 \tilde{\sigma}} \left( \frac{1 + \zeta^2}{2} \sinh 2(\eta - \zeta) \right)
\]

\[
+ \zeta \cosh 2(\eta - \zeta) + (\zeta^2 - 1) \eta - \zeta^3 \right] \right). \tag{15}
\]
Numerical simulations suggest that in this case only two possible outcomes occur: either the tumor decays to zero or it attains a steady, necrotic configuration. The type of behavior that is realized depends on the size of $\dot{\sigma}$ relative to $\sigma_x$ and $\sigma_{\text{nec}}$. For example, for small values of $\dot{\sigma}$ (i.e., strong apoptotic decay), all tumor configurations decay to zero, whereas for large values of $\dot{\sigma}$ (i.e., weak apoptotic decay), all tumors evolve to a necrotic configuration. The behavior for intermediate values of $\dot{\sigma}$ depends on $\eta(0)$: Small tumors decay to zero whereas larger tumors evolve to a necrotic configuration (Figure 2). These results, together with Figures 1a–c, demonstrate how important accurate knowledge of the proliferation rate is when assessing the growth characteristics of a tumor.

Fig. 1. (a) Evolution of $\eta$ and $\zeta$ when $\beta = 0$, $S(\sigma, \beta) = s(\sigma - \dot{\sigma})$. All initial data converge to the limiting values $\eta^* \sim 2.42$ and $\zeta \sim 0.63$. Key: $\eta(t)$ (---); $\zeta(t)$ (---). Parameter values: $\sigma_x = 0.8$, $\sigma_{\text{nec}} = 0.4$, $\dot{\sigma} = 0.5$, $\lambda = 0.1$, $\Gamma = 25$, $s = 100$. Initial scaled tumor radius: $\eta(0) = \sqrt{\Gamma} = 5.0$. (b) As for (a) but with the rate of apoptosis increased to $\dot{\sigma} = 0.7$. All initial data converge to a nonnecrotic tumour for which $\eta^* \sim 1.51$ and $\zeta = 0.00$. (c) As for (a) but with the rate of apoptosis increased to $\dot{\sigma} = 0.9$. All initial data converge to the trivial case for which $\eta^* = 0.00 = \zeta$. 
Fig. 1. (continued)
Fig. 2. Evolution of $\eta$ and $\zeta$ when $\beta = 0$, $S(\sigma, \beta) = s \sigma (1 - \sigma / \hat{\sigma})$, showing decay of the tumor to zero if $\eta(0) < 2.2$ and growth to a nontrivial configuration otherwise. Key: $\eta(t)$ (——); $\zeta(t)$ (---). Parameter values: $\alpha_x = 0.8$, $\sigma_{\text{nce}} = 0.4$, $\hat{\sigma} = 0.64$, $\lambda = 0.1$, $\Gamma = 25$, $s = 100$.

3.2. INHIBITOR-PRESENT SOLUTIONS

When $\beta > 0$, integration of Equations (1) and (2), subject to (4)–(6), yields the following expressions for $\sigma$ and $\beta$:

$$\sigma = \begin{cases} \sigma_{\text{nce}} & \text{for } r \in (0, r_{\text{in}}), \\ \frac{A_\sigma}{r} \left[ \sinh \sqrt{\Gamma} (r - r_{\text{in}}) + \sqrt{\Gamma} r_{\text{in}} \cosh \sqrt{\Gamma} (r - r_{\text{in}}) \right] + \Delta \beta & \text{for } r \in (r_{\text{in}}, R) \end{cases}$$

(16)

and

$$\beta = \begin{cases} \beta_{\text{nce}} & \text{for } r \in (0, r_{\text{in}}), \\ \frac{A_\beta}{r} \left[ \sinh \sqrt{\gamma_2} (r - r_{\text{in}}) + \sqrt{\gamma_2} r_{\text{in}} \cosh \sqrt{\gamma_2} (r - r_{\text{in}}) \right] & \text{for } r \in (r_{\text{in}}, R), \end{cases}$$

(17)
GROWTH OF NECROTIC TUMORS

where

\[ A_\alpha = \frac{\left( \sigma_\alpha - \Delta \beta_\alpha \right) R}{\sinh \sqrt{T} \left( R - r_{\text{in}} \right) + \sqrt{T} r_{\text{in}} \cosh \sqrt{T} \left( R - r_{\text{in}} \right)}, \]  

\[ A_\beta = \beta_\alpha R \left/ \left[ \sinh \sqrt{\gamma_2} \left( R - r_{\text{in}} \right) + \sqrt{\gamma_2} r_{\text{in}} \cosh \sqrt{\gamma_2} \left( R - r_{\text{in}} \right) \right] \right. \]  

and

\[ \Delta = \gamma_1 / (\gamma_2 - T) \]

and \( \beta_{\text{nec}} \) is defined in terms of \( \eta, \zeta \), and \( \theta = \sqrt{\gamma_2 / T} \) as follows:

\[ \beta_{\text{nec}} = \beta_\alpha \theta \eta / \left[ \sinh \theta (\eta - \zeta) + \theta \zeta \cosh \theta (\eta - \zeta) \right]. \]

Imposing (7) yields the following expression, which generalizes (13) to the case \( \beta > 0 \):

\[ \frac{\sigma_\alpha - \Delta \beta_\alpha}{\sigma_{\text{nec}} - \Delta \beta_{\text{nec}}} \eta = \sinh (\eta - \zeta) + \zeta \cosh (\eta - \zeta). \]

Substituting with \( \sigma \) and \( \beta \) from (16) and (17) in (3'), it is possible to derive an equation for \( \eta \) that generalizes Equation (14) to the case \( \beta > 0 \). Rather than presenting this cumbersome expression, we simply rewrite (3') in terms of \( \eta \) and \( \zeta \):

\[ \eta^2 \frac{d\eta}{dt} = s \left\{ \int_\zeta^{\eta} \left[ \sigma \left( \rho / \sqrt{T}, t \right) - \bar{\sigma} \right] \left( 1 - \frac{\beta (\rho / \sqrt{T}, t)}{\bar{\beta}} \right) \rho^2 d\rho - \lambda \zeta^3 \right\}. \]

(23)

As mentioned above, our model incorporates two mechanisms for inhibitor action: as a sink of nutrient in Equation (1) (indirect action) or by reducing the cell proliferation rate in Equation (3) (direct action). For comparison with the inhibitor-free results of Section 3.1, we examine the effect that these modes of action, taken separately and together, have on the tumor's development. Tables 1-3 summarize these results, showing how the equilibrium radii \( \eta_\alpha \) and \( \zeta_\alpha \) vary with the mode of inhibitor action.

With \( \bar{\sigma} = 0.2 < \sigma_{\text{nec}} \), Table 1 shows that the direct and indirect modes of inhibitor action have the capacity to reduce the size of the ultimate tumor radius, \( \eta_\alpha \). Indeed, in this case, the presence of the inhibitor has a beneficial effect in all cases. With the inhibitor acting in both manners (\( \gamma_1 = 0.8, \bar{\beta} = 0.5 \)), a qualitative change in the behavior of
the system occurs, with the appearance of two equilibrium states ($\eta_x = 2.38, 0.00$). From Figure 3 we observe that in this case if, prior to the inhibitor’s introduction, the tumor is sufficiently small [here $\eta(0) < 0.98$], then the tumor disappears. For larger values of $\eta(0)$, as before, the tumor evolves to a finite size.

**Table 1**

<table>
<thead>
<tr>
<th>$\gamma_1$</th>
<th>$\tilde{\beta}$</th>
<th>$\eta_x$</th>
<th>$\xi_x$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
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<td>6.00</td>
</tr>
<tr>
<td>0.01</td>
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<td>6.82</td>
<td>5.42</td>
</tr>
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<td>5.0</td>
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<td>3.77</td>
</tr>
<tr>
<td>0.01</td>
<td>0.9</td>
<td>4.10, 0.00</td>
<td>2.62, 0.00</td>
</tr>
<tr>
<td>0.80</td>
<td>0.9</td>
<td>2.38, 0.00</td>
<td>1.29, 0.00</td>
</tr>
<tr>
<td>0.01</td>
<td>0.5</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0.80</td>
<td>0.5</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Values in Figure 3.*

![Figure 3](image-url)

**Fig. 3.** Evolution of $\eta$ when $\beta > 0$ and $S(\sigma, \beta) = s(\sigma - \tilde{\sigma})(1 - \beta / \tilde{\beta})$, showing decay of the tumor to zero if $\eta(0) < 0.98$ and convergence to a nontrivial configuration otherwise. Parameter values: $\alpha_x = 0.8$, $\alpha_{nc} = 0.4$, $\tilde{\sigma} = 0.2$, $\beta_x = 1.0$, $\tilde{\beta} = 0.9$, $\lambda = 0.1$, $\gamma_1 = 0.8$, $\gamma_2 = 2.0$, $\Gamma = 25.0$, $s = 100$. 


TABLE 2

\( \hat{\sigma} = 0.7 \)

<table>
<thead>
<tr>
<th>( \gamma_1 )</th>
<th>( \hat{\beta} )</th>
<th>( \eta_\infty )</th>
<th>( \xi_\infty )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>( + \infty )</td>
<td>1.51</td>
<td>0.00</td>
</tr>
<tr>
<td>0.01</td>
<td>5.0</td>
<td>1.48</td>
<td>0.00</td>
</tr>
<tr>
<td>0.80</td>
<td>5.0</td>
<td>1.06</td>
<td>0.00</td>
</tr>
<tr>
<td>0.01</td>
<td>0.9</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0.80</td>
<td>0.9</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0.01</td>
<td>0.5</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0.80</td>
<td>0.5</td>
<td>1.90,0.00</td>
<td>0.71,0.00</td>
</tr>
</tbody>
</table>

Referring now to Table 2, with \( \sigma_{\text{neq}} < \hat{\sigma} = 0.7 < \sigma_\infty \), we note that in most cases the presence of the inhibitor has a beneficial effect, reducing \( \eta_\infty \). Indeed, if \( \gamma_1 = 0.01 \) and \( \hat{\beta} = 0.9 \), then addition of the inhibitor eradicates the tumor. However, direct action of the inhibitor may actually increase the equilibrium size of the tumor (\( \gamma_1 = 0.8, \hat{\beta} = 0.5 \)). Thus, in this case the presence of the inhibitor does not always improve the situation; if \( \eta(0) > 1.90 \), then a necrotic tumor persists.

The results presented in Table 3, with \( \sigma_{\text{neq}} < \hat{\sigma} = 0.9 \), further demonstrate how the inhibitor can sometimes exacerbate the situation. Now when \( \beta = 0 \), or when the inhibitor acts indirectly, no nontrivial tumors exist. However, direct action of the inhibitor introduces a stable, nontrivial tumor whose size and structure depend on the strength of the inhibitor. The necrotic tumor is obtained only when \( \eta(0) > 1.20 \); if \( \eta(0) < 1.20 \), then the tumor decays to zero.

TABLE 3

\( \hat{\sigma} = 0.9 \)

<table>
<thead>
<tr>
<th>( \gamma_1 )</th>
<th>( \hat{\beta} )</th>
<th>( \eta_\infty )</th>
<th>( \xi_\infty )</th>
</tr>
</thead>
<tbody>
<tr>
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4. MODEL ANALYSIS

4.1. ANALYSIS OF STEADY-STATE SOLUTIONS

The numerical results of the previous section indicate that both the parameter values and the functional forms employed in the model can affect a tumor's potential growth. For example, for the inhibitor-free model, the existence of a nontrivial steady solution having a necrotic core is predicted in Figure 1a, whereas in Figure 1c, for a different set of parameter values, the tumor disappears. In this section, by seeking time-independent solutions of Equations (1)–(8), we investigate how the existence and multiplicity of steady solutions is affected by the choice of the proliferation rate and the associated parameter values. The stability of these solutions is then discussed in Section 4.2.

With $\beta = 0$ and $d/dt = 0$, Equations (13) and (14) define the scaled steady-state tumor radii $\eta$ and $\zeta$ when no inhibitor is present:

$$(\eta - \zeta) \cosh(\eta - \zeta) + (\eta \zeta - 1) \sinh(\eta - \zeta)$$

$$= \frac{\bar{\sigma}}{3\sigma_{\text{nc}1}} (\eta^3 - \zeta^3) + \frac{\lambda}{\sigma_{\text{nc}1}} \zeta^3,$$

$$\sinh(\eta - \zeta) + \bar{\sigma} \cosh(\eta - \zeta) = \frac{\sigma_{\nu}}{\sigma_{\text{nc}1}} \eta.$$  \hspace{1cm} (24) \hspace{1cm} (25)

If $\zeta = 0$, Equations (24) and (25) reduce to give the following expression for $\eta$ [19]:

$$\tanh \eta = \frac{\eta}{1 + \bar{\sigma} \eta^2 / 3 \sigma_{\nu}}.$$ 

Figure 4 illustrates the variation of $\eta$ and $\zeta$ with $\bar{\sigma}$, holding $\sigma_{\nu}$, $\sigma_{\text{nc}1}$, and $\lambda$ fixed. From this diagram we note that whereas the trivial solution ($\eta = \zeta = 0$) persists for all parameter values, nontrivial solutions exist only when $\bar{\sigma} < \sigma_{\nu}$. (Indeed, it is possible to show that a branch of nonnecrotic solutions is created as $\bar{\sigma}$ decreases through $\sigma_{\nu}$.) We remark also that where they exist the nontrivial solutions are unique, that is, only one tumor configuration can occur.

From Equation (26) it is clear that increasing $\lambda$ has no effect on nonnecrotic tumors, for which $\zeta = 0$. Thus, changes in $\lambda$ leave the points A and B on Figure 4 fixed. However, by focusing on the limit $\bar{\sigma} \sim \delta^2 \sigma$ ($0 < \delta \ll 1$) we gain some insight into how the points $C_{\eta}$ and $C_{\zeta}$ vary with the rate of cell loss due to necrosis. For example, if $\lambda \sim \delta^3$, then we deduce from Equations (24) and (25) that the leading order
steady-state solutions can be written in the form $\eta \sim \bar{\eta}$ and $\zeta \sim \bar{\zeta}$, where

$$\frac{\sinh \bar{\eta}}{\bar{\eta}} = \frac{\sigma_e}{\sigma_{nec}} \quad \text{and} \quad \bar{\zeta}^3 = \frac{\sigma_{nec}}{\lambda} (\bar{\eta} \cosh \bar{\eta} - \sinh \bar{\eta}).$$

By continuity, we deduce further that increasing $\lambda$ reduces both $C_\eta$ and $C_\zeta$. In a similar way, it is possible to show that increasing $\sigma_{nec}$ leaves the point $A$ fixed, moves $B$ closer to $A$, and reduces both $C_\eta$ and $C_\zeta$.

When $\beta > 0$ and $d/dt = 0$, Equations (21)–(23) define $\eta$ and $\zeta$ when inhibitor is present. Figures 5a–c show how $\eta$ and $\zeta$ vary with $\bar{\sigma}$ for the three choices of $\beta$ considered in Tables 1–3 of Section 3.2. The figures not only summarize the different types of behavior that the inhibitor may induce but also provide some indication of its success in fighting the tumor. For example, comparing Figures 4 and 5a, we note that in this case the presence of the inhibitor simply reduces the inhibitor-free steady-state configuration where it exists. By contrast, the
FIG. 5. (continued)
GROWTH OF NECROTIC TUMORS

(c)

Fig. 5. (a) The effect on the scaled steady-state tumor radii \( \eta \) and \( \zeta \) of an inhibitor species \( (\beta > 0) \) is compared with the inhibitor-free situation \( (\beta = 0) \) as \( \tilde{\sigma} \) varies. The inhibitor acts both directly, via the cell proliferation rate, and indirectly, consuming the nutrient species. In this case, the inhibitor simply reduces the size of the nontrivial, inhibitor-free tumor radii. Key: inhibitor-present tumor radii (---); inhibitor-free tumor radii (----). Parameter values: \( \sigma_c = 0.8, \sigma_{nc} = 0.4, \lambda = 0.1, \beta_c = 1.0, \tilde{\beta} = 5.0, \gamma_1 = 0.8, \gamma_2 = 2.0 \). (b) The effect on \( \eta \) and \( \zeta \) increasing the strength of the direct inhibitor action \( (\tilde{\beta} = 0.9) \). In this case, when \( \tilde{\sigma} < \sigma_c \) the existence of nontrivial solutions is restricted to a smaller range of \( \tilde{\sigma} \) than for the inhibitor-free case. However, where they exist these solutions are nonunique. In addition, the existence of nonnecrotic solutions is predicted when \( \tilde{\sigma} > \sigma_c \). Key: \( \eta \) (----); \( \zeta \) (---). Parameter values as in (a) except \( \tilde{\beta} = 0.9 \). (c) The effect on \( \eta \) and \( \zeta \) of increasing the strength of the direct inhibitor action even further \( (\tilde{\beta} = 0.5) \). In this case the existence of nontrivial solutions is confined to the range \( \tilde{\sigma} > 0.6 \), with the interval \( 0 < \tilde{\sigma} < 0.6 \) now being a tumor-free region. Key: \( \eta \) (----); \( \zeta \) (---). Parameter values as in (a) and (b) except \( \tilde{\beta} = 0.5 \).

The appearance of nonunique solutions in Figure 5b marks a qualitative change in the action of the inhibitor. However, provided that \( \tilde{\sigma} < \sigma_c \) (i.e., cell loss due to apoptosis is less than the nutrient concentration on the tumor boundary), the resulting tumor steady states are smaller and possibly zero in the presence of the inhibitor. On the basis of the results presented in Tables 1–3 and the numerical simulations depicted in
Figure 3, it seems reasonable to assume that the lower branch of nontrivial solutions is unstable and separates the stable necrotic configuration from a stable, tumor-free configuration. The appearance of nontrivial solutions for $\tilde{\sigma} > \sigma_\ast$ is also new. In this case the inhibitor acts detrimentally, destabilizing the trivial solutions and enabling the system to support a tumor where the inhibitor-free system did not. Turning finally to Figure 5c, we note that in this case, provided that $\tilde{\sigma} < \sigma_\ast$, the inhibitor eliminates the tumor, whereas for $\tilde{\sigma} > \sigma_\ast$, as in Figure 5b, the presence of the inhibitor leads to the appearance of a tumor. These results demonstrate how changes in apoptotic cell loss (i.e., $\tilde{\sigma}$) can alter the nature of the solutions and hence the structure of the tumor.

4.2. ASYMPTOTIC ANALYSIS

In Section 3, expressions governing the evolution of $\eta$ and $\zeta$ were derived. Taken with the steady-state analysis presented in Section 4.1, these results provide some insight into the local stability of the different tumor configurations. For example, referring to Figure 4, with $\beta = 0$, we anticipate that, where it exists, the nontrivial steady state is stable. (In this case, any tumor whose radius is smaller/larger than the steady-state value grows/regresses monotonically to the steady state.) By contrast, referring to Figure 5b, with $\beta > 0$, we anticipate that the upper solution on each of the two branches is stable, the lower branch unstable, and the trivial solution stable where an even number of nontrivial solutions exist. (In this case, any tumor whose radius is smaller than the unstable steady-state value will disappear whereas any tumor whose radius is larger than the unstable steady-state value will evolve monotonically to the larger steady-state value.)

In practice it is possible to establish local stability properties of the steady solutions by examining the evolution of small perturbations about the steady states. Due to the complexity of the governing equations, such an approach is not particularly instructive here. Rather, we focus on the evolution of the tumor in two limiting cases that are of practical interest: immediately after the onset of necrosis ($0 < \zeta \ll 1$) and when the width of the proliferating rim is small ($0 < \eta - \zeta \ll 1$). (The case $0 < \eta \ll 1$ is not considered because it is discussed in detail in [19]. There the appearance of a nontrivial nonnecrotic solution as $\tilde{\sigma}$ decreases through $\sigma_\ast$ is shown to coincide with the loss of stability of the trivial steady state.) The asymptotic analysis enables us to investigate the effect of the different proliferation rates and modes of inhibitor action on the tumor's growth for the cases of interest. It is anticipated that the resulting approximate expressions for $\eta$ and $\zeta$ [or $R(t)$ and $r_{in}(t)$] could be used to estimate key parameters from in vitro
data on multicellular spheroids [26]. In particular, by comparing the results of the analysis for the small necrotic core and the thin proliferating rim limits, it should be possible to assess the relative importance of apoptosis and necrosis at different stages of a tumor's development. The key results of our analysis are summarized below. Details of the asymptotic analysis are contained in the Appendix.

Inhibitor-Free Analysis

When the necrotic core is small, we introduce the small parameter $0 < \varepsilon \ll 1$ and assume that the solution to (13)–(14) can be written in the form

$$
\eta \sim \eta_0 + \varepsilon \eta_1 + \varepsilon^2 \eta_2 \quad \text{and} \quad \zeta \sim \varepsilon \xi_1,
$$

where $\varepsilon$ is chosen so that $\xi_1(t = 0) = 1$ and the coefficients $\eta_0$, $\eta_1$, $\eta_2$, and $\xi_1$ are determined by substituting in (13) with the trial solutions, and equating to zero terms of $O(\varepsilon^n)$. In this way the following approximate expressions for $\eta$ and $\zeta$ are derived:

$$
\eta \sim \eta_0 + \varepsilon^2 \eta_2(0) + \Lambda t \quad (27a)
$$

and

$$
\zeta \sim \left[ \varepsilon^2 + 2 \Lambda \left( \frac{\eta_0 \operatorname{cosh} \eta_0 - \operatorname{sinh} \eta_0}{\eta_0 \operatorname{sinh} \eta_0} \right) t \right]^{1/2}. \quad (27b)
$$

In (27) $\eta_0$ and $\eta_2(0)$ are defined as

$$
\frac{\sigma_\infty}{\sigma_{\text{nec}}} = \frac{\sinh \eta_0}{\eta_0} \quad \text{and} \quad \eta_2(0) = \frac{\sinh \eta_0}{2(\cosh \eta_0 - \sigma_\infty/\sigma_{\text{nec}})},
$$

and

$$
\Lambda = \frac{5 \sigma_{\text{nec}}}{\eta_0^2} \left[ \eta_0 \operatorname{cosh} \eta_0 - \sinh \eta_0 - \frac{\bar{\sigma}}{\sigma_{\text{nec}}} \left( \frac{\eta_0}{3} \right) \right].
$$

From the expression for $\eta_0$ we deduce that, to leading order, the outer radius of the tumor is constant provided that $\sigma_\infty > \sigma_{\text{nec}}$. We remark also that growth of the tumor is predicted when $\Lambda > 0$. From the definition of $\Lambda$ we infer that growth of the tumor occurs if

$$
\frac{\bar{\sigma}}{\sigma_{\text{nec}}} < \frac{3(\eta_0 \operatorname{cosh} \eta_0 - \sinh \eta_0)}{\eta_0}.
$$
In this case the asymptotic solution remains valid until \( t \sim O(1) \), by which time the necrotic core is \( O(1) \). By contrast, if \( \Lambda < 0 \), shrinkage of the tumor is predicted and the necrotic core disappears at time \( t_D \), where, from (27),

\[
 t_D = \frac{\epsilon^2 \eta_0 \sinh \eta_0}{2|\Lambda|(\eta_0 \cosh \eta_0 - \sinh \eta_0)} .
\]

The case \( \Lambda = 0 \) arises only for particular values of the system parameters. In this special case a steady, necrotic configuration is predicted.

The above results indicate that it is the balance between the parameter groupings \( \tilde{\sigma} / \sigma_x \in (0,1) \) and \( \sigma_{\text{nec}} / \sigma_x \in (0,1) \) that governs the sign of \( \Lambda \) and hence the viability of the necrotic core. We note that if \( \tilde{\sigma} < \sigma_{\text{nec}}(\Lambda > 0) \), then persistence of the necrotic core is predicted.

When the proliferating rim is thin we introduce the small parameter \( 0 < \delta \ll 1 \) to characterize the width of the proliferating rim and assume that solutions to (13)–(14) can be written in the form

\[
 \eta \sim \eta_0 + \delta \eta_1 + \delta^2 \eta_2 \quad \text{and} \quad \zeta \sim \eta_0 + \delta \zeta_1 + \delta^2 \zeta_2.
\]

A similar expansion is adopted for the external nutrient concentration: \( \sigma_x \sim \sigma_{x0} + \delta \sigma_{x1} + \delta^2 \sigma_{x2} \). By substituting with the above trial solutions in (13)–(14) we obtain the following approximate expressions for \( \eta \), \( \eta - \zeta \), and \( \sigma_x \):

\[
 \eta \sim \eta_0 (0) e^{-s\lambda t} + \frac{\delta \phi}{\lambda} (1 - e^{-s\lambda t}) ,
\]

\[
 \eta - \zeta \sim \delta \left( \frac{2 \sigma_{x2}}{\sigma_{\text{nec}}} \right)^{1/2} = \left( \frac{2 (\sigma_x - \sigma_{\text{nec}})}{\sigma_{\text{nec}}} \right)^{1/2} ,
\]

\[
 \sigma_x \sim \sigma_{\text{nec}} + \delta^2 \sigma_{x2} > \sigma_{\text{nec}} ,
\]

with \( \phi = (\sigma_{\text{nec}} - \tilde{\sigma} + 3\lambda)(2 \sigma_{x2} / \sigma_{\text{nec}})^{1/2} \). Thus, we deduce that \( \sigma_x \sim \sigma_{\text{nec}} \) is a necessary condition for the existence of a thin proliferating rim and that the width of the proliferating rim is directly related to the difference between the external and necrotic nutrient concentrations, \( \sigma_x \) and \( \sigma_{\text{nec}} \). Indeed, the dependence of \( \eta - \zeta \) on \( \sigma_x \) and \( \sigma_{\text{nec}} \) agrees with the expression assumed by Greenspan [1].

We note further that if \( \lambda \sim O(1) \), then shrinkage of both \( \eta \) and \( \zeta \) is predicted, with the rate of necrotic cell loss dominating the regression. This contrasts with the small necrotic core analysis presented above. There the rate of apoptosis \( \tilde{\sigma} \) dominated the growth or shrinkage of the necrotic core, and the effect of necrosis was evident only as a higher order effect.
Reducing the rate of necrosis so that $\lambda = \delta \bar{\lambda}$ leaves the expressions for $\eta - \zeta$ and $\sigma_\infty$ unaltered. However, the expression for $\eta$ is modified to give

$$\eta \sim \eta_0(0) + \delta s \sigma_{\text{nec}} \left[ \left( 1 - \frac{\bar{\sigma}}{\sigma_{\text{nec}}} \right) \left( \frac{2 \sigma_\infty}{\sigma_{\text{nec}}} \right)^{1/2} - \frac{\bar{\lambda} \eta_0(0)}{\sigma_{\text{nec}}} \right] t. \quad (28)$$

As when $\lambda \sim O(1)$, if $\bar{\sigma} > \sigma_{\text{nec}}$, then tumor regression is predicted for all values of $\eta_0(0)$. By contrast, if $\bar{\sigma} < \sigma_{\text{nec}}$, then $\eta$ evolves monotonically to an equilibrium value $\eta^*$ that is given by

$$\eta^* = \frac{\sigma_{\text{nec}}}{\bar{\lambda}} \left( 1 - \frac{\bar{\sigma}}{\sigma_{\text{nec}}} \right) \left( \frac{2 \sigma_\infty}{\sigma_{\text{nec}}} \right)^{1/2}.$$ 

By considering values of $\eta_0(0)$ that are larger and smaller than $\eta^*$, it is clear that $\eta^*$ defines a stable necrotic tumor configuration that is attained in the limit $\sigma_\infty \to \sigma_{\text{nec}}$ and has a proliferating rim of width $O((\sigma_\infty - \sigma_{\text{nec}})^{1/2})$ [1].

In summary, we deduce that when the necrotic core is small, changes in the necrotic radius occur on a much larger scale than changes in the outer tumor radius. Referring to (26), the rate of growth of the necrotic radius is more rapid than that of the outer tumor radius. The balance between the rate of apoptosis and the nutrient concentration at which necrosis is initiated determines whether growth or shrinkage of the necrotic core results; the rate of cell degradation due to necrosis does not affect the results. In particular, if $\sigma_{\text{nec}} > \bar{\sigma}$, then the necrotic core persists. By contrast, for the thin proliferating rim analysis, necrosis is the dominant cell loss mechanism. If $\lambda \sim O(1)$, then regression of the tumor occurs. Reducing the rate of apoptosis, a stable necrotic steady state is predicted if $\bar{\sigma} < \sigma_{\text{nec}}$. A necessary condition for the existence of solutions having a thin proliferating rim is that $0 < \sigma_\infty - \sigma_{\text{nec}} \sim O(\delta^2)$, this difference defining the width of the proliferating rim.

Inhibitor-Present Analysis

In this section we investigate how the presence of an inhibitor affects the inhibitor-free analysis that describes the growth of tumors that have either small necrotic cores or thin proliferating rims.

Once again, when the necrotic core is small, we assume that the solution to Equations (21)--(23) can be written in the form

$$\eta \sim \eta_0 + \varepsilon^2 \eta_2, \quad \zeta \sim \varepsilon \zeta_1, \quad \beta_{\text{nec}} \sim \beta_{n0} + \varepsilon^2 \beta_{n2} \quad (0 < \varepsilon \ll 1).$$

The same qualitative behavior observed when $\beta = 0$ is recovered (see Figure 3); there is a rapid timescale $t \sim O(\varepsilon^2)$ during which the outer tumor radius remains constant to $O(\varepsilon^2)$ and the necrotic core grows (or
shrinks, depending on the parameter values) rapidly. Unfortunately, the detailed analysis is much less tractable than when \( \beta = 0 \). For example, introducing \( \theta = \sqrt{\gamma_2 / \Gamma} \), it is possible to show that when \( \beta > 0 \), \( \eta_0 \) is defined in terms of the key parameters as follows:

\[
\frac{\sigma_\infty}{\sigma_{\text{nec}}} = \frac{\sinh \eta_0}{\eta_0} + \frac{\Delta \beta_\infty}{\sigma_{\text{nec}}} \left( 1 - \frac{\theta \eta_0}{\sinh \eta_0} \right).
\]

Since the corresponding equations for \( \eta_2 \) and \( \zeta_1 \) are rather cumbersome, for simplicity any further discussion of the small necrotic core analysis is omitted.

In contrast to the small necrotic core analysis, that for the thin proliferating rim limit generalizes naturally to the case \( \beta > 0 \). With \( \lambda \sim O(1) \) and \( 0 < \eta - \zeta \ll 1 \), we obtain the following modified expressions for \( \eta \) and \( \zeta \) from (21)–(23):

\[
\eta = \eta_0(0) e^{-s\lambda t} + \frac{\delta \bar{\phi}}{\lambda} (1 - e^{-s\lambda t})
\]

and

\[
\eta - \zeta \sim \delta (\eta_1 - \zeta_1) = \delta \left( \frac{2 \sigma_{\text{nec}}}{\sigma_{\text{nec}} + (\theta^2 - 1) \Delta \beta_\infty} \right)^{1/2},
\]

where \((\theta^2 - 1)\Delta = \gamma_1 / \Gamma > 0\),

\[
\bar{\phi} = \sigma_{\text{nec}} \left[ \left( 1 - \frac{\bar{\sigma}}{\sigma_{\text{nec}}} \right) \left( 1 - \frac{\beta_\infty}{\beta} \right) + \frac{3\lambda}{\sigma_{\text{nec}}} \right],
\]

and, as for the inhibitor-free case, \( \sigma_\infty = \sigma_{\text{nec}} + O(\epsilon^2) \). The following expression for \( \beta_{\text{nec}} \) completes the solution:

\[
\frac{\beta_{\text{nec}}}{\beta_\infty} \sim 1 - \frac{\delta^2 \theta^2}{2} (\eta_1 - \zeta_1)^2.
\]

In this case, with \( \lambda \sim O(1) \), the presence of the inhibitor has no effect on the tumor’s growth: the rate of shrinkage of both \( \eta \) and \( \zeta \) is still controlled by the rate of necrotic cell loss, \( \lambda \). However, the reduction in the width of the proliferating rim that occurs when \( \beta > 0 \) corresponds to a reduction in the number of viable, or proliferating, cells, and hence we conclude that the tumor poses less of a threat to its host.

Reducing the rate of necrotic cell loss so that \( \lambda = \delta \lambda \) leaves the expressions for \( \eta - \zeta \), \( \alpha_\infty \), and \( \beta_{\text{nec}} \) unchanged, whereas the expression for \( \eta \) becomes

\[
\eta \sim \eta_0(0) + \delta s \sigma_{\text{nec}} \left[ \left( 1 - \frac{\bar{\sigma}}{\sigma_{\text{nec}}} \right) \left( 1 - \frac{\beta_\infty}{\beta} \right) (\eta_1 - \zeta_1) - \frac{\lambda \eta_0(0)}{\sigma_{\text{nec}}} \right] t.
\]
Now, provided that \((\sigma_{\text{nec}} - \tilde{\sigma})(\beta_x - \tilde{\beta}) > 0\), regression is predicted for all values of \(\eta_0(0)\). In particular, if \(\tilde{\sigma} < \sigma_{\text{nec}}\) and \(\beta_x > \tilde{\beta}\), then the inhibitor actively initiates shrinkage of the tumor (compare Figures 4 and 5c). When \((\sigma_{\text{nec}} - \tilde{\sigma})(\beta_x - \tilde{\beta}) < 0\), then, as for the inhibitor-free case, the tumor evolves to a stable configuration, for which the outer tumor radius \(\eta^{**}\) is given by

\[
\eta^{**} = \frac{\sigma_{\text{nec}}}{\lambda} \left(1 - \frac{\tilde{\sigma}}{\sigma_{\text{nec}}} \right) \left(1 - \frac{\beta_x}{\tilde{\beta}} \right) \left(\frac{2\sigma_2}{\sigma_{\text{nec}} + \gamma_1 \beta_x / \Gamma} \right)^{1/2}
\]

From the analysis presented above we note that if \(\sigma_{\text{nec}} > \tilde{\sigma}\) and \(\tilde{\beta} > \beta_x\), then presence of the inhibitor gives rise to a smaller tumor (see Figure 5a) and that increasing the factor \(\gamma_1 \beta_x / \Gamma\) reduces both the equilibrium tumor radius \(\eta^{**}\) and the width of the proliferating rim. The detrimental action of the inhibitor predicted in Table 3 and Figures 5b and 5c can also be explained. If \(\tilde{\sigma} < \sigma_{\text{nec}}\), then regression of the tumor is predicted when \(\beta = 0\), whereas the inhibitor actually enables the system to support a stable, nontrivial tumor configuration if \(\beta_x > \tilde{\beta}\).

5. CONCLUSIONS

In this paper we have developed and extended the previous work of [19] to include tumors that possess a central necrotic core. The analysis of this paper has enabled us to contrast the roles of apoptosis and necrosis, and we have shown that whichever is the dominant cell loss mechanism depends on the tumor's size and structure. For example, in the case of a small necrotic core, apoptosis dominates, whereas for the thin proliferating rim, if \(\lambda \sim O(1)\), then necrosis dominates and tumor regression results. In the special case \(0 < \lambda \ll 1\), the existence of a stable, nontrivial solution with a thin proliferating rim is predicted.

In addition to providing insight into the roles of apoptosis and necrosis, the model has enabled us to compare the action of a range of inhibitory mechanisms on the tumor's growth. Thus the inhibitor can be regarded as either an anticancer drug or a naturally occurring inhibitor stimulated by the immune system in response to the foreign body. Further the inhibitor may act either directly, by reducing the cell proliferation rate, or indirectly, by reducing the nutrient concentration.

Numerical simulations of the model in the absence of any inhibitor \((\beta = 0)\) exhibit two characteristic modes of tumor growth: either the tumor shrinks in size and eventually disappears, or it evolves to a nonzero configuration that may possess a necrotic core (see Figures 1a–c). From the simulations we observe that the type of behavior that results is strongly influenced by the relative importance of cell loss due
to apoptosis, cell loss due to necrosis, and the external nutrient concentration (i.e., the parameters $\bar{\sigma}$, $\sigma_{\text{nc}}$, and $\sigma_{e}$, respectively). For example, with $\sigma_{e}$ and $\sigma_{\text{nc}}$ fixed, as $\bar{\sigma}$ decreases, decay of the tumor to zero is superseded first by evolution of the tumor to a nonnecrotic configuration for moderate values of $\bar{\sigma}$ and to a necrotic configuration for smaller values of $\bar{\sigma}$ (see Figure 4).

Modifications to the tumor's growth characteristics may be effected by adapting the functional form of the proliferation rate and by introducing an inhibitor into the system. For example, using a logistic proliferation rate, the appearance of an unstable nontrivial steady solution, having radius $R_{U}$, say, is concomitant with the creation of a finite basin of attraction for the trivial solution. If the tumor radius is initially smaller than $R_{U}$, then the tumor disappears; otherwise the tumor evolves to a necrotic configuration (see Figure 2). Similarly, qualitative differences in the solution structure of the model may result from the inclusion of an inhibitor in the model (see Figures 5a–c). Referring to Tables 1–3, we note further that the proposed modes of inhibitor action may induce different effects on a tumor. For example, in Table 3, treatment with an inhibitor that acts indirectly can lead to the persistence of a tumor if the original tumor is sufficiently large.

In order to complement the numerical results described above, analytical techniques were used to derive results for cases of physical interest that could be validated experimentally. In particular, it is possible to prove that if the rate of apoptosis is sufficiently large (i.e., $\bar{\sigma} > \sigma_{e}$), then, in the absence of any inhibitor, no nontrivial solutions can occur and the tumor-free state persists. Directly after the onset of necrosis ($0 < r_{m} < 1$), the outer tumor radius $R$ remains approximately constant and apoptosis is the dominant cell loss mechanism, the balance between $\bar{\sigma}$ and $\sigma_{\text{nc}}$ determining the viability of the necrotic core. In particular, if $\bar{\sigma} < \sigma_{\text{nc}}$, then the necrotic core expands rapidly until an equilibrium solution, with $r_{m} > 0$, is attained. Necessary conditions for the existence of tumors that possess the thin proliferating rim characteristic of multicellular spheroids are also derived. In this case necrosis is the dominant cell loss mechanism. The dependence of the width of the proliferating rim on $\sigma_{e}$ and $\sigma_{\text{nc}}$, as predicted from the asymptotic analysis, agrees with the expression assumed by Greenspan [1]. By focusing on such asymptotic limits, it is also possible to assess whether a given mode of inhibitor acts beneficially, reducing the tumor's size.

The results discussed above derive from an admittedly simple model of tumor growth, with scope for refinements. One simple extension to the model would be to examine the effect of asymmetric variations in the dependent variables: this is the subject of work in progress [28]. We remark that in our model no mention is made of the hypoxic, or
nonproliferating, cell population that is known to play a major role in the success or failure of radiotherapy. In a well-developed multilayer tumor, radiotherapy typically targets and kills the proliferating cells located in the outer rim. This leads to recruitment of quiescent cells back into the proliferating regime. In particular, if a tumor possesses a large quiescent population, then after treatment it may recommence growing, possibly exceeding its preradiotherapy size. Whereas it would be relatively straightforward to include quiescence in our model by extending the admissible tumor structures to, say, three layers, the complexity of the two-layer necrotic model discussed in this paper suggests that such generalizations would be of limited use because similar analysis would be rendered intractable. Further, distinguishing between live and quiescent cells experimentally is known to be difficult [22].

The description of a tumor as comprising concentric shells of proliferating, quiescent, and necrotic cells is an idealization observed in in vitro experiments where control of the external environment can be manipulated. By contrast, in vivo tumors exhibit much less structure: islands of necrosis may be surrounded by regions of cell proliferation or quiescence. This hampers direct application of the results derived in this paper to in vivo situations.

Given the importance of the functional form of the proliferation rate on the qualitative behavior of the tumor, it seems particularly important to employ experimentally determined expressions for interaction terms such as $S(\sigma, \beta)$. The decision to employ simpler expressions here was taken in order to focus on a methodological approach for studying tumor growth that can be easily adapted to a particular situation. Whereas any modifications would, in general, necessitate numerical simulations, we believe that by demonstrating the existence and stability of nontrivial tumors for our simplistic model, some insight into the generic behavior of tumors can be derived.

We now discuss the practical implications of the results derived above. The asymptotic analysis could be used in conjunction with experimental data from multicellular spheroids to estimate system parameters and to assess the relative importance of apoptosis and necrosis as cell loss mechanisms at different stages of a tumor's development. For example, data tracking the evolution of the outer tumor radius and the necrotic radius could be used to validate the claims made in Section 5.1 that, directly after the onset of necrosis, the necrotic core grows more rapidly than the outer tumor radius and that apoptosis is then the dominant cell loss mechanism. Such data could also be used to estimate the ratio $\sigma / \sigma_{\text{lec}}$ and to assess the viability of the necrotic core. Data describing the limiting, or equilibrium, tumor radii could be used to
verify the claim that a necessary condition for the existence of thin proliferating rims is that \( \sigma_x \) and \( \sigma_{\text{nec}} \) are approximately equal and that in this case \( R - r_{in} \propto (\sigma_x - \sigma_{\text{nec}})^{1/2} \). Modifications to the limiting tumor radii affected by the addition of a prospective anticancer drug could also be used, in tandem with the inhibitor-present extension of the thin proliferating rim analysis, to assess the tumor’s handling of the drug. For example, the results of Section 4.2 could be used to estimate \( \gamma_\text{i}/\Gamma \), the relative rate at which the inhibitor degrades the nutrient relative to its natural decay.

More generally, given the interpretations of the inhibitor species as an immune response or an anticancer drug, the numerical simulations of Section 3 and 4 provide some insight into the way in which failure of the immune response can induce cancers (inhibitor as immune response) and also why similar patients respond different to the same treatment (inhibitor as anticancer drug). For example, from Table 2 we conclude that whereas one patient may respond favorably to treatment, another patient with different “parameter values” may deteriorate when given the same treatment. The results presented in Figure 5 further demonstrate how the intricate balance between the different physical processes affects the viability of a tumor and highlights the difficulties associated with prescribing anticancer drugs to patients. For example, the inhibitor considered in Figure 5a merely reduces the size of the tumor without eliminating it. By contrast, the inhibitor shown in Figure 5c eliminates those tumors that would persist in the absence of the inhibitor. However, treatment with this chemical runs the risk of inducing tumors in parts of the body for which \( \bar{\sigma} > \sigma_x \). The appearance of multiple steady-state solutions in Tables 1 and 2 and Figures 5b and 5c, and the concomitant stabilization of the trivial, tumor-free state, further emphasize the need for accurate monitoring of patients during treatment. In this case, a patient with two tumors of different sizes treated with an anticancer drug may find that although the smaller, less harmful tumor disappears, the larger one actually grows in size.

APPENDIX

Before presenting the asymptotic analysis, we explain why the existence of nontrivial solutions is restricted to \( \bar{\sigma} < \sigma_x \). Fixing \( S(\sigma, \beta) = s(\sigma - \bar{\sigma}) \) in (3) leads to the following equation for \( dR/dt \):

\[
R^2 \frac{dR}{dt} = s \int_{r_{in}}^{R} (\sigma - \bar{\sigma}) r^2 \, dr - \lambda r_{in}^3,
\]

where \( \sigma \) satisfies Equations (1) and (4)–(7). By the maximum principle [27], \( \sigma \) attains its maximum value at \( r = R \) where \( \sigma(R, t) = \sigma_x \). Thus if
\( \tilde{\sigma} > \sigma_{z} \), then the integrand in (29) is negative and hence \( dR/dt < 0 \ \forall \ r_{m} \in [0, R) \). In particular, for \( \tilde{\sigma} > \sigma_{z} \), no nontrivial solutions exist and the trivial, tumor-free state is stable.

**INHIBITOR-FREE ANALYSIS**

**Small Necrotic Core Analysis**

We seek solutions to the system (13)–(14) in the form

\[
\eta \sim \eta_{0} + \epsilon \eta_{1} + \epsilon^{2} \eta_{2} \quad \text{and} \quad \xi \sim \epsilon \xi_{1}, \tag{30}
\]

where \( 0 < \epsilon \ll 1 \) is a small parameter that characterizes the size of the necrotic core and is chosen so that \( \xi_{1}(t = 0) = 1 \). By substituting with (30) in (13) and equating to zero the \( O(1) \) terms, we deduce that \( \eta_{0} \) satisfies

\[
\frac{\sigma_{z}}{\sigma_{nec}} = \frac{\sinh \eta_{0}}{\eta_{0}}. \tag{31}
\]

Provided that \( \sigma_{z} > \sigma_{nec} \), Equation (31) possesses a constant nontrivial solution \( \eta_{0} \). Continuing with our expansion, we deduce that \( \eta_{1} = 0 \) and that \( \xi_{1} \) is related to \( \eta_{2} \) as follows:

\[
\xi_{1}^{2} = \frac{2(\cosh \eta_{0} - \sigma_{z}/\sigma_{nec})}{\sinh \eta_{0}} \eta_{2}. \tag{32}
\]

We remark that since \( \xi_{1}(0) = 1 \), Equation (32) automatically defines \( \eta_{2}(0) \).

Given that \( \eta_{0} \) and \( \eta_{1} \) are independent of \( t \), substituting with (30) in (14) yields a differential equation that is singular in the limit as \( \epsilon \to 0 \). In order to regularize the system we introduce the transient timescale \( \tau = t/\epsilon^{2} \) and rescale (14) accordingly. Now, equating to zero the \( O(1) \) terms, we recover the following equation for \( \eta_{2}(\tau) \):

\[
\frac{d\eta_{2}}{d\tau} = \frac{s \sigma_{nec}}{\eta_{0}^{2}} \left[ \eta_{0} \cosh \eta_{0} - \sinh \eta_{0} - \frac{\tilde{\sigma}}{\sigma_{nec}} \frac{\eta_{0}}{3} \right] = \Lambda, \quad \text{say}. \tag{33}
\]

In terms of the original timescale \( t = \epsilon^{2} \tau \), we deduce that \( \eta \) and \( \xi \) are given by

\[
\eta \sim \eta_{0} + \epsilon^{2} \eta_{2}(0) + \Lambda t \quad \text{and} \quad \xi \sim \left( \epsilon^{2} + \frac{\eta_{0} \cosh \eta_{0} - \sinh \eta_{0}}{\eta_{0} \sinh \eta_{0}} 2 \Lambda t \right)^{1/2}, \tag{34}
\]
where $\eta_0$ and $\eta_2(0)$ are defined in terms of $\sigma_x/\sigma_{\text{necc}}$ by (31) and (32). If $\Lambda > 0$, then tumor growth is predicted and our expansion (34) remains valid until $t \sim O(1)$, by which time the necrotic core is $O(1)$. Otherwise, if $\Lambda < 0$, shrinkage of the tumor is predicted and the necrotic core disappears in a finite time. Using (34) we deduce that the time $t_D$ at which the necrotic core disappears is given by

$$t_D = \frac{\varepsilon^2 \eta_0 \sinh \eta_0}{2|\Lambda|(\eta_0 \cosh \eta_0 - \sinh \eta_0)}.$$

If $\Lambda = 0$, then a steady, necrotic configuration is predicted. By considering higher order terms in the power series expansion (30) it is possible to show that this solution is stable with respect to small perturbations.

**Thin Proliferating Rim Analysis**

Introducing the small parameter $\delta$ ($0 < \delta \ll 1$), we now assume that the width of the proliferating region is $O(\delta)$ and seek solutions to (13)–(14) in the form

$$\eta \sim \eta_0 + \delta \eta_1 + \delta^2 \eta_2 \quad \text{and} \quad \zeta \sim \eta_0 + \delta \zeta_1 + \delta^2 \zeta_2. \quad (35)$$

In addition, we assume a regular expansion for the external nutrient concentration: $\sigma_x \sim \sigma_{x0} + \delta \sigma_{x1} + \delta^2 \sigma_{x2}$. The reason for adopting an expansion for $\sigma_x$ becomes clear when we substitute with (35) in (13). Equating to zero the coefficients of $O(\delta^n)$ yields the relations

$$\sigma_{x0} = \sigma_{\text{necc}}, \quad \sigma_{x1} = 0, \quad (\eta_1 - \zeta_1)^2 = 2 \sigma_{x2} / \sigma_{\text{necc}}.$$ 

Thus, we deduce that $\sigma_x = \sigma_{\text{necc}} + O(\varepsilon^2)$ is a necessary condition for the existence of a thin proliferating rim.

Substituting with (35) in (14) using the expressions derived from (13) leads to the following expressions for $\eta$, $\eta - \zeta$, and $\sigma_x$:

$$\eta \sim \eta_0(0) e^{-s\lambda t} + \frac{\delta \phi}{\lambda} (1 - e^{-s\lambda t}),$$

$$\eta - \zeta \sim \delta \left( \frac{2 \sigma_{x2}}{\sigma_{\text{necc}}} \right)^{1/2} = \left( \frac{2(\sigma_x - \sigma_{\text{necc}})}{\sigma_{\text{necc}}} \right)^{1/2},$$

$$\sigma_x \sim \sigma_{\text{necc}} + \delta^2 \sigma_{x2} > \sigma_{\text{necc}},$$

with $\phi = (\sigma_{\text{necc}} - \bar{\sigma} + 3\lambda)(2 \sigma_{x2} / \sigma_{\text{necc}})^{1/2}$. From these expressions we note that if $\lambda \sim O(1)$, then shrinkage of both $\eta$ and $\zeta$ occurs, with $\lambda$ dominating the rate of regression.
Reducing $\lambda$ so that $\lambda = \delta \lambda$ does not affect the expressions for $\eta - \zeta$ and $\sigma_e$. However, the expression for $\eta$ is modified to give

$$\eta \sim \eta_0(0) + \delta s \sigma_{nec} \left[ \left(1 - \frac{\bar{\sigma}}{\sigma_{nec}}\right) \left(\frac{2\lambda \eta_0(0)}{\sigma_{nec}}\right)^{1/2} - \frac{\bar{\lambda} \eta_0(0)}{\sigma_{nec}} \right] t. \quad (36)$$

As when $\lambda \sim O(1)$, if $\bar{\sigma} > \sigma_{nec}$, then tumor regression is predicted for all values of $\eta_0(0)$. By contrast, if $\bar{\sigma} < \sigma_{nec}$, then $\eta$ evolves monotonically to an equilibrium value $\eta^*$ that is given by

$$\eta^* = \frac{\sigma_{nec}}{\lambda} \left(1 - \frac{\bar{\sigma}}{\sigma_{nec}}\right) \left(\frac{2\lambda \eta_0(0)}{\sigma_{nec}}\right)^{1/2}.$$

By considering values of $\eta_0(0)$ that are larger and smaller than $\eta^*$, it is clear that $\eta^*$ defines a stable necrotic tumor configuration that is attained in the limit $\sigma_e \rightarrow \sigma_{nec}$ and has a proliferating rim of width $O((\sigma_e - \sigma_{nec})^{1/2})$ [1].

**INHIBITOR-PRESENT ANALYSIS**

It is possible to extend the analysis presented above to cases for which $\beta > 0$. For example, from (3') it is easy to see that if $\beta > \beta_e$, then the trivial solution is both stable and unique whenever $\bar{\sigma} > \sigma_e$ (see Figure 5a). Similarly, if $\bar{\sigma} < \sigma_{nec}$ and $\beta < \beta_{nec} = \sigma(r_{in},t)$, then the trivial solution is again unique and stable (see Figure 5c).

The asymptotic analysis for the small necrotic core and thin proliferating rim limits when $\beta > 0$ mirrors that presented above for the case $\beta = 0$. Consequently, we shall not discuss the details of the analysis here; the key results are presented in Section 4.

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