CELL CYCLE CONTROL AT THE FIRST RESTRICTION POINT AND ITS EFFECT ON TISSUE GROWTH

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ABSTRACT. Cell cycle is controlled at two restriction points, R_1 and R_2. At both points the cell will commit apoptosis if it detects irreparable damage. But at R_1 an undamaged cell also decides whether to proceed to the S phase or go into a quiescent mode, depending on the environmental conditions (e.g., overpopulation, hypoxia). We consider the effect of this decision at the population level in a spherical tissue $\{r < R(t)\}$. We prove that if the cells have full control at R_1, they can manipulate the size of $R(t)$ to ensure that $0 < c \leq R(t) \leq C < \infty$; simulations show that $R(t)$ can be made nearly stationary. In the absence of such control (e.g., if suppressor genes such as APC and SMAD have been mutated), $R(t)$, in general, will either increase to ∞ or decrease to 0. The mathematical model and analysis involve a system of PDEs in $\{r < R(t)\}$.

Keywords: Cell cycle, cell cycle check points, cell cycle control, tissue growth, free boundary problems.

1. INTRODUCTION

In a recent paper Friedman [9] developed a multiscale model of avascular tumor, based on a system of partial differential equations (PDEs) in the tumor region Ω_t. The model is spatially multiscale in the sense that it includes gene mutations at the cell level and cells densities in the tumor region; thus the model combines genetic information with continuous mechanics. The model is also temporally multiscale as it consider two times: the usual time of tumor growth and the cycling time of cells. A similar multiscale hybrid model for colorectal tumor was earlier developed by Ribba et al [18]. In that model the time s_i that a cell spends in phase i of its cycle is divided into a finite number of time steps, and the tumor region is fixed in time.

Although a large number of mutations can often be found in cancer tissues, it is commonly believed that the initiation of cancer occurs when just very few gene are mutated. In the model developed by Ribba et al [18] two such genes have been identified, SMAD and APC, both are suppressor genes. SMAD blocks cell proliferation under hypoxic conditions and APC blocks cell proliferation when the microenvironment is overpopulated with cells.

Figure 1 describes the cell cycle with phases G_1, S, G_2, M and its two restriction points (or check points). During the S phase the DNA is replicated, that is, each chromosome is duplicated. During the mitosis phase, M, the nucleus membrane breaks down, sister chromatids are separated, new nucleus membranes are formed, and the daughter cells split. S and M are separated by gap phases G_1 and G_2. The first check point R_1 is located near the end of the G_1 phase, and the second check point R_2 is located near the end of the G_2 phase.

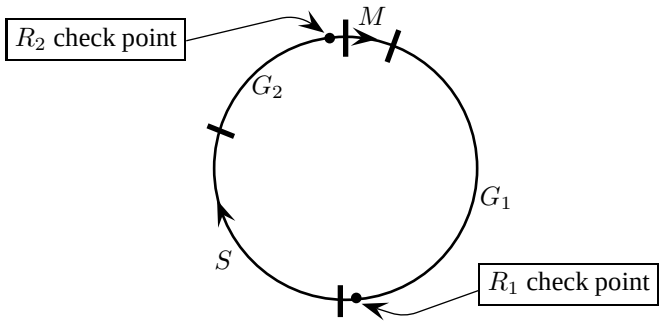

Figure 1.

Figure 2 describes the decision a cell makes at the check points R_1 and R_2. At R_1 the cell decides to commit suicide (apoptosis) if irreparable damage has occurred during its growth in the G_1 phase, to go to quiescent mode G_0 in case the microenvironment is hypoxic or overpopulated, or otherwise to proceed to the S phase. At the check point R_2 the cell decides whether to apoptose in case irreparable damage has occurred (mostly in the DNA replication) or to proceed to mitosis.

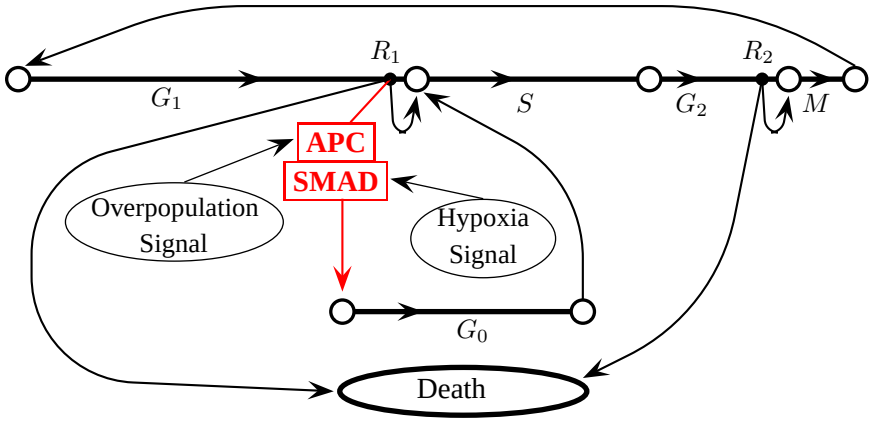

Figure 2.

A cell remains in quiescent mode for a period of time, after which it proceeds to the S phase.

For simplicity we assume that the tumor is spherical, occupying a region $\Omega_t = \{r < R(t)\}$, where $R(t)$ varies in time. As proved in Friedman [9], there exists a unique global-in-time solution to the system of PDEs and free boundary $r = R(t)$ which describe the multiscale model. In the present paper we consider decision by the cell, at the check point R_1, whether to go to quiescent mode or to proceed to S phase as a control problem. This decision, by the cell, depends, among other things, on the microenvironment. For example, if the cell receives a signal that the microenvironment is overpopulated and if the APC gene is heathy normal, then the cell may decide to go into quiescent mode, depending on the level of overpopulation; however if APC is mutated then the cell will ignore the overpopulation signal and will proceed directly to S.

The optimal control at the restriction point R_1 would be a control which keeps $R(t)$ constant, i.e., in homeostasis. However, as will be shown by simulations, such a control generally does

not exist. Thus instead we address the question of whether the control at R_1 can achieve the following minimal results:

(a) $R(t) \geq c > 0$ for all $t > 0$,

(b) $R(t) \leq C < \infty$ for all $t > 0$.

It will be shown that if all the cells have unrestricted total control at R_1 then they can simultaneously achieve both (a) and (b); the rigorous mathematical proof actually provides a bound on C/c. However, if the cells do not have any control (for example, if the tumor suppressors gene APC and SMAD are both mutated) then, in general, either $R(t) \to 0$ as $t \to \infty$ or $R(t) \to \infty$ as $t \to \infty$; the latter case may be interpreted under some circumstances (as will be explained in Remark 2.1) as the onset of cancer.

We conclude the introduction by noting that other multiscale tumor models were developed by Ayati et al [1] and by Jiang et al [12]. In a different context Nowak and Sigmund [15] and Komarova [16] showed how cellular dynamics is related to genetic dynamics.

A mathematical model of tumor with three populations of cells, namely, proliferating, quiescent, and necrotic cells, was introduced and studied numerically in [17]; mathematical analysis of the model appeared in [4] [5] [6] [7].

2. THE MATHEMATICAL MODEL

We introduce the following notation:

$p_1(r,t,s_1)$ = density of cells in phase G_1, $s_1 \in [0, A_1]$;
$p_2(r,t,s_2)$ = density of cells in phase S and G_2, $s_2 \in [0, A_2]$;
$p_3(r,t,s_3)$ = density of cells in phase M, $s_3 \in [0, A_3]$;
$p_0(r,t,s_0)$ = density of cells in state G_0, $s_0 \in [0, A_0]$;
$p_4(r,t)$=density of necrotic (dead) cells.

Here $r = |x|$, x varies in the domain $\Omega_t = \{r < R(t)\}$ in $\mathbb{R}^3$.

We denote by $w(r,t)$ the oxygen concentration and by $Q(r,t)$ the density of live cells which are not in quiescent phase. Due to cell proliferation and death, there is a velocity field $\vec{v}(r,t)$, which is assumed to be common to all the cells. By conservation of mass,

$$\frac{\partial p_i}{\partial t} + \frac{\partial p_i}{\partial s_i} + \operatorname{div}(p_i \vec{v}) = \lambda_i(w) p_i \quad \text{for} \quad 0 < s_i < A_i \ \ (i = 1,2,3), \tag{2.1}$$

$$\frac{\partial p_0}{\partial t} + \frac{\partial p_0}{\partial s_i} + \operatorname{div}(p_0 \vec{v}) = -\lambda_0 p_0 \quad \text{for} \quad 0 < s_0 < A_0, \tag{2.2}$$

$$\frac{\partial p_4}{\partial t} + \operatorname{div}(p_4 \vec{v}) = \mu_1 p_1(r,t,A_1) + \mu_2 p_2(r,t,A_2) - \lambda_4 p_4 \tag{2.3}$$

where $\lambda_i(w)$ are growth rates which depend on the oxygen concentration w,

$$\lambda_i(w) > 0 \quad \text{if } w > 0, \quad \text{for } \ i = 1,2,3, \tag{2.4}$$

λ_0 is the death rate of cells in quiescence mode, λ_4 is the clearing rate of dead cells, and μ_1, μ_2 are the rates at which cells at R_1 and R_2, respectively, decide to go into apoptosis; the rate parameters $\lambda_0, \lambda_4, \mu_1, \mu_2$ are positive numbers, and $\mu_1 < 1$, $\mu_2 < 1$. We are not including in (2.3) cell death of quiescent cells; see however Remark 5.2.

We also have:

$$p_1(r,t,0) = p_3(r,t,A_3), \tag{2.5}$$

$$p_2(r,t,0) = [1 - \beta(t) - \mu_1] p_1(r,t,A_1) + p_0(r,t,A_0), \tag{2.6}$$

$$p_3(r,t,0) = (1 - \mu_2) p_2(r,t,A_2), \tag{2.7}$$

$$p_0(r,t,0) = \beta(t) p_1(r,t,A_1). \tag{2.8}$$

Equation (2.6) expresses the assumption that at the end of the G_1 phase a fraction $\beta(t)$ of the cells goes into quiescence, and a fraction μ_1 goes into apoptosis, while the remaining fraction of cells at the end of the G_1 phase as well as the cells at the end of the quiescence period enter the S phase. The function $\beta(t)$ is viewed as a control function, $0 < \beta(t) < 1 - \mu_1$.

We introduce the total density of each population of cells:

$$Q_i(r,t) = \int_0^{A_i} p_i(r,t,s_i)ds_i \quad (i = 0,1,2,3)$$

and formally set $Q_4(r,t) = p_4(r,t)$. Then

$$Q(r,t) \equiv \sum_{i=1}^{3} Q_i(r,t)$$

is the combined density of cells in phases G_1, S, G_2 and M. Later on we shall see how the function $\beta(t)$ relates to the signals from the microenvironment which are relayed to the cell by means of APC (in case of overpopulation) and SMAD (in case of hypoxia). We shall then view $\beta(t)$ as a functional

$$\beta(t) = K[w,Q](t). \tag{2.9}$$

Although the control β shall generally depend on (r,t), rather than on t alone, we assume here, for simplicity, that β depends only on t.

We assume that the total density of cells, live and dead, is constant, and for simplicity take the constant to be 1, so that,

$$\sum_{i=0}^{4} Q_i(r,t) = \text{const.} = 1. \tag{2.10}$$

We integrate each of the equations in (2.1) and (2.2) over $s_i \in (0, A_i)$ and sum up the resulting equations and (2.3). Using (2.5)–(2.8) we find that all the boundary integrals resulting from integrating $\partial p_i/\partial s_i$ cancel out, so that

$$\sum_{i=0}^{4}\left[\frac{\partial Q_i}{\partial t} + \mathrm{div}(Q_i\vec{v})\right] = \sum_{i=1}^{3}\lambda_i(w)Q_i - \lambda_0 Q_0 - \lambda_4 Q_4 \equiv H(\vec{Q},w). \tag{2.11}$$

Assuming that $\vec{v}$ is radially symmetric, we can write it in the form

$$\vec{v} = v\vec{e}_r \quad \text{where } \vec{e}_r = \frac{x}{r},$$

so that

$$\mathrm{div}(\vec{v}p) = \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 vp) \quad \text{if } p = p(r);$$

note that $v(0) = 0$.

From (2.10), (2.11) we then obtain

$$\mathrm{div}\,\vec{v} = \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 v) = H(\vec{Q},w). \tag{2.12}$$

Finally we assume that the oxygen concentration $w(r,t)$ satisfies the diffusion equation with a positive bounded source h,

$$-\Delta w + Qw = h, \quad h(r,t) = \gamma(r,t)(\overline{w} - w) \quad \text{in } \Omega_t; \tag{2.13}$$

where $\overline{w}$ is the average oxygen concentration in a healthy tissue and the source h represents oxygen transported from the vasculature into the tissue. We prescribe the boundary condition

$$w = \overline{w} \quad \text{on } \partial\Omega_t \tag{2.14}$$

and a free boundary condition, which says that the boundary moves with the velocity of the cells,

$$\frac{dR(t)}{dt} = v(r)\Big|_{r=R(t)}. \tag{2.15}$$

We also prescribe initial data

$$p_i\Big|_{t=0} = p_{i0}(r, s_i) \quad (i = 0, 1, 2, 3), \quad p_4\Big|_{t=0} = p_{40}(r), \quad R\Big|_{t=0} = R_0 > 0 \tag{2.16}$$

that are nonnegative, namely,

$$\inf_{0<r<R_0, 0<s<A_i} p_{i0}(r, s) \geq 0 \ \ (0 \leq i \leq 3), \quad \inf_{0<r<R_0} p_{40}(r) \geq 0.$$

The following global existence and uniqueness result for radially symmetric solutions is established in Friedman [9] in case β is a function of w and Q,

$$\beta = K(w, Q). \tag{2.17}$$

Theorem 2.1. *If the p_{i0} belong to $C^1(\overline{\Omega}_0 \times [0, A_i])$, $0 \leq i \leq 3$, p_{40} belongs to $C^1(\overline{\Omega}_0)$, p_{i0} $(0 \leq i \leq 4)$ satisfy (2.5)–(2.10), and $\lambda_i(z)$ $(1 \leq i \leq 3)$ and $K(z, Q)$ belong to C^1 for $z \in \mathbb{R}^1$, $Q \in [0, 1]$ and $\gamma(r, t)$ is a continuous function for $r \geq 0$, $t \geq 0$, then there exists a unique radially symmetric solution (p_i, w, v, R) of (2.1)–(2.10), (2.12)–(2.16) with $R(t)$ in $C^1[0, \infty)$, and $p_i \geq 0$ $(0 \leq i \leq 4)$.*

Remark 2.1. In this paper we do not specify the coefficient $\gamma(r, t)$ in the source term h in the oxygen equation (2.13); γ depends directly on the blood vasculature. In a healthy normal tissue, γ is such that it ensures that the oxygen level w is typically above the necrotic level w_*, so that the cells continue to grow during the cell cycle phases G_1, S, G_2, M. Hence, the assumption (2.4) holds in healthy normal tissue. We expect that as long as the cells have full control over $\beta(t)$ and (2.4) holds, the radius $R(t)$ will remain bounded and $0 < c \leq R(t) \leq C < \infty$ will hold for all $t > 0$, with C/c "fairly close" to 1, at least for some initial data. However, if the control $\beta(t)$ is lost (in the sense that $\beta \equiv$const.) through gene mutations, then a tumor may develop. Whether the tumor will continue to grow (beyond a few millimeters) will depend on the tumor ability to induce angiogenesis, that is, the formation of new blood vessels moving into the tumor, thus providing it with oxygen (and other nutrients). The effect of angiogenesis is expressed by taking $\gamma = \gamma(r, t, e)$ in (2.13) where e is the density of the endothelial cells. Without angiogenesis, the oxygen level in the core of the tumor will decrease below the necrotic level w_* and then (2.4) will no longer hold there, and instead we shall have

$$\lambda_j(w) < 0 \quad \text{if } w < w_* \quad (j = 1, 2, 3).$$

Angiogenesis has been modeled in the literature quite extensively; see [13], [14] and the references therein. In this paper we do not include angiogenesis explicitly; instead we assume it implicitly by imposing the condition (2.4) throughout the growing tumor. Although we assume that the oxygen concentration is above the necrotic level w_*, this concentration may still be hypoxic in some regions within the tissue. We shall prove that if the control $\beta(t)$ is lost (more precisely, if $\beta(t) \equiv$const. and the constant is small) and (2.4) holds, then the radius $R(t)$ of the tumor will grow to ∞ as $t \to \infty$. We can interpret this result as the onset on cancer.

It is interesting to note (as proved in [11]) that, without angiogenesis (i.e., if $h \equiv 0$ in (2.13)), even if $w_* = 0$, that is, even if

$$\lambda_j(w) > 0 \quad \text{for } w > 0, \quad \lambda_j(0) = 0, \quad (j = 1, 2, 3),$$

then already $R(t) \leq C < \infty$ for all $t > 0$.

3. $\beta(t)$ CONSTANT

For simplicity we first consider the case

$$\lambda_1(w) = \lambda_2(w) = \lambda_3(w) = \text{ const. } = \lambda, \tag{3.1}$$

The case where $\lambda_j = \lambda_j(w)$ (for $i = 1, 2, 3$) will be considered in Section 6. It is convenient to introduce the function

$$p(r,t,s) = \begin{cases} (1-\mu_2)p_2(r,t,s), & 0 \le s \le A_2, \\ p_3(r,t,s-A_2), & A_2 \le s \le A_2 + A_3, \\ p_1(r,t,s-A_2-A_3), & A_2 + A_3 \le s \le A_1 + A_2 + A_3 \equiv A, \end{cases} \tag{3.2}$$

so that

$$Q(r,t) = \frac{1}{1-\mu_2}\int_0^{A_2} p(r,t,s)ds + \int_{A_2}^{A} p(r,t,s)ds. \tag{3.3}$$

By conservation of mass,

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial s} + \operatorname{div}(p\vec{v}) = \lambda p \quad \text{for} \quad 0 < s < A \ , \tag{3.4}$$

$$\frac{\partial p_0}{\partial t} + \frac{\partial p_0}{\partial s} + \operatorname{div}(p_0\vec{v}) = -\lambda_0 p_0 \quad \text{for} \quad 0 < s < A_0 \ , \tag{3.5}$$

$$\frac{\partial p_4}{\partial t} + \operatorname{div}(p_4\vec{v}) = \mu_1 p(r,t,A) + \frac{\mu_2}{1-\mu_2}p(r,t,A_2) - \lambda_4 p_4 \tag{3.6}$$

with

$$p(r,t,0) = (1-\mu_2)[1-\mu_1-\beta(t)]p(r,t,A) + (1-\mu_2)p_0(r,t,A_0), \tag{3.7}$$

$$p_0(r,t,0) = \beta(t)p(r,t,A). \tag{3.8}$$

Note that $p(r,t,s)$ is continuous in s, $0 \le s \le A$. It is natural to assume that the cell remains in quiescent mode for relatively long time, so that

$$A_0 > A, \tag{3.9}$$

but, mathematically, this assumption is not necessary. We introduce the volume integrals

$$\widehat{p}(t,s) = 4\pi\int_0^{R(t)} r^2 p(r,t,s)dr,$$

$$\widehat{p}_0(t,s) = 4\pi\int_0^{R(t)} r^2 p_0(r,t,s)dr,$$

$$\widehat{p}_4(t) = 4\pi\int_0^{R(t)} r^2 p_4(r,t)dr.$$

Integrating (3.4)–(3.6) over Ω_t and using (2.15), we obtain

$$\frac{\partial \widehat{p}}{\partial t} + \frac{\partial \widehat{p}}{\partial s} = \lambda\widehat{p} \quad \text{for} \quad 0 < s < A \ ,$$

$$\frac{\partial \widehat{p}_0}{\partial t} + \frac{\partial \widehat{p}_0}{\partial s} = -\lambda_0\widehat{p}_0 \quad \text{for} \quad 0 < s < A_0 \ ,$$

$$\frac{\partial \widehat{p}_4}{\partial t} = \mu_1\widehat{p}(t,A) + \frac{\mu_2}{1-\mu_2}\widehat{p}(t,A_2) - \lambda_4\widehat{p}_4.$$

From (3.7), (3.8) we also get

$$\widehat{p}(t,0) = (1-\mu_2)[1-\mu_1-\beta(t)]\widehat{p}(t,A) + (1-\mu_2)\widehat{p}_0(t,A_0), \tag{3.10}$$

$$\widehat{p}_0(t,0) = \beta(t)\widehat{p}(t,A). \tag{3.11}$$

Solving the equations for $\widehat{p}, \widehat{p}_0$ along the characteristics, we obtain

$$\widehat{p}(t+s,s) = e^{\lambda s}\widehat{p}(t,0), \qquad \text{for } t>0, \quad 0<s<A, \tag{3.12}$$

$$\widehat{p}_0(t+s,s) = e^{-\lambda_0 s}\widehat{p}_0(t,0), \qquad \text{for } t>0, \quad 0<s<A_0, \tag{3.13}$$

Define

$$\widehat{Q}(t) = \int_0^A \widehat{p}(t,s)ds \equiv \int_0^A \int_0^{R(t)} 4\pi r^2 p(r,t,s)drds;$$

then

$$\widehat{Q}(t) \le \text{total mass of cells in phases } G_1, S, G_2, M \le \frac{1}{1-\mu_2}\widehat{Q}(t).$$

We also define

$$\widehat{Q}_0(t) = \int_0^{A_0} \widehat{p}_0(t,s)ds \equiv \int_0^A \int_0^{R(t)} 4\pi r^2 p_0(r,t,s)drds$$

as the total mass of cells in phases G_0. If $t > A + A_0$, then, by (3.12), (3.10) and (3.13),

$$\begin{aligned}
\widehat{Q}(t) &= \int_0^A \widehat{p}(t,s)ds \\
&= \int_0^A e^{\lambda s}\widehat{p}(t-s,0)ds \\
&= (1-\mu_2)\int_0^A e^{\lambda s}\Big(\widehat{p}(t-s,A)[1-\mu_1-\beta(t-s)] + \widehat{p}_0(t-s,A_0)\Big)ds \\
&= (1-\mu_2)\int_0^A e^{\lambda s}\widehat{p}(t-s,A)[1-\mu_1-\beta(t-s)]ds \\
&\quad +(1-\mu_2)\int_0^A e^{\lambda s}e^{-\lambda_0 A_0}\widehat{p}_0(t-s-A_0,0)ds,
\end{aligned}$$

or, by (3.11),

$$\begin{aligned}
\widehat{Q}(t) &= (1-\mu_2)\int_0^A e^{\lambda s}\widehat{p}(t-s,A)[1-\mu_1-\beta(t-s)]ds \\
&\quad +(1-\mu_2)\int_0^A e^{\lambda s}e^{-\lambda_0 A_0}\beta(t-s-A_0)\widehat{p}(t-s-A_0,A)ds.
\end{aligned} \tag{3.14}$$

We shall now assume that

$$\beta(t) \equiv \text{const.} = \beta, \tag{3.15}$$

that is, the cells have no (viable) control at R_1 over the decision whether to go into quiescent state or to proceed to the S phase. Then, by (3.14), and (3.12), (3.13),

$$\begin{aligned}
\widehat{Q}(t) &= (1-\mu_2)(1-\mu_1-\beta)e^{\lambda A}\int_0^A \widehat{p}(t-A,s)ds \\
&\quad +\beta e^{-\lambda_0 A_0}e^{\lambda A}\int_0^A (1-\mu_2)\widehat{p}(t-A-A_0,s)ds \\
&= (1-\mu_2)(1-\mu_1-\beta)e^{\lambda A}\widehat{Q}(t-A) + (1-\mu_2)\beta e^{-\lambda_0 A_0}e^{\lambda A}\widehat{Q}(t-A-A_0),
\end{aligned}$$

or,

$$\begin{aligned}
&\widehat{Q}(t) = \alpha_1(\beta)\widehat{Q}(t-A) + \alpha_2(\beta)\widehat{Q}(t-A-A_0) \\
&\quad \text{where } \alpha_1(\beta) = (1-\mu_2)(1-\mu_1-\beta)e^{\lambda A},\ \alpha_2(\beta) = (1-\mu_2)\beta e^{-\lambda_0 A_0}e^{\lambda A}.
\end{aligned} \tag{3.16}$$

We shall assume that

$$(1-\mu_1)(1-\mu_2)e^{\lambda A} > 1, \qquad (1-\mu_1)(1-\mu_2)e^{-\lambda_0 A_0}e^{\lambda A} < 1. \tag{3.17}$$

Lemma 3.1. *Under the assumption (3.17) there exists a unique β^*, $0 < \beta^* < 1-\mu_1$, such that*
(i) if $0 \le \beta < \beta^*$, then

$$\lim_{t\to\infty} \widehat{Q}(t) = \infty; \tag{3.18}$$

(ii) if $\beta^* < \beta \le 1-\mu_1$, then

$$\lim_{t\to\infty} \widehat{Q}(t) = 0. \tag{3.19}$$

Proof. Clearly $\alpha_1(\beta)+\alpha_2(\beta)$ is monotonically decreasing in β, and from (3.16) it follows that

$$\alpha_1(\beta)+\alpha_2(\beta) = (1-\mu_2)\Big((1-\mu_1-\beta)e^{\lambda A} + \beta e^{-\lambda_0 A_0}e^{\lambda A}\Big) \begin{cases} >1 & \text{if } \beta = 0, \\ <1 & \text{if } \beta = 1-\mu_1. \end{cases}$$

Hence there is a unique β^* such that

$$\alpha_1(\beta)+\alpha_2(\beta) \begin{cases} >1 & \text{if } 0 \le \beta < \beta^*, \\ =1 & \text{if } \beta = \beta^*, \\ <1 & \text{if } \beta^* < \beta \le 1-\mu_1. \end{cases}$$

Suppose $0 \le \beta < \beta^*$, so that $\alpha_1(\beta)+\alpha_2(\beta) = 1+\delta,\ \delta > 0$. Let

$$M_j = \inf_{j(A+A_0)\le t<(j+1)(A+A_0)} \widehat{Q}(t), \quad j = 1,2,3,\cdots.$$

Then, by (3.16),

$$\widehat{Q}(t) \ge (1+\delta)M_1 \quad \text{if } 2(A+A_0) \le t \le 2(A+A_0)+A,$$

and, in particular,

$$\widehat{Q}(t) \ge M_1 \quad \text{for } (A+A_0) \le t \le 2(A+A_0)+A.$$

Repeating this procedure k times, we obtain

$$\widehat{Q}(t) \ge (1+\delta)M_1 \quad \text{for } 2(A+A_0) \le t \le 3(A+A_0)$$

if k is such that $kA > (A+A_0)$. Taking "inf" over the interval $[2(A+A_0), 3(A+A_0)]$ it follows that $M_2 \ge (1+\delta)M_1$. Similarly $M_j \ge (1+\delta)^j M_1$ and therefore $M_j \to \infty$ as $j \to \infty$.

The case $\beta^* < \beta \le 1-\mu_1$ is similar if we replace "inf" by "sup" and $1+\delta$ by $1-\delta$. □

Theorem 3.2. *Assume that (3.17) holds. (i) If $0 \le \beta < \beta^*$, then*

$$R(t) \to \infty \quad \textit{as } t \to \infty;$$

(ii) if $\beta^* < \beta \le 1-\mu_1$, then

$$R(t) \to 0 \quad \textit{as } t \to \infty.$$

Proof. If $0 \le \beta < \beta^*$, then (3.18) holds, and since

$$\begin{aligned} \widehat{Q}(t) &= 4\pi \int_0^A \Big(\int_0^{R(t)} r^2 p(r,t,s)dr \Big) ds \\ &= 4\pi \int_0^{R(t)} r^2 \Big(\int_0^A p(r,t,s)ds \Big) dr \\ &\le 4\pi \int_0^{R(t)} r^2 dr \ = \ \frac{4\pi}{3} R^3(t), \end{aligned}$$

we conclude that $R(t) \to \infty$ as $t \to \infty$.

In case $\beta^* < \beta \le 1-\mu_1$, we need, in addition to (3.19), to estimate $\widehat{Q}_0(t)$ and $\widehat{p}_4(t)$. We begin with $\widehat{Q}_0$. By (3.13), (3.8),

$$\begin{aligned}\widehat{Q}_0(t) &= \int_0^{A_0} \widehat{p}_0(t,s)ds \\ &= \int_0^{A_0} e^{-\lambda_0 s}\widehat{p}_0(t-s,0)ds \quad \text{(assuming that } t \ge A_0\text{)}, \\ &= \int_0^{A_0} e^{-\lambda_0 s}\beta(t-s)\widehat{p}(t-s,A)ds.\end{aligned}$$

We take k such that $kA < A_0 \le (k+1)A$. Then, by (3.8), (3.12),

$$\begin{aligned}\widehat{Q}_0(t) &= \int_0^{A_0} \widehat{p}_0(t,s)ds \\ &< \sum_{j=0}^{k}\int_{jA}^{(j+1)A} e^{-\lambda_0 s}\beta(t-s)\widehat{p}(t-s,A)ds \\ &= \sum_{j=0}^{k}\int_{jA}^{(j+1)A} e^{-\lambda_0 s}\beta(t-s)e^{\lambda A}\widehat{p}(t-s-A,0)ds \\ &= \sum_{j=0}^{k}\int_{jA}^{(j+1)A} e^{-\lambda_0 s}\beta(t-s)e^{\lambda A}e^{-\lambda(s-jA)}\widehat{p}(t-A-jA,s-jA)ds \\ &\le \sum_{j=0}^{k}(1-\mu_1)e^{\lambda A}\widehat{Q}\Big(t-(j+1)A\Big),\end{aligned}$$

so that, by Lemma 3.1,

$$\lim_{t\to\infty}\widehat{Q}_0(t) = 0. \tag{3.20}$$

We next estimate $\widehat{p}_4(t)$:

$$\begin{aligned}\widehat{p}_4(t) &= \widehat{p}_4(0)e^{-\lambda_4 t} + \mu_1\int_0^t e^{-\lambda_4(t-\tau)}\widehat{p}(\tau,A)d\tau + \frac{\mu_2}{1-\mu_2}\int_0^t e^{-\lambda_4(t-\tau)}\widehat{p}(\tau,A_2)d\tau \\ &\equiv I_1 + I_2 + I_3.\end{aligned}$$

Clearly I_1 goes to zero as $t\to\infty$. Next, by (3.12),

$$\begin{aligned}I_2 &= \mu_1\sum_{j=0}^{[t/A]+1}\int_{jA}^{(j+1)A} e^{-\lambda_4(t-\tau)}\widehat{p}(\tau,A)d\tau \\ &\le \mu_1\sum_{j=0}^{[t/A]+1} e^{-\lambda_4 t+\lambda_4(j+1)A}\int_{jA}^{(j+1)A}\widehat{p}(\tau,A)d\tau \\ &= \mu_1\sum_{j=0}^{[t/A]+1} e^{-\lambda_4 t+\lambda_4(j+1)A}\int_{jA}^{(j+1)A} e^{\lambda(\tau-jA)}\widehat{p}(jA,A+jA-\tau)d\tau.\end{aligned}$$

By Lemma 3.1, for any small $\varepsilon > 0$, there is a $J = J(\varepsilon)$ sufficiently large such that

$$\widehat{Q}(jA) < \varepsilon \text{ for all } j \ge J.$$

Then

$$\begin{aligned} I_2 &\leq \mu_1 \sum_{j=0}^{J} e^{-\lambda_4 t+\lambda_4(j+1)A} e^{\lambda A}\widehat{Q}(jA) + \varepsilon\mu_1 \sum_{j=J+1}^{[t/A]+1} e^{-\lambda_4 t+\lambda_4(j+1)A} e^{\lambda A} \\ &\leq \mu_1 \sum_{j=0}^{J} e^{-\lambda_4 t+\lambda_4(j+1)A} e^{\lambda A}\widehat{Q}(jA) + \varepsilon\mu_1 e^{-\lambda_4 t}\ \frac{e^{\lambda_4([t/A]+3)A}-1}{e^{\lambda_4 A}-1} e^{\lambda A} \end{aligned}$$

and the last term is bounded by

$$\varepsilon\mu_1\ \frac{e^{3\lambda_4 A}}{e^{\lambda_4 A}-1} e^{\lambda A}.$$

Hence

$$\limsup_{t\to\infty} I_2(t) \leq \varepsilon\mu_1\ \frac{e^{3\lambda_4 A}}{e^{\lambda_4 A}-1} e^{\lambda A},$$

and, since ε is arbitrary, $\lim_{t\to\infty} I_2(t) = 0$. In a similar manner one can show $\lim_{t\to\infty} I_3(t) = 0$, so that

$$\lim_{t\to\infty} \widehat{p}_4(t) = 0. \tag{3.21}$$

Since

$$\widehat{Q}(t) + \widehat{Q}_0(t) + \widehat{p}_4(t) \geq 4(1-\mu_2)\pi \int_0^{R(t)} r^2 \cdot 1\ dr = \frac{4\pi}{3}(1-\mu_2)R^3(t),$$

we conclude from (3.19)–(3.21) that

$$\lim_{t\to\infty} R(t) = 0.$$

Remark 3.1. The arguments used in the proof of Lemma 3.1 show that if $\beta = \beta^*$, then

$$0 < \liminf_{t\to\infty} \widehat{Q}(t) \leq \limsup_{t\to\infty} \widehat{Q}(t) < \infty.$$

Remark 3.2. The case $\beta(t) \equiv$ const. may arise in a situation where the cell does not respond to signals from its microenvironment, that is, when both APC and SMAD are mutated. In this case, as explained in Remark 2.1, Theorem 3.2 (i) may be interpreted as the onset of cancer.

4. $\beta(t)$ AS FREE CONTROL

In this section we continue to assume that (3.1) holds, deferring the case of $\lambda_j = \lambda_j(w)$ for $j = 1, 2, 3$ to Section 5. We also assume that (3.17) holds and wish to show that there is a control $\beta(t)$ that depends on the population Q (or rather on $\widehat{Q}$) for which

$$0 < c \leq R(t) \leq C < \infty \quad \text{for all } t. \tag{4.1}$$

We assume for simplicity that

$$A_0 = mA, \qquad m \text{ integer} \geq 1. \tag{4.2}$$

In order to define $\beta(t)$, we choose any positive constant Q^* and numbers $\underline{\beta}$, $\overline{\beta}$ such that

$$0 < \underline{\beta} < \beta^* < \overline{\beta} < 1 - \mu_1. \tag{4.3}$$

Assuming that $\beta(t)$ has already been determined for $t < t_0$ when $t_0 = jA$ (j integer ≥ 1), we take

$$\beta(t) = \begin{cases} \overline{\beta} & \text{for } t_0 \leq t < t_0 + A \text{ if } \widehat{Q}(t_0) \geq Q^* \\ \underline{\beta} & \text{for } t_0 \leq t < t_0 + A \text{ if } \widehat{Q}(t_0) < Q^*. \end{cases} \tag{4.4}$$

With this choice of $\beta(t)$ we can then extend the solution of the free boundary problem for the p_i and $R(t)$ to $jA \le t \le (j+1)A$. If we set $\widehat{Q}_j = \widehat{Q}(jA)$, $\beta_j = \beta(jA)$ then, by (3.14),

$$\widehat{Q}_j = (1-\mu_2)(1-\mu_1-\beta_{j-1})e^{\lambda A}\widehat{Q}_{j-1} + (1-\mu_2)\beta_{j-1-m}e^{\lambda A}e^{-\lambda_0 mA}\widehat{Q}_{j-1-m} \tag{4.5}$$

and

$$\beta_j = \begin{cases} \overline{\beta} & \text{if } \widehat{Q}_j \ge Q^* \\ \underline{\beta} & \text{if } \widehat{Q}_j < Q^* \end{cases} . \tag{4.6}$$

Define

$$\begin{aligned} \widehat{Q}_{min} &= \min\Big((1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A}Q^*, (1-\mu_2)\overline{\beta}e^{\lambda A}e^{-\lambda_0 mA}Q^*, \widehat{Q}_1, \cdots, \widehat{Q}_{m+1}\Big), \\ \widehat{Q}_{max} &= \max\Big(\frac{(1-\mu_2)\underline{\beta}e^{\lambda A}e^{-\lambda_0 mA}}{1-(1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A}}Q^*, \frac{(1-\mu_2)(1-\mu_1-\underline{\beta})e^{\lambda A}}{1-(1-\mu_2)\overline{\beta}e^{\lambda A}e^{-\lambda_0 mA}}Q^*, \\ &\qquad (1-\mu_2)(1-\mu_1-\underline{\beta})e^{\lambda A}Q^* + (1-\mu_2)\underline{\beta}e^{\lambda A}e^{-\lambda_0 mA}Q^*, \widehat{Q}_1, \cdots, \widehat{Q}_{m+1}\Big). \end{aligned}$$

Note that with the choices of $\underline{\beta}$ and $\overline{\beta}$, we have

$$(1-\mu_2)(1-\mu_1-\underline{\beta})e^{\lambda A} + (1-\mu_2)\underline{\beta}e^{\lambda A}e^{-\lambda_0 mA} > 1, \tag{4.7}$$

$$(1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A} + (1-\mu_2)\overline{\beta}e^{\lambda A}e^{-\lambda_0 mA} < 1. \tag{4.8}$$

Lemma 4.1. *Assume that (3.17) holds. Then*

$$\widehat{Q}_{min} \le \widehat{Q}_j \le \widehat{Q}_{max} \quad \textit{for } 0 \le j < \infty. \tag{4.9}$$

Proof. We use induction on j. It is clear that (4.9) is valid for all $1 \le j \le m+1$. Suppose that (4.9) holds for up to $j-1$ where $j \ge m+2$. There are only four possible cases for $\widehat{Q}_{j-1}, \widehat{Q}_{j-m-1}$:

i), $\widehat{Q}_{j-1} \ge Q^*, \widehat{Q}_{j-1-m} \ge Q^*$;
ii), $\widehat{Q}_{j-1} \ge Q^*, \widehat{Q}_{j-1-m} < Q^*$;
iii), $\widehat{Q}_{j-1} < Q^*, \widehat{Q}_{j-1-m} < Q^*$;
iv), $\widehat{Q}_{j-1} < Q^*, \widehat{Q}_{j-1-m} \ge Q^*$.

In case i) we have, by (4.5), (4.6),

$$\widehat{Q}_j = (1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A}\widehat{Q}_{j-1} + (1-\mu_2)\overline{\beta}e^{\lambda A}e^{-\lambda_0 mA}\widehat{Q}_{j-1-m},$$

so that, using (4.8),

$$\widehat{Q}_j \le \left\{(1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A} + (1-\mu_2)\overline{\beta}e^{\lambda A}e^{-\lambda_0 mA}\right\}\widehat{Q}_{max} < \widehat{Q}_{max},$$

whereas, by the two inequalities of case i),

$$\widehat{Q}_j \ge \left\{(1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A} + (1-\mu_2)\overline{\beta}e^{\lambda A}e^{-\lambda_0 mA}\right\}\widehat{Q}^* > \widehat{Q}_{min}.$$

In case ii) we have, by (4.5), (4.6),

$$\widehat{Q}_j = (1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A}\widehat{Q}_{j-1} + (1-\mu_2)\underline{\beta}e^{\lambda A}e^{-\lambda_0 mA}\widehat{Q}_{j-1-m},$$

so that, by the inequality $(1-\mu_2)\underline{\beta}e^{\lambda A}e^{-\lambda_0 mA}Q^* \le \left\{1-(1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A}\right\}\widehat{Q}_{max}$, we get

$$\widehat{Q}_j \le (1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A}\widehat{Q}_{max} + (1-\mu_2)\underline{\beta}e^{\lambda A}e^{-\lambda_0 mA}Q^* \le \widehat{Q}_{max}.$$

On the other hand, by the inequalities of case ii),

$$\widehat{Q}_j \ge (1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda A}\widehat{Q}^* \ge \widehat{Q}_{min}.$$

Case iii) can be treated in a similar way as case i) using (4.8), and case iv) is similar to Case ii). □

Theorem 4.2. *Assume that (3.17) holds and $\beta(t)$ is defined by (4.4). Then $R(t)$ satisfies (4.1).*

Proof. Using Lemma 4.1, one can establish the upper and lower bounds for $\widehat{Q}(t)$ for all time $0 < t < \infty$. From the lower bound on $\widehat{Q}(t)$ we derive a positive lower bound on $R(t)$. Using arguments similar to those in the proof of Theorem 3.2 we can also establish upper bounds on $\widehat{Q}_0(t)$ and $\widehat{p}_4(t)$, and therefore $R(t)$ must also be bounded from above. □

Remark 4.1. The control function used in Theorem 4.2 depends on the total population of cells, $\widehat{Q}$, in the tissue. If APC can control any situation of overpopulation, then, according to Theorem 4.2, it can ensure that the tissue $\{r < R(t)\}$ will remain bounded, without actually dying (i.e., with $R(t) \geq c > 0$). From the oxygen equation (2.13) and the boundary condition (2.14), it is clear that there is a one-to-one correspondence between Q and w. Hence we can express the strategy (4.4) also in terms of the $w(r,t)$, $t \leq t_0$. We conclude that if APC is mutated, but SMAD is healthy normal so that it can sense the oxygen level and use this to control $R(t)$, then indeed it may force $R(t)$ to satisfy (4.1).

5. The case of variable $\lambda_j(w)$

In this section we extend the results of Sections 3, 4 to the case where $\lambda_j(w)$ are functions of w, and

$$\lambda_j(w) \text{ belong to } C^1[0,\infty) \text{ for } j = 1,2,3. \tag{5.1}$$

In this case

$$\frac{\partial \widehat{p}}{\partial t} + \frac{\partial \widehat{p}}{\partial s} = \widetilde{\lambda}\widehat{p}$$

where

$$\lambda_- \equiv \min_{1\leq j\leq 3} \min_{(r,t)} \lambda_j(w(r,t)) \leq \widetilde{\lambda} \leq \max_{1\leq j\leq 3} \max_{(r,t)} \lambda_j(w(r,t)) \equiv \lambda_+.$$

It follows that

$$\frac{\partial \widehat{p}}{\partial t} + \frac{\partial \widehat{p}}{\partial s} \geq \lambda_- \widehat{p}, \tag{5.2}$$

and

$$\frac{\partial \widehat{p}}{\partial t} + \frac{\partial \widehat{p}}{\partial s} \leq \lambda_+ \widehat{p}. \tag{5.3}$$

Analogously to (3.17) we assume that

$$(1-\mu_1)(1-\mu_2)e^{\lambda_- A} > 1, \qquad (1-\mu_1)(1-\mu_2)e^{-\lambda_0 A_0}e^{\lambda_- A} < 1 \tag{5.4}$$

and set

$$\alpha_1^-(\beta) = (1-\mu_2)(1-\mu_1-\beta)e^{\lambda_- A},\ \alpha_2^-(\beta) = (1-\mu_2)\beta e^{-\lambda_0 A_0}e^{\lambda_- A}. \tag{5.5}$$

Then there exists a unique β_-^*, $0 < \beta_-^* < 1-\mu_1$ such that

$$\alpha_1^-(\beta) + \alpha_2^-(\beta) \begin{cases} > 1 & \text{if } 0 \leq \beta < \beta_-^*, \\ = 1 & \text{if } \beta = \beta_-^*, \\ < 1 & \text{if } \beta_-^* < \beta \leq 1-\mu_1. \end{cases}$$

Using (5.2) we derive the inequalities $\widehat{p}(t,s) \geq \widehat{p}(t-s,0)e^{\lambda_- s}$ for $0 \leq s \leq A$, $\widehat{p}(t-s,A) \geq \widehat{p}(t-A,s)e^{\lambda_-(A-s)}$ for $0 \leq s \leq A$, and then, analogously to (3.16),

$$\widehat{Q}(t) \geq \alpha_1^-(\beta)\widehat{Q}(t-A) + \alpha_2^-(\beta)\widehat{Q}(t-A-A_0).$$

As in the proof of Lemma 3.1, we can now show that (3.18) holds if $\beta < \beta_-^*$, so that $R(t) \to \infty$ as $t \to \infty$.

Similarly, if we assume that

$$(1-\mu_1)(1-\mu_2)e^{\lambda_+ A} > 1, \qquad (1-\mu_1)(1-\mu_2)e^{-\lambda_0 A_0}e^{\lambda_+ A} < 1 \tag{5.6}$$

and set

$$\alpha_1^+(\beta) = (1-\mu_2)(1-\mu_1-\beta)e^{\lambda_+ A},\ \alpha_2^+(\beta) = (1-\mu_2)\beta e^{-\lambda_0 A_0}e^{\lambda_+ A}, \tag{5.7}$$

then exists a unique β_+^*, $0 < \beta_+^* < 1-\mu_1$ such that

$$\alpha_1^+(\beta) + \alpha_2^+(\beta) \begin{cases} > 1 & \text{if } 0 \le \beta < \beta_+^*, \\ = 1 & \text{if } \beta = \beta_+^*, \\ < 1 & \text{if } \beta_+^* < \beta \le 1-\mu_1. \end{cases}$$

Using (5.3) we can then derive the inequality

$$\widehat{Q}(t) \le \alpha_1^+(\beta)\widehat{Q}(t-A) + \alpha_2^+(\beta)\widehat{Q}(t-A-A_0),$$

from which we deduce that, if $\beta_+^* < \beta < 1-\mu_1$, then (3.19) holds. One can next establish (3.20) and (3.21) as before, and thus conclude that $R(t) \to 0$ if $t \to \infty$.

We summarize:

Theorem 5.1. *(i) If (5.4) holds and $0 < \beta < \beta_-^*$, then*

$$R(t) \to \infty \quad \textit{if } t \to \infty.$$

(ii) If (5.6) holds and $\beta_+^* < \beta < 1-\mu_1$, then

$$R(t) \to 0 \quad \textit{if } t \to \infty.$$

As explained in Remark 2.1, case (i) may be interpreted as the onset of cancer.

Remark 5.1. Note that, in general, $\beta_-^* < \beta_+^*$. It is not clear how $R(t)$ behaves if β is a constant satisfying $\beta_-^* < \beta < \beta_+^*$.

We next turn to extension of Theorem 4.2, assuming that both (5.3) and (5.4) are satisfied. We define $\beta(t)$ as in (4.4), but with $0 < \underline{\beta} < \beta_-^* \le \beta_+^* < \overline{\beta} < 1-\mu_1$, so that

$$(1-\mu_1)(1-\mu_2-\underline{\beta})e^{\lambda_- A} + (1-\mu_2)\underline{\beta}e^{-\lambda_0 A_0}e^{\lambda_- A} > 1, \tag{5.8}$$

$$(1-\mu_1)(1-\mu_2-\overline{\beta})e^{\lambda_+ A} + (1-\mu_2)\overline{\beta}e^{-\lambda_0 A_0}e^{\lambda_+ A} < 1. \tag{5.9}$$

Lemma 4.1 then extends to this case provided $\widehat{Q}_{min}$ and $\widehat{Q}_{max}$ are replaced by

$$\begin{aligned} \widehat{Q}_{min} &= \min\Big((1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda_- A}Q^*, \\ &\qquad (1-\mu_2)\overline{\beta}e^{\lambda_- A}e^{-\lambda_0 mA}Q^*, \widehat{Q}_1, \cdots, \widehat{Q}_{m+1}\Big), \\ \widehat{Q}_{max} &= \max\Big(\frac{(1-\mu_2)\underline{\beta}e^{\lambda_+ A}e^{-\lambda_0 mA}}{1-(1-\mu_2)(1-\mu_1-\overline{\beta})e^{\lambda_+ A}}Q^*, \frac{(1-\mu_2)(1-\mu_1-\underline{\beta})e^{\lambda_+ A}}{1-(1-\mu_2)\overline{\beta}e^{\lambda_+ A}e^{-\lambda_0 mA}}Q^*, \\ &\qquad (1-\mu_2)(1-\mu_1-\underline{\beta})e^{\lambda_+ A}Q^* + (1-\mu_2)\underline{\beta}e^{\lambda_+ A}e^{-\lambda_0 mA}Q^*, \widehat{Q}_1, \cdots, \widehat{Q}_{m+1}\Big). \end{aligned}$$

We can now proceed as before to derive the following theorem.

Theorem 5.2. *Assume that (5.4), (5.6) hold and $\beta(t)$ is defined by (4.4) with $\underline{\beta}, \overline{\beta}$ as in (5.8), (5.9). Then*

$$0 < c \le R(t) \le C < \infty \quad \textit{for all } t.$$

Remark 5.2. In the model presented in this paper we have not included the death of quiescent cells in the equation for p_4; this can be done by adding some average of $p_0(r,t,s)$ with respect to s. Adding such a term does not change the results of Sections 4, 5.

6. Numerical Simulations

The proof of Theorem 5.2 provides an upper bound for C/c, that is, an upper bound on the oscillations of $R(t)$. In homeostasis $R(t)$ is nearly stationary. In this section we explore numerically how the choice of the control $\beta(t)$ can be improved to achieve nearly stationary $R(t)$. For simplicity we consider the case $\lambda_j(w) = \lambda$ for $j = 1, 2, 3$. We take the parameter values:

$$\lambda = \ln 2\,\text{day}^{-1} \approx 0.693\,\text{day}^{-1}, \quad \lambda_0 = \frac{1}{10}\ln 2\,\text{day}^{-1} \approx 0.0693\,\text{day}^{-1},$$

which corresponds to cell cycle period of 24 hours [2];

$$A = 1\,\text{day}, \quad A_1 = A_2 = A_3 = \frac{1}{3}\,\text{day}, \quad A_0 = 5\,\text{day};$$

$$\lambda_0 A_0 = \frac{1}{2}\lambda A, \quad m\lambda_0 = \frac{1}{2}\ln 2 \approx 0.347, \quad \text{and} \quad m = 5.$$

Since, according to [3], death rate is approximately $\frac{1}{2}$ of proliferation rate, we take

$$\mu_1 = \mu_2 = \frac{1}{5}.$$

We finally choose the clearing rate of death cells to be ([8])

$$\lambda_4 = \frac{1}{2}\text{day}^{-1}.$$

Note that (3.15) is actually satisfied for $\mu_1 = \mu_2 = \mu$ in the range $0.16 < \mu < 0.29$.

We shall simulate the solution of the free boundary problem for the initial values

$$p_0(r,s,0) = \frac{1}{6\frac{1}{12} + \frac{7}{6}\log(2)}(-\cos(6\pi s) + 1), \quad 0 \le s \le A_0$$

$$p(r,s,0) = \frac{1}{6\frac{1}{12} + \frac{7}{6}\log(2)}(-\cos(6\pi s) + 1), \quad 0 \le s \le A.$$

The subsequent considerations, however, can be applied to any initial data. In the numerical simulations we use finite difference upwind discretization in space x and s ($dx = ds = A_1/128$) with forward Euler method in time t ($dt = 0.5dx$) to solve the hyperbolic type equations (2.1)–(2.3) with the boundary conditions (2.5)–(2.8). The velocity $\overrightarrow{v}$ is obtained by mid-point integration of H: $\overrightarrow{v} = \frac{1}{r^2}\int_0^r r^2 H(\overrightarrow{Q},\omega)$ (where $H(\overrightarrow{Q},\omega)$ is given by (2.11)) and (2.10) through several numerical integrations of p_i.

We are going to illustrate several control strategies. We begin with the choice $\beta(t)$ =const.= β. According to Theorem 3.2, with

$$\beta^* = \frac{7}{20(2-\sqrt{2})} \approx 0.6,$$

if $\beta < \beta^*$ then $R(t) \to 0$ as $t \to \infty$ and if $\beta > \beta^*$ then $R(t) \to 0$ as $t \to \infty$. This is illustrated in Figure 3 with $\beta(t) = \beta = 0.2, 0.4, 0.6$, and 0.8.

For $\beta = 0.6$, the trend for the limit of $R(t)$ takes longer time.

The choice $\beta(t)$ =const. is of course not robust. The derive a robust control we follow the proof of Theorem 4.2, but first choose $\beta(t)$ for $0 \le t \le t_0 = A_0$ to be different from β^* in order to be in a non-stationary situation at $t = t_0$; we take $\beta(t) = 0.5$ for $0 \le t \le t_0$.

Figure 4 shows the results for different constants Q^*. The asymptotic behavior of $R(t)$ at large time strongly depends on the choice Q^*. The control β makes H fluctuate around zero

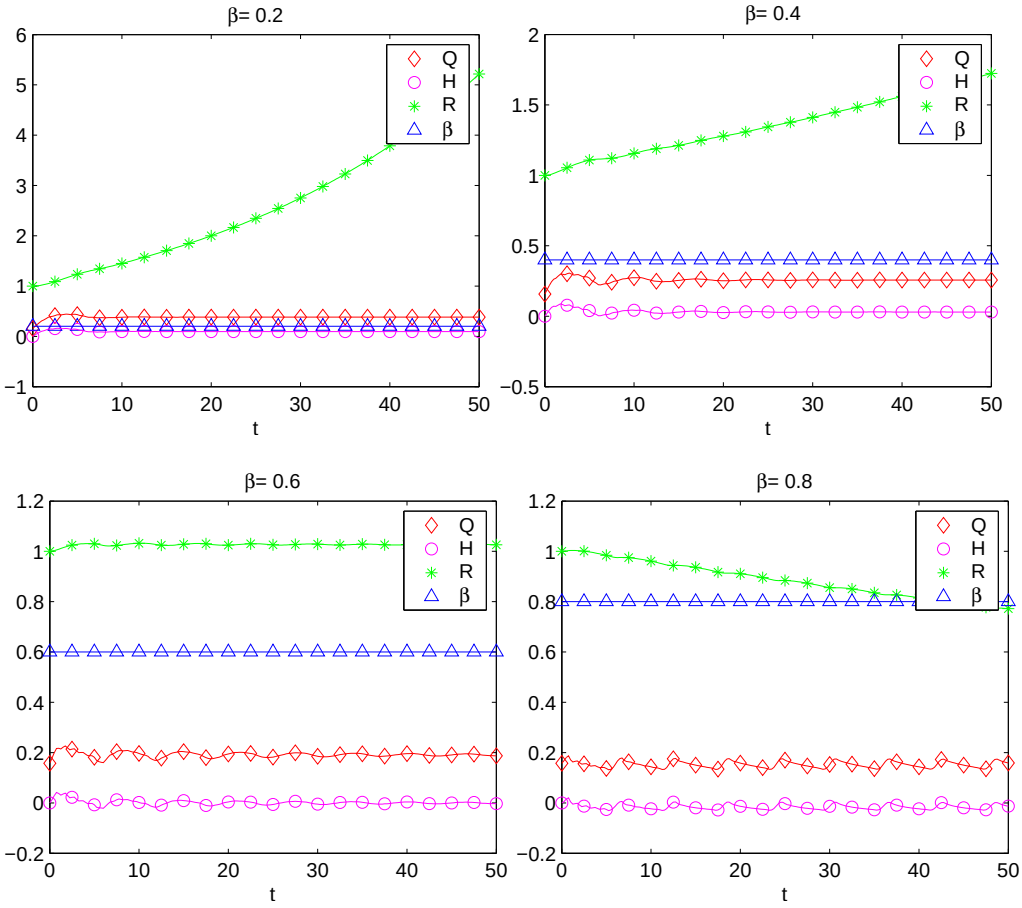

FIGURE 3.
The evolution of $R(t)$ w.r.t (a) $\beta = 0.2$ (b) $\beta = 0.4$ (c) $\beta = 0.6$ (d) $\beta = 0.8$.

and $R(t)$ fluctuate around a constant radius after certain time T. The radius $R(t)$ stabilizes for $T > 75$ when $Q^* = 0.8$ and for $T > 40$ when $Q^* = 1.4$.

Although the strategy adapted in the proof of Theorem 4.2 is robust, we can do better by an adaptive control approach, as illustrated in Figure 5.

Instead of fixing Q^* in the previous example, we choose $Q^* = \widehat{Q}(jA)$. The control is chosen as

$$\beta(t) = \begin{cases} \overline{\beta} & \text{if } \widehat{Q}(t) \geq Q^* \\ \underline{\beta} & \text{if } \widehat{Q}(t) < Q^* \end{cases} \tag{6.1}$$

where $jA \leq t \leq (j+1)A$. Due to the initial control $\beta(t) = 0.5$ for $t < A_0$ and the control at later time, the radius first grows and then stabilizes. The radius does not fluctuate as frequently as in the previous examples. A completely different approach to satisfying $R(t)$ is to choose $\beta(t)$ such that $H \equiv 0$, so that $R(t) \equiv$const. The problem with this approach is that $\beta(t)$ tends in general to exit the interval $(0, 1-\mu-1)$. Nonetheless one can achieve an improved performance hybrid method which combines this strategy as long as $\beta(t)$ remains in the interval $(0, 1-\mu_1)$, and then the adaptive control strategy of (6.1). This is illustrated in Figure 6 which shows that $R(t)$ stabilizes faster than in Figure 5.

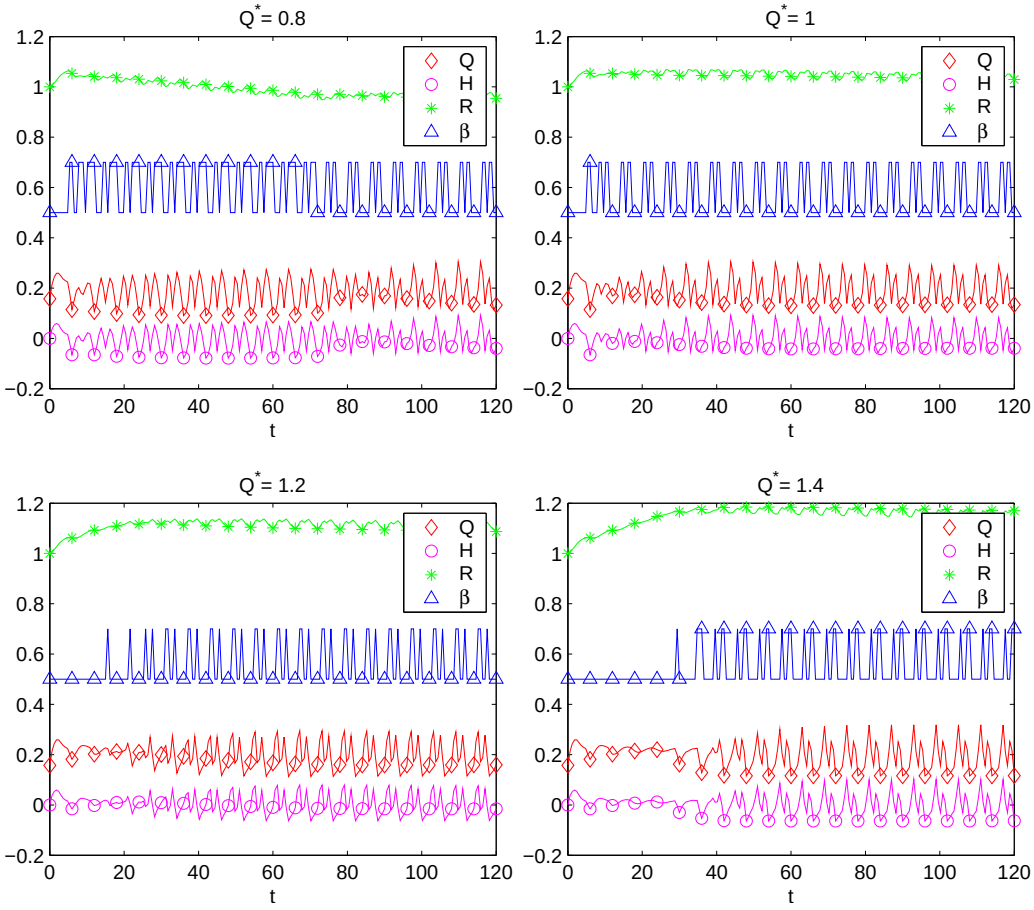

FIGURE 4.
The evolution of $R(t)$ for (a) $Q^* = 0.8$(b) $Q^* = 1.0$(c) $Q^* = 1.2$(d) $Q^* = 1.4$.

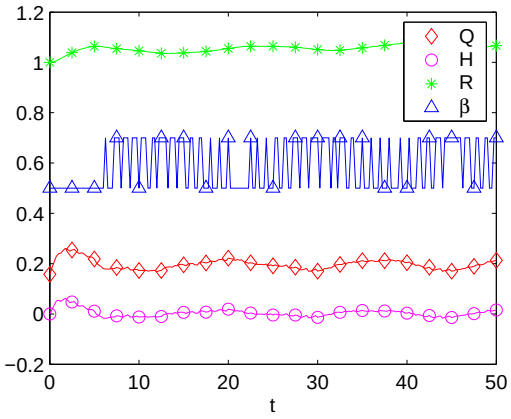

FIGURE 5.
The evolution of $R(t)$ for adaptive Q^*.

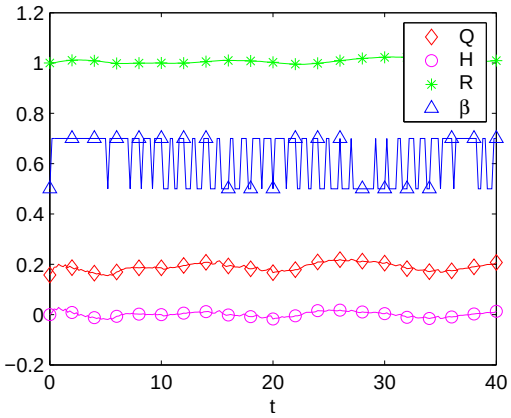

FIGURE 6.
The evolution of $R(t)$ for adaptive Q^*.

7. CONCLUSION

The growth or shrinkage of a tissue, taken as a sphere $\{r < R(t)\}$, depends on a decision that individual cells make whether to proceed directly from the restriction point R_1 in the G_1 phase to the S phase, or whether to go first into quiescent state. If the cells are healthy normal, then when the microenvironment is overpopulated (or hypoxic), and if the cells are endowed with full control at R_1, $\beta = \beta(t)$ in some interval $\underline{\beta} \leq \beta(t) \leq \overline{\beta}$ at R_1, then they can act in a way that will not increase or decrease the tissue's diameter by more than a multiplicative constant. Simulations show that this control when chosen in an adaptive manner can render $R(t)$ nearly stationary after a relatively short time. However if suppressor genes, that are designed to block proliferation when the microenvironment is unfavorable (such as APC and SMAD) are mutated, then the radius $R(t)$ may increase to ∞ (this could be interpreted as the onset of cancer in the presence of angiogenesis, as explained in Remark 2.1), or decrease to 0 (i.e., the tissue dies out).

These results are based on a multiscale model with two time scales: the usual time t, and the running time of cells in each phase of the cell cycle. The model equations are based on mass conservation for cell populations and on a diffusion equation for the oxygen. It was assumed that all the cells act in unison at R_1. However the results can be extended to two (or more) populations of cells. For example, suppose one population of cells is healthy, and co-exists with another population in which SMAD and APC are mutated so that all control at R_1 is lost for the latter population. In this case, again $R(t) \to \infty$ under the assumption of Theorem 3.2 (i); however under the conditions of Theorem 3.2 (ii), $R(t)$ will remain bounded from below by a positive constant (rather than go to zero) due to the healthy cells of the tissue.

The present model makes the implicit assumption that soon after the tumor was initiated (due to mutations of SMAD and APC) it induces angiogenesis, and thus ensures continuous supply of oxygen; see Remark 2.1. Future work should include angiogenesis directly by taking $\gamma = \gamma(r, t, e)$ in (2.13) where e is the density of the endothelial cells, and allow the $\lambda_j(w)$ to become negative whenever the oxygen concentration is below the necrotic level. The mathematical model for this situation should include additional differential equations for the concentration of tumor angiogenetic factors and for proteolytic enzymes, and for densities of endothelial cells

and macrophages; it should also included the effect of hapotaxis on the tumor cells as they migrate into the stroma.

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