

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 further show that $R(t)$ can be made nearly stationary. In the absence of such control, $R(t)$ 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

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1 Introduction

A schematic diagram of the eukaryotic cell cycle is given in Fig. 1. DNA is replicated during *S* phase (*S* for synthesis of DNA). Chromosomes condense and segregate in *M* phase (*M* for mitosis). Gap phases G_1 and G_2 separate *S* and *M* phases.

Cell-cycle checkpoints are points in the cell cycle when decisions are made whether cell-cycle progression continuous or halts. Intuitively, a cell-cycle checkpoint involve a surveillance mechanism that somehow checks whether the requirements for progression to the next cell-cycle phase are satisfied and, if not, a mechanism is triggered to arrest the process.

Figure 1 shows the R_1 checkpoint and the R_2 checkpoint; these points are also called ‘restriction’ points. At the checkpoint R_1 a cell decides whether to continue to the *S* phase, transit to quiescence mode G_0 , or, in case of irreparable damage, undergo apoptosis; for modeling of the $G_1 - S$ regulatory network about the restriction point R_1 (see [Aguda and Friedman 2008](#)). At the second restriction point R_2 a cell checks if the DNA has been correctly duplicated; here again, in case of damage, the cell may undergo apoptosis.

A cell remains in quiescence phase for a period of time after which it proceeds with the cell cycle, starting at the beginning of the *S* phase.

The decisions whether to transit to the G_0 phase and how long to remain in this phase depend on the cell’s microenvironment. In particular, if the microenvironment is hypoxic (low oxygen level) or overpopulated (by other cells) then a healthy normal cell will transit into quiescence mode. There are two important genes that control the pathway to cell proliferation: SMAD and APC. Under hypoxic conditions SMAD shuts off the pathway to proliferation, while APC does the same thing if the microenvironment is overpopulated.

Figure 2 shows a basic signaling pathway from overpopulation and hypoxia signals to cell proliferation, in which APC and SMAD are imbedded. This diagram was developed by [Ribba et al. \(2006a,b\)](#) and is based on several papers ([Fearon and Vogelstein 1990](#); [Hahn and Weinberg 2002](#); [Kanehisa 1997](#); [Kanehisa and Goto 2000](#)).

Figure 3 shows the roles APC and SMAD play at the restriction point R_1 . Under hypoxia signal SMAD induces the cell to go quiescence, and APC does the same under overpopulation signal.

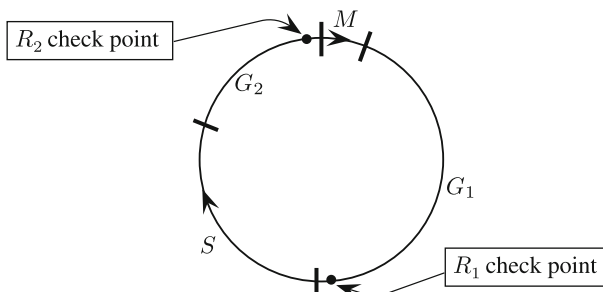


Fig. 1 Phases of the eukaryotic cell cycle. DNA is replicated in *S* phase. Duplicate chromosomes are segregated in *M* phase. G_1 and G_2 are ‘gap’ phases

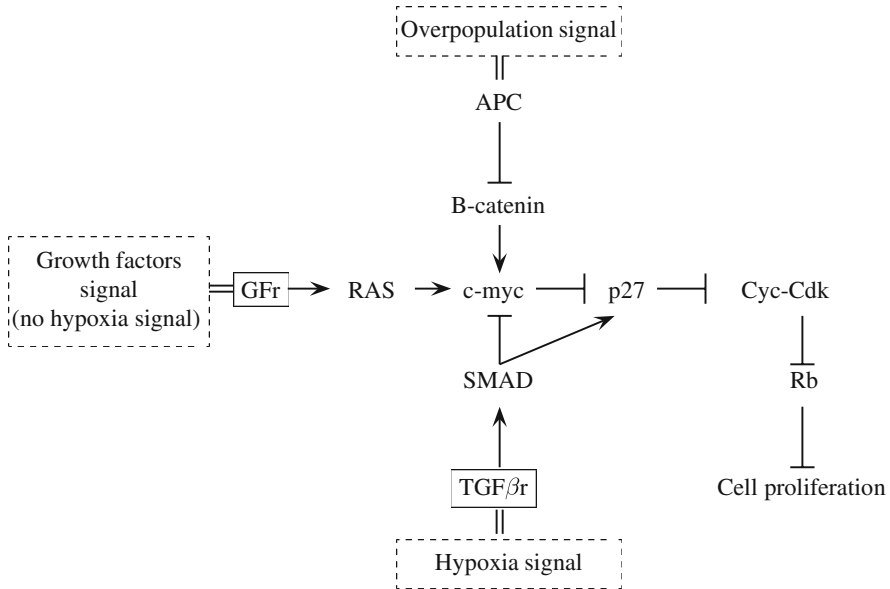


Fig. 2 Schematics (taken from Ribba et al. 2006a) shows how signals of overpopulation and hypoxia are transmitted through APC and SMAD to block cell proliferation. Arrowhead indicates activation, hammerhead indicates inhibition

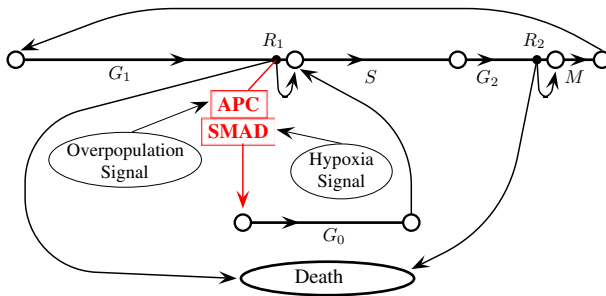


Fig. 3 Hypoxia signal sensed by SMAD, or overpopulation signal sensed by APC, sends the cell at checkpoint R_1 into quiescence model G_0 . A cell remains in G_0 for a period of time, after which the cell cycle is resumed

Cancer is a disease that develops as a result of genes mutation. Typically a cancer is associated with more than just a few mutations. However, it is believed the initiation of the disease is caused by just very few mutations. In the case of colorectal cancer it was suggested in Fearon and Vogelstein (1990), Hahn and Weinberg (2002), Kanehisa (1997) and Kanehisa and Goto (2000) that the two genes SMAD and APC are the initiators of the disease.

Ribba et al. (2006a,b) developed a mathematical model of colorectal cancer based on the regulatory network in Fig. 2 in which tumor suppressors SMAD and APC are mutated. Their study includes the effects of irradiation therapy and anti-invasive agents. In their hybrid PDE/discrete model the cell cycle clock time is divided into a

finite number of blocks, but the time t varies continuously. Although they used PDEs to describe the growth of cells as function of t , the tumor region is taken as a fixed region. Their 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, although the cycling time varies in discrete steps. More recently, Friedman (2007, 2008) developed a mathematical model in which also the cycling time varies continuously. His model assumes that the tumor's boundary is a free boundary which needs to be determined together with the solution of the PDEs.

In this paper we assume that the microenvironment is not hypoxic so that cells continue growing during all phases of the cell cycle, and SMAD is not sending cells into quiescence mode. We focus on the effect that APC has on the tissue growth. We view upregulation of APC as a control mechanism, and make the following simplifying assumptions:

1. we replace the signaling pathway from APC to cell proliferation by APC alone;
2. We assume that upregulation of APC is unconstrained, i.e., APC is viewed as a free controller.

Future work should include the complete genetic network and also impose biological constrains on the expression level of each intermediate gene in the network.

The controller APC tries to make an optimal decision on whether to take the cell into quiescence mode or let it proceed to the S phase; here, optimality is determined by homeostasis. If APC is mutated, the cell loses control at R_1 so that the probability of transition to G_0 is a fixed number (independent of population density).

In the analysis presented in this paper we assume that all the cells have precisely the same mutation. 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 (2008), there exists a unique global-in-time solution to the system of PDEs and free boundary $r = R(t)$ of the multiscale model. An 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 at least 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 APC is mutated then, in general,

$$\text{either } R(t) \rightarrow 0 \text{ or } R(t) \rightarrow \infty \text{ as } t \rightarrow \infty;$$

the second case may be interpreted as the onset of cancer (see Remark 3.3). On the other hand, if APC is not mutated, it has strategies that will result in

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

We provide rigorous mathematical proofs to the above statements. Numerical simulations also show that C/c can be made close to 1, i.e., close to homeostasis.

We conclude the introduction by noting that other multiscale tumor models were developed by Ayati et al. (2006) and Jiang et al. (2005). In a different context Nowak and Sigmund (2004) and Komarova (2007) 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 (but without including cell cycle phases), was introduced and studied numerically in Pettet et al. (2001); mathematical analysis of the model appeared in Chen and Friedman (2003), Chen et al. (2005) and Cui and Friedman (2003a,b).

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,

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

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

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

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

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

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:

$$p_1(r, t, 0) = p_3(r, t, A_3), \quad (2.5)$$

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

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

$$p_0(r, t, 0) = \beta(t)p_1(r, t, A_1). \quad (2.8)$$

Note that cell division at the end of the M phase, while increasing the number of cells does not change their density, so that $p_1(r, t, 0) = p_3(r, t, A_3)$.

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 life 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). We shall then view $\beta(t)$ as a functional

$$\beta(t) = K[Q](t). \quad (2.9)$$

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 .

Remark 2.1 The assumption that A_0 is constant is not biologically correct. In Remark 5.2 we shall consider the case where A_0 depends on the density Q in a way similar to (2.9), namely, $A_0 = A_0[Q](t)$.

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

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

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

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

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

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

so that

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

note that $v(0) = 0$.

From (2.10), (2.11) we then obtain

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

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

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

where \bar{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

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

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,

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

The following global existence and uniqueness result for radially symmetric solutions is established in [Friedman \(2008\)](#) 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)–(2.8), (2.10), (2.12)–(2.17) with $R(t)$ in $C^1[0, \infty)$, and $p_i \geq 0$ ($0 \leq i \leq 4$).*

Remark 2.2 We denote by w_* the critical concentration of oxygen below which a cell cannot sustain life. Then it is natural to assume that

$$\lambda_j(w) > 0 \text{ if } w > w_*, \lambda_j(w) < 0 \text{ if } w < w_*. \tag{2.18}$$

Applying the maximum principle to the solution of (2.13), (2.14) and recalling that $Q \leq 1$ we find that the minimum value of w in Ω_t , say $w(\bar{x}, t)$, satisfies: $0 < w(\bar{x}, t)$ and

$$w(\bar{x}, t) \geq \gamma(|\bar{x}|, t) \cdot (\bar{w} - w(\bar{x}, t)). \tag{2.19}$$

Hence if

$$w_* < \bar{w} \min \left\{ \frac{\gamma}{1 + \gamma} \right\} \tag{2.20}$$

then $w(x, t) > w_*$ so that, by (2.18), the assumption (2.4) is satisfied.

In future work we shall dispense with the assumption (2.20), so that (2.4) will generally not be satisfied, and there will be a role to play for SMAD. However, such a model will need to include angiogenesis, that is, the formation of new blood vessels in response to hypoxia signals. The effect of angiogenesis is expressed by taking $\gamma = \gamma(r, t, e)$ in (2.13) where e is the density of endothelial cells. Angiogenesis has been modeled in the literature quite extensively (see [Levine et al. 2001](#); [Mantzaris et al. 2004](#) and the references therein). By including angiogenesis we then add a system of PDEs coupled to the system of the present paper via the variable e .

It is interesting to note (as proved in [Friedman and Hu 2008](#)) that, without angiogenesis (i.e., if $h = 0$ in (2.13)), even if $w_* = 0$, that is, even if

$$\lambda_j(w) > 0 \text{ for } w > 0, \lambda_j(w) = 0 \text{ (} j = 1, 2, 3\text{)}, \tag{2.21}$$

then, regardless of the control function β , $R(t) \leq C < \infty$ 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 Sect. 6. It is convenient to introduce the function

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

so that

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

Note that $p(r, t, s)$ is continuous in s , $0 \leq s \leq A$. By conservation of mass,

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

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

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

with

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

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

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

$$\begin{aligned} \frac{\partial \widehat{p}}{\partial t} + \frac{\partial \widehat{p}}{\partial s} &= \lambda \widehat{p} \quad \text{for } 0 < s < A, \\ \frac{\partial \widehat{p}_0}{\partial t} + \frac{\partial \widehat{p}_0}{\partial s} &= -\lambda_0 \widehat{p}_0 \quad \text{for } 0 < s < A_0, \\ \frac{\partial \widehat{p}_4}{\partial t} &= \mu_1 \widehat{p}(t, A) + \frac{\mu_2}{1 - \mu_2} \widehat{p}(t, A_2) - \lambda_4 \widehat{p}_4. \end{aligned}$$

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

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

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

Define

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

then

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

We also define

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

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

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

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 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,

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

where $\alpha_1(\beta) = (1 - \mu_2)(1 - \mu_1 - \beta)e^{\lambda A}$, $\alpha_2(\beta) = (1 - \mu_2)\beta e^{-\lambda_0 A_0} e^{\lambda A}$. (3.16)

We shall assume that

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

Remark 3.1 The first inequality in (3.17) says that if none of cells go into quiescence then their density over each cycle increases, that is, $\widehat{Q}(t) > \widehat{Q}(t - A)$. Indeed, this follows from (3.16) with $\beta = 0$. Similarly, the second inequality in (3.17) says that if cells go into quiescence and stay there long enough then the total population density decreases over the period $A + A_0$, that is, $\widehat{Q}(t) < \widehat{Q}(t - A - A_0)$. Indeed, this follows from (3.16) with $\beta = 1 - \mu_1$.

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

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

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

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

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

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

Hence there is a unique β^* such that

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

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

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

We want to use (3.16). However, (3.16) only enables us to derive estimates on an interval with a time shift of length A , not $A + A_0$. To obtain estimates on the interval $[2(A + A_0), 3(A + A_0)]$, we shall repeatedly use (3.16). First, by (3.16),

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

and, in particular,

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

Repeating this procedure with $2(A + A_0) + jA < t < 2(A + A_0) + (j + 1)A$ for $j = 1, 2, \dots, k$ where k is such that $kA > (A + A_0)$, we obtain

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

Taking “inf” over the interval $[2(A + A_0), 3(A + A_0)]$ it follows that

$$M_2 \geq (1 + \delta)M_1.$$

Similarly $M_j \geq (1 + \delta)M_{j-1}$ and therefore $M_j \rightarrow \infty$ as $j \rightarrow \infty$.

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

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

$$R(t) \rightarrow \infty \quad \text{as } t \rightarrow \infty;$$

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

$$R(t) \rightarrow 0 \quad \text{as } t \rightarrow \infty.$$

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

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

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

In case $\beta^* < \beta \leq 1 - \mu_1$, 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),

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

We note that in the last integral $\beta(t - s)$ is actually a constant β . The argument used in the present proof, however, can also be used in the proof of Theorem 4.2, in which case β is not a constant. In order to avoid repeating the same argument we keep writing here $\beta = \beta(t - s)$, and refer to this proof later on.

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

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

so that, by Lemma 3.1,

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

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 $t \rightarrow \infty$. Next, by (3.12),

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

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

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

Then

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

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

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

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

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

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) to (3.21) that

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

□

Remark 3.2 The arguments used in the proof of Lemma 3.1 show that if $\beta = \beta^*$, then

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

Remark 3.3 The case $\beta(t) \equiv \text{const.}$ 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, 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 Sect. 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

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

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

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

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 $jA \leq t \leq (j + 1)A$. 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

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

Define

$$\begin{aligned} \widehat{Q}_{\min} &= \min \left((1 - \mu_2)(1 - \mu_1 - \bar{\beta})e^{\lambda A} Q^*, (1 - \mu_2)\bar{\beta}e^{\lambda A}e^{-\lambda_0 mA} Q^*, \widehat{Q}_1, \dots, \widehat{Q}_{m+1} \right), \\ \widehat{Q}_{\max} &= \max \left(\frac{(1 - \mu_2)\underline{\beta}e^{\lambda A}e^{-\lambda_0 mA}}{1 - (1 - \mu_2)(1 - \mu_1 - \bar{\beta})e^{\lambda A}} Q^*, \frac{(1 - \mu_2)(1 - \mu_1 - \underline{\beta})e^{\lambda A}}{1 - (1 - \mu_2)\bar{\beta}e^{\lambda A}e^{-\lambda_0 mA}} Q^*, \right. \\ &\quad \left. (1 - \mu_2)(1 - \mu_1 - \underline{\beta})e^{\lambda A} Q^* + (1 - \mu_2)\underline{\beta}e^{\lambda A}e^{-\lambda_0 mA} Q^*, \widehat{Q}_1, \dots, \widehat{Q}_{m+1} \right). \end{aligned}$$

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

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

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

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

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

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

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

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

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

so that, using (4.8),

$$\widehat{Q}_j \leq \left\{ (1 - \mu_2)(1 - \mu_1 - \bar{\beta})e^{\lambda A} + (1 - \mu_2)\underline{\beta}e^{\lambda A} e^{-\lambda_0 m A} \right\} \widehat{Q}_{\max} < \widehat{Q}_{\max},$$

whereas, by the two inequalities of case (i),

$$\widehat{Q}_j \geq \left\{ (1 - \mu_2)(1 - \mu_1 - \bar{\beta})e^{\lambda A} + (1 - \mu_2)\underline{\beta}e^{\lambda A} e^{-\lambda_0 m A} \right\} \widehat{Q}^* > \widehat{Q}_{\min}.$$

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

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

so that, by the inequality $(1 - \mu_2)\underline{\beta}e^{\lambda A} e^{-\lambda_0 m A} Q^* \leq \{1 - (1 - \mu_2)(1 - \mu_1 - \bar{\beta})e^{\lambda A}\} \widehat{Q}_{\max}$, we get

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

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

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

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 $R(t) \geq c > 0$).

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

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

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

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

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

and set

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

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 $R(t) \rightarrow \infty$ as $t \rightarrow \infty$.

Similarly, if we assume that

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

and set

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

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

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

Using (5.3) we can then derive the inequality

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

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 $R(t) \rightarrow 0$ if $t \rightarrow \infty$.

We summarize:

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

$$R(t) \rightarrow \infty \quad \text{if } t \rightarrow \infty.$$

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

$$R(t) \rightarrow 0 \quad \text{if } t \rightarrow \infty.$$

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 $0 < \underline{\beta} < \beta_-^* \leq \beta_+^* < \overline{\beta} < 1 - \mu_1$, 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

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

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

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

Remark 5.2 Up to now we assumed that A_0 is constant. Consider the more biologically appropriate assumption that A_0 is a function depending on the microenvironment, say

$$A_0 = A_0[Q](t).$$

If A_0 is a continuously differentiable in Q then Theorem 2.1 remains valid with some minor modifications in the proof; hence unique global solution exists. If APC is mutated, then $A_0 = \text{const.}$ and Theorem 3.2 remains valid. Finally, if APC, is not mutated then, if $A_0 = A_0(Q)$ is chosen a constant large enough to satisfy the second inequality in (3.17), then the Theorem 4.2 remains valid.

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 24h (Brooks and Riddle 1988);

$$\begin{aligned} A &= 1 \text{ day}, \quad A_1 = A_2 = A_3 = \frac{1}{3} \text{ day}, \quad A_0 = 5 \text{ days}; \\ \lambda_0 A_0 &= \frac{1}{2} \lambda A, \quad m \lambda_0 = \frac{1}{2} \ln 2 \approx 0.347, \quad \text{and } m = 5. \end{aligned}$$

Since, according to DeBoer and Perelson (2005), 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 (Fowler 1991)

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

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

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

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

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 \vec{v} is obtained by mid-point integration of H : $\vec{v} = v\vec{e}_r$, $v = \frac{1}{r^2} \int_0^r r^2 H(\vec{Q}, \omega)$ (where $H(\vec{Q}, \omega)$ 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 $\beta(t) = \text{const.} = \beta$. According to Theorem 3.2, with

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

if $\beta < \beta^*$ then $R(t) \rightarrow 0$ as $t \rightarrow \infty$ and if $\beta > \beta^*$ then $R(t) \rightarrow 0$ as $t \rightarrow \infty$. This is illustrated in Fig. 4 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 $\beta(t) = \text{const.}$ is of course not robust. To derive a robust control we follow the proof of Theorem 4.2, but first choose $\beta(t)$ for $0 \leq t \leq t_0 = A_0$ 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 $0 \leq t \leq t_0$.

Figure 5 shows simulation results for different constants Q^* . The asymptotic behavior of $R(t)$ at large times strongly depends on the choice Q^* . The control β makes H fluctuate around zero 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 employed in the proof of Theorem 4.2 is robust, we can do better by an adaptive control approach, as illustrated in Fig. 6.

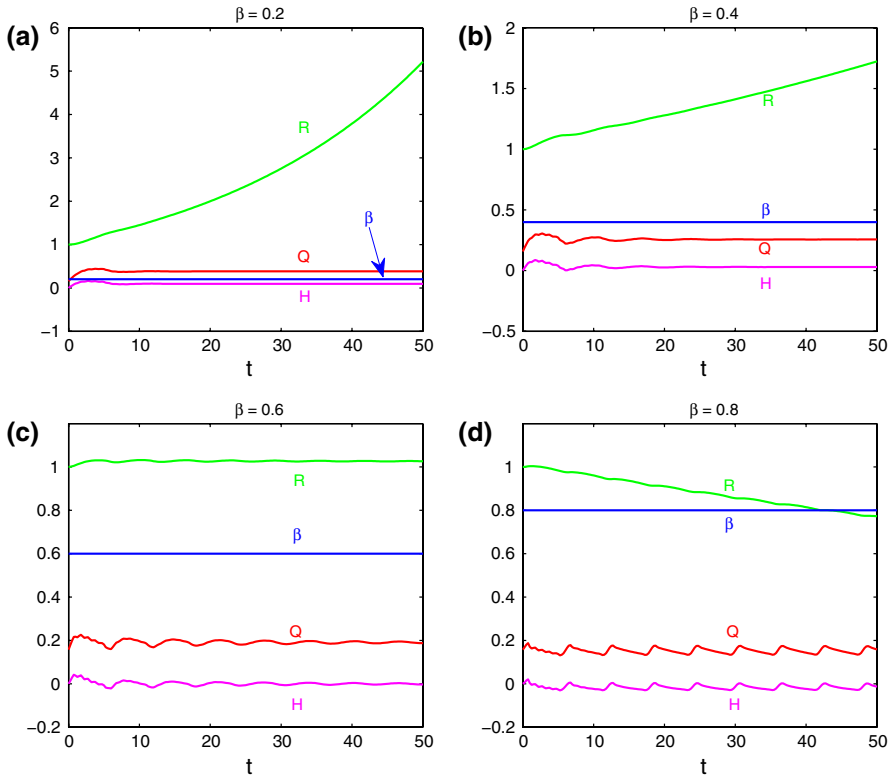


Fig. 4 The effect of different constant β (the fraction of the cell goes into quiescence) on the radius $R(t)$, the density of live cells Q , and H defined in (2.11). We see that the radius increases for $\beta < \beta^* \approx 0.6$ in **a** and **b**, converges asymptotically to a constant for $\beta = 0.6$ in **c**, and decreases for $\beta > \beta^*$ in **d**. Here $\mu_1 = \mu_2 = 0.2$. The color figure appears in <http://dx.doi.org/10.1007/s00285-009-0290-7>

Instead of fixing Q^* in the previous example, we choose $Q^* = \widehat{Q}(jA)$ so that

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

where $jA \leq t \leq (j + 1)A$. Due to the initial control $\beta(t) = 0.5$ for $t < t_0 = A_0$ and the control (6.1) at later times, the radius first grows and then stabilizes. The radius does not fluctuate as frequently as in the previous examples.

A completely different approach to stabilize $R(t)$ is to choose $\beta(t)$ such that $H \equiv 0$, so that $R(t) \equiv \text{const}$. 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 by hybrid method which combines this strategy as long as $\beta(t)$ remains in the interval $(0, 1 - \mu_1)$, and then switches to the adaptive control strategy of (6.1). This is illustrated in Fig. 7 which shows that $R(t)$ stabilizes faster than in Fig. 6.

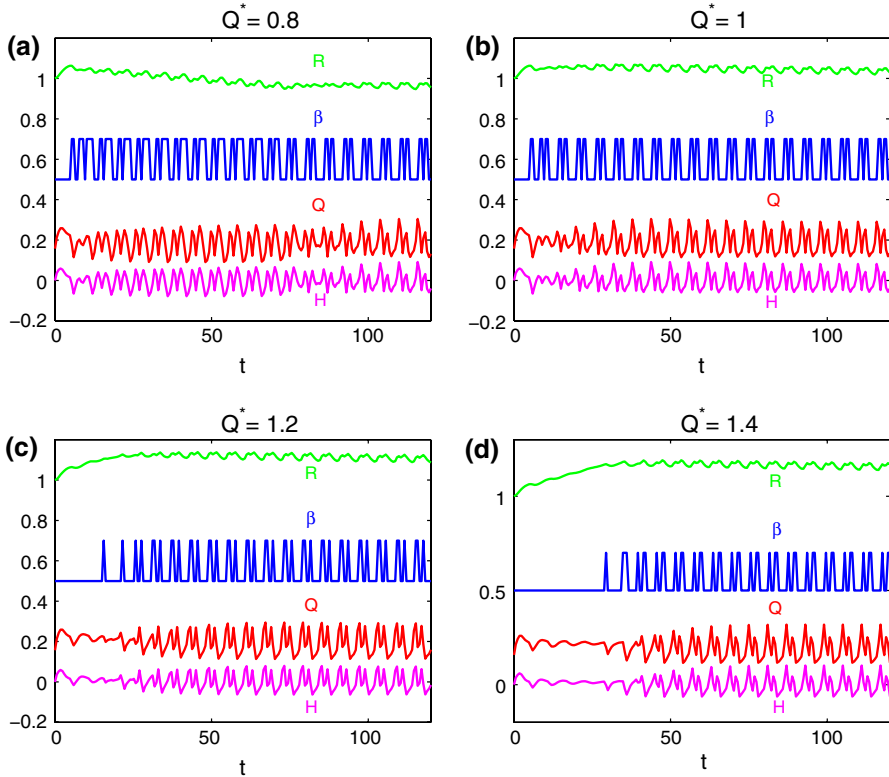


Fig. 5 The simulation results for different constant Q^* defined in (4.6) are shown. By switching β to be either $\underline{\beta} = 0.5$ or $\bar{\beta} = 0.7$, the radius R , the density of live cells Q , and H defined in (2.11) oscillate. The radius oscillates around a larger constant when Q^* is larger. The color figure appears in <http://dx.doi.org/10.1007/s00285-009-0290-7>

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 G_1 phase to S phase, or whether to go first into quiescent state. If the cells are healthy normal, then when the microenvironment is overpopulated, and if the cells are endowed with full control $\beta = \beta(t)$ in some interval $\underline{\beta} \leq \beta(t) \leq \bar{\beta}$ 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 the suppressor gene that is designed to block proliferation when the microenvironment is overpopulated is mutated, then the radius $R(t)$ may increase to ∞ (this could be interpreted as the onset of cancer), 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

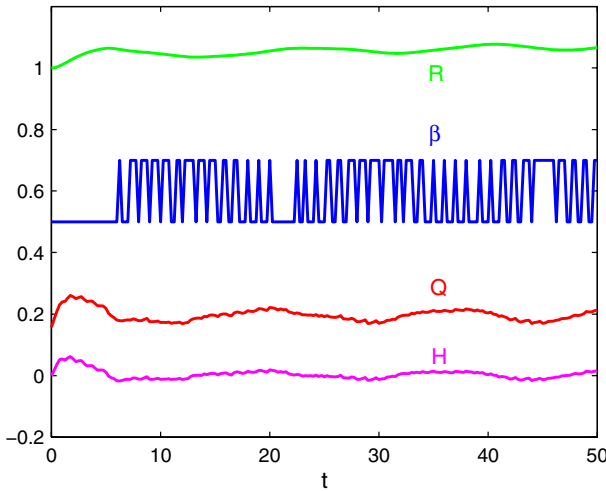


Fig. 6 The simulation result for adaptive Q^* defined in (6.1) to stabilize the radius is shown. The radius does not fluctuate as frequently as in the examples shown in Fig. 5. Here $\underline{\beta} = 0.5, \bar{\beta} = 0.7$. The color figure appears in <http://dx.doi.org/10.1007/s00285-009-0290-7>

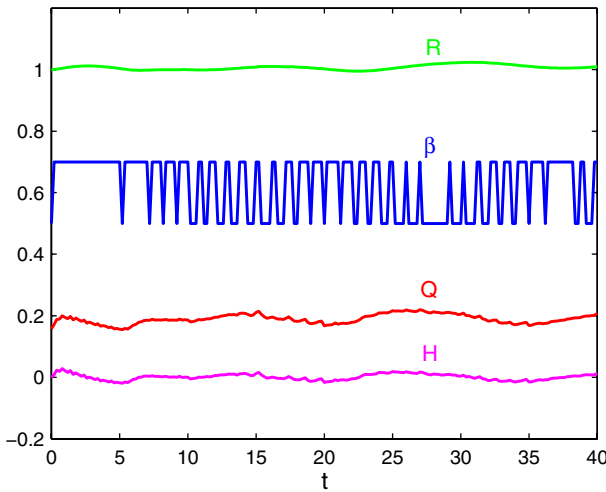


Fig. 7 Instead of switching β according to Q^* to stabilize the radius, β is chosen to make H close to zero which implies that the radius stays close to a constant. This strategy shows that $R(t)$ stabilizes faster than in Fig. 6. Here $\underline{\beta} = 0.5, \bar{\beta} = 0.7$. The color figure appears in <http://dx.doi.org/10.1007/s00285-009-0290-7>

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 APC is mutated so that all control at R_1 is lost for the latter population. In this case, again $R(t) \rightarrow \infty$ 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.

In this paper we made the simplifying assumptions that the genetic pathway from overpopulation signal to cell proliferation is represented by just one gene, namely, APC, and that the expression level of this gene is unlimited. Future work should strive to remove or relax these assumptions.

It was assumed in the present paper that the microenvironment is above the hypoxic level so that cells continue to grow unless they are quiescence. Future work should include hypoxia signal. This is a situation which on one hand gives rise to angiogenesis, prompting supply of oxygen by new blood vessels, and on the other hand signals to SMAD to block cell proliferation.

Ribba et al. (2006a,b) used their model to study therapeutic approaches to colorectal cancer. We hope to consider such therapies in a future work by means of the model of the present paper.

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References

- Aguda BD, Friedman A (2008) Models of cellular regulations. Oxford University Press, New York
- Ayati BP, Webb GF, Anderson ARA (2006) Computational methods and results for structured multiscale methods of tumor invasion. *Multiscale Model Simul* 5:1–20
- Brooks RF, Riddle PN (1988) The 3T3 cell cycle at low proliferation rates. *J Cell Sci* 90:601–612
- Chen X, Friedman A (2003) A free boundary problem for elliptic-hyperbolic system: an application to tumor growth. *SIAM J Math Anal* 35:974–986
- Chen X, Cui S, Friedman A (2005) A hyperbolic free boundary problem modeling tumor growth: asymptotic behavior. *Trans Am Math Soc* 357:4771–4804
- Cui S, Friedman A (2003a) A free boundary problem for a singular system of differential equations: an application to a model of tumor growth. *Trans Am Math Soc* 355:3537–3590
- Cui S, Friedman A (2003b) A hyperbolic free boundary problem modeling tumor growth. *Interfaces Free Bound* 5:159–181
- DeBoer RJ, Perelson AS (2005) Estimating division and death rates from CFSE data. *J Comput Appl Math* 184:140–164
- Fearon ER, Vogelstein B (1990) A genetic model for colorectal tumorigenesis. *Cell* 61:759–767
- Fowler JF (1991) The phantom of tumor treatment-continually rapid proliferation unmasked. *Radiother Oncol* 22:156–158
- Friedman A (2007) Mathematical analysis and challenges arising from models of tumor growth. *Math Models Methods Appl Sci* 17:1751–1772
- Friedman A (2008) A multiscale tumor model. *Interfaces Free Bound* 10:245–262
- Friedman A, Hu B (2008) The role of oxygen in tissue maintenance: mathematical modeling and qualitative analysis. *Math Models Methods Appl Sci* 18:1–33
- Hahn WC, Weinberg RA (2002) Modeling the molecular circuitry of cancer. *Nat Rev Cancer* 2:331–341
- Jiang J, Pjesivac-Grbovic J, Cantrell C, Freyer JP (2005) A multiscale model for avascular tumor growth. *Biophys J* 89:3884–3894
- Kanehisa M (1997) A database for post-genome analysis. *Trends Genet* 13:375–376
- Kanehisa M, Goto S (2000) KEGG: Kyoto encyclopedia of genes and genomes. *Nucleic Acid Res* 28:27–30
- Komarova N (2007) Stochastic modeling of loss- and gain-of-function mutation in cancer. *Math Models Methods Appl Sci* 17:1647–1673
- Levine HA, Pamuk SL, Sleeman BD, Nilsen-Hamilton M (2001) Mathematical modeling of capillary formation and development in tumor angiogenesis: penetration into the stoma. *Bull Math Biol* 63:801–863

- Mantzaris N, Webb S, Othmer HG (2004) Mathematical modeling of tumor-induced angiogenesis. *J Math Biol* 49:87–111
- Nowak MA, Sigmund K (2004) Evolutionary dynamics of biological games. *Science* 303:793–799
- Pettet GJ, Please CP, Tindall MJ, McElwain DLS (2001) The migration of cells in multicell tumor spheroids. *Bull Math Biol* 63:231–257
- Ribba B, Colin T, Schnell S (2006a) A multiscale model of cancer, and its use in analyzing irradiation therapies. *Theor Biol Med Model* 3(7):1–19
- Ribba B, Sant O, Colin T, Bresch D, Grenien E, Boissel JP (2006b) A multiscale model of avascular tumor growth to investigate agents. *J Theor Biol* 243:532–541