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Free Boundary Problems Associated with Multiscale Tumor Models

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Abstract. The present paper introduces a tumor model with two time scales, the time t during which the tumor grows and the cycle time of individual cells. The model also includes the effects of gene mutations on the population density of the tumor cells. The model is formulated as a free boundary problem for a coupled system of elliptic, parabolic and hyperbolic equations within the tumor region, with nonlinear and nonlocal terms. Existence and uniqueness theorems are proved, and properties of the free boundary are established.

Key words: free boundary problems, system of PDEs, tumor, cell cycle
AMS subject classification: 35Q80, 35R35, 92C50, 35Q30, 35F99, 35M99

1. Introduction

The cell cycle is divided into four phases: S (for synthesis), M (for mitosis), and gap phases G_1 and G_2; see Figure 1. During the S phase the DNA is replicated, that is, each chromosome is duplicated. During the mitosis phase, M, the nuclear membrane breaks down, sister chromatids are separated, new nuclear membranes are formed, and the cell divides into two daughter cells. S and M are separated by two gap phases, G_1 and G_2. As shown in Figure 1, the cell cycle is controlled at two check points, R_1 and R_2; R_1 and R_2 are also called *restriction points*.

We consider tumor models with two time scales: the time t during which the tumor evolves, and the time s_i during which the tumor cells progress in their i-phase of the cell cycle. The decisions on transition from one phase to another are being made at the two restriction points which are located near the end of the G_1 phase and the G_2 phase. These decisions depend on the state of the cell as

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well as on signals the cell receives from the microenvironment, such as signals of overpopulation or hypoxia. When as a result of mutations the cells ignore such cues, a tumor may develop. The models considered here are formulated as a system of PDEs for population densities of cells and concentrations of oxygen and chemokines. The tissue in which the tumor grows is assumed to have the consistency of either a porous medium to which Darcy's law applies, or a fluid-like medium for which Stokes equation holds. The tumor's boundary is a free boundary, and, in the radially symmetric case, it it given by $r = R(t)$.

At R_1 the cell decides on one of three options: (i) to commit suicide (apoptosis) if it senses that it has been damaged beyond repair during the growth phase G_1; (ii) to go into a quiescent phase G_0 and stay there for a while, if the microenvironment is hypoxic or overpopulated with other cells; or (iii) to proceed to the S phase. At R_2 the cells decides either to go into apoptosis if irreparable damage has occurred during the DNA replication, or to continue toward the M phase. A cell remains in G_0 for a period of time, at the end of which it proceeds to the S phase.

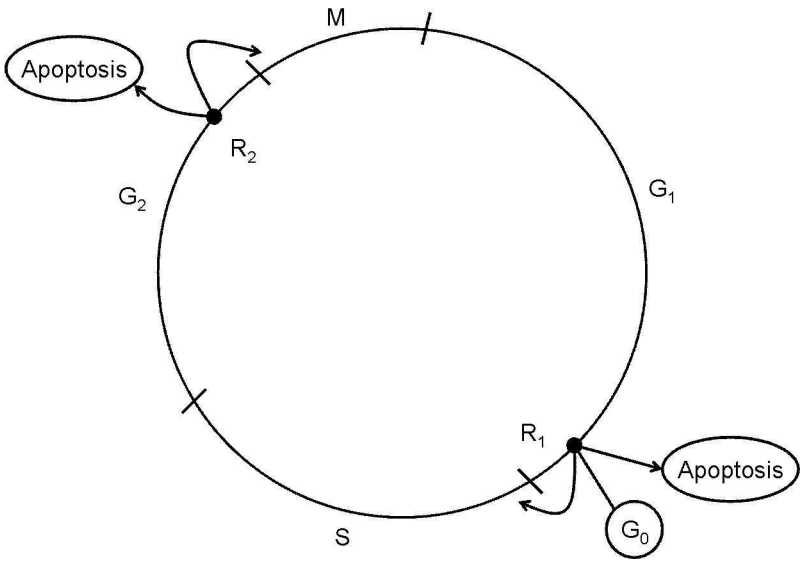

Figure 1: Cell cycle

Oncogene is a gene that normally directs cell growth; if altered or mutated, it can promote uncontrolled growth of tumor. Suppressor gene is a protective gene that normally limits the growth of a tumor. Thus, for example, if the microenvironment is hypoxic, the suppressor gene SMAD will direct the cell, at the restriction point R_1, to go into the quiescent phase G_0; similarly, if the microenvironment is overpopulated, then the suppressor gene APC will direct the cell at R_1 to go into G_0. The suppressor gene p53 sends the cell into apoptosis when the cell is irreparably damaged. Figure 2 describes the role of these three suppressor genes. For more details, see Ribba et al [27].

In this paper we focus on mathematical models of tumor growth that capture some of the genetic aspects of the disease and, at the same time, deal with the disease at the tissue level. Thus we need

to deal with (densities of) populations of cells that are at different phases of the cell cycle and with the decision they make at their restriction points. By taking the decision the individual cells make into population size considerations, our models combine genetic information with continuum mechanics. In the same spirit of Nowak and Sigmund [25] and Komarova [21], we shall show how cellular dynamics are related to genetic dynamics. Other multiscale tumor models were developed by Ayati et al. [1] and Jiang et al. [20]. A tumor model with three types of cells (proliferating, quiescent, and dead) was developed by Pettet et al [26] and analyzed by mathematical analysis in [5], [6], [7]. The underlying assumptions in our models is that all the cells which have the same set of genetic mutations make the same decisions at R_1 and at R_2. For simplicity we shall only consider the case where all the cells have the very same set of genetic mutations and thus they all make the same decisions at R_1 and at R_2. The more general case where the population of cells is divided into subpopulations, each having its own specific set of genetic mutations, will be briefly mentioned in Remark 6.2.

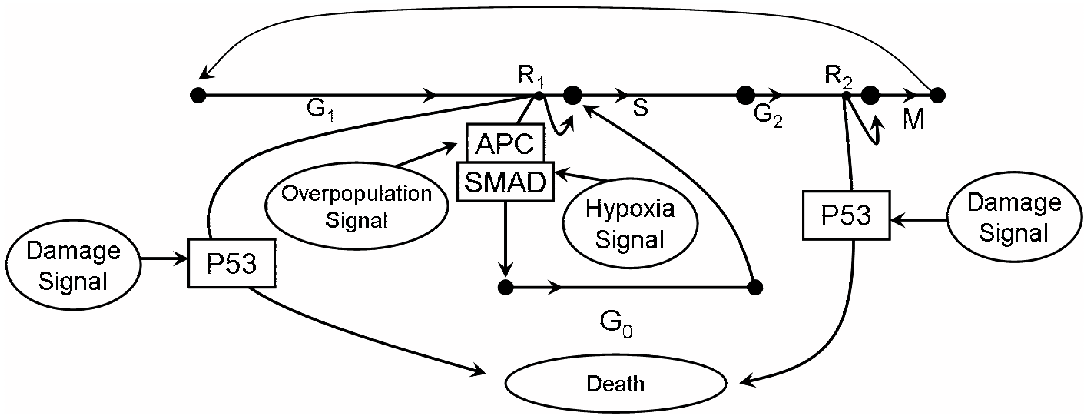

Figure 2: Gene suppressors

We shall model the evolution of tumor by means of a set of PDEs in the tumor region. This region, $\Omega(t)$, varies in time. Thus the mathematical model is that of a *free boundary problem* for a system of PDEs: We need to find both the free boundary $\Gamma(t)$ of $\Omega(t)$ and the solution of the differential equations in $\Omega(t)$. The most important questions are concerned with the free boundary: Does it grow? Does it produce "fingers"? etc.

In this paper we establish local existence and uniqueness for general initial data, and global existence in the radially symmetric case, as well as asymptotic results on the free boundary $r = R(t)$. This paper is a continuation of our earlier work in [15], [16].

2. A Mathematical Model

We introduce the following notation:

$p_1(x, t, s_1)$=density of cells in phase G_1, $s_1 \in [0, A_1]$;

$p_2(x,t,s_2)$=density of cells in phase S, $s_2 \in [0, A_2]$;
$p_3(x,t,s_3)$=density of cells in phases G_2 and M, $s_3 \in [0, A_3]$;
$p_0(x,t,s_0)$=density of cells in phase G_0, $s_0 \in [0, A_0]$;
$p_4(x,t)$=density of necrotic cells.

The variable x will vary in the tumor region $\Omega(t)$ in $\mathbb{R}^3$, with boundary $\Gamma(t)$.

We denote by $w(x,t)$ the oxygen concentration and by $Q(x,t)$ the combined density of live cells in phases G_1, S, G_2, M. Due to cells proliferation and death, there is a velocity field $\vec{v}(x,t)$, which is assumed to be common to all the cells. Then, by conservation of mass,

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

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

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

where $\lambda_i(w)$ are growth rates,

$$\lambda_i(w) = \begin{cases} > 0 & \text{if } w > w_* \\ \leq 0 & \text{if } w < w_*, w_* \geq 0 \quad (i = 1,2,3) \end{cases} \tag{2.4}$$

$$\lambda_0 = const. > 0,$$

w_* is the necrotic level of oxygen, λ_0 is the death rate of cells in quiescent mode, λ_4 is the clearance rate of dead cells, and μ_1, μ_2 are the rates at which cells are damaged and apoptose at the check points R_1, R_2, respectively.

From the diagram in Figure 2 we deduce the following relations:

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

$$p_2(x,t,0) = (1 - \mu_1 - K(w(x,t), Q(x,t)))p_1(x,t,A_1) + p_0(x,t,A_0), \tag{2.6}$$

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

$$p_0(x,t,0) = K(w(x,t), Q(x,t))p_1(x,t,A_1). \tag{2.8}$$

The function $K(w,Q)$ in (2.6) represents the effect of the microenvironment: under hypoxic or overpopulation conditions the cell, at R_1, is induced to go into quiescent mode; hence

$$K(w,Q) \geq 0, \quad K(w,Q) \downarrow \quad if \quad w \uparrow \quad or \quad Q \downarrow,$$

and, of course, $K(w,Q) + \mu_1 \leq 1$. If both genes SMAD and APC are mutated, then

$$K(w,Q) \equiv const. = \beta \geq 0$$

where β is a small positive constant, or zero.

We introduce the total density of each population of cells that are in the same phase of the cell cycle:

$$Q_i(x,t) = \int_0^{A_i} p_i(x,t,s_i)ds_i.$$

Then

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

It is convenient to define

$$p_4(x,t,s_4) = p_4(x,t), \quad s_4 \in [0,A_4], A_4 = 1$$

and introduce the vector

$$\vec{Q} = \{Q_i\}_{i=0}^4.$$

We integrate each of the equations in (2.1)-(2.3) over $s_i, 0 < s_i < A_i$ and sum up the resulting equations. Using the relations (2.5)-(2.8) we then get

$$\sum_{i=0}^{4} \left[\frac{\partial Q_i}{\partial t} + div(Q_i \vec{v}) \right] = \sum_{i=1}^{3} \lambda_i(w) Q_i - \lambda_0 Q_0 - \lambda_4 Q_4. \tag{2.9}$$

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

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

Then (2.9) yields

$$div\vec{v} = H(\vec{Q}, w) \tag{2.11}$$

where

$$H(\vec{Q}, w) = \sum_{i=1}^{3} \lambda_i(w) Q_i - \lambda_0 Q_0 - \lambda_4 Q_4. \tag{2.12}$$

Conversely, one can easily show that (2.11) together with (2.9), (2.12) imply (2.10) for all $t > 0$ provided (2.10) is satisfied at $t = 0$.

Substituting (2.11) into (2.1)-(2.3), we obtain

$$\frac{\partial p_i}{\partial t} + \frac{\partial p_i}{\partial s_i} + \vec{v} \cdot \nabla p_i = p_i f_i(\vec{Q}, w) \quad (0 \le i \le 3), \tag{2.13}$$

$$\frac{\partial p_4}{\partial t} + \vec{v} \cdot \nabla p_4 = \mu_1 p_1(x, t, A_1) + \mu_2 p_2(x, t, A_2) + p_4 f_4(\vec{Q}, w) \tag{2.14}$$

where

$$f_i(\vec{Q}, w) = \lambda_i(w) - H(\vec{Q}, w) \quad (1 \le i \le 3), \tag{2.15}$$

$$f_0(\vec{Q}, w) = -\lambda_0 - H(\vec{Q}, w), \tag{2.16}$$

$$f_4(\vec{Q}, w) = -\lambda_4 - H(\vec{Q}, w). \tag{2.17}$$

The oxygen concentration satisfies a diffusion equation

$$w_t - D_w \cdot \nabla^2 w + \lambda Q w = b(x, t)(\bar{w} - w), \quad b \ge 0, \tag{2.18}$$

where λ is a positive constant, $\bar{w}$ is the average oxygen concentration in a healthy tissue, and b is a transmission function of oxygen from the vasculature into the tissue.

In order to close the PDE system we need to prescribe a constitutive law for velocity $\vec{v}$ in the tumor tissue. If the tissue is assumed to be a porous medium, then, by Darcy's law,

$$\vec{v} = -\nabla \sigma \tag{2.19}$$

where σ is the internal pressure that is responsible for the movement of cells with their $\vec{v}$ velocity. Then, from (2.11) we obtain

$$\nabla^2 \sigma = -H(\vec{Q}, w) \tag{2.20}$$

Most mathematical models assume that the tissue is a porous medium for which Darcy's law holds; see [13], [14], [15], [16] and the references therein. Later on we shall also consider a fluid-like tumor for which we shall take a different constitutive law relating $\vec{v}$ to σ, based on the Stokes equation.

We proceed to prescribe boundary conditions. We impose the continuity condition on the movement of the free boundary, that is, the velocity V_n of the free boundary in the outward normal direction $\vec{n}$ is equal to $\vec{v} \cdot \vec{n}$:

$$V_n = \vec{v} \cdot \vec{n},$$

or, by (2.19),

$$V_n = -\frac{\partial \sigma}{\partial n} \quad on \ \ \Gamma(t). \tag{2.21}$$

Naturally, we also take

$$w = \bar{w} \quad on \ \ \Gamma(t). \tag{2.22}$$

In a solid tumor, the boundary remains intact due to cell-to-cell adhesion [2]-[4]. This fact is expressed by the boundary condition

$$\sigma = \gamma\kappa \quad on \quad \Gamma(t) \tag{2.23}$$

where κ is the mean curvature ($\kappa = 1/R$ if $\Gamma(t)$ is a sphere of radius R) and γ is proportional to the force of cell-to-cell adhesion. Since the characteristic curves of the hyperbolic system (2.13)-(2.14) initiating on the free boundary move with the same velocity as the free boundary, no boundary conditions need to be prescribed for the $p_i(x,t,s_i)$ on $\Gamma(t)$.

We finally prescribed initial conditions:

$$\begin{aligned} \Omega(t)|_{t=0} &= \Omega_0 \quad with \ \ boundary \quad \Gamma(t)|_{t=0} = \Gamma_0, \\ w|_{t=0} &= w_0(x), \ x \in \Omega_0, \\ p_i|_{t=0} &= p_{i0}(x,s_i), \ \ x \in \Omega_0, 0 < s_i < A_i \ \ (0 \le i \le 4), \end{aligned} \tag{2.24}$$

where

$$w_0 \ge 0, p_{i0} \ge 0 \quad and \quad \sum_{i=0}^{4} Q_i|_{t=0} \equiv 1. \tag{2.25}$$

Definition 2.1. The multiscale tumor problem with Darcy's law consists of the system (2.12)-(2.25) and (2.4)-(2.8).

The tumor model described above is a multiscale model. The spatial multiscale character is due to the fact that the model includes effects of gene mutations (at the cell level) as well as population densities (at the tissue level). It is also multiscale in the temporal sense, since it is concerned with the cell-cycle phase times s_i as well as the time t of tumor growth.

3. Existence Theorems Under Darcy's Law

In this section we consider the multiscale tumor model assuming Darcy's law (2.19). If the initial conditions in (2.24) satisfy the equations (2.5)-(2.8) at $t = 0$, and $w_0 = \bar{w}$ on Γ_0, then we say that the *first order compatibility conditions* are satisfied.

Before stating existence theorems we need to introduce some notation. Let $\varphi = (x,t,s), \beta = (\beta_1,\beta_2,\beta_3,\beta_4,\beta_5), \beta_i$ integers $\ge 0, |\beta| = \beta_1 + \cdots + \beta_5$. Then we write

$$D^\beta\varphi = D^\beta_{(x,t,s)}\varphi = \frac{\partial^{|\beta|}\varphi}{(\partial x_1)^{\beta_1}(\partial x_2)^{\beta_2}(\partial x_3)^{\beta_3}(\partial t)^{\beta_4}(\partial s)^{\beta_5}}$$

$$||\varphi||_0 = \sup|\varphi|, ||\varphi||_m = \sum_{|\beta|\le m} ||D^\beta\varphi||_0,$$

$$|\varphi|_{\alpha_1,\alpha_2,\alpha_3} = \sup \frac{|\varphi(x,t,s) - \varphi(\bar{x},\bar{t},\bar{s})|}{|x-\bar{x}|^{\alpha_1} + |t-\bar{t}|^{\alpha_2} + |s-\bar{s}|^{\alpha_3}},$$

$$||\varphi||_{m+\alpha_1,m+\alpha_2,m+\alpha_3} = ||\varphi||_0 + \sum_{|\beta|=m} |D^\beta\varphi|_{\alpha_1,\alpha_2,\alpha_3}; \tag{3.1}$$

here m is an integer ≥ 0 and $0 < \alpha_i < 1$. The domain in which the norms are defined will be specified later on. If φ does not depend on s, then we drop α_3 in corresponding norms. If $\varphi = \varphi(x,t)$, we define, for $0 < \alpha < 1$,

$$||\varphi||_{3+\alpha,(3+\alpha)/3} = ||\varphi||_0 + ||D_x^3\varphi||_{\alpha,\alpha/3} + ||D_t\varphi||_{\alpha,\alpha/3}, \tag{3.2}$$

Note that the norm (3.1) dominates the norm $||\varphi||_m$, and, by standard estimates, the norm (3.2) dominates the norm

$$|D_x^2\varphi|_{0,(1+\alpha)/2} + |D_x\varphi|_{0,(2+\alpha)/3}$$

where $|\psi|_{0,\alpha} = \sup_x |\psi(x,\cdot)|_\alpha$ if $\psi = \psi(x,t)$.

We say that a function $\varphi = \varphi(x,t,s)$ is in $C^{m+\alpha_1,m+\alpha_2,m+\alpha_3}$ if

$$||\varphi||_{m+\alpha_1,m+\alpha_2,m+\alpha_3} < \infty.$$

Similarly we define the notion of $\varphi = \varphi(x,t)$ in $C^{3+\alpha,(3+\alpha)/3}$.

In the sequel we assume that

$$\Gamma_0 \in C^{m+1+\alpha} \tag{3.3}$$

where $0 < \alpha < 1$ and m is an integer ≥ 0. Denote by ξ a variable point in Γ_0 and by $\vec{n}(\xi)$ the unit outward normal to Γ_0 at ξ. We shall write $\Gamma(t)$ in the form

$$\Gamma(t) = \{\xi + \rho(\xi,t)\vec{n}(\xi)\}.$$

Set $d(x) = d(x,\Gamma_0) =$ signed distance from x to Γ_0 $(d > 0$ if $x \notin \Omega_0)$. Then, for x near Γ_0 we can write

$$x = \xi + d(x)\vec{n}(\xi)$$

where ξ is uniquely determined by x.

In what follows we shall use a local coordinate transformation to flatten the boundary $\Gamma(t)$. We fix a point ξ_0 in Γ_0 and take local coordinates $y' = (y_1, y_2)$ near the origin 0 in $\mathbb{R}^2$, about ξ_0, so that any point $\xi \in \Gamma_0$ with $|\xi - \xi_0|$ small can be written in the form $\xi = S(y')$. Then any point $x \in \mathbb{R}^3$ near ξ_0 can be written in the form

$$x = S(y') + (\rho(\xi,t) + y_3)\vec{n}(S(y'))$$

where $y_3 = d(x,\Gamma_0) - \rho(\xi,t)$. This defines a local mapping $y \to x$ from a neighborhood of the origin in $\mathbb{R}^3$ into an $\mathbb{R}^3$-neighborhood of ξ_0 such that $x \in \Gamma(t)$ corresponds to $(y',0)$.

Later on we shall make the following regularity assumptions:

$$\begin{gathered}\lambda_i(z) \ \ belong \ \ to \ \ C^{m+1+\alpha}(\mathbb{R}^1),\\ K(z,\xi) \ \ belongs \ \ to \ \ C^{m+1+\alpha}(\mathbb{R}^2),\\ b(x,t) \ \ belongs \ \ to \ \ C^m(\mathbb{R}^3\times[0,\infty]),\end{gathered} \tag{3.4}$$

$$w_0 \in C^{m+1+\alpha}(\bar\Omega_0), \ and \ the \ \ p_{i0} \ \ belong \ \ to \ \ C^{m+1+\alpha}(\bar\Omega_0\times[0,A_i]) \tag{3.5}$$

where m is an integer ≥ 0.

We first consider the case $m = 0$ and assume that

the first order compatibility conditions are satisfied. (3.6)

Theorem 3.1 *Under the assumptions (3.3)-(3.5) for $m = 0$ and (3.6), there exists a unique solution of the multiscale tumor model with Darcy's law for some time interval $0 \leq t \leq T$ $(T > 0)$ such that*

$$D_\xi\rho \in C^{3+\alpha,(3+\alpha)/3}(\Gamma_0\times[0,T]),$$

and σ, w, p_i can be extended into functions satisfying:

$$\begin{gathered}D_x^2\sigma \in C^{\alpha,\alpha/3}(\mathbb{R}^3\times[0,T]),\\ w \in C^{1+\alpha,1+\alpha/3}(\mathbb{R}^3\times[0,T]),\\ p_i \in C^{1+\alpha,\alpha/3,\alpha/3}(\mathbb{R}^3\times[0,T]\times A_i).\end{gathered}$$

The proof of Theorem 3.1 is given in [15]. It is based on two lemmas. The first lemma, taken from [6], is concerned with the inhomogeneous Hele-Shaw problem: Find a function $\sigma(x,t)$ and domains $\Omega(t)$ such that

$$\Delta\sigma = h(x,t) \ \ in \ \ \Omega(t), \ \ 0 \leq t \leq T, \tag{3.7}$$

$$\sigma = \gamma\kappa, V_n = -\frac{\partial\sigma}{\partial n} \ \ on \ \ \Gamma(t), \ \ 0 \leq t \leq T \tag{3.8}$$

where $\Omega(0) = \Omega_0$ is given, and

$$h \in C^{m+\alpha,m+\alpha/3}(\mathbb{R}^3\times[0,T_0]) \tag{3.9}$$

for some $T_0 > 0$.

Lemma 3.2 ([6]). *Under the assumptions (3.3),(3.9) for some integer $m \geq 0$, there exists a unique solution of (3.7),(3.8) for some $0 < T \leq T_0$, such that*

$$D_\xi D^m_{(\xi,t)}\rho \in C^{3+\alpha,(3+\alpha)/3}(\Gamma_0 \times [0,T])$$

and σ can be extended into a function satisfying:

$$D^2_x D^m_{x,t}\sigma \in C^{\alpha,\alpha/3}(\mathbb{R}^3 \times [0,T]).$$

The second lemma is an extension of Lemma 2.2 of [14] to the case of two time variables. Consider the hyperbolic equation

$$\begin{gathered} W_t + W_s + \vec{b}(x,t)\cdot \nabla_x W = G(x,t,s,W) \\ \textit{for } \ x \in \mathbb{R}^N, 0 < t < T, 0 < s < A, \end{gathered} \tag{3.10}$$

with initial conditions

$$\begin{aligned} W|_{t=0} &= W_0(x,s) \textit{ for } \ x \in \mathbb{R}^3, 0 \leq s \leq A, \\ W|_{s=0} &= W_1(x,t) \textit{ for } \ x \in \mathbb{R}^3, 0 \leq t \leq T, \end{aligned} \tag{3.11}$$

satisfying the compatibility condition

$$W_0(x,0) = W_1(x,0), \ \ x \in \mathbb{R}^3. \tag{3.12}$$

Lemma 3.3. *Assume that*

$$\begin{gathered} \vec{b}, D_x\vec{b} \ \textit{ belong to } \ C^{\alpha_1,\alpha_2}(\mathbb{R}^3 \times [0,T]), \\ G, D_xG, D_sG, D_WG \ \textit{ belong to } \ C^{\alpha_1,\alpha_2,\alpha_2}(\mathbb{R}^3 \times [0,T] \times [0,A]), \\ \textit{for any } \ W = W(x,t,s) \ \textit{ in } \ C^{\alpha_1,\alpha_2,\alpha_2}(\mathbb{R}^3 \times [0,T] \times [0,A]), \\ D_xW_0, D_sW_0 \ \textit{ belong to } \ C^{\alpha_1,\alpha_2}(\mathbb{R}^3 \times [0,A]), \\ D_xW_1, D_tW_1 \ \textit{ belong to } \ C^{\alpha_1,\alpha_2}(\mathbb{R}^3 \times [0,T]). \end{gathered}$$

Then there exists a unique solution of (3.10)-(3.12) such that

$$W \in C^{\alpha_1,\alpha_2,\alpha_2}(\mathbb{R}^3 \times [0,T] \times [0,A]),$$

and

$$W_t, W_s, D_xW \ \textit{ belong to } \ C^{\alpha_1,\alpha_2,\alpha_2}(N_0)$$

where N_0 is the disjoint union

$$\mathbb{R}^3 \times [0,T] \times [0,A] \cap \{t < s\} \bigcup \mathbb{R}^3 \times [0,T] \times [0,A] \cap \{s < t\};$$

furthermore, if

$$||(\vec{b}, D_x\vec{b})||_{\alpha_1,\alpha_2} \le B, \;\; ||D_xW_0, D_sW_1||)||_{\alpha_1,\alpha_2} \le \gamma$$
$$||(G, D_xG, D_tG, D_sG, D_WG||_{\alpha_1,\alpha_2,\alpha_2} \le M \;\; \textit{at} \;\; W = W(x,t,s),$$

then

$$||(D_xW, D_tW, D_sW)||_{\alpha_1,\alpha_2,\alpha_2} \le c_1(B)\gamma + c_2(B,M)T \tag{3.13}$$

where the norm is taken over N_0, and $c_1(B), c_2(B,M)$ are constants depending only on B and (B,M), respectively.

For more details, see [16]. One can define m^{th} order compatibility conditions and, under these conditions, Theorem 1 can be extended to order m.

Theorem 3.1 cannot be expected to hold for all $T > 0$; indeed, for general initial data, even the homogeneous Hele-Shaw problem does not have a (regular) solution for all $t > 0$. However, in the case of radially symmetric data, a global solution does exist.

Consider the case where the initial data are radially symmetric, that is,

$$\Omega_0 \;\; \textit{is a sphere of radius } R_0, \;\; \textit{and}$$
$$w_0 = w_0(r), p_{i0} = p_{i0}(r, s_i), \tag{3.14}$$

where $r = |x|$. We seek a solution which is radially symmetric in x, with

$$\Omega(t) = \{r < R(t)\}.$$

In this special case we can relax the assumptions (3.4),(3.5) for $m = 0$ by assuming that

$$\textit{the conditions (3.4), (3.5) hold with } \; C^{m+1+\alpha} \textit{ replaced by } C^1. \tag{3.15}$$

Theorem 3.4 [16] *Under the assumptions (3.14),(3.15),(3.6) there exists a unique radially symmetric solution of the multiscale tumor model with Darcy's law for all $t > 0$, with $R(t) \in C^1[0,\infty])$, $(D_x\sigma, w)$ in $C^1(\Omega_\infty)$ where $\Omega_\infty = \{(x,t), |x| \le R(t), 0 \le t < \infty\}$, p_i in $C(\Omega_\infty \times [0,A_i])$, and $\partial p_i/\partial r, \partial p_i/\partial s_i$ in $C(\Omega_\infty \times [0,A_i]; t \ne s_i + \sum_{j=1}^{3} n_j A_j$ for any nonnegative integers $n_j)$.*

Note that in the radially symmetric case

$$\vec{v} = \frac{x}{r}u(r,t),$$
$$div(p\vec{v}) = u\frac{\partial p}{\partial r} + \frac{p}{r^2}\frac{\partial}{\partial r}(r^2u) \;\; \textit{if} \;\; p = p(r)$$

$$u(r,t) = \frac{1}{r^2}\int_0^r r^2 H(\vec{Q}, W)dr, \tag{3.16}$$

and the free boundary condition is

$$\frac{dR(t)}{dt} = u(R(t),t). \tag{3.17}$$

The proof of the Theorem 3.4 is based on a slightly different version of Lemma 3.3 and on the a priori estimates

$$|\frac{\partial u}{\partial r}| \leq \textit{const.}, \quad |\frac{1}{R}\frac{dR}{dt}| \leq \textit{const.}$$

which follow from (3.16),(3.17).

4. A Tumor Model Based on Stokes Equation

When the tumor evolves in fluid-like tissue it is more appropriate to use Stokes equation rather than Darcy's law. Indeed, several recent mathematical models on ductal carcinoma in the breast use the Stokes equation, [10]-[12]. If we denote the fluid velocity by $\vec{v} = (v_1, v_2, v_3)$ and the fluid pressure by σ, then the constitutive law is

$$\sigma_{ij} = -\sigma\delta_{ij} + 2\nu\left(e_{ij} - \frac{1}{3}\tilde{\Delta}\delta_{ij}\right)$$

where σ_{ij} is the stress tensor, $\sigma = \frac{1}{3}\sigma_{kk}$ is the fluid pressure, $\vec{v} = (v_1, v_2, v_3)$ is the fluid velocity, $e_{ij} = \frac{1}{2}\left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i}\right)$ is the strain tensor, $\tilde{\Delta} = e_{kk} = div\vec{v}$ is the dilatation, and ν is the viscosity coefficient. If there are no body forces then

$$\sum_{j=1}^{3}\frac{\partial \sigma_{ij}}{\partial x_j} = 0.$$

We can rewrite this equation as the Stokes equation

$$-\nu\Delta\vec{v} + \nabla\sigma - \frac{1}{3}\nu\nabla div\vec{v} = 0 \tag{4.1}$$

where $div\vec{v}$ is given by (2.11). Thus, instead of (2.19) we now have an entirely different relation between $\vec{v}$ and σ.

We proceed to prescribe boundary conditions. The boundary conditions (2.21),(2.22) remain unchanged, but instead of (2.23) we have

$$T\vec{n} = -\gamma\kappa\vec{n} \ \ \textit{on} \ \ \Gamma(t). \tag{4.2}$$

Here T is the stress tensor

$$T = \nu(\nabla\vec{v} + (\nabla\vec{v})^*) - \left(\sigma + \frac{2\nu}{3} div\vec{v}\right) I$$
$$\equiv \tilde{T} - \frac{2\nu}{3}(div\vec{v})I \tag{4.3}$$

where W^* denotes the transpose of a matrix W and I is the unit matrix, or $T = (T_{ij})$ where

$$T_{ij} = \nu\left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i}\right) - \left(\sigma + \frac{2\nu}{3} div\vec{v}\right)\delta_{ij}$$
$$\equiv \tilde{T}_{ij} - \frac{2\nu}{3}(div\vec{v})\delta_{ij}.$$

The initial conditions remain the same as in (2.24),(2.25). However, in order to eliminate the non-uniqueness which results from rigid motions, we need to impose two constraints:

$$\int_{\Omega(t)} \vec{v}dx = A(t), \quad \int_{\Omega(t)} \vec{v}\times\vec{x}dx = \vec{B}(t) \tag{4.4}$$

where $\vec{A}(t), \vec{B}(t)$ are given functions.

Definition 4.1. The multiscale tumor problem with Stokes equation consists of the same system as for Darcy's law with (2.19)-(2.23) replaced by (2.11), (4.1)-(4.4) and $V_n = \vec{v}\cdot\vec{n}$ on $\Gamma(t)$.

Analogously to the regularity assumptions in Section 3 we impose the following conditions:

$$\Gamma_0 \in C^{m+3+\alpha},$$
$$\lambda_i(z) \ \textit{belong to} \ C^{m+2+\alpha}(\mathbb{R}^1),$$
$$K(z,\xi) \ \textit{belongs to} \ C^{m+2+\alpha}(\mathbb{R}^2),$$
$$b(x,t) \ \textit{belongs to} \ C^{m+\alpha}(\mathbb{R}^3\times[0,\infty])$$
$$w_0 \in C^{m+3+\alpha}(\bar{\Omega}_0) \ \textit{and the} \ p_{i0} \ \textit{belong to} \ C^{m+1+\alpha}(\mathbb{R}^3\times[0,A_i]),$$
$$\vec{A}(t), \vec{B}(t) \ \textit{are in} \ C^1[0,\infty]. \tag{4.5}$$

As in [14] [28] we introduce the Lagrangian variable $\vec{\xi}$ where

$$\vec{x} = \vec{\xi} + \int_0^t \vec{u}(\vec{\xi},\tau)d\tau = X(\vec{\xi},t), \quad \vec{\xi}\in\Omega_0$$

and

$$\vec{u}(\vec{\xi},t) = \vec{v}(X(\vec{\xi},t), \quad \pi(\xi,t) = \sigma(X(\xi,t),t))$$

and, for simplicity, write ξ instead of $\vec{\xi}$.

We can now state an existence theorem similar to Theorem 3.1.

Theorem 4.2 *Assume that the conditions in (4.5) are satisfied for* $m = 0$ *and that the first compatibility condition holds (as in (3.6)). Then the multiscale tumor model with Stokes equation has a unique solution for some time interval* $0 \le t \le T$ $(T > 0)$ *such that the free boundary* $\Gamma(t)$ *belongs to* $C([0,T]; C^{3+\alpha}) \cap C^1([0,T]; C^{2+\alpha})$ *and, in Lagrangian coordinates* (ξ, t)*, the function* $\vec{u}(\xi,t) \equiv \vec{v}(x,t)$ *belongs to*

$$C([0,T]; C^{2+\alpha}(\Omega_0)) \cap C^1([0,T]; C^{1+\alpha}(\Omega_0)),$$

$\hat{w}(\xi,t) \equiv w(x,t)$ *belongs to*

$$C([0,T]; C^{2+\alpha}(\Omega_0)) \cap C^1([0,T]; C^{\alpha}(\Omega_0)),$$

the pressure $\pi(\xi,t) \equiv \sigma(x,t)$ *belongs to*

$$C([0,T]; C^{1+\alpha}(\Omega_0)) \cap C^1([0,t]; C^{\alpha}(\Omega_0)),$$

and the $\hat{p}_i(\xi,t,s_i) \equiv p_i(x,t,s_i)$ *belong to*

$$C^1([0,T] \times [0,A_i]; C^{\alpha}(\Omega_0)).$$

In order to prove the theorem we need some preparations. Consider the system (4.1), (4.2), (2.11) where $H(\vec{Q}, w)$ can actually be any prescribed function, g, so that

$$div\vec{v} = g. \tag{4.6}$$

The procedure for proving Theorem 4.2 is to first solve (4.1), (4.2), (4.6) with the constraints (4.4), and then use this result with $g = H(\vec{Q}, w)$ in order to define a new function $\tilde{Q}$ and prove that the mapping $Q \to \tilde{Q}$ together with the corresponding mapping of $p_i \to \tilde{p}_i$, has a unique fixed point.

In order to solve (4.1), (4.2), (4.6) with the constraints (4.4) we introduce a basis $\vec{w}_1(x), \cdots, \vec{w}_6(x)$ in the six-dimensional space V_0 generated by the rigid motions $\vec{a} + \vec{b} \times \vec{x}$ where $\vec{a}, \vec{b}$ are arbitrary vectors in $\mathbb{R}^3$,

$$\vec{w}_1 = (1,0,0), \vec{w}_2 = (0,1,0), \vec{w}_3 = (0,0,1), \vec{w}_4 = (0,-x_3,x_2),$$
$$\vec{w}_5 = (x_3,0,-x_1), \vec{w}_6 = (-x_2,x_1,0).$$

We can then rewrite the constraints (4.4) in the form

$$(\vec{v}, \vec{w}_k) = M_k(t) \tag{4.7}$$

where $(\vec{v}, \vec{w}_k) = \int_{\Omega(t)} \vec{v}(x,t) \cdot \vec{w}_k(x,t)dx$, and where the functions $M_k(t)$ are linearly dependent on the components of $\vec{A}(t), \vec{B}(t)$. Note that

$$div\vec{w}_j = 0 \ \textit{for all} \ \ j, \tag{4.8}$$

$$\int_{\Gamma(t)} \kappa \vec{w}_j \cdot \vec{n} = 0 \ \textit{for all} \ \ j \tag{4.9}$$

by [[19]; Lemma 6.1], and

$$\int_{\Gamma(t)} \vec{w}_j \cdot \vec{n} = 0 \ \textit{for all} \ \ j$$

since

$$\int_{\Gamma(t)} \vec{w}_j \cdot \vec{n} = \int_{\Omega(t)} div \vec{w}_j = 0 \ \textit{by} \ \ (4.8).$$

The system (4.1), (4.2), (2.11) is an elliptic system in the Agmon-Douglas-Nirenberg sense, but the homogeneous system, with $div\vec{v} = g = 0$, has the six-dimensional null space V_0. In order to ensure uniqueness we need to impose the constraints (4.4), or (4.7), and a convenient way of doing it is to follow [28], by using the Schmidt lemma [[29]:Section 21]. Accordingly, we replace the differential equation (4.1) by

$$-\nu\Delta\vec{v} + \ell(\vec{v}) + \nabla\sigma - \frac{1}{3}\nu\nabla(div\vec{v}) = 0 \tag{4.10}$$

where

$$\ell(\vec{v}) = \sum_{k=1}^{6}[(\vec{v}, \vec{w}_k) - M_k(t)]\vec{w}_k(x). \tag{4.11}$$

The the system (4.10),(4.2),(2.11) can be solved by the theory of elliptic systems. We can now follow the proof of Theorem 3.1 in [14] but apply Lemma 3.3 of the present paper instead of Lemma 3.1 of [14]. In this way we obtain a unique solution to a modified tumor model where (4.1),(4.4) have been replaced by (4.10),(4.11).

Clearly every solution of the tumor model is also a solution of the modified tumor model. In order to complete the proof of Theorem 4.2 it suffices to prove the converse:

Lemma 4.3. *Every solution of the modified tumor model is a solution of the tumor model.*

Proof. By integration by parts we have, for any functions $\vec{v}, \vec{w}, \sigma$,

$$\frac{\nu}{2}\int_{\Omega(t)} \sum \left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i}\right)\left(\frac{\partial w_i}{\partial x_j} + \frac{\partial w_j}{\partial x_i}\right) - \int_{\Omega(t)} \sigma div\vec{w}$$

$$= \int_{\Omega(t)} (-\nu\Delta\vec{v} + \nabla\sigma)\cdot\vec{w} - \int_{\Omega(t)} \nu\nabla(div\vec{v})\cdot\vec{w} + \int_{\Gamma(t)} (\tilde{T}\vec{n})\cdot\tilde{w};$$

here we have integrated out $\partial w_k/\partial x_m$ in both integrals of the left-hand side. Taking for $(\vec{v}, \sigma)$ the solution of the modified tumor model and $\vec{w} = \vec{w}_\ell$, and using (4.8),(4.10), we obtain

$$\int_{\Omega(t)} \ell(\vec{v}) \cdot w_\ell = \int_{\Omega(t)} \left(-\frac{2\nu}{3}\right) \nabla(div\vec{v}) \cdot \vec{w}_\ell + \int_{\Gamma(t)} (\tilde{T}\vec{n}) \cdot \vec{w}_\ell$$
$$= \int_{\Gamma(t)} (T\vec{n}) \cdot \vec{w}_\ell = -\gamma \int_{\Gamma(t)} \kappa\vec{n} \cdot \vec{w}_\ell = 0 \ \ by \ \ (4.9).$$

Hence

$$\sum_{k=1}^{6} [(\vec{v}, \vec{w}_k) - M_k(t)]\vec{w}_k \cdot \vec{w}_\ell = 0 \ \ for \ \ \ell = 1, \cdots, 6.$$

It follows that the expressions in brackets vanishes. Thus the constraints (4.7), or equivalently (4.4), are satisfied.

Remark 4.4. If the assumptions of Theorem 4.2 hold for $m \geq 0$ and the corresponding compatibility conditions of order m are satisfied, then the solution has additional regularity; in particular,

$$\Gamma(t) \in C([0,T]; C^{m+3+\alpha}) \cap C^1([0,T]; C^{m+2+\alpha}).$$

Consider next the radially symmetric case as in Theorem 3.4. If we set

$$\vec{v} = G(r,t)\vec{x}$$

then (2.11) becomes

$$div\vec{v} = rG_r + 3G = f(r) \ \ where \ \ f(r) = H(\vec{Q}, w),$$

(4.1) takes the form

$$-\nu \left(\Delta G + \frac{2}{r} G_r\right) + \frac{1}{r}\sigma_r = \frac{\nu}{3} \cdot H(\vec{Q}, w),$$

the boundary condition (4.2) becomes

$$\frac{4}{3}\nu r G_r - \sigma = -\frac{\gamma}{R(t)} \ \ on \ \ r = R(t),$$

and

$$\frac{1}{R}\frac{dR}{dt} = G(R(t), t).$$

Since the origin is fixed, there is no need to impose any constraints. Furthermore, the introduction of the Lagrangian variable is accomplished by a simple change of variables

$$r' = \frac{r}{R(t)}$$

which converts the free boundary into a fixed boundary, but only slightly complicates the PDE system. Proceeding analogously to the proof of Theorem 3.4, and using Lemma 3.3, we can establish the following theorem.

Theorem 4.5 *Under the assumptions of Theorem 3.4 there exists a unique radially symmetric solution of the multiscale tumor model with Stokes equation, for all $t > 0$, with $R(t) \in C^1[0,\infty]$, and with the same regularity of σ, p_i as in Theorem 3.4.*

5. Introducing Angiogenesis

When a tumor grows to a size of a few millimeters it becomes hypoxic and it begins to secrete Tumor Angiogenic Factor (TAF). TAF induces existing blood vessels to grow new vessels in a process called angiogenesis. The new blood vessels move into the tumor, by chemotaxis, and they supply the tumor with oxygen (and other nutrients) that enable it to continue to grow. We shall represent the density of the the blood capillary system by the density e of the endothelial cells (EC), i.e., by the cells that form the inner layer of the capillaries. Thus, we need to replace the transmission function $b(r,t)$ in the oxygen equation (2.18) by $b(r,t,e)$. The mathematical model needs also to include the proteolytic enzyme that "softens" the capillary walls and enables the formation of capillary tips and sprouts from the existing vasculature, and fibronectin and collagen in the extracellular matrix.

There are quite a number of mathematical models of angiogenesis. We refer, in particular, to [22], [24] and the references therein. Here we shall use a somewhat simple model, based on [22], [24], which includes the main ingredients from these papers.

Set

a=concentration of TAF,
f=concentration of fibronectin,
c=concentration of proteolytic enzyme,
c_a=active forms of c.

Then

$$c_a = \frac{c}{1+\alpha_1 f}, \tag{5.1}$$

$$\frac{\partial a}{\partial t} = D_a \nabla^2 a - \frac{\alpha_2 a}{1+\alpha_3 a} e, \tag{5.2}$$

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c + \frac{\alpha_2 a}{1+\alpha_3 a} e - \alpha_4 c, \tag{5.3}$$

$$\frac{\partial f}{\partial t} = D_f \nabla^2 f + \alpha_5 f \left(1 - \frac{f}{f_0}\right) - \frac{\alpha_6 f}{1+\alpha_7 f} c_a, \tag{5.4}$$

$$\frac{\partial e}{\partial t} = D_e \nabla \cdot \left[\nabla \ell n \frac{e}{\tau(c_a, f)} \right], \tag{5.5}$$

where

$$\tau(c_a, f) = \left(\frac{c_a + \beta_1}{c_a + \beta_2} \right)^{\gamma_1} \left(\frac{f + \delta_1}{f + \delta_2} \right)^{\gamma_2} \tag{5.6}$$

is a chemotactic function.

The diffusion coefficients D_c, D_f are extremely small and, in fact, do not appear in [22][24]. The PDE system (5.1)-(5.6) needs to be supplemented with boundary conditions and initial conditions. The boundary conditions on $\Gamma(t)$ may be taken, for instance, as no-flux conditions on a, c, f, and $e = const.$

Definition 5.1. We shall refer to the tumor model with Darcy's law coupled with (5.1)-(5.6) and corresponding initial and boundary conditions, and with $b = b(r, t, e)$ in the oxygen equation (2.18) as the *vascularized tumor model* with Darcy's law. Similarly we define the vascularized tumor model with Stokes' law.

The proofs of Theorems 3.1, 3.4 and 4.1, 4.3 extend to the vascularized tumor problem. Indeed, using parabolic estimates we can treat the additional system (5.1)-(5.6) in the same way we treat the parabolic oxygen equation.

As the vascularized tumor grows into the stroma, tumor cells may invade the blood vessel, resulting in metastasis. In modeling tumor invasion into the stroma, one needs to introduce an additional set of variables (and PDEs) coupled to the variables already introduced above; such variables are matrix metalloproteinase (MMP), urokinase plasminogen activator (UPA), plasminogen activator inhibitor (PAI), and plasmin; see Lolas [23]. The inclusion of the corresponding (parabolic) differential equations into the model does not introduce any new difficulties in the proof of an existence theorem.

6. Properties of the Free Boundary

In this section we consider the radially symmetric tumor model. Consider first the model with Darcy's law and assume that there is no angiogenesis or, more precisely, that the vasculature does not enter into the tumor, so that $b \equiv 0$ in the oxygen equation (2.18)

Theorem 6.1 ([17]). *If $b \equiv 0$ in the oxygen equation (2.18) then*

$$R(t) \leq const. < \infty \ \textit{for all} \ \ t > 0.$$

We may interpret this result as a statement asserting that without angiogenesis the tumor will remain confined, even if the genes which control $K(w, Q)$ are mutated.

We next consider the case of vascularized tumor, but instead of incorporating the system of PDEs (5.1)-(5.6) into the model we assume, more simply, that the transmission coefficient $b(r, t, e)$

is such that the oxygen level remains uniformly above the necrotic level w_* and, therefore, the $\lambda_j(w)$ are positive functions, although $\lambda_j(w)$ may become small at hypoxic levels. Then

$$\lambda_j(w) \geq \lambda > 0 \ \textit{for} \ \ j = 1, 2, 3 \ \ \textit{and for all} \ \ w. \tag{6.1}$$

We shall assume that

$$(1-\mu_1)(1-\mu_2)e^{-\lambda A} > 1, (1-\mu_1)(1-\mu_2)e^{-\lambda_0 A_0}e^{-\lambda A} < 1 \tag{6.2}$$

where $A = A_1 + A_2 + A_3$. Then there exists a unique $\beta^* \in (0, 1-\mu_1)$ such that

$$(1-\mu_2)(1-\mu_1-\beta^*)e^{-\lambda A} + \beta^*(1-\mu_2)e^{-\lambda_0 A_0}e^{-\lambda A} = 0$$

We assume that both SMAD and APC are mutated so that $K(w, Q)$ is a constant and, in fact, a small constant β:

Theorem 6.2 ([18]). *If (6.1), (6.2) hold and $K(w, Q) \equiv \beta$ where $0 < \beta < \beta^*$, then*

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

This result suggests the onset of cancer for a vascularized tumor with SMAD and APC mutated. On the other hand if only one of these two genes is mutated and the other gene (say APC) is fully active and can function as a control function $\beta(t)$ which depends on the values of $Q(s)$ where $Q(s)$ is the total mass of all cells in phases G_1, S, G_2, M at time s, for $s \leq t$, then, as proved in [18], $\beta(t)$ can be chosen in such a way that

$$R(t) \leq const. < \infty \ \ \textit{for all} \ \ t > 0. \tag{6.3}$$

Theorems 6.1, 6.2 and the assertion (6.3) (for a suitable choice of control $\beta(t)$) are valid also for the radially symmetric tumor model with Stokes law, and the proof is essentially the same.

It would be interesting to extend Theorem 6.2 to the vascularized tumor model where instead of assuming that (6.1) holds we assume that

$$\lambda_j(w) = \begin{cases} > 0 & \text{if } w > w_* \\ < 0 & \text{if } w < w_*. \end{cases}$$

and $K(w, Q) \equiv const. = \beta$ where β is small.

Remark 6.3. The existence of radially symmetric stationary solutions to the multiscale tumor model is wide open, except for one special case in [17]. The question whether a stationary spherical solution, if existing, is asymptotically stable, or whether it gives rise to symmetry-breaking bifurcation branches of stationary solutions is another challenging open problem; these questions have been considered for much simpler tumor models (see review article [16]).

Remark 6.4. So far we assumed that all the cells have the same mutations, so they all abide by the same function $K(w, Q)$. The results of Sections 3-5 can be extended to the case where we have two (or more) populations of cells, each with its own set of mutations, as in modeled in [15].

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