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A hyperbolic free boundary problem modeling tumor growth

SHANGBIN CUI†
*Department of Mathematics, Zhongshan University,
Guangzhou, Guangdong 510275, People's Republic of China*

AND

AVNER FRIEDMAN‡
*Department of Mathematics, The Ohio State University,
231 West 18th Avenue, Columbus, OH 43210-1174, USA*

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In this paper we study a free boundary problem modeling the growth of tumors with three cell populations: proliferating cells, quiescent cells and dead cells. The densities of these cells satisfy a system of nonlinear first order hyperbolic equations in the tumor, with tumor surface as a free boundary. The nutrient concentration satisfies a diffusion equation, and the free boundary $r = R(t)$ satisfies an integro-differential equation. We consider the radially symmetric case of this free boundary problem, and prove that it has a unique global solution for all the three cases $0 < K_R < \infty$, $K_R = 0$ and $K_R = \infty$, where K_R is the removal rate of dead cells. We also prove that in the cases $0 < K_R < \infty$ and $K_R = \infty$ there exist positive numbers δ_0 and M such that $\delta_0 \leqslant R(t) \leqslant M$ for all $t \geqslant 0$, while $\lim_{t\to\infty} R(t) = \infty$ in the case $K_R = 0$.

Keywords: Tumor growth; proliferating cells; quiescent cells; dead cells; free boundary problem; global solution.

1. The model

A variety of PDE models for tumor growth have been developed in the last three decades. These models are based on mass conservation laws and on reaction-diffusion processes for cell densities and nutrient concentrations within the tumor. The surface of the tumor is a free boundary, and one seeks to determine both the tumor's region and the solution of the differential equations within the tumor. Some models assume that all cells in the tumor are in proliferating state, while other models include cells in quiescent and/or in necrotic state. In some of the latter models, the cells in different states are assumed to be mixed together, while in other models it is assumed that cells in different states occupy separate regions in the tumor: The proliferating cells occupy a region near the tumor's surface, the necrotic cells lie in the tumor's central core, and the quiescent cells reside in an intermediate region; the interfaces between these regions are then also free boundaries.

We refer to [1, 5–9, 17, 18, 23] and references therein for models which are based on reaction-diffusion equations, and to [4, 19, 20, 22, 24] for models which include hyperbolic equations; the hyperbolic equations arise from mass conservation laws of concentrations of cells. Some of these articles include numerical results. Rigorous mathematical analysis including existence,

†Email: mcinst@zsu.edu.cn
‡Email: afriedman@mbi.osu.edu

uniqueness, and stability theorems, as well as properties of the free boundaries, have been obtained in [2, 3, 10–16].

In this paper we deal with a mathematical model which was introduced by Pettet, Please, Tindall and McElwain [20]. This model includes densities P, Q and D of proliferating, quiescent and dead (necrotic) cells respectively, and concentration C of nutrients. The cells in different states are assumed to be mixed within the tumor, and to have the same size. We also assume that the tumor is uniformly packed with cells, so that

$$P + Q + D = \text{const} \equiv N. \tag{1.1}$$

Due to proliferation of cells and to removal of necrotic cells, there is a continuous movement of cells within the tumor. We shall represent this movement by a velocity field $\vec{v}$. We treat the tumor tissue as a porous medium so that, by Darcy's law,

$$\vec{v} = \nabla\sigma, \quad \sigma \text{ pressure}. \tag{1.2}$$

Next we assume that living cells can change from proliferating state to quiescent state at a rate $\bar{K}_Q(C)$, and from quiescent state to proliferating state at a rate $\bar{K}_P(C)$. Clearly,

- $\bar{K}_Q(C)$ is increasing in C, since the tumor grows (i.e., proliferation increases) if the supply of nutrients increases, and similarly,
- $\bar{K}_P(C)$ is decreasing in C.

We also assume that quiescent cells become necrotic at a rate $\bar{K}_D(C)$, where

- $\bar{K}_D(C)$ is decreasing in C,

i.e., the death rate increases as the supply of nutrients decreases.

The proliferating cells also undergo proliferation as well as apoptosis (natural death). We denote the death rate by $\bar{K}_A(C)$ and the proliferation rate by $\bar{K}_B(C)$. Then,

- $\bar{K}_A(C)$ is decreasing in C, whereas
- $\bar{K}_B(C)$ is increasing in C.

Also, since the rate of proliferation is larger than the rate of apoptosis,

- $\bar{K}_B(C) > \bar{K}_A(C)$.

We finally denote by K_R the rate of removal of dead cells from the tumor; this rate is a nonnegative constant independent of C.

We assume that C satisfies a diffusion equation which, for simplicity, we take to be

$$\nabla^2 C - \lambda C = 0 \quad \text{in } \Omega(t) \quad (\lambda > 0), \tag{1.3}$$

and

$$C = C_0 \quad \text{on } \partial\Omega(t), \tag{1.4}$$

where $\Omega(t)$ is the tumor region at time t. The mass conservation laws for the densities of proliferating cells, quiescent cells and dead cells in $\Omega(t)$ take the following form:

$$\frac{\partial P}{\partial t} + \operatorname{div}(P\vec{v}) = [\bar{K}_B(C) - \bar{K}_Q(C) - \bar{K}_A(C)]P + \bar{K}_P(C)Q, \tag{1.5}$$

$$\frac{\partial Q}{\partial t} + \operatorname{div}(Q\vec{v}) = \bar{K}_Q(C)P - [\bar{K}_P(C) + \bar{K}_D(C)]Q, \tag{1.6}$$

$$\frac{\partial D}{\partial t} + \operatorname{div}(D\vec{v}) = \bar{K}_A(C)P + \bar{K}_D(C)Q - K_R D. \tag{1.7}$$

If we add (1.5)–(1.7) and use (1.1), (1.2), we obtain an equation for the pressure σ:

$$N\nabla^2\sigma = \bar{K}_B(C)P - K_R D. \tag{1.8}$$

Clearly, (1.7) may be replaced by (1.8). If we replace D by $N - P - Q$ and set

$$\bar{c} = C/C_0, \quad \bar{p} = P/N, \quad \bar{q} = Q/N,$$

we arrive at the following system of equations:

$$\nabla^2\bar{c} - \lambda\bar{c} = 0 \quad \text{in } \Omega(t), \tag{1.9}$$

$$\bar{c} = 1 \quad \text{on } \partial\Omega(t), \tag{1.10}$$

$$\frac{\partial \bar{p}}{\partial t} + \operatorname{div}(\bar{p}\nabla\sigma) = [K_B(\bar{c}) - K_Q(\bar{c}) - K_A(\bar{c})]\bar{p} + K_P(\bar{c})\bar{q} \quad \text{in } \Omega(t), \tag{1.11}$$

$$\frac{\partial \bar{q}}{\partial t} + \operatorname{div}(\bar{q}\nabla\sigma) = K_Q(\bar{c})\bar{p} - [K_P(\bar{c}) + K_D(\bar{c})]\bar{q} \quad \text{in } \Omega(t), \tag{1.12}$$

$$\nabla^2\sigma = -K_R + [K_B(\bar{c}) + K_R]\bar{p} + K_R\bar{q} \quad \text{in } \Omega(t) \tag{1.13}$$

where

$$K_i(\bar{c}) = \bar{K}_i(C_0\bar{c}) \quad \text{for } i = A, B, D, P, Q.$$

We assume that the pressure σ on the surface of the tumor is equal to the surface tension (see Greenspan [18]), that is,

$$\sigma = \gamma\kappa \quad \text{on } \partial\Omega(t) \quad (\gamma > 0), \tag{1.14}$$

where κ is the mean curvature.

The motion of the free boundary is given by the continuity equation

$$\vec{v}\cdot\vec{n} = V_n, \quad \text{or} \quad \frac{\partial\sigma}{\partial\vec{n}} = V_n \quad \text{on } \partial\Omega(t), \tag{1.15}$$

where $\vec{n}$ is the outward normal and V_n is the velocity of the free boundary in the outward normal direction.

Given initial conditions

$$\Omega(0), \quad p(x,0), \quad q(x,0), \tag{1.16}$$

we would like to determine the family of domains $\Omega(t)$ and functions $p(x,t)$, $q(x,t)$, $c(x,t)$ and $\sigma(x,t)$ satisfying the system (1.9)–(1.15).

In this paper we assume that the data (1.16) are radially symmetric and consider radially symmetric solutions. We note that tumors grown *in vitro* are typically of spherical shape, which makes the study of radially symmetric solutions quite relevant.

In §2 we reformulate the radially symmetric problem as a system of equations in a fixed domain. In §§3–4 we prove global existence and uniqueness of the solution. The rest of the paper is devoted to establishing uniform bounds from above and below for the free boundary.

2. Reformulation of the problem

We consider the radially symmetric case and set

$$\vec{v} = \frac{x}{|x|}\bar{u}, \quad \Omega(t) = \{r < R(t)\} \ (r = |x|).$$

Then the system (1.9)–(1.15) becomes:

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial \bar{c}}{\partial r}\right) = \lambda\bar{c} \quad (0 < r < R(t),\ t > 0), \tag{2.1}$$

$$\frac{\partial \bar{c}}{\partial r}(0,t) = 0, \quad \bar{c}(R(t),t) = 1 \quad (t > 0), \tag{2.2}$$

$$\frac{\partial \bar{p}}{\partial t} + \bar{u}\frac{\partial \bar{p}}{\partial r} = [K_B(\bar{c}) - K_Q(\bar{c}) - K_A(\bar{c})]\bar{p} + K_P(\bar{c})\bar{q} - [(K_B(\bar{c}) + K_R)\bar{p} + K_R\bar{q} - K_R]\bar{p} \quad (0 \leqslant r \leqslant R(t),\ t > 0), \tag{2.3}$$

$$\frac{\partial \bar{q}}{\partial t} + \bar{u}\frac{\partial \bar{q}}{\partial r} = K_Q(\bar{c})\bar{p} - [K_P(\bar{c}) + K_D(\bar{c})]\bar{q} - [(K_B(\bar{c}) + K_R)\bar{p} + K_R\bar{q} - K_R]\bar{q} \quad (0 \leqslant r \leqslant R(t),\ t > 0), \tag{2.4}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2\bar{u}) = [K_B(\bar{c}) + K_R]\bar{p} + K_R\bar{q} - K_R \quad (0 < r \leqslant R(t),\ t > 0), \tag{2.5}$$

$$\bar{u}(0,t) = 0 \quad (t > 0), \tag{2.6}$$

$$\frac{\mathrm{d}R(t)}{\mathrm{d}t} = \bar{u}(R(t),t) \quad (t > 0) \tag{2.7}$$

with initial data

$$R(0), \quad \bar{p}(r,0), \quad \bar{q}(r,0).$$

In writing up this paper we found it convenient (but it is perhaps a matter of taste) to transform the above system in the unknown domain $\{(r,t) : 0 < r < R(t),\ t > 0\}$ into a system in the fixed domain $\{(r,t) : 0 < r < 1,\ t > 0\}$. To do that we first note that, for given $R(t)$, the solution of (2.1) and (2.2) is given by

$$\bar{c}(r,t) = \frac{R(t)\sinh(\sqrt{\lambda}r)}{r\sinh(\sqrt{\lambda}R(t))} = c\left(\frac{r}{R(t)}, R(t)\right), \tag{2.8}$$

where

$$c(r,R) = \frac{\sinh(\sqrt{\lambda}Rr)}{r\sinh(\sqrt{\lambda}R)} \quad (0 < r \leqslant 1,\ R > 0), \qquad c(0,R) = \frac{\sqrt{\lambda}R}{\sinh(\sqrt{\lambda}R)} \quad (R > 0). \tag{2.9}$$

We introduce the functions

$$p(r,t) = \bar{p}(rR(t),t), \quad q(r,t) = \bar{q}(rR(t),t), \quad u(r,t) = \frac{\bar{u}(rR(t),t)}{R(t)} \quad (0 \leqslant r \leqslant 1,\ t \geqslant 0).$$

Then we obtain the following system of equations:

$$\frac{\partial p}{\partial t} + v\frac{\partial p}{\partial r} = [K_B(c) - K_Q(c) - K_A(c)]p + K_P(c)q - [(K_B(c) + K_R)p + K_Rq - K_R]p \quad (0 \leqslant r \leqslant 1,\ t > 0), \tag{2.10}$$

$$\frac{\partial q}{\partial t} + v\frac{\partial q}{\partial r} = K_Q(c)p - [K_P(c) + K_D(c)]q - [(K_B(c) + K_R)p + K_Rq - K_R]q \quad (0 \leqslant r \leqslant 1,\ t > 0), \tag{2.11}$$

where $c = c(r, R(t))$, $c(r, R)$ as in (2.9), and

$$v(r,t) = u(r,t) - ru(1,t) \quad (0 \leqslant r \leqslant 1,\ t > 0), \tag{2.12}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u) = [K_B(c) + K_R]p + K_R q - K_R \quad (0 < r \leqslant 1,\ t > 0), \tag{2.13}$$

$$u(0,t) = 0 \quad (t > 0), \tag{2.14}$$

$$\frac{\mathrm{d}R(t)}{\mathrm{d}t} = R(t)u(1,t) \quad (t > 0), \tag{2.15}$$

with initial data

$$R(0) = R_0, \quad p(r,0) = p_0(r), \quad q(r,0) = q_0(r) \quad (0 \leqslant r \leqslant 1), \tag{2.16}$$

where

$$R_0 > 0, \quad p_0(r) \geqslant 0, \quad q_0(r) \geqslant 0, \quad p_0(r) + q_0(r) \leqslant 1 \quad (0 \leqslant r \leqslant 1). \tag{2.17}$$

In what follows it will be useful to rewrite (2.13) in the integrated form

$$u(r,t) = \frac{1}{r^2}\int_0^r [(K_B(c(\rho, R(t))) + K_R)p(\rho,t) + K_R q(\rho,t) - K_R]\rho^2\,\mathrm{d}\rho, \tag{2.18}$$

and, correspondingly, rewrite (2.15) in the form

$$\frac{\mathrm{d}R(t)}{\mathrm{d}t} = R(t)\int_0^1 [(K_B(c(r, R(t))) + K_R)p(r,t) + K_R q(r,t) - K_R]r^2\,\mathrm{d}r. \tag{2.19}$$

It will also be useful to note that the normalized concentration of dead cells $d \equiv 1 - p - q$ satisfies the equation

$$\frac{\partial d}{\partial t} + v\frac{\partial d}{\partial r} = K_A(c)p + K_D(c)q - [K_B(c)p - K_R d + K_R]d \quad (0 \leqslant r \leqslant 1,\ t > 0). \tag{2.20}$$

In §3 we establish local existence and uniqueness for the system (2.10)–(2.16), and in §4 we prove global existence. The rest of the paper is devoted to the derivation of bounds on the free boundary $r = R(t)$. In §§5–6 we prove that in the case $0 < K_R < \infty$ there exist positive numbers δ_0 and M (depending on the initial data) such that $\delta_0 \leqslant R(t) \leqslant M$ for all $t \geqslant 0$. In §7 we extend the results of §§3–6 to the extreme case where the dead cells are instantly removed from the tumor, that is, $D \equiv 0$ or, formally, $K_R = \infty$. Finally, in §8 we consider the other extreme case where the dead cells are not removed at all from the tumor, that is, $K_R = 0$, and prove that $R(t) \nearrow \infty$ as $t \to \infty$. The asymptotic behavior of the solution as $t \to \infty$ remains to be explored.

To end this section we note that, by (2.9), $c(r, R)$ is strictly increasing in r and strictly decreasing in R, and

$$\begin{aligned} &\lim_{R\to 0} c(r,R) = 1 \quad \text{uniformly for } 0 \leqslant r \leqslant 1,\\ &\lim_{R\to\infty} c(r,R) = \begin{cases} 0 & \text{if } 0 \leqslant r < 1,\\ 1 & \text{if } r = 1. \end{cases} \end{aligned} \tag{2.21}$$

These properties will be frequently used later on.

3. Local existence and uniqueness

Throughout this paper we make the following assumptions:

(**a**) $K_i(c)$ $(i = A, B, D, P, Q)$ are nonnegative and continuously differentiable for $0 \leqslant c \leqslant 1$, and

$$K_B(c) > K_A(c), \quad K_B'(c) > 0, \quad K_P'(c) > 0 \quad (0 \leqslant c \leqslant 1),$$
$$K_B(0) = K_P(0) = 0,$$
$$K_A'(c) \leqslant 0, \quad K_D'(c) < 0, \quad K_Q'(c) < 0, \quad K_B'(c) + K_D'(c) > 0 \quad (0 \leqslant c \leqslant 1),$$
$$K_A(1) = K_D(1) = K_Q(1) = 0;$$

(**b**) $p_0(r)$ and $q_0(r)$ are continuously differentiable for $0 \leqslant r \leqslant 1$, and (2.17) holds.

The condition $K_B'(c) + K_D'(c) > 0$ is based on experimental data [20]. In this section and the next one we assume that $0 \leqslant K_R < \infty$.

We shall denote by **s** the vector (p, q), by $f_1(r, R, \mathbf{s})$ and $f_2(r, R, \mathbf{s})$ the right-hand sides of (2.10) and (2.11), respectively, and by **f** the vector (f_1, f_2). We shall also set

$$g(r, R, \mathbf{s}) = (K_B(c(r, R)) + K_R)p + K_R q - K_R.$$

Then the system of equations (2.10), (2.11) and (2.18) takes the following simpler form:

$$\frac{\partial \mathbf{s}(r,t)}{\partial t} + v(r,t)\frac{\partial \mathbf{s}(r,t)}{\partial r} = \mathbf{f}(r, R(t), \mathbf{s}(r,t)) \quad (0 \leqslant r \leqslant 1,\ t > 0), \tag{3.1}$$

$$u(r,t) = \frac{1}{r^2}\int_0^r g(\rho, R(t), \mathbf{s}(\rho,t))\rho^2\,\mathrm{d}\rho \quad (0 < r \leqslant 1,\ t > 0). \tag{3.2}$$

Since $v(0,t) = v(1,t) = 0$ for all $t \geqslant 0$, the lines $r = 0$ and $r = 1$ in the (r,t)-plane are characteristic curves of the hyperbolic equations in (3.1); hence all the characteristic curves starting from points in the region $0 < r < 1$, $t \geqslant 0$ remain in this region for $t > 0$, and they do not intersect each other (see the proof of Theorem 3.1).

To prove local existence we introduce, for a given $T > 0$, the space X_T of pairs of functions $(R(t), \mathbf{s}(r,t))$ defined for $0 \leqslant r \leqslant 1$, $0 \leqslant t \leqslant T$ and satisfying the following conditions:

(i) $R(t) \in C[0,T]$, $R(0) = R_0$, and

$$|R(t) - R_0| \leqslant \delta \quad (0 \leqslant t \leqslant T) \tag{3.3}$$

where $0 < \delta < R_0$ is an arbitrary but fixed number (one may take, for instance, $\delta = R_0/2$);

(ii) $\mathbf{s}(r,t) \in C([0,1] \times [0,T])$, $\mathbf{s}(r,0) = \mathbf{s}_0(r) \equiv (p_0(r), q_0(r))$, and

$$|\mathbf{s}(r,t)| \leqslant \max_{0 \leqslant r \leqslant 1}(|\mathbf{s}_0(r)| + |\mathbf{s}_0'(r)|) + 1 \equiv M_0 + 1 \quad (0 \leqslant r \leqslant 1,\ 0 \leqslant t \leqslant T). \tag{3.4}$$

We take the metric d in X_T to be the uniform metric, i.e.,

$$d((R_1, \mathbf{s}_1), (R_2, \mathbf{s}_2)) = \max_{0 \leqslant t \leqslant T}|R_1(t) - R_2(t)| + \max_{0 \leqslant r \leqslant 1,\, 0 \leqslant t \leqslant T}|\mathbf{s}_1(r,t) - \mathbf{s}_2(r,t)|.$$

It is obvious that X_T is a complete metric space.

We shall prove the existence of a local solution by using the contraction mapping theorem for a mapping $\mathcal{F}\colon X_T \to X_T$, which is defined as follows:

Given a pair $(R, \mathbf{s}) \in X_T$, define $u(r,t)$ and $v(r,t)$ by (3.2) and (2.12), respectively, and consider the initial value problems:

$$\frac{\partial \tilde{\mathbf{s}}(r,t)}{\partial t} + v(r,t)\frac{\partial \tilde{\mathbf{s}}(r,t)}{\partial r} = \mathbf{f}(r, R(t), \tilde{\mathbf{s}}(r,t)) \quad \text{for } 0 \leqslant r \leqslant 1,\ 0 < t \leqslant T, \tag{3.5}$$

$$\tilde{\mathbf{s}}(r,0) = \mathbf{s}_0(r,0) \quad \text{for } 0 \leqslant r \leqslant 1, \tag{3.6}$$

$$\frac{\mathrm{d}\tilde{R}(t)}{\mathrm{d}t} = \tilde{R}(t)u(1,t) \quad \text{for } 0 < t \leqslant T, \tag{3.7}$$

$$\tilde{R}(0) = R_0. \tag{3.8}$$

Clearly, the problem (3.7)–(3.8) has a unique solution $\tilde{R}(t) \in C^1[0,T]$; in fact,

$$\tilde{R}(t) = R_0 \exp\left(\int_0^t u(1,\tau)\,\mathrm{d}\tau\right), \qquad 0 \leqslant t \leqslant T. \tag{3.9}$$

Since

$$|g(r, R(t), \mathbf{s}(r,t))| \leqslant (K_B(1) + K_R)(M_0+1) + K_R(M_0+1) + K_R \equiv M_1,$$

we have $|u(1,t)| \leqslant M_1/3$, which implies that

$$|\tilde{R}(t) - R_0| \leqslant \tfrac{1}{3}R_0 M_1 T \mathrm{e}^{\frac{1}{3}M_1 T} \quad \text{for } 0 \leqslant t \leqslant T.$$

Hence $\tilde{R}(t)$ satisfies (3.3) if T is sufficiently small, namely, $\tilde{R}(t)$ satisfies the condition (i) if T is small.

To see that the problem (3.5)–(3.6) has a unique solution we introduce the characteristic curves $r = r(\xi,t)$ $(0 \leqslant \xi \leqslant 1, 0 \leqslant t \leqslant T)$ of the equation (3.5) by

$$\begin{cases} \dot{r} = v(r,t) & \text{for } 0 < t \leqslant T, \\ r|_{t=0} = \xi \ (0 \leqslant \xi \leqslant 1), \end{cases} \tag{3.10}$$

where $\dot{r}$ denotes the derivative of r in the time variable. Since $v(r,t)$ is continuous in (r,t) and continuously differentiable in r, these curves are uniquely defined, satisfying $0 < r(\xi,t) < 1$ for $0 < \xi < 1$, $0 \leqslant t \leqslant T$ and $r(0,t) = 0$, $r(1,t) = 1$ for $0 \leqslant t \leqslant T$. Furthermore,

$$\frac{\partial r(\xi,t)}{\partial \xi} = \exp\left(\int_0^t \frac{\partial v}{\partial r}(r(\xi,\tau),\tau)\,\mathrm{d}\tau\right),$$

so that

$$\mathrm{e}^{-AT} \leqslant \frac{\partial r(\xi,t)}{\partial \xi} \leqslant \mathrm{e}^{AT} \quad (0 \leqslant \xi \leqslant 1,\ 0 \leqslant t \leqslant T), \qquad A \text{ a constant.} \tag{3.11}$$

It follows that the mapping $(\xi,t) \mapsto (r(\xi,t),t)$ is a 1-1 correspondence of the region $[0,1]\times[0,T]$ to itself. Setting $\tilde{\tilde{\mathbf{s}}}(\xi,t) = \tilde{\mathbf{s}}(r(\xi,t),t)$, the problem (3.5)–(3.6) reduces to the initial value problem

$$\frac{\partial \tilde{\tilde{\mathbf{s}}}(\xi,t)}{\partial t} = \mathbf{f}(r(\xi,t), R(t), \tilde{\tilde{\mathbf{s}}}(\xi,t)) \quad \text{for } 0 \leqslant \xi \leqslant 1,\ 0 < t \leqslant T, \tag{3.12}$$

$$\tilde{\tilde{\mathbf{s}}}(\xi,0) = \mathbf{s}_0(\xi) \quad (0 \leqslant \xi \leqslant 1). \tag{3.13}$$

Using the standard ODE theory, we can find a unique solution $\tilde{\tilde{\mathbf{s}}}(\xi, t)$ of the problem (3.12)–(3.13) for all $0 \leqslant \xi \leqslant 1$, $0 \leqslant t \leqslant T$ if T is sufficiently small, and $\tilde{\tilde{\mathbf{s}}}(\xi, t)$ is continuously differentiable in (ξ, t). Further, from the formula

$$\tilde{\tilde{\mathbf{s}}}(\xi, t) = \mathbf{s}_0(\xi) + \int_0^t \mathbf{f}(r(\xi, \tau), R(\tau), \tilde{\tilde{\mathbf{s}}}(\xi, \tau))\,\mathrm{d}\tau$$

we can easily show that there exists a constant M_2 depending on M_0, but independent of T, such that

$$|\tilde{\tilde{\mathbf{s}}}(\xi, t)| \leqslant M_0 + M_2 T \quad (0 \leqslant \xi \leqslant 1,\ 0 \leqslant t \leqslant T). \tag{3.14}$$

Now let $\xi = \xi(r, t)$ be the inverse function of $r = r(\xi, t)$ for fixed $0 \leqslant t \leqslant T$, and let $\tilde{\mathbf{s}}(r, t) = \tilde{\tilde{\mathbf{s}}}(\xi(r, t), t)$. Then $\tilde{\mathbf{s}}(r, t)$ is the unique solution of the problem (3.5)–(3.6) for $0 \leqslant r \leqslant 1$, $0 \leqslant t \leqslant T$ which, by (3.14), satisfies

$$|\tilde{\mathbf{s}}(r, t)| \leqslant M_0 + M_2 T \leqslant M_0 + 1 \quad (0 \leqslant r \leqslant 1,\ 0 \leqslant t \leqslant T) \tag{3.15}$$

if T is sufficiently small. Hence $\tilde{\mathbf{s}}(r, t)$ satisfies the condition (ii). We now set

$$\mathcal{F}(R, \mathbf{s}) = (\tilde{R}, \tilde{\mathbf{s}}).$$

Then, for sufficiently small T, $\mathcal{F}$ is a mapping of X_T into itself.

Differentiating (3.12) with respect to ξ we find that

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}\left(\dfrac{\partial \tilde{\tilde{\mathbf{s}}}(\xi, t)}{\partial \xi}\right) = \dfrac{\partial \mathbf{f}}{\partial \mathbf{s}}(r(\xi, t), R(t), \tilde{\tilde{\mathbf{s}}}(\xi, t))\dfrac{\partial \tilde{\tilde{\mathbf{s}}}(\xi, t)}{\partial \xi} \\ \qquad\qquad + \dfrac{\partial \mathbf{f}}{\partial r}(r(\xi, t), R(t), \tilde{\tilde{\mathbf{s}}}(\xi, t)) \exp\left(\displaystyle\int_0^t \dfrac{\partial v}{\partial r}(r(\xi, \tau), \tau)\,\mathrm{d}\tau\right), \\ \dfrac{\partial \tilde{\tilde{\mathbf{s}}}(\xi, 0)}{\partial \xi} = \mathbf{s}_0'(\xi), \end{cases}$$

where $\partial \mathbf{f}/\partial \mathbf{s}$ is the Jacobian of $\mathbf{f}(r, R, \mathbf{s})$ with respect to $\mathbf{s}$. By standard ODE theory it follows that

$$\left|\frac{\partial \tilde{\tilde{\mathbf{s}}}(\xi, t)}{\partial \xi}\right| \leqslant M_0 + M_3 T \quad (0 \leqslant \xi \leqslant 1,\ 0 \leqslant t \leqslant T),$$

where M_3 is a constant independent of T (as long as T is small). Recalling (3.11) we conclude that

$$\left|\frac{\partial \tilde{\mathbf{s}}(r, t)}{\partial r}\right| \leqslant (M_0 + M_3 T)\mathrm{e}^{AT} \leqslant M_0 + 1 \quad (0 \leqslant r \leqslant 1,\ 0 \leqslant t \leqslant T) \tag{3.16}$$

provided T is sufficiently small.

We now prove that $\mathcal{F}$ is a contraction mapping for sufficiently small T. Let $(R_i, \mathbf{s}_i) \in X_T$ for $i = 1, 2$ and set

$$u_i(r, t) = \frac{1}{r^2}\int_0^r g(\rho, R_i(t), \mathbf{s}_i(\rho, t))\rho^2\,\mathrm{d}\rho,$$

$$v_i(r, t) = u_i(r, t) - r u_i(1, t),$$

$$(\tilde{R}_i, \tilde{\mathbf{s}}_i) = \mathcal{F}(R_i, \mathbf{s}_i), \qquad d = d((R_1, \mathbf{s}_1), (R_2, \mathbf{s}_2)).$$

By direct calculation we get

$$|u_1(r,t) - u_2(r,t)| \leqslant M_4 d \quad (0 \leqslant r \leqslant 1,\ 0 \leqslant t \leqslant T), \tag{3.17}$$

so that, by (3.9),

$$\max_{0\leqslant t\leqslant T} |\tilde{R}_1(t) - \tilde{R}_2(t)| \leqslant M_5 T d; \tag{3.18}$$

here and in what follows, M_i denote constants independent of T.

Next, setting $\tilde{\mathbf{s}}_* = \tilde{\mathbf{s}}_1 - \tilde{\mathbf{s}}_2$ we can write

$$\begin{cases} \dfrac{\partial \tilde{\mathbf{s}}_*}{\partial t} + v_1(r,t)\dfrac{\partial \tilde{\mathbf{s}}_*}{\partial r} - \mathbf{A}(r,t)\tilde{\mathbf{s}}_* = \mathbf{h}(r,t) & \text{for } 0 \leqslant r \leqslant 1,\ 0 < t \leqslant T, \\ \tilde{\mathbf{s}}_*(r,0) = 0 & \text{for } 0 \leqslant r \leqslant 1, \end{cases} \tag{3.19}$$

where

$$\begin{aligned} \mathbf{A}(r,t) = {} & \int_0^1 \frac{\partial \mathbf{f}}{\partial \mathbf{s}}(r, R_1(t), \theta\tilde{\mathbf{s}}_1(r,t) + (1-\theta)\tilde{\mathbf{s}}_2(r,t))\,\mathrm{d}\theta, \\ \mathbf{h}(r,t) = {} & -(v_1(r,t) - v_2(r,t))\frac{\partial \tilde{\mathbf{s}}_2}{\partial r} \\ & + (R_1(t) - R_2(t))\int_0^1 \frac{\partial \mathbf{f}}{\partial R}(r, \theta R_1(t) + (1-\theta)R_2(t), \tilde{\mathbf{s}}_2(r,t))\,\mathrm{d}\theta. \end{aligned}$$

Using the bounds (3.15), (3.16) for $\tilde{\mathbf{s}}_1$, $\tilde{\mathbf{s}}_2$ and the estimate (3.17), we deduce the norm estimates

$$\begin{aligned} \|\mathbf{A}(r,t)\| &\leqslant M_6 \quad (0 \leqslant r \leqslant 1,\ 0 \leqslant t \leqslant T), \\ |\mathbf{h}(r,t)| &\leqslant M_7 d \quad (0 \leqslant r \leqslant 1,\ 0 \leqslant t \leqslant T). \end{aligned}$$

Hence, integrating (3.19) along the characteristics determined by the equation $\mathrm{d}r/\mathrm{d}t = v_1(r,t)$ as before, we find that

$$\max_{0\leqslant r\leqslant 1,\, 0\leqslant t\leqslant T} |\tilde{\mathbf{s}}_1(r,t) - \tilde{\mathbf{s}}_2(r,t)| \leqslant M_8 T d. \tag{3.20}$$

Combining (3.18) and (3.20), we get

$$d((\tilde{R}_1, \tilde{\mathbf{s}}_1), (\tilde{R}_1, \tilde{\mathbf{s}}_1)) \leqslant \tfrac{1}{2} d((R_1, \mathbf{s}_1), (R_2, \mathbf{s}_2))$$

provided $(M_5 + M_8)T \leqslant 1/2$. This proves the desired assertion.

We summarize:

THEOREM 3.1 Let $\delta_0 \leqslant R_0 \leqslant 1/\delta_0$ ($\delta_0 > 0$) and

$$\max_{0\leqslant r\leqslant 1} (|\mathbf{s}_0(r)| + |\mathbf{s}_0'(r)|) \leqslant M_0.$$

Then there is a unique solution of the system (2.10)–(2.16) for $0 \leqslant r \leqslant 1$, $0 \leqslant t \leqslant T$ provided T is sufficiently small, depending on δ_0 and M_0. □

4. Global existence

In this section we prove the following theorem:

THEOREM 4.1 The system (2.10)–(2.16) has a unique solution for $0 \leqslant r \leqslant 1$, $0 \leqslant t < \infty$, and it has the following properties:

$$p(r,t) \geqslant 0, \quad q(r,t) \geqslant 0, \quad p(r,t)+q(r,t) \leqslant 1, \tag{4.1}$$

$$R_0 e^{-\frac{1}{3}K_R t} \leqslant R(t) \leqslant R_0 e^{\frac{1}{3}K_B(1)t}, \tag{4.2}$$

$$-\tfrac{1}{3}K_R \leqslant \frac{\dot{R}(t)}{R(t)} \leqslant \tfrac{1}{3}K_B(1). \tag{4.3}$$

Proof. In view of Theorem 3.1, the solution established for small times can be extended step-by-step to all $t > 0$ provided we can prove that if the solution exists for $0 \leqslant t < T$, $T > 0$ arbitrary, then the *a priori* estimates (4.1), (4.2) and

$$\left|\frac{\partial p(r,t)}{\partial r}\right| \leqslant M, \quad \left|\frac{\partial q(r,t)}{\partial r}\right| \leqslant M \tag{4.4}$$

hold for $0 \leqslant r \leqslant 1$, $0 \leqslant t < T$, where M is a positive constant which may depend on T.

To prove (4.1), we note that (3.12) can be written in the form

$$\frac{\partial \tilde{\tilde{p}}(\xi,t)}{\partial t} = a_{11}(\xi,t)\tilde{\tilde{p}}(\xi,t) + a_{12}(\xi,t)\tilde{\tilde{q}}(\xi,t),$$
$$\frac{\partial \tilde{\tilde{q}}(\xi,t)}{\partial t} = a_{21}(\xi,t)\tilde{\tilde{p}}(\xi,t) + a_{22}(\xi,t)\tilde{\tilde{q}}(\xi,t),$$

where $a_{ij}(\xi,t)$'s are continuous functions and

$$a_{12}(\xi,t) = K_P(c(r(\xi,t),R(t))) \geqslant 0, \quad a_{21}(\xi,t) = K_Q(c(r(\xi,t),R(t))) \geqslant 0.$$

Since $\tilde{\tilde{p}}(\xi,0) = p_0(\xi) \geqslant 0$ and $\tilde{\tilde{q}}(\xi,0) = q_0(\xi) \geqslant 0$, by a standard comparison theorem for systems of ordinary differential equations (see, for instance, [21]) we infer that

$$\tilde{\tilde{p}}(\xi,t) \geqslant 0, \quad \tilde{\tilde{q}}(\xi,t) \geqslant 0$$

for $0 \leqslant \xi \leqslant 1$, $0 \leqslant t < T$. Hence

$$p(r,t) \geqslant 0, \quad q(r,t) \geqslant 0$$

for $0 \leqslant r \leqslant 1$, $0 \leqslant t < T$. Substituting the second inequality into (2.20) we get

$$\frac{\partial d}{\partial t} + v\frac{\partial d}{\partial r} + [K_B(c)p - K_R d + K_R]d \geqslant 0 \quad (0 \leqslant r \leqslant 1,\ 0 < t < T).$$

Since $d(r,0) = 1 - p_0(r) - q_0(r) \geqslant 0$ for $0 \leqslant r \leqslant 1$, by rewriting the above inequality in characteristic form and then using a comparison theorem, we conclude that also

$$d(r,t) \geqslant 0, \quad \text{or} \quad p(r,t)+q(r,t) \leqslant 1$$

for $0 \leqslant r \leqslant 1$, $0 \leqslant t < T$.

Next, by (2.19) and (4.1) we have

$$\dot{R}(t) \geqslant -K_R R(t) \int_0^1 r^2 \, \mathrm{d}r = -\tfrac{1}{3} K_R R(t) \qquad \text{for } 0 < t < T$$

and

$$\begin{aligned} \dot{R}(t) &= R(t) \int_0^1 [K_B(c(r, R(t))) p(r,t) - K_R(1 - p(r,t) - q(r,t))] r^2 \, \mathrm{d}r \\ &\leqslant K_B(1) R(t) \int_0^1 r^2 \, \mathrm{d}r = \tfrac{1}{3} K_B(1) R(t) \qquad \text{for } 0 < t < T, \end{aligned}$$

so that (4.3) holds. (4.2) is an immediate consequence of (4.3).

Finally, (4.4) follows from an argument similar to the proof of (3.16). □

5. Lower bound on $R(t)$; $0 < K_R < \infty$

In this section and the next one we assume that $0 < K_R < \infty$.

THEOREM 5.1 There exists a $\delta_0 > 0$ such that

$$R(t) \geqslant \delta_0 \qquad \text{for all } t \geqslant 0. \tag{5.1}$$

Proof. Let $\delta > 0$ be a sufficiently small number to be determined later on. We shall prove that in any interval $[t_1, t_2]$ such that $R(t_1) = \delta$ and $R(t) \leqslant \delta$ for $t_1 \leqslant t \leqslant t_2$ we have

$$R(t) \geqslant \delta \mathrm{e}^{-\frac{1}{3} K_R T} \qquad \text{for } t_1 \leqslant t \leqslant t_2, \tag{5.2}$$

where $T = T(\delta)$ is a positive constant depending on δ but not on $[t_1, t_2]$. Clearly, if this is proved then the desired assertion follows.

Let

$$V(t) = \tfrac{1}{3} R^3(t), \qquad V_P(t) = R^3(t) \int_0^1 p(r,t) r^2 \, \mathrm{d}r, \qquad V_Q(t) = R^3(t) \int_0^1 q(r,t) r^2 \, \mathrm{d}r,$$

$$V_D(t) = R^3(t) \int_0^1 d(r,t) r^2 \, \mathrm{d}r, \qquad W(t) = V(t) + V_P(t).$$

By direct calculations,

$$\begin{aligned} \dot{V}(t) &= R^3(t) \int_0^1 K_B(c) p r^2 \, \mathrm{d}r - K_R V_D(t), \\ \dot{V}_P(t) &= R^3(t) \int_0^1 \{[K_B(c) - K_Q(c) - K_A(c)] p + K_P(c) q\} r^2 \, \mathrm{d}r, \\ \dot{V}_Q(t) &= R^3(t) \int_0^1 \{K_Q(c) p - [K_P(c) + K_D(c)] q\} r^2 \, \mathrm{d}r, \\ \dot{V}_D(t) &= R^3(t) \int_0^1 [K_A(c) p + K_D(c) q] r^2 \, \mathrm{d}r - K_R V_D(t), \end{aligned} \tag{5.3}$$

where $c = c(r, R(t))$, $p = p(r, t)$, etc. Since $c(r, R)$ is decreasing in R and increasing in r, we have

$$c(r, R(t)) \geqslant c(r, \delta) \geqslant c(0, \delta) \equiv c(\delta) \quad \text{for } 0 \leqslant r \leqslant 1,\ t_1 \leqslant t \leqslant t_2. \tag{5.4}$$

Note that $\lim_{\delta \to 0} c(\delta) = 1$, so that by the assumption (**a**) we can find a $\delta > 0$ sufficiently small such that

$$\mu = \tfrac{1}{2} \min\{2K_B(c(\delta)) - K_Q(c(\delta)) - K_A(c(\delta)), K_P(c(\delta))\} > 0.$$

Then, by (5.4) and the assumption (**a**) we have, for $t_1 \leqslant t \leqslant t_2$,

$$\begin{aligned}
\dot{W}(t) &= \dot{V}(t) + \dot{V}_P(t) \\
&= R^3(t) \int_0^1 \{[2K_B(c) - K_Q(c) - K_A(c)]p + K_P(c)q\} r^2 \, \mathrm{d}r - K_R V_D(t) \\
&\geqslant 2\mu R^3(t) \int_0^1 (p+q) r^2 \, \mathrm{d}r - K_R V_D(t) \\
&\geqslant \mu R^3(t) \int_0^1 (2p+q) r^2 \, \mathrm{d}r - K_R V_D(t) \\
&\geqslant \mu R^3(t) \int_0^1 (2p+q+d) r^2 \, \mathrm{d}r - (K_R + \mu) V_D(t) \\
&= \mu W(t) - \nu V_D(t), \qquad \nu = K_R + \mu.
\end{aligned}$$

Hence

$$\dot{W}(t) \geqslant \mu W(t) - \nu V_D(t) \quad \text{for } t_1 \leqslant t \leqslant t_2. \tag{5.5}$$

Let $\varepsilon = \max\{K_D(c(\delta)), K_A(c(\delta))\}$. Then by (5.4) and the assumption (**a**) we have, for $t_1 \leqslant t \leqslant t_2$,

$$\begin{aligned}
\dot{V}_D(t) &= R^3(t) \int_0^1 [K_A(c)p + K_D(c)q] r^2 \, \mathrm{d}r - K_R V_D(t) \\
&\leqslant \varepsilon R^3(t) \int_0^1 (p+q) r^2 \, \mathrm{d}r - K_R V_D(t) \\
&\leqslant \varepsilon W(t) - K_R V_D(t)
\end{aligned}$$

so that

$$\dot{V}_D(t) \leqslant \varepsilon W(t) - K_R V_D(t) \quad \text{for } t_1 \leqslant t \leqslant t_2. \tag{5.6}$$

From (5.5) and (5.6) we get

$$\frac{\mathrm{d}}{\mathrm{d}t}\left[V_D(t) - \frac{\varepsilon}{\mu} W(t)\right] \leqslant -\left[K_R - \frac{\nu\varepsilon}{\mu}\right] V_D(t) \quad (t_1 \leqslant t \leqslant t_2).$$

Since $\lim_{\delta \to 0} \varepsilon = 0$, we can take δ so small that also

$$\alpha \equiv K_R - \nu\varepsilon/\mu > 0.$$

It follows that

$$\frac{\mathrm{d}}{\mathrm{d}t}\left[V_D(t) - \frac{\varepsilon}{\mu} W(t)\right] \leqslant -\alpha\left[V_D(t) - \frac{\varepsilon}{\mu} W(t)\right] \quad (t_1 \leqslant t \leqslant t_2).$$

Hence

$$V_D(t) - \frac{\varepsilon}{\mu}W(t) \leqslant \left[V_D(t_1) - \frac{\varepsilon}{\mu}W(t_1)\right]e^{-\alpha(t-t_1)} \leqslant V_D(t_1)e^{-\alpha(t-t_1)},$$

and since $V_D(t_1) \leqslant V(t_1) = \delta^3/3$,

$$V_D(t) \leqslant \frac{\varepsilon}{\mu}W(t) + \frac{\delta^3}{3}e^{-\alpha(t-t_1)} \quad \text{for } t_1 \leqslant t \leqslant t_2. \tag{5.7}$$

Substituting (5.7) into (5.5) we obtain

$$\dot{W}(t) \geqslant \beta W(t) - \frac{\nu\delta^3}{3}e^{-\alpha(t-t_1)} \quad \text{for } t_1 \leqslant t \leqslant t_2, \tag{5.8}$$

where

$$\beta \equiv \mu - \nu\varepsilon/\mu > 0$$

if δ is sufficiently small.

Let $z(t)$ be the solution of the initial value problem

$$\begin{cases} \dot{z}(t) = \beta z(t) - (\nu\delta^3/3)e^{-\alpha t} & \text{for } t > 0, \\ z(0) = \delta^3/3. \end{cases} \tag{5.9}$$

Since $W(t_1) \geqslant V(t_1) = \delta^3/3$, we have, by comparison between (5.8) and (5.9),

$$W(t) \geqslant z(t - t_1) \quad \text{for } t_1 \leqslant t \leqslant t_2. \tag{5.10}$$

Clearly, $\lim_{t\to\infty} z(t) = \infty$, so that there exists a $T = T(\delta) > 0$ such that

$$z(t) \geqslant \tfrac{2}{3}\delta^3 \quad \text{for } t \geqslant T. \tag{5.11}$$

By (4.3) we have

$$R(t) \geqslant R(t_1)e^{-\frac{1}{3}K_R(t-t_1)} \geqslant \delta e^{-\frac{1}{3}K_R T} \quad \text{for } t_1 \leqslant t \leqslant t_1 + T. \tag{5.12}$$

Using the inequalities (5.10)–(5.12) we can now prove that (5.2) holds. Indeed, if $t_2 \leqslant t_1 + T$ then (5.2) is an immediate consequence of (5.12). On the other hand, if $t_2 > t_1 + T$ then for $t_1 \leqslant t \leqslant t_1 + T$ we have the estimate (5.12), and for $t_1 + T < t \leqslant t_2$ we have, by (5.10) and (5.11),

$$\tfrac{2}{3}R^3(t) = 2V(t) \geqslant W(t) \geqslant z(t - t_1) \geqslant \tfrac{2}{3}\delta^3,$$

so that $R(t) \geqslant \delta > \delta e^{-K_R T/3}$. □

6. Upper bound on $R(t)$; $0 < K_R < \infty$

THEOREM 6.1 There exists a positive constant M such that

$$R(t) \leqslant M \quad \text{for all } t \geqslant 0. \tag{6.1}$$

Before giving the proof of this theorem we need some preparations. Let $c(r, R)$ be as before (see (2.9)). Since $c(0, R)$ is strictly decreasing in R, $\lim_{R\to\infty} c(0, R) = 0$ and $c(0, 0) = 1$, for any $0 < \varepsilon < 1$ there exists a unique $R_\varepsilon > 0$ such that $c(0, R_\varepsilon) = \varepsilon$ and $c(0, R) < \varepsilon$ for all $R > R_\varepsilon$. Since $c(r, R)$ is strictly increasing in r and $c(1, R) = 1$, it follows that for any $R > R_\varepsilon$ there exists a unique $0 < r(\varepsilon, R) < 1$ such that

$$c(r, R) \begin{cases} < \varepsilon & \text{if } 0 \leqslant r < r(\varepsilon, R), \\ = \varepsilon & \text{if } r = r(\varepsilon, R), \\ \varepsilon & \text{if } r(\varepsilon, R) < r \leqslant 1. \end{cases} \tag{6.2}$$

By differentiating the implicit equation

$$c(r(\varepsilon, R), R) = \varepsilon$$

in R, we find that $\frac{\partial r(\varepsilon,R)}{\partial R} = -\frac{\partial c}{\partial R}\Big/\frac{\partial c}{\partial r} > 0$, so that $r(\varepsilon, R)$ is strictly increasing in R.

LEMMA 6.2 $\lim_{R\to\infty} r(\varepsilon, R) = 1$ for all $0 < \varepsilon < 1$.

Proof. Since $r(\varepsilon, R)$ is increasing in R and $r(\varepsilon, R) < 1$, we see that $r_\varepsilon^* \equiv \lim_{R\to\infty} r(\varepsilon, R)$ exists, and $0 < r_\varepsilon^* \leqslant 1$. Assume that $r_\varepsilon^* < 1$ for some ε. Then $r > r(\varepsilon, R)$ for all $r_\varepsilon^* \leqslant r \leqslant 1$ and $R > R_\varepsilon$, implying that $c(r, R) > \varepsilon$ for all $r_\varepsilon^* \leqslant r \leqslant 1$ and $R > R_\varepsilon$, which contradicts the fact that $\lim_{R\to\infty} c(r, R) = 0$ for all $0 \leqslant r < 1$. Hence the desired assertion follows. □

LEMMA 6.3 Let $U(t) = 3V_P(t) + 2V_Q(t) + V_D(t)$. There exist positive numbers η and M_0 such that, for any $0 \leqslant t_1 < t_2 < \infty$, if $R(t) \geqslant M_0$ for $t_1 < t < t_2$ then

$$\dot U(t) \leqslant -\frac{\eta}{4} U(t) \quad \text{for } t_1 < t < t_2. \tag{6.3}$$

Proof. By (5.3) we have the following identity:

$$\dot U(t) = R^3(t) \int_0^1 \{-[(K_Q(c)+2K_A(c))p + K_D(c)q + K_R d] + [3K_B(c)p + K_P(c)q]\} r^2 \,\mathrm{d}r. \tag{6.4}$$

Let $0 < \varepsilon < 1$ and assume that $R(t) > R_\varepsilon$. Then by (6.4) we have

$$\begin{aligned} \dot U(t) \leqslant{}& R^3(t)\bigg\{-\int_0^{r(\varepsilon,R(t))} [(K_Q(c) + 2K_A(c))p + K_D(c)q + K_R d] r^2 \,\mathrm{d}r \\ &+ \int_0^{r(\varepsilon,R(t))} [3K_B(c)p + K_P(c)q] r^2 \,\mathrm{d}r + \int_{r(\varepsilon,R(t))}^1 [3K_B(c)p + K_P(c)q] r^2 \,\mathrm{d}r\bigg\} \\ \leqslant{}& -R^3(t) \min\{K_Q(\varepsilon) + 2K_A(\varepsilon), K_D(\varepsilon), K_R\} \int_0^{r(\varepsilon,R(t))} r^2 \,\mathrm{d}r \\ &+ R^3(t)[3K_B(\varepsilon) + K_P(\varepsilon)] \int_0^1 r^2 \,\mathrm{d}r + R^3(t)[3K_B(1) + K_P(1)] \int_{r(\varepsilon,R(t))}^1 r^2 \,\mathrm{d}r. \end{aligned}$$

Hence

$$\begin{aligned} \dot U(t) \leqslant{}& -\tfrac{1}{3} R^3(t) \min\{K_Q(\varepsilon) + 2K_A(\varepsilon), K_D(\varepsilon), K_R\} r^3(\varepsilon, R(t)) + \tfrac{1}{3} R^3(t)[3K_B(\varepsilon) + K_P(\varepsilon)] \\ &+ \tfrac{1}{3} R^3(t)[3K_B(1) + K_P(1)][1 - r^3(\varepsilon, R(t))] \\ \leqslant{}& -\tfrac{1}{3} R^3(t) \min\{K_Q(\varepsilon) + 2K_A(\varepsilon), K_D(\varepsilon), K_R\} + \tfrac{1}{3} R^3(t)[3K_B(\varepsilon) + K_P(\varepsilon)] \\ &+ R^3(t)[3K_B(1) + K_P(1) + K_R][1 - r(\varepsilon, R(t))]; \end{aligned}$$

in deriving the last inequality we have used the estimate

$$r^3(\varepsilon, R(t)) \geqslant 1 - 3[1 - r(\varepsilon, R(t))].$$

Clearly,

$$\tfrac{1}{3}R^3(t) \leqslant U(t) \leqslant R^3(t).$$

Hence

$$\begin{aligned}\dot{U}(t) \leqslant\ & -\tfrac{1}{3}\min\{K_Q(\varepsilon) + 2K_A(\varepsilon), K_D(\varepsilon), K_R\}U(t) + [3K_B(\varepsilon) + K_P(\varepsilon)]U(t)\\ & + 3b[1 - r(\varepsilon, R(t))]U(t),\end{aligned} \tag{6.5}$$

where $b = 3K_B(1) + K_P(1) + K_R$. Since

$$\lim_{\varepsilon\to 0} \tfrac{1}{3}\min\{K_Q(\varepsilon) + 2K_A(\varepsilon), K_D(\varepsilon), K_R\} = \tfrac{1}{3}\min\{K_Q(0) + 2K_A(0), K_D(0), K_R\} \equiv \eta > 0$$

and $\lim_{\varepsilon\to 0}[3K_B(\varepsilon) + K_P(\varepsilon)] = 0$, we can find a sufficiently small $\varepsilon > 0$ such that

$$-\tfrac{1}{3}\min\{K_Q(\varepsilon) + 2K_A(\varepsilon), K_D(\varepsilon), K_R\} + [3K_B(\varepsilon) + K_P(\varepsilon)] \leqslant -\eta/2.$$

By (6.5), we then have

$$\dot{U}(t) \leqslant -\frac{\eta}{2}U(t) + 3b[1 - r(\varepsilon, R(t))]U(t).$$

Since $\lim_{R\to\infty} r(\varepsilon, R) = 1$, we can find an $M_0 > R_\varepsilon$ sufficiently large such that $3b[1 - r(\varepsilon, R)] \leqslant \eta/4$ for $R \geqslant M_0$, so that $\dot{U}(t) \leqslant -(\eta/4)U(t)$ if $R(t) \geqslant M_0$. □

Proof of Theorem 6.1. Let η and M_0 be as in Lemma 6.3. Take a sufficiently large positive number M such that $M^3 \geqslant 3M_1^3$, where $M_1 = \max\{R_0, M_0\}$. We claim that

$$R(t) < M \quad \text{for all } t \geqslant 0. \tag{6.6}$$

Indeed, if (6.6) does not hold then we can find two numbers t_1 and t_2 with $0 \leqslant t_1 < t_2$ such that

$$R(t_1) = M_1, \quad R(t_2) = M \quad \text{and} \quad R(t) > M_1 \geqslant M_0 \quad \text{for } t_1 < t < t_2.$$

By (6.3), we then have

$$U(t_2) \leqslant U(t_1)\mathrm{e}^{-\frac{\eta}{4}(t_2 - t_1)} < U(t_1).$$

Since however $U(t_2) \geqslant \frac{1}{3}R^3(t_2) = \frac{1}{3}M^3$ and $U(t_1) \leqslant R^3(t_1) = M_1^3$, we get $M^3 < 3M_1^3$, which contradicts the choice of M. □

7. The case $K_R = \infty$

We interpret the case $K_R = \infty$ to mean that dead cells are instantly removed from the tumor, that is, $D \equiv 0$ so that $P + Q = N$. In this case, instead of (2.10)–(2.15) we have the following system:

$$\frac{\partial p}{\partial t} + v(r, t)\frac{\partial p}{\partial r} = K_P(c) + [K_M(c) - K_N(c)]p - K_M(c)p^2, \quad 0 \leqslant r \leqslant 1,\ t \geqslant 0, \tag{7.1}$$

where $K_M(c) = K_B(c) + K_D(c) - K_A(c)$, $K_N(c) = K_Q(c) + K_P(c)$, $c = c(r, R(t))$ is as before (see (2.9)), and

$$v(r,t) = u(r,t) - ru(1,t), \quad 0 \leqslant r \leqslant 1,\ t \geqslant 0, \tag{7.2}$$

$$u(r,t) = \frac{1}{r^2}\int_0^r \{-K_D(c(\rho, R(t))) + K_M(c(\rho, R(t)))p(\rho,t)\}\rho^2\,\mathrm{d}\rho, \quad 0 < r \leqslant 1,\ t \geqslant 0, \tag{7.3}$$

$$u(0,t) = 0, \quad t \geqslant 0, \tag{7.4}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = R\int_0^1 \{-K_D(c(r, R(t))) + K_M(c(r, R(t)))p(r,t)\}r^2\,\mathrm{d}r, \quad t \geqslant 0, \tag{7.5}$$

with the initial conditions:

$$R(0) = R_0, \quad p(r,0) = p_0(r), \quad 0 \leqslant r \leqslant 1. \tag{7.6}$$

We assume that the conditions (**a**), (**b**) (in §2) hold with $p_0(r) + q_0(r) \equiv 1$; it follows, in particular, that $K_M(c) > 0$ and $K_M'(c) > 0$.

The proofs of Theorems 3.1 and 4.1 can be easily modified to establish the following result:

THEOREM 7.1 The problem (7.1)–(7.6) has a unique solution $(R(t), p(r,t))$ defined for all $0 \leqslant r \leqslant 1$ and $t \geqslant 0$. Moreover, the solution has the following properties:

$$0 \leqslant p(r,t) \leqslant 1 \quad \text{for } 0 \leqslant r < 1,\ t > 0, \tag{7.7}$$

$$R_0 \mathrm{e}^{-\frac{1}{3}K_D(0)t} \leqslant R(t) \leqslant R_0 \mathrm{e}^{\frac{1}{3}K_B(1)t} \quad \text{for } t \geqslant 0, \tag{7.8}$$

$$-\tfrac{1}{3}K_D(0) \leqslant \frac{\dot{R}(t)}{R(t)} \leqslant \tfrac{1}{3}K_B(1) \quad \text{for } t > 0. \tag{7.9}$$

□

Theorems 5.1 and 6.1 can also be extended to the system (7.1)–(7.6):

THEOREM 7.2 For the solution of (7.1)–(7.6), there exist positive numbers δ_0, M such that

$$\delta_0 \leqslant R(t) \leqslant M \quad \text{for all } t \geqslant 0. \tag{7.10}$$

To prove the lower bound in (7.10) we need a preliminary lemma. Let c_0 be a positive constant, $0 < c_0 < 1$. Consider the initial value problem

$$\begin{cases} \dfrac{\mathrm{d}\hat{z}(t)}{\mathrm{d}t} = K_P(c_0) + [K_M(c_0) - K_N(c_0)]\hat{z}(t) - K_M(c_0)\hat{z}^2(t) & \text{for } t > 0, \\ \hat{z}(0) = 0. \end{cases} \tag{7.11}$$

It is easily seen that this problem has a unique solution $\hat{z}(t)$ for all $t \geqslant 0$. We assert that $\hat{z}(t)$ is strictly increasing, and $0 < \hat{z}(t) < 1$ for all $t > 0$. Indeed, the quadratic equation

$$K_P(c_0) + [K_M(c_0) - K_N(c_0)]\sigma - K_M(c_0)\sigma^2 = 0$$

has exactly two real roots, one positive and less than 1 which we denote by σ_+, and the other negative which we denote by σ_-. The equation for $\hat{z}(t)$ can then be rewritten as

$$\frac{\mathrm{d}\hat{z}(t)}{\mathrm{d}t} = K_M(c_0)(\sigma_+ - \hat{z}(t))(\hat{z}(t) + |\sigma_-|).$$

From this formulation and the fact that $\hat{z}(0) = 0 < \sigma_+$ it follows immediately (by comparison) that $0 < \hat{z}(t) < \sigma_+$ for all $t > 0$, so that $\mathrm{d}\hat{z}(t)/\mathrm{d}t > 0$ and $0 < \hat{z}(t) < 1$ for all $t > 0$. One can further deduce that $\lim_{t\to\infty} \hat{z}(t) = \sigma_+$.

LEMMA 7.3 Let M_0 be a positive constant and let $(R(t), p(r,t))$ be the solution of the system (7.1)–(7.6). Assume that

$$R(t) \leqslant M_0 \quad \text{for } t_0 \leqslant t \leqslant t_1 \tag{7.12}$$

for some $0 \leqslant t_0 < t_1$. Then, denoting by $\hat{z}(t)$ the solution of the problem (7.11) with $c_0 = c(0, M_0)$, we have

$$\min_{0\leqslant r\leqslant 1} p(r,t) \geqslant \hat{z}(t - t_0) \quad \text{for } t_0 \leqslant t \leqslant t_1. \tag{7.13}$$

Proof. Since $c(r, R)$ is increasing in r and decreasing in R, the condition (7.12) implies that

$$c(r, R(t)) \geqslant c(0, R(t)) \geqslant c(0, M_0) = c_0 \quad \text{for } 0 \leqslant r \leqslant 1,\ t_0 \leqslant t \leqslant t_1.$$

By writing

$$K_P(c) + [K_M(c) - K_N(c)]p - K_M(c)p^2 = K_P(c)(1-p) + K_M(c)(1-p)p - K_Q(c)p, \tag{7.14}$$

one can easily verify that this function is increasing in c for every fixed $0 \leqslant p \leqslant 1$. It follows (by (7.1)) that

$$\frac{\partial p}{\partial t} + v(r,t)\frac{\partial p}{\partial r} \geqslant K_P(c_0) + [K_M(c_0) - K_N(c_0)]p - K_M(c_0)p^2 \tag{7.15}$$

for $0 \leqslant r \leqslant 1$ and $t_0 \leqslant t \leqslant t_1$. Let $r = r(t, \xi)$ ($t \geqslant 0$, $0 \leqslant \xi \leqslant 1$) denote the characteristic curves of (7.1), and let $\tilde{p}(\xi, t) = p(r(t,\xi), t)$. Then the above inequality can be rewritten as follows:

$$\frac{\partial \tilde{p}(\xi,t)}{\partial t} \geqslant K_P(c_0) + [K_M(c_0) - K_N(c_0)]\tilde{p} - K_M(c_0)\tilde{p}^2$$

($0 \leqslant \xi \leqslant 1$, $t_0 \leqslant t \leqslant t_1$). Therefore, by comparison,

$$\tilde{p}(\xi, t) \geqslant \hat{z}(t - t_0) \quad \text{for all } 0 \leqslant \xi \leqslant 1,\ t_0 \leqslant t \leqslant t_1.$$

Since $\min_{0\leqslant r\leqslant 1} p(r,t) = \min_{0\leqslant \xi\leqslant 1} \tilde{p}(\xi, t)$, the estimate (7.13) immediately follows. □

Proof of Theorem 7.2. Let $V(t)$ and $V_P(t)$ be as before. Then

$$\dot{V}_P(t) = R^3(t) \int_0^1 \{[K_B(c) - K_Q(c) - K_A(c)]p + K_P(c)q\} r^2 \, \mathrm{d}r. \tag{7.16}$$

Since the function $K_B(c) - K_Q(c) - K_A(c)$ is strictly increasing in c for $0 \leqslant c \leqslant 1$, and $K_B(0) - K_Q(0) - K_A(0) = -[K_Q(0) + K_A(0)] < 0$, $K_B(1) - K_Q(1) - K_A(1) = K_B(1) > 0$, we infer that there exists a constant $0 < c^* < 1$ such that

$$K_B(c) - K_Q(c) - K_A(c) \begin{cases} < 0 & \text{if } 0 \leqslant c < c^*, \\ = 0 & \text{if } c = c^*, \\ > 0 & \text{if } c^* < c \leqslant 1. \end{cases} \tag{7.17}$$

Since $c(0, R)$ is strictly decreasing in R and $c(0, 0) = 1$, $\lim_{R\to\infty} c(0, R) = 0$, there exists a constant $R^* > 0$ such that

$$c(0, R) \begin{cases} > c^* & \text{if } 0 \leqslant R < R^*, \\ = c^* & \text{if } R = R^*, \\ < c^* & \text{if } R > R^*. \end{cases}$$

Let $R_1 = \frac{1}{2}\min\{R_0, R^*\}$. We assert that for some $0 < \delta < R_1$, to be specified later,

$$R(t) > \delta \quad \text{for all } t \geqslant 0. \tag{7.18}$$

Indeed, if (7.18) does not hold then we can find two numbers t_1 and t_2, $0 < t_1 < t_2$, such that $R(t_1) = R_1$, $R(t_2) = \delta$ and

$$R(t) < R_1 \quad \text{for } t_1 < t < t_2. \tag{7.19}$$

Let $c_1 = c(0, R_1)$. From (7.18) we see that

$$c(r, R(t)) \geqslant c(0, R(t)) \geqslant c(0, R_1) = c_1 \quad \text{for } 0 \leqslant r \leqslant 1,\ t_1 \leqslant t \leqslant t_2,$$

so that

$$K_B(c(r, R(t))) - K_Q(c(r, R(t))) - K_A(c(r, R(t))) \geqslant K_B(c_1) - K_Q(c_1) - K_A(c_1) \equiv a$$

for $0 \leqslant r \leqslant 1$, $t_1 \leqslant t \leqslant t_2$. Note that since $R_1 < R^*$, we have $c_1 > c^*$, so that $a > 0$. Therefore, from (7.16) we get

$$\dot{V}_P(t) \geqslant R^3(t)\int_0^1 [K_B(c) - K_Q(c) - K_A(c)]pr^2\,\mathrm{d}r \geqslant aR^3(t)\int_0^1 pr^2\,\mathrm{d}r = aV_P(t)$$

for $t_1 \leqslant t \leqslant t_2$, and, by integration,

$$V_P(t_2) \geqslant V_P(t_1)\mathrm{e}^{a(t_2-t_1)}. \tag{7.20}$$

We have

$$V_P(t_2) = R^3(t_2)\int_0^1 p(r, t_2)r^2\,\mathrm{d}r \leqslant \delta^3\int_0^1 r^2\,\mathrm{d}r = \tfrac{1}{3}\delta^3,$$
$$V_P(t_1) = R^3(t_1)\int_0^1 p(r, t_1)r^2\,\mathrm{d}r \geqslant R_1^3 \min_{0\leqslant r\leqslant 1} p(r, t_1)\int_0^1 r^2\,\mathrm{d}r = \tfrac{1}{3}R_1^3 \min_{0\leqslant r\leqslant 1} p(r, t_1),$$

and, by (7.9) and the fact that $R(t_1) = R_1$ and $R(t_2) = \delta$,

$$R_1\mathrm{e}^{-\frac{1}{3}K_D(0)(t_2-t_1)} \leqslant \delta, \quad \text{or} \quad t_2 - t_1 \geqslant -\frac{3}{K_D(0)}\log\left(\frac{\delta}{R_1}\right).$$

Substituting these estimates into (7.20) we find that

$$\delta^3 \geqslant R_1^3 \min_{0\leqslant r\leqslant 1} p(r, t_1)\left(\frac{\delta}{R_1}\right)^{-3a/K_D(0)},$$

or

$$\left(\frac{\delta}{R_1}\right)^{3+3a/K_D(0)} \geqslant \min_{0\leqslant r\leqslant 1} p(r, t_1). \tag{7.21}$$

We next derive a lower bound for $\min_{0\leqslant r\leqslant 1} p(r, t_1)$.

Let $M_0 = \min\{R_0, R^*\} = 2R_1$. Since $R(t_1) = R_1 < M_0$ and $R(0) = R_0 \geqslant M_0$, there exists a t_0, $0 \leqslant t_0 < t_1$, such that

$$R(t_0) = M_0 \quad \text{and} \quad R(t) \leqslant M_0 \quad \text{for } t_0 \leqslant t \leqslant t_1.$$

By Lemma 7.3, it follows that $\min_{0\leqslant r\leqslant 1} p(r,t) \geqslant \hat{z}(t-t_0)$ for $t_0 \leqslant t \leqslant t_1$; in particular,

$$\min_{0\leqslant r\leqslant 1} p(r,t_1) \geqslant \hat{z}(t_1 - t_0). \tag{7.22}$$

Since $R(t_0) = M_0$ and $R(t_1) = R_1$, using again (7.9) we get

$$M_0 \mathrm{e}^{-\frac{1}{3}K_D(0)(t_1-t_0)} \leqslant R_1,$$

or

$$t_1 - t_0 \geqslant -\frac{3}{K_D(0)} \log\left(\frac{R_1}{M_0}\right) = \frac{3\log 2}{K_D(0)} \equiv a_0.$$

Substituting this into the right-hand side of (7.22) we obtain a lower bound on p:

$$\min_{0\leqslant r\leqslant 1} p(r,t_1) \geqslant \hat{z}(a_0),$$

which, combined with (7.21), yields

$$\left(\frac{\delta}{R_1}\right)^{3+3a/K_D(0)} \geqslant \hat{z}(a_0). \tag{7.23}$$

This is a contradiction if we take

$$\delta < R_1(\hat{z}(a_0))^{K_D(0)/(3(a+K_D(0)))}.$$

Hence the lower bound in (7.10) holds.

The upper bound in (7.10) can be established similarly to the proof of Theorem 6.1, by using the identity:

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}&[2V_P(t) + V_Q(t)]\\ &= R^3(t)\int_0^1 \{-[K_D(c)q + (K_Q(c) + 2K_A(c))p] + [2K_B(c)p + K_P(c)q]\} r^2\,\mathrm{d}r\end{aligned}$$

(recall that in the present case $V(t) = V_P(t) + V_Q(t)$). □

REMARK 7.1 The assumption $K'_B(c) + K'_D(c) > 0$ made in **(a)** is used in this paper only in the proof of Lemma 7.3, namely, in asserting that the function in (7.14) is increasing in c. This assumption (which is based on experimental data; see [20]), can actually be dropped if in (7.11) we replace $K_M(c_0)$ by $\tilde{K}_M(c_0)$ where $\tilde{K}_M = K_M - K_D$. Then $\tilde{K}_M \leqslant K_M$ and we replace (7.14) by

$$K_P(c) + [K_M(c) - K_N(c)]p - K_M(c)p^2 \geqslant K_P(c)(1-p) + \tilde{K}_M(c)(1-p)p - K_Q(c)p,$$

and observe that the right-hand side is increasing in c for fixed p, so that (7.15) holds with $K_M(c_0)$ replaced by $\tilde{K}_M(c_0)$.

8. The case $K_R = 0$

In the case $K_R = 0$, dead cells are not removed from the tumor, and from (2.19) we have

$$\dot{R}(t) = R(t) \int_0^1 K_B(c(r, R(t)))p(r,t)r^2\,\mathrm{d}r \geqslant 0, \tag{8.1}$$

so that $R(t)$ increases in t. As $R(t)$ increases, the nutrient concentration $c(r, R(t))$ decreases and therefore so does the proliferation rate. Thus, it is not *a priori* clear whether $R(t)$ tends to ∞ or whether it remains bounded. We shall prove that the first alternative occurs, at least under the assumptions that

$$p(r,0) \not\equiv 0, \quad p_r(r,0) \geqslant 0 \quad \text{and} \quad d_r(r,0) \leqslant 0 \quad (0 \leqslant r \leqslant 1), \tag{8.2}$$

$$K_D(c) \geqslant K_A(c) \quad (0 \leqslant c \leqslant 1). \tag{8.3}$$

The assumption (8.3) is natural: the rate of death of quiescent cells is larger than that of proliferating cells. The assumption (8.2) is related to the experimental fact that dead cells tend to concentrate in the inner region of the tumor whereas proliferating cells tend to concentrate in the outer region of the tumor.

THEOREM 8.1 Assume that $K_R = 0$ and that (8.2), (8.3) hold. Then

$$\lim_{t\to\infty} R(t) = \infty. \tag{8.4}$$

To prove this result, we need some preliminary lemmas.

LEMMA 8.2 Let $K_R = 0$ and assume that (8.2) and (8.3) hold. Then

$$p_r(r,t) \geqslant 0, \quad d_r(r,t) \leqslant 0 \quad \text{for all } 0 \leqslant r \leqslant 1,\ t \geqslant 0. \tag{8.5}$$

Proof. Set $w = 1 - d = p + q$. Then $w_r = -d_r$, so that by differentiating (2.20) in r and replacing q_r with $w_r - p_r$ we get

$$\frac{\partial w_r}{\partial t} + v\frac{\partial w_r}{\partial r} = b_{11}w_r + b_{12}p_r + b_{10},$$

where

$$b_{11} = -v_r - K_B(c)p - K_D(c), \quad b_{12} = K_B(c)d + K_D(c) - K_A(c),$$
$$b_{10} = [K_B'(c)dp - K_A'(c)p - K_D'(c)q]c_r.$$

Similarly, by differentiating (2.10) in r we obtain

$$\frac{\partial p_r}{\partial t} + v\frac{\partial p_r}{\partial r} = b_{21}w_r + b_{22}p_r + b_{20},$$

where

$$b_{21} = K_P(c), \quad b_{22} = -v_r + K_B(c)(1-2p) - K_P(c) - K_Q(c) - K_A(c),$$
$$b_{20} = \{[K_B'(c)(1-p) - K_Q'(c) - K_A'(c)]p + K_P'(c)q\}c_r.$$

Clearly, b_{12}, b_{10}, b_{21} and b_{20} are nonnegative, by (8.3) and the assumption (**a**) (in §2). Hence by comparison (cf. the proof of Theorem 4.1) we conclude that $w_r(r,t) \geqslant 0$, $p_r(r,t) \geqslant 0$ for all $0 \leqslant r \leqslant 1$, $t \geqslant 0$, and the desired assertion follows. □

LEMMA 8.3 Let $K_R = 0$ and assume that (8.2), (8.3) hold. Then $v(r,t) \leqslant 0$ for all $0 \leqslant r \leqslant 1$, $t \geqslant 0$.

Proof. Since $v(r,t) = u(r,t) - ru(1,t)$ and $\frac{\partial u}{\partial r} + \frac{2}{r}u = K_B(c)p$, we have

$$\frac{\partial}{\partial r}\left(\frac{\partial v}{\partial r} + \frac{2}{r}v\right) = \frac{\partial}{\partial r}\left(\frac{\partial u}{\partial r} + \frac{2}{r}u\right) = K_B(c)p_r + K_B'(c)pc_r,$$

so that, by Lemma 8.2,

$$\frac{\partial^2 v}{\partial r^2} + \frac{2}{r}\frac{\partial v}{\partial r} - \frac{2}{r^2}v \geqslant 0 \quad \text{for } 0 < r < 1,\ t > 0.$$

Since $v(0,t) = v(1,t) = 0$ for all $t \geqslant 0$, the assertion that $v \leqslant 0$ follows by the maximum principle. □

Let $\bar{p} = \bar{p}(r,t)$ be the solution of the initial value problem

$$\begin{cases} \dfrac{\partial \bar{p}(r,t)}{\partial t} = [K_B(c) - K_Q(c) - K_A(c) - K_B(c)\bar{p}]\bar{p} \quad \text{for } 0 \leqslant r \leqslant 1,\ t > 0 \\ \bar{p}(r,0) = p(r,0) \quad \text{for } 0 \leqslant r \leqslant 1, \end{cases} \tag{8.6}$$

where $c = c(r, R(t))$ as before. It is easily seen that this problem has a unique solution for all $0 \leqslant r \leqslant 1$, $t \geqslant 0$, and that the following holds:

LEMMA 8.4 Assume that $\lim_{t\to\infty} R(t) = R_\infty < \infty$, and that $p(r,0)$ is continuous, $p(r,0) \geqslant 0$ and $p(r,0) \not\equiv 0$ $(0 \leqslant r \leqslant 1)$. Then

$$\lim_{t\to\infty} \bar{p}(r,t) = \bar{p}_\infty(r) \equiv \max\left\{0, 1 - \frac{(K_Q + K_A)(c(r,R_\infty))}{K_B(c(r,R_\infty))}\right\} \quad \text{for } 0 \leqslant r \leqslant 1. \qquad \square$$

Proof of Theorem 8.1. By (8.1), $R(t)$ is increasing. If (8.4) does not hold then

$$R(t) \nearrow R_\infty \quad \text{as } t \to \infty, \quad \text{where} \quad R_\infty < \infty. \tag{8.7}$$

We shall prove that (8.7) leads to a contradiction.

Let $\bar{p}(r,t)$ be as in Lemma 8.4. By Lemmas 8.2, 8.3 and (2.10) we have

$$\frac{\partial p}{\partial t} \geqslant [K_B(c) - K_Q(c) - K_A(c) - K_B(c)p]p \quad \text{for } 0 \leqslant r \leqslant 1,\ t > 0,$$

so that, by comparison with (8.6),

$$p(r,t) \geqslant \bar{p}(r,t) \quad \text{for } 0 \leqslant r \leqslant 1,\ t \geqslant 0.$$

It follows that

$$\dot{V}(t) = R^3(t)\int_0^1 K_B(c(r,R(t)))p(r,t)r^2\,\mathrm{d}r \geqslant K_B(c(0,R_\infty)) \cdot R^3(t)\int_0^1 \bar{p}(r,t)r^2\,\mathrm{d}r,$$

where, as before, $V(t) = R^3(t)/3$. Using Lemma 8.4 and noticing that $\bar{p}_\infty(r) \geqslant 0$, $\bar{p}_\infty(r) \not\equiv 0$ for $0 \leqslant r \leqslant 1$, we conclude that

$$\liminf_{t\to\infty} \dot{V}(t) \geqslant K_B(c(0,R_\infty))R_\infty^3 \int_0^1 \bar{p}_\infty(r)r^2\,\mathrm{d}r > 0,$$

which implies that $\lim_{t\to\infty} V(t) = \infty$, thus contradicting (8.7). □

9. Conclusion

In this paper we have considered a mathematical model of tumor growth in which living cells may change from proliferating phase to quiescent phase and vice versa. The model involves also dead cells which are removed from the tumor at rate K_R. We established the existence and uniqueness of a global solution, for any given initial data. We also derived global bounds for the radius $R(t)$ of the tumor:

$$\delta_0 \leqslant R(t) \leqslant M \quad \text{for all } t > 0, \text{ if } K_R > 0, \tag{9.1}$$

and $R(t) \to \infty$ as $t \to \infty$ if $K_R = 0$; here δ_0 and M are positive constants. The inequalities in (9.1) suggest that a stationary solution with (finite) positive radius R_∞ should exist. This was recently proved (in [13]) but only for a subsystem of the model, which formally corresponds to the case $K_R = \infty$. The existence of stationary solutions for the general system, and the determination of their stability, remain open problems.

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