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FREE BOUNDARY PROBLEMS ARISING IN TUMOR MODELS

Abstract. — We consider several simple models of tumor growth, described by systems of PDEs, and describe results on existence of solutions and on their asymptotic behavior. The boundary of the tumor region is a free boundary. In §1 the model assumes three types of cells, proliferating, quiescent and necrotic, and the corresponding PDE system consists of elliptic, parabolic and hyperbolic equations. The model in §2 assumes that the tumor has only proliferating cells. Finally in §3 we consider a model for treatment of tumor, described by a system of elliptic and hyperbolic equations.

Key words: Free boundary problems; Asymptotic stability; Tumor models; Treatment of cancer.

1. A model with three populations of cells

We assume that in the tumor region $\Omega(t)$ there are three types of cells: proliferating cells with density p, quiescent cells with density q, and necrotic cells with density r. Nutrient (*e.g.* oxygen) with concentration c is diffusing in $\Omega(t)$ and affects the transition of cells from one type to another:

$$p \to q \text{ at rate } k_Q(c), \quad q \to p \text{ at rate } k_P(c),$$

$p \to r$ and $q \to r$ at rates $k_A(c)$ and $k_D(c)$ respectively, and $p \to p$ at proliferation rate $k_B(c)$. Necrotic cells are removed from the tumor at constant rate k_R. By conservation of mass,

$$\frac{\partial p}{\partial t} + \operatorname{div}(p\vec{v}) = [k_B(c) - k_Q(c) - k_A(c)]p + k_P(c)q,$$

$$\frac{\partial q}{\partial t} + \operatorname{div}(q\vec{v}) = k_Q(c)p - [k_P(c) + k_D(c)]q,$$

$$\frac{\partial r}{\partial t} + \operatorname{div}(r\vec{v}) = k_A(c)p + k_D(c)q - k_R r$$

where $\vec{v}$ is the velocity of cells, caused by motions due to proliferation and removal of cells. We assume that the tumor is a porous medium so that, by Darcy's law,

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

We further assume that the total density of the cells is constant,

$$p + q + r = \text{const} = N$$

and take, for simplicity, $N = 1$. Adding the first three equations we get an equation for σ, namely, $\Delta\sigma = -k_B(c)p + k_R r$. We can then eliminate the equation for r, and set $r = 1 - p - q$ in the equation for σ. Introducing also a diffusion equation for the nutri-

ent concentration c, we arrive at the following system of equations:

$$\varepsilon_0 \frac{\partial c}{\partial t} - \Delta c + \lambda c = 0 \text{ in } \Omega(t), \tag{1.1}$$

$$\frac{\partial p}{\partial t} + \nabla\sigma\cdot\nabla p = f(c, p, q) \text{ in } \Omega(t), \tag{1.2}$$

$$\frac{\partial q}{\partial t} + \nabla\sigma\cdot\nabla q = g(c, p, q) \text{ in } \Omega(t) \tag{1.3}$$

$$\Delta\sigma = -h(c, p, q) \text{ in } \Omega(t) \tag{1.4}$$

where $\varepsilon_0 \geqslant 0$,

$$f(c, p, q) = [k_B(c) - k_Q(c)]p + k_P(c)q + h(c, p, q)p,$$

$$g(c, p, q) = k_Q(c)p - [k_P(c) + k_D(c)]q + h(c, p, q)q,$$

$$h(c, p, q) = -k_R + [k_B(c) + k_R]p + k_R q.$$

Denote the boundary of $\Omega(t)$ by $\Gamma(t)$. Then

$$c = \bar{c} \text{ on } \Gamma(t) \quad (\bar{c} \text{ positive constant}), \tag{1.5}$$

$$\sigma = \gamma\kappa \text{ on } \Gamma(t), \tag{1.6}$$

$$\frac{\partial\sigma}{\partial n} = -V_n \text{ on } \Gamma(t) \tag{1.7}$$

where n is the outward normal and V_n is the velocity of $\Gamma(t)$ in the normal direction, κ is the mean curvature ($\kappa = 1/R$ for a ball of radius R), and γ is the surface tension coefficient. Equations (1.1)-(1.4) were first introduced by Pettet *et al.* [15] in the radially symmetric case in order to explain some experimental results. The condition (1.6) was introduced already in early tumor models (Greenspan [14]). From the definition of the various rate functions it is clear that $k_B(c)$ and $k_P(c)$ are monotone increasing in c, whereas $k_D(c)$, $k_Q(c)$ and $k_A(c)$ are monotone decreasing in c.

We complement the system (1.1)-(1.7) with initial conditions:

$$\begin{cases} \Omega(t)\big|_{t=0} = \Omega_0 \text{ is given}, \\ p\big|_{t=0} = p_0(x) \geqslant 0, \ q\big|_{t=0} = q_0(x) \geqslant 0, \ p_0(x) + q_0(x) \leqslant 1, \\ \text{and } c\big|_{t=0} = c_0(x) \text{ is given if } \varepsilon_0 > 0, \ c_0(x) \geqslant 0. \end{cases} \tag{1.8}$$

THEOREM 1 (Chen and Friedman [5]). *If $\varepsilon_0 = 0$, p_0, q_0 belong to $C^{m+1+\alpha}(\overline{\Omega}_0)$ for some integer $m \geqslant 1$ and $0 < \alpha < 1$, and $\partial\Omega_0$ belong to $C^{m+1+\alpha}$, then there exists a unique solution of* (1.1)-(1.8) *for some time interval $0 < t \leqslant T$ such that p, q, c and their first $m+1$ derivatives in (x, t) are in $C^{\alpha, \alpha/3}\left\{\bigcup_{0\leqslant t\leqslant T}\overline{\Omega}(t)\times\{t\}\right\}$ and $\left\{\bigcup_{0\leqslant t\leqslant T}\Gamma(t)\times\{t\}\right\}$ has $D_s D_{s,t}^m$ derivatives which belong to $C^{3+\alpha,(3+\alpha)/2}$ (s is a local coordinate in $\partial\Omega_0$).*

The proof requires a careful study of the inhomogeneous Hele-Shaw problem:

$$\Delta\sigma = k(x, t) \text{ in } \Omega(t),$$

subject (1.6), (1.7).

Theorem 1 extends to the case $\varepsilon_0 > 0$.

As in the Hele-Shaw problem where $\Delta\sigma = 0$ in $\Omega(t)$ subject to (1.6), (1.7), we cannot expect to have global existence for (1.1)-(1.8). However, in the case of spherically symmetric data

$$\Omega_0 = \{r < R_0\}, \quad p_0 = p_0(r), \quad q_0 = q_0(r) \tag{1.9}$$

we have:

THEOREM 2 (Cui and Friedman [8]). *Under the additional assumption* (1.9), *there exists a unique global spherically symmetric solution for the system* (1.1)-(1.8), *and the free boundary* $r = R(t)$ *satisfies*

$$\delta_0 \leqslant R(t) \leqslant A_0 \quad \forall t > 0 \tag{1.10}$$

where δ_0, A_0 *are positive constants.*

In this theorem it is assumed that the functions $k_X(c)$ satisfy the following conditions;

$$\begin{cases} k_B'(c) > 0, \quad k_P'(c) > 0, \quad k_A'(c) \leqslant 0, \quad k_D'(c) < 0, \\ k_Q'(c) < 0, \quad k_B'(c) + k_D'(c) > 0, \\ k_B(0) = k_P(0) = 0, \quad k_A(1) = k_D(1) = k_Q(1) = 0. \end{cases} \tag{1.11}$$

Theorem 2 suggests that $R(t)$ might converge to a limit as $t \to \infty$. This, however, has not been proved. Nor is it known whether spherically symmetric stationary solutions exist. But some results are known in case we assume that there are only two types of cells in the tumor, namely, proliferating and quiescent. In this case $r \equiv 0$, $q \equiv 1 - p$ and we have:

THEOREM 3 (Cui and Friedman [8]). *In the special case of two types of cells, proliferating and quiescent, there exists a unique spherically symmetric stationary solution.*

More recently it was proved by Chen, Cui and Friedman [4] that this solution is linearly asymptotically stable with respect to spherically symmetric perturbations.

2. TUMOR WITH ONLY PROLIFERATING CELLS

In this section we consider a tumor model whereby all the cells are proliferating. This means, in the notation of §1, that $p \equiv 1$, $q \equiv 0$, $r \equiv 0$. We assume that the proliferation rate is given by

$$k_B(c) = \mu(c - \tilde{c})$$

where $\tilde{c}$ is a positive constant, so that analogously to (1.4) we have

$$\Delta\sigma = -\mu(c - \tilde{c}) \text{ in } \Omega(t). \tag{2.1}$$

Note that our choice of $k_B(c)$ is different from that in (1.11). We consider the system (1.1), (2.1) with the same free boundary conditions (1.5)-(1.7) and with the initial conditions

$$\Omega(t)\,|_{t=0} = \Omega_0, \quad c\,|_{t=0} = c_0(x). \tag{2.2}$$

This model was considered by Byrne and Chaplain [3]. Friedman and Reitich [10] proved that (*i*) for initial spherically symmetric data there exists a unique global spherically symmetric solution with free boundary $v = R(t)$; (*ii*) if

$$\frac{\tilde{c}}{\bar{c}} < 1$$

then there exists a unique spherically symmetric stationary solution, and (*iii*) the stationary solution is asymptotically stable with respect to spherically symmetric small perturbations.

For the stationary solution (σ_s, c_s, R_s), in the 2-d case R_s is given by

$$\frac{I_1(R_s)}{I_0(R_s)} = \frac{\tilde{\sigma}}{2\,\bar{\sigma}} R_s$$

and $c_s(r)$ is given by

$$c_s(r) = \bar{\sigma} I_0(r)/I_0(R_s)$$

where $I_m(r)$ is the Bessel function of the second kind; similar formulas can be derived in the 3-d case.

The existence of a local solution for general initial data was established by Bazaliy and Friedman [1]; the proof uses Sobolev norms rather than the Hölder norms which were used in the proof of Theorem 1.

Consider now general perturbation of the spherically symmetric stationary solution:

$$\partial\Omega_0\colon\ r = R_s + \varepsilon f(\theta, \varphi) \qquad c_0(r) = c_s(r) + \varepsilon g(r, \theta, \varphi) \tag{2.3}$$

THEOREM 4 (Bazaliy and Friedman [2]). *If μ is sufficiently small then if $|\varepsilon|$ is sufficiently small there exists a global solution to the system* (1.1), (2.1), (1.5)-(1.7) *with initial condition* (2.2), (2.3) *and*

$$\Gamma(t) \to \{r = R_s\}$$

exponentially fast as $t \to \infty$.

It was proved by Friedman and Reitich [11, 12] in the 2-d case and by Fontelos and Friedman [9] in the 3-d case that there exist symmetry-breaking bifurcation

branches of stationary solutions, at bifurcation points

$$\mu_2 < \mu_3 < \ldots < \mu_n < \ldots \quad (\mu_n \to \infty \text{ if } n \to \infty).$$

Therefore Theorem 4 cannot be extended to $\mu = \mu_2$. The question whether Theorem 4 is valid for all $\mu < \mu_2$ remains open.

The proof of Theorem 4 is valid also if $\mu = 0$; this Hele-Shaw case is already well known.

3. Treatment of cancer

When a drug or «inhibitor» is present in the tumor, one may describe it by a diffusion process. For example, the model in §2 may be augmented by introducing a diffusion equation for the concentration of an inhibitor. This was done [3]; mathematical analysis of the model was carried out in [6]. Here we shall describe a more specific approach to tumor therapy, based on injection of genetically engineered virus into the tumor. The virus particles move into the tumor cells, infect them, and multiply inside them. When an infected cell dies, the virus particles burst out and infect adjacent tumor cells. We shall consider here only the spherically symmetric case, although the extension to general initial conditions, by analogy to §1, is straightforward.

We denote by $x(r, t)$ the density of uninfected tumor cells, by $y(r, t)$ the density of infected cells, by $z(r, t)$ the density of necrotic cells, and by $v(r, t)$ the density of free virus in the tumor. As in §1 we assume that

$$x(r, t) + y(r, t) + z(r, t) \equiv \text{const} = \theta; \tag{3.1}$$

since the virus particles are much smaller than the tumor cells, their density is neglected in (3.1). We use conservation of mass for x, y and z (as in §1), add the three equations to get (using (3.1)) an equation for the radial velocity, and finally drop the equation for z. After rescaling (taking $\theta = 1$) we obtain the following system:

$$\frac{\partial x(r, t)}{\partial t} = \lambda x(r, t) - p_0 \gamma x(r, t) v(r, t) - \frac{1}{r^2} \frac{\partial}{\partial r} [r^2 u(r, t) x(r, t)], \tag{3.2}$$

$$\frac{\partial y(r, t)}{\partial t} = p_0 \gamma x(r, t) v(r, t) - \delta y(r, t) - \frac{1}{r^2} \frac{\partial}{\partial r} [r^2 u(r, t) y(r, t)], \tag{3.3}$$

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 u(r, t)) = \lambda x(r, t) - \mu [1 - x(r, t) - y(r, t)], \quad u(0, t) = 0 \tag{3.4}$$

in the tumor region $\{r < R(t), t > 0\}$, where the left-hand side of (3.4) is $\nabla^2 \sigma$, $\sigma =$ pressure. The equation for $v(r, t)$ is

$$\frac{\partial v(r, t)}{\partial t} = \delta y(r, t) - \gamma v(r, t) + \kappa_0 R^2(t) \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial v}{\partial r} \right), \quad \frac{\partial v(0, t)}{\partial r} = 0, \quad \kappa_0 > 0. \tag{3.5}$$

In the above equations λ is the proliferation rate of uninfected cancer cells, β is the infection rate of uninfected cells, δ is the death rate of infected cells, μ is the removal rate of necrotic cells, γ is the removal rate of virus particles, and $p_0 = \beta\theta N/\gamma$ where N is the bust size of virus emerging from a dead cancer cell.

We complement the system (3.2)-(3.5) with the free boundary conditions

$$\frac{\partial v}{\partial r}(R(t), t) = 0, \tag{3.6}$$

$$\frac{dR(t)}{dt} = u(R(t), t), \tag{3.7}$$

and prescribe initial conditions

$$R(0) \text{ is given}, \quad x(r, 0) = x_0(r),\ y(r, 0) = y_0(r),\ v(r, 0) = v_0(r) \tag{3.8}$$

where $x_0(r)$, $y_0(r)$, $v_0(r)$ are nonnegative functions and $x_0(r) + y_0(r) \leqslant 1$.

The above system with $\kappa_0 = 0$ was introduced by Wu *et al.* [16]; adding the diffusion term in (3.5) is essential for making the system mathematically well posed (as shown in [13]), but it is also reasonable since the virus particles have Brownian nature.

THEOREM 5 (Friedman and Tao [13]). *The system* (3.2)-(3.8) *has a unique global solution, and*

$$\delta_0 e^{-bt} \leqslant R(t) \leqslant A_0 e^{bt} \quad \forall t > 0 \tag{3.9}$$

where δ_0, A_0, b *are positive constants.*

Note the similarity between the system (3.2)-(3.7) and (1.1)-(1.7) (in the radial case). There are of course some differences in the differential equations and in the boundary conditions. In particular notice that instead of the assertion (1.10) we have the much cruder bounds (3.9) for $R(t)$. The interesting question here is whether $R(t)$ can remain bounded, or even go to zero as $t \to \infty$, by appropriate injection $v_0(r)$ of virus particles.

In order to address this question we perform a change of variables

$$p = \frac{r}{R(t)}, \quad \tilde{x}(p, t) = x(r, t), \quad \tilde{y}(p, t) = y(r, t),$$

$$\tilde{v}(p, t) = v(r, t), \quad \tilde{u}(p, t) = u(r, t)$$

and obtain a new system for $\tilde{x}$, $\tilde{y}$, $\tilde{v}$, $\tilde{u}$ with initial values

$$\tilde{x}_0(p), \quad \tilde{y}_0(p), \quad \tilde{v}_0(p).$$

We next examine all the possible stationary solutions (x_s, y_s, v_s, u_s) with constant densities. We easily find that there are just four such solutions of (3.2)-(3.5), namely

$$(x_s, y_s) = (0, 0), (1, 0), \left(0, 1 - \frac{\delta}{\mu}\right) \text{ (provided } \delta < \mu), \tag{3.10}$$

and

$$(x_s, y_s) = \left(\frac{\lambda\mu - p_0\delta\mu + p_0\delta^2 + \mu\delta}{(p_0\delta - \lambda)p_0\delta}, \quad \frac{(\lambda + \mu)(p_0\delta - \delta - \lambda)}{(p_0\delta - \lambda)p_0\delta} \right) \tag{3.11}$$

provided each component is nonnegative, and

$$v_s = \frac{\delta}{\gamma} y_s \tag{3.12}$$

$$u_s = \frac{1}{3}(-\mu + (\lambda + \mu)x_s + \mu y_s)r \tag{3.13}$$

in all cases. Consider first the case $(x_s, y_s) = (0, 1 - \delta/\mu)$:

THEOREM 6 (Friedman and Tao [13]). *Let $R(0)$ be arbitrary, and assume that*

$$p_0 > \frac{\mu(\lambda + \delta)}{\delta(\mu - \delta)}.$$

If

$$\left\| \tilde{x}_0(p) - 0, \tilde{y}_0(p) - \left(1 - \frac{\delta}{\mu}\right), \tilde{v}_0(p) - \frac{\delta}{\gamma}\left(1 - \frac{\delta}{\mu}\right) \right\|_{C^1[0,1]}$$

is sufficiently small then $\dot{R}(t) < 0$ for all $t > 0$ and

$$R(t) \leqslant e^{-at} \text{ as } t \to \infty, \text{ for some } a > 0.$$

This result shows that no matter how large the initial tumor is, we can nontheless decrease its size at exponential rate by injecting a dose close to $\frac{\delta}{\gamma} y_s$, provided initially the density of the infected cells is approximately $1 - \delta/\mu$ and the density of uninfected cells is sufficiently small.

A similar result holds in the case (3.11), but not for the other two stationary solutions. These results suggest an interesting problem in optimal control: Given any initial values of $\tilde{x}_0(p)$, $\tilde{y}_0(p)$, find the best choice of $\tilde{v}_0(p)$ to reduce the tumor, under some constraints, such as $\|\tilde{v}_0\|_{L^\infty} \leqslant K$.

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