



## A two-phase free boundary problem with discontinuous velocity: Application to tumor model

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### ABSTRACT

We consider a two-phase free boundary problem consisting of a hyperbolic equation for  $w$  and a parabolic equation for  $u$ , where  $w$  and  $u$  represent, respectively, densities of cells and cytokines in a simplified tumor growth model. The tumor region  $\Omega(t)$  is enclosed by the free boundary  $\Gamma(t)$ , and the exterior of the tumor,  $D(t)$ , consists of a healthy normal tissue. Due to cancer cell proliferation, the convective velocity  $\vec{v}$  of cells is discontinuous across the free boundary; the motion of the free boundary  $\Gamma(t)$  is determined by  $\vec{v}$ . We prove the existence and uniqueness of a solution to this system in the radially symmetric case for a small time interval  $0 \leq t \leq T$ , and apply the analysis to the full tumor growth model.

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### 1. Introduction

Free boundary problems are widely used in modeling tumor growth. In many existing models [1–4], it is sufficient to consider the dynamics of cells and chemicals only within the tumor region. However, the normal tissue surrounding the tumor sometimes needs to be included, in order to study the process of tumor angiogenesis, during which endothelial cells, from the blood vessels outside the tumor, move (by chemotaxis) toward the tumor region. The tumor and the normal tissue typically have different biological and physical properties. This is the situation considered in the present paper, where the tumor region  $\Omega(t)$  is surrounded by healthy normal tissue  $D(t)$ . The common boundary  $\Gamma(t)$  is a free boundary to be determined, and the overall region  $\Omega(t) \cup \Gamma(t) \cup D(t)$  is assumed to be fixed. Thus, what we consider in this paper is a two-phase free boundary problem. Both regions contain a variety of cells, signaling molecules, and oxygen, but the tumor tissue contains also cancer cells. The signaling molecules and oxygen diffuse in both regions. Cell movement is induced by chemotaxis; however, since cells are relatively large in comparison with the signaling molecules, their diffusion is ignored. We also assume that cells distributed themselves in such a manner that the total cell density in  $\Omega(t)$  is a constant, independent of time  $t$ . Since proliferation of cancer cells occurs only in  $\Omega(t)$ , cells need to “spread out” and, this results in convective velocity  $\vec{v}$ ; both cells and signaling (and oxygen) molecules are subject to this velocity within  $\Omega(t)$ . On the other hand there is no such velocity outside the tumor, i.e.,  $\vec{v} = 0$  in  $D(t)$ . The abrupt discontinuity of the velocity  $\vec{v}$  across the free boundary  $\Gamma(t)$  is the novel feature of this free boundary problem.

A full tumor model was developed in [5]. It consists of a coupled system of hyperbolic equations for the cells and parabolic equations for the signaling molecules and oxygen. The model was investigated in [5] by numerical methods. In the present paper we prove existence and uniqueness of a smooth solution with smooth free boundary, for a small time interval. For clarity we shall first carry out the mathematical analysis in the special case of just two PDEs, one hyperbolic and another parabolic; this will be done in Sections 2–5. The hyperbolic PDE represents the mass conservation law of cell densities and

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it includes the effect of chemotaxis and the convective velocity field  $\vec{v}$ . The parabolic PDE is a general reaction–diffusion equation of chemical densities. In Section 6 we shall apply the analysis to the full tumor model.

**2. The model**

For simplicity, the tumor is assumed to be radially symmetric as in [5], hence the domain  $\Omega(t) \cup D(t)$  is a fixed closed spherical domain with the radius  $L$  and  $\Omega(t)$  is a spheroid with the time-dependent radius  $r = R(t)$ . We consider the following free boundary problem for a hyperbolic–parabolic system on  $[0, L]$  for  $t > 0$ :

$$\frac{\partial w}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left[ r^2 w \left( v + \frac{\partial u}{\partial r} \right) \right] = g(w, u), \quad 0 < r < L; \tag{1}$$

$$\frac{\partial u}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left[ r^2 \left( \frac{\partial u}{\partial r} - vu \right) \right] + f(w, u), \quad 0 < r < L; \tag{2}$$

$$v(r, t) = \begin{cases} \frac{1}{r^2} \int_0^r \zeta^2 Q \left( w, u, \frac{\partial u}{\partial \zeta} \right) d\zeta & \text{if } 0 < r \leq R(t), \\ 0 & \text{if } R(t) < r < L, \end{cases} \tag{3}$$

$$\dot{R}(t) = v(R(t), t); \tag{4}$$

the domain  $[0, L]$  is large enough such that  $R(t) < L$ . This abstract system represents a general cell–cytokines interaction network, in which  $w$  represents the density of cells (e.g. tumor cells) and  $u$  represents the density of cytokines (e.g. those secreted by cells) or oxygen.

The initial and boundary conditions are

$$\begin{aligned} w(r, 0) &= w_0(r), & u(r, 0) &= u_0(r) \quad \text{for } 0 \leq r \leq L, \\ v(r, 0) &= v_0(r) = \begin{cases} \frac{1}{r^2} \int_0^r \zeta^2 Q \left( w_0, u_0, \frac{\partial u_0}{\partial \zeta} \right) d\zeta, & \text{if } 0 < r \leq R_0, \\ 0, & \text{if } R_0 < r < L \end{cases} \end{aligned} \tag{5}$$

$$R(0) = R_0,$$

and

$$\frac{\partial u}{\partial r} \Big|_{r=0} = \frac{\partial u}{\partial r} \Big|_{r=L} = 0, \quad v(0, t) = 0, \quad \text{for } t \geq 0. \tag{6}$$

We assume that the functions  $g, f$  have the forms

$$g(w, u) = w\tilde{g}(w, u), \quad f(w, u) = u\tilde{f}(w, u), \tag{7}$$

where  $\tilde{g}$  and  $\tilde{f}$  are functions of  $w$  and  $u$ , and that, for some constant  $K_0 > 0$ ,

$$\begin{aligned} \left\| \frac{\partial \tilde{g}}{\partial w} \right\|_{L^\infty} + \left\| \frac{\partial \tilde{g}}{\partial u} \right\|_{L^\infty} &\leq K_0; \\ \left\| \frac{\partial \tilde{f}}{\partial w} \right\|_{L^\infty} + \left\| \frac{\partial \tilde{f}}{\partial u} \right\|_{L^\infty} &\leq K_0; \\ \sum_{i,j=1}^3 \left\| \frac{\partial^2 Q}{\partial y_i \partial y_j} \right\|_{L^\infty} &\leq K_0. \end{aligned} \tag{8}$$

Additionally, we assume that

$$w_0(r) \geq 0, \quad u_0(r) \geq 0, \quad \frac{\partial u_0}{\partial r} \Big|_{r=0} = \frac{\partial u_0}{\partial r} \Big|_{r=L} = 0, \quad v_0(R_0-) > 0, \tag{9}$$

and

$$\begin{cases} \frac{\partial u_0}{\partial r} \Big|_{r=R_0-} > 0, \\ \frac{\partial u_0}{\partial r} \Big|_{r=R_0+} < v_0(R_0). \end{cases} \tag{10}$$

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