Nonlinear Analysis: Real World Applications 19 (2014) 45–53

Contents lists available at ScienceDirect

Nonlinear Analysis: Real World Applications

journal homepage: www.elsevier.com/locate/nonrwa

Bifurcation for a free boundary problem modeling tumor growth with inhibitors

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ARTICLE INFO

Article history:
Received 25 November 2013
Accepted 4 March 2014

ABSTRACT

This paper deals with a free boundary problem modeling tumor growth with inhibitors. This problem has a unique radially symmetric stationary solution with radius $r = R_s$. The tumor aggressiveness is modeled by a positive tumor aggressiveness parameter μ. It is shown that there exist a positive integer $m^{**} \in \mathbb{R}$ and a sequence of μ_m, such that for each $\mu_m (m > m^{**})$, symmetry-breaking solutions bifurcate from the radially symmetric stationary solutions.

1. Introduction

The mathematical models of tumor growth have been developed and studied since last century, many theoretical and numerical results are established for various tumor models; see review papers [1–5] and the references therein. Among those, the growth of solid tumor models, described by partial differential equations with a free boundary, has been given considerable attention in the past forty years; see [6–18]. Growth of the solid tumor phase can be regarded as a result of various interactions within the micro-environment, such as nutrient (e.g., oxygen and glucose), inhibitors (e.g., inhibitory material developed from the immune system of healthy cells, anti-cancer drugs and radiation administered by medical treatment), etc.

In this paper, the tumor model with the presence of an inhibitor is considered, such presence has implications to assess the efficacy of certain cancer treatments. For simplicity of exposition, we assume that the nutrient and the inhibitor are single species; the inhibitor inhibits the cell proliferation but does not play any role in nutrient concentration. We denote the concentrations of nutrient and inhibitor by σ and β, respectively, and then the distribution of externally supplied nutrient may be given by the following reaction–diffusion equation (see [6,19,9,20,15]):

$$\frac{\partial \sigma}{\partial t} = D_1 \Delta \sigma + \hat{\Gamma}_1(\sigma_B - \sigma) - \lambda_1 \sigma \quad \text{in } \Omega(t), \tag{1.1}$$

where $\Omega(t)$ is the tumor domain at time t with a moving boundary $\partial\Omega(t)$, σ denotes the concentration of a nutrient which diffuses throughout the tumor, with diffusion coefficient D_1, the term $\hat{\Gamma}_1(\sigma_B - \sigma)$ accounts for the transfer of nutrient by means of the vasculature, whose presence stems from angiogenesis, see [19], and the last term on the right side describes the nutrient uptake by cells. Here $\hat{\Gamma}_1$ is the transfer rate of nutrient-in-blood-tissue; for the avascular case we have $\hat{\Gamma}_1 = 0$. σ_B is the concentration of nutrient in the vasculature and λ_1 is the rate of consumption of nutrient by the tumor cells.

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http://dx.doi.org/10.1016/j.nonrwa.2014.03.001
1468-1218/

Assume that the similar effects govern the evolution of the inhibitor in the tumor, and then from [19,21,22], it follows that:

$$\frac{\partial \beta}{\partial t} = D_2 \Delta \beta + \hat{\Gamma}_2(\beta_B - \beta) - \lambda_2 \beta \quad \text{in } \Omega(t), \tag{1.2}$$

where β_B and $\hat{\Gamma}_2$ denote the inhibitor concentration in the vasculature and the transfer rate of inhibitor-in-blood-tissue if the inhibitor is a blood-borne anti-cancer drug, respectively; $\hat{\Gamma}_2 = 0$ if the inhibitor is secreted by neighboring healthy cells. In response to the "foreign" body, the inhibitor is delivered by diffusion across the tumor boundary. Using non-dimensional scales (see [19,9,21]), Eqs. (1.1) and (1.2) can be rewritten as

$$\delta_1 \frac{\partial \sigma}{\partial t} = \Delta \sigma - \sigma \quad \text{in } \Omega(t), \tag{1.3}$$

$$\delta_2 \frac{\partial \beta}{\partial t} = \Delta \beta - \lambda \beta \quad \text{in } \Omega(t), \tag{1.4}$$

where δ_1, δ_2 are small parameters.

We assume that the pressure p within the tumor comes from the proliferation of the tumor cells. We assume that the density of tumor cells is constant; the proliferation rate of the tumor cell is linearly dependent on the nutrient and the inhibitor, and then the rate of volume change $\nabla \cdot \mathbf{u}$ ($\mathbf{u}$ is the cell velocity) is given by conservation of mass

$$\frac{1}{\mu} \nabla \mathbf{u} = \sigma - \tilde{\sigma} - \tau \beta,$$

where μ is a parameter expressing the "intensity" of the expansion by mitosis, the term $\sigma - \tilde{\sigma}$ on the right side is the proliferation rate, $\tilde{\sigma}$ is a threshold concentration and the term $\tau\beta$ is the death rate of tumor caused by the inhibitor. Combining with Darcy's law, $\mathbf{u} = -\nabla p$, we get

$$\Delta p = -\mu(\sigma - \tilde{\sigma} - \tau \beta) \quad \text{in } \Omega(t) \tag{1.5}$$

and

$$p = \kappa \quad \text{on } \partial\Omega(t)$$

due to cell-to-cell adhesiveness; see [19]. Furthermore, assuming the continuity of the velocity field through the boundary, we obtain

$$\frac{\partial p}{\partial n} = -V_n \quad \text{on } \partial\Omega(t), \tag{1.6}$$

where V_n is the velocity of the free boundary in the exterior normal direction, and n is the exterior normal vector.

Since tumors grown in vitro have a nearly spherical shape, many papers discuss the radially symmetric tumor models. Thus, it is important to study the stability of the radially symmetric stationary solutions of the tumor models. In the present paper, we are interested in the bifurcation of steady-state solutions of the above free boundary problem. Namely, we consider the existence of symmetric-breaking stationary solution of the stationary problem:

$$\Delta \sigma = \sigma \quad \text{in } \Omega, \tag{1.7}$$

$$\Delta \beta = \lambda \beta \quad \text{in } \Omega, \tag{1.8}$$

$$\Delta p = -\mu(\sigma - \tilde{\sigma} - \tau \beta) \quad \text{in } \Omega, \tag{1.9}$$

$$\sigma = \overline{\sigma} \quad \text{in } \partial\Omega, \tag{1.10}$$

$$\beta = \overline{\beta} \quad \text{on } \partial\Omega, \tag{1.11}$$

$$p = \kappa \quad \text{on } \partial\Omega, \tag{1.12}$$

$$\frac{\partial p}{\partial n} = 0 \quad \text{on } \partial\Omega, \tag{1.13}$$

where Ω is a bounded domain in $\mathbb{R}^3$, λ, μ, $\tilde{\sigma}$, τ, $\overline{\sigma}$, $\overline{\beta}$ are positive constants and $\overline{\sigma} - \tilde{\sigma} - \tau\overline{\beta} > 0$, κ is the mean curvature.

For the case of the system (1.7)–(1.13) without inhibitors, i.e., $\beta = 0$, the authors of [23,20,24] proved the existence of a unique radially symmetric solution and there exists a sequence of symmetry-breaking stationary solutions for this system in the two-dimensional case and the three-dimensional case respectively. Numerical simulations were carried out by authors such as Cristini et al. [9], and Li et al. [25], in certain circumstances a small perturbation of a radially symmetric tumor will finally evolve into a radially non-symmetric configuration. The asymptotic stability of the stationary solutions was studied in [12,26,13]. For the case $\beta \neq 0$, the existence of radially symmetric stationary solution and its asymptotical stability under radially symmetric perturbations were analyzed by Cui and Friedman in [21,22]. In [27], Wu et al. investigated the asymptotic stability of a radially symmetric stationary solution under radially and non-radially symmetric perturbations;