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Bifurcation for a free boundary problem modeling tumor growth with ECM and MDE interactions

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ABSTRACT

We study a free boundary problem modeling solid tumor growth. The simplified model contains a parameter λ. Different from previous works on bifurcation analysis, a new ingredient of the present paper is that the influence of the extracellular matrix (ECM) and matrix degrading enzymes (MDE) interactions is included in the model. We first show that for each $\lambda > 0$, there exists a unique radially symmetric stationary solution with radius $r = R_S$. Then we prove that there exist a positive integer n^* and a sequence of λ_n $(n > n^*)$ for which branches of symmetry-breaking stationary solutions bifurcate from the radially symmetric one. In particular, we discover that these λ_n are larger than those $\widetilde{\lambda}_n$ previously known when the effects of ECM and MDE are not considered in the model.

1. Introduction

The focus of this paper is the bifurcation analysis of a free boundary model describing solid tumor growth with microenvironment interactions. Let $\Omega(t)$ in $\mathbb{R}^3$ denote the tumor region at time t, $\Gamma(t)$ the boundary of $\Omega(t)$, and $\mathbf{n}$ the unit outer normal vector to $\Gamma(t)$. We next give a brief description of the model.

Assuming that the density ν of the cells depends on the concentration σ of nutrients (e.g., oxygen and glucose) and that this dependence is linear, so we identify ν with σ in this paper. Following [1], we consider that the concentration σ of nutrients satisfies the reaction diffusion equation

$$\sigma_t = \overbrace{\nabla \cdot (D_\sigma \nabla \sigma)}^{diffusion} + \overbrace{\lambda_B(\sigma_B - \sigma)}^{transfer} - \overbrace{\lambda^\sigma_{decay}\sigma}^{decay} \quad \text{in } \Omega(t), \tag{1.1}$$

with the boundary condition

$$\sigma = \sigma_\infty \quad \text{on } \Gamma(t). \tag{1.2}$$

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Here, D_σ is the nutrient diffusion coefficient, σ_B is the concentration of nutrient in the blood, λ_B is the blood-tissue transfer rate of nutrient, λ^σ_{decay} is the rate of consumption of nutrient by the tumor cells, and σ_∞ is the external nutrient concentration. For simplicity, the vasculature is assumed to be uniform, and the nutrient is also uniform outside of the tumor.

During vascular tumor growth, the viable tumor cells and endothelial cells release matrix degrading enzymes (MDE) to degrade the extracellular matrix (ECM). Denote by E the ECM density and by M the level of MDE. M satisfies the reaction diffusion equation [2]

$$\frac{\partial M}{\partial t} = \overbrace{\nabla\cdot(D_M\nabla M)}^{diffusion} + \overbrace{\lambda^M_{prod_1}(1-MM_0^{-1})}^{production} - \overbrace{\lambda^M_{decay}M}^{decay} \quad \text{in } \Omega(t),$$

or [3]

$$\frac{\partial M}{\partial t} = \overbrace{\nabla\cdot(D_M\nabla M)}^{diffusion} + \overbrace{\lambda^M_{prod_2}\sigma}^{production} - \overbrace{\lambda^M_{decay}M}^{decay} \quad \text{in } \Omega(t),$$

where D_M is the MDE diffusion coefficient, M_0 is the maximum sustainable density for MDE, λ^M_{decay} is a decay constant, $\lambda^M_{prod_1}$ and $\lambda^M_{prod_2}$ represent the rates of production due to tumor cells and nutrient, respectively. In order to cover both cases, we assume that M satisfies

$$\frac{\partial M}{\partial t} = \overbrace{\nabla\cdot(D_M\nabla M)}^{diffusion} + \overbrace{\lambda^M_{prod_1}(1-MM_0^{-1}) + \lambda^M_{prod_2}\sigma}^{production} - \overbrace{\lambda^M_{decay}M}^{decay} \quad \text{in } \Omega(t), \tag{1.3}$$

with the boundary condition

$$\frac{\partial M}{\partial \mathbf{n}} = 0 \quad \text{on } \Gamma(t). \tag{1.4}$$

Since ECM does not diffuse, its model equation does not contain any diffusion term. According to [4], the ECM density $E(x,t)$ satisfies

$$\frac{dE}{dt} = -\overbrace{\lambda^E_{degr}ME}^{degradation} + \overbrace{\lambda^E_{prod}E(1-EE_0^{-1})}^{proliferation} \quad \text{in } \Omega(t), \tag{1.5}$$

where λ^E_{degr} is the degradation rate, λ^E_{prod} the proliferation rate, and E_0 the maximum sustainable density for ECM. Note that it is assumed that MDE used up in the interaction with the ECM with the rate λ^E_{degr} are negligible with the MDE production, so the term $-\lambda^E_{degr}ME$ does not appear in the dynamics (1.3) of MDE [4].

The pressure p within the tumor stems from the proliferation of the tumor cells and is related to the velocity $\vec{V}$ of the concentration σ. Assuming Darcy's law in the tissue, the velocity satisfies $\vec{V} = -\mu\nabla p$. It is known [1] that the ECM distribution can affect the development of tumor morphologies and vascular tumor growth. In [5], Macklin et al. established a model to characterize heterogeneous response to gradients of pressure and ECM adhesion via nonconstant cell mobility dependent of E and by introducing a haptotaxis velocity proportional to ∇E. That is, the velocity satisfies

$$\vec{V} = -\overbrace{\mu\nabla p}^{pressure\ gradient\ by\ mitosis} + \overbrace{\chi_E\nabla E}^{haptotaxis}.$$

Also see [1,6,7]. For simplicity, we here assume that μ and χ_E are constants.

Representing by λ_p the cell-proliferation rate, λ_A the rate of apoptosis, and λ^σ_{prod} a measure of mitosis, by conservation of mass, we have

$$\nabla\cdot\vec{V} = \lambda_p = \lambda^\sigma_{prod}\sigma - \lambda_A.$$