Applied Mathematics and Computation 245 (2014) 152–157

Contents lists available at ScienceDirect

Applied Mathematics and Computation

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

Analysis of an integro-differential system modeling tumor growth

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ARTICLE INFO

Keywords:
Integro-differential system
Stability
Invariant set
Pattern formation
Cancer stem cell

ABSTRACT

A mathematical model of integro-differential equations is studied to describe the evolution of a heterogeneous population of cancer stem cells and tumor cells. This model has recently been analyzed by Hillen et al., who reduced the analysis to a system of ordinary differential equations to prove the so-called "tumor growth paradox". In this paper we study the reaction–diffusion systems of integro-differential equations and we have the positivity and global existence of solution by an invariant set. The stability of steady states is investigated after having proven that every spatially inhomogeneous pattern disappears by using "energy estimates".

1. Introduction

Hillen et al. have recently proposed a mathematical model to elucidate the role of cancer stem cells (CSCs) and tumor cells (TCs) in cancer progression [12]. They proposed a reaction–diffusion system of integro-differential equations (PDE) that presents a "functional" reaction, which describes birth–death dynamics while the diffusion describes random movement in a given set Ω. For general results of methods in spatial dynamics we can refer to [9,16]. Hillen et al. reduced the analysis to a system of ordinary differential equations and, using the geometric singular perturbation theory, they explained the core idea of "the tumor growth paradox". Since data from Molecular Medicine of Tumors are often difficult to analyze many mathematical models of biomedical phenomena have been proposed [7]. Models for cancer often describe the growth of cancer by the interaction between cancer stem cells and tumor cells or between the "tumor" and the immune system [2–4,8,13]. The study of coexistence of species is one of the main topics in mathematical biology so many authors had proposed models of dynamic populations [15]. In [3] a system of delay differential equations is proposed to study qualitative behavior of stem cell evolution without and with an underlying signal, taking into account the chemotactic and haptotactic effect. Chauviere et al. proposed a model for the interaction between cells, or between cells and fibrous environment. In [11], Hek explains and explores the full geometric singular perturbation theory and its use in biological practice to understand the global structure of the phases space and to construct orbits with desired properties. Dawson and Hillen in [6] proposed a mathematical model for the radiation treatment of cancer so mathematical modeling is a helpful tool not only to study growth tumor and the cancer spread, but also to study the effectiveness of specific treatments.

[1] This work was written while the author was a visiting faculty at the Department of Mathematical Sciences of The Worcester Polytechnic Institute (Massachusset, U.S.).

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http://dx.doi.org/10.1016/j.amc.2014.07.081
0096-3003/

In this paper we will study the PDE system, model proposed by Hillen et al. [12], and investigate the properties of solutions. Taking into account the assumption that cells can migrate randomly, Hillen et al. proposed a linear diffusion for CSCs and TCs. The dynamics between CSCs and TCs is described by the following system

$$\frac{\partial u}{\partial t}(x,t) = d_1 \triangle u + \delta\gamma \int_\Omega K(x,y,p(x,t))u(y,t)dy, \tag{1.1}$$

$$\frac{\partial v}{\partial t}(x,t) = d_2 \triangle v + (1-\delta)\gamma \int_\Omega K(x,y,p(x,t))u(y,t)dy + \rho \int_\Omega K(x.y,p(x,t))v(y,t)dy - \alpha v(x,t), \ in\ \Omega \times \mathbb{R}_+,$$

with Neumann homogeneous boundary conditions:

$$\frac{\partial u}{\partial \nu} = 0 \quad and \quad \frac{\partial v}{\partial \nu} = 0 \ in\ \partial\Omega \times (0,T], \tag{1.2}$$

$\frac{\partial}{\partial \nu}$ is the outward normal and initial conditions

$$u(x,0) = u_0, \ v(x,0) = v_0 \ in\Omega. \tag{1.3}$$

In (1.1), $p(x,t) = u(x,t) + v(x,t)$ is the total tumor density, $u(x,t)$ is the density of cancer stem cells CSCs, and $v(x,t)$ is the density of tumor cells TCs. We observe that $u(x,t)$ and $v(x,t)$ denote the density, in cells per unity cell space, that is the fraction of the interval $(x, x+dx)$ physically occupied by cells. $\Omega \subset \mathbb{R}^n$ is a bounded domain with boundary $\partial\Omega$ $n-1$ dimensional sufficiently smooth manifold. The diffusion coefficients d_1 e d_2, are taken as constants $\geqslant 0$. The constants $\gamma > 0$ and $\rho > 0$ denote the number of cell cycle times for unit time of CSCs and TC respectively. The kernel $K(x,y,p(x,t))$ redistributes cells only within domain Ω, hence is equal to 0 for all $x \notin \Omega$, and for $x \in \Omega$, describes the rate of progeny contribution to location x from a cell at location y, per "cell cycle time" (i.e. the defined period between divisions of freely-cycling cell). For a complete and comprehensive presentation of the model, readers may refer to [12]. In the model we suppose that the kernel $K$is monotonically decreasing in p, continuous in its variables and satisfies a local Lipschitz condition, and:

$$0 \leqslant K(x,y,p(x,t)) \leqslant 1, \quad K(x,y,p(x,t)) = 0, \quad for\ p = 1, \quad |\Omega| = 1.$$

Taking into account these assumptions, we have that the solution exists and is bounded in time, and so a global existence results. In [12] the analysis of the reduced ODE system shows the existence of three steady states of system, the pure stem cell state $(1,0)$, the pure tumor cell state $(0,1)$ and the state $(0,0)$ with zero stem cell and zero tumor cell. In this case the only asymptotically stable solution in the positively invariant region is $(1,0)$, so if time goes to infinity the tumor will consist of cancer stem cells only while the state $(0,0)$ is a saddle point or unstable node. If we take into account the diffusion process we have three equilibria solutions as for ODE, but for suitable parameters the trivial solution can become locally asymptotically stable. Hence due to diffusion process we can have, for suitable parameters, a locally asymptotically stable trivial solution. An equilibrium solution locally asymptotic stable with zero stem cell and zero tumor cell exists. This means that a successful therapy may exist in some particular cases. More specifically in the ODE case in Section 2 we briefly present the results concerning the steady states. In Section 3 the existence of an invariant bounded set proves that the solution is positive, bounded and exists globally in time. In Section 4 we prove that there is no pattern formation, and in Section 5 the asymptotic behavior of solutions is studied.

2. ODE system

On the biological assumptions of the agent-based model of [8], Hillen et al. in [12] reduce this model to a nonlinear ordinary differential system to describe the time evolution of CSCs and TCs and assume:

$$k(x,y,p(x,t)) = k(\overline{p}(t)), \quad with\ \overline{p}(t) = \int_\Omega u(x,t)dx + \int_\Omega v(x,t)dx.$$

So now we present the dynamics that can arise in the system without the presence of diffusion. The problem (1.1)–(1.3) can be reduced to the following ODE problem:

$$u_t(t) = \delta K(p(t))u(t), \tag{2.1}$$

$$v_t(t) = (1-\delta)K(p(t))u(t) + \rho K(p(t))v(t) - \alpha v(t).$$

$$u(0) = u_0, \quad v(0) = v_0. \tag{2.2}$$

The steady states of system (2.1) are

$$P_0 = (0,0), P_1 = (K^{-1}(0),0) \ and \ P_2 = \left(0, K^{-1}\left(\frac{\alpha}{\rho}\right)\right). \tag{2.3}$$

If we use a linearization in the steady states P_i which yields a linear system, we can look at the eigenvalues of matrix of linearization, the Jacobian in P_i. Routh–Hurtwitz criteria in [5] give us necessary and sufficient conditions to have eigenvalue with real part < 0. So we can state: