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Avoiding healthy cells extinction in a cancer model

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HIGHLIGHTS

- The dynamics of three interacting cell populations of tumor cells, healthy host cells and immune effector cells is discussed.
- Transient chaotic behavior for a certain choice of parameters takes place before extinction of healthy and immune cells.
- The method of partial control is applied to avoid the extinction of the healthy tissue.
- The difficulties of applying such control method at the present state-of-the-art of cancer therapies are discussed.

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ABSTRACT

We consider a dynamical model of cancer growth including three interacting cell populations of tumor cells, healthy host cells and immune effector cells. For certain parameter choice, the dynamical system displays chaotic motion and by decreasing the response of the immune system to the tumor cells, a boundary crisis leading to transient chaotic dynamics is observed. This means that the system behaves chaotically for a finite amount of time until the unavoidable extinction of the healthy and immune cell populations occurs. Our main goal here is to apply a control method to avoid extinction. For that purpose, we apply the partial control method, which aims to control transient chaotic dynamics in the presence of external disturbances. As a result, we have succeeded to avoid the uncontrolled growth of tumor cells and the extinction of healthy tissue. The possibility of using this method compared to the frequently used therapies is discussed.

1. Introduction

Cancer is the result of an uncontrolled proliferation of tumor cells within a tissue that eventually can spread to new locations in the body. The loss of cooperative behavior of cancer cells arises as a consequence of accumulated mutations, and yields a complex evolutionary scenario in which tumor and healthy cells compete for space and scarce resources. Mathematical modeling has proven to be a useful tool for the understanding of many features concerning the complex interactions between tumor and healthy cells (Bellomo et al., 2008; Bajzer et al., 1996; Kuznetsov et al., 1994; d'Onofrio, 2005). Based on how the tumor tissue is represented, a vast number of cancer growth models fall into two main categories: discrete models and continuum models. The discrete cell based models are capable of describing biophysical processes in significant detail, considering the individual cells governed by a precise series of rules. However, for large-scale-systems, this method is very demanding and requires sophisticated computer simulations. An alternative to discrete methods is provided by the continuum approach, where tumors are treated as a collection of tissue, considering, among other possible elements, the description of densities or cell volume fractions and cell substrate concentrations. More particularly, carcinogenesis population-based models have often been used to study different aspects of tumor progression and settle therapy protocols (Sachs and Hlatky, 2001; Kirschner and Panetta, 1988; De Pillis and Radunskaya, 2003; De Pillis et al., 2005, 2006; Pinho et al., 2002; Nani and Freedman, 2000; Placeres Jiménez and Hernández, 2011; Freedman and Pinho, 2009; Panetta and Adam, 1995). Among these works some use ODE models, and frequently divide the problem into two clearly differentiated parts. The first one sets and describes the model itself, which generally consists of some Lotka–Volterra equations describing growth and death of cell populations, as well as competition between them. The second part is devoted to establish a treatment protocol, mainly chemotherapy, immunotherapy or radiotherapy, to reduce the tumor population in an optimal manner. Even though most of these models deal with more than two dimensions, not many of them (Itik and Banks, 2010; Letellier et al., 2013; Saleem and Agrawal, 2012;

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Ahmed, 1993) have seriously considered the situation in which cell populations behave in a chaotic fashion. From our point of view, the main reason why this occurs is that, in spite of the fact that there is experimental evidence of deterministic chaos in tumor cell populations (Wolfrom et al., 2000), in general evidence is not abundant and clear enough. Although chaotic dynamics of a growing tumor seems to be uncommon, it is more probable to appear when therapies are considered. Therefore, we think that chaos should not be disregarded in the study of tumor progression. In particular, as far as we are concerned, no one has mentioned the possibility of finding transient chaos in the populations of these tumor models. We believe that, since complex interactions take place between neoplastic, stromal and immune response cells, it is likely for transient chaotic dynamics to happen before tumor dominates the struggle. On the other hand, several methods to control transient chaos have been proposed along the last decades (Tèl, 1991; Schwartz and Triandaf, 1996; Kapitaniak and Brindley, 1998; Yang et al., 1995; Aguirre et al., 2004). Among them, the partial control method (Zambrano and Sanjuán, 2009; Sabuco et al., 2009, 2012a, 2012b) aims to control systems displaying chaotic transients in the presence of certain external disturbances (usually noise), using smaller controls. The main idea of partial control is to take advantage of the Cantor set structure embedded in a region of phase space containing the remnant of a chaotic attractor to avoid escaping from it by small perturbations. In this manner, we prevent the occurrence of a particular dynamics.

The purpose of this work is to show and control the existence of transient chaotic dynamics for certain values of the parameter space in a three dimensional cancer model consisting of interacting cell populations, similar to the one used in De Pillis and Radunskaya (2003), Itik and Banks (2010) and Letellier et al. (2013). These three populations are the tumor cells, the healthy host cells and the immune effector cytotoxic T-cells present at the tumor site. After examining the phase space of the model for the given parameters, and the boundary crisis leading to transient chaotic dynamics, the partial control method is applied to avoid tumor escape and uncontrolled growth, preventing from extinction of the healthy tissue. We discuss the main difficulties of applying such control method at the present state of the art of cancer treatments, as well as some others inherent to chaotic behavior.

The paper is organized as follows. In Section 2 we describe the model and discuss a set of parameters for which chaos takes place. We show the phase space portrait, study the equilibria of the system and comment the boundary crisis leading to transient chaotic dynamics. In Section 3 we explain the main features of the partial control method, and apply it to the cancer model in Section 4, preventing tumor escape. Finally, Section 5 is devoted as usual to conclusions and discussions.

2. Model description and phase space analysis

2.1. The model

We develop our investigations with a model used in Itik and Banks (2010) and Letellier et al. (2013). It is the same three dimensional Lotka–Volterra model than the one described in De Pillis and Radunskaya (2003), with the only difference that no constant input of effector immune cells is considered. Such input can be used to model innate immunity (De Pillis et al., 2005) or an immunotherapy protocol (Kirschner and Panetta, 1988). Each of the variables represents a cell population, namely $T(t)$ the tumor cells, $H(t)$ the healthy host cells near the tumor site, and $E(t)$ the effector immune cells. The growth of cancer and host cells is assumed to be logistic with growth rate r_i and carrying capacity k_i. Both compete with each other, the competition terms being given by a_{ij}. The production of immune cytotoxic T-cells is triggered by antigen presenting cells. Assuming that this process occurs at a enough smaller time scale than the one corresponding to tumor growth, the stimulation of the immune system by the tumor specific antigens can be considered to act instantly and modeled by a Michaelis–Menten law. The immune effector cell production rate in response to the presence of tumor cells is given by r_3, and the steepness of the response curve is associated to k_3, the value of the tumor cells at which the immune response rate is half of the maximum production, where the response curve saturates. These cells only compete with cancer cells and in their absence they die off with a constant per capita rate d_3. Therefore, the system of differential equations is

$$\begin{aligned}\dot{T} &= r_1 T\left(1-\frac{T}{k_1}\right) - a_{12}TH - a_{13}TE\\ \dot{H} &= r_2 H\left(1-\frac{H}{k_2}\right) - a_{21}HT\\ \dot{E} &= r_3\frac{ET}{T+k_3} - a_{31}ET - d_3E.\end{aligned} \tag{1}$$

The nondimensionalization and parameter reduction of this system are thoroughly studied in Itik and Banks (2010), yielding the set of equations

$$\begin{aligned}\dot{x} &= x(1-x) - a_{12}xy - a_{13}xz\\ \dot{y} &= r_2 y(1-y) - a_{21}yx\\ \dot{z} &= r_3\frac{zx}{x+k_3} - a_{31}zx - d_3z.\end{aligned} \tag{2}$$

2.2. Equilibria of the system

An exhaustive phase space analysis has been carried out in the previously cited references (De Pillis and Radunskaya, 2003; Itik and Banks, 2010). In the following, we restrict our attention to a particular set of parameter values for which the system has a chaotic attractor close to a boundary crisis. The choice of parameters in Eq. (2) is $a_{12}=0.5$, $a_{21}=4.8$, $a_{13}=1.2$, $a_{31}=1.1$, $r_2=1.20$, $r_3=1.291$, $d_3=0.1$ and $k_3=0.3$. The only significant differences of this setting compared to the one arranged in De Pillis and Radunskaya (2003) are given by parameters a_{12} and r_3, which take higher values in the present case. The biological meaning of this choice is that tumor cells are more aggressive in their competition with normal cells, and that the recruitment or response of the immune effector cells due to the presence of tumor cells is much stronger.

We now describe all the nullclines and equilibria for the current set of parameters. The fixed points of the system are given by $\dot{x}=\dot{y}=\dot{z}=0$ which yields the set of equations

$$\begin{aligned}0 &= x(1-x-a_{12}y-a_{13}z)\\ 0 &= y(r_2-r_2y-a_{21}x)\\ 0 &= z((r_3-k_3a_{13}-d_3)x-a_{31}x^2-k_3d_3).\end{aligned} \tag{3}$$

Nullclines can be read directly from Eq. (3). There is a total of six nullclines: the x–y, y–z and x–z planes, the plane Π_1, represented by the implicit equation $x+a_{12}y+a_{13}z=1$, the plane Π_2, given by $r_2y+a_{21}x=r_2$, and the planes Π_3 and Π_4 for x the constant solutions of the quadratic equation $a_{31}x^2-(r_3-k_3a_{13}-d_3)x+k_3d_3=0$. If we focus on the positive octant $\mathbb{R}^+\times\mathbb{R}^+\times\mathbb{R}^+$, the intersections of the different nullclines yield six different fixed points x_i^*, as shown in Fig. 1. We give the numerical values of the fixed points and also analyze their stability by examining the eigenvalues of the Jacobian at each of them.

The point x_1^* is the origin $(0,0,0)$, a saddle with two positive eigenvalues corresponding to the x-axis and the y-axis, and a negative eigenvalue along the z-axis. The point $x_2^*=(0,1,0)$