Journal of Theoretical Biology 349 (2014) 74–81

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Avoiding healthy cells extinction in a cancer model

Álvaro G. López [a], Juan Sabuco [a], Jesús M. Seoane [a], Jorge Duarte [b], Cristina Januário [b], Miguel A.F. Sanjuán [a,*]

[a] Nonlinear Dynamics, Chaos and Complex Systems Group, Departamento de Física, Universidad Rey Juan Carlos, Tulipán s/n, 28933 Móstoles, Madrid, Spain
[b] Instituto Superior de Engenharia de Lisboa, Department of Mathematics, Rua Conselheiro Emídio Navarro 1, 1949-014, Lisboa, Portugal

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.

ARTICLE INFO

Article history:
Received 25 October 2013
Received in revised form
10 January 2014
Accepted 31 January 2014
Available online 7 February 2014

Keywords:
Cancer models
Partial control
Chaos
Tumor growth
Therapy

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;

* Corresponding author.

http://dx.doi.org/10.1016/j.jtbi.2014.01.040
0022-5193

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 $x_2^*=(0,1,0)$

represents the healthy state for which there are only normal cells. This fixed point is a saddle point too, but with two stable directions (negative eigenvalues) and one unstable direction (positive eigenvalues). The stable eigenvectors are contained in the $x=0$ plane, so if the dynamics enters this plane, it eventually reaches the healthy solution. The point $x_3^*=(1,0,0)$ has its three eigenvalues smaller than zero, representing a stable solution for which there are only tumor cells. Since this point is the one we want to avoid falling into, we have colored it in red. The fixed point $x_4^*=(0.75,0,0.21)$ is also a saddle fixed point with two stable and one unstable directions. A stable and an unstable direction are in the plane $y=0$, while the remaining stable direction is given by the eigenvector (0.23,0.97,0.02). The two stable directions are related to the stable manifold separating the basins of attraction of the chaotic attractor and the tumor stable fixed point. The fixed points $x_5^*=(0.04,0,0.8)$ and $x_6^*=(0.04,0.85,0.45)$ are two spiral-saddles. For x_5^* the spiral is stable and is contained in the $y=0$ plane, while the unstable direction is given by the eigenvector $(-0.02,1.00,-0.03)$, almost pointing parallel to the y-axis. The other spiral-saddle shows opposite stability, *i.e.*, the spiral is unstable and the stable direction is given by the eigenvector $(-0.02,-1.0,0.02)$. The interplay of these two "facing" spiral-saddles is responsible for the heteroclinic chaotic motion of the system, which is the reason why we paint them blue. The attractor together with the fixed points is shown in Fig. 2(a). The Lyapunov exponents of the chaotic attractor are $\lambda_1=0.022$, $\lambda_2=0$ and $\lambda_3=-0.76$, so its Kaplan–Yorke dimension is $d_L=2.027$.

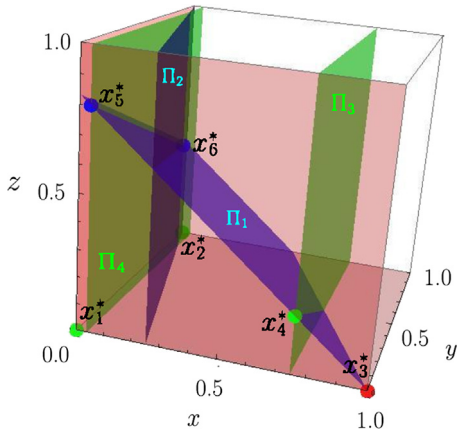

Fig. 1. This figure shows the phase space with the nullclines and the fixed points. The planes are the different nullclines, with the fixed points placed at some of their intersections. The green points are saddle fixed points, the red point is the tumor stable fixed point and the blue points are the two spiral-saddles that give rise to chaotic motion. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

2.3. Boundary crisis and transient chaos

It would be expected that, decreasing the level of the immune response to tumor cells, the cancer state x_3^* should asymptotically prevail over the chaotic attractor. As is well known, whenever two attractors coexist in phase space, the stable manifold of a saddle fixed point between them separates their basins of attraction. If one of these attractors is chaotic, when we vary a parameter, it might happen that it collides with the stable manifold of the saddle. Such phenomenon is formally known as a boundary crisis, and allows the chaotic attractor to access the basin of the stable attractor, falling into it. Indeed, when we decrease the value of the immune response r_3 from 1.291, the chaotic attractor collides with the stable manifold of x_4^* at an approximated critical value $r_3^c=1.2909$. For values of r_3 below the critical value, the dynamics of the system eventually sinks into x_3^*. However, if the value of the parameter is close to the boundary crisis, the chaotic attractor persists as a remnant (or ghost), so larger or shorter chaotic transients are observed before escaping into the stable attractor, as shown in Fig. 2(b). The use of the partial control method to avoid ending in that attractor, which corresponds to the tumor-only state, is the pursued objective through Section 4. In Fig. 3 we show a two-dimensional fold of the parameter space, corresponding to the rate of production of immune cells r_3 and the rate of

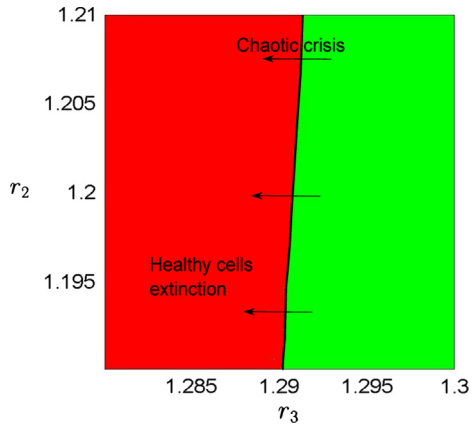

Fig. 3. A region of the parameter space showing how the variation of the parameter r_3 induces the crisis for many different values of the parameter r_2. The boundary between the two regions contains the critical values of r_3^c.

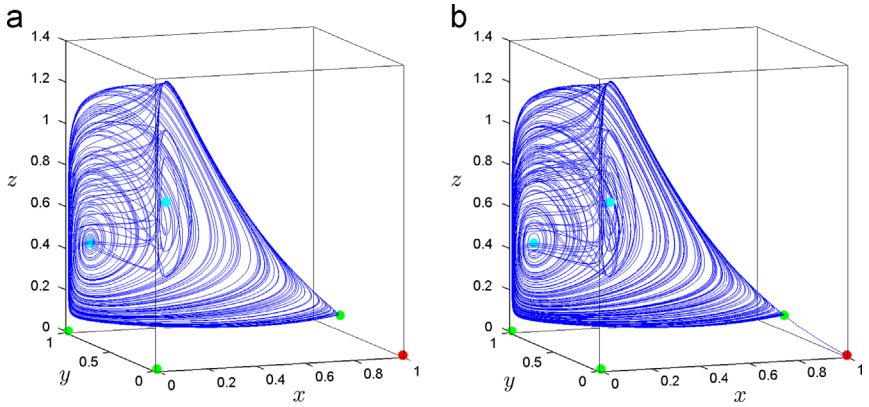

Fig. 2. (a) Chaotic attractor before the crisis. Again saddle fixed points are marked in green, the tumor attractor is shown in red, and the spiral-saddles are painted blue. (b) The same chaotic attractor and fixed points after the crisis. Now trajectories do not stay forever in the chaotic attractor, but fall into the tumor stable equilibrium after a long transient. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

growth of healthy cells r_2, making a clear distinction between parameter regions before and after the crisis.

3. The partial control method

3.1. Basic aspects

Transient chaos is a physical phenomenon that occurs in systems for which trajectories behave chaotically during some finite amount of time in a region Q of the phase space, until they move toward a final state outside Q. The underlying topological structure in Q responsible for that type of motion is a Cantor set-like structure known as the chaotic saddle. Manifestations of transient chaos are wide, and many examples can be found in the literature (Tèl and Lai, 2008; Chen and Aihara, 1995; Tèl et al., 2005). We show transient chaotic dynamics for our model in Fig. 2(b). Partial control is a feedback control method aimed to maintain the transient chaotic dynamics as long as desired, avoiding the escape from Q. Things get even more complicated if we consider the existence of some unpredictable external disturbances acting on the system. Since most physical systems interact with their environment, realistic situations always have to deal with a certain amount of noise. The striking advantage of the partial control technique is that it allows the avoidance of the undesired event sometimes using smaller controls than the disturbances. If we consider a map f modeling the dynamics of the system, the whole process is mathematically expressed as

$$q_{n+1} = f(q_n) + \xi_n + u_n, \tag{4}$$

where ξ_n is the noise at step n, and u_n is the feedback control applied at the same iteration. In our case we have a continuous system, and a Poincaré map must be arranged to apply partial control. In addition, the noise and the control are bounded and moreover the upper control bound is smaller than the upper noise bound, that is,

$$\xi_0 > u_0 > 0 \quad |u_n| \le u_0 \quad |\xi_n| \le \xi_0. \tag{5}$$

Noises and controls obeying these conditions are called admissible, and trajectories fulfilling Eq. (4) are equally named.

3.2. The safe set and the asymptotic safe set

Consider a point q_0 in the set Q, the one we want to keep the dynamics in. We say that such point is safe if for any iteration q_n of this point and any admissible disturbance ξ_n there exists an admissible feedback control u_n such that q_{n+1} remains in Q. Note that if q_0 is safe, any of its iterations is safe as well. More generally, if any point in $S \subset Q$ is a safe point, we say S is a *safe set*. Examples of safe sets for different systems can be seen in Sabuco et al. (2012a). The following lines are devoted to describe the computation of the safe set.

The computation of the safe set can be achieved by means of the *Sculpting Algorithm* (Sabuco et al., 2012a), which proceeds iteratively in the following manner. A point in the safe set has to verify that any of its images under Eq. (4) is in S, so, beginning with Q, we compute the fattened set $Q+u_0$, this is to say, we add to Q all points that are at a distance u_0 from its boundary. Then we eliminate every point in $Q+u_0$ that is at a distance ξ_0 from its boundary, obtaining $Q+u_0-\xi_0$ (see Fig. 4). All points in Q whose images are in $Q+u_0-\xi_0$ are safe for one iteration. We call this set $Q_1 \subset Q$ and insist that every point in Q_1 can be kept in Q for one iteration. Now we repeat the procedure starting with Q_1 and obtain Q_2, the set of points that are safe for two iterations. The set Q_∞ is the largest safe set in Q. Topological properties granting the convergence of the iterates are given in Sabuco et al. (2012b). Here we just recall that if Q is compact, all Q_n are compact and that the infinite intersection of non-empty compact sets $\bigcap_n^\infty Q_n$ is non-empty. In practice we have to use a grid with limited resolution to compute S, so the procedure converges for some finite n.

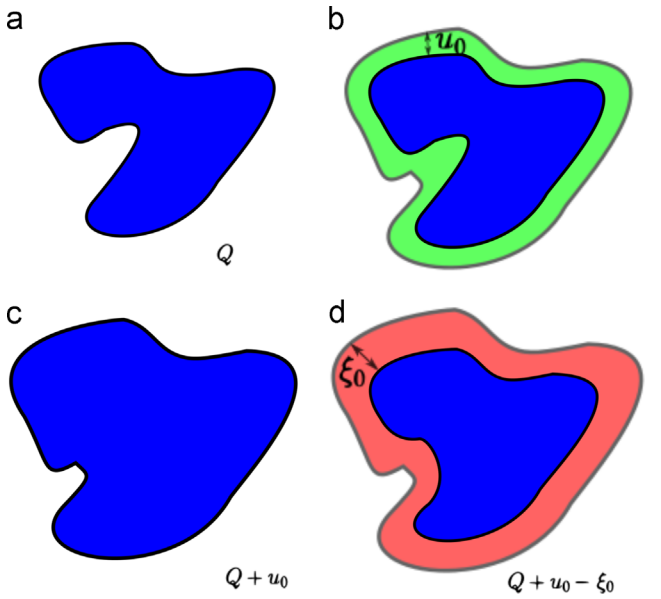

Fig. 4. An iteration of the Sculpting Algorithm. (a) An initial set Q to apply partial control. (b) Fattening realized by the addition of points at a distance u_0 from the boundary of Q. (c) The resulting set $Q+u_0$. (d) The set $Q+u_0-\xi_0$, result of the shrinking of $Q+u_0$, which is performed by eliminating the points that are at a distance ξ_0 from it. The set Q_1 would consist of all the points in Q whose images are in $Q+u_0-\xi_0$ in one iteration. Even though $\xi_0 > u_0$, as long as we sculp the successive sets Q_n, the Cantor construction of the chaotic saddle or equivalently, the sets of points that do not escape from the region Q after some particular iteration are glued together by the control if such iteration is high enough, which is related to the convergence of the Sculpting Algorithm.

Intuitively, if noises are not too high, all the partially controlled trajectories must end in some region around the original attractor (or the ghost). This means that there exists a trapping region where trajectories enter after a sufficiently high number of partially controlled iterations and never leave. This idea leads to the definition of the largest *asymptotic safe set* A. Such set is invariant under Eq. (4), so any of its points must be accessible from any other point in it by a partially controlled iteration. Clearly stated, the largest asymptotic safe set is the largest invariant set under partial control. For the rigorous mathematical formalism see Sabuco et al. (2012b). The asymptotic safe set can be computed using a similar Sculpting Algorithm to the one described in the previous paragraph. Starting with S, we compute all of the accessible points under partial control from every point in it, this is to say, we compute $(f(S)+u_0+\xi_0)\bigcap S$. We call this new set S_1 and use it to compute S_2, and so on until obtaining S_∞. Another algorithm used in Sabuco et al. (2012b), called the *Growing Algorithm*, operates locally starting at some point q in S and computing all the points accessible by any partial control iteration $(f(q)+u_0+\xi_0)\bigcap S$. However, it might happen that A contains other invariant subsets in it, so that the Growing Algorithm starting at some particular point q in A gives, as a result, a set that is smaller than the largest one. In the next section we introduce the smallest asymptotic safe set computed with the Growing Algorithm, and show that partially controlled trajectories cover it densely. Therefore, such set is the attractor of the partially controlled system.

4. Avoiding extinction of healthy cells

Although partial control could be carried out in the whole phase space, computational efficiency exhorts to use some

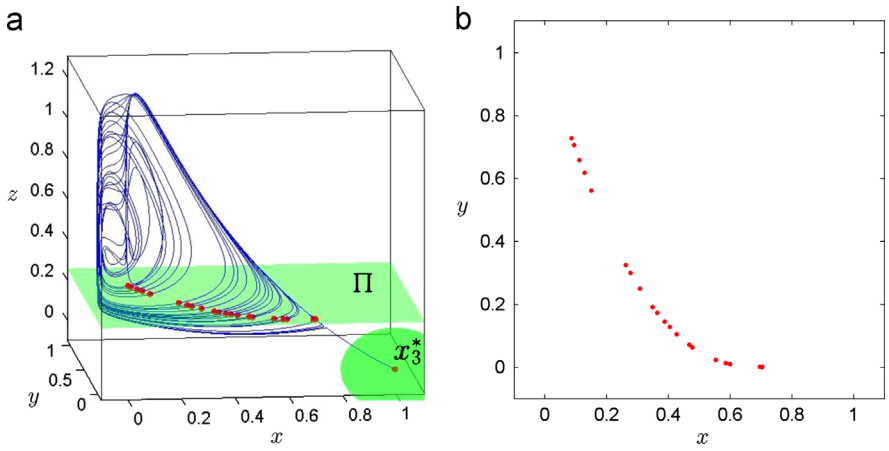

Fig. 5. (a) A Poincaré section Π for $z=0.255$. The trajectory returns to it several times (red points) before escaping to the attractor x_3^*, contained in the green ball. (b) The return map associated to the green section in (a). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

subspace with a dimension as small as possible. This way, the first thing we have to do to apply partial control is to select a Poincaré section. Any two-dimensional manifold intersecting the chaotic attractor serves for this purpose, but for simplicity, we choose a plane Π at some fixed value of the immune cell population, *i.e.*, at a constant z value. According to the reasons explained ahead, we use $z=0.255$. This Poincaré section appears in green in Fig. 5(a) and the associated Poincaré map is shown in Fig. 5(b). The value of r_3 after the crisis is set to 1.207. Since we know that eventually trajectories approach x_3^*, a simple way to avoid this event is to assure that any iteration comes back to the Poincaré section Π. With this purpose, we take Q as the set of all points in that plane that comes back to it at least once before escaping to the attractor. In fact, this set resembles very much the basin of attraction of the chaotic attractor for a parameter value of r_3 above the critical value. The set Q is shown in Fig. 6. The reason why we choose $z=0.255$ is that for such value of the immune effector cell population the set Q is the biggest, and the control/noise ratio is the smallest.

Concerning disturbances on the system, these models usually use multiplicative noises (Spagnolo et al., 2003), so that external perturbations acting on them modify the cell populations through some parameter fluctuations. Note that the use of additive noises could lead to negative values of populations, which have no physical/biological meaning. Nevertheless, partial control acting on some parameter of a dynamical system is still to be attained. For the moment, we take additive noises, considering that those leading to negative values of the cell populations are meaningless, and therefore rejected. If preferred, one can think that the noise probability distribution varies as we approach to a zero value of any coordinate of the system, which is somehow equivalent to considering multiplicative noises. Anyway, this does not require modifying the noise and control conditions given in Eq. (5), since they cover the rejected cases. Another important issue is that the use of continuous noises modifies the set Q, because some points in the non-disturbed case that would come back to Π do not return when disturbances are present. Nevertheless, to simplify things, we will suppose that noises act only on the Poincaré section and assume a correspondence between the maximum continuous noise amplitude and the discretized one, which are related by $e^{\lambda_1 \tau_{max}}$, λ_1 being the maximum Lyapunov exponent and τ_{max} the maximum recurrence time of a point in the set Q. The probability distribution of the noise is then considered uniform and takes values according to Eq. (5), with bounds $\xi_0 = 0.02$ and $u_0 = 0.013$, which means a control/noise ratio $\rho = 0.65$.

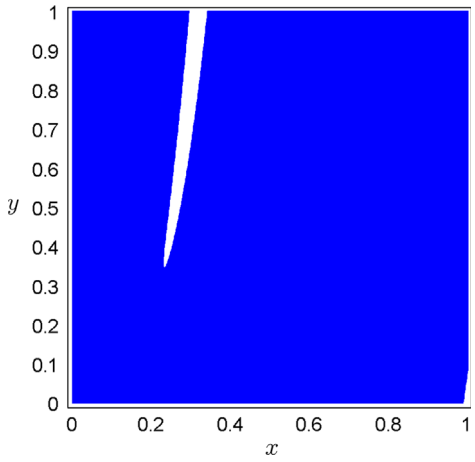

Fig. 6. The set Q, a subset of $[0,1]\times[0,1]$ formed by all initial conditions on $z=0.255$ that return at least once to the Poincaré section before escaping to the attractor. The purpose of partial control is to maintain trajectories in the blue region, avoiding the escape through the long white tusk that transverses it and the small white piece on the bottom right corner. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

The Sculpting Algorithm is applied to a 3000×3000 grid to obtain the safe set, which is shown in Fig. 7. Any trajectory starting in S can be controlled to stay in S as much time as desired. Using this safe set, we compute the largest asymptotic safe set A and also the smallest asymptotic safe set $I \subset A \subset S$. The former is computed with the Sculpting Algorithm, while the latter uses the Growing Algorithm starting with a point in A. Both sets are shown in Fig. 8.

As stated in Sabuco et al. (2012b), potentially there could be more that one asymptotic safe set. In fact, we have found up to four asymptotic safe sets with the growing procedure. One of them is the smallest asymptotic safe set, which is contained in all the remaining. We claim that there is not a smaller invariant set under partial control. Rigorously stated, I is irreducible under partial control transformations. After a sufficient amount of time trajectories enter in I and do not escape, covering it densely, as shown in Fig. 9. We perform a simulation of the partially controlled system for 6000 iterations, proving its success to prevent escape from the chaotic attractor towards the stable tumor fixed point (Fig. 10).

In spite of this mathematical and numerical achievement, it is important to give biological and medical significance to controls. The idea of tumor therapies relies on a very simple fact: kill by all possible means the tumor cells. Generally, most cancer therapies,

although designed to be as selective as possible, entail the simultaneous destruction of healthy and tumor tissues. This is in contrast with the partial control method that deals with cell populations separately and requires not only their destruction, but also to increase them according to the safe sets. Another difficulty is due to the fact that perturbations of the cell populations are practiced directly on the dynamical variables, and not through relevant parameters. In this manner, we can only provide a qualitatively relation between this method and the usual therapy mechanisms. For instance, chemotherapy treatments destroy cell populations by the injection of cytotoxic drugs. The great advance of biomedical engineering suggests that a day may come for which selective drugs allow to control cell populations in an independent way, and therefore chemotherapy could be related to the decrease of the cell populations in the application of the partial control method. On stimulation of cellular growth there is also research (Seong et al., 2006; Cottage et al., 2012), so the possibility of increasing cell populations is not harebrained. In fact, these are rather counter-intuitive things, since as we have shown, occasionally we have had to increase the number of cancer cells and destroy healthy cells to control the tumor escape. In the case of immunotherapy, a more natural choice of the Poincaré section would be a constant value for the healthy cells. In such case a

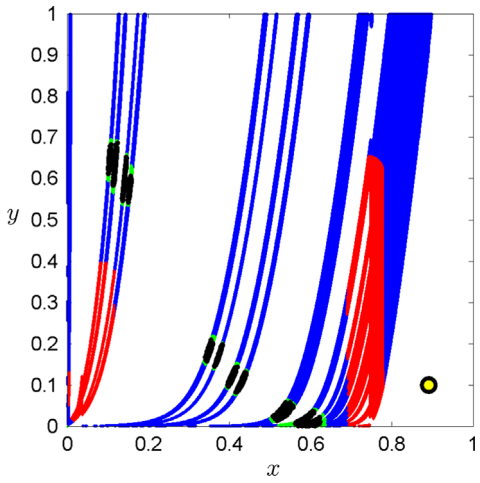

Fig. 9. A partially controlled trajectory for 6000 iterations starting close to the original attractor. The black points are the iterates, which cover densely the smallest asymptotic safe set (green). We see that the trajectory stays close to the attractor avoiding escape. The radius of the two circles in the bottom-right part of the image represents the maximum control u_0 (yellow) and the maximum noise ξ_0 (black). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

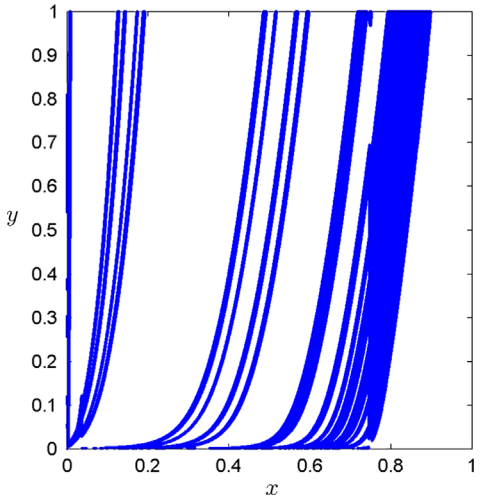

Fig. 7. The safe set obtained from Q with a maximum admissible noise of $\xi_0 = 0.02$ and a maximum admissible control $u_0 = 0.013$.

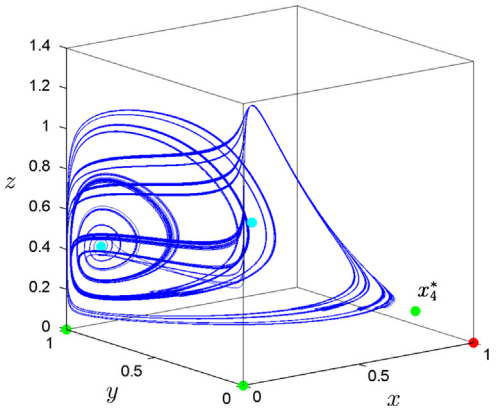

Fig. 10. The partially controlled attractor for 1000 iterations (of the Poincaré map). Note that it does not get as close to the saddle fixed point x_4^* as it does without control.

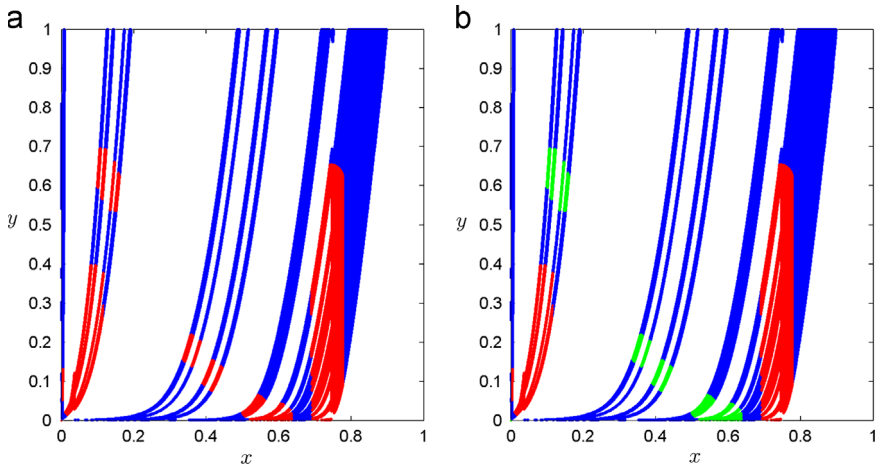

Fig. 8. (a) The safe set in blue containing the largest asymptotic safe set (red) obtained with the Sculpting Algorithm. (b) The smallest asymptotic safe set (green) obtained with the Growing Algorithm starting at some point in the largest asymptotic safe set, close to the original attractor. Note how this safe set encloses the attractor in Fig. 5(b). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

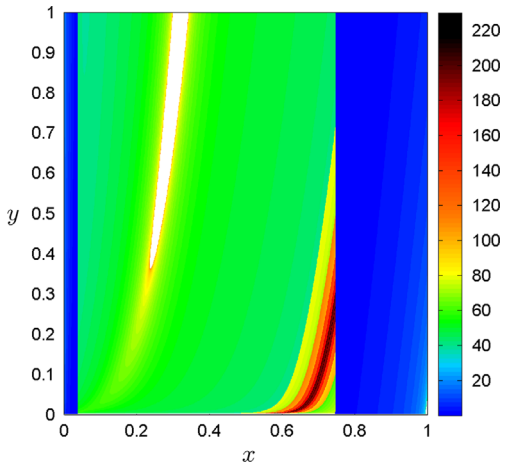

Fig. 11. The recurrence time of each point in the Poincaré section. The color bar represents the time it takes a point (x,y) in the section to return to it. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

reinforcement of the immune system could serve to carry out the increase of this cell population.

Another interesting point is that the chaotic attractor in Fig. 2(a) oscillates between regions where there is a very low number of cancer cells and a high number of healthy ones to others where the opposite situation is found. A similar oscillatory regime also appears in other works with this model (Itik and Banks, 2010; Letellier et al., 2013), and it is characteristical of Lotka–Volterra predator–prey systems. Whenever this happened at some stage of tumor growth, the precise instant of the application of a therapy would be crucial. This means that a single therapy session applied at the right time might be enough to annihilate the tumor, while many sessions wrongly applied could result in a great damage to the patient. Furthermore, the chaotic behavior of the system implies that periodic controls acting on it might not have the desired effect. Finally, suppose that we could perform the required controls, a physician would ask how much time do we have to wait until we reach the Poincaré section again, or equivalently, how often therapy controls need to be applied. Certainly, as we have stated, the recurrence time of each point is different, so, the way we have tackled the problem, no periodic or continuous protocols can be used. We show the recurrence time of every point in the Poincaré section in Fig. 11. The idea of using non-periodic protocols is not new, and cases can be found in the literature, as for example the optimal therapy protocols used in De Pillis and Radunskaya (2003), or the modeling of intermittent hormone therapy of prostate cancer developed in Ideta et al. (2008), Hirata et al. (2010) and Suzuki et al. (2010).

5. Conclusions and discussion

We have shown the possibility of preventing a tumor escape in a chaotic cancer model in the presence of some external disturbances, applying small controls to the cell populations. This has been achieved by means of the partial control method, which applies to transient chaotic situations in the presence of external disturbances. The fact that controls are smaller than the external disturbances is promising, since the side effects of drugs and radiation are well known. On the other hand, the main difficulties at the current stage of development of the partial control method to maintain healthy cell populations arise from two simple facts. It requires to be able to modify cell populations directly and all of a sudden, implying an enormous accessibility to the system, and the treatment of cells independently. This is in contrast to the regular procedure of most cancer treatments that usually decrease all cell populations by complex processes. Therefore, the implementation of partial control to parameter variations would be convenient. Another surprising aspect is that sometimes it has been required to increase cell populations. Although striking, if we consider common tumor therapies, this reveals important consequences of chaotic dynamics on tumor progression and therapy protocols.

Acknowledgment

This work was supported by the Spanish Ministry of Science and Innovation under Project number FIS 2009-09898.

References

Aguirre, J., d'Ovidio, F., Sanjuán, M.A.F., 2004. Controlling chaotic transients: Yorke's game of survival. Phys. Rev. E 69, 016203.
Ahmed, E., 1993. Fractals and chaos in cancer models. Int. J. Theor. Phys. 32, 353–355.
Bajzer, Ž., Marušić, M., Vuk-Pavlović, S., 1996. Conceptual frameworks for mathematical modelling of tumor growth dynamics. Math. Comput. Model. 23, 31–46.
Bellomo, N., Li, N.K., Maini, P.K., 2008. On the foundations of cancer modelling: selected topics, speculations, and perspectives. Math. Models Methods Appl. Sci. 18, 593–646.
Chen, L., Aihara, K., 1995. Chaotic simulated annealing by a neural network model with transient chaos. Neural Netw. 8, 915–930.
Cottage, C.T., Neidig, L., Sundararaman, B., Din, S., Joyo, A.Y., Bailey, B., Gude, N., Hariharan, N., Sussman, M.A., 2012. Increased mitotic rate coincident with transient telomere lengthening resulting from Pim-1 overexpression in cardiac progenitor cells. Stem Cells 30, 2512–2522.
d'Onofrio, A., 2005. A general framework for modelling tumor-immune system competition and immunotherapy: mathematical analysis and biomedical inferences. Physica D 208, 220–235.
De Pillis, L.G., Radunskaya, A., 2003. The dynamics of an optimally controlled tumor model: a case study. Math. Comput. Model. 37, 1221–1244.
De Pillis, L.G., Radunskaya, A.E., Wiseman, C.L., 2005. A validated mathematical model of cell-mediated immune response to tumor growth. Cancer Res. 6, 235–252.
De Pillis, L.G., Gu, W., Radunskaya, A.E., 2006. Mixed immunotherapy and chemotherapy of tumors: modelling, applications and biological interpretations. J. Theor. Biol. 238, 841–862.
Freedman, H.I., Pinho, S.T.R., 2009. Stability criteria for the cure state in a cancer model with radiation treatment. Nonlinear Anal.: Real World Appl. 10, 2709–2715.
Hirata, Y., Bruchovsky, N., Aihara, K., 2010. Development of a mathematical model that predicts the outcome of hormone therapy for prostate cancer. J. Theor. Biol. 264, 517–527.
Ideta, A.M., Tanaka, G., Takeuchi, T., Aihara, K., 2008. A mathematical model of intermittent adrogen suppression for prostate cancer. J. Nonlinear Sci. 18, 593–614.
Itik, M., Banks, S., 2010. Chaos in a three dimensional cancer model. Int. J. Bifurc. Chaos 20, 71–79.
Kapitaniak, T., Brindley, J., 1998. Preserving transient chaos. Phys. Lett. A 241, 41–45.
Kirschner, D., Panetta, J.C., 1988. Modelling immunotherapy of the tumor-immune interaction. J. Math. Biol. 37, 235–252.
Kuznetsov, V.A., Makalkin, I.A., Taylor, M.A., Perelson, A.S., 1994. Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. Bull. Math. Biol. 56, 295–321.
Letellier, C., Denis, F., Aguirre, L.A., 2013. What can be learned from a chaotic cancer model? J. Theor. Biol. 322, 7–16.
Nani, F., Freedman, H.I., 2000. A mathematical model of cancer treatment by immunotherapy. Math. Biosci. 163, 159–199.
Panetta, J.C., Adam, J., 1995. A mathematical model of cycle-specific chemotherapy. Math. Comput. Model. 22, 67–82.
Pinho, S.T.P., Freedman, H.I., Nani, F., 2002. A chemotherapy model for the treatment of cancer with metastasis. Math. Comput. Model. 36, 773–803.
Placeres Jiménez, R., Hernández, E.O., 2011. Tumor–host dynamics under radiotherapy. Chaos Solitons Fractals 44, 685–692.
Sabuco, J., Zambrano, S., Sanjuán, M.A.F., 2009. Partial control of chaotic transients using escape times. New J. Phys. 12, 113038.
Sabuco, J., Zambrano, S., Sanjuán, M.A.F., Yorke, J.A., 2012a. Finding safety in partially controllable chaotic systems. Commun. Nonlinear Sci. Numer. Simul. 17, 4274–4280.
Sabuco, J., Sanjuán, M.A.F., Yorke, J.A., 2012b. Dynamics of partial control. Chaos 22, 047507.
Sachs, R.K., Hlatky, L.R., 2001. Simple ODE models of tumor growth and anti-angiogenic or radiation treatment. Math. Comput. Model. 33, 1297–1305.
Saleem, M., Agrawal, T., 2012. Chaos in a tumor growth model with delayed feedback responses of the immune system. J. Appl. Math. 2012, 891095.

Schwartz, I.B., Triandaf, I., 1996. Sustaining chaos by using basin boundary Saddles. Phys. Rev. Lett. 77, 4740–4743.
Seong, S.R., Lee, J.W., Kim, T.I., Son, D.J., Yun, Y.W., Moon, D.C., Yun, Y.W., Yoon, D.Y., Hong, J.T., 2006. Stimulation of cell growth by erythropoietin in RAW264.7 cells: association with AP-1 activation. Arch. Pharm. Res. 29, 218–223.
Spagnolo, B., Fiasconaro, A., Valenti, D., 2003. Noise induced phenomena in a Lotka–Volterra system. Fluct. Noise Lett. 3, L177.
Suzuki, T., Bruchovsky, N., Aihara, K., 2010. Mathematical modelling of prostate cancer growth and its application to hormone therapy. Trans. R. Soc. A 368, 5045–5059.
Tèl, T., 1991. Controlling transient chaos. J. Phys. A: Math. Gen. 24, L1359–L1368.
Tèl, T., Lai, Y., 2008. Chaotic transient in spatially extended systems. Phys. Rep. 460, 245–275.
Tèl, T., de Moura, A., Grebogi, C., Károlyi, G., 2005. Chemical and biological activity in open flows: a dynamical systems approach. Phys. Rep. 413, 91–196.
Wolfrom, C., Chau, N.P., Maigné, J., Lambert, J.C., Ducot, B., Guerroui, S., Deschatrette, J., 2000. Evidence for deterministic chaos in aperiodic oscillations of proliferative activity in long-term cultured Fao hepatoma cells. J. Cell Sci. 113, 1069–1074.
Yang, W., Ding, M., Mandell, A.J., Ott, E., 1995. Preserving chaos: control strategies to preserve complex dynamics with potential relevance to biological disorders. Phys. Rev. E 51, 102–110.
Zambrano, S., Sanjuán, M.A.F., 2009. Exploring partial control. Phys. Rev. E 79, 026217.