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Research Article

Improving Clinical Conditions by Enlarging Tumor Dormant State Based on Design Equilibrium State by Lyapunov Stability Theorem

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Abstract: In this study, a novel method is proposed in which designs equilibrium point of tumor model in order to decrease the density of tumor cells as well as makes the possibility of controlling desirable clinical situation to improve desirable clinical conditions by enlarging tumor dormant state. The tumor dormancy means that all tumor cells are in cell-cycle arrest or a dynamic equilibrium state in which cells proliferation are in balance with cells undergoing apoptosis and the tumor growth is blocked. Therefore, this equilibrium represents a desirable clinical condition. If the trajectories of the describing dynamic systems belong to a specific region denoted by domain of attraction, then the convergence of system to the healthy steady state is guaranteed for this equilibrium point, the domain of attraction is a set of desired clinical conditions. This problem is indicated in form of the two layer global multi objective function optimization.

Keywords: Dormant state, enlarging domain of attraction, equilibrium point, lyapunov stability theorem, optimization control, tumor

INTRODUCTION

Cancer occurs when a group of cells has lost the ability to control growth through mutations. These cells divide rapidly to form tumors and sometimes cancer cells can spread to other parts of the body. In order to control the growth of tumor, different strategies introduced. The response of tumor to treatment depends on many factors, such as the severity of the diseases, the treatment's application and the strength of patient's own immune response. It is possible to model this process and mathematical modeling of this process is a powerful tool in the development of improved treatment regimens.

In respect of the control systems that protect against cancer, they are classified in two general groups: systems that prevent mutations and systems that cope with mutations once they occurred. To promote effective treatments, it is significant to identify the mechanisms to controlling cancer growth, how they interact and how they can most easily be manipulated to eradicate (or manage) the disease. Through the development and solution of mathematical models that describe different aspects of solid tumor growth, applied mathematics has the potential to prevent extra experimentation and also to provide biologists with complementary and valuable insight into the mechanisms that may handle the development of solid tumors (Byrne, 1999).

Tumor dormancy or dynamic equilibrium state in which tumor cells and immune cells are in balance has been recognized as a clinical phenomenon in numerous types of cancer for many years. Clinicians and experimental biologists have used the term dormancy loosely, to describe the hypothetical state of cancer cells lying in wait over a period of time after treatment of the primary tumor, pending subsequent growth and clinical recurrence.

Determining the steady states of the model and the stability of the equilibrium points for cancers is investigated by Sarkar and Banerjee (2005), Amato *et al*. (2007) and Yang (2012).

The mathematical modeling of tumor growth and treatment has been approached by a number of researchers using a variety of models over the past decades (Bajzer *et al*., 1996). These models describe interaction and competition between tumor cells and immune cells (namely Cytotoxic T-Lymphocytes (CTLs) and macrophages).

Different dynamics of the cancer development can be described in four states. Lotka-Volterra-based models are used in several papers and also in this study to explain the states of interactions and competition between normal cells and tumor cells. They are included: uncontrolled tumor growth, the populations of normal cells and malignant cells coexist together with blocked sizes in steady-state condition (tumor dormancy), tumor recurrence and tumor remission.

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Desirable clinical conditions is the cases of tumor dormancy and tumor remission since in these equilibria the population size of tumor cells can be limited to low or null values. The tumor dormancy state is occurred when the trajectories of dynamics system tends to asymptotically stable equilibrium in which the size of malignant cells and normal cells do not vary. This equilibrium represent a set of desirable clinical conditions which are domain of attraction related to stable equilibrium point in tumor growth nonlinear system (Kuznetsov *et al*., 1994; Gatenby, 1995; Michelson and Leith, 1995; Bajzer *et al*., 1996; Kirschner and Panetta, 1998; Pillis and Radunskaya, 2001; Sarkar and Banerjee, 2005; Pillis *et al*., 2005; Pillis *et al*., 2006; Byrne *et al*., 2004).

Methods which estimate Domain of Attraction (DA), can be classified in two general groups, Lyapunov based and non-Lyapunov based. The first group contains two main steps (Chesi *et al*., 1997; Zhai *et al*., 2009; Rapoport, 1999; Barreeiro *et al*., 2002; Rapoport and Morozov, 2008). At the first step a suitable Lyapunov Function (LF) based on the structure of the system is proposed and in the second step DA is estimated based on the suggested LF.

Hashemzade and Yazdanpanah (2006), Cao *et al*. (2002), Brockett and Li (2003), Chesi (2004) and Matallana *et al*. (2011) represent the methods of enlarging DA.A bi-level optimization method for the design of the operating equilibrium of a nonlinear dynamic system based on a measure of the extension of its domain of attraction is proposed by Matallana *et al*. (2011). A non-Lyapunov based approach for estimating the domain of attraction, in the form of a continuation optimization algorithm, is proposed by Moghaddam *et al*. (2012). According to the proposed algorithm, the domain of attraction is estimated with finite number of open sets. This method is also applied to design controlling parameters to extend the domain of attraction along desired directions. As it is mentioned, enlarging DA in tumor growth model means improving and enlarging the desirable clinical conditions. So, to extend DA leads to decrease cost of controlling so as to drive the tumor cell to the desirable equilibrium state. Several methods are proposed in order to drive the tumor cell to the DA of desirable equilibrium point (Ghaffari and Nasserifar, 2009; Mehmet *et al*., 2010; Pillis and Radunskaya, 2003).

In this study, we proposed a method based on design the equilibrium point in order to reach the dormant state that has smaller density tumor cells. What is more, extending desirable clinical conditions in dormant state by finding an optimum value for hunting rate of predation of the tumor cells. Hunting rate of predation of the tumor cells by hunting cells is depend on a therapeutic method such as radiation therapy, hyper thermic,… This method is indicated in the form of a two layer optimization problem. In inner layer for each allowable controlling parameter (which satisfies asymptotically stability constrain and are in acceptable range of hunting rate of predation of the tumor cells) the best estimation of DA is obtained by designing P matrix in Lyaponuv equation. Then, in outer layer the controlling parameter that leads to an equilibrium point with the largest estimation of DA and the smallest the density of tumor cells is found as optimal controlling parameter.

PRELIMINARIES

Consider the following system:

$$\dot{x} = h(x), \qquad x \in R^n, \qquad x(t_0) = x_0 \tag{1}$$

Definition 1 (equilibrium (Khalil, 2010)): A point $x_e \in R^n$ is called an equilibrium point of system (1) if $f(x_e) = 0$. The equilibrium points of system (1) correspond to the intersection of the null clines of the system, meaning the curves given by $f(x) = 0$.

In the sequel, without loss of generality, we assume that the equilibrium point under study coincides with the origin of the state space of R^n, $x_e = 0$.

Definition 2 (stability (Hahn and Band, 138 1967)): Let $x(t, x_e)$ denote the solution of system (1), which at the initial time t_0 passes through the initial point $x_e \in R^n$ The origin is defined as stable if $\forall\varepsilon>0$ there exists a $\delta>0$ such that:

$$\|x(t.x_e)\| < \varepsilon, \quad \forall t \geq t_0 \tag{2}$$

Is valid whenever $\|x_e\| <\delta$.

Definition 3 (asymptotic stability (Hahn, 1967): The origin is defined as asymptotically stable if:

- It is stable
- There exists a $\eta>0$ having the property $\lim_{t\to\infty} x(t, x_0) = 0$ whenever $\|x_0\| <\eta$

Definition 4 (positive and negative definite functions (Salle and Lefschetz, 1961)): Let $D \subseteq R^n$. A function $V(x)$: $D\rightarrow R$ is called positive definite (positive semi definite) on D if $V(0) = 0$ and $V(x) >0$ ($V(x) \geq 0$) $\forall x D\backslash$ (Yang, 2012) V (x) is called negative definite (negative semi definite) if -V (x) is positive definite (positive semi definite).

Definition 5 (Lyapunov function (Khalil, 2010): Let V (x) be a continuously differentiable real-valued function defined on a domain $D \subset R^n$ containing the equilibrium $x_e = 0$. The function V (x) is called a

Lyapunov function of equilibrium x = 0 of system (1) if the following conditions hold:

- V (x) is positive definite on D
- The time derivative of V (x) along the trajectories of system (1):

$$\dot{V}(x) = (\frac{\partial V}{\partial x})^T f(x)$$

is negative definite on R (0)

Definition 6 (domain of attraction (Khalil, 2010)): The domain of attraction of the origin is given by:

$$DA = \{x_0 \in R^n \mid \lim_{t\to\infty} x(t, x_0) = 0\}. \quad (3)$$

Definition 7 (dormancy therapy): The usage of low dose drugs in order to control tumor size to take and keep the tumor into dormancy phase (stage) for prolong Time to Progression (TTP), not to kill cancer cells.

Theorems:

Theorem 1 (Jacobean matrix spectrum (Khalil, 2010)): Let $A = \frac{\partial f}{\partial x(x)} \|_{x=0}$ (the Jacobian of system (1) at the origin) then:

- The origin is asymptotically stable if all eigenvalues of A have negative real parts.
- The origin is unstable if one or more eigenvalues of A have positive real parts.

Theorem 2 (estimation of the domain of attraction (Khalil, 2010)): Let V (x) be a Lyapunov function for the equilibrium x = 0 of system (1). R (0) can be an estimation of DA if Dv (x) /dt<0 holds in the following set:

$$S(0) = \{x : V(x) \le c, \quad c > 0\} \quad (4)$$

Hence, every trajectory initiated within region S (0) tends to x = 0 as time tends to infinity.

Theorem 3 (Lyapunov identity (Khalil, 2010)): If the equilibrium x = 0 of system (1) is asymptotically stable, then there exists a Lyapunov function of the quadratic type, v (x) = x^T Px, where *P* is a positive definite matrix which can be calculated from the so-called Lyapunov identity:

$$A_1^T P + PA_1 = -Q \quad (5)$$

A common choice is to set Q = I where *I* is the identity matrix.

Theorem 4: Consider the following representation of system (1):

$$h(x) = A_1 x + h_1(x)$$

where h_1 (x) comprises the nonlinear part of function h (x). It can be shown that if the following condition holds (Vidyasagar, 1993):

$$\|h_1(x)\| / \|x\| \le \lambda_{\min}(Q) / 2\lambda_{\max}(P), \quad \forall x \in B_r \quad (6)$$

V (x) and its time derivatives are positive and negative definite respectively within the ball Br of radius *r*. It is clear that the larger the ratio $\lambda_{min}(Q)/2\lambda_{max}(P)$ the larger the possible choice of *r*.

Proposition 1: According to the theorem 2, the best estimation of DA is that the largest the level set value c in Eq. (4). In order to find the better estimation of DA, it is necessary to maximize the set's level of V (x) which is fully contained in the region of negative definiteness of dV (x) /dt. On the other hand, the largest level to be the smallest hyper-sphere contained in dV (x) /dt = 0. Therefore, in order to find the best estimation of DA based on theorem 4, Eq. (6) can be reformulated as:

$$\|h_1(x)\| / \|x\| - \lambda_{\min}(Q) / 2\lambda_{\max}(P) = 0,$$

$\forall x \in B_r$

DYNAMICAL MODEL OF TUMOR GROWTH

The dynamical model of tumor growth is considered by Sarkar and Banerjee (2005). In this model, spontaneous tumor regression and progression are described as a prey-predator like system. Prey and predator cells in the case of tumor are clear which prey destroy the immune cells and predator is consisted in two stages, hunting cells and resting cells and as it mentioned they destroy the prey (cancerous cells).It is considered that tumor cells are destroyed at a rate proportional to the densities of hunting predator cells and tumor cells. Also, it is assumed that the resting predator cells are converted to the hunting cells either by contact with a fast diffusing substance (cytokines) produced by the hunting cells or by direct contact with antigens. When a cell has been converted, it will never return to the resting stage as well as active cells die at constant probability per unit of time. It is supposed that the proliferation of tumor cells is over the normal cells (Merola *et al.*, 2008). Hence, it is considered that two different carrying or packing capacities for resting predator cells and tumor cells, respectively, where the carrying capacity of predator cells is less than that of the tumor cells:

$$\frac{dM}{dt} = q + rM\left(1 - \frac{M}{k_1}\right) - \alpha MN$$
$$\frac{dN}{dt} = \beta NZ - k_1 N \quad (7)$$
$$\frac{dZ}{dt} = sZ\left(1 - \frac{Z}{k_2}\right) - \beta NZ - d_2 Z$$

where,

M = Tumor cells density
N = Density of hunting predator cells
Z = The resting predator cells density
r = The growth rate of tumor cells
q = The conversion of normal cells to malignant cells
k_1 = The maximum packing capacity of tumor cells
$(k_2 > 0)$ = The same as k_1 but it is for resting cells (also $k_1 > k_2$)
$\alpha > 0$ = The rate of tumor cells by hunting ones
$\beta > 0$ = The rate of conversion of $(k_2 > 0)$ cell
d_1 = The natural death of hunting cell
s = The rate of growth for predator cells
d_2 = The rate of natural death for hunting cell

Considering all biologically feasible equilibrium admitted by the system (7) and studying the dynamic of the system around each equilibrium leads to the fact that negative sign is not admissible for the existence of positive interior equilibrium (Merola *et al*., 2008). System (7) has three equilibrium points:

$$E_1 = [\frac{k_1}{2}(1 + \sqrt{1 + \frac{4q}{rk_1}}), 0, 0] \quad (8)$$

$$E_2 = [\frac{k_2}{2}(1 + \sqrt{1 + \frac{4q}{rk_1}}), 0, k_2(1 - \frac{d_2}{s})] \quad (9)$$

$$E_3 = [M_3, \frac{s}{\beta}(1 - \frac{d_1}{\beta k_2}) - \frac{d_2}{\beta}, \frac{d_1}{\beta}] \quad (10)$$

where,

$$M_3 = \frac{-[(\frac{\alpha s}{\beta})(1 - (\frac{d_1}{\beta k_2}) - (\frac{\alpha d_2}{\beta})r] + \sqrt{[(\frac{\alpha s}{\beta})(1 - (\frac{d_1}{\beta k_2}) - (\frac{\alpha d_2}{\beta}) - r]^2 + (\frac{4rq}{k_1})}}{2(\frac{r}{k_1})} \quad (11)$$

In the above equilibrium points, it is abundantly clear that the equilibrium E_1 only malignant cells are exist in comparison with E_2 which both malignant cells and predator cells are present in the organism. What is more, in equilibrium E_3, the three species of cells are present.

When E_3 belongs to the positive orthant it is possible to control the steady-state density of the tumor by varying α. Therefore, E_3 is a desirable equilibrium point.

The Jacobian of system (7) at the desirable equilibrium point is asfollows:

$$A = \begin{bmatrix} -\sqrt{[\frac{\alpha s}{\beta}(1 - \frac{d_1}{\beta k_2}) - \frac{\alpha d_2}{\beta} - r]^2 - \frac{4rq}{k_1}} & \alpha M_3 & 0 \\ 0 & 0 & s(1 - \frac{d_1}{\beta k_2}) - d_2 \\ 0 & -d_1 & \frac{sd_1}{\beta k_2} \end{bmatrix} \quad (12)$$

The state response of system (7) is determined for theinitial condition $x_0 = (4.87, 2.7, 0.1)^T$ and parameters q = 10, r = 0.9, α = 0.3, k_1 = 0.8, β = 0.1, d_1 = 0.02, s = 0.8, k_2 = 0.7, d_2 = 0.03 by Merola *et al*. (2008). The optimal estimated DA which is obtaind through a optimization alghorithm for E_3 = [3.25, 5.1, 0.2]. All parameters, except α, are assumed the values given by Merola *et al*. (2008) and the allowable range for α is considered, such that α is between 0 (absence of drug) and 0.3 (maximum value of α).

In the next section an optimization problem is proposed in order to design the eqilibrium point which is optimal in aspect to the amount of density tumor cells and the extensionof DA. It is clear that the smaller density of tumor cells and the larger DA is desirable.

PROPOSED APPROACH

In this section, the following two level global multi objective optimization is proposed. In this optimization problem, the stable equilibrium point with the smaller density tumor cells and the larger DA is designed by finding the optimal controlling parameters. In this optimization problem x_e is the equilibrium point and α is the predation's rate of the tumor cells by hunting cells which is as a controlling parameter in order to enlarge DA or maximize desirable clinical sets. What is more, *r* is the radius of the sphere which the stability is guaranteed or DA and x_e (1, 1) denotes that amount of density tumor cells in equilibrium point:

$$\underset{\alpha}{Max}\ R - |x_e(1,1)|$$

$$S.t.\quad f(\alpha, x_e(\alpha)) = 0$$
$$real(\lambda(A(\alpha, x_e(\alpha)))) < 0$$

$$R = \underset{P}{Min}\,|r| \qquad (13)$$
$$S.t.\quad r = \|x - x_e(\alpha)\|$$
$$V(x) = x^T P x > 0$$
$$A_1{}^T P + P A_1 = -Q$$
$$\frac{\|f_1(\alpha)\|}{\|x\|} - \frac{\lambda_{\min}(Q)}{2\lambda_{\max}(P)} = 0$$
$$x > 0$$
$$0 < \alpha < 0.3$$

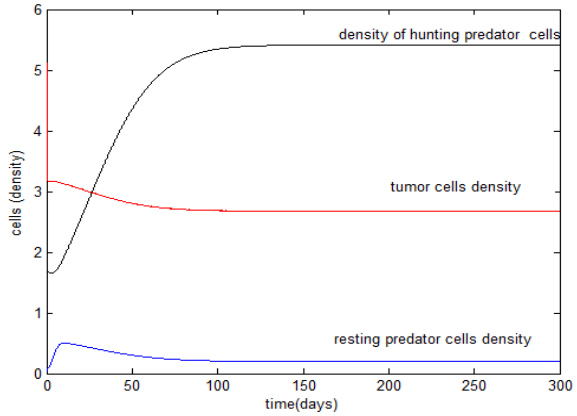

Fig. 1: State response of system (7) from an initial condition

In optimization problem (13), in the inner layer optimization for each allowable controlling parameter, the best Lyapunov function through Lyapunov identity is designed and according to theorem 4 and proposition 1, the largest estimation of DA is obtained. It should be mentioned that the allowable controlling parameters are that the parameters which are in allowable range of predation's rate of the tumor cells by hunting cells and the parameters that lead to asymptotic stable equilibrium point according to theorem 1. In the outer layer the controlling parameter that leads to an equilibrium point with the smaller density of tumor cells and larger DA is considered as optimal controlling parameter.

It should be noted that constraints (13) may have had many local solutions. In order to avoid dummy solutions, problem (13) has to be solved to global optimality therefore in this contribution a standard implementation of a genetic algorithm adopted by Haghighatnia and Moghaddam (2012).

By solving this optimization problem for Dynamical model of tumor growth at (7), the DA for this nonlinear system is the positive part of the sphere with center with coordinate equal to (2.61, 5.41, 0.2) , the radius equal to 3.66 and optimal value 0.3 for predation's rate of the tumor cells by hunting cells, this equilibrium point indicates a better tumor dormancy equilibrium rather than previous works (Merola, Cosentino *et al*., 2008) because the density of tumor cells in dormant state is smaller and the desirable conditions is larger (Fig. 1). In Fig. 1 Trajectory starting is from the initial condition x_0 (5.11, 1.7 and 0.05). As is expected, the trajectory, starting by this unfavorable state which is included into the DA of the equilibrium point, converges to the tumor dormancy equilibrium.

CONCLUSION

In this study a new method so as to improve the desirable clinical conditions in dormancy therapy is proposed. In this method, the model of tumor growth and the desirable clinical condition are considered as a nonlinear system and DA, respectively. To aim, an algorithm in order to enlarge DA based on design equilibrium point of nonlinear system and by using quadratic Lyaponuv functions is proposed. In this algorithm, controlling parameter is rate of predation of the tumor cells by hunting cells with a therapeutic method such as radiation therapy, hyper thermic…

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