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Designing Nonlinear Feedback Control for Controlling Tumor Growth

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Abstract: Tumor growth models as nonlinear systems have some equilibrium points. In clinical situations, the desirable equilibrium point is the state that the competition between the populations of tumor cells and immune cells tend to the state in which the sizes of these populations do not vary (dormancy mode) or populations of tumor are zero (free tumor mode). In this study, a feedback nonlinear control for tumor growth model is designed so as to stabilize the unstable desirable equilibrium points based on Lyapunov stability theory. The aim is to steer the state trajectories to the desirable equilibrium point in order to treat cancer disease. The efficiency of the proposed method is shown in the simulation part.

Keywords: Equilibrium point, lyapunov stability theory, nonlinear feedback control, tumor growth

INTRODUCTION

Cancer is one of the mortality diseases in the world which kills a lot of people. So, researchers have been taking it into account and have been proposing a lot of methods in order to treatment cancer diseases. The growth of tumor cells for cancer is very complex in nature as it involves many biological factors. Cancer is caused due to unnatural growth of malignant cells which form tumor. The malignant cell that causes tumor also affects the normal and immune cells of human body till treatments are started.

Different dynamics of the cancer development can be described in four states. They are included: uncontrolled tumor growth, tumor dormancy (the populations of normal cells and malignant cells coexist together with blocked sizes in steady-state condition), tumor recurrence and tumor remission. Desirable clinical conditions are 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. In other words, in desirable equilibria state, the size of tumor population is few or tends to zero (tumor free) (Merola *et al*., 2008).

To understand the behavior of complex tumor growth, mathematical modeling of cancer has been of great interest. The mathematical modeling of tumor growth and treatment has been approached by a number of researchers over the past decades (Devi and Ghosh, 2112). These models describe interaction and competition between tumor cells and immune cells (D'Onofrio *et al*., 2012; Chang *et al*., 2003; Pillis *et al*., 2006; Cappuccio *et al*., 2007; Caravagna *et al*., 2012; Pillis and Radunskaya, 2003).

As it is obvious, in real world, in some cases it is not possible to perform experiment in order to treatment on real patients because of risks. So, a model that describes the features of a system is necessary. In this case, different controlling methods in order to treat cancer diseases can be tested on models. After proving the theoretical research, scientists and clinicists try to make it applicable in real world. Tumor model as a nonlinear system has some equilibrium points, where some of them are desirable in clinical view. The goal of cancer treatment is to elimination of tumor cells. So, a controller can be design to drive the trajectories to the state which is called desirable equilibrium point. The desirable equilibrium point is the state that population of tumor cells tends to zero or the size of the populations of malignant cells and immune cells do not vary. In this study, we choose the non-dimensionalized ODE model which is presented by Pillis and Radunskaya (2003) and Lisette *et al*. (2005).

In this study, according to the model of tumor growth which is nonlinear and indisputable advantages of nonlinear control in terms of transient response, stability and robustness to uncertainties, nonlinear control methods have outweigh in comparison with linear control. So, we design a nonlinear feedback control so as to stabilize the unstable desirable equilibrium points of tumor growth model based on Lyapunov stability theory. This controller can steer the state trajectories to the desirable equilibrium point so as to eradicate tumor cell or reduce the amount of tumor cells. The simulation results show the efficiency of the presented method.

THE MATHEMATICAL MODEL

The model is basically an ordinary differential equation whose state variables are population cells which are included tumor cells and two types of

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immune cells. A tumor logistically grows in absence of immune response. The below model is an accepted growth model for tumors and is based on fitting the data in Pillis *et al*. (2006):

$$\frac{dT}{dt} = aT(1-bT) - cNT - D \tag{1}$$

$$\frac{dN}{dt} = \delta - fN + g\frac{T^2}{h+T^2}N - pNT \tag{2}$$

$$\frac{dL}{dt} = -mL + j\frac{D^2}{k+D^2}L + rNT - qLT \tag{3}$$

$$D = \frac{d(\frac{L}{T})^l}{s+(\frac{L}{T})^l}T$$

The populations at time t are represented by: T (t), the population of tumor cell, N (t), the total population of NK cell and L (t), the total population of CD8+T cell. NK and CD8+T cells are capable of killing tumor cells (Diefenbach *et al*., 2001; Kawarada *et al*., 2001; Germain, 2004). What is more, they respond to tumor cells by developing and increasing cytocytic activity (Kieper *et al*., 2001; Osada *et al*., 2004). NK cells naturally exist in the body with or without tumor cells due to their nature (Roitt and Brostoff, 1993). Active tumor-specific CD^+8 only present in large numbers when tumor cells are present (Kirschner and Panetta, 1998; Roitt and Brostoff, 1993) When NK and CD8+T cells encounters with tumor cells after some contact with tumor cells it leads to inactivation (Adam and Bellomo, 1997).

Where the constants values is as follows:

$$\begin{aligned}
&a = 5.14*10^{-1}\ \text{day}^{-1}, && b = 1.02*10^{-9},\\
&s = 2.5*10^{-1} && c = 3.23*10^{-7}\,\text{day}^{-1},\\
&h = 2.02*10^{7}, && j = 3.75*10^{-2}\,\text{day}^{-1},\\
&f = 4.12*10^{-2}\,\text{day}^{-1},\\
&g = 2.5*10^{-2}\,\text{day}^{-1},\\
&q = 3.42*10^{-10}\,\text{cell}^{-1}.\text{day}^{-1},\\
&m = 2*10^{-2} && d = 5.8\ \text{day}^{-1},\\
&\delta = 1.3*10^{4} && k = 2*10^{7},\\
&r = 1.1*10^{-7}\,\text{cell}^{-1}.\text{day}^{-1},\\
&l = 1.36, && p = 10^{-7}
\end{aligned} \tag{4}$$

And initial densities:

$$T(0) = 1000,\ N(0) = 515530,\ L(0) = 1000 \tag{5}$$

STABILITY ANALYSIS

By setting the derivatives in each of these equations to zero and examining the intersection of null surfaces, we can calculate the equlibria for the model. On each of these surfaces, each cell population is constant. Therefore, at intersections between all three surfaces, there exist equilibria since then all populations will remain constant. The equations for the three null surfaces in the model are described below in terms of N as functions of T and L:

$$\begin{aligned}
&\frac{dT}{dt} = 0: && T = 0 \quad or \quad N = \frac{abT - a + D}{c}\\
&\frac{dN}{dt} = 0: && N = \frac{\delta}{f + \frac{gT^2}{h+T^2} - pT}\\
&\frac{dL}{dt} = 0: && N = \frac{qLT + mL - j\frac{D^2}{k+D^2}L}{rT}
\end{aligned} \tag{6}$$

According to above equations for the tumor model, three equilibria exist and are included: high tumor, low tumor and tumor free. The tumor-free equilibrium for all three state variables is given by (T_E , N_E , L_E) = (0, δ/f, 0). In the case, where $T_E \neq 0$, the equilibria are determined by finding the simultaneous solutions of Eq. (1), (2) and (3) (Pillis *et al*., 2006). With respect to the fact that eradication of tumor cells (steering the trajectories to E_0) is desirable, values of equilibrium points for a non-zero tumor are not significant in our research and the best state in clinical view is the one which tumor cells are zero. Since the stability of equilibria is important from a physiological viewpoint, Stabilization of the equilibria has done by determining the stability of the linearized system. At the tumor-free equilibrium, $E_0 = \left(0, \frac{\delta}{f}, 0\right)$ the Jacobian matrix becomes:

$$\begin{bmatrix} a - \frac{c\delta}{f} & 0 & 0 \\ -\frac{p\delta}{f} & -f & 0 \\ \frac{r\delta}{f} & 0 & -m \end{bmatrix} \tag{7}$$

Therefore, the eigenvalues of the system linearized about the tumor-free equilibrium are:

$$\lambda_1 = a - \frac{c\delta}{f}, \quad \lambda_2 = -f, \quad \lambda_3 = -m$$

Since f, m>0, λ_2 and λ_3 are always negative, the tumor-free equilibrium E_0 is stable if and only if:

$$\lambda_1 = a - \frac{c\delta}{f} < 0 \Leftrightarrow c > \frac{af}{\delta}.$$

NONLINEAR FEEDBACK CONTROL AND STABILIZATION

In this section, we will study the problem of nonlinear feedback control and stabilization of tumor system about its equilibrium points. For this purpose, consider model (1-3) with controlling inputs as follows:

$$\frac{dT}{dt} = aT(1-bT) - cNT - D + u_1 \tag{8}$$

$$\frac{dN}{dt} = \delta - fN + g\frac{T^2}{h+T^2}N - pNT + u_2 \tag{9}$$

$$\frac{dL}{dt} = -mL + j\frac{D^2}{k+D^2}L + rNT - qLT + u_3 \tag{10}$$

$$D = \frac{d(\frac{L}{T})^l}{s+(\frac{L}{T})^l}T$$

where, u_i; (i = 1, 2, 3) are controlling inputs. Without loss of generality, we suppose that T = x_1; N = x_2; L = x_3 and will obtain the equations of perturbed states about the desirable equilibrium point by representing the following new variables:

$$\eta_1 = x_1 + \bar{x}_1, \quad \eta_2 = x_2 + \bar{x}_2, \quad \eta_3 = x_3 + \bar{x}_3 \tag{11}$$

where, x_i; i = 1, 2, 3 denote the coordinates of the equilibrium point E_0. Substituting (11) into (1-4) leads to the following system:

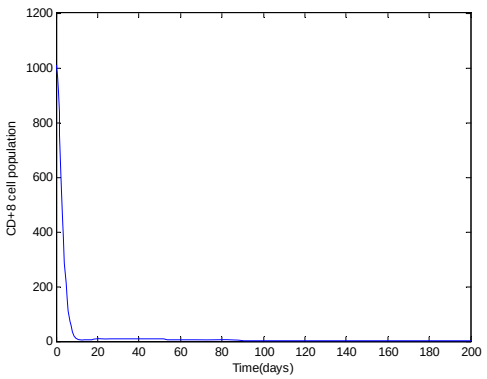
$$\dot{\eta}_1 = a\eta_1(1-b\eta_1) - c(\eta_2 - \frac{\delta}{f})\eta_1 - D + u_1 \tag{12}$$

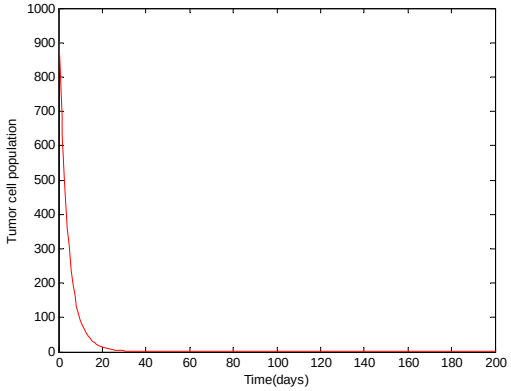
$$\dot{\eta}_2 = \delta - f(\eta_2 + \frac{\delta}{f}) + g\frac{\eta_1^2}{h+\eta_1^2}(\eta_2 + \frac{\delta}{f}) - p(\eta_2 + \frac{\delta}{f})\eta_1 + u_2 \tag{13}$$

$$\dot{\eta}_3 = -m\eta_3 + j\frac{D^2}{k+D^2}\eta_3 - q(\eta_1\eta_3) + r(\eta_2 + \frac{\delta}{f})\eta_1 + u_3 \tag{14}$$

Theorem 1: Using the nonlinear feedback control inputs:

$$u^*_1 = -a\eta_1^2 + ab\eta_1^3 + c\eta_2 + D \tag{15}$$





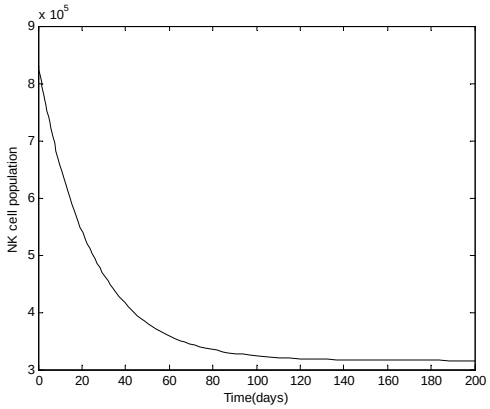


Fig. 1: Trajectories of desirable equilibrium point with controlling inputs

$$u^*_2 = -g\frac{\eta_1^2\eta_2}{h+\eta_1^2} - \frac{g\delta}{(h+\eta_1^2)f} + p\eta_1\eta_2 + \frac{p\eta_1\delta}{f} \quad (16)$$

$$u^*_3 = -\frac{jD^2\eta_3}{k+D^2} - r_1\eta_1\eta_2 + q\eta_1\eta_3 + + \frac{r\delta}{f}\eta_1 \quad (17)$$

The unstable desirable equilibrium point of the system (1-4) will be globally asymptotically stabilized.

Proof: To proof the above theorem, Lyapunov stability theorem is used to obtain the control inputs and to prove the asymptotic stability of the system (1-4) around its desirable equilibrium point. Consider the nonlinear system (12-14) with three state variables η_i; (i = 1; 2; 3) and three control inputs u_i; (i = 1; 2; 3) with $\dot{\eta}_i$ a definite functions η_i of and u_i. One choice as the candidate Lyapunov function of the system (12-14) can be V (η_1, η_2, η_3) = $\frac{1}{2}(\eta_1^2 + \eta_2^2 + \eta_3^2)$. The time derivation along the trajectories of the system (12-14) is:

$$\dot{V} = \eta_1\dot{\eta}_1 + \eta_2\dot{\eta}_2 + \eta_3\dot{\eta}_3 = (a\eta_1^2 - ab\eta_1^3 - c\eta_1\eta_2 - \frac{c\eta_1\delta}{f} - \eta_1 D + u_1\eta_1)$$
$$+(-f\eta_2^2 + \frac{g\eta_1^2\eta_2^2}{h+\eta_1^2} + \frac{g\eta_1^2\delta\eta_2}{(h+\eta_1^2)f} - p\eta_2^2\eta_1 - \frac{p\delta\eta_1\eta_2}{f} + \eta_2 u_2) +$$
$$(\frac{jD^2\eta_3^2}{k+D^2} - m\eta_3^2 - q\eta_1\eta_3^2 + r\eta_2\eta_1\eta_3 + \frac{r\delta\eta_1\eta_3}{f} + u_3\eta_3) \quad (18)$$

The optimal trajectories: In order to obtain the optimal trajectories, we substitute the control inputs (15-17) into system (12-14). Therefore, the optimal trajectories can be obtained by solving the following system:

$$\dot{\eta}_1 = -\frac{c\delta}{f}\eta_1$$
$$\dot{\eta}_2 = -f\,\eta_2$$
$$\dot{\eta}_3 = -m\,\eta_3 \quad (19)$$

Therefore the optimal trajectories $\dot{\eta}_i^*$ can be written as follows:

$$\eta_1^* = c_1 e^{-\frac{c\delta}{f}t},$$
$$\eta_2^* = c_2 e^{-ft},$$
$$\eta_3^* = c_3 e^{-mt}, \quad (20)$$

SIMULATION RESULTS

In this section, we have shown the simulation results for the tumor system (1-3) to represent the feasibility of the nonlinear control with nonlinear control inputs u_i: i = 1, 2, 3. And have concluded that the desirable unstable equilibrium point of the tumor system can be asymptotically stabilized. Numerical examples for this system were carried out for parameters values (2) and initial densities (3). The following figures display the stabilized behavior of the tumor system about the unstable equilibrium point and its control functions inputs (Fig. 1).

CONCLUSION

In this study, a nonlinear feedback control law in order to stabilize the unstable desirable equilibrium point and steering the state trajectories of system to this point is proposed. The stability of the equilibrium point of this system is studied based on the Lyapunov linearization approach. Numerical simulations are included to demonstrate the effectiveness of the proposed technique. MATLAB has been used for computations in this study.

REFERENCES

Adam, J.A. and N. Bellomo, 1997. Mathematical Modeling of Tumor Growth Kinetics. Math. G., pp: 89-133.

Cappuccio, A., F. Castiglione and B. Piccoli, 2007. Determination of the optimal therapeutic protocols in cancer immunotherapy. Math. Biosci., 209(1): 1-13.

Caravagna, G., R. Barbuti and A. D'Onofrio, 2012. Fine-tuning anti-tumor immunotherapies via stochastic simulations. BMC Bioinformatics, 13(4) DOI: 10.1186/1471-2105-13-S4-S8.

Chang, W., L. Crowl, M. Eric, T.B. Katherine, T. Lorraine and V. Michael, 2003. Advisors analyzing immunotherapy and chemotherapy of tumors through mathematical modeling. Depart. Math., pp: 1-184.

Diefenbach, A., E.R. Jensen, A.M. Jamieson and D.H. Raulet, 2001. Rae1 and H60 ligands of the NKG2D receptor stimulate tumor immunity. Nature, 413(6852): 165-171.

D'Onofrio, A., U. Ledzewicz and H. Schättler, 2012. On the dynamics of tumor- immune system interactions and combined chemo- and immunotherapy. SIMAI Springer Series, 1: 249-266.

Devi, A. and A. Ghosh, 2112. On the Stability of immune-tumor (I-T) model with the effect of drug administration. Int. J. Pure Appl. Math., 79(4): 547-560.

Germain, R.N., 2004. An innately interesting decade of research in immunology. Nat. Med., 10(12): 1307-1320.

Kawarada, Y., R. Ganss, N. Garbi, T. Sacher, B. Arnold and G.J. Hämmerling, 2001. NK- and CD8+T cell-mediate eradication of established tumors by peritumoral injection of CpG-containing oligodeoxynucleotides. J. Immunol., 167(1): 5247-5253.

Kieper, W.C., M. Prlic, C.S. Schmidt, M.F. Mescher and S.C. Jameson, 2001. Il-12 enhances CD8 T cell homeostatic expansion. J. Immunol., 166(9): 5515-5521.

Kirschner, D. and J.C. Panetta, 1998. Modeling immunotherapy of the tumor-immune interaction. J. Math. Biol., 37: 235-252.

Lisette, G., D. Pillis, A.E. Radunskaya and C.L. Wiseman, 2005. A validated mathematical model of cell-mediated immune response to tumor growth. Cancer Res., 65(17): 7950-7958.

Merola, A., C. Cosentino and F. Amato, 2008. An insight into tumor dormancy equilibrium via the analysis of its domain of attraction. Biomed. Signal Process. Control, 3(3): 212-219.

Osada, T., H. Nagawa and Y. Shibata, 2004. Tumor-infiltrating effector cells of α-galactosylceramide-induced antitumor immunity in metastatic liver tumor. J. Immune Based Ther. Vaccines., 2(7): 1-9.

Pillis, L.G.D. and A. Radunskaya, 2003. A Mathematical Model of Immune Response to Tumor Invasion. Bathe, K.J. (Ed.), Computational Fluid and Solid Mechanics, pp: 1661-1668.

Pillis, L.G.D., W. Gu and A.E. Radunskaya, 2006. Mixed immunotherapy and chemotherapy of tumors:Modeling applications and biological interpretations. J. Theor. Biol., 238(4): 841-862.

Roitt, I.M. and J. Brostoff, 1993. Immunology. Mosby, St. Louis.