Optimal Control Strategies for Tumor Cells with Immune Response

Kondala Rao.K[1], Karuna.B.N.R[2], Lakshmi Narayan.K[3]

[1]Associate Professor of Mathematics, Vidya Jyothi Institute of Technology, Hyderabad, India
[2]Assistant Professor of Mathematics, CMR college of Engineering and Technology, Hyderabd, India
[3]Professor of Mathematics, Vidya Jyothi Institute of Technology, Hyderabad, India
Email: [1]kkrao.kanaparthi@gmail.com, [2]karunakrao@gmail.com, [3]narayankunderu@yahoo.com

ABSTRACT

The recurrence of the cancer growth can be prevented by the anti- tumor activity which is found to be very crucial in developing the treatment of the cancerous cells. In the present work, we include an immune response to derive the optimal control strategies. The focus is on assessing immune cell effects on tumor progression. Applying optimal control theory, we produce continuous controls to a range of objectives and parameter choices. Applying Pontryagin's Maximum Principle we provide a practical approach and look at factors that have a reflective influence on numerical convergence. Numerical simulations have been carried out with hypothetical values to show stability of the system.

Keywords

Cancer disease, Optimal Control strategies, Pontryagin's Maximum Principle, Routh-Hurwitz criterion
Article Received: 10 August 2020, Revised: 25 October 2020, Accepted: 18 November 2020

Introduction

Cancer cells are host cells that multiply in an uncontrolled and non-specific way that leads to the development of a tumor. The characteristic feature of cancer is its ability to invade and metastatize, which comprises of tissue disruptions, which further simulates the immune system. Tumor cells are categorized by a wide number of genetic and epigenetic events leading to the appearance of specific antigens called neo antigens, triggering anti tumoral mechanism by the immune system [1,2]. All these observations led to the formation of the hypothesis that the immune system may eliminate tumors.

The growth of cells and their function are regulated with the help of antigen specific agents called cytokines during a particular immune response. They bring about the autocrine and panacrine effects i.e., changing the cells that produce them and altering the cells near them. An important cytokine is Interleukin-2 which arbitrates cell proliferation, enhancing the

production of other cytokines, and increasing the function of natural killer cells. This use of cytokines to treat cancer is generally done in combination with adoptive cellular Immunotherapy (ACI). In a treatment that includes ACI, T-cells are taken from cancer patients which are grown and activated in a manner that helps in stimulating them to react to certain antigens. These activated T-cells then immunologically reject the tumor cells when infused into the patient by attacking the tumor cite.

Progressive approaches used in other fields, specifically pest management, imply to the fact that complete elimination of an undesired species is not often possible. Similarly, in commonly found cancers (such as prostate, lung, breast, colorectal, pancreatic etc.), years of clinical observations have clearly confirmed that a cure is not possible with currently employed therapies. The goal of cancer treatment for these cancers is to be shifted to its long term control which essentially turns the cancer into a chronic disease [3].

Optimization techniques can isolate values of the controller which decreases the objective over some fixed or varied time horizon of the model. The majority of past optimal control models of cancer therapy define the objective as minimizing total tumor volume following the standard goal of "treat to cure". Swan and Vincent (1977), Swan (1980), and Swan (1988) provide the first applications of optimal control theory to treating cancer [4, 5, 6]. Optimal control theory has since been used to investigate cytotoxic chemotherapies, cell cycle chemotherapies, radiotherapy, and immune therapies [7,8,9,10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,24,25].

The deterministic model

In this section we construct the spontaneous tumor regression and progression system using a prey–predator system. The dynamical system can be described the following set of nonlinear ordinary differential equations,

$$\frac{dx}{dt} = rx\left(1-\frac{x}{k}\right) - \alpha xy - ux(t)$$

$$\frac{dy}{dt} = \beta yz - dy + \alpha xy + ux(t)$$

$$\frac{dz}{dt} = sz\left(1-\frac{z}{g}\right) - \beta yz - pz$$

Where,

- x(t) represents the densities of tumor cells
- y(t) represents the densities of hunting predator cells
- z(t) represents the densities of resting predator cells.

We have assumed that the tumor cells are being destroyed at a rate proportional to the tumor cells densities according to the law of mass action.

Next we also assume that the resting predator cells are converted to the hunting cells either by direct contact with them or by contact with a fast diffusing substance produced by hunting cells.

Here,

r is the growth rate of the tumor cells,

k is the maximum carrying capacity of tumor cells,

β is the conversion rate of resting cell to hunting cell,

d is the natural death of hunting cell,

α is the loss of tumor cells due to interaction with the hunting predator cells.

s is the growth rate of resting predator cell,

g is the maximum carrying capacity of resting cells,

p is the natural death rate of resting cell.

u is the control variable

Stability analysis:

Cancer self-remission and tumor system have to be analyzed with the initial positivity conditions x(0) > 0, y(0) > 0, z(0) > 0.

To study the stability of the steady states, we linearize system around the steady states and find the Jacobian matrices. Based on the theory of differential equations, the stability of the steady states is investigated, where det (Jacobian J) = 0 . If all the eigen values of the Jacobian matrix have negative real parts, then the steady state is locally asymptotically stable. On the other hand, if at least one of the eigen values has positive real part, then the steady state is unstable.

In the absence of control variable, i.e., u(t) = 0 in model (1) , the modified model has then two types of steady states:

(i) Tumour-free steady state, where the tumour cells population is zero, while the normal cells survive.

$$E_0\,(0,y^*,z^*) = (0,\ d/\beta,\ g-p/s).$$

(ii) Persistent-tumour steady state(s)

$$E_1\,(x^*,y^*,z^*)$$

The Jacobian matrix for system (1) around the steady state E_1 is given by

$$\begin{vmatrix} r-\frac{2rx^*}{k}-\lambda & -\alpha y^* & 0 \\ \alpha x^* & \beta z^*-d+\alpha x^*-\lambda & \beta y^* \\ 0 & -\beta y^* & s-\frac{2sz^*}{g}-p-\beta y^*-\lambda \end{vmatrix} = 0$$

The characteristic equation is given by $\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0$

In this case, the steady state E_1 is locally asymptotically stable if and only if all the roots of the characteristic equation have negative real parts which depends on the numerical values of parameters which can be shown in numerical exploration.

This is based on holding the following Routh–Hurwitz conditions.

$A_1 > 0$, $A_3 > 0$ and $A_1A_2 - A_3 > 0$. Hence the persistent tumor state is locally asymptotically stable, where the equilibrium points at persistent tumor state are given as

$$x^* = \frac{k\left(r-\alpha y^*\right)}{r}$$

$$z^* = \frac{g\left(s-\beta y^*-p\right)}{s}$$

$$y^* = \frac{\beta g\left(s-p\right)+s\left(k-d\right)}{\beta^2 g+sk\alpha r^{-1}}$$

Optimal control problem

The formulation as an optimal control problem allows us to:

(i) investigate the dynamical system of interacting cell populations being affected by the (immune) treatments;

(ii) Optimize the application of the control such that the quantity of the treatments is optimized; and

(iii) Minimize the tumour size at some end-time.

The objective function is defined as follows:

$$J\left(u\right)=\int_0^{t_f}\left(x+y+z+\frac{1}{2}Au^2\right)dt$$

With the constraint equation

$$U=\left\{\vec{u}:0\le u\left(t\right)\le 1,\forall t\in\left[0,t_f\right]\right\}$$

Then in order to get the necessary condition of optimal control , Pomtryagin's Principle is applied. The Hamiltonian function of this optimal control is

$$H\left(x,y,z,u,\lambda\right)=x+\frac{1}{2}Au^2+\lambda_1\left(rx\left(1-\frac{x}{k}\right)-\alpha xy+u\left(t\right)\right)$$
$$+\lambda_2\left(\beta yz-dy-\alpha xy+u\left(t\right)\right)$$
$$+\lambda_3\left(sz\left(1-\frac{z}{g}\right)-\beta yz-pz\right)$$

From the Hamiltonian function we get,

(i) State Equations

$$\frac{dx}{dt}=\frac{\partial H}{\partial\lambda_1}=rx\left(1-\frac{x}{k}\right)-\alpha xy-u\left(t\right)$$

$$\frac{dy}{dt}=\frac{\partial H}{\partial\lambda_2}=\beta yz-dy+\alpha xy+ux\left(t\right)$$

$$\frac{dz}{dt}=sz\left(1-\frac{z}{g}\right)-\beta yz-pz$$

with the initial conditions

$$x\left(0\right)=x_0,y\left(0\right)=y_0,z\left(0\right)=z_0$$

The co-existence state equation is

$$\frac{d\lambda_1}{dt}=\frac{\partial H}{\partial x}=-1-\lambda_1 r+\frac{2\lambda_1 rx}{k}+\lambda_1\alpha y+\lambda_2\alpha y$$

$$\frac{d\lambda_2}{dt}=\frac{\partial H}{\partial y}=\lambda_1\alpha x-\lambda_2\beta z+\lambda_2 d+\lambda_2\alpha x+\lambda_3\beta z$$

$$\frac{d\lambda_3}{dt}=\frac{\partial H}{\partial z}=-\lambda_2\beta y-\lambda_3 y+\frac{2\lambda_3 sz}{g}+\lambda_3\beta y+\lambda_3 p$$

With transversality condition

$$\lambda_1\left(t_f\right)=\lambda_2\left(t_f\right)=\lambda_3\left(t_f\right)=0$$

Stationary condition

$$\frac{\partial H}{\partial u}=0,\qquad u^*=-\frac{\lambda_1}{A}$$

Since $0\le u\left(t\right)\le 1$, we get

$$u^*=\min\left\{\max\left(0,\frac{\lambda_1}{A}\right)\right\}$$

Numerical Results:

This section aims to present the numerical solution of the controlled nonlinear cancer self-remission and tumor system to explore the possibility of the optimal control of this system.

We carry out numerical simulations to demonstrate our theoretical results and the complex dynamics of the system (1) for a set of d=0.5;g=0.4;k=13;p=1.8;r=6.5;s=0.9;u=2.5;

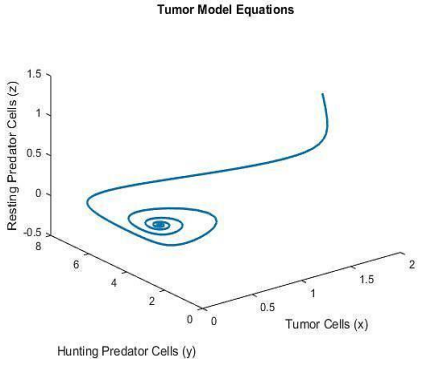

Figure1(a)

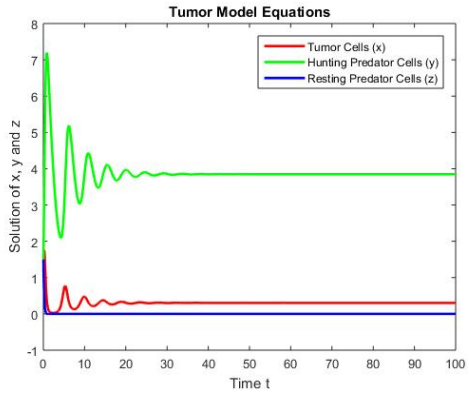

Figure1(b)

Figure 1(a) The phase portrait of the system approaching stability and **Figure 1(b)** shows the stable variations for the population under study.

Conclusion

- It is well known that the cancer is one of the greatest killers in the world and the control of tumor growth requires great attention.
- This paper is concerned with the problem of optimal control of unstable steady-states of cancer self-remission and tumor system using a nonlinear control approach. The positive steady-states are investigated. The stability of the
- steady-states of this system are studied using the linear stability approach. The aim of the optimal control is to minimize the number of tumor cells.
- Pontryagin's Principle was applied to the problem to obtain the optimal condition. Numerical simulations show that with immune response there is effective control inthe growth of tumors.

References

[1] El-Gohary A. Optimal control of the genital herpes epidemic. Chaos, Solitons & fractals 2001;12:1817–22.

[2] d'Onofrio A. Tumor evasion from immune control: strategies of a MISS to become a MASS. Chaos, Solitons & Fractals 2007;31:261–8.

[3] P. Enriquez-Navas, Y. Kam, T. Das, S. Hassan, A. Silva, P. Foroutan, E. Ruiz, G. Martinez, S. Minton, R. Gillies, R. Gatenby, Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer, Science Translational Medicine 8 (327) (2016) 327ra24.

[4] G. Swan, T. Vincent, Optimal control analysis in the chemotherapy of IgG multiple myeloma, Bulletin of Mathematical Biology 39 (3) (1977) 317–337.

[5] G. Swan, Optimal control in some cancer chemotherapy problems, International Journal of Systems Science 11 (1980) 223–227.

[6] G. Swan, General applications of optimal control theory in cancer chemotherapy, IMA J Math Appl Med Biol 5 (5) (1988) 303–316.

[7] A.Coldman, J. Murray, Optimal control for a stochastic model of cancer chemotherapy, Mathematical Biosciences 168 (2) (2000) 187–200.

[8] F. Castiglione, B. Piccoli, Optimal control in a model of dendritic cell transfection cancer immunotherapy, Bulletin of Mathematical Biology 68 (2) (2006) 255–274.

[9] A. Cappuccio, F. Castiglione, B. Piccoli, Determination of the optimal therapeutic protocols in cancer immunotherapy, Mathematical Biosciences 209 (1) (2007) 1–13.

[10] F. Castiglione, B. Piccoli, Cancer immunotherapy, mathematical modeling and optimal control, Journal of Theoretical Biology 247 (4) (2007) 723–732.

[11] U. Ledzewicz, H. Schattler, Optimal and suboptimal protocols for a class of mathematical 470 models of tumor anti-angiogenesis, Journal of Theoretical Biology 252 (2) (2008) 295–312.

[12] M. Villasana, G. Ochoa, S. Aguilar, Modeling and optimization of combined cytostatic and cytotoxic cancer chemotherapy, Artificial Intelligence in Medicine 50 (3) (2010) 163–173.

[13] S. Benzekry, P. Hahnfeldt, Maximum tolerated dose versus metronomic scheduling in the treatment of metastatic cancers, Journal of Theoretical Biology 335 (2013) 235–244.

[14] U. Ledzewicz, H. Schattler, Controlling a model for bone marrow dynamics in cancer chemotherapy, Mathematical Biosciences and Engineering 1 (1) (2004) 95–110.
[15] U. Ledzewicz, H. Schattler, The influence of pk/pd on the structure of optimal controls in cancer chemotherapy models, Mathematical Biosciences and Engineering 2 (3) (2005) 561– 578.
[16] A. Swierniak, J. Smieja, Analysis and optimization of drug resistant and phase-specific cancer chemotherapy models, Mathematical Biosciences and Engineering 2 (3) (2005) 657–670.
[17] J. Zhu, R. Liu, Z. Jiang, P.Wang, Y. Yao, Z. Shen, Optimization of drug regimen in chemotherapy based on semi-mechanistic model for myelosuppression, Journal of Biomedical Informatics 57 (2015) 20–27.
[18] J. Murray, Optimal control for a cancer chemotherapy problem with general growth and loss functions, Mathematical Biosciences 98 (2) (1990) 273–287.
[19] J. Murray, Some optimal control problems in cancer chemotherapy with a toxicity limit, Mathematical Biosciences 100 (1) (1990) 49–67.
[20] S. Nanda, H. Moore, S. Lenhart, Optimal control of treatment in a mathematical model of chronic myelogenous leukemia, Mathematical Biosciences 210 (1) (2007) 143–156.
[21] A. Ghaffari, N. Naserifar, Optimal therapeutic protocols in cancer immunotherapy, Computers in Biology and Medicine 40 (3) (2010) 261–270.
[22] B. Ainseba, C. Benosman, Optimal control for resistance and suboptimal response in cml, Mathematical Biosciences 227 (2) (2010) 81–93.
[23] U. Ledzewicz, M. Naghnaeian, S. H, Optimal response to chemotherapy for a mathematical model of tumor-immune dynamics, Journal of Mathematical Biology 64 (3) (2012) 557–577.
[24] K. Kim, G. Cho, I. Jung, Optimal treatment strategy for a tumor model under immune suppression, Computational and Mathematical Methods in Medicine 204, paper nr. 206287.
[25] U. Ledzewicz, H. Schaettler, Optimizing chemotherapeutic anti-cancer treatment and the tumor microenvironment: An analysis of mathematical models, Advances in Experimental Medicine and Biology 936 (2016) 209–223