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The combined effects of optimal control in cancer remission

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ABSTRACT

We investigate a mathematical model depicting the nonlinear dynamics of immunogenic tumors as envisioned by Kuznetsov et al. [1]. To understand the dynamics under what circumstances the cancer cells can be eliminated, we implement the theory of optimal control. We design two types of external treatment strategies, one is Adoptive Cellular Immunotherapy and another is interleukin-2. Our aim is to establish the treatment regimens that maximize the effector cell count and minimize the tumor cell burden and the deleterious effects of the total amount of drugs. We derive the existence of an optimal control by using the boundedness of solutions. We characterize the optimality system, in which the state system is coupled with co-states. The uniqueness of an optimal control of our problem is also analyzed. Finally, we demonstrate the numerical illustrations that the optimal regimens reduce the tumor burden under different scenarios.

1. Introduction

Cancer is a worldwide problem caused by the proliferation of tumor cells which destroy the surrounding tissues of our body. But, it is still an enigma about its proliferation, destruction and its mechanism of establishment. When the tumor cells can grow, it is necessary for them to take treatment depend upon their devastating nature, malignancy and their sequestered locations. In most of the cases surgery, chemotherapy, hormone therapy and radiation therapy failed to eliminate the cancerous cells. Despite the advances of clinicians, there are so much challenges remain to diagnosis and the treatment of cancers. So our aim is not only prevent the measure of cancer, but also investigate the successful treatment strategies through cancer immune reactions or immunotherapeutic approach to eliminate cancer.

The immunotherapy naturally stimulate our immune system to work harder against foreign organisms such as cancers. The immunological therapy can refer to as the antigen and non-antigen specific agents such as cytokine usually along with Adoptive Cellular Immunotherapy (ACI) [15–19]. Cytokines are protein hormones that mediate cell growth and activate our immune system response. Cytokines can provide the immune system a boost or given with different immunotherapies they can be used as adjuvants [38]. Interleukin-2 (IL-2) is the main cytokine (approved by Food and the Drug Administration (FDA) in 1992) responsible for the activation of T-cells (Lymphocytes) growth and differentiation. It is produced by Helper-T ($CD4+T$) cells and $CD8+T$ cells (Cytotoxic-T-Lymhocytes or *CTLs*). IL-2 acts on the same cells and produce them and alter the near by T-Lymphocytes. Therefore, we can infer to as an autocrine growth factor and an paracrine growth factor. IL-2 also used as a chemotherapeutic drug and has generic name Aldesleukin (http://chemocare.com/chemotherapy/drug-info/il-2.asp). IL-2 has been accepted for the

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treatment of cancer with high dosage regimen [14]. IL-2 is a paramount cytokine that mediate the proliferation of cells, enhance the production of several cytokine and stimulate CTLs activity at different stages [17,19] and also promote the functions of Natural Killer (NK) cells.

Adoptive Cellular Immunotherapy is refers to as the boosting and expansion of the immune system externally in the cultured of immune cells. In the tumor bearing host, ACI has an anti-tumor activity which can be achieved in conjunction with high dosage human recombinant interleukin-2. This can happen in two distinct ways: (a) Lymphokine - activated - killer (LAK) cell therapy and (b) Tumor Infiltrating Lymphocyte (TIL) therapy. In [20], Kirschner and Panetta discussed in detail the activity of LAK and TIL therapy.

To understand the dynamics of tumor cells and their environment from the context of mathematical modeling have been studied by numerous researchers [1,3,4,20–22,24–26,28,29]. The delay introduced to the biological system may cause the arising of phenomena such as existence of stability switches of the steady state [31], appearance of Hopf-bifurcation and periodic solutions or chaos [8,27,30]. But, our aim of this paper is to study the dynamic behavior of tumor-immune interaction through the application of optimal control technique. There is a large body of literature that addresses on the applications of optimal control strategy for immunotherapy in cancer dynamics [11,13,14,23,32–38]. Fister and Donnelly [38] implement the optimal control theory to obtain under what situations the cancer cells can be eliminated. They showed that the bang–bang control exists for two linear optimal control problem and cancer cells have cyclic nature during therapy. Chakrabarty and Banerjee [14] studied a mathematical model of cancer remission that include two external treatments of ACI and IL-2 therapy based on numerical simulations. Castiglione and Piccoli [32] presented a mathematical model of the competition between tumor cells and their environment, and after that they applied the optimal control theory to obtain when and in which extent the immune system can be stimulated by immunotherapeutic treatment regimens during the treatment period in the finite time horizon. Fister and Panetta [33] developed an optimal treatment strategies for the chemotherapeutic treatment administered by using optimal control theory. They studied the qualitative behavior of three distinct cell-kill models, both analytically and numerically. They also observed that the distinct treatment policies which depend on the distinct cost functions. De Pillis et al. [34] explored a magnificent mathematical model to understand the dynamics of cancer and immune system reactions in addition to chemotherapy. The authors developed the existence of optimal control theory and solved in both the quadratic and linear optimal control. They compared optimal treatment strategies, in quadratic control, linear control and state-constraint. In the article [34], the authors showed by graphical representations that the regions on which the singular control is optimal. Burden et al. [35] considered a mathematical model of cancer dynamics that include immune-effector cells and interleukin-2 (IL-2). The authors used the optimal control theory to obtain the optimal treatment strategy by external injections of adoptive cellular immunotherapy against tumor cells. Swan [37] studied the optimal control theory and established feedback treatment control and the characterization of drugs for tumor models under the hypothesis of quadratic control performance criteria. Murray [36] studied a mathematical model of tumor cells and the normal cells under the conjectures of logistic growth fashion and Gompertzian growth fashion, whereby the rate of administration of therapies is controlled. At the end of the treatment, the tumor cell burden is minimized, in different implementation, the level of toxicity, interpreted as the area under the concentration curve. De Pillis and Radunskaya [23] studied and improved a more pragmatic mathematical model of tumor cells, normal cells and immune cells with drug therapy and achieved a new treatment strategy which shows that the total amount of tumor mass being small at the end of the treatment period. To the best of our knowledge, the combined effects of drug therapies has not been explored so far in cancer dynamics by analytically and numerically. But, the effects of a single drug in cancer dynamics using optimal controls are done analytically by Fister and Donnelly [38], Fister and Panetta [33], De Pillis [23,34].

In this paper, we use the deterministic optimal control theory to obtain the effectiveness of an optimal treatment strategies for the two therapies ACI and IL-2. Also, we minimize the total number of tumor burden and the deleterious effect of drugs and maximize the total amount of effector cells. The subsequent part of this paper is as follows: we briefly describe the system of nonlinear differential equations which address the cancer-immune system interaction model in Section 2. By keeping the biomedical aim in our mind, we formulate the optimal control problem in Section 3. In Section 4, we investigate the existence of an optimal control pair. In the same section, we characterize the optimal control problem by using the Pontryagin's Maximum Principle. We then analyze the uniqueness of the optimality system, in which the state system coupled with co-states in Section 5. We perform numerical simulations for our problem in Section 6. The paper ends with a conclusion in Section 7.

2. Mathematical model

In this section, we will study the model of cancer dynamics originally represented by Kuznetsov et al. [1]. The mathematical model is akin to a prey-predator system which comprises a system of two nonlinear ordinary differential equation's (ODEs) namely, the activated immune - effector cells (ECs) and tumor cells (TCs) in a single tumor-site compartment model. The system of coupled nonlinear ODEs is defined as follows:

$$\begin{aligned}\frac{dE}{dt} &= s\epsilon_1(t) + \frac{pET}{g+T} - mET - dE,\\ \frac{dT}{dt} &= aT(1-bT) - nET - \epsilon_2(t)T,\end{aligned} \tag{1}$$

satisfying the initial conditions $E(0) = E_0$ and $T(0) = T_0$ are known. $\epsilon_1(t)$ and $\epsilon_2(t)$ are the time dependent drug efficacies. The cancer dynamics model system (1) without treatment [1] can be obtained by setting $\epsilon_1(t) = 1$ and $\epsilon_2(t) = 0$. All the parameter