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Proposing a Finite Duration Cancer Treatment Using Multi-Objective Optimization

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ABSTRACT: The main target of this paper is to propose an optimal method for eradicating cancer, such that it cannot be relapsed. The major issue is that the tumor-free equilibrium point at the end of chemotherapy is still unstable. Mathematically, it means that when the chemotherapy is stopped, the trajectory of the system moves away from the tumor-free equilibrium point and the tumor cells start increasing. To overcome this problem, we can either restart the process of chemotherapy or try to stabilize the equilibrium. In this article, the dynamics of the system is changed around the tumor-free equilibrium point using the vaccine therapy and the chemotherapy pushes the system to the domain of attraction of the desired point. In other words, some inputs have an effect on the parameters of the system. For optimal chemotherapy, two objective functions optimized simultaneously in order to minimize the size of the tumor as well as the side effects of the anticancer drug on the patients' body. After removing the chemotherapy, cancer does not relapse due to the change in the dynamics of the system. Simulation results show that by applying this method, the cancer cells population approaches to zero even after the cessation of chemotherapy for a long time.

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1- INTRODUCTION

Modeling and treatment of cancer are the main focus of many researchers worldwide from clinicians, biologists, mathematicians, and control engineers. Cancer mathematical models create an appropriate insight into the behavior of cells in the presence of cancer cells and their interaction with drugs. On the other hand, preparation of such drugs and medical examination has high risk and cost. These illustrate the importance of mathematical modeling and suitable control of the system for cancer treatment. The cancer treatment models, in addition, will enable researchers to forecast and adjust the behavior of the cancerous tumor. The modeling approaches to study the disease dynamics include but are not limited to the following: optimization, compartmental, and dynamical system approaches. In this study, we use a dynamical system approach which shows the interaction between cells and drugs. In order to avoid the adverse side effects of such drugs and preserve the level of drug dosage, drugs should be used based on a regular program. Different control methods have been used for solving this problem. Using these methods along with optimizing the number of drugs used yield to the effective diminishing of cancer cells. Theory of optimal control has been used in the modeling of chemotherapy treatment problems [1-14]. In this problem, the optimal controller is gained by solving a series of differential equations. Currently, many researchers presented mathematical models to simulate the behavior of the drug and its effects on the body [11]. However, these studies assumed that the dynamics of cancer during treatment is time invariant. In other words, the authors considered the effects of therapeutic inputs only on the system states. However, the dynamics of cancer changes during its progression.

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In this paper, a method for finite duration treatment is proposed such that at the end of treatment the system approaches its healthy equilibrium point. The base model used in this paper is [14]:

$$\frac{dT}{dt} = -aT\ln\frac{bT}{a} - cTL, \tag{1}$$

$$\frac{dL}{dt} = d + eLI_2 - fL, \tag{2}$$

$$\frac{dI_2}{dt} = \frac{gT}{T+l} - jLI_2 - kTI_2. \tag{3}$$

2-METHODOLOGY

The tumor-free equilibrium point is very important from the physiological viewpoint. The tumor-free equilibrium point is as follows:

$$E_0 = \left(0, \frac{d}{f}, 0\right) \tag{4}$$

The modified equations of the model with treatment are as following:

$$\frac{dT}{dt} = -aT\ln\left(\frac{bT}{a}\right) - cTL - K_T\left(\frac{1.2M}{0.8+M}\right)T, \tag{5}$$

$$\frac{dL}{dt} = d + eLI_2 - fL - K_L\left(\frac{1.2M}{0.8+M}\right)L, \tag{6}$$

$$\frac{dI_2}{dt} = \frac{gT}{T+l} - jLI_2 - kTI_2, \tag{7}$$

$$\frac{dM}{dt} = -\mu M + V_M(t), \tag{8}$$

$$\frac{dc}{dt} = \mu_c v_v(t)\left(1-\frac{c}{k_c}\right), \tag{9}$$

$$\frac{de}{dt} = \mu_e v_v(t)\left(1-\frac{e}{k_e}\right), \tag{10}$$

$$\frac{dg}{dt} = \mu_g v_v(t)\left(1-\frac{g}{k_g}\right), \tag{11}$$

$$\frac{dj}{dt} = \mu_j v_v(t)\left(1-\frac{j}{k_j}\right). \tag{12}$$

For analyzing the stability of the tumor-free equilibrium point and to find a Lyapunov function. The following scaled model is used:

$$\frac{dT}{dt} = -aT\ln(bT) - cTL \tag{13}$$

$$\frac{dL}{dt} = 1 + eLI_2 - L \tag{14}$$

$$\frac{dI_2}{dt} = \frac{gT}{T+1} - jLI_2 - kTI_2 \tag{15}$$

where;

$$T^* = \frac{T}{l}, \quad L^* = \frac{f}{d}L, \quad I_2^* = \frac{j}{f}I_2, \quad t^* = ft \tag{16}$$

By applying Lyapunov's direct method, the following Lyapunov function is selected:

$$V(x) = \frac{\alpha}{2}(L-1)^2 + \beta\ln(T+1) + \frac{\gamma}{2}I_2^2 \tag{17}$$

Where

$$\dot{V}(x) = -\alpha(L-1)^2 - \alpha eLI_2 - \gamma jLI_2^2 - \gamma kTI_2^2 + \left(-\beta a\ln bT_* + \alpha eI_{2*}L_*^2 + \gamma gI_{2*}\right)\frac{T}{T+1} + \left(\alpha eI_{2*}L_* - \beta cT_*\right)\frac{L}{T+1} \tag{18}$$

By considering the saturated value for defined parameters, the tumor-free equilibrium point is stable after vaccine therapy.

2-1-Multi-objective optimization

In this paper, we use the following cost function to minimize tumor cells during chemotherapy:

$$J_1 = \int_0^{t_f} T(t)\,dt, \tag{19}$$

$$J_2 = \int_0^{t_f} (L_0 - L(t))\,dt, \tag{20}$$

By considering another objective function to consider the effect of the injected drug on healthy cells:

Fig. 1 shows the Pareto front which the horizontal and vertical axes represent the first and second objective functions.

3-RESULTS AND DISCUSSION

3-1-The patient is young

The behavior of the system during the treatment for a young patient is shown in Fig. 2. Oncologist puts the goal of the chemotherapy to reduce cancer cells, so, an optimal drug regimen from region 1 can be selected.

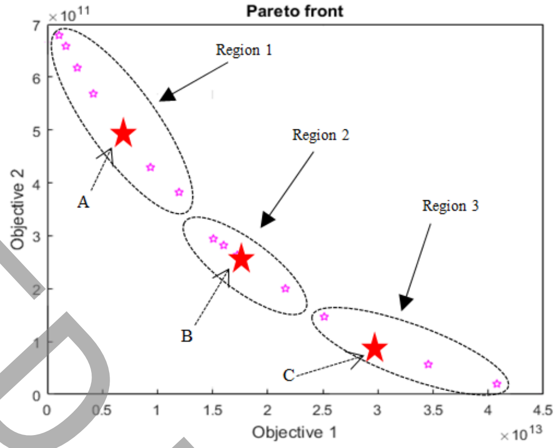

Fig. 1: Pareto front obtained by NAGA-II

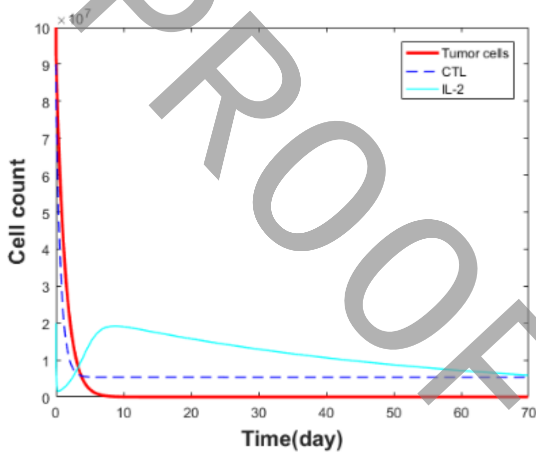

Fig. 2: The behavior of the system during the treatment for a young patient

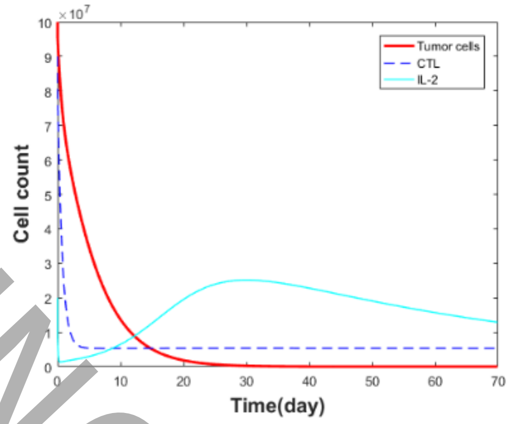

Fig. 3: The behavior of the system during the treatment for a middle-aged patient.

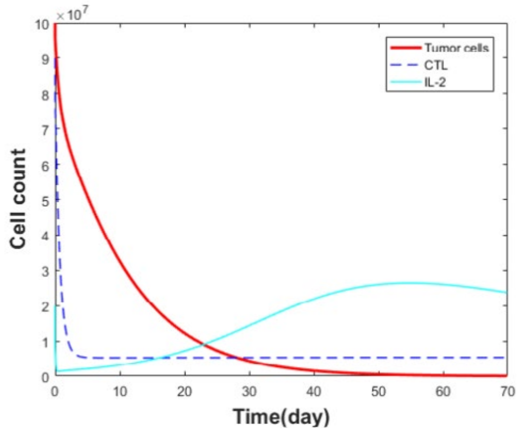

Fig. 4: The behavior of the system during the treatment for a pregnant patient

3-2-The middle-aged patient

The behavior of the system during the treatment for a middle-aged patient can be seen in Fig. 3. The doctor prescribes the chemotherapy based on both decreasing the tumor cells and protecting the healthy cells, so an optimal drug regimen from region 2 can be selected.

3-3-The patient is pregnant

The behavior of the system during the treatment for a pregnant patient can be seen in Fig. 4. The doctor chooses one of the optimal therapeutic regimens in region 3 because keeping healthy cells is more important than killing cancer cells.

4-CONCLUSION

In this paper, we showed that to obtain the finite duration treatment, a change in the dynamics of the system is necessary.

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