Mathematics

Research article

Optimal control of effector-tumor-normal cells dynamics in presence of adoptive immunotherapy

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Abstract: Interactive dynamics between effector-tumor-normal cells in a mathematical model related to the growth of cancer in presence of immunotherapy has been discussed in the present paper. Adoptive immunotherapy has been added to the original model proposed by De Pillis et al. [1]. This has been done to get rid of the tumor cells. Different dynamical behaviours of the modified systems have been studied. The existence of the solution and global stability conditions of the healthy equilibrium point is addressed. Corresponding optimal control problem has been formulated to find the best possible way of administration of adoptive immunotherapy by which cancer cells can be eradicated without putting the patient at any health-related risk. To achieve this purpose, the quadratic control principle has been adopted. The dynamical behaviour of the effector-tumor-normal cells model with control is also numerically verified and demonstrated. Through numerical simulations, it is formally shown that the optimal regimens eradicate the tumor load in less time without putting the patients' health at any risk.

Keywords: mathematical model of cancer; adoptive immunotherapy; stability analysis; optimal control problem; quadratic control principle
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1. Introduction

Cancer is still considered as one of the dreaded diseases among the human population. The majority of types of cancer precipitate through the growth of malignant tumor cells. So, special care is needed to control the growth of malignant tumors [2]. Effective treatments for cancer patients include surgery, chemotherapy, immunotherapy, and radiation therapy. There are a variety of immunosuppressive therapies including cell transfer, dendritic cells, vaccines, monoclonal antibodies, cytokines, and adjuvant therapy to name a few [3–5]. In cancer, an increase in the number of growing tumor cells kills the tissues of our body [6]. The response of a tumor to treatment depends on several factors including the severity of the tumor, the patient's response to treatment, and the location of the tumor, etc. In some cases, immunotherapy is very effective and such a treatment stimulates the immune system to fight the tumor cells and to have fewer side effects than other therapies [3, 4, 7, 8]. Therefore, our goal is not only to stop cancer but also to explore effective treatment strategies to eradicate cancer without putting the patients' health condition to further risk.

Adoptive immunotherapy targets the growth and development of antibodies by increasing the number of effectors or immune cells that help our immune system to fight cancer and other diseases. It is made up of white blood cells, tissues, and the lymphatic system. Adoptive immunotherapy, which acquires implants in the immune system to fight cancer, enhances the body's natural ability to fight tumor cells. This treatment consists of tumor antigens on cancer cells, whose molecules are identified on the face and bound with antibody proteins. Tumor antigens are usually proteins or other macronutrients (e.g., carbohydrates) and common antibodies that bind to foreign viruses, but anti-immunotherapy antibodies bind to antigen markers and target cancer cells so that the immune system blocks or kills tumors [9]. The mathematical model of tumor-immune interactions is discussed by Qomlaqi et al. [5] which can be used to develop a systematic approach to immunotherapy treatment. Interested readers are referred to the papers [8, 10–15] to have more information about the use of adoptive immunotherapy in cancer treatment.

Mathematical modeling and optimal control theory have played an important role in answering such important research questions which are found generally through experimentation, but the performance of the required experiments becomes too costly or otherwise difficult to perform. Kuznetsov et al. [16] described the cytotoxic T-lymphocyte response to tumor development. Kuznetsov and Knott [7] discussed the methods of tumor growth, its suppression, and regeneration. De Pillis and Raduskaya [1] presented the competition between normal cells and tumor cells in a model considering the role of chemotherapy into account. De Pillis et al. [17] introduced a mathematical model in tumor development using combined immunotherapy and chemotherapy. Nagata et al. [18] discussed the dynamical behaviours of T cell tumor response under the support of dendritic cells. Many researchers have worked on tumor growth models with optimal control strategies. Optimal control strategies are very helpful in finding effective treatment strategies so that the dose of the drug can be controlled with time to lessen different side effects which otherwise may put the patients' health under threat. Interested readers are referred to the papers [2, 5, 6, 9, 19–21].

In modern times, a variety of optimal control methods have been introduced to find the best treatment strategy which can cure cancer, inflicting minimum side effects [6, 22–25]. Khajanchi and Ghosh [6] demonstrated the method of combined optimal control and developed strategies that could increase the number of effector cells and minimize the overall dose of the drug that could eradicate tumor cell load. Nastitie and Khusnul Arif [22] discussed the cancer treatment process through a

combination of radiotherapy and anti-angiogenic therapy aimed at reducing cancer size by adding control doses of radiotherapy and anti-angiogenic. Glick and Mastroberradino [23] used anti-angiogenesis doses at the end of two weeks of treatment to determine the optimal dose to reduce tumor size and reduce toxicity to the patient. Bukkuri [24] carried out optimal control analysis of combined chemotherapy-immunotherapy in the case of a cancer model. Irana Ira et al. [25] discussed the dynamics of tumor cell growth and its optimal control. It is important to note the fact that the application of appropriate control theory requires a variety of populations which ultimately increases the number of equations in the mathematical model under consideration making it a difficult problem to handle with. To have an idea in this context, interested readers are referred to the papers [26–29].

In the present paper, we have discussed about a mathematical model having a cancerous cell in the form of tumors and have adopted the method of adoptive immunotherapy to get rid of the cancerous tumor cells. To make the treatment strategy a better one in which the patient's health condition does not come under threat due to different side effects, we have converted it to an optimal control problem and solved it.

The rest of this paper is as follows: In Section 2, we illustrate the model formulation. Positiveness and boundedness of the solutions of the model are verified in Section 3. The existence of equilibrium points and the local stability of those are discussed in Sections 4 and 5, respectively. In Section 6, the Lyapunov function is constructed to investigate the global stability of a locally stable healthy equilibrium point. In Section 7, we discuss the problem of optimal control concerning the model using Pontryagin's minimum principle and the Hamiltonian function. Numerical simulations and corresponding discussions are presented in Section 8. Finally, the paper ends with a detailed review in Section 9.

2. Model formulation

Our considered model in this paper is a slight modification of the model proposed by De Pillis et al. [1]. Modifications are done in the first and second equations of the model due to the incorporation of adoptive immunotherapy. In the considered model, $E(t)$, $T(t)$, and $H(t)$ denote the total density of effector or immune cells, tumor cells, and healthy or normal cells at any time $t > 0$, respectively. The system of differential equations describing the growth, death, and interactions of this population is given by

$$\frac{dE}{dt} = \mu + \frac{\rho ET}{\sigma + T} - c_1 ET - d_1 E + v_1,$$

$$\frac{dT}{dt} = r_1 T(1 - b_1 T) - c_2 ET - c_3 TH - v_2 T, \tag{2.1}$$

$$\frac{dH}{dt} = r_2 H(1 - H) - c_4 HT,$$

with initial conditions $E(0) = E_0$, $T(0) = T_0$, and $H(0) = H_0$ where each initial value is positive.

In the first equation of model (2.1), the effector cells have a constant source rate μ, while the density of effector cells is proportional to death using the term $d_1 E$. Response of tumor-specific effector cells is regulated by the Michaelis-Menten form $\rho ET/(\sigma + T)$ which gives a saturation effect. The third term $c_1 ET$ represents the decomposing rate of effector cells by tumor cells. The last

term v_1 represents the external source of adoptive cellular immunotherapy. This last term has not been applied in the model proposed by De Pillis et al. [1].

In the second equation of model (2.1), the tumor cell population is logistically increasing, as justified in [6–9], and is killed by the immune cells and normal cells through a mass-action dynamics which are represented by the terms c_2ET and c_3TH. Tumor cell growth rate is r_1 and b_1 is the maximum carrying capacity of tumor cells. The final term v_2T refers to tumor cells killed by an external injection of adoptive immunotherapy. This last term has not been used in the model introduced by De Pillis et al. [1].

In the third equation of model (2.1), the normal cell population is also growing logistically, r_2 is representing the growth rates of normal cells, and the maximum carrying capacities of normal cells is one [1]. The second term c_4TH refers to the rate of normal cell death owing to tumor cells.

3. Positive invariance and boundedness

Before we proceed with the mathematical analysis, we must show that the model is biologically feasible and that the values of all parameters are non-negative. According to the standard comparison theory, it follows

$$\frac{dE}{dt} = \mu + \frac{\rho ET}{\sigma + T} - c_1ET - d_1E + v_1 \leq \mu + v_1 - d_1E.$$

Integration of the above leads to

$$E(t) \leq \frac{\mu + v_1}{d_1} + E(0)e^{-d_1t} \implies \lim_{t \to \infty} \sup(E(t)) \leq \frac{\mu + v_1}{d_1}.$$

Again

$$\frac{dT}{dt} = r_1T(1 - b_1T) - c_2ET - c_3TH - v_2T \leq r_1T(1 - b_1T).$$

Proceeding as above, we have

$$T(t) \leq \frac{1}{b_1 + T(0)e^{-r_1t}} \implies \lim_{t \to \infty} \sup(T(t)) \leq \frac{1}{b_1},$$

and similarly, we find

$$H(t) \leq \frac{1}{1 + H(0)e^{-r_2t}} \implies \lim_{t \to \infty} \sup(H(t)) \leq 1.$$

Thus, the feasible region for model (2.1) to be realistic is defined as $\psi = \{(E, T, H) \in R_+^3\}$.

We further assume that the initial values are positive i.e. $E(0) \geq 0$, $T(0) \geq 0$, and $H(0) \geq 0$, then $E(t) \geq 0$, $T(t) \geq 0$, and $H(t) \geq 0$ for all $t \geq 0$. The trajectories evolve in the attracting regions

$$\psi = \{(E, T, H) \in R_+^3 | 0 \leq E(t) \leq \frac{\mu + v_1}{d_1}, 0 \leq T(t) \leq \frac{1}{b_1}, 0 \leq H(t) \leq 1\}.$$

The domain ψ is positive invariant for model (2.1) and thus biologically meaningful for the cell

densities. We will analyze the model quantitative behaviour in the domain ψ [30]. This verifies that model (2.1) is biologically feasible.

4. Existing of equilibrium points

We consider a case where the external source of adoptive cellular immunotherapy and tumor cells killed by an external injection of adoptive immunotherapy per day is a constant parameter [6].

Equilibrium points are found by

$$\frac{dE}{dt} = 0 \Longrightarrow \mu + \frac{\rho ET}{\sigma + T} - c_1 ET - d_1 E + v_1 = 0,$$

$$\frac{dT}{dt} = 0 \Longrightarrow r_1 T(1 - b_1 T) - c_2 ET - c_3 TH - v_2 T = 0,$$

$$\frac{dH}{dt} = 0 \Longrightarrow r_2 H(1 - H) - c_4 TH = 0.$$

The simplification of the above results shows that

(i) $S_1(E_1, T_1, H_1)$ is a healthy equilibrium (where there is no existence of tumor) point where $E_1 = (\mu + v_1)/d_1$, $T_1 = 0$, and $H_1 = 1$.

(ii) $S_2(E_2, T_2, H_2)$ is a co-existing or unhealthy equilibrium point (where there is the existence of tumor) where

$$E_2 = \frac{(\mu + v_1)(\sigma + T_2)}{(d_1 + c_1 T_2)(\sigma + T_2) - \rho T_2}, \qquad H_2 = 1 - \frac{c_4 T_2}{r_2},$$

and T_2 can be found from the solution of the equation

$$T_2 = \frac{1}{b_1} - \frac{c_2 E_2}{r_1 b_1} - \frac{c_3 H_2}{r_1 b_1} - \frac{v_2}{r_1 b_1}$$

$$= \frac{1}{b_1} - \frac{c_2}{r_1 b_1}\left(\frac{(\mu + v_1)(\sigma + T_2)}{(d_1 + c_1 T_2)(\sigma + T_2) - \rho T_2}\right) - \frac{c_3}{r_1 b_1}\left(1 - \frac{c_4 T_2}{r_2}\right) - \frac{v_2}{r_1 b_1},$$

or

$$A_1 T_2^3 + A_2 T_2^2 + A_3 T_2 + A_4 = 0,$$

where

$$A_1 = c_1(c_3 c_4 - r_1 r_2 b_1),$$

$$A_2 = (r_1 r_2 b_1 - c_3 c_4)(\rho - d_1 - \sigma c_1) + c_1 r_2(r_1 - v_2 - c_3),$$

$$A_3 = -r_2 c_2(\mu + v_1) - d_1 \sigma(r_1 r_2 b_1 - c_3 c_4) - r_2(r_1 - v_2 - c_3)(\rho - d_1 - \sigma c_1),$$

$$A_4 = d_1 \sigma r_2(r_1 - v_2 - c_3) - r_2 c_2(\mu + v_1)\sigma.$$

Note: Equilibrium points are valid if $r_2 > c_4 T_2$ and $(d_1 + c_1 T_2)(\sigma + T_2) > \rho T_2$ which can be seen easily from the above equations.

5. Local stability analysis

Without treatment case $(v_1 = v_2 = 0)$: In this section, we study the nature of stability of the equilibrium points S_1 and S_2 by considering $v_1 = 0$ and $v_2 = 0$; these equilibrium points are

$$S_1^* \left(E_1^* = \frac{\mu}{d_1}, T_1 = 0, H_1 = 1 \right),$$

and

$$S_2^* \left(E_2^* = \frac{\mu(\sigma + T_2^*)}{(d_1 + c_1 T_2^*)(\sigma + T_2^*) - \rho T_2^*}, T_2^* = \frac{1}{r_1 b_1}(r_1 - c_2 E_2^* - c_3 H_2^*), H_2^* = 1 - \frac{c_4 T_2^*}{r_2} \right).$$

The Jacobian matrix of the system (2.1) is

$$J_{S*} = \begin{pmatrix} A & D - c_1 E & 0 \\ -c_2 T & B & -c_3 T \\ 0 & -c_4 H & C \end{pmatrix},$$

where

$$A = \frac{\rho T}{\sigma + T} - c_1 T - d_1, \ B = r_1 - 2r_1 b_1 T - c_2 E - c_3 H, \ C = r_2 - 2r_2 H - c_4 T, \ D = \frac{\sigma \rho E}{(\sigma + T)^2}.$$

(i) At the first equilibrium point, the eigenvalues of the Jacobian matrix J_{S*} are

$$\lambda_1^1 = \frac{\rho T_1}{\sigma + T_1} - c_1 T_1 - d_1 = -d_1 < 0,$$

$$\lambda_2^1 = r_1 - 2r_1 b_1 T_1 - c_2 E_1^* - c_3 H_1 = r_1 - \frac{c_2 \mu}{d_1} - c_3,$$

$$\lambda_3^1 = r_2 - 2r_2 H_1 - c_4 T_1 = -r_2 < 0.$$

By applying the condition of stability, the necessary condition for asymptotic stability of equilibrium point S_1^* is found to be

$$r_1 < \frac{c_2 \mu}{d_1} + c_3,$$

and it will be unstable when $r_1 > \frac{c_2 \mu}{d_1} + c_3$.

(ii) The eigenvalues associated with co-existing equilibrium point $S_2^*(E_2^*, T_2^*, H_2^*)$ are derived from the Jacobian matrix J_{S*}. The characteristic equation is

$$\lambda^3 + A_{11}\lambda^2 + A_{12}\lambda + A_{13} = 0, \tag{5.1}$$

where (in (5.1))

$$A_{11} = -(A + B + C),$$

$$A_{12} = AB + AC + BC + c_2 D T_2^* - c_1 c_2 E_2^* T_2^* - c_3 c_4 H_2^* T_2^*,$$

$$A_{13} = c_1 c_2 C E_2^* T_2^* + c_3 c_4 A H_2^* T_2^* - ABC - c_2 CD T_2^*,$$

and

$$E_2^* = \frac{\mu(\sigma + T_2^*)}{(d_1 + c_1 T_2^*)(\sigma + T_2^*) - \rho T_2^*},$$

$$T_2^* = \frac{1}{r_1 b_1}(r_1 - c_2 E_2^* - c_3 H_2^*),$$

$$H_2^* = 1 - \frac{c_4 T_2^*}{r_2},$$

$$A = \frac{\rho T_2^*}{\sigma + T_2^*} - c_1 T_2^* - d_1,$$

$$B = r_1 - 2 r_1 b_1 T_2^* - c_2 E_2^* - c_3 H_2^* = -r_1 + c_2 E_2^* + c_3 H_2^*, \text{ (Substituting the value of } T_2^*),$$

$$C = r_2 - 2 r_2 H_2^* - c_4 T_2^* = -r_2 + c_4 T_2^*, \text{ (Substituting the value of } H_2^*),$$

$$D = \frac{\sigma \rho E_2^*}{(\sigma + T_2^*)^2}.$$

From here, we get

$$A_{11} = r_1 + r_2 + d_1 + c_1 T_2^* - c_2 E_2^* - c_3 H_2^* - c_4 T_2^* - \frac{\rho T_2^*}{\sigma + T_2^*}, \tag{5.2}$$

and

$$A_{11} A_{12} - A_{13} = \left(r_1 + r_2 + d_1 + c_1 T_2^* - c_2 E_2^* - c_3 H_2^* - c_4 T_2^* - \frac{\rho T_2^*}{\sigma + T_2^*} \right) \left((-r_2 \right.$$

$$+ c_4 T_2^*) \left((-r_1 + c_2 E_2^* + c_3 H_2^*) - \left(d_1 + c_1 T_2^* - \frac{\rho T_2^*}{\sigma + T_2^*} \right) \right) \Bigg)$$

$$- \left(d_1 + c_1 T_2^* - \frac{\rho T_2^*}{\sigma + T_2^*} \right)(-r_1 + c_2 E_2^* + c_3 H_2^*) + c_2 T_2^* \frac{\sigma \rho E_2^*}{(\sigma + T_2^*)^2} - c_1 c_2 E_2^* T_2^*$$

$$- c_3 c_4 H_2^* T_2^* \Bigg) - (-r_2 + c_4 T_2^*)(-r_1 + c_2 E_2^* + c_3 H_2^*) \left(d_1 + c_1 T_2^* - \frac{\rho T_2^*}{\sigma + T_2^*} \right)$$

$$+ c_3 c_4 H_2^* T_2^* \left(d_1 + c_1 T_2^* - \frac{\rho T_2^*}{\sigma + T_2^*} \right) - (-r_2 + c_4 T_2^*) c_2 T_2^* \left(c_1 E_2^* - \frac{\sigma \rho E_2^*}{(\sigma + T_2^*)^2} \right).$$

$$\tag{5.3}$$

By Routh-Hurwitz stability criteria, if $A_{11} > 0$ and $A_{11} A_{12} - A_{13} > 0$, then S_2^* is stable and becomes unstable when conditions are not satisfied. Validity of (5.2) and (5.3) are verified by putting the parameter values from Table 1.

With treatment case ($v_1 \neq 0$ and $v_2 \neq 0$): In this section, we study the nature of stability of the equilibrium points S_1 and S_2 of the system and here $v_1 \neq 0$ and $v_2 \neq 0$.

The Jacobian matrix of the system (2.1) is

$$J_S = \begin{pmatrix} A & D - c_1 E & 0 \\ -c_2 T & B_1 & -c_3 T \\ 0 & -c_4 H & C \end{pmatrix},$$

where

$$A = \frac{\rho T}{\sigma + T} - c_1 T - d_1, \ B_1 = r_1 - 2r_1 b_1 T - c_2 E - c_3 H - v_2, \ C = r_2 - 2r_2 H - c_4 T, \ D = \frac{\sigma \rho E}{(\sigma + T)^2}.$$

(i) At the first equilibrium point, the eigenvalues of the Jacobian matrix J_S are

$$\lambda_1^1 = \frac{\rho T_1}{\sigma + T_1} - c_1 T_1 - d_1 = -d_1 < 0,$$

$$\lambda_2^1 = r_1 - 2r_1 b_1 T_1 - c_2 E_1 - c_3 H_1 - v_2 = r_1 - \frac{c_2(\mu + v_1)}{d_1} - c_3 - v_2,$$

$$\lambda_3^1 = -r_2 < 0.$$

By applying the condition of stability, the necessary condition for asymptotic stability of equilibrium point S_1 is found to be

$$r_1 < \frac{c_2(\mu + v_1)}{d_1} + c_3 + v_2,$$

and it will be unstable when $r_1 > \frac{c_2(\mu + v_1)}{d_1} + c_3 + v_2$.

(ii) The eigenvalues associated with co-existing equilibrium point $S_2(E_2, T_2, H_2)$ are derived from the Jacobian matrix J_S. The characteristic equation is

$$\lambda^3 + B_{11}\lambda^2 + B_{12}\lambda + B_{13} = 0, \tag{5.4}$$

where (in (5.4))

$$B_{11} = -(A + B_1 + C),$$

$$B_{12} = AB_1 + AC + B_1 C + c_2 DT_2 - c_1 c_2 E_2 T_2 - c_3 c_4 H_2 T_2,$$

$$B_{13} = c_1 c_2 C E_2 T_2 + c_3 c_4 A H_2 T_2 - AB_1 C - c_2 CDT_2,$$

and

$$E_2 = \frac{(\mu + v_1)(\sigma + T_2)}{(d_1 + c_1 T_2)(\sigma + T_2) - \rho T_2},$$

$$T_2 = \frac{1}{r_1 b_1}(r_1 - c_2 E_2 - c_3 H_2 - v_2),$$

$$H_2 = 1 - \frac{c_4 T_2}{r_2},$$

$$A = \frac{\rho T_2}{\sigma + T_2} - c_1 T_2 - d_1,$$

$$B_1 = r_1 - 2r_1 b_1 T_2 - c_2 E_2 - c_3 H_2 - v_2 = -r_1 + c_2 E_2 + c_3 H_2 + v_2, \text{ (Substituting the value of } T_2),$$

$$C = r_2 - 2r_2 H_2 - c_4 T_2 = -r_2 + c_4 T_2, \text{ (Substituting the value of } H_2),$$

$$D = \frac{\sigma \rho E_2}{(\sigma + T_2)^2}.$$

From here, we get

$$B_{11} = r_1 + r_2 + d_1 - v_2 + c_1 T_2 - c_2 E_2 - c_3 H_2 - c_4 T_2 - \frac{\rho T_2}{\sigma + T_2}, \tag{5.5}$$

and

$$\begin{aligned}
B_{11} B_{12} - B_{13} = \Big(&r_1 + r_2 + d_1 - v_2 + c_1 T_2 - c_2 E_2 - c_3 H_2 - c_4 T_2 \\
&- \frac{\rho T_2}{\sigma + T_2} \Big) \Big((-r_2 + c_4 T_2) \big((-r_1 + c_2 E_2 + c_3 H_2 + v_2) - \big(d_1 + c_1 T_2 - \frac{\rho T_2}{\sigma + T_2} \big) \big) \\
&- \big(d_1 + c_1 T_2 - \frac{\rho T_2}{\sigma + T_2} \big) (-r_1 + c_2 E_2 + c_3 H_2 + v_2) + c_2 T_2 \frac{\sigma \rho E_2}{(\sigma + T_2)^2} - c_1 c_2 E_2 T_2 \\
&- c_3 c_4 H_2 T_2 \Big) - (-r_2 + c_4 T_2)(-r_1 + c_2 E_2 + c_3 H_2 + v_2) \big(d_1 + c_1 T_2 - \frac{\rho T_2}{\sigma + T_2} \big) \\
&+ c_3 c_4 H_2 T_2 \big(d_1 + c_1 T_2 - \frac{\rho T_2}{\sigma + T_2} \big) - (-r_2 + c_4 T_2) c_2 T_2 \big(c_1 E_2 - \frac{\sigma \rho E_2}{(\sigma + T_2)^2} \big).
\end{aligned}$$

$$\tag{5.6}$$

By Routh-Hurwitz stability criteria, if $B_{11} > 0$ and $B_{11} B_{12} - B_{13} > 0$, then S_2 is stable and becomes unstable when conditions are not satisfied. Validity of (5.5) and (5.6) are verified by putting the parameter values from Table 1.

Now, we conclude that S_1 and S_2 as equilibrium points are biologically feasible and stable under the condition of biological existence.

6. Global stability analysis of the healthy equilibrium point S_1 in treatment case

For the behaviour of the system (2.1) far away from the equilibrium point S_1, we analyze the global stability of S_1 in this section. Let's define the Lyapunov function of the model (2.1) as

$$L(E, T, H) = \Big(E - E_1 - E_1 \ln \frac{E}{E_1} \Big) + (T - T_1) + \Big(H - H_1 - H_1 \ln \frac{H}{H_1} \Big).$$

Now, we differentiate w.r.t. time to obtain

$$\frac{dL}{dt} = \left(1 - \frac{E_1}{E}\right)\frac{dE}{dt} + \frac{dT}{dt} + \left(1 - \frac{H_1}{H}\right)\frac{dH}{dt}$$

$$= \left(1 - \frac{E_1}{E}\right)\left(\mu + \frac{\rho ET}{\sigma + T} - c_1 ET - d_1 E + v_1\right)$$

$$+ (r_1 T(1 - b_1 T) - c_2 ET - c_3 TH - v_2 T) + \left(1 - \frac{H_1}{H}\right)(r_2 H(1 - H) - c_4 HT)$$

$$= -d_1 \frac{(E - E_1)^2}{E} - r_2(H - H_1)^2 - r_1 b_1 T^2 - (c_3 + c_4)TH$$

$$+ \left(\frac{\rho}{\sigma + T} - c_1\right)(E - E_1)T + (r_1 - v_2)T - c_2 ET - c_3 TH - c_4 T(H - H_1)$$

$$= -d_1 \frac{(E - E_1)^2}{E} - r_2(H - H_1)^2 - r_1 b_1 T^2 - (c_3 + c_4)T(H - H_1)$$

$$+ \left(\frac{\rho}{\sigma + T} - c_1 - c_2\right)(E - E_1) + [r_1 - v_2 - c_2 E_1 - c_3 H_1]T = -Y^T MY - V^T Y,$$

$$(6.1)$$

where

$$Y^T = [E - E_1, T, H - H_1],$$

$$M = \begin{pmatrix} \dfrac{d_1}{E} & \dfrac{1}{2}\left(c_1 + c_2 - \dfrac{\rho}{\sigma + T}\right) & 0 \\ \dfrac{1}{2}\left(c_1 + c_2 - \dfrac{\rho}{\sigma + T}\right) & r_1 b_1 & \dfrac{1}{2}(c_3 + c_4) \\ 0 & \dfrac{1}{2}(c_3 + c_4) & r_2 \end{pmatrix},$$

$$V^T = [0, v_2 - r_1 + c_2 E_1 + c_3 H_1, 0].$$

By noting the second component of the vector V in (6.1), we must have:

$$\frac{c_2(\mu + v_1)}{d_1} + c_3 + v_2 > r_1, \tag{6.2}$$

where such a condition, namely (6.2), results in $V^T Y > 0$. Furthermore, by considering the values of parameters from Table 1, if $E = (\mu + v_1)/d_1$ and $T = 1/b_1$, then all minors of the matrix M are positive (all eigenvalues of M are also positive) and so $Y^T MY > 0$. Now, it is clear that

$$\frac{dL}{dt} < 0.$$

Therefore, the healthy equilibrium point S_1 is globally asymptotically stable if

$$\frac{c_2(\mu + v_1)}{d_1} + c_3 + v_2 > r_1, \qquad E = \frac{\mu + v_1}{d_1}, \qquad T = \frac{1}{b_1}.$$

In biological terms, it means that the tumor cells will be killed by an external injection of the adoptive immunotherapy if

$$\frac{c_2(\mu + v_1)}{d_1} + c_3 + v_2 > r_1, \qquad E = \frac{\mu + v_1}{d_1}, \qquad T = \frac{1}{b_1}.$$

The vector field plot along with four trajectories with different initial points (with the same set of parameter values taken in Table 1) and the equilibrium point S_1 has been shown in Figure 1.
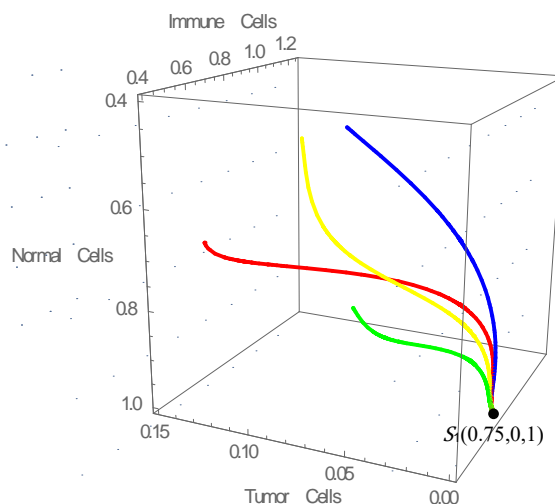

Figure 1. The vector field plot (The initial conditions of effector-tumor-normal cells are Blue [1, 0.1, 0.5], Red [0.2, 0.1, 0.6], Yellow [0.15, 0.05, 0.4], and Green [0.3, 0.04, 0.7]).

From the vector field plot, it is seen that any trajectory starting from any starting point in the basin of attraction converges to the tumor-free equilibrium point S_1 (indicated by the black dot) indicating that it is a globally stable point for the system. Biologically, this indicates the fact that the body is recovering from the tumor regardless of the initial condition which contains tumor growth.

7. Optimal control

This section is devoted to the study of the model after we administer adoptive immunotherapy treatment at a specific time. From a biomedical perspective, we have used the concept of optimal control in the model. In the earlier discussed case, the amount of injected adoptive immunotherapy remains the same even when the tumor size gets reduced. This in turn might infuse detrimental effects to the patients' immune system and other diseases may attack the patient. So, practically, the amount of injected immunotherapy should be decreased when the size of the tumor gets smaller. For this purpose, we should look into the problem with a control strategy that can lessen the health hazard for the patient. Therefore, we propose and analyze the optimal control problem applicable to model (2.1) to determine the optimal dose of adoptive immunotherapy to control the tumor. We determine control inputs v_1 and v_2 of cellular immunotherapy which are included in the first and second equations of the model (2.1); to be supplied from an external source at different times.

So, let us assume that the time-dependent form of our considered model has the following form:

$$\frac{dE}{dt} = \mu + \frac{\rho ET}{\sigma + T} - c_1 ET - d_1 E + v_1(t),$$

$$\frac{dT}{dt} = r_1 T(1 - b_1 T) - c_2 ET - c_3 TH - v_2(t)T, \tag{7.1}$$

$$\frac{dH}{dt} = r_2 H(1 - H) - c_4 HT,$$

with the initial conditions

$$E(0) = E_0, \ T(0) = T_0, \ H(0) = H_0. \tag{7.2}$$

The objective function which is to be minimized is defined as:

$$\Omega(v_1, v_2) = \int_0^{t_f} (\alpha_1 T - \alpha_2 E + \beta_1 v_1^2 + \beta_2 v_2^2) \, dt, \tag{7.3}$$

where α_1, α_2, β_1, and β_2 are non-negative constants. It should be mentioned that β_1 and β_2 represent the weight factors of the objective function and are used for balancing the size of the terms. The optimal combination of control variables v_1 and v_2 will be adequate to minimize the tumor density and negative side effects over a fixed time. The first two terms of the integrand function are the total number of tumor cells and immune cells. The third and fourth terms of the integrand show the effect of adoptive immunotherapy on the body. Here, we have used the problem of optimal control for the model to reduce the burden of tumor cells, to reduce the time period for recovery of the patient, to reduce side effects due to immunotherapy, and also to increase the effectiveness of immunotherapy to strengthen the immune system.

Here, we establish an optimal control v_1^* and v_2^* such that

$$\Omega(v_1^*, v_2^*) = \min\{\Omega(v_1, v_2) : v_1, v_2 \in \Delta\},$$

where $\Delta = \{v_1, v_2 : \text{measurable}, 0 \le v_1, v_2 \le 1, t \in [0, t_f]\}$ is the admissible control set.

7.1. Existence of optimal control

In this sub-section, the existence of optimal control of the system (7.1) is discussed. The property of supersolutions $\bar{E}$, $\bar{T}$, and $\bar{H}$ of the model (7.1) is that trajectories are given by

$$\frac{d\bar{E}}{dt} = \mu + \rho\bar{E},$$

$$\frac{d\bar{T}}{dt} = r_1 \bar{T}, \tag{7.4}$$

$$\frac{d\bar{H}}{dt} = r_2 \bar{H},$$

are bounded [9]. We rewrite (7.4) as follows:

$$\begin{pmatrix} \bar{E} \\ \bar{T} \\ \bar{H} \end{pmatrix}' = \begin{pmatrix} \rho & 0 & 0 \\ 0 & r_1 & 0 \\ 0 & 0 & r_2 \end{pmatrix} \begin{pmatrix} \bar{E} \\ \bar{T} \\ \bar{H} \end{pmatrix} + \begin{pmatrix} \mu \\ 0 \\ 0 \end{pmatrix}. \tag{7.5}$$

Since it is a linear system with bounded coefficients and the time limit is limited, we conclude that supersolutions $\bar{E}$, $\bar{T}$, and $\bar{H}$ of the above system are uniformly bounded. Using the theorem proposed by Lukes [31], we found that the admissible control class and the corresponding state equations are nonempty with initial conditions given in (7.2). Also, by the definition of the set Δ, the control set Δ is convex and closed. Since the state solutions are bounded, hence, the continuity of R.H.S of the state system (7.1) holds and is bounded above by a sum of the bounded control and state.

Now, we have to show that the convexity of the integrand of $\Omega(v_1, v_2)$ on Δ and bounded below by $\tau_1(v_1^2 + v_2^2) - \tau_2$ with $\tau_1, \tau_2 > 0$.

Let u and w are distinct elements of Ω and $0 \le p \le 1$. We have to show

$$(1-p)\Omega(t, Y, u) + p\Omega(t, Y, w) \ge \Omega(t, Y, (1-p)u + pw), \tag{7.6}$$

where

$$\Omega(t, Y, u) = \alpha_1 T - \alpha_2 E + \beta_1 v_1^2 + \beta_2 v_2^2, \tag{7.7}$$

and u and w are two control vectors and $p \in (0,1)$.

By substituting (7.7) into (7.6), we get

$$(1-p)\Omega(t, Y, u) + p\Omega(t, Y, w) - \Omega(t, Y, (1-p)u + pw)$$

$$= (1-p)(\alpha_1 T - \alpha_2 E + \beta_1 u_1^2 + \beta_2 u_2^2) + p(\alpha_1 T - \alpha_2 E + \beta_1 w_1^2 + \beta_2 w_2^2)$$

$$- \left(\alpha_1 T - \alpha_2 E + \sum_{i=1}^{2} \beta_i((1-p)u_i + pw_i)^2\right)$$

$$= p(1-p)(\beta_1(u_1 - w_1)^2 + \beta_2(u_2 - w_2)^2) \ge 0, \quad [\text{since}(1-p) > 0 \text{ and } (u_i - w_i)^2 \ge 0],$$

which implies that

$$(1-p)\Omega(t, Y, u) + p\Omega(t, Y, w) \ge \Omega(t, Y, (1-p)u + pw),$$

and

$$\Omega(t, Y, v) = \alpha_1 T - \alpha_2 E + \beta_1 v_1^2 + \beta_2 v_2^2 \ge \sum_{i=1}^{2} \beta_i(v_i)^2 \ge \tau_1(v_1^2 + v_2^2) \ge \tau_1(v_1^2 + v_2^2) - \tau_2.$$

This shows that $\tau_1(v_1^2 + v_2^2) - \tau_2$ is a lower bound of $\Omega(v_1, v_2)$.

Therefore, there exists an optimal control v_1^* and v_2^* for which $\Omega(v_1, v_2)$ is minimized. From the above analysis, we establish the following theorem.

Theorem 7.1. For given objective functional

$$\Omega(v_1, v_2) = \int_0^{t_f}(\alpha_1 T - \alpha_2 E + \beta_1 v_1^2 + \beta_2 v_2^2)\, dt, \tag{7.8}$$

where

$$\Delta = \left\{v_1, v_2 : \text{measurable}, 0 \le v_1, v_2 \le 1, t \in [0, t_f]\right\}$$

is subject to the system (7.1) with the initial conditions $E(0) = E_0$, $T(0) = T_0$, and $H(0) = H_0$, there

exists an optimal control v_1^* and v_2^* such that $\Omega(v_1^*, v_2^*) = \min\{\Omega(v_1, v_2): v_1, v_2 \in \Delta\}$.

7.2. Characterization of the optimal control

Now, we implement the procedure of applying the Pontryagin minimum principle and Hamiltonian function. We introduce the three co-state variable $p_s, s = 1, 2, 3$ and so the Hamiltonian function is given by

$$M = \alpha_1 T - \alpha_2 E + \beta_1 v_1^2 + \beta_2 v_2^2 + p_1 \dot{E} + p_2 \dot{T} + p_3 \dot{H}. \tag{7.9}$$

By substituting (7.1) and (7.2) into (7.9), we find

$$M = \alpha_1 T - \alpha_2 E + \beta_1 v_1^2 + \beta_2 v_2^2 + p_1 \left(\mu + \frac{\rho ET}{\sigma + T} - c_1 ET - d_1 E + v_1\right)$$
$$+ p_2(r_1 T(1 - b_1 T) - c_2 ET - c_3 TH - v_2 T) + p_3(r_2 H(1 - H) - c_4 TH).$$

$$\tag{7.10}$$

The Hamiltonian equations are

$$\dot{p}_1 = -\frac{\partial M}{\partial E},$$

$$\dot{p}_2 = -\frac{\partial M}{\partial T}, \tag{7.11}$$

$$\dot{p}_3 = -\frac{\partial M}{\partial H}.$$

where $p_s(t), s = 1, 2, 3$ are the adjoint functions to be determined suitably.

Adjoint equations and forms of transversality conditions are standard results from the Pontryagin minimum principle [32, 33]. In the case of our considered system, an adjoint system can be obtained in the form of:

$$\dot{p}_1 = \alpha_2 - p_1 \left(\frac{\rho T}{\sigma + T} - c_1 T - d_1\right) + p_2 c_2 T,$$

$$\dot{p}_2 = -\alpha_1 - p_1 \left(\frac{\sigma \rho E}{(\sigma + T)^2} - c_1 E\right) - p_2(r_1 - 2b_1 r_1 T - c_2 E - c_3 H - v_2) + p_3 c_4 H, \tag{7.12}$$

$$\dot{p}_3 = p_2 c_3 T - p_3(r_2 - 2r_2 H - c_4 T),$$

where $p_s(t_f) = 0, s = 1, 2, 3$ are the transversality conditions.

The optimal control functions are determined by the circumstances $\frac{\partial M}{\partial v_i} = 0, i = 1, 2$. Hence, we get

$$v_1^*(t) = -\frac{p_1}{2\beta_1}, v_1^* = v_1^*(t); \quad v_2^*(t) = \frac{p_2 T(t)}{2\beta_2}, v_2^* = v_2^*(t); \quad T = T(t). \tag{7.13}$$

Using the bounds for the control variables v_1^* and v_2^* from (7.13), we get

$$v_1^* = \begin{cases} -\dfrac{p_1}{2\beta_1}, & \text{if } 0 \leq -\dfrac{p_1}{2\beta_1} \leq 1 \\[2mm] 0, & \text{if } -\dfrac{p_1}{2\beta_1} \leq 0 \\[2mm] 1, & \text{if } -\dfrac{p_1}{2\beta_1} \geq 1 \end{cases}, \qquad v_2^* = \begin{cases} \dfrac{p_2 T}{2\beta_2}, & \text{if } 0 \leq \dfrac{p_2 T}{2\beta_2} \leq 1 \\[2mm] 0, & \text{if } \dfrac{p_2 T}{2\beta_2} \leq 0 \\[2mm] 1, & \text{if } \dfrac{p_2 T}{2\beta_2} \geq 1 \end{cases}.$$

In the compact notation, let us consider

$$v_1^* = \min\left\{\max\left\{0, -\tfrac{p_1}{2\beta_1}\right\}, 1\right\}, \tag{7.14}$$

and

$$v_2^* = \min\left\{\max\left\{0, \tfrac{p_2 T}{2\beta_2}\right\}, 1\right\}. \tag{7.15}$$

From (2.1), (7.12), (7.14), and (7.15), we get the subsequent optimal system as

$$\frac{dE}{dt} = \mu + \frac{\rho E T}{\sigma + T} - c_1 E T - d_1 E + \min\left\{\max\left\{0, -\frac{p_1}{2\beta_1}\right\}, 1\right\},$$

$$\frac{dT}{dt} = r_1 T(1 - b_1 T) - c_2 E T - c_3 T H - \min\left\{\max\left\{0, \frac{p_2 T}{2\beta_2}\right\}, 1\right\} T,$$

$$\frac{dH}{dt} = r_2 H(1 - H) - c_4 H T,$$

$$\frac{dp_1}{dt} = \alpha_2 - p_1\left(\frac{\rho T}{\sigma + T} - c_1 T - d_1\right) + p_2 c_2 T,$$

$$\frac{dp_2}{dt} = -\alpha_1 - p_1\left(\frac{\sigma \rho E}{(\sigma + T)^2} - c_1 E\right) - p_2(r_1 - 2b_1 r_1 T - c_2 E - c_3 H - v_2) + p_3 c_4 H,$$

$$\frac{dp_3}{dt} = p_2 c_3 T - p_3(r_2 - 2r_2 H - c_4 T),$$

subject to the conditions $E(0) = E_0$, $T(0) = T_0$, and $H(0) = H_0$ and $p_s(t_f) = 0, s = 1,2,3$.

Theorem 7.2. Considering optimal control variables v_1^* and v_2^* and corresponding state variables $E^*(t)$, $T^*(t)$, and $H^*(t)$, there exist ongoing specific adjoint variables $p_s(t), s = 1, 2, 3$, satisfying the following system:

$$\frac{dp_1}{dt} = \alpha_2 - p_1\left(\frac{\rho T}{\sigma + T} - c_1 T - d_1\right) + p_2 c_2 T,$$

$$\frac{dp_2}{dt} = -\alpha_2 - p_1\left(\frac{\sigma \rho E}{(\sigma + T)^2} - c_1 E\right) - p_2(r_1 - 2b_1 r_1 T - c_2 E - c_3 H - v_2) + p_3 c_4 H, \tag{7.16}$$

$$\frac{dp_3}{dt} = p_2 c_3 T - p_3(r_2 - 2r_2 H - c_4 T),$$

subject to the transversality conditions $p_s(t_f) = 0, s = 1, 2, 3.$

In addition, the following properties hold:

$$v_1^* = \min\left\{\max\left\{0, -\frac{p_1}{2\beta_1}\right\}, 1\right\}, \qquad v_2^* = \min\left\{\max\left\{0, \frac{p_2 T}{2\beta_2}\right\}, 1\right\}.$$

Next, we proceed to numerically solve the proposed model and the optimal control problem.

8. Numerical simulation

This section is devoted to numerical solutions of the system (2.1), first without drug administration, then with the introduction of external immunotherapy and ultimately optimal control model of (2.1) as defined in (7.1). We consider the parameter values in Table 1. The numerical solutions of the model are found using MATLAB, while the optimal system was solved using a fourth-order Runge-Kutta method.

The optimal system (7.1) is associated with the adjoint system (7.14) and (7.15) and separated boundary conditions at times $t = 0$ and $t = t_f$. The forward method is used to solve the optimal system (7.1) and the backward method is used to solve the respective adjoint system (7.16) for $t_f = 50$. The variables associated with optimal systems and in the objective functions have different scales. Hence, they are balanced by choosing weight constants $\alpha_1 = 2$, $\alpha_2 = 0.5$, $\beta_1 = 0.5$, and $\beta_2 = 5$ in the objective function given in (7.3).

Table 1. Parameter values considered for the model.

Parameters	Meaning	Value	Source
μ	Constant source rate of effector cells	0.05	[1]
d_1	Natural death rate of effector cells	0.2	[1]
r_1	Intrinsic growth rate of tumor cells	0.35	[1]
r_2	Intrinsic growth rate of normal cells	0.3	[1]
$1/b_1$	Tumor population carrying capacity	2/3	[1]
c_1	Decay rate of effector cells owing to tumor cells	0.2	[1]
c_2	Decay rate of tumor cells owing to effector cells	0.3	[1]
c_3	Decay rate of tumor cells owing to normal cells	0.15	[1]
c_4	Decay rate of normal cells owing to tumor cells	0.3	[1]
ρ	Maximum recruitment of effector cells by tumor cells	1	[1]

Parameters	Meaning	Value	Source
σ	Half saturation constant for the proliferation term	0.5	[1]
v_1	External source of adoptive cellular immunotherapy	0.1 (Varied)	
v_2	Tumor cells killed by an external injection	0.01 (Estimated)	[6]

Case 1: In Figure 2, we have portrayed the dynamics of effector cells (a), tumor cells (b), and the normal cells (c) in (2.1) arising out of their mutual interaction, when no external therapy ($v_1 = v_2 = 0$) is used. It gives us an insight into what happens to the system without treatment and from this we get an idea about designing various optimal control policies.
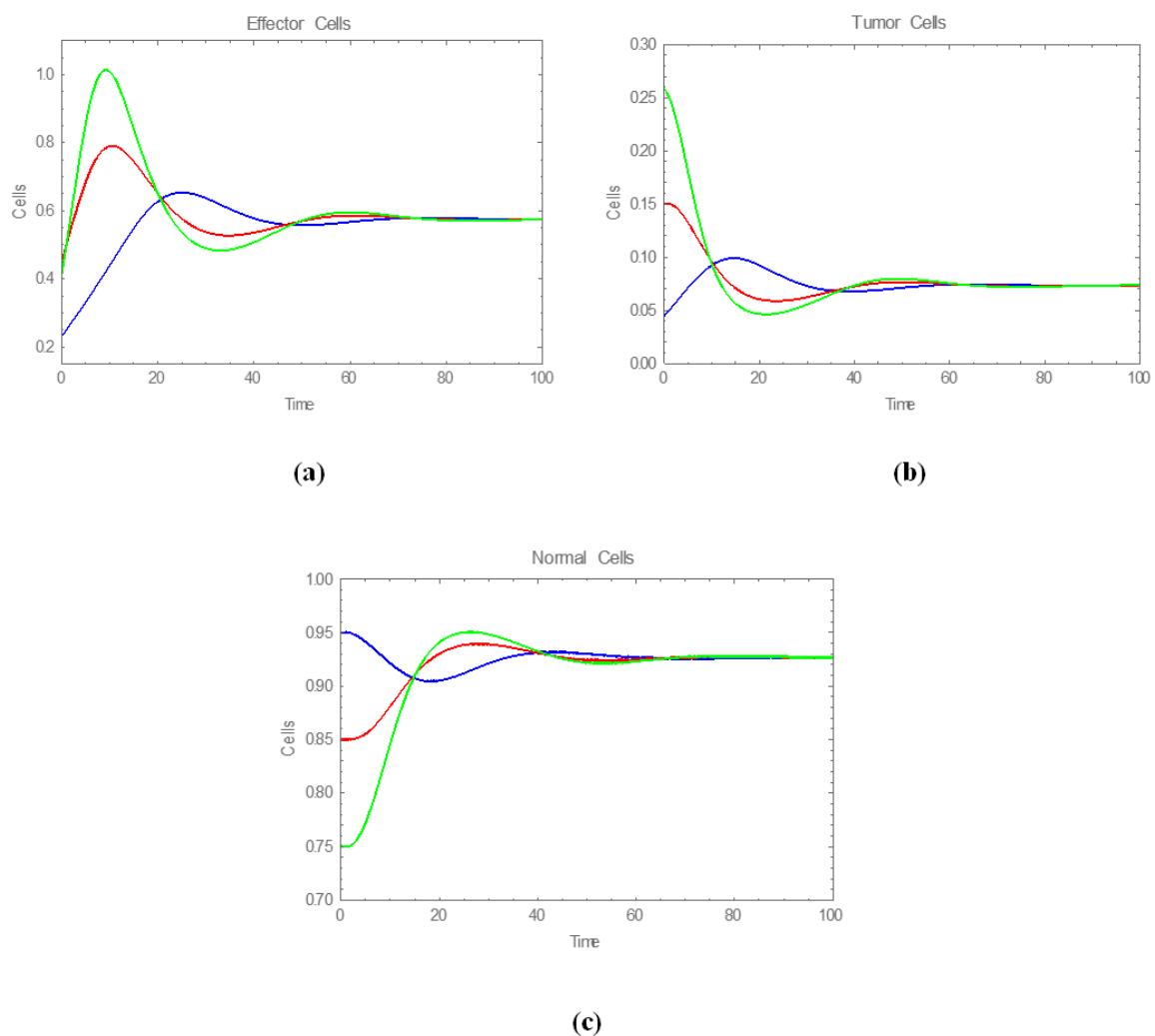

(a)

(b)

(c)

Figure 2. Without treatment: The density of effector cells, tumor cells, and normal cells (The initial values of effector-tumor-normal cells are $E(0) = 0.25, 0.5, 0.5$, $T(0) = 0.05, 0.15, 0.25$, and $H(0) = 0.95, 0.85, 0.75$).

From Figure 2, we note that without treatment, the density of effector cells, tumor cells, and

normal cells goes up and down and achieves their stable state after some time interval. As the tumor cell load gradually increases, effector cells also increase and the normal cells decrease and after some oscillation attain their steady-state and reach the unhealthy equilibrium point S_2^*. It is also clear from this that removal of tumor cells is not possible without a treatment strategy such as adoptive immunotherapy.

Case 2: In Figure 3, we have plotted the dynamics of the system (2.1) with adoptive immunotherapy treatment but without optimal control.
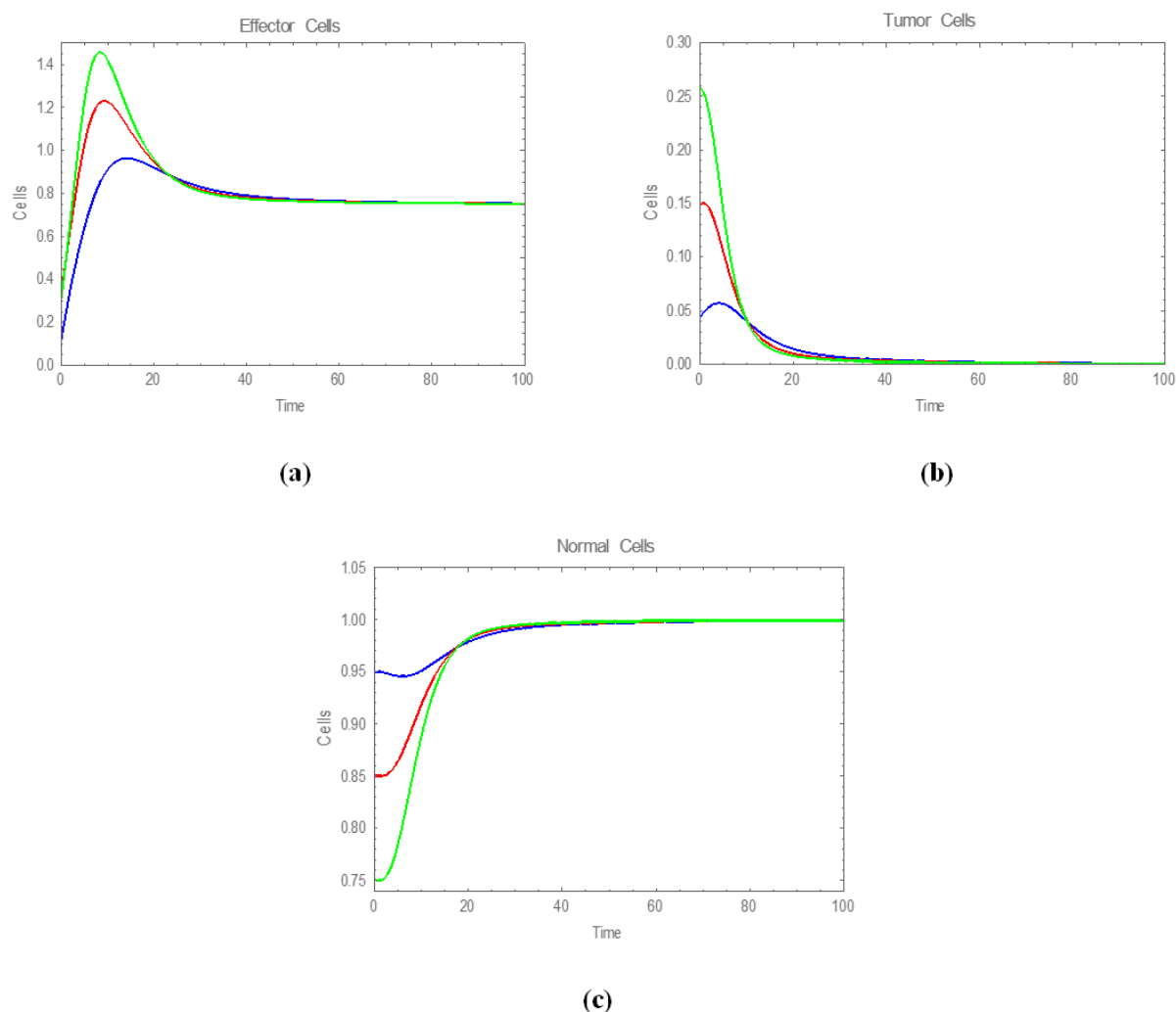
(a)

(b)

(c)

Figure 3. With treatment but without optimal control (The initial values of effector cells, tumor cells, and normalcells are $E(0) = 0.25, 0.5, 0.5$, $T(0) = 0.05, 0.15, 0.25$, and $H(0) = 0.95, 0.85, 0.75$).

From Figure 3, it is seen that when treatment is started, though for a brief period, normal cells initially decrease and tumor cells grow, the pattern changes after that time period and the tumor cell load decrease, but the effector cells and normal cells grow and ultimately settle down at the steady-state which is the tumor-free equilibrium point S_1. This shows that with the incorporation of therapeutic strategies such as adoptive immunotherapy, tumor cells can be eradicated from the body of the patient.

Case 3: In Figure 4, we have portrayed the dynamics of the system (2.1) with adoptive immunotherapy treatment when optimal control is used.
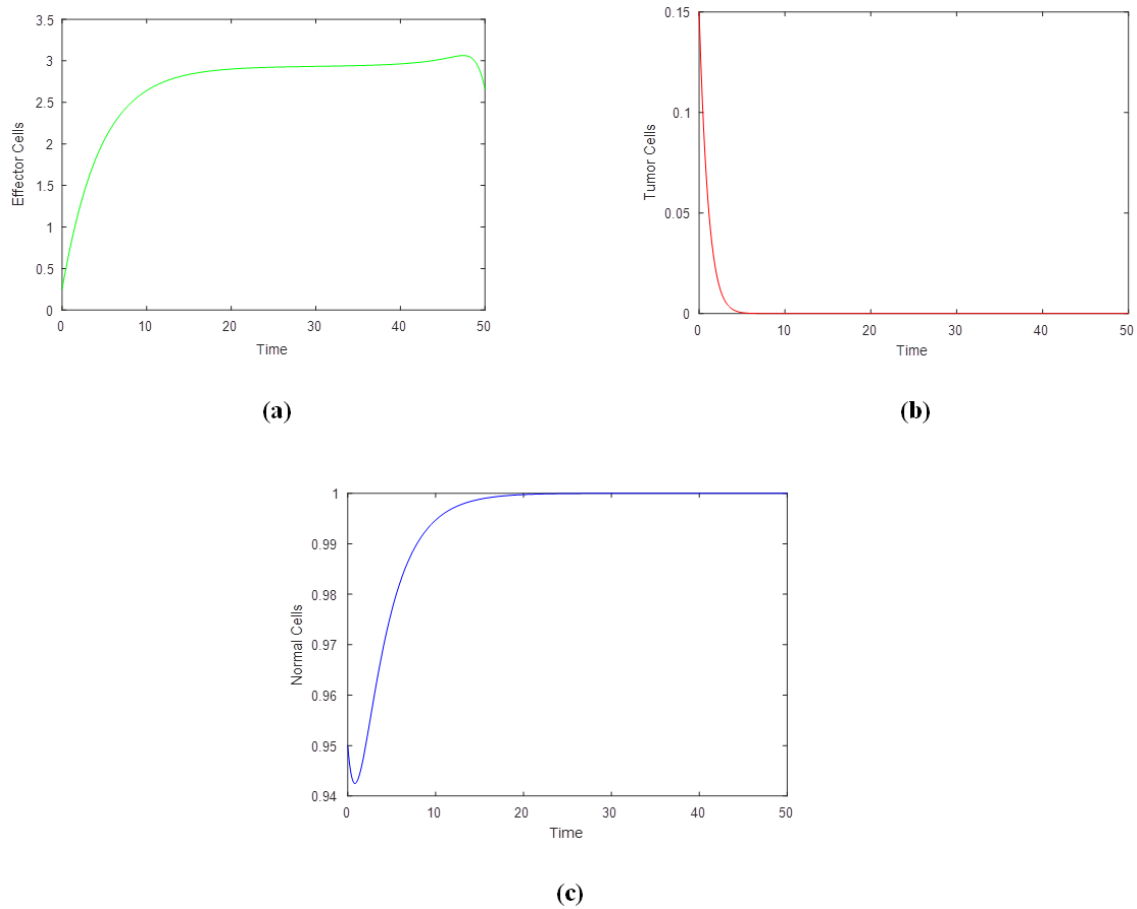
(a)

(b)

(c)

Figure 4. With both treatment and optimal control: The density of effector cells, tumor cells, and normal cells in presence of optimal drug control with initial conditions $E(0) = 0.25$, $T(0) = 0.05$, and $H(0) = 0.9$.
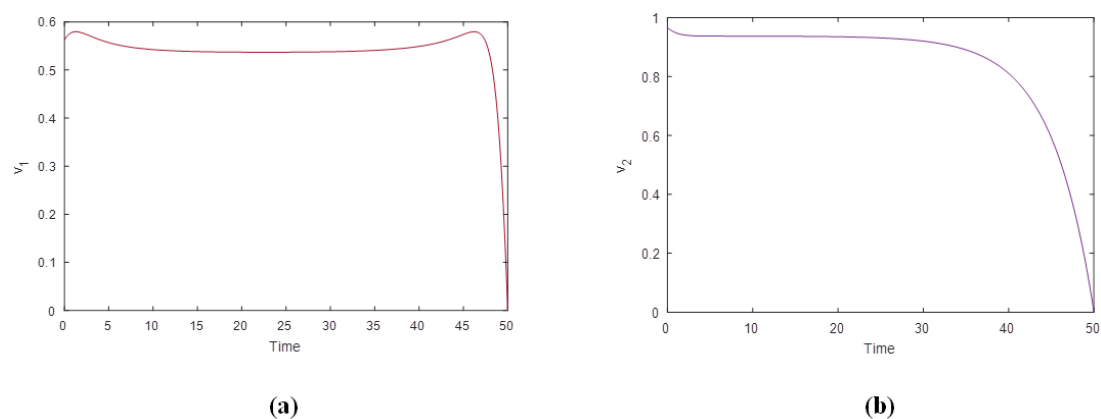
(a)

(b)

Figure 5. Components of the control inputs for the same parameter values in Table 1 with initial conditions $E(0) = 0.25$, $T(0) = 0.05$, and $H(0) = 0.9$.

From Figure 4, it is seen that the optimal treatment strategies reduce the burden of tumor cells and increase the number of effector cells without causing damage to normal cells after a certain time of introduction of treatment. From Figure 4(b), we can conclude that the incorporation of optimal control to eradicate the tumor cells is more effective as it makes the patients' body tumor-free in less time without putting the patients' health at any risk. From this perspective, we can deduce from the optimal control diagram (Figures 4 and 5) that all efforts at the onset of the disease to reduce the proliferation of tumor cells should be kept under optimal control. Figures 5(a) and 5(b) further show that control inputs v_1 and v_2 of drugs can be reduced rather than keeping those constant with the decrease in the number of tumor cells.

9. Conclusions

In this paper, we have considered a basic model related to cancer which was proposed by De Pillis et al. showing interactions between effector-tumors-normal cells in the human body. Mathematical analysis of the model demonstrated that if the system is left to itself, cancerous tumor cells cannot be eradicated. Such a result tempted the authors to incorporate external immunotherapy in the form of injection showing that the tumorous cells can be wiped out after a certain interval of timekeeping external immunotherapy input constant throughout the time. Of course, this work suffers the drawback that an unreasonable amount of external immunotherapy may put the patients' health at risk. Generally, it is expected that after the introduction of immunotherapy, when tumor cells decrease in number after a certain time, the amount of immunotherapy should also be lessened accordingly instead of keeping it fixed. Another important issue that should be kept in mind is that "can we wipe out the cancerous cells in a lesser interval of time?" To answer these issues we implemented an optimal treatment strategy with the introduction of adoptive immunotherapy. Satisfactory answers were found with regard to the above-mentioned important issues. Appropriate numerical simulations were incorporated to justify our conclusions.

Conflict of interest

The authors declare no conflict of interest.

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