International Journal of Modelling and Simulation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tjms20

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To cite this article: Anusmita Das, Kaushik Dehingia, Hemanta Kr Sarmah & Kamyar Hosseini (2022): An optimally controlled chemotherapy treatment for cancer eradication, International Journal of Modelling and Simulation, DOI: 10.1080/02286203.2022.2155601

To link to this article: https://doi.org/10.1080/02286203.2022.2155601

Published online: 18 Dec 2022.

INTERNATIONAL JOURNAL OF MODELLING AND SIMULATION
https://doi.org/10.1080/02286203.2022.2155601

An optimally controlled chemotherapy treatment for cancer eradication

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ABSTRACT

In the present study, we developed a modified immune-tumor-normal cell model, considering Lotka-Volterra-type competitions between the cell populations and the chemotherapy drugs. The local stability of the model has been examined at each equilibrium point. Also, the global stability of the model at tumor-free equilibrium has been looked at, and a range of drug administration rates has been found for which the tumor-free state is asymptotically stable globally. Also, the growth of tumor cells was kept to a minimum by setting up an optimal control policy for how drugs are given. We found that the optimal control strategy helped eliminate tumor cells with fewer adverse side effects because it kept the number of normal and immune cells high. The optimal control strategy also reduces the time needed for the treatment strategy. Finally, numerical simulations are performed to verify some of our theoretical results.

ARTICLE HISTORY
Received 10 August 2022
Accepted 2 December 2022

KEYWORDS
Cancer; mathematical model; chemotherapy; stability; optimal control

2020 AMS SUBJECT CLASSIFICATION
37M05; 37M10; 37N25; 92B05

1. Introduction

A tumor is created by the abnormal proliferation of cells, which may be classified broadly into two types: benign and malignant. Benign tumors are non-cancerous in nature and remain localized in the region where they originate. A tumor becomes cancerous when it is malignant in nature. Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts. Cancer cells can spread to other body parts through the blood and lymphatic systems. During the last several decades, cancer has been the leading cause of death among human beings [1].

The rapid proliferation of cells and tumors is not yet precise. The growth of tumor cells is a highly complex process that involves genes, the environment, radiation, viruses, the use of tobacco and alcohol, and many other things. In many cases, mainly when vital organs are attacked, or the disease is detected after a prolonged duration, cancer becomes an incurable disease which generally becomes fatal [2]. Treatment methods in response to the tumor depend upon many factors, including the severity of the tumor, location of the tumor, patient's immune response, etc.

Chemotherapy is a treatment method that uses powerful chemical drugs to kill rapidly growing malignant cells. Chemical drugs are absorbed into the bloodstream and transported to different body parts. So, chemotherapy is usually recommended for people with cancer that has already spread to other parts of the body or for people with tumors that can't be removed by surgery because of where they are. In addition, chemotherapy is used when a patient gets sick again after surgery or for radiation therapy for the first time. Chemotherapy has more potential to kill cancer cells directly and can control cancer growth or eliminate pain symptoms [3]. At the same time, chemotherapy has the drawback of killing all cells, including normal and immune cells, apart from the cancerous cells for which the therapy is intended. As a result, the patient's immune response drops alarmingly when chemotherapy drugs are used in a higher amount, making the patient susceptible to other opportunistic diseases. So, an optimally controlled chemotherapy treatment is needed for a better treatment strategy. Control theory is concerned with verifying whether the evolution of system is controllable, i.e. whether the evolution can be influenced or controlled by some external agent, called 'control'. Optimal control theory deals with finding a 'control' for the system over a period of time such that the performance criterion is optimized. Mathematically, chemotherapy dose applied for treatment of cancer can be formulated as an optimal control problem. In literature, applications of optimal control theory to mathematical models of cancer biology and role of chemotherapy began to appear in the 1980s and this continued with regularity in the subsequent years to present day [4].

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This has motivated us to investigate an optimally controlled chemotherapy treatment strategy for the eradication of cancer.

Mathematical modelling in the form of differential equations has been used during the last three decades to understand the effects of chemotherapy treatment for cancer treatment [5–8]. In 2003, de Pillis et al. [5] developed a mathematical model to study how the immune system reacts and how chemotherapy drugs affect the growth of tumors. The authors concluded that optimally controlled chemotherapy can make the system a desirable basin of attraction, whereas traditional pulse chemotherapy cannot. Itik *et al.* [6] proposed a mathematical model containing normal, tumor, and immune cells subjected to chemotherapy as a mode of treatment. Their numerical results show that using an optimal control strategy can yield positive outcomes such as fewer drug administrations and a shorter treatment period. Solis and Delgadillo [7] proposed a discrete mathematical model that included chemotherapy treatment. The authors found some helpful information about how tumors grow and how the response to treatment depends on dose amounts for the different ways drugs can be used. Sharma and Samanta [8] showed a model of how tumors grow that looked at how the immune system and the tumor interact and how chemotherapeutic drugs work. Their numerical results revealed that a high dose of a chemotherapy drug at the start is the most effective way to combat tumor cells. By giving the proper doses of drugs, optimal control helps reduce the number of tumor cells. This shortens the time it takes for a patient to get better and has few side effects [9–15]. Rihan *et al.* [9] analyzed a chemotherapy model and found that the optimal control treatment strategy reduces side effects by inhibiting the production of new tumor cells and maintaining the number of normal cells above 75% of their carrying capacity. Ku-Carrillo *et al.* [10] analyzed an optimal control protocol for chemotherapy treatments for a mathematical model of a cancerous tumor that interacts with normal-immune cells and fat stored in adipocytes, a type of cell present in the adipose tissue. Numerical results showed that losing weight can help the chemotherapy work better and gaining weight can make the chemotherapy less effective. Oke *et al.* [11] presented a mathematical model in the presence of chemotherapy treatment and the ketogenic diet. The authors used the theory of optimal control to find the best way to change the doses of the drugs as an input control for the system therapies. Badziul *et al.* [12] focused on the possibility of optimal immunotherapy based on the vaccination strategy adopted by each patient to increase the quality and quantity of their life. Researchers' interest in using optimal control theory has also shifted to discrete [16–18], fractional models [19–22], and time delay [9,23–25].

In the present paper, we have analyzed a modified version of the tumor growth model proposed by de Pillis *et al.* [5]. We assume that all kinds of cells are killed due to chemotherapy drugs in the Lotka-Volterra form. Controlling the chemo-drug is an essential part of this treatment, primarily to reduce the side effects caused by a high dose of chemotherapy and shorten the length of treatment. In this work, we have developed an optimal control policy for the immune-tumor-normal cell model. In contrast to the paper by de Pillis *et al.* [5], we have maximized chemotherapy drugs in our control strategy. These two aspects have incorporated novelty into our investigation.

The rest of the paper is organized as follows: In section 2, we have given a description of the modified version of the model under certain assumptions; positive invariance and the boundedness of the system are discussed in section 3. In section 4, we determined the conditions for the existence of the equilibrium points. The dynamical behaviour of our system by analyzing the local stability analysis of the system at each equilibrium point is discussed in Section 5. In section 6, we applied the method to globally stabilize the locally stable tumor-free equilibrium point $E1$. In section 7, we have set up an optimal control problem relative to the model to minimize the number of tumor cells and reduce the patient's recovery time. Numerical simulation to validate our results is done in section 8. Finally, concluding remarks are forwarded in section 9.

2. The model and the assumptions

We have followed the tumor growth model proposed by de Pillis *et al.* [5]. In the present paper, we have redefined the de Pillis *et al.* model by modifying the last term of the first three equations. In contrast to the paper by de Pillis *et al.*, we assume that all kinds of cells are killed due to the application of chemotherapy drugs in the Lotka-Volterra form. We have assumed the following [6] and [26].

With the above-mentioned assumption, our redefined model takes the form

$$\frac{dI}{dt} = \tau + \frac{\rho IK}{\sigma + K} - \delta_1 I - \gamma_1 IK - \mu_1 CI, \qquad (1a)$$

$$\frac{dK}{dt} = \alpha_1 K(1 - \beta K) - \gamma_2 IK - \gamma_3 KH - \mu_2 CK, \qquad (1b)$$

$$\frac{dH}{dt} = \alpha_2 H(1-H) - \gamma_4 KH - \mu_3 CH, \qquad (1c)$$

$$\frac{dC}{dt} = \varphi - \delta_2 C, \qquad (1d)$$

with initial conditions $I(0) = I_0 > 0, K(0) = K_0 \geq 0$, $H(0) = H_0 > 0$ and $C(0) = C_0 > 0$. Here, $I(t), K(t)$, $H(t)$, and $C(t)$ denote the number of immune cells, number of tumor cells, number of normal cells, and the amount of drug administrated at time t respectively.

In equation (1a), the first term τ represents the constant source rate of mature immune cells in the body. The tumor-specific immune response is regulated through the second term of first equation (1a), $\rho IK/(\sigma + K)$ which is Michaelis–Menten form, ρ is the rate at which the immune cells grow and σ represents the steepness of the immune response and the term δ_1 represents the natural mortality rate of immune cells per day. Interaction between immune cells and tumor cells that lead to the rate of decay of immune cells is provided by the term $\gamma_1 IK$.

In equation (1b), the logistic term $\alpha_1 K(1-\beta K)$ describes the growth of tumor cells, where α_1 and $1/\beta$ denote the maximal growth rate and carrying capacity of the tumor cells. The second and third terms, $\gamma_2 IK, \gamma_3 KH$, represent the loss rate of tumor cells by immune cells and normal cells interaction [5,9].

In equation (1c), the normal cells also grow logistically with the growth rate of α_2 and maximum carrying capacity is assumed to be one. The second term, $\gamma_4 KH$ represents the loss rate of normal cells by tumor cells interaction.

In equation (1d), the first term, φ represent the amount of drug administration rate and δ_2 is the per capita decay rate after the drug being injected.

We further consider that the chemotherapy drug kills all types of cells, but at different kills rates, with the response curve in all cases given by a Lotka-Volterra form. These response terms are incorporated following the relevant models of Itik *et al.* [6] and Malinzi [26]. Thus, $\mu_1 CI, \mu_2 CK$, and $\mu_3 CH$ refer to the death of immune cells, tumor cells, and normal cells owing to chemotherapy treatment.

3. Positive invariance and boundedness

Before we proceed with the mathematical analysis, we need to show that the model with considered parameters values is biologically feasible.

Lemma1: The feasible region Δ defined by $\Delta = \left\{(I,K,H,C) \in R_+^4 | I(t) \leq \frac{\tau}{\delta_1}, K(t) \leq \frac{1}{\beta}, H(t) \leq 1, C(t) \leq \frac{\varphi}{\delta_2}\right\}$, which is positive invariant for the system (1a-1d).

Proof: From equation (1a) of the system,

According to the standard comparison theory, it follows

$$\frac{dI}{dt} = \tau + \frac{\rho IK}{\sigma + K} - \delta_1 I - \gamma_1 IK - \mu_1 CI \leq \tau - \delta_1 I,$$

Integration of the above leads to

$$I(t) \leq \frac{\tau}{\delta_1} + e^{-\delta_1 t} I(0) = > \underbrace{\lim_{t\to\infty}} \sup(I(t)) \leq \frac{\tau}{\delta_1},$$

Again, from equation (1b), it follows that

$$\frac{dK}{dt} = \alpha_1 K(1-\beta K) - \gamma_2 IK - \gamma_3 KN - \mu_2 CK \leq \alpha_1 K(1-\beta K),$$

Proceeding as above, we have

$$K(t) \leq \frac{1}{\beta + K(0)e^{-\alpha_1 t}} = > \underbrace{lim_{t\to\infty}} \sup(K(t)) \leq \frac{1}{\beta},$$

and similarly, from equation (1c) and (1d), it follows that

$$\frac{dH}{dt} \leq \alpha_2 H(1-H) = > H(t) \leq \frac{1}{1 + H(0)e^{-\alpha_2 t}} = > \underbrace{\lim_{t\to\infty}} \sup(H(t)) \leq 1,$$

And $\frac{dC}{dt} \leq \varphi - \delta_2 C = > \frac{\varphi}{\delta_2} + e^{-\delta_2 t} C(0) = > \underbrace{\lim_{t\to\infty}} \sup(C(t)) \leq \frac{\varphi}{\delta_2}$.

Thus, the feasible region is defined as follows: $\Delta = \left\{(I,K,H,C) \in R_+^4\right\}$.

We assume that the initial values $I(0) \geq 0, K(0) \geq 0, H(0) \geq 0$, and $C(0) \geq 0$ then $I(t) \geq 0, K(t) \geq 0, H(t) \geq 0$, and $C(t) \geq 0$ for all $t > 0$.

The trajectories evolve in the attractive regions

$$\Delta = \left\{(I,K,H,C) \in R_+^4 | I(t) \leq \frac{\tau}{\delta_1}, K(t) \leq \frac{1}{\beta}, H(t) \leq 1, C(t) \leq \frac{\varphi}{\delta_2}\right\}.$$

The domain Δ is positive invariant for model (1a-1d) and therefore biologically meaningful.

4. Equilibrium points and their existence

Equilibrium points are found by equating the first order derivatives to zero. So, we have

$$\frac{dI}{dt} = 0 = > \tau + \frac{\rho IK}{\sigma + K} - \delta_1 I - \gamma_1 IK - \mu_1 CI = 0,$$

$$\frac{dK}{dt} = 0 = > \alpha_1 K(1-\beta K) - \gamma_2 IK - \gamma_3 KH - \mu_2 CK = 0,$$

$$\frac{dH}{dt} = 0 = > \alpha_2 H(1-H) - \gamma_4 KH - \mu_3 CH = 0,$$

$$\frac{dC}{dt} = 0 = > \varphi - \delta_2 C = 0,$$

Simplification of the above expressions give the following equilibrium points:

(i) The first equilibrium point is obtained as $E_1(I_1, 0, H_1, C_1)$,which can be termed as a Tumor Free Equilibrium point. This equilibrium point means that system is tumor-free, where $I_1 = \tau/(\delta_1 + \mu_1 C_1)$, $K_1 = 0$, $H_1 = (\alpha_2 - \mu_3 C_1)/\alpha_2$, and $C_1 = \frac{\varphi}{\delta_2}$.

Note: Equilibrium point E_1 is real if $\alpha_2 > \mu_3 C_1$.

(ii) The second equilibrium point is $E_2(I_2, K_2, H_2, C_2)$, which can be termed as a co-existing or unhealthy equilibrium point (where the tumor exists) where,

$$I_2 = \frac{\tau(\sigma + K_2)}{(\delta_1 + \gamma_1 K_2 + \mu_1 C_2)(\sigma + K_2) - \rho K_2},$$
$$H_2 = 1 - \frac{\gamma_4 K_2}{\alpha_2} - \frac{\mu_3 C_2}{\alpha_2}, C_2 = \frac{\varphi}{\delta_2},$$

and K_2 can be found from the solution of the equation.

$$K_2 = \frac{1}{\beta} - \frac{\gamma_2 I_2}{\alpha_1 \beta} - \frac{\gamma_3 H_2}{\alpha_1 \beta} - \frac{\mu_2 C_2}{\alpha_1 \beta}$$

$$= \frac{1}{\beta} - \frac{\gamma_2}{\alpha_1 \beta}\left(\frac{\tau(\sigma + K_2)}{(\delta_1 + \gamma_1 K_2 + \mu_1 C_2)(\sigma + K_2) - \rho K_2}\right) - \frac{\gamma_3}{\alpha_1 \beta}\left(1 - \frac{\gamma_4 K_2}{\alpha_2} - \frac{\mu_3 C_2}{\alpha_2}\right) - \frac{\mu_2 C_2}{\alpha_1 \beta},$$

or

$$A_1 K_2^3 + A_2 K_2^2 + A_3 K_2 + A_4 = 0,$$

where

$$A_1 = \gamma_1(\alpha_1 \alpha_2 \beta - \gamma_3 \gamma_4),$$

$$A_2 = (\delta_1 + \mu_1 C_2 + \sigma\gamma_1 - \rho)(\alpha_1 \alpha_2 \beta - \gamma_3 \gamma_4) - \gamma_1(\alpha_1 \alpha_2 - \alpha_2 \gamma_3 + \mu_3 \gamma_3 C_2 - \alpha_2 \mu_2 C_2),$$

$$A_3 = \sigma(\delta_1 + \mu_1 C_2)(\alpha_1 \alpha_2 \beta - \gamma_3 \gamma_4) - (\delta_1 + \mu_1 C_2 + \sigma\gamma_1 - \rho)(\alpha_1 \alpha_2 - \alpha_2 \gamma_3 + \mu_3 \gamma_3 C_2 - \alpha_2 \mu_2 C_2) + \tau \alpha_2 \gamma_2,$$

$$A_4 = \sigma\tau\alpha_2\gamma_2 - \sigma(\delta_1 + \mu_1 C_2)(\alpha_1 \alpha_2 - \alpha_2 \gamma_3 + \mu_3 \gamma_3 C_2 - \alpha_2 \mu_2 C_2).$$

Note: Equilibrium point E_2 is real if $\alpha_2 > \gamma_4 K_2 + \mu_3 C_2$ and $(\delta_1 + \gamma_1 K_2 + \mu_1 C_2)(\sigma + K_2) > \rho K_2$, which can be seen easily from the above equations.

5. Stability analysis of the equilibrium points

In this section, we investigate the stability of each of the equilibrium points by linearizing the system (1a-1d). Also, we will determine conditions under which equilibrium points are either stable or unstable.

Without treatment case $(C(t) = 0)$: In this section, we study the nature of stability of the equilibrium points E_1 and E_2 by considering $C(t) = 0$, i.e. before employing chemotherapy for treatment. In this case, the equilibrium points are

$E_1^*(I_1^* = \tau/\delta_1, K_1^* = 0, H_1^* = 1)$ which can be termed as a healthy equilibrium point as tumor is not present in this case and

$$E_2^*\left(\begin{array}{c} I_2^* = \frac{\tau(\sigma + K_2^*)}{(\delta_1 + \gamma_1 K_2^*)(\sigma + K_2^*) - \rho K_2^*}, \\ K_2^* = \frac{1}{\beta} - \frac{\gamma_2}{\alpha_1 \beta} I_2^* - \frac{\gamma_3}{\alpha_1 \beta} H_2^*, H_2^* = 1 - \frac{\gamma_4 K_2^*}{\alpha_2} \end{array}\right),$$

which can be termed as co-existing equilibrium point as tumor is present in this case.

The Jacobian matrix of system (1a-1c) is given by

$$P_1 = \begin{pmatrix} \frac{\rho K}{\sigma + K} - \delta_1 - \gamma_1 K & \frac{\sigma\rho I}{(\sigma + K)^2} - \gamma_1 I & 0 \\ -\gamma_2 K & \alpha_1 - 2\alpha_1 \beta K - \gamma_2 I - \gamma_3 H & -\gamma_4 H \\ 0 & -\gamma_3 K & \alpha_2 - 2\alpha_2 H - \gamma_4 K \end{pmatrix}.$$

Now, we forward the following results:

Theorem 1: The healthy equilibrium point E_1^* is locally asymptotically stable if $\alpha_1 < \frac{\gamma_2 \tau}{\delta_1} + \gamma_3$ and unstable if $\alpha_1 \geq \frac{\gamma_2 \tau}{\delta_1} + \gamma_3$ i.e. if the intrinsic tumor growth rate is less than $\frac{\gamma_2 \tau}{\delta_1} + \gamma_3$ then the healthy equilibrium is E_1^* is locally asymptotically stable otherwise unstable.

Proof: At equilibrium point $E_1^*(I_1^* = \tau/\delta_1, K_1^* = 0, H_1^* = 1)$, the eigenvalues of the jacobian matrix P_1 are

$$\lambda_{11} = -\delta_1,$$

$$\lambda_{12} = \alpha_1 - \gamma_2 I_1^* - \gamma_3 H_1^* = \alpha_1 - \gamma_2 . \frac{\tau}{\delta_1} - \gamma_3 .1 = \alpha_1 - \frac{\gamma_2 \tau}{\delta_1} - \gamma_3,$$

$$\lambda_{13} = \alpha_2 - 2\alpha_2 H_1^* = \alpha_2 - 2\alpha_2.1 = -\alpha_2,$$

By applying the condition of stability [23], the necessary condition for asymptotic stability of equilibrium point E_1^* is found to be

$$\alpha_1 < \frac{\gamma_2\tau}{\delta_1} + \gamma_3,$$

and it will be unstable when $\alpha_1 \geq \frac{\gamma_2\tau}{\delta_1} + \gamma_3$. It implies that the intrinsic tumor growth rate plays an important role on system's stability at healthy equilibrium E_1^*.

Theorem2: The coexisting equilibrium point E_2^* is locally asymptotically stable if $A_{11} > 0 \text{and} A_{11}A_{12} - A_{13} > 0$.

where,

$$A_{11} = \left(-\frac{\rho K_2^*}{\sigma + K_2^*} + \delta_1 + \gamma_1 K_2^*\right) + \left(\alpha_2 - \gamma_4 K_2^*\right) + \left(\alpha_1 - \gamma_2 I_2^* - \gamma_3 H_2^*\right),$$

and

$$A_{11}A_{12} - A_{13} = \left(\left(-\frac{\rho K_2^*}{\sigma+K_2^*} + \delta_1 + \gamma_1 K_2^*\right) + \left(\alpha_2 - \gamma_4 K_2^*\right) + \left(\alpha_1 - \gamma_2 I_2^* - \gamma_3 H_2^*\right)\right)\left(\left(-\alpha_2 + \gamma_4 K_2^*\right)\left(-\alpha_1 + \gamma_2 I_2^* + \gamma_3 H_2^*\right) + \left(\left(-\alpha_2 + \gamma_4 K_2^*\right) + \left(-\alpha_1 + \gamma_2 I_2^* + \gamma_3 H_2^*\right)\right)\left(\frac{\rho K_2^*}{\sigma+K_2^*} - \delta_1 - \gamma_1 K_2^*\right) + \gamma_2 K_2^*\left(\frac{\sigma\rho I_2^*}{\left(\sigma+K_2^*\right)^2} - \gamma_1 I_2^*\right) - \gamma_3\gamma_4 H_2^* K_2^*\right) - \left(\left(\frac{\rho K_2^*}{\sigma+K_2^*} - \delta_1 - \gamma_1 K_2^*\right)\left(\gamma_3\gamma_4 H_2^* K_2^* - \left(-\alpha_2 + \gamma_4 K_2^*\right)\left(-\alpha_1 + \gamma_2 I_2^* + \gamma_3 H_2^*\right)\right) - \gamma_2 K_2^*\left(\frac{\sigma\rho I_2^*}{\left(\sigma+K_2^*\right)^2} - \gamma_1 I_2^*\right)\left(-\alpha_2 + \gamma_4 K_2^*\right)\right)$$

Proof: At Equilibrium point, $E_2^*\left(I_2^*, K_2^*, H_2^*\right)$, the eigenvalues of the Jacobian matrix P_1 are derived from the characteristics equation:

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

where,

$$I_2^* = \frac{\tau\left(\sigma + K_2^*\right)}{\left(\delta_1 + \gamma_1 K_2^*\right)\left(\sigma + K_2^*\right) - \rho K_2^*},$$

$$K_2^* = \frac{1}{\beta} - \frac{\gamma_2}{\alpha_1\beta} I_2^* - \frac{\gamma_3}{\alpha_1\beta} H_2^*,$$

$$H_2^* = 1 - \frac{\gamma_4 K_2^*}{\alpha_2},$$

$$A_{11} = -\left(\frac{\rho K_2^*}{\sigma+K_2^*} - \delta_1 - \gamma_1 K_2^*\right) - \left(\alpha_2 - 2\alpha_2 H_2^* - \gamma_4 K_2^*\right) - \left(\alpha_1 - 2\alpha_1\beta K_2^* - \gamma_2 I_2^* - \gamma_3 H_2^*\right) = -\left(\frac{\rho K_2^*}{\sigma+K_2^*} - \delta_1 - \gamma_1 K_2^*\right) - \left(-\alpha_2 + \gamma_4 K_2^*\right) - \left(-\alpha_1 + \gamma_2 I_2^* + \gamma_3 H_2^*\right),$$

(Substituting the value of $K_2^*$and H_2^*),

$$A_{12} = \left(\alpha_2 - 2\alpha_2 H_2^* - \gamma_4 K_2^*\right)\left(\alpha_1 - 2\alpha_1\beta K_2^* - \gamma_2 I_2^* - \gamma_3 H_2^*\right) + \left(\left(\alpha_2 - 2\alpha_2 H_2^* - \gamma_4 K_2^*\right) + \left(\alpha_1 - 2\alpha_1\beta K_2^* - \gamma_2 I_2^* - \gamma_3 H_2^*\right)\right)\left(\frac{\rho K_2^*}{\sigma + K_2^*} - \delta_1 - \gamma_1 K_2^*\right) + \gamma_2 K_2^*\left(\frac{\sigma\rho I_2^*}{\left(\sigma + K_2^*\right)^2} - \gamma_1 I_2^*\right) - \gamma_3\gamma_4 H_2^* K_2^*$$

$$= \left(-\alpha_2 + \gamma_4 K_2^*\right)\left(-\alpha_1 + \gamma_2 I_2^* + \gamma_3 H_2^*\right) + \left(\left(-\alpha_2 + \gamma_4 K_2^*\right) + \left(-\alpha_1 + \gamma_2 I_2^* + \gamma_3 H_2^*\right)\right)\left(\frac{\rho K_2^*}{\sigma+K_2^*} - \delta_1 - \gamma_1 K_2^*\right) + \gamma_2 K_2^*\left(\frac{\sigma\rho I_2^*}{\left(\sigma+K_2^*\right)^2} - \gamma_1 I_2^*\right) - \gamma_3\gamma_4 H_2^* K_2^*,$$ (Substituting the value of K_2^* and H_2^*), $A_{13} = \gamma_3\gamma_4 H_2^* K_2^*\left(\frac{\rho K_2^*}{\sigma + K_2^*} - \delta_1 - \gamma_1 K_2^*\right) - \left(\frac{\rho K_2^*}{\sigma+K_2^*} - \delta_1 - \gamma_1 K_2^*\right)\left(\alpha_2 - 2\alpha_2 H_2^* - \gamma_4 K_2^*\right)\left(\alpha_1 - 2\alpha_1\beta K_2^* - \gamma_2 I_2^* - \gamma_3 H_2^*\right) - \gamma_2 K_2^*\left(\frac{\sigma\rho I_2^*}{\left(\sigma+K_2^*\right)^2} - \gamma_1 I_2^*\right)\left(\alpha_2 - 2\alpha_2 H_2^* - \gamma_4 K_2^*\right) = \left(\frac{\rho K_2^*}{\sigma+K_2^*} - \delta_1 - \gamma_1 K_2^*\right)\left(\gamma_3\gamma_4 H_2^* K_2^* - \left(-\alpha_2 + \gamma_4 K_2^*\right)\left(-\alpha_1 + \gamma_2 I_2^* + \gamma_3 H_2^*\right)\right) - \gamma_2 K_2^*\left(\frac{\sigma\rho I_2^*}{\left(\sigma+K_2^*\right)^2} - \gamma_1 I_2^*\right)\left(-\alpha_2 + \gamma_4 K_2^*\right)$, (Substituting the value of K_2^* and H_2^*),

By using Routh-Hurwitz stability criteria, if $A_{11} > 0 \text{and} A_{11}A_{12} - A_{13} > 0$, then E_2^* is stable and becomes unstable when either of the conditions are not satisfied.

In the next section, we study at the equilibrium points E_1 and E_2 when the growth rate of the tumor, $\alpha_1 \geq \frac{\gamma_2\tau}{\delta_1} + \gamma_3$. This is done so as our earlier analysis has shown that the immune system can eliminate the growth rate of tumor cells up to $\alpha_1 < \frac{\gamma_2\tau}{\delta_1} + \gamma_3$, but fails to do the same when $\alpha_1 \geq \frac{\gamma_2\tau}{\delta_1} + \gamma_3$. This suggests that some form of treatment method becomes necessary when $\alpha_1 \geq \frac{\gamma_2\tau}{\delta_1} + \gamma_3$.

With treatment case $(C(t) \neq 0)$: In this section, we study the nature of stability of the equilibrium points E_1 and E_2 of the system (1a-1d) under the assumed condition $C_2 \neq 0$.

The Jacobian matrix of the system (1a-1d):

$$P_2 = \begin{pmatrix} B_1 & \frac{\sigma\rho I}{(\sigma+K)^2} - \gamma_1 I & 0 & -\mu_1 I \\ -\gamma_2 K & B_2 & -\gamma_3 K & -\mu_2 K \\ 0 & -\gamma_4 H & B_3 & -\mu_3 H \\ 0 & 0 & 0 & -\delta_2 \end{pmatrix},$$

where, $B_1 = \frac{\rho K}{\sigma+K} - \delta_1 - \gamma_1 K - \mu_1 C, B_2 = \alpha_1 - 2\alpha_1\beta K - \gamma_2 I - \gamma_3 H - \mu_2 C, B_3 = \alpha_2 - 2\alpha_2 H - \gamma_3 K - \mu_3 C.$

We forward the following result:

Theorem 3: The tumor-free equilibrium point E_1 is locally asymptotically stable if

$\alpha_2 > \frac{\varphi\mu_3}{\delta_2}$ and $\left((\alpha_1-\gamma_3)\alpha_2+(\mu_3\gamma_3-\alpha_2\mu_2)C_1\right)(\delta_1+\mu_1C_1) < \alpha_2\gamma_2\tau$.

Proof: At equilibrium point $E_1(I_1,0,H_1,C_1)$, the eigenvalues of the Jacobian matrix P_2 are

$$\lambda_{21} = -\delta_1-\mu_1C_1,$$

$$\begin{aligned}\lambda_{22} &= \alpha_1-\gamma_2I_1-\gamma_3H_1-\mu_2C_1\\ &= \alpha_1-\gamma_2.\left(\frac{\tau}{\delta_1+\mu_1C_1}\right)-\gamma_3.\left(1-\frac{\mu_3C_1}{\alpha_2}\right)-\mu_2C_1\\ &= \alpha_1-\frac{\gamma_2\tau}{(\delta_1+\mu_1C_1)}-\gamma_3\left(1-\frac{\mu_3C_1}{\alpha_2}\right)-\mu_2C_1,\end{aligned}$$

$$\begin{aligned}\lambda_{23} &= \alpha_2-2\alpha_2H_1-\mu_3C_1\\ &= \alpha_2-2\alpha_2.\left(1-\frac{\mu_3C_1}{\alpha_2}\right)-\mu_3C_1 = -\alpha_2+\mu_3C_1,\end{aligned}$$

$$\lambda_{24} = -\delta_2,$$

So, following the standard result (related to eigenvalue and stability) we can conclude that the equilibrium point P_2 is locally asymptotically stable if the following two conditions are satisfied

$$i.\ \alpha_2 > \frac{\varphi\mu_3}{\delta_2} \text{and} \tag{2a}$$

ii.

$$\left((\alpha_1-\gamma_3)\alpha_2+(\mu_3\gamma_3-\alpha_2\mu_2)C_1\right)(\delta_1+\mu_1C_1) < \alpha_2\gamma_2\tau, \text{ where } C_1=\tfrac{\varphi}{\delta_2} \tag{2b}$$

otherwise, unstable.

We consider the chemotherapy dose φ in between the stable range from equation (2a) and (2b) to bring the system to the tumor-free equilibrium point.

Theorem 4: The coexisting equilibrium point E_2 is locally asymptotically stable if $B_{11}>0 \text{and} B_{11}B_{12}-B_{13}>0$.

where,

$$\begin{aligned}B_{11} &= \delta_1+\gamma_1K_2+\mu_1C_2+\alpha_1-\gamma_2I_2-\gamma_3H_2-\mu_2C_2\\ &\quad+\alpha_2-\gamma_3K_2-\mu_3C_2-\frac{\rho K_2}{\sigma+K_2},\end{aligned}$$

and-

$$\begin{aligned}B_{11}B_{12}-B_{13} &= \left(\delta_1+\gamma_1K_2+\mu_1C_2+\alpha_1-\gamma_2I_2-\gamma_3H_2\right.\\ &\left.-\mu_2C_2+\alpha_2-\gamma_3K_2-\mu_3C_2-\tfrac{\rho K_2}{\sigma+K_2}\right)\left(\left(\tfrac{\rho K_2}{\sigma+K_2}-\delta_1-\gamma_1K_2\right.\right.\\ &\left.\left.-\mu_1C_2-\alpha_2+\gamma_3K_2+\mu_3C_2\right)\left(-\alpha_1+\gamma_2I_2+\gamma_3H_2+\mu_2C_2\right)\right.\\ &\left.+\left(\tfrac{\rho K_2}{\sigma+K_2}-\delta_1-\gamma_1K_2-\mu_1C_2\right)\left(-\alpha_2+\gamma_3K_2+\mu_3C_2\right)+\gamma_2\right.\\ &\left.K_2\left(\tfrac{\sigma\rho I_2}{(\sigma+K_2)^2}-\gamma_1I_2\right)-\gamma_3\gamma_4H_2K_2\right)-\left(\left(\tfrac{\rho K_2}{\sigma+K_2}-\delta_1-\gamma_1\right.\right.\\ &\left.\left.K_2-\mu_1C_2\right)\left(\left(-\alpha_1+\gamma_2I_2+\gamma_3H_2+\mu_2C_2\right)\left(-\alpha_1+\gamma_2I_2\right.\right.\right.\\ &\left.\left.\left.+\gamma_3H_2+\mu_2C_2\right)-\gamma_3\gamma_4H_2K_2\right)\right)-\left(\tfrac{\sigma\rho I_2}{(\sigma+K_2)^2}-\gamma_1I_2\right)(-\alpha_1\\ &+\gamma_2I_2+\gamma_3H_2+\mu_2C_2)\gamma_2K_2.\end{aligned}$$

Proof: Atequilibriumpoint$E_2(I_2,K_2,H_2,C_2)$, i.e. coexisting steady state, one eigenvalue is $\lambda=-\delta_2<0$, and the other eigenvalues are derived from the Jacobian matrix P_2.

The characteristic equation at equilibrium point P_2 is

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

where,

$$B_{11} = -(B_1+B_2+B_3),$$

$$\begin{aligned}B_{12} &= B_1B_2+B_2B_3+B_1B_3+\gamma_2K_2\left(\frac{\sigma\rho I_2}{(\sigma+K_2)^2}-\gamma_1I_2\right)\\ &\quad-\gamma_3\gamma_4H_2K_2,\end{aligned}$$

$$\begin{aligned}B_{13} &= B_1\left(B_2B_3-\gamma_3\gamma_4H_2K_2\right)\\ &\quad-\left(\frac{\sigma\rho I_2}{(\sigma+K_2)^2}-\gamma_1I_2\right)B_3\gamma_2K_2,\end{aligned}$$

and

$$B_1 = \frac{\rho K_2}{\sigma+K_2}-\delta_1-\gamma_1K_2-\mu_1C_2,$$

$B_2 = -\alpha_1+\gamma_2I_2+\gamma_3H_2+\mu_2C_2$, (Substituting the value of K_2),

$B_3 = -\alpha_2+\gamma_3K_2+\mu_3C_2$, (Substituting the value of H_2),

By using Routh-Hurwitz stability criteria, if $B_{11}>0 \text{and} B_{11}B_{12}-B_{13}>0$, then E_2 is stable and becomes unstable when either of the conditions are not satisfied.

We know that if the tumor-free equilibrium point is globally asymptotically stable, then the disease eradication is assured regardless of the initial number of infected cells in the cell population. So, in the next section, we check whether the equilibrium point E_1 is globally stable or unstable.

6. Global stability analysis of the healthy equilibrium point E_1 in the treatment case

For analyzing the qualitative behaviour of the system (1a-1d) far away from the equilibrium point E_1, we analyze the global stability of E_1 in this section.

Theorem 5: If the healthy equilibrium point $E_1(I_1, 0, H_1, C_1)$ is locally asymptotically stable inside the positive quadrant of the *IKHC*-plane, it will be globally asymptotically stable in that region if $\left((\alpha_1-\gamma_3)\alpha_2+(\mu_3\gamma_3-\alpha_2\mu_2)\frac{\varphi}{\delta_2}\right)\left(\delta_1+\mu_1\frac{\varphi}{\delta_2}\right)<\alpha_2\gamma_2\tau$, $I=\frac{\tau}{\delta_1}, K=\frac{1}{\beta}, H=1 \text{and} C\le\frac{\varphi}{\delta_2}$.

Proof: Let's define the Lyapunov function of the model (1a-1d)

$$\text{as} P(I,K,H,C)=\left(I-I_1-I_1\ln\frac{I}{I_1}\right)+(K-K_1)+\left(H-H_1-H_1\ln\frac{H}{H_1}\right)+\left(C-C_1-C_1\ln\frac{C}{C_1}\right).$$

Differentiating w.r.t. time we get

$$\frac{dP}{dt}=\left(1-\frac{I_1}{I}\right)\frac{dI}{dt}+\frac{dK}{dt}+\left(1-\frac{H_1}{H}\right)\frac{dH}{dt}+\left(1-\frac{C_1}{C}\right)\frac{dC}{dt}$$

$$=\left(1-\frac{I_1}{I}\right)\left(\tau+\frac{\rho IK}{\sigma+K}-\delta_1 I-\gamma_1 IK-\mu_1 CI\right)+\left(\alpha_1K(1-\beta K)-\gamma_2 IK-\gamma_3 KH-\mu_2 CK\right)+\left(1-\frac{H_1}{H}\right)\left(\alpha_2H(1-H)-\gamma_4 KH-\mu_3 CH\right)+\left(1-\frac{C_1}{C}\right)(\varphi-\delta_2 C)$$

$$=\left(\frac{I-I_1}{I}\right)\left(\frac{\rho IK}{\sigma+K}-\delta_1(I-I_1)-\gamma_1 IK-\mu_1 I(C-C_1)-\mu_1C_1(I-I_1)\right)+\left(\alpha_1K-\alpha_1\beta K^2-\gamma_2K(I-I_1)-\gamma_2I_1K-\gamma_3K(H-H_1)-\gamma_3KH_1-\mu_2K(C-C_1)-\mu_2C_1K\right)+\left(\frac{H-H_1}{H}\right)\left(\alpha_2(H-H_1)-\alpha_2\left(H^2-H_1^2\right)-\gamma_4KH-\mu_3H(C-C_1)-\mu_3C_1(H-H_1)\right)+\left(\frac{C-C_1}{C}\right)(-\delta_2(C-C_1))$$

$$=\left(\frac{(-\delta_1-\mu_1C_1)}{I}(I-I_1)^2-\gamma_1K(I-I_1)-\mu_1(C-C_1)(I-I_1)+\frac{\rho K}{\sigma+K}(I-I_1)\right)-\alpha_1\beta K^2-\gamma_2K(I-I_1)-\gamma_3K(H-H_1)-\mu_2K(C-C_1)+\left(-\alpha_2(H-H_1)^2-\gamma_4K(H-H_1)-\mu_3(C-C_1)(H-H_1)\right)+\left(-\frac{\delta_2}{C}\right)(C-C_1)^2+(\alpha_1-\gamma_2I_1-\gamma_3H_1-\mu_2C_1)K$$

$$=-Y^TMY-N^TY, \tag{3}$$

where,

$$Y^T=[I-I_1,K,H-H_1,C-C_1], N^T=\left[0,-\alpha_1+\gamma_2I_1+\gamma_3H_1+\mu_2C_1,0,0\right],$$

$$M=\begin{pmatrix}\frac{(\delta_1+\mu_1C_1)}{I} & \frac{1}{2}\left(\gamma_1+\gamma_2-\frac{\rho}{\sigma+K}\right) & 0 & \frac{\mu_1}{2}\\ \frac{1}{2}\left(\gamma_1+\gamma_2-\frac{\rho}{\sigma+K}\right) & \alpha_1\beta & \frac{\gamma_3+\gamma_4}{2} & \frac{\mu_2}{2}\\ 0 & \frac{\gamma_3+\gamma_4}{2} & \alpha_2 & \frac{\mu_3}{2}\\ \frac{\mu_1}{2} & \frac{\mu_2}{2} & \frac{\mu_3}{2} & \frac{\delta_2}{C_1}\end{pmatrix}.$$

By noting the second component of the vector N in (3), for stability we must have:

$$\frac{\gamma_2\tau}{\delta_1+\mu_1C_1}+\gamma_3\left(1-\frac{\mu_3C_1}{\alpha_2}\right)+\mu_2C_1>\alpha_1$$

$$=>\left((\alpha_1-\gamma_3)\alpha_2+(\mu_3\gamma_3-\alpha_2\mu_2)C_1\right)(\delta_1+\mu_1C_1)<\alpha_2\gamma_2\tau,$$

as such a condition, namely (3), results in $N^TY>0$. Furthermore, by considering the values of parameters from Table 1, if $I=\frac{\tau}{\delta_1}, K=\frac{1}{\beta}, H=1 \text{and} C\le\frac{\varphi}{\delta_2}$, then $Y^TMY>0$. Now, it is clear that $dP/dt<0$.

Therefore, the healthy equilibrium point E_1 is globally asymptotically stable if $\left((\alpha_1-\gamma_3)\alpha_2+(\mu_3\gamma_3-\alpha_2\mu_2)\frac{\varphi}{\delta_2}\right)\left(\delta_1+\mu_1\frac{\varphi}{\delta_2}\right)<\alpha_2\gamma_2\tau, I=\frac{\tau}{\delta_1}, K=\frac{1}{\beta}, H=1,$ and

$$C\le\frac{\varphi}{\delta_2}.$$

The Tumor Free Equilibrium point E_1 must satisfy the local stability conditions, in addition to these derived conditions to become globally stable.

In the next section, we formulate the problem of determining the most effective treatment regimen after we administer chemotherapy treatment at a specific time. This has been achieved by formulating and then solving the corresponding optimal control problem.

7. Optimal control

To make the treatment regiment better, it is expected that the amount of chemotherapy drug dose should be reduced when the size of the tumor gets smaller as it can save the patient from the attack of other opportunistic diseases which may take place due to further decrease in immune and normal cells. Therefore, we propose and analyze the optimal control problem applicable to model (1a-1d). Mathematically, we assume that maximum amount of drug is given when the number of tumor cells are high and it is gradually reduced to zero with the decrease in number of of tumor cells within a prescribed treatment interval $[0, t_f]$. For achieving the same, we assume the chemotherapeutic drug in equation (1d) of the model as a function of time viz. $\varphi(t)$ and consider it as the control input. It is to be noted that in the earlier parts of our investigation we considered φ as a constant.

Under the above considerations, the objective function which is to be minimized is:

$$\Omega(\varphi) = \int_0^{t_f} \left(\beta_1 K - \beta_2 I - \beta_3 H - \beta_4 \varphi^2\right) dt, \tag{4}$$

where $\beta_1, \beta_2, \beta_3$, and β_4 are non-negative constants. It should be mentioned that $\beta_i (i = 1, 2, 3, 4)$ represents the weight factors of the objective function and are used for balancing the size of the terms. The square of the optimal combination of control variables will be adequate to minimize the tumor density and adverse side effects over a fixed time. When a high dose of chemotherapeutic drugs is administered to the patient, they are toxic to the body, which justifies the quadratic terms in the functional [8]. The first three terms of the integrand function are the total number of tumor cells, immune cells, and normal cells. The fourth term of the integrand shows the effect of chemotherapy on the body. Here, we have used the problem of optimal control for the model to reduce the burden of tumor cells while maximizing the number of immune-normal cells, to reduce the time for recovery of the patient, which can reduce side effects due to a lower amount of chemotherapy in a shorter time.

Here, we establish an optimal control φ^* such that

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

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

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

$$\begin{aligned}
\frac{dI}{dt} &= \tau + \frac{\rho IK}{\sigma + K} - \delta_1 I - \gamma_1 IK - \mu_1 CI,\\
\frac{dK}{dt} &= \alpha_1 K(1 - \beta K) - \gamma_2 IK - \gamma_3 KH - \mu_2 CK,\\
\frac{dH}{dt} &= \alpha_2 H(1 - H) - \gamma_4 KH - \mu_3 CH,\\
\frac{dC}{dt} &= \varphi(t) - \delta_2 C,
\end{aligned} \tag{5}$$

with the initial conditions

$$I(0) = I_0, K(0) = K_0, H(0) = H_0, C(0) = C_0. \tag{6}$$

7.1. The existence of optimal control

In this sub-section, the existence of optimal control of the system (5) is discussed. The property of super solutions $\bar{I}$, $\bar{K}$,$\bar{H}$, and $\bar{C}$ of the model (5) is that trajectories are given by

$$\begin{aligned}
\frac{d\bar{I}}{dt} &= \tau + \rho\bar{I},\\
\frac{d\bar{K}}{dt} &= \alpha_1 \bar{K},\\
\frac{d\bar{H}}{dt} &= \alpha_2 \bar{H},\\
\frac{d\bar{C}}{dt} &= \varphi - \delta_2 \bar{C},
\end{aligned} \tag{7}$$

are bounded [27]. We rewrite (7) as follows:

$$\begin{pmatrix} \bar{I} \\ \bar{K} \\ \bar{H} \\ \bar{C} \end{pmatrix}' = \begin{pmatrix} \rho & 0 & 0 & 0 \\ 0 & \alpha_1 & 0 & 0 \\ 0 & 0 & \alpha_2 & 0 \\ 0 & 0 & 0 & -\delta_2 \end{pmatrix} \begin{pmatrix} \bar{I} \\ \bar{K} \\ \bar{H} \\ \bar{C} \end{pmatrix} + \begin{pmatrix} \tau \\ 0 \\ 0 \\ \varphi \end{pmatrix}, \tag{8}$$

Since it is a linear system with bounded coefficients and the time limit is limited, we conclude that super solutions $\bar{I}$, $\bar{K}$, $\bar{H}$, and $\bar{C}$ of the above system are uniformly bounded. We found that the admissible control class and the corresponding state equations are nonempty with initial conditions given in (6) by using the theorem proposed by Lukes [28]. 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 (5) holds and is bounded above by a sum of the bounded control and state.

Now, we must show convexity of $\Omega(\varphi)$ on Δ and further that it is bounded below by $\tau_1(K - \varphi^2) - \tau_2$ with $\tau_1, \tau_2 > 0$.

Let p_1 and p_2 be distinct elements of Ω and $0 \le Y \le 1$. We must show

$$(1 - Y)\Omega(p_1) + Y\Omega(p_2) \ge \Omega((1 - Y)p_1 + Yp_2), \tag{9}$$

where

$$\Omega(\varphi) = \beta_1 K - \beta_2 I - \beta_3 H - \beta_4 \varphi^2, \tag{10}$$

and p_1 and p_2 are two control vectors and $Y \in (0, 1)$.

By substituting (10) into (9), we get

$$\begin{aligned}
&(1 - Y)\Omega(p_1) + Y\Omega(p_2) - \Omega((1 - Y)p_1 + Yp_2)\\
&= (1 - Y)\left(\beta_1 K - \beta_2 I - \beta_3 H - \beta_4 p_1^2\right)\\
&\quad + Y\left(\beta_1 K - \beta_2 I - \beta_3 H - \beta_4 p_2^2\right)\\
&\quad - \left(\beta_1 K - \beta_2 I - \beta_3 H - \beta_4 ((1 - Y)p_1 + Yp_2)^2\right)\\
&= -\beta_4 p_1^2 Y + 2\beta_4 Y p_1 p_2 - Y\beta_4 p_2^2 + \beta_4 Y^2 p_1^2 + \beta_4 Y^2 p_2^2\\
&\quad - 2\beta_4 Y^2 p_1 p_2
\end{aligned}$$

$$= \beta_4 Y(1-Y)(p_2-p_1)^2$$
$$\geq 0, \left[\text{since}(1-Y) > 0 \text{and}(p_1-p_2)^2 \geq 0\right],$$

which implies that

$(1-Y)\Omega(p_1) + Y\Omega(p_2) \geq \Omega((1-Y)p_1 + Yp_2)$,

which verifies the convexity of $\Omega(\varphi)$ on Δ

And further

$$\Omega(t, Y, \varphi) = \beta_1 K - \beta_2 I - \beta_3 H - \beta_4 \varphi^2 \geq \beta_1 K - \beta_4 \varphi^2$$
$$\geq \tau_1\left(K - \varphi^2\right) \geq \tau_1\left(K - \varphi^2\right) - \tau_2.$$

This shows that $\tau_1(K-\varphi^2) - \tau_2$ is a lower bound of $\Omega(\varphi)$.

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

Theorem 6. For given objective functional

$$\Omega(\varphi) = \int_0^{t_f} \left(\beta_1 K - \beta_2 I - \beta_3 H - \beta_4 \varphi^2\right) dt, \tag{11}$$

where

$$\Delta = \left\{\varphi : \text{measurable}, 0 \leq \varphi \leq 1, t \in \left[0, t_f\right]\right\},$$

is subject to the system (5) with the initial conditions $I(0) = I_0$, $\mathrm{K}(0) = \mathrm{K}_0$, $\mathrm{H}(0) = \mathrm{H}_0$ and $\mathrm{C}(0) = \mathrm{C}_0$, there exists an optimal control φ^* such that $\Omega(\varphi^*) = \min\{\Omega(\varphi) : \varphi \in \Delta\}$.

7.2. Characterization of the optimal control

Now, we implement the procedure of applying the Pontryagin maximum principle and Hamiltonian function. We introduce the four co-state variables $h_s, s = 1, 2, 3, 4$ and so the

Hamiltonian function is given by

$$X = \beta_1 K - \beta_2 I - \beta_3 H - \beta_4 \varphi^2 + h_1 \dot{I} + h_2 \dot{K} + h_3 \dot{H} + h_4 \dot{C}. \tag{12}$$

By substituting (5) into (12), we find

$$\begin{aligned} X = {} & \beta_1 K - \beta_2 I - \beta_3 H - \beta_4 \varphi^2 \\ & + h_1\left(\tau + \frac{\rho I K}{\sigma + K} - \delta_1 I - \gamma_1 I K - \mu_1 C I\right) \\ & + h_2\left(\alpha_1 K(1 - \beta K) - \gamma_2 I K - \gamma_3 K H - \mu_2 C K\right) \\ & + h_3\left(\alpha_2 H(1 - H) - \gamma_4 K H - \mu_3 C H\right) \\ & + h_4(\varphi(\mathrm{t}) - \delta_2 C), \end{aligned} \tag{13}$$

The Hamiltonian equations are

$$\dot{h}_1 = -\frac{\partial X}{\partial I},$$

$$\dot{h}_2 = -\frac{\partial X}{\partial K},$$

$$\dot{h}_2 = -\frac{\partial X}{\partial H},$$

$$\dot{h}_3 = -\frac{\partial X}{\partial C},$$

where $h_s(t), s = 1, 2, 3, 4$ are the adjoint functions to be determined suitably.

Adjoint equations and forms of transversality conditions are standard results from the Pontryagin maximum principle [29,30]. In the case of our considered system, an adjoint system can be obtained in the form of:

$$\dot{h}_1 = \beta_2 - h_1\left(\frac{\rho K}{\sigma + K} - \gamma_1 K - \mu_1 C - \delta_1\right) + h_2 \gamma_2 K,$$

$$\begin{aligned} \dot{h}_2 = {} & -\beta_1 - h_1\left(\frac{\sigma \rho I}{(\sigma + K)^2} - \gamma_1 I\right) \\ & - h_2\left(\alpha_1 - 2\alpha_1 \beta K - \gamma_2 I - \gamma_3 H - \mu_2 C\right) + h_3 \gamma_4 H, \end{aligned}$$

$$\dot{h}_3 = \beta_3 + h_2 \gamma_3 K - h_3\left(\alpha_2 - 2\alpha_2 H - \gamma_4 K - \mu_3 C\right), \tag{14}$$

$$\dot{h}_4 = h_1 \mu_1 I + h_2 \mu_2 K + h_3 \mu_3 H + h_4 \delta_2.$$

where $h_s\left(t_f\right) = 0, (s = 1, 2, 3, 4)$ are the transversality conditions.

The optimal control functions are determined by putting $\frac{\partial X}{\partial \varphi} = 0$. Hence, we get

$$\varphi^*(t) = \frac{h_4}{2\beta_4}, \ \varphi^* = \varphi^*(t) \tag{15}$$

Using the bounds for the control variable φ^* from (15), we get

$$\varphi^* = \left\{\begin{array}{c} \frac{h_4}{2\beta_4}, \text{if} 0 \leq \frac{h_4}{2\beta_4} \leq 1 \\ 0, \text{if} \frac{h_4}{2\beta_4} \leq 0 \\ 1, \text{if} \frac{h_4}{2\beta_4} \geq 1 \end{array}\right\}.$$

In the compact notation, let us consider

$$\varphi^* = \min\left\{\max\left\{0, \frac{h_4}{2\beta_4}\right\}, 1\right\}, \tag{16}$$

From (5), (14), and (16), we get the subsequent optimal system as

$$\frac{dI}{dt} = \tau + \frac{\rho IK}{\sigma + K} - \delta_1 I - \gamma_1 IK - \mu_1 CI,$$

$$\frac{dK}{dt} = \alpha_1 K(1 - \beta K) - \gamma_2 IK - \gamma_3 KH - \mu_2 CK,$$

$$\frac{dH}{dt} = \alpha_2 H(1 - H) - \gamma_4 KH - \mu_3 CH,$$

$$\frac{dC}{dt} = \min\left\{\max\left\{0, \frac{h_4}{2\beta_4}\right\}, 1\right\} - \delta_2 C,$$

$$\dot{h}_1 = \beta_2 - h_1\left(\frac{\rho K}{\sigma + K} - \gamma_1 K - \mu_1 C - \delta_1\right) + h_2\gamma_2 K,$$

$$\dot{h}_2 = -\beta_1 - h_1\left(\frac{\sigma\rho I}{(\sigma + K)^2} - \gamma_1 I\right) - h_2(\alpha_1 - 2\alpha_1\beta K - \gamma_2 I - \gamma_3 H - \mu_2 C) + h_3\gamma_4 H,$$

$$\dot{h}_3 = \beta_3 + h_2\gamma_3 K - h_3(\alpha_2 - 2\alpha_2 H - \gamma_4 K - \mu_3 C),$$

$$\dot{h}_4 = h_1\mu_1 I + h_2\mu_2 K + h_3\mu_3 H + h_4\delta_2.$$

subject to the conditions $I(0) = I_0$, $K(0) = K_0$, $H(0) = H_0$ and $C(0) = C_0$ and $h_s(t_f) = 0, s = 1, 2, 3, 4$.

Theorem 7. Considering optimal control variable φ^* and corresponding state variables $I^*(t)$, $K^*(t)$,$H^*(t)$ and $C^*(t)$, there exist ongoing specific adjoint variables $h_s(t), s = 1, 2, 3, 4$, satisfying the following system:

$$\dot{h}_1 = \beta_2 - h_1\left(\frac{\rho K}{\sigma + K} - \gamma_1 K - \mu_1 C - \delta_1\right) + h_2\gamma_2 K,$$

$$\dot{h}_2 = -\beta_1 - h_1\left(\frac{\sigma\rho I}{(\sigma + K)^2} - \gamma_1 I\right) - h_2(\alpha_1 - 2\alpha_1\beta K - \gamma_2 I - \gamma_3 H - \mu_2 C) + h_3\gamma_4 H,$$

$$\dot{h}_3 = \beta_3 + h_2\gamma_3 K - h_3(\alpha_2 - 2\alpha_2 H - \gamma_4 K - \mu_3 C),$$

$$\dot{h}_4 = h_1\mu_1 I + h_2\mu_2 K + h_3\mu_3 H + h_4\delta_2,$$

subject to the transversality conditions $h_s(t_f) = 0, s = 1, 2, 3, 4$.

In addition, the following properties hold:

$$\varphi^* = \min\left\{\max\left\{0, \frac{h_4}{2\beta_4}\right\}, 1\right\},$$

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

8. Numerical simulation

To assess the feasibility of our analytical results in terms of stability, we perform the calculations using MATLAB and Mathematica with parameter values specified in Table 1.

Case(i): when $\alpha_1 < \frac{\gamma_2\tau}{\delta_1} + \gamma_3$:

The above simulations are for 'without treatment' case when the growth rate of tumor cells,$\alpha_1 < \frac{\gamma_2\tau}{\delta_1} + \gamma_3$. Figure1 (a,b,c) show that solutions of the system with different initial points of tumor cells $(K(0) = 0.05, 0.06, 0.07, 0.08)$ have some oscillation in case of immune cells but ultimately converge to the tumor free equilibrium point E_1^*, which is on the tumor-free $(K = 0)$ plane. Biologically, the above simulation shows that if there are some pre-cancerous or potentially cancerous cells in the body then the immune system can eradicate those without application of any external therapy. Of course, this will be possible till $\alpha_1 < \frac{\gamma_2\tau}{\delta_1} + \gamma_3$.

Case(ii): when $\alpha_1 \geq \frac{\gamma_2\tau}{\delta_1} + \gamma_3$:

The above simulations are for 'without treatment' case when the growth rate of tumor cells,$\alpha_1 > \frac{\gamma_2\tau}{\delta_1} + \gamma_3$. Figures 2(a, b, c) show that solutions of the system with different initial points of tumor cells $(K(0) = 0.05, 0.06, 0.07, 0.08)$ have oscillations in all three types of cells and ultimately converge not to the tumor free equilibrium point E_1^* (as in the earlier case)

Table 1. Parameter values considered for the model.

Parameters	Meaning	Values	Source
τ	Constant source rate of immune cells	0.05	[5]
δ_1	The natural death rate of immune cells	0.2	[5]
α_1	The intrinsic tumor growth rate	varied	
α_2	The growth rate of normal cell	0.35	[5]
$1/\beta$	The tumor population carrying capacity	2/3	[5]
δ_2	The natural decay rate of drug	0.05	[5]
μ_1	Immune cells kill rate due to drug	0.2	Estimated based on [5]
μ_2	Tumor cells kill rate due to drug	0.5	Estimated based on [5]
μ_3	Normal cells kill rate due to drug	0.25	Estimated based on [5]
γ_1	The decay rate of immune cells due to tumor cells	0.2	[5]
γ_2	The decay rate of tumor cells due to immune cells	0.3	[5]
γ_3	The decay rate of tumor cells due to normal cells	0.2	[5]
γ_4	The decay rate of normal cells due to tumor cells	0.25	[5]
ρ	Maximum recruitment of immune cells by tumor cells	1	[5]
σ	Half saturation constant for the proliferation term	0.4	[5]

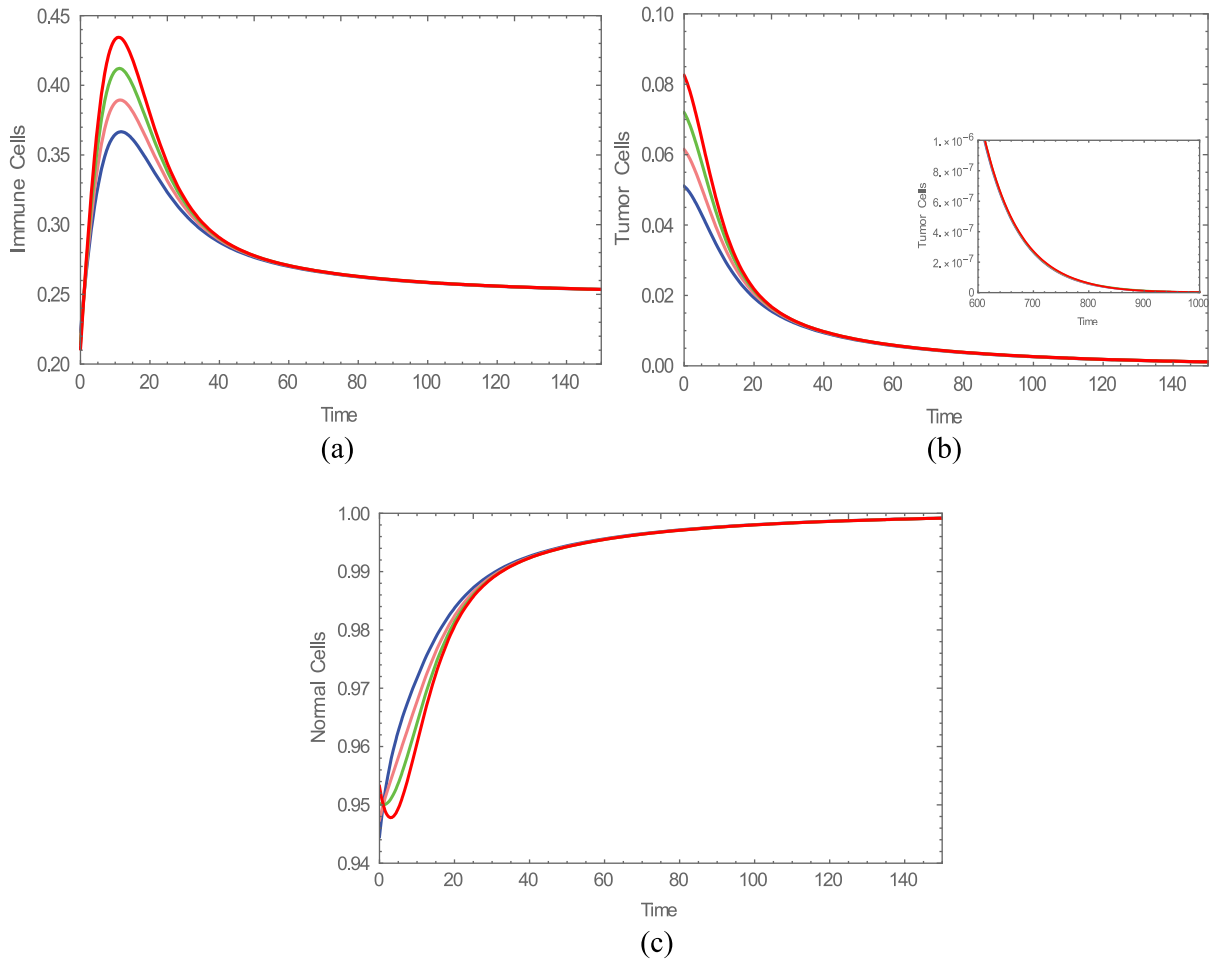

Figure 1. Numerical simulations of the model (1a-1d) showing the time variation in the size of all relative populations of the model with various initial values. For these simulations, we used the following initial values.

but to the co-existing equilibrium point E_2^*. This shows that when growth rate of the tumor is high $\alpha_1 > \frac{\gamma_2\tau}{\delta_1} + \gamma_3$, the immune system itself can't eradicate tumor cells and some kind of external therapy is required for treating the patient.

Case(iii): With treatment and $\alpha_1 \geq \frac{\gamma_2\tau}{\delta_1} + \gamma_3$:

The above simulations are for 'with treatment' case when the growth rate of tumor cells,$\alpha_1 > \frac{\gamma_2\tau}{\delta_1} + \gamma_3$. In this case, we have simulated the effect of applied chemotherapy drug on all three types of cells viz. immune, tumor and normal, when the drug dose φ of chemotherapy is increased. Figures 3(a, b, c, d) illustrate the time variations in each compartment of the model (1a-1d) with tumor growth rate, $\alpha_1 = 0.4$. From figures, it is seen that when the chemotherapy drug dose is low ($\varphi < 0.021$) and growth rate of tumor is high ($\alpha_1 = 0.4$), the solutions converge to the co-existing equilibrium point E_2. However, when growth rate of tumor remains same ($\alpha_1 = 0.4$) but drug dose is increased ($\varphi \geq 0.021$), the solutions converge to the tumor-free equilibrium point E_1. This shows that an increase in φ leads to the success for chemotherapy treatment. But one important point of consideration is that whether the tumor-free equilibrium point E_1 is globally stable as in that case we can conclude that there will be no scope for relapse of tumor. We already discussed the global stability of the point E_1 theoretically. Below, we have presented a numerical simulation which supports our theoretical finding.

Figure 4 shows that even when tumor growth rate is high ($\alpha_1 = 0.4$) if we apply a high dose of chemotherapy drug ($\varphi = 0.021$), then any trajectory starting from any initial point in the basin of attraction converges to the healthy equilibrium point E_1. This indicates that the healthy equilibrium point E_1 is globally stable. Biologically, this indicates the fact that the body is recovering from the tumor,

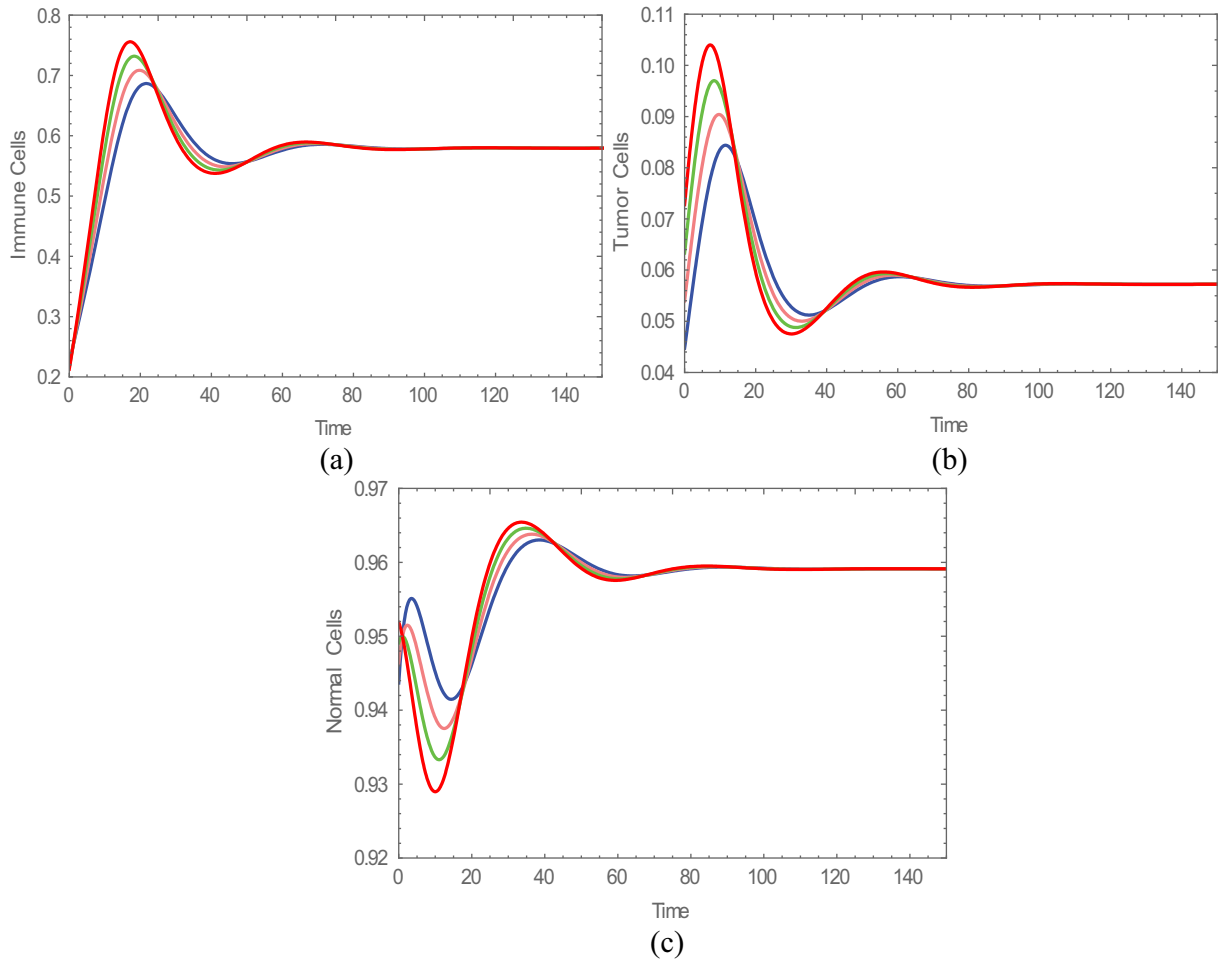

Figure 2. Numerical simulations of the model (1a-1d) showing the time variation in the size of all relative populations of the model with various initial values. For these simulations, we used the following initial values.

regardless of the initial condition which contains tumor growth.

We already mentioned that though a high dose of chemotherapy drugs can kill cancerous cells, the method also has the drawback of killing normal and immune cells. Also, when the tumor size gets smaller, as shown in Figure 3(d), the amount of chemotherapy drugs should likely be decreased instead of staying the same. This is because the number of healthy and immune cells will continue to decrease. A decrease in immune cells makes the patient susceptible to other opportunistic diseases. So, we developed the optimal control strategy considering chemotherapy drugs as the control input. We have presented the following simulations in support of our theoretical findings in Section 7, which are related to the optimal control strategy.

Case(iv): In this section, we have presented the simulations to show the effect of optimal control in the method of treatment:

From Figures 5(a, b, c, d) it is seen that the optimal treatment strategy reduces the burden of tumor cells and increases the number of immune and normal cells after a certain time of adoption of the treatment strategy. Particularly from Figure 5(b) we can conclude that the incorporation of optimal control to eradicate the tumor cells is more effective as it makes the system tumor-free in less time without putting the patients' health at risk. From this perspective, we can conclude that all efforts to reduce the proliferation of tumor cells after the onset of the disease should be kept under optimal control. Another advantage of the control strategy can be seen in Figure 5(d) which shows that control inputs $\varphi(t)$ of drugs can be reduced with the decrease in the number of tumor cells rather than keeping this constant (Figure 3 (d)). This can reduce unnecessary killing of immune and normal cells and help the system to fight against the attack of other opportunistic diseases.

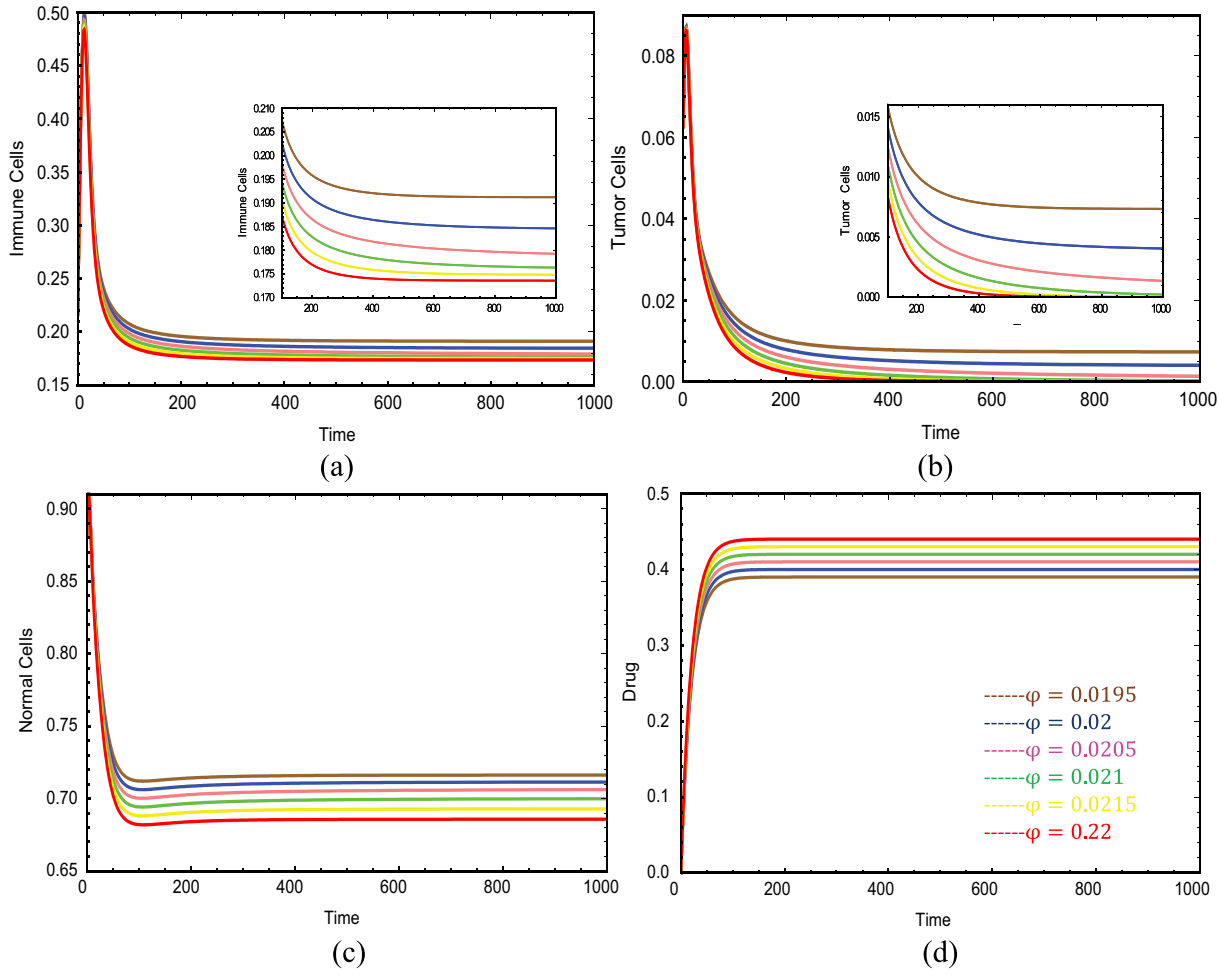

Figure 3. Numerical simulations of the model (1a-1d) showing the time variation in the size of all relative populations of the model with different chemotherapy drug dose. For these simulations, we used the following initial values.

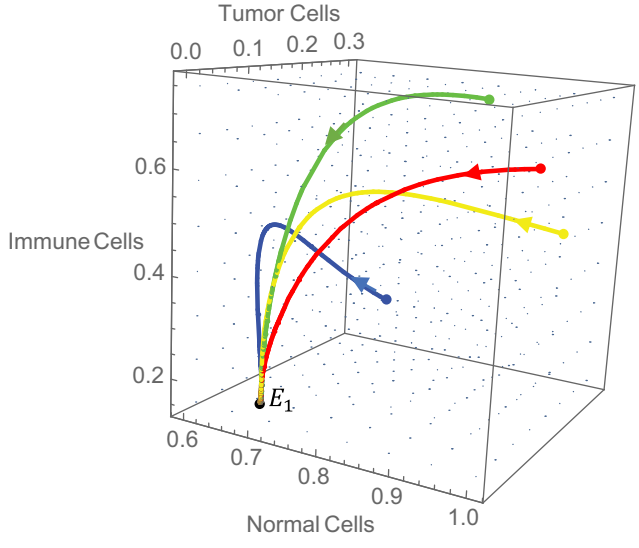

Figure 4. The vector field plot with different initial conditions of immune-tumor-normal cells (Yellow (0.5, 0.2, 0.99), Red (0.65,0.1,1), Green (0.75, 0.1, 0.9), Blue (0.27, 0.25, 0.7)) with tumor growth rate, $a_1 = 0.4$ and chemotherapy drug dose.

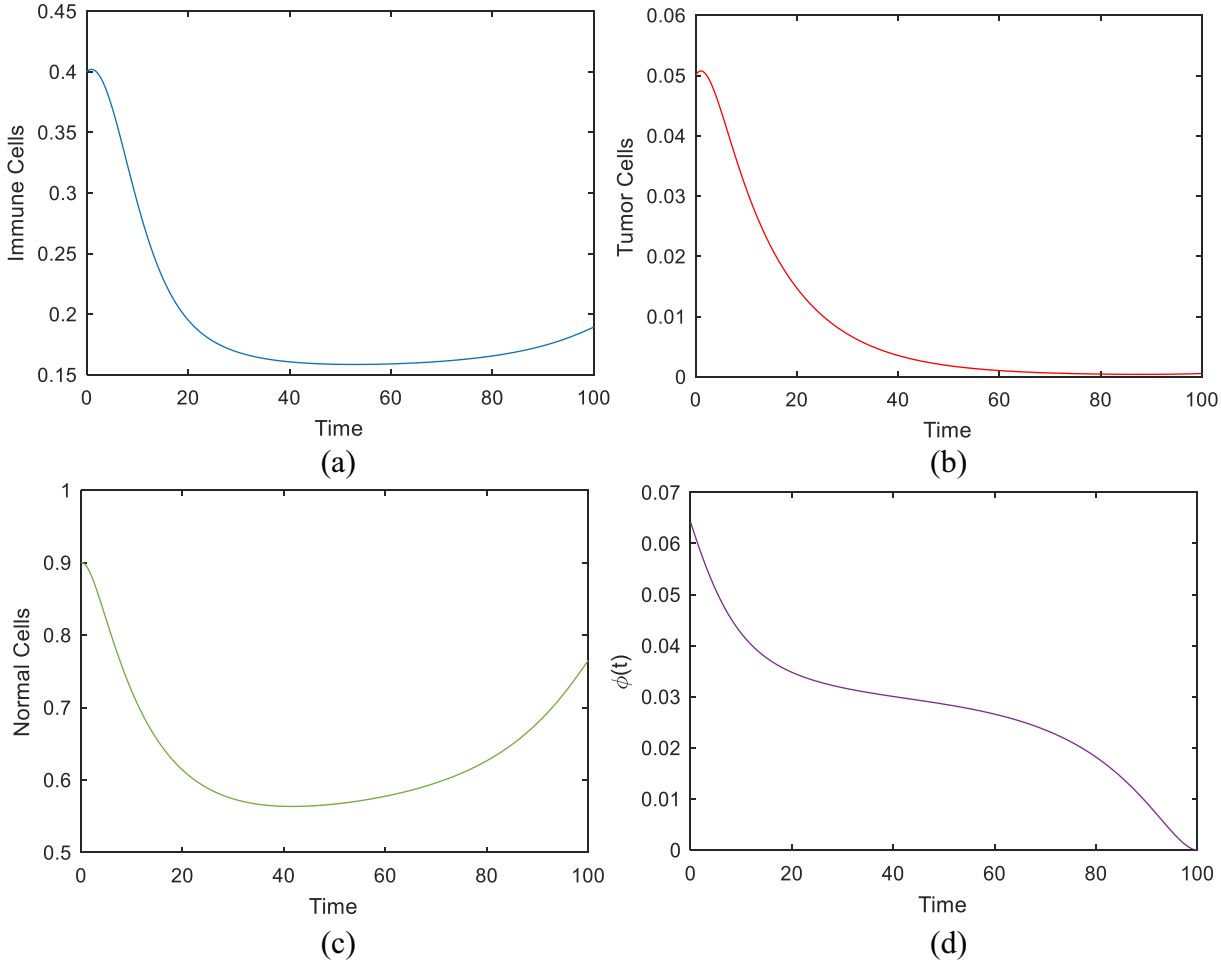

Figure 5. Numerical simulations of the model (5) showing the time variation in the size of all relative populations of the model. For these simulations, we used the following initial values.

9. Conclusion

In this study, we constructed an ODE model for analyzing cancer dynamics. The model is a modified version of [5]. The evolution of the model has been analyzed and displayed with different values of the parameters α_1 (growth rate of tumor cells) and φ (drug administration rate). The stability of equilibria without and with treatment strategy were explored.

The analysis revealed that for tumor growth rate, $\alpha_1 < \frac{\gamma_2\tau}{\delta_1} + \gamma_3$, tumor cell population can be controlled by the immune-normal cells without application of any treatment strategy. In this case, it was observed that the system gets stabilized to the tumor-free equilibrium point E_1^*. Of course, the process takes a long time.

On the contrary, it was seen that when tumor growth rate, $\alpha_1 \geq \frac{\gamma_2\tau}{\delta_1} + \gamma_3$ the immune-normal cells fail to overcome the tumor burden of their own. In this case, it was seen that the tumor cells proliferate, and the system gets stabilized to the co-existing equilibrium point E_2^*. So, some form of treatment method becomes necessary.

It was found that when the chemotherapy drug dose ($\varphi \geq 0.021$) was applied, the model approaches the tumor-free equilibrium point E_1 signifying the success of chemotherapy treatment for eradication of cancer. It was further seen that for larger values of chemotherapy drug dose (φ) the system can clean up the tumor cells in lesser time. But as high doses of chemotherapy are detrimental for the health of the patient, we implemented an optimal treatment strategy considering chemotherapy as the control input. Analysis of this strategy revealed that cancer cells can be fully eradicated by less amount of chemotherapy and that too in a lesser time interval. The amount of chemotherapy input was lessened by considering it as a function of time and reducing it with decrease in the number of tumor cells. Numerical simulations presented in the paper confirm our theoretical findings.

Modifications in the model and the optimal control strategy have given novelty to our findings. Of course, interested readers can employ other optimal control techniques like 'bang-bang control' or 'feedback control' to analyze the problem and compare the results. Readers interested in those aspects and different methodologies to investigate different realistic problems are referred to the papers [31–35].

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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