Applied Mathematics and Computation 353 (2019) 147–165

Contents lists available at ScienceDirect

Applied Mathematics and Computation

journal homepage: www.elsevier.com/locate/amc

Optimal control of tumour-immune model with time-delay and immuno-chemotherapy

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ARTICLE INFO

MSC:
92C50
93A30
37N25
37N35
34K28

Keywords:
DDEs
Hamiltonian
Immuno-chemotherapy
Optimal control
Time-delay
Tumour cells
Stability

ABSTRACT

Herein, we study an optimal control problem of delay differential model to describe the dynamics of tumour-immune interactions in presence of immuno-chemotherapy. The model includes constant delays in the mitotic phase to justify the time required to stimulate the effector cells and for the effector cells to develop a suitable response to the tumour cells. By applying optimal control theory, we seek to minimize the cost associated with the immuno-chemotherapy and to reduce load of of tumour cells. Non-Negativity of the solutions of the model and existence of an optimal control has also been proven. Optimality conditions and characterization of the control are also discussed. We numerically approximate the solution of the optimal control problem by solving the state system forward and adjoint system backward in time. The numerical simulations show that the combination of immuno-chemotherapy protocol reduces the tumour load in few months of therapy.

1. Introduction

Cancer is the leading cause of death not only in the developing countries, but also in developed countries; see the statistics of Health World Organization (WHO). Although a great research effort is being devoted to understand the interaction between tumour cells and immune system, the treatment of cancer is still one of the most challenging problems of modern medicine. Cancer treatment should kill cancer cells in the entire body and in the meantime keep the healthy cells above the minimum level. Chemotherapy is one of the most prominent cancer treatment modalities, but it is not always a comprehensive solution for tumour regression [7,37]. Now, progress is being made with an experimental form of immunotherapy to eliminate the tumour cells in the host [22].

Immunotherapy (which is sometimes referred to biological therapy) is quickly becoming one of the most important components of cancer treatments, especially in multi-pronged approaches [28]. The goal of immunotherapy is to reinforce the body's own natural ability to combat cancer by enhancing the effectiveness of the immune system to act against cancer cells, which involves the use of cytokines[1] with Adoptive Cellular Immunotherapy (ACI), derived from the body or laboratory-produced versions of such substances, to improve or restore immune system function [16,17]. Although it is not entirely clear how immunotherapy treats cancer, it may work by stopping or slowing the growth of cancer cells, stopping cancer

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[1] Cytokines: Protein hormones that mediate both natural and specific immunity, called interferons and interleukins. They increase the production of immune cells, can be made in the laboratory and given to patients as part of treatment for cancer.

https://doi.org/10.1016/j.amc.2019.02.002
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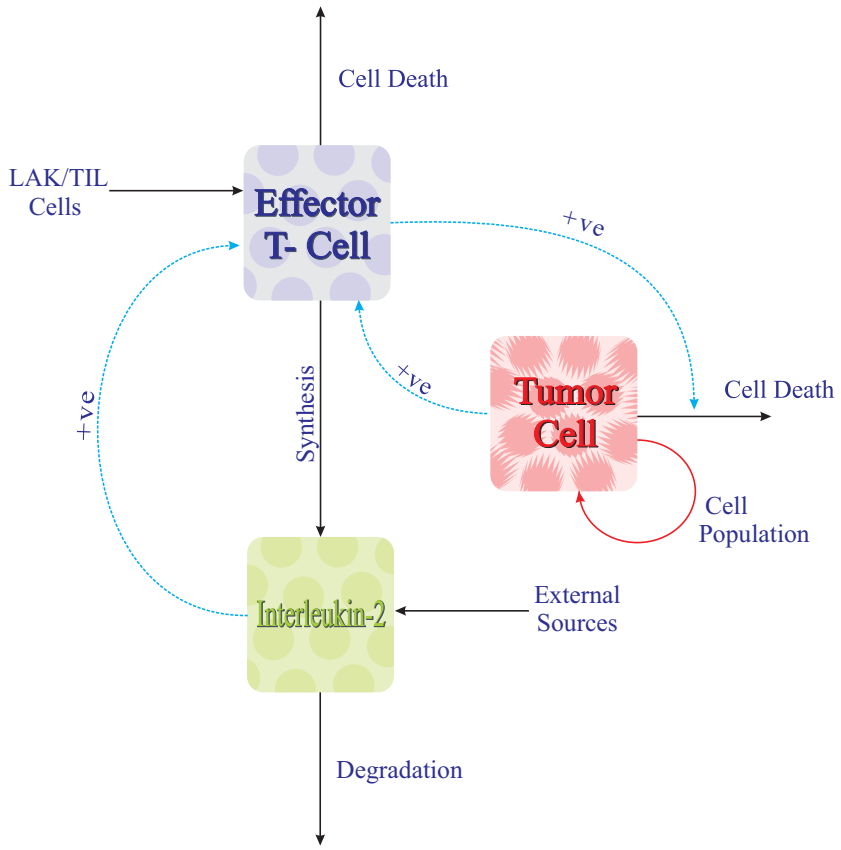

Fig. 1. Schematic diagram showing the key-players in tumour-immune interactions.

from spreading to other parts of the body, or helping the immune system increase its effectiveness at eliminating cancer cells [19]. There are, mainly, three known categories of immunotherapy: immune response modifiers (cytokines), monoclonal antibodies[2] and vaccines[3]. The most commons cytokines are IL-2 and interferon-alpha (INF-α) [20]. IL-2 does not kill tumour cells directly like classical chemotherapy. Instead, IL-2 activates and stimulates the growth of immune cells, most importantly T-cells[4], but also Natural Killer (NK) cells, both of which are capable of destroying cancer cells directly. The main role of ACI is that the T-cells are collected from a patient and grown in the laboratory. This increases the number of T-cells that are able to kill cancer cells or fight infections. These T-cells are given back to the patient to help the immune system to fight disease. This can be done in two ways, either by (i) a lymphokine-activated killer cell therapy (LAK therapy), or a tumour infiltrating lymphocyte therapy (TIL) [10] (see Fig. 1). However, we should mention that the common side-effects of IL-2 treatment include weight gain and low blood pressure, which can be treated with other medications [29,35].

Chemotherapy and radiotherapy are also common cancer therapies that have developed to fight cancer [20]. The basic idea behind chemotherapy is to kill cancerous cells faster than healthy cells, while radiotherapy uses radiation to kill cancerous cells. Immunotherapy is used as a maintenance therapy following a combination of chemotherapy or radiotherapy, and in some circumstances it is used as a single agent to treat cancer [5,6]. The combination is due to the fact that the chemotherapy treatment kills both cancerous and healthy cells and therefore it depletes the patient's immune system, making the patient prone to dangerous infections. For this and other reasons, it is desirable to strengthen the immune system after an immune-depleting course of chemotherapy. Additionally, recruiting body's own defense to fight cancer can be a powerful treatment strategy. Therefore, maintaining a strong immune system, by combining immunotherapy and chemotherapy, may be essential to successfully fight the cancer. However, the query now is how to most effectively combine cancer immunotherapy and chemotherapy?

Clearly, the interactions between tumour cells and immune system are very complex and need sophisticated models to describe such interactions. Several mathematical models have been proposed to describe the dynamics of tumour and

[2] Monoclonal antibodies: a type of immunotherapy, are made in the laboratory. Monoclonal antibodies may be used alone, or they may have an attached drug or radioactive material.

[3] Cancer vaccines, another type of immunotherapy, stimulate the bodys immune system to destroy cancer cells.

[4] T-cell: A type of white blood cell that is of key importance to the immune system and is at the core of adaptive immunity, the system that tailors the body's immune response to specific pathogens. The T-cells are like soldiers who search out and destroy the targeted invaders.

immune system over time (see e.g. [2,3,25,34]). In 1985, De Boer et al. [9] suggested a mathematical model which contained eleven *ordinary differential equations* (ODEs) with five algebraic equations to describe anti-tumour response with IL-2 taken into account. A simple version of this model is proposed by Kirschner and Panetta [17], which is based on three ODEs. Recently, in [30], the authors adopted a predator-prey formulation of the tumour immunity problem as a battle between immune cells and tumour cells (predators and prey, respectively). The time-delay was taken into account in order to achieve a better compatibility with reality [31,40]. Many research papers have been published in mathematical modeling of the interactions between tumour cells and immune cells, tumour cells and normal cells alone, or tumour cells and chemotherapy treatment; See e.g. [7,17,33,37].

Of course, there exists many research papers on delay differential models in biology and biomedicine, but only a few papers study such models in the framework of optimal control theory. The goal of this paper is to model mathematically, analyze and explore computationally potentially optimal ways to combine immuno-chemotherapy treatment strategies that can minimize a tumour while maximizing the strength of the immune system, with minimal toxicity to the patient. We formulate and analyze a delay differential model describing immune response and tumour cells under the influence of immunotherapy and the combinations of immuno-chemotherapy. Tme-delay is taken into account in order to achieve a better compatibility with reality, which exists when activated T-cells produce IL-2 and for immune system develop suitable response. We also aim to solve the optimal control problem to find the optimal control variables and identify the best treatment strategy.

The organization of this paper is as follows: in Section 2, we present a mathematical model governed by a system of Delay Differential Equations (DDEs) that includes treatment terms which represent an external source of the effectors cells by ACI and an external input of IL-2. We then extend the model to include chemotherapy and study the non-negativity of solutions of the system. In Section 3, we investigate the stability of the drug-free steady states (in the absence of chemotherapy) and existence of Hopf-bifurcation. In Section 4, we solve the optimal control problem governed by DDEs with two control variables. Existence of the solution and optimality conditions are also discussed. Numerical simulations for different weights in the objective are presented in Section 5, to verify the obtained results. Finally, we give concluding remarks in Section 6.

2. Development of the model

Mathematical models provide biologists and clinicians with the tools that may guide efforts to clarify fundamental mechanisms of cancer progress and improve current strategies of stimulate the development of new ones. A number of mathematical models, based on Marchuk's model [24] of antiviral immune response, have been developed to describe the dynamics of tumour-immune system. In our knowledge, the first attempts to consider the effects of immunotherapy within an appropriate ODEs model was made by Kirschner and Panetta in [17]. They studied the immunotherapy based on the use of IL-2 together with ACI by introducing some terms in the dynamical systems. Consider the three populations: $E(t)$, the activated immune-system cells (commonly called effector cells) such as cytotoxic T-cells, macrophages, and NK cells that are cytotoxic to the tumour cells; $T(t)$, the tumour cells; and $I_L(t)$, the concentration of IL-2 in single tumour-site compartment (See Fig. 1). The proposed model labeling the interaction between the effector cells, tumour cells, and the cytokine (IL-2) takes the form

$$\begin{aligned}
\frac{dE(t)}{dt} &= \mu T(t) - \delta E(t) + \frac{\rho_1 E(t-\tau_1) I_L(t-\tau_1)}{\eta_1 + I_L(t)} + \sigma_1,\\
\frac{dT(t)}{dt} &= \alpha_1 T(t)(1-\beta_1 T(t)) - \frac{\rho_2 E(t-\tau_2) T(t-\tau_2)}{\eta_2 + T(t)},\\
\frac{dI_L(t)}{dt} &= \frac{\rho_3 E(t) T(t)}{\eta_3 + T(t)} - b I_L(t) + \sigma_2.
\end{aligned} \tag{1}$$

In the first equation, the effector cells grow due to the direct presence of the tumour, given by the term μT, where μ is the antigenicity of the tumour. They are also stimulated by IL-2 that is produced by effector cells in an autocrine and paracrine manner $\frac{\rho_1 E(t-\tau_1) I_L(t-\tau_1)}{\eta_1 + I_L(t)}$, where ρ_1 is the rate at which the effector cells grow and η_1 is the half saturation constant[5] (the concentration supporting half the maximum rate). $\delta E(t)$ gives the natural decay of the effector cells. $\sigma_1 \geq 0$ is a treatment term that represents the external source of the effector cells such as ACI. There is a time-lag, τ_1, between the production of interleukin-2 by activated T-cells and the effector cell stimulation from treatment with IL-2. Hence, a discrete time-delay $\tau_1 \geq 0$ is being inserted to the third term of the first equation of the system. To ease the analysis, we ignored the time-delay in the denominator, due to the fact that $I_L(t^* - \tau_1) = I_L(t^*)$ and $E(t^*) = E_{max}$ (the maximum or saturated value) when $t^* \to \infty$.

The second equation represents the rate of change of the tumour cells which follows a logistic growth term $\alpha_1(1-\beta_1 T(t))$. The loss of tumour cells is denoted by an immune-effector cell interaction at rate ρ_2, modeled also by Michaelis–Menten kinetics to indicate the limited immune response to tumour, $\frac{\rho_2 E(t-\tau_2) T(t-\tau_2)}{\eta_2 + T(t)}$, η_2 is the half saturation constant. $\tau_2 \geq 0$ is the time required for the immune system to develop suitable response. (To ease the analysis, we also ignore the time-delay in the denominator.)

[5] Half saturation constant is defined as the substrate concentration at which growth $E(t)$ is occurring at $\frac{1}{2} E_{max}$.

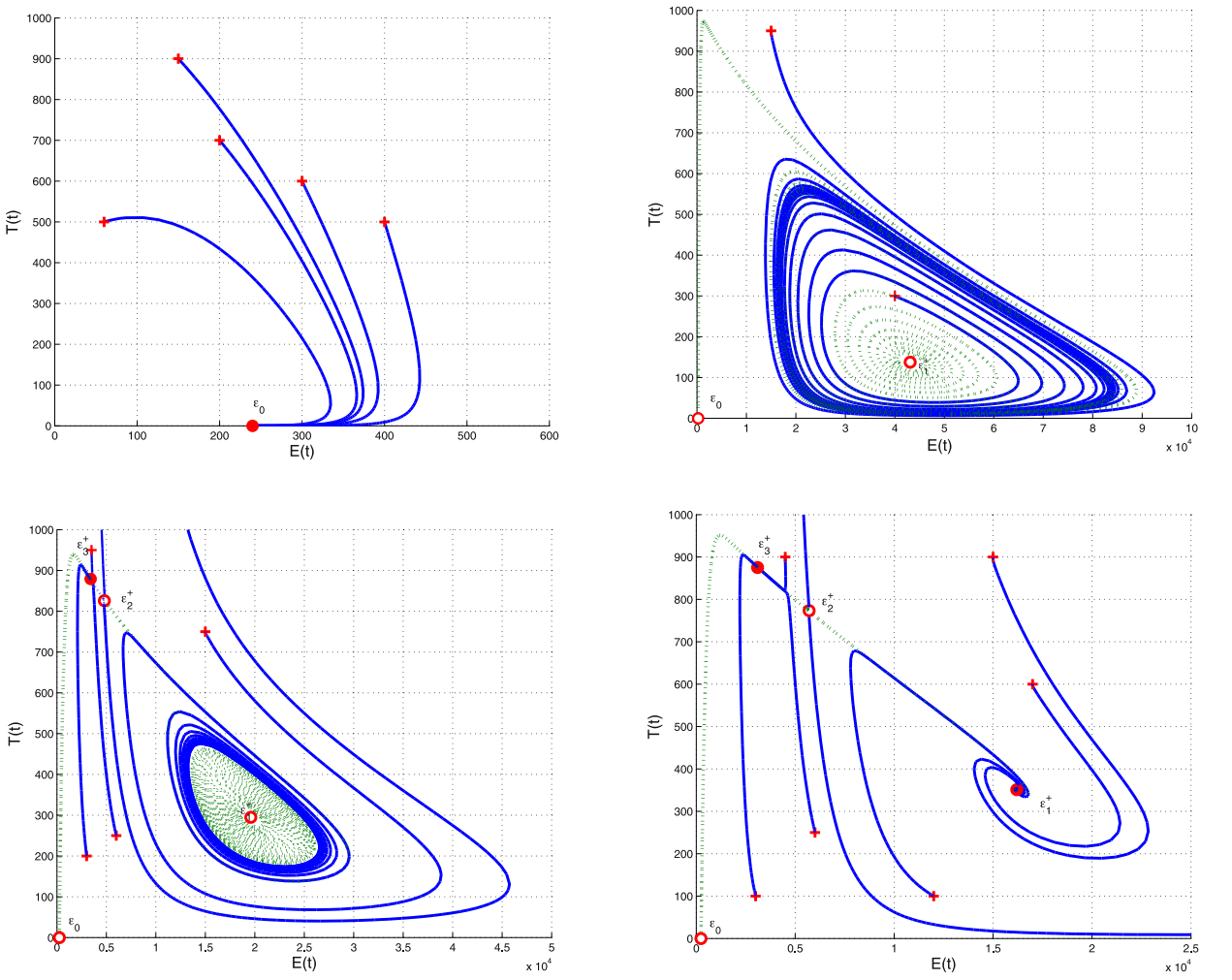

Fig. 2. Shows (from top to bottom and left to right) different steady states of model (1): tumour-free steady state $\mathcal{E}_0$ (with $\alpha_1 = 1, \rho_2 = 5 \times 10^{-3}, \tau = 0.3$), low persistent-tumour steady state $\mathcal{E}_1^+$ (with $\alpha_1 = 1, \rho_2 = 2 \times 10^{-5}, \tau = 0.3$), medium persistent-tumour steady state $\mathcal{E}_2^+$ (with $\alpha_1 = 0.5, \rho_2 = 1.8 \times 10^{-5}, \tau = 0.3$), and high persistent-tumour steady state $\mathcal{E}_3^+$ (with $\alpha_1 = 1, \rho_2 = 4 \times 10^{-5}, \tau = 0.5$). The stable steady states are [•], unstable steady states are [◦], stable manifold is [− − −] and initial conditions are [+], with external immunotherapy doses $\sigma_1 = 0.4$, $\sigma_2 = 0.1$ and parameters given in the table. For a particular set of parameters, there are up to four steady states, in the absence of treatments. It is possible that the tumour will result in either an equilibrium with (dormancy) or escape from the immune system.

The third equation represents the rate of change for the concentration of IL-2. Its source is the effector cells that are stimulated by interaction with the tumour and also has Michaelis–Menten kinetics to account for the self-limiting production of IL-2 and is represented by $\frac{\rho_3 E(t)T(t)}{\eta_3 + T(t)}$, ρ_3 being the production rate of IL-2 and η_3 a half saturation constant. b represents loss/degraded rate of IL-2 and $\sigma_2 \geq 0$ is a treatment term that represents an external input of IL-2 into the system. One meaning and parameter values of this model are described in Table 1.

According to the values of σ_1 and σ_2, there are up to four possible cases of external immunotherapy treatments: (i) no-treatment case ($\sigma_1 = \sigma_2 = 0$); (ii) adoptive cellular immunotherapy case ($\sigma_1 > 0$, $\sigma_2 = 0$); (iii) Interleukin-2 case ($\sigma_1 = 0, \sigma_2 > 0$); (iv) and immunotherapy with both effector cells and IL-2 ($\sigma_1 > 0$ and $\sigma_2 > 0$). For a particular set of parameters, there are up to four (stable and unstable) steady states: tumour-free, low-persistent, medium-persistent or high-persistent steady state. It is possible that the tumour will result in either an equilibrium with (dormancy) or escape from the immune system (See Fig. 2).

Remark 1. System (1) is an example of *stiff*[6] model [32], and needs a special care in the analysis and numerical treatment. Furthermore, the state variables of these types of models are very sensitive to small perturbations (or changes) in the parameters that occur in the model. To ease the analysis of numerical treatments and stability of the steady states with

[6] One definition of the stiffness is that the global accuracy of the numerical solution is determined by stability rather than local error and implicit methods are more appropriate for it.

meaningful parameters with less sensitive (or robust) model, we may need to non-dimensionalize the model by re-scaling the parameters and variables; See [17]. That is, without scaling, or inappropriate scalings, the numerical routines used to solve these equations will fail. This is due to very large changes in some of the variables over very short ranges of time.

Remark 2. The formulation the problem is restricted to discrete time-delays. However, 'distributed' time-delays, if they are of interest, can be approximated by a sufficiently large number of discrete time-delays.

Of course, to solve system (1), we have to provide positive initial conditions: $E(0) = E_0,\ T(0) = T_0$ and $L_L(0) = I_0,\ E(t) = \psi_1(t),\quad T(t) = \psi_2(t)$ for all $t \in [-\tau_*, 0]$, where $\psi_1(t)$ and $\psi_2(t)$ are smooth functions in $[-\tau_*, 0]$, where $\tau_* = \max\{\tau_1, \tau_2\}$. Next, we study the model with additional (presence) of chemotherapy treatments.

2.1. Immuno-chemotherapy model

To add chemotherapy treatment into the immunotherapy model (1), we should consider two extra variables namely the amount of chemotherapy, $U(t)$ and normal cells, $N(t)$ [6,8]. We also assume a homogeneity of the tumour cells and asynchronous tumour-drug interaction [36]. The modified model is

$$\begin{aligned}
\frac{dE(t)}{dt} &= \mu T(t) - \delta E(t) + \frac{\rho_1 E(t-\tau_1) I_L(t-\tau_1)}{\eta_1 + I_L(t)} + w(t)\sigma_1 - \mathcal{F}_1(U)E(t),\\
\frac{dT(t)}{dt} &= \alpha_1 T(t)(1-\beta_1 T(t)) - \frac{\rho_2 E(t-\tau_2) T(t-\tau_2)}{\eta_2 + T(t)} - c_1 N(t) T(t) - \mathcal{F}_2(U))T(t),\\
\frac{dI_L(t)}{dt} &= \frac{\rho_3 E(t) T(t)}{\eta_3 + T(t)} - b I_L(t) + \sigma_2,\\
\frac{dN(t)}{dt} &= \alpha_2 N(t)(1-\beta_2 N(t)) - c_2 T(t) N(t) - \mathcal{F}_3(U) N(t),\\
\frac{dU(t)}{dt} &= v(t) - d_1 U(t).
\end{aligned} \tag{2}$$

We assume that the drug kills all types of cells, but that the killing rate differs for each type of cells, such that $\mathcal{F}_i(U) = a_i(1-e^{-U}),\ i = 1, 2, 3,$ represents the fraction cells killed due to a given amount of drug, $U(t)$, at the tumour site, where a_i, are the different response coefficients. We assume that chemotherapy has no effect on IL-2. $v(t) > 0$ and $w(t) > 0$ represent the amounts of doses that are injected into the system, while d_1 is the decay rate of the drug once it is injected. In this case, the quantity that we should control is $v(t)$. The tumour cells and normal cells are modelled by a logistic growth law, with parameters α_i representing the growth rate of two types of cells: $i = 1$ identifies the parameter associated with tumour, and $i = 2$ identifies the one associated with the normal tissue, β_1 and β_2 are the reciprocal carrying capacities of tumour cells and host cells respectively. The two terms $-c_1 NT$ and $-c_2 NT$ represent the competition between the tumour and normal cells. To ease the analysis, we assume that $\tau_1 = \tau_2 = \tau$.

2.2. Non-negativity of the solutions

To prove the non-negativity of the solutions of model (2), let $\mathcal{C} = \mathcal{C}([-\tau, 0], \mathbb{R}^5)$ be the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^5$ with topological uniform convergence. It is easy to show that there exists a unique solution $[E, T, I_L, N, U]^T$ of system (2) with initial data $(E_0, T_0, I_0, N_0, U_0) \in \mathcal{C}$. For biological reasons, we assume that the initial data of system (2) satisfy $E_0 \geq 0,\ T_0 \geq 0,\ I_0 \geq 0,\ N_0 \geq 0,\ U_0 \geq 0$. We rewrite the system Eq. (2) in a vector form by setting [1]

$$x(t) = \begin{bmatrix} E(t) & T(t) & I_L(t) & N(t) & U(t) \end{bmatrix}^T \in \mathbb{R}^5_{+0}, F(t) = \begin{pmatrix} -\delta + \frac{\rho_1 I_L(t-\tau)}{\eta_1 + I_L(t)} - a_1(1-e^{-U(t)}) \\ \alpha_1(1-\beta_1 T(t)) - \frac{\rho_2 E(t-\tau)}{\eta_2 + T(t)} - c_1 N(t) - a_2(1-e^{-U(t)}) \\ -b \\ \alpha_2(1-\beta_2 N(t)) - c_2 T(t) - a_3(1-e^{-U(t)}) \\ -d_1 \end{pmatrix},$$

where $F : C_+ \longrightarrow \mathbb{R}^5,\ x(0) \geq 0$ and $F \in \mathbf{C}^\infty(\mathbb{R}^5_{+0})$. Therefore, from system (2), we have

$$\dot{x}(t) \geq F(t)x(t), \tag{3}$$

where $\dot{} \equiv \frac{d}{dt}$. From system (3) and using [41, Lemma 4], it is easy to prove that

$$x(t) \geq x(0) \exp\left(\int_0^t F(s)x(s)ds\right) > 0. \tag{4}$$

Therefore, for positive initials $x(0) > 0$ the solutions of (2) are positive $x(t) \in \mathbb{R}^5_{+0}$, for all $t > 0$. We may refer to [4,38], for more details and discussions about the nonnegativity of the solutions of initial value problems.

3. Drug-free steady states and stability analysis

In this Section, we study the qualitative bahaviours of the drug-free model. Stability of the steady states and bifurcation analysis for the parameter τ which plays an effective role in the model, are important in studying tumour behaviour for healthy and unhealthy states. To study the stability of the steady states, we linearize system around the steady states and find the Jacobian matrices. Based on the theory of differential equations, the stability of the steady states is investigated, where $\det(Jacobian) = 0$. If all the eigenvalues of the Jacobian matrix have negative real parts, then the steady state is locally asymptotically stable. On the other hand, if at least one of the eigenvalues has positive real part, then the steady state is unstable.

In the absence of chemotherapy drug, we put $U(t) = 0$ and $w(t) = 1$ in model (2). The modified model has then two types of steady states:

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

$$\mathcal{E}_0 = [E_*, 0, I_{L*}, N_*], \tag{5}$$

where

$$E_* = \frac{\sigma_1(b\eta_1 + \sigma_2)}{(b\eta_1 + \sigma_2)\delta - \rho_1\sigma_2} > 0, \quad I_{L*} = \frac{\sigma_2}{b} > 0, \quad N_* = \frac{1}{\beta_2} > 0.$$

(ii) Persistent-tumour steady state(s)

$$\mathcal{E}^+ = [E^*, T^*, I_L^*, N^*]^T, \tag{6}$$

where

$$\begin{aligned}
E^* &= \left[\frac{\eta_2 + T^*)}{\rho_2}\right]\left[\frac{\alpha_1\alpha_2\beta_2(1-\beta_1T^*) - c_1(\alpha_2 - c_2T^*)}{\alpha_2\beta_2}\right] > 0,\\
I_L^* &= \frac{1}{b}\left[\left(\frac{\rho_3T^*}{\eta_3 + T^*}\right)\left(\frac{\eta_2 + T^*}{\rho_2}\right)\left(\frac{\alpha_1\alpha_2\beta_2(1-\beta_1T^*) - c_1[\alpha_2 - c_2T^*]}{\alpha_2\beta_2}\right) + \sigma_2\right] > 0,\\
N^* &= \frac{\alpha_2 - c_2T^*}{\alpha_2\beta_2} > 0, \quad T^* = \frac{\delta E^*}{\mu} - \frac{\rho_1E^*I_L^*}{\mu(\eta_1 + I_L^*)} - \frac{\sigma_1}{\mu} > 0.
\end{aligned} \tag{7}$$

The Jacobian matrix for system (2) around the steady state $\mathcal{E}_0$ is then given by

$$J_{\mathcal{E}_0} = \begin{pmatrix}
-\delta + \frac{\rho_1 I_{L*}}{(\eta_1 + I_{L*})}e^{-\lambda\tau} & \mu & -\frac{\rho_1E_*I_{L*}}{(\eta_1+I_{L*})^2} + \frac{\rho_1E_*}{(\eta_1+I_{L*})}e^{-\lambda\tau} & 0\\
0 & \Pi_* & 0 & 0\\
0 & \frac{\rho_3E_*}{(\eta_3)} & -b & 0\\
0 & -c_2N_* & 0 & \alpha_2 - 2\alpha_2\beta_2N_*
\end{pmatrix}. \tag{8}$$

Here, $\Pi_* = \alpha_1 - 2 - c_1N_* - \frac{\rho_2E_*}{(\eta_2)}e^{-\lambda\tau}$; While Jacobian matrix of system (2) around the steady state $\mathcal{E}^+$ is given by

$$J_{\mathcal{E}^+} = \begin{pmatrix}
-\delta + \frac{\rho_1 I_L^*}{(\eta_1 + I_L^*)}e^{-\lambda\tau} & \mu & -\frac{\rho_1E^*I_L^*}{(\eta_1+I_L^*)^2} + \frac{\rho_1E^*}{(\eta_1+I_L^*)}e^{-\lambda\tau} & 0\\
\frac{-\rho_2T^*}{(\eta_2+T^*)}e^{-\lambda\tau} & \Pi^* & 0 & -c_1T^*\\
\frac{\rho_3T^*}{(\eta_3+T^*)} & -\frac{\rho_3E^*T^*}{(\eta_3+T^*)^2} + \frac{\rho_3E^*}{(\eta_3+T^*)} & -b & 0\\
0 & -c_2N^* & 0 & \alpha_2 - 2\alpha_2\beta_2N^* - c_2T^*
\end{pmatrix}, \tag{9}$$

where $\Pi^* = \alpha_1 - 2\alpha_1\beta_1T^* + \frac{\rho_2E^*T^*}{(\eta_2+T^*)^2} - c_1N^* - \frac{\rho_2E^*}{(\eta_2+T^*)}e^{-\lambda\tau}$.

Let us study stability of the persistent-tumour state(s) $\mathcal{E}^+$, given by Eq. (6), in which the tumour may result in either an equilibrium with 'dormancy' or 'escape' from the immune system. After some computations, the characteristic equation of (9) is

$$\varphi(\lambda, \tau) \equiv \lambda^4 + \lambda^3P_1 + \lambda^2P_2 + \lambda P_3 + P_4 + e^{-\lambda\tau}(\lambda^3Q_1 + \lambda^2Q_2 + \lambda Q_3 + Q_4) + e^{-2\lambda\tau}(\lambda^2K_1 + \lambda K_2 + K_3) = 0, \tag{10}$$

where

$$\begin{aligned}
&K_1 = -F_1F_4, \ K_2 = E_6F_1F_4 - E_4F_2F_3 - E_3F_2F_4 - F_1F_4b, \ K_3 = E_3E_6F_2F_4 + E_4E_6F_2F_3 + E_6F_1F_4b;\\
&P_1 = -E_2 - E_6 + b + \delta; \quad P_2 = -E_2b - E_6b - E_2\delta - E_6\delta + b\delta + E_1E_3 + E_2E_6 + E_5T^*c_1;\\
&P_3 = -(E_1E_2E_3 + E_1E_3E_6 - E_2E_6b - E_2E_6\delta + E_2b\delta + E_6b\delta - E_5T^*bc_1 - E_5T^*c_1\delta);\\
&P_4 = E_1E_2E_3E_6 + E_2E_6b\delta + E_5T^*bc_1\delta + E_1E_3E_5T^*c_1;\\
&Q_1 = F_4 - F_1; \quad Q_2 = F_4b - F_1b + F_4\delta - F_3\mu + E_2F_1 - E_3F_2 + E_6F_1 - E_6F_4;\\
&Q_3 = E_2E_3F_2 + E_1E_3F_4 + E_1E_4F_3 - E_2E_6F_1 + E_3E_6F_2 + E_2F_1b + E_6F_1b - E_6F_4b - E_6F_4\delta + E_6F_3\mu + F_4b\delta - F_3b\mu - E_5F_1T^*c_1;\\
&Q_4 = -E_2E_3E_6F_2 - E_1E_3E_6F_4 - E_1E_4E_6F_3 - E_2E_6F_1b - E_6F_4b\delta + E_6F_3b\mu - E_5F_1T^*bc_1 - E_3E_5F_2T^*c_1;
\end{aligned}$$

$$F_1=\frac{\rho_1 I_L^*}{(\eta_1+I_L^*)},\ F_2=\frac{\rho_1 E^*}{(\eta_1+I_L^*)},\quad F_3=\frac{-aT^*}{(\eta_2+T^*)},\quad F_4=\frac{\rho_2 E^*}{(\eta_2+T^*)},$$
$$E_1=\frac{\rho_1 E^* I_L^*}{(\eta_1+I_L^*)^2},\quad E_2=\alpha_1-2\alpha_1\beta_1 T^*+\frac{\rho_2 E^* T^*}{(\eta_2+T^*)^2}-c_1N^*,\quad E_3=\frac{\rho_3 T^*}{(\eta_3+T^*)},$$
$$E_4=-\frac{\rho_3 E^* T^*}{(\eta_3+T^*)^2}+\frac{\rho_3 E^*}{(\eta_3+T^*)},\quad E_5=-c_2N^*,\quad E_6=\alpha_2-2\alpha_2\beta_2N^*-c_2T^*.$$

When $\tau=0$, we have

$$\varphi(\lambda,0)=\lambda^4+(P_1+Q_1)\lambda^3+(P_2+Q_2+K_1)\lambda^2+(P_3+Q_3+K_2)\lambda+P_4+Q_4+K_3=0. \tag{11}$$

In this case, the steady state $\mathcal{E}^+$ is locally asymptotically stable if and only if all the roots of the characteristic Eq. (11) have negative real parts which depends on the numerical values of parameters that are shown in the numerical exploration. This is based on holding the following Routh–Hurwitz conditions:

$$(P_1+Q_1)>0,\quad (P_4+Q_4+K_3)>0,\quad D_1=(P_1+Q_1)(P_2+Q_2+K_1)-(P_3+Q_3+K_2)>0,$$
$$(P_3+Q_3+K_2)D_1>(P_1+Q_1)^2(P_4+Q_4+K_3).$$

The following Theorem provides the necessary and sufficient conditions for the persistent-tumour steady state $\mathcal{E}^+$, when $\tau>0$.

Theorem 1. *The persistent-tumour steady state $\mathcal{E}^+$ is asymptotically stable for all delay $\tau\geq 0$ if the real parts of all the roots of $\varphi(\lambda,\tau)=0$, described in (10), are negative.*

Proof. If we Multiply both sides of (10) by $e^{\lambda\tau}$, we get

$$e^{\lambda\tau}\left(\lambda^4+\lambda^3P_1+\lambda^2P_2+\lambda P_3+P_4\right)+(\lambda^3Q_1+\lambda^2Q_2+\lambda Q_3+Q_4)+e^{-\lambda\tau}(\lambda^2K_1+\lambda K_2+K_3)=0. \tag{12}$$

Assume that $\lambda=i\omega$, for all ω, and $\tau>0$, where $i=\sqrt{-1}$. Substituting $\lambda=i\omega$ $(\omega>0)$ into Eq. (12) and separating the real and imaginary parts of the equations, yields

$$(\omega^4-\omega^2P_2+P_4-K_1\omega^2+K_3)\cos(\omega\tau)+(\omega^3P_1+K_2\omega-\omega P_3)\sin(\omega\tau)=Q_2\omega^2-Q_4,$$
$$(K_2\omega-\omega^3P_1+\omega P_3)\cos(\omega\tau)+(\omega^4-\omega^2P_2+P_4+K_1\omega^2-K_3)\sin(\omega\tau)=Q_1\omega^3-Q_3\omega. \tag{13}$$

By computations, we obtain the following equations:

$$\cos(\omega\tau)=\frac{\omega^6T_1+\omega^4T_2+\omega^2T_3+T_4}{\omega^8+\omega^6S_1+\omega^4S_2+\omega^2S_3+S_4};\quad \sin(\omega\tau)=\frac{\omega^7Q_1+\omega^5R_1+\omega^3R_2+\omega R_3}{\omega^8+\omega^6S_1+\omega^4S_2+\omega^2S_3+S_4}. \tag{14}$$

where

$$T_1=Q_2-P_1Q_1,\ T_2=-Q_4+K_1Q_2-K_2Q_1+P_1Q_3-P_2Q_2+P_3Q_1,$$
$$T_3=-K_1Q_4+K_2Q_3-K_3Q_2+P_2Q_4-P_3Q_3+P_4Q_2,\quad T_4=-P_4Q_4+K_3Q_4,$$
$$R_1=-Q_3-K_1Q_1+P_1Q_2-P_2Q_1,$$
$$R_2=K_1Q_3-K_2Q_2+K_3Q_1-P_1Q_4+P_2Q_3-P_3Q_2+P_4Q_1,$$
$$R_3=K_2Q_4-K_3Q_3+P_3Q_4-P_4Q_3,$$
$$S_1=P_1^2-2P_2,\quad S_2=-2P_1P_3+P_2^2+2P_4-K_1^2,$$
$$S_3=2K_1K_3-K_2^2-2P_2P_4+P_3^2,\quad S_4=-K_3^2+P_4^2.$$

Using the property $sin^2(\omega\tau)+cos^2(\omega\tau)=1$ in Eq. (14), we have

$$\omega^{16}+\omega^{14}f_1+\omega^{12}f_2+\omega^{10}f_3+\omega^8f_4+\omega^6f_5+\omega^4f_6+\omega^2f_7+f_8=0 \tag{15}$$

where

$$f_1=2S_1-Q_1^2,\quad f_2=2S_2+S_1^2-(2Q_1R_1+T_1^2),\quad f_3=2S_1S_2+2S_3-(2Q_1R_2+R_1^2+2T_1T_2),$$
$$f_4=2S_4+2S_1S_3+S_2^2-(2Q_1R_3+2R_1R_2+2T_1T_3+T_2^2),$$
$$f_5=2S_1S_4+2S_2S_3-(2R_1R_3+R_2^2+2T_1T_4+2T_2T_3),$$
$$f_6=2S_2S_4+S_3^2-(2R_2R_3+2T_2T_4+T_3^2),\quad f_7=2S_3S_4-(2T_3T_4+R_3^2),\quad f_8=S_4^2-T_4^2.$$

Therefore, the stability condition of Theorem 1 holds if and only if Eq. (15) has no real positive roots (ω be pure imaginary).

Assume that $m=\omega^2$, then Eq. (15) takes the following form:

$$m^8+m^7f_1+m^6f_2+m^5f_3+m^4f_4+m^3f_5+m^2f_6+mf_7+f_8=0. \tag{16}$$

If $f_k<0$ (for all $k=1,\ldots,8$), then Eq. (15) has at least one positive root. However, If $f_k>0$ (for all $k=1,\ldots,8$), the roots m must be negative, accordingly ω will be pure imaginary, which completes the proof. □

3.1. Hopf bifurcation analysis

We consider the parameter τ as a bifurcation parameter, to find conditions for preservation of unstability or stability of the system. The bifurcation points help to know the necessary conditions for the coexistence of tumour cells population, effector cells population and IL-2 as an equilibrium or periodic oscillating state of system.

From Eq. (14), we have

$$\tau_k^{(j)} = \frac{1}{\omega_k}\left\{\arcsin\frac{\omega_k^7 Q_1 + \omega_k^5 R_1 + \omega_k^3 R_2 + \omega_k R_3}{\omega_k^8 + \omega_k^6 S_1 + \omega_k^4 S_2 + \omega_k^2 S_3 + S_4} + 2j\pi\right\} \tag{17}$$

where $k = 1, \ldots, 8$ and $j = 1, 2, 3, \ldots$, we choose $\tau_0 = \min(\tau_k^{(j)})$. To establish the occurrence of Hopf bifurcation at $\tau = \tau_0$, we need to show that

$$\Re\left(\frac{d\lambda}{d\tau}\right)_{\tau=\tau_0} \neq 0.$$

By differentiating Eq. (12) with respect to τ, we get

$$\frac{d\lambda}{d\tau} = \frac{\lambda e^{-\lambda\tau}\left(\lambda^2 K_1 + \lambda K_2 + K_3\right) - e^{\lambda\tau}(\lambda^5 + P_1\lambda^4 + P_2\lambda^3 + P_3\lambda^2 + \lambda P_4)}{\Theta_1 e^{\lambda\tau} + \Theta_2 \tau e^{\tau} + (3\lambda^2 Q_1 + 2\lambda Q_2 + Q_3) + (2\lambda K_1 + K_2)e^{-\lambda\tau} - \tau e^{-\lambda\tau}(\lambda^2 K_1 + \lambda K_2 + K_3)},$$

where $\Theta_1 = (4\lambda^3 + 3\lambda^2 P_1 + 2\lambda P_2 + P_3)$, $\quad \Theta_2 = \lambda^4 + \lambda^3 P_1 + \lambda^2 P_2 + \lambda P_3 + P_4$.

Then by combining Eq. (12), we have

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{(3\lambda^2 Q_1 + 2\lambda Q_2 + Q_3) + e^{\lambda\tau}(4\lambda^3 + 3\lambda^2 P_1 + 2\lambda P_2 + P_3) + (2\lambda K_1 + K_2)e^{-\lambda\tau}}{\lambda\left(e^{-\lambda\tau}(\lambda^2 K_1 + \lambda K_2 + K_3) - e^{\lambda\tau}(\lambda^4 + \lambda^3 P_1 + \lambda^2 P_2 + \lambda P_3 + P_4)\right)} - \frac{\tau}{\lambda}. \tag{18}$$

Substituting $\lambda = i\omega_0$ in Eq. (18), we have

$$\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_0} = \frac{d_1 + id_2}{d_3 + id_4} - \frac{\tau}{\lambda}$$

where

$$\begin{aligned}
d_1 =& (Q_3 - 3\omega_0^2 Q_1) + (P_3 - 3\omega_0^2 P_1 + K_2)\cos(\omega_0\tau_0) + (4\omega_0^3 - 2\omega_0 P_2 + 2\omega_0 K_1)\sin(\omega_0\tau_0),\\
d_2 =& 2\omega_0 Q_2 + (2\omega_0 P_2 - 4\omega_0^3 + 2\omega_0 K_1)\cos(\omega_0\tau_0) + (P_3 - 3\omega_0^2 P_1 - K_2)\sin(\omega_0\tau_0),\\
d_3 =& (\omega_0 P_4 + \omega_0^5 - \omega_0^3 P_2 + \omega_0 K_3 - \omega_0^3 K_1)\sin(\omega_0\tau_0) + (-\omega_0^2 K_2 - \omega_0^4 P_1 + \omega_0^2 P_3)\cos(\omega_0\tau_0),\\
d_4 =& (\omega_0 K_3 - \omega_0^3 K_1 - \omega_0 P_4 - \omega_0^5 + \omega_0^3 P_2)\omega_0\cos(\omega_0\tau_0) + (\omega_0^2 P_3 - \omega_0^4 P_1 + \omega_0^2 K_2)\sin(\omega_0\tau_0).
\end{aligned}$$

Thus

$$\Re\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_0} = \frac{d_1 d_3 + d_2 d_4}{d_3^2 + d_4^2}.$$

Notice that

$$sign\left(\Re\frac{d\lambda(t)}{d\tau}\right)\Big|_{\tau=\tau_0} = sign\left(\Re\left(\frac{d\lambda}{d\tau}\right)^{-1}\right)\Big|_{\tau=\tau_0}.$$

By summarizing the above analysis, we arrive at the following Remark:

Remark 3. The persistent-tumour steady state $\mathcal{E}^+$ of the system (2) without chemotherapy is asymptotically stable for $\tau^* \in [0, \tau_0)$ and it undergoes Hopf bifurcation at $\tau^* = \tau_0$.

4. Optimal control problem with immuno-chemotherapy

The formulation as an optimal control problem allows us to:

(i) investigate the dynamical system of interacting cell populations being affected by the (immuno-chemotherapy) treatments;
(ii) Optimize the application of the control such that the quantity of the treatments is optimized; and
(iii) Minimize the tumour size at some of end-time.

We aim to design an efficient treatment protocol, where we employ the tools of optimal control theory. This demonstrates how immunotherapy and chemotherapy might be combined for more effective treatment and to protect the patient from opportunistic infection, as well as fighting the cancer itself. Unlike chemotherapy, immunotherapy does not kill tumour cells directly, but it activates and stimulates the growth of immune cells, most importantly T-Cells, and NK Cells, which are capable of destroying cancer cells directly. Therefore, the main goal of combining immuno-chemotherapy treatment is to eradicate the tumour cells, with the minimum side-effect, while maintaining adequate amounts of healthy tissues.

Let us recall the immuno-chemotherapy model [30]

$$\begin{aligned}
\frac{dE(t)}{dt} &= \mu T(t) - \delta E(t) + \frac{\rho_1 E(t-\tau_1) I_L(t-\tau_1)}{\eta_1 + I_L(t)} + w(t)\sigma_1 - a_1(1-e^{-U})E(t),\\
\frac{dT(t)}{dt} &= \alpha_1 T(t)(1-\beta_1 T(t)) - \frac{\rho_2 E(t-\tau_2) T(t-\tau_2)}{\eta_2 + T(t)} - c_1 N(t) T(t) - a_2(1-e^{-U})T(t),\\
\frac{dI_L(t)}{dt} &= \frac{\rho_3 E(t) T(t)}{\eta_3 + T(t)} - b I_L(t) + \sigma_2,\\
\frac{dN(t)}{dt} &= \alpha_2 N(t)(1-\beta_2 N(t)) - c_2 T(t) N(t) - a_1(1-e^{-U})N(t),\\
\frac{dU(t)}{dt} &= v(t) - d_1 U(t).
\end{aligned} \tag{19}$$

The state vector of the modified model (19) of immuno-chemotherapy is given by

$$x = (E, T, I_L, N, U) \in \mathbb{R}^5.$$

In compact form, the system (19) can be written as the DDE

$$\begin{aligned}
x'(t) &= f(t, x(t), x(t-\tau), v(t), w(t)), \quad t \in [0, t_f]\\
x(t) &= \phi(t), \quad t \in [-\tau, 0].
\end{aligned} \tag{20}$$

The control functions $v(t)$ and $w(t)$ satisfy the following control constraints:

$$0 \le v(t) \le v_{max} < \infty, \quad \text{and} \quad 0 \le w(t) \le w_{max} < \infty, \quad t \in [0, t_f]. \tag{21}$$

The optimal control problem consists in determining control functions $(v(\cdot), w(\cdot)) \in L^\infty([0, t_f], \mathbb{R}^2)$ that *maximize* the objective functional

$$J_q(v, w) = \int_0^{t_f} \Big[E(t) + I_L(t) - T(t) - \frac{1}{2}(B_v v(t)^q + B_w w(t)^q)\Big] dt, \quad q = 1, 2. \tag{22}$$

subject to the DDEs (20) and the control constraints (21) Here, B_v and B_w are weight factors that describe the patient's acceptance level of chemotherapy $u(t)$ and the amount of external immunotherapy $w(t)$. For $q = 2$ we obtain the control-quadratic objective $J_2(v, w)$ of L^2 type which is often used in economic problems. We shall see in Section 5.3 that optimal controls are *continuous* functions. For $q = 1$, the objective $J_1(v, w)$ is control-affine and thus of L^1 type. In a biomedical framework, the L^1 objective may be more appropriate, since the control penalty in the objective is directly proportional to the doses administered.

The functions $v(t)$ and $w(t)$ are called admissible controls if they fulfill the inequality constraints (21). The set of all admissible controls is called the admissible set and we refer to it as

$$W = \{\, (v, w) \in L^\infty([0, t_f], \mathbb{R}^2) \mid (v(t), w(t)) \text{ satisfy (21)} \,\}. \tag{23}$$

The set of all admissible states X_{ad}, which satisfy the state equations and the state constraint, is called the set of admissible state. The optimal controls, v^* and w^*, are the functions that optimizes the objective function $J_q(v, w)$ (22).

4.1. Boundedness and existence of an optimal solution

To prove the existence of the optimal solution of (22), we use the results of Fleming and Rishel [11, Theorem 4.1, p. 68–69], and Lukes [23, Theorem 9.2.1, p. 182].

Theorem 2. *There exists an optimal solution* $(x^*, v^*, w^*) \in W^{1,\infty}([0, t_f], \mathbb{R}^5) \times L^\infty([0, t_f], \mathbb{R}^2)$ *for the optimal control problem (20)–(22) such that*

$$J(v^*, w^*) = \max_{v, w \in W} J(v, w) \tag{24}$$

where $x^* = [E^*, T^*, I_L^*, N^*, U^*]^T$, *if the following conditions are satisfied:*

1. *The set of admissible states is nonempty.*
2. *The admissible control set W (23) is nonempty, convex and closed.*
3. *The right-hand side of the state system is bounded by a linear combination of the state and control variables.*

4. *The integrand,* $L(E,T,I_L,v,w)=\left(E(t)-T(t)+I_L(t)-\left[\frac{B_v}{2}[v(t)]^q+\frac{B_w}{2}[w(t)]^q\right]\right)$, *of the objective functional is a concave on* W *for* $q=1,2$.
5. *The exist constants* $h_2, h_3>0$ *such that* $L(E,T,I_L,v,w)\le h_2-h_3(|v|+|w|)^q$ *for* $q=1,2$.

Proof. In order to verify the above conditions, we should first prove the existence of the solution for system (19). Since $\frac{\rho_1 I_L(t)}{\eta+I_L(t)}<\rho_1$, $v_{max}<\infty$ and by neglecting the negative terms in the model, we have

$$\begin{aligned}
\frac{dE(t)}{dt}&<\sigma_1+\rho_1E(t-\tau),\\
\frac{dT(t)}{dt}&<\alpha_1T,\\
\frac{dI_L(t)}{dt}&<\sigma_2+\rho_3E(t),\\
\frac{dN(t)}{dt}&<\alpha_2N,\\
\frac{dU(t)}{dt}&<v_{max}.
\end{aligned}\tag{25}$$

System (25) can be rewritten in the vector form as follows:

$$\begin{pmatrix}E(t)\\T(t)\\I_L(t)\\N(t)\\U(t)\end{pmatrix}'<\begin{pmatrix}0&0&0&0&0\\0&\alpha_1&0&0&0\\\rho_3&0&0&0&0\\0&0&0&\alpha_2&0\\0&0&0&0&0\end{pmatrix}\begin{pmatrix}E(t)\\T(t)\\I_L(t)\\N(t)\\U(t)\end{pmatrix}+\begin{pmatrix}\rho_1&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{pmatrix}\begin{pmatrix}E(t-\tau)\\T(t-\tau)\\I_L(t-\tau)\\N(t-\tau)\\U(t-\tau)\end{pmatrix}+\begin{pmatrix}\sigma_1\\0\\\sigma_2\\0\\v_{max}\end{pmatrix}$$

where $'=d/dt$. This system is linear in finite time with bounded coefficients. Then the solutions of this linear system are uniformly bounded. Therefore, the solutions of the nonlinear system (19) are bounded and exist [23]. Hence, condition one is satisfied.

Clearly, the second condition is satisfied by the definition of W. System (19) is bilinear in the control variables v, w and can be rewritten as

$$f(t,x(t),x(t-\tau),v,w)=\alpha(t,x)+\beta_1(t,x(t-\tau))+\sigma_1+\sigma_2+v+w\tag{26}$$

where $x(t)=[E(t),T(t),I_L(t),N(t),U(t)]^T$, $x(t-\tau)=[E(t-\tau),T(t-\tau),N(t-\tau),U(t-\tau)]^T$, α and β_1 are the vector valued functions of $x(t)$ and $x(t-\tau)$, respectively. The solutions are bounded, and we have

$$|f(t,x(t),x(t-\tau),v,w)|\le|M_1x(t)|+|M_2x(t-\tau)|+|M_3|+|M_4|+|M_5|\le h_1|x|+|\sigma_1|+|\sigma_2|+|v|+|w|$$

where h_1 depends on the coefficients of the system, and

$$M_1=\begin{pmatrix}0&0&0&0&0\\0&\alpha_1&0&0&0\\\rho_3&0&0&0&0\\0&0&0&\alpha_2&0\\0&0&0&0&0\end{pmatrix},\quad M_2=\begin{pmatrix}\rho_1&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{pmatrix},$$

$$M_3=\begin{pmatrix}\sigma_1\\0\\0\\0\\0\end{pmatrix},\quad M_4=\begin{pmatrix}0\\0\\\sigma_2\\0\\0\end{pmatrix},\quad M_5=\begin{pmatrix}0\\0\\0\\0\\v_{max}\end{pmatrix}.$$

We also note that the integrand of $J(v,w)$ is concave in W. Finally,

$$\begin{aligned}E(t)-T(t)+I_L(t)-\left[\frac{B_v}{2}[v(t)]^q+\frac{B_w}{2}[w(t)]^q\right]&<E(t)+I_L(t)-\left[\frac{B_v}{2}[v(t)]^q+\frac{B_w}{2}[w(t)]^q\right]\\&\le h_2-h_3(|v(t)|^q+|w(t)|^q),\end{aligned}$$

where h_2 depends on the upper bounds of $E(t)+I_L(t)$, and $h_3=[B_v+B_w]/2$. This completes the proof. □

We also conclude that there exist optimal control variables v^* and w^*.

4.2. Necessary optimality conditions

To establish the necessary conditions for the optimal solution of the optimal control problem (20)–(22), we can use a Pontryagin type Maximum Principle which has been derived by Göllmann et al. [13,14] for retarded optimal control problems with mixed control-state constraints.

To define the Hamiltonian function we introduce the state variable x_τ which is related to the state variable x by $x_\tau(t) = x(t-\tau)$. Then in view of the objective (22) the Hamiltonian is given by

$$H(x, x_\tau, \lambda, v, w) = E + I_L - T - 0.5(B_v v^q + B_w w^q) + \lambda f(x, x_\tau, v, w), \tag{27}$$

where $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5) \in \mathbb{R}^5$ is a row vector denoting the adjoint (costate) variable. Note that the formal variables N_τ and U_τ do not appear in the Hamiltonian.

To formulate the Maximum Principle, we need the indicator function $\chi_{[0,t_f-\tau]}$ of the interval $[0, t_f - \tau]$ defined by

$$\chi_{[0,t_f-\tau]}(t) = \begin{cases} 1 & \text{if } t \in [0, t_f - \tau], \\ 0 & \text{otherwise.} \end{cases}$$

Then the necessary optimality in Pontryagin's maximum principle [13,14] are given in the the following theorem:

Theorem 3. *Let $(x^*, v^*, w^*) \in W^{1,\infty}([0,t_f], \mathbb{R}^5) \times L^\infty([0,t_f], \mathbb{R}^2)$ be an optimal solution of (20)–(22), where $x^* = [E^*, T^*, I_L^*, N^*, U^*]^T$. Then there exists an adjoint state $\lambda \in W^{1,\infty}([0,t_f], \mathbb{R}^5)$ such that the following conditions are satisfied:*

1. *Adjoint equation and transversality condition*

$$\dot\lambda(t) = -\frac{\partial H}{\partial x}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial H}{\partial x_\tau}(t+\tau), \quad \lambda_1(t_f) = 0, \tag{28}$$

where $H(t)$ is defined by (27).

2. *Maximizing controls:*

$$\begin{aligned} &H(x^*(t), x_\tau^*(t), \lambda(t), v^*(t), w^*(t)) \\ &= \max_{v,w} \{H(x^*(t), x_\tau^*(t), \lambda(t), v, w) \mid 0 \le v \le v_{max}, 0 \le w \le w_{max}\}. \end{aligned} \tag{29}$$

When evaluating the adjoint equation (28), we have to take into account that there is no delay in the state variables N and U and thus the delayed variables N_τ and U_τ do not appear in the Hamiltonian (27). Then the adjoint equations read explicitly:

$$\begin{aligned}
\dot\lambda_1(t) &= -1 + \lambda_1(t)\Big[\delta + a_1(1 - e^{-U^*(t)})\Big] + \chi_{[0,t_f-\tau]}(t)\lambda_1(t+\tau)\Big[-\frac{\rho_1 I_L^*(t+\tau)}{\eta_1 + I_L^*(t+\tau)}\Big] \\
&\quad + \lambda_3(t)\Big[-\frac{\rho_3 T^*(t)}{\eta_3 + T^*(t)}\Big] + \chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)\Big[\frac{aT^*}{\eta_2 + T^*}\Big], \\
\dot\lambda_2(t) &= 1 - \mu\lambda_1(t) + \lambda_2(t)\Big[-\alpha_1 + 2\alpha_1\beta T^*(t) + c_1 N^*(t) - \frac{\rho_2 E^*(t) T^*(t)}{(\eta_3 + T^*(t))^2} + a_2(1 - e^{-U^*(t)})\Big] \\
&\quad + \lambda_3(t)\Big[\frac{\rho_3 E^*(t) T^*(t)}{(\eta + T*(t))^2} - \frac{\rho_3 E^*(t)}{\eta_3 + T^*(t)}\Big] + \lambda_4(t) c_2 N^*(t) \\
&\quad + \chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)\Big[\frac{\rho_2 E^*(t+\tau)}{\eta_2 + T^*(t+\tau)}\Big] \\
\dot\lambda_3(t) &= -1 + \lambda_1(t)\Big[\frac{\rho_1 E^*(t) I_L^*(t)}{(\eta_1 + I_L^*(t))^2}\Big] + \chi_{[0,t_f-\tau]}(t)\lambda_1(t+\tau)\Big[-\frac{\rho_1 E^*(t+\tau)}{(\eta_1 + I_L^*(t+\tau))}\Big] + b\lambda_3(t), \\
\dot\lambda_4(t) &= \lambda_2(t) c_1 T^*(t) + \lambda_4(t)\Big[-\alpha_2 + 2\alpha_2\beta_2 N^*(t) + c_2 T^*(t) + a_3(1 - e^{-U^*(t)})\Big] - \gamma, \\
\dot\lambda_5(t) &= \lambda_1(t) a_1 e^{-U^*(t)} E^*(t) + \lambda_2(t) a_2 e^{-U^*(t)} T^*(t) + \lambda_4(t) a_3 e^{-U^*(t)} N^*(t) + \lambda_5(t) d_1.
\end{aligned} \tag{30}$$

It is important to note that one is not obliged to integrate the advanced adjoint equations numerically, because a rather precise approximation of adjoint functions can be obtained from the Lagrange multipliers of the discretized control problem [13,14]. The state equations for the optimal states and controls (x^*, v^*, w^*) are given in (19). The initial conditions for the state variable $x = (E, I_L, T, N, U)$ are given by

$$x^*(t) = x_0(t) \quad \forall\, t \in [-\tau, 0]. \tag{31}$$

For the evaluation of the maximum condition (29) we consider the two cases $q = 2$ and $q = 1$ in the objective (22). In the control-quadratic case $q = 2$, we first determine the so-called free controls v_f and w_f which are defined by the equations $H_v[t] = -B_v v(t) + \lambda_5(t) = 0$ and $H_w[t] = -B_w w_f(t) + \lambda_1(t)\sigma_1 = 0$. This yields

$$v_f(t) = \lambda_5(t)/B_v, \quad w_f(t) = \lambda_1(t)\,\sigma_1/B_w\,. \tag{32}$$

Then the maximizing controls are obtained by projecting the free control $v_f(t)$ onto the interval $[0, v_{max}]$, resp., the free control $w_f(t)$ onto the interval $[0, w_{max}]$. This yields the controls

$$v^*(t) = \max\{0,\ \min\{v_{max}, v_f(t)\}\}, \quad w^*(t) = \max\{0,\ \min\{w_{max}, w_f(t)\}\}, \tag{33}$$

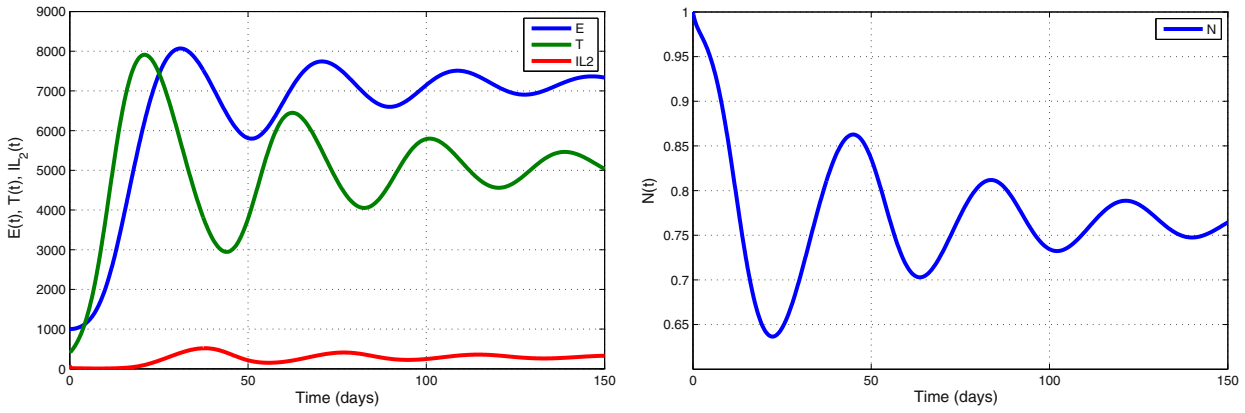

Fig. 3. Shows the numerical simulations of immuno-chemotherapy model (19) with drug-free (without control). The parameter values are given in Table 1. The parameter values of the external treatments $\sigma_1 = 0.4$ and $\sigma_2 = 0.1$.

In direct optimization methods, these formulas are used as a test of extremal solutions satisfying the necessary conditions. Namely, by computing the discrete values of the controls $v^*(t)$ and $w^*(t)$ directly and determining the adjoint variables a posteriori as Lagrange multipliers, the quantities in (33) must match with high accuracy.

The L^1 objective $J_1(v, w)$ in (22) must be handled in a different way. Here, the Hamiltonian (27) is affine in the control variables. Defining the *switching functions*

$$\phi_v(t) = H_v[t] = -0.5B_v + \lambda_5(t), \quad \phi_w(t) = H_w[t] = -0.5B_w + \lambda_1(t)\sigma_1, \tag{34}$$

the maximum condition (29) furnishes the control law

$$z^*(t) = \begin{cases} z_{max} & \text{if} \quad \phi_z(t) > 0 \\ 0 & \text{if} \quad \phi_z(t) < 0 \end{cases}, \quad z \in \{v, w\}. \tag{35}$$

The control $z \in \{v, w\}$ is called *bang-bang* in an interval $I_b \subset [0, t_f]$, if the switching function $\phi_z(t)$ has only isolated zeros on I_b. The control $z \in \{v, w\}$ is called *singular* on an interval $I_s \subset [0, t_f]$, if $\phi_z(t) = 0$ holds on I_s. For weights $B_v, B_w \leq 300$, our computations show that both controls are bang-bang. But for a larger weight B_v, we may also obtain singular arcs of the control v. In this case, the order of the singular arc is equal to 2 and thus we get a chattering junctions between a bang-bang arc and a singular arc [18,27], the example in [21] and Fig. 10.

5. Numerical solution of delayed control problem with weights in the objective

The optimal control problem with DDEs is now studied numerically to see the effect of the discrete time-delays on the system and combination of immune-chemotherapy treatments. To numerically solve the optimal control problem (20)–(22), we discretize the system and use the Applied Modeling Programming Language AMPL (cf. Fourer et al. [12]) to formulate the resulting *nonlinear programming problem* (NLP); see e.g. Göllmann and Maurer et al. [13–15]. AMPL can be linked to several optimization solvers. In particular, we use the Interior-Point Optimization Solver IPOPT; cf. Wächter, Biegler [39]. We work on a grid of $N = 1000 - 2000$ grid points with nodes $t_i = i \cdot h, h = t_f/N, i = 0, 1, \ldots, N$, and use either the implicit Euler method or the trapezoidal rule.

We choose a different set of parameter values (in stable and unstable regions). In the current simulations, we vary the three parameters σ_1, σ_2, ρ, τ, the rest of the parameters are given in Table 1. The parameter values of the external treatments are $\sigma_1 = 0.4$ and $\sigma_2 = 0.2$. We solve the optimality system to determine the optimal control situation (i.e., the drug strategy), and predict the evolution of the tumour cells, effector cells, and normal cells of each control strategy in 100 days.

Fig. 2 shows, for a particular set of parameters, that there are up to four steady states for the tumour-immune system model DDEs (1). The top left panel of the Figure shows the trajectories where there is a stable tumour-free equilibrium, while top right panel a limit cycle around the a persistent-steady state in addition to unstable tumour-free state. The bottom left panel displays the trajectories where there are three tumour-persistent equilibria (for which one of them is locally stable, one is stable limit cycles and one, and the third is unstable), and tumour-free equilibrium which is unstable. However, the bottom right panel shows the trajectories where there are three tumour-persistent equilibria (for which two of them are locally stable and one is unstable), and the tumour-free equilibrium which is unstable. The Figure shows that it is possible to get healthy steady state, equilibrium with dormancy or escape from the immune system. Fig. 3 displays the numerical simulations, for a particular set of parameters, of immuno-chemotherapy model (19) with drug-free (without control).

In the following computations, we choose the initial conditions and final time,

$$E(0) = 1000,\ T(0) = 400,\ I_L(0) = 100,\ N(0) = 0.9,\ U(0) = 0 \quad \text{and} \quad t_f = 100,$$

Table 1
Parameter definitions and estimations used in the manuscript.

Parameter	Description	Units	Value	Source
μ	Antigenicity of tumour	day^{-1}	0.103	[17]
ρ_1	Growth rate of effector cells	$cell^{-1}\ day^{-1}$	1	[17]
a_1	Killing rate of effector cells by chemotherapy	day^{-1}	0.65	
η_1	Half saturation constant	Volume	2×10^6	[17]
δ	Natural decay rate of effector cells	day^{-1}	0.08	[17]
a_2	Killing rate of tumour cells by chemotherapy	day^{-1}	0.45	
α_1	Growth rate of tumour cells	day^{-1}	0.28	[17]
c_1	Fractional (non)-ligand-transduced T-cell kill by N-cells.	$cell^{-1}day^{-1}$	1×10^{-4}	
β_1	1/carrying capacity of tumour cells	$cell^{-1}\ day^{-1}$	1×10^{-4}	[17]
ρ_2	Decay rate of tumour	day^{-1}	1.8	[17]
η_2	Half saturation constant	Volume	1×10^5	[17]
b	Natural decay rate of IL-2	day^{-1}	20	[17]
ρ_3	Growth rate of IL-2	day^{-1}	1	[17]
a_3	Killing rate of IL-2 cells	day^{-1}	2×10^{-2}	
$\sigma_i\ (i=1,2)$	External treatment terms	day^{-1}	[0,40]	[17]
β_2	1/carrying capacity of normal cells	day^{-1}	1	
η_3	Half saturation constant	Volume	1×10^3	[17]
α_2	Growth rate of normal cells	day^{-1}	1.2	
c_2	Normal cell inactivation rate by tumour cells	$cell^{-1}day^{-1}$	0.00005553	
a_3	Killing rate of normal cells by chemotherapy	day^{-1}	0.02	
d_1	Decay rate of the drug	day^{-1}	1	

and control bounds

$$v_{max} = w_{max} = 1.$$

The parameter values of the external treatments are

$$\sigma_1 = 40,\ \sigma_2 = 20.$$

We next provide numerical simulations for different wights B_v and B_w, that describe the patient's acceptance level of chemotherapy $u(t)$ and the amount of external immunotherapy $w(t)$, in the objectives $J_2(v,w)$ and $J_1(v,w)$.

5.1. Weights $B_v = B_w = 0$ and delay $\tau = 0$

Here we do not put a penalty on the control variables. The optimal immuno-therapy is $w^*(t) \equiv 0$ as expected. However, it is a bit surprising that the optimal chemotherapy is not $v^*(t) = 1$ but the bang-bang control

$$v^*(t) = \begin{cases} 1 & \text{for} \quad 0 \le t \le t_1, \\ 0 & \text{for} \quad t_1 < t \le t_f, \end{cases} \tag{36}$$

with a switch at $t_1 = 34.6$. The numerical results are

$$J_1(v^*, w^*) = 30001.1, \quad E^*(t_f) = 562.63, \quad T^*(t_f) = 220.44, \quad I_L^*(t_f) = 6.0191,$$
$$N^*(t_f) = 0.99165, \quad U^*(t_f) = 0.146 \cdot 10^{-8}.$$

The optimal trajectories, controls and switching functions are shown in Fig. 4. Note that the control law (35) is exactly satisfied. Moreover, one can show that second-order sufficient conditions in [26] are satisfied. In particular, the switching functions $\phi_v(t)$ and $\phi_w(t)$ satisfy the strict bang-bang property as can be seen from Fig. 4, bottom row (b), (c).

5.2. L^2 objective with weights $B_v = 100, B_w = 150$ and delay $\tau = 0$

We obtain the numerical results

$$J(v^*, w^*) = 21252.0,\ E(t_f) = 493.97,\ T(t_f) = 239.01,\ I_L(t_f) = 5.7210.$$

The control-quadratic objective implies that both controls $v^*(t)$ and $w^*(t)$ are *continuous*, also at the junction points with the control boundaries. The state trajectories and controls are displayed in Fig. 5. The chemotherapy control $v^*(t)$ looks like the bang-bang control (36), but in fact is a continuous control with a very steep transition between the control boundaries. The state trajectories are rather similar to those for $B_v = B_w = 0$ in Fig. 4.

In Fig. 6, it is demonstrated that both controls v^* and w^* satisfy the control law (33) involving the free controls v_f and w_f in (32).

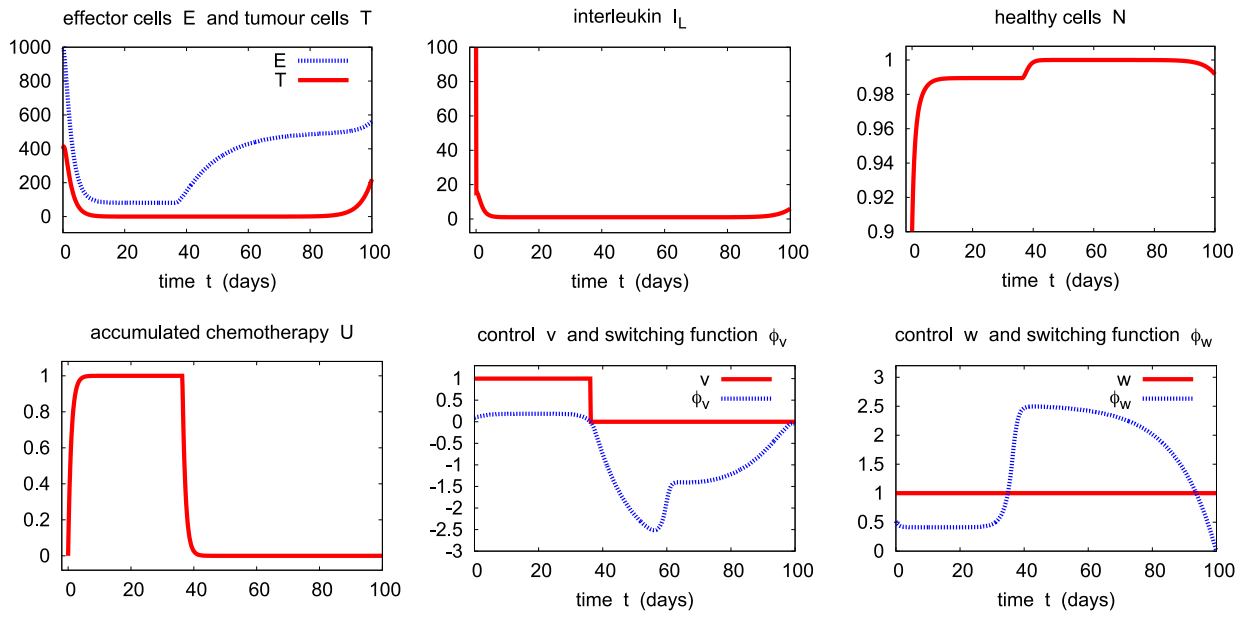

Fig. 4. L^1-objective $J_1(v,w)$ (22) with weights $B_v = B_w = 0$ and delay $\tau = 0$. *Top row*: (left) effector cells E and tumour cells T, (middle) interleukin I_L, (right) healthy cells N. *Bottom row*: (left) accumulated chemotherapy U, (middle) chemotherapy control v and scaled switching function ϕ_v satisfying the control law (35), (right)) immuno control w and scaled switching function ϕ_w satisfying the control law (35).

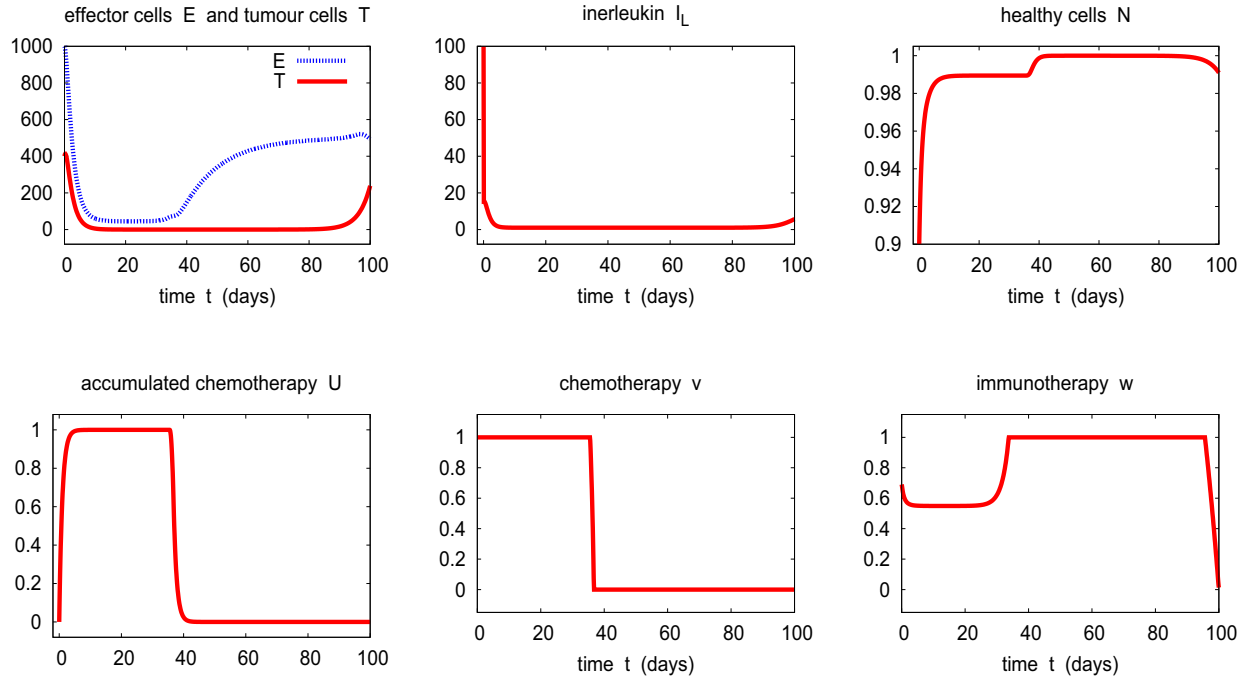

Fig. 5. L^2-objective $J_2(v,w)$ (22) with weights $B_v = 100, B_w = 150$ and delay $\tau = 0$. *Top row*: (left) effector cells E and tumour cells T, (middle) interleukin I_L, (right) healthy cells N. *Bottom row*: (left) accumulated chemotherapy U, (middle) chemotherapy control v, (right)) immuno control w.

5.3. L^1 *objective* $J_1(v,w)$ *(22) with weights* $B_v = 100, B_w = 150$*: comparison of controls for delays* $\tau = 0$ *and* $\tau = 5$

Both controls are bang-bang:

$$v^*(t) = \begin{Bmatrix} 1 & \text{for} & 0 \le t \le t_1, \\ 0 & \text{for} & t_1 < t \le t_f, \end{Bmatrix}, \quad w^*(t) = \begin{Bmatrix} 1 & \text{for} & 0 \le t \le t_2, \\ 0 & \text{for} & t_2 < t \le t_f, \end{Bmatrix} \tag{37}$$

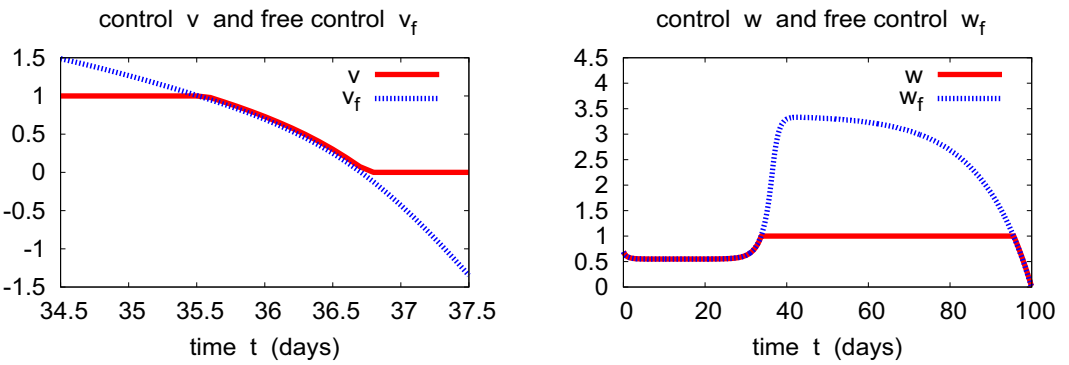

Fig. 6. L^2-objective $J_2(v,w)$ (22) with $q=2$ with weights $B_v=100, B_w=150$ and delay $\tau=0$. (left) control v and free control v_f satisfying the control law (33), (right) control w and free control w_f satisfying the control law (33).

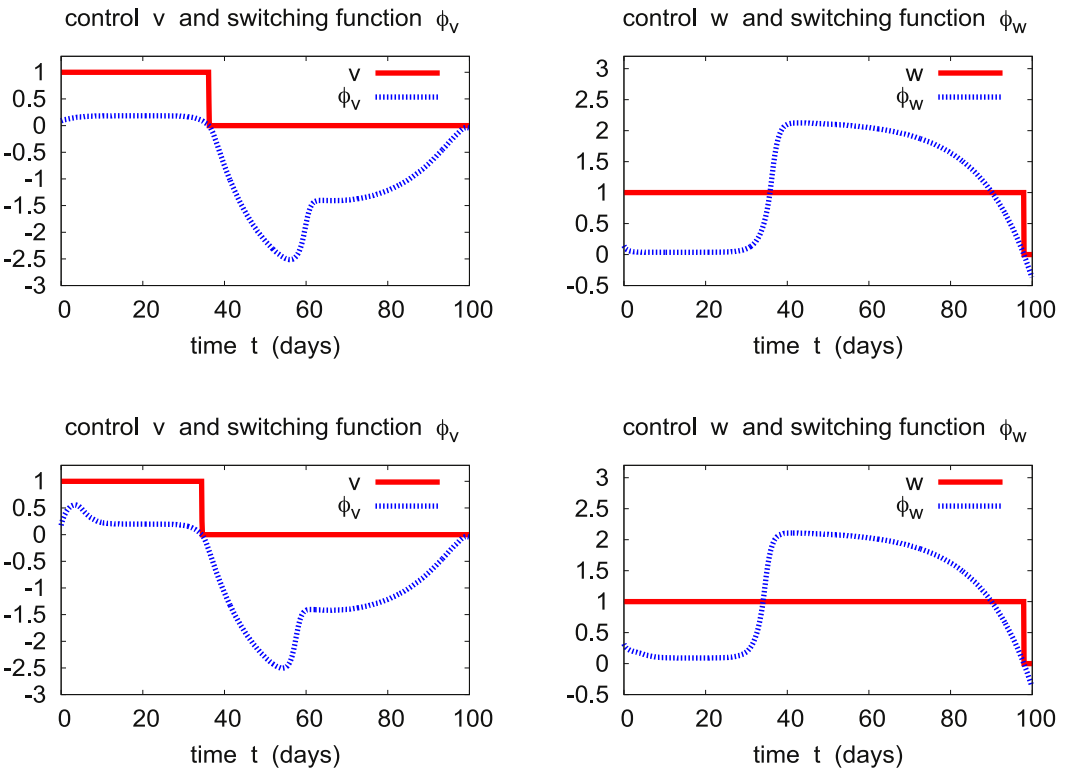

Fig. 7. L^1-objective $J_1(v,w)$ (22) with weights $B_v=100, B_w=150$: comparison of controls and switching functions for delays $\tau=0$ and $\tau=5$. *Top row*: Delay $\tau=0$: (left) control v and scaled switching function ϕ_v satisfying the control law (35), (right) control w and scaled switching function ϕ_w satisfying the control law (35). *Bottom row*: Delay $\tau=5$: (left) control v and scaled switching function ϕ_v satisfying the control law (35), (right) control w and scaled switching function ϕ_w satisfying the control law (35).

with switching times $t_1=36.2, t_2=97.9$ for $\tau=0$ and $t_1=34.5, t_2=98.0$ for $\tau=5$. Numerical results for the state variables are

$$\begin{array}{llll} \tau=0: & J_1(v^*,w^*)=20760.8, & E(t_f)=495.11, & T(t_f)=247.46, \quad I_L(t_f)=5.8663, \\ \tau=5: & J_1(v^*,w^*)=21638.5, & E(t_f)=493.15, & T(t_f)=244.52, \quad I_L(t_f)=5.7995. \end{array}$$

We have $N^*(t_f)\approx 1$ and $U^*(t_f)\approx 1$ for $\tau=0$ and $\tau=5$.

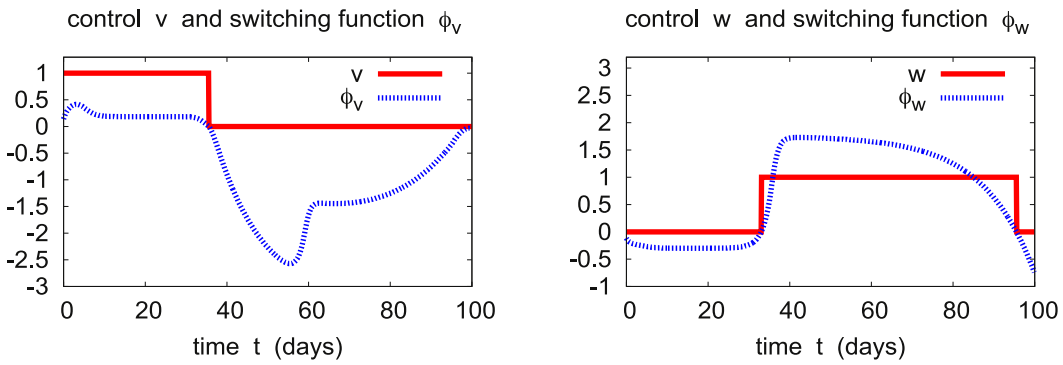

Fig. 8. L^1objective $J_1(v,w)$ (22) with weights $B_v = 100, B_w = 300$ and delay $\tau = 5$. (left) control v and scaled switching function ϕ_v satisfying the control law (35), (right) control w and scaled switching function ϕ_w satisfying the control law (35).

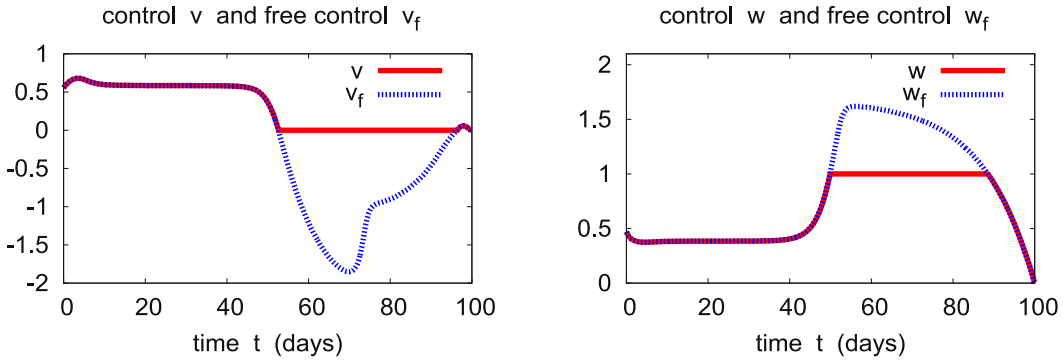

Fig. 9. L^2objective $J_2(v,w)$ (22) with weights $B_v = 1000, B_w = 300$ and delay $\tau = 5$. (left) control v and free control v_f (32) satisfying the control law (33), (right) control w and free control v_f (32) satisfying the control law (33).

5.4. L[1] objective $J_1(v,w)$ (22) with weights $B_v = 100, B_w = 300$ and delay $\tau = 5$

Both controls are bang-bang: $v^*(t)$ has only one switch at t_2 while $w^*(t)$ has two switches at t_1 and t_3 (See Fig. 8):

$$(v^*(t), w^*(t)) = \left\{ \begin{array}{lll} (0,1) & \text{for} & 0 \le t \le t_1, \\ (1,1) & \text{for} & t_1 < t \le t_2, \\ (0,1) & \text{for} & t_2 < t \le t_3, \\ (0,0) & \text{for} & t_3 < t \le t_f. \end{array} \right\}, \quad t_1 = 33.1,\ t_2 = 35.6,\ t_3 = 95.6. \tag{38}$$

Numerical results for the state variables

$$J(v^*, w^*) = 16061.2, \quad E(t_f) = 409.62, \quad T(t_f) = 213.67, \quad I_L(t_f) = 4.5705.$$

5.5. L[2] objective $J_2(v,w)$ and L[1] objective $J_1(v,w)$ for weights $B_v = 1000, B_w = 300$

Finally, we consider the rather large weights $B_v = 1000$ and $B_w = 300$. For the L^2 objective $J_2(v,w)$ and delay $\tau = 5$, we find the controls shown in Fig. 9. Despite the larger weights, the state trajectories are very similar to those for the weights $B_v = 100, B_w = 150$ and $\tau = 0$ in Fig. 5 and thus are not shown here. We get the numerical results:

$$J(v^*, w^*) = 4806.84, \quad E(t_f) = 428.45, \quad T(t_f) = 348.23, \quad I_L(t_f) = 6.4883.$$

Due to the large weight $B_v = 1000$, the control $v^*(t)$ does not attain anymore its upper bound $v_{max} = 1$. The control $v^*(t)$ has the same structure as for the weights $B_v = 100, B_w = 300$; See Fig. 5.

Now we consider the L^1 objective $J_1(v,w)$ (22). Here, we can expect that the $v^*(t)$ is no longer a simple bang-bang control but has singular arcs. Due to the pharmacological equation $\dot{U}(t) = v(t) - d_1 U(t)$, singular arcs have order two, i.e., the control v appears in the 4th derivative of the switching function for the first time. This implies that the junction between a bang-bang arc and a singular arc is a *chattering junction*; cf. [27] and the combination therapies of cancer treated in Ledzewicz, Maurer, Schättler [21]. Fig. 10 displays the controls for $\tau = 0$. One can recognize the chattering junctions.

Finally, Fig. 11 presents the evolution of system (30–34) before and after treatments, when $\tau = 7.82$. The parameters values are chosen in the stable region. We note that the presence of immuno-chemotherapy with optimal control, the effector

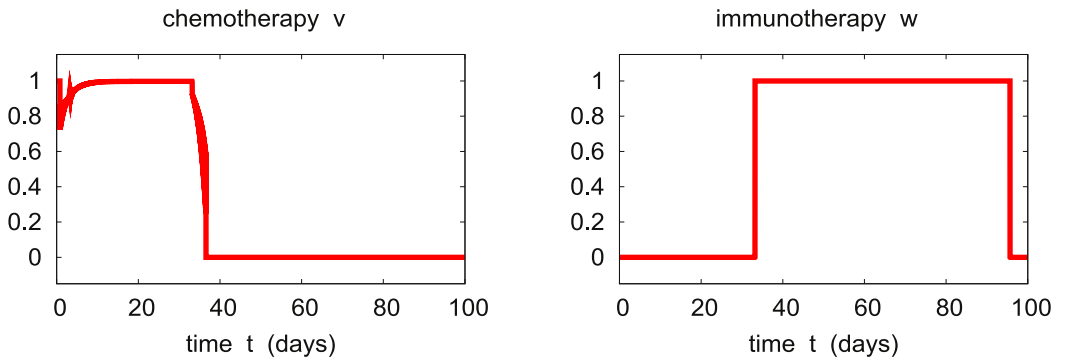

Fig. 10. L^1-objective $J_1(v, w)$ (22) with weights $B_v = 1000, B_w = 300$ and delay $\tau = 0$. (left) control v, (right) control w.

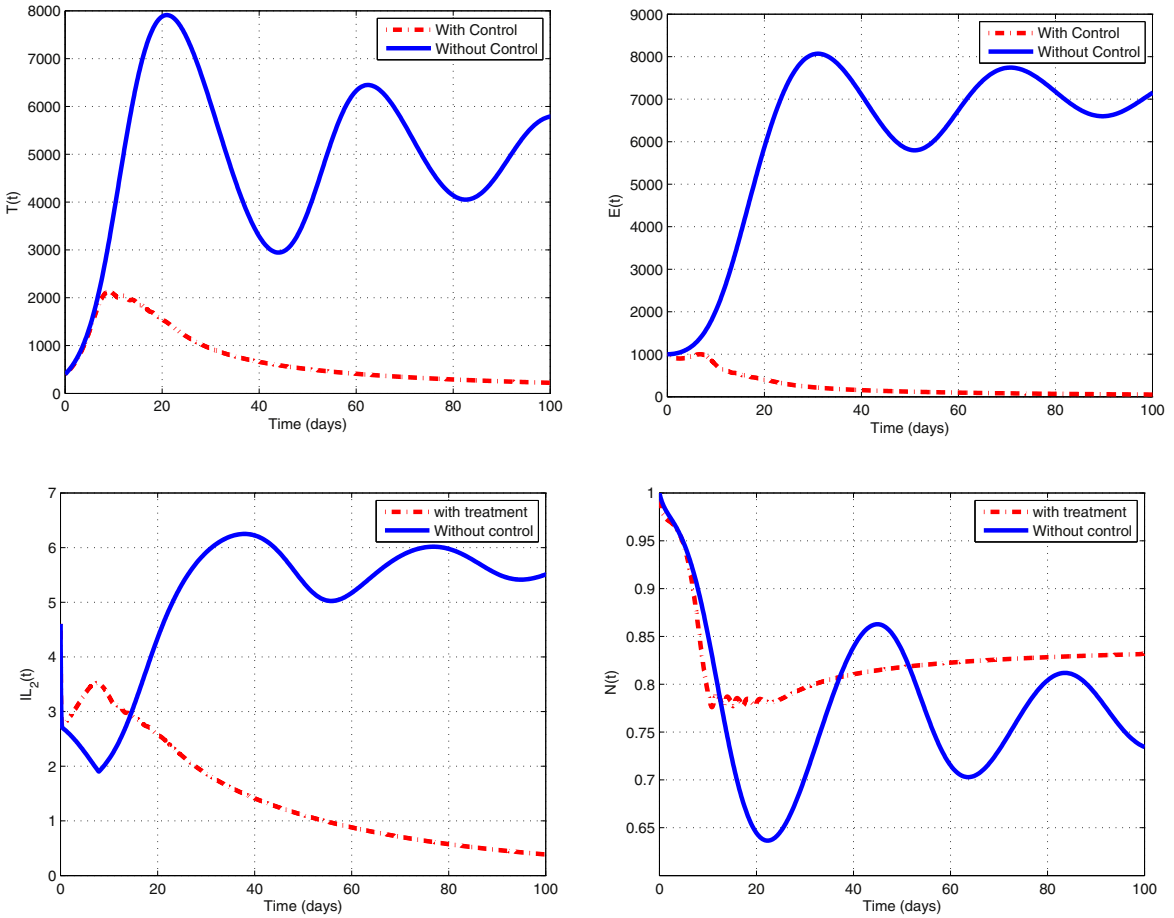

Fig. 11. Shows the numerical simulations of the optimal problem (20)–(22) with $\tau = 7.82$, in the stable region, before and after the treatments. The optimal treatment strategies reduce the tumour cells load and the immune cells approach to the normal levels in the end of time-interval.

cells population and IL-2 decrease gradually to the normal levels. The tumour cells population decreases and is almost eradicated in the end of the time period. In the meantime, the normal cells population grow up and remain over the average level.

Remark 4. It can be said that the above finding sheds some light on immuno-chemotherapy strategy and can be helpful to medical practitioners, experimental scientists and others to control this killer disease of cancer. An extension along this line of work can be done to examine the effect of other cytokines such as interferon-alpha (INF-α), which are involved in the cellular dynamics of the immune system response to tumour invasion and how these cytokines affect the dynamics of the system.

6. Concluding remarks

In this paper, we studied an optimal control problem of DDEs to describe the interactions of tumour-immune system in presence treatment of immuno-chemotherapy. Pontryagin's Maximum Principle is used to determine the representation of the control through the calculation of the adjoint system that is coupled with the state system. The model is an extension to the one presented by Kirschner and Panetta [17] by assuming the homogeneity of the tumour cells. We presented the non-negativity and boundedness of solutions, existence of steady states of our model. The model exhibits periodic solutions around the tumour-persistent steady state due to a Hopf bifurcation. In the absence of the chemotherapy, we deduced a delay threshold τ^* below which the persistent-tumour steady state is asymptotically stable and the system undergoes Hopf bifurcation at the threshold.

Control variables are introduced into the originally uncontrolled model and considered L^1 and L^2 type objective functionals to maximize the effector cells and IL-2 concentration, and minimize the tumour cells with low side-effect of the chemotherapy. We showed that an optimal control exists for this problem. We derived the necessary optimality conditions as a Pontryagin type Minimum Principle. We estimated the optimality system to determine the optimal control situation (i.e., the drug strategy), and predict the evolution of the tumour cells, effector cells, and normal cells of each control strategy in 100 days. The numerical simulations displayed in the Figures validate the existence of optimality of the control variables and show that the combination of immuno-chemotherapy protocol reduces the tumour load in a few months of therapy. Careful determination of the inclusion of the delay in the optimal control setting for the forward and backward oriented system in the numerical setting is needed.

Sensitivity analysis with respect to the parameters of the model is desirable, which will be considered in future research. It is useful to investigate how a small shift (change) in the input parameters would change the stability of the tumour-free equilibrium, and detect the most significant parameter that has a major impact on the model dynamics.

Acknowledgement

This work was supported by the UAE University. The authors are grateful to the reviewers for their constructive suggestions and valuable comments, which improved the quality of the paper.

Appendix. Numerical algorithm

Most of optimal control problems can not be solved analytically and consequently, reliable numerical methods are essentially required. Direct and indirect approaches are usually used to solve the optimal control problems. In the direct approach, the optimal control problem is transformed into a nonlinear programming problem. The algorithm of solving the optimal control problem (20)–(22) is roughly based on the following steps:

Step 1. Provide the initial guess for the control parameters v_0 and w_0 over the interval, and Declare the parameters.
Step 2. Set the initial conditions for the state variables $x_0(t)$ with the stored values of v_0 and u_0 and solve the state system forward in time, using any DDEs solver.
Step 3. Use the transversality condition $\lambda(t_f) = 0$ the stored values v_0 and u_0 and $x(t)$ and solve the adjoint system backward in time.
Step 4. Check the control by entering the new values of the state and the adjoint state into the characterization of the optimal control.
Step 5. Verify for convergence. If values of the variables in this iteration and the latest iteration are not negligible small, output the current values as solutions. If values are not small, return to Step 2.

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