Dynamics of Cancer-Immune System with External Treatment and Optimal Control

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Abstract

Herein, we present a mathematical model of tumour-immune interactions in presence of chemotherapy treatment. The model is governed by a system of delay differential equations with optimal control variables. A discrete time-delay is considered to justify the time-needed for the effector cells to develop a suitable response to the tumour cells. The control variables are included to justify the best treatment strategy with minimum side effects by reducing the production of new tumour cells and keeping the number of normal cells above the average of its carrying capacity. The numerical simulations show that the optimal treatment strategy reduces the load of tumour cells increases the effector cells after few days of therapy.

Keywords: Chemotherapy; Immune system; Mathematical modeling; Optimal control; Time-delay; Tumour

Introduction

Indeed, cancer remains a major cause of death in both developing and developed countries; see the statistics of Health World Organization (WHO) [1]. The term cancer represents numerous diseases that can affect any part of the body. It can similarly be referred to as malignant tumours and neoplasms. The unique procedure that cancer cells adopt includes their ability to multiply rapidly, exceeding their normal boundaries, and accordingly invading the adjacent organs and spreading the disease. Cancer is the most challenging disease to treat, although great research effort dedicated to revealing the relation between the tumour cells and immune system. The desired outcome from cancer treatment should be destruction of all cancer cells in the body, while maintaining the minimum level of healthy cells. Chemotherapy is one of the most highly adopted cancer treatment modalities, however, it was proved to be not the most convenient solution for tumour regression [2,3]. Progress is currently being made in attempting to eliminate tumour cells in the host by using an experimental form of immunotherapy [4,5].

Immune system (IS) is responsible for monitoring substances that be normally present the body. Any new substance in the body that the IS does not recognize raises an alarm, causing the IS to attack it. Substances that cause the IS response are called antigens1. Cancer cells are different from normal cells in the body and usually have unusual substances on their outer surfaces that can act as antigens. However, cancer cells look very much like normal cells and are tricky, as they put almost a cape over themselves so that the IS cannot recognize the cancer cell [6].

The immunity (or defence against pathogens or cancer cells) has basically two categories: innate immunity and adaptive immunity [7]. The innate immune system represents a nonspecific (no memory) response to substance to which the body regards as foreign or potentially harmful. The innate system represents the first line of defence and quickly respond to certain general signs of infection so that is unable to memorise the same pathogen should the body be exposed to it in the future. In most cases, the innate immunity can suffice to clear pathogens, but sometimes it is insufficient. In fact, pathogens possess ways to overcome the innate barrier and successfully canalize the host. The adaptive immunity is, however, very specific, it is called into action against pathogens that can evade or overcome innate immune defences. This takes time to develop, but the adaptive immune system ‘remembers’ antigens that it has previously encountered and responds immediately the next time they try to infect. There are two types of adaptive immune responses: humoral immunity, mediated by antibodies produced by B lymphocytes, and cell-mediated immunity, mediated by T-lymphocytes [8]. In fact, the innate immune response develops first and occurs on the order of minutes or hours; While adaptive immunity follows, innate and occurs on order of days or weeks. Each has inherit time-delay τ in their developments [9].

The interactions between tumour cells and immune system are very complex and need sophisticated models to describe such interactions [10]. Mathematical models, based on ordinary differential equations, delay differential equations, partial differential equations, have proven to be useful tools in analysing and understanding the IS interactions with viral, bacterial infections and cancerous cells. Several mathematical models have been suggested to describe the interactions of tumour and immune system over time (see e.g. the research papers [11–15]). Most of these papers describe the interactions between tumour cells and immune cells, tumour cells and normal cells alone [16], or consider the interactions of tumour-immune system with chemotherapy treatment [2,3]. In this paper, we provide a mathematical model of tumour-immune interactions in presence of chemotherapy treatment and optimal control variables. The control variables are incorporated to justify the best strategy of treatment and minimize side effects of the external treatment by reducing the production of new tumour cells, while keeping the number of normal cells above the average of its carrying capacity.

1Antigens may be contained within or on bacteria, viruses, other microorganisms, or cancer cells.

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Mathematical Models

We first present a simple model that describes the dynamics of tumour cells, T(t), and activated effector cells, E(t), such as cytotoxic T-cells, macrophages, and natural killer cells that are cytotoxic to the tumour cells. We adopt a predator prey formulation of the tumour immunity problem as a battle between immune cells and tumour cells (predators and prey, respectively). The model takes the form

\[
\begin{align*}
\frac{dE(t)}{dt} &= \sigma + F(E(t), T(t)) - \mu E(t)T(t) - \beta E(t), \\
\frac{dT(t)}{dt} &= -\alpha T(t)\beta E(t) - \eta E(t)T(t),
\end{align*}
\]

with initial conditions: E(0) = E_0, T(0) = T_0. Of course, the interaction between the effector and tumour cells leads to a reduction in the size of both populations with different rates, which are expressed by \(-\mu E(t)T(t)\) and \(-\eta E(t)T(t)\), respectively. Because of this interaction, the immune effector cells decrease the population of tumour cells at rate \(\mu\). While, tumour cells infect some of the effector cells and therefore, the population of infected effector cells decreases at the rate \(\mu\). If one considers T(t) as prey and E(t) as predator, then F(E,T) is assumed to be Michaelis-Menton form, so that

\[
F(E, T) = \frac{\rho E(t)T(t)}{\eta + T(t)}.
\]

In this term, \(\rho\) is the maximum immune response rate and \(\eta\) is the steepness of immune response. The presence of the tumour cells virtually initiates the proliferation of tumour-specific effector cells to reach a saturation level parallel with the increase in the tumour populations. Hence, the recruitment function should be zero in the domain of its application for sufficiently large values of time t, we recall the following Lemma:

**Lemma 1**

(Gronwall’s Lemma [19]) Let x, \(\psi\) and \(\chi\) be real continuous functions defined in [a,b], \(\chi \geq 0\) for \(t \in [a,b]\). We suppose that on [a,b] we have the inequality

\[
x(t) \leq \psi(t) + \int_a^t \psi(s) \chi(s) ds.
\]

Then

\[
x(t) \leq \psi(t) + \int_a^t \psi(s) \chi(s) e^{\int_a^s \chi(s) ds} ds \text{ in } [a,b].
\]

Therefore, we arrive at the following Proposition:

**Proposition 1**

Let \((E(t), T(t))\) be a solution of system (2), then \(E(t) < M_1\) and \(T(t) < M_2\) for all sufficiently large time t, where

\[
M_1 = E(0) + \sigma \exp(\delta T(0)) + \frac{\sigma}{\beta} \exp\left[\frac{\sigma - \beta}{\beta} T(0)\right],
\]

\[
M_2 = \frac{\max(1, T(0))}{\beta}.
\]

For the proof, we refer to [9].

**Corollary 1**

If \(\frac{\sigma}{\beta} \geq \mu\), then the solutions \((E,T)\) for model (2) are non-negative for any non-negative initial condition. However, if \(\frac{\sigma}{\beta} < \mu\), then there exist non-negative initial conditions such that \(E(t)\) becomes negative in a finite time interval.

Model with Chemotherapy and Control

To include external chemotherapy in model (2), we should consider two variables namely amount of chemotherapy \(u(t)\) and normal cells \(N(t)\) with two control variables \(v(t)\) and \(w(t)\) (Figure 1). We assume the homogeneity of the tumour cells, then the model takes the form

\[
\begin{align*}
\frac{dE(t)}{dt} &= \sigma + \rho E(t)T(t) - \mu E(t)(\eta + T(t)) - \beta E(t), \quad t \geq 0, \\
\frac{dT(t)}{dt} &= -\alpha T(t)(\eta + T(t)) - \eta E(t)T(t),
\end{align*}
\]

This model is called delay differential equations (DDEs), in which we must provide initial functions:

\[
E(t) = \psi(t) \quad \text{and} \quad E(t) = \psi(t) \quad \text{for all } t \in [-\tau, 0], \quad \text{instead of initial values.}
\]

In model (2), the presence of tumour cells stimulates the immune response, represented by the positive nonlinear growth term for the immune cells \(\rho E(t)T(t)\), \(\eta + T(t)\) and \(\eta\). \(\rho\) is the maximum immune response rate and \(\eta\) is the steepness of immune response. The presence of the tumour cells virtually initiates the proliferation of tumour-specific effector cells to reach a saturation level parallel with the increase in the tumour populations. Of course, the solution of DDEs model (2) should be bounded and nonnegative [18].

**Boundedness and Non-Negativity of the Model Solutions**

To show that the solutions of model (2) are bounded and remain non-negative in the domain of its application for sufficiently large values of time t, we recall the following Lemma:

Let \(x(t) \leq \psi(t) + \int_0^t \psi(s) \chi(s) ds\). Then

\[
x(t) \leq \psi(t) + \int_0^t \psi(s) \chi(s) e^{\int_0^s \chi(s) ds} ds \text{ in } [a,b].
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Therefore, we arrive at the following Proposition:

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For the proof, we refer to [9].

**Corollary 1**

If \(\frac{\sigma}{\beta} \geq \mu\), then the solutions \((E,T)\) for model (2) are non-negative for any non-negative initial condition. However, if \(\frac{\sigma}{\beta} < \mu\), then there exist non-negative initial conditions such that \(E(t)\) becomes negative in a finite time interval.
The existence of optimal controls \( v(t) \) and \( w(t) \) for this model is guaranteed by standard results in optimal control theory [21].

The time-delay has been considered to describe the time needed by the immune system to launch a suitable response after recognizing the tumour-immune interactions in the presence of chemotherapy treatments. Furthermore, the following properties hold

\[
\mathcal{L}_t(t_j) = 0, \quad i = [1, 2, 3, 4] \quad \text{and} \quad \mathcal{L}_{[0,t_j]} = \begin{cases} 1 & \text{if } t \in [0,t_j] \setminus \{t_j\} \\ 0 & \text{otherwise} \end{cases}
\]

(10)

Furthermore, the following properties hold

\[
\nu^* = \min \left\{ \nu_{\text{max}}, \frac{\lambda_4}{B_a} \right\}, \quad w^* = \min \left\{ w_{\text{max}}, \frac{\lambda_8 S_1}{B_a} \right\}
\]

(11)

(See the Delay Models with Optimal Control)

**Discussion and Conclusion**

In this paper, we provided a mathematical model with memory (time-delay) and optimal control variables to describe the dynamics of tumour-immune interactions in presence of chemotherapy treatments. The time-delay has been considered to describe the time needed by the immune system to launch a suitable response after recognizing the non-self-cells or foreign bodies. The numerical approximations of the optimal control problem are carried out using forward and backward Euler’s methods. Starting with an initial guess for the value of the controls on the time interval \([0, t_J]\), we solve the state system
with control variables (3) using forward Euler’s scheme. While, the adjoint system is solved using the solutions of the state system and the transversality conditions (9) backward in time. A Pontryagin-type maximum principle is derived, for optimal control problems with time-lag in the state variable. The control system is subject to a mixed control-state constraint to minimize the cost of treatment, reduce the tumour cells load, and keep the number of normal cells above 75% of its carrying capacity.

Figure 2 shows the impact of chemotherapy treatments (with optimal control) when we choose the parameter values in an unstable region ($\sigma =0.2$, $\rho =0.2$, and $\tau =1.5$). The tumour cell population is growing up over time in the absence of chemotherapy, while the presence of treatment helps the immune system to keep the growth of the tumour cells under its control.

The Figure shows that the tumour cells can be eradicated at day 10. The numerical simulations show the rationality of the model presented, which in some degree meets the natural facts.

The theoretical results presented in this paper convey a general insight to biologists and can help to gain better understanding of interaction mechanisms of tumour-immune system. They can be used to evaluate control strategies and applied for real cases in the future research work.

Delay Models with Optimal Control

Mathematical modelling with delay differential equations (DDEs) is widely used for analysis and predictions in epidemiology, immunology, physiology [23-27]. The time delays in these models consider a dependence of the present state of the modelled system on its history. In life, things are rarely so instantaneous; there is usually a propagation delay before the effects are felt. This situation can be modelled using a DDE.

$$ y'(t) = f(y(t), y(t-\tau_1), y(t-\tau_2), \ldots, y(t-\tau_d), t), \ t \geq t_0 $$  \hspace{1cm} (12)

where all the time-lags, $\tau_\alpha$, are assumed to be none negative functions of the current time $t$. Because of these delay terms it is no longer sufficient to supply an initial value, at time $t=t_0$, to completely define the problem. Instead, it is necessary to define the history of the state vector, $y(t)$, sufficiently far enough back in time from $t_0$ to ensure that all the delayed state terms, $y(t-\tau_\alpha)$, are always well defined. Thus, it is necessary to supply an initial state profile of the form:

$$ y(t) = \psi(t), \quad t_0 - \tau_{\text{max}} \leq t < t_0, \quad \text{and} \quad y(t_0) = y_0. $$  \hspace{1cm} (13)

It should be noted that $\psi(t_0)$ need not be the same as $y_0$. This immediately introduces the possibility of a discontinuity in the state, $y(t)$.

We mention here that there are many problems in biosciences (such as epidemics, harvesting, chemostat, treatment of diseases, physiological control, vaccination) which can be addressed within an optimal control framework for systems of DDEs [28-30]. However, the amount of real experience that exists with optimal control problems (OCPs) is still small. The DDE (12) can be converted into an optimal control problem by adding an $m$-dimensional control term $u(t)$

$$ y'(t) = f(y(t), y(t-\tau_1), y(t-\tau_2), \ldots, y(t-\tau_d), u(t), t), $$  \hspace{1cm} (14)

and a suitable objective functional (measure): $J_0(u)$

$$ \text{Maximize} \quad J_0(u) = \Phi(y(T)) + \int_{t_0}^{T} L(y(t), y(t-\tau_1), y(t-\tau_2), \ldots, y(t-\tau_d), u(t), t)dt, $$  \hspace{1cm} (15)

and subject to control constraint $a \leq u(t) \leq b$, and state constant $y(t) \leq c$, where $a$ and $b$ are the lower and upper bounds. The integrand, $L(\cdot)$ is called the Lagrangian of objective functional which is continuous in $[0, T]$. Additional equality or inequality constraint(s) can be imposed in terms of $J_0(u)$. 

Figure 2: Numerical simulations of populations of the tumour cells and effector cells of system (3), before and after the chemotherapy treatment with controls $v(t)$ and $w(t)$. It shows that the tumour cells population can be eradicated in day 10.
Pontryagin's Maximum Principle [22] gives necessary conditions that the control and the state need to satisfy, and introduces an adjoint function to affix to the differential equation to the objective functional. The necessary conditions needed to solve the optimal control problem are derived from the so called 'Hamiltonian' $H$ which is given by the equation

$$H(t) = L(t) + \lambda^T(t) f(t).$$

(16)

Here, $\lambda^T(t)$ is a vector of costate variables of the state variables $y(t)$, which is the solution of the equation

$$\dot{\lambda}^T(t) = - \frac{\partial H}{\partial y}(t) - \chi_{[0,t-\tau]} - \frac{\partial H}{\partial (t+\tau)}$$

(Adjoint equation)    (17)

Where

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

Given the nonlinear Hamiltonian (16) in the controls $v$ and $w$, the process of solving the optimal control problem is to solve the state system (14) together with the adjoint equation (17) and the following conditions:

$$\frac{\partial H}{\partial v} = \frac{\partial H}{\partial w} = 0$$

(Optimality conditions)

$$\lambda^T(t_f) = 0.$$  (Transversality conditions)

(18)

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