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ORIGINAL PAPER

Chemotherapy and Immunotherapy for Tumors: A Study of Quadratic Optimal Control

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Abstract
In this work, we start by Kuznetsov's model which describes the interaction between two cell populations: tumor cells and effector cells. We insert in this model controls corresponding to two types of treatment: chemotherapy and immunotherapy, which leads to a controlled dynamic system. The goal of this paper is to minimize the density of tumor cells as well as the dose of treatment. We seek for an optimal treatment which will be characterized by using Pontryagin's Maximum Principle.

Keywords Chemotherapy · Immunotherapy · Tumor cells · Dynamical system · Optimal control

Introduction

Cancer treatment aims to heal or unless to stop the evolution of the tumor as long as possible in order to allow the patient to have an almost normal life.

The main treatments are: surgery, radiotherapy, chemotherapy, hormonotherapy, and immunotherapy. These treatments can be used individually or in combination depending on the type of cancer. The purpose is to define the appropriate treatment for each patient in ordre to give the best results with least sequelae.

Chemotherapy treatment has been treated in several mathematical models [5,12,15], based on control theory, where control variable is the administered dose. It's widely known that the immune system impacts the success of chemotherapy, see [10,14]. Hence, combining chemotherapy and immunotherapy protocols attracts great interest in oncology. However, this combination is hard for patients, then it would be suitable to minimize the total amount of drugs while preserving their efficiency. In our previous work [13], we insert in

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Kuznetsov's model [11], two controls corresponding to two types of treatment: chemotherapy and immunotherapy. We study the viability of this model under states constraints. This result allows to evaluate the chances of remission of a patient depending on its state at the first diagnostic. Nevertheless, this previous study does not take into consideration side effects of treatments, which are exhibited in the present work in the form of optimal control problem.

The contribution of this work consists on defining an objective function that depends on the density of tumor cells and the total amount of drugs subject to a coupled system of ordinary differential equations presented in [13]. The goal is to explore optimal strategies combining chemotherapy and immunotherapy treatments allowing to minimize tumor cells density together with minimal toxicity in the patient body. The objective functional involves quadratic control as used in several works, since it's generally more theoretically tractable, the existence of an optimal control is obtained under mild conditions and the square in control terms models severity of the drugs side effects [1,3,8,16].

This paper is divided into five sections. The next section is devoted to mathematical formulation of the model, positivity and boundedness of the system. Section 3 deals with the existence and characterization of an optimal control. Section 4, illustrates the results theoretically obtained, by numerical simulations, where specific parameters are related to melanoma cancer. Some conclusions are drawn in Sect. 5.

Mathematical Model

Starting from kuznetsov's work [11] describing a dynamic system of two cell populations, that are, tumor cells T and effector cells E, and using interaction laws between them [1,3,4,7]: The natural growth of tumor cells is assumed to be a logistic function f_T:

$$f_T(T) = aT(1 - bT),$$

The dynamic of effector cells obeys to an affine law f_E explaining that effector cells have a constant source rate s, while death is proportional to the population of effector cells.

$$f_E(E) = s - dE.$$

The competition between cell populations is modeled by $-nET$ and $-mTE$. This model takes into account the stimulation of effector cells by the presence of tumor cells, this phenomenon is modeled by a Michaelis–Menten term $\frac{\rho TE}{g+T}$ to characterize the rate of accumulation of cytotoxic effector cells in the tumor cell localization region. The dynamic system of Kuznetsov is therefore:

$$\begin{cases} \dot{T} = a(1 - bT)T - nET \\ \dot{E} = s - dE + \frac{\rho TE}{g+T} - mTE \end{cases}$$

In order to support the praticiens in their choice of therapies, we add to this model two kinds of treatment, chemotheapy and immunotherapy. Combining the both treatments for many cancer types could potentially leads to enhance efficiency [2,6]. The goal of chemotherapy is to attack the growth factors of cancer cells and stop their proliferation. However, it also attacks healthy cells including progenitor cells, which produce effector cells. The immune system becomes therefore also affected. Hence the interest of introducing immunotherapy to boost the immune system. Mathematically speaking, we introduce two control variables $(c(t), i(t))$ corresponding to treatments (chemotherapy/immunotherapy) and leading to the

following controlled system:

$$\begin{cases} \dot{T} = a(1-bT)T - \mu c(t)T - nET, \\ \dot{E} = s - dE + \frac{\rho TE}{g+T} - mTE - hc(t)E + i(t), \\ E(0) = E_0, \text{ and } T(0) = T_0. \end{cases} \tag{1}$$

where the control i describes the direct effect of immunotherapy on effector cells while the concentration of chemotherapy is denoted by c.

We admit that the concentrations of both therapies should not exceed a maximum threshold and are limited as follow:

$$(c, i) \in U,$$

where the set U is defined as:

$$U = [0, c_{max}] \times [0, i_{max}]$$

Here we list all parameters used in the model (1), their meaning and units:

Positivity and Boundedness of Trajectories

To be biologically meaningful, trajectories of system (1) must be positively invaraint and bounded.

Proposition 1 *All trajectories of the system* (1)*, starting in* $\mathbb{R}^2_+$*, are positively invariant.*

Proof To prove the positive invariance of the trajectories, it suffices to study the behavior of the vector field $(\dot{T},\ \dot{E})$ on the boundary of $\mathbb{R}^2_+$.
If T tends to 0 then $\dot{T} = 0$.
If E tends to 0 then $\dot{E} = s + i > 0$, since $i \geq 0$ and $s > 0$.
Therefore, the vector field $(\dot{T},\ \dot{E})$ is pointed inside $\mathbb{R}^2_+$ and then trajectories T and E of the dynamic system (1) are positively invariant. □

Let us show that the dynamical system (1) provides bounded trajectories even if $t_f = +\infty$.

Proposition 2 *Assume that*

$$d - \rho > mg - \sqrt{\frac{\rho g}{m}}. \tag{2}$$

Then the positive trajectories of the system (1) *are uniformly bounded.*

Proof Recall that

$$\dot{T} = a(1-bT)T - \mu cT - nET.$$

Note that the logistic function $a(1-bT)T$ is concave and we have

$$a(1-bT)T \leq \frac{a}{4b},$$

then,

$$\dot{T}(t) \leq \frac{a}{4b} - \mu cT(t).$$

Table 1 Parameters of the cancer model (1)

Parameter	Description	Unit	Estimated value	References
T	Density of tumor cells	cells	–	[15]
E	Density of effector cells	cells	–	[15]
c	Chemotherapy drug concentration	mg L^{-1}	–	[1]
i	Immunotherapy drug concentration	IU (International Unity)	–	[1]
a	Tumor growth rate	day^{-1}	0.18	[11]
b	b^{-1} is tumor carrying capacity	$cells^{-1}$	2×10^{9}	[11]
n	Fractional tumor cell kill by effector cells	day^{-1} $cells^{-1}$	1.101×10^{-7}	[11]
s	The constant flow of effector immune cells	cells day^{-1}	1.3×10^{4}	[11]
d	Death rate of the effector cells	day^{-1}	4.12×10^{-2}	[3]
ρ	Maximum growth rate of the effector cells	day^{-1}	0.1245	[11]
g	A half-saturation constant	cells	2.019×10^{7}	[11]
m	Fractional effector cell inactivated by tumor cells	day^{-1} $cells^{-1}$	3.422×10^{-10}	[3]
μ	Fractional tumor cell kill by chemotherapy	day^{-1}	0.09	[16]
h	Fractional effector cell kill by chemotherapy	day^{-1}	0.06	Estimated

We deduce by standards calculus of the linear differential equations that

$$T(t) \leq \left(T(0) - \frac{a}{4b\mu c}\right) \exp^{-\mu ct} + \frac{a}{4b\mu c}.$$

So the state T which corresponds to the density of the tumor cells is well bounded.
For the boundedness E, we have

$$\dot{E} \leq s + i - dE + \frac{\rho TE}{g+T} - mTE,$$
$$\dot{E} \leq s + i - E\left(d + mT - \frac{\rho T}{g+T}\right).$$

Consdier i_{max} the upper bounds of i.
We obtain then the following inequality

$$\dot{E}(t) \leq s + i_{max} - E(t)\left(d + mT - \frac{\rho T}{g+T}\right). \tag{3}$$

Our hope is to prove that there exists $Q_M > 0$ such that

$$d + mT - \frac{\rho T}{g+T} \geq Q_m.$$

Consider the function

$$Q(T) := d + mT - \frac{\rho T}{g+T},$$

The analysis of Q shows that it takes a mininum at $\sqrt{\frac{\rho g}{m}} - g$ and

$$Q_m := Q\left(\sqrt{\frac{\rho g}{m}} - g\right) = d + \left(1 + \frac{1}{m}\right)\sqrt{m\rho g} - mg - \rho$$

On the other hand, according to condition (2) we have that

$$mg - \sqrt{\frac{\rho g}{m}} < d - \rho,$$
$$-\frac{1}{m}\sqrt{m\rho g} < d - \rho - mg,$$

which implies that

$$-\left(1 + \frac{1}{m}\right)\sqrt{m\rho g} < d - \rho - mg,$$

and then

$$Q_m > 0.$$

Hence, the inequality (3) becomes

$$\dot{E}(t) \leq s + i_{max} - E(t)Q_m.$$

We conclude that

$$E(t) \leq \left(E(0) - \frac{B_1}{Q_m}\right)e^{-Q_m t} + \frac{B_1}{Q_m}$$

where $B_1 = s + i_{max}$. □

Theory of Control

Let's rewrite the controlled dynamic system (1) as:

$$\begin{aligned} \dot{x} &= f(x(t), u(t)), \ \forall\, t \in [0, t_f], \\ x(0) &= x_0. \end{aligned} \tag{4}$$

where $x = (T, E)$ and $u = (c, i) \in U = [0, c_{max}] \times [0, i_{max}]$.
Moreover $f : \mathbb{R}^2_+ \times U \longrightarrow \mathbb{R}^2$ is defined as:

$$f(x, u) := (f_1(x, u),\ f_2(x, u)),$$

with

$$f_1(x, u) = a(1 - bT)T - \mu c(t)T - nET, \tag{5}$$

$$f_2(x, u) = s - dE + \frac{\rho TE}{g + T} - mTE - hc(t)E + i(t). \tag{6}$$

To dynamic (4), we associate a quadratic control objective functional, minimizing density of tumor cells and the total amount of drugs, [1,3,8,16], as follows:
For $u(\cdot) = (c(\cdot), i(\cdot)) \in L^\infty([0, t_f],\ U)$, we define

$$J(u) = \int_0^{t_f} L(x(t), u(t))dt, \tag{7}$$

where

$$L(x, u) := T + w_1 \frac{\epsilon_1}{2} c^2 + w_2 \frac{\epsilon_2}{2} i^2.$$

T is the tumor cells density, $c(t)$ describes the amount of chemotherapy agent doses and $i(t)$ is the immunotherapy injection. The weights w_1 and w_2, with values between 0 and 1, are considered to privilege one treatment over another. On the other hand, since the density of tumor cells and treatment doses do not have the same order of magnitude, we need to introduce ϵ_1 and ϵ_2 which are the scaling factors. This allows us to display more clearly population dynamics with one objective function.

The problem is to minimize the objective function J on $\mathscr{U} := L^\infty([0, t_f],\ U)$. These considerations lead to the following optimal control problem:

$$\begin{cases} \underset{u \in \mathscr{U}}{\text{Minimize}}\ J(u) = \displaystyle\int_0^{t_f} L(x(t), u(t))dt \\ \text{s.t.} \\ \dot{x} = f(x(t), u(t)), \quad \text{for } t \in [0, t_f] \\ x(0) = x_0. \end{cases} \tag{8}$$

Existence of Optimal Control

Now, we have to find a trajectory which minimizes the objective function $J(u)$. According to [9], we establish the existence of an optimal control, and then we characterized it. This existence depends on the regularity hypotheses of the studied model.

Theorem 1 *For each control $u \in \mathscr{U}$ there exists a unique solution $x = (T, E)$ of the system (4) defined on $[0, t_f]$.*

Moreover, the problem (8) *admits an optimal control* $u^* \in \mathscr{U}$ *such that*

$$\min_{u\in\mathscr{U}} J(u) = J(u^*).$$

Proof To prove this theorem we need to prove the following lemma □

Lemma 1 *The function* $f(.,u)$ *is continuous for all* $u \in U$ *and there exists positive constants* C_1 *and* C_2 *such that for all* $(x, x', u) \in (\mathbb{R}_+^2)^2 \times U$

$$| f(x,u) | \leq C_1(1+ | x | + | u |), \tag{9}$$
$$| f(x',u) - f(x,u) | \leq C_2 | x' - x | (1+ | u |). \tag{10}$$

Moreover

1. *U is closed and convex.*
2. *f is linear with respect to control u.*
3. *The integrand L of J is continuous, convex with respect the second variale, on U and is bounded below by* A_1u^2 *where* $A_1 > 0$.

Proof of the Lemma 1:
For the continuity of f and taking account of the expression (5), the right hand side of system (4) must be continuous. We see that only the right hand side of $\dot{E}$ has a chance to be discontinuous. Since both g and T are positive this eliminates the possibility of $\frac{\rho TE}{g+T}$ to be undefined. Therefore the entire system is continuous, and hence the function f is continuous. Furthermore we have

$$\begin{aligned}
&| f(t,x,u) | \\
&\leq | a(1-bT)T - \mu cT - nET | + | s - dE + \frac{\rho TE}{g+T} - mTE - hcE + i |, \\
&\leq \frac{a}{4b} + \mu c | T | + | nET | + s + d | E | + \rho | E | + m | ET | + hc | E | + | i |, \\
&\leq \frac{a}{4b} + s + (d+\rho) | E | + (nE_{max} + mE_{max}) | T | + (\mu T_{max} + hT_{max}) | c | + | i |, \\
&\leq C_1(1+ | x | + | u |)
\end{aligned}$$

where $C_1 = max(\frac{a}{4b} + s, d + \rho, E_{max} + mE_{max}, \mu T_{max} + hT_{max}, 1)$.
For the lipschitziennity of f with respect to the second variable, we have:

$$\begin{aligned}
&| f(t,x',u) - f(t,x,u) | \\
&\leq | a(1-bT)T - \mu cT - nET - a(1-bT')T' + \mu cT' - nE'T' | \\
&\quad + | -dE + \frac{\rho TE}{g+T} - mTE - hcE + dE' - \frac{\rho T'E'}{g+T'} + mT'E' + hcE' |, \\
&\leq a | T - T' | + ab | T - T' | | T + T' | + \mu c | T - T' | + nE' | T - T' | \\
&\quad + nT | E - E' | + d | E - E' | + \rho | \frac{gT(E-E') + TT'(E-E')}{(g+T)(g+T')} | \\
&\quad + mT | E - E' | + mE' | T - T' | + hc | E - E' |, \\
&\leq (a + 2abT_{max} + (m+n)E_{max}) | T - T' | \\
&\quad + | E - E' | (d + (m+n)T_{max} + 2\rho) + | c | (| T - T' | + | E - E' |), \\
&\leq C_2 | x' - x | (1+ | u |),
\end{aligned}$$

where $C_2 = \max(k_1, k_2, 1), k_1 = a + 2abT_{max} + (m+n)E_{max}$ and $k_2 = d + (m+n)T_{max} + 2\rho$.

At this stage, we must mention that the continuity of the function f and the conditions (9) and (10) assures the existence of a solution of the dynamic (4).

Now, for the second condition of the Lemma 1, we note that U is closed and convex by definition. For the convexity of the integrand L of $J(u)$ with respect to the second variable $u = (c, i)$, we need to show

$$L(T, E, (1-p)c_1 + pc_2, (1-p)i_1 + pi_2) \leq (1-p)L(T, E, c_1, i_1) + pL(T, E, c_2, i_2).$$

Then, the following difference should be negative

$$\begin{aligned} &L(T, E, (1-p)c_1 + pc_2, (1-p)i_1 + pi_2) \\ &\quad -(1-p)L(T, E, c_1, i_1) - pL(T, E, c_2, i_2) \leq 0. \end{aligned}$$

We have

$$\begin{aligned} &L(T, E, (1-p)c_1 + pc_2, (1-p)i_1 + pi_2) - (1-p)L(T, E, c_1, i_1) - pL(T, E, c_2, i_2) \\ &= w_1 \frac{\epsilon_1}{2} p(p-1)(c_1 - c_2)^2 + w_2 \frac{\epsilon_2}{2} p(p-1)(i_1 - i_2)^2, \\ &= p(p-1)\left[w_1 \frac{\epsilon_1}{2}(c_1 - c_2)^2 + w_2 \frac{\epsilon_2}{2}(i_1 - i_2)^2 \right]. \end{aligned}$$

Since $0 \leq p \leq 1$ then

$$p(p-1) \leq 0,$$

and

$$w_1 \frac{\epsilon_1}{2}(c_1 - c_2)^2 + w_2 \frac{\epsilon_2}{2}(i_1 - i_2)^2 \geq 0.$$

This implies that

$$L(T, E, (1-p)c_1 + pc_2, (1-p)i_1 + pi_2) - (1-p)L(T, E, c_1, i_1) - pL(T, E, c_2, i_2) \leq 0.$$

Moreover, for the fourth condition, we have

$$T(t) + w_1 \frac{\epsilon_1}{2} c^2 + w_2 \frac{\epsilon_2}{2} i^2 \geq w_1 \frac{\epsilon_1}{2} c^2 + w_2 \frac{\epsilon_2}{2} i^2,$$

if $\epsilon_1 w_1 \leq \epsilon_2 w_2$ then we obtain

$$w_1 \frac{\epsilon_1}{2} c^2 + w_2 \frac{\epsilon_2}{2} i^2 \geq \frac{\epsilon_1 w_1}{2}(c^2 + i^2).$$

which implies that

$$T(t) + w_1 \frac{\epsilon_1}{2} c^2 + w_2 \frac{\epsilon_2}{2} i^2 \geq A_1 \mid (c, i) \mid^2,$$

where $A_1 = \dfrac{\epsilon_1 w_1}{2}$. Else if $\epsilon_2 w_2 < \epsilon_1 w_1$, we obtain $A_1 = \dfrac{\epsilon_2 w_2}{2}$ by the same reasoning. Hence

$$L(x, u) \geq A_1 \mid u \mid^2,$$

with $x = (T, E)$ and $u = (c, i)$. □

Characterization of Optimal Control

A trajectory can be parameterized as the projection of a solution of a constrained Hamiltonian system. Consider again the controlled system :

$$\dot{x} = f(t, x(t), u(t)), x(t_0) = x_0.$$

Let (x^*, u^*) be an optimal process for the problem (8), so there exists an absolutely continuous application λ such that $\lambda : [0, t_f] \to R^2$, called the adjoint vector. The following equations are satisfied for almost all $t \in [0, t_f]$:

$$\dot{x}(t) = \frac{\partial H}{\partial \lambda}(t, x(t), \lambda(t), u(t)), \tag{11}$$

$$\dot{\lambda}(t) = -\frac{\partial H}{\partial x}(t, x(t), \lambda(t), u(t)), \tag{12}$$

$$\max_{u \in U} H(x(t), \lambda(t), u(t)) = H(x^*(t), \lambda(t), u^*(t)) = C^{te},$$

$$\lambda_1(t_f) = \lambda_2(t_f) = 0 \tag{13}$$

where H is the Hamiltonien associated with problem 8 and is defined by:

$$H = T + w_1 \frac{\epsilon_1}{2} c^2 + w_2 \frac{\epsilon_2}{2} i^2 + \lambda_1(a(1 - bT)T - \mu cT - nET) + \lambda_2 \left(s - dE + \frac{\rho TE}{g + T} - mTE - hcE + i \right),$$

and $\lambda = (\lambda_1, \lambda_2)$ such that :

$$\dot{\lambda_1} = \lambda_1(2abT + \mu c + nE - a) + \lambda_2 \left(mE - \frac{\rho gE}{(g + T)^2} \right) - 1.$$

$$\dot{\lambda_2} = n\lambda_1 T + \lambda_2 \left(d + mT + hc - \frac{\rho T}{(g + T)} \right).$$

Since the controls are bounded, we form the Lagrangian as follows:

$$L = H - W_1(t)c(t) - W_2(t)(1 - c(t)) - W_3(t)i(t) - W_4(t)(1 - i(t)),$$

where $W_i(t) \geq 0$ are penalty multipliers such that:
$W_1(t)c(t) = 0$ and $W_2(t)(1 - c(t)) = 0$ at the optimal c^*.
$W_3(t)i(t) = 0$ and $W_4(t)(1 - i(t)) = 0$ at the optimal i^*.
To characterize (c^*, i^*), we analyze the necessary optimality condition

$$\frac{\partial L}{\partial c} = 0 \text{ and } \frac{\partial L}{\partial i} = 0.$$

We have,

$$\frac{\partial L}{\partial c} = \frac{\partial H}{\partial c} - W_1 + W_2 \quad \text{or} \quad \epsilon_1 w_1 c - \lambda_1 \mu T - \lambda_2 hE - W_1 + W_2 = 0,$$

and

$$\frac{\partial L}{\partial i} = \frac{\partial H}{\partial i} - W_3 + W_4 \quad \text{or} \quad \epsilon_2 w_2 i + \lambda_2 - W_3 + W_4 = 0.$$

Using standard optimality arguments, we characterize the optimal control as:

$$c^* = min\left(1, \left(\frac{\lambda_1 \mu T + \lambda_2 hE}{\epsilon_1 w_1}\right)^+\right),$$
$$i^* = min\left(1, \left(\frac{-\lambda_2}{\epsilon_2 w_2}\right)^+\right).$$

Where:

$$r^+ = \begin{cases} r \text{ if } r \geq 0 \\ 0 \text{ if not} \end{cases}$$

Since the second derivative of the Lagrangian with respect to c and i is positive, a minimum occurs at (c^*, i^*).

At this stage, we were able to express control in term of states (T, E) and adjoint states (λ_1, λ_2), by applying Pontryagin's Maximum Principle. By re-injecting this expression of control into the dynamic of states and co-states, we obtain Hamiltonian system. In the next section, we give some numerical simulations illustrating the theoretical results.

Numerical Simulations

General model leads to qualitative properties of cancer evolution. However, it would be relevant to study particular types of cancer with specific sets of parameters. In this section, we use the data made available in [2,11]. Among the several numerical methods, we use the shooting method [17] to compute the optimal solution of (8) by solving the boundary value problem derived from the Pontryagin Maximum Principle and corresponding to the initial conditions (T_0, E_0), as well as final conditions on the adjoint states $(\lambda_1(t_f), \lambda_2(t_f)) = (0, 0)$.

Treatment doses c and i are normalized to be between zero and one, their order of magnitude is therefore 0. However, the order of magnitude of tumor cells is 6. In this numerical experiment, the system dynamics were non-dimensionalized using an order-of-magnitude concentration scale $E_0 = 10^6$ for effector cells and $T_0 = 10^6$ for tumor cells. While the time is scaled relative to the rate of tumor cell desactivation $\tau = nT_0 t$. Then, the dynamical system (1) becomes:

$$\begin{cases} \dot{z} = \alpha(1 - \beta z)z - \theta_1 c(\tau)z - yz \\ \dot{y} = \sigma - \delta y + \dfrac{pzy}{\eta + z} - rzy - \theta_2 c(\tau)y + i(\tau) \\ z(0) = 1 \text{ and } y(0) = 1 \end{cases} \tag{14}$$

With $z = \dfrac{T}{T_0}$ and $y = \dfrac{E}{E_0}$. We use parameter values in Table 1 to define the new values of the non-dimensionalized parameters of (14), as follow:

$$\alpha = \frac{a}{nT_0} = 1.636 \qquad \beta = bT_0 = 2 \times 10^{-3} \qquad \theta_1 = \frac{\mu}{nT_0} = 0.8$$
$$\sigma = \frac{s}{nE_0T_0} = 0.1181 \qquad \delta = \frac{d}{nT_0} = 0.3743 \qquad p = \frac{\rho}{nT_0} = 1.131$$
$$r = \frac{m}{n} = 0.00311 \qquad \theta_2 = \frac{h}{nT_0} = 0.6 \qquad \eta = \frac{g}{T_0} = 20.19$$

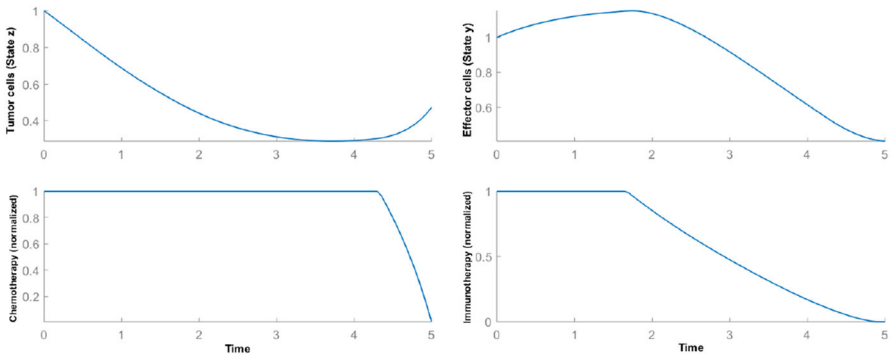

Fig. 1 Time plot of tumor cells (T), effector cells (E), normalized chemotherapy c and normalized immunotherapy i during $\tau_f = 5$, which corresponds to a treatment duration equal to 50 days. Initial tumor size is 1×10^6 cells and initial effector cell level is 1×10^6 cells. The chemotherapy is privileged by choosing weight parameters as $w_1 = 0.2$ and $w_2 = 0.8$

We find numerically the optimal control minimizing the following objective functional:

$$J(c, i) = \int_0^{\tau_f} \left(z(\tau) + w_1 \frac{\epsilon_1}{2} c^2(\tau) + w_2 \frac{\epsilon_2}{2} i^2(\tau) \right) d\tau,$$

where scaling factors ϵ_1 and ϵ_2 are equal to 1 because the order of magnitude of z is 0. Therefore, for numerical purposes, we discuss the results obtained according to the values of w_1 and w_2. At first, we use an w_1 lower than w_2 which means that we privilege chemotherapy as treatment. The Fig. 1 below shows the behavior of tumor cells and effector cells with high dose of chemotherapy and low dose of immunotherapy.

In Fig. 1 we privilige chemotherapy treatment, we can see that the maximum dose of (normalized) chemotherapy is administered throughout the treatment period of the therapeutic protocol, while the (normalized) immunotherapy is administered for a short time. Once the tumor is eradicated, the treatment is stopped, which prevents the growth of the immune cells due to the absence of immunotherapy that stimulates the effector cells. The density of tumor cells is driven near zero but resume their growth at the end.

Now we privilege immunotherapy and we get the results shown in the Fig. 2. With a high value of w_1, maximum dose of chemotherapy can not be used for a long time but immunotherapy is administered for the duration longer than that in the Fig. 1. This influences the dynamic of tumor cells that almost desappear at the end of treatment, while the effector cells maintain their gowth.

We therefore notice that the results differ according to the values of w_1 and w_2. In our case, we obtain a good results by privileging immunotherapy which means choosing w_1 higher than w_2, in this case, the tumor cells decrease definitively and tend to zero whereas the density of the effector cells remains high until the end of treatment.

For the values of parameters we used in this paper, we were able to find a therapeutic protocol that minimizes the density of tumor cells at the end of treatment with the time horizon $\tau_f = 5$. For a longer final time, the tumor cells can resume their growth, in this case we can change the therapeutic protocol at this moment or repeat it.

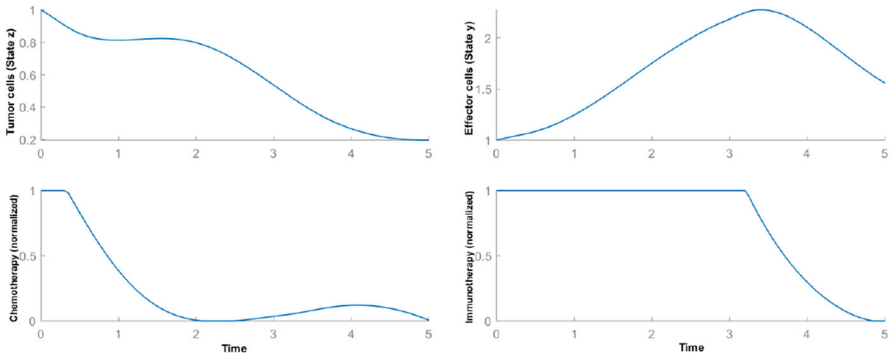

Fig. 2 The graphs of this figure represent the states and controls for weight parameter values $w_1 = 0.7$ and $w_2 = 0.3$. Initial tumor size is 1×10^6 cells and initial effector cell size is 1×10^6 cells. At the start of the treatment, a maximum dose of chemotherapy is administered and thereafter doses decrease. Whereas maximum dose of immunotherapy is administered for almost 1 month. The tumor is reduced to a very low level at the end of treatment while poulation of immune cells is increasing

Conclusion

Control theory provides an adequate conceptual framework for the analysis of evolutionary systems depending on decision variables. The system approached in our case is of biological origin: it describes the interaction between two cell populations (tumor cells and effector cells) in the presence of two types of treatment (chemotherapy and immunotherapy).

The objective is to determine optimal therapies that minimize the density of tumor cells and the dose of treatment. After modeling this issue, we verify the existence of optimal solutions, and then we applied Pontryagin's Maximum Principle to characterize it. The weight parameters w_1 and w_2, in the objective function (7), reflects an efficiency comprmis in mixed therapy protocols (Chemotherapy/Immunotherapy). One perspective of this work is to consider the cost of treatment and patient comfort. So in a next work, we approach these issues as part of a multi-objective problem.

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