Cancer therapies based on Optimal Control methods

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Abstract

Besides being an inevitability, cancer is among the leading causes of death worldwide and its incidence is expected to increase due to population ageing. At the same time, chemotherapy resistance onset continues to be the major reason for chemotherapy failing. Moreover, the schedule design of anticancer treatments are not patient tailored but rather based on trial and error approaches. There is an evident need for in silico mathematical modelling and optimization of treatments protocols.

Given the important role of the immune system in chemotherapy efficacy, in this dissertation, for the first time an ODE model combining chemotherapy, chemotherapy resistance, immunotherapy and a realistic immune response is proposed. Chemotherapy resistance is modeled as being proportional to chemotherapy blood concentration. An optimal control problem is then formulated and two proper performance indexes (linear and quadratic) are optimized using numerical methods based on the Pontryagins principle. Iteratively, the state and adjoint equations are integrated forwards and backwards, respectively, and the Hamiltonian function is optimized with respect to the control variables in a grid of time points. Two gradient based numerical methods are adapted and improved for this purpose. Finally, numerical simulations are presented and the optimal treatment schedule for the combination of chemo- and immunotherapy are analyzed. Combination therapy is able to eradicate tumors impossible to be eliminated by immunotherapy or chemotherapy alone. Both modelling of the immunosurveillance mechanism and tumor resistance fundamental prove to be essential to the design of proper treatment schedules.

Keywords: Optimal control, Chemotherapy resistance, Immunotherapy, Combination therapy, Nonlinear control, Pontyagins principle.

1. Introduction

The formation of the tumors is a complex process that usually occurs over a period of decades and rarely goes far enough to origin a clinically detectable tumor mass [1]. In fact, as the human body ages, several populations of cells throughout the body evolve into cells with increasingly neoplastic phenotypes as they complete some, but fortunately not all, of the steps of tumor progression [1]. Most of the individuals pass way from other diseases without realizing that any of these tumors progression had been initiated in their bodies and that they could have become victims of cancer in the near future [1]. Cancers are therefore an inevitability. Under these circumstances and given the increasing life expectancy and the advances in medicine, especially in developed countries, it is not surprising that cancer is currently among the leading causes of death worldwide [2]. Indeed, in 2012, 14.1 million of new cancer cases were diagnosed and there were 8.2 million cancer deaths and 32.6 million cancer patients within 5 years of diagnosis, worldwide [3]. Moreover, it is estimated that there will be 23.6 million new cases of cancer each year by 2030 [3].

Despite the significant investment in cancer research and the concomitant advance in the knowledge of cancer biology, the anticancer treatments currently in widespread use (surgery, radiotherapy and chemotherapy) were developed prior to 1975 and little progress has been made since then [1]. Since the development of cancer resistance to chemotherapy drugs has been related to the major reason for chemotherapy failure [1, 4], new therapeutic approaches have been designed, such as the anticancer immunotherapy. The latter, which first use dates back to 1893 [5], manipulates the immune

system of the patient in ways that enables it to kill the neoplastic cells that have emerged throughout the body [1]. Although it has advantages over other cancer therapy strategies, it lacks clinical efficacy [5]. At the same time, recent evidence suggests that the combination of immunotherapy and chemotherapy as a anticancer treatment may provide substantial clinical benefits for patients with advanced disease [6, 7].

All things considered, which is the best time-concentration profile for the chemo- and immunotherapy administration that led to the maximum therapeutic effect for a specific patient? Experimentally, this question is impossible to answer. It would be infeasible and both unethical to test all the possible dosing schedules in pre-clinical or clinical studies [8] using exhaustive, medically guided, expensive trial-and-error approaches [9]. his is where modern math and oncology came across, making the personalized cancer medicine and the optimization of a patient therapeutic care a realistic ambition. Mathematical modeling would not only challenge current paradigms, redefine the knowledge of mechanisms driving tumorigenesis and shape future research in cancer biology, but also enable the systematic search through these millions of possible dose administration strategies and drug combination schedules tailored for the patient [8]. By applying for instance, theory of optimal control to an anticancer therapy mathematical model, an optimal therapy for a given patient can be found.

Overall, this work aims at (i) expanding an existing Ordinary Differential Equation (ODE) mathematical model of tumor growth [10] incorporating innate and adaptive immune responses with combination of immuno- and chemotherapy as anticancer therapies, to include tumor heterogeneity and chemotherapy-drug-resistance onset; (ii) designing an optimal schedule for the expanded model using optimal control techniques.

The outline of this paper is as follows. In 2, two models from de Pillis et al. [10], and Hahnfeldt et al. [11] are combined and the assumptions underlying the resultant model specified. Finally, the system ODEs that form the mathematical model are presented. In 3, two optimal control problems regarding the minimization of two objectives with linear and quadratic dependence on the controls are formulated. Furthermore, the Pontryagin's principle necessary conditions for optimality are presented. In 4, two indirect gradient-based algorithms are proposed for the minimization of the linear and quadratic objectives presented in 3. In 5 the optimal combination therapy obtained with the aforementioned algorithms are presented for two distinct tumor burdens. Finally, in 6 some conclusions are provided, and in 7 and 8, the achievements and limitations of the work developed are discussed and suggestions are made regarding future work, respectively.

2. Model formulation

Since the development of drug resistance is the major reason behind chemotherapy failing and the immune system is implicated in the efficacy of chemotherapy, the development of tumor mathematical models that explore both realities is of utmost importance to develop effective anti-cancer therapies. So far, there is not a single model that combines immune dynamics and the development of drug resistance to chemotherapy. Accordingly, a tumor-immune ODE model from de Pillis et al. [10], and a tumor-chemotherapy ODE model from Hahnfeldt et al. [11] are combined. The resulting model is not only capable of generating the observed *in vivo* tumor behaviors exhibited by each individual model, but also some important behaviors related with the chemotherapy resistance onset.

2.1. Model assumptions

The assumptions underlining the resulting model reflect the assumptions behind the two original models [10, 11]. Some of these assumptions were modified in order to improve these models and enable their coherent combination:

- Tumor cells are considered to follow a logistic growth law in the absence of an immune response and anticancer treatment;
- The initial tumor burden T_0 is considered to be composed mostly of sensitive cells and few intrinsically resistant cells;
- Sensitive cells acquire drug resistance through (epi)genetic mutations. The higher the drug concentration, the more probable cancer cells are to develop chemotherapy resistance;
- Resistant tumor cells re-sensitization occur by chance through random (epi)genetic mutations;
- Resistant tumor cells are considered to be as sensitive to the immune response as the sensitive chemotherapeutic tumor cells.

Generally, the strategies behind the acquisition of chemotherapy resistance are different from the cancer immunoevasive strategies. Therefore, it is reasonable to admit that drug resistance does not affect the immune response. However, this conjecture may not be totally correct since the alteration of the apoptotic machinery as a strategy of drug resistance may prevent cancer cells from being killed by cytotoxic immune cells.

2.2. ODE model

The model presented here describes the kinetics of five populations (tumor cells with distinct sensibility to chemotherapy and three types of immune cells), as well as two drug bloodstream concentrations. The populations at time t are denoted by:

- $S(t)$, cancer cells sensitive to the chemotherapy treatment;
- $R(t)$, cancer cells resistant to the chemotherapy treatment;
- $N(t)$, total Natural Killer (NK) cell population;
- $L(t)$, total cytotoxic T cells (T_C) cell population;
- $W(t)$, number of white blood cells (circulating lymphocytes);
- $C(t)$, chemotherapy drug concentration in the bloodstream;
- $I(t)$, immunotherapy drug (IL-2) concentration in the bloodstream.

All things considered, the final model, further referred as the dynamic $\dot{x} = F(x,t)$, is mathematically described by the following system of equations:

$$
\begin{aligned}
\dot{S} &= r_S \left(1 - \frac{S+R}{T_{max}}\right) S - c_1 N S - D S \\
&\quad - \frac{C}{C_{max}} P_{SR} S + P_{RS} R - c_S \left(1 - e^{-C}\right) S, \\
\dot{R} &= r_R \left(1 - \frac{S+R}{T_{max}}\right) R - c_1 N R - D R \\
&\quad + \frac{C}{C_{max}} P_{SR} S - P_{RS} R - c_R \left(1 - e^{-C}\right) R, \\
\dot{N} &= a_1 W + \rho_1 \frac{T^2}{s_1 + T^2} N - d_1 N - c_2 T N \\
&\quad - c_N \left(1 - e^{-C}\right) N, \\
\dot{L} &= \rho_2 \frac{D^2 T^2}{s_2 + D^2 T^2} L + (a_2 N + a_3 W) T \\
&\quad - d_2 L - c_3 T L - c_4 N L^2 + \rho_3 \frac{L I}{s_4 + I} \\
&\quad - c_L \left(1 - e^{-C}\right) L + u_L(t), \\
\dot{W} &= a_4 - d_3 W - c_w \left(1 - e^{-C}\right) W, \\
\dot{C} &= -k_c C + u_c(t), \\
\dot{I} &= -k_i I + u_i(t),
\end{aligned}
\tag{1}
$$

The terms u_L, u_c, u_i concern the temporal administration of Tumor Infiltrating Lymphocytes (TILs), chemotherapy, and Interleukin-2 (IL-2), respectively. At day 7, 5×10^{11} TILs are administered as a bolus. Both IL-2 and TILs take part of an anticancer immunotherapy called Adoptive Cell Transfer (ACT). Table 1 presents a list of the model parameters, their meaning, their estimated value and their source.

3. Optimal control problem formulation

The main objective of this study is to design a drug schedule that eliminates the tumor level at the end of treatment, while infusing the least drug dosage (to avoid toxicity), and maintaining low tumor levels along the treatment [21]. Let $b = (1,1,0,0,0,0,0)$, $e = (1,1,0,0,0,0,0)$, $m = (2, 8 \times 10^{-7})$ be row vectors of non-negative weights and $T = 120$ days an *a priori* specified therapy horizon. The state is denoted by $x = (R, S, N, L, W, C, I)$ and the control by $u = (u_c, u_i)'$. The aforementioned goals can be translated in the following linear (L1-norm) and quadratic (L2-norm) cost functions

$$
J(u(t)) = b\,x(T) + \int_{t_0}^{T} e\,x(t) + m\,u(t)\,\mathrm{d}t, \tag{2}
$$

$$
J(u(t)) = b\,x(T) + \int_{t_0}^{T} e\,x(t) + \frac{1}{2} m\,[u(t)]^2\,\mathrm{d}t, \tag{3}
$$

respectively.

Optimal control theory is then used to minimize the linear and quadratic performance objectives imposed on the dynamical system (1) subjected to some constraints [9]. Controls (chemotherapy- and immunotherapeuthic agents) are applied to (1) inducing a system response [9]. The performance index, in other words a performance measure of the system, is evaluated based on the system response [9]. This objective function is then minimized through the Pontryagin's minimum principle. The process is repeated iteratively until some criteria are met and the optimal therapy schedule is obtained.

The two optimization problems are formulated as

[OC] For a specified terminal time T:

$$
\begin{aligned}
\min_{u(t)} \quad & J(u(t)) \qquad \text{given by (2) or (3)} \\
s.t. \quad & \dot{x}(t) = F\left(x(t), u(t)\right) \qquad \text{given by (1)}, \\
& x(t_0) = x_0, \\
& t \in [t_0, T], \\
& u(t) \in U = [0,5] \times [0, 5 \times 10^6] \subset \mathbb{R}^2,
\end{aligned}
\tag{4}
$$

where $x_0 = (0.995T_0,\ 0.05T_0,\ 10^3,\ 10,\ 6 \times 10^8,\ 0,\ 0)$. The initial tumor burdens considered are $T_0 = \{3.2 \times 10^6,\ 4.0 \times 10^7\}$.

Table 1: Description and value of the parameters used in the resulting model. Adapted from [10].

Param.	Value	Units	Description	Source
r_S	4.31×10^{-1}	day^{-1}	Growth rate of sensitive tumor cells.	M [12]
r_R	1.44×10^{-1}	day^{-1}	Growth rate of resistant tumor cells.	$\hbar$
T_{max}	9.80×10^{8}	day^{-1}	Carrying capacity.	M [12]
P_{SR}	0.15	$cell^{-1}$	Transitioning rate between the sensitive and resistant compartments.	[13]
P_{RS}	5.00×10^{-4}	$cell^{-1}$	Transitioning rate between the resistant and sensitive compartments.	$\hbar$
c_1	6.41×10^{-11}	$cell^{-1}$	Fractional tumor cell kill by NK cells.	H,M [7, 12]
c_2	3.42×10^{-6}	$cell^{-1}day^{-1}$	NK cell inactivation rate by tumor cells.	M [12]
c_3	1.42×10^{-6}	$cell^{-1}day^{-1}$	T_C cell inactivation rate by tumor cells.	M [14]
c_4	3.00×10^{-10}	$cell^{-2}day^{-1}$	Regulatory function by NK cells on T_C cells.	[10]
c_5	2.34	day^{-1}	Saturation level of fractional tumor cell kill by T_C cells.	H [7]
a_1	2.08×10^{-7}	day^{-1}	Fraction of circulating lymphocytes that become NK cells.	M [14]
a_2	1.10×10^{-7}	$cell^{-1}day^{-1}$	T_C cells production rate due to stimulation by tumor cells killed by NK cells.	M [15, 16]
a_3	6.50×10^{-11}	$cell^{-1}day^{-1}$	T_C cells production rate due to stimulation by tumor cells interacting with circulating lymphocytes.	[10]
a_4	7.5×10^{8}	$cellday^{-1}$	Constant source of circulating lymphocytes.	H?
d_1	4.12×10^{-2}	day^{-1}	Death rate of NK cells	M [14]
d_2	0.204	day^{-1}	Death rate of T_C cells.	M [15]
d_3	1.20×10^{-2}	day^{-1}	Natural death and differentiation of circulating lymphocytes.	H ?
ρ_1	1.25×10^{-2}	day^{-1}	Maximum NK cell recruitment rate by tumor cells.	H,M [7, 12]
ρ_2	2.49×10^{-2}	day^{-1}	Maximum T_C cell recruitment rate.	H,M [7, 12]
ρ_3	0.125	day^{-1}	Maximum T_C cell recruitment rate by IL-2.	[17]
c_S	0.90	day^{-1}	Fractional sensitive tumor cell kill by chemotherapy.	[18]
c_R	0.10	day^{-1}	Fractional resistant tumor cell kill by chemotherapy.	$\hbar$
c_N,c_L, c_W	0.60	day^{-1}	Fractional immune cell kill by chemotherapy.	[18]
k_c	0.90	day^{-1}	Rate of chemotherapy drug decay.	[19]
k_i	1.00	day^{-1}	Rate of IL-2 decay.	[17]
s_1	2.02×10^{7}	$cell^2$	Steepness coefficient of the NK cell recruitment curve.	M [14]
s_2	3.66×10^{7}	$cell^2$	Steepness coefficient of the T_C cell recruitment.	H,M [7, 12]
s_3	8.39×10^{-2}	none		H [7]
s_4	2.00×10^{7}	$cell^2$	Steepness of T_C cell recruitment curve by IL-2.	[17]
λ	2.09	none		H [7]
Til	5×10^{11}	$cell$	Number of TIL administered.	H [20]

[M] Mouse data; [H] Human data; [$\hbar$] Estimated; [?] Data no longer available. See Bannock (2002); Hauser (2001) from [10].

3.1. Pontryagin's principle necessary conditions for optimality

The adjoint equation and transversality condition for model (1) read

$$\dot{\lambda}'(t) = -\lambda(t)' f_x(x(t), u(t)) - e, \tag{5}$$

$$\lambda(T) = b. \tag{6}$$

regardless of the objective dependence on the control $u(t)$. The Hamiltonian $H(\lambda(t), x(t), u_c(t), u_i(t))$ for the linear and the quadratic objective are

$$H(\lambda(t), x(t), u_c(t), u_i(t)) = e\,x(t) + m_1\,u_c(t) + m_2\,u_i(t) + \lambda(t)' f(x(t), u_c(t),\, u_i(t)), \tag{7}$$

$$H(\lambda(t), x(t), u_c(t), u_i(t)) = e\,x(t) + \frac{1}{2} m_1\,[u_c(t)]^2 + \frac{1}{2} m_2\,[u_i(t)]^2 + \lambda(t)' f(x(t), u_c(t),\, u_i(t)), \tag{8}$$

respectively.

In order to decrease the complexity of the optimal control problems, singular control arcs are not considered as optimal candidates.

4. Numerical approach

In order to find the optimal combination therapy for the dynamics, four indirect numerical methods are implemented in order to found the optimal combination therapy for the dynamics (1). However, only the gradient-based algorithms are capable of converging to the optimal solution. Therefore, only these algorithms are presented. Index j represents the iteration number, N_{it} the maximum number of iterations pre-established and N_{int} the number of time subintervals accordingly with the time discretization considered. For the sake of simplicity, the temporal dependency of some functions is omitted.

4.1. Algorithm B

This algorithm is an adaptation of the gradient method from Duda [22]. The optimal solutions are considered to be a bang-bang process. Accordingly, the initial guess of $u(t)$ is an alternate function that switches from u_{max} to u_{min} and so on at the N_s switching times $(t_1^s, ..., t_{N_s}^s)$, starting in u_{max} as represented in figure 1.

Mathematically, $u(t)$ is given by

$$u(t) = \sum_{n=1}^{N_s} g(n) \left[\theta\left(t - t_n^s\right) - \theta\left(t - t_{n+1}^s\right)\right], \tag{9}$$

where θ is the heaviside step function, $t_0^s = t_0$ and $t_{N_s+1}^s = T$. If n is even then $g(n) = u_{max}$, otherwise

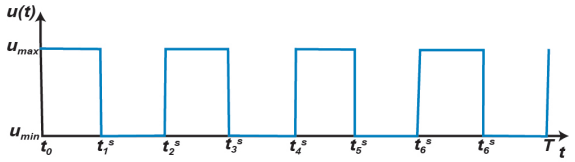


Figure 1: The initial guess of algorithm B is a bang-bang process.

$g(n) = u_{min}$. The number of switching times (N_s) is specified at the beginning. Although the switching times can collapse and thus disappear, N_s determines the maximum number of transitions. An upper limit can be assumed to N_s based on the clinical reality and the properties of the drug being used [22].

In the long run, the steps of this algorithm are described as:

1. Subdivide the interval $[t_0, T]$ into Ni_{int} equal subintervals;

2. Choose N_s, compute t_n^s and store them in vector vts. Compute the subinterval index referent to those t_n^s and store those indexes in vector $vtsi$;

3. Admitting that the control is a bang-bang process given by expression (9), compute $u(t)$ using $vtsi$;

4. Integrate the state equation $\dot{x}(t) = F(x(t), u(t))$ from $[t_0, T]$ with initial value x_0 using $u(t)$. Store the state trajectory $x(t)$;

5. Integrate the adjoint equation (5) backwards in time, i.e. $[T, t_0]$ with final condition $\lambda(T)$ using the $u(t)$ and $x(t)$ obtained in step **3.** and **4.**. Store the costate trajectory $\lambda(t)$;

6. Compute the performance index $J^{(j)}(u)$, $\frac{\partial H(t_n^s)}{\partial u}$, κ_1 and κ_2 for all the controls

$$\kappa_2 = \sum_{n=1}^{N_s} \left(\frac{\partial H(t_n^s)}{\partial u}^{(j)} - \frac{\partial H(t_n^s)}{\partial u}^{(j-1)} \right)^2. \tag{10}$$

6.1. If $J^{(j)}(u) > J^{(j-1)}(u)$:

6.1.1. Considering that $u(t) = (u_c, u_i)$, stop if

$$\begin{aligned} &(\kappa_1(u_i) \leq \varepsilon_1 \wedge \kappa_1(u_c) \leq \varepsilon_1) \vee \\ &[(\kappa_1(u_c) \leq \varepsilon_1 \vee \kappa_2(u_c) \leq \varepsilon_1) \wedge \\ &(\kappa_1(u_i) \leq \varepsilon_1 \vee \kappa_2(u_i) \leq \varepsilon_1)]; \end{aligned} \tag{11}$$

6.1.2. If $\kappa_1 > \varepsilon_1 \wedge \kappa_2 > \varepsilon_1$:

6.1.2.1. Return to the initial values of the previous iteration saved in **8.** and reduce the step size ($w_1 < 1$) according to

$$\eta(t_n^s)^{j-1} = w_1 \times \eta(t_n^s)^{j-1}; \tag{12}$$

6.1.2.2. Decrease the iteration number $j = j - 1$ and jump to step **10.**;

7. Evaluate the stopping criteria

$$\left(\left| J^{(j)}(u) - J^{(j-1)}(u) \right| \leq \varepsilon_2 \ \wedge \ \sum_{n=1}^{N_s} [\,\delta(t_n^s)\,]^2 \leq \varepsilon_1 \right) \ \vee$$
$$\text{Number of } t^s = 0 \ \vee \ j \geq N_{it}; \tag{13}$$

Note: Initialize $J^{(0)} = -\infty$ and $\delta(t_n^s)$ as a vector of $-\infty$.

Steps **8.**, **9.**, **10.**, **11.** and **12.** are only performed for the controls whose $\kappa_1 > \varepsilon_1 \vee \kappa_2 > \varepsilon_1$.

8. Save $u(t)$, vts, vts, $\frac{\partial H(t_n^s)}{\partial u}$, $J^{(j-1)}(u)$ and $J^{(j)}(u)$ in a matrix;

9. Compute the step size η for each t_n^s (w_2 is a weight)

$$\eta(t_n^s) = \begin{cases} 0, & \frac{\partial H(t_n^s)}{\partial u} = 0, \\ w_2 \times 10^{-floor\left(\log_{10}\left|\frac{\partial H(t_n^s)}{\partial u}\right|\right)-1}, & \frac{\partial H(t_n^s)}{\partial u} \neq 0; \end{cases} \tag{14}$$

10. Compute $\delta(t_n^s)$

$$\delta(t_n^s) = -\eta(t_n^s)\, ind_n\, \frac{\partial H(t_n^s)}{\partial u}, \tag{15}$$

where

$$ind_n = \begin{cases} 1, & u(t_n^s) = u_{max} \text{ on } [t_{n-1}^s, t_n^s[, \\ -1, & u(t_n^s) = u_{min} \text{ on } [t_{n-1}^s, t_n^s[; \end{cases} \tag{16}$$

11. Compute the new $\frac{\partial H(t_n^s)}{\partial u}$ one by one

$$t_n^s = t_n^s + \delta(t_n^s), \tag{17}$$

and update vts, and $vtsi$ accordingly.

11.1. If $t_1^s - t_0 \leq \varepsilon_3$ eliminate t_1^s;

11.2. If $T - t_N^s \leq \varepsilon_4$ eliminate t_N^s;

11.3. If $t_n^s - t_{n-1}^s \leq \varepsilon_3$ eliminate both t_n^s and t_{n+1}^s;

11.4. Update vts, and $vtsi$;

12. Update $u(t)$ using $vtsi$;

13. Repeat from **4.** until the stopping criteria are met. If the result is unexpected, increase the number of N_s and repeat all steps.

Note that each control has its own initial guess, N_s, vts, $vtsi$, $\kappa 1$, $\kappa 2$, η, δ, w_1, w_2, $\frac{\partial H(t_n^s)}{\partial u}$. Accordingly, the steps of algorithm B have to be performed for all the controls. By the same token the stopping criteria have to be met by all the controls.

4.2. Algorithm D

This gradient method is a modified version of the steepest descent method [23], inspired in a back-propagation algorithm for Neural Networks studied in the course Machine Learning at Instituto Superior Técnico. In this algorithm, two acceleration techniques proposed in [24, 25] are used, namely iterative step sizes and a momentum technique. Furthermore, some measures are taken for the purpose of preventing the cost function from increasing between iterations. Generally speaking, the numerical algorithm is as follows:

1. Subdivide the interval $[t_0, T]$ into N_{int} equal subintervals;

2. Make an initial guess for the control $u(t)$, which must be piecewise-constant for each subinterval;

3. Integrate the state equation $\dot{x}(t) = F(x(t), u(t))$ from $[t_0, T]$ with initial value x_0 using the $u(t)$. Store the state trajectory $x(t)$;

4. Integrate the adjoint equation (5) backwards in time, i.e. $[T, t_0]$ with final condition $\lambda(T)$ using the $u(t)$ and the $x(t)$ obtained previously. Store the costate trajectory $\lambda(t)$;

5. Compute the performance index $J^{(j)}(u)$, $\frac{\partial H}{\partial u}$ and κ_2 for all the controls

$$\kappa_2 = \sum_{t=1}^{N_{int}+1} \left(\left[\frac{\partial H(t)}{\partial u} \right]^{(j)} - \left[\frac{\partial H(t)}{\partial u} \right]^{(j-1)} \right)^2; \quad (18)$$

5.1. If $J^{(j)}(u) > J^{(j-1)}(u)$:

5.1.1. Compute κ_1

$$\kappa_1 = \sum_{t=1}^{N_{int}+1} \left[\eta(t)^{(j)} g(t)^{(j)} \right]^2, \quad (19)$$

5.1.2. Considering that $u(t) = (u_c, u_i)$, stop if

$$\begin{aligned} &(\kappa_1(u_i) \leq \varepsilon_1 \wedge \kappa_1(u_c) \leq \varepsilon_1) \vee \\ &[(\kappa_1(u_c) \leq \varepsilon_1 \vee \kappa_2(u_c) \leq \varepsilon_1) \wedge \\ &(\kappa_1(u_i) \leq \varepsilon_1 \vee \kappa_2(u_i) \leq \varepsilon_1)]; \end{aligned} \quad (20)$$

5.1.3. If $\kappa_1 > \varepsilon_1 \ \wedge \ \kappa_2 > \varepsilon_1$:

5.1.3.1. Return to the initial values of the previous iteration saved in **7.** and reduce the step size parameters $(w_3 < 1)$ according to

$$w_1 = w_3 \times w_1, \quad (21)$$

$$w_2 = w_3 \times w_2; \quad (22)$$

5.1.3.2. Set the momentum memories to zero, i.e. $g(t) = 0$ for each time subinterval;

5.1.3.3. Decrease the iteration number $j = j - 1$ and jump to step **8.**;

6. Evaluate the stopping criteria

$$\begin{aligned} &\left(\left| J^{(j)}(u) - J^{(j-1)}(u) \right| \leq \varepsilon_2 \ \wedge \right. \\ &\left. \sum_{t=1}^{N_{int}+1} \left(\left[\frac{\partial H(t)}{\partial u} \right]^{(j)} - \left[\frac{\partial H(t)}{\partial u} \right]^{(j-1)} \right)^2 \leq \varepsilon_1 \right) \vee \\ &j \geq N_{it}; \end{aligned} \quad (23)$$

Note: Initialize $J^{(0)} = -\infty$ and $\left[\frac{\partial H}{\partial u} \right]^{(j=0)}$ as a vector of $-\infty$.

Steps **7.**, **8.**, **9.**, and **10.** are only performed for the controls whose $\kappa_2 > \varepsilon_1$.

7. Save $u(t)$, $\frac{\partial H}{\partial u}$, $J^{(j-1)}(u)$ and $J^{(j)}(u)$ in a matrix;

8. Compute the weights $\eta^{(j)}$ for each subinterval

$$\eta^{(j=1)}(t) = \begin{cases} 0, & \frac{\partial H(t)}{\partial u} = 0, \\ w_4 \, 10^{-floor\left(\log_{10}\left| \frac{\partial H}{\partial u} \right|\right)-1}, & \frac{\partial H(t)}{\partial u} \neq 0; \end{cases} \quad (24)$$

$$\eta^{(j\neq 1)}(t) = \begin{cases} w_1 \, \eta^{(j-1)}(t), & \left[\frac{\partial H}{\partial u} \right]^{(j)} \left[\frac{\partial H}{\partial u} \right]^{(j-1)} > 0, \\ w_2 \, \eta^{(j-1)}(t), & \left[\frac{\partial H}{\partial u} \right]^{(j)} \left[\frac{\partial H}{\partial u} \right]^{(j-1)} < 0, \end{cases} \quad (25)$$

where $w_1 > 1$, and $w_2 < 1$.

9. Compute $g^{(j)}$ according to

$$g^{(j)}(t) = \left[\frac{\partial H}{\partial u} \right]^{(j)} + w_5 \, g^{(j-1)}(t), \quad (26)$$

where $0 \leq w_5 < 1$.

10. Update the optimal control(s) $u(t)$

$$u^{(j+1)}(t) = u^{(j)}(t) - \eta^{(j)}(t) \, g^{(j)}(t); \quad (27)$$

11. Repeat from **3.** until the stopping criteria are met.

Note that each control has its own initial guess, g, $\frac{\partial H}{\partial u}$, η, $\kappa 1$, $\kappa 2$, w_1, w_2, w_3, w_4, w_5. Accordingly, the steps of algorithm D are performed for all the controls. Finally, the stopping criteria have to be met by all the controls.

4.3. Control parameters

The choice of the control parameters for the algorithms B and D has a direct impact on the optimal solution found. Consequently, an exhaustive search for the optimal combination of the control parameters is made for each numerical simulation present below. Several combinations of the control parameters were tested. The parameters set that has resulted in the lowest objective was chosen.

5. Combination therapy Results

In this section, the results from the optimal control problems are presented. Subsequently, a comparison of the results obtained with algorithms B and D.

5.1. Algorithm B: L1-norm

Figure 2 presents the optimal controls u_c^* and u_i^* resultant from the minimization of the linear objective (2), the system dynamics response, as well as the Hamiltonian functions and the evolution of the controls towards optimality, for $T_0 = 3.2 \times 10^6$ and $T_0 = 4.0 \times 10^7$. Combination therapy is successful to eradicate $T_0 = 3.2 \times 10^6$ cells, when chemotherapy is administered between day 0.0 and day 8.5. At the same time, IL-2 is administered from day 0.0 to day 5.0. Note that TILs have been administered at day 7.0. Therefore, there is not a simultaneously administration of the IL-2 and TILs. Sensitive and resistant chemotherapeutic cells are eradicated at day 11 and day 13, respectively. The eradication of the tumor was expected since chemotherapy by itself eliminates this tumor burden. Both chemo- and immunotherapy just need to be administered until the immune system has the full capacity to eradicate the remaining tumor burden.

With regards to $T_0 = 4.0 \times 10^7$, neither immunotherapy nor chemotherapy alone cannot eradicate this tumor burden), combination therapy has successfully eradicated the tumor burden. Chemotherapy and IL-2 are administered between day 0 and day 10, and day 0 and day 7, respectively. Thus administration of IL-2 and TILs coincide in time. Sensitive and resistant chemotherapeutic cells are eradicated at day 12.0 and day 14.5, respectively. As expected, a higher period of therapy administration is obtained for $T_0 = 4.0 \times 10^7$ comparatively with $T_0 = 3.2 \times 10^6$. Moreover, tumor cells are first eradicated in the case of $T_0 = 3.2 \times 10^6$ relatively to $T_0 = 4.0 \times 10^7$. Forthwith, the value of the objective $\left(J(u^*) = 1.31 \times 10^8\right)$ is higher for $T_0 = 4.0 \times 10^7$ than it is $T_0 = 3.2 \times 10^6$ $\left(J(u^*) = 1.04 \times 10^7\right)$. Over again, both chemo- and immunotherapy are only administered until the patient immune system has the full capacity to eradicate the remaining tumor burden.

The Hamiltonian functions are not constant in the subintervals corresponding to the first 10 days, which is a signal of non-optimality. The higher the tumor burden, and by the same token the higher the cost function, the more prominent is the bad behavior of the Hamiltonian, specially for chemotherapy. These behaviors may come from numerical errors, a high discretization time (0.5 day) considered in algorithm B and D steps 1. and 1., respectively, or even a poor selection of the control parameters. Moreover, the optimal solution that would give rise to a constant Hamiltonian may not be a solution of the dynamics or it does not comply with the constraints imposed. Furthermore, a high time discretization and a poor selection of the control parameters may result in a solution distinct of the optimal one.

At last, figure 2 *Convergence to* u_i^* and 2 *Convergence to* u_c^*, top and bottom, are a reflex of the control parameters considered for each case. See the caption of figure 2 for more informations. In all these images, it is evident that the control is converging towards optimality.

5.2. Algorithm D: L2-norm

Figure 2 presents the optimal controls u_c^* and u_i^*, the system dynamics response to them, as well as the Hamiltonian functions and the evolution of the controls towards optimality, for $T_0 = 3.2 \times 10^6$ and $T_0 = 4.0 \times 10^7$, the quadratic objective (3).

As seen for algorithm B, the combination therapy also eradicates an initial tumor burden of $T_0 = 3.2 \times 10^6$ (see figure 3 top), as chemotherapy alone. Chemotherapy is administered from day 0.0 until day 12.0. However, an insignificant interruption on the chemotherapy administration seems to occur between day 10.5 and day 11.5. Meanwhile, IL-2 is given between day 7.0 and day 12.0. The TILs and IL-2 administration coincides in time. A residual administration of IL-2 exists almost during the 120 days. Sensitive and resistant chemotherapeutic cells are eradicated at day 11.5 and day 13.0, respectively.

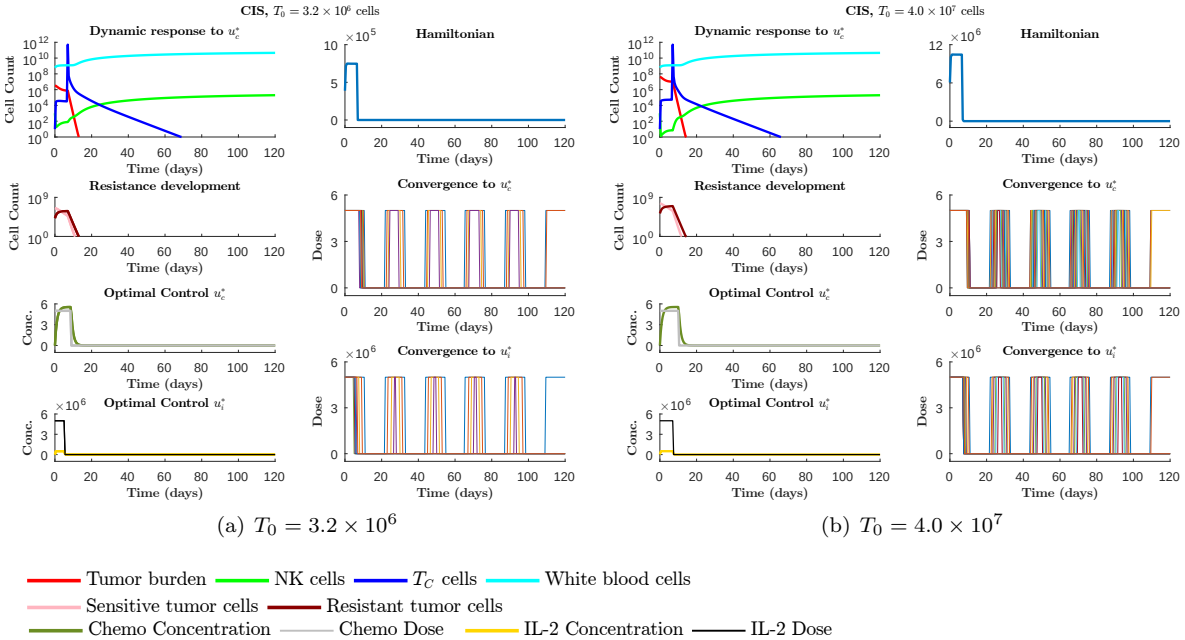
When a tumor burden of $T_0 = 4.0 \times 10^7$ cells is considered, neither immunotherapy nor chemotherapy alone cannot eradicate this tumor burden) combination therapy is capable of doing so (see figure 3 bottom). Chemotherapy and IL-2 are administered between day 0.0 and day 12.0, and day 7.5 and day 10.5, respectively. Sensitive and resistant chemotherapeutic cells are eradicated at day 12.5 and day 14.5, respectively. Accordingly, a higher therapy administration period is obtained for $T_0 = 4.0 \times 10^7$ relatively to $T_0 = 3.2 \times 10^6$. In addition, tumor cells are first eradicated for $T_0 = 3.2 \times 10^6$ than for $T_0 = 4.0 \times 10^7$. Consequently, the value of the performance index $\left(J(u^*) = 1.29 \times 10^8\right)$ is higher than the one obtained for $T_0 = 3.2 \times 10^6$ $\left(J(u^*) = 1.02 \times 10^7\right)$.

As before, the Hamiltonian functions are not constant in the beginning of the time axis. The higher the initial tumor burden, and therefore the higher the cost functions, the more pronounced is the bad behavior of the Hamiltonian functions.

Finally, figures 3 *Convergence to* u_i^* and 3 *Convergence to* u_c^*, top and bottom, reflect the control parameters considered for each T_0. The initial guess considered for the IL-2 is almost the optimal control.

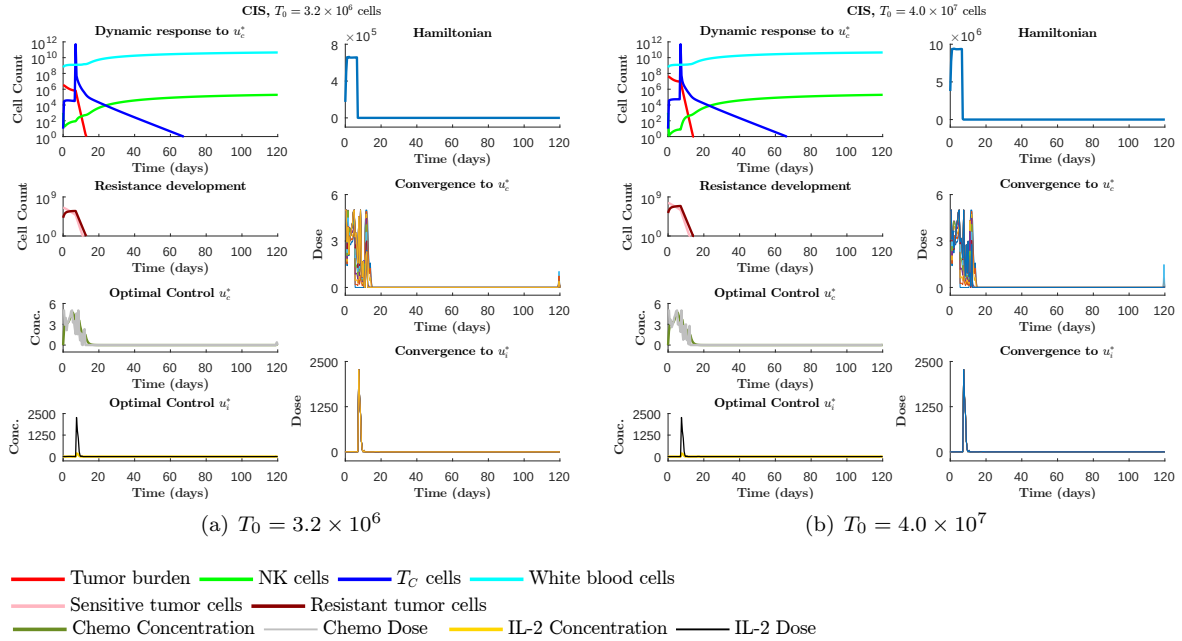
5.3. Comparison of the L1- and L2-norm performance indexes

Considering the results obtained for the two initial tumor burdens with the linear and quadratic per-



(a) $T_0 = 3.2 \times 10^6$ (b) $T_0 = 4.0 \times 10^7$

Figure 2: **(a)** and **(b)** left side: Dynamic response of model (1), resistance onset when the optimal control for chemotherapy and IL-2 are administered for $T_0 = 3.2 \times 10^6$ and $T_0 = 4.0 \times 10^7$. **(a)** and **(b)** right side: the Hamiltonian and evolution of the controls towards optimality. Simulation parameters:Compromised Immune System (CIS) initial conditions, quadratic objective, $N_{int} = 240$, $N_s = 10$, $T = 120$, $\varepsilon_1 = \varepsilon_2 = 10^{-10}$, $\varepsilon_4 = 10$, $w_1 = 0.8$ for both u_c and u_i. For u_c and $T_0 = 3.2 \times 10^6$, $\varepsilon_3 = 4$ and $w_2 = 4$. For u_c and $T_0 = 4.0 \times 10^7$, $\varepsilon_3 = 0.5$ and $w_2 = 1.5$. For u_i and $T_0 = 3.2 \times 10^6$, $\varepsilon_3 = 1$ and $w_2 = 2$. For u_i and $T_0 = 4.0 \times 10^7$, $\varepsilon_3 = 1$ and $w_2 = 0.9$. Model (1).



(a) $T_0 = 3.2 \times 10^6$ (b) $T_0 = 4.0 \times 10^7$

Figure 3: **(a)** and **(b)** left side: Dynamic response of the model (1), resistance onset when the optimal control for chemotherapy and IL-2 are administered for $T_0 = 3.2 \times 10^6$ and $T_0 = 4.0 \times 10^7$. **(a)** and **(b)** right side: the Hamiltonian and the evolution of the controls towards optimality. Simulation parameters: Compromised Immune System (CIS) initial conditions, quadratic objective, $N_{int} = 240$, $T = 120$, $w_1 = 1.2$, $w_2 = 0.99$, $w_3 = 0.41$, $w_4 = 0.94$, $w_5 = 0.61$, except for immunotherapy where $w_5 = 0.35\,\varepsilon_1 = \varepsilon_2 = 10^{-10}$. For u_i and $T_0 = 4.0 \times 10^7$, $w_4 = 0.83$. Model (1).

Table 2: Results of the minimization of the linear and quadratic performance indexes for two initial tumor burdens when a compromised IS is considered.

J Norm	T_0	**Chemo. admin. period** (day)	**Immuno. admin. period** (day)	**S cells erad.** (day)	**R cells erad.** (day)	**Cost function**	**Tumor erad.**
L1	3.2×10^6	$0.0 - 8.5$	$0.0 - 5.0$	11.0	13.0	1.04×10^7	✔
	4.0×10^7	$0.0 - 10.0$	$0.0 - 7.0$	12.0	14.5	1.31×10^8	✔
L2	3.2×10^6	$0.0 - 12.0$	$7.0 - 10.5$	11.5	13.0	1.02×10^7	✔
	4.0×10^7	$0.0 - 12.0$	$7.5 - 10.5$	12.5	14.5	1.29×10^8	✔

formance indexes (see table 2), the chemotherapy administration period is higher for the L2-norm cost function than for the linear one. Interestingly, the opposite occurs for the IL-2 administration period. The higher administration periods obtained for the L1-norm objective may have resulted from the way in which algorithm B is implemented. In fact, the initial time t_0 was not considered to be a switching time (it is fixed), and the initial guesses for the controls are considered to begin in their maximum admissible value.

Despite having the same order of magnitude, the performance indexes are higher for the L1-norm relatively to the L2-norm objectives, which favor lower drug concentrations. Even though higher chemotherapy doses are administered in the case of the L1-norm and the treatments are ceased earlier comparatively with the L2-norm objective, both sensitive and resistant tumor cells are first eradicated for the L2-objective. However, for $T_0 = 4.0 \times 10^7$, the resistant tumor cells are eliminated in the same day, regardless the objective norm considered. Provided that a lower discretization time was used, resistant tumor cells would have been eradicated in different time subintervals. Interestingly, sensitive tumor cells are first eradicated than the resistant ones, even in the case of the L1-norm.

6. Conclusions

The combination of both therapies enables the eradication of tumor burdens that are not possible to eliminate by none of these therapies *per se*. The results obtained here demonstrate that rather than aiming at fully eradicate the tumor burden, combination therapy intends to restore the equilibrium of the immunosurveillance mechanism.

These results highlight the importance of modeling anticancer therapies together with the immunosurveillance mechanism. Under those circumstances, lower drug doses are administered. Furthermore, disregarding the onset of chemotherapeutic resistance would lead to the design of inaccurate drug schedules, that in the long run could result in a worst prognosis for the patient, due to the highly genomically unstable resistant tumor cells created.

Regarding the optimal control problems formulated in this work, the minimization of L1-or L2-type objectives leads to optimal solutions with distinct mathematical characteristics. Besides favouring the administration of lower drug doses relatively to L1- cost functions, L2-objectives also privilege higher therapeutic administration periods. These solutions must not be used as a mathematical replacement or approximation of the other [26]. It is up to medical practitioners to decide which solutions best fit the specific patient biological situation and whether any of the results can be used for practical implementation [26].

In the final analysis, the development of predictive pre-clinical models of human cancer may not only reduce the expense of drug development, but also provide "personalized molecular medicine" at affordable cost in a near future [1]. Only these type of approaches will enable the administration of therapies in an optimal way, balancing the therapeutic benefits of treatment with its side effects.

7. Achievements and limitations

For the first time in the literature, an ODE model combining chemotherapy, chemotherapy resistance, immunotherapy and a realistic immune response is proposed. Although this model was born as a combination of the de Pillis et al. [10] and Hahnfeldt et al. [11] models, some novelties are introduced. Unlike anything seen so far, the onset of chemotherapeutic resistance is modeled as being proportional to the chemotherapy blood concentration.

With regards to optimal control, the linear Duda [22] algorithm is modified and improved, giving rise to Algorithm B. Concerning the L2 objective function minimization, a backpropagation algorithm for neural networks (Silva and Almeida [24, 25]) is adapted and modified, resulting in algorithm D. In both algorithms, the stopping criteria are evaluated after the computation of the new performance index, in order to avoid unnecessary steps. In addition, the step size in algorithm B and the initial step size in algorithm D, are considered as a function of $\frac{\partial H}{\partial u}$ for each time subinterval.

Despite the aforementioned achievements, there are several limitations that deserve to be addressed, namely:

- Chemotherapy is assumed to kill a fraction of tumor cells and not only the ones actively dividing;
- The number of cells the drug bloodsteam concentrations on model (1) are 'forced' to be positive in order to avoid unrealistic model behaviors;
- Most of the parameters used in this study came from murine experiments or from unknown origin [27]. As a result, the model proposed here is not suitable for generating treatment schedules useful in the clinical practice;
- The singular control arcs were not considered as optimal candidates. However, in this field singular controls cannot be ruled out [27]. As a matter of fact, they might be the prime candidates to optimality with bang-bang controls only arising where singular control arcs are either inadmissible or inexistent [28];
- The algorithms implemented have some drawbacks, namely (i) the difficult choice of the optimal control parameters, (ii) in the case of algorithm B, the initial time t_0 is not considered to be a switching time;
- Time consuming integrations with *ode45*. Whenever the tumor is not eliminated, a single state integration can take more than 3.0 hours to be accomplished. Since algorithm B and D need several iterations to found the optimal controls, some simulations ran for more than one week without results;
- The Hamiltonian functions correspondent to the optimal solutions found present high value discontinuities, rather than being constant over time, which is a signal of non optimality.

8. Future Work

In this section some suggestions are made concerning the direction of the future work. Regarding the model:

- The re-sensitization of resistant tumor cells should also depend on chemotherapy bloodstream concentration. In other words, the smaller the bloodstream concentration of chemotherapy, the more probable resistant cells are of becoming sensitive to this drug. This can be achieved by replacing $P_{RS}R$ in (1) with $\left(1-\frac{C}{C_{max}}\right)P_{RS}R$;
- The further administration of of chemotherapeutic re-sensitizations drugs would be interesting [29, 30];
- To consider other scenarios of drug resistance. For example, the addition of more tumor cell populations with distinct sensitivities to chemotherapy. Moreover, rather than directly competing with one another, cells with distinct chemotherapy sensitivities may support the growth and survival of one another [1]. With this in mind, a positive term modeling the interactions between tumor populations could be added.
- The Model (1) should account for the role of inflammation in tumor progression. This can be done by adding a positive term in tumor cell equations proportional to a portion of the white blood cells W;
- To adapt model (1) to the cancer stem cell model and compare it with the clinical reality.

Finally, regarding the optimal control:

- Singular control arcs must be considered. They may privilege the administration of small drug doses and, therefore, a small development of drug resistance;
- The administration of TILs must be explored as a third control;
- Other cost functions could be experimented;
- Algorithm B must be modified so the initial time t_0 can also be considered as a switching time.

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