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Cancer immunotherapy, mathematical modeling and optimal control

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Abstract

Clinical immunologists, among other problems, routinely face a question: what is the best time and dose for a certain therapeutic agent to be administered to the patient in order to decrease/eradicate the pathological condition?

In cancer immunotherapies the therapeutic agent is something able to elicit an immune response against cancer. The immune response has its own dynamics that depends on the immunogenicity of the therapeutic agent and on the duration of the immune response. The question then is "how can we decide *when* and *how much* of the drug to inject so to have a prolonged and effective immune response to the cancer?".

This question can be addressed in mathematical terms in two stages: first one construct a mathematical model describing the cancer-immune interaction and secondly one applies the theory of optimal control to determine when and to which extent to stimulate the immune system by means of an immunotherapeutic agent administered in discrete variable doses within the therapeutic period. The solution of this mathematical problem is described and discussed in this article.

We show that the method employed can be applied to find the optimal protocol in a variety of clinical problems where the kinetics of the drug or treatment and its influence on the physiologic/pathologic functions have been described by a system of ordinary differential equations.

Keywords: Optimal control; Drug scheduling; Cancer; Immunotherapy; Autologous cells transfection

1. Introduction

In the field of mathematical biology one constructs mathematical models of certain phenomena and tries to derive biological knowledge from it. Clinical medicine requires theoretician to do one more step: to predict the outcome of the application of a certain therapeutic regimen. This task includes the description of the phenomena by means of a mathematical model and the addition of the terms describing the effects of one or more therapeutic agents. Therapeutic agents in cancer treatments are drugs or irradiation that influence directly the life of the pathogen but also the life of host cells. In other cases, as in immunotherapy, the goal is not to target the pathogen directly, but rather to stimulate the immune system (hence the name of this class of therapies) to react strongly to the pathogenic agent thus leading to an endogenous cure. Mathematical models of immunotherapies are models in which the immune cells and the pathogen are described together with the *indirect* influence of a certain therapeutic agent. Cancer immunotherapy is based on the idea of immune surveillance, that is a physiological function of the immune system to recognize and destroy clones of transformed cells before they grow in to tumors and, potentially, to kill tumors after they are formed.

The immune system is composed by a variety of cell types. Among these, the *dendritic cells* (DC) are perhaps the best of the so-called *antigen presenting cells* (APC) in that their work consists in capturing the *antigens* and show them to other cells called *effector cells* (i.e., cytotoxic T lymphocytes). If the presented molecules are "labeled" as dangerous, then the immune system mounts a specific response to eliminate the danger. *Dendritic cell transfection* is the practice of cultivating autologous dendritic cells

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(i.e., previously extracted from the same patient), together with some known tumor-associated-antigen (TAA) and then inject them back into the patient. The resulting vaccine made by autologous TAA-loaded dendritic cells is called *dendritic cell vaccine* (DCV). The idea is that the immune system, confronted with such amount of tumor-antigen, starts to mount a response against it, in place of an otherwise weak or completely absent response. In fact, as a side effect of the immune response against the vaccine (i.e., DC loaded with the TAA), the immune system will eventually recognize the same TAA molecule on tumor cells and kill them.

Animal studies have shown that vaccination with dendritic cells pulsed with tumor antigens are potent strategies to elicit protective immunity in tumor-bearing animals (Gilboa et al., 1998). Moreover, current protocols using dendritic cells are considerably simpler than other immunotherapies and would be more widely available hence they have obvious appeal. Immunotherapy using autologous DC loaded with tumor-derived antigens emerges as a potentially powerful and broadly useful vaccination strategy for cancer patients.

The theory of optimal control has been already applied to cancer. For example Acharya and Sundareshan (1984) discuss about optimal drug delivery. Swan (1990) gives a review of the ways in which optimal control theory is applied to growth kinetic models, cell cycle models, and a classification of "other models" together with suggestions for designing better chemotherapy strategies. De Pillis and Radunskaya (2001) also face the problem of administration of chemotherapy but considering the interesting question of immune resistance.

In the present paper we deal with dendritic cell transfection immunotherapy. In so doing we use a model (already presented in Castiglione and Piccoli, to appear; Piccoli and Castiglione, 2006) to describe the immune–cancer interaction. Then we apply the theory of optimal control to determine how to optimally administer DCV as therapeutic agent. Our main concern was to develop a generic procedure to optimize the time/dosage dependent administration of the TAA so to reduce or, in the best case, to eliminate the tumor mass.

Similar works have been previously published (Castiglione and Piccoli, 2006; Martin, 1992; Kirschner and Panetta, 1998; Swierniak et al., 2003; Burden et al., 2004; Fister and Donnelly, 2005). In many of these references, the treatment is thought as a continuous process, thus the used techniques are those typical of optimal control problems in continuous time. On the contrary in Castiglione and Piccoli (to appear) discrete injection times were introduced.

In the present work, we provide a fairly complete modeling discussion on immunotherapy treatments. First, the basic requirements for a correct model are introduced. Then we show how continuous time and impulsive control approaches do not ensure the basic requirements. On the contrary, the hybrid method described herein (hybrid control) has shown to be successful also when applied to the Panetta–Kirschner model (Kirschner and Panetta, 1998; Cappuccio et al., 2006).

The model we use is essentially the same as in Castiglione and Piccoli (to appear), while the main differences are in the way we apply the control. In fact, beside the vaccination schedule, we consider also vaccination quantities as control variables. To this end, the cost includes a term measuring the tumor mass (or tumor cell count) during treatment and a term measuring the total vaccine quantity.

In the following, after a short description of the ODE system in Section 2 we illustrate three different choices for the control space: continuous-time control, impulsive controls and hybrid controls. We show how the first leads to intractability problems, while the second is unsuitable for our purposes. Finally, the hybrid approach is approximated by a finite dimensional optimization problem, so to use numerical schemes which achieve good results.

2. A model for tumor-immune interaction and vaccine

The ODE model of the tumor-immune interaction we use (Castiglione and Piccoli, to appear) is quite simple and is likely to be one of the few specialized for autologous dendritic cell transfection therapy.

Dendritic cells that are the most efficient antigen representing cells in vertebrate immune systems (Goldsby et al., 2000) and, in this model, are the source of tumor associated antigen presentation. Dendritic cells are introduced externally and ignite the immune response against themselves and, as side effect, also against the tumor cells. In fact, the clone expansion of cytotoxic T cells able to recognize the TAA loaded by DCs, also favor tumor killing since cancer cells naturally display the same TAA on their cell surface.

The system is

$$\frac{dH}{dt} = a_0 + b_0 DH\left(1 - \frac{H}{f_0}\right) - c_0 H, \tag{1}$$

$$\frac{dC}{dt} = a_1 + b_1 I(M + D)C\left(1 - \frac{C}{f_1}\right) - c_1 C, \tag{2}$$

$$\frac{dM}{dt} = b_2 M\left(1 - \frac{M}{f_2}\right) - d_2 MC, \tag{3}$$

$$\frac{dD}{dt} = -d_3 DC + u, \tag{4}$$

$$\frac{dI}{dt} = b_4 DH - e_4 IC - c_4 I, \tag{5}$$

where **H** are the tumor-specific CD4 T helper cells, **C** are the tumor-specific CD8 cytotoxic T cells, **M** are the cancer cells that expose the TAA, **D** are the mature dendritic cells loaded with the TAA and **u** is the control, i.e., the injection rate of dendritic cells. **I** is the IL-2 secreted by H and responsible for T cell growth.

The model requires the following assumptions: (i) the time resolution is of one hour; (ii) we consider only the dynamics of those clones of cells who actually recognize the TAA, neglecting the effect of cross-reactivity of other clones. Moreover, the model is meant to be valid in the range of the tumor mass for which the effects of immune escape, immune down-regulation or vascularization are

still negligible (Preziosi, 2003). More in detail, tumor formation basically follows four major phases: (i) the first phase occurs when normal cells mutate into tumor cells and begin dividing out of control; (ii) the second phase is called *carcinoma in situ* and is classified by the presence of a tumor mass that has not yet invaded other tissues. This phase is limited by the nutrient flow to the tumor; (iii) if blood vessels can be induced to grow into the tumor (angiogenesis), the tumor will progress to the next phase, called the invasive stage; (iv) metastasis, or dissemination to other tissues, is the final phase. The immune system is able to intervene *before* the cancer has reached the phase of carcinoma in situ simply because, after a solid tumor is formed, it is usually unable to get in contact and kill malignant cells that are in the inner part of the tumor mass. Therefore the efficacy of the optimized therapy discussed in the present work follows those of any other immunotherapy. In practice, however, there are other mechanisms of immune evasion of cancer due to its ability to down-regulate the immune recognition. Those mechanisms are not taken into account in the present model.

Starting from the set of values used in Kirschner and Panetta (1998) and by tuning the system to reproduce qualitatively the dynamics of the tumor-immune competition we have sorted out the parameters reported in Table 1.

3. Optimal scheduling and vaccine administration

Our aim is to consider an optimal policy for immunotherapeutic treatment. More precisely, we want to take into account the following features:

(i) The ultimate goal is both to reduce the tumor mass at the end of treatment period and to keep it under control during the treatment period (i.e., below a certain threshold).
(ii) To lessen the treatment burden of the patients the method has to take into account some constraints on the treatment policy (i.e., treatment interruption or *drug holidays*).
(iii) The cell loading procedure may happen on a short time interval, while two different loading procedures need to be well separated due to cell maturation time.
(iv) The amount of injected cells affects the equilibria of the immune system and may ultimately be dangerous. Thus we want to keep this amount as small as possible.

We model the treatment as a control problem:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = F(x,u), \tag{6}$$

where $x = (H, C, M, D, I) \in \mathbb{R}^5$ is the state variable measuring the cell populations, while $u \in U$ is the control, i.e., measures the treatment effects. More precisely u can be set to be the cell injection rate. At this point, we have various modeling choices to represent the vaccination policy and the issues (i)–(iv), listed above.

To satisfy (i), we consider an optimal control problem with a cost including a term measuring the final tumor mass and one measuring the mass exceeding a fixed level during treatment. This results in an optimal control problem in the *Bolza* form:

$$\min_{u(\cdot)\in\mathscr{U}} \int_0^T L(x(t,u),u(t))\,\mathrm{d}t + \varphi(x(T,u)), \quad x(0) = \bar{x}, \tag{7}$$

where $\mathscr{U}$ is the class of admissible controls, $x(\cdot,u)$ the solution corresponding to control u, L the running cost, φ the final cost, T the treatment period and $\bar{x}$ is the initial

Table 1
Parameters of the model in Eqs. 1–5 (same values as in Castiglione and Piccoli, to appear)

Model parameters				
Entity	Parameter	Description	Value	Units (c = cells)
H	a_0	CD4 T birth rate	10^{-4}	$\mathrm{c\,h^{-1}\,mm^{-3}}$
	b_0	CD4 T proliferation rate	10^{-1}	$\mathrm{c^{-1}\,h^{-1}\,mm^{-3}}$
	c_0	CD4 T death rate	0.005	$\mathrm{h^{-1}}$
	f_0	Carrying capacity of CD4 T	1	$\mathrm{c\,mm^{-3}}$
C	a_1	CD8 T birth rate	10^{-4}	$\mathrm{c\,h^{-1}\,mm^{-3}}$
	b_1	CD8 T proliferation rate	10^{-2}	$\mathrm{c^{-1}\,h^{-1}\,mm^{3}}$
	c_1	CD8 T death rate	0.005	$\mathrm{h^{-1}}$
	f_1	Carrying capacity of CD8 T	1	$\mathrm{c\,mm^{-3}}$
M	b_2	1/2 satur const of tumor	0.02	$\mathrm{h^{-1}}$
	d_2	Killing by CD8 of tumor	0.1	$\mathrm{c^{-1}\,h^{-1}\,mm^{3}}$
	f_2	Carrying capacity of tumor	1	$\mathrm{c\,mm^{-3}}$
D	d_3	CD8 T killing of DC	0.1	$\mathrm{c^{-1}\,h^{-1}\,mm^{3}}$
I	b_4	IL-2 production by CD4 T	10^{-2}	$\mathrm{c^{-1}\,h^{-1}\,mm^{3}}$
	c_4	IL-2 degradation rate	10^{-2}	$\mathrm{h^{-1}\,mm^{-3}}$
	e_4	IL-2 uptake by CD8 T	10^{-7}	$\mathrm{c^{-1}\,h^{-1}\,mm^{3}}$

condition. If $L \equiv 0$, then the problem is said to be in *Mayer* form and is easier to be addressed.

In our case

$$L(x,u) = w_1([M(t,u) - M^{max}]_+)^2, \quad \varphi(x(T,u)) = w_2 M(T,u), \tag{8}$$

where $M(\cdot,u)$ is the tumor mass corresponding to control u, w_1 and w_2 are weights and $[\cdot]_+$ indicates the positive part . To reduce a Bolza problem to a Mayer one, one usually introduces a new variable measuring the running cost. In this case we set

$$\frac{dx_6}{dt} = w_1([M(t,u) - M^{max}]_+)^2, \quad x_6(0) = 0. \tag{9}$$

Thus the problem (7) is reduced to the case with only the final cost given by the following equation:

$$\varphi(H,C,M,D,I,x_6) = w_2 M(T,u) + x_6. \tag{10}$$

The characteristics of treatment required by issues (ii) and (iii) affect the space $\mathscr{U}$ of admissible controls. More precisely, (ii) tells us that the control cannot be active for the whole treatment period, while (iii) further implies that the periods of control activity are short and well separated.

In Eq. (6) the control is usually thought as a continuous in time function with values in the control space U. In this case the evolution of the system is smooth; in particular, no jump is possible. However, one may also introduce more general controls to model discontinuities in the system. For instance, a Dirac delta δ in the control u would produce a unitary instantaneous jump in the corresponding controlled variable. Such choice gives rise to the so-called *impulsive control systems*.[1].

In this paper, we discuss three particular choices for the control functions:

Continuous: The control function $u : [0,T] \to [0, Q_{max}]$ is a continuous time varying function taking values between zero (no injection) and Q_{max} (maximum vaccine injection rate).

Impulsive: There are fixed injection times $0 \leqslant t_0 < t_1 < \cdots < t_N \leqslant T$ and one assigns to each fixed vaccination time t_j the amount of TAA-loaded autologous cells injected. This corresponds to a purely impulsive control, presenting a finite number of delta functions at vaccination times.

Hybrid: There exists a given vaccination procedure represented by a control function $\bar{u} : [0,\eta] \to [0, Q_{max}]$ for some $\eta > 0$. Then the control function is given by a finite set of vaccination procedures, so

$$u(t) = \sum_{j=1}^{N} \chi_{[t_j, t_j+\eta]}(t)\bar{u}(t - t_j),$$

where $\chi_{[t_j,t_j+\eta]}$ is the indicator function of $[t_j, t_j + \eta]$, i.e., $\chi_{[t_j,t_j+\eta]} = 1$ if $t \in [t_j, t_j + \eta]$ and zero otherwise. The problem in this case can be written in hybrid form introducing a discrete (boolean) variable which distinguishes vaccination periods from no treatment periods.

Notice that the first two choices are strongly different and both special cases of a general control function. More precisely, a general control function would have both a continuous in time part and a purely jump part (sum of Dirac deltas.) Also, it is clear that a delta function may be approximated by continuous in time controls, provided that the control set U is not bounded. (Otherwise, admissible controls would also be bounded and thus it would not be possible to approximate big sudden changes in the system.)

Finally, the third choice is again a particular case: it can be approximated by continuous in time controls and, as we will see in detail later, it approximates a purely jump control (as a parameter tends to zero).

We proceed by discussing the three different cases and showing how to address the issues (ii)–(iv).

3.1. Continuous in time controls with no jump

In the case of continuous in time controls, with no jump, the issue (iv) is readily obtained taking an additional cost of the form:

$$\int_0^T \psi(u)\,dt,$$

where ψ may be taken any positive increasing function of u, for example $\psi(u) = u$ or $\psi(u) = u^2$.

If the dynamics would be linear and $\psi(u) = u^2$, then we would have a so-called linear–quadratic problem, for which there is a variety of results. For example, this approach was used in Burden et al. (2004) for the immunotherapy model of Kirschner and Panetta (1998). Unfortunately, the dynamics of the system (1–5) is highly nonlinear, thus the LQ theory is not applicable. Moreover, a linearization would destroy some equilibria (typical of logistic type equations) and hence would not give useful information. Then one has to resort to the Pontryagin maximum principle (PMP, see Bressan and Piccoli, to appear). As a result, one has to solve an Hamiltonian system of the type:

$$\frac{dx}{dt} = \frac{\partial H}{\partial \lambda}, \quad \frac{d\lambda}{dt} = -\frac{\partial H}{\partial x},$$

with boundary conditions:

$$x(0) = \bar{x}, \quad \lambda(T) = \bar{\lambda}.$$

More precisely, for a Bolza problem the PMP can be written as (Bressan and Piccoli, to appear):

Theorem 1 (*PMP for Bolza problem*). *Consider the optimal control problem* (6), (7) *with* $T > 0$ *fixed and* $S = \mathbb{R}^n$. *Let* $u^* : [0, T^*] \mapsto U$ *be a bounded admissible control whose corresponding trajectory* $x^*(\cdot) = x(\cdot, u^*)$ *is optimal. Then, there exists a nontrivial adjoint vector* $p = (p_1, \ldots, p_n)$ *and*

[1]There are two different ways of modelling impulsive system. The more classical one, see Bensoussan and Lions (1984), is obtained introducing generalized controls, e.g., including a finite number of delta functions. In certain mechanical system one may control directly a variable of the system, inducing jumps on other variables: produces rise to a different theory, see Bressan (1990) and Bressan and Piccoli (to appear).

$\lambda_0 \geqslant 0$ *such that, for almost every* $t \in [0, T^*]$,

$$\frac{\mathrm{d}p}{\mathrm{d}t_i}(t) = -\sum_{j=1}^{n} p_j(t)\frac{\partial F_j}{\partial x_i}(x^*(t), u^*(t)) - \lambda_0 \frac{\partial L}{\partial x_i}(x^*(t), u^*(t)) \quad i = 1, \ldots, n, \tag{11}$$

$$0 = p(t) \cdot F(x^*(t), u^*(t)) + \lambda_0 L(x^*(t), u^*(t)) = \min_{\omega \in U}\{p(t) \cdot F(x^*(t), \omega) + \lambda_0 L(x^*(t), \omega)\}, \tag{12}$$

$$p(T^*) = \nabla\psi(x^*(T)). \tag{13}$$

The covectors equations can be compactly written as

$$\frac{\mathrm{d}p}{\mathrm{d}t} = -p \cdot DxF - \lambda_0 \nabla L$$

and in our case DF is given by:

$$\begin{pmatrix} -c_0 + b_0 D - 2b_0\frac{DH}{f_0} & 0 & 0 & b_0 H\left(1 - \frac{H}{f_0}\right) & 0 \\ 0 & -c_1 + b_1 I(M+D)\left(1 - \frac{2C}{f_1}\right) & b_1 IC\left(1 - \frac{C}{f_1}\right) & b_1 IC\left(1 - \frac{C}{f_1}\right) & b_1(M+D)C\left(1 - \frac{C}{f_1}\right) \\ 0 & -d_2 M & b_2\left(1 - \frac{2M}{f_2}\right) - d_2 C & 0 & 0 \\ 0 & -d_3 D & 0 & -d_3 C & 0 \\ b_4 D & -c_4 I & 0 & b_4 H & -e_4 C - c_4 \end{pmatrix}$$

while:

$$\nabla L = \begin{pmatrix} 0 \\ 0 \\ 2([M(t,u) - M^{max}]_+)A(M(t,u)) \\ 0 \\ 0 \end{pmatrix},$$

where $A(M(t,u)) = 1$ if $M(t,u) \geqslant M^{max}$ and is equal to 0 otherwise.

Unfortunately, such system is highly nonlinear and coupled, thus analytical solutions are not possible. Even more, also the numerical treatment is particularly challenging. This is due to the fact that the boundary conditions are not standard initial conditions, since the value of x is prescribed at initial time, while the value of p at final ones. Various numerical methods are described in Polak (1997) and Schmidt et al. (1998).

To respect issue (ii), one would have to restrict the set of admissible controls, for example, imposing the control to be equal to zero on some fixed time intervals J_is inside the treatment period. This can be obtained simply writing the equation for dendritic cells as:

$$\frac{\mathrm{d}D}{\mathrm{d}t} = -d_3 DC + \alpha(t)u,$$

where α vanishes on J_i. PMP would still be applicable.

The case of issue (iii) is more delicate. In fact, if the time intervals on which the control is active are small, then bounded controls cannot represent big changes in the system. On the other side, if we allow unbounded controls, PMP may be not applicable. This is why we investigate the other special type of controls, which will permit an easier implementation of a numerical algorithm to find optimal vaccine strategies.

3.2. Impulsive controls

In this case one would represent instant injections as delta functions. The correct formulation for generalized control is that of impulsive systems. Thus we need to consider control functions of the type

$$u(t) = \sum_{i=0}^{N} TAC_i \delta_{t_i},$$

where $0 \leqslant t_0 < t_1 < \cdots < t_N \leqslant T$ are vaccination times, TAC_i is the total amount of cells injected at time t_i and δ_{t_i} is the Dirac delta centered at time t_i. The space of controls is well determined once we fix the number N of vaccinations. In fact the space of control is finite-dimensional and parameterized by the vectors $(t_i, TAC_i)_{i=1,\ldots,N}$. Also, some bounds are natural for the quantities TAC_i.

To address issue (ii), we simply need to impose some restrictions on the vaccination times t_i. Issue (iii) is properly addressed by purely impulsive controls for what concerns the limitations on the size of control activity intervals, while the separation among vaccinations is again a restriction on t_i. The limitation in such approach regards the possibility of properly describing the vaccination procedure. Some nonlinear small effects may be neglected.

Regarding issue (iv), the cost function needs to be corrected adding the term

$$\sum_i TAC_i.$$

The investigations of optimal control problems for general impulsive systems are not an easy task, see Bensoussan and Lions (1984). Again, the statement of PMP may not hold. In next section, we discuss the case of hybrid control, which represents a convenient way to approximate purely impulsive ones.

3.3. Hybrid controls

We assume the vaccine-administration procedure to be described by a control function

$$\bar{u} : [0, \eta] \mapsto [0, \bar{Q}_{max}],$$

where $\bar{Q}_{max}$ is the maximal vaccine injection rate. The function $\bar{u}$ represents the injection rate of dendritic cells population as a function of time. Thus the total quantity injected is $\int_0^\eta \bar{u}(s)\,ds$. It is worth noting that since the time scale chosen for the system (1)–(5) is that of the cellular duplication time which is estimated about $\frac{1}{3}$ of a day and given that the time duration of the vaccine administration is often of the order of minutes, we can safely assume that η is small.

Defining Q_i to be the total injected quantity of dendritic cells at the ith vaccination, to satisfy (iii) we simply add the cost

$$\sum_i^N Q_i, \tag{14}$$

where Q_is are now new control variables. Thus we get an hybrid optimal control problem. Again the analytical solution of the problem would need the use of the hybrid maximum principle (see Garavello and Piccoli, 2005), thus facing the same problems as the approach with continuous control.

We rather use the information that η is small to reduce the problem to a finite-dimensional one. Also, we compute the trajectory variations corresponding to control variations.

Clearly, the issues (ii) and (iii) can be again properly addressed by simply imposing restrictions on the values taken by vaccination times.

The clinical treatment of a patient via immunotherapy consists in a series of injections that are scheduled over a time range of some months. We then consider a control procedure that consists in N vaccinations inoculated according to a *schedule* $S = \{(t_i, Q_i): i = 0, \dots, N-1, 0 \leqslant t_0 \leqslant t_1 - \eta < t_1 \leqslant \cdots \leqslant t_{N-1} \leqslant T - \eta, 0 \leqslant Q_i \leqslant Q_{max}\}$. Let $\mathscr{S}$ be the space of schedules, then for every $S \in \mathscr{S}$ we define u_S to be the corresponding control:

$$u_S(t) = \sum_{i=0}^{N-1} Q_i \bar{u}(t - t_i)\chi_{[t_i, t_i+\eta]},$$

where, for simplicity, we assumed $\int_0^\eta \bar{u}(s)\,ds = 1$. The control u_S corresponds to N vaccine administrations that occur at times t_i with injected quantities Q_i. Finally we set

$$\mathscr{U} = \{u_S: S \in \mathscr{S}\}.$$

We have now reached the point in which the problem described in the introduction can be formulated in mathematical terms.

Consider the cost obtained by summing up the costs (7), (8), with the cost (14) and get the problem:

(P) Given the initial condition x_0 determine a schedule $S \in \mathscr{S}$ of N injections so that the control u_S and the trajectory x_S of $dx/dt = f(x(t)) + u_S(t)g(x)$ attains the minimum of the cost:

$$\min_{S\in\mathscr{S}} w_1 \int_0^T ([M_S(t,u) - M^{max}]_+)^2\,dt + w_2 M_S(T, u_S) + w_3 \sum_{i=1}^N Q_i(S), \tag{15}$$

where w_i are weights, M_S (the tumor mass) is the fourth component of x_S.

The obtained optimization problem is indeed a finite-dimensional one. In fact, the space S can be clearly parameterized by a subset of $\mathbb{R}^{2N}$. Moreover, we will show that we can approximate this optimization problem considering the set of controls given by finite sums of delta functions centered at vaccination times of the schedule, thus formally considering $\eta = 0$.

Consider a family of controls $\tilde{u}_\varepsilon$ corresponding to a single vaccine administration procedure that takes place at time $t_\varepsilon = \bar{t} + \varepsilon$ with total injected quantity $Q_\varepsilon = \bar{Q} + \varepsilon$. We want to compute the corresponding trajectory variation, under the reduction (9) and (10). We split the problem in two parts taking first the variation of injection times and then the variation of total injected quantities.

Proposition 1. *Let u_ε be a family of controls corresponding to a single vaccine administration procedure at time $t_\varepsilon = \bar{t} + \varepsilon$ of total injected quantity $\bar{Q}$. Let us denote by v the trajectory variation and w the variation of the new variable* (9). *Then, recalling that η is the duration of the administration of the vaccine, we get*

$$\begin{cases} \frac{dv}{dt}(t) = D_x f(x_0(t)) \cdot v(t), \\ \frac{dw}{dt}(t) = D_x L(x_0(t)) \cdot v(t), \\ v(\bar{t}) = f(x_0(\bar{t})) - f(x_0(\bar{t}) + \bar{Q}\mathbf{e_4}) + o(\eta), \\ w(\bar{t}) = 0. \end{cases} \tag{16}$$

Let now U_θ be a family of controls corresponding to a single vaccine administration procedure at time $\bar{t}$ of total injected quantity $Q_\theta = \bar{Q} + \theta$. Let us denote by V the trajectory variation and W the variation of the new variable (9). *Then, recalling that η is the duration of the administration of the vaccine, we get*:

$$\begin{cases} \frac{dV}{dt}(t) = D_x f(x_0(t)) \cdot V(t), \\ \frac{dW}{dt}(t) = D_x L(x_0(t)) \cdot V(t), \\ V(\bar{t}) = \mathbf{e_4} + o(\eta), \\ W(\bar{t}) = 0. \end{cases} \tag{17}$$

The proof of the above proposition is easily obtained using Taylor expansion of the involved quantities (and can be found in Piccoli and Castiglione, 2006).

Then we can compute the gradient of the total cost (15) using Proposition 1, thus getting the following.

Proposition 2. *For the problem (P) the following holds. Let us indicate by $v_i(\cdot), w_i(\cdot)$ the solution to* (16) *for $\bar{t} = t_i$ and*

$x_0 = x_S$ and by $V_i(\cdot), W_i(\cdot)$ is the solution to (17) *for $\bar{t} = t_i$ and $x_0 = x_S$. Then*

$$\frac{\partial M(x_S(T))}{\partial t_i} = \nabla M(x_S(T)) \cdot v_i(T) = \mathbf{e_4} \cdot v_i(T) + o(\eta),$$
$$\frac{\partial M(x_S(T))}{\partial Q_i} = \nabla M(x_S(T)) \cdot V_i(T) = \mathbf{e_4} \cdot V_i(T) + o(\eta),$$
$$\frac{\partial(\int_0^T ([M(x(t,u(\cdot))) - M^{max}]_+)^2 \,\mathrm{d}t)}{\partial t_i} = w(T) + o(\eta),$$
$$\frac{\partial(\int_0^T ([M(x(t,u(\cdot))) - M^{max}]_+)^2 \,\mathrm{d}t)}{\partial Q_i} = W(T) + o(\eta),$$
$$\frac{\partial \sum_{i=1}^N Q_i(S)}{\partial t_j} = 0,$$
$$\frac{\partial \sum_{i=1}^N Q_i(S)}{\partial Q_j} = 1.$$

Proposition 2 gives the basic ingredients for the numerical solution of problem (P).

As a remark on item (iv), note that we obtain a bound on the total vaccine injected, thanks to the term $\sum_i Q_i$ in the total cost. Adjusting the weight w_3 we can get a more strict or more relaxed constraint.

In (iv), we mentioned also toxicity, which would require a bound not only on the total amount of cells injected in the whole period, but also in a bound on every time interval of a certain length. This constraint, as (iii), asks for vaccination times to be separate enough. Fortunately, the bound on the tumor mass on the whole period forces the system in the same direction, since the concentration of vaccine injections in a short period would let the tumor grow fast in the rest of the treatment time window. Therefore, such requirement will be fulfilled as a combination of the first and last term in the total cost (15).

4. The algorithm

The optimization algorithm consists of the following procedure:

step0: initialize variables
set $T \in \mathbb{R}^+$
set $M^{max} \in \mathbb{R}^+$
set $N \in \mathbb{N}^+$
set $\overline{Q} \in \mathbb{R}^+$
set $x_0 = (H(0), C(0), M(0), D(0), I(0)) \in (\mathbb{R}^+)^5$
set $S_0 = \{\binom{t_i}{Q_i}\}_{i=1,\ldots,N}$
for n:=0 **to** *optsteps* **do**
step1: Solve the system, i.e., $x_S = \text{RungeKutta}(x_0)$;
Solve the variational equations (16) and (17);
step2: Via Proposition 2 compute $\frac{\partial \varphi}{\partial t_i}$ and $\frac{\partial \varphi}{\partial Q_i}$
step3: Update the schedule by an optimization method, i.e., $\forall i$
$t_i^{n+1} = t_i^n + h_t \cdot \frac{\partial \varphi}{\partial t_i}$
$Q_i^{n+1} = Q_i^n + h_Q \cdot \frac{\partial \varphi}{\partial Q_i}$
for small parameters $h_t < 0$ and $h_Q < 0$
od

In other words, fix the time horizon T, the maximum allowed value of the tumor mass during treatment M^{max}, the number of vaccine administrations N, the vaccine quantity $\overline{Q}$, an initial value x_0 of cells populations and an initial schedule S_0 (this can be taken at random). Then iterate the following steps: solve the system (1)–(5) with x_0 as the initial value via the fourth-order Runge–Kutta integrator generating an approximation of the trajectory x_S. At the same time solve the variational equations (16) and (17); compute the derivatives of the extended cost φ (see (15)) with respect to the injection times t_i and the vaccine quantities Q_i via Proposition 2. Update the schedule by the steepest descent (or other optimization) method, for small parameters $h_t < 0$ and $h_Q < 0$.

In Step 0, a time horizon T of six months and a number of vaccine injection $N = 10$ are chosen. Moreover, we take the initial value of the tumor $M(0) = 0.1$, the H and C initial levels are set to equilibrium that is $H(0) = a_0/b_0$ and $C(0) = a_1/b_1$, while $I(0)$ and $D(0)$ are set to zero, whose biological meaning is that there is no specific immune response at time zero. The vaccine quantity injected at each administration cycle is $\bar{V} = 0.5$ (the effect on the tumor of this parameter was investigated in Castiglione and Piccoli, to appear). We start with a random vaccine injection schedule S_0 and we run the optimization schema for *optsteps* $= 5000$ (no special stopping criteria is used here).

5. Results

In Fig. 1 it is shown the evolution of the schedule during the optimization. The schedule varies in both time and dosage. Panel A shows changes in both time and dose while panels B and C show the two aspects separately. In panel B, notice that the schedule is characterized by three main issues: the first injection is brought at the beginning of the treatment period, some vaccinations are glued together, while the other ones are distributed more or less at equal distances. Moreover, the first vaccination quantity is increased considerably; the quantity of the third injection is decreased to zero; the other injection are more or less of the same quantity. Finally, the first vaccination occurs at the beginning of treatment and is the most consistent, so to readily diminish the tumor mass to a safe level. The other injections are of the same strength and equally spaced to get a smooth control on the tumor growth. To generalize what we have observed on a single run, we have repeated the optimization by starting from random schedules. Fig. 2 shows the histogram of the optimal schedule. This evidences that while the first and second injections accumulate on the first period of the therapeutic interval, the remaining injections are more or less equally spaced within the therapeutic horizon. This is somehow expected

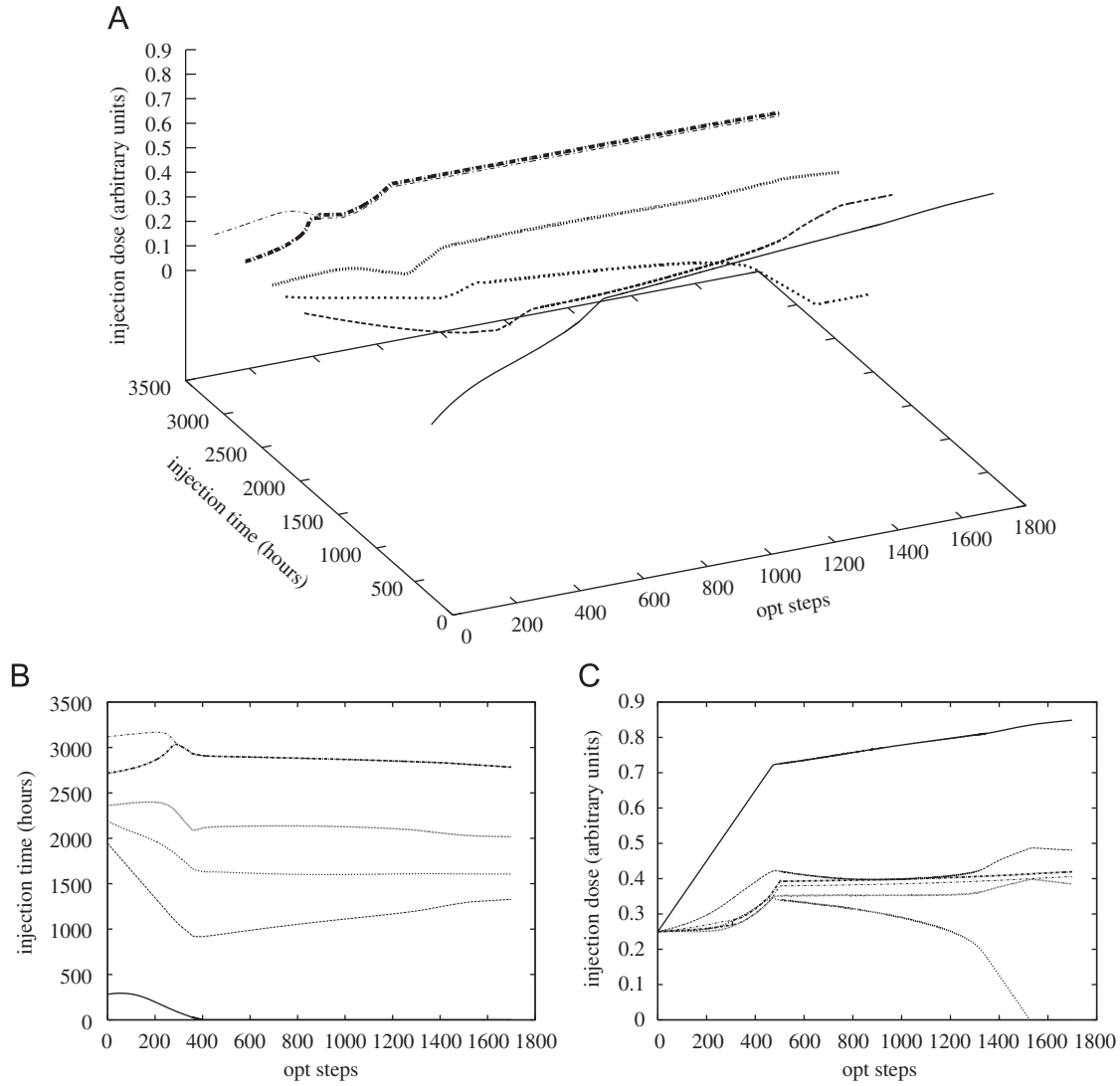

Fig. 1. Evolution of the schedule during the optimization. Panel A shows the changes with respect to time and dosage at the same time. Panels B and C show the same information but separated increase readability. It is worth to note in panel C that the optimal schedule is composed by five injections since one has dosage close to zero. It is an advantage of optimizing on the dosage in addition to the timing.

since the first injections decrease the value of the tumor mass while the remaining injections have the purpose of keeping the tumor burden below the threshold level.

At each optimization step n, of the algorithm updates the injection time t_i and the quantity $Q_i \ \forall i = \ldots$ as follows (step 3)

$$t_i^{n+1} = t_i^n + h_t \cdot \frac{\partial \varphi}{\partial t_i}, \tag{18}$$

$$Q_i^{n+1} = Q_i^n + h_Q \cdot \frac{\partial \varphi}{\partial Q_i}. \tag{19}$$

To study the dependence of the optimal solution on h_t and h_Q we repeated the optimization procedure for the same initial data but for different choices of the parameters h_t and h_Q. The outcome is reported in Fig. 3. The graphs show the final outcome of the optimization as function of these parameters, which are set to be equal. We notice that, as expected, the total (and other) costs diminish as the parameters decrease. However, this happens only up to some small values, when suddenly the cost increases again. This phenomenon is due to the very complicated structure of the cost function, with respect to the vaccine schedule and quantity. In particular, the presence of many local minima causes some problem to the optimization algorithms for small choices of the parameter. Fortunately, it is possible to isolate an "optimal" window, between 3 and 13, for which the behavior of the final and other costs is particularly good. All costs in such windows are essentially constant, except for the final tumor mass, which shows a better performance for the particular choice of $h_t = h_Q$ equal to 3.

From this analysis, one could still argue that the bad behavior of the algorithm may be due simply to a slower

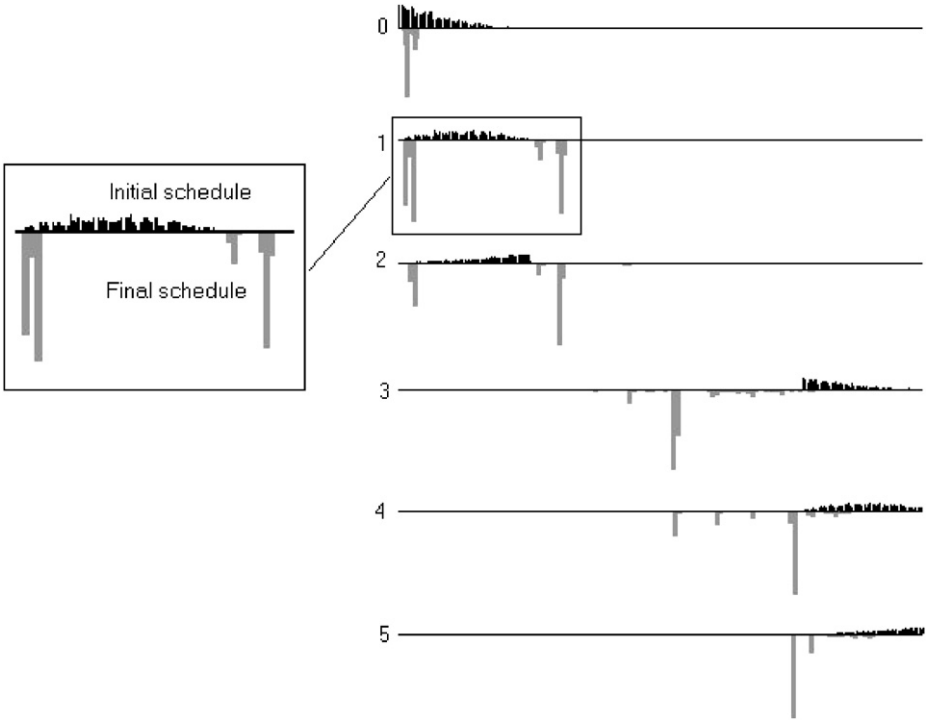

Fig. 2. This figure shows the histogram computed by running many times the optimization algorithm each time initializing the injection schedule at random. The histogram shows both the distribution of the initial and the final/optimal injection schedule. The figure evidences that while the first and second injection accumulate on the first period of the therapeutic interval, the remaining injections are more or less equally spaced within the therapeutic horizon.

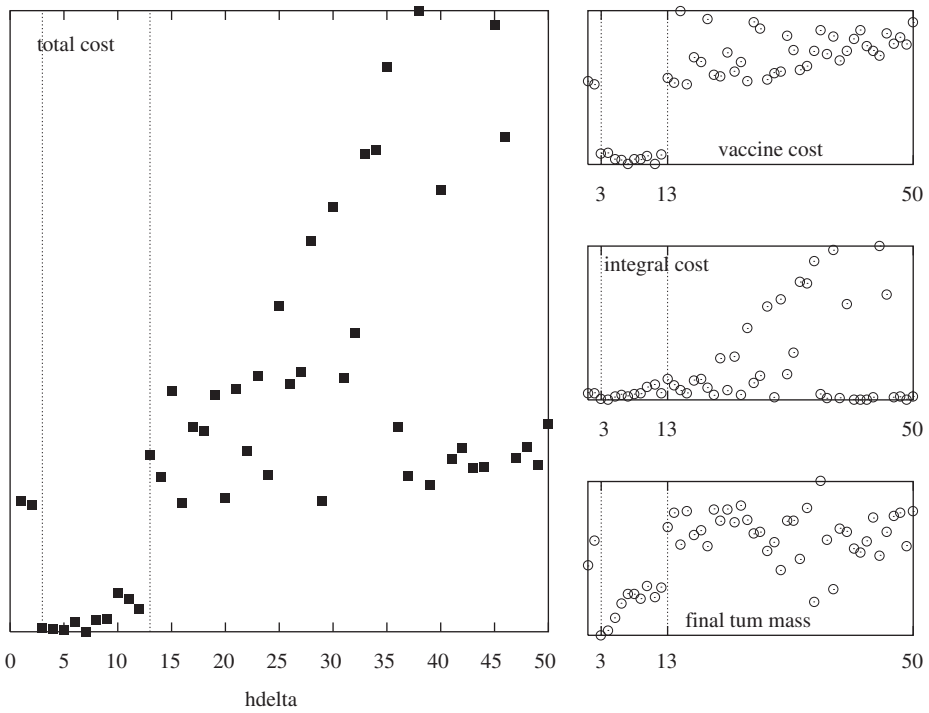

Fig. 3. How the costs are influenced by a different choice of the parameters h_t and h_Q of the optimization algorithm.

convergence rate for small h_t and h_Q. In order to solve this doubt, we reported the total cost as function of the optimization step for the choices of $h_t = h_Q = 2$, 3 and 4, in Fig. 4. The optimization procedure ends at step 2000, thus one can notice that the choice of the parameter $h_t = h_Q = 2$ occurs in a local minimum, with total cost greater than the

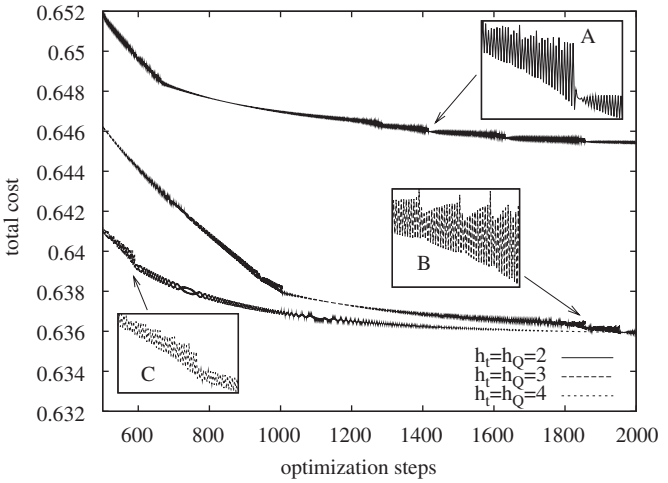

Fig. 4. Oscillations of the cost function is apparent by zooming (panels A, B and C).

value reached by the other two choices. To appreciate the complex structure of the cost function, we zoomed some part of the graph for the three different choices, revealing its oscillations.

6. Discussions

We have constructed a mathematical model of the immune–cancer interaction to study the effect of immunotherapy via dendritic cell vaccines and we asked the question of how to determine the best time/quantity allocation of the injections within the time therapeutic horizon.

Our solution was to transform it in a control problem where the cost function is the sum of the tumor mass at the end of the therapy $M(T)$, the integral of the tumor mass exceeding a certain level M^{max} and the total quantity of vaccine injected.

We discussed the modeling problem analyzing three different approach for the resulting control problem: continuous, impulsive and hybrid. The first happens to be not tractable for our system, since the population dynamic are highly nonlinear and the resulting adjoint equations are coupled. Then, we showed how the impulsive approach leads to modeling problems. Finally, the hybrid approach was used and the control set simplified to better capture the characteristic of the vaccine administration procedure and reduce the problem to a finite-dimensional one. In particular, we used tools of optimal control to compute the gradient of the cost function with respect to the schedule. The latter is obtained via the solution of a generalized variational equation.

To summarize the results we can say that the optimal schedules present the following features.

- A first vaccination with high dose is put at the beginning of the treatment period, so to promptly reduce the tumor.
- The other vaccinations present smaller doses and are distributed more or less along the rest of the treatment period.

We further analyzed the method by discussing the choice of h_t and h_Q on the steepest descent method identifying a window of optimal values.

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