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Optimal vaccine scheduling in cancer immunotherapy

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Abstract

Cancer immunotherapy aims at stimulating the immune system to react against cancer stealth capabilities. It consists of repeatedly injecting small doses of a tumor-associated molecule one wants the immune system to recognize, until a consistent immune response directed against the tumor cells is observed.

We have applied the theory of optimal control to the problem of finding the optimal schedule of injections of an immunotherapeutic agent against cancer. The method employed works for a general ODE system and 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 normal physiologic functions have been described by a mathematical model.

We show that the choice of the cost function has dramatic effects on the kind of solution the optimization algorithm is able to find. This provides evidence that a careful ODE model and optimization schema must be designed by mathematicians and clinicians using their proper different perspectives.

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

1. Introduction

According to the theory of the clonal selection, the human immune system possesses an array of cellular and molecular detection systems and associated weapons. Against most pathogens these forces mount an effective defense, but not when the disease in question involves the body's own cells. Having learned to recognize and ignore familiar proteins early in life, the immune system mostly dismisses molecules associated to disease-bearing cells such as those of cancer.

Cancer immunotherapy aims at stimulating the immune system to react against cancer stealth capabilities. It consists of injecting small doses of the molecule one wants the immune system to recognize, until a consistent immune response is observed. One technical problem consists in actually delivering the molecule to destination. For this job, the best candidate is the dendritic cell, whose normal activity is to present antigens in a way that draws the attention of immune effector cells like cytotoxic T lymphocytes. A technique called *dendritic cell transplantation* has been devised where *autologous* dendritic cells (i.e., previously extracted from

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the same patient) are cultivated together with those molecules one wants the immune system to recognize (e.g., in the case of cancer these are called *tumor-associated antigens* or TAAs) and then inject them back into the patient. The resulting vaccine made by autologous TAA-loaded dendritic cells is called *dendritic cell vaccine* (DCV).

Having a system of differential equations describing the tumor–immune dynamics, the problem of choosing the right time allocation to administer the substance to stimulate the immune system is a mathematical control problem. We have already faced this problem. In our previous work [1] we have first constructed a mathematical model of the immune–cancer interaction to study the effect of immunotherapy via DCVs, then we have considered the control problem associated to the optimal choice of the time to make the injection of DCV, with final value of tumor mass as cost function. The results obtained were very satisfactory as the optimized schedule was always able to reduce the tumor consistently within the therapeutic horizon. However, we discovered how sensible the solution was with respect to the cost function used. In fact, since the tumor recovers pretty quickly from any early vaccination given its fast growth, the optimized protocol was highly relying on the late treatment.

In the present work we show how to get rid of that problem and introduce another term in the cost function that limits the tumor mass at anytime during the treatment period. An alternative approach would consist in introducing a state constraint for the tumor mass, however, the theory, based on Pontryagin maximum principle (PMP) [2], requires a much more complex framework involving measures instead of functions [3].

In Section 2 we describe the ODE system; in Section 3 we introduce the control theory and in the Section 3.1 we describe its application to our problem. Finally, in Sections 4 and 5 the results are described and commented.

2. A model for tumor–immune interaction and vaccine

The majority of mathematical models in theoretical immunology involve relatively simple ODEs to represent reaction kinetics amongst cells and/or molecules involved in the immune response. The parameters are growth rates or affinity constants and are not always available. Nevertheless these models are quite successful in studying the dynamics of a pathogen in absence or in presence of a certain treatment and sometimes they predict interesting aspects of the disease. Other studies, like the present one, attempt to extend those mathematical applications and use the theory of the optimal control to systematically study the relation between the targeted system and the form of the solution, i.e., the optimal protocol of drug or treatment administration [1,4–7].

Among many mathematical ODE models of the tumor–immune interaction we use our own model [1] because it is quite simple and is likely to be the only one specialized for autologous dendritic cell transfection therapy. It consists of the following key immune cell populations: the lymphocytes CD4 T helper cells; lymphocyte CD8 T cytotoxic cells; cancer cells and dendritic cells that are the most efficient antigen representing cells in vertebrate immune systems [8] and, in this model, are the source of TAA presentation. Dendritic cells are introduced externally and ignite the immune response against themselves and, as side effect, also against the tumor cells.

The system is

$$\dot{H} = a_0 - b_0 H + c_0 D d_0 \gamma(H, f_0), \tag{1}$$

$$\dot{C} = a_1 - b_1 C + c_1 I(M + D) d_1 \gamma(C, f_1), \tag{2}$$

$$\dot{M} = d_2 \gamma(M, f_2) - e_2 M C, \tag{3}$$

$$\dot{D} = -e_3 D C, \tag{4}$$

$$\dot{I} = a_4 H D - c_4 C I - e_4 I, \tag{5}$$

Table 1
Parameters of the model in Eqs. (1)–(5) (same values as in Ref. [1])

Name	Description	Value	Units (c = cells,h = hours)
a_0	CD4 T birth rate	10^{-4}	$c\,h^{-1}\,mm^{-3}$
b_0	CD4 T death rate	0.005	h^{-1}
c_0	Max. proliferation of CD4 T	10	
d_0	$\frac{1}{2}$ saturation constant of CD4 T	10^{-2}	$c^{-1}\,h^{-1}\,mm^3$
f_0	Carrying capacity of CD4 T	1	$c\,mm^{-3}$
a_1	CD8 T birth rate	10^{-4}	$c\,h^{-1}\,mm^{-3}$
b_1	CD8 T death rate	0.005	h^{-1}
c_1	Max. proliferation of CD8 T	10	
d_1	$\frac{1}{2}$ saturation constant of CD8 T	10^{-2}	$h^{-1}\,(mm^3/c)^2$
f_1	Carrying capacity of CD8 T	1	$c\,mm^{-3}$
d_2	$\frac{1}{2}$ saturation constant of tumor	0.02	h^{-1}
e_2	Killing by CD8 of tumor	0.1	$c^{-1}\,h^{-1}\,mm^3$
f_2	Carrying capacity of tumor	1	$c\,mm^{-3}$
e_3	CD8 T killing of DC	0.1	$c^{-1}\,h^{-1}\,mm^3$
a_4	IL-2 production by CD4 T	10^{-2}	$c^{-1}\,h^{-1}\,mm^3$
c_4	IL-2 uptake by CD8 T	10^{-7}	$c^{-1}\,h^{-1}\,mm^3$
e_4	IL-2 degradation rate	10^{-2}	h^{-1}

where $\gamma(x,c) = x(1-x/c)$, H are the tumor-specific CD4 T helper cells, C are the tumor-specific CD8 T cells or CTLs cytotoxic cell, M are the cancer cells that expose the TAA, D are the mature dendritic cells loaded with the TAA and I is the IL-2 secreted by H and responsible for T cell growth.

The model required the following assumptions: (i) the time resolution is of 1 h; (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 (this is a common approximation in this kind of models of the immune system); (iii) the model is meant to be valid in the range of the tumor mass for which the effects of immune escape, down-regulation or vascularization, are still negligible [9].

Starting from the set of values used in Ref. [5] and by tuning the system to reproduce qualitatively the dynamics of the tumor–immune competition we [1] have sorted out the parameters reported in Table 1.

3. Optimal control

A general control system is given by the equation:

$$\dot{x} = F(x,u), \tag{6}$$

where $x \in R^n$ is the state variable and $u \in U$ the control, i.e., the source of external influence. An optimal control problem in *Bolza* form is given by

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

where $\mathscr{U}$ is the class of admissible controls, L the Lagrangian or running cost, ψ the final cost, $\bar{x}$ the initial condition and S the target set. We assume F, L and ψ to be smooth and U compact.

To deal with Bolza problems, one usually introduces a new variable x_{n+1} whose dynamics is given by

$$\dot{x}_{n+1} = L(x_1,\ldots,x_n,u), \quad x_{n+1}(0) = 0, \tag{8}$$

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

$$\varphi(x_1,\ldots,x_{n+1}) = \psi(x_1,\ldots,x_n) + x_{n+1}. \tag{9}$$

The PMP [2] provides, under suitable assumptions, a first-order necessary condition for optimality in terms of a lift of the candidate optimal trajectory to the cotangent bundle. Such lift is a trajectory of a pseudo-Hamiltonian system. For problems in Bolza form with fixed final time T and without final constraint, the PMP can be stated as follows:

Theorem 1 (*PMP for Bolza problem*). *Consider the optimal control problems* (6) *and* (7) *with* $T>0$ *fixed and* $S = R^n$. *Let* $u^* : [0, T^*] \mapsto U$ *be an 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* $\lambda_0 \geqslant 0$ *such that, for almost every* $t \in [0, T^*]$,

$$\dot{p}_i(t) = -\sum_{j=1}^{n} p_j(t)\,\frac{\partial F_j}{\partial x_i}\,(x^*(t), u^*(t)) - \lambda_0\,\frac{\partial L}{\partial x_i}\,(x^*(t), u^*(t)), \quad i = 1,\ldots,n, \tag{10}$$

$$0 = p(t)\cdot F(x^*(t), u^*(t)) + \lambda_0 L(x^*(t), u^*(t)) = \min_{\omega\in U}\{p(t)\cdot F(x^*(t),\omega) + \lambda_0 L(x^*(t),\omega)\}, \tag{11}$$

$$p(T^*) = \nabla\psi(x^*(T)). \tag{12}$$

The proof of the PMP relies on a special type of variations, called *needle variations*, of a reference trajectory. Given a candidate optimal control u^* and corresponding trajectory x^*, a time τ (of approximate continuity for $F(x^*(\cdot), u^*(\cdot))$ and $L(x^*(\cdot), u^*(\cdot))$) and $\omega \in U$, a needle variation is a family of controls u_ε obtained replacing u^* with ω on the interval $[\tau-\varepsilon, \tau]$. Needle variations give rise to trajectory variations

$$v(t) = \lim_{\varepsilon\to 0+} \frac{x_\varepsilon(t) - x^*(t)}{\varepsilon},$$

not differentiable in classical sense at time τ. Recently [10,11], it was introduced a generalized setting in which needle and other variations happen to be differentiable.

3.1. Application to cancer immunotherapy

We now consider the DCV as the control term within system (1)–(5), hence we obtain

$$\dot{x} = F(x,u) = f(x) + ug(x), \tag{13}$$

where $x = (H, C, M, D, I)$ represents the cells populations, the field f is given by (1)–(5) and, since the vaccine acts only on dendritic cells, we have $g(x) = \mathbf{e_4}$ the fourth coordinate vector.

To avoid the problems experienced by using the final tumor mass as the only optimization criteria [1], we minimize not only the final value of the tumor mass M, but also the time, during which the tumor is above a certain value M^{max} given as a parameter. In order to achieve this, we consider a cost that is the sum of two terms: the first addendum is the final value of the tumor mass M, i.e., $M(T)$ (T is the duration of the therapy), while the second is the integral (in time) of the tumor mass exceeding the fixed value M^{max} (referred herein as the integral cost). To summarize we focus on the following the optimal control problem:

$$\min_{u(\cdot)\in\mathscr{U}} (w_1 C_1 + w_2 C_2), \quad x(0) = x_0, \tag{14}$$

with

$$C_1 = \int_0^T ([M(x(t,u(\cdot))) - M^{max}]_+)^2\,\mathrm{d}t,$$

$$C_2 = M(x(T,u(\cdot))),$$

where T is the final time of the treatment period, $[\cdot]_+ = \max\{\cdot, 0\}$ indicates the positive part, x_0 is some fixed initial value of cells populations and the set $\mathscr{U}$ is still to be defined.

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

$$\bar{u} : [0, \eta] \mapsto [0, \bar{V}],$$

where $\bar{V}$ is the maximal vaccine quantity. The function $\bar{u}$ represents the value of injected dendritic cells population as a function of time. It is worth noting that since the time scale chosen for 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.

Consider now a family of controls u_ε corresponding to a single vaccine-administration procedure that take place at time $t_\varepsilon = \bar{t} + \varepsilon$. We want to compute the corresponding trajectory variation, under reduction (8) and (9). In this case

$$\dot{x}_{n+1} = L(x, u) = ([M(x(t, u(\cdot))) - M^{max}]_+)^2, \quad \varphi = M(x(T, u(\cdot))) + x_{n+1}. \tag{15}$$

Proposition 1. *Let u_ε be a family of controls corresponding to a single vaccine-administration procedure at time $t_\varepsilon = \bar{t} + \varepsilon$ with $\bar{u}$ constant. Let us denote by v the trajectory variation and w the variation of the new variable* (8). *Then, recalling that η is the duration of the administration of the vaccine, we get*

$$\begin{aligned} &\dot{v}(t) = D_x f(x_0(t)) \cdot v(t), \\ &\dot{w}(t) = D_x L(x_0(t)) \cdot v(t), \\ &v(\bar{t}) = f(x_0(\bar{t})) - f(x_0(\bar{t}) + V) + o(\eta), \\ &w(\bar{t}) = 0. \end{aligned} \tag{16}$$

where $V = \eta u(0)\mathbf{e_4}$,

The proof of the above proposition is easily obtained using Taylor expansion of the involved quantities.

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* $S = \{t_i : \ i = 0, \ldots, N-1, 0 \leqslant t_0 \leqslant t_1 - \eta < t_1 \leqslant \cdots \leqslant t_{N-1} \leqslant T - \eta\}$. Let $\mathscr{S}$ be the space of schedules, then for every $S \in \mathscr{S}$ we define $u(S)$ to be the corresponding control

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

The control u_S corresponds to N vaccine-administration procedures that occur at times t_i. Finally, we set

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

and optimal control problem (14) is now well defined:

(P) Given the initial condition x_0 determine a schedule $S \in \mathscr{S}$ of N injections so that the trajectory x_S of $\dot{x} = f(x(t)) + u_S(t)g(x)$ attains the minimum of cost (14).

It is easy to notice that such an optimal control problem is indeed a finite dimensional optimization problem. In fact the space S can be clearly parameterized by a subset of R^N.

Remark 1. Thanks to Proposition 1, 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 $\eta = 0$. This can be checked by computing the difference obtained by shifting a delta function.

The set of admissible schedules is clearly compact and the cost continuous, thus granting a solution to (P). Also from Proposition 1, we obtain:

Proposition 2. *For problem* (P) *we have*

$$\frac{\partial M(x_S(T))}{\partial t_i} = \nabla M(x_S(T)) \cdot v_i(T) = \mathbf{e_4} \cdot v_i(T) + o(\eta),$$

$$\frac{\partial\left(\int_0^T ([M(x(t,u(\cdot))) - M^{max}]_+)^2\,\mathrm{d}t\right)}{\partial t_i} = w(T) + o(\eta),$$

where $v(\cdot), w(\cdot)$ *is the solution to* (16) *for* $\bar{t} = t_i$ *and* $x_0 = x_S$.

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

4. Finding the optimal schedule

The optimization algorithm consists of the following iterative procedure:

Step 0: 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 $\bar{V}$, an initial value x_0 of cells populations and an initial schedule S_0 (the vector of vaccine-administration time).

Step 1: Solve 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 equation (16).

Step 2: Compute the derivatives of the extended cost φ (see (15)) with respect to the injection times t_i, via Proposition 2.

Step 3: Update the schedule by the steepest descent method, i.e., $\forall i$ add $h \cdot \partial\varphi/\partial t_i$ to t_i for some small parameter $h<0$. GOTO Step 1.

Notice that in Step 1 to save computer memory we compute *at the same time* the solution of system (1)–(5) and the variational equations (16). It is worth to mention that in order to correctly use a Runge–Kutta method with step Δt for the variation equations for v, the trajectory x_S must be computed with a step $\Delta t/2$. This is because the computation for v requires the knowledge of the values of x_S. Simulations based on more simple integrator, such as first order Euler, revealed to be too unstable hence erroneous.

In our particular settings a time horizon T of 6 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 Ref. [1]).

We start with a random vaccine injection schedule S_0 and we run the optimization schema for 5000 steps (no special stopping criteria is used here). In Fig. 1 panel (a) it is shown the evolution of the schedule during

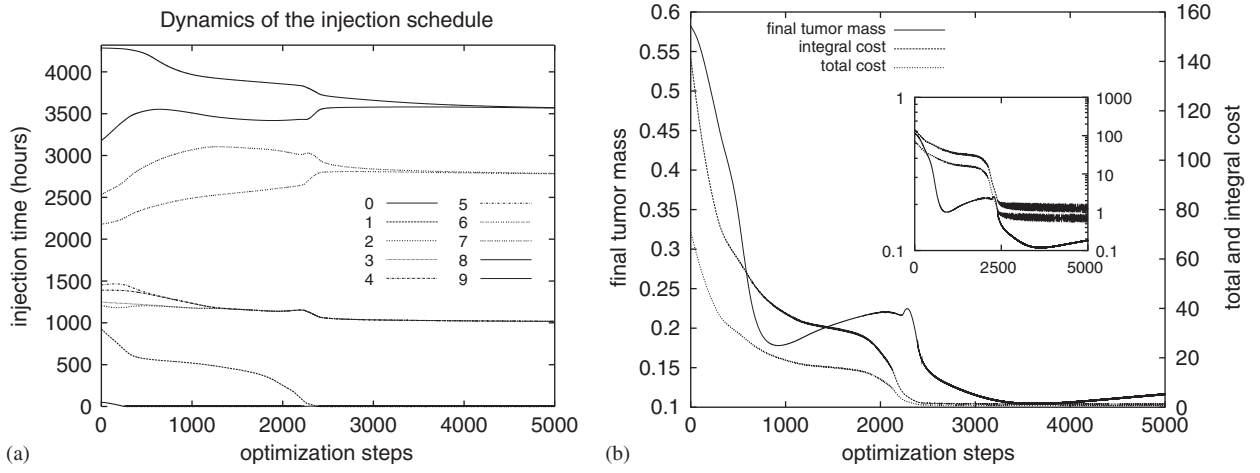

Fig. 1. Panel (a): the injection schedule (in hours, 4320 time steps is about 6 months) versus the optimization steps. The initial schedule is taken at random. In this run the dynamics shows a nontrivial aggregation of injections at almost equal intervals. Panel (b): this figure shows the two components of the cost function, the final tumor mass and the integral cost, and the weighted sum of the two (the total cost). The inset figure shows the same plot but in linear–log scale.

the iterations of the optimization algorithm. Note how the injection tends to concentrate on almost equally spaced rapid successions of injections.

In Fig. 1 panel (b) we show how the cost function changes at each iteration of the optimization procedure. In that figure both the final tumor mass and the integral cost are plotted. Note that the dynamics of the partial costs does not need to be monotonic. In this case, as in any other cases presented in this manuscript, we weighted the partial costs C_1 and C_2 equally (i.e., $w_1 = w_2 = \frac{1}{2}$) and we took $M^{max} = 0.125$.

The dynamics of the system controlled by the vaccine injections as scheduled by the optimization algorithm (i.e., S^{opt}) is shown in Fig. 2. In panel (a) the tumor mass is plotted versus time. Note how the limit M^{max} indicated by the dashed line is rarely exceeded and always for a short time. For the chosen values, the tumor is highly affected by the presence of the H (tumor-specific T helper) cells and the C (tumor-specific cytotoxic) cells. The decay of these cells is quite rapid (see panel (c)) and even more is that of dendritic cells D (panel (d)) and interleukin I (panel (b)). Note that by penalizing the solutions for which the $M > M^{max}$ (i.e., the integral cost) we force the system to find a schedule that is able to control the tumor during the *whole period of the treatment* and not by just concentrating the injections in the final period as we experienced in Ref. [1].

To study the dependence of the solution S^{opt} with respect to M^{max} we run the optimization 500 times for each of nine values of M^{max} (i.e., $M^{max} = 0.1, \ldots, 0.9$) to get a reasonable estimation of the average behavior in terms of the variation of the optimized schedule $S^{opt} = (t_0^{opt}, \ldots, t_9^{opt})$ with respect to the randomly chosen initial schedule $S^0 = (t_0^0, \ldots, t_9^0)$, $t_i^0 = rand(0, T) : t_i^0 < t_j^0, \forall i, j \in \{0, 9\}$. Then for all injection index k we compute the average over the 500 runs of the difference $t_k^{opt} - t_k^0$. Intuitively one would expect a stronger influence on the integral cost C_1 for small values of M^{max} while for large M^{max} the optimization falls into the case of using just the final tumor mass C_2 as cost function. Indeed this is what we obtain as shown in Fig. 3.

In panel (a) dark areas correspond to large negative time shifts of the injections meaning that they have been moved backward in time with respect to the initial random ones, while white areas correspond to positive variations meaning that the injections have been shifted forward in time. In particular for M^{max} approaching unity the injections cluster almost at the end of the optimization period (e.g., around injection 7) resembling what we obtained in Ref. [1]. At variance with that, for small M^{max}, the optimal solutions found are those that uniformly allocate the injection within the allowed time horizon T. To show this point more clearly, in panel (b) we show S^0 and S^{opt} for $M^{max} = 0.1$. In this case $t_k^{opt}, k = 0, \ldots, 9$ are shifted backward; in particular the first two injections are shortly distanced to immediately push the immune system to develop a strong anticancer immune response, and then the remaining injections are roughly equally spaced to sustain the

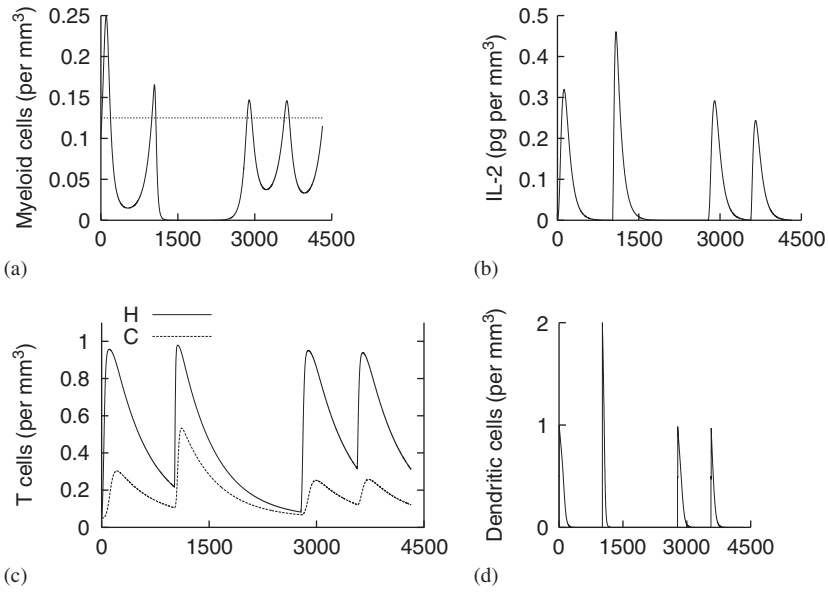

Fig. 2. Here we show the dynamic of the system that follow the vaccination schedule as computed by the optimization algorithm (i.e., S^{opt} corresponding to Fig. 1). The dashed line in the upper-left panel indicates the value of $M^{max} = 0.125$.

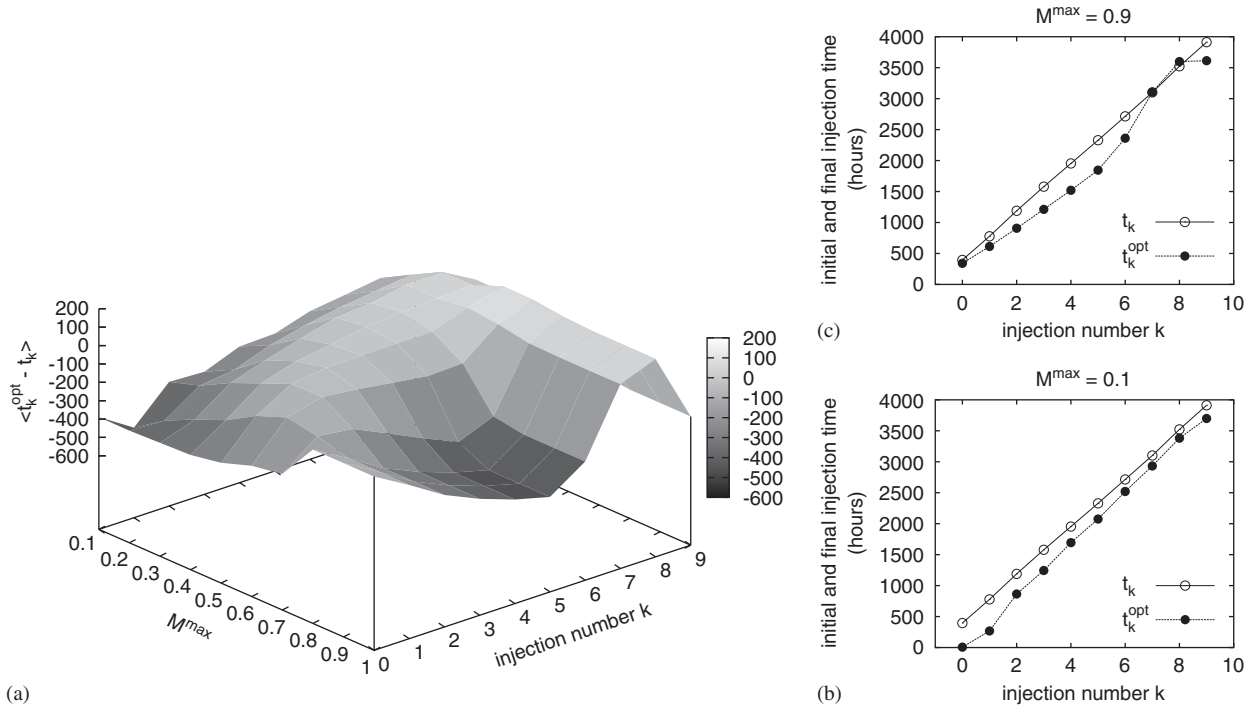

Fig. 3. Panel (a) shows $\langle t_k^{opt} - t_k^0 \rangle$ as a function of M^{max} and k. Panels (b) and (c) show t_k^{opt} and t_k^0 for $M^{max} = 0.1$ and $M^{max} = 0.9$, respectively.

immune memory and to keep the tumor under control. Panel (c), again, shows S^0 and S^{opt} for the antipodal case $M^{max} = 0.9$. In this case the optimal injections drift lightly in the first half of the duration of the therapy, and heavily close to its termination, struggling to keep the final tumor burden $M(T)$ as low as possible.

5. Discussion and conclusions

We have constructed a mathematical model of the immune–cancer interaction to study the effect of immunotherapy via DCVs and we asked the question of how to determine the best time 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 $M(T)$ and the integral of the tumor mass exceeding a certain level M^{max} given as parameter.

We used typical tools of optimal control to approximate the effect of the vaccine and compute the gradient of the cost function with respect to the schedule. The latter is obtained via the solution of a generalized variational equation. Finally, the optimization algorithm itself is based on the steepest decent method.

For what concerns the dependency of the solution of the optimization problem on the parameters' values one can divide in two the space of possible changes of the parameters, with respect to the choice in Table 1: the first subspace is that of parameters' changes that favor the tumor growth and the other is the one that makes a more effective immune system response (i.e., the ''dual'' of the first). The impact of parameters' changes that favor the tumor growth consists in a slower convergence of the optimization algorithm. In the opposite case of an increase of immune system's efficiency, the optimization algorithm converges faster but vary less the vaccination schedule just because there is no need for an optimization. In both cases the optimization procedure shows to be robust with respect to parameters' changes since a tumor reduction is always attained. The number of injections required to keep the tumor mass small is very much dependent on the choice of the parameters that define the ''balance'' of the tumor resistance with the efficacy of the immune response. In other words N is a function of all system parameters and of the initial condition. Clearly a small N is better from the clinical point of view (less burden for the patient, smaller risk of toxicity, vaccine costs, etc.) but it is

quite difficult to find its lower bound just by numerical analysis. Finally, it is worth to say that for a fixed setting of the carrying capacities in Eqs. (1)–(5), there is a threshold above which one does not have any improvements in increasing the number of injections N, simply because the immune system efficacy is limited.

The optimal solutions found are successful in controlling the tumor and tell us that the best schema is those that uniformly allocate the injection within the allowed time horizon T. However, given that the efficacy of the vaccine depends on many parameters like the grow rate of the tumor, the immunogenicity of the presented TAA, the cell counts in real patients, and so on, we evince that a certain grouping of the injections is needed to actually control the tumor mass and that such groups of shortly distanced injections need to be equally spaced in time over the whole therapeutic period. This can be seen as the need for different vaccine dosages at different time. Interestingly the question points to the possible development of our study including a variable vaccine dosage that we already started to look into.

References

[1] F. Castiglione, B. Piccoli, Optimal control in a model of dendritic cell transfection cancer immunotherapy, Bull. Math. Biol., Online version available, DOI:10-1007/s11538-005-9014-3.
[2] L.S. Pontryagin, V. Boltianski, R. Gamkrelidze, E. Mitchtchenko, The Mathematical Theory of Optimal Processes, Wiley, New York, 1961.
[3] R.B. Vinter, Optimal Control, Birkhäuser, Boston, 2000.
[4] R.B. Martin, Optimal control drug scheduling of cancer chemotherapy, Automatica 28 (1992) 1113–1123.
[5] D. Kirschner, J.C. Panetta, Modeling immunotherapy of tumor–immune interaction, J. Math. Biol. 37 (1998) 235–252.
[6] A. Swierniak, U. Ledzewicz, H. Schattler, Optimal control for a class of compartmental models in cancer chemotherapy, Int. J. Appl. Math. Comp. Sci. 13 (3) (2003) 357–368.
[7] T. Burden, J. Ernstberger, K. Renee Fister, Optimal control applied to immunotherapy, Disc. Cont. Dyn. Syst. B. 4 (1) (2004) 135–146.
[8] R.A. Goldsby, T.J. Kindt, B.A. Osborne, Kuby Immunology, fourth ed., Freeman, New York, 2000.
[9] L. Preziosi (Ed.), Cancer Modeling and Simulation, Chapman & Hall/CRC Press, (UK), London, 2003.
[10] B. Piccoli, H.J. Sussmann, Regular synthesis and sufficiency conditions for optimality, SIAM J. Control Optim. 39 (2000) 359–410.
[11] M. Garavello, B. Piccoli, Hybrid necessary principle, SIAM J. Control Optim. 43 (2005) 1867–1877.