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Mixed immunotherapy and chemotherapy of tumors: Feedback design and model updating schemes

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ABSTRACT

In this paper, a recently developed model governing the cancer growth on a cell population level with combination of immune and chemotherapy is used to develop a reactive (feedback) mixed treatment strategy. The feedback design proposed here is based on nonlinear constrained model predictive control together with an adaptation scheme that enables the effects of unavoidable modeling uncertainties to be compensated. The effectiveness of the proposed strategy is shown under realistic human data showing the advantage of treatment in feedback form as well as the relevance of the adaptation strategy in handling uncertainties and modeling errors. A new treatment strategy defined by an original optimal control problem formulation is also proposed. This new formulation shows particularly interesting possibilities since it may lead to tumor regression under better health indicator profile.

1. Introduction

This paper is based on recent works (dePillis et al. 2005a, b; dePillis and Radunskaya, 2003) where a system of ordinary differential equations (ODE's) has been proposed to model the growth of cell population levels in presence of tumor cells and under a combined immune, vaccine and chemotherapy of cancer. While modeling the entire immune system is a highly complex task (Perelson and Weisbuch, 1997), reasonably simple models can be obtained when concentrating on the reaction of the immune system to tumor growth (see dePillis et al. 2005a, b; dePillis and Radunskaya, 2003; de Boer and Hogeweg, 1986 and the references therein). In particular, the model proposed in dePillis et al. (2005a, b) and dePillis and Radunskaya (2003) enables the basic qualitative phenomenons such as tumor dormancy, oscillation in tumor size as well as bifurcation-like behavior to be reproduced under particular realistic conditions. Moreover, the tumor and the immune system responses to particular medical interventions (chemotherapy drug and immune response modifiers injection) have been modeled. Corresponding simulations show clearly the following facts (dePillis et al. 2005a, b): first combined immune and chemotherapy may be crucial to the success of cancer treatment, and also as the model parameters may heavily depend on the patient, the same open-loop injection profile can be successful for one patient and inadequate for another even when starting from the same initial state.

The resolution of optimal control problem in cancer treatment therapy is a very performing tool that already showed particularly interesting performances (Ledzewicz and Schattler, 2002; Martin, 1992; Alamir and Chareyron, 2006). However, this is generally done in an open-loop, namely, by computing the best strategy to be applied based on the model and some initial state. The specificity of NMPC scheme is to be a feedback scheme that need optimal control problem to be repeatedly solved at each decision instant in order to robustify the results against model mismatch and parameter uncertainties. To the best of our knowledge, this scheme, while widely assessed to be of a great efficiency by control systems theorists has been but rarely (if never) been used in cancer treatment computation in feedback form. Thus, the feedback scheme proposed here combines both the advantages of optimal control theory and the performances of a feedback scheme. Indeed it is a well known fact that controlled systems gain in robustness when a feedback control is applied to achieve the desired behavior. More precisely, feedback decreases the sensitivity of the overall result to parametric uncertainties and modeling errors. Moreover, when large deviations in the values of parameters are expected to hold, it may be necessary to use the available measurements in order to improve the robustness of the treatment result.

The feedback scheme proposed here is applied on the mathematical model proposed in dePillis et al. (2005a, b) and dePillis and Radunskaya (2003), but the method is very generic and such feedback scheme could be implemented for any other types of models as bidimensional models (d'Onofrio, 2000) or

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infinite dimensional model (Bellomo et al., 2004) since the model is used here only as a black-box simulator.

The aim of the present paper is to propose a complete (feedback control, adaptation) scheme that implement the above ideas on the mixed immunotherapy/chemotherapy of tumors. The paper is organized as follows. First, the model of dePillis et al. (2005a, b) and dePillis and Radunskaya (2003) is briefly described in Section 2. Follows a description of the control problem. More precisely, two possible nonlinear model predictive control (NMPC) formulations are defined using two different optimal control problems:

(1) In the first, the problem is to minimize the tumor size at the end of the prediction horizon while keeping the number of circulating lymphocytes beyond a minimal level during the whole therapy.
(2) In the second, the problem is to maximize the number of circulating lymphocytes while imposing a contraction rate on the number of tumor cells at the end of the prediction horizon compared to its value at the beginning of the prediction horizon.

Once an optimal control problem is defined, the corresponding NMPC feedback amounts to solve this optimal control problem leading to an optimal sequence of future control actions, to apply the first action in the resulting optimal sequence during the sampling period. At the next decision instant, the optimal control problem to be solved is updated based on the value of the current state, the resulting problem is solved yielding an optimal sequence of future actions, the first one is applied during the sampling period until the next decision instant and the procedure is repeated.

The use of the predictive control strategy to yield a mixed therapy in feedback form without updating scheme is proposed in Section 4 together with some validating simulations using the human data given in dePillis et al. (2005a, b) (patients 9 and 10). These simulations suggest a nice robustness behavior against parameters discrepancy up to a certain level. In Section 5, a novel updating scheme is proposed and its effectiveness in improving the robustness is assessed through dedicated simulations. Finally, the different consequences that result from the use of each one of the above two different formulations are also discussed in Section 6. The paper ends with a conclusion summarizing the paper contributions and giving guidelines for future work.

2. Model description and control related problem

2.1. The state variables

In this section, the mathematical model proposed in dePillis et al. (2005a, b) to describe the dynamic evolution of the population of cells in the presence of tumor and under the combined immune and chemotherapy treatment is briefly described. This model involves the following cell populations:

- T, tumor cell population.
- N, total NK cell population. These cells are part of the innate immune system and therefore exist even when no tumor cells are present (dePillis et al., 2005a; Roitt et al., 1993).
- L, total $CD8^+$T cell population. These are active tumor specific cells that are part of the specific immune response. Consequently, these cells are only present in large numbers when tumor cells are present (dePillis et al., 2005a; Roitt et al., 1993; Kirschner and Panetta, 1998).
- C, number of circulating lymphocytes (or white blood cells). This number can be used as a measure of the patient health (Melichar et al., 2001; Mustafa et al., 1998).
- M, chemotherapy drug concentration in the blood stream.
- I, immunotherapy drug concentration in the bloodstream.

2.2. The modeling assumptions

Before going into the model description, it is important to note that, as it is recalled in dePillis et al. (2005a), *there is no universal agreement as to the underlying dynamics or the precise cascades of events that take place in the immune response process*. The model recalled and described below is, however, based on published statements derived from clinical validations (Diefenbach et al., 2001; Dudley et al., 2002; Rosenberg and Lotze, 1986) as well as on reasonable assumptions depicted in Table 1.

2.3. Mixed immunotherapy and chemotherapy of tumor model

The considerations depicted in Table 1 lead to the following simplified model for cell population dynamics in presence of tumor cells and under mixed immune and chemotherapy medical interventions:

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T(1-e^{-M})T, \tag{1}$$

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT - K_N(1-e^{-M})N, \tag{2}$$

$$\begin{aligned}\frac{dL}{dt} = & -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T \\ & - uNL^2 - K_L(1-e^{-M})L + \frac{p_lI}{g_l+I}L + v_L(t),\end{aligned} \tag{3}$$

Table 1
Table describing the modeling assumptions on the six population evolutions and their mathematical formulations

The number of tumor cells grows logistically in the absence of immune response	$aT(1-bT)$ (in the r.h.s of (1))
Both NK and $CD8^+$T kill tumor cells	$-cNT$ and $-DT$ (in the r.h.s of (1))
The cytokine IL-2 stimulates the recruitment of $CD8^+$T cells (Roitt et al., 1993). It is naturally present in the immune system but it can also be injected therapeutically (Kirschner and Panetta, 1998). The additional amount of cytokine IL-2 that corresponds to this medical intervention is represented by the state variable I	$\frac{p_lI}{g_l+I}L$ (in the r.h.s of (6))
NK cells are normally present in the body even in the absence of tumor cells. In the model of dePillis et al. (2005a), the source of NK cells is taken to be a fraction of the circulating lymphocytes. This is clearly a simplification that aims to represent a rather complex cascade of biological events that result in the stimulation of NK cells production	eC (in the r.h.s of (2))
The fraction of cells (both tumor and healthy cells) killed by chemotherapy depends on the amount of drug present in the body	$(1-e^{-M})$ (in the r.h.s of (1)–(4))
Both the NK and the $CD8^+$T cell populations are stimulated by the presence of tumor cells	$g\frac{T^2}{h+T^2}N$ and $j\frac{D^2T^2}{k+D^2T^2}L$ (in (2) and (3), respectively)
Allcells are in competition for space and nutriments	Bilinear terms NT, LT, NL^2 in Eqs. (1)–(3)

This table has to be related to the system dynamics described by (1)–(7).

$$\frac{dC}{dt} = \alpha - \beta C - K_C(1 - e^{-M})C, \tag{4}$$

$$\frac{dM}{dt} = -\gamma M + v_M(t), \tag{5}$$

$$\frac{dI}{dt} = -\mu_I I + v_I(t), \tag{6}$$

$$D = d\frac{(L/T)^l}{s + (L/T)^l}. \tag{7}$$

To summarize, the model involves

- six measured state variables T, N, L, C M, and I,
- three manipulated (control) variables v_M, v_L and v_I,
- and 24 parameters: $a, b, c, d, s, K_T, e, f, g, h, K_N, m, j, k, q, r_1, r_2, u, K_L, \alpha, \beta, K_C, \gamma$ and l. Almost all these parameters vary from one patient to another. Two sets of experimentally estimated parameters for two different patients can be found in dePillis et al. (2005a). These sets are used in the remainder of the paper for simulation and validation purposes. Relative errors on a subset of these parameters are also simulated to evaluate the robustness of the resulting closed-loop behavior.

2.4. The control problem

The basic paradigm in cancer therapy drug administration is to decrease the number of tumor cells T while monitoring the number of circulating lymphocytes C as they are a good measure of the patient health (Fister and Panetta, 2000; Martin and Teo, 1994; DePillis and Radunskaya, 2001). There are two different ways to formally write this control objective:

(1) The first formulation is the one used by DePillis and Radunskaya (2001), Matveev and Savkin (2002) and Alamir and Chareyron (2006) among many other works. It amounts to minimize the tumor size $T(t_f)$ at the end of some prediction horizon while keeping the circulating lymphocytes above a given threshold C_{min}:

$$\mathscr{P}_1 : \min_{v_M(\cdot), v_L(\cdot), v_I(\cdot)} T(t_f)$$
$$\text{under } C(t) \geqslant C_{min}, \quad \forall t \in [0, t_f]. \tag{8}$$

This formulation aims to reduce the tumor size as faster as possible under the health constraint $C(t) \geqslant C_{min}$.

(2) The second possible formulation investigated hereafter uses a reverse logic. Namely, it aims to maximize the patient health under a contraction constraint on the tumor size at the end of the prediction horizon. More precisely, the following game is defined

$$\mathscr{P}_2 : \max_{v_M(\cdot), v_L(\cdot), v_I(\cdot)} \min_{t \in [0, t_f]} C(t)$$
$$\text{under } T(t_f) \leqslant \gamma T(0) \quad \text{with } \gamma \in]0, 1[. \tag{9}$$

This formulation focuses on the *health level* by allowing a less faster decrease of the tumor size.

To the best of our knowledge, the second formulation has never been considered and one of the contributions of the present paper is to show that the above different two formulations lead to quite different results. Namely, as shown hereafter, the second formulation may lead to huge improvement in the health indicator at the price of a imperceptibly longer treatment duration.

In the following section, it is shown how NMPC design enables the above formulations to be handled yielding two corresponding feedback schemes.

3. Recall on NMPC

This section is devoted to a brief recall on NMPC that is a state feedback design tool, refer to Alamir (2006) for a detailed presentation of NMPC. Let us consider a time-invariant system

$$x(t) = F(x_0, t, \boldsymbol{u}), \quad x(t) \in \mathbb{R}^n, \ u(t) \in \mathbb{R}^m \tag{10}$$

with $x(.)$ the state trajectory that is completely determined through the map $F(.)$ given the initial state $x_0 = x(0)$ and the control profile $\boldsymbol{u}$,

$$\boldsymbol{u} = \{u(\tau)\}_{\tau \in [0,t]}, \quad u(\tau) \in \mathbb{U}. \tag{11}$$

Let $\tau_s > 0$ be a sampling period, the NMPC is a control strategy in which the current control action is obtained by solving at each sampling instant a finite constrained horizon open-loop optimal control problem

$$\min_{\boldsymbol{u} \in \mathbb{U}^{[0,t_f]}} J(x_0, t_f, \boldsymbol{u}), \quad \sigma(x_0, \boldsymbol{u}) \leqslant 0 \tag{12}$$

with $t_f = N\tau_s$ the prediction horizon. This yields an optimal control profile. The *first part* of this profile is applied during the current sampling period until the next decision instant is reached. At this decision instant, the problem is updated according to the new initial state (equal to the current one) and the procedure is repeated yielding a state feedback.

Note that in many applications, the system dynamics is submitted to state constraints that are here described by the inequality $\sigma(x_0, \boldsymbol{u}) \leqslant 0$. In our case, the state constraints are imposed either by the threshold on the number of circulating lymphocytes in the optimal control problem $\mathscr{P}_1$ [see (8)], or by a contraction rate on the number of tumor cells at the end of the prediction horizon in the optimal control problem $\mathscr{P}_2$ [see (9)].

For the mixed immunotherapy and chemotherapy of tumors, the NMPC will either be defined using the optimal control problem $\mathscr{P}_1$ or $\mathscr{P}_2$ described, respectively, by (8) or (9). Note that in both cases, the optimal control problems are submitted to state constraints. Now, in order to reduce the optimal control problem complexity, it is interesting to consider a control parametrization that can be described by a map

$$C : \mathbb{P} \to \mathbb{U}^N$$
$$C(p) = (u^1(p) \ \ldots \ u^N(p)), \tag{13}$$

where $\mathbb{P}$ is a set of admissible parameter values, leading to a so-called $\mathbb{P}$-parameterized piecewise constant control profile

$$\boldsymbol{u} = \mathscr{U}_{pwc}(., p), \tag{14}$$

such that, if the decision instants are denoted by $\{t_i = i.\tau_s\}_{i=1}^N$, one has

$$\mathscr{U}_{pwc}(t, p) = u^i(p) \quad \text{with } i \in \{1, \ldots, N\} \text{ and } t \in [t_{i-1}, t_i]. \tag{15}$$

This way, a parameterized receding-horizon control is defined, where the new decision variable is p. The cost function is now a function of p since

$$J(x_0, t_f, \boldsymbol{u}) \ \leftrightarrow \ J(x_0, t_f, \mathscr{U}_{pwc}(., p)) \ \leftrightarrow \ J(x_0, t_f, p). \tag{16}$$

At each decision instant t_k, the solution of the parameterized optimization problem (17) over the prediction horizon t_f:

$$\min_{p \in \mathbb{P}} J(x(t_k), t_f, p), \quad \sigma(x(t_k), p) \leqslant 0 \tag{17}$$

yields the optimal parameter value $\hat{p}(x(t_k))$. The sampled receding-horizon feedback described by (15) is then obtained by applying the first element of the control sequence that is defined by the optimal parameter value

$$u(t_k) = u^1(\hat{p}(x(t_k))) = \mathscr{U}_{pwc}(0, \hat{p}(x(t_k))). \tag{18}$$

At the next decision instant t_{k+1}, a new optimal parameter $\hat{p}(x(t_{k+1}))$ is computed by minimizing the new cost function $J(x(t_{k+1}), t_f, p)$ and the resulting control

$$u(t_{k+1}) = u^1(\hat{p}(x(t_{k+1}))) = \mathscr{U}_{pwc}(0, \hat{p}(x(t_{k+1})))$$

is applied during the sampling period $[t_{k+1}, t_{k+2}]$ and so on.

4. NMPC for mixed immunotherapy and chemotherapy treatments

Recall that according to (1)–(7), the effect of chemotherapy and immunotherapy treatments (TIL and IL-2 injections) on the state variables are modeled, respectively, by $v_M(.)$, $v_L(.)$ and $v_I(.)$. These three variables correspond to the control actions, their profiles will be determined by two different ways:

- The explicit direct effects of immunotherapy treatments on the dynamical behavior of the system lead to determine the immunotherapy control $v_L(.)$ and $v_I(.)$ explicitly through a simple feedback loop as explained in Section 4.1.
- On the opposite, the effect of chemotherapy is quite complex because it induces positive effects (tumor regression) and negative effects (regression of immune system). As a result, it is necessary to implement a prediction-based implicit NMPC scheme in order to determine the chemotherapy control profile.

We will see in Section 4.2 that when considering medical applications, piecewise constant and parameterized control profiles seems particularly well-adapted.

4.1. Computation of immunotherapy treatment $v_L(.)$ and $v_I(.)$ through an explicit feedback loop

The goal of immunotherapy is to strengthen the ability of the body to fight against cancer by enhancing the effectiveness of the patient immune system. To get into more details, we can observe that through Eqs. (3) and (6), the immunotherapy treatments $v_L(.)$ and $v_I(.)$ tend to increase the CD8$^+$T cell population L. As a result, immunotherapy acts on the tumor cell population through the tumor lysis by CD8$^+$T cells described by the term D [see (7)] in Eq. (1).

Now, since the term $D(L,T)$ is a function of CD8$^+$T cells L and tumor cells T, one can observe through relation (7) that with a high rate of CD8+ cells, the tumor lysis by CD8+ cells tends to the value of the parameter d, while for a low population of CD8$^+$T the term D tends to zero.

The control objective of immunotherapy appears thus relatively simple, it aims at maximizing the tumor lysis by CD8$^+$T cells by increasing the CD8$^+$T cell population with d as a set point. Indeed, according to the model, when D approaches d, no benefit can be obtained from immunotherapy and treatment can be almost stopped.

Therefore at each decision instant t_k, the quantity of both TIL and IL-2 drugs are computed through the following expression:

$$v_L(t_k) = Sat_0^{V_{L\,max}}(\lambda(d - D(L(t_k), T(t_k))))$$
$$v_I(t_k) = Sat_0^{V_{I\,max}}(\lambda(d - D(L(t_k), T(t_k))))$$

with $\lambda > 0$ a coefficient that determines the bandwidth of the feedback. The maximum concentration of immunotherapy treatments $v_L(.)$ and $v_I(.)$ is bounded by the following values taken from dePillis et al. (2005a): a maximum boost of TILs of $V_{L\,max} = 10^9$ cells and a maximum boost of IL-2 of $V_{I\,max} = 5 \times 10^5$ cells.

4.2. Parametrization of the chemotherapy treatment

Following the control parametrization principle recalled in Section 3, the parametrization of the chemotherapy profile to be used in the implementation of the NMPC feedback is detailed in the present section.

In medical applications, a drug treatment is often defined by the following parameters: dosages, duration of the treatment, schedule (number of administrations and times of administration), way of administration, and administration profile (bolus, infusion). As a result, the parametrization of the chemotherapy treatment profile used in the NMPC related computation appears completely natural. As shown in Fig. 1 the chemotherapy control profile will be described by three parameters: the dosage (amplitude) α_M, (bounded by a maximum value $V_{M\,max}$), the duration of each dose δ_M and the period T_M.

4.3. NMPC for chemotherapy treatment

The control profile of the chemotherapeutic treatment is found by solving at each decision instant the optimal control problem $\mathscr{P}_1$ or $\mathscr{P}_2$ in the vector of unknown parameter

$$p = (\alpha_M, \delta_M, T_M).$$

In fact, for the simulations presented here, the period of the chemotherapy treatment T_M was kept constant and equal to the

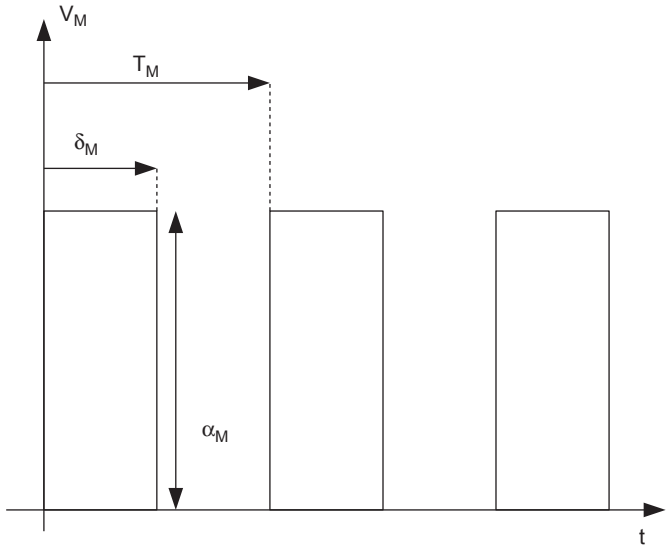

Fig. 1. Parametrization of the chemotherapy treatment.

Table 2
The set of parameters used in the control strategy

Simulation data	Value
Maximum dose of immunotherapy	$V_L^{max} = 10^9$ and $V_I^{max} = 5 \times 10^5$
Maximum dose of chemotherapy	$V_M^{max} = 1$
Prediction horizon	$t_f = 4$ days
Coefficient for immunotherapy feedback control	$\lambda = 42$
Coefficient for the updating algorithm	$\mu_0 = 10^{-6}$
Circulating lymphocytes threshold	$C_{min} = 10^6$
Initial conditions	$L_0 = 50$, $N_0 = 5 \times 10^2$ $C_0 = 4 \times C_{min}$

prediction horizon, but this parameter can easily be used as an optimizable variable.

As explained in Section 3, in order to reduce the optimal control problem complexity, the control parametrization for the NMPC feedback control for mixed chemotherapy/immunotherapy is based on a quantization of the chemotherapy treatment. The set $\mathbb{P}$ of admissible parameter values, defined in (13), is here described by the set of discretized drug quantities and treatment

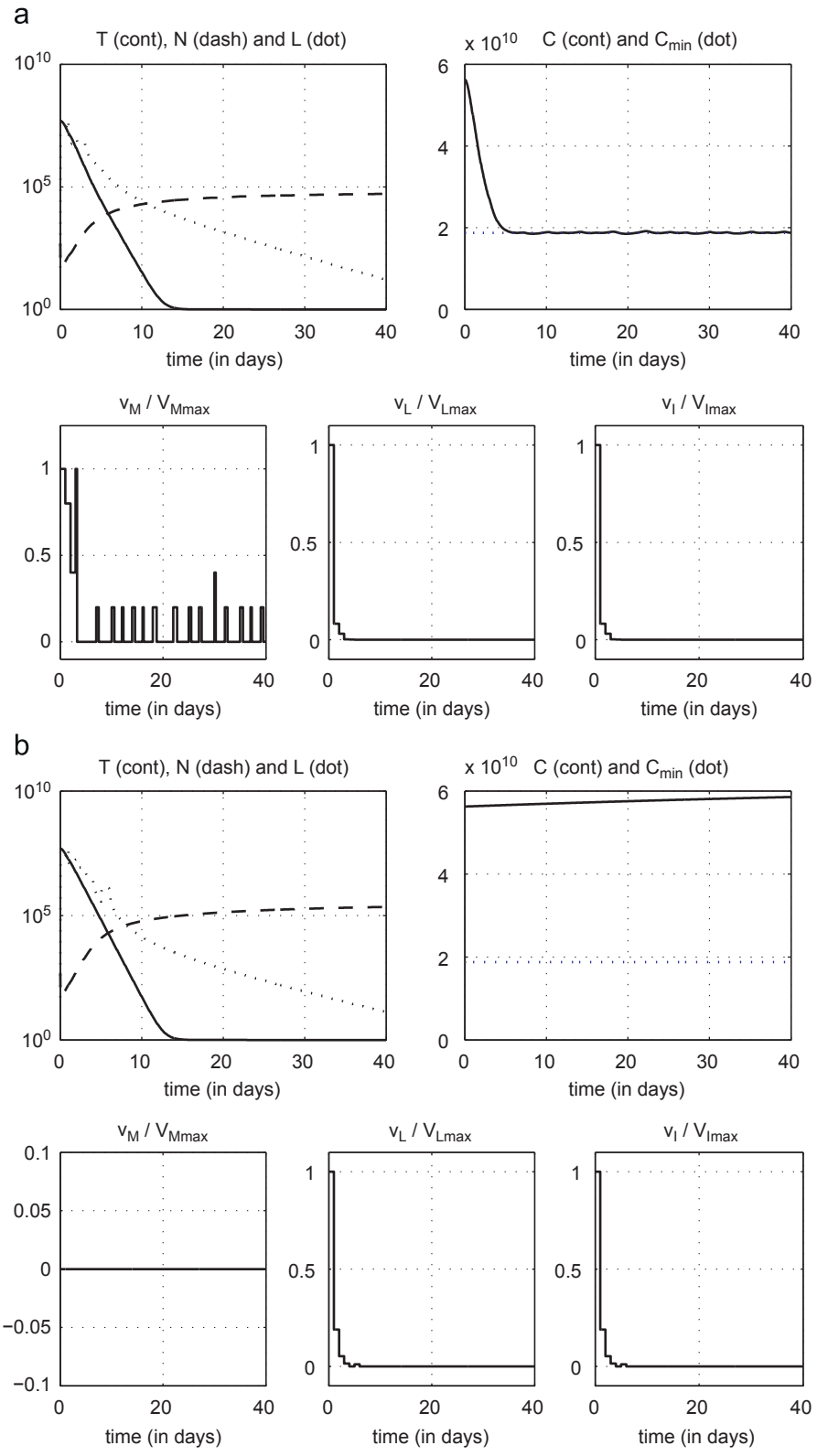

Fig. 2. Behavior of the population levels under the two treatment strategies: using the optimal control problem $\mathscr{P}_1$ (a) and $\mathscr{P}_2$ (b) under 15% of parameter discrepancy. On both cases the treatment is successful since it leads to a tumor regression. Note, however, that the treatment strategy corresponding to the optimal control problem $\mathscr{P}_2$ appears here particularly attractive since even though the treatment duration is slightly longer, the health of the patient is kept at its maximum level over the whole treatment period. (Simulation conditions $T(0) = 5 \times 10^7$, 15% of discrepancy on nine parameters.)

durations

$$(\alpha_M, \delta_M) \in \{0, 0.2, 0.4, 0.6, 0.8, 1\} \cdot V_{M\,max} \times \{0, 0.25, 0.5, 0.75, 1, 2\} \cdot \delta_{M\,max}$$

which is particularly suitable for medical applications.

4.4. Simulations of NMPC-based mixed therapy

The simulations are obtained using a routine written in C++ that uses the GSL library. For the simulations, two sets of parameters are used, their values taken from dePillis et al. (2005a) correspond to two patients (9 and 10). A brief look at these two sets of parameters allows to observe a wide range of parameter variations. It is therefore necessary to check the robustness of the mixed immunotherapy and chemotherapy of tumors.

The control parameters and the initial conditions are given in Table 2, additional parameters that vary for simulation purposes (as initial tumor cells T_0 or contraction factor γ) will be specified inside the caption of the corresponding figure. For robustness analysis, we introduce a discrepancy on nine randomly chosen parameters: a, d, c, p, q, u, r_1, r_2, pI always in the most pessimistic case. Fig. 2a shows the successful treatment for an initial tumor size of $T(0) = 5 \times 10^7$ when the optimal control problem $\mathscr{P}_1$ is used under 15% of discrepancy (Fig. 2b will be exploited in Section 6). For this simulation, the initial conditions considered on the system parameters are $N(0) = 5.0 \times 10^2$, $L(0) = 50$ and $C(0) = 5.625 \times 10^{10}$ cells. The threshold for the minimum number of lymphocytes is fixed three times smaller than the initial number of lymphocytes, namely $C_{min} = 1.875 \times 10^{10}$ cells. Despite the 15% of parameter discrepancy, the treatment strategy leads to a tumor regression while keeping above the threshold the number of circulating lymphocytes.

To quantify more systematically the robustness property of the NMPC scheme, we examine the case of a discrepancy on the parameters ranging from 0% to 50%. Fig. 3 shows a table summarizing the successful (the dark green area) or unsuccessful (all but the dark green area) treatments for an initial tumor size going from 1×10^7 cells to 1.5×10^8 cells with respect to different model uncertainties (note that Fig. 3 contains two other regions that correspond to the adaptive scheme, they are described in Section 5). The treatment is considered to be successful when the total number of cancerous cells by the end of the treatment is sufficiently low, for example less than 1×10^3, but it is to be noticed that the treatment period is extended when needed to satisfy this criterion of minimum number of cells. The initial conditions are kept identical to the above simulation. When there is no uncertainty between the patient parameters and the model, we can observe that the NMPC scheme is able to kill a tumor of initial size $T_{max}(0) = 1.3 \times 10^8$ cells. When the uncertainties increase, the maximum allowable size of the initial tumor decreases: for 10% of unmodeled uncertainties, the maximum initial size of the tumor for the treatment to succeed is of $T_{max}(0) = 9 \times 10^7$ and for 20% $T_{max}(0) = 6 \times 10^7$. Note that for high unmodeled uncertainties, the NMPC is still able to kill an initial tumor of size $T_{max}(0) = 1 \times 10^7$. Clearly, the proposed NMPC presents nice robustness properties with respect to unmodeled uncertainties.

It is interesting to notice that in a general manner, the optimal solution obtained in this work yields in applying chemotherapy at the beginning of the treatment therapy. This solution is different from the optimal solutions obtained in Fister and Panetta (2000), Martin (1992) and Swierniak et al. (2003) that lead to apply the drugs at the end of the treatment period. In Alamir and Chareyron (2006), these two different strategies were observed, and they were due to the existence of multiple solutions, the solution was thus for the considered compartmental model, sensitive to the initial guess.

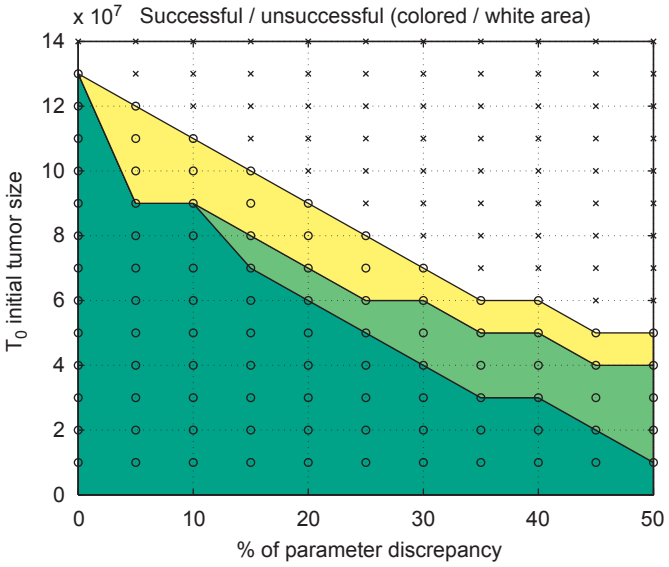

Fig. 3. Robustness analysis of the NMPC with and without updating scheme using different updating periods. Four areas appear: successful treatments with NMPC without updating mechanism (dark green), area of recovering successful treatment with one update/day (light green), area of recovering successful treatment with three updates/day (yellow) or unsuccessful treatments (white area).

5. NMPC with updating scheme

5.1. An updating scheme

It goes without saying that updating the values of the 24 parameters of the model would be illusory. Indeed, it is a well known fact in identification theory that when the system is described by a large number of parameters, the problem might be ill-conditioned unless the identification is performed under extremely rich excitation signal. Unfortunately, this is impossible to do in our case where the identification would have been performed under the on-line treatment signals that are generally insufficient to guarantee good identifiability of the model parameters.

Based on the above argumentation, a low dimensional updating scheme is proposed here. This scheme allows to reduce the number of parameters to adapt, by focusing exclusively on what is directly linked to the control objectives. Thus, we propose to correct the evolution model of the key variable T by adding a correction term on Eq. (1) (when used by the controller to perform prediction) as follows:

$$\frac{dT}{dt} = aT(1 - bT) - cNT - DT - K_T(1 - e^{-M})T - \alpha_{up}(t_i)T, \tag{19}$$

where $t_i = i\tau_{up}$ are the updating instants, while τ_{up} is the updating period. $\alpha_{up}(.)$ is a piecewise constant correction term determined according to

$$\alpha_{up}(t_{i+1}) = \alpha_{up}(t_i) + \mu_{up}(t_i)(T_{pred}(t_i) - T_{meas}(t_i)), \tag{20}$$

where $\mu_{up}(t_i) = \mu_0.T_{pred}(t_i)$ with $\mu_0 \in [0, 1]$ is a filtering coefficient and $(T_{pred}(t_i) - T_{meas}(t_i))$ corresponds to the prediction error at time t_i between the total number of tumor cells measured on the patient and the total number of tumor cells predicted by the model. After each measurement, $\alpha_{up}(.)$ is updated and implemented according to (20).

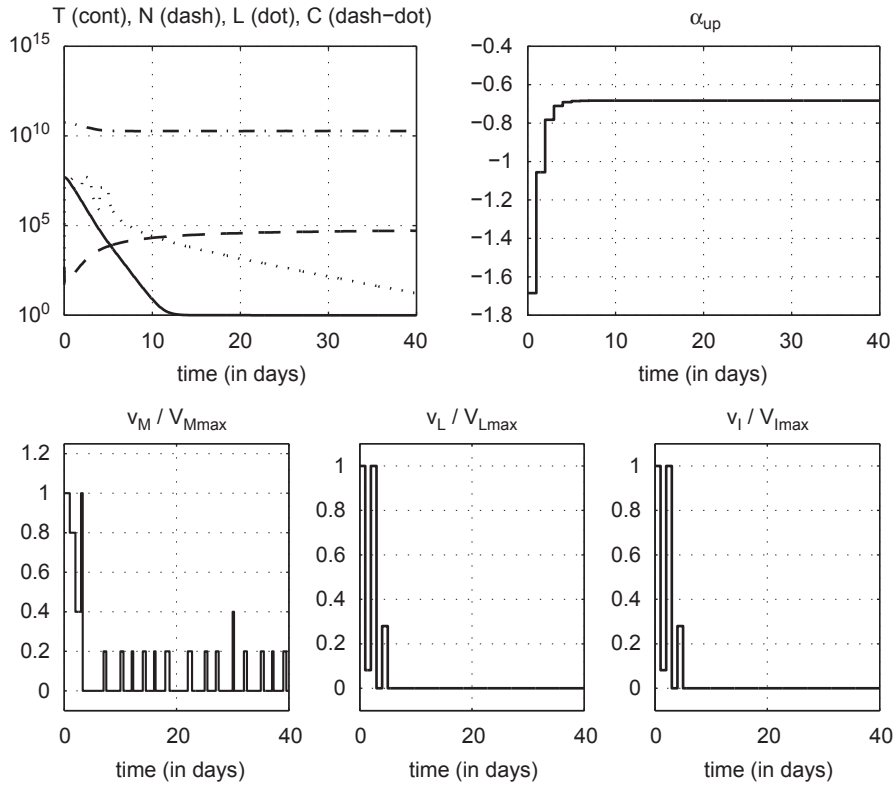

Fig. 4. Evolution of the model correction coefficient α_{up} (related to the prediction error through (20)) over the treatment period for 20% of parameter discrepancy in the case of an NMPC with updating scheme.

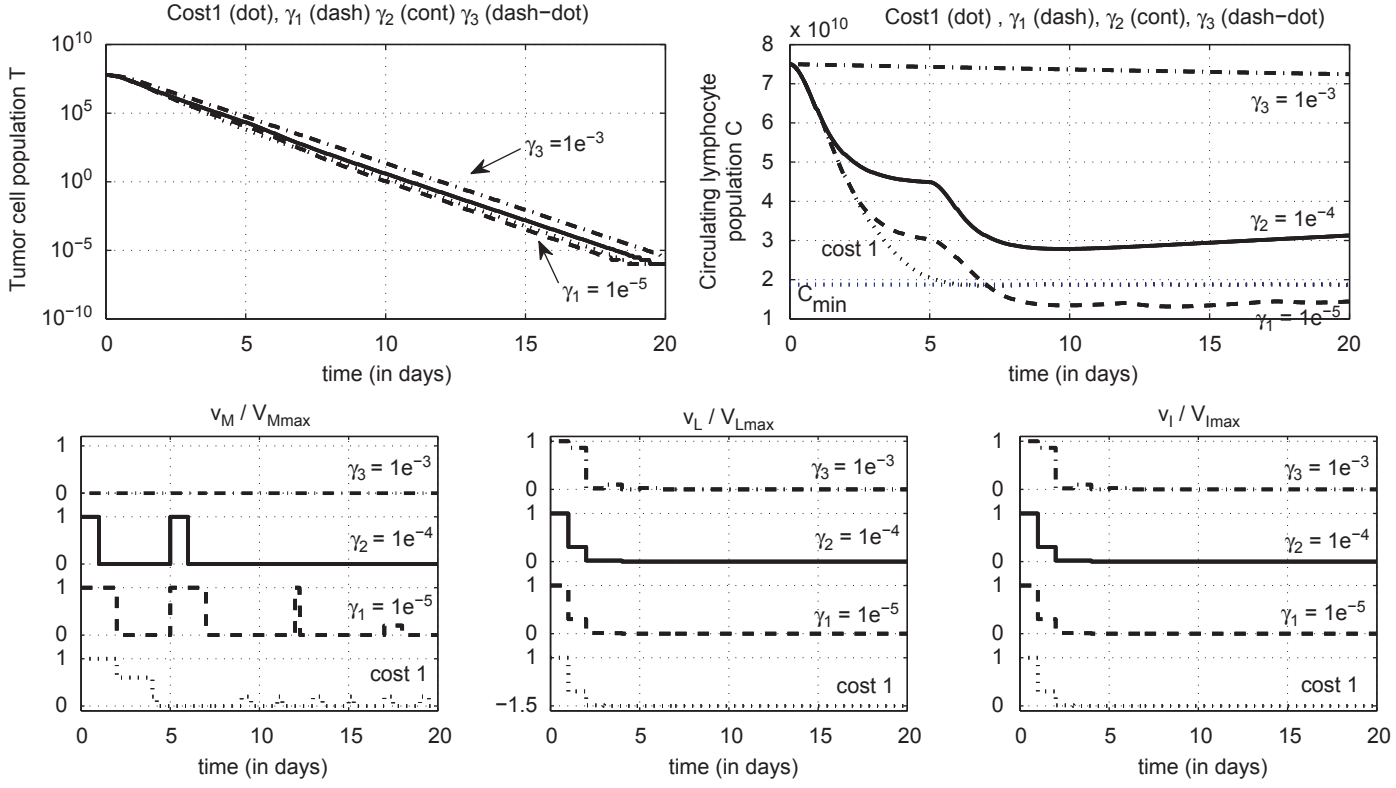

Fig. 5. Influence of the contraction factor: (simulation conditions: $T_0 = 6.10^7$, $t_f = 4$ days).

5.2. Numerical experiments

First, let us observe in Fig. 4 the evolution of the updating coefficient α_{up} over the treatment period, in the case of 20% of parameter discrepancy. Note how the value of α_{up} evolves before reaching a constant value meaning that the corrected model provides correct predictions of the tumor cells evolution (Fig. 4) quite long time before the end of the treatment period.

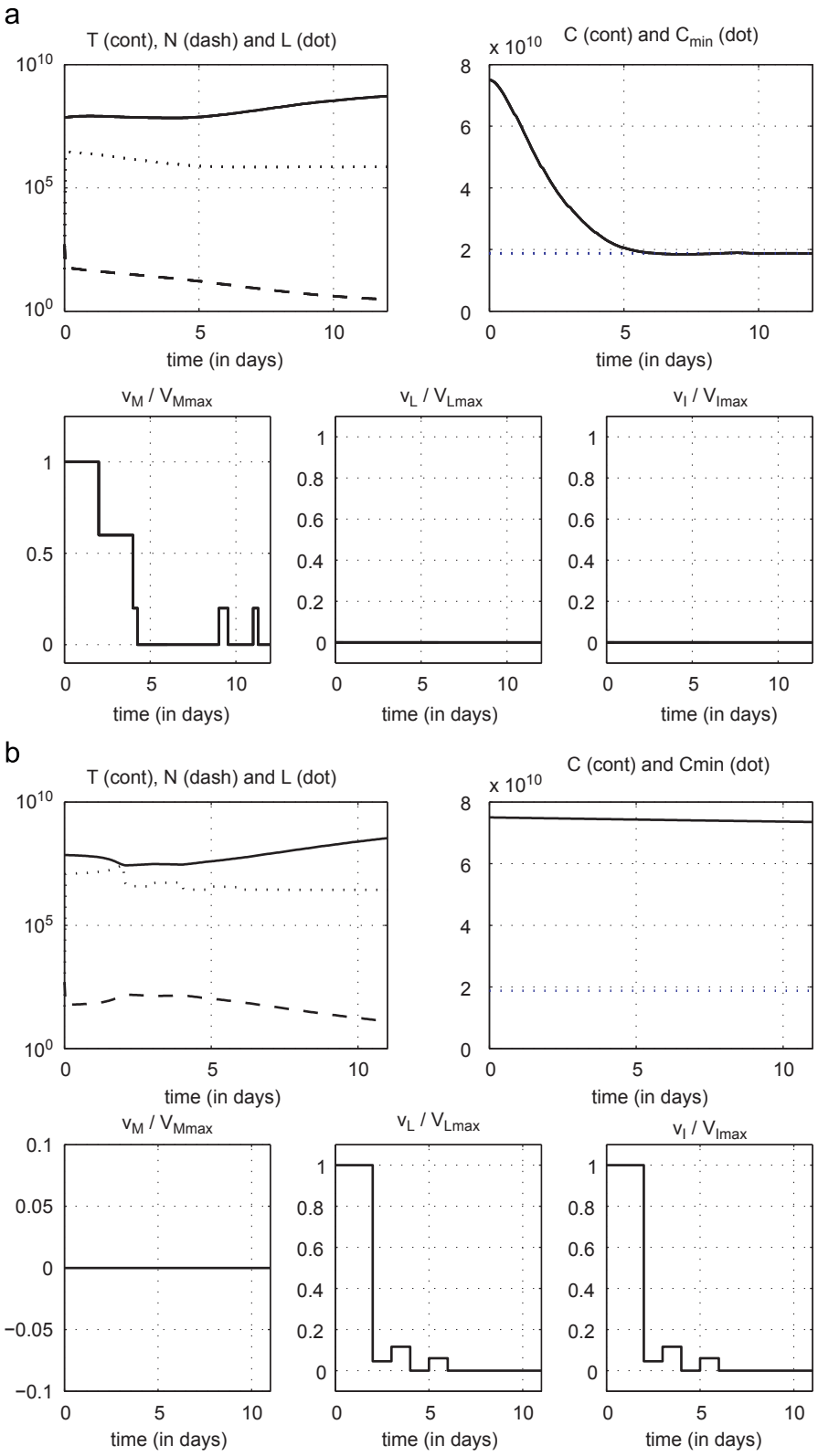

Fig. 6. Unsuccessful treatments when using exclusively chemotherapy (a) or immunotherapy (b). (Simulation conditions: $T_0 = 7e7$ cells, $C_0 = 4$. C_{min}, $t_f = 4$ days, $\gamma = 1e-3$, and 10% of parameters uncertainties.)

In addition to the results of the updating free NMPC presented in Section 4.3, Fig. 3 shows the treatment results (successful or unsuccessful) for two updating periods τ_{up}, namely: 24 or 8 h. We can observe that regardless the uncertainty level, updating always enlarge the area of recoverable initial conditions.

An other important feature is that the region of recoverable initial conditions is increased as the updating frequency increases.

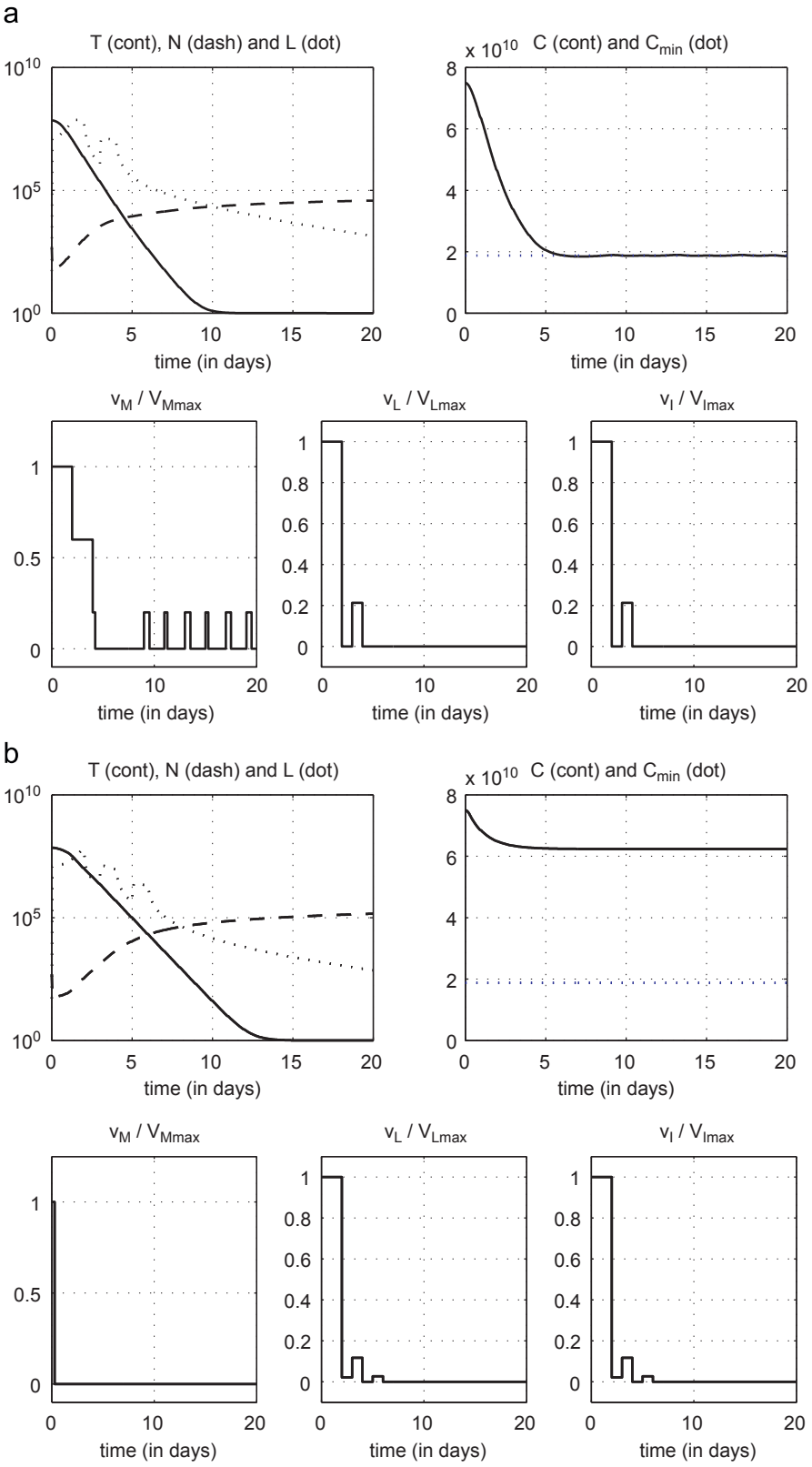

Fig. 7. Successful treatment when using combined chemotherapy and immunotherapy with optimal control problem $\mathscr{P}_2$ (a) and optimal control problem $\mathscr{P}_1$ (b). (Simulation conditions: $T_0 = 7e7$ cells, $C_0 = 4$. C_{min}, $t_f = 4$ days, $\gamma = 1e-3$, and 10% of parameters uncertainties.)

6. Interesting alternative: the control problem $\mathscr{P}_2$

6.1. The role of the contraction factor with control problem $\mathscr{P}_2$

The contraction factor $\gamma \in [0, 1]$ in (9) used in the formulation of the optimal control problem $\mathscr{P}_2$ plays a critical role for the success or failure of the treatment strategy. Depending on its value, the resulting strategy is completely different as illustrated by Fig. 5. If the contraction of the tumor cell population over the prediction horizon is fixed too low (close to zero), the circulating lymphocytes population might fail below the threshold (as for $\gamma_1 = 10^{-5}$). On the opposite if the contraction factor is fixed too high (close to one), we force the health indicator to be so good that the treatment would not use chemotherapy and as a result the treatment will not lead to a tumor regression. Therefore the contraction factor has to be chosen very carefully. If we consider only the acceptable values of γ (no constraints violation and tumor regression by the end of the treatment), this contraction factor allows to impose a minimum health level with, as a counter part, a slower tumor regression. We can observe in Fig. 5 the treatment strategy for the optimal control problem $\mathscr{P}_1$, the tumor regression slope with this strategy is close to the one obtained for a contraction factor of $\gamma_1 = 10^{-4}$ with the optimal control problem $\mathscr{P}_2$. For higher value of γ (as for $\gamma_1 = 10^{-3}$), the slope of tumor regression is lower but the population of circulation lymphocytes is consequently increased. The control problem $\mathscr{P}_2$, based on the contraction factor γ, seems therefore to be a very interesting alternative since it offers treatment strategy with higher health indicator profile for slightly longer tumor regression.

Note that in order to determine the optimal value of the contraction factor, an adaptation scheme can be simply implemented, this will be realized in future work.

6.2. The need for a combined therapy and the benefit of the control problem $\mathscr{P}_2$

First, let us precise that depending on the initial conditions (level of the populations of circulating lymphocytes and tumor cell), a combined treatment can be necessary for the success of the treatment as illustrated in Figs. 6 and 7. Fig. 6 shows unsuccessful treatments when using only chemotherapy or only immunotherapy and Fig. 7 shows, for identical initial conditions, the resulting successful treatments based on a combined therapy, obtained with the optimal control problem $\mathscr{P}_2$ in Fig. 7a and in b with the optimal control problem $\mathscr{P}_1$.

Let us recall that the optimal control problem $\mathscr{P}_2$ aims at maximizing the patient health under a contraction constraint on the tumor cell population. As a result if the required contraction of the tumor cell population is not too high, this strategy will minimize the use of chemotherapy and thus maximize the population of circulating lymphocytes. Fig. 2a and b illustrates perfectly the interesting alternative of the optimal control problem $\mathscr{P}_2$. Indeed, we can observe that no chemotherapy is needed for ensuring a successful treatment with the optimal control problem $\mathscr{P}_2$. Even though the treatment duration is slightly longer, a direct consequence of this strategy is the total number of circulating lymphocytes which is kept at its higher level, which ensures a good patient health during the whole treatment duration. On the opposite, with the optimal control problem $\mathscr{P}_1$, the total number of circulating lymphocytes lies at the minimum acceptable value, which corresponds to a threshold on the patient health.

6.3. Critical role of immunotherapy for treatment success

It is also interesting to observe in Fig. 7a that when using the optimal control problem $\mathscr{P}_2$, immunotherapy plays a critical role for the success of the strategy. The chemotherapy is only used in a single pulse of 2 h at the beginning of the treatment, the decrease of the number of tumor cells after these first hours is therefore clearly resulting from the immunotherapy action.

7. Conclusion

This paper presents a feedback scheme that aims at improving treatment strategies in the case of mixed immunotherapy and chemotherapy of tumors. This scheme is based on a reasonably simple mathematical model proposed by dePillis et al. (2005a) that enables basic qualitative phenomenons to be reproduced. The simulations proposed in the previous sections illustrate the following points:

- A mixed explicit/NMPC-based feedback design methodology has been proposed for combined therapy of cancer. This feedback strategy shows inherent robustness property against model discrepancy.
- The robustness of the proposed scheme can be significantly improved using a scalar updating scheme that concentrate on the effects of potential uncertainties on the tumor cells evolution. The region of recoverable initial conditions is hence significantly enlarged.
- A new optimal control problem has been proposed (to be used in NMPC control schemes) that amounts to maximize the patient health while imposing a contraction of the tumor size. It has been shown that under certain circumstances, the resulting NMPC feedback enables to obtain successful treatment with a huge increase of the health indicators. When compared to classical formulations that are based on the minimization of the number of tumor cells, the new proposed formulation seems to be extremely promising.

This suggest to use a more general predictive strategy in which the controller systematically evaluate the two strategies before to decide about the control to apply, this option is currently under evaluation.

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