Determination of the Pharmaceutical Treatment-Dosage for Cancer Patients Using Non-Linear Optimal Control Techniques

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***Abstract*—Cancer remains one of the most important diseases and causes of death. In this study, a non-linear mathematical model of tumor growth with immune response, under the effects of chemotherapeutic treatment is studied. Two cost-efficient optimal control approaches are presented based on direct collocation and state dependent Riccati equation methods in order to optimize the pharmaceutical treatment-dosage to the patients. Finally, the numerical results from each method are presented, providing an overall better regimen, when compared to similar previous studies, by successfully eradicating the tumor and minimizing the side-effects of chemotherapy.**

Keywords—tumor growth mathematical model, optimal drug dosage, direct collocation, SDRE control, optimal control

I. Introduction

Over the past decades, multiple efforts have been made to portray the dynamics of the cancer and to find an optimal administration strategy of the chemotherapy drug. In order to analyze these dynamics, as well as the interactions between tumor, immune and/or normal (healthy) cell populations near the tumor area under chemotherapy, numerous mathematical models have been proposed [1-5]. Based on such mathematical models, a more recent model that incorporates the interactions among tumor, normal, immune cells and chemotherapy drugs has been proposed [6,7]. Mathematical models of the above form have allowed researchers to test and compare various optimal control strategies for drug administration.

Various techniques in the literature [7-10] attempted to solve optimal control problems for non-linear systems. However, due to the computational efforts to obtain them they cannot be generalized. Another approach suggested for this kind of problems is the Linear Time Varying (LTV) approximations [11]. Thus, the well-known Linear Quadratic Regulator (LQR) techniques could take place. Despite the valid results this approach produces, it is limited due to the required pre-computation of the optimal control parameters. This issue can be dealt with a more recent technique, which is called State-Dependent Riccati Equation (SDRE) optimal control and has been applied effectively to plenty non-linear optimal control cases [12-14].

In this research article, the dynamics of a non-linear mathematical tumor growth model proposed by L. G. de Pillis and A. Radunskaya [6,7] are reviewed. Afterwards, two optimal control methods, based on the Direct Collocation (DirCol) [7] and on the SDRE methods [14] are examined for this certain mathematical model and an optimal periodic chemotherapeutic treatment is determined and applied [14], decreasing the total amount of the administrated drug, while maintaining the efficacy of the treatment against the tumor.

II. Methods

A. The Mathematical Model of the Tumor Growth

Among many mathematical models of tumor growth based on ordinary differential equations, the one proposed by De Pillis and Radunskaya [6,7] stands out, since it portrays the growth of tumor cells and their interaction with normal and immune cells, alongside with the effects of the chemotherapy. The model considers three major cell types, immune, tumor and normal cells, denoted by I, T and N respectively. The increase of immune cells in the tumor area is achieved by an external source (immune system), therefore a constant influx rate s is expected. If the tumor is eliminated, the immune cells will no longer be required, thus they will start decreasing at a per capita rate d_1, converging to a long-term population size of s/d_1 cells. The existence of a tumor triggers the defensive mechanism of the body (immune response), thus the growth rate of immune cells is described by the term

$$\rho I(t)T(t)/\big(\alpha + T(t)\big) \tag{1}$$

where ρ and α are positive constants, representing the intensity and the threshold rate of the immune system respectively. When immune and normal cells meet tumor cells (and vice versa), either the first or the second are eliminated, resulting in four competition terms c_i of the populations between the cell types. The proliferation of the tumor and normal cells follows a logistic growth law with growth rate r_i with maximum carrying capacity b_i^{-1}, where $i = \{1,2\}$ refers to the tumor and normal cells respectively. Each cell type is affected by the drug based on a coefficient denoted by a_1, a_2, a_3 for immune, tumor and normal cells respectively. Cancerous cells are the main target, followed by the immune and normal cells, as a side effect. Thus, $a_2 > a_1 > a_3$. The chemo drug, once injected into the body, is metabolized by the organism with a per capita decay rate d_2. The drug amount injected per liter of body volume (i.e. the model input) at time t is denoted by $v(t)$ (*mg/L/day*) and the concentration of the drug per liter of blood by a state $M(t)$ (*mg/L)*. A system of nonlinear ordinary differential equations that encapsulates the above is the following:

$$\begin{aligned}
\dot{N} &= r_2 N(1 - b_2 N) - c_4 TN - a_3 MN, \\
\dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 MT, \\
\dot{I} &= s + \rho IT/(\alpha + T) - c_1 IT - d_1 I - a_1 MI, \\
\dot{M} &= v(t) - d_2 M.
\end{aligned} \tag{2}$$

The units of all three cell populations (N, T, I) are rescaled, so that one unit is at the order of the carrying capacity of the normal cells at the cancerous area. A realistic number to normalize the cell population is 10^{11} cells per unit in the y axis [6]. Table I presents the normalized system parameters to the maximum carrying capacity of the normal cells [6,7,14]:

TABLE I. MODEL PARAMETERS VALUES

$a_1 = 0.2$ (L/mg)	$a_2 = 0.3$ (L/mg)	$a_3 = 0.1$ (L/mg)	$\alpha = 0.3$ (cells)
$b_1 = 1.0$ (cells^{-1})	$b_2 = 1.0$ (cells^{-1})	$s = 0.33$ (cells/day)	$\rho = 0.01$ (day^{-1})
$c_1 = 1.0$ ($\text{cells}^{-1}\text{day}^{-1}$)	$c_2 = 0.5$ ($\text{cells}^{-1}\text{day}^{-1}$)	$c_3 = 1.0$ ($\text{cells}^{-1}\text{day}^{-1}$)	$c_4 = 1.0$ ($\text{cells}^{-1}\text{day}^{-1}$)
$d_1 = 0.2$ (day^{-1})	$d_2 = 1.0$ (day^{-1})	$r_1 = 1.5$ (day^{-1})	$r_2 = 1.0$ (day^{-1})

B. The DirCol Optimization Technique

Direct Collocation is a very effective iterative non-linear programming (NLP) optimization technique where a polynomial with a number of points (collocation points) in the time domain is chosen, in order to enforce it to satisfy the equations of motion at the collocation points. A basic method of collocation is the Hermite-Simpson [15,16] (see Fig. 1). For each time segment $[t_k, t_{k+1}]$ the two knot points (dots) represent the state and control NLP variables, which correspond to $[x_k, u_k, x_{k+1}, u_{k+1}]$. The dynamics of the mathematical model are used to provide time derivative values at the two knot points, so the datasets $[x_k, x_{k+1}, f(x_k, u_k), f(x_{k+1}, u_{k+1})]$ can be used to generate a 3rd order Hermite interpolation polynomial (cubic spline), which satisfies the equations of the model at the knot points t_k, t_{k+1}. Let $[x_c, u_c]$ be the state and control at t_c and the middle point of $[t_k, t_{k+1}]$ be the collocation point (diamond). By enforcing $\Delta = \dot{x}_c - f(x_c, u_c) = 0$ it is possible to have a polynomial that also satisfies the dynamics at the collocation point. The larger the number of segments is, the closer to the real dynamics the approximation of the state is.

C. The SDRE Optimal Non-linear Control Method

The SDRE technique presents a systematic way of designing non-linear feedback controllers that approximate the solution of the infinite time horizon optimal control problem giving the time responses of the non-linear mathematical model in real time, and thus making it feasible to be implemented on-line [12-14]. Firstly, the non-linear mathematical model is converted to a pseudo-linear formulation, also referred to as extended linear form, which it is treated as a sequence of LTI mathematical models. Afterwards, the suboptimal solution is computed via solving the Algebraic Riccati Equation (ARE) for the LTI models obtained in each time step.

Any non-linear mathematical model can be represented as

$$\dot{\underline{x}} = f\left(\underline{x}(t)\right) + G\left(\underline{x}(t)\right)u(t),\ \underline{x}(0) = \underline{x_0} \qquad (3)$$

where $\underline{x} \in \mathbb{R}^n$ is the state vector and $u \in \mathbb{R}^m$ is the input vector. Equation (3) can be written in the pseudo-linear form

$$\dot{\underline{x}} = A(\underline{x})\underline{x} + B(\underline{x})u \qquad (4)$$

where $f(\underline{x}) = A(\underline{x})\underline{x},\ A(\underline{x}) \in \mathbb{R}^{nxn}$ and $G(\underline{x}) = B(\underline{x})$, $B(\underline{x}) \in \mathbb{R}^{nxm}$. $A(\underline{x})$ and $B(\underline{x})$ matrices are called state-dependent coefficient (SDC) matrices. There are many alternative parameterizations to choose from when constructing the SDC matrices, but the one which will be chosen must ensure pointwise controllability for $\forall \underline{x}$, in order to apply the SDRE control law. This can be achieved if the state-dependent controllability matrix (5)

$$\left[B(\underline{x})\ \ A(\underline{x})B(\underline{x})\ \ \cdots\ \ A^{n-2}(\underline{x})B(\underline{x})\ \ A^{n-1}(\underline{x})B(\underline{x})\right] \qquad (5)$$

has full rank for the time segment where the control is applied.

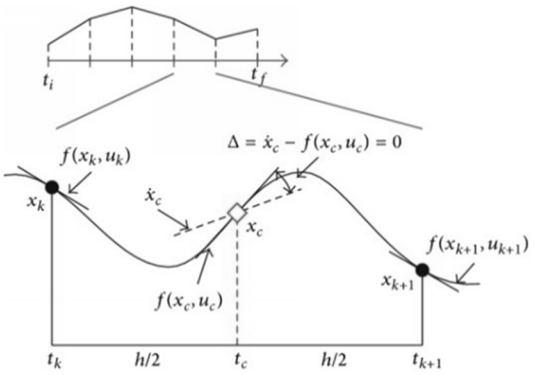

Fig. 1. A time segment of the Hermite-Simpson collocation method [16].

SDRE attempts to determine the sub-optimal controller for the state model (4), in order to minimize the cost function

$$J = \frac{1}{2}\int_0^\infty \left(\underline{x}^T Q(\underline{x})\underline{x} + u^T R(\underline{x})\, u\right)dt\,, \qquad (6)$$

where $Q(\underline{x}) \in \mathbb{R}^{nxn}$ and $R(\underline{x}) \in \mathbb{R}^{nxm}$ are state-dependent matrices and determine the weight for each state and the control, thus $Q(\underline{x}) \geq 0$ and $R(\underline{x}) \geq 0$ for $\forall x$ [12,13]. When the control of LQR is applied, if it is unbounded, the cost function J is minimized using the state-feedback controller

$$u(\underline{x}) = -R^{-1}(\underline{x})B^T(\underline{x})P(\underline{x})\underline{x} \triangleq -K(\underline{x})\underline{x}, \qquad (7)$$

where the term $-K(\underline{x})$ is referred to as feedback gain matrix and $P(\underline{x}) \in \mathbb{R}^{nxn}$ is a symmetric, positive definite matrix and the unique solution of the ARE

$$A^T(\underline{x})P(\underline{x}) + P(\underline{x})A(\underline{x}) - P(\underline{x})B(\underline{x})R^{-1}(\underline{x})B^T(\underline{x})P(\underline{x}) + Q(\underline{x}) = 0, \qquad (8)$$

The dynamics of the pseudo-linearized closed-loop nonlinear state mathematical model (4) now become

$$\dot{\underline{x}} = \left(A(\underline{x}) - B(\underline{x})K(\underline{x})\right)\underline{x}. \qquad (9)$$

In the case of a bounded control input, the sub-optimal input for the nonlinear state mathematical model (4) is

$$u_{bound}(\underline{x}) = min(max(u, u_{min})\,, u_{max})\,, \qquad (10)$$

with u_{min} and u_{max} being the lower and upper bounds.

Despite the high efficacy of the SDRE technique, it might need to be modified, so that high toxicity scenarios can be avoided when controlling dynamic systems like (2). Therefore, a periodic controller is proposed, with a period of t_p days, $t_p \geq 2$. If the control is "active" during the first t_{on} days, where $1 \leq t_{on} < t_p$, it is then "turned off" for the remaining $t_{off} = t_p - t_{on}$ days. An active controller is one which applies the control input calculated by SDRE, based on the state and control responses of the previous timestep, while an inactive controller sets the control input to zero, ignoring

what SDRE dictates as optimal dose. During the time window of "inactive" days t_{off}, the states' values change according to the mathematical model's dynamics. When a new period is about to start, the dosage (input) based on the SDRE is applied once again, during the "active" days t_{on}.

III. Results and Discussion

In this work it is studied a tumor eradication case, where the aim is to kill the tumor cells and at the same time to reduce the excessive usage of the chemo drug [17]. For brevity, the states of (2) as well as the drug input are denoted by $\{x_1, x_2, x_3, x_4\} \triangleq \{N, T, I, M\}$ and $u \triangleq v$ following the constraints

$$u_{min} \leq u, \qquad x_{min} \leq x \leq x_{max}, \tag{11}$$

where $u_{min} = 0, x_{max} = \infty$. A robust organism is one which maintains the population of its normal cells at levels above the 75% of its carrying capacity [6,7]. Thus,

$$x_{min} = [0.75, 0, 0, 0]^T. \tag{12}$$

The initial values of the states (normalized cell numbers) and the drug concentration of the mathematical model are $[x_1(0), x_2(0), x_3(0), x_4(0)] = [1,0.25,0.15,0]$. The desired final values corresponding to the tumor-free equilibrium, are $[x_1(t_f), x_2(t_f), x_3(t_f), x_4(t_f)] = [1,0,1.65,0]$ [7], where $t_f = 150$ days (approx. the 4-6 months that chemotherapy usually lasts).

A. Hermite-Simpson DirCol Optimal Control Treatment

In order to obtain a good approximation of states, the time segments are set to 149 and the iterations' limit to 50. High toxicity levels are prevented by setting $u \leq u_{max} = 1$. Previous studies have presented objective functions, which focus on the tumor size at final time $x_2(t_f)$, including the total tumor cells' population $\int_0^{t_f} x_2(t)\,dt$ and its maximum value T_{max} [6,15]. In the present study, the objective function is further evolved, including the total amount of drug given $v_{total} = \sum_{t=0}^{t_f} v(t)$, making the approach more cost-efficient. The resulting objective function weighted by $w_1 = 1500$, $w_2 = 150$, $w_3 = 1000$, $w_4 = 40$ is

$$J(u) = w_1 x_2(t_f) + w_2 \int_0^{t_f} x_2(t)dt + w_3 \max_{t\in(0,t_f)} x_2(t) + w_4 v_{total}. \tag{13}$$

The DirCol optimal control dictates a daily drug dosage, even if it is trivial (see Fig. 2). In order to avoid this, a Bang-Bang chemo drug dosage regimen can be applied

$$u_{bb}(t) = \begin{cases} u_{max}, & u(t) \geq u_{th} \\ 0, & u(t) < u_{th} \end{cases}, \tag{14}$$

where $u(t)$ is the drug dosage as DirCol dictates, $u_{max} = 1$ and $u_{bb}(t)$ is the modified drug dosage, according to a threshold u_{th}, on day t. As it is shown in Table II, DirCol satisfies the lower bound of the normal cells $N_{min} = 0.75$, but Bang-Bang approach does not. This does not mean ineffectiveness of the latter, since Bang-Bang control suggests that the drug must be given mainly at the therapy's initiatory days, a fact confirmed by the increase in the maximum drug concentration M_{max}. On the other hand, DirCol dictates a smoother regimen with a significant amount of drug being administered during the initiatory days, followed by smaller amounts for the rest of treatment. It is worth mentioning that in all cases T_{max} is very close to its initial value, indicating the efficacy of the treatment regimens. Finally, the differences between these two methods have an obvious impact on the duration of the treatment, given that the DirCol approach is 1.6 - 2 times slower than the Bang-Bang approach, when comparing the tumor at the day t_{zero} of its eradication in both cases. Also, the DirCol Bang-Bang version is preferable, mainly because it is easier to be applied in real-life scenarios.

TABLE II. DirCol Treatment Results

	Case 1		Case 2	
	DirCol	***Bang-Bang***	***DirCol***	***Bang-Bang***
I_0	0.10		0.15	
N_{min}	0.75	0.7087	0.75	0.7144
T_{max}	0.2536	0.2549	0.2521	0.2521
M_{max}	0.7227	0.9860	0.6605	0.9978
v_{total}	15.8379	16	14.9764	15
v_{th}	0.1455		0.12	
t_{zero}	118	72	122	63

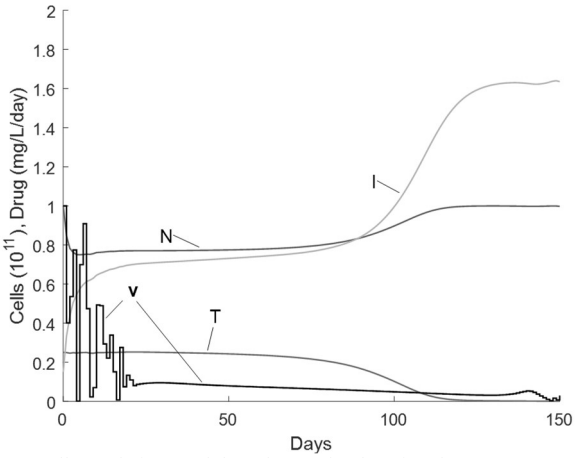

Fig. 2. Cell populations and drug dosage for the DirCol treatment (Case 2).

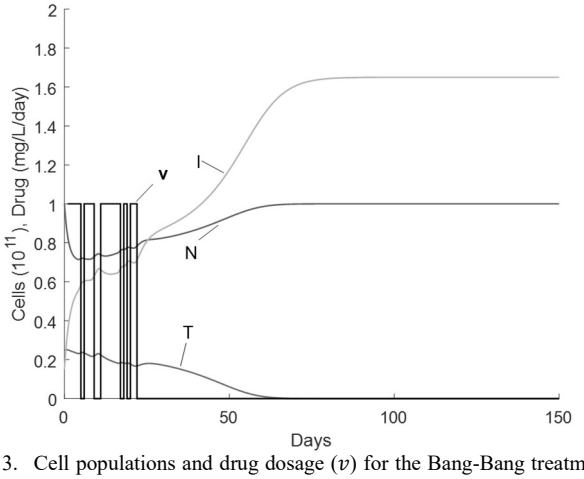

Fig. 3. Cell populations and drug dosage (v) for the Bang-Bang treatment (Case 2).

B. SDRE Optimal Control Treament

In order to implement the SDRE optimal control based tumor chemo treatment, (2) must be rewritten in the form of (4). Thus, the tumor-free equilibrium point $(1/b_2, 0, s/d_1, 0)$ is shifted to the origin [14]. The shifted state variables are now defined as follows:

$$x_1 \triangleq N - \frac{1}{b_2}, \qquad x_2 \triangleq T, \qquad x_3 \triangleq I - \frac{s}{d_1}, \qquad x_4 \triangleq M, \quad (15)$$

where $\underline{x} \triangleq [x_1, x_2, x_3, x_4]$ is the shifted state vector. As a result, the shifted state space equations (2) are rewritten as

$$\dot{x}_1 = -r_2 x_1(1 + b_2 x_1) - \frac{c_4}{b_2} x_2 - \frac{a_3}{b_2} x_4 - c_4 x_2 x_1 - a_3 x_4 x_1,$$

$$\dot{x}_2 = r_1 x_2(1 - b_1 x_2) - \left(\frac{c_2 s}{d_1} + \frac{c_3}{b_2}\right) x_2 - c_2 x_3 x_2 - c_3 x_2 x_1 - a_2 x_4 x_2,$$

$$\dot{x}_3 = -\frac{c_2 s}{d_1} x_2 - d_1 x_3 - \frac{a_1 s}{d_1} x_4 + \frac{\rho s}{d_1} \frac{x_2}{(a + x_2)} + \frac{\rho x_3 x_2}{a + x_2} - c_1 x_3 x_2 - a_1 x_4 x_3,$$

$$\dot{x}_4 = u(t) - d_2 x_4, \quad (16)$$

The non-linear mathematical model of (16) is now in the form of (3), thus it can be written in the form of (4) as follows:

$$A(\underline{x}) \triangleq \begin{bmatrix} -r_2(1 + b_2 x_1) & -c_4\left(x_1 + \frac{1}{b_2}\right) & 0 & -a_3\left(x_1 + \frac{1}{b_2}\right) \\ -c_3 x_2 & r_1(1 - b_1 x_2) - \left(\frac{c_2 s}{d_1} + \frac{c_3}{b_2}\right) & -c_2 x_2 & -a_2 x_2 \\ 0 & \frac{\rho\left(x_3 + \frac{s}{d_1}\right)}{(a + x_2)} - c_1\left(x_3 + \frac{s}{d_1}\right) - x_4 & -d_1 & -a_1\left(x_3 + \frac{s}{d_1}\right) + x_2 \\ 0 & 0 & 0 & -d_2 \end{bmatrix},$$

$$B(\underline{x})^T \triangleq [0,0,0,1]^T. \quad (17)$$

In order to end up to the tumor-free equilibrium, the tumor cells' population and the drug concentration are the states to be minimized. Thus, the form of $Q(\underline{x})$ could be chosen as

$$Q(\underline{x}) = Q = diag(0, w_2, 0, w_4), \quad (18)$$

where $w_2 = 150$ and $w_4 = 0.1$ [14]. For the weight matrix $R(\underline{x})$ three scenarios are examined:

$$R(\underline{x}) = \begin{cases} r_C, & or \\ r_C + \beta_1 x_2(t), & or \\ r_C - \beta_2 x_2(t), \end{cases} \quad (19)$$

where $r_C = 4.7, \beta_1 = 2, \beta_2 = 15$ [14]. A low value of the $R(\underline{x})$ will allow a greater amount of drug to be administered, compared to a higher one. When $R(\underline{x})$ remains constant, the drug intake rate is related only to the factor r_C. On the contrary, when $R(\underline{x})$ is a function of the tumor population (x_2), the drug input can vary according to the state value of the tumor. The estimation of both $Q(\underline{x})$ and $R(\underline{x})$ is a very delicate process (see [18]) which includes a trial and error procedure, so that the tumor can be eradicated with a lesser amount of drug, resulting in lower toxicity levels.

A summary of the results for the continuous SDRE based treatment is presented in Table III. In the first three cases all the possible scenarios regarding $R(\underline{x})$ are studied. As one can observe in these three cases, high toxicity levels ($M_{max} > 1$) are present. Case 4 (see Fig. 5) is similar to Case 3 (see Fig. 4), but with the addition of an upper bound $v_{max} = 1$ to the drug input, as a first attempt to minimize the toxicity, while maintaining the effectiveness of the treatment. The maximum drug concentration drops almost to a third of its previous value ($M_{max} = 1$) and, consequently, the minimum population of the normal cells is increased ($N_{min} = 0.7064$). However, there is an increase to the total amount of drug v_{total} given and a longer duration for the therapy t_{zero} (~10 more days).

A second attempt to tame the drug toxicity is to apply a periodic drug dosology regimen while keeping the global minimum of the normal cells' population at a relatively safe level. Cases 3 & 4 damage the normal cells the least and combat the tumor successfully, therefore they are used as a basis for the determination and application of a periodic treatment. Table IV shows the two proposed periodic regimens (i.e. the least harmful treatments based on the N_{min}), corresponding to regimens with [(total) t_p/ t_{on} (active)] days being [3/1] and [4/3] (see Figs. 6 & 7, respectively). The produced cases (5 & 6) offer further improvements when compared to cases 3 & 4, since N_{min} is increased and both the M_{max} and the total amount of drug required (v_{total}) are decreased. However, in both periodic cases there is an increased treatment duration t_{zero}. It is worth noticing that in Case 6, due to the already bounded drug dosage, the improvements are smaller, when compared to that of the unbounded case.

TABLE III. CONTINUOUS SDRE TREATMENT RESULTS

	Case 1	Case 2	Case 3	Case 4
$R(\underline{x})$	**4.7**	$\mathbf{4.7 + 2x_2(t)}$	$\mathbf{4.7 - 15x_2(t)}$	**4.7**
v_{max}	∞	∞	∞	1
N_{min}	0.6311	0.6308	0.6350	0.7064
T_{max}	0.2511	0.2512	0.2502	0.2518
v_{total}	15.118	15.071	15.564	17.897
t_{zero}	32	33	31	44
M_{max}	2.960	2.959	2.989	1

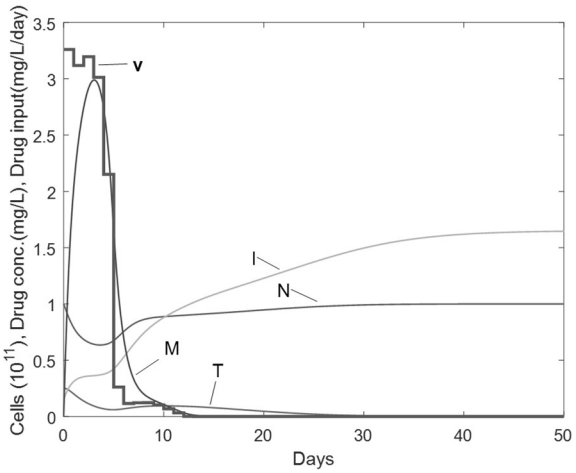

Fig. 4. Mathematical model's response and drug dosage for $R(\underline{x}(t))$ as a decreasing function of the tumor evolution, i.e. $R(\underline{x}(t)) = 4.7 - 15\ x_2(t)$.

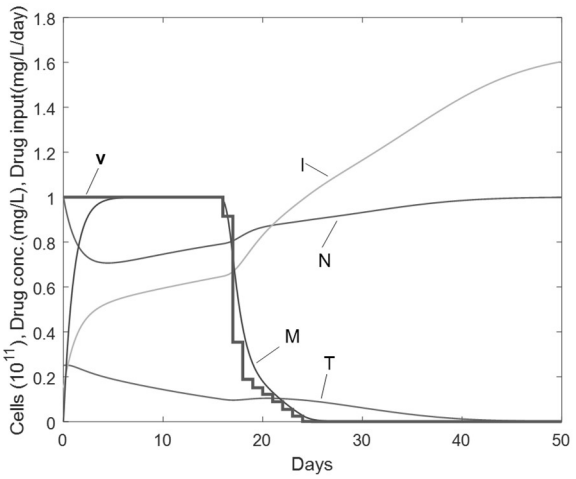

Fig. 5. Mathematical model's response and drug dosage for constant value $R(\underline{x}) = 4.7$ and bounded drug dosage ($v_{max} = 1$).

TABLE IV. PERIODIC SDRE TREATMENT RESULTS

	Case 5 – Periodic [3/1]	Case 6 – Periodic [4/3]
$R(\underline{x})$	$4.7 - 15x_2(t)$	4.7
v_{max}	∞	1
N_{min}	0.7084	0.7129
T_{max}	0.2502	0.2518
v_{total}	11.054	16.613
t_{zero}	46	49
M_{max}	2.033	0.9679

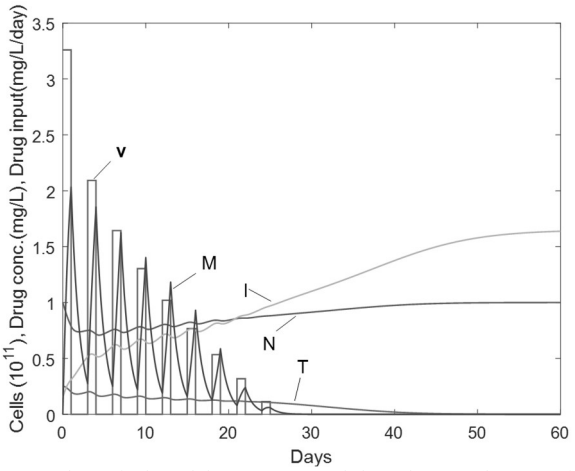

Fig. 6. Mathematical model's response and drug dosage when a periodic treatment of $[3/1]$ days is applied. The drug dosage is unbounded (Case 5).

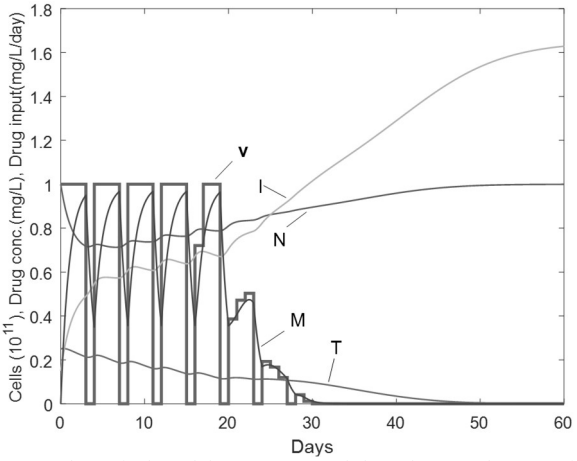

Fig. 7. Mathematical model's response and drug dosage when a periodic treatment of $[4/3]$ days is applied. The drug dosage is bounded (Case 6).

IV. CONCLUSIONS

The problem of determining an optimal chemo drug regimen to be applied in tumor growth inhibition can be very challenging. For this reason, two optimal control methods are implemented, compared and evaluated, considering a tumor growth nonlinear mathematical model proposed by De Pillis and Radunskaya [6,7]. In the first approach, the Hermite-Simpson DirCol method is used to deduce an optimal regimen. The proposed daily drug administration, for the whole treatment period, makes it impractical for clinical implementation. Thus, a Bang-Bang approach is proposed, maintaining the same amount of total drug delivered, but selecting discrete specific days for its administration. The results obtained are satisfactory, since the tumor is also eradicated, while extreme levels of toxicity are avoided, and the duration of the treatment is reduced. In the second approach, the SDRE method is applied leading to a faster simulation time compared to DirCol. However, the unconstrained optimal chemotherapy dosage determined by this method results in high toxicity, i.e. excessive drug concentration in order to eliminate the tumor. This problem is confronted successfully in the present work, either by setting an upper bound to the drug dosage, or by embedding a periodic application of the determined optimal chemotherapy treatment consisting of active and inactive days of the drug administration. Both scenarios offer more effective regimens and, particularly, the so determined optimal periodic drug dosage achieves to reduce the total drug amount administrated with the less important consequence of a slightly longer treatment period.

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