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SDRE optimal control of drug administration in cancer treatment

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Abstract

In this study, we apply State Dependent Riccati Equation (SDRE) based optimal control technique to a nonlinear tumor growth model. The model consists of three biological cells which are normal tissue, tumor and immune cells. The effect of chemotherapy treatment is also included in the model. Chemotherapy administration is considered as a control input to the nonlinear cancer dynamics and the amount of administered drug is determined by using SDRE optimal control. The optimal control is applied to the model in order not only to drive the tumor cells to the healthy equilibrium state but also to minimize the amount of the drug used. In SDRE control design, we investigate the effects of different weighting matrices in the cost function to be minimized. Simulation results show that selection of state dependent weighting matrices can yield positive outcomes such as less drug administration or control of tumor growth in a shorter time period.

Key Words: *Cancer, tumor growth, cancer model, SDRE control*

1. Introduction

Although many improvements have been obtained in the treatment of cancer, most cancer types are still incurable due to the non-responsiveness of the tumor cells to therapy, the relapse characteristics of the tumor cells, the toxicity limitations of the treatments, insufficient dose administration and inaccurate scheduling, etc. Development of treatment strategies requires many clinical experiments first on animals and then on humans in order to figure out a convenient way for the administration of the therapy. These experiments, in general, take a long time, increase the treatment costs and most importantly, may result in many deaths during the development period. Clinical experiments also reveal the fact that there is a strong relationship between the cancer state (the number and/or volume of tumor cells, tumor type), the immune system of the patient and the treatment strategy [1, 2]. Hence, understanding the dynamical behavior of cancer has been of great interest not only to the clinical scientist but also to the mathematicians, physicists and engineers.

Mathematical models of tumor growth have been used by the scientists in order to analyze the growth dynamics and to develop treatment strategies by using different mathematical control methods [3–10]. Depending on the patient's immune system and cancer type, different mathematical models are proposed some of which are validated with experimental results. These models are then incorporated into a proposed treatment strategy such as chemotherapy, immunotherapy, and radiotherapy (in some cases, combined therapies are also suggested). In general, the effect of the therapy is added to the mathematical models of tumor growth as a control input. The dynamics of cancer have a complex nature and the corresponding mathematical models are illustrated with nonlinear systems of differential equations. As a result, applications of linear control strategies to the nonlinear models, in general, fail. Linearization of the models, on the other hand, can cause undesirable outcomes such as uncontrolled spread of cancer or toxicity effects which may have a negative effect on the patients' lives or cause detrimental side effects to healthy organs. Therefore, therapy administration for the cancer is handled as a nonlinear control problem which is to be solved such that tumor level is decreased and a healthy immune system is ensured during the treatment progress.

It is stated that optimal administration of the therapy can increase the survival chance in cancer treatment [11, 12]. Various applications of optimal control to specific type or non-specific type cancer models have been investigated by different researchers [4, 7, 8, 13–15]. The techniques used in the literature to solve optimal control problems for nonlinear systems (in particular, cancer models which are highly nonlinear and high dimensional) are carefully addressed to have an optimal solution and the solution methods cannot be generalized due to the special computational efforts to obtain them. A new optimal control method for cancer treatment is suggested in [16], in which Linear Time Varying (LTV) approximations of the nonlinear cancer dynamics are used. The nonlinear cancer dynamics is approximated as a sequence of LTV models whose limit behavior converges to the behavior of the nonlinear cancer dynamics. This approach enables one to design the optimal controller for LTV approximations by using the well-known Linear Quadratic Regulator (LQR) techniques. Although the method gives globally valid results by recursively solving an infinite series of LQR problems for LTV systems, because of its recursive nature, it is an off-line method which requires pre-computation of the optimal control efforts. On the other hand, other common control techniques for nonlinear system such as feedback linearization, sliding mode control, gain scheduling, and adaptive control require strong conditions on the system [17]. One of the main issues in these control techniques is that they are not completely sufficient for drug administration problems since optimality is required to minimize a desired cost functional.

A recently developed technique which does not yet have complete theoretical background is called State Dependent Riccati Equations (SDRE) based optimal control and has been applied successfully to nonlinear systems both in theory and experimental practice [18–20]. Although there are some applications of SDRE optimal control to biological systems [21], control of drug administration in cancer dynamics using this method has not been studied yet. Due to its computational simplicity and its satisfactory simulation/experimental results, SDRE optimal control technique becomes an attractive control approach for a class of nonlinear systems and therefore many research and application results are reported (see [22] and the references therein).

In this study, we suggest SDRE based optimal control for the nonlinear cancer dynamics by extending our previous results presented in [23]. The drug administration in the cancer treatment is an optimal control problem which is defined as the minimization of drug amount and duration of the treatment. In this work, the amount of chemotherapy drug administration is considered as a control input to the system which holds the interactions between normal, tumor and immune cells. The aim of the control is to eradicate the tumor

cell population whilst minimizing the amount of chemotherapy. The cost functional for the optimal control is selected as a quadratic function of the states and control which is biologically relevant. One of the main contributions of this paper is to apply SDRE optimal control to cancer dynamics. Although there are many optimal control algorithms proposed in this field, almost all of these algorithms require the use of some special nonlinear optimization software. Unlike the other optimal control approaches which have appeared in the literature in which (Hamilton-Jacobi-Bellman) HJB equations should be solved by using numerical shooting methods or using special nonlinear optimization algorithms, the method proposed here gives a sub-optimal solution by solving the well-known linear quadratic regulator (LQR) problem. The method also gives some extra freedom in order to choose different state dependent coefficient (SDC) matrices and weighting matrices of the states and controls which may lead to better results in terms of chosen variables such as a state or a control input.

The method suggested in this paper differs from [16] in many senses, such as in its control structure and applications. In terms of the control structure, SDRE uses frozen Linear Time Invariant (LTI) models of the nonlinear dynamics at each time whereas LTV approximations are used in [16]. The results of these two different control approaches cannot be compared since the SDRE one gives the time responses of the nonlinear system directly but the method proposed in [16] gives only recursive approximations, whose converged values are the results of the nonlinear dynamics. Therefore SDRE method may be implemented on-line by using fast microprocessors in the controller structure, however the method proposed in [16] is an off-line method by nature.

The paper is organized as follows. a brief background for SDRE control design is introduced in Section 2. Section 3 represents the nonlinear cancer model with and without chemotherapy effect. The optimal control approach is summarized and different system representations are given. In section 4, we give the simulation results for SDRE based control of the tumor growth model. Finally, conclusions are drawn.

2. SDRE control outline

The optimal control problem of dynamical systems has been studied in theory for a given cost functional to be minimized. The solution of this problem is well-established for Linear Time Invariant (LTI) systems subjected to a linear quadratic functional. Mainly, the solution of Algebraic Riccati Equations (ARE) produces necessary information to compute the optimal feedback gain(s). Hence, the regulation (stabilization) problem of LTI systems, which is known as LQR (Linear Quadratic Regulator), is solved in optimal way.

The optimal control for nonlinear systems, on the other hand, cannot—in general—be handled in a way similar to LTI systems as the solutions of Hamilton Jacobi Bellman (HJB) equations do not yield a straightforward procedure. Analytical solutions for the optimal control may be obtained for only a few restricted cases since the governing equations for optimality are also nonlinear and their solutions should satisfy the terminal conditions. It is well known [24] that even numerical solutions for the optimal control cannot be obtained with precision for nonlinear systems as the number of possible candidates for the optimal solution is not known. This difficulty brings out many different approaches to approximate solutions to the HJB equation which are regarded as suboptimal solutions to the optimal control problem of nonlinear dynamical systems.

One of the approaches to the optimal control of nonlinear systems is the use of the SDRE technique. The method, which gives a systematic way of designing nonlinear feedback controllers that approximate the solution of the infinite time horizon optimal control problem, is described in detail in [18, 19]. The method is based

on the so-called pseudo-linearized or extended linearized form of the nonlinear system in which the nonlinear system is treated as a sequence of LTI systems. Then the suboptimal solution is computed via solving the ARE for the LTI systems obtained in each time step. The nonlinear system to be considered in this study is

$$\dot{x} = f(x) + G(x)u, \tag{1}$$

where $x \in R^n$ and $u \in R^m$. System (1) can be represented in the pseudo-linear form

$$\dot{x} = A(x)x + B(x)u, \tag{2}$$

where $f(x) = A(x)x$ and $G(x) = B(x)$. In equation (2), $A(x) \in R^{n\times n}$ and $B(x) \in R^{n\times m}$ are state dependent coefficient (SDC) matrices which bring the nonlinear system described by (1) into a linear-like representation. It is known that SDC parameterization of the nonlinear system is not unique; however, among the alternatives, the chosen parameterization should yield point-wise controllability to design the SDRE control law [18]. To ensure the point-wise controllability condition, the so-called "state dependent controllability matrix"

$$M(x) = \left[\begin{array}{cccc} B(x) & A(x)B(x) & \cdots & A^{n-2}(x)B(x) \quad A^{n-1}(x)B(x) \end{array}\right] \tag{3}$$

must have full rank for the domain for which the nonlinear system is controlled.

It is clear that after the parameterization, the nonlinear system representation given by equation (2) resembles the $\dot{x} = Ax + Bu$ LTI form apart from SDC matrices $A(x)$ and $B(x)$. The aim of the SDRE control is to determine the sub-optimal controller for the system (2) such that the following cost functional is minimized:

$$J = \frac{1}{2}\int_0^\infty (x^T Q(x)x + u^T R(x)u)dt. \tag{4}$$

Here, $Q(x) \in R^{n\times n}$ and $R(x) \in R^{n\times m}$ are state dependent weighting matrices which satisfy $Q(x) \geq 0$ and $R(x) > 0$ for $\forall x$. Some optimal control problems require constraints on the system states and/or control input to be satisfied. The selection of the weighting matrices $Q(x)$ and $R(x)$ as state dependent may play important role on satisfying the requirements of the optimal control problem. On the other hand, one can impose hard bounds on the control by penalizing the Hamiltonian [21]. The Hamiltonian for the optimal control problem is given by

$$H(x,u,\lambda) = \frac{1}{2}(x^T Q(x)x + u^T R(x)u) + \lambda^T(A(x)x + B(x)u) - \bar{w}^T(u - u_{\min}) - \hat{w}^T(u_{\max} - u), \tag{5}$$

where $\bar{w}$ and $\hat{w}$ are non-negative m dimensional penalty multiplier vectors. They are introduced to impose the constraints on the control inputs and must satisfy the conditions

$$\bar{w}^T(u - u_{\min}) = \hat{w}^T(u_{\max} - u) = 0. \tag{6}$$

From the Hamiltonian the necessary conditions for optimality are

$$\begin{aligned} \dot{x} &= \tfrac{\partial H}{\partial \lambda} = A(x)x + B(x)u \\ \dot{\lambda} &= -\tfrac{\partial H}{\partial x} = -Q(x) - \left[\tfrac{\mathrm{d}A(x)x}{\mathrm{d}x}\right]^T \lambda - \left[\tfrac{\mathrm{d}B(x)u}{\mathrm{d}x}\right]^T \lambda \ \cdot \\ 0 &= \tfrac{\partial H}{\partial u} = R(x)u + B^T(x)\lambda - \bar{w} + \hat{w} \end{aligned} \tag{7}$$

The last equation of Equation (7) gives the optimal control of the form

$$u(x) = -R^{-1}(x)\left(B^T(x)\lambda - \bar{w} + \hat{w}\right). \tag{8}$$

By applying the theory of LQR, the ad-joint state vector has the form given by

$$\lambda = P(x)x, \tag{9}$$

where $P(x) \in R^{n\times n}$ is a symmetric state dependent matrix. The sub-optimal control for the nonlinear system with bounded control input is obtained as

$$u(x) = \min(\max(\tilde{u}, u_{\min}), u_{\max}), \tag{10}$$

where $u_{\min}$ and $u_{\max}$ are the minimum and maximum bounds on the control, respectively, and the unbounded control is obtained as

$$\tilde{u}(x) = -R^{-1}(x)B^T(x)P(x)x, \tag{11}$$

which is a feedback control with the feedback gain matrix of $K^{op}(x) = R^{-1}(x)B^T(x)P(x)$ The symmetric, positive definite matrix $P(x)$ is obtained from the solution of algebraic Riccati equation given by the relation

$$A^T(x)P(x) + P(x)A(x) - P(x)B(x)R^{-1}(x)B^T(x)P(x) + Q(x) = 0. \tag{12}$$

In order to solve (12), the pair $(A(x), B(x))$ must be point-wise controllable $\forall x$. Dynamics of the closed-loop system is now illustrated by the relation

$$\dot{x} = (A(x) - B(x)K^{op}(x))x = A_{CL}(x)x. \tag{13}$$

Local asymptotic stability of the closed-loop system is proved in both [18] and [19] and stated in the following theorem.

Theorem [19] *Assume that the system*

$$\dot{x} = f(x) + B(x)u$$

is such that $f(x)$ *and* $\frac{\partial f(x)}{\partial x_i}$ $i = (\ 1, \ \cdots \ n\ )$ *are continuous in* x *for all* $\|x\| \leq r, r > 0$, *and that* $f(x)$ *can be written as* $f(x) = A(x)x$ *(in SDC form). Assume further that* $A(x)$ *and* $B(x)$ *are continuous and the system defined by (2) and (3) is a detectable and stabilizable parameterization in some nonempty neighborhood of the origin* $\Omega \subseteq B_r(0)$. *Then the system with the control given by (11) is locally asymptotically stable.*

The design of SDRE control is then based on the freezing of the nonlinear system which is represented in pseudo-linear form, and application of linear quadratic regulator (LQR) control to the linear systems in each time step. The state dependent quadratic cost functional is minimized at each time step and the feedback control is then applied to the nonlinear system.

3. Mathematical model of the tumor growth

Mathematical models for cancer dynamics have been studied by many scientists using different mathematical methods. Some of these models consider the growth of tumor cells as population dynamics problems which

include the interaction of tumor cells with other cells (e.g. normal cells and immune cells). In order to develop treatment strategies, the effects of therapy are also included in the models as control inputs. In this study, we analyze the model originally discussed in [4]. The model does not aim to concentrate on a specific kind of cancer and uses normalized parameters. It includes three different cell populations and chemotherapy drug concentration. Interaction of the tumor cells with normal and immune cell population in the absence of any treatment is given by the system

$$\begin{aligned} \dot{N} &= r_2 N(1 - b_2 N) - c_4 TN, \\ \dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN, \\ \dot{I} &= s + \tfrac{\rho IT}{\alpha + T} - c_1 IT - d_1 I. \end{aligned} \tag{14}$$

where $N(t)$, $T(t)$ and $I(t)$ denote the number of normal cells, the number of tumor cells and the number of immune cells at time t, respectively. The first term in the normal cell population is the logistic growth of normal cell population with growth rate r_2 and maximum carrying capacity b_2^{-1}. The second term is the loss of normal cells due to competition among tumor-normal cells for local resources. In a tumor cell population, the first term denotes the logistic growth of tumor cells in the absence of immune surveillance with the growth rate r_1 and maximum tumor carrying capacity b_1^{-1}. The second and the third terms are death terms for tumor cells due to the interaction between immune and normal cells, respectively. Immune cells have a constant source s which can be supplied from bone marrow or lymph nodes, etc. In the presence of tumor cells, immune cells are stimulated by tumor cells with a Michaelis-Menten type saturation function with the positive parameters ρ and α. Immune cells are deactivated by tumor cells at the rate c_1 and they also die at the natural death rate d_1.

There are different ways to include the effect of chemotherapy in the tumor growth model. We assume that chemotherapy kills all cell populations with different ratios using mass action term. The effect of drug therapy in the model is shown with an additional state $M(t)$ and control input $u(t)$ which denote drug concentration in the blood stream, and external drug injection respectively. The nonlinear system with the effect of drug therapy is

$$\begin{aligned} \dot{N} &= r_2 N(1 - b_2 N) - c_4 TN - a_3 MN, \\ \dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 MT, \\ \dot{I} &= s + \tfrac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 MI, \\ \dot{M} &= -d_2 M + u(t). \end{aligned} \tag{15}$$

Here, a_1, a_2, and a_3 are the different killing effects of chemotherapy on the cell populations. Chemotherapy drug decay rate in the blood stream is denoted by d_2. The system parameters which are normalized to the maximum carrying capacity of the normal cells are given in Table 1. Analysis of the model for possible equilibrium points in the absence of therapy is given in the next sub-section.

Table 1. Model parameters.

Parameter	Description	Value
a_1	Fractional normal cell kill by chemotherapy	0.05
a_2	Fractional tumor cell kill by chemotherapy	0.15
a_3	Fractional immune cell kill by chemotherapy	0.1
b_1^{-1}	tumor cell carrying capacity	1.0
b_2^{-1}	Normal cell carrying capacity	1.0
c_1	Fractional tumor cell kill by immune cells	1.0
c_2	Fractional immune cell kill by tumor cells	0.5
c_3	Fractional tumor cell kill by normal cells	1.0
c_4	Fractional normal cell kill by tumor cells	1.0
d_1	Death rate of immune cells	0.2
d_2	Decay rate of chemotherapy drug	1.0
r_1	tumor cell growth rate	1.5
r_2	Normal cell growth rate	1.0
s	Steady source rate for immune cells	0.33
α	Immune threshold rate	0.3
ρ	Immune response rate	0.01

γ0 = 10
γ1 = 5

swap
α3 <= α1 <= α2

control | no control

1.0

false, see dePillis 2003 drug-free

3.1. Analysis of the model

In the absence of therapy, equilibrium points of the system can be obtained as follows:

$$\dot{N} = 0 \Rightarrow \begin{cases} N = 0, \\ N = \frac{1}{b_2} - \left(\frac{c_4}{r_2 b_2}\right) T. \end{cases} \tag{16}$$

$$\dot{T} = 0 \Rightarrow \begin{cases} T = 0, \\ T = \frac{1}{b_1} - \left(\frac{c_2}{r_1 b_1}\right) I - \left(\frac{c_3}{r_1 b_1}\right) N. \end{cases} \tag{17}$$

$$\dot{I} = 0 \Rightarrow I = \frac{s(\alpha + T)}{(c_1 T + d_1)(\alpha + T) - \rho T}\ . \tag{18}$$

$$\dot{M} = 0 \Rightarrow M = 0, \tag{19}$$

provided that $\rho T \neq (c_1 T + d_1)(\alpha + T)$.

The system has three different types of equilibria: *Tumor-free* (no tumor cells), *Dead* (no normal tissue cells), and *Coexisting* (both normal and tumor cells exist) equilibrium points. Depending on the system parameters given in Table 1, there could be zero, one, two, or three of these equilibria types [4]. In the context of developing therapy strategy, *Tumor-free* or *Coexisting* type equilibrium points should be reached, since in these types of states, the normal cell population is close to its healthy state. In this study, our aim is to determine the therapy dosage to bring the system to the *tumor-free* equilibrium point. The *tumor-free* equilibrium point of the system is obtained as $(1/b_2, 0, s/d_1, 0)$ which gives us a healthy normal cell population of $(1/b)$ and immune cell population of (s/d_1) with zero tumor level and zero drug injection. The linearized model around this equilibrium point has stable eigenvalues which are $(-1, -0.325, -0.2, -1)$ for the given parameter set in Table 1.

One of the main issues in cancer treatment is the existence of periodic behavior; i.e., re-growth of the tumor cells after the treatment. For the given mathematical model of the cancer dynamics, existence of possible periodic orbits is explored in [4] in detail. In this study, we shall only refer to the following proposition.

Proposition [2]. *All orbits of system (9), with the parameter set given in Table 1, with initial values in the positive octant, have exactly one of the equilibria as their limit set. In particular, all orbits are bounded and the system admits no nontrivial periodic orbits.*

3.2. SDRE optimal control and pseudo-linear representation of the system

There are various optimal therapy strategies for cancer treatment proposed in the literature [4, 8, 13–15]. Almost all of these methods aim at minimizing the amount of drug during the treatment period which also results with the less toxicity effect to the healthy tissues. Therefore, a cost functional is defined in terms of drug (input) and tumor cell population (state) and then an optimal solution is suggested which minimizes the proposed functional. Nevertheless, the optimal drug administration is determined by using special computer software, since the cost functional is minimized associated with the nonlinear dynamical equations. Moreover, the existence of such an optimal control should be proved beforehand.

In this study, we apply the SDRE control method to the tumor model which requires no additional burden both in proving the existence of an optimal control and in computing the necessary drug administration. We use the classical LQR algorithm in the computation of optimal control. In order to implement SDRE based optimal control, the system is defined in the form of (2). We can rewrite the system by shifting the tumor-free equilibrium point $(1/b_2, 0, s/d_1, 0)$ to the origin in terms of the following error states:

$$x_1 = N - \frac{1}{b_2}, x_2 = T, \quad x_3 = I - \frac{s}{d_1}, \quad x_4 = M, \tag{20}$$

where $x = [x_1,\, x_2,\, x_3,\, x_4]^T$ denotes error states. The system in the new coordinates is

$$\begin{aligned}
\dot{x}_1 &= -r_2 x_1(1 + b_2 x_1) - \tfrac{c_4}{b_2} x_2 - \tfrac{a_3}{b_2} x_4 - c_4 x_1 x_2 - a_3 x_1 x_4,\\
\dot{x}_2 &= r_1 x_2(1 - b_1 x_2) - (\tfrac{c_2 s}{d_1} + \tfrac{c_3}{b_2}) x_2 - c_3 x_1 x_2 - c_2 x_2 x_3 - a_2 x_2 x_4,\\
\dot{x}_3 &= -\tfrac{c_2 s}{d_1} x_2 - d_1 x_3 - \tfrac{a_1 s}{d_1} x_4 + \tfrac{\rho s}{d_1} \tfrac{x_2}{(\alpha + x_2)} + \rho \tfrac{x_2 x_3}{(\alpha + x_2)} - c_1 x_2 x_3 - a_1 x_3 x_4,\\
\dot{x}_4 &= -d_2 x_4 + u(t).
\end{aligned} \tag{21}$$

The nonlinear system given by Equation (21) is now in the form of (1) which has equilibrium at the origin. These systems can be represented in the form of pseudo-linear given by Equation (2).

One of the main difficulties in the SDRE control is the selection of SDC matrices, as the SDC representation is not unique and there is not a straightforward selection procedure for $f(x) = A(x)x$ factorization. In fact, this difficulty can be handled advantageously to get different sub-optimal solutions provided that the selected SDC matrices are point-wise controllable. However, one should note that the point-wise controllability of the selected $(A(x), B(x))$ pair does not have any implication on the controllability of the nonlinear system

check?
η προσθεση-αφαιρεση του ιδιου ορου που κανει
είναι για να πετυχει ευσταθεια στο σύστημα

[18, 22]. In this work, we use the following pseudo-linear representation for the system (21):

$$A(x) = \begin{bmatrix} -r_2(1+b_2x_1) & -c_4(x_1+\frac{1}{b_2}) & 0 & -a_3(\frac{1}{b_2}+x_1) \\ -c_3x_2 & r_1(1-b_1x_2)-(\frac{c_2s}{d_1}+\frac{c_3}{b_2}) & -c_2x_2 & -a_2x_2 \\ 0 & \frac{\rho(x_3+\frac{s}{d_1})}{(\alpha+x_2)}-c_1(x_3+\frac{s}{d_1})-x_4 & -d_1 & -a_1(x_3+\frac{s}{d_1})+x_2 \\ 0 & 0 & 0 & -d_2 \end{bmatrix} \tag{22}$$

dx[i]/dt=A(x[i-1])x[i]

and $B(x) = [0,\, 0,\, 0,\, 1]^T$.

Note that $f(x) = A(x)x$. In this work, the SDRE control is determined for the type quadratic cost functional

$$J = \int_0^\infty \left(x^T Q(x)x + r_C(x)u^2\right) dt, \tag{23}$$

in which the weighting matrix $Q(x)$ and control weighting $r_C(x)$ are state dependent. With the state dependent weightings, it is possible to give more importance to some of the states or controls in the cost functional. This freedom is another advantage of the SDRE control method.

4. Simulations

The aim of the therapy is to kill the tumor cells whilst minimizing the amount of drug application, which also reduces the possible detrimental toxicity effect, caused by the excess usage of the chemotherapy drugs. In the simulated cancer model, the healthy equilibrium point with the parameter set $(1,\, 0,\, 1.65,\, 0)$ is locally stable, which means that the growth of cancer is controllable if a sufficient immune surveillance is guaranteed. In the absence of sufficient immune control, the tumor cells grow in number and kill the healthy tissue cells and reach the limit capacity, which is referred to as dead equilibrium point. In our simulations, in order to avoid self-control of the immune system on the cancer cells, we choose a scenario where the initial immune cell population is very small and the tumor cell population is large, so that tumor growth is inevitable unless chemotherapy is applied. The initial states, i.e., the conditions when the chemotherapy treatment is started, are assumed to be $(N(0) = 1,\, T(0) = 0.20,\, I(0) = 0.15,\, M(0) = 0)$. The response of treatment-free cancer growth with respect to normalized time scale is given in Figure 1.

One of the most important issues in the optimal control is the selection of the cost functional to be minimized. Usually systems give clues as to what the cost functional can be. In the optimal control application to cancer models, there is not a certain selection of the cost [13]. Many authors have proposed different cost functionals which can consist of the number of tumor cells, the amount of drugs or their combination. In our study, we select the weightings of the quadratic cost functional (3) as a combination of the number of tumor cells and drug, which is biologically relevant. We simulate four different cases of optimal control application to the cancer model to show the effects of different weighting matrices as well as bounded control. Toxicity is an important phenomenon is cancer chemotherapy as it reduces the patient's health quality as well as causing serious side effects which can result in death. Hence in our simulations we discuss the cases where the control input is unbounded and bounded to one unit drug $(0 \le u \le u_{\max} = 1)$. Moreover, we try to keep the number of normalized normal cell population above 0.75 to avoid the toxicity effect of excess chemotherapy injection.

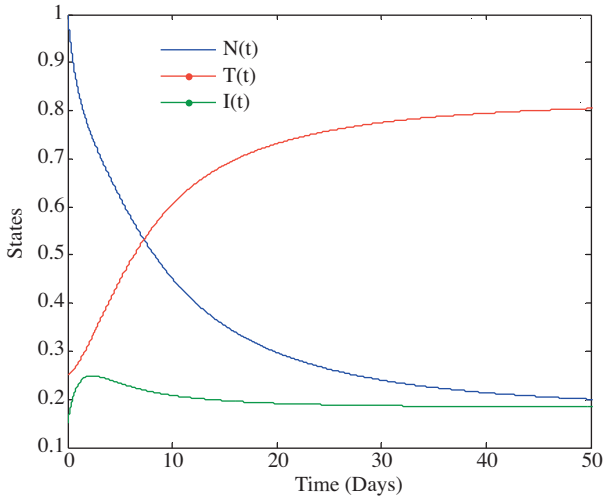

Figure 1. Response of the system in the absence of control.

We now discuss the cases below to show the effects of different weighting matrices and bounded control.

Case 1: We use constant weighting matrices Q and R selected as follows:

$$Q = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & \omega_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \omega_2 \end{bmatrix} \tag{24}$$

and $R = r_C$,
where $\omega_1 \geq 0$, $\omega_2 \geq 0$ and $r_C > 0$ must be satisfied so that $Q \geq 0$ and $R > 0$. We select the parameters as $\omega_1 = 100$, $\omega_2 = 0.1$ and $r_C = 1.2$ in order to enable a comparison with the other cases. The cost functional given by (3) becomes

$$J = \int_0^\infty \left(\omega_1 (x_2(t))^2 + \omega_2 (x_4(t))^2 + r_C (u(t))^2\right) dt. \tag{25}$$

Here, $x_2(t)$ refers to the number of tumor cells, $x_4(t)$ is the drug concentration in the blood and $u(t)$ is the amount of drug given to the patient at time t. The controlled normalized states of the system for case 1 are given by Figure 2.

Case 2: In this case we use the constant weighting matrix for states Q, given by (24), with the same parameters as in case 1, and a state dependent weighting for control, $R(x) = r_C + \gamma_0 x_2(t)$, where γ_0 is a positive constant and selected as $\gamma_0 = 10$. As it can be seen that at the beginning, $R(x)$ is greater than r_C, since $x_2(0) > 0$. However as control is applied, the number of tumor cells decreases and $R(x)$ tends to r_C as $x_2(t) \to 0$. This means that at the beginning of the treatment the weighting of the control will be high which provides less control comparing to the constant weighting case. As $x_2(t) \to 0$, the weighting of the control decreases, resulting with a higher control effort to minimize the cost functional. The aim of selecting this type of $R(x)$ is to reduce the

toxicity effects of high drug application at the beginning of the therapy. The controlled states are shown in Figure 3 for case 2. The number of normal cells is obtained very close to the toxicity limit. Also, control is lower than the bound.

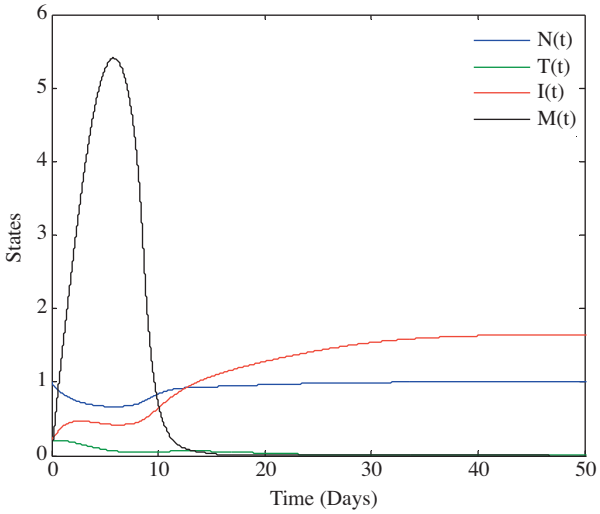

Figure 2. Case 1: System response as a function of time; Q and R are constant.

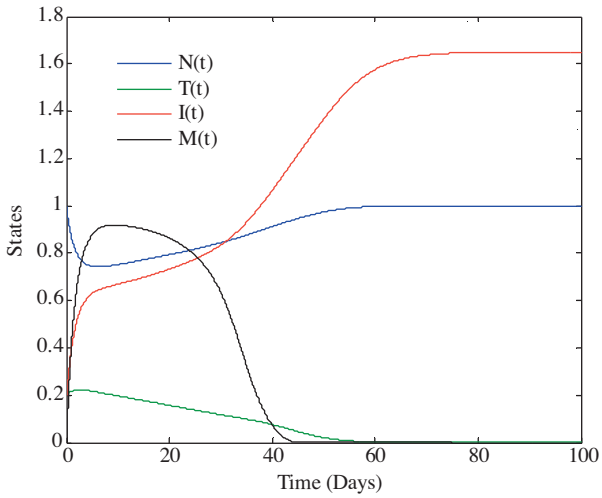

Figure 3. Case 2: System response as a function of time; $R(x) = r_C + \gamma_0 x_2(t)$.

Case 3: We use the same constant weighting matrix for states Q, given by (24) and a state dependent weighting for control, $R(x) = r_C - \gamma_1 x_2(t)$, where γ_1 is a positive constant satisfying the condition $r_C > \gamma_1 x_2(t)$. We select $\gamma_1 = 5$ so that $R(x) > 0$. $R(x)$ is less than r_C at the beginning of the therapy, since $x_2(0) = 0.20$. However as control is applied, the number of tumor cells decreases and $R(x)$ tends to r_C as $x_2(t) \to 0$. Initially this selection of $R(x)$ provides larger control values than the case of $R = r_C$. As $x_2(t) \to 0$, the weighting of the control increases resulting with a less control effort to minimize the cost functional. The controlled states are given in Figure 4. As it can be seen in Figure 4, this type of selection of $R(x)$ causes toxicity problems since much control effort is applied to reduce the number of tumor cells and also, the bound condition of the control is not satisfied.

Case 4: In this case we again consider the same weighting matrices of Case 1 with a limit on the control, i.e. $(u \leq u_{\max} = 1)$. The response of the system to the applied control is shown in Figure 5. Since the bound reduces the amount of drug application into the system, the number of normal cells is kept very close to 0.75. We should note that imposing a bound on the control does not always satisfy the sub-optimality condition [21, 25].

We compare the amounts of drug injections in Figure 6. As it can be seen from the figure, while case 2 and case 4 satisfy the maximum control bound condition, case 1 and case 3 use larger amount of drug than the maximum bound to control the tumor growth. For the sake of clarity of Figure 7, we limit the drug axes at 10, although the amount of the drug for case 3 is obtained around 20 at the beginning of the simulation. In order to show the toxicity effect caused the drug application, we give a comparison of the number of normal cells in Figure 7. As expected, high drug application causes more toxicity and results in the killing of more normal cells, which also can be seen from the figure that Case 1 and Case 3 cannot satisfy the condition of biological limit

for the normal cells. Figure 8 shows the change in the tumor cell population over time. Case 3 provides the shortest time in driving the number of tumor cell to the healthy equilibrium point. This is followed by Case 1, as expected, and the other cases give almost similar time for the eradication of cancer cells although there are some perturbations in the cancer cell numbers during time. Therefore, selection of different weighting matrices can yield positive outcomes such as less drug administration or eradication of the tumor cells in a shorter time period compared to some other alternative selections.

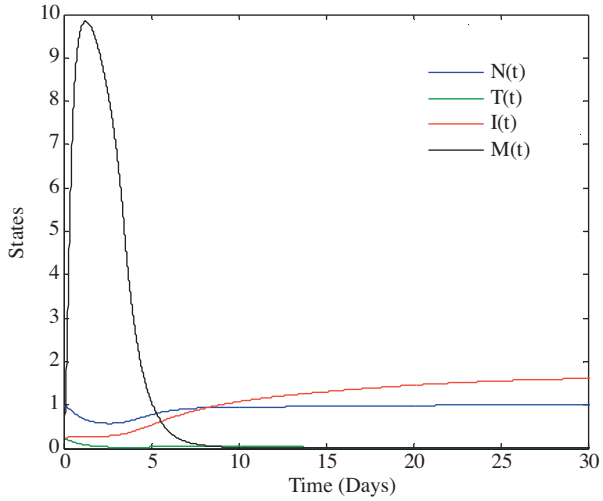

Figure 4. Case 3: System response as a function of time; $R(x) = r_C - \gamma_1 x_2(t)$.

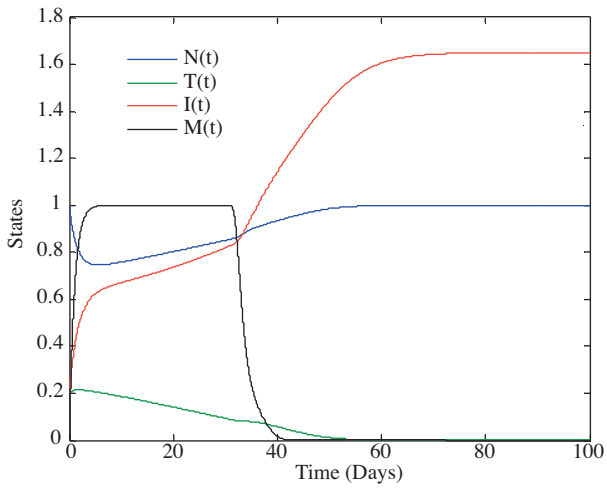

Figure 5. Case 4: System response as a function of time; Q and R are constant; $u(t)$ is bounded.

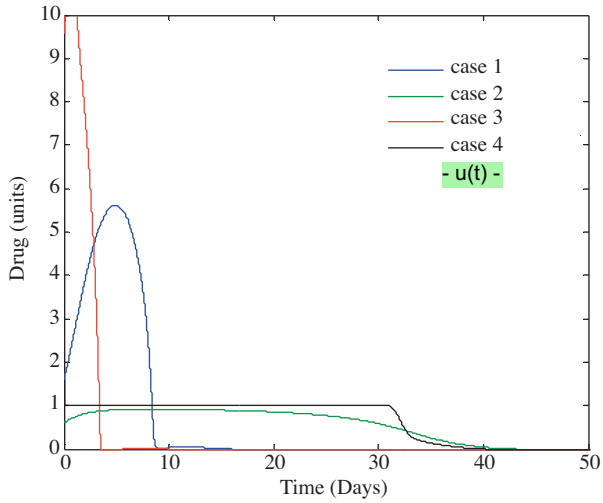

Figure 6. Comparison of the control inputs in terms of administered drug over time.

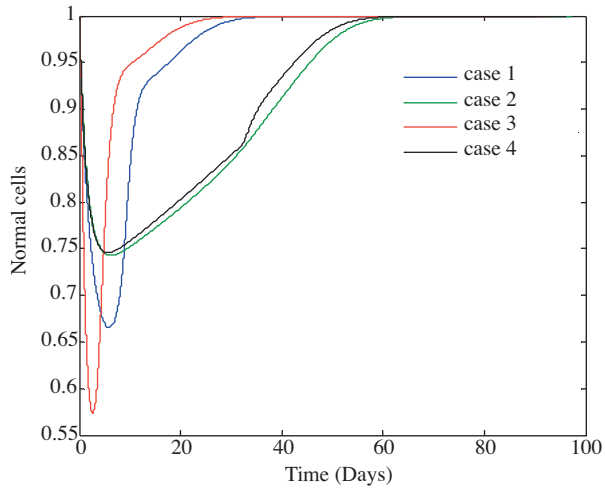

Figure 7. Comparison of normal cells in time.

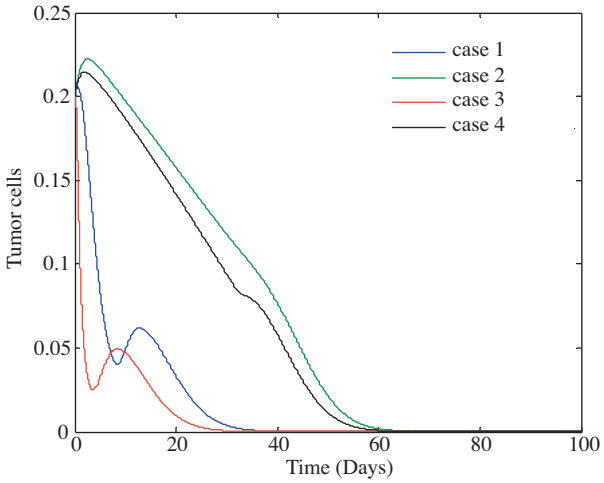

Figure 8. Comparison of the tumor cells in time.

5. Conclusion

We have developed an SDRE based optimal control and applied it to a model of cancer dynamics. We have shown that SDRE optimal control method provides fast and easy derivation of sub-optimal control for the chemotherapy administration problem. The effects of different state dependent weighting matrices to the SDRE performance have been investigated. The results show that these features of the SDRE optimal control can be advantageously used in the determination of drug administration in the simulated model. However, the selection of SDC matrices and state dependent weightings does not have a straightforward design procedure. Especially, how to select the system representation stays as an unanswered problem. On the other hand, besides tweaking the controller parameters priori and applying ad-hoc "anti-windup" schemes a posteriori to satisfy the constraints, there are other methods to impose constraints on the control problem in SDRE design [26]. We have shown that we can satisfy the required constraints on the control problem by defining state dependent weighting matrices. As a future work, this technique could be applied to a quantitative cancer model which uses real clinical parameters. Moreover, the computational advantage of the method can be used to design drug scheduling.

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