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IFAC-PapersOnLine 48-25 (2015) 265–270

State Dependent Riccati Equation controlled drug delivery for mixed therapy of cancer treatment*

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Abstract: The paper presents a drug delivery solution to the mixed therapy of cancer treatment using the State Dependent Riccati Equations (SDRE) control method. A sixth-order nonlinear ordinary differential equation describes the cancer dynamics considering the number of cells of tumor, natural killers, circulating lymphocytes and cytotoxic T-cells, together with chemotherapy drug concentration and immunotherapy drug concentration. The control problem is posed as the suboptimal solution for minimizing a quadratic objective function, which is constructed using the states and mixed therapy inputs of "chemotherapy" and "immunotherapy" drug injections. The SDRE approach provides an attractive solution to the highly nonlinear multi-input (mixed therapy) cancer dynamics problem, which is compared with the results presented in the literature.

Keywords: cancer treatment; chemotherapy; immunotherapy; mixed therapy; SDRE; optimal control.

1. INTRODUCTION

Cancer is the result of uncontrolled division of cells that leads to formation of a tumor. For years, the most significant cancer treatment method was chemotherapy. Chemotherapy kills both cancerous as well as healthy cells at different rates. Fundamental principle in chemotherapy is to kill cancerous cells faster than healthy cells, which has its unavoidable side effects in patient that persuade researchers and physicians to detect new treatment methods.

For the sake of better understanding the interaction between healthy and cancerous cells as well as drug intervention, different mathematical models have been developed by researchers for chemo, immune and mixed therapy. By understanding the interaction of each cell within the group of other cells, researchers can develop more effective treatment methodologies and protocols.

Determining optimal treatment protocols based on proposed mathematical models always has been an appealing research area. It is well-known that excessive dose of administrated anticancer drug in chemotherapy may destroy healthy tissues and cause fatal side-effects. Research by Bahrami and Kim (1975) and Swan and Vincent (1977) presented the first steps in using optimal control theories in chemotherapy for cancer treatment. Subsequently, other researchers have extended the optimal control techniques for determining optimal treatment protocols including drug dosage, administration period and frequency. Swan (1990) investigated a model of cancer chemotherapy by optimal control methods for general classes of growth and loss functions by considering lower limits for normal cells. de Pillis and Radunskaya (2001, 2003) addressed the optimal chemotherapy schedule by using a cost function for minimizing tumor cell population. de Pillis et al. (2007b) proposed a revised and improved mathematical model of cancer, and indicated the optimal solution for administering treatment by using quadratic and linear controls by considering constraints to immune cells level.

Itik et al. (2009) proposed a linear time varying approximation method for the solution of cancer treatment. One of the recent approaches that have been considered in optimal control synthesis for cancer treatment problems is the State Dependent Riccati Equations (SDRE) technique, which provides a systematic way of designing nonlinear suboptimal feedback controllers for a very general class of nonlinear systems. Algorithmically speaking, the SDRE technique relies on fixing the state of the nonlinear system and converting it to a LTI system at each instant of time, followed by controlling the system by utilizing the online feedback controller based on linear-quadratic regulator (LQR).

SDRE-based optimal control of nonlinear cancer dynamics via chemotherapy was first proposed by Itik and Salamci (2010). Çimen (2010, 2012) documented the SDRE methodology and implemented the SDRE approach to another mathematical model of cancer dynamics by considering constraints for maximum dose of drug administration and minimum level of healthy cells population. Babaei and Salamci (2014) developed a new SDRE-based model-reference adaptive control architecture for stabilizing uncertain nonlinear systems, which was used to determine optimal drug dose of chemotherapy for patient with unknown mathematical model parameters. Babaei and Salamci (2015) extended the results of their research for

* This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK) under the Project no. 112M209.

10.1016/j.ifacol.2015.11.098

determination of personalized drug delivery scenario for patients with unknown parameters.

Recently, immunotherapy related treatments have received extensive consideration in cancer treatment researches. The objective of immunotherapy is to boost the patient's immune system to eradicate the cancerous cells based on body immune response. Some studies reveal that a combination of immunotherapy and chemotherapy could lead to more effective treatment protocols (Swan, 1981; de Pillis, 2006). Combination of immunotherapy with chemotherapy not only strengthens the immune system, but also reduces unwanted side effects of chemotherapy. However, the manner of combination of immunotherapy and chemotherapy, both in drug dose and periodicity of administration, is an open area for research.

de Pillis et al. (2006) developed their former mathematical model (2003) and proposed a model for combining chemotherapy and immunotherapy. de Pillis and coworkers presented their research in mixed therapy in de Pillis et al. (2007a) and de Pillis et al. (2009).

In this paper, the solution to the delivery protocol for the nonlinear dynamics of mixed immunotherapy and chemotherapy is pursued using the SDRE technique. The main objective of this study is to determine the minimum dose of chemotherapy and immunotherapy drugs during treatment period. For this propose, the nonlinear cancer dynamics proposed by de Pillis et al. (2006) is considered in the paper. Numerical simulation results demonstrate the effectiveness of the proposed method in obtaining chemo and immune drug delivery scenario in combined therapy.

The structure of the paper is as follows; in Section II, mathematical background of the SDRE technique is presented. Section III presents the cancer dynamics for mixed therapy. SDRE-based optimal control of cancer dynamics is discussed in Section IV. Numerical simulations are presented in Section V. Conclusions are drawn in Section VI.

2. SDRE BACKGROUND

SDRE methodology has become a popular methods for optimal control of nonlinear systems, receiving a considerable amount of attention amongst control researchers in recent years. It presents a systematic and effective procedure for controlling nonlinear dynamics. In this section, mathematical backgrounds of SDRE technique are given for the input-affine class of nonlinear systems.

Consider a class of nonlinear systems, nonlinear in the state and affine in the input, described by

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}) + \mathbf{B}(\mathbf{x})\mathbf{u}(t), \quad \mathbf{x}(\mathbf{0}) = \mathbf{x}_0 \tag{1}$$

where $\mathbf{x} \in \mathbb{R}^n$ is the state vector, $\mathbf{u} \in \mathbb{R}^q$ is the input vector, $\mathbf{B}(\mathbf{x}) \in \mathbb{R}^{n\times q}$ and $\mathbf{f}(\mathbf{x}) \in \mathbb{R}^n$ where $\mathbf{B}(\mathbf{x}) \neq \mathbf{0}\ \forall \mathbf{x}$.

Condition 2.1: The system has an equilibrium point at the origin of the state, so that $\mathbf{f}(\mathbf{0}) = \mathbf{0}$.

If Assumption 2.1 is satisfied, in order to utilize the LQR technique, $\mathbf{f}(\mathbf{x})$ can be factorized as $\mathbf{f}(\mathbf{x}) = \mathbf{A}(\mathbf{x})\mathbf{x}$ with $\mathbf{A}(\mathbf{x}) \in \mathbb{R}^{n\times n}$.

Remark 2.1: In parameterization of $\mathbf{f}(\mathbf{x})$ as $\mathbf{A}(\mathbf{x})\mathbf{x}$, the method for selecting the $\mathbf{A}(\mathbf{x})$ matrix is not unique and factorization can be done in infinite number of ways.

Then, Eq. (1) can be represented in State-Dependent Coefficient (SDC) form as

$$\dot{\mathbf{x}}(t) = \mathbf{A}(\mathbf{x})\mathbf{x}(t) + \mathbf{B}(\mathbf{x})\mathbf{u}(t), \quad \mathbf{x}(\mathbf{0}) = \mathbf{x}_0 \tag{2}$$

Where $\mathbf{A}(\mathbf{x})$ and $\mathbf{B}(\mathbf{x})$ are the SDC matrices. In fact, by evaluating the SDC matrices for a given state vector, the nonlinear system is regarded as a pointwise LTI one. Therefore, at each instant of time, an LTI system is obtained, allowing one to design the control input $\mathbf{u}$ using well-known approaches for LTI systems.

Condition 2.2: $\{\mathbf{A}(\mathbf{x}), \mathbf{B}(\mathbf{x})\}$ is a pointwise stabilizable pair.

The objective of nonlinear optimal regulation by SDRE method is to drive all states to zero by minimizing the cost

$$J = \int_0^\infty \{\mathbf{x}^T(t)\mathbf{Q}(\mathbf{x})\mathbf{x}(t) + \mathbf{u}^T(t)\mathbf{R}(\mathbf{x})\mathbf{u}(t)\}\, dt \tag{3}$$

where $\mathbf{Q}(\mathbf{x}) \in \mathbb{R}^{n\times n}$ and $\mathbf{R}(\mathbf{x}) \in \mathbb{R}^{q\times q}$ are state-dependent state- and input-weighting matrices, respectively. Subsequently, similar to the LQR architecture, the cost function is minimized using the state-feedback controller

$$\mathbf{u}(\mathbf{x}) = -\mathbf{R}^{-1}(\mathbf{x})\mathbf{B}^T(\mathbf{x})\mathbf{P}(\mathbf{x})\mathbf{x} \tag{4}$$

where $\mathbf{P}(\mathbf{x})$ is the symmetric, positive-definite and unique solution for the algebraic SDRE

$$\mathbf{P}(\mathbf{x})\mathbf{A}(\mathbf{x}) + \mathbf{A}^T(\mathbf{x})\mathbf{P}(\mathbf{x}) - \mathbf{P}(\mathbf{x})\mathbf{B}(\mathbf{x})\mathbf{R}^{-1}(\mathbf{x})\mathbf{B}^T(\mathbf{x})\mathbf{P}(\mathbf{x}) + \mathbf{Q}(\mathbf{x}) = \mathbf{0} \tag{5}$$

For SDC parameterization of the system, in order to preserve the dependency of terms containing two or more states, the following parameterization is considered by using free design parameters represented by the $\boldsymbol{\theta}$ vector, where $\theta_i \in [0, 0.5, 1]$, $i \in \mathbb{N}$.

$$\mathbf{A}(\mathbf{x}, \theta_i) = \theta_i \mathbf{A}_1(\mathbf{x}) + (1-\theta_i)\mathbf{A}_2(\mathbf{x}) \tag{6}$$

Selecting a different θ_i vector affects the optimality, stability and robustness of the system, in addition to design flexibility (for details refer to Çimen, 2010). The parameter $\theta_i \in \mathbb{R}^n$ is to be selected from a pointwise stability point of view for the $\{\mathbf{A}(\mathbf{x}, \theta_i), \mathbf{B}(\mathbf{x})\}$ pair. For this purpose, the state-dependent controllability matrix $\mathbf{M}_c(\mathbf{x}) = [\mathbf{B}(\mathbf{x}) | \mathbf{A}(\mathbf{x}, \theta_i)\mathbf{B}(\mathbf{x}) | \ldots | \mathbf{A}^{n-1}(\mathbf{x}, \theta_i)\mathbf{B}(\mathbf{x})]$ is used. By determining the determinant of $\mathbf{M}_c(\mathbf{x})$ numerically, based on the state vector and different values of θ_i, the largest space of pointwise stability can be achieved.

In some control problems, systems may be nonaffine (nonlinear) in the control input, and hard bounds on the states of the system may also be required because of various limitations. Extensions of the SDRE control method for dealing with such hard nonlinearities have been discussed in Çimen (2010), and will be employed in the paper.

3. CANCER DYNAMICS

3.1. System Variables

For cancer dynamics, the model developed by de Pillis and Radunskaya (2006) for mixed immunotherapy and chemotherapy will be considered. This model contains six variables that include the kinetics of four different cell populations and two drug concentrations in the blood stream. The proposed model, in the absence of medical interventions,

comprise tumor dormancy, struggle of cancer and normal cells for nutrients and space, unchecked growth of tumor cells, and activation effect of cancerous cells on immune cells in the patient body. The model also considers two different medical interventions in cell populations including chemotherapy and immunotherapy. The multi-population nonlinear model that reflects all these consideration includes the following cell populations and drug concentrations in the blood stream at time t: (1) $T(t)$, tumor cell populations, (2) $N(t)$, total natural killer (NK) cell populations, as a part of innate immune response of body, (3) $L(t)$, total CD8$^+$T cell populations, as another part of immune response of body, also known as cytotoxic T cells or CTL, (4) $C(t)$, number of circulating lymphocytes (white blood cells), (5) $M(t)$, chemotherapy drug concentration in the blood stream, (6) $I(t)$, immunotherapy drug concentration in the bloodstream.

3.2. Immune System of Body and Framework of Immunotherapy

The task of the immune system in the body is to identify and attack tumor cells. For eradication of cancerous cells, human body has two major kinds of immune cells:

- **Non-specific immune cells** such as NK cells that belong to white blood cells. NK cells can circulate the whole body through the blood stream or lymph system and attack all foreign cells.
- **Specific immune cells** such as cytotoxic T cells (CD8$^+$T), which must prepare and activate before attacking tumor cells. Preparing procedure is done inside of lymph nodes with antigens.

In immunotherapy, the immune system of patient is boosted, thereby eradicating the tumor cells. Strengthening of the immune response of the body may be accomplished by the following methodologies.

- **IL-2 growth factor injection**
  Naturally CD4$^+$T cells secrete the IL-2 as a growth factor of CD8$^+$T cells. Injection of IL-2 causes enhancement in the population of CD8$^+$T cells, which destroy tumor cells without affecting normal cells.
- **Direct injection of highly activated specific immune cells in blood stream**
  For boosting immune cells, prepared and activated CD8$^+$T of one patient cultivate and increase, then re-inject into the patient bloodstream. Indeed by imitated enrichment of immune system, patient immune system is aided to eradicate tumor cells.

3.3. Model Formulation

The cancer dynamics must reflect the growth and death of cells, the fractional cell kill, per cell recruitment, cell inactivation and external intervention with chemotherapy and immunotherapy drugs. In the proposed mathematical model, the following assumptions have been considered:

- Tumor cells grow logistically in the absence of immune response.
- Both NK and CD8$^+$T cells kill tumor cells.
- NK cells as part of the innate immune system exist in the human body, even in absence of cancerous cells.
- CD8$^+$T cells, as part of the specific immune response, exist in large numbers in the presence of tumor cells in the body.
- Both NK and CD8$^+$T cells become inert after conflict with tumor cells.
- Circulating lymphocyte levels reflect patient health. Lymphocyte cells contribute in production of the antibody and NK cells attack cells to which antibody has attached.
- Based on anticancer drug dose in chemotherapy, fraction of tumor cells killed. This fraction is always less than one.
- Some population of NK and CD8$^+$T cells and circulating lymphocytes are also killed by chemotherapy.
- Natural killer and tumor cells influence the stimulation and elimination of activated effector cells.

These assumptions and considerations lead to the following nonlinear coupled ordinary differential equations (ODEs) for modeling cell population dynamics in the presence of mixed immune and chemotherapy drug interventions.

$$\left.\begin{aligned}
\dot{T} &= aT(1-bT) - cNT - DT - k_T(1-e^{-M})T \\
\dot{N} &= eC - fN + g\tfrac{T^2}{h+T^2}N - pNT - k_N(1-e^{-M})N \\
\dot{L} &= -mL + j\tfrac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T - uNL^2 - k_L(1-e^{-M})L \\
&\quad + \tfrac{p_I LI}{g_I+I} + v_L(t) \\
\dot{C} &= \alpha - \beta C - k_C(1-e^{-M})C \\
\dot{M} &= -\gamma M + v_M(t) \\
\dot{I} &= -\mu_I I + v_I(t) \\
\dot{D} &= d\tfrac{(L/T)^i}{s+(L/T)^i}
\end{aligned}\right\} \quad (7)$$

The proposed model contains 24 different constant parameters, which differ from one patient to another. Two sets of parameters for two different patients are mentioned by de Pillis et al. (2006), which are estimated based on fitting clinical data results. One of these sets of parameters, tabulated in Table 1, is used in the paper.

3.4. System equilibrium points

In order to determine the tumor-free equilibrium point of the system, *T*-dynamics is assumed to have equilibria at $T_{eq} = 0$ (tumor free). On the other hand, *C*-dynamics decouples from the other set of equations and simply one can determine the equilibrium point of circulating lymphocytes as $C_{eq} = \alpha/\beta$. Also NK cells equilibrium point could be determined based on T_{eq}, C_{eq} as $N_{eq} = e\alpha/f\beta$. To determine the equilibrium point of CD8$^+$T cells, considering *L*-dynamics as well as T_{eq}, C_{eq} and N_{eq}, $-mL - u\frac{e\alpha}{f\beta}L^2 = 0$. Then two different equilibrium points are achieved, given by $L_{eq1} = 0$ and $L_{eq2} = -(mf\beta)/(ue\alpha) < 0$. Since all model parameters are positive, L_{eq2} has a negative value, which is not possible for cell population. Therefore, the desired tumor-free equilibrium point, that needs to be derived by intervention of chemotherapy and immunotherapy, is $(T_{eq}, N_{eq}, L_{eq}, C_{eq}) = (0, \frac{e\alpha}{f\beta}, 0, \frac{\alpha}{\beta})$.

4. SDRE-BASED OPTIMAL CONTROL OF CANCER DYNAMICS

In cancer treatment, the system must be driven to the tumor-free equilibrium point by administering the appropriate dose

of drug and administration periodicity in the treatment duration. By defining error states, the equilibrium point of the system of Eqs. (7) is shifted to the origin (for details refer to Çimen, 2011) as follows

$$x_1 \triangleq T \quad x_2 \triangleq N - \frac{ce\alpha}{f\beta} \quad x_3 \triangleq L \quad x_4 \triangleq C - \frac{\alpha}{\beta} \quad x_5 \triangleq M \quad x_6 \triangleq I \tag{8}$$

The new state vector $[x_1\ x_2\ x_3\ x_4\ x_5\ x_6]^{\mathrm{T}}$ contains the error states, and the set of ODEs (7) can be defined in the new coordinates. Since the term e^{-x_5} is a state-dependent term, and in the new set of equations $(1-e^{-x_5})$ includes the origin, the expression $R \triangleq (e^{-x_5}-1)/x_5$ is considered. Therefore, $\lim_{x_5 \to 0} R = -1$ (for details, see Çimen, 2010). Then the new set of ODEs is represented as follows:

$$\left.\begin{aligned}
\dot{x}_1 &= ax_1(1-bx_1) - cx_1x_2 - \tfrac{ce\alpha}{f\beta}x_1 - \tfrac{dx_3^{l-1}}{sx_1^l+x_3^l}x_1x_3 + k_T R x_1 x_5 \\
\dot{x}_2 &= ex_4 - fx_2 + g\tfrac{x_1^2x_2}{h+x_1^2} + \tfrac{ce\alpha}{f\beta}\tfrac{x_1^2}{h+x_1^2} - px_1x_2 - \tfrac{pe\alpha}{f\beta}x_1 + k_N R x_2 x_5 + \tfrac{k_N Re\alpha}{f\beta}x_5 \\
\dot{x}_3 &= -mx_3 + j\tfrac{D^2x_1^2}{k+D^2x_1^2}x_3 - qx_1x_3 + \left(r_1\left(x_2+\tfrac{e\alpha}{f\beta}\right) + r_2\left(x_4+\tfrac{\alpha}{\beta}\right)\right)x_1 \\
&\quad -u\left(x_2+\tfrac{e\alpha}{f\beta}\right)x_3^2 - k_L R x_3 x_5 + \tfrac{p_I x_5 x_6}{g_I+x_6} + v_L(t) \\
\dot{x}_4 &= -\beta x_4 - k_C R x_4 x_5 + \tfrac{\alpha k_C k_5}{\beta}x_5 \\
\dot{x}_5 &= -\gamma x_5 + v_M(t) \\
\dot{x}_6 &= -\mu_I x_6 + v_I(t)
\end{aligned}\right\} \tag{9}$$

SDC parameterization of the system of Eqs. (9) is constructed by using the free $\boldsymbol{\theta}$ vector, as follows:

$$\mathbf{A}(\mathbf{x},\boldsymbol{\theta}) = \begin{bmatrix} a_{11} & a_{12} & a_{13} & 0 & a_{15} & 0 \\ a_{21} & a_{22} & 0 & e & a_{25} & 0 \\ a_{31} & a_{32} & a_{33} & a_{34} & a_{35} & a_{36} \\ 0 & 0 & 0 & a_{44} & a_{45} & 0 \\ 0 & 0 & 0 & 0 & -\gamma & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu \end{bmatrix}, \quad \mathbf{B} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \tag{10}$$

where

$$\begin{aligned}
a_{11} &= a(1-bx_1) - c\theta_1 x_2 - \tfrac{ce\alpha}{f\beta} + k_T R\theta_2 x_5 - \tfrac{dx_3^{l-1}}{sx_1^l+x_3^l}\theta_3 x_3 \\
a_{12} &= -c(1-\theta_1)x_1 \\
a_{13} &= -\tfrac{dx_3^{l-1}}{sx_1^l+x_3^l}(1-\theta_3)x_1 \\
a_{15} &= k_T R(1-\theta_2)x_1 \\
a_{21} &= -p\theta_4 x_2 - \tfrac{pe\alpha}{f\beta} + g\theta_6\tfrac{x_1x_2}{h+x_1^2} + \tfrac{ce\alpha}{f\beta}\tfrac{x_1}{h+x_1^2} \\
a_{22} &= -f - p(1-\theta_4)x_1 + k_N R\theta_5 x_5 + g(1-\theta_6)\tfrac{x_1^2}{h+x_1^2} \\
a_{25} &= k_N R(1-\theta_5)x_2 + \tfrac{k_N Re\alpha}{f\beta} \\
a_{31} &= -q\theta_7 x_3 + r_1\theta_{11}x_2 + r_1\tfrac{e\alpha}{f\beta} + r_2\theta_{12}x_4 + r_2\tfrac{\alpha}{\beta} + \theta_{13}j\tfrac{D^2x_3^{2l}}{k(sx_1^l+x_3^l)^2+D^2x_3^{2l}x_1}x_3 \\
a_{32} &= -u\theta_{10}x_3^2 \\
a_{33} &= -m - q(1-\theta_7)x_1 + k_L R\theta_8 x_5 + \tfrac{p_I\theta_9 x_6}{g_I+x_6} - u(1-\theta_{10})x_2x_3 \\
&\quad -u\tfrac{e\alpha}{f\beta}x_3 + (1-\theta_{13})j\tfrac{D^2x_3^{2l}}{k(sx_1^l+x_3^l)^2+D^2x_3^{2l}} \\
a_{34} &= r_2(1-\theta_{12})x_1 \\
a_{35} &= k_L R(1-\theta_8)x_3 \\
a_{36} &= \tfrac{p_I(1-\theta_9)x_3}{g_I+x_6} \\
a_{44} &= -\beta - k_C R\theta_{14}x_5 \\
a_{45} &= k_C k_5(1-\theta_{14})x_4 + \tfrac{\alpha k_C R}{\beta}
\end{aligned}$$

The parameter $\boldsymbol{\theta} \in \mathbb{R}^{14}$ must be selected from the pointwise stability point of view for the $\{\mathbf{A}(\mathbf{x},\boldsymbol{\theta}),\mathbf{B}\}$ pair. Assuming that $\theta_i \in [0, 0.5, 1],\ i = 1, 2, \ldots, 14$, then the maximum pointwise controllable space related to different sets of the θ parameter is numerically determined. The result of this numerical study showed that the maximum value of $|\det(\mathbf{M}_c(\mathbf{x}))|$, and consequently the largest pointwise controllable space for the pair $\{\mathbf{A}(\mathbf{x},\boldsymbol{\theta}),\mathbf{B}\}$, is achieved using (refer to Çimen, 2010):

$\theta = [0\ 0\ 1\ 0\ 0\ 0\ 0\ 0\ 0.5\ 0\ 0\ 0.5\ 1\ 0]$,

Additionally, constraints are imposed for drug dose of chemotherapy as well as administrated TIL and IL-2 in treatment: $0 \le v_L(t) \le 10^9$, $0 \le v_M(t) \le 5$, $0 \le v_I(t) \le 5\times10^5$. As these hard bounds cause nonlinearity in the control, integral control is utilized (Çimen, 2010). Then, the control inputs of $v_L(t), v_M(t)$ and $v_I(t)$ are considered as new augmented states for the system as $\tilde{\mathbf{x}}^T = [x_1\ \cdots\ x_9]$ with $x_7 \triangleq v_L$, $x_8 \triangleq v_M$, $x_9 \triangleq v_I$. The constrained input is modeled as saturation nonlinearity:

$$sat(u, u_{\max}) = \begin{cases} u_{\max}, & u > u_{\max} \\ u, & 0 < u \le u_{\max} \\ 0, & u < 0 \end{cases} \tag{11}$$

Then, a family of SDC parameterization for $\tilde{\mathbf{A}}(\tilde{\mathbf{x}},\boldsymbol{\theta})$ can be constructed with $a_{37} = sat(x_7, 10^9)/x_7$, $a_{58} = sat(x_8, 5)/x_8$ and $a_{69} = sat(x_9, 5\times10^9)/x_9$.

5. NUMERICAL SIMULATIONS

For numerical simulations, parameters and initial conditions from de Pillis et al.(2006) will be used, and the results compared. For the patient with parameters given in Table 1, and with initial conditions of $(T_0, N_0, L_0, C_0) = (2\times10^7, 1\times10^3, 10, 6\times10^8)$ de Pillis and coworkers administered the following combination therapy, which is presented in Fig. 1:

- $v_M(t)$: Injection of 9 pulses of chemotherapy with periodicity of 10 days and duration of 1 day and dose of 5.
- $v_L(t)$: Injection from day 7 through 8 with dose of 10^9.
- $v_I(t)$: Injection of 6 pulses from day 8 through 11 with dose of 5×10^5.

The cells population and administered drug delivery protocol proposed in de Pillis et al. (2006) over a 120-day time span are illustrated in Figs. 1 and 2, respectively. They have used chemotherapy and immunotherapy drug delivery as pulsed administration of drugs in a selected period of time. The tumor cells have been eradicated in 17 days and $CD8^+T$ cells go to zero in about 42 days. Also NK cells and circulating lymphocytes need more time to reach their equilibrium points. The administered drugs are illustrated in Fig 2. In this example of mixed therapy, optimal control has not been considered for the drug delivery scenario. On the other hand, the proposed SDRE approach is applied for achieving a suboptimal solution to mixed therapy of cancer. For this purpose, the same parameters and initial conditions as de Pillis et al. (2006) is considered. The objective is to eradicate tumor cells by administering minimum dose of immunotherapy and chemotherapy drugs and drive system to the tumor free equilibrium point of

$[T_{eq}\ N_{eq}\ L_{eq}\ C_{eq}]^{\mathrm{T}} = [0\ \ 3.1553\times10^5\ \ 0\ \ 6.25\times10^{10}]^{\mathrm{T}}$

Then the new (error) states are

$x_1 \triangleq T$, $x_2 \triangleq N - 3.1553\times10^5$, $x_3 \triangleq L$,
$x_4 \triangleq C - 6.25\times10^{10}$, $x_5 \triangleq M$, $x_6 \triangleq I$

The number of circulating lymphocytes reflects patient health. Therefore during cancer treatment procedure, circulating lymphocytes population in patient body must be kept above 10^6. Five different cases with different state and

input weighting matrices of $Q_i \in \mathbb{R}^{n\times n}$ and $R_i \in \mathbb{R}^{q\times q}, i =$ 1,2…5 are then considered, as shown in Table 2.

Table 1. Estimated patient parameters values (de Pillis & Radunskaya, 2006)

Parameters	Units	Description	Estimated value
a	day^{-1}	Tumor growth rate	4.31×10^{-1}
b	cells^{-1}	$1/b$ is tumor carrying capacity.	1.02×10^{-9}
c	cell^{-1}day^{-1}	Fractional (non)-ligand-transduced tumor cell kill by **NK** cells	6.41×10^{-11}
d	day^{-1}	Saturation level of fractional tumor cell kill by $CD8^+T$ cells. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	2.34
l	None	Exponent of fractional tumor cell kill by $CD8^+T$ cells. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	2.08×10^{-7}
s	None	Steepness coefficient of the tumor-($CD8^+T$ cell) lysis term $\boldsymbol{D}$. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	2.09
e	day^{-1}	Fraction of circulating lymphocytes that become **NK** cells.	4.12×10^{-2}
f	day^{-1}	Death rate of **NK** cells.	1.25×10^{-2}
g	day^{-1}	Maximum **NK** cell recruitment rate by ligand-transduced tumor cells.	2.02×10^{7}
h	cell^2	Steepness coefficient of the **NK** cell recruitment curve.	2.49×10^{-2}
p	cell^{-1}day^{-1}	**NK** cell inactivation rate by tumor cells.	3.66×10^{7}
m	day^{-1}	Death rate of $CD8^+T$ cells.	2.04×10^{-1}
j	day^{-1}	Maximum $CD8^+T$ cell recruitment rate. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	1.42×10^{-6}
k	cell^2	Steepness coefficient of the $CD8^+T$ cell recruitment curve.	3.42×10^{-6}
q	cell^{-1}day^{-1}	$CD8^+T$cell inactivation rate by tumor cells.	8.39×10^{-2}
r_1	cell^{-1}day^{-1}	Rate at which $CD8^+T$ cells are stimulated to be produced as a result of tumor cells killed by **NK** cells	1.10×10^{-7}
r_2	cell^{-1}day^{-1}	Rate at which $CD8^+T$ cells are stimulated to be produced as a result of tumor cells interacting with circulating lymphocytes.	6.50×10^{-11}
u	cell^{-2}day^{-1}	Regulatory function by **NK**-cells of $CD8^+T$ -cells.	3.00×10^{-10}
K_T	day^{-1}	Fractional tumor cell kill by chemotherapy.	9.00×10^{-1}
K_N	day^{-1}	Fractional immune cell kill by chemotherapy.	6.00×10^{-1}
K_L	day^{-1}	Fractional immune cell kill by chemotherapy.	6.00×10^{-1}
K_C	day^{-1}	Fractional immune cell kill by chemotherapy.	6.00×10^{-1}
α	cellday^{-1}	Constant source of circulating lymphocytes.	6.50×10^{-11}
β	day^{-1}	Natural death and differentiation of circulating lymphocytes.	3.00×10^{-10}
γ	day^{-1}	Rate of chemotherapy drug decay.	9.00×10^{-1}
P_I	day^{-1}	Maximum $CD8^+T$-cell recruitment rate by **IL-2**.	1.25×10^{-1}
g_I	cell^2	Steepness of $CD8^+T$-cell recruitment curve by **IL-2**.	2.00×10^{7}
μ_I	day^{-1}	Rate of **IL-2** drug decay.	1.00×10^{1}

Table 2. State and Input weighting matrices for 5 cases

	State and Input Weighting Matrices
Case 1	$Q_1 = Diag(1,1,10^3,1,1,1,10^2,1,1)\times10^{-9}$ $R_1 = diag(10^4,10^2,4)\times10^{-10}$
Case 2	$Q_2 = Diag(1,0,10^2,1,1,0,1,10^{-1},10)\times10^{-7}$ $R_2 = diag(10^4,10^2,4)\times10^{-7}$
Case 3	$Q_3 = Diag(1,0,1,1,0,10^4,10^{10},10^2,10^2)\times10^{-7}$ $R_3 = diag(10^{12},10,10^{11})\times10^{-6}$
Case 4	$Q_4 = Diag(1,1,10^5,1,1,1,1,1,1)\times10^{-9}$ $R_4 = diag(10^2,10^2,5)\times10^{-10}$
Case 5	$Q_5 = Diag(1,1,10^4,1,1,1,1,1,1)\times10^{-9}$ $R_5 = diag(1,10,5\times10^{12})\times10^{-8}$

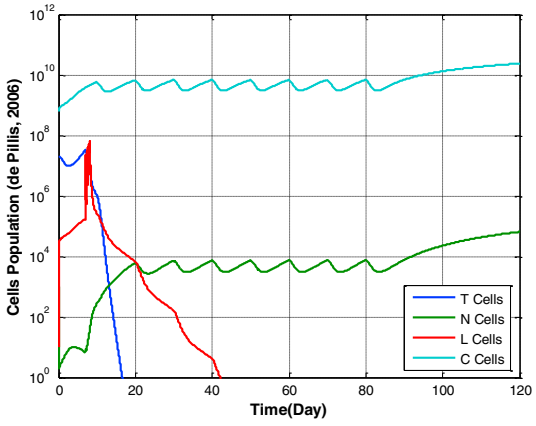

Fig. 1. Evolution of cell population of cancer patient by pulsed drug delivery (de Pillis el al., 2006).

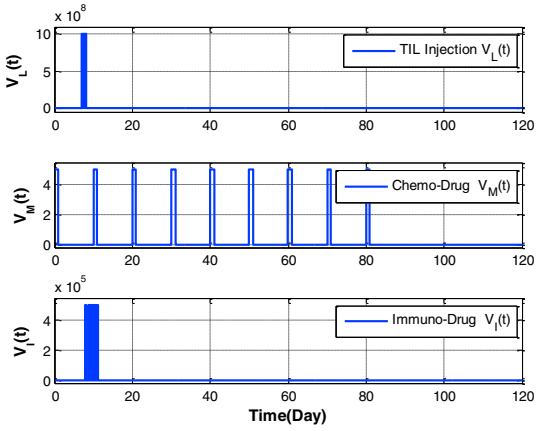

Fig. 2. Pulsed drug delivery protocol (de Pillis et al., 2006).

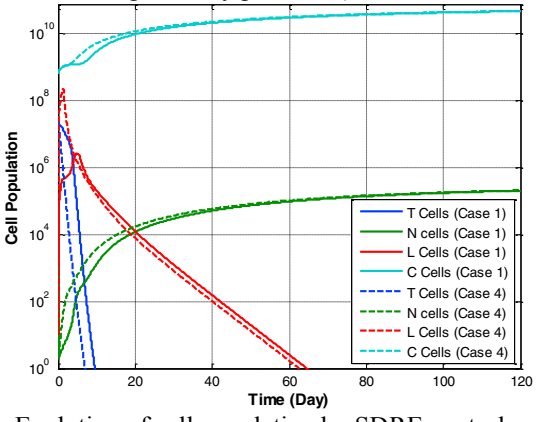

Fig. 3. Evolution of cell population by SDRE control protocol for Case 1 (solid line) and Case 4 (dashed line).

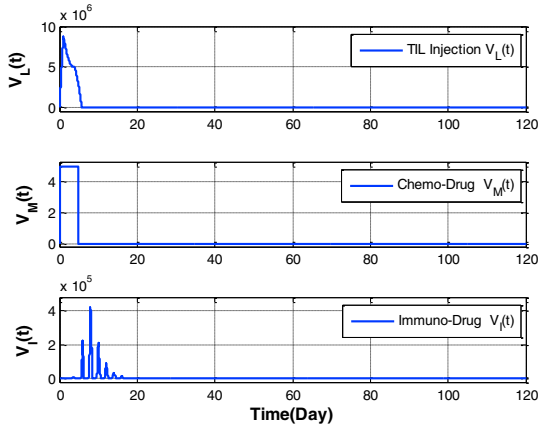

Fig. 4. Drug delivery scenario by SDRE control for Case 1.

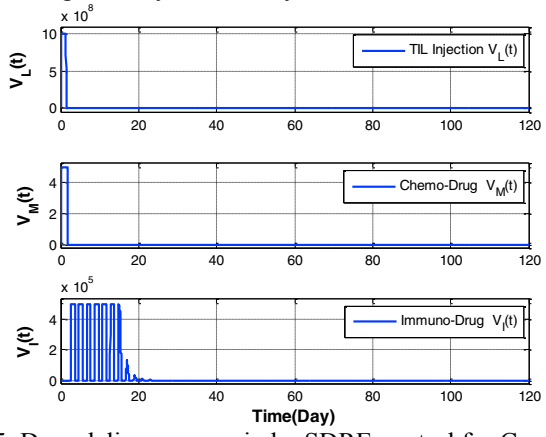

Fig. 5. Drug delivery scenario by SDRE control for Case 4.

Only the simulation results related to case 1 and case 4 are graphically presented, albeit the results of all cases are compared in Table 3. Figure 3 illustrates the achieved cells population evolution for Case 1 and case 4 by considering SDRE control. The states of Case 1 are represented by solid lines, and for case 4 by dashed lines. The tumor cells eradication period for Case 1 is about 10 days, and for Case 4 it is 7 days. Also, the time duration for reaching $CD8^{+}T$ cells population to zero is 64 days for Case 1 and 63 days for Case 4. NK cells and circulating lymphocyte population have been driven to the equilibrium points in the same time span for the two cases. In comparison with the results of de Pillis and Radunskaya (2006), SDRE method not only eradicates tumor cells in shorter time span than pulsed protocol but also with fewer fluctuations in all cell populations. The suboptimal drug delivery protocols related to SDRE control for Cases 1 and 4 are depicted in Figs. 4 and 5.

To comprise the SDRE solutions for patient 9, performance index and total dose of each drug for all 5 cases is tabulated in Table 3.

Table 3. Performance index values and total administrated drug dose for patient 9 in Cases 1 to 5

	Performance Index, J	Total Dose of v_L	Total Dose of v_M	Total Dose of v_I
Case 1	1.7546e14	2.7598e7	24.55	4.3987e5
Case 2	1.8388e16	7.2167e6	36.60	7.6339e3
Case 3	2.0162e16	0	62.25	0
Case 4	1.6731e14	1.3223e9	9.00	3.3475e6
Case 5	1.6462e14	1.2147e9	9.45	0

5. CONCLUSIONS

SDRE approach for mixed chemotherapy and immunotherapy in cancer treatment has been presented, considering a patient mathematical model with parameter set and initial conditions used by de Pillis and Radunskaya (2006). Comparison of results of the proposed SDRE control with pulsed drug administration (de Pillis and Radunskaya, 2006) reveals that the SDRE drug delivery protocol gives shorter treatment period than pulsed drug administration. SDRE control drives the system to the tumor free equilibrium point with less fluctuation in cell populations. Using the SDRE method, threshold for circulating lymphocyte level is also considered. Simulation results showed that by changing state and input weighting matrices, drug delivery protocol can be obtained for mixed therapy as only chemotherapy, or chemotherapy and TIL injection, or chemotherapy, TIL and IL-2 administration as can be seen in Table 3.

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