



Mixed therapy in cancer treatment for personalized drug administration using model reference adaptive control

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ABSTRACT

The paper presents Model Reference Adaptive Control (MRAC) design strategy to determine personalized drug delivery protocol for mixed therapy with chemotherapy and immunotherapy in cancer treatment. We consider a nonlinear mathematical ODE set for cancer dynamics that includes tumor, natural killers, circulating lymphocytes and cytotoxic T-cells population together with the interaction of chemotherapy and immunotherapy. For researchers and physicians, the main challenge in mathematical models is the determination of the exact model parameters. In order to have a drug administration policy for a patient with unknown parameter set, we develop State Dependent Riccati Equations (SDRE) based MRAC design approach to determine the personalized drug delivery protocol for patients with unknown model parameters. First of all, we determine the optimal drug delivery scenario for a reference patient with known dynamics parameters using SDRE approach. Then for any patient with unknown parameters, the personalized mixed therapy protocol is determined based on the treatment regimen of the reference patient. In the proposed methodology, unknown patients are considered as a black-box simulator in the design and the mathematical model parameters of the patient are not essential for the design of drug administration protocol. In addition, the Bang-Bang and continuous drug delivery regimens could be obtained using proper adaptation gains in the presented MRAC methodology. The simulation results demonstrate the effectiveness of the proposed MRAC approach for prescribing a treatment regimen of chemoimmunotherapy.

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1. Introduction

Although the overall cancer death rate has declined about 25% over the last 2 decades, by estimating about 1,688,780 new cases in the United States in 2017, after heart disease, cancer is the second prominent cause of death in the US, and most important health problem in the worldwide [1]. Cancer is the result of uncontrolled division and spread of abnormal cells that lead to the creation of a tumor lump. For the sake of better understanding the dynamics and treatment progress, different mathematical models (including the interaction between healthy and cancerous cells as well as drug intervention) have been developed by researchers [2–5]. Based on these mathematical models, researchers can develop more effective treatment regimens and survey them by computer simulations and optimize treatment regimens prior to the clinical trials [6–10].

For years, the most significant cancer treatment method has been chemotherapy. Extensive researches have been carried to develop optimal drug delivery strategies using optimal control theory [2,7,9,11–17]. Later, in addition to the chemotherapy, immunotherapy related treatments have received extensive consideration in cancer treatment studies. The objective of immunotherapy is to boost the patient's own immune system to eradicate the cancerous cells based on body immune response [4]. In recent decade immunotherapy is becoming an effective cancer treatment method and appealing topic in cancer treatment-related studies [4,8,18–26].

Several researchers have proposed distinct mathematical models to describe cancer cells and immune system interactions [3–5,18,22,27,28]. Some studies reveal that a combination of immunotherapy and chemotherapy could lead to more effective treatment protocols [4,29,30]. The combination of immunotherapy with chemotherapy not only strengthens the immune system but also reduces unwanted side effects of chemotherapy by boosting patient immune system [4]. Albeit lately extensive researches have been done in the mixed therapy of chemotherapy and immunotherapy [4,8,20,24–26], the manner of combination of

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immunotherapy and chemotherapy, both in drug dose and periodicity of administration, is an open area for researchers and still goes through a pre-clinical phase [30].

A model for combining chemotherapy and immunotherapy and pulsed treatment strategy for mixed therapy proposed in [4]. In [24] a feedback control strategy for the mixed therapy problem based on the mathematical model proposed in [4] was provided.

One of the recent approaches that has been considered in optimal control synthesis for cancer treatment problems is the State Dependent Riccati Equations (SDRE) technique [15,31], which provides a systematic methodology for designing nonlinear sub-optimal feedback controllers for a very general class of nonlinear systems [31,32]. SDRE-based optimal control of nonlinear cancer dynamics via chemotherapy was first proposed in [15]. Then in [31] by considering constraints for the administrated anti-cancer drug dosage and the minimum number of healthy cell population carried out the SDRE method to another mathematical model of cancer dynamics. The authors of the present paper in their earlier work [25] proposed SDRE technique to determine the optimal drug delivery protocol in the mixed therapy of chemotherapy and immunotherapy.

In all proposed cancer dynamics by distinct researchers, the mathematical model parameters vary from one patient to another patient and the optimal drug delivery protocol for one patient may not be the proper one for another patient [24]. Indeed, successful drug delivery protocol for one patient may be inadequate for the eradication of cancer cells or be excessive with fatal side effects. Thus, prescribing personalized, or individualized, optimal drug delivery protocol for cancer patients is a key point in a successful treatment regimen. The main difficulty in determining optimal treatment regimen is the need to parameter set of any patient and mostly the parameter set of a cancer patient is unknown for physicians. Also, determination of parameter set for any patient is a time-consuming and demanding task. Therefore, we are interested in developing intelligent prescribing methods for drug delivery protocols for any cancer patient without needing parameter set. The adaptive control strategies have received great interest from researchers for developing drug delivery protocols for cancer and other disease treatment for coping with uncertain or unknown parameters challenge [6,33–39].

In [36,40] a new SDRE-based Model Reference Adaptive Control (MRAC) architecture for stabilizing uncertain nonlinear systems, which was used to determine the optimal drug dose of chemotherapy for a patient with unknown mathematical model parameters and the proposed method is used in [6] for determination of personalized drug delivery scenario for patients with unknown parameters has been presented. The successive approximation approach (SAA) based model reference adaptive control for personalized drug delivery administration in chemotherapy [39,41] is introduced.

The computation of personalized drug delivery protocol in mixed therapy is more sophisticated since combination strategies for different therapeutic methods are not fully understood. The main objective of this study is to determine the optimum dose of chemotherapy and immunotherapy drugs during the treatment period. For this purpose, the nonlinear cancer dynamics proposed by de Pillis et al. [4] is considered in this study. We propose SDRE based MRAC (as studied in [25] with some preliminary results) to determine the personalized drug delivery protocol for any patient, with unknown parameter set, based on the reference drug delivery scenario which is determined by SDRE technique for a reference and known patient. In the proposed method, the unknown patient is considered as a “black box” for simulation and based on the inputs (drug intervention), we utilize the output (cell population) to achieve a unique and personalized drug delivery protocol for an unknown patient. This methodology can aid the physicians to

prescribe the sub-optimal mixed chemotherapy and immunotherapy regimens for any patients beyond traditional methods like as using body surface area. Also, the bang-bang or continuous drug delivery regimens are achievable using proper adaptation gain. Numerical simulation results demonstrate the effectiveness of the proposed method in obtaining chemo and immune drug delivery scenarios in combination therapy for the patient with an unknown parameter set.

This paper is organized as follows. In Section 2, mathematical backgrounds of the SDRE and MRAC approaches are briefly presented. In Section 3 we derive the SDRE based MRAC for nonlinear systems which contain parameter uncertainty. Section 4 presents the cancer dynamics for mixed immunotherapy and chemotherapy. Also, the stability of equilibrium points has been explored. SDRE-based optimal control of cancer dynamics of reference patient as well as personalized mixed therapy of unknown patients based on reference patient treatment regimen is discussed in Section 5. Numerical simulation results are presented in Section 6. Finally, conclusions are drawn in Section 7.

2. Mathematical preliminaries

SDRE strategy presents a systematic and effective procedure for controlling nonlinear dynamics. MRAC approaches, on the other hand, have been utilized to control systems with unmodeled dynamics or with uncertainty in model parameters for many years. In this section, mathematical backgrounds of SDRE technique for the input-affine class of nonlinear systems and MRAC approaches for LTI systems are given. Subsequently, we present the SDRE based MRAC technique for MIMO systems.

2.1. SDRE regulation of nonlinear systems

Consider the following full-state feedback, infinite-time horizon nonlinear optimal regulation problem, where the system is nonlinear in the state and affine in the input, described by

$$\dot{x}(t) = f(x) + B(x)u(t), \quad x(0) = x_0 \quad (1)$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $u(t) \in \mathbb{R}^m$, ($1 \leq m \leq n$) is the input vector, $f(x) : \mathbb{R}^n \rightarrow \mathbb{R}^n$ and $B(x) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times m}$ with $B(x) \neq 0$ for $\forall x$.

Condition 2.1. The origin is an equilibrium point of the system (1) with $u(t) = 0$, that is, $f(0) = 0$. Also $B(x) \neq 0 \forall x$.

Under Condition 2.1, $f(x)$ can be factorized as

$$f(x) = A(x)x \quad (2)$$

where $A(x) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times n}$ is the continuous (nonlinear) matrix-valued function.

Then using extended linearization, under Condition 2.1, Eq. (1) can be represented by the State-Dependent Coefficient (SDC) Matrices form as follows

$$\dot{x}(t) = A(x)x(t) + B(x)u(t) \quad (3)$$

where $A(x)$ and $B(x)$ are the SDC matrices and $\{A(x), B(x)\}$ is assumed to be a pointwise stabilizable pair. In fact, by evaluating the SDC matrices for a given state vector, the nonlinear system (3) 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 $u(t)$ using well-known approaches for LTI systems.

The objective of nonlinear optimal regulation using SDRE method is to drive all states to zero by minimizing an infinite-time performance criterion, which is non-quadratic in state x and quadratic in u , given by

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

where $Q(x) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times n}$ and $R(x) : \mathbb{R}^n \rightarrow \mathbb{R}^{m \times m}$ are state-dependent state and input weighting matrices, respectively. The state and input weighting matrices satisfy the pointwise positive semi-definiteness and positive definiteness conditions, i.e. $Q(x) = Q^T(x) \geq 0$ and $R(x) = R^T(x) > 0$. Subsequently, similar to the LQR architecture, the cost function (4) is minimized subject to (1) using the stabilizing state-feedback controller

$$u(x) = -R^{-1}(x)B^T(x)P(x)x \quad (5)$$

with

$$K(x) = R^{-1}(x)B^T(x)P(x) \quad (6)$$

where $K(x) : \mathbb{R}^n \rightarrow \mathbb{R}^{m \times n}$ is the state dependent feedback-gain matrix and it is designed at each instant of time to satisfy local stability while minimizing the cost (4), in which $P(x)$ is the symmetric, positive-definite and unique solution for the algebraic State-Dependent Riccati Equation (SDRE)

$$P(x)A(x) + A^T(x)P(x) - P(x)B(x)R^{-1}(x)B^T(x)P(x) + Q(x) = 0 \quad (7)$$

2.1.1. SDC parameterization

In the multivariable case, i.e. $n > 1$, the parameterization of $f(x)$ as $A(x)x$ is not unique and we can represent the system in the infinite number of SDC parameterization. For SDC parameterization of the system (1), in order to preserve the dependency of terms containing two or more states, the following parameterization is considered using free design parameters represented by the θ vector, where $\theta_i \in \mathbb{R}^n$, $i \in \mathbb{N}$.

$$A(x, \theta_i) = \theta_i A_1(x) + (1 - \theta_i) A_2(x) \quad (8)$$

Selecting a different θ_i vector affects the optimality, stability and robustness of the system, in addition to design flexibility (see [31] for more details). The parameter $\theta_i \in \mathbb{R}^n$ is to be selected from a pointwise stability point of view for the $\{A(x, \theta_i), B(x)\}$ pair.

2.1.2. Nonlinearity in the control

In some control problems, we may encounter with a system with non-affine (nonlinear) control. E.g. applying hard bounds on the control yields non-affine control. Consider the following system with non-affine control

$$\dot{x} = f(x) + g(x, u) \quad (9)$$

Since non-affine system (9) does not conform to the SDRE structure represented by (1), by utilizing integral control [42,43], nonlinear system dynamics in (9) can be represented in the appropriate form for conformity of SDRE standard form of (1)

$$\dot{u} = \tilde{u} \quad (10)$$

Consequently, by considering the control u as a new state which adds to the system states, the augmented system (with pseudo-control input \tilde{u}) can be represented as

$$\underbrace{\begin{bmatrix} \dot{x} \\ \dot{u} \end{bmatrix}}_{\dot{\tilde{x}}} = \underbrace{\begin{bmatrix} f(x) + g(x, u) \\ 0 \end{bmatrix}}_{\tilde{f}(\tilde{x})} + \underbrace{\begin{bmatrix} 0 \\ 1 \end{bmatrix}}_{\tilde{g}(\tilde{x})} \tilde{u} \quad (11)$$

Thus, augmented system can be presented as $\dot{\tilde{x}} = \tilde{f}(\tilde{x}) + \tilde{g}(\tilde{x})\tilde{u}$, when \tilde{u} is the pseudo control input and the actual control input u is considered as an augmented state in the system. The system represented by (11) is in line with the necessary condition of control-affine input \tilde{u} .

2.1.3. State constraints

In some realistic control problems, applying hard bounds to the states of the system may be necessary because of various limitations. We consider the following acceptable states set for the systems represented by (1),

$$\psi = \{x : h(x) \leq 0, h(x) : \mathbb{R}^n \rightarrow \mathbb{R}^p, h(\cdot) \in C^1\} \quad (12)$$

A SDRE feedback controller for nonlinear regulation problem (1) needs to be designed in such a way that $x \in \psi, \forall t > 0$, which means the trajectory of closed-loop system should not cross the boundary of ψ defined by $\partial\psi$ as

$$\partial\psi = \{x : h(x) = 0, h(x) : \mathbb{R}^n \rightarrow \mathbb{R}^p, h(\cdot) \in C^1\} \quad (13)$$

When the states of the closed-loop system come close to the boundary of (13), the controller should force the states to not intersect with the boundary of ψ and remain in acceptable states set ψ . Consequently, to keep the states in ψ , it is sufficient that the following condition holds

$$\begin{aligned} Z &\stackrel{\Delta}{=} \left(\frac{\partial h(x)}{\partial x} \right) \dot{x} = \frac{\partial h(x)}{\partial x} [f(x) + B(x)u] \\ &= \frac{\partial h(x)}{\partial x} [A(x)x + B(x)u] \\ &= C(x)x + D(x)u(x) = 0 \end{aligned} \quad (14)$$

where $Z \in \mathbb{R}^p$ is a fictitious output, $(\partial h(x)/\partial x)A(x) \stackrel{\Delta}{=} C(x)$ and $(\partial h(x)/\partial x)B(x) \stackrel{\Delta}{=} D(x)$.

If the states come close to the boundary $\partial\psi$, then algebraic equation (14), i.e. $Z = 0$, yields the following equality

$$C(x)x = -D(x)u(x) \quad (15)$$

Therefore, the following feedback control can force the states to remain in the aforementioned boundary (12)

$$u(x) = -\hat{D}(x)C(x)x \quad (16)$$

where $\hat{D}(x) = D^T(x)[D(x)D^T(x)]^{-1}$ is the right inverse of $D(x)$, that is $D(x)\hat{D}(x) = I$.

Now we consider state dependent nonlinear regulator problem where nonlinear feedback control $u(x)$ in (16) minimizes $J_\psi(x_0, u) = \frac{1}{2}Z^T W(x)Z$, $W(x) > 0$ subject to (3). That is,

$$\begin{aligned} J_\psi(x_0, u) &= \frac{1}{2} \int_0^\infty \{C(x)x + D(x)u(x)\}^T W(x) \{C(x)x + D(x)u(x)\} dt \\ J_\psi(x_0, u) &= \frac{1}{2} \int_0^\infty \{x^T Q_\psi(x)x + 2x^T S_\psi(x)u + u^T R_\psi(x)u\} dt, \end{aligned} \quad (17)$$

The quantities used in the cost functional (17) are given as follows;

$$\begin{aligned} Q_\psi(x) &\stackrel{\Delta}{=} C(x)^T W(x) C(x), \\ R_\psi(x) &\stackrel{\Delta}{=} D(x)^T W(x) D(x), \\ S_\psi(x) &\stackrel{\Delta}{=} C(x)^T W(x) D(x). \end{aligned} \quad (18)$$

In (17) and (18), $W(x) : \mathbb{R}^p \rightarrow \mathbb{R}^{p \times p}$ is a diagonal state-dependent matrix such that its i th element is large when x is close to the boundary of the i th constraint and small otherwise. For choosing $W(x)$, the distance between x and $\partial\psi$ is as

$$W(x) = \text{diag}(\phi_1(x), \dots, \phi_p(x)) \quad (19)$$

where

$$\phi_i(x) = \frac{1}{(\|h_i(x)\|_2 + \varepsilon_i)^{2N_i}}, \quad i = 1, \dots, p \quad (20)$$

And $\phi_i \in \mathbb{Z}$, $\phi_i \geq 1$ and $0 < \varepsilon_i \leq 1$. Thus, when $x \rightarrow \partial\psi$ then $h_i(x) \rightarrow 0$ and $\phi_i(x) \rightarrow \frac{1}{\varepsilon_i^{2N_i}}$. Also, when $x \rightarrow 0$ then $\phi_i(x) \rightarrow \frac{1}{(1+\varepsilon_i)^{2N_i}}$.

Generally, the minimizing of (17) leads to singular regulator and makes acceptable states set (12) positively invariant. However regulation objective is to drive the states to a desired equilibrium while remaining in the set ψ . This can be achieved by minimizing the augmented cost functional

$$J(x, u) = J_0(x, u) + J_\psi(x, u) \quad (21)$$

where $J_\psi(x, u)$ is defined in (17), and $J_0(x, u)$ given by

$$J_0(x, u) = \frac{1}{2} \int_0^\infty \{x^T Q_0(x)x + u^T R_0(x)u\} dt, \quad (22)$$

Then

$$J(x, u) = \frac{1}{2} \int_0^\infty \{x^T Q(x)x + 2x^T S(x)u + u^T R(x)u\} dt, \quad (23)$$

where

$$Q(x) \triangleq Q_0(x) + Q_\psi(x) = Q_0(x) + C^T(x)W(x)C(x),$$

$$R(x) \triangleq R_0(x) + R_\psi(x) = R_0(x) + D^T(x)W(x)D(x)$$

$$S(x) \triangleq S_\psi(x) = C^T(x)W(x)D(x)$$

Then the state feedback gain matrix that (approximately) minimizes (21) is given by

$$K(x) = R^{-1}(x)[B^T(x)P(x) + S^T(x)] = K_0(x) + K_\psi(x) \quad (24)$$

with

$$K_0(x) \triangleq [R_0(x) + D^T(x)W(x)D(x)]^{-1}B^T(x)P(x)$$

$$K_\psi(x) \triangleq [R_0(x) + D^T(x)W(x)D(x)]^{-1}D^T(x)W(x)C(x)$$

and $P(x) \geq 0$ satisfies the SDRE

$$P(x)\bar{A}(x) + \bar{A}^T(x)P(x) - P(x)B(x)\bar{R}^{-1}(x)B^T(x)P(x) + \bar{Q}(x) = 0 \quad (25)$$

where

$$\begin{aligned} \bar{A}(x) &\triangleq A(x) - B(x)R^{-1}(x)S^T(x) \\ &= A(x) - B(x)[R_0(x) + D^T(x)W(x)D(x)]^{-1}D^T(x)W(x)C(x) \end{aligned}$$

$$\begin{aligned} \bar{Q}(x) &\triangleq Q(x) - S(x)R^{-1}(x)S^T(x) \\ &= Q_0(x) + C^T(x)(W(x) - W(x)D(x)[R_0(x) \\ &\quad + D^T(x)W(x)D(x)]^{-1}D^T(x)W(x))C(x) \end{aligned}$$

$$\bar{R}(x) \triangleq R(x) \triangleq R_0(x) + D^T(x)W(x)D(x) \quad (26)$$

Remark 2.1. In (24), the state dependent control gain $K(x)$ is combined from $K_0(x)$ which is designed to stabilize the system with desired performance and $K_\psi(x)$ which is designed to satisfy the state constraints [31].

The details on how to design the controller as well as other issues related to stability and constraints for control input and state are documented comprehensively by [31,32,42].

2.2. Model reference adaptive control

The MRAC is a feedback control method with estimated variable control gains, which relies on the desired trajectory of a reference model for controlling a plant including uncertain or time varying parameters. The adaptive controller gains are estimated online by considering the tracking error, reference command and the output of the plant such a way that the plant output tracks the output of the well-behaved reference model (see [44–46] for details).

Consider the following reference LTI system with well-behaved output given by

$$\dot{x}_m(t) = A_{mcl}x_m(t), \quad x_m(0) = x_{m0} \quad (27)$$

where A_{mcl} is an asymptotically stable matrix, i.e. all eigenvalues of A_{mcl} are in the open left half complex plane.

For the plant dynamics, consider the following LTI system described by

$$\dot{x}_p(t) = A_p x_p(t) + B_p u_p(t), \quad x_p(0) = x_{p0} \quad (28)$$

where $x_p(t) \in \mathbb{R}^n$ is the plant state vector, $A_p \in \mathbb{R}^{n \times n}$ and $B_p \in \mathbb{R}^{n \times m}$ are possibly unknown constant system matrices while $\{A_p, B_p\}$ pair is assumed to be controllable. $u(t) \in \mathbb{R}^m$ is the state feedback control input for the plant which is to be designed in such a way that the plant states, $x_p(t)$, track reference model desired states, $x_m(t)$, as close as possible.

The proposed control to stabilize plant dynamics (28) is in the form

$$u_p(t) = -K_p x_p(t) \quad (29)$$

Estimation of controller gain K_p is performed using an adaptation rule, which is mainly developed based on the Lyapunov stability theorem, as follows

$$\dot{K}_p(t) = \hat{B}_p^T e(t) x_p^T(t) P_{ad} \Gamma, \quad K_p(0) = K_{p0} \quad (30)$$

where $K_{p0} \in \mathbb{R}^{m \times n}$ is an arbitrary initial estimate of the unknown parameter K_p and P_{ad} is the unique symmetric positive definite, i.e. $P_{ad} = P_{ad}^T > 0$, solution of Lyapunov equation of the asymptotically stable close-loop system of reference model (27),

$$A_{mcl}^T P_{ad} + P_{ad} A_{mcl} = -Q_{ad} \quad (31)$$

for some $Q_{ad} \in \mathbb{R}^{n \times n}$ which is symmetric, i.e. $Q_{ad} = Q_{ad}^T > 0$.

3. SDRE based MRAC for stabilization of uncertain nonlinear systems

In this section, we shall combine the SDRE and MRAC approaches to present a systematic control methodology to the regulation of nonlinear dynamical systems with unknown dynamics. Although the MRAC design methodology is established for unknown plant dynamics (either linear or nonlinear), the reference model is generally taken to be linear whose behavior is stable with desirable system responses as given in Section 2.2. In this context, unlike the classical MRAC design approach, we shall use a nonlinear reference model whose behavior is ensured to be stable in the domain of operation. In order to obtain a stable nonlinear reference model, an SDRE controller is designed for the reference dynamics first. Then by considering the reference model response, we propose MRAC for the regulation problem of the class of nonlinear plants with unknown parameters and/or unmodeled dynamics.

3.1. Optimal regulation of the nonlinear reference model using SDRE approach method

Consider the full-state feedback nonlinear optimal stabilization problem, where the n -dimensional nonlinear system is nonlinear in the state, and affine in the input, described by

$$\dot{x}_m(t) = f_m(x_m) + g_m(x_m)u_m(t), \quad x_m(0) = x_{m0} \quad (32)$$

where $x_m(t) \in \mathbb{R}^n$ is the state vector of reference model, $u_m(t) \in \mathbb{R}^m$, $(1 \leq m \leq n)$ is the (stabilizing) input vector of reference model with $f_m(x_m) : \mathbb{R}^n \rightarrow \mathbb{R}^n$ and $g_m(x_m) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times m}$

The nonlinear dynamics (32) can be factorized into linear like structure in the State-Dependent Coefficient (SDC) form

$$\dot{x}_m(t) = A_m(x_m)x_m(t) + B_m(x_m)u_m(t), \quad x_m(0) = x_{m0} \quad (33)$$

where

$$f_m(x_m) = A_m(x_m)x_m(t), \quad g_m(x_m) = B_m(x_m) \quad (34)$$

where $A_m(x_m) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times n}$ and $B_m(x_m) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times m}$ are completely known SDC matrices of the reference model.

Condition 3.1. $f_m(x_m) \in C^1$ is continuously differentiable vector-valued function, and the origin is an equilibrium point of the system (32) with $u_m(t) = 0$, that is, $f_m(0) = 0$. Under this condition the factorization of $f_m(x_m) = A_m(x_m)x_m$ is guaranteed.

Remark 3.1. If Condition 3.1 is not satisfied, i.e. $f_m(0) \neq 0$, one can shift the equilibrium point to the origin using appropriate transformation.

Condition 3.2. $B_m(x_m) \in C^0$ is continuous matrix-valued function, with $B_m(x_m) \neq 0$, $\forall x_m$.

By assuming pointwise controllability, the stabilizing full state feedback control input for the reference nonlinear system (32) using SDRE control (see Section 2.1) could be designed as follows:

$$u_m(x_m) = -K_m(x_m)x_m \quad (35)$$

with

$$K_m(x_m) = R_m^{-1}(x_m)B_m^T(x_m)P_m(x_m) \quad (36)$$

where $K_m(x_m) : \mathbb{R}^n \rightarrow \mathbb{R}^{m \times n}$ is the state-dependent feedback gain matrix determined by LQR technique for minimizing an infinite-time cost function, which is non-quadratic in state x_m and quadratic in u_m ,

$$J_m = \frac{1}{2} \int_0^\infty \{x_m^T(t)Q_m(x_m)x_m(t) + u_m^T(x_m)R_m(x_m)u_m(x_m)\} dt \quad (37)$$

where $P_m(x_m)$ is the symmetric, positive-definite and unique solution for the algebraic SDRE

$$\begin{aligned} P_m(x_m)A_m(x_m) + A_m^T(x_m)P_m(x_m) \\ - P_m(x_m)B_m(x_m)R_m^{-1}(x_m)B_m^T(x_m)P_m(x_m) + Q_m(x_m) = 0 \end{aligned} \quad (38)$$

where $Q_m(x_m) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times n}$ and $R_m(x_m) : \mathbb{R}^n \rightarrow \mathbb{R}^{m \times m}$ are state-dependent state and input-weighting matrices, respectively.

Condition 3.3. The pair $(A_m(x_m), B_m(x_m))$ is pointwise controllable for all $t \geq 0$, i.e. $[B_m(x_m) \ A_m(x_m)B_m(x_m) \ A_m^2(x_m)B_m(x_m) \ \dots \ A_m^{n-1}(x_m)B_m(x_m)]$ has full rank.

Thus, stabilized closed-loop reference model with desired state trajectory will be

$$\dot{x}_m(t) = A_{m_{cl}}(x_m)x_m(t) \quad (39)$$

where $A_{m_{cl}}(x_m) = A_m(x_m) - B_m(x_m)K_m(x_m)$ is pointwise Hurwitz closed-loop dynamics matrix of reference model, i.e. $R_e[\lambda_i(A_{m_{cl}}(x_m))] < 0$, $\forall x_m$, with desired stability characteristics.

3.2. Adaptive control design for regulation problem of the nonlinear plant with unknown parameters via SDRE based MRAC approach

Consider the following full-state feedback nonlinear dynamics, described by

$$\dot{x}_p(t) = f_p(x_p) + B_p(x_p)u_p(t), \quad x_p(0) = x_{p_0} \quad (40)$$

where $x_p \in \mathbb{R}^n$ is the state vector, $B_p(x_p) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times m}$ and $f_p(x_p) : \mathbb{R}^n \rightarrow \mathbb{R}^n$ are possibly unknown matrix and vector with $B_p(x_p) \neq 0 \ \forall x_p$. Furthermore, $u_p \in \mathbb{R}^m$, ($1 \leq m \leq n$) is the adaptive full-state feedback control vector for stabilization of the nonlinear plant which is to be designed in such a way that the plant (40) states $x_p(t)$ track closed-loop reference model (39) desired states, $x_m(t)$, as close as possible and the tracking error, $e(t) \triangleq x_p(t) - x_m(t)$, approaches zero asymptotically.

Condition 3.4. All states of the plant (40), i.e. $x_p(t)$, are assumed to be accessible for measurement.

Condition 3.5. The system has an equilibrium point at the origin of the state, so that $f_p(0) = 0$, then it can be factorized as $f_p(x) = A_p(x_p)x_p$ with $A_p(x_p) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times n}$ in infinite number of ways.

Thus, plant nonlinear dynamics (40) can be factorized as linear-like structure with SDC matrices

$$\dot{x}_p(t) = A_p(x_p)x_p + B_p(x_p)u_p(t, x_p, x_m), \quad x_p(0) = x_{p_0} \quad (41)$$

where $A_p(x_p)$ and $B_p(x_p)$ are assumed be unknown state dependent matrices.

For a known $A_p(x_p)$ and $B_p(x_p)$ matrix pair, the following full-state feedback control may exist for the perfect model following,

$$u_p(t, x_p, x_m) = -K_p^*(x_p, x_m)x_p(t) \quad (42)$$

Condition 3.6. There exists an ideal control gain matrix $K_p^*(x_p, x_m) \in \mathbb{R}^{m \times n}$, that results in perfect model following between the nonlinear reference model (39) and the nonlinear plant (41) such that $A_p(x_p) - B_p(x_p)K_p^*(x_p, x_m) = A_{m_{cl}}(x_m)$ where $A_{m_{cl}}(x_m) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times n}$ is Hurwitz matrix for all $t \geq 0$.

Remark 3.2. It is noted that the exact value of the gain $K_p^*(x_p, x_m)$ is not necessarily essential, but the existence of the gain is required.

Condition 3.7. $K_p^*(x_p, x_m)$ is continuously differentiable, and its derivative is uniformly bounded, $\|\dot{K}_p^*(x_p, x_m)\| \leq \delta < \infty$ for all $t \geq 0$.

Remark 3.3. Assuming that the pair $(A_p(x_p), B_p(x_p))$ is pointwise controllable for all $t \geq 0$, i.e. $[B_p(x_p) \ A_p(x_p)B_p(x_p) \ A_p^2(x_p)B_p(x_p) \ \dots \ A_p^{n-1}(x_p)B_p(x_p)]$ has full rank, the existence of $K_p^*(x_p, x_m)$ is satisfied.

Since $A_p(x_p)$ and $B_p(x_p)$ matrices are not known exactly, estimate of $K_p^*(x_p, x_m)$ may be used in the adaptive control for stabilization of the uncertain/unknown nonlinear plant,

$$u_p(t, x_p, x_m) = -K_p(t, x_p, x_m)x_p(t) \quad (43)$$

where $K_p(t, x_p, x_m) : \mathbb{R}^{2n} \rightarrow \mathbb{R}^{m \times n}$ is the time varying, and state dependent, estimation of the ideal $K_p^*(x_p, x_m)$ in (42) which is to be adjusted by the adaptation law.

Condition 3.8. There exists a positive definite matrix $G \in \mathbb{R}^{m \times m}$, such that $\hat{B}_p(x_p) = B_p(x_p)G$ is known.

To update adaptive control gain $K_p(t, x_p, x_m)$, we consider the following time varying and state dependent adaptation law

$$\begin{aligned} \dot{K}_p(t, x_p, x_m) &= \hat{B}_p^T(x_p)e(t)x_p^T(t)P_{ad}(x_p, x_m)\Gamma, \\ K_p(t_0, x_{p_0}, x_{m_0}) &= K_{p_0} \in \mathbb{R}^{m \times n} \end{aligned} \quad (44)$$

where K_{p_0} is an initial estimate of the unknown adaptive control gain $K_p(t, x_p, x_m)$ and matrix-valued function $P_{ad}(x_p, x_m)$ is the unique symmetric positive definite, i.e. $P_{ad}(x_p, x_m) = P_{ad}^T(x_p, x_m) > 0$, solution of algebraic Lyapunov equation for the stable closed-loop reference model (39) for some arbitrary matrix-valued functions $Q_{ad}(x_p) = Q_{ad}^T(x_p) > 0$.

$$A_{m_{cl}}^T(x_m)P_{ad}(x_p, x_m) + P_{ad}(x_p, x_m)A_{m_{cl}}(x_m) = -Q_{ad}(x_p) \quad (45)$$

Furthermore, $\hat{B}_p(x_p) : \mathbb{R}^n \rightarrow \mathbb{R}^{n \times m}$ is the estimation of the $B_p(x_p)$ and $\Gamma \in \mathbb{R}^{n \times n}$ is the positive definite adaptation rate to adjust the rate of convergence of $x_p(t)$ to $x_m(t)$ that affect the transient response and stability of the plant.

Theorem 3.1. The closed-loop of the nonlinear plant with adaptive controller (43) and the adaptation law (44), applied to the plant (40), guarantees that all closed-loop signals, including $x_p(t)$, $e(t)$ and $u_p(t)$ remain bounded and plant state $x_p(t)$ approaches to reference model state $x_m(t)$ that means the tracking error $e(t) \in \mathcal{L}^2$ and $e(t) \rightarrow 0$ as $t \rightarrow \infty$.

Proof. Define the following state and control parameter errors respectively

$$\begin{aligned} e(t) &\triangleq x_p(t) - x_m(t), \quad \tilde{K}(t, x_p, x_m) \triangleq K_p(t, x_p, x_m) - K_p^*(x_p, x_m) \end{aligned} \quad (46)$$

Then, closed-loop plant dynamics can be represented as follows

$$\begin{aligned} \dot{x}_p(t) &= A_p(x_p)x_p(t) - B_p(x_p)(K_p(t, x_p, x_m)x_p(t)) \\ \dot{x}_p(t) &= A_p(x_p)x_p(t) - B_p(x_p)(\tilde{K}(t, x_p, x_m) + K_p^*(x_p, x_m))x_p(t) \\ \dot{x}_p(t) &= A_{m_{cl}}(x_m)x_p(t) - B_p(x_p)\tilde{K}(t, x_p, x_m)x_p(t) \end{aligned} \quad (47)$$

By adding and subtracting $A_{m_{cl}}(x_m)x_m(t)$ to the right hand side of the equality, we have

$$\dot{x}_p(t) = A_{m_{cl}}(x_m)e(t) + \dot{x}_m(t) - B_p(x_p)\tilde{K}(t, x_p, x_m)x_p(t) \quad (48)$$

then the error dynamic is derived as follows;

$$\begin{aligned} \dot{e}(t) &= A_{m_{cl}}(x_m)e(t) - \hat{B}_p(x_p)G^{-1}\tilde{K}(t, x_p, x_m)x_p(t), \\ e(0) &= e_0 = x_{p_0} - x_{m_0} \end{aligned} \quad (49)$$

Therefore, there exist two error signals in the error dynamics (49) namely tracking error $e(t)$ and feedback gain estimation error $\tilde{K}(t, x_p, x_m)$. We consider the following positive definite Lyapunov function candidate for the error dynamics (49)

$$\begin{aligned} V(e(t), \tilde{K}(t, x_p, x_m)) &= e^T(t)P_{ad}(x_p, x_m)e(t) + \text{tr}(G^{-1}\tilde{K}(t, x_p, x_m)\Gamma^{-1}\tilde{K}^T(t, x_p, x_m)) \\ & \quad + G^{-1}\tilde{K}(t, x_p, x_m)\Gamma^{-1}\tilde{K}^T(t, x_p, x_m) \end{aligned} \quad (50)$$

where $\Gamma \in \mathbb{R}^{n \times n}$ is positive definite adaptation gain and $P_{ad}(x_p, x_m) : \mathbb{R}^{2n} \rightarrow \mathbb{R}^{m \times n}$ is symmetric positive definite matrix and unique solution of (45). The time derivative of $V(e(t), \tilde{K}(t, x_p, x_m))$ along the trajectories (44), (48) and (49) considering Condition 3.8 is as follows;

$$\begin{aligned} \dot{V}(e(t), \tilde{K}(.)) &= \dot{e}^T(t)P_{ad}(x_p, x_m)e(t) + e^T(t)P_{ad}(x_p, x_m)\dot{e}(t) \\ & \quad + \text{tr}(G^{-1}\dot{\tilde{K}}(t, x_p, x_m)\Gamma^{-1}\tilde{K}^T(t, x_p, x_m)) \\ & \quad + G^{-1}\tilde{K}(t, x_p, x_m)\Gamma^{-1}\dot{\tilde{K}}^T(t, x_p, x_m) \\ \dot{V}(e(t), \tilde{K}(.)) &= \dot{e}^T(t)P_{ad}(x_p, x_m)e(t) + e^T(t)P_{ad}(x_p, x_m)\dot{e}(t) \\ & \quad + 2\text{tr}(G^{-1}\dot{\tilde{K}}(t, x_p, x_m)\Gamma^{-1}\tilde{K}^T(t, x_p, x_m)) \\ \dot{V}(e(t), \tilde{K}(.)) &= e^T(t)A_{m_{cl}}^T(x_m)P_{ad}(x_p, x_m)e(t) \\ & \quad - x_p^T(t)\tilde{K}^T(t, x_p, x_m)G^{-1}\hat{B}_p^T(x_p)P_{ad}(x_p, x_m)e(t) \\ & \quad + e^T(t)P_{ad}(x_p, x_m)A_{m_{cl}}(x_m)e(t) \\ & \quad - e^T(t)P_{ad}(x_p, x_m)\hat{B}_p(x_p)G^{-1}\tilde{K}(t, x_p, x_m)x_p(t) \\ & \quad + 2\text{tr}(G^{-1}\dot{\tilde{K}}(t, x_p, x_m)\Gamma^{-1}\tilde{K}^T(t, x_p, x_m)) \\ &= e^T(t)[A_{m_{cl}}^T(x_m)P_{ad}(x_p, x_m) \\ & \quad + P_{ad}(x_p, x_m)A_{m_{cl}}(x_m)]e(t) \\ & \quad - x_p^T(t)\tilde{K}^T(t, x_p, x_m)G^{-1}\hat{B}_p^T(x_p)P_{ad}(x_p, x_m)e(t) \\ & \quad - e^T(t)P_{ad}(x_p, x_m)\hat{B}_p(x_p)G^{-1}\tilde{K}(t, x_p, x_m)x_p(t) \\ & \quad + 2\text{tr}(G^{-1}\dot{\tilde{K}}(t, x_p, x_m)\Gamma^{-1}\tilde{K}^T(t, x_p, x_m)) \\ \dot{V}(e(t), \tilde{K}(.)) &= -e^T(t)Q_{ad}(x_p)e(t) \\ & \quad + 2\text{tr}(G^{-1}\dot{\tilde{K}}(t, x_p, x_m)\Gamma^{-1}\tilde{K}^T(t, x_p, x_m)) \\ & \quad - e^T(t)P_{ad}(x_p, x_m)\hat{B}_p(x_p)G^{-1}\tilde{K}(t, x_p, x_m)x_p(t) \end{aligned}$$

Then by considering the adaptation law (44) and the Lyapunov equation (45), we get

$$\dot{V}(e(t), \tilde{K}(.)) = -e^T(t)Q_{ad}(x_p)e(t) \leq -\lambda_{min}(Q_{ad}(x_p))\|e(t)\|_2^2 \leq 0 \quad (51)$$

where $\lambda_{min}(Q_{ad}(x_p))$ denotes the minimum eigenvalue of the symmetric $Q_{ad}(x_p)$ matrix. Thus, negative semidefinite $\dot{V}(e(t), \tilde{K}(.))$ in (51), yields that the error dynamics (49) is stable and $e(t)$ and $\tilde{K}(t, x_p, x_m)$ are bounded function of time, which conclude the boundedness of $x_p(t)$ and $K_p(t, x_p, x_m)$ that guarantees the boundedness of $\dot{e}(t)$. Furthermore, $\ddot{V}(e(t), \tilde{K}(.)) = -\dot{e}^T(t)Q_{ad}(x_p)e(t) - e^T(t)Q_{ad}\dot{e}(t)$ is uniformly bounded function of time, which implies that $V(e(t), \tilde{K}(.))$ is uniformly continuous. Then, using Barbalat's Lemma one can derive that $\dot{V}(e(t), \tilde{K}(.))$ asymptotically tends to zero as time tends to infinity that implies $\lim_{t \rightarrow \infty} e(t) = 0$. \square

Remark 3.4. We consider the adaptive control problem, similar to SDRE regulation problem of reference model dynamics, from the local stability point of view. Thus, evaluating the SDC matrices, i.e. $A_{m_{cl}}(x_m)$, $A_p(x_p)$, $B_p(x_p)$ and $\hat{B}_p(x_p)$, as well as matrix-valued functions, i.e. $P_{ad}(x_p, x_m)$ and $Q_{ad}(x_p)$, for a given state vectors for plant and reference model dynamics, i.e. x_p and x_m , are reduced to constant matrices obtained from the frozen system at the state vector.

Remark 3.5. In the case of classical model reference adaptive regulation of LTI systems, we solve the adaptation law (28) for any arbitrary initial condition (most of the time zero) in order to determine the control gain matrix, $K_p(t)$. On the other hand, in the SDRE based MRAC, the values of $K_p(t, x_p, x_m)$ at each evaluation are used as a new initial condition for adaptation law (44) to evaluate the next $K_p(t, x_p, x_m)$. Thus, initial conditions for Eq. (44) are updated at each step. In the first step, we use $K_p(t_0, x_p(0), x_m(0)) = K_{p_0} \in \mathbb{R}^{m \times n}$ as an initial condition and then $K_p(t_n, x_p(t_n), x_m(t_n))$ matrix is used as initial condition for the evaluation process of $K_p(t_{n+1}, x_p(t_{n+1}), x_m(t_{n+1}))$. This issue is illustrated in Fig. 1.

Remark 3.6. To determine the $P_{ad}(x_p, x_m)$ matrix using the algebraic Lyapunov equation (45), we can consider constant Q_{ad} matrix as well as state dependent $Q_{ad}(x_p)$ matrix. In both cases, the selected matrix must be positive-definite and symmetric.

Remark 3.7. Despite the classical MRAC approach, in adaptation law (44) the state dependent $\hat{B}_p(x_p)$ matrix is updated at each step with the state vector of x_p . Then the $\hat{B}_p(x_p)$ may be considered as a constant matrix instead of state dependent matrix. Also in algebraic Lyapunov equation (45), the $A_{m_{cl}}(x_m)$ matrix and $Q_{ad}(x_p)$ are state dependent matrices and they are updated in each time instant based on x_m and x_p states. Thus, unlike to classical MRAC approach, $P_{ad}(x_p, x_m)$ is not constant matrix and it is updated in each time instant using state vectors of x_p and x_m .

4. Cancer dynamics with mixed chemo-immunotherapy effects

4.1. System variables

In this section, the mathematical model for cancer dynamics developed by de Pillis et al. [4] for mixed chemo-immunotherapy is 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, comprises tumor dormancy, struggle of cancer and host cells for nutrients and space, unchecked growth of tumor cells and activation effects of cancerous cells on immune cells in the patient's body. The model also considers medical interventions, including chemotherapy and immunotherapy. The multi-population nonlinear model that reflects all these considerations includes the following cell populations and drug concentrations in the blood stream at time t .

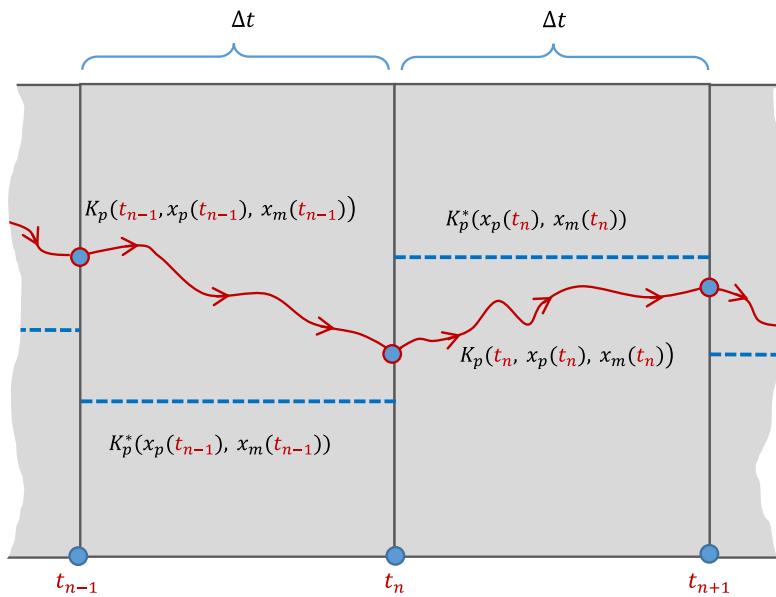


Fig. 1. Updating of initial conditions in SDRE based MRAC at each step (Remark 3.5).

- $T(t)$, the total tumor cell population,
- $N(t)$, the total of Natural Killer (NK) cell population,
- $L(t)$, the total of CD8⁺T cell population,
- $C(t)$, the total of lymphocytes (white blood) cell population,
- $M(t)$, chemotherapy drug concentration in bloodstream,
- $I(t)$, immunotherapy drug concentration in bloodstream.

4.2. The immune system of body and framework of immunotherapy

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

- **Nonspecific immunity**, also known as *innate immunity*, is the body's first and immediate defense line against all pathogens. There are distinct types of non-specific immunity in our body which begin by our skin as the first barrier against various bacteria, viruses, and pathogens. Also, different cells in body belong to non-specific immune system. NK cells are part of the non-specific immune system that belongs to white blood cells. NK cells circulate the whole body through the blood stream or lymph system to find and destroy all cells that do not similar host cells. Thus, NK cells attack all strange cells in the body and not specific ones.
- **Specific immunity**, also known as *adaptive immunity*, such as CD8⁺T cells, also known as cytotoxic T-cells or CTL, which must prepare and activate before attacking foreign cells. Preparing procedure is done inside of lymph nodes with antigens. Thus, the specific immune system activates with antigens to attack particular pathogens and specific types of foreign cells and it needs time, some kind of lag-time, to respond. Helper T-cells, cytotoxic T-cells and B-cells belong to the specific immune system. Specific immunity also contains memory T-cells that memorize the foreign cells to respond faster if they enter the body next time.

In immunotherapy, the immune system of a patient is boosted and eradication of tumor cells carries out totally by the boosted immune system. Strengthening of the immune response of the body may be accomplished by the following methodologies.

• IL-2 (interleukin 2) growth factor injection

In the body, naturally CD4⁺T cells secrete the cytokine interleukin 2 (IL-2) as a growth factor of CD8⁺T cells. IL-2 stimulates the production of CD8⁺T cells. In addition to normally produced by the body, therapeutic injection of IL-2 causes enhancement in the population of CD8⁺T cells, which destroy tumor cells without affecting normal cells.

• TIL (tumor-infiltrating lymphocytes) injection

For boosting immune cells, CD8⁺T cells removed from the cancer patient's body and then cultivate and are activated in vitro. Then highly activated CD8⁺T cells re-inject into the patient's bloodstream or tumor area. Indeed, by imitated enrichment of the immune system, the patient immune system is aided to eradicate tumor cells.

4.3. Model formulation

The cancer dynamics, which is presented by the coupled multi population equation, 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, all cells compete for space and nutrients and tumor cell population grows logistically in the absence of an immune response. NK cells are the part of the innate immune response and CD8⁺T cells are the part of the specific immune response. NK cells always present in the body, but CD8⁺T cells exist meaningfully only in the presence of tumor cells in the body [5]. Both NK and CD8⁺T cells kill tumor cells and become inert after a conflict with tumor cells. The Circulating lymphocyte (also known as white blood) levels reflect the patients' health. Since lymphocyte cells contribute in the production of the antibody and NK cells attack cells to which antibody has attached. This model includes chemotherapy and immunotherapy interventions. In chemotherapy, anticancer drug leads fraction kills of tumor cells. Since chemotherapy able to kill cancer cells in a certain stage of development, then fraction killed has a saturation point. As an undesired effect of an anti-cancer drug, some population of NK and CD8⁺T cells and circulating lymphocytes are also killed by chemotherapy. NK and tumor cells influence the stimulation and the elimination of activated effector cells.

Table 1

Description of the terms used in the mathematical equations [4].

	Description	Terms	Equation
Growth and death	Tumor growth is considered by a logistic term in the absence of an immune response For CD8 ⁺ T cells only natural death rate is considered and the CD8 ⁺ T cells exist when the tumor cells are present in the body.	$aT(1 - bT)$ $-mL$	dT/dt dL/dt
	NK cells growth term depends on population of circulating lymphocytes, which reflects the immune health levels, and extirpation of NK cells with chemotherapy.	$eC - fN$	dN/dt
	Circulating lymphocytes grow at a constant rate and die after natural lifetime.	$\alpha - \beta C$	dC/dt
	Chemotherapy drug concentration in the bloodstream decreases by an exponential decay term that proportional to its concentration in the bloodstream.	$-\gamma M$	dM/dt
	Immunotherapy drug concentration in the bloodstream decrease by exponential decay term that proportional to its concentration in the bloodstream.	$-\mu I$	dI/dt
Fractional cell kill	Tumor and NK cells struggle for the limited space and nutrients.	$-cNT$	dT/dt
	Tumor cell population decline by CD8 ⁺ T cells	$-DT (*)$	dT/dt
	The chemotherapy drug is effective during certain phases of the cell cycle and saturation term, i.e. $1 - e^{-M}$, for chemotherapy fractional cell kill for tumor, NK, CD8 ⁺ T and circulating lymphocytes have been considered.	$-k_T(1 - e^{-M})T$ $-k_N(1 - e^{-M})N$ $-k_L(1 - e^{-M})L$ $-k_C(1 - e^{-M})C$ $\frac{pLI}{g_I + I}$	dT/dt dN/dt dL/dt dC/dt dL/dt
	The production of CD8 ⁺ T cells in the immune system is related to the presence of IL-2 that is naturally occurring cytokine in the body and may be injected externally as an immunotherapy drug for stimulating production of CD8 ⁺ T		
Recruitment	NK cells recruitment term that is a modified Michaelis–Menten term, which is described the tumor–natural killer cell interactions	$g \frac{T^2}{h + T^2} N$	dN/dt
	CD8 ⁺ T cells be activated by the fraction of lysate tumor cells by other CD8 ⁺ T cells	$j \frac{D^2 T^2}{k + D^2 T^2} L *$	dL/dt
	CD8 ⁺ T cells recruitment by the lysate tumor cells by NK cells	$r_1 NT$	dL/dt
Inactivation	Presence of tumor cells, stimulate the immune system to produce CD8 ⁺ T cells.	$r_2 CT$	dL/dt
	Identification of the number of tumor cells is based on the struggles number between circulating lymphocytes and the tumor.		
Drug intervention	Inactivation of NK cell because of encounter with tumor cells	$-pNT$	dN/dt
	Inactivation of CD8 ⁺ T cell because of encounter with tumor cells	$-qLT$	dL/dt
	Regulation and suppression of excessive activated CD8 ⁺ T cells	$-uNL^2$	dL/dt
	The TIL drug intervention term for CD8 ⁺ T cell population which indicates the number of activated CD8 ⁺ T cells injected per day per liter of blood volume (in cells/L per day)	$v_L(t)$	dL/dt
	The chemotherapy drug intervention term which indicates the amount of anti-cancer drug injected per day per liter of body volume (in mg/L per day)	$v_M(t)$	dM/dt
	The immunotherapy drug intervention term which indicates the amount of IL-2 injected per day per liter of body volume (in IU/L per day).	$v_I(t)$	dI/dt

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

Recruitment of CD8⁺T cells is stimulated by IL-2, which presents in the immune system naturally and can be injected as a drug intervention in immunotherapy [5]. All these explanations are defined by mathematical equations and summarized all in Table 1.

These assumptions and considerations lead to the following multi-population nonlinear dynamics in the presence of mixed immunotherapy and chemotherapy drug interventions.

$$\dot{T} = aT(1 - bT) - cNT - DT - k_T(1 - e^{-M})T \quad (52)$$

$$\dot{N} = eC - fN + g \frac{T^2}{h + T^2} N - pNT - k_N(1 - e^{-M})N \quad (53)$$

$$\begin{aligned} \dot{L} &= -mL + j \frac{D^2 T^2}{k + D^2 T^2} L - qLT + (r_1 N + r_2 C)T - uNL^2 \\ &\quad - k_L(1 - e^{-M})L + \frac{pLI}{g_I + I} + v_L(t) \end{aligned} \quad (54)$$

$$\dot{C} = \alpha - \beta C - k_C(1 - e^{-M})C, \quad (55)$$

$$\dot{M} = -\gamma M + v_M(t), \quad (56)$$

$$\dot{I} = -\mu I + v_I(t) \quad (57)$$

$$D = d \frac{(L/T)^l}{s + (L/T)^l} \quad (58)$$

The proposed cancer dynamics mathematical model in (52)–(58) contains 24 different constant positive parameters, which are

highly dependent on the patient. Two parameter sets for two different patients are specified by de Pillis et al. for the so-called “patient 9” and “patient 10” in [4]. The parameters are estimated based on fitting clinical data results. In this study, these parameter sets are utilized in the simulations of the proposed personalized drug administration scenarios. These parameter values and related explanations are presented in Appendix A for the sake of completeness.

4.4. Equilibrium points analysis of the drug free system

In order to analyze the equilibrium points of the cancer dynamics and the stability of each equilibrium point, we consider the cancer dynamic without medical interventions. Thus, we remove all three drug intervention, i.e. $v_L(t)$, $v_M(t)$ and $v_I(t)$, and their effects from the cancer dynamic in (52)–(58) that yields the following four population cancer dynamic;

$$\dot{T} = aT(1 - bT) - cNT - DT \quad (59)$$

$$\dot{N} = eC - fN + g \frac{T^2}{h + T^2} N - pNT \quad (60)$$

$$\dot{L} = -mL + j \frac{D^2 T^2}{k + D^2 T^2} L - qLT + (r_1 N + r_2 C)T - uNL^2 \quad (61)$$

$$\dot{C} = \alpha - \beta C \quad (62)$$

where D is given in (58).

To explore the local stability of cell population dynamics in equilibrium points, we construct the Jacobian matrix of the system in (T, N, L, C) point. The Jacobian matrix is then formed as,

$$J = \begin{bmatrix} a - 2abT - cN - \Phi_1 & -cT & -\frac{d TL^{l-1} T^{l+1}}{(sT^l + L^l)^2} & 0 \\ \frac{2gTN}{(h+T^2)^2} - pN & \frac{gT^2}{h+T^2} - pT - f & 0 & e \\ \Phi_2 + r_1 N + r_2 C - qL & r_1 T - uL^2 & \Phi_3 - 2uNL - qT - m & r_2 T \\ 0 & 0 & 0 & -\beta \end{bmatrix}$$

where,

$$\begin{aligned} \Phi_1 &= \frac{d(L^2l + s(1-l)L^l T^l)}{(sT^l + L^l)^2} \\ \Phi_2 &= \frac{2jkd^2TL^{4l+1} + 2(1-l)jks^2d^2T^{2l+1}L^{2l+1} + 2(2-l)jksd^2T^{l+1}L^{3l+1}}{(ks^2T^{2l} + kL^{2l} + 2ksT^lL^l + d^2L^{2l}T^2)^2} \\ \Phi_3 &= \frac{j d^4 T^4 L^{4l} + jkd^2 T^2 L^{4l} + (2l+1) jkd^2 s^2 T^{2l+2} L^{2l} + (2l+1) jksd^2 T^{l+2} L^{3l}}{(ks^2T^{2l} + kL^{2l} + 2ksT^lL^l + d^2L^{2l}T^2)^2} \end{aligned}$$

4.4.1. Tumor-free equilibrium

In order to determine tumor-free equilibrium point, Eq. (59) is assumed to have equilibria at $T_{E_T} = 0$ (tumor-free). On the other hand, Eq. (62) decouples from the other set of equations. Therefore, simply the only equilibrium point of circulating lymphocytes can be determined as $C_{E_T} = \alpha/\beta$. Also, NK cells equilibrium point could be determined by substituting T_{E_T} , C_{E_T} into Eq. (60) that yields $N_{E_T} = e\alpha/f\beta$.

To determine the equilibrium point of CD8⁺T cells related to tumor-free equilibria, considering Eq. (61) together with T_{E_T} , C_{E_T} and N_{E_T} yields

$$-mL_{E_T} - u\frac{e\alpha}{f\beta}L_{E_T}^2 = 0 \quad (63)$$

Then, the second order equation Eq. (63) yields two distinct equilibrium points;

$$L_{E_T} = \begin{cases} 0 \\ -mf\beta/ue\alpha \end{cases}$$

Since all model parameters are positive, $-mf\beta/ue\alpha$ is a negative value and it is not acceptable from a biological point of view. Therefore, the desired tumor-free equilibrium point is

$$E_T = (T_{E_T}, N_{E_T}, L_{E_T}, C_{E_T}) = \left(0, \frac{e\alpha}{f\beta}, 0, \frac{\alpha}{\beta}\right) \quad (64)$$

The treatment procedure, using chemo and immunotherapy protocols, is expected to drive the system to this tumor-free equilibrium point. To survey the local stability of tumor-free equilibrium point, linearized Jacobian around this equilibrium point, i.e. E_T , is given by

$$J|_{E_T} = \begin{bmatrix} a - \frac{ce\alpha}{f\beta} & 0 & 0 & 0 \\ -\frac{pe\alpha}{f\beta} & -f & 0 & e \\ \frac{e\alpha r_1}{f\beta} + \frac{\alpha r_2}{\beta} & 0 & -m & 0 \\ 0 & 0 & 0 & -\beta \end{bmatrix}$$

The eigenvalues of the linearized system around tumor-free equilibrium points are

$$\lambda_1 = -\beta, \lambda_2 = -m, \lambda_3 = -f, \lambda_4 = a - \frac{ce\alpha}{f\beta}.$$

As all parameters are positive values, the λ_1 , λ_2 and λ_3 are negative eigenvalues. For local stability, all eigenvalues of the system must be negative. Thus, for λ_4 we have $a - \frac{ce\alpha}{f\beta} < 0$ which yields $< \frac{ce\alpha}{f\beta}$.

Remark 4.1. By considering the estimated parameter values in Table 2, $a < ce\alpha/f\beta$ is not satisfied and tumor free equilibrium

point is unstable for both patients. Therefore, solo chemotherapy is not sufficient to survive the patient. Since the tumor-free equilibrium point is unstable by stopping treatment after eradication of the tumor burden, the system comes back to coexisting equilibrium points. Consequently, for both patients 9 and 10 immunotherapy treatment is necessary for permanently boosting the cytolytic potential of the NK cells (for details see [4]).

4.4.2. Coexisting equilibrium

Similar to the tumor-free equilibrium point, the cancer nonlinear dynamics may have coexisting equilibria, when tumor cells exist besides host cells. Coexisting equilibrium points may be considered as tumor dormancy condition in cancer treatment [4]. Therefore, it is essential to analyze coexisting equilibria. To achieve coexisting equilibria, we shall solve (59)–(62) when all equations simultaneously are equal to zero. Since (62) is decoupled from the other three equations, similar to tumor free equilibria, the circulating lymphocyte equilibrium point beyond the populations of other cells is $C_{E_c} = \alpha/\beta$. Then we encounter the following three equations;

$$\begin{cases} \dot{N} = 0 \\ \dot{T} = 0 \\ \dot{L} = 0 \end{cases} \Rightarrow \begin{cases} a(1 - bT_{E_c}) - cN_{E_c} - D_{E_c} = 0 \\ eC_{E_c} - fN_{E_c} + g\frac{T_{E_c}^2}{h+T_{E_c}^2}N_{E_c} - pN_{E_c}T_{E_c} = 0 \\ -mL_{E_c} + j\frac{D_{E_c}^2 T_{E_c}^2}{k+D_{E_c}^2 T_{E_c}^2}L_{E_c} - qL_{E_c}T_{E_c} + (r_1 N_{E_c} + r_2 C_{E_c})T_{E_c} \\ -uN_{E_c}L_{E_c}^2 = 0 \end{cases} \quad (65)$$

where

$$D_{E_c} = \frac{d\left(\frac{L_{E_c}}{T_{E_c}}\right)^l}{s + \left(\frac{L_{E_c}}{T_{E_c}}\right)^l} \text{ and } C_{E_c} = \alpha/\beta.$$

Now using the second equation in (65), we can derive the N_{E_c} based on T_{E_c}

$$N_{E_c} = \frac{e\alpha}{\beta} \frac{h + T_{E_c}^2}{fh + hpT_{E_c} + (f - g)T_{E_c}^2 + pT_{E_c}^3} \quad (66)$$

On the other hand, considering first and third equations with the value of D_{E_c} , two different equations for L_{E_c} , are obtained which are solved simultaneously. The intersection of the solutions of these two equations determines the equilibrium point/points of

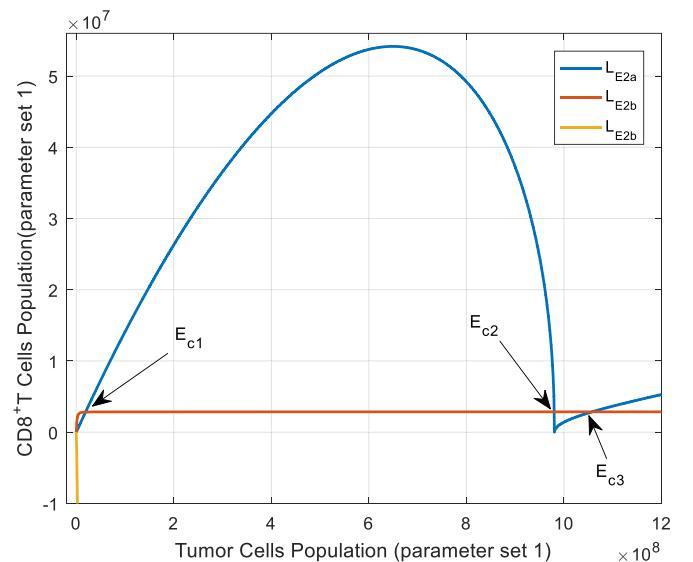


Fig. 2. Numerical solution and intersections of Eq. (67) for coexisting equilibrium points of patient 9 with parameter set 1.

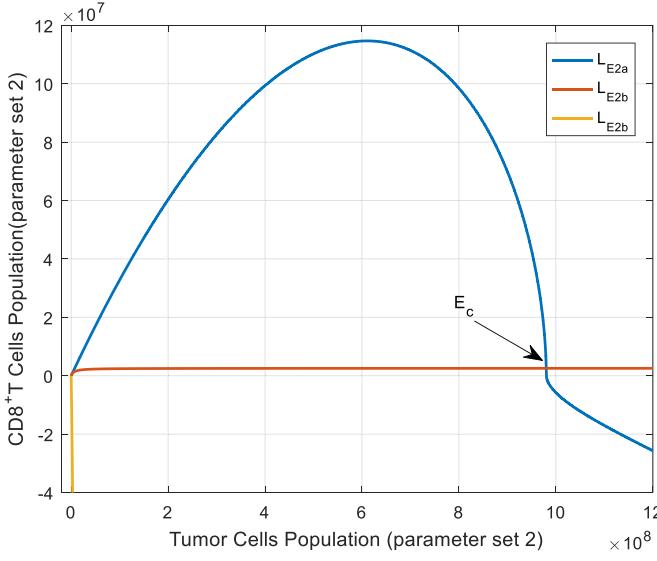


Fig. 3. Numerical solution and intersection of Eq. (67) for Coexisting equilibrium point of patient 10 with parameter set 2.

the CD8⁺T cells in coexisting equilibria.

$$\begin{cases} L_{E_c} = \left(\frac{sD_{E_c}}{d-D_{E_c}} \right)^{\frac{1}{l}} T_{E_c} \\ L_{E_c}^2 + \frac{1}{uN_{E_c}} \left(m + qT_{E_c} - \frac{j(a-abT_{E_c}-cN_{E_c})^2 T_{E_c}^2}{k+(a-abT_{E_c}-cN_{E_c})^2 T_{E_c}^2} \right) L_{E2} - \frac{T_{E_c}}{uN_{E_c}} \left(r_1 N_{E_c} + \frac{\alpha r_2}{\beta} \right) = 0 \end{cases} \quad (67)$$

Since analytically determining of coexisting equilibrium points of the system is so sophisticated task, we solve these two equations for both parameters sets given in Table 2 numerically for both patient 9 and patient 10. The numerical solutions of (67) for patient 9 and patient 10 are pictured in Figs. 2 and 3, respectively. As Fig. 2 shows, patient 9 cancer dynamics has three distinct coexisting equilibrium points, i.e. E_{ci} , $i = 1, 2, 3$, as follows

$$\text{Coexisting Equilibria} \begin{cases} E_{c1} = [T_{E_{c1}}, N_{E_{c1}}, L_{E_{c1}}, C_{E_{c1}}] = [1.906 \times 10^7, 199.3440, 2.825 \times 10^6, 6.250 \times 10^{10}] \\ E_{c2} = [T_{E_{c2}}, N_{E_{c2}}, L_{E_{c2}}, C_{E_{c2}}] = [9.801 \times 10^8, 3.8783, 2.860 \times 10^6, 6.250 \times 10^{10}] \\ E_{c3} = [T_{E_{c3}}, N_{E_{c3}}, L_{E_{c3}}, C_{E_{c3}}] = [1.058 \times 10^9, 3.5928, 2.860 \times 10^6, 6.250 \times 10^{10}] \end{cases}$$

Also, Fig. 3 shows that for cancer dynamics of patient 10, there is a unique coexisting equilibrium point, given by

$$\begin{aligned} E_c &= [T_{E_c}, N_{E_c}, L_{E_c}, C_{E_c}] \\ &= [9.801 \times 10^8, 2.5402 \times 10^6, 3.6947, 6.250 \times 10^{10}] \end{aligned}$$

5. Personalized mixed therapy for unknown patient based on reference patient

5.1. SDRE-based drug delivery for mixed therapy for cancer treatment of reference patient

The objective in the cancer treatment is to drive the system to the tumor-free equilibrium point by administering the appropriate dose of drug with correct administration periodicity in the treatment duration. To determine this sub-optimal drug delivery protocol, we use the SDRE methodology. We assume that all 24 parameters for the reference patient are known in the control design procedure. Since the cancer dynamics does not satisfy Condition 2.1, i.e. $f(0) \neq 0$, by defining error states, the equilibrium point of the system (61)–(67) is shifted to the origin (for details refer to [31]).

$$x_{m_1} \triangleq T, \quad x_{m_2} \triangleq N - \frac{e\alpha}{f\beta}, \quad x_{m_3} \triangleq L, \quad x_{m_4} \triangleq C - \frac{\alpha}{\beta}, \quad x_{m_5} \triangleq M, \quad x_{m_6} \triangleq I \quad (68)$$

The new state vector $[x_{m_1} \ x_{m_2} \ x_{m_3} \ x_{m_4} \ x_{m_5} \ x_{m_6}]^T$ contains the error states and the set of ODEs (52)–(58) can be defined in the new coordinates, based on error states. In the new set of equations we encounter with the term $e^{-x_{m_5}}$. As this term is a state-dependent term, and $1 - e^{-x_{m_5}}$ includes the origin, to overcome this difficulty the following expression is considered

$$R \triangleq \frac{e^{-x_{m_5}} - 1}{x_{m_5}} \quad (69)$$

Therefore $\lim_{x_{m_1} \rightarrow 0} R = -1$ (for details refer to [31]). Then the new set of ODEs is given by

$$\begin{aligned} \dot{x}_{m_1} &= a(1 - bx_{m_1})x_{m_1} - cx_{m_1}x_{m_2} - \frac{ce\alpha}{f\beta}x_{m_1} \\ &\quad - \frac{dx_{m_3}^{l-1}}{sx_{m_1}^l + x_{m_3}^l}x_{m_1}x_{m_3} + k_T Rx_{m_1}x_{m_5} \end{aligned} \quad (70)$$

$$\begin{aligned} \dot{x}_{m_2} &= ex_{m_4} - fx_{m_2} + g \frac{x_{m_1}^2 x_{m_2}}{h + x_{m_1}^2} + \frac{ge\alpha}{f\beta} \frac{x_{m_1}^2}{h + x_{m_1}^2} - px_{m_1}x_{m_2} \\ &\quad - \frac{pe\alpha}{f\beta}x_{m_1} + k_N Rx_{m_2}x_{m_5} + \frac{k_N Re\alpha}{f\beta}x_{m_5} \end{aligned} \quad (71)$$

$$\begin{aligned} \dot{x}_{m_3} &= -mx_{m_3} + j \frac{D^2 x_{m_1}^2}{k + D^2 x_{m_1}^2} x_{m_3} - qx_{m_3}x_{m_1} \\ &\quad + \left(r_1 \left(x_{m_2} + \frac{e\alpha}{f\beta} \right) + r_2 \left(x_{m_4} + \frac{\alpha}{\beta} \right) \right) x_{m_1} - u \left(x_{m_2} + \frac{e\alpha}{f\beta} \right) x_{m_3}^2 \\ &\quad + k_L Rx_{m_5}x_{m_3} + \frac{p_l x_{m_3}x_{m_6}}{g_l + x_{m_6}} + v_L(t) \end{aligned} \quad (72)$$

$$\begin{aligned} \dot{x}_{m_4} &= -\beta x_{m_4} + k_C Rx_{m_4}x_{m_5} + \frac{\alpha k_C k_5}{\beta} x_{m_5} \\ \dot{x}_{m_5} &= -\gamma x_{m_5} + v_M(t) \end{aligned} \quad (73) \quad (74)$$

$$\dot{x}_{m_6} = -\mu_l x_{m_6} + v_l(t) \quad (75)$$

$$D = d \frac{(x_{m_3}/x_{m_1})^l}{s + (x_{m_3}/x_{m_1})^l} \quad (76)$$

Now one can factorize the nonlinear system of (70)–(75) into a linear-like structure with SDC matrices in the form of

$$\dot{x}_m = A_m(x_m, \theta)x_m + B_m u_m$$

where the SDC matrices using the free θ vector (see Section 2.1.1) is as follows

$$A_m(x_m, \theta) = \begin{bmatrix} a_{m_{11}} & a_{m_{12}} & a_{m_{13}} & 0 & a_{m_{15}} & 0 \\ a_{m_{21}} & a_{m_{22}} & 0 & e & a_{m_{25}} & 0 \\ a_{m_{31}} & a_{m_{32}} & a_{m_{33}} & a_{m_{34}} & a_{m_{35}} & a_{m_{36}} \\ 0 & 0 & 0 & a_{m_{44}} & a_{m_{45}} & 0 \\ 0 & 0 & 0 & 0 & -\gamma & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_I \end{bmatrix},$$

$$B_m = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \quad (77)$$

where

$$\begin{aligned} a_{m_{11}} &= a(1 - bx_{m_1}) - \frac{ce\alpha}{f\beta} - c\theta_1x_{m_2} + k_T R\theta_2x_{m_5} - \frac{dx_{m_3}^{l-1}}{sx_{m_1}^l + x_{m_3}^l}\theta_3x_{m_3} \\ a_{m_{12}} &= -c(1 - \theta_1)x_{m_1} \\ a_{m_{13}} &= -\frac{dx_{m_3}^{l-1}}{sx_{m_1}^l + x_{m_3}^l}(1 - \theta_3)x_{m_1} \\ a_{m_{15}} &= k_T R(1 - \theta_2)x_{m_1} \\ a_{m_{21}} &= -p\theta_4x_{m_2} - \frac{pe\alpha}{f\beta} + g\theta_6 \frac{x_{m_1}x_{m_2}}{h + x_{m_1}^2} + \frac{ge\alpha}{f\beta} \frac{x_{m_1}}{h + x_{m_1}^2} \\ a_{m_{22}} &= -f - p(1 - \theta_4)x_{m_1} + k_N R\theta_5x_{m_5} + g(1 - \theta_6) \frac{x_{m_1}^2}{h + x_{m_1}^2} \\ a_{m_{25}} &= k_N k_5(1 - \theta_5)x_{m_2} + \frac{k_N Re\alpha}{f\beta} \\ a_{m_{31}} &= -q\theta_7x_{m_3} + r_1\theta_{11}x_{m_2} + \frac{r_1e\alpha}{f\beta} + r_2\theta_{12}x_{m_4} + \frac{r_2\alpha}{\beta} \\ &\quad + \theta_{13} \frac{jd^2x_{m_3}^{2l}}{k(sx_{m_1}^l + x_{m_3}^l)^2 + d^2x_{m_3}^{2l}}x_{m_1} \\ a_{m_{32}} &= -u\theta_{10}x_{m_3}^2 + r_1(1 - \theta_{11})x_{m_1} \\ a_{m_{33}} &= -m - q(1 - \theta_7)x_{m_1} + k_L R\theta_8x_{m_5} + \frac{p_l\theta_9x_{m_6}}{g_l + x_{m_6}} \\ &\quad - u(1 - \theta_{10})x_{m_2}x_{m_3} - \frac{ue\alpha}{f\beta}x_{m_3} \\ &\quad + (1 - \theta_{13}) \frac{jd^2x_{m_3}^{2l}}{k(sx_{m_1}^l + x_{m_3}^l)^2 + d^2x_{m_3}^{2l}} \\ a_{m_{34}} &= r_2(1 - \theta_{12})x_{m_1} \\ a_{m_{35}} &= k_L R(1 - \theta_8)x_{m_3} \\ a_{m_{36}} &= \frac{p_l(1 - \theta_9)x_{m_3}}{g_l + x_{m_6}} \\ a_{m_{44}} &= -\beta + k_c R\theta_{14}x_{m_5} \\ a_{m_{45}} &= k_c R(1 - \theta_{14})x_{m_4} + \frac{\alpha k_c R}{\beta} \end{aligned}$$

The parameter vector $\theta \in \mathbb{R}^{14}$ is selected from the pointwise stability point of view for the $\{A_m(x_m, \theta), B_m\}$ pair. Assuming that, $\theta_i \in [0, 0.5, 1]$, $i = 1, 2, \dots, 14$, 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 $|\det(M_c(x_m))|$, and consequently the largest pointwise controllable space for the pair $\{A_m(x_m, \theta), B_m\}$, is achieved using the following θ vector (for details refer to [31]).

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

5.1.1. Constrained drugs dosage for reference patient

To avoid toxicity and other fatal side effects, the following constraints are imposed for drug dose of chemotherapy as well as ad-

ministrated TIL and IL-2 in treatment [4]:

$$\begin{cases} 0 \leq v_L(t) \leq 10^9 \\ 0 \leq v_M(t) \leq 5 \\ 0 \leq v_I(t) \leq 5 \times 10^5 \end{cases} \quad (78)$$

To apply these hard bounds to controls, the constrained input is modeled as a saturation nonlinearity, which is defined by

$$Sat(u_m, u_{m(max)}) \triangleq \begin{cases} u_{m(max)}, & u_m > u_{m(max)} \\ u_m, & 0 < u_m \leq u_{m(max)} \\ 0, & u_m < 0 \end{cases} \quad (79)$$

Then input-constrained nonlinear optimal control problem of cancer dynamics is represented as

$$\dot{x}_m = A_m(x_m, \theta)x_m + B_m Sat(u_m, u_{m(max)}) \quad (80)$$

$$J = \frac{1}{2} \int_0^\infty \left\{ x_m^T(t)Q(x_m)x_m(t) + (Sat(u_m, u_{m(max)}))^T \right. \\ \left. \times R(x_m)(Sat(u_m, u_{m(max)})) \right\} dt \quad (81)$$

As hard bounds cause nonlinearity in the control, integral control is utilized, as mentioned in Section 2.1.2. Then, the control inputs of $v_L(t)$, $v_M(t)$ and $v_I(t)$ are considered as three new augmented states, i.e. $\dot{v}_L = \tilde{u}_{m_1}$, $\dot{v}_M = \tilde{u}_{m_2}$ and $\dot{v}_I = \tilde{u}_{m_3}$ and consequently augmented system states are given by

$$\tilde{x}_m^T = [x_{m_1} \ x_{m_2} \ x_{m_3} \ x_{m_4} \ x_{m_5} \ x_{m_6} \ v_L \ v_M \ v_I] \quad (82)$$

Then, the augmented system with 9 states, i.e. $\tilde{x}_m \in \mathbb{R}^9$, is constructed as follows

$$\dot{\tilde{x}}_m = \tilde{A}_m(\tilde{x}_m, \theta)\tilde{x}_m + \tilde{B}_m \tilde{u}_m \quad (83)$$

The family of SDC parameterization for $\tilde{A}_m(\tilde{x}_m, \theta)$ and \tilde{B}_m can be constructed as follows;

$$\begin{aligned} \tilde{A}_m(\tilde{x}_m, \theta) &= \begin{bmatrix} a_{m_{11}} & a_{m_{12}} & a_{m_{13}} & 0 & a_{m_{15}} & 0 & 0 & 0 & 0 \\ a_{m_{21}} & a_{m_{22}} & 0 & e & a_{m_{25}} & 0 & 0 & 0 & 0 \\ a_{m_{31}} & a_{m_{32}} & a_{m_{33}} & a_{m_{34}} & a_{m_{35}} & a_{m_{36}} & v_1 & 0 & 0 \\ 0 & 0 & 0 & a_{m_{44}} & a_{m_{45}} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\gamma & 0 & 0 & v_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu & 0 & 0 & v_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \\ \tilde{B}_m &= \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \quad (84) \end{aligned}$$

where

$$v_1 \triangleq \frac{Sat(v_L, 10^9)}{v_L}, \quad v_2 \triangleq \frac{Sat(v_M, 5)}{v_M} \text{ and } v_3 \triangleq \frac{Sat(v_I, 5 \times 10^5)}{v_I}$$

Therefore, the augmented cancer dynamics is as follows,

$$\begin{bmatrix} \dot{x}_{m_1} \\ \dot{x}_{m_2} \\ \dot{x}_{m_3} \\ \dot{x}_{m_4} \\ \dot{x}_{m_5} \\ \dot{x}_{m_6} \\ \dot{v}_L \\ \dot{v}_M \\ v_I \end{bmatrix} = \begin{bmatrix} a_{m_{11}} & a_{m_{12}} & a_{m_{13}} & 0 & a_{m_{15}} & 0 & 0 & 0 & 0 \\ a_{m_{21}} & a_{m_{22}} & 0 & e & a_{m_{25}} & 0 & 0 & 0 & 0 \\ a_{m_{31}} & a_{m_{32}} & a_{m_{33}} & a_{m_{34}} & a_{m_{35}} & a_{m_{36}} & v_1 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_{m_{44}} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma' & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu & 0 & v_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ \tilde{u}_{m_1} \\ \tilde{u}_{m_2} \\ \tilde{u}_{m_3} \end{bmatrix} \quad (85)$$

In (85), the $\tilde{u}_m = [\tilde{u}_{m_1} \quad \tilde{u}_{m_2} \quad \tilde{u}_{m_3}]^T$ is the control that stabilizes the augmented system.

5.1.2. Constrained circulating lymphocyte population for reference patient

In order to avoid weakness of the immune system of the patient, we desire the circulating lymphocyte population of the reference patient to keep above 10^6 cells. Hence we apply hard constraint of $C(t) \geq 10^6$ to the circulating lymphocyte population. Thus, $\psi = \{\tilde{x}_m \in \mathbb{R}^9 : C(t) \geq 10^6\}$ is the allowable circulating lymphocyte population sets and $h(x_{m_4}) = 10^6 - C(t)$. For the shifted

$$\left(\frac{\partial h(x_{m_4})}{\partial \tilde{x}_m} \right) \tilde{A}_m(\tilde{x}_m, \theta) = [0_{1 \times 3}, \beta, -k_c R x_{m_4} - \alpha k_c R / \beta, 0_{1 \times 4}] \quad \text{and}$$

$$D(\tilde{x}_m) \triangleq \left(\frac{\partial h(x_{m_4})}{\partial \tilde{x}_m} \right) \tilde{B}_m = [0_{1 \times 3}].$$

Then desired nonlinear feedback control \tilde{u}_m to keep circulating lymphocyte population in an allowable range, could be achieved by considering a state dependent nonlinear regulator problem which minimizes the cost function of $J_\psi = \frac{1}{2} Z^T W(\tilde{x}_m) Z$, $W(\tilde{x}_m) > 0$, subject to (94). That is,

$$J_\psi = \frac{1}{2} \int_0^\infty \{C(\tilde{x}_m)\tilde{x}_m + D(\tilde{x}_m)\tilde{u}_m\}^T W(\tilde{x}_m) \{C(\tilde{x}_m)\tilde{x}_m + D(\tilde{x}_m)\tilde{u}_m\} dt$$

By considering $Q_\psi(\tilde{x}_m) \triangleq C^T(\tilde{x}_m)W(\tilde{x}_m)C(\tilde{x}_m)$, $R_\psi(\tilde{x}_m) \triangleq D^T(\tilde{x}_m)W(\tilde{x}_m)D(\tilde{x}_m)$ and $S_\psi(\tilde{x}_m) \triangleq C^T(\tilde{x}_m)W(\tilde{x}_m)D(\tilde{x}_m)$ we have

$$J_\psi = \frac{1}{2} \int_0^\infty \{ \tilde{x}_m^T Q_\psi(\tilde{x}_m) \tilde{x}_m + 2\tilde{x}_m^T S_\psi(\tilde{x}_m) \tilde{u}_m + \tilde{u}_m^T R_\psi(\tilde{x}_m) \tilde{u}_m \} dt,$$

by considering $\varepsilon_1 = 0.1$ and $N = 210$ for cancer problem, we have $\phi(x_{m_4}) = 1/(\|h(x_{m_4})\|_2 + 0.1)^{420}$. Consequently, $W(\tilde{x}_m) = \phi(x_{m_4}) = 1/(\|h(x_{m_4})\|_2 + 0.1)^{420}$ and we have

$$Q_\psi(\tilde{x}_m) \triangleq \begin{bmatrix} 0_{3 \times 1} \\ \beta \\ -k_c R x_{m_4} - \frac{\alpha k_c R}{\beta} \\ 0_{4 \times 1} \end{bmatrix} \frac{1}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} \begin{bmatrix} 0_{3 \times 1} \\ \beta \\ -k_c R x_{m_4} - \frac{\alpha k_c R}{\beta} \\ 0_{4 \times 1} \end{bmatrix}^T$$

Then

$$Q_\psi(\tilde{x}_m) \triangleq \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta^2}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} & \frac{-\beta(k_c R x_{m_4} + \frac{\alpha k_c R}{\beta})}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{-\beta(k_c R x_{m_4} + \frac{\alpha k_c R}{\beta})}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} & \frac{(k_c R x_{m_4} + \frac{\alpha k_c R}{\beta})^2}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$R_\psi(\tilde{x}_m) \triangleq D^T(\tilde{x}_m)W(\tilde{x}_m)D(\tilde{x}_m) = 0_{3 \times 3}$$

$$S_\psi(\tilde{x}_m) \triangleq C^T(\tilde{x}_m)W(\tilde{x}_m)D(\tilde{x}_m) = 0_{9 \times 3}$$

Thus, minimization of the following cost function by singular regulator guarantees that x_{m_4} remains in the set ψ .

$$J_\psi(\tilde{x}_m, \tilde{u}_m) = \frac{1}{2} \int_0^\infty \frac{1}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} \times \left\{ x_{m_4} \beta + x_{m_5} \left(-k_c R x_{m_4} - \frac{\alpha k_c R}{\beta} \right) \right\}^2 dt \quad (87)$$

However, regulation objective is to drive the states to a desired equilibrium while remaining in the set ψ . Driving the states to the desired equilibrium point, here is a origin, can be achieved by minimizing the augmented cost functional $J = J_0 + J_\psi$ where $J_\psi(\tilde{x}_m, \tilde{u}_m)$ is defined in (87), and $J_0 = \int_0^\infty \{\tilde{x}_m^T Q_0(\tilde{x}_m) \tilde{x}_m + \tilde{u}_m^T R_0(\tilde{x}_m) \tilde{u}_m\} dt$, Then

$$J(\tilde{x}_m, \tilde{u}_m) = \frac{1}{2} \int_0^\infty \{ \tilde{x}_m^T Q(\tilde{x}_m) \tilde{x}_m + 2\tilde{x}_m^T S(\tilde{x}_m) \tilde{u}_m + \tilde{u}_m^T R(\tilde{x}_m) \tilde{u}_m \} dt, \quad (88)$$

system (70)–(75), we have $C(t) \triangleq x_{m_4} + \alpha/\beta$ and by considering that $\alpha/\beta = 6.25 \times 10^{10}$ for both parameter sets of Table 2, acceptable domain for x_{m_4} is given by

$$h(x_{m_4}) = 10^6 - x_{m_4} - \frac{\alpha}{\beta} = -6.2499 \times 10^{10} - x_{m_4} \quad (86)$$

Consequently, for the nonlinear regulation case, the allowable state set is $\psi = \{\tilde{x}_m \in \mathbb{R}^9, x_{m_4}(t) \geq -6.2499 \times 10^{10}\}$ and circulating lymphocytes trajectory of the closed-loop system should not cross the boundary of ψ which is defined as $\partial\psi = \{\tilde{x}_m \in \mathbb{R}^9, h(x_{m_4}) = 0, h(x_{m_4}) \in \mathbb{R}^1\}$.

Thus, to keep the state x_{m_4} inside ψ , it is sufficient that the following condition holds

$$Z \triangleq \left(\frac{\partial h(x_{m_4})}{\partial \tilde{x}_m} \right) \dot{\tilde{x}}_m = 0$$

$$Z = \underbrace{[0_{1 \times 3}, -1, 0_{1 \times 5}]}_{\frac{\partial h(x_{m_4})}{\partial \tilde{x}_m}} \underbrace{[\tilde{A}_m(\tilde{x}_m, \theta) \tilde{x}_m + \tilde{B}_m \tilde{u}_m]}_{\dot{\tilde{x}}_m}$$

$$= C(\tilde{x}_m, \theta) \tilde{x}_m + D(\tilde{x}_m) \tilde{u}_m = 0$$

Considering $(\frac{\partial h(x_{m_4})}{\partial \tilde{x}_m}) \tilde{A}_m(\tilde{x}_m, \theta) \triangleq C(\tilde{x}_m, \theta)$, $(\frac{\partial h(x_{m_4})}{\partial \tilde{x}_m}) \tilde{B}_m \triangleq D(\tilde{x}_m)$ and $\frac{\partial h(x_{m_4})}{\partial \tilde{x}_m} = [0_{1 \times 3}, -1, 0_{1 \times 5}]$, yields $C(\tilde{x}_m, \theta) \triangleq$

where

$$\begin{aligned} Q(\tilde{x}_m) &\triangleq Q_0(\tilde{x}_m) + Q_\psi(\tilde{x}_m) = Q_0(\tilde{x}_m) + C^T(\tilde{x}_m)W(\tilde{x}_m)C(\tilde{x}_m) \\ R(\tilde{x}_m) &\triangleq R_0(\tilde{x}_m) + R_\psi(\tilde{x}_m) = R_0(\tilde{x}_m) \\ S(\tilde{x}_m) &= 0_{9 \times 3} \end{aligned}$$

Then the state feedback gain matrix that minimizes (88) is given by $K(\tilde{x}_m) = K_0(\tilde{x}_m) + K_\psi(\tilde{x}_m)$, where

$$\begin{aligned} K_0(\tilde{x}_m) &\triangleq [R_0(\tilde{x}_m) + D^T(\tilde{x}_m)W(\tilde{x}_m)D(\tilde{x}_m)]^{-1}\tilde{B}_m^TP(\tilde{x}_m) \\ &= R_0^{-1}(\tilde{x}_m)\tilde{B}_m^TP(\tilde{x}_m) \\ K_\psi(\tilde{x}_m) &\triangleq [R_0(\tilde{x}_m) + D^T(\tilde{x}_m)W(\tilde{x}_m)D(\tilde{x}_m)]^{-1}S(\tilde{x}_m) = 0 \end{aligned}$$

Then $K(\tilde{x}_m) = K_0(\tilde{x}_m) = R_0^{-1}(\tilde{x}_m)\tilde{B}_m^TP(\tilde{x}_m)$ with $P(\tilde{x}_m) \geq 0$ satisfies the SDRE

$$\begin{aligned} P(\tilde{x}_m)\tilde{A}_m(\tilde{x}_m) + \tilde{A}_m^T(\tilde{x}_m)P(\tilde{x}_m) \\ - P(\tilde{x}_m)\tilde{B}_mR_0^{-1}(\tilde{x}_m)\tilde{B}_m^TP(\tilde{x}_m) + Q(\tilde{x}_m) = 0 \end{aligned}$$

5.2. MRAC-based personalized drug delivery for mixed therapy of unknown patient

For the unknown patient, we consider the same dynamics and the same mathematical model as reference patient in (52)–(58) but with different parameter set. While the mathematical models and states are the same, for the sake of avoiding any confusion, we consider all parameters and states with bar accent, i.e. (\cdot) . Therefore, unknown patient states are $\bar{T}(t)$, $\bar{N}(t)$, $\bar{L}(t)$, $\bar{C}(t)$, $\bar{M}(t)$ and $\bar{I}(t)$ which describe the tumor cell, natural killer cell, CD8⁺T cell and circulating lymphocyte population as well as chemotherapy and immunotherapy drug concentration in blood stream related to unknown patient respectively.

We assume that all parameters of the unknown patient are unknown. Therefore, we cannot factorize the nonlinear dynamics of unknown patient as a linear-like structure with SDC matrices. However, we can consider the nonlinear dynamics of unknown patient as

$$\dot{x}_p(t) = f_p(x_p) + B_p u_p(t), \quad x_p(0) = x_{p_0}, \quad (89)$$

Where $x_{p_1} \triangleq \bar{T}$, $x_{p_2} \triangleq \bar{N}$, $x_{p_3} \triangleq \bar{L}$, $x_{p_4} \triangleq \bar{C}$, $x_{p_5} \triangleq \bar{M}$, $x_{p_6} \triangleq \bar{I}$, and $x_p \in \mathbb{R}^6$, i.e. $x_p = [x_{p_1} \ x_{p_2} \ x_{p_3} \ x_{p_4} \ x_{p_5} \ x_{p_6}]^T$, is the state vector of unknown patient, $u_p \in \mathbb{R}^3$ is the input vector (drug intervention), $B_p \in \mathbb{R}^{3 \times 6}$, $f_p(x_p) : \mathbb{R}^6 \rightarrow \mathbb{R}^6$. Since all parameters in dynamical system (89) are unknown, then $f_p(x_p)$ in (89) is unknown. On the other hand, the B_p is the constant matrix that equals to B_m matrix. Thus, the B_p matrix is not dependent to any state or parameter, given by

$$B_p = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

Consequently, we can represent unknown patient nonlinear dynamic as follows

$$\begin{aligned} \begin{bmatrix} \dot{x}_{p_1} \\ \dot{x}_{p_2} \\ \dot{x}_{p_3} \\ \dot{x}_{p_4} \\ \dot{x}_{p_5} \\ \dot{x}_{p_6} \end{bmatrix} &= \underbrace{\begin{bmatrix} \bar{a}x_{p_1} - \bar{a}\bar{b}x_{p_1}^2 - \bar{c}x_{p_1}x_{p_2} - \bar{d}\bar{D}x_{p_1} - \bar{k}_T(1 - e^{-x_{p_5}})x_{p_1} \\ \bar{e}x_{p_4} - \bar{f}x_{p_2} + \frac{\bar{g}x_{p_1}^2x_{p_2}}{\bar{h}+x_{p_1}^2} - \bar{p}x_{p_1}x_{p_2} - \bar{k}_N(1 - e^{-x_{p_5}})x_{p_2} \\ -\bar{m}x_{p_3} + \frac{\bar{j}\bar{D}^2x_{p_1}^2x_{p_3}}{\bar{k}+\bar{D}^2x_{p_1}^2} - \bar{q}x_{p_1}x_{p_3} + \bar{r}_1x_{p_1}x_{p_2} + \bar{r}_2x_{p_1}x_{p_4} - \bar{u}x_{p_2}x_{p_3}^2 - \bar{k}_L(1 - e^{-x_{p_5}})x_{p_3} + \frac{\bar{p}_1x_{p_3}x_{p_6}}{\bar{g}_l+x_{p_6}} \\ \bar{\alpha} - \bar{\beta}x_{p_4} - \bar{k}_C(1 - e^{-x_{p_5}})x_{p_4} \\ -\bar{\gamma}x_{p_5} \\ -\bar{\mu}_I x_{p_6} \end{bmatrix}}_{\text{Unknown } f_p(x_p)} \\ &+ \underbrace{\begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}}_{\text{Known } B_p} \underbrace{\begin{bmatrix} \bar{v}_L(t) \\ \bar{v}_M(t) \\ \bar{v}_I(t) \end{bmatrix}}_{u_p(t)} \end{aligned} \quad (90)$$

where

$$\bar{D} = \bar{d} \frac{(x_{p_3}/x_{p_1})^{\bar{l}}}{\bar{s} + (x_{p_3}/x_{p_1})^{\bar{l}}} \quad (91)$$

Since parameters and consequently $f_p(x_p)$ is not known, then we cannot factorize it as a linear like structure. Then we try to stabilize the unknown patient via MRAC approach. Therefore, in (90) we consider $u_p(t)$ as an adaptive feedback control to stabilize the system. Indeed, here $u_p(t)$ represent personalized drug delivery protocol for the unknown patient to drive it to the tumor-free equilibrium point. The state feedback control is given by

$$u_p(t) = K_p(t)x_p(t) \quad (92)$$

where the adaptive control gain $K_p(t)$ is updated based on the adaptation rule at each time instant. The proposed adaptation rule is given by

$$\begin{aligned} \dot{K}_p(t, x_p, x_m) &= B_p^T e(t) x_p^T(t) P_{ad}(x_p, x_m) \Gamma, \quad K_p(t_0, x_{p_0}, x_{m_0}) \\ &= K_{p_0} \in \mathbb{R}^{m \times n} \end{aligned} \quad (93)$$

where

$$e = [\bar{T}, \bar{N}, \bar{L}, \bar{C}, \bar{M}, \bar{I}] - [T, N, L, C, M, I] \quad (94)$$

and $P_{ad}(x_p, x_m)$ is the solution of the algebraic Lyapunov equation of

$$A_{m_{cl}}^T(x_m)P_{ad}(x_p, x_m) + P_{ad}(x_p, x_m)A_{m_{cl}}(x_m) = -Q_{ad}(x_p) \quad (95)$$

Remark 5.1. Since for reference patient x_m is shifted to the origin by the appropriate transformation as described in (68), thus, considering the $e(t) = x_p(t) - x_m(t)$ does not represent the correct error for adaptation rule (93). Therefore, to compute the error, we consider the difference of the state of the original system in (94).

Similar to the reference patient, the hard bounds are applied to the administrated drug dose for the unknown patient

$$\begin{cases} 0 \leq \bar{v}_L(t) \leq 10^9 \\ 0 \leq \bar{v}_M(t) \leq 5 \\ 0 \leq \bar{v}_I(t) \leq 5 \times 10^5 \end{cases}$$

The constrained input for the unknown patient is modeled as a saturation nonlinearity, similar to reference patient, which is defined by (88).

Remark 5.2. As the parameter set is unknown, then $f_p(x_p)$ is unknown. Therefore, the nonlinear dynamics of unknown patient is used as a black-box simulator in the procedure of determining the drug delivery protocol for the unknown patient.

The diagram of the proposed algorithm to determine the drug delivery for the unknown patient based on the drug delivery protocol of the reference patient is depicted in Fig. 4.

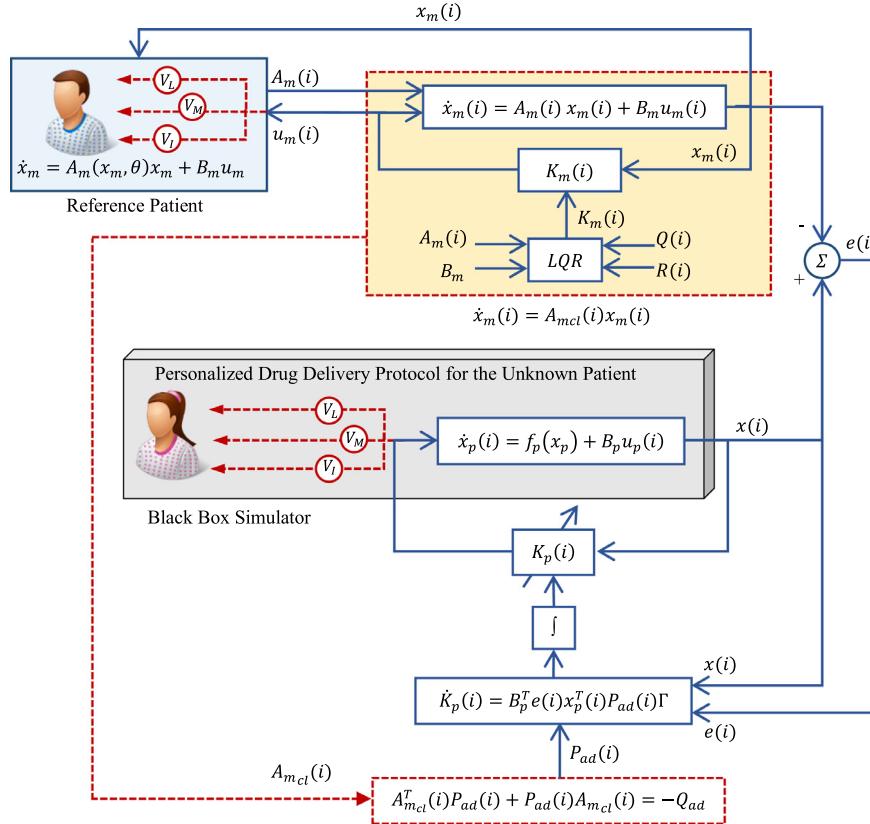


Fig. 4. The diagram of the personalized drug delivery of unknown patient (via MRAC) based on the drug delivery regimen of the reference patient (via SDRE).

6. Numerical results

For numerical simulations, parameters and initial conditions from [4] are used. The proposed parameter sets for two distinct patients (patient 9 and patient 10) are presented in Appendix A. To survey the effectiveness of the proposed methodology, we present the numerical results for two conditions. In the first simulation, we consider patient 9 as a reference patient with known parameter set and the patient 10 as an unknown patient with an unknown parameter set. Conversely, in the second simulation, we consider patient 10 as reference patient and patient 9 as an unknown patient. In both conditions, for reference patient, the drug delivery protocol is determined by SDRE approach. Then, based on the archived drug delivery scenario for reference patient, we figure out the personalized drug delivery for the unknown patient via addressed MRAC methodology. Under each condition, we consider two distinct cases with different state and input weighting matrices to demonstrate the effectiveness of the SDRE based MRAC to figure out a personalized drug delivery scenario for an unknown patient.

In all simulations, for reference and unknown patients, we consider the initial condition proposed in [4] that is $[T_0, N_0, L_0, C_0] = [2 \times 10^7, 1 \times 10^3, 10, 6 \times 10^8]$ and the objective is to eradicate tumor cells by administering an optimum dose of chemotherapy and immunotherapy drugs and drive the system to the tumor-free equilibrium point of $[T_{eq}, N_{eq}, L_{eq}, C_{eq}] = [0, 3.1553 \times 10^5, 0, 6.25 \times 10^{10}]$. To avoid depletion of the immune system of the patient, we desire to keep circulating lymphocyte population above the predetermined threshold, i.e. $C(t) \geq 10^6$. Since the tumor-free equilibrium point is not at the origin, for reference patient, the tumor-free equilibrium point is transferred to

the origin using the following error states,

$$\begin{aligned} x_{m_1} &\triangleq T, \quad x_{m_2} \triangleq N - 3.1553 \times 10^5, \quad x_{m_3} \triangleq L, \\ x_{m_4} &\triangleq C - 6.25 \times 10^{10}, \quad x_{m_5} \triangleq M, \quad x_{m_6} \triangleq I. \end{aligned}$$

6.1. Patient 9 is considered as reference patient and patient 10 is considered as unknown patient

For simulation, we consider two different cases with distinct Q_0 and R_0 weighting matrices for LQR problem of SDRE control.

Case 1. In this case of the nonlinear regulation problem of the reference patient (patient 9), SDRE method is utilized. We assume that all parameters as well as cancer dynamics of reference patient (patient 9) are known. By following the procedure, which is described in Section 4, we can design SDRE control for nonlinear regulation problems of reference patient treatment. For LQR problem of the SDC factorization of reference patient, we consider the following state and input weighting matrices for the augmented system;

$$\begin{cases} Q_{01} = \text{diag}(1, 1, 10^4, 1, 1, 10, 1, 10) \times 10^{-7} \\ R_{01} = \text{diag}(1, 10^{-2}, 4 \times 10^{-4}) \times 10^{-3} \end{cases}$$

Next by considering the hard bounds for control and threshold for circulating lymphocytes (see Section 4), we can determine the drug delivery protocol for the reference patient. The cell population and mixed chemo and immunotherapy drug delivery protocol are pictured in Figs. 5 and 6 respectively. Fig. 6 shows that the tumor burden shrinks rapidly and disappears in less than 9 days. SDRE controlled drug delivery scenario presented in Fig. 6 contains

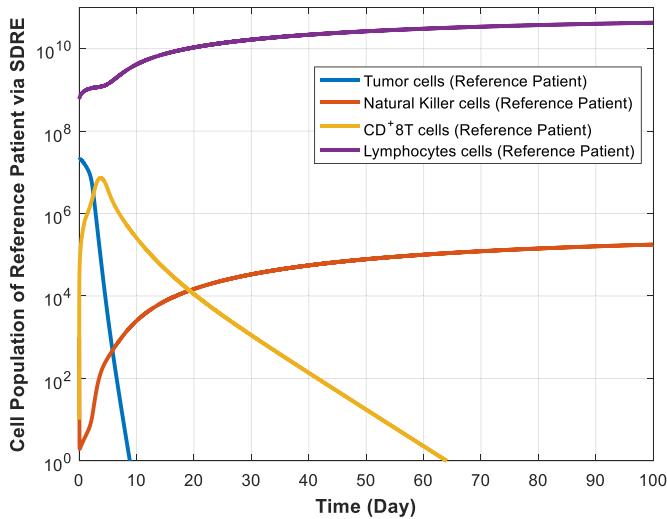


Fig. 5. Evolution of cell population of reference patient (patient 9) by SDRE control for [Case 1](#).

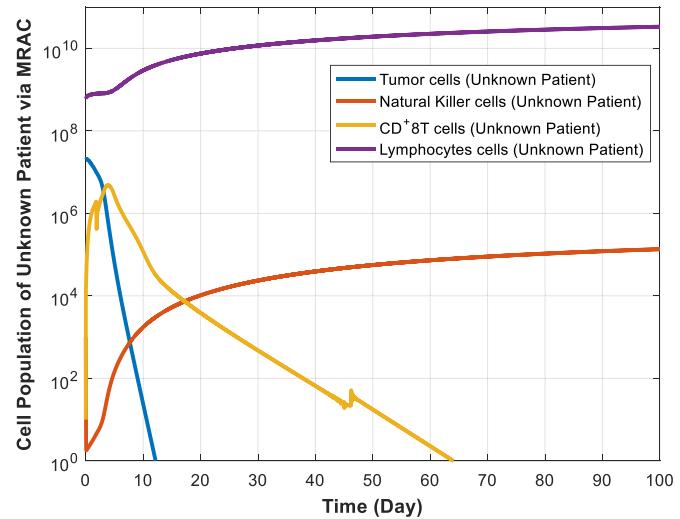


Fig. 7. Evolution of cell population of unknown patient (patient 10) by MRAC control for [Case 1](#).

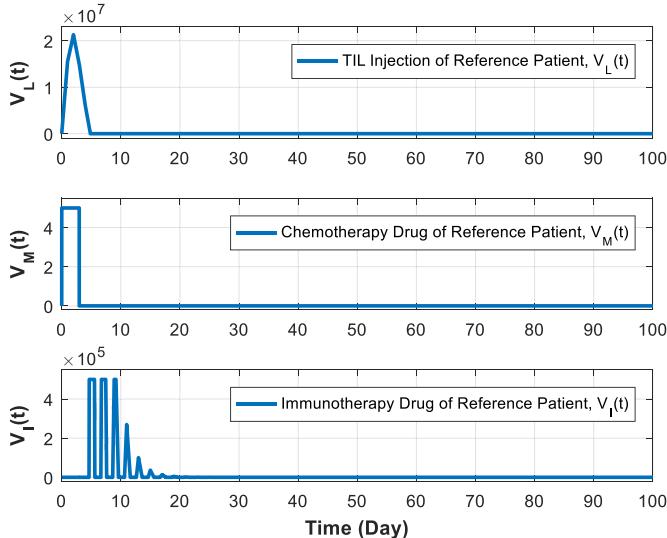


Fig. 6. Drug delivery protocol of reference patient (patient 9) by SDRE control for [Case 1](#).

3 days full-dose chemotherapy administration in addition to TIL and IL-2 injection. TIL administration begins from the first day of treatment, together with chemotherapy, and gradually increase to 2.1×10^7 in two days, then in 3 days it is decreased and administration is stopped. Also immune drug (IL-2) administration is situated between days 5–20. The TIL injection begins with a bang-bang like administration, and after 3 full-dose administration, which is gradually decreased.

In the second stage based on the drug delivery scenario of the reference patient, we compute the drug delivery protocol for mixed therapy of unknown patient (patient 10) with proposed SDRE based MRAC approach. For MRAC problem, we use the adaptation rate $\Gamma_1 = 10^{-17} \times I_{6 \times 6}$ and $Q_{ad_1} = \text{diag}(1, 1, 2, 10, 10, 10)$. Cell population and personalized drug delivery scenario for mixed-therapy of unknown patient are presented in [Figs. 7](#) and [8](#), respectively.

Simulation results in [Fig. 7](#) presents the eradication of the tumor cells in 12 days. In addition, mixed-drug delivery protocol of unknown patient is a full dose chemotherapy administration for 3 days besides administration of immunotherapy including TIL and

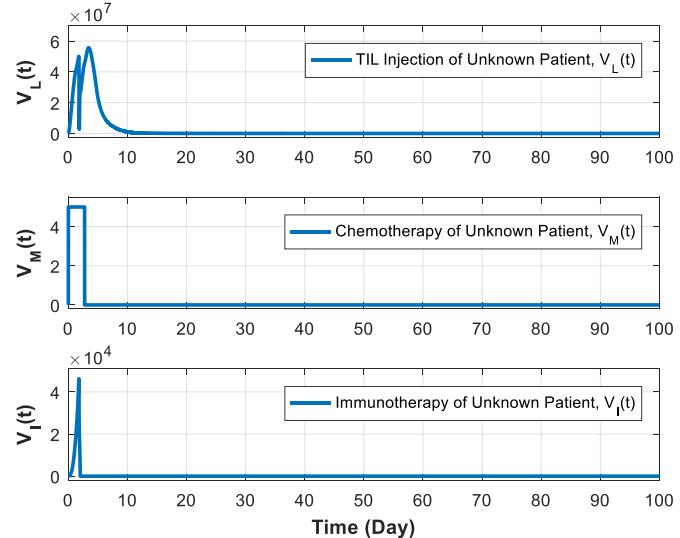


Fig. 8. Personalized drug delivery protocol of unknown patient (patient 10) by MRAC control for [Case 1](#).

IL-2 during 14 and 2 days, respectively. Thus, achieved personalized drug delivery using MRAC successfully eradicates the tumor burden of unknown patient ([10](#)). It should be mentioned that by increasing the adaptation rate Γ_1 , we can change the drug delivery of the unknown patient to totally bang-bang (full dose or no dose) drug administration for all three drug intervention.

Case 2. In this case, like as [Case 1](#), we consider the patient 9 as reference patient and using different state and input weighting matrices we present another drug delivery protocol via SDRE approach. Indeed, we want to intensify the effect of weighting matrices in achieving drug delivery for a reference patient (patient 9). The following state and input weighting matrices are considered for the augmented system in SDRE control;

$$\begin{cases} Q_{02} = \text{diag}(1, 1, 10^5, 1, 1, 1, 1, 1, 1) \times 10^{-9} \\ R_{02} = \text{diag}(100, 100, 5) \times 10^{-10} \end{cases}$$

Following the procedure described in [Section 4](#), with the same initial conditions and control bounds as well as circulating lymphocytes threshold, the following cell population and mixed-drug

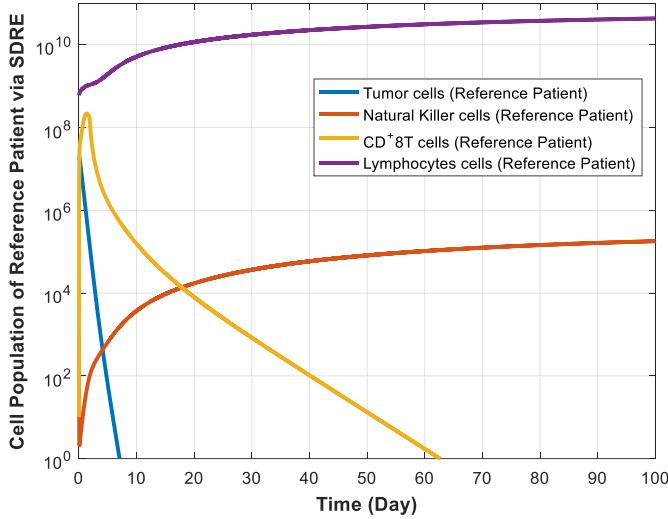


Fig. 9. Evolution of cell population of reference patient (patient 9) by SDRE control for Case 2.

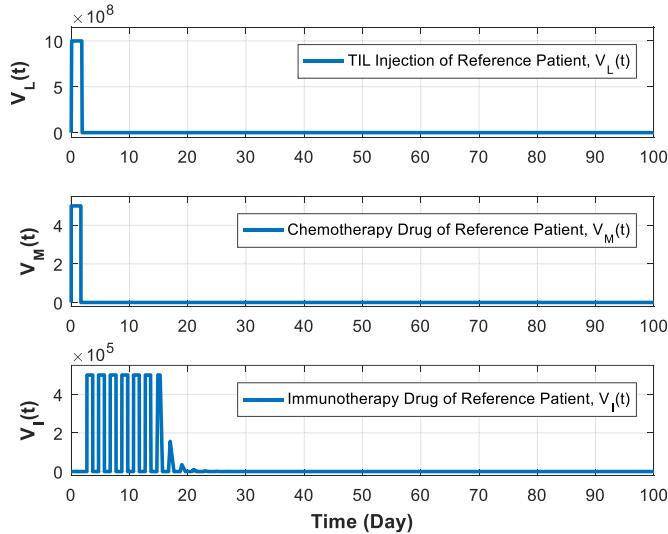


Fig. 10. Drug delivery protocol of reference patient (patient 9) by SDRE control for Case 2.

delivery protocol for reference patient (patient 9) are presented in Figs. 9 and 10, respectively.

Consequently, we desire to determine the personalized drug delivery protocol for the unknown patient (patient 10) using MRAC based on the drug delivery protocol of reference patient (patient 9). For the MRAC problem, we consider the adaptation rate $\Gamma_2 = \text{diag}(1, 5, 5 \times 10^4, 5, 1, 5 \times 10^{-2}) \times 10^{-18}$ and $Q_{ad_2} = \text{diag}(1, 10, 2, 15, 10, 10)$. The simulation results of unknown patient are presented in Figs. 11 and 12. In Fig. 11 we depict the evolution of cell population of unknown patient. The figure shows that the tumor burden of unknown patient is erad-

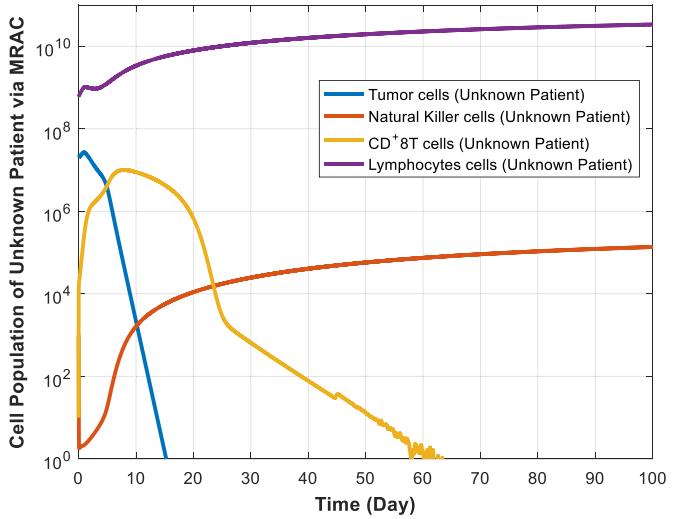


Fig. 11. Evolution of cell population of unknown patient (patient 10) by MRAC control for Case 2.

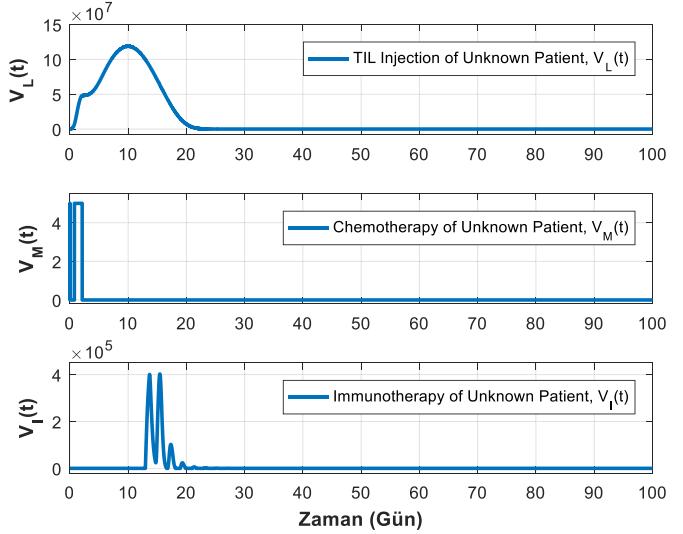


Fig. 12. Personalized drug delivery protocol of unknown patient (patient 10) by MRAC control for Case 2.

icated in about 16 days using the achieved drug delivery scenario by MRAC. Personalized drug delivery protocol of the unknown patient (patient 10) is pictured in Fig. 12. The achieved drug delivery protocol contains bang-bang administration of chemotherapy for 3 days, bang-bang administration of IL-2 from days 13–16 which is decreased gradually up to day 23. Also, administration of TIL is continuous in the first 22 days of treatment.

By considering simulation results, we can see that different weighting input and state matrices in SDRE control lead to totally different drug delivery protocol for reference patient that also affects the drug delivery scenario of the unknown patient. To compare the two cases, in Table 2 we present cost functions and to-

Table 2
Cost function and total administrated drugs for reference and unknown patients in Case 1 and Case 2.

		Approach	Total v_L	Total v_M	Total v_I	Cost function
Case 1	Reference Patient (patient 9)	SDRE	5.7088×10^7	14.80	1.4216×10^6	1.6847×10^{16}
	Unknown Patient (Patient 10)	MRAC	2.1748×10^8	13.75	2.7123×10^4	2.2074×10^{16}
Case 2	Reference Patient (patient 9)	SDRE	1.8073×10^9	8.30	3.4037×10^6	1.7374×10^{16}
	Unknown Patient (Patient 10)	MRAC	1.3861×10^9	6.80	7.6845×10^5	2.1862×10^{16}

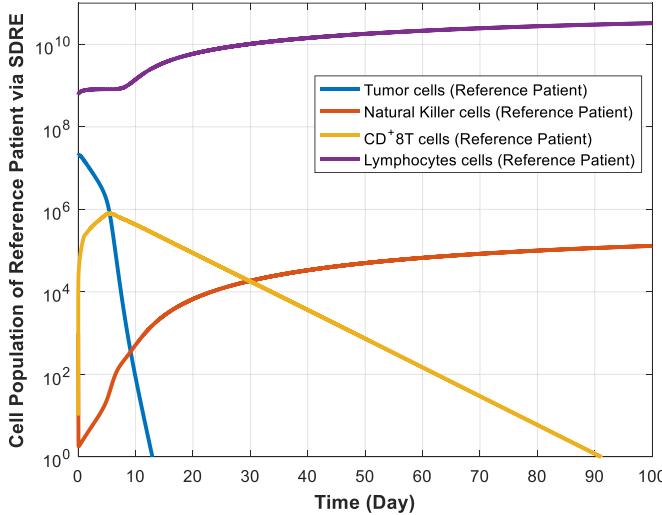


Fig. 13. Evolution of cell population of reference patient (patient 10) by SDRE control for [Case 3](#).

tal administrated drugs amount related to [Case 1](#) and [Case 2](#). To compute the total administrated chemotherapy and immunotherapy drugs, we consider the following integrals in the simulation time span,

$$V_L = \int_0^{100} v_L(t) dt, \quad V_M = \int_0^{100} v_M(t) dt, \quad V_I = \int_0^{100} v_I(t) dt$$

For computation of the cost function of reference patient, we must compute the values of J_0 and J_ψ and the augmented cost function value will be $J = J_0 + J_\psi$. By considering the $J_\psi(\tilde{x}_{m_0}, \tilde{u}_m)$ that is defined in [\(87\)](#) we have

$$J_\psi(\tilde{x}_{m_0}, \tilde{u}_m) = \frac{1}{2} \int_0^\infty \frac{1}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} \times \left\{ x_{m_4} \beta + x_{m_5} \left(-k_c R x_{m_4} - \frac{\alpha k_c R}{\beta} \right) \right\}^2 dt$$

In [Case 1](#) for patient 9 we have $\alpha = 7.50 \times 10^8$, $\beta = 1.20 \times 10^{-2}$, $k_c = 6.00 \times 10^{-1}$ and $R \triangleq \frac{e^{-x_{m_5}} - 1}{x_{m_5}}$ (see Appendix 1)

Therefore

$$J_\psi(\tilde{x}_{m_0}, \tilde{u}_m) = \frac{1}{2} \int_0^\infty \frac{1}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} \times \left\{ 0.012 x_{m_4} + (e^{-x_{m_5}} - 1)(-0.6 x_{m_4} - 3.75 \times 10^{10}) \right\}^2 dt$$

On the other hand $J_0 = \int_0^\infty \{\tilde{x}_m^T Q_{01}(\tilde{x}_m) \tilde{x}_m + \tilde{u}_m^T R_{01}(\tilde{x}_m) \tilde{u}_m\} dt$ and by substituting of Q_{01} and R_{01} in this equation we have

$$J_0 = \int_0^\infty \left\{ \left(\begin{bmatrix} x_{m_1} \\ x_{m_2} \\ x_{m_3} \\ x_{m_4} \\ x_{m_5} \\ x_{m_6} \\ v_L \\ v_M \\ v_I \end{bmatrix}^T \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 10^4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 10 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 10 \end{bmatrix} \begin{bmatrix} x_{m_1} \\ x_{m_2} \\ x_{m_3} \\ x_{m_4} \\ x_{m_5} \\ x_{m_6} \\ v_L \\ v_M \\ v_I \end{bmatrix} \right) \times 10^{-7} + \left(\begin{bmatrix} \tilde{u}_{m_1} \\ \tilde{u}_{m_2} \\ \tilde{u}_{m_3} \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 \\ 0 & 10^{-2} & 0 \\ 0 & 0 & 4 \times 10^{-4} \end{bmatrix} \begin{bmatrix} \tilde{u}_{m_1} \\ \tilde{u}_{m_2} \\ \tilde{u}_{m_3} \end{bmatrix}^T \right) \times 10^{-3} \right\} dt$$

$$J_0 = \int_0^\infty \left\{ (x_{m_1}^2 + x_{m_2}^2 + 10^4 \times x_{m_3}^2 + x_{m_4}^2 + x_{m_5}^2 + x_{m_6}^2 + 10 \times v_L^2 + v_M^2 + 10 \times v_I^2) \times 10^{-7} + (\tilde{u}_{m_1}^2 + 10^{-2} \times \tilde{u}_{m_2}^2 + 4 \times 10^{-4} \times \tilde{u}_{m_3}^2) \times 10^{-3} \right\} dt$$

[Case 1](#) and for J_ψ we have

$$J_\psi(\tilde{x}_{m_0}, \tilde{u}_m) = \frac{1}{2} \int_0^\infty \frac{1}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} \times \left\{ 0.012 x_{m_4} + (e^{-x_{m_5}} - 1)(-0.6 x_{m_4} - 3.75 \times 10^{10}) \right\}^2 dt$$

$$J_0 = \int_0^\infty \left\{ (x_{m_1}^2 + x_{m_2}^2 + 10^5 \times x_{m_4}^2 + x_{m_5}^2 + x_{m_6}^2 + v_L^2 + v_M^2 + v_I^2) \times 10^{-9} + (10^2 \times \tilde{u}_{m_1}^2 + 10^2 \times \tilde{u}_{m_2}^2 + 5 \times \tilde{u}_{m_3}^2) \times 10^{-10} \right\} dt$$

In both cases, by considering the cell population and administrated drug doses, we use numerical integration for calculating of cost function values in the simulation time span which is presented in [Table 2](#).

6.2. Patient 10 is considered as reference patient and patient 9 is considered as unknown patient

In this simulation series, unlike simulation 5.1, we consider patient 10 as reference patient and patient 9 as unknown patient with the parameters given in [Table 4](#). As dynamics and parameters of reference patient (patient 10) are known, we utilize SDRE method for the nonlinear regulation problem of reference patient (patient 10). For simulation, we consider two different cases with distinct Q_0 and R_0 weighting matrices for LQR problem.

Case 3. In this case, we consider the following state and input weighting matrices for LQR problem of SDRE control for the augmented system;

$$\begin{cases} Q_{03} = \text{diag}(1, 1, 10^4, 1, 1, 1, 100, 1, 10) \times 10^{-8} \\ R_{03} = \text{diag}(10^4, 100, 4) \times 10^{-7} \end{cases}$$

Then we consider the same hard bounds for control and threshold for circulating lymphocytes like as [Case 1](#) and [Case 2](#). [Figs. 13](#) and [14](#) depict the cell population and mixed chemo and immune drug delivery protocol for reference patient (patient 10), respectively. [Fig. 13](#) shows that the tumor cell population disappear in less than 13 days using the achieved drug delivery protocol by SDRE control, which is presented in [Fig. 14](#). The TIL administration is started and increase during 6 days to the 10×10^6 and then decrease gradually in 30 days. The anti-cancer drug is administrated as full dose in 7 days. In addition, IL-2 is administrated in several pulses with different doses during 28 days.

Using drug delivery protocol of the reference patient (patient 10), we determine the drug delivery scenario for the unknown patient (patient 9) with MRAC approach. For MRAC problem, we use the adaptation rate $\Gamma_3 = 10^{-17} \times I_{6 \times 6}$ and $Q_{ad3} = \text{diag}(1, 1, 2, 50, 10, 10)$. Cell population and personalized drug

In the same manner to determine the cost function for [Case 2](#), because of similar parameters, the J_ψ is determined exactly as

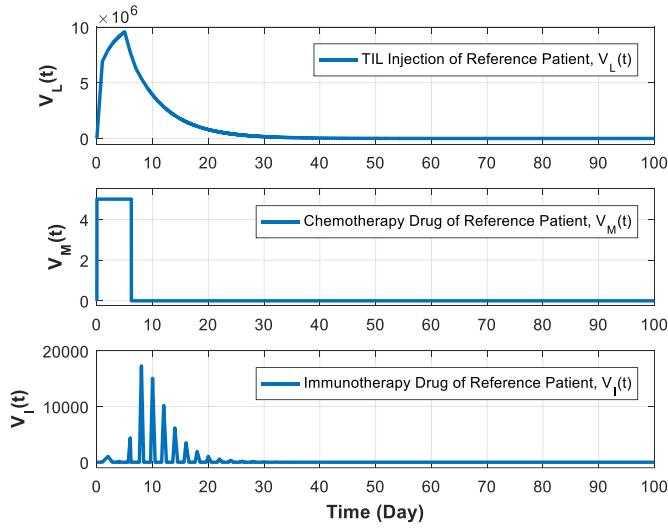


Fig. 14. Drug delivery protocol of reference patient (patient 10) by SDRE control for Case 3.

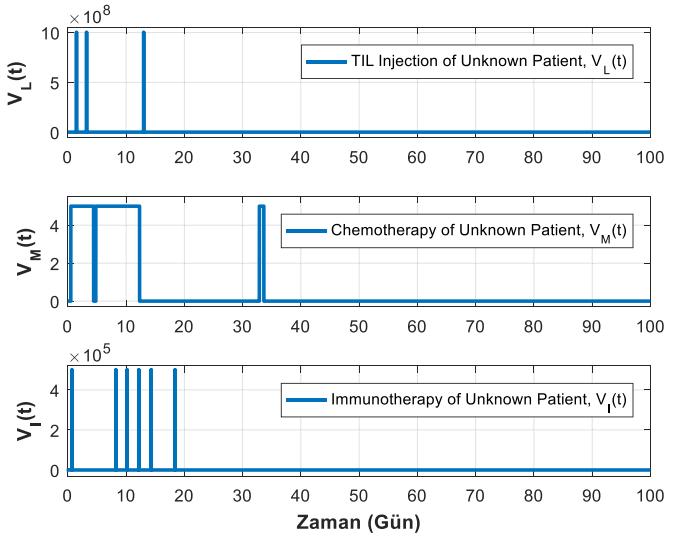


Fig. 16. Personalized drug delivery protocol of unknown patient (patient 9) by MRAC control for Case 3.

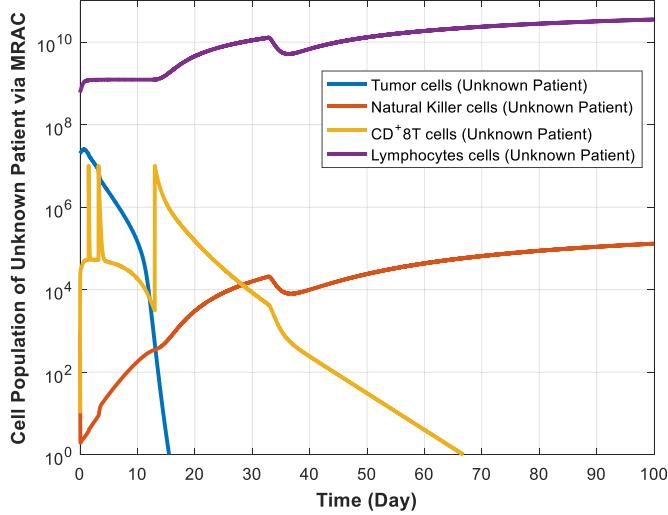


Fig. 15. Evolution of cell population of unknown patient (patient 9) by MRAC control for Case 3.

delivery scenario for mixed-therapy of unknown patient are presented in Figs. 15 and 16, respectively.

Fig. 15 shows that the eradication time of tumor burden is 16 days. The achieved drug delivery protocol for unknown patient is bang-band control for all 3 drug interventions. During 13 days, we have 3 full doses TIL injection. The chemotherapy drug delivery protocol contains 4 days administration of the full dose, then stop administration for 1 day and again there is full-dose administration up to 12th day and finally administration of full dose for one day in day 33. In addition, IL-2 contains 5 full dose pulses during 18 days.

Therefore, achieved personalized drug delivery using MRAC has bang-bang administration structure. If the continuous administration is in consideration, we can decrease the adaptation gain Γ_3 .

Case 4. In this case, we consider the patient 10 as reference patient and patient 9 as unknown patient. Thus, this case is similar to Case 3 and we only consider the different state and input weighting matrices to achieve distinct drug delivery protocol for reference patient via SDRE method. We consider the following state and in-

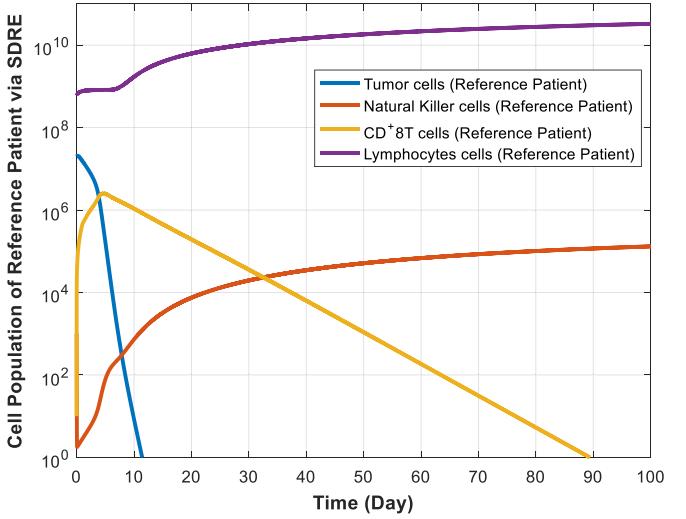


Fig. 17. Evolution of cell population of reference patient (patient 10) by SDRE control for Case 4.

put weighting matrices;

$$\begin{cases} Q_{04} = \text{diag}(10^2, 1, 10^9, 10^5, 15 \times 10^5, 10^5, 12 \\ \quad \times 10^5, 20, 15 \times 10^5) \times 10^{-8} \\ R_{04} = \text{diag}(5 \times 10^3, 1, 4 \times 10^2) \times 10^{-7} \end{cases}$$

Subsequently, we follow the procedure of Section 4 to stabilize cancer dynamics of reference patient (patient 9) with SDRE method. The cell population of reference patient (patient 9) is pictured in Fig. 17. The simulation results show the tumor lump is eradicated in 12 days. The personalized drug delivery protocol for the unknown patient, which is obtained using MRAC is depicted in Fig. 18. The TIL and IL-2 administrations are continuous during 33 and 5 days, respectively. In addition, the chemotherapy protocol is full dose administration for 6 days.

Then, we determine the personalized drug delivery protocol for the unknown patient (patient 9) using MRAC based on the drug delivery protocol of reference patient (patient 10). For MRAC, we consider the adaptation rate of $\Gamma_4 = 10^{-10} \times \text{diag}(1000, 1, 1000, 1, 10, 1)$ and $Q_{ad4} = \text{diag}(1, 1, 2, 500, 1, 100)$. The simulation results for the unknown patient are

Table 3
Cost function and total administrated drugs for reference and unknown patients in **Case 3** and **Case 4**.

		Approach	Total v_L	Total v_M	Total v_I	Cost function
Case 3	Reference Patient (patient 10)	SDRE	9.2715×10^7	30.90	2.5359×10^4	2.1631×10^{16}
	Unknown Patient (Patient 9)	MRAC	3.0×10^8	50.20	2.5005×10^4	2.3088×10^{16}
Case 4	Reference Patient (patient 10)	SDRE	2.3933×10^8	27.00	1.2552×10^4	2.1404×10^{16}
	Unknown Patient (Patient 9)	MRAC	9.0×10^8	58.45	2.5031×10^4	2.3035×10^{16}

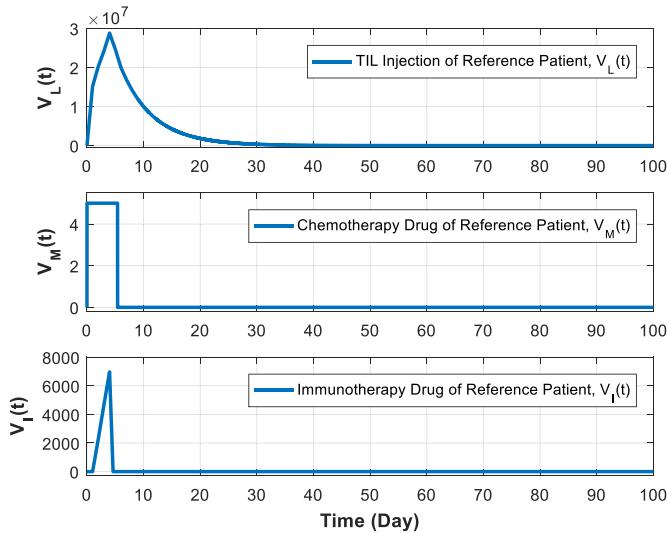


Fig. 18. Drug delivery protocol of reference patient (patient 10) by SDRE control for **Case 4**.

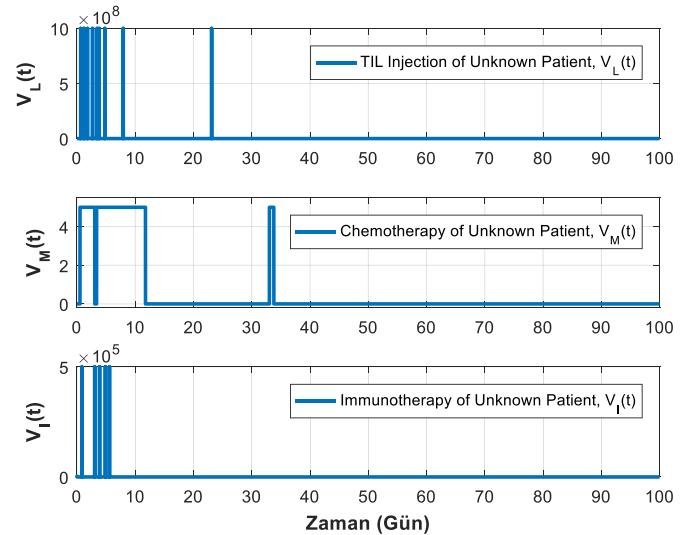


Fig. 20. Personalized drug delivery protocol of unknown patient (patient 9) by MRAC control for **Case 4**.

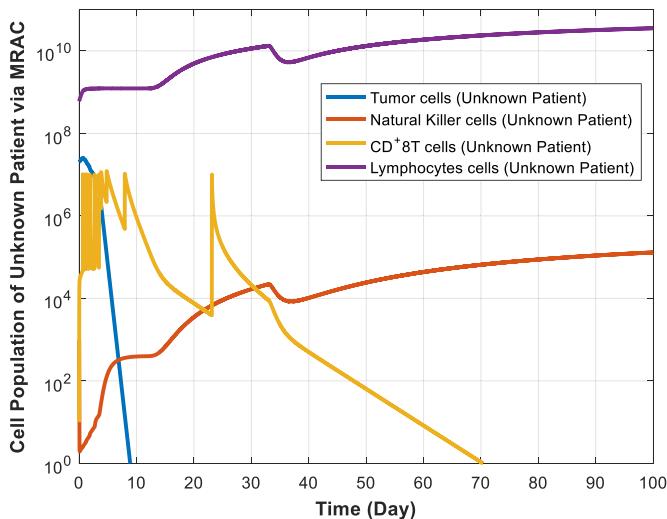


Fig. 19. Evolution of cell population of unknown patient (patient 9) by MRAC control for **Case 4**.

presented in Figs. 19 and 20. The cell population of unknown patient is given in Fig. 19 and shows that the tumor burden of unknown patient (patient 9) disappears in 9 days using the archived personalized drug delivery scenario by MRAC. Fig. 20 illustrates the personalized drug delivery for unknown patient. The drug delivery of unknown patient via MRAC is bang-bang for all 3 drug interventions. To compare two cases, we present cost function and total drugs amount related to **Case 3** and **Case 4** in Table 3. Similar to **Case 1** and **Case 2**, by considering $\alpha = 5.00 \times 10^8$, $\beta = 8.00 \times 10^{-3}$, $k_c = 6.00 \times 10^{-1}$, the cost

function of **Case 3** is determined as follows

$$J_{\psi}(\tilde{x}_{m_0}, \tilde{u}_m) = \frac{1}{2} \int_0^{\infty} \frac{1}{(\|h(x_{m_4})\|_2 + 0.1)^{420}} \\ \times \{0.008x_{m_4} + (e^{-x_{m_5}} - 1)(-0.6x_{m_4} - 3.75 \times 10^{10})\}^2 dt$$

$$J_0 = \int_0^{\infty} \{(x_{m_1}^2 + x_{m_2}^2 + 10^4 \times x_{m_3}^2 + x_{m_4}^2 + x_{m_5}^2 + x_{m_6}^2 \\ + 10^2 \times v_L^2 + v_M^2 + 10 \times v_I^2) \times 10^{-8} \\ + (10^4 \times \tilde{u}_{m_1}^2 + 10^2 \times \tilde{u}_{m_2}^2 + 4 \times \tilde{u}_{m_3}^2) \times 10^{-7}\} dt$$

In **Case 4** value of J_{ψ} is determined exactly like as **Case 3** and J_0 is determined as follows

$$J_0 = \int_0^{\infty} \{(10^2 \times x_{m_1}^2 + x_{m_2}^2 + 10^9 \times x_{m_3}^2 + 10^5 \times x_{m_4}^2 + 15 \times 10^5 \\ \times x_{m_5}^2 + 10^5 \times x_{m_6}^2 + 12 \times 10^5 \times v_L^2 + 20 \times v_M^2 \\ + 15 \times 10^5 \times v_I^2) \times 10^{-8} + (5 \times 10^3 \times \tilde{u}_{m_1}^2 + \tilde{u}_{m_2}^2 \\ + 4 \times 10^2 \times \tilde{u}_{m_3}^2) \times 10^{-7}\} dt$$

Therefore, we can determine cost function values for **Case 3** and **Case 4** using numerical integration in treatment time intervals which are mentioned in Table 3.

For better comparison, besides cost function values of 4 cases which are presented in Tables 3 and 4, the cost function modifications during 100 days for reference and unknown patients in all cases are depicted in Fig. 21. Indeed, we compute the immediate value of the cost function for every day in the treatment period. Therefore, the area under each graph presents the cost function values that are presented in Tables 2 and 3. This Figure shows that immediate cost function values are altered for reference and unknown patient in **Cases 1** and **2**, by as well as **Cases 3** and **4** are very

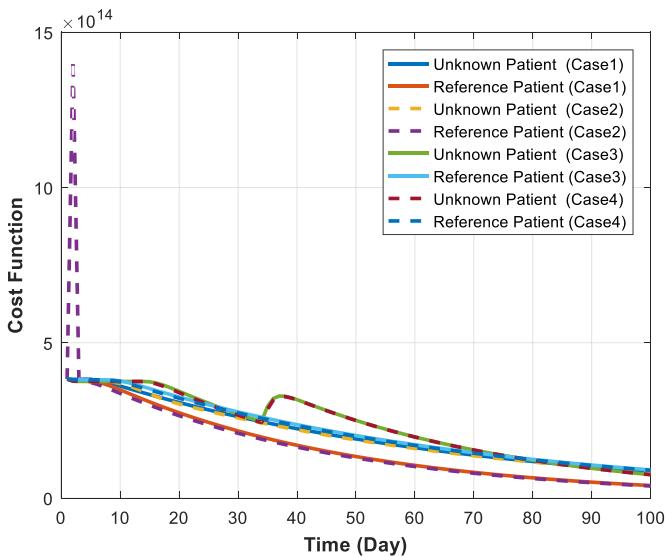


Fig. 21. Modification of instant cost function values for reference and unknown patients.

similar to each other. The only immediate cost function of reference patient in [Case 2](#) has different behavior in comparison with reference patient in [Case 1](#) in the first two days and after two days the cost functions change like each other.

7. Conclusions

In this study, SDRE based model reference adaptive control design strategy for nonlinear MIMO systems is developed to determine the personalized drug delivery protocol for mixed therapy with chemotherapy and immunotherapy in cancer treatment. The

6th order nonlinear ODE model with 3 inputs, including administration of one chemotherapy drug and two immunotherapy drugs of TIL and IL-2 has been taken and by considering two distinct model parameter sets, two patients (patient 9 and patient 10) have been considered as reference and unknown patients. Reference patient's drug delivery protocol is determined via SDRE method. Then personalized drug delivery scenario for an unknown patient (with unknown parameter set) is determined using MRAC method based on the treatment strategy of reference patient. To emphasize the effectiveness of the proposed approach, firstly we considered patient 9 as reference patient and patient 10 as an unknown patient ([Case 1](#) and [Case 2](#)) and later patient 10 is considered as reference patient and patient 9 is considered as an unknown patient ([Case 3](#) and [Case 4](#)). The simulation results reveal that in both cases the presented SDRE based MRAC approach successfully eradicate tumor cells via mixed therapy. Moreover, it has been confirmed that using different weight matrices in SDRE control for reference patient and different adaptation gains in MRAC for unknown patient results totally distinct drug delivery protocols both in drugs dosage and periodicity of administration. Particularly the adaptation gain is the fundamental point of obtaining continuous or bang-bang drug delivery protocols for both chemotherapy and immunotherapy. Besides, simulations revealed that by selecting proper reference patient and proper reference drug delivery protocol, the cost function value of the unknown patient is close to the reference patient cost function value as mentioned in [Tables 2](#) and [3](#). Considering the fact that parameter sets are different from one patient to another, the MRAC based approach present straightforward manner to determine the personalized drug delivery for each patient by considering the patient as a black box simulator according to the patient biologically situation instead of the physical appearance of a patient such as weight, height and body surface area (BSA).

In future studies, the proposed approach can be presented as a software package to aid oncologist as a useful tool in prescribing the proper and near-optimal drug delivery scenarios in the mixed

Table 4
Estimated patient parameters values [[4](#)].

Parameters	Units	Description	Patient 9 (parameter set 1)	Patient 10 (parameter set 2)
<i>a</i>	day ⁻¹	Tumor growth rate	4.31×10^{-1}	4.31×10^{-1}
<i>b</i>	cells ⁻¹	1/b is tumor carrying capacity	1.02×10^{-9}	1.02×10^{-9}
<i>c</i>	cell ⁻¹ day ⁻¹	Fractional (non)-ligand-transduced tumor cell kill by NK cells	6.41×10^{-11}	6.41×10^{-11}
<i>d</i>	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	1.88
<i>e</i>	day ⁻¹	Fraction of circulating lymphocytes that become NK cells.	2.08×10^{-7}	2.08×10^{-7}
<i>f</i>	None	Exponent of fractional tumor cell kill by CD8 ⁺ T cells. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	2.09	1.81
<i>f</i>	day ⁻¹	Death rate of NK cells.	4.12×10^{-2}	4.12×10^{-2}
<i>g</i>	day ⁻¹	Maximum NK cell recruitment rate by ligand-transduced tumor cells.	1.25×10^{-2}	1.25×10^{-2}
<i>h</i>	cell ²	Steepness coefficient of the NK cell recruitment curve.	2.02×10^7	2.02×10^7
<i>j</i>	day ⁻¹	Maximum CD8 ⁺ T cell recruitment rate. Primed with ligand-transduced cells, challenged with ligand-transduced cells.	2.49×10^{-2}	2.49×10^{-2}
<i>k</i>	cell ²	Steepness coefficient of the CD8 ⁺ T cell recruitment curve.	3.66×10^7	5.66×10^7
<i>m</i>	day ⁻¹	Death rate of CD8 ⁺ T cells.	2.04×10^{-1}	9.12
<i>q</i>	cell ⁻¹ day ⁻¹	CD8 ⁺ Tcell inactivation rate by tumor cells.	1.42×10^{-6}	1.59×10^{-6}
<i>p</i>	cell ⁻¹ day ⁻¹	NK cell inactivation rate by tumor cells.	3.42×10^{-6}	3.59×10^{-6}
<i>s</i>	none	Steepness coefficient of the tumor-(CD8 ⁺ T cell) lysis term D. Primed with ligand-transduced cells, challenged with ligand-transduced cells. (Smaller s → steeper curve)	8.39×10^{-2}	5.12×10^{-1}
<i>r</i> 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}	1.10×10^{-7}
<i>r</i> 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}	6.50×10^{-11}
<i>u</i>	cell ⁻² day ⁻¹	Regulatory function by NK cells of CD8 ⁺ T cells.	3.00×10^{-10}	3.00×10^{-10}
<i>K_T</i>	day ⁻¹	Fractional tumor cell kill by chemotherapy.	9.00×10^{-1}	9.00×10^{-1}
<i>K_N</i>	day ⁻¹	Fractional immune cell kill by chemotherapy.	6.00×10^{-1}	6.00×10^{-1}
<i>K_L</i>	day ⁻¹	Fractional immune cell kill by chemotherapy.	6.00×10^{-1}	6.00×10^{-1}
<i>K_C</i>	day ⁻¹	Fractional immune cell kill by chemotherapy.	6.00×10^{-1}	6.00×10^{-1}

(continued on next page)

Table 4 (continued)

Parameters	Units	Description	Patient 9 (parameter set 1)	Patient 10 (parameter set 2)
α	cellday ⁻¹	Constant source of circulating lymphocytes.	7.50×10^8	5.00×10^8
β	day ⁻¹	Natural death and differentiation of circulating lymphocytes.	1.20×10^{-2}	8.00×10^{-3}
γ	day ⁻¹	Rate of chemotherapy drug decay.	9.00×10^{-1}	9.00×10^{-1}
P_l	day ⁻¹	Maximum CD8 ⁺ T-cell recruitment rate by IL-2.	1.25×10^{-1}	1.25×10^{-1}
g_l	cell ²	Steepness of CD8 ⁺ T-cell recruitment curve by IL-2.	2.00×10^7	2.00×10^7
μ_l	day ⁻¹	Rate of IL-2 drug decay.	1.00×10^1	1.00×10^1

therapy for cancer treatment and increase the survival chance of patient by administration of an adequate drug dose and avoiding overdose or insufficient dose administration during treatment. Also, the authors are working on a new study to comprise the results of using different adaptive control methods on prescribing personalized drug delivery protocols.

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Appendix A. Estimated parameters values for two different patient

Two parameter sets for two different patients, i.e. patient 9 and patient 10, which are studied by de Pillis et al. [4] are given in Table 4.

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