Decentralized Model Reference Adaptive Control Design for Nonlinear Systems; Application to Cancer Treatment

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Abstract— **The paper gives an approach to decentralized Model Reference Adaptive Control (MRAC) design for nonlinear dynamical systems and illustrates the method with an application to cancer treatment. The nonlinear mathematical model of the cancer dynamics is described by a set of differential equations each of which defines the variation of different cell numbers. The model also includes the treatment effects which are specifically defined by immune, vaccine and chemotherapy. The proposed MRAC design methodology is based upon a stable nonlinear reference model which is produced by a state feedback controller using the so called State Dependent Riccati Equation (SDRE) techniques. The plant dynamics is nonlinear by nature and an adaptation methodology is designed such that response of the nonlinear reference model is followed. The adaptation is performed on a state dependent basis mainly using the adaptation mechanism designed for multi input multi output (MIMO) linear time invariant (LTI) systems. The proposed technique is illustrated to develop mixed immunotherapy, chemotherapy and vaccine therapy drug administration for cancer treatment using a tumor growth mathematical model. Simulation results show the effectiveness of the SDRE based MRAC for MIMO nonlinear systems.**

Keywords— Nonlinear Systems, State Dependent Riccati Equations, Decentralized Model Reference Adaptive Control, Cancer Treatment

I. INTRODUCTION

Adaptive control methodologies are widely used to control dynamical systems and processes. The recent efforts on the adaptive control theory are focused on developing adaptation mechanisms to improve the behavior or performance of physical systems by collecting and exploiting knowledge about the system's function. Within this context, Model Reference Adaptive Control (MRAC) plays an important role in the adaptive controller design schemes. One of the most important advantages of MRAC system is its high-speed of adaptation. The characteristics of high-speed of adaptation of MRAC are valuable for the design of adaptive control of nonlinear systems. It is well-known that the nonlinear systems are more complex and need more calculation than linear systems in the MRAC design. A MRAC of a nonlinear system can be demonstrated via a nonlinear transformation as an equivalent feedback system which is a linear time invariant system.

State Dependent Riccati Equation (SDRE) has been an emerging technique for stabilization of nonlinear systems. Although there are a number of other methods for stabilization of nonlinear systems, the SDRE based control strategy is one of the few successful approaches that have important properties, such as applicability to a large class of nonlinear systems, systematic formulation and allowing the control designer to make tradeoff between control effort and state errors. Autopilot design [1], MRAC design for nonlinear systems [5], satellite and spacecraft control [2], control of pendulum on a cart [6], control of aero elastic systems [3] and optimal administration of drug in Cancer treatment [4] are some of the applications of SDRE techniques in recent years.

In the MRAC schemes, many scientists and engineers explore the context of decentralized adaptive control. Decentralized control has been widely used in industry due to ease of implementation, fault tolerance, and reduced computational effort. These advantages make decentralized control techniques attractive for applications in complex dynamical systems. In particular, decentralized adaptive control is employed to stabilize and track the nonlinear, interconnected subsystems with unknown parameters.

In this paper, we extend the SDRE method to decentralized MRAC design for MIMO nonlinear systems and illustrate the method with an application to cancer treatment. For this purpose, we consider a patient with known mathematical model and model parameters and regard the patient as the reference model of the MRAC. The plant model is composed of coupling matrix, therefore they can be treated as modeling error term in the control design. The design of adaptive controllers for multi input multi output (MIMO) plant models is more complex than in the SISO case. This means that instead of designing an adaptive controller for the MIMO plant, we can design N adaptive controllers for N SISO plant models. This approach is known as decentralized adaptive control. Then the objective is to follow the response of stable reference model for the closed-loop subsystems. The proposed MRAC design

978-1-4673-8606-7/16/$31.00 ©2016 IEEE

methodology is based upon a stable nonlinear reference model which is produced by a state feedback controller using the SDRE technique. The plant dynamics is nonlinear by nature and an adaptation methodology is designed such that response of the nonlinear reference model is followed. The adaptation is performed on a state dependent basis mainly using the adaptation mechanism designed for MIMO linear time invariant (LTI) systems. The proposed technique is illustrated to develop mixed immunotherapy, chemotherapy and vaccine therapy drug administration for cancer treatment using a tumor growth mathematical model.

The paper is organized as follows. Section II contains brief review of decentralized MRAC systems. In section III, the proposed SDRE based decentralized MRAC scheme for MIMO nonlinear systems. An application of the suggested control methodology is given in section IV with simulation results for cancer treatment. Section V draws the conclusions.

II. Decentralized MRAC For Systems With State Feedback

The decentralized MRAC for LTI systems are well documented in the literature (see [7-11] for more details). The LTI MIMO system given by

$$\tilde{S}_P: \quad \dot{x}_P = \tilde{A}_P x_P + \tilde{B}_P u_P \tag{1}$$

is described as a collection of *N* MIMO subsystems

$$S_{P_i}: \ \dot{x}_{P_i} = A_{P_i} x_{P_i} + b_{P_i} u_{P_i} + \sum_{j=1}^{N} A_{P_{ij}} x_{P_j} \quad i,j \in N\,; \quad i \neq j \tag{2}$$

The system S_P, which is composed of subsystems S_{P_i} interconnected as in (2), can be given in a compact form as,

$$S_P: \quad \dot{x}_P = A_P x_P + B_P u_P + A_{D_P} x_P \tag{3}$$

where $x_P = (x_1^T, x_2^T, \dots, x_N^T)^T, u_P = (u_1^T, u_2^T, \dots, u_N^T)^T$ are the state and input vectors of S_P at time $t \in R$. In addition to, $A_P = diag(A_{P_i}), B_P = diag(b_{P_i})$, and the coupling block matrices are $A_{D_P} = diag\left(A_{P_{ij}}\right)$.

For each subsystem S_{P_i}, a linear reference model is considered such that

$$\tilde{S}_M: \quad \dot{x}_M = \tilde{A}_M x_M + \tilde{B}_M u_M \tag{4}$$

The LTI system which is described as an interconnection of N subsystems,

$$S_{M_i}: \ \dot{x}_{M_i} = A_{M_i} x_{M_i} + b_{M_i} u_{M_i} + \sum_{j=1}^{N} A_{M_{ij}} x_{M_j} \quad i,j \in N\,; \quad i \neq j \tag{5}$$

The overall system S_M, which is composed of subsystems S_{M_i} interconnected as in (5), can be given in a compact form:

$$S_M: \quad \dot{x}_M = A_M x_M + B_M u_M + A_{D_M} x_M \tag{6}$$

where $x_M = \left(x_{M_1}^T, x_{M_2}^T, \dots, x_{M_N}^T\right)^T$ is the state vector and $u_M = \left(u_{M_1}^T, u_{M_2}^T, \dots, u_{M_N}^T\right)^T$ is the input vector of S_{M_α} at time $t \in R$. In addition to, $A_M = diag(A_{M_i})$, $B_M = diag(b_{M_i})$ and the coupling block matrices are $A_{D_M} = diag\left(A_{M_{ij}}\right)$.

The following adaptive controller is proposed;

$$u_{P_i} = M_i r_i + L_i x_{P_i} \qquad i \in N \tag{7}$$

where $M_i(t) \in R^{q_i \times q_i}$ and $L_i(t) \in R^{q_i \times n_i}$ are time-varying adaptation gains at time $t > t_0$. The control is given in a compact form as $u_P = Mr + Lx_P$. The adaptation gains are formulated as follows;

$$\begin{aligned} \dot{M}_i &= -\sigma_i \Gamma_i M_i - \gamma_i \Gamma_i b_{M_i}^T P_i e_i r_i^T \\ \dot{L}_i &= -\sigma_i \Gamma_i L_i - \gamma_i \Gamma_i b_{M_i}^T P_i e_i x_{P_i}^T \qquad i \in N \end{aligned} \tag{8}$$

where σ_i and γ_i are given positive scalars and $\Gamma_i \in R^{n_i \times n_i}$ is the constant symmetric positive definite matrix (see [17] for the derivation of adaptation gains).

III. SDRE Based Decentralized MRAC For MIMO Nonlinear Systems

State Dependent Riccati Equation (SDRE) based control techniques are widely used to design controllers for nonlinear systems [1, 3, 4, 13, 15]. The details of the SDRE methods are given in [13]. The methodology defined for LTI systems in Section II is extended to nonlinear systems in this section. For this purpose, the following MIMO nonlinear systems are considered

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

where $x = [x_1, x_2, \dots, x_n]^T \in R^n$ is the vector of state variables and $u = [u_1, u_2, \dots, u_q]^T \in R^q$ is the input vector. Also $f(x)$ and $g(x)$ are nonlinear vector functions. Rewriting the nonlinear dynamics (9) in the state dependent coefficient (SDC) matrix form such that $f(x) = A(x)x$, $g(x) = B(x)$, we have

$$\dot{x} = A(x)x + B(x)u \tag{10}$$

Actually, by appraising the SDC matrices for a given state vector, the nonlinear system could be considered as an LTI one which is like a frozen system at the state vector. For this reason for each state vector, an LTI system is acquired allowing one to design the control input u with known approaches for LTI systems. A state dependent feedback control law can then be designed as follows;

$$u(x) = -K(x)x \tag{11}$$

where $K(x)$ is the state dependent feedback gain matrix which can be determined by LQR, pole placement, etc. algorithms. One of the basic assumptions about the SDRE based control design is, $A(x)$ and $B(x)$ should be pointwise controllable [6]. The point-wise controllability condition can be checked from the controllability matrix

$$W(x) = \left[B(x)\ A(x)B(x)\ \dots\ A^{(n-1)}(x)B(x)\right] \tag{12}$$

$Rank[W(x)] = n$ for all x.

In this paper, we consider the N interconnected MIMO nonlinear subsystems. Accordingly, the system equations are recast in the SDC form as follows;

$$S_P(x): \quad \dot{x}_P = A_P(x_P)x_P + B_P(x_P)u_P + A_{D_P}(x_P)x_P \tag{13}$$

where $A_P(x_P)$ and $B_P(x_P)$ are SDC matrices of the decoupled

matrix and $A_{D_P}(x_P)$ the coupling block matrices of the plant with appropriate dimensions. Also the reference model is modified in SDC form as follows;

$$S_M(x_m): \dot{x}_m = A_m(x_m)x_m + B_m(x_m)u_m + A_{D_M}(x_m)x_M \quad (14)$$

where $A_m(x_m)$ and $B_m(x_m)$ are SDC matrices of the reference model with appropriate dimensions. In order to have a desirable reference response, the control law for the reference nonlinear system could be designed as follows;

$$u_m(x_m) = -K_m^T(x_m)x_m + r(x_m) \quad (15)$$

where $K_m^T(x_m)$ is the state feedback gain matrix which may be determined by pole placement technique for each frozen state. Here $r(x_m)$ is the reference model signal to be tracked. The adaptive controller for the nonlinear plant can then be designed as follows;

$$u = M(x)r(x_m) + L(x)x \quad (16)$$

where $M(x)$ and $L(x)$ are state dependent adaptation gains which are regulated by the following adaptation rules;

$$\dot{M}(x) = -\sigma\Gamma\mathrm{M}(x) - \gamma\Gamma B_m^T(x_m)P(x_m)e(x_m, x)r^T(x_m)$$
$$\dot{L}(x) = -\sigma\Gamma\mathrm{L}(x) - \gamma\Gamma B_m^T(x_m)P(x_m)e(x_m, x)x^T \quad (17)$$

Note that the adaptation gains are modified in two different ways; one is the adaptation due to state dependent nature and the second is the adaptation mechanisms defined by (17) which may be considered as an additional adaptation for nonlinear plants.

IV. Mixed Drug Administration for Cancer Treatment

We consider the cancer mathematical model, in the absence of therapy, proposed by de Pillis and Radunskaya (2003) [16], which is compound from six components of follows;

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T(1-e^{-M})T \quad (18)$$

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT - K_N(1-e^{-M})N \quad (19)$$

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T - uNL^2 - K_L(1-e^{-M})L + \frac{P_lLI}{g_I+I} + v_L(t) \quad (20)$$

$$\frac{dC}{dt} = \alpha - \beta C - K_C(1-e^{-M})C \quad (21)$$

$$\frac{dM}{dt} = -\gamma M + v_M(t) \quad (22)$$

$$\frac{dI}{dt} = -\mu_I I + v_I(t) \quad (23)$$

$$D = d\frac{(L/T)^l}{s+(L/T)^l} \quad (24)$$

The tumor-free equilibrium for all six state variables is given by $(T_E, N_E, L_E, C_E, M_E, I_E) = (0, \frac{e\alpha}{\beta f}, 0, \frac{\alpha}{\beta}, 0, 0)$. We shift the equilibrium point to the origin by employing the error states, as follows: $x_1 \triangleq T$, $x_2 \triangleq N - \frac{e\alpha}{\beta f}$, $x_3 \triangleq L$, $x_4 \triangleq C - \frac{\alpha}{\beta}$, $x_5 \triangleq M$, $x_6 \triangleq I$. The new $[x_1\ x_2\ x_3\ x_4\ x_5\ x_6]^T$ state denotes the error state and SDC parameterization of system by using free θ vector will be as follows (see [17] for details):

$$\dot{x}_1 = ax_1(1-bx_1) - cx_1x_2\theta_1 - cx_1x_2(1-\theta_1) - \frac{ce\alpha}{\beta f}x_1 - \frac{dx_3^lx_1\theta_3}{sx_1^l+x_3^l} - \frac{dx_3^lx_1(1-\theta_3)}{sx_1^l+x_3^l} + K_TQx_5x_1\theta_2 + K_TQx_5x_1(1-\theta_2) \quad (25)$$

$$\dot{x}_2 = ex_4 - fx_2 + \frac{ge\alpha}{\beta f}\left(\frac{x_1^2}{h+x_1^2}\right) + \frac{gx_1^2x_2\theta_6}{h+x_1^2} + \frac{gx_1^2x_2(1-\theta_6)}{h+x_1^2} - Px_1x_2\theta_4 - Px_1x_2(1-\theta_4) - \frac{Pe\alpha}{\beta f}x_1 + K_NQx_2x_5\theta_5 + K_NQx_2x_5(1-\theta_5) + K_N\frac{e\alpha Q}{\beta f}x_5 \quad (26)$$

$$\dot{x}_3 = -mx_3 + \frac{jd^2x_3^{2l}x_1^2\theta_{13}}{h\left(sx_1^l+x_3^l\right)^2 + d^2x_3^{2l}x_1^2}x_3 + \frac{jd^2x_3^{2l}x_1^2(1-\theta_{13})}{h\left(sx_1^l+x_3^l\right)^2 + d^2x_3^{2l}x_1^2}x_3 - qx_3x_1\theta_7 - qx_3x_1(1-\theta_7) + r_1x_1x_2\theta_{11} + r_1x_1x_2(1-\theta_{11}) + \frac{r_1\alpha Q}{\beta f}x_1 + r_2x_1x_4\theta_{12} + r_2x_1x_4(1-\theta_{12}) + \frac{r_2\alpha}{\beta}x_1 - ux_3^2x_2\theta_{10} - ux_3^2x_2(1-\theta_{10}) - \frac{u\alpha Q}{\beta f}x_3^2 + K_LQx_5x_3\theta_8 + K_LQx_5x_3(1-\theta_8) + \frac{P_Ix_6x_3\theta_9}{g_I+x_6} + \frac{P_Ix_6x_3(1-\theta_9)}{g_I+x_6} + V_L(t) \quad (27)$$

$$\dot{x}_4 = -\beta x_4 + K_CQx_4x_5\theta_{14} + K_CQx_4x_5(1-\theta_{14}) + \frac{K_C\alpha Q}{\beta}x_5 \quad (28)$$

$$\dot{x}_5 = -\gamma x_5 + V_M(t) \quad (29)$$

$$\dot{x}_6 = -\mu_I x_6 + V_I(t) \quad (30)$$

The parameter $\theta\epsilon\mathbb{R}^{14}$ is selected from the pointwise stability point of view for $\{A(x,\theta), B\}$ pair. We assumed that $\theta_i \in [0,1]$; $i = 1; 2; \ldots; 14$. Then we numerically determine that maximum pointwise controllable space related to different sets of θ parameter. The result of this numerical study showed that by selecting $\theta = [0{,}5\ 0{,}5\ 0{,}5\ 0\ 0{,}5\ 0\ 0\ 0\ 0{,}5\ 0\ 1\ 1\ 1\ 0]$, the maximum value of $\left|det\left(M_c(x)\right)\right|$ and consequently the largest pointwise controllable space for the pair $\{A(x,\theta), B\}$ is achieved [13, 14]. We can now write the SDC matrices as follows;

$$A(x) = \begin{bmatrix} a_{11} & a_{12} & a_{13} & 0 & a_{15} & 0 \\ a_{21} & a_{22} & 0 & e & a_{25} & 0 \\ a_{31} & a_{32} & a_{33} & a_{34} & a_{35} & a_{36} \\ 0 & 0 & 0 & a_{44} & a_{45} & 0 \\ 0 & 0 & 0 & 0 & -\gamma & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu_I \end{bmatrix} \qquad B(x) = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

For stabilizing of reference model (cancer patient which all model parameters are known as table I.) we use SDRE optimal control by using LQR method like as [4]. For this propose, the SDRE control is determined for the type quadratic cost functional $J(x) = \int_0^\infty (x^TQ(x)x + u^TR(x)u)dt$,
In which the weighting matrix $Q(x)$ and control weighting $R(x)$ are state dependent. For simplicity of problem we use constant weighting matrices Q and R as follows:

$$Q = 10^8 \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}, \qquad R = 10^6 \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

In this section, to show the effectiveness of proposed algorithm, we consider two cancer patients, first patient with known parameters (Table I.) as reference model and the second patient with different nonlinear mathematical model and unknown parameters as unknown plant dynamics. Initial conditions and model parameters for both models are 2×10^7 Tumor cells, 1×10^3 NK cells, 10 CD8$^+$T cells, and 6×10^8 number of circulating lymphocytes. $v_L = 10^9$, for the CD8$^+$T cell population represents an immunotherapy in which immune cell levels are boosted. The drug intervention terms in the equations for $v_M = 5$ and $v_I = 5 \times 10^6$ reflect the amount of chemotherapy and immunotherapy drug given over time.

By using the SDRE based decentralized MRAC for MIMO nonlinear systems defined in Section III, we apply the suggested algorithm to develop mixed immunotherapy, chemotherapy and vaccine therapy drug administration for cancer treatment using a tumor growth mathematical model [16]. The plant dynamics, reference model, the controller and the control input of the reference model are as follows;

Nonlinear plant system; $\dot{x} = A_P(x_P)x_P + B_P(x_P)u_P$

Decentralized plant dynamics;

$$\dot{x}_{P_i} = A_{P_i}(x_P)x_{P_i} + b_{P_i}(x_P)u_{P_i} + A_{D_{P_j}}(x_P)x_{P_j}$$

Model reference nonlinear system;

$$\dot{x}_M = A_m(x_m)x_m + B_m(x_m)u_m$$

Decentralized model reference dynamics;

$$\dot{x}_{M_i} = A_{M_i}(x_M)x_{M_i} + b_{M_i}(x_M)u_{M_i} + A_{D_{M_j}}(x_M)x_{M_j}$$

The decentralized control law; $u_{P_i} = M_i(x_P)r_i + L_i(x_P)x_{P_i}$

The control input of the reference model is given by

$$u_{M_i}(x_M) = -K_{M_i}^T(x_M)x_{M_i}$$

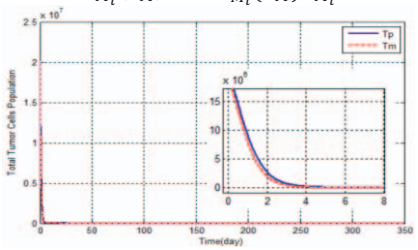

Fig. 1. Tumor cells population of unknown and reference patient

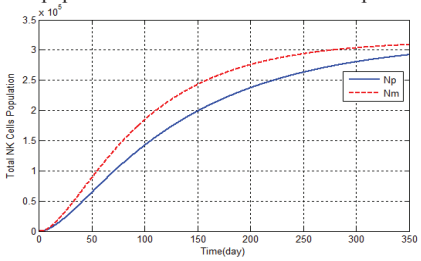

Fig. 2. Total NK cells population of unknown and reference patient

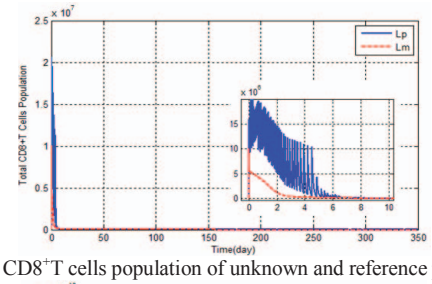

Fig. 3. Total CD8$^+$T cells population of unknown and reference patient

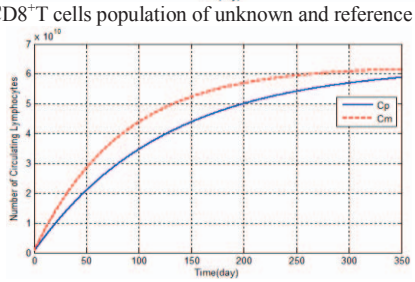

Fig. 4. Number of circulating lymphocytes of unknown and reference patient

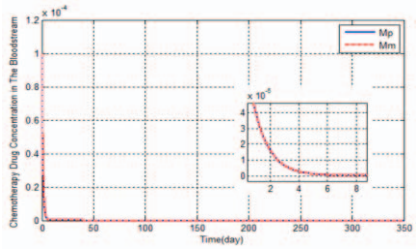

Fig. 5. Chemotherapy drug concentration in the bloodstream of unknown and reference patient

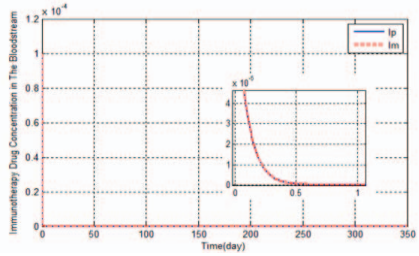

Fig. 6. Immunotherapy drug concentration in the bloodstream of unknown and reference patient

Figures 1 to 6 illustrate the responses of both the "reference patient" and the "unknown patient". Clearly the number of tumor cells for both patients eradicate in a short period of treatment as given in Fig.1. The proposed decentralized MRAC scheme adjusts the drug amounts to stabilize the other cells of the unknown patient. Fig. 2 shows that the NK cell of the unknown patient reaches to the normal level and follows the response of reference patient. Similarly, $CD8^+T$ cell of the unknown patient and circulating lymphocytes of the unknown patient follow the responses of the reference patient as seen in Figs. 3 and 4 respectively. Figs 5 and 6 illustrate the drug concentrations in the bloodstream which are the 5th and 6th states of the nonlinear dynamics.

Figures 7, 8 and 9 give the control inputs of the reference patient which are VLm, VIm and VMm respectively. The figures give the simulation results when the bounds on the drugs are considered. Figures 10, 11 and 12 illustrate the control inputs

for the treatment of the reference patient when the bounds on the drugs are released.

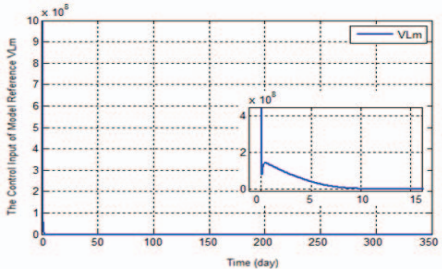

Fig. 7. The control input of reference patient VLm (If $v_{Lm} < 0 \Rightarrow v_{Lm} = 0$, and $v_{Lm} > 10^9 \Rightarrow v_{Lm} = 10^9$.)

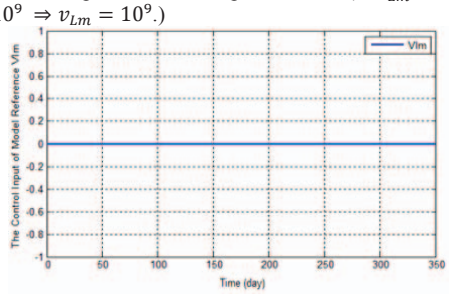

Fig. 8. The control input of reference patient VIm (If $v_{Im} < 0 \Rightarrow v_{Im} = 0$, and $v_{Im} > 5 \times 10^6 \Rightarrow v_{Im} = 5 \times 10^6$.)

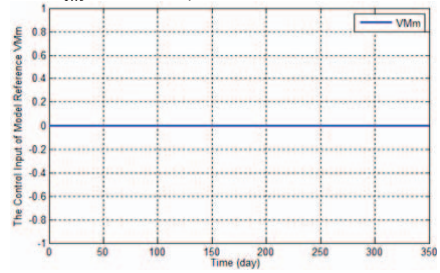

Fig. 9. The control input of reference patient VMm (If $v_{Mm} < 0 \Rightarrow v_{Mm} = 0$, and $v_{Mm} > 5 \Rightarrow v_{Mm} = 5$.)

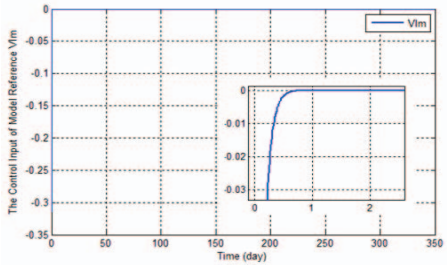

Fig. 10. The control input of reference patient VIm ($v_{Im} = 5 \times 10^6$ at t time of the chemotherapy drug)

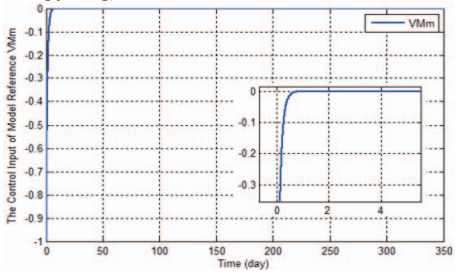

Fig. 11. The control input of reference patient VMm ($v_{Mm} = 5$ at t time of the immunotherapy drug)

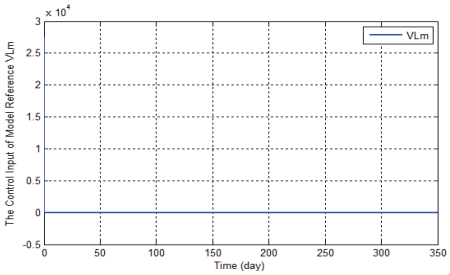

Fig. 12. The control input of reference patient VLm ($v_{Lm} = 10^9$ at t time of the $CD8^+T$ cell population an immunotherapy in which immune cell levels are boosted.

Figures 13, 14 and 15 give the control inputs of the unknown patient which are VLp, VIp and VMp respectively. The figures give the simulation results when the bounds on the drugs are considered. Figures 16, 17 and 18 illustrate the control inputs for the treatment of the unknown patient when the bounds on the drugs are released.

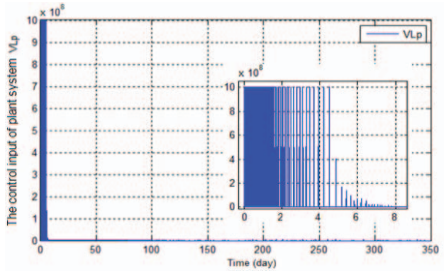

Fig. 13. The control input of unknown patient VLp (If $v_{Lp} < 0 \Rightarrow v_{Lp} = 0$, and $v_{Lp} > 10^9 \Rightarrow v_{Lp} = 10^9$.)

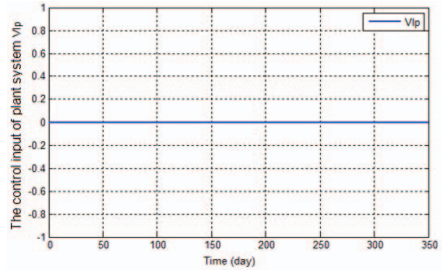

Fig. 14. The control input of unknown patient VIp (If $v_{Ip} < 0 \Rightarrow v_{Ip} = 0$, and $v_{Ip} > 5 \times 10^6 \Rightarrow v_{Ip} = 5 \times 10^6$.)

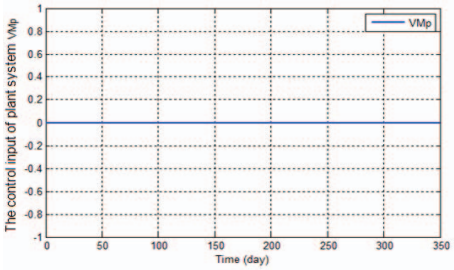

Fig. 15. The control input of unknown patient VMp (If $v_{Mp} < 0 \Rightarrow v_{Mp} = 0$, and $v_{Mp} > 5 \Rightarrow v_{Mp} = 5$.)

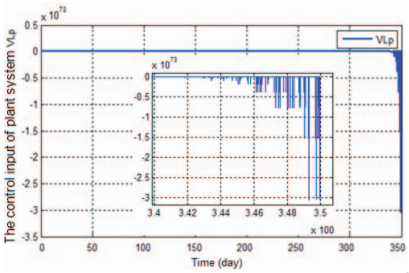

Fig. 16. The control input of unknown patient VLp ($v_{Lp} = 10^9$ at t time of the $CD8^+T$ cell population an immunotherapy in which immune cell levels are boosted.

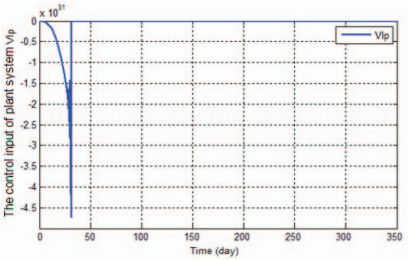

Fig. 17. The control input of unknown patient VIp ($v_{Ip} = 5 \times 10^6$ at t time of the chemotherapy drug)

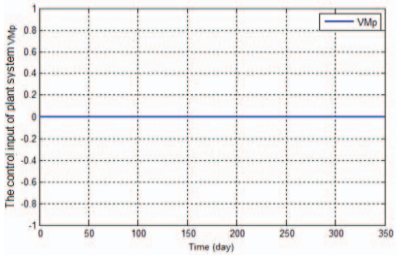

Fig. 18. The control input of unknown patient VMp ($v_{Mp} = 5$ at t time of the immunotherapy drug)

TABLE I. DIFFERENT PARAMETER VALUES OF REFERENCE AND UNKNOWN PATIENT [16]

Reference Patient	Unknown Real Patients
$d_m = 2.34$; $l_m = 2.09$	$d_p = 1.88$; $l_p = 1.81$
$k_m = 3.66 \times 10^7$	$k_p = 5.66 \times 10^7$
$m_m = 2.04 \times 10^{-1}$	$m_p = 9.12$
$q_m = 1.42 \times 10^{-6}$	$q_p = 1.59 \times 10^{-6}$
$p_m = 3.42 \times 10^{-6}$	$p_p = 3.59 \times 10^{-6}$
$s_m = 8.39 \times 10^{-2}$	$s_p = 5.12 \times 10^{-1}$

V. CONCLUSIONS

The paper gives an approach to decentralized MRAC design for nonlinear dynamical systems and illustrates the method with an application to cancer treatment. The model also includes the treatment effects which are specifically defined by immune, vaccine and chemotherapy. The method is based on SDRE techniques and combines SDRE with MRAC. By using the state dependent coefficient matrices, the nonlinear system is transformed into an LTI system allowing one to apply the well-known design techniques to nonlinear systems. The plant dynamics is nonlinear by nature and an adaptation methodology is designed such that response of the nonlinear reference model is followed. The adaptation is performed on a state dependent basis mainly using the adaptation mechanism designed for MIMO LTI systems. The nonlinear reference model is first stabilized by using SDRE based control methods and the response of the stable reference model is followed by the nonlinear plant using an adaptation which gives flexibility to the adaptation of the control gains for the nonlinear systems.

ACKNOWLEDGEMENTS

This work is supported by The Scientific and Technological Research Council of Turkish (TUBITAK) under the Project no: 112M209.

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