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State Dependent Riccati Equation Based Model Reference Adaptive Stabilization of Nonlinear Systems with Application to Cancer Treatment*

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Abstract: The paper suggests a new approach to Model Reference Adaptive Control (MRAC) design for stabilization of a class of uncertain nonlinear systems. 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. Based on states of the reference model, the designed stabilizer for the nonlinear reference model is then adapted for the nonlinear plant dynamics with a suitable adaptation mechanism, again by using the SDRE methodology. The proposed technique is illustrated to develop an optimal chemotherapy drug administration for cancer treatment using a tumor growth mathematical model. Simulation results show the effectiveness of the proposed SDRE-based MRAC method for the stabilization of nonlinear systems.

Keywords: Model reference adaptive control, Nonlinear systems, Cancer treatment, Optimal control, State dependent Riccati equation.

1. INTRODUCTION

Adaptive control methods are widely studied for linear time invariant (LTI), time varying and nonlinear systems to deal with plant uncertainty and/or time-varying plant parameters (Åström, & Wittenmark, 1995), (Ioannou & Sun, 1996). The methods may be classified under two main streamlines; Model Reference Adaptive Control (MRAC) and Self-Tuning Regulators (STR). In the MRAC design, the objective is to push the response(s) of unknown plant to track the output of a reference plant asymptotically by adjusting controller gains recursively. MRAC has been proposed for continuous-time systems (Narendra & Annaswamy, 1988; Åström & Wittenmark, 1995; Ioannou & Sun, 1996; Tao, 2003) and extended for discrete-time systems (Goodwin et al., 1980; Goodwin & Sin, 1984; Tao, 2003; Akhtar & Bernstein, 2005; Hoagg et al., 2008). The adaptive control architecture has also been studied for various classes of nonlinear systems (Sastry & Bodson, 1989; Krstic et al., 1995).

State Dependent Riccati Equation (SDRE) based control methods, on the other hand, have been investigated since SDRE strategy has emerged as a very attractive tool for the systematic design of nonlinear controllers. The SDRE methodologies provide an effective way for synthesizing nonlinear feedback controls by allowing nonlinearities in the system states while additionally offering great design flexibility through design matrices (Çimen, 2010). SDRE techniques are used in a wide variety of nonlinear control applications, such as autopilot design (Mracek, 2007), satellite and spacecraft control (Stansbery & Cloutier, 2000), robotics (Erdem & Alleyne, 2001), control of aeroelastic systems (Tadi, 2003) and optimal administration of drug in Cancer treatment (Itik et al., 2010).

In this paper, we propose a new MRAC design method for a class of nonlinear systems by extending the SDRE method to adaptive control. We consider a stable nonlinear reference model which is created by designing a sub-optimal control. The control for the reference model is designed by using SDRE method giving an "*implicit adaptation rule*" in such a way that the control is updated for the SDRE reference model. Then the control signal for the nonlinear plant is generated by using a recursive adaptation procedure such that the plant states tracks the states of nonlinear reference model. The plant dynamics is assumed to be nonlinear and have some uncertain parameters and plant nonlinear structure differ from reference model. The main objective here is to develop an adaptation mechanism for the MRAC of nonlinear systems which is based on the adaptation of SDRE model. The proposed method allows one to design a new adaptive control algorithm for a class of uncertain nonlinear systems. The method has a systematic structure combining the MRAC and SDRE control approaches. The proposed method is applied to a tumor growth model to determine the optimal administrated drug dose.

The paper is organized as follows. Section 2 contains backgrounds of MRAC for LTI systems, and SDRE control methodology for nonlinear systems. The proposed SDRE based MRAC scheme for nonlinear systems is introduced in Section 3. An application of the proposed control methodology to develop a chemotherapy drug administration is given in Section 4. Section 5 gives the conclusions.

2. BACKGROUND FOR MRAC AND SDRE CONTROLS

In this section, basic backgrounds of MRAC and SDRE control methodologies are revisited for the sake of completeness.

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2.1. MRAC Algorithm for Linear Time Invariant Systems

The MRAC relies on a reference model whose desired output or state is taken as a reference trajectory for a plant (see Narendra & Annaswamy, 1988; Åström & Wittenmark, 1995; Ioannou & Sun, 1996; Tao, 2003 for details). The objective of the control design is to adapt the reference model control command for the plant dynamics such that plant output tracks reference model output asymptotically. The controller gains are updated recursively based on the tracking error, reference command and output or state of the plant. Recursive estimation of controller gains is performed using an adaptive law which is, in general, developed from the Lyaponuv stability theorem. Therefore, similar to the stability synthesis of dynamical systems by using a positive definite Lyapunov function, parameter adaptation law is generated.

2. 2. Problem formulation for tracking

Consider the following reference LTI system

$$\dot{x}_m(t) = A_m x_m(t) + B_m u_r(t)\ x_m(0) = x_{m0},\ \ t \geq 0. \qquad (1)$$

where $x_m(t) \in \mathbb{R}^n$ is the state vector for the reference system, $A_m \in \mathbb{R}^{n\times n}$ and $B_m \in \mathbb{R}^{n\times q}$ are system matrices and A_m is Hurwitz. $u_r(t) \in \mathbb{R}^q$ is a bounded reference signal to be followed. The plant is also an LTI system described by

$$\dot{x}(t) = Ax(t) + Bu(t) \quad x(0) = x_0,\ \ t \geq 0. \qquad (2)$$

where $x(t) \in \mathbb{R}^n$ is plant state vector, $A \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times q}$ are possibly unknown constant system matrices while (A, B) are controllable. $u(t) \in \mathbb{R}^q$ is the control input for the plant which is to be designed such that the plant states $x(t)$, track reference model desired states, $x_m(t)$, as close as possible and the tracking error, $e(t) \triangleq x(t) - x_m(t)$, approaches to zero asymptotically. Suppose that all states of the plant, $x(t)$, are accessible for measurement. Then, the proposed adaptive control law for the linear system is in the form

$$u(t) = M(t)u_r(t) - K(t)x(t) \qquad (3)$$

where $M(t) \in \mathbb{R}^{q\times q}$ and $K(t) \in \mathbb{R}^{q\times n}$ are control gain matrices to be estimated recursively for the control of plant dynamics. Control gain matrices $M(t)$ and $K(t)$, and therefore plant input vector $u(t)$ are to be updated in such a way that all signals in the closed loop plant system kept bounded and plant states track reference model states asymptotically. Then the plant closed loop system with the control is given by

$$\dot{x}(t) = \big(A - BK(t)\big)x(t) + BM(t)u_r(t).$$

With known plant system matrices, A and B, *Perfect Model Following* is achieved if the algebraic equations $A - BK^* = A_m$, $BM^* = B_m$ (which are termed as *matching conditions*) are satisfied. By satisfying the matching condition, the system matrices (therefore transfer functions) of the closed loop plant system and reference model are the same and states of the plant approach to the reference states exponentially.

Remark 1. (Åström & Wittenmark, 1995; Ioannou & Sun, 1996) There may not exist K^* and M^* for given A, B, A_m and B_m matrices. For the existence of K^* and M^*, the columns of B_m and $(A - A_m)$ matrices must be the linear combination of B matrix and B and B_m must be linearly independent. For the existence of K^* and M^* for perfect model following, all A, B, A_m and B_m matrices should be in canonical form.

Since the plant matrices A and B are not known exactly, then $K(t)$ and $M(t)$ matrices, those are estimates of K^* and M^* respectively, are used in control law (3).

Assumption 1: *There exists $K^* \in \mathbb{R}^{q\times n}$ and $M^* \in \mathbb{R}^{q\times q}$ matrices so that the matching conditions are satisfied and the sign of M^* is known.*

The adaptation rule for estimating $K(t)$ and $M(t)$ matrices in each iteration can be derived by using the Lyapunov stability theory such that the error dynamics ($\dot{e}(t)$) approaches to zero. The adaptation law for $K(t)$ and $M(t)$ are as follows (see Åström & Wittenmark, 1995 for details):

$$\dot{M}(t) = -sgn(M^*)\,\Gamma_m u_r(t) e^T(t) P B_m \quad M(0) = M_0\,, t \geq 0 \quad (4)$$

$$\dot{K}(t) = sgn(M^*)\Gamma_k x(t) e^T(t) P B_m \quad K(0) = K_0,\ \ t \geq 0 \qquad (5)$$

2.3. Model Reference Adaptive Stabilization Algorithm for Linear Time Invariant Systems with full State Feedback

Now consider the following reference LTI system given by

$$\dot{x}_m(t) = A_m x_m(t) + B_m u_m(t) \quad x_m(0) = x_{m0},\ \ t \geq 0. \quad (6)$$

where $x_m(t) \in \mathbb{R}^n$ is the reference model state vector, $A_m \in \mathbb{R}^{n\times n}$ and $B_m \in \mathbb{R}^{n\times q}$ are system matrices.

Assumption 2. *The $\{A_m, B_m\}$ pair is controllable. A_m may have positive eigenvalues and $u_m(t) \in \mathbb{R}^q$ is a bounded reference control input for the stabilization of closed loop reference system.*

$u_m \in \mathbb{R}^n$ is a bounded state feedback control input (i.,e, $u_m(t) = -K_m x_m(t)$) which is obtained by either using pole placement or optimal control methods such that x_m states in the closed loop system asymptotically approaches to zero. The closed loop system is given by

$$\dot{x}_m(t) = (A_m - B_m K_m)x_m(t) = A_{m_{cl}} x_m(t) \qquad (7)$$

where $A_{m_{cl}}$ is now a Hurwitz matrix and all eigenvalues of $A_{m_{cl}}$ are in the open left half complex plane. Therefore the reference model with desired response will be characterized by $\dot{x}_m(t) = A_{m_{cl}} x_m(t)\ \ x_m(0) = x_{m0},\ \ t \geq 0$. In the reference model proposed by (6), contrary to (1), there is no external reference signal to be followed and $u_r(t) \equiv 0$. Indeed unstable reference model given in (6) is changed to a stable linear autonomous system.

On the other hand, the plant is also assumed to be an LTI system described by (2). Since there is no reference signal, the proposed control law for this linear system is in the form of $u(t) = -K^* x(t)$, where K^* is a state feedback gain matrix for the matching condition. Since A and B matrices are not known exactly, we use the estimate of K^* as follows

$$u(t) = -K(t)x(t) \qquad (8)$$

where $K(t) \in \mathbb{R}^{q\times n}$ is the gain matrix to be recursively estimated for the control of plant dynamics.

Assumption 3: *There exists a $K^* \in \mathbb{R}^n$ so that $A_{m_{cl}} = A - BK^*$. Also, there exists a known or unknown positive definite G matrix where $G \in \mathbb{R}^{q\times q}$, so that $\hat{B} = BG$ is known.*

The following adaptation law is considered,

$$\dot{K}(t) = -\Gamma x(t) e^T(t) P \hat{B}(t) \quad (9)$$

where P satisfies the following Lyapunov equation for the closed loop (stable) reference model (7) for some $Q = Q^T > 0$.

$$A_{m_{cl}}^T P + P A_{m_{cl}} = -Q$$

On the other hand, the following state and control parameter errors are considered

$$e(t) \triangleq x(t) - x_m(t), \quad \widetilde{K}(t) \triangleq K(t) - K^* \quad (10)$$

The error dynamics, $\dot{e}(t)$, is then,

$$\dot{e}(t) = \dot{x}(t) - \dot{x}_m(t) = A_{m_{cl}} e(t) + B\widetilde{K}(t) x(t) \quad (11)$$

Theorem 1: If $u(t)$ and $x(t)$ for all $t \geq 0$ are bounded, then, parameter errors and state error vectors defined by (10) and (11) respectively, are stable at large.

Proof. See Ioannou & Sun, 1996 for the proof of the theorem. □

The block diagram of the model reference adaptive stabilization by state feedback is illustrated in Fig. 1.

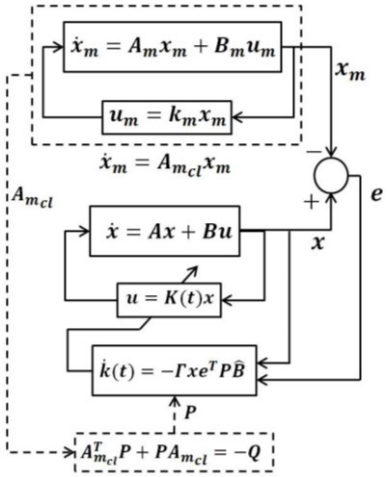

Fig. 1. Block diagram of model reference adaptive stabilization.

Remark 2. It should be noted that the state feedback gain of the adaptive controller given by (8) is determined from (9) which uses the solution of Lyapunov equation giving a constant P matrix for LTI systems. Once the constant P matrix is determined, then the adaptation is characterized by the error between the states of reference model and the plant.

2.4. SDRE Based Control Algorithms for Nonlinear Systems

SDRE based control methods are suggested for a class of nonlinear systems such that the system is described by the following type of nonlinear systems (Çimen, 2010);

$$\dot{x}(t) = f(x) + B(x)u(t), \quad x(0) = x_0 \quad (12)$$

where $x \in \mathbb{R}^n$ is the state vector, $B(x) \in \mathbb{R}^{n \times q}$ and $u \in \mathbb{R}^q$. Suppose that $f(0) = 0$, and $B(x) \neq 0$, $\forall x$, then $f(x)$ can be factorized as $f(x) = A(x)x$, where $A(x) \in \mathbb{R}^{n \times n}$ which yields the following type of equations;

$$\dot{x}(t) = A(x)x(t) + B(x)u(t) \quad (13)$$

where $A(x)$ and $B(x)$ are State Dependent Coefficient (SDC) matrices. In fact, by evaluating the SDC matrices for a given state vector, the nonlinear system is regarded as an LTI one which is like a frozen system at the state vector. Therefore for each state vector, an LTI system is obtained allowing one to design the control input u with the well known approaches for LTI systems. For instance, a state dependent feedback control may be designed as $u(x) = -K(x)x(t)$ where $K(x) \in \mathbb{R}^{q \times n}$ is the state dependent feedback gains and is designed at each instant to satisfy the local stability. It is clear that an optimal control design may also be achieved by solving algebraic state dependent Riccati equations. The details on how to design the controller as well as other issues related to stability are well documented in Çimen (2010). It should be noted that one of the basic assumptions about the SDRE based control design is, $\{A(x), B(x)\}$ pair should be point-wise controllable.

3. SDRE BASED MRAC FOR STABILIZATION OF UNCERTAIN NONLINEAR SYSTEMS

Consider now a nonlinear plant dynamics whose mathematical model is given by (13). The main objective here is to design a model reference adaptive controller for the plant where the reference model is also nonlinear and is given by

$$\dot{x}_m(t) = A_m(x_m)x_m(t) + B_m(x_m)u_m(t) \quad (14)$$

where $A_m(x_m)$ and $B_m(x_m)$ are SDC matrices of the reference model with proper dimensions. By assuming point-wise controllability, the stabilizing full state feedback control law for the reference nonlinear system may be designed as $u_m(x_m) = -K_m(x_m)x_m$ where $K_m(x_m)$ is the state dependent feedback gain matrix which may be determined by pole placement, LQR, etc. For the MRAC of unknown nonlinear plant dynamics defined by (13) and nonlinear reference model (14), we consider the following assumptions.

Assumption 4:

1. *$\{A(x), B(x)\}$ and $\{A_m(x_m), B_m(x_m)\}$ pairs are point-wise controllable,*
2. *There exist a $K^*(x) \in \mathbb{R}^n$ so that $A_{m_{cl}}(x) = A(x) - B(x)K^{*T}(x)$. There also exists a known or unknown positive definite matrix $W \in \mathbb{R}^{q \times q}$, so that $\hat{B}(x) = B(x)W$ is known.*

By applying full state feedback controller in (14) we have

$$\dot{x}_m = (A_m(x_m) - B_m(x_m)K_m(x_m))x_m \triangleq A_{m_{cl}}(x_m)x_m \quad (15)$$

where $A_{m_{cl}}(x)$ is a point-wise Hurwitz with desired (exponential) stability characteristics. Then, we propose the following controller for the uncertain/unknown nonlinear plant $u(t) = -K(x)x(t)$, where $K(x)$ is a state dependent gain which is adjusted by the following adaptation rule;

$$\dot{K}(x) = -\Gamma x e^T(x, x_m) P(x_m) \hat{B}(x_m), \quad K(0) = K_0, \quad (16)$$

Adaptation laws structure is similar to that of LTI systems adaptation rule (which is defined by (9)).

Remark 3. In the model reference adaptive stabilization of LTI case, we solve the differential equation (9) for a zero initial condition in order to determine the control gain matrix, K. On the other hand, in the SDRE based MRAC, the values of $K(x)$ at each evaluation is used as a new initial condition in

order to evaluate the new $K(x)$. In point of fact initial conditions for $K(x)$ are updated at each step of iteration and $K(x_n)$ values are used as initial conditions for the evaluation process of $K(x_{n+1})$. Despite the classical MRAC approach, the state dependent $B_m(x_m)$ and $P(x_m)$ matrices are altered at each iteration and these matrices are evaluated at each iteration with the state vector of x_m. The $P(x_m)$ matrix is the solution of frozen Lyapunov equations giving one another adaptation (an implicit adaptation) for the adaptation of state feedback gain.

The main objective of the proposed algorithm is to stabilize unknown/uncertain nonlinear plant dynamics based on stabilization process of nonlinear reference model, which has totally different structure and parameters. Indeed the proposed method eliminates twice effort for designing another stabilization controller for the nonlinear plant.

4. SDRE BASED MODEL REFERENCE ADAPTIVE STABILIZATION IN CANCER TREATMENT

4.1. Mathematical model of tumor growth

We consider the cancer mathematical model, in the absence of therapy, proposed by de Pillis and Radunskaya (2003), which is compound from three components of $N(t), I(t),$ and $T(t)$.

$$\begin{aligned}\dot{N} &= r_2 N(1 - B_2 N) - C_4 TN \\ \dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN \\ \dot{I} &= s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I\end{aligned} \tag{17}$$

where $I(t)$, $T(t)$, and $N(t)$ denote the number of immune cells, tumor cells and normal cells at time *t*, respectively. The proposed mathematical model does not belong to any specific kind of cancer (see de Pillis and Radunskaya, 2003). It should be mentioned that in this model the effect of drug does not take into account in system and there is no chemotherapy. Considering the fact that chemotherapy kills all cells populations with different rate, the chemotherapy effects in the model is considered with an additional state $M(t)$ and control input $u(t)$ which denote drug concentration in the blood stream and external injected drug respectively. The model with chemotherapy which proposed by Itik et al. (2010) is as follows;

$$\begin{aligned}\dot{N} &= r_2 N(1 - B_2 N) - C_4 TN - a_3 MN \\ \dot{T} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2 MT \\ \dot{I} &= s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1 MI \\ \dot{M} &= u(t) - d_2 M\end{aligned} \tag{18}$$

The parameter sets and variation range of parameters which proposed by de Pillis and Radunskaya (2003), are given in Table 1. The parameter set may vary from one type of cancer to another type as well as for different patients.

In the absence of chemotherapy, the cancer system has three different types of equilibrium points which are (1) Tumor-free (no tumor cells), (2) Dead (no normal cells), and (3) Coexisting (both normal and tumor cells exist). In chemotherapy, we try to bring the system to the tumor-free equilibrium point $(1/b_2, 0, s/d_1, 0)$ by determining the appropriate dose of drug in treatment period. In tumor-free equilibrium point with the given parameters in Table 1, we have the normal cells population of $N = 1/b_2 = 1$ and immune cells population of $I = s/d_1 = 1.65$ with zero tumor cells population level, $T = 0$, and zero drug concentration in blood, $M = 0$. By employing the following error states, we shift the tumor-free equilibrium point $(1/b_2, 0, s/d_1, 0)$ of the system to the origin as $x_1 \triangleq N - \frac{1}{b_2}, x_2 \triangleq T, x_3 \triangleq I - \frac{s}{d_1}, x_4 \triangleq M$. The new $[x_1\ x_2\ x_3\ x_4]^T$ states denote the error states and system (18) can be defined in the new coordinates as follows.

$$\dot{x}_1 = -r_2 x_1(1 + b_2 x_1) - \frac{c_4}{b_2} x_2 - \frac{a_3}{b_2} x_4 - c_4 x_1 x_2 - a_3 x_1 x_4 \tag{19}$$

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

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

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

Table 1. Parameter values and their variation range (de Pillis and Radunskaya, 2003)

Para-meters	Description	Value	Considerations
a_1	Immune cell kill by chemotherapy	0.2	$0 \le \alpha_i \le 0.5$ $a_3 \le a_1 \le a_2$
a_2	Tumor cell kill by chemotherapy	0.3	
a_3	Normal cell kill by chemotherapy	0.1	
b_1	Tumor cell carrying capacity	1.0	$b_1^{-1} \le b_2^{-1}$
b_2	Normal cell carrying capacity	1.0	
c_1	Immune cell kill by tumor cells	1.0	$c_i > 0$
c_2	Tumor cell kill by immune cells	0.5	
c_3	Tumor cell kill by normal cells	1.0	
c_4	Normal cell kill by tumor cells	1.0	
d_1	Death rate of immune cells	0.2	
d_2	Death rate of chemotherapy drug	1.0	
r_1	Tumor cells growth rate	1.5	$r_1 > r_2$
r_2	Normal cells growth rate	1.0	
s	Immune cells steady source rate	0.33	$0 \le s \le 0.5$
α	Immune threshold rate	0.3	
ρ	Immune response rate	0.01	$0 \le \rho \le 2.5$

We use the following pseudo-linear representation as SDC matrices for the system (19):

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

$$B(x) = [0, 0, 0, 1]^T. \tag{20}$$

4.2. Optimal Control of Cancer Treatment

For stabilizing (19), we take the parameters from Table 1 and use SDRE optimal control method suggested by Itik et al. (2010). For this purpose, the SDRE control is determined to minimize the following cost functional;

$$J(x) = \int_0^\infty (x^T Q(x) x + R(x) u^2) dt, \tag{21}$$

The weighting matrix $Q(x)$ and control weighting $R(x)$ are state dependent. For simplicity, we use constant Q and R matrices in the simulations. The weighting matrices are

selected as $Q = \text{diag}\{12 \quad 6 \quad 0 \quad 0.1\}$, $R = 1$. Since the control input is the dosage of external injected drug, buy considering the fact that maximum dosage of injected drug should be limited in healthy amount, we apply constraint to the control signal as: $0 \leq u \leq u_{max} = 1$.

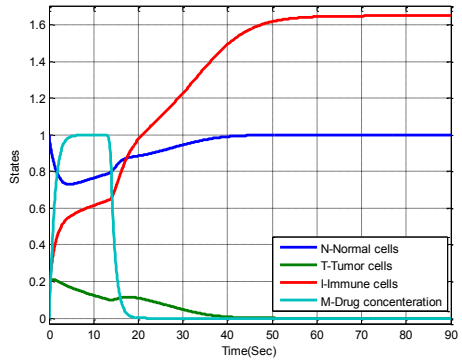

Fig. 2. Response of the system with optimal control input.

The simulation result for optimal control of reference model (with the parameter set of Table 1) is given in Fig. 2.

4.3. SDRE Based Model Reference Adaptive Stabilization for Cancer Treatment

In this section, in order to show the effectiveness of the proposed algorithm we consider two cancer patients. The first patient is described by (19) with known parameters (Table 1.). The second patient, on the other hand, is described by a different nonlinear mathematical model with unknown parameters which is considered as the unknown patient. For the plant model, we consider the mathematical model proposed by de Pillis and Radunskaya (2003), as follows:

$$\dot{N} = r_2 N(1 - b_2 N) - c_4 TN - a_3(1 - e^{-M})N \tag{22}$$

$$\dot{T} = r_1 T(1 - b_1 T) - c_2 IT - c_3 TN - a_2(1 - e^{-M})T$$

$$\dot{I} = s + \frac{\rho IT}{\alpha + T} - c_1 IT - d_1 I - a_1(1 - e^{-M})I$$

$$\dot{M} = u(t) - d_2 M$$

By applying the same procedure for the reference model, we can rewrite the model in the state space form with new error states as follows;

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

$$B_m(x) = [0, 0, 0, 1]^T \tag{23}$$

where $g = 1 - e^{-M} = 1 - e^{-x_4}$

Different nonlinear dynamics are selected for "reference model" and "plant" in order to demonstrate the sufficiency and capability of proposed algorithm in stabilizing unknown/uncertain nonlinear plant dynamics based on reference model with different nonlinear structures and parameters. The main objective of the given algorithm is to generate the stabilization signal (administrated drug dosage) to the unknown patient (plant) based on the reference patient (model), for bringing tumor cells population to zero and normal cell population to healthy level with determined administrated drug value for the unknown patient. To determine the proper administrated drug dose for unknown patient, the gains of state feedback controller, K, is adjusted by using (16). In order to demonstrate the effectiveness of proposed algorithm, we consider the following scenario in the simulations.

Parameters of reference patient are not equal to parameters of unknown patient. However initial conditions of reference patient are equal to initial condition of unknown patient. To show the effects of adaptation rate (Γ) on response of plant and administrated drug dose (control signal), we consider two different adaptation rates as $\Gamma_1 = 0.1$ and $\Gamma_2 = 1$. Initial conditions and different model parameters for both models are given in Table 2 and Table 3 respectively. The parameters which are not given in Table 3, are equal to each other. These parameters are given as $b_1 = 1$, $b_2 = 1$, $c_1 = 1$, $c_3 = 1$, $c_4 = 1$, $d_1 = 0.2$, $d_2 = 1$, $s = 0.33$.

Table 2. Initial conditions.

	Normal cells	Tumor cells	Immune cells
Reference patient	1	0.2	0.15
Unknown patient	1	0.2	0.15

Table 3. Parameters of reference and unknown patient.

	Reference patient	Unknown patient
a_1	0.2	0.1
a_2	0.3	0.5
a_3	0.1	0.06
c_2	0.5	0.58
r_1	1.5	1.7
r_2	1	1.3
α	0.3	0.5
ρ	0.01	0.06

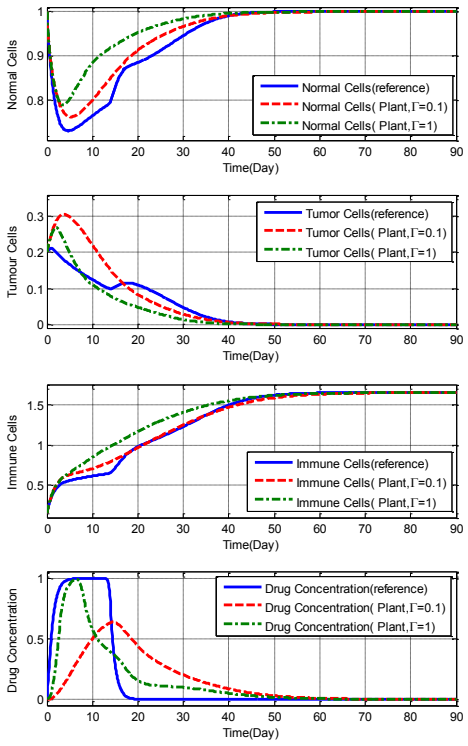

Fig. 3. Responses of reference and plant models.

The simulation results are shown in Figures 3-5. In Fig. 3, the stabilization of plant dynamics based on reference model is illustrated. The administrated drug dose for the unknown patient is determined by the adaptation of reference model sub-optimal controller. As shown, stabilization with $\Gamma_2 = 1$ gives faster convergence for the state vector $x(t)$ than the adaptation rate $\Gamma_1 = 0.1$. With big values of adaptation rate, dose of administrated drug increases without any tangible decreasing in stabilization time. Reference and adapted administrated drug dosages are illustrated in Fig. 4. Control signal for case with $\Gamma = 1$ is more than the case with $\Gamma = 0.1$. Fig. 5 shows the control gain matrix, K(t), parameters for $\Gamma = 1$. As indicated, the big value of Γ results in faster adaptation but causes more fluctuation in the gain matrix parameters and consequently in control signal.

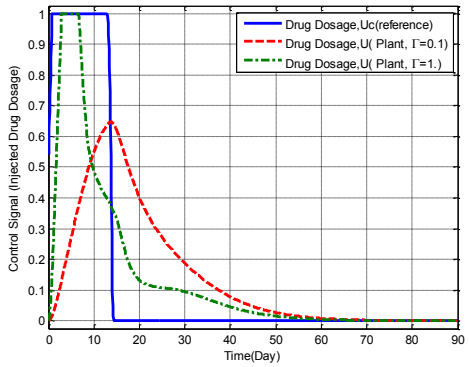

Fig. 4. Control signal (administrated drug) for reference and unknown plant models.

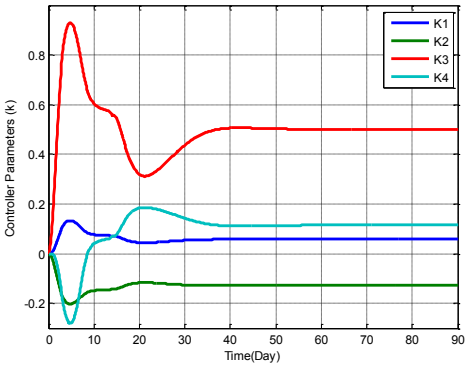

Fig. 5. Controller parameters with $\Gamma = 1$.

5. CONCLUSIONS

A new MRAC algorithm for the stabilization of uncertain nonlinear systems is proposed. The method is based on SDRE techniques and combines SDRE with MRAC such that plant states track a stabilized reference model states. With the design flexibility of SDRE, the adaptation rule is extended to nonlinear SDC matrices. At each step of evaluation, the nonlinear system is transformed into an LTI system by using the state values in SDC matrices. Then MRAC for LTI systems is used to design the adaptive controller. The proposed algorithm is used to determine chemotherapy administration of a patient whose tumor growth dynamics is unknown. Simulation results show that the algorithm successfully determines the proper drug dosage for another patient with uncertain/unknown plant model or parameters.

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