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Adaptive fuzzy back-stepping control of drug dosage regimen in cancer treatment

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ABSTRACT

This paper presents an intelligent controller for MIMO cancer immunotherapy system. The treatment objective is obtaining a suitable scheduling scheme for drug dosage to decrease the tumor cells. Utilizing the back-stepping technique and property of universal approximation of the fuzzy systems, an adaptive fuzzy back-stepping controller for the MIMO cancer immunotherapy system is proposed. The response of closed-loop system is valid for any initial conditions and robust performance of the overall system for a wide range of the parameter uncertainties can be guaranteed. Simulation results clarify the efficiency of the suggested approach in the reduction of the number of tumor cells in the cancer model.

1. Introduction

The second cause of death in the human is cancer [1]. Radiotherapy, immunotherapy, chemotherapy, surgery or multiple therapies can be employed to cancer treatment. In some cases, the side effects of treatment are extremely high. In some cases, even after the expiration of the treatment, there is a possibility of recurrence. These therapies must be scheduling carefully to achieve tumor elimination. Immunotherapy in cancer is a common mode of treatment which enhances the immune system to eradicate tumors. Nowadays, the major contribution of researchs are allocated to development mathematical equations of the describing tumor–immune dynamics [2–5]. Also in these models, the relations between tumor and immune system are understandable. In this paper, the Kirschner and Penetta model is used to describe the tumor-immune dynamics which despite its Simplicity, it has the most important conceptions of cancer-immune dynamics including immunity Interleukin-2 dynamics. Already various nonlinear control methods have been presented to achieve the optimal schedule in many of pharmaceutic therapy [6–9]. Optimal schedules for drug administration in immunotherapy has become one of the most common approaches in recent studies.

The goal of [10] is to formulate an optimal control issue and solve it. The chemotherapeutic schedule is obtained as minimizes the tumor load, the negative aspects of drugs on healthy cells is considered. The novel Feedback Linearization Control is presented for MIMO Cancer Immunotherapy in [11]. In [12], a model predictive control with moving horizon has been used to determine an optimal dosing of cancer chemotherapy. [13] proposes an optimal immunotherapy control of aggressive tumors growth. In [14] an adaptive control method has been used to control the drug usage, and the performance of the three uncertain models have been compared. [15] benefits the optimal control theory and displays the stability and usefulness of the optimization approach to reduce cancer load but the tumor is not eliminated completely.

In recent decades, considerable improvements have been made in the control of nonlinear systems. The adaptive fuzzy control method is one of modern and almost the most effective methods for the nonlinear control. This paper aims to demonstrate that adaptive fuzzy based on the back-stepping design is a proper and effective approach for scheduling cancer therapy and ensuring that the stability is satisfied. According to our suggested method in this research, the amount of tumor cell is reduced to around zero when the achieved suitable schedule of injections of LAK or TIL is applied.

This paper is organized as follows: In Section 2, the description of the Panetta Kirschner model is presented. In Section 3, a brief description of fuzzy systems is expressed, Section 4 develops the proposed control method. In Section 5, the results are shown and finally, the conclusion is given in Section 6.

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Table 1
System parameters.

c	Antigenicity
μ_2	Death rate of immune cells
p_1	Proliferation rate of immune cells
g_2	Half-sat. for cancer clearance
r_2	Cancer growth rate
b	Logistic growth of cancer capacity
μ_3	Half-life of effector molecule
p_2	Production rate of effector molecule
g_1	Half sat. for proliferation term
a	Cancer clearance term
g_3	Half-sat. of production

Table 2
Parameters value.

Eq. (1)	$g_1 = 2 * 10^7$	$p_1 = 0.1245$	$\mu_2 = 0.03$	$0 \le c \le 0.05$
Eq. (2)	$a = 1$	$b = 1 * 10^{-9}$	$r_2 = 0.18$	$g_2 = 1 * 10^5$
Eq. (3)		$g_3 = 1 * 10^3$	$p_2 = 5$	$\mu_3 = 10$

2. Kirschner model

A tumor–immune model that contains a set of differential equation is represented by Kuznetsov. Tumor cells and effector cells are two main populations in this model [16]. In 1998 this model was developed by Kirschner and Panetta. They constructed a mathematical model by combining (IL-2) dynamics with tumor–immune dynamics. The tumor and the immune system interactions well have been explained by this effort. With despite the simple form of this model most important concepts of cancer such as tumor relapse and the oscillations in tumor sizes are exhibited.

This model is expressed by the following differential equations

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L} + u_1 \tag{1a}$$

$$\frac{dT}{dt} = r_2(1 - bT)T - \frac{aET}{g_2 + T} \tag{1b}$$

$$\frac{dI_L}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 I_L + u_2 \tag{1c}$$

Parameters of the system and their values are given in Table 1 and 2.

Where E, T, and I_L represent the number of effector cells, tumor cells, and the concentration of IL-2, respectively. The parameter c models the antigenicity of the tumor. The second term in (1a) represents natural death and p_1 is the maximal production rate of an effector cell and g_1 is the semi-saturation point. Third is the proliferative enhancement effect of the cytokine I_L Lastly u_1 represents an external source of effector cells such as lymphokine-activated killer (LAK) or tumor infiltrating lymphocyte (TIL) cells. In Eq. (1b), the first term represents tumor growth and the second term is a clearance term by the immune effector cells at rate a. This rate is constant, $g_1$represents the strength of the immune response. Eq. (1c) gives the rate of change in the concentration of I_L, while the meanings of g_2, g_3, a, and p_2 are similar to g_1 and p_1. The term μ_3 indicates the degraded rate of IL-2.the final term is u_2 indicate an external source of effector cells such as LAK or TIL cells.

3. Fuzzy system and fuzzy control

Most practical systems are multivariable and nonlinear. Control of the nonlinear multivariable systems is widely investigated and become one of the most important topics in control system. Designing a robust controller for complex and ill-defined systems is facing many difficulties and challenges in the domain of system and control. To overcome this issue, already some techniques such as fuzzy control have been employed [17].

It is evident that the fuzzy systems can approximate nonlinear continuous functions with an arbitrary accuracy. A fuzzy inference system comprises of four parts: the knowledge base, the fuzzifier, the fuzzy inference engine and the defuzzifier. The knowledge base of a zero order TSK fuzzy system [17] includes a set of fuzzy IF–THEN rules as

$$R^l : \text{IF } x_1 \text{ is } F_1^l \text{ and } \ldots \text{ and } x_n \text{ is } F_n^l \text{ THEN } y = \bar{y}^l, \quad l = 1, 2, \ldots, N$$

Where $\boldsymbol{X} = [x_1, \ldots, x_n]^T \varepsilon R^n$ and yεR are the input and output of the fuzzy system, respectively. $F_i^l$is the fuzzy set of input $x_i\,(i = 1, 2, \ldots, n)$ and $\bar{y}^l$ is a constant, both in rule l and N is number of fuzzy rules.

Through a singleton fuzzification, a product inference and a weighted average [17], the output of the fuzzy system can be expressed as follows

$$y(X|\theta) = \frac{\sum_{l=1}^{N} \overline{y_l} \prod_{i=1}^{n} \mu_{F_i^l}(x_i)}{\sum_{l=1}^{N} [\prod_{i=1}^{n} \mu_{F_i^l}(x_i)]} = \theta^T \varphi(X) \tag{2}$$

$\boldsymbol{\theta} = \left[\bar{y}^1, \ldots, \bar{y}^N\right]^T \varepsilon R^N$ is the vector of output singleton membership functions and $\mu_{F_i^l}$ is the membership function of fuzzy set F_i^l. Also $\boldsymbol{\varphi}(\boldsymbol{X}) = [\varphi^1, \ldots, \varphi^N]^T$ is the vector of fuzzy basis functions. Each element of $\boldsymbol{\varphi}(\boldsymbol{X})$ is defined as

$$\varphi^l(\boldsymbol{X}) = \frac{\prod_{i=1}^{n} \mu_{F_i^l}(x_i)}{\sum_{l=1}^{N} [\prod_{i=1}^{n} \mu_{F_i^l}(x_i)]}$$

The optimal parameters vector θ* is defined as

$$\boldsymbol{\theta}^* = \underset{\boldsymbol{\theta} \epsilon R^N}{argmin}(\sup_{X \epsilon R^n} |y(\boldsymbol{X}|\boldsymbol{\theta}) - y(X)|) \tag{3}$$

The minimum approximation error for the fuzzy system can be expressed in terms of the optimal parameters vector as:

$$\omega = y\left(\boldsymbol{X}|\boldsymbol{\theta}^*\right) - y\left(\boldsymbol{X}\right)$$

The universal approximation property of the fuzzy inference system is expressed by the following lemma.

Lemma 1[16]: For any continuous function $f(\boldsymbol{X})$ on the compact set ΩX and arbitrary small positive constant ε, a fuzzy inference system $y\left(\boldsymbol{X}|\boldsymbol{\theta}\right)$ given by (2) can be found such that: $\sup_{\boldsymbol{X} \in \Omega_{\boldsymbol{X}}} |y\left(\boldsymbol{X}|\boldsymbol{\theta}\right) - f(\boldsymbol{X})| \le \varepsilon$.

To ensure the robust performance of the systems, uncertainty should be compensated. Recently, active research has been carried out in adaptive control [18–20] in order to bring robustness against uncertainties in nonlinear systems with parametric uncertainties and external disturbance [18]. Several stable adaptive fuzzy control schemes have been developed for single-input–single-output (SISO) and multiple-input–multiple-output (MIMO) nonlinear systems [19–26].

For designing a fuzzy adaptive control system, two distinct scheme are considered: direct and indirect [27–29]. In the direct adaptive fuzzy control design, a fuzzy system is used to approximate the ideal controller [27,28]. In the indirect method, a controller is generated by the estimated system dynamics that is obtained based on fuzzy systems [29]. For both methods, some adaptive laws based on Lyapunov theory methods are employed to adjust the fuzzy parameters directly.

Nowadays, back-stepping controls have been extensively investigated among various control approaches. Also, some adaptive fuzzy controllers have been constructed for nonlinear systems with unknown nonlinear functions based on back-stepping methodology [30]. The controller can cope with unknown parameters and unknown nonlinear functions by means of the back-stepping

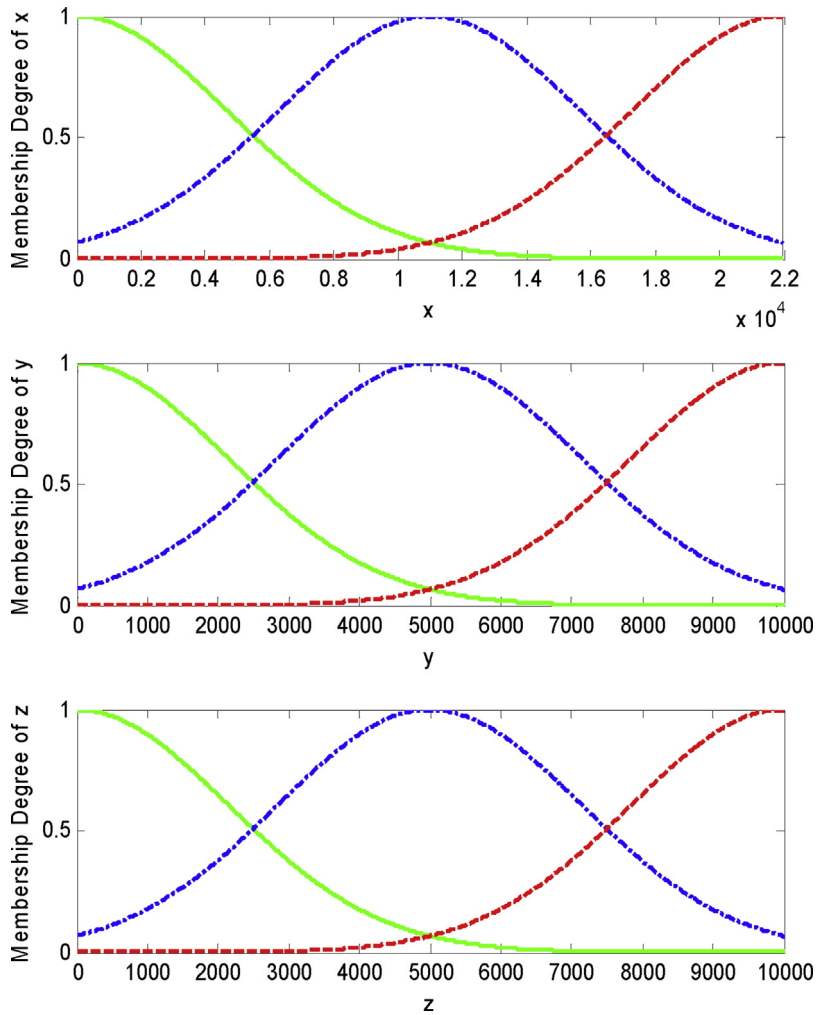

Fig. 1. The membership functions for variables x, y and z.

approach [19,31,32]. The other advantage of this scheme is that uncertainties in systems need not satisfy the matching conditions.

Compared with the other adaptive control schemes, the control methods using fuzzy systems have a main advantage that a linear parameterization condition is not required. So in this paper an adaptive fuzzy back-stepping scheme is used to control the system. The controller is MIMO and it is assumed that all states of the systems are measurable. In other word, the goal of this study is to design an adaptive fuzzy back-stepping controller for the proposed immunotherapy model, such that the asymptotic stability of the number of tumor cells to zero is guaranteed and the all signals of the closed loop system remain bounded.

4. Methodology

Now it will be shown how to design a controller that causes the number of tumor cells converge to zero asymptotically. The system model (1) is written as

$$\frac{dx}{dt} = cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + u_1 \tag{4a}$$

$$\frac{dy}{dt} = r_2(1 - by)y - \frac{axy}{g_2 + y} \tag{4b}$$

$$\frac{dz}{dt} = \frac{p_2 xy}{g_3 + y} - \mu_3 z + u_2 \tag{4c}$$

in which $[xyz] = [ETI_L]$. Now (4b) is rewritten as

$$\dot{y} = f_y(y) - g_y(y)x \tag{5}$$

where $f_y(y) = r_2(1 - by)y$, and $g_y(y) = \frac{ay}{g_2+y}$. Desired scenario i.e. yd for the tumor reduction is considered as

$$y_d = \left(y_0 - y_f\right)\exp(-\lambda t) + y_f \tag{6}$$

Where λ is the rate of tumor reduction. y0 and yf are the initial and desired values of tumor volume, respectively. In the previous optimal controls [14,19,33,34] the exponential functions have been used for Desired scenario of the tumor reduction.

For the tumor volume y, the tracking error variable ey is introduced as

$$e_y = y - y_d \tag{7}$$

Then its time derivative with noticing (5) is given by

$$\dot{e}_y = \dot{y} - \dot{y}_d = f_y(y) - g_y(y)x - \dot{y}_d \tag{8}$$

Now, the desired dynamic error equation is proposed as

$$\dot{e}_y + k_y e_y = 0 \tag{9}$$

Where ky is a designing positive constant. By choosing the virtual control input α^* as follows

$$\alpha^* = x = \frac{-1}{g_y(y)}\left[-f_y(y) + \dot{y}_d - k_y e_y\right] \tag{10}$$

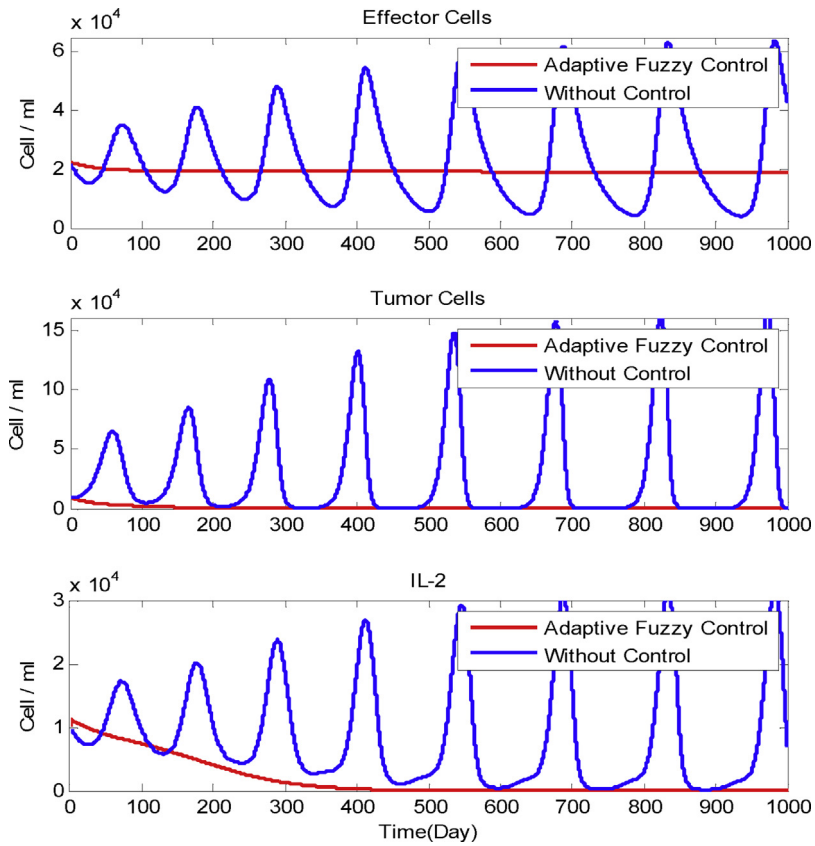

Fig. 2. Comparison the concentrations of effector cells, the tumor cells, and IL-2 with proposed and without control.

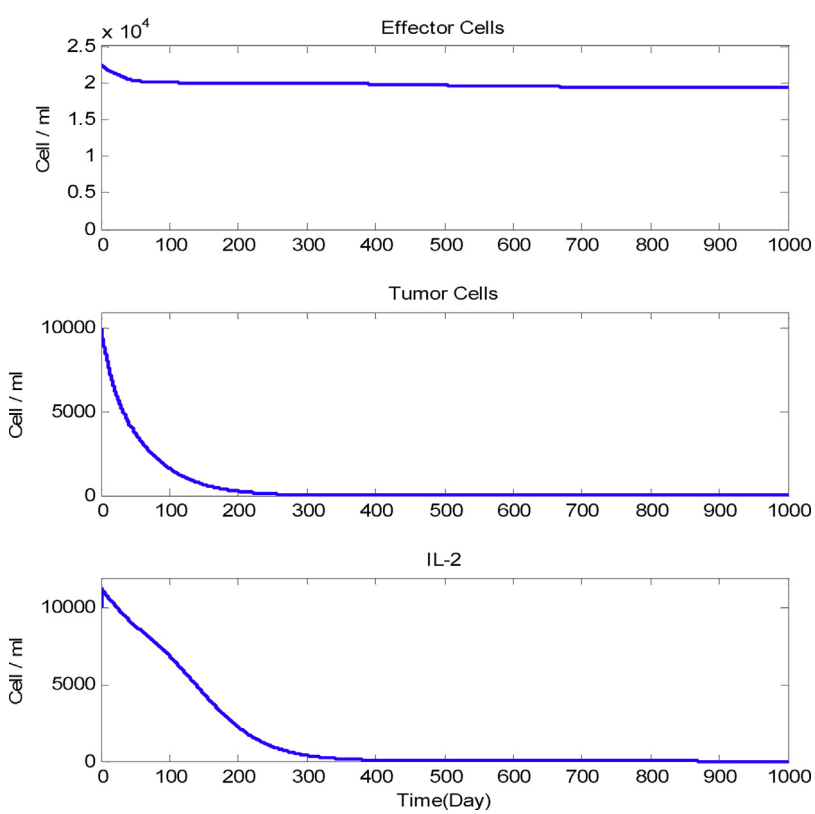

Fig. 3. The concentrations of effector cells, the tumor cells, and IL-2 with proposed control scheme.

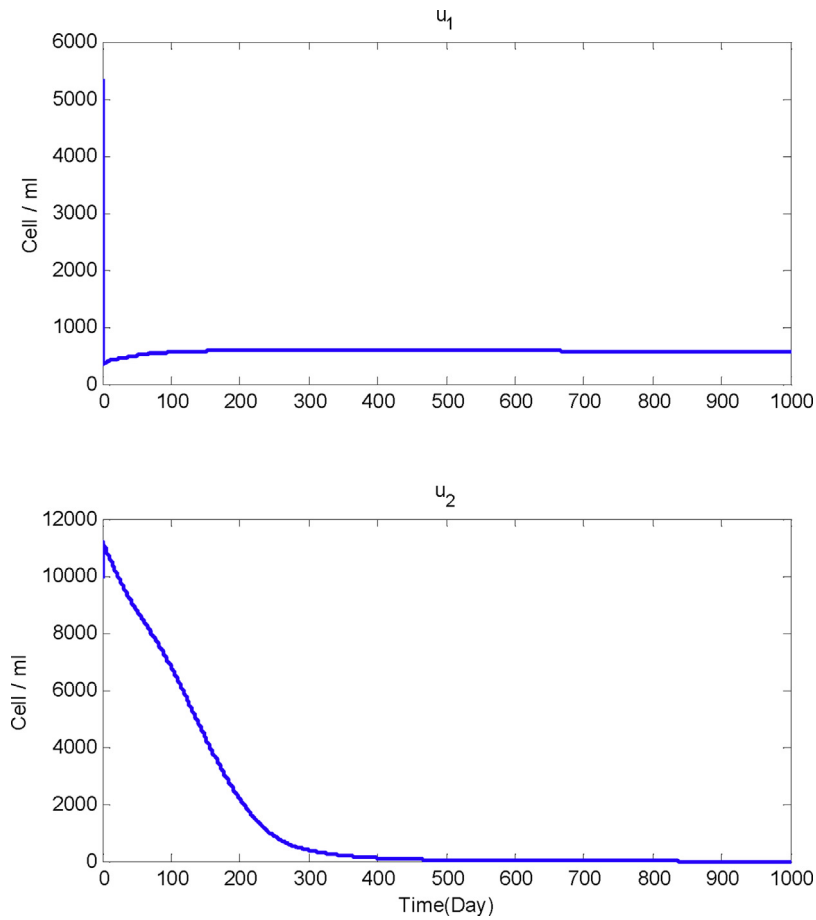

Fig. 4. Drugs usage (u1 and u2).

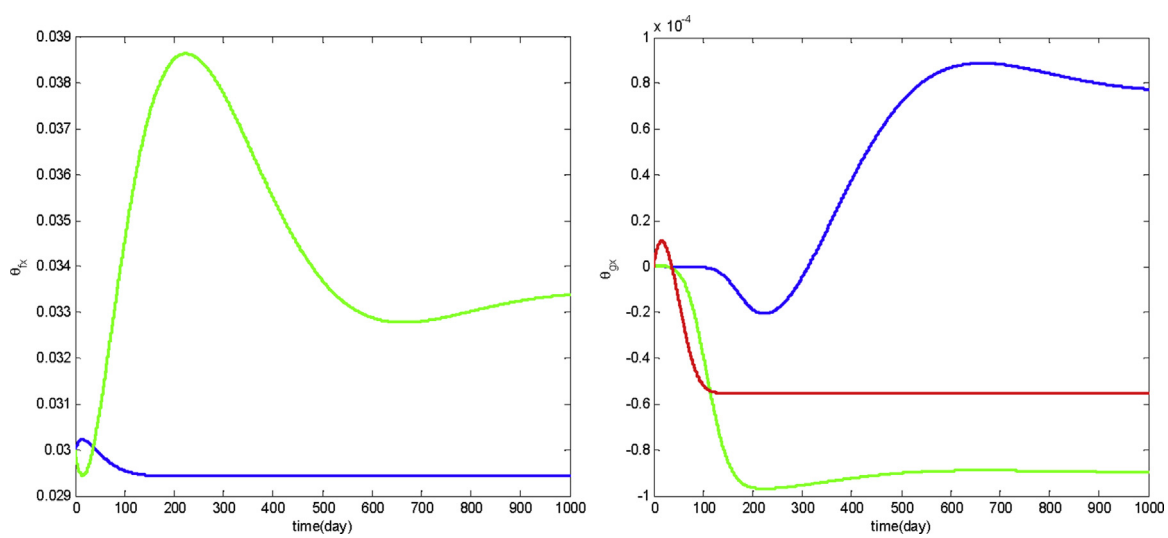

Fig. 5. Parameters adaptation for $f_x(.)$ and $g_x(.)$.

It can conclude that $\lim_{t\to\infty} e_y(t) = 0$. However, the nonlinear functions $f_y(y)$ and $g_y(y)$ are unknown. Therefore they are approximated adaptively. So virtual control input α is defined as below

$$\alpha = \frac{-1}{\hat{g}_y(y)}\left[-\hat{f}_y(y) + \dot{y}_d - k_y e_y\right] \tag{11}$$

In above equation $\hat{f}_y(y)$ and $\hat{g}_y(y)$ are estimates of $f_y(y)$ and $g_y(y)$, respectively. Regarding Lemma 1, by fuzzy systems can approximate each smooth function on a compact set. Thus each nonlinear terms $f_y(y)$ and $g_y(y)$ in (11) can be approximated by a fuzzy model. Therefore $\hat{f}_y(y)$ is chosen as follows

$$\hat{f}_y(y|\boldsymbol{\theta}_{f_y}) = \boldsymbol{\theta}_{f_y}^T \boldsymbol{\eta}_y(y) \tag{12}$$

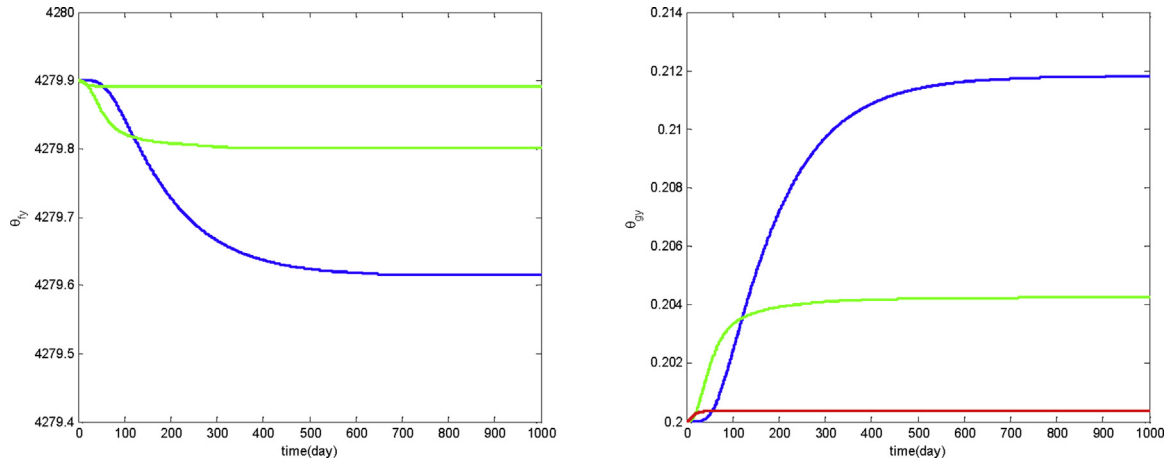

Fig. 6. Parameters adaptation for $f_y(.)$ and $g_y(.)$.

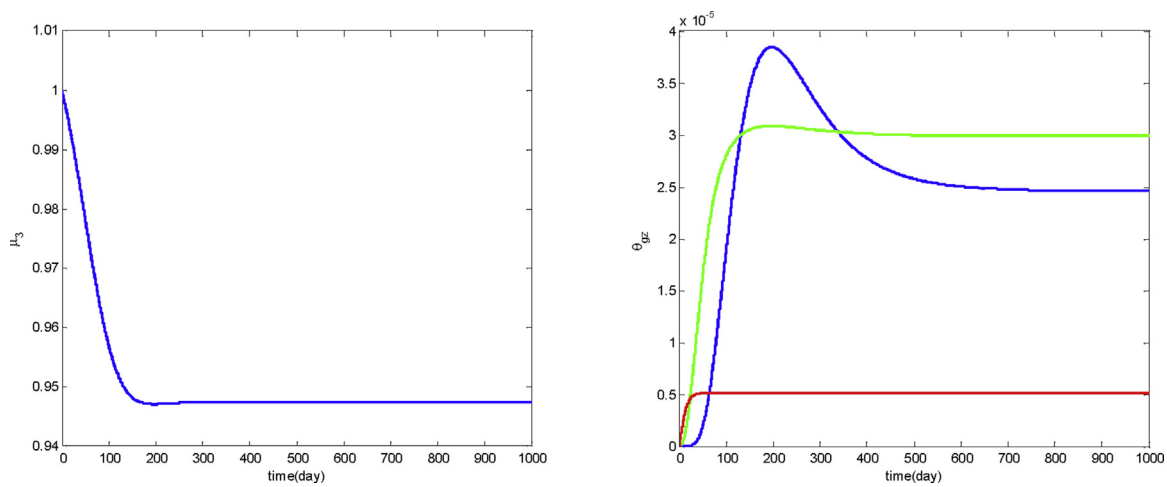

Fig. 7. Parameters adaptation for μ3 and $g_z(.)$.

where $\boldsymbol{\theta}_{f_y} = (\theta_{fy_1}, \ldots, \theta_{fy_M})^T$ is the adjustable parameters vector and

$$\boldsymbol{\eta}_y(y) = \left[\eta_y^1(y) \ldots\ldots \eta_y^M(y)\right]^T \tag{13}$$

where $\boldsymbol{\eta}_y(y)$ is a fuzzy basis function vector as

$$\eta_y^l(y) = \frac{\mu_{F^l}(y)}{\sum_M^{l=1} \mu_{F^l}(y)}, \quad l = 1, 2, \ldots, M \tag{14}$$

Also $\hat{g}_y(y)$ is approximation of $g_y(y)$ by the fuzzy systems as

$$\hat{g}_y(y|\boldsymbol{\theta}_{g_y}) = \boldsymbol{\theta}_{g_y}^T \boldsymbol{\xi}_y(y) \tag{15}$$

where $\boldsymbol{\theta}_{g_y} = (\theta_{gy_1}, \ldots, \theta_{gy_M})^T$ is the adjustable parameters vector and

$$\boldsymbol{\xi}_y(y) = \left[\xi_y^1(y) \ldots\ldots \xi_y^M(y)\right]^T$$

where

$$\xi_y^l(y) = \frac{\mu_{F^l}(y)}{\sum_M^{l=1} \mu_{F^l}(y)}, \quad l = 1, 2, \ldots, M$$

Since the above fuzzy systems cannot exactly represent the nonlinear functions, approximation error exists, therefore the control term of (11) may not ensure the stability of the closed loop system. So a robust compensator u_{r_y} is introduced to overcome the reconstruction error and the control signal (11) is modified as below

$$\alpha = \frac{-1}{\hat{g}_y(y)} \left(-\hat{f}_y(y) + \dot{y}_d - k_y e_y - u_{r_y}\right) \tag{16}$$

Now (8) is rewritten as

$$\dot{e}_y = f_y(y) - g_y(y)(x - \alpha) - g_y(y)\alpha + \hat{g}_y(y)\alpha - \dot{y}_d - \hat{g}_y(y)\alpha \tag{17}$$

And ex is defined as below

$$e_x = x - \alpha \tag{18}$$

Regarding (18) and substituting the control law (16) in (17) yields

$$\dot{e}_y = -g_y(y)e_x + \left[f_y(y) - \hat{f}_y(y)\right] - \left[g_y(y) - \hat{g}_y(y)\right]\alpha - k_y e_y - u_{r_y} \tag{19}$$

The optimal parameters $\boldsymbol{\theta}_{f_y}^*$ and $\boldsymbol{\theta}_{g_y}^*$ in (12) is introduced as follow

$$\begin{aligned} \boldsymbol{\theta}_{f_y}^* &= \arg \min_{\boldsymbol{\theta}_{f_y} \epsilon \Omega_{\boldsymbol{\theta}_{f_y}}} \left(\sup_{y \epsilon R} |\hat{f}_y(y|\boldsymbol{\theta}_{f_y}) - f_y(y)|\right) \\ \boldsymbol{\theta}_{g_y}^* &= \arg \min_{\boldsymbol{\theta}_{g_y} \epsilon \Omega_{\boldsymbol{\theta}_{g_y}}} \left(\sup_{y \epsilon R} |\hat{g}_y(y|\boldsymbol{\theta}_{g_y}) - g_y(y)|\right) \end{aligned} \tag{20}$$

By considering (20), using (12) and (15), then (19) can be written as

$$\dot{e}_y = g_y(y)e_x - \tilde{\boldsymbol{\theta}}_{f_y}^T \boldsymbol{\eta}_y(y) + \tilde{\boldsymbol{\theta}}_{g_y}^T \boldsymbol{\xi}_y(y)\alpha + \left[f_y(y) - \hat{f}_y(y|\boldsymbol{\theta}_{f_y}^*)\right] - \left[g_y(y) - \hat{g}_y(y|\boldsymbol{\theta}_{g_y}^*)\right]\alpha - k_y e_y - u_{r_y} \tag{21}$$

where $\tilde{\boldsymbol{\theta}}_{f_y} = \boldsymbol{\theta}_{f_y} - \boldsymbol{\theta}_{f_y}^*$ and $\tilde{\boldsymbol{\theta}}_{g_y} = \boldsymbol{\theta}_{g_y} - \boldsymbol{\theta}_{g_y}^*$ are the error vectors for parameters estimation. $\boldsymbol{\theta}_{f_y}^*$ and $\boldsymbol{\theta}_{g_y}^*$ are the ideal parameter vectors that result the minimum approximation error defined as (20). Now the total uncertainty i.e. $w_y(t)$ is considered as

$$w_y(t) = g_y(y)e_x + \left[f_y(y) - \hat{f}_y(y|\boldsymbol{\theta}_{f_y}^*)\right] - \left[g_y(y) - \hat{g}_y(y|\boldsymbol{\theta}_{g_y}^*)\right]\alpha \tag{22}$$

Also suppose $|w_y(t)| \le D_y$, where Dy is an unknown positive constant. Therefore (21) can be rewritten as

$$\dot{e}_y = -k_y e_y - \tilde{\boldsymbol{\theta}}_{f_y}^T \boldsymbol{\eta}_y(y) + \tilde{\boldsymbol{\theta}}_{g_y}^T \boldsymbol{\xi}_y(y)\alpha + w_y(t) - u_{r_y} \tag{23}$$

Now the following Lyapunov-like positive function is candidate

$$V_y = \frac{1}{2}e_y^2 + \frac{1}{2\gamma_{f_y}}\tilde{\boldsymbol{\theta}}_{f_y}^T\tilde{\boldsymbol{\theta}}_{f_y} + \frac{1}{2\gamma_{g_y}}\tilde{\boldsymbol{\theta}}_{g_y}^T\tilde{\boldsymbol{\theta}}_{g_y} + \frac{1}{2\gamma_y}\tilde{D}_y^2 \tag{24}$$

where γ_{f_y}, γ_{g_y} and γy are positive design parameters. Also $\tilde{D}_y = \hat{D}_y - D_y$, and $\hat{D}_y$ is the estimate of Dy. The time derivative of Vy is

$$\dot{V}_y = e_y\dot{e}_y + \frac{1}{\gamma_{f_y}}\tilde{\boldsymbol{\theta}}_{f_y}^T\dot{\boldsymbol{\theta}}_{f_y} + \frac{1}{\gamma_{g_y}}\tilde{\boldsymbol{\theta}}_{g_y}^T\dot{\boldsymbol{\theta}}_{g_y} + \frac{1}{\gamma_y}\tilde{D}_y\dot{\hat{D}}_y \tag{25}$$

Substituting (23) in (25) yields

$$\begin{aligned}
\dot{V}_y &= -k_y e_y^2 - \tilde{\boldsymbol{\theta}}_{f_y}^T \boldsymbol{\eta}_y(y)e_y + \tilde{\boldsymbol{\theta}}_{g_y}^T \boldsymbol{\xi}_y(y)\alpha e_y + w_y(t)e_y - u_{r_y}e_y \\
&\quad + \frac{1}{\gamma_{f_y}}\tilde{\boldsymbol{\theta}}_{f_y}^T\dot{\boldsymbol{\theta}}_{f_y} + \frac{1}{\gamma_{g_y}}\tilde{\boldsymbol{\theta}}_{g_y}^T\dot{\boldsymbol{\theta}}_{g_y} + \frac{1}{\gamma_y}\tilde{D}_y\dot{\hat{D}}_y \\
&= -k_y e_y^2 + \tilde{\boldsymbol{\theta}}_{f_y}^T\left(\frac{1}{\gamma_{f_y}}\dot{\boldsymbol{\theta}}_{f_y} - \boldsymbol{\eta}_y(y)e_y\right) + \tilde{\boldsymbol{\theta}}_{g_y}^T\left(\frac{1}{\gamma_{g_y}}\dot{\boldsymbol{\theta}}_{g_y} + \boldsymbol{\xi}_y(y)\alpha e_y\right) \\
&\quad + w_y(t)e_y - u_{r_y}e_y + \frac{1}{\gamma_y}\tilde{D}_y\dot{\hat{D}}_y \\
&\le -k_y e_y^2 + \tilde{\boldsymbol{\theta}}_{f_y}^T\left(\frac{1}{\gamma_{f_y}}\dot{\boldsymbol{\theta}}_{f_y} - \boldsymbol{\eta}_y(y)e_y\right) \\
&\quad + \tilde{\boldsymbol{\theta}}_{g_y}^T\left(\frac{1}{\gamma_{g_y}}\dot{\boldsymbol{\theta}}_{g_y} + \boldsymbol{\xi}_y(y)\alpha e_y\right) + D_y|e_y| - u_{r_y}e_y + \frac{1}{\gamma_y}\tilde{D}_y\dot{\hat{D}}_y
\end{aligned}$$

By defining u_{r_y} as follows

$$u_{r_y} = \hat{D}_y \operatorname{sgn}(e_y) \tag{26}$$

The latter will become

$$\begin{aligned}
\dot{V}_y &\le -k_y e_y^2 + \tilde{\boldsymbol{\theta}}_{f_y}^T\left(\frac{1}{\gamma_{f_y}}\dot{\boldsymbol{\theta}}_{f_y} - \boldsymbol{\eta}_y(y)e_y\right) \\
&\quad + \tilde{\boldsymbol{\theta}}_{g_y}^T\left(\frac{1}{\gamma_{g_y}}\dot{\boldsymbol{\theta}}_{g_y} + \boldsymbol{\xi}_y(y)\alpha e_y\right) + D_y|e_y| - \hat{D}_y|e_y| + \frac{1}{\gamma_y}\tilde{D}_y\dot{\hat{D}}_y \\
&\le -k_y e_y^2 + \tilde{\boldsymbol{\theta}}_{f_y}^T\left(\frac{1}{\gamma_{f_y}}\dot{\boldsymbol{\theta}}_{f_y} - \boldsymbol{\eta}_y(y)e_y\right) \\
&\quad + \tilde{\boldsymbol{\theta}}_{g_y}^T\left(\frac{1}{\gamma_{g_y}}\dot{\boldsymbol{\theta}}_{g_y} + \boldsymbol{\xi}_y(y)\alpha e_y\right) + \tilde{D}_y\left(-|e_y| + \frac{1}{\gamma_y}\dot{\hat{D}}_y\right)
\end{aligned} \tag{27}$$

By considering the following adaptation laws

$$\begin{aligned}
\dot{\boldsymbol{\theta}}_{f_y} &= \gamma_{f_y}\boldsymbol{\eta}_y(y)e_y \\
\dot{\boldsymbol{\theta}}_{g_y} &= -\gamma_{g_y}\boldsymbol{\xi}_y(y)\alpha e_y \\
\dot{\hat{D}}_y &= \gamma_y|e_y|
\end{aligned} \tag{28}$$

from (27) will have

$$\dot{V}_y \le -k_y e_y^2 \tag{29}$$

Now u1 in (4a) should be determined such that x tends to α. Thus the following error dynamic is proposed

$$\dot{e}_x + k_x e_x = 0 \rightarrow \dot{x} - \dot{\alpha} + k_x e_x = 0 \tag{30}$$

Substituting the dynamic of (4a) into (30) results

$$cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + u_1 - \dot{\alpha} + k_x e_x = 0 \tag{31}$$

By defining $g_x(z) = \frac{p_1 z}{z+g_1}$ and $f_x(x,y) = \begin{bmatrix} c & \mu_2 \end{bmatrix}\begin{bmatrix} y \\ -x \end{bmatrix} = \boldsymbol{\theta}_{f_x}^T\boldsymbol{\eta}_x(x,y)$, then (31) can be written as

$$\boldsymbol{\theta}_{f_x}^T\boldsymbol{\eta}_x(x,y) + xg_x(z) + u_1 - \dot{\alpha} + k_x e_x = 0 \tag{32}$$

If u1 is chosen as below and be applied to (4a), then the error dynamic (30) is satisfied

$$u_1^* = -\boldsymbol{\theta}_{f_x}^T\boldsymbol{\eta}_x(x,y) - xg_x(z) + \dot{\alpha} - k_x e_x \tag{33}$$

By reason of $\boldsymbol{\theta}_{f_x}$ and $g_x(z)$ are unknown, the ideal control signal u1∗ may not be realized. Since a fuzzy system is a universal approximator thus the nonlinear term $g_x(z)$ in (33) can be approximated by a fuzzy model. Now the following control input is proposed

$$u_1 = -\hat{\boldsymbol{\theta}}_{f_x}^T\boldsymbol{\eta}_x(x,y) - x\hat{g}_x(z|\boldsymbol{\theta}_{g_x}) + \dot{\alpha} - k_x e_x - u_{rx} \tag{34}$$

In the above equation $\hat{\boldsymbol{\theta}}_{f_x}$ is the estimate of $\boldsymbol{\theta}_{f_x}$ and $\hat{g}_x(z|\boldsymbol{\theta}_{g_x})$ is the approximation of $g_x(z)$ by the fuzzy systems as

$$\hat{g}_x(z|\boldsymbol{\theta}_{g_x}) = \boldsymbol{\theta}_{g_x}^T\boldsymbol{\xi}_x(z) \tag{35}$$

where $\boldsymbol{\theta}_{g_x} = (\theta_{gx_1}, \ldots, \theta_{gx_M})^T$ is the adjustable parameters vector and $\boldsymbol{\xi}_x(z) = \left[\xi_x^1(z)\ldots\ldots\xi_x^M(z)\right]^T$ is the fuzzy basis function vector i.e. $\xi_x^l(z) = \frac{\mu_{Fl}(z)}{\sum_{l=1}^{M}\mu_{Fl}(z)}$, $l = 1, 2, \ldots, M$.

Also for compensating the fuzzy approximation error, the robust term urx has been added to control signal in (34). By applying the controller (34) to (4a) yields

$$\begin{aligned}
\dot{e}_x = \dot{x} - \dot{\alpha} &= \left(\boldsymbol{\theta}_{f_x}^T - \hat{\boldsymbol{\theta}}_{f_x}^T\right)\boldsymbol{\eta}_x(x,y) \\
&\quad + x\left(g_x(z) - \hat{g}_x(z|\boldsymbol{\theta}_{g_x})\right) + d_x(t) - k_x e_x - u_{rx}
\end{aligned} \tag{36}$$

If optimal parameters $\boldsymbol{\theta}_{g_x}^*$ in (35) is introduced as

$$\boldsymbol{\theta}_{g_x}^* = \arg\min_{\boldsymbol{\theta}_{g_x}\epsilon\Omega_{\theta_{g_x}}}\left(\sup_{z\epsilon R}|\hat{g}_x(z|\boldsymbol{\theta}_{g_x}) - g_x(z)|\right) \tag{37}$$

then (36) can be written as

$$\begin{aligned}
\dot{e}_x &= -\tilde{\boldsymbol{\theta}}_{f_x}^T\boldsymbol{\eta}_x(x,y) - \tilde{\boldsymbol{\theta}}_{g_x}^T\boldsymbol{\xi}_x(z)x \\
&\quad + \left[g_x(z) - \hat{g}_x(z|\boldsymbol{\theta}_{g_x}^*)\right]x - k_x e_x - u_{rx}
\end{aligned} \tag{38}$$

where $\tilde{\boldsymbol{\theta}}_{f_x} = \hat{\boldsymbol{\theta}}_{f_x} - \boldsymbol{\theta}_{f_x}$ and $\tilde{\boldsymbol{\theta}}_{g_x} = \boldsymbol{\theta}_{g_x} - \boldsymbol{\theta}_{g_x}^*$ are the parameters estimation error vectors. In this case the uncertainty is considered as

$$w_x(t) = \left[g_x(z) - \hat{g}_x(z|\boldsymbol{\theta}_{g_x}^*)\right]x \tag{39}$$

Also let $|w_x(t)| \le D_x$, where Dx is an unknown positive constant. Hence (38) can be rewritten as

$$\dot{e}_x = -k_x e_x - \tilde{\boldsymbol{\theta}}_{f_x}^T\boldsymbol{\eta}_x(x,y) - \tilde{\boldsymbol{\theta}}_{g_x}^T\boldsymbol{\xi}_x(z)x + w_x(t) - u_{rx} \tag{40}$$

Now consider the following positive function

$$V_x = \frac{1}{2}e_x^2 + \frac{1}{2\gamma_{f_x}}\tilde{\boldsymbol{\theta}}_{f_x}^T\tilde{\boldsymbol{\theta}}_{f_x} + \frac{1}{2\gamma_{g_x}}\tilde{\boldsymbol{\theta}}_{g_x}^T\tilde{\boldsymbol{\theta}}_{g_x} + \frac{1}{2\gamma_x}\tilde{D}_x^2 \tag{41}$$

where γ_{f_x}, γ_{g_x} and γx are positive design parameters. Also $\tilde{D}_x = \hat{D}_x - D_x$, and $\hat{D}_x$ is the estimate of Dx. The derivative of Vx respect to time results

$$\dot{V}_x = e_x\dot{e}_x + \frac{1}{\gamma_{f_x}}\tilde{\boldsymbol{\theta}}_{f_x}^T\dot{\hat{\boldsymbol{\theta}}}_{f_x} + \frac{1}{\gamma_{g_x}}\tilde{\boldsymbol{\theta}}_{g_x}^T\dot{\boldsymbol{\theta}}_{g_x} + \frac{1}{\gamma_x}\tilde{D}_x\dot{\hat{D}}_x \tag{42}$$

Replacing (40) in (42) yields

$$\begin{aligned}\dot{V}_x &= -k_xe_x^2 - \tilde{\boldsymbol{\theta}}_{f_x}^T\boldsymbol{\eta}_x(x,y)e_x - \tilde{\boldsymbol{\theta}}_{g_x}^T\boldsymbol{\xi}_x(z)xe_x + w_x(t)e_x - u_{r_x}e_x \\ &\quad + \frac{1}{\gamma_{f_x}}\tilde{\boldsymbol{\theta}}_{f_x}^T\dot{\hat{\boldsymbol{\theta}}}_{f_x} + \frac{1}{\gamma_{g_x}}\tilde{\boldsymbol{\theta}}_{g_x}^T\dot{\boldsymbol{\theta}}_{g_x} + \frac{1}{\gamma_x}\tilde{D}_x\dot{\hat{D}}_x \\ &= -k_xe_x^2 + \tilde{\boldsymbol{\theta}}_{f_x}^T\left(\frac{1}{\gamma_{f_x}}\dot{\hat{\boldsymbol{\theta}}}_{f_x} - \boldsymbol{\eta}_x(x,y)e_x\right) \\ &\quad + \tilde{\boldsymbol{\theta}}_{g_x}^T\left(\frac{1}{\gamma_{g_x}}\dot{\boldsymbol{\theta}}_{g_x} - \boldsymbol{\xi}_x(z)xe_x\right) + w_x(t)e_x - u_{r_x}e_x + \frac{1}{\gamma_x}\tilde{D}_x\dot{\hat{D}}_x \\ &\le -k_xe_x^2 + \tilde{\boldsymbol{\theta}}_{f_x}^T\left(\frac{1}{\gamma_{f_x}}\dot{\hat{\boldsymbol{\theta}}}_{f_x} - \boldsymbol{\eta}_x(x,y)e_x\right) \\ &\quad + \tilde{\boldsymbol{\theta}}_{g_x}^T\left(\frac{1}{\gamma_{g_x}}\dot{\boldsymbol{\theta}}_{g_x} - \boldsymbol{\xi}_x(z)xe_x\right) + D_x|e_x| - u_{r_x}e_x + \frac{1}{\gamma_x}\tilde{D}_x\dot{\hat{D}}_x\end{aligned}$$

By defining u_{r_x} as

$$u_{r_x} = \hat{D}_x\mathrm{sgn}(e_x) \tag{43}$$

the latter will become

$$\begin{aligned}\dot{V}_x &\le -k_xe_x^2 + \tilde{\boldsymbol{\theta}}_{f_x}^T\left(\frac{1}{\gamma_{f_x}}\dot{\hat{\boldsymbol{\theta}}}_{f_x} - \boldsymbol{\eta}_x(x,y)e_x\right) \\ &\quad + \tilde{\boldsymbol{\theta}}_{g_x}^T\left(\frac{1}{\gamma_{g_x}}\dot{\boldsymbol{\theta}}_{g_x} - \boldsymbol{\xi}_x(z)xe_x\right) + D_x|e_x| - \hat{D}_x|e_x| + \frac{1}{\gamma_x}\tilde{D}_x\dot{\hat{D}}_x \\ &\le -k_xe_x^2 + \tilde{\boldsymbol{\theta}}_{f_x}^T\left(\frac{1}{\gamma_{f_x}}\dot{\hat{\boldsymbol{\theta}}}_{f_x} - \boldsymbol{\eta}_x(x,y)e_x\right) \\ &\quad + \tilde{\boldsymbol{\theta}}_{g_x}^T\left(\frac{1}{\gamma_{g_x}}\dot{\boldsymbol{\theta}}_{g_x} - \boldsymbol{\xi}_x(z)xe_x\right) + \tilde{D}_x\left(-|e_x| + \frac{1}{\gamma_x}\dot{\hat{D}}_x\right)\end{aligned} \tag{44}$$

By the following adaptation laws

$$\begin{aligned}\dot{\hat{\boldsymbol{\theta}}}_{f_x} &= \gamma_{f_x}\boldsymbol{\eta}_x(x,y)e_x \\ \dot{\boldsymbol{\theta}}_{g_x} &= \gamma_{g_x}\boldsymbol{\xi}_x(z)xe_x \\ \dot{\hat{D}}_x &= \gamma_x|e_x|\end{aligned} \tag{45}$$

(44) will result

$$\dot{V}_x \le -k_xe_x^2 \tag{46}$$

Similar to previous steps, u2 can be determined so that z converges to zd. First is defined as below

$$e_z = z - z_d \tag{47}$$

and the desirable error dynamic is chosen as

$$\dot{e}_z + k_ze_z = 0 \tag{48}$$

where kz is a positive designing constant. Now the following control input is proposed

$$u_2 = \hat{\mu}_3z - x\hat{f}_z(y|\boldsymbol{\theta}_{f_z}) + \dot{z}_d - k_ze_z - u_{r_z} \tag{49}$$

In above equation $\hat{\mu}_3$ is the estimate of μ3 and $\hat{f}_z(y|\boldsymbol{\theta}_{f_z})$ is the approximation of $f_z(y) = \frac{p_2y}{g_3+y}$ by the fuzzy systems as

$$\hat{f}_z(y|\boldsymbol{\theta}_{f_z}) = \boldsymbol{\theta}_{f_z}^T\boldsymbol{\xi}_z(y) \tag{50}$$

where $\boldsymbol{\theta}_{f_z} = (\theta_{f_{z1}}, \ldots, \theta_{f_{zM}})^T$ is the adjustable parameters vector and $\boldsymbol{\xi}_z(y) = \left[\xi_z^1(y)\ldots\ldots\xi_z^M(y)\right]^T$ is the fuzzy basis function vector *i.e.* $\xi_z^l(y) = \frac{\mu_{F^l}(y)}{\sum_{l=1}^{M}\mu_{F^l}(y)}$, $l = 1, 2, \ldots, M$. The robust term u_{r_z} in (49) is for compensating the fuzzy approximation error. By applying the controller (49) to (4c) yields

$$\dot{e}_z = \dot{z} - \dot{z}_d = \left(\hat{\mu}_3 - \mu_3\right)z + x\left(f_z(y) - \hat{f}_z(y|\boldsymbol{\theta}_{f_z})\right) - k_ze_z - u_{r_z} \tag{51}$$

If the optimal parameters vector $\boldsymbol{\theta}_{f_z}^*$ in (50) is introduced as follows

$$\boldsymbol{\theta}_{f_z}^* = \arg\min_{\theta_{f_z}\epsilon\Omega_{\theta_{f_z}}}\left(\sup_{y\epsilon R}|\hat{f}_z(y|\boldsymbol{\theta}_{f_z}) - f_z(y)|\right) \tag{52}$$

then (51) can be written as

$$\dot{e}_z = \tilde{\mu}_3z - \tilde{\boldsymbol{\theta}}_{f_z}^T\boldsymbol{\xi}_z(y)x + \left[f_z(y) - \hat{f}_z(y|\boldsymbol{\theta}_{f_z}^*)\right]x - k_ze_z - u_{r_z} \tag{53}$$

where $\tilde{\mu}_3 = \hat{\mu}_3 - \mu_3$ and$\tilde{\boldsymbol{\theta}}_{f_z} = \boldsymbol{\theta}_{f_z} - \boldsymbol{\theta}_{f_z}^*$ are the scalar and vector of the parameter estimation error, respectively. Also the uncertainty is

$$w_z(t) = \left[f_z(y) - \hat{f}_z(y|\boldsymbol{\theta}_{f_z}^*)\right]x \tag{54}$$

Also let $|w_z(t)| \le D_z$, where Dz is an unknown positive constant. Hence (53) can be rewritten as

$$\dot{e}_z = \tilde{\mu}_3z - \tilde{\boldsymbol{\theta}}_{f_z}^T\boldsymbol{\xi}_z(y)x + w_z(t) - k_ze_z - u_{r_z} \tag{55}$$

Now consider the positive function as below

$$V_z = \frac{1}{2}e_z^2 + \frac{1}{2\gamma_\mu}\tilde{\mu}_3^2 + \frac{1}{2\gamma_{f_z}}\tilde{\boldsymbol{\theta}}_{f_z}^T\tilde{\boldsymbol{\theta}}_{f_z} + \frac{1}{2\gamma_z}\tilde{D}_z^2 \tag{56}$$

where γ_{f_z}, γμ and γz are positive design parameters. Also $\tilde{D}_z = \hat{D}_z - D_z$, and $\hat{D}_z$ is the estimate of Dz. The time derivative of Vz results

$$\dot{V}_z = e_z\dot{e}_z + \frac{1}{\gamma_\mu}\tilde{\mu}_3\dot{\hat{\mu}}_3 + \frac{1}{\gamma_{f_z}}\tilde{\boldsymbol{\theta}}_{f_z}^T\dot{\boldsymbol{\theta}}_{f_z} + \frac{1}{\gamma_z}\tilde{D}_z\dot{\hat{D}}_z \tag{57}$$

Replacing (55) in (57) yields

$$\begin{aligned}\dot{V}_z &= -k_ze_z^2 + \tilde{\mu}_3ze_z - \tilde{\boldsymbol{\theta}}_{f_z}^T\boldsymbol{\xi}_z(y)xe_z + w_z(t)e_z - u_{r_z}e_z \\ &\quad + \frac{1}{\gamma_\mu}\tilde{\mu}_3\dot{\hat{\mu}}_3 + \frac{1}{\gamma_{f_z}}\tilde{\boldsymbol{\theta}}_{f_z}^T\dot{\boldsymbol{\theta}}_{f_z} + \frac{1}{\gamma_z}\tilde{D}_z\dot{\hat{D}}_z \\ &= -k_ze_z^2 + \tilde{\mu}_3\left(\frac{1}{\gamma_\mu}\dot{\hat{\mu}}_3 + ze_z\right) + \tilde{\boldsymbol{\theta}}_{f_z}^T\left(\frac{1}{\gamma_{f_z}}\dot{\boldsymbol{\theta}}_{f_z} - \boldsymbol{\xi}_z(y)xe_z\right) \\ &\quad + w_z(t)e_z - u_{r_z}e_z + \frac{1}{\gamma_z}\tilde{D}_z\dot{\hat{D}}_z \\ &\le -k_ze_z^2 + \tilde{\mu}_3\left(\frac{1}{\gamma_\mu}\dot{\hat{\mu}}_3 + ze_z\right) + \tilde{\boldsymbol{\theta}}_{f_z}^T\left(\frac{1}{\gamma_{f_z}}\dot{\boldsymbol{\theta}}_{f_z} - \boldsymbol{\xi}_z(y)xe_z\right) \\ &\quad + D_z|e_z| - u_{r_z}e_z + \frac{1}{\gamma_z}\tilde{D}_z\dot{\hat{D}}_z\end{aligned}$$

Let u_{r_z} as

$$u_{r_z} = \hat{D}_z\mathrm{sgn}(e_z) \tag{58}$$

The latter will become

$$\begin{aligned}\dot{V}_z &\le -k_z e_z^2 + \tilde{\mu}_3\left(\frac{1}{\gamma_\mu}\dot{\hat{\mu}}_3 + z e_z\right) + \tilde{\boldsymbol{\theta}}_{f_z}^T\left(\frac{1}{\gamma_{f_z}}\dot{\boldsymbol{\theta}}_{f_z} - \boldsymbol{\xi}_z(y)\,x e_z\right)\\ &\quad + D_z|e_z| - \hat{D}_z|e_z| + \frac{1}{\gamma_z}\tilde{D}_z\dot{\hat{D}}_z\\ &\le -k_z e_z^2 + \tilde{\mu}_3\left(\frac{1}{\gamma_\mu}\dot{\hat{\mu}}_3 + z e_z\right) + \tilde{\boldsymbol{\theta}}_{f_z}^T\\ &\quad \left(\frac{1}{\gamma_{f_z}}\dot{\boldsymbol{\theta}}_{f_z} - \boldsymbol{\xi}_z(y)\,x e_z\right) + \tilde{D}_z\left(-|e_z| + \frac{1}{\gamma_z}\dot{\hat{D}}_z\right)\end{aligned} \tag{59}$$

Now choose the following adaptation laws

$$\begin{aligned}\dot{\hat{\mu}}_3 &= -\gamma_\mu z e_z\\ \dot{\boldsymbol{\theta}}_{f_z} &= \gamma_{f_z}\boldsymbol{\xi}_z(y)\,x e_z\\ \dot{\hat{D}}_z &= \gamma_z|e_z|\end{aligned} \tag{60}$$

Thus (59) leads to

$$\dot{V}_z \le -k_z e_z^2 \tag{61}$$

The above results are presented as the subsequent theorem.

Theorem: Consider the uncertain nonlinear system in form of (4). Using the control signals (34) and (49), adaptation laws (28), (45) and (60), and robust terms (26), (43) and (58), the tracking errors of the closed loop system tends to zero asymptotically.

Proof: From (24), (41) and (56), the following Lyapunov-like function can be held for the overall closed loop system

$$V = V_x + V_y + V_z \tag{62}$$

Regarding (29), (46) and (61), the time derivative of V will become

$$\dot{V} = \dot{V}_x + \dot{V}_y + \dot{V}_z \le -k_x e_x^2 - k_y e_y^2 - k_z e_z^2 \tag{63}$$

By defining$E = \begin{bmatrix} e_x & e_y & e_z \end{bmatrix}^T$,$K = \mathrm{Diag}\left(k_x, k_y, k_z\right)$, and $k_{min} = \min\left(k_x, k_y, k_z\right)$, (63) can be written as

$$\dot{V} \le -E^T K E \le -k_{min}\|E\|^2 \tag{64}$$

Since $\dot{V}$is negative semi-definite ($\dot{V} \le 0$), therefore$V(t) \le V(0)$, also$V(t) \ge 0$, i.e. $V(t)$ is decreasing and bounded. It results from the all right handed variables and parameters in (24), (41) and (56) are bounded. Also by integrating from both sides of (64), can conclude E ∈ L2. Lastly, from (23), (40) and (55) can infer$\dot{E} \in L_\infty$. This means E is uniformly continuous, therefore from the lemma of Barbalat [35] can result $\lim_{t\to\infty} E = 0$. This concludes the asymptotic stability of the closed-loop system and the proof is completed.

According to the mentioned theorem, the suggested control approach ensures the global stability of the closed loop system, also tracking error of the outputs converges to zero asymptotically. In another word, the volume of the tumor (i.e. y) decreases to around zero if the therapy based on the proposed controller is applied.

Remark: Due to the existing sign function in the control signals, hard switching occurs in the system and creates the unwanted phenomenon so-called chattering. Thus for avoiding it, usually a continuous function such as saturation function is used [35].

5. Simulation results

A simulation study is employed to demonstrate the effectiveness of the presented adaptive fuzzy controller. To show the validity of suggested scheme, numerical simulation via Matlab software is presented. To solve the deferential equations of the system, Fourth-order Runge-Kutta method is utilized with step size 0.001.

Three Gaussian membership functions are defined equally distributed on the interval [0,2.2 × 10^4] for x and [0,10^4] for y and z as shown in Fig. 1. Also, yd and zd are chosen as yd = y0e−t/60 and zd = z0e−t/60.

For simulating, the initial conditions are selected as [4] i.e. $[x_0 y_0 z_0] = [\ 22000 \quad 10000 \quad 10000\ ]$. Simulation results are shown in Figs. 2–7. All tuning parameters and initial conditions are selected by trial and error to achieve the best transient response performance. Fig. 2 shows the results when the proposed adaptive fuzzy control is applied in contrast of no control. As can see the system is unstable without control, while by applying the proposed control immunotherapy, the tumor load decreases and holds in near the zero value level after only 300 days that the immunotherapy is applied. Through the exploiting of the presented control treatment the recycle does not exist. Similarly, the number of IL-2 is converged to near zero and remains stable and the effector cell population are held bounded. Also in order to show more precisely the behavior of the closed loop system, in Fig. 3, only the results in the case of controlled by the proposed method have been depicted.

Fig. 4 illustrates the prescribed drug dosages that can be consumed to impose the tumor cells and IL-2 to zero. It can see the control signals are bounded and appropriate. Also Figs. 5–7 show the behavior of the adaptive parameters for the estimated functions in each dynamical equation of (4). It must be noted that, based on the adaptive control point of view [36], for converging the estimated parameters to their nominal values, the control signals of the system must be PE (Persistently Exciting) which often do not happen in closed loop control systems. In this study, in order to attain the appropriate response of the system, the initial conditions for the adaptive parameters have been tuned as shown in Fig. 5–7.

6. Conclusion

This study presents an adaptive fuzzy back-stepping control for MIMO tumor-immune system. The controller adjusts the drug delivery schedule to accomplish the desired behavior for tumor reduction in cancer immunotherapy. The global stability of the closed-loop system is guaranteed and tracking error of the outputs of the system asymptotically go to zero. The simulation results confirm this conclusion. Also, the effector cell population is held at the proper level and the volume of tumor is decreased near zero after treatment. According to this simulation, the control structure can be successfully applied to the tumor-immune system. Also, it convinces that the suggested methodology can be employed on other similar health treatments and biomedical areas that related to immunotherapy.

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