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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 $y \varepsilon R$ 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

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

$\boldsymbol{\theta} = \left[\bar{y}^1, \ldots, \bar{y}^N\right]^T \varepsilon R^N$ 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

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

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

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

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