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Control of the Amount of Oncolytic Virus Injection by Considering Time Delay

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ABSTRACT: Oncolytic viral therapy is a new promising strategy against cancer. Oncolytic viruses can replicate in cancer cells rather than in normal cells, leading to lysis of the tumor mass and stimulate the immune system. During cancer viral therapy, there is a time delay from the initial virus infection of the tumor cells up to the time those infected cells reach the stage of being able to infect other cells. It is important to understand how the delay affects cancer viral therapy. For this purpose, a mathematical model is introduced to identify this delay. To analyze the effects of delay on virus therapy, the model was reconstructed by adding both virus therapy and immunotherapy control. Finally, using a numerical simulation, a fuzzy parallel distributed compensation controller was designed for the first time. Numerical results showed that with proper control, the tumor cell population decreased to below 10% over time. It is also observed that the use of a delay-independent stability criterion for the design of the parallel distributed compensation controller has reduced the sensitivity of the system response to increasing time delay to an acceptable level. Since the studied system is introduced only in one reference and only the optimal controller is applied, the comparison shows the superiority and power of the designed fuzzy parallel distributed compensation controller.

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1. INTRODUCTION

Owing to the high mortality rate caused by cancers worldwide, many different therapeutic approaches against tumors are being studied, including chemotherapy, immunotherapy, and radiotherapy. Chemotherapy drugs are transported through the blood to cancer cells and all parts of the body. They also have a detrimental effect on healthy cells, which can have side effects. One of the most important side effects of chemotherapy is a decrease in the number of blood cells. The importance of this complication is to the extent that it can cause the patient to die. Radiotherapy is a treatment that uses high-energy rays, such as X-rays, gamma rays, electron or proton rays, to kill or damage cancer cells and prevent their growth and proliferation. The rays used in radiotherapy have high energy so that they can destroy the DNA of cancer cells and cause their death and destruction. This is a lasting impact. In addition to the destruction of cancer cells' DNA, healthy cells are also killed. In immunotherapy, the goal is to get the immune system to act against the tumor, either by strengthening or training the immune system, in other words, T cells (a type of white blood cell). T cells are one of the body's most important weapons in the fight against diseases, especially infections and cancer. In the meantime, a virus-based treatment approach has recently been considered, in which an oncolytic virus acts as a treatment agent by targeting and invading cancer cells using the virus itself or its genetic modification [1]. The term cancer-causing viruses are used for viruses that are capable of proliferating and destroying cancer cells, in particular, and have little effect on normal cells. This ability can be inherited or associated with viruses through genetic engineering [2].

Since cancer viral therapy applies a virus infection, its complex dynamics should be analyzed using a mathematical model to identify its most effective treatment mechanism. Moreover, the mathematical model should provide an understanding of the interaction between the number of viruses and immune cells under various environments [3].

During cancer viral therapy, there is a time delay from the initial virus infection of the tumor cells up to the time those infected cells reach the stage of being able to infect other cells. Because the duration of this "time delay" varies with each virus, it is important to understand how the delay affects cancer viral therapy. Therefore, a mathematical model is needed to explain the effects of this time delay. Wang et al. [4] proposed a mathematical model for explaining the dynamics of oncolytic virus therapy, which involves the combination of the lytic cycle of the virus. Their results showed that the time course of virus outbreak size and intracellular viral life cycle had an inverse relationship. They proved the existence of a Hopf bifurcation with stability and time delay.

Since the model investigated in this study is directly related to people's health, it is not sufficient to provide local stability conditions. Therefore, there is a need to provide global stability conditions for success equilibrium point of treatment. Therefore, the long-term behavior of the system should be investigated. In this paper, the system model

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is defined based on the Takagi-Sugeno [5] fuzzy model. The stability criterion can be categorized based on delay dependence into two categories: delay-dependent stability criterion and delay independent stability criterion, the former being less conservative. This study investigates the stability independent of the delay of this model. The model-based fuzzy stabilizer is designed using the concept of Parallel Distributed Compensation (PDC). The basic idea behind the design of this controller is to produce a control law to compensate for each law of a fuzzy system. The problem of finding the control signal is formulated as a Linear Matrix Inequality (LMI) problem.

2. METHODOLOGY

2-1. Mathematical model formulation

Similar to the time delay being an important factor in virus dynamics, the cellular infection process can be divided into multiple steps during cancer viral therapy, and each step requires a certain time for successful completion [6-8]. Therefore, to describe the time delay between the entry of virus particles into uninfected tumor cells and the production of new viral particles, the delay τ is incorporated in the model proposed by Kim et al. [9] The proposed model is Eq. (1):

$$\begin{cases} \dfrac{dT_i(t)}{dt} = \beta T_u(t-\tau)V(t-\tau) - d_1 T_i(t) - a_2 T_i(t) I(t) \\ \dfrac{dV(t)}{dt} = \pi T_i(t) - d_2 V(t) + u_v(t) \\ \dfrac{dI(t)}{dt} = r_1 T_u(t) I(t) + r_2 T_i(t) I(t) - d_3 I(t) + u_i(t) \\ \dfrac{dT_u(t)}{dt} = a T_u(t)(1 - b(T_u(t) + T_i(t))) - \beta T_u(t) V(t) - a_1 T_u(t) I(t) \end{cases} \quad (1)$$

where a is the maximal production rate per uninfected tumor cells and $1/b$ is the carrying capacity. Uninfected tumor cells are infected at a rate $\beta T_u V$, and infected tumor cells are destroyed at a rate $d_1 T_i$. Also, uninfected tumor cells and infected tumor cells are eliminated by immune cells at a rate $a_1 T_u I$ and $a_2 T_i I$. Viruses are released by infected tumor cells at a rate πT_i and removed at a rate $d_2 V$. Immune cells are produced by uninfected and infected tumor cells at a rate $r_1 T_u I$ and $r_2 T_i I$, die at a rate $d_3 I$. Note that the term corresponding to the absorption of viruses by tumor cells ($-\beta T_u V$) was not directly shown in the second line in Eq. (1). However, the effects of the absorption of viruses are included in the parameter (d_2), and the numerical results are not sensitive to the parameter.

Kim et al. [9] showed that the above model has two equilibrium points. They called E_0 the treatment failure equilibrium point and E_1 the treatment success equilibrium point and discussed the conditions for each local asymptotic stability. By designing the optimal controller, they presented their optimal value for each of the control inputs.

2-2. Design of fuzzy controller

For the fuzzy controller design, the system model (1) is considered as the reference model, except that in this paper the immunotherapy ($u_i(t)$) and viral therapy ($u_v(t)$) control inputs will be determined.

The state feedback stabilization design problem can be stated as follows: Given a plant described by Eq. (1) model, find a PDC control that quadratically stabilizes the closed-loop system. The design variables in this problem are the gain matrices $F_i (0 \le i \le 1)$. The following theorem states conditions that are sufficient for the existence of such a PDC controller. Taken together, these conditions form an LMI feasibility problem. If this problem is analyzed numerically and a feasible solution is found, then a set of stabilizing gain matrices can be computed directly from the solution data [10].

THEOREM A sufficient condition for the existence of a PDC controller that quadratically stabilizes the T-S model is that there exist matrices $X > 0$, $W_1 > 0$, and $M_i, (1 \le i \le r)$, such that the following two LMI conditions hold: (a) For $1 \le i \le r$, the following equation is satisfied:

$$\begin{bmatrix} \begin{pmatrix} A_i X + X A_i^T + A_{id} W A_{id}^T \\ -B_i M_i - M_i^T B_i^T \end{pmatrix} & X \\ X & -W \end{bmatrix} < 0 \quad (2)$$

(b) For every pair of indices satisfying $1 \le i \le j \le r$, the equation

$$\begin{bmatrix} U_{ij} + V_{ij} + W_{ij} & X \\ X & -\dfrac{1}{2} W \end{bmatrix} \le 0 \quad (3)$$

holds, where

$$U_{ij} = A_i X + X A_i^T + A_j X + X A_j^T$$

$$W_{ij} = A_{id} W A_{id}^T + A_{jd} W A_{jd}^T$$

$$V_{ij} = -B_i M_j - M_j^T B_i - B_j M_i - M_i^T B_j$$

3. DISCUSSION AND RESULTS

Figs. 1 (a, b) show the changes of closed-loop system states by applying the resulting control signal under the same initial conditions and various delays. It is observed that over time even at high delays the system states tend to zero, which means that the system (1) is directed toward the equilibrium point of the treatment success.

It is observed that by applying the calculated control signal, the states of the system move towards a healthy equilibrium. As the treatment process begins, that is, the injection of virus particles and immunotherapy, the virus-infected tumor cells gradually increase and the non-infected tumor cells decrease. It is also observed that with the increase in the number of oncolytic virus particles, the number of immune cells has been increasing, confirming the basic assumptions that the virus affects enhancing the efficiency of immune cells and proliferation of tumor antigens. Over time, the tumor cells became more infected with the oncolytic virus as well as with the help of immune cells, reducing the tumor cell population and moving the system toward the health equilibrium point. As can be seen, by increasing the amount of time delay, the system states need more time to balance.

4. CONCLUSIONS

The purpose of this paper is to design and present a fuzzy PDC controller to reduce the number of tumor cells presented in the delayed model and ultimately move to a health equilibrium point. To this end, by fuzzy system modeling, the application of fuzzy control rules and the

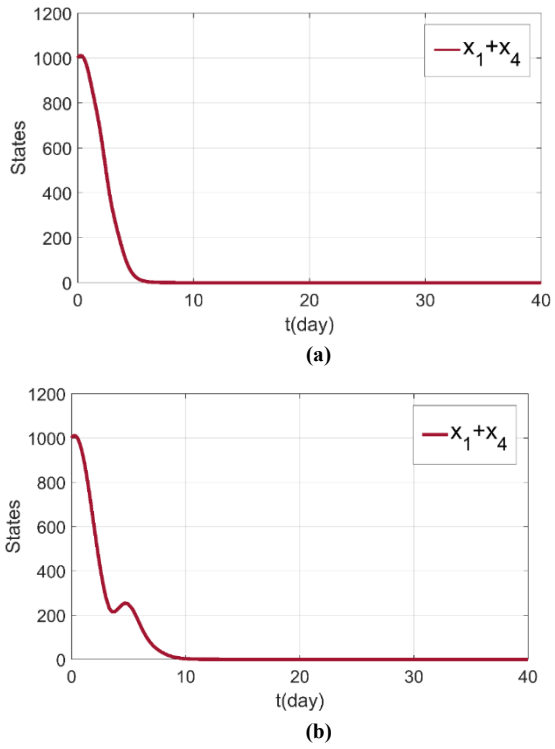

Fig. 1. Changes of sum of the states x_1 and x_4 under initial conditions $(0,1,2,1000)$ and (a) $\tau = 1$, (b) $\tau = 4$

design of a PDC controller, thereby designing an appropriate delay-independent control signal, namely determining the appropriate rate of the virus and drug injection to minimize tumor cells, for each, The amount of time delay was obtained. Numerical results showed that with proper control, over time, the tumor cell population decreased to below 10% and the system moved to a health equilibrium point. The results also support the claim that the PDC controller provides a more efficient performance than the optimal control results presented in reference [9]. It is also observed that the use of delay-independent stability criterion for the design of a PDC controller has reduced the sensitivity of the response of the system to the time delay increase to an acceptable level. Since the system studied is introduced in reference [9] and applied only to the optimal controller, the comparison shows the superiority and power of the designed fuzzy PDC controller.

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