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Super-twisting sliding mode control approach for tumor growth by immunotherapy

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Abstract. Cancer is the second leading cause of death after heart disease in the world and the third leading cause of death after heart disease and accidents in Iran. In general, cancer is a disorder of the rate of proliferation and cell differentiation that can occur in any tissue of the body and at any age and by invading healthy tissues may exacerbate the disease and eventually cause death. In a word, one of the most commonly used treatments for cancer is the use of chemotherapy. The drugs of the aforementioned chemotherapy are transported through the blood to cancer cells and all parts of the body. In addition to cancer cells, these drugs also have a detrimental effect on healthy cells, which can be seen as side effects. It is to note that they are temporary and can stop at the end of treatment. The subject behind this research is to propose super-twisting sliding mode control approach without chattering for mathematical model of cancer by immunotherapy with the aim of stabilizing the closed-loop system, as long as determining the optimal drug dose is taken into consideration as the innovation of this study to conclude which controller has the better performance in the presence of uncertainties and disturbances.

Keywords. Super-twisting sliding mode control approach; cancer treatment; tumor modeling; immunotherapy.

1. Introduction

Although new treatments have been developed by scientists working in gene therapy and immunotherapy, they are still in their infancy. In the clinical treatment for cancer, the amount of medication prescribed and how it is prescribed for the patient is crucial. Because drug treatment not only kills the tumor cells, it also kills some healthy cells. Therefore, in order to minimize damage to healthy tissues, the maximum dose of drug should be carefully determined. Scientists have studied mathematical models of tumor growth in order to analyze the dynamics of tumor growth and also to develop cancer treatment strategies through various mathematical control strategies. Due to the type of the patient's immune system and also the type of cancer, different mathematical models have been proposed. Some researchers have studied the tumor growth model using cellular automatons, which incorporate very specific features of the tumor, patient and drug. As an example, Swanson *et al* have modeled the growth of a malignant type of brain tumor using partial differential equations. Gerlee and Anderson have presented an evolutionary hybrid cellular automaton model of solid tumor growth, while Anderson *et al* have used a combination of partial differential equations and cellular automata to study the tumor growth model. In one such case, De Phillis *et al* have presented a general tumor growth model, using ordinary differential equations showing the dynamics of tumor growth by tumor cell numbers, normal and immune, and using chemotherapy in the model through optimal bang-bang control to adjust the rate. It should be noted that medicines have been also covered in these investigations [1–4]. Regarding the control strategies realized in this area, in line with information presented in [5, 6], they have been focused on designing a sliding mode controller for nonlinear systems with delay in control input. Also, the design of sliding mode controllers for delay systems is discussed in [7, 8]. Finally, a series of the related materials are given in [9–11], as well. The rest of the present paper is organized as follows. The proposed control approach is first given in section 2. The simulation results and concluding remarks are presented in sections 3 and 4, respectively.

2. The proposed control approach

The appropriate design of the sliding mode control approach for nonlinear delay systems is a problem that has been nearly addressed in various literatures. Given the classification, it is clear that different sliding mode controllers including super-twisting one have been proposed

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for so many classes of these delay systems with the disease model. In this section, a sliding surface for hand-driven indefinite nonlinear delay systems is going to be designed using the linearization method and also based on the scroll controller. Subsequently, the switching law is acquired to stabilize this sliding surface. The asymptotic stability of the closed loop system should also be examined. Now, consider the nonlinear delay system, its disease model is identified through the quasi-linear form. Hereafter, utilization of the relative degree of sliding mode control approach, it is tried to find the rate of interleukin concentration to reach normal production. We are going to have the patient's cell after the interleukin concentration. Based on the simulation results for the conditions of the patient model, which are carried out in the proceeding section, in order to detect the variable cell reference signal $q(t)$, it is represented in Eq. (1) along with other system's states.

$$\begin{cases} \dfrac{dG(t)}{dt} = -K_{xgi}I(t)G(t) + \dfrac{T_{gh}}{V_g} + D(t) \\ \dfrac{dI(t)}{dt} = -K_{xi}I(t) + \dfrac{T_{igmax}}{V_i} f\big(G(t-\tau_g)\big) + u(t) \\ \dfrac{dq(t)}{dt} = G_{ref} - G(t) \end{cases} \tag{1}$$
$$G(\tau) = G_0(\tau), I(\tau) = I_0(\tau),\ \tau \in [-\tau_g, 0]$$

Furthermore, consider the well-known quasi-linearization model as

$$\tilde{A}(\tilde{X}_t) = \begin{bmatrix} -K_{xgi}I(t) & \dfrac{T_{gh}}{V_g}\left(\dfrac{1}{I(t)}\right) & 0 \\ \dfrac{T_{igmax}}{V_i G(t)}\left(\dfrac{\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}{1+\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}\right) & -K_{xi} & 0 \\ -1 & 0 & 0 \end{bmatrix}$$
$$\tilde{B}(\tilde{X}_t) = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}$$
$$\Phi = \begin{bmatrix} 0 & \dfrac{T_{gh}}{V_g}\left(\dfrac{1}{I(t)}\right) & -\dfrac{T_{gh}}{V_g}\left(\dfrac{1}{I(t)}\right)(K_{xi}+K_{xgi}) \\ 1 & -K_{xi} & \dfrac{T_{igmax}}{V_i G(t)}\left(\dfrac{\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}{1+\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}\right)\dfrac{T_{gh}}{V_g}\left(\dfrac{1}{I(t)}\right) + K_{xi}^2 \\ 0 & 0 & -\dfrac{T_{gh}}{V_g}\left(\dfrac{1}{I(t)}\right) \end{bmatrix}$$
$$|\phi| = \left(\frac{T_{gh}}{V_g}\right)^2\left(\frac{1}{I(t)}\right)^2 \neq 0 \tag{2}$$

The parameters of the nonlinear disease model for the studied patients are obtained based on the generalized least squares fitting to the experimental data presented in [9–11]. Values like G_b and I_b are directly measurable, some parameters such as G^* and V_i are constant and known, and parameters such as $K_{xgi}, \tau_g, K_{xi}, V_g$ and γ are estimated for each patient. T_{igmax} and T_{gh} parameters can be taken as well as those ones that are determined based on the condition of each patient's physical state based on algebraic relationships.

3. Simulation results

The delay model of the patient is first given in Eq. (3), as long as the required parameters to carry out the simulation programs are given in table 1 [9]. As is the case, the patient's target mass index is taken above the patient's normal limit and $K_{xgi} < 10^{-4}$ is taken as an interleukin resistance index. These factors indicate a sub-normal interleukin concentration rate for the patient. The reference signal of cell proliferation is shown to be a

$$\Phi = G_{ref}(t) = 5.2 + (6.14 - 5.2).e^{-0.02t} \tag{3}$$

subtraction of the patient's initial cell ($G_b = 6.14$ mM) to a normal value 5.2 mM ($\lambda = 1$). Figures 1, 2, 3, 4, 5 illustrate the sliding surface, the tracking of the effective cells to its reference signal, the rate of interleukin concentration as a control signal, the cell proliferation changes in the closed loop control system, and finally $G_{ref} - G(t)$, respectively, while $\lambda = 10$ is taken. In fact, after less than 80 minutes, the patient's condition is stable. The amplitude of the

Table 1. The parameter's initialization.

The parameters	The values	The parameters	The values
G_b	6.14	V_g	0.187
I_b	93.669	K_{xi}	$1.211 * 10^{-2}$
T_{igmax}	1.573	T_{gh}	0.003
γ	3.205	V_i	0.25
G^*	9	K_{xgi}	$3.11 * 10^{-5}$
τ_g	24		

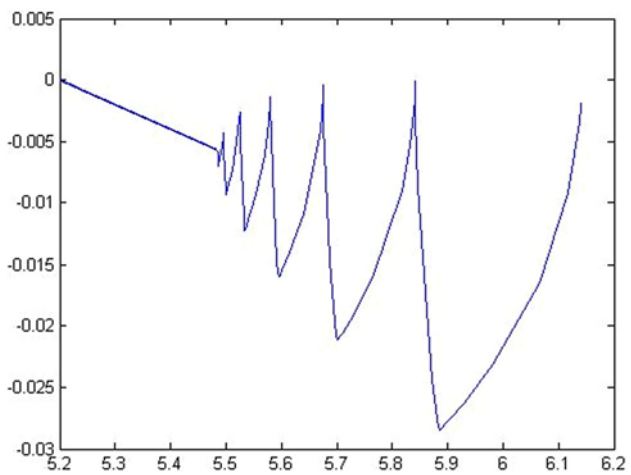

Figure 1. The sliding surface $s = 0$.

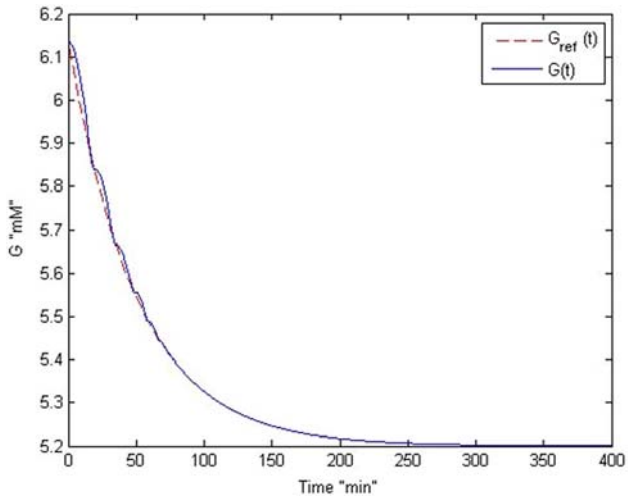

Figure 2. The tracking reference cell.

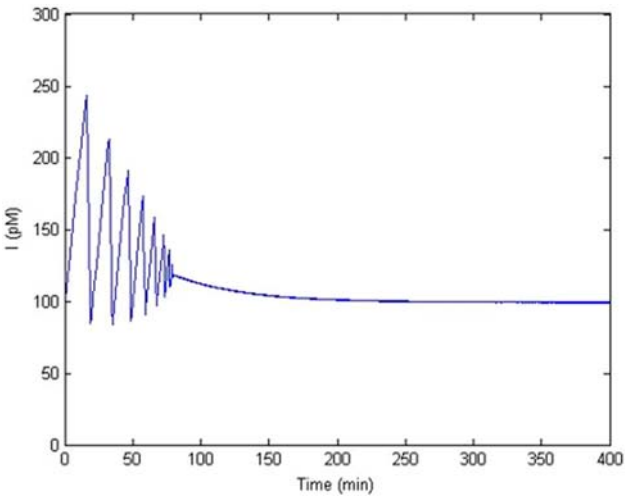

Figure 4. The patient interleukin.

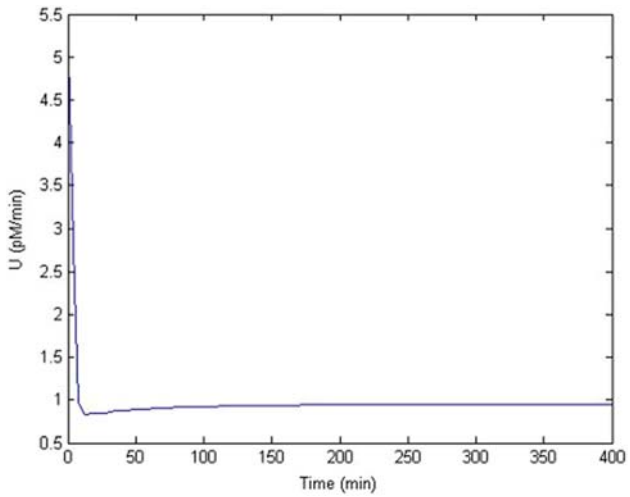

Figure 3. The interleukin concentration rate.

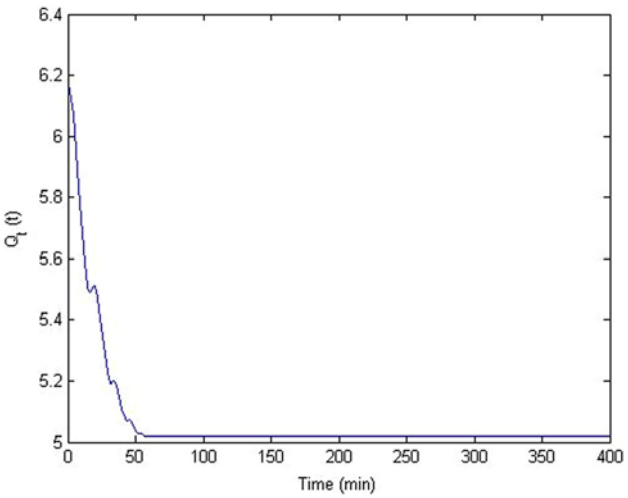

Figure 5. The $G_{ref} - G(t) = Q(t)$.

control signal is also less than 1 pm/min in less than 30 seconds. And under these conditions, the patient is in a completely stable state.

4. Conclusion

One of the strategies used in the control of brain tumor cancer is known as the sliding mode control approach. In this research, the design of super-twisting sliding mode control approach for delay nonlinear model is considered. In the investigation presented here, the sliding mode of a continuous and pervasive controller is designed to maintain the effective cell at the base surface. Using the idea of quasi-linearization method in association with sliding mode control theory, the convergence of cells to their normal level in a cancer patient is obtained and the rate of injection is observed. It is to reach the patient's effective cells to their normal level by adjusting the rate of interleukin concentration. The simulation results illustrate that by modifying the sliding mode structure via optimizing it, the control of delay biological systems have the better performance with respect to its traditional ones.

List of symbols

γ	Fixed and positive parameter in effective cell rotation
$u(t)$	Effective cell external source rate
τ_g	Delay in interleukin concentration
V_g	Cell distribution rate
V_i	Interleukin concentration rate

K_{xgi} Interleukin-dependent tumor cell rate
T_{gh} Effective cell and tumor cell communication index
T_{igmax} The maximum rate of interleukin secretion in phase II
G_b Target mass index

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