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RESEARCH ARTICLE

Event-Triggered Based Feedback Impulse Control for the Tumor Growth Model With Chemotherapy

KUN TIAN AND CHAO BAI
Electronics and Information Engineering, Xi'an Technological University, Xi'an 710021, China
Corresponding author: Chao Bai (baic@xatu.edu.cn)

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ABSTRACT This paper presents a novel approach for cancer treatment using the event-triggered impulse control approach. The proposed approach primarily focuses on adjusting the interval of the chemotherapy regimen, followed by implementing state feedback control to administer flexible chemotherapy dosage based on the last measurement of the patient during each interval. In this way, less total dose and shorter tumor eradicated time are achieved as compared to similar recent work. Different from other researches, as the hidden characteristic of tumor cells often inhibits the immune system's effective recognition and feasibility measurement, we guide chemotherapy in terms of the state of immune cells in our proposed method, providing practical feasibility for treatment. To ensure the effectiveness of the proposed method, we investigate three novel theorems based on the Lyapunov stability theorem. Simulation and results have verified the correctness and superiority of the proposed scheme.

INDEX TERMS Tumor therapy, impulse control, event-triggered impulse control, chemotherapy interval.

I. INTRODUCTION

Tumor is a critical disease threatening human health. Therefore, it is of great significance to explore effective treatment techniques to reduce the rate of death. For high-grade tumor, chemotherapy is an absolutely necessary therapy technique to kill rapidly growing cells. Depending on the age, height and weight, type and size of tumor, the chemotherapy regimen has formulated a paradigm protocol in the clinical treatment. In fact, chemotherapy drugs are often injected at a fixed time interval for treatment [1]. However, this treatment lacks personalized customization and flexibility. Therefore, it is necessary to adjust the protocol for chemotherapy regimen according to the state of the patient.

Recently, numerous scholars from various fields, including medical and theoretical disciplines, have been drawn to investigate the treatment of tumors. However, the current limitations of theoretical research in cancer treatment restrict the ability to administer more precise chemotherapy-dose, while fixed-dose methods are more commonly used due to their broader application scope. A recent clinical study compared the potential of multi-cycle and standard-cycle temozolomide chemotherapy in patients with glioblastoma and concluded that multi-cycle temozolomide chemotherapy can prolong the overall survival and progression-free survival time of patients with glioblastoma [2]. This finding makes more significance of the precise chemotherapy dose in treating the tumor, which could ultimately minimize patient harm and improve treatment outcomes. From the view of cybernetics, such kind of issues can be considered as impulse control, therefore, they could be solved with impulse control theory. Most issues involve the amount of drug and the interval between each drug. According to the impulse control theorem, various chemotherapy regimens have been proposed. A tumor growth model with impulse chemotherapy has been explored in [3] and [4]. The impulse chemotherapy in the tumor immune model has been investigated with consideration of random perturbations in both [5] and [6]. In addition, Yang et al. have presented impulse control conditions for a three-phases stochastic model of cancer immunity [7]. The hybrid model of tumor has been studied, including its complicated dynamic behavior and impulse

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periodic solutions in [8]. However, one may observe that most of existing results focus on the chemotherapy regimen, where the drug dose and chemotherapy period are predetermined in advance. It indicates that the drug is injected at the regular time, whether it is required or not. In other words, cancer treatment is always depending on the experience of doctors and medication guidelines. From the view of application, the chemotherapy methods lack flexibility. For this reason, some researchers have proposed the optimal impulse chemotherapy protocols resulting in minimal drug usage for fixed resting time, but the impulse interval is not optimized [9], [10], [11]. To optimize the impulse interval, a tumour-immune model with different frequency impulse therapy is proposed, and the benefit of the impulsive period on the dynamical behavior of the system is investigated [12].

Event-triggered control allows the control input enabled when the state of the system satisfies the event trigger rule, which could improve flexibility for the chemotherapy treatment. In recent years, Event-Triggered Impulse Control (ETIC) approach has been successfully developed in the nonlinear systems [13], [14], [15], [16], [17], [18], [19]. It is proved that the event-triggered algorithm is popular. In [13], the exponential synchronization issue of neural networks utilizing ETIC is investigated, which is designed to efficiently reduce the communication load and economic cost. The synchronization of fractional-order coupled neural networks is investigated with ETIC, in which synchronization conditions are given by Lyapunov stability theory [14]. In [15], the event-triggered control is used to investigate the globally exponential stability of nonlinear systems which involve hybrid impulses. The event-triggered algorithms are widely proposed to solve the consensus problem of the uncertain nonlinear multiagent systems [16], [17], [18], [19]. Aghaeeyan and Yazdanpanah have designed a self-triggered impulse control for chemotherapy [20], but they assumed that the dose to be administered as a linear function of cancer cells, and no constraint on the administrated dose is considered. Besides this, they have improved the regimen in [21]. As we all know, although the control is activated at the discrete time, the regular detection of the states of systems (or patient's blood chemistry in this paper) is necessary. But the detection variable is cancer cells, which are difficult to diagnose through chemical tests and analysis, especially, the expensive physical examination, which increases the complexity and cost of the treatment. Therefore, there is a need for alternative approaches that consider other variables that are easier and less expensive to measure.

In this paper, motivated by the provided arguments, we propose the ETIC for tumor growth model with chemotherapy. The contribution of this work is listed as the following. Firstly, to the best of our knowledge, it is the first time that the ETIC for the 4-dimensional tumor growth model with chemotherapy is designed, which focuses on adjusting the interval of the chemotherapy regimen. The results about the total dose and tumor eradicated time are better than that in the similar recent work. Secondly, with the help of the Lyapunov theorem, the positive solution and boundedness theorem are derived, which guarantees the boundedness of system with chemotherapeutic drugs. In addition, the immune cells are taken as the feedback information in this paper which the leukocytes are usually indicated for immune cells and easy to measure in practice. Thus it is more practical. Finally, the rational state feedback impulse control is proposed, which can be implemented in practice.

The organization of this paper is as follows: Section II provides the tumor model and preliminaries. Section III introduces the arrangement of ETIC. Section IV derives the theoretical results. Section V provides the simulation results and discussions. Conclusions are given in Section VI.

II. MODEL AND PRELIMINARIES

A. TUMOR MODEL WITH CHEMOTHERAPY

Tumor cells and hunting cells are based on predator-prey models, where the hunting cells act as the predator and the tumor cells as the prey. Due to the presence of cytokines released by hunting cells, resting cells can undergo direct or indirect conversion into hunting cells, which also eliminates tumor cells. Following chemotherapy treatment, the tumor-chemotherapy model becomes a four-dimensional system consisting of tumor cells, hunting cells, resting cells, and the chemotherapeutic agent. To do so, we consider a model inspired by reference [3], which has been identified by experimental results. Particularly, this model was able to reproduce the results obtained by Michor and colleagues [22]. The model is given by,

$$\begin{aligned}
\frac{dx_1(t)}{dt} &= q_1x_1(t)\left(1-\frac{x_1(t)}{K_1}\right) \\
&\quad - \alpha_1x_1(t)x_2(t) - \frac{p_1x_1(t)}{a_1+x_1(t)}x_4(t) \\
\frac{dx_2(t)}{dt} &= \beta_1x_2(t)x_3(t-\tau) - d_1x_2(t) \\
&\quad - \alpha_2x_1(t)x_2(t) - \frac{p_2x_2(t)}{a_2+x_2(t)}x_4(t) \\
\frac{dx_3(t)}{dt} &= q_2x_3(t)\left(1-\frac{x_3(t)}{K_2}\right) \\
&\quad - \beta_1x_2(t)x_3(t-\tau) - \frac{p_3x_3(t)}{a_3+x_3(t)}x_4(t) \\
\frac{dx_4(t)}{dt} &= -\left(\xi + \frac{g_1x_1(t)}{a_1+x_1(t)} + \frac{g_2x_2(t)}{a_2+x_2(t)} + \frac{g_3x_3(t)}{a_3+x_3(t)}\right) \\
&\quad \times x_4(t)
\end{aligned} \tag{1}$$

where $x_1(t), x_2(t), x_3(t), x_4(t) \in R^4$ are the number of tumor cells, hunting cells, resting cells and the concentration of the chemotherapeutic agent, respectively. R^4 is the 4-dimensional real space. The values of these parameters according to the references are shown in the Table 1.

TABLE 1. Dimensionless parameters of system (1).

Parameter	Value	Description
q_1	0.18	Growth rate of tumor cells [23]
q_2	0.0245	Growth rate of resting cells [24]
K_1	1/3	Carrying capacity of tumor cells [23]
K_2	2/3	Carrying capacity of resting cells [24]
α_1	1.6516	Decay rate of tumour cells by hunting cells [25]
α_2	$5.133 * 10^{-3}$	Decay rate of hunting cells by tumour cells [25]
$P_{1,2,3}$	10^{-3}	Predation coefficients of chemotherapeutic agent on tumor cell, the hunting cell, the resting cells [26]
d_1	0.0412	Death rate of hunting cells [25]
β_1	0.093	Conversion rate from resting to hunting cells [25]
$a_{1,2,3}$	10^{-4}	The carrying rate of tumor cells, hunting cells and resting cells in the absence of competition [26]
τ	45.6	Time delay in conversion from resting cells to hunting cells [24]
$g_{1,2,3}$	0.1	Combination rate of the chemotherapeutic agent with cells [26]
ξ	0.2	Washout of chemotherapeutic agent [26]

We extend the $x_4(t)$ of the model (1) with impulse chemotherapy as follows:

$$\begin{aligned}\frac{dx_4(t)}{dt} &= -\left(\xi + \frac{g_1x_1(t)}{a_1+x_1(t)} + \frac{g_2x_2(t)}{a_2+x_2(t)} + \frac{g_3x_3(t)}{a_3+x_3(t)}\right) \\ &\quad \times x_4(t) + u(t) \\ u(t) &= k_2x_2(t), \quad t = t_k \\ u(t) &= 0, \quad t \neq t_k \end{aligned} \tag{2}$$

where $u \in R^4$ is the impulse control input, $k \in R^4$ is the feedback control gain. The impulse time instant $t_k, k = 1, 2, 3, \ldots$ should be designed by the event-triggered, and the trigger rule based on the measurement of system state $x_2(t)$. At the same time, the dosage of chemotherapy agents is depending on the state $x_2(t)$.

B. PRELIMINARIES

Define R as the set of real numbers and R_+ as the set of nonnegative reals. Next, we introduce some basic definitions and lemmas that will be used from the references [27], [28], [29].

Definition 1 (Upper Right Derivative [27]): For an m-dimensional system $\dot{\mathbf{x}} = f(t, \mathbf{x})$ and a positive function $V(t, \mathbf{x}(t)) : R_+ \times R_+^m \to R_+$, the upper right derivative of $V(t, \mathbf{x}(t))$ regarding to the system is defined as: $D^+V(t, \mathbf{x}(t)) = \lim_{h\to 0^+} \sup \frac{1}{h}(V(t+h, \mathbf{x}(t+h)) - V(t, \mathbf{x}(t)))$.

Definition 2 (Boundedness [28]): If $\mathbf{x}(t, t_0, \mathbf{x}_0)$ is a solution of the system $\dot{\mathbf{x}} = f(t, \mathbf{x})$ with initial condition $\mathbf{x}(t_0) = x_0$. If for any positive real $\chi > 0$ and initial time t_0, there exists $B > 0$ such that $|\mathbf{x}(t, t_0, \mathbf{x}_0)| \leqslant B, t \geqslant \chi + t_0$, then the solution $\mathbf{x}(t, t_0, \mathbf{x}_0)$ is ultimately bounded.

Definition 3 (Positive Solution): Suppose $\mathbf{x}(t, t_0, \mathbf{x}_0) \in (x_1(t), x_2(t), \ldots, x_m(t))$ is a solution of a system. If there has $x_1(t) > 0, x_2(t) > 0, \ldots, x_m(t) > 0$, then $\mathbf{x}(t, t_0, \mathbf{x}_0)$ is defined as a positive solution of system.

TABLE 2. Event-triggered strategy.

1	If $\bar{t}_{k+1} - t_k > N$, then activate the impulse control u at time $\bar{t}_{k+1}$.
2	If $\bar{t}_{k+1} - t_k \leqslant N$, then activate the impulse control at time t_k + N, i.e., $t_{k+1} = t_k + \mathrm{N}$.

Definition 4 (Zeno Behavior [29]): If there exists $\rho > 0$ such that $\rho = \inf\{t_{k+1} - t_k\} > 0$ then the system is said to exclude Zeno behavior.

III. ETIC DESIGN

This section introduces an ETIC of the tumor growth model with chemotherapy. In Section III-A, we design the event-triggered method, and then the Zeno behavior is ensured to be excluded in Section III-B.

A. EVENT-TRIGGERED REGIMEN DESIGN

We propose the time triggered regimen. The basic triggered event is defined as follows:

$$\bar{t}_{k+1} = \inf\{t > t_k | x_2(t) \geq h_{\max}\}, \tag{3}$$

where $\bar{t}_{k+1}$ is the time of the event happened. Let t_k as the time to activate the impulse controller u with a minimum fixed-impulse interval $N > 0$. In other words, the patients have the minimum recovery interval for the normal cells. $h_{\max}$ is the detection threshold of immune cells. It is noticed that the decreased immune cells predispose to myelosuppression, so the next chemotherapy must be started after the immune cells increasing. Therefore, as long as $x_2(t) \geq h_{\max}$, the controller is activated. The triggering time is according to the inter-state $x_2(t)$ of the system. We display the execution rule of ETIC, as shown in Table 2.

It can be seen from the event-triggered strategy, that the lower bound of impulse control execution interval times $\{t_{k+1} - t_k\}_{k\in N}$ is $N > 0$. Then the system (2) can exclude

Zeno behavior under an event-triggered strategy. The detailed theoretical analysis will be given in Section III-B.

Algorithm 1 is the pseudocode of the ETIC application of chemotherapy with state feedback. That is, the dosage in the regimens is not constant. The details of algorithm 1 is as follows. The stop criterion of algorithm 1 can be determined by the quantities of the remained tumor cells.

Algorithm 1 Event-Triggered With the State Feedback

Input: Dose and interval parameter; d_{max} (Maximum Tolerated Dose (MTD))
Output: trigger control time t_{k+1}

```
k = 0;
while stop condition is not met do
    Measure x2(t);
    if x2(t) ≥ h_max then
        Calculate the t_{k+1} to be administered based on algebraic expression (3);
        Inject the drug intravenously with k2 x2(t);
        k = k + 1;
    end
end
```

B. EXCLUDING ZENO BEHAVIOR VIA ETIC

In this section, we objective is to show that the proposed ETIC for the system (2) is designed to exclude Zeno behavior.

Theorem 1: Assume that there exist a constant $\tau \in R^+$ and $n \times n$ matrices W such that $t_{k+1} - t_k \geq \frac{\ln(\tau+1)}{2\lambda_{\max}(W)}$, then there is no Zeno behavior for system (2) under ETIC.

Proof of Theorem 1: Consider the Lyapunov function as:$V_1(t) = x_i^2$.

The upper right derivative of $V_1(t)$ is

$$\begin{aligned} D^+(V(t)) &= 2(x_1\dot{x}_1 + x_2\dot{x}_2 + x_3\dot{x}_3 + x_4\dot{x}_4) \\ &\leq 2q_1x_1^2(1-x_1) - 2d_1x_2^2 \\ &\quad + 2q_2x_3^2(1-x_3) - 2\xi x_4^2 \\ &\leq 2\lambda_{\max}(W)x(t)x^T(t), \end{aligned} \tag{4}$$

where

$$W = \begin{bmatrix} q_1 & & & \\ & -d_1 & & \\ & & q_2 & \\ & & & -\xi \end{bmatrix}.$$

Integrating the equation (4), we have,

$$V(t) \leq \frac{1}{\tau}V(t_k)(\exp(2\lambda(t-t_k)) - 1). \tag{5}$$

The event is triggered when $x_2(t) \geq h_{\max}$. Thus, we have

$$t_{k+1} - t_k \geq \frac{\ln(\tau+1)}{2\lambda_{\max}(W)} > 0. \tag{6}$$

Therefore, there is no Zeno behavior for system (2) under ETIC.

End of proof.

IV. THEORETICAL ANALYSIS

In the above sections, the dynamic system and actuator have been given. The aim is to design the input controller such that the system's trajectory is globally ultimately bounded. The positivity and boundedness of the system (2) with ETIC will be discussed in this section.

Theorem 2: The solution $(x_1(t), x_2(t), x_3(t), x_4(t))$ of the system (2) is positive, i.e. $x(t) \in R_+^4 = (x_1(t), x_2(t), x_3(t), x_4(t))$.

Proof of Theorem 2: Integrating each formula from 0 to t in the system (2), we can get

$$\begin{aligned} x_1(t) &= x_1(0^+)\exp\left\{\int_0^t\left[q_1\left(1-\frac{x_1(t)}{K_1}\right) - \alpha_1x_2(t) \right.\right. \\ &\quad \left.\left. - \frac{p_1}{a_1+x_1(t)}x_4(t)\right]ds\right\} \\ x_2(t) &= x_2(0^+)\exp\left\{\int_0^t\left[\beta_1x_3(t-\tau) - d_1 - \alpha_2x_1(t) \right.\right. \\ &\quad \left.\left. - \frac{p_2}{a_2+x_2(t)}x_4(t)\right]ds\right\} \\ x_3(t) &= x_3(0^+)\exp\left\{\int_0^t\left[q_2\left(1-\frac{x_3(t)}{K_2}\right) - \frac{p_3}{a_3+x_3(t)}x_4(t)\right]ds \right. \\ &\quad \left. - \int_{-\tau}^{t-\tau}\beta_1x_2(t)ds\right\} \\ x_4(t) &= x_4(0^+)\exp\left\{-\int_0^t\left[\left(\xi + \frac{g_1x_1(t)}{a_1+x_1(t)} + \frac{g_2x_2(t)}{a_2+x_2(t)} \right.\right.\right. \\ &\quad \left.\left.\left. + \frac{g_3x_3(t)}{a_3+x_3(t)}\right)x_4(t)\right]ds\right\}. \end{aligned} \tag{7}$$

As we all know, the solution (7) is always positive when $x_i(0^+) > 0$, $(i = 1, 2, 3, 4)$ (it has been demonstrated in [9]). Therefore, the solutions of the system (2) is constantly positive when $t \to \infty$.

End of proof.

Theorem 3: If there exists a positive constant $M > 0$ and $\lambda > 0$ such that $\lambda \leq \xi$, the solution of the system (2) are globally ultimately bounded.

Proof of Theorem 3: Let $x_i(t)$ be any positive solution of system (2). The Lyapunov function is defined as:

$$V(t,x) = \sum_{i=1}^{3}\frac{p_i}{a_ig_i}x_i + x_4. \tag{8}$$

Because of the positivity of $x_i(t)$, the Lyapunov function (8) is positive.

For $t \neq t_k$, we have the upper right derivative of $V(t,x)$ along the system (2) is,

$$\begin{aligned} D^+V(t,x) &= \frac{p_1}{a_1g_1}\dot{x}_1 + \frac{p_2}{a_2g_2}\dot{x}_2 + \frac{p_3}{a_3g_3}\dot{x}_3 + \dot{x}_4 \\ &\leq T_a\left[q_1\left(1-\frac{x_1}{K_1}\right)x_1 - d_1x_2 + q_2\left(1-\frac{x_3}{K_2}\right)x_3\right] \\ &\quad - \xi x_4 \\ &\leq T_a[T_bx_1 - d_1x_2 + T_cx_3] - \xi x_4, \end{aligned} \tag{9}$$

where $T_a = \max\left(\frac{p_1}{a_1 g_1}, \frac{p_2}{a_2 g_2}, \frac{p_3}{a_3 g_3}\right)$, $T_b = q_1\left(1 - \frac{x_1}{K_1}\right)$, $T_c = q_2\left(1 - \frac{x_3}{K_2}\right)$.

For any constant $\lambda > 0$,

$$\begin{aligned} &D^+V(t,x) + \lambda V(t,x) \\ &\quad \le T_a\left[(\lambda + T_b)x_1 + (\lambda - d_1)x_2 + (\lambda + T_c)x_3\right] \\ &\qquad + (\lambda - \xi)x_4. \end{aligned} \tag{10}$$

Since the positive properties of the solutions, the equation (10) is boundedness for $\lambda \le \xi$. Thus, for any $t > t_0$, there exist a constant M that makes the following holds,

$$D^+V(t,x) + \lambda V(t,x) \le M. \tag{11}$$

Now, for discussing the boundary of the solution of system (2), the two cases are considered.

Case I: $t_{k+1} = t_k + N$

We will have

$$V\left(t_k^+\right) = V\left(t_k^-\right) + k_2 x_2\left(t_k^-\right), t = t_k. \tag{12}$$

By equations (11) and (12), we have

$$\begin{cases} D^+V(t,x) \le M - \lambda V(t,x), & t \ne t_k \\ V\left(t_k^+\right) \le V\left(t_k^-\right) + k_2 V\left(t_k^-\right), & t = t_k. \end{cases} \tag{13}$$

Integrating the equation (13), we have

$$\begin{cases} V(t,x) \le V\left(0^+\right)e^{-\lambda t} + \dfrac{M}{\lambda}\left(1 - e^{-\lambda t}\right), \\ \qquad\qquad t \ne t_k \\ V(t,x) \le V\left(0^+\right)e^{-\lambda(1+k_2)t} + \dfrac{M}{\lambda(1+k_2)}\left(1 - e^{-\lambda(1+k_2)t}\right), \\ \qquad\qquad t = t_k \end{cases} \tag{14}$$

Thus, the conclusion from the equation (14) is

$$\begin{cases} V(t,x) \to \dfrac{M}{\lambda}, & t \ne t_k, \\ V(t,x) \to \dfrac{M}{\lambda(1+k_2)}, & t = t_k. \end{cases} \tag{15}$$

Hence, the system (2) is boundedness for Case I.

Case II: $t_{k+1} > t_k + N$

We will show that the $x_i(t)$ is boundedness for $t \in (t_k + N, t_{k+1})$.

According to the fouth equation of system (2), we have

$$\frac{dx_4(t)}{dt} \le -\xi x_4. \tag{16}$$

Considering the comparison equation,

$$\begin{cases} \dfrac{dy(t)}{dt} \le -\xi y(t), & t \ne t_{k+1}, \\ \Delta y(t) = k_2 x_2(t), & t = t_{k+1}, \\ y(0^+) = x_4(0^+) \ge 0, \end{cases} \tag{17}$$

we have $x_4(t) < y(t)$. Defining $y(t) = \tilde{y}(t) + \varepsilon$, we have $y(t) = \tilde{y}(t) + \varepsilon \ge x_4(t)$ for $t \to \infty$. Therefore, $\exists \varepsilon_4 > 0$ such that $x_4(t) \to \xi + \varepsilon_4$ as $t \to \infty$. By the same method, we can prove $\exists \varepsilon_1 > 0, \varepsilon_2 > 0, \varepsilon_3 > 0$ such that $x_1(t) \to K_1 + \varepsilon_1$, $x_2(t) \to \varepsilon_2, x_3(t) \to K_2 + \varepsilon_3$ as $t \to \infty$. Therefore, the $x_i(t)$ is boundedness for Case II with $t \to \infty$.

End of proof.

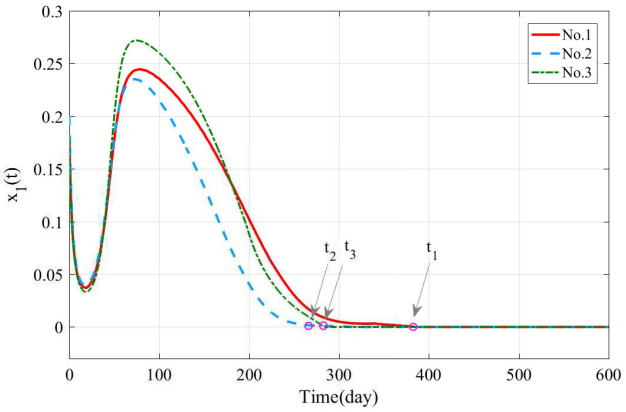

FIGURE 1. The number of tumor cells under three different chemotherapy protocols.

TABLE 3. Chemotherapy regimen.

Parameters	Values
k_2	0.69
h_{max}	0.1
N	5

V. SIMULATION RESULTS AND DISCUSSION

The majority dosage of chemotherapy drugs are depending on body surface area. Commonly consider the body surface of a standard is about $1.79m^2$(cubic centimeter of tumor contains 108 cells, which indicates the shape of tumor is a spherical with diameter of 62 mm [30]). One of the established dose regimens is intravenous injection drug 100-140mg/m^2 over 30 min in every three weeks [21]. According to the principle for calculating the MTD of the drug, the MTD is defined as $d_{\max} = 140 \times 1.79 = 250.6mg$. The $d_{\max} = 250.6mg$ is equal to $d_{\max}/\Delta_M = 250.6mg$ in the dimensionless model, where $\Delta_M = 1mg\ m^2 day^{-1}$.

The results are reported for three different protocols, namely event-triggered with fixed dosage, No.1, event-triggered with the state feedback, No.2, and comparison scheme, No.3. No.1 is based on the event-triggered strategy and the fixed dosage of each chemotherapy interval is 5 mg. No.2 is Algorithm 1, which has the state feedback of hunting cells for adjusting the dose. No.3 implements the protocol of reference [21]. The parameters of the No.2 chemotherapy protocols are shown in Table 3. The simulation results of the three protocols are shown in the following figures.

Figure 1 depicts the tumor cells reaction to three different chemotherapy protocols. It can be seen from Fig. 1 that the tumor cells are almost eradicated with protocols.

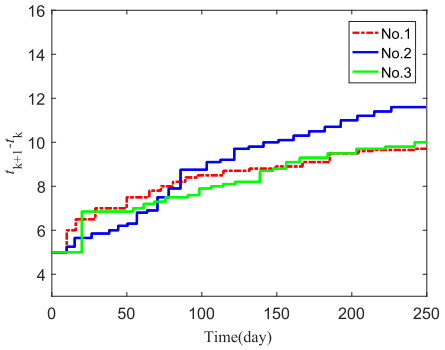

FIGURE 2. Drug injection time interval.

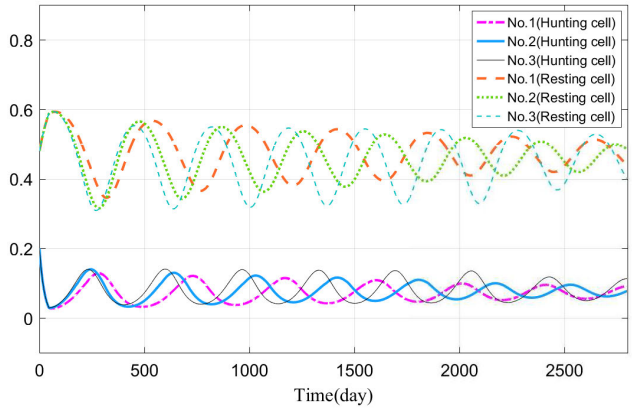

FIGURE 3. The number of hunting cells and resting cells under three different chemotherapy protocols.

TABLE 4. The comparison of three different therapy protocols.

Therapy protocols	Total administered dose(mg)	Tumor eradicated time(day)
No.1	118	t_1=379
No.2	71.1	t_2=269
No.3	102	t_3=282

Nevertheless, No. 1 and No.3 take more time on treatment than No. 2. The time interval between consecutive injections, $t_{k+1} - t_k$, for each therapy protocol is shown in Fig. 2, in which all minimum fixed-impulse interval N is 5 days, including 1 day for injection and 4 days for normal cells recovery time. As we can see from Fig. 2, the intensive injections in the early-stage effectively suppress the growth of tumor cells, indicating that the injection interval is a critical factor. While the interval can be amplified appropriately in the later treatment. Table 4 gives the quantitative comparison of the total administered dose in each therapy protocol. The total dose for No.2, which is 40% lower than that of No.1, and 30% lower than that of No.3, provides evidence for the significance of the method proposed in this article.

Figure 3 depicts the hunting cells of No.1, No.2, and No.3 with the magenta dotted line, the blue solid line and the black thin solid line, respectively. While the green thin dotted line, the orange dashed line and the light blue dotted line show the resting cells of No.1, No.2 and No.3, respectively. The results show that the immune cells are maintained at a certain value and the boundedness theorem is verified.

VI. CONCLUSION

In this paper, the ETIC is proposed for the tumor chemotherapy regimen, which execution rules out Zeno behavior. To derive the sufficient condition for eradicating the tumor and preserving the immune cells, the positive solution and boundedness theorem are investigated rigorously. The numerical simulations show the efficiency of the proposed method.

The approach adjusts the interval between each drug injection by the ETIC method, which reduces the pain that the patient suffers from the toxic side-effects of chemotherapy. Our hope is that with further theoretical analysis, the results can not only be verified by the simulation, but also guide medical practice in cancer diagnosis and treatment in future endeavors.

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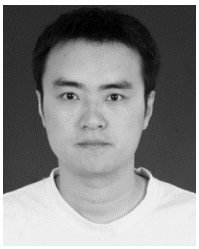
KUN TIAN was born in Hebei, China, in 1989. She received the M.S. and Ph.D. degrees in control science and engineering from the Xi'an University of Technology, in 2016 and 2021, respectively. She is currently with Xi'an Technological University. She has published eight journal articles.



CHAO BAI was born in Xi'an, China, in 1988. He received the B.S. degree in automation from Xi'an Polytechnic University, in 2010, and the M.S. and Ph.D. degrees in control science and engineering from the Xi'an University of Technology, in 2014 and 2019, respectively. He is a Postdoctoral Researcher with Xi'an Technological University. He has published more than ten journal articles and held eight patents. His current research interest includes chaotic communication.