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Tumour chemotherapy strategy based on impulse control theory

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Chemotherapy is a widely accepted method for tumour treatment. A medical doctor usually treats the patients periodically with an amount of drug according to empirical medicine guides. From the point of view of cybernetics, this procedure is an impulse control system, where the amount and frequency of drug used can be determined analytically using the impulse control theory. In this paper, the stability of a chemotherapy treatment of a tumour is analysed applying the impulse control theory. The globally stable condition for prescription of a periodic oscillatory chemotherapeutic agent is derived. The permanence of the solution of the treatment process is verified using the Lyapunov function and the comparison theorem. Finally, we provide the values for the strength and the time interval that the chemotherapeutic agent needs to be applied such that the proposed impulse chemotherapy can eliminate the tumour cells and preserve the immune cells. The results given in the paper provide an analytical formula to guide medical doctors to choose the theoretical minimum amount of drug to treat the cancer and prevent harming the patients because of over-treating.

1. Introduction

In a healthy individual, a new produced body cell replaces a damaged or dead one in an orderly and sustainable way. Cancer cells break this balanced order by multiplying themselves in an uncontrolled way, invading the space and demanding the nutrients of the normal cells. The result is the death of the normal cells. ...ncy for Research on ...cancer cases in 2008, it is predicted that there will be 21.4 million cases of cancer and 13.5 million deaths by 2030 [1]. Cancer ranks the number one killer in the world, therefore, it is of great significance to explore the effective mass of treatment techniques in order to reduce the rate of death due to cancer. It is no surprise that cancer treatment receives great attention around the scientific world [2,3].

For most types of cancers, a wide range of chemotherapeutic drug treatments are available, such as chorionic carcinoma and heterogeneous tumour [4]. Recently, there has been growing interest to understand not only from the medical experimental point of view, but also from a theoretical perspective the effects of the chemotherapy on the cells [5–7]. Fundamental issues involve the amount of drug used and the periodical interval determination. From the view point of cybernetics, the tumour-immune interaction system with the periodical impulse chemotherapy can be considered as an impulse control procedure (or system), therefore, it should be studied using impulse control theory and be treated using cybernetics strategy.

The immune system plays an important role to identify and eliminate tumours. This is called immune surveillance. Our body defence against disease caused by a virus, bacteria or tumour is the destruction of infected cells or tumours by actived cytotoxic T-lymphocytes cells (CTL), also called hunter lymphocytes. CTL [8] can kill cells or make a programmed cell death. The biological activation process occurs efficiently when the CTL receive impulses generated by T-helper cells (TH). The stimuli occur through the release of cytokines. This process involves the time delay for converting resting T-lymphocytes into CTL. The presence of time delay makes the stability analysis to become complicate in the tumour-immune interaction model. Reference [9] proposed a tumour growth model with time delay. The authors investigated the treatment of cancer when impulse chemotherapy treatment was considered. This model is a time delay non-autonomous system, the non-autonomous nature being provide by the impulse treatment. The impulse control (treatment) of a dynamical system with delay introduces more difficulty for the cybernetic strategy design and the stability analysis of the controlled system.

In this paper, the model of reference [9] is extended by treating the impulsive chemotherapy as a dynamical variable. The extended system becomes a higher dimensional delay differential system of equations concerning the tumour-immune interaction and the treatment of chemotherapy. Firstly, after some basic notations are defined in section II and the impulse control system model is formulated in section III, the stability of the steady state (a periodic solution) of the extended system is studied in section IV, which shows conditions for when the chemotherapy kills all cells. Secondly, the solution of the studied system is verified to be bounded using Lyapunov function and comparison theorem in section V. And the periodic solution is verified to be stable in the sense of the (definition of) permanence in section VI, which is guaranteed by a derived theorem (formula). Finally, a chemotherapy strategy supported by our simulations show the correctness of the formula in section VII. In conclusion, we provide a strategy to tell what parameters of the impulsive chemotherapy can eliminate tumour cells and preserve the permanence of the immune cells, i.e they are not completely destroyed. Therefore, this work provides useful information for practical chemotherapy.

2. Notations and definitions

In this section we give some definitions.

Definition 1. *r-order piecewise continuous function [10]: Let $PC(D,F)$ represents a piecewise continuous function mapping D onto F, where $D \subset R$, $F \subset R$. $\phi \in PC(D,F)$, $t \in D$, satisfies that ϕ is a continuous function for $t \neq t_k$, and that ϕ is discontinuous and left continuous for $t = t_k = kT$, where T is the impulse period, $t_k \to \infty$ as $k \to \infty$. An r-order piecewise continuous function, $PC^r(D,F)$, represents a differentiable function of ϕ, which satisfies $\phi \in PC(D,F)$ and $\frac{d^r\phi}{dt^r} \in PC(D,F)$, $r \in N$, where R is real, N is integer.*

Definition 2. *Upper right derivative: For a m-dimensional system* $\dot{\boldsymbol{x}} = f(t, \boldsymbol{x})$ *and a positive function* $V : R_+ \times R_+^m \to R_+$, *where* $\boldsymbol{x} = (x_1, x_2, \cdots, x_m)$. *The upper right derivative of* $V(t, \boldsymbol{x})$ *with respect to the system is defined as*

$$D^+V(t, \boldsymbol{x}) = \lim_{h \to 0^+} \sup \frac{1}{h} \left[V(t + h, \boldsymbol{x}(t) + hf(t, \boldsymbol{x}(t))) - V(t, \boldsymbol{x}(t)) \right]$$

Definition 3. *Boundedness: Suppose* $\phi(t) = x(t, t_0, x(t_0))$ *is a solution of a dynamical system with* $x(t_0) = x_0$, *if for any positive real* $B > 0$, *and the initial time* t_0, *there exists* $\gamma > 0$, *such that* $|x(t, t_0, x(t_0))| \leq B$ *for* $t \geq \gamma + t_0$, *then, the solution is ultimately bounded.*

Definition 4. *Positive solution: Assume* $u_1(t), u_2(t), \ldots, u_m(t)$ *is a solution of an m-dimensional systems* U. *If* $u_i(t) > 0$, $i = 1, 2, \ldots, m$, *then* $(u_1(t), u_2(t), \ldots u_m(t))$ *is defined as a positive solution of system* U.

Definition 5. *Permanence [11]: If there exists constants* ς *and* M, *such that the solution of a system,* $u_i(t)$, *satisfies* $\varsigma \leq \lim_{t \to \infty} \inf u_i(t) \leq \lim_{t \to \infty} \sup u_i(t) \leq M$, *then the system is permanence,* ς *is ultimately lower bound and* M *is the ultimately upper bound.*

3. Tumour growth model with impulse chemotherapy

A mathematical model describing tumour growth under a treatment of chemotherapy was proposed recently [9]. The model is based on the predator-prey system [12]. The T-lymphocyte is the predator, while the tumour cell is the prey that is being attacked. The predators can be in a hunting or a resting state. The resting cells do not kill tumour cells, but they can become hunters after activation. The chemotherapeutic agent is treated as activation. The chemotherapeutic agent acts as a predator on both cancerous and lymphocytes cells. The model is described by

$$\begin{cases} \frac{dC(t)}{dt} = q_1 C(t) \left(1 - \frac{C(t)}{K_1}\right) - \alpha_1 C(t) H(t) - \frac{p_1 C(t)}{a_1 + C(t)} Z(t) \\ \frac{dH(t)}{dt} = \beta_1 H(t) R(t - \tau) - d_1 H(t) - \alpha_2 C(t) H(t) - \frac{p_2 H(t)}{a_2 + H(t)} Z(t) \\ \frac{dR(t)}{dt} = q_2 R(t) \left(1 - \frac{R(t)}{K_2}\right) - \beta_1 H(t) R(t - \tau) - \frac{p_3 R(t)}{a_3 + R(t)} Z(t) \\ \frac{dZ(t)}{dt} = \Delta - \left(\xi + \frac{g_1 C(t)}{a_1 + C(t)} + \frac{g_2 H(t)}{a_2 + H(t)} + \frac{g_3 R(t)}{a_3 + R(t)}\right) Z(t) \end{cases} \tag{3.1}$$

where C, H and R are the number of cancerous, hunting and resting cells, respectively, t is the time and Z is the concentration of the chemotherapeutic agent. q_1, q_2, α_1, α_2, K_1, K_2, p_1, p_1, p_3, a_1, a_1, a_3, g_1, g_1, g_3, d_1, β_1, ξ where values can be seen in Table 1. Δ represents the infusion rate of chemotherapy. τ is the time delay of the conversion from resting cells to hunting cells. To make a clear distinction between parameters and variable, we define $C = x_1$, $H = x_2$, $R = x_3$, $Z = x_4$. Then, the extended tumour growth model with impulsive chemotherapy as a dynamical variable described by

$$\begin{cases} \frac{dx_1(t)}{dt} = q_1 x_1(t) \left(1 - \frac{x_1(t)}{K_1}\right) - \alpha_1 x_1(t) x_2(t) - \frac{p_1 x_1(t)}{a_1 + x_1(t)} x_4(t) \\ \frac{dx_2(t)}{dt} = \beta_1 x_2(t) x_3(t - \tau) - d_1 x_2(t) - \alpha_2 x_1(t) x_2(t) - \frac{p_2 x_2(t)}{a_2 + x_2(t)} x_4(t) \\ \frac{dx_3(t)}{dt} = q_2 x_3(t) \left(1 - \frac{x_3(t)}{K_2}\right) - \beta_1 x_2(t) x_3(t - \tau) - \frac{p_3 x_3(t)}{a_3 + x_3(t)} x_4(t) & t \neq nT \\ \frac{dx_4(t)}{dt} = -\left(\xi + \frac{g_1 x_1(t)}{a_1 + x_1(t)} + \frac{g_2 x_2(t)}{a_2 + x_2(t)} + \frac{g_3 x_3(t)}{a_3 + x_3(t)}\right) x_4(t) \\ \Delta x_1 = 0 \\ \Delta x_2 = 0 \\ \Delta x_3 = 0 & t = nT \\ \Delta x_4 = \Delta \end{cases} \tag{3.2}$$

where $\Delta x_i(t) = x_i(nT^+) - x_i(nT^-)(i = 1, 2, 3, 4)$, T is the period of the impulse, $n = 1, 2, 3, ...$ is a positive integer. This model means that at $t = nT$, an impulse drug treatment is applied with amplitude Δ.

Using the techniques to calculate equilibrium in time delay systems [13], the first formula of equation (3.2) has an equilibrium point given by (0,0,0,0) as $t \neq nT$. From the Jacobian matrix of system (3.2) evaluated at the equilibrium point (0,0,0,0), i.e.

$$J(0,0,0,0) = \begin{bmatrix} q_1 & 0 & 0 & 0 \\ 0 & -d_1 & 0 & 0 \\ 0 & 0 & q_2 & 0 \\ 0 & 0 & 0 & -\xi \end{bmatrix} \tag{3.3}$$

implying that two eigenvalues of the Jacobian matrix have positive real part. Therefore, the equilibrium point (0,0,0,0) is unstable.

4. The stability of periodic solutions of the chemotherapeutic agent

In this section, we study the stability of periodic solutions [14] of system (3.2), when $x_1 = 0, x_2 = 0$, $x_3 = 0$. Our interest is to demonstrate that the impulse perturbation creates a periodic solution in the chemotherapeutic variable, $x_4(t)$. For such a case, system (3.2) is described by the following equations

$$\begin{cases} \dfrac{dx_4(t)}{dt} = -\xi x_4(t) & t \neq nT \\ \Delta x_4 = \Delta & t = nT \end{cases} \tag{4.1}$$

Lemma 1. *[15] System (4.1) has a positive periodic solution $\tilde{x}_4(t)$, i.e., for any solution $x_4(t)$ with initial condition $x_4(0^+) > 0$, $x_4(t) \to \tilde{x}_4(t)$ as $t \to \infty$, where $\tilde{x}_4(t) = \frac{\Delta e^{-\varepsilon(t-nT)}}{1-e^{-\varepsilon T}}$, $t = (nT, (n+1)T]$.*

proof: Integrating the first formula of equation (4.1) on $(nT, (n+1)T]$ yields

$$\int_{nT^+}^{t} \frac{dx_4}{x_4} = \int_{nT^+}^{t} -\varepsilon dt$$

and we get

$$x_4(t) = x_4(nT^+) e^{-\varepsilon(t-nT)} \quad nT < t \leq (n+1)T.$$

From the second formula of equation (4.1),we obtain Stroboscopic Map:

$$x_4((n+1)T) = x_4\left(nT^+\right) e^{-\varepsilon T} = (x_4(nT) + \Delta)e^{-\varepsilon T}.$$

This map has the only positive fixed points

$$\tilde{x}_4(T) = \frac{\Delta e^{-\varepsilon T}}{1 - e^{-\varepsilon T}}$$

or

$$\tilde{x}_4\left(0^+\right) = \frac{\Delta}{1 - e^{-\varepsilon T}}.$$

The corresponding (4.1) has a periodic positive solution with period T, namely,

$$\tilde{x}_4(t) = \tilde{x}_4\left(0^+\right) e^{-\varepsilon(t-nT)} = \frac{\Delta e^{-\varepsilon(t-nT)}}{1 - e^{-\varepsilon T}}.$$

End the proof.

Theorem 1. *Let $(x_1(t), x_2(t), x_3(t), x_4(t))$ be any solution of (3.2), then $(0, 0, 0, \tilde{x}_4(t))$ is globally asymptotically stable provided $T \leq \hat{T}$, $\hat{T} \triangleq \min\left\{\frac{p_1\Delta}{q_1 a_1}, \frac{p_3\Delta}{q_2 a_3}\right\}$.*

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proof: Firstly, we prove the local stability of a periodic solution $(0,0,0,\tilde{x}_4(t))$ by considering the behavior of small-amplitude perturbations about the periodic solution.

Define

$$x_1(t)=u(t),x_2(t)=v(t),x_3(t)=l(t),x_4(t)=w(t)+\tilde{x}_4(t)$$

where $(u(t),v(t),l(t),w(t))$ are small perturbations. We expand system (3.2) according to Taylor's formula, ignore higher-order terms, and obtain the linearized equation

$$\begin{cases} \frac{du(t)}{dt}=(q_1-\frac{p_1}{a_1}\tilde{x}_4(t))u(t) & \\ \frac{dv(t)}{dt}=(-d_1-\frac{p_2}{a_2}\tilde{x}_4(t))v(t) & t\neq nT \\ \frac{dl(t)}{dt}=(q_2-\frac{p_3}{a_3}\tilde{x}_4(t))l(t) & \\ \frac{dw(t)}{dt}=-\frac{g_1\tilde{x}_4(t)u(t)}{a_1}-\frac{g_2\tilde{x}_4(t)v(t)}{a_2}-\frac{g_3\tilde{x}_4(t)l(t)}{a_3}-\xi w(t) & \\ u(nT^+)=u(nT^-) & \\ v(nT^+)=v(nT^-) & \\ l(nT^+)=l(nT^-) & t=nT \\ w(nT^+)=w(nT^-) & \end{cases} \tag{4.2}$$

Defined $\Phi(t)$ is the fundamental solution matrix of system (4.2) (the first to fourth equations), hence

$$\begin{pmatrix} u(t)\\ v(t)\\ l(t)\\ w(t)\end{pmatrix}=\Phi(t)\begin{pmatrix} u(0)\\ v(0)\\ l(0)\\ w(0)\end{pmatrix}$$

where $\Phi(t)$ satisfy

$$\frac{d\Phi(t)}{dt}=A(t)\Phi(t) \tag{4.3}$$

and

$$A(t)=\begin{pmatrix} q_1-\frac{p_1}{a_1}\tilde{z}(t) & 0 & 0 & 0\\ 0 & -d_1-\frac{p_2}{a_2}\tilde{z}(t) & 0 & 0\\ 0 & 0 & q_2-\frac{p_3}{a_3}\tilde{z}(t) & 0\\ -\frac{g_1\tilde{z}(t)}{a_1} & -\frac{g_2\tilde{z}(t)}{a_2} & -\frac{g_3\tilde{z}(t)}{a_3} & -\xi \end{pmatrix}$$

with $\Phi(0)=I$, where I is the identity matrix. The impulsive conditions of (4.2) (the fifth to eighth equations) becomes

$$\begin{pmatrix} u(nT^+)\\ v(nT^+)\\ l(nT^+)\\ w(nT^+)\end{pmatrix}=\begin{pmatrix} 1&0&0&0\\ 0&1&0&0\\ 0&0&1&0\\ 0&0&0&1\end{pmatrix}\begin{pmatrix} u(nT^-)\\ v(nT^-)\\ l(nT^-)\\ w(nT^-)\end{pmatrix}$$

Hence, if the absolute values of all eigenvalues of

$$M=\begin{pmatrix} 1&0&0&0\\ 0&1&0&0\\ 0&0&1&0\\ 0&0&0&1\end{pmatrix}\Phi(T)=\Phi(T)$$

are smaller than one, the periodic solution is locally stable (since $[u(t),v(t),\ l(t),w(t)]^{\mathrm{T}}\to[0,0,0,0]^{\mathrm{T}}$ for $t\to\infty$). By calculating (4.3), we have

$$\Phi(T)=\Phi(0)\exp\left(\int_0^T A(s)\,ds\right)\triangleq\Phi(0)\exp\left(\bar{A}\right)$$

where $\bar{A} = \int_0^T A(s)\,ds$, namely

$$M = \exp\left(\bar{A}\right) = \exp\left(\int_0^T A(s)\,ds\right)$$

then,

$$\bar{A} = \int_0^T \begin{pmatrix} q_1 - \frac{p_1}{a_1}\tilde{z}(s) & 0 & 0 & 0 \\ 0 & -d_1 - \frac{p_2}{a_2}\tilde{z}(s) & 0 & 0 \\ 0 & 0 & q_2 - \frac{p_3}{a_3}\tilde{z}(s) & 0 \\ -\frac{g_1\tilde{z}(s)}{a_1} & -\frac{g_2\tilde{z}(s)}{a_2} & -\frac{g_3\tilde{z}(s)}{a_3} & -\varepsilon \end{pmatrix} ds,$$

we have

$$\bar{A} = \begin{pmatrix} \int_0^T (q_1 - \frac{p_1}{a_1}\tilde{z}(s))ds & 0 & 0 & 0 \\ 0 & \int_0^T (-d_1 - \frac{p_2}{a_2}\tilde{z}(s))ds & 0 & 0 \\ 0 & 0 & \int_0^T (q_2 - \frac{p_3}{a_3}\tilde{z}(s))ds & 0 \\ \int_0^T (-\frac{g_1\tilde{z}(s)}{a_1})ds & \int_0^T (-\frac{g_2\tilde{z}(s)}{a_2})ds & \int_0^T (-\frac{g_3\tilde{z}(s)}{a_3})ds & \int_0^T (-\varepsilon)ds \end{pmatrix}$$

assume that λ_1, λ_2, λ_3 and λ_4 are the eigenvalues of $\bar{A}$, then we have

$$\lambda_1 = \int_0^T (q_1 - \frac{p_1}{a_1}\tilde{z}(s))ds = q_1 T - \frac{p_1}{a_1}\int_0^T \tilde{z}(s)ds = q_1 T - \frac{p_1}{a_1}\left(\frac{\Delta}{1-e^{-\varepsilon T}} - \frac{\Delta e^{-\varepsilon T}}{1-e^{-\varepsilon T}}\right) = \frac{q_1 a_1 T - p_1 \Delta}{a_1}$$

$$\lambda_2 = \int_0^T (-d_1 - \frac{p_2}{a_2}\tilde{z}(s))ds = -d_1 T - \frac{p_2}{a_2}\int_0^T \tilde{z}(s)ds = -d_1 T - \frac{p_2 \Delta}{a_2} < 0$$

$$\lambda_3 = \int_0^T (q_2 - \frac{p_3}{a_3}\tilde{z}(s))ds = q_2 T - \frac{p_3}{a_3}\int_0^T \tilde{z}(s)ds = q_2 T - \frac{p_3}{a_3}\left(\frac{\Delta}{1-e^{-\varepsilon T}} - \frac{\Delta e^{-\varepsilon T}}{1-e^{-\varepsilon T}}\right) = q_2 T - \frac{p_3 \Delta}{a_3}$$

$$\lambda_4 = \int_0^T (-\varepsilon)ds = -\varepsilon T < 0$$

the absolute value of eigenvalues e^{λ_1}, e^{λ_2}, e^{λ_3}, e^{λ_4} of M are less than one provided that $T \le \hat{T}$. Therefore, according to Floquet theory, the periodic solution $(0, 0, 0, \tilde{x}_4(t))$ is locally asymptotically stable.

In the following, we prove the global stability of $(0, 0, 0\ \ \tilde{x}_4(t))$. Choose an $\varepsilon > 0$ such that

$$\sigma = q_1 T + \frac{p_1 \varepsilon}{a_1} T - \frac{p_1 \Delta}{a_1} < 0$$

According to the fourth equation of system (3.2), we have $\frac{dx_4(t)}{dt} \le -\xi x_4(t)$, consider the following impulsive differential equation

$$\begin{cases} \frac{dy(t)}{dt} = -\xi y(t) & t \ne nT \\ \Delta y(t) = \Delta & t = nT \\ y\left(0^+\right) = x_4\left(0^+\right) \ge 0 \end{cases}$$

Using comparison theory, we have that $y(t) \ge x_4(t)$. Defining $y(t) = \tilde{y}(t) + \varepsilon$, then $\tilde{y}(t) + \varepsilon \ge x_4(t) > \tilde{x}_4(t) - \varepsilon$ for large enough t.

Let $\varepsilon \to 0$, we get $\tilde{y}(t) \to \tilde{x}_4(t)$, $x_4(t) \to \tilde{x}_4(t)$ as $t \to \infty$.

From the first equation of (3.2) we get

$$\frac{dx_1(t)}{dt} \le x_1(t)\left(q_1 - \frac{p_1}{a_1}\left(\tilde{x}_4(t) - \varepsilon\right)\right) \tag{4.4}$$

integrating (4.4) on $(nT, (n+1)T]$ yields

$$x_1((n+1)T) \le T_n = x_1(nT)\exp(\sigma)$$

where

$$T_n = x_1(nT)\exp\left(\int_{nT}^{(n+1)T}\left(q_1 - \frac{p_1}{a_1}\left(\tilde{x}_4(t) - \varepsilon\right)\right)\right)$$

Thus $x_1(nT) \le x_1(0^+)\exp(n\sigma)$ and $x_1(nT) \to 0$ as $n \to \infty$. Therefore, $x_1(t) \to 0$ as $n \to \infty$ (since $0 < x_1(t) \le x_1(nT)\exp(q_1 T)$, for $nT < t < (n+1)T$). By the same method, we can prove $x_2(t) \to 0$, $x_3(t) \to 0$ as $n \to \infty$.

Next, we prove that $x_4(t) \to \tilde{x}_4(t)$ as $t \to \infty$, if $\lim_{t\to\infty} x_1(t) = 0$, $\lim_{t\to\infty} x_2(t) = 0$ and $\lim_{t\to\infty} x_3(t) = 0$. For $0 < \varepsilon_1 < \xi$, there exist $\hat{T} > 0$ such that $0 < x_1(t) < \varepsilon_1$, $0 < x_2(t) < \varepsilon_2$, $0 < x_3(t) < \varepsilon_3$ for $t \ge \hat{T}$. From the fourth equation of system (3.2), we have

$$-\left(\xi + \frac{g_1\varepsilon_1}{a_1} + \frac{g_2\varepsilon_1}{a_2} + \frac{g_3\varepsilon_1}{a_3}\right)x_4(t) \le \frac{dx_4(t)}{dt} \le -\xi x_4(t)$$

Using comparison theory, we obtain $y_1(t) \le x_4(t) \le y(t)$, $y_1(t) \to \tilde{y}_1(t)$, $y(t) \to \tilde{y}(t)$ as $n \to \infty$, where $y_1(t)$ are solution of

$$\begin{cases} \dfrac{dy_1(t)}{dt} = -\left(\xi + \dfrac{g_1\varepsilon_1}{a_1} + \dfrac{g_2\varepsilon_1}{a_2} + \dfrac{g_3\varepsilon_1}{a_3}\right)y_1(t) & t \ne nT \\ \Delta y_1(t) = \Delta & t = nT \\ y_1\left(0^+\right) = x_4\left(0^+\right) \ge 0 \end{cases}$$

and

$$\tilde{y}_1(t) = \frac{\Delta\exp\left(\xi + \frac{g_1\varepsilon_1}{a_1} + \frac{g_2\varepsilon_1}{a_2} + \frac{g_3\varepsilon_1}{a_3}\right)(t - nT)}{1 - \exp\left(\left(\xi + \frac{g_1\varepsilon_1}{a_1} + \frac{g_2\varepsilon_1}{a_2} + \frac{g_3\varepsilon_1}{a_3}\right)T\right)}$$

for $nT < t \le (n+1)T$.

Therefore, there exists a $\varepsilon_2 > 0$ such that $\tilde{x}_4(t) - \varepsilon_2 < y_1(t) < x_4(t)$, for t being large enough. Let $\varepsilon_1 \to 0$, we get $\tilde{y}_1(t) \to \tilde{x}_4(t)$.

End the proof.

5. Boundedness

Now we show that all the solutions of system (3.2) are uniformly ultimately bounded.

Lemma 2. *[16] Let the function $W \in PC^1([0, +\infty), R)$ satisfies the following inequalities*

$$\begin{cases} \dot{W}(t) \le f(t)W(t) + g(t) & t \ne nT, t > 0 \\ W\left(nT^+\right) \le f_n W(nT) + g_n & t = nT \\ W\left(0^+\right) \le W_0 \end{cases}$$

where $f(t), g(t) \in C(R_+, R)$, $f_n > 0$, g_n and W_0 are constants. Then

$$W(t) \le W\left(0^+\right)e^{f(t)t} + \int_0^t g(t)e^{f(t)(t-s)}ds + \sum_{0<nT<t} g_n e^{-f(t)(t-nT)} \quad t > 0$$

Theorem 2. *There exists a constant $M>0$, such that $x_i(t)\le M$, $i=1,2,3,4$, for each positive solution $\Psi(t)=(x_1(t),x_2(t),x_3(t),x_4(t))$ of system (3.2) with large enough t.*

proof: Let $\Psi(t)=(x_1(t),x_2(t),x_3(t),x_4(t))$ be any positive solution of (3.2), and defined a function $W(t,x)=x_4+\sum_{i=1}^{3}\frac{p_i}{a_ig_i}x_i$. Then $W(t,x)\in V_0$.

Because $\Psi(t)$ is a positive solution of (3.2), from the third equation of system (3.2), we have $\dot{x}_3(t)<q_2x_3(t)$. Integrating $\dot{x}_3(t)<q_2x_3(t)$ on $(t-\tau,t)$, yields $x_3(t)\le x_3(t-\tau)e^{q_2\tau}$, we obtain $x_3(t-\tau)\ge x_3(t)e^{-q_2\tau}$. Then the upper right derivative of $W(t,x)$ along the solution of (3.2) is described as

$$D^+W(t)=\frac{p_1}{a_1g_1}\dot{x}_1+\frac{p_2}{a_2g_2}\dot{x}_2+\frac{p_3}{a_3g_3}\dot{x}_3+\dot{x}_4$$

For any $\lambda>0$, ignoring the third and fourth terms of the first equation, the first, the third and the fourth terms of the second equation, the third and the fourth items of the third equation, and the second, the third and the fourth terms of the fourth equation of (3.2), for $t\ne nT$, we get

$$\begin{aligned}
&D^+W(t)+\lambda W(t)=(q_1+\lambda)\tfrac{p_1}{a_1g_1}x_1-\tfrac{q_1}{K_1}\cdot\tfrac{p_1}{a_1g_1}{x_1}^2+(-d_1+\lambda)\tfrac{p_2}{a_2g_2}x_2+(q_2+\lambda)\tfrac{p_3}{a_3g_3}x_3\\
&-\tfrac{q_2}{K_2}\cdot\tfrac{p_3}{a_3g_3}{x_3}^2+(\lambda-\xi)x_4\\
&=-\tfrac{q_1}{K_1}\cdot\tfrac{p_1}{a_1g_1}\left({x_1}^2-\tfrac{K_1}{q_1}(q_1+\lambda)x_1+\left(\tfrac{K_1(q_1+\lambda)}{2q_1}\right)^2-\left(\tfrac{K_1(q_1+\lambda)}{2q_1}\right)^2\right)+(-d_1+\lambda)\tfrac{p_2}{a_2g_2}x_2\\
&-\tfrac{q_2}{K_2}\cdot\tfrac{p_3}{a_3g_3}\left({x_3}^2-\tfrac{K_2}{q_2}(q_2+\lambda)x_3+\left(\tfrac{K_2(q_2+\lambda)}{2q_2}\right)^2-\left(\tfrac{K_2(q_2+\lambda)}{2q_2}\right)^2\right)+(\lambda-\xi)x_4\\
&=-\tfrac{q_1}{K_1}\cdot\tfrac{p_1}{a_1g_1}\left(x_1-\tfrac{K_1(q_1+\lambda)}{2q_1}\right)^2+\tfrac{p_1K_1(q_1+\lambda)^2}{4a_1g_1q_1}+(-d_1+\lambda)\tfrac{p_2}{a_2g_2}x_2\\
&-\tfrac{q_2}{K_2}\cdot\tfrac{p_3}{a_3g_3}\left(x_3-\tfrac{K_2(q_2+\lambda)}{2q_2}\right)^2+\tfrac{p_3K_2(q_2+\lambda)^2}{4a_3g_3q_2}+(\lambda-\xi)x_4
\end{aligned}$$

in the above equation, the second and fifth terms are positive constants. Define the sum of them as K, because q_1, q_2, p_1, p_2, p_3, K_1, K_2, a_1, a_2, a_3, g_1, g_2, g_3 are all positive (as shown in Table 1, which is determined by their biological meaning), at the same time, the first and fourth terms are negative, we have then

$$D^+W(t)+\lambda W(t)\le K+(-d_1+\lambda)\frac{p_2}{a_2g_2}x_2+(\lambda-\xi)x_4. \tag{5.1}$$

If $\lambda<\min(d_1,\xi)$, for any positive solution $\Psi(t)$ (that means that $x_2>0$ and $x_4>0$),

$$D^+W(t)+\lambda W(t)\le K.$$

For $t=nT$, we obtain

$$W\left(nT^+\right)=W\left(nT^-\right)+\Delta$$

where

$$W\left(nT^-\right)=\frac{p_1}{a_1g_1}x_1\left(nT^-\right)+\frac{p_2}{a_2g_2}x_2\left(nT^-\right)+\frac{p_3}{a_3g_3}x_3\left(nT^-\right)+x_4\left(nT^-\right)+\Delta$$

we have

$$\begin{cases} D^+W(t)\le-\lambda W(t)+K & t\ne nT\\ W\left(t^+\right)=W(t)+\Delta & t=nT\end{cases} \tag{5.2}$$

According to Lemma 2, we have

$$W(t) \leq W\left(0^{+}\right) e^{-\lambda t} + \int_{0}^{t} K e^{-\lambda(t-s)} ds \quad + \sum_{0<nT<t} \Delta e^{-\lambda(t-nT)}$$

and

$$\sum_{n=0}^{\frac{t}{T}} \Delta e^{-\lambda(t-nT)} = \Delta e^{-\lambda t} \frac{e^{\lambda T}\left(1-e^{\lambda t}\right)}{1-e^{\lambda T}} \quad = \frac{\Delta e^{-\lambda(t-T)}}{1-e^{\lambda T}} + \frac{\Delta e^{\lambda T}}{e^{\lambda T}-1}$$

then we have

$$W(t) \leq W\left(0^{+}\right) e^{-\lambda t} + \frac{K}{\lambda}\left(1-e^{-\lambda t}\right) + \frac{\Delta e^{-\lambda(t-T)}}{1-e^{\lambda T}} + \frac{\Delta e^{\lambda T}}{e^{\lambda T}-1}$$

The right-hand side of the inequality is $\frac{K}{\lambda} + \frac{\Delta e^{\lambda T}}{e^{\lambda T}-1}$ as $t \to \infty$.

Hence, $W(t)$ is ultimately bounded for any positive solution of system (3.2).

End the proof.

6. Permanence of the solution

Theorem 3. *System (3.2) is permanent if* $\beta_1 K_2 e^{(-q_2\tau)} > \alpha_2 K_1$ *and* $T > \max\left\{ \frac{\frac{p_1}{a_1 q_1}\Delta}{\xi + \frac{g_1}{a_1} + \frac{g_2}{a_2} + \frac{g_3}{a_3+K_2}}, \frac{\frac{p_2}{a_2\left(\beta_1 K_2 e^{(-q_2\tau)} - \alpha_2 K_1\right)}\Delta}{\xi + \frac{g_3}{a_3+K_2} + \frac{g_2}{a_2} + \frac{g_1}{a_1+K_1}}, \frac{\frac{p_3}{a_3 q_2}\Delta}{\xi + \frac{g_3}{a_3} + \frac{g_2}{a_2} + \frac{g_1}{a_1+K_1}} \right\} \triangleq \hat{T}_2$, *where* K_1, K_2 *are parameters of (3.2).*

proof: Suppose that $x(t)$ is a solution of (3.2) with $x(0) > 0$. From Theorem 2, we can assume $x_4(t) \leq M$. According to the first equation of (3.2), we get $\frac{dx_1(t)}{dt} \leq q_1 x_1(t)\left(1 - \frac{x_1(t)}{K_1}\right)$ for any positive solution of the system.

Considering the following comparison equation

$$\begin{cases} \dfrac{dw(t)}{dt} = w(t)\left(q_1 - \dfrac{q_1}{K_1} w(t)\right) \\ w(0) = x_1(0) \end{cases}$$

we have $x_1(t) \leq w(t)$ and $w(t) \to K_1$ as $t \to \infty$. Similarly, we can get the comparison equation for the second equation of (3.2)

$$\begin{cases} \dfrac{dn(t)}{dt} = -d_1 n(t) \\ n(0) = x_2(0) \end{cases}$$

and the comparison equation for the third equation of (3.2)

$$\begin{cases} \dfrac{dm(t)}{dt} = m(t)\left(q_2 - \dfrac{q_2}{K_2} m(t)\right) \\ m(0) = x_3(0) \end{cases}$$

Thus, there exists an $\varepsilon_1 > 0$, such that $x_1(t) < K_1 + \varepsilon_1$ for large enough t. Without loss of generality, we assume $x_2(t) < \varepsilon_2$, $x_3(t) < K_2 + \varepsilon_3$ $(t > 0)$.

Let $m_4 = \frac{\Delta e^{-\xi T}}{1-e^{-\xi T}} - \varepsilon_4 > 0, \varepsilon_4 > 0$. According to the comparison theorem, we have $x_4(t) > m_4$ for large enough t. In the following, we want to find $\bar{m}_1 > 0$, $\bar{m}_2 > 0$, $\bar{m}_3 > 0$, such that $x_1(t) \geq \bar{m}_1$, $x_2(t) \geq \bar{m}_2$, $x_3(t) \geq \bar{m}_3$ for large enough t. We will do it in the following two steps.

Step I: Let $m_1 > 0$, $m_2 > 0$, $m_3 > 0$, we will prove that there exist $t_1, t_2, t_3 \in (0, \infty)$, such that $x_1(t_1) \geq m_1$, $x_2(t_2) \geq m_2$, $x_3(t_3) \geq m_3$.

Firstly, we prove there exist $t_1 \in (0,\infty)$, such that $x_1(t_1) \geq m_1$. We use proof by contradiction and suppose that for any $t_1 \in (0,\infty)$, $x_1(t_1) \leq m_1$.

proof: Let $\varepsilon_1 > 0$ small enough so that

$$\bar{\sigma}_1 = \left(q_1 - \frac{q_1}{K_1}m_1 - \alpha_2\varepsilon_2 - \frac{p_1}{a_1}\varepsilon_1\right)T - \frac{\frac{p_1}{a_1}\Delta}{\xi + \frac{g_1}{a_1+m_1} + \frac{g_2}{a_2+\varepsilon_2} + \frac{g_3}{a_3+(K_2+\varepsilon_2)}} > 0$$

According to the above assumption, we get

$$\frac{dx_4(t)}{dt} \leq x_4(t)\left(-\xi - \frac{g_1}{a_1+m_1} - \frac{g_2}{a_2+\varepsilon_2} - \frac{g_3}{a_3+(K_2+\varepsilon_3)}\right)$$

According to the comparison theorem, we have $x_4(t) \leq y_3(t)$. By Lemma 1, we get $y_3(t) \to \tilde{y}_3(t)$ as $t \to \infty$, where $y_3(t)$ is the solution of

$$\begin{cases} \frac{dy_3(t)}{dt} = y_3(t)\left(-\xi - \frac{g_1}{a_1+m_1} - \frac{g_2}{a_2+\varepsilon_2} - \frac{g_3}{a_3+(K_2+\varepsilon_3)}\right) & t \neq nT \\ \Delta y_3(t) = \Delta & t = nT \\ y_3\left(0^+\right) = x_4(0) \geq 0 \end{cases} \tag{6.1}$$

Similarly to the periodic solution $\tilde{x}_4(t)$ of equation (4.1), we have

$$\tilde{y}_3(t) = \frac{\Delta \exp\left(-\xi - \frac{g_1}{a_1+m_1} - \frac{g_2}{a_2+\varepsilon_2} - \frac{g_3}{a_3+(K_2+\varepsilon_3)}\right)(t-nT)}{1 - \exp\left(\left(-\xi - \frac{g_1}{a_1+m_1} - \frac{g_2}{a_2+\varepsilon_2} - \frac{g_3}{a_3+(K_2+\varepsilon_3)}\right)T\right)}$$

for $t \in (nT, (n+1)T]$.

Thus, there exists $T_1 > 0$ such that $x_4(t) \leq y_3(t) \leq \tilde{y}_3(t) + \varepsilon_1$. In the first equation of system (3.2), replace x_4 with $\tilde{y}_3 + \varepsilon_1$, x_2 with ε_2, and x_1 with m_1. For $t \geq T_1$, we have

$$\frac{dx_1(t)}{dt} \geq x_1(t)\left(q_1 - \frac{q_1 m_1}{K_1} - \alpha_2\varepsilon_2 - \frac{p_1}{a_1}(\tilde{y}_3(t) + \varepsilon_1)\right) \tag{6.2}$$

Let $N_1 \in Z_+$ be positive integer, and $N_1 T \geq T_1$, integrating (6.2) on $(nT,(n+1)T]$ (for $n \geq N_1$), we get

$$x_1((n+1)T) \geq Tz = x_1(nT)\exp(\bar{\sigma}_1)$$

where

$$T_z = x_1(nT)\exp\left(\int_{nT}^{(n+1)T}\left(q_1 - \frac{q_1}{K_1}m_1 - \alpha_2\varepsilon_2 - \frac{p_1}{a_1}\tilde{y}_3(t) - \frac{p_1}{a_1}\varepsilon_1\right)dt\right)$$

similarly to the above case, for $k \to \infty$

$$x_1((N_1+k)T) \geq x_1(N_1 T)\exp(k\bar{\sigma}_1) \to \infty \tag{6.3}$$

which is a contradiction to the boundedness of the solution. We conclude that there exists a t_1 ($t_1 > 0$), such that $x_1(t) \geq m_1$. By the same way, we can get similar conclusions for $x_2(t)$, $x_3(t)$.

From the above discussion, we get that there exists $t_1, t_2, t_3 \in (0,\infty)$, such that $x_1(t_1) \geq m_1$, $x_2(t_2) \geq m_2$, $x_3(t_3) \geq m_3$.

Step II: If $x_1(t) \geq m_1$ for all $t \geq t_1$, then our aim is obtained. Otherwise, $x_1(t) < m_1$, for some $t \geq t_1$.

Setting $t^* = \inf_{t > t_1}\{x_1(t) < m_1\}$, we have $x_1(t) \geq m_1$ for $t \in [t_1, t^*)$. It is easy to see that $x_1(t^*) = m_1$, since $x_1(t)$ is continuous at $t^* \in (n_1 T, (n_1+1)T]$ for $n_1 \in Z_+$. Select n_2, $n_3 \in Z_+$

such that

$$n_2 T > \frac{1}{-\xi - \frac{g_1}{a_1+m_1} - \frac{g_2}{a_2+\varepsilon_2} - \frac{g_3}{a_3+(K_2+\varepsilon_3)}} \ln \frac{\varepsilon_4}{M+\Delta}$$

and

$$\exp\left(\delta\left(n_2+1\right)T\right)\exp\left(n_3\bar{\sigma}_1\right) > 1$$

where

$$\delta = q_1 - \frac{q_1 m_1}{K_1} - \alpha_2\varepsilon_2 - \frac{p_1}{a_1}M < 0$$

Setting $T' = n_2 T + n_3 T$, we claim that there must exist $t' \in ((n_1+1)T, (n_1+1)T{+}T']$, such that $x_1(t') \geq m_1$. Otherwise, $x_1(t) < m_1$ (for $t \in \left((n_1+1)T, (n_1+1)T + T'\right]$), considering (6.1) and $y_3\left((n_1+1)\ T^+\right) = x_4\left((n_1+1)T^+\right)$, we have

$$y_3(t) = y_3\left((n_1+1)T^+\right) - \frac{\Delta}{1-\exp\left(\left(-\xi - \frac{g_1}{a_1+m_1} - \frac{g_2}{a_2+\varepsilon_2} - \frac{g_3}{a_3+(K_2+\varepsilon_3)}\right)T\right)}$$
$$\exp\left(\left(-\xi - \frac{g_1}{a_1+m_1} - \frac{g_2}{a_2+\varepsilon_2} - \frac{g_3}{a_3+(K_2+\varepsilon_3)}\right)(t-(n_1+1)T)\right) + \tilde{y}_3(t)$$

for $t \in (nT, (n+1)T]$, $n_1+1 \leq n \leq n_1+1+n_2+n_3$

According to $y_3\left((n_1+1)T^+\right) = y_3\left((n_1+1)T^-\right) + \Delta$ and $x_4(t) \leq M$, we get

$$|y_3(t) - \tilde{y}_3(t)| < (M+\Delta)T_e < \varepsilon_1$$

where

$$T_e = \exp\left(\left(-\xi - \frac{g_1}{a_1+m_1} - \frac{g_2}{a_2+\varepsilon_2} - \frac{g_3}{a_3+(K_2+\varepsilon_3)}\right)(t-(n_1+1)T)\right)$$

and

$x_4(t) \leq y_3(t) < \tilde{y}_3(t) + \varepsilon_1$, for $(n_1+1+n_2)T \leq t \leq (n_1\ \ +1)T + T'$. which implies that (6.2) holds for $(n_1+1+n_2)T \leq t \leq (n_1+1)T + T'$. Similarly to (6.3), we have

$$x_1(n_1+1+n_2+n_3)T \geq x_1((n_1+1+n_2)T)\exp(n_3\bar{\sigma}_1)$$

There are two possible cases for $t \in (t^*, (n_1+1)T]$:

Case(1) (x_1 has an upper bound for a finite time internal $((t^*, (n_1+1)]T)$)

If $x_1(t) < m_1$ for $t \in (t^*, (n_1+1)T]$, then $x_1(t) < m_1$ for all $t \in (t^*, (n_1+1+\ \ n_2)T]$. According to system (3.2), we have

$$\frac{dx_1(t)}{dt} \geq x_1(t)\left(q_1 - \frac{q_1 m_1}{K_1} - \alpha_2\varepsilon_2 - \frac{p_1}{a_1}M\right) = \delta x_1(t) \tag{6.4}$$

Integrating (6.4) on $(t^*, (n_1+1+n_2)T]$ yields

$$x_1((n_1+1+n_2)T) \geq m_1\exp(\delta(n_2+1)T)$$

Then

$$x_1((n_1+1+n_2+n_3)T) \geq x_1((n_1+1+n_2)T)\exp(n_3\bar{\sigma}_1)$$
$$\geq m_1\exp(\delta(n_2+1)T)\exp(n_3\bar{\sigma}_1) > m_1$$

which is a contradiction to the boundedness of $x_1(t)$. Therefore, assumption $x_1(t) < m_1$ for all $t \in (t^*,\ (n_1+1)T]$ is invalid.

Set $\bar{t} = \inf_{t > t^*}\{x_1(t) \geq m_1\}$, then $x_1(\bar{t}) = m_1$ and (6.4) holds if only $t \in [t^*, \bar{t})$. Then integrating (6.4) on $t \in [t^*, \bar{t})$ yields

$$x_1(t) \geq x_1(t^*)\exp\left(\delta\left(t - t^*\right)\right) \geq m_1\exp(\delta(1+n_2+n_3)T) \stackrel{\Delta}{=} \bar{m}_1$$

for $t > \bar{t}$, the similar argument can be done (since $x_1(\bar{t}) \geq m_1$). Hence $x_1(t) \geq \bar{m}_1$for all $t > t_1$.

Case(2) (x_1 still has an upper bound when a finite time internal $((t^*,\ (n_1\ \ +1)]$) is smaller than Case (1))

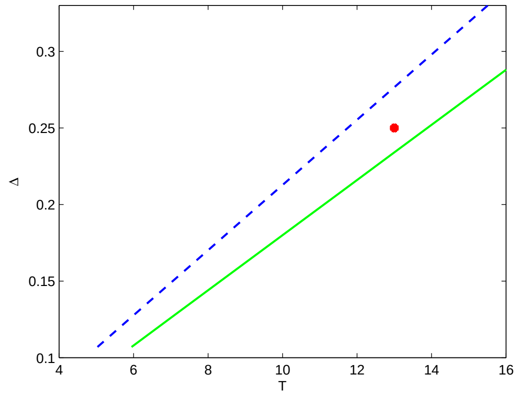

Figure 1. Relationship of minimum drug intensity, Δ, to suppress cancer and pulse interval T. Solid line is the result obtained from Theorem 4, dashed line is the result obtained in reference [11]

There exists a $t^{''} \in (t^*, (n_1+1)T]$ such that $x_1\left(t^{''}\right) \geq m_1$. Let $\hat{t} = \underset{t>t^*}{inf}\{x_1 \ \ (t) \geq m_1\}$, then $x_1(t) < m_1$ for $t \in \left[t^*, \hat{t}\right)$ and $x_1\left(\hat{t}\right) = m_1$. By integrating (6.4) on $\left[t^*, \hat{t}\right)$, we have

$$x_1(t) \geq x_1(t^*) \exp\left(\delta\left(t - t^*\right)\right) \geq m_1 \exp(\delta T) > \bar{m}_1$$

This process can be continued since $x_1\left(\hat{t}\right) \geq m_1$ and we have $x_1(t) \geq \bar{m}_1$ for all $t \geq t_1$.

For both cases, we conclude $x_1(t) \geq \bar{m}_1$ for all $t \geq t_1$. Similarly, we can prove $x_2(t) \geq \bar{m}_2$ for all $t \geq t_2$ and $x_3(t) \geq \bar{m}_3$ for all $t \geq t_3$.

End the proof.

Theorem 4. *Let $(x_1(t), x_2(t), x_3(t), x_4(t))$ be any solution of (3.2), then x_2, x_3 and x_4 are permanence, $x_1(t) \to 0$ as $t \to \infty$ provided that $\beta_1 K_2 e^{(-q_2\tau)} > \alpha_2 K_1$ and* $\max\left\{\frac{\frac{p_2}{a_2\left(\beta_1 K_2 e^{(-q_2\tau)} - \alpha_2 K_1\right)}\Delta}{\xi + \frac{g_3}{a_3+K_2} + \frac{g_2}{a_2} + \frac{g_1}{a_1+K_1}}, \frac{\frac{p_3}{a_3 q_2}\Delta}{\xi + \frac{g_3}{a_3} + \frac{g_2}{a_2} + \frac{g_1}{a_1+K_1}}\right\} < T < \frac{p_1}{a_1 q_1}\Delta$.

proof: By the proving process of Theorem 1, when $\sigma = q_1 T + \frac{p_1\varepsilon}{a_1}T - \frac{p_1\Delta}{a_1} < 0$, we have

$$T < \frac{p_1\Delta}{a_1\left(q_1 + \frac{p_1\varepsilon}{a_1}\right)}$$

integrating (4.4) on $nT < t < (n\ +1)T$, we get

$$x_1((n+1)T) \leq T_m = x_1(nT)\exp(\sigma)$$

where

$$T_m = x_1(nT)\exp\left(\int_{nT}^{(n+1)T}\left(q_1 - \frac{p_1}{a_1}\left(\tilde{x}_4(t) - \varepsilon\right)\right)\right)$$

Then $x_1(nT) \leq x_1\left(0^+\right)\exp(n\sigma)$, and $x_1(nT) \to 0$ as $n \to \infty$. Therefore, $x_1(t) \to 0$ as $n \to \infty$ (since $0 < x_1(t) \leq x_1(nT)\exp(b_1 T)$) (for $nT < t < (n+1)T$). By the proving process of Theorem 3, we get $x_1(t) > m_1$, and according to permanence condition, let $n \to \infty$, $m_1 \to 0$, $\varepsilon \to 0$, $\varepsilon_1 \to 0$, $\varepsilon_2 \to 0$, we can verify the conclusion of Theorem 4.

End the proof.

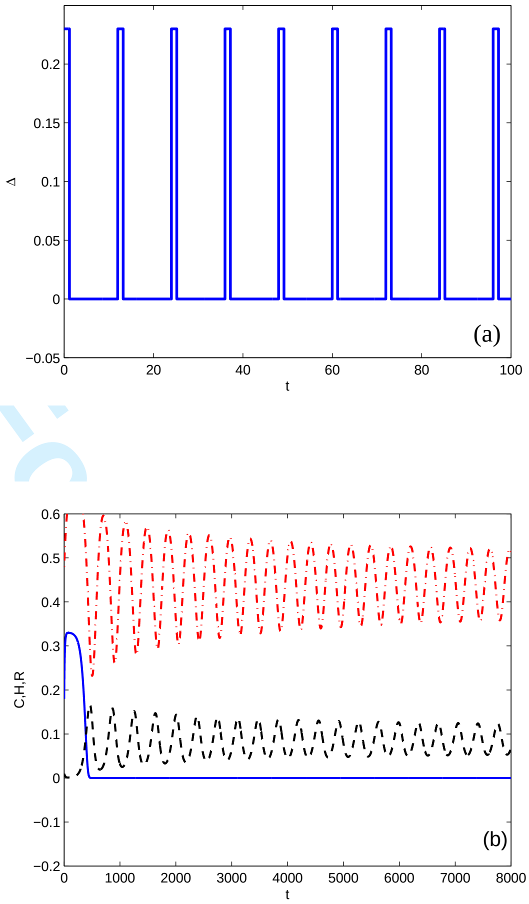

Figure 2. Impulse chemotherapy results using the parameters suggested by Theorem 4. Subplot (a) shows the infusion rate of the impulse chemotherapy. Subplot (b) gives the concentration of cancer cells (solid line), the hunter cells (dashed line), and resting cells (dash-dotted) plot, respectively.

7. Simulation

Considering the parameters in Table 1 for system (3.2), reference [11] gives the dashed line in Fig.1 (numerically obtained) to show the relationship of the time interval T of the pulsed chemotherapy, and the minimum value of Δ for which cancer can be suppressed. According to Theorem 4, we know that the infusion rate Δ is linearly related to the period T of the impulsive chemotherapy to suppress the cancer. When T increases, it is necessary to increase the intensity of the chemotherapy to obtain the cancer suppression. According to Theorem 4 and parameters in Table 1, we obtain the solid line in Fig.1 by considering the upper bound of Theorem 4, i.e. $\Delta = \frac{a_1 q_1}{p_1} T$. The solid line is below the dashed line, which indicates that the infusion rate of chemotherapy give by Theorem 4 is lower than that given in reference [11].

Using the parameters determined by the principle of Theorem 4, we obtain the simulation results shown in Fig.2, where the parameters are $\Delta = 0.23$ and $P = 12$, marked by the point in Fig.1.

Table 1. Dimensionless parameters

Parameter	Value	Parameter	Value
q_1	0.18	K_1	1/3
α_1	1.6515	α_2	5.133×10^{-3}
d_1	0.0412	q_2	0.0245
τ	45.6	K_2	2/3
β_1	9.3×10^{-2}	p_1	1×10^{-3}
p_2	1×10^{-3}	p_3	1×10^{-3}
a_1	1×10^{-4}	a_2	1×10^{-4}
a_3	1×10^{-4}	g_1	0.1
g_2	0.1	g_3	0.1
Δ	$0 \sim 10^4$	ξ	0.2

8. Conclusion

Tumour chemotherapy procedure is a cybernetical system using impulse control in the field of the cybernetic physics. In this paper, we investigate the stability of a tumour growth model with time delay and impulse chemotherapy using impulse control theory. We show the stability of the equilibrium point (chemotherapy kills all cells), the stability of the periodic oscillation of the chemotherapeutic agent (so the impulse chemotherapy function has a well-defined shape), the permanence of the immune cells (i.e., they are not completely destroyed by the chemotherapy), and the condition under which the chemotherapy can eliminate the cancer cells and preserve the immune cells. The theorem about the relationship between impulse treatment period and the intensity of the drug can be used for a doctor to determine minimum drugs applied to the patient to eliminate the cancer and minimize the harm to the immune cells and patient's body.

Data Accessibility. It is a condition of publication that supporting data are made available either as supplementary information or in a suitable repository. If your article has any supporting data, this section should state where it can be accessed. This section should also include details, where possible, of where to access other relevant research materials such as statistical tools, protocols, software etc. If the data has been deposited in an external repository this section should list the database, accession number and link to the DOI for all data from the article that has been made publicly available. Data sets that have been deposited in an external repository and have a DOI should also be appropriately cited in the manuscript and included in the reference list.

Competing Interests. The author(s) declare that they have no competing interests.

Authors' Contributions. H P Ren designed the study, and carried out theoretical analysis, paper writing and editing. Y Yang performed equation deduction, numerical simulation and drafted the manuscript. M S Baptista provided some background knowledge and edited the paper. C Grebogi gave valuable advices in discussion and edited the paper. All authors read and approved the manuscript.

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