Research article

Stability and Hopf bifurcations in a competitive tumour-immune system with intrinsic recruitment delay and chemotherapy

Qingfeng Tang and Guohong Zhang[*]

School of Mathematics and Statistics, Southwest University, Chongqing 400715, China

* **Correspondence:** Email: zgh711@swu.edu.cn.

Abstract: In this paper, a three-dimensional nonlinear delay differential system including Tumour cells, cytotoxic-T lymphocytes, T-helper cells is constructed to investigate the effects of intrinsic recruitment delay and chemotherapy. It is found that the introduction of chemotherapy and time delay can generate richer dynamics in tumor-immune system. In particular, there exists bistable phenomenon and the tumour cells would be cleared if the effect of chemotherapy on depletion of the tumour cells is strong enough or the side effect of chemotherapy on the hunting predator cells is under a threshold. It is also shown that a branch of stable periodic solutions bifurcates from the coexistence equilibrium when the intrinsic recruitment delay of tumor crosses the threshold which is new mechanism, which can help understand the short-term oscillations in tumour sizes as well as long-term tumour relapse. Numerical simulations are presented to illustrate that larger intrinsic recruitment delay of tumor leads to larger amplitude and longer period of the bifurcated periodic solution, which indicates that there exists longer relapse time and then contributes to the control of tumour growth.

Keywords: bistable phenomenon; tumor relapse; intrinsic recruitment delay; chemotherapy; Hopf bifurcation; numerical simulations

1. Introduction

Cancer or malignant tumor results from uncontrolled growth of normal cells [1]. According to the report of World Health Organization, there are about 14.1 million new cancer cases and 8.2 million deaths in the world and it is expected that annual cancer cases will rise from 14 million in 2012 up to 22 million in the following two decades [2].

The immune system can monitor and protect the host from tumor evasion. However, the mechanisms of tumor evasion and immune response are still not completely understood. One of the adaptive immune responses is cell-mediated immunity(CMI). Cell-mediated immunity involves the production of cytotoxic T-lymphocytes (CTLs) and release of various cytokines in response to an antigen mediated

by T-lymphocytes. CTLs are able to recognize and destroy tumor cells. The immune system can be classified into two subclasses, namely, the hunting cells (cytotoxic T lymphocytes) and the resting cells (T Helper cells). Most CTLs require cytokines from helper (resting) T-cells in order to be activated efficiently [3, 4].

Different mathematical models have been constructed to understand the complex interaction between tumor and anti-tumor elements [5–11]. Kuznetsov et al. [12] proposed a classical tumor-immune model to explain the phenomena of "sneaking through" of the tumor and formation of a tumor "dormant state". Letellier et al. [13] found there exist chaotic attractor in a simple model of three competing cell populations (host, immune and tumour cells). Assia and Wang [14] investigated the effects of stochastic noises on tumors dynamics under treatment.

In [3], Sarkar et al. classified the immune system into two subclasses and proposed the following system

$$
\begin{cases}
\frac{dM}{dt} = q + r_1 M(1 - \frac{M}{k_1}) - \alpha MN, \\
\frac{dN}{dt} = \beta NZ - dN, \\
\frac{dZ}{dt} = r_2 Z(1 - \frac{Z}{k_2}) - \beta NZ.
\end{cases}
\tag{1.1}
$$

Here M, N and Z represent the densities of tumor cells, hunting predator cells (cytotoxic T-lymphocytes) and resting predator cells (T-Helper cells), respectively; q is the conversion of normal cells to malignant ones (fixed input), r_1 is the growth rate of tumor cells, k_1 and k_2 are the maximum capacity of tumor cells and resting cells, respectively; α is the predation/destruction rate of tumor cells by the hunting cells, β is the conversion rate of resting cells to hunting cells, d is the natural death rate of hunting cells. The authors obtained some thresholds to control the malignant tumor growth.

In order to prolong the survival of patients it is essential to initiate a specific treatment regimen such as surgery, radiotherapy and chemotherapy [15–20]. Among various treatment methods, chemotherapy is very important and widely used in practice. However chemotherapy also has some side effects and it may kill the normal cells and immune cells [21, 22]. Some mathematical models have been proposed to evaluate the effects of chemotherapy on tumor-immune dynamical behavior [23, 24]. We also refer to [25] and the references therein for related works.

To derive more realistic models, recent papers [26–33] focus on delayed-induced oscillations in tumor-immune system dynamics to explain the short-term oscillations as well as long-term tumour relapse during the progress of the disease. Particularly, following [3], Subhas et al. [4] proposed the following tumor-immune competitive system with time delay

$$
\begin{cases}
\frac{dM}{dt} = r_1 M(1 - \frac{M}{k_1}) - \alpha MN, \\
\frac{dN}{dt} = \beta_1 N(t - \tau)Z(t - \tau) - d_1 N, \\
\frac{dZ}{dt} = r_2 Z(1 - \frac{Z}{k_2}) - \beta_2 N(t - \tau)Z(t - \tau) - d_2 Z.
\end{cases}
\tag{1.2}
$$

They neglect the fixed input term q of tumor in original Eq (1.1) by assuming that the tumour cells are not benign but malignant. Another modification to original Eq (1.1) is that a discrete time delay is added to prescribe the convention time from resting predator cells to hunting predator cells. It is found in Eq (1.2) that the introduction of time delay can lead to appearance of periodic solution. Some other tumor immune models with time delay were investigated in [34, 35].

Considering the necessary times for molecule production and proliferation, the authors of [36–39] introduced the intrinsic recruitment delay of tumor. In fact, as a type of special population, the growth of tumor also need supply of nutrition and food and thus there exist intrinsic recruitment delay. In this paper, based on the models of Sarkar et al. [3], when considering the intrinsic recruitment delay and the effects of chemotherapy, we propose a new deterministic model describing tumor-immune responses as

$$
\begin{cases}
\frac{dM}{dt} = r_1 M(1 - \frac{M(t-\tau)}{k_1}) - \alpha_1 MN - c_1 M, \\
\frac{dN}{dt} = \beta_1 NZ - dN - \alpha_2 MN - c_2 N, \\
\frac{dZ}{dt} = r_2 Z(1 - \frac{Z}{k_2}) - \beta_2 NZ - c_3 Z.
\end{cases}
\tag{1.3}
$$

Here c_1 reflects the chemotherapy effect on the depletion rate of tumour cells, c_2 and c_3 represent the side effect of chemotherapy on the hunting predator cells and resting predator cells, respectively. The term $r_1 M(1 - \frac{M(t-\tau)}{k_1})$ describes the intrinsic recruitment of tumor and the positive time delay constant τ describes the necessary times for molecule production, proliferation, etc. We also modify the Eq (1.1) by adding the term $-\alpha_2 MN$ in the second equation, which represents the loss of hunting predator cells due to competition and destructive influence of tumour cells and is an important characteristic of cancer[12].

In order to simplify the analysis, we non-dimensionalize the Eq (1.3) by using the following rescaling

$$
x = \frac{M}{k_1}, \ y = \frac{N}{k_1}, \ z = \frac{Z}{k_2}, \ \bar{t} = k_1 \alpha_1 t, \ m_1 = \frac{c_1}{\alpha_1 k_1}, \ m_2 = \frac{c_2}{\alpha_1 k_1}, \ m_3 = \frac{c_3}{\alpha_1 k_1},
$$

$$
\alpha = \frac{\alpha_2}{\alpha_1}, \ \mu_1 = \frac{r_1}{\alpha_1 k_1}, \ \mu_2 = \frac{r_2}{\alpha_1 k_1}, \ \rho = \frac{\beta_1 k_2}{\alpha_1 k_1}, \ k = \frac{d}{\alpha_1 k_1}, \ \gamma = \frac{\beta_2}{\alpha_1}.
$$

After dropping the over bar notation for notational clarity, we obtain the following renormalization model

$$
\begin{cases}
\frac{dx}{dt} = \mu_1 x(1 - x(t - \tau)) - xy - m_1 x, \\
\frac{dy}{dt} = \rho yz - ky - \alpha xy - m_2 y, \\
\frac{dz}{dt} = \mu_2 z(1 - z) - \gamma yz - m_3 z.
\end{cases}
\tag{1.4}
$$

The rest of this paper is organized as follows. In Section 2, we obtain the non-negativity and boundeness of solutions of Eq (1.4). In Section 3, we study the existence and stability of possible steady states of the model. In Section 4, we study the changes in the stability of positive equilibrium though the Hopf bifurcation analysis. The direction and stability of the bifurcated periodic solution is also obtained. In Section 5, we carry out some numerical simulations and provide some biological interpretations. Conclusions and discussions are then presented in Section 6.

2. Non-negativity and boundeness

In this section, we discuss the non-negativity and boundedness of the solutions of Eq (1.4). For $\tau > 0$, let $C = C([-\tau, 0], \mathbb{R}^3_+)$ denote the Banach space of continuous function mapping the interval

$[-\tau, 0]$ into $\mathbb{R}_+^3$ with the topology of uniform convergence. The initial conditions are given by

$$x(\xi) = \phi_1(\xi), y(\xi) = \phi_2(\xi), z(\xi) = \phi_3(\xi) \tag{2.1}$$

with $\phi_i(\xi) \geq 0$, $\xi \in [-\tau, 0]$ and $\phi_i(0) > 0$ $(i = 1, 2, 3)$.

Theorem 2.1. *The solutions of Eq (1.4) satisfying the initial conditions Eq (2.1) are non-negative and ultimately bounded.*

Proof. We first define the right-hand side function of Eq (1.4) as

$$G(t, K(t)) = \begin{bmatrix} \mu_1 x(1 - x(t - \tau)) - xy - m_1 x \\ \rho yz - ky - \alpha xy - m_2 y \\ \mu_2 z(1 - z) - \gamma yz - m_3 z \end{bmatrix},$$

where $K(t) = (K_1(t), K_2(t), K_3(t))^T$ and $K_1(t) = x$, $K_2(t) = y$, $K_3(t) = z$. It is obvious that the function $G(t, K(t))$ is locally Lipschitz and by the standard theory of functional differential equation, we know that there exists a unique solution for a given initial conditions. To prove the non-negativity of solutions of Eq (1.4), we first prove the non-negativity over the time interval $[0, \tau]$. Considering the right-hand side functions of Eq (1.4) over the time interval $[0, \tau]$, we have

$$G(t, K(t)) = \begin{bmatrix} G_1(t, K(t)) \\ G_2(t, K(t)) \\ G_3(t, K(t)) \end{bmatrix}_{K_i(t)=0} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

It follows that the solutions of Eq (1.4) remain nonnegative in $[0, \tau]$. Similarly, we can repeat the process over $[\tau, 2\tau]$ and so on by using the method of steps, it can be proved that for any finite interval $[0, t]$, the solutions of Eq (1.4) remains non-negative.

Now we consider the boundeness of the solutions. It follows from the non-negativity of the solutions and the first equation of Eq (1.4) that

$$\frac{dx}{dt} \leq \mu_1 x(1 - x(t - \tau)). \tag{2.2}$$

Note that the solution is bounded for delay-logistic equation (refer to [41]). We know from Eq (2.2) and the comparison principle that $x(t)$ is ultimately bounded for any nonnegative initial conditions. Define a new variable $U(t) = y(t) + \frac{\rho}{\gamma} z(t)$, and let $d = \min\{k + m_2, m_3\}$. By the non-negativity of the solutions of Eq (1.4), we have

$$\begin{aligned} \frac{dU}{dt} &= -ky - \alpha xy - m_2 y + \frac{\rho\mu_2}{\gamma} z(1 - z) - \frac{\rho m_3}{\gamma} z \\ &\leq \frac{\rho\mu_2}{4\gamma} - (k + m_2)y - \frac{\rho m_3}{\gamma} z \\ &\leq \frac{\rho\mu_2}{4\gamma} - dU. \end{aligned} \tag{2.3}$$

Taking $Q = \frac{\rho\mu_2}{4\gamma}$, we know from Eq (2.3) and comparison principle that $\limsup\limits_{t \to \infty} U(t) \leq \frac{Q}{d}$. So the solutions of Eq (1.4) are ultimately bounded.

3. Existence and stability of equilibria

In this section, we investigate the existence and stability of equilibria for Eq (1.4) as delay is absent, that is

$$
\begin{cases}
\frac{dx}{dt} = \mu_1 x(1-x) - xy - m_1 x, \\
\frac{dy}{dt} = \rho yz - ky - \alpha xy - m_2 y, \\
\frac{dz}{dt} = \mu_2 z(1-z) - \gamma yz - m_3 z.
\end{cases}
\tag{3.1}
$$

Clearly, some of equilibria of Eq (3.1) can be obtained easily as follows:

- There always exists extinction equilibrium $E_0^{xyz}(0,0,0)$.
- If $m_1 < \mu_1$, the Eq (3.1) exists immunity-free equilibrium $E_0^{yz}(\frac{\mu_1-m_1}{\mu_1}, 0, 0)$.
- If $m_3 < \mu_2$, the Eq (3.1) exists axial equilibrium $E_0^{xy}(0, 0, \frac{\mu_2-m_3}{\mu_2})$.
- If $m_1 > \mu_1$ and $m_3 < \mu_2$, the Eq (3.1) exists equilibrium $E_0^y(\frac{\mu_1-m_1}{\mu_1}, 0, \frac{\mu_2-m_3}{\mu_2})$.
- If $\mu_2 m_2 + \rho m_3 < \mu_2(\rho - k)$, the Eq (3.1) exists tumor-free equilibrium $E_0^x(0, y_1, z_1)$, where

$$
y_1 = \frac{\mu_2\rho - \mu_2 k - \mu_2 m_2 - \rho m_3}{\rho\gamma}, z_1 = \frac{k + m_2}{\rho}.
$$

For the existence of coexistence equilibrium, we have the following theorem.

Theorem 3.1. *If Eqs* (3.6) *and* (3.7) *hold, the Eq* (3.1) *exists a unique coexistence equilibrium* $E^*(x^*, y^*, z^*)$.

Proof. The coexistence equilibrium $E^*(x^*, y^*, z^*)$ of Eq (3.1) satisfies the following equations:

$$
\begin{cases}
\mu_1(1-x^*) - y^* - m_1 = 0, \\
\rho z^* - k - \alpha x^* - m_2 = 0, \\
\mu_2(1-z^*) - \gamma y^* - m_3 = 0.
\end{cases}
\tag{3.2}
$$

From the first equation of (3.2), we have

$$
y^* = \mu_1 - m_1 - \mu_1 x^*.
\tag{3.3}
$$

Substituting Eq (3.3) into the third equation of (3.2) comes to

$$
z^* = \frac{\gamma\mu_1 x^* + \mu_2 + \gamma m_1 - \gamma\mu_1 - m_3}{\mu_2}.
\tag{3.4}
$$

Substituting Eqs (3.3) and (3.4) into the second equation of (3.2) yields

$$
x^* = \frac{\mu_2 m_2 + \rho m_3 + \mu_1\gamma\rho + k\mu_2 - \rho\mu_2 - \gamma\rho m_1}{\mu_1\rho\gamma - \alpha\mu_2}.
\tag{3.5}
$$

It is easy to see from Eqs (3.3) and (3.4) that $y^* > 0, z^* > 0$ if and only if

$$
\mu_1 x^* < \mu_1 - m_1 < \mu_1 x^* + \frac{\mu_2 - m_3}{\gamma},
\tag{3.6}
$$

which indicates that

$$\mu_1 - m_1 > 0, \mu_2 - m_3 > 0.$$

It follows from Eq (3.5) that $x^* > 0$ if and only if

$$(\mu_2 m_2 + \rho m_3 - \mu_2(\rho - k) + \gamma\rho(\mu_1 - m_1))(\mu_1\gamma\rho - \mu_2\alpha) > 0. \tag{3.7}$$

To study the stability of the equilibria above when $\tau = 0$, we evaluate the Jacobian matrix of Equation (3.1) to get

$$J = \begin{bmatrix} \mu_1 - 2\mu_1 x - y - m_1 & -x & 0 \\ -\alpha y & \rho z - k - \alpha x - m_2 & \rho y \\ 0 & -\gamma z & \mu_2 - 2\mu_2 z - \gamma y - m_3 \end{bmatrix}. \tag{3.8}$$

Theorem 3.2. *If $m_1 > \mu_1$ and $m_3 > \mu_2$, then $E_0^{xyz}(0,0,0)$ is globally asymptotically stable.*

Proof. It follows from Eq (3.8) that the characteristic equation of (3.1) at extinction equilibrium $E_0^{xyz}(0,0,0)$ is

$$(\lambda - \mu_1 + m_1)(\lambda + k + m_2)(\lambda - \mu_2 + m_3) = 0.$$

It is easy to see that the eigenvalues are

$$\lambda_1 = \mu_1 - m_1, \quad \lambda_2 = -k - m_2 < 0, \quad \lambda_3 = \mu_2 - m_3.$$

So if $m_1 > \mu_1$, and $m_3 > \mu_2$, equilibrium $E_0^{xyz}(0,0,0)$ is locally asymptotically stable.

Now we prove the global stability of $E_0^{xyz}(0,0,0)$. Note that $m_1 > \mu_1$ and $m_3 > \mu_2$. It follows that $\frac{dx}{dt} < 0$, $\frac{dz}{dt} < 0$, which implies that

$$\lim_{t\to\infty} x(t) \to 0, \quad \lim_{t\to\infty} z(t) \to 0. \tag{3.9}$$

Then from Eq (3.9) and the second equation of (3.1) we have

$$\lim_{t\to\infty} y(t) \to 0. \tag{3.10}$$

It follows from Eqs (3.9) and (3.10) that $E_0^{xyz}(0,0,0)$ is globally attractive. The proof is completed.

Theorem 3.3. *Assume that $m_1 < \mu_1$. If $m_3 > \mu_2$, then $E_0^{yz}(\frac{\mu_1-m_1}{\mu_1},0,0)$ is globally asymptotically stable.*

Proof. It follows from Eq (3.8) that the characteristic equation of (3.1) at $E_0^{yz}(\frac{\mu_1-m_1}{\mu_1},0,0)$ is

$$(\lambda - m_1 + \mu_1)\left(\lambda + k + m_2 + \frac{\alpha(\mu_1 - m_1)}{\mu_1}\right)(\lambda - \mu_2 + m_3) = 0.$$

Clearly the eigenvalues

$$\lambda_1 = m_1 - \mu_1 < 0, \quad \lambda_2 = -k - m_2 - \frac{\alpha(\mu_1 - m_1)}{\mu_1} < 0.$$

So if $\mu_2 < m_3$, we have $\lambda_3 = \mu_2 - m_3 < 0$. We know that $E_0^{yz}(\frac{\mu_1-m_1}{\mu_1}, 0, 0)$ is locally asymptotically stable.

Now we prove the global stability of $E_0^{yz}(\frac{\mu_1-m_1}{\mu_1}, 0, 0)$. It follows from $m_3 > \mu_2$ that $\frac{dz}{dt} < 0$, which implies that

$$z(t) \to 0 \quad \text{as} \quad t \to \infty. \tag{3.11}$$

Then from Eq (3.11) and the second equation of (3.1), we have $\frac{dz}{dt} < 0$ for large t, which indicates that

$$y(t) \to 0 \quad \text{as} \quad t \to \infty. \tag{3.12}$$

There exists $T_1(\epsilon) > 0$ such that $0 \le y(t) \le \epsilon$ as $t > T_1(\epsilon)$. Then from the first equation of (3.1), we have

$$(\mu_1 - m_1 - \epsilon)x - \mu_1 x^2 \le \frac{dx}{dt} \le (\mu_1 - m_1)x - \mu_1 x^2. \tag{3.13}$$

It follow from Eq (3.13), comparison principle and the arbitrariness of ϵ that

$$\lim_{t \to \infty} x(t) = \frac{\mu_1 - m_1}{\mu_1}. \tag{3.14}$$

We know from Eqs (3.11), (3.12) and (3.14) that $E_0^{yz}(\frac{\mu_1-m_1}{\mu_1}, 0, 0)$ is globally attractive. The proof is completed.

Theorem 3.4. *Assume that $m_3 < \mu_2$. If $m_1 > \mu_1$ and $\mu_2 m_2 + \rho m_3 > \mu_2(\rho - k)$, then $E_0^{xy}(0, 0, \frac{\mu_2-m_3}{\mu_2})$ is globally asymptotically stable.*

Proof. It follows from Eq (3.8) that the characteristic equation of (3.1) at equilibrium E_0^{xy} is

$$(\lambda - m_3 + \mu_2)(\lambda - \mu_1 + m_1)(\lambda - \frac{\rho\mu_2 - \rho m_3 - \mu_2 k - \mu_2 m_2}{\mu_2}) = 0.$$

The eigenvalues are

$$\lambda_1 = m_3 - \mu_2, \quad \lambda_2 = \mu_1 - m_1 \quad \lambda_3 = \frac{\rho\mu_2 - \rho m_3 - \mu_2 k - \mu_2 m_2}{\mu_2}.$$

So if $m_1 > \mu_1$ and $\mu_2 m_2 + \rho m_3 > \mu_2(\rho - k)$, E_0^{xy} is locally asymptotically stable.

Now we prove the global stability of $E_0^{xy}(0, 0, \frac{\mu_2-m_3}{\mu_2})$. It follows from $m_1 > \mu_1$ that $\frac{dx}{dt} < 0$, which implies that

$$\lim_{t \to \infty} x(t) = 0. \tag{3.15}$$

From the third equation of (3.1) we have

$$\frac{dz}{dt} \le (\mu_2 - m_3)z - \mu_2 z^2,$$

which indicates that

$$\limsup_{t \to \infty} z(t) \le \frac{\mu_2 - m_3}{\mu_2}. \tag{3.16}$$

Then from the second equation of (3.1) we have

$$\frac{dy}{dt} \le (\rho z - k - m_2)y \le \left(\frac{\rho(\mu_2 - m_3)}{\mu_2} - k - m_2\right)y$$

for large t. Since $\mu_2 m_2 + \rho m_3 > \mu_2(\rho - k)$, we have $\frac{dy}{dt} < 0$, which indicates that

$$\lim_{t \to \infty} y(t) = 0. \tag{3.17}$$

There exists $T_2(\epsilon) > 0$ such that $0 \le y(t) \le \epsilon$ as $t > T_2(\epsilon)$. It follows from the third equation of (3.1) that

$$\frac{dz}{dt} \ge (\mu_2 - m_3 - \epsilon)z - \mu_2 z^2,$$

which implies that

$$\liminf_{t \to \infty} z(t) \ge \frac{\mu_2 - m_3 - \epsilon}{\mu_2}. \tag{3.18}$$

It follow from Eqs (3.16) and (3.18), the arbitrariness of ϵ that

$$\lim_{t \mapsto \infty} z(t) = \frac{\mu_2 - m_3}{\mu_2}. \tag{3.19}$$

Then from Eqs (3.15), (3.17) and (3.19), we know that $E_0^{xy}(0, 0, \frac{\mu_2 - m_3}{\mu_2})$ is globally attractive. The proof is completed.

Theorem 3.5. *Assume that* $m_1 < \mu_1$ *and* $m_3 < \mu_2$. *If* $\mu_2 m_2 + \rho m_3 > \mu_2(\rho - k) + \frac{\mu_2 \alpha}{u_1}(m_1 - \mu_1)$, $E_0^y(\frac{\mu_1 - m_1}{\mu_1}, 0, \frac{\mu_2 - m_3}{\mu_2})$ *is locally asymptotically stable.*

Proof. It follow from Eq (3.8) that the characteristic equation of (3.1) at equilibrium E_0^y is

$$(\lambda - m_3 + \mu_2)(\lambda - m_1 + \mu_1)(\lambda - \frac{A}{\mu_1 \mu_2}) = 0,$$

where

$$A = \mu_2(\rho - k) + \frac{\mu_2 \alpha}{\mu_1}(m_1 - \mu_1) - \mu_2 m_2 - \rho m_3.$$

Note that eigenvalues

$$\lambda_1 = m_3 - \mu_2 < 0, \lambda_2 = m_1 - \mu_1 < 0$$

since $m_1 < \mu_1$ and $m_3 < \mu_2$. Thus if eigenvalue $\lambda_3 = \frac{A}{\mu_1 \mu_2} < 0$, that is

$$\mu_2 m_2 + \rho m_3 > \mu_2(\rho - k) + \frac{\mu_2 \alpha}{u_1}(m_1 - \mu_1),$$

the equilibrium E_0^y is locally asymptotically stable.

Theorem 3.6. *Assume that* $\mu_2 m_2 + \rho m_3 < \mu_2(\rho - k)$. *If* $\mu_2 m_2 + \rho m_3 < \mu_2(\rho - k) + \rho \gamma(m_1 - \mu_1)$, *then* $E_0^x(0, y_1, z_1)$ *is locally asymptotically stable.*

Proof. It follows from Eq (3.8) that the characteristic equation of (3.1) at tumor-free equilibrium $E_0^x(0, y_1, z_1)$ is

$$(\lambda - \mu_1 + m_1 + y_1)(\lambda^2 + \mu_2 z_1 \lambda + \gamma\rho y_1 z_1) = 0.$$

One of the eigenvalues is

$$\lambda_1 = \mu_1 - m_1 - y_1 = \mu_1 - m_1 - \frac{\mu_2\rho - \mu_2 k - \mu_2 m_2 - \rho m_3}{\rho\gamma}.$$

The other two eigenvalues λ_2 and λ_3 are determined by the following equation

$$\lambda^2 + \mu_2 z_1 \lambda + \gamma\rho y_1 z_1 = 0.$$

Note that

$$\lambda_2 + \lambda_3 = -\mu_2 z_1 < 0, \quad \lambda_2 \lambda_3 = \gamma\rho y_1 z_1 > 0.$$

Then the real parts of eigenvalues λ_2 and λ_3 are negative. So if $\lambda_1 < 0$, that is

$$\mu_2 m_2 + \rho m_3 < \mu_2(\rho - k) + \rho\gamma(m_1 - \mu_1),$$

the tumor-free equilibrium $E_0^x(0, y_1, z_1)$ is locally asymptotically stable.

Remark 3.7. It can be seen from Theorem 3.5 and Theorem 3.6 that there exist bistable phenomenon in the Eq (3.1). Both E_0^x and E_0^y are locally asymptotically stable if $m_1 < \mu_1$, $m_3 < \mu_2$ and

$$(A1) \quad \mu_2(\rho - k) + \frac{\mu_2}{\mu_1}\alpha(m_1 - \mu_1) < \mu_2 m_2 + \rho m_3 < \mu_2(\rho - k) + \rho\gamma(m_1 - \mu_1),$$

which indicates that if the tumor can be cleared or not depends on the initial densities of different types of cells.

Theorem 3.8. *Assume that Eqs (3.6) and (3.7) hold. The coexistence equilibrium E^* is locally asymptotically stable if and only if the following conditions hold:*

$$(H1) \quad \mu_1\gamma\rho - \mu_2\alpha > 0;$$
$$(H2) \quad \mu_2\gamma\rho y^*(z^*)^2 + \mu_1(\mu_2)^2 x^*(z^*)^2 + \mu_1(x^*)^2(\mu_1\mu_2 z^* - \alpha y^*) > 0.$$

Proof. It follows from Eq (3.8) that the characteristic equation of (3.1) at coexistence equilibrium E^* is

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,$$

where

$$a_1 = \mu_1 x^* + \mu_2 z^*,$$
$$a_2 = \mu_1\mu_2 x^* z^* + \rho\gamma y^* z^* - \alpha x^* y^*,$$
$$a_3 = (\mu_1\gamma\rho - \alpha\mu_2)x^* y^* z^*.$$

Clearly $a_1 > 0$. Then by Routh-Hurwitz Criterion, if $a_3 > 0$ and $a_1 a_2 - a_3 > 0$, that is the conditions $(H1)$ and $(H2)$ hold, E^* is locally asymptotically stable.

Remark 3.9. It can be seen from Theorem 3.8 that if the destructive influence of tumor cells is small, that is α is small enough, the conditions $(H1)$ and $(H2)$ hold, and the coexistence equilibrium E^* is locally asymptotically stable.

Theorem 3.10. *If the coexistence equilibrium E^* is asymptotically stable, all the other boundary equilibria are unstable.*

Proof. If E^* exist, we have $\mu_1 > m_1$, $\mu_2 > m_3$, which indicates that equilibria E_0^{xyz}, E_0^{xy} and E_0^{xy} can not be stable. It follows from Eq (3.6) that

$$\mu_2(\rho - k) + \frac{\mu_2\alpha}{\mu_1}(m_1 - \mu_1) - \frac{\mu_2 - m_3}{\gamma\mu_1}(\mu_1\rho\gamma - \mu_2\alpha) < \mu_2 m_2 + \rho m_3 < \mu_2(\rho - k) + \frac{\mu_2\alpha}{\mu_1}(m_1 - \mu_1),$$

which indicates that E_0^y can not be stable. It follows from the stability of E^* and Eq (3.7) that

$$\mu_2 m_2 + \rho m_3 > \mu_2(\rho - k) + \rho\gamma(m_1 - \mu_1),$$

which indicates that E_0^x can not be stable.

Remark 3.11. It is believed that, although it is difficulty to complete the proof, the coexistence equilibrium E^* is globally asymptotically stable when it is locally asymptotically stable. However, we can obtain the result about uniform persistence of Eq (3.1), which indicates that three types of cells can coexist.

Theorem 3.12. *If the axial and planer singular points exist and*
(a)$m_1 < \mu_1$,
(b)$m_3 < \mu_2$,
(c)$\mu_2(\rho - k) + \rho\gamma(m_1 - \mu_1) < \mu_2 m_2 + \rho m_3 < \mu_2(\rho - k) + \frac{\mu_2\alpha}{\mu_1}(m_1 - \mu_1)$,
then the Eq (3.1) is uniformly persistent.

Proof. In order to prove the theorem we shall employ the method of average Lyapunov function [42]. Let us consider the following average Lyapunov function for the Eq (3.1)

$$\psi(x, y, z) = x^{\xi_{11}} y^{\xi_{22}} z^{\xi_{33}},$$

where $\xi_{11}, \xi_{22}, \xi_{33}$ are all nonnegative constants to be chosen suitably in the subsequent steps. It can be noted that $\psi(x, y, z)$ is a positive continuous function defined in the positive quadrant $\mathbf{R}_+^3$. Taking the time derivative along the solution of Eq (3.1), we have

$$\begin{aligned}
\Gamma(x, y, z) &= \frac{\dot{\psi}(x, y, z)}{\psi(x, y, z)} \\
&= \xi_{11}\frac{\dot{x}}{x} + \xi_{22}\frac{\dot{y}}{y} + \xi_{33}\frac{\dot{z}}{z} \\
&= \xi_{11}[\mu_1(1 - x) - y - m_1] + \xi_{22}[\rho z - k - \alpha x - m_2] + \xi_{33}[\mu_2(1 - z) - \gamma y - m_3].
\end{aligned}$$

It is easy to show that the ω-limit sets for Eq (3.1) on the boundary of the positive cone consists of fixed points. Thus to prove the uniform persistence of the Eq (3.1), it is sufficient to verify that $\Gamma(x, y, z)$

is positive for all singular points and the suitable choice of $\xi_{11}, \xi_{22}, \xi_{33} > 0$, that is, the following conditions must be satisfied:

$$\Gamma(E_0^{xyz}) = \xi_{11}(\mu_1 - m_1) + \xi_{22}(-k - m_2) + \xi_{33}(\mu_2 - m_3) > 0, \tag{3.20}$$

$$\Gamma(E_0^{yz}) = \xi_{22}(-k - m_2 - \alpha\frac{\mu_1 - m_1}{\mu_1}) + \xi_{33}(\mu_2 - m_3) > 0, \tag{3.21}$$

$$\Gamma(E_0^{xy}) = \xi_{11}(\mu_1 - m_1) + \xi_{22}(\rho\frac{\mu_2 - m_3}{\mu_2} - k - m_2) > 0, \tag{3.22}$$

$$\Gamma(E_0^{y}) = \xi_{22}(\rho\frac{\mu_2 - m_3}{\mu_2} - \alpha\frac{\mu_1 - m_1}{\mu_1} - k - m_2) > 0, \tag{3.23}$$

and

$$\Gamma(E_0^{x}) = \xi_{11}(\mu_1 - m_1 - \frac{\mu_2\rho - \mu_2 k - \mu_2 m_2 - \rho m_3}{\rho\gamma}) > 0. \tag{3.24}$$

Noting $\mu_1 - m_1 > 0$ and $\mu_2 - m_3 > 0$, we can take large ξ_{11} and ξ_{33} and small ξ_{22} such that Eqs (3.20), (3.21) and (3.22) are satisfied. It follows that if

$$\mu_2(\rho - k) + \rho\gamma(m_1 - \mu_1) < \mu_2 m_2 + \rho m_3 < \mu_2(\rho - k) + \frac{\mu_2\alpha}{\mu_1}(m_1 - \mu_1),$$

Equations (3.23) and (3.24) hold. The proof is completed.

Remark 3.13. It is found that if the effect of chemotherapy on depletion of tumor cells is strong enough ($m_1 > \mu_1$), tumor cells would be cleared. While if the effect of chemotherapy is relatively weak ($m_1 < \mu_1$), the dynamics of Eq (3.1) rely on the side effects of chemotherapy on the hunting predator cells (m_2) and resting predator cells (m_3), respectively. Then to control or clear the tumor, it is important to increase the effect of chemotherapy on tumor cells and let the side effect of chemotherapy on the predator cells be under a threshold.

4. Hopf bifurcation

In this section, we take the discrete time delay τ as a bifurcation parameter and show that when E^* loses its stability and a Hopf bifurcation occurs when the time delay passes through a critical value.

4.1. Existence of Hopf bifurcation

In order to study the stability of the coexistence equilibrium E^* of Eq (1.4), we first compute the Jacobian matrix as following

$$J(E^*) = \begin{bmatrix} -\mu_1 x^* e^{-\lambda\tau} & -x^* & 0 \\ -\alpha y^* & 0 & \rho y^* \\ 0 & -\gamma z^* & -\mu_2 z^* \end{bmatrix}.$$

Then the characteristic equation at E^* is

$$\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 + (b_4\lambda^2 + b_5\lambda + b_6)e^{-\lambda\tau} = 0, \tag{4.1}$$

where

$$b_1 = \mu_2 z^*, \qquad b_2 = \gamma\rho y^* z^* - \alpha x^* y^*, \qquad b_3 = -\alpha\mu_2 x^* y^* z^*,$$
$$b_4 = \mu_1 x^*, \qquad b_5 = \mu_1\mu_2 x^* z^*, \qquad\qquad b_6 = \mu_1\rho\gamma x^* y^* z^*.$$

Putting $\lambda = i\omega$ into the characteristic Eq (4.1) and separating the real and imaginary parts, we have

$$\omega^3 - b_2\omega = b_5\omega\cos(\omega\tau) + (b_4\omega^2 - b_6)\sin(\omega\tau) \tag{4.2}$$

and

$$b_1\omega^2 - b_3 = b_5\omega\sin(\omega\tau) + (-b_4\omega^2 + b_6)\cos(\omega\tau). \tag{4.3}$$

Adding up the squares of the corresponding sides of Eqs (4.2) and (4.3) yields the following algebra equation with respect to ω

$$\omega^6 + p_1\omega^4 + p_2\omega^2 + p_3 = 0, \tag{4.4}$$

where

$$p_1 = b_1^2 - 2b_2 - b_4^2,$$
$$p_2 = b_2^2 - 2b_1 b_3 + 2b_4 b_6 - b_5^2,$$
$$p_3 = b_3^2 - b_6^2.$$

Let $u = \omega^2$. Then Eq (4.4) becomes

$$Q(u) \equiv u^3 + p_1 u^2 + p_2 u + p_3 = 0. \tag{4.5}$$

If Eq (4.5) has a positive real root u, the characteristic Eq (4.1) has a purely imaginary root $i\omega = \sqrt{u}$; otherwise, Eq (4.1) has no purely imaginary root.

Note that

$$p_3 = b_3^2 - b_6^2 = (\alpha\mu_2 - \mu_1\rho\gamma)(\alpha\mu_2 + \mu_1\rho\gamma)x^{*2}y^{*2}z^{*2}.$$

We have $p_3 < 0$ if and only if (H1) is satisfied. We know that the stability of coexistence equilibrium E^* as $\tau = 0$ implies that Eq (4.5) has at least one positive real root. If we further assume that $p_2 < 0$, by Descartes sign rule, we know that Eq (4.5) has a unique positive real root u_0. In addition it can be shown that $Q'(u_0) > 0$.

Let $\omega_0 = \sqrt{u_0}$. It follows from Eqs (4.2) and (4.3) that

$$\tau_j = \frac{1}{\omega_0}\arccos\left(\frac{(b_4\omega_0^2 - b_6)(\omega_0^3 - b_2\omega_0) + b_5\omega_0(b_1\omega_0^2 - b_3)}{(b_4\omega_0^2 - b_6)^2 + (b_5\omega_0)^2}\right) + \frac{2\pi n}{\omega_0}, j = 0, 1, 2, \ldots \tag{4.6}$$

Then at increasing sequences of τ values,

$$\tau_0 < \tau_1 < \tau_2 < \cdots < \tau_j \cdots,$$

Equation (4.1) has a pair of purely imaginary roots $\pm i\omega_0$.

Now, it remain to check the transversality condition required by the Hopf bifurcation theorem. Substituting $\lambda(\tau)$ into Eq (4.1) and differentiating the resulting equation in τ, we obtain

$$\left[3\lambda^2 + 2b_1\lambda + b_2 + (2b_4\lambda + b_5)e^{-\lambda\tau} + (b_4\lambda^2 + b_5\lambda + b_6) \cdot (-\tau)e^{-\lambda\tau}\right]\frac{d\lambda}{d\tau} = \lambda e^{-\lambda\tau}(b_4\lambda^2 + b_5\lambda + b_6).$$

Then we have

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2b_1\lambda + b_2 + (2b_4\lambda + b_5)e^{-\lambda\tau} + (b_4\lambda^2 + b_5\lambda + b_6) \cdot (-\tau)e^{-\lambda\tau}}{\lambda e^{-\lambda\tau}(b_4\lambda^2 + b_5\lambda + b_6)}$$

$$= \frac{(3\lambda^2 + 2b_1\lambda + b_2)e^{\lambda\tau}}{\lambda(b_4\lambda^2 + b_5\lambda + b_6)} + \frac{2b_4\lambda + b_5}{\lambda(b_4\lambda^2 + b_5\lambda + b_6)} - \frac{\tau}{\lambda},$$

which indicates that

$$\text{sign}\left\{\frac{d(\text{Re}\lambda)}{d\tau}\right\}\Big|_{\lambda=i\omega_0} = \text{sign}\left\{\text{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\right\}\Big|_{\lambda=i\omega_0}$$

$$= \text{sign}\left\{\frac{3\omega_0^4 + 2(b_1^2 - 2b_2 - b_4^2)\omega_0^2 + (b_2^2 + 2b_4b_6 - b_5^2 - 2b_1b_3)}{(b_6 - b_4\omega_0^2)^2 + b_5^2\omega_0^2}\right\}$$

$$= \text{sign}\left\{\frac{Q'(\omega_0^2)}{(b_6 - b_4\omega_0^2)^2 + b_5^2\omega_0^2}\right\}.$$

Since $Q'(u_0) > 0$, then for $j = 0, 1, 2, ...,$ we have

$$\text{sign}\left\{\frac{d(\text{Re}\lambda)}{d\tau}\Big|_{\tau=\tau_j}\right\} = \text{sign}\left\{\text{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\Big|_{\tau=\tau_j}\right\} > 0.$$

We know that at each τ_j, $j = 0, 1, 2, \cdots$, a pair of characteristic roots of Eq (4.1) cross the imaginary axis to the right. Then the transversality condition required by the Hopf bifurcation theorem is satisfied. We thus obtain the following result.

Theorem 4.1. *Assume that the conditions in Theorem 3.8 hold.*
(i) If $p_2 > 0$, E^* is locally asymptotically stable for $\tau \in [0, \tau_0]$ and unstable for $\tau > \tau_0$.
(ii) Equation (1.4) undergoes a Hopf bifurcation at E^* when $\tau = \tau_0$. That is, Eq (1.4) has a branch of nonconstant periodic solutions bifurcating from E^* near $\tau = \tau_0$.

4.2. Direction and stability of the Hopf bifurcation

In the previous section, we studied the stability of the coexistence equilibrium E^* of Eq (1.4) and the existence of Hopf bifurcations. We know Eq (1.4) has a branch of nonconstant periodic solutions bifurcating from E^* near $\tau = \tau_0$. It is interesting to further determine the direction, stability of bifurcated periodic solutions.

Let $\mu = \tau - \tau_0$ and then $\mu = 0$ is the Hopf bifurcation value of Eq (1.4) at E^*. Introduce the change of variables

$$x_1(t) = x - x^*, x_2(t) = y - y^*, x_3(t) = z - z^*.$$

Let $\bar{x}_i(t) = x_i(\tau t)$ and drop the bars for simplicity of notation. Define operators $L(\mu) : C \longrightarrow \mathbb{R}^3$ and $F(\mu, \phi) : \mathbb{R} \times C \longrightarrow \mathbb{R}^3$ by

$$L(\mu)\phi = (\mu + \tau_0)\begin{bmatrix} 0 & -x^* & 0 \\ -\alpha y^* & 0 & \rho y^* \\ 0 & -\gamma z^* & -\mu_2 z^* \end{bmatrix}\begin{bmatrix} \phi_1(0) \\ \phi_2(0) \\ \phi_3(0) \end{bmatrix} + (\mu + \tau_0)\begin{bmatrix} -\mu_1 x^* & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}\begin{bmatrix} \phi_1(-1) \\ \phi_2(-1) \\ \phi_3(-1) \end{bmatrix},$$

and

$$F(\mu, \phi) = (\mu + \tau_0)\begin{bmatrix} -\mu_1\phi_1(0)\phi_1(-\tau) - \phi_1(0)\phi_2(0) \\ \rho\phi_2(0)\phi_3(0) - \alpha\phi_1(0)\phi_2(0) \\ -\mu_2\phi_3^2(0) - \gamma\phi_2(0)\phi_3(0) \end{bmatrix}$$

respectively, where $\phi(\theta) = (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta))^T \in C$. Then Eq (1.4) may be transformed into a FDE in $C = C([-1, 0], \mathbb{R}^3)$ as

$$\dot{X}(t) = L(\mu)X_t + F(\mu, X_t(\cdot)), \tag{4.7}$$

where

$$X(t) = (x_1(t), x_2(t), x_3(t))^T, \quad X_t(\theta) = X(t + \theta), \theta \in [-1, 0].$$

By Riesz representation theorem, there exists bounded variation function $\eta(\theta, \mu) : [-1, 0] \to \mathbb{R}^3$ such that

$$L(\mu)\phi = \int_{-1}^{0} d\eta(\theta, \mu)\phi(\theta),$$

where

$$\eta(\theta, \mu) = (\mu + \tau_0)\begin{bmatrix} 0 & -x^* & 0 \\ -\alpha y^* & 0 & \rho y^* \\ 0 & -\gamma z^* & -\mu_2 z^* \end{bmatrix}\delta(\theta) + (\mu + \tau_0)\begin{bmatrix} -\mu_1 x^* & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}\delta(\theta + 1)$$

and $\delta(\theta)$ is the Dirac delta function. For $\phi \in C([-1, 0], \mathbb{R}^3)$, we define

$$A(\mu)\phi(\theta) = \begin{cases} \dfrac{d\phi(\theta)}{d\theta}, & \theta \in [-1, 0), \\ \displaystyle\int_{-1}^{0} d\eta(\xi, \mu)\phi(\xi), & \theta = 0, \end{cases}$$

and

$$R(\mu)\phi(\theta) = \begin{cases} 0, & \theta \in [-1, 0), \\ F(\mu, X_t(\cdot)), & \theta = 0. \end{cases}$$

Then Eq (4.7) is equivalent to the following operator equation

$$\dot{X}_t(\theta) = A(\mu)X_t(\theta) + R(\mu)X_t(\theta).$$

For $\varphi \in C([0, 1], (\mathbb{R}^3)^*)$, we define

$$A^*(0)\varphi(s) = \begin{cases} -\dfrac{d\varphi(s)}{ds}, & s \in (0, 1], \\ \displaystyle\int_{-1}^{0} d\eta^{\mathrm{T}}(\xi, 0)\phi(-\xi), & s = 0. \end{cases}$$

For $\varphi \in C([0,1], (\mathbb{R}^3)^*)$ and $\phi \in C([-1,0], \mathbb{R}^3)$, we define a bilinear form as

$$< \varphi, \phi > = \bar{\varphi}^{\mathrm{T}}(0)\phi(0) - \int_{-1}^{0} \int_{0}^{\theta} \bar{\varphi}^{T}(\xi - \theta) d\eta(\theta)\phi(\xi)d\xi,$$

where $\eta(\theta) = \eta(\theta, 0)$. Then it is not difficult to show that $A^*(0)$ is the adjoint operator of $A(0)$. By the discussion at the beginning of this section, we know that $\pm i\omega_0\tau_0$ are eigenvalues of $A(0)$. Thus, they are also eigenvalues of $A^*(0)$.

Let $q(\theta) = (1, q_2, q_3)^{\mathrm{T}} e^{i\omega_0\tau_0\theta}$ be the eigenvectors of matric A corresponding to eigenvalue $i\omega_0\tau_0$. Then we have

$$\tau_0 \begin{bmatrix} i\omega_0 + \mu_1 x^* e^{-i\omega_0\tau_0} & x^* & 0 \\ \alpha y^* & i\omega_0 & -\rho y^* \\ 0 & \gamma z^* & i\omega_0 + \mu_2 z^* \end{bmatrix} \begin{bmatrix} 1 \\ q_2 \\ q_3 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

It follows that

$$q_2 = -\frac{\mu_1 x^* e^{-i\omega_0\tau_0} + i\omega_0}{x^*}, \qquad q_3 = \frac{\gamma z^* (i\omega_0 + \mu_1 x^* e^{-i\omega_0\tau_0})}{x^*(\mu_2 z^* + i\omega_0)}.$$

Let $q^*(s) = D(1, q_2^*, q_3^*)^{\mathrm{T}} e^{i\omega_0\tau_0 s}$ be the eigenvectors of matric A^* corresponding to eigenvalue $-i\omega_0\tau_0$. Then we have

$$\tau_0 \begin{bmatrix} -i\omega_0 + \mu_1 x^* e^{i\omega_0\tau_0} & \alpha y^* & 0 \\ x^* & -i\omega_0 & \gamma z^* \\ 0 & -\rho y^* & -i\omega_0 + \mu_2 z^* \end{bmatrix} \begin{bmatrix} 1 \\ q_2^* \\ q_3^* \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

It follows that

$$q_2^* = \frac{i\omega_0 - \mu_1 x^* e^{i\omega_0\tau_0}}{\alpha y^*}, \qquad q_3^* = \frac{\rho y^* (\mu_1 x^* e^{i\omega_0\tau_0} - i\omega_0)}{\alpha y^* (i\omega_0 - \mu_2 z^*)},$$

Note that

$$< q^*(s), q(\theta) > = \bar{D}(1, \bar{q}_2^*, \bar{q}_3^*)(1, q_2, q_3)^{\mathrm{T}} - \int_{-1}^{0} \int_{s=0}^{\theta} \bar{D}(1, \bar{q}_2^*, \bar{q}_3^*) e^{-(s-\theta)i\omega_0\tau_0} d\eta(\theta)(1, q_2, q_2)^{\mathrm{T}} e^{i\omega_0\tau_0 s} ds$$

$$= \bar{D}(1 + q_2\bar{q}_2^* + q_3\bar{q}_3^* - \int_{-1}^{0} (1, \bar{q}_2^*, \bar{q}_3^*)\theta e^{i\omega_0\tau_0\theta} d\eta(\theta)(1, q_2, q_2)^{\mathrm{T}})$$

$$= \bar{D}(1 + q_2\bar{q}_2^* + q_3\bar{q}_3^* - \mu_1 x^* \tau_0 e^{-i\omega_0\tau_0}).$$

Then we can choose

$$\bar{D} = (1 + q_2\bar{q}_2^* + q_3\bar{q}_3^* - \mu_1 x^* \tau_0 e^{-i\omega_0\tau_0})^{-1}.$$

such that $< q^*(s), q(\theta) > = 1$.

Now following the standard notations and algorithms given in [44] and using a computation process similar to that of Wei and Ruan [43], we can obtain the following coefficients which will be used for determining the important qualities:

$$g_{20} = 2\bar{D}\tau_0\{(\bar{q}_2^*\rho - \bar{q}_3^*\gamma)q_2q_3 - \mu_1 e^{-i\omega_0\tau_0} - (1 + \bar{q}_2^*\alpha)q_2 - \bar{q}_3^*\mu_2 q_3^2\},$$

$$g_{11} = \bar{D}\tau_0\{(\bar{q}_2^*\rho - \bar{q}_3^*\gamma)(\bar{q}_2 q_3 + q_2\bar{q}_3) - \mu_1(e^{i\omega_0\tau_0} + e^{-i\omega_0\tau_0}) - (1 + \bar{q}_2^*\alpha)(\bar{q}_2 + q_2) - 2\bar{q}_3^*\mu_2 q_3\bar{q}_3\},$$

$$g_{02} = 2\bar{D}\tau_0\{(\bar{q}_2^*\rho - \bar{q}_3^*\gamma)\bar{q}_2\bar{q}_3 - \mu_1 e^{i\omega_0\tau} - (1 + \bar{q}_2^*\alpha)\bar{q}_2 - \bar{q}_3^*\mu_2\bar{q}_3^2\},$$

$$g_{21} = 2\bar{D}\tau_0\Big\{-\mu_1[W_{11}^{(1)}(-1) + \frac{1}{2}W_{20}^{(1)}(-1) + \frac{1}{2}W_{20}^{(1)}(0)e^{i\omega_0\tau} + W_{11}^{(1)}(0)e^{-i\omega_0\tau_0}]$$

$$+ (\bar{q}_2^*\rho - \bar{q}_3^*\gamma)[q_3 W_{11}^{(2)}(0) + \frac{1}{2}\bar{q}_3 W_{20}^{(2)}(0) + \frac{1}{2}W_{20}^{(3)}(0)\bar{q}_2 + W_{11}^{(3)}(0)q_2]$$

$$- (1 + \bar{q}_2^*\alpha)[W_{11}^{(2)}(0) + \frac{1}{2}W_{20}^{(2)}(0) + \frac{1}{2}W_{20}^{(1)}(0)\bar{q}_2 + W_{11}^{(1)}(0)q_2]$$

$$- \bar{q}_3^*\mu_2[2q_3 W_{11}^{(3)}(0) + \bar{q}_3 W_{20}^{(3)}(0)]\Big\},$$

where $W_{11}^{(1)}(-1)$, $W_{20}^{(i)}(0)$ and $W_{11}^{(i)}(0)$ are given, respectively, by

$$W_{20}(\theta) = \frac{ig_{20}}{\omega_0\tau_0}e^{i\omega_0\tau_0\theta}q(0) + \frac{i\bar{g}_{02}}{3\omega_0\tau_0}e^{-i\omega_0\tau_0\theta}\bar{q}(0) + E_{20}e^{2i\omega_0\theta}$$

and

$$W_{11}(\theta) = -\frac{ig_{11}}{\omega_0\tau_0}e^{i\omega_0\tau_0\theta}q(0) + \frac{i\bar{g}_{11}}{\omega_0\tau_0}e^{-i\omega_0\tau_0\theta}\bar{q}(0) + E_{11}.$$

Furthermore the constant vector E_{20} satisfy the following equation

$$\begin{bmatrix} 2i\omega_0 + \mu_1 x^* e^{-2i\omega_0\tau_0} & x^* & 0 \\ \alpha y^* & 2i\omega_0 & -\rho y^* \\ 0 & \gamma z^* & 2i\omega_0 + \mu_2 z^* \end{bmatrix} E_{20} = 2\begin{bmatrix} -\mu_1 e^{-i\omega_0\tau_0} - q_2 \\ \rho q_2 q_3 - \alpha q_2 \\ -\mu_2 q_3^2 - \gamma q_2 q_3 \end{bmatrix}.$$

It follows that

$$E_{20} = 2\begin{bmatrix} 2i\omega_0 + \mu_1 x^* e^{-2i\omega_0\tau_0} & x^* & 0 \\ \alpha y^* & 2i\omega_0 & -\rho y^* \\ 0 & \gamma z^* & 2i\omega_0 + \mu_2 z^* \end{bmatrix}^{-1}\begin{bmatrix} -\mu_1 e^{-i\omega_0\tau_0} - q_2 \\ \rho q_2 q_3 - \alpha q_2 \\ -\mu_2 q_3^2 - \gamma q_2 q_3 \end{bmatrix}.$$

The constant vector E_{20} satisfy the following equation

$$\begin{bmatrix} \mu_1 x^* e^{-2i\omega_0\tau_0} & x^* & 0 \\ \alpha y^* & 0 & -\rho y^* \\ 0 & \gamma z^* & \mu_2 z^* \end{bmatrix} E_{11} = 2\begin{bmatrix} -\mu_1 Re\{e^{-i\omega_0\tau_0}\} - Re\{q_2\} \\ \rho Re\{q_2 q_3\} - \alpha Re\{q_2\} \\ -\mu_2 Re\{q_3^2\} - \gamma Re\{q_2 q_3\} \end{bmatrix}.$$

It follows that

$$E_{11} = 2\begin{bmatrix} \mu_1 x^* e^{-2i\omega_0\tau_0} & x^* & 0 \\ \alpha y^* & 0 & -\rho y^* \\ 0 & \gamma z^* & \mu_2 z^* \end{bmatrix}^{-1}\begin{bmatrix} -\mu_1 Re\{e^{-i\omega_0\tau_0}\} - Re\{q_2\} \\ \rho Re\{q_2 q_3\} - \alpha Re\{q_2\} \\ -\mu_2 Re\{q_3^2\} - \gamma Re\{q_2 q_3\} \end{bmatrix}.$$

So far, we have calculated $g_{20}, g_{11}, g_{02}, g_{21}$ and then we can obtain

$$
\begin{aligned}
c_1(0) &= \frac{i}{2\omega_0\tau_0}\Big(g_{11}g_{20} - 2\mid g_{11}\mid^2 - \frac{\mid g_{02}\mid^2}{3}\Big) + \frac{g_{21}}{2}, \\
\nu_2 &= -\frac{\mathrm{Re}(c_1(0))}{\mathrm{Re}(\lambda'(\tau_0))}, \\
\beta_2 &= 2\mathrm{Re}(c_1(0)), \\
T_2 &= \frac{-(\mathrm{Im}\{c_1(0)\} + \nu_2\mathrm{Im}\{\lambda'(\tau_0)\})}{\omega_0\tau_0}.
\end{aligned}
\tag{4.8}
$$

It is known that ν_2 and β_2 will determine the direction and stability of the Hopf bifurcation, and T_2 determines the period of the bifurcated periodic solutions. In particular, if $\nu_2 > 0(\nu_2 < 0)$, the Hopf bifurcation is supercritical (subcritical) and the bifurcated periodic solutions exist for $\tau > \tau_0(\tau < \tau_0)$. If $\beta_2 < 0(\beta_2 > 0)$, the bifurcated periodic solutions are stable(unstable). The period will become longer(shorter) if $T_2 > 0(T_2 < 0)$.

5. Numerical simulations

In this section, we carry out some numerical simulations to display the qualitative behaviours of Eq (1.4) and confirm the theoretical results obtained in the above sections. We perform simulations by using MATLAB software with realistic parameter values given in Table 1.

**Table 1.** Meanings and units of parameters.

Parameters	Descriptions	Ranges	Units
r_1	growth rate of malignant tumor cells	$0.05 - 0.5$	day^{-1} [30]
k_1	carrying capacity of tumor cells	$10^6 - 5 \times 10^9$	cells [30]
α_1	decay rate of tumor cells by hunting cells	$10^{-12} - 5 \times 10^{-7}$	cell^{-1}day^{-1} [30]
α_2	decay rate of hunting cells by tumor cells	$10^{-12} - 5 \times 10^{-7}$	cell^{-1}day^{-1} [30]
d	death rate of hunting cells	$0.01 - 0.1$	day^{-1} [30]
r_2	growth rate of resting cells	0.0245	day^{-1} [27]
k_2	carrying capacity of resting cells	10^7	cells [27]
β	conversion rate from resting to hunting cells	10^{-9}	cell^{-1}day^{-1}[27]
c_1	decay rate of tumor cells by chemotherapy	$10^5 - 10^6$	cell^{-1}day^{-1}[15]
c_2	decay rate of resting cells by chemotherapy	$10^5 - 10^6$	cell^{-1}day^{-1}[15]
c_3	decay rate of hunter cells by chemotherapy	$10^5 - 10^6$	cell^{-1}day^{-1}[15]

Note: GAS means globally asymptotically stable; LAS means locally asymptotically stable.

According to the ranges of parameters in Table 1, we first take the following normalized parameter values

$$
\mu_1 = 0.2, \mu_2 = 0.6, k = 0.4, \alpha = 0.1, \rho = 0.48, \gamma = 0.1, m_1 = 0.01, m_2 = 0.02, m_3 = 0.026.
\tag{5.1}
$$

Then we obtain the boundary equilibria $E_0^x = (0, 0.49, 0.8750)$, $E_0^y = (0.95, 0, 0.9567)$. It is easy to check that the conditions in Theorems 3.5 and 3.6 are satisfied. Then both E_0^x and E_0^y are locally
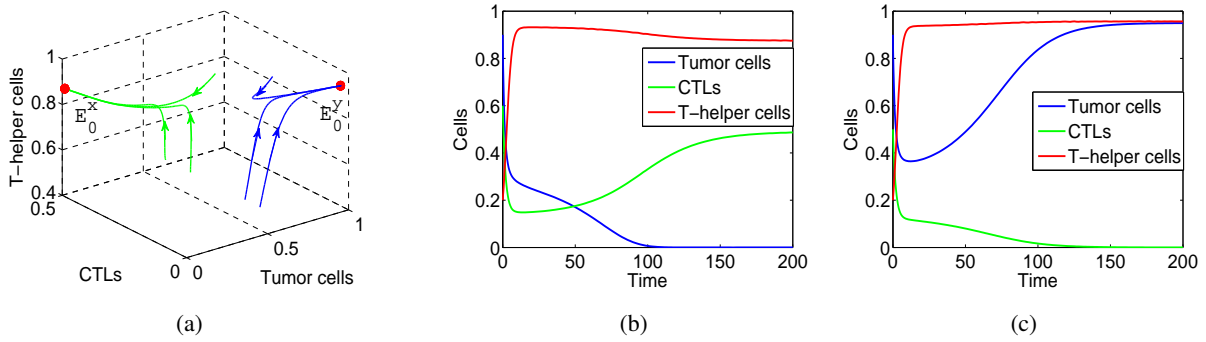
Figure 1. (a) Basins of attraction of E_0^x and E_0^y. (b) (c)Trajectories are shown to converge to either E_0^x or E_0^y depending on their initial positions. The initial values in 1(b) is $[x(0), y(0), z(0)] = [0.9, 0.6, 0.2]$ and in 1(c) is $[x(0), y(0), z(0)] = [0.9, 0.5, 0.2]$. Normalized parameters are given in Eq (5.1). One can note that when the initial density of hunting predator cells is small, the tumour cells tend to be persistent; when the initial density of hunting predator cells is relatively large, the tumour cells will be cleared.
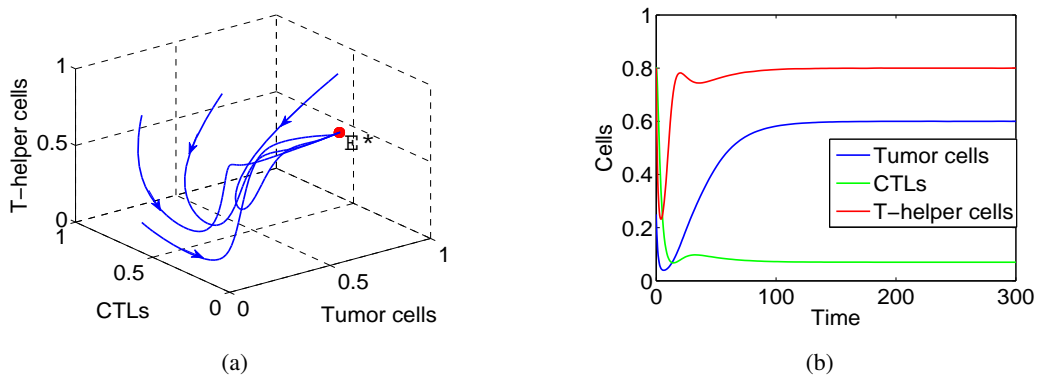

Figure 2. The coexistence equilibrium $E^* = (0.6, 0.07, 0.8)$ is locally asymptotically stable when time delay is absent. Normalized parameters are given in Eq (5.2).

asymptotically stable and E^* is unstable. Figure 1 presents a phase diagram and time series of the solutions of Eq (1.4). One can see that the trajectories converge to either E_0^x or E_0^y with different initial positions. Specially, when the initial density of hunting predator cells is small, the tumour cells tend to be persistent; when the initial density of hunting predator cells is relatively large, the tumour cells will be cleared.

To investigate the stability of coexistence equilibrium E^*, we choose a slightly different set of the normalized parameter values as following

$$\mu_1 = 0.2, \mu_2 = 0.48, k = 0.4, \alpha = 0.1, \rho = 0.6, \gamma = 1, m_1 = 0.01, m_2 = 0.02, m_3 = 0.026. \qquad (5.2)$$

The coexistence equilibrium is $E^* = (0.6, 0.07, 0.8)$. One can show that the conditions in Theorem 3.8 are satisfied and then E^* is locally asymptotically stable when $\tau = 0$, which implies that all the boundary equilibria including E_0^x and E_0^y are unstable. One can see that the trajectories around E^* converge to it (see Figure 2).
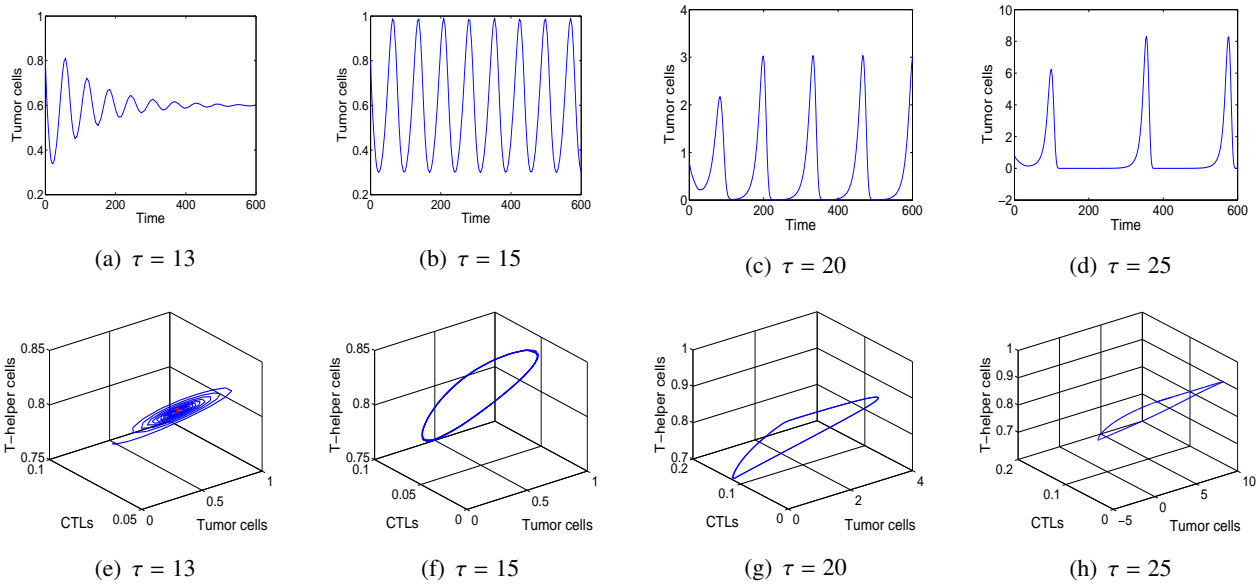
Figure 3. Time series and phase diagrams of the solutions of Eq (1.4) with different time delays τ. (a) (d):the positive equilibrium $E^* = (0.6, 0.07, 0.8)$ of Eq (1.4) is local asymptotically stable when $\tau = 14 < \tau_0 = 14.5117$. (b) (c) (e) (f): the bifurcated periodic solutions occur through Hopf bifurcations when $\tau = 15, 20, 25 > \tau_0$. Normalized parameters are given in Equation (5.2).

From Eq (4.6), we can obtain the Hopf bifurcation point $\tau_0 = 14.5117$. By Eq (4.8), we obtain the Hopf bifurcation parameters $\nu_2 = 40.3056$, $\beta_2 = -0.3561$, $T_2 = 5.8354$. Then we know that the Hopf bifurcation at E^* is supercritical, the bifurcated periodic solutions is stable and the period will increase with the increase of time delay. Figure 3 gives the time series and phase diagrams of the solutions of Equation (1.4) with different time delays. One can see that when the time delay is under the threshold, that is $\tau = 14 < \tau_0$, E^* is a stable focus(see Figure 3(a),(e)), which can explain the short-term oscillations in tumour sizes; when $\tau = 15, 20, 25 > \tau_0$, a branch of stable periodic solutions bifurcate from E^* and the period become larger with the increase of τ (see Figure 3(b)–(d), 3(f)–(h)), which can explain the long-term tumour relapse.

Figure 4 presents the amplitude and period of the bifurcated periodic solutions of Eq (1.4) with respect to different time delay τ. One can see that, larger intrinsic recruitment delay lead to larger amplitude and longer period of the bifurcated periodic solutions, which indicates that the period of tumor relapse become longer and then can provide us with a longer period to control or delete the tumor. Furthermore, with the increase of time delay, the minimum of the periodic tumor tends to zero, which indicates larger delay τ contributes to the control of tumor growth.

Figure 5 shows the sensitivity of state variable $x(t)$ (tumour cells) to the parameters m_1, m_2, m_3 and α. The oscillation behaviour indicates that the tumour cells population is very sensitive in the early time intervals. Note that $\frac{\partial x}{\partial m_1} < 0$. We know that the increase of m_1 is beneficial to control and clear the tumor (see Figure 5(a)). On the other hand, the positivity of $\frac{\partial x}{\partial m_i} 0$ ($i = 1, 2$) indicates that stronger side effect of chemotherapy on hunting predator cells and resting predator cells leads to increase of tumor cells (see Figure 5(b),(d)). The positivity of $\frac{\partial x}{\partial \alpha}$ implies that larger destructive influence of tumor cells
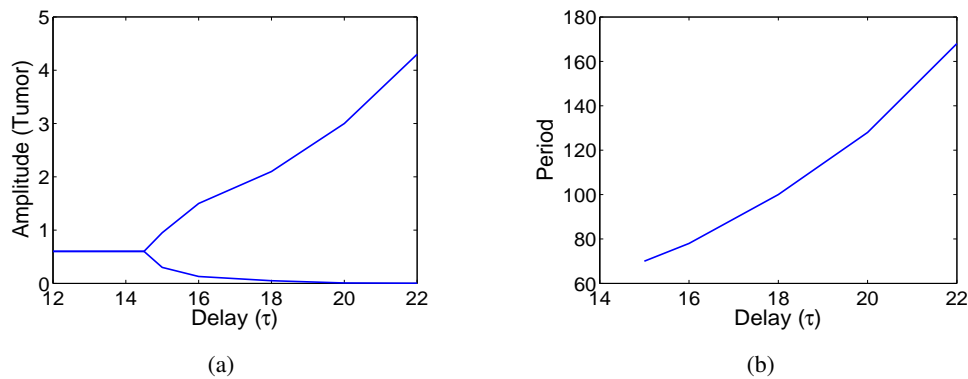
Figure 4. Amplitude and period of tumor cells population for the bifurcated periodic solutions of Eq (1.4) with respect to time delay τ. One can note that larger intrinsic recruitment delay lead to larger amplitude and longer period of the bifurcated periodic solution. Normalized parameters are given in Eq (5.2).

is not conductive to the control of tumor. Here we have used the so called "direct approach" to find sensitivity functions of Eq (1.4) (refer to [40]).

6. Conclusions

The long-term relapse phenomenon of tumor, that is the appearance of periodic solution in a system including tumor, is interesting for the control or deletion of tumor. In this paper, we construct a three-dimensional nonlinear delay differential system including Tumor cells, cytotoxic-T lymphocytes, T-helper cells with recruitment delay and chemotherapy to investigate long-term relapse phenomena of tumor.

We first show that the existence and stability of the equilibria are influenced by the effects of chemotherapy and destructive influence of tumor cells and the results are summarized in the following Table 2.

Table 2. Equilibria and their stability of Eq (1.4).

Case	Conditions	Equilibria and stability
$m_1 > \mu_1$	$m_3 > \mu_2$	E_0^{xyz} is GAS
	$m_3 < \mu_2, \mu_2 m_2 + \rho m_3 \geq \mu_2(\rho - k)$	E_0^{xy} is GAS
	$\mu_2 m_2 + \rho m_3 < \mu_2(\rho - k)$	E_0^x is LAS
$m_1 < \mu_1$	$m_3 > \mu_2$	E_0^{yz} is GAS
	$m_3 < \mu_2, \mu_2 m_2 + \rho m_3 > \mu_2(\rho - k) + \frac{\mu_2 \alpha(m_1 - \mu_1)}{\mu_1}$	E_0^y is LAS
	$\mu_2 m_2 + \rho m_3 < \mu_2(\rho - k) + \rho\gamma(m_1 - \mu_1)$	E_0^x is LAS

Note: GAS means globally asymptotically stable; LAS means locally asymptotically stable.

It is found that there exist bistable phenomenon in Eq (1.4). Both tumor-free equilibrium E_0^x and E_0^y are locally asymptotically stable at the same time, which indicates that if the tumour cells can be eradicated or not rely on the initial density of the hunting predator cells (see Figure 1). We point out
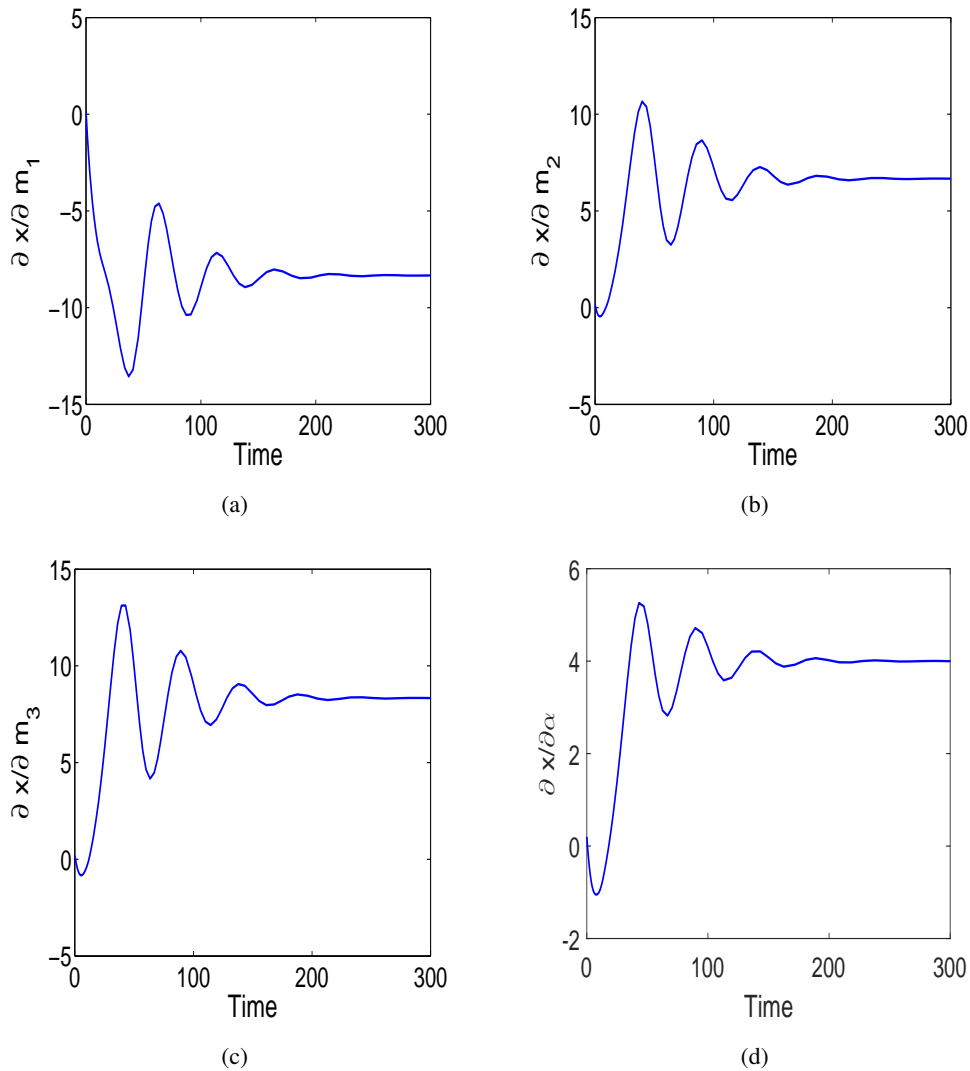
Figure 5. Sensitivity functions $\frac{\partial x}{\partial m_1}$, $\frac{\partial x}{\partial m_2}$, $\frac{\partial x}{\partial m_3}$ and $\frac{\partial x}{\partial \alpha}$ for Eq (1.4). Normalized parameters are given in Eq (5.2). One can see that the tumour cells population is very sensitive to the perturbation of the chosen set of parameters in the early time intervals and the sensitivity decreases by time. The increase of m_1 is beneficial to control and clear the tumor. However stronger side effect of chemotherapy and destructive influence of tumor cells on predator cells leads to increase of tumor cells.

that the bistable phenomenon appearing in this paper is a new dynamical behavior compared with the results in [27] and [28], which indicates that the introduction of chemotherapy and destructive influence of tumor cells can generate richer dynamics in tumor-immune system.

It is found that the coexistence equilibrium is locally asymptotically stable if the destructive influence of tumor cells is small enough (see Figure 2). We also show that the introduction of intrinsic recruitment delay of tumor can leads to the appearance of periodic solutions through Hopf bifurcation, which is a different factor that explain the long-term relapse phenomena of tumor compared with the factor in [27] and [28] (see Figure 3). We further investigate the direction and stability of bifurcated periodic solutions by applying normal form method and center manifold theory. Finally, by numerical simulations, it is shown that, with the increase of delay τ, the amplitude and period of the bifurcated periodic solutions increase and the minimum of the periodic tumor cells tend to zero, which indicates that the increase of delay τ is beneficial to the control of the growth of tumor (see Figure 4). The sensitivity of tumour cells population to small perturbations in m_1, m_2, m_3 and α are also investigated. It follows that tumour cells is negatively proportion with increasing the parameter m_1 and is positively proportion with increasing the parameter m_2, m_3 and α and they are very sensitive in the early time intervals and the sensitivity decreases by time to be insensitive in the steady state (see Figure 5).

Some aspects of the problem remain to be examined and studied in the future. For instance, we plan to extend our analysis to global Hopf bifurcation analysis. Some other factors that influence the dynamics of tumor including the biological heterogeneity of tumor and the resistance to immunotherapy or chemotherapy may be investigated.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest in this paper.

References

1. L. M. F. Merlo, J. W. Pepper, B. J. Reid, C. C. Maley, Cancer as an evolutionary and ecological process, *Nat. Rev. Cancer*, **6** (2006), 924–935.

2. A. Jemal, F. Bray, M. M. Center, Global cancer statistics, *Ca. Cancer. J. Clin.*, **61** (2011), 69–90.

3. R. R. Sarkar, S. Banerjee, Cancer self remission and tumor stability-a stochastic approach, *Math. Biosci.*, **196** (2005), 65–81.

4. K. Subhas, J. J. Nieto, Mathematical modeling of tumor-immune competitive system, considering the role of time delay, *Appl. Math. Comput.*, **340** (2019), 180–205.

5. D. Kirschner, J. Panetta, Modelling immunotherapy of the tumor-immune interaction, *J. Math. Biol.*, **37** (1998), 235–252.

6. L. G. de Pillis, A. Radunskaya, The dynamics of an optimally controlled tumor model: A case study, *Math. Comput. Model.*, **37** (2003), 1221–1244.

7. N. Tsur, Y. Kogana, M. Rehmc, Z. Agur, Response of patients with melanoma to immune checkpoint blockade-insights gleaned from analysis of a new mathematical mechanistic model, *J. Theor. Biol.*, **485** (2020), 110033.

8. M. A. Owen, J. A. Sherratt, Mathematical modelling macrophage dynamics in tumors, *Math. Model. Meth. Appl. Sci.*, **9** (1999), 513–539.

9. J. L. Yu, S. R. J. Jang, A mathematical model of tumor-immune interactions with an immune checkpoint inhibitor, *Appl. Math. Comput.*, **362** (2019), 124532.

10. R. A. Ku-Carrillo, S. E. Delgadillo, B. M. Chen-Charpentier, A mathematical model for the effect of obesity on cancer growth and on the immune system response, *Appl. Math. Model.*, **40** (2016), 4908–4920.

11. N. Bellomo, L. Preziosi, Modelling and mathematical problems related to tumor evolution and its interaction with the immune system, *Math. Comput. Model.*, **32** (2000), 413–452.

12. V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor, A. S. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis, *Bull. Math. Biol.*, **56** (1994), 295–321.

13. C. Letellier, F. Denis, L. A. Aguirre, What can be learned from a chaotic cancer model?, *J. Theor. Biol.*, **322** (2013), 7–16.

14. A. Zazoua, W. D. Wang, Analysis of mathematical model of prostate cancer with androgen deprivation therapy, *Commun. Nonlinear. Sci. Numer. Simul.*, **66** (2019), 41–60.

15. L. Y. Pang, Z. Zhao, X. Y. Song, Cost-effectiveness analysis of optimal strategy for tumor treatment, *Chaos Solitons Fractals*, **87** (2016), 293–301.

16. S. Khajanchi, S. Banerjee, Quantifying the role of immunotherapeutic drug T11 target structure in progression of malignant gliomas: Mathematical modeling and dynamical perspective, *Math. Biosci.*, **289** (2017), 69–77.

17. S. Banerjee, S. Khajanchi, S. Chaudhur, A mathematical model to elucidate brain tumor abrogation by immunotherapy with T11 target structure, *PLoS One*, **10** (2015), 1–21.

18. J. Arciero, T. Jackson, D. Kirschner, A mathematical model of tumor-immune evasion and siRNA treatment, *Discret. Contin. Dyn. Syst. Ser. B.*, **4** (2004), 39–58.

19. L. G. depillis, A. Eladdadi, A. E. Radunskaya, Modeling cancer-immune responses to therapy, *J. Pharmacokinet. Pharmacodyn.*, **41** (2014), 461–0478.

20. M. Itik, M. U. Salamci, S. P. Banks, Optimal control of drug therapy in cancer treatment, *Nonlinear Anal.*, **71** (2009), 1473–1486.

21. X. D. Liu, Q. Z. Li, J. X. Pan, A deterministic and stochastic model for the system dynamics of tumor-immune responses to chemotherapy, *Phys. A*, **500** (2018), 162–176.

22. L. G. depillis, W. Gu, K. R. Fister, T. Head, K. Maples, A. Murugan, et al., Chemotherapy for tumors: An analysis of the dynamics and a study of quadratic and linear optimal controls, *Math. Biosci.*, **209** (2007), 292–315.

23. P. Rokhforoz, A. A. Jamshidi, N. N. Sarvestani, Adaptive robust control of cancer chemotherapy with extended Kalman filter observer, *Inform. Med. Unlock.*, **8** (2017), 1–7.

24. L. G. de Pillis, W. Gu, A. E. Radunskaya, Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations, *J. Theor. Biol.*, **238** (2006), 841–862.

25. R. Eftimie, J. J. Gillard, D. A. Cantrell, Mathematical models for immunology: Current state of the art and future research directions, *Bull. Math. Biol.*, **78** (2016), 2091–2134.

26. M. Villasana, A. Radunskaya, A delay differential equation model for tumor growth, *J. Math. Biol.*, **47** (2003), 270–294.

27. Y. Radouane, Hopf bifurcation in differential equations with delay for tumor-immune system competition model, *SIAM J. Appl. Math.*, **67** (2007), 1693–1703.

28. F. A. Rihan, D. H. Abdel Rahman, S. Lakshmanan, A. S. Alkhajeh, A time delay model of tumour-immune system interactions: Global dynamics, parameter estimation, sensitivity analysis, *Appl. Math. Comput.*, **232** (2014), 606–623.

29. M. Yu, Y. P. Dong, Y. Takeuchi, Dual role of delay effects in a tumour-immune system, *J. Biol. Dyn.*, **11** (2017), 334–347.

30. S. Khajanchi, S. Banerjee, Stability and bifurcation analysis of delay induced tumor immune interaction model, *Appl. Math. Comput.*, **248** (2014), 652–671.

31. S. Khajanchi, Bifurcation analysis of a delayed mathematical model for tumor growth, *Chaos Solitons Fractals*, **77** (2015), 264–276.

32. S. Khajanchi, S. Banerjee, Influence of multiple delays in brain tumor and immune system interaction with T11 target structure as a potent stimulator, *Math. Biosci.*, **302** (2018), 116–130.

33. M. J. Piotrowska, M. Bodnar, Influence of distributed delays on the dynamics of a generalized immune system cancerous cells interactions model, *Commun. Nonlinear. Sci. Numer. Simul.*, **54** (2018), 389–415.

34. S. Banerjee, R. R. Sarkar, Delay-induced model for tumor-immune interaction and control of malignant tumor growth, *BioSystems*, **91** (2008), 268–288.

35. A. E. Gohary, Chaos and optimal control of cancer self-remission and tumor system steady states, *Chaos Solitons Fractals*, **37** (2008), 1305–1316.

36. H. Mayer, K. Zaenker, U. an der Heiden, A basic mathematical model of the immune response, *Chaos*, **5** (1995), 155–161.

37. H. M. Byrne, The effect of time delay on the dynamics of avascular tumor growth, *Math. Biosci.*, **144** (1997), 83–117.

38. P. Bi, S. G. Ruan, Bifurcations in delay differential equations and applications to tumor and immune system interaction models, *SIAM J. Appl. Dyn.*, **12** (2014), 1847–1888.

39. S. G. Ruan, Nonlinear dynamics in tumor-immune system interaction models with delays, *Discret. Contin. Dyn. Syst. Ser. B.*, **26** (2021), 541–602.

40. F. A. Rihan, Sensitivity analysis of dynamic systems with time lags, *J. Comput. Appl. Math.*, **151** (2003), 445–462.

41. K. Gopalsamy, Nonoscillation in a delay-logistic equation, *Quart. Appl. Math.*, **43** (1985), 189–197.

42. D. Mukherjee, P. C. Bhakta, A. B. Roy, Uniform persistence in Kolmogorov models with convex growth functions, *Nonlinear Anal.*, **34** (1998), 427–432.

43. J. J. Wei, S. G. Ruan, Stability and bifurcation in a neural network model with two delays, *Phys. D*, **130** (1998), 255–272.

44. B. D. Hassard, N. D. Kazarinoff, Y. H. Wan, *Theory and Application of Hopf Bifurcation*, London Mathematical Society Lecture Note Series, Cambridge University Press, 1981.