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Periodic and chaotic oscillations in a tumor and immune system interaction model with three delays

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In this paper, a tumor and immune system interaction model consisted of two differential equations with three time delays is considered in which the delays describe the proliferation of tumor cells, the process of effector cells growth stimulated by tumor cells, and the differentiation of immune effector cells, respectively. Conditions for the asymptotic stability of equilibria and existence of Hopf bifurcations are obtained by analyzing the roots of a second degree exponential polynomial characteristic equation with delay dependent coefficients. It is shown that the positive equilibrium is asymptotically stable if all three delays are less than their corresponding critical values and Hopf bifurcations occur if any one of these delays passes through its critical value. Numerical simulations are carried out to illustrate the rich dynamical behavior of the model with different delay values including the existence of regular and irregular long periodic oscillations. © *2014 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4870363]

It is very important to study how the immune system responds to cancer development and progression. On one hand, innate and adaptive immune cells can suppress tumor growth by destroying cancer cells or restraining their outgrowth. On the other hand, the immune system can also promote tumor progression. Recently, various mathematical models have been developed to study the immune response to tumor cells. Following Mayer *et al.*,[25] Burić *et al.*,[4] and Yu and Wei,[39] in this paper, we propose a tumor and immune system interaction model consisted of two differential equations with three time delays in which the delays describe the times necessary for molecule production, proliferation, differentiation of cells, transport, etc. It is well known that systems with multiple delays are difficult to deal with. Here, we provide some analysis on the existence and stability of equilibria and existence of Hopf bifurcations in the model with three delays. We follow the technique of Wei and Ruan[38] (see also Ref. 1) to study the stability of the positive equilibrium: First, we start by considering the model with one delay and obtain a stable interval for the delay; Second, fixing the first delay in its stable interval, we then introduce the second delay and obtain a stable interval for it as well; Finally, we fix the first two delays in their stable intervals and determine the stability for the third delay. The stability of the positive equilibrium is thus obtained when the three delays are restricted in their corresponding intervals and Hopf bifurcations occur if any one of these delays passes through its critical value. Numerical simulations indicate that the model exhibits regular and irregular periodic oscillations (and chaotic behaviors), which demonstrate the phenomenon of long-term tumor relapse. The regular periodic oscillations describe the equilibrium process of cancer immunoediting in the dual host-protective and tumor-promoting actions of immunity. The time delay effects may make the immune-tumor interaction more irregular.

I. INTRODUCTION

The immune state of a patient with tumor often looks rather irregular and is unpredictable due to its complex interactions with the tumor. How the immune system responds to cancer development and progression is an interesting and important question in immunology and cancer research. It is known that innate and adaptive immune cells not only suppress tumor growth but also promote tumor progression.[13,14,21,33,36] Elimination (immunity functions as an extrinsic tumor suppressor in naive hosts), equilibrium (expansion of transformed cells is held in check by immunity), and escape (tumor cells attenuate immune responses and grow into cancers) are the three processes in the dual host-protective and tumor-promoting actions of immunity, called *cancer immunoediting*.

Recently, there has been much interest in mathematical modeling of immune response to tumor cells, see for example, Refs. 5, 6, 11, 20, 22–27, 32, 34, and 35 and the references cited therein. An ideal model can provide insights into the dynamics of interactions of the immune response with the tumor and may play a significant role in understanding the cancer and developing effective drug therapy strategies against it. However, it is almost impossible to develop realistic models to describe such complex processes. In fact, mathematical models for the dynamics of the interaction of the

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immune components with tumor cells are very idealized. Thus, it is feasible to propose simple models, which can display some of the essential immunological phenomena.

In 1997, Mayer *et al.*[25] (see also Refs. 4 and 39) proposed a very simple model of the typical immune response with two ordinary differential equations (ODEs), which is capable of describing a variety of possible situations. Although the model is very simple, it demonstrates how the combination of a few proposed nonlinear interaction rules between the immune system and the tumor are able to generate various kinds of immune response. Mayer *et al.*[25] also pointed out that time delays should be taken into account to describe the times necessary for molecule production, proliferation, differentiation of cells, transport, etc. However, they did not go into any analysis of the delay model they mentioned. In fact, tumor and immune system interaction models with delay have been studied extensively, see Refs. 2, 5, 6, 9, 11, 12, 15, 16, 25, 28, 29, and 37 and the references cited therein.

From the above references, we know it is necessary to consider time delays in the tumor growth model with immune response. In this article, following Mayer *et al.*,[25] Byrne,[5] d'Onofrio and Gandolfi,[11] d'Onofrio *et al.*,[12] Burić *et al.*,[4] and Yu and Wei,[39] we consider the following tumor and immune system interaction model with three time delays (see Fig. 1)

$$\begin{cases} \dfrac{dT}{dt} = rT(t-\tau) - kT(t)E(t) \\ \dfrac{dE}{dt} = f(aT(t) + (1-a)T(t-\delta)) + g(bE(t) + (1-b)E(t-\Delta)) - dE(t), \end{cases} \tag{1}$$

where $T(t)$ describes the concentration of tumor cells at time t, $E(t)$ measures the concentration of relevant active immune effector cells at time t, r is the intrinsic growth rate of tumor cells, and $\tau \geq 0$ is the time delay in the proliferation of tumor cells.[5,11,25] The term kTE is the inactivation of tumor cells by the immune effector cells. The corresponding inactivation term TE in the equation for E can be neglected since it should be orders of magnitude smaller than the first two terms, which are given by the nonlinear functions $f(T)$ and $g(E)$. f describes the velocity of the stimulation by the presence of tumor cells and g is the corresponding function because of autocatalytic effects in the immune system, where

$$f(T) = \frac{pT^u}{m^v + T^v}, \quad g(E) = \frac{sE^n}{c^n + E^n}$$

with $p, s, u, m, n, v > 0, u \geq v, n \geq 1$ being constants. Following Refs. 4 and 39, we write the variable of f as a combination of $T(t)$ and $T(t-\delta)$, which shows the dependence of the rate of creating immunocompetent cells not only on the size of $T(t)$ but also on the value of $T(t-\delta)$, where $\delta \geq 0$ is the time delay describing the process of effector cells growth with respect to stimulus by the tumor cells growth.[12] Similarly, we allow the function g to depend on the combination of $E(t)$ and $E(t-\Delta)$, where $\Delta \geq 0$ is the time delay appearing in the differentiation of immune effector cells.[25] a, b are constants, and d is the death rate of the immune effector cells.

Note that some special cases of model (1) have been considered in the literature. (i) When $a = 0$ and $b = 0$, the model was first proposed by Mayer *et al.*[25] to describe the immune response to tumor cells who showed that the model has only regular solutions, such as fixed points, periodic orbits, and orbits asymptotic to these, but the model cannot describe frequently observed, irregular or chaotic, behavior. (ii) When $\tau = 0, d = 1, u = v = 4, n = 3, m = 1$, and $c = 1$, Burić *et al.*[4] illustrated that a time delay could introduce chaotic dynamics in the model (i.e., with $f(T) = \frac{pT^4}{1+T^4}$, $g(E) = \frac{sE^3}{1+E^3}$). (iii) When $\tau = 0$, $u = v = 2m_1, n = 2n_1$, $m = 1$, and $c = 1$, Yu and Wei[39] studied stability switch and Hopf bifurcations of the model (i.e., with $f(T) = \frac{pT^{2m_1}}{1+T^{2m_1}}$, $g(E) = \frac{sE^{2n_1}}{1+E^{2n_1}}$). In this paper, without loss of generality we consider the case of $m = c = 1$.

It is well known that systems with multiple delays are difficult to deal with. Various biological models with two delays have been studied by many researchers and very interesting dynamics have been observed, see Refs. 1–3, 7, and 39, for example. For biological models with three or more delays, Glass *et al.*[17] showed numerically that multiple negative feedback loops with different delays may generate complex periodic and aperiodic,

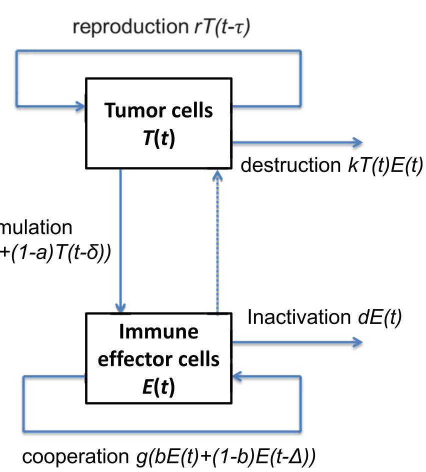

FIG. 1. The essential mechanisms of interaction between the tumor cells $T(t)$ and the immune effector cells $E(t)$.

chaotic rhythms, as delays vary. Glass and Malta[18] gave the possibility of chaos for normal physiological control in multi-looped negative feedback systems. We also refer to the online Wolfram Demonstrations Project,[19] which presents simulations of chaos in tumor growth models with time delayed immune response. However, there are very few studies on the mathematical analysis of biological models with more than two different delays. In this paper, we provide detailed mathematical analysis on the existence and stability of equilibria and existence of Hopf bifurcations in model (1) with three delays. We follow the technique of Wei and Ruan[38] (see also Ref. 1) to study the stability of the positive equilibria and the existence of Hopf bifurcations: we start by considering the corresponding ODE model when all delays are equal to zero and obtaining conditions for the stability of the positive equilibrium. Then, we introduce the three delays into the model one by one and obtain a stable interval for each of them. The stability of the positive equilibrium is thus obtained when the three delays are restricted within their corresponding intervals and a Hopf bifurcation can occur if any of these three delays passes through a critical value. Numerical simulations indicate that the model exhibits regular and irregular periodic oscillations (and chaotic behaviors), which demonstrate the phenomenon of long-term tumor relapse.

The rest of this paper is organized as follows. In Sec. II, we consider the existence and linear stability of equilibria, some results for the stability and Hopf bifurcation of the model with multiple delays are given. Section III devotes to the numerical analysis and simulations of the main results of this paper. A brief discussion and more numerical simulations are given in Sec. IV.

II. STABILITY AND BIFURCATION ANALYSIS

In this section, we discuss the existence of equilibria and determine their stabilities by analyzing the distribution of eigenvalues of the variational system of (1). Noting the forms of the functions f and g, system (1) has three types of equilibria:

(a) Trivial (virgin state) equilibrium (0, 0);

(b) Semi-trivial (tumor-free or immune state) equilibrium $(0, E_i)$ with $dE_i^n - sE_i^{n-1} + d = 0$;

(c) Positive (tumor-present or coexistence) equilibrium $(T_i, \frac{r}{k})$, where T_i satisfies $\bar{m}T_i^v - pT_i^u + \bar{m} = 0$ with $\bar{m} = \frac{dr}{k} - \frac{sr^n}{k^n + r^n}$.

Let $\bar{m} = \frac{r}{k}(d - \frac{skr^{n-1}}{k^n + r^n}), T_1 = \sqrt[v]{\frac{u}{v-u}}, B = \frac{pT_1^u}{1+T_1^v}$. The existence of all possible equilibria of system (1) can be summarized as follows.

(i) System (1) always has a trivial equilibrium (0,0).

(ii) (a) If $n = 1$, then system (1) has no semi-trivial equilibrium when $s < d$ and a unique semi-trivial equilibrium $(0, \frac{s}{d} - 1)$ when $s > d$. (b) If $n > 1$, then system (1) has no semi-trivial equilibrium when $\frac{d}{s} > \frac{1}{n}\sqrt[n]{(n-1)^{n-1}}$; a unique semi-trivial equilibrium when $\frac{d}{s} = \frac{1}{n}\sqrt[n]{(n-1)^{n-1}}$; and two semi-trivial equilibria when $\frac{d}{s} < \frac{1}{n}\sqrt[n]{(n-1)^{n-1}}$.

(iii) (a) System (1) has no positive equilibrium when $u = v$ and $\bar{m} < 0$ or $\bar{m} \geq p$; a unique positive equilibrium $(\sqrt[u]{\frac{\bar{m}}{p-\bar{m}}}, \frac{r}{k})$ when $u = v$ and $0 < \bar{m} < p$; and two positive equilibria $(T^{2*}, \frac{r}{k})$ and $(T^{3*}, \frac{r}{k})$ when $0 < u < v$ and $0 < \bar{m} < B$, where T^{2*} and T^{3*} are the positive roots of $\bar{m}T^v - pT^u + \bar{m} = 0$ with $T^{2*} < \sqrt[v]{\frac{u}{v-u}} < T^{3*}$. (b) When $\bar{m}$ increases to B, the two positive equilibria $(T^{2*}, \frac{r}{k})$ and $(T^{3*}, \frac{r}{k})$ merge into one $(\bar{m}, \frac{r}{k})$, and when $\bar{m}$ is greater than B, this positive equilibrium disappears.

Cases (i) and (ii) are easy to see. To see case (iii), assume $u < v$, then $f'(t) = \frac{T^{-1}(u+(u-v)T^v)}{(1+T^v)^2}$; that is, $f(T)$ is increasing when $0 < T < T_1$ and decreasing when $T > T_1$, where $T_1 = \sqrt[v]{\frac{u}{v-u}}$. On the other hand, we know $\lim_{T\to\infty} \frac{pT^u}{1+T^v} = 0$. In fact, the three different shapes of the stimulation function $f(T)$ can be illustrated as in Figs. 2(a)–2(c), that is, the equilibria are the intersect points of the horizontal line $\bar{m} = c$ (constant) and the curve of $f(T)$. If $u = v$, it is easy to obtain that $f'(T) > 0$ and $\lim_{T\to\infty} \frac{pT^u}{1+T^u} = p$.

Let (T_0, E_0) be any equilibrium of system (1). Assume $\bar{T} = T - T_0, \bar{E} = E - E_0$. For convenience, removing the overbars, then the linearized system of (1) at an equilibrium (T_0, E_0) is

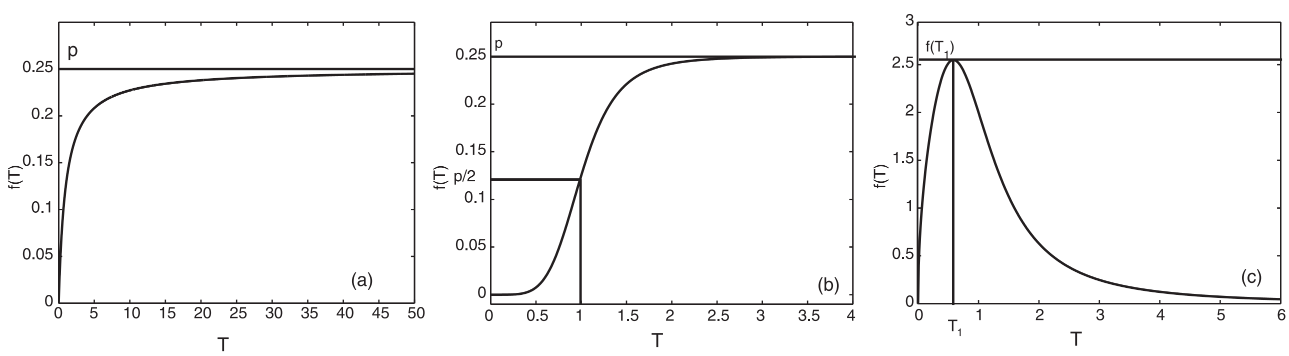

FIG. 2. Graphs of $f(T)$ for three different parameter sets: (a) $u = v = 1$; (b) $u = v = 5 > 1$; (c) $u = \frac{1}{2} < 1 < v = 2$.

$$\begin{cases} \dfrac{dT}{dt} = rT(t-\tau) - kE_0T(t) - kT_0E(t) \\ \dfrac{dE}{dt} = f'(T_0)(aT(t) + (1-a)T(t-\delta)) + g'(E_0)(bE(t) + (1-b)E(t-\Delta)) - dE(t). \end{cases} \tag{2}$$

Then, the stability of the equilibrium (T_0, E_0) is equivalent to the stability of the trivial equilibrium (0,0) of the linearized system (2).

In order to understand the dynamics of the model, we now discuss the stability of the equilibria one by one.

A. The trivial (virgin state) equilibrium

For any $u, v > 0$, $n > 0$, the first equation of the variational system of (2) at the trivial equilibrium (0,0) is

$$\frac{dT}{dt} = rT(t-\tau).$$

Noting that $r > 0$, it is easy to see that the trivial equilibrium of (1) is unstable for all $\tau, \delta, \Delta \geq 0$. That is, if there are no immune effector cells, the tumor cells will not die out once they invade, this is an obvious result.

B. The semi-trivial (tumor-free) equilibrium

For the stability of the semi-trivial or tumor-free equilibrium $(0, E_i)$, the characteristic equation of (2) is

$$(\lambda - re^{-\lambda\tau} + kE_i)(\lambda - g'(E_i)(1-b)e^{-\lambda\Delta} + (d - g'(E_i)b)) = 0, \tag{3}$$

then the characteristic roots of (3) satisfy

$$\lambda + A - re^{-\lambda\tau} = 0 \quad \text{or} \quad \lambda + C_1 - C_2e^{-\lambda\Delta} = 0, \tag{4}$$

where $A = kE_i > 0$, $C_1 = d(1 - \frac{nb}{1+E_i^n})$, $C_2 = \frac{nd}{1+E_i^n}(1-b) \geq 0$.

If $\tau = \Delta = 0$, then the roots of (3) are $\lambda_1 = r - A$ and $\lambda_2 = C_2 - C_1$. Thus, $\lambda_1 < 0$ and $\lambda_2 < 0$ as $r < A$ and $C_2 < C_1$. On the other hand, for $\tau \geq 0$, $\Delta \geq 0$, it is easy to see that (3) has no zero root and purely imaginary root when $r < A$ and $C_2 < C_1$.

Assume $r > A$ and $C_1 < C_2$, we can see that (3) has positive roots $\lambda_1 = r - A$ and $\lambda_2 = C_2 - C_1$ when $\tau = \Delta = 0$. If $-C_2 < C_1 < C_2$, then (3) has a pair of purely imaginary roots $\pm i\omega_{1,2}$, which satisfy

$$\tan \omega_1\tau = -\frac{\omega_1}{A}, \quad \tan \omega_2\Delta = -\frac{\omega_2}{C_1}. \tag{5}$$

Thus

$$\tau_0 = \frac{1}{\sqrt{r^2 - A^2}} \arccos\frac{A}{r}, \quad \Delta_0 = \frac{1}{\sqrt{C_2^2 - C_1^2}} \arccos\frac{C_1}{C_2}.$$

Recalling (4) and (5), we know that $\sin \omega_1\tau = \frac{-\omega}{r} < 0$, $\sin \omega_2\Delta = \frac{-\omega}{C_2} < 0$, hence $\tau_j = 2\pi - \tau_0 + 2j\pi$, $\Delta_j = 2\pi - \Delta_0 + 2j\pi$, $j = 0, 1, 2 \ldots$. If n is given, E_i can be obtained from (1), then the distribution of λ_i can be given as follows:

(i) If $r < A$ and $C_2 < C_1$, then all roots of (3) have negative real parts for all $\tau \geq 0$ and $\Delta \geq 0$.

(ii) If $C_1 < -C_2$, then (3) has roots with positive real part for $\tau \geq 0, \Delta \geq 0$.

(iii) If $r > A$ or $-C_2 < C_1 < C_2$, then (3) has roots with positive real part when $\tau = \Delta = 0$; moreover, (3) has purely imaginary roots $\pm i\omega_1$ and $\pm i\omega_2$ when $\tau = \tau_j$, $\Delta = \Delta_j$, respectively, where

$$\begin{aligned} \tau_j &= 2\pi - \frac{1}{\sqrt{r^2 - A^2}} \arccos\frac{A}{r} + 2j\pi, \\ \Delta_j &= 2\pi - \frac{1}{\sqrt{C_2^2 - C_1^2}} \arccos\frac{C_1}{C_2} + 2j\pi, \quad j = 0, 1, 2, \ldots \end{aligned} \tag{6}$$

(iv) If there exists n such that $n = E_i^n + 1$, then (3) has a zero root, the other roots have negative real parts when $r < A$ and positive parts when $r > A$.

(v) If $A = r$ and there exists n such that $n = (\frac{r}{k})^n + 1$, then (3) has two zero roots, that is the semi-trivial equilibrium degenerates to the trivial equilibrium.

On the other hand, it is easy to see that (3) has a pair of purely imaginary roots $\pm i\omega_\tau$ when $\tau = \tau_j$, $\Delta < \Delta_j$ or $\pm i\omega_\Delta$ when $\tau < \tau_j$, $\Delta = \Delta_j$. To verify whether a Hopf bifurcation occurs, we study the transversality condition as follows. Let $\lambda(\tau, \Delta) = \alpha(\tau, \Delta) + i\beta(\tau, \Delta)$ be a root of (3) satisfying $\alpha(\tau, \Delta_j) = 0$, $\alpha(\tau_j, \Delta) = 0$, $\beta(\tau_j, \Delta) = \omega_1$, $\beta(\tau, \Delta_j) = \omega_2$. If $r^2 - A^2 \neq C_2^2 - C_1^2$, by a direct computation, one has

$$\begin{aligned} \left.\frac{d\alpha(\tau,\Delta)}{d\tau}\right|_{\tau=\tau_j,\Delta\neq\Delta_j} &= \frac{\omega_1^2}{(1+\tau A)^2 + \omega_1^2\tau^2} > 0, \\ \left.\frac{d\alpha(\tau,\Delta)}{d\Delta}\right|_{\tau\neq\tau_j,\Delta=\Delta_j} &= \frac{\omega_2^2}{(1+C_1\Delta)^2 + \omega_2^2\Delta^2} > 0, \\ \left.\frac{d\alpha(\tau,\Delta)}{d\tau}\right|_{\tau=\tau_j,\Delta=\Delta_j} &= \frac{\omega_1^2}{(1+\tau A)^2 + \omega_1^2\tau^2} > 0, \\ \left.\frac{d\alpha(\tau,\Delta)}{d\Delta}\right|_{\tau=\tau_j,\Delta=\Delta_j} &= \frac{\omega_2^2}{(r+C_1\Delta)^2 + (\Delta\omega_2)^2} > 0. \end{aligned} \tag{7}$$

Noting $\pm i\omega_1$ and $\pm i\omega_2$ are purely imaginary roots of (3), then the result follows. From the above discussions, we have the following stability results.

Theorem 2.1.

(i) *If $r < A$ and $C_1 > C_2$, then the semi-trivial equilibrium $(0, E_i)$ of (1) is asymptotical stable for all $\tau \geq 0$, $\Delta \geq 0$;*

(ii) *If $C_1 < -C_2$, then the semi-trivial equilibrium $(0, E_i)$ of (1) is unstable for $\Delta \geq \Delta_0$, $\tau \geq \tau_0$;*

(iii) *If $r > A$, $-C_2 < C_1 < C_2$, then the semi-trivial equilibrium $(0, E_i)$ of (1) is unstable for $0 < \tau < \tau_0$, $0 < \Delta < \Delta_0$, $r^2 - A^2 \neq C_2^2 - C_1^2$; and*

(1) undergoes Hopf bifurcation at $(0, E_i)$ as $\tau = \tau_j$, $\Delta \neq \Delta_j$, or $\tau \neq \tau_j$, $\Delta = \Delta_j$, where $\tau_j = 2\pi - \tau_0 + 2j\pi$, $\Delta_j = 2\pi - \Delta_0 + 2j\pi$, $j = 0, 1, 2\ldots.$

(iv) *Let $r > A$, $-C_2 < C_1 < C_2$. If there is no integer k_1 such that $r^2 - A^2 \neq k_1(C_2^2 - C_1^2)$, then system (1) undergoes Hopf-Hopf bifurcation at $\tau = \tau_j$, $\Delta = \Delta_j$, $j = 0, 1, 2\ldots.$*

(v) *Let $r > A$, $-C_2 < C_1 < C_2$. If there exist integers m_2 and n_2 such that $m_2^2(r^2 - A^2) = n_2^2(C_2^2 - C_1^2)$, then system (1) undergoes $m_2 : n_2$ resonant bifurcation at $\tau = \tau_j$, $\Delta = \Delta_j(\tau_j)$, $j = 0, 1, 2\ldots.$*

The above results indicate that the stability of the semi-trivial equilibrium $(0, E_i)$ depends on the delays τ and Δ. In fact, when the delays take some critical values, the stability of the semi-trivial equilibrium will change and various types of bifurcations such as Hopf, Hopf-Hopf, and resonant bifurcations will occur at the semi-trivial equilibrium. These demonstrate that the immune system exhibits various types of oscillatory behavior.

C. The positive (tumor-present) equilibrium

In this section, following the technique of Wei and Ruan[38] (see also Ref. 1), we present detailed study on the stability of the positive (tumor-present) equilibrium (T^*, E^*) and the existence of Hopf bifurcations of system (1) with three time delays. We start by considering the ODE model when all three delays are zero and analyze the cases with one, two, and three delays, respectively. The first result is about the saddle-node bifurcation in system (1), which indicates the possible types of the equilibria and the number of positive equilibria.

Theorem 2.2. *If $0 < u < v$ and $m = f(T_1)$, then (1) undergoes a saddle-node bifurcation, where m and f(T) are defined as above and $T_1 = \sqrt[v]{\frac{u}{v-u}}$.*

We first consider the model when all delays τ, δ and Δ are zero; that is, the ODE model. The characteristic equation reduces to

$$\lambda\left(\lambda + d + g'\left(\frac{r}{k}\right)\right) + kT^* f'(T^*) = 0. \qquad (8)$$

Thus, $\lambda_1 + \lambda_2 = -(d + g'(\frac{r}{k})) < 0$ and $\lambda_1\lambda_2 = kT^* f'(T^*)$. We have the following results.

Theorem 2.3. *Let $\tau = \delta = \Delta = 0$.*

(i) *When $u = v$, the unique positive equilibrium (T^*, E^*) of system (1) is a stable node.*

(ii) *When $0 < u < v$, system (1) has two positive equilibria (T^{1*}, E^*) and (T^{2*}, E^*), where (T^{1*}, E^*) is a stable node and (T^{2*}, E^*) is a saddle.*

When τ, δ, Δ increase from zero, it is possible to have Hopf bifurcations. Hence, in order to study whether (1) undergoes Hopf bifurcations when the delays τ, δ, Δ increase from zero, for the sake of simplicity, we only consider the case $u = v$ in the rest of this paper. At first, we discuss the existence of equilibria when $u = v$:

(i) If $m \geq p$ or $m < 0$, then (1) has only one equilibrium, the trivial equilibrium (0,0);

(ii) If $m = 0$, then (1) has two equilibria, the trivial equilibrium (0,0) and a semi-trivial equilibrium $(0, \frac{r}{k})$;

(iii) If $0 < m < p$, then (1) has two equilibria, the trivial equilibrium (0,0) and a positive equilibrium $(\frac{m}{p-m}, \frac{r}{k})(u = v = 1)$ or $(\sqrt[u]{\frac{m}{p-m}}, \frac{r}{k})(u = v > 1)$.

Recall that the trivial equilibrium (0, 0) is always unstable and the semi-trivial equilibrium $(0, \frac{r}{k})$ is stable, while the stability of the positive equilibrium changes depending on the parameter values, which is what we will study next.

If $u = v$ and $0 < m < p$, $m = \frac{k}{r}(d - \frac{skr^{n-1}}{k^n + r^n})$, then (1) has only one positive equilibrium (T^*, E^*) with $E^* = \frac{r}{k}$. The characteristic equation at (T^*, E^*) is

$$\begin{vmatrix} \lambda - re^{-\lambda\tau} + kE^*, & kT^* \\ -f'(T^*)a - f'(T^*)(1-a)e^{-\delta\lambda}, & \lambda - (g'(E^*)b - d) - (1-b)g'(E^*)e^{-\Delta\lambda} \end{vmatrix} = 0, \qquad (9)$$

where $(T^*, E^*) = (\frac{m}{p-m}, \frac{r}{k})$ as $u = v = 1$ and $(T^*, E^*) = (\sqrt[u]{\frac{m}{p-m}}, \frac{r}{k})$ as $u = v > 1$ are defined as above. If $b = 1, \tau = \delta$, system (1) is studied in Bi and Ruan,[2] codimension one and codimension two bifurcations, including Hopf, Bautin, and Hopf-Hopf bifurcations, were obtained. In this section, we consider the stability and Hopf bifurcation in the case $\tau \neq \delta$. We establish the main results in two steps: (i) $b = 1$ and $g'(E^*)b = d$; and (ii) $g'(E^*)b \neq d$.

1. *b=1 and $g'(E^*)b=d$*

Notice that in this case, the term involving $e^{-\Delta\lambda}$ disappears, so that the problem becomes a model with two delays τ and δ. There are two subcases: $a = 1$ and $a \neq 1$.

(a) If $a = 1$, then the terms containing $e^{-\delta\lambda}$ also vanish and we have the special case with only a single delay τ. From (9), the characteristic equation at (T^*, E^*) is

$$\lambda^2 + r\lambda + A_1 - \lambda re^{-\lambda\tau} = 0, \qquad (10)$$

where $A_1 = f'(T^*)kT^* \geq 0$. Noting $r = kE^* \geq 0$. The distribution of the roots of Eq. (A1) can be analyzed using standard techniques (see Appendix), we know that there are critical values of the delay τ so that the characteristic Eq. (A1) has purely imaginary roots.

However, the positive equilibrium remains stable if the delay τ is less than the first critical value 2π.

(b) If $a \neq 1$, the second delay δ appears and the characteristic Eq. (9) becomes

$$\lambda^2 + \lambda(-re^{-\lambda\tau} + kE^*) + A_1(a + (1-a)e^{-\lambda\delta}) = 0. \quad (11)$$

From the Hopf bifurcation theorem and the results of Ruan,[30] we obtain the following results on the existence of a Hopf bifurcation when the second delay takes some critical values.

Theorem 2.4. *Assume $A_1 > 0$, if $|a - \frac{1}{2}| \ll 1$, $\tau \in (0, \tau')$, then (11) has purely imaginary roots $\pm i\omega_n$ with $\delta = \delta_j^n$, $j = 0, 1, 2\ldots$, where ω_n are the positive roots of*

$$g(\omega, h) = \omega^4 + \omega^2(2r^2 - 2A_1 a + 2\omega r \sin\omega\tau - 2r^2\cos\omega\tau) - 2\omega A_1 ar\sin\omega\tau + A_1^2 a^2(1 - h^2)$$

with $h = \frac{1-a}{a}$ and

$$\delta_j^n = \begin{cases} \dfrac{1}{\omega_n}\left(2\pi - \arccos\dfrac{\omega^2 - aA_1 + \omega r\sin\omega\tau}{A_1(1-a)} + 2j\pi\right), & r > \cos\omega\tau \\ \dfrac{1}{\omega_n}\left(\arccos\dfrac{\omega^2 - aA_1 + \omega r\sin\omega\tau}{A_1(1-a)} + 2j\pi\right), & r < \cos\omega\tau. \end{cases} \quad (12)$$

Moreover, if

$$2\omega\cos\delta\omega + \omega r\tau\cos\omega(\delta-\tau) + r(\sin\delta\omega - \sin\omega(\delta-\tau)) \neq 0, \quad (13)$$

then *Eq. (1) undergoes a Hopf bifurcation at (T^*, E^*).*

The above results indicate that system (1) is more likely to undergo Hopf bifurcations at the positive equilibrium when the two delays τ and δ increase. Thus, the population densities of the tumor cells and immune effector cells oscillate around their steady state values.

Remark 2.5. We use the parameter a to show that the change of $E(t)$ at time t is decided by the qualities of $E(t)$ not only at time t but also at time $t - \tau$. In the analysis, we choose $a = \frac{1}{2}$, which shows that the qualities of $E(t)$ at time t and $t - \tau$ have the same effect to the change of $E(t)$. For $a < \frac{1}{2}$, it is easy to obtain $g(0, h) < 0$, then (11) has purely imaginary roots obviously, which shows that the change of $E(t)$ depends more on time $t - \tau$ when $a < \frac{1}{2}$.

The result of the remark is relevant to the model of Mayer *et al.*,[25] which is as follows. Noting (A3), we have $g(\omega, 0)|_{\omega=0} = -A_1^2 < 0$, then we have the following result.

Corollary 2.6. If $a = 0$ and (13) holds, then (1) undergoes a Hopf bifurcation at (T^*, E^*).

2. $g'(E^*)b \neq d$

In this case, all three delays appear in the characteristic Eq. (9). We further consider three subcases: (a) $\tau \neq 0, \delta = \Delta = 0$ (one delay); (b) $\tau \neq 0, \delta \neq 0, \Delta = 0$ (two delays); (c) $\tau\delta\Delta \neq 0$ (three delays).

(a) If $\tau \neq 0, \delta = \Delta = 0$, the characteristic equation at (T^*, E^*) is

$$\lambda^2 + B_1\lambda + B_2 + (B_3\lambda + B_4)e^{-\lambda\tau} = 0, \quad (14)$$

where $B_1 = r + d - g'(E^*)$, $B_2 = r(d - g'(E^*)) + A_1$, $B_3 = -r < 0$, and $B_4 = -r(d - g'(E^*))$. First, we make the following assumptions:

(H_1) $B_4 + B_2 > 0$, $B_3 + B_1 > 0$.
(H_2) $B_3^2 - B_1^2 + 2B_2 < 0, B_2^2 - B_4^2 > 0$ or $(B_3^2 - B_1^2 + 2B_2)^2 < 4(B_2^2 - B_4^2)$.
(H_3) $B_2^2 - B_4^2 \leq 0$ or $B_3^2 - B_1^2 + 2B_2 > 0$ and $(B_3^2 - B_1^2 + 2B_2)^2 = 4(B_2^2 - B_4^2)$.
(H_4) $B_3^2 - B_1^2 + 2B_2 > 0, B_2^2 - B_4^2 > 0$ and $(B_3^2 - B_1^2 + 2B_2)^2 > 4(B_2^2 - B_4^2)$.

Define

$$\omega_\pm^2 = \frac{1}{2}(B_3^2 - B_1^2) + B_2 \pm \sqrt{\frac{(B_3^2 - B_1^2)^2}{4} + B_2(B_3^2 - B_1^2) + B_4^2}$$

and $\tau_j^\pm (j = 0, 1, 2)$ as functions of ω and other parameters by

$$\tau_j^\pm = \begin{cases} \tau_{1j}^\pm = \dfrac{1}{\omega_\pm}\left(2j\pi + \arccos\left\{\dfrac{(B_4 - B_1B_3)\omega_\pm^2 - B_4B_2}{B_3^2\omega_\pm^2 \pm B_4^2}\right\}\right), & \text{if } B_4B_1 + B_3(\omega_\pm^2 - B_2) > 0, \\ \tau_{2j}^\pm = \dfrac{1}{\omega_\pm}\left((2j+1)\pi - \arccos\left\{\dfrac{(B_4 - B_1B_3)\omega_\pm^2 - B_4B_2}{B_3^2\omega_\pm^2 \pm B_4^2}\right\}\right), & \text{if } B_4B_1 + B_3(\omega_\pm^2 - B_2) < 0. \end{cases} \quad (15)$$

Using the results of Bi and Ruan,[2] Cooke and Grossman,[8] and Ruan,[30] we can obtain the following results on the stability, Hopf bifurcation, and stability switch in the case of one delay.

Theorem 2.7. *Let (H_1) hold and $\tau_j^{\pm}(j=1,2,\ldots)$ be defined by (15).*

(i) *If (H_2) holds, then the positive equilibrium (T^*,E^*) of (1) is asymptotically stable for all $\tau \geq 0$.*

(ii) *If (H_3) holds, then (T^*,E^*) is stable for all $\tau \in (0,\tau_0^+)$ and unstable for $\tau > \tau_0^+$. Moreover, system (1) undergoes Hopf bifurcation at (T^*,E^*) as $\tau = \tau_j^+$, $j = 0,1,2\cdots$.*

(iii) *If (H_4) holds, then there is a positive integer l such that (T^*,E^*) is stable for*

$$\tau \in [0,\tau_0^+) \cup [\tau_0^-,\tau_1^+) \cup \cdots \cup [\tau_{l-1}^-,\tau_l^+)$$

and unstable for

$$\tau \in [\tau_0^+,\tau_0^-) \cup [\tau_1^+,\tau_1^-) \cup \cdots \cup [\tau_{l-1}^+,\tau_{l-1}^-).$$

(b) If $\tau \neq 0, \delta \neq 0, \Delta = 0$ $(a \neq 1)$, then the characteristic equation can be written as

$$\lambda^2 + B_1\lambda + B_2 - A_1(1-a) + e^{-\lambda\tau}(B_3\lambda + B_4) + A_1(1-a)e^{-\lambda\delta} = 0. \tag{16}$$

Now assume that the first delay τ lies in its stable interval, we discuss the stability and Hopf bifurcation using the second delay δ as the bifurcation parameter. Then, we have the following results.

Theorem 2.8. *Assume that (H_1) holds, if $B_2^2 - B_4^2 < 0$, $\tau < \tau_0, \tau_0 = min\{\tau_0^+,\tau'\}$, then (16) has purely imaginary roots $\pm i\omega_{1n}$ with $\delta = \delta_j^n, j = 0,1,2,\cdots$, where ω_{1n} are the positive roots of*

$$g_1(\omega) = (B_2 - \omega^2 - A_1(1-a) + B_4\cos\omega\tau + B_3\omega\sin\omega\tau)^2 + (B_1\omega_{1n} + B_3\omega\cos\omega\tau - B_4\sin\omega\tau)^2 - A_1^2(1-a)^2 \tag{17}$$

and

$$\delta_j^n = \begin{cases} \dfrac{1}{\omega_{1n}}\left(2\pi - \arccos\dfrac{\omega^2 - B_2 + A_1(1-a) - B_4\cos(\omega\tau) - B_3\omega\sin(\omega\tau)}{A_1(1-a)} + 2j\pi\right), & \sin\omega_{1n}\delta < 0, \\ \dfrac{1}{\omega_{2n}}\left(\arccos\dfrac{\omega^2 - B_2 + A_1(1-a) - B_4\cos(\omega\tau) - B_3\omega\sin(\omega\tau)}{A_1(1-a)} + 2j\pi\right), & \sin\omega_{1n}\delta > 0. \end{cases} \tag{18}$$

Moreover, if

$$B_3\omega_{1n}\tau\cos\omega_{1n}(\delta-\tau) + (B_4\tau - B_3)\sin\omega_{1n}(\delta-\tau) - 2\omega_{1n}\cos\delta\omega_{1n} - B_1\sin\delta\omega_{1n} \neq 0,$$

then Eq. (1) undergoes a Hopf bifurcation at (T^*,E^*) as $\delta = \delta_n$.

(c) If $\tau\delta\Delta \neq 0$, all three delays are present and the characteristic equation is

$$\lambda^2 + B_1'\lambda + B_2' - A_1(1-a) + e^{-\lambda\tau}(B_3\lambda + B_4' + rB_5e^{-\Delta\lambda}) - (\lambda + kE^*)B_5e^{-\Delta\lambda} + A_1(1-a)e^{-\lambda\delta} = 0, \tag{19}$$

where $B_1' = B_1 + B_5$, $B_2' = B_2 + rB_5$, $B_4' = B_4 - rB_5$, and $B_5 = g'(E^*)(1-b)$. In the case of three delays, fixing the first two delays in their stable intervals, we finally discuss the stability and Hopf bifurcation by using the third delay Δ as the bifurcation parameter.

Lemma A3 (see Appendix) gives the existence of Δ^*, in fact, we can compute Δ^* in a similar way as above for other critical delay values and have the following main result.

Theorem 2.9. *Assume (H_1) and $B_2^2 < B_4^2$ hold, if $\tau < \tau_0, \delta < \delta_0$, then (16) has purely imaginary roots $\pm i\omega_{2n}$ with $\Delta = \Delta_j^n, j = 0,1,2,\ldots$, where ω_{2n} are the positive roots of*

$$\begin{aligned} g_3(\omega_{2n}) = {} & (B_2' - \omega_{2n}^2 - A_1(1-a)(1-\cos\omega_{2n}\delta) - B_5r\cos\omega_{2n}\Delta + B_5\omega_{2n}\sin\omega_{2n}\Delta)^2 \\ & + (B_1'\omega_{2n} + rB_5\sin\omega_{2n}\Delta - \omega B_5\cos\omega_{2n}\Delta - A_1(1-a)\sin\omega_{2n}\delta)^2 \\ & - B_4'^2 - B_3^2\omega_{2n}^2 - B_5^2r^2 - 2B_4'B_5r\cos\omega_{2n}\Delta + 2B_3'B_5\omega_{2n}r\sin\omega_{2n}\Delta, \end{aligned} \tag{20}$$

where

$$\Delta_j^n = \begin{cases} \dfrac{1}{\omega_{2n}}\left(2\pi - \arccos\dfrac{G(\omega_{2n})}{B_5(\omega_{2n} + r\sin\omega_{2n}\tau)^2 + B_5(r\cos\omega_{2n}\tau - kE^*)^2} + 2j\pi\right), & \sin\omega_{2n}\Delta < 0 \\ \dfrac{1}{\omega_{2n}}\left(\arccos\dfrac{G(\omega_{2n})}{B_5(\omega_{2n} + r\sin\omega_{2n}\tau)^2 + B_5(r\cos\omega_{2n}\tau - kE^*)^2} + 2j\pi\right), & \sin\omega_{2n}\Delta > 0 \end{cases} \tag{21}$$

with

$$\begin{aligned}G(\omega_{2n}) = {} & (A_1(1-a)+\omega_{2n}^2 - B_2')E^*k + \omega_{2n}^2 B_1' + A_1(1-a)r\cos\omega_{2n}(\delta+\tau)\\ & + \cos\omega_{2n}\tau((B_3-r)\omega_{2n}^2 - A_1(1-a)(ek+r) - ekB_4' + rB_2')\\ & + \omega_{2n}\sin\omega_{2n}\tau(rB_1' - B_3ek - B_4') + B_3\omega_{2n}r\sin 2\omega_{2n}\tau\\ & - A_1(1-a)\omega_{2n}\sin\delta\omega_{2n} + rB_4'\cos 2\omega_{2n}\tau. \end{aligned} \tag{22}$$

Moreover, if

$$\begin{aligned} & -\omega(2E^*k + B_3r\tau)\cos\delta\omega + (-1+a)A_1\delta\omega\cos(\Delta-\delta)\omega - B_5\omega r\tau\cos\omega\tau\\ & +(B_3\omega - B_4'\omega\tau + B_3E^*k\omega\tau)\cos\omega(\Delta-\tau) + 2\omega r\cos\omega(\Delta+\tau)\\ & +(B_3r - B_1'E^*k - 2\omega^2 - B_4'r\tau)\sin\Delta\omega + A_1\delta E^*k(1-a)\sin(\Delta-\delta)\omega\\ & +(B_4'E^*k\tau - B_3E^*k + B_3\omega^2\tau)\sin\omega(\Delta-\tau) + B_1'r\sin\omega(\Delta+\tau)\\ & -B_5r(1+E^*k\tau)\sin\omega\tau - A_1(1-a)\delta r\sin\omega(\Delta-\delta+\tau) \neq 0, \end{aligned} \tag{23}$$

then Eq. (1) undergoes a Hopf bifurcation at (T^*, E^*).

The above results demonstrate that to have stability of the positive equilibrium (T^*, E^*), all three delays have to be in their corresponding stable intervals, while a Hopf bifurcation occurs at (T^*, E^*) if any one of the three delays passes through its critical values.

III. NUMERICAL SIMULATIONS

In this section, we present some numerical simulations to illustrate the results obtained in Sec. II. Before presenting the numerical results, we would like to make a couple of remarks. First, the initial value for model (1) with three delays takes the form: $x(\theta) = \phi(\theta), \theta \in [-\tau^*, 0]$, where $\tau^* = \max\{\tau, \delta, \Delta\}$ and $\phi(\theta)$ is a continuous function defined on $[-\tau^*, 0]$. For the sake of simplicity, in all simulations, we choose $\phi(\theta) = \phi(0)$ as a constant defined at $\theta = 0$. Second, the asymptotic behavior of the solutions to the delay model (1) depends on the initial values, as the further numerical simulations in Sec. IV demonstrate.

A. The model of Mayer *et al.*

To compare our results with that of Mayer *et al.*[25] and to see how delays affect the dynamics of the model, we first choose two parameter sets that were used in Mayer *et al.*[25]

(I) $a = 0, b = 0, n = 1, u = v = 1, r = 1.8, k = 3, p = 2, s = 1.5, d = 1$.
(II) $a = 0, b = 0, n = u = v = k = d = 1, r = 1.2, p = 0.28, s = 2$.

From the above analysis, we know that the semi-trivial equilibrium is unstable and the positive equilibrium is stable; and certainly, the trivial equilibrium is unstable. For $\tau = 0.3$, $\delta = 0.3$, $\Delta = 1$, the simulations are given in Fig. 3, which indicate the instability of the trivial and semi-trivial equilibria and the stability of the positive equilibrium for both parameter sets.

B. The model with one or two delays

In the following, we give simulations on the results in Theorems 2.7 and 2.8. We consider the third set of parameters as follows:

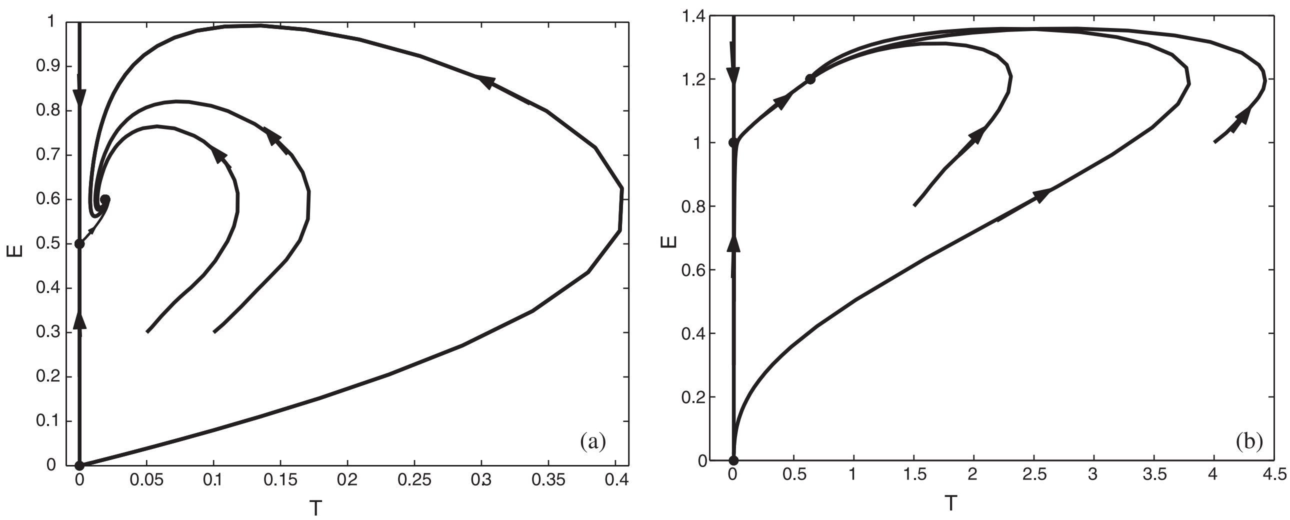

FIG. 3. The phase portraits of system (1) in the form of Mayer *et al.*:[25] (a) with parameter set (I); (b) with parameter set (II).

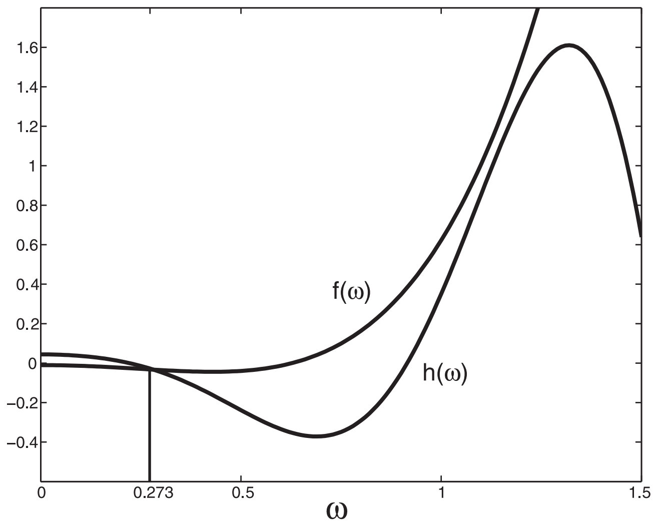

FIG. 4. The roots of (24) which are the intersection points of $f(\omega)$ and $h(\omega)$.

(III) $a=0.1,\ n=3,\ u=2,\ v=2,\ r=0.6,\ k=1.3,\ p=0.3,\ s=0.2,\ d=0.5.$

For this case, (1) has two equilibria (0,0) and (1.563, 0.461538). Since (0,0) is unstable, we only need to consider the properties of the positive equilibrium (1.563, 0.461538). If $\delta=\Delta=0$, from (15), by Theorem 2.7, we know (14) has only a pair of purely imaginary roots $\pm i\omega$ with $\omega=0.416274$ as $\tau_0=3.8641$, and the positive equilibrium (1.563, 0.461538) is locally stable as $\tau<\tau_0$. According to Theorem 2.8, the imaginary roots $\pm i\omega_{1n}$ of (16) are the roots of

$$\begin{aligned}&-0.010245-0.36749\omega^2+\omega^4+(0.0558983+0.36\omega^2)\\&\quad\times\cos^2(3.8641\omega)+(-0.142236\omega+1.2\omega^3)\\&\quad\times\sin(3.8641\omega)+(0.0558983+0.36\omega^2)\sin^2(3.8641\omega)\\&\quad+\cos(3.8641\omega)(-0.100101+0.189143\omega^2)=0,\end{aligned}\tag{24}$$

which are the points of intersection of functions (see Fig. 4)

$$f(\omega)=\omega^4-0.36749\omega^2-0.010245$$

and

$$\begin{aligned}h(\omega)=&-(0.0558983+0.36\omega^2)\cos^2(3.8641\omega)\\&+(0.142236\omega-1.2\omega^3)\sin(3.8641\omega)\\&-(0.0558983+0.36\omega^2)\sin^2(3.8641\omega)\\&+\cos(3.8641\omega)(0.100101-0.189143\omega^2).\end{aligned}$$

Then, we can see that the only pair of purely imaginary roots are $\pm 0.273i$ from Fig. 4.

When $\tau=\tau_0=3.8641$, recalling (18), by a direct computation, we have $\delta_0=15.1378$. We also know that the positive equilibrium (T^*,E^*) is stable when $\tau<\tau_0$, $\delta<\delta_0$. With the above chosen parameters, by Theorem 2.8, we know that model (1) exhibits a Hopf bifurcation when $\delta_0=15.1378$ and has bifurcated periodic solutions when $\delta=15.898>\delta_0=15.1378$, as shown in Fig. 5.

The dynamical behaviors of the positive equilibrium (T^*,E^*) (stable or unstable) can be seen in Fig. 6. The critical boundary respects the possible bifurcation values, which are given by (18). On the other hand, one can see rich dynamical behaviors of the positive equilibrium as τ (respectively δ) increases, a finite number of stability switches may occur.

C. The effect of parameter *a*

For the above parameters, if a increases from 0.1 to 0.5, the dynamical behavior of the model does not change compared with Figs. 5 and 6. If a keeps increasing from 0.5 to 0.9, then the functions $f(\omega)$ and $h(\omega)$ have no points of intersection, see Fig. 7. That is when $\tau<\tau_0$, as a increases to 0.9, there are no characteristic roots passing through the imaginary axis. Hence, we have the following result.

Proposition 3.1. Let $r=0.6,\ k=1.3,\ p=0.3,\ s=0.2,\ d=0.5,\ n=3,\ u=2,\ v=2$. *If* $a=0.9$, *then the positive equilibrium (0.26087, 4.14083) of (1) is stable when* $\tau<\tau_0$ *and* $\delta>0$.

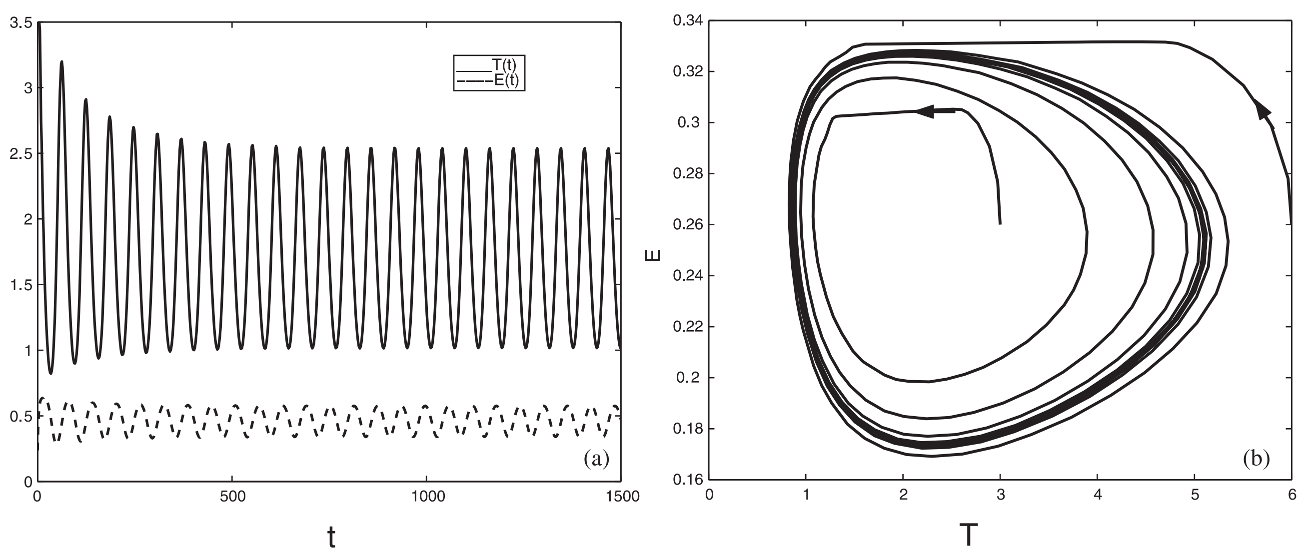

FIG. 5. Numerical simulations of system (1) with two delays (τ and δ) and parameter set (III): (a) Periodic solutions of system (1) in terms of t via a Hopf bifurcation with $(T(0),E(0))=(3.7191,0.2376)$; (b) Solution trajectories spiral toward the stable limit cycle of system (1) in the (T,E)-plane with $(T_1(0),E_1(0))=(3.7191,0.2376)$ and $(T_2(0),E_2(0))=(6.1,0.26)$. Here, $\tau=3.8641=\tau_0$, $\delta=15.898>\delta_0=15.1378$, $\Delta=0$.

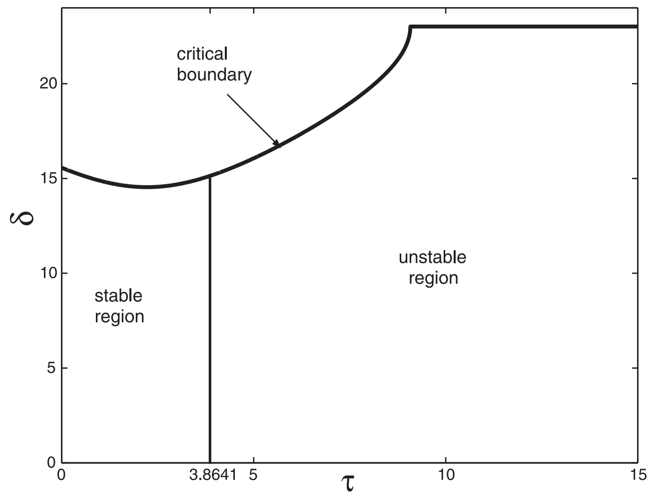

FIG. 6. Stability diagram of system (1) with two delays in the (τ, δ)-delay parameter space.

In fact, the stable region of the positive equilibrium becomes bigger and bigger when a increases from 0.1 to 0.5 then to 0.9. The Hopf bifurcation may occur when τ and δ are on the critical boundary; that is, the dynamical behavior of the positive equilibrium changes when the parameter a increases from 0 to 1. Thus, it is necessary to introduce a new parameter a into the model of Mayer *et al.*[25]

D. The model with three delays

At the end of this section, we will simulate the results in Theorem 2.9. For convenience, we still use the above parameter set. First, we need to compute the roots of (20). Still using the above method, for simplicity, we only consider the case $a = 0.1, b = 0.1$. Similarly, from Fig. 8, we know that (20) has two pairs of imaginary roots $\pm i\omega_{10}$ and $\pm i\omega_{20}$ with $\omega_{10} = 0.2651$ and $\omega_{20} = 0.2809$. But for $\omega_{10} = 0.2651$, there is no Δ defined in (21) can be found. Hence, the characteristic equation of (2) has only one pair of purely imaginary roots $\pm i\omega_{20}$ with $\Delta_0 = 2.0592$.

Let $\tau_0 = 3.8641$, $\delta_0 = 15.1378$, and $\Delta_0 = 2.0592$. From the result in last section, we know that the solutions of (1) are stable when $\tau = 3.8 < \tau_0$, $\delta = 13.5 < \delta_0$, and $\Delta = 2 < \Delta_0$, the simulations are presented in Fig. 9. If $\tau = \tau_0$, $\delta = \delta_0$, $\Delta = \Delta_0$, then system (1) undergoes a Hopf bifurcation, the bifurcating periodic solutions can be seen in Fig. 10.

Note that we have the following property.

Proposition 3.2. Let $r = 0.6$, $k = 1.3$, $p = 0.3$, $s = 0.2$, $d = 0.5$, $n = 3$, $u = 2$, *and* $v = 2$. *If* $a = 0.1$, $b = 0.1$, *then the positive equilibrium* $(1.563, 0.461538)$ *of (1) is stable when* $\tau < \tau_0$, $\delta < \delta_0$ *and* $\Delta < \Delta^*(\tau, \delta)$, *where*

$$\Delta^*(\tau, \delta) = \frac{F(\tau, \delta)}{\omega_{10}} \arccos \frac{1}{(0.6(1 - \cos(0.2809\tau))^2 + (0.2809 + 0.6\sin(0.2809\tau))^2}$$

with

$$\begin{aligned} F(\tau, \delta) = {} & 10.4869(-0.002547 - 0.101124\cos(0.2809\tau)^2 - 0.133564\sin(0.2809\delta) \\ & + \cos(0.2809\tau)(0.074559 + 0.133564\sin(0.2809\delta)) - 0.101124\sin(0.2809\tau)^2 \\ & + \cos(0.2809\delta)(-0.0625301 - 0.133564\sin(0.2809\tau)) - 0.109526\sin(0.2809\tau)). \end{aligned}$$

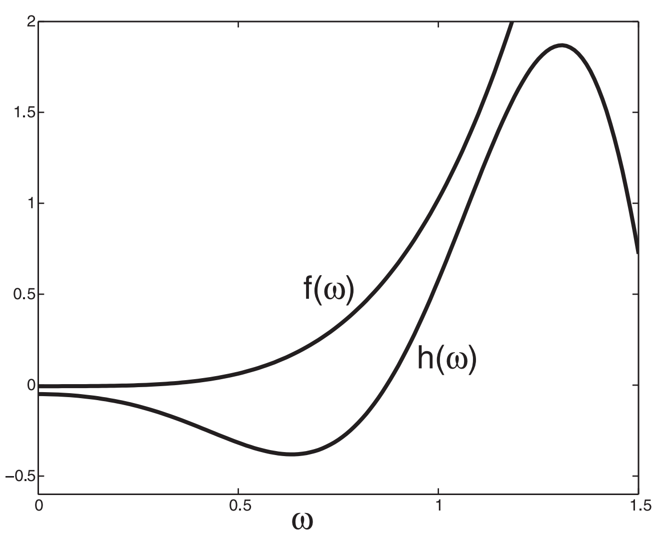

FIG. 7. The curves $f(\omega)$ and $h(\omega)$ do not intersect when $a = 0.9$.

With the above given parameter values, the stable region of (1) is given in Fig. 11 in the (τ, δ, Δ) parameter space. Therefore, to have stability of the positive equilibrium, all three delays τ, δ, and Δ have to be lying in their corresponding stable intervals. If any one of these three delays changes so that (τ, δ, Δ) lies outside the stable region, the positive equilibrium will become unstable, a Hopf bifurcation will occur, and the densities of the tumor cells and immune cells will fluctuate around their equilibrium values. If the delays increase further, more complex dynamical behavior (irregular long oscillations and chaos) can occur as the numerical simulations in Sec. IV indicate.

IV. DISCUSSIONS AND MORE SIMULATIONS

In this paper, we considered a tumor and immune system interaction model consisted of two differential equations with three time delays in which the delays describe the times necessary for molecule production, proliferation, differentiation of

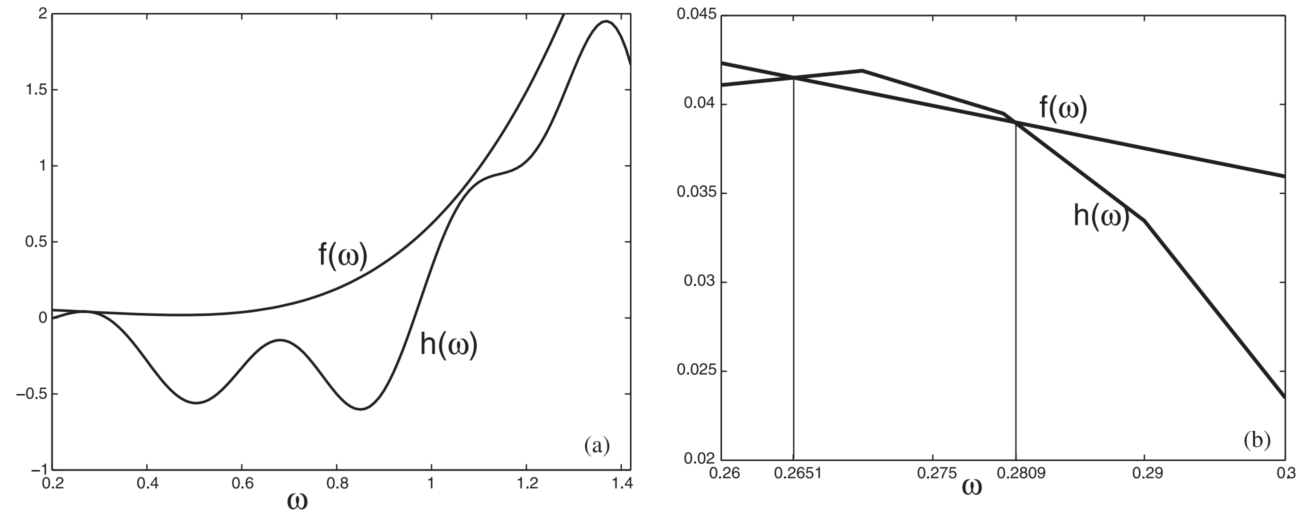

FIG. 8. (a) The locations of $f(\omega)$ and $h(\omega)$ when $a = 0.1, b = 0.1$. (a) For $0.2 < \omega < 1.5$ and (b) $0.26 < \omega < 0.3$.

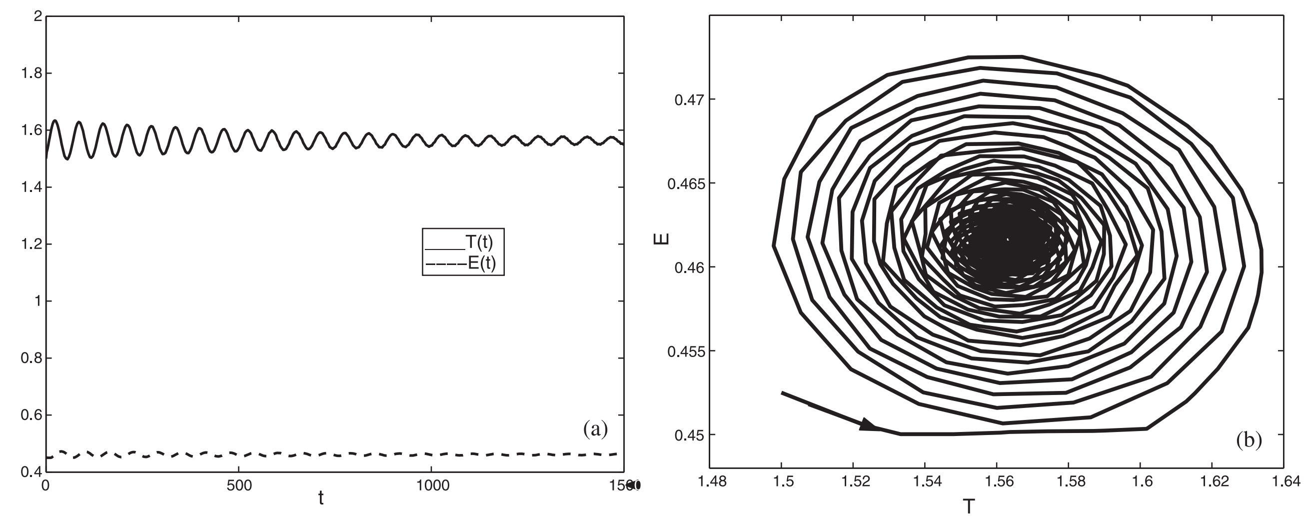

FIG. 9. Numerical simulations of system (1) with three delays and parameter set (III). (a) Solutions $T(t)$ and $E(t)$ of system (1) converge to the equilibrium values and (b) solution trajectories of system (1) spiral toward the positive equilibrium in the (T, E)-plane. Here, $\tau = 3.8 < \tau_0, \delta = 13.5 < \delta_0, \Delta = 2 < \Delta_0$, and $(T(0), E(0)) = (1.5, 0.4523)$.

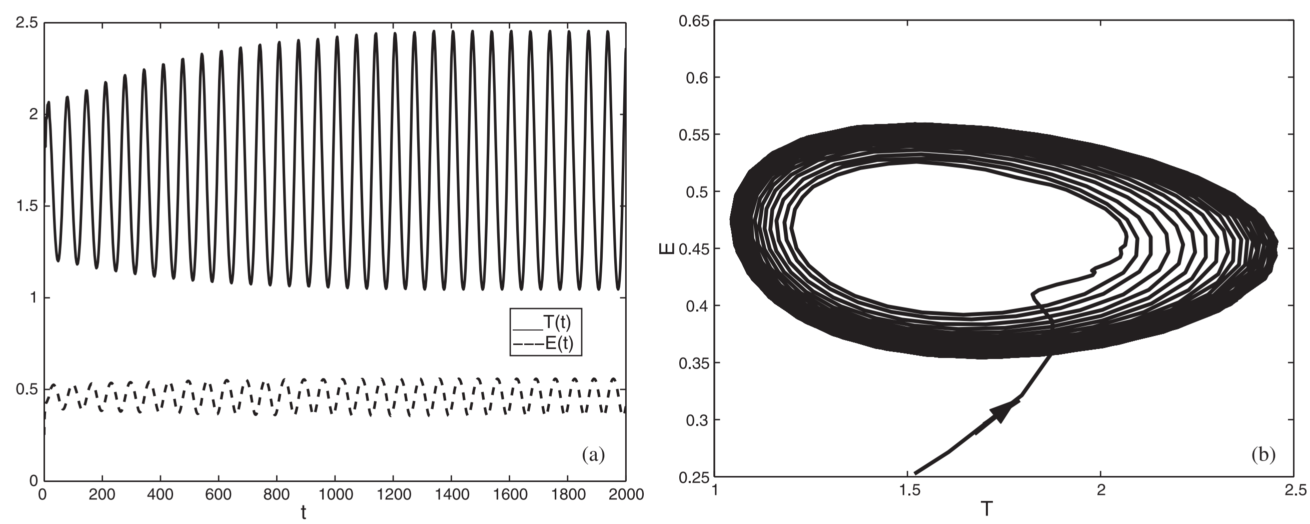

FIG. 10. Numerical simulations of system (1) with three delays and parameter set (III). (a) Periodic solutions $T(t)$ and $E(t)$ of system (1) in terms of t and (b) solution trajectories of system (1) spiral toward a periodic orbit in the (T, E)-plane. Here, $\tau = \tau_0 = 3.8641, \delta = \delta_0 = 15.1378, \Delta = \Delta_0 = 2.0592$, and $(T(0), E(0)) = (1.6, 0.2699)$.

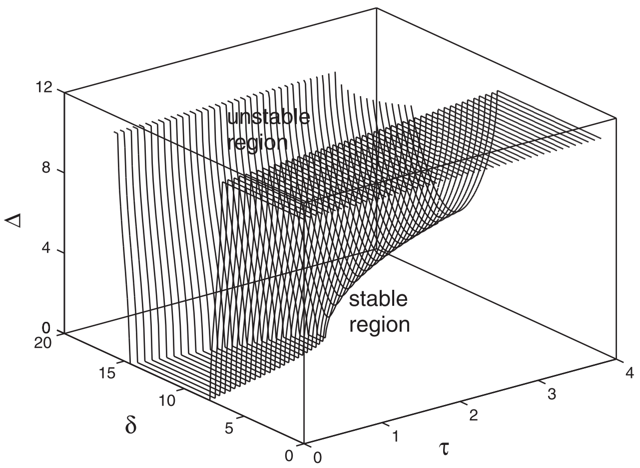

FIG. 11. The stability diagram of the positive equilibrium for system (1) with three delays in the (τ, δ, Δ) parameter space.

cells, transport, etc. Following the techniques of Bélair and Campbell,[3] Campbell *et al.*,[7] Ruan and Wei,[31] and Yu and Wei,[39] we studied stability and Hopf bifurcation in the tumor-immune system model. In Sec. II, we provided detailed analysis on the existence and stability of equilibria and existence of Hopf bifurcations in the model with one, two, or three delays. In Sec. III, we presented some numerical simulations of the model in the case when the model (1) only has one positive equilibrium. Roughly speaking, the positive equilibrium is stable when all three delays are less than their corresponding critical values. The positive equilibrium becomes unstable and a Hopf bifurcation occurs if any one of the three delays passes through its critical values. Our mathematical analysis and numerical simulations demonstrate that the nonlinear dynamics of the tumor-immune system interaction model with three delays are very complex and difficult to study even for the simple case when there is one positive equilibrium.

In fact, model (1) exhibits more complicated dynamical behavior than that proved and observed in Secs. II and III when two or three delays vary. Now, we give more simulations to show the existence of irregular long periodic oscillations. For this purpose, we introduce our fourth set of parameter values as follows:

(IV) $a = 0.5, b = 0.9, n = 3, u = 1, v = 3, r = 2, k = 3, p = 2, s = 1, d = 1.2.$

When $\tau = \delta = \Delta = 0$, numerical simulations of system (1) show that the positive equilibrium is asymptotically stable (see Fig. 12).

Now we have the following simulations with different values of the delays τ, δ, and Δ.

These simulations demonstrate that the tumor and immune system interaction model with three time delays exhibits very rich and complex dynamical behaviors. The positive equilibrium is stable when $\tau < \tau_0$, $\delta < \delta_0$, and $\Delta < \Delta_0$; but when the delays increase, the dynamical behavior becomes more and more complex. When we fix the $\tau = 0.5$ and increase δ and Δ gradually, the dynamical behavior changes from regular periodic (Fig. 13) to irregular long periodic (Fig. 14), and finally chaotic (Fig. 15). Therefore, the time delays play a crucial role in determining the nonlinear dynamics of the tumor and immune system interaction model (1). Notice that Mayer *et al.*[25] provided some empirical data on the number of phenotypically identified natural killer cells ($CD16^+$, $CD56^+$) versus total tumor size during the course of a metastatic disease (*Fibrosarcoma*), which exhibit chaotic behavior: they fluctuate irregularly and unpredictably. Mayer *et al.*[25] pointed out that their model is unable to produce any kind of chaotic behavior since it is only two-dimensional. By modifying their model, we are able to demonstrate numerically that the two-dimensional model with three delays can produce chaotic behavior which, in some sense, supports the empirical data provided by Mayer *et al.*[25]

The existence of regular and irregular periodic oscillations in the tumor and immune interaction model demonstrates the phenomenon of long-term tumor relapse and has been observed in some related tumor and immune system models.[12,20,22] The regular periodic oscillations describe the equilibrium process (expansion of transformed cells is held in check by immunity) of cancer immunoediting in the dual

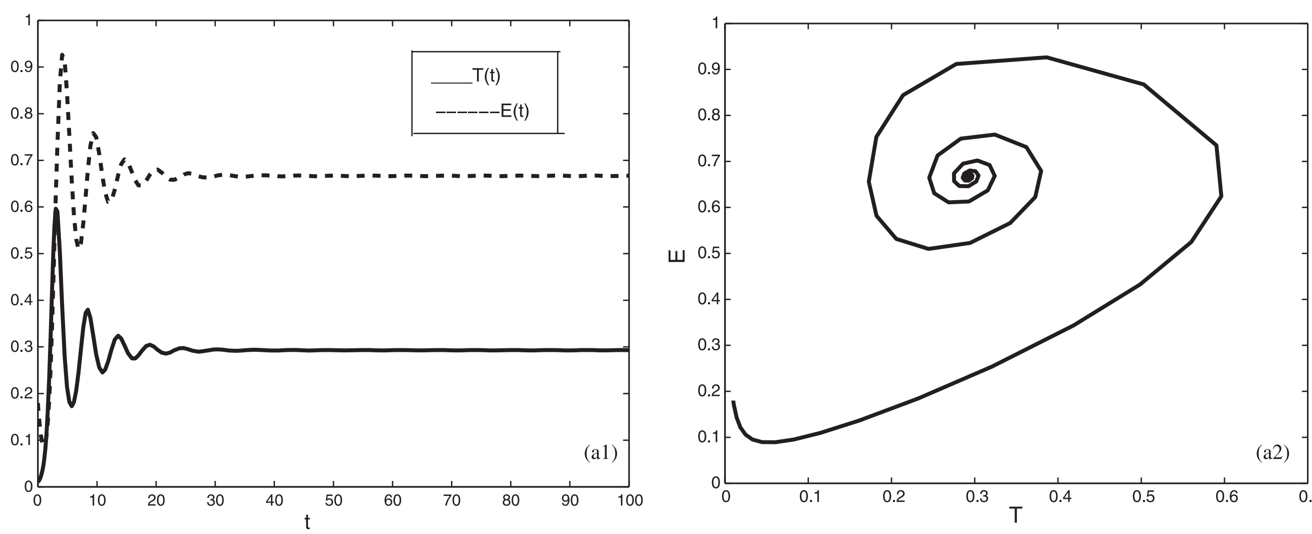

FIG. 12. (a1) The stable solutions of system (1) when $\tau = \delta = \Delta = 0$ (a2) The solution trajectory of system (1) converges to the positive equilibrium in the (T, E) plane. Here, $(T(0), E(0)) = (0.01, 0.18)$.

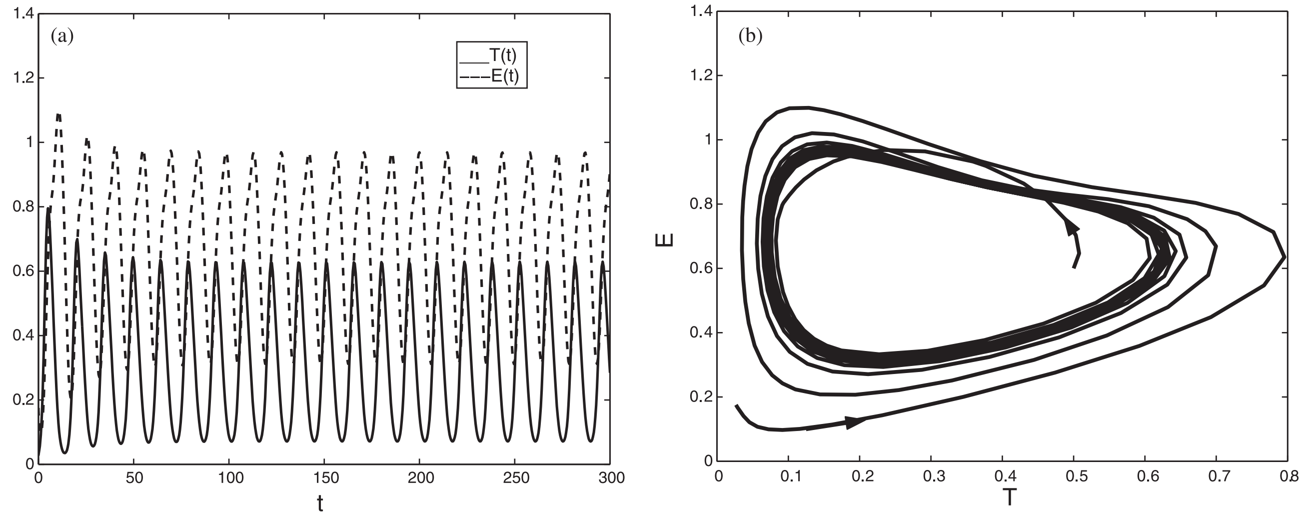

FIG. 13. The regular periodic oscillations in system (1) with parameter set (IV) and $\tau = 0.5, \delta = 5, \Delta = 8$. Here, (a) $(T(0), E(0)) = (0.01, 0.18)$; (b) $(T_1(0), E_1(0)) = (0.01, 0.18)$ and $(T_2(0), E_2(0)) = (0.5, 0.45)$.

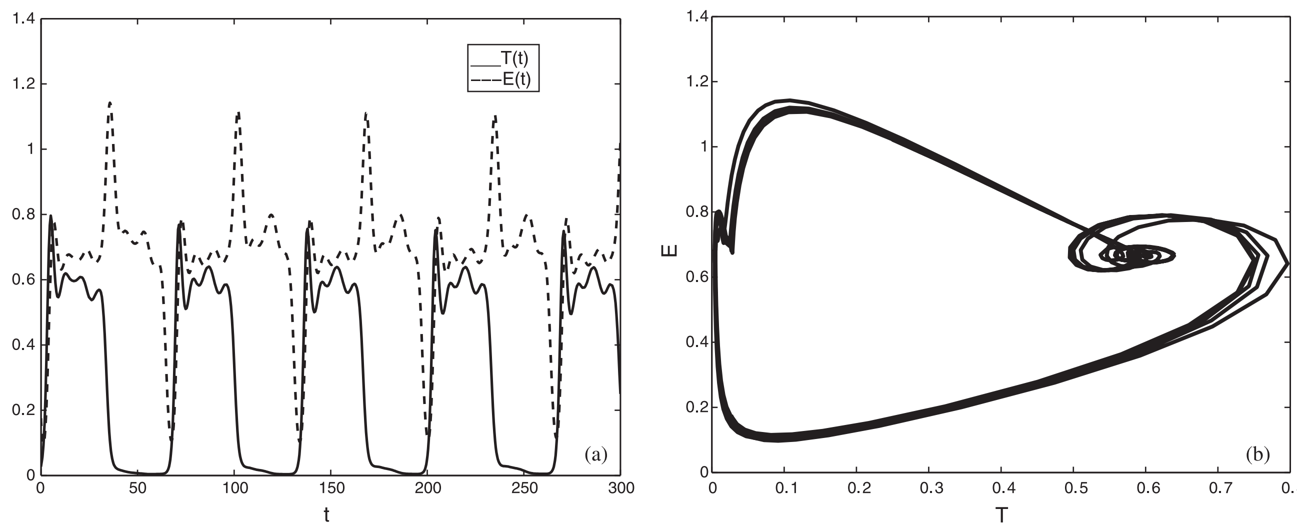

FIG. 14. The irregular long periodic oscillations in system (1) with parameter set (IV) and $\tau = 0.5, \delta = 30, \Delta = 18$. Here, $(T(0), E(0)) = (0.5, 0.61)$.

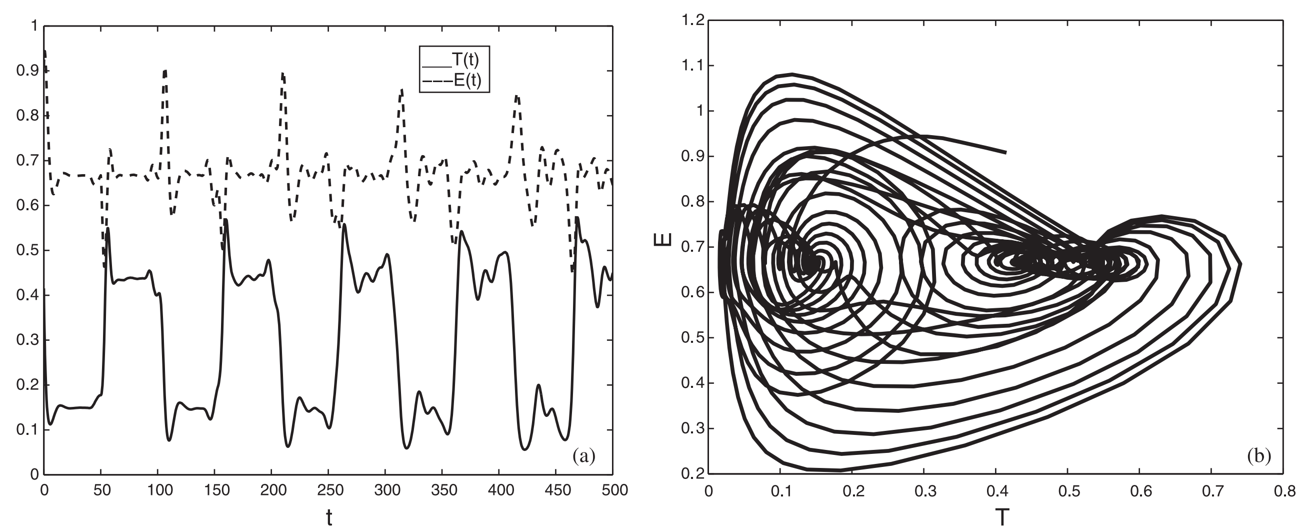

FIG. 15. The chaotic solutions in system (1) with parameter set (IV) and $\tau = 0.5, \delta = 50, \Delta = 38$. Here, $(T(0), E(0)) = (0.4, 0.91)$.

host-protective and tumor-promoting actions of immunity and support the experimental observations of Koebel *et al.*[21] that the immune system of a naive mouse can restrain cancer growth for extended time periods. The existence of irregular long periodic oscillations suggests that with temporal delay in the immune response cancer may progress to a more aggressive state. It would be interesting to obtain clinical or experimental data on tumor and immune cells and see if our modeling results and simulations apply to the data.

It should be pointed out that we did not prove the existence of chaos in system (1) theoretically. Instead, following similar observations in Refs. 17, 18, and 32, we observed numerically that solutions of system (1) exhibit chaotic behavior when delays take different values. We believe that the technique and results in Desch *et al.*[10] may be used to prove the existence of chaos in system (1) with three delays and leave this for future consideration. Also, our mathematical analysis and numerical simulations were carried out based on the assumptions that system (1) has only one positive equilibrium (when $u = v$). The case that system (1) has multiple positive equilibria (when $u < v$) deserves further investigation.

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APPENDIX: ANALYSIS ABOUT THE POSITIVE EQUILIBRIUM

Here, we provide some analysis and give the proofs of some results about the positive equilibrium. If $u = v$ and $0 < m < p$, $m = \frac{k}{r}(d - \frac{skr^{n-1}}{k^n + r^n})$, then (1) has only one positive equilibrium (T^*, E^*) with $E^* = \frac{r}{k}$. The characteristic equation at (T^*, E^*) is given by Eq. (9). The main results were established in two steps: (i) $b = 1$ and $g'(E^*)b = d$; and (ii) $g'(E^*)b \neq d$.

(i) $b = 1$ and $g'(E^*)b = d$. In this case, the term involving $e^{-\Delta\lambda}$ disappears, so it becomes a model with two delays τ and δ. There are two subcases: $a = 1$ and $a \neq 1$.

(a) If $a = 1$, the terms containing $e^{-\delta\lambda}$ also vanish and it further reduces to a model with a single delay τ. From (9), the characteristic equation at (T^*, E^*) is

$$\lambda^2 + r\lambda + A_1 - \lambda r e^{-\lambda\tau} = 0, \tag{A1}$$

where $A_1 = f'(T^*)kT^* \geq 0$. Noting $r = kE^* \geq 0$, in order to consider the distribution of the roots of Eq. (A1), we give a result as follows.

Lemma A1. Let $\tau = \tau_j^0$. Then, (A1) has a pair of purely imaginary roots $\pm i\omega_0$ with $\omega_0^2 = A_1$, where $\tau_j^0 = 2j\pi$, $j = 0, 1, 2\cdots$.

Proof. Let $i\omega$ be a root of (A1). Then,

$$-\omega^2 + r\omega i + A_1 - r\omega i(\cos\omega\tau - i\sin\omega\tau) = 0.$$

Separating the real and imaginary parts of above equality, we have

$$-\omega^2 + A_1 = r\omega\sin\omega\tau, \quad r\omega = r\omega\cos\omega\tau. \tag{A2}$$

Hence, $\omega^2 = A_1$. From the second equation of (A2), it is easy to obtain that $\tau_j^0 = 2j\pi$, $j = 0, 1, 2\cdots$. □

Let $\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$ be the root of (A1) satisfying $\alpha(\tau_{\pm j}^1) = 0$, $\omega(\tau_{\pm j}^1) = \omega_\pm$, then we have the following results.

Lemma A2.

(i) *Since $A_1 > 0$, we have $\alpha'(\tau_j^0) = 0$ and $\alpha''(\tau_j^0) < 0$. Hence, all roots of (A1) have negative real parts except the purely imaginary roots $\pm i\omega$, and all purely imaginary roots $\pm i\omega$ are obtained as $\tau_j^0 = 2j\pi$, $j = 0, 1, 2\cdots$.*

(ii) *There exists a $\tau' < 2\pi$ such that (T^*, E^*) is stable as $\tau \in (0, \tau')$.*

Proof. Differentiating both sides of (A1), it follows that

$$\frac{d\lambda}{d\tau} = \frac{-\lambda^2 r e^{-\lambda\tau}}{2\lambda + kE^* - re^{-\lambda\tau} + \lambda r\tau e^{-\lambda\tau}},$$

then

$$\left(\frac{d\mathrm{Re}\{\lambda\}}{d\tau}\right)^{-1} = \frac{2\lambda + kE^* - re^{-\lambda\tau}}{-\lambda^2 re^{-\lambda\tau}} - \frac{\tau}{\lambda}.$$

Hence,

$$\left(\frac{d\mathrm{Re}\{\lambda\}}{d\tau}\right)^{-1}\Bigg|_{\lambda=i\omega} = \frac{1}{\omega^2 r^2}\left(k^2E^{*2} - 2A_1 + 2\omega_{\pm j}^2 - r^2\right) = 0\cdot$$

Differentiating both sides of (A1) once again, we have

$$\frac{\mathrm{Re}\{d^2\lambda\}}{d\tau^2}\Bigg|_{\lambda=i\omega} = \frac{-\omega^2 r}{2 + r\tau} < 0.$$

Hence, $\alpha(0) = \alpha(2\pi) = \alpha'(0) = 0$ and $\alpha''(0) < 0$. Noting that (A1) has no zero roots, then there must exist a $\tau' < 2\pi$ such that $\alpha(\tau) < 0$ for $\tau \in (0, \tau')$. The proof is complete. □

(b) If $a \neq 1$, the second delay δ appears and the characteristic Eq. (9) becomes Eq. (11).

Proof of Theorem 2.4. Substituting $i\omega(\omega > 0)$ into (11), we have

$$\begin{aligned}&-\omega^2 + i\omega(kE^* - r\cos\omega\tau + ir\sin\omega\tau)\\&\quad + aA_1(1 + h\cos\omega\delta - ih\sin\omega\delta) = 0,\end{aligned}$$

where $h = \frac{1-a}{a}$. Separating the real and imaginary parts, it follows that

$$\begin{cases}-\omega^2 - \omega r\sin\omega\tau + aA_1 + aA_1 h\cos\omega\delta = 0\\ \omega kE^* - \omega r\cos\omega\tau - aA_1 h\sin\omega\delta = 0,\end{cases} \tag{A3}$$

that is

$$(\omega^2 - A_1 a + \omega r \sin \omega\tau)^2 + (\omega r - \omega r \cos \omega\tau)^2 = A_1^2 a^2 h^2.$$

Let

$$g(\omega, h) = \omega^4 + \omega^2(2r^2 - 2A_1 a + 2\omega r \sin \omega\tau - 2r^2 \cos \omega\tau) \\ -2\omega A_1 ar \sin \omega\tau + A_1^2 a^2(1 - h^2).$$

Then, $g(\omega, h)|_{(0,1)} = 0$, $\frac{\partial g(\omega,h)}{\partial \omega}|_{(0,1)} = 0$ and

$$\frac{\partial^2 g(\omega, h)}{\partial \omega^2}\bigg|_{(0,1)} = -2A_1 a(1 + r\tau) < 0.$$

Hence $g(\omega, 1)$ has at least one positive solution, at most finite solutions denoted by ω_n. Since $g(\omega, h)$ is continuous with respect to h, then $g(\omega, h)$ also has positive solutions as $|a - \frac{1}{2}| \ll 0$. On the other hand, differentiating both sides of (11) with respect to δ, noting (13), we have

$$\frac{\mathrm{Re}\{d\lambda\}}{d\delta}\bigg|_{\lambda=i\omega_n} = \frac{2\omega_n \cos \delta\omega_n + \omega_n r\tau \cos \omega_n(\delta - \tau) + ek \sin \delta\omega_n - r \sin \omega_n(\delta - \tau)}{(1 - a)A_1\omega_n} \neq 0.$$

Then the results are proved.

(ii) $g'(E^*)b \neq d$. In this case, all three delays appear in the characteristic Eq. (9). We further consider three subcases: (a) $\tau \neq 0, \delta = \Delta = 0$ (one delay); (b) $\tau \neq 0, \delta \neq 0, \Delta = 0$ (two delays); (c) $\tau\delta\Delta \neq 0$ (three delays).

(a) If $\tau \neq 0, \delta = \Delta = 0$, the characteristic equation at (T^*, E^*) reduces to Eq. (14).

Proof of Theorem 2.7. We only need to prove the transversality condition as follows:

$$\left(\frac{d\mathrm{Re}\lambda}{d\tau}\right)^{-1}\bigg|_{\tau=\tau_j^{\pm}} = \frac{2\lambda + B_1 + B_3 e^{-\lambda\tau}}{\lambda e^{-\lambda\tau}(B_3\lambda + B_4)}\bigg|_{\tau=\tau_j^{\pm}} = \begin{cases} \frac{1}{2}\left((B_3^2 - B_1^2 + 2B_2)^2 - 4(B_2^2 - B_4^2)\right)^{1/2} > 0, & \tau = \tau_j^+ \\ -\frac{1}{2}\left((B_4^2 - B_1^2 + 2B_2)^2 - 4(B_2^2 - B_4^2)\right)^{1/2} < 0, & \tau = \tau_j^-. \end{cases}$$

This completes the proof.

(b) If $\tau \neq 0, \delta \neq 0, \Delta = 0$ $(a \neq 1)$, then the characteristic equation becomes Eq. (16).

Proof of Theorem 2.8. Let $i\omega_{1n}(\omega_{1n} > 0)$ be a root of (16), then

$$\begin{aligned} &-\omega_{1n}^2 + B_1\omega_{1n} i + B_2 - A_1(1 - a) + (B_3\omega_{1n} i + B_4)(\cos \omega_{1n}\tau - i \sin \omega_{1n}\tau) \\ &\quad + A_1(1 - a)(\cos \omega_{1n}\delta - i \sin \omega_{1n}\delta) = 0. \end{aligned} \tag{A4}$$

Separating the real and imaginary parts, we have

$$\begin{cases} -\omega_{1n}^2 + B_2 - A_1(1 - a) + B_4 \cos \omega_{1n}\tau + B_3\omega_{1n} \sin \omega_{1n}\tau + A_1(1 - a)\cos \omega_{1n}\delta = 0 \\ B_1\omega_{1n} + B_3\omega_{1n} \cos \omega_{1n}\tau - B_4 \sin \omega_{1n}\tau - A_1(1 - a)\sin \omega_{1n}\delta = 0. \end{cases} \tag{A5}$$

Then,

$$(-\omega_{1n}^2 + B_2 - A_1(1 - a)(1 - \cos \omega_{1n}\delta))^2 + (B_1\omega_{1n} - A_1(1 - a)\sin \omega_{1n}\delta)^2 = B_3^2\omega_{1n}^2 + B_4^2.$$

Let

$$g_2(\omega_{1n}) = (-\omega_{1n}^2 + B_2 - A_1(1 - a) + A_1(1 - a)\cos \omega_{1n}\delta)^2 + (B_1\omega_{1n} - A_1(1 - a)\sin \omega_{1n}\delta)^2 - B_3^2\omega_{1n}^2 - B_4^2.$$

It is easy to see that $g_2(0) = B_2^2 - B_4^2 < 0$ and $\lim_{\omega\to\infty} g_2(\omega) > 0$. Thus, $g_2(\omega) = 0$ has at least one positive solution, denoting all positive solutions by ω_{1n}. On the other hand, from (A5), we also know that the purely roots $\pm i\omega_{1n}$ are the roots of

$$(B_2 - \omega^2 - A_1(1 - a) + B_4 \cos \omega\tau + B_3\omega \sin \omega\tau)^2 + (B_1\omega_{1n} + B_3\omega \cos \omega\tau - B_4 \sin \omega\tau)^2 = A_1^2(1 - a)^2.$$

That is, ω_{1n} are the positive roots of $g_1(\omega)$. Differentiating both sides of (16) with respect to δ, we have

$$\left.\frac{\mathrm{Re}\{d\lambda\}}{d\delta}\right|_{\lambda=i\omega_{1n}} = \frac{B_3\omega_{1n}\tau\cos\omega_{1n}(\delta_j^n-\tau)+(B_4\tau-B_3)\sin\omega_{1n}(\delta_j^n-\tau)-B_1\sin\delta_j^n\omega_{1n}-2\omega_{1n}\cos\delta_j^n\omega_{1n}}{(-1+a)A_1\omega_{1n}}.$$

Then, Eq. (1) undergoes a Hopf bifurcation at (T^*, E^*).

(c) If $\tau\delta\Delta \neq 0$, all three delays are present and the characteristic equation is given by Eq. (19). The technique is to fix the first two delays in their stable intervals and discuss the stability and Hopf bifurcation by using the third delay Δ as the bifurcation parameter. In order to study the stability of (T^*, E^*) for $\Delta \neq 0$, we need a result which can be proved similarly as Theorem 7 of Adimy *et al.*[1]

Lemma A3. If all roots of Eq. (16) *have negative real parts for* $\tau \in (0, \tau_0^+)$ *and* $\delta \in (0, \delta_0)$, *where* $\delta_0 = \min_{n\in N}\{\delta_0^n\}$, *then there exists* $\Delta^* = \Delta(\tau,\delta)$ *such that all roots of* (19) *have negative real parts when* $\Delta \in (0, \Delta^*(\tau,\delta))$, *and the positive equilibrium* (T^*, E^*) *of* (1) *is locally asymptotically stable.*

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