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*Research Article*

# Bifurcations of Tumor-Immune Competition Systems with Delay

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A tumor-immune competition model with delay is considered, which consists of two-dimensional nonlinear differential equation. The conditions for the linear stability of the equilibria are obtained by analyzing the distribution of eigenvalues. General formulas for the direction, period, and stability of the bifurcated periodic solutions are given for codimension one and codimension two bifurcations, including Hopf bifurcation, steady-state bifurcation, and B-T bifurcation. Numerical examples and simulations are given to illustrate the bifurcations analysis and obtained results.

## 1. Introduction

In this century, cancer remains one of the most dangerous killers of humankind; every year millions of people suffer from cancer and die from this disease throughout the world; see Boyle et al. [1]. Recently, there has been much interest in mathematical modeling of immune response with the intruder (see, e.g., Liu et al. [2, 3], Yafia [4], d'Onofrio et al. [5, 6], and the references cited therein). In fact, mathematical models are feasible to propose simple models which are capable of displaying some of the essential immunological phenomena. The delayed models of tumor and immune response interactions have been studied extensively; we refer to Bi and Ruan [7], Yafia [8], Mayer et al. [9], Yafia [10], and the references cited therein, which have shown that various bifurcations can occur in such models. It is interesting to consider the nonlinear dynamics of the delayed tumor-immune model.

In 1994, Kuznetsov et al. [11] took into account the penetration of tumor cells (TCs) by effector cells (ECs) and proposed a model describing the response of ECs to the growth of TCs. They assumed that interactions between ECs and TCs *in vitro* can be described by the kinetic scheme shown in Figure 1, where $E, T, C, T^*$, and $E^*$ are the local concentrations of ECs, TCs, EC-TC complexes, inactivated ECs, and lethally hit TCs, respectively. Then the Kuznetsov and Taylor model is as follows:

$$\begin{aligned} \frac{\mathrm{d}E}{\mathrm{d}t} &= c + F(C,T) - d_1 E - k_1 ET + (k_{-1} + k_3) C, \\ \frac{\mathrm{d}T}{\mathrm{d}t} &= aT(1 - bT_{\mathrm{tot}}) - k_1 ET + (k_{-1} + k_2) C, \\ \frac{\mathrm{d}C}{\mathrm{d}t} &= k_1 ET - (k_{-1} + k_2 + k_3) C, \\ \frac{\mathrm{d}T^*}{\mathrm{d}t} &= k_3 C - d_2 T^*, \\ \frac{\mathrm{d}E^*}{\mathrm{d}t} &= k_2 C - d_3 E^*, \end{aligned} \tag{1}$$

where $c$ is the normal rate of the flow of adult ECs into the tumor site, $F(C,T)$ describes the accumulation of effector cells in the tumor cells localization due to the presence of the tumor, $d_1, d_2$, and $d_3$ are the coefficients of the processes of destruction and migration for E, EC, and TC, respectively, $a$ is the coefficient of the maximal growth of tumor, and $b$ is the environment capacity. Kuznetsov et al. [11] claimed that experimental observations motivate the approximation $dC/dt \approx 0$; therefore, it is reasonable to assume that $C \approx KET$

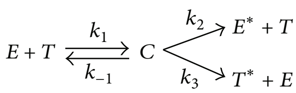


FIGURE 1: Kinetic scheme describing interactions between ECs and TCs.

with $K = k_1/(k_1 + k_2 + k_3)$. Kuznetsov et al. [11] also suggested that the function $F$ is in the Michaelis-Menten form $F(C,T) = F(E,T) = (fC/(g+T))(f, g > 0)$. In 2003, Gałach [12] suggested that the function $F$ should be in a Lotka-Volterra form $F(C,T) = F(E,T) = n_1 ET$; then the model (1) can be reduced to

$$\frac{dx}{dt} = c + n_1 xy - m_1 xy - d_1 x,$$
$$\frac{dy}{dt} = ay(1 - by) - m_2 xy, \tag{2}$$

where $x$ denotes the dimensionless density of ECs, $y$ stands for the dimensionless density of the population of TCs, $m_1 = kk_2$, $m_2 = kk_3$, and all coefficients are positive. Set $x = x_0 x'$, $y = y_0 y'$, $t = (1/m_2 x_0)t'$, $x_0 > 0$, $y_0 > 0$. Replace $x$ with $x'$ and $y$ with $y'$. Then (2) can be written as

$$\frac{dx}{dt} = \sigma + nxy - mxy - \delta x,$$
$$\frac{dy}{dt} = \alpha y(1 - \beta y) - xy, \tag{3}$$

where $\sigma = s/m_2 x_0^2$, $n = n_1 y_0/m_2 x_0$, $m = m_1 y_0/m_2 x_0$, $\delta = d_1/m_2 x_0$, $\alpha = a/m_2 x_0$, and $\beta = by_0$.

Mayer et al. [9] and Asachenkov et al. [13] pointed out that the delays should be taken into account to describe the times necessary for molecule production, proliferation, differentiation of cells, transport, and so forth. In fact, the immune system needs time to develop a suitable response after the invasion of tumor cells; the binding of EC and TC also needs time. Therefore, we introduce time delays into the model of immune response. Integrating models [9–11], we will consider the model as follows:

$$\frac{dx}{dt} = \sigma + \zeta x(t - \tau_1) y(t - \tau_1) - \delta x,$$
$$\frac{dy}{dt} = \alpha y(1 - \beta_2 y) - x(t - \tau_2) y(t - \tau_2), \tag{4}$$

where $\zeta = n - m$; if the stimulation coefficient of the immune system exceeds the neutralization coefficient of ECs in the process of the formation of EC-TC complexes, then $\zeta > 0$. Yafia [4] studied the linear stability of the equilibria and the existence of Hopf bifurcation for model (4) with $\tau_1 = \tau_2 = 0$. Yafia [10] and Gałach [12] obtained similar results as those of Yafia [4] for (4) with $\tau_2 = 0$. Recently, Bi and Xiao [14] give conditions for the properties of Hopf bifurcated periodic solution and existence of the global Hopf bifurcation for (4) with $\tau_2 = 0$.

In this paper, we will consider the dynamical behaviors of model (4) with $\tau_1 = \tau_2 = \tau$. The rest of this paper is organized as follows. In Section 2, the linear analysis of the model is carried out and local stability of the equilibria and the conditions of Hopf bifurcation are given. Section 3 is devoted to the analysis of Hopf, steady-state bifurcations, and B-T bifurcation. Numerical results and simulations are carried out to illustrate the main results. A brief discussion and more numerical simulations are given in Section 4.

## 2. Local Analysis

In this section, we will study the local stability of the equilibria and the Hopf bifurcations of system

$$\frac{dx}{dt} = \sigma + \zeta x(t - \tau) y(t - \tau) - \delta x,$$
$$\frac{dy}{dt} = \alpha y(1 - \beta_2 y) - x(t - \tau) y(t - \tau). \tag{5}$$

It is easy to obtain that system (5) have three equilibria $P_0(\sigma/\delta, 0)$, $P_1(x_1, y_1)$, and $P_2(x_2, y_2)$, where

$$x_1 = \frac{-\alpha(\beta\delta - \zeta) - \sqrt{\Delta}}{2\zeta},$$
$$y_1 = \frac{\alpha(\beta\delta + \zeta) + \sqrt{\Delta}}{2\alpha\beta\zeta},$$
$$x_2 = \frac{-\alpha(\beta\delta - \zeta) + \sqrt{\Delta}}{2\zeta},$$
$$y_2 = \frac{\alpha(\beta\delta + \zeta) - \sqrt{\Delta}}{2\alpha\beta\zeta}, \tag{6}$$

$\Delta = \alpha^2(\beta\delta - \zeta)^2 + 4\alpha\beta\zeta\sigma > 0$. It is easy to see that $x_1 < 0$. Because the number of tumor cells or effect cells is positive, we only consider the dynamical behaviors of the equilibria $P_0$ (tumor-free point) and $P_2$ in the rest of the paper.

Let $z_1(t) = x(t) - x^*$, $z_2(t) = y(t) - y^*$. System (5) can be written as

$$z_1'(t) = \alpha_1 z_1(t) + \alpha_2 z_1(t - \tau) + \alpha_3 z_2(t - \tau) + \zeta z_1(t - \tau) z_2(t - \tau),$$
$$z_2'(t) = \beta_1 z_1(t - \tau) + \beta_2 z_2(t) + \beta_3 z_2(t - \tau) - \alpha\beta z_2^2(t) - z_1(t - \tau) z_2(t - \tau), \tag{7}$$

where $\alpha_1 = -\delta < 0$, $\alpha_2 = \zeta y^* \geq 0$, $\alpha_3 = \zeta x^* > 0$, $\beta_1 = -y^* \leq 0$, $\beta_2 = \alpha - 2\alpha\beta y^*$, $\beta_3 = -x^* < 0$ and $(x^*, y^*)$ is the coordinate of the equilibrium.

It is easy to see that the linear system of system (7) is

$$z_1'(t) = \alpha_1 z_1(t) + \alpha_2 z_1(t - \tau) + \alpha_3 z_2(t - \tau),$$
$$z_2'(t) = \beta_1 z_1(t - \tau) + \beta_2 z_2(t) + \beta_3 z_2(t - \tau), \tag{8}$$

where $\alpha_1, \alpha_2, \alpha_3, \beta_1, \beta_2$, and $\beta_3$ are the same as those in (7).

*2.1. Tumor-Free Point.* The characteristic equation of system (8) at the tumor-free equilibrium $P_0$ is

$$\Delta(\lambda) = (\lambda + \delta)\left(\lambda - \alpha + \frac{\sigma}{\delta}e^{-\lambda\tau}\right) = 0. \tag{9}$$

Then we have the following results.

**Lemma 1.** *(I) If $\alpha = \sigma/\delta$, then*

(1) *Equation* (9) *has a simple zero root, and all other roots have negative real parts as $0 \le \tau < \delta/\sigma$;*

(2) *Equation* (9) *has a double zero root, and all other roots have negative real parts as $\tau = \delta/\sigma$;*

(3) *Equation* (9) *has at least one root with positive real parts as $\tau > \delta/\sigma$.*

*(II) If $\alpha < \sigma/\delta$, then*

(1) *all roots of* (9) *have negative real parts as $0 \le \tau < \tau_0$;*

(2) *Equation* (9) *has a pair of conjugate purely imaginary roots $\pm i\omega_+$, and all other roots have negative real parts as $\tau = \tau_0$;*

(3) *Equation* (9) *has at least one root with positive real parts as $\tau > \tau_0$.*

*(III) Equation* (9) *has a negative root $-\delta$, and all other roots have positive real parts as $\alpha > \sigma/\delta$.*

*Proof.* $\lambda = 0$ is a root of (9) if and only if $\alpha = \sigma/\delta$. If $\tau = 0$, (9) has two roots $\lambda_1 = -\delta$ and $\lambda_2 = \alpha - \sigma/\delta$. Then there are three cases: (1) $\lambda_2 = 0$ as $\alpha = \sigma/\delta$; (2) $\lambda_2 < 0$ as $\alpha < \sigma/\delta$; (3) $\lambda_2 > 0$ as $\alpha > \sigma/\delta$.

We will consider the case $\tau > 0$ as follows. If $\alpha = \sigma/\delta$, $\tau = \delta/\sigma$, then

$$\Delta'(\lambda) = 2\lambda - \alpha + \frac{\sigma}{\delta}e^{-\lambda\tau} - \tau\lambda\frac{\sigma}{\delta}e^{-\lambda\tau} + \delta - \sigma\tau e^{-\lambda\tau}; \tag{10}$$

hence, $\Delta'(\lambda)|_{\lambda=0} = 0$, and $\Delta''(\lambda)|_{\lambda=0} = \delta^2/\sigma > 0$. Thus $\lambda = 0$ is the double zero root of (9).

If (9) has purely imaginary roots, then the roots must be the solution of

$$\Delta_0(\lambda) = \lambda - \alpha + \frac{\sigma}{\delta}e^{-\lambda\tau} = 0. \tag{11}$$

Assume that $\lambda = i\omega(\omega > 0)$ is the root of (11); that is,

$$\begin{aligned} -\alpha + \frac{\sigma}{\delta}\cos\omega\tau &= 0, \\ \omega - \frac{\sigma}{\delta}\sin\omega\tau &= 0; \end{aligned} \tag{12}$$

that is $\omega^2 = \sigma^2/\delta^2 - \alpha^2$. Hence (11) has a positive root $\omega_+ = \sqrt{\sigma^2/\delta^2 - \alpha^2}$ if and only if $\alpha < \sigma/\delta$, and the corresponding critical values are

$$\tau_k = \frac{1}{\omega_+}\left\{\text{arc cos}\frac{\alpha\delta}{\sigma} + 2k\pi\right\}, \quad k = 0, 1, 2, \ldots. \tag{13}$$

Using Rouché theorem, we know that conclusions (II)(1), (II)(2), and (III) hold.

If $0 < \tau < \delta/\sigma$, $\alpha = \sigma/\delta$, we can obtain $\Delta'_0(\lambda)|_{\lambda=0} = 1 - (\sigma/\delta)\tau > 0$, $\Delta_0(0) = 0$. Noting the continuous of the function $\Delta_0(\lambda)$, we know that there is at least a $\lambda < 0$ such that $\Delta_0(\lambda) < 0$. On the other hand, it is easy to see that $\lim_{\lambda\to-\infty}\Delta_0(\lambda) = +\infty$; then there exists $\lambda < 0$ such that $\Delta_0(\lambda) = 0$.

Differentiating both sides of (11) with respect to $\tau$, we have

$$\frac{d\lambda}{d\tau} = \frac{\lambda(\sigma/\delta)e^{-\lambda\tau}}{1 - (\sigma/\delta)\tau e^{-\lambda\tau}}. \tag{14}$$

If $\tau \ne \delta/\sigma$, then

$$\left.\frac{d\lambda}{d\tau}\right|_{\lambda=0} = \left.\frac{\lambda(\sigma/\delta)e^{-\lambda\tau}}{1 - (\sigma/\delta)\tau e^{-\lambda\tau}}\right|_{\lambda=0} = 0. \tag{15}$$

Using Rouché theorem, we know that the conclusions of (I)(1) and (I)(2) are true.

If $\tau = \delta/\sigma$, then

$$\lim_{\lambda\to0}\frac{d\tau}{d\lambda} = \lim_{\lambda\to0}\frac{-\tau(\sigma/\delta)(-\tau)e^{-\lambda\tau}}{(\sigma/\delta)e^{-\lambda\tau} - (\sigma/\delta)\tau\lambda e^{-\lambda\tau}} = \tau^2. \tag{16}$$

Thus

$$\text{sgn}\left\{\text{Re}\left(\frac{d\lambda}{d\tau}\right)\bigg|_{\lambda=0}\right\} = \text{sgn}\left\{\text{Re}\left(\frac{d\tau}{d\lambda}\right)\bigg|_{\lambda=0}\right\} = 1 > 0. \tag{17}$$

Hence the conclusion (I)(3) is true.

Noting

$$\begin{aligned} \text{sgn}\left\{\text{Re}\left(\frac{d\lambda}{d\tau}\right)\bigg|_{\lambda=i\omega_+}\right\} &= \text{sgn}\left\{\text{Re}\left(\frac{d\tau}{d\lambda}\right)\bigg|_{\lambda=i\omega_+}\right\} \\ &= \text{sgn}\left\{\frac{\sin\omega_+\tau}{(\sigma/\delta)\omega_+}\right\} \\ &= \text{sgn}\left\{\left(\frac{\delta}{\sigma}\right)^2\right\} = 1 > 0, \end{aligned} \tag{18}$$

then (II)(3) is proved. Then all the proof is finished. □

Thus the following results can be obtained by Lemma 1.

**Theorem 2.** *(I) If $\alpha = \sigma/\delta$, then*

(1) *system* (5) *undergoes a codimension one steady-state bifurcation at the tumor-free equilibrium $P_0$ as $0 < \tau < \delta/\sigma$;*

(2) *the tumor-free equilibrium $P_0$ is a B-T singular equilibrium as $\tau = \delta/\sigma$.*

*(II) If $\alpha < \sigma/\delta$, then*

(1) *the tumor-free equilibrium $P_0$ is asymptotically stable as $0 \le \tau < \tau_0$;*

(2) *the tumor-free equilibrium $P_0$ is unstable as $\tau > \tau_0$;*

(3) *system* (5) *undergoes Hopf bifurcation at the tumor-free equilibrium $P_0$ as $\tau = \tau_k$.*

*(III) The tumor-free equilibrium $P_0$ is unstable as $\alpha > \sigma/\delta$.*

*2.2. Positive Equilibrium.* If $\alpha\delta - \sigma > 0$, then the positive equilibrium $P_2$ exists. The characteristic equation of system (8) at the point $P_2$ is

$$\lambda^2 + p\lambda + q\lambda e^{-\lambda\tau} + r + le^{-\lambda\tau} = 0, \quad (19)$$

where

$$\begin{gathered} p = -(\alpha - \delta - 2\alpha\beta y_2), \\ q = x_2 - \zeta y_2, \\ r = -\delta(\alpha - 2\alpha\beta y_2), \\ l = \delta x_2 + \zeta y_2(\alpha - 2\alpha\beta y_2). \end{gathered} \quad (20)$$

**Lemma 3.** *If $\alpha\delta - \sigma > 0$, $\beta < \alpha\delta/2(\alpha\delta - \sigma)$, then*

(1) *all roots of* (19) *have negative real parts as $0 \le \tau < \tau_0'$;*

(2) *Equation* (19) *has a pair of conjugate purely imaginary roots $i\tilde{\omega}_+$, and all other roots have negative real parts as $\tau = \tau_0'$;*

(3) *Equation* (19) *has at least one root with positive real parts as $\tau > \tau_0'$.*

*Proof.* Noting $\beta < \alpha\delta/2(\alpha\delta - \sigma)$, $1 - 2\beta y_2 > 0$, one has

$$r + l = \zeta\alpha y_2(1 - 2\beta y_2) + \delta\alpha\beta y_2 > 0; \quad (21)$$

thus (19) has no zero root.

If $\tau = 0$, then (19) can be written as

$$\lambda^2 + (p + q)\lambda + r + l = 0. \quad (22)$$

It is easy to see

$$p + q = \delta - \alpha(1 - 2\beta y_2) + x_2 - \zeta y_2 = \delta + (\alpha\beta - \zeta)y_2 > 0, \quad (23)$$

and then all roots of (22) have negative real parts.

If $\tau > 0$, we assume that (19) has a pair of purely imaginary roots $\lambda = i\omega$ $(\omega > 0)$; thus

$$\begin{gathered} -\omega^2 + l\cos\omega\tau + q\omega\sin\omega\tau + r = 0, \\ p\omega + q\omega\cos\omega\tau - l\sin\omega\tau = 0, \end{gathered} \quad (24)$$

and hence

$$\omega^4 + (p^2 - 2r - q^2)\omega^2 + r^2 - l^2 = 0. \quad (25)$$

Noting $r + l > 0$, $r < 0$, then we have $r - l < 0$ and $r^2 - l^2 = (r + l)(r - l) < 0$. That is to say, (25) has only one positive root

$$\tilde{\omega}_+ = \sqrt{\frac{-(p^2 - 2r - q^2) + \sqrt{(p^2 - 2r - q^2)^2 - 4(r^2 - l^2)}}{2}}, \quad (26)$$

and the corresponding critical value is

$$\tau_k' = \begin{cases} \dfrac{1}{\tilde{\omega}_+}\left\{\arctan\dfrac{lp\tilde{\omega}_+ + q\tilde{\omega}_+(\tilde{\omega}_+^2 - r)}{l(\tilde{\omega}_+^2 - r) - pq\tilde{\omega}_+^2} + 2k\pi\right\} \\ \quad if\ l(\tilde{\omega}_+^2 - r) - pq\tilde{\omega}_+^2 > 0; \\ \dfrac{1}{\tilde{\omega}_+}\left\{\arctan\dfrac{lp\tilde{\omega}_+ + q\tilde{\omega}_+(\tilde{\omega}_+^2 - r)}{l(\tilde{\omega}_+^2 - r) - pq\tilde{\omega}_+^2} + (2k+1)\pi\right\}, \\ \quad if\ l(\tilde{\omega}_+^2 - r) - pq\tilde{\omega}_+^2 < 0. \end{cases} \quad k \in \mathbb{N}. \quad (27)$$

We can also give the following transversal condition:

$$\begin{aligned} &\operatorname{sgn}\left\{\operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)\Big|_{\lambda=i\tilde{\omega}_+}\right\} \\ &= \operatorname{sgn}\left\{\operatorname{Re}\left(\frac{d\tau}{d\lambda}\right)\Big|_{\lambda=i\tilde{\omega}_+}\right\} \\ &= \operatorname{sgn}\left\{\operatorname{Re}\left(\frac{2\lambda + p}{\lambda(q\lambda + l)e^{-\lambda\tau}} + \frac{q}{\lambda(q\lambda + l)}\right)\Big|_{\lambda=i\tilde{\omega}_+}\right\} \\ &= \operatorname{sgn}\left\{2(\tilde{\omega}_+^2 - r) + p^2 - q^2\right\} \\ &= \operatorname{sgn}\left\{-(p^2 - 2r - q^2) + (p^2 - 2r - q^2) \right. \\ &\qquad \left. + \sqrt{(p^2 - 2r - q^2)^2 - 4(r^2 - l^2)}\right\} \\ &= 1 > 0. \end{aligned} \quad (28)$$

Then all results of this theorem have been proven. □

From Lemma 3, the following theorem can be obtained directly.

**Theorem 4.** *Suppose that $\alpha\delta - \sigma > 0$, $\beta < \alpha\delta/2(\alpha\delta - \sigma)$; then*

(1) *the positive equilibrium $P_2$ is stable as $0 \le \tau < \tau_0'$;*

(2) *the positive equilibrium $P_2$ is unstable as $\tau > \tau_0'$;*

(3) *system* (5) *undergoes a Hopf bifurcation at the equilibrium $P_2$ as $\tau = \tau_k'$.*

## 3. Direction and Stability of the Bifurcations

*3.1. Hopf Bifurcation.* In the previous section, we know that system (5) undergoes Hopf bifurcation at the tumor-free equilibrium $P_0$ and positive equilibrium $P_2$ under certain conditions. In this section, we will study the stability and direction of the Hopf bifurcated periodic solution by using the center manifold reduction and normal form theory of retarded functional differential equations due to the ideals of Faria and Magalhães [15, 16]. Throughout this section, we always assume that system (5) undergoes Hopf bifurcations at the equilibrium $P$ ($P_0$ or $P_2$) as the critical parameter $\tau = \tau_k$ and the corresponding purely imaginary roots are $\pm i\omega_k$.

Normalizing the delay $\tau$ in system (7) by the time-scaling $t \to t/\tau$, then (7) is transformed into

$$\begin{aligned} z_1'(t) &= \tau\left[\alpha_1 z_1(t) + \alpha_2 z_1(t-1) + \alpha_3 z_2(t-1) + \zeta z_1(t-1) z_2(t-1)\right], \\ z_2'(t) &= \tau\left[\beta_1 z_1(t-1) + \beta_2 z_2(t) + \beta_3 z_2(t-1) - \alpha\beta z_2^2(t) - z_1(t-1) z_2(t-1)\right]. \end{aligned} \tag{29}$$

This scaling is irrelevant for the study of the stability of the equilibrium but will be crucial for the Hopf bifurcation analysis.

Let $z(t) = \begin{cases} z_1(t) \\ z_2(t) \end{cases}$. we transformed (29) into an FDE in $C([-1,0],\mathbb{R}^2)$:

$$\dot{z}(t) = N(\tau)(z_t) + F(z_t,\tau), \tag{30}$$

where $N(\varphi) : C([-1,0],\mathbb{R}^2) \to \mathbb{R}^2$, $F(\varphi) : C([-1,0]\mathbb{R}^2) \to \mathbb{R}^2$, are given by

$$\begin{aligned} N(\tau)(\varphi) &= \tau\begin{pmatrix} \alpha_1\varphi_1(0) + \alpha_2\varphi_1(-1) + \alpha_3\varphi_2(-1) \\ \beta_1\varphi_1(-1) + \beta_2\varphi_2(0) + \beta_3\varphi_2(-1) \end{pmatrix}, \\ F(\varphi,\tau) &= \tau\begin{pmatrix} \zeta\varphi_1(-1)\varphi_2(-1) \\ -\alpha\beta\varphi_2^2(0) - \varphi_1(-1)\varphi_2(-1) \end{pmatrix}, \end{aligned} \tag{31}$$

where $\varphi = \operatorname{col}(\varphi_1,\varphi_2) \in C([-1,0],\ \mathbb{R}^2)$. Let $\Lambda = \{i\omega_k, -i\omega_k\}$. Setting the new parameter $\gamma = \tau - \tau_k$, then (30) can be written as

$$\dot{z}(t) = N(\tau_k)(z_t) + \widetilde{F}(z_t,\gamma), \tag{32}$$

where $\widetilde{F}(z_t,\gamma) = N(\gamma)(z_t) + F(z_t,\tau_k+\gamma)$.

Assume that $A$ is the infinitesimal generator of $\dot{z}(t) = N(\tau_k)(z_t)$ satisfying $A\Phi = \Phi B$ with

$$B = \begin{pmatrix} i\omega_k & 0 \\ 0 & -i\omega_k \end{pmatrix}, \tag{33}$$

and $A$ has a pair of conjugate purely imaginary roots $\pm i\omega_k$. Denote that $P$ is the invariant space of $A$ associated with $\Lambda$; then $\dim P = 2$. We can decompose $C := C([-1,0],\mathbb{R}^2)$ to $C = P\bigoplus Q$ by the formal adjoint theory for FDEs by Hale [17]. Considering complex coordinates, we still denote $C$ as $([-1,0],C^2)$. Let $\Phi = (\Phi_1,\Phi_2)$ be the bases of $P$, where

$$\Phi_1 = e^{i\omega_k\theta}v, \quad \Phi_2 = \overline{\Phi}_1, \quad \theta \in [-1,0], \tag{34}$$

$v = \binom{v_1}{v_2}$ is a vector in $C^2$ and $N(\tau_k)\Phi_1 = i\omega_k v$.

Choose a basis $\Psi$ for the adjoint space $P^*$, such that $(\Psi,\Phi) = I_2$, where $(\cdot,\cdot)$ is the bilinear form on $C^* \times C$ associated with the adjoint equation. Thus, $\Psi = \operatorname{col}(\Psi_1,\Psi_2)$ with

$$\Psi_1 = e^{-i\omega_k\widetilde{\theta}}u^T, \quad \Psi_2 = \overline{\Psi}_1, \quad u = \begin{pmatrix} u_1 \\ u_2 \end{pmatrix}, \quad \widetilde{\theta} \in [0,1], \tag{35}$$

such that $(\Psi_1,\Phi_1) = 1$, $(\Psi_1,\Phi_2) = 0$. Then

$$\begin{aligned} v &= \begin{pmatrix} 1 \\ \dfrac{i\omega_k - \left(\alpha_1 + \alpha_2 e^{-i\omega_k}\right)\tau_k}{\tau_k\alpha_3 e^{-i\omega_k}} \end{pmatrix}, \\ u &= u_1\begin{pmatrix} 1 \\ \dfrac{i\omega_k - \left(\alpha_1 + \alpha_2 e^{-i\omega_k}\right)\tau_k}{\tau_k\beta_1 e^{-i\omega_k}} \end{pmatrix}, \end{aligned} \tag{36}$$

and $1/u_1 = 1 + (1 + \beta_3 e^{-i\omega_k})v_2((i\omega_k - (\alpha_1 + \alpha_2 e^{-i\omega_k})\tau_k)/\tau_k\beta_1 e^{-i\omega_k}) + (\alpha_2 + 2\alpha_3 v_2)e^{-i\omega_k}$.

Take the enlarged phase space $BC$, defined as

$$BC := \left\{\varphi : [-1,0] \longrightarrow \mathbb{C}^2 \mid \varphi \text{ is continuous on } [-1,0),\ \lim_{\theta\to 0^-}\varphi(\theta) \text{ exists}\right\}. \tag{37}$$

The projection $\pi : BC \to P$ is defined as

$$\pi(\varphi + X_0 b) = \Phi\left[(\Psi,\varphi) + \Psi(0)b\right], \quad \forall\varphi \in C,\ b \in \mathbb{R}^2; \tag{38}$$

thus we have the decomposition $BC = P\bigoplus \operatorname{Ker}\pi$. Let $z_t = \Phi x + y$, $x \in \mathbb{C}^2$, $y \in \ker(\pi)\cap C^1 := Q^1$, we can decompose (32) to

$$\begin{aligned} \dot{x} &= Bx + \Psi(0)\widetilde{F}(\Phi x + y,\gamma), \\ \frac{\mathrm{d}y}{\mathrm{d}x} &= A_{Q^1}y + (I-\pi)X_0\widetilde{F}(\Phi x + y,\gamma), \end{aligned} \tag{39}$$

where

$$X_0(\theta) = \begin{cases} I, & \theta = 0; \\ 0, & -1 \le \theta < 0. \end{cases} \tag{40}$$

We write the Taylor expansion as follows:

$$\begin{aligned} \Psi(0)\widetilde{F}(\Phi x + y,\gamma) &= \frac{1}{2}f_2^1(x,y,\gamma) + \frac{1}{3!}f_3^1(x,y,\gamma) + \text{h.o.t.}, \\ (I-\pi)X_0\widetilde{F}(\Phi x + y,\gamma) &= \frac{1}{2}f_2^2(x,y,\gamma) + \frac{1}{3!}f_3^2(x,y,\gamma) + \text{h.o.t.}, \end{aligned} \tag{41}$$

where $f_k^1$ and $f_k^2$ are homogeneous polynomials in $x$, $y$, and $\gamma$ of degree $k$, $k = 2,3$, with coefficients in $\mathbb{C}^2$ and $\operatorname{Ker}\pi$, h.o.t. stands for higher order terms. The normal form method implies a normal form on the center manifold of the origin for (32) which is

$$\dot{x} = Bx + \frac{1}{2}g_2^1(x,0,\gamma) + \frac{1}{3!}g_3^1(x,0,\gamma) + \text{h.o.t.}, \tag{42}$$

where $g_2^1(x,0,\gamma)$ and $g_3^1(x,0,\gamma)$ are homogeneous polynomials in $x$ and $\gamma$, respectively.

From (39), it follows that

$$f_2^1(x,0,\gamma) = 2\Psi(0)\left[N(\gamma)(\Phi x) + F(\Phi x, \tau_k)\right]; \tag{43}$$

that is,

$$f_2^1(x,0,\gamma) = 2\begin{pmatrix} A_1x_1\gamma + A_2x_2\gamma + a_{20}x_1^2 + a_{11}x_1x_2 + a_{02}x_2^2 \\ \overline{A}_1x_2\gamma + \overline{A}_2x_1\gamma + \overline{a}_{02}x_1^2 + \overline{a}_{11}x_1x_2 + \overline{a}_{20}x_2^2 \end{pmatrix}, \tag{44}$$

where

$$\begin{aligned} A_1 &= \frac{i\omega_k}{\tau_k}u^T v, \qquad A_2 = \frac{-i\omega_k}{\tau_k}u^T\overline{v}, \\ a_{20} &= \tau_k\left[u_1e^{-2i\omega_k}\zeta v_1v_2 + u_2\left(-\alpha\beta v_2^2 - e^{-2i\omega_k}v_1v_2\right)\right], \\ a_{11} &= \tau_k\left[\zeta u_1\left(v_1\overline{v}_2 + \overline{v}_1v_2\right) - u_2\left(2\alpha\beta v_2\overline{v}_2 + v_1\overline{v}_2 + \overline{v}_1v_2\right)\right], \\ a_{02} &= \tau_k\left[u_1e^{2i\omega_k}\zeta\overline{v}_1\overline{v}_2 + u_2\left(-\alpha\beta\overline{v}_2^2 - e^{2i\omega_k}\overline{v}_1\overline{v}_2\right)\right]. \end{aligned} \tag{45}$$

Thus

$$g_2^1(x,0,\gamma) = \text{Proj}_{\text{Ker}(M_2^1)}f_2^1(x,0,\gamma) = \begin{pmatrix} 2A_1x_1\gamma \\ 2\overline{A}_1x_2\gamma \end{pmatrix}. \tag{46}$$

We will compute the cubic terms $g_3^1(x,0,\gamma)$ as follows.

Since $O(|x|\gamma^2)$ are irrelevant to determine the generic Hopf bifurcation, then

$$J = \text{span}\left\{\begin{pmatrix} x_1^2x_2 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ x_1x_2^2 \end{pmatrix}\right\}; \tag{47}$$

hence

$$g_3^1(x,0,\gamma) = \text{Proj}_J\overline{f}_3^1(x,0,0) + o\left(|x|\gamma^2\right), \tag{48}$$

where $\overline{f}_3^1(x,0,0) = (3/2)[(D_xf_2^1)u_2^1 - (D_xu_2^1)g_2^1]_{(x,0,0)} + (3/2)[(D_yf_2^1)u_2^2]_{(x,0,0)}$. In order to obtain $g_3^1(x,0,\gamma)$, we need to compute $f_3^1(x,0,0)$; that is, $\text{Proj}_J[(D_xf_2^1)u_2^1]_{(x,0,0)}$, $\text{Proj}_J[(D_xu_2^1)g_2^1]_{(x,0,0)}$, and $\text{Proj}_J[(D_yf_2^1)u_2^2]_{(x,0,0)}$ should be given; we will compute them as follows.

Firstly, knowing that

$$\begin{aligned} f_2^1(x,0,0) &= 2\begin{pmatrix} a_{20}x_1^2 + a_{11}x_1x_2 + a_{02}x_2^2 \\ \overline{a}_{02}x_1^2 + \overline{a}_{11}x_1x_2 + \overline{a}_{20}x_2^2 \end{pmatrix}, \\ u_2^1(x,0) &= \frac{2}{i\omega_k}\begin{pmatrix} a_{20}x_1^2 - a_{11}x_1x_2 - \frac{1}{3}a_{02}x_2^2 \\ \frac{1}{3}\overline{a}_{02}x_1^2 + \overline{a}_{11}x_1x_2 - \overline{a}_{20}x_2^2 \end{pmatrix}, \end{aligned} \tag{49}$$

then

$$\begin{aligned} &\text{Proj}_J\left[\left(D_xf_2^1\right)u_2^1\right]_{(x,0,0)} \\ &= \frac{4}{i\omega_k}\begin{pmatrix} \left(-a_{20}a_{11} + \frac{2}{3}|a_{02}|^2 + |a_{11}|^2\right)x_1^2x_2 \\ \left(-\frac{2}{3}|a_{02}|^2 - |a_{11}|^2 + \overline{a_{20}a_{11}}\right)x_1x_2^2 \end{pmatrix} \\ &= 4\begin{pmatrix} A_3x_1^2x_2 \\ \bar{A}_3x_1x_2^2 \end{pmatrix}. \end{aligned} \tag{50}$$

Secondly, noting (46), we know that $g_2^1(x,0,0) = 0$; then $\text{Proj}_J[(D_xu_2^1)g_2^1]_{(x,0,0)} = 0$.

Lastly, we will compute $\text{Proj}_J[(D_yf_2^1)u_2^2]_{(x,0,0)}$ as follow.

Let $h = u_2^2 = h_{200}x_1^2 + h_{020}x_2^2 + h_{002}\gamma^2 + h_{110}x_1x_2 + h_{101}x_1\gamma + h_{011}x_2\gamma$. Noting $g_2^2 = 0$, one has

$$\begin{aligned} M_2^2h(x,\gamma) &= f_2^2 = 2(I-\pi)X_0\widetilde{F}(\Phi x,\gamma) \\ &= 2(I-\pi)X_0\left[N(\gamma)(\Phi x) + F(\Phi x,\tau_k)\right]. \end{aligned} \tag{51}$$

On the other hand, we know that

$$\begin{aligned} &M_2^2h(x,\gamma) \\ &= D_xh(x,\gamma)Bx - A_{Q^1}h(x,\gamma) \\ &= D_xh(x,\gamma)Bx \\ &\quad - \left[\dot{h}(x,\gamma) + X_0\left(L(\tau_k)(h(x,\gamma)) - \dot{h}(x,\gamma)(0)\right)\right]. \end{aligned} \tag{52}$$

If $\gamma = 0$, then

$$\begin{aligned} \dot{h}(x) - D_xh(x)Bx &= 2\Phi\Psi(0)F(\Phi x,\tau_k), \\ \dot{h}(x)(0) - L(\tau_k)(h(x)) &= 2F(\Phi x,\tau_k). \end{aligned} \tag{53}$$

Let

$$\begin{aligned} W(\theta) &= \Phi x + y = \Phi_1x_1 + \Phi_2x_2 + y(\theta) \\ &= e^{i\omega_k\theta}vx_1 + e^{-i\omega_k\theta}\overline{v}x_2 + y(\theta), \\ \widetilde{W}(\theta) &= \Phi x = \Phi_1x_1 + \Phi_2x_2 = e^{i\omega_k\theta}vx_1 + e^{-i\omega_k\theta}\overline{v}x_2. \end{aligned} \tag{54}$$

From

$$\begin{aligned} &f_2^1(x,y,0) \\ &= 2\tau_k\begin{pmatrix} u^T\begin{pmatrix} \zeta W_1(-1)W_2(-1) \\ -\alpha\beta W_2^2(0) - W_1(-1)W_2(-1) \end{pmatrix} \\ \overline{u}^T\begin{pmatrix} \zeta W_1(-1)W_2(-1) \\ -\alpha\beta W_2^2(0) - W_1(-1)W_2(-1) \end{pmatrix} \end{pmatrix}, \end{aligned} \tag{55}$$

we obtain

$$\left[\left(D_y f_2^1\right) h\right]_{(x,0,0)} = 2\begin{pmatrix} \tau_k u^T \begin{pmatrix} \zeta\widetilde{W}_2(-1)h^1(-1)+\zeta\widetilde{W}_1(-1)h^2(-1) \\ -\widetilde{W}_2(-1)h^1(-1)-\widetilde{W}_1(-1)h^2(-1)-2\alpha\beta\widetilde{W}_2(0)h^2(0)\end{pmatrix} \\ \tau_k \bar{u}^T \begin{pmatrix} \zeta\widetilde{W}_2(-1)h^1(-1)+\zeta\widetilde{W}_1(-1)h^2(-1) \\ -\widetilde{W}_2(-1)h^1(-1)-\widetilde{W}_1(-1)h^2(-1)-2\alpha\beta\widetilde{W}_2(0)h^2(0)\end{pmatrix} \end{pmatrix}, \quad (56)$$

$$\operatorname{Proj}_J\left[\left(D_y f_2^1\right) u_2^2\right]_{(x,0,0)} = 2\begin{pmatrix} A_4 x_1^2 x_2 \\ \overline{A}_4 x_1 x_2^2 \end{pmatrix}, \quad (57)$$

where

$$\begin{aligned} A_4 = {} & \tau_k \Big[u_1\zeta\Big(e^{-i\omega_k}v_2h_{110}^1(-1) + e^{i\omega_k}\bar{v}_2h_{200}^1(-1) \\ & \quad + e^{-i\omega_k}v_1h_{110}^2(-1) + e^{i\omega_k}\bar{v}_1h_{200}^2(-1)\Big)\Big] \\ & + u_2\tau_k\Big[-e^{-i\omega_k}v_2h_{110}^1(-1) - e^{i\omega_k}\bar{v}_2h_{200}^1(-1) \\ & \quad - e^{-i\omega_k}v_1h_{110}^2(-1) - e^{i\omega_k}\bar{v}_1h_{200}^2(-1)\Big] \\ & - u_2\tau_k\Big[2\alpha\beta\Big(v_2h_{110}^2(0) + \bar{v}_2h_{200}^2(0)\Big)\Big]. \end{aligned} \quad (58)$$

In order to obtain $A_4$, we need to compute $h_{110}(\theta)$, $h_{200}(\theta)$. From (53), it follows that

$$\begin{aligned} \dot{h}_{110} &= 2(\Phi_1,\Phi_2)\begin{pmatrix} a_{11} \\ \bar{a}_{11}\end{pmatrix}, \\ \dot{h}_{110}(0) - L(\tau_k)(h_{110}) &= \tau_k\begin{pmatrix} a_1 \\ b_1\end{pmatrix}, \\ \dot{h}_{200} - 2i\omega_k h_{200} &= 2(\Phi_1,\Phi_2)\begin{pmatrix} a_{20} \\ \bar{a}_{02}\end{pmatrix}, \\ \dot{h}_{200}(0) - L(\tau_k)(h_{200}) &= \tau_k\begin{pmatrix} a_2 \\ b_2\end{pmatrix}, \end{aligned} \quad (59)$$

where $a_1 = 2[\zeta(v_1\bar{v}_2+\bar{v}_1v_2)]$, $b_1 = 2[-2\alpha\beta v_2\bar{v}_2-(v_1\bar{v}_2+\bar{v}_1v_2)]$, $a_2 = 2[\zeta v_1v_2e^{-2i\omega_k}]$, and $b_2 = 2[-\alpha\beta v_2^2 - e^{-2i\omega_k}v_1v_2]$. Solving (59), we can obtain

$$\begin{aligned} h_{110} &= 2\left[\frac{a_{11}}{i\omega_k}\Phi_1 - \frac{\bar{a}_{11}}{i\omega_k}\Phi_2\right] + C_1, \\ h_{200} &= 2\left[\frac{a_{20}}{-i\omega_k}\Phi_1 + \frac{\bar{a}_{02}}{-3i\omega_k}\Phi_2\right] + C_2e^{2i\omega_k\theta}, \end{aligned} \quad (60)$$

where

$$\begin{aligned} C_1 &= \begin{pmatrix} C_1^1 \\ C_1^2 \end{pmatrix}, \\ C_1^1 &= \frac{\begin{vmatrix} a_1 & -\alpha_3 \\ b_1 & -(\beta_2+\beta_3)\end{vmatrix}}{\begin{vmatrix} -(\alpha_1+\alpha_2) & -\alpha_3 \\ -\beta_1 & -(\beta_2+\beta_3)\end{vmatrix}}, \\ C_1^2 &= \frac{\begin{vmatrix} -(\alpha_1+\alpha_2) & a_1 \\ -\beta_1 & b_1\end{vmatrix}}{\begin{vmatrix} -(\alpha_1+\alpha_2) & -\alpha_3 \\ -\beta_1 & -(\beta_2+\beta_3)\end{vmatrix}}, \\ C_2 &= \begin{pmatrix} C_2^1 \\ C_2^2 \end{pmatrix}, \\ C_2^1 &= \frac{\begin{vmatrix} \tau_k a_2 & -\tau_k\alpha_3e^{-2i\omega_k} \\ \tau_k b_2 & 2i\omega_k+\tau_k\beta_2+\tau_k\beta_3e^{-2i\omega_k}\end{vmatrix}}{\begin{vmatrix} 2i\omega_k-\tau_k\alpha_1-\tau_k\alpha_2e^{-2i\omega_k} & -\tau_k\alpha_3e^{-2i\omega_k} \\ -\tau_k\beta_1e^{-2i\omega_k} & 2i\omega_k+\tau_k\beta_2+\tau_k\beta_3e^{-2i\omega_k}\end{vmatrix}}, \\ C_2^2 &= \frac{\begin{vmatrix} 2i\omega_k-\tau_k\alpha_1-\tau_k\alpha_2e^{-2i\omega_k} & \tau_k a_2 \\ -\tau_k\beta_1e^{-2i\omega_k} & \tau_k b_2\end{vmatrix}}{\begin{vmatrix} 2i\omega_k-\tau_k\alpha_1-\tau_k\alpha_2e^{-2i\omega_k} & -\tau_k\alpha_3e^{-2i\omega_k} \\ -\tau_k\beta_1e^{-2i\omega_k} & 2i\omega_k+\tau_k\beta_2+\tau_k\beta_3e^{-2i\omega_k}\end{vmatrix}}. \end{aligned} \quad (61)$$

Hence

$$g_3^1(x,0,0) = \begin{pmatrix} \left(6A_3+3A_4\right)x_1^2x_2 \\ \left(6\overline{A}_3+3\overline{A}_4\right)x_1x_2^2 \end{pmatrix}. \quad (62)$$

Thus, the normal form of system (42) has the form

$$\begin{aligned} \dot{x} = {} & Bx + \begin{pmatrix} A_1x_1\gamma \\ \overline{A}_1x_2\gamma \end{pmatrix} + \frac{1}{3!}\begin{pmatrix} \left(6A_3+3A_4\right)x_1^2x_2 \\ \left(6\overline{A}_3+3\overline{A}_4\right)x_1x_2^2 \end{pmatrix} \\ & + o\left(|x|^4 + |x|\gamma^2\right). \end{aligned} \quad (63)$$

Let $x_1 = \xi_1 - i\xi_2$, $x_2 = \xi_1 + i\xi_2$, $\xi_1 = \rho\cos\omega$, and $\xi_2 = \rho\sin\omega$. Then the normal form becomes

$$\begin{aligned} \dot{\rho} &= r_1\gamma\rho + r_2\rho^3 + O\left(\gamma^2\rho + |(\rho,\gamma)|^4\right), \\ \dot{\omega} &= -\omega_k - \operatorname{Im}(A_1)\gamma - \operatorname{Im}\left(A_3 + \frac{1}{2}A_4\right)\rho^2 + o\left(\left|\left(\rho^2,\gamma\right)\right|\right), \end{aligned} \quad (64)$$

where $r_1 = \operatorname{Re} A_1$, $r_2 = \operatorname{Re}(A_3 + (1/2)A_4)$.

Summarizing all above, we have the following theorem.

**Theorem 5.** *The flow on the center manifold of the equilibrium $P$ at $\gamma = 0$ is given by* (64). *Also the following results hold:*

(1) *the Hopf bifurcation is supercritical if $r_1r_2 < 0$ and subcritical if $r_1r_2 > 0$;*

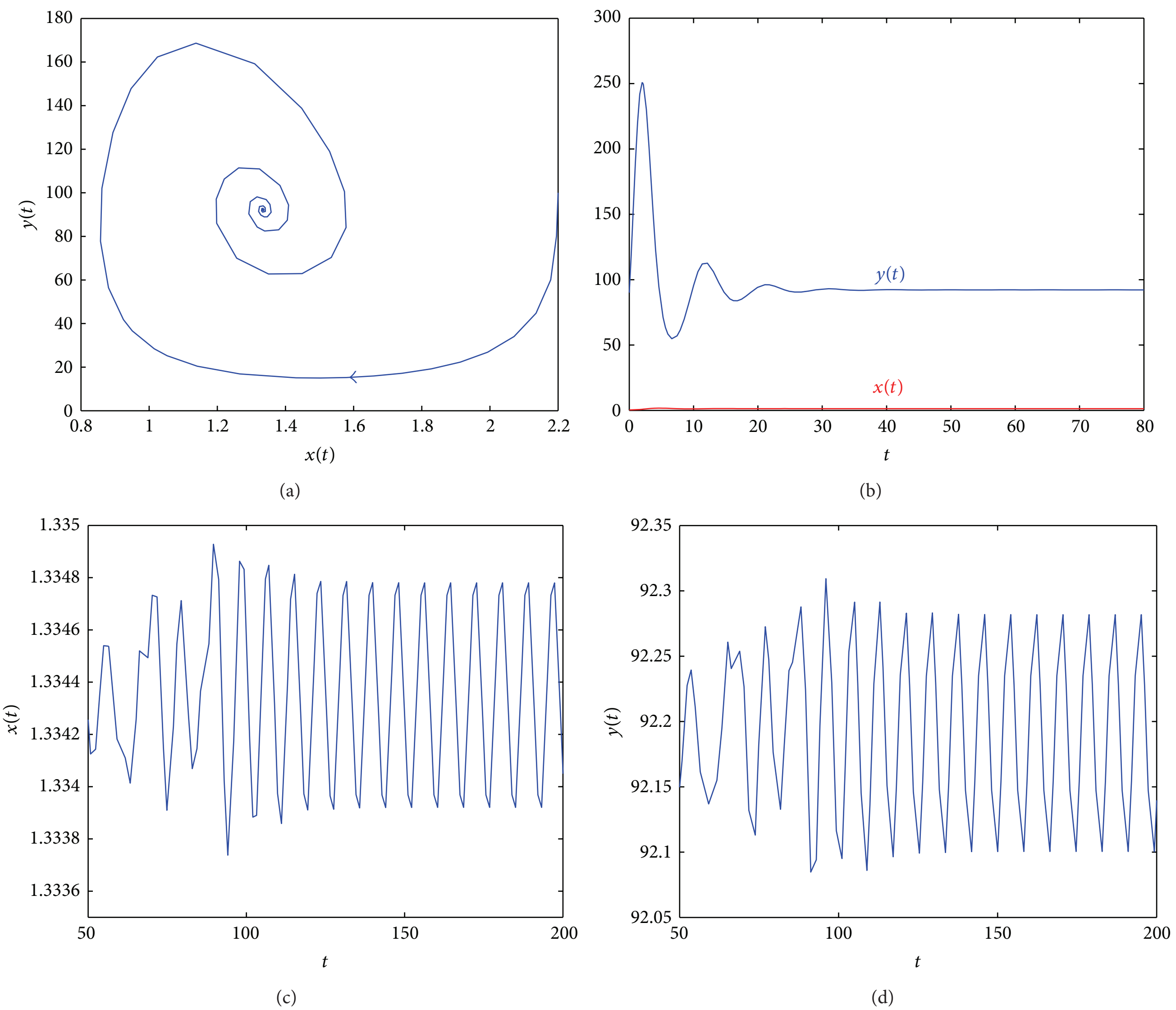


FIGURE 2: (a) The equilibrium (1.3344, 92.1911) is stable when $\tau = 0.2$. (b) The oscillation solutions $x(t)$ and $y(t)$ in terms of time $t$ when $\tau = 0.2 < \tau_0$. (c) The oscillation solution $x(t)$ in terms of $t$ when $\tau = 0.372892$. (d) The oscillation solution $y(t)$ in terms of $t$.

(2) *the bifurcated periodic solution is stable if* $r_2 < 0$ *and unstable if* $r_2 > 0$;

(3) *the period of the bifurcated periodic solution is*

$$p(\gamma) = \frac{2\pi}{\omega_k} - \frac{2\pi\gamma\left(r_2 \operatorname{Im}(A_1) - r_1 \operatorname{Im}(A_3 + (1/2)A_4)\right)}{r_2\omega_k^2} + O(\gamma^2). \tag{65}$$

In the following, we will give some simulations to illustrate the results of Theorems 4 and 5 for model (4). We cite the parameters in [11], that is, $\sigma = 0.1181$, $\zeta = 0.0031$, $\delta = 0.3743$, $\alpha = 1.636$, and $\beta = 0.002$. Then (4) has a tumor-free equilibrium $(0.3155, 0)$, which is unstable, and a positive equilibrium $(1.33435, 92.1911)$, which is locally asymptotically stable. We only simulate local properties of the stable equilibrium $(1.33435, 92.1911)$ here in Figures 2(a) and 2(b).

*Remark 6.* From Figures 2(c) and 2(d), we can see that the amplitude vibration for $x(t)$ is much bigger than that of $y(t)$; also both $x(t)$ and $y(t)$ with respect to $t$ are not so smooth. Then the Hopf bifurcated periodic solution on $(x(t), y(t))$ plan is not given here. At the same time, we can see that the dynamical behaviors of the system have been changed although $\tau$ is small.

*3.2. Steady-State Bifurcation.* From Section 2, we know that system (5) undergoes a steady-state bifurcation at the tumor-free equilibrium $P_0$ as $\alpha = \sigma/\delta$, $0 < \tau < \delta/\sigma$. In this section, we will discuss the properties of the steady-state bifurcation by using the center manifold reduction and normal form theories of retarded functional differential equations.

At the tumor-free equilibrium $P_0$, we write system (5) as an FDE:

$$\dot{z}(t) = N(z_t) + F(z_t), \tag{66}$$

where

$$N(\varphi) = \tau \begin{pmatrix} -\delta\varphi_1(0) + \zeta\dfrac{\sigma}{\delta}\varphi_2(-1) \\ \alpha\varphi_2(0) - \dfrac{\sigma}{\delta}\varphi_2(-1) \end{pmatrix},$$
$$F(\varphi) = \tau \begin{pmatrix} \zeta\varphi_1(-1)\varphi_2(-1) \\ -\alpha\beta\varphi_2^2(0) - \varphi_1(-1)\varphi_2(-1) \end{pmatrix}. \tag{67}$$

Letting $\alpha = (\sigma/\delta) + \gamma$, then (66) can be written as

$$\dot{z}(t) = N\left(\frac{\sigma}{\delta}\right)(z_t) + \widetilde{F}(z_t, \gamma), \tag{68}$$

where $\widetilde{F}(z_t, \gamma) = N(\gamma)(z_t) + F(z_t, \gamma)$.

Assuming that $A$ is the infinitesimal generator of $\dot{z}(t) = N(\sigma/\delta)(z_t)$, then $A$ has a simple zero root. Set $\Lambda = \{0\}$ and we denote by $P$ the invariant space of $A$ associated with $\Lambda$; then $\dim P = 1$. We can decompose $C := C([-1, 0], \mathbb{R}^2)$ to $C = P \bigoplus Q$ by the formal adjoint theory for FDEs by Hale [17]. Let $P = \mathrm{span}(\Phi)$ be the bases for $P$, where $\Phi = \binom{\nu_1}{\nu_2}$, which is a vector in $\mathbb{R}^2$ satisfying

$$N\left(\frac{\sigma}{\delta}\right)\Phi = \dot{\Phi}(0). \tag{69}$$

Choose a basis $\Psi$ for the adjoint space $P^*$, where $\Psi = (u_1, u_2)$, which is a vector in $\mathbb{R}^{2*}$ satisfying $\Psi N(\sigma/\delta) = -\dot{\Psi}(0)$. Thus we can obtain

$$\Phi = \begin{pmatrix} 1 \\ \dfrac{\delta^2}{\zeta\sigma} \end{pmatrix}, \qquad \Psi = \left(0, \frac{1}{(\delta^2/\zeta\sigma) - (\tau\delta/\zeta)}\right). \tag{70}$$

According to the method of Faria and a similar computation in the last section, we can obtain

$$\begin{aligned} f_2^1(x, 0, \gamma) &= 2\Psi(0)\left[N(\gamma)(\Phi x) + F(\Phi x, \tau_k)\right] \\ &= 2\frac{\tau}{\delta/\sigma - \tau}\left[\gamma\frac{\delta}{\sigma}x - \left(\left(\beta\delta^2\right)/\zeta\sigma + \delta/\sigma\right)x^2\right]. \end{aligned} \tag{71}$$

Noting

$$\mathrm{Ker}\left(M_2^1\right) = \mathrm{span}\left\{x^2, x\gamma, \gamma^2\right\}, \tag{72}$$

one has

$$\begin{aligned} g_2^1(x, 0, \gamma) &= \mathrm{Proj}_{\mathrm{Ker}(M_2^1)} f_2^1(x, 0, \gamma) \\ &= 2\frac{\tau}{\delta/\sigma - \tau}\left[\gamma\frac{\delta}{\sigma}x - \left(\frac{\beta\delta^2}{\zeta\sigma} + \frac{\delta}{\sigma}\right)x^2\right]. \end{aligned} \tag{73}$$

Thus, the normal form of system (5) is

$$\dot{x} = \frac{\tau}{\delta/\sigma - \tau}\left[\gamma\frac{\delta}{\sigma}x - \left(\frac{\beta\delta^2}{\zeta\sigma} + \frac{\delta}{\sigma}\right)x^2\right] + o\left(x^2\right). \tag{74}$$

Then the following two results are obvious.

**Theorem 7.** *If $\alpha = \sigma/\delta$, $0 < \tau < \delta/\sigma$, then the tumor-free equilibrium $P_0$ is stable.*

**Theorem 8.** *If $0 < \tau < \delta/\sigma$, $\alpha = \sigma/\delta + \gamma$, and $\gamma$ is small enough, then*

(1) *the tumor-free equilibrium $P_0$ is stable as $\gamma > 0$ and unstable as $\gamma < 0$;*

(2) *system (5) undergoes transcritical bifurcation at the tumor-free equilibrium $P_0$.*

*3.3. Bogdanov-Takens Bifurcation.* From Theorem 2 we know that the tumor-free equilibrium $P_0$ is a B-T singular equilibrium of the system (5) as $\alpha = \sigma/\delta$, $\tau = \delta/\sigma$. In this section, we will discuss the bifurcations of the system (5) at $P_0$.

At tumor-free equilibrium $P_0$, we can write (5) as an FDE:

$$\dot{z}(t) = N(z_t) + F(z_t), \tag{75}$$

where

$$N(\varphi) = \tau \begin{pmatrix} -\delta\varphi_1(0) + \zeta\dfrac{\sigma}{\delta}\varphi_2(-1) \\ \alpha\varphi_2(0) - \dfrac{\sigma}{\delta}\varphi_2(-1) \end{pmatrix},$$
$$F(\varphi) = \tau \begin{pmatrix} \zeta\varphi_1(-1)\varphi_2(-1) \\ -\alpha\beta\varphi_2^2(0) - \varphi_1(-1)\varphi_2(-1) \end{pmatrix}. \tag{76}$$

Let $\alpha = \sigma/\delta + \gamma_1$, $\tau = \delta/\sigma + \gamma_2$. Then system (75) can be written as

$$\dot{z}(t) = N\left(\frac{\sigma}{\delta}\right)(z_t) + \widetilde{F}(z_t, \gamma), \tag{77}$$

where $\widetilde{F}(z_t, \gamma) = N(\gamma)(z_t) + F(z_t, \gamma)$, $\gamma = \binom{\gamma_1}{\gamma_2}$.

Assuming that $A$ is the infinitesimal generator of $\dot{z}(t) = N(\sigma/\delta)(z_t)$, then $A$ has double zero roots. Set $\Lambda = \{0\}$ and denote by $P$ the invariant space of $A$ associated with $\Lambda$; then $\dim P = 2$. We can decompose $C := C([-1, 0], \mathbb{R}^2)$ as $C = P \bigoplus Q$ by the formal adjoint theory for FDEs by Hale [17]. Assume that $P = \mathrm{span}(\Phi)$ and $P^* = \mathrm{span}(\Psi)$. On the other hand, we know that $A\Phi = \Phi B$, where

$$B = \begin{pmatrix} 0 & 1 \\ 0 & 0 \end{pmatrix}, \tag{78}$$

that is, $N\Phi = \dot{\Phi}(0) = \Phi B$, $\Psi N = -\dot{\Psi}(0) = -B\Psi$, and $(\Psi, \Phi) = I_2$.

Let

$$A' = \begin{pmatrix} -\dfrac{\delta^2}{\sigma} & 0 \\ 0 & 1 \end{pmatrix}, \qquad B' = \begin{pmatrix} 0 & \zeta \\ 0 & -1 \end{pmatrix}. \tag{79}$$

From Lemma 3.1 by Xu and Huang [18], we can get

$$\Phi(\theta) = \begin{pmatrix} \frac{\sigma}{\delta^2} & \frac{\sigma}{\delta^2}\theta - \frac{\sigma^2}{\delta^4} \\ \frac{1}{\zeta} & \frac{1}{\zeta}(\theta+1) \end{pmatrix}, \quad (80)$$

$$\Psi(\tilde{\theta}) = \begin{pmatrix} 0 & -\frac{4}{3}\zeta - 2\zeta\tilde{\theta} \\ 0 & 2\zeta \end{pmatrix}. \quad (81)$$

Using the method of Faria and the last section, we can obtain

$$\begin{aligned} f_2^1(x,0,\gamma) &= 2\Psi(0)\left[N(\gamma)(\Phi x) + F(\Phi x, \tau_k)\right] \\ &= 2\begin{pmatrix} -\frac{4}{3}\left[\frac{\delta}{\sigma}\gamma_1 x_1 + \left(\frac{\delta}{\sigma}\gamma_1 + \frac{\sigma}{\delta}\gamma_2\right)x_2 - \left(\frac{\beta}{\zeta} + \frac{1}{\delta}\right)x_1^2 + \left(-\frac{2\beta}{\zeta} + \frac{\sigma}{\delta^3} + \frac{1}{\delta}\right)x_1x_2 - \frac{\beta}{\zeta}x_2^2\right] \\ 2\left[\frac{\delta}{\sigma}\gamma_1 x_1 + \left(\frac{\delta}{\sigma}\gamma_1 + \frac{\sigma}{\delta}\gamma_2\right)x_2 - \left(\frac{\beta}{\zeta} + \frac{1}{\delta}\right)x_1^2 + \left(-\frac{2\beta}{\zeta} + \frac{\sigma}{\delta^3} + \frac{1}{\delta}\right)x_1x_2 - \frac{\beta}{\zeta}x_2^2\right] \end{pmatrix}. \end{aligned} \quad (82)$$

On the other hand, the basis of $\mathrm{Ker}(M_2^1)$ is

$$\begin{pmatrix} 0 \\ x_1\gamma_1 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ x_2\gamma_1 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ x_1^2 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ x_1x_2 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ x_1\gamma_2 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ x_2\gamma_2 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ \gamma_1^2 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ \gamma_2^2 \end{pmatrix}, \quad \begin{pmatrix} 0 \\ \gamma_1\gamma_2 \end{pmatrix}, \quad (83)$$

and then we can obtain

$$\begin{aligned} g_2^1(x,0,\gamma) &= \mathrm{Proj}_{\mathrm{Ker}(M_2^1)} f_2^1(x,0,\gamma) \\ &= 2\begin{pmatrix} 0 \\ 2\left[\frac{\delta}{\sigma}\gamma_1 x_1 + \left(\frac{\delta}{\sigma}\gamma_1 + \frac{\sigma}{\delta}\gamma_2\right)x_2 - \left(\frac{\beta}{\zeta} + \frac{1}{\delta}\right)x_1^2 + \left(-\frac{2\beta}{\zeta} + \frac{\sigma}{\delta^3} + \frac{1}{\delta}\right)x_1x_2\right] \end{pmatrix}. \end{aligned} \quad (84)$$

Thus, the normal form of the system (5) is

$$\begin{aligned} \dot{x}_1 &= x_2, \\ \dot{x}_2 &= a_1x_1 + a_2x_2 + b_1x_1^2 + b_2x_1x_2 + \text{h.o.t}, \end{aligned} \quad (85)$$

where

$$\begin{aligned} a_1 &= 2\frac{\delta}{\sigma}\gamma_1, \qquad a_2 = 2\left(\frac{\delta}{\sigma}\gamma_1 + \frac{\sigma}{\delta}\gamma_2\right), \\ b_1 &= -2\left(\frac{\beta}{\zeta} + \frac{1}{\delta}\right), \qquad b_2 = 2\left(-\frac{2\beta}{\zeta} + \frac{\sigma}{\delta^3} + \frac{1}{\delta}\right). \end{aligned} \quad (86)$$

From above, we know that the following result can be obtained with the help of the theories of Xu and Huang [18] and Chow and Hale [19].

**Theorem 9.** *Assume that $\alpha = \sigma/\delta + \gamma_1$, $\tau = \delta/\sigma + \gamma_2$, $b_2 > 0$, and $\gamma$ is small enough; then system (5) undergoes Bogdanov-Takens bifurcation at the tumor-free equilibrium $P_0$. Furthermore, on the $(a_1, a_2)$-parameter plane, both H and HL are located in the area $a_1 > 0$, $a_2 < 0$ and H is on the left of HL, where H is Hopf bifurcation curve defined by*

$$H = \left\{(\gamma_1,\gamma_2) : a_2(\gamma_1,\gamma_2) = \frac{b_2}{b_1}a_1(\gamma_1,\gamma_2) + h.o.t., a_1(\gamma_1,\gamma_2) > 0\right\}, \quad (87)$$

*HL is the homoclinic bifurcation curve defined by*

$$HL = \left\{0(\gamma_1,\gamma_2) : a_2(\gamma_1,\gamma_2) = \mu\left(\sqrt{a_1(\gamma_1,\gamma_2)}\right)a_1(\gamma_1,\gamma_2) + h.o.t., a_1(\gamma_1,\gamma_2) > 0\right\}, \quad (88)$$

*and $\mu$ is a continuously differentiable function with $\mu(0) = 6b_2/7b_1$.*

Take the same parameter in last section, that is, $\sigma = 0.1181$, $\zeta = 0.0031$, $\delta = 0.3743$, and $\beta = 0.002$; then

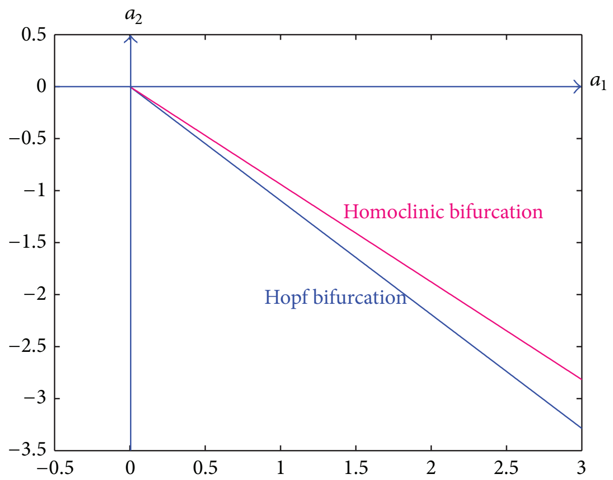


FIGURE 3: The bifurcation diagram of system (5) at the tumor-free equilibrium $P_0$.

the tumor-free equilibrium is $(0.3155, 0)$. From Theorem 9, we can obtain that the Hopf bifurcation curve is $a_2 = -1.0955a_1$ and the homoclinic bifurcation is $a_2 = -0.939a_1$. Then on $(a_1, a_2)$-parameter plane, the bifurcation diagram of system (5) at the equilibrium $P_0$ is in Figure 3.

## 4. Discussion

We have studied the nonlinear dynamics of Kuznetsov, Makalkin, and Taylor's model with delay, which is a two-dimensional model of tumor cells and immune system. We first provided linear analysis of the model with delays at the possible equilibria, namely, the tumor-free and positive equilibria, and discussed the existence of Hopf bifurcation at the equilibria. We investigated the Hopf bifurcation, Bogdanov-Takens bifurcation, and steady-state bifurcation in the model. Numerical simulations were presented to illustrate the theoretical analysis and results.

Our analysis on the existence and stability of the tumor-free equilibrium corresponds to this elimination process and on the existence and stability of the positive equilibrium corresponds to coexistence of the immune system and the tumor system. Our results on the existence and stability of the Hopf bifurcated periodic solutions of $P_2$ describe the equilibrium process. When a stable periodic orbit exists, it can be understood that the tumor and the immune system can coexist although the cancer is not eliminated. The conditions for the parameters provide theories basis to control the development or progression of the tumors. The phenomena have been observed in some models as d'Onofrio [5], Kuznetsov et al. [11], and Bi and Xiao [14]. In particular, Bi and Ruan [7] have shown that various bifurcations, including Hopf bifurcation, Bautin bifurcation, and Hopf-Hopf bifurcation, can occur in such models. Our results on the existence and stability of the bifurcated (Hopf, Bogdanov-Takens, and steady-state) periodic solutions describe rich dynamical behaviors of $P_0$, which show that the elimination process is so complex and difficult to control.

Finally, we should point out that we have studied the local dynamical behaviors of $P_0$ and $P_2$. As the example in our paper showed these two equilibria may coexist. Correspondingly, the system can exhibit more degenerate bifurcations including Hopf-Hopf and resonant higher codimension bifurcations. It would be interesting to consider these dynamics of the delayed model.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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## References


[1] P. Boyle, A. d'Onofrio, P. Maisonneuve et al., "Measuring progress against cancer in Europe: has the 15% decline targeted for 2000 come about?" *Annals of Oncology*, vol. 14, no. 8, pp. 1312–1325, 2003.

[2] D. Liu, S. Ruan, and D. Zhu, "Bifurcation analysis in models of tumor and immune system interactions," *Discrete and Continuous Dynamical Systems B*, vol. 12, no. 1, pp. 151–168, 2009.

[3] D. Liu, S. Ruan, and D. Zhu, "Stable periodic oscillations in a two-stage cancer model of tumor and immune system interactions," *Mathematical Biosciences and Engineering*, vol. 9, no. 2, pp. 347–368, 2012.

[4] R. Yafia, "Hopf bifurcation analysis and numerical simulations in an ODE model of the immune system with positive immune response," *Nonlinear Analysis. Real World Applications*, vol. 8, no. 5, pp. 1359–1369, 2007.

[5] A. d'Onofrio, "A general framework for modeling tumor-immune system competition and immunotherapy: mathematical analysis and biomedical inferences," *Physica D*, vol. 208, no. 3-4, pp. 220–235, 2005.

[6] A. d'Onofrio, "Tumor-immune system interaction: modeling the tumor-stimulated proliferation of effectors and immunotherapy," *Mathematical Models & Methods in Applied Sciences*, vol. 16, no. 8, pp. 1375–1401, 2006.

[7] P. Bi and S. Ruan, "Bifurcations in delay differential equations and applications to tumor and immune system interaction models," *SIAM Journal on Applied Dynamical Systems*, vol. 12, no. 4, pp. 1847–1888, 2013.

[8] R. Yafia, "Hopf bifurcation in differential equations with delay for tumor-immune system competition model," *SIAM Journal on Applied Mathematics*, vol. 67, no. 6, pp. 1693–1703, 2007.

[9] H. Mayer, K. S. Zaenker, and U. An Der Heiden, "A basic mathematical model of the immune response," *Chaos*, vol. 5, no. 1, pp. 155–161, 1995.

[10] R. Yafia, "Hopf bifurcation in a delayed model for tumor-immune system competition with negative immune response," *Discrete Dynamics in Nature and Society*, vol. 2006, Article ID 95296, 9 pages, 2006.

[11] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor, and A. S. Perelson, "Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis," *Bulletin of Mathematical Biology*, vol. 56, no. 2, pp. 295–321, 1994.

[12] M. Gałach, "Dynamics of the tumor-immune system competition—the effect of time delay," *International Journal of Applied Mathematics and Computer Science*, vol. 13, no. 3, pp. 395–406, 2003.

[13] A. L. Asachenkov, G. I. Marchuk, R. R. Mohler, and S. M. Zuev, "Immunology and disease control: a systems approach," *IEEE Transactions on Biomedical Engineering*, vol. 41, no. 10, pp. 943–953, 1994.

[14] P. Bi and H. Xiao, "Hopf bifurcation for tumor-immune competition systems with delay," *Electronic Journal of Differential Equations*, vol. 2014, no. 27, pp. 1–13, 2014.

[15] T. Faria and L. T. Magalhães, "Normal forms for retarded functional-differential equations and applications to Bogdanov-Takens singularity," *Journal of Differential Equations*, vol. 122, no. 2, pp. 201–224, 1995.

[16] T. Faria and L. T. Magalhães, "Normal forms for retarded functional-differential equations with parameters and applications to Hopf bifurcation," *Journal of Differential Equations*, vol. 122, no. 2, pp. 181–200, 1995.

[17] J. Hale, *Theory of Functional Differential Equations*, Springer, New York, NY, USA, 1977.

[18] Y. Xu and M. Huang, "Homoclinic orbits and Hopf bifurcations in delay differential systems with T-B singularity," *Journal of Differential Equations*, vol. 244, no. 3, pp. 582–598, 2008.

[19] S. N. Chow and J. K. Hale, *Methods of Bifurcation Theory*, Springer, New York, NY, USA, 1982.