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Bifurcations in Delay Differential Equations and Applications to Tumor and Immune System Interaction Models*

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Abstract. In this paper, we consider a two-dimensional delay differential system with two delays. By analyzing the distribution of eigenvalues, linear stability of the equilibria and existence of Hopf, Bautin, and Hopf–Hopf bifurcations are obtained in which the time delays are used as the bifurcation parameter. General formula for the direction, period, and stability of the bifurcated periodic solutions are given for codimension one and codimension two bifurcations, including Hopf bifurcation, Bautin bifurcation, and Hopf–Hopf bifurcation. As an application, we study the dynamical behaviors of a model describing the interaction between tumor cells and effector cells of the immune system. Numerical examples and simulations are presented to illustrate the obtained results.

Key words. delay differential equations, Hopf bifurcation, Bautin bifurcation, Hopf–Hopf bifurcation, tumor–immune system interaction

AMS subject classifications. 34K18, 34K60, 92C37

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1. Introduction.

One of the most important and challenging questions in immunology and cancer research is to understand how the immune system affects cancer development and progression (Schreiber, Old, and Smyth [42]). In the 1950s, based on an emerging understanding of the cellular basis of transplantation and tumor immunity, Burnet [4] and Thomas [45] predicted that lymphocytes were responsible for eliminating continuously arising nascent transformed cells and introduced the concept *cancer immunosurveillance*. Recent data on both mice and humans with cancer suggest that innate and adaptive immune cell types, effector molecules, and pathways can suppress tumor growth by destroying cancer cells or inhibiting their outgrowth. On the other hand, the immune system can also promote tumor progression either by selecting tumor cells that are more fit to survive in an immunocompetent host or by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth (Dunn, Old, and Schreiber [17], Pardoll [36], Schreiber, Old, and Smyth [42], Sotolongo-Costa et al. [43], Vesely et al. [46]). Together, the dual host-protective and tumor-promoting actions of immunity are referred to as *cancer immunoediting*, which has three processes: 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

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responses and grow into cancers) (Dunn et al. [16, 17], Koebel et al. [25], Schreiber, Old, and Smyth [42]).

The theoretical study of tumor–immune system interaction dynamics has a long history (Adam and Bellomo [1]). In an attempt to make the models closer to reality, more and more models have been developed (Arciero, Jackson, and Kirschner [2], de Pillis, Radunskaya, and Wiseman [10], Kirschner and Panetta [24], Kuznetsov et al. [26], Lejeune, Chaplaina, and Akili [28], Nani and Freedman [34], Owen and Sherratt [35]). We refer the reader to a recent survey by Eftimie, Bramson, and Earn [18] on spatially homogeneous mathematical models describing the interactions between a malignant tumor and the immune system. However, mathematical models for the interaction dynamics of the immune components with a target population are very idealized. It is almost impossible to construct realistic models due to the complexity of the processes involved; thus it is feasible to propose simple low dimensional models which are capable of displaying some of the essential immunological phenomena, in particular the two-dimensional ODE models for the interaction of tumor cells and effector cells of the immune system (d'Onofrio [11, 12, 13]). The basic modeling idea is to assume that effector cells attack tumor cells, and their proliferation is stimulated, in turn, by the presence of tumor cells. However, tumor cells also induce a loss of effector cells, and there is an influx of effector cells, whose intensity may depend on the size of the tumor.

Delayed responses cannot be ignored for the tumor–immune system interaction, just as Asachenkov et al. [3] and Mayer, Zaenker, and an der Heiden [32] pointed out that the delays should be taken into account to describe the times necessary for molecule production, proliferation, differentiation of cells, transport, etc. In fact, tumor–immune system interaction models with delay have been studied extensively; see Asachenkov et al. [3], Byrne [5], Byrne and Gourley [6], d'Onofrio and Gandolfi [14], d'Onofrio et al. [15], Galach [19], Liu, Hillen, and Freedman [31], Mayer, Zaenker, and an der Heiden [32], Piotrowska and Foryś [37], Rordriguez-Perez et al. [39], Villasana and Radunskaya [47], and the references cited therein.

In this article, based on the models of d'Onofrio et al. [15] and followed by Asacheukov et al. [3] and Mayer, Zaenker, and an der Heiden [32], we consider a delayed model of tumor–immune system interaction of the following form:

$$\begin{cases} x'(t) = x(t)[\nu(x(t-\tau)) - \phi(x(t), y(t))], \\ y'(t) = \beta(x(t-\rho))y(t) - \mu(x(t))y(t) + \sigma q(x(t)) + \theta(t), \end{cases} \tag{1.1}$$

where $x(t)$ and $y(t)$ are the density of tumor cells and immune effector cells at time t, respectively. τ and ρ are positive constants, and $\nu(x), \beta(x), \mu(x), q(x) \in C^r(\mathbb{R})$, $\phi(x,y) \in C^r(\mathbb{R}, \mathbb{R})$, $r \geq 5$, are interpreted as follows:

(i) $\nu(x)$ describes the relative baseline growth of tumor cells and satisfies $0 < \nu(0) \leq +\infty$, $\nu'(x) \leq 0$, and $\lim_{x\to 0^+} x\nu(x) = 0$, and in some relevant cases, we shall suppose that there exists a $0 < \bar{x} \leq +\infty$ such that $\nu(\bar{x}) = 0$. Prototype examples include the exponential growth $\nu(x) = k > 0$ (Wheldon [49]); the Gompertz growth $\nu(x) = k\ln(a/x)$ (Laird [27]); and the logistic growth $\nu(x) = k(1-(x/a)^n)$ (Marusic et al. [33]). We assume that there is a time delay $\tau \geq 0$ in the proliferation of tumor cells (Mayer, Zaenker, and an der Heiden [32], Byrne [5], d'Onofrio and Gandolfi [14]).

(ii) $\phi(x,y)$ models the loss rate of tumor cells due to the attack by effector cells of the immune system and satisfies $\phi(x,0) = 0$, $\phi(0,y) > 0$, $\partial_x\phi(x,y) \leq 0$, and $\partial_y\phi(x,y) > 0$.

An example is the Beddington–DeAngelis function $\phi(x,y) = \frac{ay}{1+bx+cy}$ (Huisman and De Boer [23] and d'Onofrio [11]), where a is the rate or possibility of successful removal of tumor cells by immunity effector cells, $1/b$ is a saturation constant, and c scales the impact of the immune response.

(iii) $\beta(x)$ represents the tumor-stimulated proliferation rate of the effector cells and satisfies $\beta(x) \geq 0$, $\beta(0) = 0$, and $\beta'(x) \geq 0$. The Michaelis–Menten–Monod function $\beta(x) = \frac{ax}{m+x}$ has been used (Kuznetsov et al. [26]). A time delay $\rho \geq 0$ is introduced into $\beta(x)$ to reflect the process of effector cell growth with respect to stimulus by the tumor cell growth (d'Onofrio et al. [15]).

(iv) The term $\sigma q(x) > 0$ describes the influx of effector cells of the immune system in the tumor in situ, which may depend on the tumor size. It is assumed that $q(0) = 1$ and $q'(x) < 0$ for $x \gg 1$ (d'Onofrio et al. [15]).

(v) $\mu(x)$ is the loss rate of immune effector cells due to the interaction with tumor cells and satisfies $\mu(x) > 0, \mu'(x) > 0$ (d'Onofrio et al. [15]).

(vi) $\theta(t) \geq 0$ models the effect of immunotherapy, which could be periodic, constant, or zero (in the absence of immunotherapy). In this paper, we consider only constant immunotherapy (that is, $\theta(t) = \theta_0$, where θ_0 is the nonnegative constant) or no immunotherapy (that is, $\theta(t) = 0$).

We can see that model (1.1) with $\phi(x,y) = \phi(x)\pi(y)$ and $\tau = \rho = 0$ reduces to the model considered by d'Onofrio [11, 12, 13] who studied the local stability of the equilibria and the uniqueness of stable limit cycles. When $\tau = 0$, $\rho \neq 0$, model (1.1) becomes the delay model proposed in d'Onofrio et al. [15], in which the stability of equilibria and the onset of sustained oscillations through Hopf bifurcations was investigated. Model (1.1) can be regarded as an extension of the models of d'Onofrio [11, 12, 13], d'Onofrio et al. [15], and Mayer, Zaenker, and an der Heiden et al. [32].

In order to study the nonlinear dynamics of model (1.1), in this paper we first consider a general two-dimensional delay differential system with two delays,

$$\begin{cases} x'(t) = f(x(t), x(t-\tau), y(t)), \\ y'(t) = g(x(t), x(t-\rho), y(t)), \end{cases} \tag{1.2}$$

where $x(t), y(t)$ are scalar variables, $f, g \in C^r(\mathbb{R}^3, \mathbb{R}), r \geq 3$, with $f(0,x,y) = 0$ and $g(x,x,0) \geq 0$. From the biological point of view, we will focus on the dynamical behaviors of (1.2) in the domain $D = \{(x,y) \in \mathbb{R}^2 | x \geq 0, y \geq 0\}$. We will study the local stability of the equilibria, the existence of Hopf bifurcation, Bautin bifurcation, and Hopf–Hopf bifurcation for system (1.2) and provide detailed calculations for the normal form of the Hopf bifurcation and Hopf–Hopf bifurcation. Then we will apply these results to the tumor–immune response interaction model (1.1).

The rest of this paper is organized as follows. In section 2, for the general delay differential system (1.2), the linear analysis will be carried out, and local stability of the equilibria and the existence of Hopf bifurcation, Bautin bifurcation, and Hopf–Hopf bifurcation will be studied. Detailed calculations for the normal form of the Hopf bifurcation and Hopf–Hopf bifurcation will be given. In section 3, all theories will be used to study the dynamical behaviors of the tumor–immune system interaction model (1.1). In section 4, we summarize the methods and conclusions and make some remarks about more general results on degenerated bifurcations.

2. Bifurcations in the general delay differential equations.

In this section, we study the local stability of the equilibria and the existence of Hopf bifurcation, Bautin bifurcation, and Hopf–Hopf bifurcation in the general delay differential system (1.2) and give detailed calculations for the normal form of the Hopf bifurcation and Hopf–Hopf bifurcation.

2.1. Local analysis.

In this subsection, we provide some local analysis for system (1.2) in the domain D. It has three types of equilibria.

(1) Semitrivial ($x(t)$-absence) equilibrium $E_1(0, y_1)$ with $f(0, 0, y_1) = g(0, 0, y_1) = 0$.

(2) Positive equilibria $E_2^k(x_2^k, y_2^k)$ ($x_2^k, y_2^k \neq 0,\ k \in Z$), which are the intersecting points of the nullclines $f(x_2^k, x_2^k, y_2^k) = g(x_2^k, x_2^k, y_2^k) = 0$ with $x_2^k y_2^k \neq 0$.

(3) Semitrivial ($y(t)$-absence) equilibrium $E_3(x_3, 0)$, where x_3 satisfies $f(x_3, x_3, 0) = g(x_3, x_3, 0) = 0$.

Let (x_i, y_i) be the coordinates of the equilibrium $E_i, i = 1, 2, 3$. The linearizing system of (1.2) at the equilibrium is

$$\begin{cases} x'(t) = a_{11}x(t-\tau) + a_{12}x(t) + a_{13}y(t), \\ y'(t) = a_{21}x(t-\rho) + a_{22}x(t) + a_{23}y(t), \end{cases} \tag{2.1}$$

where

$$\begin{cases} a_{11} = \dfrac{\partial f(x_i, x_i, y_i)}{\partial x(t-\tau)}, & a_{12} = \dfrac{\partial f(x_i, x_i, y_i)}{\partial x(t)}, \\ a_{13} = \dfrac{\partial f(x_i, x_i, y_i)}{\partial y(t)}, & a_{21} = \dfrac{\partial g(x_i, x_i, y_i)}{\partial x(t-\rho)}, \\ a_{22} = \dfrac{\partial g(x_i, x_i, y_i)}{\partial x(t)}, & a_{23} = \dfrac{\partial g(x_i, x_i, y_i)}{\partial y(t)}. \end{cases} \tag{2.2}$$

It is obvious that the stability of E_i depends on the distribution of characteristic roots of (2.1). The characteristic equation of (2.1) is

$$\lambda^2 + A_1\lambda + A_2 + (B_1\lambda + B_{21})e^{-\lambda\tau} + B_{22}e^{-\lambda\rho} = 0, \tag{2.3}$$

where

$$\begin{aligned} &A_1 = -a_{12} - a_{23}, \quad A_2 = a_{12}a_{23} - a_{13}a_{22}, \\ &B_1 = -a_{11}, \quad B_{21} = a_{11}a_{23}, \quad B_{22} = -a_{13}a_{21}. \end{aligned}$$

We now study the distribution of the roots of the transcendental equation (2.3) in two cases, that is, $\tau = \rho$ and $\tau \neq \rho$. We will give the local analysis in the following two cases.

2.1.1. Equal delays $\tau = \rho$.

In this case, the characteristic equation (2.3) becomes

$$\lambda^2 + A_1\lambda + A_2 + (B_1\lambda + B_2)e^{-\lambda\tau} = 0, \tag{2.4}$$

where $B_2 = B_{21} + B_{22} = a_{13}a_{21} - a_{11}a_{23} \geq 0$. Analyzing the distribution of eigenvalues, we obtain the following results.

Lemma 2.1. (1) *If*

$$A_1 + B_1 > 0, \qquad A_2 + B_2 > 0, \tag{2.5}$$

and

$$B_1^2 - A_1^2 + 2A_2 < 0, \quad A_2^2 - B_2^2 > 0 \ \text{ or } \ (B_1^2 - A_1^2 + 2A_2)^2 < 4(A_2^2 - B_2^2), \tag{2.6}$$

then all roots of (2.4) *have negative real parts for all* $\tau \geq 0$.

(2) *If*

$$A_2^2 - B_2^2 < 0 \ \text{ or } \ B_1^2 - A_1^2 + 2A_2 > 0 \ \text{ and } \ (B_1^2 - A_1^2 + 2A_2)^2 = 4(A_2^2 - B_2^2), \tag{2.7}$$

then (2.4) *has a pair of purely imaginary roots* $\pm i\omega_+$ *at* $\tau = \tau_j^+$.

(3) *If*

$$B_1^2 - A_1^2 + 2A_2 > 0, \quad A_2^2 - B_2^2 > 0, \ \text{ and } \ (B_1^2 - A_1^2 + 2A_2)^2 > 4(A_2^2 - B_2^2), \tag{2.8}$$

then (2.4) *has a pair of purely imaginary roots* $\pm i\omega_+$ *(*$\pm i\omega_-$*, respectively) at* $\tau = \tau_j^+$ *(*$\tau = \tau_j^-$*, respectively), where*

$$\omega_\pm^2 = \frac{1}{2}(B_1^2 - A_1^2) + A_2 \pm \sqrt{\frac{(B_1^2 - A_1^2)^2}{4} + A_2(B_1^2 - A_1^2) + B_2^2} \tag{2.9}$$

and

$$\tau_j^\pm = \begin{cases} \frac{1}{\omega_\pm}\left(2j\pi + \arccos\left\{\frac{(B_2 - A_1B_1)\omega_\pm^2 - B_2A_2}{B_1^2\omega_\pm^2 \pm B_2^2}\right\}\right) & \text{if } B_2A_1 + B_1(\omega_\pm^2 - A_2) > 0, \\ \frac{1}{\omega_\pm}\left((2j+1)\pi - \arccos\left\{\frac{(B_2 - A_1B_1)\omega_\pm^2 - B_2A_2}{B_1^2\omega_\pm^2 \pm B_2^2}\right\}\right) & \text{if } B_2A_1 + B_1(\omega_\pm^2 - A_2) < 0. \end{cases} \tag{2.10}$$

Let

$$F(\lambda_\pm, \tau) = \lambda^2 + A_1\lambda + A_2 + e^{-\lambda\tau}(B_1\lambda + B_2).$$

Noting that $F(i\omega_\pm, \tau_0) = 0$, it is easy to prove that $i\omega$ is not a root of $F'_\tau(\lambda, \tau) = 0$. The following result can be obtained from the implicit function theorem.

Theorem 2.2. *Assume that* (2.7) *or* (2.8) *holds; then we have the following conclusions.*

(i) *The characteristic function* $F(\lambda, \tau)$ *is continuously differentiable with respect to* τ.

(ii) *There exist a constant* $\delta > 0$ *and a smooth curve* $\lambda(\tau) : (\tau_0^\pm - \delta, \tau_0^\pm + \delta) \to \mathbb{C}$ *such that* $\lambda(\tau_0^\pm) = i\omega_\pm$ *and* $F(i\omega_\pm, \tau_0^\pm) = 0$ *for all* $\tau \in (\tau_0^\pm - \delta, \tau_0^\pm + \delta)$. *Moreover,* $\frac{d}{d\tau}\mathrm{Re}\lambda(\tau)|_{\tau=\tau_0^\pm} > 0$.

In fact, if the characteristic roots of (2.4)

$$\lambda_j^\pm = \alpha_j^\pm(\tau) + i\omega_j^\pm(\tau), \qquad j = 0, 1, 2\ldots, \tag{2.11}$$

satisfy $\alpha_j^\pm(\tau_j^\pm) = 0, \ \omega_j^\pm(\tau_j^\pm) = \omega_\pm$, then a pair of complex roots crosses the imaginary axis and

$$\begin{aligned} \left(\frac{d\mathrm{Re}\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau=\tau_j^\pm} &= \frac{2\lambda + A_1 + B_1e^{-\lambda\tau}}{\lambda e^{-\lambda\tau}(B_1\lambda + B_2)}\Big|_{\tau=\tau_j^\pm} \\ &= \begin{cases} \frac{1}{2}\left((B_1^2 - A_1^2 + 2A_2)^2 - 4(A_2^2 - B_2^2)\right)^{1/2} > 0, & \tau = \tau_j^+, \\ -\frac{1}{2}\left((B_1^2 - A_1^2 + 2A_2)^2 - 4(A_2^2 - B_2^2)\right)^{1/2} < 0, & \tau = \tau_j^-. \end{cases} \end{aligned} \tag{2.12}$$

It follows that $\tau_j^{\pm}$ are bifurcation values. Thus we have the following results on the distribution of the characteristic roots of (2.4).

Theorem 2.3. *Let* (2.5) *hold and* $\tau_j^{\pm}$ $(j = 1, 2 \dots)$ *be defined by* (2.10).

(i) *If* (2.6) *holds, then all roots of* (2.4) *have negative real parts for all* $\tau \geq 0$.

(ii) *If* (2.7) *holds, then all roots of* (2.4) *have negative real parts as* $\tau \in [0, \tau_0^+)$; (2.4) *has a pair of purely imaginary roots as* $\tau = \tau_0^+$; *and* (2.4) *has at least one root with positive real part as* $\tau > \tau_0^+$;

(iii) *If* (2.8) *holds, then there is a positive integer* k *such that the sign of the real part* $\alpha(\tau)$ *switches* k *times from negative to positive and then to negative; that is, when*

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

all roots of (2.4) *have negative real parts, and when*

$$\tau \in [\tau_0^+, \tau_1^-) \cup [\tau_1^+, \tau_2^-) \cup \cdots \cup [\tau_{k-1}^+, \tau_k^-) \qquad \text{and} \quad \tau > \tau_k^+,$$

(2.4) *has at least one root with positive real part.*

Correspondingly, we have the following results on the stability of the positive equilibrium $E_2(x_2, y_2)$.

Theorem 2.4. *Assume* (2.5) *holds and* $\tau_j^{\pm}$ $(j = 1, 2 \dots)$ *are defined by* (2.10).

(i) *If* (2.6) *holds, then the positive equilibrium* $E_2(x_2, y_2)$ *of* (1.2) *is asymptotically stable for all* $\tau \geq 0$.

(ii) *If* (2.7) *holds, then* $E_2(x_2, y_2)$ *is stable for* $\tau \in (0, \tau_0^+)$ *and unstable for* $\tau > \tau_0^+$.

(iii) *If* (2.8) *holds, then there is a positive integer* k *such that* $E_2(x_2, y_2)$ *is stable for*

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

and unstable for

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

(iv) *If* $A_2^2 < B_2^2$, *then system* (1.2) *undergoes Hopf bifurcation at* $E_2(x_2, y_2)$ *as* $\tau = \tau_k^+$ *such that* $\tau_k \neq \tau_l$ *for any nonnegative integer* $k \neq l$.

Remark 2.5. Results similar to those in Theorems 2.2–2.4 have been obtained in Cooke and Grossman [9], Ruan [40] and Ruan and Wei [41].

Noting (2.3), we know that B_2 is the constant coefficient of $e^{-\lambda\tau}$, which is critical in affecting the dynamical behaviors of (1.2). Thus we chose B_2 and τ as parameters to determine the stability regions of the positive equilibrium E_2.

If $B_2 = 0$, we know that the stability regions of the positive equilibrium E_2 are

(1) $A_1 > B_1, \quad A_2 > 0, \ \tau > 0;$

(2) $A_1 = B_1, \quad A_2 > 0, \quad \tau < \tau_0^+;$

(3) $B_1 > |A_1|, \quad A_2 > 0, \quad \tau \in [0, \tau_0^+) \cup [\tau_0^-, \tau_1^+) \cup \cdots \cup [\tau_{k-1}^-, \tau_k^+),$

where

$$\tau_j^{\pm} = \begin{cases} \frac{1}{\omega_\pm}\left(2j\pi + \arccos\{\frac{-A_1}{B_1}\}\right), & A_2 - \omega_\pm^2 < 0, \\[2ex] \frac{1}{\omega_\pm}\left((2j+1)\pi - \arccos\{\frac{-A_1}{B_1}\}\right), & A_2 - \omega_\pm^2 > 0. \end{cases} \tag{2.13}$$

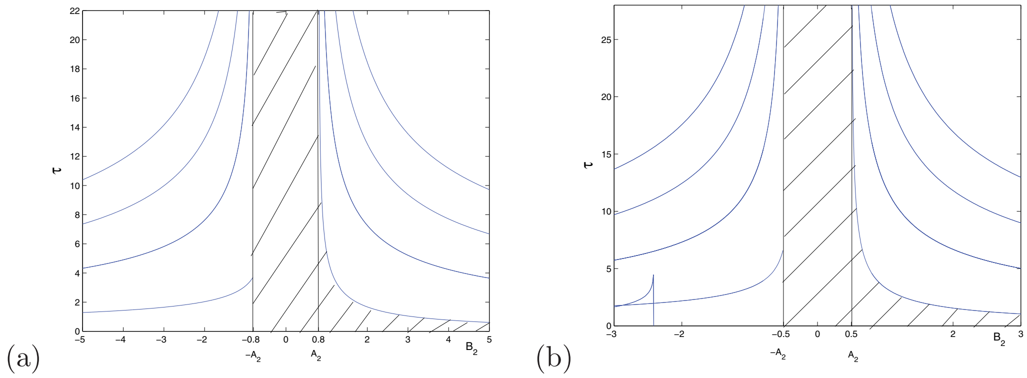


Figure 1. *The stability regions.* (a) *For case* (i) *in* (2.15) *with* $A_1 = 2, A_2 = 0.8,$ *and* $B_1 = 1$. (b) *For case* (ii) *in* (2.14) *with* $A_1 = 2, A_2 = 0.5,$ *and* $B_1 = \sqrt{2}$, *where the blue curves represent* $\tau_{1j}^{+}, i = 0, 1, 2, \dots,$ *from bottom to top.*

For fixed $\tau > 0$, E_2 will remain stable for $B_2 \neq 0$ until B_2 reaches a value for which one of the corresponding characteristic roots has zero real part, which occurs as $B_2 = -A_2$ (corresponding to the zero root) or a pair of complex eigenvalues crosses the imaginary axis ($\tau = \tau_j^{\pm}$). In the following, we will consider the stable region in terms of parameters B_2 and τ.

(a) If $A_1 > B_1$, recalling (2.9), we have $B_2^2 = \omega_+^4 + (A_1^2 - B_1^2 - 2A_2)\omega_+^2 + A_2^2$; then B_2^2 is an increasing function of ω_+. Note that $\lim_{\omega \to 0} B_2^2 = A_2^2$, if B_2 increases from 0; then the stability regions are given by

$$\text{(2.14)} \qquad \begin{array}{ll} \text{(i)}\ -|A_2| < B_2 < |A_2|, & \tau > 0, \\ \text{(ii)}\ B_2 > |A_2|, \quad B_2 A_1 + B_1(\omega_\pm^2 - A_2) > 0, & \tau < \tau_{10}^{+}. \end{array}$$

The stable regions are illustrated by the shadowed areas bounded by the dashed curves in Figure 1.

(2) For $A_1 \leq B_1$, if B_2 varies from 0, then the stability region is when B_2 reaches A_2 or $\tau = \tau_k^{\pm}$—whichever occurs first; that is,

$$\text{(2.15)} \qquad \begin{array}{lll} \text{(i)}\ B_2 > |A_2|, & B_2 A_1 + B_1(\omega_\pm^2 - A_2) > 0, & \tau < \tau_{10}^{+}, \\ \text{(ii)}\ -|A_2| < B_2 < |A_2|, & \tau_{2j}^{-} < \tau < \tau_{1(j+1)}^{+}. & \end{array}$$

This regions are illustrated by the shadowed areas bounded by the dashed curves in Figure 2.

(3) From the expressions of $\omega_\pm$, we still need to consider the case $A_1^2 - 2A_2 < B_1^2 < A_1^2$, $A_1 > 0$. The stability region is when B_2 reaches A_2 or $\tau = \tau_k^{\pm}$—whichever occurs first. If B_2 increases from 0, the stability regions can be given by

$$\text{(2.16)} \qquad \begin{array}{ll} \text{(i)}\ -|B^*| < B_2 < |B^*|, & \tau > 0, \\ \text{(ii)}\ -|A_2| < B_2 < -|B^*|, & 0 < \tau < \tau_{20}^{+},\ \tau_{2j}^{-} < \tau < \tau_{2(j+1)}^{+}, \\ \text{(iii)}\ |B^*| < B_2 < |A_2|, & 0 < \tau < \tau_{10}^{+},\ \tau_{1j}^{-} < \tau < \tau_{1j}^{+}, \end{array}$$

where $B^* = \sqrt{(A_1^2 - B_1^2)(A_2 - \frac{A_1^2 - B_1^2}{4})}$. Let $A_1 = 2, A_2 = 1$, and $B_1 = \sqrt{3}$; then $B^* = \frac{\sqrt{3}}{2}$. Choose the other parameters as $A_1 = 2, A_2 = 1.5$, and $B_1 = 1.5$; then $B^* \doteq 1.36359$, and the stable regions are the shadowed areas bounded by the dashed curves in Figure 3.

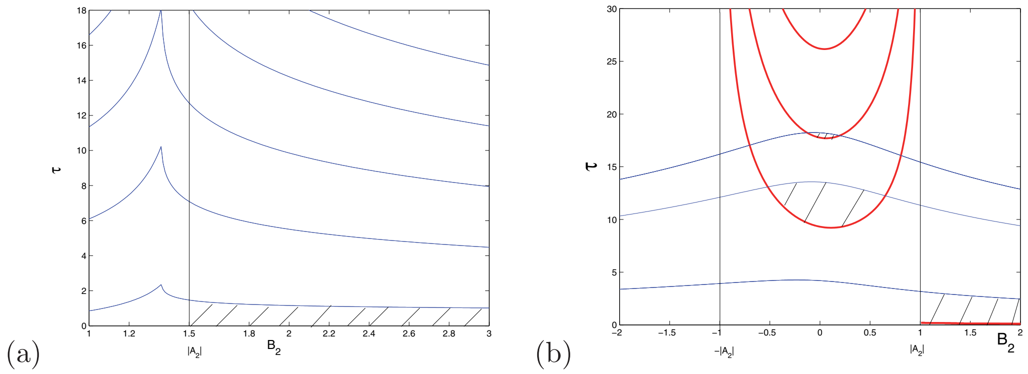


Figure 2. *The stability regions.* (a) $A_1 = 1, A_2 = 1.5,\ B_1 = 1$. (b) $A_1 = 0.8, A_2 = 1,\ B_1 = 1$. *In* (a) *the blue curves represent* $\tau_{1j}^{+}, i = 0, 1, 2, \ldots,$ *from bottom to top. In* (b) *the blue curves represent* $\tau_{1j}^{+},\ i = 0, 1, 2\ldots,$ *and the red curves represent* $\tau_{2j}^{-},\ i = 0, 1, 2, \ldots,$ *from bottom to top.*

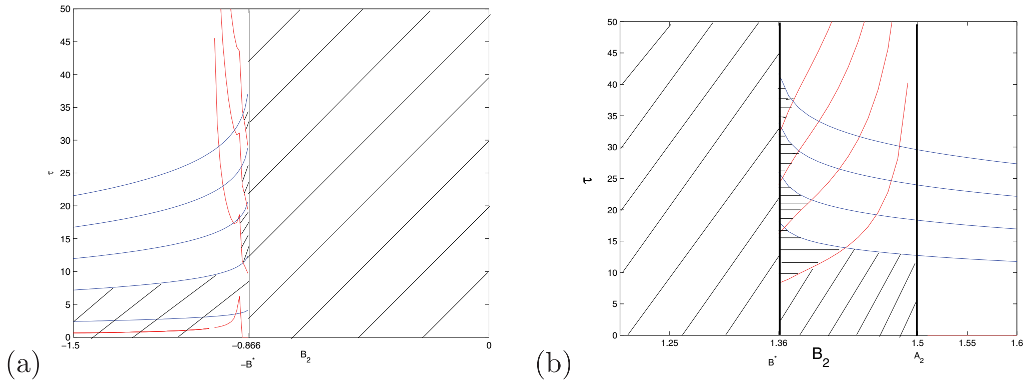


Figure 3. *The stability regions.* (a) *For cases* (i)–(ii) *in* (2.16). (b) *For case* (iii) *in* (2.16). *In* (a) *the blue curves represent* $\tau_{2j}^{+},\ i = 0, 1, 2\ldots,$ *and the red curves represent* $\tau_{2j}^{-},\ i = 0, 1, 2, \ldots,$ *from bottom to top. In* (b) *the blue curves represent* $\tau_{1j}^{+},\ i = 0, 1, 2\ldots,$ *and the red curves represent* $\tau_{1j}^{-},\ i = 0, 1, 2, \ldots,$ *from bottom to top.*

The only point that may have significant influence on the dynamical behaviors is when $j = 0$, which is on the border of the stability region of the equilibrium point. Further results will be given in the following sections.

2.1.2. Distinct delays $\tau \neq \rho$. To study the characteristic equation (2.3) with two delays, we use a technique developed in Wei and Ruan [48]. Namely, we first let $\rho = 0$ and analyze the characteristic equation with one delay τ. As in the previous subsection, we can obtain sufficient conditions for all eigenvalues having negative real parts either for all $\tau \geq 0$ or when $\tau \in [0, \tau_0)$, where τ_0 is the first bifurcation value. Then we fix τ^*, in either $[0, \infty)$ or $[0, \tau_0)$, and consider the characteristic equation (2.3) regarding ρ as a bifurcation value. Once again, we can find a critical value $\rho_0(\tau^*) > 0$ such that the real parts of all eigenvalues are still negative when $\rho \in [0, \rho_0(\tau^*))$. Therefore, we can obtain sufficient conditions such that the positive equilibrium of system (1.2) with two delays is asymptotically stable when either $\tau \in [0, \infty)$ and $\rho \in [0, \rho_0(\tau^*))$ or $\tau \in [0, \tau_0)$ and $\rho \in [0, \rho_0(\tau^*))$.

Case (a) $\tau \geq 0$ *and* $\rho = 0$. In this case, the characteristic equation (2.3) reduces to

$$\lambda^2 + A_1\lambda + (A_2 + B_{22}) + (B_1\lambda + B_{21})e^{-\lambda\tau} = 0. \tag{2.17}$$

Following the analysis of (2.4) in the previous subsection, we obtain the following results.

Lemma 2.6. *Let* (2.5) *hold.*

(i) *If*

$$\begin{aligned} &B_1^2 - A_1^2 + 2(A_2 + B_{22}) < 0, \quad (A_2 + B_{22})^2 - B_{21}^2 > 0, \\ &\textit{or} \quad (B_1^2 - A_1^2 + 2(A_2 + B_{22}))^2 < 4((A_2 + B_{22})^2 - B_{21}^2), \end{aligned} \tag{2.18}$$

then all roots of (2.17) *have negative real parts for all* $\tau \in [0, \infty)$.

(ii) *If*

$$\begin{aligned} &(A_2 + B_{22})^2 - B_{21}^2 < 0 \quad \textit{or} \quad B_1^2 - A_1^2 + 2(A_2 + B_{22}) > 0 \\ &\textit{and} \quad (B_1^2 - A_1^2 + 2(A_2 + B_{22}))^2 = 4((A_2 + B_{22})^2 - B_{21}^2), \end{aligned} \tag{2.19}$$

then all roots of (2.17) *have negative real parts when* $\tau \in [0, \tau_0)$, *where*

(2.20)

$$\tau_0 = \begin{cases} \frac{1}{\omega_+} \arccos\left\{\frac{(B_{21} - A_1B_1)\omega_+^2 - B_{21}(A_2 + B_{22})}{B_1^2\omega_+^2 \pm B_{21}^2}\right\} & \textit{if } B_{21}A_1 + B_1(\omega_+^2 - A_2 - B_{22}) > 0, \\ -\frac{1}{\omega_+} \arccos\left\{\frac{(B_{21} - A_1B_1)\omega_+^2 - B_{21}(A_2 + B_{22})}{B_1^2\omega_+^2 \pm B_{21}^2}\right\} & \textit{if } B_{21}A_1 + B_1(\omega_+^2 - A_2 - B_{22}) < 0, \end{cases}$$

and

(2.21)

$$\omega_+^2 = \frac{1}{2}(B_1^2 - A_1^2) + (A_2 + B_{22}) + \sqrt{\frac{(B_1^2 - A_1^2)^2}{4} + (A_2 + B_{22})(B_1^2 - A_1^2) + B_{21}^2}.$$

Case (b) $\tau \geq 0$ *and* $\rho \geq 0$. We assume that the conditions in Lemma 2.1 are satisfied. Fix $\tau^* \in [0, \infty)$ if (2.18) holds or $\tau^* \in [0, \tau_0)$ if (2.19) holds. Then the characteristic equation (2.3) can be written as

$$\lambda^2 + (A_1 + B_1e^{-\lambda\tau^*})\lambda + (A_2 + B_{21}e^{-\lambda\tau^*}) + B_{22}e^{-\lambda\rho} = 0. \tag{2.22}$$

Next, we consider (2.17) with τ in its stable intervals. Take ρ as a parameter; then we have the following lemma.

Lemma 2.7. *If* $\tau^* \in [0, \tau_0)$, *then there exists a* $\rho_0(\tau^*) > 0$, *such that all roots of* (2.22) *have negative real parts when* $\rho \in [0, \rho_0(\tau^*))$.

Summarizing the above analysis, we can obtain some conditions, to ensure that all roots of the characteristic equation (2.3) with two delays have negative real parts, which imply the asymptotic stability of the positive equilibrium of system (1.2). That is, we have the following results.

Theorem 2.8. *Let* (2.5) *hold.*

(i) *If* (2.18) *holds, then for any* $\tau^* > 0$ *there exists a* $\rho_0(\tau^*) > 0$ *such that the positive equilibrium* $E_2(x_2, y_2)$ *of system* (1.2) *is asymptotically stable for* $\rho \in [0, \rho_0(\tau^*))$.

(ii) *If* (2.19) *holds, then for any* $\tau^* \in [0, \tau_0)$ *there exists a* $\rho_0(\tau^*) > 0$ *such that the positive equilibrium* $E_2(x_2, y_2)$ *of system* (1.2) *is asymptotically stable for* $\rho \in [0, \rho_0(\tau^*))$.

2.2. Codimension one bifurcations. In this subsection, for the sake of simplicity we consider system (1.2) with equal delay ($\tau = \rho$). We shall study codimension one bifurcations of the positive equilibrium E_2, including Hopf bifurcation and Bautin bifurcation. The other equilibria can be studied similarly, and so we omit them here.

2.2.1. Hopf bifurcation. In the previous subsection, we obtained conditions under which a family of periodic solutions bifurcated from the positive equilibrium E_2 at critical values τ_k. As pointed out in Hassard, Kazarinoff, and Wan [22], it is interesting and important to determine the direction, stability, and period of these bifurcated periodic solutions. We will derive explicit formulae determining these factors at critical values τ_k using the normal form and the center manifold theory in Hassard, Kazarinoff, and Wan [22]. In this section, we always assume that (2.7) holds, and $\pm i\omega$ are the only purely imaginary roots, where $\omega = \omega_+$.

Let $a = \tau - \tau_k$. Then $a = 0$ is a Hopf bifurcation value of (1.2) with $\tau = \rho$. Set $\bar{t} = \tau t$, $\bar{y} = y - y_2$, and $\bar{x} = x - x_2$, dropping the bars; then (1.2) can be written as a functional differential equation in $\mathcal{C} = C([-1, 0), \mathbb{R}^2)$ as

$$x'(t) = L_a(x_t) + R(a, x_t), \tag{2.23}$$

where $x(t) = (x_1, x_2)^T \in \mathbb{R}^2$, $L_a : \mathcal{C} \to \mathbb{R}$, $R : \mathbb{R} \times \mathcal{C} \to \mathbb{R}$ are given by

$$L_a(\phi) = (\tau_k + a)\begin{pmatrix} -a_{12} & -a_{13} \\ a_{22} & a_{23} \end{pmatrix}\begin{pmatrix} \phi_1(0) \\ \phi_2(0) \end{pmatrix} + (\tau_k + a)\begin{pmatrix} a_{11} & 0 \\ a_{21} & 0 \end{pmatrix}\begin{pmatrix} \phi_1(-1) \\ \phi_2(-1) \end{pmatrix},$$

(2.24)

$$\begin{aligned}
R(a, \phi) = (\tau_k + a)\big[&D_1(\phi_1^2(0), \phi_1(0)\phi_2(0), \phi_2^2(0))^T \\
&+ D_2(\phi_1^2(-1), \phi_1(0)\phi_1(-1), \phi_2(0)\phi_1(-1))^T \\
&+ E_1(\phi_1^3(0), \phi_1^2(0)\phi_2(0), \phi_1(0)\phi_2^2(0), \phi_2^3(0))^T \\
&+ E_2(\phi_1^3(-1), \phi_1(0)\phi_1^2(-1), \phi_2(0)\phi_1^2(-1), \\
&\quad \phi_1^2(0)\phi_1(-1), \phi_2^2(0)\phi_1(-1), \phi_2(0)\phi_2(0)\phi_1(-1))^T \\
&+ F_1(\phi_1^4(0), \phi_1^3(0)\phi_2(0), \phi_1^2(0)\phi_2^2(0), \phi_1(0)\phi_2^3(0), \phi_2^4(0))^T \\
&+ F_2(\phi_1^4(-1), \phi_1^3(-1)\phi_1(0), \phi_1^3(-1)\phi_2(0), \phi_1^2(-1)\phi_1^2(0), \phi_1^2(-1)\phi_2^2(0), \\
&\quad \phi_1^2(-1)\phi_1(0)\phi_2(0), \phi_1(-1)\phi_1^3(0), \phi_1(-1)\phi_2^3(0), \\
&\quad \phi_1(-1)\phi_1^2(0)\phi_2(0), \phi_1(-1)\phi_1(0)\phi_2^2(0))^T \\
&+ H_1(\phi_1^5(0), \phi_1^4(0)\phi_2(0), \phi_1^3(0)\phi_2^2(0), \phi_1^2(0)\phi_2^3(0), \phi_1(0)\phi_2^4(0), \phi_2^5(0))^T \\
&+ H_2(\phi_1^5(-1), \phi_1^4(-1)\phi_1(0), \phi_1^4(-1)\phi_2(0), \phi_1^3(-1)\phi_1^2(0), \\
&\quad \phi_1^3(-1)\phi_2^2(0), \phi_1^3(-1)\phi_1(0)\phi_2(0), \\
&\phi_1^2(-1)\phi_1^3(0), \phi_1^2(-1)\phi_1^2(0)\phi_2(0), \phi_1^2(-1)\phi_1(0)\phi_2^2(0), \phi_1^2(-1)\phi_2^3(0), \phi_1(-1)\phi_1^4(0), \\
&\phi_1(-1)\phi_1^3(0)\phi_2(0), \phi_1(-1)\phi_1^2(0)\phi_2^2(0), \phi_1(-1)\phi_1(0)\phi_2^3(0), \phi_1(-1)\phi_2^4(0))^T\big],
\end{aligned}$$

$$D_1 = \begin{pmatrix} f_{22}, & f_{23}, & f_{33} \\ g_{22}, & g_{23}, & g_{33} \end{pmatrix}, \qquad D_2 = \begin{pmatrix} f_{11}, & f_{12}, & f_{13} \\ g_{11}, & g_{12}, & g_{13} \end{pmatrix},$$

$$E_1 = \begin{pmatrix} f_{222}, & f_{223}, & f_{233}, & f_{333} \\ g_{222}, & g_{223}, & g_{233}, & g_{333} \end{pmatrix}, \qquad E_2 = \begin{pmatrix} f_{111}, & f_{112}, & f_{113}, & f_{122}, & f_{133}, & f_{123} \\ g_{111}, & g_{112}, & g_{113}, & g_{122}, & g_{133}, & g_{123} \end{pmatrix},$$

$$F_1 = \begin{pmatrix} f_{2222}, & f_{2223}, & f_{2233}, & f_{2333}, & f_{3333} \\ g_{2222}, & g_{2223}, & g_{2233}, & g_{2333}, & g_{3333} \end{pmatrix},$$

$$F_2 = \begin{pmatrix} f_{1111}, & f_{1112}, & f_{1113}, & f_{1122}, & f_{1133}, & f_{1123}, & f_{1222}, & f_{1223}, & f_{1233}, & f_{1333} \\ g_{1111}, & g_{1112}, & g_{1113}, & g_{1122}, & g_{1133}, & g_{1123}, & g_{1222}, & g_{1223}, & g_{1233}, & g_{1333} \end{pmatrix},$$

$$H_1 = \begin{pmatrix} f_{22222}, & f_{22223}, & f_{22233}, & f_{22333}, & f_{33333} \\ g_{22222}, & g_{22223}, & g_{22233}, & g_{22333}, & g_{33333} \end{pmatrix},$$

$$H_2 = \left(\begin{matrix} f_{11111}, & f_{11112}, & f_{11113}, & f_{11122}, & f_{11133}, & f_{11123}, & f_{11222}, & f_{11223}, & f_{11233}, & f_{11333}, \\ g_{11111}, & g_{11112}, & g_{11113}, & g_{11122}, & g_{11133}, & g_{11123}, & g_{11222}, & g_{11223}, & g_{11233}, & g_{11333}, \\ f_{12222}, & f_{12223}, & f_{12233}, & f_{12333}, & f_{13333} \\ g_{12222}, & g_{12223}, & g_{12233}, & g_{12333}, & g_{13333} \end{matrix} \right).$$

By the Riesz representation theorem, there exists a bounded variation matrix $\eta(\theta, a)$ whose components are functions of bounded variation in $\theta \in [-\tau_0, 0]$ such that

$$L_a\phi = \int_{-1}^{0} d\eta(\theta, 0)\phi(\theta) \quad \text{for} \quad \phi \in \mathcal{C}. \tag{2.25}$$

For $\varphi \in C^1([-1, 0], R^3)$, define

$$A(a)\varphi = \begin{cases} \frac{d\varphi}{d\theta}, & \theta \in [-1, 0), \\ \int_{-1}^{0} d\eta(a, s)\varphi(s), & \theta = 0, \end{cases} \quad \text{and} \quad R(a)\varphi = \begin{cases} 0, & \theta \in [-1, 0), \\ R(a, \varphi), & \theta = 0. \end{cases}$$

Then (2.23) can be written as

$$x_t' = A(a)x_t + R(a)x_t, \tag{2.26}$$

where $x_t(t) = x(t + \theta)$ for $\theta \in [-1, 0]$. For $\varphi \in C^1([0, 1], (\mathbb{R}^2)^*)$, define

$$A^*\psi(s) = \begin{cases} -\frac{d\psi}{d\theta}, & s \in (0, 1], \\ \int_{-1}^{0} d\eta^T(t, 0)\psi(-t), & s = 0, \end{cases}$$

and a bilinear inner product

$$\langle \psi(s), \varphi(\theta) \rangle = \overline{\psi}(0)\varphi(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \overline{\psi}^T(\xi - \theta)d\eta(\theta)\varphi(\xi)d\xi,$$

where $\eta(\theta) = \eta(\theta, 0)$; then $A(0)$ and A^* are adjoint operators. By the analysis in the last section, we know that $\pm i\omega\tau_k$ are eigenvalues of $A(0)$; thus they are also eigenvalues of A^*. We first need to compute the eigenvectors of $A(0)$ and A^* corresponding to $i\omega\tau_k$ and $-i\omega\tau_k$, respectively. For $A(0)$, it is easy to obtain that the eigenvector basis of $i\omega_0$ is $p(\theta)$ and that of $p^*(\theta)$, which ensure that $\langle p^*(\theta), p(\theta)\rangle = 1$.

In the following, we will compute the coordinates on the center manifold C_a at $a = 0$ with the method of Hassard, Kazarinoff, and Wan [22]. Let x_t be the solution of (2.23) when $a = 0$. Define $z = \langle p^*, x_t\rangle$, $W(t, \theta) = x_t(\theta) - 2\mathrm{Re}\{z(t)p(\theta)\}$. On the center manifold C_0, $W(t, \theta) = W(z(t), \overline{z}(t), \theta)$ with the form $W(z(t), \overline{z}(t), \theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\overline{z} + W_{02}(\theta)\frac{\overline{z}^2}{2} +$

$W_{30}(\theta)\frac{z^3}{6} + \cdots$, where z and $\overline{z}$ are local coordinates for C_0 in the direction of p^* and $\overline{p^*}$, respectively. For the solution $x_t \in C_0$ of (2.23), we have

$$z'(t) = i\omega\tau_k z + g(z, \overline{z}, a), \tag{2.27}$$

where

$$\begin{aligned} g(z,\overline{z}) = {} & \frac{g_{20}(\theta)}{2}z^2 + g_{11}(\theta)z\overline{z} + \frac{g_{02}(\theta)}{2}\overline{z}^2 + \frac{g_{30}(\theta)}{6}z^3 + \frac{g_{21}(\theta)}{2}z^2\overline{z} + \frac{g_{12}(\theta)}{2}z\overline{z}^2 \\ & + \frac{g_{03}(\theta)}{6}\overline{z^3} + \frac{g_{31}(\theta)}{6}z^3\overline{z} + \frac{g_{40}(\theta)}{24}z^4 + \frac{g_{31}(\theta)}{4}z^3\overline{z} + \frac{g_{22}(\theta)}{6}z^2\overline{z}^2 + \frac{g_{13}(\theta)}{4}z\overline{z}^3 \\ & + \frac{g_{04}(\theta)}{24}\overline{z}^4 + \frac{g_{41}(\theta)}{24}z^4\overline{z} + \frac{g_{32}(\theta)}{12}z^3\overline{z}^2 + \cdots . \end{aligned} \tag{2.28}$$

Noting that $x_t = (x_{1t}(\theta), x_{2t}(\theta)) = W(t,\theta) + zp(\theta) + \overline{zp(\theta)}$ and $q(\theta) = (1, \alpha)^T e^{i\omega\theta}$ and recalling (2.27), one has

$$g(z, \overline{z}) = \overline{p^*(0)}R(0, z, \overline{z}). \tag{2.29}$$

Inserting (x_{1t}, x_{2t}) into (2.29) and comparing the coefficients of $z^i\overline{z}^j$ $(i + j \geq 2)$ with that of (2.28), all $g_{ij}(i + j \geq 2)$ can be obtained. Thus (2.27) can be transformed into an equation of the form

$$z'(t) = \lambda_1(a)z + \tfrac{1}{2}C_1(a)z^2\overline{z} + \tfrac{1}{12}C_2(a)z^3\overline{z}^2 + (o|z|^5), \tag{2.30}$$

where $\lambda_1(a) = i\omega\tau_k + a\lambda'(0) + (o|a|^3)$ with $\lambda(a)$ being a smooth function defined by Theorem 2.2 and

$$C_1(0) = \frac{i}{2\omega}\left(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2\right) + \frac{1}{2}g_{21},$$

$$\begin{aligned} C_2(0) = {} & \mathrm{Re}\{g_{32}\} + \tfrac{1}{\omega}\mathrm{Im}\left\{g_{20}\bar{g}_{31} - g_{11}(4g_{31} + 3\bar{g}_{22}) - \tfrac{1}{3}g_{02}(g_{40} + \bar{g}_{13}) - g_{30}g_{12})\right\} \\ & + \tfrac{1}{\omega^2}\mathrm{Re}\left\{g_{20}(\bar{g}_{11}(3g_{12} - \bar{g}_{30}) + g_{02}(\bar{g}_{12} - \tfrac{1}{3}g_{30}) + g_{03}\bar{g}_{02}))\right\} \\ & + \tfrac{1}{\omega^2}\mathrm{Re}\left\{g_{11}(\bar{g}_{02}(\tfrac{5}{3}\bar{g}_{30} + 3g_{12}) + \tfrac{1}{3}\bar{g}_{03}g_{02} - 4g_{11}g_{30})\right\} \\ & + \tfrac{3}{\omega^2}\mathrm{Im}\{g_{20}g_{11}\}\mathrm{Im}\{g_{21}\} + \tfrac{1}{\omega^3}\mathrm{Im}\{\bar{g}_{02}g_{11}(\bar{g}_{02}^2 - 3\bar{g}_{20}g_{11} - 4g_{11}^2)\} \\ & + \tfrac{1}{\omega^3}\mathrm{Im}\{g_{20}g_{11}\}(3\mathrm{Re}\{g_{11}g_{20}\} - 2|g_{02}|^2). \end{aligned}$$

Let $z = re^{i\theta}$. Then (2.30) can be written as

$$\begin{cases} \dfrac{dr}{dt} = ar\mathrm{Re}\lambda'(0) + \dfrac{1}{2}r^3\mathrm{Re}\{C_1(0)\} + \dfrac{1}{12}r^5\mathrm{Re}\{C_2(0)\} + \text{h.o.t.} \\ \dfrac{d\theta}{dt} = \omega\tau_k + a\mathrm{Im}\lambda'(0) + \dfrac{1}{2}r^2\mathrm{Im}\{C_1(0)\} + \dfrac{1}{12}r^4\mathrm{Im}\{C_2(0)\} + \text{h.o.t.} \end{cases} \tag{2.31}$$

Hence

$$\begin{aligned} \frac{dr}{d\theta} &= \frac{ar\mathrm{Re}\{\lambda'(0)\} + \frac{1}{2}r^3\mathrm{Re}\{C_1(0)\} + \frac{1}{12}r^5\mathrm{Re}\{C_2(0)\} + \text{h.o.t.}}{\omega\tau_k + a\mathrm{Im}\{\lambda'(0)\} + \frac{1}{2}r^2\mathrm{Im}\{C_1(0)\} + \frac{1}{12}r^4\mathrm{Im}\{C_2(0)\} + \text{h.o.t.}} \\ &= \frac{1}{A(\tau_k, a)}\left(a\mathrm{Re}\{\lambda'(0)\}r + B(\tau_k, a)r^3 + C(\tau_k, a)r^5\right) + \text{h.o.t.}, \end{aligned} \tag{2.32}$$

where $A(\tau_k, a) = \omega\tau_k + a\mathrm{Im}\{\lambda'(0)\}$,

$$B(\tau_k, a) = \frac{1}{2}\mathrm{Re}\{C_1(0)\} - \frac{\mathrm{Im}\{C_1(0)\}\mathrm{Re}\{\lambda'(0)\}a}{2A(\tau_k, a)},$$

and

$$C(\tau_k, a) = \frac{\mathrm{Re}\{C_2(0)\}}{12} - \frac{a\mathrm{Re}\lambda'(0)}{12A(\tau_k, a)}\left(\mathrm{Im}\{C_2(0)\} - \frac{3\mathrm{Im}^2\{C_1(0)\}}{A(\tau_k, a)}\right) - \frac{\mathrm{Re}\{C_1(0)\}\mathrm{Im}\{C_1(0)\}}{4A(\tau_k, a)}.$$

Let

$$r(\theta, r_0) = r_1(\theta)r_0 + r_2(\theta)r_0^2 + r_3(\theta)r_0^3 + r_4(\theta)r_0^4 + r_5(\theta)r_0^5 + O(r_0^6)$$

be a solution of (2.32) satisfying $r(0, r_0) = r_0$. Then $r_1(0) = 1$, $r_i(0) = 0$ for $i \geq 2$. Inserting the above into (2.32), we have

$$\begin{aligned} &r_1'(\theta)r_0 + r_2'(\theta)r_0^2 + r_3'(\theta)r_0^3 + r_4'(\theta)r_0^4 + r_5'(\theta)r_0^5 + O(r_0^6) \\ &\quad = \frac{1}{A(\tau_k, a)}\left(a\mathrm{Re}\{\lambda'(0)\}r + B(\tau_k, a)r^3 + C(\tau_k, a)r^5\right) + \text{h.o.t.} \end{aligned}$$

Thus $r_2'(\theta) = 0, r_4'(\theta) = 0$, and

$$r_1'(\theta) = \frac{a\mathrm{Re}\{\lambda'(0)\}}{A(\tau_k, a)}, \quad r_3'(\theta) = \frac{B(\tau_k, a)}{A(\tau_k, a)}, \qquad r_5'(\theta) = \frac{C(\tau_k, a)}{A(\tau_k, a)}.$$

Hence

$$r_1(\theta) = \frac{a\mathrm{Re}\{\lambda'(0)\}}{A(\tau_k, a)}\theta + 1, \quad r_2(\theta) = 0, \quad r_4(\theta) = 0,$$
$$r_3(\theta) = \frac{B(\tau_k, a)}{A(\tau_k, a)}\theta, \qquad r_5(\theta) = \frac{C(\tau_k, a)}{A(\tau_k, a)}\theta.$$

Then the Poincaré map $P(r_0) = r(2\pi, r_0)$ has the form

$$P(r_0) = \left(\frac{2a\mathrm{Re}\{\lambda'(0)\}\pi}{A(\tau_k, a)} + 1\right) r_0 + \frac{2\pi B(\tau_k, a)}{A(\tau_k, a)}r_0^3 + \frac{2\pi C(\tau_k, a)}{A(\tau_k, a)}r_0^5 + O(r_0^7). \tag{2.33}$$

Near $r_0 = 0$, the map has a unique fixed point

$$r_0^* = \sqrt{\frac{-a\mathrm{Re}\{\lambda'(0)\}}{B(\tau_k, a)}}(1 + O(|a|)). \tag{2.34}$$

We can compute the period of the bifurcated periodic solution as

$$\begin{aligned} T(\tau_k, a) &= \int_0^{2\pi} \frac{d\theta}{A(\tau_k, a) + \frac{1}{2}\mathrm{Im}\{C_1(0)\}r^2 + \text{h.o.t.}} \\ &= \frac{1}{A(\tau_k, a)}\int_0^{2\pi}\left(1 + \frac{\mathrm{Im}\{C_1(0)\}\mathrm{Re}\{\lambda'(0)\}a}{2A(\tau_k, a)B(\tau_k, a)}\right)d\theta + o(|a|) \\ &= \frac{2\pi}{\omega\tau_k}\left(1 + N(\tau_k)a + o(|a|)\right), \end{aligned} \tag{2.35}$$

where

$$N(\tau_k) = \frac{\mathrm{Im}\{C_1(0)\}\mathrm{Re}\{\lambda'(0)\} - \mathrm{Re}\{C_1(0)\}\mathrm{Im}\{\lambda'(0)\}}{\omega\tau_k \mathrm{Re}\{C_1(0)\}}.$$

Then we can obtain the following result from the above analysis and Hassard, Kazarinoff, and Wan [22].

Theorem 2.9. *If* $\mathrm{Re}\{C_1(0)\} \neq 0$, *then system* (1.2) *has a branch of Hopf bifurcated solutions for* $\tau = \tau_k + a$ *with* a *satisfying* $a\mathrm{Re}\{\lambda'(0)\}B(\tau_k, a) < 0$. *Also, the bifurcated periodic solutions have the following properties:*

(i) *they are orbitally stable (resp., unstable) if* $\mathrm{Re}\{C_1(0)\} < 0$ *(resp.,* $\mathrm{Re}\{C_1(0)\} > 0$*);*

(ii) *the bifurcated periodic solution is supercritical (resp., subcritical) if* $\frac{\mathrm{Re}\{C_1(0)\}}{\mathrm{Re}\{\lambda'(0)\}} > 0$ *(resp.,* $\frac{\mathrm{Re}\{C_1(0)\}}{\mathrm{Re}\{\lambda'(0)\}} < 0$*).*

(iii) *the period of the bifurcated periodic solution is* $\frac{2\pi}{\omega\tau_k}$ *as* $a = 0$, *and the period* $T(\tau_k, a)$ *is increasing in parameter* a *(resp., decreasing) if* $N(\tau_k) > 0$ *(resp.,* $N(\tau_k) < 0$*).*

2.2.2. Bautin bifurcation. From the last subsection, we know that (1.2) undergoes Hopf bifurcation if $\mathrm{Re}\{C_1(0)\} \neq 0$. If $\mathrm{Re}\{C_1(0)\} = 0$ but $\mathrm{Re}\{C_2(0)\} \neq 0$, then Bautin bifurcation occurs, which will be analyzed in this subsection. Just as in the previous subsection, we can obtain (2.30), and (2.31) can be written as

$$\begin{cases} \dfrac{dr}{dt} = ar\mathrm{Re}\lambda'(0) + \dfrac{1}{2}r^3\mathrm{Re}\{C_1(a)\} + \dfrac{1}{12}r^5\mathrm{Re}\{C_2(0)\} + \text{h.o.t.}, \\ \dfrac{d\theta}{dt} = \omega\tau_k + a\mathrm{Im}\lambda'(0) + \dfrac{1}{2}r^3\mathrm{Im}\{C_1(a)\} + \dfrac{1}{12}r^5\mathrm{Im}\{C_2(0)\} + \text{h.o.t.} \end{cases} \tag{2.36}$$

Similarly, we have the Poincaré map $P(r_0) = r(2\pi, r_0)$ of the form

$$P(r_0) = \left(\frac{2a\mathrm{Re}\{\lambda'(0)\}\pi}{A(\tau_k, a)} + 1\right) r_0 + \frac{2\pi\bar{B}(\tau_k, a)}{A(\tau_k, a)} r_0^3 + \frac{2\pi\bar{C}(\tau_k, a)}{A(\tau_k, a)} r_0^5 + O(r_0^7), \tag{2.37}$$

where

$$\bar{B}(\tau_k, a) = \frac{1}{2}\mathrm{Re}\{C_1(a)\} - \frac{\mathrm{Im}\{C_1(a)\}\mathrm{Re}\{\lambda'(0)\}a}{2A(\tau_k, a)},$$

$$\bar{C}(\tau_k, a) = \frac{\mathrm{Re}\{C_2(0)\}}{12} - \frac{a\mathrm{Re}\lambda'(0)}{12A(\tau_k, a)}\left(\mathrm{Im}\{C_2(0)\} - \frac{3\mathrm{Im}^2\{C_1(a)\}}{A(\tau_k, a)}\right) - \frac{\mathrm{Re}\{C_1(a)\}\mathrm{Im}\{C_1(a)\}}{4A(\tau_k, a)}.$$

Since $C_1(a)$ is a continuously differentiable function of the parameter a, we have

$$P(r_0) = r_0 + \frac{1}{A(\tau_k, a)}\left(2a\mathrm{Re}\{\lambda'(0)\}\pi r_0 + 2\pi\bar{B}(\tau_k, a)r_0^3 + 2\pi\bar{C}(\tau_k, a)r_0^5\right) + O(r_0^7). \tag{2.38}$$

Hence the number of periodic solutions of system (2.30) equals the number of positive fixed points of the Poincaré map $P(r_0)$. Now we analyze the distribution of roots of $P(r_0) = r_0$. Finding fixed points of $P(r_0) = r_0$ is equivalent to finding positive roots of

$$P_1(r_0) \triangleq \frac{A(\tau_k, a)}{\pi r_0}(P(r_0) - r_0) = \alpha_0 + \alpha_1 r_0^2 + \alpha_2 r_0^4 + O(a^2, r_0^5) = 0, \tag{2.39}$$

which can have zero, one, or two positive solutions of r_0. These solutions are branched from the trivial solution, where

$$\alpha_0 = 2a\mathrm{Re}\{\lambda'(0)\}, \quad \alpha_1 = \mathrm{Re}\{C_1(a)\},$$
$$\alpha_2 = \frac{1}{6}\left(\mathrm{Re}\{C_2(0)\} - \frac{\mathrm{Re}\{\lambda'(0)\}\mathrm{Im}\{C_2(0)\}a}{\omega\tau_k}\right) - \frac{\mathrm{Re}\{C_1(a)\}\mathrm{Im}\{C_1(a)\}}{4\omega\tau_k}.$$

We will give conditions for the existence of positive solutions as follows. The implicit function theorem implies that a unique function $r^2 = -\frac{\alpha_1}{2\alpha_2}(1 + O(\alpha_1)) \equiv r_0^2(a)$ exists such that $P'_{1r_0^2}(a, r_0^2(a)) = 0$; then we have

$$P_1(a, r^2) = \frac{1}{2\alpha_2}(2\alpha_0\alpha_2 - \alpha_1^2 + O(\alpha_1^3)). \tag{2.40}$$

Substituting $\alpha_0, \alpha_1, \alpha_2$ into (2.40) yields

$$\begin{aligned} P_1(a, r_0(a)) &= 2\mathrm{Re}\{\lambda'(0)\}a - \tfrac{3\mathrm{Re}\{C_1(a)\}^2}{2\mathrm{Re}\{C_2(0)\}} + O(C_1(a)^3) \\ &= \alpha_0 - \tfrac{3\alpha_1^2}{2\mathrm{Re}\{C_2(0)\}} + O(C_1(a)^3). \end{aligned}$$

Let $P_1(a, r_0^2(a)) \triangleq M(a)$. Noting that $P'_{1r_0^2}(a, 0) = \alpha_1(a)$, $P_1(a, 0) = \alpha_0(a)$, we obtain the following results for $\alpha_2(a) > 0$.

(1) For $|a| \ll 1$, $P_1(a, r_0)$ has no positive solution if one of the following two cases holds: (i) $M(a) > 0$; (ii) $\alpha_0(a) \geq 0, \alpha_1(a) \geq 0,\ M(a) \leq 0$.

(2) For $|a| \ll 1$, $P_1(a, r_0)$ has one positive root if one of the following two cases holds: (i) $\alpha_0(a) = 0, \alpha_1(a) < 0,\ M(a) < 0$; (ii) $\alpha_0(a) < 0,\ \ M(a) < 0$.

(3) For $|a| \ll 1$, $P_1(a, r_0)$ has two positive roots as $\alpha_0(a) > 0, \alpha_1(a) < 0$, $M(a) < 0$, and the two roots become one as $M(a) = 0$, $\alpha_0(a) > 0$, and $\alpha_1(a) < 0$.

Define

$$\begin{aligned} D'_1 &= \{M(a) > 0\} \bigcup \{\alpha_0(a) \geq 0, \alpha_1(a) \geq 0, M(a) \leq 0\}, \\ D'_2 &= \{\ \alpha_0(a) = 0, \alpha_1(a) < 0,\ M(a) < 0\} \bigcup \{\alpha_0(a) < 0,\ M(a) < 0\}, \\ D'_3 &= \{\alpha_0(a) > 0, \alpha_1(a) < 0, M(a) < 0\}, \\ l &= \{\alpha_0(a) > 0, \alpha_1(a) < 0, M(a) = 0\}, \\ D'_{21} &= \{\alpha_0(a) < 0, \alpha_1(a) > 0,\ M(a) < 0\}, \\ D'_{22} &= \{\alpha_0(a) < 0, \alpha_1(a) < 0,\ M(a) < 0\}. \end{aligned}$$

That is, $l : \alpha_0 = \frac{3\alpha_1^2}{2\mathrm{Re}\{C_2(0)\}}$, $\alpha_1 < 0$. Recalling the first equation of (2.36), the above analysis can be summarized as follows.

(a) If $(\alpha_0, \alpha_1) \in D'_1$, (2.39) has no positive root, which means that system (2.30) has no periodic solution in a sufficiently small neighborhood of the unstable equilibrium $z = 0$.

(b) If $(\alpha_0, \alpha_1) \in D'_2$, (2.39) has only one positive root, which means that system (2.30) has one periodic solution in a sufficiently small neighborhood of the stable equilibrium $z = 0$. The periodic solution is stable as $(\alpha_0, \alpha_1) \in D'_{22}$ and unstable as $(\alpha_0, \alpha_1) \in D'_{21}$.

(c) If $(\alpha_0,\alpha_1)\in D'_3$, (2.39) has two positive roots, which means that system (2.30) has two periodic solutions in a sufficiently small neighborhood of the unstable equilibrium $z=0$; one is stable, and the other is unstable.

Therefore, we can summarize the above discussions as follows.

Theorem 2.10. *If* $\mathrm{Re}\{C_1(0)\}=0$ *but* $\mathrm{Re}\{C_2(0)\}\neq 0$, *then* (1.1) *undergoes a Bautin bifurcation for* $\tau=\tau_k+a$. *On the* (α_0,α_1)*-parameter plane, the half-parabola* l *and the line* $l_1:\alpha_0=0$ *are bifurcation curves. When* $\alpha_2>0$, *the bifurcations are outlined as follows:*

(i) *On the* (α_0,α_1)*-parameter plane, if a point* (α_0,α_1) *crosses the positive* α_1*-axis from the region* D'_1 *to the region* D'_2, *then* (2.30) *undergoes Hopf bifurcation and an unstable periodic solution* Γ_1 *with period* T_1 *bifurcates from* $z=0$. *When the point* (α_0,α_1) *crosses* D'_2 *counterclockwise in* D'_{21}, *the periodic solution* Γ_1 *expands with the same periodic* T_1, *and* Γ_1 *attaches the maximum when* (α_0,α_1) *reaches the negative* α_0*-axis. When* (α_0,α_1) *crosses the negative* α_0*-axis from* D'_{21} *to* D'_{22}, *then the stability of* Γ_1 *changes from unstable to stable; meanwhile, the period changes from* T_1 *to* T_2, *and at the same time, an unstable periodic solution* Γ_2 *bifurcates from* Γ_1 *and locates inside* Γ_1, *where*

$$T_1=\frac{2\pi}{\omega\tau_k}\left(1+N_1(\tau_k)a+o(|a|^2)\right),\quad T_2=\frac{2\pi}{\omega\tau_k}\left(1+N_2(\tau_k)+o(|a|,|C_1(a)|^2)\right),$$

$$N_1(\tau_k)=\frac{\mathrm{Re}\{\lambda'(0)\}\mathrm{Im}\{C_1(a)\}-\mathrm{Re}\{C_1(a)\}\mathrm{Im}\{\lambda'(0)\}}{\omega\tau_k\mathrm{Re}\{C_1(a)\}},$$

and

$$N_2(\tau_k)=\frac{3\mathrm{Re}\{C_1(a)\}\mathrm{Im}\{C_1(a)\}-\mathrm{Im}\{\lambda'(0)\}\mathrm{Re}\{C_2(0)\}a}{\omega\tau_k\mathrm{Re}\{C_2(0)\}}.$$

(ii) *On the* (α_0,α_1)*-parameter plane, if a point* (α_0,α_1) *crosses the negative* α_1*-axis from the region* D'_2 *to the region* D'_3, *then* (2.30) *undergoes Hopf bifurcation, and an unstable periodic solution* Γ_3 *with period* T_1 *bifurcates from* $z=0$, *and* Γ_2 *coincides with* Γ_3 *and disappears, which means that there are two periodic solutions in* D'_3; *one is stable with period* T_2, *and the other is unstable with period* T_1.

(iii) *On the* (α_0,α_1)*-parameter plane, if a point* (α_0,α_1) *goes from region* D'_3 *to* l, *the two periodic solutions of* (2.30) *coincide to become one. If the point* (α_0,α_1) *crosses the line* l *to* D'_1, *the new periodic solution of* (2.30) *disappears; that is, if a point* (α_0,α_1) *crosses the region* D'_3 *to the region* D'_1, *then periodic solutions of* (2.30) *undergo saddle-node bifurcation, that is, a saddle-node type periodic solution bifurcated from the trivial solution* $z=0$.

Proof. First, we will compute the periods T_1 and T_2 as follows: when $(\alpha_0,\alpha_1)\in D'_2$, noting that $\alpha_0\le 0$, near $r_0=0$ the Poincaré map has positive fixed points with

$$r_i^{*2}=\begin{cases}-\dfrac{\alpha_0}{\alpha_1}+\text{h.o.t.}, & \alpha_1>0,\\[2mm] \dfrac{\alpha_0}{\alpha_1}-\dfrac{\alpha_1}{\alpha_2}+\text{h.o.t.}, & \alpha_1<0.\end{cases}\tag{2.41}$$

Since

$$T_i = \int_0^{2\pi} \frac{d\theta}{A(\tau_k, a) + \frac{1}{2}\mathrm{Im}\{C_1(a)\}r_i^{*2} + \text{h.o.t.}}$$
$$= \frac{2\pi}{\omega\tau_k}\left(1 - \frac{a\mathrm{Im}\{\lambda'(0)\}}{\omega\tau_k} - \frac{\mathrm{Im}\{C_1(a)\}}{2A(\tau_k, a)} r_i^{*2} + o(|a|^2)\right),$$

we have

$$T_1 = \frac{2\pi}{\omega\tau_k}\left(1 + N_1(\tau_k)a + o(|a|^2)\right), \quad i = 1, 2,$$

with

$$N_1(\tau_k) = \frac{\mathrm{Re}\{\lambda'(0)\}\mathrm{Im}\{C_1(a)\} - \mathrm{Re}\{C_1(a)\}\mathrm{Im}\{\lambda'(0)\}}{\omega\tau_k \mathrm{Re}\{C_1(a)\}}.$$

Similarly, we have

$$T_2 = \frac{2\pi}{\omega\tau_k}\left(1 + N_2(\tau_k) + o(|C_1(a)|^2)\right)$$

with

$$N_2(\tau_k) = \frac{3\mathrm{Re}\{C_1(a)\}\mathrm{Im}\{C_1(a)\} - \mathrm{Im}\{\lambda'(0)\}\mathrm{Re}\{C_2(0)\}a}{\omega\tau_k \mathrm{Re}\{C_2(0)\}}.$$

In the following, we will prove that the stability of the periodic solutions will change with the change of $\alpha_1(a)$. Set $r = r_i^* + b$, $|b| \ll 0$. From the first equation of (2.36), we have

$$\frac{dr}{dt} = \alpha_1 b r_i^{*2} + O(b^2). \tag{2.42}$$

Hence, the stability of the bifurcated periodic solution Γ_1 will change when α changes from $\alpha_1 > 0$ to $\alpha_1 < 0$; that is, a new periodic solution Γ_2 will bifurcate from the periodic solution Γ_1. On the other hand, we know that $z = 0$ is a stable equilibrium as $(\alpha_0, \alpha_1) \in D_2'$; then the bifurcated periodic solution Γ_2 is unstable and located between Γ_1 and the equilibrium $z = 0$. The bifurcation diagram is given in Figure 4.

Combing the above analysis, all results of this theorem have been proven. ■

On the other hand, define

$$\begin{aligned}
D_1'' &= \{M(a) < 0\} \bigcup \{\alpha_0(a) \le 0, \alpha_1(a) \le 0, M(a) \ge 0\},\\
D_2'' &= \{\ \alpha_0(a) = 0, \alpha_1(a) > 0\ M(a) > 0\} \bigcup \{\alpha_0(a) > 0,\ M(a) > 0\},\\
D_3'' &= \{\alpha_0(a) < 0, \alpha_1(a) > 0, M(a) > 0\},\\
l' &= \{\alpha_0(a) < 0, \alpha_1(a) > 0, M(a) = 0\},\\
D_{21}'' &= \{\alpha_0(a) > 0, \alpha_1(a) < 0,\ M(a) > 0\},\\
D_{22}'' &= \{\alpha_0(a) > 0, \alpha_1(a) > 0,\ M(a) > 0\}.
\end{aligned}$$

Similarly to Theorem 2.10, we obtain the following bifurcation results for the case $\alpha_2 < 0$.

Theorem 2.11. *If* $\mathrm{Re}\{C_1(0)\} = 0$ *but* $\mathrm{Re}\{C_2(0)\} \neq 0$, *then* (1.1) *undergoes a Bautin bifurcation for* $\tau = \tau_k + a$. *On the* (α_0, α_1)*-parameter plane, the half-parabola* l' *and the line* $l_1' : \alpha_0 = 0$ *are bifurcation curves. When* $\alpha_2 < 0$, *the bifurcations are outlined as follows:*

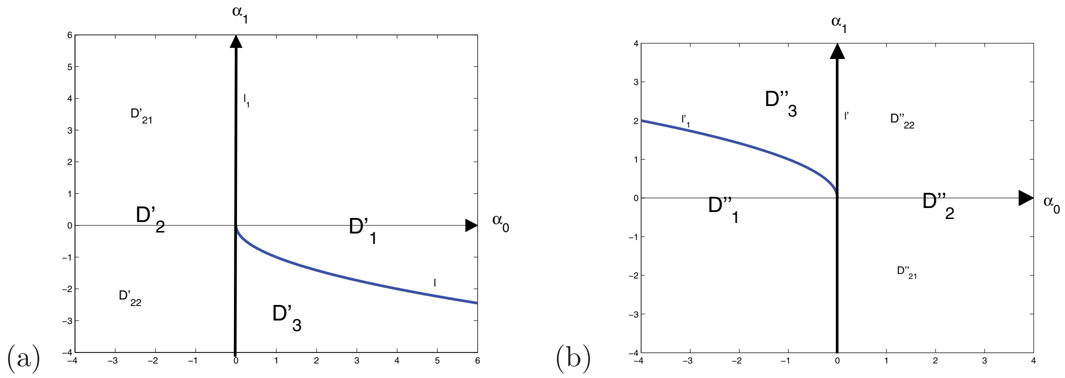


Figure 4. *The bifurcation diagram for system* (2.30). (a) $\alpha_2 > 0$. (b) $\alpha_2 < 0$.

(i) *On the* (α_0, α_1)*-parameter plane, if a point* (α_0, α_1) *crosses the negative* α_1*-axis from the region* D_1'' *to the region* D_2''*, then* (2.30) *undergoes Hopf bifurcation, and a stable periodic solution* Γ_1' *with period* T_1 *bifurcates from* $z = 0$*. When the point* (α_0, α_1) *crosses* D_2'' *counterclockwise in* D_{21}''*, the periodic solution* Γ_1' *expands with the same periodic* T_1*, and* Γ_1' *attaches the maximum when* (α_0, α_1) *reaches the positive* α_0*-axis. When* (α_0, α_1) *crosses the positive* α_0*-axis from* D_{21}'' *to* D_{22}''*, then the stability of* Γ_1' *changes from stable to unstable; meanwhile, the period changes from* T_1 *to* T_2*, and at the same time, an unstable periodic solution* Γ_2' *bifurcates from* Γ_1' *and locates inside* Γ_1'*.*

(ii) *On the* (α_0, α_1)*-parameter plane, if a point* (α_0, α_1) *crosses the negative* α_1*-axis from the region* D_2'' *to the region* D_3''*, then* (2.30) *undergoes Hopf bifurcation, and a stable periodic solution* Γ_3' *with period* T_1 *bifurcates from* $z = 0$*, and* Γ_2' *coincides with* Γ_3' *and disappears, which means that there are two periodic solutions in* D_3''*; one is stable with period* T_2*, and the other is unstable with period* T_1*.*

(iii) *On the* (α_0, α_1)*-parameter plane, if a point* (α_0, α_1) *goes from region* D_3'' *to* l'*, the two periodic solutions of* (2.30) *coincide to become one. If the point* (α_0, α_1) *crosses the line* l' *to* D_1''*, the new periodic solution of* (2.30) *disappears; that is, if a point* (α_0, α_1) *crosses* l' *from region* D_3'' *to the region* D_1''*, then periodic solutions of* (2.30) *undergo saddle-node bifurcation, that is, a saddle-node type periodic solution bifurcated from the trivial solution* $z = 0$*.*

2.3. Codimension two bifurcation: Hopf–Hopf.

In section 2.1, we knew that the characteristic equation (2.4) has two different pairs of purely imaginary roots when (2.8) holds. Take A_1, A_2, B_1, B_2 as parameters. If there exist integers k, j such that $\tau_j^+ = \tau_k^-$, then (2.4) will have two pairs of purely imaginary roots $\pm i\omega_+$ and $\pm i\omega_-$. Let $\omega_1 = \omega_+,\ \omega_2 = \omega_-$; then one important codimension two bifurcation, Hopf–Hopf bifurcation, may occur. In general, these points are not easy to solve; however, they can be computed numerically and can be seen in Figures 1–3, where they appear at intersection points of two Hopf bifurcation curves.

Lemma 2.12. *For any* $k_1, k_2 \in \mathcal{Z}$ *and* $0 < |k_1| + |k_2| \le 6$*, it must hold that* $k_1\omega_1 + k_2\omega_2 \ne 0$*, where* $\omega_1 = \omega^+,\quad \omega_2 = \omega^-$*.*

Proof. If $\pm i\omega_i, i = 1, 2$, are purely imaginary roots of (2.4), then $i\omega_i$ satisfies

$$\begin{cases} -A_2 + \omega_i^2 = B_2 \cos\omega_i\tau + B_1\omega_i \sin\omega_i\tau, \\ \quad -A_1\omega_i = B_1\omega_i \cos\omega_i\tau - B_2 \sin\omega_i\tau. \end{cases}$$

Differentiating the last two equations with respect to ω_i twice separately on both sides, we have

$$\begin{cases} 2 = (2B_1\tau - B_2\tau^2)\cos\omega_i\tau - B_1\tau^2\omega_i \sin\omega_i\tau, \\ 0 = (B_2\tau^2 - 2B_1\tau)\sin\omega_i\tau - B_1\tau^2\omega_i \cos\omega_i\tau. \end{cases}$$

Thus we have

$$\cos\omega_i\tau = \frac{2(2B_1\tau - B_2\tau^2)}{(2B_1\tau - B_2\tau^2)^2 + (B_1\tau^2\omega_i)^2}, \ \sin\omega_i\tau = \frac{-2B_1\tau^2\omega_i}{(2B_1\tau - B_2\tau^2)^2 + (B_1\tau^2\omega_i)^2}; \tag{2.43}$$

hence

$$\tan\omega_i\tau = \frac{B_1\tau\omega_i}{B_2\tau - 2B_1}. \tag{2.44}$$

Then we prove $k_1\omega_1 + k_2\omega_2 \neq 0$ for $|k_1| + |k_2| \leq 6$. If not, assume that there exist $k_1, k_2 \in Z^+$ such that $k_1\omega_1 = k_2\omega_2$ and $|k_1| + |k_2| \leq 6$. It is easy to see that $\omega_1 \neq \omega_2$. Without loss of generality, we assume that $\omega_1 > \omega_2$, $\omega_i > 0$; then $k_1 < k_2$; that is, we need only prove the following cases.

(i) If $\omega_1 = 2\omega_2$, then (2.44) yields

$$\tan\omega_1\tau = \frac{B_1\tau\omega_1}{B_2\tau - 2B_1} = \tan 2\omega_2\tau = \frac{\frac{2B_1\tau\omega_2}{B_2\tau - 2B_1}}{1 - (\frac{B_1\tau\omega_2}{B_2\tau - 2B_1})^2},$$

which leads to $\omega_2 = 0$, which is a contradiction; thus $\omega_1 \neq 2\omega_2$.

(ii) If $\omega_1 = 3\omega_2$, then (2.44) yields

$$\tan\omega_1\tau = \frac{B_1\omega_1\tau}{B_2\tau - 2B_1} = \tan 3\omega_2\tau = \frac{\tan\tau\omega_2(3 - \tan^2\omega_2\tau)}{1 - 3\tan^2\omega_2\tau},$$

which leads to $\tan^2\omega_2\tau = 0$, which is a contradiction; hence $\omega_1 \neq 3\omega_2$.

(iii) If $\omega_1 = 4\omega_2$, then (2.44) yields

$$\tan\omega_1\tau = \frac{B_1\tau\omega_1}{B_2\tau - 2B_1} = \tan 4\omega_2\tau = \frac{\frac{4\tan\omega_2\tau}{(1 - \tan^2\omega_2\tau)}}{1 - (\frac{2\tan\omega_2\tau}{1 - \tan^2\omega_2\tau})^2},$$

which has real roots $\tan^2\tau\omega_2 = 0$, $\tan^2\tau\omega_2 = 5$. If $\tan^2\tau\omega_2 = 5$, then $\cos\tau\omega_1 = \frac{1}{9}$, $\cos\tau\omega_2 = \frac{1}{\sqrt{6}}$. With the help of (2.43), we have

$$\frac{\sqrt{6}}{9} = \frac{(2B_1\tau - B_2\tau^2)^2 + (B_1\tau^2\omega_2)^2}{(2B_1\tau - B_2\tau^2)^2 + (4B_1\tau^2\omega_2)^2}.$$

Thus $(\frac{B_1\tau\omega_2}{B_2\tau - 2B_1})^2 = \frac{9 - \sqrt{6}}{16\sqrt{6} - 9}$, which contradicts $\tan\omega_2\tau = \frac{B_1\tau\omega_2}{B_2\tau - 2B_1} = \sqrt{5}$, that is, $\omega_1 \neq 4\omega_2$.

(iv) If $\omega_1 = 5\omega_2$, then (2.44) yields

$$\tan\omega_1\tau = \frac{B_1\tau\omega_1}{B_2\tau - 2B_1} = \tan 5\omega_2\tau = \frac{\tan\omega_2\tau + \frac{4\tan\omega_2\tau(1-\tan^2\omega_2\tau)}{(1-\tan^2\omega_2\tau)^2-4\tan^2\omega_2\tau}}{1-\frac{4\tan^2\omega_2\tau(1-\tan^2\omega_2\tau)}{(1-\tan^2\omega_2\tau)^2-4\tan^2\omega_2\tau}},$$

which leads to $\tan^2\omega_2\tau = 0$ and $\tan^2\omega_2\tau = \frac{5}{3}$. Similar to the proof of case (iii), it follows that $\omega_1 \neq 5\omega_2$.

(v) If $2\omega_1 = 3\omega_2$, then $\tan 2\omega_1\tau = \tan 3\omega_2\tau$. Noting (2.44), one has $\tan\omega_1\tau = \frac{3}{2}\tan\omega_2\tau$, and, similarly to the above, we can get

$$8\tan^2\omega_2\tau + \tan^2\omega_2\tan^2\omega_1\tau - 3\tan^2\omega_1\tau = 0,$$

which leads to $\tan^2\omega_2\tau = 0$, which is a contradiction.

(vi) If $2\omega_1 = 4\omega_2$, then $\omega_1 = 2\omega_2$, which is proved in case (i).

Therefore, there are two pairs of purely imaginary roots $\pm i\omega_1$ and $\pm i\omega_2$ which are not resonant in low orders. ■

In the following, we present the normal form of Hopf–Hopf bifurcation on the center manifold C_a. Noting (2.12), we know that the eigenvalues $\pm i\omega_j, j = 1,2$, of (2.4) are simple. On the other hand, we know that $A(a)$ has simple eigenvalues $\lambda_1(a)$ and $\lambda_2(a)$ with $\lambda_i(0) = i\omega_j,\ j = 1,2$. From section 2.2.1, we know that $A(a)$ has two eigenvectors $p_1(a,\theta)$ and $p_2(a,\theta)$ corresponding to the eigenvalues $\lambda_1(a)$ and $\lambda_2(a)$ such that

$$A(a)p_j(a,\theta) = \lambda_j(a)p_j(a,\theta), \quad j = 1,2,$$

and the adjoint eigenvectors $q_j(a,\theta),\ j = 1,2$, corresponding to the eigenvalues $\bar\lambda_j(a)$ such that

$$A^*(a)q_j(a,\theta) = \bar\lambda_j(a)q_j(a,\theta), \quad j = 1,2.$$

Suppose $p_j(\theta) \triangleq p_j(0,\theta),\ q_j(\theta) \triangleq q_j(0,\theta),\ j = 1,2$, are the eigenvectors of $A(0)$ and $A^*(0)$, respectively; then

$$p_j(\theta) = (1,\ \gamma_j)^T e^{i\omega_j\tau_k\theta}, \qquad q_j(\xi) = D_j(1,\ \beta_j)^T e^{i\omega_j\tau_k\xi},$$

with $\langle q_j^*(\theta), q_j(\theta)\rangle = 1$. Define $z_j = \langle q_j, X\rangle,\ j = 1,2,\quad W(t,\theta) = X_t(\theta) - 2\mathrm{Re}\{z_1(t)q_1(\theta) + z_2(t)q_2(\theta)\}$, where $z = (z_1,z_2) \in \mathcal{C}_a$, and z_j and $\bar z_j$ are the local coordinates for $\mathcal{C}_a$ in the direction of q_j and $\bar q_j$, $j = 1,2$. If $X_t \in \mathcal{C}_a$ is a solution of (2.26), then on the center manifold $\mathcal{C}_a$, one has the normal form

$$z' = \Lambda z(t) + g(z,a), \tag{2.45}$$

where $\Lambda = \mathrm{diag}(i\omega_1\tau_k,\ i\omega_2\tau_k)$,

$$g(z,a) = (g^1(z,a),\ g^2(z,a))^T = \left(\sum_{i+j+k+l\geq 2}\frac{1}{i!j!l!k!}g^1_{ijkl},\ \sum_{i+j+k+l\geq 2}\frac{1}{i!j!l!k!}g^2_{ijkl}\right)^T. \tag{2.46}$$

Similar to the computation of Hopf bifurcation, we can obtain

$$g(z,a) = \begin{pmatrix} C_{10}(a)z_1 + C_{11}(a)|z_1|^2 z_1 + C_{12}(a)|z_2|^2 z_1 + O(|z|^5) \\ C_{20}(a)z_2 + C_{21}(a)|z_2|^2 z_2 + C_{22}(a)|z_1|^2 z_2 + O(|z|^5) \end{pmatrix},$$

where $C_{10}(a) = a\lambda_1'(a),\ C_{20}(a) = a\lambda_2'(a),$

$$\begin{aligned}
C_{10}(a) &= a\lambda_1'(a),\\
C_{20}(a) &= a\lambda_2'(a),\\
C_{11}(a) &= \tfrac{1}{2}g^1_{2100} + \tfrac{i}{2\omega_1}g^1_{1100}g^1_{2000} + \tfrac{i}{\omega_2}(g^1_{1010}g^2_{1100} - g^1_{1001}\overline{g^2_{1100}}) - \tfrac{i}{4\omega_1+2\omega_2}g^1_{0101}\overline{g^2_{0200}}\\
&\quad - \tfrac{i}{4\omega_1-2\omega_2}g^1_{0110}g^2_{2000} - \tfrac{i}{\omega_1}|g^1_{1100}|^2 - \tfrac{i}{6\omega_1}|g^1_{0200}|^2,\\
C_{12}(a) &= g^1_{1011} + \tfrac{i}{\omega_2}(g^1_{1010}g^2_{0011} - g^1_{1001}\overline{g^2_{0011}}) - \tfrac{i}{\omega_1+2\omega_2}g^1_{0002}\overline{g^2_{0101}} - \tfrac{i}{\omega_1-2\omega_2}g^1_{0020}g^2_{1001}\\
&\quad + \tfrac{i}{\omega_1}(g^1_{2000}g^1_{0011} - g^1_{1100}\overline{g^1_{0011}} - g^1_{0011}\overline{g^2_{0110}} - g^1_{0011}g^1_{1010})\\
&\quad - \tfrac{i}{2\omega_1-\omega_2}|g^1_{0110}|^2 - \tfrac{i}{2\omega_1+\omega_2}|g^1_{0101}|^2,\\
C_{21}(a) &= \tfrac{1}{2}g^2_{0021} + \tfrac{i}{2\omega_2}g^2_{0011}g^2_{0020} + \tfrac{i}{\omega_1}(g^1_{0011}g^2_{1010} - \overline{g^1_{0011}}g^2_{0110}) - \tfrac{i}{4\omega_2-2\omega_1}g^1_{0020}\overline{g^2_{1001}}\\
&\quad - \tfrac{i}{4\omega_2+2\omega_1}\overline{g^1_{0002}}g^2_{0101} - \tfrac{i}{\omega_2}|g^2_{0011}|^2 - \tfrac{i}{6\omega_2}|g^2_{0002}|^2,\\
C_{22}(a) &= g^2_{1110} + \tfrac{i}{\omega_1}(g^1_{1100}g^2_{1010} - g^2_{0110}\overline{g^1_{0110}}) - \tfrac{i}{2\omega_1+\omega_2}g^2_{0200}\overline{g^1_{0101}} + \tfrac{i}{2\omega_1-\omega_2}g^1_{0110}g^2_{2000}\\
&\quad + \tfrac{i}{\omega_2}(g^2_{0020}g^2_{1100} - g^2_{0011}\overline{g^2_{1100}} - g^1_{1010}g^2_{1100} - \overline{g^1_{1001}}g^2_{1100})\\
&\quad + \tfrac{i}{\omega_1-2\omega_2}|g^2_{1001}|^2 - \tfrac{i}{\omega_1+2\omega_2}|g^2_{0101}|^2,
\end{aligned}$$

where $g_{ijkl},\ i+j+k+l \geq 2$, can be obtained similarly to the above. As shown in Takens [44] and Wiggins [50], we assume that the following nondegeneracy conditions are satisfied: $\mathrm{Re}\{C_{ij}(a)\} \neq 0$ and $\mathrm{Re}\{C_{11}(a)\}\mathrm{Re}\{C_{22}(a)\} - \mathrm{Re}\{C_{12}(a)\}\mathrm{Re}\{C_{21}(a)\} \neq 0,\ i,j = 1,2$. Let $z_1 = r_1 e^{i\theta_1}$, $z_2 = r_2 e^{i\theta_2}$. Then (2.45) can be changed into

$$\begin{cases} r_1' = a\mathrm{Re}\lambda_1'(0)r_1 + \mathrm{Re}\{C_{11}(0)\}r_1^3 + \mathrm{Re}\{C_{12}(0)\}r_1 r_2^2 + O(\|r_1,r_2\|)^5,\\ r_2' = a\mathrm{Re}\lambda_2'(0)r_2 + \mathrm{Re}\{C_{21}(0)\}r_2^3 + \mathrm{Re}\{C_{22}(0)\}r_1^2 r_2 + O(\|r_1,r_2\|)^5,\\ \theta_1' = \omega_1 + a\mathrm{Im}\lambda_1'(0) + \mathrm{Im}\{C_{11}(0)\}r_1^2 + \mathrm{Im}\{C_{12}(0)\}r_2^2 + O(\|r_1,r_2\|)^4,\\ \theta_2' = \omega_1 + a\mathrm{Im}\lambda_2'(0) + \mathrm{Im}\{C_{21}(0)\}r_2^2 + \mathrm{Im}\{C_{22}(0)\}r_1^2 + O(\|r_1,r_2\|)^4. \end{cases}$$

Then the truncation of the amplitude equation to quadratic order is

$$\begin{cases} \theta_1' = \omega_1 + a\mathrm{Im}\lambda_1'(0) + \mathrm{Im}\{C_{11}(0)\}r_1^2 + \mathrm{Im}\{C_{12}(0)\}r_2^2 + O(\|r_1,r_2\|)^4,\\ \theta_2' = \omega_1 + a\mathrm{Im}\lambda_2'(0) + \mathrm{Im}\{C_{21}(0)\}r_2^2 + \mathrm{Im}\{C_{22}(0)\}r_1^2 + O(\|r_1,r_2\|)^4, \end{cases} \tag{2.47}$$

and the truncation of the phase equations to cubic order is

$$\begin{cases} r_1' = a\mathrm{Re}\lambda_1'(0)r_1 + \mathrm{Re}\{C_{11}(0)\}r_1^3 + \mathrm{Re}\{C_{12}(0)\}r_1 r_2^2 + O(\|r_1,r_2\|)^5,\\ r_2' = a\mathrm{Re}\lambda_2'(0)r_2 + \mathrm{Re}\{C_{21}(0)\}r_2^3 + \mathrm{Re}\{C_{22}(0)\}r_1^2 r_2 + O(\|r_1,r_2\|)^5. \end{cases} \tag{2.48}$$

Let $r_1 = \frac{\overline{r_1}}{\sqrt{|\mathrm{Re}\{C_{11}(0)\}|}}$, $r_2 = \frac{\overline{r_2}}{\sqrt{|\mathrm{Re}\{C_{22}(0)\}|}}$, dropping the bars; then (2.48) can be written as

$$\begin{cases} r_1' = (\mu_1 + er_1^2 + br_2^2)r_1,\\ r_2' = (\mu_2 + cr_1^2 + dr_2^2)r_2, \end{cases} \tag{2.49}$$

where $d = \frac{\mathrm{Re}\{C_{22}(a)\}}{|\mathrm{Re}\{C_{22}(a)\}|} = \pm 1, \quad c = \frac{\mathrm{Re}\{C_{21}(a)\}}{|\mathrm{Re}\{C_{11}(a)\}|}, \quad b = \frac{\mathrm{Re}\{C_{12}(a)\}}{|\mathrm{Re}\{C_{22}(a)\}|}, \quad e = \frac{\mathrm{Re}\{C_{11}(a)\}}{|\mathrm{Re}\{C_{11}(a)\}|} = \pm 1$, and $\mu_1 = a\mathrm{Re}\lambda_1'(0), \quad \mu_2 = a\mathrm{Re}\lambda_2'(0)$.

Similar to the previous subsection, we know that system (2.47) determines the period and direction of the bifurcated solutions. As Guckhenheimer and Holmes [20] and Choi and LeBlanc [8] pointed out, the possible phase portraits in the neighborhood of the Hopf–Hopf bifurcation points are classified by the dynamical behaviors of the phase equations; we need only study the truncation equation of phase equations (2.48) and obtain the following results.

Theorem 2.13.

(i) *If* (2.49) *has an equilibrium* $(r_1^*, 0)$ *(resp.,* $(0, r_2^*)$*), then in the neighborhood of the positive equilibrium* E_2*, system* (1.2) *has a periodic solution with period* $T = \frac{2\pi}{\omega_1\tau_k}(1 - \frac{\mathrm{Im}\{C_{11}\}r_1^{*2}}{2\omega_1\tau_k}) + o(a)$ *(resp.,* $T = \frac{2\pi}{\omega_2\tau_k}(1 - \frac{\mathrm{Im}\{C_{21}\}r_2^{*2}}{2\omega_2\tau_k}) + o(a)$*). The stability of the periodic solution is same as that of the equilibrium.*

(ii) *If* (2.49) *has a equilibrium* $(r_1^*,\ r_2^*)$ *with* $r_1^* > 0$, $r_2^* > 0$ *in the interior of the positive quadrant, then* (1.2) *has quasi-periodic solutions in the neighborhood of the positive equilibrium* E_2.

(iii) *If* (2.49) *has a limit cycle in the interior of the positive quadrant, then* (1.2) *has a three-dimensional invariant torus in the neighborhood of the positive equilibrium* E_2.

In order to analyze the qualitative properties of (2.49), there are four cases to be considered: (1) $e > 0, \quad d > 0$; (2) $e > 0, \quad d < 0$; (3) $e < 0, \quad d > 0$; (4) $e < 0, \quad d < 0$. Here, we consider only the second case, since the other cases can be analyzed similarly. In this case, system (2.49) takes the form

$$\left\{ \begin{array}{l} r_1' = (\mu_1 + r_1^2 + br_2^2)r_1, \\ r_2' = (\mu_2 + cr_1^2 - r_2^2)r_2. \end{array} \right. \tag{2.50}$$

It is easy to see that (2.50) has nonzero equilibria $E_1'(\sqrt{-\mu_1}, 0)$ with $\mu_1 < 0$, $E_2'(0, \sqrt{\mu_2})$ with $\mu_2 > 0$, and $E_3'(\sqrt{\frac{b\mu_2+\mu_1}{-1-bc}}, \sqrt{\frac{\mu_2-c\mu_1}{1+bc}})$ with $\frac{b\mu_2+\mu_1}{1+bc} < 0$ and $\frac{\mu_2-c\mu_1}{1+bc} > 0$. The stability of the equilibria E_i can be determined by the eigenvalues of the linearized matrix of (2.50) at E_i' :

$$\begin{pmatrix} \mu_1 + 3r_1^{*2} + br_2^{*2}, & 2br_1^*r_1^* \\ 22r_1^*r_1^*, & \mu_2 + cr_1^{*2} + 3r_2^{*2} \end{pmatrix}. \tag{2.51}$$

The determinant of this matrix is

$$3\mu_2 r_1^2 + 3cr_1^4 + b\mu_2 r_2^2 + 9r_1^2 r_2^2 - 3bcr_1^2 r_2^2 + 3br_2^4 + \mu_1(\mu_2 + cr_1^2 + 3r_2^2)|_{E_i'},$$

and the trace of this matrix is

$$\mu_1 + \mu_2 + 3r_1^2 + cr_1^2 + 3r_2^2 + br_2^2|_{E_i'}.$$

Hence, with the help of (2.51), we know that the Hopf bifurcation can occur only as $\mu_2 = c\mu_1$, $\mu_1 = -b\mu_2$, and $\mu_2 = \frac{\mu_1(c-1)}{cb+1}$. It is well known that the signs of b, c, d determine the complex dynamical behaviors of (2.50). Guckhenheimer and Holmes [20] pointed out that there are 12 unfolding cases for the nonresonant Hopf–Hopf bifurcation for E_i', which are summarized in Table 1 (Table 7.5.2 of [20]).

Table 1
The 12 unfolding cases of (2.49).

Case	Ia	Ib	II	III	IVa	IVb	V	VIa	VIb	VIIa	VIIb	VIII
d	$+1$	$+1$	$+1$	$+1$	$+1$	$+1$	-1	-1	-1	-1	-1	-1
b	$+$	$+$	$+$	$-$	$-$	$-$	$+$	$+$	$+$	$-$	$-$	$-$
c	$+$	$+$	$-$	$+$	$-$	$-$	$+$	$-$	$-$	$+$	$+$	$-$
$d-bc$	$+$	$-$	$(+)$	$4(+)$	$+$	$-$	$4(-)4$	$4+$	$-$	$+$	$-$	$(-)$

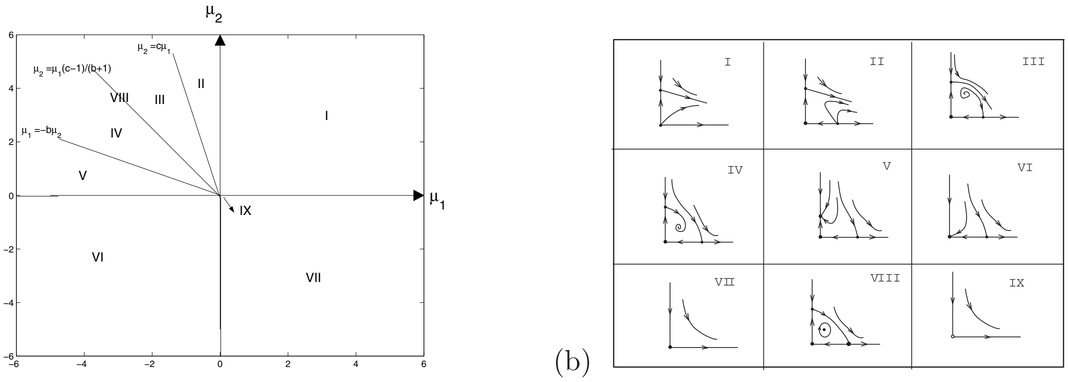
(a) (b)


Figure 5. *Phase portraits for the case* VIa *in Table* 1. (a) *Bifurcation diagram in* (μ_1, μ_2). (b) *Phase portraits of* (2.50).

We choose only VIa as an example; that is, $e = 1, d = -1, b > 0, c < 0$, and $-1 - bc > 0$. From $-1 - bc > 0$, it is easy to obtain $c < \frac{c-1}{b+1} < \frac{-1}{b}$; then the line $\mu_2 = \frac{c-1}{b+1}\mu_1$ must lie between the lines $\mu_2 = c\mu_1$ and $\mu_1 = -b\mu_2$. As shown in Guckhenheimer and Holmes [20], the partial bifurcation sets and the phase portraits for the unfoldings of this case are given in Figure 5.

From (2.43) and Figure 5, we have the following results.

Theorem 2.14. *Assume that* $\mathrm{Re}\{C_{11}(a)\} > 0$, $\mathrm{Re}\{C_{12}(a)\} > 0$, $\mathrm{Re}\{C_{21}(a)\} < 0$, $\mathrm{Re}\{C_{22}(a)\} < 0$, *and* $\mathrm{Re}\{C_{11}(a)\}\mathrm{Re}\{C_{22}(a)\} > 0 \neq \mathrm{Re}\{C_{21}(a)\}\mathrm{Re}\{C_{12}(a)\}$. *Then on the* (μ_1, μ_2)*-parameter plane, we have the following cases:*

(i) *If a point* (μ_1, μ_2) *crosses the positive* μ_1*-axis from* D_7 *to* D_1*, Hopf bifurcation occurs, an unstable periodic solution* Γ_1 *is bifurcated from the trivial solution, and* Γ_1 *persists for* (μ_1, μ_2) *in regions* $D_1 - D_5$*.*

(ii) *If a point* (μ_1, μ_2) *crosses the positive* μ_2*-axis from* D_1 *to* D_2*, another Hopf bifurcation occurs, an unstable periodic solution* Γ_2 *is bifurcated from the trivial solution.* Γ_2 *persists for* (μ_1, μ_2) *in regions* $D_2 - D_6$*.*

(iii) *If a point* (μ_1, μ_2) *crosses the line* $\mu_2 = c\mu_1$ *from* D_2 *to* D_3*, a stable quasi-periodic solution* Θ_1 *is bifurcated from* Γ_1*, and* Θ_1 *persists for* (μ_1, μ_2) *in regions* D_3 *and* D_4*.*

(iv) *If a point* (μ_1, μ_2) *crosses the line* $(b + 1)\mu_2 = (c - 1)\mu_1$ *from* D_3 *to* D_4*, a torus* Θ_2 *is bifurcated from* Θ_1*, and the bifurcated torus* Θ_2 *exists in a small neighborhood of*

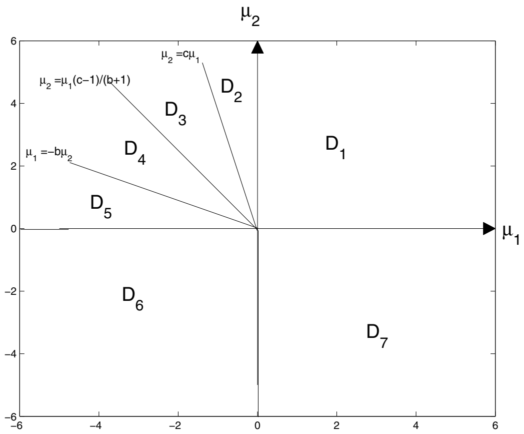


Figure 6. *The bifurcation diagram of* (2.50) *on the* (μ_1, μ_2)*-plane.*

$(\mu_1, \frac{(c-1)\mu_1}{b+1})$ *when* (μ_1, μ_2) *goes anticlockwise in* D_4. Θ_2 *will coincide with* Θ_1 *and disappear.*

(v) *If a point* (μ_1, μ_2) *crosses the line* $\mu_1 = -b\mu_2$ *from* D_4 *to* D_5*, the quasi-periodic solution* Θ_1 *coincides with* Γ_2 *and disappears.*

(vi) *If a point* (μ_1, μ_2) *crosses the line* $\mu_1 = -b\mu_2$ *from* D_5 *to* D_6*, the bifurcated periodic solution* Γ_1 *coincides with the trivial solution and disappears.*

(vii) *If a point* (μ_1, μ_2) *crosses the line* $\mu_1 = -b\mu_2$ *from* D_6 *to* D_7*, the bifurcated periodic solution* Γ_2 *coincides with the trivial solution and disappears.*

The bifurcation diagram is given in Figure 6.

Finally, we need to point out again that B_2 is an important parameter for the dynamical behaviors of (1.2). By Lemma 2.12, we know that ω_1 and ω_2 are not resonant in low order as $B_2 \neq 0$. But as $B_2 = 0$, from Theorem 3.5 of Campbell and Bélair [7], we know that ω_1 and ω_2 are resonant with any possible ratio. The result can be described as follows.

Theorem 2.15. *For* $A_2 > 0$*, system* (1.2) *possesses Hopf–Hopf points with frequencies having all possible ratios* $\omega_1 : \omega_2 = m : n$*,* $m < n \in Z$.

3. Applications to tumor-immune system interaction models.

In this section we apply the results obtained in last section to study the nonlinear dynamics in the tumor–immune system interaction model (1.1) in terms of the model parameters. This will be helpful in determining the model parameters that are crucial in controlling the development and progression of tumor.

3.1. Local analysis.

Model (1.1) has the following possible equilibria:

(1) Tumor-free equilibrium $E_1(0, y_1)$ with $y_1 = \frac{\sigma+\theta}{\mu(0)}$.

(2) Tumor-present equilibria $E_2^k(x_2^k, y_2^k)$ $(x_2^k, y_2^k \neq 0,\ k \in Z)$, which are the intersecting points of the nullclines $\nu(x) = \phi(x, y)$ and $y(\beta(x) - \mu(x)) + \sigma q(x) + \theta = 0$. x_2^k and y_2^k satisfy $\nu(x_2^k) = \phi(x_2^k, y_2^k)$, $y_k = \frac{\sigma q(x_k)+\theta}{\mu(x_2^k)-\beta(x_2^k)}$.

(3) Immune-free equilibrium $E_3(x_3, 0)$ for $\sigma q(x_3) > 0, \theta \geq 0$.

First, we consider (1.1) without immunotherapy; then the linearizing system of (1.1) can be obtained as

$$\begin{cases} x'(t) = x_i\nu'(x_i)x(t-\tau) + (-x_i\phi'_x(x_i,y_i) + (\nu(x_i) - \phi(x_i,y_i)))x(t) - x_i\phi'_y(x_i,y_i)y(t), \\ y'(t) = y_i\beta'(x_i)x(t-\rho) + (\sigma q'(x_i) - y_i\mu'(x_i))x(t) + (\beta(x_i) - \mu(x_i))y(t), \end{cases} \tag{3.1}$$

where (x_i, y_i) are the coordinates of the equilibrium $E_i, i = 1, 2, 3$. It is well known that the stability of E_i depends on the distribution of characteristic roots of (3.1). We now analyze the stability of the equilibrium E_i of (1.1) separately as follows.

3.1.1. Tumor-free equilibrium. It is easy to see that the linearizing system (3.1) at the tumor-free equilibrium $E_1(0, y_0)$ becomes

$$\begin{cases} x'(t) = (\nu(0) - \phi(0,y_0))x(t), \\ y'(t) = y_0\beta'(0)x(t-\rho) + (\sigma q'(0) - y_0\mu'(0))x(t) - \mu(0)y(t). \end{cases} \tag{3.2}$$

Since $\sigma > 0$, for any initial point (x'_0, y'_0) with $x'_0 > 0,\ y'_0 > 0$, the condition for the asymptotic annihilation of x is

$$\nu(0) < \phi(0, y_0).$$

Then $y' \to -\mu(0)y$; that is, $y \to 0$.

From the above analysis, we have the following results.

Theorem 3.1. *In the absence of immunotherapy* ($\theta = 0$) *in* (1.1), *we have the following conclusions:*

(i) *If* $\nu(0) < \phi(0, y_0)$, *then the tumor-free equilibrium* E_1 *is a stable node.*

(ii) *If* $\nu(0) > \phi(0, y_0)$, *then the tumor-free equilibrium* E_1 *is a saddle.*

The results in Theorem 3.1 indicate that when the influx rate σ of the immune effect cells is not zero, if the relative growth rate of tumor cells is less than their loss rate due to the attraction by immune effector cells ($\nu(0) < \phi(0, y_0)$), then tumor cells will die out. Otherwise ($\nu(0) > \phi(0, y_0)$), the tumor-free equilibrium is unstable and tumor cells will appear either at the immune-free equilibrium or at the tumor-present equilibrium. The result also indicates that the stability of the tumor-free equilibrium E_1 will not change for all values of $\tau \geq 0$ and $\rho \geq 0$; that is to say, the Hopf bifurcation will not occur at the tumor-free equilibrium E_1 in the absence of immunotherapy.

Remark 3.2. (a) The linearizing system (3.2) is same as that in d'Onofrio [13] and d'Onofrio et al. [15], so the linear stability of the tumor-free equilibrium for these systems are same. Lemma 2.1 summarized the results and presented more concrete classifications.

(b) In the case of constant immunotherapy, the tumor-free equilibrium of (3.2) is $E_1(0, \frac{\theta+\sigma q(0)}{\mu(0)})$. Because θ is a constant, the tumor-free equilibrium E_1 is locally asymptotically stable if $\theta + \sigma \neq 0, \nu(0) < \phi(0, \frac{\theta+\sigma}{\mu(0)})$ and unstable in the other cases.

3.1.2. Tumor-present equilibrium. The positive (tumor-present) equilibrium $E_2(x_2, y_2)$ of (1.1) is the intersecting point of the two nullclinies. In the absence of immunotherapy, the linearizing system (3.1) at E_2 is

$$\begin{cases} x'(t) = a_{11}x(t-\tau) - a_{12}x(t) - a_{13}y(t), \\ y'(t) = a_{21}x(t-\rho) + a_{22}x(t) + a_{23}y(t), \end{cases} \tag{3.3}$$

where

$$\begin{aligned} a_{11} &= x_2\nu'(x_2) < 0, & a_{12} &= x_2\phi'_x(x_2,y_2) \le 0,\\ a_{13} &= x_2\phi'_y(x_2,y_2) > 0, & a_{21} &= \beta'(x_2)y_2 \ge 0,\\ a_{22} &= \sigma q'(x_2) - \mu'(x_2)y_2, & a_{23} &= \beta(x_2)-\mu(x_2) = \tfrac{-\sigma q(x_2)}{y_2} < 0. \end{aligned}$$

Then the characteristic equation of (3.3) is

$$\lambda^2 + A_1\lambda + A_2 + (B_1\lambda + B_{21})e^{-\lambda\tau} + B_{22}e^{-\lambda\rho} = 0, \tag{3.4}$$

where

$$\begin{aligned} A_1 &= a_{12} - a_{23} = x_2\phi'_x(x_2,y_2) - \beta(x_2) + \mu(x_2),\\ A_2 &= a_{13}a_{22} - a_{12}a_{23} = x_2(\phi'_y(x_2,y_2)(\sigma q'(x_2) - \mu'(x_2)y_2) - (\beta(x_2)-\mu(x_2))\phi'_x(x_2,y_2)),\\ B_1 &= -a_{11} = -x_2\nu'(x_2) > 0,\\ B_{21} &= a_{11}a_{23} = -\tfrac{\sigma x_2 q(x_2)\nu'(x_2)}{y_2} > 0,\\ B_{22} &= a_{13}a_{21} = x_2y_2\phi'_y(x_2,y_2)\beta'(x_2) \ge 0. \end{aligned}$$

Let

$$\begin{aligned} f_1 &= x_2\phi'_x(x_2,y_2) - \beta(x_2) + \mu(x_2) - x_2\nu'(x_2),\\ f_2 &= x_2\phi'_x(x_2,y_2) - \beta(x_2) + \mu(x_2) + x_2\nu'(x_2),\\ f_3 &= x_2(\phi'_y(x_2,y_2)(\sigma q'(x_2) - \mu'(x_2)y_2 + y_2\beta'(x_2)) + (\beta(x_2)-\mu(x_2))(\nu'(x_2) - \phi'_x(x_2,y_2))),\\ f_4 &= x_2(\phi'_y(x_2,y_2)(\sigma q'(x_2) - \mu'(x_2)y_2 - y_2\beta'(x_2)) - (\beta(x_2)-\mu(x_2))(\nu'(x_2) + \phi'_x(x_2,y_2))),\\ f_5 &= 2x_2(\phi'_y(x_2,y_2)(\sigma q'(x_2) - \mu'(x_2)y_2) + (\beta(x_2)-\mu(x_2))\phi'_x(x_2,y_2)),\\ f_6 &= x_2(y_2\phi'_y(x_2,y_2)\beta'(x_2) + (\beta(x_2)-\mu(x_2))\phi'_x(x_2,y_2)). \end{aligned}$$

In the following, we consider the case $\tau = \rho$; then the characteristic equation of (3.3) is

$$\lambda^2 + A_1\lambda + A_2 + (B_1\lambda + B_2)e^{-\lambda\tau} = 0. \tag{3.5}$$

Define

$$\omega_\pm^2 = \frac{1}{2}\left[(f_5 - f_1f_2) \pm \sqrt{(f_1f_2)^2 + 2f_5f_1f_2 + 4f_6^2}\right] \tag{3.6}$$

and

(3.7)
$$\tau_j^\pm = \begin{cases} \frac{1}{\omega_\pm}\left(2j\pi + \arccos\left\{\frac{(f_6+f_1f_2)\omega_\pm^2 - f_5f_6}{(f_1+x_2\nu'(x_2))^2\omega_\pm^2 \pm f_6^2}\right\}\right) & \text{if } f_6f_1 + x_2\nu'(x_2)(f_6 - \omega_\pm^2 + f_5) > 0,\\ \frac{1}{\omega_\pm}\left((2j+1)\pi - \arccos\left\{\frac{(f_6+f_1f_2)\omega_\pm^2 - f_5f_6}{(f_1+x_2\nu'(x_2))^2\omega_\pm^2 \pm f_6^2}\right\}\right) & \text{if } f_6f_1 + x_2\nu'(x_2)(f_6 - \omega_\pm^2 + f_5) < 0. \end{cases}$$

By Theorems 2.2–2.4, we have the following stability results.

Theorem 3.3. *Let $\tau_j^\pm (j = 1, 2, \dots)$ be defined by (3.7), and assume that*

$$f_1 > 0, \;\; f_3 > 0. \tag{3.8}$$

(i) *If*

$$f_5 - f_1 f_2 < 0, \quad f_3 f_4 > 0, \quad or \quad f_5 - f_1 f_2 < 4 f_3 f_4, \tag{3.9}$$

then $E_2(x_2, y_2)$ *of* (1.1) *is asymptotically stable for all* $\tau \geq 0$.

(ii) *If*

$$f_3 f_4 < 0 \quad or \quad f_5 - f_1 f_2 > 0 \quad and \quad (f_5 - f_1 f_2)^2 = 4 f_3 f_4, \tag{3.10}$$

then $E_2(x_2, y_2)$ *is stable for all* $\tau \in (0, \tau_0^+)$ *and unstable for* $\tau > \tau_0$.

(iii) *If*

$$f_5 - f_1 f_2 > 0, \quad f_3 f_4 > 0, \quad and \quad (f_5 - f_1 f_2)^2 > 4 f_3 f_4, \tag{3.11}$$

then there is a positive integer k *such that* E_2 *is stable for*

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

and unstable for

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

(iv) *If* $f_5^2 < f_6^2$ *holds, then system* (1.1) *undergoes a Hopf bifurcation at* $E_2(x_2, y_2)$ *as* $\tau = \tau_k^+$ *such that* $\tau_k \neq \tau_l$ *for any nonnegative integer number* $s \neq l$.

In order to analyze the stability of the positive equilibria of model (1.1), we use the functions proposed in d'Onofrio [11] as an example, that is, $\nu(x) = 1.636(1-0.002x)$, $\phi(x, y) = y$, $\beta(x) = \frac{1.131x}{20.19+x}$, $\sigma q(x) = 0.1181$, $\mu(x) = 0.00311x + 0.3743$. Then (1.1) has a tumor-free equilibrium (0, 0.315522) which is a saddle and three positive equilibria: a microscopic equilibrium point (8.18971, 1.6092) which is locally asymptotically stable, an unstable saddle (267.798, 0.759765), and a macroscopic equilibrium point (447.134, 0.17298) which is also locally asymptotically stable. Since the stability of the saddle does not change with small perturbation, we analyze only the local stability of the two stable equilibria (8.18971, 1.6092) and (447.134, 0.172977) as follows.

(a) For the equilibrium (8.18971, 1.6092), we know that $a_{11} = -0.0268, a_{12} = 0$, $a_{13} = 1.6902, a_{21} = 0.0456, a_{22} = -0.005$, and $a_{23} = -0.0734$; then $A_1 = 0.0734$, $A_2 = -0.008451$, $B_1 = 0.0268$, $B_2 = 0.07904$, and $\omega^2 = 0.0685379$. It is obvious that $A_1 > B_1$, $B_2 > |A_2|$, and $B_2 A_1 + B_1(\omega_\pm^2 - A_2) = 0.00786484 > 0$. If B_2 varies from 0, then the stability region is when B_2 reaches $\tau = \tau_0^+$. The stable regions are illustrated by the shadowed areas bounded by the dashed lines in Figure 7. In this case, $B_2 = 0.07904$; then we can obtain that the equilibrium is stable as $\tau < 1.27248$.

(2) For the equilibrium (447.134, 0.172977), we know that $a_{11} = -1.46302, a_{12} = 0$, $a_{13} = 0.172977, a_{21} = 0.000169, a_{22} = -0.000537958$, and $a_{23} = -0.68275$; then $A_1 = -0.68275$, $A_2 = -0.00009$, $B_1 = 1.46302$, $B_2 = 0.998906$, and $\omega^2 = 2.1403$. It is obvious that $A_1 < B_1$, $B_2 > |A_2|$, and $B_2 A_1 + B_1(\omega_\pm^2 - A_2) = 2.44943 > 0$. If B_2 varies from 0, then the stability region is when B_2 reaches $\tau = \tau_0^+$. The stable regions are illustrated by the

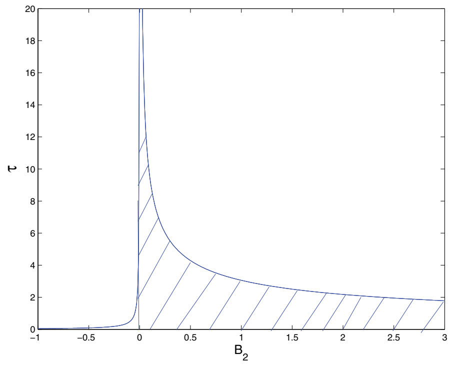


Figure 7. *The local stability regions of the equilibrium* $(8.18971, 1.6092)$ *with blue dashed lines.*

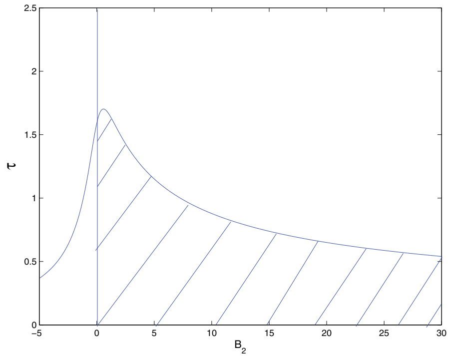


Figure 8. *The local stability regions of the equilibrium* $(447.134, 0.172977)$ *with blue dashed lines.*

blue shadowed areas bounded by the dashed lines in Figure 8. Since $B_2 = 0.998906$, we can see that the equilibrium is stable as $\tau < 0.476779$.

Remark 3.4. If the immunotherapy is constant, then the variational system of (1.1) at E_2 is same as (3.3); we need only replace (x_2, y_2) with (x_2', y_2'), and then we can analyze the stability of E_2 in a similar way, where (x_2', y_2') is the positive equilibrium of (1.1) with immunotherapy.

3.1.3. Hopf bifurcation. Let $a = \tau - \tau_k$. Then $a = 0$ is a Hopf bifurcation value of (1.1) with $\tau = \rho$. Set $\bar{t} = \tau t$, $\bar{y} = y - y_2$, and $\bar{x} = x - x_2$, dropping the bars; then (1.1) can be written as a functional differential equation in $\mathcal{C} = C([-1, 0), \mathbb{R}^2)$ as

$$x'(t) = L_a(x_t) + R(a, x_t), \tag{3.12}$$

where $x(t) = (x_1, x_2)^T \in \mathbb{R}^2$, $L_a : \mathcal{C} \to \mathbb{R}$, and $R : \mathbb{R} \times \mathcal{C} \to \mathbb{R}$ are given in (2.24), where a_{ij} are defined in subsection 3.1.2, in which

$$D_1 = \begin{pmatrix} d_{11}, & d_{12}, & d_{13} \\ d_{21} & d_{22} & 0 \end{pmatrix} \tag{3.13}$$

with

$$\begin{aligned}
d_{11} &= \tfrac{\partial\phi(x_2,y_2)}{\partial x} + \tfrac{x_2\partial^2\phi(x_2,y_2)}{2\partial x^2}, & d_{12} &= \tfrac{\partial\phi(x_2,y_2)}{\partial y} + \tfrac{x_2\partial^2\phi(x_2,y_2)}{\partial x\partial y},\\
d_{13} &= \tfrac{x_2\partial^2\phi(x_2,y_2)}{\partial y^2}, & d_{21} &= \tfrac{1}{2}(\sigma q''(x_2) - \mu''(x_2)y_2),\\
d_{22} &= -\mu'(x_2), & &0,
\end{aligned}$$

$$D_2 = \begin{pmatrix} \frac{x_2}{2}\nu''(x_2), & \nu'(x_2), & 0\\ \frac{y_2}{2}\beta''(x_2), & 0, & \beta'(x_2)\end{pmatrix},$$

$$E_1 = \begin{pmatrix} e_{11}, & e_{12}, & e_{13}, & e_{14}\\ \frac{\sigma q^{(3)}(x_2)-\mu^{(3)}(x_2)y_2}{6}, & -\frac{\mu''(x_2)}{2}, & 0, & 0\end{pmatrix}, \tag{3.14}$$

with

$$\begin{aligned}
e_{11} &= \tfrac{\partial^2\phi(x_2,y_2)}{2\partial x^2} + \tfrac{x_2\partial^3\phi(x_2,y_2)}{6\partial x^3}, & e_{12} &= \tfrac{\partial^2\phi(x_2,y_2)}{\partial x\partial y} + \tfrac{x_2\partial^3\phi(x_2,y_2)}{2\partial x^2\partial y},\\
e_{13} &= \tfrac{\partial^2\phi(x_2,y_2)}{2\partial y^2} + \tfrac{x_2\partial^3\phi(x_2,y_2)}{2\partial x\partial y^2}, & e_{14} &= \tfrac{x_2\partial^3\phi(x_2,y_2)}{6\partial y^3},\\
e_{21} &= \tfrac{\sigma q^{(3)}(x_2)-\mu^{(3)}(x_2)y_2}{6}, & e_{22} &= -\tfrac{\mu''(x_2)}{2},
\end{aligned}$$

$$E_2 = \begin{pmatrix} \frac{x_2}{6}\nu^{(3)}(x_2), & \frac{\nu''(x_2)}{2}, & 0, & 0, & 0, & 0\\ \frac{y_2}{6}\beta^{(3)}(x_2), & 0, & \frac{\beta''(x_2)}{2}, & 0, & 0, & 0\end{pmatrix},$$

$$F_1 = \begin{pmatrix} f_{11}, & f_{12}, & f_{13}, & f_{14}, & f_{15}\\ \frac{\sigma q^{(4)}(x_2)-\mu^{(4)}(x_2)y_2}{24}, & -\frac{\mu^{(3)}(x_2)}{6}, & 0, & 0, & 0\end{pmatrix},$$

with

$$\begin{aligned}
f_{11} &= \tfrac{\partial^3\phi(x_2,y_2)}{6\partial x^3} + \tfrac{x_2\partial^4\phi(x_2,y_2)}{24\partial x^4}, & f_{12} &= \tfrac{\partial^3\phi(x_2,y_2)}{2\partial x^2\partial y} + \tfrac{x_2\partial^4\phi(x_2,y_2)}{6\partial x^3\partial y},\\
f_{13} &= \tfrac{\partial^3\phi(x_2,y_2)}{2\partial x\partial y^2} + \tfrac{x_2\partial^4\phi(x_2,y_2)}{4\partial x^2\partial y^2}, & f_{14} &= \tfrac{\partial^3\phi(x_2,y_2)}{6\partial y^3} + \tfrac{x_2\partial^4\phi(x_2,y_2)}{6\partial x\partial y^3}, \quad f_{15} = \tfrac{x_2\partial^4\phi(x_2,y_2)}{24\partial y^4},
\end{aligned}$$

$$F_2 = \begin{pmatrix} \frac{x_2}{24}f^{(4)}(x_2), & \frac{1}{6}\nu^{(3)}(x_2), & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0\\ \frac{y_2}{24}\beta^{(4)}(x_2), & 0, & \frac{1}{6}\beta^{(3)}(x_2), & 0, & 0, & 0, & 0, & 0, & 0, & 0\end{pmatrix},$$

$$H_1 = \begin{pmatrix} h_{11}, & h_{12}, & h_{13}, & h_{14}, & h_{15}, & h_{16}\\ \frac{\sigma q^{(5)}(x_2)-\mu^{(5)}(x_2)y_2}{120}, & -\frac{\mu^{(4)}(x_2)}{24}, & 0, & 0, & 0, & 0\end{pmatrix},$$

in which

$$\begin{aligned}
h_{11} &= \tfrac{\partial^4\phi(x_2,y_2)}{24\partial x^4} + \tfrac{x_2\partial^5\phi(x_2,y_2)}{120\partial x^5}, & h_{12} &= \tfrac{\partial^4\phi(x_2,y_2)}{6\partial^3 x\partial y} + \tfrac{x_2\partial^5\phi(x_2,y_2)}{24\partial x^4\partial y},\\
h_{13} &= \tfrac{\partial^4\phi(x_2,y_2)}{4\partial x^2\partial y^2} + \tfrac{x_2\partial^5\phi(x_2,y_2)}{12\partial x^3\partial y^2}, & h_{14} &= \tfrac{\partial^4\phi(x_2,y_2)}{6\partial x^2\partial y^2} + \tfrac{x_2\partial^5\phi(x_2,y_2)}{12\partial x^3\partial y^2},\\
h_{15} &= \tfrac{\partial^4\phi(x_2,y_2)}{24\partial y^4} + \tfrac{x_2\partial^4\phi(x_2,y_2)}{24\partial x\partial y^4}, & h_{16} &= \tfrac{x_2\partial^5\phi(x_2,y_2)}{120\partial y^5},
\end{aligned}$$

$$H_2 = \begin{pmatrix} \frac{x_2}{120}f^{(5)}(x_2), & \frac{1}{24}f^{(4)}(x_2), & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0\\ \frac{y_2}{120}\beta^{(5)}(x_2), & 0, & \frac{1}{24}\beta^{(4)}(x_2), & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0\end{pmatrix}.$$

By the Riesz representation theorem, there exists a bounded variation matrix $\eta(\theta, a)$ whose components are functions of bounded variation in $\theta \in [-\tau_0, 0]$ such that

$$L_a\phi = \int_{-1}^{0} d\eta(\theta, 0)\phi(\theta) \quad \text{for} \quad \phi \in \mathcal{C}. \tag{3.15}$$

In fact, we can choose

$$\eta(\theta, a) = (\tau_k + a)\begin{pmatrix} -a_{12} & -a_{13} \\ a_{22} & a_{23} \end{pmatrix}\delta(\theta) - (\tau_k + a)\begin{pmatrix} a_{11} & 0 \\ a_{21} & 0 \end{pmatrix}\delta(\theta + 1), \tag{3.16}$$

where δ is defined by

$$\delta(\theta) = \begin{cases} 0, & \theta \neq 0 \\ 1, & \theta = 0. \end{cases}$$

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

$$A(a)\varphi = \begin{cases} \frac{d\varphi}{d\theta}, & \theta \in [-1, 0), \\ \int_{-1}^{0} d\eta(a, s)\varphi(s), & \theta = 0, \end{cases} \quad \text{and} \quad R(a)\varphi = \begin{cases} 0, & \theta \in [-1, 0), \\ R(a, \varphi), & \theta = 0. \end{cases}$$

Then (3.12) can be written as

$$x_t' = A(a)x_t + R(a)x_t, \tag{3.17}$$

where $x_t(t) = x(t + \theta)$ for $\theta \in [-1, 0]$. For $\varphi \in C^1([0, 1], (\mathbb{R}^2)^*)$, define

$$A^*\psi(s) = \begin{cases} -\frac{d\psi}{d\theta}, & s \in (0, 1], \\ \int_{-1}^{0} d\eta^T(t, 0)\psi(-t), & s = 0, \end{cases}$$

and a bilinear inner product

$$\langle \psi(s), \varphi(\theta)\rangle = \overline{\psi}(0)\varphi(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \overline{\psi}^T(\xi - \theta)d\eta(\theta)\varphi(\xi)d\xi,$$

where $\eta(\theta) = \eta(\theta, 0)$; then $A(0)$ and A^* are adjoint operators. By the analysis in the last section, we know that $\pm i\omega\tau_k$ are eigenvalues of $A(0)$; thus they are also eigenvalues of A^*. We first need to compute the eigenvectors of $A(0)$ and A^* corresponding to $i\omega\tau_k$ and $-i\omega\tau_k$, respectively. For $A(0)$, it is easy to obtain that the eigenvector basis of $i\omega_0$ is $p(\theta) = (1, \alpha)^T e^{i\omega\theta\tau_k}$ and $p^*(\theta) = D(1, \alpha^*)^T e^{is\omega\tau_k}$, where $\alpha = \frac{a_{21}e^{-i\omega\tau_k} + a_{22}}{i\omega - a_{23}}$, $\alpha^* = \frac{a_{13}}{i\omega + a_{23}}$. In order to ensure that $\langle p^*(\theta), p(\theta)\rangle = 1$, we have

$$D = \left(1 + \overline{\alpha}\alpha^* - \tau_k(a_{21}\alpha^* + a_{11})e^{i\omega\tau_k}\right)^{-1}. \tag{3.18}$$

In the following, we will compute the coordinates on the center manifold C_a at $a = 0$. Let x_t be the solution of (3.12) when $a = 0$. Define $z = \langle p^*, x_t\rangle$, $W(t, \theta) = x_t(\theta) - 2\mathrm{Re}\{z(t)p(\theta)\}$.

On the center manifold C_0, $W(t,\theta) = W(z(t),\overline{z}(t),\theta)$ with the form $W(z(t),\overline{z}(t),\theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\overline{z} + W_{02}(\theta)\frac{\overline{z}^2}{2} + W_{30}(\theta)\frac{z^3}{6} + \cdots$. For the solution $x_t \in C_0$ of (3.12), we have

$$z'(t) = i\omega\tau_k z + g(z,\overline{z},a), \tag{3.19}$$

where

$$\begin{aligned}
g(z,\overline{z}) = {} & \frac{g_{20}(\theta)}{2}z^2 + g_{11}(\theta)z\overline{z} + \frac{g_{02}(\theta)}{2}\overline{z}^2 + \frac{g_{30}(\theta)}{6}z^3 + \frac{g_{21}(\theta)}{2}z^2\overline{z} + \frac{g_{12}(\theta)}{2}z\overline{z}^2 \\
& + \frac{g_{03}(\theta)}{6}\overline{z^3} + \frac{g_{31}(\theta)}{6}z^3\overline{z} + \frac{g_{40}(\theta)}{24}z^4 + \frac{g_{31}(\theta)}{4}z^3\overline{z} + \frac{g_{22}(\theta)}{6}z^2\overline{z}^2 + \frac{g_{13}(\theta)}{4}z\overline{z}^3 \\
& + \frac{g_{04}(\theta)}{24}\overline{z}^4 + \frac{g_{41}(\theta)}{24}z^4\overline{z} + \frac{g_{32}(\theta)}{12}z^3\overline{z}^2 + \cdots,
\end{aligned} \tag{3.20}$$

$$\begin{aligned}
g_{20} = {} & \tau_k\overline{D}\Bigg(\frac{\partial\phi(x_2,y_2)}{\partial x} + \frac{x_2\partial^2\phi(x_2,y_2)}{2\partial x^2} + \left(\frac{\partial\phi(x_2,y_2)}{\partial y} + \frac{x_2\partial^2\phi(x_2,y_2)}{\partial x\partial y}\right)\alpha \\
& + \left(\frac{x_2\partial^2\phi(x_2,y_2)}{\partial y^2}\right)\alpha^2 + \frac{1}{2}(\sigma q''(x_2) - \mu''(x_2)y_2)\overline{\alpha^*} - \mu'(x_2)\overline{\alpha^*}\alpha \\
& + \frac{x_2}{2}\nu''(x_2)e^{-2i\omega\tau_k} + \nu'(x_2)e^{-i\omega\tau_k} + \frac{y_2}{2}\beta''(x_2)\overline{\alpha^*}e^{-2i\omega\tau_k} + \overline{\alpha^*}\alpha\beta'(x_2)e^{-i\omega\tau_k}\Bigg),
\end{aligned}$$

$$\begin{aligned}
g_{11} = {} & \tau_k\overline{D}\Bigg(\frac{2\partial\phi(x_2,y_2)}{\partial x} + \frac{x_2\partial^2\phi(x_2,y_2)}{\partial x^2} + \left(\frac{\partial\phi(x_2,y_2)}{\partial y} + \frac{x_2\partial^2\phi(x_2,y_2)}{\partial x\partial y}\right)(\alpha+\overline{\alpha}) \\
& + \left(\frac{2x_2\partial^2\phi(x_2,y_2)}{\partial y^2})\alpha\overline{\alpha} + (\sigma q''(x_2) - \mu''(x_2)y_2\right)\overline{\alpha^*} - \mu'(x_2)\overline{\alpha^*}(\alpha+\overline{\alpha}) \\
& + x_2\nu''(x_2) + \nu'(x_2)(e^{-i\omega\tau_k} + e^{i\omega\tau_k}) + y_2\beta''(x_2)\overline{\alpha^*} \\
& + \overline{\alpha^*}\beta'(x_2)(e^{-i\omega\tau_k}\overline{\alpha} + e^{i\omega\tau_k}\alpha)\Bigg),
\end{aligned}$$

$$\begin{aligned}
g_{02} = {} & \tau_k\overline{D}\Bigg(\frac{\partial\phi(x_2,y_2)}{\partial x} + \frac{x_2\partial^2\phi(x_2,y_2)}{2\partial x^2} + \left(\frac{\partial\phi(x_2,y_2)}{\partial y} + \frac{x_2\partial^2\phi(x_2,y_2)}{\partial x\partial y}\right)\overline{\alpha} \\
& + \left(\frac{x_2\partial^2\phi(x_2,y_2)}{\partial y^2}\right)\overline{\alpha^2} + \frac{1}{2}(\sigma q''(x_2) - \mu''(x_2)y_2)\overline{\alpha^*} - \mu'(x_2)\overline{\alpha^*}\overline{\alpha} \\
& + \frac{x_2}{2}\nu''(x_2)e^{2i\omega\tau_k} + \nu'(x_2)e^{i\omega\tau_k} + \frac{y_2}{2}\beta''(x_2)\overline{\alpha^*}e^{2i\omega\tau_k} + \overline{\alpha^*}\overline{\alpha}\beta'(x_2)e^{i\omega\tau_k}\Bigg),
\end{aligned}$$

$$\begin{aligned}
g_{21} = {} & \tau_k\overline{D}(3e_{11} + (2\alpha+\overline{\alpha})e_{12} + (\alpha^2 + 2\alpha\overline{\alpha})e_{13} + 3\alpha^2\overline{\alpha}e_{14} + 3\overline{\alpha^*}e_{21} + \overline{\alpha^*}(2\alpha+\overline{\alpha})e_{22} \\
& + \frac{x_2}{2}\nu^{(3)}(x_2)e^{-i\omega\tau_k} + \frac{\nu''(x_2)}{2}(e^{-2i\omega\tau_k} + 2) + \frac{\overline{\alpha^*}}{2}\beta^{(3)}(x_2)e^{-i\omega\tau_k} \\
& + \frac{\overline{\alpha^*}}{2}\beta''(x_2)(\overline{\alpha}e^{-2i\omega\tau_k} + 2\alpha) + d_{12}\left(\frac{W_{20}^{(1)}(0)}{2}\overline{\alpha} + \frac{W_{20}^{(2)}(0)}{2} + \alpha W_{11}^{(1)}(0) + W_{11}^{(2)}(0)\right) \\
& + d_{11}(W_{20}^{(1)}(0) + 2W_{11}^{(1)}(0)) + d_{13}(W_{20}^{(2)}(0)\overline{\alpha} + 2\alpha W_{11}^{(2)}(0)) + d_{21}\overline{\alpha^*}(W_{20}^{(1)}(0) \\
& + 2W_{11}^{(1)}(0)) + d_{22}\overline{\alpha^*}\left(\frac{W_{20}^{(1)}(0)}{2}\overline{\alpha} + \frac{W_{20}^{(2)}(0)}{2} + W_{11}^{(1)}(0)\alpha + W_{11}^{(2)}(0)\right)
\end{aligned}$$

$$
\begin{aligned}
&+\frac{x_2}{2}\nu''(x_2)(W_{20}^{(1)}(-1)e^{i\omega\tau_k}+2W_{11}^{(1)}(-1)e^{-i\omega\tau_k})\\
&+\nu'(x_2)\left(\frac{W_{20}^{(1)}(-1)}{2}+\frac{W_{20}^{(1)}(0)}{2}e^{i\omega\tau_k}+W_{11}^{(1)}(-1)+e^{-i\omega\tau_k}W_{11}^{(1)}(0)\right)\\
&+\frac{y_2}{2}\beta''(x_2)\overline{\alpha^*}(W_{20}^{(1)}(-1)e^{i\omega\tau_k}+2W_{11}^{(1)}(-1)e^{-i\omega\tau_k})\\
&+\overline{\alpha^*}\beta'(x_2)(W_{20}^{(1)}(-1)\overline{\alpha}+2W_{11}^{(1)}(-1)\alpha+W_{20}^{(2)}(0)e^{i\omega\tau_k}+2W_{11}^{(2)}(0)e^{-i\omega\tau_k})),
\end{aligned}
$$

$$
\begin{aligned}
g_{12}=\tau_k\overline{D}\Bigg(&3e_{11}+(\alpha+2\overline{\alpha})e_{12}+(\overline{\alpha}^2+2\alpha\overline{\alpha})e_{13}+3\alpha\overline{\alpha}^2e_{14}+3\overline{\alpha^*}e_{21}+\overline{\alpha^*}(\alpha+2\overline{\alpha})e_{22}\\
&+\frac{x_2}{2}\nu^{(3)}(x_2)e^{i\omega\tau_k}+\frac{\nu''(x_2)}{2}(e^{2i\omega\tau_k}+2)+\frac{\overline{\alpha^*}}{2}\beta^{(3)}(x_2)e^{i\omega\tau_k}\\
&+\frac{\overline{\alpha^*}}{2}\beta''(x_2)(\alpha e^{2i\omega\tau_k}+2\overline{\alpha})+d_{12}\Bigg(\frac{W_{02}^{(1)}(0)}{2}\alpha+\frac{W_{02}^{(2)}(0)}{2}\\
&\qquad\qquad+\overline{\alpha}W_{11}^{(1)}(0)+W_{11}^{(2)}(0)\Bigg)\\
&+d_{11}(W_{02}^{(1)}(0)+2W_{11}^{(1)}(0))+d_{13}(W_{02}^{(2)}(0)\alpha+2\overline{\alpha}W_{11}^{(2)}(0))+d_{21}\overline{\alpha^*}(W_{02}^{(1)}(0)\\
&+2W_{11}^{(1)}(0))+d_{22}\overline{\alpha^*}\left(\frac{W_{02}^{(1)}(0)}{2}\alpha+\frac{W_{02}^{(2)}(0)}{2}+W_{11}^{(1)}(0)\overline{\alpha}+W_{11}^{(2)}(0)\right)\\
&+\frac{x_2}{2}\nu''(x_2)(W_{02}^{(1)}(-1)e^{-i\omega\tau_k}+2W_{11}^{(1)}(-1)e^{i\omega\tau_k})\\
&+\nu'(x_2)\left(\frac{W_{02}^{(1)}(-1)}{2}+\frac{W_{02}^{(1)}(0)}{2}e^{-i\omega\tau_k}+W_{11}^{(1)}(-1)+e^{i\omega\tau_k}W_{11}^{(1)}(0)\right)\\
&+\frac{y_2}{2}\beta''(x_2)\overline{\alpha^*}(W_{02}^{(1)}(-1)e^{-i\omega\tau_k}+2W_{11}^{(1)}(-1)e^{+i\omega\tau_k})\\
&+\overline{\alpha^*}\beta'(x_2)(W_{02}^{(1)}(-1)\alpha+2W_{11}^{(1)}(-1)\overline{\alpha}+W_{02}^{(2)}(0)e^{-i\omega\tau_k}+2W_{11}^{(2)}(0)e^{i\omega\tau_k})\Bigg),
\end{aligned}
$$

$$
\begin{aligned}
g_{30}=\tau_k\overline{D}\Bigg(&e_{11}+\alpha e_{12}+\alpha^2e_{13}+\alpha^3e_{14}+\overline{\alpha^*}e_{21}+\overline{\alpha^*}\alpha e_{22}+\frac{x_2}{6}\nu^{(3)}(x_2)e^{-3i\omega\tau_k}\\
&+\frac{\nu''(x_2)}{2}\alpha e^{-2i\omega\tau_k}+\frac{y_2\overline{\alpha^*}}{6}\beta^{(3)}(x_2)e^{-3i\omega\tau_k}+\frac{\overline{\alpha^*}}{2}\beta''(x_2)\alpha e^{-2i\omega\tau_k}+d_{11}W_{20}^{(1)}(0)\\
&+d_{12}\left(\frac{W_{20}^{(1)}(0)}{2}\alpha+\frac{W_{20}^{(2)}(0)}{2}\right)+d_{13}W_{20}^{(1)}(0)\alpha+d_{22}\overline{\alpha^*}\left(\frac{W_{20}^{(1)}(0)}{2}\alpha+\frac{W_{20}^{(2)}(0)}{2}\right)\\
&+d_{21}\overline{\alpha^*}W_{20}^{(1)}(0)+x_2\nu''(x_2)W_{20}^{(2)}(-1)e^{-i\omega\tau_k}\\
&+\nu'(x_2)(W_{20}^{(1)}(-1)+W_{20}^{(1)}(0)e^{-i\omega\tau_k})\\
&+\frac{y_2}{2}\beta''(x_2)\overline{\alpha^*}W_{20}^{(1)}(-1)e^{-i\omega\tau_k}+\overline{\alpha^*}\beta'(x_2)(W_{20}^{(1)}(-1)\alpha+W_{20}^{(0)}(0)e^{-i\omega\tau_k})\Bigg),
\end{aligned}
$$

$$
\begin{aligned}
g_{03} = \tau_k \overline{D}\Bigg(& e_{11} + \overline{\alpha} e_{12} + \overline{\alpha}^2 e_{13} + \overline{\alpha}^3 e_{14} + \overline{\alpha^*} e_{21} + \overline{\alpha^*}\,\overline{\alpha} e_{22} + \frac{x_2}{6}\nu^{(3)}(x_2) e^{3i\omega\tau_k} \\
& + \frac{\nu''(x_2)}{2}\overline{\alpha} e^{2i\omega\tau_k} + \frac{y_2\overline{\alpha^*}}{6}\beta^{(3)}(x_2)e^{3i\omega\tau_k} + \frac{\overline{\alpha^*}}{2}\beta''(x_2)\overline{\alpha}e^{2i\omega\tau_k} + d_{11}W_{02}^{(1)}(0) \\
& + d_{12}\left(\frac{W_{02}^{(1)}(0)}{2}\overline{\alpha} + \frac{W_{02}^{(2)}(0)}{2}\right) \\
& + d_{13}W_{02}^{(1)}(0)\overline{\alpha} + d_{22}\overline{\alpha^*}\left(\frac{W_{02}^{(1)}(0)}{2}\overline{\alpha} + \frac{W_{02}^{(2)}(0)}{2}\right) \\
& + d_{21}\overline{\alpha^*}W_{02}^{(1)}(0) + x_2\nu''(x_2)W_{02}^{(2)}(-1)e^{i\omega\tau_k} + \nu'(x_2)(W_{02}^{(1)}(-1) + W_{02}^{(1)}(0)e^{i\omega\tau_k}) \\
& + \frac{y_2}{2}\beta''(x_2)\overline{\alpha^*}W_{02}^{(1)}(-1)e^{i\omega\tau_k} + \overline{\alpha^*}\beta'(x_2)(W_{20}^{(1)}(-1)\overline{\alpha} + W_{02}^{(0)}(0)e^{i\omega\tau_k})\Bigg).
\end{aligned}
$$

Similarly, we can give the expression of g_{31}, g_{22}, g_{40}, and g_{32}; then all useful g_{ij}'s are given. The W_{ij}'s can be obtained with the constant variation formula; we will not go into the details of them here.

To show the results of Theorem 2.9, we still consider the model proposed in d'Onofrio [11] as an example, that is, $\nu(x) = 1.636(1 - 0.002x)$, $\phi(x, y) = y$, $\beta(x) = \frac{1.131x}{20.19+x}$, $\sigma q(x) = 0.1181$, $\mu(x) = 0.00311x + 0.3743$.

It is easy to see $\nu''(x) = \frac{\partial\phi(x,y)}{\partial x} = \frac{\partial^2\phi(x,y)}{\partial y^2} = q'(x) = \mu''(x) = 0$. For the microscopic equilibrium (8.18971, 1.6092), we know that the equilibrium will undergo Hopf bifurcation when $\tau = \tau_0^+$. Then we have $\alpha = -0.0149845 - 0.149707i$, $\alpha^* = -1.67819 - 5.98562i$, and $D = 0.511595 - 0.0555238i$. Also, $g_{20} = 0.013352 - 0.0989036i$, $g_{11} = 0.0140638 - 0.104576i$, and $g_{02} = -0.0332515 + 0.0830015i$. In order to compute g_{21}, we need to give W_{11} and W_{20} first. From

$$
W' = x_t' - z'p - \overline{z}'p = \begin{cases} A_0W - 2\mathrm{Re}\{\bar{p}^T(0)R_0p(\theta)\}, & \theta \in [-\tau_1, 0), \\ A_0W - 2\mathrm{Re}\{\bar{p}^T(0)R_0p(\theta)\} + R_0, & \theta = 0, \end{cases} \stackrel{\text{def}}{=} A_0W + H(z, \bar{z}, \theta), \tag{3.21}
$$

where

$$
H(z, \overline{z}) = H_{20}(\theta)\frac{z^2}{2} + H_{11}(\theta)z\overline{z} + H_{02}(\theta)\frac{\overline{z}^2}{2} + H_{30}(\theta)\frac{z^3}{6} + \cdots,
$$

we can obtain

$$
W_{20}(\theta) = \frac{ig_{20}}{\omega_0}p(0)e^{i\omega_0\theta} + \frac{i\overline{g_{02}}}{3\omega_0}\overline{p(0)}e^{-i\omega_0\theta} + K_1e^{2i\omega_0\theta}. \tag{3.22}
$$

Similarly,

$$
W_{11}(\theta) = \frac{ig_{11}}{\omega_0}p(0)e^{i\omega_0\theta} + \frac{i\overline{g_{11}}}{\omega_0}\overline{p(0)}e^{-i\omega_0\theta} + K_2, \tag{3.23}
$$

where $K_i = (K_i^{(1)}, K_i^{(2)})^T \in R^2, i = 1, 2$, are constant vectors. With the boundary conditions, we can obtain $K_1 = (0.281858 - 1.72499i, -0.129063 + 0.0178572i)$ and $K_2 = (0.178478 - 1.70488i, -0.128644 + 0.0179399i)$.

Hence

$$W_{20}^1(0) = 0.479785 - 1.67155i, \qquad W_{20}^2(0) = - - 0.128029 - 0.0422056i,$$
$$W_{20}^1(-1) = 0.451428 - 1.60976i, \qquad W_{20}^2(-1) = -0.104795 - 0.0115331i,$$

and

$$W_{11}^1(0) = 0.178478 - 1.70488i, \qquad W_{11}^2(0) = -0.138052 + 0.0166747i,$$
$$W_{11}^1(-1) = 0.744189 - 1.41978i, \qquad W_{11}^2(-1) = -0.125589 - 0.07208i.$$

Then $g_{21} = -0.222815 - 0.0610833i$ and $C_1(0) = -0.107224 - 0.0832058$. Now we have the following results.

Theorem 3.5. *The system* (1.1) *has a supercritical Hopf bifurcation at the equilibrium* $(8.18971, 1.6092)$ *for* $\tau = \tau_0$*, the bifurcating periodic solution is stable.*

Similarly, we can give the results about the macroscopic equilibrium point (447.134, 0.17298). We simulate the periodic solutions bifurcated from the two stable equilibria (8.18971, 1.6092) and (447.134, 0.172977) with bifurcation parameters $\tau_k = 2.08803$ and $\tau_k = 0.333814$, which are given in (a)(b) and (c)(d) in Figure 9, respectively.

For the model proposed in d'Onofrio [11], which we have analyzed, we can obtain all positive equilibria. Then the results of the Bautin bifurcation can be obtained similarly; we will not provide the details here for the sake of simplicity.

3.1.4. Hopf–Hopf bifurcation. In the following, we consider Hopf–Hopf bifurcation in the tumor–immune system interaction model (1.1). Noting (2.12), we know that the eigenvalues $\pm i\omega_j, j = 1, 2$, of (2.4) are simple. On the other hand, we know that $A(a)$ has simple eigenvalues $\lambda_1(a)$ and $\lambda_2(a)$ with $\lambda_i(0) = i\omega_j,\ j = 1, 2$. From Theorem 2.2, we know that $A(a)$ has two eigenvectors $p_1(a, \theta)$ and $p_2(a, \theta)$ corresponding to the eigenvalues $\lambda_1(a)$ and $\lambda_2(a)$ and the adjoint eigenvectors $q_j(a, \theta),\ j = 1, 2$, corresponding to the eigenvalues $\bar{\lambda}_j(a)$. Suppose $p_j(\theta) \triangleq p_j(0, \theta),\ q_j(\theta) \triangleq q_j(0, \theta),\ j = 1, 2$, are the eigenvectors of $A(0)$ and $A^*(0)$, respectively; then

$$p_j(\theta) = (1,\ \gamma_j)^T e^{i\omega_j\tau_k\theta}, \qquad q_j(\xi) = D_j(1,\ \beta_j)^T e^{i\omega_j\tau_k\xi},$$

where $\gamma_j = \frac{a_{21}e^{-i\omega_j\tau_k}+a_{22}}{i\omega_j - a_{23}}$, $\quad \beta_j = \frac{a_{23}}{i\omega_j + a_{23}}$, and

$$D_j = (1 + \overline{\gamma}_j\beta_j + \tau_k(a_{21}\beta_j + a_{11})e^{i\omega_j\tau_k})^{-1}. \tag{3.24}$$

Define $z_j = \langle q_j, X\rangle,\ j = 1, 2,\quad W(t, \theta) = X_t(\theta) - 2\mathrm{Re}\{z_1(t)q_1(\theta) + z_2(t)q_2(\theta)\}$, where $z = (z_1, z_2) \in \mathcal{C}_a$, and z_j and $\bar{z}_j$ are the local coordinates for $\mathcal{C}_a$ in the direction of q_j and $\bar{q}_j$,

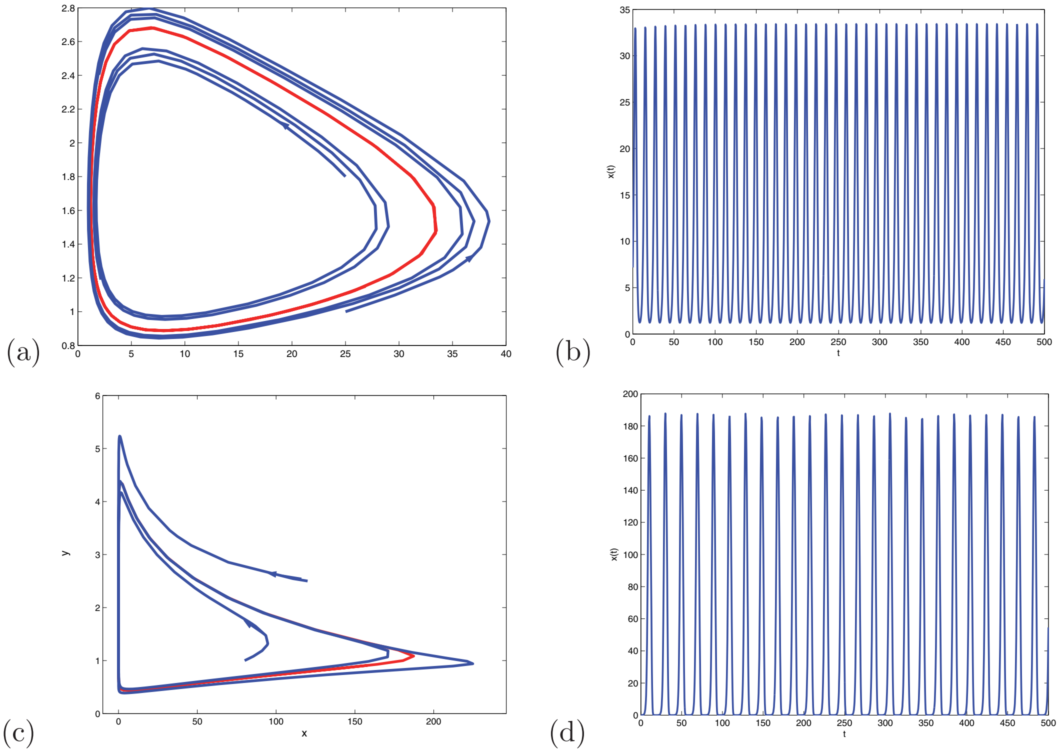


Figure 9. (a) *The periodic solution* $(x(t), y(t))$ *bifurcated from the microscopic equilibrium* $(8.18971, 1.6092)$ *with* $\tau = 0.333814$. (b) *The corresponding solution* $x(t)$ *in terms of time* t. (c) *The periodic solution* $(x(t), y(t))$ *bifurcated from the macroscopic equilibrium* $(447.134, 0.172977)$ *as* $\tau = 2.08803$. (d) *The corresponding solution* $x(t)$ *in terms of time* t.

$j = 1, 2$. If $X_t \in \mathcal{C}_a$ is a solution of (2.26), then on the center manifold $\mathcal{C}_a$, one has the normal form

$$z' = \Lambda z(t) + g(z, a). \tag{3.25}$$

In order to derive the concrete expressions for $g_{ijkl}, i + j + k + l \geq 2$, we will use the normal form and the center manifold theory in Hassard, Kazarinoff, and Wan [22] and derive the explicit formulae determining these properties at the critical value of $a = 0$. From last section, we know that at $a = 0$,

$$\begin{aligned} z_j(t) = \langle q^*, x_t' \rangle &= i\omega_j z_j(t) + \overline{q}_j^{*T} R(W + 2\mathrm{Re}\{z_1 q_1 + z_2 q_2\}) \\ &\triangleq i\omega_j z_j(t) + g(z_1, \overline{z_1}, z_2, \overline{z_2}), \qquad j = 1, 2, \end{aligned}$$

where $g(z_1, \overline{z_1}, z_2, \overline{z_2}) = (g^1(z, a), g^2(z, a))^T, \quad z = (z_1, z_2)^T$. Thus,

$$g^j(z, a) = \overline{q}_j^{*T} R_0(W + 2\mathrm{Re}\{z_1 q_1 + z_2 q_2\}), \tag{3.26}$$

where $R_0(z_1, z_2) = R(0, z_1, z_2)$. Noting that $x_t = (x_{1t}(\theta), x_{2t}(\theta)) = W(t, \theta) + z_1 q(\theta) + \overline{z_1 q(\theta)} + z_2 q(\theta) + \overline{z_2 q(\theta)}$ and $q_j(\theta) = (1, \beta_j)^T e^{i\omega\theta}$, comparing the coefficients of (3.26) and (2.46), g_{ijkl}

can be obtained as follows:

$$
\begin{aligned}
g^1_{2000} &= \tau_k\overline{D}(d_{11} + d_{12}\beta_1 + d_{13}\beta_1^2 + \frac{x_2\nu''(x_2)}{2}e^{-2i\omega_1\tau_k} + \nu'(x_2)e^{-i\omega_1\tau_k}),\\
g^1_{0200} &= \tau_k\overline{D}(d_{11} + d_{12}\overline{\beta_1} + d_{13}\overline{\beta_1^2} + \frac{x_2\nu''(x_2)}{2}e^{2i\omega_1\tau_k} + \nu'(x_2)e^{i\omega_1\tau_k}),\\
g^1_{0020} &= \tau_k\overline{D}(d_{11} + d_{12}\beta_2 + d_{13}\beta_2^2 + \frac{x_2\nu''(x_2)}{2}e^{-2i\omega_2\tau_k} + \nu'(x_2)e^{-i\omega_2\tau_k}),\\
g^1_{0002} &= \tau_k\overline{D}(d_{11} + d_{12}\overline{\beta_2} + d_{13}\overline{\beta_2^2} + \frac{x_2\nu''(x_2)}{2}e^{2i\omega_2\tau_k} + \nu'(x_2)e^{i\omega_2\tau_k}),\\
g^1_{1100} &= \tau_k\overline{D}(2d_{11} + d_{12}(\beta_1 + \overline{\beta_1}) + 2d_{13}\beta_1\overline{\beta_1} + x_2\nu''(x_2)\\
&\quad + \nu'(x_2)(e^{i\omega_1\tau_k} + e^{-i\omega_1\tau_k})),\\
g^1_{1010} &= \tau_k\overline{D}(2d_{11} + d_{12}(\beta_2 + \beta_1) + 2d_{13}\beta_1\beta_2 + x_2\nu''(x_2)e^{-i(\omega_1+\omega_2)\tau_k}\\
&\quad + \nu'(x_2)(e^{-i\omega_2\tau_k} + e^{-i\omega_1\tau_k})),\\
g^1_{1001} &= \tau_k\overline{D}(2d_{11} + d_{12}(\overline{\beta_2} + \beta_1) + 2d_{13}\beta_1\overline{\beta_2} + x_2\nu''(x_2)e^{i(\omega_2-\omega_1)\tau_k}\\
&\quad + \nu'(x_2)(e^{i\omega_2\tau_k} + e^{-i\omega_1\tau_k})),\\
g^1_{0110} &= \tau_k\overline{D}(2d_{11} + d_{12}(\overline{\beta_1} + \beta_2) + 2d_{13}\beta_2\overline{\beta_1} + x_2\nu''(x_2)e^{i(\omega_1-\omega_2)\tau_k}\\
&\quad + \nu'(x_2)(e^{-i\omega_2\tau_k} + e^{i\omega_1\tau_k})),\\
g^1_{0101} &= \tau_k\overline{D}(2d_{11} + d_{12}(\overline{\beta_1} + \overline{\beta_2}) + 2d_{13}\overline{\beta_2\beta_1} + x_2\nu''(x_2)e^{i(\omega_1+\omega_2)\tau_k}\\
&\quad + \nu'(x_2)(e^{i\omega_2\tau_k} + e^{i\omega_1\tau_k})),\\
g^1_{0011} &= \tau_k\overline{D}(2d_{11} + d_{12}(\beta_2 + \overline{\beta_2}) + 2d_{13}\overline{\beta_2}\beta_2 + x_2\nu''(x_2) + \nu'(x_2)(e^{-i\omega_2\tau_k} + e^{i\omega_2\tau_k})),\\
g^1_{2100} &= \tau_k\overline{D}(d_{11}(W^{(1)}_{2000} + 2W^{(1)}_{1100}) + d_{12}(\frac{1}{2}W^{(1)}_{2000}\overline{\beta_1} + \frac{1}{2}W^{(2)}_{2000} + W^{(1)}_{1100}\beta_1 + W^{(2)}_{1100})\\
&\quad + d_{13}(\overline{\beta_1}W^{(2)}_{2000} + 2\beta_1W^{(1)}_{1100}) + \frac{x_2\nu''(x_2)}{2}(W^{(1)}_{2000}(-1)e^{i\omega_1\tau_k} + 2W^{(1)}_{1100}e^{-i\omega_1\tau_k})\\
&\quad + \nu'(x_2)(\frac{1}{2}W^{(1)}_{2000}e^{i\omega_1\tau_k} + \frac{1}{2}W^{(1)}_{2000}(-1) + W^{(1)}_{1100}(-1) + W^{(1)}_{1100}e^{-i\omega_1\tau_k})\\
&\quad + 3e_{11} + e_{12}(\overline{\beta_1} + 2\beta_1) + e_{13}(2\beta_1\overline{\beta_1} + \beta_1^2) + 3e_{14}\overline{\beta_1}\beta_1^2\\
&\quad + \frac{x_2\nu^{(3)}(x_2)}{2}e^{-i\omega_1\tau_k} + \frac{\nu''(x_2)}{2}(e^{-2i\omega_1\tau_k} + 2)),\\
g^1_{1011} &= \tau_k\overline{D}(2d_{11}(W^{(1)}_{0011} + W^{(1)}_{1010} + W^{(1)}_{1001}) + 2d_{13}(\beta_1W^{(2)}_{0011} + \overline{\beta_2}W^{(2)}_{1010} + \beta_2W^{(2)}_{1001})\\
&\quad + d_{12}(W^{(2)}_{0011} + W^{(2)}_{1010} + W^{(2)}_{1001} + \beta_2W^{(1)}_{1001} + \beta_1W^{(1)}_{0011} + \overline{\beta_2}W^{(1)}_{1010})\\
&\quad + x_2\nu''(x_2)(W^{(1)}_{0011}(-1)e^{-i\omega_1\tau_k} + W^{(1)}_{1010}(-1)e^{i\omega_2\tau_k} + W^{(1)}_{1001}(-1)e^{-i\omega_2\tau_k})\\
&\quad + \nu'(x_2)(W^{(1)}_{0011}e^{-i\omega_1\tau_k} + W^{(1)}_{1010}e^{i\omega_2\tau_k} + W^{(1)}_{1001}e^{-i\omega_2\tau_k} + W^{(1)}_{0011}(-1)\\
&\quad + W^{(1)}_{1010}(-1) + W^{(1)}_{1001}(-1)) + 6e_{11} + 2e_{12}(\overline{\beta_1} + \beta_2 + \overline{\beta_2}) + 6e_{14}\overline{\beta_2}\beta_1\beta_2\\
&\quad + 2e_{13}(\overline{\beta_2}\beta_1 + \beta_1\beta_2 + \overline{\beta_2}\beta_2) + x_2\nu^{(3)}(x_2)e^{-i\omega_1\tau_k}\\
&\quad + \nu''(x_2)(1 + e^{-i(\omega_1+\omega_2)\tau_k} + e^{i(\omega_2-\omega_1)\tau_k})),\\
g^2_{2000} &= \tau_k\overline{D}(d_{21} + d_{22}\beta_1 + \frac{y_2\beta''(x_2)}{2}e^{-2i\omega_1\tau_k} + \beta'(x_2)\beta_1e^{-i\omega_1\tau_k}),
\end{aligned}
$$

$$
\begin{aligned}
g^2_{0200} &= \tau_k\overline{D}(d_{21}+d_{22}\overline{\beta_1}+\frac{y_2\beta''(x_2)}{2}e^{2i\omega_1\tau_k}+\beta'(x_2)\overline{\beta_1}e^{i\omega_1\tau_k}),\\
g^2_{0020} &= \tau_k\overline{D}(d_{21}+d_{22}\beta_2+\frac{y_2\beta''(x_2)}{2}e^{-2i\omega_2\tau_k}+\beta'(x_2)\beta_2e^{-i\omega_2\tau_k}),\\
g^2_{0002} &= \tau_k\overline{D}(d_{21}+d_{22}\overline{\beta_2}+\frac{y_2\beta''(x_2)}{2}e^{2i\omega_2\tau_k}+\beta'(x_2)\overline{\beta_2}e^{i\omega_2\tau_k}),\\
g^2_{1100} &= \tau_k\overline{D}(2d_{21}+d_{22}(\beta_1+\overline{\beta_1})+y_2\beta''(x_2)+\beta'(x_2)(\beta_1e^{i\omega_1\tau_k}+\overline{\beta_1}e^{-i\omega_1\tau_k})),\\
g^2_{1010} &= \tau_k\overline{D}(2d_{21}+d_{22}(\beta_2+\beta_1)+y_2\beta''(x_2)e^{-i(\omega_1+\omega_2)\tau_k}\\
&\quad+\beta'(x_2)(\beta_1e^{-i\omega_2\tau_k}+\beta_2e^{-i\omega_1\tau_k})),\\
g^2_{1001} &= \tau_k\overline{D}(2d_{21}+d_{22}(\overline{\beta_2}+\beta_1)+y_2\beta''(x_2)e^{i(\omega_2-\omega_1)\tau_k}\\
&\quad+\beta'(x_2)(\beta_1e^{i\omega_2\tau_k}+\overline{\beta_2}e^{-i\omega_1\tau_k})),\\
g^2_{0110} &= \tau_k\overline{D}(2d_{21}+d_{22}(\overline{\beta_1}+\beta_2)+y_2\beta''(x_2)e^{i(\omega_1-\omega_2)\tau_k}\\
&\quad+\beta'(x_2)(\overline{\beta_1}e^{-i\omega_2\tau_k}+\beta_2e^{i\omega_1\tau_k})),\\
g^2_{0101} &= \tau_k\overline{D}(2d_{21}+d_{22}(\overline{\beta_1}+\overline{\beta_2})+y_2\beta''(x_2)e^{i(\omega_1+\omega_2)\tau_k}\\
&\quad+\beta'(x_2)(\overline{\beta_1}e^{i\omega_2\tau_k}+\overline{\beta_2}e^{i\omega_1\tau_k})),\\
g^2_{0011} &= \tau_k\overline{D}(2d_{21}+d_{22}(\beta_2+\overline{\beta_2})+y_2\beta''(x_2)+\beta'(x_2)(\beta_2e^{i\omega_2\tau_k}+\overline{\beta_2}e^{-i\omega_2\tau_k})),\\
g^2_{0021} &= \tau_k\overline{D}(d_{21}(W^{(1)}_{0020}+2W^{(1)}_{0011})+d_{22}(\frac{1}{2}W^{(1)}_{0020}\overline{\beta_2}+\frac{1}{2}W^{(2)}_{0020}+W^{(1)}_{0011}\beta_2+W^{(2)}_{0011})\\
&\quad+\frac{y_2\beta''(x_2)}{2}(W^{(1)}_{0020}(-1)e^{i\omega_2\tau_k}+2W^{(1)}_{0011}(-1)e^{-i\omega_2\tau_k})\\
&\quad+\beta'(x_2)(\frac{1}{2}W^{(2)}_{0020}e^{i\omega_2\tau_k}+\frac{1}{2}\overline{\beta_2}W^{(1)}_{0020}(-1)+\beta_2W^{(1)}_{0011}(-1)+W^{(2)}_{0011}e^{-i\omega_2\tau_k})\\
&\quad+3e_{21}+e_{22}(\overline{\beta_2}+2\beta_2)+\frac{y_2\beta^{(3)}(x_2)}{2}e^{-i\omega_2\tau_k}+\frac{\beta''(x_2)}{2}(\overline{\beta_2}e^{-2i\omega_2\tau_k}+2\beta_2)),\\
g^2_{1110} &= \tau_k\overline{D}(2d_{21}(W^{(1)}_{1100}+W^{(1)}_{1010}+W^{(1)}_{0110})\\
&\quad+d_{22}(\beta_2W^{(1)}_{1100}+\beta_1W^{(1)}_{0110}+\overline{\beta_1}W^{(1)}_{1010}+W^{(2)}_{1100}+W^{(2)}_{0110}+W^{(2)}_{1010})\\
&\quad+\beta'(x_2)(W^{(2)}_{1100}e^{-i\omega_2\tau_k}+W^{(2)}_{1010}e^{i\omega_1\tau_k}+W^{(2)}_{0110}e^{-i\omega_1\tau_k}+\beta_2W^{(1)}_{1100}(-1)\\
&\quad+\overline{\beta_1}W^{(1)}_{1010}(-1)+\beta_1W^{(1)}_{0110})+y_2\beta''(x_2)(W^{(1)}_{1100}(-1)e^{-i\omega_2\tau_k}+W^{(1)}_{1010}(-1)e^{i\omega_1\tau_k}\\
&\quad+W^{(1)}_{0110}(-1)e^{-i\omega_1\tau_k})+6e_{21}+2e_{22}(\overline{\beta_1}+\beta_1+\beta_2)+y_2\beta^{(3)}(x_2)e^{-i\omega_2\tau_k}\\
&\quad+\beta''(x_2)(\overline{\beta_2}+\overline{\beta_1}e^{-i(\omega_1+\omega_2)\tau_k}+\beta_1e^{i(\omega_1-\omega_2)\tau_k})),
\end{aligned}
$$

where D and E are defined in (3.13) and (3.14), respectively. Since W_{2000}, W_{0020}, W_{1100}, W_{1010}, W_{1001}, W_{0110}, W_{0101}, and W_{0011} appear in g_{ijkl}, $i+j+k+l=3$, we still need to compute them. It is easy to see that

(3.27)
$$
\begin{aligned}
W' &= X'_t - z'_1q_1-\overline{z'_1q_1}-z'_2q_2-\overline{z'_2q_2}\\
&= \begin{cases} A_0W-2\mathrm{Re}\{q_1^{*T}(0)R_0q_1\}-2\mathrm{Re}\{q_2^{*T}(0)R_0q_2\}, & \theta\in[-\tau,0),\\ A_0W-2\mathrm{Re}\{q_1^{*T}(0)R_0q_1\}-2\mathrm{Re}\{q_2^{*T}(0)R_0q_2\}+R_0(z_1,\overline{z_1},z_2,\overline{z_2}), & \theta=0,\end{cases}\\
&\triangleq A_0W+H(z_1,\overline{z_1},z_2,\overline{z_2},\theta),
\end{aligned}
$$

where $H(z_1, \overline{z_1}, z_2, \overline{z_2}, \theta) = \sum_{i+j+k+l\geq 2} \frac{1}{i!j!k!l!} H_{ijkl} z_1^i \overline{z_1}^j z_2^k \overline{z_2}^l$. On the other hand, we have $W' = W_{z_1} z_1' + W_{z_2} z_2' + W_{\overline{z_1'}} \overline{z_1'} + W_{\overline{z_2}} \overline{z_2'}$. Then

$$(3.28)\qquad \begin{aligned} (A_0 - 2i\omega_1\tau_k)W_{2000}(\theta) &= -H_{2000}(\theta), & (A_0 - 2i\omega_2)W_{0020}(\theta) &= -H_{0020}(\theta),\\ A_0 W_{1100}(\theta) &= -H_{1100}(\theta), & A_0 W_{0011}(\theta) &= -H_{0011}(\theta), \end{aligned}$$

$$\begin{aligned} (A_0 - i\omega_1\tau_k - i\omega_2\tau_k)W_{1010}(\theta) &= -H_{1010}(\theta),\\ (A_0 - i\omega_1\tau_k + i\omega_2\tau_k)W_{1001}(\theta) &= -H_{1001}(\theta),\\ (A_0 + i\omega_1\tau_k - i\omega_2\tau_k)W_{1010}(\theta) &= -H_{0110}(\theta),\\ (A_0 + i\omega_1\tau_k + i\omega_2\tau_k)W_{1001}(\theta) &= -H_{0101}(\theta). \end{aligned}$$

From (3.27), it is easy to see that

$$(3.29)\qquad \begin{aligned} H(z_1, \overline{z_1}, z_2, \overline{z_2}, \theta) &= -2\mathrm{Re}\{q_1^{*T}(0)R_0 q_1\} - 2\mathrm{Re}\{q_2^{*T}(0)R_0 q_2\}\\ &= -g^1(z,\overline{z})q_1(\theta) - \overline{g^1(z,\overline{z})q_1(\theta)} - g^2(z,\overline{z})q_2(\theta) - \overline{g^2(z,\overline{z})q_2(\theta)}. \end{aligned}$$

From the definition of A_0, (3.28), and (3.29), it follows that

$$W_{2000}' = 2i\omega_1 W_{2000} - g_{2000}^1 q_1(\theta) - \overline{g_{0200}^1 q_1(\theta)} - g_{0020}^2 q_2(\theta) - \overline{g_{0002}^2 q_2(\theta)}.$$

Noting the definition of $q(\theta)$, we have

$$(3.30)\qquad \begin{aligned} W_{2000}(\theta) = {}& \frac{ig_{2000}^1 q_1(0)}{\omega_1\tau_k} e^{i\omega_1\theta\tau_k} + \frac{i\overline{g_{0200}^1 q_1(0)}}{3\omega_1\tau_k} e^{-i\omega_1\theta\tau_k}\\ & - \frac{ig_{0020}^2 q_2(0)}{(\omega_2 - 2\omega_1)\tau_k} e^{i\omega_2\theta\tau_k} + \frac{i\overline{g_{0002}^1 q_2(0)}}{(\omega_2 + 2\omega_1)\tau_k} e^{-i\omega_2\theta\tau_k} + Ke^{2i\omega_1\theta\tau_k}, \end{aligned}$$

where $K = (K^{(1)}, K^{(2)}) \in R^3$ is a constant vector which still needs to be obtained. The definition of A_0 and (3.29) yield

$$(3.31)\qquad \int_1^0 d\eta(\theta)W_{2000}(0) = 2i\omega_1 W_{2000}(\theta) - H_{2000}(0).$$

From (3.27), it is easy to obtain $H_{2000}(0)$ as follows:

$$(3.32)\qquad H_{2000}(0) = -g_{2000}^1 q_1(0) - \overline{g_{0200}^1 q_1(0)} - g_{2000}^2 q_2(0) - \overline{g_{0200}^2 q_2(0)} + R_0.$$

Submitting (3.29) and (3.32) into (3.31) and noting that $\pm i\omega_1$, $\pm i\omega_2$ are characteristic roots of (3.5) but $2i\omega_1$ is not, we obtain

$$(3.33)\qquad K = \begin{pmatrix} 2\omega_1 i + a_{12} + a_{11}e^{-2i\omega_1\theta}, & a_{13}\\ -a_{22} - a_{21}e^{-2i\omega_1\theta}, & 2\omega_1 i - a_{23} \end{pmatrix}^{-1} R_0.$$

From (3.29), we know that W_{2000} is obtained. Similarly, we can obtain other W_{ijkl}'s. Thus, all g_{ijkl}'s are obtained, where $i + j + k + l = 2$. Thus, we can analyze the Hopf–Hopf bifurcation as we analyzed the Hopf bifurcation. We should point out that it is usually difficult to find the Hopf–Hopf bifurcation parameter τ_k, and we can find it only by numerical methods.

4. Discussion. We have studied the nonlinear dynamics of a two-dimensional general delay differential system. We first provided linear analysis of the system with two delays at the possible equilibria, namely, the semitrivial and positive equilibria, and discussed the existence of Hopf bifurcation at the positive equilibrium. In the case when the two delays are equal, we investigated Hopf bifurcation, Bautin bifurcation, and Hopf–Hopf bifurcation in the system. The existence and stability of periodic solutions created in these three types of bifurcations were studied. We then applied the obtained results to a model for the interaction between tumor cells and effector cells of the immune system. The model is described by a system of two differential equations with two delays, which describe the proliferation delay (τ) of tumor cells and the growth delay (ρ) of immune effector cells stimulated by tumor cells, respectively. Numerical simulations were presented to illustrate the theoretical analysis and results.

Cancer immunosurveillance functions as an important defense against cancer. If the immune system can successfully survey the body for tumor cells based on their acquisition of neoantigens consequent to genetic alterations, these nascent tumor cells will be destroyed (Pardoll [36]). This is the elimination process of cancer immunoediting (Dunn et al. [16, 17]). Our analysis of the existence and stability of the tumor-free equilibrium corresponds to this elimination process. If tumor cells actively acquire resistant mechanisms that attenuate immune responses, then tumor survival occurs, and tumor cells continue to grow and expand in an uncontrolled manner and may eventually lead to malignancies (Pardoll [36]). This is the escape process of cancer immunoediting (Dunn et al. [16, 17]). Our analysis of the immune-free equilibrium describes this escape process. There are extensive experiments to support the existence of the elimination and escape processes because immunodeficient mice develop more carcinogen-induced and spontaneous cancers than wild-type mice, and tumor cells from immunodeficient mice are more immunogenic than those from immunocompetent mice (Dunn et al. [16, 17], Schreiber, Old, and Smyth [42]). Recently, Koebel et al. [25] used a mouse model of primary chemical carcinogenesis and demonstrated that equilibrium occurs. Their results reveal that the immune system of a naive mouse can restrain cancer growth for extended time periods; that is, the tumor cells and effector cells of the immune system coexist for a long time. Our results on the existence and stability of the bifurcated (Hopf, Bautin, and Hopf–Hopf) periodic solutions describe the equilibrium process. When a stable periodic orbit exists, it can be understood that the tumor and the immune system can coexist for a long term although the cancer is not eliminated. The conditions for the existence of the bifurcations indicate the parameters that are important in controlling the development and progression of the tumor.

The existence of oscillatory modes in the tumor–immune system interaction models demonstrate the phenomenon of long-term tumor relapse and have been observed in some related tumor and immune system models (d'Onofrio et al. [15], Kirschner and Panetta [24], Kuznetsov et al. [26], Lejeune, Chaplaina, and Akili [28], and Liu, Ruan, and Zhu [29, 30]). We should point out, though, that the oscillatory coexistence of the tumor cells and the effector cells really depends on the initial values. Numerical simulations indicate that when the initial values are close to the microscopic (small) positive equilibrium, both the tumor cells and the effector cells oscillate rapidly with small amplitude. However, when the initial values are close to the macroscopic (large) positive equilibrium, both the tumor cells and the effector cells oscillate slowly with very large amplitude.

We not only presented detailed analysis for the Hopf, Bautin, and Hopf–Hopf bifurcations but also gave the computation procedures for the normal forms on the center manifold for these bifurcations in general delay differential equations. These procedures can be used to analyze other degenerated bifurcations in such delay differential equations, and we mention a couple of general cases here.

If the linearizing system has eigenvalue sets Λ as follows,

$$\begin{aligned}
&\Lambda_1 = \{\pm\omega_1,\ \pm\omega_2, \dots, \pm\omega_p, \quad \tfrac{\omega_i}{\omega_j} \neq \tfrac{m}{n}, \quad p, m, n \in \mathcal{Z}^+, \quad i, j = 1, \dots, p\},\\
&\Lambda_2 = \{0\} \bigcup \{\pm\omega_1,\ \pm\omega_2, \dots, \pm\omega_p, \quad \tfrac{\omega_i}{\omega_j} \neq \tfrac{m}{n}, \quad p, m, n \in \mathcal{Z}^+, \quad i, j = 1, \dots, p\},
\end{aligned}$$

where 0 is a simple root, and ω_i and ω_j are nonresonant roots, then by the results of this paper and in Choi and LeBlanc [8] and Guo, Chen, and Wu [21], we can obtain the following results.

(1) If system (1.1) has nonresonant purely imaginary roots set Λ_1, then the truncation equations of the phase equations on the center manifold in cubic orders have the form

$$\text{(4.1)} \qquad \begin{cases} r_1' = (\mu_1 + b_{11}r_1^2 + b_{12}r_2^2 + \cdots + b_{1p}r_p^2)r_1 \\ \vdots \\ r_p' = (\mu_p + b_{p1}r_1^2 + b_{p2}r_2^2 + \cdots + b_{pp}r_p^2)r_p. \end{cases}$$

(2) If system (1.1) has nonresonant root set Λ_2, then the truncation equations to phase equations on the center manifold in cubic orders are of the form

$$\text{(4.2)} \qquad \begin{cases} r_0' = r_0(a_0 + b_0r_0) + b_{01}r_1^2 + b_{02}r_2^2 + \cdots + b_{0p}r_p^2, \\ r_1' = r_1(a_1 + b_1r_0) + (b_{10}r_0^2 + b_{11}r_1^2 + b_{12}r_2^2 + \cdots + b_{1p}r_p^2)r_1 \\ \vdots \\ r_1' = r_p(a_p + b_pr_0) + (b_{p0}r_0^2 + b_{p1}r_1^2 + b_{p2}r_2^2 + \cdots + b_{pp}r_p^2)r_p. \end{cases}$$

All b_{ij}'s, $1 \leq i, j \leq p$, in (4.1) and (4.2) can be given with the methods of Hassard, Kazarinoff, and Wan [22], although they are tedious.

Finally, we should point out that we have studied system (1.1) under the assumption that it has only one positive equilibrium. As the example in section 3.1 showed, it could have multiple positive equilibria. Correspondingly, the system can exhibit more degenerate bifurcations including Bogdanov–Takens bifurcation (see Liu, Ruan, and Zhu [29] for an ODE model of tumor–immune system interaction) and higher codimension bifurcations. Also, throughout the paper we assumed that $\theta(t) = 0$; that is, we studied only model (1.1) in the absence of immunotherapy. As the recent clinical data on the immunotherapy of chronic lymphoid leukemia were very encouraging (Porter, Levine, and Kalos [38]), it will be very interesting (and challenging) to study the effect of immunotherapy (periodic or impulsive) on the nonlinear dynamics of the tumor–immune system interaction models with delay effect. We leave these for future investigation.

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