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NONLINEAR DYNAMICS IN TUMOR-IMMUNE SYSTEM INTERACTION MODELS WITH DELAYS

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In memory of my Ph.D. thesis supervisor
Professor Herbert I. Freedman (1940 - 2017)

Abstract. In this paper, we review some recent results on the nonlinear dynamics of delayed differential equation models describing the interaction between tumor cells and effector cells of the immune system, in which the delays represent times necessary for molecule production, proliferation, differentiation of cells, transport, etc. First we consider a tumor-immune system interaction model with a single delay and present results on the existence and local stability of equilibria as well as the existence of Hopf bifurcation in the model when the delay varies. Second we investigate a tumor-immune system interaction model with two delays and show that the model undergoes various possible bifurcations including Hopf, Bautin, Fold-Hopf (zero-Hopf), and Hopf-Hopf bifurcations. Finally we discuss a tumor-immune system interaction model with three delays and demonstrate that the model exhibits more complex behaviors including chaos. Numerical simulations are provided to illustrate the nonlinear dynamics of the delayed tumor-immune system interaction models. More interesting issues and questions on modeling and analyzing tumor-immune dynamics are given in the discussion section.

Contents

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1. **Introduction.** Cancer is one of the most dangerous killers of humankind in the new century. According to a World Health Organization report in 2018 (WHO [121]), every year millions of people die from cancer throughout the world. A recent study found that in some countries cancer has overtaken heart disease as the leading cause of death (Dagenais et al. [32]). It is believed that immunological deficiency is one of the main causes of a remarkably high incidence of neoplasia. Studies show that about ten percent of patients who have spontaneous immunodeficiency diseases may develop cancer (Melief and Schwartz [88]).

To understand how the immune system affects cancer development and progression is one of the most important and challenging questions in immunology and cancer research (Schreiber et al. [106]). Based on an emerging understanding of the cellular basis of transplantation and tumor immunity, Burnet [23] and Thomas [112] reported that lymphocytes were responsible for eliminating continuously arising nascent transformed cells and introduced the concept *cancer immunosurveillance*. On one hand, recent studies 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 for 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 et al. [45], Matsushita et al. [86], Mohme et al. [91], Pardoll et al. [95], Schreiber et al. [106], Vesely et al. [114]). 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 responses and grow into cancers) (Dunn [44, 45], Koebel et al. [71], Schreiber et al. [106]), see Figure 1.

In order to simulate the host's own immune response to destroy and eliminate tumor cells, various types of mathematical models have been proposed, see for example Adam and Bellomo [3], Arciero et al. [8], Byrne et al. [24], de Pillis et al. [35], Dritschel et al. [43], Frascoli et al. [52], Hu and Jang [64], Kirschner and Panetta [70], Kuznetsov et al. [74], Lejeune et al. [78], Nani and Freedman [92], Nikolopoulou et al. [93], Owen and Sherratt [94], Robertson-Tessi et al. [100], Stepanova [109], and the references cited therein. We refer to reviews by Anderson and Maini [7], Cristini et al. [31], dePillis et al. [34], Eftimie et al. [47], Freedman [53], Friedman [54], Konstorum et al. [72], Mahlbacher et al. [84], Szymańska et al. [110], Wilkie [120] and the references cited therein on modeling tumor-immune system interactions and tumor growth, proceedings of d'Onofrio et al. [41] and

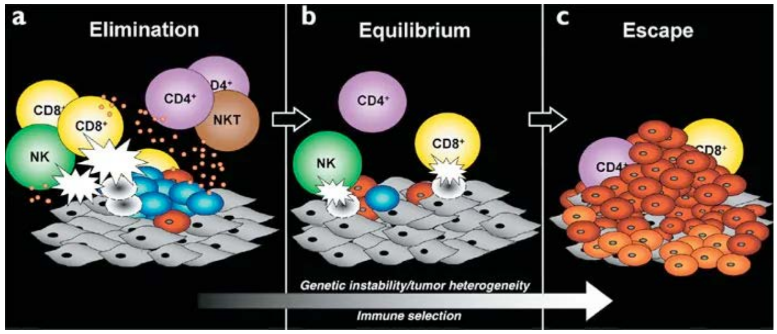


FIGURE 1. Three processes in cancer immunoediting: (a) **Elimination** corresponds to immunosurveillance; (b) **Equilibrium** represents the process by which the immune system iteratively selects and/or promotes the generation of tumor cell variants with increasing capacities to survive immune attack; (c) **Escape** is the process wherein the immunologically sculpted tumor expands in an uncontrolled manner in the immunocompetent host. Adapted from Dunn [44].

Eladdadi et al. [48], and a monograph of Kuang et al. [73] on this subject. However, 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. Two-dimensional ODE models for the interaction of tumor cells and effector cells of the immune system have been extensively used (Adam [2], Albert et al. [5], DeLisi and Rescigno [33], d'Onofrio [37, 38, 39], Sotolongo et al. [107]). 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 (see Figure 2).

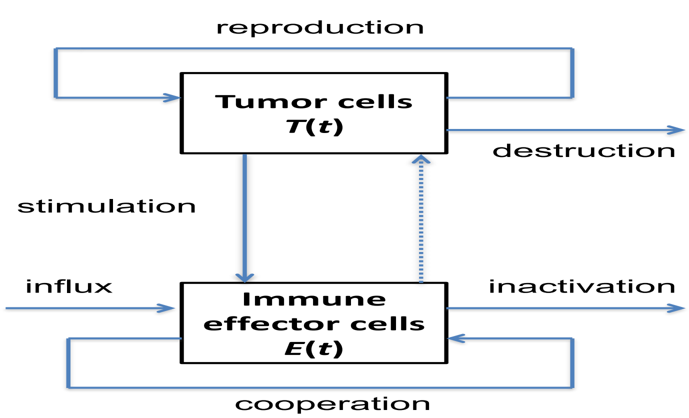


FIGURE 2. Scheme of the essential mechanisms of interaction between the tumor cells and immune effector cells.

Delayed responses are very crucial and important for the tumor and immune system interaction, just as Asachenkov et al. [10] and Mayer et al. [87] 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 and immune system interaction models with delay have been studied considerably, in particular two-dimensional delay differential equations model, see Abdulrashid et al. [1], Asachenkov et al. [10], Banerjee and Sarkar [11], Barbarossa et al. [12], Bi et al. [13, 14, 15, 16], Bodnar and Foryś [18], Buric [22], Dong et al. [36], d'Onofrio [37, 38, 39], d'Onofrio and Gandolfi [40], d'Onofrio et al. [42], Galach [56], Grossman and Berke [57], Khajanchi and Banerjee [69], Liu et al. [81], Mayer et al. [87], Mendonça et al. [90], Piotrowska [96], Piotrowska and Foryś [97], Rordriguez-Perez et al. [101], Villasana and Radunskaya [115], Yu and Wei [126], Yu et al. [127, 128], and the references cited therein.

Delay differential equations exhibit very richer bifurcation phenomena, including Hopf bifurcation (Hale and Verduyn Lunel [62], Hassard et al. [63], Faria and Magalhães [49], Guo and Wu [60]), Bautin bifurcation (Bi and Ruan [13], Ion [66]), Bogdanov-Takens bifurcation (Faria and Magalhães [50], Xiao and Ruan [125]), Fold-Hopf (zero-Hopf) bifurcation (Choi and LeBlanc [27], Guo et al. [59], Jiang et al. [67], Jiang and Wang [68], Wu and Wang [122]), Hopf-Hopf bifurcation (Campbell and Belair [25], Bruno and Bélair [21], Wu and Wang [124]), and triple zero singularities (Campbell and Yuan [26], LeBlanc [77]). In applications it is usually interesting but difficult to show that a specific biological or physical model undergoes any of these bifurcations in particular the degenerate ones.

The goal of this paper is to review some recent results on the nonlinear dynamics of delayed differential equation models describing the interaction between tumor cells and effector cells of the immune system. First we consider a tumor-immune system interaction model with a single delay, which is a reduced model of Kuznetsov et al. [74] with a single delay and was considered by Gałach [56] and Bi and Xiao [15], and present results on the existence and local stability of equilibria as well as the existence of Hopf bifurcation in the model when the delay varies. Second we investigate a tumor-immune system interaction model with two delays, which is a generalized model of d'Onofrio et al. [42] and was studied by Bi and Ruan [13], and show that the model undergoes various possible bifurcations including Hopf, Bautin, Fold-Hopf (zero-Hopf), and Hopf-Hopf bifurcations. Finally we discuss a tumor-immune system interaction model with three delays, which was proposed by Mayer et al. [87] and analyzed by Bi et al. [14], and demonstrate that the model exhibits more complex behaviors including chaos. Numerical simulations are provided to illustrate the nonlinear dynamics of the delayed tumor-immune system interaction models. Some interesting issues and questions on modeling and analyzing tumor-immune dynamics are given in the discussion section.

2. Dynamics in a tumor-immune system interaction model with a delay.

2.1. The reduced model of Kuznetsov et al. [74] with a delay. To develop schemes for immunotherapy or its combination with other therapy methods directed at lowering tumor mass, heightening tumor immunogenicity, and removal of immunosuppression induced in an organism in the process of tumor growth, Kuznetsov et al. [74] construct a model for the interaction between effector cells and a growing immunogenic tumor *in vivo* involving unbound effector cells, unbound tumor cells, effector cell-tumor cell complexes, inactivated effector cells, and lethally hit tumor cells. Based on some experimental observations and approximations, Kuznetsov et al. [74] further suggested that their original five-dimensional system can be reduced to the following two-dimensional system:[1]

$$\begin{cases} \dfrac{dT}{dt} = aT(t)(1 - bT(t)) - nT(t)E(t), \\ \dfrac{dE}{dt} = s + \dfrac{pT(t)E(t)}{g + T(t)} - mE(t)T(t) - dE(t), \end{cases} \tag{1}$$

where $T(t)$ and $E(t)$ are the density of tumor cells and immune effector cells at time t, respectively; the parameter a is the maximal growth rate of the tumor cell population; the maximal carrying capacity of the biological environment for tumor cells (i.e. the maximum number of cells due, for example, to competition for resources such as oxygen, glucose, etc.) is b^{-1}; n describes the effect of effector cells on the growth of tumor cells; s is the "normal" (non-enhanced by tumor cells presence) rate of flow of mature effector cells into the region of tumor cells localization; d is a positive constants representing the rate of elimination of effector cells; the Michaelis-Menten-Monon function $\frac{pT(t)E(t)}{g+T(t)}$ characterizes the rate at which cytotoxic effector cells accumulate in the region of tumor cell localization due to the presence of the tumor in which p and g are positive constants; and m represents the effect of tumor cells on the growth of effector cells. By comparing the model with experimental data, Kuznetsov et al. [74] derived numerical estimates of parameters describing processes that cannot be measured *in vivo*. Local and global bifurcations were calculated for realistic values of the parameters. For a large set of parameters Kuznetsov et al. [74] predicted that the course of tumor growth and its clinical manifestation have a recurrent profile with a 3- to 4-month cycle, similar to patterns seen in certain leukemias.

Variants of model (1) with delay have been constructed and studied in the literature. For example, Gałach [56] assumed that, in the equation for $E(t)$, the Michaelis-Menten-Monon function $\frac{pT(t)E(t)}{g+T(t)}$ is replaced by the Lotka-Volterra function $pT(t)E(t)$. Rescaling the parameters by

$$\sigma = \frac{s}{n},\ \zeta = \frac{p-m}{n},\ \alpha = \frac{a}{n},\ \beta = b,\ \delta = \frac{d}{n}$$

and incorporating a time delay τ into the term $\zeta E(t)T(t)$ of the E-equation, Gałach [56] considered the following delayed model:

$$\begin{cases} \dfrac{dT}{dt} = \alpha T(t)(1 - \beta T(t)) - T(t)E(t), \\ \dfrac{dE}{dt} = \sigma + \zeta E(t-\tau)T(t-\tau) - \delta E(t), \end{cases} \tag{2}$$

where $\tau > 0$ is a constant meaning that the immune system needs some time to develop a suitable response after the recognition of tumor cells. Gałach [56] studied the stability of equilibria and the existence of periodic solutions induced by Hopf bifurcation in his delayed model. Bi and Xiao [15] gave the general formula for the direction of Hopf bifurcation, the estimation formula for periods and stability of bifurcated periodic solutions. They also obtained conditions for the global existence of periodic solutions bifurcating from Hopf bifurcations and presented numerical simulations to illustrate the obtained results.

[1] In order to be consistent with the models in sections 2 and 3, the order of the two equations (4a) and (4b) of Kuznetsov et al. [74] is interchanged in model (1).

TABLE 1. Existence and stability chart for the ODE model (Gałach [56])

Sign of ζ	Conditions		P_0	P_1	P_2
$\zeta > 0$	$\alpha\delta < \sigma$		stable	–	–
	$\alpha\delta > \sigma$		unstable	–	stable
$\zeta < 0$	$\alpha(\beta\delta - \zeta)^2 + 4\beta\zeta\sigma < 0$		stable	–	–
	$\alpha(\beta\delta - \zeta)^2 + 4\beta\zeta\sigma > 0$	$\alpha\delta > \sigma$	unstable	–	stable
		$\alpha\delta < \sigma$ $\zeta + \beta\delta < 0$	stable	unstable	stable

2.2. **Analysis of the ODE model (Gałach [56]).** Note that $\zeta = \frac{p-m}{n}$, so the sign of ζ depends on the relation between p and m : If the stimulation coefficient p of the immune system exceeds the neutralization coefficient m of effector cells in the process of the formation of effector cell-tumor cell complexes, then $\zeta > 0$; otherwise $\zeta < 0$. The sign of ζ will in fact affect the number of equilibria and their stabilities.

The ODE version of model (2) has up to three equilibria: the tumor-free (semitrivial) equilibrium $P_0 = (0, \frac{\sigma}{\delta})$ and two possible tumor-present (positive) equilibria:

$$P_1 = \left(\frac{\alpha(\beta\delta + \zeta) + \sqrt{\Delta}}{2\alpha\beta\zeta}, \ \frac{-\alpha(\beta\delta - \zeta) - \sqrt{\Delta}}{2\zeta} \right),$$

$$P_2 = \left(\frac{\alpha(\beta\delta + \zeta) - \sqrt{\Delta}}{2\alpha\beta\zeta}, \ \frac{-\alpha(\beta\delta - \zeta) + \sqrt{\Delta}}{2\zeta} \right),$$

where $\Delta = \alpha^2(\beta\delta - \zeta)^2 + 4\alpha\beta\zeta\sigma$. Gałach [56] analyzed the existence and stability of these equilibria, which can be summarized in Table 1.

2.3. **Linear analysis of the delayed model.** Since the delay does not affect the existence of equilibria, the number and existence of equilibria for the delayed model (2) are same for the ODE model as listed in Table 1. In the case when

$$\zeta > 0, \quad \alpha\delta > \sigma, \tag{3}$$

the delay model (2) also has two equilibria: the tumor-free (semitrivial) equilibrium P_0 and the positive equilibrium P_2. Gałach [56] and Bi and Xiao [15] briefly discussed the stability of these two equilibria, here we provide some details.

For an equilibrium $P^* = (T^*, E^*)$ of the delay model (2), let

$$x(t) = T(t) - T^*, \ y(t) = E(t) - E^*.$$

Then the linearized system at P^* takes the following form:

$$\frac{d}{dt}\begin{pmatrix} x(t) \\ y(t) \end{pmatrix} = \begin{bmatrix} -\alpha\beta T^* & -T^* \\ 0 & -\delta \end{bmatrix} \begin{pmatrix} x(t) \\ y(t) \end{pmatrix} + \begin{bmatrix} 0 & 0 \\ \zeta E^* & -\zeta T^* \end{bmatrix} \begin{pmatrix} x(t-\tau) \\ y(t-\tau) \end{pmatrix}. \tag{4}$$

The characteristic equation is given by

$$\lambda^2 + (\delta + \alpha\beta T^*)\lambda + \delta\alpha\beta T^* + [-\zeta T^* \lambda + \zeta\alpha T^*(1 - 2\beta T^*)]e^{-\lambda\tau} = 0. \tag{5}$$

Before considering the stability of the equilibria, we recall some results from Ruan [102]. Consider a second-order transcendental polynomial equation of the form:

$$\lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0, \tag{6}$$

where p, r, q, s are real numbers. Now we make the following assumptions:

(H_1) $p + s > 0$;

(H_2) $q + r > 0$;
(H_3) $s^2 - p^2 + 2r < 0$ and $r^2 - q^2 > 0$ or $(s^2 - p^2 + 2r)^2 < 4(r^2 - q^2)$;
(H_4) $r^2 - q^2 < 0$ or $s^2 - p^2 + 2r > 0$ and $(s^2 - p^2 + 2r)^2 = 4(r^2 - q^2)$;
(H_5) $r^2 - q^2 > 0, s^2 - p^2 + 2r > 0$ and $(s^2 - p^2 + 2r)^2 > 4(r^2 - q^2)$.

Define

$$\tau_j^{\pm} = \frac{1}{\omega_{\pm}} \arccos\left\{\frac{q(\omega_{\pm}^2 - r) - ps\omega_{\pm}^2}{s^2\omega_{\pm}^2 + q^2}\right\} + \frac{2j\pi}{\omega_{\pm}}, \quad j = 0, 1, 2, \cdots, \tag{7}$$

where

$$\omega_{\pm}^2 = \frac{1}{2}(s^2 - p^2 + 2r) \pm \frac{1}{2}[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)]^{\frac{1}{2}}. \tag{8}$$

We have the following theorem about the distribution of the characteristic roots of equation (6) (Ruan [102]).

Lemma 2.1. *Let $\tau_j^{\pm}(j = 0, 1, 2, \cdots)$ be defined by (7).*

(i) If (H_1)-(H_3) hold, then all roots of equation (6) have negative real parts for all $\tau \geq 0$;

(ii) If (H_1), (H_2) and (H_4) hold, then when $\tau \in [0, \tau_0^+)$ all roots of equation (6) have negative real parts, when $\tau = \tau_0^+$ equation (6) has a pair of purely imaginary roots $\pm i\omega_+$, and when $\tau > \tau_0^+$ equation (6) has at least one root with positive real part;

(iii) If (H_1), (H_2) and (H_5) hold, then there is a positive integer k such that

$$0 < \tau_0^+ < \tau_0^- < \tau_1^+ < \cdots < \tau_{k-1}^- < \tau_k^+,$$

when

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

all roots of equation (6) have negative real parts, and when

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

equation (6) has at least one root with positive real part.

At the tumor-free equilibrium P_0, the characteristic equation (5) reduces to

$$\lambda^2 + (\delta + \alpha\beta T^*)\lambda + \delta\alpha\beta T^* = (\lambda + \delta)(\lambda + \alpha\beta T^*) = 0.$$

The eigenvalues are $\lambda_1 = \delta < 0$ and $\lambda_2 = -\alpha\beta T^* < 0$. Thus, we have the following result.

Proposition 1. *Under the conditions (3), the tumor-free equilibrium $P_0 = (0, \frac{\sigma}{\delta})$ of the delay model (2) is asymptotically stable for all delay $\tau \geq 0$.*

At the positive equilibrium $P_2 = (T_2, E_2) = \left(\frac{\alpha(\beta\delta+\zeta)-\sqrt{\Delta}}{2\alpha\beta\zeta}, \frac{-\alpha(\beta\delta-\zeta)+\sqrt{\Delta}}{2\zeta}\right)$, the characteristic equation takes the form of equation (6) with

$$\begin{aligned} p &= \delta + \alpha\beta T_2 > 0, \quad & r &= \delta\alpha\beta T_2 > 0, \\ s &= -\zeta T_2 < 0, \quad & q &= \zeta\alpha T_2(1 - 2\beta T_2). \end{aligned}$$

Condition (H_1) yields $p + s = \delta + (\alpha\beta - \zeta)T_2 > 0$ if

$$\alpha\beta > \zeta. \tag{9}$$

Condition (H_2) implies $q + r = \alpha T_2(\delta\beta + \zeta - 2\beta T_2) > 0$ if

$$\delta\beta + \zeta - 2\beta T_2 > 0 \tag{10}$$

By (H_3), we have

$$\begin{aligned}
s^2-p^2+2r &= \zeta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2+2\delta\alpha\beta T_2,\\
r^2-q^2 &= \delta^2\alpha^2\beta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2,\\
(s^2-p^2+2r)^2-4(r^2-q^2) &= [\zeta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2+2\delta\alpha\beta T_2]^2\\
&\quad -4[\delta^2\alpha^2\beta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2].
\end{aligned}$$

Therefore, following the arguments in Ruan [102, 103], we have the following results on the stability and Hopf bifurcation in the delay model (2).

Theorem 2.2. *Assume that the conditions (3), (9), (10) are satisfied.*

(i) If

$$\zeta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2+2\delta\alpha\beta T_2<0, \tag{11}$$

and

$$\delta^2\alpha^2\beta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2>0 \tag{12}$$

or

$$\begin{aligned}&[\zeta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2+2\delta\alpha\beta T_2]^2\\ &\qquad -4[\delta^2\alpha^2\beta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2]<0,\end{aligned} \tag{13}$$

then the positive equilibrium P_2 of the delay model (2) is asymptotically stable for all delay $\tau \geq 0$;

(ii) If

$$\delta^2\alpha^2\beta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2<0 \tag{14}$$

or

$$\zeta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2+2\delta\alpha\beta T_2>0 \tag{15}$$

and

$$\begin{aligned}&[\zeta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2+2\delta\alpha\beta T_2]^2\\ &\qquad -4[\delta^2\alpha^2\beta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2]=0,\end{aligned} \tag{16}$$

then the positive equilibrium P_2 of the delay model (2) is asymptotically stable for $\tau \in [0, \tau_0^+)$ and unstable for $\tau > \tau_0^+$; a Hopf bifurcation occurs at P_2 when $\tau = \tau_0^+$ and a family of periodic solutions bifurcates from P_2 when τ passes through τ_0^+ which is defined by (7);

(iii) If (12), (15) and

$$\begin{aligned}&[\zeta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2+2\delta\alpha\beta T_2]^2\\ &\qquad -4[\delta^2\alpha^2\beta^2T_2^2-\zeta^2\alpha^2T_2^2(1-2\beta T_2)^2]>0\end{aligned} \tag{17}$$

hold, then stability switch occurs at P_2; that is, P_2 is asymptotically stable when

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

and unstable when

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

Bi and Xiao [15] studied the direction of the Hopf bifurcation and stability of the bifurcated periodic solutions as well as the existence of global Hopf bifurcation at the positive equilibrium P_2.

Remark 1. In Theorem 2.2, only the case when $\zeta > 0$ was considered. From Table 1, one can see that when $\zeta < 0$ there are up to three equilibria and one expects that Bogdanov-Takens bifurcation may occur when

$$\alpha(\beta\delta - \zeta)^2 + 4\beta\zeta\sigma = 0,$$

that is, when the two positive equilibria coalesce to a unique degenerate equilibrium

$$P_c = (T_c, E_c) = \left(\frac{\alpha(\beta\delta+\zeta)}{2\alpha\beta\zeta}, \frac{-\alpha(\beta\delta-\zeta)}{2\zeta}\right),$$

which may be studied by using the results of Faria and Magalhaés [50] and following the procedure of Xiao and Ruan [125].

Remark 2. We only considered a simplified version (2) of the Kuznetsov et al.'s model with delay. Recently, Bi et al. [16] incorporated a time delay into the original model (1) of Kuznetsov et al. [74]:

$$\begin{cases} \dfrac{dT}{dt} = aT(t)(1-bT(t)) - nT(t)E(t) \\ \dfrac{dE}{dt} = s + \dfrac{pT(t)E(t)}{g+T(t)} - mE(t-\tau)T(t-\tau) - dE(t) \end{cases} \tag{18}$$

and obtained some results. We believe that model (18) exhibits much more complex dynamical properties which deserve further consideration.

2.4. **Numerical simulations.** We provide the simulations of Hopf bifurcation at P_2 using the parameter values in [74]. Take $\sigma = 0.1181$, $\zeta = 0.0031$, $\delta = 0.3743$, $\alpha = 1.636$, $\beta = 0.002$, then system (2) has a tumor-free equilibrium $P_0 = (0, 0.3155)$ and a positive equilibrium $P_2 = (92.1911, 1.33435)$, which is locally stable. A Hopf bifurcation occurs when $\tau_0 = 1.8760$, P_0 becomes unstable when $\tau_0 > 1.8760$, and there is a periodic solution bifurcated from P_2 (see Fig. 3).

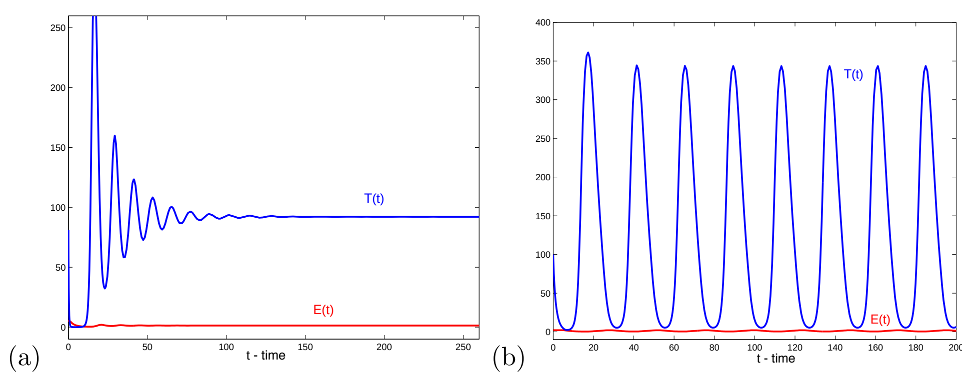


FIGURE 3. (a) Solution trajectories converge to the stable equilibrium $P_2 = (92.1911, 1.3344)$; (b) Periodic solutions bifurcated from the positive equilibrium when $\tau = 2.0 > \tau_0$.

3. Bifurcations in a tumor-immune system interaction model with two delays.

3.1. The generalized model of d'Onofrio et al. [42].

Based on the ODE models of Sotolongo-Costa et al. [107] and d'Onofrio [37] and the DDE model of d'Onofrio et al. [42], Bi and Ruan [13] proposed the following tumor and immune system interaction model with two delays:

$$\begin{cases} \dfrac{dT}{dt} = T(t)[\nu(T(t-\tau)) - \phi(T(t), E(t))] \\ \dfrac{dE}{dt} = \beta(T(t-\rho))E(t) - \mu(T(t))E(t) + \sigma q(E(t)), \end{cases} \tag{19}$$

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

(i) $\nu(T)$ describes the relative baseline growth of tumor cells and satisfies $0 < \nu(0) \leq +\infty$, $\nu'(T) \leq 0$, $\lim\limits_{T\to 0^+} T\nu(T) = 0$, and in some relevant cases, we shall suppose that there exists a $0 < \bar{T} \leq +\infty$ such that $\nu(\bar{T}) = 0$. Prototype examples include the exponential growth $\nu(T) = k > 0$ (Wheldon [118]); the Gompertz growth $\nu(T) = k\ln(a/T)$ (Laird [76]); the logistic growth $\nu(T) = k(1-(T/a)^n)$ (Marusic et al. [85]); etc. We assume that there is a time delay $\tau \geq 0$ in the proliferation of tumor cells (Mayer et al. [87], d'Onofrio and Gandolfi [40]).

(ii) $\phi(T, E)$ models the loss rate of tumor cells due to the attack by effector cells of the immune system and satisfies $\phi(T, 0) = 0$, $\phi(0, E) > 0$, $\partial_T\phi(T, E) \leq 0$ and $\partial_E\phi(T, E) > 0$. An example is the Beddington-DeAngelis function $\phi(T, E) = \frac{aE}{1+bT+cE}$ (Huisman and De Boer [65] and d'Onofrio [37]), 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 immune response.

(iii) $\beta(T)$ represents the tumor-stimulated proliferation rate of the effector cells and satisfies $\beta(T) \geq 0$, $\beta(0) = 0$ and $\beta'(T) \geq 0$. The Michaelis-Menten-Monod function $\beta(T) = \frac{aT}{m+T}$ has been used (Kuznetsov et al. [74]). A time delay $\rho \geq 0$ is introduced into $\beta(x)$ to reflect the process of effector cells growth with respect to stimulus by the tumor cells growth (d'Onofrio et al. [42]).

(iv) The term $\sigma q(T) > 0$ 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 $q'(T) < 0$ for $T \gg 1$ (d'Onofrio et al. [42]).

(v) $\mu(T)$ is the loss rate of immune effector cells due to the interaction with tumor cells and satisfies $\mu(T) > 0, \mu'(T) > 0$ (d'Onofrio et al. [42]).

When $\phi(T, E) = \phi(T)\pi(E)$ and $\tau = \rho = 0$ model (19) reduces to the model considered by d'Onofrio [37, 38, 39] who studied the local stability of the equilibria and the uniqueness of stable limit cycles. When $\tau = 0$, $\rho \neq 0$, model (19) becomes the delay model proposed in d'Onofrio et al. [42], in which the stability of equilibria and the onset of sustained oscillations through Hopf bifurcations were investigated. Thus, model (19) can be regarded as an extension of the models of d'Onofrio [37, 38, 39], d'Onofrio et al. [42] and Mayer et al. [87].

3.2. **Bifurcation analysis.** In this subsection, we present the analyses and results from Bi and Ruan [13] on the nonlinear dynamics of the tumor-immune system interaction model (19).

Model (19) has the following possible equilibria:

(1) Tumor-free equilibrium $P_1(0, E_1)$, where $E_1 = \frac{\sigma+\theta}{\mu(0)}$;
(2) Positive equilibria $P_2^k(T_2^k, E_2^k)$ $(T_2^k, E_2^k \neq 0,\ k \in \mathbb{Z})$, which are the intersecting points of the nullclines $\nu(T) = \phi(T, E)$ and $E(\beta(T) - \mu(T)) + \sigma q(T) + \theta = 0$. T_2^k and E_2^k satisfy $\nu(T_2^k) = \phi(T_2^k, E_2^k)$, $E_2^k = \frac{\sigma q(T_2^k)+\theta}{\mu(T_2^k)-\beta(T_2^k)}$;
(3) Immune-free equilibrium $P_3(T_3, 0)$ for $\sigma q(T_3) > 0, \theta \geq 0$.

Firstly, the linearized system of (19) can be obtained as $(x(t) = T(t) - T_i,\ y(t) = E(t) - E_i)$

$$\begin{cases} x'(t) = T_i\nu'(T_i)x(t-\tau) + (-T_i\phi'_T(T_i, E_i) + (\nu(T_i) - \phi(T_i, E_i)))x(t) \\ \qquad\quad - T_i\phi'_E(T_i, E_i)y(t), \\ y'(t) = E_i\beta'(T_i)x(t-\rho) + (\sigma q'(T_i) - E_i\mu'(T_i))x(t) + (\beta(T_i) - \mu(T_i))y(t), \end{cases} \tag{20}$$

where (T_i, E_i) are the coordinates of the equilibrium $P_i, i = 1, 2, 3$. It is well known that the stability of P_i depends on the distribution of characteristic roots of (20). We now analyze the stability of the equilibria $P_i (i = 1, 2, 3)$ of (19) separately.

3.2.1. *Tumor-Free Equilibrium.* The linearized system (20) at the tumor-free equilibrium $P_1(0, E_1)$ becomes

$$\begin{cases} x'(t) = (\nu(0) - \phi(0, E_1))x(t) \\ y'(t) = E_1\beta'(0)x(t-\rho) + (\sigma q'(0) - E_1\mu'(0))x(t) - \mu(0)y(t). \end{cases} \tag{21}$$

Since $\sigma > 0$, then for any initial point (T'_0, E'_0) with $T'_0 > 0,\ E'_0 > 0$, the condition for the asymptotic annihilation of T is

$$\nu(0) < \phi(0, E_1).$$

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

From the above analysis, we have the following results.

Theorem 3.1. *For system (19), we have the following conclusions:*

(i) If $\nu(0) < \phi(0, E_1)$, then the tumor-free equilibrium P_1 is a stable node.
(ii) If $\nu(0) > \phi(0, E_1)$, then the tumor-free equilibrium P_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 ($\nu(0) < \phi(0, E_1)$), then tumor cells will die out. Otherwise ($\nu(0) > \phi(0, E_1)$), the tumor-free equilibrium is unstable and tumor cells will appear either at the immune-free equilibrium or at the tumor-present equilibrium. These results also show that the stability of the tumor-free equilibrium P_1 will not change for all values of $\tau \geq 0$ and $\rho \geq 0$; that is, Hopf bifurcation will not occur at the tumor-free equilibrium P_1 in the absence of immunotherapy.

3.2.2. *Positive Equilibria.* The linearized system (20) at a positive equilibrium P_2 (T_2, E_2) of (19) takes the form

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

where

$$\begin{array}{ll} a_{11}=T_2\nu'(T_2)<0, & a_{12}=T_2\phi'_T(T_2,E_2)\le 0,\\ a_{13}=T_2\phi'_E(T_2,E_2)>0, & a_{21}=\beta'(T_2)E_2\ge 0,\\ a_{22}=\sigma q'(T_2)-\mu'(T_2)E_2, & a_{23}=\beta(T_2)-\mu(T_2)=\frac{-\sigma q(T_2)}{E_2}<0. \end{array}$$

Then the characteristic equation of (22) is

$$\lambda^2+A_1\lambda+A_2+(B_1\lambda+B_{21})e^{-\lambda\tau}+B_{22}e^{-\lambda\rho}=0, \tag{23}$$

where

$$\begin{aligned} A_1&=a_{12}-a_{23}=T_2\phi'_T(T_2,E_2)-\beta(T_2)+\mu(T_2),\\ A_2&=a_{13}a_{22}-a_{12}a_{23}\\ &=T_2(\phi'_E(T_2,E_2)(\sigma q'(T_2)-\mu'(T_2)E_2)-(\beta(T_2)-\mu(T_2))\phi'_T(T_2,E_2)), \end{aligned}$$

$$\begin{aligned} B_1&=-a_{11}=-T_2\nu'(T_2)>0,\\ B_{21}&=a_{11}a_{23}=-\frac{\sigma T_2 q(T_2)\nu'(T_2)}{E_2}>0,\\ B_{22}&=a_{13}a_{21}=T_2E_2\phi'_E(T_2,E_2)\beta'(T_2)\ge 0. \end{aligned}$$

Let

$$\begin{aligned} f_1&=T_2\phi'_T(T_2,E_2)-\beta(T_2)+\mu(T_2)-T_2\nu'(T_2),\\ f_2&=T_2\phi'_T(T_2,E_2)-\beta(T_2)+\mu(T_2)+T_2\nu'(T_2),\\ f_3&=T_2(\phi'_E(x_2,E_2)(\sigma q'(T_2)-\mu'(T_2)E_2+E_2\beta'(T_2))\\ &\quad+(\beta(T_2)-\mu(T_2))(\nu'(T_2)-\phi'_T(T_2,E_2))),\\ f_4&=T_2(\phi'_E(T_2,E_2)(\sigma q'(T_2)-\mu'(T_2)E_2-E_2\beta'(T_2))\\ &\quad-(\beta(T_2)-\mu(T_2))(\nu'(T_2)+\phi'_T(T_2,E_2)))\\ f_5&=2T_2(\phi'_E(T_2,E_2)(\sigma q'(T_2)-\mu'(T_2)E_2)+(\beta(T_2)-\mu(T_2))\phi'_T(T_2,E_2))\\ f_6&=T_2(E_2\phi'_E(T_2,E_2)\beta'(T_2)+(\beta(T_2)-\mu(T_2))\phi'_T(T_2,E_2)). \end{aligned}$$

In the following, we consider the case $\tau=\rho$, then the characteristic equation of (22) is

$$\lambda^2+A_1\lambda+A_2+(B_1\lambda+B_2)e^{-\lambda\tau}=0, \tag{24}$$

Define

$$\omega_\pm^2=\frac{1}{2}\left[(f_5-f_1f_2)\pm\sqrt{(f_1f_2)^2+2f_5f_1f_2+4f_6^2}\right]. \tag{25}$$

and

$$\tau_j^\pm=\begin{cases} \frac{1}{\omega_\pm}\left(2j\pi+\arccos\left\{\frac{(f_6+f_1f_2)\omega_\pm^2-f_5f_6}{(f_1+x_2\nu'(x_2))^2\omega_\pm^2\pm f_6^2}\right\}\right)\\ \quad\text{if } f_6f_1+x_2\nu'(x_2)(f_6-\omega_\pm^2+f_5)>0,\\ \frac{1}{\omega_\pm}\left((2j+2)\pi-\arccos\left\{\frac{(f_6+f_1f_2)\omega_\pm^2-f_5f_6}{(f_1+x_2\nu'(x_2))^2\omega_\pm^2\pm f_6^2}\right\}\right)\\ \quad\text{if } f_6f_1+x_2\nu'(x_2)(f_6-\omega_\pm^2+f_5)<0. \end{cases} \tag{26}$$

We have the following stability results.

Theorem 3.2. *Let $\tau_j^\pm (j=1,2\cdots)$ be defined by (26) and assume that*

$$f_1>0,\ f_3>0. \tag{27}$$

(i) If

$$f_5 - f_1 f_2 < 0, \quad f_3 f_4 > 0 \ \text{ or } \ f_5 - f_1 f_2 < 4 f_3 f_4, \tag{28}$$

then the positive equilibrium $P_2(T_2, E_2)$ of (19) is asymptotically stable for all $\tau \geq 0$;

(ii) If

$$f_3 f_4 < 0 \ \text{ or } \ f_5 - f_1 f_2 > 0 \ \text{ and } \ (f_5 - f_1 f_2)^2 = 4 f_3 f_4, \tag{29}$$

then $P_2(T_2, E_2)$ is stable for all $\tau \in (0, \tau_0^+)$ and unstable for $\tau > \tau_0$;

(iii) If

$$f_5 - f_1 f_2 > 0, \quad f_3 f_4 > 0 \ \text{ and } \ (f_5 - f_1 f_2)^2 > 4 f_3 f_4, \tag{30}$$

then there is a positive integer k such that $P_2(T_2, E_2)$ is stable for

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

and unstable for

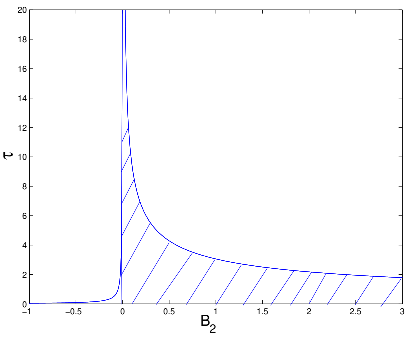
$$\tau \in [\tau_0^+, \tau_0^-) \cup [\tau_1^+, \tau_1^-) \cup \cdots \cup [\tau_{k-1}^+, \tau_{k-1}^-);$$

(iv) If $f_5^2 < f_6^2$ hold, then system (19) undergoes a Hopf bifurcation at the positive equilibrium $P_2(T_2, E_2)$ 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 (19), we use the functions proposed in d'Onofrio [37] as an example, that is, $\nu(T) = 1.636(1 - 0.002T)$, $\phi(T, E) = E$, $\beta(T) = \frac{1.131T}{20.19+T}$, $\sigma q(T) = 0.1181$, $\mu(T) = 0.00311T + 0.3743$. Then (19) has a tumor-free equilibrium $P_1(0, 0.315522)$, which is a saddle and three positive equilibria: a microscopic equilibrium point $P_2^1(8.18971, 1.6092)$ which is locally asymptotically stable, an unstable saddle $P_2^2(267.798, 0.759765)$, and a macroscopic equilibrium point $P_2^3(447.134, 0.17298)$ which is also locally asymptotically stable. Since the stability of the saddle does not change with small perturbation, we only analyze the stability regions of the two stable equilibria $P_2^1(8.18971, 1.6092)$ and $P_2^3(447.134, 0.17298)$ as follows.

(a) For the equilibrium $P_2^1(8.18971, 1.6092)$, 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 region is illustrated by the blue shadowed areas bounded by the dashed lines in Fig. 4(a). In this case $B_2 = 0.07904$, then we can obtain that the equilibrium is stable as $\tau < 1.27248$.

(b) 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 blue shadowed areas bounded by the dashed lines in Fig. 4(b). Since $B_2 = 0.998906$, then we can see that the equilibrium is stable as $\tau < 0.476779$.



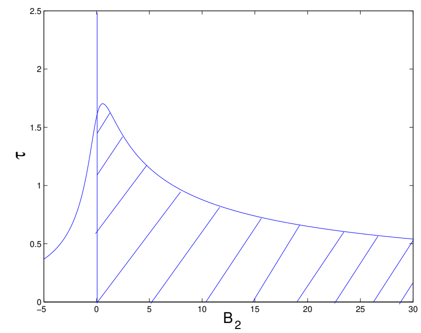


FIGURE 4. The stability regions of the equilibria (a) $P_2^1(8.18971, 1.6092)$ and (b) $P_2^3(447.134, 0.17298)$ with blue dashed lines in the (B_2, τ)-parameter plane.

3.2.3. *Hopf Bifurcation.* In order to further consider Hopf bifurcation at the positive equilibrium $P_2(T_2, E_2)$, let $a = \tau - \tau_k$. Then $a = 0$ is a Hopf bifurcation value of equation (19) with $\tau = \rho$. Set $\bar{t} = \tau t$, $\bar{x}_1 = x_1 - T_2$, $\bar{x}_2 = x_2 - E_2$, dropping the bars, then (19) can be written as a functional differential equation in $\mathcal{C} = C([-1, 0), \mathbb{R}^2)$ as follows

$$x'(t) = L_a(x_t) + R(a, x_t), \tag{31}$$

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

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

in which a_{ij} are defined in subsection 3.2.2, $R : \mathbb{R} \times \mathcal{C} \to \mathbb{R}^2$ denotes the higher order terms.

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

$$L_a\phi = \int_{-1}^{0} d\eta(\theta, 0)\phi(\theta) \quad \text{for} \quad \phi \in \mathcal{C}. \tag{32}$$

In fact, we can choose

$$\eta(\theta, a) = (\tau_k + a)\begin{pmatrix} -a_{12} & -a_{13} \\ a_{22} & a_{23} \end{pmatrix}\delta(\theta) - (\tau_k + a)\begin{pmatrix} a_{11} & 0 \\ a_{21} & 0 \end{pmatrix}\delta(\theta + 1), \tag{33}$$

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 (31) can be written as

$$x_t' = A(a)x_t + R(a)x_t, \tag{34}$$

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 last subsection, 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 assure $\langle p^*(\theta), p(\theta) \rangle = 1$, we have

$$D = \left(1 + \overline{\alpha}\alpha^* - \tau_k(a_{21}\alpha^* + a_{11})e^{i\omega\tau_k}\right)^{-1}. \tag{35}$$

In the following, we will compute the coordinates on the center manifold C_a at $a = 0$. Let x_t be the solution of (31) 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 (31), we have

$$z'(t) = i\omega\tau_k z + g(z, \overline{z}, a), \tag{36}$$

where

$$\begin{aligned} g(z, \overline{z}) =& \frac{g_{20}(\theta)}{2}z^2 + g_{11}(\theta)z\overline{z} + \frac{g_{02}(\theta)}{2}\overline{z}^2 + \frac{g_{30}(\theta)}{6}z^3 + \frac{g_{21}(\theta)}{2}z^2\overline{z} + \frac{g_{12}(\theta)}{2}z\overline{z}^2 \\ &+ \frac{g_{03}(\theta)}{6}\overline{z^3} + \frac{g_{31}(\theta)}{6}z^3\overline{z} + \frac{g_{40}(\theta)}{24}z^4 + \frac{g_{31}(\theta)}{4}z^3\overline{z} + \frac{g_{22}(\theta)}{6}z^2\overline{z}^2 \\ &+ \frac{g_{13}(\theta)}{4}z\overline{z}^3 + \frac{g_{04}(\theta)}{24}\overline{z}^4 + \frac{g_{41}(\theta)}{24}z^4\overline{z} + \frac{g_{32}(\theta)}{12}z^3\overline{z}^2 + \cdots. \end{aligned} \tag{37}$$

The coefficients $g_{ij}(\theta)$ are given by

$$\begin{aligned} g_{20} =& \tau_k\overline{D}\left[\frac{\partial\phi(T_2,E_2)}{\partial T} + \frac{T_2}{2}\frac{\partial^2\phi(T_2,E_2)}{\partial T^2} + \left(\frac{\partial\phi(T_2,E_2)}{\partial E} + T_2\frac{\partial^2\phi(T_2,E_2)}{\partial T\partial E}\right)\alpha\right. \\ &+ \left(T_2\frac{\partial^2\phi(T_2,E_2)}{\partial E^2}\right)\alpha^2 + \frac{1}{2}(\sigma q''(T_2) - \mu''(T_2)E_2)\overline{\alpha^*} - \mu'(T_2)\overline{\alpha^*}\alpha \\ &+ \frac{T_2}{2}\nu''(T_2)e^{-2i\omega\tau_k} + \nu'(T_2)e^{-i\omega\tau_k} \\ &\left.+ \frac{E_2}{2}\beta''(T_2)\overline{\alpha^*}e^{-2i\omega\tau_k} + \overline{\alpha^*}\alpha\beta'(T_2)e^{-i\omega\tau_k}\right], \end{aligned}$$

$$\begin{aligned} g_{11} =& \tau_k\overline{D}\left[2\frac{\partial\phi(T_2,E_2)}{\partial T} + T_2\frac{\partial^2\phi(T_2,E_2)}{\partial T^2} + \left(\frac{\partial\phi(T_2,E_2)}{\partial E} + T_2\frac{\partial^2\phi(T_2,E_2)}{\partial T\partial E}\right)(\alpha + \overline{\alpha})\right. \\ &+ \left(2T_2\frac{\partial^2\phi(T_2,E_2)}{\partial E^2}\right)\alpha\overline{\alpha} + (\sigma q''(T_2) - \mu''(T_2)E_2)\overline{\alpha^*} - \mu'(T_2)\overline{\alpha^*}(\alpha + \overline{\alpha}) \end{aligned}$$

$$+ T_2\nu''(T_2) + \nu'(T_2)(e^{-i\omega\tau_k} + e^{i\omega\tau_k})$$
$$+ E_2\beta''(T_2)\overline{\alpha^*} + \overline{\alpha^*}\beta'(T_2)(e^{-i\omega\tau_k}\overline{\alpha} + e^{i\omega\tau_k}\alpha)\Big],$$

$$\begin{aligned} g_{02} =& \tau_k\overline{D}\left[\frac{\partial\phi(T_2,E_2)}{\partial T} + T_2\frac{\partial^2\phi(T_2,E_2)}{2\partial T^2} + \left(\frac{\partial\phi(T_2,E_2)}{\partial E} + T_2\frac{\partial^2\phi(T_2,E_2)}{\partial T\partial y}\right)\overline{\alpha}\right. \\ &+ \left(T_2\frac{\partial^2\phi(T_2,E_2)}{\partial E^2}\right)\overline{\alpha^2} + \frac{1}{2}(\sigma q''(T_2) - \mu''(T_2)E_2)\overline{\alpha^*} - \mu'(T_2)\overline{\alpha^*}\overline{\alpha} \\ &\left. + \frac{T_2}{2}\nu''(T_2)e^{2i\omega\tau_k} + \nu'(T_2)e^{i\omega\tau_k} + \frac{E_2}{2}\beta''(T_2)\overline{\alpha^*}e^{2i\omega\tau_k} + \overline{\alpha^*}\overline{\alpha}\beta'(T_2)e^{i\omega\tau_k}\right], \end{aligned}$$

$$\begin{aligned} g_{21} =& \tau_k\overline{D}\Big[3e_{11} + (2\alpha+\overline{\alpha})e_{12} + (\alpha^2 + 2\alpha\overline{\alpha})e_{13} + 3\alpha^2\overline{\alpha}e_{14} + 3\overline{\alpha^*}e_{21} \\ &+ \overline{\alpha^*}(2\alpha+\overline{\alpha})e_{22} + \frac{T_2}{2}\nu^{(3)}(T_2)e^{-i\omega\tau_k} + \frac{\nu''(T_2)}{2}(e^{-2i\omega\tau_k} + 2) \\ &+ \frac{\overline{\alpha^*}}{2}\beta^{(3)}(T_2)e^{-i\omega\tau_k} + \frac{\overline{\alpha^*}}{2}\beta''(T_2)(\overline{\alpha}e^{-2i\omega\tau_k} + 2\alpha) \\ &+ d_{12}\left(\frac{W_{20}^{(1)}(0)}{2}\overline{\alpha} + \frac{W_{20}^{(2)}(0)}{2} + \alpha W_{11}^{(1)}(0) + W_{11}^{(2)}(0)\right) \\ &+ d_{11}(W_{20}^{(1)}(0) + 2W_{11}^{(1)}(0)) + d_{13}(W_{20}^{(2)}(0)\overline{\alpha} + 2\alpha W_{11}^{(2)}(0)) \\ &+ d_{21}\overline{\alpha^*}(W_{20}^{(1)}(0) + 2W_{11}^{(1)}(0)) \\ &+ d_{22}\overline{\alpha^*}\left(\frac{W_{20}^{(1)}(0)}{2}\overline{\alpha} + \frac{W_{20}^{(2)}(0)}{2} + W_{11}^{(1)}(0)\alpha + W_{11}^{(2)}(0)\right) \\ &+ \frac{T_2}{2}\nu''(T_2)\left(W_{20}^{(1)}(-1)e^{i\omega\tau_k} + 2W_{11}^{(1)}(-1)e^{-i\omega\tau_k}\right) \\ &+ \nu'(T_2)\left(\frac{W_{20}^{(1)}(-1)}{2} + \frac{W_{20}^{(1)}(0)}{2}e^{i\omega\tau_k} + W_{11}^{(1)}(-1) + e^{-i\omega\tau_k}W_{11}^{(1)}(0)\right) \\ &+ \frac{y_2}{2}\beta''(x_2)\overline{\alpha^*}\left(W_{20}^{(1)}(-1)e^{i\omega\tau_k} + 2W_{11}^{(1)}(-1)e^{-i\omega\tau_k}\right) \\ &+ \overline{\alpha^*}\beta'(x_2)\left(W_{20}^{(1)}(-1)\overline{\alpha} + 2W_{11}^{(1)}(-1)\alpha + W_{20}^{(2)}(0)e^{i\omega\tau_k} + 2W_{11}^{(2)}(0)e^{-i\omega\tau_k}\right)\Big], \end{aligned}$$

$$\begin{aligned} g_{12} =& \tau_k\overline{D}\Big[3e_{11} + (\alpha+2\overline{\alpha})e_{12} + (\overline{\alpha}^2 + 2\alpha\overline{\alpha})e_{13} + 3\alpha\overline{\alpha}^2e_{14} + 3\overline{\alpha^*}e_{21} \\ &+ \overline{\alpha^*}(\alpha+2\overline{\alpha})e_{22} + \frac{T_2}{2}\nu^{(3)}(T_2)e^{i\omega\tau_k} + \frac{\nu''(x_2)}{2}(e^{2i\omega\tau_k} + 2) + \frac{\overline{\alpha^*}}{2}\beta^{(3)}(T_2)e^{i\omega\tau_k} \\ &+ \frac{\overline{\alpha^*}}{2}\beta''(T_2)(\alpha e^{2i\omega\tau_k} + 2\overline{\alpha}) \\ &+ d_{12}\left(\frac{W_{02}^{(1)}(0)}{2}\alpha + \frac{W_{02}^{(2)}(0)}{2} + \overline{\alpha}W_{11}^{(1)}(0) + W_{11}^{(2)}(0)\right) \\ &+ d_{11}(W_{02}^{(1)}(0) + 2W_{11}^{(1)}(0)) + d_{13}(W_{02}^{(2)}(0)\alpha + 2\overline{\alpha}W_{11}^{(2)}(0)) \end{aligned}$$

$$
\begin{aligned}
&+ d_{21}\overline{\alpha^*}(W_{02}^{(1)}(0) + 2W_{11}^{(1)}(0))\\
&+ d_{22}\overline{\alpha^*}\left(\frac{W_{02}^{(1)}(0)}{2}\alpha + \frac{W_{02}^{(2)}(0)}{2} + W_{11}^{(1)}(0)\overline{\alpha} + W_{11}^{(2)}(0)\right)\\
&+ \frac{T_2}{2}\nu''(T_2)\left(W_{02}^{(1)}(-1)e^{-i\omega\tau_k} + 2W_{11}^{(1)}(-1)e^{i\omega\tau_k}\right)\\
&+ \nu'(T_2)\left(\frac{W_{02}^{(1)}(-1)}{2} + \frac{W_{02}^{(1)}(0)}{2}e^{-i\omega\tau_k} + W_{11}^{(1)}(-1) + e^{i\omega\tau_k}W_{11}^{(1)}(0)\right)\\
&+ \frac{y_2}{2}\beta''(x_2)\overline{\alpha^*}\left(W_{02}^{(1)}(-1)e^{-i\omega\tau_k} + 2W_{11}^{(1)}(-1)e^{+i\omega\tau_k}\right)\\
&+ \overline{\alpha^*}\beta'(x_2)\left(W_{02}^{(1)}(-1)\alpha + 2W_{11}^{(1)}(-1)\overline{\alpha} + W_{02}^{(2)}(0)e^{-i\omega\tau_k} + 2W_{11}^{(2)}(0)e^{i\omega\tau_k}\right)\Bigg],
\end{aligned}
$$

$$
\begin{aligned}
g_{30} =&\tau_k\overline{D}\Bigg[e_{11} + \alpha e_{12} + \alpha^2 e_{13} + \alpha^3 e_{14} + \overline{\alpha^*}e_{21} + \overline{\alpha^*}\alpha e_{22} + \frac{T_2}{6}\nu^{(3)}(T_2)e^{-3i\omega\tau_k}\\
&+ \frac{\nu''(T_2)}{2}\alpha e^{-2i\omega\tau_k} + \frac{y_2\overline{\alpha^*}}{6}\beta^{(3)}(x_2)e^{-3i\omega\tau_k} + \frac{\overline{\alpha^*}}{2}\beta''(T_2)\alpha e^{-2i\omega\tau_k}\\
&+ d_{11}W_{20}^{(1)}(0) + d_{12}\left(\frac{W_{20}^{(1)}(0)}{2}\alpha + \frac{W_{20}^{(2)}(0)}{2}\right) + d_{13}W_{20}^{(1)}(0)\alpha\\
&+ d_{22}\overline{\alpha^*}\left(\frac{W_{20}^{(1)}(0)}{2}\alpha + \frac{W_{20}^{(2)}(0)}{2}\right) + d_{21}\overline{\alpha^*}W_{20}^{(1)}(0)\\
&+ T_2\nu''(x_2)W_{20}^{(2)}(-1)e^{-i\omega\tau_k} + \nu'(T_2)(W_{20}^{(1)}(-1) + W_{20}^{(1)}(0)e^{-i\omega\tau_k})\\
&+ \frac{E_2}{2}\beta''(T_2)\overline{\alpha^*}W_{20}^{(1)}(-1)e^{-i\omega\tau_k} + \overline{\alpha^*}\beta'(T_2)(W_{20}^{(1)}(-1)\alpha + W_{20}^{(0)}(0)e^{-i\omega\tau_k})\Bigg],
\end{aligned}
$$

$$
\begin{aligned}
g_{03} =&\tau_k\overline{D}\Bigg[e_{11} + \overline{\alpha}e_{12} + \overline{\alpha}^2 e_{13} + \overline{\alpha}^3 e_{14} + \overline{\alpha^*}e_{21} + \overline{\alpha^*}\overline{\alpha}e_{22} + \frac{T_2}{6}\nu^{(3)}(T_2)e^{3i\omega\tau_k}\\
&+ \frac{\nu''(T_2)}{2}\overline{\alpha}e^{2i\omega\tau_k} + \frac{E_2\overline{\alpha^*}}{6}\beta^{(3)}(T_2)e^{3i\omega\tau_k} + \frac{\overline{\alpha^*}}{2}\beta''(T_2)\overline{\alpha}e^{2i\omega\tau_k} + d_{11}W_{02}^{(1)}(0)\\
&+ d_{12}\left(\frac{W_{02}^{(1)}(0)}{2}\overline{\alpha} + \frac{W_{02}^{(2)}(0)}{2}\right) + d_{13}W_{02}^{(1)}(0)\overline{\alpha}\\
&+ d_{22}\overline{\alpha^*}\left(\frac{W_{02}^{(1)}(0)}{2}\overline{\alpha} + \frac{W_{02}^{(2)}(0)}{2}\right) + d_{21}\overline{\alpha^*}W_{02}^{(1)}(0)\\
&+ T_2\nu''(T_2)W_{02}^{(2)}(-1)e^{i\omega\tau_k} + \nu'(T_2)(W_{02}^{(1)}(-1) + W_{02}^{(1)}(0)e^{i\omega\tau_k})\\
&+ \frac{E_2}{2}\beta''(T_2)\overline{\alpha^*}W_{02}^{(1)}(-1)e^{i\omega\tau_k} + \overline{\alpha^*}\beta'(T_2)(W_{20}^{(1)}(-1)\overline{\alpha} + W_{02}^{(0)}(0)e^{i\omega\tau_k})\Bigg],
\end{aligned}
$$

in which

$$
\begin{array}{ll}
d_{11} = \frac{\partial\phi(T_2,E_2)}{\partial T} + \frac{1}{2}\frac{T_2\partial^2\phi(T_2,E_2)}{\partial T^2}, & d_{12} = \frac{\partial\phi(T_2,E_2)}{\partial E} + T_2\frac{\partial^2\phi(T_2,E_2)}{\partial T\partial E},\\
d_{13} = T_2\frac{\partial^2\phi(T_2,E_2)}{\partial E^2}, & d_{21} = \frac{1}{2}(\sigma q''(T_2) - \mu''(T_2)E_2),\\
d_{22} = -\mu'(T_2), & \\
e_{11} = \frac{1}{2}\frac{\partial^2\phi(T_2,E_2)}{\partial T^2} + \frac{T_2}{6}\frac{\partial^3\phi(T_2,E_2)}{\partial T^3}, & e_{12} = \frac{\partial^2\phi(T_2,E_2)}{\partial T\partial E} + \frac{T_2}{2}\frac{\partial^3\phi(T_2,E_2)}{\partial T^2\partial E},\\
e_{13} = \frac{1}{2}\frac{\partial^2\phi(T_2,E_2)}{\partial E^2} + \frac{T_2}{2}\frac{\partial^3\phi(T_2,E_2)}{\partial T\partial E^2}, & e_{14} = \frac{T_2}{6}\frac{\partial^3\phi(T_2,E_2)}{\partial E^3},\\
e_{21} = \frac{\sigma q^{(3)}(T_2) - \mu^{(3)}(T_2)E_2}{6}, & e_{22} = -\frac{\mu''(T_2)}{2}.
\end{array}
\qquad (38)
$$

Similarly we can give the expressions of g_{31}, g_{22}, g_{40} and g_{32}, then all useful g_{ij} are given.

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 (36), one has

$$g(z,\overline{z}) = \overline{p^*(0)}R(0,z,\overline{z}). \tag{39}$$

Inserting (x_{1t}, y_{2t}) into (39) and comparing the coefficients of $z^i\overline{z}^j (i+j \geq 2)$ with that of (37), we obtain all $g_{ij}(i+j \geq 2)$. Thus, (36) can be transformed into an equation of the form

$$z'(t) = \lambda_1(a)z + \tfrac{1}{2}C_1(a)z^2\overline{z} + \tfrac{1}{12}C_2(a)z^3\overline{z}^2 + (o|z|^5), \tag{40}$$

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

$$\begin{array}{rcl} C_1(0) & = & \frac{i}{2\omega}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{1}{2}g_{21}, \\ C_2(0) & = & \mathrm{Re}\{g_{32}\} + \frac{1}{\omega}\mathrm{Im}\left\{g_{20}\bar{g}_{31} - g_{11}(4g_{31} + 3\bar{g}_{22}) - \frac{1}{3}g_{02}(g_{40} + \bar{g}_{13})\right. \\ & & \left. -g_{30}g_{12})\right\} + \frac{1}{\omega^2}\mathrm{Re}\left\{g_{20}(\bar{g}_{11}(3g_{12} - \bar{g}_{30}) + g_{02}(\bar{g}_{12} - \frac{1}{3}g_{30}) + g_{03}\bar{g}_{02}))\right\} \\ & & +\frac{1}{\omega^2}\mathrm{Re}\left\{g_{11}(\bar{g}_{02}(\frac{5}{3}\bar{g}_{30} + 3g_{12}) + \frac{1}{3}\bar{g}_{03}g_{02} - 4g_{11}g_{30})\right\} \\ & & +\frac{3}{\omega^2}\mathrm{Im}\{g_{20}g_{11}\}\mathrm{Im}\{g_{21}\} + \frac{1}{\omega^3}\mathrm{Im}\{\bar{g}_{02}g_{11}(\bar{g}_{02}^2 - 3\bar{g}_{20}g_{11} - 4g_{11}^2)\} \\ & & +\frac{1}{\omega^3}\mathrm{Im}\{g_{20}g_{11}\}(3\mathrm{Re}\{g_{11}g_{20}\} - 2|g_{02}|^2). \end{array}$$

Let $z = re^{i\theta}$. Then (40) can be written as

$$\left\{ \begin{array}{l} \dfrac{dr}{dt} = ar\mathrm{Re}\lambda'(0) + \dfrac{1}{2}r^3\mathrm{Re}\{C_1(0)\} + \dfrac{1}{12}r^5\mathrm{Re}\{C_2(0)\} + h.o.t. \\ \dfrac{d\theta}{dt} = \omega\tau_k + a\mathrm{Im}\lambda'(0) + \dfrac{1}{2}r^2\mathrm{Im}\{C_1(0)\} + \dfrac{1}{12}r^4\mathrm{Im}\{C_2(0)\} + h.o.t. \end{array} \right. \tag{41}$$

Hence

$$\begin{array}{rcl} \dfrac{dr}{d\theta} & = & \dfrac{ar\mathrm{Re}\{\lambda'(0)\} + \frac{1}{2}r^3\mathrm{Re}\{C_1(0)\} + \frac{1}{12}r^5\mathrm{Re}\{C_2(0)\} + h.o.t.}{\omega\tau_k + a\mathrm{Im}\{\lambda'(0)\} + \frac{1}{2}r^2\mathrm{Im}\{C_1(0)\} + \frac{1}{12}r^4\mathrm{Im}\{C_2(0)\} + h.o.t.} \\ & = & \dfrac{1}{A(\tau_k,a)}\left(a\mathrm{Re}\{\lambda'(0)\}r + B(\tau_k,a)r^3 + C(\tau_k,a)r^5\right) + h.o.t., \end{array} \tag{42}$$

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

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

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 (42) satisfying $r(0, r_0) = r_0$. Then $r_1(0) = 1$, $r_i(0) = 0$ for $i \geq 2$. Inserting the above into (42), we have

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

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

$$P(r_0)=\left(\frac{2a\mathrm{Re}\{\lambda'(0)\}\pi}{A(\tau_k,a)}+1\right)r_0+\frac{2\pi B(\tau_k,a)}{A(\tau_k,a)}r_0^3+\frac{2\pi C(\tau_k,a)}{A(\tau_k,a)}r_0^5+O(r_0^7). \tag{43}$$

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

$$r_0^*=\sqrt{\frac{-a\mathrm{Re}\{\lambda'(0)\}}{B(\tau_k,a)}}(1+O(|a|)). \tag{44}$$

We can compute the period of the bifurcated periodic solution as follows

$$\begin{aligned} T(\tau_k,a) &= \int_0^{2\pi}\frac{d\theta}{A(\tau_k,a)+\frac{1}{2}\mathrm{Im}\{C_1(0)\}r^2+h.o.t.} \\ &= \frac{1}{A(\tau_k,a)}\int_0^{2\pi}\left(1+\frac{\mathrm{Im}\{C_1(0)\}\mathrm{Re}\{\lambda'(0)\}a}{2A(\tau_k,a)B(\tau_k,a)}\right)d\theta+o(|a|) \\ &= \frac{2\pi}{\omega\tau_k}\left(1+N(\tau_k)a+o(|a|)\right), \end{aligned} \tag{45}$$

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 et al. [63].

Theorem 3.3. *If* $\mathrm{Re}\{C_1(0)\}\neq 0$*, then system (19) 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* $a=0$*, the period* $T(\tau_k,a)$ *is increasing in parameter a (resp., decreasing) if* $N(\tau_k)>0$ *(resp.,* $N(\tau_k)<0$*).*

3.2.4. *Bautin Bifurcation.* The *Bautin bifurcation* of an equilibrium in a two-parameter family of differential equations is a bifurcation at which the critical equilibrium has a pair of purely imaginary eigenvalues and the first Lyapunov coefficient for the Hopf bifurcation vanishes (Kuznetsov [75]). This phenomenon is also called the *generalized Hopf bifurcation.* For system (19), Theorem 3.3 implies that it 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 (40), and (41) can be written as

$$\begin{cases} \dfrac{dr}{dt} = ar\mathrm{Re}\lambda'(0) + \dfrac{1}{2}r^3\mathrm{Re}\{C_1(a)\} + \dfrac{1}{12}r^5\mathrm{Re}\{C_2(0)\} + h.o.t. \\ \dfrac{d\theta}{dt} = \omega\tau_k + a\mathrm{Im}\lambda'(0) + \dfrac{1}{2}r^3\mathrm{Im}\{C_1(a)\} + \dfrac{1}{12}r^5\mathrm{Im}\{C_2(0)\} + h.o.t. \end{cases} \tag{46}$$

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

$$P(r_0) = \left(\frac{2a\mathrm{Re}\{\lambda'(0)\}\pi}{A(\tau_k,a)} + 1\right) r_0 + \frac{2\pi\bar{B}(\tau_k,a)}{A(\tau_k,a)} r_0^3 + \frac{2\pi\bar{C}(\tau_k,a)}{A(\tau_k,a)} r_0^5 + O(r_0^7), \tag{47}$$

where

$$\begin{aligned} \bar{B}(\tau_k,a) =& \frac{1}{2}\mathrm{Re}\{C_1(a)\} - \frac{\mathrm{Im}\{C_1(a)\}\mathrm{Re}\{\lambda'(0)\}a}{2A(\tau_k,a)}, \\ \bar{C}(\tau_k,a) =& \frac{\mathrm{Re}\{C_2(0)\}}{12} - \frac{\mathrm{Re}\{C_1(a)\}\mathrm{Im}\{C_1(a)\}}{4A(\tau_k,a)} \\ & - \frac{a\mathrm{Re}\lambda'(0)}{12A(\tau_k,a)}\left(\mathrm{Im}\{C_2(0)\} - \frac{3\mathrm{Im}^2\{C_1(a)\}}{A(\tau_k,a)}\right). \end{aligned}$$

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

$$P(r_0) = r_0 + \frac{1}{A(\tau_k,a)}\left(2a\mathrm{Re}\{\lambda'(0)\}\pi r_0 + 2\pi\bar{B}(\tau_k,a)r_0^3 + 2\pi\bar{C}(\tau_k,a)r_0^5\right) + O(r_0^7). \tag{48}$$

Hence the number of periodic solutions of system (40) equals the number of positive fixed points of the Poincaré map $P(r_0)$. Now we analyze the distribution of roots of $P(r_0) = r_0$. To find fixed points of $P(r_0) = r_0$ is equivalent to find positive roots of

$$P_1(r_0) \triangleq \frac{A(\tau_k,a)}{\pi r_0}\left(P(r_0) - r_0\right) = \alpha_0 + \alpha_1 r_0^2 + \alpha_2 r_0^4 + O(a^2, r_0^5) = 0, \tag{49}$$

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

$$P_1(a, r^2) = \frac{1}{2\alpha_2}(2\alpha_0\alpha_2 - \alpha_1^2 + O(\alpha_1^3)). \tag{50}$$

Substituting $\alpha_0, \alpha_1, \alpha_2$ into (50) 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 $P'_{1r_0^2}(a, 0) = \alpha_1(a)$, $P_1(a, 0) = \alpha_0(a)$, 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

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

That is, $l : \alpha_0 = \frac{3\alpha_1^2}{2\mathrm{Re}\{C_2(0)\}},\ \alpha_1 < 0$. Recalling the first equation of (46), the above analysis can be summarized as follows:

(a) If $(\alpha_0, \alpha_1) \in D_1'$, (49) has no positive root, which means that system (40) has no periodic solution in a sufficiently small neighborhood of the unstable equilibrium $z = 0$.

(b) If $(\alpha_0, \alpha_1) \in D_2'$, (49) has only one positive root, which means that system (40) 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 $(\alpha_0, \alpha_1) \in D_3'$, (49) has two positive roots, which means that system (40) has two periodic solutions in a sufficiently small neighborhood of the unstable equilibrium $z = 0$, one is stable and the other is unstable.

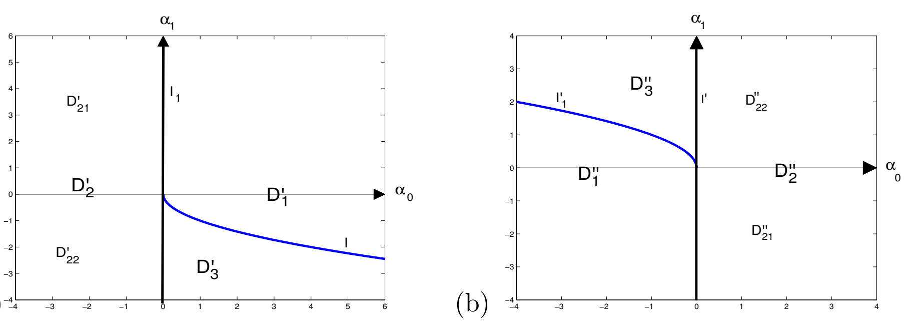


FIGURE 5. The bifurcation diagram for system (40). (a) $\alpha_2 > 0$. (b) $\alpha_2 < 0$.

Therefore, we can summarize the above discussions as follows.

Theorem 3.4. *If $\mathrm{Re}\{C_1(0)\} = 0$ but $\mathrm{Re}\{C_2(0)\} \neq 0$, then (19) 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 (40) 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, at the same time, an unstable periodic solution Γ_2 bifurcates from Γ_1 and locates inside Γ_1, where

$$\begin{aligned} T_1 &= \frac{2\pi}{\omega\tau_k}\left(1 + N_1(\tau_k)a + o(|a|^2)\right), \\ T_2 &= \frac{2\pi}{\omega\tau_k}\left(1 + N_2(\tau_k) + o(|a|, |C_1(a)|^2)\right), \\ N_1(\tau_k) &= \frac{\mathrm{Re}\{\lambda'(0)\}\mathrm{Im}\{C_1(a)\} - \mathrm{Re}\{C_1(a)\}\mathrm{Im}\{\lambda'(0)\}}{\omega\tau_k \mathrm{Re}\{C_1(a)\}}, \end{aligned}$$

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 (40) undergoes Hopf bifurcation and an unstable periodic solution Γ_3 with period T_1 bifurcates from $z = 0$, 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 (40) coincide to become one; If the point (α_0, α_1) crosses the line l to D'_1, the new periodic solution of (40) disappears, that is if a point (α_0, α_1) crosses the region D'_3 to the region D'_1, then periodic solutions of (40) undergo saddle-node bifurcation, that is, a saddle-node type periodic solution bifurcated from the trivial solution $z = 0$.

Similarly bifurcation results can be obtained for the case $\alpha_2 < 0$.

3.2.5. *Fold-Hopf (Zero-Hopf) Bifurcation.* In this subsection we explore the possibility that the characteristic equation (23) of the linearized system (22) at a positive equilibrium $P_2(T_2, E_2)$ has a simple zero eigenvalue and a pair of purely imaginary eigenvalues; that is, the existence of Fold-Hop (zero-Hopf) bifurcation of the double delayed model (19) at P_2. Note that the condition for the existence of a limit cycle does not exist anymore, so we have to use different approaches to handle this singularity (Wu and Wang [123]). First, we find the condition under which the characteristic equation of (22) has a simple zero eigenvalue. Second, under this condition, we consider the existence of a pair of purely imaginary eigenvalues and the distribution of the remaining eigenvalues of the characteristic equation of (22). Hence, we obtain the conditions for the existence of a Fold-Hopf (zero-Hopf) bifurcation.

Let ωi ($\omega > 0$) be a root of (23). Plugging it into (23) and separating the real and imaginary parts, we obtain that

$$\left\{ \begin{array}{rcl} -\omega^2 + A_2 + B_{22}\cos(\rho\omega) &=& -\omega B_1 \sin(\tau\omega) - B_{21}\cos(\tau\omega), \\ \omega A_1 - B_{22}\sin(\rho\omega) &=& -\omega B_1 \cos(\tau\omega) + B_{21}\sin(\tau\omega). \end{array} \right. \tag{51}$$

(i) If $\tau = \rho = 0$, $A_1 + B_1 > 0$, and $A_2 + B_{21} + B_{22} = 0$, then the characteristic equation (23) has a zero root and a negative root. In order to discuss Fold-Hopf bifurcation, we make the following assumption:

(H_1) $A_1 + B_1 > 0$, $A_2 + B_{21} + B_{22} = 0$.

(ii) If $\tau = 0, \rho > 0$, and assumption (H$_1$) holds, then system (51) reduces to

$$\begin{aligned} -\omega^2 - B_{22} &= -B_{22}\cos(\rho\omega), \\ \omega(A_1 + B_1) &= B_{22}\sin(\rho\omega). \end{aligned}$$

Squaring both sides and adding them together yields

$$\omega^4 + b_0\omega^2 = 0,$$

where

$$b_0 = (A_1 + B_1)^2 + 2B_{22}. \tag{52}$$

We know that if $b_0 \geq 0$, then (23) has a simple root zero and all other roots have negative real parts for all $\rho \geq 0$; If $b_0 < 0$, note that in this case $B_{22} < 0$, then (23) has a simple root zero and a pair of purely imaginary roots $\pm i\omega^+$ at $\rho = \rho_j^+,\ j = 0, 1, 2, \cdots$, where

$$\omega^+ = \sqrt{-b_0}$$

and

$$\rho_j^+ = \frac{1}{\omega^+}\left(2(j+1)\pi + \arcsin\frac{\omega^+(A_1 + B_1)}{B_{22}}\right). \tag{53}$$

One can also obtain that

$$\mathrm{Re}\left(\frac{d\lambda}{d\rho}\right)^{-1}\Bigg|_{\rho=\rho_j^+} = \frac{\pm|b_0|}{B_{22}^2}.$$

Hence, we have the following results on the stability of the equilibrium $P_2(T_2, E_2)$.

Theorem 3.5. *Let assumption (H$_1$) hold and $\rho_j^+, j = 0, 1, 2, \cdots$, be defined by (53).*

(a) If $b_0 \geq 0$, then P_2 is stable for all $\rho \geq 0$;
(b) If $b_0 < 0$, then P_2 is stable for all $\rho \in [0, \rho_0^+)$, unstable for $\rho > \rho_0^+$, and system (19) (with $\tau = 0, \rho > 0$) undergoes a Fold-Hopf bifurcation at P_2 as ρ passes through ρ_0^+.

(iii) If $\tau > 0, \rho > 0$, squaring both sides of (51) and adding them up gives

$$2B_{22}(A_1\omega\sin(\omega\rho) + (\omega^2 - A_2)\cos(\omega\rho)) = \omega^4 + (A_1^2 - B_1^2 - 2A_2)\omega^2 + A_2^2 + B_{22}^2 - B_{21}^2.$$

Assuming $B_{22} \neq 0$ and noticing that $A_2 + B_{21} + B_{22} = 0$, the above equation can be rewritten as follows:

$$A_1\omega\sin(\omega\rho) + (\omega^2 - A_2)\cos(\omega\rho) = \frac{\omega^4 + (A_1^2 - B_1^2 - 2A_2)\omega^2 - 2A_2B_{22}}{2B_{22}}.$$

Define

$$\begin{aligned} F(\omega) &= \frac{\omega^4 + (A_1^2 - B_1^2 - 2A_2)\omega^2 - 2A_2B_{22}}{2B_{22}\sqrt{A_1^2\omega^2 + (\omega^2 - A_2)^2}}, \\ G(\omega) &= \frac{A_1\omega\sin(\omega\rho) + (\omega^2 - A_2)\cos(\omega\rho)}{\sqrt{A_1^2\omega^2 + (\omega^2 - A_2)^2}} \end{aligned}$$

for any $\rho \geq 0$. To consider the existence of the purely imaginary eigenvalue $i\omega$ of the characteristic equation (22), we now need to discuss the existence of the positive solutions of the following equation

$$F(\omega) = G(\omega) \tag{54}$$

and make the second assumption as follows.

(H$_2$) $A_2 > 0$.

Now we have

$$F(0) = G(0) = -\frac{A_2}{|A_2|}, \quad F'(0) = G'(0) = 0,$$

$$F''(0) = \frac{A_1^2(A_2 + B_{22}) - A_2(2A_2 + 2B_{22} + B_1^2)}{A_2|A_2|B_{22}}, \quad G''(0) = \frac{(A_1 + A_2\rho)^2}{A_2|A_2|},$$

and the following results (Wu and Wang [123]).

Lemma 3.6. *Let assumptions (H_1) and (H_2) hold.*

(i) Let $B_{22} > 0$. Assume $F''(0) < 0$, then (54) always has at least one positive solution for any $\rho \geq 0$; Assume $F''(0) > 0$, (a) if $F''(0) > \frac{A_1^2}{A_2|A_2|}$, then there exist $\rho^* > 0$ and $\rho^{**} > \rho^*$ such that (54) has no positive solutions for $\rho \in [0, \rho^*)$, one positive solution for $\rho \in [\rho^*, \rho^{**}]$ and two or more positive solutions for $\rho > \rho^{**}$; (b) if $F''(0) < \frac{A_1^2}{A_2|A_2|}$, then (54) always has positive solutions for any $\rho \geq 0$ if $A_1 \geq 0$ and has positive solutions for ρ small and large but no solutions in between if $A_1 < 0$.

(ii) Let $B_{22} < 0$. Assume $F''(0) < 0$, then Eq.(54) has no positive solutions for any $\rho \geq 0$; Assume $F''(0) > 0$, (a) if $F''(0) > \frac{A_1^2}{A_2|A_2|}$, then there exist $\rho^* > 0$ and $\rho^{**} > \rho^*$ such that (54) has one positive solution for $\rho \in [0, \rho^*)$, no positive solutions for $\rho \in (\rho^*, \rho^{**})$ and at least one positive solution for $\rho > \rho^{**}$; (b) if $F''(0) < \frac{A_1^2}{A_2|A_2|}$, and (1) $A_1 > 0$ then there exist $\rho^* > 0$ such that (54) has no positive solutions for any $\rho \in [0, \rho^*)$ and at least one positive solution for $\rho > \rho^*$; and (2) $A_1 < 0$, then (54) has no positive roots for small ρ, as ρ increases positive root appears, as ρ continues to increase, positive root disappears, and for all ρ big enough there are always positive roots.

Now from (51), solving for $\sin(\tau\omega)$ and $\cos(\tau\omega)$ we have

$$\begin{aligned}
\sin(\tau\omega) &= \ell_1(\omega) := -\frac{-A_1B_{21}\omega + A_2B_1\omega + B_1B_{22}\omega\cos(\rho\omega) - B_1\omega^3 + B_{21}B_{22}\sin(\rho\omega)}{B_1^2\omega^2 + B_{21}^2}, \\
\cos(\tau\omega) &= \ell_2(\omega) := -\frac{A_1B_1\omega^2 + A_2B_{21} - B_1B_{22}\omega\sin(\rho\omega) + B_{21}B_{22}\cos(\rho\omega) - B_{21}\omega^2}{B_1^2\omega^2 + B_{21}^2}.
\end{aligned}$$

Let $\bar{\rho} \geq 0$ be such that (54) has positive solution(s). Without loss of generality, suppose that equation (54) has n positives solutions $\omega_1 < \omega_2 < \cdots < \omega_n$. For each $j = 1, 2, \cdots, n$, define

$$\tau_j = \begin{cases} \frac{1}{\omega_j}\arccos \ell_2(\omega_j) & \text{if } \ell_1(\omega_j) \geq 0, \\ \frac{1}{\omega_j}(2\pi - \arccos \ell_2(\omega_j)) & \text{if } \ell_1(\omega_j) < 0 \end{cases}$$

and let

$$\tau^+ = \min\{\tau_j : j = 1, 2, \cdots, n\} \geq 0. \tag{55}$$

Let $\lambda(\tau, \bar{\rho}) = \sigma(\tau, \bar{\rho}) + i\omega(\tau, \bar{\rho})$ to be the solution of (23) such that $\sigma(\tau^+, \bar{\rho}) = 0$ and $\omega(\tau^+, \bar{\rho}) = \omega_k$, respectively. Differentiating both sides of (23) with respect to τ yields

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{(2\lambda + A_1)e^{\lambda\tau} - B_{22}\bar{\rho}e^{\lambda(\tau - \bar{\rho})} - B_{21}\tau - B_1(\lambda\tau - 1)}{\lambda(B_1\lambda + B_{21})}.$$

Denote

$$\sigma'(\tau^+, \bar{\rho}) = \operatorname{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\Bigg|_{\tau = \tau^+}. \tag{56}$$

We have the following results.

Theorem 3.7. *Assume that* (H_1) *and* (H_2) *hold. Let* b_0 *be defined in (52) and* ρ_0^+ *be defined in (53). Also let* $\tau^+ > 0$ *and* $\sigma'(\tau^+, \bar{\rho})$ *be defined by (55) and (56), respectively.*

(i) Let $B_{22} > 0$.

(a) If $F''(0) < 0$, *then* P_2 *is stable for all* $\rho \in [0, \bar{\rho}]$ *and* $\tau \in [0, \tau^+)$; *If* $\sigma'(\tau^+, \bar{\rho}) > 0$, *then model (19) undergoes a Fold-Hopf bifurcation at* P_2 *when* $\rho = \bar{\rho}$ *and* τ *passes through* τ^+;

(b) If $F''(0) > 0$,

(1) when $F''(0) > \frac{A_1^2}{A_2|A_2|}$, *then there exists* $\rho^* > 0$ *such that* P_2 *is stable for all* $\rho \in [0, \bar{\rho})$ *and* $\tau \geq 0$; *For any* $\rho \geq \rho^*$, P_2 *is stable for all* $\rho \in [0, \bar{\rho}]$ *and* $\tau \in [0, \tau^+)$; *If* $\sigma'(\tau^+, \rho) > 0$, *model (19) undergoes a Fold-Hopf bifurcation at* P_2 *when* $\rho = \bar{\rho}$ *and* τ *passes through* τ^+;

(2) when $F''(0) < \frac{A_1^2}{A_2|A_2|}$ *and* $A_1 \geq 0$, *then for any* $\bar{\rho} > 0$, P_2 *is stable for all* $\rho \in [0, \bar{\rho}]$ *and* $\tau \in [0, \tau^+)$; *If* $\sigma'(\tau^+, \bar{\rho}) > 0$, *model (19) undergoes a Fold-Hopf bifurcation at* P_2 *when* $\rho = \bar{\rho}$ *and* τ *passes through* τ^+; *If* $A_1 < 0$, *then there exist* $0 < \rho^* < \rho^{**}$ *such that* P_2 *is stable for all* $\rho \in (\rho^*, \rho^{**})$ *and* $\tau \geq 0$. *For any* $\rho \in (0, \rho^*]$ *and* $\rho \geq \rho^{**}$, P_2 *is stable for all* $\rho \in [0, \bar{\rho}]$ *and* $\tau \in [0, \tau^+)$; *If* $\sigma'(\tau^+, \rho) > 0$, *model (19) undergoes a Fold-Hopf bifurcation at* E *when* $\rho = \bar{\rho}$ *and* τ *passes through* τ^+.

(ii) Let $B_{22} < 0$.

(a) If $F''(0) < 0$, *then* P_2 *is stable for all* $\rho \geq 0$ *and* $\tau \geq 0$;

(b) If $F''(0) > 0$,

(1) when $F''(0) > \frac{A_1^2}{A_2|A_2|}$ *and* $b_0 < 0$, *then for any* $\bar{\rho} < \min\{\rho^*, \rho_0^+\}$, P_2 *is stable for all* $\rho \in [0, \bar{\rho}]$ *and* $\tau \in [0, \tau^+)$; *If* $\sigma'(\tau^+, \bar{\rho}) > 0$, *model (19) undergoes a Fold-Hopf bifurcation at* P_2 *when* $\rho = \bar{\rho}$ *and* τ *passes through* τ^+;

(2) when $F''(0) < \frac{A_1^2}{A_2|A_2|}$ *and* $b_0 < 0$, *if* $A_1 > 0$, *then* P_2 *is stable for all* $\rho \in [0, \bar{\rho}]$ *and* $\tau \geq 0$.

In order to derive the normal form of Fold-Hopf bifurcation in model (19) under the above assumptions, let

$$f_1(z, u, v) = a_{11} z + a_{12} u + a_{13} v + \sum_{i+j+k=2,3} a_{ijk}^{(1)} z^i u^j v^k + \mathcal{O}(|w|^4),$$
$$f_2(z, u, v) = a_{21} z + a_{22} u + a_{23} v + \sum_{i+j+k=2,3} a_{ijk}^{(2)} z^i u^j v^k + \mathcal{O}(|w|^4).$$

Let $X = (u, v)^T$. Then the linearized system (22) at the equilibrium P_2 can be written as

$$X'(t) = \mathbb{A}X(t) + \mathbb{B}_1 X(t-\tau) + \mathbb{B}_2 X(t-\rho) + F(X(t-\tau), X(t-\rho), X(t)), \tag{57}$$

where

$$\mathbb{A} = \begin{pmatrix} a_{12} & a_{13} \\ a_{22} & a_{23} \end{pmatrix}, \mathbb{B}_1 = \begin{pmatrix} a_{11} & 0 \\ 0 & 0 \end{pmatrix}, \mathbb{B}_2 = \begin{pmatrix} 0 & 0 \\ a_{21} & 0 \end{pmatrix},$$

$$F(X(t-\tau), X(t-\rho), X(t)) = \sum_{i+j+k=2,3} \begin{pmatrix} a_{ijk}^{(1)} u^i(t-\tau) u^j(t) v(t)^k \\ a_{ijk}^{(2)} u^i(t-\rho) u^j(t) v(t)^k \end{pmatrix} + \mathcal{O}(|X|^4).$$

Theorem 3.7 implies that if (H_1), (H_2) and certain conditions hold, then system (22) undergoes a Fold-Hopf bifurcation at P_2 as τ passes through τ^+ when $\rho = \bar{\rho}$. From (H_1), we have

$$a_{11} = a_{11}^* \equiv \frac{a_{13}(a_{22} - a_{21}) - a_{12}a_{23}}{a_{23}}$$

provided $a_{23} \neq 0$ (If $a_{23} = 0$, one can assume $a_{21} = a_{22}$ provided $a_{13} \neq 0$). Now we use a_{11} and τ as bifurcation parameters to study Fold-Hopf bifurcation of (19). Let

$$a_{11} = a_{11}^* + \mu_1, \quad \tau = \tau^+ + \mu_2, \quad \mathbb{B}_{\mu_1} = \begin{pmatrix} a_{11}^*+\mu_1 & 0 \\ 0 & 0 \end{pmatrix}.$$

For simplicity, we still use a_{11} and τ to denote a_{11}^* and τ^+, respectively. Without loss of generality, assume that $\tau > \bar{\rho}$ and $\mu_2 < \tau^+ - \bar{\rho}$ since the case $\tau < \bar{\rho}$ can be treated similarly. Now $\mu = (\mu_1, \mu_2)$ is the bifurcation parameter of the following system

$$X'(t) = \mathbb{A}X(t) + \mathbb{B}_{\mu_1}X(t-\tau-\mu_2) + \mathbb{B}_2X(t-\rho) + F(X(t-\tau-\mu_2), X(t-\rho), X(t)), \quad (58)$$

where $\mathbb{B}_{\mu_1} = \begin{pmatrix} a_{11}+\mu_1 & 0 \\ 0 & 0 \end{pmatrix}$. System (58) can be written as

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

where

$$\begin{aligned} L(\mu)\varphi &= \int_{-\tau}^{0} d\eta(\theta,\mu)\varphi(\theta), \ \forall \varphi \in \mathcal{C} = C([-\tau,0), \mathbb{C}^2), \\ \eta(\theta,\nu) &= \mathbb{A}\delta(\theta) + \mathbb{B}_{\mu_1}\delta(\tau+\mu_2) + \mathbb{B}_2\delta(\rho), \\ F(X_t) &= F(X(t-\tau), X(t-\rho), X(t)). \end{aligned}$$

The Taylor expansion of F takes the form

$$F(\varphi) = \frac{1}{2!}F_2(\varphi) + \frac{1}{3!}F_3(\varphi) + \mathcal{O}(\|\varphi\|^4),$$

where

$$\begin{aligned} \frac{1}{2!}F_2(\varphi) &= \sum_{i+j+k=2} \begin{pmatrix} a_{ijk}^{(1)} x^i(t-\tau)x^j(t)y^k(t) \\ a_{ijk}^{(2)} x^i(t-\rho)x^j(t)y^k(t) \end{pmatrix}, \\ \frac{1}{3!}F_3(\varphi) &= \sum_{i+j+k=3} \begin{pmatrix} a_{ijk}^{(1)} x^i(t-\tau)x^j(t)y^k(t) \\ a_{ijk}^{(2)} x^i(t-\rho)x^j(t)y^k(t) \end{pmatrix}. \end{aligned}$$

Take the enlarged space of $\mathcal{C}$

$$BC = \{\varphi : [-\tau, 0] \to \mathbb{C}^2 : \ \varphi \text{ is continuous on } [-\tau,0), \ \exists \lim_{\theta\to 0^-} \varphi(\theta) \in \mathbb{C}^2\}.$$

Then the elements of BC can be expressed as $\psi = \varphi + X_0\nu$, $\varphi \in \mathcal{C}, \nu \in \mathbb{C}^2$ and

$$X_0(\theta) = \begin{cases} 0, & -\tau \leq \theta < 0, \\ I, & \theta = 0, \end{cases}$$

where I is the identity matrix in $\mathcal{C}$ and the norm of BC is $|\varphi + X_0\nu| = |\varphi|_\infty + |\nu|$. Let $\mathcal{C}^1 = C^1([-\tau,0), \mathbb{C}^2)$. Then the infinitesimal generator $\mathcal{A}_\mu : \mathcal{C}^1 \to BC$ associated with L is given by

$$\mathcal{A}_\mu\varphi = \dot{\varphi} + X_0[L(\mu)\varphi - \dot{\varphi}(0)] = \begin{cases} \dot{\varphi}, & \text{if } -\tau \leq \theta < 0, \\ \int_{-\tau}^{0} d\eta(t,\mu)\varphi(t), & \text{if } \theta = 0, \end{cases}$$

and its adjoint is given by

$$\mathcal{A}_\mu^*\psi = \begin{cases} -\dot{\psi}, & \text{if } 0 < s \le \tau, \\ \int_0^\tau \psi(-t)d\eta(t,\mu), & \text{if } s = 0, \end{cases}$$

for $\forall \psi \in \mathcal{C}^{1*}$, where $\mathcal{C}^{1*} = C^1((0,\tau],\mathbb{C}^{2*})$. Let $\mathcal{C}' = C((0,\tau],\mathbb{C}^{2*})$ and define a bilinear inner product between $\mathcal{C}$ and $\mathcal{C}'$ by

$$\langle \psi, \varphi\rangle = \psi(0)\varphi(0) + \int_{-\tau}^0 \psi(\xi+\tau)\mathbb{B}_1\varphi(\xi)d\xi + \int_{-\rho}^0 \psi(\xi+\rho)\mathbb{B}_2\varphi(\xi)d\xi.$$

We know that $\pm i\omega$ and 0 are eigenvalues of $\mathcal{A}_0$ and $\mathcal{A}_0^*$. Now we compute eigenvectors of $\mathcal{A}_0$ associated with $i\omega$ and 0, and eigenvectors of $\mathcal{A}_0^*$ associated with $-i\omega$ and 0, respectively. Let $\varphi_1(\theta) = (\sigma,1)^T e^{i\omega\theta}$, $\varphi_2(s) = (\alpha,1)^T$ be eigenvectors of $\mathcal{A}_0$ associated with $i\omega$ and 0, respectively. Then $\mathcal{A}_0\varphi_1(\theta) = i\omega\varphi_1(\theta)$ and $\mathcal{A}_0\varphi_2 = 0$. It follows from the definition of $\mathcal{A}_0$ that

$$(i\omega I - \mathbb{A} - \mathbb{B}_1 e^{-i\tau\omega} - \mathbb{B}_2 e^{-i\rho\omega})q_1(0) = 0, (\mathbb{A} + \mathbb{B}_1 + \mathbb{B}_2)q_2 = 0,$$

from which we obtain $\sigma = -\frac{e^{i\rho\omega}(-a_{23}+i\omega)}{a_{21}+e^{i\rho\omega}a_{22}}$ and $\alpha = \frac{a_{13}}{a_{11}+a_{12}}$.

Similarly, we can find eigenvectors $\psi_1(s)$ and $\psi_2(s)$ of $\mathcal{A}_0^*$ associated with $-i\omega$ and 0, respectively, as follows

$$\psi_1(s) = \frac{1}{D_1}(\gamma,1)e^{i\omega s}, \quad \psi_2(s) = \frac{1}{D_2}(\beta,1),$$

where $\beta = -\frac{a_{23}}{a_{13}}, \gamma = -\frac{a_{23}+\omega i}{a_{13}}$ with D_1 and D_2 being constants to be determined such that $\langle \bar{\psi}_1(s), q_1(\theta)\rangle = 1$. In fact,

$$D_1 = \gamma\left(\bar{\sigma} + a_{11}\sigma\tau e^{i\tau\omega}\right) + a_{21}\bar{\rho}\bar{\sigma}e^{i\rho\omega} + 1, \; D_2 = \alpha a_{11}\beta\tau + \alpha a_{21}\rho + \alpha\beta + 1.$$

Let $\mathbb{P}$ be spanned by $q_1, \bar{q}_1, q_2$ and $\mathbb{P}^*$ by $p_1, \bar{p}_1, p_2$. Then $\mathcal{C}$ can be decomposed as

$$\mathcal{C} = \mathbb{P} \oplus \mathbb{Q} \text{ where } \mathbb{Q} = \{\varphi \in \mathcal{C} : \langle\psi,\varphi\rangle = 0, \forall\psi \in \mathbb{P}^*\}.$$

Define $\mathbb{Q}^1 = \mathbb{Q} \cap \mathcal{C}^1$. Let $\Phi(\theta) = (\varphi_1(\theta), \bar{\varphi}_1(\theta), \varphi_2(s))$ and $\Psi(s) = (\bar{\psi}_1(s), \psi_1(s), \psi_2(s))^T$. Then

$$\dot{\Phi} = \Phi J, \dot{\Psi} = -J\Psi, \langle\Psi,\Phi\rangle = I, \text{ where } J = \mathrm{diag}(i\tau\omega, -i\tau\omega, 0).$$

We can verify that the pairing $\langle\Psi,\Phi\rangle = I$ is equivalent to the following identities

$$\begin{aligned}
&\bar{\psi}_1(0)\phi_1(0) + \textstyle\int_{-\tau}^0 \bar{\psi}_1(t+\tau)\mathbb{B}_1\phi_1(t)dt + \int_{-\rho}^0 \bar{\psi}_1(t+\rho)\mathbb{B}_2\phi_1(t)dt = 1,\\
&\psi_2(0)\phi_2(0) + \textstyle\int_{-\tau}^0 \psi_2(t+\tau)\mathbb{B}_1\phi_2(t)dt + \int_{-\rho}^0 \psi_2(t+\rho)\mathbb{B}_2\phi_2(t)dt = 1,\\
&\bar{\psi}_1(0)\bar{\phi}_1(0) + \textstyle\int_{-\tau}^0 \bar{\psi}_1(t+\tau)\mathbb{B}_1\bar{\phi}_1(t)dt + \int_{-\rho}^0 \bar{\psi}_1(t+\rho)\mathbb{B}_2\bar{\phi}_1(t)dt = 0,\\
&\bar{\psi}_1(0)\phi_2(0) + \textstyle\int_{-\tau}^0 \bar{\psi}_1(t+\tau)\mathbb{B}_1\phi_2(t)dt + \int_{-\rho}^0 \bar{\psi}_1(t+\rho)\mathbb{B}_2\phi_2(t)dt = 0,\\
&\psi_2(0)\phi_1(0) + \textstyle\int_{-\tau}^0 \bar{\psi}_2(t+\tau)\mathbb{B}_1\phi_1(t)dt + \int_{-\rho}^0 \psi_2(t+\rho)\mathbb{B}_2\phi_1(t)dt = 0,\\
&\psi_2(0)\bar{\phi}_1(0) + \textstyle\int_{-\tau}^0 \bar{\psi}_2(t+\tau)\mathbb{B}_1\bar{\phi}_1(t)dt + \int_{-\rho}^0 \psi_2(t+\rho)\mathbb{B}_2\bar{\phi}_1(t)dt = 0,
\end{aligned}$$

respectively.

Define the projection $\pi : BC \to \mathbb{P}$ by

$$\pi(\varphi + X_0\mu) = \Phi[(\Psi,\varphi) + \Psi(0)\mu].$$

Write $X = \Phi x + y$, namely

$$u_1(\theta) = \sigma e^{i\omega\theta}x_1 + \bar{\sigma}e^{-i\omega\theta}x_2 + \alpha x_3 + y_1(\theta), \quad u_2(\theta) = e^{i\omega\theta}x_1 + e^{-i\omega\theta}x_2 + x_3 + y_2(\theta).$$

Then (58) can be decomposed as

$$\begin{aligned}\dot{x} &= Jx + \Psi(0)F(\Phi x + y, \mu),\\ \dot{y} &= A_{\mathbb{Q}^1}y + (I-\pi)X_0F(\Phi x + y, \mu),\end{aligned}$$

which can be further rewritten as

$$\begin{aligned}\dot{x} &= Jx + \tfrac{1}{2}f_2^1(x,y,\mu) + \tfrac{1}{3!}f_3^1(x,y,\mu) + \mathcal{O}(|\mu|(|x|^2+|y|^2) + |\mu|^2(|x|+|y|)),\\ \dot{y} &= A_{\mathbb{Q}^1}y + \tfrac{1}{2}f_2^2(x,y,\mu) + \tfrac{1}{3!}f_3^2(x,y,\mu) + \mathcal{O}(|\mu|(|x|^2+|y|^2) + |\mu|^2(|x|+|y|)),\end{aligned} \tag{59}$$

where

$$\begin{aligned}f_2^1(x,y,\mu) &= \Psi(0)[(L(\mu)-L(0))(\Phi x + y) + F_2(\Phi x + y, \mu)],\\ f_2^2(x,y,\mu) &= (I-\pi)X_0[(L(\mu)-L(0))(\Phi x + y) + F_2(\Phi x + y, \mu)],\\ f_j^1(x,y,\mu) &= \Psi(0)F_j(\Phi x + y, \mu),\\ f_j^2(x,y,\mu) &= (I-\pi)X_0F_j(\Phi x + y, \mu), \quad j = 3, 4, \cdots.\end{aligned}$$

By the normal form theory of Faria and Magalhães [49, 50], on the center manifold system (59) can be transformed into the following normal form

$$\dot{x} = Jx + \frac{1}{2}g_2^1(x,0,\mu) + \frac{1}{3!}g_3^1(x,0,\mu) + \mathcal{O}(|\mu||x|^2 + |\mu|^2|x|), \tag{60}$$

where $g_j^1(x,0,\mu)$ are homogeneous polynomials of degree j in (x,μ). Let Y be a normed space and $j, p \in \mathbb{N}$. Let

$$V_j^p(Y) = \left\{ \sum_{|q|=j} c_q x^q : q \in \mathbb{N}_0^q, c_q \in Y \right\}$$

with norm $|\sum_{|q|=j} c_q x^q| = \sum_{|q|=j} |c_q|_Y$. Define M_j to be the operator in $V_j^5(\mathbb{C}^2 \times \ker \pi)$ with the range in the same space by

$$M_j(p,h) = (M_j^1 p, M_j^2 h),$$

where

$$\begin{aligned}M_j^1 p &= [J, p(\cdot,\mu)](x) = D_x p(x,\mu)Jx - Jp(x,\mu) = i\omega \begin{pmatrix} x_1\frac{\partial p_1}{\partial x_1} - x_2\frac{\partial p_1}{\partial x_2} - p_1 \\ x_1\frac{\partial p_2}{\partial x_1} - x_2\frac{\partial p_2}{\partial x_2} + p_2 \\ x_1\frac{\partial p_3}{\partial x_1} - x_2\frac{\partial p_3}{\partial x_2} \end{pmatrix},\\ M_j^2 h &= M_j^2 h(x,\mu) = D_x h(x,\mu) - A_{Q^1}h(x,\mu),\end{aligned}$$

with $p(x,\mu) \in V_j^5(\mathbb{C}), h(x,\mu) \in V_j^5(\ker \pi)$. One can check that

$$V_j^5(\mathbb{C}^3) = \mathrm{Im}(M_j^1) \oplus \mathrm{Ker}(M_j^1)$$

and

$$\mathrm{Ker}(M_j^1) = \{\mu^p x^q e_k : (q, \bar{\lambda}) = \lambda_k, k = 1,2,3, q \in \mathbb{N}_0^3, |(p,q)| = j\},$$

where $e_1 = (1,0,0)^T, e_2 = (0,1,0)^T, e_3 = (0,0,1)^T$ are the base of $\mathbb{C}^3$. By the above decompositions, $g_2^1(x,0,\mu)$ and $g_3^1(x,0,\mu)$ can be expressed as

$$\begin{aligned}g_2^1(x,0,\mu) &= \mathrm{Proj}_{\ker(M_2^1)} f_2^1(x,0,\mu) = \mathrm{Proj}_{S_1} f_2^1(x,0,\mu) + \mathcal{O}(|\mu|^2),\\ g_3^1(x,0,\mu) &= \mathrm{Proj}_{\ker(M_3^1)} \tilde{f}_3^1(x,0,\mu) = \mathrm{Proj}_{S_2} \tilde{f}_3^1(x,0,0) + \mathcal{O}(|\mu|^2|x|),\end{aligned}$$

where

$$\tilde{f}_3^1(x,0,\mu) = f_3^1(x,0,\mu) + \frac{3}{2}[(D_x f_2^1)(x,0,\mu)U_2^1(x,\mu) + (D_y f_2^1)(x,0,\mu)U_2^2(x,\mu)].$$

Here U_2^1 and U_2^2 are determined by

$$U_2^1(x,\mu) = (M_2^1)^{-1}\mathrm{Proj}_{\mathrm{Im}(M_2^1)} f_2^1(x,0,\mu) = (M_2^1)^{-1} f_2^1(x,0,\mu),$$
$$(M_2^2 U_2^2)(x,\mu) = f_2^2(x,0,\mu),$$

and S_1 and S_2 are spanned, respectively, by (see [122] for details)

$$\mu_i x_1 e_1,\ \ x_1x_3e_1,\ \ \mu_i x_2 e_2,\ \ x_2x_3e_2,\ \ x_1x_2e_3,\ \ \mu_i x_3 e_3,\ \ x_3^2 e_3,\ \ i=1,2,$$

and

$$x_1^2x_2e_1,\ \ x_1x_3^2e_1,\ \ x_1x_2^2e_2,\ \ x_2x_3^2e_2,\ \ x_1x_2x_3e_3,\ \ x_3^3e_3.$$

For simplicity, write

$$\begin{aligned}\frac{1}{2!}F_2(\Phi x+y,\mu) = &\sum_{i+j+k=2}\begin{pmatrix}A_{ijk}^{(1)}\\ A_{ijk}^{(2)}\end{pmatrix}x_1^ix_2^jx_3^k\\ &+\sum_{j=1}^{3}\sum_{k=1}^{2}\left[\begin{pmatrix}B_{jk}^{(1)}\\ B_{jk}^{(2)}\end{pmatrix}x_jy_k(0)+\begin{pmatrix}C_{jk}^{(1)}\\ 0\end{pmatrix}x_jy_k(-\tau)+\begin{pmatrix}0\\ C_{jk}^{(2)}\end{pmatrix}x_jy_k(-\rho)\right]\\ &+\sum_{j=1}^{2}\left[\begin{pmatrix}D_{j}^{(1)}\\ D_{j}^{(2)}\end{pmatrix}y_j^2(0)+\begin{pmatrix}E_{j}^{(1)}\\ 0\end{pmatrix}y_j^2(-\tau)+\begin{pmatrix}0\\ E_{j}^{(2)}\end{pmatrix}y_j^2(-\rho)\right]\\ &+\sum_{j=1}^{2}\sum_{k=1}^{2}\left[\begin{pmatrix}F_{jk}^{(1)}\\ 0\end{pmatrix}y_j(0)y_k(-\tau)+\begin{pmatrix}0\\ F_{jk}^{(2)}\end{pmatrix}y_j(0)y_k(-\rho)\right]\end{aligned}$$

and

$$\frac{1}{3!}F_3(\Phi x,0) = \sum_{i+j+k=3}\begin{pmatrix}A_{ijk}^{(1)}\\ A_{ijk}^{(2)}\end{pmatrix}x_1^ix_2^jx_3^k.$$

Let

$$\Psi(0) = \begin{pmatrix}\bar\psi_{11} & \bar\psi_{12}\\ \psi_{11} & \psi_{12}\\ \psi_{21} & \psi_{22}\end{pmatrix}.$$

Then we have

$$\begin{aligned}\frac{1}{2}g_2^1(x,0,\mu) &= \frac{1}{2}\mathrm{Proj}_{S_1} f_2^1(x,0,\mu)\\ &= \frac{1}{2}\mathrm{Proj}_{S_1}\Psi(0)F_2(\Phi x,\mu)+\text{h.o.t.}\\ &= \begin{pmatrix}\theta_1x_1+\alpha_{101}^{(1)}x_1x_3\\ \bar\theta_1x_2+\bar\alpha_{101}^{(1)}x_2x_3\\ \theta_2x_3+\alpha_{110}^{(2)}x_1x_2+\alpha_{002}^{(2)}x_3^2\end{pmatrix}+\text{h.o.t.}\end{aligned}$$

where

$$\theta_1 = \tfrac{e^{-i\tau\omega}\sigma\bar\gamma}{\bar D_1}\mu_1 - \tfrac{ie^{i\tau\omega}\sigma\omega\bar\gamma a_{11}}{\bar D_1}\mu_2,\ \ \theta_2=\tfrac{\alpha\beta\mu_1}{D_2},$$
$$\alpha_{101}^{(1)} = \bar\psi_{11}A_{101}^{(1)}+\bar\psi_{12}A_{101}^{(2)},\ \ \alpha_{110}^{(2)} = \psi_{21}A_{110}^{(1)}+\psi_{22}A_{110}^{(2)},$$
$$\alpha_{002}^{(2)} = \psi_{21}A_{002}^{(1)}+\psi_{22}A_{002}^{(2)}.$$

Next we compute $g_3^1(x,0,\mu)$. Note that

$$\frac{1}{6}g_3^1(x,0,\mu) = \frac{1}{6}\mathrm{Proj}_{\ker(M_2^1)}\tilde f_3^1(x,0,\mu)$$

$$\begin{aligned} &= \frac{1}{6}\mathrm{Proj}_{S_2}\tilde{f}_3^1(x,0,0) + \mathcal{O}(|x||\mu|^2 + |x|^2|\mu|),\\ &= \frac{1}{6}\mathrm{Proj}_{S_2} f_3^1(x,0,0) + \frac{1}{4}\mathrm{Proj}_{S_2}[(D_x f_2^1)(x,0,0)U_2^1(x,0)\\ &\quad +(D_y f_2^1)(x,0,0)U_2^2(x,0)] + \mathcal{O}(|\mu|^2|x| + |\mu||x|^2). \end{aligned}$$

First we have

$$\begin{aligned} \frac{1}{3!}\mathrm{Proj}_{S_2} f_3^1(x,0,0) &= \frac{1}{3!}\mathrm{Proj}_{S_2}\Psi(0)F_3(\Phi x,0) + \text{h.o.t.}\\ &= \begin{pmatrix} \alpha_{210}^{(1)}x_1^2x_2 + \alpha_{102}^{(1)}x_1x_3^2\\ \bar{\alpha}_{210}^{(1)}x_1x_2^2 + \bar{\alpha}_{102}^{(1)}x_2x_3^2\\ \alpha_{111}^{(2)}x_1x_2x_3 + \alpha_{003}^{(2)}x_3^3 \end{pmatrix} + \text{h.o.t.} \end{aligned}$$

where

$$\begin{aligned} &\alpha_{210}^{(1)} = \bar{\psi}_{11}F_{210}^{(1)} + \bar{\psi}_{12}F_{210}^{(2)}, \quad \alpha_{102}^{(1)} = \bar{\psi}_{11}F_{102}^{(1)} + \bar{\psi}_{12}F_{102}^{(2)},\\ &\alpha_{111}^{(2)} = \psi_{21}F_{111}^{(1)} + \psi_{22}F_{111}^{(2)}, \quad \alpha_{003}^{(2)} = \psi_{21}F_{003}^{(1)} + \psi_{22}F_{003}^{(2)}. \end{aligned}$$

Since $f_2(x,0,0) = \Psi(0)F_2(\Phi x,0)$, we have

$$\begin{aligned} &U_2^1(x,0) = U_2^1(x,\mu)|_{\mu=0} = (M_2^1)^{-1}\mathrm{Proj}_{\mathrm{Im}(M_2^1)} f_2^1(x,0,0)\\ &\quad = 2(M_2^1)^{-1}\mathrm{Proj}_{\mathrm{Im}(M_2^1)}\sum_{j=1}^{2}\Bigg[\begin{pmatrix}\bar{\psi}_{1j}A_{200}^{(j)}\\ \psi_{1j}A_{200}^{(j)}\\ \psi_{2j}A_{200}^{(j)}\end{pmatrix}x_1^2 + \begin{pmatrix}\bar{\psi}_{1j}A_{020}^{(j)}\\ \psi_{1j}A_{020}^{(j)}\\ \psi_{2j}A_{020}^{(j)}\end{pmatrix}x_2^2 + 2\begin{pmatrix}\bar{\psi}_{1j}A_{002}^{(j)}\\ \psi_{1j}A_{002}^{(j)}\\ \psi_{2j}A_{002}^{(j)}\end{pmatrix}x_3^2\\ &\qquad + \begin{pmatrix}\bar{\psi}_{1j}A_{110}^{(j)}\\ \psi_{1j}A_{110}^{(j)}\\ \psi_{2j}A_{110}^{(j)}\end{pmatrix}x_1x_2 + \begin{pmatrix}\bar{\psi}_{1j}A_{101}^{(j)}\\ \psi_{1j}A_{101}^{(j)}\\ \psi_{2j}A_{101}^{(j)}\end{pmatrix}x_1x_3 + \begin{pmatrix}\bar{\psi}_{1j}A_{011}^{(j)}\\ \psi_{1j}A_{011}^{(j)}\\ \psi_{2j}A_{011}^{(j)}\end{pmatrix}x_2x_3\Bigg]\\ &\quad = \frac{1}{3i\omega}\sum_{j=1}^{2}\Bigg[\begin{pmatrix}6\bar{\psi}_{1j}A_{200}^{(j)}\\ 2\psi_{1j}A_{200}^{(j)}\\ 3\psi_{2j}A_{200}^{(j)}\end{pmatrix}x_1^2 + \begin{pmatrix}-2\bar{\psi}_{1j}A_{020}^{(j)}\\ -6\psi_{1j}A_{020}^{(j)}\\ -3\psi_{2j}A_{020}^{(j)}\end{pmatrix}x_2^2 + \begin{pmatrix}-6\bar{\psi}_{1j}A_{002}^{(j)}\\ 6\psi_{1j}A_{002}^{(j)}\\ 0\end{pmatrix}x_3^2\\ &\qquad + \begin{pmatrix}-6\bar{\psi}_{1j}A_{110}^{(j)}\\ 6\psi_{1j}A_{110}^{(j)}\\ 0\end{pmatrix}x_1x_2 + \begin{pmatrix}0\\ 3\psi_{1j}A_{101}^{(j)}\\ 6\psi_{2j}A_{101}^{(j)}\end{pmatrix}x_1x_3 + \begin{pmatrix}-3\bar{\psi}_{1j}A_{011}^{(j)}\\ 0\\ -6\psi_{2j}A_{011}^{(j)}\end{pmatrix}x_2x_3\Bigg]. \end{aligned}$$

We also have

$$\frac{1}{4}\mathrm{Proj}_{S_2}[(D_x f_2^1(x,0,0))U_2^1(x,0)] = \begin{pmatrix} \beta_{210}^{(1)}x_1^2x_2 + \beta_{102}^{(1)}x_1x_3^2\\ \bar{\beta}_{210}^{(1)}x_1x_2^2 + \bar{\beta}_{012}^{(1)}x_2x_3^2\\ \beta_{111}^{(2)}x_1x_2x_3 + \beta_{003}^{(2)}x_3^3 \end{pmatrix} + \text{h.o.t.}$$

where

$$\begin{aligned} \beta_{210}^{(1)} = &-\frac{i}{12\omega}[12(\psi_{11}A_{110}^{(1)} + \psi_{12}A_{110}^{(2)})(\bar{\psi}_{11}A_{110}^{(1)} + \bar{\psi}_{12}A_{110}^{(2)}) + 12(\bar{\psi}_{11}A_{200}^{(1)}\\ &+ \bar{\psi}_{12}A_{200}^{(2)}) \times (\bar{\psi}_{11}A_{110}^{(1)} + \bar{\psi}_{12}A_{110}^{(2)}) - 12(2\bar{\psi}_{11}A_{200}^{(1)}\\ &+ 2\bar{\psi}_{12}A_{200}^{(2)})(\bar{\psi}_{11}A_{110}^{(1)} + \bar{\psi}_{12}A_{110}^{(2)}) + 4(\psi_{11}A_{200}^{(1)} + \psi_{12}A_{200}^{(2)})\\ &(2\bar{\psi}_{11}A_{020}^{(1)} + 2\bar{\psi}_{12}A_{020}^{(2)}) + 6(\psi_{21}A_{200}^{(1)} + \psi_{22}A_{200}^{(2)})(\bar{\psi}_{11}A_{011}^{(1)} + \bar{\psi}_{12}A_{011}^{(2)})],\\ \beta_{102}^{(1)} = &-\frac{i}{12\omega}[6(\psi_{11}A_{101}^{(1)} + \psi_{12}A_{101}^{(2)})(\bar{\psi}_{11}A_{011}^{(1)} + \bar{\psi}_{12}A_{011}^{(2)}) + 12(\psi_{21}A_{101}^{(1)} + \psi_{22}A_{101}^{(2)})\\ &\times (2\bar{\psi}_{11}A_{002}^{(1)} + 2\bar{\psi}_{12}A_{002}^{(2)}) + 12(\psi_{11}A_{002}^{(1)} + \psi_{12}A_{002}^{(2)})(\bar{\psi}_{11}A_{110}^{(1)} + \bar{\psi}_{12}A_{110}^{(2)})\\ &- 12(\bar{\psi}_{11}A_{002}^{(1)} + \bar{\psi}_{12}A_{002}^{(2)})(2\bar{\psi}_{11}A_{200}^{(1)} + 2\bar{\psi}_{12}A_{200}^{(2)})], \end{aligned}$$

$$\beta_{111}^{(2)} = -\frac{i}{6\omega}[-6(\psi_{21}A_{101}^{(1)} + \psi_{22}A_{101}^{(2)})(\bar{\psi}_{11}A_{110}^{(1)} + \bar{\psi}_{12}A_{110}^{(2)}) - 6(\psi_{21}A_{200}^{(1)} + \psi_{22}A_{200}^{(2)}) \times (\bar{\psi}_{11}A_{011}^{(1)} + \bar{\psi}_{12}A_{011}^{(2)}) + 6(\psi_{21}A_{020}^{(1)} + \psi_{22}A_{020}^{(2)})(\psi_{11}A_{101}^{(1)} + \psi_{12}A_{101}^{(2)}) + 6(\psi_{21}A_{011}^{(1)} + \psi_{22}A_{011}^{(2)})(\psi_{11}A_{110}^{(1)} + \psi_{12}A_{110}^{(2)})],$$

$$\beta_{003}^{(2)} = -\frac{i}{36\omega}[36(\psi_{11}A_{002}^{(1)} + \psi_{12}A_{002}^{(2)})(\psi_{21}A_{011}^{(1)} + \psi_{22}A_{011}^{(2)}) - 36(\psi_{21}A_{101}^{(1)} + \psi_{22}A_{101}^{(2)})(\bar{\psi}_{11}A_{002}^{(1)} + \bar{\psi}_{12}A_{002}^{(2)})].$$

Finally we compute the last term of the third order. This is the most difficult part since its computation involves solving linear systems with singular coefficient matrices. Define $h = h(x)(\theta) = U_2^2(x, 0)$ and write

$$h(\theta) = \begin{pmatrix} h^{(1)}(\theta) \\ h^{(2)}(\theta) \end{pmatrix} = h_{200}x_1^2 + h_{020}x_2^2 + h_{002}x_3^2 + h_{110}x_1x_2 + h_{101}x_1x_3 + h_{011}x_2x_3,$$

where $h_{200}, h_{020}, h_{002}, h_{110}, h_{101}, h_{011} \in Q^1$. The coefficients of h are determined by $(M_2^2 h)(x) = f_2^2(x, 0, 0)$, which is equivalent to

$$D_x hJx - A_{Q^1}(h) = (I - \pi)X_0 F_2(\Phi x, 0).$$

Applying the definitions of A_{Q^1} and π, we obtain

$$\dot{h} - D_x hJx = \Phi(\theta)\Psi(0)F_2(\Phi x, 0), \quad \dot{h}(0) - Lh = F_2(\Phi x, 0),$$

where $\dot{h}$ denotes the derivative of $h(\theta)$ in θ. Comparing the coefficients of x_1^2, x_2^2, x_3^2, x_1x_2, x_1x_3, x_2x_3, we have that $\bar{h}_{020} = h_{200}, \bar{h}_{011} = h_{101}$ and that $h_{200}, h_{101}, h_{110}, h_{002}$ satisfy the following differential equations, respectively,

$$\begin{cases} \dot{h}_{200} - 2i\omega h_{200} = 2\Phi(\theta)\Psi(0)A_{200}, \\ \dot{h}_{200}(0) - L(h_{200}) = 2A_{200}, \end{cases} \tag{61}$$

$$\begin{cases} \dot{h}_{101} - i\omega h_{101} = 2\Phi(\theta)\Psi(0)A_{101}, \\ \dot{h}_{101}(0) - L(h_{101}) = 2A_{101}, \end{cases} \tag{62}$$

$$\begin{cases} \dot{h}_{110} = 2\Phi(\theta)\Psi(0)A_{110}, \\ \dot{h}_{110}(0) - L(h_{110}) = 2A_{110}, \end{cases} \tag{63}$$

$$\begin{cases} \dot{h}_{002} = 2\Phi(\theta)\Psi(0)A_{002}, \\ \dot{h}_{002}(0) - L(h_{002}) = 2A_{002}, \end{cases} \tag{64}$$

where $A_{ijk} = \binom{A_{ijk}^{(1)}}{A_{ijk}^{(2)}}$. Thus, we have

$$\frac{1}{4}\mathrm{Proj}_{S_2} D_y f_2^1|_{y=0,\mu=0} U_2^2 = \begin{pmatrix} \gamma_{210}^{(1)}x_1^2x_2 + \gamma_{102}^{(1)}x_1x_3^2 \\ \bar{\gamma}_{210}^{(1)}x_1x_2^2 + \bar{\gamma}_{102}^{(1)}x_2x_3^2 \\ \gamma_{111}^{(2)}x_1x_2x_3 + \gamma_{003}^{(2)}x_3^3 \end{pmatrix}$$

where

$$\gamma_{210}^{(1)} = \bar{\psi}_{11}(h_{110}^{(1)}(0)B_{11}^{(1)} + h_{200}^{(1)}(0)B_{21}^{(1)} + h_{110}^{(2)}(0)B_{12}^{(1)} + h_{200}^{(2)}(0)B_{22}^{(1)} + C_{11}^{(1)}h_{110}^{(1)}(-\tau) + C_{21}^{(1)}h_{200}^{(1)}(-\tau) + C_{12}^{(1)}h_{110}^{(2)}(-\tau) + C_{22}^{(1)}h_{200}^{(2)}(-\tau) + C_{11}^{(2)}h_{110}^{(1)}(-\rho) + C_{21}^{(2)}h_{200}^{(1)}(-\rho) + C_{12}^{(2)}h_{110}^{(2)}(-\rho) + C_{22}^{(2)}h_{200}^{(2)}(-\rho)) + \bar{\psi}_{12}(h_{110}^{(1)}(0)B_{11}^{(2)} + h_{200}^{(1)}(0)B_{21}^{(2)} + h_{110}^{(2)}(0)B_{12}^{(2)} + h_{200}^{(2)}(0)B_{22}^{(2)}),$$

$$\begin{aligned}\gamma_{102}^{(1)} =&\bar{\psi}_{11}(h_{002}^{(1)}(0)B_{11}^{(1)} + h_{101}^{(1)}(0)B_{31}^{(1)} + h_{002}^{(2)}(0)B_{12}^{(1)} + h_{101}^{(2)}(0)B_{32}^{(1)} + C_{11}^{(1)}h_{002}^{(1)}(-\tau)\\ &+ C_{31}^{(1)}h_{101}^{(1)}(-\tau) + C_{12}^{(1)}h_{002}^{(2)}(-\tau) + C_{32}^{(1)}h_{101}^{(2)}(-\tau) + C_{11}^{(2)}h_{002}^{(1)}(-\rho)\\ &+ C_{31}^{(2)}h_{101}^{(1)}(-\rho) + C_{12}^{(2)}h_{002}^{(2)}(-\rho) + C_{32}^{(2)}h_{101}^{(2)}(-\rho)) + \bar{\psi}_{12}(h_{002}^{(1)}(0)B_{11}^{(2)}\\ &+ h_{101}^{(1)}(0)B_{31}^{(2)} + h_{002}^{(2)}(0)B_{12}^{(2)} + h_{101}^{(2)}(0)B_{32}^{(2)}),\end{aligned}$$

$$\begin{aligned}\gamma_{111}^{(2)} =&\psi_{21}(h_{011}^{(1)}(0)B_{11}^{(1)} + h_{101}^{(1)}(0)B_{21}^{(1)} + h_{110}^{(1)}(0)B_{31}^{(1)} + h_{011}^{(2)}(0)B_{12}^{(1)} + h_{101}^{(2)}(0)B_{22}^{(1)}\\ &+ h_{110}^{(2)}(0)B_{32}^{(1)} + C_{11}^{(1)}h_{011}^{(1)}(-\tau) + C_{21}^{(1)}h_{101}^{(1)}(-\tau) + C_{31}^{(1)}h_{110}^{(1)}(-\tau)\\ &+ C_{12}^{(1)}h_{011}^{(2)}(-\tau) + C_{22}^{(1)}h_{101}^{(2)}(-\tau) + C_{32}^{(1)}h_{110}^{(2)}(-\tau) + h_{101}^{(2)}(0)B_{2,2}^{(2)}\\ &+ C_{11}^{(2)}h_{011}^{(1)}(-\rho) + C_{21}^{(2)}h_{101}^{(1)}(-\rho) + C_{31}^{(2)}h_{110}^{(1)}(-\rho) + C_{12}^{(2)}h_{011}^{(2)}(-\rho)\\ &+ C_{22}^{(2)}h_{2101}(-\rho) + C_{32}^{(2)}h_{110}^{(2)}(-\rho)) + \psi_{22}(h_{011}^{(1)}(0)B_{11}^{(2)}\\ &+ h_{101}^{(1)}(0)B_{21}^{(2)} + h_{110}^{(1)}(0)B_{31}^{(2)} + h_{011}^{(2)}(0)B_{12}^{(2)} + h_{101}^{(2)}(0)B_{22}^{(2)} + h_{110}^{(2)}(0)B_{32}^{(2)}),\\ \gamma_{003}^{(2)} =&\psi_{21}(h_{002}^{(1)}(0)B_{31}^{(1)} + h_{002}^{(2)}(0)B_{32}^{(1)} + C_{31}^{(1)}h_{002}^{(1)}(-\tau) + C_{32}^{(1)}h_{002}^{(2)}(-\tau)\\ &+ C_{31}^{(2)}h_{002}^{(1)}(-\rho) + C_{32}^{(2)}h_{002}^{(2)}(-\rho)) + \psi_{22}(h_{002}^{(1)}(0)B_{31}^{(2)} + h_{002}^{(2)}(0)B_{32}^{(2)}).\end{aligned}$$

To compute h_{ijk}, we recall the following result.

Lemma 3.8 (Kuznetsov [75]). *For a linear system $Mw = v$ where M is a singular $n \times n$ matrix, there is a unique solution for the following bordered system*

$$\begin{pmatrix} M & q \\ p & 0 \end{pmatrix}\begin{pmatrix} w \\ u \end{pmatrix} = \begin{pmatrix} v \\ 0 \end{pmatrix}$$

where p, q satisfy the following conditions

$$Mq = 0,\ pM = 0,\ (p, q) = 1,\ (p, v) = 0$$

where $(\cdot,\cdot)$ is defined by

$$(x, y) = \sum_{j=1}^{n} x_j y_j,\ x = (x_1, \cdots, x_n),\ y = (y_1, \cdots, y_n)^T.$$

Write the unique solution as $w = M^{INV}v$.

Using Lemma 3.8, we can compute the rest of $h_{101}(\theta), h_{110}(\theta)$ and $h_{002}(\theta)$ and obtain that (see Wu and Wang [123])

$$\begin{aligned}h_{200}(\theta) =&2e^{2i\omega\theta}\int_0^\theta e^{-2i\omega t}\Phi(t)\Psi(0)A_{200}dt + c_{200}e^{2i\omega\theta},\\ h_{101}(\theta) =&2e^{i\omega\theta}\int_0^\theta e^{-i\omega t}\Phi(t)\Psi(0)A_{101}dt + c_{101}e^{i\omega\theta},\\ h_{110}(\theta) =&2\int_0^\theta \Phi(t)\Psi(0)A_{110}dt\\ &+ (L(1))^{INV}\left[(\Phi(0)\Psi(0) - I)A_{110} + \mathbb{B}_1\int_{-1}^{0}\Phi(t)\Psi(0)A_{110}dt\right],\end{aligned}$$

$$
\begin{aligned}
h_{002}(\theta) =& 2\int_0^\theta \Phi(t)\Psi(0)A_{002}dt \\
&+ (L(1))^{INV}\left[(\Phi(0)\Psi(0)-I)A_{002} + \mathbb{B}_1\int_{-1}^0 \Phi(t)\Psi(0)A_{002}dt\right],
\end{aligned}
$$

where

$$
\begin{aligned}
c_{200} =& 2(2i\omega I - L(e^{2i\omega\theta}))^{-1}\left[(I-\Phi(0)\Psi(0))A_{200}\right. \\
&+ \mathbb{B}_1\int_{-\tau}^0 e^{-2i\omega(t+\tau)}\Phi(t)\Psi(0)A_{200}dt \\
&\left.+\mathbb{B}_2\int_{-\rho}^0 e^{-2i\omega(t+\rho)}\Phi(t)\Psi(0)A_{200}dt\right], \\
c_{101} =& 2(L(1))^{INV}\left[(\Phi(0)\Psi(0)-I)A_{110}\right. \\
&\left.+\mathbb{B}_1\int_{-\tau}^0 \Phi(t)\Psi(0)A_{110}dt + 2\mathbb{B}_2\int_{-\rho}^0 \Phi(t)\Psi(0)dt\right].
\end{aligned}
$$

Putting these results together, we have

$$
\begin{aligned}
\frac{1}{6}g_3^1(x,0,\mu) =& \begin{pmatrix} (\alpha_{210}^1+\beta_{210}^1+\gamma_{210}^1)x_1^2x_2 + (\alpha_{102}^1+\beta_{102}^1+\gamma_{102}^1)x_1x_3^2 \\ (\bar{\alpha}_{210}^1+\bar{\beta}_{210}^1+\bar{\gamma}_{210}^1)x_1x_2^2 + (\bar{\alpha}_{102}^1+\bar{\beta}_{102}^1+\bar{\gamma}_{102}^1)x_2x_3^2 \\ (\alpha_{111}^2+\beta_{111}^2+\gamma_{111}^2)x_1x_2x_3 + (\alpha_{003}^2+\beta_{003}^2+\gamma_{003}^2)x_3^3 \end{pmatrix} \\
&+ \mathcal{O}(|\mu|^2|x| + |\mu||x|^2).
\end{aligned}
$$

So we can express system (60) as the following truncated normal form

$$
\begin{cases}
\dot{x}_1 = \theta_1 x_1 + \alpha_{101}^1 x_1x_3 + (\alpha_{210}^1+\beta_{210}^1+\gamma_{210}^1)x_1^2x_2 \\
\qquad +(\alpha_{102}^1\beta_{102}^1+\gamma_{102}^1)x_1x_3^2, \\
\dot{x}_2 = \bar{\theta}_1 x_2 + \bar{\alpha}_{101}^1 x_2x_3 + (\bar{\alpha}_{210}^1+\bar{\beta}_{210}^1+\bar{\gamma}_{210}^1)x_1x_2^2 \\
\qquad +(\bar{\alpha}_{102}^1+\bar{\beta}_{102}^1+\bar{\gamma}_{102}^1)x_2x_3^2, \\
\dot{x}_3 = \theta_2 x_3 + \alpha_{110}^2 x_1x_2 + \alpha_{002}^2 x_3^2 + (\alpha_{111}^2+\beta_{111}^2+\gamma_{111}^2)x_1x_2x_3 \\
\qquad +(\alpha_{003}^2+\beta_{003}^2+\gamma_{003}^2)x_3^3
\end{cases} \tag{65}
$$

after truncating higher order terms. Since $x_1 = \bar{x}_2$, through the change of variables $x_1 = w_1 - iw_2, x_2 = w_1 + iw_2, x_3 = w_3$, and then a change to cylindrical coordinates according to $w_1 = r\cos\xi, w_2 = r\sin\xi, w_3 = \zeta$, system (65) becomes

$$
\begin{cases}
\dot{r} = \alpha_1(\mu)r + \beta_{11}r\zeta + \beta_{30}r^3 + \beta_{12}r\zeta^2 + \text{h.o.t.}, \\
\dot{\zeta} = \alpha_2(\mu)\zeta + \gamma_{20}r^2 + \gamma_{02}\zeta^2 + \gamma_{21}r^2\zeta + \gamma_{03}\zeta^3 + \text{h.o.t.}, \\
\dot{\xi} = -\omega + \mathrm{Im}[\theta_1]\zeta + \text{h.o.t.},
\end{cases}
$$

where

$$
\begin{aligned}
&\alpha_1(\mu) = \mathrm{Re}[\theta_1], \quad \beta_{11} = \mathrm{Re}[\alpha_{110}^1], \quad \beta_{30} = \mathrm{Re}[\alpha_{210}^1+\beta_{210}^1+\gamma_{210}^1], \\
&\beta_{12} = \mathrm{Re}[\alpha_{102}^1+\beta_{102}^1+\gamma_{102}^1], \quad \alpha_2(\mu) = \theta_2, \gamma_{20} = \alpha_{110}^2, \quad \gamma_{02} = \alpha_{002}^2 \\
&\gamma_{21} = \alpha_{111}^2+\beta_{111}^2+\gamma_{111}^2, \quad \gamma_{03} = \alpha_{003}^2+\beta_{003}^2+\gamma_{003}^2,
\end{aligned}
$$

Since the third equation describes a rotation around the ζ-axis, it is irrelevant and omitted. Hence, we obtain an amplitude system in the (r,ζ)-plane up to the third order

$$
\begin{cases}
\dot{r} = \alpha_1 r + \beta_{11}r\zeta + \beta_{30}r^3 + \beta_{12}r\zeta^2 + \text{h.o.t.}, \\
\dot{\zeta} = \alpha_2\zeta + \gamma_{20}r^2 + \gamma_{02}\zeta^2 + \gamma_{21}r^2\zeta + \gamma_{03}\zeta^3 + \text{h.o.t.}.
\end{cases} \tag{66}
$$

Therefore, we have the following result.

Theorem 3.9. *Under the assumptions (H_1), (H_2), and the conditions for Fold-Hopf bifurcation given in Theorem 3.7, model (19) near the equilibrium P_2 is locally topologically equivalent to system (66) near the origin.*

3.2.6. *Hopf-Hopf Bifurcation.* In the following, we consider Hopf-Hopf bifurcation in the tumor-immune system interaction model (19). Note that the eigenvalues $\pm i\omega_j, j = 1, 2$, of (24) are simple. On the other hand, we know that $A(a)$ has simple eigenvalues $\lambda_1(a)$ and $\lambda_2(a)$ with $\lambda_i(0) = i\omega_j,\ j = 1, 2$. We also know $A(a)$ 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

$$D_j = (1 + \overline{\gamma}_j\beta_j + \tau_k(a_{21}\beta_j + a_{11})e^{i\omega_j\tau_k})^{-1}. \tag{67}$$

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 $z = (z_1, z_2) \in \mathcal{C}_a$, 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 (34), then on the center manifold $\mathcal{C}_a$, one has the normal form

$$z' = \Lambda z(t) + g(z, a), \tag{68}$$

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

$$g(z, a) = (g^1(z, a),\ g^2(z, a))^T = (\sum_{i+j+k+l\geq 2} \frac{1}{i!j!l!k!} g^1_{ijkl}, \sum_{i+j+k+l\geq 2} \frac{1}{i!j!l!k!} g^2_{ijkl})^T. \tag{69}$$

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 et al. [63] and derive the explicit formulae determining these properties at the critical value of $a = 0$. From last section, we know that at $a = 0$,

$$\begin{aligned} z_j(t) &= < q^*, x_t' >= i\omega_j z_j(t) + \overline{q}_j^{*T} R(W + 2\mathrm{Re}\{z_1q_1 + z_2q_2\}) \\ &\triangleq i\omega_j z_j(t) + g(z_1, \overline{z_1}, z_2, \overline{z_2}), \qquad j = 1, 2, \end{aligned}$$

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,

$$g^j(z, a) = \overline{q}_j^{*T} R_0(W + 2\mathrm{Re}\{z_1q_1 + z_2q_2\}), \tag{70}$$

where $R_0(z_1, z_2) = R(0, z_1, z_2)$. Noting $x_t = (x_{1t}(\theta), x_{2t}(\theta)) = W(t, \theta) + z_1q(\theta) + \overline{z_1q(\theta)} + z_2q(\theta) + \overline{z_2q(\theta)}$ and $q_j(\theta) = (1, \beta_j)^T e^{i\omega\theta}$, comparing the coefficients of (70) and (69), g_{ijkl} can be obtained as follows:

$$\begin{aligned} g^1_{2000} &= \tau_k\overline{D}[d_{11} + d_{12}\beta_1 + d_{13}\beta_1^2 + \tfrac{x_2\nu''(x_2)}{2} e^{-2i\omega_1\tau_k} + \nu'(x_2)e^{-i\omega_1\tau_k}], \\ g^1_{0200} &= \tau_k\overline{D}[d_{11} + d_{12}\overline{\beta_1} + d_{13}\overline{\beta_1^2} + \tfrac{x_2\overline{\nu''}(x_2)}{2} e^{2i\omega_1\tau_k} + \nu'(x_2)e^{i\omega_1\tau_k}], \\ g^1_{0020} &= \tau_k\overline{D}[d_{11} + d_{12}\beta_2 + d_{13}\beta_2^2 + \tfrac{x_2\overline{\nu''}(x_2)}{2} e^{-2i\omega_2\tau_k} + \nu'(x_2)e^{-i\omega_2\tau_k}], \end{aligned}$$

$$
\begin{aligned}
g^1_{0002} &= \tau_k\overline{D}[d_{11} + d_{12}\overline{\beta_2} + d_{13}\overline{\beta_2^2} + \tfrac{x_2\nu''(x_2)}{2}e^{2i\omega_2\tau_k} + \nu'(x_2)e^{i\omega_2\tau_k}],\\
g^1_{1100} &= \tau_k\overline{D}[2d_{11} + d_{12}(\beta_1 + \overline{\beta_1}) + 2d_{13}\beta_1\overline{\beta_1} + x_2\nu''(x_2)\\
&\quad +\nu'(x_2)(e^{i\omega_1\tau_k} + e^{-i\omega_1\tau_k})],\\
g^1_{1010} &= \tau_k\overline{D}[2d_{11} + d_{12}(\beta_2 + \beta_1) + 2d_{13}\beta_1\beta_2 + x_2\nu''(x_2)e^{-i(\omega_1+\omega_2)\tau_k}\\
&\quad +\nu'(x_2)(e^{-i\omega_2\tau_k} + e^{-i\omega_1\tau_k})],\\
g^1_{1001} &= \tau_k\overline{D}[2d_{11} + d_{12}(\overline{\beta_2} + \beta_1) + 2d_{13}\beta_1\overline{\beta_2} + x_2\nu''(x_2)e^{i(\omega_2-\omega_1)\tau_k}\\
&\quad +\nu'(x_2)(e^{i\omega_2\tau_k} + e^{-i\omega_1\tau_k})],\\
g^1_{0110} &= \tau_k\overline{D}[2d_{11} + d_{12}(\overline{\beta_1} + \beta_2) + 2d_{13}\beta_2\overline{\beta_1} + x_2\nu''(x_2)e^{i(\omega_1-\omega_2)\tau_k}\\
&\quad +\nu'(x_2)(e^{-i\omega_2\tau_k} + e^{i\omega_1\tau_k})],
\end{aligned}
$$

$$
\begin{aligned}
g^1_{0101} &= \tau_k\overline{D}[2d_{11} + d_{12}(\overline{\beta_1} + \overline{\beta_2}) + 2d_{13}\overline{\beta_2\beta_1} + x_2\nu''(x_2)e^{i(\omega_1+\omega_2)\tau_k}\\
&\quad +\nu'(x_2)(e^{i\omega_2\tau_k} + e^{i\omega_1\tau_k})],\\
g^1_{0011} &= \tau_k\overline{D}[2d_{11} + d_{12}(\beta_2 + \overline{\beta_2}) + 2d_{13}\overline{\beta_2}\beta_2 + x_2\nu''(x_2)\\
&\quad +\nu'(x_2)(e^{-i\omega_2\tau_k} + e^{i\omega_2\tau_k})],
\end{aligned}
$$

$$
\begin{aligned}
g^1_{2100} &= \tau_k\overline{D}[d_{11}(W^{(1)}_{2000} + 2W^{(1)}_{1100}) + d_{12}(\tfrac{1}{2}W^{(1)}_{2000}\overline{\beta_1} + \tfrac{1}{2}W^{(2)}_{2000} + W^{(1)}_{1100}\beta_1\\
&\quad +W^{(2)}_{1100}) + d_{13}(\overline{\beta_1}W^{(2)}_{2000} + 2\beta_1W^{(1)}_{1100})\\
&\quad +\tfrac{x_2\nu''(x_2)}{2}(W^{(1)}_{2000}(-1)e^{i\omega_1\tau_k} + 2W^{(1)}_{1100}e^{-i\omega_1\tau_k})\\
&\quad +\nu'(x_2)(\tfrac{1}{2}W^{(1)}_{2000}e^{i\omega_1\tau_k} + \tfrac{1}{2}W^{(1)}_{2000}(-1) + W^{(1)}_{1100}(-1) + W^{(1)}_{1100}e^{-i\omega_1\tau_k})\\
&\quad +3e_{11} + e_{12}(\overline{\beta_1} + 2\beta_1) + e_{13}(2\beta_1\overline{\beta_1} + \beta_1^2) + 3e_{14}\overline{\beta_1}\beta_1^2\\
&\quad +\tfrac{x_2\nu^{(3)}(x_2)}{2}e^{-i\omega_1\tau_k} + \tfrac{\nu''(x_2)}{2}(e^{-2i\omega_1\tau_k} + 2)],
\end{aligned}
$$

$$
\begin{aligned}
g^1_{1011} &= \tau_k\overline{D}[2d_{11}(W^{(1)}_{0011} + W^{(1)}_{1010} + W^{(1)}_{1001}) + 2d_{13}(\beta_1W^{(2)}_{0011} + \overline{\beta_2}W^{(2)}_{1010}\\
&\quad +\beta_2W^{(2)}_{1001}) + d_{12}(W^{(2)}_{0011} + W^{(2)}_{1010} + W^{(2)}_{1001} + \beta_2W^{(1)}_{1001}+\\
&\quad \beta_1W^{(1)}_{0011} + \overline{\beta_2}W^{(1)}_{1010}) + x_2\nu''(x_2)(W^{(1)}_{0011}(-1)e^{-i\omega_1\tau_k}+\\
&\quad W^{(1)}_{1010}(-1)e^{i\omega_2\tau_k} + W^{(1)}_{1001}(-1)e^{-i\omega_2\tau_k})\\
&\quad +\nu'(x_2)(W^{(1)}_{0011}e^{-i\omega_1\tau_k} + W^{(1)}_{1010}e^{i\omega_2\tau_k} + W^{(1)}_{1001}e^{-i\omega_2\tau_k} + W^{(1)}_{0011}(-1)\\
&\quad +W^{(1)}_{1010}(-1) + W^{(1)}_{1001}(-1)) + 6e_{11} + 2e_{12}(\overline{\beta_1} + \beta_2 + \overline{\beta_2}) + 6e_{14}\overline{\beta_2}\beta_1\beta_2\\
&\quad +2e_{13}(\overline{\beta_2}\beta_1 + \beta_1\beta_2 + \overline{\beta_2}\beta_2) + x_2\nu^{(3)}(x_2)e^{-i\omega_1\tau_k}\\
&\quad +\nu''(x_2)(1 + e^{-i(\omega_1+\omega_2)\tau_k} + e^{i(\omega_2-\omega_1)\tau_k})],
\end{aligned}
$$

$$
\begin{aligned}
g^2_{2000} &= \tau_k\overline{D}[d_{21} + d_{22}\beta_1 + \tfrac{y_2\beta''(x_2)}{2}e^{-2i\omega_1\tau_k} + \beta'(x_2)\beta_1e^{-i\omega_1\tau_k}],\\
g^2_{0200} &= \tau_k\overline{D}[d_{21} + d_{22}\overline{\beta_1} + \tfrac{y_2\beta''(x_2)}{2}e^{2i\omega_1\tau_k} + \beta'(x_2)\overline{\beta_1}e^{i\omega_1\tau_k}],\\
g^2_{0020} &= \tau_k\overline{D}[d_{21} + d_{22}\beta_2 + \tfrac{y_2\beta''(x_2)}{2}e^{-2i\omega_2\tau_k} + \beta'(x_2)\beta_2e^{-i\omega_2\tau_k}],\\
g^2_{0002} &= \tau_k\overline{D}[d_{21} + d_{22}\overline{\beta_2} + \tfrac{y_2\beta''(x_2)}{2}e^{2i\omega_2\tau_k} + \beta'(x_2)\overline{\beta_2}e^{i\omega_2\tau_k}],\\
g^2_{1100} &= \tau_k\overline{D}[2d_{21} + d_{22}(\beta_1 + \overline{\beta_1}) + y_2\beta''(x_2) + \beta'(x_2)(\beta_1e^{i\omega_1\tau_k} + \overline{\beta_1}e^{-i\omega_1\tau_k})],\\
g^2_{1010} &= \tau_k\overline{D}[2d_{21} + d_{22}(\beta_2 + \beta_1) + y_2\beta''(x_2)e^{-i(\omega_1+\omega_2)\tau_k}\\
&\quad +\beta'(x_2)(\beta_1e^{-i\omega_2\tau_k} + \beta_2e^{-i\omega_1\tau_k})],\\
g^2_{1001} &= \tau_k\overline{D}[2d_{21} + d_{22}(\overline{\beta_2} + \beta_1) + y_2\beta''(x_2)e^{i(\omega_2-\omega_1)\tau_k}\\
&\quad +\beta'(x_2)(\beta_1e^{i\omega_2\tau_k} + \overline{\beta_2}e^{-i\omega_1\tau_k})],\\
g^2_{0110} &= \tau_k\overline{D}[2d_{21} + d_{22}(\overline{\beta_1} + \beta_2) + y_2\beta''(x_2)e^{i(\omega_1-\omega_2)\tau_k}\\
&\quad +\beta'(x_2)(\overline{\beta_1}e^{-i\omega_2\tau_k} + \beta_2e^{i\omega_1\tau_k})],
\end{aligned}
$$

$$
\begin{aligned}
g^2_{0101} &= \tau_k\overline{D}[2d_{21} + d_{22}(\overline{\beta_1} + \overline{\beta_2}) + y_2\beta''(x_2)e^{i(\omega_1+\omega_2)\tau_k}\\
&\quad +\beta'(x_2)(\overline{\beta_1}e^{i\omega_2\tau_k} + \overline{\beta_2}e^{i\omega_1\tau_k})],\\
g^2_{0011} &= \tau_k\overline{D}[2d_{21} + d_{22}(\beta_2 + \overline{\beta_2}) + y_2\beta''(x_2) + \beta'(x_2)(\beta_2e^{i\omega_2\tau_k} + \overline{\beta_2}e^{-i\omega_2\tau_k})],
\end{aligned}
$$

$$\begin{aligned} g^2_{0021} \;=\;& \tau_k\overline{D}[d_{21}(W^{(1)}_{0020}+2W^{(1)}_{0011})+d_{22}(\tfrac{1}{2}W^{(1)}_{0020}\overline{\beta_2}+\tfrac{1}{2}W^{(2)}_{0020}+W^{(1)}_{0011}\beta_2\\ &+W^{(2)}_{0011})+\tfrac{y_2\beta''(x_2)}{2}(W^{(1)}_{0020}(-1)e^{i\omega_2\tau_k}+2W^{(1)}_{0011}(-1)e^{-i\omega_2\tau_k})\\ &+\beta'(x_2)(\tfrac{1}{2}W^{(2)}_{0020}e^{i\omega_2\tau_k}+\tfrac{1}{2}\overline{\beta_2}W^{(1)}_{0020}(-1)+\beta_2W^{(1)}_{0011}(-1)\\ &+W^{(2)}_{0011}e^{-i\omega_2\tau_k})+3e_{21}+e_{22}(\overline{\beta_2}+2\beta_2)+\tfrac{y_2\beta^{(3)}(x_2)}{2}e^{-i\omega_2\tau_k}\\ &+\tfrac{\beta''(x_2)}{2}(\overline{\beta_2}e^{-2i\omega_2\tau_k}+2\beta_2)], \end{aligned}$$

$$\begin{aligned} g^2_{1110} \;=\;& \tau_k\overline{D}[2d_{21}(W^{(1)}_{1100}+W^{(1)}_{1010}+W^{(1)}_{0110})\\ &+d_{22}(\beta_2W^{(1)}_{1100}+\beta_1W^{(1)}_{0110}+\overline{\beta_1}W^{(1)}_{1010}+W^{(2)}_{1100}+W^{(2)}_{0110}+W^{(2)}_{1010})\\ &+\beta'(x_2)(W^{(2)}_{1100}e^{-i\omega_2\tau_k}+W^{(2)}_{1010}e^{i\omega_1\tau_k}+W^{(2)}_{0110}e^{-i\omega_1\tau_k}+\beta_2W^{(1)}_{1100}(-1)\\ &+\overline{\beta_1}W^{(1)}_{1010}(-1)+\beta_1W^{(1)}_{0110})\\ &+y_2\beta''(x_2)(W^{(1)}_{1100}(-1)e^{-i\omega_2\tau_k}+W^{(1)}_{1010}(-1)e^{i\omega_1\tau_k}+W^{(1)}_{0110}(-1)e^{-i\omega_1\tau_k})\\ &+6e_{21}+2e_{22}(\overline{\beta_1}+\beta_1+\beta_2)+y_2\beta^{(3)}(x_2)e^{-i\omega_2\tau_k}\\ &+\beta''(x_2)(\overline{\beta_2}+\overline{\beta_1}e^{-i(\omega_1+\omega_2)\tau_k}+\beta_1e^{i(\omega_1-\omega_2)\tau_k})], \end{aligned}$$

where d_{ij} and e_{ij} are defined in (38). 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. We can see that

$$\begin{aligned} W' \;&=\; X'_t - z'_1q_1-\overline{z'_1q_1}-z'_2q_2-\overline{z'_2q_2}\\ &=\begin{cases} A_0W-2\mathrm{Re}\{q_1^{*T}(0)R_0q_1\}-2\mathrm{Re}\{q_2^{*T}(0)R_0q_2\}, & \theta\in[-\tau,0)\\ A_0W-2\mathrm{Re}\{q_1^{*T}(0)R_0q_1\}-2\mathrm{Re}\{q_2^{*T}(0)R_0q_2\} & \\ \quad +R_0(z_1,\overline{z_1},z_2,\overline{z_2}), & \theta=0 \end{cases}\\ &\triangleq\; A_0W+H(z_1,\overline{z_1},z_2,\overline{z_2},\theta), \end{aligned} \tag{71}$$

where

$$H(z_1,\overline{z_1},z_2,\overline{z_2},\theta)=\sum_{i+j+k+l\geq 2}\frac{1}{i!j!k!l!}H_{ijkl}z_1^i\overline{z_1}^jz_2^k\overline{z_2}^l.$$

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

$$\begin{aligned} &(A_0-2i\omega_1\tau_k)W_{2000}(\theta)=-H_{2000}(\theta),\\ &(A_0-2i\omega_2)W_{0020}(\theta)=-H_{0020}(\theta)\\ &A_0W_{1100}(\theta)=-H_{1100}(\theta),\\ &A_0W_{0011}(\theta)=-H_{0011}(\theta) \end{aligned} \tag{72}$$

and

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

From (71), it is easy to see that

$$\begin{aligned} H(z_1,\overline{z_1},z_2,\overline{z_2},\theta)=&-2\mathrm{Re}\{q_1^{*T}(0)R_0q_1\}-2\mathrm{Re}\{q_2^{*T}(0)R_0q_2\}\\ =&-g^1(z,\overline{z})q_1(\theta)-\overline{g^1(z,\overline{z})q_1(\theta)}\\ &-g^2(z,\overline{z})q_2(\theta)-\overline{g^2(z,\overline{z})q_2(\theta)}. \end{aligned} \tag{73}$$

From the definition of A_0, (72) and (73), it follows that

$$W'_{2000}=2i\omega_1W_{2000}-g^1_{2000}q_1(\theta)-\overline{g^1_{0200}q_1(\theta)}-g^2_{0020}q_2(\theta)-\overline{g^2_{0002}q_2(\theta)},$$

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

$$\begin{aligned} W_{2000}(\theta) = & \frac{ig^1_{2000}q_1(0)}{\omega_1\tau_k}e^{i\omega_1\theta\tau_k} + \frac{\overline{ig^1_{0200}q_1(0)}}{3\omega_1\tau_k}e^{-i\omega_1\theta\tau_k} \\ & - \frac{ig^2_{0020}q_2(0)}{(\omega_2-2\omega_1)\tau_k}e^{i\omega_2\theta\tau_k} + \frac{\overline{ig^1_{0002}q_2(0)}}{(\omega_2+2\omega_1)\tau_k}e^{-i\omega_2\theta\tau_k} + Ke^{2i\omega_1\theta\tau_k}, \end{aligned} \tag{74}$$

where $K = (K^{(1)}, K^{(2)}) \in \mathbb{R}^3$ is a constant vector, which still need to be obtained. The definition of A_0 and (73) yield

$$\int_1^0 d\eta(\theta)W_{2000}(0) = 2i\omega_1 W_{2000}(\theta) - H_{2000}(0). \tag{75}$$

From (71), it is easy to obtain $H_{2000}(0)$ as follows

$$H_{2000}(0) = -g^1_{2000}q_1(0) - \overline{g^1_{0200}q_1(0)} - g^2_{2000}q_2(0) - \overline{g^2_{0200}q_2(0)} + R_0. \tag{76}$$

Submitting (73) and (76) into (75) and noting $\pm i\omega_1$, $\pm i\omega_2$ are characteristic roots of (24) but $2i\omega_1$ is not, we obtain

$$K = \begin{pmatrix} 2\omega_1 i + a_{12} + a_{11}e^{-2i\omega_1\theta}, & a_{13} \\ -a_{22} - a_{21}e^{-2i\omega_1\theta}, & 2\omega_1 i - a_{23} \end{pmatrix}^{-1} R_0. \tag{77}$$

From (73), we know that W_{2000} is obtained. Similarly, we can obtain other W_{ijkl}, that is, all g_{ijkl} are obtained.

Similar to the computation of Hopf bifurcation, we can obtain

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

where

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

where $g_{ijkl},\ i+j+k+l \geq 2$ can be obtained similar as above. As shown in Takens [111] and Wiggins [119], we assume that the following non-degeneracy 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 (68) can be changed into

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

Then the truncation of the amplitude equations to the quadratic order is

$$\left\{\begin{array}{l} \theta_1' = \omega_1 + a\mathrm{Im}\lambda_1'(0) + \mathrm{Im}\{C_{11}(0)\}r_1^2 + \mathrm{Im}\{C_{12}(0)\}r_2^2 + O(\|r_1, r_2\|)^4 \\ \theta_2' = \omega_1 + a\mathrm{Im}\lambda_2'(0) + \mathrm{Im}\{C_{21}(0)\}r_2^2 + \mathrm{Im}\{C_{22}(0)\}r_1^2 + O(\|r_1, r_2\|)^4, \end{array}\right. \tag{78}$$

and the truncation of the phase equations to the cubic order is

$$\left\{\begin{array}{l} r_1' = a\mathrm{Re}\lambda_1'(0)r_1 + \mathrm{Re}\{C_{11}(0)\}r_1^3 + \mathrm{Re}\{C_{12}(0)\}r_1 r_2^2 + O(\|r_1, r_2\|)^5 \\ r_2' = a\mathrm{Re}\lambda_2'(0)r_2 + \mathrm{Re}\{C_{21}(0)\}r_2^3 + \mathrm{Re}\{C_{22}(0)\}r_1^2 r_2 + O(\|r_1, r_2\|)^5. \end{array}\right. \tag{79}$$

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 (79) can be written as

$$\left\{\begin{array}{l} r_1' = (\mu_1 + er_1^2 + br_2^2)r_1 \\ r_2' = (\mu_2 + cr_1^2 + dr_2^2)r_2. \end{array}\right. \tag{80}$$

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

Similar to the previous subsection, we know that system (78) determines the period and direction of the bifurcated solutions. As Guckhenheimer and Holmes [58] and Choi and LeBlanc [27] 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 only need to study the truncation equation of phase equations (79) and obtain the following results.

Theorem 3.10. *(i) If (80) has an equilibrium $(r_1^*,\ 0)$ (resp., $(0,\ r_2^*)$), then in the neighborhood of the positive equilibrium P_2, system (19) 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 (80) has an equilibrium $(r_1^*,\ r_2^*)$ with $r_1^* > 0$, $r_2^* > 0$ in the interior of the positive quadrant, then (19) has quasi-periodic solutions in the neighborhood of the positive equilibrium P_2.

(iii) If (80) has a limit cycle in the interior of the positive quadrant, then (19) has a three-dimensional invariant torus in the neighborhood of the positive equilibrium P_2.

In order to analyze the qualitative properties of (80), there are four cases to be considered: (1) $e > 0,\ \ d > 0$; (2) $e > 0,\ \ d < 0$; (3) $e < 0,\ \ d > 0$; (4) $e < 0,\ \ d < 0$. Here, we only consider the second case, the other cases can be analyzed similarly. In this case, system (80) takes the form

$$\left\{\begin{array}{l} r_1' = (\mu_1 + r_1^2 + br_2^2)r_1 \\ r_2' = (\mu_2 + cr_1^2 - r_2^2)r_2. \end{array}\right. \tag{81}$$

It is easy to see that (81) 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 (81) at E_i' :

$$\begin{pmatrix} \mu_1 + 3r_1^{*2} + br_2^{*2}, & 2br_1^* r_1^* \\ 22r_1^* r_1^*, & \mu_2 + cr_1^{*2} + 3r_2^{*2} \end{pmatrix}. \tag{82}$$

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 (82), 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 give the complex dynamical behaviors of (81), Guckhenheimer and Holmes [58] pointed out that there are 12 unfolding cases for the nonresonant Hopf-Hopf bifurcation for E_i', which were summarized in Table 7.5.2 of [58].

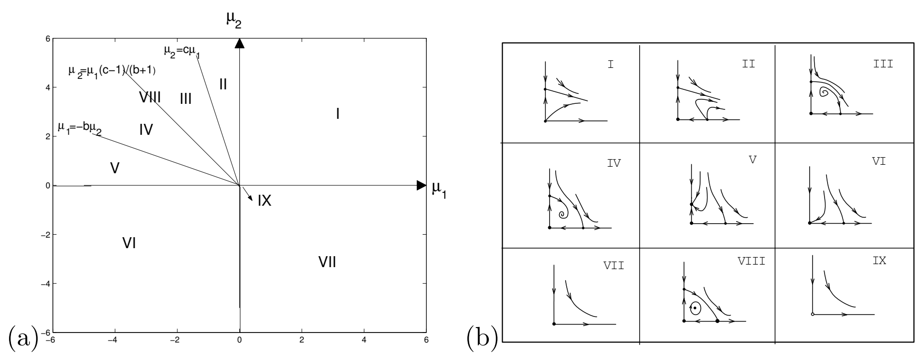


FIGURE 6. Phase portraits for the case VIa in Table 7.5.2 of [58]: (a) Bifurcation diagram in (μ_1, μ_2); (b) Phase portraits of (81).

We choose case VIa in Table 7.5.2 of [58] 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 [58], the partial bifurcation sets and the phase portraits for the unfoldings of this case are given in Fig. 6.

From Fig. 6, we have the following results.

Theorem 3.11. *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 results:*

(i) If a point (μ_1, μ_2) *crosses the positive* μ_1*-axis from* D_7 *to* D_1*, Hopf bifurcation occurs and a unstable periodic solution* Γ_1 *is bifurcated from the trivial solution,* 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 and a 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 qusa-periodic solution Θ_1 is bifurcated from Γ_1, 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, the bifurcated torus Θ_2 exists in a small neighborhood of $(\mu_1, \frac{(c-1)\mu_1}{b+1})$, 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 Fig. 7.

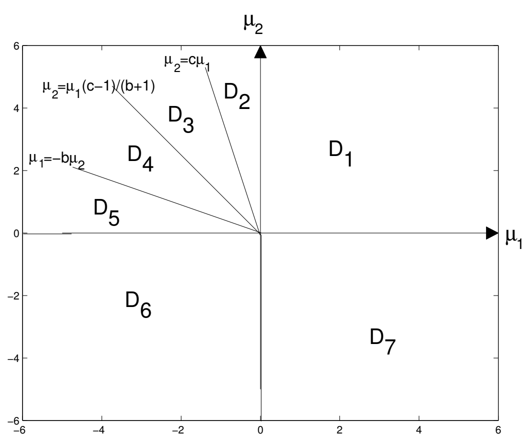


FIGURE 7. The bifurcation diagram of (81) on the (μ_1, μ_2)-plane.

Theorem 3.12. *For $A_2 > 0$, system (19) possesses Hopf-Hopf points with frequencies having all possible ratios $\omega_1 : \omega_2 = m : n$, $m < n \in Z$.*

3.3. **Numerical simulations.** To show the results of Theorem 3.3, we still consider the model proposed in d'Onofrio [37] 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 $\tau = \tau_0^+$ (Fig. 8(a)(b)). Then we have $\alpha = -0.0149845 - 0.149707i$, $\alpha^* = -1.67819 - 5.98562i$ and $D = 0.511595 - 0.0555238i$. Also, $g_{20} = 0.013352 - 0.0989036i$, $g_{11} = 0.0140638 - 0.104576i$, $g_{02} = -0.0332515 + 0.0830015i$. In order to compute g_{21}, we need give W_{11} and W_{20} first. We have

$$\begin{aligned} W' &= x_t' - z'p - \bar{z}'p = \begin{cases} A_0W - 2\mathrm{Re}\{\bar{p}^T(0)R_0p(\theta)\} & \theta \in [-\tau_1, 0) \\ A_0W - 2\mathrm{Re}\{\bar{p}^T(0)R_0p(\theta)\} + R_0 & \theta = 0 \end{cases} \\ &\stackrel{\text{def}}{=} A_0W + H(z, \bar{z}, \theta) \end{aligned} \tag{83}$$

where

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

Hence we obtain

$$W_{20}(\theta) = \frac{ig_{20}}{\omega_0}p(0)e^{i\omega_0\theta} + \frac{i\overline{g_{02}}}{3\omega_0}\overline{p(0)}e^{-i\omega_0\theta} + K_1e^{2i\omega_0\theta} \tag{84}$$

Similarly,

$$W_{11}(\theta) = \frac{ig_{11}}{\omega_0}p(0)e^{i\omega_0\theta} + \frac{i\overline{g_{11}}}{\omega_0}\overline{p(0)}e^{-i\omega_0\theta} + K_2, \tag{85}$$

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 $K_2 = (0.178478 - 1.70488i, -0.128644 + 0.0179399i)$.

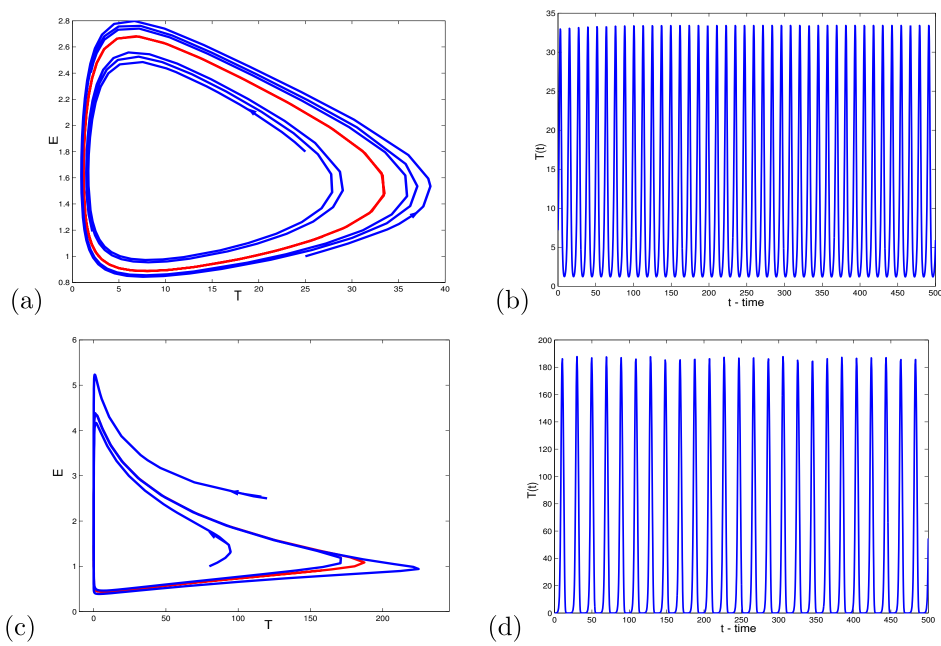


FIGURE 8. (a) The periodic solution $(x(t), y(t))$ bifurcated from the microscopic equilibrium $(8.18971, 1.6092)$ with $\tau = 0.333814$. (b) The corresponding solution $x(t)$ in terms of time t. (c) The periodic solution $(x(t), y(t))$ bifurcated from the macroscopic equilibrium $(447.134, 0.172977)$ as $\tau = 2.08803$. (d) The corresponding solution $x(t)$ in terms of time t.

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 $C_1(0) = -0.107224 - 0.0832058$. Thus, system (19) 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 discuss the stability of 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 $\tau_k = 0.333814$, respectively (Fig. 8).

For the model proposed in d'Onofrio [37], we can obtain all positive equilibria. Then the results of Bautin, Fold-Hopf, and Hopf-Hopf bifurcations can be obtained similarly, we will not provide the details here for the sake of simplicity.

4. **Periodic and chaotic oscillations in a tumor-immune system interaction model with three delays.**

4.1. **The basic model of Mayer et al. [87].**

Let $T(t)$ describe the concentration of the tumor cells and $E(t)$ measure the concentration of relevant active immune effector cells at time t, respectively. $E(t)$ may be measured, for example, by the concentration of certain immune cells, like cytotoxic T-cells, natural killer cells, or by the concentration of certain antibodies. In 1996, Mayer et al. [87] first proposed the following tumor and immune system interaction model with two time delays:

$$\begin{cases} \dfrac{dT}{dt} = rT(t-\tau) - kT(t)E(t) \\ \dfrac{dE}{dt} = f(T(t-\delta)) + g(E(t-\Delta)) - dE(t), \end{cases} \tag{86}$$

where r is the intrinsic growth rate of the tumor cells and $\tau \geq 0$ is the time delay in the proliferation of tumor cells. The term $kT(t)E(t)$ is the inactivation of the tumor cells by the immune effector cells. The corresponding inactivation term $T(t)E(t)$ in the equation for E can be neglected since it should be orders of magnitude smaller than the first two terms, which are given by the nonlinear functions $f(T)$ and $g(E)$.

The immune competence $E(t)$ is supposed to be constituted by three factors:

(i) The tumor cells trigger processes in the immune system leading to competence against them. The velocity of this simulation is described by a function $f(T)$ which is specifically given by

$$f(T) = \frac{pT^u}{m^v + T^v},$$

where p, s, u, m, n are positive constants with $u \geq v$. Depending on the parameters u and v there are three different shapes of the stimulation function $f(T)$ illustrated as in Fig. 9(a), (b) and (c). All these functions are bounded accounting for the fact that the precursor population is limited. The sigmoid increase in the case $u > 1$ emphasizes that a small amount of tumor cells may be more or less ignored by the immune system. This effect is known as low-zone unresponsiveness. The high-zone unresponsiveness, $u < v$, is characterized by a decrease of immune response stimulation under high tumor burden. The parameter p describes the precursor pool size. Assume that this process is delayed and let $\delta \geq 0$ be the time delay describing the process of effector cells growth with respect to stimulus by the tumor cells growth.

(ii) The immune reaction is additionally strengthened by autocatalytic and/or cooperative reinforcement of immune activation processes. That is, the competent immune effector cells proliferate and/or stimulate themselves or precursor

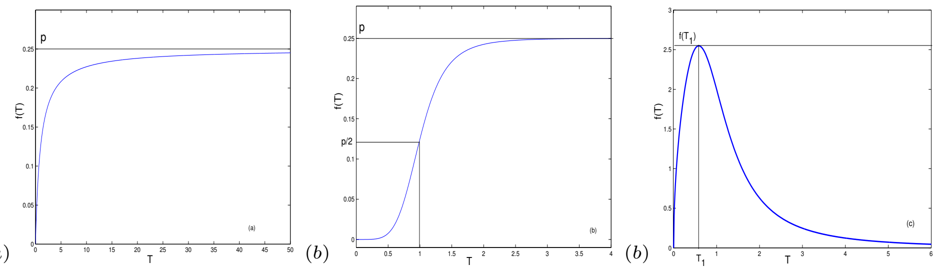


FIGURE 9. Graphs of $f(T)$ for three different parameter sets: (a) $u = v = 1$; (b) $u = v = 5 > 1$; (c) $u = \frac{1}{2} < 1 < v = 2$.

cells for increased proliferation or differentiation. The resulting increase rate of immune competence is described by a function

$$g(E) = \frac{sE^n}{c^n + E^n}$$

where $n \geq 1$ is a constant. The graph of $g(E)$ is qualitatively similar to Fig. 9(a) ($n = 1$) or (b) ($n > 1$). The sigmoid shape takes into account that a critical number of immune cells may be necessary for realizing the cooperative and autocatalytic effect. This process is also assumed to be delayed and $\Delta \geq 0$ is the time delay appearing in the differentiation of immune effector cells.

(iii) The term $-dE(t)$ models that finite lifetime of the immune competent cells with a positive death rate constant d.

Mayer et al.[87] did not analyze the delayed model (86). Instead they provided detailed analysis of the ODE version when all delays are zero. In particular, they showed that solutions of the model equations correspond to states described by immunologists as "virgin state," "immune state" and "state of tolerance." They demonstrated that the model successfully replicates the so-called primary and secondary response and predicts the existence of a threshold level for the amount of pathogen germs or of transplanted tumor cells below which the host is able to eliminate the infectious organism or to reject the tumor graft. They found a long time coexistence of tumor cells and immune competent cells including damped and undamped oscillations of both. They also observed that if the number of transformed cells or pathogens exceeds definable values the immune system fails to keep the disease under control. On the other hand, there is an increased chance of tumor survival despite enhanced immune activity or therapeutically achieved tumor reduction. Their study demonstrates how the combination of a few proposed nonlinear interaction rules between the immune system and tumor cells in a very simple model are able to generate a considerable variety of different kinds of immune responses, many of which are observed both experimentally and clinically.

In order to study the original delay model (86), Buric et al. [22] and Yu and Wei [126] expressed the variable of f as a combination of $T(t)$ and $T(t-\delta)$, that is $f(aT(t) + (1-a)T(t-\delta))$ with $a (0 \leq a \leq 1)$ being a constant, and allowed the function g to depend on the combination of $E(t)$ and $E(t-\Delta)$, that is $g(bE(t) + (1-b)E(t-\Delta))$, where $b (0 \leq b \leq 1)$ is a constant.

(a) When $\tau = 0, d = 1, u = v = 4, n = 3, m = 1$, and $c = 1$, $f(aT(t)+(1-a)T(t-\delta)) = \frac{p[aT(t)+(1-a)T(t-\delta)]^4}{1+[aT(t)+(1-a)T(t-\delta)]^4}$, $g(bE(t) + (1-b)E(t-\Delta)) = \frac{s[bE(t)+(1-b)E(t-\Delta)]^3}{1+[bE(t)+(1-b)E(t-\Delta)]^3}$, Burić et al. [22] studied the stability of the equilibria and showed that the time delay could introduce chaotic dynamics in the model.

(b) When $\tau = 0$, $u = v = 2m_1, n = 2n_1, m = 1$, and $c = 1$, $f(aT(t)+(1-a)T(t-\delta)) = \frac{p[aT(t)+(1-a)T(t-\delta)]^{2m_1}}{1+[aT(t)+(1-a)T(t-\delta)]^{2m_1}}$, $g(bE(t)+(1-b)E(t-\Delta)) = \frac{s[bE(t)+(1-b)E(t-\Delta)]^{2n_1}}{1+[bE(t)+(1-b)E(t-\Delta)]^{2n_1}}$, Yu and Wei [126] studied the stability switch and Hopf bifurcation of model.

(c) When $u = v, d = 1$, $f(T(t-\delta)) = \frac{pT(t-\delta)^u}{1+T(t-\delta)^u}$, $g(E(t-\Delta)) = \frac{sE(t-\Delta)^n}{1+E(t-\Delta)^n}$, recently Mendonça et al. [90] performed detailed linear stability analysis of original delayed model (86) to investigate possible stability switches induced by the existence of characteristic delay times of the dynamical processes and showed that stability switches of stable periodic cycle solutions can be induced by enforcing appropriated time delays in the tumor cell reproduction as well as in the cooperative immune response. They also provided numerical simulations of the corresponding set of delayed differential equations to support the analytical results, showing bifurcations and quasi-chaotic behavior.

In this section, we present the analyses and results on the periodic and chaotic oscillations in the delayed model (86) of Mayer et al. [87] obtained by Bi, Ruan and Zhang [14]. Following Buric et al. [22] and Yu and Wei [126], the variable of f is expressed as a combination of $T(t)$ and $T(t-\delta)$, that is $f(aT(t)+(1-a)T(t-\delta))$ with $a(0 \le a \le 1)$ being a constant, meaning that the dependence of the rate of creating immunocompetent cells not only on the rate of variations of $T(t)$ at the current time but also on the value of $T(t-\delta)$ at an earlier time $t-\delta$. Similarly, the function g depends on the combination of $E(t)$ and $E(t-\Delta)$, that is $g(bE(t)+(1-b)E(t-\Delta))$, where $b(0 \le b \le 1)$ is a constant. Consider the following tumor and immune system interaction model with three time delays

$$\begin{cases} \dfrac{dT}{dt} = rT(t-\tau) - kT(t)E(t), \\ \dfrac{dE}{dt} = f(aT(t) + (1-a)T(t-\delta)) + g(bE(t) + (1-b)E(t-\Delta)) - dE(t). \end{cases} \tag{87}$$

The technique of Adimy et al. [4] is used to study the stability of the positive equilibrium: it starts by considering the model with one delay and obtain a stable interval for the delay; fixing the first delay in its stable interval one then introduces the second delay and obtains a stable interval for it as well; next fix the first two delays in their stable intervals and determine the stability for the third delay. The stability of the positive equilibrium is thus obtained when the three delays are restricted in their corresponding intervals. Further numerical simulations indicate that the model exhibits long irregular oscillations and chaotic behaviors.

4.2. **Local analysis.** System (87) has equilibria (0, 0), $(0, E_i)$ and $(T_i, \frac{r}{k})$, where E_i is the positive root of $E_i^n - sE_i^{n-1} + 1 = 0$, and T_i is the positive root of equation $mT_i^v - pT_i^u + m = 0$ with $m = \frac{dr}{k} - \frac{sr^n}{k^n + r^n}$. The variational system of (87) at an equilibrium $(T_0,\ E_0)$ is

$$\begin{aligned} \frac{dT}{dt} &= rT(t-\tau) - kE_0T(t) - kT_0E(t), \\ \frac{dE}{dt} &= f'(T_0)(aT(t) + (1-a)T(t-\delta)) + g'(E_0)(bE(t) + (1-b)E(t-\Delta)) - dE(t). \end{aligned} \tag{88}$$

4.2.1. *The Trivial (Virgin State) Equilibrium.* For any $u, v > 0,\ n = 1$, the first equation of the variational system of (87) at the trivial equilibrium $(0, 0)$ is

$$\begin{cases} \dfrac{dT}{dt} = rT(t-\tau). \\ \dfrac{dE}{dt} = f'(0)T(t) + g'(0)E(t) - dE(t). \end{cases} \tag{89}$$

Noting $r > 0$, from the first equation of (89) it is easy to see that the trivial equilibrium of (87) is unstable for all $\tau, \delta, \Delta \geq 0$. That is, if there is no immune effector cells, the foreign cells will not die out once they invade, this is an obvious result.

4.2.2. *The Semi-Trivial (Immune State) Equilibrium.* For the stability of the semi-trivial or immune state equilibria $(0, E_i)$, it is easy to see that the characteristic equation of (88) at $(0, E_i)$ is

$$(\lambda - re^{-\lambda\tau} + kE_i)(\lambda - g'(E_i)(1-b)e^{-\lambda\Delta} + (d - g'(E_i)b)) = 0, \tag{90}$$

then the characteristic roots of (90) satisfy

$$\lambda + A - re^{-\lambda\tau} = 0 \ \text{ or } \ \lambda + C_1 - C_2 e^{-\lambda\Delta} = 0, \tag{91}$$

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

$$\begin{aligned} \tau_j &= 2\pi - \frac{1}{\sqrt{r^2 - A^2}} \arccos \frac{A}{r} + 2j\pi, \\ \Delta_j &= 2\pi - \frac{1}{\sqrt{C_2^2 - C_1^2}} \arccos \frac{C_1}{C_2} + 2j\pi, j = 0, 1, 2, ... \end{aligned} \tag{92}$$

One has the following stability and bifurcation results:

Theorem 4.1. *(i) Assume that $r < A$.*

(i-1) If $C_1 > C_2$, then the semi-trivial equilibrium $(0, E_i)$ of (87) is asymptotical stable for all $\tau \geq 0,\ \Delta \geq 0$;

(i-2) If $C_1 < -C_2$, then the semi-trivial equilibrium $(0, E_i)$ of (87) is unstable for $\Delta \geq \Delta_0,\ \tau \geq \tau_0$;

(ii) Assume that $r > A$ and $-C_2 < C_1 < C_2$.

(ii-1) Then the semi-trivial equilibrium $(0, E_i)$ of (87) is unstable for $0 < \tau < \sigma_0,\ 0 < \Delta < \sigma_0,\ r^2 - A^2 \neq C_2^2 - C_1^2$; and (87) undergoes Hopf bifurcation at $(0, E_i)$ as $\tau = \tau_j,\ \Delta \neq \Delta_j$ or $\tau \neq \tau_j,\ \Delta = \Delta_j$, where $\tau_j = 2\pi - \tau_0 + 2j\pi,\ \Delta_j = 2\pi - \Delta_0 + 2j\pi,\ j = 0, 1, 2 \cdots$;

(ii-2) If there is no integer k_1 such that $r^2 - A^2 \neq k_1(C_2^2 - C_1^2)$, then system (87) undergoes Hopf-Hopf bifurcation at $\tau = \tau_j,\ \Delta = \Delta_j,\ j = 0, 1, 2 \cdots$;

(ii-3) If there exist integers m_2 and n_2 such that $m_2^2(r^2 - A^2) = n_2^2(C_2^2 - C_1^2)$, then system (87) undergoes $m_2 : n_2$ resonant bifurcation at $\tau = \tau_j,\ \Delta = \Delta_j(\tau_j),\ j = 0, 1, 2 \cdots$.

Remark 3. If $A = r$ and there exists n such that $n = (\frac{r}{k})^n + 1$, then (90) has two zero roots, that is the semi-trivial equilibrium degenerates to the trivial equilibrium.

4.2.3. *The Positive (Coexistence) Equilibrium.* In this subsection, the stability and Hopf bifurcation of the positive (coexistence) equilibrium (T^*, E^*) of (87) is considered. The following results are on the number of positive equilibria.

Lemma 4.2. *Let $m = \frac{r}{k}(d - \frac{skr^{n-1}}{k^n + r^n}),\ T_1 = \sqrt[v]{\frac{u}{v-u}},\ B = \frac{pT_1^u}{1+T_1^v}$.*

(i) *System (87) has only one positive equilibrium* $(\frac{m}{p-m}, \frac{r}{k})$ *when* $u = v = 1$ *and* $0 < m < p$;
(ii) *System (87) has only one positive equilibrium* $(\sqrt[v]{\frac{m}{p-m}}, \frac{r}{k})$ *when* $u = v > 1$ *and* $0 < m < p$;
(iii) *System (87) has no positive equilibrium when* $u = v$ *and* $m < 0$ *or* $m \geq p$;
(iv) *System (87) has two positive equilibria* $(T^{2*}, \frac{r}{k})$ *and* $(T^{3*}, \frac{r}{k})$ *when* $0 < u < v$ *and* $0 < m < B$, *where* T^{2*} *and* T^{3*} *are the positive roots of* $mT^v - pT^u + m = 0$;
(v) *As* m *increases to* B, *the two positive equilibria* $(T^{2*}, \frac{r}{k})$ *and* $(T^{3*}, \frac{r}{k})$ *merge into one, and as* $m > B$, *this positive equilibrium disappears.*

In fact, the three different shapes of the stimulation function $f(T)$ can be illustrated as in Fig. 9(a), (b) and (c), that is, the number of the equilibria are the intersect points of the horizontal line $m = c$ (constant) and the curve of $f(T)$. Hence, the above results are obvious from Fig. 9. Then one can state the following results.

Theorem 4.3. *If* $0 < u < v$ *and* $m = f(T_1)$, *then (87) undergoes saddle-node bifurcation, where* m *and* $f(T)$ *are defined as above and where* $T_1 = \sqrt[v]{\frac{u}{v-u}}$.

If the delays τ, δ and Δ are zero, then the characteristic equation reduces to

$$\lambda(\lambda + d + g'(\frac{r}{k})) + kT^* f'(T^*) = 0, \tag{93}$$

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

Theorem 4.4. *Let* $\tau = \delta = \Delta = 0$.

(i) *When* $u = v$, *then the unique positive equilibrium* (T^*, E^*) *of (87) is a stable node.*
(ii) *When* $0 < u < v$, *(87) has two positive equilibria,* (T^{1*}, E^*) *and* (T^{2*}, E^*), *where* (T^{1*}, E^*) *is a stable node and* (T^{2*}, E^*) *is a saddle.*

When τ, δ, Δ increase from zero, it is possible to have Hopf bifurcation. Hence, in order to study whether (87) undergoes Hopf bifurcation when the delays τ, δ, Δ increase from zero, the case $u = v$ is considered in the rest of this section. Firstly, one has the results for the existence of the equilibria as $u = v$.

Theorem 4.5. *Let* $u = v$.

(i) *If* $m = 0$, *then (87) has two equilibria* $(0, 0)$ *and* $(0, \frac{r}{k})$;
(ii) *If* $m \geq p$ *or* $m < 0$, *then (87) has only one equilibrium* $(0, 0)$;
(iii) *If* $0 < m < p$, *then (87) has two equilibria* $(0, 0)$ *and* $(\frac{m}{p-m}, \frac{r}{k})(u = v = 1)$ *or* $(\sqrt[u]{\frac{m}{p-m}}, \frac{r}{k})(u = v > 1)$.

The dynamical behavior of the positive equilibrium in case (iii) is important and difficult and is considered in the following. If $u = v$ and $0 < m < p$, $m = \frac{k}{r}(d - \frac{skr^{n-1}}{k^n + r^n})$, then (87) has only one positive equilibrium (T^*, E^*) with $E^* = \frac{r}{k}$. The characteristic equation of (88) at (T^*, E^*) is

$$\begin{vmatrix} \lambda - re^{-\lambda\tau} + kE^*, & kT^* \\ -f'(T^*)a - f'(T^*)(1-a)e^{-\delta\lambda}, & \lambda - (g'(E^*)b - d) - (1-b)g'(E^*)e^{-\Delta\lambda} \end{vmatrix} = 0, \tag{94}$$

where $(T^*, E^*) = (\frac{m}{p-m}, \frac{r}{k})$ as $u = v = 1$ and $(T^*, E^*) = (\sqrt[u]{\frac{m}{p-m}}, \frac{r}{k})$ as $u = v > 1$ are defined as above. The main results are established in two steps.

Step I. Firstly, consider the case $b = 1$ and $g'(E^*)b = d$.

(a) If $a = 1$, from (94), the characteristic equation of (88) at (T^*, E^*) is

$$\lambda^2 + r\lambda + A_1 - \lambda r e^{-\lambda\tau} = 0, \tag{95}$$

where $A_1 = f'(T^*)kT^* \geq 0$. Noting $r = kE^* \geq 0$, in order to consider the distribution of the roots of equation (95), we give a result as follows.

Lemma 4.6. *Let $\tau = \tau_j^0$. Then (95) has a pair of purely imaginary roots $\pm i\omega_0$ with $\omega_0^2 = A_1$, where $\tau_j^0 = 2j\pi,\ j = 0, 1, 2\cdots$.*

Let $\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$ be the root of (95) satisfying $\alpha(\tau^1_{\pm j}) = 0$, $\omega(\tau^1_{\pm j}) = \omega_\pm$, then we have the following results.

Lemma 4.7. *(i) If $A_1 > 0$, then $\alpha'(\tau_j^0) = 0$, $\alpha''(\tau_j^0) < 0$. Hence, all roots of (95) have negative real parts except the purely imaginary roots $+i\omega$, and all purely imaginary roots $\pm i\omega$ are obtained as $\tau_j^0 = 2j\pi,\ j = 0, 1, 2\cdots$.*
(ii) There exists a $\tau' < 2\pi$ such that (T^*, E^*) is stable as $\tau \in (0, \tau')$.

(b) If $a \neq 1$, then the characteristic equation (94) is

$$\lambda^2 + \lambda(-re^{-\lambda\tau} + kE^*) + A_1(a + (1-a)e^{-\lambda\delta}) = 0. \tag{96}$$

From Hopf bifurcation theorem and the results of Ruan [102], we obtain the following results.

Theorem 4.8. *Assume $A_1 > 0$, if $|a - \frac{1}{2}| \ll 1$, $\tau \in (0, \tau')$, then (96) has purely imaginary roots $\pm i\omega_n$ with $\delta = \delta_j^n, j = 0, 1, 2\cdots$, where ω_n are the positive roots of*

$$\begin{aligned} g(\omega, h) =& \omega^4 + \omega^2(2r^2 - 2A_1 a + 2\omega r \sin\omega\tau - 2r^2\cos\omega\tau) \\ & - 2\omega A_1 ar\sin\omega\tau + A_1^2 a^2(1 - h^2). \end{aligned}$$

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

$$\delta_j^n = \begin{cases} \frac{1}{\omega_n}(2\pi - \arccos\frac{\omega_n^2 - aA_1 + \omega_n r\sin\omega_n\tau}{A_1(1-a)} + 2j\pi), & r > \cos\omega_n\tau \\ \frac{1}{\omega_n}(\arccos\frac{\omega_n^2 - aA_1 + \omega_n r\sin\omega_n\tau}{A_1(1-a)} + 2j\pi), & r < \cos\omega_n\tau. \end{cases} \tag{97}$$

Moreover, if

$$2\omega\cos\delta\omega + \omega r\tau\cos\omega(\delta - \tau) + r(\sin\delta\omega - \sin\omega(\delta - \tau)) \neq 0, \tag{98}$$

then equation (87) undergoes a Hopf bifurcation at (T^*, E^*).

Remark 4. The parameter a is to show that the change of $E(t)$ at time t is decided by the qualities of $E(t)$ not only at time t but also at time $t - \tau$. In fact, it was chosen $a = \frac{1}{2}$, which shows that the qualities of $E(t)$ at time t and $t - \tau$ have the same effect to the change of $E(t)$. For $a < \frac{1}{2}$, it is easy to obtain $g(0, h) < 0$, then (96) has purely imaginary roots obviously, which shows that the change of $E(t)$ depends more on time $t - \tau$ as $a < \frac{1}{2}$. This is relevant to the model of Mayer et al. [87]. Note that $g(\omega, 0)|_{\omega=0} = -A_1^2 < 0$, then one has the following result on Hopf bifurcation in the original delayed model (86) of Mayer et al. [87].

Corollary 1. *If $a = 0$ and (98) hold, then (87) undergoes a Hopf bifurcation at (T^*, E^*).*

Step II. In the second step, consider the more general case $g'(E^*)b \neq d$. There are three subcases. (a) $\Delta = 0, \delta = 0$; (b) $\Delta = 0$, $\delta \neq 0$; (c) $\Delta\tau\delta \neq 0$.

(a) If $\Delta = 0, \delta = 0$, the characteristic equation of (88) at (T^*, E^*) is

$$\lambda^2 + B_1\lambda + B_2 + (B_3\lambda + B_4)e^{-\lambda\tau} = 0, \tag{99}$$

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

(H_1) $B_4 + B_2 > 0$, $B_3 + B_1 > 0$.

(H_2) $B_3^2 - B_1^2 + 2B_2 < 0$, $B_2^2 - B_4^2 > 0$ or $(\mathrm{B}_3^2 - \mathrm{B}_1^2 + 2\mathrm{B}_2)^2 < 4(\mathrm{B}_2^2 - \mathrm{B}_4^2)$.

(H_3) $B_2^2 - B_4^2 \leq 0$ or $\mathrm{B}_3^2 - \mathrm{B}_1^2 + 2\mathrm{B}_2 > 0$ and $(\mathrm{B}_3^2 - \mathrm{B}_1^2 + 2\mathrm{B}_2)^2 = 4(\mathrm{B}_2^2 - \mathrm{B}_4^2)$.

(H_4) $B_3^2 - B_1^2 + 2B_2 > 0$, $B_2^2 - B_4^2 > 0$ and $(\mathrm{B}_3^2 - \mathrm{B}_1^2 + 2\mathrm{B}_2)^2 > 4(\mathrm{B}_2^2 - \mathrm{B}_4^2)$.

Define

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

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

$$\tau_j^\pm = \begin{cases} \frac{1}{\omega_\pm}\left(2j\pi + \arccos\{\frac{(B_4 - B_1B_3)\omega_\pm^2 - B_4B_2}{B_3^2\omega_\pm^2 \pm B_4^2}\}\right), \\ \qquad\qquad\qquad \text{if } B_4B_1 + B_3(\omega_\pm^2 - B_2) > 0, \\ \frac{1}{\omega_\pm}\left((2j+2)\pi - \arccos\{\frac{(B_4 - B_1B_3)\omega_\pm^2 - B_4B_2}{B_3^2\omega_\pm^2 \pm B_4^2}\}\right), \\ \qquad\qquad\qquad \text{if } B_4B_1 + B_3(\omega_\pm^2 - B_2) < 0. \end{cases} \tag{100}$$

Using the results of Cooke and Grossman [29], and Ruan [102], one obtains the following results.

Theorem 4.9. *Let (H_1) hold and $\tau_j^\pm (j = 1, 2, \cdots)$ be defined by (100).*

- *(i) If (H_2) holds, then the positive equilibrium (T^*, E^*) of (87) is asymptotically stable for all $\tau \geq 0$.*
- *(ii) If (H_3) holds, then (T^*, E^*) is stable for all $\tau \in (0, \tau_0^+)$ and unstable for $\tau > \tau_0^+$. Moreover, system (87) undergoes Hopf bifurcation at (T^*, E^*) as $\tau = \tau_j^+$, $j = 0, 1, 2 \cdots$.*
- *(iii) If (H_4) holds, then there is a positive integer l such that (T^*, E^*) is stable for*

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

and unstable for

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

(b) If $\Delta = 0$, $\delta \neq 0$ $(a \neq 1)$, then the characteristic equation (99) can be written as

$$\lambda^2 + B_1\lambda + B_2 - A_1(1-a) + e^{-\lambda\tau}(B_3\lambda + B_4) + A_1(1-a)e^{-\lambda\delta} = 0. \tag{101}$$

Then one has the following result.

Theorem 4.10. *Assume that (H_1) holds, if $B_2^2 - B_4^2 < 0$, $\tau < \tau_0, \tau_0 = \min\{\tau_0^+, \tau'\}$, then (101) has purely imaginary roots $\pm i\omega_{1n}$ with $\delta = \delta_j^n, j = 0, 1, 2, \cdots$, where ω_{1n} are the positive roots of*

$$\begin{aligned} g_1(\omega) =&(B_2 - \omega^2 - A_1(1-a) + B_4\cos\omega\tau + B_3\omega\sin\omega\tau)^2 \\ &+ (B_1\omega_{1n} + B_3\omega\cos\omega\tau - B_4\sin\omega\tau)^2 - A_1^2(1-a)^2 \end{aligned} \tag{102}$$

and

$$\delta_j^n = \begin{cases} \frac{1}{\omega_{1n}}\left(2\pi - \arccos\frac{\omega^2 - B_2 + A_1(1-a) - B_4\cos(\omega\tau) - B_3\omega\sin(\omega\tau)}{A_1(1-a)} + 2j\pi\right), & \sin\omega_{1n}\delta < 0, \\ \frac{1}{\omega_{2n}}\left(\arccos\frac{\omega^2 - B_2 + A_1(1-a) - B_4\cos(\omega\tau) - B_3\omega\sin(\omega\tau)}{A_1(1-a)} + 2j\pi\right), & \sin\omega_{1n}\delta > 0. \end{cases} \tag{103}$$

Moreover, if

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

then equation (87) undergoes Hopf bifurcation at (T^*, E^*) *as* $\delta = \delta_n$.

(c) If $\Delta\tau\delta \neq 0$, the characteristic equation of (88) is

$$\begin{aligned} &\lambda^2 + B_1'\lambda + B_2' - A_1(1-a) + e^{-\lambda\tau}(B_3\lambda + B_4' + rB_5 e^{-\Delta\lambda}) \\ &\quad - (\lambda + kE^*)B_5 e^{-\Delta\lambda} + A_1(1-a)e^{-\lambda\delta} = 0, \end{aligned} \tag{104}$$

where $B_1' = B_1 + B_5,\ B_2' = B_2 + rB_5,\ B_4' = B_4 - rB_5$, and $B_5 = g'(E^*)(1-b)$. In order to study the stability of (T^*, E^*) for $\Delta \neq 0$, we introduce a result which can be proved similarly as Theorem 7 of Adimy et al. [4].

Lemma 4.11. *If all roots of equation (101) have negative real parts for* $\tau \in (0, \tau_0^+)$ *and* $\delta \in (0, \delta_0)$, *where* $\delta_0 = \min_{n\in N}\{\delta_0^n\}$, *then there exists* $\Delta^* = \Delta(\tau, \delta)$ *such that all roots of (104) have negative real parts when* $\Delta \in (0, \Delta^*(\tau, \delta))$, *and the positive equilibrium* (T^*, E^*) *of (87) is locally asymptotically stable.*

Lemma 4.11 gives the existence of Δ^*, in fact, one can compute Δ^* in a similar way as above for other critical delay values and have the following result.

Theorem 4.12. *Assume* (H_1) *and* $B_2^2 < B_4^2$ *hold, if* $\tau < \tau_0, \delta < \delta_0$, *then (101) has purely imaginary roots* $\pm i\omega_{2n}$ *with* $\Delta = \Delta_j^n, j = 0, 1, 2, \cdots$, *where* ω_{2n} *are the positive roots of*

$$\begin{aligned} & g_3(\omega_{2n}) \\ = \ & (B_2' - \omega_{2n}^2 - A_1(1-a)(1-\cos\omega_{2n}\delta) - B_5 r\cos\omega_{2n}\Delta + B_5\omega_{2n}\sin\omega_{2n}\Delta)^2 \\ & + (B_1'\omega_{2n} + rB_5\sin\omega_{2n}\Delta - \omega B_5\cos\omega_{2n}\Delta - A_1(1-a)\sin\omega_{2n}\delta)^2 \\ & - B_4'^2 - B_3^2\omega_{2n}^2 - B_5^2 r^2 - 2B_4' B_5 r\cos\omega_{2n}\Delta + 2B_3' B_5\omega_{2n} r\sin\omega_{2n}\Delta, \end{aligned} \tag{105}$$

where

$$\Delta_j^n = \begin{cases} \frac{1}{\omega_{2n}}\left(2\pi - \arccos\frac{G(\omega_{2n})}{B_5(\omega_{2n} + r\sin\omega_{2n}\tau)^2 + B_5(r\cos\omega_{2n}\tau - kE^*)^2} + 2j\pi\right), & \sin\omega_{2n}\Delta < 0 \\ \frac{1}{\omega_{2n}}\left(\arccos\frac{G(\omega_{2n})}{B_5(\omega_{2n} + r\sin\omega_{2n}\tau)^2 + B_5(r\cos\omega_{2n}\tau - kE^*)^2} + 2j\pi\right), & \sin\omega_{2n}\Delta > 0 \end{cases} \tag{106}$$

with

$$\begin{aligned} G(\omega_{2n}) = & (A_1(1-a) + \omega_{2n}^2 - B_2')E^* k + \omega_{2n}^2 B_1' + A_1(1-a)r\cos\omega_{2n}(\delta+\tau) \\ & + \cos\omega_{2n}\tau((B_3 - r)\omega_{2n}^2 - A_1(1-a)(ek + r) - ekB_4' + rB_2') \\ & + \omega_{2n}\sin\omega_{2n}\tau(rB_1' - B_3 ek - B_4') + B_3\omega_{2n} r\sin 2\omega_{2n}\tau \\ & - A_1(1-a)\omega_{2n}\sin\delta\omega_{2n} + rB_4'\cos 2\omega_{2n}\tau. \end{aligned} \tag{107}$$

Moreover, if

$$\begin{aligned}&-\omega(2E^*k+B_3r\tau)\cos\delta\omega+(-1+a)A_1\delta\omega\cos(\Delta-\delta)\omega-B_5\omega r\tau\cos\omega\tau\\&\quad+(B_3\omega-B_4'\omega\tau+B_3E^*k\omega\tau)\cos\omega(\Delta-\tau)+2\omega r\cos\omega(\Delta+\tau)\\&\quad+(B_3r-B_1'E^*k-2\omega^2-B_4'r\tau)\sin\Delta\omega+A_1\delta E^*k(1-a)\sin(\Delta-\delta)\omega\\&\quad+(B_4'E^*k\tau-B_3E^*k+B_3\omega^2\tau)\sin\omega(\Delta-\tau)+B_1'r\sin\omega(\Delta+\tau)\\&\quad-B_5r(1+E^*k\tau)\sin\omega\tau-A_1(1-a)\delta r\sin\omega(\Delta-\delta+\tau)\neq 0,\end{aligned}\tag{108}$$

then equation (87) undergoes Hopf bifurcation at (T^*, E^*).

4.3. **Numerical simulations.** In this subsection, some numerical simulations are presented to illustrate the results obtained in section 4.2. Choose two parameter sets as in Mayer et al. [87], i.e.,
(I): $a = 0,\ b = 0,\ n = 1,\ u = v = 1,\ r = 1.8,\ k = 3,\ p = 2,\ s = 1.5,\ d = 1$;
(II): $a = 0,\ b = 0,\ n = u = v = k = d = 1,\ r = 1.2,\ p = 0.28,\ s = 2$.
From the above analysis one knows that the the trivial and semi-trivial equilibria are unstable and the positive equilibrium is stable. For $\tau = 0.3,\ \delta = 0.3,\ \Delta = 1$ the simulations are given in Fig. 10.

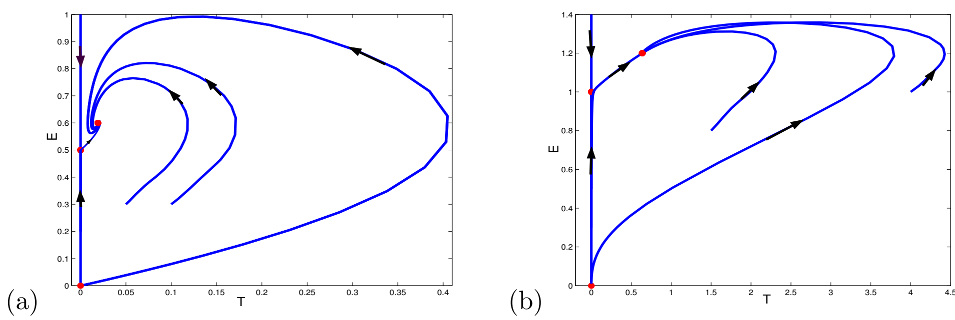


FIGURE 10. The phase portraits of system (87): (a) with parameter set (I); (b) with parameter set (II).

(i) First we simulate the results in Theorems 4.9 and 4.10. Let $r = 0.6,\ k = 1.3,\ p = 0.3,\ s = 0.2,\ d = 0.5,\ a = 0.1,\ n = 3,\ u = 2,\ v = 2$. For this case, (87) has two equilibria $(0, 0)$ and $(1.563,\ 0.461538)$. Since $(0, 0)$ is unstable, one only needs to consider the properties of the positive equilibrium $(1.563,\ 0.461538)$. If $\delta = \Delta = 0$, (100) implies that (99) has only a pair of purely imaginary roots $\pm i\omega$ with $\omega = 0.416274$ as $\tau_0 = 3.8641$, and the positive equilibrium $(1.563,\ 0.461538)$ is locally stable as $\tau < \tau_0$. According to Theorem 4.10, the imaginary roots $\pm i\omega_{1n}$ of (101) are the roots of

$$\begin{aligned}&-0.010245-0.36749\omega^2+\omega^4+(0.0558983+0.36\omega^2)\cos^2(3.8641\omega)\\&\quad+(-0.142236\omega+1.2\omega^3)\sin(3.8641\omega)+(0.0558983+0.36\omega^2)\sin^2(3.8641\omega)\\&\quad+\cos(3.8641\omega)(-0.100101+0.189143\omega^2)=0,\end{aligned}\tag{109}$$

which are the points of intersection of functions

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

and

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

Then the only one pair of purely imaginary roots are $\pm 0.273i$.

When $\tau = \tau_0$, recalling (103), by a direct computation one has $\delta_0 = 15.1378$. Thus, the positive equilibrium (T^*, E^*) is stable when $\tau < \tau_0$, $\delta < \delta_0$. In fact, choose delays as $\tau = 4 < \tau_0$, $\delta = 20 < \delta_0$, then the positive equilibrium is stable (Fig. 11(a)(b)). Choose parameters as $\tau = \tau_0 = 3.8641$, one knows that (87) has bifurcated periodic solutions (see Fig. 11(c)(d)).

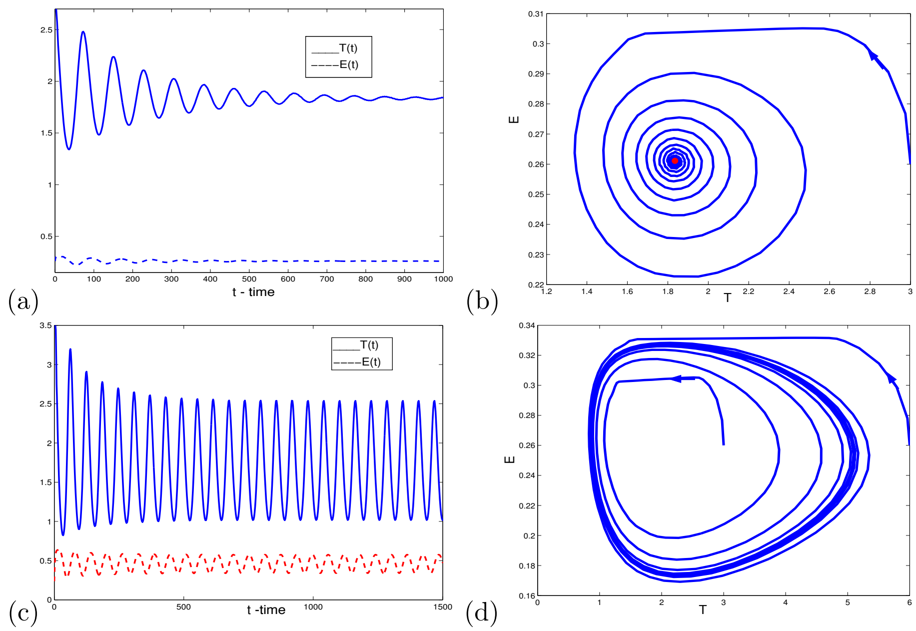


FIGURE 11. (a) The converging solutions of system (87) in terms of t when $\tau = 4, \delta = 20$; (b) The solution trajectories of system (87) spiral toward the positive equilibrium in the (T, E)-plane when $\tau = 4, \delta = 20$; (c) The periodic solutions of system (87) in terms of t when $\tau = \tau_0$; (d) The periodic trajectories of system (87) in the (T, E)-plane.

The dynamical behavior of the positive equilibrium (T^*, E^*) (stable or unstable) can be seen in Fig. 12. The critical boundary respects the possible bifurcation values, which are given by (103). On the other hand, one can see rich dynamical behaviors of the positive equilibrium as τ(respectively δ) increases, a finite number of stability switches may occur.

For the above parameters, if a increases from 0.1 to 0.5, the dynamical behavior of the model does not change compared with Fig. 11. If a keeps increasing from 0.5 to 0.9, then the functions $f(\omega)$ and $h(\omega)$ have no points of intersection. That is, when $\tau < \tau_0$, as a increases to 0.9, there are no characteristic roots passing through the imaginary axis. Hence, the positive equilibrium $(0.26087,\ 4.14083)$ of (87) is stable when $\tau < \tau_0$ and $\delta > 0$.

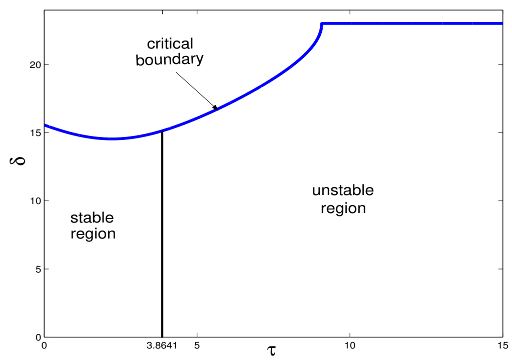


FIGURE 12. Stability diagram of system (87) on the (τ, δ)-delay parameter space.

The stable region of the positive equilibrium becomes bigger and bigger when a increases from 0.1 to 0.5 then to 0.9. Hopf bifurcation may occur when τ and δ are on the critical boundary; that is, the dynamical behavior of the positive equilibrium changes when the parameter a from 0 to 1. Thus, it is necessary to consider a in the model of Mayer et al. [87].

(ii) To simulate the results in Theorem 4.12 using the above parameter set, one needs to compute the roots of (105). For simplicity, only consider the case $a = 0.1, b = 0.1$. Similarly, from Fig. 13 one knows that (105) has two pairs of imaginary roots $\pm i\omega_{10}$ and $\pm i\omega_{20}$ with $\omega_{10} = 0.2651$ and $\omega_{20} = 0.2809$. But for $\omega_{10} = 0.2651$, there is no Δ defined in (106) can be found. Hence, the characteristic equation of (88) has only one pair of purely imaginary roots $\pm i\omega_{20}$ with $\Delta_0 = 2.0592$.

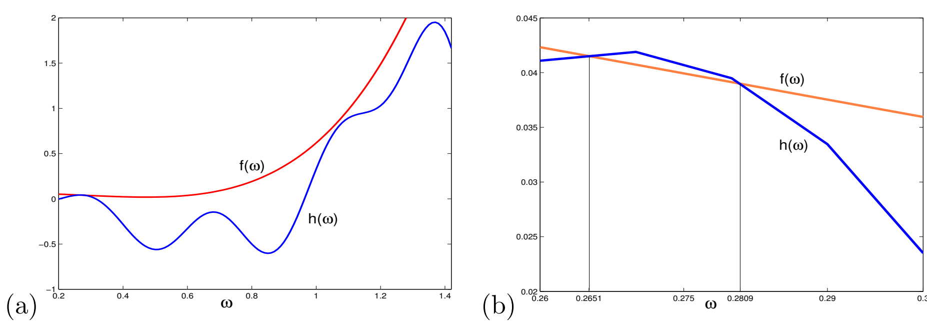


FIGURE 13. (a) The locations of $f(\omega)$ and $h(\omega)$ when $a = 0.1, b = 0.1$. (a) $0.2 < \omega < 1.5$; (b) $0.26 < \omega < 0.3$.

Let $\tau_0 = 3.8641$, $\delta_0 = 15.1378$, $\Delta_0 = 2.0592$. From the result in last section, one knows that the solutions of (87) are stable when $\tau < \tau_0$, $\delta < \delta_0$, $\Delta < \Delta_0$, choose $\tau = 3.8, \delta = 13.5$, $\Delta = 2$, the simulations are presented in Fig. 14(a)(b). If $\tau = \tau_0$, $\delta = \delta_0$, $\Delta = \Delta_0$, then system (87) undergoes Hopf bifurcation, the bifurcating periodic solutions can be seen in Fig. 14(c)(d).

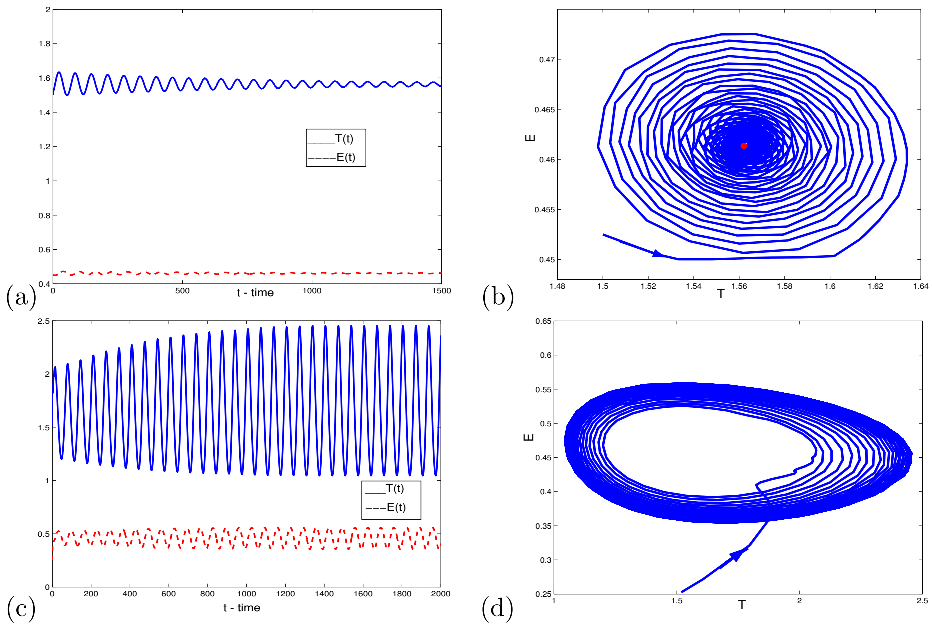


FIGURE 14. (a) The stable solutions of system (87) when $\tau = 3.8, \delta = 13.5,\ \Delta = 2$; (b) The solution trajectory of system (87) converges to the positive equilibrium in the (T, E) plane; (c) The periodic solutions $T(t)$ and $E(t)$ of system (87) in terms of t when $\tau = \tau_0 = 3.8641,\ \delta = \delta_0 = 15.1378,\ \Delta = \Delta_0 = 2.0592$; (d) The periodic trajectories of system (87) in the (T, E) plane.

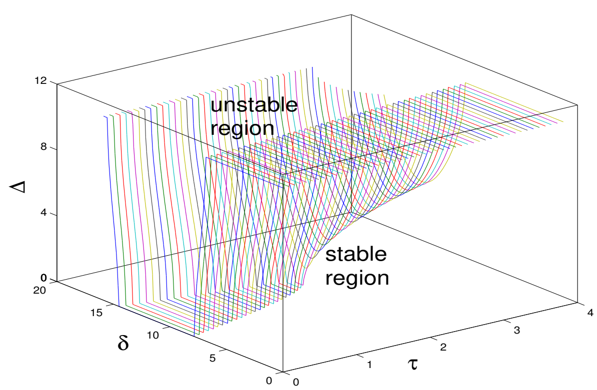


FIGURE 15. The stability diagram of the positive equilibrium for system (87) in the $(\tau, \delta,\ \Delta)$ parameter space.

Noting Lemma 4.7, let $r = 0.6,\ k = 1.3,\ p = 0.3,\ s = 0.2,\ d = 0.5,\ n = 3,\ u = 2,\ v = 2$. If $a = 0.1,\ b = 0.1$, then we know that the positive equilibrium $(1.563,\ 0.461538)$ of (87) is stable when $\tau < \tau_0$, $\delta < \delta_0$ and $\Delta < \Delta^*(\tau, \delta)$, where

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

with

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

With the above parameters, the stable region of (87) is given in Fig. 15 in the $(\tau, \delta,\ \Delta)$ parameter space.

(iii) In fact, model (87) exhibits more complicated dynamical behavior than that observed in Mayer et al. [87]. Now we give more simulations to show the existence of irregular long periodic oscillations. Ripples can be observed in the figures. If $a \neq 0, b \neq 0$, choose parameters set $a = 0.5, b = 0.9, n = 3, u = 1, v = 3, r = 2, k = 3, p = 2, s = 1, d = 1.2$. Then we have the following simulations with different values of the time delays τ, δ and Δ.

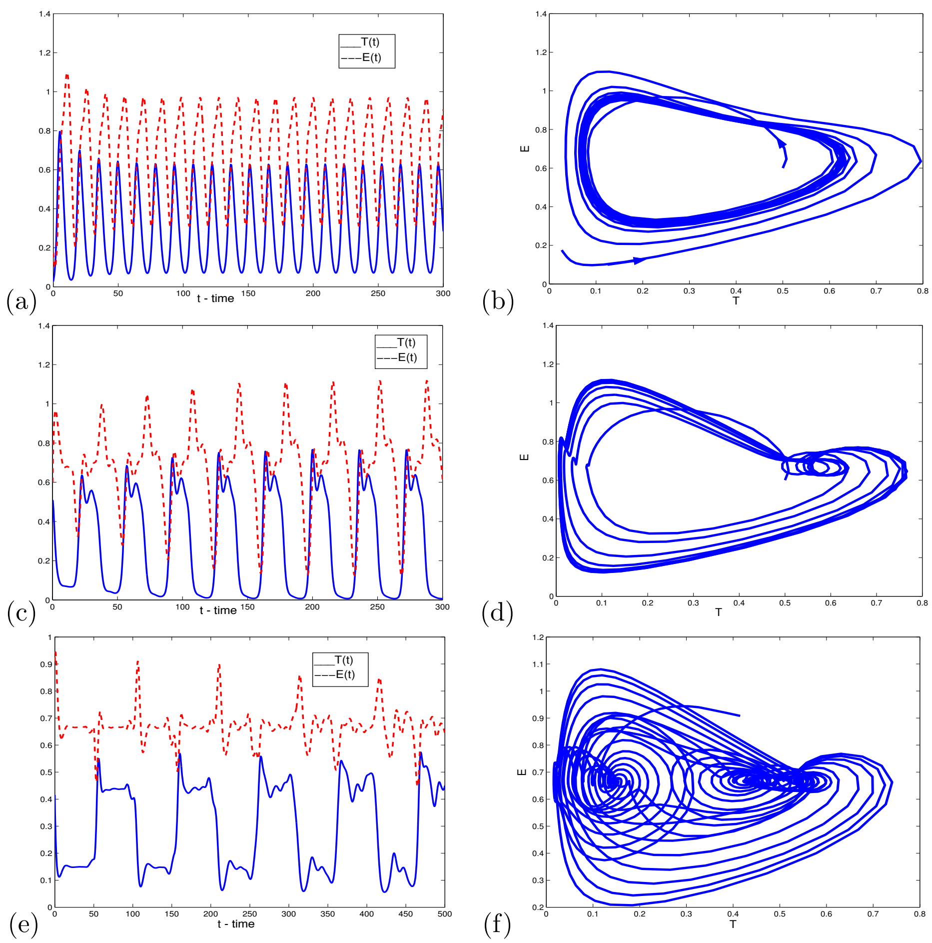


Figure 16. (a)(b) The regular periodic oscillations in system (87) with $\tau = 0.5, \delta = 5, \Delta = 8$; (c)(d) The irregular long periodic oscillations in system (87) with $\tau = 0.5, \delta = 15, \Delta = 8$; (e)(f) The chaotic solutions in system (87) with $\tau = 0.5, \delta = 50, \Delta = 38$.

These simulations demonstrate that the tumor and immune system interaction model with three time delays exhibits very rich and complex dynamical behaviors. Although the positive equilibrium is stable when $\tau < \tau_0$, $\delta < \delta_0$ and $\Delta < \Delta_0$, but when the delays increase, the dynamical behavior becomes more and more complex. When we fix the $\tau = 0.5$ and increase δ and Δ gradually, the dynamical behavior changes from regular periodic (Fig. 16(a)(b)) to irregular long periodic (Fig. 16(c)(d)) and finally chaotic (Fig. 16(e)(f)). Therefore, the time delays play a crucial role in determining the nonlinear dynamics of the tumor and immune system interaction model (87). Notice that Mayer et al. [87] provided some empirical data on the number of phenotypically identified natural killer cells ($CD16^+$, $CD56^+$) versus total tumor size during the course of a metastatic disease (Fibrosarcoma) which exhibit chaotic behavior: they fluctuate irregularly and unpredictably. Mayer et al. [87] pointed out that their model is unable to produce any kind of chaotic behavior since it is only two-dimensional. By modifying their model, we are able to demonstrate numerically that the two-dimensional model with three delays can produce chaotic behavior which, in some sense, supports the empirical data provided by Mayer et al. [87].

5. **Discussion.** We have reviewed some recent results on the nonlinear dynamics of two-dimensional differential equations with multiple delays which model the interactions between tumor cells and effector cells of the immune system. In section 2 we discussed a tumor-immune system interaction model with a single delay (which is a reduced model of Kuznetsov et al. [74] with a single delay and was considered by Gałach [56] and Bi and Xiao [15]) and provided results on the existence and local stability of equilibria as well as the existence of Hopf bifurcation in the model when the delay varies. In section 3 we studied a tumor-immune system interaction model with two delays (which is a generalized model of d'Onofrio et al. [42] and was studied by Bi and Ruan [13]) and demonstrated that the model undergoes various possible bifurcations including Hopf, Bautin, Fold-Hopf (zero-Hopf), and Hopf-Hopf bifurcations. In section 4 we considered a tumor-immune system interaction model with three delays (which was proposed by Mayer et al. [87] and analyzed by Bi et al. [14]) and showed that the model exhibits more complex behaviors including chaos. Various numerical simulations were presented to illustrate the nonlinear dynamics of the delayed tumor-immune system interaction models.

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 [95]). This is the elimination process of the cancer immunoediting (Dunn [44, 45]). Our analysis on the existence and stability of the tumor-free equilibrium in all three models (2), (19) and (87) 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 [95]). This is the escape process of the cancer immunoediting (Dunn [44, 45]). Our analysis on the immune-free equilibrium $P_3(T_3, 0)$ of the model (19) with two delays 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 [44, 45], Schreiber et al. [106]). Koebel et al.

[71] used a mouse model of primary chemical carcinogenesis to demonstrate that equilibrium occurs. Their results reveal that the immune system of a naive mouse can restrain cancer growth for extended time periods, that it, the tumor cells and effector cells of the immune system coexist for a long time. Our results on the existence of periodic solutions via bifurcations (Hopf, Bautin, Fold-Hopf (zero-Hopf), Hopf-Hopf) in all three models 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 regular and irregular periodic oscillations in the tumor and immune interaction model (87) with three delays demonstrates the phenomenon of long-term tumor relapse which have been observed in some related tumor and immune system models (d'Onofrio [42], Kirschner and Panetta [70], Kuznetsov et al. [74]). Cancer dormancy is a state in which cancer cells persist in a host without significant growth (Wilkie [120]). The regular periodic oscillations describe the equilibrium process (expansion of transformed cells is held in check by immunity) of cancer immunoediting in the dual host-protective and tumor-promoting actions of immunity and support the experimental observations of Koebel et al. [71] that the immune system of a naive mouse can restrain cancer growth for extended time periods. The irregular periodic oscillations suggest that with temporarily delay the immune response may progress the cancer to a more aggressive state.

We should emphasize that the literature on modeling tumor-immune system interactions is huge, see reviews by Anderson and Maini [7], Cristini et al. [31], dePillis et al. [34], Eftimie et al. [47], Freedman [53], Friedman [54], Konstorum et al. [72], Mahlbacher et al. [84], Szymańska et al. [110], Wilkie [120], and books of d'Onofrio et al. [41], Eladdadi et al. [48], and Kuang et al. [73]. In order to understand the nonlinear dynamics in particular various bifurcations in the tumor-immune system interaction models, we focused only on two-dimensional delay differential equations. There are many interesting issues and questions on modeling and analyzing tumor-immune dynamics.

(a) The effect of therapies. In analyzing models (2), (19) and (87), the effect of therapies (chemotherapy, immunotherapy, radiotherapy) was completely ignored (Abdulrashid et al. [1], Barbarossa et al. [12], d'Onofrio [37, 38, 39], Rordriguez-Perez et al. [101]). It will be very interesting and challenging to study the effect of therapies in particular immunotherapy (constant, periodic or impulsive) (Konstorum et al. [72]) on the nonlinear dynamics of the tumor and immune system interaction models with delays (see d'Onofrio et al. [42] for example). In particular, immunotherapy is now very effective and promising in harnessing the immune system to battle tumors (Couzin-Frankel [30], Mellman et al. [89]), it will be very important to help design therapies (constant, periodic or impulsive) and seek for optimal treatments. From the dynamical system point of view, one particular interesting question is the existence of resonance when periodic chemotherapy (Andersen and Mackey [6], Webb [116]) is applied to delayed tumor-immune system interaction models.

(b) Bogdanov-Takens bifurcation. We studied system (19) under the assumption that it has only one positive equilibrium. As Table 1 and the examples showed such models could have multiple positive equilibria. Correspondingly, the systems can exhibit more degenerate bifurcations including Bogdanov-Takens bifurcation (see Liu et al. [79] for an ODE model of tumor and immune system interaction and Xiao and Ruan [125] for a delayed predator-prey model) and higher codimension bifurcations. In fact, even for the reduced ODE model (1) we expect that it could exhibit bifurcations of co-dimension three.

(c) Three- and higher-dimensional models with delays. The two-dimensional models are over-simplified as the tumor-immune system interactions are very complex and involve more components, more reasonable models should include three or more variables. For instance, Grossman and Berke [57] proposed a three-dimensional model with delay consisting of specific precursor T-cells, proliferating cells that are stimulated by antigenic tumor cells, and mature cytotoxic (killer) cells. Villasana and Radunskaya [115] considered a three-dimensional delay differential equations model consisting of immune cells, tumor cells during interphase, and population of tumor during mitosis. Dong et al. [36] considered a three-dimensional model with delay which describes the interactions between effector cells, cytotoxic T lymphocytes and helper T cells. The techniques and results used in treating the third-order transcendental equations in Ruan et al. [105] can be employed to analyze the stability and bifurcations in such three-dimensional models with delays. Higher-dimensional models with delays can be found in Abdulrashid et al. [1], Barbarossa et al. [12], Feyissa and Banerjee [51], Qomlaqi et al. [99], Yu and Wei [126], Yu et al. [127, 128], and the references cited therein.

(d) Age-structured tumor models. Once the growth and proliferation of tumor cells is concerned, different stages (quiescent phase G_0, first gap G_1, synthesis stage S, second gap G_2, and mitosis stage M) of the cell-cycle need to be considered (Vermeulen et al. [113]) and age-structured models play a crucial role in describing the population dynamics of tumor cells, see for example Arino et al. [9], Billy et al. [17], Brikci et al. [20], Clairambault et al. [28], Dyson et al. [46], Gabriel et al. [55], Gyllenberg and Webb [61], Liu et al. [82], Spinelli et al. [108], and the references cited therein. This also brings various challenges in analyzing (mathematically and computationally) these age-structured tumor models. For instance, even for a linear age-structured model of tumor growth with quiescence, Gyllenberg and Webb [61] observed the existence of periodic solutions which seems to be induced by Hopf bifurcation. To show the existence of Hopf bifurcation in such age-structured tumor model, one may apply the recent developed theory in Magal and Ruan [83]. It should be pointed out that the above mentioned age-structured models focused on the growth and proliferation of tumor cells and did not include the interaction of tumor cells and the immune system (which is the focus of this review paper). It becomes interesting to propose reasonable age-structured models to characterize tumor-immune dynamics.

(e) Combine models with clinical data. A mathematical model is only suitable to simulate and predict novel treatment protocols if it can fit and predict the data of known therapies (Brady and Enderling [19], Konstorum et al. [72]). Thus it is desirable to combine models with clinical data; that is, the models have to be validated by calibrating the data. The mathematical analysis and numerical simulation will help in understand the properties of the models. The utmost goal of using mathematical models to describe the interactions between tumors and immune system and studying the nonlinear dynamics of these models is to provide scientific insights on the dynamics of tumor growth and immune response, and to help design optimal scheduling and dosage of treatment.

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