Available online at www.sciencedirect.com

ScienceDirect

Mathematics and Computers in Simulation 198 (2022) 289–311

MATHEMATICS AND COMPUTERS IN SIMULATION

www.elsevier.com/locate/matcom

Original Articles

Bifurcations and multistability in a virotherapy model with two time delays

Qinrui Dai, Mengjie Rong, Ren Zhang*

School of information and Engineering, Wuhan Huaxia University of Technology, Wuhan 430000, China

Received 10 September 2021; received in revised form 3 December 2021; accepted 20 February 2022
Available online 4 March 2022

Abstract

In this paper, we establish a delayed virotherapy model including infected tumor cells, uninfected tumor cells and free virus. In this model, both infected and uninfected tumor cells have special growth patterns, and there are at most two positive equilibria. We mainly analyze the stability and Hopf bifurcation of the model under different time delays. For the model without delay, we study the Hopf and Bogdanov–Takens bifurcations. For the delayed model, by center manifold theorem and normal form theory of functional differential equation, we study the direction of Hopf bifurcation and stability of the bifurcated periodic solution. Moreover, we prove the existence of Zero-Hopf bifurcation. Finally, some numerical simulations show the results of our theoretical calculations, and the dynamic behaviors near Zero-Hopf and Bogdanov–Takens point of the system are also observed in the simulations, such as bistability, periodic coexistence and chaotic behavior.

Keywords: Virotherapy; Double time delays; Bogdanov–Takens bifurcation; Zero-Hopf bifurcation

1. Introduction

With the development of genetic engineering, the virotherapy has become a new therapy for cancer [5,15]. Under the action of free virus, tumor cells are divided into two parts, one for infected tumor cells and the other for uninfected tumor cells [1]. To study the effect of viral therapy on tumor development, a series of mathematical models have been established. For example, a delay differential equation model for cell cycle-specific cancer virotherapy is studied, and its stability is analyzed and numerically simulated in [7]. Elaiw et al. [11] added immune response and diffusion effect to the virotherapy model, and analyzed the global stability of the model. The authors in [25] proposed a mathematical model:

$$\begin{cases} \frac{dx}{dt} = rx\left(1-\frac{x+y}{k}\right)-\beta xv, \\ \frac{dy}{dt} = \beta xv-\delta y, \\ \frac{dv}{dt} = dy-\beta xv-\alpha v, \end{cases} \tag{1}$$

where x, y and v represent the density of uninfected tumor cells, infected tumor cells and free virus at time t, respectively. r, β stand for the growth rate and infection rate of uninfected tumor cells, respectively. The infected

* Corresponding author.
E-mail addresses: dqrhit@qq.com (Q. Dai), rzhang@qq.com (R. Zhang).

https://doi.org/10.1016/j.matcom.2022.02.028
0378-4754/

tumor cells die with the apoptosis rate δ. The reproduction rate and apoptosis rate of virus are d and α, respectively. The maximum carrying capacity of uninfected tumor cells in human body is defined as k. This model well describes the growth law of tumor cells, but the author only analyzes its stability. In [2], it is considered that the infected tumor cells not only originate from the transformation of uninfected tumor cells, but also have their own growth. Therefore, we can obtain the following three-dimensional ordinary differential model:

$$\begin{cases} \frac{dx}{dt} = rx\left(1 - \frac{x+y}{k}\right) - \beta xv, \\ \frac{dy}{dt} = \beta xv + sy\left(1 - \frac{x+y}{k}\right) - \delta y, \\ \frac{dv}{dt} = dy - \beta xv - \alpha v, \end{cases} \tag{2}$$

where s represents the growth rate of infected tumor cells. Moreover, the time delay is also very common in tumor models [3,32]. For the blocking growth model, in general, the capacity of human individual resources, medical measures and patients' life attitude play a blocking role in the growth of tumor, and with the increase of the number of tumor cells, the blocking effect becomes greater and greater. More specifically, in model (2), rx reflects the growth trend of tumor itself, while $\left(1 - \frac{x+y}{k}\right)$ shows the blocking effect of environment and resources on the growth of tumor. However, this blocking effect does not occur immediately, and there is usually a time delay. Therefore, this paper assumes that the production delay of uninfected tumor cells is τ_1. Some medical studies and mathematical model have also explained the production delay of biological individual [17,18]. For the delay τ_2 of virus apoptosis, similar to the apoptosis of cells, we followed the model in literature [8,19]. Thus, considering the production delay of uninfected tumor cells and the apoptosis delay of virus, the following delayed virotherapy model is also studied in this paper:

$$\begin{cases} \frac{dx}{dt} = rx\left(1 - \frac{x(t-\tau_1)+y(t-\tau_1)}{k}\right) - \beta xv, \\ \frac{dy}{dt} = \beta xv + sy\left(1 - \frac{x+y}{k}\right) - \delta y, \\ \frac{dv}{dt} = dy - \beta xv - \alpha v(t-\tau_2), \end{cases} \tag{3}$$

where the production delay of uninfected tumor cells and the apoptosis delay of virus are τ_1 and τ_2, respectively. For more information about such models, please refer to [10,27,28]. Although most scholars have studied tumor models similar to model (2), they mostly analyze them from the biological point of view, and rarely involve the analysis of stability and bifurcation, especially Co-dimension two bifurcations. Therefore, this paper improves these models and tries to study some interesting dynamic phenomena from the perspective of bifurcation, such as multistability, periodic coexistence and chaos, which have not been studied in the previous models.

Based on the above analysis, in this paper, we mainly study the bifurcations and stability of model (2) and its corresponding delayed model (3). For model (2), in Section 2, the boundedness of the solutions and the existence and stability of the positive equilibriums are first proved. Moreover, the Hopf bifurcation and Bogdanov–Takens bifurcation of positive equilibrium are also studied. For model (3), in Section 3, we focus on the Hopf bifurcation and Zero-Hopf bifurcation of the positive equilibrium, and by center manifold theorem and normal form theory, we study the direction of Hopf bifurcation and stability of the bifurcated periodic solution. In Section 4, we simulate the dynamic phenomena of system (2) near Bogdanov–Takens point and system (3) near Zero-Hopf point, such as bistability, periodic coexistence and chaotic behavior.

2. Stability and bifurcations of model (2)

In this section, we study the stability and bifurcations behavior of model (2), mainly involving the boundedness of solutions, the existence and stability of positive equilibriums, Hopf and Bogdanov–Takens bifurcations.

2.1. Stability

To ensure the biological validity of the model, we must give that the solutions of system (2) are bounded. For this, we obtain the region of attraction in Lemma 1.

Lemma 1. *All the solutions of system (2) initiating in the $\mathbb{R}^3_+$ are nonnegative and are attracted to the subset of $\mathbb{R}^3_+$ defined by*

$$K = \left\{(x, y, v) \in \mathbb{R}^3_+ : 0 \le x + y \le k, 0 \le v \le \frac{dk}{\alpha}\right\}.$$

Proof. From the first two equations of model (2), we have

$$\frac{dx}{dt}+\frac{dy}{dt}=\frac{d(x+y)}{dt}=(rx+sy)\left(1-\frac{x+y}{k}\right)-\delta y\le \bar{M}(x+y)\left(1-\frac{x+y}{k}\right). \tag{4}$$

where $\bar{M}=\max\{r,s\}$. Let $z=x+y$, and inequality (4) is equivalent to $\frac{dz}{dt}\le \bar{M}z\left(1-\frac{z}{k}\right)$. It is easy for solving $\frac{dU}{dt}=\bar{M}U\left(1-\frac{U}{k}\right)$ to get $\lim_{t\to\infty}\sup U(t)=k$. Due to $\dot{z}(t)\le \dot{U}(t)$, and by the comparison theorem of ordinary differential equation, we have $\lim_{t\to\infty}\sup z(t)\le \lim_{t\to\infty}\sup U(t)=k$, namely $\lim_{t\to\infty}\sup(x(t)+y(t))\le k$. Similarly, for the boundedness of v, we have $-\alpha v\le \frac{dv}{dt}\le dy-\alpha v\le dk-\alpha v$. Hence, $0\le v\le \frac{dk}{\alpha}$.

Obviously, there is a zero equilibrium $E_0\,(0,0,0)$ and two boundary equilibriums $E_{01}\left(0,k(1-\frac{\delta}{s}),\frac{kd}{\alpha}(1-\frac{\delta}{s})\right)$ and $E_{02}\,(k,0,0)$ in model (2). The rest of this section mainly studies the stability and Hopf bifurcation of equilibriums.

Lemma 2. *The zero equilibrium E_0 is unstable, and if $\delta(\beta k+\alpha)-d\beta k>0$ and $\beta k+\alpha+d>0$ hold, then the boundary equilibrium E_{02} is locally asymptotically stable.*

Proof. The Jacobian matrix of system (2) at zero equilibrium E_0 is

$$J_{E_0}=\begin{pmatrix} r & 0 & 0\\ 0 & s-\delta & 0\\ 0 & d & -\alpha\end{pmatrix}. \tag{5}$$

It is clear that the eigenvalues of the Jacobi matrix (5) are $(r,s-\delta,-\alpha)$, and since not all real parts of the eigenvalues are negative, the E_0 is unstable. Similarly, the Jacobian matrix of system (2) at boundary equilibrium E_{02} is

$$J_{E_{02}}=\begin{pmatrix} -r & -r & -\beta k\\ 0 & -\delta & \beta k\\ 0 & d & -\beta k-\alpha\end{pmatrix}. \tag{6}$$

The characteristic polynomial of (6) is

$$P(\lambda)=(\lambda+r)\left[\lambda^2+(\beta k+\alpha+d)\lambda+\delta(\beta k+\alpha)-d\beta k\right].$$

There is a negative eigenvalue $-r$, and the other two eigenvalues have a negative real part if and only if $\delta(\beta k+\alpha)-d\beta k>0$ and $\beta k+\alpha+d>0$ hold. Therefore, the proof is completed.

Lemma 3. *The boundary equilibrium E_{02} is globally asymptotically stable when the following conditions hold: (a) $\alpha\ge\beta+r$, (b) $s\ge dk$, (c) $\delta\ge s$.*

Proof. The Lyapunov function V on K is defined as follows: $V=xv+y$. Obviously, V is continuous on K and positive definite with respect to E_{02}. Calculating the derivative of V with respect to time t, we get

$$\begin{aligned}\frac{dV}{dt}&=v\frac{dx}{dt}+x\frac{dv}{dt}+\frac{dy}{dt}=(\beta+r-\alpha)xv+\left(d-\frac{s}{k}\right)xy+(s-\delta)y-\frac{rxv(x+y)}{k}\\&\quad-\beta xv^2-\beta x^2v-\frac{s}{k}y^2.\end{aligned}$$

It is apparent that if conditions (a), (b) and (c) hold, then $\frac{dV}{dt}<0$. That is, E_{02} is globally asymptotically stable.

The positive equilibrium $E\,(x^*,y^*,v^*)$ of system (2) satisfies

$$\begin{cases} rx^*\left(1-\frac{x^*+y^*}{k}\right)-\beta x^*v^*=0,\\ \beta x^*v^*+sy^*\left(1-\frac{x^*+y^*}{k}\right)-\delta y^*=0,\\ dy^*-\beta x^*v^*-\alpha v^*=0.\end{cases} \tag{7}$$

Sorting (7), we have

$$m_1\left(y^*\right)^2+m_2y^*+m_3=0, \tag{8}$$

where

$$m_1 = \frac{\delta r^2}{k},$$
$$m_2 = r\left(r+d+\frac{\alpha r}{k\beta}-\delta\right)^2 + \frac{r}{k}\left(\frac{\alpha r}{\beta}-rk+1\right)\left(r+d+\frac{\alpha r}{k\beta}-\delta\right) + \frac{\alpha r^2}{k^2\beta} - 2\frac{\alpha^2 r^3}{k^2\beta^2} - \frac{\alpha r^2\delta}{k\beta} - 3\frac{d\alpha r^2}{k\beta} - 2\frac{\alpha r^3}{k\beta},$$
$$m_3 = \left(\frac{\alpha r^2}{\beta} - \frac{2\alpha r}{\beta} - \frac{\alpha^2 r^2}{k\beta^2}\right)\left(r+d+\frac{\alpha r}{k\beta}-\delta\right) + \frac{\alpha^3 r^3}{k^2\beta^3} + \frac{d\alpha^2 r^2}{k\beta^2} + 3\frac{\alpha^2 r^3}{k\beta^2},$$

and the discriminant $\Delta = (m_2)^2 - 4m_1m_3$. In this way, the two roots of Eq. (8) can be easily given

$$y_1 = \frac{-m_2-\sqrt{\Delta}}{2m_1}, \quad y_2 = \frac{-m_2+\sqrt{\Delta}}{2m_1}.$$

Then, by simple analysis, we have

Theorem 1. *For system (2).*

(1) *There are two different positive equilibriums when $\Delta > 0$, $-\frac{m_2}{2m_1} > 0$ and $m_3 > 0$, defined by $E_1(x_1, y_1, v_1)$ and $E_2(x_2, y_2, v_2)$, where*

$$x_1 = \frac{rk-(r+s)y_1 + k\sqrt{\left(r-\frac{(r+s)}{k}y_1\right)^2 + 4\frac{r}{k}\left(\frac{sy_1^2}{k}+(s-\delta)y_1\right)}}{2r}, \quad v_1 = \frac{dy_1}{\beta x_1+\alpha},$$
$$x_2 = \frac{rk-(r+s)y_2 + k\sqrt{\left(r-\frac{(r+s)}{k}y_2\right)^2 + 4\frac{r}{k}\left(\frac{sy_2^2}{k}+(s-\delta)y_2\right)}}{2r}, \quad v_2 = \frac{dy_2}{\beta x_2+\alpha}.$$

(2) *There is a unique positive equilibrium $E_2(x_2, y_2, v_2)$ when $m_3 < 0$.*

Remark 1. In fact, if $\Delta = 0$, $-\frac{m_2}{2m_1} > 0$ and $m_3 > 0$ are satisfied, then system (2) admits an instantaneous equilibrium $E_2^*\left(x_2^*, y_2^*, v_2^*\right)$ formed by the collision of equilibriums E_1 and E_2, where $y_2^* = -\frac{m_2}{2m_1}$ and the forms of x_2^* and v_2^* are same as x_2 and v_2 in Theorem 1.

This paper mainly focuses on the stability and bifurcation behavior of positive equilibrium E_2. Therefore, the linearized system of (3) at positive equilibrium E_2 is

$$\begin{pmatrix}\dot{x}\\ \dot{y}\\ \dot{v}\end{pmatrix} = B_1\begin{pmatrix}x\\ y\\ v\end{pmatrix} + B_2\begin{pmatrix}x(t-\tau_1)\\ y(t-\tau_1)\\ v(t-\tau_1)\end{pmatrix} + B_3\begin{pmatrix}x(t-\tau_2)\\ y(t-\tau_2)\\ v(t-\tau_2)\end{pmatrix}, \tag{9}$$

where

$$B_1 = \begin{pmatrix}a_{11} & 0 & -a_{12}\\ a_{21} & a_{22} & a_{12}\\ -a_{31} & -a_{32} & -a_{12}\end{pmatrix}, \quad B_2 = \begin{pmatrix}-b_{11} & -b_{11} & 0\\ 0 & 0 & 0\\ 0 & 0 & 0\end{pmatrix}, \quad B_3 = \begin{pmatrix}0 & 0 & 0\\ 0 & 0 & 0\\ 0 & 0 & -c_{11}\end{pmatrix},$$

and

$$a_{11} = r\left(1-\frac{x_2+y_2}{k}\right) - \beta v_2, \; a_{12} = \beta x_2, \; a_{21} = \beta v_2 - \frac{s}{k}y_2,$$
$$a_{22} = s\left(1-\frac{x_2+2y_2}{k}\right) - \delta, \; a_{31} = \beta v_2, \; a_{32} = -d, \; b_{11} = \frac{rx_2}{k}, \; c_{11} = \alpha.$$

Then the characteristic equation is obtained

$$\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0 + \left(n_2\lambda^2 + n_1\lambda + n_0\right)e^{-\lambda\tau_1} + \left(e_2\lambda^2 + e_1\lambda + e_0\right)e^{-\lambda\tau_2} + \left(g_1\lambda + g_0\right)e^{-\lambda(\tau_1+\tau_2)} = 0, \tag{10}$$

where

$$p_2 = a_{12} - a_{11} - a_{22},\ \ p_1 = a_{12}a_{32} + a_{11}a_{22} - a_{11}a_{12} - a_{12}a_{31} - a_{22}a_{12},$$
$$p_0 = a_{12}a_{31}a_{22} + a_{11}a_{12}a_{22} - a_{21}a_{12}a_{32} - a_{12}a_{32}a_{11},\ \ e_2 = c_{11},\ \ e_1 = -a_{11}c_{11} - a_{22}c_{11},$$
$$e_0 = a_{11}a_{22}c_{11},\ \ n_2 = b_{11},\ \ n_1 = a_{12}b_{11} + a_{21}b_{11} - a_{22}b_{11},$$
$$n_0 = a_{12}a_{32}b_{11} + a_{12}a_{21}b_{11} - a_{31}a_{12}b_{11} - a_{12}a_{22}b_{11},$$
$$g_1 = c_{11}b_{11},\ \ g_0 = a_{21}b_{11}c_{11} - a_{22}b_{11}c_{11}.$$

When $\tau_1 = \tau_2 = 0$, the characteristic equation of system (2) is

$$\lambda^3 + m_{12}\lambda^2 + m_{11}\lambda + m_{10} = 0, \tag{11}$$

where

$$m_{12} = p_2 + n_2 + e_2,\ \ m_{11} = p_1 + n_1 + e_1 + g_1,\ \ m_{10} = p_0 + n_0 + e_0 + g_0.$$

For convenience, we make the following hypotheses

(H1) $\qquad m_{12}m_{11} = m_{10},\ \ m_{12} > 0,\ \ m_{11} > 0,$

and

(H2) $\qquad m_{11} = m_{10} = 0.$

Following from the Routh–Hurwitz criteria and the Hopf bifurcation theory of ordinary differential equation [16,24,29], we have

Lemma 4. *For $\tau_1 = \tau_2 = 0$, the positive equilibrium E_2 is locally asymptotically stable when $m_{12} > 0$ and $m_{12}m_{11} > m_{10}$. System (2) undergoes a Hopf bifurcation with β as bifurcation parameter when hypothesis* (H1) *and* $\mathrm{Re}\left(\frac{d\lambda}{d\beta}\right)^{-1}_{\beta=\beta^*} \neq 0$ *hold.*

Remark 2. Here, β^* is the critical value of β for Hopf bifurcation. The hypothesis (H1) guarantees that system (2) has a pair of pure imaginary roots $\pm\omega_0$ (clearly, $\omega_0 = \sqrt{m_{11}} = \sqrt{\frac{m_{12}}{m_{10}}}$) and a root with negative real part. $\mathrm{Re}\left(\frac{d\lambda}{d\beta}\right)^{-1}_{\beta=\beta^*} \neq 0$ is for transversality condition.

Remark 3. The calculation of the critical value of β is actually to find the value satisfied hypothesis (H1). To this end, we substitute the parameter values into (H1) to solve β,

$$f_2(x_2 + v_2)\beta^2 + [f_1 f_2 + f_3(x_2 + v_2) - f_4]\,\beta + f_1 f_3 - f_5 = 0, \tag{12}$$

where

$$f_1 = \frac{r}{k}x_2 + \alpha + \delta - r\left(1 - \frac{x_2 + y_2}{k}\right) - s\left(1 - \frac{x_2 + 2y_2}{k}\right),$$
$$f_2 = \frac{r}{k}x_2v_2 + \frac{r}{k}x_2^2 + \alpha v_2 - dx_2 - \left[s\left(1 - \frac{x_2 + 2y_2}{k}\right) - \delta\right](x_2 + v_2) - rx_2\left(1 - \frac{x_2 + y_2}{k}\right),$$
$$f_3 = r\left(1 - \frac{2x_2 + y_2}{k}\right)\left[s\left(1 - \frac{x_2 + 2y_2}{k}\right) - \delta\right] + \frac{r\alpha x_2}{k} - \alpha\left[s\left(1 - \frac{x_2 + 2y_2}{k}\right) - \delta\right]$$
$$- \alpha r\left(1 - \frac{x_2 + y_2}{k}\right) - \frac{srx_2y_2}{k^2},$$
$$f_4 = x_2r\left(1 - \frac{x_2 + y_2}{k}\right) + \frac{\alpha r x_2 v_2}{k} + dx_2r\left(1 - \frac{x_2 + y_2}{k}\right) - \frac{dsx_2y_2 + rdx_2^2}{k} - \frac{rsx_2^2y_2}{k^2}$$
$$- \left(\frac{rx_2^2}{k} - \alpha v_2\right)\left[s\left(1 - \frac{x_2 + 2y_2}{k}\right) - \delta\right],$$

$$f_5 = \alpha r \left(1 - \frac{2x_2 + y_2}{k}\right)\left[s\left(1 - \frac{x_2 + 2y_2}{k}\right) - \delta\right] - \frac{r\alpha s}{k^2}x_2 y_2.$$

Since Eq. (12) is a quadratic equation with respect to β, there are at most two critical values, this is

$$\beta_1^* = -\frac{f_1 f_2 + f_3(x_2 + v_2) - f_4 + \sqrt{\Delta_2}}{2f_2(x_2 + v_2)},\ \ \beta_2^* = -\frac{f_1 f_2 + f_3(x_2 + v_2) - f_4 - \sqrt{\Delta_2}}{2f_2(x_2 + v_2)},$$

where

$$\Delta_2 = [f_1 f_2 + f_3(x_2 + v_2) - f_4]^2 - 4f_2(x_2 + v_2)\left(f_1 f_3 - f_5\right).$$

For transversality condition, with reference to Eq. (11), we have

$$3\lambda^2 \frac{d\lambda}{d\beta} + 2m_{12}\lambda\frac{d\lambda}{d\beta} + (x_2 + v_2)\lambda^2 + m_{11}\frac{d\lambda}{d\beta} + f_2\lambda = 0,$$

then

$$\frac{d\lambda}{d\beta} = \frac{\omega_0^2(x_2 + v_2)(m_{11} - 3\omega_0^2) - 2m_{12}\omega_0^2 f_2}{\left(m_{11} - 3\omega_0^2\right)^2 + 4m_{12}^2\omega_0^2} - i\frac{\omega_0 f_2(m_{11} - 3\omega_0^2) + 2\omega_0^2(x_2 + v_2)m_{12}\omega_0}{\left(m_{11} - 3\omega_0^2\right)^2 + 4m_{12}^2\omega_0^2}.$$

Thus,

$$\mathrm{Re}\left(\frac{d\lambda}{d\beta}\right)_{\beta=\beta^*} = \frac{\omega_0^2(x_2 + v_2)(m_{11} - 3\omega_0^2) - 2m_{12}\omega_0^2 f_2}{\left(m_{11} - 3\omega_0^2\right)^2 + 4m_{12}^2\omega_0^2}.$$

2.2. Bogdanov–Takens bifurcation

In this subsection, by using the theory in [21], we calculate the normal form of Bogdanov–Takens bifurcation of system (2) at positive equilibrium E_2 with β and d as bifurcation parameters. For the existence of Bogdanov–Takens bifurcation, we first give Lemma 5.

Lemma 5. *If the hypothesis (H2) holds, then the characteristic equation of system (2) has a pair of zero eigenvalues.*

For convenience, we rewrite system (2) as follows

$$\begin{pmatrix}\dot{x}\\ \dot{y}\\ \dot{v}\end{pmatrix} = B\begin{pmatrix}x\\ y\\ z\end{pmatrix} + \begin{pmatrix}F_1(x, y, v)\\ F_2(x, y, v)\\ F_3(x, y, v)\end{pmatrix}, \tag{13}$$

where

$$B = \begin{pmatrix} a_{11} - b_{11} & -b_{11} & -a_{12}\\ a_{21} & a_{22} & a_{12}\\ -a_{31} & -a_{32} & -a_{12} - c_{11}\end{pmatrix},$$

and

$$F_1(x, y, v) = -\frac{r}{k}x^2 - \frac{r}{2k}xy - \frac{\beta}{2}xv - \frac{r}{k}x_2^2 - \frac{r}{2k}x_2 y_2 - \frac{\beta}{2}x_2 v_2 + h.o.t,$$
$$F_2(x, y, v) = \frac{\beta}{2}xv - \frac{s}{k}y^2 - \frac{s}{2k}xy + \frac{\beta}{2}x_2 v_2 - \frac{s}{k}y_2^2 - \frac{s}{2k}x_2 y_2 + h.o.t,$$
$$F_3(x, y, v) = -\frac{\beta}{2}xv - \frac{\beta}{2}x_2 v_2 + h.o.t.$$

To reduce system (13) to the center manifold, we consider the following transformation,

$$\begin{pmatrix}U\\ V\\ Z\end{pmatrix} = \begin{pmatrix} q_{111} & q_{112} & q_{113}\\ q_{211} & q_{212} & q_{213}\\ q_{311} & q_{312} & q_{313}\end{pmatrix}\begin{pmatrix}x\\ y\\ v\end{pmatrix}, \tag{14}$$

where

$$\begin{aligned}
q_{211} &= -[(a_{11}-b_{11})a_{12}+a_{21}a_{12}],\\
q_{311} &= [(a_{11}-b_{11})a_{22}+a_{21}b_{11}],\\
q_{213} &= -[(a_{11}-b_{11}+m_{12})a_{12}+a_{21}a_{12}],\\
q_{313} &= [(a_{11}-b_{11}+m_{12})(a_{22}+m_{12})+a_{21}b_{11}],
\end{aligned}$$

$$\begin{aligned}
q_{111} &= \frac{a_{32}[(a_{11}-b_{11})a_{12}+a_{21}a_{12}]-(a_{12}+c_{11})[(a_{11}-b_{11})a_{22}+a_{21}b_{11}]}{a_{31}},\\
q_{113} &= \frac{a_{32}[(a_{11}-b_{11}+m_{12})a_{12}+a_{21}a_{12}]-(a_{12}+c_{11}+m_{12})[(a_{11}-b_{11}+m_{12})(a_{22}+m_{12})+a_{21}b_{11}]}{a_{31}},\\
q_{112} &= \frac{a_{12}a_{22}(q_{111}-q_{311})-a_{12}a_{32}(q_{111}+q_{211})+a_{12}b_{11}(q_{211}+q_{311})+a_{22}c_{11}q_{111}+b_{11}c_{11}q_{211}}{a_{11}a_{12}(a_{22}-a_{32})+a_{12}a_{21}(b_{11}-a_{32})+a_{12}a_{22}(b_{11}-a_{31})+a_{12}b_{11}(a_{32}-a_{31})+a_{22}c_{21}(a_{11}-a_{22})+a_{21}b_{11}c_{11}},\\
q_{212} &= \frac{a_{12}a_{31}(q_{111}+q_{211})+a_{12}a_{21}(q_{311}-q_{111})+a_{12}a_{11}(q_{211}+q_{311})-a_{12}b_{11}(q_{211}+q_{311})+c_{11}[q_{211}(a_{11}-b_{11})-a_{21}q_{111}]}{a_{11}a_{12}(a_{22}-a_{32})+a_{12}a_{21}(b_{11}-a_{32})+a_{12}a_{22}(b_{11}-a_{31})+a_{12}b_{11}(a_{32}-a_{31})+a_{22}c_{21}(a_{11}-a_{22})+a_{21}b_{11}c_{11}},\\
q_{312} &= \frac{b_{11}q_{311}(a_{22}-a_{21})+b_{11}q_{211}(a_{32}-a_{31})+(a_{21}a_{32}-a_{22}a_{31})q_{111}+a_{11}(q_{211}+q_{311})}{a_{11}a_{12}(a_{22}-a_{32})+a_{12}a_{21}(b_{11}-a_{32})+a_{12}a_{22}(b_{11}-a_{31})+a_{12}b_{11}(a_{32}-a_{31})+a_{22}c_{21}(a_{11}-a_{22})+a_{21}b_{11}c_{11}}.
\end{aligned}$$

Using transformation (14), system (13) is equivalent to the following standard form

$$\begin{pmatrix}\dot U\\ \dot V\\ \dot Z\end{pmatrix}=\begin{pmatrix}0&1&0\\0&0&0\\0&0&-m_{12}\end{pmatrix}\begin{pmatrix}U\\V\\Z\end{pmatrix}+\begin{pmatrix}W_1\\W_2\\W_3\end{pmatrix}, \tag{15}$$

where

$$\begin{aligned}
W_1 = &\left(\gamma_{11}p_{111}^2+\gamma_{12}p_{211}^2+\gamma_{13}p_{111}p_{211}+\gamma_{14}p_{111}p_{311}\right)U^2\\
&+\left(\gamma_{11}p_{112}^2+\gamma_{12}p_{212}^2+\gamma_{13}p_{112}p_{212}+\gamma_{14}p_{112}p_{312}\right)V^2\\
&+(2\gamma_{11}p_{111}p_{112}+2\gamma_{12}p_{211}p_{212}+\gamma_{13}(p_{111}p_{212}+p_{112}p_{211})+\gamma_{14}(p_{111}p_{312}+p_{112}p_{311}))UV\\
&+(2\gamma_{11}p_{111}p_{113}+2\gamma_{12}p_{211}p_{213}+\gamma_{13}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{14}(p_{111}p_{313}+p_{112}p_{313}))UZ\\
&+(2\gamma_{11}p_{112}p_{113}+2\gamma_{12}p_{212}p_{213}+\gamma_{13}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{14}(p_{112}p_{313}+p_{212}p_{313}))VZ\\
&+\left(\gamma_{11}p_{113}^2+\gamma_{12}p_{213}^2+\gamma_{13}p_{113}p_{213}+\gamma_{14}p_{113}p_{313}\right)Z^2+C_1,\\
W_2 = &\left(\gamma_{21}p_{111}^2+\gamma_{22}p_{211}^2+\gamma_{23}p_{111}p_{211}+\gamma_{24}p_{111}p_{311}\right)U^2\\
&+\left(\gamma_{21}p_{112}^2+\gamma_{22}p_{212}^2+\gamma_{23}p_{112}p_{212}+\gamma_{24}p_{112}p_{312}\right)V^2\\
&+(2\gamma_{21}p_{111}p_{112}+2\gamma_{22}p_{211}p_{212}+\gamma_{23}(p_{111}p_{212}+p_{112}p_{211})+\gamma_{24}(p_{111}p_{312}+p_{112}p_{311}))UV\\
&+(2\gamma_{21}p_{111}p_{113}+2\gamma_{22}p_{211}p_{213}+\gamma_{23}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{24}(p_{111}p_{313}+p_{112}p_{313}))UZ\\
&+(2\gamma_{21}p_{112}p_{113}+2\gamma_{22}p_{212}p_{213}+\gamma_{23}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{24}(p_{112}p_{313}+p_{212}p_{313}))VZ\\
&+\left(\gamma_{21}p_{113}^2+\gamma_{22}p_{213}^2+\gamma_{23}p_{113}p_{213}+\gamma_{24}p_{113}p_{313}\right)Z^2+C_2,\\
W_3 = &\left(\gamma_{31}p_{111}^2+\gamma_{32}p_{211}^2+\gamma_{33}p_{111}p_{211}+\gamma_{34}p_{111}p_{311}\right)U^2\\
&+\left(\gamma_{31}p_{112}^2+\gamma_{32}p_{212}^2+\gamma_{33}p_{112}p_{212}+\gamma_{34}p_{112}p_{312}\right)V^2\\
&+(2\gamma_{31}p_{111}p_{112}+2\gamma_{32}p_{211}p_{212}+\gamma_{33}(p_{111}p_{212}+p_{112}p_{211})+\gamma_{34}(p_{111}p_{312}+p_{112}p_{311}))UV\\
&+(2\gamma_{31}p_{111}p_{113}+2\gamma_{32}p_{211}p_{213}+\gamma_{33}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{34}(p_{111}p_{313}+p_{112}p_{313}))UZ\\
&+(2\gamma_{31}p_{112}p_{113}+2\gamma_{32}p_{212}p_{213}+\gamma_{33}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{34}(p_{112}p_{313}+p_{212}p_{313}))VZ\\
&+\left(\gamma_{31}p_{113}^2+\gamma_{32}p_{213}^2+\gamma_{23}p_{113}p_{213}+\gamma_{34}p_{113}p_{313}\right)Z^2+C_3,
\end{aligned}$$

and

$$\gamma_{11}=\frac{\beta q_{112}}{2}-\frac{rq_{111}}{k},\ \gamma_{12}=-\frac{rq_{111}}{2k}-\frac{sq_{112}}{k},\ \gamma_{13}=-\frac{\beta q_{111}}{2}-\frac{sq_{112}}{2k},\ \gamma_{14}=-\frac{\beta q_{113}}{2},$$
$$\gamma_{21}=\frac{\beta q_{212}}{2}-\frac{rq_{211}}{k},\ \gamma_{22}=-\frac{rq_{211}}{2k}-\frac{sq_{212}}{k},\ \gamma_{23}=-\frac{\beta q_{211}}{2}-\frac{sq_{212}}{2k},\ \gamma_{24}=-\frac{\beta q_{213}}{2},$$
$$\gamma_{31}=\frac{\beta q_{312}}{2}-\frac{rq_{311}}{k},\gamma_{32}=-\frac{rq_{311}}{2k}-\frac{sq_{312}}{k},\ \gamma_{33}=-\frac{\beta q_{311}}{2}-\frac{sq_{312}}{2k},\gamma_{34}=-\frac{\beta q_{313}}{2},$$
$$C_1=-q_{111}\left(\frac{r}{k}x_2^2+\frac{r}{2k}x_2y_2+\frac{\beta}{2}x_2v_2\right)+q_{112}\left(\frac{\beta}{2}x_2v_2-\frac{s}{k}y_2^2-\frac{s}{2k}x_2y_2\right)-\frac{\beta}{2}x_2v_2q_{113},$$

$$C_2=-q_{211}\left(\frac{r}{k}x_2^2+\frac{r}{2k}x_2y_2+\frac{\beta}{2}x_2v_2\right)+q_{212}\left(\frac{\beta}{2}x_2v_2-\frac{s}{k}y_2^2-\frac{s}{2k}x_2y_2\right)-\frac{\beta}{2}x_2v_2q_{213},$$
$$C_3=-q_{311}\left(\frac{r}{k}x_2^2+\frac{r}{2k}x_2y_2+\frac{\beta}{2}x_2v_2\right)+q_{312}\left(\frac{\beta}{2}x_2v_2-\frac{s}{k}y_2^2-\frac{s}{2k}x_2y_2\right)-\frac{\beta}{2}x_2v_2q_{313},$$

and

$$p_{111}=\frac{q_{212}q_{313}-q_{213}q_{312}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}},$$
$$p_{112}=\frac{q_{113}q_{312}-q_{112}q_{312}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}},$$
$$p_{113}=\frac{q_{112}q_{213}-q_{113}q_{212}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}},$$
$$p_{211}=\frac{q_{213}q_{311}-q_{211}q_{313}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}},$$
$$p_{212}=\frac{q_{111}q_{313}-q_{113}q_{311}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}},$$
$$p_{213}=\frac{q_{113}q_{211}-q_{111}q_{213}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}},$$

$$p_{311}=\frac{q_{211}q_{312}-q_{212}q_{311}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}},$$
$$p_{312}=\frac{q_{112}q_{311}-q_{111}q_{312}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}},$$
$$p_{313}=\frac{q_{111}q_{212}-q_{112}q_{211}}{q_{111}q_{212}q_{313}-q_{111}q_{213}q_{312}-q_{112}q_{211}q_{313}+q_{112}q_{213}q_{311}+q_{113}q_{211}q_{312}-q_{113}q_{212}q_{311}}.$$

Thus there exists a center manifold for (15) which can locally be represented as follows

$$W^c_{loc}(0)=\left\{(U,V,Z)\in\mathbb{R}^3_+|Z=h(U,V),|U|<\delta_1,|V|<\delta_2,h(0,0)=0\right\},$$

for δ_1, δ_2 sufficiently small, and we assume that $h(U,V)$ has the following form

$$Z=h(U,\ \mathrm{V})=r_1U^2+s_1UV+t_1V^2+h.o.t.$$

Then, we have

$$\frac{dZ}{dt}=2r_1U\frac{dU}{dt}+s_1U\frac{dU}{dt}+s_1V\frac{dU}{dt}+2t_1V\frac{dV}{dt}=-m_{12}Z+W_3, \tag{16}$$

Comparing the coefficients of U^2, UV and V^2 on the left and right sides of the above Eq. (16) yields

$$\begin{aligned}
r_1 &= -\frac{\left(\gamma_{31}p_{111}^2+\gamma_{32}p_{211}^2+\gamma_{33}p_{111}p_{211}+\gamma_{34}p_{111}p_{311}\right)}{m_{12}},\\
s_1 &= -\frac{\left(\gamma_{31}p_{111}^2+\gamma_{32}p_{211}^2+\gamma_{33}p_{111}p_{211}+\gamma_{34}p_{111}p_{311}\right)}{m_{12}^2}\\
&\quad -\frac{(2\gamma_{31}p_{111}p_{112}+2\gamma_{32}p_{211}p_{212}+\gamma_{33}(p_{111}p_{212}+p_{112}p_{211})+\gamma_{34}(p_{111}p_{312}+p_{112}p_{311}))}{m_{12}},\\
t_1 &= -\frac{2\left(\gamma_{31}p_{111}^2+\gamma_{32}p_{211}^2+\gamma_{33}p_{111}p_{211}+\gamma_{34}p_{111}p_{311}\right)}{m_{12}^3}\\
&\quad -\frac{\left(\gamma_{31}p_{112}^2+\gamma_{32}p_{212}^2+\gamma_{33}p_{112}p_{212}+\gamma_{34}p_{112}p_{312}\right)}{m_{12}}\\
&\quad -\frac{(2\gamma_{31}p_{111}p_{112}+2\gamma_{32}p_{211}p_{212}+\gamma_{33}(p_{111}p_{212}+p_{112}p_{211})+\gamma_{34}(p_{111}p_{312}+p_{112}p_{311}))}{m_{12}^2}.
\end{aligned}$$

Then, the dynamics of system (13) restricted to the center manifold is determined by

$$\begin{pmatrix}\dot U\\ \dot V\end{pmatrix}=\begin{pmatrix}0&1\\0&0\end{pmatrix}\begin{pmatrix}U\\V\end{pmatrix}+\begin{pmatrix}G_1\\G_2\end{pmatrix}, \tag{17}$$

where

$$\begin{aligned}
G_1 &= \left(\gamma_{11}p_{111}^2+\gamma_{12}p_{211}^2+\gamma_{13}p_{111}p_{211}+\gamma_{14}p_{111}p_{311}\right)U^2\\
&\quad+\left(\gamma_{11}p_{112}^2+\gamma_{12}p_{212}^2+\gamma_{13}p_{112}p_{212}+\gamma_{14}p_{112}p_{312}\right)V^2\\
&\quad+(2\gamma_{11}p_{111}p_{112}+2\gamma_{12}p_{211}p_{212}+\gamma_{13}(p_{111}p_{212}+p_{112}p_{211})+\gamma_{14}(p_{111}p_{312}+p_{112}p_{311}))\,UV\\
&\quad+[s_1\,(2\gamma_{11}p_{111}p_{113}+2\gamma_{12}p_{211}p_{213}+\gamma_{13}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{14}(p_{111}p_{313}+p_{112}p_{313}))\\
&\quad+r_1\,(2\gamma_{11}p_{112}p_{113}+2\gamma_{12}p_{212}p_{213}+\gamma_{13}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{14}(p_{112}p_{313}+p_{212}p_{313}))]U_2V\\
&\quad+[t_1\,(2\gamma_{11}p_{111}p_{113}+2\gamma_{12}p_{211}p_{213}+\gamma_{13}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{14}(p_{111}p_{313}+p_{112}p_{313}))\\
&\quad+s_1\,(2\gamma_{11}p_{112}p_{113}+2\gamma_{12}p_{212}p_{213}+\gamma_{13}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{14}(p_{112}p_{313}+p_{212}p_{313}))]V_2U\\
&\quad+r_1\,(2\gamma_{11}p_{111}p_{113}+2\gamma_{12}p_{211}p_{213}+\gamma_{13}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{14}(p_{111}p_{313}+p_{112}p_{313}))\,U_3\\
&\quad+t_1\,(2\gamma_{11}p_{112}p_{113}+2\gamma_{12}p_{212}p_{213}+\gamma_{13}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{14}(p_{112}p_{313}+p_{212}p_{313}))\,V_2+C_1,\\
G_2 &= \left(\gamma_{21}p_{111}^2+\gamma_{22}p_{211}^2+\gamma_{23}p_{111}p_{211}+\gamma_{24}p_{111}p_{311}\right)U^2\\
&\quad+\left(\gamma_{21}p_{112}^2+\gamma_{22}p_{212}^2+\gamma_{23}p_{112}p_{212}+\gamma_{24}p_{112}p_{312}\right)V^2\\
&\quad+(2\gamma_{21}p_{111}p_{112}+2\gamma_{22}p_{211}p_{212}+\gamma_{23}(p_{111}p_{212}+p_{112}p_{211})+\gamma_{24}(p_{111}p_{312}+p_{112}p_{311}))\,UV\\
&\quad+[s_1\,(2\gamma_{21}p_{111}p_{113}+2\gamma_{22}p_{211}p_{213}+\gamma_{23}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{24}(p_{111}p_{313}+p_{112}p_{313}))\\
&\quad+r_1\,(2\gamma_{21}p_{112}p_{113}+2\gamma_{22}p_{212}p_{213}+\gamma_{23}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{24}(p_{112}p_{313}+p_{212}p_{313}))]U_2V\\
&\quad+[t_1\,(2\gamma_{21}p_{111}p_{113}+2\gamma_{22}p_{211}p_{213}+\gamma_{23}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{24}(p_{111}p_{313}+p_{112}p_{313}))\\
&\quad+s_1\,(2\gamma_{21}p_{112}p_{113}+2\gamma_{22}p_{212}p_{213}+\gamma_{23}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{24}(p_{112}p_{313}+p_{212}p_{313}))]V_2U\\
&\quad+r_1\,(2\gamma_{21}p_{111}p_{113}+2\gamma_{22}p_{211}p_{213}+\gamma_{23}(p_{111}p_{213}+p_{112}p_{213})+\gamma_{24}(p_{111}p_{313}+p_{112}p_{313}))\,U_3\\
&\quad+t_1\,(2\gamma_{21}p_{112}p_{113}+2\gamma_{22}p_{212}p_{213}+\gamma_{23}(p_{112}p_{213}+p_{113}p_{213})+\gamma_{24}(p_{112}p_{313}+p_{212}p_{313}))\,V_2+C_2.
\end{aligned}$$

The normal form of Bogdanov–Takens bifurcation can be obtained by using the following transformation

$$\begin{cases} z_1 = U,\\ z_2 = V + G_1. \end{cases}$$

Then we have

$$\begin{cases}\dot{z}_1 = z_2,\\ \dot{z}_2 = \beta_{11}z_1^2 + \beta_{22}z_1z_2 + O(\|(z_1,z_2)^3\|),\end{cases} \tag{18}$$

where

$$\begin{aligned}\beta_{11} &= \left(\gamma_{11}p_{111}^2 + \gamma_{12}p_{211}^2 + \gamma_{13}p_{111}p_{211} + \gamma_{14}p_{111}p_{311}\right),\\ \beta_{22} &= 2\left(\gamma_{11}p_{111}^2 + \gamma_{12}p_{211}^2 + \gamma_{13}p_{111}p_{211} + \gamma_{14}p_{111}p_{311}\right)\\ &\quad + (2\gamma_{21}p_{111}p_{112} + 2\gamma_{22}p_{211}p_{212} + \gamma_{23}(p_{111}p_{212}\\ &\quad + p_{112}p_{211}) + \gamma_{24}(p_{111}p_{312} + p_{112}p_{311})).\end{aligned}$$

Theorem 2. *Here, we omit a coefficient transformation, which can eliminate the z_2^2 term and reparameterize the time. Moreover, if the hypothesis (H2) holds, $\beta_{11} \neq 0$ and $\beta_{22} \neq 0$, then positive equilibrium E_2^* is a cusp of co-dimension two, that is, a Bogdanov–Takens singularity.*

3. Bifurcations analysis of model (3)

In this section, we consider the influence of delay effect on the dynamic properties of the model. Hence, we mainly analyze the Hopf bifurcation and Zero-Hopf bifurcation of system (3).

3.1. Existence of Hopf bifurcation

Next, according to the values of τ_1 and τ_2, we study the stability and Hopf bifurcation of system (3) in following two cases.

Case I. $\tau_1 = 0$ and $\tau_2 > 0$. In this case, the characteristic equation is rewritten as follows

$$\lambda^3 + (p_2+n_2)\lambda^2 + (p_1+n_1)\lambda + p_0 + n_0 + \left(e_2\lambda^2 + (e_1+g_1)\lambda + e_0 + g_0\right)e^{-\lambda\tau_2} = 0. \tag{19}$$

Let $i\omega_2(\omega_2 > 0)$ be the root of (19). We have

$$\begin{cases}\left(e_0+g_0-e_2\omega_2^2\right)\cos\omega_2\tau_2 + (e_1+g_1)\,\omega_2\sin\omega_2\tau_2 = (p_2+n_2)\omega_2^2 - (p_0+n_0),\\ (e_1+g_1)\,\omega_2\cos\omega_2\tau_2 - \left(e_0+g_0-e_2\omega_2^2\right)\sin\omega_2\tau_2 = \omega_2^3 - (p_1+n_1)\omega_2,\end{cases}$$

then the following equation can be obtained

$$\omega_2^6 + p_{22}\omega_2^4 + p_{21}\omega_2^2 + p_{20} = 0, \tag{20}$$

where

$$\begin{aligned}p_{22} &= (p_2+n_2)^2 - 2(p_1+n_1) - e_2^2,\\ p_{21} &= (p_1+n_1)^2 + 2e_2(e_0+g_0) - (e_1+g_1)^2 - 2(p_0+n_0)(p_2+n_2),\\ p_{20} &= (p_0+n_0)^2 - (e_0+g_0)^2.\end{aligned}$$

Let $u = \omega_2^2$, then (20) becomes

$$u^3 + p_{22}u^2 + p_{21}u + p_{20} = 0. \tag{21}$$

Define $f(u) = u^3 + p_{22}u^2 + p_{21}u + p_{20}$, then we have

Lemma 6. *For the polynomial (21).*

(1) *If $p_{20} < 0$, then (21) has at least one positive root. In particular, Eq. (21) has three different roots when $\Delta_1 = p_{22}^2 - 3p_{21} > 0$, $u_1 > 0$ and $f(u_1) > 0$, $f(u_2) < 0$ are all true, where $u_1 = \frac{-p_{22}-\sqrt{\Delta_1}}{3}$ and $u_2 = \frac{-p_{22}+\sqrt{\Delta_1}}{3}$.*

(2) *If* $p_{20} \geq 0$, *then* (21) *has two positive roots when* $\Delta_1 = p_{22}^2 - 3p_{21} > 0$ *and* $f(u_2) < 0$ *are satisfied, or a unique positive root when* $\Delta_1 = p_{22}^2 - 3p_{21} > 0$ *and* $f(u_2) = 0$ *are satisfied, where* $u_2 = \frac{-p_{22}+\sqrt{\Delta_1}}{3}$.

Without loss of generality, we assume that (21) has three positive roots that are denoted as u_1, u_2 and u_3, respectively, and the corresponding roots of (20) is $\omega_{2n} = \sqrt{u_n}$, $n = 1, 2, 3$. By calculation, we have

$$\tau_{2n}^j = \frac{1}{\omega_{2n}} \left\{ arc\cos\left[\frac{\left((p_2+n_2)\omega_{2n}^2 - (p_0+n_0)\right)\left(e_0+g_0-e_2\omega_{2n}^2\right) + \left(\omega_{2n}^3 - (p_1+n_1)\omega_{2n}\right)(e_1+g_1)\,\omega_{2n}}{\left(e_0+g_0-e_2\omega_{2n}^2\right)^2 + (e_1+g_1)^2\omega_{2n}^2} \right] \right.$$
$$\left. +2j\pi \right\},$$
$$j = 1, 2, 3, \ldots.$$

Let $\tau_{20} = \min\left\{\tau_{2n}^0\right\}$ and the corresponding $\omega_{20} = \omega_{2n}\,|_{\tau_2=\tau_{20}}$. By differentiating two sides of (19) with respect to τ_2, we have

$$\left(\frac{d\lambda}{d\tau_2}\right)^{-1} = \frac{3\lambda^2 + 2(p_2+n_2) + (p_1+n_1)}{\lambda[\left(e_2\lambda^2 + (e_1+g_1)\lambda + e_0 + g_0\right)e^{-\lambda\tau_2}]} + \frac{2e_2\lambda + e_1 + g_1}{\lambda\left[e_2\lambda^2 + (e_1+g_1)\lambda + e_0 + g_0\right]} - \frac{\tau_2}{\lambda}.$$

Then we can get

$$\mathrm{Re}\left(\frac{d\lambda}{d\tau_2}\right)^{-1}_{\tau_2=\tau_{20}} = \frac{f'(\omega_{20}^2)}{(e_0+g_0)^2\omega_{20}^2 + \left(e_2\omega_{20}^2 - e_0 - g_0\right)^2}.$$

It is obvious that the transversality condition $\mathrm{Re}\left(\frac{d\lambda}{d\tau_2}\right)^{-1}_{\tau_2=\tau_{20}} \neq 0$ if and only if $f'(\omega_{20}^2) \neq 0$.

Theorem 3. *If the conditions in Lemma 6 and* $f'(\omega_{20}^2) \neq 0$ *hold, then the positive equilibrium* E_2 *of system* (3) *is locally asymptotically stable for* $\tau_2 \in [0, \tau_{20})$ *and system* (3) *undergoes a Hopf bifurcation at* $\tau_2 = \tau_{20}$.

The analysis method of $\tau_2 = 0$, $\tau_1 > 0$ and $\tau_1 = \tau_2 \neq 0$ is similar to that of *CaseI*, so we omit here.

Case II. $\tau_1 > 0$ and $\tau_2 > 0$. We consider $\tau_2 = [0, \tau_{20})$ and regard τ_1 as a bifurcation parameter. Let $i\omega_2$ be the root of (10). Then we have

$$\begin{cases} (n_1\omega_2 - g_0\sin\omega_2\tau_2 + g_1\omega_2\cos\omega_2\tau_2)\cos\omega_2\tau_1 - (g_0\cos\omega_2\tau_2 + g_1\omega_2\sin\omega_2\tau_2 \\ \qquad +n_0 - n_2\omega_2^2)\sin\omega_2\tau_1 = e_1\omega_2\cos\omega_2\tau_2 + p_1\omega_2 - (e_0 - e_2\omega_2^2)\sin\omega_2\tau_2 - \omega_2^3, \\ (n_1\omega_2 - g_0\sin\omega_2\tau_2 + g_1\omega_2\cos\omega_2\tau_2)\sin\omega_2\tau_1 + (g_0\cos\omega_2\tau_2 + g_1\omega_2\sin\omega_2\tau_2 \\ \qquad +n_0 - n_2\omega_2^2)\cos\omega_2\tau_1 = p_2\omega_2^2 - e_1\omega_2\sin\omega_2\tau_2 - (e_0 - e_2\omega_2^2)\cos\omega_2\tau_2 - p_0. \end{cases} \tag{22}$$

From (22), we can obtain

$$\omega_2^6 + q_{24}\omega_2^4 + q_{23}\omega_2^2 + q_{22} + q_{21}\cos\omega_2\tau_2 + q_{20}\sin\omega_2\tau_2 = 0, \tag{23}$$

where

$$q_{21} = {p_2}^2 + e_2^2 - 2p_1 - n_2^2,\; q_{23} = {p_1}^2 + e_1^2 + 2n_2n_0 - 2e_2e_0 - 2p_2p_0 - g_1^2,$$
$$q_{21} = 2(e_1 + e_2p_2)\omega_2^4 + 2(e_1p_1 + n_2g_0 - p_0e_2 - p_2e_0 - n_1g_1)\omega_2^2 + 2\left((p_0+n_0)e_0 - n_0g_0\right),$$
$$q_{20} = -2e_2\omega_2^5 + 2(p_1e_2 + e_0 + n_2g_1 - p_2e_1)\omega_2^3 + 2(p_0e_1 - e_0p_1 - n_1g_0 - n_0g_1)\omega_2.$$

Define $f_1(\omega_2) = \omega_2^6 + q_{24}\omega_2^4 + q_{23}\omega_2^2 + q_{22} + q_{21}\cos\omega_2\tau_2 + q_{20}\sin\omega_2\tau_2 = 0$. If $q_{22} + q_{21} < 0$, then $f_1(0) < 0$ and apparently, $\lim_{\omega_2\to+\infty} f_1(\omega_2) = +\infty$. Therefore, (23) has at most six positive roots ω_{2n}, $n = 1, 2, \ldots, 6$. For every fixed ω_{2n}, the critical values of τ_1 are

$$\tau_{1n}^j = \frac{1}{\omega_{2n}}\left\{ arc\cos\left(\frac{e_{44}\omega_{2n}^4 + e_{43}\omega_{2n}^3 + e_{42}\omega_{2n}^2 + e_{41}\omega_{2n} + e_{40}}{p_{44}\omega_{2n}^4 + p_{43}\omega_{2n}^3 + p_{42}\omega_{2n}^2 + p_{41}\omega_{2n} + p_{40}} \right) + 2j\pi \right\},\; j = 1, 2, 3, \ldots,$$

where

$$e_{40} = g_0 e_0 \sin^2\omega_2\tau_2 - (n_0 + g_0\cos\omega_2\tau_2)(p_0 + e_0\cos\omega_2\tau_2),$$
$$e_{41} = -2(e_0 g_1 + e_1 g_0)\cos\omega_2\tau_2\sin\omega_2\tau_2 + (p_0 g_1 - p_1 g_0 - n_1 e_0 - n_0 e_1)\sin\omega_2\tau_2,$$
$$e_{42} = p_1 n_1 + p_2 n_0 + (p_1 g_1 + p_2 g_0 + n_1 e_1 + n_0 e_2)\cos\omega_2\tau_2 + 2\cos^2\omega_2\tau_2 + n_2(e_0\cos\omega_2\tau_2 + p_0),$$
$$e_{43} = n_0 p_2 + n_0 e_2\cos\omega_2\tau_2 + (n_2 e_1 + p_2 g_1)\sin\omega_2\tau_2 + e_2 g_1\sin 2\omega_2\tau_2,$$
$$e_{44} = n_1 - n_2 p_2 + (g_1 - e_2 n_2)\cos\omega_2\tau_2,$$
$$p_{40} = n_0^2 + g_0^2 - 2n_0 g_0\cos\omega_2\tau_2,\ p_{41} = 2(n_0 g_1 - n_1 g_0)\sin\omega_2\tau_2,$$
$$p_{42} = n_1^2 + g_1^2 - 2n_0 n_2 + 2(n_1 g_1 - n_0 n_2)\cos\omega_2\tau_2,\ p_{43} = -2n_2 g_1\sin\omega_2\tau_2,\ p_{44} = n_2^2.$$

Let $\tau_{10} = \min\left\{\tau_{1n}^0\right\}$ and $\omega_{20} = \omega_{2n}|_{\tau_1=\tau_{10}}$, and the transversality condition is actually

$$\mathrm{Re}\left(\frac{d\lambda}{d\tau_1}\right)^{-1}_{\tau_1=\tau_{10}} = \frac{M_1M_3 + M_2M_4}{M_1^2 + M_2^2},$$

where

$$M_1 = g_0\omega_{20}\sin\left(\omega_{20}(\tau_2 + \tau_{10}^0)\right) - g_1\omega_{20}^2\cos\left(\omega_{20}(\tau_2 + \tau_{10}^0)\right) + \left(n_0\omega_{20} - n_2\omega_{20}^3\right)\sin\omega_{20}\tau_{10}^0 - n_1\omega_{20}^2\cos\omega_{20}\tau_{10}^0,$$
$$M_2 = g_0\omega_{20}\cos\left(\omega_{20}(\tau_2 + \tau_{10}^0)\right) + g_1\omega_{20}^2\sin\left(\omega_{20}(\tau_2 + \tau_{10}^0)\right) + \left(n_0\omega_{20} - n_2\omega_{20}^3\right)\cos\omega_{20}\tau_{10}^0 + n_1\omega_{20}^2\sin\omega_{20}\tau_{10}^0,$$
$$\begin{aligned}M_3 = {}& -3\omega_{20}^2 + p_1 + (2e_2\omega_{20} - \tau_3 e_1\omega_{20})\sin\omega_{20}\tau_2 + 2n_2\omega_{20}\sin\omega_{20}\tau_{10}^0 + (g_1 - \tau_2 g_0)\cos\left(\omega_{20}(\tau_2 + \tau_{10}^0)\right)\\ &+ (e_1 + \tau_2 e_2 - \tau_2 e_0)\cos\omega_{20}\tau_2 + n_0\cos\omega_{20}\tau_{10}^0 - \tau_2 g_1\omega_{20}\sin\left(\omega_{20}(\tau_2 + \tau_{10}^0)\right),\end{aligned}$$
$$\begin{aligned}M_4 = {}& 2p_2\omega_{20} + (2e_2\omega_{20} - \tau_2 e_1\omega_{20})\cos\omega_{20}\tau_2 + \left(\tau_2 e_0 - e_1 - \tau_2 e_2\omega_{20}^2\right)\sin\omega_{20}\tau_2\\ &+ 2n_2\omega_{20}\cos\omega_{20}\tau_{10}^0 - n_1\sin\omega_{20}\tau_{10}^0 - \tau_2 g_1\omega_{20}\cos\left(\omega_{20}(\tau_2 + \tau_{10}^0)\right) + (\tau_2 g_0 - g_1)\sin\left(\omega_{20}(\tau_2 + \tau_{10}^0)\right).\end{aligned}$$

The $\mathrm{Re}\left(\frac{d\lambda}{d\tau_1}\right)^{-1}_{\tau_1=\tau_{10}} \neq 0$ if and only if $M_1M_3 + M_2M_4 \neq 0$. So we have

Theorem 4. *For $\tau_2 \in [0, \tau_{20})$, if $q_{22} + q_{21} < 0$ and $M_1M_3 + M_2M_4 \neq 0$ hold, then the positive equilibrium E_2 is locally asymptotically stable when $\tau_1 \in [0, \tau_{10})$ and unstable when $\tau_1 > \tau_{10}$. System (3) undergoes Hopf bifurcation at positive equilibrium E_2 when $\tau_1 = \tau_{10}$.*

3.2. Direction and stability of the Hopf bifurcation

In this subsection, by the normal form theory and center manifold theorem of functional differential equation, we calculate the direction of Hopf bifurcation and the stability of bifurcated periodic solution in $Case II$. For $\tau_2 \in (0, \tau_{20})$, we denote any of the critical values $\tau_{1n}^j(n = 1,2,\ldots,6,\ j = 1,2,\ldots)$ by τ_{1n}^*. After scaling $t = {}^t/_{\tau_1}$ and introducing $u_1 = x - x_2$, $u_2 = y - y_2$, $u_3 = v - v_2$, $\mu = \tau_1 - \tau_{10}^*$, we have the following functional differential equation in $C\left([-1, 0], \mathbb{R}^3\right)$

$$\dot{u}(t) = L_\mu(u_t) + z(\mu, u_t), \tag{24}$$

where $u \in (u_1, u_2, u_3)^T \in \mathbb{R}^3$ and $L_\mu(\phi) : C \to \mathbb{R}^3$ is

$$L_\mu(\phi) = (\tau_{10}^* + \mu)B_1\begin{pmatrix}\phi(0)\\ \phi(0)\\ \phi(0)\end{pmatrix} + (\tau_{10}^* + \mu)B_2\begin{pmatrix}\phi(-1)\\ \phi(-1)\\ \phi(-1)\end{pmatrix} + (\tau_{10}^* + \mu)B_3\begin{pmatrix}\phi(-\frac{\tau_2}{\tau_{10}^*})\\ \phi(-\frac{\tau_2}{\tau_{10}^*})\\ \phi(-\frac{\tau_2}{\tau_{10}^*})\end{pmatrix},$$

and $z(\mu, u_t)$ is given by

$$z(\mu, \phi) = (\tau_{10}^* + \mu)\begin{pmatrix}z_1\\ z_2\\ z_3\end{pmatrix},$$

where for $\phi \in (\phi_1, \phi_2, \phi_3)^T \in C\left([-1,0], \mathbb{R}^3\right)$,

$$z_1 = -\frac{\beta}{2}\phi_1(0)\phi_3(0),\ z_2 = \frac{\beta}{2}\phi_1(0)\phi_3(0) - \frac{s}{2k}\phi_1(0)\phi_2(0) - \frac{s}{k}\phi_2^2(0),\ z_3 = -\frac{\beta}{2}\phi_1(0)\phi_3(0).$$

By the Riesz representation theorem, there exists a 3×3 matrix function $\eta(\theta, \mu)$ such that

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

and $\eta(\theta, \mu)$ is actually

$$d\eta(\theta, \mu) = (\tau_{10}^* + \mu)\left[B_1\delta(\theta) + B_2\delta(\theta+1) + C_3\delta(\theta + \frac{\tau_2}{\tau_{10}^*})\right],$$

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

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

and

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

For $\theta = 0$, system (24) is equivalent to

$$\dot{u}_t = A(\mu)u_t + R(\mu)u_t,$$

where $u_t = u(t+\theta)$ for $\theta \in [-1, 0]$.

Next, we define the adjoint operator A^* of A

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

associated with the bilinear form

$$\langle \psi(s), \phi(\theta) \rangle = \bar{\psi}(0)\phi(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \bar{\psi}(\xi - \theta)d\eta(\theta)\phi(\xi)d\xi.$$

Let $\vartheta(\theta)$ be the eigenvector corresponding to eigenvalue $i\omega_{10}$ of $A(0, 0)$ and $\vartheta^*(s)$ be the eigenvector corresponding to eigenvalue $-i\omega_{10}$ of A^*, and define $\vartheta(\theta) = (1, \vartheta_1, \vartheta_2)e^{i\theta\omega_{10}\tau_{10}^*}$, $\vartheta^*(s) = D(1, \vartheta_1^*, \vartheta_2^*)e^{i\theta\omega_{10}\tau_{10}^*}$. By simple calculation, we have

$$\vartheta_1 = \frac{-a_{21}a_{12} - a_{12}\left(a_{11} - b_{11}e^{-i\omega_{10}\tau_{10}^*} - i\omega_{10}\tau_{10}^*\right)}{-a_{12}b_{11}e^{-i\omega_{10}\tau_{10}^*} + a_{12}\left(a_{22} - i\omega_{10}\tau_{10}^*\right)},$$

$$\vartheta_2 = \frac{-b_{11}a_{21}e^{-i\omega_{10}\tau_{10}^*} - (a_{22} - i\omega_{10}\tau_{10}^*)(a_{11} - b_{11}e^{-i\omega_{10}\tau_{10}^*} - i\omega_{10}\tau_{10}^*)}{a_{12}b_{11}e^{-i\omega_{10}\tau_{10}^*} - a_{12}(a_{22} - i\omega_{10}\tau_{10}^*)}.$$

From $\langle \vartheta^*(s), \vartheta(\theta) \rangle = \bar{D}(1, \vartheta_1, \vartheta_2)(1, \vartheta_1, \vartheta_2)^T$, we can get

$$\bar{D} = \frac{1}{1 + \vartheta_1\bar{\vartheta}_1^* + \vartheta_2\bar{\vartheta}_2^* - \tau_{10}^*e^{-i\omega_{10}\tau_{10}^*}(b_{11} + b_{11}\vartheta_1) - \tau_2 c_{11}\vartheta_2\bar{\vartheta}_2^* e^{-i\omega_{10}\tau_2}}.$$

To calculate key values of Hopf bifurcation, we define $w(t) = \langle \vartheta^*, u_t \rangle$ and $W(t, \theta) = u_t(\theta) - 2\,\mathrm{Re}\,\{w(t)\vartheta(\theta)\}$.

On the center manifold C_0, $W(t, \theta)$ is

$$W(t, \theta) = W(w(t), \bar{w}(t), \theta) = W_{20}(\theta)\frac{w^2}{2} + W_{11}(\theta)w\bar{w} + W_{02}(\theta)\frac{\bar{w}^2}{2} + W_{30}(\theta)\frac{w^3}{6} + h.o.t.$$

For the solution $u_t \in C_0$ of (24), we have

$$\begin{aligned}\dot{w} &= i\omega_{10}\tau_{10}^{*}w + \left\langle \vartheta^{*}(\theta), z(0, W(w(t), \bar{w}(t), \theta)) + 2\operatorname{Re}\{w(t)\vartheta(\theta)\}\right\rangle \\ &= i\omega_{10}\tau_{10}^{*}w + \vartheta^{*}(0)z(0, W(w(t), \bar{w}(t), \theta)) + 2\operatorname{Re}\{w(t)\vartheta(0)\} \\ &= i\omega_{10}\tau_{10}^{*}w + \vartheta^{*}(0)z_0(w(t), \bar{w}(t)) \triangleq i\omega_{10}\tau_{10}^{*}w + g(w(t), \bar{w}(t)),\end{aligned}$$

where

$$g(w(t), \bar{w}(t)) = \vartheta^{*}(0)z_0(w(t), \bar{w}(t)) = g_{20}\frac{w^2}{2} + g_{11}w\bar{w} + g_{02}\frac{\bar{w}^2}{2} + g_{21}\frac{w^2\bar{w}}{2} + h.o.t. \tag{25}$$

It follows from the definitions of $w(t)$ and $z(\mu, \phi)$ that

$$g(w(t), \bar{w}(t)) = \bar{D}\tau_{10}^{*}(1, \vartheta_1^{*}, \vartheta_2^{*})(w_1^{(0)}, w_2^{(0)}, w_3^{(0)})^{T}. \tag{26}$$

Comparing the coefficients of (25) and (26) leads to

$$\begin{aligned}g_{20} &= 2\left[\frac{\beta}{2}(\bar{\vartheta}_1^{*} - \bar{\vartheta}_2^{*} - 1)\vartheta_2 - \frac{s}{2k}\bar{\vartheta}_1^{*}\vartheta_1 - \frac{s}{k}\vartheta_1^{*}\vartheta_1^{2}\right]e^{2i\omega_{10}\tau_{10}^{*}\theta}, \\ g_{11} &= \frac{\beta}{2}(\bar{\vartheta}_1^{*} - \bar{\vartheta}_2^{*} - 1)(\vartheta_2 + 1) - \frac{s}{2k}\bar{\vartheta}_1^{*}(\vartheta_1 + 1) - \frac{2s}{k}\bar{\vartheta}_1^{*}\vartheta_2, \\ g_{02} &= 2\left[\frac{\beta}{2}(\bar{\vartheta}_1^{*} - \bar{\vartheta}_2^{*} - 1) - \frac{s}{2k}\bar{\vartheta}_1^{*}\frac{s}{k}\vartheta_1^{*}e^{-2i\omega_{10}\tau_{10}^{*}\theta}\right], \\ g_{21} &= \beta(\bar{\vartheta}_1^{*} - \bar{\vartheta}_2^{*} - 1)\left[\frac{W_{20}^{(1)}(0)}{2}e^{-i\omega_{10}\tau_{10}^{*}\theta} + W_{11}^{(1)}(0)\vartheta_2e^{i\omega_{10}\tau_{10}^{*}\theta} + \frac{W_{20}^{(3)}(0)}{2}e^{-i\omega_{10}\tau_{10}^{*}\theta} + W_{11}^{(3)}(0)e^{i\omega_{10}\tau_{10}^{*}\theta}\right] \\ &\quad - \frac{s}{k}\bar{\vartheta}_1^{*}\left[\frac{W_{20}^{(1)}(0)}{2}e^{-i\omega_{10}\tau_{10}^{*}\theta} + W_{11}^{(1)}(0)\vartheta_2e^{i\omega_{10}\tau_{10}^{*}\theta} + \frac{W_{20}^{(2)}(0)}{2}e^{-i\omega_{10}\tau_{10}^{*}\theta} + W_{11}^{(2)}(0)e^{i\omega_{10}\tau_{10}^{*}\theta}\right] \\ &\quad - \frac{2s}{k}\vartheta_1^{*}\left[W_{20}^{(2)}(0)e^{-i\omega_{10}\tau_{10}^{*}\theta} + 2W_{11}^{(2)}(0)\vartheta e^{i\omega_{10}\tau_{10}^{*}\theta}\right].\end{aligned}$$

Here, we omit the calculation of unknown terms $W_{20}^{(1)}$, $W_{20}^{(2)}$, $W_{20}^{(3)}$ and $W_{11}^{(2)}$, $W_{11}^{(3)}$ in coefficient g_{21}. In fact, these can be easily obtained by solving some differential equations. Furthermore, we have

$$\mu_2 = -\frac{\operatorname{Re}(C_1(0))}{\operatorname{Re}(\lambda'(\tau_{10}^{*}))}, \quad \beta_2 = \operatorname{Re}(C_1(0)),$$

where

$$.C_1(0) = \frac{i}{2\omega_{10}\tau_{10}^{*}}\left(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2}.$$

From the Hopf bifurcation theory of functional differential equations [4,22], we know that the direction of the Hopf bifurcation is determined by μ_2, and β_2 is for the stability of periodic solutions. so we have

Theorem 5. *The Hopf bifurcation is supercritical (subcritical) when $\mu_2 > 0$($\mu_2 < 0$) and the periodic solutions bifurcated from hopf bifurcation are stable (unstable) when $\beta_2 < 0$($\beta_2 > 0$).*

3.3. Zero-Hopf bifurcation

In this subsection, we study the existence of Zero-Hopf bifurcation of system (3). For $\tau_2 = 0$, if the characteristic equation has a simple zero root and a pair of pure imaginary roots, and the other roots have strictly negative real parts, then system (3) undergoes Zero-Hopf bifurcation [6,30,33]. For convenience, let

$$H(\lambda, \tau_1) = \lambda^3 + (p_2 + e_2)\lambda^2 + (p_1 + e_1)\lambda + p_0 + e_0 + \left(n_2\lambda^2 + (n_1 + g_1)\lambda + n_0 + g_0\right)e^{-\lambda\tau_1}. \tag{27}$$

For (27), we have the following result

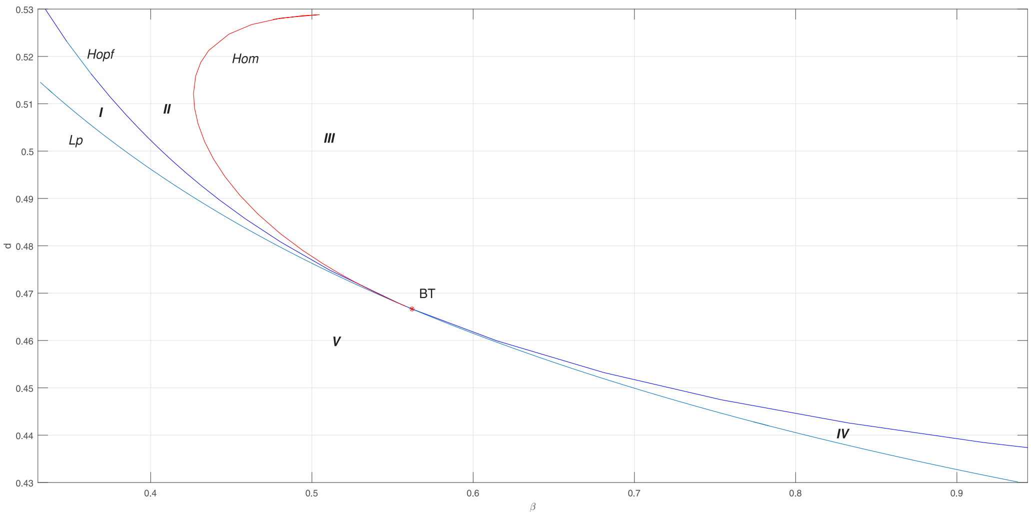


Fig. 1. Bifurcation diagram of Bogdanov–Takens bifurcation point in β–d plane. Hopf bifurcation curve and saddle–node bifurcation curve intersect, and the intersection point is Bogdanov–Takens point. Moreover, there are one homoclinic bifurcation curve originating from Bogdanov–Takens point. The β–d plane is divided into five regions, defined as I–V.

Lemma 7. *If $p_0 = -(e_0 + g_0 + n_0)$ and $\frac{p_1+e_1+g_1+n_1}{n_0+g_0} < 0$ hold, then the characteristic equation of system (3) has a simple zero root for all $\tau_1 > 0$.*

Proof. From (27), due to $p_0 = -(e_0 + g_0 + n_0)$, it is obvious that

$$H(0, \tau_1) = p_0 + (e_0 + g_0 + n_0) = 0,$$

and

$$\frac{\partial H(0, \tau_1)}{\partial \lambda} = p_1 + e_1 + g_1 + n_1 - \tau_1(n_0 + g_0).$$

Then $\frac{\partial H(0,\tau_1)}{\partial \lambda} \neq 0$ if and only if $\tau_1 = \frac{p_1+e_1+g_1+n_1}{n_0+g_0} < 0$. So the characteristic equation of system (3) has a simple zero root for all $\tau_1 > 0$ when $p_0 = -(e_0 + g_0 + n_0)$ and $\frac{p_1+e_1+g_1+n_1}{n_0+g_0} < 0$ hold.

Following $CaseII$ in Section 2, we can obtain

Theorem 6. *For $\tau_1 = \tau_{10}$, if $p_0 = -(e_0 + g_0 + n_0)$ and $\frac{p_1+e_1+g_1+n_1}{n_0+g_0} < 0$ hold, then (27) has a simple zero root and a pair of purely imaginary roots $\pm i\omega_{20}$ and the other roots of (27) have negative real parts. Namely, system (3) undergoes a Zero-Hopf bifurcation around the non-trivial equilibrium E_2.*

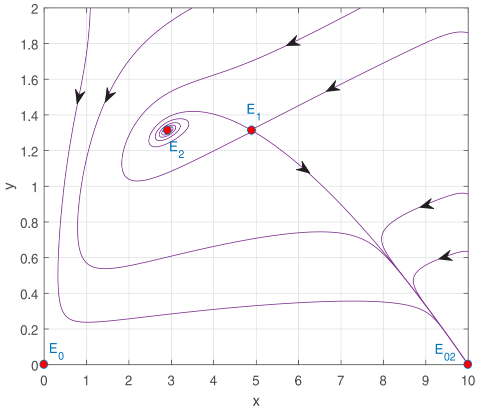
4. Numerical simulations

In this section, we simulate Bogdanov–Takens bifurcation in model (2) and Zero-Hopf bifurcation in model (3), respectively. Due to these Co-dimension two bifurcations, there are bistability, periodic coexistence and chaotic behavior in system. All these dynamic phenomena are shown in this section.

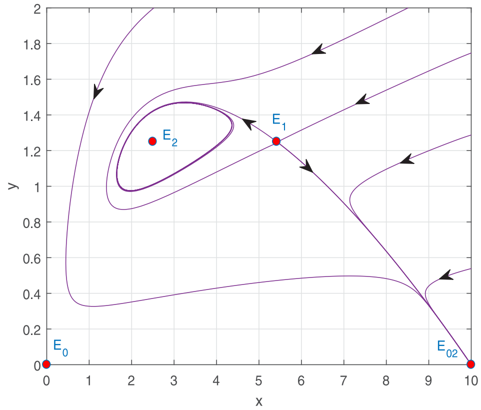
4.1. Simulations of Bogdanov–Takens bifurcation in model (2)

We regard β and d as the Bogdanov–Takens bifurcation parameters, and the values of other parameters are as follows

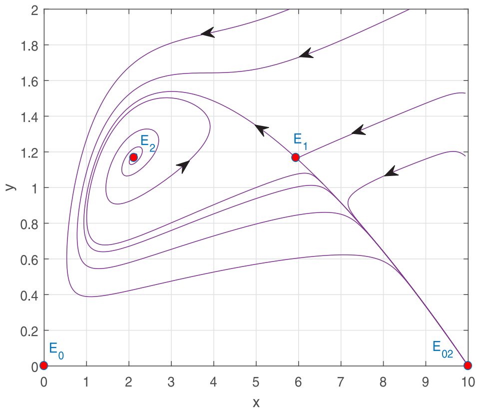
$$r = 0.3, \; k = 10, \; s = 0.2, \; \delta = 0.5, \; \alpha = 0.35.$$



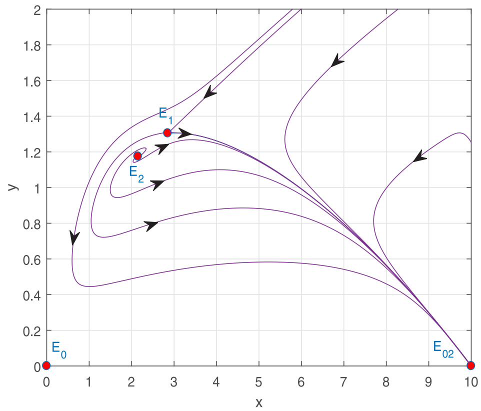
(a) $I : (\beta, d) = (0.4, 0.5)$



(b) $II : (\beta, d) = (0.42, 0.5)$



(c) $III : (\beta, d) = (0.45, 0.5)$



(d) $IV : (\beta, d) = (0.76, 0.445)$

Fig. 2. Trajectories of system (2) with different β and d. (a) Bistability between the asymptotically stable equilibrium E_2 and E_{02}. (b) Bistability between a stable periodic solution near the positive equilibrium point E_2 and E_{02}. (c) With the emergence of homoclinic orbit, the periodic solution of system (2) disappears. (d) All solutions are stable to the boundary equilibrium E_{02}.

It can be calculated that the hypothesis (H2) is satisfied, and the critical values of β and d for Bogdanov–Takens bifurcation are $\beta^* = 0.562086$ and $d^* = 0.466656$, respectively, and $E_2 = (2.999945, 1.322285, 0.303052)$. By using MATCONT [9,20], the normal form of Bogdanov–Takens bifurcation of system (2) is

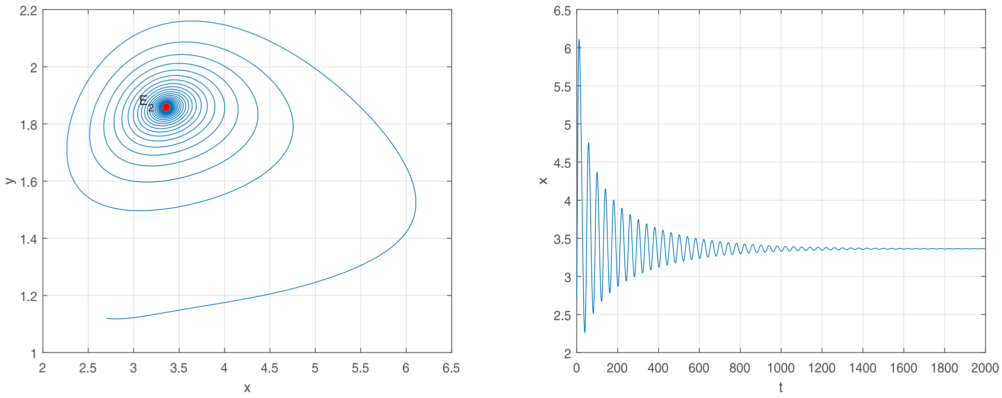
$$\begin{cases} \dot{z}_1 = z_2, \\ \dot{z}_2 = -0.0024862+0.043738z_1 + z_1^2 + z_1 z_2, \end{cases}$$

and the two parameters bifurcation diagram is shown in Fig. 1. For region I, there is bistability between the asymptotically stable equilibrium E_2 and E_{02} (see Fig. 2(a)). There is bistability phenomenon between a stable periodic solution near the positive equilibrium point E_2 and E_{02} in region II (see Fig. 2(b)). As for region III, with the emergence of homoclinic orbit, the periodic solution of system (2) disappears (see Fig. 2(c)). For region IV, all solutions are stable to the boundary equilibrium E_{02} (see Fig. 2(d)). Finally, there is only a boundary equilibrium E_{02} in region V.

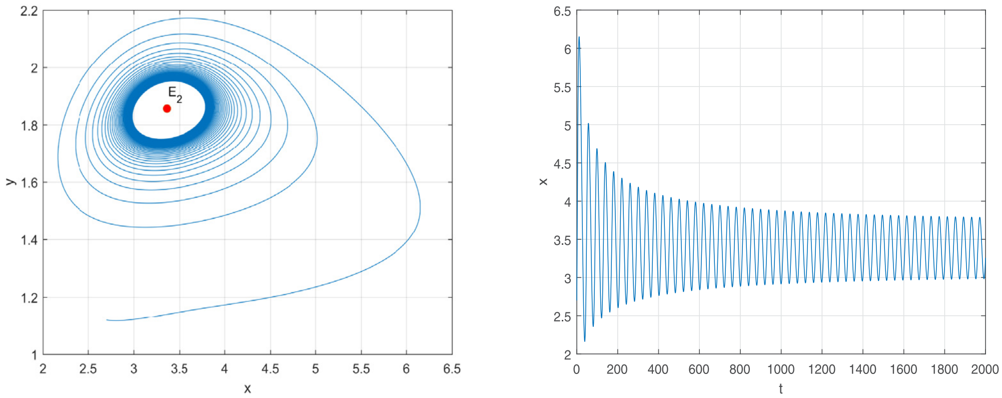
4.2. *Simulations of Zero-Hopf bifurcation in model (3)*

For $\tau_1 = 0$ and $\tau_2 > 0$, the parameter values are as follows:

$$r = 0.55,\ k = 10,\ \beta = 0.4,\ s = 0.05,\ \delta = 0.5,\ d = 0.6,\ \alpha = 0.35.$$



(a) $\tau_2 = 2$



(b) $\tau_2 = 2.2$

Fig. 3. Numerical results for system (3) with different τ_2. (a) The positive equilibrium E_2 is asymptotically stable. (b) There is a stable periodic solution of system (3).

By calculation, we get the critical value $\tau_{20} = 1.969$, and when $\tau_2 > \tau_{20}$, system (3) has a stable periodic solution (see Fig. 3), and the positive equilibrium E_2 is asymptotically stable when $\tau_2 < \tau_{20}$. For $\tau_1 > 0$ and $\tau_2 > 0$, we take the following parameters

$$r = 0.3,\ k = 10,\ \beta = 0.3,\ s = 0.05,\ \delta = 0.5,\ d = 0.6,\ \alpha = 0.35,\ \tau_2 = 3.$$

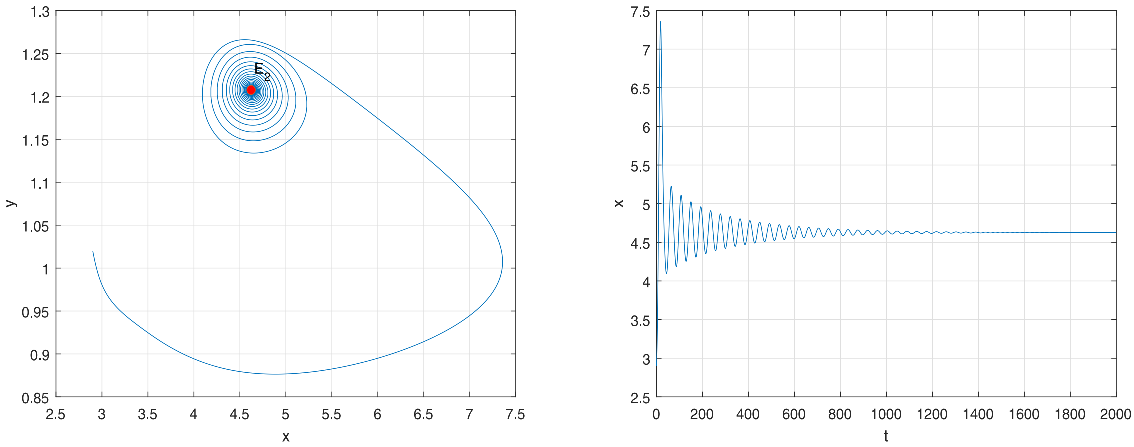
The critical values $\tau_{10} = 4.1252$, $\mu_2 = 0.1245 > 0$ and $\beta_2 = -0.018598 < 0$ are easily obtained. From Theorem 4, the positive equilibrium E_2 is asymptotically stable when $\tau_1 < \tau_{10}$, and system (3) has a stable periodic solution when $\tau_1 > \tau_{10}$ (see Fig. 4).

Finally, we regard τ_1 and r as bifurcation parameters to simulate Zero-Hopf bifurcation. The parameters we selected are as follows

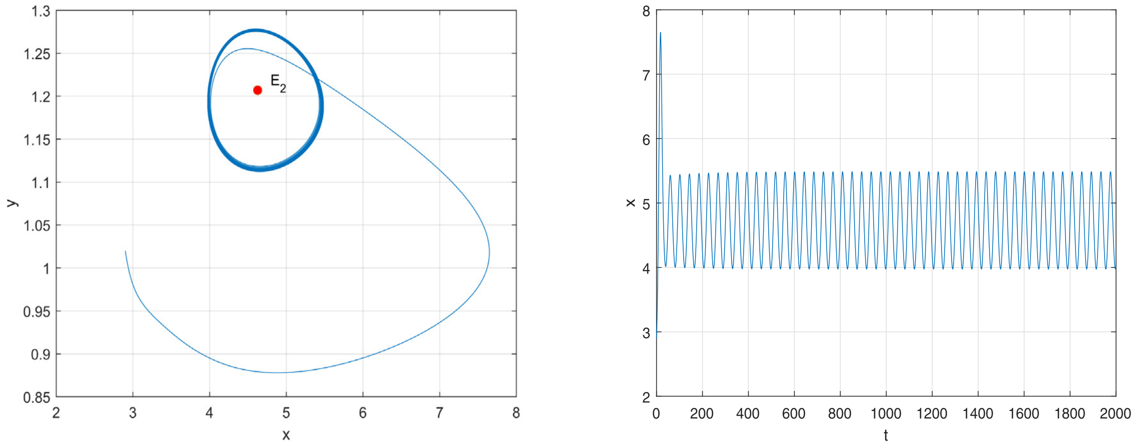
$$k = 10,\ \beta = 0.3,\ s = 0.2,\ \delta = 0.5,\ d = 0.53,\ \alpha = 0.35.$$

By using DDE-BIFTOOL [12,13,26], the normal form of Zero-Hopf bifurcation of system (3) is

$$\begin{cases} \dot{z}_0 = -0.017601 z_0^2 + (0.0013746 - 0.030339\mathrm{i})|z_1|^2 - 0.012044 z_0^3 - 0.031473 z_0 |z_1|^2, \\ \dot{z}_1 = 0.1397 i z_1 + (0.0013746 - 0.030339\mathrm{i}) z_0 z_1 + (0.012766 - 0.013735\mathrm{i}) z_0^2 z_1 + (0.0041182 \\ \qquad -0.016159\mathrm{i}) z_1 |z_1|^2, \end{cases}$$



(a) $\tau_1 = 3.9$



(b) $\tau_1 = 4.3$

Fig. 4. Numerical results for system (3) with different τ_1. (a) The positive equilibrium E_2 is asymptotically stable. (b) There is a stable periodic solution of system (3).

and the two quantities that characterize the Zero-Hopf bifurcation are $s = sign(0.00075406) = 1$ and $\theta = -0.078096 < 0$. The τ_1–r plane bifurcation diagram is shown in Fig. 5 and the plane is divided into five regions. By calculation, the values of τ_1 and r of Zero-Hopf point are $\tau_1^* = 7.677634$ and $r^* = 0.3666754$, respectively.

For region $D1$, the positive equilibrium E_2 is asymptotically stable, and when the initial value is far away from E_2, the solution finally converges to the boundary equilibrium E_{02}, and system (3) also has bistability between E_{02} and E_2 (see Fig. 6(a)). In this case, all infected tumor cells disappear, and the number of uninfected tumor cells reaches the maximum carrying capacity k. In regions $D2$ and $D5$, system (3) also has the similar convergence (see Figs. 6(b), 10 and 11). For region $D2$, due to the different values of τ_1 and r, system (3) either has a stable periodic solution (see Fig. 6(b), and there is a bistability between the stable periodic solution near E_2 and E_{02}) or chaotic behavior [14,23,31] near E_2 (see Figs. 7 and 8, respectively). Moreover, with the appearance of chaotic behavior, system (3) has a stable periodic solution near the boundary equilibrium E_{02} (see Figs. 7 and 8(a)), that is, in this case, system (3) coexists two periodic solutions. As for region $D3$, system (3) has two stable periodic solutions near E_{02} and E_2, respectively (see Fig. 9(a)), and for region $D4$, different degrees of oscillation behavior is shown in Fig. 9(b). System (3) has a saddle point E_2^* on the fold bifurcation curve $D6$ (see Fig. 11), and there are two periodic solutions bifurcated from the Zero-Hopf equilibrium point (see Fig. 12).

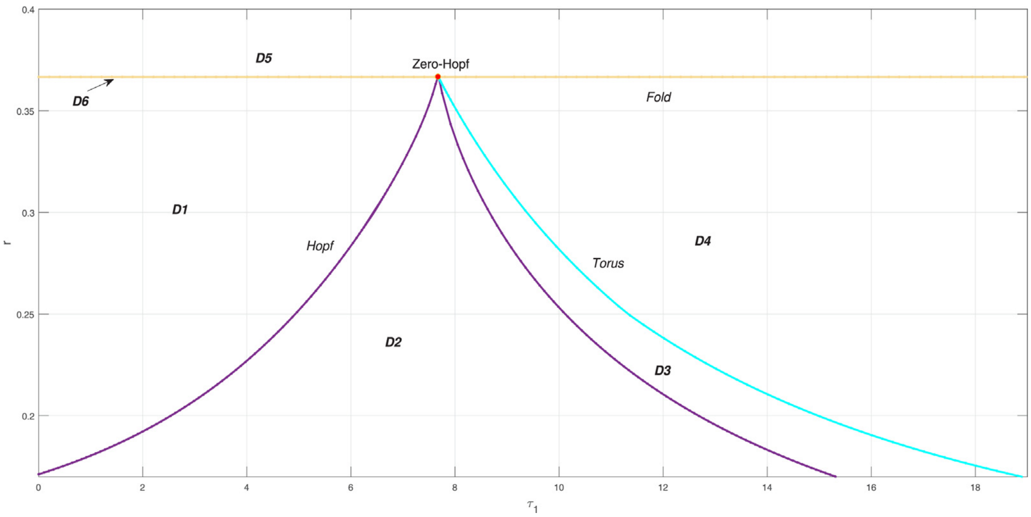
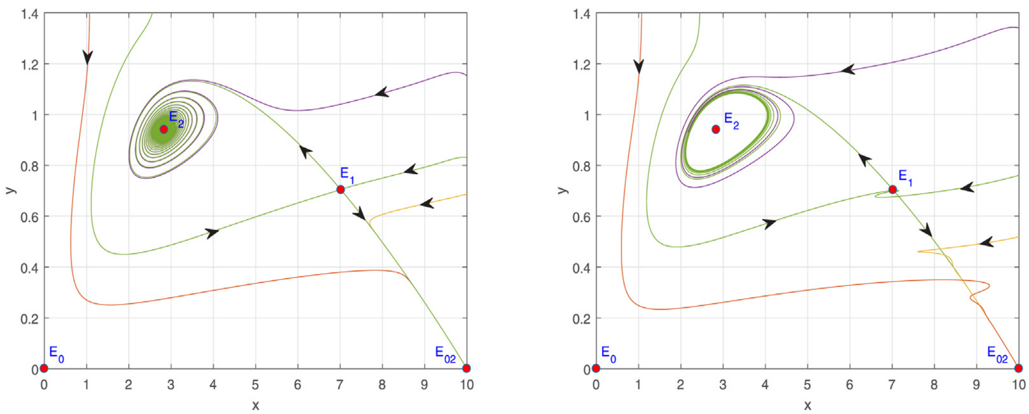


Fig. 5. Bifurcation diagram of Zero-Hopf point. Hopf bifurcation curve and Fold bifurcation curve intersect, and the intersection point is Zero-Hopf point. Moreover, there are one torus bifurcation curve originating from Zero-Hopf point. The τ_1–r plane is divided into five regions, defined as $D1$–$D5$.



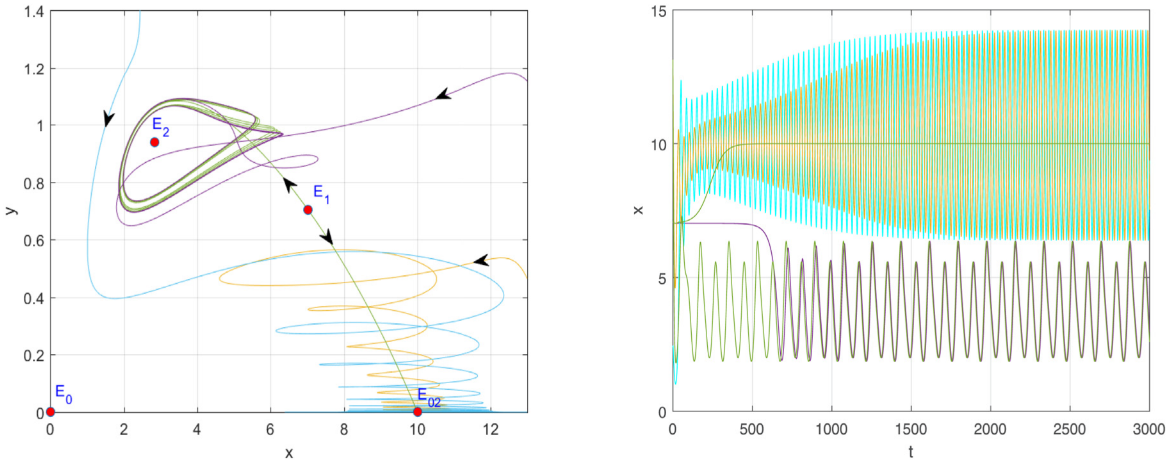
(a) $D1 : (\tau_1, r) = (2, 0.2)$ (b) $D2 : (\tau_1, r) = (4, 0.2)$

Fig. 6. Numerical results for system (3) in regions $D1$ and $D2$.

5. Conclusion

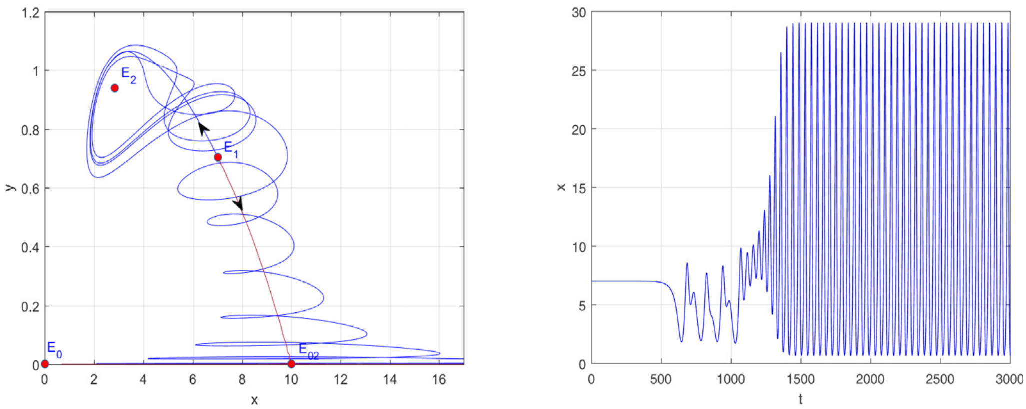
In this paper, we study a virotherapy model with two time delays and analyze the existence of positive equilibrium of the system and prove the existence of Hopf bifurcation and Zero-Hopf bifurcation. Moreover, for the model without delay, we analyze the Hopf and Bogdanov–Takens bifurcations. Both model (2) and model (3) have bistability phenomenon, and the difference is that model (3) has chaotic behavior and periodic coexistence. Finally, some numerical experiments are also carried out for theoretical calculation. Thus, in the process of virus treatment, different delays will lead to interesting dynamic phenomena, such as asymptotic stability and periodic solution, for uninfected tumor cells and infected tumor cells, which is conducive to tumor treatment in the future.

In conclusion, the growth rate of uninfected tumor cells and the production delay of uninfected tumor cells play a key role in the number of infected and uninfected tumor cells.

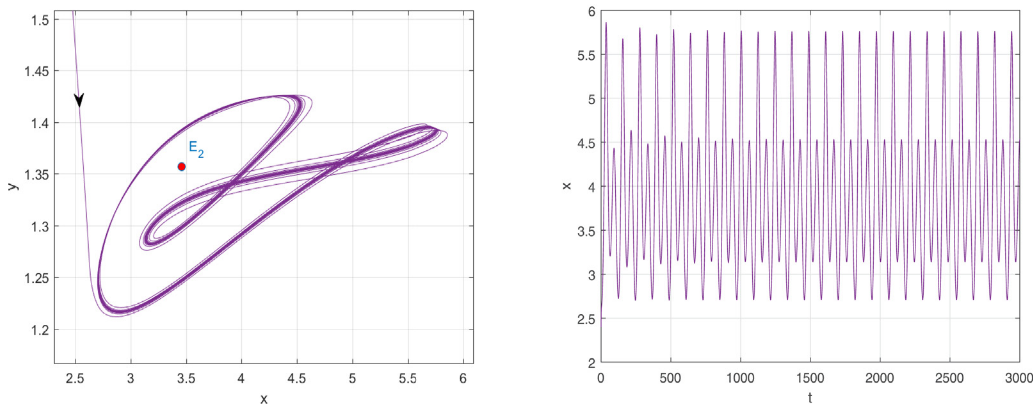


(a) $D2 : (\tau_1, r) = (8, 0.2)$

Fig. 7. Numerical results for system (3) in region $D2$.

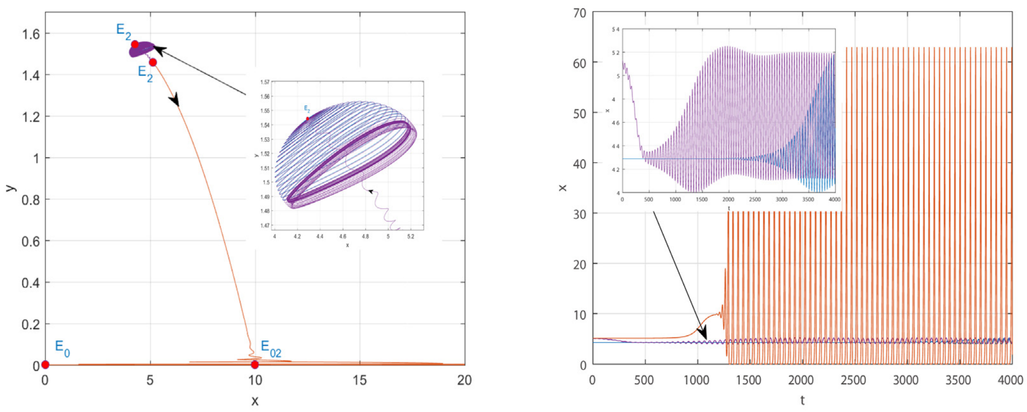


(a) $D2 : (\tau_1, r) = (10, 0.2)$

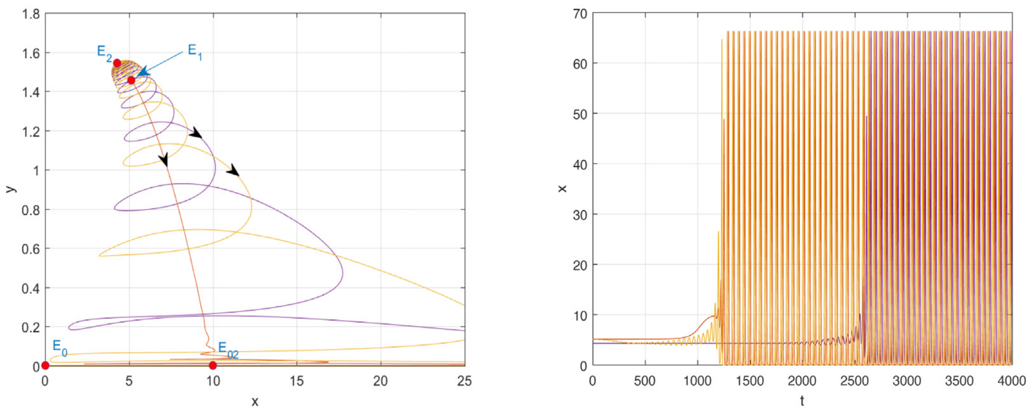


(b) $D2 : (\tau_1, r) = (8, 0.3)$

Fig. 8. Numerical results for system (3) in region $D2$.

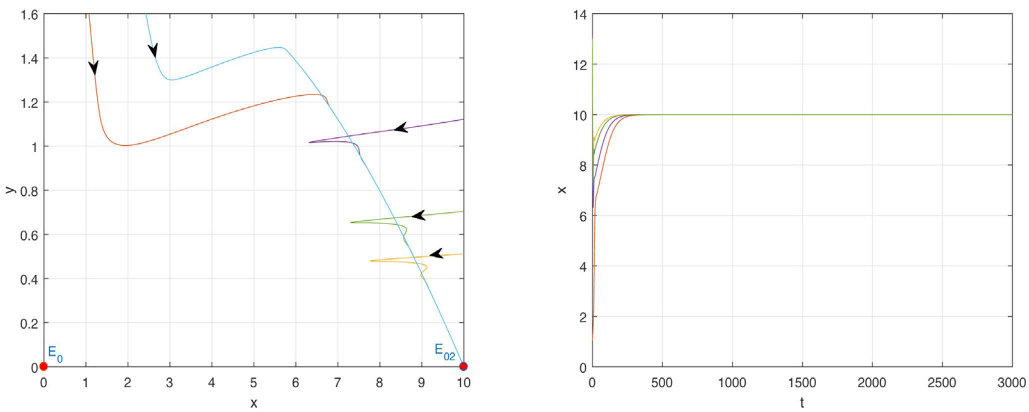


(a) $D3 : (\tau_1, r) = (7.8, 0.36)$



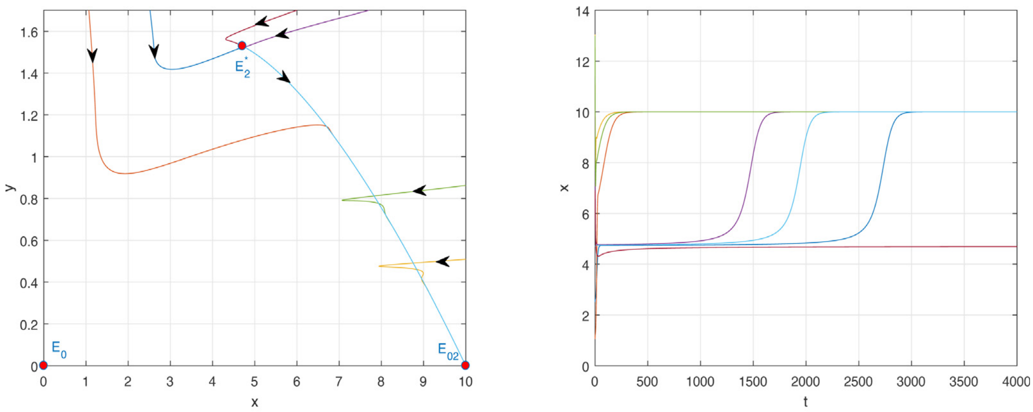
(b) $D4 : (\tau_1, r) = (7.95, 0.36)$

Fig. 9. Numerical results for system (3) in regions $D3$ and $D4$.



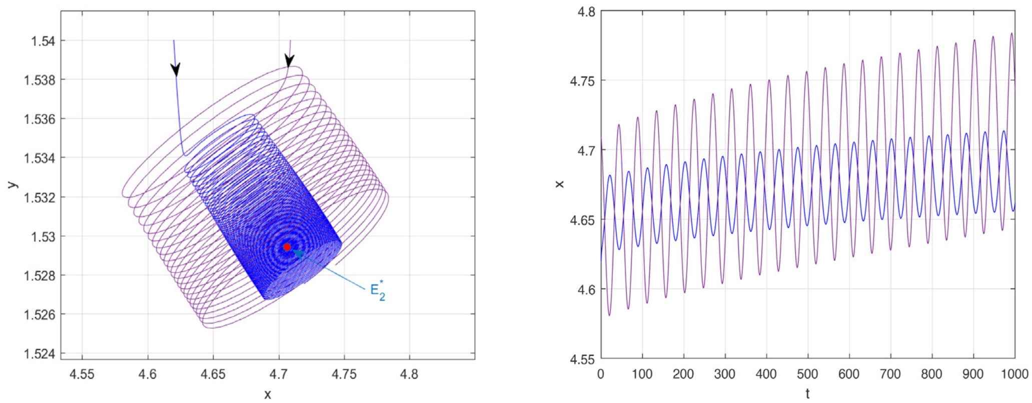
(a) $D5 : (\tau_1, r) = (2, 0.4)$

Fig. 10. Numerical results for system (3) in region $D3$.



(a) $D6:(\tau_1, r) = (2, 0.3666754)$

Fig. 11. Numerical results for system (3) in Fold curve $D6$.



(a) $Zero-Hopf\,point:(\tau_1, r) = (7.677634, 0.3666754)$

Fig. 12. The two periodic solutions bifurcated from the Zero-Hopf equilibrium point.

Acknowledgments

The authors are grateful to all anonymous reviewers for their valuable comments, which has provided great help for the improvement of the paper.

Funding

This work is supported by the Science Foundation of Education Department of HuBei Province (No. B2017389).

References

[1] Salma M. Al-Tuwairqi, Najwa O. Al-Johani, Eman A. Simbawa, Modeling dynamics of cancer radiovirotherapy, J. Theoret. Biol. 506 (2020) 110405.

[2] Akram Ashyani, Hajimohammad Mohammadinejad, Omid RabieiMotlagh, Hopf bifurcation analysis in a delayed system for cancer virotherapy, Indag. Math. (N.S.) 27 (1) (2016) 318–339.

[3] Sandip Banerjee, Alexei Tsygvintsev, Stability and bifurcations of equilibria in a delayed Kirschner–Panetta model, Appl. Math. Lett. 40 (2015) 65–71.

[4] Meriem Bentounsi, Imane Agmour, Naceur Achtaich, Youssef El Foutayeni, The Hopf bifurcation and stability of delayed predator–prey system, J. Comput. Appl. Math. 37 (5) (2018) 5702–5714.

[5] Matt Biesecker, Jung-Han Kimn, Huitian Lu, David Dingli, Željko Bajzer, Optimization of virotherapy for cancer, Bull. Math. Biol. 72 (2) (2010) 469–489.

[6] Jason Bramburger, Benoit Dionne, Victor G. LeBlanc, Zero-Hopf bifurcation in the van der Pol oscillator with delayed position and velocity feedback, Nonlinear Dynam. 78 (4) (2014) 2959–2973.
[7] Joseph J. Crivelli, Juraj Földes, Peter S. Kim, Joanna R. Wares, A mathematical model for cell cycle-specific cancer virotherapy, J. Biol. Dyn. 6 (sup1) (2012) 104–120.
[8] Lisette G. De Pillis, Ami Radunskaya, The dynamics of an optimally controlled tumor model: A case study, Math. Comput. Model. 37 (11) (2003) 1221–1244.
[9] Annick Dhooge, Willy Govaerts, Yu A. Kuznetsov, MATCONT: A MATLAB package for numerical bifurcation analysis of ODEs, ACM Trans. Math. Softw. 29 (2) (2003) 141–164.
[10] David Dingli, Matthew D. Cascino, Krešimir Josić, Stephen J. Russell, Željko Bajzer, Mathematical modeling of cancer radiovirotherapy, Math. Biosci. 199 (1) (2006) 55–78.
[11] A.M. Elaiw, A.D. Al Agha, Analysis of a delayed and diffusive oncolytic M1 virotherapy model with immune response, Nonlinear Anal. Real World Appl. 55 (2020) 103116.
[12] Koen Engelborghs, Tatyana Luzyanina, Dirk Roose, Numerical bifurcation analysis of delay differential equations using DDE-BIFTOOL, ACM Trans. Math. Softw. 28 (1) (2002) 1–21.
[13] Koen Engelborghs, T. Luzyanina, G. Samaey, et al., DDE-BIFTOOL: A Matlab package for bifurcation analysis of delay differential equations, TW Rep. 305 (2000) 1–36.
[14] Y. Gao, K.T. Chau, Hopf bifurcation and chaos in synchronous reluctance motor drives, IEEE Trans. Energy Convers. 19 (2) (2004) 296–302.
[15] Kevin Harrington, Daniel J. Freeman, Beth Kelly, James Harper, Jean-Charles Soria, Optimizing oncolytic virotherapy in cancer treatment, Nat. Rev. Drug Discov. 18 (9) (2019) 689–706.
[16] Wentao Huang, Qinlong Wang, Aiyong Chen, Hopf bifurcation and the centers on center manifold for a class of three-dimensional circuit system, Math. Methods Appl. Sci. 43 (4) (2020) 1988–2000.
[17] Xiaowei Jiang, Xiangyong Chen, Tingwen Huang, Huaicheng Yan, Bifurcation and control for a predator-prey system with two delays, IEEE Trans. Circuits Syst. I. 68 (1) (2020) 376–380.
[18] G.K. Katara, A. Kulshrestha, M.K. Jaiswal, S. Pamarthy, A. Gilman-Sachs, K.D. Beaman, Inhibition of vacuolar ATPase subunit in tumor cells delays tumor growth by decreasing the essential macrophage population in the tumor microenvironment, Oncogene 35 (8) (2016) 1058–1065.
[19] Subhas Khajanchi, Sandip Banerjee, Stability and bifurcation analysis of delay induced tumor immune interaction model, Appl. Math. Comput. 248 (2014) 652–671.
[20] K. Kobravi, W. Kinsner, S. Filizadeh, Analysis of bifurcation and stability in a simple power system using MATCONT, in: 2007 Canadian Conference on Electrical and Computer Engineering, IEEE, 2007, pp. 1150–1154.
[21] Yuri A. Kuznetsov, Elements of Applied Bifurcation Theory, Vol. 112, Springer Science & Business Media, 2013.
[22] Qinglian Li, Yunxian Dai, Xingwei Guo, Xingyong Zhang, Hopf bifurcation analysis for a model of plant virus propagation with two delays, Adv. Differ. Equ. 2018 (1) (2018) 1–22.
[23] Stephen C. Lubkemann, Culture in Chaos, University of Chicago Press, 2010.
[24] B.O. Sang, Hopf bifurcation formular and applications to the genesio-tesi system, J. Nonlinear Funct. Anal. 2019 (2019) 34.
[25] Jianjun Paul Tian, The replicability of oncolytic virus: Defining conditions in tumor virotherapy, Math. Biosci. Eng. 8 (3) (2011) 841.
[26] B.I. Wage, Normal form computations for delay differential equations in DDE-BIFTOOL (Master's thesis), 2014.
[27] Dominik Wodarz, Viruses as antitumor weapons: Defining conditions for tumor remission, Cancer Res. 61 (8) (2001) 3501–3507.
[28] Dominik Wodarz, Gene therapy for killing p53-negative cancer cells: Use of replicating versus nonreplicating agents, Hum. Gene. Ther. 14 (2) (2003) 153–159.
[29] K. Marcel Wouapi, B. Hilaire Fotsin, K. Florent Feudjio, T. Zeric Njitacke, Hopf bifurcation, offset boosting and remerging Feigenbaum trees in an autonomous chaotic system with exponential nonlinearity, SN Appl. Math. 1 (12) (2019) 1–22.
[30] Xiaoqin Wu, Liancheng Wang, Zero-Hopf bifurcation for van der Pol's oscillator with delayed feedback, J. Comput. Appl. Math. 235 (8) (2011) 2586–2602.
[31] Xuebing Zhang, Honglan Zhu, Hopf bifurcation and chaos of a delayed finance system, Complexity 2019 (2019).
[32] Xinyue Evelyn Zhao, Bei Hu, The impact of time delay in a tumor model, Nonlinear Anal. Real World Appl. 51 (2020) 103015.
[33] Bin Zhen, Jian Xu, Fold–Hopf bifurcation analysis for a coupled FitzHugh–Nagumo neural system with time delay, Int. J. Bifurc. Chaos 20 (12) (2010) 3919–3934.