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Research Article

Hopf bifurcation analysis in a delayed model of tumor therapy with oncolytic viruses

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Abstract

The stability and Hopf bifurcation of a nonlinear mathematical model are described by the delay differential equation proposed by Wodarz for interaction between uninfected tumor cells and infected tumor cells with the virus. By choosing τ as a bifurcation parameter, we show that the Hopf bifurcation can occur for a critical value τ. Using the normal form theory and the center manifold theory, formulas are given to determine the stability and the direction of bifurcation and other properties of bifurcating periodic solutions. Then, by changing the infection rate to two nonlinear infection rates, we investigate the stability and existence of a limit cycle for the appropriate value of τ, numerically. Lastly, we present some numerical simulations to justify our theoretical results.

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Keywords: Hopf bifurcation; Delay model; Oncolytic viruses; Tumor cells.

1 Introduction

Cancer is a significant cause of death in the world. Thus, it is essential to discover some practical ways to prevail over it. Many studies have been made on cancer treatments, tumor cells behavior, clinical care, and so on. The primary purpose of cancer treatment is to reduce the destructive effects of cell behaviors [7]. The routine therapeutic substances for cancer are surgery,

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radiation, and chemotherapies. The first two treatments are excellent choices for tumor cells when they have metastatic behavior [16]. The conventional therapies are not only efficient but also highly toxic, so most efforts focus on establishing tumor cells targeted treatments. For this reason, the biological encountering is the most up to date practice [11]. An Oncolytic virus is a type of virus that infects a cell and then explodes it. In this process, the cell dies, and new virus particles are produced. The main problem with Oncolytic virus therapy is that the virus stays in the blood for a short time due to the secretion of the immune system [6, 15]. Oncolytic viruses that specifically target tumor cells are promising anti-cancer therapeutic agents. Due to our lack of understanding of the Oncolytic virus's dynamic spread in cancer cells, it is challenging to continuously control or eradicate cancer cells. The interaction between an Oncolytic virus and tumor cells, a type of virus-cell interaction, can be described by the mathematical models. The interplay between populations of uninfected tumor cells and infected tumor cells with the virus is complex and nonlinear. In this context, some mathematical models for the virus therapies of cancer cells can be seen as a tool for perceiving cancer-virus dynamics and finding better strategies for treatment; see [3, 4, 9].

In the proposed mathematical models, some parameters play a crucial role in the model's qualitative analysis. For example, an average and optimal rate of virus-infected cell death may optimize the treatment success, or the lower the number of uninfected cancer cells in the stable state can better predict the treatment process; see [11, 12]. Here, we recall a set of mathematical models that describe the virus's spread through the tumor cells in different ways [1]. First, we consider a general model as follows:

$$\begin{aligned} \frac{dx}{dt} &= xF(x,y) - \beta y G(x,y), \\ \frac{dy}{dt} &= \beta y G(x,y) - ay. \end{aligned} \tag{1}$$

This model consists of two populations: the population of uninfected tumor cells x and the infected tumor cells population by the virus y. The function $F(x,y)$ denotes the growth rate of noninfected cells, and the function $G(x,y)$ represents which the uninfected cells become infected with the virus. The coefficient β represents the infectivity of the virus. Virus-infected cells die with a rate of ay. Assuming that the growth of tumor cells approaches the carrying capacity and after a while, slows down and that the cell growth rate reaches zero, $F(x,y) = rx(1-(x+y))$ can be expressed by the logistic function. The $G(x,y)$ function plays a crucial role in determining the system's stability and helps us to make long-term predictions about treatment outcomes. Also, $G(x,y)$ can be divided into two different classes. In the class I, if the number of noninfected cells is greater than the number of infected cells and the tumor cells are not solid, then the virus replicates and increases the number of infected cells. Biologically, the growth of the virus is exponential and is called "fast virus spread." In class II, when the number of infected cells increases, the virus's growth rate decreases. The situation occurs in solid tumors because, as the number of infected cells increases, internal cells are surrounded by outer cells. Therefore, they cannot spread the virus. This type of infection is known as the "slow virus spread" [14].

We choose the following rates of infection given by [14]:

$$\begin{aligned} G_1(x,y) &= x, \\ G_2(x,y) &= \frac{(1+\varepsilon)x}{(x+y+\varepsilon)}, \\ G_3(x,y) &= \frac{x}{(xy^{\frac{1}{3}}+\varepsilon)}. \end{aligned}$$

Here G_1 and G_2 belong to class of "fast virus spread" and G_3 belongs to class of "slow virus spread". By replacing $F(x,y) = rx(1-\frac{x+y}{\omega})$ and $G = G_1$ in (1), we get

$$\begin{aligned} \frac{dx}{dt} &= rx(1-\frac{x+y}{\omega}) - \beta xy, \\ \frac{dy}{dt} &= \beta xy - ay. \end{aligned} \tag{2}$$

In 2016, the following model was developed by Wodarz, similar to (2) in which tumor cells death rate was considered (see [13]) as

$$\begin{aligned} \frac{dx}{dt} &= rx(1-\frac{x+y}{\omega}) - \delta x - \beta xy, \\ \frac{dy}{dt} &= \beta xy - ay, \end{aligned} \tag{3}$$

so that δ is defined the death rate for the uninfected tumor cells. Since (3) is an extension of (2), we introduce a delay time τ for entering virus in (3), such that it changes into

$$\begin{aligned} \frac{dx}{dt} &= rx(1-\frac{x+y}{\omega}) - \delta x - \beta xy, \\ \frac{dy}{dt} &= \beta x(t-\tau)y(t-\tau) - ay. \end{aligned} \tag{4}$$

Because of the simplicity of the delay calculations in system (4), first, we perform the calculations the delay equation of (4) analytically, and we find the appropriate parameter of τ to produce the limit cycle in (4). Now, by changing the linear infection rate of (4) to G_2 and G_3 and entering τ, we obtain, respectively,

$$\frac{dx}{dt} = rx(1 - \frac{x+y}{\omega}) - \delta x - \frac{\beta(1+\varepsilon)xy}{(x+y+\varepsilon)}, \quad (5)$$
$$\frac{dy}{dt} = \frac{\beta(1+\varepsilon)x(t-\tau)y(t-\tau)}{(x(t-\tau)+y(t-\tau)+\varepsilon)} - ay,$$

and

$$\frac{dx}{dt} = rx(1 - \frac{x+y}{\omega}) - \delta x - \frac{\beta xy}{(xy^{\frac{1}{3}}+\varepsilon)}, \quad (6)$$
$$\frac{dy}{dt} = \frac{\beta x(t-\tau)y(t-\tau)}{(x(t-\tau)y(t-\tau)^{\frac{1}{3}}+\varepsilon)} - ay.$$

By placing the parameter τ obtained from (4) and changing ε, we simulate the existence of a limit cycle in (5) and (6), numerically. The parameters r, ω, ε, β, and a are all positive and independent of the time. The state variables $x(t)$ and $y(t)$ are nonnegative. The parameter r is the reproduction rate of tumor cells, ω is the maximum carrying capacity of tumor cells, and the coefficient β denotes the virus's replication rate. Moreover, a is a death rate for the population y that are killed by the virus and ε is a positive parameter that is expressed only to fit the data to the model better.

In [10], the mathematical model

$$\frac{dx}{dt} = rx(1 - \frac{x+y}{K}) - bxy,$$
$$\frac{dy}{dt} = bx(t-\tau)y(t-\tau)e^{-n\tau} - ay,$$

for tumor virotherapy with the viral life-cycle is considered. In this model, the delay parameter displays the period of the viral life-cycle. The two parameters, b and a, are dominant factors in virotherapy. When $b < a$, the tumor cells reach their maximum size and the equilibrium solution $(1, 0)$, for $\tau \geq 0$, is stable. So, the therapy fails, but for $b > a$, the model's dynamic is much complicated, where the viral life-cycle comes to play an important role. As $b > a$, the viruses cannot exterminate the tumor cells without the viral life-cycle period. When the delay parameter value is small, the tumor cells and the viruses coexist, and their equilibrium solution is locally asymptotical stable. If the value of the delay parameter is longer than the period of viral life-cycle, the coexisting solution will be unstable, then the population of the tumor cells and the viruses will not rest on a fixed level. The model has a stable period solution for the value of the delay parameter in the middle range.

In appearance, by supposing $\delta = 0$, the model of (4) is similar to [10] for $n = 0$, but they are different in some ways. Firstly, in (4), there is the mortality rate of uninfected cells, which results in different reproduction rates with [10]. In this article, we investigate the stability of equilibrium points of (3) for different values of the reproduction rate by using the Lyapunov function. Then, with the Dulak theorem, we prove the absence of a limit cycle in (4) for $\tau = 0$. Another difference between this work and [10] is the use of the center manifold theory in the study of the stability, direction, and period of periodic solutions of bifurcation at (4) for critical values of τ, analytically.

In [2], another mathematical model

$$\frac{dx}{dt} = rx(1 - \frac{x+y}{k}) - dx - \beta xy,$$
$$\frac{dy}{dt} = \beta xy + sy(1 - \frac{x+y}{k}) - ay(t-\tau),$$

for tumor virotherapy is proposed. Wodarz in his article has stated that the infection rate and death rate of virus-infected cells play a key role in model dynamics. In that article, there is the time delay in death of infected cells and it entered in the linear sentence. Also, the Hopf bifurcation for linear infection rate is investigated. Our article's innovation is that the time delay in the arrival of the virus to tumor cells, and it entered in the nonlinear sentence. Also we have used three models with different Wodarz infection rates, two of them belong to the class of nonsolid tumors, and the other belongs to solid tumors. Using the obtained value τ suitable for the existence of a limit cycle in the initial model and its placement in the next two models, we have numerically shown that this dynamic depicts the general biological conditions of solid and nonsolid tumor cells and the effect of viral therapy on them.

In this article, we study the stability and Hopf bifurcation of system (4); then we compare it with (5) and (6). At first, in Theorem 1, we investigate the stability of the equilibrium points for system (4) for $\tau = 0$. Then in Lemma 2 and Theorem 3, we consider the existence of periodic solutions and the Hopf bifurcation for system (4) by inserting τ into the second equation (3) as a delayed time for importing Oncolytic viruses to the body and countering it with cancer cells. In Section 4, we describe the stability, direction, and period of the bifurcating periodic solutions at critical values of τ, by using the center manifold theory introduced in [5]. In Section 5, we substitute the appropriate value of τ obtained from (4) into (5) and (6). Then we simulate (5) and (6) for different values of ε. Finally, we discuss about them.

2 Stability of equilibrium points

In this section, we obtain equilibrium points of system (4) for $\tau = 0$ and study the conditions for the existence of positive equilibrium points. It is obvious that system (4) has equilibrium points $E_0 = (0,0)$, $E_1 = \left(\frac{\omega(r-\delta)}{r}, 0\right)$, and $E_2 = \left(\frac{a}{\beta}, \frac{\beta\omega(r-\delta)-ra}{\beta(r+\beta\omega)}\right)$.
The Jacobian matrix of system (4) is denoted by

$$J(x,y)=\begin{pmatrix}(r-\delta)-\frac{2rx}{\omega}-(\frac{r}{\omega}+\beta)y & -(\frac{r}{\omega}+\beta)x\\ \beta y & \beta x-a\end{pmatrix}.$$

Theorem 1. Suppose $\mathcal{R}_0=\frac{r}{\delta}$; then for $\tau=0$, we have the following properties:

(a) If $\mathcal{R}_0\leqslant 1$, then E_0 is a unique equilibrium point that is a stable node.

(b) If $1-\frac{1}{\mathcal{R}_0}<\frac{a}{\beta\omega}$ and $\mathcal{R}_0>1$, then there exist two equilibrium points E_0 and E_1 such that E_0 is a saddle point and E_1 is a stable focus.

(c) If $1-\frac{1}{\mathcal{R}_0}>\frac{a}{\beta\omega}$ and $\mathcal{R}_0>1$, then there exist three equilibrium points E_0, E_1, and E_2 such that E_0 and E_1 are saddle points and E_2 is a stable focus.

(d) If $1-\frac{1}{\mathcal{R}_0}=\frac{a}{\beta\omega}$, then $E_1=E_2$ and we have two equilibrium points such that E_0 is a saddle point and E_1 is locally asymptotically stable.

Proof.

(a) The Jacobian matrix of system (4) at the origin is

$$J(0,0)=\begin{pmatrix}r-\delta & 0\\ 0 & -a\end{pmatrix}, \tag{7}$$

which has the eigenvalues $\lambda_1=r-\delta<0$ and $\lambda_1=-a<0$, when $\mathcal{R}_0=\frac{r}{\delta}<1$. This shows that E_0 is a stable node.

(b) When $\mathcal{R}_0>1$, for $\tau=0$, there exists the equilibrium point E_1 and the Jacobian matrix of system (4) at E_1 is

$$J(E_1)=\begin{pmatrix}-r+\delta & -(r-\delta)(1+\frac{\beta\omega}{r})\\ 0 & \frac{\beta\omega(r-\delta)-ra}{r}\end{pmatrix}. \tag{8}$$

It has the characteristic polynomial

$$\lambda^2+m_1\lambda+m_2=0,$$

where

$$m_1=a-\beta\omega+\beta\omega\frac{\delta}{r}+(r-\delta),$$
$$m_2=(r-\delta)(a-\beta\omega+\beta\omega\frac{\delta}{r}).$$

For $a>\beta\omega-\beta\omega\frac{\delta}{r}$ or $1-\frac{1}{\mathcal{R}_0}<\frac{a}{\beta\omega}$, we have that $m_k>0$ $(k=1,2)$ and this implies that E_1 is a stable focus.

(c) For $\mathcal{R}_0>1$ and $a<\beta\omega-\beta\omega\frac{\delta}{r}$, there exist two positive equilibrium points E_1 and E_2 such that the Jacobian matrix of system (4) at E_2 is

$$J(E_2) = \begin{pmatrix} -\frac{ra}{\beta\omega} & -a(\frac{r+\beta\omega}{\beta\omega}) \\ \frac{\beta\omega(r-\delta)-ra}{r+\beta\omega} & 0 \end{pmatrix}.$$

Since $tr(J(E_2)) = \frac{-ra}{\beta\omega} < 0$ and $det(J(E_2)) = \frac{a(\beta\omega(r-\delta)-ra)}{\beta\omega} > 0$, then E_2 is a stable focus.

(d) By substituting $1 - \frac{1}{\mathcal{R}_0} = \frac{a}{\beta\omega}$ in (8), we obtain $\lambda_1 = -(r-\delta) < 0$ and $\lambda_2 = 0$. Hence, E_1 is a nonhyperbolic fixed point with a zero eigenvalue. To show its stability, we use a suitable Lyapunove function. In the set $\Delta = \{(x(t), y(t))|x(t) \geq 0, y(t) \geq 0\}$, we define a Lyapunov function

$$V(x,y) = x - \frac{\omega(r-\delta)}{r} - \frac{\omega(r-\delta)}{r}\ln\frac{rx}{\omega(r-\delta)} + \frac{\beta\omega + r}{\beta\omega}y,$$

such that $V(E_1) = 0$ and $V(x,y) > 0$ for all $(x,y) \in \Delta \setminus \{E_1\}$. We now show $\frac{dV}{dt} \leq 0$ for all $(x,y) \in \Delta$. By differentiating $V(x,y)$ along the solutions $(x(t), y(t))$ of (4), we have

$$\begin{aligned}\frac{dV}{dt} &= \frac{\partial V}{\partial x}\frac{dx}{dt} + \frac{\partial V}{\partial y}\frac{dy}{dt} = \left(1 - \frac{\omega(r-\delta)}{rx}\right)\dot{x} + \frac{r+\beta\omega}{\beta\omega}\dot{y} \\ &= \left(1 - \frac{\omega(r-\delta)}{rx}\right)\left((r-\delta)x - \frac{r}{\omega}x^2 - (\frac{r+\beta\omega}{\omega})xy\right) + \left(\frac{r+\beta\omega}{\beta\omega}\right)(\beta xy - ay) \\ &= 2(r-\delta) - \frac{r}{\omega}x^2 - \frac{\omega(r-\delta)^2}{r} + (r+\beta\omega)\left(\frac{(r-\delta)}{r} - \frac{a}{\beta\omega}\right)y \\ &= -\frac{\omega}{r}\left(\frac{r^2}{\omega^2}x^2 - 2\frac{r}{\omega}(r-\delta)x + (r-\delta)^2\right) + \left(\frac{r+\beta\omega}{\beta\omega}\right)\left(\frac{\beta\omega(r-\delta)-ra}{r}\right)y \\ &= -\frac{\omega}{r}\left(\frac{r}{\omega}x - (r-\delta)\right)^2 + \left(\frac{r+\beta\omega}{\beta\omega}\right)\left(\frac{\beta\omega(r-\delta)-ra}{r}\right)y.\end{aligned}$$

As $1 - \frac{1}{\mathcal{R}_0} = \frac{a}{\beta\omega}$, then $\frac{\beta\omega(r-\delta)-ra}{r} = 0$ and $\frac{dV}{dt} = -\frac{\omega}{r}\left(\frac{r}{\omega}x - (r-\delta)\right)^2 \leq 0$. If we set $\frac{dV}{dt} = 0$, then $x = \frac{\omega(r-\delta)}{r}$, and by substituting in system (4), we get $y = 0$. Therefore, E_1 is asymptotically stable. □

Theorem 2. System (3) in the set $\Delta = \{(x(t), y(t))|\ x(t) \geq 0, y(t) \geq 0\}$ does not have any periodic solutions.

Proof. We define $F_1 = (r-\delta)x - \frac{r}{\omega}x^2 - (\frac{r+\beta\omega}{\omega})xy$ and $F_2 = \beta xy - ay$. By considering the Dulac function $L(x,y) = \frac{1}{xy}$, we have

$$\frac{\partial(LF_1)}{\partial x} + \frac{\partial(LF_2)}{\partial y} = -\frac{r}{\omega y} < 0.$$

Thus, by the Bendixson's criterion, system (3) has no closed orbits lying entirely in Δ. □

We have now shown that system (3) has no periodic solutions. We consider system (4) and show that the Hopf bifurcation exists under special conditions for $\tau > 0$. First, we suppose that $E^* = (x^*, y^*)$ is a positive equilibrium point for the system (4). The characteristic equation of any equilibrium point $E^* = (x^*, y^*)$ of system (4) for $\tau > 0$, is given by

$$D(\lambda, \tau) = det(\lambda I - Q_1 - Q_2 e^{-\lambda\tau}) = 0,$$

where

$$Q_1 = \begin{pmatrix} r - \delta - \frac{2rx}{\omega} - (\frac{r}{\omega} + \beta)y & -(\frac{r}{\omega} + \beta)x \\ 0 & -a \end{pmatrix}, \quad Q_2 = \begin{pmatrix} 0 & 0 \\ \beta y & \beta x \end{pmatrix}.$$

Then

$$\begin{aligned} D(\lambda, \tau) &= det \begin{pmatrix} \lambda - r + \delta + \frac{2rx^*}{\omega} + (\frac{r}{\omega} + \beta)y^* & (\frac{r}{\omega} + \beta)x^* \\ -\beta y^* e^{-\lambda\tau} & \lambda - \beta x^* e^{-\lambda\tau} + a \end{pmatrix} \\ &= \lambda^2 + A_1\lambda + A_2 - (\lambda + B_1)B_2 e^{-\lambda\tau}, \end{aligned}$$

where

$$\begin{aligned} A_1 &= a - (r - \delta) + \frac{2rx^*}{\omega} + \frac{ry^*}{\omega} + \beta y^*, \\ A_2 &= a((r - \delta) + \frac{2rx^*}{\omega} + \frac{ry^*}{\omega} + \beta y^*), \\ B_1 &= (r - \delta) + \frac{2rx^*}{\omega}, \\ B_2 &= \beta x^* + a. \end{aligned}$$

Lemma 1. Let $x(\theta) = \phi_1(\theta) \geq 0$ and let $y(\theta) = \phi_2(\theta) \geq 0$, for $\theta \in [-\tau, 0]$, where $\phi = (\phi_1, \phi_2) \in C([-\tau, 0]; \mathbb{R}^2)$. Then the solution $(x(t), y(t))$ of system (4), defined on the interval $\Lambda = [0, T]$ for some $0 < T < \infty$, is positive and uniformly bounded on Λ.

Proof. The first equation of system (4) is a Bernouli equation, which can be written as

$$\dot{x}(t) - x(t) \left\{ (r - \delta) - (\frac{r}{\omega} + \beta)y(t) \right\} = -\frac{r}{\omega} x^2(t).$$

Its solution with the initial data $x(0) = x_0$ is

$$x(t) = x_0 e^{\int_0^t \left\{ (r-\delta) - (\frac{r}{\omega} + \beta)y(\gamma) \right\} d\gamma} \left\{ x_0 \int_0^t \frac{r}{\omega} e^{\int_0^s \left\{ (r-\delta) - (\frac{r}{\omega} + \beta)y(\gamma) \right\} d\gamma} ds + 1 \right\}^{-1}.$$

Thus, $x(t) \geq 0$ when $x(0) = x_0 \geq 0$. We know $y(\theta) \geq 0$ for $\theta \in [-\tau, 0]$; then $y(t - \tau) \geq 0$ for $t \in [0, \tau]$. Thus, by the second equation of system (4), we have $y(t) \geq y(0)e^{-at} \geq 0$, for $t \in [0, \tau]$. In a similar way, we obtain $y(t) \geq 0$ for $t \in [\tau, 2\tau]$. By repeating this process, we conclude that $y(t)$ is nonnegative for all $t \geq 0$. To prove the boundedness property of the solutions, we will first show that $x(t)$ is bounded. By the first equation of system (4), we have

$$\dot{x}(t) \leq (r-\delta)x(t) - \frac{r}{\omega}x^2(t),$$

and hence

$$x(t) \leq \frac{\omega(r-\delta)}{r + \left(\frac{\omega(r-\delta)}{x_0} - r\right)e^{-(r-\delta)t}}.$$

Putting $\beta_0 = \frac{\omega(r-\delta)}{x_0} - r$, we have

$$x(t) \leq \frac{\omega(r-\delta)}{r + \beta_0 e^{-(r-\delta)t}},$$

and therefore $\limsup_{t\to\infty} x(t) \leq \frac{\omega(r-\delta)}{r}$. Now by supposing $\Omega(t) = x(t) + y(t+\tau)$ and $\gamma = r - \delta > 0$, we have $\limsup_{t\to\infty} x(t) \leq \frac{\omega\gamma}{r} =: \beta_1$ and

$$\begin{aligned}
\dot{\Omega}(t) &= \dot{x}(t) + \dot{y}(t+\tau) \\
&= \gamma x(t) - \frac{r}{\omega}x^2(t) - \frac{r}{\omega}x(t)y(t) - \beta x(t)y(t) + \beta x(t)y(t) - ay(t+\tau) \\
&= \gamma x(t) - \frac{r}{\omega}x^2(t) - \frac{r}{\omega}x(t)y(t) - ay(t+\tau) - ax(t) + ax(t) \\
&\leq \beta_1(\gamma + a) - \frac{r}{\omega}x^2(t) - \frac{r}{\omega}x(t)y(t) - ay(t+\tau) - ax(t) \\
&\leq \beta_1(\gamma + a) - a(y(t+\tau) + x(t)) \\
&\leq \beta_1(\gamma + a) - a\Omega(t).
\end{aligned}$$

Hence, $\dot{\Omega}(t) + a\Omega(t) \leq \beta_1(\gamma + a)$, which gives $\Omega(t) \leq \frac{\beta_1(\gamma+a)}{a} - (\frac{\beta_1(\gamma+a)}{a} + \Omega(0))e^{-at}$. This implies that $\limsup_{t\to\infty} \Omega(t) \leq \frac{\beta_1(\gamma+a)}{a}$, for $r > \delta$. As a consequence, the functions $x(t)$ and $y(t)$ are uniformly bounded. □

3 Hopf bifurcation

We claim that for some $\tau > 0$, a Hopf bifurcation occurs. The interior equilibrium point E_2 exists when $\beta\omega(r-\delta) - ra > 0$. We move this point to the point $(1, 1)$ by setting

$$\begin{aligned}
x &= \frac{a}{\beta}X, \\
y &= \frac{\beta\omega(r-\delta) - ra}{\beta(r+\beta\omega)}Y, \qquad (9)\\
t &= T.
\end{aligned}$$

Applying the transformation (9) to (4), we get

$$\begin{aligned}\frac{dX}{dT} &= X(\gamma - mX) - nXY, \\ \frac{dY}{dT} &= -aY + aX(T-\tau)Y(T-\tau),\end{aligned} \tag{10}$$

where

$$\gamma = r - \delta, \qquad m = \frac{ra}{\omega\beta}, \qquad n = \frac{\beta\omega(r-\delta) - ra}{\beta\omega}. \tag{11}$$

Therefore, $(X, Y) = (1, 1)$ is an equilibrium point for system (10). Writing t instead of T and considering $u_1(t) = X(T) - 1$ and $u_2(t) = Y(T) - 1$ in system (10), we find that

$$\begin{aligned}\dot{u}_1(t) &= (u_1(t)+1)(\gamma - m(u_1(t)+1) - n(u_2(t)+1)), \\ \dot{u}_2(t) &= -a(u_2(t)+1) + a(u_1(t-\tau)+1)(u_2(t-\tau)+1).\end{aligned} \tag{12}$$

From (11), we know $\gamma - m - n = 0$, and by simplifying the right side of (12), the linear part of system (12) around $u = 0$ is given by

$$\begin{aligned}\dot{u}_1(t) &= -mu_1(t) - nu_2(t), \\ \dot{u}_2(t) &= -au_2(t) + au_1(t-\tau) + au_2(t-\tau).\end{aligned} \tag{13}$$

We know that the characteristic equation for system (13) is given by

$$D(\lambda, \tau) = det(\lambda I - Q_1 - Q_2 e^{-\lambda\tau}) = 0,$$

where

$$Q_1 = \begin{pmatrix} -m & -n \\ 0 & -a \end{pmatrix}, \qquad Q_2 = \begin{pmatrix} 0 & 0 \\ a & a \end{pmatrix}.$$

By the above assumptions, we can write

$$D(\lambda, \tau) = \lambda^2 + p_1\lambda + p_2 - (\lambda + q_1)q_2 e^{-\lambda\tau}, \tag{14}$$

in which

$$p_1 = m + a, \qquad p_2 = ma, \qquad q_1 = m - n, \qquad q_2 = a.$$

For $\tau > 0$, we show that under some conditions on parameters, a Hopf bifurcation happens. We suppose that $i\xi$ for some $\xi > 0$ is a root of (14) so that

$$\begin{aligned} D(i\xi,\tau) &= (i\xi)^2 + (i\xi)p_1 + p_2 - (i\xi + q_1)q_2 e^{-(i\xi)\tau} \\ &= -\xi^2 + i\xi p_1 + p_2 - (i\xi + q_1)q_2(\cos(\xi\tau) - i\sin(\xi\tau)) \\ &= -\xi^2 + i\xi p_1 + p_2 - i\xi q_2 \cos(\xi\tau) \\ &\quad - q_1 q_2 \cos(\xi\tau) - \xi q_2 \sin(\xi\tau) + i q_1 q_2 \sin(\xi\tau) \\ &= 0. \end{aligned} \tag{15}$$

Separating the imaginary and real parts of (15) gives that

$$p_2 - \xi^2 = q_1 q_2 \cos(\xi\tau) + \xi q_2 \sin(\xi\tau), \tag{16}$$

$$\xi p_1 = \xi q_2 \cos(\xi\tau) - q_1 q_2 \sin(\xi\tau). \tag{17}$$

Eliminating $\sin(\xi\tau)$ and $\cos(\xi\tau)$ from (16) and (17) implies that

$$\xi^4 + A\xi^2 + B = 0, \tag{18}$$

where

$$A = p_1^2 - 2p_2 - q_2^2, \qquad B = p_2^2 - q_1^2 q_2^2.$$

By assuming $Z = \xi^2$, equation (18) changes into

$$Z^2 + AZ + B = 0, \tag{19}$$

which has the solutions

$$Z_{1,2} = \frac{-(p_1^2 - 2p_2 - q_2^2) \pm \sqrt{(p_1^2 - 2p_2 - q_2^2)^2 - 4(p_2^2 - q_1^2 q_2^2)}}{2}.$$

We suppose that $h(Z) = Z^2 + AZ + B$ has two positive roots Z_k, $k = 0, 1$ such that

$$0 < Z_0 < Z_1,$$

and

$$\xi_0 = \sqrt{Z_0}, \qquad \xi_1 = \sqrt{Z_1}.$$

Then we have the following result.

Lemma 2. Suppose that $h'(Z_k) \neq 0$ and $Z_k = \xi_k^2$. Then $\frac{dr}{d\tau}(\tau_k^{(j)}) \neq 0$ and its sign is given by the sign of $h'(Z_k)$. In particular, we have

$$h'(Z_0) < 0, \qquad h'(Z_1) > 0,$$

such that

$$\frac{dr(\tau_0^{(j)})}{d\tau} < 0, \qquad \frac{dr(\tau_1^{(j)})}{d\tau} > 0, \qquad j = 0, 1, 2, \ldots. \tag{20}$$

Proof. Multiplying (16) by q_1 and (17) by ξ, we have

$$p_2 q_1 - \xi^2 q_1 = q_1^2 q_2 \cos(\xi\tau) + \xi q_1 q_2 \sin(\xi\tau),$$
$$p_1 \xi^2 = \xi^2 q_2 \cos(\xi\tau) - \xi q_1 q_2 \sin(\xi\tau),$$

and hence

$$\cos(\xi\tau) = \frac{p_2 q_1 - \xi^2 q_1 + p_1 \xi^2}{q_1^2 q_2 + \xi^2 q_2} = \frac{p_2 q_1 - \xi^2 q_1 + p_1 \xi^2}{q_2(q_1^2 + \xi^2)}.$$

Consequently,

$$\tau_k^{(j)} = \frac{1}{\xi_k}\left[\arccos\left(\frac{p_2 q_1 - \xi^2 q_1 + p_1 \xi^2}{q_2(q_1^2 + \xi^2)}\right)\right] + 2j\pi, \quad for \quad j \in \mathbb{Z}.$$

Therefore, $\pm i\xi_k$ for $k = 0, 1$ are two pairs of imaginary eigenvalues for $\tau = \tau_k^{(j)}$.
Let $\lambda(\tau) = r(\tau) + i\xi(\tau)$ be a root of (14). Then for $\tau = \tau_k^{(j)}$, we have

$$\lambda(\tau_k^{(j)}) = r(\tau_k^{(j)}) + i\xi(\tau_k^{(j)}) \qquad such\ that \qquad r(\tau_k^{(j)}) = 0, \qquad \xi(\tau_k^{(j)}) = \xi_k > 0.$$

We substitute $\lambda(\tau)$ into (14), and we get

$$\lambda^2(\tau) + p_1\lambda(\tau) + p_2 - (\lambda(\tau) + q_1)q_2 e^{-\lambda(\tau)\tau} = 0.$$

Differentiating this equality with respect to τ leads to the identity

$$(2\lambda(\tau) + p_1)\frac{d\lambda(\tau)}{d\tau} - (1 - \tau(\lambda(\tau) + q_1))q_2 e^{-\lambda(\tau)\tau}\frac{d\lambda(\tau)}{d\tau} + \lambda(\tau)(\lambda(\tau) + q_1)q_2 e^{-\lambda(\tau)\tau} = 0.$$

This gives

$$\begin{aligned}\left(\frac{d\lambda(\tau)}{d\tau}\right)^{-1} &= \frac{1}{\lambda(\tau)(\lambda(\tau) + q_1)} - \frac{2\lambda(\tau) + p_1}{\lambda(\tau)(\lambda(\tau) + q_1)q_2 e^{-\lambda(\tau)\tau}} - \frac{\tau}{\lambda(\tau)} \\ &= \frac{\lambda(\tau)}{\lambda^2(\tau)(\lambda(\tau) + q_1)} - \frac{2\lambda^2(\tau) + p_1\lambda(\tau)}{\lambda^2(\tau)(\lambda(\tau) + q_1)q_2 e^{-\lambda(\tau)\tau}} - \frac{\tau}{\lambda(\tau)}.\end{aligned}$$

Now, by using (14), we obtain that

$$\left(\frac{d\lambda(\tau)}{d\tau}\right)^{-1} = \frac{-q_1}{\lambda^2(\tau)(\lambda(\tau) + q_1)} - \frac{\lambda^2(\tau) - p_2}{\lambda^2(\tau)(\lambda^2(\tau) + p_1\lambda(\tau) + p_2)} - \frac{\tau}{\lambda(\tau)},$$

and therefore,

$$\begin{aligned}&\left(\frac{dRe\lambda(\tau)}{d\tau}\right)^{-1}\Big|_{\tau=\tau_k^{(j)}}\\&\quad=\left(Re\left[\frac{-q_1}{\lambda^2(\tau)(\lambda(\tau)+q_1)}\right]+Re\left[\frac{p_2-\lambda^2(\tau)}{\lambda^2(\tau)(\lambda^2(\tau)+p_1\lambda(\tau)+p_2)}\right]\right.\\&\qquad\left.+Re\left[\frac{-\tau}{\lambda(\tau)}\right]\right)\Big|_{\tau=\tau_k^{(j)}}.\end{aligned}$$

Since, $\lambda(\tau_k^{(j)})=r(\tau_k^{(j)})+i\xi(\tau_k^{(j)})=i\xi_k$, hence

$$\begin{aligned}Re\left(\frac{-q_1}{\lambda^2(\tau)(\lambda(\tau)+q_1)}\right)\Big|_{\tau=\tau_k^{(j)}}&=Re\left[\frac{q_1(-i\xi_k+q_1)}{\xi_k^2(i\xi_k+q_1)(-i\xi_k+q_1)}\right]\\&=\frac{q_1^2}{\xi_k^2(\xi_k^2+q_1^2)},\\Re\left(\frac{p_2-\lambda^2(\tau)}{\lambda^2(\tau)(\lambda^2(\tau)+p_1\lambda(\tau)+p_2)}\right)\Big|_{\tau=\tau_k^{(j)}}&=Re\left[\frac{p_2+\xi_k^2}{-\xi_k^2(-\xi_k^2+i\xi_kp_1+p_2)}\right]\\&=\frac{(p_2^2-\xi_k^4)}{-\xi_k^2((-\xi_k^2+p_2)^2+p_1^2\xi_k^2)},\\Re\left(\frac{-\tau}{\lambda(\tau)}\right)\Big|_{\tau=\tau_k^{(j)}}&=Re\left[\frac{-\tau}{i\xi_k}\right]=0.\end{aligned}$$

By the above relations, we get

$$\left(\frac{dRe\lambda(\tau)}{d\tau}\right)^{-1}\Big|_{\tau=\tau_k^{(j)}}=\frac{q_1^2}{\xi_k^2(\xi_k^2+q_1^2)}-\frac{p_2^2-\xi_k^4}{\xi_k^2((-\xi_k^2+p_2)^2+\xi_k^2p_1^2)}.$$

Let $\xi_k^2=Z_k$. Then

$$\left(\frac{dRe\lambda(\tau)}{d\tau}\right)^{-1}\Big|_{\tau=\tau_k^{(j)}}=\frac{q_1^2}{Z_k(Z_k+q_1^2)}-\frac{p_2^2-Z_k^2}{Z_k((-Z_k+p_2)^2+Z_kp_1^2)}.$$

Since Z_k is a root of (19), we have

$$\begin{aligned}&(-Z_k+p_2)^2-Z_kp_1^2=Z_k^2+(p_1^2-2p_2)Z_k+p_2^2=q_2^2Z_k+q_1^2q_2^2=q_2^2(Z_k+q_1^2),\\&Z_k^2+(p_1^2-2p_2-q_2^2)Z_k=-p_2^2+q_1^2q_2^2.\end{aligned}$$

Consequently,

$$\begin{aligned}\left(\frac{dRe\lambda(\tau)}{d\tau}\right)^{-1}\Big|_{\tau=\tau_k^{(j)}}&=\frac{Z_k^2-p_2^2+q_1^2q_2^2}{Z_kq_2^2(Z_k+q_1^2)}=\frac{2Z_k^2+(p_1^2-2p_2-q_2^2)Z_k}{Z_kq_2^2(Z_k+q_1^2)}\\&=\frac{2Z_k+p_1^2-2p_2-q_2^2}{q_2^2(Z_k+q_1^2)}=\frac{h'(Z_k)}{\Gamma_k},\end{aligned}$$

where

$$\Gamma_k = q_2^2(Z_k + q_1^2) > 0,$$
$$h'(Z_k) = 2Z_k + p_1^2 - 2p_2 - q_2^2.$$

Therefore,

$$sign\left[\frac{dr(\tau)}{d\tau}\right]^{-1}_{\tau=\tau_k^{(j)}} = sign\left[\frac{dRe\lambda(\tau)}{d\tau}\right]^{-1}_{\tau=\tau_k^{(j)}} = sign\left[\frac{h'(Z_k)}{\Gamma_k}\right] = sign\left[h'(Z_k)\right].$$

□

Theorem 3. Let (19) have at least a positive root. Then system (4) has a Hopf bifurcation at $\tau = \tau_*^{(j)}$ and has one periodic solution surrounding E^*, where

$$\tau_*^{(j)} = \frac{1}{\sqrt{Z^*}}\left[\cos^{-1}\left(\frac{p_2 q_1 - Z^* q_1 + p_1 Z^*}{q_2(q_1^2 + Z^*)}\right)\right] + 2j\pi.$$

Proof. This result easily follows from Lemma 2. □

We recall the results stated in [8] on the roots of (14) for $\tau > 0$.

Lemma 3. ([8]) Consider the following assumptions:

(A1) $p_1 - q_2 > 0$;

(A2) $p_2 - q_1 q_2 > 0$;

(A3) $p_1^2 - 2p_2 - q_2^2 > 0$ and $p_2^2 - q_1^2 q_2^2 > 0$ or $(p_1^2 - 2p_2 - q_2^2)^2 < 4(p_2^2 - q_1^2 q_2^2)$;

(A4) $p_1^2 - 2p_2 - q_2^2 < 0$ or $p_2^2 - q_1^2 q_2^2 < 0$ and $(p_1^2 - 2p_2 - q_2^2)^2 = 4(p_2^2 - q_1^2 q_2^2)$;

(A5) $p_1^2 - 2p_2 - q_2^2 < 0$, $p_2^2 - q_1^2 q_2^2 > 0$ or $(p_1^2 - 2p_2 - q_2^2)^2 > 4(p_2^2 - q_1^2 q_2^2)$.

Then the following properties hold:

(i) If $(A1) - (A3)$ are satisfied, then the real parts of all roots of (14) are negative for $\tau \geq 0$.

(ii) If $(A1)$, $(A2)$, and $(A4)$ are satisfied, then (14) at $\tau = \tau_k^{(j)}$, has a pair of imaginary roots $\pm i\xi_k$, such that the real parts of all roots except $\pm i\xi_k$ are negative.

(iii) If $(A1)$, $(A2)$, and $(A5)$ are satisfied, then (14) at $\tau = \tau_k^{(j)}$, has a pair of imaginary roots $\pm i\xi_k$, such that the real parts of all roots except $\pm i\xi_k$ are negative.

Theorem 4. If there are no positive roots for $h(Z) = Z^2 + AZ + B$ and $\mathcal{R}_0 > 1$, then E_2 is locally asymptotically stable for any $\tau \geq 0$.

Proof. Lemma 3 states that the real parts all of roots of (14) are negative, and this shows that E_2 is locally asymptotically stable for any $\tau \geq 0$. □

4 Stability of the Hopf bifurcation

In the previous section, we derived some conditions on Hopf bifurcation at the equilibrium point $E^* = (1,1)$, when $\tau = \tau_k^{(j)}, (j = 0, 1, 2 \ldots)$. In this section, we obtain stability, direction, and period of periodic solution bifurcating from certain values of τ. We use the center manifold and normal form theory recognized in [5]. Let system (4) have a pair of imaginary roots when $\tau = \tau^*$ and let the system have a Hopf bifurcation from E^*. We set

$$u_1(t) = X(\tau t) - 1, \qquad u_2(t) = Y(\tau t) - 1, \qquad \tau = \tau^* + \nu, \qquad \nu \in \mathbb{R}.$$

Then, from (10), we get

$$\begin{aligned} \dot{u}_1(t) &= (\tau^* + \nu)(u_1(t) + 1)(-m u_1(t) - n u_2(t)), \\ \dot{u}_2(t) &= a(\tau^* + \nu)(-u_2(t) + u_1(t-1)u_2(t-1) + u_1(t-1) + u_2(t-1)). \end{aligned} \tag{21}$$

Equation (21) can be written in the form

$$\dot{u}(t) = L_\nu(u_t) + f(\nu, u_t), \qquad u(t) = (u_1(t), u_2(t)) \in \mathbb{R}^2.$$

Let $C = C([-1, 0]; \mathbb{R}^2)$ be the Banach space of continuous functions on $[-1, 0]$ with values in $\mathbb{R}^2$. Then for $\phi = (\phi_1, \phi_2) \in C$, we define

$$L_\nu : C \longrightarrow \mathbb{R}^2, \qquad f : \mathbb{R} \times C \longrightarrow \mathbb{R}^2,$$

through

$$\begin{aligned} L_\nu \phi &= (\tau^* + \nu) \begin{pmatrix} -m & -n \\ 0 & -a \end{pmatrix} \begin{pmatrix} \phi_1(0) \\ \phi_2(0) \end{pmatrix} + (\tau^* + \nu) \begin{pmatrix} 0 & 0 \\ a & a \end{pmatrix} \begin{pmatrix} \phi_1(-1) \\ \phi_2(-1) \end{pmatrix}, \\ f(\nu, \phi) &= (\tau^* + \nu) \left[-m \begin{pmatrix} \phi_1^2(0) \\ 0 \end{pmatrix} - n \begin{pmatrix} \phi_1(0)\phi_2(0) \\ 0 \end{pmatrix} + a \begin{pmatrix} 0 \\ \phi_1(-1)\phi_2(-1) \end{pmatrix} \right] \\ &= (\tau^* + \nu) \begin{pmatrix} -m\phi_1^2(0) - n\phi_1(0)\phi_2(0) \\ a\phi_1(-1)\phi_2(-1) \end{pmatrix}. \end{aligned} \tag{22}$$

By the Rise representation theorem, there exists a bounded variation function $\eta(\theta, \nu)$ for $\theta \in [-1, 0]$, such that

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

with

$$\eta(\theta, \nu) = (\tau^* + \nu) \begin{pmatrix} -m & -n \\ 0 & -a \end{pmatrix} \delta(\theta) - (\tau^* + \nu) \begin{pmatrix} 0 & 0 \\ a & a \end{pmatrix} \delta(\theta + 1),$$

where δ is Dirac delta function. For $\phi \in C^1([-1, 0]; \mathbb{R}^2)$, we define

$$A(\nu)\phi = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \theta \in [-1, 0), \\ \int_{-1}^{0} d\eta(\theta, s)\phi(s), & \theta = 0, \end{cases} \tag{23}$$

and

$$R(\nu)\phi = \begin{cases} 0, & \theta \in [-1, 0), \\ f(\nu, \phi), & \theta = 0. \end{cases} \tag{24}$$

By the above notations, system (21) can be written as

$$\dot{u}_t = A(\nu)u_t + R(\nu)u_t, \tag{25}$$

in which $u_t(\theta) = u(t + \theta)$ for $\theta \in [-1, 0]$. For $\psi \in C^1([0, 1]; (\mathbb{R}^2)^*)$, define

$$(A^*\psi)(s) = \begin{cases} -\frac{d\psi(s)}{ds}, & s \in (0, 1], \\ \int_{-1}^{0} d\eta(t, 0)\psi(-t), & s = 0, \end{cases} \tag{26}$$

and denote the bilinear inner product by

$$< \psi(s), \phi(\theta) >= \overline{\psi(0)}\phi(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \overline{\psi}(\xi - \theta)d\eta(\theta)\phi(\xi)d\xi. \tag{27}$$

We suppose that $\eta(\theta) = \eta(\theta, 0)$ and that A^* is the adjoint operator of the linear map $A(0)$. From Section 3, we have that $\pm i\xi^*\tau^*$ are the eigenvalues of $A(0)$ and that also the eigenvalues of A^*. Assume that $q(\theta)$ is an eigenvector of $A(0)$ for $i\xi^*\tau^*$ and that $q^*(s)$ is an eigenvector of A^* for $-i\xi^*\tau^*$. Then by the definition of eigenvalue and using (23), we have

$$A(0)q(\theta) = i\xi^*\tau^*q(\theta) \quad \Longrightarrow \quad q'(\theta) = i\xi^*\tau^*q(\theta) \quad \mathit{for} \quad \theta \in [-1, 0),$$

and hence

$$\begin{aligned} q(\theta) &= q(0)e^{i\xi^*\tau^*\theta}, \qquad -1 \le \theta < 0, \\ q(-1) &= q(0)e^{-i\xi^*\tau^*}, \\ A_0q(0) + B_0q(-1) &= i\xi^*\tau^*q(0). \end{aligned}$$

Thus,

$$\begin{pmatrix} -m - i\xi^* & -n \\ ae^{-i\xi^*\tau^*} & -a - i\xi^* + ae^{-i\xi^*\tau^*} \end{pmatrix} \begin{pmatrix} q_1(0) \\ q_2(0) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}. \tag{28}$$

It is easily seen that a nontrivial solution of (28) is as follows:

$$q_2(0) = \frac{-m - i\xi^*}{n}q_1(0), \qquad q_1(0) = 1 \neq 0,$$

so that

$$q(\theta) = (q_1(0), q_2(0))\, e^{i\xi^*\tau^*\theta} = \left(1, \frac{-m - i\xi^*}{n}\right) e^{i\xi^*\tau^*\theta}.$$

Similarly, we obtain $q^*(s) = E\left(q_1^*(0), q_2^*(0)\right)^T e^{i\xi^*\tau^* s}$ as an eigenvector of A^* corresponding to the eigenvalue $-i\xi^*\tau^*$. Indeed, by using (26), we have

$$A^*q^*(s) = -i\xi^*\tau^*q^*(s) \qquad \Longrightarrow \qquad -q^{*\prime}(s) = -i\xi^*\tau^*q(s) \quad for \qquad s \in (0,1],$$

and therefore

$$\begin{aligned} q^*(s) &= q^*(0)e^{i\xi^*\tau^* s}, \qquad 0 < s \leq 1,\\ q^*(1) &= q^*(0)e^{i\xi^*\tau^*},\\ A_0^*q^*(0) + B_0^*q^*(1) &= -i\xi^*\theta^*q^*(0). \end{aligned}$$

Hence

$$\begin{pmatrix} -m + i\xi^* & ae^{i\xi^*\tau^*} \\ -n & -a + i\xi^* + ae^{i\xi^*\tau^*} \end{pmatrix} \begin{pmatrix} q_1^*(0) \\ q_2^*(0) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}. \tag{29}$$

Equation (29) shows that

$$q_1^*(0) = \frac{i\xi^* - a + ae^{i\xi^*\tau^*}}{n} q_2^*(0), \qquad \qquad q_2^*(0) = 1 \neq 0.$$

Thus, we find that

$$q^*(s) = E\left(q_1^*(0), q_2^*(0)\right) e^{i\xi^*\tau^* s} = E\left(\frac{i\xi^* - a + ae^{i\xi^*\tau^*}}{n}, 1\right) e^{i\xi^*\tau^* s}.$$

For normalizing q and q^*, we assume that $< q^*(s), q(\theta) >= 1$ and by using (27), we get

$$\begin{aligned} < q^*(s), q(\theta) >=& \overline{E}(\overline{q^*}_1(0), 1)(1, q_2(0))^T \\ &- \int_{-1}^{0}\int_{\xi=0}^{\theta} \overline{E}(\overline{q^*}_1(0), 1)e^{-i\xi^*\tau^*(\xi-\theta)}d\eta(\theta)(1, q_2(0))d\xi \\ =& \overline{E}\Big\{ \left(\frac{-i\xi^* - a + ae^{-i\xi^*\tau^*}}{n}, 1\right)\left(1, \frac{-m - i\xi^*}{n}\right) \\ &- \int_{-1}^{0}\int_{\xi=0}^{\theta} \left(\frac{-i\xi^* - a + ae^{-i\xi^*\tau^*}}{n}, 1\right) e^{-i\xi^*\tau^*(\xi-\theta)}d\eta(\theta) \\ &\quad \times \left(1, \frac{-m - i\xi^*}{n}\right) e^{i\xi^*\tau^*\theta}d\xi\Big\} \\ =& \overline{E}\Big\{ \frac{-2i\xi^* - a + ae^{-i\xi^*\tau^*} - m}{n} \\ &- \int_{-1}^{0} \left(\frac{-i\xi^* - a + ae^{-i\xi^*\tau^*}}{n}, 1\right) \theta e^{i\xi^*\tau^*\theta}d\eta(\theta) \begin{pmatrix} 1 \\ \frac{-m - i\xi^*}{n} \end{pmatrix} \Big\} \end{aligned}$$

$$
\begin{aligned}
&= \overline{E}\Big\{ \frac{-2i\xi^* - a + ae^{-i\xi^*\tau^*} - m}{n} - \tau^* \frac{a(m-n) + ia\xi^*}{n} e^{-i\xi^*\tau^*} \Big\} \\
&= 1,
\end{aligned}
$$

which gives

$$
\overline{E} = \Big\{ \frac{-2i\xi^* - a + ae^{-i\xi^*\tau^*} - m - \tau^*(a(m-n) + ia\xi^*)e^{-i\xi^*\tau^*}}{n} \Big\}^{-1}.
$$

We now describe the solutions of (21) on the center manifold C_0 at $\nu = 0$. Let $u(t)$ be the solution of (21) at $\nu = 0$. Then

$$
u(t) = u_0(t) + \Psi(u_0(t)),
$$

for $u_0(t) \in E_0$ and $E_0 = span\{q(\theta), q^*(\theta)\}$. Thus

$$
u_0(t) = z(t)q(\theta) + \bar{z}(t)q^*(\theta) = z(t)q(\theta) + \bar{z}(t)\bar{q}(\theta),
$$

and hence $u_t(\theta)$ on the center manifold can be written as

$$
\begin{aligned}
u_t(\theta) &= z(t)q(\theta) + \bar{z}(t)\bar{q}(\theta) + \Psi(z(t), \bar{z}(t)) \\
&= 2Re\{z(t)q(\theta)\} + W(t, \theta),
\end{aligned} \tag{30}
$$

where

$$
W(t, \theta) = u_t(\theta) - 2Re\{z(t)q(\theta)\}.
$$

It is clear that if $u_t(\theta)$ is real, then W is also real. Now, we set

$$
W(t, \theta) = W(z, \bar{z}, \theta) = W_{20}\frac{z^2}{2} + W_{11}z\bar{z} + W_{02}\frac{\bar{z}^2}{2} + W_{30}\frac{z^3}{6} + \cdots, \tag{31}
$$

in which $z, \bar{z}$ are the coordinates of u_t with respect to q, q^*. The reduced equations up to order three for $(z, \bar{z})$ will be computed in the following. Equation (25) used with $\nu = \theta = 0$ yields

$$
\dot{u}(t) = A(0)u(t) + R(0)u(t),
$$

which is, by (30), equivalent to

$$
\dot{z}(t)q(0) + \dot{\bar{z}}(t)\bar{q}(0) + \dot{W}(t, 0) = A(0)u(t) + R(0)u(t). \tag{32}
$$

Since the inner product of the left-hand side of (32) with $q^*(0)$ is equal to $\dot{z}(t)$, then

$$\begin{aligned}
\dot{z}(t) &=< q^*(0), A(0)u(t) + R(0)u(t) > \\
&=< q^*(0), A(0)u(t) > + < q^*(0), R(0)u(t) > \\
&=< A^*(0)q^*(0), u(t) > + < q^*(0), R(0)u(t) > \\
&=< -i\xi^*\tau^* q^*(0), u(t) > + < q^*(0), R(0)u(t) > \\
&= i\xi^*\tau^* < q^*(0), u(t) > + < q^*(0), f(0, u(t)) > \\
&= i\xi^*\tau^* z(t) + \bar{q}^*(0) f(0, u(t)) \\
&= i\xi^*\tau^* z(t) + \bar{q}^*(0) f(0, z(t)q(0) + \bar{z}(t)\bar{q}(0) + W(t,0)) \\
&= i\xi^*\tau^* z(t) + g(z(t), \bar{z}(t)),
\end{aligned}$$

where

$$g(z(t), \bar{z}(t)) = g_{20}\frac{z^2}{2} + g_{11} z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2} + \cdots . \tag{33}$$

To simplify the computations, we let

$$q_2(0) = \frac{-m - i\xi^*}{n} = M, \qquad q_1^*(0) = \frac{i\xi^* - a + ae^{i\xi^*\tau^*}}{n} = N.$$

Then (30) reads as

$$\begin{aligned}
u_t(\theta) &= z(t)q(\theta) + \bar{z}(t)\bar{q}(\theta) + W(t,\theta) \\
&= (1, M)^T e^{i\xi^*\tau^*\theta} z(t) + (1, \overline{M})^T e^{-i\xi^*\tau^*\theta}\bar{z}(t) \\
&\quad + W_{20}\frac{z^2}{2} + W_{11} z\bar{z} + W_{02}\frac{\bar{z}^2}{2} + \cdots .
\end{aligned} \tag{34}$$

It follows from (34) that

$$\begin{aligned}
u_1(t) &= z + \bar{z} + W^{(1)}(0), \\
u_2(t) &= Mz + \overline{M}\bar{z} + W^{(2)}(0), \\
u_1(t-1) &= ze^{-i\xi^*\tau^*} + \bar{z}e^{i\xi^*\tau^*} + W^{(1)}(-1), \\
u_2(t-1) &= Mze^{-i\xi^*\tau^*} + \overline{M}\bar{z}e^{i\xi^*\tau^*} + W^{(2)}(-1),
\end{aligned}$$

so that $W(t,\theta) = (W^{(1)}(\theta), W^{(2)}(\theta)) \in \mathbb{R}^2$. By replacing $\phi(\theta) = u_t(\theta)$ into (22) for $\nu = 0$ and the above relations, we have

$$
\begin{aligned}
&g(z,\bar{z})\\
&=\overline{q^*(0)}f(0,u_t)\\
&=\overline{q^*(0)}\tau^*\begin{pmatrix}-mu_1^2(t)-nu_1(t)u_2(t)\\ au_1(t-1)u_2(t-1)\end{pmatrix}\\
&=\overline{E}(\overline{N},1)\tau^*\begin{pmatrix}-m(z+\bar{z}+W^{(1)}(0))^2-n(z+\bar{z}+W^{(1)}(0))(Mz+\overline{M}\bar{z}+W^{(2)}(0))\\ a(ze^{-i\xi^*\tau^*}+\bar{z}e^{i\xi^*\tau^*}+W^{(1)}(-1))(Mze^{-i\xi^*\tau^*}+\overline{M}\bar{z}e^{i\xi^*\tau^*}+W^{(2)}(-1))\end{pmatrix}\\
&=-\overline{EN}\tau^*\{m(z+\bar{z}+W^{(1)}(0))^2+n(z+\bar{z}+W^{(1)}(0))(Mz+\overline{M}\bar{z}+W^{(2)}(0))\}\\
&\quad+\overline{E}\tau^*\{a(ze^{-i\xi^*\tau^*}+\bar{z}e^{i\xi^*\tau^*}+W^{(1)}(-1))(Mze^{-i\xi^*\tau^*}+\overline{M}\bar{z}e^{i\xi^*\tau^*}+W^{(2)}(-1))\}\\
&=-\overline{EN}\tau^*\Big\{2\left(m+nM\right)\frac{z^2}{2}+\left(2m+nRe\{M\}\right)z\bar{z}+2\left(m+n\overline{M}\right)\frac{\bar{z}^2}{2}\\
&\quad+2\Big(2mW_{11}^{(1)}(0)+2mW_{20}^{(1)}(0)+nMW_{11}^{(1)}(0)+n\overline{M}W_{20}^{(1)}(0)+nW_{11}^{(2)}(0)\\
&\quad+nW_{20}^{(2)}(0)\Big)\frac{z^2\bar{z}}{2}\Big\}+\overline{E}\tau^*\Big\{2\left(aMe^{-2i\xi^*\tau^*}\right)\frac{z^2}{2}+\left(aRe\{M\}\right)z\bar{z}+2\left(a\overline{M}e^{2i\xi^*\tau^*}\right)\frac{\bar{z}^2}{2}\\
&\quad+2\Big(ae^{-i\xi^*\tau^*}W_{11}^{(2)}(-1)+ae^{i\xi^*\tau^*}W_{20}^{(2)}(-1)+aMe^{-i\xi^*\tau^*}W_{11}^{(1)}(-1)\\
&\quad+a\overline{M}e^{i\xi^*\tau^*}W_{20}^{(1)}(-1)\Big)\frac{z^2\bar{z}}{2}\Big\}+\cdots.
\end{aligned}\tag{35}
$$

We now replace (33) in the left-hand side of (35), and we get

$$
\begin{aligned}
g_{20}&=-2\overline{EN}\tau^*(m+nM)+2\overline{E}\tau^*(aMe^{-2i\xi^*\tau^*}),\\
g_{11}&=\overline{EN}\tau^*(2m+n\overline{M}+nM)+\overline{E}\tau^*(aM+a\overline{M}),\\
g_{02}&=-2\overline{EN}\tau^*(m+n\overline{M})+2\overline{E}\tau^*(a\overline{M}e^{2i\xi^*\tau^*}),\\
g_{21}&=-2\overline{EN}\tau^*\{(2m+nM)W_{11}^{(1)}(0)+(2m+n\overline{M})W_{20}^{(1)}(0)+nW_{11}^{(2)}(0)\\
&\quad+nW_{20}^{(2)}(0)\}+2\overline{E}\tau^*\{ae^{-i\xi^*\tau^*}W_{11}^{(2)}(-1)+ae^{i\xi^*\tau^*}W_{20}^{(2)}(-1)\\
&\quad+aMe^{-i\xi^*\tau^*}W_{11}^{(1)}(-1)+a\overline{M}e^{i\xi^*\tau^*}W_{20}^{(1)}(-1)\}.
\end{aligned}\tag{36}
$$

As $W_{11}(\theta)$ and $W_{20}(\theta)$ are unknown, we should calculate them. To this end, we consider

$$\dot{W}=\dot{u}_t-q\dot{z}-\bar{q}\dot{\bar{z}},\tag{37}$$

with

$$
\begin{aligned}
\dot{u}_t&=A(0)u_t+R(0)u_t=(A(0)+R(0))(qz+\bar{q}\bar{z}+W),\\
\dot{z}&=i\xi^*\tau^*z+\bar{q}^*(0)f_0,\\
\dot{\bar{z}}&=-i\xi^*\tau^*\bar{z}+q^*(0)\bar{f}_0.
\end{aligned}
$$

Then (37) becomes

$$\begin{aligned}\dot{W} =& A(0)(W + qz + \bar{q}\bar{z}) - (i\xi^*\tau^* z + \bar{q}^*(0)f_0)q - (-i\xi^*\tau^*\bar{z} + q^*(0)\bar{f}_0)\bar{q} \\ &+ R(0)u_t \\ =& A(0)W + A(0)qz + A(0)\bar{q}\bar{z} - (i\xi^*\tau^* z)q + (i\xi^*\tau^*\bar{z})\bar{q} \\ &- \bar{q}^*(0)f_0 q - q^*(0)\bar{f}_0\bar{q} + R(0)u_t \\ =& A(0)W + (i\xi^*\tau^* q)z - (i\xi^*\tau^*\bar{q})\bar{z} - (i\xi^*\tau^* z)q + (i\xi^*\tau^*\bar{z})\bar{q} \\ &- \bar{q}^*(0)f_0 q - q^*(0)\bar{f}_0\bar{q} + R(0)u_t \\ =& A(0)W - \bar{q}^*(0)f_0 q + \overline{\bar{q}^*(0)f_0 q} + R(0)u_t \\ =& A(0)W - 2Re\{\bar{q}^*(0)f_0 q\} + R(0)u_t. \end{aligned} \tag{38}$$

Next, from (24) and (38), we find that

$$\begin{aligned}\dot{W} &= \begin{cases} AW - 2Re\{\bar{q}^*(0)f_0 q\} & \theta \in [-1, 0), \\ AW - 2Re\{\bar{q}^*(0)f_0 q\} + f(0, u_t) & \theta = 0, \end{cases} \\ &= AW + H(z, \bar{z}, \theta), \end{aligned} \tag{39}$$

where

$$H(z, \bar{z}, \theta) = H_{20}(\theta)\frac{z^2}{2} + H_{11}(\theta)z\bar{z} + H_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots . \tag{40}$$

By replacing (31) and (40) into (39), we obtain that

$$\begin{aligned} &W_{20}(\theta)z\dot{z} + W_{11}(\theta)\dot{z}\bar{z} + W_{11}(\theta)z\dot{\bar{z}} + W_{02}(\theta)\bar{z}\dot{\bar{z}} + \cdots \\ &\quad = A(W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}(\theta)\frac{\bar{z}^2}{2}) + H_{20}(\theta)\frac{z^2}{2} \\ &\qquad + H_{11}(\theta)z\bar{z} + H_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots . \end{aligned}$$

Also,

$$\begin{aligned} &W_{20}(\theta)z(i\xi^*\tau^* z + g(z, \bar{z})) + W_{11}(\theta)\bar{z}(i\xi^*\tau^* z + g(z, \bar{z})) \\ &\quad + W_{11}(\theta)z(-i\xi^*\tau^*\bar{z} + \overline{g(z, \bar{z})}) + W_{20}(\theta)\bar{z}(-i\xi^*\tau^*\bar{z} + \overline{g(z, \bar{z})}) \\ &\qquad = (AW_{20}(\theta) + H_{20}(\theta))\frac{z^2}{2} + (AW_{11}(\theta) + H_{11}(\theta))z\bar{z} \\ &\qquad\quad + (AW_{02}(\theta) + H_{02}(\theta))\frac{\bar{z}^2}{2} + \cdots . \end{aligned}$$

Thus,

$$\begin{aligned} &(2i\xi^*\tau^* W_{20}(\theta))\frac{z^2}{2} + (-2i\xi^*\tau^* W_{20}(\theta))\frac{\bar{z}^2}{2} + \cdots \\ &= (AW_{20}(\theta) + H_{20}(\theta))\frac{z^2}{2} + (AW_{11}(\theta) + H_{11}(\theta))z\bar{z} + \cdots . \end{aligned} \tag{41}$$

Comparing the similar terms in both sides of equality (41) leads to

$$AW_{20}(\theta) + H_{20}(\theta) = 2i\xi^*\tau^* W_{20}(\theta) \implies (A - 2i\xi^*\tau^*)W_{20}(\theta) = -H_{20}(\theta), \tag{42}$$

$$AW_{11}(\theta) + H_{11}(\theta) = 0 \qquad \implies \qquad AW_{11}(\theta) = -H_{11}(\theta). \tag{43}$$

From (39) for $\theta \in [-1, 0)$, we have that

$$\begin{aligned} H(z, \bar{z}, \theta) &= -2Re\{\bar{q}^*(0) f_0 q(\theta)\} \\ &= -\bar{q}^*(0) f_0 q(\theta) - \overline{\bar{q}^*(0) f_0 q(\theta)} \\ &= -g(z, \bar{z}) q(\theta) - \overline{g(z, \bar{z}) q(\theta)}. \end{aligned} \tag{44}$$

Then by comparing the coefficients of (33) and (40), we get

$$H_{20}(\theta) = -g_{20} q(\theta) - \bar{g}_{02} \bar{q}(\theta), \tag{45}$$

$$H_{11}(\theta) = -g_{11} q(\theta) - \bar{g}_{11} \bar{q}(\theta). \tag{46}$$

By substituting (45) into (42), we obtain

$$\begin{aligned} AW_{20}(\theta) &= 2i\xi^*\tau^* W_{20}(\theta) - H_{20}(\theta) \\ &= 2i\xi^*\tau^* W_{20}(\theta) + g_{20} q(\theta) + \bar{g}_{02} \bar{q}(\theta). \end{aligned} \tag{47}$$

By the definition of $A(\nu)$ for $\theta \in [-1, 0)$, we have $AW_{20}(\theta) = \dot{W}_{20}(\theta)$, and by replacing it into (47), we get

$$\begin{aligned} \dot{W}_{20}(\theta) &= 2i\xi^*\tau^* W_{20}(\theta) + g_{20} q(\theta) + \bar{g}_{02} \bar{q}(\theta) \\ &= 2i\xi^*\tau^* W_{20}(\theta) + g_{20} q(0) e^{i\xi^*\tau^*\theta} + \bar{g}_{02} \bar{q}(0) e^{-i\xi^*\tau^*\theta}, \end{aligned}$$

where $q(\theta) = q(0)e^{i\xi^*\tau^*\theta}$. Hence,

$$\begin{aligned} W_{20}(\theta) &= e^{2i\xi^*\tau^*\theta} \left\{ \int_0^\theta \left(g_{20} q(0) e^{i\xi^*\tau^*\theta} + \bar{g}_{02} \bar{q}(0) e^{-i\xi^*\tau^*\theta} \right) e^{-2i\xi^*\tau^*\theta} d\theta + C_1 \right\} \\ &= \frac{i g_{20}}{\xi^*\tau^*} q(0) e^{i\xi^*\tau^*\theta} + \frac{i\bar{g}_{02}}{3\xi^*\tau^*} \bar{q}(0) e^{-i\xi^*\tau^*\theta} + C_1 e^{2i\xi^*\tau^*\theta}. \end{aligned} \tag{48}$$

Similarly, it follows from (43), (46) and the definition of $A(\nu)$ that

$$\begin{aligned} &AW_{11}(\theta) = -H_{11}(\theta), \\ &\dot{W}_{11}(\theta) = g_{11} q(\theta) + \bar{g}_{11} \bar{q}(\theta) = g_{11} q(0) e^{i\xi^*\tau^*\theta} + \bar{g}_{11} \bar{q}(0) e^{-i\xi^*\tau^*\theta}. \end{aligned}$$

Then

$$W_{11}(\theta) = \left\{ \int_0^\theta \left(g_{11} q(0) e^{i\xi^*\tau^*\theta} + \bar{g}_{11} \bar{q}(0) e^{-i\xi^*\tau^*\theta} \right) d\theta + C_2 \right\}$$
$$= -\frac{ig_{11}}{\xi^*\tau^*} q(0) e^{i\xi^*\tau^*\theta} + \frac{i\bar{g}_{11}}{\xi^*\tau^*} \bar{q}(0) e^{-i\xi^*\tau^*\theta} + C_2. \tag{49}$$

We now need to find appropriate C_1 and C_2 for (48) and (49). From the definition of $A(\nu)$ for $\theta = 0$ and (42) we have that

$$\int_{-1}^0 d\eta(\theta) W_{20}(\theta) = 2i\xi^*\tau^* W_{20}(0) - H_{20}(0), \tag{50}$$

where $\eta(0,\theta) = \eta(\theta)$. From the definition of $H(z, \bar{z}, \theta)$ at (39) and (44) for $\theta = 0$, we have

$$H_{20}(0) = -\bar{q}^*(0) f_0 q(0) - q^*(0) \bar{f}_0 \bar{q}(0) + f(0, u_t)$$
$$= -g_{20} q(0) - \bar{g}_{02} \bar{q}(0) + \tau^* \begin{pmatrix} 2(m+nM) \\ -2aMe^{-2i\xi^*\tau^*} \end{pmatrix}. \tag{51}$$

Now, we substitute (48) and (51) into (50), and we get

$$\tau^* \begin{pmatrix} -m & -n \\ 0 & -a \end{pmatrix} \left(\frac{ig_{20}}{\xi^*\tau^*} q(0) + \frac{i\bar{g}_{02}}{3\xi^*\tau^*} \bar{q}(0) + C_1 \right)$$
$$- \tau^* \begin{pmatrix} 0 & 0 \\ -a & -a \end{pmatrix} \left(\frac{ig_{20}}{\xi^*\tau^*} q(0) e^{-i\xi^*\tau^*} + \frac{i\bar{g}_{02}}{3\xi^*\tau^*} \bar{q}(0) e^{i\xi^*\tau^*} + C_1 e^{-2i\xi^*\tau^*} \right)$$
$$= 2i\xi^*\tau^* (\frac{ig_{20}}{\xi^*\tau^*} q(0) + \frac{i\bar{g}_{02}}{3\xi^*\tau^*} \bar{q}(0) + C_1) + g_{20} q(0) + \bar{g}_{02} \bar{q}(0)$$
$$+ \tau^* \begin{pmatrix} 2(m+nM) \\ -2aMe^{-2i\xi^*\tau^*} \end{pmatrix}.$$

It reduces to

$$\tau^* \{ \frac{ig_{20}}{\xi^*\tau^*} \begin{pmatrix} -m & -n \\ ae^{-i\xi^*\tau^*} & -a + ae^{-i\xi^*\tau^*} \end{pmatrix} q(0) + \frac{i\bar{g}_{02}}{3\xi^*\tau^*} \begin{pmatrix} -m & -n \\ ae^{i\xi^*\tau^*} & -a + ae^{i\xi^*\tau^*} \end{pmatrix} \bar{q}(0)$$
$$+ \begin{pmatrix} -m & -n \\ ae^{-2i\xi^*\tau^*} & -a + ae^{-2i\xi^*\tau^*} \end{pmatrix} C_1 \}$$
$$= -g_{20} q(0) - \bar{g}_{02} \bar{q}(0) + 2i\xi^*\tau^* C_1 + \tau^* \begin{pmatrix} 2(m+nM) \\ -2aMe^{-2i\xi^*\tau^*} \end{pmatrix}.$$

Then we use the characteristic $(\lambda I - Q_1 - Q_2 e^{-\lambda\tau}) q(0) = 0$ and obtain

$$\tau^*\left\{\frac{ig_{20}}{\xi^*\tau^*}(i\xi^* q(0)) + \frac{i\bar{g}_{02}}{3\xi^*\tau^*}(-i\xi^*\bar{q}(0)) + \begin{pmatrix} -m & -n \\ ae^{-2i\xi^*\tau^*} & -a+ae^{-2i\xi^*\tau^*}\end{pmatrix} C_1\right\}$$
$$= -g_{20}q(0) - \bar{g}_{02}\bar{q}(0) + 2i\xi^*\tau^* C_1 + \tau^*\begin{pmatrix} 2(m+nM) \\ -2aMe^{-2i\xi^*\tau^*}\end{pmatrix}.$$

Therefore,

$$\begin{pmatrix} -m & -n \\ ae^{-2i\xi^*\tau^*} & -a+ae^{-2i\xi^*\tau^*}\end{pmatrix} C_1 = +2i\xi^* I C_1 + \begin{pmatrix} 2(m+nM) \\ -2aMe^{-2i\xi^*\tau^*}\end{pmatrix},$$

which is equivalent to

$$\begin{pmatrix} -m-2i\xi^* & -n \\ ae^{-2i\xi^*\tau^*} & -a+ae^{-2i\xi^*\tau^*}-2i\xi^*\end{pmatrix}\begin{pmatrix} C_1^{(1)} \\ C_1^{(2)}\end{pmatrix} = \begin{pmatrix} 2(m+nM) \\ -2aMe^{-2i\xi^*\tau^*}\end{pmatrix}.$$

It follows that

$$C_1^{(1)} = \frac{-2(ame^{-2i\xi^*\tau^*} - (a+2i\xi)(m+nM))}{ae^{-2i\xi^*\tau^*}(2i\xi+m-n) - 2i\xi(a+2\xi+m) - am},$$
$$C_1^{(2)} = \frac{2a(m+nM-2Mi\xi - mM)}{a(2i\xi+m-n) - (2i\xi(a+2\xi+m)+am)e^{2i\xi^*\tau^*}}.$$

Similarly, from (43) and the definition of $A(\nu)$, we have

$$\int_{-1}^{0} d\eta(\theta) W_{11}(\theta) = -H_{11}(0), \tag{52}$$

and also from (39), we have

$$H_{11}(0) = -g_{11}q(0) - \bar{g}_{11}\bar{q}(0) + \tau^*\begin{pmatrix} 2m + nRe\{M\} \\ -aRe\{M\}\end{pmatrix}. \tag{53}$$

Now we substitute (49) and (53) into (52), and we get

$$\tau^*\begin{pmatrix} -m & -n \\ 0 & -a\end{pmatrix}(-\frac{ig_{11}}{\xi^*\tau^*}q(0) + \frac{i\bar{g}_{11}}{\xi^*\tau^*}\bar{q}(0) + C_2)$$
$$-\tau^*\begin{pmatrix} 0 & 0 \\ -a & -a\end{pmatrix}(-\frac{ig_{11}}{\xi^*\tau^*}q(0)e^{-i\xi^*\tau^*} + \frac{i\bar{g}_{11}}{\xi^*\tau^*}\bar{q}(0)e^{i\xi^*\tau^*} + C_2)$$
$$= g_{11}q(0) + \bar{g}_{11}\bar{q}(0) + \tau^*\begin{pmatrix} 2m + nRe\{M\} \\ -aRe\{M\}\end{pmatrix}.$$

Thus, we have

$$\begin{pmatrix} -m & -n \\ a & 0\end{pmatrix} C_2 = \begin{pmatrix} 2m + nRe\{M\} \\ -aRe\{M\}\end{pmatrix},$$

which gives

$$C_2 = \begin{pmatrix} C_2^{(1)} \\ C_2^{(2)} \end{pmatrix} = \begin{pmatrix} -Re\{M\} \\ \frac{1}{n}((m-n)Re\{M\} - 2m) \end{pmatrix}.$$

By the above computations, we obtain coefficients of (36) and we can now determine the following quantities:

$$\begin{aligned} c_1(0) &= \frac{i}{2\xi^*\tau^*}\left(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2}, \\ \mu_2 &= -\frac{Re(c_1(0))}{Re(\frac{d\lambda(\tau^*)}{d\tau})}, \\ \beta_2 &= 2Re(c_1(0)), \\ T_2 &= -\frac{Im(c_1(0) + \mu_2 Im(\frac{d\lambda(\tau^*)}{d\tau})}{\xi^*}. \end{aligned} \tag{54}$$

These values describe the bifurcating periodic solutions for the critical value $\tau = \tau^*$. The direction of the Hopf bifurcation is determined by μ_2, that is, when μ_2 is positive (negative), we have a supercritical (subcritical) Hopf bifurcation. For $\tau > \tau^*$ ($\tau < \tau^*$), there exist bifurcating periodic solutions, and β_2 determines the stability of the bifurcating periodic solutions: if $\beta_2 < 0$ ($\beta_2 > 0$), then bifurcating periodic solutions in the center manifold are stable (unstable). Period of the bifurcating periodic solutions is determined by T_2, the period increases (decrease) when $T_2 > 0$ ($T_2 < 0$). Thus (20) and (54) imply that the results of the direction the Hopf bifurcations satisfy.

5 Numerical Simulation

In this section, we study numerical results of system (4) at different values of τ. By choosing $r = 21,\ \omega = 21,\ \delta = 1,\ \beta = 3,\ a = 15$ in system (4), we have

$$\begin{aligned} \frac{dx}{dt} &= 21x(1 - \frac{x+y}{21}) - x - 3xy, \\ \frac{dy}{dt} &= 3x(t-\tau)y(t-\tau) - 15y. \end{aligned}$$

For $\tau = 0$, $E_2 = (5, 3.75)$ is an interior unique equilibrium point. These values show that (19) has a positive root $z = 129.6297769$, and then Theorem 3 shows that $\tau^* = 0.2648100601$. From the formulas in Section 4, we get

$$
\begin{aligned}
M &= -0.3333333334 - 0.7241971227\, i,\\
N &= -0.1467688360 + 1.245730037\, i,\\
\overline{E} &= -0.3353048563 - 2.701455914\, i,\\
g_{20} &= 0.07001726116 + 0.0679380362\, i,\\
g_{11} &= 0.02285330684 - 0.1841225970\, i,\\
g_{02} &= 0.03920150800 - 0.9478826122\, i,\\
C_1^{(1)} &= 0.4358591088 + 0.5440217450\, i,\\
C_1^{(2)} &= -0.6386367604 - 0.1582198462\, i,\\
W_{20}^{(1)}(0) &= -0.2638607674 + 0.6954569963\, i,\\
W_{20}^{(2)}(0) &= -0.3302243769 - 0.5360810164\, i,\\
W_{20}^{(1)}(-1) &= 0.1400340404 - 0.2463831080\, i,\\
W_{20}^{(2)}(-1) &= 1.192302058 - 0.4408369488\, i,\\
C_2^{(1)} &= -0.3333333334,\\
C_2^{(2)} &= -0.4444444444,\\
W_{11}^{(1)}(0) &= -1.004521703 + 0.0\, i,\\
W_{11}^{(2)}(0) &= -0.1699352452 + 0.0\, i,\\
W_{11}^{(1)}(-1) &= -0.9494599988 + 0.0\, i,\\
W_{11}^{(2)}(-1) &= 0.0740685228 + 0.0\, i,\\
g_{21} &= -0.5523573046 + 1.0418494\, i.
\end{aligned}
$$

By replacing the above values in (54), we obtain $c_1(0) = -0.2658449039 + 0.4681490320\, i$, which implies $\mu_2 = 49.95991907 > 0$, $\beta_2 = -0.5316898078 < 0$ and $T_2 = 0.04309591200 > 0$. The fact $T_2 > 0$ shows that the period of the bifurcating periodic solution increases, and finally, the periodic solution disappears. Now, by substituting the values of $r = 21,\ \omega = 21,\ \delta = 1,\ \beta = 3,\ a = 15$ and $\tau = 0.2648100601$ in system (5) and (6), we can simulate their dynamics by changing ε, numerically.

In Figure 1, we see that for $\tau = 0.05 < \tau^*$ and $\varepsilon = 100$, $E = (20, 0)$ in (6) and $E = (5, 3.75)$ in (4) and (5) are stable focus. Figure 2 shows that for $\tau = 0.2648100601$ and $\varepsilon = 0.001$, (5) and (6) in $E = (20, 0)$ have stable focus, but (4) has a periodic solution in $E = (5, 3.75)$. In Figure 3, with a slight increase in the amount of ε, no change in the dynamics of (5) and (6) is observed. In Figure 4, with increasing $\varepsilon = 10$, the stable focus of $E = (20, 0)$ in (6) remains unchanged. In contrast, the stable focus of (5) changes from $E = (20, 0)$ to $E = (12, 3.75)$, which is a sign of the effectiveness of viral therapy and reduction of tumor cells levels. In Figure 5, for $\varepsilon = 100$, around $E = (5, 3.75)$, a family of stable periodic solutions appears in (5) with period less than periodic solutions around $E = (5, 3.75)$ in (4), which indicates the coexistence between uninfected and infected cells, but $E = (20, 0)$ is a stable focus in (6). In Figures 6 and 7, we see that with increasing $\varepsilon = 1000$ and $\varepsilon = 1000000$, a family of stable periodic solutions with the same period will appear around $E = (5, 3.75)$, which shows at high values of ε, (4) and (5) have the same dynamic. While in (6), no change in equilibrium point and its dynamic is observed and indicate the ineffectiveness of viral therapy in reducing the number of infected tumor cells. In Figure 8, for $\varepsilon = 1000$ and $\tau = 1$, in (4) and (5), the periodic solution disappears. We have used Mathematica and Maple software for numerical simulating.

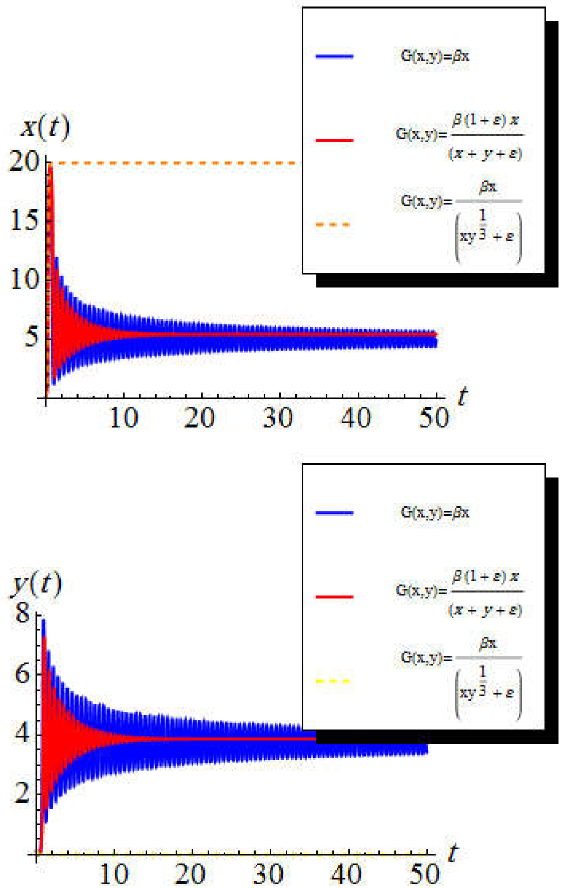


Figure 1: For $\varepsilon = 100$ and $\tau^* = 0.05$, $E = (20, 0)$ in (6), and $E = (5, 3.75)$ in (4) and (5) are stable focus.

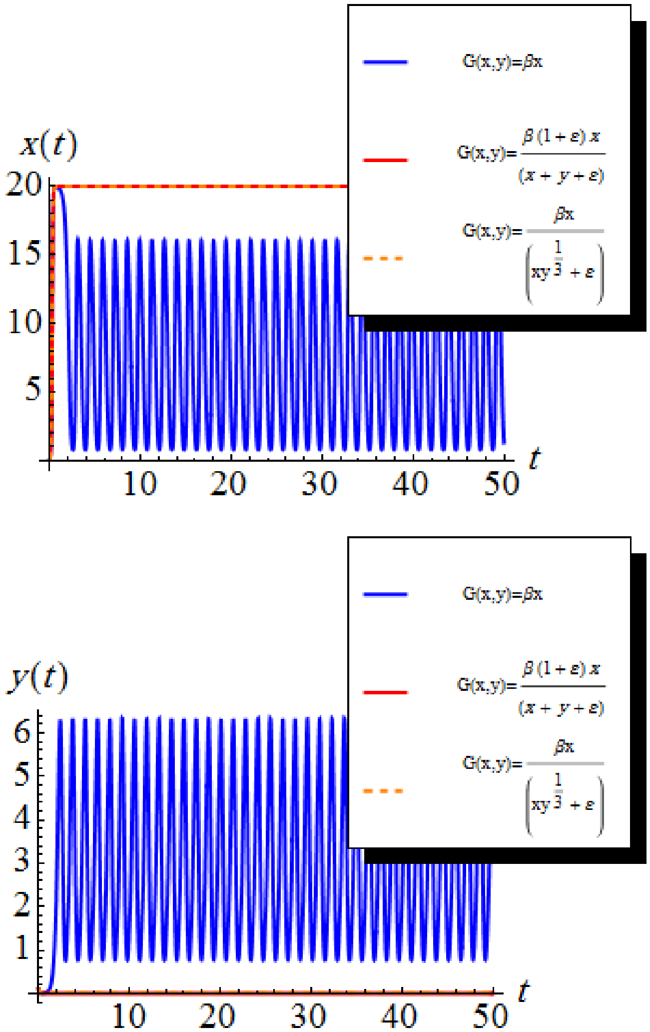


Figure 2: For $\varepsilon = 0.001$ and $\tau^* = 0.2648100601$ $E = (20, 0)$ in (5), and (6) is a stable focus and in (4) $E = (5, 3.75)$ enclosed by a periodic solution.

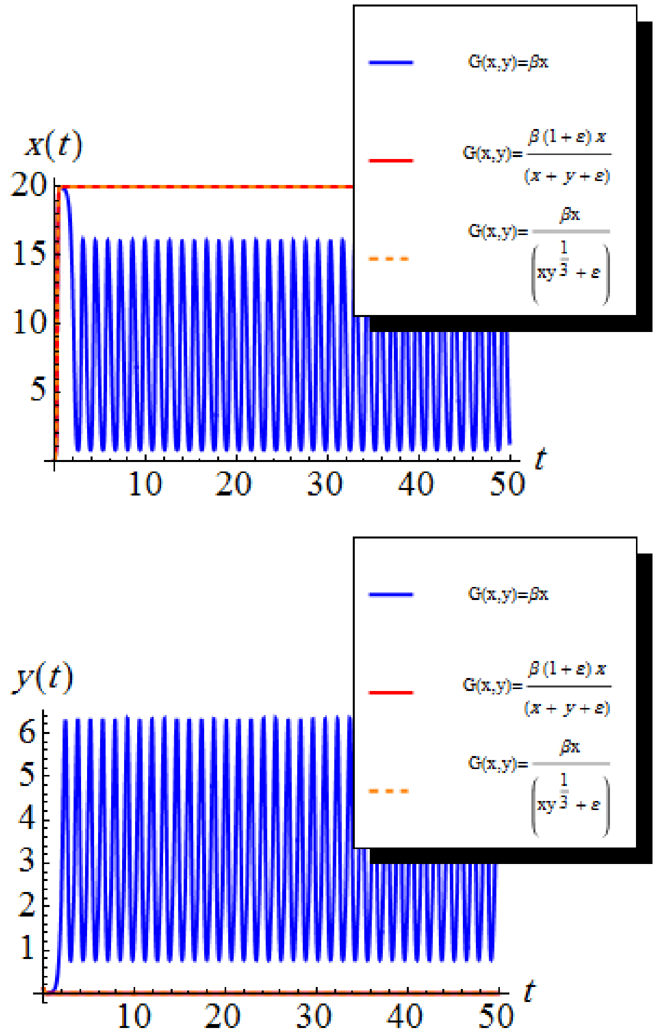
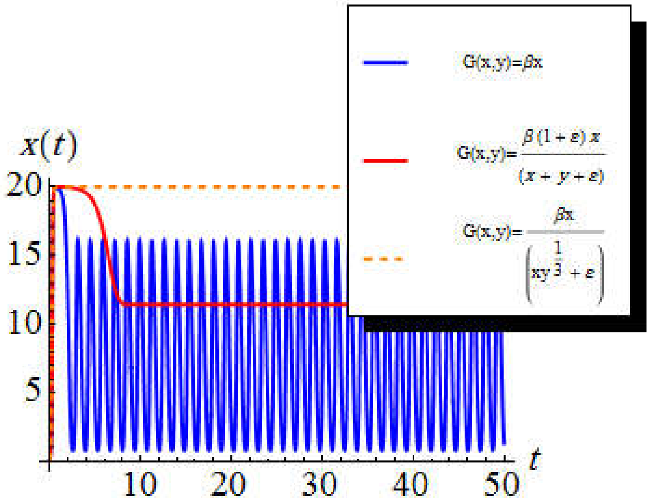


Figure 3: For $\varepsilon = 1$ and $\tau^* = 0.2648100601$ $E = (20, 0)$ in (5) and (6) is a stable focus and $E = (5, 3.75)$ in (4) enclosed by a periodic solution.



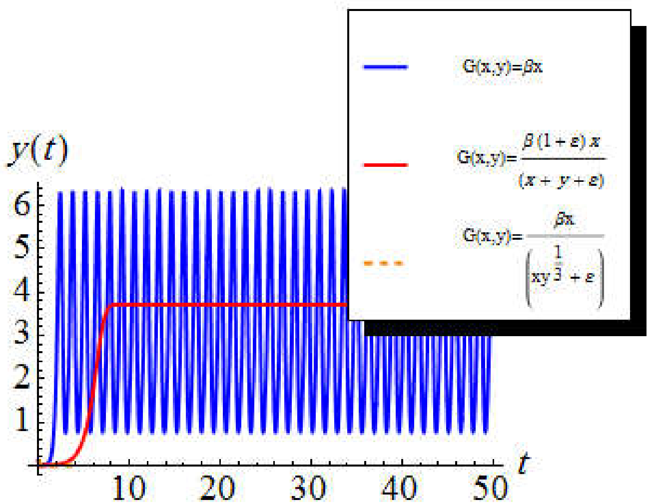


Figure 4: For $\varepsilon = 10$ and $\tau^* = 0.2648100601$ $E = (20, 0)$ in (6) is a stable focus, $E = (5, 3.75)$ in (4) enclosed by a periodic solution and $E = (12, 3.75)$ in (5) is a stable focus.

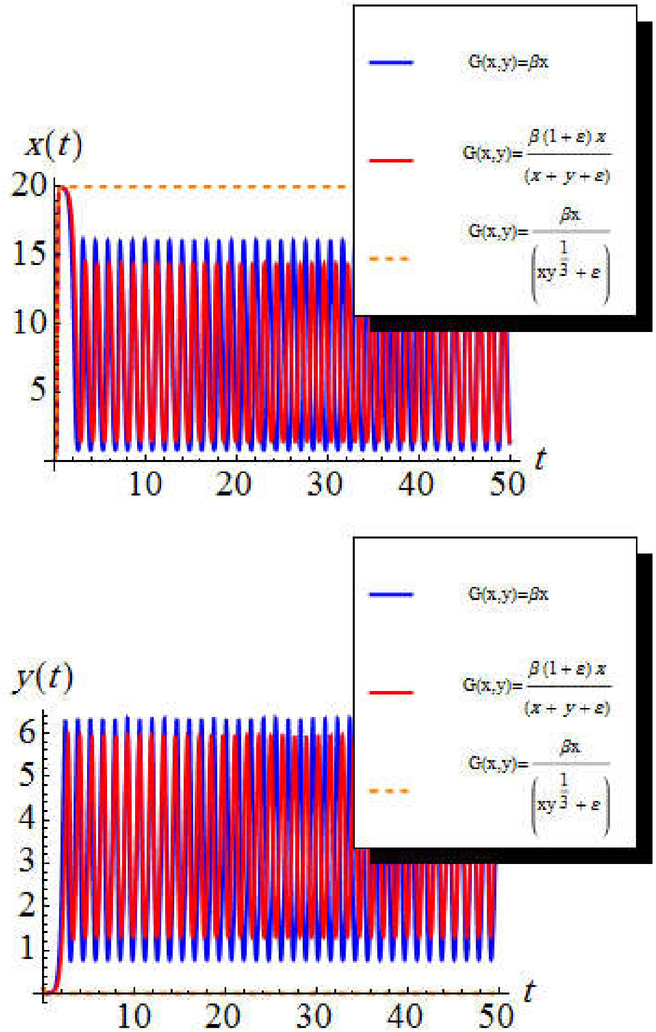


Figure 5: For $\varepsilon = 100$ and $\tau^* = 0.2648100601$ $E = (20, 0)$ in (6) is a stable focus, $E = (5, 3.75)$ in (4) and in (5) enclosed by a periodic solution with different period of the bifurcating.

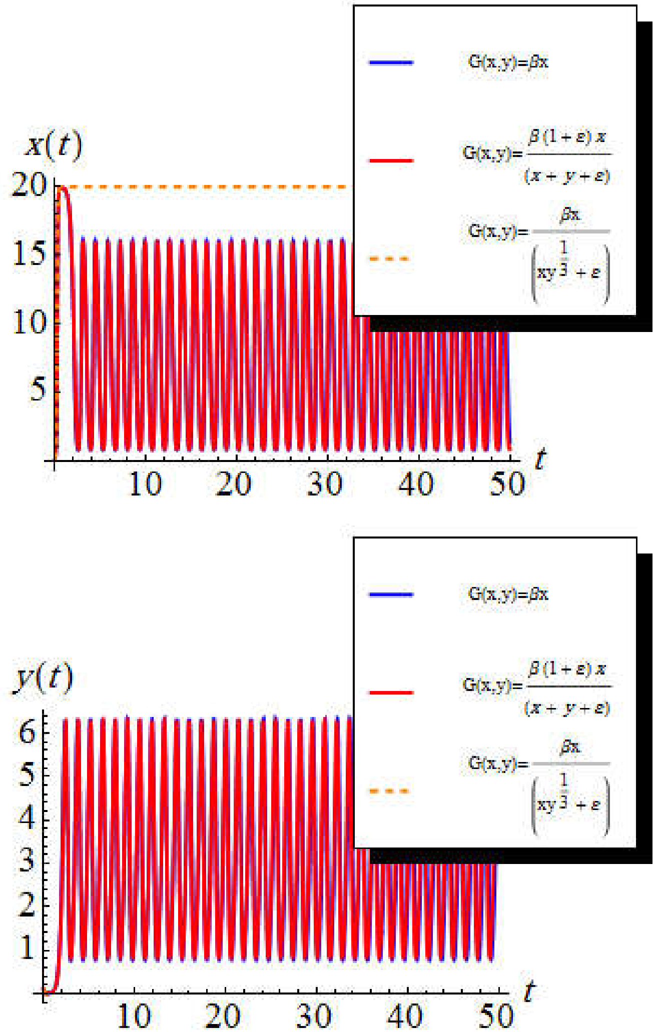


Figure 6: For $\varepsilon = 1000$ and $\tau^* = 0.2648100601\, E = (20, 0)$ in (6) is a stable focus, $E = (5, 3.75)$ in (4) and in (5) enclosed by a periodic solution with almost the same period.

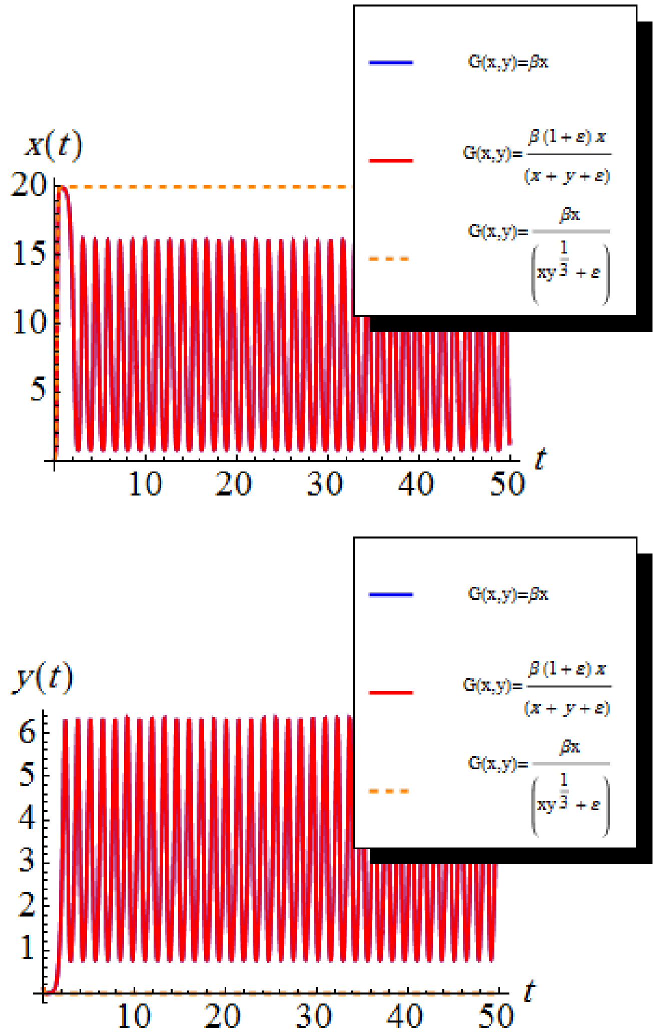


Figure 7: For $\varepsilon = 1000000$ and $\tau^* = 0.2648100601$ $E = (20, 0)$ in (6) is a stable focus, $E = (5, 3.75)$ in (4) and (5) enclosed by the same periodic solution.

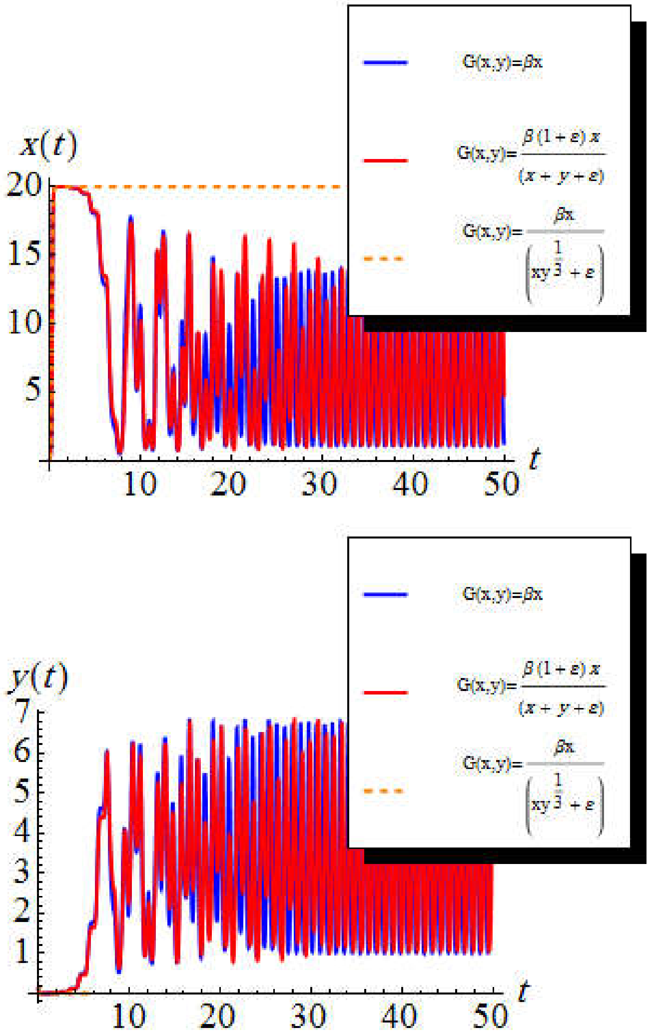


Figure 8: For $\varepsilon = 1000$ and $\tau = 1$ $E = (20, 0)$ in (6) is a stable focus, and in (4) and (5) the periodic solution disappears.

6 Discussion

Three nonlinear mathematical models were expressed with delayed differential equations. Two rates of infection, "rapid spread of the virus," and one rate of infection, "slow spread of the virus," are proposed. Due to the simplicity of calculating the mathematical model with a linear infection rate, the equilibrium points stability was studied without time delay. By introducing a time delay τ to the second equation in (4), we obtained a periodic solution and (4) undergoes a Hopf bifurcation. The existence of periodic solutions showed a coexistence between uninfected tumor cells and infected tumor cells, leading to a dynamical balance between in growth of uninfected cancer cells and infected ones. Now by placing the appropriate value τ obtained from (4) and different values of ε in (5) and (6), we simulated the existence of a periodic solution, numerically. In the simulation obtained from these three models, we found that in (4) and (5) with "rapid virus spread" rate, a periodic solution can be observed. From a biological point of view, it was stated that viral therapy in models with a "rapid virus spread" rate can create a coexistence interaction between uninfected and infected tumor cells. While simulation (6) showed that no limit cycles are observed for these values, viral treatment may not reduce tumor cells. By increasing the time delay, in (4) and (5), the period of the created periodic solutions increased until oscillations between two populations vanish. Hence, the growth of tumor cancer cells became stable.

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