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Hopf Bifurcation in Oncolytic Therapeutic Modeling: Viruses as Anti-Tumor Means with Viral Lytic Cycle

Fatiha Najm* and Radouane Yafia†
Department of Mathematics Faculty of Sciences,
Ibn Tofail University Campus Universitaire,
BP 133, Kénitra, Morocco
**faiha.najm@uit.ac.ma*
†*yafia1@yahoo.fr*

M. A. Aziz-Alaoui
Normandie Univ, France; ULH, LMAH,
F-76600 Le Havre; FR-CNRS-3335, ISCN,
25 rue Ph. Lebon, 76600 Le Havre, France
aziz.alaoui@univ-lehavre.fr

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In this paper, we propose a delayed mathematical model describing oncolytic virotherapy treatment of a tumour that proliferates according to the logistic growth function, incorporating viral lytic cycle. The tumour population cells are divided into uninfected and infected cell subpopulations and the virus spreading is supposed to be in a direct mode (i.e. from cell to cell). Depending on the time delay, we analyze the positivity and boundedness of solutions and the stability of tumour, infected and uninfected free equilibria (TFE, IFE, UFE) and uninfected–infected equilibrium (UIE) is established. We prove that, delay can lead to "Jeff's phenomenon" observed in a laboratory which causes oscillations in tumour size whose phase and period change over time. With nonlinear dependence of UIE equilibrium on time delay, we develop a more general algorithm determining the stability/instability of the oscillating periodic solutions bifurcating from the UIE equilibrium. Finally, we present numerical simulations illustrating our theoretical results.

Keywords: Anti-tumour virus; delay differential equation; stability/instability of equilibria; Jeff's phenomenon; Hopf bifurcation.

1. Introduction

In the case of gene therapy, genetically modified viruses are used for the transfer of genes that can facilitate tumor suppression, apoptosis, or the release of oncolytic cytokines. In the case of oncolytic virotherapy (OV), genetically altered viruses that are capable of intruding selectively into the cancer cells to facilitate targeted annihilation of cancer cells are used. These oncolytic viruses can then replicate within the cancer cells to cause viral burden to the cell which in turn leads to cell death [Hulou *et al.*, 2016; Jenner *et al.*, 2018]. Moreover, the oncolytic viruses that are released from the virus-infected and lysed cancer cells can infect and kill other cancer cells. Many oncolytic viruses are used in clinical trials to evaluate their efficacy in relieving cancers of ovary, sarcoma, pancreas, prostate, and bladder [Jenner *et al.*, 2018]. Adenoviruses, retroviruses, herpes viruses, paramyxoviruses, measles, vesicular stomatitis virus, etc., are some of the oncolytic viruses used to facilitate cancer cure. Some viruses are capable of infecting and killing cancer cells with defective genes. For instance, ONYX-15, a modified adenovirus can selectively kill cancer cells with an abnormal p53 gene. There are several ways by which a therapeutic virus mediates the regression of cancer. Replicating oncolytic viruses are able to infect and lyse cancer cells and spread through the tumor while leaving normal cells largely unharmed. A variety of viruses have shown promising results in clinical trials [Komarova & Wodarz , 2010]. Among the oncolytic viruses with potential use for virotherapy are the adenovirus Onyx-015 [Garber, 2006], the herpes simplex virus HSV-1 [Markert *et al.*, 2000], the Newcastle disease virus NDV [Csatary *et al.*, 2004] and M1 virus [Lin *et al.*, 2014]. Even though most suggested approaches in oncolytic virotherapy are premature and experimental, the fact that the FDA has already given its approval for the use of oncolytic virus therapy (T-VEC, Imlygic) in 2015 shows its potential [Jenner *et al.*, 2018]. In short, virotherapy based anti-cancer approaches make use of the potential of oncolytic viruses in [Farera Sal *et al.*, 2020; Li *et al.*, 2020; Novozhilov *et al.*, 2006] to

- replicate repeatedly in the cancer cells to eventually burden the cancer cells and cause cell death,
- produce cytotoxic protein while they are inside the cancer cells and thus cause cell death, and
- to infect the cancer cells in such a way that it will induce or boost anti-tumor immunity of the body.

Replication selective anti-tumour viruses was tested for head, neck cancers [Nemunaitis *et al.*, 2001] and metastatic colon carcinoma [Reid *et al.*, 2001; Reid *et al.*, 2002] and for other tumour types [Pecora *et al.*, 2002]. There are many research papers that involve ordinary and delay differential equation mathematical models for the treatment of different types of cancers [Enderling & Chaplain, 2014; Oroji *et al.*, 2016; Choi *et al.*, 2015; Crivelli *et al.*, 2012]. However, there are very few mathematical models that deal with virotherapy [Bajzera *et al.*, 2008; Dingli *et al.*, 2006; Wodarz & Komarova, 2008] and references therein.

The current paper is organized as follows: In Sec. 2, we introduce the mathematical model. In Sec. 3, we study the positivity and boundedness of solutions and the conditions of existence of equilibria. In Secs. 4 and 5, we prove the stability of equilibria and the occurrence of Hopf bifurcation at IFE equilibrium and at UIE equilibrium by considering time delay as the parameter of bifurcation. As the UIE equilibrium depends on time delay which induces a nonlinearity of the linearized operator, in Sec. 6 we develop a more general algorithm for determining the stability of bifurcating branch and the direction of Hopf bifurcation. In Sec. 7, we have carried out some numerical simulations illustrating the theoretical results. We end our paper with a conclusion.

2. Mathematical Model

In the case of oncolytic virotherapy, the mode of transmission of virus infection is an important factor that specifies the treatment efficacy [Novozhilov *et al.*, 2006]. We suppose that the spread of virus into the tumour site by a direct transmission (cell to cell) and that the tumour cells grow following the logistic low at a rate r (for uninfected cells) and s (for infected cells). The maximum sizes of the two tumour populations u and v are given by the same carrying capacity k. β is the spread rate of the virus into the tumour site. Infected tumour cells population is killed by the virus at a rate a. τ is the viral lytic cycle. $e^{-d\tau}$ models the survival function. The mathematical model is given by

$$\begin{cases} \dfrac{du(t)}{dt} = ru(t)\left(1 - \dfrac{N(t)}{k}\right) - du(t) - \beta u(t)v(t), \\ \dfrac{dv(t)}{dt} = \beta e^{-d\tau} u(t-\tau)v(t-\tau) \\ \qquad\qquad + sv(t)\left(1 - \dfrac{N(t)}{k}\right) - av(t), \\ N = u + v, \\ u(s) = \varphi(s) \geq 0, \quad v(s) = \psi(s) \geq 0, \quad s \in [-\tau, 0]. \end{cases} \tag{1}$$

$u :=$ Tumor cells that are not infected by the virus, $v :=$ Tumor cells that are infected by the virus, $N = u + v :=$ Total number of cells in the tumor micro-environment.

The model without delay was introduced and studied biologically and numerically on the effect of cytotoxicity a [Wodarz & Komarova, 2008]. Based on this model other authors introduced the indirect transmission, see [Wodarz & Komarova, 2008; Li & Xi, 2022].

We note that in [Wodarz & Komarova, 2008; Komarova & Wodarz , 2010], the authors did not provide rigorous mathematical proofs of the stability of equilibria of the above model without delay. In the last decades, some mathematical models with intracellular viral lifecycle have been introduced [Wang *et al.*, 2013]. At the molecular level, a great deal of phenomena on intracellular viral life cycles have been found experimentally. Indeed, there are several stages in a typical viral lifecycle: viral entry, viral replication, viral shedding and viral latency. For the details of the viral lifecycle, we refer the reader to [Wang *et al.*, 2013; Beretta & Kuang, 2002; Dix *et al.*, 2000; Hall *et al.*, 1998; Harada & Berk, 1999; Ramachandra *et al.*, 2001].

To the best of our knowledge and from literature, Wodarz was the first to model oncolytic virotherapy using a simple ODE system [Wodarz & Komarova, 2008]. Thus, in this work we formulate for the first time, an oncolytic virotherapy model with both viral lifecycle "delay" and cytotoxicity and survival function.

3. Properties of Solutions and Steady States

Proposition 1. *Let* $\varphi(0) > 0$ *and* $\psi(0) > 0$, *then there exist a constant* $\sigma > 0$, *for* $t \in [0, \sigma[$, *such that*

(i) *All solutions of system* (*1*) *with positive initial conditions uniquely exist and are positive.*
(ii) $\limsup_{t\to+\infty} u(t) \le k$ *and* $\limsup_{t\to+\infty} v(t) \le L$, *where* $L = \frac{k(r+a)^2}{4ra} + \frac{kse^{d\tau}}{4a}$.
(iii) $\liminf_{t\to+\infty} u(t) \ge M$, *where* $M = k(1 - \frac{Lr+k(d+\beta L)}{kr})$, *with* $kr > Lr + k(d + \beta L)$.

Proof. From Theorems 2.1 and 2.3 in [Hale & Lunel, 1993], the solutions of system (1) with positive initial conditions uniquely exist on $[0, \sigma[$. Suppose that $(u(t), v(t))$ is a solution of system (1) for $t \in [0, \sigma[$. Without loss of generality, we assume that $t \in [0, \sigma[$ is the maximum internal of the solution and $\sigma = \infty$ if the solution exists for any $t > 0$. Integrating the first equation of system (1) gives

$$\begin{aligned} u(t) &= u(0)e^{\int_0^t (r(1-\frac{N(s)}{k})-d-\beta v(s))ds} \\ &> 0, \quad t \in [0, \sigma[. \end{aligned}$$

To prove the positivity of $v(t)$ for any $t \in [0, \sigma[$, we use the method of contradiction. Suppose that there exists a $t^* \in [0, \sigma[$ such that $v(t^*) = 0$, $\frac{dv(t^*)}{dt} \le 0$ and $v(t) > 0$ for any $t \in [0, t^*[$. Taking t^* to the second equation of system (1), we have

$$\begin{aligned} \left.\frac{dv(t)}{dt}\right|_{t=t^*} &= \beta e^{-d\tau} u(t^* - \tau)v(t^* - \tau) \\ &\quad + sv(t^*)\left(1 - \frac{N(t^*)}{k}\right) - av(t^*), \\ &= \beta e^{-d\tau} u(t^* - \tau)v(t^* - \tau) \\ &> 0. \end{aligned}$$

which leads to a contradiction. Therefore, $v(t) > 0$ for all $t \in [0, \sigma[$. This completes the proof of (i).

To prove the boundedness of the solutions, we firstly see that it follows from the first equation of system (1) that $\frac{du(t)}{dt} \le ru(t)(1-\frac{u(t)}{k})$, which implies that $\limsup_{t\to+\infty} u(t) \le k$. Next, we demonstrate the boundedness of $v(t)$. Define

$$W(t) = u(t) + e^{d\tau} v(t + \tau),$$

whose derivative with respect to t yields

$$\begin{aligned} \frac{W}{dt}(t) &= \frac{du}{dt}(t) + e^{-d\tau}\frac{v(t+\tau)}{dt}, \\ &= ru(t)\left(1 - \frac{N(t)}{k}\right) - du(t) - \beta u(t)v(t) + \beta u(t)v(t) + se^{d\tau}v(t+\tau)\left(1 - \frac{N(t+\tau)}{k}\right) - ae^{d\tau}v(t+\tau), \\ &= ru(t) - \frac{r}{k}u^2(t) - \frac{r}{k}u(t)v(t) - du(t) - \beta u(t)v(t) + \beta u(t)v(t) + se^{d\tau}v(t+\tau) - \frac{se^{d\tau}}{k}v^2(t+\tau) \\ &\quad - \frac{se^{d\tau}}{k}v(t+\tau)u(t+\tau) - ae^{d\tau}v(t+\tau), \\ &\le ru(t) - \frac{r}{k}u^2(t) + se^{d\tau}v(t+\tau)\left(1 - \frac{v(t+\tau)}{k}\right), \end{aligned}$$

$$\leq -aW(t) + (r+a)u(t) - \frac{r}{k}u^2(t) + se^{d\tau}v(t+\tau)\left(1 - \frac{v(t+\tau)}{k}\right),$$

$$\leq -aW(t) + \frac{k(r+a)^2}{4r} + \frac{kse^{d\tau}}{4}.$$

Let

$$L_0 = \frac{k(r+a)^2}{4r} + \frac{kse^{d\tau}}{4}$$

and applying the theorem of differential inequality, we have

$$0 < W(t) < \frac{L_0}{a} - \left(\frac{L_0}{a} - W(0)\right)e^{-dt}.$$

By the positivity of $v(t)$, it holds that

$$\limsup_{t\to+\infty} v(t) \leq \frac{L_0}{a} = L.$$

This completes the proof of (ii).

From the first equation of system (1), we take notice of

$$\frac{du(t)}{dt} = ru(t)\left(1 - \frac{N(t)}{k}\right) - du(t) - \beta u(t)v(t),$$

$$\geq ru(t)\left(1 - \frac{u(t)}{k}\right) - \frac{r}{k}u(t)v(t) - du(t)$$

$$- \beta u(t)v(t),$$

$$\geq ru(t)\left(1 - \frac{u(t)}{k}\right) - \frac{rL}{k}u(t) - du(t)$$

$$- \beta L u(t),$$

$$\geq u(t)\left(r - \frac{rL}{k} - d - \beta L - \frac{r}{k}u(t)\right),$$

which implies that $\liminf_{t\to+\infty} u(t) \geq k(1 - \frac{L}{k} - \frac{d}{r} - \frac{\beta L}{r}) = k(1 - \frac{Lr + k(d+\beta L)}{kr}) = M$ with $kr > Lr + k(d+\beta L)$. This completes the proof of (iii). ■

From [Hale & Lunel, 1993], we get the following result.

Theorem 1. *The solution of system (1) with positive initial condition is existent, unique, positive and bounded on* $[0, +\infty)$ *and* $\Upsilon = \{(\varphi(s), \psi(s)) \in \mathcal{C}\backslash M \leq \varphi(s) \leq k, 0 \leq \psi(s) \leq L\}$ *is a positively invariant set for system (1).*

Let

$$R_1 = \beta k(a-s) + ar - sd,$$

$$R(\tau) = \beta(e^{-d\tau}(r + \beta k) - s),$$

$$R_2(\tau) = \beta k e^{-d\tau}(r-d) - ar + sd.$$

The possible steady states are given by $E_0 = (0,0)$ (tumour free equilibrium TFE), $E_1 = (u_1, 0) = (\frac{k}{r}(r-d), 0)$ (infected free equilibrium IFE), $E_2 = (0, v_2) = (0, \frac{k(s-a)}{s})$ (uninfected free equilibrium UFE), $E^*(\tau) = (u^*(\tau), v^*(\tau)) = (\frac{R_1}{R(\tau)}, \frac{R_2(\tau)}{R(\tau)})$ (uninfected–infected equilibrium UIE).

Define $\bar{\tau} = \frac{1}{d}\ln(\frac{r+\beta k}{s})$, $\hat{\tau} = \frac{1}{d}\ln(\frac{\beta k(r-d)}{ar-sd})$ and $\tau_{\min} = \min(\bar{\tau}, \hat{\tau})$, $\tau_{\max} = \max(\bar{\tau}, \hat{\tau})$.

Let the hypotheses

$$(\mathrm{H})_0: \ \frac{r+\beta k}{s} > 1$$

$$(\mathrm{H})_1: \ \frac{\beta k(r-d)}{ar - sd} > 1$$

$$(\mathrm{H})_2: \ 0 < \tau < \tau_{\min} \quad \text{and} \quad \beta k(a-s) > sd - ar$$

$$(\mathrm{H})_3: \ \tau > \tau_{\max} \quad \text{and} \quad \beta k(a-s) < sd - ar.$$

Note that, the hypotheses $(\mathrm{H})_0$ and $(\mathrm{H})_1$ guarantee the existence and positivity of $\bar{\tau}$ and $\hat{\tau}$ respectively. The hypotheses $(\mathrm{H})_2$ and $(\mathrm{H})_3$ guarantee the positivity and nonpositivity respectively of R, $R(\tau)$ and $R_1(\tau)$. Then we deduce the following result.

Lemma 1

(i) *If* $s > a$, E_1 *exists and is positive.*
(ii) *If* $r > d$, E_2 *exists and is positive.*
(iii) *If* $(H)_0$–$(H)_2$ *or* $(H)_0$, $(H)_1$, $(H)_3$ *are satisfied,* E^* *exists and is positive.*
(iv) *If* $\tau \in (\tau_{\min}, \tau_{\max})$, E^* *exists but is not positive.*

4. Stability of Boundary Equilibria

Linearizing system (1) around any equilibrium point $E = (u, v)$, we get the linearized system

$$\frac{dX(t)}{dt} = JX(t) + J_\tau X(t-\tau), \qquad (2)$$

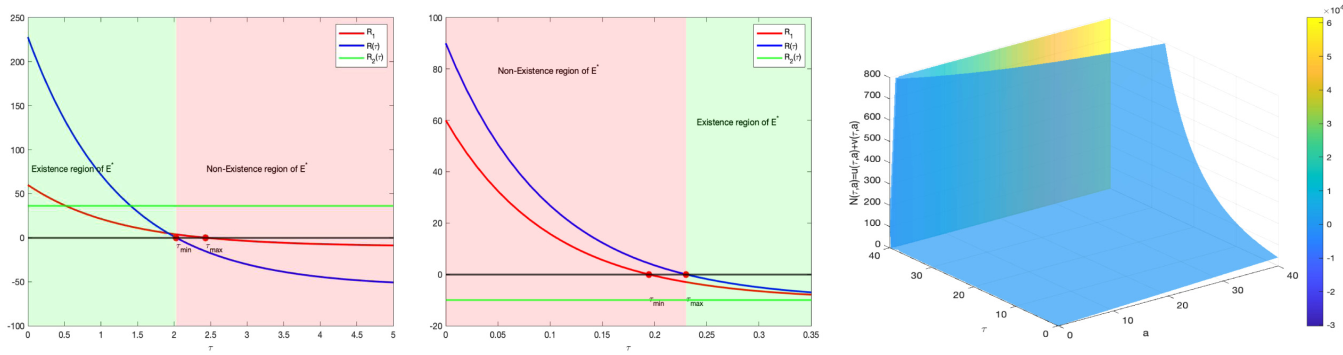

Fig. 1. The existence and nonexistence regions (left and center) of $E^*(\tau)$ depending on time delay τ, and the signs of R_1, $R(\tau)$ and $R_2(\tau)$ with parameters values $r = 15$; $s = 5$; $\beta = 2$; $d = 0.8$; (resp., $d = 10$) $a = 4$; $k = 10$. We see that, $E^*(\tau)$ exists if R_1, $R(\tau)$ and $R_2(\tau)$ have the same sign, which agree with the hypotheses $(\mathrm{H})_0$–$(\mathrm{H})_2$ or $(\mathrm{H})_0$, $(\mathrm{H})_1$, $(\mathrm{H})_3$. On the right, the 3D plot of the total size of the UIE equilibrium point for $r = 0.2$; $s = 0.2$; $\beta = 1$; $d = 0.10$; $k = 10$.

where

$$J^E = \begin{pmatrix} r\left(1 - \frac{N}{k}\right) - \frac{r}{k}u - d - \beta v & -\frac{r}{k}u - \beta u \\ -\frac{s}{k}v & s\left(1 - \frac{N}{k}\right) - \frac{s}{k}v - a \end{pmatrix}; \quad J_\tau^E = \begin{pmatrix} 0 & 0 \\ \beta e^{-d\tau}v & \beta e^{-d\tau}u \end{pmatrix}.$$

Then we deduce the stability of E_0 and E_2.

Proposition 2

(i) *If $r < d$ and $s < a$, E_0 is a stable node and unstable otherwise.*
(ii) *If $s > a$ and $r\frac{a}{s} - d - \beta v_2 < 0$, E_2 is a stable node.*

For the stability of E_1, suppose $r > d$ and we have

$$J^{E_1} = \begin{pmatrix} -\frac{r}{k}u_1 & -\left(\frac{r}{k} + \beta\right)u_1 \\ 0 & s\frac{d}{r} - a \end{pmatrix};$$

$$J_\tau^{E_1} = \begin{pmatrix} 0 & 0 \\ 0 & \beta e^{-d\tau}u_1 \end{pmatrix}.$$

The associated characteristic equation is

$$\left(\lambda + \frac{r}{k}u_1\right)(\lambda - a_1 - b_1(\tau)e^{-\lambda\tau}) = 0, \tag{3}$$

where $a_1 = s\frac{d}{r} - a$ and $b_1(\tau) = \beta e^{-d\tau}u_1$. As $\frac{r}{k}u_1 > 0$, then the stability of E_1 is deduced from

$$\Delta(\lambda, \tau) = \lambda - a_1 - b_1(\tau)e^{-\lambda\tau} = 0. \tag{4}$$

Then, we have the following result.

Proposition 3. *Suppose $r > d$;*

(i) *If $a_1 < 0$ and $b_1(\tau) < -a_1$, $\forall\, \tau > 0$, E_1 is asymptotically stable for all $\tau > 0$.*
(ii) *If $a_1 < 1$ and $|a_1| < b_1(\tau)$, the steady state E_1 is asymptotically stable for $\tau = 0$ and there exist τ_0 such that, it is asymptotically stable for $\tau < \tau_0$ and unstable for $\tau > \tau_0$.*

Proof

(i) Let $\lambda = \mu + i\nu$ be a root of Eq. (4), we have:

$$\begin{cases} \mu - a_1 - b_1(\tau)e^{-\mu\tau}\cos(\nu) = 0, \\ \nu + b_1(\tau)e^{-\mu\tau}\sin(\nu) = 0. \end{cases} \tag{5}$$

If there exist a root $\mu_0 \geq 0$ of (5), then:

$$-a_1 \leq b_1(\tau)e^{-\mu_0}\cos(\nu).$$

As $-1 \leq \cos(\nu) \leq 1$, $0 < e^{-\mu_0} < 1$ and $b_1(\tau) > 0$ imply $b_1(\tau) > -a_1$, which contradicts the assumption $b_1(\tau) < -a_1$. So the roots of Eq. (6) have negative real parts and E_1 is asymptotically stable for all $\tau > 0$.

(ii) To obtain the switch of stability of E_1, one need to find the imaginary root of Eq. (4).

Let $\lambda = i\zeta$, then

$$\Delta(i\zeta,\tau)=0 \Leftrightarrow \begin{cases} \zeta = \dfrac{1}{\tau}\arccos\left(-\dfrac{a_1}{b_1(\tau)}\right) \in (0,\pi) \quad \text{for } 0 < \left|\dfrac{a_1}{b_1(\tau)}\right| < 1 \\ \qquad\qquad \text{and} \\ \sqrt{b_1^2(\tau)-a_1^2} = \arccos\left(-\dfrac{a_1}{b_1(\tau)}\right). \end{cases} \tag{6}$$

Then, we need the following lemmas.

Lemma 2 (see [Hale & Lunel, 1993]). *All roots of the equation $(z+c)e^z + d = 0$, where c and d are real, have negative real parts if and only if*

(i) $c > -1$
(ii) $c + d > 0$
(iii) $d < \zeta \sin\zeta - c\cos\zeta$

where ζ is the root of $\zeta = -c\tan\zeta$, $0 < \zeta < \pi$, if $c \neq 0$ and $\zeta = \frac{\pi}{2}$ if $c = 0$.

Lemma 3. *Under the hypotheses of (ii) and for sufficiently d close to 0, there exists a unique solution τ_0 of Eq. $(6)_2$ such that $i\zeta_0$ is a purely imaginary root of Eq. (4), with $\zeta_0 = \arccos(-\frac{a_1}{b_1(\tau_0)})$. Furthermore*

$$\begin{cases} \sqrt{b_1^2(\tau)-a_1^2} < \arccos\left(-\dfrac{a_1}{b_1(\tau)}\right) \\ \qquad \textit{for } \tau \in (0,\tau_0), \\ \sqrt{b_1^2(\tau)-a_1^2} > \arccos\left(-\dfrac{a_1}{b_1(\tau)}\right) \\ \qquad \textit{for } \tau \in (\tau_0,+\infty). \end{cases} \tag{7}$$

Remark 4.1. Let $f_1 : (0,\pi) \to \mathbb{R}$; be defined by $f_1(\zeta) = \alpha\tan\zeta$, $\alpha < 1$ and $\alpha \neq 0$. Then f_1 has a unique fixed point $\bar\zeta \in (0,\pi)$, such that for $0 < \alpha < 1$; $f_1(\zeta) < \zeta$ if $\zeta \in (0,\bar\zeta) \cup (\frac{\pi}{2},\pi)$ and $f_1(\zeta) > \zeta$ if $\zeta \in (\bar\zeta,\frac{\pi}{2})$, and for $\alpha < 0$; $f_1(\zeta) < \zeta$ if $\zeta \in (0,\frac{\pi}{2}) \cup (\bar\zeta,\pi)$ and $f_1(\zeta) > \zeta$ if $\zeta \in (\frac{\pi}{2},\bar\zeta)$.

Then, we only have to verify conditions (i)–(iii) of Lemma 2.

The assertions (i) and (ii) follow from the hypotheses of (ii). For (iii), let $\tau \in (0,\tau_0)$ and $f_1(\zeta) = a_1\tan\zeta$. From $(7)_1$ we have; If $a_1 = 0$, the inequality $(7)_1$ becomes $-b_1(\tau) < b_1(\tau) < \frac{\pi}{2}$, and (iii) is satisfied.

If $0 < a_1 < 1$ or $a_1 < 0$, as

$$f_1\left(\arccos\left(-\frac{a_1}{b_1(\tau)}\right)\right) = \sqrt{b_1^2(\tau)-a_1^2},$$

$(7)_1$ imply that

$$f_1\left(\arccos\left(-\frac{a_1}{b_1(\tau)}\right)\right) < \arccos\left(-\frac{a_1}{b_1(\tau)}\right),$$

$$\text{with } \arccos\left(-\frac{a_1}{b_1(\tau)}\right) \in (0,\pi).$$

From Remark 4.1 and the graph of f_1, if $\bar\zeta$ is the fixed point of f_1 in $(0,\pi)$, we have:

$$f_1\left(\arccos\left(-\frac{a_1}{b_1(\tau)}\right)\right) < \bar\zeta, \tag{8}$$

that is

$$\sqrt{b_1^2(\tau)-a_1^2} < \bar\zeta$$

which leads to the desired assertion. This complete the stability of E_1 for $0 < \tau < \tau_0$.

To prove the unstability of E_1 in (2) (ii), for $\tau > \tau_0$ we will show that the characteristic equation (4) has at least one root with positive real part.

Let $\tau \in (\tau_0,+\infty)$. If all roots of the characteristic equation (4) have negative real parts, the properties (i)–(iii) of Lemma 2 are satisfied. From $(7)_2$ and (8) we have

$$\begin{cases} f_1\left(\arccos\left(-\dfrac{a_1}{b_1(\tau)}\right)\right) > \arccos\left(-\dfrac{a_1}{b_1(\tau)}\right) \\ \qquad\qquad \text{and} \\ f_1\left(\arccos\left(-\dfrac{a_1}{b_1(\tau)}\right)\right) < \bar\zeta. \end{cases}$$

So, from Remark 4.1 and the graph of f_1, we have

$$\begin{cases} \arccos\left(-\dfrac{a_1}{b_1(\tau)}\right) < \bar{\zeta} \quad \text{and} \\ \arccos\left(-\dfrac{a_1}{b_1(\tau)}\right) > \bar{\zeta} \end{cases}$$

which is impossible. Now, suppose that there is one root with zero real part and all the remaining roots have negative real parts. From (6) and Lemma 3 we deduce that $\tau = \tau_0$, which contradicts the assumption $\tau > \tau_0$. Then E_1 is unstable for $\tau > \tau_0$. ■

Proof (of Lemma 3). In view of hypotheses in (ii) Proposition 3, find a root of Eq. $(6)_2$ that is equivalent to finding a root of the equation

$$\tau = -\frac{\arccos\left(-\dfrac{a_1}{b(\tau)}\right)}{b_1(\tau)\sin\left(\arccos\left(-\dfrac{a_1}{b_1(\tau)}\right)\right)}. \tag{9}$$

Let

$$y(\tau) = \arccos\left(-\frac{a_1}{b_1(\tau)}\right) \quad \text{and}$$

$$F_1(\tau) = -\frac{y(\tau)}{b_1(\tau)\sin(y(\tau))}.$$

As F is continuously differentiable on $[0, +\infty)$, we have $F_1(0) > 0$ and $F_1(+\infty) < 0$ for d close to 0. Then there exists at least one solution τ_0 of Eq. (9) in $(0, +\infty)$. For the uniqueness of τ_0, let $g(\tau) = \tau - F_1(\tau)$, then

$$g'(\tau) = 1 - \frac{y'(\tau)b_1(\tau)\sin(y(\tau)) - y(\tau)b_1'(\tau)\sin(y(\tau)) - y(\tau)b_1(\tau)\cos((\tau))y'(\tau)}{(b_1(\tau)\sin(y(\tau)))^2},$$

where

$$y'(\tau) = -\sqrt{1 - \left(\frac{a_1}{b_1(\tau)}\right)^2}\,\frac{a_1'b_1(\tau) - a_1b_1'(\tau)}{b_1^2(\tau)}.$$

From the definitions of a_1 and $b_1(\tau)$, we have $\lim_{d\to 0} b_1'(\tau) = 0$ and $a_1' = 0$. Then $\lim_{d\to 0} g'(\tau) = 1 > 0$, for all $\tau > \tau_0$. So as, $g' > 0$ and g is a strictly increasing function on the interval $(0, +\infty)$ for d close to 0, τ_0 is unique in $(0, +\infty)$. By the continuity property of F_1, we have $F_1(\tau) > \tau$ for $\tau \in (0, \tau_0)$ and $F_1(\tau) < \tau$ for $\tau \in (\tau_0, +\infty)$. ■

Theorem 2. *Assume $r > d$, $a_1 < 1$, $|a_1| < b_1(\tau)$, and d is sufficiently small. There exists $\varepsilon_0 > 0$ such that: for each $0 \le \varepsilon < \varepsilon_0$, Eq. (1) has a family of periodic solutions $p(\varepsilon)$ with period $T = T(\varepsilon)$, for the values of the parameter $\tau = \tau(\varepsilon)$ such that $p(0) = E_1$, $T(0) = \frac{2\pi}{\zeta_0}$ and $\tau(0) = \tau_0$ where τ_0 is stated in Lemma 3 and $\zeta_0 = \arccos(-\frac{a_1}{b(\tau_0)})$.*

Proof. We only need to verify the transversality condition $\mathrm{Re}\,\lambda'(\tau)_{/\tau=\tau_0} > 0$. From (4) $\Delta(\lambda_0, \tau_0) = 0$ and $\frac{\partial}{\partial\lambda}\Delta(\lambda_0, \tau_0) = 1 + \tau_0(\lambda_0 - a_1) \neq 0$. According to the implicit function theorem, there exist $\eta > 0$ close to 0, and a function $\lambda : I :=]\tau_0 - \eta, \tau_0 + \eta[\to \mathbb{C}$, with $\lambda(\tau_0) = \lambda_0$ such that $\Delta(\lambda(\tau), \tau) = 0$ for all $\tau \in I$ and

$$\lambda'(\tau) = -\frac{\dfrac{\partial\Delta(\lambda,\tau)}{\partial\tau}}{\dfrac{\partial\Delta(\lambda,\tau)}{\partial\lambda}}, \quad \text{for all } \tau \in I. \tag{10}$$

Let $\lambda(\tau) = p(\tau) + iq(\tau)$. From (10) we have:

$$p'(\tau)_{/\tau=\tau_0} = \frac{\zeta_0^2}{(1 - \tau_0 a_1)^2 + \tau_0^2\zeta_0^2} > 0. \quad ■$$

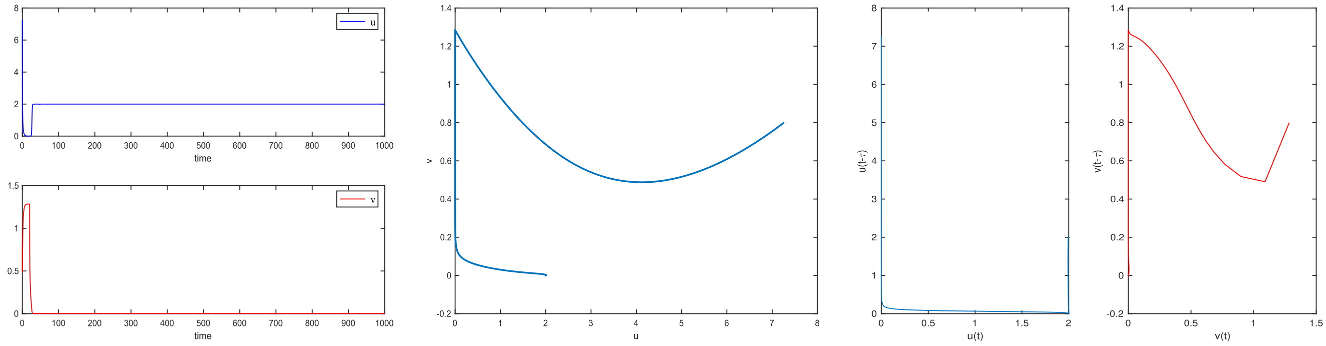

Fig. 2. Stability of the boundary equilibrium point E_1 with parameter values $r = 2$; $s = 4$; $\beta = 1.9$; $d = 0.1$; $a = 5.5$; $k = 2$; $\tau = 20.09$.

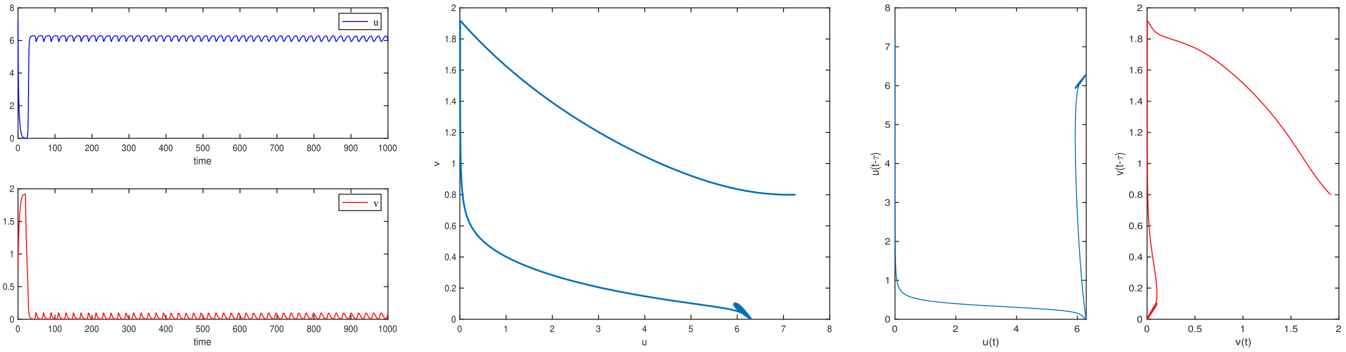

Fig. 3. Hopf bifurcation at the boundary equilibrium point E_1 with parameter values $r = 2$; $s = 4$; $\beta = 1.9$; $d = 0.1$; $a = 5.5$; $k = 6.3$; $\tau = 20.09$.

5. Stability of UIE Equilibrium

Without loss of generality, we denote (u^*, v^*) instead of $(u^*(\tau), v^*(\tau))$. Then we get

$$J^{E^*} = \begin{pmatrix} -\frac{r}{k}u^* & -\left(\frac{r}{k}+\beta\right)u^* \\ -\frac{s}{k}v^* & -\beta e^{-d\tau}u^* - \frac{s}{k}v^* \end{pmatrix}; \tag{11}$$

$$J_\tau^{E^*} = \begin{pmatrix} 0 & 0 \\ \beta e^{-d\tau}v^* & \beta e^{-d\tau}u^* \end{pmatrix},$$

$$\Delta_1(\lambda,\tau) = D_1(\lambda,\tau) + D_2(\lambda,\tau)e^{-\lambda\tau},$$

where

$$D_1(\lambda,\tau) = \lambda^2 + A(\tau)\lambda + B(\tau),$$

$$D_2(\lambda,\tau) = C(\tau)\lambda + D(\tau),$$

$$A(\tau) = \frac{r}{k}u^* + \beta e^{-d\tau}u^* + \frac{s}{k}v^*,$$

$$B(\tau) = -u^*\left(\frac{r}{k}+\beta\right)\frac{s}{k}v^*,$$

$$C(\tau) = -\beta e^{-d\tau}u^*,$$

$$D(\tau) = \left(\frac{r}{k}+\beta\right)u^*\beta e^{-d\tau}v^*.$$

Then

$$\Delta_1(\lambda,0) = \lambda^2 + (A(0)+C(0))\lambda + B(0) + D(0). \tag{12}$$

From Routh–Hurwitz criterion we deduce that, all solutions of Eq. (12) have negative real parts if and only if

$$A(0) + C(0) = \frac{r}{k}u^* + \frac{s}{k}v^* > 0$$

and

$$B(0) + D(0) = u^*v^*\left(\frac{r}{k}+\beta\right)\left(\beta - \frac{s}{k}\right) > 0.$$

Next we will investigate the existence of purely imaginary roots $\lambda = iw$ $(w = w(\tau) > 0)$. Easily we have the following relations:

(i) $D_1(0,\tau) + D_2(0,\tau) \neq 0$
(ii) $D_1(iw,\tau) + D_2(iw,\tau) \neq 0$
(iii) $\lim\sup\{|\frac{D_2(\lambda,\tau)}{D_1(\lambda,\tau)}| : |\lambda| \to \infty, \Re(\lambda) \geq 0\} < 1$
(iv) Let $H(w,\tau) = |D_1(iw,\tau)|^2 - |D_2(iw,\tau)|^2$, then it has finite roots
(v) If $w > 0$ exists satisfying $F(w,\tau) = 0$, then it is continuous and differentiable in τ.

Substituting $\lambda = iw$ into (11), we get

$$\begin{cases} D(\tau)\cos(w\tau) + C(\tau)w\sin(w\tau) = w^2 - B(\tau), \\ C(\tau)w\cos(w\tau) - D(\tau)\sin(w\tau) = -A(\tau)w. \end{cases}$$

Then, we have

$$\begin{cases} \sin(w\tau) = \dfrac{(w^2 - B(\tau))C(\tau)w + wA(\tau)D(\tau)}{w^2C^2(\tau) + D^2(\tau)}, \\[2ex] \cos(w\tau) = -\dfrac{(B(\tau) - w^2)D(\tau) + w^2A(\tau)C(\tau)}{w^2C^2(\tau) + D^2(\tau)}. \end{cases}$$

This yields

$$H(w,\tau) = w^4 + \chi_1(\tau)w^2 + \psi_2(\tau) = 0 \tag{13}$$

and their roots are given by

$$w_\pm^2 = \frac{1}{2}(-\chi_1(\tau) \pm \sqrt{\delta(\tau)}), \tag{14}$$

where

$$\chi_1(\tau) = A^2(\tau) - 2B(\tau) - C^2(\tau),$$

$$\chi_2(\tau) = B^2(\tau) - D^2(\tau),$$

$$\delta(\tau) = \chi_1^2(\tau) - 4\chi_2(\tau).$$

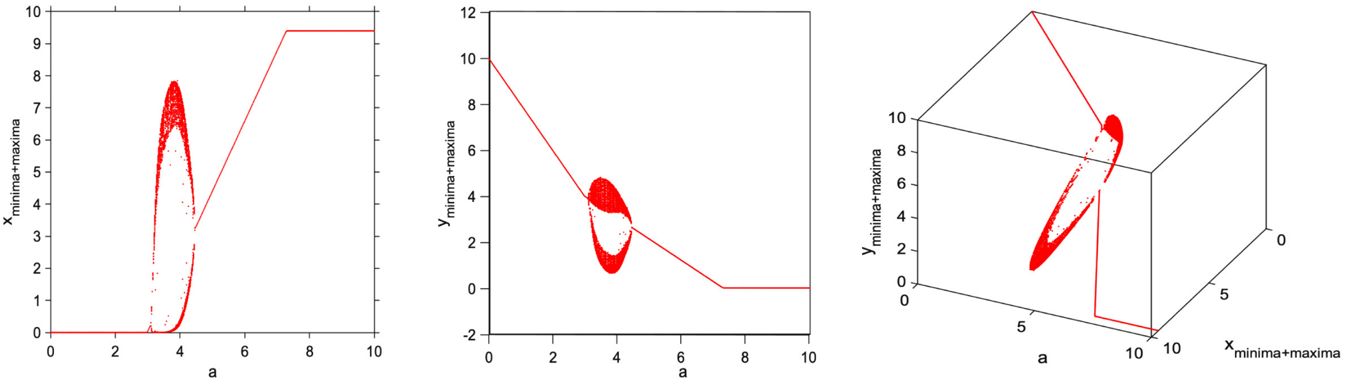

Fig. 4. Bifurcation diagrams in 2D and 3D when taking a as a parameter of bifurcation with parameter values $r = 15$; $s = 5$; $\beta = 2$; $d = 0.9$; $k = 10$; $\tau = 1.1$.

Since

$$\chi_1(\tau) = \left(\frac{r}{k}u^* + \beta e^{-d\tau}u^* + \frac{s}{k}v^*\right)^2 + 2u^*\left(\frac{r}{k}+\beta\right)\frac{s}{k}v^* - (\beta e^{-d\tau}u^*)^2 > 0$$

and

$$\begin{aligned}\chi_2(\tau) &= \left(u^*\left(\frac{r}{k}+\beta\right)\frac{s}{k}v^*\right)^2 - \left(\left(\frac{r}{k}+\beta\right)u^*\beta e^{-d\tau}v^*\right)^2 \quad (15)\\ &= \left(u^*\left(\frac{r}{k}+\beta\right)v^*\right)^2\left(\left(\frac{s}{k}\right)^2 - \beta^2 e^{-2d\tau}\right) \quad (16)\\ &= \left(u^*\left(\frac{r}{k}+\beta\right)v^*\right)^2\left(\frac{s}{k}+\beta e^{-d\tau}\right) \times \left(\frac{s}{k}-\beta e^{-d\tau}\right), \quad (17)\end{aligned}$$

then (13) has uniquely positive real root w_+ if and only if $\frac{s}{k} - \beta e^{-d\tau} < 0$.

Define $\tau_l = \frac{1}{d}\ln(\frac{k\beta}{s})$ and the set

$$\alpha_\tau = \{\tau \in \mathbb{R} \,|\, \tau \in [0, \min(\tau_{\min}, \tau_l))\}.$$

Remark 5.1. $\forall \tau \in \alpha_\tau$, w verifies (14) and w does not exist if $\tau \notin \alpha_\tau$.

Consider $\tau \in \alpha_\tau$, and suppose $\varphi_+(\tau) \in [0, 2\pi)$ defined by

$$\begin{cases}\sin(\varphi_+(\tau)) = \dfrac{(w_+^2 - B(\tau))C(\tau)w_+ + w_+A(\tau)D(\tau)}{w_+^2C^2(\tau) + D^2(\tau)},\\ \cos(\varphi_+(\tau)) = -\dfrac{(B(\tau) - w_+^2)D(\tau) + w_+^2A(\tau)C(\tau)}{w_+^2C^2(\tau) + D^2(\tau)}\end{cases}$$

and the function $\tau_n(\tau) : \alpha_\tau \to \mathbb{R}_+$ is defined as follows

$$\tau_n(\tau) := \frac{\varphi_+(\tau) + 2n\pi}{w_+(\tau)} n \in \mathbb{N}.$$

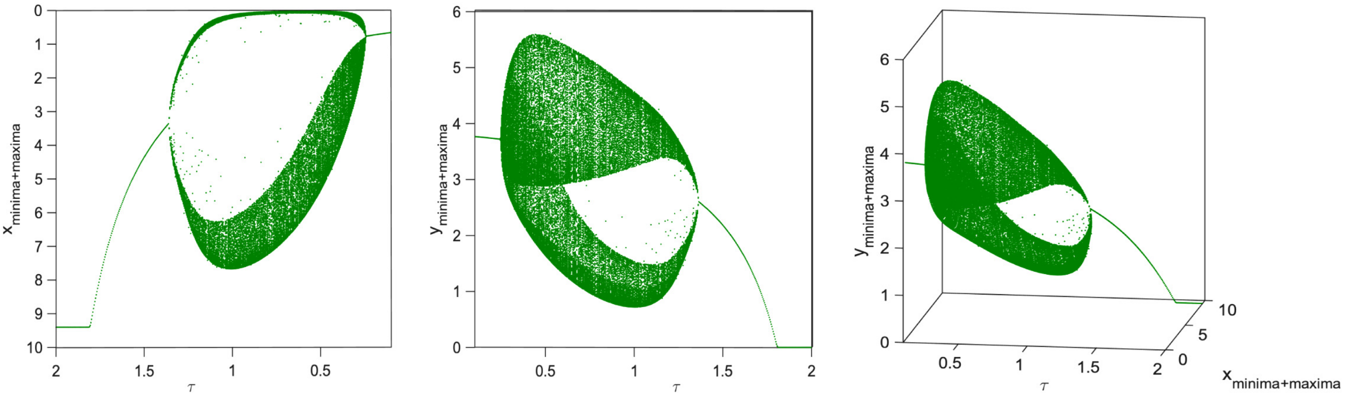

Fig. 5. Bifurcation diagrams in 2D and 3D when taking τ as a parameter of bifurcation with parameter values $r = 15$; $s = 5$; $\beta = 2$; $d = 0.9$; $k = 10$; $a = 4$.

Let us introduce the following continuous and differentiable function $\mathcal{S}_n$ defined by

$$\mathcal{S}_n(\tau) = \tau - \tau_n(\tau), \quad \tau \in \alpha_\tau, \ n \in \mathbb{N}.$$

Then we have the following theorems.

Theorem 3. *Equation (11), has a pair of purely imaginary roots $\lambda = \pm i w_+$, w_+ is real for $\tau \in \alpha_\tau$ and at some $\tau_c \in \alpha_\tau$, such that $\mathcal{S}_n(\tau_c) = 0$ for some $n \in \mathbb{N}$. This pair of roots cross the imaginary axis from left (resp., right) to the right (resp., left) if* $\text{sign}(\Re'(\lambda(\tau))|_{\tau=\tau_c}) > 0$ *(resp.,* $\text{sign}(\Re'(\lambda(\tau))|_{\tau=\tau_c}) < 0$*).*

Define $\tau_{c\,\min} = \min\{\tau \in \mathbb{R}_+ \,|\, \mathcal{S}_n(\tau) = 0\}$ and $\tau_{c\,\max} = \max\{\tau \in \mathbb{R}_+ \,|\, \mathcal{S}_n(\tau) = 0\}$.

Theorem 4. *Assume that $(H)_2$ and $\beta > \frac{s}{k}$ are verified, system (1) has the following properties*

(i) *if $\alpha_\tau = \emptyset$ or $\alpha_\tau \neq \emptyset$, but $\mathcal{S}_n(\tau) = 0$ has no positive roots in α_τ, E^* is asymptotically stable for all $\tau \in [0, \tau_{\min})$.*

(ii) *If $\alpha_\tau \neq \emptyset$ and $\mathcal{S}_n(\tau) = 0$ has positive roots $\tau_c \in \alpha_\tau$ such that,* $\text{sign}(\Re'(\lambda(\tau))|_{\tau=\tau_c}) > 0$ *for some $n \in \mathbb{N}$, then E^* is asymptotically stable for all $\tau \in [0, \tau_{c\,\min}) \cup (\tau_{c\,\max}, \tau_{\min})$ and unstable for $\tau \in (\tau_{c\,\min}, \tau_{c\,\max})$, where $\tau_{c\,\min}$ and $\tau_{c\,\max}$ are the Hopf bifurcation values.*

6. Direction of Hopf Bifurcation

Normalizing the delay τ by the time scaling $t \to \frac{t}{\tau}$, and $u = u - u^*$, $v = v - v^*$; (1) is written as a FDE in $C := C([-1, 0], \mathbb{R}^2)$ as (see [Yafia *et al.*, 2015])

$$\dot{X}(t) = l(\tau) X_t + f(\tau, X_t), \tag{18}$$

where $X_t(\theta) = X(t + \theta)$, $\forall\, \theta \in [-1, 0]$ and $l(\tau) : C \to \mathbb{R}^2$, $f : C \times \mathbb{R}^+ \to \mathbb{R}^2$ are given by

$$l(\tau)\varphi = \tau \begin{pmatrix} -\dfrac{r}{k} u^*(\tau)\varphi_1(0) - \left(\dfrac{r}{k} + \beta\right) u^*(\tau)\varphi_2(0) \\ \left(-\dfrac{s}{k} v^*(\tau)\varphi_1(0) + \left(s\left(1 - \dfrac{N^*(\tau)}{k}\right) - \dfrac{s}{k} v^*(\tau) - a\right)\varphi_2(0)\right. \\ + \beta e^{-d\tau} v^*(\tau)\varphi_1(-1) + \beta e^{-d\tau} u^*(\tau)\varphi_2(-1) \end{pmatrix} \tag{19}$$

$$= \tau \begin{pmatrix} A_{11}(\tau)\varphi_1(0) + A_{12}(\tau)\varphi_2(0) \\ A_{21}(\tau)\varphi_1(0) + A_{22}(\tau)\varphi_2(0) \end{pmatrix} + \tau \begin{pmatrix} 0 \\ B_{21}(\tau)\varphi_1(-1) + B_{22}(\tau)\varphi_2(-1) \end{pmatrix}, \tag{20}$$

where

$$A_{11} = -\frac{r}{k} u^*(\tau), \quad A_{12} = -\frac{r}{k} u^*(\tau) - \beta u^*(\tau), \quad A_{21} = -\frac{s}{k} v^*(\tau), \quad A_{22} = -\frac{s}{k} v^*(\tau) - \beta e^{-d\tau} u^*(\tau),$$

$$B_{21}(\tau) = \beta e^{-d\tau} v^*(\tau), \quad B_{22}(\tau) = \beta e^{-d\tau} u^*(\tau)$$

and

$$f(\tau, \varphi) = \tau \begin{pmatrix} \left(-\beta + \dfrac{r}{k}\right)\varphi_1^2(0) + \dfrac{r}{k}\varphi_1(0)\varphi_2(0) \\ \beta e^{-d\tau}\varphi_1(-1)\varphi_2(-1) - \dfrac{s}{k}\varphi_1(0)\varphi_2(0) - \dfrac{s}{k}\varphi_2^2(0) \end{pmatrix}, \tag{21}$$

where $\varphi = (\varphi_1, \varphi_2) \in C$ and $E^*(\tau) = (u^*(\tau), v^*(\tau)) = (\frac{R_1}{R(\tau)}, \frac{R_2(\tau)}{R(\tau)})$ and $R_1 = \beta k(a - s) + ar - sd$, $R(\tau) = \beta(e^{-d\tau}(r + \beta k) - s)$, $R_2(\tau) = \beta k e^{-d\tau}(r - d) - ar + sd$.

Consider (18) in the phase space C, let $\Lambda = \{-i\omega_+, i\omega_+\}$.

Introducing the new parameter $\alpha = \tau - \tau_c$, (18) is rewritten as

$$\frac{dz}{dt}(t) = L(\alpha) z_t + F(z_t, \alpha), \tag{22}$$

where $L(\alpha) = l(\alpha + \tau_c)$ and $F(\varphi, \alpha) = f(\varphi, \tau_c + \alpha)$.

By using the Taylor expansion of $u^*(\alpha+\tau_c)$ and $v^*(\alpha+\tau_c)$, we have

$$u^*(\alpha+\tau_c) = \alpha_0 + \alpha_1\alpha + \frac{\alpha_2}{2}\alpha^2 + O(\alpha^3), \quad v^*(\alpha+\tau_c) = \beta_0 + \beta_1\alpha + \frac{\beta_2}{2}\alpha^2 + O(\alpha^3),$$

where

$$\alpha_0 = \frac{R_1}{R(\tau_c)}, \quad \alpha_1 = R_1\frac{\beta d(r+\beta k)e^{-d\tau_c}}{R^2(\tau_c)}, \quad \alpha_2 = R_1\frac{2(\beta d(r+\beta k)e^{-d\tau_c})^2 - R(\tau_c)\beta d^2(r+\beta k)e^{-d\tau_c}}{2R^3(\tau_c)},$$

$$\beta_0 = \frac{R_2(\tau_c)}{R(\tau_c)}, \quad \beta_1 = \frac{R_2(\tau_c)}{R(\tau_c)}\left(-\frac{d\beta k e^{-d\tau_c}(r-d)}{R_2(\tau_c)} - \frac{\beta d(r+\beta k)e^{-d\tau_c}}{R(\tau_c)}\right),$$

$$\beta_2 = \frac{R_2(\tau_c)}{R(\tau_c)}\left[\left(\frac{d^2\beta k e^{-d\tau_c(r-d)}}{2R_2(\tau_c)} - \frac{d^2\beta(r+\beta k)e^{-d\tau_c}}{2R(\tau_c)}\right)\right.$$
$$\left. - \frac{\beta d(r+\beta k)e^{-d\tau_c}}{R(\tau_c)}\left(-\frac{d\beta k e^{-d\tau_c}(r-d)}{R_2(\tau_c)} - \frac{\beta d(r+\beta k)e^{-d\tau_c}}{R(\tau_c)}\right)\right].$$

Then we have:

$$L(\alpha) = L_0 + \alpha L_1 + \alpha^2 L_2 + O(\alpha^3)$$

where

$$L_0\varphi = L(0)\varphi = l(\tau_c)\varphi = A_0\varphi(0) + B_0\varphi(-1),$$
$$L_1\varphi = (A_0 + \tau_c A_1)\varphi(0) + (B_0 + \tau_c B_1)\varphi(-1),$$
$$L_2\varphi = (A_1 + \tau_c A_2)\varphi(0) + (B_1 + \tau_c B_2)\varphi(-1),$$

where

$$A_0 = \tau_c\begin{pmatrix} -\frac{r}{k}\alpha_0 & -\left(\frac{r}{k}+\beta\right)\alpha_0 \\ -\frac{s}{k}\beta_0 & -\frac{s}{k}\beta_0 - \beta e^{-d\tau_c}\end{pmatrix}, \quad A_i = \begin{pmatrix} -\frac{r}{k}\alpha_i & -\left(\frac{r}{k}+\beta\right)\alpha_i \\ -\frac{s}{k}\beta_i & -\frac{s}{k}\beta_i - \beta e^{-d\tau_c}\end{pmatrix}; \quad i = 1, 2,$$

$$B_0 = \tau_c\beta e^{-d\tau_c}\begin{pmatrix} 0 & 0 \\ \beta_0 & \alpha_0\end{pmatrix}, \quad B_1 = \beta e^{-d\tau_c}\begin{pmatrix} 0 & 0 \\ \beta_0 + \tau_c(\beta_1 - d\beta_0) & \alpha_0 + \tau_c(\alpha_1 - d\alpha_0)\end{pmatrix},$$

$$B_2 = \beta e^{-d\tau_c}\begin{pmatrix} 0 & 0 \\ \beta_1 - d\beta_0 + \tau_c\left(\beta_2 - d\beta_1 + \frac{d^2}{2}\beta_0\right) & \alpha_1 - d\alpha_0 + \tau_c\left(\alpha_2 - d\alpha_1 + \frac{d^2}{2}\alpha_0\right)\end{pmatrix}$$

and

$$F(\varphi,\alpha) = \tau_c\begin{pmatrix} \left(-\beta + \frac{r}{k}\right)\varphi_1^2(0) + \frac{r}{k}\varphi_1(0)\varphi_2(0) \\ \beta e^{-d\tau_c}\varphi_1(-1)\varphi_2(-1) - \frac{s}{k}\varphi_1(0)\varphi_2(0) - \frac{s}{k}\varphi_2^2(0)\end{pmatrix}$$

$$+\begin{pmatrix} \left(-\beta+\frac{r}{k}\right)\varphi_1^2(0)+\frac{r}{k}\varphi_1(0)\varphi_2(0) \\ \beta e^{-d\tau_c}\varphi_1(-1)\varphi_2(-1)-\frac{s}{k}\varphi_1(0)\varphi_2(0)-\frac{s}{k}\varphi_2^2(0)-\tau_c d\beta e^{-d\tau_c}\varphi_1(-1)\varphi_2(-1)\end{pmatrix}\alpha$$

$$+\begin{pmatrix} 0 \\ -d\beta e^{-d\tau_c}\varphi_1(-1)\varphi_2(-1)+\tau_c\frac{d^2}{2}\beta e^{-d\tau_c}\varphi_1(-1)\varphi_2(-1)\end{pmatrix}\alpha^2+\text{h.o.t}$$

$$=\tau_c\begin{pmatrix} \zeta_1\varphi_1^2(0)+\zeta_2\varphi_1(0)\varphi_2(0) \\ \delta_1\varphi_1(-1)\varphi_2(-1)+\delta_2\varphi_1(0)\varphi_2(0)+\delta_2\varphi_2^2(0)\end{pmatrix}$$

$$+\begin{pmatrix} \zeta_1\varphi_1^2(0)+\zeta_2\varphi_1(0)\varphi_2(0) \\ \delta_1\varphi_1(-1)\varphi_2(-1)+\delta_2\varphi_1(0)\varphi_2(0)+\delta_2\varphi_2^2(0)+\delta_3\varphi_1(-1)\varphi_2(-1)\end{pmatrix}\alpha$$

$$+\begin{pmatrix} 0 \\ \delta_4\varphi_1(-1)\varphi_2(-1)+\delta_5\varphi_1(-1)\varphi_2(-1)\end{pmatrix}\alpha^2+\text{h.o.t}$$

$$=F_2(\varphi,\alpha)+F_3(\varphi,\alpha)+\text{h.o.t},$$

where $\gamma_1=-\beta+\frac{r}{k}$, $\gamma_2=\frac{r}{k}$, $\delta_1=\beta e^{-d\tau_c}$, $\delta_2=-\frac{s}{k}$, $\delta_3=-\tau_c d\beta e^{-d\tau_c}$, $\delta_4=-d\beta e^{-d\tau_c}$, $\delta_5=\tau_c\beta\frac{d^2}{2}e^{-d\tau_c}$, and $F_i(\varphi,\alpha)$ is a homogenuous polynomial of degree i in (φ,α).

Using the formal adjoint theory for FDEs in [Hale & Lunel, 1993], we decompose C by Λ as $C=P\oplus Q$, where P is the center space for

$$\frac{dz}{dt}(t)=L_0z_t.$$

By Riesz representation theorem, there exist a $n\times n$ matrix function η on $[-1,0]$ of bounded variation such that

$$L_0\phi=\int_{-1}^0 d\eta(\theta)\phi(\theta),$$

where

$$\eta(\theta)=\begin{cases}-\tau_cA-\tau_cB, & \theta=-1,\\ -\tau_cA, & -1<\theta<0,\\ 0, & \theta=0.\end{cases}$$

Considering complex coordinates, $P=\text{span}\{\phi_1,\phi_2\}$, with $\phi_1(\theta)=e^{i\omega_+\theta}v$, $\phi_2(\theta)=\overline{\phi_1(\theta)}$, $-1\le\theta\le 0$, where the bar means complex conjugation, and v is a vector in $\mathbb{C}^2$ that satisfies

$$L_0(\phi_1)=i\omega_+v, \tag{23}$$

then we have

$$v=(v_1,v_2)=\left(1,\frac{i\omega_+-\tau_cA_{11}}{\tau_cA_{12}}\right).$$

For $\Phi=[\phi_1,\phi_2]$, note that $\dot{\Phi}=B\Phi$, where B is the 2×2 diagonal matrix

$$B=\begin{pmatrix} i\omega_+ & 0\\ 0 & -i\omega_+\end{pmatrix}.$$

Choose a basis Ψ for the adjoint space P^*, such that $(\Psi,\Phi)=(\psi_i,\phi_j)_{i,j=1}^2$, where $(\cdot,\cdot)$ is the bilinear form on $C^*\times C$ associated with the adjoint equation. Thus, $\Psi(s)=\text{col}(\psi_1(s),\psi_2(s))=\text{col}(u^Te^{-i\omega_+s},\overline{u}^Te^{i\omega_+s})$, $s\in[0,1]$, for $u\in\mathbb{C}^2$ such that

$$(\psi_1,\phi_1)=1,\quad (\psi_1,\phi_2)=0, \tag{24}$$

where, $(\cdot,\cdot)$ is the duality pairing between ψ and ϕ defined by

$$(\psi,\phi)=\psi(0)\phi(0)-\int_{-1}^0\int_0^\theta\psi(\xi-\theta)d[\eta(\theta)]\phi(\xi)d\xi.$$

A further computation leads to

$$u=(u_1,u_2)=u_1(1,H),$$

where

$$H=\frac{1-\tau_c(A_{11}+A_{12}\overline{v_2})}{-\overline{v_2}+\tau_cA_{22}\overline{v_2}+\tau_c\frac{\sin(w_+)}{w_+}(B_{21}+B_{22}\overline{v_2})}$$

and

$$\frac{1}{u_1} = 1 + Hv_2 - \tau_c(A_{11} + A_{12}v_2) - \tau_c H A_{22} v_2 - \tau_c H e^{-iw_+}(B_{21} + B_{22}v_2).$$

We take the enlarged phase space

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

we can see that the projection of C upon P, associated with the decomposition $C = P \oplus Q$, is now replaced by $\pi : BC \to P$, which leads to the decomposition

$$BC = P \oplus \operatorname{Ker}\pi.$$

Using the decomposition

$$z_t = \Phi X(t) + Y_t,$$

where $X(t) \in \mathbb{C}^2$, $Y_t \in Q^1$, we decompose (22) as

$$\begin{cases} \dfrac{dX}{dt} = BX + \Psi(0)F(\Phi X + Y, \alpha), \\ \dfrac{dY}{dt} = A_{Q^1}Y + (I-\pi)X_0 F(\Phi X + Y, \alpha) \end{cases} \tag{25}$$

and

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

Throughout this section we refer to [Faria & Magalhaes, 1995] for results and explanations of several notations involved. We write the Taylor formulas

$$\Psi(0)F(\Phi X + Y, \alpha) = \frac{1}{2}f_2^1(X,Y,\alpha) + \frac{1}{3!}f_3^1(X,Y,\alpha) + \text{h.o.t.},$$

$$(I-\pi)X_0F(\Phi X + Y, \alpha) = \frac{1}{2}f_2^2(X,Y,\alpha) + \frac{1}{3!}f_3^2(X,Y,\alpha) + \text{h.o.t.},$$

where $f_j^1(X,Y,\alpha)$, $f_j^1(X,Y,\alpha)$ are homogeneous polynomials in (X,Y,α) of degree j, $j = 1,3$, with coefficients in $\mathbb{C}^2$, $\operatorname{Ker}\pi$, respectively.

The normal form method gives for (22) a normal form on the center manifold of the origin at $\alpha = 0$, written as

$$\frac{dX}{dt} = BX + \frac{1}{2}g_2^1(X,0,\alpha) + \frac{1}{3!}g_3^1(X,0,\alpha) + \text{h.o.t.}, \tag{26}$$

where g_2^1, g_3^1 are the second and third order terms in (X,α), respectively, and h.o.t. stands for higher order terms.

The normal form procedure will show that these terms have the form

$$\frac{1}{2}g_2^1(X,0,\alpha) = \begin{pmatrix} A_1X_1\alpha \\ B_1X_2\alpha \end{pmatrix}$$

and

$$\frac{1}{3!}g_3^1(X,0,\alpha) \begin{pmatrix} A_2X_1^2X_2 \\ B_2X_1X_2^2 \end{pmatrix} + O(|X|\alpha^2).$$

Moreover, it will turn out that $B_1 = \overline{A_1}$, $B_2 = \overline{A_2}$, because the coefficients in (22) are real.

We continue this section with the computation of g_2^1, g_3^1, omitting some details.

Always following [Faria & Magalhaes, 1995], we first recall the operators, M_j^1,

$$M_j^1(p)(X,\alpha) = D_Xp(X,\alpha)BX - Bp(X,\alpha), \quad j \ge 2.$$

In particular,

$$M_j^1(\alpha^l X^q e_k) = i\omega_+(q_1 - q_2 + (-1)^k)\alpha^l X^q e_k, \quad l + q_1 + q_2 = j, \; k = 1,2,$$

for $j = 1,2$, $q = (q_1,q_2) \in \mathbb{N}_0^2$, $l \in \mathbb{N}_0$, and e_1, e_2 the canonical basis for $\mathbb{C}^2$.

Hence,

$$\operatorname{Ker}(M_2^1) = \operatorname{span}\left\{\begin{pmatrix} X_1\alpha \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ X_2\alpha \end{pmatrix}\right\},$$

$$\operatorname{Ker}(M_3^1) = \operatorname{span}\left\{\begin{pmatrix} X_1^2X_2 \\ 0 \end{pmatrix}, \begin{pmatrix} X_1\alpha^2 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ X_1X_2^2 \end{pmatrix} \begin{pmatrix} 0 \\ X_2\alpha^2 \end{pmatrix}\right\}. \tag{27}$$

From Eq. (22), we get

$$f_2^1(X,Y,\alpha) = 2\Psi(0)[L(\alpha)(\Phi X + Y) + f(\Phi X + y, \alpha)] \tag{28}$$

and we have

$$f_2^1(X,0,\alpha) = 2\tau_c \begin{pmatrix} D_1\alpha X_1 + \overline{E_1}\alpha X_2 + u_1(M_1+HN_1)X_1^2 + u_1(M_2+HN_2)X_1X_2 \\ \quad + u_1(M_3+HN_3)X_2 \\ \overline{D_1}\alpha X_2 + E_1\alpha X_1 + \overline{u_1}(M_1+\overline{H}N_1)X_1^2 + \overline{u_1}(M_2+\overline{H}N_2)X_1X_2 \\ \quad + \overline{u_1}(M_3+\overline{H}N_3)X_2 \end{pmatrix},$$

where

$$\begin{aligned}
&D_1 = u_1\Lambda_1 + u_2\Lambda_2, \quad E_1 = \overline{u_1}\Lambda_1 + \overline{u_2}\Lambda_2,\\
&\Lambda_1 = -\gamma_2\alpha_4 + \delta_1\alpha_4 v_2,\\
&\Lambda_2 = \beta_4 v_2 + \beta_5 e^{-iw_+} + \alpha_5 v_2 e^{-iw_+},\\
&M_1 = \gamma_1 + \gamma_2 v_2, \quad M_2 = 2\gamma_1 + \gamma_2\overline{v_2} + \gamma_2 v_2,\\
&M_3 = \gamma_1 + \gamma_2\overline{v_2},\\
&N_1 = \delta_1 v_2 e^{-2iw_+} + \delta_2 + \delta_2 v_2^2,\\
&N_2 = \delta_1\overline{v_2} + \delta_1 v_2 + 2\delta_2 + 2\delta_2|v_2|^2,\\
&N_3 = \delta_1\overline{v_1}e^{2iw_+} + \delta_2 + \delta_2\overline{v_2}^2,\\
&\alpha_4 = \alpha_0 + \tau_c\alpha_1, \quad \alpha_5 = 2\alpha_0 + \tau_c(\alpha_1 - d\alpha_0),\\
&\beta_4 = \beta_0 + \tau_c\beta_1, \quad \beta_5 = 2\beta_0 + \tau_c(\beta_1 - d\beta_0).
\end{aligned}$$

Therefore, the second order terms in (X,α) of the normal form on the center manifold are given by

$$\begin{aligned}
g_2^1(X,0,\alpha) &= \mathrm{Proj}_{\mathrm{Ker}(M_2^1)} f_2^1(X,0,\alpha)\\
&= 2\tau_c \begin{pmatrix} D_1X_1\alpha \\ \overline{D_1}X_2\alpha \end{pmatrix}.
\end{aligned}$$

Since the terms $O(|X|\alpha^2)$ are irrelevant to determine the generic Hopf bifurcation, we assume

$$L = \mathrm{span}\left\{\begin{pmatrix} X_1^2X_2 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ X_1X_2^2 \end{pmatrix}\right\}.$$

Then

$$g_3^1(x,0,\alpha) = \mathrm{Proj}_L\, \overline{f}_3^1(X,0,0) + o(|X|\alpha^2),$$

where

$$\begin{aligned}
\overline{f}_3^1(x,0,0) &= \frac{3}{2}[(D_X f_2^1)u_2^1 - (D_X u_2^1)g_2^1]_{(X,0,0)}\\
&\quad + \frac{3}{2}[(D_Y f_2^1)u_2^2]_{(X,0,0)}.
\end{aligned}$$

Hence we will compute $g_3^1(X0,\alpha)$ as follows. Firstly, noting

$$f_2^1(X,0,0) = 2\begin{pmatrix} b_{20}X_1^2 + b_{11}X_1X_2 + b_{02}X_2^2 \\ \bar{b}_{02}X_1^2 + \bar{b}_{11}X_1X_2 + \bar{b}_{20}X_2^2 \end{pmatrix},$$

$$u_2^1(X,0) = \frac{2}{i\omega_+}\begin{pmatrix} b_{20}X_1^2 - b_{11}X_1X_2 - \dfrac{1}{3}b_{02}X_2^2 \\ \dfrac{1}{3}\bar{b}_{02}X_1^2 + \bar{b}_{11}X_1X_2 - \bar{b}_{20}X_2^2 \end{pmatrix}$$

one has

$$\begin{aligned}
&\mathrm{Proj}_L[(D_X f_2^1)u_2^1]_{(X,0,0)}\\
&\quad = \frac{4}{i\omega_+}\begin{pmatrix} \left(-b_{20}b_{11} + \dfrac{2}{3}|b_{02}|^2 + |b_{11}|^2\right) b_1^2 X_2 \\ \left(-\dfrac{2}{3}|b_{02}|^2 - |b_{11}|^2 + \overline{b_{20}b_{11}}\right) X_1X_2^2 \end{pmatrix}\\
&\quad = 4\begin{pmatrix} D_3X_1^2X_2 \\ \overline{D}_3X_1X_2^2 \end{pmatrix}.
\end{aligned}$$

Secondly, from (2.15) we know $g_2^1(X,0,0) = 0$, then $\mathrm{Proj}_L[(D_X u_2^1)g_2^1]_{(X,0,0)} = 0$.

Lastly, we will compute $\mathrm{Proj}_L[(D_Y f_2^1)u_2^2]_{(X,0,0)}$ as follows. Let

$$\begin{aligned}
h = u_2^2 &= h_{200}X_1^2 + h_{020}X_2^2 + h_{002}\alpha^2\\
&\quad + h_{110}X_1X_2 + h_{101}x_1\alpha + h_{011}X_2\alpha.
\end{aligned}$$

Noting that $g_2^2 = 0$, one has

$$\begin{aligned}
M_2^2 h(X,\alpha) &= f_2^2 = 2(I-\pi)X_0F(\Phi X,\alpha)\\
&= 2(I-\pi)X_0[L(\alpha)(\Phi X) + F(\Phi X,\tau_c)].
\end{aligned}$$

On the other hand, we know

$$\begin{aligned}
M_2^2 h(X,\alpha) &= D_X h(X,\alpha)BX - A_{Q^1}h(X,\alpha)\\
&= D_X h(X,\alpha)BX - [h(X,\alpha)\\
&\quad + X_0(L(\tau_c)(h(X,\alpha)) - \dot{h}(X,\alpha)(0))].
\end{aligned}$$

If $\alpha = 0$, then

$$\dot{h}(X) - D_X h(X)Bx = 2\Phi\Psi(0)F(\Phi X, \tau_c), \quad \dot{h}(X)(0) - L(\tau_c)(h(X)) = 2F(\Phi X, \tau_c).$$

Let

$$\begin{aligned}\Gamma(\theta) &= \Phi X + Y = \Phi_1 X_1 + \Phi_2 X_2 + Y(\theta) = e^{i\omega_+\theta} v X_1 + e^{-i\omega_+\theta}\overline{v} X_2 + Y(\theta),\\ \Upsilon(\theta) &= \Phi X = \Phi_1 X_1 + \Phi_2 X_2 = e^{i\omega_+\theta} v X_1 + e^{-i\omega_+\theta}\overline{v} X_2.\end{aligned}$$

From

$$f_2^1(X, Y, 0) = 2\tau_c \begin{pmatrix} u^T \begin{pmatrix} \gamma_1\Gamma_1^2(0) + \gamma_2\Gamma_1(0)\Gamma_2(0) \\ \delta_1\Gamma_1(-1)\Gamma_2(-1) + \delta_2\Gamma_1(0)\Gamma_2(0) + \delta_2\Gamma_2^2(0 \end{pmatrix} \\ \overline{u}^T \begin{pmatrix} \gamma_1\Gamma_1^2(0) + \gamma_2\Gamma_1(0)\Gamma_2(0) \\ \delta_1\Gamma_1(-1)\Gamma_2(-1) + \delta_2\Gamma_1(0)\Gamma_2(0) + \delta_2\Gamma_2^2(0 \end{pmatrix} \end{pmatrix}$$

we obtain

$$[(D_y f_2^1)h]_{(x,0,0)} = 2 \begin{pmatrix} \tau_c u^T \begin{pmatrix} 2\gamma_1\Upsilon_1(0)h^1(0) + \gamma_2\Upsilon_1(0)h^2(0) + \gamma_2\Upsilon_2(0)h^1(0) \\ \delta_1\Upsilon_1(-1)h^2(-1) + \delta_1\Upsilon_2(-1)h^1(-1) \\ + \delta_2\Upsilon_1(0)h^2(0) + \delta_2\Upsilon_2(0)h^1(0) + 2\delta_2\Upsilon_2(0)h^2(0) \end{pmatrix} \\ \tau_c \overline{u}^T \begin{pmatrix} 2\gamma_1\Upsilon_1(0)h^1(0) + \gamma_2\Upsilon_1(0)h^2(0) + \gamma_2\Upsilon_2(0)h^1(0) \\ \delta_1\Upsilon_1(-1)h^2(-1) + \delta_1\Upsilon_2(-1)h^1(-1) \\ + \delta_2\Upsilon_1(0)h^2(0) + \delta_2\Upsilon_2(0)h^1(0) + 2\delta_2\Upsilon_2(0)h^2(0) \end{pmatrix} \end{pmatrix}.$$

By a direct computation, we have

$$\begin{aligned}\Upsilon_1(0)h^1(0) &= (h_{020}^1(0) + h_{110}^1(0))X_1X_2^2 + (h_{110}^1(0) + h_{200}^1(0))X_1^2X_2 + R,\\ \Upsilon_1(0)h^2(0)) &= (h_{020}^2(0) + h_{110}^2(0))X_1X_2^2 + (h_{110}^2(0) + h_{200}^2(0))X_1^2X_2 + R,\\ \Upsilon_2(0)h^1(0) &= (v_1h_{020}^1(0) + \overline{v_1}h_{110}^1(0))X_1X_2^2 + (v_1h_{110}^1(0) + \overline{v_1}h_{200}^1(0))X_1^2X_2 + R,\\ \Upsilon_1(-1)h^2(-1)) &= (e^{-iw_+}h_{020}^2(-1) + e^{iw_+}h_{110}^2(-1))X_1X_2^2 + (e^{-iw_+}h_{110}^2(-1) + e^{iw_+}h_{110}^2(-1))X_1^2X_2 + R,\\ \Upsilon_2(-1)h^1(-1) &= (e^{-iw_+}v_1h_{020}^2(-1) + e^{iw_+}\overline{v_1}h_{110}^2(-1))X_1X_2^2 + (e^{-iw_+}v_1h_{110}^2(-1)\\ &\quad + e^{iw_+}\overline{v_1}h_{110}^2(-1))X_1^2X_2 + R,\\ \Upsilon_2(0)h^2(0) &= (v_1h_{020}^2(0) + \overline{v_1}h_{110}^2(0))X_1X_2^2 + (v_1h_{110}^2(0) + \overline{v_1}h_{200}^2(0))X_1^2X_2 + R,\end{aligned}$$

where R is a polynomial in X_1^3 and X_2^3, and

$$\mathrm{Proj}_L[(D_y f_2^1)u_2^2]_{(x,0,0)} = 2\begin{pmatrix} D_2X_1^2X_2 \\ \overline{D}_2X_1X_2^2 \end{pmatrix},$$

where

$$\begin{aligned}D_2 = \tau_c[&u_1(2\gamma_1(h_{110}^1(0) + h_{200}^1(0) + \gamma_2(h_{110}^2(0) + h_{200}^2(0)) + \gamma_2(v_1h_{110}^2(0) + \overline{v_1}h_{200}^2(0)))\\ &+ u_1H(\delta_1(e^{i\omega_+}h_{200}^2(-1) + e^{-i\omega_+}h_{110}^2(-1)) + \delta_1(e^{i\omega_+}\overline{v_1}h_{200}^2(-1) + e^{-i\omega_+}v_1h_{110}^2(-1))\\ &+ \delta_2(h_{200}^1(0) + h_{110}^1(0)) + \delta_2(\overline{v_1}h_{200}^1(0) + v_1h_{110}^1(0)) + 2\delta_2(\overline{v_1}h_{200}^2(0) + v_1h_{110}^2(0)))].\end{aligned}$$

To compute A_4, we should get $h_{110}(\theta), h_{200}(\theta)$ firstly. From (2.18), it follows

$$\dot{h}_{110} = 2(\Phi_1, \Phi_2)\begin{pmatrix} b_{11} \\ \bar{b}_{11} \end{pmatrix}$$

$$\dot{h}_{110}(0) - L(\tau_c)(h_{110}) = \tau_c \begin{pmatrix} a_1 \\ b_1 \end{pmatrix}$$

and

$$\dot{h}_{200} - 2i\omega h_{200} = 2(\Phi_1, \Phi_2)\begin{pmatrix} b_{20} \\ \bar{b}_{02} \end{pmatrix},$$

$$\dot{h}_{200}(0) - L(\tau_c)(h_{200}) = \tau_c \begin{pmatrix} a_2 \\ b_2 \end{pmatrix},$$

where

$$a_1 = 2[2\gamma_1 + \gamma_2\overline{v_1} + \gamma_2 v_1],$$

$$b_1 = 2[\delta_1\overline{v_1} + \delta_1 v_1 + \gamma_2 v_1 + \gamma_2\overline{v_1} + 2\delta_2 v_1\overline{v_1}],$$

$$a_2 = 2[\gamma_1 + \gamma_2 v_1],$$

$$b_2 = 2[\delta_1 v_1 e^{-2i\omega_+} + \gamma_2 v_1 + \delta_2 v_1^2 e^{2i\omega_+}].$$

Solving the above equations (2.20) and (2.21), we obtain

$$h_{110} = 2\left[\frac{a_{11}}{i\omega_+}\Phi_1 - \frac{\bar{a}_{11}}{i\omega_+}\Phi_2\right] + C_1,$$

$$h_{200} = 2\left[\frac{a_{20}}{-i\omega_+}\Phi_1 + \frac{\bar{a}_{02}}{-3i\omega_+}\Phi_2\right] + C_2 e^{2i\omega_+\theta},$$

where

$$C_1 = \begin{pmatrix} C_1^1 \\ C_1^2 \end{pmatrix}, \quad C_1^1 = \frac{\begin{vmatrix} a_1 & \left(\frac{r}{k} + \beta\right)\alpha_0 \\ b_1 & \frac{s}{k}\beta_0 - \tau_c\beta e^{-d\tau_c}\alpha_0 \end{vmatrix}}{\begin{vmatrix} \frac{r}{k}\alpha_0 & \left(\frac{r}{k} + \beta\right)\alpha_0 \\ -\beta_0\tau_c e^{-d\tau_c} & \frac{s}{k}\beta_0 - \tau_c\beta e^{-d\tau_c}\alpha_0 \end{vmatrix}}, \quad C_1^2 = \frac{\begin{vmatrix} \frac{r}{k}\alpha_0 & a_1 \\ -\beta_0\tau_c e^{-d\tau_c} & b_1 \end{vmatrix}}{\begin{vmatrix} \frac{r}{k}\alpha_0 & \left(\frac{r}{k} + \beta\right)\alpha_0 \\ -\beta_0\tau_c e^{-d\tau_c} & \frac{s}{k}\beta_0 - \tau_c\beta e^{-d\tau_c}\alpha_0 \end{vmatrix}},$$

$$C_2 = \begin{pmatrix} C_2^1 \\ C_2^2 \end{pmatrix}, \quad C_2^1 = \frac{\begin{vmatrix} a_2 & \left(\frac{r}{k} + \beta\right)\alpha_0 \\ b_2 & 2iw_+ + \frac{s}{k}\beta_0 - \tau_c\beta e^{-d\tau_c}\alpha_0 e^{-2iw_+} \end{vmatrix}}{\begin{vmatrix} 2iw_+ + \frac{r}{k}\alpha_0 & \left(\frac{r}{k} + \beta\right)\alpha_0 \\ -\beta_0\tau_c e^{-d\tau_c}e^{-2iw_+} & 2iw_+ + \frac{s}{k}\beta_0 - \tau_c\beta e^{-d\tau_c}\alpha_0 e^{-2iw_+} \end{vmatrix}},$$

$$C_2^2 = \frac{\begin{vmatrix} 2iw_+ + \frac{r}{k}\alpha_0 & a_2 \\ -\beta_0\tau_c e^{-d\tau_c}e^{-2iw_+} & b_2 \end{vmatrix}}{\begin{vmatrix} 2iw_+ + \frac{r}{k}\alpha_0 & \left(\frac{r}{k} + \beta\right)\alpha_0 \\ -\beta_0\tau_c e^{-d\tau_c}e^{-2iw_+} & 2iw_+ + \frac{s}{k}\beta_0 - \tau_c\beta e^{-d\tau_c}\alpha_0 e^{-2iw_+} \end{vmatrix}}.$$

Hence

$$g_3^1(x, 0, 0) = \begin{pmatrix} (6D_3 + 3D_4)X_1^2 X_2 \\ (6\overline{D}_3 + 3\overline{D}_4)X_1 X_2^2 \end{pmatrix}.$$

Thus, the normal form of the system (2.12) has the form

$$\dot{x} = Bx + \begin{pmatrix} D_1 X_1 \alpha \\ \overline{D}_1 X_2 \alpha \end{pmatrix} + \frac{1}{3!}\begin{pmatrix} (6D_3 + 3D_4)X_1^2 X_2 \\ (6\overline{D}_3 + 3\overline{D}_4)X_1 X_2^2 \end{pmatrix} + o(|X|^4 + |X|\alpha^2).$$

Let $x_1 = \xi_1 - i\xi_2$, $x_2 = \xi_1 + i\xi_2$, $\xi_1 = \rho\cos\omega$, $\xi_2 = \rho\sin\omega$. Then system (2.22) can be written as

$$\dot{\rho} = r_1\alpha\rho + r_2\rho^3 + O(\alpha^2\rho + |(\rho,\alpha)|^4),$$

$$\dot{\omega} = -\omega_+ - \mathrm{Im}(D_1)\alpha - \mathrm{Im}\left(D_3 + \frac{1}{2}D_4\right)\rho^2 + o(|(\rho^2,\alpha)|),$$

where $r_1 = \mathrm{Re}\,D_1$, $r_2 = \mathrm{Re}(D_3 + \frac{1}{2}D_4)$. Summarizing, we have the following theorem.

Theorem 5. *The flow on the center manifold of the equilibrium $E^*(\tau)$ at $\alpha = 0$ is given by (26). And also we can draw the following conclusion.*

(1) *The Hopf bifurcation is supercritical if $r_1 r_2 < 0$, and subcritical if $r_1 r_2 > 0$.*

(2) *The nontrivial periodic solution is stable if $r_2 < 0$, and unstable if $r_2 > 0$.*

(3) *The period of the nontrivial solution is*

$$T(\alpha) = \frac{2\pi}{\omega_+}\left(1 - \frac{\mathrm{Im}(D_1)\alpha - \dfrac{r_1\alpha}{r_2}\mathrm{Im}\left(D_3 + \dfrac{1}{2}D_4\right)}{\omega_+}\right) + O(\alpha^3)$$

with $T(0) = 2\pi/\omega_+$.

7. Numerical Simulations

By Matlab software, we plot curves illustrating the stability of the steady states E_2 and E^* and by applying the Mikhailov criterion, we show the stability of the two equilibrium points. To plot the corresponding Mikhailov hodograph, we give the following result.

Lemma 4 (Mikhailov Criterion). *Assume that W has no pair imaginary roots. Then the steady state of the system with the characteristic equation is locally stable if and only if*

$$[\arg(W(iw))]_{w=0}^{w=+\infty} = n\frac{\pi}{2}.$$

The calculation of total change of argument of the complex function $W(iw)$ when w increases from 0 to $+\infty$ gives the stability of the corresponding steady state. In delay differential equations, the characteristic equation is written as

$$W(\lambda) = P(\lambda) + \sum_{i=0}^{k} a_i\lambda^i e^{\lambda\tau_i},$$

where P is a polynomial function with $\deg(P) = n > k$. Then, the condition which ensures the local stability of the corresponding steady state is given as follows:

$$[\arg(W(iw))]_{w=0}^{w=+\infty} = n\frac{\pi}{2}.$$

From Eqs. (4), we can write

$$\sin(\Delta(i\zeta,\tau_0)) = \frac{\mathrm{Im}(\Delta(i\zeta,\tau_0))}{\sqrt{\mathrm{Re}(\Delta(i\zeta,\tau_0))^2 + \mathrm{Im}(\Delta(i\zeta,\tau_0))^2}} \xrightarrow[\zeta\to+\infty]{} 0,$$

$$\cos(\Delta(i\zeta,\tau_0)) = \frac{\mathrm{Re}(\Delta(i\zeta,\tau_0))}{\sqrt{\mathrm{Re}\Delta(i\zeta,\tau_0))^2 + \mathrm{Im}(\Delta(i\zeta,\tau_0))^2}} \xrightarrow[\zeta\to+\infty]{} 1$$

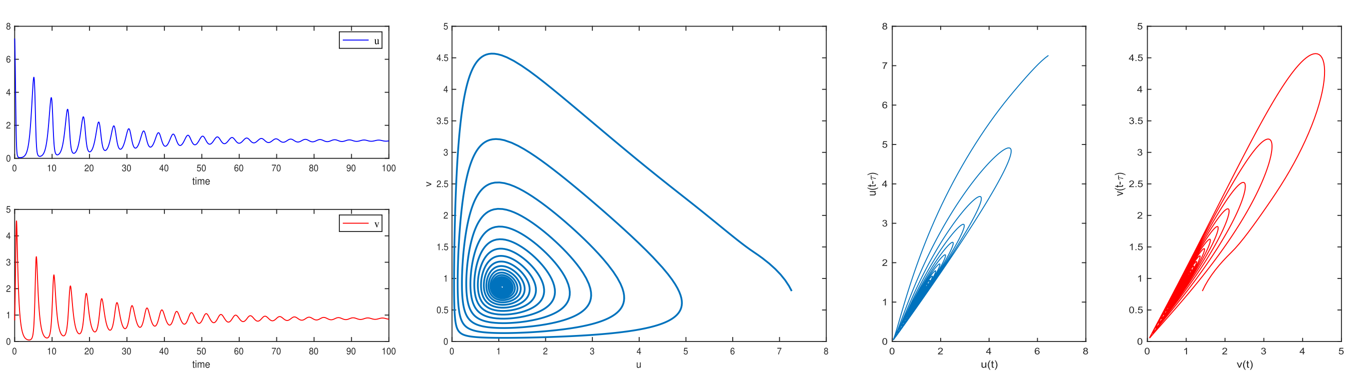

Fig. 6. Stability of the UIE equilibrium point with parameter values $r = 2$; $s = 4$; $\beta = 1.9$; $d = 0.1$; $a = 5.5$; $k = 15$; $\tau = 0.09$.

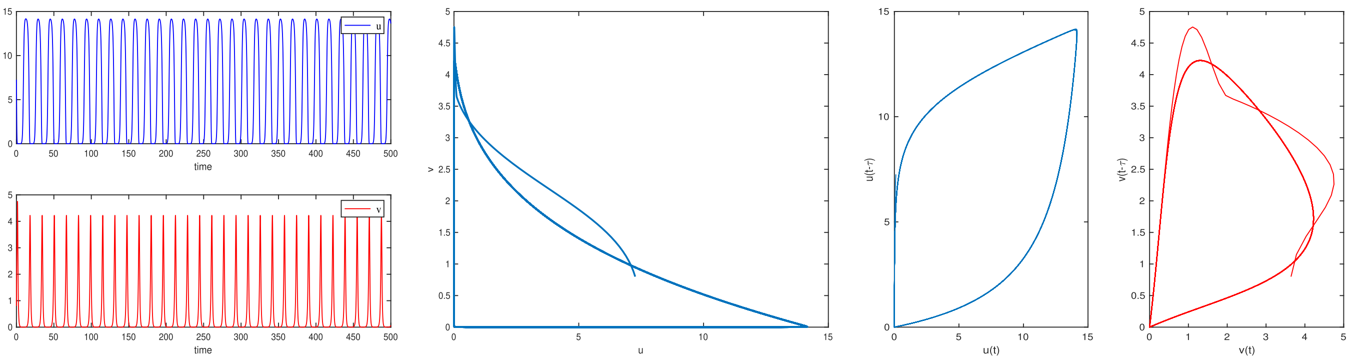

Fig. 7. The occurrence of Hopf bifurcation around the UIE equilibrium point (i.e. existence of periodic solution) with parameter values $r = 2$; $s = 4$; $\beta = 1.9$; $d = 0.1$; $a = 5.5$; $k = 15$; $\tau = \tau_c = 1.09$.

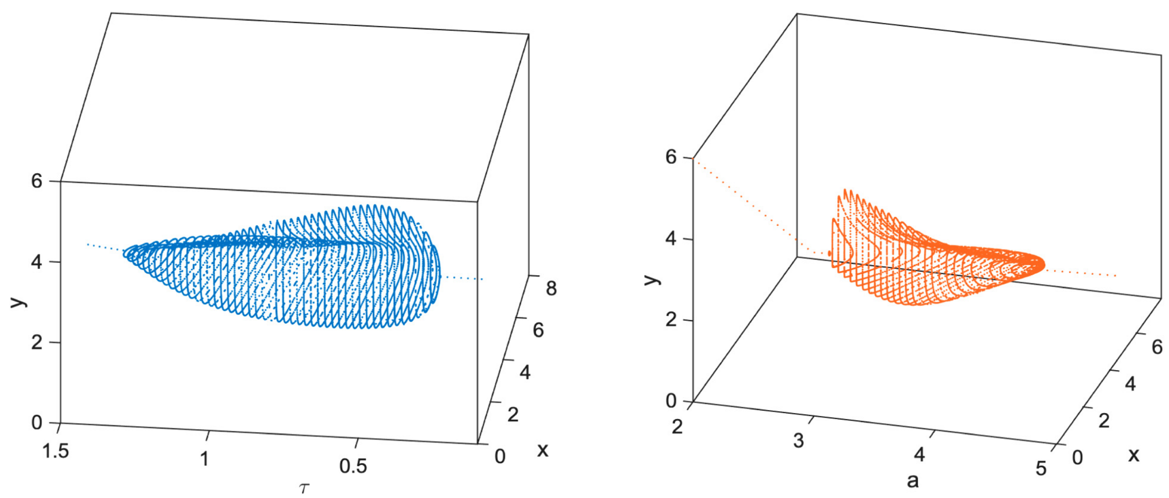

Fig. 8. The occurrence of Hopf bifurcation around the UIE equilibrium point (i.e. existence of periodic solution) by varying τ and a with parameter values $r = 2$; $s = 5$; $\beta = 2$; $d = 0.9$; $a = 4$; $k = 15$, $\tau = 1.1$.

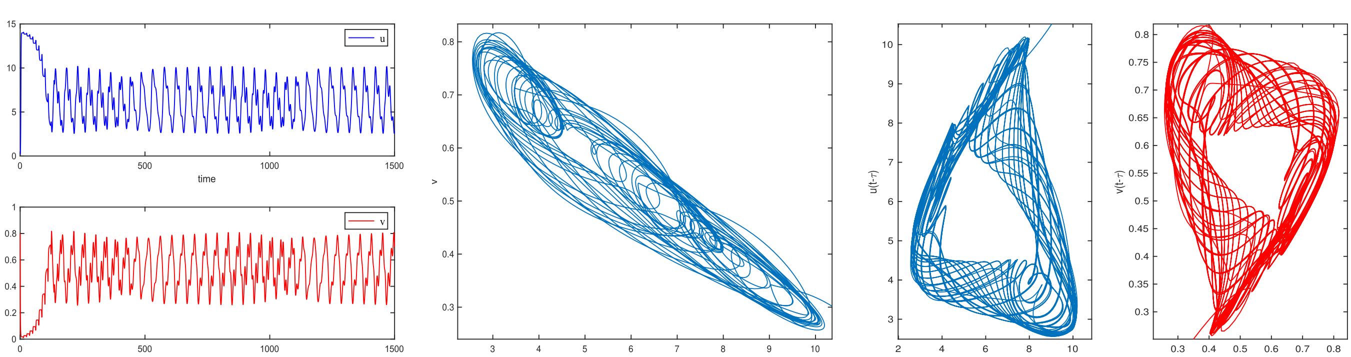

Fig. 9. The existence of choatic solutions for the delay bigger than the critical value τ_c with parameter values $r = 2$; $s = 4$; $\beta = 1.9$; $d = 0.1$; $a = 5.5$; $k = 15$; $\tau = 12.08$.

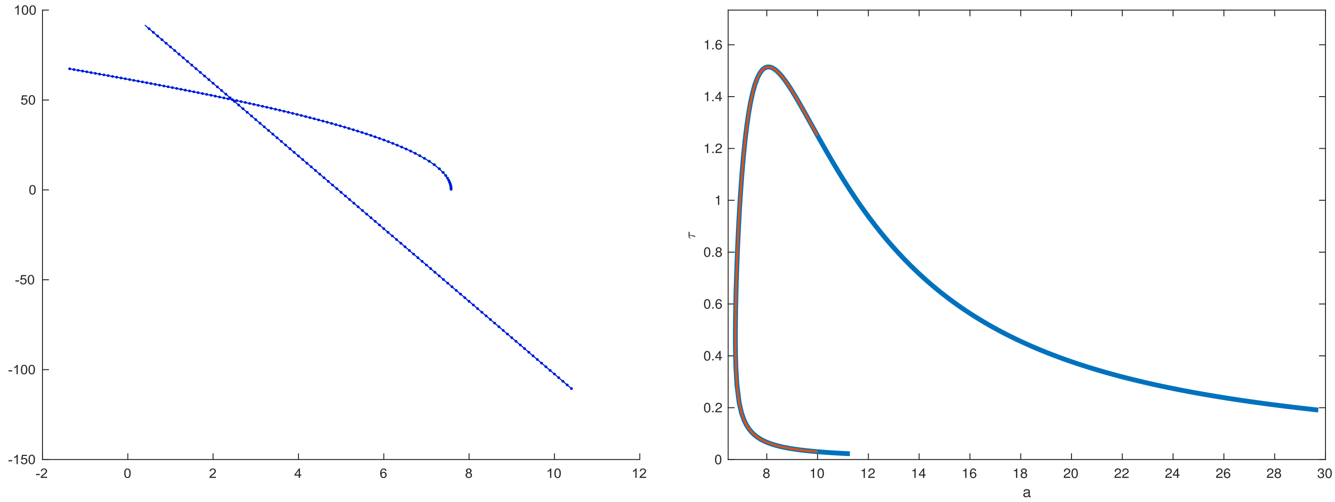

Fig. 10. Two-parameter Hop bifurcation diagram in (a, τ) parameters involving two branches of bifurcation. (Left) Branch of nontrivial equilibria. (Right) Blue line: Hopf bifurcation, red line: period doubling bifurcations.

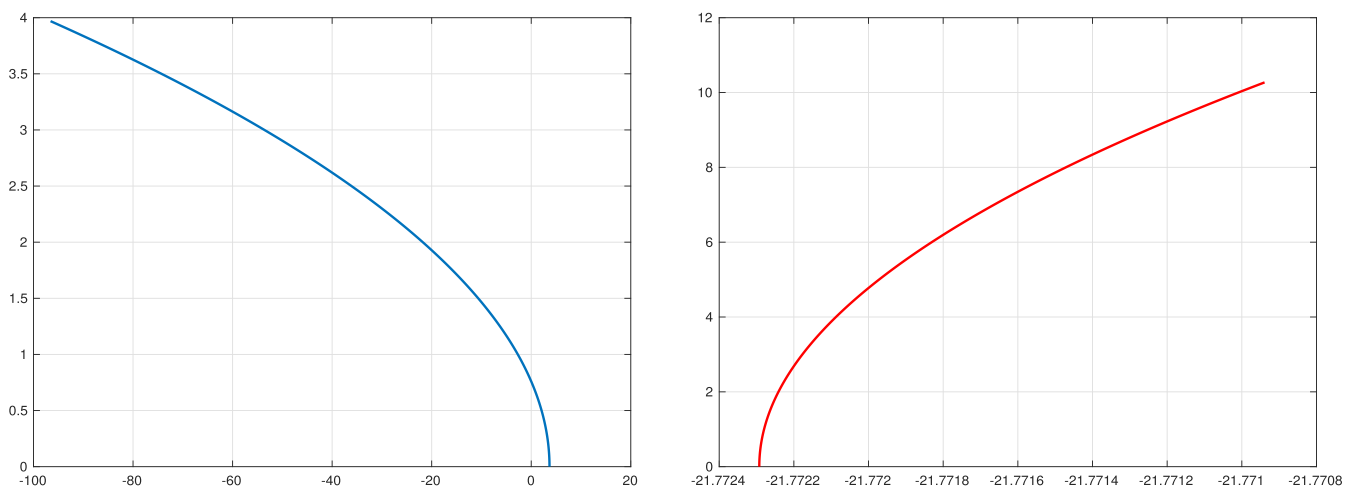

Fig. 11. Mikhailov hodographs indicating the satbilty of E^* (left) and the instability of E_1 (right) with parameter values $r = 2$; $s = 4$; $\beta = 1.9$; $d = 0.1$; $a = 5.5$; $k = 15$; $\tau = 0.001$.

and

$$\Delta(0, \tau_0) = q.$$

Then

$$\arg(\Delta(i\zeta, \tau_0)) \xrightarrow[\zeta \to +\infty]{} = \pi.$$

As $q > 0$, then $\arg(\Delta(0, \tau_0)) = 0$ and

$$[\arg(\Delta(i\zeta, \tau_0))]_{\zeta=0}^{\zeta=+\infty} = 2\frac{\pi}{2} = \pi$$

which implies that the steady state E_1 is asymptotically stable for $\tau < \tau_0$.

In the same way as in Eq. (11), we deduce that $E^*(\tau)$ is asymptotically stable for $\tau < \tau_c$.

8. Conclusions

Tumour virotherapy is a promising new approach for cancer treatment instead of surgery, chemotherapy and radiotherapy. Since, many viruses preferentially infect and destroy tumor cells, here we proposed a nonlinear mathematical model which takes into account the effect of viral lytic cycle. We have shown that under some parameter conditions the viral lytic cycle and the cytotoxicity rate induce periodic oscillations “called Jeff’s phenomenon” with small amplitude for some critical values and these oscillations can be asymptotically stable. Our model suggests that it is very much important to control these two parameters which can influence the dynamics of the system and a careful use of these parameters determines the success of virotherapy.

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