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Dedicated to Professor Ioan A. RUS on the occasion of his 70^{th} anniversary

Hopf bifurcation analysis of immune response against pathogens interaction dynamics with delays

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ABSTRACT. The aim of this paper is to study the steady states of the mathematical models with delays which describe pathogen-immune dynamics of many kinds of infectious diseases. In the study of mathematical models of infectious diseases it is an important problem to predict whether the infection disappears or the pathogens and the immune system persist. The delays are described by the memory function that reflect the influence of the past density of pathogen in blood. By using the coefficients of delays, as a bifurcation parameter, the models are found to undergo a sequence of Hopf bifurcation. The direction and the stability criteria of bifurcation periodic solutions are obtained by applying the normal form theory and the center manifold theorems. Some numerical simulation examples for justifying the theoretical results are also given.

1. INTRODUCTION

The purpose of this paper is to study Hopf bifurcation of immune response against pathogens interaction dynamics with delays. Dynamical systems with delays have been studied for population dynamics, neural networks [4] etc. In [8], we studied the Hopf bifurcation for two basic mathematical models with delay kernels which contain the density of uninfected cells, that of infected cells and that of pathogens.

In this paper, we add the effect of humoral immunity for the two models in [9] and we consider immune response against pathogens. Here we take only humoral immunity into account. When pathogens go into blood, the B cells are activated and secrete antibody. Immune system removes pathogens in blood with aid of antibody. More precisely, consider the following system of differential functional equations:

$$\begin{aligned} \dot{x}(t) &= a_1 - a_2 x(t) - a_3 x(t) p(t-\tau_2) \\ \dot{y}(t) &= -a_4 y(t) + a_3 x(t) p(t-\tau_2) \\ \dot{z}(t) &= -a_5 z(t-\tau_1) + a_6 z(t-\tau_1) p(t-\tau_2) \\ \dot{p}(t) &= a_4 a_7 y(t) - a_8 p(t-\tau_2) - a_9 x(t) p(t-\tau_2) - a_{10} z(t-\tau_1) p(t-\tau_2), \end{aligned} \tag{1.1}$$

where a_i, $i = 1, \cdots, 10$ are positives constants and the delays $\tau_1, \tau_2 \geq 0$ have parameters which denotes the effect of the past memories.

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It is also assumed that the system (1.1) is supplemented with initial conditions of the form:

$$x(0) = x^*,\ y(0) = y^*,\ z(s) = \varphi_1(s),\ s \in [-\tau_1, 0],\ p(s) = \varphi_2(s),\ s \in [-\tau_2, 0] \tag{1.2}$$

φ_i are bounded and continuous on $[-\tau_i, 0]$.

The model contains four variables: the density of uninfected cells x, the density of infected cells y, the density of pathogens specific lymphocytes z and the density of pathogens in blood p.
If $a_9 = 0$ the loss of pathogens by the absorption is ignored and if $a_3 = a_9$ the loss of pathogens by the absorption is considered. If $a_9 \neq 0$ and $a_3 \neq a_9$, the model is more realistic because only a part of the pathogen is absorbed.

2. Local stability analysis and Hopf bifurcation

In this section, we consider the local stability of the equilibrium solution of system (1.1). The equilibrium solution (x_0, y_0, z_0, p_0) of (1.1) is given by the solution of the system:

$$\begin{aligned} &a_1 - a_2 x - a_3 x p = 0 \\ &a_4 y - a_3 x p = 0 \\ &a_5 z - a_6 z p = 0 \\ &a_4 a_7 y - a_8 p - a_9 x p - a_{10} z p = 0. \end{aligned} \tag{2.3}$$

Straightforward computations lead us to the following result:

Proposition 2.1. *If*

$$a_1 \in (0,1), \quad \frac{a_2 a_6}{a_3 a_5} < \frac{a_1}{1 - a_1}, \quad a_3 a_7 > a_9 + \frac{a_8(a_2 a_6 + a_3 a_5)}{a_6},$$

the system (2.3) *has three solutions, given by* $X_{0i} = (x_{0i}, y_{0i}, z_{0i}, p_{0i})$, $i = 1, 2, 3$, *where*

$$\begin{aligned} &x_{01} = \frac{a_1}{a_2}, \quad x_{02} = \frac{a_8}{a_3 a_7 - a_9}, \quad x_{03} = \frac{a_1 a_6}{a_2 a_6 + a_3 a_5} \\ &y_{01} = 0, \quad y_{02} = \frac{a_1(a_3 a_7 - a_9) - a_2 a_8}{a_4(a_3 a_7 - a_9)}, \quad y_{03} = \frac{a_1 a_3 a_5}{a_4(a_2 a_6 + a_3 a_5)} \\ &z_{01} = 0, \quad z_{02} = 0, \quad z_{03} = \frac{a_6(a_3 a_7 - a_9) - a_8(a_2 a_6 + a_3 a_5)}{a_{10}(a_2 a_6 + a_3 a_5)} \\ &p_{01} = 0, \quad p_{02} = \frac{a_1(a_3 a_7 - a_9) - a_2 a_8}{a_3 a_8}, \quad p_{03} = \frac{a_5}{a_6}. \end{aligned} \tag{2.4}$$

The first solution X_1 represents the state where the pathogens are absent. The second solution X_2 represents the state where the pathogens are present and the lymphocytes are absent. The third solution X_3 is in the interior of the first quadrant and represents the state where both the pathogens and the lymphocytes are present.

Let $X_0 = (x_0, y_0, z_0, p_0)$ be one of the solutions given by (2.4). With respect of transformation

$$x_1(t) = x(t) - x_0,\ x_2(t) = y(t) - y_0,\ x_3(t) = z(t) - z_0,\ x_4(t) = p(t) - p_0 \tag{2.5}$$

the system (1.1) becomes:

(2.6) $$\dot{x}(t) = Ax(t) + Bx(t-\tau_1) + Cx(t-\tau_2) + F(x(t), x(t-\tau_1), x(t-\tau_2)),$$

where

$$x(t) = (x_1(t), x_2(t), x_3(t), x_4(t))^T,$$
$$x(t-\tau_1) = (x_1(t-\tau_1), x_2(t-\tau_1), x_3(t-\tau_1), x_4(t-\tau_1))^T,$$
$$x(t-\tau_2) = (x_1(t-\tau_2), x_2(t-\tau_2), x_3(t-\tau_2), x_4(t-\tau_2))^T$$

(2.7)
$$A = \begin{pmatrix} -b_1 & 0 & 0 & 0 \\ b_2 & -b_3 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ -b_6 & b_5 & 0 & 0 \end{pmatrix}, B = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -b_6 & 0 \\ 0 & 0 & -b_7 & 0 \end{pmatrix}, C = \begin{pmatrix} 0 & 0 & 0 & -b_8 \\ 0 & 0 & 0 & b_8 \\ 0 & 0 & 0 & b_9 \\ 0 & 0 & 0 & -b_{10} \end{pmatrix}$$

$F(x(t), x(t-\tau_1), x(t-\tau_2) = (F_1(x(t), x(t-\tau_1), x(t-\tau_2)), F_2(x(t), x(t-\tau_1), x(t-\tau_2)), F_3(x(t), x(t-\tau_1), x(t-\tau_2)), F_4(x(t), x(t-\tau_1), x(t-\tau_2)))^T$ and

(2.8)
$$b_1 = a_2 + a_3 p_0,\ b_2 = a_3 p_0,\ b_3 = a_4,\ b_4 = a_3 p_0,\ b_5 = a_4 a_7,\ b_6 = a_5 - a_6 p_0,$$
$$b_7 = a_{10} p_0,\ b_8 = a_3 x_0,\ b_9 = a_6 z_0,\ b_{10} = a_8 + a_9 x_0 + a_{10} z_0$$

and

(2.9)
$$F_1(x(t), x(t-\tau_1), x(t-\tau_2)) = -a_3 x_1(t) x_4(t-\tau_2)$$
$$F_2(x(t), x(t-\tau_1), x(t-\tau_2)) = a_3 x_1(t) x_4(t-\tau_2)$$
$$F_3(x(t), x(t-\tau_1), x(t-\tau_2)) = a_6 x_3(t-\tau_1) x_4(t-\tau_2)$$
$$F_4(x(t), x(t-\tau_1), x(t-\tau_2)) = (a_6 - a_{10}) x_3(t-\tau_1) x_4(t-\tau_2) - a_9 x_1(t) x_4(t-\tau_2).$$

The associated characteristic equation of the linearized system of the system (2.6) is given by:

(2.10) $$P(\lambda, \tau_1, \tau_2) = P_0(\lambda) + P_1(\lambda) e^{-\lambda\tau_1} + P_2(\lambda) e^{-\lambda\tau_2} + P_3(\lambda) e^{-\lambda(\tau_1+\tau_2)} = 0,$$

where

(2.11)
$$P_0(\lambda) = \lambda^4 + p_{03}\lambda^3 + p_{02}\lambda^2,\ P_1(\lambda) = p_{13}\lambda^3 + p_{12}\lambda^2 + p_{11}\lambda,$$
$$P_2(\lambda) = p_{22}\lambda^2 + p_{21}\lambda,\ P_3(\lambda) = p_{32}\lambda^2 + p_{31}\lambda + p_{30}$$

and

(2.12)
$$p_{03} = b_1 + b_3,\ p_{02} = b_1 b_3,\ p_{13} = b_6,\ p_{12} = b_6(b_1 + b_3),\ p_{11} = b_1 b_3 b_6$$
$$p_{22} = -b_8(b_4 + b_5),\ p_{21} = b_{10} + b_8(b_2 b_5 - b_1 b_5 - b_3 b_4),\ p_{32} = b_7 b_9 + b_6 b_{10}$$
$$p_{31} = (b_1 + b_3)(b_6 b_{10} + b_7 b_9) - b_6 b_8 (b_4 + b_5)$$
$$p_{30} = b_1 b_3 (b_9 + b_{10}) + b_6 b_8 (b_2 b_5 - b_1 b_5 - b_3 b_4).$$

Because of the presence of two different delays τ_1 and τ_2 in equation (2.10), the analysis of the sign of the real parts of eigenvalues is very complicated and a direct approach cannot be considered. We will use a method consisting of determining the stability of the equilibrium point when one delay is equal to zero and using similar analytic arguments as in [10], [1], we will deduce conditions for the stability of the equilibrium point when both time delays are nonzero.

Using the Routh-Hurwitz criterion, we have:

Proposition 2.2. *If $\tau_1 = 0, \tau_2 = 0$, then the characteristic equation (2.10) is given by*

$$P(\lambda, 0, 0) = \lambda^4 + (p_{03} + p_{13})\lambda^3 + (p_{02} + p_{12} + p_{22} + p_{32})\lambda^2 + (p_{11} + p_{31} + p_{21})\lambda + p_{30} = 0. \tag{2.13}$$

All eigenvalues of (2.13) have negative real parts if and only if

$$\begin{aligned} &p_{02} + p_{12} + p_{22} + p_{32} > 0,\ p_{11} + p_{31} + p_{21} > 0,\ p_{30} > 0 \\ &(p_{11} + p_{31} + p_{21})((p_{02} + p_{12} + p_{22} + p_{32})(p_{03} + p_{13}) - (p_{11} + p_{31} + p_{21})) \\ &> p_{30}(p_{03} + p_{13})^2. \end{aligned} \tag{2.14}$$

If (2.14) holds, then the equilibrium point X_0 is locally asymptotically stable. When $\tau_1 = 0$ and τ_2 increases, the stability of the equilibrium point X_0 can only be lost if pure imaginary roots appear. Hence, we look for imaginary roots $\lambda = \pm i\omega$, $\omega > 0$ of the characteristic equation

$$P(\lambda, 0, \tau_2) = \lambda^4 + m_3\lambda^3 + m_2\lambda^2 + m_1\lambda + (n_1\lambda^2 + n_2\lambda + n_0)e^{-\lambda\tau_2} = 0, \tag{2.15}$$

where

$$\begin{aligned} &m_3 = p_{03} + p_{13},\ m_2 = p_{02} + p_{12},\ m_1 = p_{11} \\ &n_2 = p_{22} + p_{32},\ n_1 = p_{31} + p_{21},\ n_0 = p_{30}. \end{aligned} \tag{2.16}$$

For $\lambda = i\omega$, $\omega > 0$, from (2.15) results:

$$\begin{aligned} &\omega^4 - m_2\omega^2 = (n_1\omega^2 - n_0)\cos(\omega\tau_2) - n_2\omega\sin(\omega\tau_2) \\ &m_3\omega^3 - m_1\omega = n_2\omega\cos(\omega\tau_1) + (n_1\omega^2 - n_0)\sin(\omega\tau_2). \end{aligned} \tag{2.17}$$

From (2.17) results:

Proposition 2.3. *For $\tau_2 = \tau_{20}$ given by*

$$\tau_{20} = \frac{1}{\omega_{20}} \arctan \frac{(m_3\omega_{20}^3 - m_1\omega_{20})(n_1\omega_{20}^2 - n_0) - (\omega_{20}^4 - m_2\omega_{20}^2)n_2\omega_{20}}{(\omega_{20}^4 - m_2\omega_{20}^2)(n_1\omega_{20}^2 - n_0) + (m_3\omega_{20}^3 - m_1\omega_{20})n_2\omega_{20}}, \tag{2.18}$$

where ω_{20} is the positive root of the equation

$$x^8 + (m_3^2 - 2m_2)x^6 + (m_2^2 - 2m_1m_3 - n_1^2)x^4 + (m_1^2 - n_2^2 + 2n_1n_0x^2) - n_0^2 = 0 \tag{2.19}$$

exists a Hopf bifurcation.

We return now to the study of equation (2.10) with $\tau_1, \tau_2 > 0$. Following Theorem 2.1 from [10], results:

Proposition 2.4. *If all roots of the equation (2.15) have negative real parts for $\tau_2 > 0$, then there exists $\tau_1^*(\tau_2) > 0$ such that all the roots of equation (2.10) have negative real parts when $\tau_1 < \tau_1^*(\tau_2)$.*

Using Proposition 2.3, we have the following result about the asymptotic stability of the equilibrium point X_0.

Proposition 2.5. *Assume that (2.14) holds. Let τ_{20} given by (2.18). Then for every $\tau_2 \in [0, \tau_{20})$, there exists $\tau_1^*(\tau_{20}) > 0$ such that the equilibrium point X is locally asymptotically stable when $\tau_2 \in [0, \tau_1^*(\tau_{20}))$.*

When $\tau_2 = 0$ and τ_1 increases, the stability of the equilibrium point X can only be lost if pure imaginary roots appear. Hence we look for purely imaginary roots $\lambda = \pm i\omega$, $\omega > 0$ of the characteristic equation

$$P(\lambda, \tau_1, 0) = \lambda^4 + r_3\lambda^3 + r_2\lambda^2 + r_1\lambda + (s_3\lambda^3 + s_2\lambda^2 + s_1\lambda + s_0)e^{-\lambda\tau_1} = 0, \tag{2.20}$$

where

$$\begin{aligned} &r_3 = p_{03},\ r_2 = p_{02} + p_{22},\ r_1 = p_{21} \\ &s_3 = p_{13},\ s_2 = p_{12} + p_{32},\ s_1 = p_{11} + p_{31},\ s_0 = p_{30}. \end{aligned} \tag{2.21}$$

For $\lambda = i\omega$, $\omega > 0$, from (2.20) results:

$$\begin{aligned} \omega^4 - r_2\omega^2 &= (s_2\omega^2 - s_0)\cos(\omega\tau_1) + (s_3\omega^2 - s_1\omega)\sin(\omega\tau_1) \\ r_3\omega^3 - r_1\omega &= (s_2\omega^2 - s_0)\sin(\omega\tau_1) - (s_3\omega^2 - s_1\omega)\cos(\omega\tau_1). \end{aligned} \tag{2.22}$$

From (2.21) results:

Proposition 2.6. *For $\tau_1 = \tau_{10}$ given by*

$$\tau_{10} = \frac{1}{\omega_{10}} \arctan \frac{(r_3\omega_{10}^3 - r_1\omega_{10})(s_2\omega_{10}^2 - s_0) + (\omega_{10}^4 - r_2\omega_{10}^2)(s_3\omega_{10}^2 - s_1\omega_{10})}{(\omega_{10}^4 - r_2\omega_{10}^2)(s_2\omega_{10}^2 - s_0) - (r_3\omega_{10}^3 - r_1\omega_{10})(s_3\omega_{10}^2 - s_1\omega_{10})}, \tag{2.23}$$

where ω_{10} is the positive root of the equation

$$x^8 + (r_3^2 - 2r_2)x^6 + (r_2^2 - 2r_1r_3 - s_2^2 - s_3^2)x^4 + 2s_1s_3x^3 + (2s_2s_0 - s_1^2)x^2 - s_0^2 = 0 \tag{2.24}$$

exists a Hopf bifurcation.

Following Theorem 2.1 from [10], we obtain:

Proposition 2.7. *If all the roots of the equation* (2.20) *have negative real parts for τ_1, then there exists $\tau_2^*(\tau_1) > 0$ such that all the roots of the equation* (2.10) *have negative real parts when $\tau_2 < \tau_2^*(\tau_1)$.*

Using Proposition 2.6, we have the following result about the asymptotic stability of the equilibrium point X_0.

Proposition 2.8. *Assume that* (2.14) *hold true. Let τ_{10} given by* (2.23). *Then for every $\tau_1 \in [0, \tau_{10})$, there exists $\tau_2^*(\tau_{10}) > 0$ such that the equilibrium point X is locally asymptotically stable when $\tau_2 \in [0, \tau_2^*(\tau_{10}))$.*

3. Direction and local stability of the Hopf bifurcation

In the previous section, we obtained some conditions which guarantee that the system (1.1) have Hopf bifurcation in τ_{10}, τ_{20}. In this section, we study the direction, stability and the period of the bifurcating periodic solutions. The method we use is based on the normal form theory and on the center manifold theorem [3], [7].

3.1. **Direction and stability of the Hopf bifurcation for system (2.6), with** $\tau_1 = 0$**.** From Section 2.1, we know that if $\tau_1 = 0$ and $\tau_2 = \tau_{20}$ given by (2.18) then all the roots of equation (2.15) other than $\pm i\omega_{20}$ have negative real part. For notational convenience, let $\tau_2 = \tau_{20} + \mu$, $\mu \in (-\varepsilon, \varepsilon)$. Then $\varepsilon = 0$ is the Hopf bifurcation value of system (2.6). In the study of the Hopf bifurcation problem, first we transform system (2.6) with $\tau_1 = 0$ into an operator equation of the form

$$\dot{x}_t = \mathcal{A}_{02}(\mu)x_t + \mathcal{R}_{02}x_t, \tag{3.25}$$

where

$$x = (x_1, x_2, x_3, x_4)^T, \quad x_t = x(t+\theta), \quad \theta \in [-\tau_2, 0].$$

The operators $\mathcal{A}_{02}$ and $\mathcal{R}_{02}$ are defined as

$$\mathcal{A}_{02}(\mu)\phi(\theta) = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \theta \in [-\tau_2, 0) \\ (A+B)\phi(0) + C\phi(-\tau_2), & \theta = 0 \end{cases}, \tag{3.26}$$

where $\phi \in C^1([-\tau_2, 0], \mathbb{C}^4)$ and A, B, C are given by (2.7) and

$$\mathcal{R}_{02}\phi(\theta) = \begin{cases} (0,0,0,0)^T, & \theta \in [-\tau_2, 0) \\ (F_1(\mu,\phi), F_2(\mu,\phi), F_3(\mu,\phi), F_4(\mu,\phi))^T, & \theta = 0 \end{cases} \tag{3.27}$$

$$\begin{aligned} &F_1(\mu,\phi) = -a_3\phi_1(0)\phi_4(-\tau_2),\ F_2(\mu,\phi) = a_3\phi_1(0)\phi_4(-\tau_2), \\ &F_3(\mu,\phi) = a_6\phi_3(0)\phi_4(-\tau_2), \\ &F_4(\mu,\phi) = (a_6 - a_{10})\phi_3(0)\phi_4(-\tau_2) - a_9\phi_1(0)\phi_4(-\tau_2). \end{aligned} \tag{3.28}$$

For $\psi \in C^1([0, \tau_2], \mathbb{C}^4)$, the adjoint operator $\mathcal{A}^*_{02}$ of $\mathcal{A}_{02}$ is define as

$$\mathcal{A}^*_{02}(\psi(s)) = \begin{cases} \frac{-d\psi(s)}{ds}, & s \in [0, \tau_2) \\ (A+B)\psi^T(0) + C\psi^T(\tau_2), & s = \tau_2. \end{cases} \tag{3.29}$$

For $\phi \in C^1([-\tau_2, 0], \mathbb{C}^4)$ and $\psi \in C^1([0, \tau_2], \mathbb{C}^4)$ define the bilinear form

$$< \psi, \phi >= \overline{\psi}^T\phi(0) - \int_{-\tau_{20}}^{0} \int_{\xi=0}^{\theta} \overline{\psi}^T(\xi - \theta)C\phi(\xi)d\xi d\theta. \tag{3.30}$$

To determine the Poincare normal form of operator $\mathcal{A}_0$, we need to calculate the eigenvector ϕ of $\mathcal{A}_{02}$ associated with eigenvalue $\lambda_1 = i\omega_{20}$ and the eigenvector ϕ^* of $\mathcal{A}^*_{02}$ associated with eigenvalue $\lambda_2 = \overline{\lambda_1}$.

Proposition 3.9. (i) *The eigenvector* ϕ *of* $\mathcal{A}_{02}$ *associated with eigenvalue* $\lambda_1 = i\omega_{20}$ *is given by* $\phi(\theta) = ve^{\lambda_1\theta}$, $\theta \in [-\tau_2, 0]$, *where* $v = (v_1, v_2, v_3, v_4)^T$ *and*

$$v_1 = -b_8e^{\lambda_1\tau_2},\ v_2 = \frac{b_8(\lambda_1 + b_1 - b_2)}{\lambda_1 + b_3}e^{\lambda_1\tau_2},\ v_3 = \frac{b_9(\lambda_1 + b_1)}{\lambda_1 + b_6},\ v_4 = \lambda_1 + b_1; \tag{3.31}$$

(ii) *The eigenvector* ϕ^* *of* $\mathcal{A}_{02}^*$ *associated with eigenvalue* $\lambda_2 = \overline{\lambda_1}$ *is given by* $\phi^*(s) = we^{\lambda_2 s}$, $s \in [0, \tau_2]$, *where* $w = (w_1, w_2, w_3, w_4)^T$ *and*

$$\begin{aligned} &w_1 = \frac{b_2 b_5 - b_4(\lambda_2 + b_3)}{b_5(\lambda_2 + b_1)\eta},\ w_2 = \frac{1}{\eta},\ w_3 = -\frac{b_7(\lambda_2 + b_3)}{b_5(\lambda_2 + b_6)\eta},\ w_4 = \frac{(\lambda_2 + b_3)}{b_5\eta} \\ &\eta = \frac{b_2 b_5 - b_4(\lambda_2 + b_3)}{b_5(\lambda_2 + b_1)}\overline{v}_1 + \overline{v}_2 - \frac{b_7(\lambda_2 + b_3)}{b_5(\lambda_2 + b_6)}\overline{v}_3 + \frac{(\lambda_2 + b_3)}{b_5}\overline{v}_4 \\ &+ \frac{\lambda_2\tau_2 e^{\lambda_1\tau_2} + 1 - \lambda_2^2 e^{\lambda_1\tau_2}}{\lambda_2^2}(-b_8\frac{b_2 b_5 - b_4(\lambda_2 + b_3)}{b_5(\lambda_2 + b_1)} + b_8 - b_9\frac{b_7(\lambda_2 + b_3)}{b_5(\lambda_2 + b_6)} \\ &- b_{10}\frac{\lambda_2 + b_3}{b_5})\overline{v}_4; \end{aligned} \tag{3.32}$$

(iii) *With respect of* (3.30) *we have:*

$$< \phi^*, \phi >= 1, \quad < \phi^*, \overline{\phi} >=< \overline{\phi}, \phi^* >= 0, \quad < \overline{\phi}^*, \overline{\phi} >= 1.$$

Next, we construct the coordinates of the center of the manifold Ω_{02} at $\varepsilon = 0$ [3], [7]. Let

$$\begin{aligned} z(t) &=< \phi^*, x_t > \\ w(t,\theta) &= x_t - 2Re\{z(t)\phi(\theta)\}. \end{aligned} \tag{3.33}$$

On the center manifold Ω_{02}, $w(t,\theta) = w(z(t), \overline{z}(t), \theta)$, where

$$w(z, \overline{z}, \theta) = w_{20}(\theta)\frac{z^2}{2} + w_{11}(\theta)z\overline{z} + w_{02}(\theta)\frac{\overline{z}^2}{2} + \cdots \tag{3.34}$$

and z and $\overline{z}$ are the local coordinates of the center manifold Ω_{02} in the direction of ϕ and ϕ^*, respectively.
For the solution $x_t \in \Omega_{02}$ of (3.25), notice that for $\varepsilon = 0$, we have:

$$\dot{z}(t) = \lambda_1 z(t) + \langle \phi^*, \mathcal{R}_{02}(w(t,\theta) + 2Re\{z(t)\phi(\theta)\}) \rangle . \tag{3.35}$$

Rewrite this as

$$\dot{z}(t) = \lambda_1 z(t) + g(z, \overline{z}) \tag{3.36}$$

with

$$g(z, \overline{z}) = \overline{\phi^*(0)}^T \mathcal{R}_{02}(w(z, \overline{z}, \theta) + 2Re\{z\phi(\theta)\}). \tag{3.37}$$

Further expand the function $g(z, \overline{z})$ on the center manifold Ω_{02} in powers of z and $\overline{z}$:

$$g(z, \overline{z}) = g_{20}\frac{z^2}{2} + g_{11}z\overline{z} + g_{21}\frac{\overline{z}^2}{2} + g_{21}\frac{z^2\overline{z}}{2} + \cdots \tag{3.38}$$

Proposition 3.10. *For the system* (3.25) *we have*

$$\begin{aligned} g_{20} &= \overline{w}_1 F_{120} + \overline{w}_2 F_{220} + \overline{w}_3 F_{320} + \overline{w}_4 F_{420} \\ g_{11} &= \overline{w}_1 F_{111} + \overline{w}_2 F_{211} + \overline{w}_3 F_{311} + \overline{w}_4 F_{411} \\ g_{02} &= \overline{w}_1 F_{102} + \overline{w}_2 F_{202} + \overline{w}_3 F_{302} + \overline{w}_4 F_{402} \\ g_{21} &= \overline{w}_1 F_{121} + \overline{w}_2 F_{221} + \overline{w}_3 F_{321} + \overline{w}_4 F_{421}, \end{aligned} \tag{3.39}$$

where

$$
\begin{aligned}
&F_{120} = -2a_3 v_1 v_4 e^{\lambda_2\tau_2},\ F_{220} = -F_{120},\ F_{320} = 2a_6 v_3 v_4 e^{\lambda_2\tau_2},\\
&F_{420} = \frac{a_6 - a_{10}}{2a_6}F_{320} + \frac{a_9}{2a_3}F_{120},\\
&F_{111} = -2a_3 Re(v_1\overline{v}_4 e^{\lambda_1\tau_2}),\ F_{211} = -F_{111},\ F_{311} = 2a_6 Re(v_3\overline{v}_4 e^{\lambda_1\tau_2}),\\
&F_{411} = \frac{a_6 - a_{10}}{2a_6}F_{311} + \frac{a_9}{2a_3}F_{111},\\
&F_{121} = -a_3(2v_1 w_{411}(-\tau_2) + \overline{v}_1 w_{420}(-\tau_2) + \overline{v}_4 w_{120}(0)e^{\lambda_2\tau_2} + 2v_4 w_{111}(0)e^{\lambda_1\tau_2}),\\
&F_{221} = -F_{121},\\
&F_{321} = a_6(2v_3 w_{411}(-\tau_2) + \overline{v}_3 w_{420}(-\tau_2) + \overline{v}_4 w_{320}(0)e^{\lambda_1\tau_2} + 2v_4 w_{311}(0)e^{\lambda_2\tau_2}),\\
&F_{421} = \frac{a_6 - a_{10}}{a_6}F_{321} + \frac{a_9}{a_3}F_{121},\\
&F_{102} = \overline{F}_{120},\ F_{202} = \overline{F}_{220},\ F_{302} = \overline{F}_{320},\ F_{402} = \overline{F}_{420}
\end{aligned}
\tag{3.40}
$$

and

$$
\begin{aligned}
w_{20}(\theta) &= (w_{120}(\theta), w_{220}(\theta), w_{320}(\theta), w_{420}(\theta))^T\\
w_{11}(\theta) &= (w_{111}(\theta), w_{211}(\theta), w_{311}(\theta), w_{411}(\theta))^T
\end{aligned}
$$

are given by

$$
\begin{aligned}
w_{20}(\theta) &= \frac{g_{20}}{\lambda_1} v e^{\lambda_1\theta} - \frac{\overline{g}_{20}}{3\lambda_1}\overline{v} e^{\lambda_2\theta} + E_1 e^{2\lambda_1\theta}\\
w_{11}(\theta) &= \frac{g_{11}}{\lambda_1} v e^{\lambda_1\theta} - \frac{\overline{g}_{11}}{\lambda_1}\overline{v} e^{\lambda_2\theta} + E_2, \quad \theta \in [-\tau_{20}, 0],
\end{aligned}
\tag{3.41}
$$

where $E_i = (E_{i1}, E_{i2}, E_{i3}, E_{i4})^T, i = 1, 2$ *are the solutions of the systems*

$$
\begin{aligned}
&(A + B + e^{2\lambda_1\tau_{20}}C - 2\lambda_1 I)E_1 = -(F_{120}, F_{220}, F_{320}, F_{420})^T\\
&(A + B + C)E_2 = -(F_{111}, F_{211}, F_{311}, F_{411})^T.
\end{aligned}
\tag{3.42}
$$

Therefore, we can compute the following parameters:

$$
\begin{aligned}
c_{20}(0) &= \frac{i}{2\omega_0}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{g_{21}}{2}\\
\mu_{20} &= -\frac{Re\,(c_{20}(0))}{Re\,(\lambda'(\tau_{20}))}\\
\beta_{20} &= 2Re\,(c_{20}(0))\\
T_{20} &= -\frac{Im\,(c_{20}(0)) + \mu_{20} Im\,(\lambda'(\tau_{20}))}{\omega_{20}},
\end{aligned}
\tag{3.43}
$$

where

$$
\begin{aligned}
\lambda'(\tau_{20}) &= \frac{d\lambda}{d\tau_2}|_{\tau_2=\tau_{20},\lambda=\lambda_1}\\
&= (\lambda_1(n_1\lambda_1^2 + n_2\lambda_1 + n_0))/((4\lambda_1^3 + 3m_3\lambda_1^2 + 2m_2\lambda_1 + m_1)e^{\lambda_1\tau_{20}}\\
&- n_1\tau_{20}\lambda_1^2 + (2n_1 - n_2\tau_{20})\lambda_1 + n_2 - n_0\tau_{20}).
\end{aligned}
$$

Proposition 3.11. *In formulas* (3.43), μ_{20} *determines the direction of the Hopf bifurcation: if* $\mu_{20} > 0(< 0)$ *the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for* $\tau_2 > \tau_{20}(< \tau_{20})$*;* β_{20} *determines the stability of the bifurcation periodic solutions: the solutions are orbitally stable (unstable) if* $\beta_{20} < 0(> 0)$*.* T_2 *determines the period of the bifurcating periodic solutions: the period increases (decreases) if* $T_2 > 0(< 0)$*.*

3.2. **Direction and stability of the Hopf bifurcation for system (2.6), with** $\tau_2 = 0$**.** From section 2, we know that if $\tau_2 = 0$ and $\tau_1 = \tau_{10}$ given by (2.23), then all the roots of the equation (2.20) other than $\pm i\omega_{10}$ have negative real part. For notational convenience, let $\tau_1 = \tau_{10} + \mu$, $\mu \in (-\varepsilon, \varepsilon)$. Then $\varepsilon = 0$ is the Hopf bifurcation value of the system (2.6). In the study of the Hopf bifurcation problem, first we transform system (2.6) with $\tau_2 = 0$ into an operator equation of the form

$$\dot{x}_t = \mathcal{A}_{10}(\mu)x_t + \mathcal{R}_{10}x_t, \tag{3.44}$$

where

$$x = (x_1, x_2, x_3, x_4)^T, \quad x_t = x(t+\theta), \quad \theta \in [-\tau_1, 0]$$

The operators $\mathcal{A}_{10}$ and $\mathcal{R}_{10}$ are define as

$$\mathcal{A}_{10}(\mu)\phi(\theta) = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \theta \in [-\tau_1, 0) \\ (A+C)\phi(0) + B\phi(-\tau_1), & \theta = 0 \end{cases}, \tag{3.45}$$

where $\phi \in C^1([-\tau_1, 0], \mathbb{C}^4)$ and A, B, C are given by (14) and

$$\mathcal{R}_{10}\phi(\theta) = \begin{cases} (0,0,0,0)^T, & \theta \in [-\tau_1, 0) \\ (F_1(\mu,\phi), F_2(\mu,\phi), F_3(\mu,\phi), F_4(\mu,\phi))^T, & \theta = 0 \end{cases} \tag{3.46}$$

$$\begin{aligned} &F_1(\mu,\phi) = -a_3\phi_1(0)\phi_4(0),\ F_2(\mu,\phi) = a_3\phi_1(0)\phi_4(0), \\ &F_3(\mu,\phi) = a_6\phi_3(-\tau_1)\phi_4(0), \\ &F_4(\mu,\phi) = (a_6 - a_{10})\phi_3(-\tau_1)\phi_4(0) - a_9\phi_1(0)\phi_4(0). \end{aligned} \tag{3.47}$$

For $\psi \in C^1([0, \tau_1], \mathbb{C}^4)$, the adjoint operator $\mathcal{A}^*_{10}$ of $\mathcal{A}_{10}$ is defined as

$$\mathcal{A}^*_{10}\psi(s) = \begin{cases} \frac{-d\psi(s)}{ds}, & s \in [0, \tau_1) \\ (A+C)\psi^T(0) + B\psi^T(\tau_1), & s = \tau_1. \end{cases} \tag{3.48}$$

For $\phi \in C^1([-\tau_1, 0], \mathbb{C}^4)$ and $\psi \in C^1([0, \tau_1], \mathbb{C}^4)$ define the bilinear form

$$< \phi, \psi >= \overline{\psi}^T(0)\phi(0) - \int\limits_{-\tau_{10}}^{0} \int\limits_{\xi=0}^{\theta} \overline{\psi}^T(\xi - \theta)B\phi(\xi)d\xi d\theta. \tag{3.49}$$

Similarly to section 3.1, we obtain:

Proposition 3.12. (i) *The eigenvector* ϕ *of* $\mathcal{A}_{10}$ *associated with eigenvalue* $\lambda_1 = i\omega_{10}$ *is given by* $\phi(\theta) = ve^{\lambda_1\theta}$*,* $\theta \in [-\tau_1, 0]$*, where* $v = (v_1, v_2, v_3, v_4)^T$ *and*

$$v_1 = -b_8,\ v_2 = \frac{b_8(\lambda_1 + b_1 - b_2)}{\lambda_1 + b_1},\ v_3 = \frac{b_9(\lambda_1 + b_1)}{\lambda_1 + b_6 e^{\lambda_2\tau_1}},\ v_4 = \lambda_1 + b_1; \tag{3.50}$$

(ii) *The eigenvector ϕ^* of $\mathcal{A}^*_{10}$ associated with eigenvalue $\lambda_2 = \overline{\lambda_1}$ is given by $\phi^*(s) = we^{\lambda_1 s}$, $s \in [0, \tau_1]$, where $w = (w_1, w_2, w_3, w_4)^T$ and*

(3.51)

$$w_1 = \frac{b_2b_5 - b_4(\lambda_2 + b_3)}{b_5(\lambda_2 + b_1)\eta},\ w_2 = \frac{1}{\eta},\ w_3 = -\frac{b_7e^{\lambda_1\tau_1}(\lambda_2 + b_3)}{b_5(\lambda_2 + b_6e^{\lambda_1\tau_1})\eta},\ w_4 = \frac{(\lambda_2 + b_3)}{b_5\eta}$$

$$\eta = \frac{b_2b_5 - b_4(\lambda_2 + b_3)}{b_5(\lambda_2 + b_1)}\overline{v}_1 + \overline{v}_2 + [\frac{-b_7e^{\lambda_1\tau_1}(\lambda_2 - b_3)}{b_5(\lambda_2 + b_6e^{\lambda_1\tau_1})}(1 - \frac{b_6(1 + \lambda_1\tau_1e^{\lambda_2\tau_1}e^{\lambda_2\tau_1})}{\lambda_1^2}) - \frac{(\lambda_2 + b_3)b_7(1 + \lambda_1\tau_1e^{\lambda_2\tau_1} - e^{\lambda_2\tau_1})}{\lambda_1^2}]\overline{v}_3 + \frac{\lambda_2 + b_3}{b_5}\overline{v}_4;$$

(iii) *With respect of* (3.48) *we have:*

$$< \phi^*, \phi >= 1, \quad < \phi^*, \overline{\phi} >=< \overline{\phi}^*, \phi >= 0, \quad < \overline{\phi}^*, \overline{\phi} >= 1.$$

Proposition 3.13. *For the system* (2.6) *with $\tau_2 = 0$, $\tau_1 = \tau_{10}$ result:*

(3.52)

$$\begin{aligned} g_{20} &= \overline{w}_1F_{120} + \overline{w}_2F_{220} + \overline{w}_3F_{320} + \overline{w}_4F_{420} \\ g_{11} &= \overline{w}_1F_{111} + \overline{w}_2F_{211} + \overline{w}_3F_{311} + \overline{w}_4F_{411} \\ g_{02} &= \overline{w}_1F_{102} + \overline{w}_2F_{202} + \overline{w}_3F_{302} + \overline{w}_4F_{402} \\ g_{21} &= \overline{w}_1F_{121} + \overline{w}_2F_{221} + \overline{w}_3F_{321} + \overline{w}_4F_{421} \end{aligned}$$

where

(3.53)

$$\begin{aligned} F_{120} &= -2a_3v_1v_4,\ F_{220} = -F_{120},\ F_{320} = 2a_6v_3v_4e^{\lambda_2\tau_2}, \\ F_{420} &= \frac{a_6 - a_{10}}{2a_6}F_{320} + \frac{a_9}{2a_3}F_{120}, F_{111} = -2a_3Re(v_1\overline{v}_4),\ F_{211} = -F_{111}, \\ F_{311} &= 2a_6Re(\overline{v}_3v_4e^{\lambda_2\tau_1}),\ F_{411} = \frac{a_6 - a_{10}}{2a_6}F_{311} + \frac{a_9}{2a_3}F_{111}, \\ F_{121} &= -a_3(2v_1w_{411}(0) + \overline{v}_1w_{420}(0) + \overline{v}_4w_{120}(0) + 2v_4w_{111}(0)), \\ F_{221} &= -F_{121}, \\ F_{321} &= a_6(2v_3w_{411}(0) + \overline{v}_3w_{420}(0) + \overline{v}_4w_{320}(-\tau_1) + 2v_4w_{311}(-\tau_1)), \\ F_{421} &= \frac{a_6 - a_{10}}{a_6}F_{321} + \frac{a_9}{a_3}F_{121}, \\ F_{102} &= \overline{F}_{120},\ F_{202} = \overline{F}_{220},\ F_{302} = \overline{F}_{320},\ F_{402} = \overline{F}_{420} \end{aligned}$$

and

$$\begin{aligned} w_{20}(\theta) &= (w_{120}(\theta), w_{220}(\theta), w_{320}(\theta), w_{420}(\theta))^T \\ w_{11}(\theta) &= (w_{111}(\theta), w_{211}(\theta), w_{311}(\theta), w_{411}(\theta))^T \end{aligned}$$

are given by

(3.54)

$$\begin{aligned} w_{20}(\theta) &= \frac{g_{20}}{\lambda_1}ve^{\lambda_1\theta} - \frac{\overline{g}_{20}}{3\lambda_1}\overline{v}e^{\lambda_2\theta} + E_1e^{2\lambda_1\theta} \\ w_{11}(\theta) &= \frac{g_{11}}{\lambda_1}ve^{\lambda_1\theta} - \frac{\overline{g}_{11}}{\lambda_1}\overline{v}e^{\lambda_2\theta} + E_2, \quad \theta \in [-\tau_1, 0], \end{aligned}$$

where $E_i = (E_{i1}, E_{i2}, E_{i3}, E_{i4})^T, i = 1, 2$ *are the solutions of the systems*

$$(A + C + e^{2\lambda_1\tau_{10}} B - 2\lambda_1 I)E_1 = -(F_{120}, F_{220}, F_{320}, F_{420})^T$$
$$(A + B + C)E_2 = -(F_{111}, F_{211}, F_{311}, F_{411})^T. \tag{3.55}$$

Therefore, we can compute the following parameters:

$$\begin{aligned} c_{10}(0) &= \frac{i}{2\omega_{10}}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{g_{21}}{2} \\ \mu_{10} &= -\frac{Re\, c_{10}(0)}{Re\, \lambda'(\tau_{10})} \\ \beta_{10} &= 2Re\, c_{10}(0) \\ T_{10} &= -\frac{Im\, c_{10}(0) + \mu_{10} Im\, \lambda'(\tau_{10})}{\omega_{10}}, \end{aligned} \tag{3.56}$$

where

$$\begin{aligned} \lambda'(\tau_{10}) = \frac{d\lambda}{d\tau_1}|_{\tau_1=\tau_{10},\lambda=\lambda_1} &= (\lambda_1(s_3\lambda_1^3 + s_2\lambda_1^2 + s_1\lambda_1 + s_0)) \\ &/((4\lambda_1^3 + 3r_3\lambda_1^2 + 2r_2\lambda_1 + r_1)e^{\lambda_1\tau_{10}} \\ &- r_3\tau_{10}\lambda_1^3 + (3s_3 - \tau_{10}s_2)\lambda_1^2 + (2s_2 - s_1\tau_{10})\lambda_1 - s_0\tau_{10}). \end{aligned} \tag{3.57}$$

In formulas (3.56), μ_{10} determines the direction of the Hopf bifurcation, β_{10} determines the stability of the bifurcating periodic solutions and T_{10} determines the period of the bifurcating periodic solutions.

4. Numerical examples

For the numerical simulations we use Maple 9.5. and the following data: $a_1 = 0.5$, $a_2 = 0.00833$, $a_3 = 0.1$, $a_4 = 0.5$, $a_5 = 5$, $a_6 = 0.2$, $a_7 = 8$, $a_8 = 0.02$, $a_9 = 0.5$, $a_{10} = 0.1$. For this data we obtain the equilibrium point: $x_{03} = 0.1993358131$, $y_{03} = 0.9966790654$, $z_{03} = 0.9960148784$, $p_{03} = 25$. We consider two cases: $\tau_1 = 0$ and $\tau_2 = 0$.

For $\tau_1 = 0$ we obtain: $\omega_{20} = 2.202844776$, $\tau = 0.4280270376$, $\beta_2 = -0.02266361$, $\mu_2 = 0.007144287767$, $T_2 = -0.01127085186$. Then the Hopf bifurcation is supercritical and the bifurcating periodic solutions exist for $\tau_1 > \tau_{20}$; the solutions are orbitally stable and the period of the solution is decreasing.

In the second case, $\tau_2 = 0$, we obtain: $\omega_{10} = 1.628434095$, $\tau_{10} = 0.7350389977$, $\beta_2 = 0.3262802166$, $\mu_2 = -0.1738884119$, $T_2 = 0.04059104967$. Then the Hopf bifurcation is supercritical and the bifurcating periodic solutions exist for $\tau_1 > \tau_{10}$; the solutions are orbitally unstable and the period of the solution is increasing.

5. Conclusion

In this paper, we introduce a model which describes infections diseases and malaria infection with delays. We consider two cases: $\tau_1 = 0$, $\tau_2 > 0$ and $\tau_1 > 0$, $\tau_2 = 0$. By using the time delay as a parameter, it has been proved that the Hopf bifurcation occurs when this parameter passes through a critical value. The case $\tau_1 > 0$, $\tau_2 > 0$ we will analyze in a future paper.

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