Hopf bifurcation analysis of pathogen-immune interaction dynamics with delay kernel

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Abstract

The aim of this paper is to study the steady states of the mathematical models with delay kernels which describe pathogen-immune dynamics of many kinds of infectious diseases. In the study of mathematical models of infectious diseases it is important to predict whether the infection disappears or the pathogens persist. The delay kernel is described by the memory function that reflects the influence of the past density of pathogen in the blood and it is given by a nonnegative bounded function $k$ defined on $[0, \infty)$ and is normated. By using the coefficient of kernel $k$, 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.

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1 Introduction

The purpose of this paper is to study the Hopf bifurcation of pathogen-immune dynamics in the steady states of the mathematical model with delay kernel. Dynamical systems with delay kernel have been studied for population dynamics and neural networks [2].

We introduce a model which describes one of most known infectious diseases, namely malaria infection. Our model is based on the model from [6]. The model, as it was created, without delay, has the feature that the interior equilibrium is always asymptotically stable if it exists. For obtaining the natural behavior which was observed experimentally, i.e. oscillatory behavior, it is needed to make some adjustments to the model. One way is to introduce some extra terms into the equations for a better description of the interaction pathogens-immune system or other way is to introduce the delay. Our contribution to the model lies in introduction of the delay kernel, which is a natural thing to do, because it is obvious for everyone that biological processes do not take place instantaneous.

System (1) without the last term in the third equation, which implies the effect of absorption of the pathogens into uninfected cells, could be used for describing another well-known infectious disease, the HIV infection, as was done in [3,7,10] or other infectious diseases as hepatitis B virus infection [9] or hepatitis C virus infection [7]. Because our model deals with malaria infection in what follows we will say some words about this disease. Malaria ranks high on the list of world health problems by causing massive human and economic loss. The parasite in this disease is called Plasmodium Falciparum and has a high virulence which can cause even death. Malaria has some important features that should be mentioned: first, the amount of variation in disease severity observed in the field is remarkably high, second, the immunity is virtually never sufficient to prevent infection and third, transmission intensity in the field is highly variable both temporally and geographically [4].
More precisely, consider the following system:

\[
\begin{align*}
\dot{x}(t) &= a_1 - a_2 x(t) - a_3 x(t) \int_{-\infty}^{0} z(s) k(t - s) ds \\
\dot{y}(t) &= -a_4 y(t) + a_3 x(t) \int_{-\infty}^{0} z(s) k(t - s) ds \\
\dot{z}(t) &= a_4 a_5 y(t) - a_6 \int_{-\infty}^{0} z(s) k(t - s) ds - a_7 x(t) \int_{-\infty}^{0} z(s) k(t - s) ds,
\end{align*}
\]

where \( a_i, \ i = 1, \cdots, 7 \) are positives constants and the delay kernel, \( k : [0, \infty) \to [0, \infty) \), \( k \) is piecewise continuous, is assumed to satisfy the following properties:

\[
\int_{0}^{\infty} k(s) ds = 1, \quad \int_{0}^{\infty} sk(s) ds < \infty.
\]

It is also assumed that the system (1) is supplemented with initial conditions of the form:

\[
\begin{align*}
x(0) &= x^*, \\
y(0) &= y^*, \\
z(s) &= \varphi_1(s), \quad s \in (-\infty, 0],
\end{align*}
\]

\( \varphi_1 \) is bounded and continuous on \([0, \infty)\).

The model contains three variables: the density of uninfected cells \( x \), the density of infected cells \( y \) and the density of pathogens in blood \( z \). Uninfected cells are recruited at a constant rate \( a_1 \) from the source within the body, such as the bone marrow and have the natural life expectancy of \( \frac{1}{a_1} \) days. Cells are infected by contact with pathogens and turn to infected cells at rate \( a_3 \int_{-\infty}^{0} z(s) k(t - s) ds \). Infected cells die at rate \( a_4 \). The death of the cells results in the release of \( a_5 \) pathogens per an infected cell and these pathogens have a life expectancy of \( \frac{1}{a_6} \). For \( a_7 = 0 \) we obtain the model of HIV infection with delay kernel and for \( a_3 = a_7 \) we obtain the model of malaria infection with delay kernel.
In system (1), if the delay kernel has the form

$$k(s) = \delta(s - \tau), \quad \tau \geq 0,$$

where \( \tau \) is a parameter which denotes the effect of the past memories, then system (1) becomes:

$$\begin{align*}
\dot{x}(t) &= a_1 - a_2 x(t) - a_3 x(t) z(t - \tau) \\
\dot{y}(t) &= -a_4 y(t) + a_3 x(t) z(t - \tau) \\
\dot{z}(t) &= a_4 a_5 y(t) - a_6 z(t - \tau) - a_7 x(t) z(t - \tau) \\
x(0) &= x^*, \quad y(0) = y^*, \quad z(s) = \varphi_1(s), \quad s \in [-\tau, 0]\end{align*}$$

(3)

For \( \tau = 0 \) the system has been studied in [6].

In system (1), if the kernel \( k \) has the form

$$k(s) = qe^{-qs},$$

called weak kernel, where \( q \) is a parameter varying in \((0, \infty)\) which denotes the decay rate of the effect of the post memories, then system (1) becomes:

$$\begin{align*}
\dot{x}(t) &= a_1 - a_2 x(t) - a_3 x(t) u(t) \\
\dot{y}(t) &= -a_4 y(t) + a_3 x(t) u(t) \\
\dot{z}(t) &= a_4 a_5 y(t) - a_6 u(t) - a_7 x(t) u(t) \\
\dot{u}(t) &= q(z(t) - u(t)) \\
x(0) &= x^*, \quad y(0) = y^*, \quad z(s) = z^*, \quad u(0) = z^*\end{align*}$$

(4)

In system (1), if the kernel \( k \) has the form

$$k(s) = q^2 se^{-qs},$$

then system (1) becomes:

$$\begin{align*}
\dot{x}(t) &= a_1 - a_2 x(t) - a_3 x(t) v(t) \\
\dot{y}(t) &= -a_4 y(t) + a_3 x(t) v(t) \\
\dot{z}(t) &= a_4 a_5 y(t) - a_6 v(t) - a_7 x(t) v(t) \\
\dot{u}(t) &= q(z(t) - u(t)) \\
\dot{v}(t) &= q(u(t) - v(t)) \\
x(0) &= x^*, \quad y(0) = y^*, \quad z(0) = z^*, \quad u(0) = z^*, \quad v(0) = z^*.\end{align*}$$

(5)
This paper is organized as follows: in Section 2, the local stability property and Hopf bifurcation of models (3), (4), (5) are discussed and some sufficient conditions for stability are derived. In Section 3, model (1) containing the general kernel is further studied and both the direction and the stability of Hopf bifurcation are analyzed by the normal form theory and the center manifold theorem and some criteria for stability are derived. Then, we consider two cases: in the first case $k$ is delta function and in the second $k = q e^{-q s}$. Numerical simulations will be shown, in order to justify the theoretical results. Finally, conclusions are drawn with further research directions given in Section 5.

2 Local stability analysis and the Hopf bifurcation

In this section, consider the local stability of the equilibrium solution of system (1). From the special nature of the delay kernel (2) embedded in system (1), we found out that an equilibrium solution $(x_0, y_0, z_0)$ of (1) is given by the solution of the system:

\begin{align}
 a_1 - a_2 x - a_3 x z &= 0 \\
 a_4 y - a_3 x z &= 0 \\
 a_4 a_5 y - a_6 z - a_7 x z &= 0.
\end{align} \tag{6}

From (6) it results that if $0 \leq a_7 < a_3 a_5$, $0 < a_2 a_6 < a_1 (a_3 a_5 - a_7)$, then system (6) has two equilibria. The first one is $X_1 = (\frac{a_1}{a_2}, 0, 0)$ and it represents the state in which the pathogens are absent. The second is $X_2 = (x_0, y_0, z_0)$, where

\begin{align}
 x_0 &= \frac{a_6}{a_3 a_5 - a_7}, \quad y_0 = \frac{a_1 (a_3 a_5 - a_7) - a_2 a_6}{a_4 (a_3 a_5 - a_7)}, \quad z_0 = \frac{a_1 (a_3 a_5 - a_7) - a_2 a_6}{a_3 a_6}.
\end{align}

The equilibrium $X_2$ lies in the interior of the first quadrant. Then we say that $X_2$ is an interior equilibrium and represents the state in which the pathogens are present.

In what follows, the equilibrium $(x_0, y_0, z_0)$ is transformed to the origin, so
the system (1) becomes:

\[
\begin{align*}
\dot{u}_1(t) &= -b_1 u_1(t) - b_2 \int_{-\infty}^{0} k(-s) u_3(t + s) ds - b_3 u_1(t) \int_{-\infty}^{0} k(-s) u_3(t + s) ds \\
\dot{u}_2(t) &= b_4 u_1(t) - b_5 u_2(t) + b_2 \int_{-\infty}^{0} k(-s) u_3(t + s) ds + b_3 u_1(t) \int_{-\infty}^{0} k(-s) u_3(t + s) ds \\
\dot{u}_3(t) &= -b_6 u_1(t) + b_7 u_2(t) - b_8 \int_{-\infty}^{0} k(-s) u_3(t + s) ds - b_9 u_1(t) \int_{-\infty}^{0} k(-s) u_3(t + s) ds,
\end{align*}
\]

(7)

where

\[
\begin{align*}
b_1 &= a_2 + a_3 z_0, & b_2 &= a_3 x_0, & b_3 &= a_3, & b_4 &= a_3 z_0, & b_5 &= a_4, \\
b_6 &= a_7 x_0, & b_7 &= a_4 a_5, & b_8 &= a_6 + a_7 x_0, & b_9 &= a_7
\end{align*}
\]

and

\[
\begin{align*}
u_1(t) &= x(t) - x_0, & u_2(t) &= y(t) - y_0, & u_3(t) &= z(t) - z_0.
\end{align*}
\]

Rewrite system (7) in the following matrix form:

\[
\dot{u}(t) = Lu(t) + \int_{-\infty}^{0} F(s) u(t + s) ds + H(u(t)),
\]

where

\[
\begin{align*}
u(t) &= (u_1(t), u_2(t), u_3(t))^T, \\
L &= \begin{pmatrix} -b_1 & 0 & 0 \\
        b_4 & -b_5 & 0 \\
        -b_6 & b_7 & 0 \end{pmatrix}, \\
F(s) &= k(-s) \begin{pmatrix} 0 & 0 & -b_2 \\
                         0 & b_2 & 0 \\
                        0 & 0 & -b_8 \end{pmatrix}, \\
H(u(t)) &= \begin{pmatrix} -b_3 u_1(t) \int_{-\infty}^{0} u_3(t + s) k(-s) ds \\
b_3 u_1(t) \int_{-\infty}^{0} u_3(t + s) k(-s) ds \\
-b_9 u_1(t) \int_{-\infty}^{0} u_3(t + s) k(-s) ds \end{pmatrix}.
\end{align*}
\]

(8)
The associated characteristic equation of the linearized system is given by:
\[
\lambda^3 + p_2 \lambda^2 + p_1 \lambda + (r_2 \lambda^2 + r_1 \lambda + r_0) \int_{-\infty}^{0} k(-s)e^{\lambda s} ds = 0, \tag{9}
\]
where
\[
p_2 = b_1 + b_5, \quad p_1 = b_1 b_5, \quad r_2 = b_8, \quad r_1 = b_8 (b_1 + b_5) - b_2 b_6 - b_2 b_7, \quad r_0 = b_4 b_7 - b_1 b_2 b_7 - b_1 b_3 b_8 - b_2 b_6 b_6.
\]

**Proposition 2.1.** If \( k(s) = \delta(s - \tau) \), then

(i) The characteristic equation (9) is given by
\[
\lambda^3 + p_2 \lambda^2 + p_1 \lambda + (r_2 \lambda^2 + r_1 \lambda + r_0) e^{-\lambda \tau} = 0; \tag{10}
\]

(ii) For \( \tau = 0 \) the characteristic equation (10) is given by
\[
\lambda^3 + m_2 \lambda^2 + m_1 \lambda + m_0 = 0,
\]
where
\[
m_2 = p_2 + r_2, \quad m_1 = p_1 + r_1, \quad m_0 = r_0;
\]

(iii) If \( \tau = 0 \), the equilibrium \( X_2 \) is asymptotically stable if and only if
\[
m_2 > 0, \quad m_1 > 0, \quad m_0 > 0, \quad m_1 m_2 - m_0 > 0;
\]

(iv) For \( \tau = \tau_0 \), given by
\[
\tau_0 = \frac{1}{\omega_0} \arctan \left( \frac{r_1 p_2 \omega_0^3 - (\omega_0^3 - \omega_0 p_1)(r_0 - r_2 \omega_0^2)}{p_2 \omega_0^2 (r_0 - r_2 \omega_0^2) + r_1 \omega_0 (\omega_0^3 - \omega_0 p_1)} \right),
\]
where \( \omega_0 \) is the positive root of the equation
\[
x^6 + n_1 x^4 + n_2 x^2 + n_3 = 0,
\]
with
\[
n_1 = p_2^2 - 2 p_1 - r_2^2, \quad n_2 = p_1^2 - r_1^2 + 2 r_0 r_2, \quad n_3 = -r_0^2,
\]
there is a Hopf bifurcation.
Proposition 2.2. If \( k(s) = q e^{-qs}, s > 0, q > 0 \), then

(i) The characteristic equation (9) is given by:
\[
\lambda^4 + (p_2 + q)\lambda^3 + (p_1 + q(p_2 + r_2))\lambda^2 + q(p_1 + r_1)\lambda + r_0 q = 0;
\]

(ii) The equilibrium \( X_2 \) is asymptotically stable if and only if
\[
D_3(q) = ((p_1 + r_1)(p_2 + r_2) - r_0)q^2 + ((p_1 + r_1)(p_2(p_2 + r_2) - r_1) - 2p_2r_0)q + p_2(p_1 - r_0) > 0;
\]

(iii) If there exists \( q_0 > 0 \) so that \( D_3(q_0) = 0 \) and \( \frac{dD_3(q)}{dq}|_{q=q_0} \neq 0 \), then a Hopf bifurcation occurs at \( X_2 \) as \( q \) passes through \( q_0 \).

3 Stability of the bifurcating periodic solutions: the general kernel case

In this section, the stability of the bifurcating periodic solutions of system (1) with the kernel satisfying (2) is studied. For convenience, in the study of the Hopf bifurcation problem, first we transform system (7) into an operator equation of the form
\[
\dot{u}_t = A(\mu)u_t + R u_t,
\]
where
\[
u = (u_1, u_2, u_3)^T, \quad u_t = u(t + \theta), \quad \theta \in (-\infty, 0), \quad \mu = a - a_0
\]
and operators \( A \) and \( R \) are defined as
\[
A(\mu)\phi(\theta) = \left\{ \begin{array}{ll}
\frac{d\phi(\theta)}{d\theta}, & \theta \in (-\infty, 0) \\
L\phi(\theta) + \int_{-\infty}^{0} F(s)\phi(s)ds, & \theta = 0
\end{array} \right.
\]
\[
R\phi(\theta) = \left\{ \begin{array}{ll}
(0, 0, 0)^T, & \theta \in (-\infty, 0) \\
(-b_3f_1, b_3f_1, -b_9f_1)^T, & \theta = 0
\end{array} \right.
\]
where
\[
f_1 = -\phi_1(0) \int_{-\infty}^{0} k(-s)\phi_3(s)ds,
\]
with \( L, F \) defined in (8).

As in [1], [5], the bifurcating periodic solutions \( x(t, \mu) \) of (1) are indexed by a small parameter \( \varepsilon \geq 0 \). A solution \( x(t, \mu(\varepsilon)) \) has amplitude \( O(\varepsilon) \), period \( T(\varepsilon) \) and nonzero Floquet exponent \( \beta(\varepsilon) \) with \( \beta(0) = 0 \). Under the present assumptions, \( \mu, T \) and \( \beta \) have expansions:

\[
\begin{align*}
\mu &= \mu_2 \varepsilon^2 + \mu_4 \varepsilon^4 + \cdots \\
T &= \frac{2\pi}{\omega} (1 + T_2 \varepsilon^2 + T_4 \varepsilon^4 + \cdots) \\
\beta &= \beta_2 \varepsilon^2 + \beta_4 \varepsilon^4 + \cdots .
\end{align*}
\]

The sign of \( \mu_2 \) determines the direction of bifurcation, while \( \beta_2 \) determines the stability of \( x(t, \mu(\varepsilon)) \): asymptotically orbitally stable if \( \beta_2 < 0 \), but unstable if \( \beta_2 > 0 \).

Next, the question of how to derive the coefficients in these expansions is addressed. For the applications from this paper, only \( \mu_2, \tau_2 \) and \( \beta_2 \) are computed here.

We define the adjoint operator \( A^* \) of \( A \) as:

\[
A^* \psi(s) = \begin{cases} 
-\frac{d\psi(s)}{ds}, & s \in (0, \infty) \\
L^T \psi(0) + \int_{-\infty}^{0} F^T(s) \psi(-s) ds, & s = 0,
\end{cases}
\]

where \( L^T \) and \( F^T \) are transposes of matrices \( L \) and \( F \) respectively.

Note that the operator \( A \) depends on the bifurcation parameter \( a \). According to Propositions 2.1, 2.2, Hopf bifurcation occurs when \( a \) passes through \( a_0 \). Let \( \mu = a - a_0 \). Then, Hopf bifurcation occurs when \( \mu = 0 \). It is therefore reasonable to assume that \( \varphi, \psi : [0, \infty) \to \mathbb{C}^3 \). Define the bilinear form:

\[
< \phi, \psi > = \overline{\psi(0)^T} \phi(0) - \int_{-\infty}^{\theta} \int_{\xi=0}^{\theta} \overline{\psi^T(\xi - \theta)} F(\theta) \phi(\xi) d\xi d\theta.
\]

To determine the Poincare normal form of operator \( A \), we need to calculate the eigenvector \( \phi \) of \( A \) associated with eigenvalue \( \lambda_1 = i\omega_0 \) and the eigenvector \( \phi^* \) of \( A^* \) associated with eigenvalue \( \lambda_2 = \overline{\lambda_1} \).
Proposition 3.1. (i) The eigenvector $\phi$ of $A$ associated with eigenvalue $\lambda_1 = i\omega_0$ is given by $\phi(\theta) = ve^{\lambda_1 \theta}$, $\theta \in (-\infty, 0]$, where $v = (v_1, v_2, v_3)^T$ and

$$v_1 = -b_2(\lambda_1 + b_5)k^1, v_2 = b_2(\lambda_1 + b_1 - b_4)k^1, v_3 = (\lambda_1 + b_1)(\lambda_1 + b_5),$$

where

$$k^1 = \int_{-\infty}^{0} k(-s)e^{\lambda_1 s}ds;$$

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

$$w_1 = \frac{b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)\eta}, \quad w_2 = \frac{1}{\eta}, \quad w_3 = \frac{\lambda_2 + b_5}{b_7\eta},$$

$$\eta = \frac{b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)}v_1 + v_2 + \left(\frac{\lambda_2 + b_5}{b_7}\right) - \left(-b_2\frac{b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)}\right) \eta + b_2 - b_8\frac{\lambda_2 + b_5}{b_7})k^{(-1)}v_3,$$

where

$$k^{(-1)} = \int_{-\infty}^{0} k(-s)e^{\lambda_2 s}ds;$$

(iii) 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 $\Omega_0$ at $\mu = 0$ ($a = a_0$) [1], [5]. Let

$$z(t) = <\phi^*, x_t>$$

$$w(t, \theta) = x_t - 2Re\{z(t)\phi(\theta)\}. $$
On the center manifold $\Omega_0$, $w(t, \theta) = w(z(t), \bar{z}(t), \theta)$, where

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

$z$ and $\bar{z}$ are the local coordinates of the center manifold $\Omega_0$ in the direction of $\phi$ and $\phi^*$, respectively.

For the solution $x_t \in \Omega_0$ of (1), notice that for $\mu = 0$ we have:

$$\dot{z}(t) = \lambda_1 z(t) + <\phi^*, R(\omega + 2\text{Re}\{z(t)\phi(\theta)\})>$$

Rewrite this as

$$\dot{z}(t) = \lambda_1 z(t) + g(z, \bar{z})$$

with

$$g(z, \bar{z}) = \overline{\phi^*(0)^T} R(w(z, z, 0) + 2\text{Re}\{z(t)\phi(0)\})$$

Further, expand the function $g(z, \bar{z})$ on the center manifold $\Omega_0$ in powers of $z$ and $\bar{z}$:

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

**Proposition 3.2.** For the system (1) we have:

(i) 

$$g_{20} = -2b_3v_1v_3(\bar{w}_1 - \bar{w}_2 + \frac{b_9}{b_3}\bar{w}_3)k^1$$

$$g_{11} = -b_3(\bar{v}_1v_3 + v_1\bar{v}_3)(\bar{w}_1 - \bar{w}_2 + \frac{b_9}{b_3}\bar{w}_3)(k^1 + k^{(-1)}) \quad (13)$$

$$g_{02} = -2b_3\bar{v}_1\bar{v}_3(\bar{w}_1 - \bar{w}_2 + \frac{b_9}{b_3}\bar{w}_3)k^{(-1)};$$

(ii) 

$$w_{20}(\theta) = \frac{g_{20}}{\lambda_1}e^{\lambda_1 \theta} - \frac{g_{20}}{3\lambda_1}e^{2\lambda_1 \theta} + E_1 e^{2\lambda_1 \theta}$$

$$w_{11}(\theta) = \frac{g_{11}}{\lambda_1}e^{\lambda_1 \theta} - \frac{g_{11}}{\lambda_1}e^{2\lambda_1 \theta} + E_2,$$
where $E_1, E_2$ are the solutions of the following system:

\[
\begin{align*}
(A + k^{(2)} B - 2\lambda_1 I) E_1 &= b_3 v_1 v_3 k^1 (1, -1, -b_9/b_3^2)^T \\
(A + B) E_2 &= b_3 (\overline{v}_1 v_3 + v_1 \overline{v}_3) (k^1 + k^{(-1)}) (1, -1, -b_9/b_3^2)^T \\
k^{(1)} &= \int_{-\infty}^{0} k(-s) e^{\lambda_1 s} ds, \\
k^{(2)} &= \int_{-\infty}^{0} k(-s) e^{2\lambda_1 s} ds;
\end{align*}
\]

(iii)

\[
g_{21} = -2b_3 (\overline{w}_1 - \overline{w}_2) + b_9 \overline{w}_3 (v_1 \int_{-\infty}^{0} k(-s) w_{311}(s) ds + \\
\frac{1}{2} \overline{v}_1 \int_{-\infty}^{0} k(-s) w_{320}(s) ds + v_3 w_{111}(0) k^1 + \frac{1}{2} \overline{v}_3 w_{120}(0) k^{(-1)}),
\]

with $w_{20}(\theta) = (w_{120}(\theta), w_{220}(\theta), w_{320}(\theta))^T$ and $w_{11}(\theta) = (w_{111}(\theta), w_{211}(\theta), w_{311}(\theta))^T$.

Therefore, we will compute the following parameters:

\[c_1(0) = \frac{i}{2\omega_0} (g_{20} g_{11} - 2|g_{11}|^2 - \frac{1}{3} |g_{02}|^2) + \frac{g_{21}}{2};\]

\[\mu_2 = -\frac{\text{Re} c_1(0)}{\text{Re} \lambda'(a_0)};\]

\[T_2 = -\frac{\text{Im} c_1(0) + \mu_2 \text{Im} \lambda'(a_0)}{\omega_0};\]

\[\beta_2 = 2\text{Re} c_1(0);\]

\[T = \frac{2\pi}{\omega_0} (1 + T_2 \varepsilon^2 + O(\varepsilon^4)), \quad \varepsilon^2 = \frac{a - a_0}{\mu} + O(a - a_0)^2.\]

We have:

**Theorem 3.1.** The sign of $\mu_2$ determines the directions of the Hopf bifurcations: if $\mu_2 > 0 (< 0)$ the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $a > a_0 (< a_0)$. The sign of $\beta_2$ determines the stability of the bifurcation periodic solutions. They are both
asymptotically orbitally stable if $\beta_2 < 0$, but unstable if $\beta_2 > 0$. $T_2$ determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0(<0)$.

If $k(s) = \delta(s - \tau), \tau \geq 0$, then $k^1 = e^{\lambda_1 \tau}, k^{(-1)} = e^{\lambda_2 \tau}, k^2 = e^{2\lambda_1 \tau}$ and $a_0 = \tau_0$, where $\tau_0$ is given by (20). In this case

$$\lambda'(\tau_0) = \left. \frac{d\lambda}{dt} \right|_{\tau=\tau_0, \lambda=\lambda_1} = \frac{\lambda_1 (r_2 \lambda_1^2 + r_1 \lambda_1 + r_0)}{(3\lambda_1^2 + 2p_2 \lambda_1 + p_1)e^{\lambda_1 \tau_0} + 2r_2 \lambda_1 + r_1 - (r_2 \lambda_1^2 + r_1 \lambda_1 + r_0)\tau_0}.$$  

If $k(s) = qe^{-qs}, s > 0, q > 0$, then $k^1 = \frac{q}{\lambda_1 + q}, k^{(-1)} = \frac{q}{\lambda_2 + q}$ and $a_0 = q_0$, where $q_0$ satisfies $D_3(q_0) = 0 (D_3(q_0)$ from Proposition 2.2), $\lambda_1 = i\omega_0, \lambda_2 = \lambda_1$ and $\omega_0$ is given by

$$\omega_0^2 = \frac{q_0(p_1 + r_1)}{p_2 + q_0}.$$  

In this case

$$\lambda'(q_0) = \left. \frac{d\lambda}{dq} \right|_{q=q_0, \lambda=\lambda_1} = -\frac{\lambda^3 + (p_2 + r_2)\lambda_1^2 + (p_1 + r_1)\lambda_1 + r_0}{4\lambda_1^3 + 3(p_2 + q_0)\lambda^2_1 + 2(p_1 + q_0(p_2 + r_2))\lambda_1 + q_0(p_1 + r_1)}.$$  

From (11), (12), (13), (14) it results:

**Proposition 3.3.** If $k(s) = qe^{-qs}, s > 0, q > 0$, then for system (1) we have:

$$v_1 = -\frac{b_2(\lambda_1 + b_5)q_0}{\lambda_1 + q_0}, v_2 = \frac{b_2(\lambda_1 + b_1 - b_4)q_0}{\lambda_1 + q_0}, v_3 = (\lambda_1 + b_1)(\lambda_1 + b_5),$$

$$w_1 = \frac{b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)\eta}, w_2 = \frac{1}{\eta}, w_3 = \frac{\lambda_2 + b_5}{b_7\eta}.$$  

$$\eta = \frac{b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)}\overline{v}_1 + \overline{v}_2 + \left(\frac{\lambda_2 + b_5}{b_7}\right)\frac{-b_2 b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)}$$

$$+ b_2 - b_8 \frac{\lambda_2 + b_5}{b_7}(\lambda_2 + q_0)\overline{v}_3.$$  

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where $E_a = 2$.

Because $\mu_2 > 0$, the Hopf bifurcation is supercritical for $\tau > \tau_0$; as $\beta_2 < 0$ the bifurcating periodic solution is asymptotically orbitally stable; as $T_2 > 0$ the period increases. Here are the computer simulations. Fig.1 represents time vs uninfected cells $(t, x(t))$, Fig.2 time vs infected cells $(t, y(t))$.

4 Numerical simulations

For numerical simulations, we use Maple 9.5. We consider system (3) with $a_1 = 2, a_2 = 0.02, a_3 = 0.5, a_4 = 2, a_5 = 1.5, a_6 = 0.03, a_7 = 0.5$. The equilibrium point is: $x_0 = 0.12, \quad y_0 = 0.99, \quad z_0 = 33.29$.

In the first case $k(s) = \delta(s - \tau)$, we obtain: $\tau_0 = 0.8975032747, \quad \omega_0 = 1.140149275, \quad g_20 = -0.1032034629 + 0.8542910112i, \quad g_{11} = 0.6157126005 - 0.5196432315i, \quad g_{02} = -0.1015565689 + 0.8738154402i, \quad g_{21} = -0.2181868792 + 0.9831278086i, \quad c_1(0) = -0.1197163151 + 0.2827563802i, \quad \mu_2 = 0.2857035314, \quad \beta_2 = -0.2394326302, \quad T_2 = 0.1030243826$.

Because $\mu_2 > 0$, the Hopf bifurcation is supercritical for $\tau > \tau_0$; as $\beta_2 < 0$ the bifurcating periodic solution is asymptotically orbitally stable; as $T_2 > 0$ the period increases. Here are the computer simulations. Fig.1 represents time vs uninfected cells $(t, x(t))$, Fig.2 time vs infected cells $(t, y(t))$,
Fig. 3 time vs pathogens in blood \((t, z(t))\), Fig. 4 pathogens vs infected cells \((z(t), x(t))\), Fig. 5 pathogens vs infected cells \((z(t), y(t))\), Fig. 6 uninfected cells vs infected cells \((x(t), y(t))\).
In the second case $k(s) = qe^{-qs}$, we obtain:

$q_0 = 0.1881852832$, $\omega_0 = 0.1872904846$, $g_{20} = -0.1146541958 - 0.3262916164i$, $g_{11} = 0.2100798781 - 0.2554625514i$, $g_{02} = -0.1034928343 + 0.5915640328i$, $g_{21} = -0.1382064847 - 0.2196567760i$, $c_1(0) = -0.6909931661 - 0.1103278787i$, $\mu_2 = -0.4372331513$, $\beta_2 = -0.1381986332$, $T_2 = 0.8650529366$.

Because $\mu_2 < 0$, the Hopf bifurcation is subcritical for $q > q_0$; as $\beta_2 < 0$ the bifurcating periodic solution is asymptotically orbitally stable; as $T_2 > 0$ the period increase. Here are the computer simulations: Fig.7 represents time vs uninfected cells ($t, x(t)$), Fig.8 time vs infected cells ($t, y(t)$), Fig.9 time vs pathogens in blood ($t, z(t)$), Fig.10 pathogens vs infected cells ($z(t), x(t)$), Fig.11 pathogens vs infected cells ($z(t), y(t)$), Fig.12 uninfected cells vs infected cells ($x(t), y(t)$).
5 Conclusion

In this paper we introduce a model which describes infectious diseases and malaria infection with delay kernel. By using the average time delay as a parameter, it has been proved that the Hopf bifurcation occurs when this parameter passes through a critical value. A similarly study will be made for the models which describe infectious diseases, who takes into account immune response against pathogens and the effect of involvement. This study will be made in a future work.

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