Math. Model. Nat. Phenom.
Vol. 2, No. 1, 2007, pp. 44-61

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 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 and normated function k defined on $[0, \infty)$. By using the coefficient of the 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.

Key words: delay differential equation, stability, Hopf bifurcation, pathogen-immune interaction
AMS subject classification: 34C23, 34C25, 37G05, 37G15, 92D30

1. Introduction

The purpose of this paper is to study the Hopf bifurcation of pathogen-immune dynamics in the steady states of a mathematical model with delay kernel. Dynamical systems with delay kernel

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Article available at http://www.mmnp-journal.org or http://dx.doi.org/10.1051/mmnp:2008010

have been studied for population dynamics and neural networks [3]. Various dynamical models modeling the pathogen-immune interaction have been proposed and investigated ([4,5,7-16]).

We introduce a model which describes one of most known infectious diseases, namely malaria infection. Our model is based on the model from [7]. 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 pathogens-immune system interaction or, other way is to introduce a delay. Our contribution to the model lies in introduction of the delay kernel, which is a natural thing to do, according to the fact that biological processes are not 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 [4,9,10,16] or other infectious diseases as hepatitis B virus infection [13] or hepatitis C virus infection [11].

In what follows, because our model deals with malaria infection, 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. Plasmodium Falciparum is not the only one agent that cause malaria, there are another three, but it is the most common and virulent one, so from now on we will refer to it as malaria agent. 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 [5].

More precisely, consider the following system:

$$\begin{aligned}
\dot{x}(t) &= a_1 - a_2 x(t) - a_3 \int_{-\infty}^{t} x(s)z(s)k(t-s)ds \\
\dot{y}(t) &= -a_4 y(t) + a_3 \int_{-\infty}^{t} x(s)z(s)k(t-s)ds \\
\dot{z}(t) &= a_4 a_5 y(t) - a_6 \int_{-\infty}^{t} z(s)k(t-s)ds - a_7 \int_{-\infty}^{t} x(s)z(s)k(t-s)ds,
\end{aligned} \tag{1.1}$$

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:

$$\int_0^{\infty} k(s)ds = 1, \quad \int_0^{\infty} sk(s)ds < \infty. \tag{1.2}$$

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

$$x(0) = \varphi_1(s), \quad y(0) = y^*, \quad z(s) = \varphi_2(s), \quad s \in (-\infty, 0],$$
$$\varphi_1, \varphi_2 \quad \text{is bounded and continuous on } [0, \infty).$$

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 $a_3 \int_{-\infty}^{t} z(s)k(t-s)ds$. 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 what follows we will consider this infection. Other assumptions for model (1) are: pathogens either die or successfully infect new cells; we are taking into account the absorption of pathogens into uninfected cells; we will discuss only the dynamics of uninfected cells, infected cells and parasites (Plasmodium Falciparum) in the blood of the hosts.

The number of cells implied in our model varies in the manner described below: in the absence of the disease (malaria in our case), the number of uninfected cells (erythrocytes) is quite constant and is given by the difference between the constant rate of production (a_1) and the constant rate of death (a_2). In the presence of the disease the number of erythrocytes decreases because they are infected by malaria agent (Plasmodium Falciparum). This action, i.e. infection, is represented in our model by the last term in the right side of the first equation.

If we are moving to the second equation, describing the variation of the number of infected cells (y) we can notice that the variation is given by the difference between the "production" rate given by the last term from the first equation and the rate of destruction of these cells due to the completion of the cell cycle of the parasite.

The third equation refers to the number of the pathogens in the blood of the hosts (in our case Plasmodium Falciparum). In this case the "production rate" is proportional with the destruction rate of the infected cells. Every infected cell who dies releases a_5 parasites leading to the production rate $a_5 a_4 y(t)$. To obtain the number of pathogens in blood we have to subtract from the total number of the parasites produced, the number of those that dies naturally (second term in the right side of the equation) and also the number of those that disappear from the blood by infecting the erythrocytes (last term of the equation).

We consider that it is not useless to make some comments regarding the delay kernel. It is obvious that the biological processes do not take place instantaneous and of course neither the interactions described by this model make exception. So in every equation, each of them describing a biological process, we will have a delay. In all three we will find the delay in the last term (right side), except the third equation where we can find two terms with delay (the last two). The delay we can find in the last term of all three equations rely on the interaction between the uninfected cells ($x(t)$) and the pathogens ($z(t)$). The process of interaction between uninfected cells and pathogens needs time, because the pathogens have to cross the cell membrane. For a smoother

modeling we choose the type of delay as a kernel delay because in this manner we can better describe the biological process which is a heterogeneous one. By heterogeneous process, we are meaning that the infection, which take place all over the body, is not in the same phase in every cell at a given moment in time: some cells are just infected, others are in the phase of multiplication of the pathogens, and other cells are in the final phase and start to release parasites in the blood. Having this in mind, it is now natural to use an integral form to describe this process with delay, because as it is known, the integral form, in a "raw" way of speaking is a mean of a function on a interval.

The delay kernel is a general form to describe a delay and to support this affirmation we will make some further comments about delay kernel in what follows.

If the delay kernel has the form

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

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

$$\begin{aligned} \dot{x}(t) &= a_1 - a_2 x(t) - a_3 x(t-\tau) z(t-\tau) \\ \dot{y}(t) &= -a_4 y(t) + a_3 x(t-\tau) z(t-\tau) \\ \dot{z}(t) &= a_4 a_5 y(t) - a_6 z(t-\tau) - a_7 x(t-\tau) z(t-\tau) \\ x(0) &= \varphi_1(s), \quad y(0) = y^*, \quad z(s) = \varphi_2(s), \quad s \in [-\tau, 0]. \end{aligned} \tag{1.3}$$

For $\tau = 0$ the system has been studied in [7] and has the following form:

$$\begin{aligned} \dot{x}(t) &= a_1 - a_2 x(t) - a_3 x(t) z(t) \\ \dot{y}(t) &= -a_4 y(t) + a_3 x(t) z(t) \\ \dot{z}(t) &= a_4 a_5 y(t) - a_6 z(t) - a_7 x(t) z(t) \\ x(0) &= x^*, \quad y(0) = y^*, \quad z(s) = \varphi_2(s), \quad s \in [-\tau, 0]. \end{aligned}$$

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 past memories, then system (1) becomes:

$$\begin{aligned} \dot{x}(t) &= a_1 - a_2 x(t) - a_3 x(t) u(t) \\ \dot{y}(t) &= -a_4 y(t) + a_3 x(t) u(t) \\ \dot{z}(t) &= a_4 a_5 y(t) - a_6 u(t) - a_7 x(t) u(t) \\ \dot{u}(t) &= q(x(t) - u(t)) \\ x(0) &= x^*, \quad y(0) = y^*, \quad z(s) = z^*, \quad u(0) = z^*. \end{aligned} \tag{1.4}$$

This paper is organized as follows: in Section 2, the local stability property and Hopf bifurcation of models (3), (4) 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 $k = qe^{-qs}$. Numerical simulations will be shown, in order to justify the theoretical results. Finally, some conclusions are drawn with further research directions 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 of (1) is given by the solution of the system:

$$\begin{aligned} &a_1 - a_2x - a_3xz = 0 \\ &a_4y - a_3xz = 0 \\ &a_4a_5y - a_6z - a_7xz = 0. \end{aligned} \tag{2.1}$$

From (5) it results that if $0 \leq a_7 < a_3a_5$, $0 < a_2a_6 < a_1(a_3a_5 - a_7)$, then system (5) 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

$$x_0 = \frac{a_6}{a_3a_5 - a_7}, \quad y_0 = \frac{a_1(a_3a_5 - a_7) - a_2a_6}{a_4(a_3a_5 - a_7)}, \quad z_0 = \frac{a_1(a_3a_5 - a_7) - a_2a_6}{a_3a_6}.$$

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 system (1) becomes:

$$\begin{aligned} \dot{u}_1(t) &= -b_1u_1(t) - b_2\int_{-\infty}^{0} k(-s)u_3(t+s)ds - b_3\int_{-\infty}^{0} k(-s)u_1(t+s)u_3(t+s)ds \\ \dot{u}_2(t) &= b_4u_1(t) - b_5u_2(t) + b_2\int_{-\infty}^{0} k(-s)u_3(t+s)ds + b_3\int_{-\infty}^{0} k(-s)u_1(t+s)u_3(t+s)ds \\ \dot{u}_3(t) &= -b_6u_1(t) + b_7u_2(t) - b_8\int_{-\infty}^{0} k(-s)u_3(t+s)ds - b_9\int_{-\infty}^{0} k(-s)u_1(t+s)u_3(t+s)ds, \end{aligned} \tag{2.2}$$

where

$$b_1 = a_2 + a_3 z_0, \quad b_2 = a_3 x_0 \quad b_3 = a_3, \quad b_4 = a_3 z_0, \quad b_5 = a_4,$$
$$b_6 = a_7 x_0, \quad b_7 = a_4 a_5, \quad b_8 = a_6 + a_7 x_0, \quad b_9 = a_7$$

and

$$u_1(t) = x(t) - x_0, \quad u_2(t) = y(t) - y_0, \quad u_3(t) = z(t) - z_0.$$

Rewrite system (6) in the following matrix form:

$$\dot{u}(t) = Lu(t) + \int_{-\infty}^{0} F(s)u(t+s)ds + H(u(t)), \tag{2.3}$$

where

$$u(t) = (u_1(t), u_2(t), u_3(t))^T,$$

$$L = \begin{pmatrix} -b_1 & 0 & 0 \\ b_4 & -b_5 & 0 \\ -b_6 & b_7 & 0 \end{pmatrix}, F(s) = k(-s) \begin{pmatrix} 0 & 0 & -b_2 \\ 0 & 0 & b_2 \\ 0 & 0 & -b_8 \end{pmatrix},$$
$$H(u(t)) = \begin{pmatrix} -b_3 \int_{-\infty}^{0} u_1(t+s)u_3(t+s)k(-s)ds \\ b_3 \int_{-\infty}^{0} u_1(t+s)u_3(t+s)k(-s)ds \\ -b_9 \int_{-\infty}^{0} u_1(t+s)u_3(t+s)k(-s)ds \end{pmatrix}. \tag{2.4}$$

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

$$\lambda^3 + p_2\lambda^2 + p_1\lambda + (r_2\lambda^2 + r_1\lambda + r_0) \int_{-\infty}^{0} k(-s)e^{\lambda s}ds = 0, \tag{2.5}$$

where

$$p_2 = b_1 + b_5, \quad p_1 = b_1 b_5, \quad r_2 = b_8, \quad r_1 = b_8(b_1 + b_5) - b_2 b_6 - b_2 b_7$$
$$r_0 = b_4 b_7 - b_1 b_2 b_7 - b_1 b_5 b_8 - b_2 b_5 b_6.$$

It can be directly verified that the following two proposition take place.

Proposition 2..1. *If $k(s) = \delta(s - \tau)$, then*

(i) The characteristic equation (9) is given by

$$\lambda^3 + p_2\lambda^2 + p_1\lambda + (r_2\lambda^2 + r_1\lambda + r_0)e^{-\lambda\tau} = 0; \tag{2.6}$$

(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

$$m_2 > 0, \quad m_1 > 0, \quad m_0 > 0, \quad m_1m_2 - m_0 > 0;$$

(iv) For $\tau = \tau_0$, given by

$$\tau_0 = \frac{1}{\omega_0}\arctan\frac{r_1p_2\omega_0^3 - (\omega_0^3 - \omega_0p_1)(r_0 - r_2\omega_0^2)}{p_2\omega_0^2(r_0 - r_2\omega_0^2) + r_1\omega_0(\omega_0^3 - \omega_0p_1)},$$

where ω_0 is the positive root of the equation

$$x^6 + n_1x^4 + n_2x^2 + n_3 = 0,$$

with

$$n_1 = p_2^2 - 2p_1 - r_2^2, \quad n_2 = p_1^2 - r_1^2 + 2r_0r_2, \quad n_3 = -r_0^2,$$

there is a Hopf bifurcation.

Proposition 2..2. *If $k(s) = qe^{-qs}$, $s > 0$, $q > 0$, then*

(i) The characteristic equation (9) is given by:

$$\lambda^4 + (p_2 + q)\lambda^3 + (p_1 + q(p_2 + r_2))\lambda^2 + q(p_1 + r_1)\lambda + r_0q = 0;$$

(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.

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, we consider the abstract differential equation [1]:

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

where

$$u = (u_1, u_2, u_3)^T, u_t(\theta) = u(t+\theta), \theta \in (-\infty, 0], \dot{u}_t(\theta) = \frac{du(t+\theta)}{dt}, \mu = a - a_0.$$

The operators A and R are defined as:

$$A(\mu)\phi(\theta) = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \theta \in (-\infty, 0) \\ L\phi(0) + \int\limits_{-\infty}^{0} F(s)\phi(s)ds, & \theta = 0 \end{cases}$$

$$R(\mu)\phi(\theta) = \begin{cases} (0,0,0)^T, & \theta \in (-\infty, 0) \\ (-b_3 f_1, b_3 f_1, -b_9 f_1)^T, & \theta = 0 \end{cases}$$

where

$$f_1 = -\int\limits_{-\infty}^{0} k(-s)\phi_1(s)\phi_3(s)ds,$$

with L, F defined in (8).

With respect to the parameter a_0 we will study the Hopf bifurcation.

As in [2], [6], 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, μ, T and β have expansions:

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

The sign of μ_2 determines the direction of bifurcation, while β_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 μ_2, τ_2 and β_2 are computed here.

We define the adjoint operator A^* of A as:

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

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

Note that the operator A depends on the system 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:

$$< \phi, \psi >= \overline{\psi(0)}^T \phi(0) - \int\limits_{\theta=-\infty}^{0} \int\limits_{\xi=0}^{\theta} \overline{\psi}^T(\xi - \theta)F(\theta)\phi(\xi)d\xi d\theta.$$

To determine the Poincare normal form of operator A, we need to calculate the eigenvector ϕ of A associated with eigenvalue $\lambda_1 = i\omega_0$ and the eigenvector ϕ^* of A^* associated with eigenvalue $\lambda_2 = \overline{\lambda_1}$. We can easily obtain:

Proposition 3..1. *(i) The eigenvector ϕ 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*

$$v_1 = -b_2(\lambda_1 + b_5)k^1, v_2 = b_2(\lambda_1 + b_1 - b_4)k^1, v_3 = (\lambda_1 + b_1)(\lambda_1 + b_5), \tag{3.1}$$

where

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

(ii) The eigenvector ϕ^* 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

$$\begin{aligned} w_1 &= \frac{b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)\eta}, \quad w_2 = \frac{1}{\eta}, \quad w_3 = \frac{\lambda_2 + b_5}{b_7\eta} \\ \eta &= \frac{b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)}\overline{v}_1 + \overline{v}_2 + (\frac{\lambda_2 + b_5}{b_7} - (-b_2\frac{b_4b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)} \\ &+ b_2 - b_8\frac{\lambda_2 + b_5}{b_7})k^{(-1)})\overline{v}_3, \end{aligned} \tag{3.2}$$

where

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

(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 manifold Ω_0 at $\mu = 0$ ($a = a_0$) [2], [6]. Let

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

On the center manifold Ω_0, $w(t,\theta) = w(z(t), \overline{z}(t), \theta)$, where

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

z and $\overline{z}$ are the local coordinates of the center manifold Ω_0 in the direction of ϕ and ϕ^*, respectively. For the solution $x_t \in \Omega_0$ of (1), notice that for $\mu = 0$ we have:

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

Rewrite this as

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

with

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

Further, expand the function $g(z, \overline{z})$ on the center manifold Ω_0 in powers of z and $\overline{z}$:

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

Proposition 3..2. *For the system (1) we have:*

(i)

$$\begin{aligned} g_{20} &= -2b_3v_1v_3(\overline{w}_1 - \overline{w_2} + \frac{b_9}{b_3}\overline{w}_3)k^{(2)} \\ g_{11} &= -b_3(\overline{v}_1v_3 + v_1\overline{v_3})(\overline{w}_1 - \overline{w}_2 + \frac{b_9}{b_3}\overline{w}_3) \\ g_{02} &= -2b_3\overline{v}_1\overline{v_3}(\overline{w}_1 - \overline{w}_2 + \frac{b_9}{b_3}\overline{w}_3)k^{(-2)}; \end{aligned} \tag{3.3}$$

(ii)

$$\begin{aligned} w_{20}(\theta) &= \frac{g_{20}}{\lambda_1}ve^{\lambda_1\theta} - \frac{\overline{g_{20}}}{3\lambda_1}\overline{v}e^{\lambda_2\theta} + E_1e^{2\lambda_1\theta} \\ w_{11}(\theta) &= \frac{g_{11}}{\lambda_1}ve^{\lambda_1\theta} - \frac{\overline{g_{11}}}{\lambda_1}\overline{v}e^{\lambda_2\theta} + E_2, \end{aligned}$$

where E_1, E_2 are the solutions of the following system:

$$(A + k^{(2)}B - 2\lambda_1 I)E_1 = b_3 v_1 v_3 k^{(2)}(1, -1, -b_9/b_3^2)^T$$
$$(A + B)E_2 = b_3(\overline{v}_1 v_3 + v_1 \overline{v}_3)(1, -1, -b_9/b_3^2)^T$$
$$k^{(2)} = \int_{-\infty}^{0} k(-s)e^{2\lambda_1 s}ds, k^{(-2)} = \int_{-\infty}^{0} k(-s)e^{2\lambda_2 s}ds;$$

(iii)

$$g_{21} = -2b_3(\overline{w}_1 - \overline{w_2} + \frac{b_9}{b_3}\overline{w}_3)(v_1 \int_{-\infty}^{0} k(-s)w_{311}(s)e^{\lambda_1 s}ds +$$
$$+ \frac{1}{2}\overline{v}_1 \int_{-\infty}^{0} k(-s)w_{320}(s)e^{\lambda_2 s}ds + v_3 \int_{-\infty}^{0} k(-s)w_{111}(s)e^{\lambda_1 s}ds + \quad (3.4)$$
$$+ \overline{v}_3 \int_{-\infty}^{0} k(-s)w_{120}(s)e^{\lambda_2 s}ds),$$

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:

$$c_1(0) = \frac{i}{2\omega_0}(g_{20}g_{11} - 2|g_{11}|^2 - \frac{1}{3}|g_{02}|^2) + \frac{g_{21}}{2}$$
$$\mu_2 = -\frac{Re\, c_1(0)}{Re\, \lambda'(a_0)}$$
$$T_2 = -\frac{Im\, c_1(0) + \mu_2 Im\, \lambda'(a_0)}{\omega_0}$$
$$\beta_2 = 2Re\, c_1(0)$$
$$T = \frac{2\pi}{\omega_0}(1 + T_2\varepsilon^2 + O(\varepsilon^4)), \quad \varepsilon^2 = \frac{a - a_0}{\mu} + O(a - a_0)^2.$$

We have:

Theorem 3.1. The sign of μ_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 β_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 $k^{(2)}=e^{2\lambda_1\tau}$ and $a_0=\tau_0$, where τ_0 is given by Proposition 2.1. In this case

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

If $k(s)=qe^{-qs},s>0,q>0$, then $k^{(2)}=\frac{q}{2\lambda_1+q}$, $k^{(-2)}=\frac{q}{2\lambda_2+q}$and $a_0=q_0$, where q_0 satisfies $D_3(q_0)=0$ ($D_3(q_0)$ from Proposition 2.2), $\lambda_1=i\omega_0$, $\lambda_2=\overline{\lambda_1}$ and ω_0 is given by

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

In this case

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

From (10), (11), (12), (13), (14) it results:

Proposition 3..3. *If $k(s)=\delta(s-\tau)$, $\tau\geq 0$, then for system (4) we have:*

$$v_1=-b_2(\lambda_1+b_5)e^{\lambda_1\tau},\ v_2=b_2(\lambda_1+b_1-b_4)e^{\lambda_1\tau},\ v_3=(\lambda_1+b_1)(\lambda_1+b_5),$$
$$w_1=\frac{b_4b_7-b_6(\lambda_2+b_5)}{b_7(\lambda_2+b_1)\eta},\ w_2=\frac{1}{\eta},\ w_3=\frac{\lambda_2+b_5}{b_7\eta}$$
$$\eta=\frac{b_4b_7-b_6(\lambda_2+b_5)}{b_7(\lambda_2+b_1)}\overline{v}_1+\overline{v}_2+(\frac{\lambda_2+b_5}{b_7}-(-b_2\frac{b_4b_7-b_6(\lambda_2+b_5)}{b_7(\lambda_2+b_1)}$$
$$+b_2-b_8\frac{\lambda_2+b_5}{b_7})e^{\lambda_2\tau})\overline{v}_3$$
$$g_{20}=-2b_3v_1v_3(\overline{w}_1-\overline{w_2}+\frac{b_9}{b_3}\overline{w}_3)e^{2\lambda_1\tau}$$
$$g_{11}=-b_3(v_1\overline{v}_3+\overline{v}_1v_3)(\overline{w}_1-\overline{w}_2+\frac{b_9}{b_3}\overline{w}_3)$$
$$g_{02}=-2b_3\overline{v}_1\overline{v_3}(\overline{w}_1-\overline{w}_2+\frac{b_9}{b_3}\overline{w}_3)e^{2\lambda_2\tau}$$
$$g_{21}=-2b_3(\overline{w}_1-\overline{w}_2+\frac{b_9}{b_3}\overline{w}_3)[v_1(\frac{g_{11}v_3}{\lambda_1}e^{2\lambda_2\tau}-\frac{\overline{g}_{11}\overline{v}_3}{\lambda_1}+E_{32}e^{\lambda_1\tau})$$
$$+\frac{1}{2}\overline{v}_1(\frac{g_{20}v_3}{\lambda_1}-\frac{\overline{g}_{20}\overline{v}_3}{3\lambda_1}e^{2\lambda_2\tau}+E_{31}e^{\lambda_1\tau})$$
$$+v_3(\frac{g_{11}e^{2\lambda_2\tau}v_1}{\lambda_1}-\frac{\overline{g}_{11}}{\lambda_1}\overline{v}_1+E_{12}e^{\lambda_1\tau})+\frac{1}{2}\overline{v}_3(\frac{g_{20}v_1}{\lambda_1}-\frac{\overline{g}_{20}\overline{v}_1}{3\lambda_1}e^{2\lambda_2\tau}+E_{11}e^{\lambda_1\tau})],$$

where $E_1 = (E_{11}, E_{21}, E_{31})^T$, $E_2 = (E_{12}, E_{22}, E_{32})^T$ *satisfy the systems:*

$$(A + e^{2\lambda_1\tau}B - 2\lambda_1 I)E_1 = b_3 v_1 v_3 e^{2\lambda_1\tau}(1, -1, -\frac{b_9}{b_3^2})^T$$
$$(A + B)E_2 = b_3(\overline{v}_1 v_3 + v_1\overline{v}_3)(1, -1, -\frac{b_9}{b_3^2})^T.$$

Using (11), (12), (13), (14) we have:

Proposition 3..4. *If* $k(s) = qe^{-qs}$, $s > 0$, $q > 0$, *then for system (5) we have:*

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

$$w_1 = \frac{b_4 b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)\eta},\ w_2 = \frac{1}{\eta},\ w_3 = \frac{\lambda_2 + b_5}{b_7\eta}$$

$$\eta = \frac{b_4 b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)}\overline{v}_1 + \overline{v}_2 + (\frac{\lambda_2 + b_5}{b_7} - (-b_2\frac{b_4 b_7 - b_6(\lambda_2 + b_5)}{b_7(\lambda_2 + b_1)}$$
$$+ b_2 - b_8\frac{\lambda_2 + b_5}{b_7})\frac{q_0}{\lambda_2 + q_0})\overline{v}_3$$

$$g_{20} = -2b_3 v_1 v_3(\overline{w}_1 - \overline{w_2} + \frac{b_9}{b_3}\overline{w}_3)\frac{q_0}{2\lambda_1 + q_0}$$
$$g_{11} = -b_3(\overline{v}_1 v_3 + v_1\overline{v_3})(\overline{w}_1 - \overline{w}_2 + \frac{b_9}{b_3}\overline{w}_3)$$
$$g_{02} = -2b_3\overline{v}_1\overline{v_3}(\overline{w}_1 - \overline{w}_2 + \frac{b_9}{b_3}\overline{w}_3)\frac{q_0}{2\lambda_2 + q_0}$$

$$g_{21} = -2b_3(\overline{w}_1 - \overline{w}_2 + \frac{b_9}{b_3}\overline{w}_3)[v_1(\frac{g_{11}q_0}{\lambda_1(2\lambda_1 + q_0)}v_3 - \frac{\overline{g}_{11}}{\lambda_1}\overline{v}_3 + E_{32}\frac{q_0}{\lambda_1 + q_0})+$$
$$+ \frac{1}{2}\overline{v}_1(\frac{g_{20}}{\lambda_1}v_3 - \frac{\overline{g}_{20}q_0}{3\lambda_1(2\lambda_2 + q_0)}\overline{v}_3 + E_{31}\frac{q_0}{\lambda_1 + q_0})+$$
$$+ v_3(\frac{g_{11}}{\lambda_1}v_1\frac{q_0}{2\lambda_1 + q_0} - \frac{\overline{g}_{11}}{\lambda_1}\overline{v}_1 + E_{12}\frac{q_0}{\lambda_1 + q_0}) + \frac{1}{2}\overline{v}_3(\frac{g_{20}v_1}{\lambda_1} - \frac{\overline{g}_{11}\overline{v}_1}{3\lambda_1}\frac{q_0}{2\lambda_2 + q_0}+$$
$$+ E_{11}\frac{q_0}{\lambda_1 + q_0})],$$

where $E_1 = (E_{11}, E_{21}, E_{31})^T$, $E_2 = (E_{12}, E_{22}, E_{32})^T$ *satisfy the systems:*

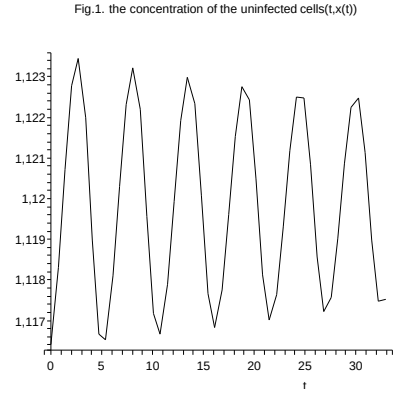
$$(A + \frac{q_0}{2\lambda_1 + q_0}B - 2\lambda_1 I)E_1 = b_3 v_1 v_3\frac{q_0}{2\lambda_1 + q_0}(1, -1, -\frac{b_9}{b_3^2})^T$$
$$(A + B)E_2 = b_3(\overline{v}_1 v_3 + v_1\overline{v}_3)(1, -1, -\frac{b_9}{b_3^2})^T.$$

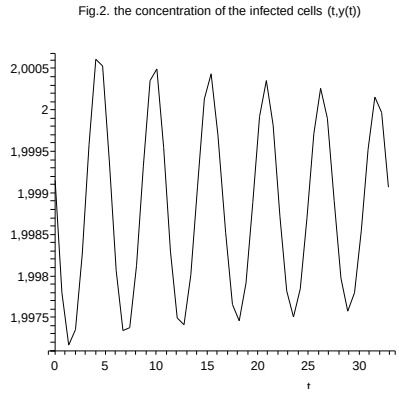
4. Numerical simulations

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: $x_0 = 0.12, \quad y_0 = 0.99, \quad z_0 = 33.29$.

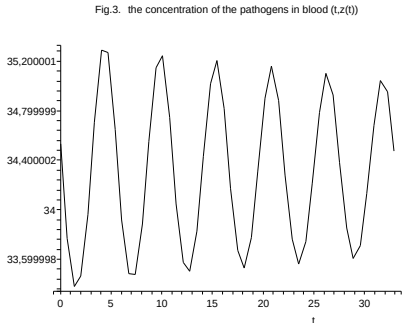
In the first case $k(s) = \delta(s - \tau)$, we obtain: $\tau_0 = 0.81$, $\omega_0 = 1.14$, $g_{20} = -2.41 + 4.73i$, $g_{11} = 3.43 + 0.11i$, $g_{02} = -2.38 - 4.74i$, $g_{21} = -170.67 + 18.30i$, $c_1(0) = -101.55 - 32.18i$, $\mu_2 = 223.34$, $\beta_2 = -203.11$, $T_2 = 129.39$.

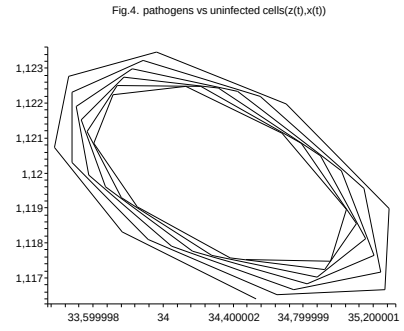
Because $\mu_2 > 0$, the Hopf bifurcation is supercritical for $\tau > \tau_0$; as $\beta_2 < 0$ the bifurcating periodic solution is asymptotically orbitally stable; as $T_2 > 0$ the period increases. We have the following figures: Fig.1 represents the concentration of the uninfected cells $(t, x(t))$, Fig.2 the concentration of the infected cells $(t, y(t))$, Fig.3 the concentration of the pathogens in blood $(t, z(t))$, Fig.4 pathogens vs uninfected cells $(z(t), x(t))$, Fig.5 pathogens vs infected cells $(z(t), y(t))$, Fig.6 uninfected cells vs infected cells $(x(t), y(t))$.



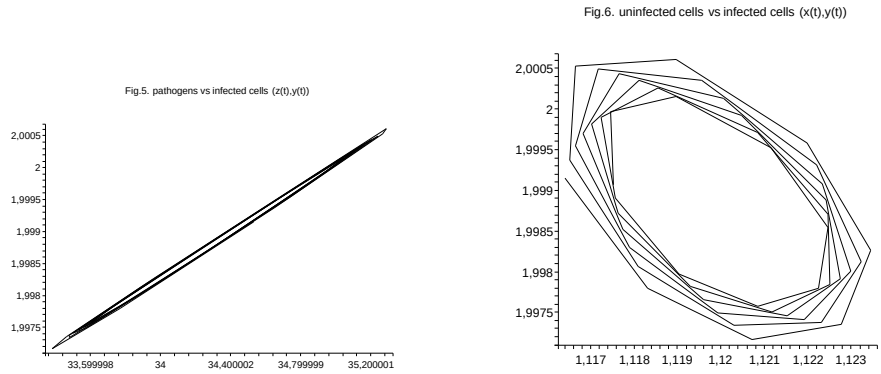


Figures 1 (left) and 2 (right).





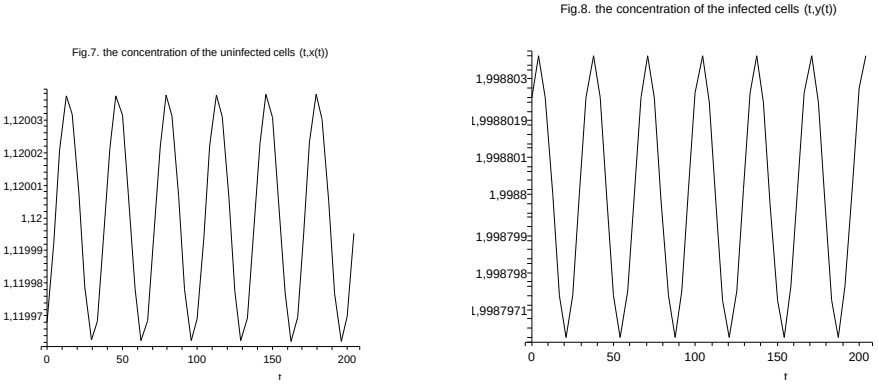
Figures 3 (left) and 4 (right).



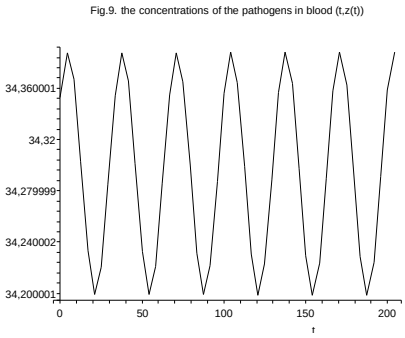
Figures 5 (left) and 6 (right).

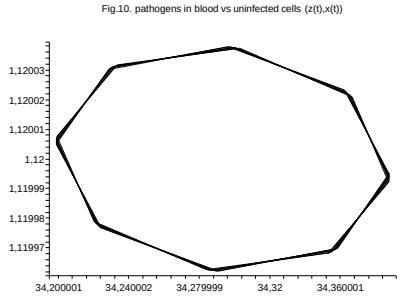
In the second case $k(s) = qe^{-qs}$, we obtain: $q_0 = 0.18$, $\omega_0 = 0.18$, $g_{20} = -0.23 - 0.95i$, $g_{11} = 0.45$, $g_{02} = -0.23 + 0.85i$, $g_{21} = 1.72 + 0.35i$, $c_1(0) = 0.86 + 0.17i$, $\mu_2 = 7.90$, $\beta_2 = 1.72$, $T_2 = -143.55$.

Because $\mu_2 > 0$, the Hopf bifurcation is supercritical for $q > q_0$; as $\beta_2 > 0$ the bifurcating periodic solution is asymptotically orbitally unstable; as $T_2 < 0$ the period decreases. We have the following figures: Fig.7 represents the concentration of the uninfected cells $(t, x(t))$, Fig.8 the concentration of the infected cells $(t, y(t))$, Fig.9 the concentration of the pathogens in blood $(t, z(t))$, Fig.10 pathogens vs uninfected cells $(z(t), x(t))$, Fig.11 pathogens vs infected cells $(z(t), y(t))$, Fig.12 uninfected cells vs infected cells $(x(t), y(t))$.

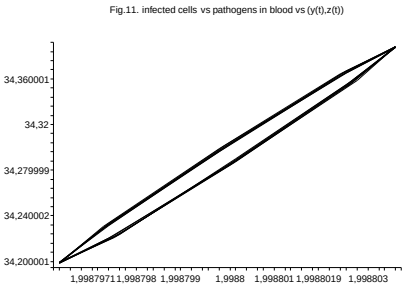


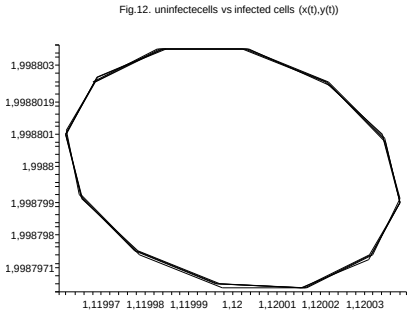
Figures 7 (left) and 8 (right).





Figures 9 (left) and 10 (right).





Figures 11 (left) and 12 (right).

5. Conclusion

In this paper we introduce a model with delay kernel which describes infectious diseases and malaria infection, in particular. 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. The biological meaning of this mathematical property of the model implies that the infection does not disappear, the immune system persists and the disease(in our case malaria) varies periodically. This finding is biologically consistent, in reality malaria does vary periodically. We also have to emphasized that the introduction of the delay in the model plays a key role, without it the interior equilibrium of the system is stable as it was shown in [7]. In the subsequent works we intend to take into account the immune response to pathogens and the effect of involvement of the uninfected cells in the immune response to pathogens.

Acknowledgements

We thank professor Vitaly Volpert for his support and his helpful advice. This work is supported by Grant no 53(2006), ”Mathematical models in hematology and P53-Mdm2 dynamics with distributed time”, The National University Research Council from Ministry of Education and Research of Romania.

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