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Analysis of Pathogen-Immune Interaction Dynamics with Three Time delays

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Abstract. Mathematical model for the effect of pathogen infection model with three delays are proposed and analyzed. Some analytical results on the global stability of pathogen free equilibrium and pathogen present equilibrium are obtained. The stability/instability of the positive steady state and associated Hopf bifurcation are investigated by analyzing the characteristic equations.

Key words: Pathogen, Bifurcation, Delays, Global stability, Lyapunov functionals.

AMS Subject classification: 92B05, 92B99, 34C23, 93D30, 34D23.

1. Introduction

Many works have been developed for various infectious diseases using different types of delay differential equation models [1–9]. Simple models are useful for verifying the various hypotheses and for determining the method of medical treatments. In the last few decades some mathematical models have been developed to understand the dynamics of interactions of pathogens with host's immune response in vivo. This has helped us to predict reduction of viral load or eradication of infection and to get a better insight of spread of infection within the body. The mechanisms of immune response and pathogen interaction are discussed by Denise [10] and the references cited therein. The loss of pathogens or effect of absorption has not been considered in pathogen-immune interaction

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models [10–12]. Consider the basic mathematical model for HIV infection containing the density of uninfected cells, that of infected cells, and that of virus cells in [11]. They also present models which incorporate the effect of the cell-mediated immunity to this model. Similarly, we refer the reader to Perelson and Nelson [13] for other models of HIV infection. For instance, Nowak et. al. [14] and Neumann et al. [15] present similar models for hepatitis B virus (HBV) infection, and hepatitis C virus (HCV) infection which have been studied respectively. In recent, some viral infection with mathematical models along with therapy intervention have been studied in [4, 16–20].

Murase et al. [21] proposed a mathematical model with immune response and absorption of pathogens into uninfected cells. They studied the local stability of equilibria to get an insight of the persistence of infection and considered different cases in their models. Firstly they considered the basic virus dynamics model and then in the next model, they incorporated immune response and ignored the effect of absorption. Further, in third case they incorporated the effect of absorption of pathogens into uninfected cells and found that absorption of pathogens may disturb the stability of interior equilibrium point. Recently, B. Dubey et. al., [22] investigated the intracellular pathogen-immune interaction with cure rate. They observed that the effect of cure in infected cells through non-cytolytic process has also been observed and found a decrease in infected cells and subsequent increase in uninfected cells.

The purpose of this paper is to study the stability of the equilibria, or the steady states, of the mathematical models which describe pathogen-immune dynamics. Motivated by the above work [21], we analyze global stability analysis of pathogen-immune dynamics with three discrete delays, we consider our model only for the loss of pathogens by the absorption is ignored. Because, absorption of pathogens may disturb the stability of interior equilibrium point.

The rest of this paper is organized as follows: In the next section, we analyze the positivity and boundedness of pathogen dynamics. We discuss the local and global stability of pathogen-immune dynamical model in Section 3. Finally, we draw our conclusions in Section 4.

2. Mathematical model

In the beginning, we introduce one of them, which is developed by Nowak and Bangham [11], and is used as a model of HIV infection. The model contains three variables: the density of uninfected cells x, the density of infected cells y and the density of pathogen's in blood p. Uninfected cells are recruited at a constant rate s from the source within the body, such as the bone marrow, and have the natural life expectancy of $1/d$ days. Cells are infected by contact with pathogen's, and turn to infected cells at rate βp. Infected cells die at rate a. Death of the cell results in the release of r pathogen's per an infected cell, and these pathogen's have a life-expectancy $1/b$ in the blood. Pathogens either die or successfully infect new cells. The amount of the absorption of pathogens into uninfected cells is small compared to those of decrease of pathogens in the case of HIV [23], and Nowak and Bangham [11] also ignore the loss of pathogens due to the absorption. These assumptions lead to the following system of differential equations:

$$\begin{aligned} \dot{x} &= s - dx - \beta xp, \\ \dot{y} &= \beta xp - ay, \\ \dot{p} &= ary - bp. \end{aligned} \tag{1}$$

Now, we consider immune response against pathogen's. Here we take only humoral immunity into account. When pathogen's go into blood, the B cells are activated and secrete antibody. Immune system removes pathogen's in blood with the aid of antibody. Here we take only the loss of pathogen's by the absorption is ignored and also we added the time delay into the above model as follows:

$$\begin{aligned} \dot{x} &= s - dx - \beta xp, \\ \dot{y} &= \beta x(t-\tau_1)p(t-\tau_1) - ay, \\ \dot{p} &= ary(t-\tau_2) - bp - \mu pz, \\ \dot{z} &= kp(t-\tau_3)z(t-\tau_3) - cz, \end{aligned} \tag{2}$$

where we represent the density of the pathogen's-specific lymphocytes by a new variable z. The pathogen's are removed at rate μz by the immune system. The

pathogen's-specific lymphocytes proliferate at rate kp by contact with the pathogen's, and die at rate c. τ_1 represents the time delay between uninfected cells by contact with pathogen's. τ_2 represents the period between complete production of pathogens, τ_3 describes the time delay between immune cells by contact with pathogen's.

2.1. **Positiveness of the solution.** Let $\tau_0 = \max\{\tau_1, \tau_2, \tau_3\}$; we denote by $C = C([-\tau_0, 0], \mathbb{R}^4)$ the Banach space of continuous real-valued functions on the interval $[-\tau_0, 0]$ with norm

$$||\phi|| = \sup_{-\tau \le \theta \le 0} |\phi(\theta)|, \quad \text{for } \phi \in C.$$

The non negative cone of C is defined as

$$C^+ = C([-\tau_0, 0], \mathbb{R}^4_+).$$

The initial conditions for system (2) are chosen at $t = 0$ as

$$\phi \in C^+, \ \phi = \{\phi_1, \phi_2, \phi_3, \phi_4\}, \ \phi_i > 0, \ i = 1, 2, 3, 4.$$

Theorem 2.1. *All solutions of system (2) are positive and bounded in C^+, for all $t > 0$. Furthermore, all solutions eventually enter and remain in the following bounded region:*

$$\Gamma = \left\{ (x, y, p, z) \in C^+ : \left|\left| x + y + \frac{1}{2r}p + \frac{\mu}{2kr}z \right|\right| \le \frac{s}{\tilde{q}} + \epsilon \right\}$$

where $\tilde{q} = \min\{d, \frac{a}{2}, b, c\}$, and ϵ is an arbitrarily small positive number.

Proof. It can easily show that $x(t)$ is positive, we proceed by contradiction. Let t_0 be the first value of time such that $x(t_0) = 0$, so $x(t) > 0$ for all $0 \le t < t_0$. By the first equation of the system (2) see that $\dot{x}(t_0) = s > 0$ which is a contradiction to $x(t_0) = 0, \ x(t) > 0$ for all $0 \le t < t_0$. It follows that $x(t)$ is always positive. With a similar argument, we see that $y(t), \ p(t)$ and $z(t)$ are positive for $t > 0$.
Next we prove the ultimate boundedness of the solutions, we define

$$\Omega(t) = x(t) + y(t + \tau_1) + \frac{1}{2r}p(t + \tau_1 + \tau_2) + \frac{\mu}{2kr}z(t + \tau_1 + \tau_2 + \tau_3)$$

and $\tilde{q} = \min\{d, \frac{a}{2}, b, c\}$. By non-negativity of the solution, it follows that

$$\begin{aligned}\dot{\Omega}(t) &= s - \Big(dx(t) + \frac{a}{2}y(t+\tau_1) + \frac{b}{2r}p(t+\tau_1+\tau_2) + \frac{\mu}{2kr}cz(t+\tau_1+\tau_2+\tau_3)\Big) \\ &< s - \tilde{q}\Omega(t).\end{aligned}$$

This implies that $\Omega(t)$ is bounded. Thus

$$\lim_{t\to\infty}\Big(x(t) + y(t+\tau_1) + \frac{1}{2r}p(t+\tau_1+\tau_2) + \frac{\mu}{2kr}z(t+\tau_1+\tau_2+\tau_3)\Big) \leq \frac{s}{\tilde{q}}.$$

Therefore $x(t),\ y(t),\ p(t)$ and $z(t)$ are ultimately bounded in C^+. □

The basic reproduction number:

The basic reproduction number, denoted R_0, is 'the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual' [24]. If $R_0 < 1$, then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection cannot grow. Conversely, if $R_0 > 1$, then each infected individual produces, on average, more than one new infection, and the disease can invade the population. Now, we will calculate the basic reproduction number of the system (2). Let $X = (x, y, p, z)^T$, then the system (2) can be written as

$$\frac{dX}{dt} = \mathscr{F}(X) - \mathscr{V}(X),$$

where

$$\mathscr{F}(X) = \begin{bmatrix} \beta xp \\ 0 \\ 0 \\ 0 \end{bmatrix},$$

$$\mathscr{V}(X) = \begin{bmatrix} ay \\ -ary + p + \mu pz \\ -kpz + cz \\ -s + dx \end{bmatrix}.$$

We can get,

$$\mathscr{F} = \begin{bmatrix} 0 & \beta x_0 \\ 0 & 0 \end{bmatrix}, \quad \mathscr{V} = \begin{bmatrix} a & 0 \\ -ar & b \end{bmatrix}.$$

giving

$$\mathscr{V}^{-1} = \begin{bmatrix} \frac{1}{a} & 0 \\ \frac{r}{b} & \frac{1}{b} \end{bmatrix}.$$

$\mathscr{F}\mathscr{V}^{-1}$ is the next generation matrix for model (2). It then follows that the spectral radius of matrix $\mathscr{F}\mathscr{V}^{-1}$ is, $\rho(\mathscr{F}\mathscr{V}^{-1}) = R_0 = \frac{\beta sr}{db}$. According to Theorem 2 in [25], the reproduction number of model (2) is

$$R_0 = \frac{\beta sr}{db}. \tag{3}$$

It is easy to see that if $R_0 < 1$, then the pathogen free equilibrium $I_0(x_0, 0, 0, 0)$ (where $x_0 = \frac{s}{d}$) is the unique steady state, corresponding to the extinction of the pathogen free equilibrium.

Now we have the following result for concerning the existence of equilibria.

Theorem 2.2. *If $R_0 > 1$, then the system (2) has a pathogen present equilibrium $I_1(x^*, y^*, p^*, z^*)$ (i.e., $x^* > 0, y^* > 0, p^* > 0, z^* > 0$) where x^*, y^*, p^* and z^* are given in the proof.*

Proof. If $R_0 > 1$, then the system (2) becomes as follows,

$$\begin{aligned} s - dx^* - \beta x^* p^* &= 0, \\ \beta x^* p^* - ay^* &= 0, \\ ary^* - bp^* - \mu p^* z^* &= 0, \\ kp^* z^* - cz^* &= 0. \end{aligned} \tag{4}$$

From the above equation (4), we easily get

$$\begin{aligned} x^* &= \frac{sk}{kd + \beta c}, \\ y^* &= \frac{\beta c}{ka} x^*, \\ p^* &= \frac{c}{k} \\ z^* &= \frac{1}{\mu}\Big(\frac{kar}{c} y^* - b\Big). \end{aligned}$$

Hence,the system (2) has a pathogen present equilibrium $I_1(x^*, y^*, p^*, z^*)$ if $R_0 > 1$. □

Summarizing the above analysis, we have the following result.

Theorem 2.3. *Consider the system (2) with R_0 defined in (3). If $R_0 < 1$, then there is unique equilibrium, which is the pathogen free equilibrium I_0; while if $R_0 > 1$, then there is unique equilibrium, which is the pathogen present equilibrium I_1.*

3. Stability Analysis

We investigate stability of the equilibria and the Hopf bifurcation in this section. First, we consider I_0 is locally asymptotically stable. The characteristic equation associated with the linearization of system (2) at I_0 is given by

$$(-d-\lambda)(-c-\lambda)\{(-a-\lambda)(-b-\lambda)-\beta x_0 a r e^{-\lambda\bar{\tau}}\} = 0, \tag{5}$$

where $\bar{\tau} = \tau_1 + \tau_2$.

Obviously, we have

$$\lambda_1 = -d < 0, \quad \lambda_2 = -c < 0$$

and we consider the equation

$$\lambda^2 + \lambda(a+b) + ab\left(1 - \frac{\beta s r}{db}e^{-\lambda\bar{\tau}}\right) = 0,$$

it implies that,

$$\lambda^2 + \lambda(a+b) + ab\left(1 - R_0 e^{-\lambda\bar{\tau}}\right) = 0. \tag{6}$$

Theorem 3.1. *The pathogen free equilibrium I_0 of model (2) is globally asymptotically stable when $R_0 < 1$. If $R_0 > 1$, I_0 is unstable.*

Proof. The characteristic equation (6) at the pathogen free equilibrium can be rewritten as

$$(\lambda + a)(\lambda + b) = abR_0 e^{-\lambda\bar{\tau}}. \tag{7}$$

If the eigenvalue of λ in (7) has a non-negative real part, then the modulus of the LHS of (7) satisfies,

$$|(\lambda + a)(\lambda + b)| \geq ab$$

while the modulus of the RHS of (7) satisfies $|abR_0 e^{-\lambda\bar{\tau}}| < abR_0 < ab$.

This leads a contradiction to (7). Thus, all the eigenvalues of (7) have negative real part and hence the pathogen free equilibrium I_0 of the model (2) is locally asymptotically stable when $R_0 < 1$. □

When $R_0 > 1$, we define a function,

$$f(\lambda) = (\lambda + a)(\lambda + a) - abR_0 e^{-\lambda\bar{\tau}}.$$

It is clear that $f(0) < 0$ and $f(\lambda) \to \infty$ when $\lambda \to \infty$. By the continuity, we know that, there exist at least one positive root when $R_0 > 1$. Thus, the pathogen free equilibrium I_0 of the model (2) is is unstable when $R_0 > 1$.

Next, we prove I_0 is globally attractive in if $R_0 < 1$. To prove this, we consider a Lyapunov functional $L : C \to \mathbb{R}$ given by

$$\begin{aligned} L(x_t, y_t, p_t, z_t) &= x_t(0) - x_0 \ln x_t(0) + y_t(0) + \frac{1}{r} p_t(0) + \frac{\mu}{rk} z_t(0) \\ &\quad + \beta \int_{-\tau_1}^{0} x_t(\theta) p_t(\theta) d\theta + a \int_{-\tau_2}^{0} y_t(\theta) d\theta + \frac{\mu}{r} \int_{-\tau_3}^{0} p_t(\theta) z_t(\theta) d\theta \end{aligned}$$

Here $x_t(s) = x(t + s)$,for $s \in [tau, 0]$,and thus $x(t) = x_t(0)$ in this notation.

Calculating the time derivative of L along solution of system(2), it follows that

$$\begin{aligned} \dot{L}|_{(2)} &= \dot{x}(t) - x_0 \ln \frac{\dot{x}(t)}{x(t)} + \dot{y}(t) + \frac{1}{r}\dot{p}(t) + \frac{\mu}{rk}\dot{z}(t) \\ &\quad + \beta \left(x(t)p(t) - x(t - \tau_1)p(t - \tau_1) \right) + a \left(y(t) - y(t - \tau_2) \right) \\ &\quad + \frac{\mu}{r} \left(p(t)z(t) - p(t - \tau_3)z(t - \tau_3) \right) \\ &= s \left(2 - \frac{x_0}{x(t)} - \frac{x}{x_0} \right) + p \left(\beta \frac{s}{d} - \frac{b}{r} \right) - \frac{\mu c}{kr} z \\ &= s \left(2 - \frac{x_0}{x(t)} - \frac{x}{x_0} \right) + \frac{b}{r} \left(R_0 - 1 \right) p - \frac{\mu c}{kr} z \end{aligned}$$

$R_0 < 1$ ensures that $\dot{L}|_{(2)} \leq 0$ and $\dot{L} = 0$ if and only if

$$x(t) = x_0, \quad y(t) = 0, \quad p(t) = 0, \quad z(t) = 0,$$

it can be verified that the maximal invariant set in $\dot{L}|_{(2)} = 0$ is the set

$$U = \{(x_0, 0, 0, 0)\}.$$

By the LaSalle-Lyapunov theorem, we conclude that U is globally attractive in Γ if $R_0 < 1$. So I_0 is globally attractive in Γ. Therefore, I_0 is globally asymptotically stable in Γ.

3.1. **Dynamics when $R_0 > 1$.** When $R_0 > 1$, there exists a pathogen present equilibrium

$$x^* = \frac{sk}{kd + \beta c},\ y^* = \frac{\beta c}{ka}x^*,\ p^* = \frac{c}{k},\ z^* = \frac{1}{\mu}\left(\frac{kar}{c}y^* - b\right).$$

The characteristic equation associated with the linearization of system (2) at I_1 is given by

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 + e^{-\lambda\tau_3}(B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4)$$
$$-e^{-\lambda(\tau_1+\tau_2)}(C_1\lambda^2+C_2\lambda+C_3) + e^{-\lambda(\tau_2+\tau_3)}(D_1\lambda+D_2) - e^{-\lambda(\tau_1+\tau_2+\tau_3)}(E_1\lambda + E_2) = 0 \quad (8)$$

where

$$\begin{aligned}
A_1 &= a + b + c + d + \beta p^* + \mu z^*;\\
A_2 &= a(d + \beta p^*) + (a + d + \beta p^*)(b + \mu z^* + c) + c(b + \mu z^*);\\
A_3 &= a(d + \beta p^*)(b + \mu z^* + c) + (a + d + \beta p^*)c(b + \mu z^*);\\
A_4 &= ac(d + \beta p^*)(b + \mu z^*);\\
B_1 &= kp^*;\\
B_2 &= kp^*(a + b + d + \beta p^* + 2\mu z^*);\\
B_3 &= kp^*(a(d + \beta p^*) + (a + d + \beta p^*)b + 2\mu z^*(a + d + \beta p^*));\\
B_4 &= kp^*(a(d + \beta p^*)(b + \mu z^*) + a\mu z^*(d + \beta p^*));\\
C_1 &= \beta x^* ar;\\
C_2 &= \beta x^* ar(c + d);\\
C_3 &= \beta x^* ar(cd);\\
D_1 &= a^2 rkz^*;\\
D_2 &= a^2 rkz^*(d + \beta p^*);\\
E_1 &= \beta x^* arkp^*;\\
E_2 &= \beta x^* arkp^*(d + \beta p^*) - \beta^2 x^* arx^* kp^{*2}.
\end{aligned}$$

Local stability and Hopf Bifurcation:

Consider the case for $\tau_1 = \tau_2 = 0$ and $\tau_3 > 0$, then the equation (2) becomes as follows:

$$\begin{aligned} \dot{x} &= s - dx - \beta xp, \\ \dot{y} &= \beta xp - ay, \\ \dot{p} &= ary - bp - \mu pz, \\ \dot{z} &= kp(t-\tau_3)z(t-\tau_3) - cz, \end{aligned} \tag{9}$$

The characteristic equation of (9) at I_1 is given by

$$\begin{aligned} &\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 + e^{-\lambda\tau_3}(B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4) \\ &\quad -(C_1\lambda^2 + C_2\lambda + C_3) + e^{-\lambda\tau_3}(D_1\lambda + D_2) - e^{-\lambda\tau_3}(E_1\lambda + E_2) = 0, \end{aligned} \tag{10}$$

that implies that,

$$\begin{aligned} &\lambda^4 + A_1\lambda^3 + (A_2 - C_1)\lambda^2 + (A_3 - C_2)\lambda + A_4 - C_3 \\ &\quad + e^{-\lambda\tau_3}\{B_1\lambda^3 + B_2\lambda^2 + (B_3 + D_1 - E_1)\lambda + (B_4 + D_2 - E_2)\} = 0. \end{aligned} \tag{11}$$

When $\tau_3 = 0$, (11) becomes

$$\begin{aligned} &\lambda^4 + (A_1 + B_1)\lambda^3 + (A_2 + B_2 - C_1)\lambda^2 + (A_3 + B_3 + D_1 - C_2 - E_1)\lambda \\ &\qquad + (A_4 + B_4 + D_2 - C_3 - E_2) = 0. \end{aligned} \tag{12}$$

Which is equivalent to

$$\lambda^4 + \nu_1\lambda^3 + \nu_2\lambda^2 + \nu_3\lambda + \nu_4 = 0,$$

where

$$\begin{aligned} \nu_1 &= A_1 + B_1; \\ \nu_2 &= A_2 + B_2 - C_1; \\ \nu_3 &= A_3 + B_3 + D_1 - C_2 - E_1; \\ \nu_4 &= A_4 + B_4 + D_2 - C_3 - E_2; \end{aligned}$$

and $\nu_1\nu_2\nu_3 > \nu_3^2 + \nu_1^2\nu_4$, i.e., $\nu_1\nu_2\nu_3 - \nu_3^2 - \nu_1^2\nu_4 > 0$. By the Routh-Hurwitz criteria, all roots of this equation have negative real parts. Clearly, 0 is not the root of (11).

3.2. **Criterion for preservation of stability or instability and bifurcation results.** Now, we put $\lambda = \gamma(\tau_3) + i\omega(\tau_3)$ in equation (11) and to determine the change of stability of I_1 of (2) for some τ_3 for which $\gamma(\tau_3) = 0, \omega(\tau_3) \neq 0$, i.e.,., when λ will be purely imaginary. Let τ_3^* be such that $\gamma(\tau_3^*) = 0$ and $\omega(\tau_3^*) = \omega_0 \neq 0$. In this case the steady state loses stability and eventually become unstable when $\gamma(\tau_3^*)$ becomes positive. However, if such a $\omega(\tau_3^*)$ does not exists i.e. if λ be not purely imaginary for $\tau_3 = \tau_3^*$, then I_1 of (2) is always stable. We will show that it is the case with equation (11). Now we let $\lambda = i\omega$ be a purely imaginary in (11) reduce to

$$\omega^4 - \omega^2(A_2 - C_1) + A_4 - C_3 = (B_2\omega^2 - (B_4 + D_2 - E_2))\cos(\omega\tau_3) + (B_1\omega^3 - \omega(B_3 + D_1 - E_1))\sin(\omega\tau_3), \tag{13}$$

$$\omega(A_3 - C_2) - \omega^3 A_1 = -(B_2\omega^2 - (B_4 + D_2 - E_2))\sin(\omega\tau_3) + (B_1\omega^3 - \omega(B_3 + D_1 - E_1))\cos(\omega\tau_3). \tag{14}$$

Now squaring and adding above equation (13) and (14) we get,

$$\omega^8 + f_1\omega^6 + f_2\omega^4 + f_3\omega^2 + f_1 = 0. \tag{15}$$

Putting $\omega^2 = u^*$ into (15), we can get the following equation:

$$F(u^*) = u^{*4} + f_1u^{*3} + f_2u^{*2} + f_3u^* + f_4 = 0, \tag{16}$$

where

$f_1 = A_1^2 - 2(A_2 - C_1) - B_1^2;$

$f_2 = (A_2 - C_1)^2 + 2(A_4 - C_3) - 2A_1(A_3 - C_2) - B_2^2 + 2B_1(B_3 + D_1 - E_1);$

$f_3 = (A_3 - C_2)^2 - 2(A_2 - C_1)(A_4 - C_3) + 2B_2(B_4 + D_2 - E_2) - (B_3 + D_1 - E_1)^2;$

$f_4 = (A_4 - C_3)^2 - (B_4 + D_2 - E_2)^2,$

Taking derivative with respect to u^* of equation (16), we get

$$\dot{F}(u^*) = 4u^{*3} + 3u^{*2}f_1 + 2u^*f_2 + f_3 = 0, \tag{17}$$

Set

$$4u^{*3} + 3u^{*2}f_1 + 2u^*f_2 + f_3 = 0. \tag{18}$$

Let $m^* = u^* + \dfrac{f_1}{4}$, then (18) becomes

$$m^{*3} + \alpha_1 m^* + \alpha_2 = 0, \tag{19}$$

where

$$\alpha_1 = \frac{f_2}{2} - \frac{3f_1^2}{16}, \quad \alpha_2 = \frac{f_1^3}{32} - \frac{f_1 f_2}{8} + \frac{f_3}{4}.$$

Define

$$\begin{aligned}
\Delta &= \left(\frac{\alpha_2}{2}\right)^2 + \left(\frac{\alpha_1}{3}\right)^3; \quad \delta = \frac{-1 + i\sqrt{3}}{2}; \\
m_1^* &= \sqrt[3]{-\frac{\alpha_2}{2} + \sqrt{\Delta}} + \sqrt[3]{-\frac{\alpha_2}{2} - \sqrt{\Delta}}; \\
m_2^* &= \sqrt[3]{-\frac{\alpha_2}{2} + \sqrt{\Delta\delta}} + \sqrt[3]{-\frac{\alpha_2}{2} - \sqrt{\Delta\delta^2}}; \\
m_3^* &= \sqrt[3]{-\frac{\alpha_2}{2} + \sqrt{\Delta\delta^2}} + \sqrt[3]{-\frac{\alpha_2}{2} - \sqrt{\Delta\delta}}; \\
u_i^* &= m_i^* - \frac{f_1}{4}, \quad i = 1, 2, 3.
\end{aligned}$$

We cite the results in [26] about the existence of positive roots of the fourth-degree polynomial equation, namely, we have the following lemma.

Lemma 3.2. (1) *If $f_4 < 0$, then (16) has at least one positive root.*

(2) *If $f_4 \geq 0$ and $\Delta \geq 0$ then (16) has positive roots if and only if $u_1 > 0$ and $F(u_1) < 0$.*

(3) *If $f_4 \geq 0$ and $\Delta < 0$, then (16) has positive roots if and only if there exists at least one $u^* \in \{u_1, u_2, u_3\}$ such that $u^* > 0$ and $F(u^*) < 0$.*

Supposing one of the above three cases in Lemma 5, is satisfied, (16) has finite positive rootss $u_1, u_2, u_3, ..., u_k, k \leq 4$. Therefore (15) has finite positive roots.

$$\omega_1 = \sqrt{u_1}, \ \omega_2 = \sqrt{u_2}, ..., \ \omega_k = \sqrt{u_k}, \quad k \leq 4.$$

For every fixed $\omega_i (i = 1, 2, ...k), \ k \leq 4)$, there exists a sequence

$$\tau_{3i}^j = \frac{1}{\omega_i} \arccos\left(\frac{\eta_1}{\eta_2}\right)$$

where $j = 0, 1, 2, ..., i = 1, 2, ..., k, \quad k \leq 4,$

where

$$\begin{aligned}\eta_1 &= \omega_i^{*4} - (A_2 - C_1)\omega_i^{*2} + A_4 - C_3)(B_2\omega_i^{*2} + E_2 - (B_4 + D_2)) \\ &\quad +(-A_1\omega_i^{*3} + (A_3 - C_2)\omega_i)(B_1\omega_i^{*3} + E_1 - (B_3 + D_1)\omega_i \\ \eta_2 &= (B_1\omega_i^3 - E_1 + B_3 + D_1\omega_i)^2 + (-B_2\omega_i^2 + B_4 + D_2 - E_2)^2.\end{aligned}$$

Now, we determine sign $\left(\frac{dRe(\lambda)}{d\tau_3}\right)\Big|_{\tau_3=\tau_3^*}$ where sign is the signum function and $Re(\lambda)$ is a real part of λ. By using the following mathematical calculation we can say that the pathogen present equilibrium of model (2) remains stable for $\tau_3 < \tau_3^*$ and Hopf bifurcation occurs when $\tau_3 = \tau_3^*$.

After some findings, we get the following lemma.

Lemma 3.3.

$$\left(\frac{dRe(\lambda)}{d\tau_3}\right)^{-1}\Big|_{\tau_3=\tau_{3i}^j} = \frac{\dot{F}(\omega_i)^2}{(B_1\omega^3 - E_1 + B_3 + D_1\omega)^2 + (-B_2\omega^2 + B_4 + D_2 - E_2)^2}$$

Especially,supposing $\dot{F}((\omega)^{*2}) \neq 0$, *then*

$$\left(\frac{dRe(\lambda)}{d\tau_3}\right)^{-1}\Big|_{\tau_3=\tau_3^*} = \frac{\dot{F}(\omega^{*2})}{(B_1\omega^{*3} - E_1 + B_3 + D_1\omega^*)^2 + (-B_2\omega^{*2} + B_4 + D_2 - E_2)^2} > 0.$$

⊡

From Lemma 6, we can get the following result.

Theorem 3.4. *For the system (9), there exists* $\tau_3^* = \min\{\tau_{3i}^0 | i = 1, 2, ..., k,\ k \leq 4\}$, *such that* I_1 *is asymptotically stable, when* $\tau_3 \in [0, \tau_3^*)$. *Furthermore, if* $\dot{F}(\omega^{*2}) \neq 0$ *holds, and system (11) undergoes a Hopf bifurcation at* I_1 *when* $\tau_3 = \tau_3^*$.

Remark 3.5. *We find that incorporating an immune delay can destroy the global intractability of* I_1 *on proper conditions when* $R_0 > 1$, *and a Hopf bifurcation occurs. That is, a periodic oscillation appears. Stability switches can appear when* $k \geq 2$. *Those results show immune delay dominates intracellular delays in this class of pathogen infection models. Those indicate the human immune system has a special effect in pathogen infection models with a CTLs response, and the human immune system itself is very complicated.*

Theorem 3.6. *If $R_0 > 1$, then the pathogen free equilibrium I_0 of (2) is unstable and the pathogen present equilibrium I_1 of (2) is globally asymptotically stable.*

Proof. Let

$$g(u) = u - 1 - \ln u,\ u > 0.$$

Define Lyapunov functional $U : C \to \mathbb{R}$ given by

$$\begin{aligned} U_1(x_t, y_t, p_t, z_t) \ = \ & x^* g\left(\frac{x_t(0)}{x^*}\right) + y^* g\left(\frac{y_t(0)}{y^*}\right) + \frac{1}{r}p^* g\left(\frac{p_t(0)}{p^*}\right) + \frac{\mu}{kr}z^* g\left(\frac{z_t(0)}{z^*}\right) \\ & + \beta x^* p^* \int_{-\tau_1}^{0} g\left(\frac{x_t(\theta)p_t(\theta)}{x^*p^*}\right) d\theta + a y^* \int_{-\tau_2}^{0} g\left(\frac{y_t(\theta)}{y^*}\right) d\theta \\ & + \frac{\mu}{r}p^* z^* \int_{-\tau_3}^{0} g\left(\frac{p_t(\theta)z_t(\theta)}{p^*z^*}\right) d\theta \end{aligned}$$

Calculating the time derivative of U_1 along solution of system (2), it follows that

$$\begin{aligned} \dot{U_1}|_{(2)} = \ & \dot{x}(t)\left(1 - \frac{x^*}{x(t)}\right) + \dot{y}(t)\left(1 - \frac{y^*}{y(t)}\right) + \frac{1}{r}\dot{p}(t)\left(1 - \frac{p^*}{p(t)}\right) \\ & + \frac{\mu}{kr}\dot{z}(t)\left(1 - \frac{z^*}{z(t)}\right) + \beta x^* p^* \left(\frac{x(t)p(t) - x(t-\tau_1)p(t-\tau_1)}{x^*p^*} - \ln\frac{x(t)p(t)}{x^*p^*}\right. \\ & \left. + \ln\frac{x(t-\tau_1)p(t-\tau_1)}{x^*p^*}\right) + a y^*\left(\frac{y(t) - y(t-\tau_2)}{y^*} + \ln\frac{y(t-\tau_2)}{y(t)}\right) \\ & + \frac{\mu}{r}p^*z^*\Big(\frac{p(t)z(t) - p(t-\tau_3)z(t-\tau_3)}{p^*z^*} - \ln\frac{p(t)z(t)}{p^*z^*} + \ln\frac{p(t-\tau_3)z(t-\tau_3)}{p^*z^*}\Big). \end{aligned}$$

Using

$$s = dx^* + \beta x^* p^*,\ a y^* = \beta x^* p^*,\ p^* = \frac{c}{k},\ y^* = \frac{(b + \mu z^*)c}{ark}.$$

It follows that

$$\begin{aligned} \dot{U_1}|_{(2)} = \ & dx^*\left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) + \beta x^* p^*\left(1 - \frac{x^*}{x} + \ln\frac{x^*}{x}\right) - \beta x^* p^* \ln\frac{x^*}{x} \\ & + \beta x^* p^*\left(1 - \frac{y^* x(t-\tau_1)p(t-\tau_1)}{x^*p^*y} + \ln\frac{y^* x(t-\tau_1)p(t-\tau_1)}{x^*p^*y}\right) \\ & - \beta x^* p^* \frac{y^* x(t-\tau_1)p(t-\tau_1)}{x^*p^*y} - \beta x^* p^* - a y^* + a y^*\left(1 - \frac{y(t-\tau_2)p^*}{y^*p}\right. \\ & \left. + \ln\frac{y(t-\tau_2)p^*}{y^*p} - \ln\frac{y^*p}{yp^*}\right) - \beta x^* p^* \ln\frac{xp}{x^*p^*} + \beta x^* p^* \ln\frac{x(t-\tau_1)p(t-\tau_1)}{x^*p^*} - \frac{\mu}{r}p^* \\ & + \frac{\mu}{r}p^*\left(1 - \frac{p(t-\tau_3)z(t-\tau_3)z^*}{zp^*} + \ln\frac{p(t-\tau_3)z(t-\tau_3)z^*}{zp^*}\right) - \frac{\mu}{r}p^* \ln\frac{p(t-\tau_3)z(t-\tau_3)z^*}{zp^*} \end{aligned}$$

$$
\begin{aligned}
= \; & dx^* \left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) - \beta x^* p^* g\left(\frac{x^*}{x}\right) - \beta x^* p^* g\left(\frac{y^* x(t-\tau_1) p(t-\tau_1)}{x^* p^* y}\right) \\
& - a y^* g\left(\frac{y(t-\tau_2) p^*}{y^* p}\right) - a y^* \ln \frac{y^* p}{y p^*} - \frac{\mu}{r} p^* g\left(\frac{p(t-\tau_3) z(t-\tau_3) z^*}{z p^*}\right) \\
\leq \; & 0.
\end{aligned}
$$

This implies that

$$\dot{U_1}|_{(2)} = 0 \Leftrightarrow x(t) = x^*,\ y(t) = y^*,\ p(t) = p^*,\ z(t) = z^*.$$

and thus the maximal invariant set in the set $\{\dot{U_1} = 0\}$ is the singleton $\{I_1\}$. Therefore, I_1 is globally attractive. Hence the pathogen present equilibrium (x^*, y^*, p^*, z^*) of model (2) is globally asymptotically stable when $R_0 > 1$, in the case of $\tau_3 < \tau_3^*$. □

4. Conclusion

In this paper, we have proposed and analyzed a model for pathogen-immune interaction dynamics with intracellular time delays. We point out the essential differences between our results and the results in [21]. In their model shows that local stability analysis for pathogen immune interaction. But our model shows that global asymptotic stability of the pathogen present equilibrium in the presence of immune delay. The positive immune delay, τ_3 is able to destabilize the pathogen present equilibrium. We showed that for this simplified model (9), pathogen present equilibrium equilibrium is locally asymptotically stable for $\tau_3 < \tau_3^*$ and bifurcation leads when $\tau_3 = \tau_3^*$. Further we show that bifurcation analysis at $\tau_3 = \tau_3^*$ and proofs on this issue are needed and we will concern about this problem in our further studies.

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