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Mathematical Analysis of an HIV/AIDS Epidemic Model with delay

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Abstract In this paper we consider a five compartmental HIV/AIDS epidemic model with delay. We first investigate the existence and stability of the equilibria and then we study the effect of the time delay as the stability of the infected equilibrium. Criteria are given to ensure that the infected equilibrium is asymptotically stable for all delay. Morever by applying Nyquist criteria, the, length of delay is estimated for which stability continues to hold. By using a delay τ as a bifurcation parameter, the existence of Hopf-bifurcation is also investigated.

Keywords: HIV model, delay differential equation, stability, Hopf bifurcation.

1 Introduction

In the last decade, many mathematical models have been developed to describe the immunological response to infection with human immunodeficiency virus (HIV) (for example, [1 - 11] and so on). These models have been used to explain different phenomena. For more references and some detailed mathematical analysis on such models, we refer to the survey papers by Kirschner [12] and Perelson and Nelson [13].

Human immunodeficiency virus (HIV) is the causative agent of acquired immun- odeficiency syndrome (AIDS), a disease that causes progressive failure of the immune system. HIV is an RNA retrovirus. That is, to enter a cell, HIV translates its RNA to DNA with a viral enzyme called reverse transcriptase. The target cell of HIV is $CD4+$ T cells. A healthy human body has about $1000/mm^3$ of $CD4+$ T cells. When the CD4 T cells of a patient decline to $200/mm^3$ or below, then that person is classified as having AIDS. When the CD4 T cells decline, they cannot mount a strong response. This results in weak responses from CTL and antibodies which cannot clear the infection.

There are three states for HIV infection:
1. The primary infection occurs within a few weeks of acquiring the virus and is the first stage. Usually the virus load increases during this stage. This stage is similar to the symptoms of u. The number of $CD4+$ T cells significantly decrease and then return to almost normal level.

2. The chronic stage of asymptomatic infection in which there are no considerable symptoms of disease is the second stage. The immune system is active. This stage lasts an average of 10 years. 3. The acute stage in which there are symptoms of the disease is the final stage, leading to AIDS. The immune system can no longer defend the body and one or more other infections occur. Eventually a patient dies from these other infections.

Time delays of one type or another have been incorporated into biological models by many authors (for example, [14 - 16] and the references cited therein). In general, delay-differential equations exhibit much more complicated dynamics than ordinary differential equations since a time delay could cause a stable equilibrium to become unstable and cause the populations to fluctuate.

Swarnali Sharma and Samanta [17] consider the model

$$\begin{aligned}
\frac{dS}{dt} &= \wedge - (\beta_1 I_1 + \beta_2 I_2)S - \mu S, \\
\frac{dI_1}{dt} &= (\beta_1 I_1 + \beta_2 I_2)S + \eta(I_1 + I_2) - (\alpha + \mu)I_1, \\
\frac{dI_2}{dt} &= \alpha I_1 - (\sigma + \rho + \mu)I_2, \\
\frac{dT}{dt} &= \rho I_2 - (\gamma + \mu)T, \\
\frac{dA}{dt} &= \gamma T + \sigma I_2 - (d + \mu)A,
\end{aligned} \tag{1}$$

with initial densities

$$S(0) > 0,\ I_1(0) > 0,\ I_2(0) \geq 0,\ T(0) \geq 0,\ A(0) \geq 0.$$

Here $S(t),\ I_1(t),\ I_2(t),\ T(t)$, and A(t) represent population densities (or fractions) of susceptible population, infective population in asymptomatic phase, infective population in symptomatic phase, infective population in treatment and full-blown AIDS group. So, $N(t) = S(t) + I_1(t) + I_2(t) + T(t) + A(t)$ denotes the total number of high-risk human population at time t.
The model parameters are as follows:

- $\wedge$: the recruitment rate of susceptible population from the larger embedding population,

- β_1 : horizantal transmission rate coefficient of infection when susceptible humans come in contact with the infective in the first stage (asymptomatic stage) and the rate transmission is of the form $\beta_1 S(t)I_1(t)$,

- β_2 : horizontal transmission rate coefficient of infection when susceptible humans come in contact with the infective in the second stage (symptomatic stage) and the rate transmission is of the form $\beta_2 S(t)I_2(t)$,

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- η : vertical transmission rate coefficient, i.e., the rate of recruitment of new borne infected children into the first infectious stage (asymptomatic stage),

- α : progression rate to second stage (symptomatic stage) infectious class from the first stage (asymptomatic stage) infectious class,

- ρ : the proportion of infective poppulation in symptomatic phase who enter into treatment,

- σ : progression rate to full-blown AIDS class from the second stage (symptomatic stage) infectious class,

- γ : rate of transfer from treatment class to a full-blown AIDS group,

- d : disease related death rate of the full-blown AIDS group,

- μ: natural death rate of population.

This model involves certain assumptions which consists of the following:

1. The susceptible population (S) is composed of individuals who have not yet been infected by HIV but may be infected through sexual interrcourse or other ways with both types of infectives (infectives in asymptomatic phase (I_1) and symptomatic phase (I_2)).
2. The infective population in asymptomatic phase (I_1) is composed of individuals who have HIV infection without any symptoms.
3. The infective population in symptomatic phase (I_2) is composed of individuals who have developed HIV infection with complications and various symptoms.
4. The infective population in treatment class (T) is composed of infective individuals who are in symptomatic phase, but become aware of their infection and enter into the drug therapy.
5. The full-blown AIDS class (A) is composed of individuals whose body's immune system has been totally suppressed by HIV infection and they are in the final stage of AIDS.
6. For simplicity, only two stages of HIV infection are considered according to clinic stages [23, 48], i.e., the asymptomatic phase (I_1) and symptomatic phase (I_2).
7. The susceptible individuals become infected by adequate contact with infective individuals both in asymptomatic phase and symptomatic phase.

8. Vertical transmission is considered only into the first infectious stage (asymptomatic stage) transmitted by infective individuals who are in asymptomatic phase and symptomatic phase.

9. The infective population in treatment do not contribute viral transmission horizontally and vertically due to stringent measures.

10. The full-blown AIDS class is considered to be too ill to remain sexually active. So, they do not contribute viral transmission both horizontally and vertically.

11. Natural death rate of the populations (μ) is considered as greater than the vertical transmission coefficient (η), i.e., $\mu > \eta$ and $\eta < \frac{(\alpha+\mu)(\rho+\sigma+\mu)}{(\rho+\sigma+\mu+\alpha)}$.

In order to make model (1) more realistic, time delay should be included in the following model:

$$\begin{aligned}
\frac{dS}{dt} &= \wedge - \beta_1 I_1 S - \beta_2 I_2(t-\tau)S(t-\tau) - \mu S, \\
\frac{dI_1}{dt} &= \beta_1 I_1 S + \beta_2 I_2(t-\tau)S(t-\tau) + \eta(I_1+I_2) - (\alpha+\mu)I_1, \\
\frac{dI_2}{dt} &= \alpha I_1 - (\rho+\sigma+\mu)I_2. \\
\frac{dT}{dt} &= \rho I_2 - (\gamma+\mu)T, \\
\frac{dA}{dt} &= \gamma T + \sigma I_2 - (d+\mu)A.
\end{aligned} \tag{2}$$

with initial conditions are given by

$$S(\vartheta) = \varphi_1(\vartheta),\ I_1(\vartheta) = \varphi_2(\vartheta), I_2(\vartheta) = \varphi_3(\vartheta), T(\vartheta) = \varphi_4(\vartheta), A(\vartheta) = \varphi_5(\vartheta) \tag{3}$$

such that $\varphi_i(\vartheta) \geq 0 (i = 1, 2, 3, 4, 5)$, for all $\vartheta \epsilon [-\tau, 0]$,
where $\varphi_i(\vartheta) \geq 0 (i = 1, 2, 3, 4, 5)$ are non-negative continuous functions on $\vartheta \epsilon [-\tau, 0]$.

The outline of the present paper is as follows. The next section is devoted to the wellposedness and positivity of the solution. In Section 3, we study the qualitative behavior of the model via stability of the steady states and Hopf bifurcation when time delay is considered as a bifurcation parameter. In Section 4, the length of delay to preserve stability are established

2 Basic Properties

Theorem 1. *The feasible region* Γ *defined by*

$$\Gamma = \left\{ (S(t), I_1(t), I_2(t), T(t), A(t))\, \epsilon R^5_+ : 0 < N \leq \frac{\wedge}{\mu - \eta} \right\}$$

with initial conditions $S(0) > 0,\ I_1(0) > 0,\ I_2(0) \geq 0,\ T(0) \geq 0,\ A(0) \geq 0,$ *is positively invariant.*

Proof:

Adding the equations of the system (2) we obtain

$$\begin{aligned}\frac{dN}{dt} &= \wedge + \eta(I_1 + I_2) - \mu N - dA \\ &= \wedge + \eta(N - S - T - A) - \mu N - dA \\ &\leq \wedge - (\mu - \eta)N.\end{aligned}$$

The solution N(t) of the above differential equation has the following property:

$$0 < N(t) \leq N(0)e^{-(\mu-\eta)t} + \frac{\wedge}{\mu - \eta}(1 - e^{-(\mu-\eta)t}),$$

where N(0) represents the sum of the initial values of the variables. As $t \to \infty . 0 < N \leq \frac{\wedge}{\mu-\eta}$. So if $N(0) \leq \frac{\wedge}{\mu-\eta}$ then $\lim_{t\to\infty} N(t) \leq \frac{\wedge}{\mu-\eta}$. This means that $\frac{\wedge}{\mu-\eta}$ is the upper bound of N. On the other hand, if $N(0) > \frac{\wedge}{\mu-\eta}$, then N(t) will decrease to $\frac{\wedge}{\mu-\eta}$. This means that if $N(0) > \frac{\wedge}{\mu-\eta}$, then the solution $(S(t),\ I_1(t),\ I_2(t),\ T(t),\ A(t))$ enters Γ or approaches it asymptotically. Hence it is positively invariant under the flow induced by the system (1).

Theorem 2. *Every solutions of system (1) with initial conditions (2) exists in the intervel* $[0, \infty)$ *and* $S(t) > 0,\ I_1(t) > 0,\ I_2(t) \geq 0.$ *T(t)* ≥ 0 *and A(t)* ≥ 0*, for all* $t \geq 0$.

Since the variables T and A of the system (2) do not appear in the first three equations, in the subsequent analysis we only consider the following subsystem:

$$\begin{aligned}\frac{dS}{dt} &= \wedge - \beta_1 I_1 S - \beta_2 I_2(t-\tau)S(t-\tau) - \mu S, \\ \frac{dI_1}{dt} &= \beta_1 I_1 S + \beta_2 I_2(t-\tau)S(t-\tau) + \eta(I_1 + I_2) - (\alpha + \mu)I_1, \\ \frac{dI_2}{dt} &= \alpha I_1 - (\alpha + \rho + \mu)I_2,\end{aligned} \tag{4}$$

with initial conditions are given by

$$S(\vartheta) = \varphi_1(\vartheta),\ I_1(\vartheta) = \varphi_2(\vartheta), I_2(\vartheta) = \varphi_3(\vartheta), \tag{5}$$

such that $\varphi_i(\vartheta) \geq 0 (i = 1, 2, 3)$, for all $\vartheta \epsilon [-\tau, 0]$,
where $\varphi_i(\vartheta) \geq 0 (i = 1, 2, 3)$ are non-negative continuous functions on $\vartheta \epsilon [-\tau, 0]$.

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3 Steady States

We can obtain the steady state values by setting $\frac{dS}{dt} = \frac{dI_1}{dt} = \frac{dI_2}{dt} = 0$. The steady state value of the infection-free steady sate E_0 is given by $E_0 = (\frac{\wedge}{\mu}, 0, 0)$ while the infected steady state E^* is given by $E^* = (S^*, I_1^*, I_2^*)$, where,

$$\begin{aligned} S^* &= \frac{(\alpha+\mu-\eta)(\rho+\sigma+\mu)-\alpha\eta}{\beta_1(\rho+\sigma+\mu)+\alpha\beta_2} \\ &= \frac{\wedge}{\mu}\frac{1}{R_0} > 0 \qquad [since R_0 > 0] \end{aligned}$$

$$\begin{aligned} I_1^* &= \frac{\wedge(\rho+\sigma+\mu)}{S^*[\beta_1(\rho+\sigma+\mu)+\beta_2\alpha]}\left(1-\frac{1}{R_0}\right) \\ I_2^* &= \frac{\alpha I_1^*}{\rho+\sigma+\mu}. \end{aligned}$$

3.1. Stability and Hopf Bifurcation Analysis of Infected Steady State E^*.

In order to study full dynamics of model (4) by using time delay as a bifurcation parameter, we need to linearize the model around the steady state E^* and determine the characteristic equation of the Jacobian matrix.The roots of the characteristic equation determine the asymptotic stability and existence of Hopf bifurcation for the model.The characteristic equation of the linearized system is given by

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + (A_4\lambda^2 + A_5\lambda + A_6)e^{-\lambda\tau} = 0 \tag{6}$$

where

$$\begin{aligned} A_1 &= -a_{33} - a_{22} - a_{11}, \\ A_2 &= a_{22}a_{33} - a_{23}a_{32} + a_{11}a_{33} + a_{11}a_{22} - a_{12}a_{21}, \\ A_3 &= a_{11}a_{23}a_{32} - a_{11}a_{22}a_{33} + a_{12}a_{21}a_{33}, \\ A_4 &= -b_{11}, \\ A_5 &= -a_{32}b_{23} + b_{11}a_{33} + b_{11}a_{22} - a_{12}b_{21}, \\ A_6 &= a_{11}a_{32}b_{23} - b_{11}a_{22}a_{33} + b_{11}a_{23}a_{32} + a_{12}a_{33}b_{21}, \end{aligned}$$

It is well known that the stability of the equilibrium of delay differential equation depends on the distribution of the zeros of characteristic equation. In the following we shall use the main results in Ruan and Wei [18], which is a generalization of the lemma in Cook and Grossman [19], to analyze the distribution of characteristic roots for (6), we first state the useful lemma as follows:

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Lemma: 1 Consider the following exponential polynomial

$$\begin{aligned} p(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2}, ..., e^{-\lambda\tau_m}) \\ &= \lambda^n + p_1^0\lambda^{n-1} + p_2^0\lambda^{n-2} + ... + p_n^0 \\ &+ [p_1^1\lambda^{n-1} + p_{n-2}^1 + ... + p_n^1]e^{-\lambda\tau_1} \\ &+ ...+ \\ &+ [p_1^m\lambda^{n-1} + p_{n-2}^m\lambda^{n-2} + ... + p_n^m]e^{\lambda\tau_m} \end{aligned}$$

where $\tau_i \geq 0.(i = 1, 2, ..., m)$ and $p_j^i(i = o, 1, ...m; j = 1, 2, ...n)$ are constants as $(\tau_1, \tau_2, ...\tau_m)$ vary the sum of the zeros of $p(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2}, ...e^{-\lambda\tau_m})$ in the open right half plane can change only if a zero appears on or crosses the imaginary axis.

This means that the number of characteristic roots with positive real parts can chage only if there exists purely imaginary roots.

Theorem 3. For $\tau = 0$, the unique nontrivial equilibrium is locally asymptotically stable if the real parts of all the roots of (4) are negative.

3.2 Existence of Hopf Bifurcation. We here study the impact of the time-delay parameter on the stability of HIV infection model. We deduce criteria that ensure the asymptotic stability of infected steady state E^*, for all $\tau > 0$.

For $\tau \neq 0$, we consider τ as bifurcation parameter and assume a purely imaginary solution of (6) is the form $\lambda = i\omega(\omega \neq 0)$. Therefore, substituting $\lambda = i\omega$ in equation (6) and then separating real and imaginary parts, we get

$$\omega^3 - A_2\omega = \sin\omega\tau(A_4\omega^2 - A_6) + A_5\omega\cos\omega\tau \quad (7)$$

$$-A_1\omega^2 + A_3 = \cos\omega\tau(A_4\omega^2 - A_6) - A_5\omega\sin\omega\tau. \quad (8)$$

Eliminating τ by squaring and adding, we get the equation for determining ω as

$$\omega^6 + d_1\omega^4 + d_2\omega^2 + d_3 = 0 \quad (9)$$

where

$$\begin{aligned} d_1 &= A_1^2 - 2A_2 - A_4^2, \\ d_2 &= A_2^2 - 2A_1A_3 + 2A_4A_6 - A_5^2, \\ d_3 &= A_3^2 - A_6^2 \end{aligned}$$

substituting $\omega^2 = z$ in (9), we set a cubic equation given by

$$h(z) \equiv z^3 + d_1z^2 + d_2z + d_3 = 0 \quad (10)$$

The roots of equation (10) are the square of the roots of equation (9) and therefore are positive.

Now we have assumed that the time delay τ is bifurcation parameter. Since the stability change

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occurs for the change of delay parameter value, we can assume that the eigenvalue λ is a function of τ. Again let

$$\lambda(\tau) = \gamma(\tau) + i\omega(\tau)$$

be a root of characteristic equation (6) such that the following two conditions hold;

$$\gamma(\tau_k) = 0,$$
$$\omega(\tau_k) = \omega_0$$

at some value of $\tau = \tau_k$.
Now, from equations(7) and (8), we get

$$\tau_k = \frac{1}{\omega_0} \arccos\left(\frac{(a_4\omega_0^2 - a_6)(a_3 - a_1\omega_0^2) + a_5\omega_0^2(\omega_0^2 - a_2)}{(a_4\omega_0^2 - a_6)^2 + a_5^2\omega_0^2}\right) + \frac{2k\pi}{\omega_0}, \quad k = 0, 1, 2, ... \tag{11}$$

Next we determine sign $\left\{\left(\frac{d(Re\lambda)}{d\tau}\right)_{\lambda=i\omega_0}\right\}$
where sign is the sign function and $Re(\lambda)$ is the real part of λ.

Taking the derivative of the characteristic equation (6) with respect to τ, we get

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{3\lambda^2 + 2a_1\lambda + a_2}{\lambda e^{-\lambda\tau}(a_4\lambda^2 + a_5\lambda + a_6)} + \frac{2\lambda a_4 + a_5}{\lambda(a_4\lambda^2 + a_5\lambda + a_6)} - \frac{\tau}{\lambda}$$

Evaluating $\left(\frac{d\lambda}{d\tau}\right)^{-1}$ at $\lambda = i\omega_0$ and taking the real part, we have

$$\begin{aligned} Re\left[\left(\frac{d\lambda}{d\tau}\right)^{-1}_{\lambda=i\omega_0}\right] &= \frac{1}{\omega_0^2(a_4\omega_0^2 - a_6)^2 + a_5^2\omega_0^4}\left[-a_5\omega_0^2\left\{(a_2 - 3\omega_0^2)\cos(\omega_0\tau)\right.\right. \\ &\quad \left. -2a_1\omega_0\sin(\omega_0\tau)\right\} - \omega_0(a_4\omega_0^2 - a_6)\left\{(a_2 - 3\omega_0^2)\sin(\omega_0\tau)\right. \\ &\quad \left.\left. +2a_1\omega_0\cos(\omega_0\tau)\right\} + 2\omega_0^2 a_4(a_6 - a_4\omega_0^2 - a_5^2\omega_0^2\right] \\ &= \frac{1}{(a_4\omega_0^2 - a_6)^2 + a_5^2\omega_0^2}\left[-(a_2 - 3\omega_0^2)(\omega_0^2 - a_2)\right. \\ &\quad \left. -2a_1(a_3 - a_1\omega_0^2) + 2a_4(a_6 - a_4\omega_0^2) - a_5^2\right] \\ &= \frac{\left[\frac{dh(z)}{dz}\right]_{z=\omega_0^2}}{(a_4\omega_0^2 - a_6)^2 + a_5^2\omega_0^2} \end{aligned}$$

Therefore, we get

$$\begin{aligned} sign\left\{\left(\frac{d(Re\lambda)}{d\tau}\right)_{\lambda=i\omega_0}\right\} &= sign\left\{Re\left(\frac{d\lambda}{d\tau}^{-1}\right)_{\lambda=i\omega_0}\right\} \\ &= sign\left(\frac{dh(z)}{dz}\right)_{z=\omega_0^2} \end{aligned}$$

Now, if $z = \omega_0^2$ is the first positive root of equation (9)

$$sign\left\{\left(\frac{d(Re\lambda)}{d\tau}\right)_{\lambda=i\omega_0}\right\} > 0 \quad as\left[\frac{dh(z)}{dz}\right]_{z=\omega_0^2} > 0.$$

Thus, the transversility condition is satisfied and the steady state becomes unstable when $\tau > \tau^*$, where τ^* is the smallest positive value of τ_k given in (11). Moreover, a Hopf-bifurcation occurs when τ passes through the critical value τ^*.

The above results can be summarized in the following theorem:

Theorem 4. *If E^* exists with the conditions $A_1 > 0$, $A_3 > 0$, and $A_1A_2 - A_3 > 0$, and $z_0 = \omega_0^2$ be a root of (10), then there exists a $\tau = \tau^*$ such that*
(i) E^* is locally asymptotically stable for $0 \leq \tau \leq \tau^*$,
(ii) E^* is unstable for $\tau > \tau^*$,
(iii) the system (2) undergoes a Hopf-bifurcation around E^* at $\tau = \tau^*$,

$$\tau^* = \min g(\omega_0),$$

where

$$g(\omega_0) = \frac{1}{\omega_0}\arccos\left[\frac{(a_4\omega_0^2 - a_6)(a_3 - a_1\omega_0^2) + a_5\omega_0^2(\omega_0^2 - a_2)}{(a_4\omega_0^2 - a_6)^2 + a_5^2\omega_0^2}\right]$$

and the minimum is taken over all positive ω_0 such that ω_0^2 is a solution of Eq. (10).

4 Estimation of the Length of Delay to Preserve Stability

In this section we shall try to estimate the length of delay to preserve the stability. We consider the system (2) and the space of all real valued continuous functions defined on $[-\tau, \infty)$ satisfying the initial conditions on $[-\tau, 0]$. We linearize the system (2) about its interior equilibrium $E^*(S^*, I_1^*, I_2^*)$ and get

$$\begin{aligned}
\frac{dx_1}{dt} &= a_{11}x_1 + b_{11}x_1(t-\tau) + a_{12}y_1 + b_{13}z_1(t-\tau),\\
\frac{dy_1}{dt} &= a_{21}x_1 + b_{21}x_1(t-\tau) + a_{22}y_1 + a_{23}z_1 + b_{23}z_1(t-\tau),\\
\frac{dz_1}{dt} &= a_{31}x_1 + a_{32}y_1 + a_{33}z_1.
\end{aligned} \tag{12}$$

where

$$\begin{aligned}
S(t) &= x_1(t) + S^*,\\
I_1(t) &= y_1(t) + I_1^*,\\
I_2(t) &= z_1(t) + I_2^*.
\end{aligned}$$

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Taking Laplace transform of the system (2) we get

$$\begin{aligned}(s-a_{11}-b_{11}e^{-s\tau})\bar{x_1}(s) &= b_{11}e^{-s\tau}k_1(s)+a_{12}\bar{y_1}(s)+b_{13}e^{-s\tau}\bar{z_1}(s)+b_{13}e^{-s\tau}k_1(s)+x_1(0),\\ (s-a_{22})\bar{y_1}(s) &= a_{21}\bar{x_1}(s)+b_{21}e^{-s\tau}(\bar{x_1}(s))+b_{21}e^{-s\tau}k_1(s)+a_{23}\bar{z_1}(s)\\ &\quad +b_{23}\bar{z_1}(s)e^{-s\tau}+b_{23}e^{-s\tau}k_1(s)+y_1(0),\\ (s-a_{33})\bar{z_1}(s) &= a_{33}\bar{x_1}(s)+a_{32}\bar{y_1}(s)+z_1(0)\end{aligned}$$

where

$$k_1(s)=\int_{-\tau}^{0}e^{-st}y_1(t)dt$$

where

$$\begin{aligned}&a_{11}=-\beta_1 I_1^*-\mu; && a_{21}=\beta_1 I_1^*; && a_{31}=0;\\ &a_{12}=-\beta_1 S^*; && a_{22}=\beta_1 S^*; && a_{23}=\eta;\\ &a_{13}=0; && a_{23}=\eta; && a_{33}=-(\rho+\sigma+\mu);\end{aligned}$$

and,

$$\begin{aligned}&b_{11}=-\beta_2 I_2^*(t-\tau); && b_{21}=\beta_2 I_2^*(t-\tau)\\ &b_{13}=\beta_2 S(t-\tau); && b_{23}=\beta_2 S(t-\tau)\end{aligned}$$

and all other $b_{ij}=0$.
and $\bar{x_1}(s),\ \bar{y_1}(s),\ \bar{z_1}(s)$ are the Laplace transforms of $x_1(t),\ y_1(t),\ z_1(t)$ respectively.

Now, we will use the Nyquist theorem [16] which states that if s is the arc length along a curve encirc ling the right half of the plane, then a curve $\bar{x_1}(s)$ will encircle the origin a number of times equal to the difference between the number of poles and the number of zeroes of $\bar{x_1}(s)$ in the right half of the plane.

Using Nyquist theorem [15, 16], it can be shown that the conditions for local asymptotic stability of $E^*(S^*,\ I_1^*,\ I_2^*)$ are given by [14]

$$ImH(i\omega_0) > 0, \tag{13}$$
$$ReH(i\omega_0) = 0, \tag{14}$$

where

$$H(s) = s^3+A_1s^2+A_2s+A_3+(A_4s^2+A_5s+A_6)e^{-s\tau} \tag{15}$$

and ω_0 is the smallest positive root of (14).

We have already shown that $E^*(S^*,I_1^*,I_2^*)$ is stable in absence of delay. Hence, by continuity,

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all eigenvalues will continue to have negative real parts for sufficiently small $\tau > 0$ provided one can guarantee that no eigenvalue with positive real parts bifurcates from infinity as τ increases from zero. This can be proved by using Butler's lemma [14].

In this case, conditions (13) and (14) give

$$a_2\omega_0 - \omega_0^3 > -(a_4\omega_0^2 - a_6)\sin(\omega_0\tau) - a_5\omega_0\cos(\omega_0\tau), \tag{16}$$

$$a_3 - a_1\omega_0^2 = (a_4\omega_0^2 - a_6)\cos(\omega_0\tau) - a_5\omega_0\sin(\omega_0). \tag{17}$$

Now,(16) and (17), if satisfied simultaneously, are sufficient conditions to guarantee stability. We shall utilize them to get an estimate on the length of the delay. Our aim is to find an upper bound ω_+ on ω_0 independent of τ so that (16) holds for all values of ω, $0 \le \omega \le \omega_+$ and hence in particular at $\omega = \omega_0$.
we rewrite (17) as

$$a_1\omega_0^2 \;=\; a_3 + (a_6 - a_4\omega_0^2)cos(\omega_0\tau) + a_5\omega_0 sin(\omega_0\tau). \tag{18}$$

Maximizing $a_3 + (a_6 - a_4\omega_0^2)\cos(\omega_0\tau) + a_5\omega_0\sin(\omega_0\tau)$ subject to $|\sin(\omega_0\tau)| \le 1, |\cos(\omega_0\tau)| \le 1$, we obtain

$$\begin{aligned} a_1\omega_0^2 &\le a_3 + \left|(a_6 - a_4\omega_0^2)\right| + |a_5|\,\omega_0 \\ &\le a_3 + |a_6| + a_4\omega_0^2 + |a_5|\,\omega_0 \end{aligned}$$

Therefore

$$(a_1 - a_4)\omega_0^2 \le |a_5|\,\omega_0 + (a_3 + |a_6|). \tag{19}$$

Hence, if

$$\omega_+ \;=\; \frac{1}{2(a_1 - a_4)}\left[|a_5| + \sqrt{a_5^2 + 4(a_1 - a_4)(a_3 + |a_6|)}\right], \tag{20}$$

then clearly from (19).we have $\omega_0 \le \omega_+$. From the inequality (16) we get

$$\omega_0^2 \;<\; a_2 + a_5\cos(\omega_0\tau) - \frac{(a_6 - a_4\omega_0^2)}{\omega_0}\sin(\omega_0\tau). \tag{21}$$

As $E^*(S^*, I_1^*, I_2^*)$ is locally asymptotically stable for $\tau = 0$, for sufficiently small $\tau > 0$, (21) will continue to hold. Substituting (18) into (21) and rearranging we get

$$\begin{aligned} \left\{a_1a_5 - (a_6 - a_4\omega_0^2)\right\}\{1 - \cos(\omega_0\tau)\} \;&+\; \left\{a_5\omega_0 + \frac{a_1}{\omega_0}(a_6 - a_4\omega_0^2)\right\}\sin(\omega_0\tau) \\ &< a_1a_2 + a_1a_5 - a_3 - (a_6 - a_4\omega_0^2). \end{aligned} \tag{22}$$

Using the bounds we obtain

$$\begin{aligned} \left\{a_1a_5 - (a_6 - a_4\omega_0^2)\right\}\{1 - \cos(\omega_0\tau)\} &= a_aa_5 - (a_6 - a_4\omega_0^2)2\sin^2(\frac{\omega_0\tau}{2}) \\ &\le \frac{1}{2}\left|a_1a_5 - (a_6 - a_4\omega_+^2)\right|\omega_+^2\tau^2, \end{aligned} \tag{23}$$

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and

$$\left\{a_5\omega_0 + \frac{a_1}{\omega_0}(a_6 - a_4\omega_0^2)\right\}\sin(\omega_0\tau) \le a_5\omega_+^2 + a_1(a_6 - a_4\omega_+^2)\tau \tag{24}$$

Now, from (22) to (24) we get

$$l_1\tau^2 + l_1\tau < l_3 \tag{25}$$

where

$$\begin{aligned} l_1 &= \frac{1}{2}\left|a_1a_5 - (a_6 - a_4\omega_+^2)\right|\omega_+^2, \\ l_2 &= a_5\omega_+^2 + a_1(a_6 - a_4\omega_+^2), \\ l_3 &= a_1a_2 + a_1a_5 - a_3 - (a_6 - a_4\omega_0^2) \end{aligned} \tag{26}$$

Hence, if

$$\tau_+ = \frac{1}{2l_1}\left[-l_2 + \sqrt{l_2^2 + 4l_1l_3}\right] \tag{27}$$

then stability is preserved for $0 \le \tau < \tau_+$. Summarizing the above discussions we come to the following result:

Theorem 5 *The delayed model (2) will be locally asymptotically stable at $E^*(S^*,\ I_1^*,\ I_2^*)$ if the delay τ lies within the interval $(0, \tau_+)$ where τ_+ is given by (27).*

5 Conclusion

The model includes a discrete time delay in the immune activation response, which plays an important role in the dynamics of the model. The infection-free and endemic steady states of the model are determined. The stability of steady states is analyzed. We deduced a formula that determines the critical value (branch value) τ_0. Necessary and sufficient conditions for the equilibrium to be asymptotically stable for all positive delay values are proved. We have seen that if the time delay exceeds the critical value τ_0, model (4) undergoes a Hopf bifurcation. The length of delay preserving the stability is estimated using Nyquist creteria and existence conditions of the Hopf-bifurcation for the time delay are investigated by choosing the time delay τ as a bifurcation parameter.

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