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MODIFIED HIV-1 INFECTION MODEL WITH DELAY IN SATURATED CTL IMMUNE RESPONSE

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Abstract. We propose a HIV-1 dynamics model with CTL immune response and both infected and immune cell infections. Both actively infected cells and immune cells are incorporated with two time delays. The infected-susceptible and immune-susceptible infection rates are given by saturated incidence. By calculation, we obtain immunity-inactivated reproduction number R_0 and immunity-activated reproduction number R_1. By analyzing the distribution of roots of the corresponding characteristic equations, we study the local stability of an infection-free equilibrium, an immunity-inactivated equilibrium and an immunity-activated equilibrium of the model. We discuss the persistence theory for addressing the long term survival of all components of system.

Keywords: HIV-1 model; delays; stability analysis; bifurcation.

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1. Introduction

Delay differential equations (DDEs), are the subject of active research for more than 60 years and has been studied by many different mathematicians. Delay differential equations are

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equations which have a delayed argument [1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12]. These equations constitute a large and important class of dynamical systems. Time delays are natural components of the dynamic processes of biology, ecology, physiology, economics, epidemiology and mechanics and so a realistic model of these processes must include time delays. Delay differential equations arise in situations where some hereditary function appears in the ordinary differential equation. Detailed studies of the real world compel us to take account of the fact that the rate of change of physical systems depends not only on their present state, but also on their past history [13].

In many real world phenomena, the initial conditions or boundary conditions are not enough to predict the future behaviour of the function. Hence to deal with such complexities, it is necessary to have some knowledge of the earlier behaviour of the function. The last few decades have witnessed a substantial increase in the application of mathematical models to HIV-1 viral infection model. Many authors are interested in studying the HIV infection models (see, for example,[14, 15, 16, 17, 18, 19, 20, 21] and the references cited therein). Several mathematical models have been used to investigate the dynamics of viral infections, the majority using a set of ordinary differential equations for the time evolution of the population of healthy and infected cells, as well as virus load and Lymphocities cells of the immune system [22].

In general, the interaction of viruses with uninfected cells are considered to be as ”mass-action” which suggests that rate of infection is directly proportional to the product of concentrations of uninfected cells and viruses. But this principle is not always true in real life. For example, the law of mass-action will not be followed if the concentration of viruses is greater than that of concentration of uninfected cells. In such case, increase in concentration of viruses will not increase infection. Taking this into consideration, we suggest that infection rate can be taken as nonlinear infection rate. Here in the proposed model we have considered saturated infection rate, also known as Holling type II infection rate and represented by the term $\frac{\beta x v}{1+\alpha v}; \beta > 0, \alpha \geq 0$. Let us we consider the following saturated infection rate on a four-dimensional equations with two delays are as follows:

$$
\begin{aligned}
\dot{x} &= \lambda - d_1 x(t) - \frac{\beta x(t)v(t)}{1+\alpha v(t)},\\
\dot{y} &= \frac{\beta x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - d_2 y(t) - \mu y(t)z(t),\\
\dot{v} &= k y(t) - d_3 v(t),\\
\dot{z} &= \frac{\gamma y(t-\tau_2)z(t-\tau_2)}{h+z(t-\tau_2)} - d_4 z(t).
\end{aligned} \tag{1}
$$

where the interaction between activated $CD4^+$ T cells, $x(t)$, infected $CD4^+$ T cells, $y(t)$, viruses, $v(t)$ and immune cells, $z(t)$. where activated $CD4^+$ T cells are produced at a rate of λ cells day^{-1}, decay at a rate d_1 day^{-1} and can become infected at a rate that is proportional to the number of infected $CD4^+$ T cells $y(t)$ with a infection rate constant β day^{-1}cell^{-1}. The infected $CD4^+$ T cells are assumed to decay at the rate of d_2 day^{-1} . The CTL responses eliminate at a rate that is proportional to the number of CTLs with a killing rate constant μ day^{-1}cell^{-1}. Free viruses produced from infected cells at the rate k, decay at a rate d_3 day^{-1}. The CTLs immune response to the infection rate γ, d_4 is a decay rate of CTLs immune response . We considered saturated immune response function $\frac{\gamma y(t)z(t)}{h+z(t)}$ to replace the bilinear rate, here h is a saturation constant. Namely, we incorporate a time delay τ_1 to describe the period between healthy cells contacting with viruses and complete production of viral RNA and protein. τ_2 represents the period between infected cells and contacting with CTL's immune cells.

This paper is organized as follows: In section 2, we describe that the solutions of (1) with positive initial conditions will remain positive for all time and their boundedness. stability analysis of disease-free, immunity inactivate and immunity activated equilibrium are analyzed in section 3. In section 4, we present the permanence of the system with the help of steady state. Finally, we draw our conclusion in section 5.

2. Properties of Solutions

We denote by C the Banach space of continuous function $\phi : [-\tau, 0] \to \mathbb{R}^4$ with norm

$$||\phi|| = \sup_{-\tau\le\theta\le 0} \{|\phi_1(\theta)|, |\phi_2(\theta)|, |\phi_3(\theta)|, |\phi_4(\theta)|\},$$

where $\phi = (\phi_1, \phi_2, \phi_3, \phi_4)$ and $\tau = \max\{\tau_1, \tau_2\}$. Further, let

$$C_+ = \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in C, \ \ \phi_i \geq 0 \ \text{ for all } \ \theta \in [-\tau, 0], i = 1,2,3,4\}.$$

The initial condition for system (1) is given as

$$x(\theta) = \phi_1(\theta), \ y(\theta) = \phi_2(\theta), \ v(\theta) = \phi_3(\theta), \ z(\theta) = \phi_4(\theta), \ -\tau \leq \theta \leq 0 \tag{2}$$

where $\phi = (\phi_1, \phi_2, \phi_3, \phi_4)$.

Theorem 1. *Let $x(t), y(t), v(t), z(t)$ be the solution of the system (1) with initial conditions (2) then $x(t), y(t), v(t)$ and $z(t)$ are all positive and bounded for $t > 0$ at which the solution exists.*

3. Stability Analysis

In this section, we perform the stability analysis of the steady states to study the long term behavior of the solution trajectories of the system (1). We study the local stability analysis of an immunity inactivated equilibrium, immunity activated equilibrium and a disease-free equilibrium of system (1) by analyzing the corresponding characteristic equations respectively. System (1) has a disease free equilibrium

$$I_0(x_0, y_0, v_0, z_0) = \left(\frac{\lambda}{d_1}, 0, 0, 0\right).$$

Further, if $\lambda \beta k > d_1 d_2 d_3$, then the system has a unique immunity-inactivated equilibrium

$$I_1(x_1, y_1, v_1, 0) = \left(\frac{\lambda\left(1 + \alpha \frac{k y_1}{d_3}\right)}{d_1\left(1 + \alpha \frac{k y_1}{d_3}\right) + \beta \frac{k y_1}{d_3}}, \ \frac{d_3 d_1 (R_0 - 1)}{k(\alpha d_1 + \beta)}, \ \frac{k y_1}{d_3}, \ 0 \right)$$

Let $R_0 = \dfrac{\lambda \beta k}{d_1 d_2 d_3}$. It is well known the importance of the value R_0, which is called as the basic reproductive ration of system (1). It represents the average number of secondary infection caused by a single infected T cells in an entirely susceptible T cells population throughout its infectious period. And it determines the dynamical properties of system (1) over a long period of time.

Denote $R_1 = \dfrac{\gamma d_3 d_1 (R_0 - 1)}{khd_4(\alpha d_1 + \beta)}$ where R_1 is called immunity-activated reproduction number of system (1). Besides, we can show that if $R_1 > 1$, system (1) has an immunity-activated equilibrium

$$I_2(x_2,y_2,v_2,z_2) = \left(\frac{(d_2+\mu z_2)(\gamma d_3 + \alpha d_4 k(h+z_2))}{\gamma\beta k}, \frac{d_4(h+z_2)}{\gamma}, \frac{d_4 k(h+z_2)}{\gamma d_3}, \frac{-b+\sqrt{\Delta}}{2a} \right)$$

$$a = d_4\mu k(\alpha d_1+\beta); \quad b = d_4 k(\alpha d_1+\beta)(d_2+h\mu) + d_1\mu\gamma d_3;$$

$$\Delta = (d_4 k(\alpha d_1+\beta)(d_2+h\mu)+d_1\mu\gamma d_3)^2 + 4d_2 {d_4}^2 k^2 h\mu(\alpha d_1+\beta)^2(R_1-1).$$

Theorem 2. *If $R_0 < 1$, I_0 of model (1) is locally asymptotically stable for any time delay $\tau > 0$. If $R_0 > 1$, I_0 of model (1) is unstable for any time delay $\tau > 0$.* □

When $R_0 > 1$, the system (1) has a immunity inactivated steady state $I_1 = (x_1, y_1, v_1, 0)$. Then the linearized system (1) at I_1 yields

$$\begin{aligned}
\dot{u_{11}} &= -d_1 u_{11}(t) - \frac{\beta v_1}{1+\alpha v_1} u_{11}(t) - \frac{\beta x_1}{(1+\alpha v_1)^2} u_{31}(t), \\
\dot{u_{21}} &= \frac{\beta v_1}{1+\alpha v_1} u_{11}(t-\tau_1) + \frac{\beta x_1}{(1+\alpha v_1)^2} u_{31}(t-\tau_1) - d_2 u_{21}(t) - \mu u_{21}(t) z_1 - \mu u_{41}(t) y_1, \\
\dot{u_{31}} &= k u_{21}(t) - d_3 u_{31}(t), \\
\dot{u_{41}} &= \frac{\gamma y_1}{(h+z_1)^2} u_{41}(t-\tau_2) + \frac{\gamma z_1}{(h+z_1)} u_{21}(t-\tau_2) - d_4 u_{41}(t).
\end{aligned} \tag{3}$$

The characteristic equation of the above linear system is given by

$$\begin{vmatrix}
-\left(d_1 + \frac{\beta v_1}{1+\alpha v_1}\right) - \wp & 0 & -\frac{\beta x_1}{(1+\alpha v_1)^2} & 0 \\
\frac{\beta v_1}{1+\alpha v_1} e^{-\wp\tau_1} & -(d_2+\mu z_1) - \wp & \frac{\beta x_1}{(1+\alpha v_1)^2} e^{-\wp\tau_1} & -\mu y_1 \\
0 & k & -d_3 - \wp & 0 \\
0 & \frac{\gamma z_1}{(h+z_1)} e^{-\wp\tau_2} & 0 & \frac{\gamma y_1}{(h+z_1)^2} e^{-\wp\tau_2} - d_4 - \wp
\end{vmatrix} = 0,$$

From the above Jacobian matrix, we conclude the following theorem

Theorem 3. *If $R_1 < 1 < R_0$, then the immunity inactivated steady state I_1 of model (3) is locally asymptotically stable in the case of $\tau_2 = 0$.* [23]

When $R_1 < 1 < R_0$, the system (1) has a immunity activated steady state $I_2 = (x_2, y_2, v_2, z_2)$. Then the linearized system (1) at I_2 yields

$$\begin{aligned}
\dot{u_1} &= -d_1u_1(t) - \frac{\beta v_2}{1+\alpha v_2}u_1(t) - \frac{\beta x_2}{(1+\alpha v_2)^2}u_3(t), \\
\dot{u_2} &= \frac{\beta v_2}{1+\alpha v_2}u_1(t-\tau_1) + \frac{\beta x_2}{(1+\alpha v_2)^2}u_3(t-\tau_1) - d_2u_2(t) - \mu u_2(t)z_2 - \mu u_4(t)y_2, \\
\dot{u_3} &= ku_2(t) - d_3u_3(t), \\
\dot{u_4} &= \frac{\gamma y_2}{(h+z_2)^2}u_4(t-\tau_2) + \frac{\gamma z_2}{(h+z_2)}u_2(t-\tau_2) - d_4u_4(t).
\end{aligned} \tag{4}$$

The characteristic equation of the above linear system is given by

$$\begin{vmatrix}
-\left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right) - \wp & 0 & -\frac{\beta x_2}{(1+\alpha v_2)^2} & 0 \\
\frac{\beta v_2}{1+\alpha v_2}e^{-\wp\tau_1} & -(d_2+\mu z_2) - \wp & \frac{\beta x_2}{(1+\alpha v_2)^2}e^{-\wp\tau_1} & -\mu y_2 \\
0 & k & -d_3 - \wp & 0 \\
0 & \frac{\gamma z_2}{(h+z_2)}e^{-\wp\tau_2} & 0 & \frac{\gamma y_2}{(h+z_2)^2}e^{-\wp\tau_2} - d_4 - \wp
\end{vmatrix} = 0,$$

From the above Jacobian matrix, we conclude the following theorem

Theorem 4. *Suppose*

(1) $R_1 > 1$

(2) If $\tau_1 = 0$ *and* $\tau_2 > 0$*, then the infected steady state* I_2 *of model (4) is locally asymptotically stable when* $\tau_2 < \tau_2^*$.

Proof. For $\tau_2 > 0$ and $\tau_1 = 0$ the characteristic equation (4) becomes

$$\wp^4 + k_1^*\wp^3 + k_2^*\wp^2 + k_3^*\wp + k_4^* + e^{-\wp\tau_2}(m_1\wp^2 + m_2\wp + m_3) = 0, \tag{5}$$

where

$$\begin{aligned}
k_1^* &= d_1 + \frac{\beta v_2}{1+\alpha v_2} + d_2 + \mu z_2 + d_3 + d_4, \\
k_2^* &= \left(d_1 + \frac{\beta v_2}{1+\alpha v_1}\right)(d_2+\mu z_2) + d_3d_4 + \left(d_1 + \frac{\beta v_2}{1+\alpha v_2} + d_2 + \mu z_2\right)(d_3+d_4) \\
&\quad - \frac{\beta k x_2}{(1+\alpha v_2)^2},
\end{aligned}$$

$$\begin{aligned}
k_3^* &= \left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right)(d_2+\mu z_2)(d_3+d_4) + \left(d_1 + \frac{\beta v_2}{1+\alpha v_2} + d_2 + \mu z_2\right) d_3 d_4 - \\
&\quad \frac{\beta k x_2}{(1+\alpha v_2)^2}\left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right) d_4 + \left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right) d_3, \\
k_4^* &= \left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right)(d_2+\mu z_2)(d_3+d_4) - \left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right) d_4 + \frac{\beta^2 v_2 k x_2 d_4}{(1+\alpha v_2)^3 (h+z_2)^2}, \\
m_1 &= \frac{\mu y_2 \gamma z_2}{h+z_2} - \frac{y_2\gamma}{(h+z_2)^2} - \frac{d_3 y_2 \gamma}{(h+z_2)^2}, \\
m_2 &= \frac{\mu y_2 \gamma z_2}{h+z_2}\left(d_1 + \frac{\beta v_2}{1+\alpha v_2} + d_3\right) \\
&\quad - \frac{d_3 \gamma y_2}{(h+z_2)^2}\left(d_1 + \frac{\beta v_2}{1+\alpha v_2} + d_2 + \mu z_2\right) - \frac{d_3 \gamma y_2}{(h+z_2)^2}\left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right) - (d_2 + \mu z_2), \\
m_3 &= \left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right) \frac{\beta k \gamma x_2 y_2}{(1+\alpha v_2)^2 (h+z_2)^2} + \frac{\beta k \gamma x_2 y_2}{(1+\alpha v_2)^2 (h+z_2)^2} \\
&\quad + \frac{\mu y_2 \gamma z_2}{h+z_2}\left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right) d_3 - \frac{\beta^2 v_2 k x_2 y_2}{(1+\alpha v_2)^3 (h+z_2)^2} \\
&\quad - \left(d_1 + \frac{\beta v_2}{1+\alpha v_2}\right)(d_2+\mu z_2) d_3 \frac{\gamma y_2}{(h+z_2)^2}
\end{aligned}$$

Let $\wp = i\omega^*$ $(\omega^* > 0)$ be a root of (5), and separating the real and imaginary parts, we have

(6) $$\omega^{*4} - \omega^{*2} k_2^* + k_4^* = (m_1 \omega^{*2} - m_3)\ \cos(\omega^* \tau_3) - m_2\ \omega^*\ \sin(\omega^* \tau_3)$$

(7) $$\omega^* k_3^* - \omega^{*3} k_1^* = (m_1 \omega^{*2} - m_3)\ \sin(\omega^* \tau_3) + m_2\ \omega^*\ \cos(\omega^* \tau_3).$$

Squaring and adding both equations of (6) and (7), we can obtain the following Eight-degree equation for ω^*:

(8) $$\omega^{*8} + \omega^{*6}(k_1^{*2} - 2k_2^*) + \omega^{*4}(k_2^{*2} - m_1^2 + 2k_4^* - 2k_1^* k_3^*) + \omega^{*2}(k_3^{*2} - 2k_2^* k_4^* - m_2^2) + k_4^{*2} - m_3^2 = 0.$$

Putting $\omega^{*2} = u^{**}$ into (8), we can get the following equation:

(9) $$F(u^{**}) = u^{**4} + A_1^* u^{**3} + A_2^* u^{**2} + A_3^* u^{**} + A_4^* = 0.$$

Where

$$\begin{aligned}
A_1^* &= k_1^{*2} - 2k_2^* \\
A_2^* &= k_2^{*2} - m_1^2 + 2k_4^* - 2k_1^* k_3^* \\
A_3^* &= k_3^{*2} - 2k_2^* k_4^* - m_2^2 \\
A_4^* &= k_4^{*2} - m_3^2.
\end{aligned}$$

Taking derivative with respect to u^{**} of equation (9), we get

$$\dot{F}(u^{**}) = 4u^{**3} + 3u^{**2}A_1^* + 2u^{**}A_2^* + A_3^* = 0. \tag{10}$$

Set

$$4u^{**3} + 3u^{**2}A_1^* + 2u^{**}A_2^* + A_3^* = 0. \tag{11}$$

Let $m^* = u^{**} + \frac{A_1^*}{4}$, then (11) becomes

$$m^{*3} + \alpha_1 m^* + \alpha_2 = 0, \tag{12}$$

where

$$\alpha_1 = \frac{A_2^*}{2} - \frac{3A_1^*2}{16}, \quad \alpha_2 = \frac{A_1^*3}{32} - \frac{A_1^*A_2^*}{8} + \frac{A_3^*}{4}.$$

Define

$$\begin{aligned}
\Delta &= \left(\frac{\alpha_2}{2}\right)^2 + \left(\frac{\alpha_1}{3}\right)^3; \;\; \delta = \frac{-1+i\sqrt{3}}{2}; \\
m_1^* &= \sqrt[3]{-\frac{\alpha_2}{2} + \sqrt{\Delta}} + \sqrt[3]{-\frac{\alpha_2}{2} - \sqrt{\Delta}}; \\
m_2^* &= \sqrt[3]{-\frac{\alpha_2}{2} + \sqrt{\Delta\delta}} + \sqrt[3]{-\frac{\alpha_2}{2} - \sqrt{\Delta\delta^2}}; \\
m_3^* &= \sqrt[3]{-\frac{\alpha_2}{2} + \sqrt{\Delta\delta^2}} + \sqrt[3]{-\frac{\alpha_2}{2} - \sqrt{\Delta\delta}}; \\
u_i^{**} &= m_i^* - \frac{A_1^*}{4}, \;\; i = 1,2,3.
\end{aligned}$$

We cite the results in [24] about the existence of positive roots of the fourth-degree polynomial equation, namely, we have the following lemma.

Lemma 5. *(1) If $A_4^* < 0$, then (9) has at least one positive root.*

(2) If $A_4^* \geq 0$ and $\Delta \geq 0$ then (9) has positive roots if and only if $u_1^* > 0$ and $F(u_1^*) < 0$.

(3) If $A_4^* \geq 0$ and $\Delta < 0$, then (9) 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, (9) has finite positive rootss $u_1, u_2, u_3, ..., u_k, k \leq 4$. Therefore (8) 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

$$\tau_{2i}^j = \frac{1}{\omega_i} \arccos\left(\frac{\eta_1}{\eta_2}\right)$$

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

where

$$\eta_1 = (\omega_i^{*4} - k_2^* \omega_i^{*2} + k_4^*)(m_1 \omega_i^{*2} - m_3)) + (\omega_i^{*2} k_3^* - \omega_i k_1^*) m_2$$
$$\eta_2 = (m_1 \omega_i^2 - m_3)^2 + \omega_i^{*2} m_2^2.$$

Now, we determine sign $\left(\dfrac{dRe(\lambda)}{d\tau_3}\right)\Bigg|_{\tau_2 = \tau_2^*}$ 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 immunity activated steady state of model (1) remains stable for $\tau_2 < \tau_2^*$ and Hopf bifurcation occurs when $\tau_2 = \tau_2^*$.

When $\tau_2 > 0$ we show the existence of bifurcating periodic solutions. We already proved that the characteristic equation (5) has a purely imaginary eigenvalues $i\omega^*$, now we shall verify the transversality condition only.

Differentiating (5) with respect to τ_2, we get

$$\left\{(4\wp^3 + 3\wp^2 k_1^* + 2\wp k_2^* + k_3^*) + e^{-\wp\tau_2}(2\wp m_1 + m_2) - \tau_2 e^{-\wp\tau_2}(m_1\wp^2 + m_2\wp + m_3)\right\}$$
$$\frac{d\wp}{d\tau_2} = \wp e^{-\wp\tau_2}(m_1\wp^2 + m_2\wp + m_3)$$

which implies,

$$\begin{aligned}\left(\frac{d\wp}{d\tau_2}\right)^{-1} &= \frac{4\wp^3+3\wp^2k_1^*+2\wp k_2^*+k_3^*}{\wp e^{-\wp\tau_2}(m_1\wp^2+m_2\wp+m_3)}+\frac{2\wp m_1+m_2}{\wp(m_1\wp^2+m_2\wp+m_3)}-\frac{\tau_2}{\wp},\\ &= \frac{4\wp^3+3\wp^2k_1^*+2\wp k_2^*+k_3^*}{-\wp(\wp^4+k_1^*\wp^3+k_2^*\wp^2+k_3^*\wp+k_4^*)}+\frac{2\wp m_1+m_2}{\wp(m_1\wp^2+m_2\wp+m_3)}-\frac{\tau_2}{\wp},\\ &= \frac{3\wp^4+2k_1^*\wp^3+k_2^*\wp^2-k_4^*}{-\wp^2(\wp^4+k_1^*\wp^3+k_2^*\wp^2+k_3^*\wp+k_4^*)}+\frac{\wp^2m_1-m_3}{\wp^2(m_1\wp^2+m_2\wp+m_3)}-\frac{\tau_2}{\wp}.\end{aligned}$$

Therefore,

$$\begin{aligned}\Xi &= sign\left\{Re\left(\frac{3\wp^4+2k_1^*\wp^3+k_2^*\wp^2-k_4^*}{-\wp^2(\wp^4+k_1^*\wp^3+k_2^*\wp^2+k_3^*\wp+k_4^*)}+\frac{\wp^2m_1-m_3}{\wp^2(m_1\wp^2+m_2\wp+m_3)}-\frac{\tau_2}{\wp}\right)\right\}_{\wp=i\omega_0^*}\\ &= sign\left\{Re\left(\frac{(3\omega_0^{*4}-\omega_0^{*2}k_2^*-k_4^*)+i(-2\omega_0^{*3}k_1^*)}{\omega_0^{*2}(\omega_0^{*4}-\omega_0^{*2}k_2^*+k_4^*)+i(\omega_0^*k_3^*-\omega_0^{*3}k_1^*)}+\frac{m_1\omega_0^{*2}+m_3}{\omega_0^{*2}(m_3-m_1\omega_0^{*2})+i(m_2\omega_0^*)}-\frac{\tau_2}{i\omega_0^*}\right)\right\}\\ &= \frac{1}{\omega_0^{*2}}sign\left\{\frac{(3\omega_0^{*4}-\omega_0^{*2}k_2^*-k_4^*)(\omega_0^{*4}-\omega_0^{*2}k_2^*+k_4^*)-2\omega_0^{*3}k_1^*(\omega_0^*k_3^*-\omega_0^{*3}k_1^*)}{(\omega_0^{*4}-\omega_0^{*2}k_2^*+k_4^*)^2+(\omega_0^*k_3^*-\omega_0^{*3}k_1^*)^2}\right.\\ &\quad\left.+\frac{(m_1\omega_0^{*2}+m_3)(m_3-m_1\omega_0^{*2})}{(m_3-m_1\omega_0^{*2})^2+(m_2\omega_0^*)^2}\right\}\\ &= \frac{1}{\omega_0^{*2}}sign\left\{\frac{(3\omega_0^{*4}-\omega_0^{*2}k_2^*-k_4^*)(\omega_0^{*4}-\omega_0^{*2}k_2^*+k_4^*)-2\omega_0^{*3}k_1^*(\omega_0^*k_3^*-\omega_0^{*3}k_1^*)}{(m_3-m_1\omega_0^{*2})^2+(m_2\omega_0^*)^2}\right.\\ &\quad\left.+\frac{(m_1\omega_0^{*2}+m_3)(m_3-m_1\omega_0^{*2})}{(m_3-m_1\omega_0^{*2})^2+(m_2\omega_0^*)^2}\right\}\\ &= \frac{1}{\omega_0^{*2}}sign\left\{\frac{3\omega_0^{*8}+(k_1^{*2}-2k_2)\omega_0^{*6}+(k_2^{*2}-2k_1^*k_3^*+2k_4^*-m_1^2)\omega_0^{*4}+k_4^{*2}-m_3^2}{(m_3-m_1\omega_0^{*2})^2+(m_2\omega_0^*)^2}\right\}.\end{aligned}$$

As $k_1^{*2}-2k_2^*$, $k_2^{*2}-2k_1^*k_3^*+2k_4^*-m_1^2$ and $k_4^{*2}-m_3^2$ are both positive by virtue of equation (8), we have

$$\left(\frac{dRe(\wp)}{d\tau_2}\right)\Bigg|_{\omega^*=\omega_0^*,\tau_2=\tau_2^*}>0.$$

Therefore the transversality condition holds and hence Hopf bifurcation occurs at $\omega^*=\omega_0^*,\tau_2=\tau_2^*$.

□

4. Permanence of System

Persistence (or permanence) is an important property of dynamical systems and of the systems in ecology, epidemics etc., they are modeling. Persistence addresses the long-term survival of some or all components of a system, while permanence also deals with the limits of growth for some (or all) components of the system. In this section, we shall present the permanence of the system (1).

Definition 6. *The system* (1) *is said to be persistent if there are positive constants* P_1, P_2 *such that each positive solution* $(x(t), y(t), v(t), z(t))$ *of the system (1) with initial conditions* (2) *satisfies*

$$P_1 \leq \liminf_{t\to\infty} x(t) \leq \limsup_{t\to\infty} x(t) \leq P_2,$$
$$P_1 \leq \liminf_{t\to\infty} y(t) \leq \limsup_{t\to\infty} y(t) \leq P_2,$$
$$P_1 \leq \liminf_{t\to\infty} v(t) \leq \limsup_{t\to\infty} v(t) \leq P_2,$$
$$P_1 \leq \liminf_{t\to\infty} z(t) \leq \limsup_{t\to\infty} z(t) \leq P_2. \tag{13}$$

Definition 7. *(Metzler matrix) (see* [25]*, 6) Matrix* J_{ij} *is a Metzler matrix if and only if all its off-diagonal elements are non-negative.*

Lemma 8. *(Perron-Frobenius Theorem) (see* [25]*, 6) Let* J_{ij} *be an irreducible Metzler matrix. Then,* λ_M *the eigenvalue of* J_{ij} *of largest real part is real, and the elements of its associated eigenvector* v_M *are positive. Moreover, any eigenvector of* J_{ij} *with non-negative elements belongs to span* v_M.

In order to prove the permanence of the system (1), we present the permanence theory for inifinite dimensional system from Theorem 4.1 [25]. Let X be a compact metric space. Suppose that $X^0 \in X,\ X_0 \in X,\ X^0 \bigcap X_0 = \emptyset$. Assume that $x(t)$ is a C_0 semigroup on X satisfying:

$$x(t) : X^0 \to X^0,$$
$$x(t) : X_0 \to X_0. \tag{14}$$

Let $x_b(t) = x(t)|_{X_0}$ and let A_b be the global attractor for $x_b(t)$.

Theorem 9. *(See* [26]*) Suppose that* $x(t)$ *satisfies (14) and we have the following:*

(1) there is a $t_0 \geq 0$ *such that* $x(t)$ *is compact for* $t > t_0$*;*

(2) $x(t)$ *is dissipative in* X*;*

(3) $\bar{A_b} = \cup_{\hat{x}\in\mathscr{A}_b}\omega(\hat{x})$ *is isolated and has an acyclic covering* $Q = \cup_{i=1}^{k} Q_i$.

(4) *For each* $Q_i \in Q, W^s(Q_i) \cap X^0 = \emptyset$, *where* W^s *refers to the stable set.*

Then $x(t)$ *is uniformly repeller with respect to* X^0, *i.e., there is a* $\sigma > 0$ *such that for any* $\hat{x} \in X^0$,

$$\liminf_{t\to\infty} d(x(t)\hat{x}, X_0) \geq \sigma,$$

where d is the distance of $x(t)\hat{x}$ *from* X_0.

Theorem 10. *If* $R_0 > 1$*, then the system (1) is permanent.*

Proof. The result follows from the above Theorem 9, Let us define Z_1 be the interior of $\mathbb{R}^4_+$ and Z_2 be the boundary of $\mathbb{R}^4_+, i.e., Z_1 = \text{int}(\mathbb{R}^4_+)$ and $Z_2 = \text{bd}(\mathbb{R}^4_+)$. This choice is in accordance with the conditions stated in this theorem. We begin by showing that sets Z_1 and Z_2 repel the positive solution of the system (1) uniformly. Furthermore, note that by using theorem 1, there exists a compact set B in which all solutions of the system (1) initiated in $\mathbb{R}^4_+$ ultimately enter and remain forever after. Denoting the Ω limit set of the solution $\tilde{z}(t,\tilde{z}_0)$ of the system (1) starting in $\tilde{z}_0 \in \mathbb{R}^4_+$ by $\Omega(\tilde{z}_0)$, we need to determine the following set:

$$\Theta = \bigcup_{\kappa_1 \in Y_2} \Omega(\kappa_1), \;\; Y_2 = \{\tilde{z}_0 \in Z_2 | \tilde{z}(t,\tilde{z}_0) \in Z_2, \forall t > 0\}.$$

From the system (1), it follows that all solutions starting in $\text{bd}(\mathbb{R}^4_+)$, but not on the x- axis leave $\text{bd}(\mathbb{R}^4_+)$ and that the x- axis is an invariant set, implying that $Y_2 = \{(x,y,v,z) \in \text{bd}(\mathbb{R}^4_+) | y = v = z = 0\}$. Furthermore, it is easy to see that $\{I_0\}$ as all solutions initiated on the x- axis converges to I_0, in fact, in the set Y_2, the system (1) becomes

$$\frac{dx}{dt} = \lambda - d_1 x.$$

It is easy to see that I_0 is globally asymptotically stable if $R_0 < 1$. Hence any solution $(x(t),y(t),v(t),z(t))$ of the system (1) initiating from Y_2 is such that $(x(t),y(t),v(t),z(t))$ $\to I_0(x,0,0,0)$. Obviously, I_0 is isolated invariant, $\{I_0\}$ is isolated and is an acyclic covering. Next, we show that $W^s(I_0) \bigcap Z_1 = \emptyset \;\; i.e., I_0$ is a weak repeller for Z_1.

By the definition of I_0 is a weak repeller for Z_1, if for every solution starting in $\tilde{z}_0 \in Z_1$,

$$\lim_{t\to\infty} d(x(t,\tilde{z}_0), I_0) \geq \sigma, \tag{15}$$

We claim that (15) is satisfied if the following holds:

$$W^s(I_0)\bigcap int(\mathbb{R}^4_+) = \emptyset. \tag{16}$$

To see this, suppose (15) does not hold for some solution $x(t,\tilde{z_0})$ starting in $\tilde{z_0} \in Z_1$. In view of the fact that the closed positive orthant is positively invariant for system (1), it follows that $\lim_{t\to\infty} d(x(t,\tilde{z_0}), I_0) = 0$ and thus that $\lim_{t\to\infty} x(t,\tilde{z_0}) = I_0$, which is clearly impossible if (16) holds. What remains to show is that (16) holds. Now the jacobian matrix of the system (1) at I_0 is given in the following:

$$J_0 = \begin{bmatrix} -d_1 & 0 & -\beta\frac{\lambda}{d_1} & 0 \\ 0 & -d_2 & \beta\frac{\lambda}{d_1}e^{-\lambda\tau_1} & 0 \\ 0 & k & -d_3 & 0 \\ 0 & 0 & 0 & -d_4 \end{bmatrix}. \tag{17}$$

It is easy to see that J_0 is unstable if $R_0 > 1$. In particular, J_0 possesses one eigenvalue with positive real part, which we denote as λ_+, and two eigenvalues with negative real part which we denote as λ_-. We proceed by determining the location of $E^s(I_0)$, the stable eigen space of I_0. Clearly, $(1,0,0,0)^T$ is an eigenvector of J_0 associated to $-\mu$. If $\lambda_- \neq -d_1$, then the eigenvector associated to λ_- has the following structure: $(0,q_2,q_3,q_4)^T$, where q_2,q_3,q_4 satisfy the eigenvector equation

$$\begin{bmatrix} -d_2 & \beta\frac{\lambda}{d_1}e^{-\lambda\tau_1} & 0 \\ k & -d_3 & 0 \\ 0 & 0 & -d_4 \end{bmatrix}\begin{bmatrix} q_2 \\ q_3 \\ q_4 \end{bmatrix} = \lambda_- \begin{bmatrix} q_2 \\ q_3 \\ q_4 \end{bmatrix}. \tag{18}$$

If $\lambda_- = -d_1$, then λ_- is a repeated eigenvalue, and associated generalized eigenvector will possess the following structure $(*,q_2,q_3,q_4)^T$, where the value of $*$ is irrelevant for what follows and q_2, q_3 and q_4 also satisfy (18).

We claim that in both case, the vector $(q_2,q_3,q_4)^T \notin \mathbb{R}^3_+$. Obviously, the matrix in (18) is an irreducible Metzler matrix. From Definition 7, we know that it is a matrix with non-negative off-diagonal entries. By using Lemma 8, we get the real eigenvalue which is larger then the real part of any other eigenvalue, also called the dominant eigenvalue. Clearly, the dominant eigenvalue here is λ_+. But, the Perron-Frobenius Theorem also implies that every eigenvector that is not associated with the dominant eigenvalue does not belong to the closed positive orthant, this means that $(*, q_2, q_3, q_4)^T \notin \mathbb{R}^3_+$. Consequently, $E^s(I_0) \bigcap \mathrm{int}(\mathbb{R}^3_+) = \emptyset$ and therefore also $W^s(I_0) \bigcap Z_1 = \emptyset$, which concludes the proof. □

5. CONCLUSION

We conclude with a brief discussion of our results. In this paper, we considered two incorporated delays in a model to study HIV-1 dynamics for viral infection with CTL immune response and both infected and immune cell infections. Incorporating the immune response delay into the model generates rich dynamics. In our model shows that the positive immune delay, τ_2 is able to destabilize the immunity activated equilibrium. We showed that for this simplified model (1), immunity activated steady state is locally asymptotically stable for $\tau_2 < \tau_2^*$ and bifurcation leads when $\tau_2 = \tau_2^*$. Further we show that bifurcation analysis at $\tau_2 = \tau_2^*$ and proofs on this issue are needed and we will concern about this problem in our further studies.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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