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DYNAMIC ANALYSIS OF HUMORAL IMMUNITY HIV FOR BOTH VIRUS-TO-CELL AND CELL-TO-CELL TRANSMISSIONS WITH RTI

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Abstract. In this paper, we have fabricated an HIV RTI model accompanied with humoral immunity. Positivity solution for the model and boundedness of the model were derived. Stability analysis of the constructed model about its steady states has been deliberated. Sensitivity analysis is performed on a delay differential equation model for human immunodeficiency virus (HIV) with reverse transcription inhibitors (RTI) model.

Keywords: HIV infection; cell to cell transmission; virus to cell transmission; delays; stability analysis; bifurcation.

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1. INTRODUCTION

Mathematical models have been used extensively in research into the epidemiology of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) to improve our understanding of major contributing factors in a giving epidemic. It has been more than three decades that the HIV has reached a pandemic state. The worldwide emergence of this infectious agent coincided with the advent of new modeling techniques in epidemiology, e.g. the adaptive

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dynamics framework. Consider the basic mathematical model for HIV infection containing the density of uninfected cells, that of infected cells, and that of virus cells in [1]. They also present models which incorporate the effect of the cell-mediated immunity to this model. It is observed that, no HIV infection model with this type of infected-to-target infection has considered the effect of immune response. In recent, some viral infection with mathematical models along with therapy intervention have been studied in [2–6]. Recently, Virgin and Walker [7] and Roederer et al. [8] revealed that humoral immunity plays an important role in the whole human immunity and considered that only by understanding the both two immune responses in unprecedented depth can we develop a protective HIV vaccine. Hence, mathematical modeling and analysis of virus dynamics with humoral immunity can be helpful to design treatment strategies and to provide insights on evaluating effective antiviral drug therapies. To prevent the dispersal of infection within a host cell to cell and virus to cell, we expend reverse transcriptase inhibitor therapy for our model. Moreover the model incorporated for RTI with different drug efficacies on uninfected and infected cells and humoral immunity as:

$$
\begin{aligned}
\frac{dT}{dt} &= s - d_1 T(t) - (1-\eta_1)\beta_1 T(t)V(t) - (1-\eta_2)\beta_2 T(t)T^*(t) \\
\frac{dT^*}{dt} &= (1-\eta_1)\beta_1 T(t-\tau_1)V(t-\tau_1) + (1-\eta_2)\beta_2 T(t-\tau_2)T^*(t-\tau_2) - d_2 T^*(t) \\
\frac{dV}{dt} &= bT^*(t-\tau_3) - d_3 V(t) - pV(t)Z(t), \\
\frac{dZ}{dt} &= gV(t)Z(t) - d_4 Z(t). \qquad (1)
\end{aligned}
$$

The model describes four populations. These include: uninfected target cells $T(t)$, productively infected cells $T^*(t)$, free virus, $V(t)$ and B cells, $Z(t)$. 's' represents the rate at which new T cells are created from sources. Parameter 'd_i', $(i = 1,2,3,4)$ are death rate of the $T(t), T^*(t), V(t)$ and $Z(t)$. Target cells are infected by free viral particles and infectious cells (productively infected cells) at rates $\beta_1 T(t)V(t)$ and $\beta_2 T(t)T^*(t)$ respectively. 'b' denotes the average production rate of virus from an infected cell. $pV(t)Z(t)$ and $gV(t)Z(t)$ are used to describe the virus killed by B cells and the new B cells produced by antigenic stimulation. Where 'η_1' denotes the efficacy of the RTI inhibiting the virus to cell infection and 'η_2' represents the

efficacy of the RTI with respect to the cell to cell channel. Parameters $\eta_1, \eta_2 \in [0,1]$, the value of 0 is associated with non-treatment and a value of 1 with full efficacy in the treatment. Drug resistance is a result of genetic mutations. $t-\tau_1$ describes the time delay between healthy cells and containing with viruses and complete production of viral RNA and protein. $t-\tau_2$ describes the period between healthy cells and containing with infected cells. In addition, a cell that is infected at time $t-\tau_3$ starts to generate new infectious HIV-1 particles at time t.

Humoral immunity has been incorporated into virus dynamics models in several works [9, 10]. however, in these papers, only virus-to-cell transmission has been considered. Therefore, reasonable mathematical models for HIV-1 with virus-to-target and infected-to-target infections should take humoral immunity into consideration. Model 1 has three steady states, infection-free steady state, immune inactivated and immune activated steady state. Moreover, the dynamics is governed by only one threshold parameter R_0 (the basic reproduction number) which is defined as the average total number of newly infected cells that arise from any one infected cell in the beginning of the infection. All parameters are assumed to be positive.

We adopt the following notation: $\mathbb{R}^4$ is a four-dimensional real Euclidean space with norm $|.|$. For $\tau > 0$, we denote by $C = C([-\tau,0],\mathbb{R}^4_+)$, the Banach space of continuous function mapping the interval $[-\tau,0]$ into $\mathbb{R}^4_+$ with the topology of uniform convergence, where $\tau = \max\{\tau_1,\tau_2,\tau_3\}$. By the standard theory of functional differential equation [11–13], we know that for any $\phi \in C([-\tau,0],\mathbb{R}^4_+)$, there exists a unique solution

$$Y(t,\phi) = (T(t,\phi),T^*(t,\phi),V(t,\phi),Z(t,\phi)),$$

of the delayed system (1), which satisfy $Y_0 = \phi$, where $\phi = (\phi_1,\phi_2,\phi_3,\phi_4) \in \mathbb{R}^4_+$ with $\phi_i(\xi) \geq 0 : (\xi \in [-\tau,0], i = 1,...,4)$, and $\phi_1(0),\phi_2(0),\phi_3(0),\phi_4(0) > 0$. And the initial conditions are given by,

$$T(\xi) = \phi_1(\xi), \quad T^*(\xi) = \phi_2(\xi), \quad V(\xi) = \phi_3(\xi), \quad Z(\xi) = \phi_4(\xi). \tag{2}$$

This paper is structured as follows. In Section 2, we perform the stability analysis on system (1). Sensitivity analysis is discussed in Section 3 and Section 4 is the conclusion.

2. Feasible Equilibria and Boundedness of Solutions

Clearly, system (1) always has an infection-free equilibrium $E_0\left(\frac{s}{d_1},0,0,0\right)$, we define the basic reproduction number as follows:

$$\begin{aligned} R_0 &= R_{01}+R_{02} \\ &= \frac{(1-\eta_1)\beta_1 T_0 b}{d_2 d_3}+\frac{(1-\eta_2)\beta_2 T_0}{d_2} \end{aligned} \tag{3}$$

R_0 is called the immune inactivated reproduction rate of system (1), which represents the number of newly infected cells produced by one infected cell during its lifespan. In fact, $\frac{(1-\eta_1)\beta_1 T_0 b}{d_2 d_3}$ is the average number of secondary viruses caused by a virus, that is the basic reproduction number corresponding to virus to cell transmission mode, while $\frac{(1-\eta_2)\beta_2 T_0}{d_2}$ is the average number of secondary infected cells caused by an infected cell, that is the basic reproduction number corresponding to cell to cell transmission mode.

It is easy to show that if $R_0>1$ system (1) has an immunity inactivated equilibrium $E_1(T_1,T_1^*,V_1,Z_1)$, where

$$(T_1,T_1^*,V_1,Z_1)=\left(\frac{T_0}{R_0},\frac{d_1 d_3}{b\beta_1+d_3\beta_2}(R_0-1),\frac{b}{d_3}\hat{T_1^*},0\right).$$

Denote $R_1=\frac{bT_2^*}{d_3 v_2}$ which is called immune-activated reproduction rate. If $R_1>1$, except for E_0 and E_1 , system (1) has an immunity-activated equilibrium $E_2(T_2,T_2^*,V_2,Z_2)$, where

$$(T_2,T_2^*,V_2,Z_2)=\left(\frac{d_2 T_2^*}{(1-\eta_1)\beta_1 V_2+(1-\eta_2)\beta_2 T_2^*},\frac{-B\pm\sqrt{B^2-4AC}}{2A},\frac{d_4}{g},\frac{d_3}{p}(R_1-1)\right)$$

where

$$\begin{aligned} A &= (1-\eta_2)\beta_2 d_2, \\ B &= (1-\eta_1)\beta_1 V_2 d_2+d_1 d_2-s(1-\eta_2)\beta_2, \\ C &= -s(1-\eta_1)\beta_1 V_2 \end{aligned}$$

Next we discuss the positivity and boundedness of the solution to system (1)

Theorem 1. *Let $Y(t,\phi)$ be the solution of the delayed system (1) with the initial conditions (2). Then $T(t), T^*(t), V(t)$ and $Z(t)$ are all non-negative and ultimately uniformly bounded $(\forall\, t \geq 0)$ at which the solution exists.*

Proof. Let $M_1(t) = d_1 + (1-\eta_1)\beta_1 V(t) + (1-\eta_2)\beta_2 T^*(t)$ and $M_2(t) = d_2; M_3(t) = d_3 + pV(t)$ From (1), we have

$$\begin{aligned}
T(t) &= e^{-\int_0^t M_1(\zeta)d\zeta} T(0) + \int_0^t s e^{-\int_\gamma^t M_1(\zeta)d\zeta} d\gamma, \\
T^*(t) &= e^{-d_2 t} T^*(0) + \int_0^t \{(1-\eta_1)\beta_1 T(\gamma-\tau_1)V(\gamma-\tau_1) \\
&\quad + (1-\eta_2)\beta_2 T(\gamma-\tau_2)T^*(\gamma-\tau_2)\} e^{-d_2(t-\gamma)} d\gamma. \\
V(t) &= e^{\int_0^t M_3(\zeta)d\zeta} V(0) + \int_0^t b T^*(\gamma-\tau_3) e^{\int_\gamma^t M_3(\zeta)d\zeta} d\gamma \\
Z(t) &= Z(0) e^{\int_0^t (gV(\gamma)-d_4)d\gamma}
\end{aligned}$$

To prove the boundedness, first by the positivity of solutions we've

$$\frac{dT}{dt} < s - d_1 T(t).$$

It follows that $\limsup_{t\to\infty} T(t) \leq \dfrac{s}{d_1}$, implying that $T(t)$ is bounded.

Next, we prove the boundedness of $T^*(t)$. Here, we define

$$H_1(t) = T(t-\tau_1) + T(t-\tau_2) + T^*(t).$$

Choose a positive constant $\bar{d_2}$ small enough such that $d_2 < \bar{d_2}$ and $\bar{d_2}\bar{T} < m_0$, where $m_0 := \max_{T\in[0,\bar{T}]}(s - d_1 T(t))$. Then for small $\sigma_1 > 0$, there is a $t_1 > 0$ such that $T(t-\tau) < \bar{T} + \sigma_1$ for $t \geq t_1$ and

$$\frac{dH_1(t)}{dt} \leq 2m_0 - \bar{d_2} H_1(t) - m_0 + \sigma_1 + \bar{d_2}.$$

Since σ_1 is an arbitrary constant, it implies

$$\limsup_{t\to\infty} H_1(t) \leq \frac{2m_0}{\bar{d_2}} = Q_1$$

From the positivity of $T^*(t)$, it holds that $\limsup_{t\to\infty} T^*(t) \leq Q_1$. Then for arbitrary $\sigma_2 > 0$, then there is a $t_2 > 0$ such that $T^*(t) \leq Q_1 + \sigma_2$ for $t \geq t_2$.

We define $H_2(t) = V(t+\tau_3) + \frac{p}{g}Z(t)$

$$\begin{aligned} \frac{dH_2(t)}{dt} &= bT^*(t) - min(d_3,d_4)H_2(t), \\ &\leq b(Q_1+\sigma_2) - min(d_3,d_4). \end{aligned}$$

Therefore, the solutions of the system (1) with initial condition in (2) are ultimately uniformly bounded. □

2.1. Stability analysis. In this section, we are concerned with the local asymptotic stability of feasible equilibria. Corresponding results can be certified by analyzing the distribution of characteristic equation roots.

Proposition 2. *The immune inactivated equilibrium E_1 of (1), is positive if and only if $R_0 > 1$.*

Proof. The coordinates of the immune inactivated equilibrium E_1, if they exist, satisfy the equalities:

$$\begin{aligned} s &= d_1T_1 + (1-\eta_1)\beta_1T_1V_1 + (1-\eta_2)\beta_2T_1T_1^* \\ (1-\eta_1)\beta_1T_1V_1 + (1-\eta_2)\beta_2T_1T_1^* &= d_2T_1^*, \\ bT_1^* &= d_3V_1. \end{aligned}$$

□

Proposition 3. *The immune activated equilibrium E_2 of (1), is positive if and only if $R_1 < 1$.*

Proof. The coordinates of the immune activated equilibrium E_2, if they exist, satisfy the equalities:

$$\begin{aligned} s &= d_1T_2 + (1-\eta_1)\beta_1T_2V_2 + (1-\eta_2)\beta_2T_2T_2^* \\ (1-\eta_1)\beta_1T_2V_2 + (1-\eta_2)\beta_2T_2T_2^* &= d_2T_2^*, \\ bT_2^* &= d_3V_2 + pV_2Z_2, \\ gV_2Z_2 &= d_4Z_2. \end{aligned} \tag{4}$$

□

Theorem 4. *If $R_0 < 1$, E_0 of model (1) is locally asymptotically stable for any time delay $\tau_i > 0$. If $R_0 > 1$, E_0 of model (1) is unstable for any time delay $\tau_i > 0$ $(i = 1,2,3)$.* □

Now, we have to ascertain the stability at E_1 so the linearization of the system (1) at E_1 and obtain the characteristic equation as follows.

$$\begin{vmatrix} -a_{11}-\lambda & -(1-\eta_2)\beta_2 T_1 & -(1-\eta_1)\beta_1 T_1 & 0 \\ a_{21} & -a_{22}-\lambda & (1-\eta_1)\beta_1 T_1 e^{-\lambda\tau_1} & 0 \\ 0 & be^{-\lambda\tau_3} & -d_3-\lambda & 0 \\ 0 & 0 & 0 & -d_4-\lambda \end{vmatrix} = 0,$$

where

$$a_{11} = d_1 + (1-\eta_1)\beta_1 V_1 + (1-\eta_2)\beta_2 T_1^*,\ a_{21} = (1-\eta_1)\beta_1 V_1 e^{-\lambda\tau_1} + (1-\eta_2)\beta_2 T_1^* e^{-\lambda\tau_2}$$

$$a_{22} = -(1-\eta_2)\beta_2 T_1 e^{-\lambda\tau_2} + d_2.$$

The stationary equation of (1)

$$s = d_1 T_1 + (1-\eta_1)\beta_1 T_1 V_1 + (1-\eta_2)\beta_2 T_1 T_1^*,$$

$$(1-\eta_1)\beta_1 T_1 V_1 + (1-\eta_2)\beta_2 T_1 T_1^* = d_2 T_1^*,$$

$$bT_1^* = d_3 V_1.$$

Thus, the characteristic equation as follows

$$\begin{aligned} &\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 + e^{-\lambda\tau_1}(C_1\lambda^2 + C_2\lambda + C_3) \\ &+e^{-\lambda\tau_2}(B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4) + e^{-\lambda(\tau_1+\tau_3)}(D_1\lambda^2 + D_2\lambda + D_3) \\ &+e^{-\lambda(\tau_2+\tau_3)}(F_1\lambda + F_2) = 0, \end{aligned} \tag{5}$$

where $A_i = A_i(\tau_1,\tau_2,\tau_3)$, $B_i = B_i(\tau_1,\tau_2,\tau_3)$, $C_i = C_i(\tau_1,\tau_2,\tau_3)$, $D_i = D_i(\tau_1,\tau_2,\tau_3)$, $F_i = F_i(\tau_1,\tau_2,\tau_3)$, and

$$\begin{aligned}
A_1 &= d_4 + a_{11} + d_3 + d_2;\\
A_2 &= d_4a_{11} + d_3d_2 + (d_4 + a_{11})(a_{11} + d_3 + d_2);\\
A_3 &= d_4 + a_{11} + (d_4 + a_{11})(a_{11} + d_3 + d_2);\\
A_4 &= d_4a_{11}d_3d_2;\\
B_1 &= (1-\eta_2)\beta_2T_1;\\
B_2 &= (d_4 + a_{11})(1-\eta_2)\beta_2T_1 + (1-\eta_2)\beta_2T_1d_3 + (1-\eta_2)^2\beta_2T_1T_1^*;\\
B_3 &= (1-\eta_2)\beta_2T_1d_4a_{11} + (1-\eta_2)\beta_2T_1d_3(d_4 + a_{11}) + (d_3 + d_4)(1-\eta_2)^2\beta_2T_1T_1^*;
\end{aligned}$$

$$\begin{aligned}
B_4 &= (1-\eta_2)\beta_2T_1d_3d_4a_{11} + d_3d_4(1-\eta_2)^2\beta_2T_1T_1^*;\\
C_1 &= (1-\eta_2)\beta_2T_1(1-\eta_1)\beta_1V_1;\\
C_2 &= (d_3 + d_4)(1-\eta_2)\beta_2T_1(1-\eta_1)\beta_1V_1;\\
C_3 &= d_3d_4(1-\eta_2)\beta_2T_1(1-\eta_1)\beta_1V_1;\\
D_1 &= -(1-\eta_1)\beta_1T_1;\\
D_2 &= (1-\eta_1)^2{\beta_1}^2T_1V_1b - (d_4 + a_{11})(1-\eta_1)\beta_1T_1;\\
D_3 &= (1-\eta_1)^2{\beta_1}^2T_1V_1bd_4 - a_{11}d_4(1-\eta_1)\beta_1T_1;\\
F_1 &= (1-\eta_1)\beta_1T_1b(1-\eta_2)\beta_2T_1^*;\\
F_2 &= (1-\eta_1)\beta_1T_1b(1-\eta_2)\beta_2T_1^*d_4;
\end{aligned}$$

Theorem 5. *If $\tau_1 = \tau_2 = \tau_3 = 0$ vanishes and $R_1 < 1$, then the immune inactivated steady state of the system (5) is stable.*

2.2. Stability of the endemic steady state. To determine the stability of the delayed model, we linearized, the system (1) around E_2 and obtained the characteristic equation as,

$$\begin{vmatrix} -a_{11}-\lambda & -(1-\eta_2)\beta_2 T_2 & -(1-\eta_1)\beta_1 T_2 & 0 \\ a_{21} & -a_{22}-\lambda & (1-\eta_1)\beta_1 T_2 e^{-\lambda\tau_1} & 0 \\ 0 & be^{-\lambda\tau_3} & -d_3-pZ_2-\lambda & -pV_2 \\ 0 & 0 & gZ_2 & gV_2-d_4-\lambda \end{vmatrix} = 0,$$

The stationary equation of (1)as

$$s = d_1 T_2 + (1-\eta_1)\beta_1 T_2 V_2 + (1-\eta_2)\beta_2 T_2 T_2^*,$$

$$(1-\eta_1)\beta_1 T_2 V_2 + (1-\eta_2)\beta_2 T_2 T_2^* = d_2 T_2^*,$$

$$bT_2^* = d_3 V_2 + pV_2 Z_2,$$

$$gV_2 Z_2 = d_4 Z_2.$$

Thus, the characteristic equation as follows

$$\begin{aligned} &\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4 + e^{-\lambda\tau_1}(c_1\lambda^2 + c_2\lambda + c_3) \\ &+e^{-\lambda\tau_2}(f_0\lambda^3 + f_1\lambda^2 + f_2\lambda + f_3) + e^{-\lambda(\tau_1+\tau_3)}(g_1\lambda^2 + g_2\lambda + g_3) \\ &+e^{-\lambda(\tau_2+\tau_3)}(h_1\lambda + h_2) + e^{-\lambda(\tau_1+\tau_2+\tau_3)}k_1 = 0, \end{aligned} \tag{6}$$

where $b_i = b_i(\tau_1,\tau_2,\tau_3)$, $c_i = c_i(\tau_1,\tau_2,\tau_3)$, $g_i = g_i(\tau_1,\tau_2,\tau_3)$, $f_i = f_i(\tau_1,\tau_2,\tau_3)$, $h_i = h_i(\tau_1,\tau_2,\tau_3)$, $k_i = k_i(\tau_1,\tau_2,\tau_3)$, and

$$\begin{aligned} b_1 &= -gV_2 + d_4 + d_3 + pZ_2 + d_2 + d_1 + (1-\eta_1)\beta_1 V_2 + (1-\eta_2)\beta_2 T_2^*; \\ b_2 &= (d_1 + (1-\eta_1)\beta_1 V_2 + (1-\eta_2)\beta_2 T_2^*)d_2; \\ b_3 &= (d_3 + pZ_2)(-gV_2 + d_4)(d_1 + (1-\eta_1)\beta_1 V_2 + (1-\eta_2)\beta_2 T_2^* + d_2) \\ &\quad -(1-\eta_1)\beta_1 T_2 bgZ_2(d_1 + (1-\eta_1)\beta_1 V_2 + (1-\eta_2)\beta_2 T_2^* + d_2) \\ &\quad +gpV_2 Z_2(d_1 + (1-\eta_1)\beta_1 V_2 + (1-\eta_2)\beta_2 T_2^* + d_2); \end{aligned}$$

$$
\begin{aligned}
b_4 &= gpV_2Z_2(d_1+(1-\eta_1)\beta_1V_2+(1-\eta_2)\beta_2T_2^*+d_2)\\
&\quad +(-gV_2+d_4+d_3+pZ_2)(d_1+(1-\eta_1)\beta_1V_2+(1-\eta_2)\beta_2T_2^*)d_2\\
&\quad +(d_3+pZ_2)(-gV_2+d_4)(d_1+(1-\eta_1)\beta_1V_2+(1-\eta_2)\beta_2T_2^*)d_2;\\
f_0 &= (1-\eta_2)\beta_2T_2;\\
f_1 &= (1-\eta_2)\beta_2T_2(d_1+(1-\eta_1)\beta_1V_2+(1-\eta_2)\beta_2T_2^*)+(1-\eta_2)^2\beta_2^2T_2T_2^*;\\
f_2 &= (d_3+pZ_2)(-gV_2+d_4)(1-\eta_2)\beta_2T_2+gpV_2Z_2(1-\eta_2)\beta_2T_2\\
&\quad +(1-\eta_2)^2\beta_2^2T_2T_2^*(-gV_2+d_4+d_3+pZ_2);\\
f_3 &= (1-\eta_2)^2\beta_2^2T_2T_2^*gpV_2Z_2-(1-\eta_1)\beta_1\beta_2^2pgV_2Z_2(1-\eta_2)T_2^*\\
&\quad +(1-\eta_2)^2\beta_2^2T_2T_2^*(d_3+pZ_2)(-gV_2+d_4)\\
&\quad +gpV_2Z_2(1-\eta_2)\beta_2T_2(d_1+(1-\eta_1)\beta_1V_2+(1-\eta_2)\beta_2T_2^*)\\
&\quad +(-gV_2+d_4+d_3+pZ_2)(1-\eta_2)\beta_2T_2(d_1+(1-\eta_1)\beta_1V_2+(1-\eta_2)\beta_2T_2^*)\\
&\quad +(d_3+pZ_2)(-gV_2+d_4)(1-\eta_2)\beta_2T_2(d_1+(1-\eta_1)\beta_1V_2\\
&\quad +(1-\eta_2)\beta_2T_2^*);\\
c_1 &= (1-\eta_2)\beta_2T_2(1-\eta_1)\beta_1V_2;\\
c_2 &= (-gV_2+d_4+d_3+pZ_2)(1-\eta_2)\beta_2T_2(1-\eta_1)\beta_1V_2;\\
c_3 &= (1-\eta_2)\beta_2T_2gpZ_2(1-\eta_1)\beta_1V_2^2-(1-\eta_1)^2\beta_1^2\beta_2V_2^2gpZ_2\\
&\quad +(d_3+pZ_2)(-gV_2+d_4)(1-\eta_2)\beta_2T_2(1-\eta_1)\beta_1V_2;\\
g_1 &= -(1-\eta_1)\beta_1T_2bgZ_2;\\
g_2 &= (1-\eta_1)^2{\beta_1}^2T_2V_2b-(1-\eta_1)\beta_1T_2^2bgZ_2(1-\eta_2)\beta_2;\\
g_3 &= (1-\eta_1)\beta_1T_2b(1-\eta_1)\beta_1V_2(-gV_2+d_4)-d_2(d_1+(1-\eta_1)\beta_1V_2+(1-\eta_2)\beta_2T_2^*)\\
&\quad (1-\eta_1)\beta_1T_2bgZ_2;
\end{aligned}
$$

$$\begin{aligned} h_1 &= (1-\eta_1)\beta_1 T_2 b(1-\eta_2)\beta_2 T_2^*; \\ h_2 &= (1-\eta_1)\beta_1 T_2 b(1-\eta_2)\beta_2 T_2^*(-gV_2+d_4); \\ k_1 &= -(1-\eta_1)\beta_1 T_2^2 bgZ_2(1-\eta_2)\beta_2 \end{aligned}$$

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

$$\lambda^4 + \nu_1\lambda^3 + \nu_2\lambda^2 + \nu_3\lambda + \nu_4 + e^{-\lambda\tau_3}(m_1\lambda^2 + m_2\lambda + m_3) = 0. \tag{7}$$

where

$$\begin{aligned} \nu_1 &= b_1 + f_0; \\ \nu_2 &= b_2 + c_1 + f_1; \\ \nu_3 &= b_3 + c_2 + f_2; \\ \nu_4 &= b_4 + c_3 + f_3; \\ m_1 &= g_1; \\ m_2 &= g_2 + h_1; \\ m_3 &= g_3 + h_2 + k_1; \end{aligned}$$

2.3. Criterion for preservation of stability or instability and bifurcation Analysis. Now, we put $\lambda = \gamma(\tau_3) + i\omega(\tau_3)$ in equation (7) and to determine the change of stability of E_2 of (1) 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 E_2 of (1) is always stable. We will show that it is the case with equation (7). Now we let $\lambda = i\omega$ be a purely imaginary in (7) reduce to

$$\omega^4 - \omega^2\nu_2 + \nu_4 = (m_1\omega^2 - m_3)\cos(\omega\tau_3) - m_2\omega\sin(\omega\tau_3), \tag{8}$$

$$\omega\nu_3 - \omega^3\nu_1 = (m_1\omega^2 - m_3)\sin(\omega\tau_3) - m_2\omega\cos(\omega\tau_3). \tag{9}$$

Now squaring and adding above equation (8) and (9) we get,

$$\omega^8 + f_{11}\omega^6 + f_{22}\omega^4 + f_{33}\omega^2 + f_{44} = 0. \tag{10}$$

Putting $\omega^2 = u^*$ into (10), we can get the following equation:

$$F(u^*) = u^{*4} + f_{11}u^{*3} + f_{22}u^{*2} + f_{33}u^* + f_{44} = 0, \tag{11}$$

where

$$\begin{aligned} f_{11} &= \nu_1^2 - 2\nu_2; \\ f_{22} &= \nu_2^2 - m_1^2 + 2\nu_4 - 2\nu_1\nu_3; \\ f_{33} &= \nu_3^2 - 2\nu_2\nu_4 - m_2^2; \\ f_{44} &= \nu_4^2 - m_3^2, \end{aligned}$$

Taking derivative with respect to u^* of equation (11), we get

$$\dot{F}(u^*) = 4u^{*3} + 3u^{*2}f_{11} + 2u^* f_{22} + f_{33} = 0, \tag{12}$$

Set

$$4u^{*3} + 3u^{*2}f_{11} + 2u^* f_{22} + f_{33} = 0. \tag{13}$$

Let $m^* = u^* + \dfrac{f_{11}}{4}$, then (13) becomes

$$m^{*3} + \alpha_1 m^* + \alpha_2 = 0, \tag{14}$$

where

$$\alpha_1 = \frac{f_{22}}{2} - \frac{3f_{11}^2}{16}, \quad \alpha_2 = \frac{f_{11}^3}{32} - \frac{f_{11}f_{22}}{8} + \frac{f_{33}}{4}.$$

Define

$$\begin{aligned}
\Delta &= \left(\frac{\alpha_2}{2}\right)^2+\left(\frac{\alpha_1}{3}\right)^3;\ \ \delta=\frac{-1+i\sqrt{3}}{2};\\
m_1^* &= \sqrt[3]{-\frac{\alpha_2}{2}+\sqrt{\Delta}}+\sqrt[3]{-\frac{\alpha_2}{2}-\sqrt{\Delta}};\\
m_2^* &= \sqrt[3]{-\frac{\alpha_2}{2}+\sqrt{\Delta\delta}}+\sqrt[3]{-\frac{\alpha_2}{2}-\sqrt{\Delta\delta^2}};\\
m_3^* &= \sqrt[3]{-\frac{\alpha_2}{2}+\sqrt{\Delta\delta^2}}+\sqrt[3]{-\frac{\alpha_2}{2}-\sqrt{\Delta\delta}};\\
u_i^* &= m_i^*-\frac{f_{11}}{4},\ \ i=1,2,3.
\end{aligned}$$

We cite the results in [14] about the existence of positive roots of the fourth-degree polynomial equation, namely, we have the following lemma.

Lemma 6. *(1) If $f_{44}<0$, then (11) has at least one positive root.*

(2) If $f_{44}\geq 0$ and $\Delta\geq 0$ then (11) has positive roots if and only if $u_1>0$ and $F(u_1)<0$.

(3) If $f_{44}\geq 0$ and $\Delta<0$, then (11) 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 6, is satisfied, (11) has finite positive roots $u_1,u_2,u_3,...,u_k,k\leq 4$. Therefore (10) 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 $j=0,1,2,...,i=1,2,...,k,\ \ k\leq 4,$

where

$$\begin{aligned}
\eta_1 &= (\omega_i^{*4}-\nu_2\omega_i^{*2}+\nu_4)(m_1\omega_i^{*2}-m_3)+(\nu_3\omega_i^{*2}-\nu_1\omega_i^{*4})b_2\\
\eta_2 &= (m_1\omega_i^2-m_3)^2+m_2^2\omega_i^2.
\end{aligned}$$

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 immune activated equilibrium of model (1) remains stable for $\tau_3 < \tau_3^*$ and Hopf bifurcation occurs when $\tau_3 = \tau_3^*$.

Differentiating (7) with respect to τ_3, we get

$$\left\{(4\lambda^3+3\lambda^2\nu_1+2\lambda\nu_2+\nu_3)+e^{-\lambda\tau_3}(2\lambda m_1+m_2)-\tau_3 e^{-\lambda\tau_3}(m_1\lambda^2+m_2\lambda+m_3)\right\}\frac{d\lambda}{d\tau_3}=\lambda e^{-\lambda\tau_3}(m_1\lambda^2+m_2\lambda+m_3)$$

which implies,

$$\begin{aligned}\left(\frac{d\lambda}{d\tau_3}\right)^{-1} &= \frac{4\lambda^3+3\lambda^2\nu_1+2\lambda\nu_2+\nu_3}{\lambda e^{-\lambda\tau_3}(m_1\lambda^2+m_2\lambda+m_3)}+\frac{2\lambda m_1+m_2}{\lambda(m_1\lambda^2+m_2\lambda+m_3)}-\frac{\tau_3}{\lambda},\\ &= \frac{4\lambda^3+3\lambda^2\nu_1+2\lambda\nu_2+\nu_3}{-\lambda(\lambda^4+\nu_1\lambda^3+\nu_2\lambda^2+\nu_3\lambda+\nu_4)}+\frac{2\lambda m_1+m_2}{\lambda(m_1\lambda^2+m_2\lambda+m_3)}-\frac{\tau_3}{\lambda},\\ &= \frac{3\lambda^4+2\nu_1\lambda^3+\nu_2\lambda^2-\nu_4}{-\lambda^2(\lambda^4+\nu_1\lambda^3+\nu_2\lambda^2+\nu_3\lambda+\nu_4)}+\frac{\lambda^2 m_1-m_3}{\lambda^2(m_1\lambda^2+m_2\lambda+m_3)}-\frac{\tau_3}{\lambda}.\end{aligned}$$

Therefore,

$$\begin{aligned}\Xi &= sign\left\{Re\left(\frac{3\lambda^4+2\nu_1\lambda^3+\nu_2\lambda^2-\nu_4}{-\lambda^2(\lambda^4+\nu_1\lambda^3+\nu_2\lambda^2+\nu_3\lambda+\nu_4)}+\frac{\lambda^2 m_1-m_3}{\lambda^2(m_1\lambda^2+m_2\lambda+m_3)}-\frac{\tau_3}{\lambda}\right)\right\}_{\lambda=i\omega^*}\\ &= sign\left\{Re\left(\frac{(3\omega^{*4}-\omega^{*2}\nu_2-\nu_4)+i(-2\omega^{*3}\nu_1)}{\omega^{*2}(\omega^{*4}-\omega^{*2}\nu_2+\nu_4)+i(\omega^*\nu_3-\omega^{*3}\nu_1)}+\frac{m_1\omega^{*2}+m_3}{\omega^{*2}(m_3-m_1\omega^{*2})+i(m_2\omega^*)}-\frac{\tau_3}{i\omega^*}\right)\right\}\\ &= \frac{1}{\omega^{*2}}sign\left\{\frac{(3\omega^{*4}-\omega^{*2}\nu_2-\nu_4)(\omega^{*4}-\omega^{*2}\nu_2+\nu_4)-2\omega^{*3}\nu_1(\omega^*\nu_3-\omega^{*3}\nu_1)}{(\omega^{*4}-\omega^{*2}\nu_2+\nu_4)^2+(\omega^*\nu_3-\omega^{*3}\nu_1)^2}\right.\\ &\quad\left.+\frac{(m_1\omega^{*2}+m_3)(m_3-m_1\omega^{*2})}{(m_3-m_1\omega^{*2})^2+(m_2\omega^*)^2}\right\}\\ &= \frac{1}{\omega^{*2}}sign\left\{\frac{(3\omega^{*4}-\omega^{*2}\nu_2-\nu_4)(\omega^{*4}-\omega^{*2}\nu_2+\nu_4)-2\omega^{*3}\nu_1(\omega^*\nu_3-\omega^{*3}\nu_1)}{(m_3-m_1\omega^{*2})^2+(m_2\omega^*)^2}\right.\\ &\quad\left.+\frac{(m_1\omega^{*2}+m_3)(m_3-m_1\omega^{*2})}{(m_3-m_1\omega^{*2})^2+(m_2\omega^*)^2}\right\}\\ &= \frac{1}{\omega^{*2}}sign\left\{\frac{3\omega^{*8}+(\nu_1^2-2\nu_2)\omega^{*6}+(\nu_2^2-2\nu_1\nu_3+2\nu_4-m_1^2)\omega^{*4}+\nu_4^2-m_3^2}{(m_3-m_1\omega^{*2})^2+(m_2\omega^*)^2}\right\}\end{aligned}$$

and this determines a set of possible eigenvalues of ω^*. Our aim is to determine the direction of motion of λ as τ_3 is varied. i.e., we determine

$$\Xi = sign\left\{\left(\frac{d(Re(\lambda))}{d\tau_3}\right)\right\}_{\lambda=i\omega^*} = sign\left\{Re\left(\frac{d\lambda}{d\tau_3}\right)^{-1}\right\}_{\lambda=i\omega^*}$$

As $\nu_1^2 - 2\nu_2$, $\nu_2^2 - 2\nu_1\nu_3 + 2\nu_4 - m_1^2$ and $\nu_4^2 - m_3^2$ are both positive by virtue of equation (10), we have $\left(\frac{dRe(\lambda)}{d\tau_3}\right)\Big|_{\tau_3=\tau_3^*} > 0$. Thus, the solution curve of the characteristic equation (10) crosses the imaginary axis. This shows that a Hopf bifurcation occurs at $0 < \tau_3 = \tau_3^*$. By continuity, the chronic infection equilibrium is locally asymptotically stable when $\tau_3 < \tau_3^*$.

Remark 1. *We find that incorporating of an delay can destroy the global intractability of E_2 on proper conditions when $R_1 > 1$, and a Hopf bifurcation occurs (i.e., a periodic oscillation appears). Those results show new infectious of HIV-1 particles dominates intracellular delays in this class of free viral particles.*

3. Sensitivity Analysis

In order to get an insight on the correct strategies to control the HIV described by model (1), we perform a sensitivity analysis. The sensitivities of a system provide temporal information on how states of the system respond to changes in the parameters [15]. They can, therefore, be used to identify time intervals where the system is most sensitive to such changes. Noting that the sensitivities are used to calculate the standard errors in estimates of parameters, direct observation of the sensitivity function provides an indication of time intervals in which data points carry more or less information for the estimation process. For instance, if the sensitivity to some parameter is close to zero in some time interval, changes in the value of the parameter would have little impact on the state variable. Conversely, more accurate knowledge of the state variable at that time could not cause the estimated parameter value to change by much. Consider model (1), with vector parameter $\mathbf{q} = [s, d_1, \beta_1, \beta_2, \eta_1, \eta_2, d_2, b, d_3, p, g, d_4]^T$. The sensitivity

functions with respect to the parameter $\mathbf{q_i}$ $(i = 1, ..., 12)$, for the model (1) are denoted by,

$$\begin{aligned} u_{1,\mathbf{q_i}} &= \frac{\partial u_1(t)}{\partial \mathbf{q_i}}, \\ u_{2,\mathbf{q_i}} &= \frac{\partial u_2(t)}{\partial \mathbf{q_i}}, \\ u_{3,\mathbf{q_i}} &= \frac{\partial u_3(t)}{\partial \mathbf{q_i}}, \\ u_{4,\mathbf{q_i}} &= \frac{\partial u_4(t)}{\partial \mathbf{q_i}}. \end{aligned} \tag{15}$$

The corresponding sensitivity of system (1), with respect to the parameter 's' is as follows,

$$\begin{aligned} \left(\frac{du_1}{dt}\right)_{t,s} &= 1 - d_1 u_{1,s}(t,s) - (1-\eta_1)(\beta_1 u_{1,s}(t,s)V_2 + \beta_1 u_{3,s}(t,s)T_2) \\ &\quad -(1-\eta_2)(\beta_2 u_{2,s}(t,s)T_2 + \beta_2 u_{1,s}(t,s)T_2^*), \\ \left(\frac{du_2}{dt}\right)_{t,s} &= (1-\eta_1)(\beta_1 u_{1,s}(t-\tau_1,s)V_2 + \beta_1 u_{3,s}(t-\tau_1,s)T_2) \\ &\quad +(1-\eta_2)(\beta_2 u_{2,s}(t-\tau_2,s)T_2 + \beta_2 u_{1,s}(t-\tau_2,s)T_2^*) - d_2 u_{2,s}(t,s), \\ \left(\frac{du_3}{dt}\right)_{t,s} &= b u_{2,s}(t-\tau_3,s) - p u_3(t,s)Z_2 - p u_4(t,s)V_2, \\ \left(\frac{du_4}{dt}\right)_{t,s} &= g u_3(t,s)Z_2 + g u_4(t,s)V_2 - d_4 u_{4,s}(t,s). \end{aligned} \tag{16}$$

The corresponding sensitivity of system (1), with respect to the parameter 'd_1' is as follows,

$$\begin{aligned} \left(\frac{du_1}{dt}\right)_{t,d_1} &= -u_1(t) - (1-\eta_1)(\beta_1 u_{1,d_1}(t,d_1)V_2 + \beta_1 u_{3,d_1}(t,d_1)T_2) \\ &\quad -(1-\eta_2)(\beta_2 u_{2,d_1}(t,d_1)T_2 + \beta_2 u_{1,d_1}(t,d_1)T_2^*), \\ \left(\frac{du_2}{dt}\right)_{t,d_1} &= (1-\eta_1)(\beta_1 u_{1,d_1}(t-\tau_1,d_1)V_2 + \beta_1 u_{3,d_1}(t-\tau_1,d_1)T_2) \\ &\quad +(1-\eta_2)(\beta_2 u_{2,d_1}(t-\tau_2,d_1)T_2 + \beta_2 u_{1,d_1}(t-\tau_2,d_1)T_2^*) - d_2 u_{2,d_1}(t,d_1), \\ \left(\frac{du_3}{dt}\right)_{t,d_1} &= b u_{2,d_1}(t-\tau_3,d_1) - p u_3(t,d_1)Z_2 - p u_4(t,d_1)V_2, \\ \left(\frac{du_4}{dt}\right)_{t,d_1} &= g u_3(t,d_1)Z_2 + g u_4(t,d_1)V_2 - d_4 u_{4,d_1}(t,d_1). \end{aligned} \tag{17}$$

The corresponding sensitivity of system (1), with respect to the parameter 'β_1' is as follows,

$$\begin{aligned}
\left(\frac{du_1}{dt}\right)_{t,\beta_1} &= -d_1 u_{1,\beta_1}(t,\beta_1) - (1-\eta_1)(u_{1,\beta_1}(t,\beta_1)V_2 + u_{3,\beta_1}(t,\beta_1)T_2) \\
&\quad -(1-\eta_2)(\beta_2 u_{2,\beta_1}(t,\beta_1)T_2 + \beta_2 u_{1,\beta_1}(t,\beta_1)T_2^*), \\
\left(\frac{du_2}{dt}\right)_{t,\beta_1} &= (1-\eta_1)(\beta_1 u_{1,\beta_1}(t-\tau_1,\beta_1)V_2 + \beta_1 u_{3,\beta_1}(t-\tau_1,\beta_1)T_2) \\
&\quad +(1-\eta_2)(\beta_2 u_{2,\beta_1}(t-\tau_2,\beta_1)T_2 + \beta_2 u_{1,\beta_1}(t-\tau_2,\beta_1)T_2^*) - d_2 u_{2,\beta_1}(t,\beta_1), \\
\left(\frac{du_3}{dt}\right)_{t,\beta_1} &= b u_{2,\beta_1}(t-\tau_3,\beta_1) - p u_3(t,\beta_1)Z_2 - p u_4(t,\beta_1)V_2, \\
\left(\frac{du_4}{dt}\right)_{t,\beta_1} &= g u_3(t,\beta_1)Z_2 + g u_4(t,\beta_1)V_2 - d_4 u_{4,\beta_1}(t,\beta_1).
\end{aligned} \tag{18}$$

The corresponding sensitivity of system (1), with respect to the parameter 'β_2' is as follows,

$$\begin{aligned}
\left(\frac{du_1}{dt}\right)_{t,\beta_2} &= -d_1 u_{1,\beta_2}(t,\beta_2) - (1-\eta_1)\beta_1(u_{1,\beta_2}(t,\beta_2)V_2 + u_{3,\beta_2}(t,\beta_2)T_2) \\
&\quad -(1-\eta_2)(u_{2,\beta_2}(t,\beta_2)T_2 + u_{1,\beta_2}(t,\beta_2)T_2^*), \\
\left(\frac{du_2}{dt}\right)_{t,\beta_2} &= (1-\eta_1)(\beta_2 u_{1,\beta_2}(t-\tau_1,\beta_2)V_2 + \beta_2 u_{3,\beta_2}(t-\tau_1,\beta_2)T_2) \\
&\quad +(1-\eta_2)(\beta_2 u_{2,\beta_2}(t-\tau_2,\beta_2)T_2 + \beta_2 u_{1,\beta_2}(t-\tau_2,\beta_2)T_2^*) - d_2 u_{2,\beta_2}(t,\beta_2), \\
\left(\frac{du_3}{dt}\right)_{t,\beta_2} &= b u_{2,\beta_2}(t-\tau_3,\beta_2) - p u_3(t,\beta_2)Z_2 - p u_4(t,\beta_2)V_2, \\
\left(\frac{du_4}{dt}\right)_{t,\beta_2} &= g u_3(t,\beta_2)Z_2 + g u_4(t,\beta_2)V_2 - d_4 u_{4,\beta_2}(t,\beta_2).
\end{aligned} \tag{19}$$

The corresponding sensitivity of system (1), with respect to the parameter 'b' is as follows,

$$\begin{aligned}
\left(\frac{du_1}{dt}\right)_{t,b} &= -d_1 u_{1,b}(t,b) - (1-\eta_1)\beta_1(u_{1,b}(t,b)V_2 + u_{3,b}(t,b)T_2) \\
&\quad -(1-\eta_2)\beta_2(u_{2,b}(t,b)T_2 + u_{1,b}(t,b)T_2^*), \\
\left(\frac{du_2}{dt}\right)_{t,b} &= (1-\eta_1)(b u_{1,b}(t-\tau_1,b)V_2 + b u_{3,b}(t-\tau_1,b)T_2) \\
&\quad +(1-\eta_2)(b u_{2,b}(t-\tau_2,b)T_2 + b u_{1,b}(t-\tau_2,b)T_2^*) - d_2 u_{2,b}(t,b), \\
\left(\frac{du_3}{dt}\right)_{t,b} &= u_{2,b}(t-\tau_3,b) - p u_3(t,b)Z_2 - p u_4(t,b)V_2, \\
\left(\frac{du_4}{dt}\right)_{t,b} &= g u_3(t,b)Z_2 + g u_4(t,b)V_2 - d_4 u_{4,b}(t,b).
\end{aligned} \tag{20}$$

Similarly, the sensitivity functions to perturbations in the rest of the parameters can also be obtained. The semi-relative sensitivity solutions are calculated by simply multiplying the

unmodified sensitivity solutions by a chosen parameter which provides information concerning the amount the state will change when that parameter is doubled. It is best to calculate this type of sensitivity solution to obtain a more thorough understanding of the dynamics.

4. Conclusion

In this study, we have considered the HIV RTI model with humoral immunity. We have described the new HIV RTI model with humoral immunity and discussed the non-negativity and boundedness of the solution of the developed model. We have also analyzed the stability of the developed model about the infection-free, immune-free and endemic steady states of the system individually. We have also obtained the sensitivity functions of the model due to perturbing the parameters appearing in delay differential system (1) using the direct approach. This work can be extended in finding the global stability of HIV-1 RTI model with general incidence rate and humoral immunity, which is considered as our future work.

Conflict of Interests

The author(s) declare that there is no conflict of interests.

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