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Analysis of time delay model for drug therapy on HIV dynamics

Vinoth Sivakumar[*]
Department of Mathematics,
Sri Ramakrishna Mission Vidyalaya
College of Arts and Science,India.
E-mail: vinothsivaruth@gmail.com

Dumitru Baleanu
Cankaya University, Turkey.
Institute of Space Sciences, Romania.
E-mail: dumitru.baleanu@gmail.com

Jayakumar Thippan
Department of Mathematics,
Sri Ramakrishna Mission Vidyalaya
College of Arts and Science,India.
E-mail: jayakumar.thippan68@gmail.com

Prasantha Bharathi Dhandapani
Department of Mathematics,
Sri Ramakrishna Mission Vidyalaya
College of Arts and Science ,India.
E-mail: d.prasanthabharathi@gmail.com

Abstract We present and investigate the delayed model of HIV infection for drug therapy. The stability of the equilibrium states, disease free and infected equilibrium states are derived and the existence of Hopf bifurcation analysis is studied. We show that the system is asymptotically stable and the stability is lost in a range due to length of the delay, then Hopf bifurcation occurs when τ exceeds the critical value. At last numerical simulations are provided to verify the theoretical results.

Keywords. HIV infection, Stability, Hopf bifurcation, Time delay.
2010 Mathematics Subject Classification. 34D20; 74H60 ; 93D20.

1. Introduction

In recent years, many researchers proved some important results to understand HIV diseases [1, 8, 13, 16, 20]. One of the best tools to proceed to analyze the spread and control of the infection is mathematical modeling. Numerous viral dynamic models exist for the interaction between viral infection, immune response reaction against the virus [3, 15, 19]. In normal it will take approximately 10 years for the HIV infection to become AIDS. Still now, there are no cure mechanisms for those who are HIV positive. So, they remain HIV throughout their lives. The presence of the virus in the blood when the anti-retroviral drugs are regulated and provides insights into

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∗ corresponding.

the host pathogenesis interactions of HIV and $CD4^+$ T-cells. Most of the viruses having genetic material are deoxyribonucleic acid (DNA). DNA contains the genetic instructions specifying the biological development of cellular life. But the Human Immunodeficiency Virus (HIV) has ribonucleic acid (RNA) as the genetic material. For this reason, HIV is called retroviruses and it belongs to lentiviruses. Lentivirus in humans takes a long period to develop the disease to affect the immune system in our body [7, 10, 11]. HIV has to enter cells to reproduce. These cells reproduce more viral particles and are converting viral RNA to DNA in the cells. These cells are producing many RNA copies and the conversion made through an enzyme called Reverse Transcriptase (RT). HIV affects the cells of the immune system. In particular, HIV attacks $CD4^+$ cells. There are two types of $CD4^+$ cells. The first one is to organize the body's overall immune response to invades diseases and infections. Macrophages are the second types that engulf foreign invaders in the body and the immune system will recognize them in the future. R.V Culshaw et al. [4] proposed the delay differential equation (DDE) model of HIV dynamics, mostly represented the interaction between viral population and healthy $CD4^+$ T-cells. Numerous mathematical models have been discussed to develop the drug (ex. RT inhibitor, fusion inhibitors, and proteases inhibitors) to attack the life cycle of the virus during the infection [6, 9, 12]. Drug therapy always depends on the life cycle of the virus.

In this paper, our purpose is to analyze stability and Hopf bifurcation for Reverse transcriptase inhibitor (RTI) of HIV infection with time delay and this model based on DDE with logistic growth term. Bifurcation analysis is studied to describe the behavior of equilibria and make predictions on the outcome of the epidemic for the prevention and control of diseases. The dynamics of HIV infection contain three components, the healthy $CD4^+$ T-cells, infected $CD4^+$ T-cells, and free virus particles. The development of infected $CD4^+$ T-cells made the interaction between the healthy $CD4^+$ T-cells and free virus populations. The infected $CD4^+$ T-cells divide into two subcomponents that are Pre-RT in which the reverse transcriptase is not completed and Post-RT in which reverse transcriptase is completed. If the post-RT process is successfully completed then the infected cells are producing the new virus. The presence of RT inhibitor rate ($u_1\alpha I_1$) in pre-RT revert back to healthy cells and rest of them $(1-u_1)\alpha I_1$ go to post-RT and these cells are productively infected, then the efficacy of RTI drug to be considered $0 < u_1 < 1$.

The structure of the paper is as follows. In section 2, the mathematical model is described by containing all the factors as discussed in diagrammatic representations. In section 3, non-negative solution and equilibria are discussed. In section 4, the stability analysis of steady states of the model is presented and a Hopf bifurcation analysis is investigated. In section 5, the numerical studies of the analytical results are verified and the periodic solutions are shown. In section 6, the above discussions are concise.

2. Model formation

A basic model to describe that without treatment changes in the viral load consists of three components: healthy cells, infected cells and free virus particles [2]. The

model is,

$$\begin{aligned} T^{'}(t) &= s - kV(t)T(t) - d_T T(t), \\ I^{'}(t) &= kV(t)T(t) - \rho I(t), \\ V^{'}(t) &= N\rho I(t) - d_V V(t), \end{aligned} \tag{2.1}$$

where, s is the rate at which new target cells are produced, d_T, ρ and d_V are the death rate of healthy cells, death rate of infected cells and infectious viral clearance rate respectively. k is constant rate that characterizing the target cell infection. N is a new virus particle.

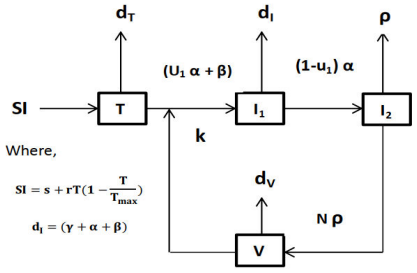

FIGURE 1. Graphical representation describes the development of the model

Thus, we are using (2.1), R. V Culshaw et al. [4] and P. K Srivastava et al. [14] and reconstructed the proposed model with an applied time delay as the interaction between healthy cells and free virus particles.

$$\begin{aligned} T^{'}(t) &= s - kV(t)T(t) - d_T T(t) + rT(t)(1 - \frac{T(t)}{T_{max}}) + (u_1\alpha + \beta)I_1(t), \\ I_1^{'}(t) &= kV(t-\tau)T(t-\tau) - (\gamma + \alpha + \beta)I_1(t), \\ I_2^{'}(t) &= (1-u_1)\alpha I_1(t) - \rho I_2(t), \\ V^{'}(t) &= N\rho I_2(t) - d_V V(t). \end{aligned} \tag{2.2}$$

With the initial conditions,

$$T(\theta) = \phi_1, I_1(\theta) = \phi_2, I_2(\theta) = \phi_3, V(\theta) = \phi_4, \theta \in [-\tau, 0]. \tag{2.3}$$

The parameter s denotes the source rate of $CD4^+$ T-cells and d_T is the natural death rate. k represents the interaction infection rate of $CD4^+$ T-cells and γ denotes the death rate of infected cells. α is representing the transition rate from pre-RT to post-RT. β represents the return rate of infected cells to uninfected cells owing to the non-completion of RT. Let ρ denotes the death rate of actively infected and contains the possibility of death by bursting of infected cells, d_V denotes the rate of virus clearance and N represents the total number of virus production from infected cells.

Table 1.

Terms	Parameters and Constants	Default Values
s	Source term for healthy CD4$^+$ T-cells	5 day^{-1}(mm^{-3}) [19]
r	Growth rate of CD4$^+$ T-cells	0.8 day^{-1}[19]
d_T	Death rate of heathy CD4$^+$ T-cells	0.01day^{-1} [19]
k	Rate at which CD4$^+$ T-cells become infected with virus	0.00002 day^{-1}(mm^{-3}) [4]
T_{max}	Maximal CD4$^+$ T-cell population level	1300 mm^{-3}[assumed]
α	Transition rate from Pre-RT to Post-RT	0.4 day^{-1} [14]
β	Reverting rate from infected class to uninfected class	0.05 day^{-1} [14]
γ	Death rate of infected T-cells	0.015 day^{-1} [14]
ρ	Death rate of actively infected T-cells	0.24 day^{-1} [4]
d_V	Rate of free virus clearance	2.4 day^{-1} [14]
N	Number of virions produced infected CD4$^+$ T-cells	Varies[assumed]
u_1	Efficiency of Reverse transcriptase inhibitor	0.1 [assumed]

3. Existence of non-negative solution and Equilibria analysis

It is important to exhibit that the system (2.2) with the initial functions, required to be specified and well-posedness, required to be presented. Let $C([-\tau,0],R_4^+)$ be the Banach space of continuous functions mapping the interval $[-\tau,0]$ into R_4^+, where $R_4^+ =(T(t),I_1(t),I_2(t),V(t))$, for the system having the initial conditions (2.3). For the initial conditions as considered the biological reasons, $T(\theta)=\phi_1(\theta)\geq 0.,I_1(\theta)=\phi_2(\theta)\geq 0,I_2(\theta)=\phi_3(\theta)\geq 0,V(\theta)=\phi_4(\theta)\geq 0$, $\theta\in[\tau,0]$. Where $\phi_i(\theta)\in\chi^1$, are the smooth functions for all $i=1,2,3,4$. The system (2.2) with the initial conditions, by the fundamental theory of functional differential equations [5] and (T,I_1,I_2,V) having a unique solution. Further, we present the solution of the system (2.2) with initial conditions are non-negative. For system (2.2) can be written into matrix form

$$\dot{Y(t)} = F(Y(t))$$

$$\begin{aligned} F(Y(t)) &= \begin{pmatrix} F_1(Y(t)) \\ F_2(Y(t)) \\ F_3(Y(t)) \\ F_4(Y(t)) \end{pmatrix} \\ &= \begin{pmatrix} s-kV(t)T(t)-d_TT(t)+rT(t)(1-\frac{T(t)}{T_{max}})+(u_1\alpha+\beta)I_1(t) \\ kV(t-\tau)T(t-\tau)-(\gamma+\alpha+\beta)I_1(t) \\ (1-u_1)\alpha I_1(t)-\rho I_2(t) \\ N\rho I_2(t)-d_VV(t) \end{pmatrix}, \end{aligned}$$

where $Y(\theta)=(\phi_1(\theta),\phi_2(\theta),\phi_3(\theta),\phi_4(\theta))\in R_4^+$, and $\phi_1(\theta),\phi_2(\theta),\phi_3(\theta),\phi_4(\theta)\geq 0$. It is verified that the system (2.2) whenever considering $Y(\theta)\in R_4^+$. $F:R_+^{4+1}\to R_4^+$,

it satifies the conditions, $F_i(Y(t))|_{y_i(t)=0}, Y(t) \in R_+^4 \geq 0$, where $y_1 = T(t), y_2 = I_1(t), y_3 = I_2(t), y_4 = V(t)$. In the lemma [18], any solution of (2.2) with $Y(\theta) \in C_+$, say $Y(t) = Y(t, Y(\theta))$, is such that $Y(t) \in R_+^4$ for all $t \geq 0$.
Obviously, the system (2.2) has two positive equilibria, namely disease-free (E_0) and infected (E_1) equilibrium.
The disease free equilibrium is given by, $E_0 = (T_0, 0, 0, 0)$, where

$$T_0 = \frac{(r - d_T) + \sqrt{(r - d_T)^2 + 4rsT_{max}^{-1}}}{2rT_{max}^{-1}}.$$

The infection equilibrium is given by, $(E_1) = (T^*, I_1^*, I_2^*, V^*)$, where

$$T^* = \frac{d_V(\gamma + \alpha + \beta)}{(1 - u_1)\alpha N k}, \qquad I_1^* = \frac{s - d_T T^* + rT^*(1 - \frac{T^*}{T_{max}})}{(\gamma + \alpha(1 - u_1))},$$
$$I_2^* = \frac{(1 - u_1)\alpha I_1^*}{\rho}, \qquad V^* = \frac{N\rho I_2^*}{d_V}.$$

The basic reproductive number is a number of newly infected cells produced by one infected cell during the lifetime is given as $R_0 = \frac{T_0}{T^*}$. Note that when $R_0 > 1$, infected (E_1) equilibrium exists.

4. Stability and Hopf bifurcation analysis

In this section, we shall discuss the stability and Hopf bifurcation analysis of disease-free and infected steady states.

Theorem 4.1. *For system (2.2), the disease free steady state E_0 is locally asymptotically stable when $R_0 < 1$ for $\tau \geq 0$ and it is unstable when $R_0 > 1$ for $\tau \geq 0$. When $R_0 = 1$, it is a critical case.*

Proof. Let us consider the system (2.2) to be linearized, then the Jacobian matrix $J(E_0)$ at disease free equilibrium E_0 is as follows,

$$J(E_0) = \begin{pmatrix} -H_0 & u_1\alpha + \beta & 0 & -kT_0 \\ 0 & -\gamma - \alpha - \beta & 0 & kT_0 e^{-\lambda\tau} \\ 0 & (1 - u_1)\alpha & -\rho & 0 \\ 0 & 0 & N\rho & -d_V \end{pmatrix}. \tag{4.1}$$

At equilibrium E_0 and the characteristic equation is as follows,

$$(H_0 - \lambda)[A(\lambda) + B(\lambda)e^{-\lambda\tau}] = 0,$$

where
$H_0 = d_T + \frac{2rT_0}{T_{max}} - r$, $A(\lambda) = \lambda^3 + \lambda^2 a_1 + \lambda a_2 + a_3$,$B(\lambda) = b_1$ and
$a_1 = \gamma + \alpha + \beta + \rho + d_V$, $a_2 = (\gamma + \alpha + \beta)(\rho + d_V)(\rho d_V)$

$a_3 = (\gamma + \beta + \alpha)\rho d_V$, $b_1 = -kT_0 e^{-\lambda\tau} N\rho(1-u_1)\alpha$.
Thus, the characteristic equation has a characteristic root,

$$\lambda = r - d_T - \frac{2rT_0}{T_{max}} = ((r - d_T^2 + 4rsT_{max}^{-1}))^{\frac{1}{2}} < 0.$$

Since we have the transcendental equation

$$\lambda^3 + \lambda^2 a_1 + \lambda a_2 + a_3 + b_1 e^{-\lambda\tau} = 0 \tag{4.2}$$

when $\tau = 0$ (4.2) becomes

$$\lambda^3 + \lambda^2 a_1 + \lambda a_2 + a_3 + b_1 = 0.$$

By Routh Hurwitz criteria, $a_1 > 0$, $a_2 > 0$, $a_3 + b_1 > 0$ and $a_1 a_2 - (a_3 + b_1) > 0$ is satisfied. This implies that all the roots have negative real parts. The system (4.1) at the equilibrium E_0 is locally asymptotically stable when $R_0 < 1$. In order to investigate the existence of pure imaginary roots,
$\lambda = \pm i\omega(\tau)$ for some $\omega > 0$ and $\tau > 0$, we have

$$\begin{aligned} -a_1\omega^2 + a_3 &= -b_1 cos\omega\tau \\ -\omega^3 + a_2\omega &= b_1 sin\omega\tau. \end{aligned} \tag{4.3}$$

It is described that if $R_0 < 1$, then (4.3) becomes

$$\omega^6 + \omega^4(a_1^2 - 2a_2) + \omega^2(a_2^2 - 2a_2a_3) + (a_3^2 - b_1^2) = 0.$$

Let $y = \omega^2$,

$$y^3 + y^2(a_1^2 - 2a_2) + y(a_2^2 - 2a_2a_3) + (a_3^2 - b_1^2) = 0.$$

Since $a_3^2 - b_1^2 > 0$ has no positive real roots. Then, (4.2) must have a negative real part. Therefore, the disease free equilibrium E_0 is locally asymptotically stable for $\tau \geq 0$. Let us consider the function f, defined as

$$f(\lambda) = \lambda^3 + \lambda^2 a_1 + \lambda a_2 + a_3 + b_1 e^{-\lambda\tau} = 0, for \lambda \in R.$$

If $R_0 > 1$, then we get $f(0) = (a_3 + b_1) < 0$ and $lim_{t\to\infty} f(\lambda) = +\infty$. We show that if $f(\lambda) = 0$ has at least one positive root then E_0 becomes unstable. When $R_0 > 1$ if possible, we consider that (4.2) has imaginary roots, then $\lambda = \eta(\tau) + i\omega(\tau)$ for $\eta(\tau) \geq 0$, $\omega(\tau) \geq 0$ and $\tau \geq 0$. We get

$$\begin{aligned} \eta^3 - 3\eta\omega^2 + a_1(\eta^2 - \omega^2) + a_2\eta + a_3 &= b_1 e^{-\eta\tau} cos\omega\tau, \\ -\omega^3 + 3\eta^2\omega + 2a_1\eta\omega + a_2\omega &= -b_1 e^{-\eta\tau} sin\omega\tau. \end{aligned}$$

Adding up the square together with $\eta > 0$, we obtain

$$M^2 + N^2 = b_1^2 e^{-2\eta\tau} \leq b_1^2,$$

where $M = \eta^3 - 3\eta\omega^2 + a_1(\eta^2 - \omega^2) + a_2\omega$ and $N = -\omega^3 + 3\eta^2\omega + 2a_1\eta\omega + a_2\omega$.
Since the above inequality is not true, it describes that (4.2) has a negative real part apart from $\lambda = 0$. Therefore, E_0 is unstable. □

Theorem 4.2. *If $\tau = 0$, the infected steady state E_1 is locally asymptotically stable when $R_0 > 1$, then τ increases from zero, there is a value τ_0 implies that unique infected state E_1 is locally asymptotically stable when $\tau \in [0, \tau_0]$ and it is unstable when $\tau > \tau_0$. When $\tau = \tau_0$ at equilibrium E_1 from the system (2.2) undergoes Hopf bifurcation.*

Proof. For the linearized system from (2.2). The Jacobian matrix of infected steady state, $J(E_1)$ becomes,

$$J(E_1) = \begin{pmatrix} -H_1 & u_1\alpha + \beta & 0 & -kT^* \\ kV^*e^{-\lambda\tau} & -\gamma - \alpha - \beta & 0 & kT^*e^{-\lambda\tau} \\ 0 & (1-u_1)\alpha & -\rho & 0 \\ 0 & 0 & N\rho & -d_V \end{pmatrix}, \tag{4.4}$$

where $H_1 = d_T + \frac{2rT^*}{T_{max}} - r + kV^*$.
The Jacobian matrix calculated at E_1 leads as,

$$C(\lambda) + D(\lambda)e^{-\lambda\tau} = 0, \tag{4.5}$$

where $C(\lambda) = \lambda^4 + \lambda^3 c_1 + \lambda^2 c_2 + \lambda c_3 + c_4$, $D(\lambda)(\lambda^2 d_1 + \lambda d_2 + d_3)e^{-\lambda\tau} = 0$,
and
$c_1 = H_1 + \gamma + \alpha + \beta + d_V + \rho$,
$c_2 = H_1(\gamma + \alpha + \beta) + \rho + d_V + (\gamma + \alpha + \beta)(\rho + d_V) + \rho d_V$,
$c_3 = H_1(\gamma + \alpha + \beta)(\rho + d_V) + (H_1 + (\gamma + \alpha + \beta))(\rho d_V)$,
$c_4 = H_1(\gamma + \alpha + \beta)\rho d_V$,
$d_1 = -(u_1\alpha + \beta)kV^*$,
$d_2 = -(kV^*(u_1\alpha + \beta)\rho d_V + kT^*(1-u_1)\alpha N\rho)$,
$d_3 = k^2T^*V^*(1-u_1)\alpha N\rho - H_1kT^*(1-u_1)\alpha N\rho - (u_1\alpha + \beta)kV^*\rho d_V$.
It is easy to show that (4.5) is stable in the absence of delay i.e., $\tau = 0$. Then (4.5) becomes

$$\lambda^4 + \lambda^3 c_1 + \lambda^2(c_2 + d_1) + \lambda(c_3 + d_2) + (c_4 + d_3) = 0,$$

By Routh Hurwitz Criteria, $c_1 > 0$, $(c_3 + d_2) > 0$, $(c_4 + d_3) > 0$ and $c_1(c_2 + d_1)(c_3 + d_2) - (c_3 + d_2)^2 + c_1^2(c_4 + d_3) > 0$, implies that E_1 is asymptotically stable when $\tau = 0$. Next we shall determine if (4.5) has unique pair of pure imaginary roots $\pm i\omega$ at equilibrium E_1. Let $\lambda = i\omega \quad (\omega > 0)$ in (4.5), then seperating real and imaginary parts, we obtain

$$\omega^4 - c_2\omega^2 + c_4 = (d_1\omega^2 - d_3)cos\omega\tau - d_2\omega sin\omega\tau \tag{4.6}$$

$$\omega^3 c_1 - c_3\omega = d_2\omega cos\omega\tau + (d_1\omega^2 - d_3)sin\omega\tau \tag{4.7}$$

Squaring and adding both the equation (4.6) and (4.7), we have
$\omega^8 + \omega^6(c_1^2 - 2c_2) + \omega^4(c_2^2 + 2c_4 - 2c_1c_3 - d_1^2) + \omega^2(c_3^2 - 2c_2c_4 - d_2^2 + 2d_1d_3) + (c_4^2 - d_3^2) = 0.$
Let us consider $z = \omega^2$
$H(z) = z4 + z^3(c_1^2 - 2c_2) + z^2(c_2^2 + 2c_4 - 2c_1c_3 - d_1^2) + z(c_3^2 - 2c_2c_4 - d_2^2 + 2d_1d_3) + (c_4^2 - d_3^2)$
since,if (4.5) has a purely imaginary root $i\omega$ then $H(z) = 0$ has a positive real root ω^2. By [17], we obtain

$$cos\sqrt{z_n}\tau = A_n = \frac{(z_n^2 - c_2z_n + c_4)(d_1z_n - d_3) - c_3d_2z_n + c_1d_2z_n}{(d_1z_n - d_3)^2 + d_2^2z_n}$$
$$sin\sqrt{z_n}\tau = B_n = \frac{(z_n^2 - c_2z_n + c_4)(d_2\sqrt{z_n}) + (\sqrt{z_n}(c_1z_n - c_3)(d_1z_n - d_3))}{d_2^2z_n + (d_1z_n - d_3)^2}$$

Denote

$$\tau_n^{(k)} = \begin{cases} \frac{1}{\sqrt{z_n}}(arccosA_n + 2k\pi), if B_n \geq 0, \\ \frac{1}{\sqrt{z_n}}(2\pi - arccosA_n + 2k\pi), if B_n < 0, \end{cases}$$

where $1 \leq n \leq 4$and $k = 1, 2, 3...$, therefore, it is described that the characteristic equation (4.5) has a pair of purley imaginary roots $\pi i\sqrt{z_n}$. Let $\lambda_n^{(k)} = \eta_n^{(k)}(\tau) + i\omega_n^{(k)}(\tau)$, the root of characteristic equation (4.5) satisfying $\eta_n^{(k)}(\tau_n^{(k)}) = 0, \omega_n^{(k)}(\tau_n^{(k)}) = \sqrt{z_n}$. Where $\eta_n^{(k)}(\tau_n^{(k)})$ and $\omega_n^{(k)}(\tau_n^{(k)})$ depends on $(\tau_n^{(k)})$.
Then, we determine

$$sign(\frac{d(Re\lambda)}{d\tau})|_{\tau=\tau_0} = sign(Re(\frac{d\lambda}{d\tau})^{-1})|_{\tau=\tau_0}.$$

we consider the characteristic equation (4.5), now differentiating with respect to τ,

$$C^{'}(\lambda)\frac{d\lambda}{d\tau} + D^{'}(\tau)\frac{d\lambda}{d\tau}e^{-\lambda\tau} - (\lambda + \tau\frac{d\lambda}{d\tau}D(\lambda)e^{-\lambda\tau}) = 0,$$

Then,

$$[\frac{d\lambda}{d\tau}]^{-1} = \frac{C'(\lambda) + D^{'}(\lambda)e^{-\lambda\tau} - \tau D(\lambda)e^{-\lambda\tau}}{\lambda D(\lambda)e^{-\lambda\tau}}. \tag{4.8}$$

Substituting $\lambda = i\omega_0$ in (4.8). We have

$$(\frac{d\lambda}{d\tau})^{-1}|_{\tau=\tau_0} = \frac{P_1 + iP_2}{P_3 + iP_4} - \frac{\tau}{\lambda},$$

where

$$P_1 = (c_3 - 2c_1\omega_0^2) + d_2cos\omega_0\tau_0 + 2d_1\omega_0sin\omega_0\tau_0$$
$$P_2 = (2c_1 - 4\omega_0^3) + 2d_1\omega_0cos\omega_0\tau_0 - d_2cos\omega_0\tau_0$$
$$P_3 = d_2\omega_0^2cos\omega_0\tau_0 - (d_3\omega_0 - d_1\omega_0^3)sin\omega_0\tau_0$$
$$P_4 = (d_3\omega_0 - d_1\omega_0^3)cos\omega_0\tau_0 + d_2\omega_0^2sin\omega_0\tau_0.$$

Thus,

$$\frac{dRe(\lambda)}{d\tau}|_{\tau=\tau_0} = \frac{P_1P_3 + P_2P_4}{P_3^2 + P_4^2}.$$

Therefore,

$$sign[\frac{dRe(\lambda)}{d\tau}|_{\tau=\tau_0}] = signRe[\frac{d\lambda}{d\tau}|_{\tau=\tau_0}] = signRe[\frac{d\lambda}{d\tau}|_{\tau=\tau_0}]^{-1},$$
$$\frac{dRe(\lambda)}{d\tau}|_{\omega=\omega_0,\tau=\tau_0} > 0.$$

Thus, transversality condition holds and this implies that the Hopf bifurcation occurs for the system (4.4). Moreover, Hopf bifurcation is present when τ passes to the critical value τ_0 and theorem is proved. □

5. Numerical simulations

In this section, we verified the theoretical stability conditions using the particular parameter values and numerical simulations provided to the system (2.2) to show the impact of the delay effect. The parameter values are in Table (1) and initial conditions: $T(\theta) = T_0$ $I_1(\theta) = I_{1_0}$, $I_2(\theta) = I_{2_0}$, $V(\theta) = V_0$ for $\theta \in [-\tau, 0]$.

Case 1: In this case, when $\tau = 0$, the numerical simulations describe that healthy cells,infected cells(Pre-RT and Post-RT) and free virus particles approach towards the equilibrium $E_1 = (T^*, I_1^*, I_2^*, V^*) = (155, 300.44, 450.66, 45066.2)$, which is locally asymptotically stable. The roots of the characteristic equations (4.4) have the negative real parts which are $(-0.0133649 \pm 0.279188i, -1.08626, -2.2941)$ in (See Fig. (2) and Fig. (3).

Case 2: In this case, when $\tau \neq 0$, by using the theorem 4.2. It is describes that

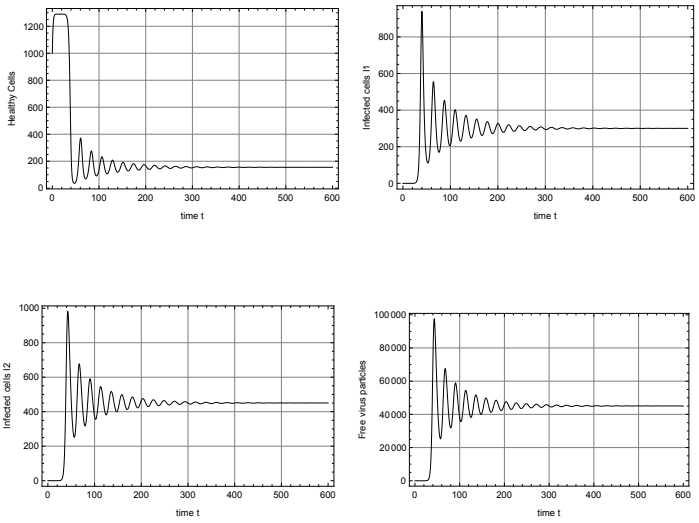

Figure 2. The solution T, I_1, I_2 and V of the system (2.2) is convergence to E_1 when $\tau = 0$

equilibrium E_1 is locally asymptotically stable for $(\tau < \tau_0)$(See Fig. (4) and Fig. (5).

Case 3: When $\tau = \tau_0$, Hopf bifurcation occurs at E_1 becomes unstable (or) lose the stability and exists the periodic oscillations for $\tau > \tau_0$ (See Fig. (6). Next Fig. (7),

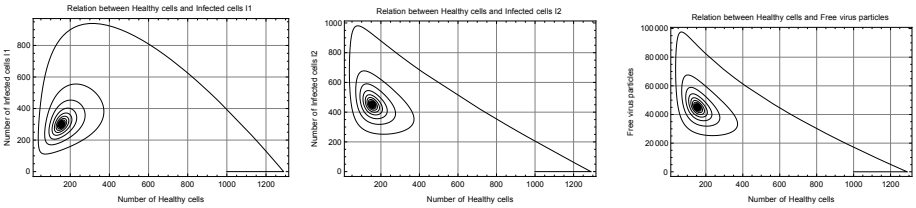

FIGURE 3. Equilibrium E_1 of the system (2.2) is locally asymptotically stable when $\tau = 0$

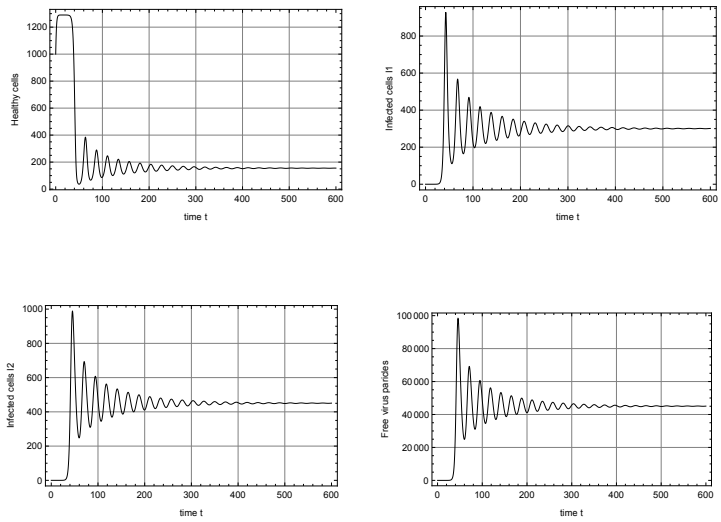

FIGURE 4. The solution T, I_1, I_2 and V of the system (2.2) is convergence to E_1 when $\tau = 0.24$

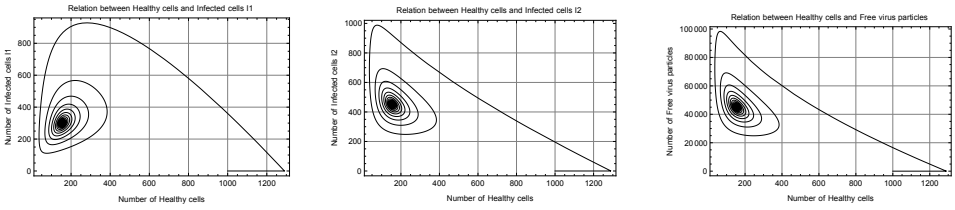

FIGURE 5. Equilibrium E_1 of the system (2.2) is locally asymptotically stable when $\tau = 0.24$

shows that all the healthy cells, infected cells (Pre-RT and Post-RT), viral particles approach periodic oscillations around the equilibrium E_1 which bifurcating periodic oscillations are orbitally asymptotically stable.

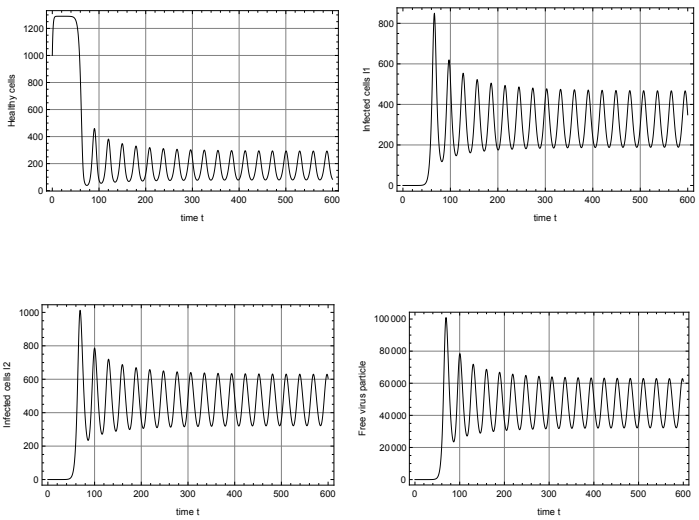

FIGURE 6. The solution T, I_1, I_2 and V of the system (2.2) occurs the periodic solution when $\tau = 2.4$

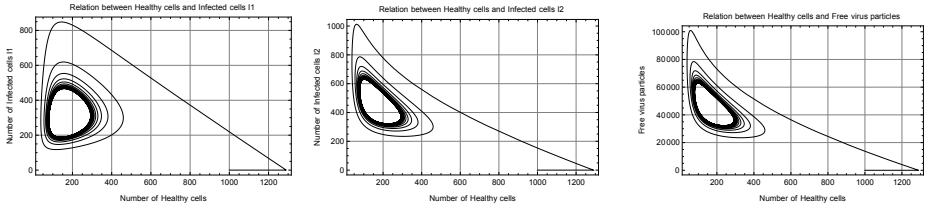

FIGURE 7. Equilibrium E_1 of the system (2.2) is undergoes bifurcation when imposed the length of the delay value $\tau = 2.4$

6. Conclusion

We present and discussed a time delay in the drug therapy model of HIV dynamics. Further, we studied how an intercellular effect progression affects the overall dynamical system. From the results of the model (2.2), we show that the time delay increases, the system proceeds to appear instability or oscillatory. Since our analysis, we determined local stability of disease-free steady state E_0 is independent of the size of time delay. An infected steady state E_1 is depended on the size of time delay and delay effects progression leading to a Hopf bifurcation. By analyzing mathematically, it was helped to understand the intercellular delay effect that describes the time between infection cells and the emission of the viral particle. The graphical representations are provided to observe and to predict the physical changes in healthy cells, infected cells, and free virus particles. In future research, we shall study the conduct of the system when the time delay increases too long.

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