Int. J. Nonlinear Anal. Appl. 13 (2022) 2, 1927–1936
ISSN: 2008-6822 (electronic)
http://dx.doi.org/110.22075/ijnaa.2021.22444.2364

Analysis of a delayed HIV pathogenesis model with saturation incidence, both virus-to-cell and cell-to-cell transmission

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(Communicated by Javad Damirchi)

Abstract

In this paper, we proposed and studied a delayed HIV pathogenesis model with saturation incidence, both virus-to-cell and cell-to-cell transmission. We address the basic reproduction number R_0, the characteristic equations, and local stability of feasible equilibria are established. Where the delay incorporates both virus-to-cell and cell-to-cell transmission. Moreover, we discuss the existence of Hopf Bifurcation when a delay is used as a bifurcation parameter. Numerical simulations are performed to satisfy our theoretical results.

Keywords: Cell-to-cell transmission, Intracellular delay, Hopf bifurcation, Saturation incidence
2010 MSC: Primary 34D20, Secondary 34C23

1 Introduction

In past decades, the study of HIV dynamics has been attracted by many researchers. There are many works proposed on HIV infection from different points of view, such as [2, 8, 10, 4, 5, 13, 15]. Mathematical models are an important tool to explain the complex processes, make an assumption, and suggest new experiments. The basic Mathematical model for studying the HIV dynamics in healthy cells, infected cells, and viral load can be written as

$$\begin{aligned}\frac{dT(t)}{dt} &= s - d_1T(t) - \beta T(t)V(t),\\ \frac{dI(t)}{dt} &= \beta T(t)V(t) - d_2I(t),\\ \frac{dV(t)}{dt} &= Nd_2I(t) - d_3V(t).\end{aligned}$$

AIDS (Acquired Immunodeficiency Syndrome) which is caused by HIV (Human Immunodeficiency Virus), is a globally problematic disease. Viruses do not have cell walls, are parasitic, and it needs the host to replicate the virus [6]. When HIV enters into a body, it targets $CD4^+$ T-cells and destroys the white blood cells of the immune system. There is

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Received: January 2021 *Accepted:* May 2021

no cure mechanism of HIV-AIDS still now unexplained. M.Y. Li and H. Shu [7] have explained the delay differential model for the joint effects of target cells and intracellular delay, that is

$$\begin{aligned}\frac{dT(t)}{dt} &= s - d_1T(t) + aT(t)(1 - \frac{T(t)}{K}) - \beta T(t)V(t),\\ \frac{dI(t)}{dt} &= \beta e^{-m\tau}T(t)V(t) - d_2I(t),\\ \frac{dV(t)}{dt} &= Nd_2I(t) - d_3V(t).\end{aligned}$$

The authors [11, 14, 17, 18, 19, 20] discussed the infection equilibrium loses stability and occurs the Hopf bifurcation when τ passes through the critical value. F. Li and J. Wang [9] proposed the following model leads to understanding the effect of bifurcation analysis which incorporates virus-to-cell transmission and cell-to-cell transmission as follows,

$$\begin{aligned}\frac{dT(t)}{dt} &= s - d_1T(t) + aT(t)(1 - \frac{T(t)}{K}) - \beta_1 T(t)V(t) - \beta_2 T(t)I(t),\\ \frac{dI(t)}{dt} &= \beta_1 e^{-m\tau}T(t)V(t) - \beta_2 e^{-m\tau}T(t)I(t) - d_2I(t),\\ \frac{dV(t)}{dt} &= Nd_2I(t) - d_3V(t).\end{aligned}$$

Motivated by [3, 9, 16], we modified their models, which considered only the three components: uninfected $CD4^+$ T-cells, infected $CD4^+$ T-cells, and free virus particle. We have constructed an HIV pathogenesis model with saturation incidence, virus-to-cell and cell-to-cell transmission as follows,

$$\begin{aligned}\frac{dT(t)}{dt} &= s - d_1T(t) + aT(t)(1 - \frac{T(t)}{K}) - \frac{\beta_1 T(t)V(t)}{1+\alpha_1 V(t)} - \frac{\beta_2 T(t)I(t)}{1+\alpha_2 I(t)},\\ \frac{dI(t)}{dt} &= \frac{\beta_1 e^{-m\tau}T(t-\tau)V(t-\tau)}{1+\alpha_1 V(t-\tau)} + \frac{\beta_2 e^{-m\tau}T(t-\tau)I(t-\tau)}{1+\alpha_2 I(t-\tau)} - d_2I(t),\\ \frac{dV(t)}{dt} &= Nd_2I(t) - d_3V(t),\end{aligned} \tag{1.1}$$

where T, I denote the number of target and infected cells, V is the viral load of the virions. β indicates the infection rate constant, s indicates the rate at which new T-cells are produced from the source. d_1 and d_2 are death rates of target and infected cells respectively. d_3 is clearance rate of virions. Where the term $e^{-m\tau}$ denotes the number of the infected cells at time t but die before productively infected t time unit later. It means that the conscription of virus producing at time t given by the number of cells that were newly infected at time (t - τ) and still alive at time t. β_1 is the infection rate by virus-to-cell transmission, β_2 is the infection rate by cell-to-cell transmission. The population density denoted by K. N is considered to be the average number of virus particles produced by infected cells.
In this paper, we shall discuss the existence of equilibria, local stability of the infected steady state. Further, we introduce the discrete time delay for the proposed model to describe the time between cell-to-virus transmission and cell-to-cell transmission. In addition, we investigate the existence of Hopf bifurcation analysis for this model. Numerical simulations are provided to illustrate the obtained results.

2 Existence of equilibria and local stability analysis

We denote the Banach space of continuous real valued function $\phi : [-\tau, 0] \to R_3$, with the norm,

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

The initial conditions for the system (1.1) is given as

$T(\theta) = \phi_1(\theta), I(\theta) = \phi_2(\theta), V(\theta) = \phi_3(\theta)$, where $\phi_i(\theta) \ge 0$, $\theta \in [-\tau, 0]$.

This system (1.1) has two nonnegative equilibria exists. An infection free equilibrium $E_0 = [T_0, 0, 0]$ and infection equilibrium $E_1 = [\overline{T}, \overline{I}, \overline{V}]$, where

$$T_0 = \frac{K}{2a}\left((a - d_1) + \sqrt{(a - d_1)^2 + 4asK^{-1}}\right),$$

Table 1: Variables and Parameters

Parameters	Range of the Parameters	Source
s	$0-10$ cells mm^{-3} day^{-1}	[12]
d_1	$0.007-0.1$ day^{-1}	[20]
a	$0.03-3$ day^{-1}	[12]
d_2	$0.5-1$ day^{-1}	[20]
d_3	$2.4-5$ day^{-1}	[20]
β_1	$0.00025-0.5$ virons mm^{-3} day^{-1}	[19]
β_2	0.0001 virons mm^{-3} day^{-1}	assumed
α_1	$0.00005-0.5$ virons mm^{-3} day^{-1}	[11]
α_2	0.00002 virons mm^{-3} day^{-1}	assumed
K	1300 mm^{-3}	[20]
N	10-2500 virons/cell	[12]
m	1.2 day^{-1}	[20]

$$\overline{T} = \frac{e^{-m\tau}[d_3d_2 - N\alpha_1 d_2 - d_3\alpha_2]}{d_3\beta_2 + Nd_2\beta_1}, \quad \overline{I} = \frac{e^{-m\tau}(s + a\overline{T} - d_1\overline{T})K - a\overline{T}^2}{K\delta}, \quad \overline{V} = \frac{N\overline{I}d_2}{d_3}.$$

The basic reproductive number is given as,$R_0 = \dfrac{T_0}{\overline{T}}$, which describes the number of newly infected cells formed by one infected cell throughout its life span. In order to show the locally asymptotically stable for an infection free equilibrium E_0.

Theorem 2.1. If $R_0 < 1$, then infection-free equilibrium E_0 is locally asymptotically stable, it is unstable, when $R_0 > 1$ and $R_0 = 1$, it is a critical case for any time $\tau \geq 0$.

Proof . Suppose $R_0 < 1$, the linearized system of (1.1) for E_0 follows;

$$J_1 = \begin{pmatrix} M_0 & -\beta_2 T_0 & -\beta_1 T_0 \\ 0 & -(d_2 - \beta_2 e^{-m\tau}T_0 e^{-\lambda\tau}) & \beta_1 e^{-m\tau}T_0 e^{-\lambda\tau} \\ 0 & Nd_2 & -d_3 \end{pmatrix}, \tag{2.1}$$

where, $M_0 = (a - d_1 - \frac{2aT_0}{K})$. Thus, the characteristic equation as E_0 is given by

$$(M_0 - \lambda)\left[\lambda^2 + \lambda(d_2 + d_3 - \beta_2 e^{-m\tau}T_0 e^{-\lambda\tau}) + d_2d_3 - (\beta_1 Nd_2 + \beta_2 d_3)e^{-m\tau}T_0 e^{-\lambda\tau}\right] = 0, \tag{2.2}$$

It is easily shown that (2.2) has a characteristic root, $\lambda = M_0$. Then, the characteristic roots for the transcendental polynomial,

$$\lambda^2 + \lambda a_0 + b_0 + \lambda c_0 e^{-m\tau}e^{-\lambda\tau} + d_0 e^{-m\tau}e^{-\lambda\tau} = 0, \tag{2.3}$$

where $a_0 = d_2 + d_3$, $b_0 = d_3d_2$, $c_0 = -\beta_2 e^{-m\tau}T_0 e^{-\lambda\tau}$, $d_0 = -(\beta Nd_2 + \beta_2 d_3)e^{-m\tau}T_0 e^{-\lambda\tau}$.
In this case, $\tau = 0$, if $R_0 < 1$, then the roots of (2.3) have negative real parts. By analyzing the Routh-Hurwitz criteria conditions $(a_0 + c_0) > 0$, $(b_0 + d_0) > 0$ are satisfied. Suppose (2.3) has pure imaginary roots, $\lambda = i\omega(\omega > 0)$ for some $\tau > 0$. We get in the form

$$\begin{aligned} -\omega^2 + b_0 &= -c_0\omega sin\omega\tau - d_0 cos\omega\tau, \\ a_0\omega &= -d_0 sin\omega\tau - c_0\omega cos\omega\tau. \end{aligned} \tag{2.4}$$

If $R_0 < 1$, then (2.4) becomes

$$\omega^4 + \omega^2(c_0^2 - a_0^2 - 2b_0^2) + (b_0^2 + d_0^2) = 0, \tag{2.5}$$

Let $y = \omega^2$, $y^2 + y(c_0^2 - a_0^2 - 2b_0^2) + (b_0^2 + d_0^2) = 0$,

$$y = \frac{-(c_0^2 - a_0^2 - 2b_0^2) + \sqrt{(c_0^2 - a_0^2 - 2b_0^2)^2 - 4(b_0^2 + d_0^2)}}{2} < 0,$$

It implies that the root of (2.3) must have a negative real part. Hence the infection free equilibrium E_0 is locally asymptotically stable for any time $\tau \geq 0$. Here we denote

$$f(\lambda) = \lambda^2 + \lambda a_0 + b_0 + \lambda c_0 e^{-\lambda\tau} + d_0 e^{-\lambda\tau} = 0,$$

If $R_0 < 1$, then

$$f(0) = (b_0 + d_0 e^{-\lambda\tau}) < 0 \quad and \quad \lim_{t\to\infty}(f(\lambda)) = +\infty. \tag{2.6}$$

From the continuity of the function f that the equation $f(\lambda) = 0$ has at least one positive root. Hence, the characteristic equation (2.3) has at least one positive real root. So that case E_0 is unstable. When, $R_0 = 1$, Eq.(2.3) becomes,

$$g(\lambda) = \lambda^2 + \lambda a_0 + b_0 + \lambda c_0 e^{-\lambda\tau} + d_0 e^{-\lambda\tau} = 0, \tag{2.7}$$

It was known that $\lambda = 0$ is a simple root of (2.7). In order to show that any root of (2.7) must have a negative real part except from $\tau = 0$. Suppose (2.7) has imaginary roots, $\lambda = u \pm i\omega$ for some $u \geq 0$, $\omega \geq 0$ and $\tau \geq 0$. From (2.4) becomes,

$$\begin{aligned} u^2 - \omega^2 + b_0 &= -(c_0 u + d_0)e^{-u\tau} cos\omega\tau - \omega c_0 e^{-u\tau} sin\omega\tau, \\ -2\omega - a_0\omega &= (c_0 u + d_0)e^{-u\tau} sin\omega\tau - \omega c_0 e^{-u\tau} cos\omega\tau. \end{aligned} \tag{2.8}$$

Reduce the (2.8) with $u \geq 0$, we have

$$(u^2 - \omega^2 + b_0)^2 + (2\omega - a_0\omega)^2 - c_0^2(u^2 + \omega^2) = e^{-2u\tau} d_0^2 \leq d_0^2. \tag{2.9}$$

From the above analysis, the inequality (2.9) is not true. Hence it shows that any root of (2.7) has a negative real part except from $\tau = 0$. Therefore, theorem (2.1) is proved. □

3 The Stability of positive equilibrium and Hopf bifurcation

In this section, we shall consider the basic reproduction number $R_0 > 1$ and τ as a parameter to study the existence of Hopf bifurcation for an infected equilibrium E_1.

Theorem 3.1. If $\tau = 0$, then the infected steady state E_1 is locally asymptotically stable when $R_0 > 1$.

Proof . Let us consider the Jacobian matrix for an infected equilibrium E_1 is

$$J_2 = \begin{pmatrix} M_1 & -\dfrac{\beta_2\overline{I}}{(1+\alpha_2\overline{I})^2} & -\dfrac{\beta_1\overline{T}}{(1+\alpha_1\overline{V})^2} \\ \left(\dfrac{e^{-m\tau}\beta_1\overline{V}e^{-\lambda\tau}}{(1+\alpha_1\overline{V})} + \dfrac{e^{-m\tau}\beta_2\overline{I}e^{-\lambda\tau}}{(1+\alpha_2\overline{I})}\right) & -\left(d_2 - \dfrac{\beta_2 e^{-m\tau}\overline{T}e^{-\lambda\tau}}{(1+\alpha_2\overline{I})^2}\right) & \dfrac{\beta_1 e^{-m\tau}\overline{T}e^{-\lambda\tau}}{(1+\alpha_1\overline{V})^2} \\ 0 & Nd_2 & -d_3 \end{pmatrix}, \tag{3.1}$$

where, $M_1 = (d_1 - a + \dfrac{2a\overline{T}}{K} + \dfrac{\beta_1\overline{V}}{(1+\alpha_1\overline{V}} + \dfrac{\beta_2\overline{I}}{(1+\alpha_2\overline{I})})$.

The characteristic equation of the system (3.1) is given by

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau} = 0, \tag{3.2}$$

where,

$$P(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3, \quad Q(\lambda) = b_1\lambda^2 + b_2\lambda + b_3,$$

$$
\begin{aligned}
a_1 &= d_2 + d_3 + M_1,\\
a_2 &= d_3 d_2 + M_1(d_2 + d_3),\\
a_3 &= M_1 d_2,\\
b_1 &= \frac{\beta_2 \overline{T}}{(1+\alpha_2 \overline{V})^2},\\
b_2 &= M_1\left(\frac{\beta_2 \overline{T}}{(1+\alpha_2 \overline{V})^2} + \frac{d_2\beta_1 N\overline{T}}{(1+\alpha_2 \overline{V})^2} + \frac{\beta_1 \overline{TI}}{(1+\alpha_2 \overline{V})^3}\right) - \frac{d_3\beta_2 \overline{I}}{(1+\alpha_2 \overline{I})^2},\\
b_3 &= M_1 d_3\left(-\frac{\beta_1 \overline{T}}{(1+\alpha_2 \overline{I})^2} - \frac{d_2\beta_1 N\overline{T}}{(1+\alpha_1 \overline{V})^2} + \frac{\beta_1^2 \overline{TV} N d_2}{(1+\alpha_1 \overline{V})^3} + \frac{\beta_1\beta_2 \overline{TI} N d_2}{(1+\alpha_1 \overline{I})(1+\alpha_1 \overline{V})^2}\right)\\
&\quad + \frac{\beta_1\beta_2 \overline{TV} d_3}{(1+\alpha_1 \overline{V})(1+\alpha_2 \overline{I})^2} + \frac{d_3\beta_2^2 \overline{TI}}{(1+\alpha_2 \overline{I})^3}.
\end{aligned}
$$

By the Routh-Hurwitz criteria conditions are satisfied for the characteristic equations (3.2) and it implies that all the roots of the characteristic equations have the negative real parts. In order to studies the possible bifurcation for the system. If $\tau = 0$, then the above analysis confirmed that the system is locally asymptotically stable. Suppose the value of τ is varying and analysis the possible bifurcation. Then if τ is increasing, then infection equilibrium E_1 becomes unstable and the characteristic roots have to cross the imaginary axis.
In order to investigate the existence of purely imaginary roots and results that can be provided as follows, from (3.2), let us consider $\lambda = i\omega(\omega > 0)$. In (3.2), all the coefficients P and Q is depending on τ. E. Beretta and Y. Kuang [1] explained a geometrical criterion and it provides the existence of purely imaginary roots of characteristic polynomials with delay depend on the coefficients. The below properties need to investigate for all $\tau \in [0, K)$. □

Proposition 3.2.

(a) $P(0,\tau) + Q(0,\tau) \neq 0$,

(b) $P(i\omega,\tau) + Q(i\omega,\tau) \neq 0$,

(c) $\limsup\{|\frac{P(\lambda,\tau)}{Q(\lambda,\tau)}| : |\lambda| \to \infty, \quad Re \quad \lambda \geq 0\} < 1$,

(d) $F(\omega,\tau) = |P(i\omega,\tau)|^2 - |Q(i\omega,\tau)|^2$, has a finite number of zeros.

(e) Each positive root $\omega(\tau)$ of $F(\omega,\tau) = 0$, is continuous and differentiate in τ whenever it exists.

From (a), it gives $P(0,\tau) + Q(0,\tau) = a_3(\tau) + b_3(\tau) = 0$. Then, (b) describes,

$$
\begin{aligned}
P(i\omega,\tau) + Q(i\omega,\tau) &= -i\omega^3 - a_1(\tau)\omega^2 + ia_2(\tau)\omega + a_3(\tau) - b_1(\tau)\omega^2 + ib_2(\tau)\omega + b_3(\tau),\\
&= [a_3(\tau) + b_3(\tau) - (a_1(\tau) + b_1(\tau))\omega^2] + i\omega[b_2(\tau) + a_2(\tau) - \omega^2],\\
&\neq 0,
\end{aligned}
$$

the above analysis (a) and (b) are satisfied. From (3.2), it is well-known that $\lim_{\lambda\to\infty} |\frac{Q(\lambda,\tau)}{P(\lambda,\tau)}| = 0$, which implies (c) is verified. From (d), F is already defined, then we know that $\lambda = i\omega(\omega > 0)$ be the pure imaginary root of (3.2). Separating real and imaginary parts after applying the pure imaginary value $\lambda = i\omega(\omega > 0)$ in (3.2).

$$
\begin{aligned}
a_3(\tau) - a_1(\tau)\omega^2 &= (b_3(\tau) - b_1(\tau)\omega^2)\cos\omega\tau - b_2(\tau)\omega\sin\omega\tau,\\
a_2(\tau)\omega - \omega^3 &= (b_3(\tau) - b_1(\tau)\omega^2)\sin\omega\tau + b_2(\tau)\omega\cos\omega\tau,
\end{aligned}
\tag{3.3}
$$

Squaring and adding both side of (3.3), then it becomes

$$F(\omega,\tau) = \omega^6 + \eta_1(\tau)\omega^4 + \eta_2(\tau)\omega^2 + \eta_3(\tau) = 0,$$

where
$\eta_1(\tau) = a_1^2(\tau) - 2a_2(\tau) - b_1^2(\tau), \quad \eta_2(\tau) = a_2^2(\tau) - 2a_1(\tau)a_3(\tau) + 2b_1(\tau)b_3(\tau) - b_3^2(\tau), \quad \eta_3(\tau) = a_3^2(\tau) - b_3^2(\tau).$

By the above analysis, now it is clear that the property (d) is satisfied. Then by implicit function theorem, (e) is also satisfied. We have

$$\sin\omega\tau = \frac{\omega^5 b_1(\tau) + \omega^3(a_1(\tau)b_2(\tau) - b_3(\tau)) - \omega^2(a_2(\tau)b_1(\tau)) + \omega(a_2(\tau)b_3(\tau) - a_3(\tau)b_2(\tau))}{(b_1(\tau)\omega^2 - b_3(\tau))^2 + b_2^2(\tau)\omega^2} = g_1(\tau) \tag{3.4}$$

$$\cos\omega\tau = \frac{\omega^4(a_1(\tau)b_1(\tau) - b_2(\tau)) + \omega^2(a_2(\tau)b_2(\tau) - a_1(\tau)b_3(\tau) - a_3(\tau)b_1(\tau)) + a_3(\tau)b_3(\tau)}{(b_1(\tau)\omega^2 - b_3(\tau))^2 + b_2^2(\tau)\omega^2} = g_2(\tau) \tag{3.5}$$

From the definition of P and Q in (3.2), then using the property (a), (3.3) becomes,

$$\sin\omega\tau = Im\frac{P(i\omega,\tau)}{Q(\omega,\tau)} \quad and \quad \cos\omega\tau = Re\frac{P(i\omega,\tau)}{Q(i\omega,\tau)}, \tag{3.6}$$

which yields,$|P(i\omega,\tau)|^2 = |Q(i\omega,\tau)|^2$, and $\tau \neq I$, $\omega(\tau)$ is not defined then $\omega(\tau)$ satisfies $F(\omega,\tau) = 0$. Further the polynomial function F can be written in the form of $F(\omega,\tau) = z(\omega^2,\tau)$, here τ represents the third degree polynomial, which gives,

$$z(x,\tau) = x^3 + \eta_1 x^2 + \eta_2 x + \eta_3. \tag{3.7}$$

It is well known that the number of positive roots (3.7) based on the sign η_1. If $\eta_1 \geq 1$, then (e) has three positive roots. Further we assume that $\eta_1 > 0$ and define $\theta(\tau) \in [0, 2\pi)$. It follows that the relation between the argument θ and $\omega\tau$ in (3.7) for $\tau > 0$ must be

$$\omega\tau = \theta + 2n\pi, \quad n = 0, 1, 2, ... \tag{3.8}$$

Hence, we define $\theta(\tau) \in (-\pi, \pi]$ as

$$\theta(\tau) = arcsin(g_1(\tau)) \;\; sign(g_2(\tau)), \quad and$$
$$s_n(\tau) = \tau - \frac{\theta + 2n\pi}{\omega(\tau)}, \quad t \in (0,\tau), \quad n \in N.$$

Then $\pm i\omega(\tau_0)$ are a purely imaginary roots (3.2), if and only if τ_0 is zero of function S_n for some $n \in N$.

Theorem 3.3. Assume that the function S_n has a positive root $\tau_0 \in (0,\tau)$ for some $n \in N$. Then a pair of simple conjugate purely imaginary roots $\lambda = \pm i\omega_0$ exists at $\tau = \tau_0$ which cross the imaginary axis from left to right if $S_n < 0$, where

$$sign\left\{\frac{dR(\lambda)}{d\tau}|_{\lambda=i\omega_0(\tau_0)}\right\} = sign\left\{\frac{dS_n(\tau)}{d\tau}|_{\tau=\tau_0}\right\}.$$

Proof .

$$sign\left\{\frac{dR(\lambda)}{d\tau}|_{\lambda=i\omega_0(\tau_0)}\right\} = sign\left\{\frac{\partial F}{\partial w}(\omega_0,\tau_0)\right\}\left\{\frac{dS_n(\tau)}{d\tau}|_{\tau=\tau_0}\right\}.$$

In fact $\frac{\partial F}{\partial w}(\omega_0,\tau_0) > 0$, then differentiate (3.2) with respect to τ, which yield.

$$R\left[\frac{d\lambda}{d\tau}\right]^{-1}|_{\tau=\tau_0} = \frac{1}{\omega_0} sign\left\{\frac{2\omega_0^6 + \omega^4(a_1^2 - 2a_2 - b_2^2) + b_3^2 - a_3^2}{(b_3 - b_1\omega_0^2)^2 + b_2^2\omega_0^2}\right\}.$$

In this case $(a_1^2 - 2a_2 - b_2^2 + b_3^2 - a_3^2) > 0$, $(b_3^2 - a_3^2) > 0$ and $\eta_1 > 0$, $\eta_2 > 0$ respectively. By our analysis, it is clear that

$$R\frac{d\lambda}{d\tau}|_{\omega=\omega_0, \;\; \tau=\tau_0} > 0. \tag{3.9}$$

It has implied that the transversality condition holds. Hence, Hopf bifurcation occurs at $\omega = \omega_0, \tau = \tau_0$. The proof is completed. □

4 Numerical simulations

In this section, we investigate the dynamic behaviour of (1.1) through numerical simulations. The parameter values are s = 5mm^{-3} day^{-1}, $d_1 = 0.01$ day^{-1}, $d_2 = 0.5$ day^{-1}, $\alpha_1 = 0.00002$ day^{-1} mm $^{-3}$, $\alpha_2 = 0.00001$ day $^{-1}$ mm $^{-3}$, d_3 = 5 day^{-1}, N = 1200, m = 1.2 day^{-1}, $\beta_1 = 0.0001$ day^{-1},$\beta_2 = 0.0002$ day^{-1} , K = 1300. The three cases to discuss the dynamics of the system (1.1) as follows,
Case (1): When $\tau = 0$, there is no time delay for the system (1.1). It is easily shown that in Fig. (1), the system is locally asymptotically stable.

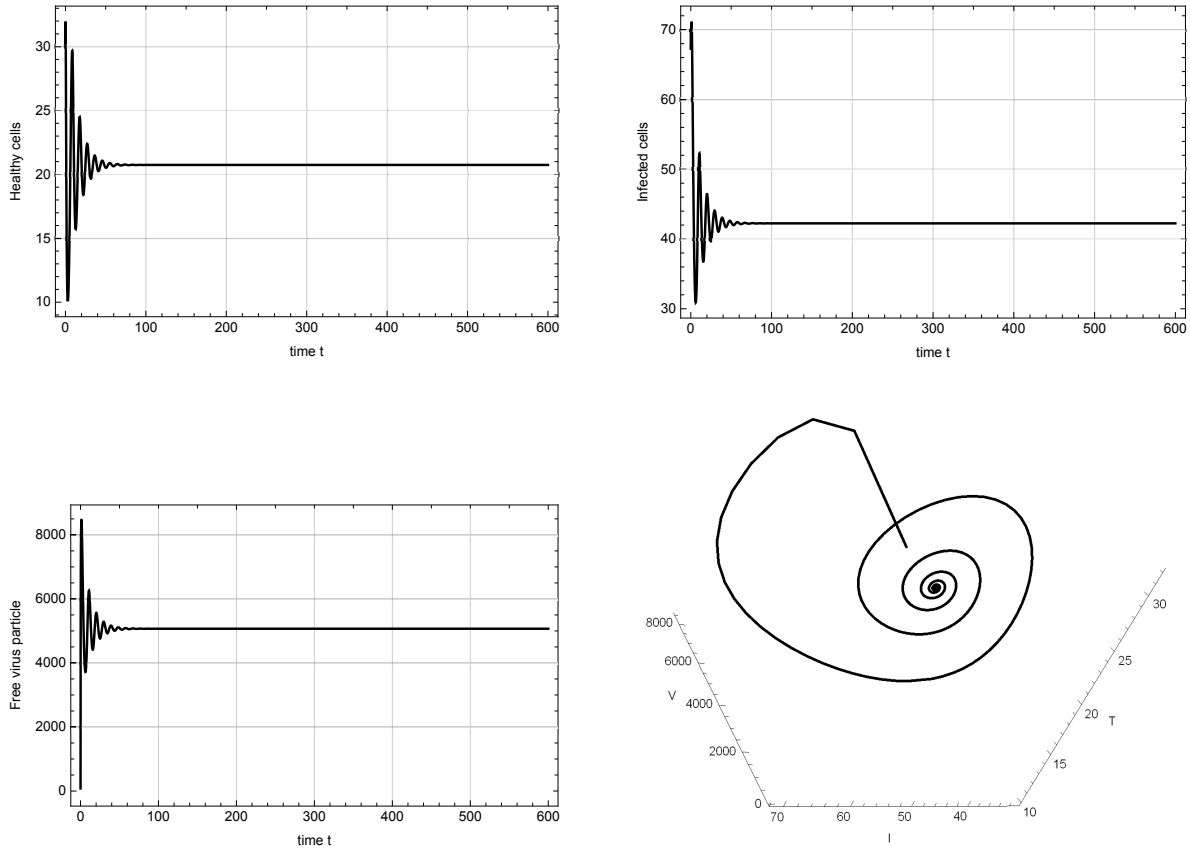
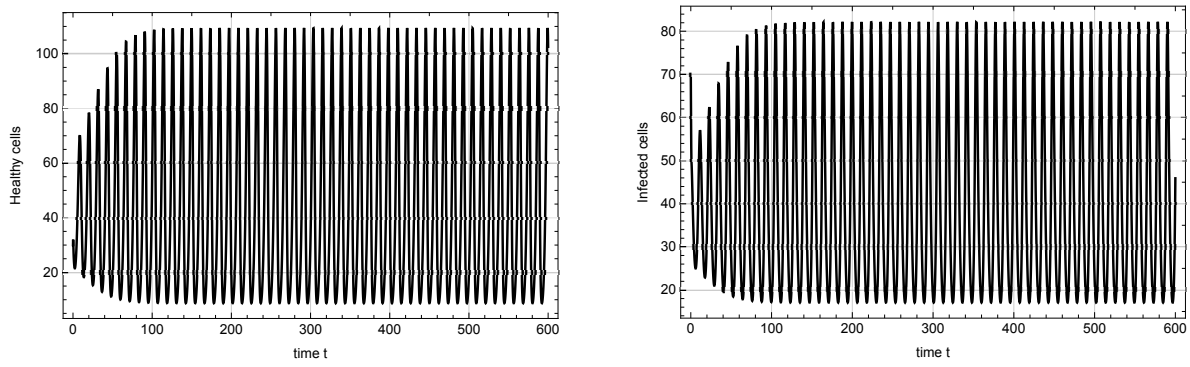


Figure 1: The solution T, I and V of the system (1.1) is convergence to E_1 when $\tau = 0$.

Case.(2): When $\tau > 0$, the time delay exists, such that the equilibrium E_1 is asymptotically stable for $0 \leq \tau < \tau_0$. If the system (1.1) become unstable for τ hold on in some neighborhood of τ_0, then a Hopf bifurcation occurring for $\tau = \tau_0$. In this case, by increasing the value of the delay as $\tau = 0.5$, Fig. (2) shows that the existence of Hopf bifurcation.



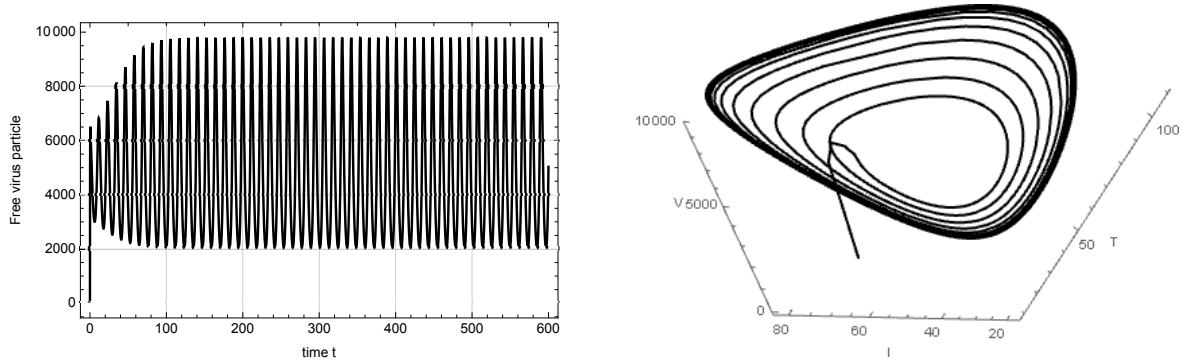


Figure 2: Equilibrium E_1 of the system (1.1) occurs the Hopf bifurcation when $\tau = 0.5$.

Case.(3): In this case, the time delay increasing the value of the delay as $\tau = 2.5$ and Fig. (3) shows that the infection equilibrium asymptotically stable again.

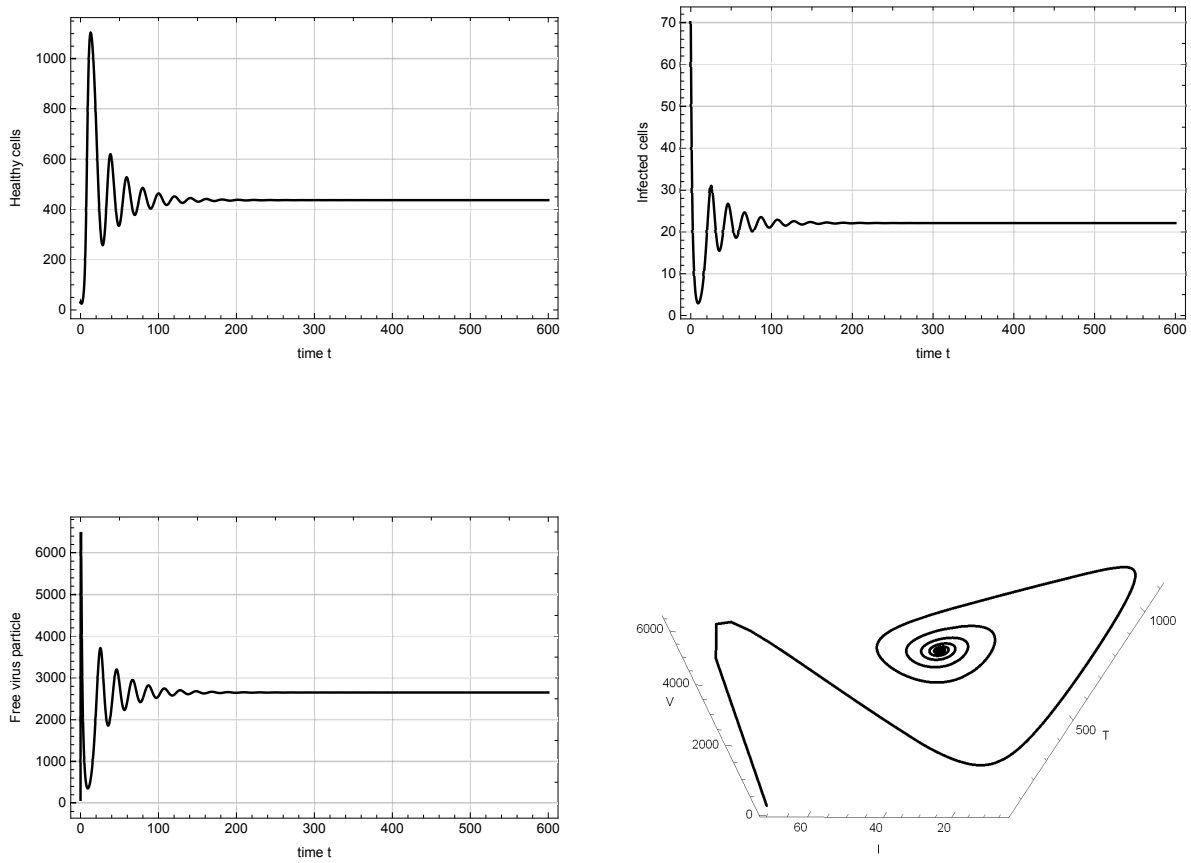


Figure 3: Equilibrium E_1 of the system (1.1) is locally asymptotically stable when $\tau = 2.5$.

According to the numerical simulation, Fig.(4) demonstrates the behavior of the phase plot for increasing the value of τ. Biologically, a small biological maturation period τ implies showing the affected of the dynamical system (1.1).

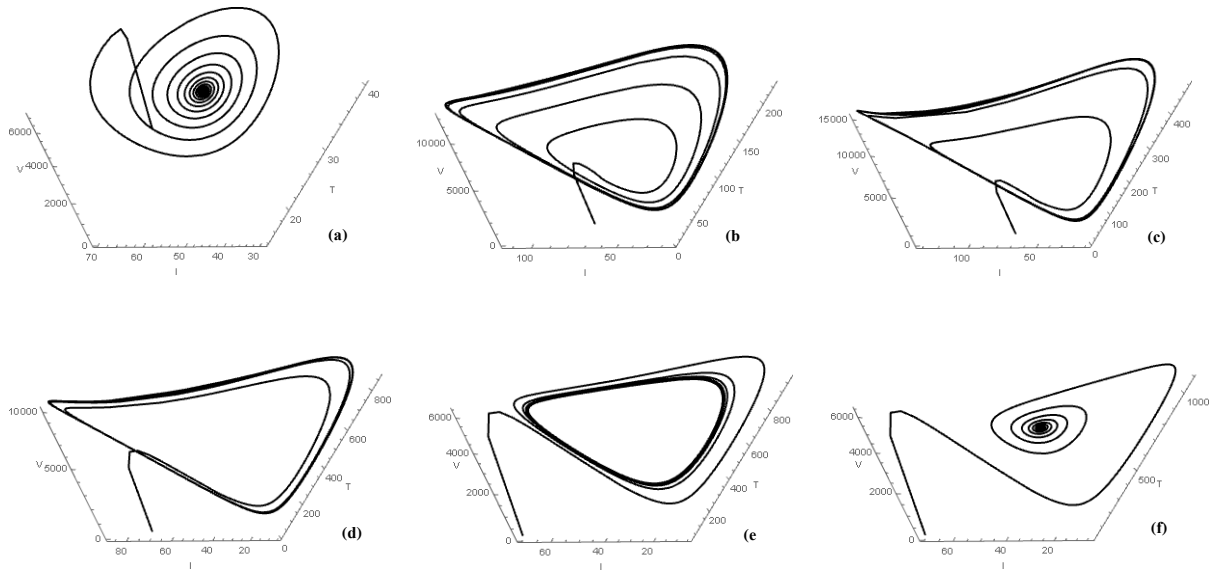


Figure 4: The behaviour of phase plots for the system (1.1) between the value of $\tau = 0.2$ to $\tau = 2.5$, $\tau = 0.2(a)$,$\tau = 0.8(b)$,$\tau = 1.2(c)$,$\tau = 1.8(d)$,$\tau = 2.2(e)$ and $\tau = 2.5(f)$.

5 Conclusion

In this paper, we studied the delayed model of HIV pathogenesis with saturation incidence, virus -to-cell and cell-to-cell transmission. We established the basic reproduction number R_0 and if $R_0 < 1$, the infection free equilibrium E_0 is locally asymptotically stable. If $R_0 > 1$, E_0 is unstable and E_1 exists. Further, the intracellular delay describing the time between viral into a target cell and direct cell into cell. In our analysis, we know that the local stability of infection free equilibrium is independent of the size of the delay, as well as the size of the delay can influence the infected equilibrium directing to a Hopf bifurcation. Moreover, sufficient conditions are established for the infection free and positive infection equilibrium. From our analysis, when the time delay τ is too long, the periodic solution disappears from the infected equilibrium, the system (1.1) is reverted to the stable.

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