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# Stability study of virus replication model

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## Abstract

An HIV infection model with time delay in which uninfected cells become infected cells is analysed. We studied conditions under which steady states will be asymptotically stable. We also examined that for endemically infected equilibrium a critical value of time delay may occur. The steady state will be asymptotically stable when delay is less than a critical value. Else the uninfected cells, infected cells, free virus, and CTLs may undergo cyclic oscillations. We estimate the delay length to maintain stability. Numerical simulations are done to aid mathematical findings.

**Keywords:** Stability, bifurcation, virus, time-delay.

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## 1. Introduction

Population dynamics of immune response requires the help of mathematical models and cannot be explained only with molecular techniques. In HIV and hepatitis B virus (HBV) infection, mathematical models of drug dynamics have provided estimates for the turnover rates of infected cells and free viruses. Here viral reproduction and immune response dynamics are expressed by simple mathematical models with the smallest number of essential assumptions. Antibodies, cytokines, natural killer cells, and T cells are essential components of a normal immune response to a virus. Cytotoxic T lymphocytes (CTLs) play a critical part in antiviral defence by attacking virus-infected cells. It is believed that they are the main host immune factor that limits the extent of virus replication in life and this determines virus load. The clearest evidence for the role of these cells comes from the passive transfer of immune CTLs, to mice and humans. There is circumstantial evidence for the control of viruses by CTLs in natural infection with HIV-1, HTLV-1, HBV, and Epstein-Barr virus. CTL response and viral load are likened to each other in a density-dependent fashion. A strong CTL response may reduce viral load, but the resulting small virus load will provide less stimulation and in time the CTL response will decline.

We now summarise previous findings to describe the immunological response to HIV infection with and without time delays. Wein et al. [34] studied a system often non-linear differential equations model.

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They performed steady-state and dynamic analysis of the model and used the results to assess what happens when therapy is switched to a less intensive maintenance regime. Ding and Hulin [8] showed with a mathematical derivation that the two viral decay rates are monotone functions of the treatment effects of the antiviral therapies. They derived formulas for the relationship between the viral decay rates and treatment effect. These formulas may be used to study what factors affect the viral decay rates. The patient's viral load may rebound due to drug resistance and in such a case, it would be difficult to estimate viral decay in plasma viruses. Nowak et al. [28] provided mathematical models for designing the treatment of HIV and suggested that HIV should be hit as early as possible and as hard as possible. By these models, one can understand the effect of antiviral treatment on the decline of infected cells and the emergence of drug-resistant viruses. Ding et al. [8] used a mathematical model to interpret the correlations regarding the viral decay rates. They evaluated the relationship between viral decay rates and treatments for efficacy in two infected cell compartments. Phillips [30] suggested that the sharp decline in virus concentration is due to a limited number of cells susceptible to HIV infection. Stafford et al. [32] illustrated that CTL destructs infected target cells and the decline in the virus is also due to cytokine suppression of viral replication. These could account for declines of viral load. Callaway and Perelson [4] presented three mathematical models for HIV-1 infection. In one the rate that governs infected cells clearance is a function of infected cell density. In the other two, the authors made use of heterogeneities in drug efficacy. They claimed that if these models reflected reality many patients should have cleared the virus, contrary to observation. Bajaria et al. [1] developed mathematical models and explored mechanisms describing differences in disease progression based on the differential interaction of HIV-1 with $CD4^+$ T cells. During disease progression, they presented simulations of structured treatment interruption (STI). Huang et al. [16] proposed mathematical models and methods to be useful in AIDS clinical trial simulations. Using the viral dynamic model they evaluated the effect of time varying drug exposure and drug susceptibility to the antiviral response. They developed a viral dynamic model with time-varying drug efficacies, which is a system of non-linear differential equations, to describe the antiviral responses. The two thresholds were shown to predict viral outcome. Using Lyapunov functions global stability of the Nowak-Bangham models [27] were studied by Korobeinikov [19].

Time delays of one type or another have been incorporated into biological models by many authors. Tam [33] in a three variables virus replication model assumed time lag between viral particles and infected cells. The author confirmed Nowak and Bangham [27] statement that the introduction of delay does not disturb stability. Herz et al. [14] discussed a mathematical model containing uninfected cells, infected cells, and plasma virus. They introduced time delay in the infection of a cell and virus production. This model predicts that plasma virus declines after a time lag. Kumnungkit [20] examined the three variables model by Nowak and Bangham [27] using the delay between infected cells and viral emission. Hopf bifurcation analysis was done using delay as a bifurcation parameter. Huang et al. [17] investigated a viral infection model consisting of target cells, infected cells, and free viruses respectively with two-time delays. Using Lyapunov functions global stability conditions were found. They discussed the effects of delays. Motivated by the work of Nowak and Bangham [27]. Li et al. [22] studied a two-time delays model. The first time delay $\tau_1$ represents viral entry into a targeted cell and the production of new viruses is delayed by $\tau_2$. Constructing suitable Lyapunov functions, conditions for global stabilities were studied for an infection-free equilibrium. They established that delays $\tau_1$ and $\tau_2$ will not produce Hopf bifurcation. Zhu et al. [36] analyzed an HIV infection model with a delay in CTL response. They studied the effects of time delay on the dynamics of the model. Balasubramaniam et al. [2] dealt with an HIV infection model of CD4 T-cells. They considered a logistic growth of uninfected cells and used time delay in the immune response. They found bifurcation about the infected steady state and derived formulae to determine the direction and stability of bifurcating periodic solutions. Li et al. [21] analyzed the dynamics of a delayed CTL response HIV infection model. Using Lyapunov function they discussed the global stability of infected and uninfected equilibrium. They also investigated Hopf bifurcation at infected equilibrium with CTL response. Geetha and Balamuralitharam [12] examined the dynamics of an infected mathematical model having a delay in CTL response. They described the existence of Hopf bifurcation

with delay in CTL response and estimated the maximum delay value to maintain stability.

In this paper, the existence and stability of the equilibrium of Nowak and Bangham [27] model is considered after introducing time delays in uninfected cell and virus particles. Tam [33] investigated a similar model but excluded the consequences of an immune response on the virus load. CTLs have an important role in antiviral defence by attacking virus-infected cells and they mainly determine the virus load. Our model includes the effect of CTLs in the system and has four delay differential equations. We explained that under certain conditions on the coefficients, the steady state is asymptotically stable for all delay values. However, for endemically infected equilibrium if the conditions on coefficients are not satisfied, then there is a critical value of the time delay. The steady state is asymptotically stable when the delay is less than the critical value and unstable when the delay is greater than the critical value. When delay passes through the critical value then there is a Hopf bifurcation at the steady state. Thus we explained that uninfected cells, infected cells, free viruses, and CTLs undergo cyclic fluctuations for some parameter values. Further, we find the maximum delay for the interior equilibrium to remain asymptotically stable.

## 2. Immune response to reduce virus load with time delay

The following model developed by Nowak and Bangham [27] describes the immune response against the infected cells.

$$\begin{aligned} \frac{dx}{dt} &= \gamma - dx - \beta xv, & \frac{dy}{dt} &= \beta xv - ay - pyz, \\ \frac{dv}{dt} &= ky - lv, & \frac{dz}{dt} &= cyz - bz. \end{aligned} \tag{2.1}$$

Here $x(t)$ represents uninfected cell, $y(t)$ represents infected cell, $v(t)$ represents virus particles, $\beta$ is the rate of production of the infected cell, $k$ is the rate by which infected cell produced virus particles, $\gamma$ is the constant influx of uninfected cell, $l$ is the death rate of virus particles, $a$ is the death rate of the infected cell and $d$ is the death rate of uninfected cell. The variable $z$ denotes the magnitude of the CTLs response. That is the abundance of virus-specific CTLs. The rate of CTLs proliferation in response to an antigen is given by $cyz$. In the absence of stimulation, CTLs decay at a rate $bz$. Infected cells are killed by CTLs at a rate $pyz$. This dynamic is derived from the kinetic interaction between CTLs and infected cells. The parameter $c$ denotes the CTLs responsiveness to the growth rate of specific CTLs after encountering infected cells. The parameter $p$ specifies the rate at which CTLs kill infected cells. In the model, there is a minimum level of infected cells necessary to stimulate the CTLs response. If $cy > b$, the CTLs response will increase. The system (2.1) has three types of equilibrium points. They are:

1. $\bar{E}_0 = (\frac{\gamma}{d}, 0, 0, 0)$, uninfected steady state which always exits.
2. $\bar{E}_1 = \left( \dfrac{al}{k\beta} , \dfrac{k\gamma\beta - adl}{ka\beta} , \dfrac{k\gamma\beta - adl}{al\beta} , 0 \right)$. This equilibrium exists if $k\gamma\beta > adl$.
3. $\bar{E}_2 = \left( \dfrac{\gamma lc}{dlc + \beta kb} , \dfrac{b}{c} , \dfrac{kb}{lc} , \dfrac{\beta\gamma kc}{p(dlc + \beta kb)} - \dfrac{a}{p} \right)$. This equilibrium exists if $\dfrac{\beta\gamma kc}{dlc + \beta kb} > a$ or $\beta\gamma kc > adlc + \beta kba$.

In this paper, we incorporate a time delay which helps to bring the model close to reality. The infected cells at time $t$ are not given by density $\beta xv$ but by the density of infected cells that are newly infected at time $t - \tau$. The population dynamics of the interaction of uninfected cells, infected cells, virus particles, and CTLs cells can be described by the following system of differential equations.

$$\begin{aligned} \frac{dx}{dt} &= \gamma - dx - \beta xv, & \frac{dy}{dt} &= \beta x(t-\tau)v(t-\tau) - ay - pyz, \\ \frac{dv}{dt} &= ky - lv, & \frac{dz}{dt} &= cyz - bz. \end{aligned} \tag{2.2}$$

All the variables and parameters have the same meaning as given in (2.1). The positive constant $\tau$ represents the length of the delay in hours. Here $\gamma$, $d$, $a$, $b$ and $c$ are cells per cubic millimeter of blood per day, $k$ and $l$ are virions per cubic millimeter of blood per day, and $\beta$ is cell/virion per cubic millimeter of blood per day.

We consider a small perturbation about the equilibrium point, i.e., $x = \bar{x} + u_1$, $y = \bar{y} + u_2$, $v = \bar{v} + u_3$, $z = \bar{z} + u_4$ where $\bar{x}, \bar{y}, \bar{v}, \bar{z}$ are the equilibrium values of $x, y, v, z$, respectively. The stability matrix for system (2.2) is

$$\begin{bmatrix} -d-\beta\bar{v}-\lambda & 0 & -\beta\bar{x} & 0 \\ \beta\bar{v}(t-\tau)e^{-\lambda\tau} & -a-p\bar{z}-\lambda & \beta\bar{x}(t-\tau)e^{-\lambda\tau} & -p\bar{y} \\ 0 & k & -l-\lambda & 0 \\ 0 & c\bar{z} & 0 & c\bar{y}-b-\lambda \end{bmatrix}.$$

*2.1. Stability of* $\bar{E}_0$

The characteristic equation of the linearized system of $\bar{E}_0 = (\frac{\gamma}{d}, 0, 0, 0)$ is

$$(d+\lambda)(b+\lambda)\left\{(a+\lambda)(l+\lambda) - k\beta\bar{x}e^{-\lambda\tau}\right\} = 0,$$

which can be simplified to get $(d+\lambda)(b+\lambda)\left\{\lambda^2 + (a+l) + al - k\beta\bar{x}e^{-\lambda\tau}\right\} = 0$. The eigenvalues $\lambda = -d$ and $\lambda = -b$ are always negative. The other eigenvalues are given by the solutions of

$$\lambda^2 + (a+l)\lambda + al - k\beta\bar{x}e^{-\lambda\tau} = 0. \tag{2.3}$$

The quantity of interest is the sign of the real parts of the solution $\lambda$ of the above equation that determines the stability of $\bar{E}_0$. We have proved in a previous section that when $\tau = 0, \bar{E}_0$ is stable if $k\beta\bar{x} < al$. We shall derive conditions on the parameters to ensure that the steady state of the delay model is still stable. Using Rouche's Theorem 9.17.4 as stated in [7] and the continuity in $\tau$, the equation (2.3) has roots with positive real parts if and only if it has purely imaginary roots from which we then shall be able to find conditions for all eigenvalues to have negative real parts.

Let $\lambda = u + iv$ and substituting into (2.3), we obtain the following equations:

$$-\hat{v}_1^2 + al = k\beta\bar{x}\cos(\hat{\tau}_1\hat{v}_1), \qquad \hat{v}_1(a+1) = -k\beta\bar{x}\sin(\hat{\tau}_1\hat{v}_1),$$

where $\hat{\tau}_1$ be such that $u(\hat{\tau}_1) = 0$ and $v(\hat{\tau}_1) = \hat{v}_1$. Squaring and adding both equations, we get $\hat{v}_1^4 + \hat{v}_1^2(m^2 - 2al) + (a^2l^2 - N^2) = 0$. Here $m = a + l$ and $k\beta\bar{x} = N$. Letting $\omega = \hat{v}_1^2$, the above equation can be rewritten as

$$\omega^2 + \omega(m^2 - 2al) + (a^2l^2 - N^2) = 0.$$

The roots of the above equation will be

$$\omega_{1,2} = \frac{-(m^2 - 2al) \pm \sqrt{(m^2 - 2al)^2 - 4(a^2l^2 - N^2)}}{2}.$$

Here $m^2 > 2al$ and $a^2l^2 > N^2$. i.e., $a^2l^2 > k^2\beta^2\bar{x}^2$, is the condition of stability of $\bar{E}_0$ when $\tau = 0$. Hence, neither $\omega_1$ nor $\omega_2$ is positive. Thus both the roots will not be positive. Hence we have established that there is no $\hat{v}_1$ such that $i\hat{v}_1$ is an eigenvalue of the characteristic equation (2.3). Therefore, the real parts of all the eigenvalues of (2.3) are negative for all delays where $\tau > 0$. Thus we summarize the above results in the following theorem.

**Theorem 2.1.** *If* $k\beta\bar{x} < al$, *then steady state* $\bar{E}_0$ *is asymptotically stable for all* $\tau \geqslant 0$.

*2.2. Stability of* $\bar{E}_1$

The characteristic equation of the linearized system of $\bar{E}_1 = \left(\frac{al}{k\beta}, \frac{k\gamma\beta - adl}{ka\beta}, \frac{k\gamma\beta - adl}{al\beta}, 0\right)$ is

$$(c\bar{y} - b - \lambda)\left[(-d - \beta\bar{v} - \lambda)\left\{(a+\lambda)(\lambda+l) - \beta k\bar{x}e^{-\lambda\tau}\right\} - \beta^2\bar{x}\bar{v}ke^{-\lambda\tau}\right] = 0.$$

The eigenvalue $\lambda_1 = c\bar{y} - b < 0$ if $\bar{y} < \frac{b}{c}$. The other three eigenvalues will be the roots of the following

cubic equation

$$\lambda^3+\lambda^2(a+l-A)-\lambda(Aa+Al-al+ale^{-\lambda\tau})+e^{-\lambda\tau}(Aal+\beta\bar{v}al)-Aal=0, \tag{2.4}$$

where $A=-d-\beta\bar{v}$. This can be rewritten as

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3=e^{-\lambda\tau}(T_2\lambda+T_3), \tag{2.5}$$

where $a_1=a+l-A$, $a_2=al-Aa-Al$, $a_3=-Aal$, $T_2=al$, and $T_3=-Aal-\beta\bar{v}al$.

Let $\lambda=u+iv$, substituting in equation (2.5) and taking the real and imaginary parts separately, gives

$$\left.\begin{aligned}(u^3-3uv)+a_1(u^2-v^2)+a_2u+a_3&=e^{-\tau u}\left[(T_2u+T_3)\cos(\tau v)+(T_2v)\sin(\tau v)\right]\\(3u^2v-v^3)+2a_1uv+a_2v&=e^{-\tau u}\left\{(T_2v)\cos(\tau v)-(T_2u+T_3)\sin(\tau v)\right\}\end{aligned}\right\} \tag{2.6}$$

respectively. Let $\hat{\tau}_1$ be such that $u(\hat{\tau}_1)=0$ and $v(\hat{\tau}_1)=\hat{v}$. Then the equation (2.6) reduces to

$$-a_1\hat{v}_1^2+a_3=T_3\cos(\tau\hat{v})+T_2\hat{v}_1\sin(\tau\hat{v}_1)\quad\text{and}\quad-\hat{v}_1^3+a_2\hat{v}_1=-T_3\sin(\tau\hat{v}_1)+T_2\hat{v}_1\cos(\tau v),$$

respectively. Adding up the squares of both the equations gives

$$\hat{v}_1^6+\hat{v}_1^4(a_1^2-2a_2)+\hat{v}_1^2(a_2^2-2a_1a_3-T_2^2)+(a_3^2-T_3^2)=0. \tag{2.7}$$

This equation can be written as

$$h(\omega)=\omega^3+b_1\omega^2+b_2\omega+b_3=0 \tag{2.8}$$

where $\omega=\hat{v}_1^2$, $b_1=a_1^2-2a_2$, $b_2=a_2^2-2a_1a_3-T_2^2$ and $b_3=a_3^2-T_3^2$. Equation (2.8) gives

$$\frac{dh}{d\omega}=3\,\omega^2+2\,b_1\omega+b_2=0. \tag{2.9}$$

The roots of equation (2.9) can be expressed as

$$\omega_{1,2}=\frac{-b_1\pm\sqrt{b_1^2-3b_2}}{3},$$

where $b_1=a_1^2-2a_2>0$. If $b_2>0$, then $\sqrt{b_1^2-3b_2}<b_1$. Hence, neither $\omega_1$ nor $\omega_2$ is positive. Thus both the roots will not be positive. If we assume $b_3\geqslant 0$ then equation (2.7) has no positive roots. Hence we have established that there is no $\hat{v}_1$ such that $i\hat{v}_1$ is an eigenvalue of the characteristic equation (2.4). Therefore, the real parts of all the eigenvalues of (2.4) are negative for all delay $\tau\geqslant 0$. We summarize the above results in the following.

**Theorem 2.2.** *If* $\bar{y}<\frac{b}{c}$ $b_3\geqslant 0$ *and* $b_2>0$, *then infected steady state* $\bar{E}_1$ *is asymptotically stable for all* $\tau\geqslant 0$.

### 2.3. *Stability of* $\bar{E}_2$

The equilibrium $\bar{E}_2$ is $\bar{E}_2=\left(\frac{\gamma lc}{dlc+\beta kb},\frac{b}{c},\frac{kb}{lc},\frac{\beta\gamma kc}{p(dlc+\beta kb)}-\frac{a}{p}\right)$ and the characteristic equation of the linearized system is given by

$$\lambda^4+k_1\lambda^3+k_2\lambda^2+k_3\lambda+k_4=e^{-\tau\lambda}(T_2\lambda^2+T_3\lambda), \tag{2.10}$$

where $k_1=-A-D+l$, $k_2=AD-Al-Dl+cp\bar{y}\bar{z}$, $k_3=ADl-cp\bar{y}\bar{z}A+cl\bar{y}\bar{z}$, $k_4=-Aclp\bar{y}\bar{z}$, $T_2=k\beta\bar{x}$, $T_3=-Ak\beta\bar{x}-\beta^2k\bar{x}\bar{v}$, $A=-d-\beta\bar{v}$, and $D=-a-p\bar{z}$.

Let $\lambda = u + iv$ where $u = u(\tau)$ and $v = v(\tau)$. Substituting in equation (2.10) we get

$$\begin{aligned} u^4 + 4u^3vi - 6u^2v^2 - 4uv^3i + v^4 + k_1(u^3 + 3u^2vi - 3uv^2 - v^3i) + k_2(u^2 + 2uvi - v^2) + k_3(u + iv) + k_4 \\ = e^{-u\tau}\left[(\cos(\tau v) - i\sin(\tau v))(T_2(u^2 - v^2) + T_2uvi + T_3(u + iv))\right]. \end{aligned}$$

The real and imaginary parts are given by

$$\left.\begin{aligned} u^4 - 6u^2v^2 + v^4 + k_1(u^3 - 3uv^2) + k_2(u^2 - v^2) + k_3u + k_4 \\ = e^{-u\tau}\left[\cos(\tau v)(T_2(u^2 - v^2) + T_3u) + \sin(\tau v)(2uvT_2 + vT_3)\right] \\ 4u^3v - 4uv^3 + k_1(3u^2v - v^3) + 2uvk_2 + k_3v \\ = e^{-u\tau}\left[\cos(\tau v)(2uvT_2 + T_3v) - \sin(\tau v)(T_2(u^2 - v^2) + uT_3)\right] \end{aligned}\right\} \tag{2.11}$$

respectively. Let $\tau_1^*$ be such that $u(\tau_1^*) = 0$. Then equation (2.11) reduces to

$$\begin{aligned} v_1^{*4} - k_2v_1^{*2} + k_4 &= (-v_1^{*2}T_2)\cos(\tau_1^*v_1^*) + (v_1^*T_3)\sin(\tau_1^*v_1^*), \\ -v_1^{*3}k_1 + v_1^*k_3 &= (v_1^*T_3)\cos(\tau_1^*v_1^*) + (v_1^{*2}T_2)\sin(\tau_1^*v_1^*). \end{aligned} \tag{2.12}$$

On simplification after squaring and adding the above two equations in (2.12) we get

$$v_1^{*8} + v_1^{*6}(-2k_2 + k_1^2) + v_1^{*4}(2k_4 + k_2^2 - 2k_1k_3 - T_2^2) + v_1^{*2}(-2k_2k_4 + k_3^2 - T_3^2) + k_4^2 = 0. \tag{2.13}$$

It was shown in the previous section that $\bar{E}_2$ is stable when $\tau = 0$. Hence the sign of the real parts of the roots of the equation

$$\lambda^4 + k_1\lambda^3 + (k_2 - T_2)\lambda^2 + (k_3 - T_3)\lambda + k_4 = 0$$

have negative real parts according to the Routh-Hurwitz criterion. We can see from equation (2.13) that left hand side is positive for $v_1^* = 0$. Therefore there will be either zero, two, or four positive real roots. We assume that $v_1^*$ is the biggest positive root of the equation (2.13) and it can be proved that $v_1^*$ is a simple root. Since $v_1^*$ is a simple root, this equation is analytic. Thus by the analytic version of the implicit theorem [5] that $u(\tau) + iv(\tau)$ is defined and analytic in a neighbourhood of $\tau = \tau_1^*$.

**Theorem 2.3.** *Let $v_1^*$ be the biggest positive simple root of equation (2.12). Then $iv(\tau_1^*) = iv_1^*$ is a simple root of equation (2.10) and $u(\tau) + iv(\tau)$ is differentiable with respect to $\tau$ in the neighborhood of $\tau = \tau_1^*$.*

To establish Hopf bifurcation at $\tau = \tau_1^*$ as stated in [5] and referred to by [11, 13, 18], we need to show that

$$\frac{du}{d\tau}|_{\tau=\tau_1^*} \neq 0.$$

Differentiating the equations in (2.11) with respect to $\tau$ and keeping $v(\tau_1^*) = v_1^*$ and $u(\tau_1^*) = 0$ gives

$$\begin{aligned} &\frac{du}{d\tau}\left[-3k_1v_1^{*2} + k_3 - \cos(\tau_1^*v_1^*)(T_3 + \tau_1^*T_2v_1^{*2}) + \sin(\tau_1^*v_1^*)(\tau_1^*T_3v_1^* - 2T_2v_1^*)\right] \\ &\quad + \frac{dv}{d\tau}\left[4v_1^{*3} - 2k_2v_1^* + \cos(\tau_1^*v_1^*)(2T_2v_1^* - \tau_1^*T_3v_1^*) - \sin(\tau_1^*v_1^*)(T_3 + T_2v_1^*)\right] \\ &= (T_3v_1^{*2})\cos(\tau_1^*v_1^*) + (T_2v_1^{*3})\sin(\tau_1^*v_1^*) \end{aligned} \tag{2.14}$$

and

$$\begin{aligned} &\frac{du}{d\tau}\left[-4v_1^{*3} + 2k_2v_1^* - \cos(\tau_1^*v_1^*)(2T_2v_1^* - \tau_1^*T_3v_1^*) + \sin(\tau_1^*v_1^*)(T_3 + T_2v_1^*)\right] \\ &\quad + \frac{dv}{d\tau}\left[-3k_1v_1^{*2} + k_3 - \cos(\tau_1^*v_1^*)(T_3 + \tau_1^*T_2v_1^{*2}) + \sin(\tau_1^*v_1^*)(\tau_1^*T_3v_1^* - 2T_2v_1^*)\right] \\ &= (v_1^{*2}T_3)\cos(\tau_1^*v_1^*) + (v_1^{*3}T_2)\sin(\tau_1^*v_1^*), \end{aligned} \tag{2.15}$$

respectively. Equations (2.14) and (2.15) can be rewritten as

$$J_1 \frac{du}{d\tau} + J_2 \frac{dv}{d\tau} = F, \quad -J_2 \frac{du}{d\tau} + J_1 \frac{dv}{d\tau} = G, \tag{2.16}$$

where

$$\begin{aligned}
J_1 &= -3k_1 v_1^{*2} + k_3 - \cos(\tau_1^* v_1^*)(T_3 + \tau_1^* T_2 v_1^{*2}) + \sin(\tau_1^* v_1^*)(\tau_1^* T_3 v_1^* - 2T_2 v_1^*),\\
J_2 &= 4v_1^{*3} - 2k_2 v_1^* + \cos(\tau_1^* v_1^*)(2T_2 v_1^* - \tau_1^* T_3 v_1^*) - \sin(\tau_1^* v_1^*)(T_3 + T_2 v_1^*),\\
F &= (T_3 v_1^{*2})\cos(\tau_1^* v_1^*) + (T_2 v_1^{*3})\sin(\tau_1^* v_1^*),\\
G &= (v_1^{*2} T_3)\cos(\tau_1^* v_1^*) + (v_1^{*3} T_2)\sin(\tau_1^* v_1^*).
\end{aligned}$$

Solving equations in (2.16) for $\frac{du}{d\tau}$ at $\tau = \tau_1^*$ gives

$$\frac{du}{d\tau} = \frac{v_1^* \begin{bmatrix} (R - T_3\cos(\tau_1^* v_1^*) - 2T_2 v_1^* \ \sin(\tau_1^* v_1^*))\,(-k_1 v_1^{*3} + k_3 v_1^*) \\ + \\ \{S + 2T_2 v_1^* \cos(\tau_1^* v_1^*) - T_3 \ \sin(\tau_1^* v_1^*)\}\,(v_1^{*4} - k_2 v_1^{*2} + k_4) \end{bmatrix}}{J_1^2 + J_1^2}, \tag{2.17}$$

where $R = -3k_1 v_1^{*2} + k_3 + \tau_1^*(v_1^{*4} - k_2 v_1^{*2} + k_4)$ and $S = 4v_1^{*3} - 2k_2 v_1^* - \tau_1^*(-k_1 v_1^{*3} + k_3 v_1^*)$. Using equation (2.12), the equation (2.17) can be rewritten as

$$\frac{du}{d\tau} = \frac{v_1^{*2}\left[4v_1^{*6} + v_1^{*4}(3k_1^2 - 6k_2) + v_1^{*2}(2k_2^2 + 4k_4 - 4k_1k_3 - 2T_2^2) + (k_3^2 - 2k_2k_4 - T_3^2)\right]}{J_1^2 + J_1^2}.$$

Let $\xi = v_1^{*2}$, then

$$v_1^{*8} + v_1^{*6}(k_1^2 - 2k_2) + v_1^{*4}(k_2^2 + 2k_4 - 2k_1k_3 - T_2^2) + v_1^{*2}(k_3^2 - 2k_2k_4 - T_3^2) + k_4^2$$

can be written as

$$\Phi(\xi) = \xi^4 + \xi^3(k_1^2 - 2k_2) + \xi^2(k_2^2 + 2k_4 - 2k_1k_3 - T_2^2) + \xi(k_3^2 - 2k_2k_4 - T_3^2) + k_4^2,$$

and therefore

$$\frac{d\Phi}{d\xi} = 4\xi^3 + 3\xi^2(k_1^2 - 2k_2) + 2\xi(k_2^2 + 2k_4 - 2k_1k_3 - T_2^2) + (k_3^2 - 2k_2k_4 - T_3^2).$$

If $v_1^{*2}$ is the last positive single root of equation $\xi = v_1^{*2} = 0$, then

$$\frac{d\Phi}{d\xi}|_{\xi = v_1^{*2}} > 0 \quad \text{giving} \quad \frac{du}{d\tau}|_{\tau=\tau_1^*} = \frac{v_1^{*2}}{J_1^2 + J_1^2}\frac{d\Phi}{d\xi}|_{\xi = v_1^{*2}} > 0.$$

If equation (2.13) has no positive real roots, then $u(\tau) \neq 0$ for any $\tau$. As the equilibrium point $\bar{E}_2$ is locally asymptotically stable when $\tau = 0$, the roots of the characteristic equation have negative real parts when $\tau = 0$. Hence if $\lambda(\tau) = u(\tau) + iv(\tau)$ is a root of equation (2.10) are continuous functions of $\tau$, we must have $u(\tau) < 0$ for all $\tau$ and thus the endemic equilibrium is locally asymptotically stable for all $\tau$.

## 3. Maximum delay to preserve stablity

Let $x(t) = \bar{x} + u_1$, $y(t) = \bar{y} + v_1$, $v(t) = \bar{v} + w_1$ and $z(t) = \bar{z} + s_1$. Linearizing the system (2.2) at the co-existing equilibrium $\bar{E}_2$ gives

$$\begin{aligned}
\frac{du_1}{dt} &= \gamma - d(\bar{x}+u_1) - \beta(\bar{x}+u_1)(\bar{v}+w_1),\\
\frac{dv_1}{dt} &= \beta(\bar{x}+u_1(t-\tau))(\bar{v}+w_1(t-\tau)) - a(\bar{y}+v_1) - p(\bar{y}+v_1)(\bar{z}+s_1),\\
\frac{dw_1}{dt} &= k(\bar{y}+v_1) - l(\bar{v}+w_1),\\
\frac{ds_1}{dt} &= c(\bar{y}+v_1)(\bar{z}+s_1) - b(\bar{z}+s_1).
\end{aligned} \tag{3.1}$$

At equllibrium $\gamma - d\bar{x} - \beta\bar{x}\bar{v} = 0$, $\beta\bar{x}\bar{v} - a\bar{y} - p\bar{y}\bar{z} = 0$, $k\bar{y} - l\bar{v} = 0$, and $c\bar{y}\bar{z} - b\bar{z} = 0$. Therefore equation (3.1) becomes

$$\begin{aligned}
\frac{du_1}{dt} &= (-d-\beta\bar{v})u_1 + (-\beta\bar{x})w_1,\\
\frac{dv_1}{dt} &= \beta\bar{v}u_1(t-\tau) - av_1 - p\bar{z}v_1 + \beta\bar{x}w_1(t-\tau) - p\bar{y}s_1,\\
\frac{dw_1}{dt} &= kv_1 - lw_1,\\
\frac{ds_1}{dt} &= (c\bar{z})v_1 + (c\bar{y}-b)s_1.
\end{aligned} \tag{3.2}$$

Taking Laplace transform of equation (3.2) gives

$$\begin{aligned}
s\mathcal{L}\{u_1(t)\} - u_1(0) &= (-d-\beta\bar{v})\mathcal{L}\{u_1(t)\} + (-\beta\bar{x})\mathcal{L}\{w_1(t)\},\\
s\mathcal{L}\{v_1(t)\} - v_1(0) &= \beta\bar{v}\mathcal{L}\{u_1(t-\tau)\} - a\mathcal{L}\{v_1(t)\} - p\bar{z}\mathcal{L}\{v_1(t)\} + \beta\bar{x}\mathcal{L}\{w_1(t-\tau)\} - p\bar{y}\mathcal{L}\{s_1(t)\},\\
s\mathcal{L}\{w_1(t)\} - w_1(0) &= k\mathcal{L}\{v_1(t)\} - l\mathcal{L}\{w_1(t)\},\\
s\mathcal{L}\{s_1(t)\} - s_1(0) &= (c\bar{z})\mathcal{L}\{v_1(t)\} + (c\bar{y}-b)\mathcal{L}\{s_1(t)\},
\end{aligned}$$

where

$$\mathcal{L}\{u_1(t-\tau)\} = \int_0^\infty e^{-st}u_1(t-\tau)dt = \int_0^\tau e^{-st}u_1(t-\tau)dt + \int_\tau^\infty e^{-st}u_1(t-\tau)dt.$$

Let $t = t_1 + \tau$. Then

$$\mathcal{L}\{u_1(t-\tau)\} = \int_{-\tau}^0 e^{-s(t_1+\tau)}u_1(t_1)dt_1 + \int_0^\infty e^{-s(t_1+\tau)}u_1(t_1)dt_1 = L_1\left(e^{-s\tau}\right) + e^{-s\tau}\mathcal{L}\{u_1(t_1)\}.$$

Similarly,

$$\mathcal{L}\{v_1(t-\tau)\} = L_2\left(e^{-s\tau}\right) + e^{-s\tau}\mathcal{L}\{v_1(t_1)\} \quad \text{and} \quad \mathcal{L}\{w_1(t-\tau)\} = L_3\left(e^{-s\tau}\right) + e^{-s\tau}\mathcal{L}\{w_1(t_1)\},$$

where

$$\begin{aligned}
L_1 &= \int_{-\tau}^0 e^{-st_1}u_1(t_1)dt_1 = \int_{-\tau}^0 e^{-st}u_1(t)dt,\\
L_2 &= \int_{-\tau}^0 e^{-st_1}v_1(t_1)dt_1 = \int_{-\tau}^0 e^{-st}v_1(t)dt,\\
L_3 &= \int_{-\tau}^0 e^{-st_1}w_1(t_1)dt_1 = \int_{-\tau}^0 e^{-st}w_1(t)dt.
\end{aligned}$$

If $\mathcal{L}\{u_1(t)\}$, $\mathcal{L}\{v_1(t)\}$, and $\mathcal{L}\{w_1(t)\}$ have roots with positive real parts, then inverse Laplace transform of $\mathcal{L}\{u_1(t)\}$, $\mathcal{L}\{v_1(t)\}$, $\mathcal{L}\{w_1(t)\}$, and $\mathcal{L}\{s_1(t)\}$ will have terms which increases exponentially with time. Thus $\bar{E}_2$ is locally asymptotically stable if and only if all roots of $\mathcal{L}\{u_1(t)\}$, $\mathcal{L}\{v_1(t)\}$, $\mathcal{L}\{w_1(t)\}$, and $\mathcal{L}\{s_1(t)\}$ have

negative real parts. Using Nyquist criterion [10, 12], $\bar{E}_2$ will be asymptotically stable if it satisfies the following two conditions

$$\operatorname{Re} G(i\omega_0) = 0, \tag{3.3a}$$
$$\operatorname{Im} G(i\omega_0) > 0, \tag{3.3b}$$

where, using (2.10),

$$G(\lambda) = \lambda^4 + k_1\lambda^3 + k_2\lambda^2 + k_4 = e^{-\tau\lambda}(T_2\lambda^2 + T_3\lambda)$$

and $\omega_0$ is the largest positive root of (3.3a). Equating the real and imaginary parts gives

$$\omega_0^4 - k_2\omega_0^2 + k_4 = -T_2\omega_0^2\cos(\tau\omega_0) + T_3\omega_0\sin(\tau\omega_0), \tag{3.4a}$$
$$-k_1\omega_0^3 > T_3\omega_0\cos(\tau\omega_0) + T_2\omega_0^2\sin(\tau\omega_0). \tag{3.4b}$$

Using equation (3.4b) we get $|k_1|\omega_0^2 - T_2\omega_0 - |T_3| \leqslant 0$ since $|\cos(\tau\omega_0)| \leqslant 1$ and $|\sin(\tau\omega_0)| \leqslant 1$. If $\omega_L \geqslant \omega_0$, then

$$\omega_L = \frac{T_2 \pm \sqrt{T_2^2 + 4|k_1||T_3|}}{2k_1}.$$

To find the length of maximum delay so that stability can be preserved, we rewrite the equations (3.4a) and (3.4b) as

$$\omega^4 - k_2\omega^2 + k_4 = -T_2\omega^2\cos(\tau\omega) + T_3\omega\sin(\tau\omega), \tag{3.5a}$$
$$-k_1\omega^3 > T_3\omega\cos(\tau\omega) + T_2\omega^2\sin(\tau\omega), \tag{3.5b}$$

respectively. Using equation (3.5b) we get

$$\omega^2 < -\frac{T_3}{k_1}\cos(\tau\omega) - \frac{T_2}{k_1}\omega\sin(\tau\omega). \tag{3.6}$$

Using inequality (3.6) and equation (3.5a) we obtain

$$\left[\frac{T_3}{k_1}\cos(\tau\omega) + \frac{T_2}{k_1}\omega\sin(\tau\omega)\right]^2 > \omega^2\left(k_2 - T_2\cos(\tau\omega)\right) + T_3\omega\sin(\tau\omega) - k_4.$$

This is simplified and rearranged to get

$$\begin{aligned}\left(\frac{T_3}{k_1}\right)^2 + T_2\omega^2 - k_2\omega^2 + k_4 > {} & T_3\omega\sin(\tau\omega) + T_2\omega^2(1-\cos(\tau\omega)) \\ & + \left(\frac{T_3}{k_1}\right)^2\sin^2(\tau\omega) - \left(\frac{T_2}{k_1}\right)^2\omega^2\sin^2(\tau\omega) - \frac{|T_2||T_3|}{k_1^2}\omega\sin(2\tau\omega).\end{aligned} \tag{3.7}$$

Now, using $\sin(\tau\omega) \leqslant \tau\omega$, $(1-\cos(\tau\omega)) = 2\sin^2\left(\frac{\tau\omega}{2}\right) \leqslant \frac{\tau^2\omega^2}{2}$ and $\omega_0 \leqslant \omega \leqslant \omega_L$, the inequality (3.7) will be transformed into

$$\left|\frac{T_2\omega_L^4}{2} - \left(\frac{T_2}{k_1}\right)^2\omega_L^4 + \left(\frac{T_3}{T_1}\right)^2\omega_L^2\right|\tau^2 + \left|T_3\omega_L^2 - 2\frac{|T_3||T_1|}{k_1^2}\omega_L^2\right|\tau \leqslant \left|\left(\frac{T_3}{k_1}\right)^2 - k_2\omega_L^2 + T_2\omega_L^2 + k_4\right|. \tag{3.8}$$

Inequality (3.8) can be expressed as

$$A_1\tau^2 + A_2\tau - A_3 \leqslant 0,$$

where

$$A_1 = \left|\frac{T_2\omega_L^4}{2} - \left(\frac{T_2}{k_1}\right)^2\omega_L^4 + \left(\frac{T_3}{T_1}\right)^2\omega_L^2\right|,$$

$$A_2 = \left| T_3\omega_L^2 - 2\frac{|T_3||T_1|}{k_1^2}\omega_L^2 \right|,$$
$$A_3 = \left| \left(\frac{T_3}{k_1}\right)^2 - k_2\omega_L^2 + T_2\omega_L^2 + k_4 \right|.$$

Let $\hat{\tau}$ be the positive root of

$$A_1\tau^2 + A_2\tau - A_3 = 0.$$

That is,

$$\hat{\tau} = \frac{-A_2 \pm \sqrt{A_2^2 + 4A_1A_3}}{2A_1}.$$

Now we summarize the above discussion in the following theorem.

**Theorem 3.1.** *If Nyquist criterion is satisfied and* $0 < \tau < \hat{\tau}$, *then* $\hat{\tau}$ *will be the maximum length of delay for which the stability will be preserved.*

## 4. Numerical results

In this section we give some numerical results to illustrate the findings on the existence of Hopf birfurcation. The parameter values $\gamma = 1.8$, $\beta = 10$, $k = 1$, $c = 9$, $p = 4$, $d = 0.02$, $a = 4$, $l = 4$, and $b = 1$ satisfy the condition $\beta\gamma kc > adlc + \beta kba$ which ensures the existence of $\bar{E}_2$, and the endemically infected equilibrium is $\bar{E}_2 = (\bar{x},\ \bar{y},\ \bar{v},\ \bar{z}) = (6.045,\ 0.111,\ 0.028,\ 2.778)$. Equation (2.13) has 4 real positive roots and 4 complex roots, and $\nu_1^* = 0.7541$ is the biggest positive simple root and $\tau_1^* = 2.48$.

The behavior of $x(t)$, $y(t)$, $v(t)$, and $z(t)$ versus time are given in Figure 1 for $\tau = 2.4$ and Figure 2 for $\tau = 2.6$ . Figures 3 and 4 give the behavior for varying $\tau$. These illustrations show that the endemic equilibrium $\bar{E}_2$ is asymptotically stable for $0 < \tau < \tau_1^*$ and the system (2.2) undergoes Hopf bifurcation at $\tau = \tau_1^*$, when the chosen parameters satisfies the condition for the existence of $\bar{E}_2$.

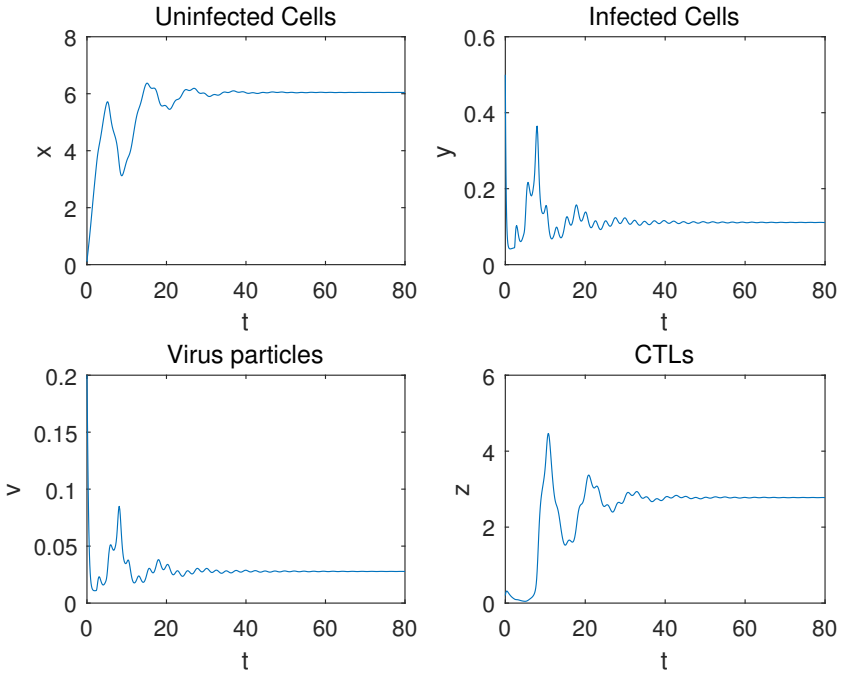


Figure 1: Solutions to (2.2), when $\tau = 2.4$.

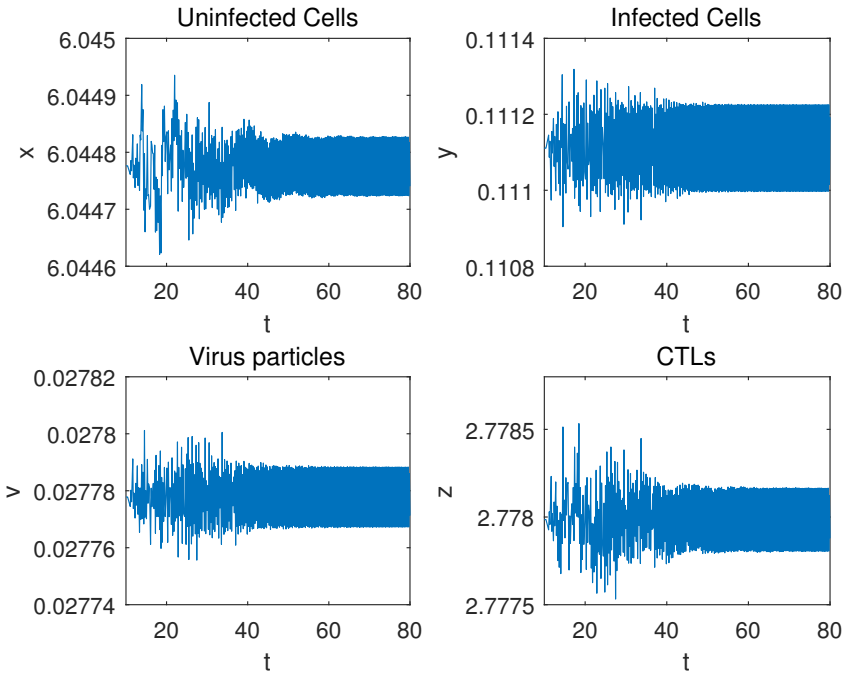


Figure 2: Solutions to (2.2), when $\tau = 2.6$.

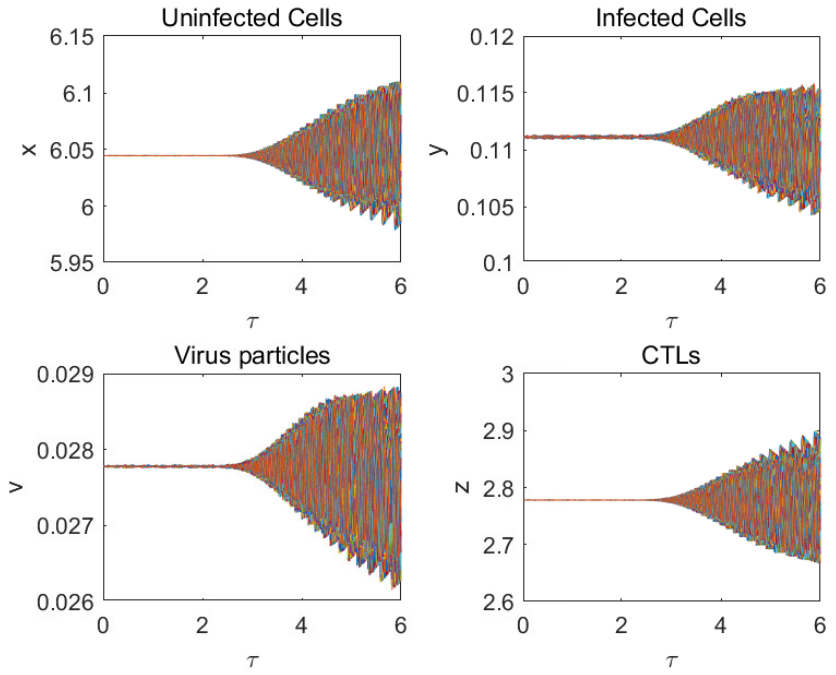


Figure 3: Solutions to (2.2) for varying $\tau$.

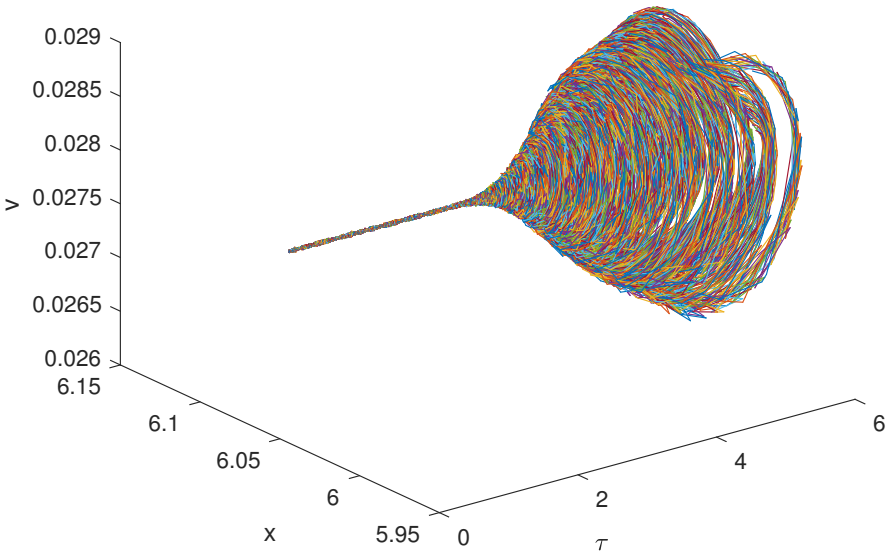


Figure 4: Hopf bifurcation - $\tau = 2.6$.

## 5. Conclusions

Over the past decades, several mathematical models have been developed to explain the immunological response to infection with human immunodeficiency virus (HIV). Different phenomena have been described through these models. In considering the outcome of infection by many viruses, the abundance of the virus that is the viral load is always an important factor. For instance, in HIV-1, the viral load is correlated with the pathogenicity disease stage and progression of the disease. It is found that in most virus infections cytotoxic T lymphocytes (CTLs) play a crucial part in antiviral defense by attacking virus-infected cells. They are believed to be the main host immune factor that limits the extent of virus replication, and these determine the viral load.

The model considered here explores the relationship between antiviral immune responses, viral load, and virus diversity. The model contains four variables, uninfected cells, infected cells, free virus particles, and the cytotoxic lymphocytes. Infected cells are produced from uninfected cells and free virus interactions. The cytotoxic lymphocytes (CTLs) play a crucial part in antiviral defence by attacking virus-infected cells, and they are believed to be the main host immune factor that subsequently determines virus load. Infected cells production may lag by the intracellular time delay between the infected cell and emission of viral partials. In this model, it is assumed that the recruitment of infected cells and time $t$ is not given by density $\beta x(t)v(t)$, but rather by the density of cells that were newly infected at time $(t-\tau)$ and are still alive at time $t$. In other words, the rate of growth of infected cells for the equation $y$ becomes a delay-differential equation while the other equations remain unchanged. The delay effect is able to incorporate the more realistic physiology associated with the time lag between uninfected cells and the emission of viral particles. We determine how much the stability of equilibrium is affected by the introduction of time delay. We studied conditions governing parameters values of the model. With these conditions, we are able to restrict the values of the parameters which are chosen so that the model remains stable. Using Nyquist criterion, we get the maximum length of delay to maintain stability.

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