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A delay-differential equation model of HIV infection of CD4$^+$ T-cells ☆

Rebecca V. Culshaw [a], Shigui Ruan [a,b,*]

[a] *Department of Mathematics and Statistics, Dalhousie University, Halifax, Nova Scotia, Canada B3H 3J5*
[b] *School of Biomedical Engineering, Dalhousie University, Halifax, Nova Scotia, Canada B3H 3J5*

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Abstract

A.S. Perelson, D.E. Kirschner and R. De Boer (Math. Biosci. 114 (1993) 81) proposed an ODE model of cell-free viral spread of human immunodeficiency virus (HIV) in a well-mixed compartment such as the bloodstream. Their model consists of four components: uninfected healthy CD4$^+$ T-cells, latently infected CD4$^+$ T-cells, actively infected CD4$^+$ T-cells, and free virus. This model has been important in the field of mathematical modeling of HIV infection and many other models have been proposed which take the model of Perelson, Kirschner and De Boer as their inspiration, so to speak (see a recent survey paper by A.S. Perelson and P.W. Nelson (SIAM Rev. 41 (1999) 3–44)). We first simplify their model into one consisting of only three components: the healthy CD4$^+$ T-cells, infected CD4$^+$ T-cells, and free virus and discuss the existence and stability of the infected steady state. Then, we introduce a discrete time delay to the model to describe the time between infection of a CD4$^+$ T-cell and the emission of viral particles on a cellular level (see A.V.M. Herz, S. Bonhoeffer, R.M. Anderson, R.M. May, M.A. Nowak [Proc. Nat. Acad. Sci. USA 93 (1996) 7247]). We study the effect of the time delay on the stability of the endemically infected equilibrium, criteria are given to ensure that the infected equilibrium is asymptotically stable for all delay. Numerical simulations are presented to illustrate the results.

Keywords: HIV infection; Intercellular delay; Steady state; Characteristic equation; Stability

1. Introduction

In the last decade, many mathematical models have been developed to describe the immunological response to infection with human immunodeficiency virus (HIV) (for example, [1–21] and

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* Tel.: +902-494 6635/2572; fax: +902-494 5130.
E-mail addresses: rebecca@mscs.dal.ca (R.V. Culshaw), ruan@mscs.dal.ca (S. Ruan).

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so on). These models have been used to explain different phenomena. For more references and some detailed mathematical analysis on such models, we refer to the survey papers by Kirschner [22] and Perelson and Nelson [23].

HIV targets, among others, the $CD4^+$ T lymphocytes, which are the most abundant white blood cells of the immune system (referred to as helper T-cells or $CD4^+$ T-cells, which is the term we will use in this paper). It is thought that HIV, although attacking many different cells, wreaks the most havoc on the $CD4^+$ T-cells by causing their destruction and decline, and decreasing the body's ability to fight infection.

We assume that peripheral blood CD4 counts (generally $1000/mm^3$) are a good indicator for CD4 densities in the body. When HIV enters the body, it targets all the cells with $CD4^+$ receptors, including the $CD4^+$ T-cells. The gp120 protein on the viral particle binds to the $CD4^+$ receptors on the $CD4^+$ T-cell and injects its core. After an intracellular delay associated with reverse transcription, integration, and the production of capsid proteins, the infected cell releases hundreds of virions that can infect other $CD4^+$ T-cells.

In 1989, Perelson [16] developed a simple model for the interaction between the human immune system and HIV. Perelson et al. [17] extended Perelson's model and proved mathematically some of the model's behavior. They observed that the model exhibits many of the symptoms of AIDS seen clinically: the long latency period, low levels of free virus in the body, and the depletion of $CD4^+$ T-cells. They defined the model by considering four compartments: cells that are uninfected, cells that are latently infected, cells that are actively infected and free virus. They described the dynamics of these populations by a system of four ordinary differential equations.

Time delays of one type or another have been incorporated into biological models by many authors (for example, [24–29] and the references cited therein). In general, delay-differential equations exhibit much more complicated dynamics than ordinary differential equations since a time delay could cause a stable equilibrium to become unstable and cause the populations to fluctuate. Recently, in studying the viral clearance rates Perelson et al. [18] assumed that there are two types of delays that occur between the administration of drug and the observed decline in viral load: a pharmacological delay that occurs between the ingestion of drug and its appearance within cells and an intracellular delay that is between initial infection of a cell by HIV and the release of new virions. Herz et al. [30] used a discrete delay to model the intracellular delay in a HIV model and showed that the incorporation of a delay would substantially shorten the estimate for the half-life of free virus. Mittler et al. [31] argued that a γ-distribution delay would be more realistic to model the intracellular delay phenomenon and introduced such a delay into the model of Perelson et al. [18]. They derived an analytic expression for the rate of decline of virus following drug treatment by assuming the drug to be completely efficacious. See also Mittler et al. [32] and Tam [33] for related work.

In this paper, we first simplify the ODE model proposed by Perelson et al. [17] by considering only three components: the uninfected $CD4^+$ T-cells, infected $CD4^+$ T-cells, and free virus. The existence and stability of the infected steady state are considered. We then incorporate a discrete delay to the model to describe the time between infection of a $CD4^+$ T-cell and the emission of viral particles on a cellular level as proposed by Herz et al. [30]. The resulting model is a system of three delay-differential equations. To determine the dynamics of the delay model, we study the transcendental characteristic equation of the linearized system at the positive infected steady state

and obtain analytic conditions on the parameters under which the infected steady state is asymptotically stable for all delay. Numerical simulations are carried out to illustrate the obtained results.

2. The ODE model

We first reduce the dimension of Perelson et al.'s system by assuming that all the infected cells are capable of producing virus. Similar reduction has been done in [10,23], etc. The reduced ODE model is

$$\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= s - \mu_{\mathrm{T}} T + rT\left(1 - \frac{T+I}{T_{\max}}\right) - k_1 VT,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= k_1' VT - \mu_{\mathrm{I}} I,\\
\frac{\mathrm{d}V}{\mathrm{d}t} &= N\mu_{\mathrm{b}} I - k_1 VT - \mu_{\mathrm{V}} V,
\end{aligned} \tag{2.1}$$

where $T(t)$ represents the concentration of healthy CD4$^+$ T-cells at time t, $I(t)$ represents the concentration of infected CD4$^+$ T-cells, and $V(t)$ the concentration of free HIV at time t.

To explain the parameters, we note that s is the source of CD4$^+$ T-cells from precursors, μ_{T} is the natural death rate of CD4$^+$ T-cells, r is their growth rate (thus, $r > \mu_{\mathrm{T}}$ in general), and $T_{\max}$ is their carrying capacity. The parameter k_1 represents the rate of infection of T-cells with free virus and so is given as a loss term for both healthy cells and virus, since they are both lost by binding to one another, and is the source term for infected cells. k_1' is the rate at which infected cells become actively infected (the ratio k_1'/k_1 is the proportion of T-cells, which ever become actively infected). μ_{I} is a blanket death term for infected cells, to reflect the assumption that we do not initially know whether the cells die naturally or by bursting. In addition, μ_{b} is the lytic death rate for infected cells. Since N viral particles are released by each lysing cell, this term is multiplied by the parameter N to represent the source for free virus (assuming a one-time initial infection). Finally, μ_{V} is the loss rate of virus.

In the absence of virus, the T-cells population has a steady state value

$$T_0 = \frac{r - \mu_{\mathrm{T}} + \left[(r-\mu_{\mathrm{T}})^2 + 4rsT_{\max}^{-1}\right]^{1/2}}{2rT_{\max}^{-1}}. \tag{2.2}$$

Thus reasonable initial conditions for infection by free virus only are

$$T(0) = T_0, \quad I(0) = 0, \quad V(0) = V_0. \tag{2.3}$$

System (2.1) has two steady states: the uninfected steady state $E_0 = (T_0, 0, 0)$ and the (positive) infected steady state $\overline{E} = (\overline{T}, \overline{I}, \overline{V})$, where

$$\begin{aligned}
\overline{T} &= \frac{\mu_V \mu_I}{k_1' N \mu_b - k_1 \mu_I}, \\
\overline{I} &= \frac{k_1' \overline{TV}}{\mu_I}, \\
\overline{V} &= \frac{\mu_I \left[(s + (r - \mu_T)\overline{T}) T_{max} - r\overline{T}^2 \right]}{\overline{T}\left[k_1' r \overline{T} + k_1 \mu_I T_{max} \right]}.
\end{aligned} \tag{2.4}$$

Following the analysis in [17], we can see that N is a bifurcation parameter. When

$$N < N_{crit} = \frac{\mu_I(\mu_V + k_1 T_0)}{k_1' \mu_b T_0}, \tag{2.5}$$

the uninfected steady state E_0 is stable and the infected steady state $\overline{E}$ does not exist (unphysical). When $N = N_{crit}$, the uninfected and infected steady states collide and there is a transcritical bifurcation. When $N > N_{crit}, E_0$ becomes unstable and $\overline{E}$ exists.

To discuss the local stability of the positive infected steady states $\overline{E}$ for $N > N_{crit}$, we consider the linearized system of (2.1) at $\overline{E}$. The Jacobian matrix at $\overline{E}$ is given by

$$A = \begin{pmatrix} -\left(\mu_T + \frac{r(2\overline{T}+\overline{I})}{T_{max}} + k_1 \overline{V} - r\right) & -\frac{r\overline{T}}{T_{max}} & -k_1 \overline{T} \\ k_1' \overline{V} & -\mu_I & k_1' \overline{T} \\ -k_1 \overline{V} & N\mu_b & -(k_1 \overline{T} + \mu_V) \end{pmatrix}.$$

Denote

$$M = \mu_T + \frac{r(2\overline{T} + \overline{I})}{T_{max}} + k_1 \overline{V} - r. \tag{2.6}$$

Then the characteristic equation of the linearized system is

$$\lambda^3 + a_1 \lambda^2 + (a_2 + a_4)\lambda + (a_3 + a_5) = 0, \tag{2.7}$$

where

$$\begin{aligned}
a_1 &= \mu_I + \mu_V + k_1 \overline{T} + M, \\
a_2 &= M\left(k_1 \overline{T} + \mu_I + \mu_V\right) + \mu_I\left(\mu_V + k_1 \overline{T}\right) - k_1^2 \overline{TV}, \\
a_3 &= k_1' \overline{T}\left(k_1 N \mu_b \overline{V} + \frac{r\mu_V \overline{V}}{T_{max}} - MN\mu_b\right), \\
a_4 &= k_1' \overline{T}\left(\frac{r\overline{V}}{T_{max}} - N\mu_b\right), \\
a_5 &= M\mu_I\left(\mu_V + k_1 \overline{T}\right) - \mu_I k_1^2 \overline{TV}.
\end{aligned} \tag{2.8}$$

We should point out that writing the coefficients in Eq. (2.7) as $a_2 + a_4$ and $a_3 + a_5$ is for the sake of convenience and comparison, since the characteristic equation (3.3) of the corresponding delay equation in Section 3 has all five a_is as coefficients.

By the Routh–Hurwitz criterion, it follows that all eigenvalues of Eq. (2.7) have negative real parts if and only if

$$a_1 > 0, \quad a_3 + a_5 > 0, \quad a_1(a_2 + a_4) - (a_3 + a_5) > 0. \tag{2.9}$$

Proposition 1. *The infected steady state* $\overline{E}$ *is asymptotically stable if the inequalities in* (2.9) *are satisfied.*

For the parameter values given in Table 1, $N_{\text{crit}} = 131.3$. The number of infectious viruses released, N, varies in the literature. It has been suggested to be hundreds (see [37,38]) and even thousands (see [39]). We first take $N = 500$, then

$$a_1 = 2.71, \quad a_2 = 0.7418, \quad a_3 = -0.0003, \quad a_4 = -0.6238, \quad a_5 = 0.0273 \tag{2.10}$$

and

$$a_3 + a_5 = 0.027 > 0, \quad a_1(a_2 + a_4) - (a_3 + a_5) = 0.2928 > 0. \tag{2.11}$$

Thus, all the conditions in (2.9) are satisfied and the infected steady state $\overline{E} = (260.7, 42.5, 1768.2)$ is asymptotically stable. Numerical simulations show that trajectories of system (2.1) approach to the steady state (Fig. 1(A1)–(A3)). Increasing the N value will decrease the numbers of uninfected $CD4^+$ T-cells and virus and increases the number of infected cells substantially, but does not change the stability of the steady state. With $N = 1000$, the steady state becomes $\overline{E} = (130.2, 34.9, 3480.1)$, which is asymptotically stable (see Fig. 1(B1)–(B3)).

We should point out that though the dynamics of system (2.1) are very similar to that of Perelson et al.'s model, the actual steady state values in our model (2.1) are different. Our bifurcation value N_{crit} is lower, the equilibrium level of healthy $CD4^+$ T-cells is lower, and the equilibrium level of free virus is higher, than that in Perelson et al.'s model.

Table 1
Variables and parameters for viral spread

Parameters and variables		Values
Dependent variables		
T	Uninfected $CD4^+$ T-cell population size	1000 mm^{-3}
I	Infected $CD4^+$ T-cell density	0
V	Initial density of HIV RNA	10^{-3} mm^{-3}
Parameters and Constants		
μ_{T}	Natural death rate of $CD4^+$ T-cells	0.02 day^{-1}
μ_{I}	Blanket death rate of infected $CD4^+$ T-cells	0.26 day^{-1}
μ_{b}	Lytic death rate for infected cells	0.24 day^{-1}
μ_{V}	Death rate of free virus	2.4 day^{-1}
k_1	Rate $CD4^+$ T-cells become infected with virus	2.4×10^{-5} mm^3 day^{-1}
k_1'	Rate infected cells becomes active	2×10^{-5} mm^3 day^{-1}
r	Growth rate of $CD4^+$ T-cell population	0.03 day^{-1}
N	Number of virions produced by infected $CD4^+$ T-cells	Varies
$T_{\max}$	Maximal population level of $CD4^+$ T-cells	1500 mm^{-3}
s	Source term for uninfected $CD4^+$ T-cells	10 $(\text{day})^{-1}(\text{mm}^{-3})$
Derived quantities		
T_0	$CD4^+$ T-cell population for HIV-negative persons	1000 mm^{-3}

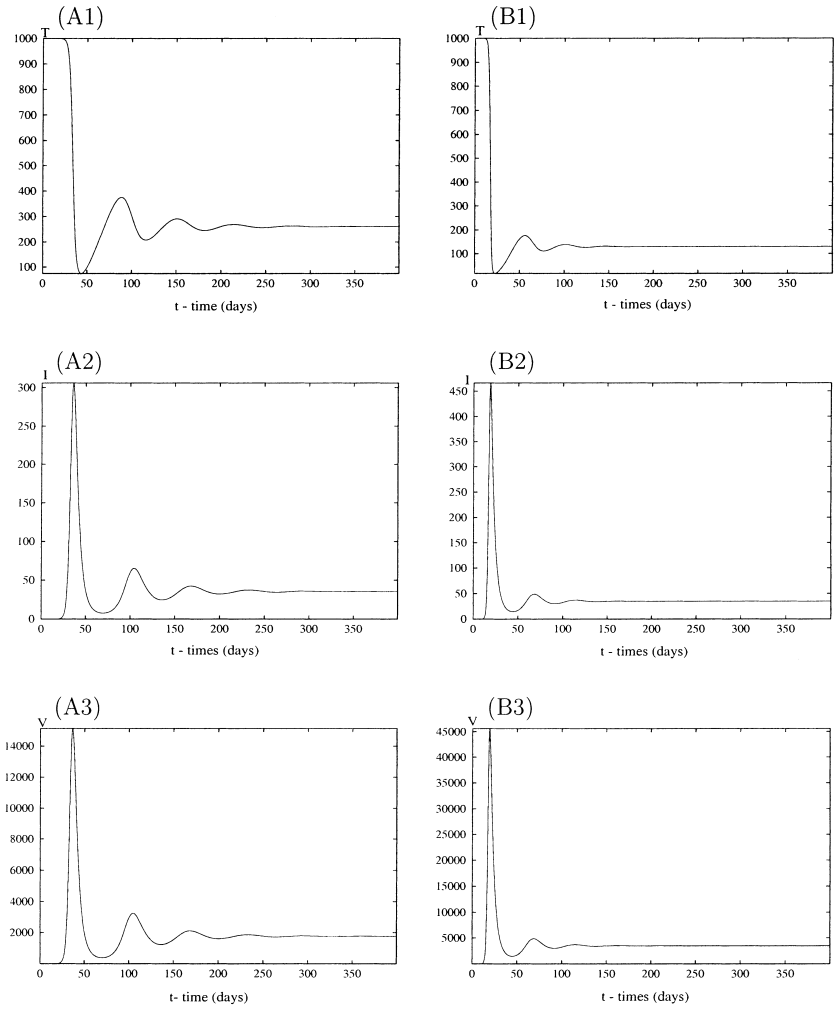

Fig. 1. The ODE model: in (A1)–(A3) $N = 500$ and in (B1)–(B3) $N = 1000$. All other parameters are given in Table 1.

3. The delay model

In this section, we introduce a time delay into system (2.1) to represent the viral eclipse phase. The model is given as follows:

$$\begin{aligned}
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= s - \mu_{\mathrm{T}} T(t) + rT(t)\left(1 - \frac{T(t)+I(t)}{T_{\max}}\right) - k_1 T(t)V(t),\\
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= k_1' T(t-\tau)V(t-\tau) - \mu_{\mathrm{I}} I(t),\\
\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= N\mu_{\mathrm{b}} I(t) - k_1 T(t)V(t) - \mu_{\mathrm{V}} V(t)
\end{aligned} \tag{3.1}$$

under the initial values

$$T(\theta) = T_0, \qquad I(0) = 0, \qquad V(\theta) = V_0, \quad \theta \in [-\tau, 0].$$

All parameters are the same as in system (2.1) except that the positive constant τ represents the length of the delay in days.

We find, again, an uninfected steady state $E_0 = (T_0, 0, 0)$ and an infected steady state $\overline{E} = (\overline{T}, \overline{I}, \overline{V})$, where $\overline{T}, \overline{I}$ and $\overline{V}$ are the same as in Section 2, given by (2.4). Since the uninfected steady state E_0 is unstable when $\tau = 0$ and $N > N_{\text{crit}}$, incorporation of a delay will not change the instability. Thus, E_0 is unstable if $N > N_{\text{crit}}$, which is also the feasibility condition for the infected steady state $\overline{E}$.

To study the stability of the steady states $\overline{E}$, let us define

$$x(t) = T(t) - \overline{T}, \quad y(t) = I(t) - \overline{I}, \quad z(t) = V(t) - \overline{V}.$$

Then the linearized system of (3.1) at $\overline{E}$ is given by

$$\begin{aligned}
\frac{\mathrm{d}x(t)}{\mathrm{d}t} &= -\left(\mu_{\mathrm{T}} + \frac{2r\overline{T} + r\overline{I}}{T_{\max}} + k_1\overline{V} - r\right)x(t) - \frac{r\overline{T}}{T_{\max}}y(t) - k_1\overline{T}z(t),\\
\frac{\mathrm{d}y(t)}{\mathrm{d}t} &= k_1'\overline{V}x(t-\tau) - \mu_{\mathrm{I}}y(t) + k_1\overline{T}z(t-\tau),\\
\frac{\mathrm{d}z(t)}{\mathrm{d}t} &= -k_1\overline{V}x(t) + N\mu_{\mathrm{b}}y(t) - (k_1\overline{T} + \mu_{\mathrm{V}})z(t).
\end{aligned} \tag{3.2}$$

We then express system (3.2) in matrix form as follows:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} x(t)\\ y(t)\\ z(t)\end{pmatrix} = A_1\begin{pmatrix} x(t)\\ y(t)\\ x(t)\end{pmatrix} + A_2\begin{pmatrix} x(t-\tau)\\ y(t-\tau)\\ z(t-\tau)\end{pmatrix},$$

where A_1 and A_2 are 3×3 matrices given by

$$A_1 = \begin{pmatrix} -M & -\frac{r\overline{T}}{T_{\max}} & -k_1\overline{T}\\ 0 & -\mu_{\mathrm{I}} & 0\\ -k_1\overline{V} & N\mu_{\mathrm{b}} & -(k_1\overline{T} + \mu_{\mathrm{V}})\end{pmatrix}, \quad A_2 = \begin{pmatrix} 0 & 0 & 0\\ k_1'\overline{V} & 0 & k_1'\overline{T}\\ 0 & 0 & 0\end{pmatrix},$$

where M is defined by (2.6). The characteristic equation of system (3.2) is given by

$$\Delta(\lambda) = \left|\lambda I - A_1 - \mathrm{e}^{-\lambda\tau}A_2\right| = 0,$$

that is,

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3\mathrm{e}^{-\lambda\tau} + a_4\lambda\mathrm{e}^{-\lambda\tau} + a_5 = 0, \tag{3.3}$$

where a_i $(i = 1, \ldots, 5)$ are defined in (2.8).

It is known that $\overline{E}$ is asymptotically stable if all roots of the corresponding characteristic equation (3.3) have negative real parts (see [34]). However, compared with the polynomial characteristic equation (2.7) for the ODE model, Eq. (3.3) is much more difficult to deal with. First, it is a transcendental equation and has infinitely many eigenvalues. Second, since it is transcendental the classical Routh–Hurwitz criterion cannot be used to discuss Eq. (3.3) anymore. Third, though there are some general tests (see [29], for example) that can be used to determine

when all eigenvalues of the transcendental equations have negative real parts, applying such a general test to specific transcendental equations is very complicated and far from trivial ([35]).

We shall study the distribution of the roots of the transcendental Eq. (3.3) analytically. Recall that for the ODE model (2.1), the infected steady state $\overline{E}$ is stable for the parameter values given in Table 1. Our starting point is to assume that the steady state of the ODE model (2.1) is stable, then we shall derive conditions on the parameters to ensure that the steady state of the delay model is still stable.

To proceed, we consider Eq. (3.3) with $\tau = 0$, that is Eq. (2.7), and assume that all the roots of Eq. (2.7) have negative real parts. This is equivalent to the assumption (2.9). By Rouché's Theorem [36, Theorem 9.17.4] and the continuity in τ, the transcendental equation (3.3) has roots with positive real parts if and only if it has purely imaginary roots. We shall determine if (3.3) has purely imaginary roots, from which we then shall be able to find conditions for all eigenvalues to have negative real parts.

Denote $\lambda = \eta(\tau) + i\omega(\tau)$ $(\omega > 0)$, the eigenvalue of the characteristic equation (3.3), where $\eta(\tau)$ and $\omega(\tau)$ depend on the delay τ. Since the equilibrium $\overline{E}$ of the ODE model is stable, it follows that $\eta(0) < 0$ when $\tau = 0$. By continuity, if $\tau > 0$ is sufficiently small we still have $\eta(\tau) < 0$ and $\overline{E}$ is still stable. If $\eta(\tau_0) = 0$ for certain value $\tau_0 > 0$ (so that $\lambda = i\omega(\tau_0)$ is a purely imaginary root of (3.3), then the steady state $\overline{E}$ loses its stability and eventually becomes unstable when $\eta(\tau)$ becomes positive. In other words, if such an $\omega(\tau_0)$ does not exist, that is, if the characteristic equation (3.3) does not have purely imaginary roots for all delay, then the steady state $\overline{E}$ is always stable. We shall show that this indeed is true for the characteristic equation (3.3).

Clearly, $i\omega$ $(\omega > 0)$ is a root of Eq. (3.3) if and only if

$$-i\omega^3 - a_1\omega^2 + ia_2\omega + a_3(\cos\omega\tau - i\sin\omega\tau) + a_4\omega(\sin\omega\tau + i\cos\omega\tau) + a_5 = 0. \tag{3.4}$$

Separating the real and imaginary parts, we have

$$a_1\omega^2 - a_5 = a_3\cos\omega\tau + a_4\omega\sin\omega\tau, \tag{3.5}$$

$$\omega^3 - a_2\omega = -a_3\sin\omega\tau + a_4\omega\cos\omega\tau. \tag{3.6}$$

Adding up the squares of both the equations, we obtain

$$\omega^6 + (a_1^2 - 2a_2)\omega^4 + (a_2^2 - 2a_1a_5 - a_4^2)\omega^2 + (a_5^2 - a_3^2) = 0. \tag{3.7}$$

Let

$$z = \omega^2, \quad \alpha = a_1^2 - 2a_2, \quad \beta = a_2^2 - 2a_1a_5 - a_4^2, \quad \gamma = a_5^2 - a_3^2.$$

Then Eq. (3.7) becomes

$$h(z) = z^3 + \alpha z^2 + \beta z + \gamma = 0. \tag{3.8}$$

Since $\gamma = a_5^2 - a_3^2 > 0$ for the parameter values given in Table 1, we assume that $\gamma \geqslant 0$ and have the following claim.

Claim 1. If

$$\gamma \geqslant 0 \tag{3.9}$$

and

$$\beta > 0, \tag{3.10}$$

then Eq. (3.8) has no positive real roots.

In fact, notice that

$$\frac{\mathrm{d}h(z)}{\mathrm{d}z} = 3z^2 + 2\alpha z + \beta.$$

Set

$$3z^2 + 2\alpha z + \beta = 0. \tag{3.11}$$

Then the roots of Eq. (3.11) can be expressed as

$$z_{1,2} = \frac{-\alpha \pm \sqrt{\alpha^2 - 3\beta}}{3}. \tag{3.12}$$

If $\beta > 0$, then $\alpha^2 - 3\beta < \alpha^2$; that is, $\sqrt{\alpha^2 - 3\beta} < \alpha$. Hence, neither z_1 nor z_2 is positive. Thus, Eq. (3.11) does not have positive roots. Since $h(0) = \gamma \geqslant 0$, it follows that the Eq. (3.8) has no positive roots.

Claim 1 thus implies that there is no ω such that $\mathrm{i}\omega$ is an eigenvalue of the characteristic equation (3.3). Therefore, the real parts of all the eigenvalues of (3.3) are negative for all delay $\tau \geqslant 0$. Summarizing the above analysis, we have the following proposition.

Proposition 2. *Suppose that*

(i) $a_1 > 0,\ a_3 + a_5 > 0,\ a_1(a_2 + a_4) - (a_3 + a_5) > 0$;

(ii) $\gamma \geqslant 0$ *and* $\beta > 0$.

Then the infected steady state $\overline{E}$ *of the delay model* (3.1) *is absolutely stable*; *that is*, $\overline{E}$ *is asymptotically stable for all* $\tau \geqslant 0$.

Notice that for the given parameter values in Table 1 all the conditions in Proposition 2 are satisfied. Thus, the infected steady state $\overline{E}$ is asymptotically stable for all $\tau \geqslant 0$. Take $N = 500, \tau = 1$, and other parameter values given in Table 1, numerical simulations show that the infected steady state $\overline{E} = (260.7, 42.5, 1768.2)$ is asymptotically stable (Fig. 2(A4)–(A6)). Compared with Fig. 1(A1)–(A3), we can see that though the delay causes transient oscillations in the components, the steady state $\overline{E}$ is still stable. Moreover, when N is larger ($N = 1000$), the effect of the delay is not as strong as for small N (Fig. 2(B4)–(B6)).

Remark. Proposition 2 indicates that if the parameters satisfy the conditions (i) and (ii), then the steady state of the delay model (3.1) is asymptotically stable for all delay values; that is, independent of the delay. However, we should point out that if the conditions (condition (ii)) in Proposition 2 are not satisfied, then the stability of the steady state depends on the delay value and the delay could even induce oscillations.

For example, if (a) $\gamma < 0$, then from Eq. (3.8) we have $h(0) < 0$ and $\lim_{z\to\infty} h(z) = \infty$. Thus, Eq. (3.8) has at least one positive root, say z_0. Consequently, Eq. (3.7) has at least one positive root, denoted by ω_0. If (b) $\beta < 0$, then $\sqrt{\alpha^2 - 3\beta} > \alpha$. By (3.12), $z_1 = \frac{1}{3}(-\alpha + \sqrt{\alpha^2 - 3\beta}) > 0$. It follows

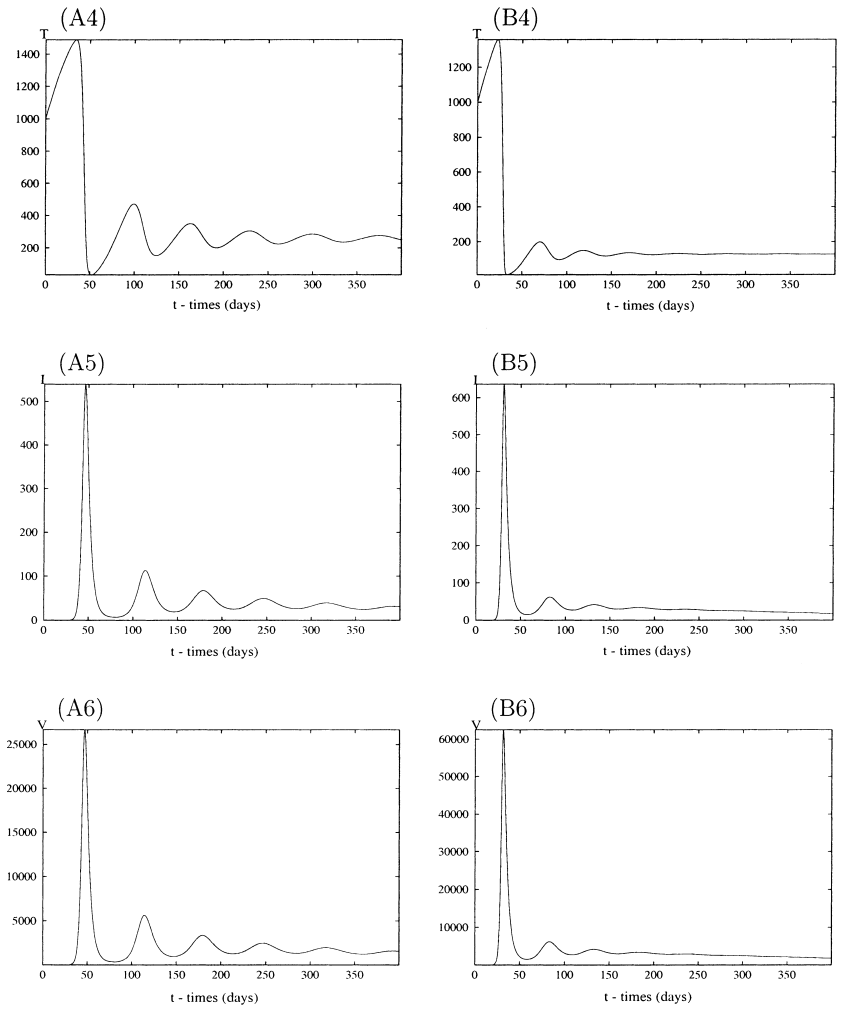

Fig. 2. The delay model with $\tau = 1$: in (A4)–(A6) $N = 500$ and in (B4)–(B6) $N = 1000$. All other parameter values are given in Table 1.

that Eq. (3.8), hence Eq. (3.7), has a positive root ω_0. This implies that the characteristic equation (3.3) has a pair of purely imaginary roots $\pm i\omega_0$.

Let $\lambda(\tau) = \eta(\tau) + i\omega(\tau)$ be the eigenvalue of Eq. (3.3) such that $\eta(\tau_0) = 0,\ \omega(\tau_0) = \omega_0$. From (3.5) and (3.6) we have

$$\tau_j = \frac{1}{\omega_0} \arccos\left(\frac{a_4\omega_0^4 + (a_1a_3 - a_2a_4)\omega_0^2 - a_3a_5}{a_3^2 + a_4^2\omega_0^2}\right) + \frac{2j\pi}{\omega_0}, \quad j = 0, 1, 2, \ldots$$

Also, we can verify that the following transversality condition:

$$\frac{\mathrm{d}}{\mathrm{d}\tau} Re\lambda(\tau)\|_{\tau=\tau_0} = \frac{\mathrm{d}}{\mathrm{d}\tau}\eta(\tau)|_{\tau=\tau_0} > 0$$

holds. By continuity, the real part of $\lambda(\tau)$ becomes positive when $\tau > \tau_0$ and the steady state becomes unstable. Moreover, a Hopf bifurcation occurs when τ passes through the critical value τ_0 (see [40]).

The above analysis can be summarized into the following proposition.

Proposition 3. *Suppose that*

(i) $a_1 > 0,\ a_3 + a_5 > 0,\ a_1(a_2 + a_4) - (a_3 + a_5) > 0.$

If either

(ii) $\gamma < 0$

or

(iii) $\gamma \geqslant 0$ and $\beta < 0$

is satisfied, then the infected steady state $\overline{E}$ *of the delay model* (3.1) *is asymptotically stable when* $\tau < \tau_0$ *and unstable when* $\tau > \tau_0$, *where*

$$\tau_0 = \frac{1}{\omega_0} \arccos\left(\frac{a_4\omega_0^4 + (a_1a_3 - a_2a_4)\omega_0^2 - a_3a_5}{a_3^2 + a_4^2\omega_0^2} \right).$$

When $\tau = \tau_0$, *a Hopf bifurcation occurs*; *that is, a family of periodic solutions bifurcates from* $\overline{E}$ *as* τ *passes through the critical value* τ_0.

Proposition 3 indicates that the delay model could exhibit Hopf bifurcation at certain value of the delay if the parameters satisfy the conditions in (ii) and (iii). However, for the parameter values given in Table 1, neither (ii) nor (iii) holds.

4. Discussion

Incorporating a time delay into HIV infection models has been done by some researchers (see [30–33,35]).It is still an interesting exercise to determine how the intercellular delay affects overall disease progression and, mathematically, how the delay effects the dynamics of systems.

We first modified the ODE model proposed by Perelson et al. [17] into a system of three equations. Similar to the analysis in [17], we obtained a restriction on the number of viral particles released per infectious cell in order for infection to be sustained. Under this restriction, the system has a positive equilibrium – the infected steady state. By using stability analysis we obtained sufficient conditions on the parameters for the stability of the infected steady state. For parameter values reported by others (see Table 1), our stability conditions are all satisfied and numerical simulations confirmed the analysis. Though our value of the number of viral particles released per infectious cell is smaller than that observed by Perelson et al. [17], it does not affect the existence and stability of the infected steady state.

We then introduced a time delay into the model which describes the time between infection of a $CD4^+$ T-cell and the emission of viral particles on a cellular level. The same restriction on the number of viral particles released per infectious cell is required. By analyzing the transcendental characteristic equation, we analytically derived stability conditions for the infected steady state in terms of the parameters and independent of the delay. Using the parameter values in Table 1, we

found that all the conditions are satisfied. Thus, the infected steady state is stable, independent of the size of the delay, though the time delay does cause transient oscillations in all components. Computer simulations confirmed our analysis. Biologically, it implies that the intercellular delay can cause the cell and virus populations to fluctuate in the early stage of infection, in a longer term they will converge to the infected steady state values.

Though the parameter values in Table 1 gave us a stable steady state independent of the delay, the delay model (3.1) itself could exhibit rich dynamics. Under another set of assumptions on the parameters, the stability of the steady state depends on the delay and even delay-induced oscillations could occur via instability.

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