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DYNAMICS OF A HIV-1 INFECTION MODEL WITH CELL-MEDIATED IMMUNE RESPONSE AND INTRACELLULAR DELAY

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Abstract. In this paper, we consider a mathematical model for HIV-1 infection with intracellular delay and cell-mediated immune response. A novel feature is that both cytotoxic T lymphocytes (CTLs) and the intracellular delay are incorporated into the model. We obtain a necessary and sufficient condition for the global stability of the infection-free equilibrium and give sufficient conditions for the local stability of the two infection equilibria: one without CTLs being activated and the other with. We also perform some numerical simulations which support the obtained theoretical results. These results show that larger intracellular delay may help eradicate the virus, while the activation of CTLs can only help reduce the virus load and increase the healthy CD_4^+ cells population in the long term sense.

1. **Introduction.** In the past decade, there has been much interest in mathematical modeling of HIV dynamics (see, for example, [14, 18, 19]). This is because HIV mathematical models can provide insights into the dynamics of viral load in vivo and may play a significant role in the development of a better understanding of HIV/AIDs and drug therapies.

A simple, standard yet classic model (probably the first) for HIV dynamics was proposed by Perelson et al. in [18, 19] as follows:

$$\begin{aligned} \frac{dx(t)}{dt} &= s - dx(t) - kv(t)x(t), \\ \frac{dy(t)}{dt} &= kv(t)x(t) - \delta y(t), \\ \frac{dv(t)}{dt} &= N\delta y(t) - \mu v(t). \end{aligned} \tag{1}$$

The variables $x(t), y(t)$, and $v(t)$ denote the concentrations of uninfected cells, infected cells and virus, respectively. The parameter s is the rate at which new target cells are generated, d is the death rate of the susceptible cells and k is the constant

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characterizing the infection rate. The infected cells are assumed to die at a rate δ (say, via lysis) due to the action of virus, each releasing N new virus particles as the lysis of infected cells occurs. Thus, on average, virus is instantaneously produced at rate $N\delta y(t)$. Lastly, virus particles are cleared from the system at rate μ per virion.

Note that the immune response after viral infection is universal and necessary to eliminate or control the disease. Antibodies, cytokines, natural killer cells, B cells and T cells are all essential components of a normal immune response to viral infection. However, in HIV-1 infection, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking virus-infected cells. Indeed, it is believed that CTLs are the main host immune factor that determines virus load (e.g.,[1]). Therefore, the dynamics of HIV-1 infection with CTLs response has recently drawn much attention of researchers in the related areas (see, e.g., [1, 15, 21, 7] and the references therein), and is also the main concern of this research. Letting $z(t)$ be the concentration of CTLs, model (1) can be modified to

$$\begin{aligned}
\frac{dx(t)}{dt} &= s - dx(t) - kv(t)x(t),\\
\frac{dy(t)}{dt} &= kv(t)x(t) - \delta y(t) - py(t)z(t),\\
\frac{dv(t)}{dt} &= N\delta y(t) - \mu v(t),\\
\frac{dz(t)}{dt} &= f(x,y,z) - bz(t),
\end{aligned} \tag{2}$$

where p accounts for the strength of the lytic component and b is the death rate for CTLs. The function $f(x,y,z)$ describes the rate of immune response activated by the infected cells. Arnaout et al.[1] and Wang et al.[21] assumed that the production of CTLs depends only on the concentration of infected cells and chose the linear dependent former $f(x,y,z) = cy(t)$. In [15], Nowak and Bangham assumed that the production of CTLs is also dependent upon the concentration of CTL cells, and used $f(x,y,z) = cy(t)z(t)$, leading to the following concrete model:

$$\begin{aligned}
\frac{dx(t)}{dt} &= s - dx(t) - kv(t)x(t),\\
\frac{dy(t)}{dt} &= kv(t)x(t) - \delta y(t) - py(t)z(t),\\
\frac{dv(t)}{dt} &= N\delta y(t) - \mu v(t),\\
\frac{dz(t)}{dt} &= cy(t)z(t) - bz(t).
\end{aligned} \tag{3}$$

Using symbolic calculation software on computers, Liu [13] gave stability analysis of model (3). By simple algebraic manipulations, Kajiwara and Sasaki [11] presented pure theoretic results on the stability of model (3).

Culshaw et al. [7] further assumed that the production of CTLs is also related the healthy cells' help and accordingly chose $f(x,y,z) = cx(t)y(t)z(t)$. With the extra assumption that the viral load is proportional to the level of infected cells,

they proposed and studied the following HIV-1 infection model:

$$\begin{aligned}\frac{dx(t)}{dt} &= s - dx(t) - kx(t)y(t),\\ \frac{dy(t)}{dt} &= k'x(t)y(t) - \delta y(t) - py(t)z(t),\\ \frac{dz(t)}{dt} &= cx(t)y(t)z(t) - bz(t).\end{aligned} \tag{4}$$

Here the ratio $k' : k$ is the proportion of infected cells that survive the incubation period (average time between the new infection of a CD_4^+ T cell and the time it becomes infectious). Model (4) may have up to three equilibria and the local stability of the three equilibria were analyzed in [7].

As pointed out in [22], time delays can not be ignored in models for immune response, since antigenic stimulation generating CTLs may need a period of time, that is, the activation rate of CTL response at time t may depend on the population of antigen at a previous time. Based on such a reality, in [5, 6, 22], a time delay was incorporated into the the immune activation term $f(x, y, z)$ for $f(x, y, z) = cy$ and $f(x, y, z) = cyz$ respectively, and the effects of the delay on the dynamics of the corresponding models was investigated. It has been found (in [22]) that the delay in activating immune response could lead to very complicated dynamics including stable periodic solutions and chaos, and such complicated dynamical behaviors may well explain irregular real time series data for the immune state of a patient.

The aforementioned models can capture some essential features of the immune system and are able to produce a variety of immune responses. On the other hand, it has been realized recently that there are also delays in the process of cell infection and virus production, and thus, delays should be incorporated into the infection equation and/or the virus production equation of a model. In the absence of immune responses, Nelson et al.[16] added a *discrete delay* in the y equation of model (1), and presented detailed analysis of the resulting delay differential equation model. By comparing their results to those from the corresponding model without delay (i.e., (1)), they showed that the predicted rate of decline in plasma virus concentration depends on the length of the delay. Nelson and Perelson [17] further generalized the model by considering a *general delay distribution*, and suggested incorporating delays in both cell infection equation and virus replication. As a follow-up of [17], Zhu and Zou [23] investigated a model with a discrete delay in the infection equation and another discrete delay in the virus production equation, by analyzing the two delay model, they found that large delays can help eliminate the virus.

In this paper, following the line of [16], we incorporate a delay into the cell infection equation in model (3). That is, we propose the following model:

$$\begin{aligned}\frac{dx(t)}{dt} &= s - dx(t) - kv(t)x(t),\\ \frac{dy(t)}{dt} &= ke^{-\delta\tau}v(t-\tau)x(t-\tau) - \delta y(t) - py(t)z(t),\\ \frac{dv(t)}{dt} &= N\delta y(t) - \mu v(t),\\ \frac{dz(t)}{dt} &= cy(t)z(t) - bz(t),\end{aligned} \tag{5}$$

where τ denotes the lag between the time the virus contacts a target cell and the time the cell becomes actively infected (including the steps of successful attachment of virus to the cell, and penetration of virus into the cell). The novelty of the model (5) is that it includes both the main immune response factor CTLs in HIV infection and the intracellular delay in virus production. For other viral infections, as long as there is an intracellular delay in virus replication and the CTLs plays the main role in the immune response to the virus, we believe the model is also appropriate. In the rest of this paper, we investigate the impact of the delay τ and CTLs on the the dynamics of model (5). In Section 2, the positivity and boundedness of solutions of the system (5) are presented. The stability analysis for the three equilibria are given in Section 3, and some numerical simulations are given in Section 4. Finally, in Section 5, some conclusions are drawn from the obtained results in previous sections, revealing both qualitatively and quantitatively the positive role of the CTLs and the intracellular delay.

2. **Positivity and boundedness of solutions.** Model (5) is a system of delay differential equations. For such a system, initial functions need to be specified and well-posedness needs to be addressed. Let $X = C([-\tau, 0]; R^4)$ be the Banach space of continuous mapping from $[-\tau, 0]$ to R equipped with the sup-norm. By the fundamental theory of FDEs (see Hale and Verduyn Lunel [10]), we know that there is a unique solution $(x(t), y(t), v(t), z(t))$ to system (5) with initial conditions

$$(x(\theta), y(\theta), v(\theta), z(\theta)) \in X. \tag{6}$$

For biological reasons, the initial functions $x(\theta)$, $y(\theta)$, $v(\theta)$ and $z(\theta)$ are assumed to be non-negative:

$$x(\theta) \geq 0, \;\; y(\theta) \geq 0, \;\; v(\theta) \geq 0, \;\; z(\theta) \geq 0, \;\; \text{for } \theta \in [-\tau, 0]. \tag{7}$$

The following theorem establish the positivity and boundedness of solutions of (5) with initial functions satisfying (6) and (7).

Theorem 2.1. *Let $(x(t), y(t), v(t), z(t))$ be the solution of system (5) satisfying conditions (6) and (7). Then $x(t)$, $y(t)$, $v(t)$ and $z(t)$ are all non-negative and bounded for all $t \geq 0$ at which the solution exists.*

Proof. Note that from (5), we have

$$x(t) = x(0)e^{-\int_0^t (d+kv(\xi))d\xi} + \int_0^t s e^{-\int_\eta^t (d+kv(\xi))d\xi} d\eta,$$

$$y(t) = y(0)e^{-\int_0^t (\delta+pz(\xi))d\xi} + \int_0^t kx(\eta-\tau)v(\eta-\tau)e^{-\delta\tau} e^{-\int_\eta^t (\delta+pz(\xi))d\xi} d\eta,$$

$$v(t) = v(0)e^{-\mu t} + \int_0^t N\delta y(\eta) e^{-\mu(t-\eta)} d\eta$$

and

$$z(t) = z(0)e^{\int_0^t (cy(\xi)-b)d\xi}.$$

Positivity immediately follows from the above integral forms and (6) and (7).

For boundedness of the solution, we define

$$G(t) = cNe^{-\delta\tau}x(t) + cNy(t+\tau) + \frac{c}{2}v(t+\tau) + Npz(t+\tau)$$

and $q = \min\{d, \delta/2, \mu, b\}$. By non-negativity of the solution, it follows that

$$\begin{aligned}
\tfrac{d}{dt}[G(t)] &= cNe^{-\delta\tau}[s - dx(t) - kv(t)x(t)] \\
&\quad + cNke^{-\delta\tau}v(t)x(t) - \delta cNy(t+\tau) - cNpy(t+\tau)z(t+\tau) \\
&\quad + \tfrac{\delta cN}{2}y(t+\tau) - \tfrac{c\mu}{2}v(t+\tau) + cNpy(t+\tau)z(t+\tau) - Npbz(t+\tau) \\
&= cNse^{-\delta\tau} - cdNe^{-\delta\tau}x(t) - \tfrac{\delta}{2}cNy(t+\tau) - \tfrac{c\mu}{2}v(t+\tau) - Npbz(t+\tau) \\
&< cNse^{-\delta\tau} - qG(t).
\end{aligned}$$

This implies that $G(t)$ is bounded, and so are $x(t), y(t), v(t)$ and $z(t)$. This completes the proof of this theorem. □

Remark 1. (i) From the proof, one can see that in addition to (6) and (7), if either $y(0) > 0$ or $v(0) > 0$, then $x(t)$, $y(t)$, $v(t)$ and $z(t)$ are actually positive; (ii) The existence theory from [10] only guarantees local existence, and the boundedness established in Theorem 2.1 indeed ensures that the solution exist for all $t \geq 0$.

3. **Equilibria and their stability.** System (5) has an infection-free equilibrium $E_0 = (s/d, 0, 0, 0)$, corresponding to the maximal level of healthy CD_4^+ T cells. This is the only biologically meaningful equilibrium if

$$\mathcal{R}_0 = ke^{-\delta\tau}\frac{sN}{d\mu} < 1.$$

However, if $\mathcal{R}_0 > 1$, in addition to E_0, there is another biologically meaningful equilibrium

$$E_1 = \left(\frac{\mu e^{\delta\tau}}{Nk}, \frac{s}{\delta e^{\delta\tau}} - \frac{d\mu}{N\delta k}, \frac{sN}{\mu e^{\delta\tau}} - \frac{d}{k}, 0\right) = \left(\frac{\mu e^{\delta\tau}}{Nk}, \frac{d\mu}{N\delta k}(\mathcal{R}_0 - 1), \frac{d}{k}(\mathcal{R}_0 - 1), 0\right),$$

which corresponds to positive levels of healthy CD_4^+ T cells, infected CD_4^+ T cells and virus, but no CTL response. If

$$\mathcal{R}_1 = ke^{-\delta\tau}\frac{scN}{dc\mu + kN\delta b} > 1,$$

or equivalently

$$\mathcal{R}_0 > 1 + \frac{kN\delta b}{dc\mu},$$

system (5) also has an interior equilibrium

$$E_2 = \left(\frac{sc\mu}{c\mu d + kN\delta b}, \frac{b}{c}, \frac{N\delta b}{c\mu}, \frac{\delta}{p}(\mathcal{R}_1 - 1)\right),$$

accounting for the presence of all four components: uninfected CD_4^+ T and infected CD_4^+ T cells, virus, and CTL response.

3.1. **Stability of the infection-free equilibrium E_0.** Linearizing (5) at the infection-free equilibrium E_0 leads to

$$\begin{aligned}
\frac{dx(t)}{dt} &= -dx(t) - k\frac{s}{d}v(t),\\
\frac{dy(t)}{dt} &= ke^{-\delta\tau}\frac{s}{d}v(t-\tau) - \delta y(t),\\
\frac{dv(t)}{dt} &= N\delta y(t) - \mu v(t),\\
\frac{dz(t)}{dt} &= -bz(t).
\end{aligned} \tag{8}$$

The characteristic equation for (8) is

$$(\lambda+b)(\lambda+d)[\lambda^2+(\delta+\mu)\lambda+\delta\mu-\frac{Nks\delta}{d}e^{-\delta\tau}e^{-\lambda\tau}]=0. \tag{9}$$

Obviously, $\lambda=-b$ and $\lambda=-d$ are eigenvalues for (8), and hence, the stability of E_0 is determined by the distribution of the roots of equation

$$\lambda^2+(\delta+\mu)\lambda+\delta\mu-\frac{Nks\delta}{d}e^{-\delta\tau}e^{-\lambda\tau}=0. \tag{10}$$

If $\mathcal{R}_0<1$, then $\lambda=0$ is not a root of the equation (10) since

$$\delta\mu-\frac{Nks\delta}{d}e^{-\delta\tau}>0.$$

When $\tau=0$, then equation (10) becomes

$$\lambda^2+(\delta+\mu)\lambda+\delta\mu-\frac{Nks\delta}{d}=0. \tag{11}$$

In this case, $\mathcal{R}_0<1$ reduces to $\frac{ksN}{d\mu}<1$. Clearly, if $\frac{ksN}{d\mu}<1$, then $\delta\mu-Nks\delta/d>0$ under which all roots of (11) have negative real parts. Note that all roots of (10) depend continuously on τ (see [3]). Notice also that the assumption (ii) of [4] holds and this ensures $Re(\lambda)<+\infty$ for any root of (10). Therefore, as the delay τ increases, the roots of (10) can only enter the right-half in complex plane by crossing the imaginary axis. Let $\lambda=iw$ with $w>0$ be a purely imaginary root of (10), then,

$$-w^2+iw(\delta+\mu)+\delta\mu=N\frac{ks\delta}{d}e^{-\delta\tau}e^{-iw\tau}.$$

Taking moduli in both sides of the above equation gives

$$w^4+(\delta^2+\mu^2)w^2+\delta^2\mu^2-\left(\frac{Nks\delta e^{-\delta\tau}}{d}\right)^2=0.$$

Letting $y=w^2$ yields

$$y^2+(\delta^2+\mu^2)y+\delta^2\mu^2-(N\frac{ks\delta}{d}e^{-\delta\tau})^2=0. \tag{12}$$

If $\mathcal{R}_0<1$, then (12) has no non-negative real root. Therefore, there is no root $\lambda=iw$ with $w\geq 0$ for (10), implying that the roots of (10) can not cross the purely imaginary axis. Hence all roots of (10) have negative real parts provided $\mathcal{R}_0<1$. On the other hand, it is easy to see that (10) has a real positive root if $\mathcal{R}_0>1$.

Summarizing the above, we have established the following

Theorem 3.1. *If $\mathcal{R}_0 < 1$, then the infection-free equilibrium E_0 is locally asymptotical stable; if $\mathcal{R}_0 > 1$, then the infection-free equilibrium E_0 becomes unstable and there occurs the equilibrium E_1.*

Theorem 3.1 only establishes local stability of E_0 under $\mathcal{R}_0 < 1$. By constructing a Lyapunov functional, we can actually obtain globally asymptotic stability of the infection-free equilibrium E_0 under the condition $\mathcal{R}_0 < 1$.

Theorem 3.2. *The infection-free equilibrium E_0 is indeed globally asymptotically stable if $\mathcal{R}_0 < 1$.*

Proof. Define

$$V = \frac{e^{-\delta\tau}}{2}\left(x(t) - \frac{s}{d}\right)^2 + \frac{s}{d}y(t) + \frac{s}{Nd}v(t) + \frac{sp}{cd}z(t) + \frac{s}{d}ke^{-\delta\tau}\int_{t-\tau}^{t} x(\theta)v(\theta)d\theta.$$

Calculating the time derivative of V along the solution of (5), we obtain

$$\begin{aligned}
V'|_{(5)} &= e^{-\delta\tau}(x(t) - \tfrac{s}{d})\left[-d(x(t) - \tfrac{s}{d}) - kv(t)(x(t) - \tfrac{s}{d})\right] \\
&\quad -e^{-\delta\tau}k\tfrac{s}{d}(x(t) - \tfrac{s}{d})v(t) + e^{-\delta\tau}k\tfrac{s}{d}x(t-\tau)v(t-\tau) \\
&\quad -\tfrac{\delta s}{d}y(t) - \tfrac{ps}{d}y(t)z(t) + \tfrac{s}{Nd}N\delta y(t) - \tfrac{s}{Nd}\mu v(t) \\
&\quad +\tfrac{sp}{cd}cy(t)z(t) - \tfrac{sp}{cd}bz(t) + \tfrac{s}{d}ke^{-\delta\tau}[x(t) - \tfrac{s}{d}]v(t) \\
&\quad +\tfrac{s^2}{d^2}ke^{-\delta\tau}v(t) - \tfrac{s}{d}ke^{-\delta\tau}x(t-\tau)v(t-\tau) \\
&= -(d + kv(t))\,e^{-\delta\tau}[x(t) - \tfrac{s}{d}]^2 - \tfrac{s\mu}{dN}(1 - \mathcal{R}_0)v(t) - \tfrac{spb}{cd}z(t) \\
&\le -de^{-\delta\tau}[x(t) - \tfrac{s}{d}]^2.
\end{aligned}$$

Here we have used the fact that $x(t), y(t), v(t)$ and $z(t)$ are non-negative and $\mathcal{R}_0 < 1$. The globally asymptotic stability of the infection-free equilibrium E_0 follows from the above inequality and LaSalle Invariance principle (see e.g., [12]). □

3.2. **Stability of the CTL-inactivated infection equilibrium E_1.** In this subsection, we assume $\mathcal{R}_0 > 1$. Thus, E_1 exists and the linearization of (5) at E_1 is

$$\begin{aligned}
\frac{dx(t)}{dt} &= -\frac{ksN}{\mu e^{\delta\tau}}x(t) - \frac{\mu e^{\delta\tau}}{N}v(t), \\
\frac{dy(t)}{dt} &= ke^{-\delta\tau}(\frac{sN}{\mu e^{\delta\tau}} - \frac{d}{k})x(t-\tau) + \frac{\mu}{N}v(t-\tau) - \delta y(t) - p(\frac{s}{\delta e^{\delta\tau}} - \frac{d\mu}{N\delta k})z(t), \\
\frac{dv(t)}{dt} &= N\delta y(t) - \mu v(t), \\
\frac{dz(t)}{dt} &= \left[c(\frac{s}{\delta e^{\delta\tau}} - \frac{d\mu}{N\delta k}) - b\right]z(t).
\end{aligned} \tag{13}$$

The characteristic equation for (13) is

$$\left[\lambda + b - c\left(\frac{s}{\delta e^{\delta\tau}} - \frac{d\mu}{N\delta k}\right)\right]\left[(\lambda+\delta)(\lambda+\mu)\left(\lambda + \frac{ksN}{\mu e^{\delta\tau}}\right) - \delta\mu(\lambda+d)e^{-\lambda\tau}\right] = 0. \tag{14}$$

The first factor on the left hand side of (14) gives a real root

$$\lambda_1 = c(\frac{s}{\delta e^{\delta\tau}} - \frac{d\mu}{N\delta k}) - b.$$

which is negative if $\mathcal{R}_1 < 1$ and positive if $\mathcal{R}_1 > 1$. The remaining roots of (14) are obtained by considering

$$(\lambda+\delta)(\lambda+\mu)\left(\lambda + \frac{ksN}{\mu e^{\delta\tau}}\right) - \delta\mu(\lambda+d)e^{-\lambda\tau} = 0. \tag{15}$$

Rewrite equation (15) as

$$\lambda^3 + a_2(\tau)\lambda^2 + a_1(\tau)\lambda + a_0(\tau) - [b_1\lambda + b_0]e^{-\lambda\tau} = 0, \tag{16}$$

where

$$a_2(\tau) = \mu + \delta + \tfrac{ksN}{\mu e^{\delta\tau}}, \quad a_1(\tau) = \mu\delta + (\mu+\delta)\tfrac{ksN}{\mu e^{\delta\tau}}, \quad a_0(\tau) = \mu\delta\tfrac{ksN}{\mu e^{\delta\tau}},$$
$$b_1 = \mu\delta, \qquad b_0 = d\mu\delta.$$

Clearly, under $\mathcal{R}_0 > 1$, $\lambda = 0$ is not a root of (16) since

$$a_0(\tau) - b_0 = \mu\delta\frac{ksN}{\mu e^{\delta\tau}} - d\mu\delta = \mu\delta d(\mathcal{R}_0 - 1) > 0.$$

For $\tau = 0$, Eq. (16) reduces to

$$h(\lambda) := \lambda^3 + a_2(0)\lambda^2 + [a_1(0) - b_1]\lambda + a_0(0) - b_0 = 0$$

to which, the Routh-Hurwitz Theorem [9] for cubic polynomials is applicable. Note that under $\mathcal{R}_0 > 1$,

$$a_2(0) = \tfrac{Nks}{\mu} + \delta + \mu > 0,$$
$$a_0(0) - b_0 = \delta ksN - d\mu\delta = d\mu\delta(\tfrac{ksN}{d\mu} - 1) = \mu\delta d\,(\mathcal{R}_0(0) - 1) > 0,$$
$$a_2(0)[a_1(0) - b_1] - [a_0(0) - b_0] = (\tfrac{Nks}{\mu})^2(\delta+\mu) + \tfrac{Nks}{\mu}(\delta^2 + \mu^2 + \delta\mu) + d\delta\mu > 0.$$

Hence all roots of (16) have negative real parts when $\tau = 0$. Note that a root of (16) depends continuously on τ (see [3]). Notice also that the assumption (ii) of [4] holds and this ensures that $Re(\lambda) < +\infty$ for any root λ of (16). Therefore, as delay τ increases, a root of (16) can only enter the right-half of the complex plane by crossing the imaginary axis. Let $\lambda = iw$ with $w \geq 0$ be a purely imaginary root of (16). Then,

$$-w^3 i - a_2(\tau)w^2 + a_1(\tau)wi + a_0(\tau) = [b_1 wi + b_0]\, e^{-\tau wi}.$$

Taking moduli in the above equation and grouping in terms of the powers of w gives

$$w^6 + [a_2(\tau) - 2a_1(\tau)]w^4 + [a_1^2(\tau) - 2a_0(\tau)a_2(\tau) - b_1^2]w^2 + a_0^2(\tau) - b_0^2 = 0. \tag{17}$$

Let $z = w^2$ and denote

$$p(\tau) = a_2(\tau) - 2a_1(\tau),$$
$$q(\tau) = a_1^2(\tau) - 2a_0(\tau)a_2(\tau) - b_1^2,$$
$$r(\tau) = a_0^2(\tau) - b_0^2.$$

Then, Eq. (17) becomes

$$H(z) := z^3 + p(\tau)z^2 + q(\tau)z + r(\tau) = 0. \tag{18}$$

Straightforward calculations shows that

$$\begin{aligned} p(\tau) &= \delta^2 + \mu^2 + (\tfrac{ksN}{\mu e^{\delta\tau}})^2 > 0, \\ q(\tau) &= (\delta^2 + \mu^2)(\tfrac{ksN}{\mu e^{\delta\tau}})^2 > 0, \\ r(\tau) &= (\tfrac{ksN}{e^{\delta\tau}} + d\mu)d\mu(\mathcal{R}_0 - 1)\delta^2 > 0 \quad \text{under} \quad \mathcal{R}_0 > 1. \end{aligned}$$

Thus the function $H(z)$ is monotonically increasing in $z \in [0, \infty)$ with $H(0) = r(\tau) > 0$ and hence (18) has no real non-negative root. This implies that no root can cross the imaginary axis as τ increases, ensuring that under $\mathcal{R}_0 > 1$ all roots of (15) have negative real parts for all $\tau \geq 0$.

Summarizing the above, we have obtained the following

Theorem 3.3. *Assume $\mathcal{R}_0 > 1$. If $\mathcal{R}_1 < 1$ (equivalently $\mathcal{R}_0 < 1 + KN\delta b/dc\mu$), then the CTL-inactivated infection equilibrium E_1 is asymptotically stable; if $\mathcal{R}_1 > 1$ (equivalently $\mathcal{R}_0 > 1 + KN\delta b/dc\mu$), then E_1 becomes unstable and there occurs the interior equilibrium E_2.*

3.3. **Stability of the CTL-activated infection equilibrium E_2.** In this subsection, we consider the case $\mathcal{R}_1 > 1$ (equivalently $\mathcal{R}_0 > 1 + k\delta bN/dc\mu$) and discuss the stability of the CTL-activated infection equilibrium $E_2 = (\bar{x}, \bar{y}, \bar{v}, \bar{z})$. To this end, we linearize (5) at E_2 to obtain

$$\begin{aligned} \frac{dx(t)}{dt} &= -(d + k\bar{v})x(t) - k\bar{x}v(t), \\ \frac{dy(t)}{dt} &= ke^{-\delta\tau}\bar{v}x(t-\tau) + ke^{-\delta\tau}\bar{x}v(t-\tau) - (\delta + p\bar{z})y(t) - p\bar{y}z(t), \\ \frac{dv(t)}{dt} &= N\delta y(t) - \mu v(t), \\ \frac{dz(t)}{dt} &= c\bar{z}y(t) + (c\bar{y} - b)z(t). \end{aligned} \tag{19}$$

The characteristic equation of (19) is given by $|\lambda I - J| = 0$, where

$$J = \begin{pmatrix} -d - k\bar{v} & 0 & -k\bar{x} & 0 \\ k\bar{v}e^{-\delta\tau}e^{-\lambda\tau} & -\delta - p\bar{z} & k\bar{x}e^{-\delta\tau}e^{-\lambda\tau} & -p\bar{y} \\ 0 & \delta N & -\mu & 0 \\ 0 & c\bar{z} & 0 & c\bar{y} - b \end{pmatrix}.$$

At E_2, we have $c\bar{y} - b = 0$, and $k\bar{x} = \frac{\mu}{\delta N e^{-\delta\tau}}(\delta + p\bar{z})$. Let $k' = k\bar{v}, u = d + k' > k'$ and $v = \delta + p\bar{z}$. Then the characteristic equation of system (5) at E_2 can be calculated as

$$\begin{aligned} \lambda^4 + \left[u + (\mu + v)\right]\lambda^3 + \left[u(\mu + v) + \mu v + pc\bar{y}\bar{z}\right]\lambda^2 + \left[u\mu v + pc\bar{y}\bar{z}(u + \mu)\right]\lambda \\ + pc\bar{y}\bar{z}\mu u - \mu v\left[\lambda^2 + (u - k')\lambda\right]e^{-\tau\lambda} = 0. \end{aligned} \tag{20}$$

When $\tau = 0$, E_2 has been proved in [11, 13] to be asymptotically stable, implying that all roots of (20) with $\tau = 0$ have negative real parts.

Next, we show that E_2 is also asymptotically stable for small $\tau > 0$. Rewrite equation (20) as

$$D(\lambda) = \lambda^4 + A_3\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 - [B_2\lambda^2 + B_1\lambda]e^{-\tau\lambda} = 0, \tag{21}$$

where

$$\begin{aligned}
A_3 &= A_3(\tau) = u + \mu + \delta\mathcal{R}_1,\\
A_2 &= A_2(\tau) = (\mu + \delta\mathcal{R}_1)u + \mu\delta\mathcal{R}_1 + \delta b(\mathcal{R}_1 - 1),\\
A_1 &= A_1(\tau) = \delta\mathcal{R}_1\mu u + b\delta(\mathcal{R}_1 - 1)u + b\delta(\mathcal{R}_1 - 1)\mu,\\
A_0 &= A_0(\tau) = \mu b\delta(\mathcal{R}_1 - 1)u,\\
B_2 &= B_2(\tau) = \mu\delta\mathcal{R}_1,\\
B_1 &= B_2(\tau) = d\mu\delta\mathcal{R}_1.
\end{aligned}$$

Since the characteristic equation (21) is a transcendental equation of degree four, the discussion of the distributions of its roots becomes harder. At least, excluding crossing of its roots over the the pure imaginary axis in the complex plane (as was done to (10) and (15) in subsections 3.1 and 3.2) is very challenging, if not impossible. In what follows, we choose to apply the theory developed in [20] to obtain conditions for the stability of E_2. To this end, we first introduce some notations corresponding to Corollary 2.38 in [20].

For the characteristic function $D(\lambda)$ defined by (21), let $R(\omega)$ and $S(\omega)$ be, respectively, the real and pure imaginary parts of $D(i\omega)$, i.e.,

$$R(\omega) = ReD(i\omega) = \omega^4 - A_2\omega^2 + A_0 + B_2\omega^2\cos\omega\tau - B_1\omega\sin\omega\tau,$$

and

$$S(\omega) = ImD(i\omega) = -A_3\omega^3 + A_1\omega - B_1\omega\cos\omega\tau - B_2\omega^2\sin\omega\tau.$$

Then, it is easy to see that

$$R^-(\omega) \le R(\omega) \le R^+(\omega), \quad \omega \in [0, +\infty),$$

and

$$S^-(\omega) \le S(\omega) \le S^+(\omega), \quad \omega \in [0, +\infty),$$

where

$$\begin{aligned}
R^-(\omega) &= \omega^4 - (A_2 + B_2 + B_1\tau)\omega^2 + A_0,\\
R^+(\omega) &= \omega^4 - (A_2 - B_2 - B_1\tau)\omega^2 + A_0,\\
S^-(\omega) &= \omega(A_1 - B_1 - A_3\omega^2 - B_2\omega^2\tau),\\
S^+(\omega) &= \omega(A_1 + B_1 - A_3\omega^2 + B_2\omega^2\tau).
\end{aligned}$$

Note that when

$$\tau < \bar{\tau} = \min\left\{\frac{1}{\mu}, \frac{1}{\delta}\ln\frac{kscN}{c\mu d + k\delta bN}\right\}, \tag{22}$$

we have

$$A_2 - B_2 - B_1\tau = \mu d + (\mu + \delta\mathcal{R}_1)k' + \delta b(\mathcal{R}_1 - 1) + \delta\mathcal{R}_1 d(1 - \mu\tau) > 0$$

and

$$\begin{aligned}
&(A_2 - B_2 - B_1\tau)^2 - 4A_0\\
&= [(\mu + \delta\mathcal{R}_1)u + \delta b(\mathcal{R}_1 - 1) - d\mu\delta\mathcal{R}_1\tau]^2 - 4\mu b\delta(\mathcal{R}_1 - 1)u\\
&\ge 2\delta[d(1 - \tau\mu) + k'][\mu\mathcal{R}_1 u + \mathcal{R}_1 b\delta(\mathcal{R}_1 - 1)] > 0.
\end{aligned}$$

Hence, $R^+(\omega)$ has two real positive zeros ρ_1^+ and ρ_2^+, where

$$\begin{aligned}
(\rho_1^+)^2 &= \frac{(A_2 - B_2 - B_1\tau) + \sqrt{(A_2 - B_2 - B_1\tau)^2 - 4A_0}}{2}\\
(\rho_2^+)^2 &= \frac{(A_2 - B_2 - B_1\tau) - \sqrt{(A_2 - B_2 - B_1\tau)^2 - 4A_0}}{2}
\end{aligned} \tag{23}$$

Clearly, $\rho_2^+ < \rho_1^+$. Similarly, if $\tau < \bar{\tau}$, we can show that $R^-(\omega)$ has two real positive zeros ρ_2^- and ρ_1^-, where

$$\left(\rho_1^-\right)^2 = \frac{(A_2+B_2+B_1\tau)+\sqrt{(A_2+B_2+B_1\tau)^2-4A_0}}{2}$$

$$\left(\rho_2^-\right)^2 = \frac{(A_2+B_2+B_1\tau)-\sqrt{A_2+B_2+B_1\tau)^2-4A_0}}{2}$$

and $\rho_2^- < \rho_1^-$. Thus, under (22), both $R^-(\omega)$ and $R^+(\omega)$ have exactly the same number (two) of real zeros. It is also easy to verify the following:

$$I_{R2} = [\min(\rho_2^-, \rho_2^+), \max(\rho_2^-, \rho_2^+)] = [\rho_2^-, \rho_2^+],$$

$$I_{R1} = [\min(\rho_1^-, \rho_1^+), \max(\rho_1^-, \rho_1^+)] = [\rho_1^+, \rho_1^-].$$

Hence, the intervals I_{R2} and I_{R1} are disjoint.

Furthermore, when $\tau < \bar{\tau}$, we have

$$A_3 - B_2\tau = u + \mu + \delta\mathcal{R}_1(1 - \mu\tau) > 0$$

and

$$A_1 - B_1 = \delta\mathcal{R}_1\mu k' + b\delta(\mathcal{R}_1 - 1)u + b\delta(\mathcal{R}_1 - 1)\mu > 0.$$

Hence, $S^+(\omega)$ only has one positive zero $\eta^+ = \sqrt{\frac{A_1+B_1}{A_3-B_2\tau}}$, and $S^-(\omega)$ also only has one positive zero $\eta^- = \sqrt{\frac{A_1-B_1}{A_3+B_2\tau}}$, with $\eta^- < \eta^+$ if $\tau < \bar{\tau}$.

Combining the above, we see that Corollary 2.38 in [20] is applicable, provided that one can verify the following two conditions

: (i) $R^-(0) > 0$;
: (ii) $S^-(\omega) > 0$ for $\omega \in I_{R2}$.

Obviously, $R^-(0) = A_0 = \mu b\delta(\mathcal{R}_1 - 1)u > 0$ (since $\mathcal{R}_1 > 1$). Moreover, $S^-(\omega) = \omega(A_1 - B_1 - A_3\omega^2 - B_2\omega^2\tau) > 0$ when $\omega \in (0, \eta^-)$. Note that $I_{R2} = [\rho_2^-, \rho_2^+]$. Thus, if $\rho_2^+ \le \eta^-$, then $S^-(\omega) > 0$ for $\omega \in I_{R2}$. From (23) and the formula for η^-, we know that $\rho_2^+ \le \eta^-$ is equivalent to $\Delta > 0$, where

$$\Delta = \Delta(\tau) = (A_1 - B_1)(A_3 + B_2\tau)(A_2 - B_2 - B_1\tau) - (A_1 - B_1)^2 - A_0(A_3 + B_2\tau)^2.$$

Therefore, by Corollary 2.38 in [20], we have established the following

Theorem 3.4. *Assume $\mathcal{R}_1 > 1$ (or equivalently $\mathcal{R}_0 > 1 + kN\delta b/dc\mu$) and (22)(i.e., $\tau < \bar{\tau}$) hold. If $\Delta(\tau) > 0$, then E_2 is locally asymptotically stable.*

4. **Numerical simulations.** In the conditions of Theorem 3.4, (22) is an explicit one for τ, but $\Delta(\tau) > 0$ is an implicit inequality with respect to τ. In order to illustrate feasibility of the results of Theorem 3.4, we perform some numerical simulations by using the software Matlab.

Consider system (5) with $s = 5, d = 0.03, k = 0.0014453, \delta = 0.32, N = 480, \mu = 1.8, p = 0.05, c = 0.2, b = 0.3$. For the parameters chosen, $\mathcal{R}_1 = 7.167$, $\Delta = 4.452 > 0$ when $\tau = 0.5$. Numeric simulations confirm that the CTL-activated infection equilibrium E_2 is asymptotically stable. See Figure 1 .

Also in Theorem 3.4, $\Delta(\tau) > 0$ is a sufficient condition needed to ensure that the condition (ii) is satisfied so that Corollary 2.38 can be applied. Our numeric simulations show that even if $\Delta(\tau) < 0$, E_2 may still be asymptotically stable, as is shown in Figure 2, where the parameters are set to $\tau = 0.3, s = 5, d = 0.03, k = 0.001, \delta = 0.32, N = 50, \mu = 3, p = 0.05, c = 0.2, b = 0.3$ leading to

$\bar{\tau} = 0.333$, $\mathcal{R}_1 = 1 + 0.267$, and $\Delta = -0.0087657 < 0$. We conjecture that the stability of E_2 is indeed implied by the condition (22).

5. **Conclusions.** We have studied a HIV-1 infection model with cell-mediated immune response and intracellular delay, that is, model (5). By combining the analysis of the characteristic equation and the Lyapunov-LaSalle method, we have proved that the infection-free equilibrium E_0, corresponding to the absence of virus, is globally asymptotically stable when the basic reproduction number $\mathcal{R}_0 < 1$. In this case the virus is unable to maintain the infection and will go extinct (the uninfected cell population will converge to the value $\frac{s}{d}$). When $\mathcal{R}_0 > 1$, E_0 becomes unstable and there occurs the CTL-inactivated infection equilibrium E_1. The stability of E_1 depends on how much $\mathcal{R}_0$ is larger than 1: when $R_0 \in (1, 1 + kN\delta b/cd\mu)$, E_1 is asymptotically stable; when $\mathcal{R}_0 > 1 + kN\delta b/cd\mu$, E_1 becomes unstable and there occurs the third biologically meaningful equilibrium, that is, the CTL-activated infection equilibrium E_2. We have proved and numerically confirmed the stability of E_2 under additional conditions (22) and $\Delta(\tau) > 0$. For the case $\Delta(\tau) < 0$ under (22), we are unable to make a conclusion, but numeric simulations have shown the possibility that E_2 may still be stable.

From the theoretical and numeric results summarized above, we see that the basic reproduction number $\mathcal{R}_0$ determines the dynamics of the model. Considering $\mathcal{R}_0 = \mathcal{R}_0(\tau) = \frac{ksN}{d\mu} e^{-\delta\tau}$ as a function of τ, we see that it is decreasing in τ with $\mathcal{R}_0(\infty) = 0$. An implication of this observation is that the intracellular delay τ plays a positive role in preventing the virus, because with all other parameters fixed, larger τ can bring $\mathcal{R}_0$ to a level lower than 1 (regardless of either $\mathcal{R}_0(0) < 1$ or $\mathcal{R}_0(0) > 1$), making the infection free equilibrium globally asymptotically stable.

We point out that $\mathcal{R}_0$ is independent of the CTLs related parameters b, c and p, meaning that CTLs does not help eliminate the virus. However, the activation of CTLs does help reduce the virus load and increase the healthy cell population, the latter being crucial because when the population of healthy CD_4^+ cells drops below certain level (e.g.,[18]), an HIV carrying person becomes an AIDS patient. This can be seen by comparing the virus load components and the healthy cell population components in the immune-inactivated infection equilibrium $E_1 = (x_1, y_1, v_1, 0)$ and the immune-activated infection equilibrium $E_2 = (\bar{x}, \bar{y}, \bar{v}, \bar{z})$: under the condition $\mathcal{R}_0 > 1 + kN\delta b/dc\mu$, simple calculations show that

$$v_1 = \frac{sN}{\mu e^{\delta\tau}} - \frac{d}{k} > \bar{v} = \frac{N\delta b}{c\mu}$$

and

$$x_1 = \frac{\mu e^{\delta\tau}}{Nk} < \bar{x} = \frac{sc\mu}{c\mu d + kN\delta b}.$$

Notice that v_1 and x_1 are independent of c and b, while $\bar{x}$ is increasing in c and decreasing in b, and $\bar{v}$ is decreasing in c and increasing in b. These dependence and independence explicitly explain, both qualitatively and quantitatively, the positive role of CTLs in maintaining the level of the healthy cells as well as in controlling the load of HIV virus.

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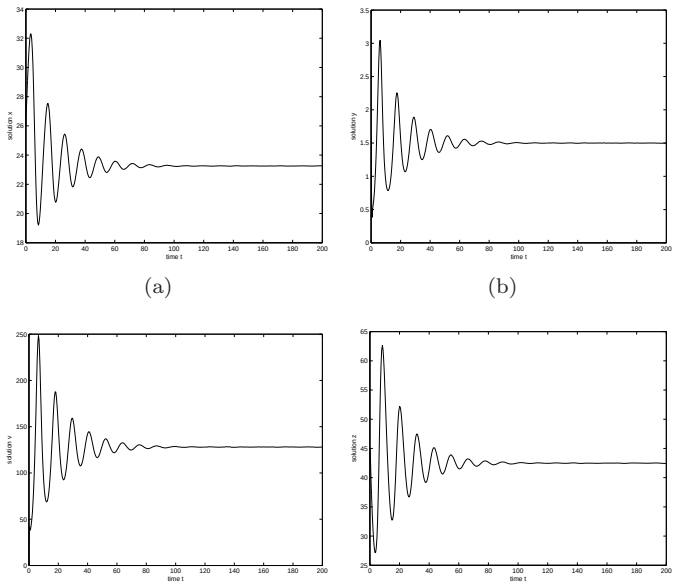

(a) (b)

(c) (d)

FIGURE 1. The interior equilibrium E_2 is asymptotically stable when (22) holds and $\Delta(\tau) > 0$, where delay $\tau = 0.5, s = 5, d = 0.03, k = 0.0014453, \delta = 0.32, N = 480, \mu = 1.8, p = 0.05, c = 0.2, b = 0.3$ and $\Delta = 4.452 > 0$, with (a) for $x(t)$; (b) for $y(t)$; (c) for $v(t)$ and (d) for $z(t)$.

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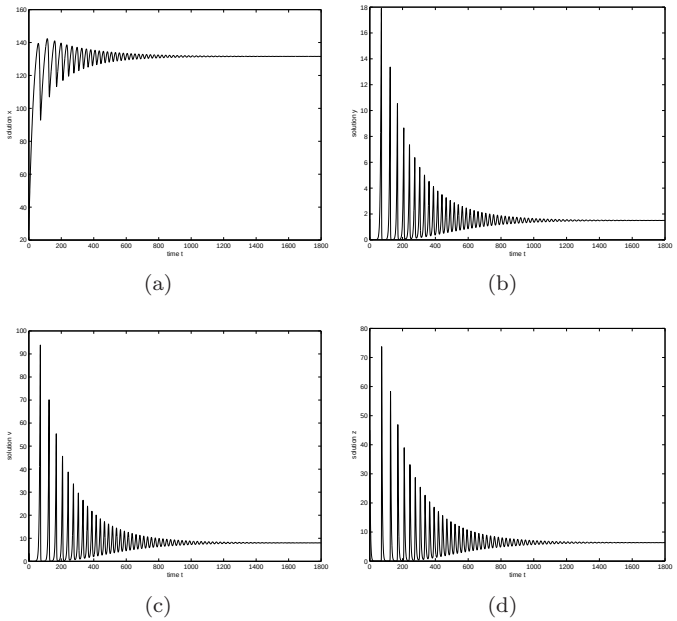

FIGURE 2. The interior equilibrium E_2 is asymptotically stable when (22) holds but $\Delta(\tau) > 0$ does not hold, where $\tau = 0.3, s = 5, d = 0.03, k = 0.001, \delta = 0.32, N = 50, \mu = 3, p = 0.05, c = 0.2, b = 0.3$ and $\Delta = -0.0087657 < 0$, with (a) for $x(t)$; (b) for $y(t)$; (c) for $v(t)$ and (d) for $z(t)$.

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