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Impact of delays in cell infection and virus production on HIV-1 dynamics

HUIYAN ZHU
School of Mathematics and Physics, Nanhua University, Hengyang, Hunan 421001, People's Republic of China

AND

XINGFU ZOU†
Department of Applied Mathematics, University of Western Ontario, London, Ontario N6A 5B7, Canada

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Analysed is a mathematical model for HIV-1 infection with two delays accounting, respectively, for (i) a latent period between the time target cells are contacted by the virus particles and the time the virions enter the cells and (ii) a virus production period for new virions to be produced within and released from the infected cells. For this model, the basic reproduction number $\mathcal{R}_0$ is identified and its threshold property is discussed: the uninfected steady state is proved to be globally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. In the latter case, an infected steady state occurs and is proved to be locally asymptotically stable. The formula for $\mathcal{R}_0$ shows that increasing either of the two delays will decrease $\mathcal{R}_0$. This may suggest a new direction for new drugs—drugs that can prolong the latent period and/or slow down the virus production process.

Keywords: HIV-1; cells; virus; delays; stability.

1. Introduction

In the last decade or so, it has been realized that mathematical modelling can provide valuable insight into HIV-1 pathogenesis. By using differential equations to quantitatively model the dynamics of the HIV-1 virus, target cells (infected and uninfected) and even possibly the immune responses, researchers have gained much knowledge about the mechanism of the interactions of these components in the immune system and have thereby enhanced the progress in understanding the HIV-1 infection (see Culshaw *et al.*, 2003; Herz *et al.*, 1996; Nowak & May, 2000; Perelson & Nelson, 1999; Perelson *et al.*, 1996, 1993). Such understanding may offer guidance for developing new drugs and for designing optimal combination of therapies available (see, e.g. Nelson *et al.*, 2001, 2000; Nelson & Perelson, 2002; Kepler & Perelson, 1998, and the references therein).

Most existing mathematical models for HIV infection are by systems of ordinary differential equations (ODEs) (see, e.g. Nowak & May, 2000; Perelson & Nelson, 1999). A standard and classic one of

†Email: xzou@uwo.ca

this type is the following ODE system:

$$\begin{cases} \frac{dT(t)}{dt} = s - \mu_T T(t) - kV(t)T(t), \\ \frac{dT^*(t)}{dt} = kV(t)T(t) - \mu T^*(t), \\ \frac{dV(t)}{dt} = \mu N T^*(t) - cV(t), \end{cases} \tag{1.1}$$

where $T(t)$, $T^*(t)$ and $V(t)$ are the densities of uninfected target cells, infected target cells and the free virus, respectively. The constant parameters in the equations are explained as below. The positive constant s is the rate at which new target cells are generated, μ_T is their specific death rate and k is the constant rate at which a T-cell is contacted by the virus. It is assumed that once cells are infected, they may die instantaneously at rate μ due to the action of either the virus or the immune system, and in the mean time, they each produces N new virus particles during their life, which on average has length $\frac{1}{\mu}$. Thus, on average, virus is instantaneously produced at rate μN. Alternatively, one can view virus as being produced in a burst of N particles when an infected cell dies via lysis, thus producing virus at rate $N\mu$. Lastly, virus particles are cleared from the system at rate c. There are other similar versions of this model in which target cells proliferate logistically or virus also disappears by infecting cells (Perelson *et al.*, 1993; Kepler & Perelson, 1998). Other variations can also be considered in which virus spreads by cell-to-cell infection (Culshaw *et al.*, 2003), infected cells can proliferate or an explicit immune response is followed. Here, we only consider the variants of (1.1). An underlying assumption in such an ODE model is that infection of cells by virions is instantaneous and the production of new virions by infected cells is also instantaneous.

However, in the real situation, there may be a lag between the time target cells are contacted by the virus particles and the time the contacted cells become actively affected meaning that the contacting virions enter cells. This can be explained by the initial (or eclipse) phase of the virus life cycle, which include all stages from viral attachment until the time that the host cell contains the infectious viral particles in its cytoplasm. Attachment is a specific binding between the two sets of proteins (also known as anti-receptors) called gp120 and gp41 on the surface of the HIV and the two sets of proteins (known as receptors), i.e. CD4 receptor and a beta-chemokine receptor (either CCR5 or CXCR4), on the surface of the T-cell. After the attachment is completed, the virus seeks to penetrate into the cell via fusion. Penetration allows the genetic core of virus (called the nucleocapsid) to be injected directly into the cell's cytoplasm. gp120 actually contains three sugar-coated proteins (glycoproteins) and once gp120 attaches itself to CD4 receptor, these three proteins spread apart, allowing the gp41 protein, which is normally hidden by the gp120 proteins, to become exposed and bind to the chemokine receptor. Once this has occurred, the viral envelope and the cell membrane are brought into direct contact and essentially melt into each other, completing the penetration. The above-stated processes take time. Realizing this time lag, Kirschner *et al.* (1997) divided infected cells into two classes: inactively infected cells and actively infected cells, and the 3D ODE system of the form (1.1) was accordingly modified into a 4D ODE system. This is equivalent to assuming that the probability that a cell still remains inactively infected t time units after being contacted by the virus obeys an exponentially decay probability density function.

In addition to the above time lag, there is also a period between the time the virus has penetrated into a cell and the time the new virions are created within the cell and are released from the cell. This is because the virus production process within a cell consists of several stages as well: (i) uncoating of viral RNA, (ii) reverse transcription of viral RNA into DNA, (iii) transport of the newly made DNA into the nucleus, (vi) integration of the viral DNA into the chromosome, (v) production of viral RNA and

protein and finally (vi) creation of new virus from these newly synthesized RNA molecules and proteins; see Mittler *et al.* (1998) for details.

Mittler *et al.* (1998) combined the aforementioned two lags into a single one and used a gamma probability distribution function to describe all the above multiple stages. Note that not every contacting viral particle can get through the eclipse phase, meaning that viral attachment is sometimes reversible. That is, some virions may not attach to the cell successfully. This happens in particular when drugs (or vaccines) called attachment inhibitors and/or fusion inhibitors such as T-20 (enfuvirtide, Fuzeon) are applied. Therefore, before entering the cell, a contacting virion should still be considered a free virion because it may fail to enter the cell and may contact other cells. Thus, in modelling the HIV-1 infection dynamics, the latent period and the virus production period within cells should be treated differently. Recently, in studying the efficacy of a protease inhibitor drug, Nelson *et al.* (2000) incorporated into (1.1) a discrete delay to account for the lag between inactively infected and actively infected. Assuming a constant uninfected T-cell density and an imperfect drug efficacy, their analysis to the delayed model shows that the delay does affect the rate of decline in plasma virus concentration. As a continuation of Nelson *et al.* (2000) and in studying the efficacy of 'two drugs'—the protease inhibitor and the reverse transcriptase inhibitor—Nelson & Perelson (2002) further generalized the model in Nelson *et al.* (2000) by including two delays for the aforementioned 'two periods'. The general model in Nelson & Perelson (2002) is given by the following system of differential–integral equations:

$$\begin{cases} \frac{\mathrm{d}T(t)}{\mathrm{d}t} = s - \mu_T T(t) - (1-n_{\mathrm{rt}})kV(t)T(t), \\ \frac{\mathrm{d}T^*(t)}{\mathrm{d}t} = (1-n_{\mathrm{rt}})k\int_0^\infty f_1(\xi)V(t-\xi)T(t-\xi)\mathrm{d}\xi - \mu T^*(t), \\ \frac{\mathrm{d}V(t)}{\mathrm{d}t} = (1-n_{\mathrm{p}})\mu N\int_0^\infty f_2(\xi)T^*(t-\xi)\mathrm{d}\xi - cV(t). \end{cases} \tag{1.2}$$

Here, the meanings of the variables and parameters appeared in (1.1) remain the same except that T^* now stands for the density of cells with 'integrated' HIV-1 DNA. The new parameters n_{p} and n_{rt} measure the efficacies of the protease inhibitor and the reverse transcriptase inhibitor, respectively. As mentioned in Nelson & Perelson (2002), the kernels $f_1(\xi)$ and $f_2(\xi)$ are the results of incorporating probability functions for the two processes and the death rate factors of the form $\mathrm{e}^{-\mu\tau}$. When 'only one discrete delay' is present in (1.2), i.e. either $f_1(\xi) = \mathrm{e}^{-\mu\tau}\delta(\xi-\tau_1)$ and $f_2(\xi) = \delta(\xi-0)$ or $f_1(\xi) = \delta(\xi-0)$ and $f_2(\xi) = \mathrm{e}^{-\mu\tau}\delta(\xi-\tau_2)$, where $\delta(\cdot)$ is the Dirac delta function, by analysing the characteristic equations, Nelson & Perelson (2002) were able to obtain some local stability results showing the impact of the delay on the virus dynamics.

When both delays are present in (1.2), the analysis of the model becomes harder and the dynamics of (1.2) in such a general case still remains an open problem. The purpose of this paper is to analyse (1.2) when there are two delays. In order to avoid the key ideas to be hidden behind too complicated analysis due to the general form of the two general probability distribution functions f_1 and f_2, we only consider two 'discrete delays'. In addition, we prefer to retrieve the death factors in $f_1(\xi)$ and $f_2(\xi)$. In other words, we take

$$f_1(\xi) = \mathrm{e}^{-\mu\xi}\delta(\xi-\tau_1) \quad \text{and} \quad f_2(\xi) = \mathrm{e}^{-\mu_2\xi}\delta(\xi-\tau_2).$$

Then, (1.2) reduces to

$$\begin{cases} \frac{\mathrm{d}T(t)}{\mathrm{d}t} = s - \mu_T T(t) - (1-n_{\mathrm{rt}})kV(t)T(t), \\ \frac{\mathrm{d}T^*(t)}{\mathrm{d}t} = (1-n_{\mathrm{rt}})k\,\mathrm{e}^{-\mu\tau_1}V(t-\tau_1)T(t-\tau_1) - \mu T^*(t), \\ \frac{\mathrm{d}V(t)}{\mathrm{d}t} = (1-n_{\mathrm{p}})\mu N\,\mathrm{e}^{-\mu_2\tau_2}T^*(t-\tau_2) - cV(t). \end{cases} \tag{1.3}$$

Here, τ_1 can be regarded as the average time for a viral particle to go through the eclipse phase (or average latent period) and τ_2 may be treated as the average time between the entry of a virion into a cell and the creation and release of new virions from this cell. Realistically, μ_2 may differ from μ. For convenience of notations, we set

$$\begin{aligned} \bar{k} &= (1 - n_{\mathrm{rt}})k, \\ \bar{N} &= (1 - n_{\mathrm{p}})N, \end{aligned} \tag{1.4}$$

which further reduces (1.3) to the following system:

$$\begin{cases} \frac{\mathrm{d}T(t)}{\mathrm{d}t} = s - \mu_T T(t) - \bar{k}V(t)T(t), \\ \frac{\mathrm{d}T^*(t)}{\mathrm{d}t} = \bar{k}\,\mathrm{e}^{-\mu\tau_1}V(t-\tau_1)T(t-\tau_1) - \mu T^*(t), \\ \frac{\mathrm{d}V(t)}{\mathrm{d}t} = \mu\bar{N}\,\mathrm{e}^{-\mu_2\tau_2}T^*(t-\tau_2) - cV(t). \end{cases} \tag{1.5}$$

In the rest of this paper, we will analyse system (1.5). In Section 2, we address the well-posedness of the model by proving the positivity and boundedness of solutions. We also identify the basic reproduction number $\mathcal{R}_0$ which determines whether or not there is an infected equilibrium. Section 3 is dedicated to the stability of the infection-free equilibrium. In addition to local stability under the condition $\mathcal{R}_0 < 1$, which is obtained by analysing the characteristic equation, we also obtain the global stability by employing the fluctuation lemma and the asymptotically autonomous system theory, the latter being in contrast to the previous work (Nelson *et al.*, 2000; Nelson & Perelson, 2002). In Section 4, we show that under the condition $\mathcal{R}_0 > 1$, the infected equilibrium is asymptotically (locally) stable. Simulations are provided in Section 5 to confirm our analytical theory. Conclusion and discussion will be given in Section 6.

2. Well-posedness and basic reproduction number

Let $X = C([-\max(\tau_1, \tau_2), 0]; R^3)$ be the Banach space of continuous functions from $[-\max(\tau_1, \tau_2), 0]$ to R^3 equipped with the sup-norm. It is biologically reasonable to consider the following initial conditions for (1.5):

$$\begin{cases} (T(\theta), T^*(\theta), V(\theta)) \in X, \\ T(\theta) \geqslant 0, T^*(\theta) \geqslant 0, V(\theta) \geqslant 0, \quad \theta \in [-\max(\tau_1, \tau_2), 0]. \end{cases} \tag{2.1}$$

By the fundamental theory of functional differential equations (see, e.g. Hale & Verduyn Lunel, 1993), we know that there is a unique solution $(T(t), T^*(t), V(t))$ to system (1.5–2.1). The following theorem establishes the non-negativity and boundedness of solutions to (1.5–2.1).

THEOREM 2.1 Let $(T(t), T^*(t), V(t))$ be any solution of system (1.5–2.1). Then, we have the following:

(i) $T(t) > 0$, $T^*(t) \geqslant 0$ and $V(t) \geqslant 0$ for $t > 0$.

(ii) There exists an $M > 0$ such that $T(t) \leqslant M$, $T^*(t) \leqslant M$, $V(t) \leqslant M$ for sufficiently large time t.

Proof. From the first equation in (1.5), it follows that

$$T(t) = T(0)\mathrm{e}^{-\int_0^t(\mu_T + \bar{k}V(\xi))\mathrm{d}\xi} + \int_0^t s\,\mathrm{e}^{-\int_\eta^t(\mu_T+\bar{k}V(\xi))\mathrm{d}\xi}\,\mathrm{d}\eta,$$

which indicates that $T(t) > 0$ for all $t > 0$. Similarly, by the second and the third equations in (1.5), we have, respectively,

$$T^*(t) = T^*(0)\mathrm{e}^{-\mu t} + \int_0^t \bar{k}\,\mathrm{e}^{-\mu(t-\xi)}T(\xi-\tau_1)V(\xi-\tau_1)\mathrm{e}^{-\mu\tau_1}\,\mathrm{d}\xi$$

and

$$V(t) = V(0)\mathrm{e}^{-ct} + \int_0^t \bar{N}\mu\,\mathrm{e}^{-c(t-\xi)}T^*(\xi-\tau_2)\mathrm{e}^{-\mu_2\tau_2}\,\mathrm{d}\xi,$$

confirming $T^*(t) \geqslant 0, V(t) \geqslant 0$ for $t \in [0, \max\{\tau_1, \tau_2\}]$. By a recursive argument, we then obtain $T^*(t) \geqslant 0, V(t) \geqslant 0$ for all $t > 0$, proving (i).

To prove (ii), let

$$G(t) = \bar{N}\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}T(t) + \bar{N}\,\mathrm{e}^{-\mu_2\tau_2}T^*(t+\tau_1) + \frac{1}{2}V(t+\tau_1+\tau_2)$$

and denote $q = \min\{\mu_T, \mu/2, c\}$. Simple calculation leads to

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}G(t) &= \bar{N}\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}[s-\mu_T T(t)-\bar{k}V(t)T(t)] + \bar{N}\,\mathrm{e}^{-\mu_2\tau_2}[\bar{k}V(t)T(t)\mathrm{e}^{-\mu\tau_1}-\mu T^*(t+\tau_1)]\\ &\quad + \frac{1}{2}\bar{N}\mu T^*(t+\tau_1)\mathrm{e}^{-\mu_2\tau_2} - \frac{c}{2}V(t+\tau_1+\tau_2)\\ &= \bar{N}s\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2} - \mu_T\bar{N}\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}T(t) - \frac{\mu}{2}\bar{N}\,\mathrm{e}^{-\mu_2\tau_2}T^*(t+\tau_1) - \frac{c}{2}V(t+\tau_1+\tau_2)\\ &\leqslant \bar{N}s\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2} - qG(t),\end{aligned}$$

which shows that $G(t) < \frac{\bar{N}s\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}}{q} + 1$ for all large t. This in turn implies, by the non-negativity confirmed in (i), that $T(t)$, $T^*(t)$ and $V(t)$ are ultimately bounded by some positive constant M, completing the proof of the theorem. □

System (1.5) has the infection-free equilibrium $E_0 = (T_0, T_0^*, V_0) = (s/\mu_T, 0, 0)$. This is the only biologically meaningful equilibrium if

$$\mathcal{R}_0 \triangleq \bar{k}\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}\frac{s\bar{N}}{c\mu_T} < 1.$$

However, if $\mathcal{R}_0 > 1$, in addition to E_0, there is also an infected equilibrium

$$E_1 = (T_1, T_1^*, V_1) = \left(\frac{c\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}}{\bar{N}\bar{k}}, \frac{s}{\mu\,\mathrm{e}^{\mu\tau_1}} - \mathrm{e}^{\mu_2\tau_2}\frac{\mu_T c}{\mu\bar{N}\bar{k}}, \frac{s\bar{N}}{c\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}} - \frac{\mu_T}{\bar{k}}\right).$$

The parameter $\mathcal{R}_0$ can be rewritten as

$$\mathcal{R}_0 = \frac{s}{\mu_T}\cdot\frac{\bar{k}\,\mathrm{e}^{-\mu\tau_1}}{\mu}\cdot\frac{\bar{N}\mu\,\mathrm{e}^{-\mu_2\tau_2}}{c}, \tag{2.2}$$

with the first term being the average number of healthy cells available for infection, the second term giving the average number of cells that each virion infects, while the last term accounting for the average number of virions that an infected cell produces. Therefore, $\mathcal{R}_0$ is indeed the basic reproduction number.

3. Stability of the infection-free equilibrium

Let $r = \frac{\tau_2}{\tau_1}$. Then, system (1.5) can be reduced to the following one with dimensionless time $\frac{t}{\tau_1}$, which, for simplicity, we again denote by t:

$$\begin{cases} \frac{\mathrm{d}T(t)}{\mathrm{d}t} = \tau_1[s - \mu_T T(t) - \bar{k}V(t)T(t)], \\ \frac{\mathrm{d}T^*(t)}{\mathrm{d}t} = \tau_1[\bar{k}V(t-1)T(t-1)\mathrm{e}^{-\mu\tau_1} - \mu T^*(t)], \\ \frac{\mathrm{d}V(t)}{\mathrm{d}t} = \tau_1[\bar{N}\mu T^*(t-r)\mathrm{e}^{-\mu_2\tau_2} - cV(t)]. \end{cases} \tag{3.1}$$

The linearization of (3.1) at E_0 is

$$\begin{cases} \frac{\mathrm{d}T}{\mathrm{d}t} = \tau_1\big[- \mu_T T(t) - \frac{\bar{k}s}{\mu_T}V(t)\big], \\ \frac{\mathrm{d}T^*}{\mathrm{d}t} = \tau_1\big[\frac{\bar{k}s}{\mu_T}V(t-1)\mathrm{e}^{-\mu\tau_1} - \mu T^*(t)\big], \\ \frac{\mathrm{d}I}{\mathrm{d}t} = \tau_1[\bar{N}\mu T^*(t-r)\mathrm{e}^{-\mu_2\tau_2} - cV(t)], \end{cases} \tag{3.2}$$

from which we obtain the characteristic equation as below:

$$\left(\lambda + \mu_T\frac{\tau_2}{r}\right)\left[\left(\lambda + \mu\frac{\tau_2}{r}\right)\left(\lambda + c\frac{\tau_2}{r}\right) - \frac{s\bar{k}\bar{N}\mu}{\mu_T}\left(\frac{\tau_2}{r}\right)^2 \mathrm{e}^{-\mu\frac{\tau_2}{r}\left(r\frac{\mu_2}{\mu}+1\right)}\mathrm{e}^{-\lambda(r+1)}\right] = 0. \tag{3.3}$$

Letting

$$\tilde{\mu}_T = \mu_T\frac{\tau_2}{r}, \quad \tilde{\mu} = \mu\frac{\tau_2}{r}, \quad \tilde{c} = c\frac{\tau_2}{r}, \quad \tilde{s} = s\frac{\tau_2}{r}, \quad \tilde{k} = \bar{k}\frac{\tau_2}{r}, \quad \tilde{\tau} = r\frac{\mu_2}{\mu} + 1 \quad \text{and} \quad \tau = r + 1, \tag{3.4}$$

(3.3) can be rewritten as

$$(\lambda + \tilde{\mu}_T)\left[\lambda^2 + (\tilde{\mu} + \tilde{c})\lambda + \tilde{\mu}\tilde{c} - \bar{N}\frac{\tilde{k}\tilde{s}\tilde{\mu}}{\tilde{\mu}_T}\mathrm{e}^{-\tilde{\mu}\tilde{\tau}}\mathrm{e}^{-\lambda\tau}\right] = 0. \tag{3.5}$$

Hence, the stability of E_0 is totally determined by the roots of

$$\lambda^2 + (\tilde{\mu} + \tilde{c})\lambda + \tilde{\mu}\tilde{c} - \bar{N}\frac{\tilde{k}\tilde{s}\tilde{\mu}}{\tilde{\mu}_T}\mathrm{e}^{-\tilde{\mu}\tilde{\tau}}\mathrm{e}^{-\lambda\tau} = 0. \tag{3.6}$$

Note that when $\tau = 0$, (3.6) becomes the following quadratic equation:

$$\lambda^2 + (\tilde{\mu} + \tilde{c})\lambda + \tilde{\mu}\tilde{c} - \bar{N}\frac{\tilde{k}\tilde{s}\tilde{\mu}}{\tilde{\mu}_T}\mathrm{e}^{-\tilde{\mu}\tilde{\tau}} = 0, \tag{3.7}$$

whose roots all have negative real parts under the condition $\tilde{\mu}\tilde{c} - \bar{N}\tilde{k}\tilde{s}\tilde{\mu}\,\mathrm{e}^{-\tilde{\mu}\tilde{\tau}}/\tilde{\mu}_T > 0$, which is equivalent to $\mathcal{R}_0 < 1$. Note also that all roots of (3.6) depend continuously on τ (see Busenberg & Cooke, 1993), and when τ increases, roots can only possibly enter the right half plane by crossing the imaginary axis in the complex plane (see, e.g. Beretta & Kuang, 2002). Since $\lambda = 0$ is not a root of (3.6) when $\mathcal{R}_0 < 1$, the roots of (3.6) can cross the imaginary axis only through a pair of non-zero purely imaginary roots. Assume that $\lambda = \mathrm{i}w$ is a purely imaginary root of (3.6) with $w > 0$. Then,

$$-w^2 + \mathrm{i}w(\tilde{\mu} + \tilde{c}) + \tilde{\mu}\tilde{c} = \bar{N}\frac{\tilde{k}\tilde{s}\tilde{\mu}}{\tilde{\mu}_T}\mathrm{e}^{-\tilde{\mu}\tilde{\tau}}\mathrm{e}^{-\mathrm{i}w\tau}.$$

Rewriting the above equation and taking moduli give

$$|-w^2+\mathrm{i}w(\tilde{\mu}+\tilde{c})+\tilde{\mu}\tilde{c}| = \bar{N}\frac{\tilde{k}\tilde{s}\tilde{\mu}}{\tilde{\mu}_T}\mathrm{e}^{-\tilde{\mu}\tilde{\tau}}.$$

Letting $y = w^2$ yields

$$y^2+(\tilde{\mu}^2+\tilde{c}^2)y+\tilde{\mu}^2\tilde{c}^2-\left(\bar{N}\frac{\tilde{k}\tilde{s}\tilde{\mu}}{\tilde{\mu}_T}\mathrm{e}^{-\tilde{\mu}\tilde{\tau}}\right)^2 = 0, \tag{3.8}$$

which has no positive solution when $\mathcal{R}_0 < 1$. This is a contradiction, showing that all roots of (3.7) remain in the left half plane for all $\tau > 0$ as long as $\mathcal{R}_0 < 1$.

On the other hand, when $\mathcal{R}_0 > 1$, (3.6) has a positive root. This can be easily seen by looking at the properties of the two functions $f(\lambda) = \lambda^2+(\tilde{\mu}+\tilde{c})\lambda+\tilde{\mu}\tilde{c}$ and $g(\lambda) = \bar{N}\frac{\tilde{k}\tilde{s}\tilde{\mu}}{\tilde{\mu}_T}\mathrm{e}^{-\tilde{\mu}\tilde{\tau}}\,\mathrm{e}^{-\lambda\tau}$.

From the above analysis, we see that $\mathcal{R}_0 = 1$ plays a role of threshold: if $\mathcal{R}_0 < 1$, the infection-free equilibrium E_0 is locally asymptotically stable; if $\mathcal{R}_0 > 1$, the infection-free equilibrium E_0 is unstable. Indeed, we can show that if $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable. To prove this, we only need to show that E_0 is also globally attractive if $\mathcal{R}_0 < 1$.

Following the convention, we use the following notations: for a continuous and bounded function $f(t)$ defined on $[0,\infty)$,

$$f^\infty \triangleq \limsup_{t\to\infty} f(t) \quad \text{and} \quad f_\infty \triangleq \liminf_{t\to\infty} f(t).$$

Now, let $(T(t), T^*(t), V(T))$ be any solution of (1.5) and (2.1). By Theorem 2.1, we know

$$\begin{aligned} &0 \leqslant T_\infty \leqslant T^\infty < \infty,\\ &0 \leqslant T^*_\infty \leqslant T^{*\infty} < \infty,\\ &0 \leqslant V_\infty \leqslant V^\infty < \infty. \end{aligned} \tag{3.9}$$

By the fluctuation lemma (see, e.g. Hirsch *et al.*, 1985), there is a sequence t_n with $t_n \to \infty$ as $n \to \infty$ such that

$$T(t_n) \to T^\infty \quad \text{and} \quad T'(t_n) \to 0 \quad \text{as } n \to \infty.$$

Substituting the sequence $\{t_n\}$ into the first equation of (1.5) and taking limit give

$$\mu_T T^\infty \leqslant s. \tag{3.10}$$

Applying a similar argument to the second and third equations of (1.5), we have

$$\mu T^{*\infty} \leqslant \bar{k}\,\mathrm{e}^{-\mu\tau_1}V^\infty T^\infty \tag{3.11}$$

and

$$cV^\infty \leqslant \bar{N}\mu\,\mathrm{e}^{-\mu_2\tau_2}T^{*\infty}. \tag{3.12}$$

Combining with (3.10), (3.11) and (3.12), we obtain

$$cV^\infty \leqslant \bar{N}\mu\,\mathrm{e}^{-\mu_2\tau_2}T^{*\infty} \leqslant \bar{N}\bar{k}\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}V^\infty T^\infty \leqslant \frac{s\bar{N}\bar{k}\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}}{\mu_T}V^\infty.$$

Now, if $V^\infty > 0$, then the above inequality yields

$$c \leqslant \frac{s\bar{N}\bar{k}\,\mathrm{e}^{-\mu\tau_1-\mu_2\tau_2}}{\mu_T},$$

contradicting $R_0 < 1$. Therefore, $V^\infty = 0$, implying $\lim_{t\to\infty} V(t) = V^\infty = V_\infty = 0$ by (3.9). By (3.11), this in turn implies $T^{*\infty} = 0$, and hence $\lim_{t\to\infty} T^*(t) = T^{*\infty} = T_{*\infty} = 0$ by (3.9). Finally, applying the theory of asymptotically autonomous system (see, e.g. Castillo-Chavez & Thieme, 1995) to the first equation of (1.5), we conclude that $\lim_{t\to\infty} T(t) = s/\mu_T$.

Summarizing the above, we have proved the following theorem.

THEOREM 3.1 Let $\mathcal{R}_0$ be the basic reproduction number given by (2.2).

(i) If $\mathcal{R}_0 < 1$, then the infection-free equilibrium E_0 is globally asymptotically stable.

(ii) If $\mathcal{R}_0 > 1$, then the infection-free equilibrium E_0 is unstable.

4. Stability of the infected equilibrium

When $\mathcal{R}_0 > 1$, we know that E_0 becomes unstable and (1.5) also has an infected equilibrium E_1, in addition to E_0. In this section, we discuss the stability of this infected equilibrium. To this end, we find the linearization of (3.1) at E_1 as below:

$$\begin{cases} \frac{\mathrm{d}T}{\mathrm{d}t} = \tau_1[-(\mu_T + kV_1)T(t) - \bar{k}T_1V(t)], \\ \frac{\mathrm{d}T^*}{\mathrm{d}t} = \tau_1[\bar{k}V_1T(t-1)\mathrm{e}^{-\mu\tau_1} + kT_1V(t-1)\mathrm{e}^{-\mu\tau_1} - \mu T^*(t)], \\ \frac{\mathrm{d}I}{\mathrm{d}t} = \tau_1[\bar{N}\mu T^*(t-r)\mathrm{e}^{-\mu_2\tau_2} - cV(t)]. \end{cases} \tag{4.1}$$

The characteristic equation for (4.1) is

$$\left[\lambda + (\mu_T + \bar{k}V_1)\frac{\tau_2}{r}\right]\left(\lambda + \mu\frac{\tau_2}{r}\right)\left(\lambda + c\frac{\tau_2}{r}\right) - \bar{k}T_1\bar{N}\mu\left(\frac{\tau_2}{r}\right)^2\left(\lambda + \mu_T\frac{\tau_2}{r}\right)$$
$$\times\, \mathrm{e}^{-(\mu\tau_1+\mu_2\tau_2)}\,\mathrm{e}^{-\lambda(r+1)} = 0. \tag{4.2}$$

Using the expressions for $E_1 = (T_1, T_1^*, V_1)$ obtained in Section 2, (4.2) can be reduced to

$$\left(\lambda + \bar{N}\frac{\tilde{k}\tilde{s}}{\tilde{c}\,\mathrm{e}^{\tilde{\tau}\tilde{\mu}}}\right)(\lambda+\tilde{\mu})(\lambda+\tilde{c}) - (\lambda+\tilde{\mu}_T)\tilde{c}\tilde{\mu}\,\mathrm{e}^{-\lambda\tau} = 0, \tag{4.3}$$

where the re-scaling (3.4) of parameters has been preserved. Obviously, (4.3) is equivalent to

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 - (b_1\lambda + b_0)\mathrm{e}^{-\lambda\tau} = 0, \tag{4.4}$$

where

$$a_2 = \bar{N}\frac{\tilde{k}\tilde{s}}{\tilde{c}\,\mathrm{e}^{\tilde{\tau}\tilde{\mu}}} + \tilde{\mu} + \tilde{c},$$
$$a_1 = \tilde{\mu}\tilde{c} + \bar{N}\frac{\tilde{k}\tilde{s}}{\tilde{c}\,\mathrm{e}^{\tilde{\tau}\tilde{\mu}}}(\tilde{\mu} + \tilde{c}),$$

$$a_0 = \bar{N}\tilde{\mu}\frac{\tilde{k}\tilde{s}}{\mathrm{e}^{\tilde{\tau}\tilde{\mu}}},$$
$$b_1 = \tilde{\mu}\tilde{c},$$
$$b_0 = \tilde{\mu}\tilde{c}\tilde{\mu}_T.$$

We first prove that when $\tau = 0$, then all roots of (4.4) have negative real parts. Indeed, if $\tau = 0$, (4.4) can be written as

$$h(\lambda) := \lambda^3 + a_2\lambda^2 + (a_1 - b_1)\lambda + a_0 - b_0 = 0. \tag{4.5}$$

Note that if $R_0 > 1$,

$$a_2 = \bar{N}\frac{\tilde{k}\tilde{s}}{\tilde{c}\,\mathrm{e}^{\tilde{\tau}\tilde{\mu}}} + \tilde{\mu} + \tilde{c} > 0,$$

$$a_0 - b_0 = \bar{N}\tilde{\mu}\frac{\tilde{k}\tilde{s}}{\mathrm{e}^{\tilde{\tau}\tilde{\mu}}} - \tilde{\mu}\tilde{c}\tilde{\mu}_T = \tilde{\mu}\tilde{c}\tilde{\mu}_T(\mathcal{R}_0 - 1) > 0,$$

$$a_2(a_1 - b_1) - (a_0 - b_0) = \left(\bar{N}\frac{\tilde{k}\tilde{s}}{\tilde{c}\,\mathrm{e}^{\tilde{\tau}\tilde{\mu}}}\right)^2(\tilde{c} + \tilde{\mu}) + \bar{N}\frac{\tilde{k}\tilde{s}}{\tilde{c}\,\mathrm{e}^{\tilde{\tau}\tilde{\mu}}}(\tilde{\mu}^2 + \tilde{c}^2 + \tilde{\mu}\tilde{c}) + \tilde{\mu}\tilde{c}\tilde{\mu}_T > 0.$$

By the Routh–Hurwitz theorem (see, e.g. Gantmacher, 1959), all roots of $h(\lambda)$ have negative real parts, i.e. all roots of (4.5) have negative real parts.

Note that all roots of (4.4) depend continuously on τ (see Busenberg & Cooke, 1993), and as τ increases, a root of (4.4) may enter the right half plane only by crossing the imaginary axis (see, e.g. Beretta & Kuang, 2002). Clearly, if $\mathcal{R}_0 > 1$, then $\lambda = 0$ is not a root of (4.4) since $a_0 - b_0 > 0$. Thus, as $\tau > 0$ increases, roots of (4.4) may cross the imaginary axis only through a pair of non-zero purely imaginary roots. Assume that $\lambda = \mathrm{i}w$, with $w > 0$, is a purely imaginary root of (4.4). Then,

$$-w^3\mathrm{i} - a_2w^2 + a_1w\mathrm{i} + a_0 = (b_1w\mathrm{i} + b_0)\mathrm{e}^{-\tau w\mathrm{i}}. \tag{4.6}$$

Grouping the real part and pure imaginary part of (4.6) and taking moduli give

$$w^6 + (a_2^2 - 2a_1)w^4 + (a_1^2 - 2a_0a_2 - b_1^2)w^2 + a_0^2 - b_0^2 = 0. \tag{4.7}$$

Thus, $z = w^2$ satisfies the following cubic equation:

$$H(z) \triangleq z^3 + pz^2 + qz + r = 0, \tag{4.8}$$

where

$$p = a_2^2 - 2a_1,$$
$$q = a_1^2 - 2a_0a_2 - b_1^2,$$
$$r = a_0^2 - b_0^2. \tag{4.9}$$

Simplifying (4.9), we can easily verify that when $R_0 > 1$,

$$p = \tilde{\mu}_T^2R_0^2 + \tilde{\mu}^2 + \tilde{c}^2 > 0,$$
$$q = \tilde{\mu}_T^2\mathcal{R}_0^2(\tilde{c}^2 + \tilde{\mu}^2) > 0,$$
$$r = \tilde{\mu}^2\tilde{c}^2\tilde{\mu}_T^2(\mathcal{R}_0 - 1)(\mathcal{R}_0 + 1) > 0.$$

It follows that

$$\frac{\mathrm{d}}{\mathrm{d}z}H(z) = 3z^2 + 2pz + q > 0, \quad \text{for all } z > 0,$$

and hence, $H(z)$ is increasing for $z > 0$. This together with the fact that $H(0) = r > 0$ shows that (4.8) has no positive solutions, implying that (4.4) has no pure imaginary roots for $\tau > 0$ as long as $\mathcal{R}_0 > 1$. Therefore, all roots of (4.4) have negative real parts for $\tau > 0$ provided $\mathcal{R}_0 > 1$. Thus, we have proved.

THEOREM 4.1 If $\mathcal{R}_0 > 1$, then the infected equilibrium E_1 is asymptotically stable.

5. Numeric simulations

In this section, we perform some numeric simulations to demonstrate the theoretical results obtained in Sections 3 and 4, by using the delay differential equation solver dde23 built in the Matlab 7.0. We have seen in previous sections that the basic reproduction number $\mathcal{R}_0$ plays a decisive rule in determining the virus dynamics. Thus, for convenience of computations, we substitute (1.4) back into (2.2) to obtain an explicit formula of $\mathcal{R}_0$ in terms of the original parameters in (1.3):

$$\mathcal{R}_0 = \frac{(1 - n_{\mathrm{rt}})(1 - n_{\mathrm{p}})skN\,\mathrm{e}^{-\mu\tau_1 - \mu_2\tau_2}}{c\mu_T}. \tag{5.1}$$

Take $\tau_1 = 1.5$, $\tau_2 = 0.5$, $\mu = 0.33$, $\mu_2 = 0.28$, $N = 250$, $k = 0.0028906$, $c = 3$, $\mu_T = 0.2$, $s = 5$, $n_{\mathrm{p}} = 0.6$ and $n_{\mathrm{rt}} = 0.5$. Straightforward calculations show that the infection-free equilibrium $E_0 = (25, 0, 0)$ and the basic reproduction number $\mathcal{R}_0 = 0.63 < 1$. Simulation shows that E_0 is asymptotically stable, meaning that virus dies out eventually (see Fig. 1). This confirms the result in Theorem 3.1.

Next, we take another set of values for the parameters: $\tau_1 = 1.5, \tau_2 = 0.5, \mu = 0.33, \mu_2 = 0.28, N = 1200, k = 0.0028906, c = 3, \mu_T = 0.2, s = 5, n_{\mathrm{p}} = 0.6$ and $n_{\mathrm{rt}} = 0.5$. For these values, $\mathcal{R}_0 = 3.05 > 1$, and in addition to the infection-free equilibrium $E_0 = (25, 0, 0)$, there is an infected equilibrium $E_1 = (8.2, 2.280, 5)$. Simulation shows that E_0 is unstable and E_1 is asymptotically stable, confirming the results in Theorems 3.1 and 4.1 (see Fig. 2).

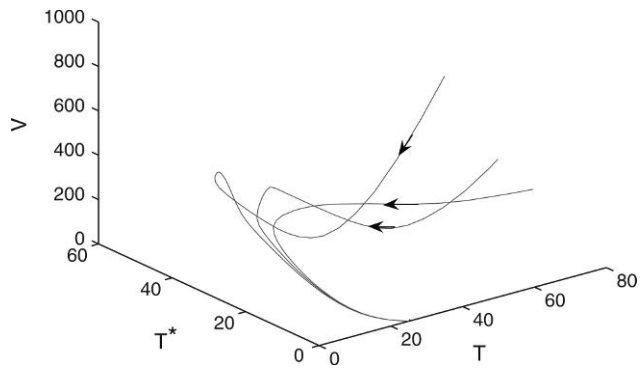

FIG. 1. Solutions of system (1.5) with $\tau_1 = 1.5$, $\tau_2 = 0.5$, $\mu = 0.33$, $\mu_2 = 0.28$, $k = 0.0028906$, $c = 3$, $\mu_T = 0.2$, $s = 5$, $n_{\mathrm{p}} = 0.6$, $n_{\mathrm{rt}} = 0.5$ and $N = 250$ giving $\mathcal{R}_0 = 0.63$. Initial conditions are $T(\theta) = 80$, $T^*(\theta) = 20$, $V(\theta) = 20$; $T(\theta) = 36$, $T^*(\theta) = 16$, $V(\theta) = 16$ and $T(\theta) = 10$, $T^*(\theta) = 6$, $V(\theta) = 6$, respectively, for $\theta \in [-1.5, 0]$.

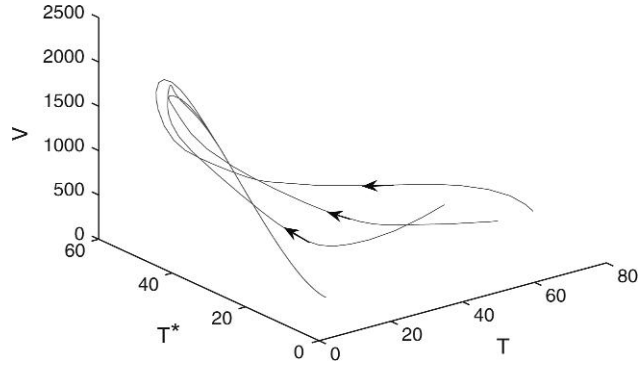

FIG. 2. Solutions of system (1.5) with $\tau_1 = 1.5, \tau_2 = 0.5, \mu = 0.33, \mu_2 = 0.28, k = 0.0028906, c = 3, \mu_T = 0.2, s = 5$, $n_p = 0.6, n_{rt} = 0.5$ and $N = 1200$ giving $\mathcal{R}_0 = 3.05$. Initial conditions are $T(\theta) = 1, T^*(\theta) = 30, V(\theta) = 200$; $T(\theta) = 5$, $T^*(\theta) = 40, V(\theta) = 1000$ and $T(\theta) = 30, T^*(\theta) = 10, V(\theta) = 500$, respectively, for $\theta \in [-1.5, 0]$.

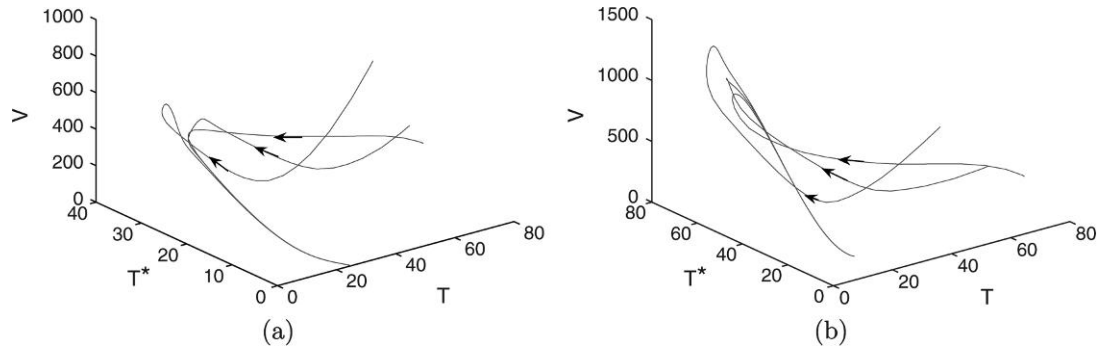

FIG. 3. Solutions of system (1.5) with $\tau_1 = 1.5, \tau_2 = 0.5, \mu = 0.33, \mu_2 = 0.28, N = 320, k = 0.0028906, c = 3, \mu_T = 0.2$ and $s = 5$. (a) $n_p = 0.5$ and $n_{rt} = 0.6$ leading to $\mathcal{R}_0 = 0.81 < 1$. Initial conditions are $T(\theta) = 50, T^*(\theta) = 2, V(\theta) = 2$; $T(\theta) = 40, T^*(\theta) = 1, V(\theta) = 1$ and $T(\theta) = 2, T^*(\theta) = 1, V(\theta) = 1$, respectively, for $\theta \in [-1.5, 0]$. (b) $n_p = 0.2$ and $n_{rt} = 0.3$ leading to $\mathcal{R}_0 = 2.28 > 1$. Initial conditions are $T(\theta) = 16, T^*(\theta) = 10, V(\theta) = 180$; $T(\theta) = 12, T^*(\theta) = 6, V(\theta) = 200$ and $T(\theta) = 2, T^*(\theta) = 10, V(\theta) = 160$, respectively, for $\theta \in [-1.5, 0]$.

In Fig. 3, we observe the impact of the two efficacy constants n_p and n_{rt} on the dynamics. To this end, we fix $\tau_1 = 1.5, \tau_2 = 0.5, \mu = 0.33, \mu_2 = 0.28, N = 320, k = 0.0028906, c = 3, \mu_T = 0.2$ and $s = 5$. Then, we take $n_p = 0.5$ and $n_{rt} = 0.6$, giving $\mathcal{R}_0 = 0.81 < 1$. The solutions all converge to the infection-free equilibrium $E_0 = (25, 0, 0)$ as is shown in Fig. 3(a). Next, we decrease n_p and n_{rt} to 0.2 and 0.3, respectively, giving $\mathcal{R}_0 = 2.28 > 1$. In this case, solutions converge to the infection equilibrium $E_1 = (12.5, 5.5, 128)$, as is shown in Fig. 3(b).

In Fig. 4, we numerically investigate the impact of the two delays τ_1 and τ_2 on the dynamics. For this purpose, we fix $\mu = 0.33, \mu_2 = 0.28, N = 500, k = 0.0028906, c = 3, \mu_T = 0.2, s = 5, n_p = 0.6$ and $n_{rt} = 0.5$. Then, we choose $\tau_1 = 3.2$ and $\tau_2 = 2.2$ giving $\mathcal{R}_0 = 0.35 < 1$. The solutions converge to the infection-free equilibrium $E_0 = (25, 0, 0)$, as is shown in Fig. 4(a). Decreasing τ_1 and τ_2 to 1.5 and 0.5, respectively, gives $\mathcal{R}_0 = 1.27 > 1$, and this destroy the stability of E_0 and solutions now converge to the infection equilibrium $E_1 = (19.7, 1.9, 45.1)$ as is shown in Fig. 4(b).

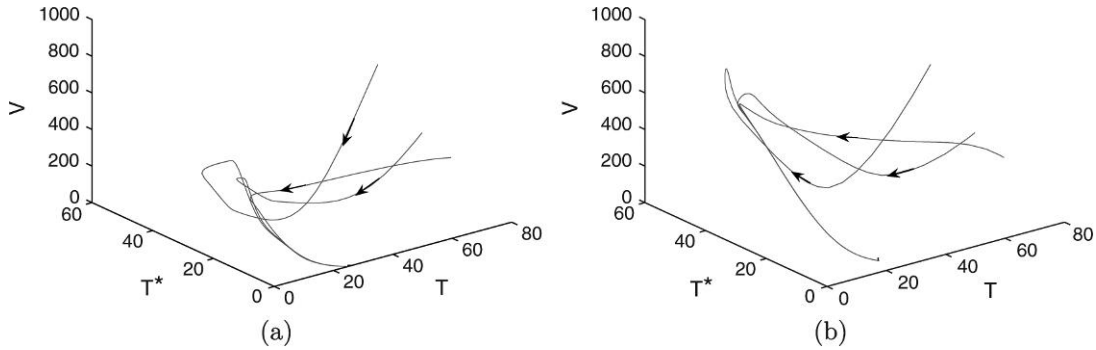

FIG. 4. Solutions of system (1.5) with $\mu = 0.33$, $\mu_2 = 0.28$, $N = 500$, $k = 0.0028906$, $c = 3$, $\mu_T = 0.2$, $s = 5$, $n_p = 0.6$ and $n_{rt} = 0.5$. (a) $\tau_1 = 3.2$ and $\tau_2 = 2.2$ giving $\mathcal{R}_0 = 0.35 < 1$. Initial conditions are $T(\theta) = 50$, $T^*(\theta) = 10$, $V(\theta) = 12$; $T(\theta) = 30$, $T^*(\theta) = 10$, $V(\theta) = 12$ and $T(\theta) = 5$, $T^*(\theta) = 15$, $V(\theta) = 20$, respectively, for $\theta \in [-3.2, 0]$. (b) $\tau_1 = 1.5$ and $\tau_2 = 0.5$ giving $\mathcal{R}_0 = 1.27 > 1$. Initial conditions are $T(\theta) = 10$, $T^*(\theta) = 15$, $V(\theta) = 60$; $T(\theta) = 40$, $T^*(\theta) = 8$, $V(\theta) = 80$ and $T(\theta) = 5$, $T^*(\theta) = 5$, $V(\theta) = 25$, respectively, for $\theta \in [-1.5, 0]$.

6. Conclusion and discussion

We have analysed an HIV-1 infection differential equation model with two concentrated delays, one accounts for the average latent period for cell infection (time between the contact of a cell by a virus particle and the entry of the virion into the cell) and the other explains the average time needed for the virus production after a virion enters a cell. We have identified the basic reproduction number $\mathcal{R}_0$, and proved that if $\mathcal{R}_0 < 1$, the infection-free steady state is globally asymptotically stable; if $\mathcal{R}_0 > 1$, the infection-free steady state becomes unstable and there occurs an infected steady state which is asymptotically stable. Thus, $\mathcal{R}_0 = 1$ plays a role of threshold value that determines whether or not the HIV-1 virus in host will be persistent or will go to extinction.

From our results, we conclude that to control the concentrations of the virus and the infected cells, a strategy should aim to reduce the value of the basic reproduction number to below one. By the explicit formula (5.1) for $\mathcal{R}_0$, we see that $\mathcal{R}_0$ can be decreased by increasing the efficacy of the protease inhibitor and the reverse transcriptase inhibitor (i.e. increasing n_p and n_{rt}). Another way to reduce $\mathcal{R}_0$ is to increase the latent period and/or postponing the production period (i.e. increase τ_1 and τ_2). While increasing the efficacy of drugs for HIV has been the goal of scientists, the 'biological significance' of the latter is that it suggests a new direction for new drugs. In other words, any drugs that can prolong the latent period or slow down virus production process may also help control the HIV-1 infection.

We point out the essential differences between our results and the results in Nelson & Perelson (2002) by which this work is motivated. Firstly, while Nelson & Perelson (2002) proposed the model with two delayed terms, the analysis was done only for the situation when one delay vanishes. Our results allow both delays to be present, and it is well known that the analysis of equations with multiple delays is in general much more challenging. Secondly, our results are in contrast to those in Nelson & Perelson (2002) as well in the following two aspects: (i) All theoretic results in Nelson & Perelson (2002) (also other existing works known by us) are for 'local' stability, but we have obtained a 'global' stability result for the infection-free equilibrium by applying the fluctuation lemma. It is well known that local stability generally does not imply global stability in systems of higher dimensions, let alone infinite-dimensional systems (delay differential equations are infinite-dimensional systems), and coexistence of a local stable equilibrium and other asymptotic structure is also possible. (ii) The main theoretic result in Nelson &

Perelson (2002, Theorem 1) claims that when 'only one single discrete delay' is present, this delay will not affect the stability of the equilibrium determined in the non-delay case, as long as the delay is small or large. For the stability of the infection-free equilibrium E_0, our corresponding result shows that the restrictions of 'a single delay' and 'small delay or large delay' are indeed not needed. As for the stability of infected equilibrium, our corresponding result would 'exclude' the 'large' part, even for a single delay case. To see this, we consider $\mathcal{R}_0 = \mathcal{R}_0(\tau_1, \tau_2)$ as a function of τ_1 and τ_2 given by (5.1). Obviously, $\mathcal{R}_0(\tau_1, \tau_2)$ is continuous and decreasing in τ_1 and τ_2. We choose values of all parameters other than τ_1 and τ_2 such that

$$\mathcal{R}_0(0, 0) = \frac{(1 - n_{\mathrm{rt}})(1 - n_{\mathrm{p}})skN}{c\mu_T} < 1, \tag{6.1}$$

implying that the infection-free equilibrium E_0 is stable when $\tau_1 = 0$ and $\tau_2 = 0$. The decreasing property of $\mathcal{R}_0(\tau_1, \tau_2)$ ensures that $\mathcal{R}_0(\tau_1, \tau_2) < 1$ for all $\tau_1 \geqslant 0$ and $\tau_2 \geqslant 0$, implying that E_0 remains stable for all $\tau_1 \geqslant 0$ and $\tau_2 \geqslant 0$. Next, we choose another set of values for all parameters other than τ_1 and τ_2 such that $\mathcal{R}_0(\tau_1, \tau_2) > 1$ ensuring existence and stability of E_1. By the continuity of $\mathcal{R}_0(\tau_1, \tau_2)$ on τ_1 and τ_2, we know that for small τ_1 and τ_2, $\mathcal{R}_0(\tau_1, \tau_2) > 1$ still holds and thus E_1 is still stable. But for large τ_1 and/or τ_2, $\mathcal{R}_0(\tau_1, \tau_2) < 1$ and thus E_1 does not exists, let alone its stability.

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