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Global dynamics of an HIV-1 infection model with distributed intracellular delays

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ABSTRACT

In this paper, an HIV-1 infection model with distributed intracellular delays is investigated, where the intracellular delays account for the time the target cells are contacted by the virus particles and the time the contacted cells become actively infected meaning that the contacting virions enter cells and 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, respectively. By analyzing the characteristic equations, the local stability of an infection-free equilibrium and a chronic-infection equilibrium of the model is established. By using suitable Lyapunov functionals and LaSalle's invariance principle, it is proved that if the basic reproduction ratio is less than unity, the infection-free equilibrium is globally asymptotically stable; and if the basic reproduction ratio is greater than unity, the chronic-infection equilibrium is globally asymptotically stable.

1. Introduction

Mathematical modeling combined with experimental measurements has yielded important insights into HIV-1 pathogenesis and has enhanced progress in the understanding of HIV-1 infection (see, for example, [1–7]). Models used to study HIV-1 infection have involved the concentrations of uninfected target cells, x, infected cells that are producing virus, y, and virus, v. After protease inhibitors are given, virus is classified as either infectious, v_I, i.e., not influenced by the protease inhibitor, or as non-infectious, v_{NI}, due to the action of the protease inhibitor which prevents virion maturation into infectious particles. A basic mathematical model describing HIV-1 infection dynamics that has been studied in [3,6,8] is of the form

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \bar{\beta}x(t)v(t), \\ \dot{y}(t) &= \bar{\beta}x(t)v(t) - ay(t), \\ \dot{v}(t) &= \bar{k}y(t) - uv(t), \end{aligned} \tag{1.1}$$

where uninfected, susceptible cells are produced at a rate, λ, uninfected cells die at rate d, and become infected at rate $\bar{\beta}xv$, where $\bar{\beta}$ is the rate constant describing the infection process; infected cells are produced at rate $\bar{\beta}xv$ and die at rate ay; free virions are produced from infected cells at rate $\bar{k}y$ and are removed at rate uv.

The binding of a viral particle to a receptor on a target cell initiates a cascade of events that ultimately lead to the target cell becoming productively infected, i.e. producing new virus. We note that in model (1.1) this process was assumed to occur instantaneously: as soon as virus contacts a target cell the cell begins producing virus. However, in the real situation, there

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may be a lag between the time the target cells are contacted by the virus particles and the time the contacted cells become actively infected 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. In addition to the above time delay, there may be 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, for example, [9]). There has been some work on the effect of intracellular delays on the dynamics of virus infection (see, for example, [9–19]).

In [15], Nelson and Perelson further generalized the model in [14] by including two delays modeling the "two periods" mentioned above. The general model in [15] is given by the following system of delay differential equations

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - (1 - n_{rt})\bar{\beta}x(t)v(t),\\
\dot{y}(t) &= (1 - n_{rt})\bar{\beta}\int_0^\infty f_1(\tau)e^{-m\tau}x(t-\tau)v(t-\tau)d\tau - ay(t),\\
\dot{v}(t) &= (1 - n_p)\bar{k}\int_0^\infty f_2(\tau)y(t-\tau)d\tau - uv(t).
\end{aligned} \tag{1.2}$$

Here, the parameters a, d, $\bar{k}$, u, λ, $\bar{\beta}$ and the variables $x(t)$, $v(t)$ are defined as those in (1.1), $y(t)$ now represents 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. It is assumed in (1.2) that cells, which are infected by virus at time t, begin producing virus, i.e., become productively infected, τ time units later, where τ is distributed according to a probability distribution $f_1(\tau)$. The recruitment of virus-producing cells at time t is given by the number of cells that were newly infected at time $t - \tau$ and are still alive at time t. Here, m is assumed to be a constant death rate for infected but not yet virus-producing cells. Thus, the probability of surviving the time period from $t - \tau$ to t is $e^{-m\tau}$. On the other hand, it is assumed in (1.2) that the virus penetrated into a cell at time t, τ time units later, the new virions are created within the cell and are released from the cell, where τ is distributed according to a probability distribution $f_2(\tau)$. With the assumptions $f_1(\tau) = \delta(\tau - \tau_1), f_2(\tau) = \delta(\tau)$ and $f_1(\tau) = \delta(\tau), f_2(\tau) = \delta(\tau - \tau_2)$, respectively, where $\delta(\cdot)$ is the Dirac delta function, by analyzing the corresponding characteristic equations, the local stability of feasible equilibria was discussed in [15]. By assuming $f_1(\tau) = \delta(\tau - \tau_1), f_2(\tau) = \delta(\tau)$ and by using suitable Lyapunov functionals and LaSalle's invariance principle, the global stability of the infection-free and the chronic-infection equilibrium has been established in [19].

Motivated by the work of Nelson and Perelson [15], in this paper, we further consider the effect of intracellular delays on the global dynamics of model (1.2). To this end, we consider the following more general delay differential equation model

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t),\\
\dot{y}(t) &= \beta\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau - ay(t),\\
\dot{v}(t) &= k\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau - uv(t)
\end{aligned} \tag{1.3}$$

where $\beta = (1 - n_{rt})\bar{\beta}$, $k = (1 - n_p)\bar{k}$, the term $e^{-m_2\tau}$ is incorporated in the third equation to describe the death rate factors. In (1.3), the delay kernel, $f_i : [0, \infty) \to [0, \infty)$, is assumed to be piecewise continuous and to satisfy the following properties:

$$\int_0^\infty f_i(\tau)d\tau = 1, \qquad \int_0^\infty \tau f_i(\tau)d\tau < \infty, \quad i = 1, 2.$$

The initial conditions for system (1.3) take the form

$$\begin{aligned}
&x(\theta) = \phi_1(\theta), \qquad y(\theta) = \phi_2(\theta), \qquad v(\theta) = \phi_3(\theta),\\
&\phi_i(\theta) \geq 0, \quad \theta \in (-\infty, 0), \quad \phi_i(0) > 0 \quad (i = 1, 2, 3),
\end{aligned} \tag{1.4}$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta)) \in C((-\infty, 0], \mathbb{R}^3_{+0})$, the space of continuous functions mapping the interval $(-\infty, 0]$ into $\mathbb{R}^3_{+0}$, where $\mathbb{R}^3_{+0} = \{(x_1, x_2, x_3) : x_i \geq 0, i = 1, 2, 3\}$.

In this paper, our primary goal is to carry out a complete mathematical analysis of system (1.3) and establish its global dynamics. It is well known by the fundamental theory of functional differential equations [20], system (1.3) admits a unique solution $(x(t), y(t), v(t))$ satisfying the initial conditions (1.4). It is easy to show that all solutions of system (1.3) with initial conditions (1.4) are defined on $[0, +\infty)$ and remain positive for all $t \geq 0$.

The organization of this paper is as follows. In the next section, by analyzing the corresponding characteristic equations, we study the local asymptotic stability of an infection-free equilibrium and a chronic-infection equilibrium of system (1.3).

In Section 3, we discuss the global stability of the infection-free equilibrium and the chronic-infection equilibrium by means of suitable Lyapunov functionals and LaSalle's invariance principle, respectively. The global stability of the chronic-infection equilibrium rules out any possibility for the existence of Hopf bifurcations and sustained oscillations in system (1.3). A brief remark is given in Section 4 to conclude this work.

2. Equilibria and local stability

In this section, we study the local stability of each of feasible equilibria of model (1.3).

Clearly, system (1.3) always has an infection-free equilibrium $E_1(\lambda/d, 0, 0)$. Denote

$$\mathscr{R}_0 = \frac{k\lambda\beta \int_0^\infty f_1(\tau)e^{-m_1\tau}d\tau \int_0^\infty f_2(\tau)e^{-m_2\tau}d\tau}{adu}. \tag{2.1}$$

Here, $\mathscr{R}_0$ is called the basic reproduction ratio of model (1.3). $\mathscr{R}_0$ denotes the average number of secondary virus produced from a single virus for system (1.3). Noting that $\int_0^\infty f_i(\tau)d\tau = 1$, we have $\int_0^\infty f_i(\tau)e^{-m_i\tau}d\tau < 1$ for $m_i > 0$ $(i = 1, 2)$. Hence, biologically, the delay representing the time for a viral particle to go through the eclipse phase (or latent period) and/or the delay representing the time between the entry of a virion into a cell and the creation and release of new virions from this cell may decrease the basic reproduction ratio $\mathscr{R}_0$.

It is easy to show that if $\mathscr{R}_0 > 1$, system (1.3) admits a unique chronic-infection equilibrium $E^*(x^*, y^*, v^*)$, where

$$\begin{aligned} x^* &= \frac{au}{k\beta \int_0^\infty f_1(\tau)e^{-m_1\tau}d\tau \int_0^\infty f_2(\tau)e^{-m_2\tau}d\tau}, \\ y^* &= \frac{du}{k\beta \int_0^\infty f_2(\tau)e^{-m_2\tau}d\tau}(\mathscr{R}_0 - 1), \qquad v^* = \frac{d}{\beta}(\mathscr{R}_0 - 1). \end{aligned} \tag{2.2}$$

The characteristic equation of system (1.3) at the infection-free equilibrium E_1 is of the form

$$(s + d)\left[s^2 + (a + u)s + au - k\beta\frac{\lambda}{d}F_1(s)F_2(s)\right] = 0, \tag{2.3}$$

where

$$F_i(s) = \int_0^\infty f_i(\tau)e^{-m_i\tau}e^{-s\tau}d\tau, \quad i = 1, 2. \tag{2.4}$$

Clearly, Eq. (2.3) always has a negative real root $s_1 = -d$. Other roots of (2.3) are determined by the following equation

$$s^2 + (a + u)s + au - k\beta\frac{\lambda}{d}F_1(s)F_2(s) = 0, \tag{2.5}$$

where $F_i(s)$ $(i = 1, 2)$ are defined in (2.4).

Let

$$f(s) = s^2 + (a + u)s + au - k\beta\frac{\lambda}{d}F_1(s)F_2(s).$$

Note that $|F_i(s)| \le 1$ $(i = 1, 2)$. If $\mathscr{R}_0 > 1$, it is easy to show that, for s real,

$$f(0) = au(1 - \mathscr{R}_0) < 0, \qquad \lim_{s\to+\infty} f(s) = +\infty.$$

Hence, $f(s) = 0$ has at least one positive real root. Therefore, if $\mathscr{R}_0 > 1$, the infection-free equilibrium E_1 is unstable.

If $\mathscr{R}_0 < 1$, we prove that the equilibrium E_1 is locally asymptotically stable.

When $f_i(\tau) = \delta(\tau)$, the Dirac delta function, we have $F_i(s) = 1$ $(i = 1, 2)$. In this case, (2.5) becomes

$$s^2 + (a + u)s + au(1 - \mathscr{R}_0) = 0. \tag{2.6}$$

Hence, if $\mathscr{R}_0 < 1$, Eq. (2.6) has two negative real roots. Accordingly, the equilibrium E_1 is locally asymptotically stable when $f_i(\tau) = \delta(\tau)$ $(i = 1, 2)$.

If $\mathrm{i}\omega(\omega > 0)$ is a solution of Eq. (2.5), it follows that

$$-\omega^2 + (a + u)\omega\mathrm{i} + au - k\beta\frac{\lambda}{d}F_1(\mathrm{i}\omega)F_2(\mathrm{i}\omega) = 0, \tag{2.7}$$

which yields

$$\omega^4 + (a^2 + u^2)\omega^2 + (au)^2 - \left(k\beta\frac{\lambda}{d}\right)^2 |F_1(\mathrm{i}\omega)|^2|F_2(\mathrm{i}\omega)|^2 = 0. \tag{2.8}$$

We note that, for $i = 1, 2$,

$$|F_i(\mathrm{i}\omega)| = \left| \int_0^\infty f_i(\tau) e^{-m_i\tau} (\cos\omega\tau - \mathrm{i}\sin\omega\tau) d\tau \right| \le \int_0^\infty f_i(\tau) e^{-m_i\tau} d\tau. \tag{2.9}$$

Hence, we have that

$$(au)^2 - \left(k\beta\frac{\lambda}{d}\right)^2 |F_1(\mathrm{i}\omega)|^2 |F_2(\mathrm{i}\omega)|^2 \ge (au)^2(1 - \mathscr{R}_0^2).$$

Therefore, if $\mathscr{R}_0 < 1$, Eq. (2.8) has no positive roots. Noting that the equilibrium E_1 is locally asymptotically stable when $f_i(\tau) = \delta(\tau)$ $(i = 1, 2)$, by the general theory on characteristic equations of delay differential equations from [21] (Theorem 3.4.1), we see that if $\mathscr{R}_0 < 1$, E_1 is always locally asymptotically stable.

The characteristic equation of system (1.3) at the chronic-infection equilibrium E^* takes the form

$$s^3 + p_2 s^2 + p_1 s + p_0 + (q_1 s + q_0) F_1(s) F_2(s) = 0, \tag{2.10}$$

where

$$\begin{aligned} p_0 &= au(d + \beta v^*), \\ p_1 &= (a + u)(d + \beta v^*) + au, \\ p_2 &= a + u + d + \beta v^*, \\ q_0 &= -dk\beta x^*, \\ q_1 &= -k\beta x^*. \end{aligned} \tag{2.11}$$

When $f_i(\tau) = \delta(\tau)$, we have $F_i(s) = 1$ $(i = 1, 2)$. In this case, Eq. (2.10) becomes

$$s^3 + p_2 s^2 + (p_1 + q_1)s + p_0 + q_0 = 0. \tag{2.12}$$

It is easy to show that, if $\mathscr{R}_0 > 1$,

$$p_0 + q_0 = adu(\mathscr{R}_0 - 1) > 0, \qquad p_1 + q_1 = \frac{k\lambda\beta(a + u)}{au} > 0,$$

$$p_2(p_1 + q_1) - (p_0 + q_0) = \frac{1}{au}\{k\lambda\beta[a^2 + u^2 + au + (a + u)(d + \beta v^*)] + d(au)^2\} > 0.$$

By Routh–Hurwitz criterion, we see that all roots of Eq. (2.12) have negative real parts. Hence, the equilibrium E^* is locally asymptotically stable when $f_i(\tau) = \delta(\tau)$ $(i = 1, 2)$.

If $\mathrm{i}\omega(\omega > 0)$ is a solution of Eq. (2.10), it follows that

$$-\omega^3\mathrm{i} - p_2\omega^2 + p_1\omega\mathrm{i} + p_0 + (q_1\omega\mathrm{i} + q_0)F_1(\mathrm{i}\omega)F_2(\mathrm{i}\omega) = 0, \tag{2.13}$$

which yields

$$\omega^6 + (p_2^2 - 2p_1)\omega^4 + (p_1^2 - 2p_0p_2)\omega^2 + p_0^2 - (q_0^2 + q_1^2\omega^2)|F_1(\mathrm{i}\omega)|^2|F_2(\mathrm{i}\omega)|^2 = 0. \tag{2.14}$$

Noting the fact in (2.9), by calculation, we have that

$$\begin{aligned} p_2^2 - 2p_1 &= a^2 + u^2 + (d + \beta v^*)^2 > 0, \\ p_1^2 - 2p_0p_2 - q_1^2|F_1(\mathrm{i}\omega)|^2|F_2(\mathrm{i}\omega)|^2 &= (a^2 + u^2)(d + \beta v^*)^2 + a^2u^2 - (k\beta x^*)^2|F_1(\mathrm{i}\omega)|^2|F_2(\mathrm{i}\omega)|^2 \\ &\ge (a^2 + u^2)(d + \beta v^*)^2, \\ p_0^2 - q_0^2|F_1(\mathrm{i}\omega)|^2|F_2(\mathrm{i}\omega)|^2 &= [au(d + \beta v^*)]^2 - (dk\beta x^*)^2|F_1(\mathrm{i}\omega)|^2|F_2(\mathrm{i}\omega)|^2 \\ &\ge au\beta v^*[au(d + \beta v^*) + dk\beta x^*|F_1(\mathrm{i}\omega)||F_2(\mathrm{i}\omega)|]. \end{aligned}$$

Hence, if $\mathscr{R}_0 > 1$, Eq. (2.14) has no positive roots. Noting that the equilibrium E^* is locally asymptotically stable when $f_i(\tau) = \delta(\tau)$ $(i = 1, 2)$, by the general theory on characteristic equations of delay differential equations from [21] (Theorem 3.4.1), we see that if $\mathscr{R}_0 > 1$, the chronic-infection equilibrium E^* is locally asymptotically stable.

From what has been discussed above, we have the following result.

Theorem 2.1. *For system (1.3), if $\mathscr{R}_0 < 1$, the infection-free equilibrium $E_1(\lambda/d, 0, 0)$ is locally asymptotically stable; if $\mathscr{R}_0 > 1$, $E_1(\lambda/d, 0, 0)$ is unstable and the chronic-infection equilibrium $E^*(x^*, y^*, v^*)$ exists and is locally asymptotically stable.*

3. Global stability

In this section, we study the global stability of each of feasible equilibria of system (1.3). The strategy of proofs is to use suitable Lyapunov functionals and LaSalle's invariance principle.

We first state and prove our result on the global stability of the infection-free equilibrium $E_1(\lambda/d, 0, 0)$.

Theorem 3.1. *The disease-free equilibrium $E_1(\lambda/d, 0, 0)$ of system (1.3) is globally asymptotically stable if $\mathscr{R}_0 < 1$.*

Proof. Let $(x(t), y(t), v(t))$ be any positive solution of system (1.3) with initial conditions (1.4). Denote $x_0 = \lambda/d$
Define

$$V_{11}(t) = x - x_0 - x_0 \ln \frac{x}{x_0} + k_1 y + k_2 v, \tag{3.1}$$

where

$$k_1 = \frac{1}{\int_0^\infty f_1(\tau) e^{-m_1\tau} d\tau}, \qquad k_2 = \frac{a}{k \int_0^\infty f_1(\tau) e^{-m_1\tau} d\tau \int_0^\infty f_2(\tau) e^{-m_2\tau} d\tau}. \tag{3.2}$$

Calculating the derivative of $V_{11}(t)$ along positive solutions of system (1.3), it follows that

$$\begin{aligned} \frac{d}{dt} V_{11}(t) &= \left(1 - \frac{x_0}{x}\right)[\lambda - dx(t) - \beta x(t) v(t)] + k_1 \left[\beta \int_0^\infty f_1(\tau) e^{-m_1\tau} x(t-\tau) v(t-\tau) d\tau - a y(t)\right] \\ &\quad + k_2 \left[k \int_0^\infty f_2(\tau) e^{-m_2\tau} y(t-\tau) d\tau - u v(t)\right]. \end{aligned} \tag{3.3}$$

On substituting $\lambda = dx_0$ into (3.3), we obtain that

$$\begin{aligned} \frac{d}{dt} V_{11}(t) &= \left(1 - \frac{x_0}{x}\right)[-d(x(t) - x_0) - \beta x(t) v(t)] + k_1 \left[\beta \int_0^\infty f_1(\tau) e^{-m_1\tau} x(t-\tau) v(t-\tau) d\tau - a y(t)\right] \\ &\quad + k_2 \left[k \int_0^\infty f_2(\tau) e^{-m_2\tau} y(t-\tau) d\tau - u v(t)\right] \\ &= -d \frac{(x(t) - x_0)^2}{x} - \beta x(t) v(t) + k_1 \beta \int_0^\infty f_1(\tau) e^{-m_1\tau} x(t-\tau) v(t-\tau) d\tau - k_1 a y(t) \\ &\quad + k_2 k \int_0^\infty f_2(\tau) e^{-m_2\tau} y(t-\tau) d\tau + k_2 u(\mathscr{R}_0 - 1) v(t). \end{aligned} \tag{3.4}$$

Define

$$V_1(t) = V_{11}(t) + k_1 \beta \int_0^\infty f_1(\tau) e^{-m_1\tau} \int_{t-\tau}^t x(s) v(s) ds d\tau + k_2 k \int_0^\infty f_2(\tau) e^{-m_2\tau} \int_{t-\tau}^t y(s) ds d\tau. \tag{3.5}$$

We derive from (3.4) and (3.5) that

$$\frac{d}{dt} V_1(t) = -d \frac{(x - x_0)^2}{x} + \frac{a u (\mathscr{R}_0 - 1) v(t)}{k \int_0^\infty f_1(\tau) e^{-m_1\tau} d\tau \int_0^\infty f_2(\tau) e^{-m_2\tau} d\tau}. \tag{3.6}$$

If $\mathscr{R}_0 < 1$, it follows from (3.6) that $V_1'(t) \le 0$. By Theorem 5.3.1 in [20], solutions limit to $\mathcal{M}$, the largest invariant subset of $\{V_1'(t) = 0\}$. Clearly, it follows from (3.6) that $V_1'(t) = 0$ if and only if $x = x_0$, $v = 0$. Noting that $\mathcal{M}$ is invariant, for each element in $\mathcal{M}$, we have $v = 0$, $v'(t) = 0$. We therefore derive from the third equation of system (1.3) that

$$0 = v'(t) = k \int_0^\infty f_2(\tau) e^{-m_2\tau} y(t-\tau) d\tau.$$

This yields $y = 0$. Hence, $V_1'(t) = 0$ if and only if $(x, y, v) = (x_0, 0, 0)$. Accordingly, the global asymptotic stability of E_1 follows from LaSalle's invariance principle. This completes the proof. □

We now study the global stability of the chronic-infection equilibrium E^* of system (1.3).

Theorem 3.2. *If $\mathscr{R}_0 > 1$, then the chronic-infection equilibrium $E^*(x^*, y^*, v^*)$ of system (1.3) is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t))$ be any positive solution of system (1.3) with initial conditions (1.4).
Define

$$V_{21}(t) = x - x^* - x^* \ln \frac{x}{x^*} + k_1 \left(y - y^* - y^* \ln \frac{y}{y^*}\right) + k_2 \left(v - v^* - v^* \ln \frac{v}{v^*}\right),$$

where k_1 and k_2 are defined as in (3.2).

Calculating the derivative of $V_{21}(t)$ along positive solutions of system (1.3) we derive that

$$\begin{aligned}\frac{d}{dt}V_{21}(t) &= \left(1-\frac{x^*}{x}\right)[\lambda - dx(t) - \beta x(t)v(t)] + k_1\left(1-\frac{y^*}{y}\right)\left[\beta\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau - ay(t)\right]\\ &\quad + k_2\left(1-\frac{v^*}{v}\right)\left[k\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau - uv(t)\right]. \end{aligned} \tag{3.7}$$

On substituting $\lambda = dx^* + \beta x^* v^*$ into (3.7), it follows that

$$\begin{aligned}\frac{d}{dt}V_{21}(t) &= \left(1-\frac{x^*}{x}\right)[-d(x(t)-x^*) - \beta x(t)v(t) + \beta x^* v^*]\\ &\quad + k_1\left(1-\frac{y^*}{y}\right)\left[\beta\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau - ay(t)\right]\\ &\quad + k_2\left(1-\frac{v^*}{v}\right)\left[k\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau - uv(t)\right]\\ &= -d\frac{(x(t)-x^*)^2}{x} - \beta x(t)v(t) + \beta x^* v^*\left(1-\frac{x^*}{x}\right) + k_1\beta\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau - k_1 ay(t)\\ &\quad - k_1\frac{\beta y^*}{y(t)}\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau + \beta x^* v^* + k_2 k\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau\\ &\quad - k_2 k\frac{v^*}{v(t)}\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau + \beta x^* v^*. \end{aligned} \tag{3.8}$$

Define

$$\begin{aligned}V_2(t) &= V_{21}(t) + k_1\beta\int_0^\infty f_1(\tau)e^{-m_1\tau}\int_{t-\tau}^t\left[x(s)v(s) - x^*v^* - x^*v^*\ln\frac{x(s)v(s)}{x^*v^*}\right]ds d\tau\\ &\quad + k_2 k\int_0^\infty f_2(\tau)e^{-m_2\tau}\int_{t-\tau}^t\left[y(s) - y^* - y^*\ln\frac{y(s)}{y^*}\right]ds d\tau. \end{aligned} \tag{3.9}$$

We derive from (3.8) and (3.9) that

$$\begin{aligned}\frac{d}{dt}V_2(t) &= -d\frac{(x(t)-x^*)^2}{x} - \beta x(t)v(t) + \beta x^* v^*\left(1-\frac{x^*}{x}\right) + k_1\beta\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau - k_1 ay(t)\\ &\quad - k_1\frac{\beta y^*}{y(t)}\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)v(t-\tau)d\tau + \beta x^* v^* + k_2 k\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau\\ &\quad - k_2 k\frac{v^*}{v(t)}\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)d\tau + \beta x^* v^*\\ &\quad + k_1\beta\int_0^\infty f_1(\tau)e^{-m_1\tau}\left[x(t)v(t) - x(t-\tau)v(t-\tau) + x^*v^*\ln\frac{x(t-\tau)v(t-\tau)}{x(t)v(t)}\right]d\tau\\ &\quad + k_2 k\int_0^\infty f_2(\tau)e^{-m_2\tau}\left[y(t) - y(t-\tau) + y^*\ln\frac{y(t-\tau)}{y(t)}\right]d\tau\\ &= -d\frac{(x(t)-x^*)^2}{x} + \beta x^* v^*\left(1-\frac{x^*}{x}\right) - k_1\beta x^* v^*\int_0^\infty f_1(\tau)e^{-m_1\tau}\frac{y^*x(t-\tau)v(t-\tau)}{x^*v^*y(t)}d\tau + \beta x^* v^*\\ &\quad - k_2 k y^*\int_0^\infty f_2(\tau)e^{-m_2\tau}\frac{v^*y(t-\tau)}{y^*v(t)}d\tau + \beta x^* v^* + k_1\beta x^* v^*\int_0^\infty f_1(\tau)e^{-m_1\tau}\ln\frac{x(t-\tau)v(t-\tau)}{x(t)v(t)}d\tau\\ &\quad + k_2 k y^*\int_0^\infty f_2(\tau)e^{-m_2\tau}\ln\frac{y(t-\tau)}{y(t)}d\tau\\ &= -d\frac{(x(t)-x^*)^2}{x} + \beta x^* v^*\left(1-\frac{x^*}{x} - \ln\frac{x^*}{x}\right)\\ &\quad - k_1\beta x^* v^*\int_0^\infty f_1(\tau)e^{-m_1\tau}\left[\frac{y^*x(t-\tau)v(t-\tau)}{x^*v^*y(t)} - 1 - \ln\frac{y^*x(t-\tau)v(t-\tau)}{x^*v^*y(t)}\right]d\tau\\ &\quad - k_2 k y^*\int_0^\infty f_2(\tau)e^{-m_2\tau}\left[\frac{v^*y(t-\tau)}{y^*v(t)} - 1 - \ln\frac{v^*y(t-\tau)}{y^*v(t)}\right]d\tau. \end{aligned} \tag{3.10}$$

Noting that $x^*, y^*, v^* > 0$, we have that $V_2'(t) \leq 0$. By Theorem 5.3.1 in [20], solutions limit to $\mathcal{M}$, the largest invariant subset of $\{V_2'(t) = 0\}$. It is readily seen from (3.10) that $V_2'(t) = 0$ if and only if $x = x^*$, $\frac{y^*x(t-\tau)v(t-\tau)}{x^*v^*y(t)} = \frac{v^*y(t-\tau)}{y^*v(t)} = 1$. Using a similar argument as that in the proof of Theorem 3.1 and by LaSalle's invariance principle, the global asymptotic stability of E^* follows. This completes the proof. □

4. Concluding remark

In this paper, we have studied the global dynamics of an HIV-1 infection model with distributed intracellular delays accounting for the time between viral entry into a target cell and the production of new virus particles and the time between infection of a cell and the emission of viral particle. By analyzing the corresponding characteristic equations, it was shown that if the basic reproduction ratio $\mathscr{R}_0$ is less than unity, the infection-free equilibrium is locally asymptotically stable; if the basic reproduction ratio $\mathscr{R}_0$ is greater than unity, the chronic-infection equilibrium exists and is locally asymptotically stable. The global stability of the infection-free equilibrium and the chronic-infection equilibrium of system (1.3) has been completely established by using the Lyapunov–LaSalle type theorem. By Theorem 3.1 we see that if $\mathscr{R}_0 < 1$, the infection-free equilibrium is globally asymptotically stable. In this case, the virus is cleared up. By Theorem 3.2 we see that if $\mathscr{R}_0 > 1$, the chronic-infection equilibrium is globally asymptotically stable. From Theorems 3.1 and 3.2, we see that the intracellular delays describing the time between viral entry into a target cell and the production of new virus particles and the time between infection of a cell and the emission of viral particle have no effect on the stability of feasible equilibria and therefore do not induce periodic oscillations and the possibility of Hopf bifurcations is therefore ruled out.

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