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Global dynamics of a delayed within-host viral infection model with both virus-to-cell and cell-to-cell transmissions☆

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ABSTRACT

A within-host viral infection model with both virus-to-cell and cell-to-cell transmissions and three distributed delays is investigated, in which the first distributed delay describes the intracellular latency for the virus-to-cell infection, the second delay represents the intracellular latency for the cell-to-cell infection, and the third delay describes the time period that viruses penetrated into cells and infected cells release new virions. The global stability analysis of the model is carried out in terms of the basic reproduction number $\mathcal{R}_0$. If $\mathcal{R}_0 \leq 1$, the infection-free (semi-trivial) equilibrium is the unique equilibrium and is globally stable; if $\mathcal{R}_0 > 1$, the chronic infection (positive) equilibrium exists and is globally stable under certain assumptions. Examples and numerical simulations for several special cases are presented, including various within-host dynamics models with discrete or distributed delays that have been well-studied in the literature. It is found that the global stability of the chronic infection equilibrium might change in some special cases when the assumptions do not hold. The results show that the model can be applied to describe the within-host dynamics of HBV, HIV, or HTLV-1 infection.

1. Introduction

When a virus enters the human body, it targets cells with specific receptors. The viral capsid protein binds to the specific receptors on the host cellular surface and injects its core. For example, human immunodeficiency virus (HIV) infects vital cells in the human immune system such as helper T cells (specifically CD4+ T-cells). Its surface protein, gp120, specifically interacts with the chemokine receptors on the surface of CD4+ T-cells. Once bound to the target cell, the HIV RNA and various enzymes are injected into the cell. The hepatitis B virus (HBV) gains entry into the cell by binding to the surface receptor NTCP on the surface. Because HBV multiplies via RNA made by a host enzyme, the viral genomic DNA is transferred to the cell nucleus by host proteins called chaperones. After an intracellular period associated with transcription, integration, and the production of capsid proteins, the infected cell releases hundreds of virions that can infect other cells.

Mathematical models have been developed to describe the within-host dynamics of various viral infections, mostly focusing on virus-to-cell spread in the bloodstream, such as human immunodeficiency virus (HIV) (Kirschner and Webb [23], Müller et al. [30], Nowak and Bangham [34], Nowak and May [35], Perelson et al. [37], Perelson and Nelson [38], Wodarz et al. [48]), hepatitis C virus (HCV) (Dixit et al. [12], Neumann et al. [33], Dahari et al. [8], DebRoy et al. [9]), human T-cell lymphotropic virus I (HTLV-1) (Stilianakis and Seydel [45], Wodarz et al. [49]), etc. The basic within-host viral infection model consists of three components: uninfected target cells, infected target cells and free virus (Bonhoeffer et al. [5], Nowak and May [35]).

On the other hand, great attention has also been paid to the study of *in vitro* cell-to-cell spread of virus since many features are easier to determine experimentally in tissue cultures than in the bloodstream. For example, HIV is thought to be active in areas such as the lymph nodes and the brain where cell-to-cell spread would be a much more important mode of infection than virus-to-cell spread (Dimitrov et al. [11], Sturdevant et al. [47]). The data of Gummuluru et al. [18] demonstrate that cell-to-cell spread of HIV is the predominant route of viral spread since viral replication in a system with rapid cell turnover kinetics depends on cell-to-cell transfer of virus. Sigal et al. [43] examined replication from cell-to-cell spread of HIV in the presence of clinical drug concentrations using a stochastic infection model and found that replication is intermittent without substantial accumulation of mutations. Also, Bangham [2] reported that HTLV-I infection is achieved primarily through cell-to-cell contact. Cell-to-cell

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spread not only facilitates rapid viral dissemination but may also promote immune evasion and influence disease (Sattentau [41]). Based on these observations, researchers have constructed within-host viral infection models for the dynamics of cell-to-cell transmission of HIV (Culshaw et al. [7]).

Upon infection with viruses, there is a short intracellular "eclipse phase", during which the cell is infected but has not yet begun producing virus. For HIV infection, Spouge et al. [44] pointed out that there are two methods to model this eclipse phase, by a time delay or by an explicit class of latently infected cells, but did not consider it in their models. Perelson et al. [37] studied a system with an explicit class of latently infected cells. Herz et al. [21] assumed that cells become productively infected τ time units after initial infection and found that including an intracellular delay did change the estimates of the viral clearance rate but did not change the productively infected T cell loss rate. Culshaw and Ruan [6] showed that such an intracellular delay did not change the stability of the infected steady state for clinically reported parameter values. Mittler et al. [29] assumed that the intracellular delay was continuous and varied according to a gamma distribution and observed dramatic changes in the estimates of viral clearance. See also Banks et al. [3], Dixit et al. [13], Grossman et al. [15–17], Lloyd [28], Nelson et al. [31,32], Lai and Zou [25], Li and Shu [26], Pawelek et al. [36], Shu et al. [42], Wang et al. [46], and Zhu and Zou [50] for HIV infection model with delay; Katri and Ruan [22] for HTLV-1 infection models with delay; and Eikenberry et al. [14] for HBV infection models with delay.

Culshaw et al. [7] proposed a two-dimensional model of cell-to-cell spread of HIV in tissue cultures, in which the intracellular incubation period is modeled by a gamma distribution, and found out that, differing from the cell-to-free virus spread models, the cell-to-cell spread models can produce infective oscillations in typical tissue culture parameter regimes and the latently infected cells are instrumental in sustaining the infection.

To have a better and complete understanding of the within-host infection dynamics inside the whole body, it is necessary to take both virus-to-cell and cell-to-cell transmissions into consideration in modeling viral infections. In fact, recently Lai and Zou [25] proposed a delay differential equations model to include both infection modes of viral infection and spread, in which infection ages via viruses and infected cells are described by two distributed delays. They observed that the basic reproduction number of their model might be underevaluated if either cell-to-cell spread or virus-to-cell infection is neglected. Pourbashash et al. [39] used ordinary differential equations to model the two mechanisms of viral infection and conducted the local and global stability analysis of the model. In general, there are very few studies considering both virus-to-cell and cell-to-cell transmissions on viral infections.

In this paper we consider a within-host viral infection model with both virus-to-cell and cell-to-cell transmissions and three distributed delays, in which the first distributed delay describes the intracellular latency for the virus-to-cell infection (Mittler et al. [29]), the second delay represents the intracellular latency for the cell-to-cell infection (Culshaw et al. [7]), and the third delay describes the time period that viruses penetrated into cells and infected cells release new virions (Nelson and Perelson [32]). The mathematical model is constructed in Section 2. In Section 3, preliminaries are introduced, including the positivity and boundedness of solutions, as well as the existence of an infection-free equilibrium and a chronic infection equilibrium. The global stability of equilibria is obtained in Section 4. Finally, examples and numerical simulations for several special cases of the main model are presented, including various within-host dynamics models with discrete or distributed delays that have been well-studied in the literature. Besides the stability of equilibria under some conditions, it is also shown that periodic oscillations occur via Hopf bifurcations.

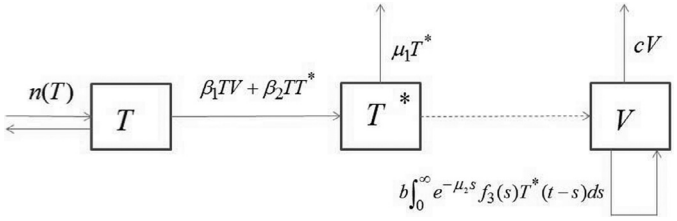

Fig. 1. Transfer diagram of the within-host viral infection.

2. Mathematical model

The compartmental model includes the concentrations of healthy target cells $T(t)$ which are susceptible to infection, infected cells $T^*(t)$ that produces viruses, and viruses $V(t)$. As assumed in De Leenheer and Smith [10], if there is no infection in the healthy target cells, the dynamics of T satisfy the equation

$$\frac{dT(t)}{dt} = n(T(t)), \tag{2.1}$$

where $n(T)$ is a function describing the natural change (including both production and turnover) of healthy target cells. Furthermore, the function $n(T)$ is assumed to satisfy the following properties:

(H_1) $n(T)$ is continuously differentiable and there exists $T^0 > 0$ such that $n(T^0) = 0$ and $n(T)(T - T^0) < 0,\ \forall T \neq T^0$;
(H_2) $n'(T) < 0, \forall T \in [0, T^0]$.

There are two typical functions for $n(T)$: $n(T) = h - d_T T$ and $n(T) = h - d_T T + rT(1 - \frac{T}{K})$ with $h, d_T, r, K > 0$, see Culshaw and Ruan [6], Li and Shu [26], Nowak and Bangham [34], Perelson and Nelson [38], Shu et al. [42], Wang et al. [46], for example.

Let β_1 be the virus-to-cell infection rate, β_2 be the cell-to-cell infection rate, μ_1 and c be death rates of actively infected cells and viruses, respectively. $e^{-\mu_1 s_1}$ is the survival rate of cells that are infected by viruses at time t and become activated infected s_1 time later with a probability distribution $f_1(s_1)$. Then $\int_0^\infty \beta_1 T(t - s_1)V(t - s_1)f_1(s_1)e^{-\mu_1 s_1}ds_1$ describes the newly activated infected target cells which are infected by free viruses s_1 time ago (Mittler et al. [29]). Similarly, $\int_0^\infty \beta_2 T(t - s_2)T^*(t - s_2)f_2(s_2)e^{-\mu_1 s_2}ds_2$ represents the newly activated infected target cells which are infected by infected cells s_2 time ago (Culshaw et al. [7]). Let s_3 be the random variable that is the time between viral RNA transcription and viral release and maturation with a probability distribution $f_3(s_3)$. The integral $\int_0^\infty e^{-\mu_2 s_3} f_3(s_3)T^*(t - s_3)ds_3$ describes the mature viral particles produced at time t (Nelson and Perelson [32]). b is the average number of viruses that bud out from an infected cell, and $e^{-\mu_2 s_3}$ is the survival rates of cells that start budding from activated infected cells at time t and become free mature viruses s_3 time later. Note that s_1, s_2, and s_3 are all integration variables, without loss of generality, they all will be represented by s.

A transfer diagram for the vivo infection of viruses is shown in Fig. 1. The model is given as follows:

$$\begin{aligned}
\frac{dT(t)}{dt} &= n(T(t)) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t),\\
\frac{dT^*(t)}{dt} &= \int_0^\infty \beta_1 T(t - s)V(t - s)f_1(s)e^{-\mu_1 s}ds\\
&\quad + \int_0^\infty \beta_2 T(t - s)T^*(t - s)f_2(s)e^{-\mu_1 s}ds - \mu_1 T^*(t),\\
\frac{dV(t)}{dt} &= b\int_0^\infty e^{-\mu_2 s} f_3(s)T^*(t - s)ds - cV(t).
\end{aligned} \tag{2.2}$$

$f_i(s) : [0, \infty) \to [0, \infty)$ are probability distributions with compact support, $f_i(s) \geq 0$, and $\int_0^\infty f_i(s)ds = 1,\ i = 1, 2, 3$. The distribution was

chosen as a gamma distribution in Mittler et al. [29]:

$$\frac{s^{n-1}}{(n-1)!b^n}e^{-s/b}, \tag{2.3}$$

and the model was converted into a set of ordinary differential equations. The distributions can also be delta functions as in Zhu and Zou [50], in such a case the model reduces to differential equations with discrete delays.

3. Preliminaries

Define the Banach space of fading memory type (see Atkinson and Haddock [1], Hale and Kato [19], Kuang [24])

$$\mathcal{C} = \left\{\phi \in C((-\infty, 0], \mathbb{R}) \middle| \phi(\theta)e^{\alpha\theta} \text{ is uniformly continuous for } \theta \in (-\infty, 0] \text{ and } \|\phi\| < \infty\right\},$$

where α is a positive constant and the norm $\|\phi\| = \sup_{\theta\le 0}|\phi(\theta)|e^{\alpha\theta}$. The nonnegative cone of $\mathcal{C}$ is defined by $\mathcal{C}_+ = \mathcal{C}((-\infty, 0], \mathbb{R}_+)$. For $\phi \in \mathcal{C}$, let $\phi_t \in \mathcal{C}$ as $\phi_t(\theta) = \phi(t+\theta)$, $\theta \in (-\infty, 0]$. We consider solutions $(T(t), T^*(t), V(t))$ of system (2.2) with initial conditions

$$(T_0, T_0^*, V_0) \in \mathcal{C}_+^3 := \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+. \tag{3.1}$$

By the standard theory of functional differential equations (Hale and Verduyn Lunel [20], Kuang [24]), we can obtain the existence of solutions for $t > 0$. Let

$$\eta_i = \int_0^\infty e^{-\mu_1 s} f_i(s)ds \quad i = 1, 2,$$

$$\eta_3 = \int_0^\infty e^{-\mu_2 s} f_3(s)ds.$$

Theorem 3.1. *Solutions of system (2.2) with initial conditions (3.1) are positive and ultimately uniformly bounded for $t > 0$.*

Proof. First, we prove that $T(t) > 0$ for all $t \ge 0$. Assume the contrary and let $t_1 > 0$ such that $T(t_1) = 0$. Then from the first equation of system (2.2), we have $\dot{T}(t_1) = n(0) > 0$. Therefore $T(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$ and $\varepsilon > 0$ is sufficiently small. This contradicts with the fact of $T(t) > 0$ for $t \in [0, t_1)$. It follows that $T(t) > 0$ for $t \ge 0$. Let $r(t)$ be the sum of the two integral terms in the second equation of system (2.2). From the second and the third equations in (2.2), we have

$$T^*(t) = \left[T^*(0) + \int_0^t r(\xi)e^{\mu_1\xi}d\xi\right]e^{-\mu_1 t},$$

$$V(t) = \left[V(0) + \int_0^t be^{c\xi}\int_0^\infty f_3(s)e^{-\mu_2 s}T^*(\xi - s)dsd\xi\right]e^{-ct},$$

which yield that $T^*(t) > 0$, $V(t) > 0$ for small $t > 0$. Now we prove that $T^*(t) > 0$ and $V(t) > 0$ for all $t > 0$. In fact, assume the contrary and let $t_2 > 0$ be the first time such that $\min\{T^*(t_2), V(t_2)\} = 0$. If $T^*(t_2) = 0$, $T^*(t) > 0$ for $0 \le t < t_2$, and $V(t) > 0$ for $0 \le t \le t_2$, then we have

$$\frac{dT^*(t_2)}{dt} = \int_0^\infty [\beta_1 T(t_2 - s)V(t_2 - s)f_1(s) + \beta_2 T(t_2 - s)T^*(t_2 - s)f_2(s)]e^{-\mu_1 s}ds > 0.$$

This contradicts $T^*(t_2) = 0$ and $T^*(t) > 0$ for $0 \le t < t_2$. If $V(t_2) = 0$, $V(t) > 0$ for $0 \le t < t_2$, and $T^*(t) > 0$ for $0 \le t \le t_2$, then we obtain

$$\frac{dV(t_2)}{dt} = b\int_0^\infty e^{-\mu_2 s}f_3(s)T^*(t_2 - s)ds > 0,$$

which is also a contradiction. Hence, $T^*(t) > 0$ and $V(t) > 0$ for all $t > 0$.

Assumptions (H_1) and (H_2) and the first equation of (2.2) imply that

$$\limsup_{t\to\infty} T(t) \le T^0.$$

Let

$$W(t) = \int_0^\infty f_1(s)e^{-\mu_1 s}T(t-s)ds + \int_0^\infty f_2(s)e^{-\mu_1 s}T(t-s)ds + T^*(t).$$

Choose $\bar{\mu}_1 \le \mu_1$ sufficiently small such that $T^0\bar{\mu}_1 < \lambda_0$, where $\lambda_0 = \sup_{T\in[0,T^0]} n(T)$. Then

$$\begin{aligned}\dot{W}(t) &= \int_0^\infty (f_1(s) + f_2(s))e^{-\mu_1 s}n(T(t-s))ds \\ &\quad - \int_0^\infty \beta_1 T(t-s)V(t-s)f_2(s)e^{-\mu_1 s}ds \\ &\quad - \int_0^\infty \beta_2 T(t-s)T^*(t-s)f_1(s)e^{-\mu_1 s}ds - \mu_1 T^*(t) \\ &\le \lambda_0(\eta_1 + \eta_2) - \mu_1 T^*(t) \\ &< 2\lambda_0(\eta_1 + \eta_2) - \bar{\mu}_1 W(t).\end{aligned}$$

It is obvious that

$$\limsup_{t\to\infty} W(t) \le \frac{2\lambda_0(\eta_1 + \eta_2)}{\bar{\mu}_1},$$

which implies that $\limsup_{t\to\infty} T^*(t) \le \frac{2\lambda_0(\eta_1+\eta_2)}{\bar{\mu}_1}$. Then, from the third equation of system (2.2), we have

$$\begin{aligned}\dot{V}(t) &= b\int_0^\infty f_3(s)e^{-\mu_2 s}T^*(t-s)ds - cV(t) \\ &\le \frac{2b\lambda_0(\eta_1 + \eta_2)\eta_3}{\bar{\mu}_1} - cV(t).\end{aligned}$$

Thus, $\limsup_{t\to\infty} V(t) \le \frac{2b\lambda_0(\eta_1+\eta_2)\eta_3}{c\bar{\mu}_1}$. Therefore, $T(t)$, $T^*(t)$ and $V(t)$ are ultimately uniformly bounded. □

Theorem 3.1 implies that omega limit sets of system (2.2) are contained in the following bounded feasible region:

$$\Gamma = \left\{(T, T^*, V) \in \mathcal{C}_+^3 : \|T\| \le T^0,\ \|T^*\| \le \frac{2\lambda_0(\eta_1 + \eta_2)}{\bar{\mu}_1},\ \|V\| \le \frac{2b\lambda_0(\eta_1 + \eta_2)\eta_3}{c\bar{\mu}_1}\right\}.$$

It can be verified that the region Γ is positively invariant with respect to system (2.2) and the system is well posed.

System (2.2) has an infection-free equilibrium $E_0 = (T^0, 0, 0)$. We define the basic reproduction number as follows:

$$\mathcal{R}_0 = \frac{b\beta_1 T^0\eta_1\eta_3}{c\mu_1} + \frac{\beta_2 T^0\eta_2}{\mu_1},$$

which represents the average number of secondary infections. In fact, $\frac{b\beta_1 T^0\eta_1\eta_3}{c\mu_1}$ is the average number of secondary viruses caused by a virus, that is the basic reproduction number corresponding to virus-to-cell infection mode, while $\frac{\beta_2 T^0\eta_2}{\mu_1}$ is the average number of secondary infected cells that caused by an infected cell, that is the basic reproduction number corresponding to cell-to-cell infection mode. The factors have the biological interpretations as follows:

- $\beta_1 T^0\eta_1$ is the number of new infections caused by a virus in target susceptible cells;
- $\frac{1}{\mu_1}$ is the average time that an infectious cell survives;
- $b\eta_3$ is the rate at which infected cells bud into viruses;
- $\frac{1}{c}$ gives the average life-span of a virus;
- $\beta_2 T^0\eta_2$ represents the number of new infections caused by an infected cell in target susceptible cells.

Then we have the following result.

Theorem 3.2. *If $\mathcal{R}_0 < 1$, then the infection-free equilibrium $E_0 = (T^0, 0, 0)$ is the only equilibrium of system (2.2). If $\mathcal{R}_0 > 1$, then E_0 is*

unstable and system (2.2) has a unique chronic infection equilibrium $\bar{E} = (\bar{T}, \bar{T}^*, \bar{V})$, *where*

$$\bar{T} = \frac{T^0}{\mathcal{R}_0}, \quad \bar{T}^* = \frac{cn(\bar{T})}{(b\beta_1\eta_3 + c\beta_2)\bar{T}}, \quad \bar{V} = \frac{b\eta_3\bar{T}^*}{c}.$$

Proof. The characteristic equation of system (2.2) at the equilibrium E_0 is

$$(\lambda - n'(T^0))[\lambda^2 - (\beta_2 T^0\bar{\eta}_2 - c - \mu_1)\lambda - (c\beta_2 T^0\bar{\eta}_2 + b\beta_1 T^0\bar{\eta}_1\bar{\eta}_3 - c\mu_1)] = 0,$$

where $\bar{\eta}_i = \int_0^\infty e^{-(\mu_1+\lambda)s} f_i(s)ds$, $i = 1, 2$, and $\bar{\eta}_3 = \int_0^\infty e^{-(\mu_2+\lambda)s} f_3(s)ds$. Since $n'(T^0) < 0$, we only need to consider the following equation

$$\lambda^2 - (\beta_2 T^0\bar{\eta}_2 - c - \mu_1)\lambda - (c\beta_2 T^0\bar{\eta}_2 + b\beta_1 T^0\bar{\eta}_1\bar{\eta}_3 - c\mu_1) = 0,$$

which is equivalent to

$$\left(\frac{\lambda}{\mu_1}+1\right)(\lambda+c) - \mathcal{R}_0\left(\frac{\bar{\eta}_2}{\eta_2}\frac{\mathcal{R}_{02}}{\mathcal{R}_0}\lambda + c\left(\frac{\bar{\eta}_2}{\eta_2}\frac{\mathcal{R}_{02}}{\mathcal{R}_0} + \frac{\mathcal{R}_{01}}{\mathcal{R}_0}\frac{\bar{\eta}_1}{\eta_1}\frac{\bar{\eta}_3}{\eta_3}\right)\right) = 0, \tag{3.2}$$

where

$$\mathcal{R}_{01} = \frac{b\beta_1 T^0\eta_1\eta_3}{c\mu_1}, \quad \mathcal{R}_{02} = \frac{\beta_2 T^0\eta_2}{\mu_1}.$$

Let

$$\psi(\lambda) = \left(\frac{\lambda}{\mu_1}+1\right)(\lambda+c) - \mathcal{R}_0\left(\frac{\bar{\eta}_2}{\eta_2}\frac{\mathcal{R}_{02}}{\mathcal{R}_0}\lambda + c\left(\frac{\bar{\eta}_2}{\eta_2}\frac{\mathcal{R}_{02}}{\mathcal{R}_0} + \frac{\mathcal{R}_{01}}{\mathcal{R}_0}\frac{\bar{\eta}_1}{\eta_1}\frac{\bar{\eta}_3}{\eta_3}\right)\right).$$

Thus, $\psi(0) = c(1-\mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$. Note that

$$\bar{\eta}_i \le \int_0^\infty f_i(s)ds = 1, \quad i = 1, 2, 3.$$

Then, we have

$$\psi(\lambda) \ge \left(\frac{\lambda}{\mu_1}+1\right)(\lambda+c) - \mathcal{R}_0\left(\frac{1}{\eta_2}\frac{\mathcal{R}_{02}}{\mathcal{R}_0}\lambda + c\left(\frac{1}{\eta_2}\frac{\mathcal{R}_{02}}{\mathcal{R}_0} + \frac{\mathcal{R}_{01}}{\mathcal{R}_0}\frac{1}{\eta_1}\frac{1}{\eta_3}\right)\right) \to +\infty$$

as $\lambda \to +\infty$. This yields that equation (3.2) has at least one positive root. Therefore, the infection-free equilibrium E_0 is unstable if $\mathcal{R}_0 > 1$.

The chronic infection equilibrium $\bar{E} = (\bar{T}, \bar{T}^*, \bar{V})$ satisfies

$$\begin{aligned} n(\bar{T}) - \beta_1\bar{T}\bar{V} - \beta_2\bar{T}\bar{T}^* &= 0,\\ \eta_1\beta_1\bar{T}\bar{V} + \eta_2\beta_2\bar{T}\bar{T}^* - \mu_1\bar{T}^* &= 0,\\ b\eta_3\bar{T}^* - c\bar{V} &= 0. \end{aligned} \tag{3.3}$$

From the third equation of (3.3), we have $\bar{V} = b\eta_3\bar{T}^*/c$. Substituting it into the first equation, we have $\bar{T}^* = \frac{cn(\bar{T})}{(b\beta_1\eta_3+c\beta_2)\bar{T}}$. Substituting $\bar{T}^*$ and $\bar{V}$ into the second equation, we obtain that

$$\bar{T} = \frac{c\mu_1}{b\beta_1\eta_1\eta_3 + c\eta_2\beta_2} = \frac{T^0}{\mathcal{R}_0}.$$

Thus, $\bar{E}$ exists if and only if $n(\bar{T}) > 0$. Since $n(T^0) = 0$ and $0 < \bar{T} < T^0$ when $\mathcal{R}_0 > 1$, we conclude that $n(\bar{T}) > 0$ and $\bar{E}$ is the unique chronic infection equilibrium. □

Using a similar argument as in the proof of Theorem 6.1 of Róst and Wu [40], Theorem 2 of Liu et al. [27] and Theorem 4.2 of Lai and Zou [25], we can prove the following theorem.

Theorem 3.3. *If* $\mathcal{R}_0 > 1$, *then system (2.2) is uniformly persistent, that is, there exists a constant* $\sigma_0 > 0$ *such that*

$$\liminf_{t\to\infty} T(t) \ge \sigma_0, \quad \liminf_{t\to\infty} T^*(t) \ge \sigma_0, \quad \liminf_{t\to\infty} V(t) \ge \sigma_0.$$

4. Global stability of equilibria

In this section, we construct a suitable Lyapunov function to investigate the global stability of the infection-free equilibrium and chronic infection equilibrium for system (2.2).

Theorem 4.1. *If* $\mathcal{R}_0 < 1$ *and* $f_1(s) = f_2(s)$, *then the infection-free equilibrium* $E_0(T^0, 0, 0)$ *of system (2.2) is globally asymptotically stable in* Γ.

Proof. We define a Lyapunov function as follows:

$$\begin{aligned} L(t) &= T(t) - T^0\ln\frac{T(t)}{T^0} + \frac{1}{\eta_1}T^*(t) + \frac{\beta_1 T^0}{c}V(t)\\ &\quad + \frac{1}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\int_{-s}^0 [\beta_1 T_t(\tau)V_t(\tau) + \beta_2 T_t(\tau)T_t^*(\tau)]d\tau ds\\ &\quad + \frac{b\beta_1 T^0}{c}\int_0^\infty f_3(s)e^{-\mu_2 s}\int_{-s}^0 T_t^*(\tau)d\tau ds. \end{aligned}$$

Then the time derivative of $L(t)$ along solutions of system (2.2) satisfies

$$\begin{aligned} &\frac{dL(t)}{dt}\Big|_{(2.2)}\\ &= \left(1-\frac{T^0}{T}\right)(n(T) - \beta_1 TV - \beta_2 TT^*) - \frac{\mu_1}{\eta_1}T^* - \beta_1 T^0 V\\ &\quad + \frac{1}{\eta_1}\int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)]f_1(s)e^{-\mu_1 s}ds\\ &\quad + \frac{b\beta_1 T^0}{c}\int_0^\infty f_3(s)e^{-\mu_2 s}T^*(t-s)ds + \beta_1 TV + \beta_2 TT^*\\ &\quad - \frac{1}{\eta_1}\int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)]f_1(s)e^{-\mu_1 s}ds\\ &\quad + \frac{b\beta_1 T^0}{c}\int_0^\infty f_3(s)e^{-\mu_2 s}(T^* - T^*(t-s))ds\\ &= \left(1-\frac{T^0}{T}\right)n(T) + \left(\beta_2 T^0 + \frac{b\beta_1 T^0\eta_3}{c} - \frac{\mu_1}{\eta_1}\right)T^*\\ &= \left(1-\frac{T^0}{T}\right)n(T) + \frac{\mu_1}{\eta_1}(\mathcal{R}_0 - 1)T^*. \end{aligned}$$

If $\mathcal{R}_0 < 1$, then from (H_1), $\frac{dL(t)}{dt}|_{(2.2)} = 0$ implies that $T = T^0$ and $T^* = 0$. It is clear that the largest invariant set $\mathcal{M}_0 \subseteq \mathcal{M} = \{(T, T^*, V) : \frac{dL(t)}{dt}|_{(2.2)} = 0\}$ is the singleton $\{E_0\}$. By the Lyapunov–LaSalle invariance principle (see Kuang [24]), E_0 is globally asymptotically stable. □

Next, we investigate the global stability of the chronic infection equilibrium $\bar{E}$ for system (2.2) when $\mathcal{R}_0 > 1$. Let

$$g(x) := x - 1 - \ln x.$$

Thus, the function g has a global minimum at 1 and satisfies $g(1) = 0$.

Theorem 4.2. *If* $\mathcal{R}_0 > 1$ *and* $f_1(s) = f_2(s)$, *then the unique chronic infection equilibrium* $\bar{E}(\bar{T}, \bar{T}^*, \bar{V})$ *of system (2.2) is globally asymptotically stable in the interior* $\overset{\circ}{\Gamma}$ *of* Γ.

Proof. We define a Lyapunov function as follows:

$$U(t) = U_1(t) + U_2(t) + U_3(t),$$

where

$$\begin{aligned} U_1(t) &= T(t) - \bar{T}\ln\frac{T(t)}{\bar{T}} + \frac{1}{\eta_1}\left(T^*(t) - \bar{T}^*\ln\frac{T^*(t)}{\bar{T}^*}\right)\\ &\quad + \frac{\beta_1\bar{T}\bar{V}}{b\eta_3\bar{T}^*}\left(V(t) - \bar{V}\ln\frac{V(t)}{\bar{V}}\right), \end{aligned}$$

$$U_2(t) = \frac{\beta_1\bar{T}\bar{V}}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\int_{-s}^0 g\left(\frac{T_t(\tau)V_t(\tau)}{\bar{T}\bar{V}}\right)d\tau ds + \frac{\beta_2\bar{T}\bar{T}^*}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\int_{-s}^0 g\left(\frac{T_t(\tau)T_t^*(\tau)}{\bar{T}\bar{T}^*}\right)d\tau ds,$$

and

$$U_3(t) = \frac{\beta_1\bar{T}\bar{V}}{\eta_3}\int_0^\infty f_3(s)e^{-\mu_2 s}\int_{-s}^0 g\left(\frac{T_t^*(\tau)}{\bar{T}^*}\right)d\tau ds.$$

Calculating the time derivative of U_1, U_2 and U_3 along solutions of system (2.2), we have

$$\begin{aligned}
&\frac{dU_1(t)}{dt}\Big|_{(2.2)}\\
&= \left(1-\frac{\bar{T}}{T}\right)(n(T)-n(\bar{T}) + \beta_1\bar{T}\bar{V} + \beta_2\bar{T}\bar{T}^* - \beta_1 TV - \beta_2 TT^*)\\
&\quad + \frac{1}{\eta_1}\left(1-\frac{\bar{T}^*}{T^*}\right)\left(\int_0^\infty [\beta_1 T(t-s)V(t-s)\right.\\
&\quad \left. + \beta_2 T(t-s)T^*(t-s)]f_1(s)e^{-\mu_1 s}ds - \mu_1 T^*\right)\\
&\quad + \frac{\beta_1\bar{T}\bar{V}}{b\eta_3\bar{T}^*}\left(1-\frac{\bar{V}}{V}\right)\left(b\int_0^\infty f_3(s)e^{-\mu_2 s}T^*(t-s)ds - cV\right)\\
&= \left(1-\frac{\bar{T}}{T}\right)(n(T)-n(\bar{T})) + \beta_1\bar{T}\bar{V} + \beta_2\bar{T}\bar{T}^* - \beta_1 TV - \beta_2 TT^*\\
&\quad - \beta_1\bar{T}\bar{V}\frac{\bar{T}}{T} - \beta_2\bar{T}\bar{T}^*\frac{\bar{T}}{T} + \beta_1\bar{T}V + \beta_2\bar{T}T^* + \frac{1}{\eta_1}\int_0^\infty [\beta_1 T(t-s)V(t-s)\\
&\quad + \beta_2 T(t-s)T^*(t-s)]f_1(s)e^{-\mu_1 s}ds - \frac{\mu_1}{\eta_1}T^*\\
&\quad - \frac{1}{\eta_1}\frac{\bar{T}^*}{T^*}\int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)]f_1(s)e^{-\mu_1 s}ds\\
&\quad + \frac{\mu_1}{\eta_1}\bar{T}^* + \frac{\beta_1\bar{T}\bar{V}}{\eta_3\bar{T}^*}\int_0^\infty f_3(s)e^{-\mu_2 s}T^*(t-s)ds - \frac{c\beta_1\bar{T}\bar{V}}{b\eta_3\bar{T}^*}V\\
&\quad - \frac{\beta_1\bar{T}\bar{V}}{\eta_3\bar{T}^*}\frac{\bar{V}}{V}\int_0^\infty f_3(s)e^{-\mu_2 s}T^*(t-s)ds + \frac{c\beta_1\bar{T}\bar{V}}{b\eta_3\bar{T}^*}\bar{V},
\end{aligned}$$

$$\begin{aligned}
&\frac{dU_2(t)}{dt}\Big|_{(2.2)}\\
&= \beta_1 TV - \frac{1}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\beta_1 T(t-s)V(t-s)ds\\
&\quad + \frac{\beta_1\bar{T}\bar{V}}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\ln\frac{T(t-s)V(t-s)}{TV}ds\\
&\quad + \beta_2 TT^* - \frac{1}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\beta_2 T(t-s)T^*(t-s)ds\\
&\quad + \frac{\beta_2\bar{T}\bar{T}^*}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\ln\frac{T(t-s)T^*(t-s)}{TT^*}ds,
\end{aligned}$$

and

$$\frac{dU_3(t)}{dt}\Big|_{(2.2)} = \beta_1\bar{T}\bar{V}\frac{T^*}{\bar{T}^*} - \frac{\beta_1\bar{T}\bar{V}}{\eta_3\bar{T}^*}\int_0^\infty f_3(s)e^{-\mu_2 s}T^*(t-s)ds + \frac{\beta_1\bar{T}\bar{V}}{\eta_3}\int_0^\infty f_3(s)e^{-\mu_2 s}\ln\frac{T^*(t-s)}{T^*}ds.$$

By using

$$n(\bar{T}) = \beta_1\bar{T}\bar{V} + \beta_2\bar{T}\bar{T}^* = \frac{\mu_1}{\eta_1}\bar{T}^* = \frac{c\mu_1}{b\eta_1\eta_3}\bar{V},$$

we obtain that

$$\begin{aligned}
&\frac{dU(t)}{dt}\Big|_{(2.2)}\\
&= \left(1-\frac{\bar{T}}{T}\right)(n(T)-n(\bar{T})) + \beta_1\bar{T}\bar{V} - \beta_1\bar{T}\bar{V}\frac{\bar{T}}{T}\\
&\quad + \frac{\beta_1\bar{T}\bar{V}}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\left[2 - \frac{T(t-s)V(t-s)\bar{T}^*}{\bar{T}\bar{V}T^*}\right.\\
&\quad \left. + \ln\frac{T(t-s)V(t-s)}{TV}\right]ds\\
&\quad + \frac{\beta_2\bar{T}\bar{T}^*}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}\left[2 - \frac{\bar{T}}{T} - \frac{T(t-s)T^*(t-s)}{\bar{T}T^*}\right.\\
&\quad \left. + \ln\frac{T(t-s)T^*(t-s)}{TT^*}\right]ds\\
&\quad - \frac{\beta_1\bar{T}\bar{V}}{\eta_3}\int_0^\infty f_3(s)e^{-\mu_2 s}\frac{\bar{V}T^*(t-s)}{V\bar{T}^*}ds\\
&\quad + \frac{\beta_1\bar{T}\bar{V}}{\eta_3}\int_0^\infty f_3(s)e^{-\mu_2 s}\ln\frac{T^*(t-s)}{T^*}ds\\
&= \left(1-\frac{\bar{T}}{T}\right)(n(T)-n(\bar{T})) - \frac{\beta_1\bar{T}\bar{V}}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}g\left(\frac{\bar{T}}{T}\right)ds\\
&\quad - \frac{\beta_1\bar{T}\bar{V}}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}g\left(\frac{T(t-s)V(t-s)\bar{T}^*}{\bar{T}\bar{V}T^*}\right)ds\\
&\quad - \frac{\beta_2\bar{T}\bar{T}^*}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}g\left(\frac{\bar{T}}{T}\right)ds\\
&\quad - \frac{\beta_2\bar{T}\bar{T}^*}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}g\left(\frac{T(t-s)T^*(t-s)}{\bar{T}T^*}\right)ds + \beta_1\bar{T}\bar{V}\\
&\quad + \beta_1\bar{T}\bar{V}\ln\frac{\bar{V}T^*}{V\bar{T}^*} - \frac{\beta_1\bar{T}\bar{V}}{\eta_3}\int_0^\infty f_3(s)e^{-\mu_2 s}\frac{\bar{V}T^*(t-s)}{V\bar{T}^*}ds\\
&\quad + \frac{\beta_1\bar{T}\bar{V}}{\eta_3}\int_0^\infty f_3(s)e^{-\mu_2 s}\ln\frac{T^*(t-s)}{T^*}ds\\
&= \left(1-\frac{\bar{T}}{T}\right)(n(T)-n(\bar{T})) - \frac{\beta_1\bar{T}\bar{V}}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}g\left(\frac{\bar{T}}{T}\right)ds\\
&\quad - \frac{\beta_1\bar{T}\bar{V}}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}g\left(\frac{T(t-s)V(t-s)\bar{T}^*}{\bar{T}\bar{V}T^*}\right)ds\\
&\quad - \frac{\beta_2\bar{T}\bar{T}^*}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}g\left(\frac{\bar{T}}{T}\right)ds\\
&\quad - \frac{\beta_2\bar{T}\bar{T}^*}{\eta_1}\int_0^\infty f_1(s)e^{-\mu_1 s}g\left(\frac{T(t-s)T^*(t-s)}{\bar{T}T^*}\right)ds\\
&\quad - \frac{\beta_1\bar{T}\bar{V}}{\eta_3}\int_0^\infty f_3(s)e^{-\mu_2 s}g\left(\frac{\bar{V}T^*(t-s)}{V\bar{T}^*}\right)ds.
\end{aligned}$$

From (H_1) and (H_2), we know that

$$\left(1-\frac{\bar{T}}{T}\right)(n(T)-n(\bar{T})) \le 0.$$

According to the property of $g(x)$, we obtain that $\frac{dU(t)}{dt}|_{(2.2)} \le 0$. It can be verified that $\frac{dU(t)}{dt}|_{(2.2)} = 0$ if and only if

$$\frac{\bar{T}}{T} = \frac{T(t-s)V(t-s)\bar{T}^*}{\bar{T}\bar{V}T^*} = \frac{T(t-s)T^*(t-s)}{\bar{T}T^*} = \frac{\bar{V}T^*(t-s)}{V\bar{T}^*} = 1.$$

It means that the largest invariant set

$$\mathcal{M}_0 \subseteq \mathcal{M} = \left\{(T,T^*,V) : \frac{dU(t)}{dt}\Big|_{(2.2)} = 0\right\}$$

is the singleton $\{\bar{E}\}$. Again by the Lyapunov–LaSalle invariance principle, the chronic infection equilibrium $\bar{E}$ of system (2.2) is globally asymptotically stable. □

Remark 4.3. If Assumption (H_2) does not hold, the chronic infection equilibrium $\bar{E}$ may lose its stability and periodic oscillations can occur because of Hopf bifurcation. We will give an example in the next section.

5. Some special cases

System (2.2) was set up as a general model to describe the virus-to-cell and cell-to-cell transmissions of certain viruses within the host. There are three distributed delay terms. By choosing some specific kernels, the model reduces to various viral infection models (with discrete or distributed delays) studied in the literature. In this section, we present some such examples.

Example 5.1. Consider the special forms $f_1(s) = f_2(s) = \delta(s-\tau_1)$ and $f_3(s) = \delta(s-\tau_2)$, where $\delta(\cdot)$ is the Dirac delta function. Then system (2.2) reduces to

$$\begin{aligned}\frac{dT(t)}{dt} &= n(T(t)) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t),\\ \frac{dT^*(t)}{dt} &= e^{-\mu_1\tau_1}[\beta_1 T(t-\tau_1)V(t-\tau_1) + \beta_2 T(t-\tau_1)T^*(t-\tau_1)]\\ &\quad - \mu_1 T^*(t),\\ \frac{dV(t)}{dt} &= be^{-\mu_2\tau_2}T^*(t-\tau_2) - cV(t)\end{aligned} \tag{5.1}$$

with $\tau_1, \tau_2 \geq 0$. Applying Theorems 4.1 and 4.2 to system (5.1) yields the following result.

Theorem 5.2. *If* $\mathcal{R}_0 = \frac{b\beta_1 T^0 e^{-(\mu_1\tau_1+\mu_2\tau_2)}}{c\mu_1} + \frac{\beta_2 T^0 e^{-\mu_1\tau_1}}{\mu_1} < 1$, *then the infection-free equilibrium* E_0 *of system (5.1) is globally asymptotically stable; if* $\mathcal{R}_0 > 1$, *then the chronic infection equilibrium* $\bar{E}$ *of system (5.1) is globally asymptotically stable.*

Remark 5.3. If $\tau_1 = \tau_2 = 0$, then system (5.1) reduces to an ODE model for HIV infection considered in Pourbashash et al. [39] and the global dynamics are completely determined by $\mathcal{R}_0$.

Example 5.4. Consider $n(T(t)) = h - d_T T(t)$, $f_1(s) = f_2(s)$ and $f_3(s) = \delta(s-\tau_1)$, system (2.2) becomes to

$$\begin{aligned}\frac{dT(t)}{dt} &= h - d_T T(t) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t),\\ \frac{dT^*(t)}{dt} &= \int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)]e^{-\mu_1 s} f_1(s)ds\\ &\quad - \mu_1 T^*(t),\\ \frac{dV(t)}{dt} &= be^{-\mu_2\tau_1}T^*(t-\tau_1) - cV(t),\end{aligned} \tag{5.2}$$

where $h, d_T > 0$ and $\tau_1 \geq 0$. It is obvious that $n(T)$ satisfies Assumptions (H_1) and (H_2). By Theorems 4.1 and 4.2, we have the following result.

Theorem 5.5. *If* $\mathcal{R}_0 = \frac{b\beta_1 T^0 \eta_1 e^{-\mu_2\tau_1}}{c\mu_1} + \frac{\beta_2 T^0 \eta_1}{\mu_1} < 1$, *then the infection-free equilibrium* E_0 *of system (5.2) is globally asymptotically stable; if* $\mathcal{R}_0 > 1$, *then the chronic infection equilibrium* $\bar{E}$ *of system (5.2) is globally asymptotically stable.*

Remark 5.6. If $\tau_1 = 0$, then system (5.2) reduces to the system describing the virus-to-cell and cell-to-cell transmissions of HIV studied in Lai and Zou [25]. It is shown in [25] that E_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$ while $\bar{E}$ is globally asymptotically stable if $\mathcal{R}_0 > 1$.

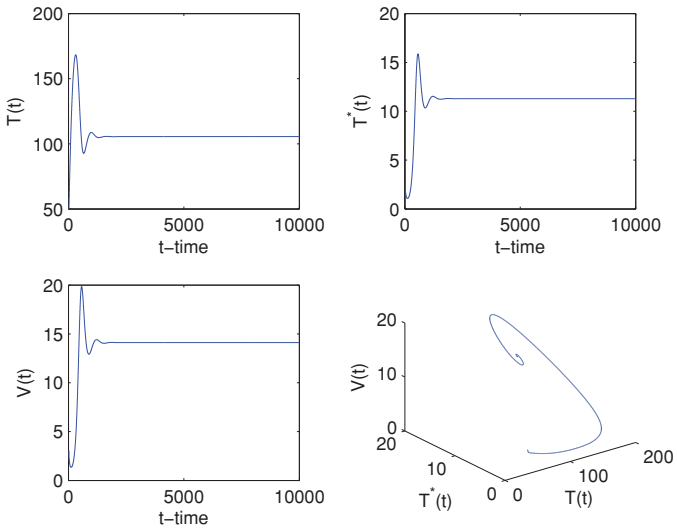

Fig. 2. Parameter values are $h = 1$, $d_T = 0.02$, $r = 0.018$, $K = 1500$, $\beta_1 = 0.0002$, $\beta_2 = 0.0003$, $\mu_1 = 0.03$, $b = 3$, $c = 2.4$ and $\tau = 22$, then $\mathcal{R}_0 = 2.0574 > 1$ and the chronic infection equilibrium $\bar{E}$ of system (5.3) is globally asymptotically stable.

Example 5.7. Consider $n(T(t)) = h - d_T T(t) + rT(t)(1 - \frac{T(t)}{K})$, $f_1(s) = f_2(s) = \delta(s-\tau)$ and $f_3(s) = \delta(s)$, system (2.2) becomes

$$\begin{aligned}\frac{dT(t)}{dt} &= h - d_T T(t) + rT(t)\left(1 - \frac{T(t)}{K}\right) - \beta_1 T(t)V(t)\\ &\quad - \beta_2 T(t)T^*(t),\\ \frac{dT^*(t)}{dt} &= e^{-\mu_1\tau}[\beta_1 T(t-\tau)V(t-\tau) + \beta_2 T(t-\tau)T^*(t-\tau)]\\ &\quad - \mu_1 T^*(t),\\ \frac{dV(t)}{dt} &= bT^*(t) - cV(t),\end{aligned} \tag{5.3}$$

where h, d_T, r, K, $\mu_1 > 0$ and $\tau \geq 0$. Clearly, $n(T)$ satisfies the Assumption (H_1). Further, $n(T)$ satisfies Assumption (H_2) if $d_T \geq r$. From Theorem 4.1 and Theorem 4.2, we have the following result.

Theorem 5.8. *If* $\mathcal{R}_0 = \frac{b\beta_1 T^0 e^{-\mu_1\tau}}{c\mu_1} + \frac{\beta_2 T^0 e^{-\mu_1\tau}}{\mu_1} < 1$, *then the infection-free equilibrium* E_0 *of system (5.3) is globally asymptotically stable; If* $\mathcal{R}_0 > 1$, *then the chronic infection equilibrium* $\bar{E}$ *of system (5.3) is globally asymptotically stable.*

Fig. 2 presents the numerical simulations of system (5.3) following the above theorem. In fact, the characteristic equation of system (5.3) at $\bar{E}$ is

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 + (b_2(\tau)\lambda^2 + b_1(\tau)\lambda + b_0(\tau))e^{-\lambda\tau} = 0, \tag{5.4}$$

where

$$\begin{aligned}a_2 &= c + \mu_1 + d_T + \frac{2r}{K}\bar{T} + \beta_1\bar{V} + \beta_2\bar{T}^* - r,\\ a_1 &= c\mu_1 + (c+\mu_1)\left(d_T + \frac{2r}{K}\bar{T} + \beta_1\bar{V} + \beta_2\bar{T}^* - r\right),\\ a_0 &= c\mu_1\left(d_T + \frac{2r}{K}\bar{T} + \beta_1\bar{V} + \beta_2\bar{T}^* - r\right),\\ b_2(\tau) &= -\beta_2\bar{T}e^{-\mu_1\tau},\\ b_1(\tau) &= -\left(\beta_2\left(d_T + \frac{2r}{K}\bar{T} - r\right) + b\beta_1 + c\beta_2\right)\bar{T}e^{-\mu_1\tau},\\ b_0(\tau) &= -(b\beta_1 + c\beta_2)\left(d_T + \frac{2r}{K}\bar{T} - r\right)\bar{T}e^{-\mu_1\tau}.\end{aligned}$$

When $\tau = 0$, equation (5.4) becomes

$$\lambda^3 + (a_2 + b_2(0))\lambda^2 + (a_1 + b_1(0))\lambda + a_0 + b_0(0) = 0.$$

Since $d_T \geq r$, we have

$$a_2 + b_2(0) > 0, \quad a_1 + b_1(0) > 0, \quad a_0 + b_0(0) > 0. \tag{5.5}$$

By calculation, we obtain

$$(a_1 + b_1(0))(a_2 + b_2(0)) - (a_0 + b_0(0)) > 0. \tag{5.6}$$

Using the Routh–Hurwitz criterion, all roots of equation (5.4) have negative real parts when $\tau = 0$. Let $\lambda = i\omega(\omega > 0)$ be a purely imaginary root of equation (5.4). Substituting it into (5.4) and separating the real and imaginary parts, we have

$$\begin{aligned}(b_0(\tau) - b_2(\tau)\omega^2)\cos\omega\tau + b_1(\tau)\omega\sin\omega\tau &= a_2\omega^2 - a_0,\\ -(b_0(\tau) - b_2(\tau)\omega^2)\sin\omega\tau + b_1(\tau)\omega\cos\omega\tau &= \omega^3 - a_1\omega.\end{aligned} \tag{5.7}$$

Squaring and adding both equations of (5.7) gives

$$F(\omega, \tau) := \omega^6 + p_2(\tau)\omega^4 + p_1(\tau)\omega^2 + p_0(\tau) = 0, \tag{5.8}$$

where

$$\begin{aligned}p_2(\tau) &= a_2^2 - 2a_1 - b_2^2(\tau),\\ p_1(\tau) &= a_1^2 - 2a_0a_2 - b_1^2(\tau) + 2b_0(\tau)b_2(\tau),\\ p_0(\tau) &= a_0^2 - b_0^2(\tau).\end{aligned}$$

After some computations we obtain that

$$\begin{aligned}p_2(\tau) &= a_2^2 - 2a_1 - b_2^2(\tau)\\ &= c^2 + \mu_1^2 + \left(\frac{h}{\bar{T}} + \frac{r}{K}\bar{T}\right)^2 - (\beta_2\bar{T}e^{-\mu_1\tau})^2\\ &> c^2 + \mu_1^2 + \left(\frac{h}{\bar{T}} + \frac{r}{K}\bar{T}\right)^2 - \mu_1^2\\ &= c^2 + \left(\frac{h}{\bar{T}} + \frac{r}{K}\bar{T}\right)^2 > 0,\end{aligned}$$

$$\begin{aligned}p_1(\tau) &= a_1^2 - 2a_0a_2 - b_1^2(\tau) + 2b_0(\tau)b_2(\tau)\\ &= (c^2 + \mu_1^2)\left(\frac{h}{\bar{T}} + \frac{r}{K}\bar{T}\right)^2 - \left(\beta_2\bar{T}e^{-\mu_1\tau}\left(d_T + \frac{2r}{K}\bar{T} - r\right)\right)^2\\ &> (c^2 + \mu_1^2)\left(\frac{h}{\bar{T}} + \frac{r}{K}\bar{T}\right)^2 - \mu_1^2\left(\frac{h}{\bar{T}} + \frac{r}{K}\bar{T}\right)^2\\ &= c^2\left(\frac{h}{\bar{T}} + \frac{r}{K}\bar{T}\right)^2 > 0,\end{aligned}$$

and

$$\begin{aligned}p_0(\tau) &= a_0^2 - b_0^2(\tau)\\ &= c^2\mu_1^2(\beta_1\bar{V} + \beta_2\bar{T}^*)\left(2\left(\frac{h}{\bar{T}} + \frac{r}{K}\bar{T}\right) - \beta_1\bar{V} - \beta_2\bar{T}^*\right).\end{aligned}$$

It is easy to obtain that $p_0(\tau) > 0$ if $d_T \geq r$. Thus, if $d_T \geq r$, the chronic infection equilibrium is locally asymptotically stable.

However, the stability may change when $d_T < r$. If both (5.5) and (5.6) hold, then all roots of equation (5.4) have negative real parts when $\tau = 0$. From the above discussion, it follows that $F(\omega, \tau) = 0$ has positive roots if and only if $p_0(\tau) < 0$, which is equivalent to

(H_3) $\frac{h}{\bar{T}} + d_T - r\left(1 - \frac{3\bar{T}}{K}\right) < 0.$

If (H_3) holds, then $F(0, \tau) = p_0(\tau) < 0$. Since $\lim_{\omega\to+\infty} F(\omega, \tau) = +\infty$ and

$$\frac{\partial F(\omega, \tau)}{\partial\omega} = 6\omega^5 + 4p_2(\tau)\omega^3 + 2p_1(\tau)\omega^2 > 0, \quad \text{for} \quad \omega > 0,$$

the Implicit Function Theorem implies that there exists a unique C^1 function $\omega = \omega(\tau) > 0$ such that $F(\omega(\tau), \tau) = 0$ for $\tau > 0$.

Let $\omega = \omega(\tau) > 0$ be the unique positive root of $F(\omega(\tau), \tau) = 0$. From equation (5.7), it follows that

$$\begin{aligned}\sin\omega(\tau)\tau &= \frac{b_1(\tau)\omega(\tau)(a_2\omega^2(\tau) - a_0) - (\omega^3(\tau) - a_1\omega(\tau))(b_0(\tau) - b_2(\tau)\omega^2(\tau))}{b_1^2(\tau)\omega^2(\tau) + (b_0(\tau) - b_2(\tau)\omega^2(\tau))^2},\\ \cos\omega(\tau)\tau &= \frac{(a_2\omega^2(\tau) - a_0)(b_0(\tau) - b_2(\tau)\omega^2(\tau)) + b_1(\tau)\omega(\tau)(\omega^3(\tau) - a_1\omega(\tau))}{b_1^2(\tau)\omega^2(\tau) + (b_0(\tau) - b_2(\tau)\omega^2(\tau))^2}.\end{aligned} \tag{5.9}$$

Define $\theta(\tau) \in [0, 2\pi]$ such that $\sin\theta(\tau)$ and $\cos\theta(\tau)$ are given by the right-hand sides of equation (5.9), respectively. Following Beretta and Kuang [4], we define

$$S_n(\tau) = \tau - \frac{\theta(\tau) + 2n\pi}{\omega(\tau)}, \quad n \in \mathbb{N}, \quad \tau \in (0, \tau_{\max}), \tag{5.10}$$

where $\tau_{\max} = \frac{1}{\mu_1}\ln\frac{(b\beta_1 + c\beta_2)T^0}{c\mu_1}$. Clearly, $i\omega(\tau^*)$ is a purely imaginary root of equation (5.4) if and only if τ^* is a root of function S_n for some $n \in \mathbb{N}$.

The following result is due to Beretta and Kuang [4].

Theorem 5.9. *The characteristic equation (5.4) admits a pair of simple and conjugate roots $\lambda_+(\tau^*) = i\omega(\tau^*)$ and $\lambda_-(\tau^*) = -i\omega(\tau^*)$, $\omega(\tau^*) > 0$ at $\tau^* \in (0, \tau_{\max})$ if $S_n(\tau^*) = 0$ for some $n \in \mathbb{N}$. This pair of simple conjugate pure imaginary roots crosses the imaginary axis from left to right if $\kappa(\tau^*) > 0$ and crosses the imaginary axis from right to left if $\kappa(\tau^*) < 0$, where*

$$\kappa(\tau^*) = \text{sign}\left\{\frac{d\text{Re}\lambda}{d\tau}\Big|_{\lambda=i\omega(\tau^*)}\right\} = \text{sign}\left\{\frac{dS_n(\tau)}{d\tau}\Big|_{\tau=\tau^*}\right\}.$$

Based on the above analysis, we obtain the following results by Theorem 5.9 and the Hopf bifurcation theorem in Hale and Verduyn Lunel [20].

Theorem 5.10. *Assume that $R_0 > 1$ and (H_3) holds, we have the following conclusions.*

(i) *If the function $S_0(\tau)$ has no positive zeros in $\tau \in (0, \tau_{\max})$, then the chronic infection equilibrium $\bar{E}$ of system (5.3) is asymptotically stable for all $0 \leq \tau < \tau_{\max}$;*

(ii) *If the function $S_n(\tau)$ has positive simple zeros such that $\tau_1 < \tau_2 < \cdots < \tau_m$ and $S'_{n_j}(\tau_j) \neq 0$, then the chronic infection equilibrium $\bar{E}$ of system (5.3) is asymptotically stable for $\tau \in [0, \tau_1) \cup (\tau_m, \tau_{\max})$ and unstable when $\tau \in (\tau_1, \tau_m)$, with a Hopf bifurcation occurring when $\tau = \tau_j$, $j = 1, 2, \cdots, m$.*

In the following, we choose a set of parameters $h = 1$, $d_T = 0.02$, $r = 0.06$, $K = 1500$, $\beta_1 = 0.0002$, $\beta_2 = 0.0003$, $b = 3$, $c = 2.4$, and $\mu_1 = 0.03$. Then we have $\tau_{\max} \approx 97.761$ and (H_3) holds when $\tau \in (0, \tau_2)$, here $\tau_2 \approx 57.497$. We draw the graphs of S_0 and S_1 versus τ on $(0, \tau_2)$, see Fig. 3. It is clear that there is a critical value of the delay τ, denoted by τ_1, and $\tau_1 \approx 20.526$. From Theorem 5.10, we conclude that the equilibrium $\bar{E}$ is asymptotically stable for $\tau \in [0, \tau_1) \cup (\tau_2, \tau_{\max})$ and unstable for $\tau \in (\tau_1, \tau_2)$, which are shown in Figs. 4–6.

Example 5.11. Assume $\beta_2 = 0$. Then system (2.2) becomes

$$\begin{aligned}\frac{dT(t)}{dt} &= n(T(t)) - \beta_1 T(t)V(t),\\ \frac{dT^*(t)}{dt} &= \int_0^\infty \beta_1 T(t-s)V(t-s)e^{-\mu_1 s}f_1(s)ds - \mu_1 T^*(t),\\ \frac{dV(t)}{dt} &= b\int_0^\infty e^{-\mu_3 s}f_3(s)T^*(t-s)ds - cV(t).\end{aligned} \tag{5.11}$$

Applying Theorems 4.1 and 4.2 to system (5.11) yields the following result.

Theorem 5.12. *If $R_0 = \frac{b_1\beta T^0\eta_1\eta_3}{c\mu_1} < 1$, then the infection-free equilibrium E_0 of system (5.11) is globally asymptotically stable; if $R_0 > 1$, then the chronic infection equilibrium $\bar{E}$ of system (5.11) is globally asymptotically stable.*

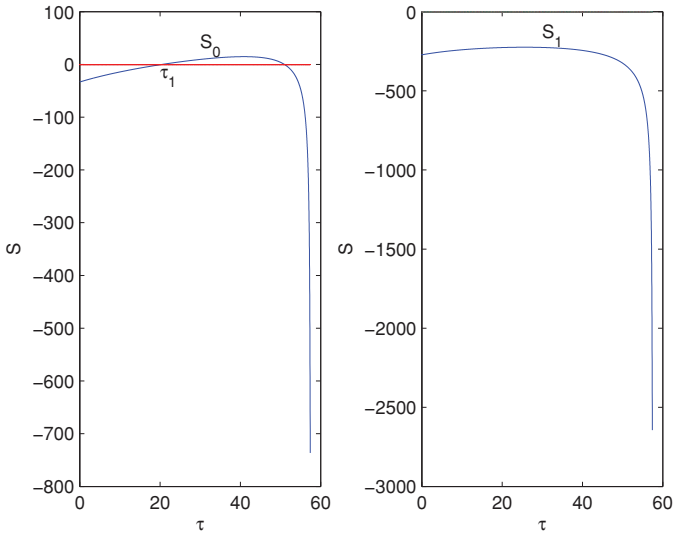

Fig. 3. Graphs of functions $S_0(\tau)$ and $S_1(\tau)$ for $\tau \in [0, \tau_2)$.

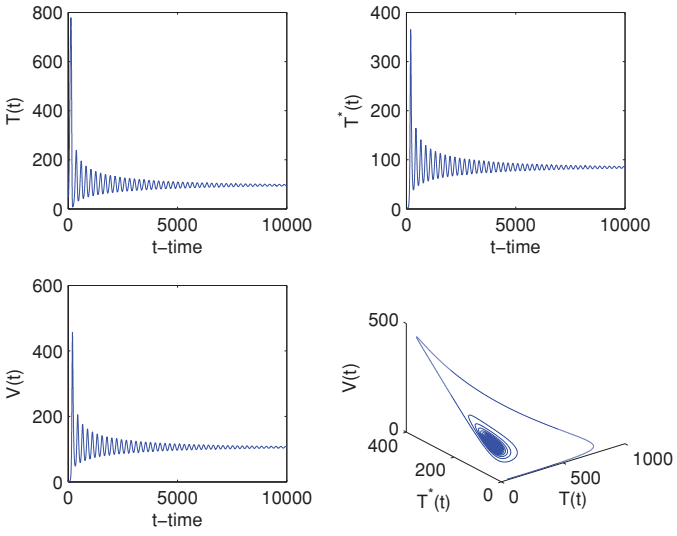

Fig. 4. The chronic infection equilibrium $\tilde{E}$ of system (5.3) is asymptotically stable when $\tau \in [0, \tau_1)$. Here $\tau = 19$.

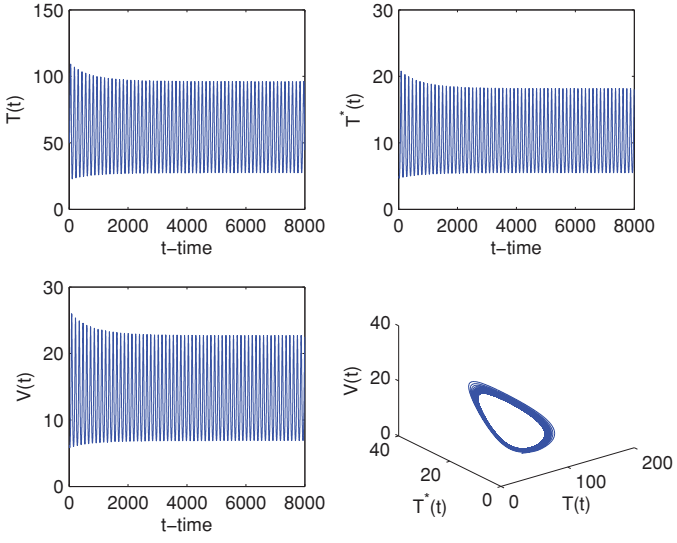

Fig. 5. There are periodic solutions bifurcated from the chronic infection equilibrium $\tilde{E}$ of system (5.3) when $\tau = 23$.

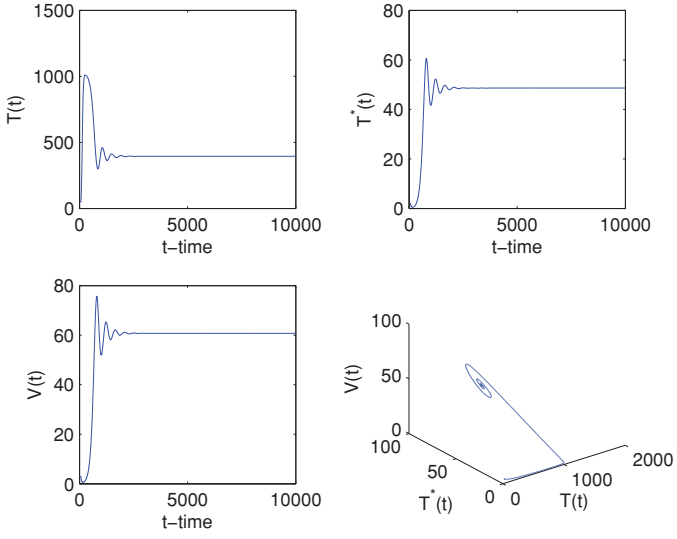

Fig. 6. The chronic infection equilibrium $\tilde{E}$ of system (5.3) becomes asymptotically stable again when $\tau \in (\tau_2, \tau_{\max})$. Here $\tau = 66$.

Remark 5.13. Let $h(x, v) = \beta_1 xv$, then the system studied in Li and Shu [26] is the same as system (5.11). The stabilities of equilibria of system (5.11) obtained in Theorem 5.12 are the same as Theorem 3.1 and 3.2 in [26].

6. Discussion

When a virus (HBV, HIV, HTLV-1, etc.) enters the human body, it first targets specific cells in the bloodstream. After an intracellular period associated with transcription, integration, and the production of capsid proteins, the infected cell releases hundreds of virions that can infect other cells. At the same time, in lymph nodes and the brain the infected cells can spread the virus to other healthy cells directly. In this article we considered a within-host viral infection model with both virus-to-cell and cell-to-cell transmissions and three distributed delays, in which the first distributed delay describes the intracellular latency for the virus-to-cell infection, the second delay represents the intracellular latency for the cell-to-cell infection, and the third delay describes the time period that viruses penetrated into cells and infected cells release new virions. After giving some preliminary results on the positivity and boundedness of solutions, we presented some sufficient conditions to ensure the global stability of the infection-free equilibrium and the chronic infection equilibrium. Since our model is a general system describing the virus-to-cell and cell-to-cell transmissions of certain viruses within the host with three distributed delay terms, it can be reduced to various viral infection models (with discrete or distributed delays) studied in the literature by selecting some specific kernels, some such examples and numerical simulations were given.

The global dynamics of the general model indicate that, under certain conditions, the chronic infection equilibrium is globally asymptotically stable. This shows that the model can be applied to describe the within-host dynamics of HBV, HIV, or HTLV-1 infection, since the main character of these viruses is that there is no specific treatment for such infections which are lifetime. Note that when the intracellular periods for the virus-to-cell and cell-to-cell spreads are described by discrete delays (see model (5.3)), Hopf bifurcation may occur, which could induce oscillations in the cell and virus populations (see Theorem 5.10). However, as pointed out in Culshow and Ruan [6] and Culshaw et al. [7], an intracellular delay for the virus-to-cell transmission does not change the stability of the infected steady state for clinically reported parameter values in the bloodstream whereas

the cell-to-cell spread models can produce infective oscillations in typical tissue culture parameter regimes and the latently infected cells are instrumental in sustaining the infection. This shows that the oscillations in our general model are caused by the cell-to-cell transmission, which further demonstrates that it is necessary to consider both virus-to-cell and cell-to-cell transmissions in order to better understand the within-host dynamics of these viral infections.

Our results also indicate that the target-cell dynamics, i.e., the function $n(T)$ in the model, is important to determine dynamics of the model. If the function $n(T)$ satisfies Assumption (H_1) and Assumption (H_2), no Hopf bifurcations occur. If Assumption (H_2) does not hold, the dynamics of the model will be more complicated. Moreover, if Assumption (H_1) does not hold, the uniqueness of the infection-free equilibrium is not guaranteed, the dynamics of the model are not clear and deserve further consideration.

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