Age-structured within-host HIV dynamics with multiple target cells

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HIV can infect various types of cell populations such as $CD4^+$ T cells and macrophages. The heterogeneity of these target cells implies different birth, death, infection rates, and so on. To investigate the within host dynamics of HIV which can infect n different types of target cells, a theoretical model with infection-age structure for each type of target cells and a general nonlinear incidence rate is proposed in this manuscript. The model, in the form of a hyperbolic system of partial differential equations (for infected target cells) coupled with several ordinary differential equations, is shown to be biologically reasonable with the establishment of existence, positivity and boundedness of solutions. Although the PDE form poses novel challenges to theoretical investigation, rigorous analysis is performed to show the uniform persistence of the virus when the basic reproduction number is greater than one. Furthermore, by constructing suitable Lyapunov functionals, we show that the infection-free steady state is globally asymptotically stable when the basic reproduction number is less than unity, while the positive steady state is globally asymptotically stable when the basic reproduction number is greater than one.

1. Introduction

Since the discovery of human immunodeficiency virus type 1 (HIV-1) in the early 1980s, nearly 78 million people have been infected and about 39 million people have died due to HIV infection. It was estimated that about 35 million people were living with HIV and 2.1 million people were newly infected worldwide in 2013 (World Health Organization, 2014 [56]).

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Due to the obstacles to effective HIV control measures, including lack of prevention, care coverage and lack of rigorous evaluations, HIV infection still remains a serious health problem in the world. Theoretical in-host as well as between-host models have been proposed to provide new insights into the virus transmission and control measures, such as those in [1, 11, 32, 37, 38, 41, 48, 52], among many others.

Most of the previous models were formulated based on the model in [36] (see also in [34]). In recent years, the time delay between viral entry into a target cell and viral production was considered, by using a model with discrete and distributed delays [16, 33], or an age-structured model in the infected cell [31, 40, 57]. The incorporation of an age structure (generally described by partial differential equations in theoretical models) allows us to have a good description of produced viral particles and of the infected cells mortality ([15, 49]). For example, an HIV-1 infection model with age-structured infected cells to account for the mechanism of AZT (Zidovudine) treatment of HIV infection was proposed in [17], and the cost-effectiveness of treatments with combined therapies involving reverse transcriptase, protease, and entry/fusion inhibitors could also be evaluated by age-structured models [40]. These age-structured within-host virus models with the consideration of age-dependent infected cell death rates and viral production rates have attracted many recent investigations, see for example, the models in the literatures [2, 3, 5, 7, 8, 13, 22, 24, 25, 26, 27, 29, 30, 44, 47, 50, 55].

When modelling the infection incidence between the virus and target cells, the mass action term $\beta T(t)V(t)$ is almost always used. However, debates exist for the infection incidence term, with some literatures arguing that the incidence rate should not be strictly linear in each variable over the entire range of virions $V(t)$ and target cells $T(t)$ and nonlinear contact rates are much more appropriate [10, 19, 20]. For example, a virus infection rate with the Beddington-DeAngelis functional response $\beta TV/(1 + k_1T + k_2V)$ was adopted in [53, 57]. Georgescu and Hsieh [10] and Wang, Zhang and Kuniya [50] considered a nonlinear infection rate in the form of $c(T)f(V)$, where $c(T)$ is the contact rate function dependent on susceptible cell density T and $f(V)$ represents the force of infection by virus at density V. Korobeinikov [19, 20] assumed the incidence rate to be a more general form $\varphi(T, V)$.

Most of the above-mentioned HIV infection models only focused on the infection of $CD4^+$ T cells by HIV. However, it was reported that, in addition to $CD4^+$ T cells, other cells such as macrophages [18] and dendritic cells [39] are also susceptible to HIV infection. For example, HIV can infect macrophages through binding of gp120 to CD4 and CCR5 receptors, and macrophages are identified to be a highly productive source of HIV during the latter stage of viral infection [35]. In this case, with

the consideration of different types of target cells, models with more compartments can be proposed, such as those in [6, 37, 42]. Recently, the global dynamics of the steady states of HIV models with multiple target cells was investigated in [51, 52].

In the present paper, we propose a mathematical model with age structure in the infected n types of target cell populations and general nonlinear rates of viral infection. The model is shown to be biologically well posed with the establishment of existence, uniqueness and nonegativeness of solutions. We analyze the model by deriving the basic reproduction number and proving the global stability of steady states. The manuscript is organized as follows. In Section 2, we formulate the mathematical model, propose some biologically meaningful assumptions and establish preliminary results on the existence and uniqueness of solutions by using an equivalent integral formulation. The boundedness of solutions is also obtained in this section. Section 3 presents the uniform persistence of the model system. Furthermore, by constructing suitable Lyapunov functionals, the global stability of equilibria, dependent on the basic reproduction number, is established in Section 4. This paper ends with numerical results and a brief conclusion in Section 5.

2. The model and preliminary results

With the consideration of heterogeneity of target cells and infected cells, for example distinct growth and infection rates [43] between macrophages and $CD4^+$ T cells, the nonlinear infection rates, as well as the age-structured heterogeneity of viral reproduction rates, we extend the well-accepted in-host virus model in [37] to an age-structured model with n types of target cells as follows:

$$\begin{cases} \dfrac{dT_i(t)}{dt} = \lambda_i - d_i T_i(t) - h_i(T_i(t), V(t)), \\ \dfrac{dV(t)}{dt} = \displaystyle\sum_{i=1}^{n} \int_0^\infty p_i(a) I_i(t,a) da - cV(t), \\ \dfrac{\partial I_i(t,a)}{\partial t} + \dfrac{\partial I_i(t,a)}{\partial a} = -\delta_i(a) I_i(t,a), \\ I_i(t,0) = h_i(T_i(t), V(t)),\ i = 1, 2, \cdots, n, \\ T_i(0) = T_i^0 \in R_+, I_i(0,a) \in L_+[0,\infty), V(0) = V^0 \in R_+, \end{cases} \tag{1}$$

where $T_i(t)$ and $V(t)$ denote the concentrations of uninfected target cells of class i ($i = 1, 2, \cdots, n$) and free virus particles at time t, respectively. The variable $I_i(t,a)$ denotes the concentration of infected target cells of

Table 1
Parameter definitions for the model system.

Parameter	Definition
λ_i	Reproduction rate of the i-th uninfected target cells
d_i	Removal rate of the i-th uninfected target cells
$h_i(T_i, V)$	Infection incidence of i-th uninfected target cells by virus
$\delta_i(a)$	Age-dependent per capita death rate of i-th infected cells
c	The clearance rate of virus
$p_i(a)$	The viral production rate of i-th infected cells with age a

class i with infection age a at time t. All parameters are summarized in Table 1 for easy reference. We assume that the function $p_i(\cdot)$ belongs to $L_+[0,\infty)\backslash\{\mathbf{0}\}$, and $\delta_i(\cdot)$ belongs to $L_+[0,\infty)$, where $L_+[0,\infty)$ represents the set of all integrable functions from R_+ to $[0,\infty)$. Moreover, we assume individuals in all ages are subject to death, that is $0 < \bar{\delta} := \min_i\{\bar{\delta}_i\}$, where $\bar{\delta}_i := \inf_{a\in[0,\infty)}\{\delta_i(a)\}$. For system (1), there should be an inherent relationship between the initial value and boundary value for the partial differential equation, that is $I_i(t,0) = I_i(0,a)$ when $t = a = 0$. Hence, we assume

$$h_i(T_i(0), V(0)) = I_i(0,0).$$

The formulation of an infection incidence term $h(T,V)$ plays an important role in modeling virus dynamics. Biologically, the infection happens when T and V are positive while it vanishes when $T = 0$ or $V = 0$. Moreover, the infection rate becomes larger when there are more target cells T or larger viral loads V. Therefore, we impose the following two natural assumptions:

(H$_1$) $h_i(T_i,V) > 0$, $\dfrac{\partial h_i(T_i,V)}{\partial T_i} > 0$, $\dfrac{\partial h_i(T_i,V)}{\partial V} > 0$ for all $T_i > 0$, $V > 0$.
(H$_2$) $h_i(0,V) = h_i(T_i,0) = 0$.

Based on Assumptions H$_1$ and H$_2$, we have $\frac{\partial h_i(T_i,0)}{\partial V} > 0$ and $\frac{\partial h_i(T_i,0)}{\partial T_i} = 0$ for $T_i > 0$. Furthermore, the per capita infection rate $\frac{h(T,V)}{V}$ is a decreasing function on V since virus compete effectively for a limited supply of target cells. Mathematically, we impose the following concavity property for infection incidence terms:

(H$_3$) $\dfrac{\partial^2 h_i(T_i,V)}{\partial V^2} \le 0$ for any T_i, $V > 0$, or $h_i(T_i,V) \le V\dfrac{\partial h_i(T_i,0)}{\partial V}$ for all $V > 0$, and $\dfrac{\partial h_i(T_i,0)}{\partial V}$ is strictly increasing with respect to $T_i > 0$.

In addition, in order to ensure the uniqueness of solutions, the following technical assumption is imposed, which is well-accepted for any term in a biological differential system:

(H$_4$) $h_i(T_i, V),\ i = 1, 2, \cdots, n$ are all Lipschitz continuous on R^2_+.

It turns out that these four assumptions are shared by many incidence terms in various literatures, for example: Holling Type II functional response $\frac{\beta_i T_i V}{1+b_i V}$ [46], Beddington-DeAngelis functional response $\frac{\beta_i T_i V}{1+a_i T_i+b_i V}$ [14], Crowley-Martin functional response $\frac{\beta_i T_i V}{(1+a_i T_i)(1+b_i V)}$ [58] and the contact rate $\beta_i T_i \ln(1 + \frac{a_i V}{1+\beta_i})$ [4], and so on. Later, we will show that Assumption H$_3$ and other assumptions also ensure the uniqueness of the positive equilibrium state when it exists (see Lemma 4).

2.1. Existence of solutions

Note that the partial differential equation in system (1) is a linear transport equation with decay, and therefore by the methods of integration along characteristics, the following partial differential equation with boundary conditions:

$$\begin{cases} \dfrac{\partial I_i(t,a)}{\partial t} + \dfrac{\partial I_i(t,a)}{\partial a} = -\delta_i(a) I_i(t,a), \\ I_i(t,0) = h_i(T_i(t), V(t)),\ t \geq 0, \end{cases}$$

can be solved with the explicit solution:

$$I_i(t,a) = \begin{cases} \sigma_i(a) h_i(T_i(t-a), V(t-a)), & \text{if } t > a \geq 0, \\ \dfrac{\sigma_i(a)}{\sigma_i(a-t)} I_i(0, a-t), & \text{if } a \geq t \geq 0, \end{cases} \tag{2}$$

where $\sigma_i(a) = \exp(-\int_0^a \delta_i(s)ds)$ represents the probability that an infected cell of class i survives till age a. Therefore, the following system of integro-differential equations is equivalent to the system (1):

$$\begin{cases} \dfrac{dT_i(t)}{dt} = \lambda_i - d_i T_i(t) - h_i(T_i(t), V(t)),\ i = 1, 2, \cdots, n, \\ \dfrac{dV(t)}{dt} = \displaystyle\sum_{i=1}^{n} \int_0^\infty p_i(a) I_i(t,a) da - cV(t), \\ I_i(t,a) = \sigma_i(a) h_i(T_i(t-a), V(t-a)) \mathbf{1}_{t>a} + \dfrac{\sigma_i(a)}{\sigma_i(a-t)} I_i(0, a-t) \mathbf{1}_{a>t}, \end{cases} \tag{3}$$

where

$$\mathbf{1}_{t>a} = \begin{cases} 1, & \text{if } t > a \geq 0, \\ 0, & \text{if } a \geq t \geq 0, \end{cases} \quad \text{and} \quad \mathbf{1}_{a>t} = \begin{cases} 0, & \text{if } t > a \geq 0, \\ 1, & \text{if } a \geq t \geq 0. \end{cases}$$

We now show the local existence and uniqueness of solutions to system (3) and hence to system (1). We would like to address reader's attention that our arguments on the uniqueness and nonnegativeness of solutions (Lemmas 1 and 2) are highly motivated by recent work [5].

LEMMA 1. *Let*

$$x_0 = (T_1(0), \cdots, T_n(0), V(0), I_1(0,\cdot), \cdots, I_n(0,\cdot)) \in R_+^{n+1} \times L_+^n[0,\infty).$$

Then there exists $\varepsilon > 0$ and an open neighborhood $B_0 \subset R^{n+1} \times L_+^n[0,\infty)$ with $x_0 \in B_0$ such that there exists a unique continuous function, $\chi : [0,\varepsilon) \times B_0 \longrightarrow R^{n+1} \times L_+^n[0,\infty)$, where $\chi(t,x)$ is the solution to system (3) with $\chi(0,x) = x$.

Proof: It is easy to see that any solution of system (3) must satisfy the following integral equation:

$$\begin{cases} T_i(t) = T_i(0) + \displaystyle\int_0^t (\lambda_i - d_i T_i(s) - h_i(T_i(s), V(s)))ds, \ i = 1, 2, \cdots, n, \\ V(t) = V(0) + \displaystyle\int_0^t \sum_{i=1}^n \int_0^\infty p_i(a) I_i(s,a) da ds - c\int_0^t V(s)ds, \\ I_i(t,a) = \sigma_i(a) h_i(T_i(t-a), V(t-a))\mathbf{1}_{t>a} + \dfrac{\sigma_i(a)}{\sigma_i(a-t)} I_i(0, a-t)\mathbf{1}_{a>t}. \end{cases}$$

We set $Y = C([0,\varepsilon) \times B_0, R^{n+1} \times L^n[0,\infty))$, the set of all continuous functions from $[0,\varepsilon) \times B_0$ to $R^{n+1} \times L^n[0,\infty)$, where $\varepsilon > 0$ and $B_0 \subset R^{n+1} \times L_+^n[0,\infty)$ is a neighborhood containing x_0, which will be determined later. Let $\mathcal{B}$ be a subset of Y containing functions whose ranges lie in $B \subset R^{n+1} \times L^n[0,\infty)$, where

$$B = \overline{U}((T_1(0), \cdots, T_n(0), V(0), I_1(0,\cdot), \cdots, I_n(0,\cdot)), r)$$

is the closed ball of radius r centered around the initial condition with $r > 0$ being determined later.

Now, we define an operator Λ on $\mathcal{B}$ as follows. Let

$$x = (x_1, \cdots, x_n, x_{n+1}, l_1(\cdot), \cdots, l_n(\cdot)) \in B_0,$$

and the vector valued function $\eta \in \mathcal{B}$ as

$$\eta(s,x) = ((\eta(s,x))_1, \cdots, (\eta(s,x))_n, (\eta(s,x))_{n+1}, (\widetilde{\eta}(s,x))_1, \cdots, (\widetilde{\eta}(s,x))_n).$$

For notational simplicity, we denote $\eta_j(s,x) = (\eta(s,x))_j$ for all $j = 1, 2, \cdots, n+1$ and $\widetilde{\eta}_i(s,x) = (\widetilde{\eta}(s,x))_i$ for all $i = 1, 2, \cdots, n$ in the proof.

For any $\eta \in \mathcal{B}$, define $\Lambda(\eta)(t,x)$ as

$$((\Lambda(\eta)(t,x))_1, \cdots, (\Lambda(\eta)(t,x))_{n+1}, (\Lambda(\eta)(t,x))_{n+2}(\cdot), \cdots, (\Lambda(\eta)(t,x))_{2n+1}(\cdot))^{\mathrm{T}}$$

with

$$\begin{pmatrix} (\Lambda(\eta)(t,x))_1 \\ \vdots \\ (\Lambda(\eta)(t,x))_n \\ (\Lambda(\eta)(t,x))_{n+1} \\ (\Lambda(\eta)(t,x))_{n+2}(a) \\ \vdots \\ (\Lambda(\eta)(t,x))_{2n+1}(a) \end{pmatrix} = \begin{pmatrix} x_1 + \int_0^t (\lambda_1 - d_1\eta_1(s,x) - h_1(\eta_1(s,x), \eta_{n+1}(s,x)))ds \\ \vdots \\ x_n + \int_0^t (\lambda_n - d_n\eta_n(s,x) - h_n(\eta_n(s,x), \eta_{n+1}(s,x)))ds \\ x_{n+1} + \int_0^t \left[\sum_{i=1}^n \int_0^\infty p_i(a)\widetilde{\eta}_i(s,x)(a)da - c\eta_{n+1}(s,x)\right] ds \\ \sigma_1(a)h_1(\eta_1(t-a,x), \eta_{n+1}(t-a,x))\mathbf{1}_{t>a} \\ +\frac{\sigma_1(a)}{\sigma_1(a-t)} l_1(a-t)\mathbf{1}_{a>t} \\ \vdots \\ \sigma_n(a)h_n(\eta_n(t-a,x), \eta_{n+1}(t-a,x))\mathbf{1}_{t>a} \\ +\frac{\sigma_n(a)}{\sigma_n(a-t)} l_n(a-t)\mathbf{1}_{a>t} \end{pmatrix}.$$

If there is η such that $\Lambda(\eta) = \eta$, then $\eta(s,x)$ is a solution to (3). We first show $\Lambda(\eta) \in Y$. In fact, since

$$\begin{aligned} &\int_0^\infty \left|\sigma_i(a)h_i(\eta_i(t-a,x), \eta_{n+1}(t-a,x))\mathbf{1}_{t>a} + \frac{\sigma_i(a)}{\sigma_i(a-t)} l_i(a-t)\mathbf{1}_{a>t}\right| da \\ &\leq \int_0^t \sigma_i(a)|h_i(\eta_i(t-a,x), \eta_{n+1}(t-a,x))|da + \int_t^\infty \frac{\sigma_i(a)}{\sigma_i(a-t)}|l_i(a-t)|da \\ &\leq \frac{1}{\bar{\delta}}(1-e^{-\bar{\delta}t})h_i(|T_i(0)+r|, |V(0)+r|) + \|l_i\| < \infty, \end{aligned}$$

where $0 < \bar{\delta} := \min_i\{\bar{\delta}_i\}$, where $\bar{\delta}_i := \inf_{a\in[0,\infty)}\{\delta_i(a)\}$ is defined as in the description of model parameters, and $\|\cdot\|$ is defined as

$$\|x\| = |x_1| + \cdots + |x_n| + |x_{n+1}| + \|l_1\|_{L[0,\infty)} + \cdots + \|l_n\|_{L[0,\infty)}.$$

Taking $B_0 = U((T_1(0), \cdots, T_n(0), V(0), I_1(0,\cdot), \cdots, I_n(0,\cdot)), \frac{r}{2})$, then we have

$$
\begin{aligned}
&\|\Lambda(\eta)(t,x) - x_0\| \\
&= \sum_{i=1}^{n} \left| x_i - T_i(0) + \int_0^t (\lambda_i - d_i\eta_i(s,x) - h_i(\eta_i(s,x), \eta_{n+1}(s,x)))ds \right| \\
&\quad + \left| x_{n+1} - V(0) + \int_0^t \sum_{i=1}^{n} \int_0^\infty p_i(a)\widetilde{\eta}_i(s,x)(a)dads - c\int_0^t \eta_{n+1}(s,x)ds \right| \\
&\quad + \sum_{i=1}^{n} \int_0^\infty \left| \sigma_i(a)h_i(\eta_i(t-a,x), \eta_{n+1}(t-a,x))\mathbf{1}_{t>a} + \frac{\sigma_i(a)}{\sigma_i(a-t)} l_i(a-t)\mathbf{1}_{a>t} - I_i(0,a) \right| da \\
&\le \sum_{i=1}^{n} |x_i - T_i(0)| + \varepsilon \sum_{n=1}^{n} (\lambda_i + d_i|T_i(0) + r| + h_i(|T_i(0) + r|, |V(0) + r|)) \\
&\quad + |x_{n+1} - V(0)| + \varepsilon \sum_{i=1}^{n} \hat{p}(\|I_i(0,a)\| + r) + \varepsilon c|V(0) + r| \\
&\quad + \sum_{i=1}^{n} \frac{1}{\bar{\delta}}(1 - e^{-\bar{\delta}t}) h_i(|T_i(0) + r|, |V(0) + r|) \\
&\quad + \sum_{i=1}^{n} \int_0^\infty \frac{\sigma_i(a)}{\sigma_i(a-t)} \mathbf{1}_{a>t} |l_i(a-t) - I_i(0, a-t)| da \\
&\quad + \sum_{i=1}^{n} \int_0^\infty \left| \frac{\sigma_i(a)}{\sigma_i(a-t)} \mathbf{1}_{a>t} I_i(0, a-t) - I_i(0,a) \right| da,
\end{aligned}
$$

where $\hat{p} = \sup_{1 \le i \le n, a \ge 0} \{p_i(a)\}$.

Note that

$$
\int_0^\infty \frac{\sigma_i(a)}{\sigma_i(a-t)} \mathbf{1}_{a>t} |l_i(a-t) - I_i(0,a-t)| da \le \|l_i(\cdot) - I_i(0,\cdot)\|
$$

and

$$
\begin{aligned}
&\int_0^\infty \left| \frac{\sigma_i(a)}{\sigma_i(a-t)} \mathbf{1}_{a>t} I_i(0,a-t) - I_i(0,a) \right| da \\
&\le \int_0^\infty \mathbf{1}_{a \ge t} I_i(0,a-t) \left| \frac{\sigma_i(a)}{\sigma_i(a-t)} - 1 \right| da + \int_0^\infty \mathbf{1}_{a>t} \left| I_i(0,a-t) - I_i(0,a) \right| da.
\end{aligned}
$$

According to the dominated-convergence theorem, we get

$$
\lim_{t \to 0} \int_0^\infty \mathbf{1}_{a>t} I_i(0,a-t) \left| \frac{\sigma_i(a)}{\sigma_i(a-t)} - 1 \right| da = 0.
$$

Hence,

$$
\int_0^\infty \mathbf{1}_{a>t} I_i(0,a-t) \left| \frac{\sigma_i(a)}{\sigma_i(a-t)} - 1 \right| da < \frac{r}{16}
$$

for all $t \in [0, \varepsilon)$ provided ε small enough.

Let ξ_i be a continuous function with compact support in $[0, \infty)$ such that

$$
\|I_i(0,\cdot) - \xi_i\| < \frac{r}{16}.
$$

Note that the existence of ξ_i follows from the fact that the set of all continuous functions with compact support is dense in L^1. Then

$$\begin{aligned}
&\int_0^\infty \mathbf{1}_{a>t}|I_i(0,a-t)-I_i(0,a)|da\\
&\leq \int_0^t |I_i(0,a)|da+\int_0^\infty |I_i(0,a)-\xi_i(a)|da+\int_0^\infty |\xi_i(a)-\xi_i(a+t)|da\\
&\quad+\int_t^\infty |I_i(0,a)-\xi_i(a)|da\\
&\leq 2\int_0^\infty |I_i(0,a)-\xi_i(a)|da+\int_0^t |I_i(0,a)|da+\int_0^\infty |\xi_i(a)-\xi_i(a+t)|da\\
&< 2\cdot\frac{r}{16}+\frac{r}{32}+\frac{r}{32}\\
&=\frac{3r}{16}.
\end{aligned}$$

Therefore,

$$\begin{aligned}
&\int_0^\infty \mathbf{1}_{a>t}I_i(0,a-t)\left|\frac{\sigma_i(a)}{\sigma_i(a-t)}-1\right|da+\int_0^\infty \mathbf{1}_{a>t}\left|I_i(0,a-t)-I_i(0,a)\right|da\\
&<\frac{r}{16}+\frac{3r}{16}=\frac{r}{4}.
\end{aligned}$$

In summary, we have

$$\begin{aligned}
&\|\Lambda(\eta)(t,x)-x_0\|\\
&\leq \|x-x_0\|+\varepsilon M_1+\varepsilon M_2+\frac{r}{4}\\
&<\frac{r}{2}+\frac{r}{4}+\frac{r}{4}=r,
\end{aligned}$$

for constants M_1, M_2 and $\varepsilon>0$ small enough.

Thus, $\Lambda : \mathcal{B} \to \mathcal{B}$. We next show that Λ is a contraction on $\mathcal{B}$ when ε is small enough. Let η, $\zeta \in \mathcal{B}$. Then

$$
\begin{aligned}
&\|\Lambda(\eta)(t,x) - \Lambda(\zeta)(t,x)\| \\
&\le \int_0^t |d_1\eta_1(s,x) - d_1\zeta_1(s,x)|ds + \int_0^t |h_1(\zeta_1(s,x), \zeta_{n+1}(s,x)) - h_1(\eta_1(s,x), \eta_{n+1}(s,x))|ds \\
&\quad + \cdots \\
&\quad + \int_0^t |d_n\eta_n(s,x) - d_n\zeta_n(s,x)|ds + \int_0^t |h_n(\zeta_n(s,x), \zeta_{n+1}(s,x)) - h_n(\eta_n(s,x), \eta_{n+1}(s,x))|ds \\
&\quad + \int_0^t \sum_{i=1}^n \int_0^\infty p_i(a)|\widetilde{\eta}_i(s,x)(a) - \widetilde{\zeta}_i(s,x)(a)|dads + \int_0^t c|\eta_{n+1}(s,x) - \zeta_{n+1}(s,x)|ds \\
&\quad + \int_0^t e^{-\bar{\delta}a}|h_1(\eta_1(t-a,x), \eta_{n+1}(t-a,x)) - h_1(\zeta_1(t-a,x), \zeta_{n+1}(t-a,x))|da \\
&\quad + \cdots \\
&\quad + \int_0^t e^{-\bar{\delta}a}|h_n(\eta_n(t-a,x), \eta_{n+1}(t-a,x)) - h_n(\zeta_n(t-a,x), \zeta_{n+1}(t-a,x))|da \\
&\le \varepsilon \sum_{i=1}^n d_i\|\eta_i - \zeta_i\| + \varepsilon \sum_{i=1}^n L_i\|\eta_i - \zeta_i\| + \varepsilon \sum_{i=1}^n L_i\|\eta_{n+1} - \zeta_{n+1}\| \\
&\quad + \varepsilon\hat{p} \sum_{i=1}^n \|\eta_i - \zeta_i\| + c\varepsilon\|\eta_{n+1} - \zeta_{n+1}\| \\
&\quad + \varepsilon \sum_{i=1}^n L_i\|\eta_i - \zeta_i\| + \|\eta_{n+1} - \zeta_{n+1}\| \\
&\le \varepsilon M\|\eta - \zeta\|,
\end{aligned}
$$

with some constant $M > 0$. Therefore Λ is a contraction mapping on $\mathcal{B}$ when ε is small enough. By the contraction mapping theorem there exists a unique fixed point of Λ in $\mathcal{B}$, denoted as χ. Then $\chi(t,x)$ solves the initial value problem and is continuous on $[0,\varepsilon] \times B_0$. ■

2.2. Nonnegativeness and boundedness of solutions

In this subsection, we show the wellposedness of the model as a biological system.

LEMMA 2. *Any solution to (3) through a nonnegative initial value remains non-negative for every $a \ge 0$ and all $t \ge 0$.*

Proof: Suppose $(T_1(t), \cdots, T_n(t), V(t), I_1(t,\cdot), \cdots, I_n(t,\cdot))$ is a solution to system (3) and hence a solution to (1) through a nonnegative initial value on the interval $[0,\rho]$, where $\rho < \beta$ and $[0,\beta)$ is the maximal interval of existence guaranteed to exist from Lemma 1 (β is allowed to be ∞). It is easy to see from (3) that $T_i(t)$ and $V(t)$ are differentiable by the fundamental theorem of calculus, and $\int_0^\infty I_i(t,a)da$ is differentiable in t by the smoothness properties of convolution. We first prove that $T_i(t) > 0$, $i = 1, 2, \cdots, n$ for all $t \in [0,\rho]$. Assume that $T_j(t)$ loses its nonnegativity on $[0,\rho]$ for some j, and let $t_0 \in [0,\rho]$ be the first time such that $T_j(t_0) = 0$. By continuity of solutions any such value of t_0 must be greater

than zero and $\dot{T}_j(t_0) \leq 0$. Revisiting system (1), we get $\dot{T}_j(t_0) = \lambda_i > 0$, a contradiction. Therefore, no such t_0 exists and $T_j(t) > 0$ for all $t \in [0, \rho]$.

Next, we show that $V(t) > 0$ and $I_i(t, a) > 0$ for all $t \in [0, \rho]$, $a \geq 0$. To do that, we first define

$$\begin{aligned}\tau = \quad & \min\{\inf\{t \in [0,\rho] : V(t) < 0\}, \inf\{t \in [0,\rho] : I_1(t,\cdot) \notin L_+[0,\infty)\}, \cdots, \\ & \inf\{t \in [0,\rho] : I_n(t,\cdot) \notin L_+[0,\infty)\}\}.\end{aligned}$$

Suppose that

$$\tau = \inf\{t \in [0,\rho] : I_i(t,\cdot) \notin L_+[0,\infty) \text{ for some } i\}.$$

Based on the last equation of (3), we have $I_i(\tau, a) \geq 0$ for all $a \geq 0$, which is a contradiction. Hence $\tau = \inf\{t \in [0, \rho] : V(t) < 0\}$. At the time instant τ, we have $\dot{V}(\tau) \leq 0$. However, according to system (1), we have $I_i(t, \cdot) > 0$, and

$$\dot{V}(\tau) = \sum_{i=1}^{n} \int_0^\infty p_i(a) I_i(\tau, a) da - cV(\tau) > 0,$$

which leads to a contradiction. Therefore, $V(t) > 0$ and $I_i(t, a) \geq 0$ for all $t \geq 0$ and $a \geq 0$. Hence the solution must remain non-negative on $[0, \rho]$. Since $\rho < \beta$ is arbitrary, we conclude that the solution remains non-negative on its maximal interval of existence $[0, \beta)$. ■

Next, we consider the boundedness of solutions. Denote

$$G(t) = \sum_{i=1}^{n} (T_i(t) + \int_0^\infty I_i(t, a) da),$$

then

$$\begin{aligned}\frac{dG(t)}{dt} &= \sum_{i=1}^{n} (\lambda_i - d_i T_i(t) - \int_0^\infty \delta_i(a) I_i(t, a) da) \\ &\leq \sum_{i=1}^{n} \lambda_i - d \sum_{i=1}^{n} (T_i(t) + \int_0^\infty I_i(t, a) da),\end{aligned}$$

where $d = \min\{d_1, \cdots, d_n, \bar{\delta}\}$, and $0 < \bar{\delta} := \min_i\{\bar{\delta}_i\}$, where $\bar{\delta}_i := \inf_{a \in [0,\infty)} \{\delta_i(a)\}$ is defined as in the description of model parameters. Therefore, we have

$$\limsup_{t \to +\infty} G(t) \leq \sum_{i=1}^{n} \lambda_i / d.$$

From the second equation of system (1), we get

$$\frac{dV(t)}{dt} \leq \sum_{i=1}^{n} \hat{p}\lambda_i/d - cV(t),$$

when t is large enough, which implies that

$$\limsup_{t\to+\infty} V(t) \leq \frac{\hat{p}}{dc}\sum_{i=1}^{n}\lambda_i,$$

where $\hat{p} = \sup_{1\leq i\leq n, a\geq 0}\{p_i(a)\}$.

Hence, the boundedness of solutions follows from non-negativity of solutions. Furthermore, the following set attracts all nonnegative solutions and is positively invariant for system (1):

$$\begin{aligned} X = \{(T_1,\cdots,T_n,V,I_1(\cdot),\cdots,I_n(\cdot)) \in \overbrace{R_+\times\cdots\times R_+}^{n+1} \times \underbrace{L_+[0,\infty)\times\cdots\times L_+[0,\infty)}_{n} \\ \Big| T_i \leq T_i^0 = \lambda_i/d_i,\ \sum_{i=1}^{n}(T_i + \textstyle\int_0^\infty I_i(a)da) \leq \sum_{i=1}^{n}\lambda_i/d,\ V \leq \frac{\hat{p}}{cd}\sum_{i=1}^{n}\lambda_i\}. \end{aligned} \tag{4}$$

Since the function set X is invariant, in what follows, we will focus on this set as the phase space.

2.3. Equilibria and the basic reproduction number

Let N_i be the total number of viral particles produced by the i-th type infected target cells during its lifespan, which can be evaluated by

$$N_i = \int_0^\infty p_i(a)\sigma_i(a)da,$$

where $\sigma_i(a) = \exp(-\int_0^a \delta_i(s)ds)$ is the probability that i-th target infected cells survive up to age a. Denote

$$R_0 = \sum_{i=1}^{n}\frac{N_i}{c}\frac{\partial h_i(T_i^0,0)}{\partial V} = \sum_{i=1}^{n}\frac{\int_0^\infty p_i(a)\sigma_i(a)da}{c}\frac{\partial h_i(T_i^0,0)}{\partial V}$$

as the basic reproduction number of system (1), which represents the number of virions produced by one virion in its lifespan.

It is easy to verify that the system (1) always has an infection-free equilibrium $E^0 = (T_1^0,\cdots,T_n^0,V^0,I_1^0(\cdot),\cdots,I_n^0(\cdot)) \in X$, where $T_i^0 = \lambda_i/d_i$, $I_i^0(\cdot) = 0$ and $i = 1,2,\cdots,n$, $V^0 = 0$. If $R_0 > 1$, then there may exist an infection equilibrium $E^* = (T_1^*,\cdots,T_n^*,V^*,I_1^*(\cdot),\cdots,I_n^*(\cdot))$ satisfying

the equations:

$$\begin{cases} \lambda_i - d_i T_i^* - h_i(T_i^*, V^*) = 0, \\ \sum_{i=1}^{n} \int_0^{\infty} p_i(a) I_i^*(a) da - cV^* = 0, \\ \dfrac{dI_i^*(a)}{da} = -\delta_i(a) I_i^*(a), \\ I_i^*(0) = h_i(T_i^*, V^*). \end{cases} \tag{5}$$

Solving the third equation of (5), we have

$$I_i^*(a) = I_i^*(0) \exp(-\int_0^a \delta_i(s) ds) = \sigma_i(a) h_i(T_i^*, V^*).$$

From the second equation of (5), we have

$$\sum_{i=1}^{n} \int_0^{\infty} p_i(a) \sigma_i(a) h_i(T_i^*, V^*) da = cV^*,$$

which implies

$$\sum_{i=1}^{n} N_i h_i(T_i^*, V^*) = cV^*.$$

In the following, we will investigate the existence and uniqueness of positive equilibrium. To this end, we need the following Lemmas.

LEMMA 3. *If $f(0) = 0$, $f'(x) > 0$ and $f''(x) < 0$, then $f(\frac{1}{\beta}x) > \frac{1}{\beta} f(x)$ for all $x > 0$ and $\beta > 1$.*

Nest, we show the existence and uniqueness of positive equilibrium if and only if $R_0 > 1$.

LEMMA 4. *There exists a unique positive equilibrium*

$$E^* = (T_1^*, \cdots, T_n^*, V^*, I_1^*(\cdot), \cdots, I_n^*(\cdot))$$

if and only if $R_0 > 1$.

Proof: We first prove the existence of E^* when $R_0 > 1$, which also shows the nonexistence when $R_0 \leq 1$. From the first equation of Eq. (5), the positive equilibrium satisfies $\lambda_i - d_i T_i - h_i(T_i, V) = 0$, which gives $T_i = g_i(V)$ according to the implicit function theorem and

$$\frac{dT_i}{dV} = -\frac{\partial h_i(T_i, V)}{\partial V} / (d_i + \frac{\partial h_i(T_i, V)}{\partial T_i}) < 0.$$

Plugging $T_i = g_i(V)$ into the second of (5), we obtain the equation for V:

$$F(V) = \sum_{i=1}^{n} \int_0^\infty p_i(a)\sigma_i(a)h_i(g_i(V), V)da - cV.$$

It is obvious that $F(0) = 0$, and when $g_i(V_0) = 0$ for some $V_0 > 0$, we have $F(V_0) = -cV_0 < 0$. Since $F(V)$ is differentiable for $V \geq 0$, we have that

$$\begin{aligned} F'(0) &= \lim_{V\to 0+} \frac{F(V) - F(0)}{V} \\ &= \sum_{i=1}^{n} \int_0^\infty p_i(a)\sigma_i(a)\Big(\frac{\partial h_i(T_i^0, 0)}{\partial V} + \frac{\partial h_i(T_i^0, 0)}{\partial T_i} \cdot \Big(- \frac{\frac{\partial h_i(T_i^0,0)}{\partial V}}{d_i + \frac{\partial h_i(T_i^0,0)}{\partial T_i}}\Big)da - c \\ &= c\Big(\frac{\sum\limits_{i=1}^{n} \int_0^\infty p_i(a)\sigma_i(a)da}{c} \cdot \frac{\partial h_i(T_i^0, 0)}{\partial V} - 1\Big) \\ &= c(R_0 - 1) > 0, \text{ when } R_0 > 1. \end{aligned}$$

Thus, $F'(0) > 0$ implies that there exists some $V^* \in (0, V_0)$ such that $F(V^*) = 0$. Therefore, $T_i^* = g_i(V^*)$, and $I_i^*(a) = \sigma_i(a)h_i(T_i^*, V^*)$ also can be computed.

Next, we claim that E^* is unique. Suppose, by way of contradiction that this is not true and there is another equilibrium

$$(\overline{T}_1, \cdots, \overline{T}_n, \overline{V}, \overline{I}_1(\cdot), \cdots, \overline{I}_n(\cdot)).$$

Without loss of generality, we suppose there exists $\overline{V} > V^* > 0$ and $\overline{V} = \beta V^*$, $\beta > 1$ such that $F(\overline{V}) = F(V^*) = 0$. By the last equation of Eq. (5), and conditions $(H_1) - (H_4)$, together with Lemma 3, we have

$$I_i^*(0) = h_i(T_i^*, V^*) = h_i(T_i^*, \frac{1}{\beta}\overline{V}) > \frac{1}{\beta}h_i(T_i^*, \overline{V}).$$

Since $g_i'(V) < 0$, then $T_i^* = g_i(V^*) > g_i(\overline{V}) = \overline{T}_i$ when $\overline{V} > V^*$ and hence, we obtain

$$I_i^*(0) > \frac{1}{\beta}h_i(T_i^*, \overline{V}) > \frac{1}{\beta}h_i(\overline{T}_i, \overline{V}) = \frac{1}{\beta}\overline{I}_i(0), \ i = 1, 2, \cdots, n.$$

Thus, $I_i^*(a) > \frac{1}{\beta}\overline{I}_i(a)$ for all $a \geq 0$, which implies that

$$V^* = \frac{\sum\limits_{i=1}^{n} \int_0^\infty p_i(a)I_i^*(a)da}{c} > \frac{1}{\beta}\frac{\sum\limits_{i=1}^{n} \int_0^\infty p_i(a)\overline{I}_i(a)da}{c} = \frac{1}{\beta}\overline{V},$$

a contradiction. Therefore, system (1) admits a unique positive equilibrium E^* if and only if $R_0 > 1$. ■

3. Uniform persistence

In this section, we investigate the uniform persistence of system (1) by applying the results of Hale and Waltman [12] and Magal and Zhao [28]. Our arguments are highly motivated by those in [5] when showing the relative compactness of the solution semiflow (Propositions 1 and 2) and uniform persistence (Theorem 1). We first claim that the solution semiflow is compact, which maps a bounded set to a precompact set.

3.1. Relative compactness

Define the phase space X as in (4). Then X is complete. For $t \geq 0$, define the solution operator:

$$\Phi(t) : X \to X \text{ as } \Phi(t)x = u(t, x),$$

that is,

$$\Phi(t)x = (T_1(t), \cdots, T_n(t), V(t), I_1(t, \cdot), \cdots, I_n(t, \cdot))$$

with

$$x = (T_1(0), \cdots, T_n(0), V(0), I_1(0, \cdot), \cdots, I_n(0, \cdot)) \in X.$$

Clearly, $\Phi(0)x = x$, $u(t, u(s, x)) = u(t + s, x)$ and $\Phi(t)$ is a semiflow on X.

The operator

$$\Phi(t) : X \to X$$

can be divided into two operators $\Phi_1(t)$ and $\Phi_2(t)$ such that $\Phi(t)x{=}\Phi_1(t)x + \Phi_2(t)x$, $\forall t \geq 0$ with

$$\Phi_1(t)x := (0, \cdots, 0, 0, \widetilde{\varphi}_1(t, \cdot), \cdots, \widetilde{\varphi}_n(t, \cdot)),$$

and

$$\Phi_2(t)x := (T_1(t), \cdots, T_n(t), V(t), \widetilde{I}_1(t, \cdot), \cdots, \widetilde{I}_n(t, \cdot)),$$

where $\widetilde{\varphi}_i$ and $\widetilde{I}_i$ are defined by

$$\widetilde{\varphi}_i(t, a) = \begin{cases} 0, & t > a \geq 0, \\ I_i(t, a) = \frac{\sigma_i(a)}{\sigma_i(a-t)} I_i(0, a - t), & a \geq t \geq 0, \end{cases}$$

and

$$\widetilde{I}_i(t, a) = \begin{cases} I_i(t, a) = \sigma_i(a) h_i(T_i(t - a), V(t - a)), & t > a \geq 0, \\ 0, & a \geq t \geq 0. \end{cases} \tag{6}$$

To show the relative compactness of $\Phi(t)$, we will establish the following two results for $\Phi_1(t)$ and $\Phi_2(t)$ respectively.

PROPOSITION 1. *For any $r_1 > 0$ and $t \geq 0$, we have $\|\Phi_1(t)x\| \leq e^{-\bar{\delta}t} r_1$ provided that $x \in X$ with $\|x\| \leq r_1$.*

Proof: It follows from (2) that

$$\widetilde{\varphi}_i(t,a) = \begin{cases} 0, & t > a \geq 0, \\ I_i(0, a-t)\exp(-\int_0^t \delta_i(a-t+\tau)d\tau), & a \geq t \geq 0. \end{cases}$$

For any $x \in X$ with $\|x\| \leq r_1$, we have

$$\begin{aligned} \|\Phi_1(t)x\| &= \sum_{i=1}^{n} \int_t^{\infty} I_i(0, a-t)\exp(-\int_0^t \delta_i(a-t+\tau)d\tau)da \\ &\leq e^{-\bar{\delta}t} \sum_{i=1}^{n} \int_t^{\infty} I_i(0, a-t)da \\ &\leq e^{-\bar{\delta}t}(\|I_1(0,\cdot)\| + \cdots + \|I_n(0,\cdot)\|) \\ &\leq e^{-\bar{\delta}t}\|x\| < e^{-\bar{\delta}t} r_1, \quad \forall t \geq 0, \end{aligned}$$

which completes the proof. ■

Based on the expression of $\widetilde{\varphi}_i(t,a)$, we can easily obtain that $\Phi_1(t)$ is compact. Next, we establish the following proposition for $\Phi_2(t)$.

PROPOSITION 2. *For any $t \geq 0$, $\Phi_2(t)$ maps any bounded set of X into a set with compact closure in X.*

Proof: By the definition of X, it is obvious that $T_i(t)$ and $V(t)$ remain in the compact set $[0, (1+\frac{\hat{p}}{c})\sum_{i=1}^{n} \lambda_i/d]$. Thus, we only need to prove that $\widetilde{I}_i(t,\cdot)$ remains in a precompact subset of $L_+[0,\infty)$, independent of initial value $x \in X$. To do that, it suffices to show that the following four facts hold for $\widetilde{I}_i(t,\cdot)$ (see [5, 45]):

(i) The supremum of $\int_0^{\infty} \widetilde{I}_i(t,a)da$ is finite with respect to $x \in X$;
(ii) $\lim_{h\to\infty} \int_h^{\infty} \widetilde{I}_i(t,a)da = 0$ uniformly with respect to $x \in X$;
(iii) $\lim_{h\to 0^+} \int_0^{\infty} |\widetilde{I}_i(t,a+h) - \widetilde{I}_i(t,a)|da = 0$ uniformly with respect to $x \in X$;
(iv) $\lim_{h\to 0^+} \int_0^{h} \widetilde{I}_i(t,a)da = 0$ uniformly with respect to $x \in X$.

It follows from (2) and (6) that

$$\widetilde{I}_i(t,a) = \begin{cases} \sigma_i(a)h_i(T_i(t-a), V(t-a)), & t > a \geq 0, \\ 0, & a \geq t \geq 0. \end{cases}$$

Then, the assumption (H_3) in section 2 and (4) imply

$$\begin{aligned}\sigma_i(a)h_i(T_i(t-a),V(t-a)) &= \sigma_i(a)\cdot\frac{h_i(T_i(t-a),V(t-a))}{V(t-a)}\cdot V(t-a)\\ &\le \sigma_i(a)\frac{\partial h_i(T_i(t-a),0)}{\partial V}V(t-a)\\ &\le \sigma_i(a)\frac{\partial h_i(T_i^0,0)}{\partial V}\frac{\hat{p}}{cd}\sum_{i=1}^{n}\lambda_i.\end{aligned}$$

Thus, conditions (i), (ii) and (iv) hold.

It remains to show that condition (iii) is satisfied. For any sufficiently small $h\in(0,t)$, we have

$$\begin{aligned}&\int_0^\infty |\widetilde{I}_i(t,a+h)-\widetilde{I}_i(t,a)|da\\ &=\int_0^t |\widetilde{I}_i(t,a+h)-\widetilde{I}_i(t,a)|da\\ &=\int_0^{t-h}|h_i(T_i(t-a-h),V(t-a-h))\sigma_i(a+h)-h_i(T_i(t-a),V(t-a))\sigma_i(a)|da\\ &\quad+\int_{t-h}^{t}|0-h_i(T_i(t-a),V(t-a))\sigma_i(a)|da\\ &\le\int_0^{t-h}h_i(T_i(t-a-h),V(t-a-h))|\sigma_i(a+h)-\sigma_i(a)|da\\ &\quad+\int_0^{t-h}|h_i(T_i(t-a-h),V(t-a-h))-h_i(T_i(t-a),V(t-a))|\sigma_i(a)da\\ &\quad+h\cdot\frac{\partial h_i(T_i^0,0)}{\partial V}\frac{\hat{p}}{cd}\sum_{i=1}^{n}\lambda_i\\ &\le\frac{\partial h_i(T_i^0,0)}{\partial V}\frac{\hat{p}}{cd}\sum_{i=1}^{n}\lambda_i\int_0^{t-h}|\sigma_i(a+h)-\sigma_i(a)|da\\ &\quad+\int_0^{t-h}|h_i(T_i(t-a-h),V(t-a-h))-h_i(T_i(t-a),V(t-a))|\sigma_i(a)da\\ &\quad+h\cdot\frac{\partial h_i(T_i^0,0)}{\partial V}\frac{\hat{p}}{cd}\sum_{i=1}^{n}\lambda_i.\end{aligned}\tag{7}$$

Since $\sigma_i(a)=\exp(-\int_0^a\delta_i(s)ds)$ is strictly decreasing with respect to a, we obtain

$$\begin{aligned}&\int_0^{t-h}|\sigma_i(a+h)-\sigma_i(a)|da=\int_0^{t-h}(\sigma_i(a)-\sigma_i(a+h))da\\ &=\int_0^h\sigma_i(a)da+\int_h^{t-h}\sigma_i(a)da-\int_0^{t-h}\sigma_i(a+h)da\\ &=\int_0^h\sigma_i(a)da-\int_{t-h}^{t}\sigma_i(a)da\\ &\le\int_0^h\sigma_i(a)da\le h.\end{aligned}\tag{8}$$

The Lipschitz continuity of $h_i(T_i, V)$ on T_i and V implies that there exist M_i^V, M_i^T such that

$$\begin{aligned} |h_i(T_i, V) - h_i(T_i, \widetilde{V})| &\le M_i^V |V - \widetilde{V}|, \\ |h_i(T_i, V) - h_i(\widetilde{T}_i, V)| &\le M_i^T |T_i - \widetilde{T}_i|. \end{aligned} \tag{9}$$

Moreover, the equations for V and T_i in system (1) on the phase space X show that there exist L^V and L^T such that

$$\begin{aligned} |V(x) - V(y)| &\le L^V |x - y|, \\ |T_i(x) - T_i(y)| &\le L^T |x - y|. \end{aligned} \tag{10}$$

Therefore, from (7), (9) and (10), we have

$$\begin{aligned} &|h_i(T_i(t-a-h), V(t-a-h)) - h_i(T_i(t-a), V(t-a))| \\ &\le |h_i(T_i(t-a-h), V(t-a-h)) - h_i(T_i(t-a-h), V(t-a))| \\ &\quad + |h_i(T_i(t-a-h), V(t-a)) - h_i(T_i(t-a), V(t-a))| \\ &\le (M_i^V L^V + M_i^T L^T) h. \end{aligned} \tag{11}$$

In summary, from (7), (8) and (11), we obtain

$$\begin{aligned} &\int_0^\infty |\widetilde{I}_i(t, a+h) - \widetilde{I}_i(t, a)| da \\ &\le 2 \cdot \frac{\partial h_i(T_i^0, 0)}{\partial V} \frac{h\hat{p}}{cd} \sum_{i=1}^n \lambda_i + (M_i^V L^V + M_i^T L^T) h \\ &= (2\frac{\hat{p}}{cd} \sum_{i=1}^n \lambda_i \cdot \frac{\partial h_i(T_i^0, 0)}{\partial V} + M_i^V L^V + M_i^T L^T) h. \end{aligned}$$

Since this upper bound is independent of $x \in X$ and converges to 0 as $h \to 0^+$, condition (iii) holds too. Consequently, $\widetilde{I}_i(t, \cdot)$ remains in a precompact subset of $L_+[0, \infty)$ and $\Phi_2(t)$ maps any bounded set of X into a set with compact closure in X. ■

3.2. Uniform persistence

We first introduce the two definitions. A set $\Gamma_0 \subset X$ attracts [28] a set $\Gamma \subset X$, if

$$d(\Phi(t)\Gamma, \Gamma_0) \to 0 \text{ as } t \to \infty,$$

where d is the distance from set $\Phi(t)\Gamma$ to Γ_0, i.e., $d(\Phi(t)\Gamma, \Gamma_0) := \inf\{\|x - y\| : x \in \Phi(t)\Gamma,\ y \in \Gamma_0\}$. The stable manifold of a compact invariant set $\Gamma_0 \subset X$ is defined as

$$W^s(\Gamma) = \{x \in X : \omega(x) \neq \emptyset \text{ and } \omega(x) \subset \Gamma_0\},$$

where $\omega(x)$ represents the omega limit set of x. To obtain the uniform persistence result, we also need the following lemma on the linear scalar integro-differential equations.

LEMMA 5. *([5]) Consider the following scalar integro-differential equation:*

$$\dot{Y}(t) = \int_0^t H(a)Y(t-a)da - \gamma Y(t),\ Y(0) > 0,$$

where $H(\cdot) \in L_+[0,\infty)$, *and* $\int_0^\infty H(a)da > \gamma > 0$. *Then there exists a unique solution* $Y(t)$, *which is unbounded.*

Set

$$A_i = \sup\{a \in (0,\infty) : p_i(a) > 0,\ i = 1, 2, \cdots n\}.$$

Note that, A_i can be chosen as ∞. We can write a point in the phase space X as

$$x = (x_1, \cdots, x_n, x_{n+1}, l_1(\cdot), \cdots, l_n(\cdot)) \in X.$$

Define

$$X^0 = \{x \in X : x_{n+1} > 0 \text{ and } \int_0^{A_i} p_i(a)l_i(a)da > 0 \text{ for all } i\},\ \text{and}$$
$$\partial X^0 = X \backslash X^0 = \{x \in X : x_{n+1} = 0 \text{ or } \int_0^{A_i} p_i(a)l_i(a)da = 0 \text{ for some } i = 1, 2, \cdots, n\}.$$

Obviously, X^0 is an open set relative to X, where X is defined in (4). Then we have the following claim on the uniform persistence of system (1).

THEOREM 1. *If* $R_0 > 1$, *then the system is uniformly persistent with respect to* ∂X^0. *That is, there exists a constant* $\mu > 0$, *such that*

$$\liminf_{t\to\infty} d(\Phi(t)x, \partial X^0) \geq \mu,\ \forall x \in X^0.$$

Proof: Note that for any $x \in X^0$, we have $u(t) := \Phi(t)x \in X^0$, $\forall t > 0$, that is, $u_{n+1}(t) > 0$ and $\int_0^{A_i} p_i(a)u_{n+1+i}(t)(a)da > 0$, for all $i = 1, 2, \cdots, n$. Indeed, if it is not true, then either (i) $u_{n+1}(t) = 0$ which implies $u_{n+1}(s) = 0$ and $\int_0^{A_i} p_i(a)u_{n+1+i}(t)(a)da = 0$ for all $i = 1, 2, \cdots, n$ and $s < t$. Therefore $x \notin X^0$, a contradiction; or (ii) $\int_0^{A_j} p_j(a)u_{n+1+j}(t)(a)da = 0$ for some j and t, then for all $s < t$, we can obtain either

$$u_{n+1}(s) \equiv 0 \text{ or } \int_0^{A_i} p_i(a)u_{n+1+i}(s)(a)da = 0$$

for all $i = 1, 2, \cdots, n$ according to the system (3). Therefore $x \notin X^0$. Hence, $\Phi(t)X^0 \subset X^0$, $\forall t > 0$.

Define

$$M_\partial = \{x \in \partial X^0 : \Phi(t)x \in \partial X^0,\ t \geq 0\}.$$

Then it is easy to see that

$$M_\partial = \{(x_1, \cdots, x_n, 0, l_1(\cdot), \cdots, l_n(\cdot)) \in X : l_i(a) = 0 \text{ for all } a \leq A_i,\ i = 1, \cdots, n\}.$$

Let $\omega(x)$ be the omega limit set of the orbit $\gamma^+(x) := \{\Phi(t)x : \forall t > 0\}$, and set $E^0 = (T_0, \cdots, T_n, 0, 0, \cdots, 0)$. Then we can easily obtain that $\forall x \in M_\partial$,

$$\omega(x) = \{E^0\} = (T_0, \cdots, T_n, 0, 0, \cdots, 0)$$

the infection-free equilibrium.

Since $R_0 > 1$, there exists some $\delta > 0$ such that

$$\sum_{i=1}^{n} N_i \Big(\frac{\partial h_i(T_i^0 - \delta, 0)}{\partial V} - \delta \Big) - c > 0.$$

In order to establish the uniform persistence, we only need to show that $W^s(E^0) \cap X^0 = \emptyset$. If not, then there exists $x \in X^0$ such that $\Phi(t)x \to E^0$ as $t \to \infty$. That is, for any ϵ $(0 < \epsilon < \delta)$, there exists $t_0 > 0$ such that

$$\|\Phi(t)x - E^0\| < \epsilon, \text{ when } t > t_0.$$

Hence, $T_i(t) > T_i^0 - \epsilon$, and $V(t) < \epsilon$ for all $i = 1, \cdots, n$ and $t > t_0$. Using a time shift if necessary, without loss of generality, we can assume $T_i(t) > T_i - \epsilon$, $V(t) < \epsilon$ for all $t > 0$. Therefore, for $t > a$, we have $T_i(t-a) > T_i^0 - \epsilon$, $V(t-a) < \epsilon$. By the assumptions of $h_i(T_i, V)$ in $(H_1) - (H_4)$, we have

$$\lim_{V(t-a) \to 0} \frac{h_i(T_i(t-a), V(t-a)) - h_i(T_i(t-a), 0)}{V(t-a)} = \frac{\partial h_i(T_i(t-a), 0)}{\partial V}.$$

Therefore, if we choose $\epsilon > 0$ small enough, we have

$$\frac{h_i(T_i(t-a), V(t-a))}{V(t-a)} > \frac{\partial h_i(T_i(t-a), 0)}{\partial V} - \epsilon > \frac{\partial h_i(T_i^0 - \epsilon, 0)}{\partial V} - \epsilon > \frac{\partial h_i(T_i^0 - \delta, 0)}{\partial V} - \delta,$$

for $t > a$. In this case, combining the second and third equations of system (3), when $t > a$, we get

$$\begin{cases} \dfrac{dV(t)}{dt} &= \sum\limits_{i=1}^{n} \int_0^\infty p_i(a) I_i(t,a) da - cV(t) \\ &\geq \int_0^\infty \sum\limits_{i=1}^{n} p_i(a)\sigma_i(a) h_i(T_i(t-a), V(t-a)) \mathbf{1}_{t>a} da - cV(t) \\ &\geq \int_0^t \sum\limits_{i=1}^{n} p_i(a)\sigma_i(a) h_i(T_i(t-a), V(t-a)) da - cV(t) \\ &\geq \int_0^t \sum\limits_{i=1}^{n} p_i(a)\sigma_i(a) \Big(\frac{\partial h_i(T_i(t-a),0)}{\partial V} - \epsilon \Big) V(t-a) da - cV(t) \\ &\geq \int_0^t \sum\limits_{i=1}^{n} p_i(a)\sigma_i(a) \Big(\frac{\partial h_i(T_i^0-\delta,0)}{\partial V} - \delta \Big) V(t-a) da - cV(t). \end{cases}$$

Since $\int_0^\infty \sum\limits_{i=1}^{n} p_i(a)\sigma_i(a) \frac{\partial h_i(T_i^0,0)}{\partial V} da > c$, there exists a solution $w(t)$ going infinity based on Lemma 5 for the following system

$$\frac{dw(t)}{dt} = \int_0^t \sum_{i=1}^{n} p_i(a)\sigma_i(a) \Big(\frac{\partial h_i(T_i^0 - \delta, 0)}{\partial V} - \delta \Big) w(t-a) da - cw(t).$$

A simple comparison argument, similar to that in [23], show the variable $V(t)$ goes infinity, which contradicts to the boundedness of solutions. Therefore, $W^s(E^0) \cap X^0 = \emptyset$.

According to the results of [12], $\Phi(t)$ is uniformly persistent, and there exists a compact set $\Gamma^0 \subset X^0$ which is a global attractor for $\{\Phi(t)\}_{t\geq 0}$ in X^0 [28]. Moreover, there exists $\mu > 0$ such that

$$\liminf_{t\to\infty} V(t) \geq \mu \text{ and } \liminf_{t\to\infty} \|I_i(t,\cdot)\| \geq \mu \text{ for all } 1 \leq i \leq n.$$

■

4. Global stability

In this section, we prove the global stability of the infection-free equilibrium (infection equilibrium) when $R_0 < 1$ ($R_0 > 1$, respectively) with the help of Lyapunov functional technique combined with the invariance principle, highly inspired by the paper [26].

THEOREM 2. *If $R_0 < 1$, then the infection-free equilibrium E^0 of system (1) is globally asymptotically stable.*

Proof: Define a function

$$\alpha_i(a) = \int_a^\infty p_i(\theta) e^{-\int_a^\theta \delta_i(s) ds} d\theta.$$

Clearly, $\alpha_i(a)$ is bounded and satisfies

$$\alpha_i'(a) = \delta_i(a)\alpha_i(a) - p_i(a), \text{ for all } a \geq 0,$$

and

$$N_i = \alpha_i(0) = \int_0^\infty p_i(\theta) e^{-\int_0^\theta \delta_i(s)ds} d\theta.$$

In the following, we define a Lyapunov functional $W_0 = W_0(T_1, \cdots, T_n, V, I_1(\cdot), \cdots, I_n(\cdot))$ as follows:

$$\begin{aligned} W_0 &= \sum_{i=1}^n N_i \Big(T_i(t) - T_i^0 - \int_{T_i^0}^{T_i(t)} \lim_{V\to 0^+} \frac{h_i(T_i^0, V)}{h_i(\eta_i, V)} d\eta_i \Big) \\ &\quad + \sum_{i=1}^n \int_0^\infty \alpha_i(a) I_i(t,a) da + V(t). \end{aligned}$$

Then W_0 is non-negative and $W_0(E^0) = 0$ at the infection-free equilibrium E^0. Calculating the time derivative of W_0 along the solution of system (1), we obtain

$$\begin{aligned} \frac{dW_0}{dt}\Big|_{(1)} &= \sum_{i=1}^n N_i \Big(1 - \lim_{V\to 0^+} \frac{h_i(T_i^0, V)}{h_i(T_i, V)} \Big) \frac{dT_i(t)}{dt} \\ &\quad + \sum_{i=1}^n \int_0^\infty \alpha_i(a) \frac{\partial I_i(t,a)}{\partial t} da + \frac{dV(t)}{dt} \\ &= \sum_{i=1}^n N_i \Big(1 - \lim_{V\to 0^+} \frac{h_i(T_i^0, V)}{h_i(T_i, V)} \Big) (\lambda_i - d_i T_i - h_i(T_i, V)) \\ &\quad - \sum_{i=1}^n \int_0^\infty \alpha_i(a) \Big(\frac{\partial I_i(t,a)}{\partial a} + \delta_i(a) I_i(t,a) \Big) da \\ &\quad + \sum_{i=1}^n \int_0^\infty p_i(a) I_i(t,a) da - cV(t). \end{aligned} \tag{12}$$

Note that $d_iT_i^0=\lambda_i$ and $R_0=\sum\limits_{i=1}^{n}\dfrac{N_i}{c}\dfrac{\partial h_i(T_i^0,0)}{\partial V}$. We have

$$\begin{aligned}
\frac{dW_0}{dt}\Big|_{(1)} &= \sum_{i=1}^{n} N_i d_i T_i\Big(\frac{T_i^0}{T_i}-1\Big)\Big(1-\lim_{V\to 0^+}\frac{h_i(T_i^0,V)}{h_i(T_i,V)}\Big)\\
&\quad -\sum_{i=1}^{n} N_i h_i(T_i,V)\Big(1-\lim_{V\to 0^+}\frac{h_i(T_i^0,V)}{h_i(T_i,V)}\Big)-\sum_{i=1}^{n}\int_0^{\infty}\alpha_i(a)dI_i(t,a)\\
&\quad -\sum_{i=1}^{n}\int_0^{\infty}(\alpha_i(a)\delta_i(a)-p_i(a))I_i(t,a)da-cV\\
&= \sum_{i=1}^{n} N_i d_i T_i\Big(\frac{T_i^0}{T_i}-1\Big)\Big(1-\lim_{V\to 0^+}\frac{h_i(T_i^0,V)}{h_i(T_i,V)}\Big)\\
&\quad -\sum_{i=1}^{n} N_i h_i(T_i,V)+\sum_{i=1}^{n} N_i h_i(T_i,V)\lim_{V\to 0^+}\frac{h_i(T_i^0,V)}{h_i(T_i,V)}\\
&\quad -\sum_{i=1}^{n}(\alpha_i(a)I_i(t,a))\Big|_0^{\infty}+\int_0^{\infty} I_i(t,a)\alpha_i'(a)da)\\
&\quad -\sum_{i=1}^{n}\int_0^{\infty}(\alpha_i(a)\delta_i(a)-p_i(a))I_i(t,a)da-cV\\
&= \sum_{i=1}^{n} N_i d_i T_i\Big(\frac{T_i^0}{T_i}-1\Big)\Big(1-\lim_{V\to 0^+}\frac{h_i(T_i^0,V)}{h_i(T_i,V)}\Big)\\
&\quad -\sum_{i=1}^{n}(\alpha_i(a)I_i(t,a))\Big|_{a=\infty}+\sum_{i=1}^{n} N_i h_i(T_i,V)\lim_{V\to 0^+}\frac{h_i(T_i^0,V)}{h_i(T_i,V)}-cV\\
&\le \sum_{i=1}^{n} N_i d_i T_i\Big(\frac{T_i^0}{T_i}-1\Big)\Big(1-\lim_{V\to 0^+}\frac{h_i(T_i^0,V)}{h_i(T_i,V)}\Big)-\sum_{i=1}^{n}(\alpha_i(a)I_i(t,a))\Big|_{a=\infty}\\
&\quad +cV\left(\sum_{i=1}^{n}\frac{N_i}{c}\frac{h_i(T_i,V)}{V}\lim_{V\to 0^+}\frac{\frac{h_i(T_i^0,V)-h_i(T_i^0,0)}{V}}{\frac{h_i(T_i,V)-h_i(T_i,0)}{V}}-1\right).
\end{aligned}$$

By assumption (H_3), we can easily obtain

$$\left(\frac{T_i^0}{T_i}-1\right)\left(1-\lim_{V\to 0^+}\frac{h_i(T_i^0,V)}{h_i(T_i,V)}\right)=\left(\frac{T_i^0}{T_i}-1\right)\left(1-\frac{\frac{\partial h_i(T_i^0,0)}{\partial V}}{\frac{\partial h_i(T_i,0)}{\partial V}}\right)\le 0. \tag{13}$$

Note that $\dfrac{\partial h_i(T_i^0,0)}{\partial V}\Big/\dfrac{\partial h_i(T_i,0)}{\partial V}\neq 1$ for $T_i\neq T_i^0$, $T_i>0$, $V>0$. The equality in (13) holds only if $T_i=T_i^0$. Since (H_3) holds, then $\frac{\partial h_i(T_i,0)}{\partial V}>0$ and $h_i(T_i,V)\le V\frac{\partial h_i(T_i,0)}{\partial V}$, thus, we have

$$\sum_{i=1}^{n}\frac{N_i}{c}\frac{h_i(T_i,V)}{V}\frac{\frac{\partial h_i(T_i^0,0)}{\partial V}}{\frac{\partial h_i(T_i,0)}{\partial V}}\le\sum_{i=1}^{n}\frac{N_i}{c}\frac{\partial h_i(T_i^0,0)}{\partial V}=R_0. \tag{14}$$

It follows from (12)–(14) that $\frac{dW_0}{dt}\Big|_{(1)}\le 0$ when $R_0\le 1$. If $R_0<1$, from Corollary 5.2 in Kuang [21], E^0 is globally asymptotically stable. If $R_0=1$, $\frac{dW_0}{dt}=0$ implies that $T_i(t)=T_i^0$, hence $\{E^0\}$ is the largest

invariant set in $\{\frac{dW_0}{dt}\Big|_{(1)} = 0\}$. By the LaSalle invariance Principle (see for example [21]), E^0 is globally asymptotically stable. ■

The following result shows that when $R_0 > 1$ the infection equilibrium is globally asymptotically stable.

THEOREM 3. *If $R_0 > 1$, then the infection equilibrium E^* of system (1) is globally asymptotically stable.*

Proof: Let $g(z) = z - 1 - \ln z,\ z \in R_+$. Then function $g(z)$ is non-negative for any $z > 0$, and $g(z) = 0$ if and only if $z = 1$. Define another Lyapunov functional $W = W(T_1, \cdots, T_n, V, I_1(\cdot), \cdots, I_n(\cdot))$ as follows:

$$W = W_1 + W_2 + V^* g\left(\frac{V(t)}{V^*}\right),$$

with

$$W_1 = \sum_{i=1}^{n} N_i\Big(T_i(t) - T_i^* - \int_{T_i^*}^{T_i(t)} \frac{h_i(T_i^*, V^*)}{h_i(\xi_i, V^*)} d\xi_i\Big),$$
$$W_2 = \sum_{i=1}^{n} \int_0^\infty \alpha_i(a) I_i^*(a) g\left(\frac{I_i(t,a)}{I_i^*(a)}\right) da.$$

Then this functional is well-defined based on the uniform persistence of the system. It is clear that W is non-negative and $W(E^*) = 0$ at the infection equilibrium E^*.

The time derivative of W along the solution of system (1) yields

$$\frac{dW}{dt}\Big|_{(1)} = \frac{dW_1}{dt}\Big|_{(1)} + \frac{W_2}{dt}\Big|_{(1)} + \Big(1 - \frac{V^*}{V(t)}\Big)\frac{dV(t)}{dt},$$

where

$$\frac{dW_1}{dt} = \sum_{i=1}^{n} N_i\Big(1 - \frac{h_i(T_i^*, V^*)}{h_i(T_i, V^*)})(\lambda_i - d_i T_i - h_i(T_i, V)\Big),$$

and

$$\begin{aligned}\frac{dW_2}{dt} &= \sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)\frac{\partial I_i(t,a)}{\partial t}da\\ &= \sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)\Big(-\delta_i(a)I_i(t,a)-\frac{\partial I_i(t,a)}{\partial a}\Big)da\\ &= -\sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\delta_i(a)I_i(t,a)\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)da\\ &\quad -\sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)\frac{\partial I_i(t,a)}{\partial a}da.\end{aligned} \tag{15}$$

In order to obtain $\frac{dW_2}{dt}$, we consider the following formulation:

$$\begin{aligned}&I_i^*(a)\frac{\partial}{\partial a}\Big(\frac{I_i(t,a)}{I_i^*(a)}-1-\ln\frac{I_i(t,a)}{I_i^*(a)}\Big)\\ &=\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)\frac{\partial}{\partial a}\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\\ &=\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)\Big(\frac{\partial I_i(t,a)}{\partial a}-\frac{\partial I_i^*(a)}{\partial a}\cdot\frac{I_i(t,a)}{I_i^*(a)}\Big).\end{aligned}$$

Thus, we have

$$\begin{aligned}&\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)\frac{\partial I_i(t,a)}{\partial a}\\ &=I_i^*(a)\frac{\partial}{\partial a}\Big(g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big)+\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)(-\delta_i(a)I_i(t,a))\\ &=I_i^*(a)\frac{\partial}{\partial a}\Big(g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big)-\delta_i(a)I_i(t,a)+\delta_i(a)I_i^*(a).\end{aligned}$$

From (15), we have

$$
\begin{aligned}
&-\sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\Big(1-\frac{I_i^*(a)}{I_i(t,a)}\Big)\frac{\partial I_i(t,a)}{\partial a}da\\
&=-\sum_{i=1}^{n}\alpha_i(a)I_i^*(a)g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big|_0^\infty\\
&\quad+\sum_{i=1}^{n}\int_0^\infty g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big(\alpha_i'(a)I_i^*(a)+\alpha_i(a)\frac{dI_i^*(a)}{da}\Big)da\\
&\quad+\sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\delta_i(a)I_i(t,a)da-\sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\delta_i(a)I_i^*(a)da\\
&=\sum_{i=1}^{n}\alpha_i(0)I_i^*(0)g(\frac{I_i(t,0)}{I_i^*(0)})-\sum_{i=1}^{n}\alpha_i(a)I_i^*(a)g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big|_{a=\infty}\\
&\quad+\sum_{i=1}^{n}\int_0^\infty g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big(\alpha_i'(a)-\alpha_i(a)\delta_i(a)\Big)I_i^*(a)da\\
&\quad+\sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\delta_i(a)I_i(t,a)da-\sum_{i=1}^{n}\int_0^\infty \alpha_i(a)\delta_i(a)I_i^*(a)da.
\end{aligned}
$$

Then, it follows from (15) that

$$
\begin{aligned}
\frac{W_2}{dt}\Big|_{(1)} &=\sum_{i=1}^{n}\alpha_i(0)I_i^*(0)g\Big(\frac{I_i(t,0)}{I_i^*(0)}\Big)-\sum_{i=1}^{n}\alpha_i(a)I_i^*(a)g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big|_{a=\infty}\\
&\quad+\sum_{i=1}^{n}\int_0^\infty g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)(-p_i(a))I_i^*(a)da.
\end{aligned}
$$

Note that

$$
\begin{aligned}
&\lambda_i=d_iT_i^*+h_i(T_i^*,V^*),\ \alpha_i(0)=N_i,\ I_i(t,0)=h_i(T_i,V),\\
&\sum_{i=1}^{n}N_ih_i(T_i^*,V^*)=cV^*,\ I_i^*(0)=h_i(T_i^*,V^*).
\end{aligned}
$$

After some complicated calculations, we obtain

$$\begin{aligned}
\frac{dW}{dt} &= \sum_{i=1}^{n} N_i d_i T_i^* \Big(1-\frac{T_i}{T_i^*}\Big)\Big(1-\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}\Big) \\
&\quad + \sum_{i=1}^{n} N_i h_i(T_i^*,V^*)\Big(1-\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}\Big) \\
&\quad - \sum_{i=1}^{n} N_i h_i(T_i,V)\Big(1-\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}\Big) \\
&\quad + \sum_{i=1}^{n} N_i h_i(T_i^*,V^*) g\Big(\frac{h_i(T_i,V)}{h_i(T_i^*,V^*)}\Big) \\
&\quad - \sum_{i=1}^{n} \alpha_i(a) I_i^*(a) g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big|_{a=\infty} \\
&\quad - \sum_{i=1}^{n} \int_0^\infty p_i(a) I_i^*(a) g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big) da \\
&\quad + (\sum_{i=1}^{n} \int_0^\infty p_i(a) I_i(t,a) da + \sum_{i=1}^{n} N_i h_i(T_i^*,V^*))(1-\frac{V}{V^*}) \\
&= \sum_{i=1}^{n} N_i d_i T_i^* \Big(1-\frac{T_i}{T_i^*}\Big)\Big(1-\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}\Big) \\
&\quad + \sum_{i=1}^{n} N_i h_i(T_i^*,V^*)\Big(1-\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}+\ln\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}\Big) \\
&\quad + \sum_{i=1}^{n} N_i h_i(T_i^*,V^*)\Big(\frac{h_i(T_i,V)}{h_i(T_i,V^*)}-1-\ln\frac{h_i(T_i,V)}{h_i(T_i,V^*)}\Big) \\
&\quad + \sum_{i=1}^{n} N_i h_i(T_i^*,V^*)\Big(1-\frac{V}{V^*}+\ln\frac{V}{V^*}\Big) \\
&\quad - \sum_{i=1}^{n} \alpha_i(a) I_i^*(a) g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big|_{a=\infty} \\
&\quad - \sum_{i=1}^{n} \int_0^\infty p_i(a) I_i^*(a) g\Big(\frac{V^* I_i(t,a)}{V I_i^*(a)}\Big) da \\
&= \sum_{i=1}^{n} N_i d_i T_i^* \Big(1-\frac{T_i}{T_i^*}\Big)\Big(1-\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}\Big) \\
&\quad - \sum_{i=1}^{n} N_i h_i(T_i^*,V^*) g\Big(\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}\Big) \\
&\quad - \sum_{i=1}^{n} N_i h_i(T_i^*,V^*)\Big(g\Big(\frac{V}{V^*}\Big)-g\Big(\frac{h_i(T_i,V)}{h_i(T_i,V^*)}\Big)\Big) \\
&\quad - \sum_{i=1}^{n} \int_0^\infty p_i(a) I_i^*(a) g\Big(\frac{V^* I_i(t,a)}{V I_i^*(a)}\Big) da \\
&\quad - \sum_{i=1}^{n} \alpha_i(a) I_i^*(a) g\Big(\frac{I_i(t,a)}{I_i^*(a)}\Big)\Big|_{a=\infty}.
\end{aligned}$$

By the monotonicity of the function $h_i(T_i,V)$ with respect to T_i, we have

$$\Big(1-\frac{T_i}{T_i^*}\Big)\Big(1-\frac{h_i(T_i^*,V^*)}{h_i(T_i,V^*)}\Big) \le 0.$$

Furthermore, from the concavity and monotonicity of the function $h_i(T_i, V)$ on V, the inequalities

$$\begin{cases} \dfrac{V}{V^*} \le \dfrac{h_i(T_i,V)}{h_i(T_i,V^*)} \le 1, & 0 < V \le V^*, \\ 1 \le \dfrac{h_i(T_i,V)}{h_i(T_i,V^*)} \le \dfrac{V}{V^*}, & V \ge V^* > 0, \end{cases}$$

hold, and we have

$$g\left(\frac{h_i(T_i,V)}{h_i(T_i,V^*)}\right) \le g\left(\frac{V}{V^*}\right)$$

from the monotonicity of the function g. The above argument shows that $\frac{dW}{dt} \le 0$ and the largest invariant subset of $\{\frac{dW}{dt} = 0\}$ is a singleton set $\{E^*\}$. Hence, by the Lyapunov-LaSalle asymptotic stability theorem [21], the infection equilibrium E^* is globally asymptotically stable when $R_0 > 1$. ■

5. Simulation and conclusions

In this section, we first present numerical simulations to validate theoretical results. To perform numerical simulation, parameter values should be appropriately chosen. We assume there are two types of target cells, $CD4^+$ T cells (type 1) and macrophages (type 2).

For the $CD4^+$ T cells, we assume the functional forms for the viral production kernel $p_1(a)$ and death rate of infected cells $\delta_1(a)$ take similar forms as those in [40], that is

$$\begin{cases} p_1(a) = p_1^*(1 - \exp(-\theta_1(a - a_1)) \text{ and } \delta_1(a) = \Delta_1 + \mu_1 & \text{if } a \ge a_1, \\ p_1(a) = 0 \text{ and } \delta_1(a) = \Delta_1 & \text{if } 0 \le a < a_1, \end{cases}$$

where a_1 is the age at which reverse transcription is completed while θ_1 determines how quickly $p_1(a)$ reaches the saturation level p_1^*, Δ_1 represents a background death rate of cells and μ_1 is an extra death rate for productively infected cells due to either viral cytopathicity or cell-mediated immune responses. Other parameters are set as [40]: $\lambda_1 = 10^4$ ml^{-1}day^{-1}, d_1 =0.01 day^{-1}, $c = 23$ day^{-1}, $h_1(T_1, V) = 2.4 \times 10^{-8} T_1 V$ ml^{-1}day^{-1}, $\Delta_1 = 1$ day^{-1}, $a_1 = 0.25$ day, $\mu_1 = 0.5$ day^{-1}, $p_1^* = 6.4201 \times 10^3$ day^{-1} and $\theta_1 = 1$.

For the macrophages, we choose the following parameter set [9]: $\lambda_2 = 0.024 \times 3.6 \times 10^5$ ml^{-1}day^{-1}, with $d_2 = 0.024$ day^{-1} such that the number of macrophage is 3.6×10^5 ml^{-1} without infection. The death rate for infected cells is assumed to be independent of age and $\delta_2(a) = 1/14.1$ day^{-1}. The kernel $p_2(a) = 0.1 \times \exp(-3 \times 0.00028a)$ [9]. For the infection

term, we set $h_2(T_2, V) = \frac{1.19VT_2}{c_2+V}$ with c_2 being Michaelis-Menten half saturation coefficient for virus in thymus (10^6 ml^{-1}) and the rate of infection of healthy macrophages being 1.19 per day [54].

When performing the numerical codes, we use the maximum age of infected cells as 10 days [40], for both types of target cells. Then the solutions are clearly shown to stabilize at a positive steady state for two different sets of initial data (Figure 1) since in this parameter set, the basic reproduction number R_0=1.4007 with R_1=1.3874 and R_2=0.0133, where $R_i = \frac{\int_0^\infty p_i(a)\sigma_i(a)da}{c} \frac{\partial h_i(T_i^0,0)}{\partial V}$ represent the reproduction numbers of HIV-CD4$^+$ T cell infection ($i = 1$) and HIV-macrophages infection ($i = 2$) modes, respectively. Using the similar simulation codes, we can also verify that all solutions approach to the infection free equilibrium when the basic reproduction number is smaller than unity (results haven't been shown here). From the basic reproduction numbers R_1 and R_2 for two different target cell types, the contribution of HIV-macrophages infection does exist, although not so strong relative to HIV-CD4$^+$ T cell infection with its relative contribution being very sensitive to the measurement of corresponding parameter values.

Existing theoretical models of HIV infection have greatly improved our understanding on the the HIV viral infection dynamics and production in CD4$^+$ T cells. Experiments and clinical data suggest that HIV can also infect other cells such as macrophages, monocytes, dendritic cells and so on, which is the main focus of the current manuscript. Here, we have analyzed the dynamic behaviors of a general within-host virus model concerning age structures in multiple infected target cells and a general nonlinear incidence rate $h_i(T_i, V)$. Since the lack of practical tools, it is normally not easy to study the global properties of age-structured models with the form of PDEs. In the current paper, the existence, uniqueness and relative compactness of solutions are investigated by following the idea in [5]. By further employing the approach developed in Magal, McCluskey and Webb [26] via constructing Lyapunov functionals, we investigate the global stability of equilibria. The infection-free steady state is globally asymptotically stable when the basic reproduction number is less than or equal to unity, and the infected steady state is globally asymptotically stable when the basic reproduction number is greater than one. Our analysis extends some existing results in the sense that the global stability was analyzed for a model with various types of target cell populations, and the general nonlinear rates, while some specific infection incidence assumptions, such as βTV, $F(T)G(V)$ and $\beta TV/(1 + k_1T + k_2V)$, were used in [13, 50, 57]. In addition, since our model was based on the HIV infection models which have convergent asymptotic dynamics in the long term, the

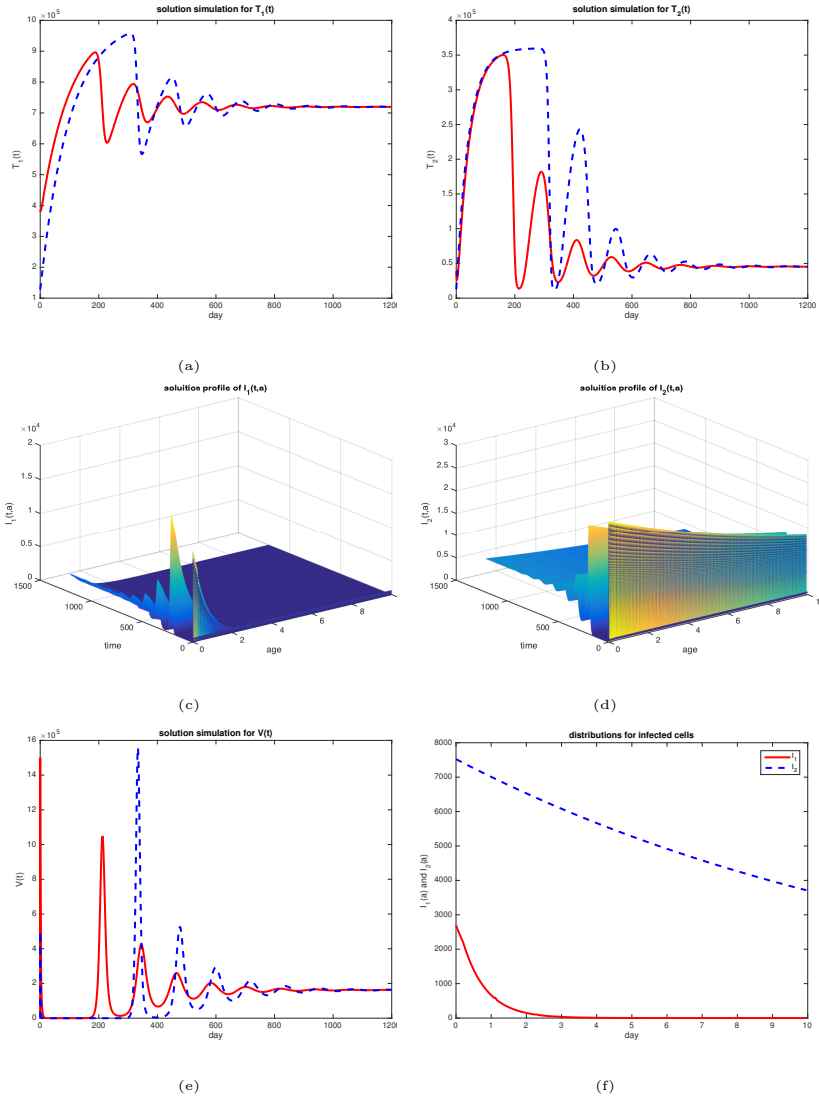

Figure 1. Panels (a)-(e) show the time evolution of solutions for all variables with two different initial data sets. Panel (f) illustrates the age-dependent steady state for infected cell loads of two different types.

result of this paper further shows that the incorporation of age-infection does not change the global dynamics of within-host virus infection model.

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