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Research article

Dynamic analysis of a cytokine-enhanced viral infection model with infection age

Jinhu Xu*

School of Sciences, Xi'an University of Technology, Xi'an 710048, China

* **Correspondence:** Email: xujinhu09@163.com.

Abstract: Recent studies reveal that pyroptosis is associated with the release of inflammatory cytokines which can attract more target cells to be infected. In this paper, a novel age-structured virus infection model incorporating cytokine-enhanced infection is investigated. The asymptotic smoothness of the semiflow is studied. With the help of characteristic equations and Lyapunov functionals, we have proved that both the local and global stabilities of the equilibria are completely determined by the threshold $\mathcal{R}_0$. The result shows that cytokine-enhanced viral infection also contributes to the basic reproduction number $\mathcal{R}_0$, implying that it may not be enough to eliminate the infection by decreasing the basic reproduction number of the model without considering the cytokine-enhanced viral infection mode. Numerical simulations are carried out to illustrate the theoretical results.

Keywords: viral infection; age-structured; cytokine-enhanced; Lyapunov functionals; global stability

1. Introduction

In recent years, much attention have been paid on the mathematical modeling for HIV infection [1–10]. However, most of the above mentioned models assumed that the death rate and virus production rate of infected cells are constants. In reality, the results in [11,12] shown that the death rate of infected cells should depend on the infection age of infected cells, i.e., the time since the infection of the cell. When taking the effect of infection age into a model, Nelson et al. [13] proposed and studied the following age-structured viral infection model

$$\begin{cases} T'(t) = \Lambda - dT(t) - \beta T(t)V(t), \\ \frac{\partial i}{\partial t} + \frac{\partial i}{\partial a} = -\delta(a)i(t,a), \\ V'(t) = \int_0^\infty p(a)i(t,a) - cV(t), \end{cases} \tag{1.1}$$

with boundary condition $i(t,0) = \beta TV$. Here, T and V denote the concentration of uninfected target cells and free virions, respectively. $i(t,a)$ denotes the density of infected cells of infection age a at time t. $\delta(a)$ is the age-dependent death rate of infected cells, $p(a)$ is the viral production rate of an infected cell with age a. The global dynamics of model (1.1) has been investigated by constructing Lyapunov functions in [14]. Then, many age-structured viral infection models have been studied by researchers [15–26] and references cited in.

Virus-to-cell infection has been regarded as the main infection mode for HIV infection for a long time. However, literature reveals that cell-to-cell infection is a more potent and efficient way of virus propagation rather than virus-to-cell infection [27–31]. Motivated by this fact that many models have been proposed to study the virus dynamics for a model with cell-to-cell infection [32–45], and references cited in. For example, Xu et al. [45] studied a viral infection model by taking cell-to-cell infection into consideration in model (1.1) and the global dynamics have been investigated.

As in the above just mentioned references, most of the existing work just considering the death of $CD4^+$ T cells caused by apoptosis. However, it is reported recently that $CD4^+$ T cells death caused by pyroptosis has a larger percentage than apoptosis [46–49]. Pyroptosis is a kind of programmed cell death triggered during the procedure of infection, in which the cytoplasmic content of infected cells and pro-inflammatory cytokines are released. When virus enters the $CD4^+$T cells that are unlicensed to viral infection, then the caspase-1 pathway will be activated to induce pyroptosis, which can secrete inflammatory cytokines, and then these inflammatory cytokines establish a chronic inflammation state and can attract more $CD4^+$ T cells to the inflammatory state resulting in more infection and cell death [46–49]. In recent years, though some researchers have paid attention on the cytokine-enhanced infection [49–52]. However, to the best of our knowledge the above mentioned work have not taken the infection age into consideration. Therefore, motivated by [13, 49–52], we propose a novel age-structured viral infection model incorporating virus-to-cell, cell-to-cell and cytokine-enhanced viral infection modes. Namely, we consider

$$\begin{cases} T'(t) = \Lambda - d_1T(t) - \beta_1T(t)V(t) - \beta_2T(t)M(t) - T(t)\int_0^\infty \beta_3(a)i(t,a)da, \\ \dfrac{\partial i(t,a)}{\partial t} + \dfrac{\partial i(t,a)}{\partial a} = -(\alpha_1(a) + d_2(a))i(t,a), \\ i(t,0) = \beta_1T(t)V(t) + \beta_2T(t)M(t) + T(t)\int_0^\infty \beta_3(a)i(t,a)da, \\ M'(t) = \int_0^\infty \alpha_2(a)i(t,a)da - d_3M(t), \\ V'(t) = \int_0^\infty p(a)i(t,a)da - d_4V(t), \end{cases} \tag{1.2}$$

with initial condition

$$\begin{aligned} &T(0) = T_0 > 0, \ \ i(0,a) = i_0(a) =: \varphi(a) \in L^1_+(0,+\infty), \\ &V(0) = V_0 > 0, \ \ M(0) = M_0 > 0, \end{aligned}$$

where $M(t)$ denotes the concentration of inflammatory cytokines. Here, β_1TV and β_2TM are the free-virus infection and cytokine-enhanced viral infection, respectively. Λ is the uninfected target cell production rate. d_1, d_3 and d_4 are the natural death rates of uninfected cells, inflammatory cytokines and virus, respectively. $\beta_3(a)$ is the infection-age specific transmission rate of productively infected cells. $d_2(a)$ is the natural death rate of infected cells with age a. $\alpha_1(a)$ is the death rate of infected cells which are caused by pyroptotis with age a. $\alpha_2(a)$ and $p(a)$ are the production rates of inflammatory cytokines released from infected cells and virus production rate with age a. All parameters in system (1.2) are positive, and $\alpha_1(a)$, $\beta_3(a)$, $d_2(a)$, $\alpha_2(a)$ and $p(a)$ are all Lipschitz continuous and belong to

$L_+^\infty(0,\infty)$. Assume $i(t,a)$ is expected to be small for large a which reflecting the fact that it is essentially zero for large age. Actually, it can be shown that $I(t)$ is bounded. Thus, assume that there exists a maximum age $0 < a_\dagger < +\infty$ such that $i(t,a) = 0$ for all $a \geq a_\dagger$ implying that no cells can live forever. It is worth mentioning that model (1.2) includes the existing models in [13,36,45]. The aim of this paper is to investigate the global dynamics of model (1.2).

The organization of this paper is as follows. Some preliminaries results of the system (1.2) are presented in Section 2. The existence and stability of steady states are analyzed in Section 3. Some numerical simulations are carried out for evaluating the results in Section 4. A brief discussion is presented at the end of the paper.

2. Preliminaries

Denote $\bar{\delta} = ess \sup_{a\in\mathbb{R}_+} \delta(a)$ and $\underline{\delta} = ess \inf_{a\in\mathbb{R}_+} \delta(a) > 0$, where $\delta \in \{\alpha_1(a), \beta_3(a), d_1(a), \alpha_2(a), p(a)\}$. Let $\mathbb{X} = \mathbb{R} \times L^1(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R} \times \mathbb{R}$, $\mathbb{X}_0 = \mathbb{R} \times \{0\} \times L^1(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R} \times \mathbb{R}$, $\mathbb{X}_+ = \mathbb{R}_+ \times L^1(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R}_+ \times \mathbb{R}_+$, $\mathbb{X}_{0+} = \mathbb{X}_+ \cap \mathbb{X}_0$ with the norm $\|\psi_1, \varphi(\cdot), \psi_2, \psi_3\|_{\mathbb{X}} = |\psi_1| + \int_0^\infty |\varphi(a)|da + |\psi_2| + |\psi_3|$. Define a linear operator $\mathcal{B} : Dom(\mathcal{B}) \subset \mathbb{X} \to \mathbb{X}$ with the form

$$\mathcal{B}\begin{pmatrix} \psi_1 \\ \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \psi_2 \\ \psi_3 \end{pmatrix} = \begin{pmatrix} -d_1\psi_1 \\ \begin{pmatrix} -\varphi(0) \\ -\varphi' - (\alpha_1(a) + d_2(a))\varphi \end{pmatrix} \\ -d_3\psi_2 \\ -d_4\psi_3 \end{pmatrix},$$

with $Dom(\mathcal{B}) = \mathbb{R} \times \{0\} \times W^{1,1}(0,\infty) \times \mathbb{R} \times \mathbb{R}$, where $W^{1,1}(0,\infty)$ is a Sobolev space. The nonlinear operator $\mathcal{F} : Dom(\mathcal{B}) \subset \mathbb{X} \to \mathbb{X}$ is given by

$$\mathcal{F}\begin{pmatrix} \psi_1 \\ \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \psi_2 \\ \psi_3 \end{pmatrix} = \begin{pmatrix} \Lambda - \beta_1\psi_1\psi_3 - \beta_2\psi_1\psi_2 - \int_0^\infty \psi_1\beta_3(a)\varphi(a)da \\ \begin{pmatrix} \beta_1\psi_1\psi_3 + \beta_2\psi_1\psi_2 + \int_0^\infty \psi_1\beta_3(a)\varphi(a)da \\ 0 \end{pmatrix} \\ \int_0^\infty \alpha_2(a)\varphi(a)da \\ \int_0^\infty p(a)\varphi(a)da \end{pmatrix},$$

and $\mathcal{F}$ is Lipschitz continuous on bounded sets. Let

$$u(t) = \left(T(t), \begin{pmatrix} 0 \\ i(t,a) \end{pmatrix}, M(t), V(t)\right)^{\mathrm{T}},$$

where T represents transposition of a vector. Then, we can reformulate model (1.2) as the following abstract Cauchy problem:

$$\frac{du(t)}{dt} = \mathcal{B}u(t) + \mathcal{F}(u(t)), \quad \text{for } t \geq 0, \quad \text{with} \quad u(0) = u_0 \in \mathcal{X}_{0+}. \tag{2.1}$$

Denote $\rho(\mathcal{B})$ as the resolvent set of $\mathcal{B}$. We will show $\mathcal{B}$ is a Hille-Yosida operator.

Definition 2.1. *([53]) A linear operator $\mathcal{B} : Dom(\mathcal{B}) \subset \mathbb{X} \to \mathbb{X}$ on a Banach space $(\mathbb{X}, \|\cdot\|)$ is called Hille-Yosida operator if there exist real constants $M_1 \geq 1$ and $\omega \in \mathbb{R}$ such that $(\omega, +\infty) \subseteq \rho(\mathcal{B})$ and*

$$\|(\lambda\mathbb{I} - \mathcal{B})^{-n}\| \leq \frac{M_1}{(\lambda - \omega)^n}, n \in \mathbb{N}_+, \lambda > \omega.$$

Lemma 2.1. *The operator $\mathcal{B}$ is a Hille-Yosida operator.*

Proof. It follows from the definition of $\mathcal{B}$ that

$$(\lambda\mathbb{I} - \mathcal{B})^{-1} \begin{pmatrix} \tilde{\psi}_1 \\ \begin{pmatrix} \tilde{\varphi}_0 \\ \tilde{\varphi}(a) \end{pmatrix} \\ \tilde{\psi}_2 \\ \tilde{\psi}_3 \end{pmatrix} = \begin{pmatrix} \psi_1 \\ \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \psi_2 \\ \psi_3 \end{pmatrix}.$$

Then, we have

$$\begin{aligned} \psi_1 =& \frac{\tilde{\psi}_1}{\lambda + d_1}, \psi_2 = \frac{\tilde{\psi}_2}{\lambda + d_3}, \psi_3 = \frac{\tilde{\psi}_3}{\lambda + d_4}, \\ \varphi(a) =& \tilde{\varphi}_0 e^{-\int_0^a (\lambda + \alpha_1(s) + d_2(s))ds} + \int_0^a \tilde{\varphi}(\tau) e^{-\int_\tau^a (\lambda + \alpha_1(s) + d_2(s))ds} d\tau. \end{aligned}$$

Let $\xi = \left(\tilde{\psi}_1, \begin{pmatrix} \tilde{\varphi}_0 \\ \tilde{\varphi}(a) \end{pmatrix}, \tilde{\psi}_2, \tilde{\psi}_3\right)^{\mathrm{T}}$. Then, we have

$$\begin{aligned} \|(\lambda\mathbb{I} - \mathcal{B})^{-1}\xi\|_{\mathbb{X}} =& |\psi_1| + |0| + |\int_0^\infty \varphi(a)da| + |\psi_2| + |\psi_3| \\ =& \frac{|\tilde{\psi}_1|}{\lambda + d_1} + \int_0^\infty \varphi(a)da + \frac{|\tilde{\psi}_2|}{\lambda + d_3} + \frac{|\tilde{\psi}_3|}{\lambda + d_4} \\ \leq& \frac{|\tilde{\psi}_1|}{\lambda + d_1} + \frac{|\tilde{\psi}_0|}{\lambda + \underline{\alpha}_1 + \underline{d}_2} + \frac{\|\tilde{\varphi}\|_{L^1}}{\lambda + \underline{\alpha}_1 + \underline{d}_2} + \frac{|\tilde{\psi}_2|}{\lambda + d_3} + \frac{|\tilde{\psi}_3|}{\lambda + d_4} \\ \leq& \frac{\|\xi\|_{\mathbb{X}}}{\lambda + \mu_0}, \end{aligned}$$

where $\mu_0 = \min\{d_1, \underline{\alpha}_1 + \underline{d}_2, d_3, d_4\}$. Hence, it follows from the Definition 2.1 that $\mathcal{B}$ is a Hille-Yosida operator. □

Let $\chi_0 = \left(T_0, \begin{pmatrix} 0 \\ i_0 \end{pmatrix}, M_0, V_0\right)^{\mathrm{T}} \in \mathbb{X}_{0+}$. Then it follows from [53] that the following result holds.

Theorem 2.1. *There exists a uniquely determined semi-flow $\{U(t)\}_{t\geq 0}$ on $\mathbb{X}_{0+}$ such that for each χ_0, there exists a unique continuous map $U \in C([0, \infty), \mathbb{X}_{0+})$ which is an integrated solution of Cauchy problem* (2.1)*, that is*

$$\begin{aligned} &\int_0^t U(s)\chi_0 ds \in Dom(\mathcal{B}), \forall t \geq 0, \\ &U(t)\chi_0 = \chi_0 + \mathcal{B} \int_0^t U(s)\chi_0 ds + \int_0^\infty \mathcal{F}(U(s)\chi_0)ds, \forall t \geq 0. \end{aligned}$$

Let $\mathcal{D} = \{(T(t), i(t,a), M(t), V(t)) \in \mathbb{X}_{0+} | T(t) \le \frac{\Lambda}{d_1}, T(t) + \int_0^\infty i(t,a)da \le \frac{\Lambda}{d_0}, M(t) \le \frac{\Lambda\bar{\alpha}_2}{d_0 d_3}, V(t) \le \frac{\Lambda\bar{p}}{d_0 d_4}\}$, where $d_0 = \min\{d_1, \underline{\alpha_1} + \underline{d_2}\}$. Then, it can be shown that $\mathcal{D}$ is a positively invariant set under semi-flow $\{U(t)\}_{t\ge 0}$.

Integrating the second equation of model (1.2) along the characteristic line yields

$$i(t,a) = \begin{cases} i(t-a, 0)\Gamma(a), t \ge a > 0, \\ i_0(a-t)\frac{\Gamma(a)}{\Gamma(a-t)}, 0 < t < a, \end{cases}$$

where $\Gamma(a) = e^{-\int_0^a (\alpha_1(\tau) + d_2(\tau))d\tau}$. Consequently, we have $I(t) = \int_0^t i(t-a,0)\Gamma(a)da + \int_t^\infty i_0(a-t)\frac{\Gamma(a)}{\Gamma(a-t)}da$. It follows from model (1.2) that $\frac{dT(t)}{dt} \le \Lambda - d_1 T$, which implies $\limsup_{t\to\infty} T(t) \le \frac{\Lambda}{d_1}$. From the first two equations of model (1.2), then we have

$$\frac{d(T(t) + I(t))}{dt} = \Lambda - d_1 T - \int_0^\infty (\alpha_1(a) + d_2(a))i(t,a)da \le \Lambda - d_0(T(t) + I(t)),$$

which yields

$$\limsup_{t\to\infty}(T + \int_0^\infty i(t,a)da) \le \frac{\Lambda}{d_0},$$

where $d_0 = \min\{d_1, \underline{\alpha_1} + \underline{d_2}\}$. Therefore, $U(t)\chi_0 \in \mathcal{D}$ for $\chi_0 \in \mathcal{D}$, which implies $\mathcal{D}$ is a positively invariant set. Moreover, the semi-flow $U(t)_{t\ge 0}$ is point dissipative and $\mathcal{D}$ attracts all positive solutions of model (1.2) in $\mathbb{X}_{0+}$. Thus, we have the following result.

Theorem 2.2. *$\mathcal{D}$ is positively invariant set under the semi-flow $\{U(t)\}_{t\ge 0}$. Moreover, the semi-flow $\{U(t)\}_{t\ge 0}$ is point dissipative and attracts all positive solutions of model* (1.2).

Furthermore, we can show that the semi-flow $\{U(t)\}_{t\ge 0}$ is asymptotically smooth. In order to give the proof, we rewrite $U = \Phi + \Psi$ where

$$\Phi(t)\chi_0 = (0, w_1(t,\cdot), 0, 0), \quad \Psi(t)\chi_0 = (T(t), w_2(t,\cdot), M(t), V(t)),$$

with

$$w_1(t,\cdot) = \begin{cases} 0, \ t > a \ge 0, \\ i(t,a), \ a \ge t \ge 0, \end{cases} \quad w_2(t,\cdot) = \begin{cases} i(t,a), \ t > a \ge 0, \\ 0, \ a \ge t \ge 0. \end{cases}$$

Theorem 2.3. *$U(t)\chi_0 : t \ge 0$ has compact closure in $\mathbb{X}$ for $\forall \chi_0 \in \mathcal{D}$ if the following two conditions hold: (i) There exists a function $\Delta : \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+$ such that $\lim_{t\to\infty} \Delta(t,r) = 0, \forall r > 0$, and if $\chi_0 \in \mathcal{D}$ with $\|\chi_0\|_{\mathbb{X}} \le r$, then $\|\Phi(t)\chi_0\|_{\mathbb{X}} \le \Delta(t,r)$ for $t \ge 0$; (ii) For $t \ge 0$, $\Psi(t)\chi_0$ maps any bounded sets of $\mathcal{D}$ into sets with compact closure in $\mathbb{X}$.*

Proof. (i) Let $\Delta(t,r) = re^{-(\underline{\alpha_1} + \underline{d_2})t}$, then we have $\lim_{t\to\infty} \Delta(t,r) = 0$. For $\chi_0 \in \mathcal{D}$ satisfying $\|\chi_0\|_{\mathbb{X}} \le r$, we have

$$\|\Phi(t)\chi_0\|_{\mathbb{X}} = |0| + \int_0^\infty |w_1(t,a)|da + |0| + |0|$$

$$= \int_t^\infty \left| i_0(a-t) \frac{\Gamma(a)}{\Gamma(a-t)} \right| da = \int_0^\infty \left| i_0(s) \frac{\Gamma(s+t)}{\Gamma(s)} \right| ds$$
$$\le e^{-(\underline{\alpha_1}+\underline{d_2})t} \int_0^\infty |i_0(s)| ds \le e^{-(\underline{\alpha_1}+\underline{d_2})t} \|\chi_0\|_{\mathbb{X}} \le \Delta(t,r), t \ge 0.$$

This completes the proof of (i).

(ii) In order to show (ii) is true. We just need to show that the following conditions hold [54].

(a) The supremum of $\int_0^\infty w_2(t,a)da$ with respect to $\chi_0 \in \mathcal{D}$ is finite;

(b) $\lim\limits_{h\to\infty} \int_h^\infty w_2(t,a)da = 0$ uniformly with respect to $\chi_0 \in \mathcal{D}$;

(c) $\lim\limits_{h\to 0^+} \int_0^\infty (w_2(t,a+h) - w_2(t,a))da = 0$ uniformly with respect to $\chi_0 \in \mathcal{D}$;

(d) $\lim\limits_{h\to 0^+} \int_h^\infty w_2(t,a)da = 0$ uniformly with respect to $\chi_0 \in \mathcal{D}$.

It follows from the definition of $\mathcal{D}$ that (a), (b) and (d) hold. Thus, we only to show the condition (c) holds. For convenience, denote $K(t) = \int_0^\infty \beta_3(a)i(t,a)da$. For sufficiently small $h \in (0,t)$, we have

$$\begin{aligned}
&\int_0^\infty |w_2(t,a+h) - w_2(t,a)|da \\
=&\int_0^{t-h} \Big| [\beta_1 T(t-a-h)V(t-a-h) + \beta_2 T(t-a-h)M(t-a-h) + K(t-a-h)T(t-a-h)]\Gamma(a+h) \\
&- [\beta_1 T(t-a)V(t-a) + \beta_2 T(t-a)M(t-a) + K(t-a)T(t-a)]\Gamma(a) \Big| da \\
&+ \int_{t-h}^t |0 - [\beta_1 T(t-a)V(t-a) + \beta_2 T(t-a)M(t-a) + K(t-a)T(t-a)]|\Gamma(a)da \\
\le&\int_0^{t-h} |(\beta_1 V(t-a-h) + \beta_2 M(t-a-h))T(t-a-h) + K(t-a-h)T(t-a-h)||\Gamma(a+h) - \Gamma(a)|da \\
&+ \int_0^{t-h} |\beta_1 T(t-a-h)V(t-a-h) - \beta_1 T(t-a)V(t-a)|\Gamma(a)da \\
&+ \int_0^{t-h} |\beta_2 T(t-a-h)M(t-a-h) - \beta_2 T(t-a)M(t-a)|\Gamma(a)da \\
&+ \int_0^{t-h} |K(t-a-h)T(t-a-h) - K(t-a)T(t-a)|\Gamma(a)da \\
&+ \left(\frac{\beta_1 \bar{p}\Lambda}{d_0 d_4} + \frac{\beta_2 \bar{\alpha}_2 \Lambda}{d_0 d_3} + \frac{\bar{\beta}_3 \Lambda}{d_0} \right) \frac{\Lambda}{d_1} h \\
\le&\left(\frac{\beta_1 \bar{p}\Lambda}{d_0 d_4} + \frac{\beta_2 \bar{\alpha}_2 \Lambda}{d_0 d_3} + \frac{\bar{\beta}_3 \Lambda}{d_0} \right) \frac{\Lambda}{d_1} \int_0^{t-h} |\Gamma(a+h) - \Gamma(a)|da + \left(\frac{\beta_1 \bar{p}\Lambda}{d_0 d_4} + \frac{\beta_2 \bar{\alpha}_2 \Lambda}{d_0 d_3} + \frac{\bar{\beta}_3 \Lambda}{d_0} \right) \frac{\Lambda}{d_1} h + \Theta,
\end{aligned} \tag{2.2}$$

where

$$\begin{aligned}
\Theta =& \int_0^{t-h} |\beta_1 T(t-a-h)V(t-a-h) - \beta_1 T(t-a)V(t-a)|\Gamma(a)da \\
&+ \int_0^{t-h} |\beta_2 T(t-a-h)M(t-a-h) - \beta_2 T(t-a)M(t-a)|\Gamma(a)da \\
&+ \int_0^{t-h} |K(t-a-h)T(t-a-h) - K(t-a)T(t-a)|\Gamma(a)da.
\end{aligned}$$

We note that $\Gamma(a)$ is a decreasing function and satisfies $0 \le \Gamma(a) \le 1$. Thus,

$$\begin{aligned}\int_0^{t-h} |\Gamma(a+h) - \Gamma(a)| da &= \int_0^{t-h} (\Gamma(a) - \Gamma(a+h)) da \\ &= \int_0^h \Gamma(a) da - \int_{t-h}^t \Gamma(a) da \le h.\end{aligned} \tag{2.3}$$

Then, it follows from (2.2) and (2.3) that

$$\int_0^\infty |w_2(t, a+h) - w_2(t, a)| da \le 2\left(\frac{\beta_1 \bar{p}\Lambda}{d_0 d_4} + \frac{\beta_2 \bar{\alpha}_2 \Lambda}{d_0 d_3} + \frac{\bar{\beta}_3 \Lambda}{d_0}\right)\frac{\Lambda}{d_1} h + \Theta.$$

It follows from [38, 55] that TV, TM and KT are Lipschitz on $\mathbb{R}_+$. Assume L_{TV}, L_{TM} and L_{KT} be the Lipschitz coefficients of TV, TM and KT, respectively. Similar techniques as [56], then we have

$$\Theta \le (\beta_1 L_{TV} + \beta_2 L_{TM} + L_{KT}) h \int_0^{t-h} \Gamma(a) da \le \frac{(\beta_1 L_{TV} + \beta_2 L_{TM} + L_{KT}) h}{\underline{\alpha_1} + \underline{d_2}}.$$

Thus,

$$\int_0^\infty |w_2(t, a+h) - w_2(t, a)| da \le 2\left(\beta_1 \frac{\bar{p}\Lambda}{d_0 d_4} + \beta_2 \frac{\bar{\alpha}_2 \Lambda}{d_0 d_3} + \frac{\bar{\beta}_3 \Lambda}{d_0}\right)\frac{\Lambda}{d_1} h + \frac{(\beta_1 L_{TV} + \beta_2 L_{TM} + L_{KT}) h}{\underline{\alpha_1} + \underline{d_2}},$$

which converges to 0 as $h \to 0^+$. Therefore, condition (iii) holds. This completes the proof. □

3. Stability of steady states

Define the basic reproduction number of model (1.2) as follows:

$$\mathcal{R}_0 = \frac{\beta_1 \Lambda}{d_1 d_4} \int_0^\infty p(a)\Gamma(a) da + \frac{\beta_2 \Lambda}{d_1 d_3} \int_0^\infty \alpha_2(a)\Gamma(a) da + \frac{\Lambda}{d_1} \int_0^\infty \beta_3(a)\Gamma(a) da.$$

Clearly, model (1.2) always has an infection-free steady state $E_0 = (T^0, 0, 0, 0)$ with $T^0 = \frac{\Lambda}{d_1}$. If $\mathcal{R}_0 \neq 1$, then there exists a unique infection steady state $E_* = (T^*, i^*(a), V^*, M^*)$, which satisfies

$$\begin{aligned} &T^* = \frac{T^0}{\mathcal{R}_0}, i^*(0) = \Lambda(1 - \frac{1}{\mathcal{R}_0}), i^*(a) = \Lambda\Gamma(a)(1 - \frac{1}{\mathcal{R}_0}), \\ &M^* = \frac{i^*(0)}{d_3} \int_0^\infty \alpha_2(a)\Gamma(a) da, V^* = \frac{i^*(0)}{d_4} \int_0^\infty p(a)\Gamma(a) da. \end{aligned} \tag{3.1}$$

Theorem 3.1. *If $\mathcal{R}_0 < 1$, then the infection-free steady state E^0 is locally stable.*

Proof. Denote $\tilde{T}(t) = T(t) - T^0$, $\tilde{i}(t, a) = i(t, a)$, $\tilde{M}(t) = M(t)$ and $\tilde{V}(t) = V(t)$. Linearizing model (1.2) at E^0, then we have

$$\begin{cases} \frac{d\tilde{T}}{dt} = -d_1 \tilde{T} - \beta_1 T^0 \tilde{V} - \beta_2 T^0 \tilde{M} - T^0 \int_0^\infty \beta_3(a)\tilde{i}(t, a) da, \\ \frac{\partial \tilde{i}}{\partial t} + \frac{\partial \tilde{i}}{\partial a} = -(\alpha_1(a) + d_2(a))\tilde{i}(t, a), \\ \tilde{i}(t, 0) = \beta_1 T^0 \tilde{V} + \beta_2 T^0 \tilde{M} + T^0 \int_0^\infty \beta_3(a)\tilde{i}(t, a) da, \\ \frac{d\tilde{M}}{dt} = \int_0^\infty \alpha_2(a)\tilde{i}(t, a) da - d_3 \tilde{M}, \\ \frac{d\tilde{V}}{dt} = \int_0^\infty p(a)\tilde{i}(t, a) da - d_4 \tilde{V}. \end{cases}$$

In order to analyze the stability of E_0, we look for solutions of the form $\tilde{T} = \tilde{T}_0 e^{\mu t}$, $\tilde{i}(t,a) = \tilde{i}_0(a)e^{\mu t}$, $\tilde{M} = \tilde{M}_0 e^{\mu t}$ and $\tilde{V} = \tilde{V}_0 e^{\mu t}$. Substituting the solutions into the above linearized model yields

$$\begin{cases} (\mu + d_1)\tilde{T}_0 = -\beta_1 T^0 \tilde{V}_0 - \beta_2 T^0 \tilde{M}_0 - T^0 \int_0^\infty \beta_3(a)\tilde{i}_0(a)da, \\ \frac{d\tilde{i}_0(a)}{da} = -(\mu + \alpha_1(a) + d_2(a))\tilde{i}(a), \\ (\mu + d_3)\tilde{M}_0 = \int_0^\infty \alpha_2(a)\tilde{i}_0(a)da, \\ (\mu + d_4)\tilde{V}_0 = \int_0^\infty p(a)\tilde{i}_0(a)da, \\ \tilde{i}_0(0) = \beta_1 T^0 \tilde{V}_0 + \beta_2 T^0 \tilde{M}_0 + T^0 \int_0^\infty \beta_3(a)\tilde{i}_0(a)da. \end{cases} \tag{3.2}$$

Then we have $\tilde{i}_0(a) = \tilde{i}_0(0)\Gamma(a)e^{-\mu a}$, $\tilde{M}_0 = \frac{1}{\mu+d_3}\int_0^\infty \alpha_2(a)\tilde{i}_0(a)da$, $\tilde{V}_0 = \frac{1}{\mu+d_4}\int_0^\infty p(a)\tilde{i}_0(a)da$, substituting $\tilde{i}_0(a)$, $\tilde{M}_0$ and $\tilde{V}_0$ into the last equation of (3.2), we have

$$1 = \frac{\beta_1 T^0}{\mu + d_4}\int_0^\infty p(a)\Gamma(a)e^{-\mu a}da + \frac{\beta_2 T^0}{\mu + d_3}\int_0^\infty \alpha_2(a)\Gamma(a)e^{-\mu a}da + T^0\int_0^\infty \beta_3(a)\Gamma(a)e^{-\mu a}da \triangleq G(\mu). \tag{3.3}$$

Obviously, $\lim_{\mu\to\infty} G(\mu) = 0$, $G(0) = \mathcal{R}_0$, and a simple computation shows that $G(\mu)$ is a decreasing function with respect to μ. Therefore, if $\mathcal{R}_0 < 1$, then any real root of (3.3) is negative. Thus, E_0 is unstable for $\mathcal{R}_0 > 1$. Moreover, we claim that (3.3) has no complex roots with nonnegative real part if $\mathcal{R}_0 < 1$. In fact, if there exists a root $\mu = \xi + \eta i$ with $\xi \geq 0$. Then,

$$\begin{aligned} |G(\mu)| \leq & \frac{\beta_1 T^0}{|\mu + d_4|}\left|\int_0^\infty p(a)\Gamma(a)e^{-\mu a}da\right| + \frac{\beta_2 T^0}{|\mu + d_3|}\left|\int_0^\infty \alpha_2(a)\Gamma(a)e^{-\mu a}da\right| \\ & + T^0\left|\int_0^\infty \beta_3(a)\Gamma(a)e^{-\mu a}da\right| \\ = & \frac{\beta_1 T^0}{\sqrt{(\xi + d_4)^2 + \eta^2}}\int_0^\infty \left|e^{-(\xi+\eta i)a}\right| p(a)\Gamma(a)da + \frac{\beta_2 T^0}{\sqrt{(\xi + d_3)^2 + \eta^2}}\int_0^\infty \left|e^{-(\xi+\eta i)a}\right| \alpha_2(a)\Gamma(a)da \\ & + T^0\int_0^\infty \beta_3(a)\Gamma(a)\left|e^{-(\xi+\eta i)a}\right| da \\ \leq & \frac{\beta_1 T^0}{\xi + d_4}\int_0^\infty e^{-\xi a}p(a)\Gamma(a)da + \frac{\beta_2 T^0}{\xi + d_3}\int_0^\infty e^{-\xi a}\alpha_2(a)\Gamma(a)da + T^0\int_0^\infty \beta_3(a)\Gamma(a)e^{-\xi a}da \\ = & G(\xi) \leq G(0) = \mathcal{R}_0 < 1. \end{aligned}$$

Thus, the above arguments imply that every root of (3.3) must have a negative real part, which implies that E_0 is locally stable for $\mathcal{R}_0 < 1$. □

Theorem 3.2. *If $\mathcal{R}_0 > 1$, then E_* is locally stable.*

Proof. With the same technique of Theorem 3.1. Let $x(t) = T - T^*$, $y(t,a) = i(t,a) - i^*(a)$, $z = M(t) - M^*$ and $v(t) = V(t) - V^*$. Linearizing model (1.2) at E_* and looking for solutions of the form $x = \tilde{x}e^{\mu t}$,

$y(t,a) = \tilde{y}(a)e^{\mu t}$, $z = \tilde{z}e^{\mu t}$ and $v = \tilde{v}e^{\mu t}$ leads to

$$\begin{cases} \mu\tilde{x} = -(d_1 + \beta_1 V^* + \beta_2 M^* + \int_0^\infty \beta_3(a)i_*(a)da)\tilde{x} - \beta_1 T^*\tilde{v} - \beta_2 T^*\tilde{z} - T^* \int_0^\infty \beta_3(a)y(t,a)da, \\ \frac{d\tilde{y}(a)}{da} = -(\mu + \alpha_1(a) + d_2(a))\tilde{y}, \\ \mu\tilde{z} = \int_0^\infty \alpha_2(a)\tilde{y}(a)da - d_3\tilde{z}, \\ \mu\tilde{v} = \int_0^\infty p(a)\tilde{y}(a)da - d_4\tilde{v}, \\ \tilde{y}(0) = (\beta_1 V^* + \beta_2 M^* + \int_0^\infty \beta_3(a)i^*(a)da)\tilde{x} + \beta_1 T^*\tilde{v} + \beta_2 T^*\tilde{z} + T^* \int_0^\infty \beta_3(a)y(t,a)da. \end{cases}$$

A simple calculation leads to $\tilde{y}(a) = \tilde{y}(0)e^{-\mu a}\Gamma(a)$, $\tilde{x} = -\frac{\tilde{y}(0)}{\mu+d_1}$, $\tilde{z} = \frac{\tilde{y}(0)}{\mu+d_3}\int_0^\infty \alpha_2(a)e^{-\mu a}\Gamma(a)da$, and $\tilde{v} = \frac{\tilde{v}(0)}{\mu+d_4}\int_0^\infty p(a)e^{-\mu a}\Gamma(a)da$. Then we have

$$\begin{aligned} &\frac{\mu + d_1 + \beta_1 V^* + \beta_2 M^* + \int_0^\infty \beta_3(a)i^*(a)da}{\mu + d_1} \\ =&\frac{\beta_1 T^*}{\mu + d_4}\int_0^\infty p(a)\Gamma(a)e^{-\mu a}da + \frac{\beta_2 T^*}{\mu + d_3}\int_0^\infty \alpha_2(a)\Gamma(a)e^{-\mu a}da + T^*\int_0^\infty \beta_3(a)\Gamma(a)e^{-\mu a}da. \end{aligned} \tag{3.4}$$

Obviously, for $Re\mu \geq 0$ then

$$\left|\frac{\mu + d_1 + \beta_1 V^* + \beta_2 M^* + \int_0^\infty \beta_3(a)i^*(a)da}{\mu + d_1}\right| > 1, \tag{3.5}$$

and

$$\begin{aligned} &\left|\frac{\beta_1 T^*}{\mu + d_4}\int_0^\infty p(a)\Gamma(a)e^{-\mu a}da + \frac{\beta_2 T^*}{\mu + d_3}\int_0^\infty \alpha_2(a)\Gamma(a)e^{-\mu a}da + T^*\int_0^\infty \beta_3(a)\Gamma(a)e^{-\mu a}da\right| \\ \leq&\frac{\beta_1 T^*}{|\mu + d_4|}\left|\int_0^\infty p(a)\Gamma(a)e^{-\mu a}da\right| + \frac{\beta_2 T^*}{|\mu + d_3|}\left|\int_0^\infty \alpha_2(a)\Gamma(a)e^{-\mu a}da\right| + T^*\left|\int_0^\infty \beta_3(a)\Gamma(a)e^{-\mu a}da\right| \\ \leq&\frac{\beta_1 T^*}{d_4}\int_0^\infty p(a)\Gamma(a)da + \frac{\beta_2 T^*}{d_3}\int_0^\infty \alpha_2(a)\Gamma(a)da + T^*\int_0^\infty \beta_3(a)\Gamma(a)da \\ =&\frac{T^*}{T^0}\mathcal{R}_0 = 1. \end{aligned} \tag{3.6}$$

It follows from (3.4)–(3.6) that there are no characteristic roots with non-negative real part. Thus, E_* is locally stable. □

Before we discuss the global stability of model (1.2) by constructing Lyapunov functionals. We present the following result by a procedure similar to [22, 23], so we omit the proof.

Theorem 3.3. *If $\mathcal{R}_0 > 1$, then for each $\chi_0 \in \mathbb{X}$ there exists a constant $\rho > 0$ such that*

$$\lim_{t\to\infty} T(t) \geq \rho, \lim_{t\to\infty} \|i(t,a)\|_{L^1} \geq \rho, \lim_{t\to\infty} M(t) \geq \rho, \lim_{t\to\infty} V(t) \geq \rho.$$

Now, we are in position to investigate the global stability of steady states.

Theorem 3.4. *If $\mathcal{R}_0 < 1$, then the infection-free steady state E_0 is globally asymptotically stable.*

Proof. Define

$$H_1(t) = T - T^0 - T^0 \ln\frac{T}{T^0} + \int_0^\infty \Phi(a)i(t,a)da + \frac{\beta_2 T^0}{d_3}M + \frac{\beta_1 T^0}{d_4}V,$$

where

$$\Phi(a) = \int_a^\infty \left(\frac{\beta_1 T^0}{d_4}p(\tau) + \frac{\beta_2 T^0}{d_3}\alpha_2(\tau) + \beta_3(\tau)T^0\right)e^{-\int_a^\tau(\alpha_1(\theta)+d_2(\theta))d\theta}d\tau.$$

It is easy to show that $\Phi(0) = \mathcal{R}_0$, and

$$\begin{aligned}\int_0^\infty \Phi(a)i(t,a)da =& \int_0^t \Phi(a)i(t-a,0)e^{-\int_0^a(\alpha_1(\tau)+d_2(\tau))d\tau}da \\ &+ \int_t^\infty \Phi(a)i_0(a-t)e^{-\int_{a-t}^a(\alpha_1(\tau)+d_2(\tau))d\tau}da \\ =& \int_0^t \Phi(t-r)i(r,0)e^{-\int_0^{t-r}(\alpha_1(\tau)+d_2(\tau))d\tau}dr \\ &+ \int_0^\infty \Phi(t+r)i_0(r)e^{-\int_r^{t+r}(\alpha_1(\tau)+d_2(\tau))d\tau}dr.\end{aligned} \tag{3.7}$$

Furthermore, we can obtain

$$\left(\int_0^\infty \Phi(a)i(t,a)da\right)' = \Phi(0)i(t,0) + \int_0^\infty (\Phi'(a) - (\alpha_1(a) + d_2(a))\Phi(a))i(t,a)da. \tag{3.8}$$

Thus, by using (3.7) and (3.8) and noting that $T^0 = \frac{\Lambda}{d_1}$, we have

$$\begin{aligned}H'(t) =& \left(1 - \frac{T}{T^0}\right)(\Lambda - d_1 T - i(t,0)) + \int_0^\infty (\Phi'(a) - (\alpha_1(a) + d_2(a))\Phi(a))i(t,a)da \\ &+ \Phi(0)i(t,0) + \frac{\beta_2 T^0}{d_3}\left(\int_0^\infty \alpha_2(a)i(t,a)da - d_3 M\right) \\ &+ \frac{\beta_1 T^0}{d_4}\left(\int_0^\infty p(a)i(t,a)da - d_4 V\right) \\ =& d_1 T^0\left(1 - \frac{T}{T^0}\right)\left(1 - \frac{T^0}{T}\right) + i(t,0)(\mathcal{R}_0 - 1) \le 0, \text{ for } \mathcal{R}_0 < 1.\end{aligned}$$

Therefore, if $\mathcal{R}_0 < 1$, we have $H'(t) \le 0$ and $H'(t) = 0$ implies that $T = T^0$, $i(t,a) = 0$, $M(t) = 0$ and $V(t) = 0$. Hence, the largest invariant subset of $\{H'(t) = 0\}$ is a singleton $\{E_0\}$, which means E_0 is global asymptotically stable for $\mathcal{R}_0 < 1$ by Lyapunov-LaSalle theorem [57]. This completes the proof. □

Theorem 3.5. *If $\mathcal{R}_0 > 1$, then the infection steady state E_* is globally asymptotically stable.*

Proof. Define

$$H_2(t) = T - T^* - T^* \ln\frac{T}{T^*} + \int_0^\infty \Phi(a)\left(i(t,a) - i^*(a) - i^*(a)\ln\frac{i(t,a)}{i^*(a)}\right)da$$

$$+\frac{\beta_2 T^*}{d_3}\left(M - M^* - M^* \ln \frac{M}{M^*}\right) + \frac{\beta_1 T^*}{d_4}\left(V - V^* - V^* \ln \frac{V}{V^*}\right),$$

where

$$\Phi(a) = \int_a^\infty \left(\frac{\beta_1 T^* p(\tau)}{d_4} + \frac{\beta_1 T^* \alpha_2(\tau)}{d_3} + \beta_3(\tau) T^*\right) e^{-\int_a^\tau (\alpha_1(\theta)+d_2(\theta))d\theta} da,$$

and satisfies

$$\Phi'(a) = -\left(\frac{\beta_1 T^* p(a)}{d_4} + \frac{\beta_1 T^* \alpha_2(a)}{d_3} + \beta_3(a) T^*\right) + (\alpha_1(a) + d_2(a))\Phi(a),\ \Phi(0) = 1. \tag{3.9}$$

Differentiating and using the steady state identities (3.1) and (3.9), then we have

$$\begin{aligned}
H_2'(t) =& d_1 T^*\left(1 - \frac{T}{T^*}\right)\left(1 - \frac{T^*}{T}\right) - i^*(0)\left(\frac{T^*}{T} + \ln \frac{i(t,0)}{i^*(0)}\right) + \beta_1 T^* V^* + \beta_2 T^* M^* \\
&+ \int_0^\infty \frac{\beta_1 T^* p(a) i^*(a)}{d_4}\left(1 + \ln \frac{i(t,a)}{i^*(a)}\right) da - \frac{\beta_1 T^*}{d_4}\int_0^\infty p(a) i(t,a) \frac{V^*}{V} da \\
&+ \int_0^\infty \frac{\beta_2 T^* \alpha_2(a) i^*(a)}{d_3}\left(1 + \ln \frac{i(t,a)}{i^*(a)}\right) da - \frac{\beta_2 T^*}{d_3}\int_0^\infty \alpha_2(a) i(t,a) \frac{M^*}{M} da \\
&+ \int_0^\infty \beta_3(a) T^* i^*(a)\left(1 + \ln \frac{i(t,a)}{i^*(a)}\right) da \\
=& d_1 T^*\left(1 - \frac{T}{T^*}\right)\left(1 - \frac{T^*}{T}\right) + \int_0^\infty \frac{\beta_1 T^*}{d_4} p(a) i^*(a)\left[2 - \frac{T^*}{T} - \frac{i(t,a)V^*}{i^*(a)V} + \ln \frac{i(t,a)i^*(0)}{i^*(a)i(t,0)}\right] da \\
&+ \int_0^\infty \frac{\beta_2 T^*}{d_3}\alpha_2(a) i^*(a)\left[2 - \frac{T^*}{T} - \frac{i(t,a)M^*}{i^*(a)M} + \ln \frac{i(t,a)i^*(0)}{i^*(a)i(t,0)}\right] da \\
&+ \int_0^\infty \beta_3(a) T^* i^*(a)\left[1 - \frac{T^*}{T} + \ln \frac{i(t,a)i^*(0)}{i^*(a)i(t,0)}\right] da \\
=& d_1 T^*\left(1 - \frac{T}{T^*}\right)\left(1 - \frac{T^*}{T}\right) + \int_0^\infty \frac{\beta_1 T^*}{d_4} p(a) i^*(a)\left[\phi\left(\frac{T}{T^*}\right) + \phi\left(\frac{V^* i(t,a)}{V i^*(a)}\right)\right. \\
&\left. + \phi\left(\frac{T V i^*(0)}{T^* V^* i(t,0)}\right) + \left(\frac{i^*(0) T V}{i(t,0) T^* V^*} - 1\right)\right] da + \int_0^\infty \frac{\beta_2 T^*}{d_3}\alpha_2(a) i^*(a)\left[\phi\left(\frac{T}{T^*}\right)\right. \\
&\left. + \phi\left(\frac{M^* i(t,a)}{M i^*(a)}\right) + \phi\left(\frac{T M i^*(0)}{T^* M^* i(t,0)}\right) + \left(\frac{i^*(0) T M}{i(t,0) T^* M^*} - 1\right)\right] da \\
&+ \int_0^\infty \beta_3(a) T^* i^*(a)\left[\phi\left(\frac{T^*}{T}\right) + \phi\left(\frac{i(t,a) i^*(0) T}{i^*(a) i(t,0) T^*}\right) + \left(\frac{i(t,a) i^*(0) T}{i^*(a) i(t,0) T^*} - 1\right)\right] da.
\end{aligned}$$

Since,

$$\begin{aligned}
&\int_0^\infty \frac{\beta_1 T^*}{d_4} p(a) i^*(a)\left(\frac{i^*(0) T V}{i(t,0) T^* V^*} - 1\right) da + \int_0^\infty \frac{\beta_2 T^*}{d_3}\alpha_2(a) i^*(a)\left(\frac{i^*(0) T M}{i(t,0) T^* M^*} - 1\right) da \\
&+ \int_0^\infty \beta_3(a) T^* i^*(a)\left(\frac{i(t,a) i^*(0) T}{i^*(a) i(t,0) T^*} - 1\right) da
\end{aligned}$$

$$=i^*(0) - i(t,0)\frac{i^*(0)}{i(t,0)} = 0.$$

Then we have

$$\begin{aligned}
H_2'(t) =& d_1 T^*\left(1 - \frac{T}{T^*}\right)\left(1 - \frac{T^*}{T}\right) + \int_0^\infty \frac{\beta_1 T^*}{d_4} p(a) i^*(a)\left[\phi\left(\frac{T}{T^*}\right) + \phi\left(\frac{V^* i(t,a)}{V i^*(a)}\right)\right.\\
&\left. + \phi\left(\frac{T V i^*(0)}{T^* V^* i(t,0)}\right)\right] da + \int_0^\infty \frac{\beta_2 T^*}{d_3}\alpha_2(a) i^*(a)\left[\phi\left(\frac{T}{T^*}\right) + \phi\left(\frac{M^* i(t,a)}{M i^*(a)}\right)\right.\\
&\left. + \phi\left(\frac{T M i^*(0)}{T^* M^* i(t,0)}\right)\right] da + \int_0^\infty \beta_3(a) T^* i^*(a)\left[\phi\left(\frac{T^*}{T}\right) + \phi\left(\frac{i(t,a) i^*(0) T}{i^*(a) i(t,0) T^*}\right)\right] da\\
&\le 0,
\end{aligned}$$

where $\phi(x) = 1 + \ln x - x$ satisfies $\phi(x) \le 0$ for $x > 0$ and $\phi(x) = 0$ if and only if $x = 1$. Thus, $H_2' \le 0$. Furthermore, it can be shown that the largest compact invariant set of $H_2' = 0$ is the singleton $\{E_*\}$, which implies E_* is globally asymptotically stable. □

4. Numerical simulations

In this part, we carry out some numerical simulations to illustrate the above obtained theoretical results. Most of the parameters are from [13], and the functions $p(a)$, $\alpha_2(a)$, $d_2(a)$ are given with the following forms:

$$p(a) = \begin{cases} 0, \ a < a_1, \\ p_{max}\left(1 - e^{-\gamma_1(a-a_1)}\right), \ a \ge a_1, \end{cases} \quad \alpha_2(a) = \begin{cases} 0, \ a < a_1, \\ \alpha_{20}\left(1 - e^{-\gamma_2(a-a_1)}\right), \ a \ge a_1, \end{cases}$$

$$d_2(a) = \begin{cases} \delta_0, \ a < a_2, \\ \delta_0 + \delta_m\left(1 - e^{-\gamma(a-a_1)}\right), \ a \ge a_2. \end{cases}$$

For simulation, we assume $\alpha_1(a) = 0.1$ and $\beta_3(a) = 0.0000075$, $\Lambda = 100$, $\beta_1 = 0.0000046$, $\beta_2 = 0.0000065$, $d_1 = 0.1$, $d_3 = 6.6$, $d_4 = 2.4$, $a_1 = 0.2$, $a_2 = 0.5$, $a_{max} = 15$, $\gamma_1 = 10$, $\gamma_2 = 5$, $\delta_0 = 0.05$, $\delta_m = 0.35$, $\alpha_{20} = 1000$, $\gamma = 1$, $p_{max} = 850$, computation yields $\mathcal{R}_0 = 0.4557 < 1$, which implies that the infection-free steady state is globally asymptotically stable as shown in Figure 1. When $\Lambda = 10$, $\beta_1 = 0.0000046$, $\beta_2 = 0.0000065$, $d_1 = 0.01$, $d_3 = 6.6$, $d_4 = 2.4$, $a_1 = 0.2$, $a_2 = 0.5$, $a_{max} = 15$, $\gamma_1 = 10$, $\gamma_2 = 5$, $\delta_0 = 0.05$, $\delta_m = 0.35$, $\alpha_{20} = 1000$, $\gamma = 1$, $p_{max} = 1880$, computation yields $\mathcal{R}_0 = 14.7759 > 1$, which implies that the infection steady state is globally asymptotically stable as shown in Figure 2. Moreover, it follows from Figure 3 that the existence of cytokine-enhanced effect can lead to a higher peak of viral load. Also, the formula of the basic reproduction number implies that it may be under-evaluated without considering cytokine-enhanced viral infection.

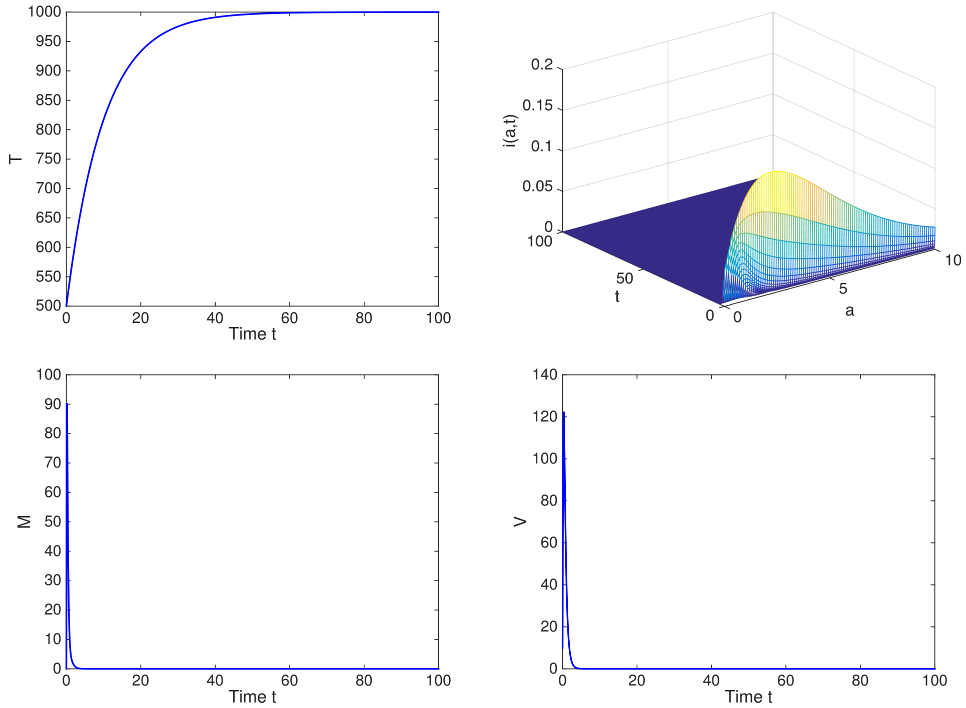

Figure 1. $\mathcal{R}_0 = 0.4347 < 1$, the infection-free steady state E_0 is globally asymptotically stable.

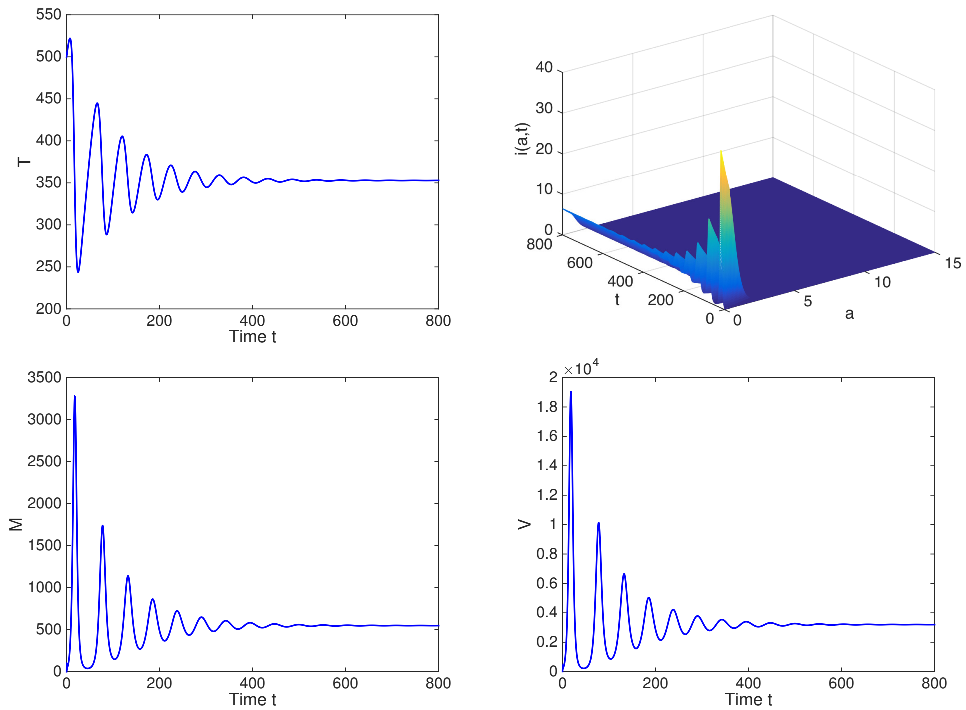

Figure 2. $\mathcal{R}_0 = 14.7494 > 1$, the infection steady state E_* is globally asymptotically stable.

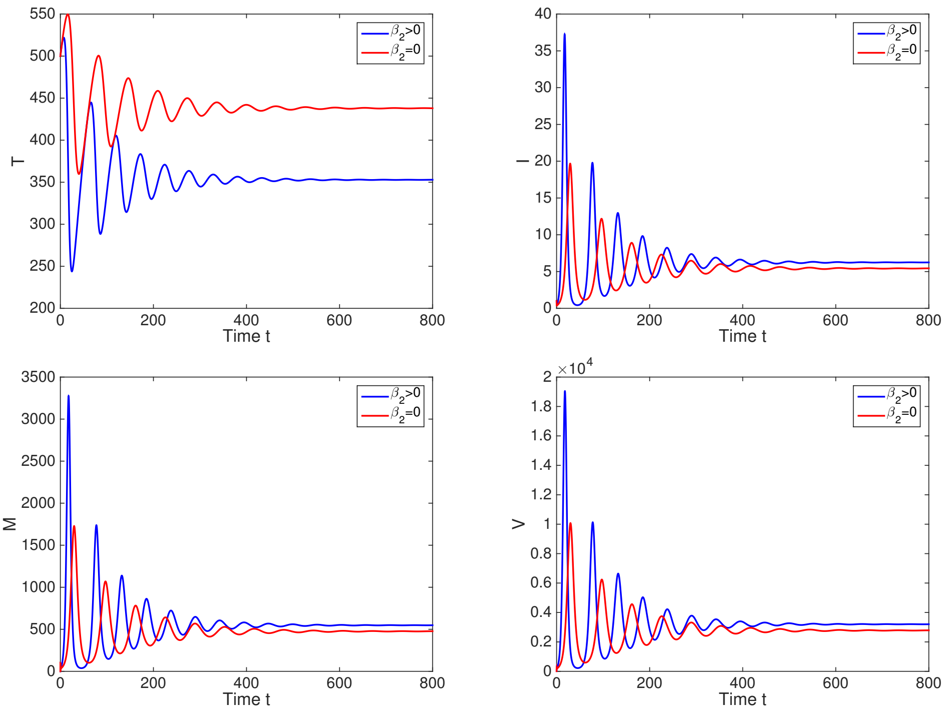

Figure 3. The dynamics of model (1.2) with ($\beta_2 > 0$) or without ($\beta_2 = 0$) cytokine-enhanced viral infection.

5. Summary and discussion

In this paper, an age-structured virus infection model in which the cytokine-enhanced viral infection have been taken into consideration. By constructing Lyapunov functionals, we show that the global properties of the model are completely determined by the basic reproduction numbers $\mathcal{R}_0$: if $\mathcal{R}_0 < 1$, then the infection-free equilibrium is globally asymptotically stable and the infection dies out; if $\mathcal{R}_0 > 1$, there exists a unique infection steady state which is globally asymptotically stable. Recall that

$$\mathcal{R}_0 = \frac{\beta_1 \Lambda}{d_1 d_4} \int_0^\infty p(a)\Gamma(a)da + \frac{\beta_2 \Lambda}{d_1 d_3} \int_0^\infty \alpha_2(a)\Gamma(a)da + \frac{\Lambda}{d_1} \int_0^\infty \beta_3(a)\Gamma(a)da.$$

The first term of $\mathcal{R}_0$ is induced by viral infection, the second term is induced by cytokine-enhanced viral infection, and the third term corresponds to the cell-to-cell infection mode. Thus, the basic reproduction number will be under-evaluated without considering cytokine-enhanced viral infection, and it may not be enough to eliminate the infection by decreasing the basic reproduction number just for virus-to-cell or cell-to-cell infection.

In most virus infection process, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking virus-infected cells. Thus, it would be very interesting to improve the current work by considering both CTL responses and antibody response in an age-structured viral infection model. Besides, the motion of the virus should also be taken into consideration. This will result in a reaction-diffusion model with age-structure. Whether the improved models can preserve these global results is an interesting problem and we leave this as a future work.

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Conflict of interest

The authors declare there is no conflict of interest.

References

1. A. S. Perelson, A. Neumann, M. Markowitz, J. M. Leonard, D. D. Ho, HIV-1 dynamics *in vivo*: Virion clearance rate, infected cell life-span, and viral generation time, *Science*, **271** (1996), 158–286. https://doi.org/10.1126/science.271.5255.1582
2. A. S. Perelson, P. W. Nelson, Mathematical analysis of HIV-1 dynamics *in vivo*, *SIAM Rev.*, **41** (1999), 3–44. https://doi.org/10.1137/S0036144598335107
3. J. Mittler, B. Sulzer, A. Neumann, A. S. Perelson, Influence of delayed virus production on viral dynamics in HIV-1 infected patients, *Math. Biosci.*, **152** (1998), 143–163. https://doi.org/10.1016/S0025-5564(98)10027-5
4. P. W. Nelson, J. Murray, A. S. Perelson, A model of HIV-1 pathogenesis that includes an intracellular delay, *Math. Biosci.*, **163** (2000), 201–215. https://doi.org/10.1016/S0025-5564(99)00055-3
5. P. de Leenheer, H. L. Smith, Virus dynamics: A global analysis, *SIAM J. Appl. Math.*, **63** (2003), 1313–1327. https://doi.org/10.1137/S0036139902406905
6. Y. Wang, Y. C. Zhou, Oscillatory viral dynamics in a delayed HIV pathogenesis model, *Math. Biosic.*, **219** (2009), 104–112. https://doi.org/10.1016/j.mbs.2009.03.003
7. M. Y. Li, H. Shu, Global dynamics of an in-host viral model with intracellular delay, *Bull. Math. Biol.*, **72** (2010), 1492–1505. https://doi.org/10.1007/s11538-010-9503-x
8. D. S. Callaway, A. S. Perelson, HIV-1 infection and low steady state viral loads, *Bull. Math. Biol.*, **64** (2002), 29–64. https://doi.org/10.1006/bulm.2001.0266
9. Y. Shang, Analytical solution for an in-host viral infection model with time-inhomogeneous rates, *Acta. Phys. Pol. B*, **46** (2015), 1567–1577. https://doi.org/10.5506/APhysPolB.46.1567
10. Y. Shang, Global stability of disease-free equilibria in a two-group SI model with feedback control, *Nonlinear Anal. Model.*, **20** (2015), 501–508. https://doi.org/10.15388/NA.2015.4.3
11. M. A. Gilchrist, D. Coombs, A. S. Perelson, Optimizing within-host viral fitness: Infected cell lifespan and virion production rate, *J. Theor. Biol.*, **229** (2004), 281–288. https://doi.org/10.1016/j.jtbi.2004.04.015
12. C. L. Althaus, A. S. de Vos, R. J. De Boer, Reassessing the human immunodeficiency virus type 1 life cycle through age-structured modeling: Life span of infected cells, viral generation time, and basic reproductive number, r_0, *J. Virol.*, **83** (2009), 7659–7667. https://doi.org/10.1128/JVI.01799-08

13. P. W. Nelson, M. A. Gilchrist, D. Coombs, J. M. Hyman, A. Perelson, An age-structured model of HIV infection that allows for variations in the production rate of viral particles and the death rate of productively infected cells, *Math. Biosci. Eng.*, **1** (2004), 267–288. https://doi.org/10.3934/mbe.2004.1.267

14. G. Huang, X. Liu, Y. Takeuchi, Lyapunov functions and global stability for age-structured HIV infection model, *SIAM J. Appl. Math.*, **72** (2012), 25–38. https://doi.org/10.1137/110826588

15. L. Rong, Z. Feng, A.S. Perelson, Mathematical analysis of age-structured HIV-1 dynamics with combination antiretroviral therapy, *SIAM J. Appl. Math.*, **67** (2007), 731–756. https://doi.org/10.1137/060663945

16. Y. Yang, S. Ruan, D. Xiao, Global stability of an age-structured virus dynamics model with Beddington-DeAngelis infection function, *Math. Biosci. Eng.*, **12** (2015), 859–877. https://doi.org/10.3934/mbe.2015.12.859

17. S. Wang, X. Song, Global properties for an age-structured within-host model with Crowley-Martin functional response, *Int. J. Biomath.*, **10** (2017), 1750030. https://doi.org/10.1142/S1793524517500309

18. J. Wang, R. Zhang, T. Kuniya, Global dynamics for a class of age-infection HIV models with nonlinear infection rate, *J. Math. Anal. Appl.*, **432** (2015), 289–313. https://doi.org/10.1016/j.jmaa.2015.06.040

19. X. Wang, Y. Lou, X. Song, Age-structured within-host HIV dynamics with multiple target cells, *Stud. Appl. Math.*, **138** (2017), 43–76. https://doi.org/10.1111/sapm.12135

20. J. Wang, R. Zhang, T. Kuniya, Mathematical analysis for an age-structured HIV infection model with saturation infection rate, *Electron. J. Differ. Equations*, **2015** (2015), 1–19.

21. L. Zou, S. Ruan, W. Zhang, An age-structured model for the transmission dynamics of hepatitis B, *SIAM J. Appl. Math.*, **70** (2010), 3121–3139.https://doi.org/10.1137/090777645

22. S. Liu, R. Zhang, On an age-structured hepatitis B virus infection model with HBV DNA-containing capsids, *Bull. Malays. Math. Sci. Soc.*, **44** (2021), 1345–1370. https://doi.org/10.1007/s40840-020-01014-6

23. X. Tian, R. Xu, J. Lin, Mathematical analysis of an age-structured HIV-1 infection model with CTL immune response, *Math. Biosci. Eng.*, **16** (2019), 7850–7882. https://doi.org/10.3934/mbe.2019395

24. X. Duan, S. Yuan, K. Wang, Dynamics of a diffusive age-structured HBV model with saturating incidence, *Math. Biosci. Eng.*, **13** (2016), 935–968. https://doi.org/10.3934/mbe.2016024

25. J. Yang, X. Wang, Dynamics and asymptotical profiles of an age-structured viral infection model with spatial diffusion, *Appl. Math. Comput.*, **360** (2019), 236–254. https://doi.org/10.1016/j.amc.2019.05.007

26. J. Wang, R. Zhang, Y. Gao, Global threshold dynamics of an infection age-space structured HIV infection model with neumann boundary condition, *J. Dyn. Differ. Equations*, **2021** (2021), 1–33. https://doi.org/10.1007/s10884-021-10086-2

27. N. Martin, Q. Sattentau, Cell-to-cell HIV-1 spread and its implications for immune evasion, *Curr. Opin. HIV AIDS.*, **4** (2009), 143–149. https://doi.org/10.1097/COH.0b013e328322f94a

28. B. K. Titanji, M. Aasa-Chapman, D. Pillay, C. Jolly, Protease inhibitors effectively block cell-to-cell spread of HIV-1 between T cells, *Retrovirology*, **10** (2013), 161. https://doi.org/10.1186/1742-4690-10-161

29. H. Sato, J. Orenstein, D. S. Dimitrov, M. Martin, Cell-to-cell spread of HIV-1 occurs with minutes and may not involve the participation of virus particles, *Virology*, **186** (1992), 712–724. https://doi.org/10.1016/0042-6822(92)90038-Q

30. D. S. Dimitrov, R. L. Willey, H. Sato, L. J. Chang, R. Blumenthal, M. A. Martin, Quantitation of human immunodeficiency virus type 1 infection kinetics, *J. Virol.*, **67** (1993), 2182–2190. https://doi.org/10.1128/jvi.67.4.2182-2190.1993

31. M. Sourisseau, N. Sol-Foulon, F. Porrot, F. Blanchet, O. Schwartz, Inefficient human immunodeficiency virus replication in mobile lymphocytes, *J. Virol.*, **81** (2007), 1000–1012. https://doi.org/10.1128/JVI.01629-06

32. X. L. Lai, X. F. Zou, Modeling HIV-1 virus dynamics with both virus-to-cell infection and cell-to-cell transmission, *SIAM J. Appl. Math.*, **74** (2014), 898–917. https://doi.org/10.1137/130930145

33. X. L. Lai, X. F. Zou, Modeling cell-to-cell spread of HIV-1 with logistic target cell growth, *J. Math. Anal. Appl.*, **426** (2015), 563–584. https://doi.org/10.1016/j.jmaa.2014.10.086

34. Y. Yang, L. Zou, S. Ruan, Global dynamics of a delayed within-host viral infection model with both virus-to-cell and cell-to-cell transmissions, *Math. Biosci.*, **270** (2015), 183–191. https://doi.org/10.1016/j.mbs.2015.05.001

35. J. Wang, M. Guo, X. Liu, Z. Zhao, Threshold dynamics of HIV-1 virus model with cell-to-cell transmission, cell-mediated immune responses and distributed delay, *Appl. Math. Comput.*, **291** (2016), 149–161. https://doi.org/10.1016/j.amc.2016.06.032

36. J. Wang, J. Yang, T. Kuniya, Dynamics of a PDE viral infection model incorporating cell-to-cell tranmission, *J. Math. Anal. Appl.*, **444** (2016), 1542–1564. https://doi.org/10.1016/j.jmaa.2016.07.027

37. F. Li, J. Wang, Analysis of an HIV infection model with logistic target-cell growth and cell-to-cell transmission, *Chaos Solitons Fractals*, **81** (2015), 136–145. https://doi.org/10.1016/j.chaos.2015.09.003

38. R. Zhang, S. Liu, Global dynamics of an age-structured within-host viral infection model with cell-to-cell transmission and general humoral immunity response, *Math. Biosci. Eng.*, **17** 2020, 1450–1478. https://doi.org/10.3934/mbe.2020075

39. W. Wang, X. Wang, K. Guo, W. Ma, Global analysis of a diffusive viral model with cell-to-cell infection and incubation period, *Math. Method Appl. Sci.*, **43** (2020), 5963–5978. https://doi.org/10.1002/mma.6339

40. X. Ren, Y. Tian, L. Liu, X. Liu, A reaction-diffusion within-host HIV model with cell-to-cell transmission, *J. Math. Biol.*, **76** (2018), 1831–1872. https://doi.org/10.1007/s00285-017-1202-x

41. Y. Xu, Z. Zhu, Y. Yang, F. Meng, Vectored immunoprophylaxis and cell-to-cell transmission in HIV dynamics, *Int. J. Bifurcation Chaos*, **30** (2020), 1–19. https://doi.org/10.1142/S0218127420501850
42. T. Guo, Z. Qiu, L. Rong, Modeling the role of macrophages in HIV persistence during antiretroviral therapy, *J. Math. Biol.*, **81** (2020), 369–402. https://doi.org/10.1007/s00285-020-01513-x
43. Y. Gao, J. Wang, Threshold dynamics of a delayed nonlocal reaction-diffusion HIV infection model with both cell-free and cell-to-cell transmissions, *J. Math. Anal. Appl.*, **488** (2020), 124047. https://doi.org/10.1016/j.jmaa.2020.124047
44. C. Y. Cheng, Y. Dong, Y. Takeuchi, An age-structured virus model with two routes of infection in heterogeneous environments, *Nonlinear Anal. RWA.*, **39** (2018), 464–491. https://doi.org/10.1016/j.nonrwa.2017.07.013
45. J. Xu, Y. Geng, Y. Zhou, Global dynamics for an age-structured HIV virus infection model with cellular infection and antiretroviral therapy, *Appl. Math. Comput.*, **305** (2017), 62–83. https://doi.org/10.1016/j.amc.2017.01.064
46. G. Doitsh, N. Galloway, X. Geng, Z. Yang, K. M. Monroe, O. Zepeda, et al., Pyroptosis drives CD4 T-cell depletion in HIV-1 infection, *Nature*, **505** (2014), 509–514. https://doi.org/10.1038/nature12940
47. G. Doitsh, M. Cavrois, K.G. Lassen, O. Zepeda, Z. Yang, M. L. Santiago, et al., Abortive HIV infection mediates CD4 T cell depletion and inflammation in human lymphoid tissue, *Cell*, **143** (2010), 789–801. https://doi.org/10.1016/j.cell.2010.11.001
48. A. L. Cox, R. F. Siliciano, HIV: Not-so-innocent bystanders, *Nature*, **505** (2014), 492–493. https://doi.org/10.1038/505492a
49. S. Wang, P. Hottz, M. Schechter, L. Rong, Modeling the slow CD4+ T cell decline in HIV-infected individuals, *PLoS Comput. Biol.*, **11** (2015), 1–25. https://doi.org/10.1371/journal.pcbi.1004665
50. W. Wang, T. Zhang, Caspase-1-mediated pyroptosis of the predominance for driving CD4+ T cells death: a nonlocal spatial mathematical model, *Bull. Math. Biol.*, **80** (2018), 540–582. https://doi.org/10.1007/s11538-017-0389-8
51. W. Wang, Z. Feng, Global dynamics of a diffusive viral infection model with spatial heterogeneity, *Nonlinear Anal. RWA.*, **2022** 2022, 103763. https://doi.org/10.1016/j.nonrwa.2022.103763
52. Y. Jiang, T. Zhang, Global stability of a cytokine-enhanced viral infection model with nonlinear incidence rate and time delays, *Appl. Math. Letters.*, **132** (2022), 108110. https://doi.org/10.1016/j.aml.2022.108110
53. P. Magal, S. Ruan, *Theory And Applications of Abstract Semilinear Cauchy Problems*, Springer International Publishing, 2018.
54. H. L. Smith, H. R. Thieme, *Dynamical Systems and Population Persistence*, American Mathematical Society, Providence, 2011.
55. C. C. McCluskey, Global stability for an SEI epidemiological model with continuous age-structure in the exposed and infectious classes, *Math. Biosci. Eng.*, **9** (2012), 819–841. https://doi.org/10.3934/mbe.2012.9.819

56. Y. Shang, The limit behavior of a stochastic logistic model with individual time-dependent rates, *J. Math.*, **2013** (2013), 1–7. https://doi.org/10.1155/2013/502635

57. J. P. LaSalle, *T*he Stability of Dynamical Systems, SIAM, 1976. ttps://doi.org/10.21236/ADA031020