MATHEMATICAL ANALYSIS FOR AN AGE-STRUCTURED HIV INFECTION MODEL WITH SATURATION INFECTION RATE

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ABSTRACT. In this article, we study a continuous age-structured HIV infection model. For the case of the saturation infection rate, the basic reproduction number $\Re_0$ is shown to be a sharp threshold value for the global dynamics; that is, the infection-free equilibrium is globally stable if $\Re_0 < 1$, while a unique infection equilibrium is so if $\Re_0 > 1$. For the proof, we use Lyapunov functional techniques based on the relative compactness of the orbit and uniform persistence of the system.

1. INTRODUCTION

During the past decades, mathematical analysis of within-host dynamics of HIV has been extensively done by many authors (see, for example, [4, 5, 7, 9, 14, 15, 16, 22] and the references therein). These studies have enriched our knowledge of in-host models. The classical and basic viral infection models proposed by Nowak and May [14], Perelson and Nelson [16] have widely been developed in several directions including, in particular, immune response and oscillations (see [6, 7]). However, most of the models might neglect an important character that the mortality rate and viral production rate of infected cells are functions of the infection age of cells [4], where age is defined as the time since the infection.

The evidence that the number of virus production increases exponentially with the age of the infected cell [17] and the death rate of infected cells varies all time [2] has been found from the recent studies. Investigating the impact of the age dependent mortality rate and viral production rate are a neglected activity of significant importance. The age structure will allow us to have a good description of the viral particles and the mortality of infected cells [8]. Age structure allows more realistic representations of the biology of HIV-1 infection [15]. Therefore, it is necessary to study in-host models with age structure.

One of the basic age-structured HIV models presented by Nelson et al [15] was governed by the first order partial differential equations system. By evaluating eigenvalues and its related characteristic equation, local stability of the equilibria has been analyzed. The global asymptotic stability of the equilibria was established by Huang et al [4] by using suitable Lyapunov functions and Lasalle's invariance

principle. Based on the model studied in [15], Rong et al [18] considered two models with age-of-infection and combination therapies involving reverse transcriptase, protease, and entry/fusion inhibitors and study the impact of drugs on viral dynamics.

The model we shall consider in this study is an extension of the model proposed by Nelson et al [15] and Huang et al [4]. It incorporates with the saturation infection rate. Based on the existing age-structured HIV infection models formulated in [4, 15, 18], and motivated by the works in [1, 3, 9, 10, 11, 12, 22], the main concern of this research is to prove the global stability of the following age-structured model with saturated infection rate:

$$
\begin{aligned}
\frac{dT(t)}{dt} &= s - dT(t) - kT(t)\frac{V(t)}{1+\alpha V(t)}, \\
\frac{\partial i(a,t)}{\partial a} + \frac{\partial i(a,t)}{\partial t} &= -\delta(a)i(a,t), \\
\frac{dV(t)}{dt} &= \int_0^\infty p(a)i(a,t)da - cV(t).
\end{aligned}
\tag{1.1}
$$

The boundary and initial conditions are

$$
i(0,t) = kT(t)\frac{V(t)}{1+\alpha V(t)},
$$
$$
T(0) = T_s, \quad i(a,0) = i_s(a), \quad V(0) = V_s,
\tag{1.2}
$$

where $T(t)$ and $V(t)$ denote the densities of uninfected target T cells and infectious free virion at time t. $i(a,t)$ denotes the density of infected T cells of infection age a at time t and $i_s(a)$ is a given non-negative function. The meanings of the other parameters in the system (1.1) are listed in Table 1.

Parameter	Meaning
a	Age of infection, i.e., the time since an HIV virion penetrated cell;
s	Recruitment rate of healthy T cells;
d	Per capita death rate of uninfected cells;
c	Clearance rate of virions;
α	Saturation constant;
k	Rate at which an uninfected cell becomes infected by an infectious virus;
$\delta(a)$	Age-dependent per capita death rate of infected cells;
$p(a)$	Viral production rate of an infected cell with age a.

TABLE 1. The definition of the different parameters in Section 1.

For the models describing age-structured viral infection, local stability can be proved by linearizing the systems at their equilibrium states and verifying the eigenvalues of the corresponding characteristic equations. While, for models described by PDEs, the global stability analysis of equilibrium is often very challenging if not impossible. The global stability approach used in this paper is related to ones used in [4, 12, 11].

In this paper, we focus not only on proving the global stability properties for the case of continuous age by constructing suitable Lyapunov functions, but also on giving rigorous mathematical analysis on technical materials and necessary arguments to the proofs including the relative compactness of the orbit and uniform persistence of system (1.1).

The result in the present paper can be regarded as a supplement and generalization of the works in [15] and [4]. The basic reproduction number shall be defined and proved to be a sharp threshold determining whether or not infection dies out. More precisely, if $\Re_0 < 1$ the infection-free equilibrium is globally asymptotically stable; if $\Re_0 > 1$, a unique infection equilibrium exists and is globally asymptotically stable.

The organization of this article is as follows. In Section 2, we present some preliminary results on system (1.1). In Section 3, we prove that the global stability of the infection-free equilibrium for $\Re_0 < 1$ by constructing a suitable Lyapunov function. In Section 4, for the proof of global stability of the infection equilibrium, we present some preliminary results on the uniform persistence. In Section 5, we give the proof of the global stability of infection equilibrium for $\Re_0 > 1$.

2. Preliminaries

Let us define a functional space $\mathcal{X} := \mathbb{R} \times L^1(0,\infty) \times \mathbb{R}$ equipped with norm

$$\|(x,\varphi,y)\|_{\mathcal{X}} := |x| + \int_0^\infty |\varphi(a)|da + |y|, \quad x,y \in \mathbb{R},\ \varphi \in L^1(0,\infty). \qquad (2.1)$$

The initial condition (1.2) for system (1.1) can be represented as

$$X_0 := (T(0), i(\cdot,0), V(0)) = (T_s, i_s(\cdot), V_s) \in \mathcal{X}_+, \qquad (2.2)$$

where $\mathcal{X}_+ := \mathbb{R}_+ \times L^1_+(0,\infty) \times \mathbb{R}_+$ denotes the positive cone of $\mathcal{X}$.

It is necessary to make the following assumption on the parameters of system (1.1), which makes the model to be biologically relevant.

Assumption 2.1. We assume that:
  (i) $s > 0$, $d > 0$, $k > 0$, $\alpha > 0$ and $c > 0$;
  (ii) $\delta, p \in L^\infty_+(0,\infty)$ and

$$\delta^+ := \operatorname{ess\,sup}_{a\in[0,\infty)} \delta(a) < +\infty, \quad p^+ := \operatorname{ess\,sup}_{a\in[0,\infty)} p(a) < +\infty;$$

  (iii) There exists a positive constant $\delta_0 \in (0, d]$ such that $\delta(a) \ge \delta_0$ for all $a \ge 0$;
  (iv) There exists a maximum age $a_\dagger > 0$ for the viral production such that $p(a) > 0$ for $a \in (0, a_\dagger)$.

Integrating the second equation in (1.1) along the characteristic line $t - a = \text{const.}$, we have

$$i(a,t) = \begin{cases} kT(t-a)\dfrac{V(t-a)}{1+\alpha V(t-a)} e^{-\int_0^a \delta(\epsilon)d\epsilon}, & t > a \ge 0; \\ i_s(a-t) e^{-\int_0^t \delta(a-t+\epsilon)d\epsilon}, & a \ge t \ge 0. \end{cases} \qquad (2.3)$$

As mentioned in Section 1, we shall focus on the global stability of (1.1). To this end, we first define the continuous semi-flow associated with the system. Using standard methods, we can verify the existence and uniqueness of solutions to the system (1.1). Moreover, we can show that all solutions with nonnegative initial

conditions $X_0 \in \mathcal{X}_+$ will remain nonnegative for all $t > 0$. Thus, we can obtain a continuous semi-flow $\Phi : \mathbb{R}_+ \times \mathcal{X}_+ \to \mathcal{X}_+$ defined by system (1.1) such that

$$\Phi(t, X_0) := (T(t), i(\cdot, t), V(t)), \quad t \geq 0, \ X_0 \in \mathcal{X}_+. \tag{2.4}$$

Thus

$$\|\Phi(t, X_0)\|_{\mathcal{X}} = \|\Phi(T(t), i(\cdot, t), V(t))\|_{\mathcal{X}} = T(t) + \int_0^\infty i(a, t) da + V(t). \tag{2.5}$$

Define the state space for system (1.1) by

$$\Omega := \left\{ (x, \varphi, y) \in \mathcal{X}_+ : \ \|(x, \varphi, y)\|_{\mathcal{X}} \leq (1 + \frac{p^+}{c})\frac{s}{\delta_0} \right\}. \tag{2.6}$$

Now, we are in a position to show the positive invariance of Ω.

Proposition 2.2. *Let Φ and Ω be defined by (2.4) and (2.6), respectively. Ω is positively invariant for Φ; that is,*

$$\Phi(t, X_0) \subset \Omega, \quad \forall t \geq 0, \ X_0 \in \Omega.$$

Proof. It can be easily checked from the second equation of (1.1) that

$$\frac{d}{dt} \int_0^\infty i(a, t) \, da = kT(t)\frac{V(t)}{1 + \alpha V(t)} - \int_0^\infty \delta(a)i(a, t) \, da.$$

Thus, from the first equation of (1.1) and (iii) of Assumption 2.1, we have

$$\frac{d}{dt}\Big(T(t) + \int_0^\infty i(a, t) \, da\Big) = s - dT(t) - \int_0^\infty \delta(a)i(a, t) \, da$$

$$\leq s - \delta_0\Big(T(t) + \int_0^\infty i(a, t) \, da\Big).$$

Using the variation of constants formula, we obtain

$$T(t) + \int_0^\infty i(a, t) \, da \leq \frac{s}{\delta_0} - e^{-\delta_0 t}\Big\{\frac{s}{\delta_0} - \Big(T_s + \int_0^\infty i_s(a) \, da\Big)\Big\}.$$

It is easy to see that for all $t \geq 0$,

$$T(t) + \int_0^\infty i(a, t) \, da \leq \frac{s}{\delta_0} \tag{2.7}$$

holds for any $X_0 \in \Omega$. Moreover, the third equation of (1.1) and (ii) of Assumption 2.1 lead to

$$\frac{dV(t)}{dt} \leq p^+ \int_0^\infty i(a, t) \, da - cV(t).$$

From (2.7), it follows that

$$\frac{dV(t)}{dt} \leq p^+ \frac{s}{\delta_0} - cV(t).$$

Hence, using the variation of constants formula again, we obtain

$$V(t) \leq \frac{p^+}{c}\frac{s}{\delta_0}, \quad \forall t \geq 0, \tag{2.8}$$

for all $X_0 \in \Omega$. Consequently, from (2.7) and (2.8), we have

$$T(t) + \int_0^\infty i(a, t) \, da + V(t) \leq (1 + \frac{p^+}{c})\frac{s}{\delta_0}, \quad \forall t \geq 0,$$

which implies $\Phi(t, X_0) \subset \Omega$ for all $t \geq 0$. $\square$

2.1. **Equilibria and basic reproductive number.** Let N denote the burst size; that is, the total number of viral particles produced by an infected cell in its lifespan. Then,

$$N \equiv \int_0^\infty p(a)\sigma(a)da \ \Big(= \int_0^{a_\dagger} p(a)\sigma(a)\,da\Big), \tag{2.9}$$

where

$$\sigma(a) = e^{-\int_0^a \delta(\epsilon)d\epsilon} \tag{2.10}$$

denotes the fraction at which an infected cell survives up to age a.

System (1.1) has at most two equilibria. There always exists an infection-free equilibrium $E_1^0 = (T_0, i_0(a), V_0) \in \Omega$, where $T_0 = s/d$, $i_0(a) = 0$, $V_0 = 0$. An infection equilibrium $E_1^* = (T^*, i^*(a), V^*) \in \Omega$ possibly exists satisfying the following equations:

$$\begin{aligned}
s - dT^* - kT^* \frac{V^*}{1+\alpha V^*} &= 0, \\
\frac{di^*(a)}{da} &= -\delta(a)i^*(a), \\
\int_0^\infty p(a)i^*(a)da &= cV^*, \\
i^*(0) &= kT^* \frac{V^*}{1+\alpha V^*}.
\end{aligned} \tag{2.11}$$

Integrating the second equation of (2.11) from 0 to a yields

$$i^*(a) = i^*(0)e^{-\int_0^a \delta(s)ds}. \tag{2.12}$$

Thus, from the fourth equation of (2.11), we have

$$i^*(a) = \sigma(a)kT^* \frac{V^*}{1+\alpha V^*}. \tag{2.13}$$

Substituting (2.13) in the third equation of (2.11) and using the equality in (2.9) gives

$$\int_0^\infty p(a)\sigma(a)kT^* \frac{V^*}{1+\alpha V^*}da = NkT^* \frac{V^*}{1+\alpha V^*} = cV^*, \tag{2.14}$$

and thus $T^* = \frac{c(1+\alpha V^*)}{Nk}$. The basic reproduction number of system (1.1) is

$$\Re_0 = \frac{Nks}{dc}, \tag{2.15}$$

which is defined by the number of newly infected cells produced by one infected cell during its lifespan. As will be shown in the next sections, the qualitative and quantitative behaviors of the model (1.1) is completely determined by $\Re_0$.

Solving the first equation of (2.11) with respect to V^*, we can easily obtain

$$V^* = \frac{Nks - dc}{dc\alpha + kc} = \frac{dc}{dc\alpha + kc}\Big(\frac{Nks}{dc} - 1\Big) = \frac{dc}{dc\alpha + kc}(\Re_0 - 1),$$

Thus, we have infection equilibrium $E_1^* = (T^*, i^*(a), V^*)$ if and only if $\Re_0 > 1$.

2.2. **Relative compactness of the orbit.** As we are now concerned with the infinite dimensional Banach space $\mathcal{X}$ including $L^1(0, \infty)$, the issue one fist faces is to show the relative compactness of the orbit $\{\Phi(t, X_0) : t \geq 0\}$ in $\mathcal{X}$ in order to make use of the invariance principle (see e.g., [20, Theorem 4.2 of Chapter IV]). To this end, we first decompose $\Phi : \mathbb{R}_+ \times \mathcal{X}_+ \to \mathcal{X}_+$ into the following two operators $\Theta, \Psi : \mathbb{R}_+ \times \mathcal{X}_+ \to \mathcal{X}_+$:

$$\Theta(t, X_0) := (0, \tilde{\varphi}_i(\cdot, t), 0), \tag{2.16}$$

$$\Psi(t, X_0) := (T(t), \tilde{i}(\cdot, t), V(t)), \tag{2.17}$$

where

$$\tilde{\varphi}_i(a, t) := \begin{cases} 0, & t > a \geq 0, \\ i(a, t), & a \geq t \geq 0, \end{cases} \quad \text{and} \quad \tilde{i}(a, t) := \begin{cases} i(a, t), & t > a \geq 0, \\ 0, & a \geq t \geq 0. \end{cases} \tag{2.18}$$

It is easy to see that

$$\Phi(t, X_0) = \Theta(t, X_0) + \Psi(t, X_0), \quad \forall t \geq 0,$$

and from [21, Proposition 3.13] and Proposition 2.2, we arrive at the following lemma.

Lemma 2.3. *Let Φ, Ω, Θ and Ψ be defined by (2.4), (2.6), (2.16) and (2.17), respectively. If the following two conditions hold, then $\{\Phi(t, X_0) : t \geq 0\}$ for $X_0 \in \Omega$ has compact closure in $\mathcal{X}$.*

   (i) *There exists a function $\Delta : \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+$ such that for any $r > 0$, $\lim_{t \to \infty} \Delta(t, r) = 0$, and if $X_0 \in \Omega$ with $\|X_0\|_\mathcal{X} \leq r$, then $\|\Theta(t, X_0)\|_\mathcal{X} \leq \Delta(t, r)$ for $t \geq 0$;*
   (ii) *For $t \geq 0$, $\Psi(t, \cdot)$ maps any bounded sets of Ω into sets with compact closure in $\mathcal{X}$.*

To show that conditions (i) and (ii) in Lemma 2.3 hold, we first prove the following lemma.

Lemma 2.4. *Let Ω and Θ be defined by (2.6) and (2.16), respectively. For $r > 0$, let $\Delta(t, r) := e^{-\delta_0 t} r$. Then, $\lim_{t \to \infty} \Delta(t, r) = 0$ and for $t \geq 0$, $\|\Theta(t, X_0)\|_\mathcal{X} \leq \Delta(t, r)$ provided $X_0 \in \Omega$ with $\|X_0\|_\mathcal{X} \leq r$.*

Proof. $\lim_{t \to \infty} \Delta(t, r) = 0$ is obvious. From (2.3), we have

$$\tilde{\varphi}_i(a, t) = \begin{cases} 0, & t > a \geq 0; \\ i_s(a - t) e^{- \int_0^t \delta(a - t + \epsilon) d\epsilon}, & a \geq t \geq 0. \end{cases}$$

Then, for $X_0 \in \Omega$ satisfying $\|X_0\|_\mathcal{X} \leq r$, we have

$$\|\Theta(t, X_0)\|_\mathcal{X} = |0| + \int_0^\infty |\tilde{\varphi}_i(a, t)| da + |0|$$

$$= \int_t^\infty |i_s(a - t) e^{- \int_0^t \delta(a - t + \epsilon) d\epsilon}| da$$

$$\leq e^{-\delta_0 t} \int_0^\infty |i_s(a)| da$$

$$\leq e^{-\delta_0 t} \|X_0\|_\mathcal{X}$$

$$\leq e^{-\delta_0 t} r = \Delta(t, r), \quad \forall t \geq 0,$$

which completes the proof. $\qquad \square$

Lemma 2.5. *Let Ω and Ψ be defined by (2.6) and (2.17), respectively. Then, for $t \geq 0$, $\Psi(t, \cdot)$ maps any bounded sets of Ω into sets with compact closure in $\mathcal{X}$.*

Proof. It follows from Proposition 2.2 that $T(t)$ and $V(t)$ remain in the compact set $[0, (1 + p^+/c)s/\delta_0]$. Thus, we are in a position to show that $\tilde{i}(a, t)$ remains in a precompact subset of $L^1_+(0, \infty)$, which is independent of $X_0 \in \Omega$. To this end, it suffices to verify the following conditions (see e.g., [19, Theorem B.2]).

   (i) The supremum of $\int_0^\infty \tilde{i}(a, t) \, da$ with respect to $X_0 \in \Omega$ is finite;
   (ii) $\lim_{h \to \infty} \int_h^\infty \tilde{i}(a, t) da = 0$ uniformly with respect to $X_0 \in \Omega$;
   (iii) $\lim_{h \to 0+} \int_0^\infty |\tilde{i}(a + h, t) - \tilde{i}(a, t)| da = 0$ uniformly with respect to $X_0 \in \Omega$;
   (iv) $\lim_{h \to 0+} \int_0^h \tilde{i}(a, t) \, da = 0$ uniformly with respect to $X_0 \in \Omega$.

In fact, from (2.3) and (2.18), it follows that

$$\tilde{i}(a, t) = \begin{cases} kT(t - a)\frac{V(t-a)}{1+\alpha V(t-a)}e^{-\int_0^a \delta(\epsilon)d\epsilon}, & t > a \geq 0; \\ 0, & a \geq t \geq 0, \end{cases} \tag{2.19}$$

and hence, from Proposition 2.2 and the fact that $f(x) = x/(1 + \alpha x)$ is monotone increasing with respect to x, we obtain the inequality

$$0 \leq \tilde{i}(a, t) \leq k(1 + \frac{p^+}{c})\frac{s}{\delta_0}\frac{1}{\alpha}e^{-\int_0^a \delta(\epsilon)d\epsilon}. \tag{2.20}$$

Thus, the aforementioned conditions (i), (ii) and (iv) follow immediately from (2.20).

We claim that (iii) holds. In fact, for sufficiently small $h \in (0, t)$, we have

$$\int_0^\infty |\tilde{i}(a + h, t) - \tilde{i}(a, t)| da$$

$$= \int_0^{t-h} \left| kT(t - a - h)\frac{V(t - a - h)}{1 + \alpha V(t - a - h)}\sigma(a + h) \right.$$

$$\left. - kT(t - a)\frac{V(t - a)}{1 + \alpha V(t - a)}\sigma(a) \right| da$$

$$+ \int_{t-h}^t |0 - kT(t - a)\frac{V(t - a)}{1 + \alpha V(t - a)}\sigma(a)| da$$

$$\leq \int_0^{t-h} kT(t - a - h)\frac{V(t - a - h)}{1 + \alpha V(t - a - h)}|\sigma(a + h) - \sigma(a)| da$$

$$+ \int_0^{t-h} \left| kT(t - a - h)\frac{V(t - a - h)}{1 + \alpha V(t - a - h)} - kT(t - a)\frac{V(t - a)}{1 + \alpha V(t - a)} \right|\sigma(a) da$$

$$+ k(1 + \frac{p^+}{c})\frac{s}{\delta_0}\frac{1}{\alpha}h$$

$$\leq k(1 + \frac{p^+}{c})\frac{s}{\delta_0}\frac{1}{\alpha}\int_0^{t-h} |\sigma(a + h) - \sigma(a)| da$$

$$+ k\int_0^{t-h} \left| T(t - a - h)\frac{V(t - a - h)}{1 + \alpha V(t - a - h)} - T(t - a)\frac{V(t - a)}{1 + \alpha V(t - a)} \right|\sigma(a) da$$

$$+ k(1 + \frac{p^+}{c})\frac{s}{\delta_0}\frac{1}{\alpha}h. \tag{2.21}$$

Noticing that $\sigma(a) = e^{-\int_0^a \delta(\epsilon)d\epsilon}$ is monotone decreasing with respect to a, we have

$$\int_0^{t-h} |\sigma(a+h) - \sigma(a)|da = \int_0^{t-h} \{\sigma(a) - \sigma(a+h)\}da$$
$$= \int_0^h \sigma(a)\,da - \int_{t-h}^t \sigma(a)\,da \leq h. \tag{2.22}$$

Moreover, we have

$$\left|T(t-a-h)\frac{V(t-a-h)}{1+\alpha V(t-a-h)} - T(t-a)\frac{V(t-a)}{1+\alpha V(t-a)}\right|$$
$$\leq \left|T(t-a-h)V(t-a-h)\{1+\alpha V(t-a)\}\right.$$
$$\left. - T(t-a)V(t-a)\{1+\alpha V(t-a-h)\}\right| \tag{2.23}$$
$$\leq \left|T(t-a-h)V(t-a-h) - T(t-a)V(t-a)\right|$$
$$+ |T(t-a-h) - T(t-a)|\alpha V(t-a-h)V(t-a).$$

Now, the Lipschitz continuity of $T(\cdot)$ and $V(\cdot)$ on $\mathbb{R}_+$ is easily verified from (1.1) and the boundedness of the solution (Proposition 2.2) and thus, the product $T(\cdot)V(\cdot)$ of these two Lipschitz functions is also Lipschitz (see e.g., [13, Proposition 6]). Therefore, there exists a positive constant $M_{TV} > 0$ such that (2.23) becomes

$$\left|T(t-a-h)\frac{V(t-a-h)}{1+\alpha V(t-a-h)} - T(t-a)\frac{V(t-a)}{1+\alpha V(t-a)}\right| \leq M_{TV}h. \tag{2.24}$$

From (2.21), (2.22) and (2.24), we obtain

$$\int_0^\infty |\tilde{i}(a+h,t) - \tilde{i}(a,t)|da$$
$$\leq k(1+\frac{p^+}{c})\frac{s}{\delta_0}\frac{1}{\alpha}h + kM_{TV}h\int_0^{t-h}\sigma(a)\,da + k(1+\frac{p^+}{c})\frac{s}{\delta_0}\frac{1}{\alpha}h$$
$$\leq 2k(1+\frac{p^+}{c})\frac{s}{\delta_0}\frac{1}{\alpha}h + kM_{TV}h\int_0^{t-h}e^{-\delta_0 a}da \tag{2.25}$$
$$\leq k\left\{2(1+\frac{p^+}{c})\frac{s}{\delta_0}\frac{1}{\alpha} + \frac{M_{TV}}{\delta_0}\right\}h.$$

Since this upper bound is independent of $X_0 \in \Omega$ and converges to 0 as $h \to 0+$, the condition (iii) holds. Consequently, $\tilde{i}(a,t)$ remains in a precompact subset C^i of $L_+^1(0,\infty)$, and thus

$$\Psi(t,C) \subseteq [0, (1+\frac{p^+}{c})\frac{s}{\delta_0}] \times C^i \times [0, (1+\frac{p^+}{c})\frac{s}{\delta_0}]$$

holds for any bounded subset $C \subset \Omega$ of Ω. This completes the proof. $\square$

In summary, from Lemmas 2.3-2.5, we have proved the following result on the relative compactness of the orbit $\{\Phi(t,X_0): t \geq 0\}$.

Proposition 2.6. *Let Φ and Ω be defined by (2.4) and (2.6), respectively. For $X_0 \in \Omega$, $\{\Phi(t,X_0): t \geq 0\}$ has compact closure in $\mathcal{X}$.*

3. Global stability of the infection-free equilibrium

In this section, we study the global stability of the infection-free equilibrium E_1^0 of (1.1) by constructing a suitable Lyapunov function. Our principal result in this section can be stated as follows.

Theorem 3.1. *Let $\Re_0$ be defined by (2.15). The infection-free equilibrium E_1^0 of (1.1) is globally asymptotically stable if $\Re_0 \le 1$.*

Proof. Define

$$\alpha(a) = \int_a^\infty p(\epsilon) e^{-\int_a^\epsilon \delta(s)ds} d\epsilon \quad \Big(= \int_a^{a_\dagger} p(\epsilon) e^{-\int_a^\epsilon \delta(s)ds} d\epsilon \Big). \tag{3.1}$$

Note that from (iv) of Assumption 2.1 and (2.9) it follows that $\alpha(a) > 0$ for $0 \le a < a_\dagger$ and $\alpha(0) = N$. It is easy to see that $\alpha(a)$ is bounded and its derivative is given by

$$\alpha'(a) = \delta(a)\alpha(a) - p(a). \tag{3.2}$$

We define a Lyapunov function

$$U_1(t) = T_0 g\Big(\frac{T(t)}{T_0}\Big) + \frac{1}{N} \int_0^{a_\dagger} \alpha(a) i(a,t) da + \frac{1}{N} V(t), \tag{3.3}$$

where

$$g(z) = z - 1 - \ln z, \quad z \in \mathbb{R}_+, \tag{3.4}$$

which has the global minimum at $z = 1$ and $g(1) = 0$. Thus, $U_1(t)$ reaches its global minimum at E_1^0, and therefore it is a Lyapunov function, which is nonnegative.

Differenting $U_1(t)$ along the solutions of (1.1) yields

$$\begin{aligned}
\frac{dU_1(t)}{dt} &= \Big(1 - \frac{T_0}{T(t)}\Big)\Big(dT_0 - dT(t) - kT(t)\frac{V(t)}{1+\alpha V(t)}\Big) \\
&\quad - \frac{1}{N} \int_0^{a_\dagger} \alpha(a)\Big(\frac{\partial i(a,t)}{\partial a} + \delta(a)i(a,t)\Big)da \\
&\quad + \frac{1}{N} \int_0^{a_\dagger} p(a)i(a,t)da - \frac{cV(t)}{N} \\
&= -\frac{d}{T(t)}(T(t) - T_0)^2 + kT_0\frac{V(t)}{1+\alpha V(t)} - kT(t)\frac{V(t)}{1+\alpha V(t)} \\
&\quad - \frac{1}{N} \int_0^{a_\dagger} \alpha(a)\frac{\partial i(a,t)}{\partial a}da - \frac{1}{N} \int_0^{a_\dagger} \alpha'(a)i(a,t)da - \frac{cV(t)}{N}.
\end{aligned}$$

Recall that $\alpha(0) = N$, $\alpha(a_\dagger) = 0$ and $i(0,t) = kT(t)\frac{V(t)}{1+\alpha V}$. Using the integration by parts, we have

$$\begin{aligned}
\int_0^{a_\dagger} \alpha(a)\frac{\partial i(a,t)}{\partial a}da &= \alpha(a)i(a,t)\big|_{a=0}^{a=a_\dagger} - \int_0^{a_\dagger} \alpha'(a)i(a,t)da \\
&= -NkT(t)\frac{V(t)}{1+\alpha V} - \int_0^{a_\dagger} \alpha'(a)i(a,t)da.
\end{aligned}$$

It follows that

$$\frac{dU_1(t)}{dt} = -\frac{d}{T(t)}(T(t) - T_0)^2 - \frac{c\alpha V^2(t)}{N(1+\alpha V(t))} + (\Re_0 - 1)\frac{cV(t)}{N(1+\alpha V(t))}.$$

Therefore, $\Re_0 \le 1$ ensures that $U_1' \le 0$ holds. Similar to the arguments in [4, Theorem 3.1], the largest invariant set of $\{\frac{dU_1(t)}{dt} = 0\}$ is singleton $\{E_1^0\}$. Thus, by

the invariance principle for relatively compact orbit $\{\Phi(t, X_0) : \ t \geq 0\}$ (see [20, Theorem 4.2, Chapter IV] and Proposition 2.6), the infection-free equilibrium is globally asymptotically stable when $\Re_0 \leq 1$. $\square$

4. Uniform persistence

In Section 5, we will prove the global stability of the infection equilibrium E_1^* for $\Re_0 > 1$. For the proof, as in the proof of Theorem 3.1, we will use function g defined by (3.4) in a Lyapunov functional. To make $g(\frac{i(t,a)}{i^*(a)})$ well-defined, one faces an issue that we have to show that $i(t, a)/i^*(a)$ is bounded below and above by some positive constants. To this end, we show that the limit infimum of $T(t)$ and $V(t)$ is bounded below by some constants independent from the choice of the initial condition (uniform persistence). We first prove the following lemma.

Lemma 4.1. *There exists a positive lower bound $\underline{T} > 0$ such that*

$$\liminf_{t \to \infty} T(t) \geq \underline{T}.$$

Here, $\underline{T}$ is independent from the choice of initial value $X_0 = (T_s, i_s(\cdot), V_s) \in \Omega$.

Proof. It follows from the monotonicity of $V/(1 + \alpha V)$ with respect to V and the first equation of (1.1) that

$$\frac{dT(t)}{dt} \geq s - dT(t) - \frac{k}{\alpha}T(t).$$

Hence, the variation of constants formula yields

$$T(t) \geq \frac{s}{d + \frac{k}{\alpha}}\Big(1 - e^{-(d + \frac{k}{\alpha})t}\Big) + e^{-(d + \frac{k}{\alpha})t}T_s \to \frac{s}{d + \frac{k}{\alpha}}, \quad \text{as } t \to \infty,$$

which implies $\liminf_{t \to \infty} T(t) \geq \underline{T} > 0$ with $\underline{T} := s/(d + k/\alpha)$. $\square$

Next we show that the limit infimum of $V(t)$ is bounded below by a constant if $\Re_0 > 1$. Before the proof, we need the following lemma.

Lemma 4.2. *Let $\Re_0$ be defined by (2.15). If $\Re_0 > 1$ and $V_s > 0$, then there exists a positive constant $\epsilon_0 > 0$ such that*

$$\limsup_{t \to \infty} V(t) \geq \epsilon_0.$$

Here, ϵ_0 is independent from the choice of initial value $X_0 = (T_s, i_s(\cdot), V_s) \in \Omega$ with $V_s > 0$.

Proof. From $\Re_0 = \frac{Nks}{dc} > 1$, we can choose $\epsilon_0 > 0$ sufficiently small such that

$$\frac{Nks}{(d + k\frac{\epsilon_0}{1 + \alpha\epsilon_0})c}\frac{1}{1 + \alpha\epsilon_0} > 1 \tag{4.1}$$

holds. For this ϵ_0, we show that $\limsup_{t \to \infty} V(t) \geq \epsilon_0$. Suppose for the contrary, if $\limsup_{t \to \infty} V(t) < \epsilon_0$, then there exists a positive constant $t_0 > 0$ such that $V(t) < \epsilon_0$ holds for all $t \geq t_0$. From the first equation of (1.1), one gets

$$\frac{dT(t)}{dt} \geq s - dT(t) - kT(t)\frac{\epsilon_0}{1 + \alpha\epsilon_0}, \quad \forall t \geq t_0.$$

The variation of constants formula yields

$$T(t) \geq e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})t} \Big\{ s \int_{t_0}^t e^{(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})\tau} \mathrm{d}\tau + T(t_0) \Big\}$$
$$\geq \frac{s}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}} \Big(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(t-t_0)} \Big), \quad \forall t \geq t_0. \tag{4.2}$$

From (4.1), it follows that there exists a sufficiently large $\tilde{t}_0 \geq t_0$ such that

$$\frac{Nks}{(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})c} \Big(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(\tilde{t}_0-t_0)} \Big) \frac{1}{1+\alpha\epsilon_0} > 1. \tag{4.3}$$

Moreover, recalling that the right-hand side of (4.2) is monotone increasing with respect to t, we have

$$T(t) \geq \frac{s}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}} \Big(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(\tilde{t}_0-t_0)} \Big), \quad V(t) < \epsilon_0, \quad \forall t \geq \tilde{t}_0. \tag{4.4}$$

Here, without loss of generality, we can perform a time-shift of $\tilde{t}_0$ on the solution being studied. That is, we can replace the initial condition X_0 with $X_1 := \Phi(\tilde{t}_0, X_0)$. Then, from (4.4), the solution passing through X_1 at time $t = 0$ satisfies

$$T(t) \geq \frac{s}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}} \Big(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(\tilde{t}_0-t_0)} \Big), \quad V(t) < \epsilon_0, \ \forall t \geq 0. \tag{4.5}$$

Integrating the third equation of (1.1) yields

$$V(t) = e^{-ct} \Big\{ \int_0^t e^{c\tau} \int_0^\infty p(a)i(a,\tau) \, da \, d\tau + V(0) \Big\}$$
$$\geq \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)i(a,\tau) \, da \, d\tau.$$

It follows from (2.3) and (4.5) that

$$V(t) \geq \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)kT(\tau-a)\frac{V(\tau-a)}{1+\alpha V(\tau-a)}\sigma(a) \, da \, d\tau$$
$$\geq k\frac{s}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}} \Big(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(\tilde{t}_0-t_0)} \Big) \frac{1}{1+\alpha\epsilon_0} \tag{4.6}$$
$$\times \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)\sigma(a)V(\tau-a) \, da \, d\tau.$$

Taking the Laplace transform to each side of above equation yields

$$\hat{V}(\lambda) \geq \frac{ks}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}} \Big(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(\tilde{t}_0-t_0)} \Big) \frac{1}{1+\alpha\epsilon_0}$$
$$\times \int_0^\infty e^{-\lambda t} \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)\sigma(a)V(\tau-a) \, da \, d\tau \, dt. \tag{4.7}$$

Using the fact that the Laplace transform of a convolution of functions equals the product of the Laplace transforms of each of the functions, we have

$$
\int_0^\infty e^{-\lambda t} \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)\sigma(a)V(\tau-a)\,da\,d\tau\,dt
$$
$$
= \int_0^\infty e^{-\lambda t}e^{-ct}dt \times \int_0^\infty e^{-\lambda t}\int_0^t p(a)\sigma(a)V(t-a)\,da\,dt \qquad (4.8)
$$
$$
= \frac{1}{\lambda+c}\int_0^\infty e^{-\lambda t}p(t)\sigma(t)\,dt \times \hat{V}(\lambda).
$$

Substituting (4.8) into (4.7) and dividing both sides by $\hat{V}(\lambda)$, we have

$$
1 \geq \frac{ks}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}}\Big(1-e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(\tilde{t}_0-t_0)}\Big)\frac{1}{1+\alpha\epsilon_0}\frac{1}{\lambda+c}\int_0^\infty e^{-\lambda t}p(t)\sigma(t)dt.
$$

Thus, taking $\lambda \to 0$, we obtain

$$
1 \geq \frac{Nks}{(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})c}\Big(1-e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(\tilde{t}_0-t_0)}\Big)\frac{1}{1+\alpha\epsilon_0},
$$

which contradicts to (4.3). This completes the proof. $\qquad\square$

Under Lemma 4.2, we prove the following lemma about the lower bound of the limit infimum of V.

Lemma 4.3. *Let $\Re_0$ be defined by (2.15). If $\Re_0 > 1$ and $V_s > 0$, then there exists a positive lower bound $\underline{V} > 0$ such that*

$$
\liminf_{t\to\infty} V(t) \geq \underline{V}. \qquad (4.9)
$$

Here, $\underline{V}$ is independent from the choice of initial value $X_0 = (T_s, i_s(\cdot), V_s) \in \Omega$ with $V_s > 0$.

Proof. Let us choose $\epsilon_0 > 0$ as in Lemma 4.2. It follows that $\limsup_{t\to\infty} V(t) \geq \epsilon_0$ holds, and hence, we only have the following two possibilities.

 (i) There exists a positive constant $\tilde{t} > 0$ such that $V(t) \geq \epsilon_0$ for all $t \geq \tilde{t}$;
 (ii) Eventually $V(t)$ oscillates around ϵ_0.

For (i), we have $\liminf_{t\to\infty} V(t) \geq \epsilon_0$ and hence (4.9) holds with $\underline{V} = \epsilon_0$. We consider (ii). In this case, there exist two positive constants $t_1 > 0$ and $t_2 > t_1$ such that

$$
V(t_1) = V(t_2) = \epsilon_0;
$$
$$
V(t) \leq \epsilon_0, \quad \forall t \in (t_1, t_2). \qquad (4.10)
$$

Now let $C_0 > 0$ be a positive constant defined below, which is independent of the choice of t_1 and t_2. For such C_0, if we show

$$
V(t) > \epsilon_0 e^{-cC_0}, \quad \forall t \in (t_1, t_2), \qquad (4.11)
$$

then (4.9) holds with $\underline{V} = \epsilon_0 e^{-cC_0}$. Therefore, in the remainder of this proof, we prove (4.11).

First we consider the case where $t_2 - t_1 \leq C_0$. Since we have from the third equation of (1.1) that

$$
\frac{dV(t)}{dt} > -cV(t).
$$

With the help of variation of constants formula and the first equation of (4.10), we obtain

$$V(t) > V(t_1)e^{-c(t-t_1)} \geq \epsilon_0 e^{-cC_0} = \underline{V}, \quad \forall t \in (t_1, t_2).$$

Hence (4.11) holds.

Next we consider the case where $t_2 - t_1 > C_0$. Similar to the above, we have

$$V(t) > \underline{V}, \quad \forall t \in [t_1, t_1 + C_0]$$

and hence, we are left to show that

$$V(t) > \underline{V}, \quad \forall t \in (t_1 + C_0, t_2). \tag{4.12}$$

Suppose for the contrary, if there exists a positive constant $\tilde{C}_0 \in (0, t_2 - t_1 - C_0)$ such that

$$V(t) > \underline{V} \quad \forall t \in (t_1 + C_0, t_1 + C_0 + \tilde{C}_0);$$
$$V(t_1 + C_0 + \tilde{C}_0) = \underline{V} \tag{4.13}$$

and show a contradiction. Now, from the second equation of (4.10), we have

$$V(t) \leq \epsilon_0, \quad \forall t \in [t_1, \ t_1 + C_0 + \tilde{C}_0] \tag{4.14}$$

and hence, from the first equation of (1.1), this implies that

$$\frac{dT(t)}{dt} \geq s - dT(t) - kT(t)\frac{\epsilon_0}{1 + \alpha\epsilon_0}, \quad \forall t \in [t_1, \ t_1 + C_0 + \tilde{C}_0],$$

which leads to the inequality

$$T(t) \geq \frac{s}{d + k\frac{\epsilon_0}{1+\alpha\epsilon_0}}\left(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})(t-t_1)}\right) \quad \forall t \in [t_1, \ t_1 + C_0 + \tilde{C}_0].$$

Since the right-hand side of this inequality is monotone increasing with respect to t, we have

$$T(t) \geq \frac{s}{d + k\frac{\epsilon_0}{1+\alpha\epsilon_0}}\left(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})\frac{C_0}{2}}\right), \quad \forall t \in [t_1 + \frac{C_0}{2}, \ t_1 + C_0 + \tilde{C}_0]. \tag{4.15}$$

Here, without loss of generality, we can perform a time-shift of $t_1 + C_0/2$ of the solution being studied. That is, we can replace the initial condition X_0 with $X_2 := \Phi(t_1 + C_0/2, X_0)$. Then, from (4.13), (4.14) and (4.15), the solution passing through $\mathcal{X}_2$ at time $t = 0$ satisfies

$$T(t) \geq \frac{s}{d + k\frac{\epsilon_0}{1+\alpha\epsilon_0}}\left(1 - e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})\frac{C_0}{2}}\right), \quad \forall t \in [0, \frac{C_0}{2} + \tilde{C}_0];$$
$$V(t) \leq \epsilon_0, \quad V(t) > \underline{V}, \quad \forall t \in [0, \frac{C_0}{2} + \tilde{C}_0); \tag{4.16}$$
$$V(\frac{C_0}{2} + \tilde{C}_0) = \underline{V}.$$

Now, from first inequality in (4.6) we obtain

$$V(t) \geq \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)kT(\tau - a)\frac{V(\tau - a)}{1 + \alpha V(\tau - a)}\sigma(a)\, da\, d\tau.$$

With the help of (4.16), we have

$$\underline{V} = V(\frac{C_0}{2} + \tilde{C}_0)$$

$$\geq \int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{-c(\frac{C_0}{2}+\tilde{C}_0-\tau)} \int_0^\tau p(a)kT(\tau-a)\frac{V(\tau-a)}{1+\alpha V(\tau-a)}\sigma(a)\,da\,d\tau$$

$$\geq k\frac{s}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}}\Big(1-e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})\frac{C_0}{2}}\Big)\frac{\underline{V}}{1+\alpha\epsilon_0}$$

$$\times \int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{-c(\frac{C_0}{2}+\tilde{C}_0-\tau)}\int_0^\tau p(a)\sigma(a)\,da\,d\tau.$$

Dividing both sides by $\underline{V}$ and performing integration by parts yield

$$1 \geq k\frac{s}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}}\Big(1-e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})\frac{C_0}{2}}\Big)\frac{1}{1+\alpha\epsilon_0}$$
$$\times \frac{1}{c}\Big\{\int_0^{\frac{C_0}{2}+\tilde{C}_0} p(a)\sigma(a)\,da - e^{-c(\frac{C_0}{2}+\tilde{C}_0)}\int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{c\tau}p(\tau)\sigma(\tau)\,d\tau\Big\}. \tag{4.17}$$

Now, noticing that from (iv) of Assumption 2.1,

$$\int_0^{\frac{C_0}{2}+\tilde{C}_0} p(a)\sigma(a)\,da \quad \text{and} \quad \int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{c\tau}p(\tau)\sigma(\tau)\,d\tau$$

become finite,

$$\int_0^{a_\dagger} p(a)\sigma(a)\,da \ (= N) \quad \text{and} \quad \int_0^{a_\dagger} e^{c\tau}p(\tau)\sigma(\tau)\,d\tau$$

for sufficiently large C_0. Thus the right-hand side of (4.17) converges to

$$\frac{Nks}{(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})c}\frac{1}{1+\alpha\epsilon_0}$$

as $C_0 \to \infty$. Consequently, from (4.1), we see that this value is greater than 1 and thus, for sufficiently large $C_0 > 0$,

$$k\frac{s}{d+k\frac{\epsilon_0}{1+\alpha\epsilon_0}}\Big(1-e^{-(d+k\frac{\epsilon_0}{1+\alpha\epsilon_0})\frac{C_0}{2}}\Big)\frac{1}{1+\alpha\epsilon_0}$$
$$\times \frac{1}{c}\Big\{\int_0^{\frac{C_0}{2}+\tilde{C}_0} p(a)\sigma(a)\,da - e^{-c(\frac{C_0}{2}+\tilde{C}_0)}\int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{c\tau}p(\tau)\sigma(\tau)\,d\tau\Big\} > 1 \tag{4.18}$$

holds. In fact, since C_0 is an arbitrary large constant, we can assume without loss of generality that C_0 satisfies (4.18), which contradicts with (4.17). Therefore, there exists no $\tilde{C}_0 \in (0, t_2 - t_1 - C_0)$ satisfying (4.13) and thus, (4.12) holds. This completes the proof. $\square$

5. Global stability of infection equilibrium

With the above preparation, we are ready to study the stability of equilibria. Now, from (2.3) and (2.13), we can easily see that for $t - a > 0$,

$$\frac{i(a,t)}{i^*(a)} = \frac{T(t-a)}{T^*}\frac{V(t-a)}{\frac{V^*}{1+\alpha V^*}}\frac{1}{1+\alpha V(t-a)}$$

holds. Thus, it follows from Lemmas 4.1 and 4.3 that for sufficiently small $\varepsilon > 0$, there exists $t_3 > 0$ such that

$$\frac{i(a,t)}{i^*(a)} \geq \frac{\underline{T}-\varepsilon}{T^*}\frac{\underline{V}-\varepsilon}{\frac{V^*}{1+\alpha V^*}}\frac{1}{1+\alpha(\underline{V}-\varepsilon)} \quad (>0)$$

holds for all $t \geq \max(t_3, a)$. Thus, letting $t_4 := \max(t_3, a_\dagger)$, the integral

$$\int_0^{a_\dagger} \alpha(a) i^*(a) g\left(\frac{i(a,t)}{i^*(a)}\right) da \tag{5.1}$$

is well-defined for any $t \geq t_4$, where g is a function defined by (3.4). In what follows, without loss of generality, we can perform a time-shit of t_4 on the solution being studied. That is, we can replace the initial condition X_0 with $X_3 := \Phi(t_4, X_0)$. Under this setting, using a Lyapunov functional which includes the integral (5.1), we prove the following main theorem.

Theorem 5.1. *Let $\Re_0$ be defined by (2.15). The infection equilibrium E_1^* of (1.1) is globally asymptotically stable if $\Re_0 > 1$.*

Proof. We define a Lyapunov function

$$U_2(t) = T^* g\left(\frac{T(t)}{T^*}\right) + \frac{1}{N} \int_0^{a_\dagger} \alpha(a) i^*(a) g\left(\frac{i(a,t)}{i^*(a)}\right) da + \frac{1}{N} g\left(\frac{V(t)}{V^*}\right).$$

where $g(z) = z - 1 - \ln z$ and has global minimum value in 1, $g(1) = 0$. It is easy to see that $U_2(t)$ is nonnegative and infection equilibrium E_1^* is the global minimum point.

Using the equilibrium equations (2.11), differentiating $U_2(t)$ along the solutions of (1.1) gives

$$\frac{dU_2(t)}{dt}$$
$$= \left(1 - \frac{T^*}{T(t)}\right)\left(dT^* + kT^* \frac{V^*}{1 + \alpha T^*} - dT(t) - kT(t)\frac{V(t)}{1 + \alpha V(t)}\right)$$
$$+ \frac{1}{N} \int_0^{a_\dagger} \alpha(a)\left(1 - \frac{i^*(a)}{i(a,t)}\right)\frac{\partial i(a,t)}{\partial t} da$$
$$+ \frac{1}{N}\left(1 - \frac{V^*}{V(t)}\right)\left(\int_0^{a_\dagger} p(a) i(a,t) da - cV(t)\right)$$
$$= -\frac{d}{T(t)}(T(t) - T^*)^2 + kT^* \frac{V^*}{1 + \alpha V^*} - kT^* \frac{T^* V^*}{T(t)(1 + \alpha V^*)} - kT(t)\frac{V(t)}{1 + \alpha V(t)}$$
$$+ kT^* \frac{V(t)}{1 + \alpha V(t)} - \frac{1}{N}\int_0^{a_\dagger} \alpha(a)\left(1 - \frac{i^*(a)}{i(a,t)}\right)\left(\frac{\partial i(a,t)}{\partial a} + \delta(a)i(a,t)\right) da$$
$$+ \frac{1}{N}\int_0^{a_\dagger} p(a)i(a,t) da - \frac{cV(t)}{N} - \frac{1}{N}\frac{V^*}{V(t)}\int_0^{a_\dagger} p(a)i(a,t) da + \frac{cV^*}{N}.$$

It is useful to note that

$$\frac{d}{da}\left(\frac{i(a,t)}{i^*(a)} - 1 - \ln\frac{i(a,t)}{i^*(a)}\right) = \left(1 - \frac{i^*(a)}{i(a,t)}\right)\left(\frac{i_a(a,t)}{i^*(a)} - \frac{i(a,t)i_a^*(a)}{[i^*(a)]^2}\right), \tag{5.2}$$

and

$$i_a^*(a) = -\delta(a)i^*(a). \tag{5.3}$$

It follows that

$$\left(1 - \frac{i^*(a)}{i(a,t)}\right)\frac{\partial i(a,t)}{\partial a} = i^*(a)\frac{d}{da}\left(\frac{i(a,t)}{i^*(a)} - 1 - \ln\frac{i(a,t)}{i^*(a)}\right) + \delta(a)i^*(a) - \delta(a)i(a,t).$$

Using integration by part, we have

$$\int_0^{a_\dagger} \alpha(a)\left(1 - \frac{i^*(a)}{i(a,t)}\right)\frac{\partial i(a,t)}{\partial a} da \tag{5.4}$$

$$=\alpha(a)i^*(a)\Big(\frac{i(a,t)}{i^*(a)}-1-\ln\frac{i(a,t)}{i^*(a)}\Big)\Big|_{a=0}^{a=a_\dagger} \tag{5.5}$$

$$-\int_0^{a_\dagger}\Big(\frac{i(a,t)}{i^*(a)}-1-\ln\frac{i(a,t)}{i^*(a)}\Big)(\alpha'(a)i^*(a)+\alpha(a)i_a^*(a))\,da \tag{5.6}$$

$$+\int_0^{a_\dagger}\alpha(a)(\delta(a)i^*(a)-\delta(a)i(a,t))da. \tag{5.7}$$

We infer from

$$\alpha(0)=N,\quad \alpha(a_\dagger)=0,$$

$$i^*(0)=kT^*\frac{V^*}{1+\alpha V^*},\quad i(0,t)=kT(t)\frac{V(t)}{1+\alpha V(t)},$$

$$i_a^*(a)=-\delta(a)i^*(a),\quad \alpha'(a)=\delta(a)\alpha(a)-p(a)$$

that

$$\alpha(0)i^*(0)\Big(\frac{i(0,t)}{i^*(0)}-1-\ln\frac{i(0,t)}{i^*(0)}\Big)=NkT^*\frac{V^*}{1+\alpha V^*}g\Big(\frac{T(t)V(t)(1+\alpha V^*)}{T^*V^*(1+\alpha V(t))}\Big),$$

$$\alpha(a_\dagger)i^*(a_\dagger)\Big(\frac{i(a_\dagger,t)}{i^*(a_\dagger)}-1-\ln\frac{i(a_\dagger,t)}{i^*(a_\dagger)}\Big)=0, \alpha'(a)i^*(a)+\alpha(a)i_a^*(a)=-p(a)i^*(a).$$

Hence, it follows that

$$\int_0^{a_\dagger}\alpha(a)\Big(1-\frac{i^*(a)}{i(a,t)}\Big)\Big(\frac{\partial i(a,t)}{\partial a}+\delta(a)i(a,t)\Big)da$$

$$=-NkT^*\frac{V^*}{1+\alpha V^*}g\Big(\frac{T(t)V(t)(1+\alpha V^*)}{T^*V^*(1+\alpha V(t))}\Big) \tag{5.8}$$

$$+\int_0^{a_\dagger}\Big(\frac{i(a,t)}{i^*(a)}-1-\ln\frac{i(a,t)}{i^*(a)}\Big)p(a)i^*(a)da.$$

Note that $kT^*=\frac{c(1+\alpha V^*)}{N}$ and $\int_0^{a_\dagger}p(a)i^*(a)da=NkT^*\frac{V^*}{1+\alpha V^*}$, one gets

$$\frac{dU_2(t)}{dt}$$

$$=-\frac{d}{T(t)}(T(t)-T^*)^2+kT^*\frac{V^*}{1+\alpha V^*}-kT^*\frac{T^*V^*}{T(t)(1+\alpha V^*)}$$

$$+kT^*\frac{V(t)}{1+\alpha V(t)}-kT(t)\frac{V(t)}{1+\alpha V(t)}+kT^*\frac{V^*}{1+\alpha V^*}g\Big(\frac{T(t)V(t)(1+\alpha V^*)}{T^*V^*(1+\alpha V(t))}\Big)$$

$$-\frac{1}{N}\int_0^{a_\dagger}\Big(\frac{i(a,t)}{i^*(a)}-1-\ln\frac{i(a,t)}{i^*(a)}\Big)p(a)i^*(a)da$$

$$+\frac{1}{N}\int_0^{a_\dagger}p(a)i(a,t)da-\frac{kT^*V(t)}{1+\alpha V^*}-\frac{1}{N}\frac{V^*}{V(t)}\int_0^{a_\dagger}p(a)i(a,t)da+\frac{kT^*V^*}{1+\alpha V^*}$$

$$=-\frac{d}{T(t)}(T(t)-T^*)^2-\frac{1}{N}\int_0^{a_\dagger}p(a)i^*(a)g\Big(\frac{V^*i(a,t)}{V(t)i^*(a)}\Big)da$$

$$-\frac{1}{N}\int_0^{a_\dagger}p(a)i^*(a)g\Big(\frac{T^*}{T(t)}\Big)da-\frac{1}{N}\int_0^{a_\dagger}p(a)i^*(a)g\Big(\frac{1+\alpha V(t)}{1+\alpha V^*}\Big)da$$

$$+\frac{1}{N}\int_0^{a_\dagger}p(a)i^*(a)\Big(-1-\frac{1+\alpha V(t)}{1+\alpha V^*}+\frac{V(t)(1+\alpha V^*)}{V^*(1+\alpha V(t))}-\frac{V(t)}{V^*}\Big)da$$

$$= -\frac{d}{T(t)}(T(t) - T^*)^2 - \frac{1}{N}\int_0^{a_\dagger} p(a)i^*(a)g\Big(\frac{V^*i(a,t)}{V(t)i^*(a)}\Big)da$$

$$- \frac{1}{N}\int_0^{a_\dagger} p(a)i^*(a)g\Big(\frac{T^*}{T(t)}\Big)da - \frac{1}{N}\int_0^{a_\dagger} p(a)i^*(a)g\Big(\frac{1+\alpha V(t)}{1+\alpha V^*}\Big)da$$

$$- \frac{1}{N}\int_0^{a_\dagger} p(a)i^*(a)\frac{\alpha(V(t)-V^*)^2}{V^*(1+\alpha V(t))(1+\alpha V^*)}da.$$

Hence, positive-definite function $U_2(t)$ has negative derivative $\frac{dU_2(t)}{dt}$ with the property of function $g(z) = z - 1 - \ln z$. Furthermore, one can obtain the equality $\frac{dU_2(t)}{dt} = 0$ holds if and only if $(T(t), i(a,t), V(t) = T^*, i^*(a), V^*)$. Hence, from the invariance principle for relatively compact orbit $\{\Phi(t, X_0) : t \geq 0\}$ (see [20, Theorem 4.2 of Chapter IV]), the infection equilibrium E_1^* is globally asymptotically stable whenever it exists.   □

Discussion

Considering age as a continuous variable will leads to partial differential equations (PDEs) formulation, where age is defined as the time that has passed since the infection of the cell. Due to the greater flexibility, both experimentally and mathematically, Nelson et al. [15] formulated an age-structured model of HIV infection allowing for death rate and virus production rate of infected cells are infection-age-dependent variable. With a specific form of the viral production function and constant death rate of infected cells, they studied local stability of the model without or with drug treatment, respectively utilizing the Jacobian matrix to calculate the characteristic equation. Actually, global stability is one of the challenging problems in the analysis of biological models and it is essential to rule out other dynamical scenarios such as periodic solutions. Huang et al [4] established global dynamical properties of model in [15] without (or with) drug treatment by constructing suitable Lyapunov functions. However, for the proof of the global stability of endemic equilibrium, we have to show first the relative compactness of the orbit generated by model in order to make use of the invariance principle. Furthermore, uniform persistence of system must be shown, which is extremely important in constructing the Lyapunov functional. The main contribution of this paper has twofold. First, we give analytic result on the global stability of endemic equilibrium, that is, the relative compactness of the orbit generated by model and uniform persistence of system. Second, we perform a rigorous mathematical analysis on the global dynamics for a continuous age-structured HIV infection model with saturation infection rate. The results obtain in this paper can be regarded as a supplement and extension to [4] and [15]. According to [18], system (1.1) with (1.2) can be used to study the possible impact of drug treatment of HIV-1 infections on evolution of the pathogen. The impact of combination therapy using RT and protease inhibitors on the emergence of drug-resistant HIV-1 strains and the effect of drug efficacy on viral dynamics by numerical simulations will be left as future work.

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