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PDF issue: 2025-12-04

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Kuniya, Toshikazu

(Citation)
Journal of Mathematical Analysis and Applications,432(1):289-313

(Issue Date)
2015-12-01

(Resource Type)
journal article

(Version)
Accepted Manuscript

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(URL)
https://hdl.handle.net/20.500.14094/90003816

Global dynamics for a class of age-infection HIV models with nonlinear infection rate

Jinliang Wang[a,1], Ran Zhang[a], Toshikazu Kuniya[b,2,*]

[a]School of Mathematical Science, Heilongjiang University, Harbin 150080, China
[b]Graduate School of System Informatics, Kobe University, 1-1 Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan

Abstract

In this paper, we study the global stability of a class of HIV viral infection models with continuous age-structure using the direct Lyapunov method. In each of the cases where the incidence rates are given by nonlinear infection rate $F(T)G(V)$, Holling type II functional response and Crowley-Martin functional response, we define the basic reproduction number and prove that it is a sharp threshold determining whether the infection dies out or not. We give a rigorous mathematical analysis on technical materials and necessary arguments, including relative compactness of the orbit and uniform persistence of system, by reformulating the system as a system of Volterra integral equations. We further investigate global behaviors of HIV viral infection models with Holling type II functional response and Crowley-Martin functional response through numerical simulations.

Keywords: Age-structured model, Nonlinear incidence rate, Relative compactness, Uniform persistence, Lyapunov function
2010 MSC: 92D30, 34D23, 34K20

1. Introduction

In the past decades, many authors expressed much interest in mathematical modeling and analysis to the in-host dynamics of HIV. It is the fact that a large number of issues had widely been investigated, based on the classical and basic viral infection models proposed by Nowak and May [27], Perelson and Nelson [30], with various mathematical formulations. Denote by $x(t)$, $y(t)$, and $v(t)$ the numbers of target cells, infected cells, and free viruses. Uninfected target cells are assumed to be produced at a constant rate s and die at rate d. Infection of target cells by free virus is assumed to occur at rate $\beta x(t)v(t)$ and infected cells die at rate a. New virus particles are produced by infected cells at rate k and die at rate u. Thus, the average life-spans of uninfected cells, infected cells, and free virus particles are given by $1/d$, $1/a$ and $1/u$, respectively. This lead to the basic viral infection model takes the following form:

$$\begin{cases} \dfrac{dx(t)}{dt} = s - dx(t) - \beta x(t)v(t), \\ \dfrac{dy(t)}{dt} = \beta x(t)v(t) - ay(t), \\ \dfrac{dv(t)}{dt} = ky(t) - uv(t), \end{cases} \tag{1.1}$$

*Corresponding author.
Email addresses: jinliangwang@hlju.edu.cn (Jinliang Wang), ranzhang90@aliyun.com (Ran Zhang), tkuniya@port.kobe-u.ac.jp (Toshikazu Kuniya)

[1]The research was supported by National Natural Science Foundation of China (nos. 11401182, 11471089), Natural Science Foundation of Heilongjiang Province (no. A201415), Science and Technology Innovation Team in Higher Education Institutions of Heilongjiang Province (No. 2014TD005).

[2]The research was partially supported by Grant-in-Aid for Research Activity Start-up, No.25887011 of Japan Society for the Promotion of Science.

The global dynamics of system (1.1) was fully established in [17, 33]: the system is infection free if $R_0 \leq 1$ and if $R_0 > 1$, then the chronic-infection equilibrium is globally asymptotically stable. Here R_0 denotes the basic reproductive number of the virus for system (1.1) and it is given as $R_0 = \lambda k\beta/(dau)$, representing the average number of newly infected cells generated from one infected cell at the beginning of the infection process. There have been numerous works on pathogen in-host dynamics describing HIV infection. The pioneer work of Nowak and May [27], Perelson and Nelson [30] have been further developed by incorporating some biological features as a realistic attempt, such as, immune response and delays (see e.g., Hellriegel [13], Hetzel and Anderson [14], Bairagi and Adak [1] and Huang *et al.* [10]). However almost works had not taken into account an important picture of the mortality rate and viral production rate of infected cells dependent on the infection age of cells. This suggests that ODE models may be an unreasonable model for describing HIV viral infection since it implies that mortality rate and viral production rate of infected cells be constant other than be functions of infection age of cells. Until recently, incorporating this issue to model (1.1), Nelson et al. [28] and Huang et al. [11] have studied age-structured model of HIV infection by considering age to be a continuous variable. The age structure (generally leads to partial differential equations) will allow us to have a good description of produced viral particles and of the infected cells mortality (for a famous book on age-structured models, see Iannelli [15] and for a recent paper, see Vargas-De-León *et al.* [36]).

Let $i(t,a)$ be the density of infected cells with respect to the infection age a at time t, where the infection age $a \geq 0$ implies the time since the infection began. Thus, for two given age values $a_1, a_2 : 0 \leq a_1 < a_2 < +\infty$, the number of infected cells with infection age a between a_1 and a_2 is $\int_{a_1}^{a_2} i(t,a)da$. It can be found as an evidence in the literature that virus production increases exponentially with the infection age of cell [31]. In the paper [7], the authors give a confirmed result that the death rate of infected cells should be vary with some variable. It is easy to see that when we consider infection age as a continuous variable, i.e., production rate of viral particles and the death rate of productively infected cells be two continuous functions of age, $p(a)$ and $\delta(a)$, respectively, model (1.1) will be modeled to the following one order partial differential equations system (see, Nelson et al. [28]):

$$\begin{cases} \dfrac{dT(t)}{dt} = s - dT(t) - kT(t)V(t), \\ \dfrac{\partial i(a,t)}{\partial a} + \dfrac{\partial i(a,t)}{\partial t} = -\delta(a)i(a,t), \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty p(a)i(a,t)da - cV(t), \end{cases} \tag{1.2}$$

with boundary condition

$$i(0,t) = kV(t)T(t), \tag{1.3}$$

and initial condition

$$T(0) = T_s, \;\; i(a,0) = i_s(a), \;\; V(0) = V_s, \tag{1.4}$$

where $T(t)$ and $V(t)$ denotes the population of uninfected target T cells and infectious free virion at time t. k and c have the same meaning with β, u in (1.1). By using the Jacobian matrix and its characteristic equation, local stability of the equilibria of (1.2) has been analyzed in Nelson et al. [28]. The global asymptotic stability of the infection-free equilibrium and the infection equilibrium of (1.2) was established in Huang et al. [11] by constructing suitable Lyapunov functions and LaSalle's invariance principle. In [5, 32], the model (1.2) was further developed in combining drug therapy to study the impact of drugs on viral dynamics.

It is also important to highlight the fact that global properties of equilibria of in-host viral infection models can help us to understand virus ultimate development in patient [11]. For models of describing age-structured viral infection (these models are normally formulated in the form of first-order partial differential equations), their local stability can be proved by linearizing the systems at their equilibrium states and verifying the eigenvalues of the corresponding characteristic equations. While global stability analysis of equilibrium is often very challenging, even if it is not impossible. The commonly used method to obtain global stability for epidemic and viral infection dynamics is to construct a Lyapunov function (for ODE) or functional (for DDE).

Thus, it is a challenging topic that attracts many authors to study global stability of age-structured models from both the mathematical and epidemiological points of view (we point here that some perspectives and results from the global stability theory for SIR and SEIR models would also be relevant for our discussion, for example, the

work of Magal, McCluskey and Webb in [22]). In [24], by utilizing Volterra-type of function, McCluskey obtained the global stability of a disease transmission model with continuous age-structure for latently infected individuals and for infectious individuals. Recently, studies on constructing Lyapunov functionals to obtain global stability for McKendrick-von Foerster equation and age-dependent SIR and SEIR models have been done by Melnik and Korobeinikov in [23].

Due to the difficulty in determining the global stability of age-structured models, stage progression/multi-stage ODE models are commonly formulated in the literature to approximate the infection-age dependent infectivity from these PDE models, such as multi-stage cholera models [35] and HIV infection models [12]. Another approach to achieve the global stability of age-structured model is to discretize it with respect to the age variable a and rewrite models into a higher dimensional ODE system, and then study the global stability of each equilibria by constructing Lyapunov functions [18].

The model we shall consider in this paper is a generalization of the model proposed by Huang et al. in [11] by taking into account nonlinear incidence rate. It is well known that nonlinear incidence rates are frequently used to describe the viral infection process based on experiments data and reasonable assumptions [21] and be important to account for a number of nonlinear features of the biological phenomena involved, which is influenced by the availability of susceptible cells and by the force of infection of viral cells. For example, Holling type II functional response [10], Saturation infection rate [20, 39], Beddington-DeAngelis functional response [8], Crowley-Martin functional response [40, 41] and general nonlinear incidence $c(x)f(v)$ [6], where $c(x)$ denotes the contact rate function at concentration of the target cells x and $f(v)$ denotes the force of infection by virus at concentration v. Motivated by the works mentioned above (see, [6, 8, 11, 20, 22–24, 39]), in this paper, we develop the model (1.2) with nonlinear incidence rate and investigate the global stability of their equilibrium.

For the proof of the global stability properties of equilibria, it is often necessary to use more mathematical arguments, for example, (i) In order to make use of the invariance principle, we have to show first the relative compactness of the orbit generated by models; (ii) In order to construct a well-posed Lyapunov functions, the state space has to be discussed in more details. Furthermore, uniform persistence of system must be shown, which is extremely extremely important because the Lyapunov functional that is used integrates as the age-of-infection a goes from 0 to infinity, using an integrand that is infinite if $i(a,t) = 0$. Thus, if the number of infected cells is 0 on some set of infection ages (where this set has positive measure - an interval, for example), then the Lyapunov functional is infinite. Similarly, if $i(a,t)$ is positive, but close enough to 0, then the functional is infinite.

In the present paper, we not only focus on proving global stability properties by constructing Lyapunov functionals for age-infection models, but also give rigorous mathematical analysis on technical materials and necessary arguments to the proofs, including relative compactness of the orbit and uniform persistence of the systems. The results in present paper serve as a supplement and generalization of the works in [28] and [11]. The basic reproduction number is defined for each model and proved that it is a sharp threshold determining whether or not infection dies out.

The plan of this article is as follows. In Section 2, we introduce the age-structured model of viral infection model with general incidence rate $F(T)G(V)$ and study its basic properties and global asymptotic stability. For the analysis, we construct some proper Lyapunov functionals and use some subtle estimates of the derivatives of them. In Section 3, we introduce two age-infection models with Holling type II functional response and Crowley-Martin functional response, which can be regarded as special cases of the general model studied in Section 2. In Section 4, we perform numerical simulation to verify the validity of our main theoretical results. In Section 5, a brief discussion is given to conclude this work.

2. The age-infection model with nonlinear infection rate $F(T)G(V)$

The aim of this section is to prove the global stability of the following age-infection model with general nonlinear incidence rate, which can be regarded as a generalization of model (1.2).

$$\begin{cases} \dfrac{dT(t)}{dt} = s - dT(t) - F(T(t))G(V(t)), \\ \dfrac{\partial i(a,t)}{\partial t} + \dfrac{\partial i(a,t)}{\partial t} = -\delta(a)i(a,t), \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty p(a)i(a,t)da - cV(t), \end{cases} \tag{2.1}$$

with boundary condition

$$i(0,t) = F(T(t))G(V(t)) \tag{2.2}$$

and initial condition

$$X_0 := (T(0), i(\cdot,0), V(0)) = (T_s, i_s(\cdot), V_s) \in \mathscr{X}_+. \tag{2.3}$$

Here $\mathscr{X} = \mathbb{R} \times L^1(0,\infty) \times \mathbb{R}$ is a functional space equipped with norm

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

and $\mathscr{X}_+ := \mathbb{R}_+ \times L^1_+(0,\infty) \times \mathbb{R}_+$ is the positive cone of $\mathscr{X}$. We make the following assumption on parameters, which is thought to be biologically relevant.

Assumption 2.1. We assume that:

(i) $s > 0$, $d > 0$ 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 $\delta(a) \geq \delta_0$ for all $a \geq 0$;

(iv) There exists a maximum age $a_\dagger > 0$ for the viral production such that $p(a) > 0$ for $a \in (0,a_\dagger)$ and $p(a) = 0$ for $a > a_\dagger$.

We further make the following assumption on functions $F, G : \mathbb{R}_+ \to \mathbb{R}_+$ (see also [6, 9, 16]).

Assumption 2.2. We assume that:

(i) $F(0) = G(0) = 0$;

(ii) $F'(T) > 0, G'(V) > 0$ and

$$\frac{\partial^2 G(V)}{\partial V^2} \leq 0; \tag{2.4}$$

(iii) $F(T)/T$ and $G(V)/V$ are monotone nonincreasing with respect to $T > 0$ and $V > 0$, respectively. Moreover, there exist positive constants $k_1, k_2 > 0$ such that

$$\lim_{T\to+0} \frac{F(T)}{T} = k_1, \quad \lim_{V\to+0} \frac{G(V)}{V} = k_2.$$

Let $k := k_1 k_2$;

(iv) F and G are Lipschitz continuous on $\mathbb{R}_+$. That is, there exist positive constants $M_F, M_G > 0$ such that

$$|F(x) - F(y)| \leq M_F |x-y| \quad \text{and} \quad |G(x) - G(y)| \leq M_G |x-y|$$

for all $x, y \in \mathbb{R}_+$.

From (2.2) and (2.3), integration of the second equation in (2.1) along the characteristic line $t-a=$ const. yields

$$i(a,t) = \begin{cases} F(T(t-a))G(V(t-a))e^{-\int_0^a \delta(\varepsilon)d\varepsilon}, & t > a \geq 0; \\ i_s(a-t)e^{-\int_0^a \delta(a-t+\varepsilon)d\varepsilon}, & a \geq t > 0. \end{cases} \tag{2.5}$$

As mentioned in Section 1, we shall focus on the global stability of (2.1). To achieve the goal, we first define the continuous semiflow associated with this system. It follows from Assumptions 2.1-2.2 and (2.5), we easily see that system (2.1) has a unique nonnegative solution for any initial condition $X_0 \in \mathscr{X}_+$. Thus, we can obtain a continuous semi-flow $\Phi : \mathbb{R}_+ \times \mathscr{X}_+ \to \mathscr{X}_+$ defined by system (2.1) such that

$$\Phi(t, X_0) := (T(t), i(\cdot,t), V(t)), \quad t \geq 0, \ X_0 \in \mathscr{X}_+. \tag{2.6}$$

Thus

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

Let us define the state space for system (2.1) by

$$\Omega := \left\{ (x, \varphi, y) \in \mathscr{X}_+ : \ \|(x,\varphi,y)\|_{\mathscr{X}} \leq \left(1 + \frac{p^+}{c}\right) \frac{s}{\delta_0} \right\}. \tag{2.7}$$

Then, the following proposition holds true:

Proposition 2.1. *Let Φ and Ω be defined by (2.6) and (2.7), 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 follows from the second equation of (2.1) that

$$\frac{d}{dt} \int_0^\infty i(a,t)da = F(T(t))G(V(t)) - \int_0^\infty \delta(a) i(a,t)da.$$

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

$$\begin{aligned} \frac{d}{dt}\left(T(t) + \int_0^\infty i(a,t)da\right) &= s - dT(t) - \int_0^\infty \delta(a)i(a,t)da \\ &\leq s - \delta_0 \left(T(t) + \int_0^\infty i(a,t)da\right). \end{aligned}$$

The variation of constants formula yields

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

and hence,

$$T(t) + \int_0^\infty i(a,t)da \leq \frac{s}{\delta_0} \quad \forall t \geq 0 \tag{2.8}$$

holds for any $X_0 \in \Omega$. Moreover, it follows from the third equation of (2.1) and (ii) of Assumption 2.1 that

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

Hence, from (2.8),

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

and similar to the above discussion, we can use the variation of constants formula to obtain

$$V(t) \leq \frac{p^+}{c}\frac{s}{\delta_0} \quad \forall t \geq 0 \tag{2.9}$$

for all $X_0 \in \Omega$. Consequently, from (2.8) and (2.9), we have

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

which implies $\Phi(t, X_0) \subset \Omega \ \ \forall t \geq 0$.

2.1. Equilibria and basic reproductive number

Let N denote the burst size, i.e, the total number of viral particles produced by an infected cell in its lifespan. Then,

$$N \equiv \int_0^\infty p(a)\sigma(a)da \ \left(= \int_0^{a_\dagger} p(a)\sigma(a)da\right), \tag{2.10}$$

where

$$\sigma(a) = e^{-\int_0^a \delta(\varepsilon)d\varepsilon} \tag{2.11}$$

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

System (2.1) has at most two kinds of equilibria. There always exists an infection-free equilibrium $E^0 = (T_0, i_0(a), V_0) \in \Omega$, where $T_0 = s/d$, $i_0(a) = 0$, $V_0 = 0$. Moreover, there exists possibly an infection equilibrium $E^* = (T^*, i^*(a), V^*) \in \Omega$, satisfying the following equations:

$$\begin{cases} s - dT^* - F(T^*)G(V^*) = 0, \\ \dfrac{di(a)}{da} = -\delta(a)i^*(a), \\ \displaystyle\int_0^\infty p(a)i^*(a)da = cV^*, \\ i^*(0) = F(T^*)G(V^*), \end{cases} \tag{2.12}$$

The basic reproduction number of system (2.1) is given by

$$\mathfrak{R}_0 = \frac{NF(T_0)}{c}\frac{\partial G(0)}{\partial V}, \tag{2.13}$$

which is defined by the number of newly infected cells produced by one infected cell during its lifespan. It follows from the lemmas of [6, 9, 16] that we can claim that model (2.1) admits unique infection equilibrium $E^* = (T^*, i^*(a), V^*)$ when $\mathfrak{R}_0 > 1$.

2.2. Relative compactness of the orbit

In the proof of the global stability of each equilibrium, we will use a Lyapunov functional technique combined with the invariance principle. Since we are now concerned with the infinite dimensional Banach space $\mathscr{X}$ including $L^1(0,\infty)$, we have to show first the relative compactness of the orbit $\{\Phi(t, X_0) : \ t \geq 0\}$ in $\mathscr{X}$ in order to make use of the invariance principle (see e.g., [37, Theorem 4.2 of Chapter IV]). To this end, we first decompose $\Phi : \ \mathbb{R}_+ \times \mathscr{X}_+ \to \mathscr{X}_+$ into the following two operators $\Theta, \Psi : \ \mathbb{R}_+ \times \mathscr{X}_+ \to \mathscr{X}_+$:

$$\Theta(t, X_0) := (0, \tilde{\varphi}_i(\cdot, t), 0), \tag{2.14}$$

$$\Psi(t, X_0) := \left(T(t), \tilde{i}(\cdot, t), V(t)\right), \tag{2.15}$$

where $\tilde{\varphi}_i$ and $\tilde{i}$ are defined by

$$\tilde{\varphi}_i(a,t) := \begin{cases} 0, & t > a \geq 0; \\ i(a,t), & a \geq t \geq 0 \end{cases} \quad \text{and} \quad \tilde{i}(a,t) := \begin{cases} i(a,t), & t > a \geq 0; \\ 0, & a \geq t \geq 0. \end{cases} \tag{2.16}$$

Then, we have $\Phi(t,X_0) = \Theta(t,X_0) + \Psi(t,X_0)$ $\forall t \geq 0$ and from [38, Proposition 3.13] and Proposition 2.1, the following Proposition is obtained.

Lemma 2.1. *Let Φ, Ω, Θ and Ψ be defined by (2.6), (2.7), (2.14) and (2.15), respectively. If the following two conditions hold, then $\{\Phi(t,X_0) : t \geq 0\}$ for $X_0 \in \Omega$ has compact closure in $\mathscr{X}$.*

(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 $\|X_0\|_{\mathscr{X}} \leq r$, then $\|\Theta(t,X_0)\|_{\mathscr{X}} \leq \Delta(t,r)$ for $t \geq 0$;

(ii) For $t \geq 0$, $\Psi(t,\cdot)$ maps any bounded sets of Ω into sets with compact closure in $\mathscr{X}$.

To show that the conditions (i) and (ii) in Lemma 2.1 hold, we first prove the following lemma.

Lemma 2.2. *Let Ω and Θ be defined by (2.7) and (2.14), respectively. For $r > 0$, let $\Delta(t,r) := e^{-\delta_0 t} r$. Then, $\lim_{t\to\infty} \Delta(t,r) = 0$ and for $t \geq 0$, $\|\Theta(t,X_0)\|_{\mathscr{X}} \leq \Delta(t,r)$ provided $X_0 \in \Omega$ with $\|X_0\|_{\mathscr{X}} \leq r$.*

PROOF. $\lim_{t\to\infty} \Delta(t,r) = 0$ is obvious. From (2.5), we have

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

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

$$\begin{aligned} \|\Theta(t,X_0)\|_{\mathscr{X}} &= |0| + \int_0^\infty |\tilde{\varphi}_i(a,t)|\,da + |0| \\ &= \int_t^\infty \left| i_s(a-t)e^{-\int_0^t \delta(a-t+\varepsilon)d\varepsilon} \right| da \\ &\leq e^{-\delta_0 t} \int_0^\infty |i_s(a)|\,da \\ &\leq e^{-\delta_0 t} \|X_0\|_{\mathscr{X}} \leq e^{-\delta_0 t} r = \Delta(t,r), \quad \forall t \geq 0, \end{aligned}$$

which completes the proof.

We next prove the following lemma.

Lemma 2.3. *Let Ω and Ψ be defined by (2.7) and (2.15), respectively. Then, for $t \geq 0$, $\Psi(t,\cdot)$ maps any bounded sets of Ω into sets with compact closure in $\mathscr{X}$.*

PROOF. From Proposition 2.1, it is easily seen that $T(t)$ and $V(t)$ remain in the compact set $[0,(1+p^+/c)s/\delta_0]$. Thus, we only have 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., [34, 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) $\lim_{h\to 0+} \int_0^\infty \left|\tilde{i}(a+h,t) - \tilde{i}(a,t)\right| da = 0$ 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 $X_0 \in \Omega$.

Now, from (2.5) and (2.16), we have

$$\tilde{i}(a,t) = \begin{cases} F(T(t-a))G(V(t-a))\sigma(a), & t > a \geq 0; \\ 0, & a \geq t > 0. \end{cases} \tag{2.17}$$

It follows from Assumption 2.2 and Proposition 2.1 that

$$\begin{aligned} F(T(t-a))G(V(t-a))\sigma(a) &= \frac{F(T(t-a))}{T(t-a)}\frac{G(V(t-a))}{V(t-a)}T(t-a)V(t-a)\sigma(a) \\ &\leq k_1k_2T(t-a)V(t-a)\sigma(a) \\ &\leq k\left\{\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}\right\}^2\sigma(a) \end{aligned}$$

for any solutions of system (2.1) with $X_0 \in \Omega$. Thus, we can easily check that (i), (ii) and (iv) in the proof of Lemma 2.3 hold.

We are in a position to show (iii). For sufficiently small $h \in (0,t)$, we have

$$\begin{aligned} &\int_0^\infty \left|\tilde{i}(a+h,t)-\tilde{i}(a,t)\right| da \\ =& \int_0^{t-h} |F(T(t-a-h))G(V(t-a-h))\sigma(a+h) \\ &-F(T(t-a))G(V(t-a))\sigma(a)|da + \int_{t-h}^t |F(T(t-a))G(V(t-a))\sigma(a)|da \\ \leq& \int_0^{t-h} F(T(t-a-h))G(V(t-a-h))|\sigma(a+h)-\sigma(a)|da \\ &+\int_0^{t-h} |F(T(t-a-h))G(V(t-a-h))-F(T(t-a))G(V(t-a))|\sigma(a)da \\ &+k\left\{\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}\right\}^2 h \\ \leq& k\left\{\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}\right\}^2 \int_0^{t-h}|\sigma(a+h)-\sigma(a)|da \\ &+\int_0^{t-h} |F(T(t-a-h))G(V(t-a-h))-F(T(t-a))G(V(t-a))|da \\ &+k\left\{\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}\right\}^2 h. \end{aligned} \tag{2.18}$$

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

$$\begin{aligned} \int_0^{t-h} |\sigma(a+h)-\sigma(a)|da &= \int_0^{t-h}\{\sigma(a)-\sigma(a+h)\}da \\ &= \int_0^h \sigma(a)da - \int_{t-h}^t \sigma(a)da \leq h. \end{aligned} \tag{2.19}$$

Moreover, from (iv) of Assumption 2.2, we have

$$\begin{aligned} &|F(T(t-a-h))G(V(t-a-h))-F(T(t-a))G(V(t-a))| \\ \leq\ & |F(T(t-a-h))-F(T(t-a))||G(V(t-a-h))| \\ &+|G(V(t-a-h))-G(V(t-a))||F(T(t-a))| \\ \leq\ & M_F|T(t-a-h)-T(t-a)|\left|\frac{G(V(t-a-h))}{V(t-a-h)}\right||V(t-a-h)| \\ &+M_G|V(t-a-h)-V(t-a)|\left|\frac{F(T(t-a))}{T(t-a)}\right||T(t-a)|. \end{aligned} \tag{2.20}$$

Now, the Lipschitz continuity of $T(\cdot)$ and $V(\cdot)$ on $\mathbb{R}_+$ is easily verified from (2.1) and the boundedness of the solution (Proposition 2.1). Thus, there exist some positive constants $M_T, M_V > 0$ such that

$$|T(x)-T(y)| \le M_T\,|x-y| \quad \text{and} \quad |V(x)-V(y)| \le M_V\,|x-y|.$$

Hence, we have from (2.20) that

$$\begin{aligned} & |F(T(t-a-h))G(V(t-a-h)) - F(T(t-a))G(V(t-a))| \\ \le\ & M_F M_T h k_2 \left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0} + M_G M_V h k_1 \left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0} \\ =\ & M_{TV} h, \end{aligned} \tag{2.21}$$

where $M_{TV} := (M_F M_T k_2 + M_G M_V k_1)(1+p^+/c)s/\delta_0$. Thus, from (2.18), (2.19) and (2.21), we obtain

$$\int_0^\infty \left|\tilde{i}(a+h,t)-\tilde{i}(a,t)\right| da \ \le\ \left[M_{TV} + 2k\left\{\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}\right\}^2\right] h.$$

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,

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

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

From Lemmas 2.1-2.3, we can apply [38, Proposition 3.13] to obtain the following proposition on the relative compactness of the orbit of system (2.1).

Proposition 2.2. *Let Φ and Ω be defined by (2.6) and (2.7), respectively. For $X_0 \in \Omega$, $\{\Phi(t,X_0) :\ t \ge 0\}$ has compact closure in $\mathscr{X}$.*

2.3. Global stability of the infection-free equilibrium

In this subsection, we prove the following theorem on the global stability of the infection-free equilibrium E^0 of system (2.1) when $\mathfrak{R}_0 \le 1$.

Theorem 2.1. *Let $\mathfrak{R}_0$ be defined by (2.13). The infection-free equilibrium E^0 of system (2.1) is globally asymptotically stable if $\mathfrak{R}_0 \le 1$.*

PROOF. Define

$$\alpha(a) \ =\ \int_a^\infty p(\varepsilon)e^{-\int_a^\varepsilon \delta(s)ds}d\varepsilon \ \left(= \int_a^{a_\dagger} p(\varepsilon)e^{-\int_a^\varepsilon \delta(s)ds}d\varepsilon\right). \tag{2.22}$$

Note from (iv) of Assumption 2.1 and (2.10) 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

$$\alpha'(a) = \delta(a)\alpha(a) - p(a). \tag{2.23}$$

We define a Lyapunov function

$$U_1(t) = \left(T(t) - \int_{T_0}^{T(t)} \frac{F(T_0)}{F(\eta)}d\eta\right) + \frac{1}{N}\int_0^{a_\dagger} \alpha(a)i(a,t)da + \frac{1}{N}V(t).$$

Calculating the derivative of $U_1(t)$ along the trajectories of system (2.1) gives

$$\begin{aligned}
\frac{dU_1(t)}{dt} &= \left(1-\frac{F(T_0)}{F(T(t))}\right)\frac{dT(t)}{dt}+\frac{1}{N}\int_0^{a_\dagger}\alpha(a)\frac{\partial i(a,t)}{\partial t}da+\frac{1}{N}\frac{dV(t)}{dt} \\
&= \left(1-\frac{F(T_0)}{F(T(t))}\right)(dT_0-dT(t)-F(T(t))G(V(t)) \\
&\quad -\frac{1}{N}\int_0^{a_\dagger}\alpha(a)\left(\frac{\partial i(a,t)}{\partial a}+\delta(a)i(a,t)\right)da+\frac{1}{N}\int_0^{a_\dagger}p(a)i(a,t)da-\frac{cV(t)}{N} \\
&= \frac{d}{F(T(t))}(F(T(t))-F(T_0))(T_0-T(t))-F(T(t))G(V(t))+F(T_0)G(V(t)) \\
&\quad -\frac{1}{N}\int_0^{a_\dagger}\alpha(a)di(a,t)-\frac{1}{N}\int_0^{a_\dagger}(\alpha(a)\delta(a)-p(a))i(a,t)da-\frac{cV(t)}{N} \\
&= \frac{d}{F(T(t))}(F(T(t)-F(T_0))(T_0-T(t))+F(T_0)G(V(t))-\frac{cV(t)}{N}.
\end{aligned}$$

Here,

$$(F(T(t))-F(T_0))(T_0-T(t))\le 0,$$

and the assumption (2.4) ensures that $G(V(t))\le \frac{\partial G(0)}{\partial V(t)}V(t)$ for all $V>0$. Hence, we have

$$\begin{aligned}
F(T_0)G(V)-\frac{cV(t)}{N} &\le \left(F(T_0)\frac{\partial G(0)}{\partial V(t)}-\frac{c}{N}\right)V(t) \\
&= \left(\frac{NF(T_0)}{c}\frac{\partial G(0)}{\partial V(t)}-1\right)\frac{cV(t)}{N}.
\end{aligned}$$

Then

$$\frac{dU_1(t)}{dt} \le \frac{d}{F(T(t))}(F(T(t))-F(T_0))(T_0-T(t))+(\mathfrak{R}_0-1)\frac{cV(t)}{N}.$$

Therefore, it follows from $\mathfrak{R}_0\le 1$ that $U_1'\le 0$ holds true. Similar to the arguments in Theorem 3.1 in [11], the largest invariant set of $\{\frac{dU_1(t)}{dt}=0\}$ is singleton $\{E^0\}$. Thus, by the invariance principle for relatively compact orbit $\{\Phi(t,X_0):\ t\ge 0\}$ (see [37, Theorem 4.2 of Chapter IV] and Proposition 2.2), the infection-free equilibrium is globally asymptotically stable when $\mathfrak{R}_0\le 1$.

2.4. Global stability of the infection equilibrium

In this subsection, we prove the global stability of the infection equilibrium E^* for $\mathfrak{R}_0>1$. For the proof, we will use a function g defined by

$$g(z)=z-1-\ln z,\ \ z\in R_+ \tag{2.24}$$

in a Lyapunov functional. In order to make $g\left(\frac{i(t,a)}{i^*(a)}\right)$ well-defined, 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 2.4. *For $T(t)$ of system (2.1), there exists a positive lower bound $\underline{T}>0$ such that*

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

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 first equation of system (2.1) that

$$\begin{aligned}\frac{dT(t)}{dt} &= s-\left\{d+\frac{F(T(t))}{T(t)}\frac{G(V(t))}{V(t)}V(t)\right\}T(t)\\ &\geq s-\left\{d+k\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}\right\}T(t).\end{aligned}$$

Hence, the variation of constants formula yields

$$\begin{aligned}T(t) &\geq \frac{s}{d+k\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}}\left(1-e^{-\left\{d+k\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}\right\}t}\right)+e^{-\left\{d+k\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}\right\}t}T_s\\ &\to \frac{s}{d+k\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}},\ \ as\ t\to\infty.\end{aligned}$$

This implies that $\liminf_{t\to+\infty}T(t)\geq \underline{T}>0$ with

$$\underline{T}:=\frac{s}{d+k\left(1+\frac{p^+}{c}\right)\frac{s}{\delta_0}}.$$

We next prove the following lemma.

Lemma 2.5. *Let $\mathfrak{R}_0$ be defined by (2.13). If $\mathfrak{R}_0>1$ and $V_s>0$, then there exists a positive constant $\varepsilon_0>0$ such that*

$$\limsup_{t\to\infty}V(t)\geq\varepsilon_0.$$

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

PROOF. Noticing from Assumption 2.2 that

$$\frac{\partial G(0)}{\partial V} = \lim_{h\to+0}\frac{G(h)-G(0)}{h} = \lim_{h\to+0}\frac{G(h)}{h}$$

and $G(V)/V$ is monotone decreasing, we see from $\mathfrak{R}_0=\frac{N}{c}F(T_0)\frac{\partial G(0)}{\partial V}>1$ that there exists a sufficiently small positive constant $\varepsilon_0>0$ such that

$$\frac{N}{c}F(T_0)\frac{1}{T_0}\frac{s}{d+k\varepsilon_0}\frac{G(\varepsilon_0)}{\varepsilon_0}>1. \tag{2.25}$$

Here note that $T_0=s/d$. For this ε_0, we shall show $\limsup_{t\to\infty}V(t)\geq\varepsilon_0$. On the contrary, we suppose that $\limsup_{t\to\infty}V(t)<\varepsilon_0$ and show a contradiction. In this case, there exists a sufficiently large $t_0\geq 0$ such that $V(t)<\varepsilon_0$ for all $t\geq t_0$. Then, it follows from the first equation of (2.1) that

$$\begin{aligned}\frac{dT(t)}{dt} &= s-\left\{d+\frac{F(T(t))}{T(t)}\frac{G(V(t))}{V(t)}V(t)\right\}T(t)\\ &\geq s-(d+k\varepsilon_0)T(t).\end{aligned}$$

Hence, from the variation of constants formula, we have

$$T(t)\geq\frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(t-t_0)}\right) \tag{2.26}$$

for all $t\geq t_0$. From (2.25) we see that there exists a sufficiently large $\tilde{t}_0\geq t_0$ such that

$$\frac{N}{c}\frac{F(T_0)}{T_0}\frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(\tilde{t}_0-t_0)}\right)\frac{G(\varepsilon_0)}{\varepsilon_0}>1. \tag{2.27}$$

For this $\tilde{t}_0$, we have

$$T(t) \geq \frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(\tilde{t}_0-t_0)}\right), \quad V(t) < \varepsilon_0, \quad \forall t \geq \tilde{t}_0 \tag{2.28}$$

since the right-hand side of (2.26) is monotone decreasing with respect to t. 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 (2.28), the solution passing through X_1 at time $t = 0$ satisfies

$$T(t) \geq \frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(\tilde{t}_0-t_0)}\right), \quad V(t) < \varepsilon_0, \quad \forall t \geq 0. \tag{2.29}$$

Now, integration of the third equation in (2.1) gives

$$V(t) \geq \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a) i(a,\tau) da d\tau$$

and hence, it follows from (2.5) and (2.29) that

$$\begin{aligned} V(t) &\geq \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a) F(T(\tau-a)) G(V(\tau-a)) \sigma(a) da d\tau \\ &= \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a) \frac{F(T(\tau-a))}{T(\tau-a)} \frac{G(V(\tau-a))}{V(\tau-a)} T(\tau-a) V(\tau-a) \sigma(a) da d\tau \\ &\geq \frac{F(T_0)}{T_0} \frac{G(\varepsilon_0)}{\varepsilon_0} \frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(\tilde{t}_0-t_0)}\right) \\ &\quad \times \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a) \sigma(a) V(\tau-a) da d\tau. \end{aligned} \tag{2.30}$$

Then, taking the Laplace transform of each side, we have

$$\begin{aligned} \hat{V}(\lambda) &\geq \frac{F(T_0)}{T_0} \frac{G(\varepsilon_0)}{\varepsilon_0} \frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(\tilde{t}_0-t_0)}\right) \\ &\quad \times \int_0^\infty e^{-\lambda t} \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a) \sigma(a) V(\tau-a) da d\tau dt. \end{aligned} \tag{2.31}$$

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

$$\begin{aligned} &\int_0^\infty e^{-\lambda t} \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a) \sigma(a) V(\tau-a) da d\tau dt \\ &= \int_0^\infty e^{-\lambda t} e^{-ct} dt \times \int_0^\infty e^{-\lambda t} \int_0^t p(a) \sigma(a) V(t-a) da dt \\ &= \frac{1}{\lambda+c} \int_0^\infty e^{-\lambda t} p(t) \sigma(t) dt \times \hat{V}(\lambda). \end{aligned} \tag{2.32}$$

Substituting (2.32) into (2.31) and dividing both sides by $\hat{V}(\lambda)$, we have

$$1 \geq \frac{F(T_0)}{T_0} \frac{G(\varepsilon_0)}{\varepsilon_0} \frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(\tilde{t}_0-t_0)}\right) \frac{1}{\lambda+c} \int_0^\infty e^{-\lambda t} p(t) \sigma(t) dt.$$

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

$$1 \geq \frac{N}{c} \frac{F(T_0)}{T_0} \frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(\tilde{t}_0-t_0)}\right) \frac{G(\varepsilon_0)}{\varepsilon_0},$$

which contradicts to (2.27). The proof is complete.

Next, under Lemma 2.5, we prove the following lemma on the lower bound of the limit infimum of $V(t)$.

Lemma 2.6. *Let $\mathfrak{R}_0$ be defined by (2.13). If $\mathfrak{R}_0 > 1$ and $V_s > 0$, then there exists a positive lower bound $\underline{V} > 0$ such that*

$$\liminf_{t\to\infty} V(t) \geq \underline{V}. \tag{2.33}$$

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

PROOF. Let us choose ε_0 as in Lemma 2.5. Then, $\limsup_{t\to\infty} V(t) \geq \varepsilon_0$ holds and hence, we only have the following two possibilities.

(i) There exists a positive constant $\tilde{t} > 0$ such that $V(t) \geq \varepsilon_0$ for all $t \geq \tilde{t}$;

(ii) Eventually $V(t)$ oscillates around ε_0.

Since (2.33) holds in (i), we only have to consider (ii). In this case, there exist two positive constants $t_1, t_2 > 0$ $(t_2 > t_1)$ such that

$$\begin{cases} V(t_1) \;=\; V(t_2) \;=\; \varepsilon_0; \\ V(t) \;\leq\; \varepsilon_0, \quad \forall t \in (t_1, t_2)\,. \end{cases} \tag{2.34}$$

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

$$V(t) > \varepsilon_0 e^{-cC_0}, \quad \forall t \in (t_1, t_2)\,, \tag{2.35}$$

then (2.33) holds with $\underline{V} = \varepsilon_0 e^{-cC_0}$. Therefore, in the remainder of this proof, we prove (2.35).

First we consider the case where $t_2 - t_1 \leq C_0$. Since we have from the third equation of (2.1) that

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

we can use the variation of constants formula and the first equation of (2.34) to obtain

$$\begin{aligned} V(t) \;&>\; V(t_1)e^{-c(t-t_1)} \\ &\geq\; \varepsilon_0 e^{-cC_0} \;=\; \underline{V}, \quad \forall t \in (t_1, t_2)\,. \end{aligned}$$

Hence (2.35) 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

$$V(t) > \underline{V}, \quad \forall t \in (t_1 + C_0, t_2)\,. \tag{2.36}$$

On the contrary, if it does not hold, then there exists a positive constant $\tilde{C}_0 \in (0, t_2 - t_1 - C_0)$ such that

$$\begin{cases} V(t) \;>\; \underline{V}, \quad \forall t \in \left(t_1 + C_0,\, t_1 + C_0 + \tilde{C}_0\right); \\ V(t_1 + C_0 + \tilde{C}_0) \;=\; \underline{V}. \end{cases} \tag{2.37}$$

Now, it follows from the second equation of (2.34) that

$$V(t) \leq \varepsilon_0, \quad \forall t \in \left[t_1, t_1 + C_0 + \tilde{C}_0\right] \tag{2.38}$$

and hence, from the first equation of (2.1) and Assumption 2.2 we have

$$\begin{aligned} \frac{dT(t)}{dt} \;&=\; s - \left\{ d + \frac{F(T(t))}{T(t)} \frac{G(V(t))}{V(t)} V(t) \right\} T(t) \\ &\geq\; s - (d + k\varepsilon_0)\, T(t), \quad \forall t \in \left[t_1, t_1 + C_0 + \tilde{C}_0\right]. \end{aligned}$$

Thus, by using the variation of constants formula, we obtain

$$T(t) \geq \frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)(t-t_1)}\right), \quad \forall t \in \left[t_1, t_1+C_0+\tilde{C}_0\right].$$

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

$$T(t) \geq \frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)\frac{C_0}{2}}\right), \quad \forall t \in \left[t_1+\frac{C_0}{2},\ t_1+C_0+\tilde{C}_0\right]. \tag{2.39}$$

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 (2.37)-(2.39), the solution passing through X_2 at time $t=0$ satisfies

$$\begin{cases} T(t) \geq \dfrac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)\frac{C_0}{2}}\right), \quad \forall t \in \left[0,\ \dfrac{C_0}{2}+\tilde{C}_0\right]; \\ V(t) \leq \varepsilon_0,\ V(t) > \underline{V}, \quad \forall t \in \left[0,\ \dfrac{C_0}{2}+\tilde{C}_0\right); \\ V\left(\dfrac{C_0}{2}+\tilde{C}_0\right) = \underline{V}. \end{cases} \tag{2.40}$$

Recalling that it follows from the first inequality of (2.30) that

$$V(t) \geq \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)F(T(\tau-a))G(V(\tau-a))\sigma(a)dad\tau,$$

we have from Assumption 2.2 and (2.40) that

$$\begin{aligned} \underline{V} &= V\left(\frac{C_0}{2}+\tilde{C}_0\right) \\ &\geq \int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{-c\left(\frac{C_0}{2}+\tilde{C}_0-\tau\right)} \\ &\quad \times \int_0^\tau p(a)\frac{F(T(\tau-a))}{T(\tau-a)}\frac{G(V(\tau-a))}{V(\tau-a)}T(\tau-a)V(\tau-a)\sigma(a)dad\tau \\ &\geq \int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{-c\left(\frac{C_0}{2}+\tilde{C}_0-\tau\right)} \int_0^\tau p(a)\frac{F(T_0)}{T_0}\frac{G(\varepsilon_0)}{\varepsilon_0}T(\tau-a)\underline{V}\sigma(a)dad\tau \\ &\geq \frac{F(T_0)}{T_0}\frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)\frac{C_0}{2}}\right)\frac{G(\varepsilon_0)}{\varepsilon_0}\underline{V} \\ &\quad \times \int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{-c\left(\frac{C_0}{2}+\tilde{C}_0-\tau\right)} \int_0^\tau p(a)\sigma(a)dad\tau. \end{aligned}$$

Dividing both sides of this inequality by $\underline{V}$, we obtain

$$\begin{aligned} 1 &\geq \frac{F(T_0)}{T_0}\frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)\frac{C_0}{2}}\right)\frac{G(\varepsilon_0)}{\varepsilon_0} \\ &\quad \times \frac{1}{c}\left\{\int_0^{\frac{C_0}{2}+\tilde{C}_0} p(a)\sigma(a)da - e^{-c\left(\frac{C_0}{2}+\tilde{C}_0\right)}\int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{c\tau}p(\tau)\sigma(\tau)d\tau\right\}. \end{aligned} \tag{2.41}$$

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, we see that the right-hand side of (2.41) converges to

$$\frac{N}{c}\frac{F(T_0)}{T_0}\frac{s}{d+k\varepsilon_0}\frac{G(\varepsilon_0)}{\varepsilon_0}$$

as $C_0 \to \infty$. From (2.25), we see that this value is greater than 1 and thus, for sufficiently large $C_0 > 0$,

$$\begin{aligned}&\frac{F(T_0)}{T_0}\frac{s}{d+k\varepsilon_0}\left(1-e^{-(d+k\varepsilon_0)\frac{C_0}{2}}\right)\frac{G(\varepsilon_0)}{\varepsilon_0}\underline{V}\\ &\times\frac{1}{c}\left\{\int_0^{\frac{C_0}{2}+\tilde{C}_0} p(a)\sigma(a)da - e^{-c\left(\frac{C_0}{2}+\tilde{C}_0\right)}\int_0^{\frac{C_0}{2}+\tilde{C}_0} e^{c\tau}p(\tau)\sigma(\tau)d\tau\right\} > 1 \end{aligned} \tag{2.42}$$

holds. In fact, since C_0 is an arbitrary large constant, we can assume without loss of generality that C_0 satisfies (2.42). However, this contradicts with (2.41). Therefore, there exists no $\tilde{C}_0 \in (0, t_2 - t_1 - C_0)$ satisfying (2.37) and thus, (2.36) holds. This completes the proof.

Now, from (2.5) and (2.12), we have for $t - a > 0$ that

$$\frac{i(a,t)}{i^*(a)} = \frac{F(T(t-a))G(V(t-a))}{F(T^*)G(V^*)}.$$

Hence, it follows from Lemmas 2.4 and 2.6 that for an arbitrary small constant $\varepsilon > 0$, there exists a positive constant $t_3 > 0$ such that

$$\frac{i(a,t)}{i^*(a)} = \frac{F(\underline{T}-\varepsilon)\,G(\underline{V}-\varepsilon)}{F(T^*)G(V^*)} > 0 \tag{2.43}$$

for any $t \geq \max(t_3, a)$. Therefore, in what follows, let $t_4 := \max(t_4, a_\dagger)$ and without loss of generality, we perform a time-shift of t_4 setting $X_3 := \Phi_3(t_4, X_0)$ as a new initial condition for system (2.1). Then, from (2.43), we see that the integral

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

is well-defined for all $t \geq 0$. Using this integral, we prove the following theorem.

Theorem 2.2. *Let $\mathfrak{R}_0$ be defined by (2.13). The infection equilibrium E^* of system (2.1) is globally asymptotically stable if $\mathfrak{R}_0 > 1$.*

PROOF. We define a Lyapunov function

$$\begin{aligned} U_2(t) \quad = \quad & T(t) - \int_{T^*}^{T(t)} \frac{F(T^*)}{F(\eta)}d\eta + \frac{1}{N}\left(V(t) - \int_{V^*}^{V(t)} \frac{G(V^*)}{G(\eta)}d\eta\right) \\ & + \frac{1}{N}\int_0^{a_\dagger} \alpha(a)i^*(a)g\left(\frac{i(a,t)}{i^*(a)}\right)da. \end{aligned}$$

It is easy to see that $U_2(t)$ has global minimum point at E^*, and this function satisfies

$$\begin{aligned}
\frac{dU_2(t)}{dt} &= \left(1-\frac{F(T^*)}{F(T(t))}\right)\frac{dT(t)}{dt}+\frac{1}{N}\left(1-\frac{G(V^*)}{G(V(t))}\right)\frac{dV(t)}{dt} \\
&\quad +\frac{1}{N}\int_0^{a_\dagger}\alpha(a)\left(1-\frac{i^*(a)}{i(a,t)}\right)\frac{\partial i(a,t)}{\partial t}da \\
&= \frac{d}{F(T(t))}(F(T(t))-F(T^*))(T^*-T)+F(T^*)G(V^*)-F(T(t))G(V(t)) \\
&\quad -F(T^*)G(V^*)\frac{F(T^*)}{F(T(t))}+F(T^*)G(V(t))+\frac{1}{N}\int_0^{a_\dagger}p(a)i(a,t)da-\frac{cV(t)}{N} \\
&\quad -\frac{1}{N}\frac{G(V^*)}{G(V(t))}\int_0^{a_\dagger}p(a)i(a,t)da+\frac{G(V^*)}{G(V(t))}\frac{V(t)F(T^*)G(V^*)}{V^*} \\
&\quad -\frac{1}{N}\int_0^{a_\dagger}\alpha(a)i^*(a)\left(1-\frac{i^*(a)}{i(a,t)}\right)\left(\frac{\partial i(a,t)}{\partial a}+\delta(a)i(a,t)\right)da.
\end{aligned} \tag{2.44}$$

It follows from the calculation in [11] that we can easily check that

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

Hence, using integration by parts yields

$$\begin{aligned}
\int_0^{a_\dagger}\alpha(a)\left(1-\frac{i^*(a)}{i(a,t)}\right)\frac{\partial i(a,t)}{\partial a}da &= \alpha(a)i^*(a)\left(\frac{i(a,t)}{i^*(a)}-1-\ln\frac{i(a,t)}{i^*(a)}\right)\Big|_{a=0}^{a=a_\dagger} \\
&\quad -\int_0^{a_\dagger}\left(\frac{i(a,t)}{i^*(a)}-1-\ln\frac{i(a,t)}{i^*(a)}\right)(\alpha'(a)i^*(a)+\alpha(a)i_a^*(a))da \\
&\quad +\int_0^{a_\dagger}\alpha(a)(\delta(a)i^*(a)-\delta(a)i(a,t))da.
\end{aligned} \tag{2.45}$$

We infer from

$$\begin{aligned}
\alpha(0) &= N, \quad \alpha(a_\dagger)=0, \\
i^*(0) &= F(T^*)G(V^*), \quad i(0,t)=F(T(t))G(V(t)), \\
i_a^*(a) &= -\delta(a)i^*(a),
\end{aligned}$$

and (2.23) that

$$\begin{aligned}
&\alpha(0)i^*(0)\left(\frac{i(0,t)}{i^*(0)}-1-\ln\frac{i(0,t)}{i^*(0)}\right)=NF(T^*)G(V^*)g\left(\frac{F(T(t))G(V(t))}{F(T^*)G(V^*)}\right), \\
&\alpha(a_\dagger)i^*(a_\dagger)\left(\frac{i(a_\dagger,t)}{i^*(a_\dagger)}-1-\ln\frac{i(a_\dagger,t)}{i^*(a_\dagger)}\right)=0,
\end{aligned}$$

and

$$\alpha'(a)i^*(a)+\alpha(a)i_a^*(a)=-p(a)i^*(a).$$

Hence, it follows that

$$\begin{aligned}
&\int_0^{a_\dagger}\alpha(a)\left(1-\frac{i^*(a)}{i(a,t)}\right)\left(\frac{\partial i(a,t)}{\partial a}+\delta(a)i(a,t)\right)da \\
&= -NF(T^*)G(V^*)g\left(\frac{F(T(t))G(V(t))}{F(T^*)G(V^*)}\right) \\
&\quad +\int_0^{a_\dagger}\left(\frac{i(a,t)}{i^*(a)}-1-\ln\frac{i(a,t)}{i^*(a)}\right)p(a)i^*(a)da.
\end{aligned} \tag{2.46}$$

Substituting (2.46) to (2.44) and rearranging the equation, we have

$$\begin{aligned}
\frac{dU_2(t)}{dt} &= \frac{d}{F(T(t))}(F(T(t))-F(T^*))(T^*-T) \\
&\quad +F(T^*)G(V^*)\left(1+\ln\frac{G(V^*)i(a,t)}{G(V(t))i^*(a)}-\frac{G(V^*)i(a,t)}{G(V(t))i^*(a)}\right) \\
&\quad +F(T^*)G(V^*)\left(1+\ln\frac{F(T^*)}{F(T(t))}-\frac{F(T^*)}{F(T(t))}\right) \\
&\quad +F(T^*)G(V^*)\left(\frac{G(V(t))}{G(V^*)}-\frac{V(t)}{V^*}+\frac{V(t)G(V^*)}{V^*G(V(t))}-1\right) \\
&= \frac{d}{F(T(t))}(F(T(t))-F(T^*))(T^*-T) \\
&\quad -F(T^*)G(V^*)g\left(\frac{G(V^*)i(a,t)}{G(V(t))i^*(a)}\right)-F(T^*)G(V^*)g\left(\frac{F(T^*)}{F(T(t))}\right) \\
&\quad +F(T^*)G(V^*)\left(\frac{G(V(t))}{G(V^*)}-1\right)\left(\frac{V(t)}{V^*}-\frac{G(V^*)}{G(V(t))}\right).
\end{aligned}$$

Here we used the fact $\int_0^{a_\dagger} p(a)i^*(a)da = NF(T^*)G(V^*)$. Hence, from the monotonousness of $F(T)$, and the concaveness of $G(V)$, we have

$$(T-T^*)(F(T)-F(T^*)) \le 0,$$
$$\left(\frac{G(V)}{G(V^*)}-1\right)\left(\frac{V}{V^*}-\frac{G(V^*)}{G(V)}\right) \le 0.$$

This shows that $U_2'(t) \le 0$ and the largest invariant subset of set $\{U_2' = 0\}$ is singleton E^*. Hence, from the invariance principle ([37, Theorem 4.2 of Chapter IV]), we conclude that the infection equilibrium E^* is globally asymptotically stable.

3. Special cases

In this section, as special cases for the age-infection model (2.1)-(2.2) with general nonlinear infection rate $F(T)G(V)$, we introduce two kinds of age-infection models with Holling type II functional response and Crowley-Martin functional response.

3.1. The age-infection model with Holling type II functional response

First, we consider the following model with Holling type II functional response:

$$\begin{cases}
\dfrac{dT(t)}{dt} = s - dT(t) - k\dfrac{T(t)}{1+\alpha T(t)}V(t), \\
\dfrac{\partial i(a,t)}{\partial t} + \dfrac{\partial i(a,t)}{\partial t} = -\delta(a)i(a,t), \\
\dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty p(a)i(a,t)da - cV(t),
\end{cases} \tag{3.1}$$

where $k, \alpha > 0$. The boundary condition is as follows:

$$i(0,t) = k\frac{T(t)}{1+\alpha T(t)}V(t). \tag{3.2}$$

The initial condition of system (1.2) is similar to that of system (2.1). The coefficients s, d, c, $\delta(a)$ and $p(a)$ are assumed to satisfy Assumption 2.1. Then, setting $F(x) = x/(1+\alpha x)$ and $V(x) = kx$, $x \in \mathbb{R}_+$ in the original system

(2.1)-(2.2), we can easily see that (3.1)-(3.2) is a special case of (2.1)-(2.2). In fact, it is obvious that such F and G satisfy Assumption 2.2 (i)-(iv).

The infection-free equilibrium of system (3.1) is similar to the previous one, $E_2^0 = (T_0, i_0(a), V_0)$, where $T_0 = s/d$, $i_0(a) = 0$, $V_0 = 0$. Following (2.13), we obtain the basic reproduction number of system (3.1) as

$$\mathfrak{R}_2 \;=\; \frac{N}{c}\frac{s/d}{1+\alpha s/d}k \;=\; \frac{Nsk}{cd+c\alpha s}. \tag{3.3}$$

Then, from Theorems 2.1 and 2.2, we obtain the following corollary:

Corollary 3.1. (i) *If $\mathfrak{R}_2 \le 1$, then the infection-free equilibrium E_2^0 of system (3.1) is globally asymptotically stable.*
(ii) *If $\mathfrak{R}_2 > 1$, then the infection equilibrium $E_2^* = (T^*, i^*(a), V^*)$ of system (3.1) is globally asymptotically stable.*

3.2. The age-infection model with Crowley-Martin functional response

Next, we consider the following model with Crowley-Martin functional response:

$$\begin{cases} \dfrac{dT(t)}{dt} = s - dT(t) - k\dfrac{T(t)}{1+\alpha T(t)}\dfrac{V(t)}{1+\beta V(t)}, \\ \dfrac{\partial i(a,t)}{\partial t} + \dfrac{\partial i(a,t)}{\partial t} = -\delta(a)i(a,t), \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty p(a)i(a,t)da - cV(t), \end{cases} \tag{3.4}$$

where $\beta > 0$ and the other coefficients are similar as in the above system (3.1). The boundary condition is

$$i(0,t) = k\frac{T(t)}{1+\alpha T(t)}\frac{V(t)}{1+\beta V(t)}. \tag{3.5}$$

Similar to the above case, it is easy to see that $F(x) = x/(1+\alpha x)$ and $V(x) = kx/(1+\beta x)$ satisfy Assumption 2.2 (i)-(iv) and therefore, system (3.4)-(3.5) is also a special case of the original system (2.1)-(2.2).

The infection-free equilibrium of system (3.4) is also similar to the previous one, $E_3^0 = (T_0, i_0(a), V_0)$, where $T_0 = s/d$, $i_0(a) = 0$, $V_0 = 0$. From (2.13), the basic reproduction number of system (3.4) is obtained by

$$\mathfrak{R}_3 \;=\; \frac{N}{c}\frac{s/d}{1+\alpha s/d}k \;=\; \frac{Nsk}{cd+c\alpha s},$$

which is equal to $\mathfrak{R}_2$. Then, from Theorems 2.1 and 2.2, we obtain the following corollary:

Corollary 3.2. (i) *If $\mathfrak{R}_3 \le 1$, then the infection-free equilibrium E_3^0 of system (3.4) is globally asymptotically stable.*
(ii) *If $\mathfrak{R}_3 > 1$, then the infection equilibrium $E_3^* = (T^*, i^*(a), V^*)$ of system (3.4) is globally asymptotically stable.*

4. Numerical simulation

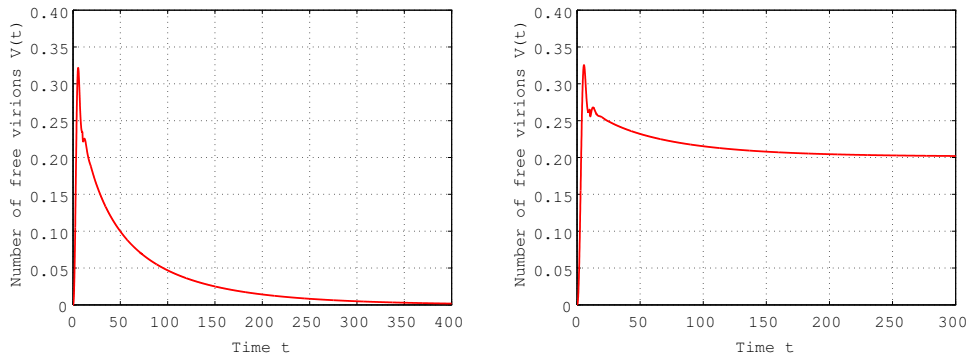
In this section, to verify the validity of the theoretical result of this paper, we perform numerical simulation. Specifically, we focus on the age-infection model with Crowley-Martin functional response (3.4)-(3.5) in Section 3.2.

Following [41] and references therein ([2–4, 19, 25, 29]), we fix the following coefficients:

$$s = 10,\;\; d = 0.09,\;\; k = 0.0025,\;\; c = 2.4.$$

Furthermore, we set the maximum age for the viral production as $a_\dagger = 10$ and

$$\delta(a) = 0.4\left(1+\sin\frac{(a-5)\pi}{10}\right),\;\; p(a) = 300\left(1+\sin\frac{(a-5)\pi}{10}\right),\;\; 0 \le a \le 10,$$



(a) For $\alpha = 0.8$ ($\mathfrak{R}_3 \simeq 0.9480 < 1$). (b) For $\alpha = 0.7$ ($\mathfrak{R}_3 \simeq 1.0817 > 1$).

Figure 1: The dynamical behavior of the number of free virions $V(t)$ of system (3.4)-(3.5). (a) From Corollary 3.2 (i), the infection-free equilibrium E_3^0 is globally asymptotically stable. (b) From Corollary 3.2 (ii), the infection equilibrium E_3^* is globally asymptotically stable.

so that each of the averages is equal to 0.4 and 300, respectively, which were used in [41]. Let $\beta = 0.4$ as in [41] and observe the dynamical behavior of solutions when α varies.

First, let $\alpha = 0.8$. Then, $\mathfrak{R}_3$ is approximately calculated as 0.9480 and less than 1. Therefore, from Corollary 3.2 (i), we can expect that the infection-free equilibrium E_3^0 is globally asymptotically stable. In fact, we can observe in Figure 1 (a) that the number of free virions $V(t)$ converges to $V_0 = 0$.

On the other hand, when $\alpha = 0.7$, the approximate value of $\mathfrak{R}_3$ is 1.0817 and greater than 1. Therefore, from Corollary 3.2 (ii) we can expect that the infection equilibrium E_3^* is globally asymptotically stable. In fact, in Figure 1 (b), the number of free virions $V(t)$ converges to the positive steady state V^*.

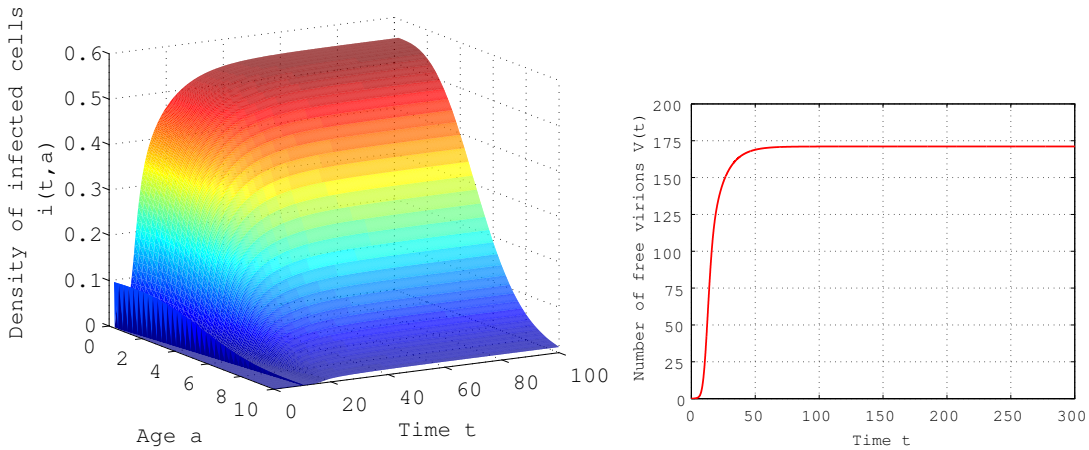
Finally, we set $\alpha = 0.0015$ as in [41]. In this case, $\mathfrak{R}_3$ is about 73.0402 and greater than 1. Therefore, from Corollary 3.2 (ii), we can expect that the infection equilibrium E_3^* is globally asymptotically stable. In fact, Figure 2 shows an example in which $i(t,a)$ and $V(t)$ converge to the positive steady states $i^*(a)$ and V^*, respectively.

5. Discussion

In this paper, we considered an age-infection model of HIV where the infection rate is given by nonlinear infection rate $F(T)G(V)$. As special examples of the model, we considered the age-infection models with Holling type II functional response and Crowley-Martin functional response (see Section 3). We have shown that the global stability of equilibria of these models are determined by the corresponding basic reproduction numbers. That is, we have shown that the infection-free equilibrium is globally asymptotically stable if the basic reproduction number is less than one, while an infection equilibrium is so if the basic reproduction number is greater than one. To prove these properties, we used the direct Lyapunov methods, which was recently developed by [11, 22–24] in epidemic and viral dynamics. It is should pointed here that $\alpha(a)$ is included to function type $\int_0^\infty \alpha(a) i^*(a) g\left(\frac{i(a,t)}{i^*(a)}\right) da$, which play the key role in estimating the derivative of Lyapunov function. It is expected to be useful and fundamental for the analysis of more complicated PDE systems. In Section 4, we have performed numerical simulation to show the validity of our theoretical result.

Finally, we remark that the results in the present paper can be applicable to the following model:

$$\begin{cases} \dfrac{dT(t)}{dt} = s - dT(t) - kT(t)V(t), \\ \dfrac{\partial y(a,t)}{\partial a} + \dfrac{\partial y(a,t)}{\partial t} = -(\delta(a)+d)y(a,t), \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty \gamma(a)\delta(a)y(a,t)da - cV(t), \end{cases} \tag{5.1}$$



(a) (b)

Figure 2: The dynamical behavior of (a) the age-distribution of infected cells $i(t,a)$ and (b) the number of free virions $V(t)$ for $\alpha = 0.0015$ ($\mathfrak{R}_3 \simeq 73.0402 > 1$).

with boundary condition

$$y(0,t) = kV(t)T(t),$$

where $\delta(a)$ denotes the additional death rate of infected cells due to infection at age a. The death of infected cells at age a results in the release of an average number $\gamma(a)$ of viral particles, so that susceptible cells infected by free viral particles then produce, at age a, viral particles with the rate $\gamma(a)\delta(a)$. In fact, by introducing the following function $i(a,t) = y(a,t)e^{\int_0^a \delta(l)dl}$, we can easily obtain that

$$\begin{aligned} \frac{\partial i(a,t)}{\partial t} + \frac{\partial i(a,t)}{\partial t} &= \left[\frac{\partial y(a,t)}{\partial t} + \frac{\partial y(a,t)}{\partial t} + \delta(a)\right] e^{\int_0^a \delta(l)dl} \\ &= -dy(a,t)e^{\int_0^a \delta(l)dl} = -di(a,t). \end{aligned}$$

Denote $p(a) = \gamma(a)\delta(a)e^{-\int_0^a \delta(l)dl}$, it follows that

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

Note that $i(0,t) = y(0,t)$, then system (5.1) rewrites as

$$\begin{cases} \dfrac{dT(t)}{dt} = s - dT(t) - kT(t)V(t), \\ \dfrac{\partial i(a,t)}{\partial a} + \dfrac{\partial i(a,t)}{\partial t} = -di(a,t), \\ \dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty p(a)i(a,t)da - cV(t), \end{cases} \tag{5.2}$$

with boundary condition

$$i(0,t) = kV(t)T(t),$$

supplemented together with initial condition

$$T(0) = T_s, \;\; i(.,0) = i_0(.) \in L^1(0,\infty;\mathbb{R}^n_+), \;\; V(0) = V_s$$

If we further assume $p(a) = p$ for a constant, then the model (5.2) will reduce to the model studied in [27, 28].

Acknowledgments

The authors would like to thank the editor and anonymous reviewer for their helpful comments and suggestions to improve the previous version of the manuscript.

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