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Analysis of an age structured HIV infection model with virus-to-cell infection and cell-to-cell transmission[☆]

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ABSTRACT

Recent studies reveal that cell-to-cell transmission via formation of virological synapses can contribute significantly to virus spread, and hence, may play a more important role than virus-to-cell infection in some situations. Age-structured models can be employed to study the variations w.r.t. infection age in modeling the death rate and virus production rate of infected cells. Considering the above characteristics for within-host dynamics of HIV, in this paper, we formulate an age-structured hybrid model to explore the effects of the two infection modes in viral production and spread. We offer a rigorous analysis for the model, including addressing the relative compactness and persistence of the solution semiflow, and existence of a global attractor. By subtle construction and estimates of Lyapunov functions, we show that the global attractor actually consists of an singleton, being either the infection free steady state if the basic reproduction number is less than one, or the infection steady state if the basic reproduction number is larger than one.

1. Introduction

Over the past decade, significant progress has been made in the mathematical modeling of HIV infection and antiretroviral therapy. It has been realized that mathematically modeling within-host virus dynamics may significantly contribute to the understanding of the effects of antiretroviral drugs treatment. Much of the work on this and related topics builds upon the pioneering work of Ho et al. [1] and Perelson et al. [2] where a three-dimensional system of ordinary differential equations (ODEs) was used to describe the inter-

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action of uninfected target cells, infected cells, and free virus particles. Since [1,2], there have been a lot of efforts in modifying/improving the model by incorporating various factors.

Nelson et al. [3] formulated a model for HIV infection in the form of initial–boundary-value problem, allowing death rate and virus production rate of infected cells to be infection-age-dependent, denoted by $\theta(a)$ and $p(a)$ respectively, the model reads

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = h - dT(t) - \beta_1 T(t)V(t), \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\right) i(a,t) = -\theta(a)i(a,t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \displaystyle\int_0^{\infty} p(a)i(a,t)\mathrm{d}a - cV(t), \\ i(0,t) = \beta_1 T(t)V(t), \\ T(0) = T_s, \qquad i(a,0) = i_s(a), \quad \text{and} \quad V(0) = V_s, \end{cases} \tag{1.1}$$

where $T(t)$ denotes the concentration of uninfected target T cells at time t, $i(a,t)$ denotes the concentration of infected T cells of infection age a at time t, and $V(t)$ denotes the concentration of infectious virus at t. The parameters of model (1.1) are explained as below: h is the constant recruitment rate, β_1 is the rate at which an uninfected cell becomes infected by an infectious virus, d is the natural death rate of uninfected cells, $\theta(a)$ is the infection-age-dependent per capita death rate of infected cells, c is the clearance rate of virions, and $p(a)$ is the viral production rate of an infected cell with infection age a. Mathematically, for a specific form of $p(a)$ and constant $\theta(a)$, Nelson et al. [3] analyzed the *local* stability of the model without or with drug treatment, respectively. They also performed some numerical simulations to illustrate that the time to reach the peak viral level depends not only on the initial conditions but also on the speed at which viral production achieves its maximum value. Subsequently, Rong et al. [4] and Feng and Rong [5] further modified this age-structured model by including three different classes of drugs to assess the effects of different combination of therapies on viral dynamics. They also extended the *local* stability analysis in [3] for general forms of both $p(a)$ and $\theta(a)$ by reformulating the system to a system of Volterra integral equations. However, the *global* behavior is left as an open problem in the above works. Actually, *global* stability is one of the challenging problems in the analysis of biological models and yet it is essential to rule out other dynamical scenarios such as periodic solutions. By constructing suitable Lyapunov functions, Huang et al. [6] were able to complete a global analysis for the model (1.1) without (or with) drug treatment. The age-structured model (1.1) was also used by Qesmi et al. [7] to study the dynamical behaviors of hepatitis B or C virus.

On the other hand, recent experimental work shows that direct cell-to-cell spread via formation of virological synapses can contribute significantly to virus spread in vivo [8]. In fact, the high efficiency of infection by large numbers of virions is likely to result in a transfer of multiple virions to a target cell [8]. The cell-to-cell infection mechanism through transfer of viral particles from infected cells to uninfected cells has also been investigated by some other researchers, among which are [9,10] and [11] from the virological view points. More specifically, in [9], Dimitrov et al. found that the infection rate constant is the critical parameter that affects the kinetics of HIV-1 infection, and furthermore, the infectivity of HIV-1 during cell-to-cell transmission is greater than the infectivity of cell-free viruses; in [10], Sigal et al. claimed that cell-to-cell spread of HIV-1 does reduce the efficacy of antiretroviral therapy, because cell-to-cell infection can cause multiple infections of target cells, which can in turn reduce the sensitivity to the antiretroviral drugs; in [11], Sattentau showed that Herpes simplex virus type-1 (HSV-1) can spread between a fibroblast and a T cell via a virological synapse while it can also move between fibroblasts by assembling and budding at basolateral intercellular junctions.

The above works suggest that the cell-to-cell transmission mechanism is significant. In response to these evidences, there have been some recent works by mathematical models quantitatively exploring the effect of the co-existence of the two modes on the virus dynamics. For example, [12–17] all used ordinary differential equation models to study the virus dynamics with the two modes. In particular, Pourbashash et al. [17] proposed a 3-dimensional ODE system with both virus-to-cell and cell-to-cell transmission modes incorporated, and by analyzing the system, showed that the model demonstrates a global threshold dynamics. Interestingly, the ODE model in [16] is similar to that in [17] with production function for healthy cells replaced by a logistic type function, yet, this model allows sustained oscillations (via Hopf bifurcation) around the positive equilibrium, strongly contrasting to the result in [17]. This difference shows the necessity of exploring the global dynamics of a dynamical system model.

With the two transmission modes and the infection age in mind, Lai and Zou [18] proposed and studied the following model in the form of distributed delay differential equations:

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} &= h - dT(t) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t), \\ \dfrac{\mathrm{d}T^*(t)}{\mathrm{d}t} &= \displaystyle\int_0^\infty [\beta_1 T(t-s)V(t-s) + \beta_2 T(t-s)T^*(t-s)]e^{-\mu s} f(s)\mathrm{d}s - \theta T^*(t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} &= bT^*(t) - cV(t). \end{cases} \tag{1.2}$$

Here β_2 is the infection rate of productively infected cells, $e^{-\mu s}$ is the survival probability for a time period of length s, $f(s) : [0,\infty) \to [0,\infty)$ accounts for the probability that a cell becomes productively infected s time units after infection which is assumed to have a compact support and satisfy $f(s) \geq 0$ and $\int_0^\infty f(s)ds = 1$, θ is the constant death rate for the productively infected cells. By a rigorous analysis of the model, the authors identified basic reproduction number explicitly, and proved that as in the ODE model in [17], the global threshold dynamics also remains true for this mode.

Note that (1.2) is a simplified way to consider infection age in the sense that the parameters β_1, β_2, θ and b are all *independent of the infection age*. However, the works in [3–5,7] show that infection age dependence plays an important role in virus dynamics. Inspired by the aforementioned works, in this paper we consider a model that captures the main features of the model (1.1) and the model (1.2): containing the two modes of infection and allowing age-dependent death rate and age-dependent production rate. Moreover, we also consider the variance in the infectivity with respect to the infection age of the infected cells in the cell-to-cell mode. These considerations naturally lead to the following model system

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = h - dT(t) - \beta_1 T(t)V(t) - \beta_2 T(t)\displaystyle\int_0^\infty q(a)i(a,t)\mathrm{d}a, \\ \left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\right) i(a,t) = -\theta(a)i(a,t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \displaystyle\int_0^\infty p(a)i(a,t)\mathrm{d}a - cV(t), \end{cases} \tag{1.3}$$

with the boundary and initial conditions

$$\begin{cases} i(0,t) = \beta_1 T(t)V(t) + \beta_2 T(t)\displaystyle\int_0^\infty q(a)i(a,t)\mathrm{d}a, \\ T(0) = x_0 > 0, \qquad i(a,0) = i_0(a) \in L^1_+(0,\infty), \qquad V(0) = V_0 > 0, \end{cases} \tag{1.4}$$

where $q(a)$ measure variance of the infectivity of infected cell with respect to the infection age a. Our goal is to investigate how the rate functions $p(a)$, $q(a)$ and $\theta(a)$ affect the global dynamics.

Note that (1.3)–(1.4) is a hybrid and infinite dimensional system, and hence, as expected, the analysis of this system is more challenging than that of (1.2) and the ODE models in [12–15,17]. Next, we will first state our main theorem for this model. To this end, we need the following preparation.

Integrating the second equation in (1.3) along the characteristic line $t-a=constant$ and making use of (1.4) yields

$$i(a,t)=\begin{cases} T(t-a)e^{-\int_0^a \theta(\omega)\mathrm{d}\omega}\left(\beta_1 V(t-a)+\beta_2\int_0^\infty q(v)i(v,t-a)\mathrm{d}v\right), & t>a;\\ i_0(a-t)e^{-\int_{a-t}^a \theta(\omega)\mathrm{d}\omega}, & t\le a.\end{cases} \tag{1.5}$$

Obviously, system (1.3) always has the infection-free equilibrium $E_0=(T_0,0,0)$, where $T_0=h/d$. An infection equilibrium $E^*=(T^*,i^*(a),V^*)$ of (1.3) is a positive solution to the following equations

$$\begin{cases} h-dT^*-\beta_1T^*V^*-\beta_2T^*\int_0^\infty q(a)i^*(a)\mathrm{d}a=0,\\ \frac{\mathrm{d}}{\mathrm{d}a}i^*(a)=-\theta(a)i^*(a),\\ \int_0^\infty p(a)i^*(a)\mathrm{d}a=cV^*,\\ i^*(0)=\beta_1T^*V^*+\beta_2T^*\int_0^\infty q(a)i^*(a)\mathrm{d}a.\end{cases} \tag{1.6}$$

To simplify expressions, we introduce the following notations:

$$K=\int_0^\infty q(a)e^{-\int_0^a\theta(\omega)\mathrm{d}\omega}\mathrm{d}a,\qquad Q=\int_0^\infty p(a)e^{-\int_0^a\theta(\omega)\mathrm{d}\omega}\mathrm{d}a. \tag{1.7}$$

Note that the term $e^{-\int_0^a\theta(\omega)\mathrm{d}\omega}$ is typically interpreted as the probability that an infected cell can survive to age a, and thus, Q accounts for the total number of virus particles produced by an infected cell during its life-span, i.e., the burst size.

After some simple calculations, we can solve (1.6) to obtain

$$T^*=\frac{T_0}{\Re_0}>0,\qquad i^*(a)=dT_0\left(1-\frac{1}{\Re_0}\right)e^{-\int_0^a\theta(\omega)\mathrm{d}\omega}\qquad V^*=\frac{1}{c}\int_0^\infty p(a)i^*(a)\mathrm{d}a, \tag{1.8}$$

where

$$\Re_0=\frac{\beta_1T_0Q}{c}+\beta_2T_0K, \tag{1.9}$$

is nothing but the basic reproduction number for the model (1.3). Biologically, β_1T_0Q/c accounts for the total number of newly infected cells resulted from a single viron through the virus-to-cell infection mode, which is the basic reproduction number for the corresponding model with virus-to-cell infection only. Similarly, β_2T_0K gives the total number of newly infected cells that arise from a single infected cell, which is the basic reproduction number for the corresponding model with cell-to-cell transmission only. It follows from (1.8) that (1.3) has a unique endemic equilibrium $E^*=(T^*,i^*(a),V^*)$ if and only if $\Re_0>1$.

Age-structured viral infection models have been of recent interest in the literature. Determining sharp threshold conditions for the global stability of equilibria of these models remains one of the *most challenging problems*. In the rest of this paper, we will tackle this problem for the model (1.3). It turns out that this model actually also demonstrates a global threshold dynamic in the sense of the following main theorem:

Theorem 1.1. *Consider system (1.3) with (1.4) and $\Re_0$ defined in (1.9).*

(a) *The infection-free equilibrium E_0 is globally asymptotically stable if $\Re_0\le 1$ while it is unstable if $\Re_0>1$.*
(b) *If $\Re_0>1$, the infection equilibrium E^* is globally asymptotically stable with respect to solutions with initial conditions $T_0>0$ and $i_0(a)>0$, $V_0>0$ bounded away from zero.*

To prove this main theorem, we need to do a lot of preparations, including addressing *the relative compactness* of the solution semiflow generated by System (1.3) and *the uniform persistence* under the condition $\Re_0 > 1$ for the solution semiflow. These are *two major challenges* in applying the main results in [19] to our model, because the model is an infinite dimensional hybrid system involving a time delay and a PDE, and as such, *they themselves constitute important mathematical problems*. To achieve our goal, we reformulate System (1.3) to a Volterra integral equation so that we can apply a functional-analytic approach. The existence of a global attractor is also obtained, as a result of the relative compactness. The persistence allows us to construct an appropriate Lyapunov function on the compact attractor to prove the global stability of E^* under $\Re_0 > 1$. The construction and estimate of the two Lyapunov functions require subtle choices of some kernel functions and inequality techniques. Our theoretical analysis makes use of the techniques laid out in [19].

We point out that introducing age structure into HIV models is a crucial point as this enables us to deal with realistic situations allowing for infection-age-dependent death rate and virus production rate of infected cells. Since the continuous age-structured model is described by first order PDEs, it is generally difficult to analyze the dynamics of such a model, particularly the global stability. As such, this work is of both mathematical and biological interest and importance. We will also discuss some biological implications of our main results in the conclusion section, Section 6.

2. Preliminary results

For mathematical tractability, we make the following assumption on parameters, which is thought to be biologically relevant.

Assumption 2.1. Consider system (1.3) with (1.4), we assume that:

(i) $h, d, \beta_1, \beta_2, c > 0$;
(ii) $q(a), \theta(a), p(a) \in L^\infty_+(0, \infty)$, with respective essential upper bounds $\bar{q}, \bar{\theta}, \bar{p}$, i.e.,

$$\bar{q} := \operatorname*{ess.sup}_{a\in[0,\infty)} q(a) < +\infty, \qquad \bar{\theta} := \operatorname*{ess.sup}_{a\in[0,\infty)} \theta(a) < +\infty, \qquad \bar{p} := \operatorname*{ess.sup}_{a\in[0,\infty)} p(a) < +\infty$$

(iii) $q(a), p(a)$ are Lipschitz continuous on $\mathbb{R}_+$ with Lipschitz coefficients M_q, M_p respectively;
(iv) For any $a > 0$, there exists a_q such that $q(a)$ are positive in a neighborhood of a_q;
(v) There exists $\mu_0 \in (0, d]$ such that $\theta(a) \geq \mu_0$ for all $a \geq 0$;
(vi) There exists a maximum age $a^+ > 0$ for the viral production such that $p(a) > 0$ for $a \in (0, a^+)$ and $p(a) = 0$ for $a > a^+$.

Let us define the phase space for system (1.3):

$$\mathcal{Y} = \mathbb{R}_{\geq 0} \times L^1(0, +\infty) \times \mathbb{R}_{\geq 0} \quad \text{and} \quad \mathcal{Y}^+ = \mathbb{R}_{>0} \times L^1_+(0, +\infty) \times \mathbb{R}_{>0},$$

where L^1_+ is the space of functions on $(0, \infty)$ that are non-negative and Lebesgue integrable, equipped with the norm

$$\|(x, \varphi, y)\|_{\mathcal{Y}} := |x| + \int_0^\infty |\varphi(a)| \mathrm{d}a + |y|.$$

The initial conditions in (1.4) for the system can be rewritten as $X_0 := (T_0, i_0(\cdot), V_0) \in \mathcal{Y}^+$.

2.1. Notations

Let

$$\Omega(a) = \mathrm{e}^{-\int_0^a \theta(\tau)\mathrm{d}\tau}. \tag{2.1}$$

It follows from (ii) and (v) of Assumption 2.1 that

$$0 \le \Omega(a) \le \mathrm{e}^{-\mu_0 a}, \quad a \ge 0, \tag{2.2}$$

and furthermore, $\Omega'(a) = -\theta(a)\Omega(a)$ holds for almost all $a \ge 0$.

For $t \ge 0$, let

$$P(t) = \int_0^\infty q(a)i(a,t)\mathrm{d}a, \qquad L(t) = \int_0^\infty p(a)i(a,t)\mathrm{d}a.$$

Thus (1.5) can be rewritten as

$$i(a,t) = \begin{cases} T(t-a)[\beta_1 V(t-a) + \beta_2 P(t-a)]\Omega(a), & 0 \le a \le t; \\ i_0(a-t)\dfrac{\Omega(a)}{\Omega(a-t)}, & 0 \le t \le a. \end{cases} \tag{2.3}$$

It is useful to note that

$$i(a,t) = i(0,t-a)\Omega(a) \quad \text{for } 0 \le a \le t, \tag{2.4}$$

and the boundary condition given in (1.4) can be rewritten as

$$i(0,t) = \beta_1 T(t)V(t) + \beta_2 T(t)P(t).$$

2.2. Volterra formulation

Substituting (2.4) into the T and V equations in (1.3) yields

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = h - dT(t) - \beta_1 T(t)V(t) - \beta_2 T(t)P(t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \displaystyle\int_0^t p(a)\Omega(a)T(t-a)(\beta_1 V(t-a) + \beta_2 P(t-a))\mathrm{d}a - cV(t) + F_1(t), \end{cases} \tag{2.5}$$

where

$$F_1(t) = \int_t^\infty p(a)i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)}\mathrm{d}a.$$

Clearly, $F_1(t) \to 0$ as $t \to \infty$. Integrating the T equation in (1.3) yields

$$\begin{aligned} T(t) &= x_0 e^{-\int_0^t (d+\beta_1 V(s)+\beta_2 P(s))\mathrm{d}s} + \int_0^t h e^{-\int_u^t (d+\beta_1 V(s)+\beta_2 P(s))\mathrm{d}s}\mathrm{d}u \\ &= \int_0^t h e^{-\int_u^t (d+\beta_1 V(s)+\beta_2 P(s))\mathrm{d}s}\mathrm{d}u + F_2(t), \\ &= \int_0^t h e^{-\int_0^{t-u} (d+\beta_1 V(s+u)+\beta_2 P(s+u))\mathrm{d}s}\mathrm{d}u + F_2(t), \end{aligned} \tag{2.6}$$

where $F_2(t) = x_0 e^{-\int_0^t (d+\beta_1 V(s)+\beta_2 P(s))\mathrm{d}s}$. Similarly, integrating the V equation in (1.3) yields

$$\begin{aligned} V(t) &= V_0 e^{-ct} + \int_0^t e^{-c(t-u)}\left[\int_0^u p(\tau)\Omega(\tau)T(u-\tau)(\beta_1 V(u-\tau) + \beta_2 P(u-\tau))\mathrm{d}\tau + F_1(u)\right]\mathrm{d}u \\ &= \int_0^t T(u)(\beta_1 V(u) + \beta_2 P(u))H_2(t-u)\mathrm{d}u + F_3(t), \end{aligned} \tag{2.7}$$

where

$$H_2(t) = e^{-ct}\int_0^t e^{c\tau}p(\tau)\Omega(\tau)\mathrm{d}\tau, \qquad F_3 = V_0 e^{-ct} + \int_0^t e^{-c(t-u)}F_1(u)\mathrm{d}u.$$

Eqs. (2.6) and (2.7) form a system of volterra integral equations that are equivalent to the original system (1.3).

Denote $Y(t) = (T(t), V(t))^T$ and $g(Y) = (1, \beta_1 TV + \beta_2 TP)^T \in C(\mathbb{R}^2, \mathbb{R}^2)$. Let $f(t) = (F_2(t), F_3(t))^T \in C([0,\infty), \mathbb{R}^2)$ and

$$\nabla(t) = \begin{pmatrix} he^{-\int_0^t (d+\beta_1 V(s+u)+\beta_2 P(s+u))\mathrm{d}s} & 0 \\ 0 & H_2(t) \end{pmatrix},$$

which belongs to $L^1_{\mathrm{loc}}([0,\infty); \mathbb{R}^{2\times 2})$. Obviously, Eqs. (2.6) and (2.7) can be rewritten as

$$Y(t) = \int_0^t \nabla(t-u) g(Y(u))\mathrm{d}u + f(t).$$

It follows from the standard results in Gripenberg et al. [20, Theorem 1.1] that a continuous solution exists on a maximal interval such that the solution goes to infinity if this maximal interval is finite. Moreover, similar to the proof in [21, Lemma 2.2], it is easy to check that $T(t)$ and $V(t)$ remain nonnegative for all positive initial data.

Next, we define a continuous semi-flow $\Phi : \mathbb{R}_+ \times \mathcal{Y} \to \mathcal{Y}$ generated by system (1.3) such that

$$\Phi(t, X_0) = \Phi_t(X_0) := (T(t), i(\cdot,t), V(t)), \quad t \geq 0,\ X_0 \in \mathcal{Y}. \tag{2.8}$$

Thus

$$\|\Phi_t(X_0)\|_{\mathcal{Y}} = \|\Phi(T(t), i(\cdot,t), V(t))\|_{\mathcal{Y}} = T(t) + \int_0^\infty i(a,t)\mathrm{d}a + V(t). \tag{2.9}$$

Let

$$\tilde{\mu}_0 = \frac{\mu_0}{1+\bar{p}/c} > 0$$

and define a subset in the state space for system (1.3) by

$$\Omega = \left\{ (T(t), i(\cdot,t), V(t)) \in \mathcal{Y}^+ :\ T(t) + \int_0^\infty i(a,t)\mathrm{d}a \leq \frac{h}{\mu_0},\ \|\Phi_t(X_0)\|_{\mathcal{Y}^+} \leq \frac{h}{\tilde{\mu}_0} \right\}. \tag{2.10}$$

The following proposition shows that Ω is positively invariant for (1.3).

Proposition 2.1. *Let Φ and Ω be defined by (2.8) and (2.10), respectively. Ω is positively invariant for Φ, that is,*

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

Moreover, Φ is point dissipative and Ω attracts all points in $\mathcal{Y}^+$.

Proof. First we have

$$\frac{\mathrm{d}}{\mathrm{d}t}\|\Phi_t(X_0)\|_{\mathcal{Y}} = \frac{\mathrm{d}T(t)}{\mathrm{d}t} + \frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty i(a,t)\mathrm{d}a + \frac{\mathrm{dV(t)}}{\mathrm{d}t}. \tag{2.11}$$

It follows from Eq. (2.3) that

$$\int_0^\infty i(a,t)\mathrm{d}a = \int_0^t T(t-a)(\beta_1 V(t-a) + \beta_2 P(t-a))\Omega(a)\mathrm{d}a + \int_t^\infty i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)}\mathrm{d}a.$$

Using substitution $a = t - \sigma$ in the first integral, and $a = t + \tau$ in the second integral, and differentiating with respect to t yield

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty i(a,t)\mathrm{d}a = \frac{\mathrm{d}}{\mathrm{d}t}\int_0^t T(\sigma)(\beta_1 V(\sigma) + \beta_2 P(\sigma))\Omega(t-\sigma)\mathrm{d}\sigma + \frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty i_0(\tau)\frac{\Omega(t+\tau)}{\Omega(\tau)}\mathrm{d}\tau$$

$$= T(t)(\beta_1 V(t) + \beta_2 P(t))\Omega(0) + \int_0^\infty i_0(\tau)\frac{\Omega'(t+\tau)}{\Omega(\tau)}\mathrm{d}\tau$$
$$+ \int_0^t T(\sigma)(\beta_1 V(\sigma) + \beta_2 P(\sigma))\Omega'(t-\sigma)\mathrm{d}\sigma.$$

Note that $\Omega(0) = 1$ and $\Omega'(a) = -\theta(a)\Omega(a)$, we have

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_0^\infty i(a,t)\mathrm{d}a = T(t)(\beta_1 V(t) + \beta_2 P(t)) - \int_0^\infty \theta(a) i(a,t)\mathrm{d}a. \tag{2.12}$$

Adding the first equation of (1.3) and (2.12), we have from (v) of Assumption 2.1 that

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(T(t) + \int_0^\infty i(a,t)\mathrm{d}a\right) = h - dT(t) - \int_0^\infty \theta(a) i(a,t)\mathrm{d}a$$
$$\le h - \mu_0\left(T(t) + \int_0^\infty i(a,t)\mathrm{d}a\right), \quad t \ge 0.$$

Making use of the integration factor $e^{-\mu_0 t}$, we obtain

$$T(t) + \int_0^\infty i(a,t)\mathrm{d}a \le \frac{h}{\mu_0} - e^{-\mu_0 t}\left\{\frac{h}{\mu_0} - \left(T(0) + \int_0^\infty i(a,0)\mathrm{d}a\right)\right\}, \quad t \ge 0. \tag{2.13}$$

This implies that for any solutions of (1.3) satisfying $X_0 \in \Omega$,

$$T(t) + \int_0^\infty i(a,t)\mathrm{d}a \le \frac{h}{\mu_0}, \quad t \ge 0. \tag{2.14}$$

Then, it follows from (2.14) and (ii) of Assumption 2.1 that

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} \le \bar{p}\int_0^\infty i(a,t)\mathrm{d}a - cV(t) \le \bar{p}\frac{h}{\mu_0} - cV(t).$$

This together with (v) of Assumption 2.1 implies

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} \le \frac{\bar{p}}{c}\frac{h}{\mu_0} - e^{-ct}\left\{\frac{\bar{p}}{c}\frac{h}{\mu_0} - V(0)\right\} \le \frac{\bar{p}}{c}\frac{h}{\mu_0} - e^{-\mu_0 t}\left\{\frac{\bar{p}}{c}\frac{h}{\mu_0} - V(0)\right\}. \tag{2.15}$$

Adding (2.13) and (2.15), we have

$$\|\Phi_t(X_0)\|_{\mathcal{Y}} \le \left(1 + \frac{\bar{p}}{c}\right)\frac{h}{\mu_0} - e^{-\mu_0 t}\left\{\left(1 + \frac{\bar{p}}{c}\right)\frac{h}{\mu_0} - \|(X_0)\|_{\mathcal{Y}}\right\}$$
$$= \frac{h}{\tilde{\mu}_0} - e^{-\mu_0 t}\left\{\frac{h}{\tilde{\mu}_0} - \|(X_0)\|_{\mathcal{Y}}\right\}, \quad t \ge 0. \tag{2.16}$$

From (2.14) and (2.15), it follows that for any solution of (1.3) satisfying $X_0 \in \Omega$, $\Phi_t(X_0) \in \Omega$ for all $t \ge 0$. This concludes the positive invariance of set Ω for semi-flow Φ.

Moreover, it follows from (2.13) and (2.15) that

$$\limsup_{t\to\infty}\{T(t) + \|i(\cdot,t)\|_{L^1}\} \le \frac{h}{\mu_0} \quad \text{and} \quad \limsup_{t\to\infty}\|\Phi_t(X_0)\|_{\mathcal{Y}} \le \frac{h}{\tilde{\mu}_0},$$

for any $X_0 \in \mathcal{Y}$. Therefore, Φ is point dissipative and Ω attracts all points in $\mathcal{Y}$. This completes the proof. □

By (v) of Assumption 2.1 and the proof of Proposition 2.1, we can actually have the following proposition.

Proposition 2.2. *For any $A \ge \frac{h}{\tilde{\mu}_0}$. If $X_0 \in \mathcal{Y}$ and $\|X_0\|_{\mathcal{Y}} \le A$, then the following statements hold true for all $t \ge 0$:*

(1) $T(t) \le A$, $\int_0^\infty i(a,t)\mathrm{d}a \le A$, *and* $V(t) \le A$;
(2) $P(t) \le \bar{q}A$ *and* $L(t) \le \bar{p}A$;
(3) $i(0,t) \le \bar{\beta}A^2$, *where* $\bar{\beta} = \beta_1 + \beta_2\bar{q}$.

As presented in (iii) of Assumption 2.1, functions $q(\cdot)$ and $p(\cdot)$ are assumed to be Lipschitz continuous. This allows the initial conditions for i to be taken in $L_+^1(0,\infty)$. Then, the functions $P(t)$ and $L(t)$, related to the boundary conditions $i(0,t)$, can be shown to be Lipschitz continuous.

Proposition 2.3. *The functions $P(t)$ and $L(t)$ are Lipschitz continuous on $\mathbb{R}_+$.*

Proof. Let $A \ge \max\{\frac{h}{\bar{\mu}_0}, \|X_0\|_{\mathcal{Y}}\}$. It follows from Proposition 2.1 that $\|\Phi_t(X_0)\|_{\mathcal{Y}} \le A$ for all $t \ge 0$.

Let $t \ge 0$ and $u > 0$. We can check that

$$\begin{aligned} P(t+u) - P(t) &= \int_0^\infty q(a)i(a,t+u)\mathrm{d}a - \int_0^\infty q(a)i(a,t)\mathrm{d}a \\ &= \int_0^u q(a)i(a,t+u)\mathrm{d}a + \int_u^\infty q(a)i(a,t+u)\mathrm{d}a - \int_0^\infty q(a)i(a,t)\mathrm{d}a \\ &= \int_0^u q(a)i(0,t+u-a)\Omega(a)\mathrm{d}a + \int_u^\infty q(a)i(a,t+u)\mathrm{d}a - \int_0^\infty q(a)i(a,t)\mathrm{d}a. \end{aligned} \tag{2.17}$$

By applying $q(a) \le \bar{q}$, $i(0,t+u-a) \le \bar{\beta}A^2$ and $\Omega(a) \le 1$ for the first integral, and making the substitution $\sigma = a - u$ for the second integral to (2.17), we get

$$P(t+u) - P(t) \le \bar{q}\bar{\beta}A^2 h + \int_0^\infty q(\sigma+u)i(\sigma+h,t+u)\mathrm{d}\sigma - \int_0^\infty q(a)i(a,t)\mathrm{d}a.$$

It follows from (2.3) that

$$i(\sigma+u,t+u) = i(\sigma,t)\frac{\Omega(\sigma+u)}{\Omega(\sigma)}.$$

Thus,

$$\begin{aligned} P(t+u) - P(t) &\le \bar{q}\bar{\beta}A^2 u + \int_0^\infty \left(q(a+u)\frac{\Omega(a+u)}{\Omega(a)} - q(a)\right) i(a,t)\mathrm{d}a \\ &= \bar{q}\bar{\beta}A^2 u + \int_0^\infty \left(q(a+u)e^{-\int_a^{a+u}\theta(\tau)\mathrm{d}\tau} - q(a)\right) i(a,t)\mathrm{d}a \\ &= \bar{q}\bar{\beta}A^2 u + \int_0^\infty q(a+u)\left(e^{-\int_a^{a+u}\theta(\tau)\mathrm{d}\tau} - 1\right) i(a,t)\mathrm{d}a \\ &\quad + \int_0^\infty (q(a+u) - q(a))i(a,t)\mathrm{d}a. \end{aligned} \tag{2.18}$$

From (ii) of Assumption 2.1, it is easy to check that $-\bar{\theta}u \le -\int_a^{a+u}\theta(\tau)\mathrm{d}\tau \le 0$. Note that $1 \ge e^{-\int_a^{a+u}\theta(\tau)\mathrm{d}\tau} \ge e^{-\bar{\theta}u} \ge 1 - \bar{\theta}u$. Therefore,

$$0 \le q(a+u)|e^{-\int_a^{a+u}\theta(\tau)\mathrm{d}\tau} - 1| \le \bar{q}\bar{\theta}u.$$

Recall that $\int_0^\infty i(a,t)\mathrm{d}a \le \|\Phi_t(X_0)\|_{\mathcal{Y}} \le A$. By the Lipschitz continuity of function $q(\cdot)$ on $\mathbb{R}_+$ with Lipschitz coefficients M_q (see (iii) of Assumption 2.1), we have $\int_0^\infty (q(a+u) - q(a))i(a,t)\mathrm{d}a \le M_q uA$. Combining the above inequalities, we obtain

$$P(t+u) - P(t) \le \bar{q}\bar{\beta}A^2 u + \bar{q}\bar{\theta}Au + M_q Au, \tag{2.19}$$

implying that $P(t)$ is Lipschitz continuous with coefficient $L_P = (\bar{q}\bar{\beta}A + \bar{q}\bar{\theta} + M_q)A$. The proof of Lipschitz continuity of $L(t)$ is similar to that of $P(t)$. Furthermore, $L(t)$ is Lipschitz continuous with coefficient $L_L = (\bar{p}\bar{\beta}A + \bar{p}\bar{\theta} + M_p)A$. The proof is completed. $\square$

The following proposition will be used in the next section, which comes from [22].

Proposition 2.4. *Let $D \subseteq \mathbb{R}$. For $j = 1, 2$, suppose $f_j : D \to \mathbb{R}$ is a bounded Lipschitz continuous function with bound K_j and Lipschitz coefficient M_j. Then the product function $f_1 f_2$ is Lipschitz with coefficient $K_1M_2 + K_2M_1$.*

3. Relative compactness of the orbit

The proof of the global stability of each equilibrium will reply on the Lyapunov function technique combined with the LaSalle invariance principle. Since the phase space is the infinite dimensional Banach space $\mathcal{Y}$, according to [23, Theorem 4.2 of Chapter IV], we first need to confirm the relative compactness of the orbit $\{\Phi(t, X_0) : t \geq 0\}$ in $\mathcal{Y}$ in order to make use of the invariance principle. To this end, we decompose $\Phi : \mathbb{R}_+ \times \mathcal{Y} \to \mathcal{Y}$ into the following two operators $\Theta, \Psi : \mathbb{R}_+ \times \mathcal{Y} \to \mathcal{Y}$:

$$\Theta\,(t, X_0) := (0, \tilde{\varphi}_i(\cdot, t), 0)\,, \tag{3.1}$$

$$\Psi\,(t, X_0) := \left(T(t), \tilde{i}(\cdot, t), V(t)\right), \tag{3.2}$$

where

$$\tilde{\varphi}_i\,(a, t) := \begin{cases} 0, & t > a \geq 0; \\ i\,(a, t)\,, & a \geq t \geq 0. \end{cases} \quad \text{and} \quad \tilde{i}\,(a, t) := \begin{cases} i\,(a, t)\,, & t > a \geq 0; \\ 0, & a \geq t \geq 0. \end{cases} \tag{3.3}$$

Then we have $\Phi\,(t, X_0) = \Theta\,(t, X_0) + \Psi\,(t, X_0)\,,\ \forall t \geq 0$. Note that $\tilde{i}(a, t)$ can be written as

$$\tilde{i}\,(a, t) := \begin{cases} (\beta_1 V(t-a) + \beta_2 P(t-a))T(t-a)\Omega(a), & t > a \geq 0; \\ 0, & a \geq t \geq 0. \end{cases} \tag{3.4}$$

Following the line of [24, Proposition 3.13], we are now in the position to state and prove the following main Theorem of this section.

Theorem 3.1. *Let Φ, Ω, Θ and Ψ be defined by (2.8), (2.10), (3.1) and (3.2), respectively. Then for any $X_0 \in \Omega$, $\{\Phi\,(t, X_0) : t \geq 0\}$ has compact closure in $\mathcal{Y}$ if the following two conditions hold:*

(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 $\|X_0\|_{\mathcal{Y}} \leq r$, then $\|\Theta\,(t, X_0)\|_{\mathcal{Y}} \leq \Delta\,(t, r)$ for $t \geq 0$;*
(ii) *For $t \geq 0$, $\Psi\,(t, \cdot)$ maps any bounded sets of Ω into sets with compact closure in $\mathcal{Y}$.*

To give the proof of Theorem 3.1, we turn to prove the following two lemmas.

Lemma 3.1. *Let Ω and Θ be defined by (2.10) and (3.1), respectively. For $r > 0$, let $\Delta\,(t, r) := e^{-\mu_0 t} r$. Then, $\lim_{t\to\infty} \Delta\,(t, r) = 0$ and for $t \geq 0$, $\|\Theta\,(t, X_0)\|_{\mathcal{Y}} \leq \Delta\,(t, r)$ provided $X_0 \in \Omega$ with $\|X_0\|_{\mathcal{Y}} \leq r$.*

Proof. It is obvious that $\lim_{t\to\infty} \Delta\,(t, r) = 0$. It follows from (2.3) that

$$\tilde{\varphi}_i(a, t) = \begin{cases} 0, & t > a \geq 0; \\ i_0(a-t)\dfrac{\Omega(a)}{\Omega(a-t)}, & a \geq t \geq 0. \end{cases}$$

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

$$\begin{aligned}\|\Theta(t, X_0)\|_{\mathcal{Y}} &= |0| + \int_0^\infty |\tilde{\varphi}_i(a,t)|\,\mathrm{d}a + |0| \\ &= \int_t^\infty \left| i_0(a-t)\frac{\Omega(a)}{\Omega(a-t)} \right| \mathrm{d}a \\ &= \int_0^\infty \left| i_0(\sigma)\frac{\Omega(\sigma+t)}{\Omega(\sigma)} \right| \mathrm{d}\sigma \\ &= \int_0^\infty \left| i_0(\sigma) e^{-\int_\sigma^{\sigma+t}\theta(\tau)\mathrm{d}\tau} \right| \mathrm{d}\sigma \\ &\le e^{-\mu_0 t}\int_0^\infty |i_0(\sigma)|\,\mathrm{d}\sigma \\ &\le e^{-\mu_0 t}\|X_0\|_{\mathcal{Y}} \le e^{-\mu_0 t} r = \Delta(t,r), \quad t \ge 0\end{aligned}$$

which completes the proof. □

We next prove the following lemma, which is based on Theorem B.2 from [19].

Lemma 3.2. *Let Ω and Ψ be defined by (2.10) and (3.2), respectively. Then, for $t \ge 0$, $\Psi(t,\cdot)$ maps any bounded set of Ω into a set with compact closure in $\mathcal{Y}$.*

Proof. From Proposition 2.1, it is easily seen that $T(t)$ and $V(t)$ remain in the compact set $[0, h/\tilde{\mu}_0] \subset [0, A]$. Thus, we only have to show that $\tilde{i}(a,t)$ remain 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) $\lim_{u\to\infty}\int_u^\infty \tilde{i}(a,t)\,da = 0$ uniformly with respect to $X_0 \in \Omega$;
(iii) $\lim_{u\to 0^+}\int_0^\infty \left|\tilde{i}(a+u,t) - \tilde{i}(a,t)\right| da = 0$ uniformly with respect to $X_0 \in \Omega$;
(iv) $\lim_{u\to 0^+}\int_0^u \tilde{i}(a,t)\,da = 0$ uniformly with respect to $X_0 \in \Omega$.

Let $A \ge a/\tilde{\mu}_0$. Combining (2.2), (2.3), and (3.4) with Proposition 2.2, we have

$$\tilde{i}(a,t) \le (\beta_1 + \beta_2\bar{q})A^2 e^{-\mu_0 a}, \tag{3.5}$$

from which the aforementioned conditions (i), (ii) and (iv) follow.

Next, we verify condition (iii). For sufficiently small $u \in (0,t)$, we have

$$\begin{aligned}&\int_0^\infty \left|\tilde{i}(a+u,t) - \tilde{i}(a,t)\right| \mathrm{d}a \\ &= \int_0^{t-u} |(\beta_1 T(t-a-u)V(t-a-u) + \beta_2 T(t-a-u)P(t-a-u))\Omega(a+u) \\ &\quad - (\beta_1 T(t-a)V(t-a) + \beta_2 T(t-a)P(t-a))\Omega(a)|\,\mathrm{d}a \\ &\quad + \int_{t-u}^t |0 - (\beta_1 T(t-a)V(t-a) + \beta_2 T(t-a)P(t-a))\Omega(a)|\mathrm{d}a \\ &\le \int_0^{t-u} \big|(\beta_1 T(t-a-u)V(t-a-u) + \beta_2 T(t-a-u)P(t-a-u))\Omega(a+u) \\ &\quad - (\beta_1 T(t-a)V(t-a) + \beta_2 T(t-a)P(t-a))\Omega(a)\big|\mathrm{d}a + \bar{\beta}A^2 u \\ &\le \bar{\beta}A^2 u + \Delta + \Xi,\end{aligned} \tag{3.6}$$

where

$$\varDelta = \int_0^{t-u} (\beta_1 T(t-a-u)V(t-a-u) + \beta_2 T(t-a-u)P(t-a-u))|\varOmega(a+u) - \varOmega(a)|\mathrm{d}a$$

and

$$\begin{aligned}\varXi &= \int_0^{t-u} |(\beta_1 T(t-a-u)V(t-a-u) + \beta_2 T(t-a-u)P(t-a-u)) \\ &\quad - (\beta_1 T(t-a)V(t-a) + \beta_2 T(t-a)P(t-a))|\varOmega(a)\mathrm{d}a \\ &\le \int_0^{t-u} |\beta_1 T(t-a-u)V(t-a-u) - \beta_1 T(t-a)V(t-a)|\varOmega(a)\mathrm{d}a \\ &\quad + \int_0^{t-u} |\beta_2 T(t-a-u)P(t-a-u) - \beta_2 T(t-a)P(t-a)|\varOmega(a)\mathrm{d}a := \varXi_1.\end{aligned}$$

Noting that $0 \le \varOmega(a) = \mathrm{e}^{-\int_0^a \theta(\tau)\mathrm{d}\tau} \le \mathrm{e}^{-\mu_0 a}$, and $\varOmega(a)$ is non-increasing function with respect to a, we have

$$\begin{aligned}\int_0^{t-a} |\varOmega(a+u) - \varOmega(a)|\mathrm{d}a &= \int_0^{t-u} (\varOmega(a) - \varOmega(a+u))\mathrm{d}a \\ &= \int_0^{t-u} \varOmega(a)\mathrm{d}a - \int_0^{t-u} \varOmega(a+u)\mathrm{d}a \\ &= \int_0^{t-u} \varOmega(a)\mathrm{d}a - \int_u^{t} \varOmega(a)\mathrm{d}a \\ &= \int_0^{t-u} \varOmega(a)\mathrm{d}a - \int_u^{t-u} \varOmega(a)\mathrm{d}a - \int_{t-u}^{t} \varOmega(a)\mathrm{d}a \\ &= \int_0^{u} \varOmega(a)\mathrm{d}a - \int_{t-u}^{t} \varOmega(a)\mathrm{d}a \le u.\end{aligned}$$

Hence, combining the above with (3.6) yields

$$\int_0^{\infty} \left|\tilde{i}(a+u,t) - \tilde{i}(a,t)\right| \mathrm{d}a \le 2\bar{\beta}A^2 u + \varXi_1.$$

For $\varXi_1$, combining Proposition 2.2 with the expression for $\frac{\mathrm{d}T(t)}{\mathrm{d}t}$, we find that $|\frac{\mathrm{d}T(t)}{\mathrm{d}t}|$ is bounded by $M_T = u + dA + \beta_1 A^2 + \beta_2 \bar{q} A^2$, and therefore $T(\cdot)$ is Lipschitz on $[0,\infty)$ with coefficient M_T. By Proposition 2.4, there exist two Lipschitz coefficients M_V, M_P for V, P respectively. Thus, $T(\cdot)V(\cdot)$ and $T(\cdot)P(\cdot)$ are Lipschitz on $[0,\infty)$ with coefficient $M_{TV} = AM_V + AM_T$ and $M_{TP} = AM_P + \bar{q}AM_T$. Setting $M = \beta_1 M_{TV} + \beta_2 M_{TP}$, we then have

$$\varXi_1 \le Mu \int_0^{t-u} e^{-\mu_0 a}\mathrm{d}a \le \frac{Mu}{\mu_0}.$$

Finally, we get

$$\int_0^{\infty} |\tilde{i}(a+u,t) - \tilde{i}(a,t)|\mathrm{d}a \le \left(2\bar{\beta}A^2 + \frac{M}{\mu_0}\right) u,$$

which converges to 0 as $u \to 0^+$. Let $Y_0 \subset \mathcal{Y}$ be a bounded closed set and $A > h/\mu_0$ be a bound for Y_0. We note that M depends on A, which depends on the set Y_0, but not on X_0. Therefore, the above inequality holds for any $X_0 \in Y_0$. This implies that $\tilde{i}$ remains in a pre-compact subset C_i of L^1_+. Thus, $\varPsi(t, Y_0) \subseteq [0, A] \times C_i \times [0, A]$, which has compact closure in $\mathcal{Y}$. This completes the proof. □

Combining Proposition 2.1, Lemmas 3.1 and 3.2 with the theory of global attractors in Hale [25] and Smith and Thieme [19], we obtain the following theorem for the semi-flow $\{\varPhi(t)\}_{t\ge 0}$.

Theorem 3.2. *The semi-flow $\{\Phi(t)\}_{t\geq 0}$ has a global attractor $\mathcal{A}$ in $\mathcal{Y}$, which attracts all bound subsets of $\mathcal{Y}$.*

4. Uniform persistence

In this section we prove the uniform persistence of system (1.3) under $\Re_0 > 1$. To this end, we let $\hat{i}(t) := i(0,t)$ and rewrite (1.5) as

$$i(a,t) = \begin{cases} \hat{i}(t-a)\Omega(a), & t \geq a \geq 0; \\ i_0(a-t)\dfrac{\Omega(a)}{\Omega(a-t)}, & a \geq t \geq 0, \end{cases} \tag{4.1}$$

where $\Omega(a)$ is defined by (2.1).

Substituting (4.1) into the boundary condition in (1.4), we obtain the following system of integral equations of $\hat{i}(t)$:

$$\hat{i}(t) = \beta_1 T(t)V(t) + \beta_2 T(t)\left\{\int_0^t q(a)\Omega(a)\hat{i}(t-a)\mathrm{d}a + \int_t^\infty q(a)\frac{\Omega(a)}{\Omega(a-t)}i_0(a-t)\mathrm{d}a\right\}. \tag{4.2}$$

In addition, note that the first equation of (1.3) can be rewritten as

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = h - dT(t) - \hat{i}(t). \tag{4.3}$$

So we have the following result on the weak persistence of $\hat{i}(t)$.

Lemma 4.1. *If $\Re_0 > 1$, then there exists a positive constant $\epsilon_0 > 0$ such that*

$$\limsup_{t\to\infty} \hat{i}(t) > \epsilon_0. \tag{4.4}$$

Proof. By (4.2) and the positivity of coefficients, we obtain

$$\hat{i}(t) \geq \beta_1 T(t)V(t) + \beta_2 T(t)\int_0^t q(a)\Omega(a)\hat{i}(t-a)\mathrm{d}a. \tag{4.5}$$

From the third equation of (1.3), we have

$$V(t) \geq \int_0^t e^{-c(t-\tau)}\int_0^\tau p(a)i(a,\tau)\mathrm{d}a\mathrm{d}\tau = \int_0^t e^{-c(t-\tau)}\int_0^\tau p(a)\Omega(a)\hat{i}(\tau-a)\mathrm{d}a\mathrm{d}\tau. \tag{4.6}$$

Combining (4.5) and (4.6), we obtain the following integral inequality for $\hat{i}(t)$:

$$\hat{i}(t) \geq \beta_1 T(t)\int_0^t e^{-c(t-\tau)}\int_0^\tau p(a)\Omega(a)\hat{i}(\tau-a)\mathrm{d}a\mathrm{d}\tau + \beta_2 T(t)\int_0^t q(a)\Omega(a)\hat{i}(t-a)\mathrm{d}a. \tag{4.7}$$

In what follows, we prove that for the solution $\hat{i}(t)$ satisfying (4.7), there exists a positive constant $\epsilon_0 > 0$ such that (4.4) holds.

Since $\Re_0 > 1$, by (1.7)–(1.9) and (2.1), for sufficiently small $\epsilon_0 \in (0,h)$, there holds

$$\frac{\beta_1}{c}\frac{h-\epsilon_0}{d}\int_0^\infty p(a)\Omega(a)\mathrm{d}a + \beta_2\frac{h-\epsilon_0}{d}\int_0^\infty q(a)\Omega(a)\mathrm{d}a > 1. \tag{4.8}$$

For such an ϵ_0, we show that (4.4) holds. For the sake of contradiction, assume that there exists a sufficiently large constant $T > 0$ such that $\hat{i}(t) \leq \epsilon_0$ for all $t \geq T$. Then, it follows from (4.3) that

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} \geq h - dT(t) - \epsilon_0 \quad \text{for all } t \geq T,$$

implying that $\liminf_{t\to\infty} T(t) \geq \frac{h-\epsilon_0}{d}$. Thus, for any $\epsilon_1 > 0$, there exists $T_1 > 0$ such that $T(t) \geq \frac{h-\epsilon_0-\epsilon_1}{d}$ for all $t \geq T_1$. It follows from (4.7) that

$$\begin{aligned} \hat{i}(t) &\geq \beta_1 \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)\Omega(a)\hat{i}(\tau-a)\mathrm{d}a\mathrm{d}\tau \\ &\quad + \beta_2 \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^t q(a)\Omega(a)\hat{i}(t-a)\mathrm{d}a, \quad \text{for } t \geq T_1. \end{aligned} \tag{4.9}$$

Note that one can always perform a time-shift to system (1.3) with respect to T_1, that is, replacing the initial condition for system (1.3) by $X_1 := \Phi(T, X_0) \in \mathcal{Y}^+$, and we are interested in the long time behavior of the system. Thus, without loss of generality, we can assume that (4.9) holds for all $t \geq 0$. Taking the Laplace transforms in both sides of (4.9) and making use of the convolution theorem, we then obtain

$$\begin{aligned} \mathcal{L}[\hat{i}] &\geq \beta_1 \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^{+\infty} e^{-\lambda t} \int_0^t e^{-c(t-\tau)} \int_0^\tau p(a)\Omega(a)\hat{i}(\tau-a)\mathrm{d}a\mathrm{d}\tau\mathrm{d}t \\ &\quad + \beta_2 \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^\infty q(a)\Omega(a)e^{-\lambda a}\mathrm{d}a\ \mathcal{L}[\hat{i}], \\ &= \beta_1 \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^{+\infty} e^{-\lambda t}e^{-ct}\mathrm{d}t \times \int_0^{+\infty} e^{-\lambda t} \int_0^t p(a)\Omega(a)\hat{i}(t-a)\mathrm{d}a\mathrm{d}t \\ &\quad + \beta_2 \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^\infty q(a)\Omega(a)e^{-\lambda a}\mathrm{d}a\ \mathcal{L}[\hat{i}], \\ &= \beta_1 \frac{h-\epsilon_0-\epsilon_1}{d} \frac{1}{c+\lambda} \int_0^{+\infty} e^{-\lambda t}p(a)\Omega(a)\mathrm{d}a\ \mathcal{L}[\hat{i}] + \beta_2 \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^\infty q(a)\Omega(a)e^{-\lambda a}\mathrm{d}a\ \mathcal{L}[\hat{i}], \end{aligned}$$

where $\mathcal{L}[\hat{i}]$ denotes the Laplace transform of $\hat{i}$, which is strictly positive because of (4.2) and Assumption 2.1. Dividing both sides by $\mathcal{L}[\hat{i}]$ and letting $\lambda \to 0$, we obtain

$$1 \geq \frac{\beta_1}{c} \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^\infty p(a)\Omega(a)\mathrm{d}a + \beta_2 \frac{h-\epsilon_0-\epsilon_1}{d} \int_0^\infty q(a)\Omega(a)\mathrm{d}a. \tag{4.10}$$

Since $\epsilon_1 > 0$ is arbitrary, letting $\epsilon_1 \to 0^+$, we then obtain

$$1 \geq \frac{\beta_1}{c} \frac{h-\epsilon_0}{d} \int_0^\infty p(a)\Omega(a)\mathrm{d}a + \beta_2 \frac{h-\epsilon_0}{d} \int_0^\infty q(a)\Omega(a)\mathrm{d}a, \tag{4.11}$$

which contradicts (4.8). This completes the proof. $\square$

Next, in order to apply the technique used in Smith and Thieme [19, Chapter 9] (see also McCluskey [22, Section 8]), we consider total Φ-trajectories of system (1.3) in space $\mathcal{Y}$, where Φ is a continuous semi-flow defined by (2.8). Let $\phi : \mathbb{R} \to \mathcal{Y}$ be a total Φ-trajectory such that $\phi(r) := (T(r), i(\cdot, r), V(r))$, $r \in \mathbb{R}$. Then, it follows that $\phi(r+t) = \Phi(t, \phi(r))$, $t \geq 0$, $r \in \mathbb{R}$ and

$$i(a, r) = i\,(0, r-a)\,\Omega(a) = \hat{i}(r-a)\Omega(a), \quad r \in \mathbb{R},\ a \geq 0.$$

Hence, from (4.2)–(4.3), we have

$$\begin{cases} \dfrac{\mathrm{d}T(r)}{\mathrm{d}r} &= h - dT(r) - \hat{i}(r), \\ \hat{i}(r) &= \beta_1 T(r)V(r) + \beta_2 T(r) \displaystyle\int_0^\infty q(a)\Omega(a)\hat{i}(r-a)\mathrm{d}a, \quad r \in \mathbb{R}. \\ \dfrac{\mathrm{d}V(r)}{\mathrm{d}r} &= \displaystyle\int_0^\infty p(a)\Omega(a)\hat{i}(r-a)\mathrm{d}a - cV(r). \end{cases} \tag{4.12}$$

From the above, we can establish the following lemma.

Lemma 4.2. *Let ϕ be a total Φ-trajectory in $\mathcal{Y}$. Then* (I) *$T(r)$ is strictly positive on $\mathbb{R}$, and* (II) *$\hat{\imath}(r) = 0$ for all $r \geq 0$ if $\hat{\imath}(r) = 0$ for all $r \leq 0$.*

Proof. We first prove that $T(r)$ is strictly positive on $\mathbb{R}$. By way of contradiction, suppose (i) is not true. Then, there exists a number $r^* \in \mathbb{R}$ such that $T(r^*) = 0$. By (4.12), we then have $T'(r^*) = h > 0$. Thus, for sufficiently small $\eta > 0$, $T(r^* - \eta) < 0$. This contradicts to the fact that the total Φ-trajectory ϕ remains in $\mathcal{Y}$. Thus, $T(r)$ must be strictly positive on $\mathbb{R}$, proving (I).

To prove (II), assume that $\hat{\imath}(r) = 0$ for all $r \leq 0$. Then, by the positivity of $T(r)$ and the second equation in (4.12), we know that $V(r) = 0$ for $r \leq 0$. This together with the third equation in (4.12) further implies that $V(r) = 0$ for all $r \in \mathbb{R}$, and accordingly, reduces the second equation to

$$\hat{\imath}(r) = \beta_2 T(r) \int_{-\infty}^{r} q(r-a)\Omega(r-a)\hat{\imath}(a)\mathrm{d}a, \quad r \in \mathbb{R}.$$

By this integral equation and the condition that $\hat{\imath}(r) = 0$ for all $r \leq 0$, we then conclude that we actually have $\hat{\imath}(r) = 0$ for all $r \in \mathbb{R}$. □

A total Φ-trajectory ϕ enjoys the following nice properties:

Lemma 4.3. *For a total Φ-trajectory ϕ in $\mathcal{Y}$, $\hat{\imath}(r)$ is either strictly positive or identical to zero on $\mathbb{R}$.*

Proof. For any $r^* \in \mathbb{R}$, by Lemma 4.2 and a shift, we see that $\hat{\imath}(r) = 0$ for all $r \geq r^*$ if $\hat{\imath}(r) = 0$ for all $r \leq r^*$. This implies that either (A) $\hat{\imath}(r)$ is identically zero on $\mathbb{R}$; or (B) there exists a decreasing sequence $\{r_j\}_{j=1}^{\infty}$ such that $r_j \to -\infty$ as $j \to \infty$ and $\hat{\imath}(r_j) > 0$. For the case (B), denoting $\hat{\imath}_j(t) := \hat{\imath}(t + r_j)$, $t \geq 0$, we have

$$\hat{\imath}_j(t) \geq \beta_2 \underline{T} \int_0^t q(a)\Omega(a)\hat{\imath}_j(t-a)\mathrm{d}a + \hat{\jmath}_j(t), \quad t \geq 0,$$

where $\underline{T} := \inf_{r\in\mathbb{R}} T(r) > 0$ and

$$\hat{\jmath}_j(t) := \beta_1 T(t + r_j)V(t + r_j) + \beta_2 T(t + r_j) \int_t^{\infty} q(a)\Omega(a)\hat{\imath}_j(t-a)\mathrm{d}a, \quad t \geq 0.$$

Then, since $\hat{\jmath}_j(0) = \hat{\imath}(r_j) > 0$ and $\hat{\jmath}_j(t)$ is continuous at 0. It follows from Corollary B.6 of Smith and Thieme [19] that there exists a number $r^* > 0$, which depends only on $\beta_2\underline{T}q(a)\Omega(a)$, such that $\hat{\imath}_j(t) > 0$ for all $t > r^*$. From the definition of $\hat{\imath}_j$, it follows that $\hat{\imath}(t) > 0$ for all $t > r^* + r_j$. By $r_j \to -\infty$ as $j \to \infty$, we obtain that $\hat{\imath}(r) > 0$ for all $r \in \mathbb{R}$. □

Now, let us define a function $\rho : \mathcal{Y} \to \mathbb{R}_+$ on $\mathcal{Y}$ by

$$\rho(x, \varphi, \psi) := \beta_1 x\psi + \beta_2 x \int_0^{\infty} q(a)\varphi(a)\mathrm{d}a, \quad (x, \varphi, \psi) \in \mathcal{Y}.$$

Then, it is obvious that $\rho(\Phi_t(X_0)) = \hat{\imath}(t)$. Under $\Re_0 > 1$, Lemma 4.1 has established uniform weak ρ-persistence for the semi-flow Φ. Now Theorem 3.2, Lemmas 4.2–4.3 and the Lipschitz continuity of $\hat{\imath}$ (see Proposition 2.3) allow us to apply the results in [19, Theorem 5.2] to conclude that the uniform weak ρ-persistence of semi-flow Φ indeed implies the uniform (strong) ρ-persistence, as stated in the following theorem.

Theorem 4.1. *If $\Re_0 > 1$, then semi-flow Φ is uniformly (strongly) ρ-persistent.*

We can easily pass the ρ-persistence (i.e., with respect to $\hat{\imath}(a)$) to the persistence of $i(\cdot, t)$ with respect to $\|\cdot\|_{L^1}$. In fact, by (4.1) we have

$$\|i(\cdot, t)\|_{L^1} \geq \int_0^t \hat{\imath}(t-a)\Omega(a)\mathrm{d}a.$$

Hence, from a variation of the Lebesgue–Fatou lemma [26, Section B.2], we obtain

$$\liminf_{t\to\infty} \|i(\cdot,t)\|_{L^1} \geq \hat{i}^\infty \int_0^\infty \Omega(a)\mathrm{d}a,$$

where $\hat{i}^\infty := \liminf_{t\to\infty} \hat{i}(t)$. By Theorem 4.1, there exists a positive constant $\epsilon > 0$ such that $\hat{i}^\infty > \epsilon$ if $\Re_0 > 1$, and hence, the persistence of $i(a,t)$ with respect to $\|\cdot\|_{L^1}$ follows.

The combining the persistence of $\hat{i}(r)$ and the first and the third equation in (4.12), we can easily see that $T(t)$ and $V(t)$ are also persistent with respect to $|\cdot|$ and $|\cdot|$. Therefore, we have actually proved the following theorem.

Theorem 4.2. *Assume that $\Re_0 > 1$. Then, the semiflow $\{\Phi(t)\}_{t\geq 0}$ generated by (1.3) is uniformly persistent in $\mathcal{Y}$ in the sense that there exists a constant $\epsilon > 0$ such that*

$$\liminf_{t\to+\infty} T(t) \geq \epsilon, \qquad \liminf_{t\to+\infty} \|i(\cdot,t)\|_{L^1} \geq \epsilon, \qquad \liminf_{t\to+\infty} V(t) \geq \epsilon$$

for each $X_0 \in \mathcal{Y}$.

5. Global stability of equilibria of (1.3)

In this section, we prove the global stability of the infection-free equilibrium E^0 under $\Re_0 \leq 1$ and that of the infection equilibrium E^* when $\Re_0 > 1$, as stated in Theorem 1.1.

5.1. Proof of Theorem 1.1-(i)

Let $g(x) = x - 1 - \ln x$. Note that $g : \mathbb{R}_+ \to \mathbb{R}_+$ is continuous and concave up. Also, g has a unique minimum at 1, with $g(x) \geq g(1) = 0$ for $x \in \mathbb{R}_+$.

We construct the following Lyapunov function $L = L_1 + L_2 + L_3$, where

$$L_1 = T_0 g\left(\frac{T}{T_0}\right), \qquad L_2 = \int_0^\infty \phi(a)i(a,t)\mathrm{d}a, \quad \text{and} \quad L_3 = \frac{\beta_1 T_0}{c}V(t).$$

Here, the nonnegative kernel functions $\phi(a)$ will be determined later. We calculate the time derivative of L_1 along the positive solutions of (1.3) and show that $\frac{\mathrm{d}L}{\mathrm{d}t}\big|_{(1.3)} \leq 0$. First, we get

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t}\Big|_{(1.3)} &= \left(1 - \frac{T_0}{T}\right)\left(dT_0 - dT - \beta_1 TV - \beta_2 T\int_0^\infty q(a)i(a,t)\mathrm{d}a\right)\\ &= -\frac{d(T-T_0)^2}{T} - \beta_1 TV - \beta_2 T\int_0^\infty q(a)i(a,t)\mathrm{d}a + \beta_1 T_0 V + \beta_2 T_0\int_0^\infty q(a)i(a,t)\mathrm{d}a\\ &= -\frac{d(T-T_0)^2}{T} - i(0,t) + \beta_1 T_0 V + \beta_2 T_0 \int_0^\infty q(a)i(a,t)\mathrm{d}a.\end{aligned}$$

Secondly, using the second equation of (1.3) and the method of integration by parts yield

$$\begin{aligned}\frac{\mathrm{d}L_2}{\mathrm{d}t}\Big|_{(1.3)} &= \int_0^\infty \phi(a)\frac{\partial i(a,t)}{\partial t}\mathrm{d}a = -\int_0^\infty \phi(a)\left[\theta(a)i(a,t) + \frac{\partial i(a,t)}{\partial a}\right]\mathrm{d}a\\ &= -\phi(a)i(a,t)\big|_0^\infty + \int_0^\infty \frac{\mathrm{d}\phi(a)}{\mathrm{d}a}i(a,t)\mathrm{d}a - \int_0^\infty \phi(a)\theta(a)i(a,t)\mathrm{d}a\\ &= \phi(0)i(0,t) + \int_0^\infty \left(\frac{\mathrm{d}\phi(a)}{\mathrm{d}a} - \phi(a)\theta(a)\right)i(a,t)\mathrm{d}a.\end{aligned}$$

For L_3 we have

$$\frac{\mathrm{d}L_3}{\mathrm{d}t}\Big|_{(1.3)} = \frac{\beta_1 T_0}{c}\left(\int_0^\infty p(a)i(a,t)\mathrm{d}a - cV\right) = \frac{\beta_1 T_0}{c}\int_0^\infty p(a)i(a,t)\mathrm{d}a - \beta_1 T_0 V.$$

Consequently, we obtain

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t}\Big|_{(1.3)} &= -\frac{d(T-T_0)^2}{T} - i(0,t) + \beta_1 T_0 V + \beta_2 T_0 \int_0^\infty q(a)i(a,t)\mathrm{d}a \\ &\quad + \phi(0)i(0,t) + \int_0^\infty \left(\frac{\mathrm{d}\phi(a)}{\mathrm{d}a} - \phi(a)\theta(a)\right) i(a,t)\mathrm{d}a + \frac{\beta_1 T_0}{c}\int_0^\infty p(a)i(a,t)\mathrm{d}a - \beta_1 T_0 V \\ &= -\frac{d(T-T_0)^2}{T} - i(0,t) + \phi(0)i(0,t) \\ &\quad + \int_0^\infty \left(\frac{\mathrm{d}\phi(a)}{\mathrm{d}a} - \phi(a)\theta(a) + \beta_2 T_0 q(a) + \frac{\beta_1 T_0}{c}p(a)\right) i(a,t)\mathrm{d}a.\end{aligned}$$

Now choose

$$\phi(a) = \int_a^\infty \left(\frac{\beta_1 T_0}{c}p(u) + \beta_2 T_0 q(u)\right) e^{-\int_a^u \theta(\omega)d\omega}\mathrm{d}u.$$

Differentiation gives

$$\frac{\mathrm{d}\phi(a)}{\mathrm{d}a} = \phi(a)\theta(a) - \beta_2 T_0 q(a) - \frac{\beta_1 T_0}{c}p(a).$$

Note that

$$\begin{aligned}\phi(0) &= \int_0^\infty \left(\frac{\beta_1 T_0}{c}p(u) + \beta_2 T_0 q(u)\right) e^{-\int_0^u \theta(\omega)d\omega}\mathrm{d}u \\ &= \frac{\beta_1 T_0}{c}\int_0^\infty p(u)\Omega(u)du + \beta_2 T_0 \int_0^\infty q(u)\Omega(u)\mathrm{d}u \\ &= \frac{\beta_1 T_0 Q}{c} + \beta_2 T_0 K = \Re_0.\end{aligned} \tag{5.1}$$

Adopting this $\phi(a)$, we obtain

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t}\Big|_{(1.3)} &= -\frac{d(T-T_0)^2}{T} + \big(\phi(0)-1\big)i(0,t) \\ &= -\frac{d(T-T_0)^2}{T} + \big(\Re_0 - 1\big)i(0,t) \le 0, \quad \text{if } \Re_0 \le 1.\end{aligned} \tag{5.2}$$

Notice that $\frac{\mathrm{d}L}{\mathrm{d}t}\big|_{(1.3)} = 0$ implies that $T = T_0$. It can be verified that the largest invariant subset of $\{\frac{\mathrm{d}L}{\mathrm{d}t}\big|_{(1.3)} = 0\}$ is the singleton $\{E_0\}$. Therefore, by the Lyapunov–LaSalle asymptotic stability theorem [23, Theorem 4.2 of Chapter IV], the infection-free equilibrium E_0 is globally asymptotically stable if $\Re_0 \le 1$. If $\Re_0 > 1$, then by continuity and (5.2), $\frac{\mathrm{d}L}{\mathrm{d}t}\big|_{(1.3)} > 0$ in a neighborhood of E_0. Positive solutions of (1.3) close to E_0 move away from E_0, implying that E_0 is unstable. This completes the proof.

5.2. Proof Theorem 1.1-(ii)

In this subsection, we prove the global stability of the infection equilibrium E^* under $\Re_0 > 1$. Our next lemma is a computational result that will be used in what follows to simply the calculation of Lyapunov arguments.

Lemma 5.1. *The following equation holds.*

$$\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\left[1 - \frac{i^*(0)TV}{i(0,t)T^*V^*}\right]\mathrm{d}a + \int_0^\infty \beta_2 T^* q(a) i^*(a)\left[1 - \frac{Ti^*(0)i(a,t)}{T^* i(0,t) i^*(a)}\right]\mathrm{d}a = 0. \tag{5.3}$$

Proof. It follows from (1.8) that

$$\begin{aligned}
&\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\left[1-\frac{i^*(0)TV}{i(0,t)T^*V^*}\right]\mathrm{d}a+\int_0^\infty \beta_2 T^* q(a) i^*(a)\left[1-\frac{Ti^*(0)i(a,t)}{T^*i(0,t)i^*(a)}\right]\mathrm{d}a\\
&=\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)da+\int_0^\infty \beta_2 T^* q(a) i^*(a)\mathrm{d}a\\
&\quad-\frac{i^*(0)}{i(0,t)}\left[\frac{\int_0^\infty \beta_1 p(a) i^*(a) TV\mathrm{d}a}{cV^*}+\int_0^\infty \beta_2 T q(a) i(a,t)\mathrm{d}a\right]\\
&=i^*(0)-\frac{i^*(0)}{i(0,t)} i(0,t)=0.
\end{aligned}$$

This completes the proof. □

We now give the proof of (ii) of Theorem 1.1. Let $G[x,y]=x-y-y\ln(x/y)$ for $x,y>0$. It is easy to verify that $xG_x[x,y]+yG_y[x,y]=G[x,y]$.

Next, we construct a Lyapunov function $W=W_1+W_2+W_3$, where

$$W_1=G[T,T^*],\qquad W_2=\int_0^\infty \psi(a)G[i(a,t),i^*(a)]\mathrm{d}a,\quad \text{and}\quad W_3=\frac{\beta_1 T^*}{c}G[V,V^*].$$

Here nonnegative kernel functions $\psi(a)$ will be determined later. Now we calculate the differentiation of $W_i, i=1,2,3$, along the solutions of (1.3), respectively. First, we have

$$\begin{aligned}
\frac{\mathrm{d}W_1}{\mathrm{d}t}\Big|_{(1.3)}&=\left(1-\frac{T^*}{T}\right)\left(h-dT-\beta_1 TV-\beta_2 T\int_0^\infty q(a)i(a,t)\mathrm{d}a\right)\\
&=\left(1-\frac{T^*}{T}\right)\Big(h-dT-i(0,t)\Big)\\
&=\left(1-\frac{T^*}{T}\right)\Big(dT^*-dT+i^*(0)-i(0,t)\Big)\\
&=-\frac{d(T-T^*)^2}{T}+i^*(0)-i(0,t)-i^*(0)\frac{T^*}{T}+i(0,t)\frac{T^*}{T}.
\end{aligned}$$

Using (2.3) and (2.4), we can rewrite W_2 as

$$\begin{aligned}
W_2&=\int_0^t \psi(a)G[i(0,t-a)\Omega(a),i^*(a)]\mathrm{d}a+\int_t^\infty \psi(a)G\left[i_0(a-t)e^{-\int_{a-t}^a\theta(\omega)d\omega},i^*(a)\right]\mathrm{d}a\\
&=\int_0^t \psi(t-r)G[i(0,r)\Omega(t-r),i^*(t-r)]\mathrm{d}r+\int_0^\infty \psi(t+r)G\left[i_0(r)e^{-\int_r^{t+r}\theta(\omega)d\omega},i^*(t+r)\right]\mathrm{d}r.
\end{aligned}$$

It follows from the relations $i^*(a)=i^*(0)e^{-\int_0^a\theta(\omega)\mathrm{d}\omega}$ and $\Omega(0)=1$ that

$$\begin{aligned}
\frac{\mathrm{d}W_2}{\mathrm{d}t}\Big|_{(1.3)}=\psi(0)G[i(0,t),i^*(0)]&+\int_0^t \psi'(t-r)G\left[i(0,r)e^{-\int_0^{t-r}\theta(\omega)\mathrm{d}\omega},i^*(t-r)\right]\mathrm{d}r\\
&-\int_0^t \psi(t-r)\theta(t-r)\Bigg[i(0,r)e^{-\int_0^{t-r}\theta(\omega)\mathrm{d}\omega}G_x\left[i(0,r)e^{-\int_0^{t-r}\theta(\omega)\mathrm{d}\omega},i^*(t-r)\right]\\
&+i^*(t-r)G_y[i(0,r)e^{-\int_0^{t-r}\theta(\omega)d\omega},i^*(t-r)]\Bigg]\mathrm{d}r\\
&+\int_0^\infty \psi'(t+r)G\left[i_0(r)e^{-\int_r^{t+r}\theta(\omega)\mathrm{d}\omega},i^*(t+r)\right]\mathrm{d}r\\
&-\int_0^\infty \psi(t+r)\theta(t+r)\left[i_0(r)e^{-\int_r^{t+r}\theta(\omega)\mathrm{d}\omega}G_x[i_0(r)e^{-\int_r^{t+r}\theta(\omega)\mathrm{d}\omega},i^*(t+r)]\right.
\end{aligned}$$

$$+ i^*(t+r)G_y\left[i_0(r)e^{-\int_r^{t+r}\theta(\omega)d\omega}, i^*(t+r)\right]\Bigg] \mathrm{d}r$$

$$= \psi(0)G[i(0,t), i^*(0)] + \int_0^\infty \Big[\psi'(a) - \psi(a)\theta(a)\Big] G[i(a,t), i^*(a)]\mathrm{d}a.$$

The last equality follows from (2.3) and the fact that $xG_x[x,y] + yG_y[x,y] = G[x,y]$. For W_3, we have

$$\begin{aligned}
\frac{\mathrm{d}W_3}{\mathrm{d}t}\Big|_{(1.3)} &= \frac{\beta_1 T^*}{c}\left(1 - \frac{V^*}{V}\right)\left[\int_0^\infty p(a)i(a,t)\mathrm{d}a - cV(t)\right] \\
&= \frac{\beta_1 T^*}{c}\int_0^\infty p(a)i(a,t)\mathrm{d}a - \beta_1 T^* V + \beta_1 T^* V^* - \frac{\beta_1 T^* V^*}{cV}\int_0^\infty p(a)i(a,t)\mathrm{d}a.
\end{aligned}$$

Now we choose

$$\varphi(a) = \int_a^\infty \left(\frac{\beta_1 T^*}{c}p(u) + \beta_2 T^* q(u)\right)e^{-\int_a^u \theta(\omega)d\omega}\mathrm{d}u.$$

Differentiating the above equation gives

$$\frac{\mathrm{d}\varphi(a)}{\mathrm{d}a} = \varphi(a)\theta(a) - \beta_2 T^* q(a) - \frac{\beta_1 T^* p(a)}{c},$$

that is,

$$\frac{\mathrm{d}\varphi(a)}{\mathrm{d}a} - \varphi(a)\theta(a) = -\left[\frac{\beta_1 T^*}{c}p(a) + \beta_2 T^* q(a)\right]. \tag{5.4}$$

Similar to (5.1), we have

$$\begin{aligned}
\varphi(0) &= \int_0^\infty \left(\frac{\beta_1 T^*}{c}p(u) + \beta_2 T^* q(u)\right)e^{-\int_0^u \theta(\omega)d\omega}\mathrm{d}u \\
&= \frac{\beta_1 T^*}{c}\int_0^\infty p(u)\Omega(u)\mathrm{d}u + \beta_2 T^*\int_0^\infty q(u)\Omega(u)\mathrm{d}u \\
&= \frac{\beta_1 T^* Q}{c} + \beta_2 T^* K = T^*\frac{\Re_0}{T_0} = 1.
\end{aligned}$$

Hence

$$\begin{aligned}
\frac{\mathrm{d}W_2}{\mathrm{d}t}\Big|_{(1.3)} &= \int_0^\infty \left[\frac{\beta_1 T^*}{c}p(a) + \beta_2 T^* q(a)\right]\left(i^*(a) - i(a,t) + i^*(a)\ln\frac{i(a,t)}{i^*(a)}\right)\mathrm{d}a \\
&\quad + i(0,t) - i^*(0) - i^*(0)\ln\frac{i(0,t)}{i^*(0)}.
\end{aligned}$$

Consequently, we obtain

$$\begin{aligned}
\frac{\mathrm{d}W}{\mathrm{d}t}\Big|_{(1.3)} &= -\frac{d(T-T^*)^2}{T} + i^*(0) - i(0,t) - i^*(0)\frac{T^*}{T} + i(0,t)\frac{T^*}{T} \\
&\quad + \int_0^\infty \left[\frac{\beta_1 T^*}{c}p(a) + \beta_2 T^* q(a)\right]\left(i^*(a) - i(a,t) + i^*(a)\ln\frac{i(a,t)}{i^*(a)}\right)\mathrm{d}a \\
&\quad + i(0,t) - i^*(0) - i^*(0)\ln\frac{i(0,t)}{i^*(0)} \\
&\quad + \frac{\beta_1 T^*}{c}\int_0^\infty p(a)i(a,t)\mathrm{d}a - \beta_1 T^* V + \beta_1 T^* V^* - \frac{\beta_1 T^* V^*}{cV}\int_0^\infty p(a)i(a,t)\mathrm{d}a \\
&= -\frac{d(T-T^*)^2}{T} - i^*(0)\frac{T^*}{T} + i(0,t)\frac{T^*}{T} - i^*(0)\ln\frac{i(0,t)}{i^*(0)} \\
&\quad + \int_0^\infty \frac{\beta_1 T^* p(a)}{c}\left(i^*(a) - i(a,t) + i^*(a)\ln\frac{i(a,t)}{i^*(a)}\right)\mathrm{d}a
\end{aligned}$$

$$+\int_0^\infty \beta_2 T^* q(a)\left(i^*(a)-i(a,t)+i^*(a)\ln\frac{i(a,t)}{i^*(a)}\right)\mathrm{d}a$$
$$+\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i(a,t)\mathrm{d}a-\int_0^\infty \frac{\beta_1 T^* V^* p(a)}{cV} i(a,t)\mathrm{d}a-\beta_1 T^* V+\beta_1 T^* V^*.$$

Using the equilibrium equations $V^*=\int_0^\infty \frac{p(a)i^*(a)}{c}\mathrm{d}a$ and $i^*(0)=\beta_1 T^* V^*+\beta_2 T^*\int_0^\infty q(a)i^*(a)\mathrm{d}a$, we have

$$\begin{aligned}\frac{\mathrm{d}W}{\mathrm{d}t}\Big|_{(1.3)}&=-\frac{d(T-T^*)^2}{T}-\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\frac{T^*}{T}\mathrm{d}a-\int_0^\infty \beta_2 T^* q(a) i^*(a)\frac{T^*}{T}\mathrm{d}a\\
&\quad+\beta_1 T^* V+\int_0^\infty \beta_2 T^* q(a) i(a,t)\mathrm{d}a\\
&\quad-\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\ln\frac{i(0,t)}{i^*(0)}\mathrm{d}a-\int_0^\infty \beta_2 T^* q(a) i^*(a)\ln\frac{i(0,t)}{i^*(0)}\mathrm{d}a\\
&\quad+\int_0^\infty \frac{\beta_1 T^* p(a)}{c}\left(i^*(a)-i(a,t)+i^*(a)\ln\frac{i(a,t)}{i^*(a)}\right)\mathrm{d}a\\
&\quad+\int_0^\infty \beta_2 T^* q(a)\left(i^*(a)-i(a,t)+i^*(a)\ln\frac{i(a,t)}{i^*(a)}\right)\mathrm{d}a\\
&\quad+\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i(a,t)\mathrm{d}a-\int_0^\infty \frac{\beta_1 T^* p(a)}{c}\frac{V^*}{V} i(a,t)\mathrm{d}a-\beta_1 T^* V\\
&\quad+\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\mathrm{d}a.\end{aligned}$$

Canceling and rearranging the terms in the above yield

$$\begin{aligned}\frac{\mathrm{d}W}{\mathrm{d}t}\Big|_{(1.3)}&=-\frac{d(T-T^*)^2}{T}+\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\left(2+\ln\frac{i(a,t)}{i^*(a)}-\frac{T^*}{T}-\ln\frac{i(0,t)}{i^*(0)}-\frac{V^* i(a,t)}{V i^*(a)}\right)\mathrm{d}a\\
&\quad+\int_0^\infty \beta_2 T^* q(a) i^*(a)\left(1+\ln\frac{i(a,t)}{i^*(a)}-\frac{T^*}{T}-\ln\frac{i(0,t)}{i^*(0)}\right)\mathrm{d}a\\
&=-\frac{d(T-T^*)^2}{T}\\
&\quad+\int_0^\infty \beta_2 T^* q(a) i^*(a)\left(1-\frac{T^*}{T}+\ln\frac{T^*}{T}+1-\frac{T i^*(0) i(a,t)}{T^* i(0,t) i^*(a)}+\ln\frac{T i^*(0) i(a,t)}{T^* i(0,t) i^*(a)}\right)\mathrm{d}a\\
&\quad+\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\left(1-\frac{T^*}{T}+\ln\frac{T^*}{T}+1-\frac{V^* i(a,t)}{V i^*(a)}+\ln\frac{V^* i(a,t)}{V i^*(a)}\right.\\
&\quad\left.+1-\frac{i^*(0)TV}{i(0,t)T^*V^*}+\ln\frac{i^*(0)TV}{i(0,t)T^*V^*}\right)\mathrm{d}a\\
&\quad-\left\{\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\left[1-\frac{i^*(0)TV}{i(0,t)T^*V^*}\right]\mathrm{d}a+\int_0^\infty \beta_2 T^* q(a) i^*(a)\left[1-\frac{T i^*(0) i(a,t)}{T^* i(0,t) i^*(a)}\right]\mathrm{d}a\right\}.\end{aligned}$$

Using the equality in Lemma 5.1, we obtain

$$\begin{aligned}\frac{\mathrm{d}W}{\mathrm{d}t}\Big|_{(1.3)}&=-\frac{d(T-T^*)^2}{T}-\int_0^\infty \frac{\beta_1 T^* p(a)}{c} i^*(a)\left[g\left(\frac{T^*}{T}\right)+g\left(\frac{V^* i(a,t)}{V i^*(a)}\right)+g\left(\frac{i^*(0)TV}{i(0,t)T^*V^*}\right)\right]\mathrm{d}a\\
&\quad-\int_0^\infty \beta_2 T^* q(a) i^*(a)\left[g\left(\frac{T^*}{T}\right)+g\left(\frac{T i^*(0) i(a,t)}{T^* i(0,t) i^*(a)}\right)\right]\mathrm{d}a\le 0.\end{aligned}$$

It follows from the non-negativity of g that $\frac{\mathrm{d}W}{\mathrm{d}t}\big|_{(1.3)}\le 0$. Combining the equation expressions of system (1.3) and boundary conditions in (1.4), we can verify that $\frac{\mathrm{d}W}{\mathrm{d}t}\big|_{(1.3)}=0$ leads to $T=T^*$ and

$$\frac{i(a,t)}{i^*(a)}=\frac{i(0,t)}{i^*(0)}=\frac{V}{V^*}=1,\quad \text{for all } a\ge 0.$$

That is, the largest invariant subset of $\{\frac{\mathrm{d}W}{\mathrm{d}t}\big|_{(1.3)} = 0\}$ is the singleton $\{E^*\}$. By [23, Theorem 4.2 of Chapter IV], every positive solution of (1.3) approaches E^* when $\Re_0 > 1$, meaning that E^* is globally asymptotically stable with respect to solutions with initial conditions $T_0, V_0 > 0$ and $i_0(a) > 0$ bounded away from zero.

Remark 5.1. The key technique for constructing the suitable Lyapunov function in the proof of Theorem 1.1 is to choose proper $\phi(a)$ and $\psi(a)$, which is mathematically determined according to coefficient function $\theta(a)$, $p(a)$ and $q(a)$ with respect to the infection age a.

6. Discussion

In this paper, we have formulated an age-structured model for HIV-1 infection with two modes of viral infection. One is the traditional virus-to-cell infection, and the other is cell-to-cell transmission via formation of virological synapses. We have given a rigorous analysis on this model system, addressing issues such as relative compactness, existence of a global attractor, and persistence; and most significantly, we have shown that the global attractor is indeed a singleton, being either the infection free equilibrium if $\Re_0 \le 1$, or the infection equilibrium if $\Re_0 > 1$. Thus, the global dynamics is fully determined by $\Re_0$.

A biological implication (importance) of such a global threshold dynamics is that one only needs to focus on the dependence of the basic reproduction number on the model parameters. For example, if one wants to focus on the impact of the virus kernel function $p(a)$, one can follow the recent work Lai–Zou [27]. Indeed, [27] explored, among other things, how $p(a)$, in conjunction with the death rate function $\theta(a)$, affects the burst size Q and hence the basic reproduction number $\mathcal{R}_0$. To be more specific, the following two forms of functions for $p(a)$ are used in [27]:

$$\gamma(a) = \begin{cases} m_1\left(1 - e^{-m_2(a-\tau)}\right) & \text{if } a \ge \tau, \\ 0 & \text{if } a < \tau. \end{cases} \tag{6.1}$$

and

$$\gamma(a) = \begin{cases} \dfrac{k_1(a-\tau)}{k_2 + (a-\tau)^2} & \text{if } a \ge \tau, \\ 0 & \text{if } a < \tau. \end{cases} \tag{6.2}$$

With the above given forms, the results in [27] showed how the initial release time τ of the newly replicated virus particles, in conjunction with the other two model parameters in (6.1) and (6.2), will affect the burst size Q (and hence, $\mathcal{R}_0$). Similar things can be done on the impact of the kernel function $q(a)$ on $\mathcal{R}_0$ through K. The parameter values in (6.1) and (6.2) should be virus specific, and other forms of the kernels are also possible depending on the virus. We will not go into too much details along this. The message is that such results indicate that the age structure characterized by the kernel functions $p(a)$, $q(a)$ and $\theta(a)$ can have significant impacts on the virus dynamics.

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References

[1] D.D. Ho, A.U. Neumann, A.S. Perelson, W. Chen, J.M. Leonard, M. Markowitz, Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection, Nature 373 (1995) 123–126.

[2] A.S. Perelson, A.U. Neumann, M. Markowitz, J.M. Leonard, D.D. Ho, HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time, Science 271 (1996) 1582–1586.

[3] P.W. Nelson, M.A. Gilchrist, D. Coombs, J.M. Hyman, A.S. Perelson, An age-structured model of HIV infection that allow for variations in the production rate of viral particles and the death rate of productively infected cells, Math. Biosci. Eng. 1 (2) (2004) 267–288.

[4] L. Rong, Z. Feng, A.S. Perelson, Mathematical analysis of age-structured HIV-1 dynamics with combination antiretroviral therapy, SIAM J. Appl. Math. 67 (3) (2007) 731–756.

[5] Z. Feng, L. Rong, The influence of anti-viral drug therapy on the evolution of HIV-1 pathogens, DIMACS Ser. Discrete Math. Theoret. Comput. Sci. 71 (2006) 261–279.

[6] G. Huang, X. Liu, Y. Takeuchi, Lyapunov functions and global stability for age-structured HIV infection model, SIAM J. Appl. Math. 72 (2012) 25–38.

[7] R. Qesmi, S. Elsaadany, J.M. Heffernan, J. Wu, A hepatitis B and C virus model with age since infection that exhibits backward bifurcation, SIAM J. Appl. Math. 71 (2011) 1509–1530.

[8] W. Hübner, G.P. McNerney, P. Chen, B.M. Dale, R.E. Gordan, F.Y.S. Chuang, X.D. Li, D.M. Asmuth, T. Huser, B.K. Chen, Quantitative $3D$ video microscopy of HIV transfer across T cell virological synapses, Science 323 (2009) 1743–1747.

[9] D.S. Dimitrov, R.L. Willey, H. Sato, L. Chang, R. Blumenthal, M.A. Martin, Quantitation of human immunodeficiency virus type 1 infection kinetics, J. Virol. 67 (1993) 2182–2190.

[10] A. Sigal, J.T. Kim, A.B. Balazs, E. Dekel, A. Mayo, R. Milo, D. Baltimore, Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy, Nature 477 (2011) 95–98.

[11] Q. Sattentau, The direct passage of animal viruses between cells, Curr. Opin. Virol. 1 (2011) 396–402.

[12] N.L. Komarova, D. Anghelina, I. Voznesensky, B. Trinite, D.N. Levy, D. Wodarz, Relative contribution of free-virus and synaptic transmission to the spread of HIV-1 through target cell populations, Biol. Lett. 9 (2012) 1049–1055.

[13] N.L. Komarova, D.N. Levy, D. Wodarz, Effect of synaptic transmission on viral fitness in HIV infection, PLoS One 7 (2012) 1–11.

[14] N.L. Komarova, D. Wodarz, Virus dynamics in the presence of synaptic transmission, Math. Biosci. 242 (2013) 161–171.

[15] N.L. Komarova, D.N. Levy, D. Wodarz, Synaptic transmission and the susceptibility of HIV infection to anti-vrial drugs, Sci. Rep. 3 (2013) 1–8.

[16] X. Lai, X. Zou, Modeling cell-to-cell spread of HIV-1 with logistic target cell growth, J. Math. Anal. Appl. 426 (2015) 563–584.

[17] H. Pourbashash, S.S. Pilyugin, P. De Leenheer, C. McCluskey, Global analysis of within host virus models with cell-to-cell viral transmission, Discrete Contin. Dyn. Syst. Ser. B 10 (2014) 3341–3357.

[18] X. Lai, X. Zou, Modeling HIV-1 virus dynamics with both virus-to-cell infection and cell-to-cell transmission, SIAM J. Appl. Math. 74 (3) (2014) 898–917.

[19] H.L. Smith, H.R. Thieme, Dynamical Systems and Population Persistence, Amer. Math. Soc., Providence, 2011.

[20] G. Gripenberg, S.O. Londen, O. Staffans, Volterra Integral and Functional Equation, Cambridge University Press, New York, 1990.

[21] C.J. Browne, S.S. Pilyugin, Global analysis of age-structured within-host virus model, Discrete Contin. Dyn. Syst. Ser. B 18 (2013) 1999–2017.

[22] C.C. McCluskey, Global stability for an SEI epidemiological model with continuous age-structure in the exposed and infectious classes, Math. Biosci. Eng. 9 (2012) 819–841.

[23] J.A. Walker, Dynamical Systems and Evolution Equations, Plenum Press, New York and London, 1980.

[24] G.F. Webb, Theory of Nonlinear Age-Dependent Population Dynamic, Marcel Dekker, New York and Basel, 1985.

[25] J.K. Hale, Asymptotic Behavior of Dissipative Systems, in: Mathematical Surveys and Monographs, vol. 25, American Mathematical Society, Providence, RI, 1988.

[26] H.L. Smith, Mathematics in Population Biology, Princeton University Press, 2003.

[27] X. Lai, X. Zou, Dynamics of evolutionary competition between budding and lytic viral release strategies, Math. Biol. Eng. 11 (2014) 1091–1113.