GLOBAL DYNAMICS OF AN AGE-STRUCTURED HIV INFECTION MODEL INCORPORATING LATENCY AND CELL-TO-CELL TRANSMISSION

JINLIANG WANG¹, JIYING LANG¹ AND YUMING CHEN²,*
¹School of Mathematical Science, Heilongjiang University
Harbin 150080, China
²Department of Mathematics, Wilfrid Laurier University
Waterloo, ON N2L 3C5 Canada

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ABSTRACT. In this paper, we are concerned with an age-structured HIV infection model incorporating latency and cell-to-cell transmission. The model is a hybrid system consisting of coupled ordinary differential equations and partial differential equations. First, we address the relative compactness and persistence of the solution semi-flow, and the existence of a global attractor. Then, applying the approach of Lyapunov functionals, we establish the global stability of the infection-free equilibrium and the infection equilibrium, which is completely determined by the basic reproduction number.

1. Introduction. Acquired immunodeficiency syndrome (AIDS) is a condition in human in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. AIDS is considered as a pandemic—a disease outbreak which is present over a large area and is actively spreading. By 2010, more than 30 million people worldwide had died of AIDS (UNAIDS2010). In 2013, it resulted in about 1.34 million deaths.

In 1984, the human immunodeficiency virus (HIV) infection was identified as the cause of AIDS. HIVs are intracellular parasites that depend on the host cells, CD4⁺ T-cells, to survive and replicate. CD4⁺ T-cells can be damaged either directly by the virus or by immune responses to the virus [22]. It is believed that CTLs, also known as CD8⁺ T-cells or killer T-cells, are the main host immune factor that limits the virus replication in vivo, blocks up virus into target cells, and determines the viral load [23]. These cells cannot become infected with the virus, but do destroy infected cells.

The last few decades have witnessed a substantial increase in the application of mathematical models to understand HIV infection at both the population level and within-host level. Models of HIV infection at the population level can be used
to predict the future prevalence and suggest possible control strategies while viral
dynamic models characterizing the interaction between CD4\(^+\) T cells and viruses
and studying the effects of drug therapy are aimed to guide treatment strategies.
In this paper, we focus on within-host HIV models. We refer to Perelson and
Nelson [25] for a review of such models built and analyzed before 1995.

Most within-host HIV models are described by ordinary differential equations (ODEs) for uninfected CD4\(^+\) T cells, actively infected CD4\(^+\) T cells, free
infectious viruses, (CTLs response). For example, Perelson et al. [24] examined a
model for the interaction of HIV with CD4\(^+\) T cells that consists of four populations: uninfected T cells \((T(t))\), latently infected T cells \((T^\ast(t))\), actively infected T cells \((T^{**}(t))\), and free viruses \((V(t))\). The model is as follows,

\[
\begin{align*}
\frac{dT(t)}{dt} &= s - \mu T + r T \left(1 - \frac{T+T^\ast+T^{**}}{T_{\max}}\right) - k_1 VT, \\
\frac{dT^\ast(t)}{dt} &= k_1 VT - \mu T^\ast - k_2 T^\ast, \\
\frac{dT^{**}(t)}{dt} &= k_2 T^\ast - \mu b T^{**}, \\
\frac{dV(t)}{dt} &= N_0 T^{**} - \mu b VT - \mu V.
\end{align*}
\]

Let \(N_{\text{crit}} = \frac{(k_2 + \mu b)(\mu V + k_1 T_0)}{\mu b + \mu V}\), where \(T_0 = \frac{(r - \mu^2)T_{\max} + \sqrt{(r - \mu^2)^2 T_{\max}^2 + 4\mu^2 T_{\max}}}{2\mu^2}\). Denote by \(N\) the total number of new virus particles produced by each infected cell
during its life time. It is shown that if \(N < N_{\text{crit}}\), then the uninfected steady state
is the only steady state in the nonnegative orthant and this steady state is stable;
while if \(N > N_{\text{crit}}\), then the uninfected steady state is unstable and the endemically
infected steady state can be either stable, or unstable and surrounded by a stable
limit cycle. Recently, Wang et al. [36] studied the following HIV-1 infection model
with the mass-action infection rate and latent cells,

\[
\begin{align*}
\frac{dT(t)}{dt} &= \lambda - dT - \beta TV, \\
\frac{dT^\ast(t)}{dt} &= (1 - q)\beta TV - eT^\ast - \delta T^\ast, \\
\frac{dT^{**}(t)}{dt} &= q\beta TV - a T^{**} + \delta T^\ast, \\
\frac{dV(t)}{dt} &= kT^{**} - uV.
\end{align*}
\]

(Note that we have changed the symbols for state variables in order to be consistent
with [1.1].) If the basic reproduction number \(R_0 = \frac{k_1\lambda\beta(q + \delta)}{a \mu(q + \delta)} \leq 1\) then the infection-free equilibrium of [1.2]
is globally asymptotically stable while if \(R_0 > 1\) then its chronic-infection equilibrium is globally asymptotically stable.

As in the above just mentioned references, most of the existing work on within-host
HIV infection only considers the cell-free spread. However, it is reported recently
that cell-to-cell transmission of viruses also occurs when a healthy cell comes
into contact with an infected cell [27]. Productive cell-to-cell infection requires
interaction between the viral envelop glycoproteins on the surface of the infected
cell and HIV receptors on the surfaces of target cells, leading to the formation of
virological synapses. For details on the infection mechanism via cell-to-cell contact,
we refer the readers to [16] [19] and the references therein. Though direct cell-to-
cell transmission of HIV is a more potent and efficient means of virus propagation
than infection by cell-free particles, this mode of viral propagation is less studied
by using mathematical models [13] [14] [18] [28] [42]. The models in [13] [14] [28] consist
of equations for three populations (uninfected, infected and virus) while those in [18] [42] also include another population, the latently infected cells. Roughly,
there is a threshold dynamics with/without additional conditions besides those on
the existence of endemic equilibria [13, 18, 28, 42]. Sometimes, Hopf bifurcation can occur [14].

It is well-known that the HIV virus may not reveal any symptoms for many years. According to health professionals, this could be around 10 years. However, the virus will still be active, infecting new cells and making copies. Due to the virus persisting in reservoirs, there will be a long-term low viral load persistence in patients on antiretroviral therapy. It has been reported in [2] that latently infected CD4+ T cells are the best known reservoir. The latently infected CD4+ T cells are neither interfered with antiretroviral therapy nor affected by immune responses. However, they can produce virus when activated by relevant antigens. Over time this will cause a lot of damage to the immune system. Moreover, in the study of HIV/AIDS epidemic, early infectivity experiments and the measurements of antigen and antibody titers suggest the possibility of an early infectivity peak (a few weeks after exposure) and a late infectivity plateau (one year or so before the onset of “full-blown” AIDS) for HIV-infected individuals. One realistic way to describe such phenomena is to introduce age structures. The idea of using age-structured models to study the spread of infectious diseases already has a long history. At the heart of an age-structured epidemic model is a coupled system of hyperbolic partial differential equations (PDEs) with/without ODEs, which is a generalization of those of standard differential equations and of delay differential equations. The introduction of PDEs enhances the interconnectivity and accuracy of the model. The resulting system is substantially complicated to analyze. For some background of age-structured epidemic models, see the books by Cushing [5] and Webb [41]. By now, lots have been done for age-structured HIV infection models only with cell-free spread (to name a few, see [3, 6, 8, 10, 12, 21, 29, 34, 38, 39]). In spite of this, to the best of our knowledge, only Wang et al. [37] studied the following age-structured HIV infection model with both cell-free infection and cell-to-cell transmission,

\[
\begin{align*}
\frac{dT(t)}{dt} &= h - dT(t) - \beta_1 T(t)V(t) - \beta_2 T(t) \int_0^\infty q(a)i(a, t)da, \\
\left(\frac{d}{dt} + \frac{\partial}{\partial a}\right)i(a, t) &= -\theta(a)i(a, t), \\
\frac{dV(t)}{dt} &= \int_0^\infty p(a)i(a, t)da - cV(t), \\
i(0, t) &= \beta_1 T(t)V(t) + \beta_2 T(t) \int_0^\infty q(a)i(a, t)da, \\
T(0) &= T_0 > 0, i(a, 0) = i_0(a) \in L_1^1(0, \infty), V(0) = V_0 > 0,
\end{align*}
\]  

(1.3)

where \(T(t)\) denotes the concentration of uninfected target T cells at time \(t\), \(i(a, t)\) denotes the density of target T cells of infection age \(a\) at time \(t\), and \(V(t)\) denotes the concentration of infectious virus at \(t\). Here \(L_1^1(0, \infty)\) is the set of all nonnegative integrable functions on \(\mathbb{R}_+ := [0, \infty)\). A threshold dynamics is established by applying the technique of Lyapunov functionals.

Considering that antigen specificity plays an important role in the activation of latently infected cells. Mathematical models have been formulated to study the decay dynamics of the latent reservoir. See, for example, [11, 20, 4]. It has been reported in [31, 32] that “cells specific to frequently encountered antigens can be activated quickly while cells specific to rarely encountered antigens need more time to be activated. Thus, the more time elapsed since the establishment of latent infection, the more likely the latently infected cell is specific to a rarer antigen, and the less likely it is to be activated”. In a recent work [1], the authors assumed that the activation rate of latently infected cells should depend on the age of latent infection (the time elapsed since latent infection). They incorporated this structure into infection model with latency proposed by Perelson et al. [20] to study the
second phase viral load decline during combination therapy. Some stability results of the infection-free and infected steady states are obtained in terms of the basic reproductive number.

Motivated by the above discussions and based on (1.2) and (1.3), in this paper, we propose and study an age-structured HIV infection model with latency and both cell-free and cell-to-cell infection modes. Let \( e(a, t) \) be the density of infected T cells of latency age \( a \) at time \( t \). The model to be analyzed is as follows,

\[
\begin{align*}
\frac{dT(t)}{dt} &= h - dT(t) - \beta T(t)V(t) - \beta_1 T(t) \int_0^\infty q_1(a)e(a, t)da \\
&\quad - \beta_2 T(t) \int_0^\infty q_2(b)i(b, t)db, \\
\frac{e(0, t)}{dt} &= -\theta_1(a)e(a, t), \\
\frac{e(t)}{dt} &= -\theta_2(b)i(b, t), \\
\frac{dV(t)}{dt} &= \int_0^\infty p(b)i(b, t)db - cV(t),
\end{align*}
\]

with boundary conditions

\[
\begin{align*}
e(0, t) &= \beta T(t)V(t) + \beta_1 T(t) \int_0^\infty q_1(a)e(a, t)da \\
&\quad + \beta_2 T(t) \int_0^\infty q_2(b)i(b, t)db \\
i(0, t) &= \int_0^\infty \xi(a)e(a, t)da
\end{align*}
\]

and initial conditions

\[
T(0) = T_0 \in \mathbb{R}_+, \quad e(\cdot, 0) = e_0 \in L^1_+(0, \infty), \quad i(\cdot, 0) = i_0 \in L^1_+(0, \infty), \quad V(0) = V_0 \in \mathbb{R}_+
\]

The meanings of the parameters in (1.4) are summarized in Table 1.

| Parameter | Meaning |
|-----------|---------|
| \( h \)  | Constant recruitment rate of uninfected CD4⁺ T cells |
| \( d \)  | Death rate of uninfected CD4⁺ T cells |
| \( \beta \) | Infection rate of CD4⁺ T cells by infectious virus |
| \( \beta_1 \) | Infection rate of CD4⁺ T cells by latently infected T cells |
| \( \beta_2 \) | Infection rate of CD4⁺ T cells by infectious T cells |
| \( q_1(a) \) | Infectivity of a latently infected T cell with latency age \( a \) |
| \( q_2(b) \) | Infectivity of an infectious T cell with infection age \( b \) |
| \( \theta_1(a) \) | Sum of death rate and activation rate \( \xi(a) \) of latently infected T cells with latency age \( a \) |
| \( \theta_2(b) \) | Death rate of infectious T cells with infection age \( b \) |
| \( p(b) \) | Viral production rate of an infectious T cell with infection age \( b \) |
| \( c \)   | Clearance rate of virions |
| \( \xi(a) \) | Activation rate of latently infected T cells with latency age \( a \) |

The disease transmission diagram is depicted in Fig. 1.

In what follows, we always make the following assumptions on parameters in (1.4) and (1.5).

**Assumption 1.1.**
(i) \( h, d, \beta, \beta_1, \beta_2, c > 0 \);
(ii) \( q_i, \theta_i \ (i = 1, 2), p, \xi \in L^\infty_+(0, \infty) \) satisfy

\[
\tilde{q}_i := \text{ess sup} q_i < \infty, \quad \tilde{\theta}_i := \text{ess sup} \theta_i < \infty, \\
\tilde{p} := \text{ess sup} p < \infty, \quad \tilde{\xi} := \text{ess sup} \xi < \infty,
\]

Table 1. Biological meanings of parameters in (1.4) and (1.5)
where \( L_+^\infty (0, \infty) \) is the set of all nonnegative essentially bounded functions on \((0, \infty)\);

(iii) \( q_i (i = 1, 2), p \neq 0, \xi \neq 0 \) are Lipschitz continuous on \( \mathbb{R}_+ \) with Lipschitz constants \( M_{q_i}, M_p, M_\xi \) respectively;

(iv) There exists \( \mu_0 \in (0, d] \) such that \( \theta_1 (a) - \xi (a), \theta_2 (b) \geq \mu_0 \) for all \( a, b \in \mathbb{R}_+ \).

Our goal is to show that (1.4) possesses a threshold dynamics. Roughly speaking, if the basic reproduction number is less than one then the infection-free equilibrium is globally asymptotically stable otherwise the infection equilibrium attracts all solutions with initial active infection.

The remaining of this paper is organized as follows. First, in Section 2, we present some preliminary results including properties of solutions and the existence of equilibria. Then we show the relative compactness of orbits in Section 3 and the uniform persistence of (1.4) in Section 4. The coming three sections are devoted to the global dynamics of (1.4). First, we obtain the local stability of the infection-free equilibrium and the infection equilibrium in Section 5. Then we establish their global attractivity in Section 6 and Section 7, respectively. The main results are demonstrated with numerical examples in Section 8. The paper concludes with a brief summary and discussion.

2. Preliminaries.

2.1. The solution semi-flow. From the biological background of the model, define the state space of (1.4) as

\[ Y = \mathbb{R}_+ \times L^1_+ (0, \infty) \times L^1_+ (0, \infty) \times \mathbb{R}_+ , \]

which is a subset of the Banach space \( \mathbb{R} \times L^1 (0, \infty) \times L^1 (0, \infty) \times \mathbb{R} \) equipped with the norm \( \|(x, \varphi, \psi, y)\| = |x| + \|\varphi\|_{L^1} + \|\psi\|_{L^1} + |y| \) for \( (x, \varphi, \psi, y) \in \mathbb{R} \times L^1 (0, \infty) \times L^1 (0, \infty) \times \mathbb{R} \). If any initial value \( X_0 = (T_0, e_0, i_0, V_0) \in Y \) satisfies the coupling equations

\[ e(0, 0) = \beta T_0 V_0 + \beta_1 T_0 \int_0^\infty q_1 (a) e_0 (a) da + \beta_2 T_0 \int_0^\infty q_2 (b) i_0 (b) db \]

and

\[ i(0, 0) = \int_0^\infty \xi (a) e_0 (a) da , \]

then (1.4) is well-posed under Assumption 1.1 due to Iannelli [9] and Magal [15]. In fact, for such solutions, it is not difficult to show that \( (T(t), e(\cdot, t), i(\cdot, t), V(t)) \in Y \) for each \( t \in \mathbb{R}_+ \). In what follows, we always assume that the initial values satisfy the
coupling equations. Thus we can get a continuous solution semi-flow \( \Phi : \mathbb{R}_+ \times \mathcal{Y} \to \mathcal{Y} \) defined by

\[
\Phi(t, X_0) = \Phi_t(X_0) := (T(t), e(\cdot, t), i(\cdot, t), V(t)), \quad (t, X_0) \in \mathbb{R}_+ \times \mathcal{Y}.
\]

In what follows, we denote

\[
\Omega(a) = e^{-\int_0^a \theta_1(\tau)d\tau} \quad \text{and} \quad \Gamma(b) = e^{-\int_0^b \theta_2(\tau)d\tau} \quad \text{for} \quad a, b \in \mathbb{R}_+.
\]

It follows from (iii) and (iv) of Assumption 1.1 that for all \( a, b \in \mathbb{R}_+ \),

\[
0 \leq \Omega(a) \leq e^{-\mu_0 a} \quad \text{and} \quad 0 \leq \Gamma(b) \leq e^{-\mu_0 b},
\]

\[
\Omega'(a) = -\theta_1(a) \Omega(a) \quad \text{and} \quad \Gamma'(b) = -\theta_2(b) \Gamma(b).
\]

For ease of notations, associated with each solution of (1.4), we introduce the following functions on \( \mathbb{R}_+ \),

\[
P(t) = \int_0^\infty q_1(a)e(a, t)da, \quad \quad Q(t) = \int_0^\infty q_2(b)i(b, t)db,
\]

\[
M(t) = \int_0^\infty \xi(a)e(a, t)da, \quad \quad N(t) = \int_0^\infty p(b)i(b, t)db.
\]

Integrating the second and third equations of (1.4) respectively along the characteristic lines \( t - a = \text{const} \) and \( t - b = \text{const} \) gives us

\[
e(a, t) = \begin{cases} 
T(t - a)[\beta V(t - a) + \beta_1 P(t - a) + \beta_2 Q(t - a)]\Omega(a) & \text{if } 0 \leq a \leq t \\
0 & \text{if } 0 \leq t \leq a
\end{cases}
\]

and

\[
i(b, t) = \begin{cases} 
M(t - b)\Gamma(b) = i(0, t - b)\Gamma(b) & \text{if } 0 \leq b \leq t, \\
i_0(b - t)\Gamma(b) & \text{if } 0 \leq t \leq b.
\end{cases}
\]

**Proposition 2.1.** Define

\[
\Xi = \left\{ X_0 = (T_0, e_0, i_0, V_0) \in \mathcal{Y} \big| T_0 > 0, T_0 + \| e_0 \|_{L^1} + \| i_0 \|_{L^1} \leq \frac{h}{\mu_0}, V_0 \leq \frac{pb}{\mu_0 e} \right\}.
\]

Then \( \Xi \) is a positively invariant and attractive subset of \( \Phi \).

**Proof.** Clearly, for a solution \((T(t), e(\cdot, t), i(\cdot, t), V(t))\) of (1.4) with initial condition \(X_0 \in \Xi\), we have \(T(t) > 0\) for \( t > 0 \).

It follows from (2.2) and changes of variables that

\[
\| e(\cdot, t) \|_{L^1} = \frac{\int_0^t e(0, t - a)\Omega(a)da}{\int_0^t \frac{e_0(a - t)}{\Omega(a - t)}da} + \left( \int_0^t e(0, \sigma)\Omega(t - \sigma) d\sigma \right) + \int_0^t e_0(\tau)\frac{\Omega(t + \tau)}{\Omega(\tau)}d\tau, \quad t \in \mathbb{R}_+,
\]

which yields

\[
\frac{d}{dt}\| e(\cdot, t) \|_{L^1} = e(0, t)\Omega(0) + \int_0^\infty e_0(\tau)\frac{d\Omega(t + \tau)}{d\tau}d\tau + \int_0^t e(0, \sigma)\frac{d\Omega(t - \sigma)}{d\sigma}d\sigma
\]

for \( t \in \mathbb{R}_+ \). With the help of (2.1) and changing of variables, one can easily get

\[
\frac{d}{dt}\| e(\cdot, t) \|_{L^1} = e(0, t)\Omega(0) - \int_0^\infty e_0(\tau)\frac{\theta_1(t + \tau)\Omega(t + \tau)}{\Omega(\tau)}d\tau
\]

\[
- \int_0^t e(0, \sigma)\theta_1(t - \sigma)\Omega(t - \sigma)d\sigma.
\]
for \( t \in \mathbb{R}_+ \). Similarly, we can get
\[
\frac{d||i(\cdot,t)||_{L^1}}{dt} = \int_0^\infty \xi(a)e(a,t)da - \int_0^\infty \theta_2(b)i(b,t)db, \quad t \in \mathbb{R}_+.
\]
Therefore, with the help of (iv) of Assumption \[1.1\] we have
\[
\frac{d(T(t) + ||e(\cdot,t)||_{L^1} + ||i(\cdot,t)||_{L^1})}{dt} \leq h - \mu_0(T(t) + ||e(\cdot,t)||_{L^1} + ||i(\cdot,t)||_{L^1})
\]
for \( t \in \mathbb{R}_+ \). It follows that, for \( t \in \mathbb{R}_+ \),
\[
T(t) + ||e(\cdot,t)||_{L^1} + ||i(\cdot,t)||_{L^1} \leq \frac{h}{\mu_0} - e^{-\mu_0 t} \left( \frac{h}{\mu_0} - (T_0 + ||e_0||_{L^1} + ||i_0||_{L^1}) \right), \quad (2.4)
\]
This, combined with the fourth equation of (1.4), tells us that, for \( t \in \mathbb{R}_+ \),
\[
\frac{dV(t)}{dt} \leq \bar{p} \left( \frac{h}{\mu_0} - e^{-\mu_0 t} \left( \frac{h}{\mu_0} - (T_0 + ||e_0||_{L^1} + ||i_0||_{L^1}) \right) \right) - eV(t)
\]
and consequently
\[
V(t) \leq e^{-ct}V_0 + \bar{p}e^{-ct} \int_0^t e^{cs} \left( \frac{h}{\mu_0} - e^{-\mu_0 s} \left( \frac{h}{\mu_0} - (T_0 + ||e_0||_{L^1} + ||i_0||_{L^1}) \right) \right) ds.
\]
Then
\[
V(t) \leq \frac{\bar{p}h}{\mu_0 c} - e^{-ct} \left( \frac{\bar{p}h}{\mu_0 c} - V_0 \right) - \bar{p}e^{-ct}t \left( \frac{h}{\mu_0} - e^{-\mu_0 t} \left( \frac{h}{\mu_0} - (T_0 + ||e_0||_{L^1} + ||i_0||_{L^1}) \right) \right)
\]
if \( c = \mu_0 \) and
\[
V(t) \leq \frac{\bar{p}h}{\mu_0 c} - e^{-ct} \left( \frac{\bar{p}h}{\mu_0 c} - V_0 \right) - \frac{\bar{p}}{c} \left( e^{-\mu_0 t} - e^{-ct} \right) \left( \frac{h}{\mu_0} - (T_0 + ||e_0||_{L^1} + ||i_0||_{L^1}) \right)
\]
if \( c \neq \mu_0 \). Now, the required results follow easily from (2.4) and the above inequalities.

According to Proposition \[2.1\] we only need to consider (1.4) with initial conditions in \( \Xi \) for the limiting behavior. The next result is a direct consequence of Proposition \[2.1\].

**Proposition 2.2.** Let \( A \geq \max \left\{ \frac{h}{\mu_0}, \frac{\bar{p}h}{\mu_0 c} \right\} \) be given. If \( X_0 \in \Xi \), then the following statements hold for all \( t \in \mathbb{R}_+ \).

(i) \( T(t), \|e(\cdot,t)\|_{L^1}, \|i(\cdot,t)\|_{L^1}, V(t) \leq A \);
(ii) \( P(t) \leq \bar{q}_1 A, Q(t) \leq \bar{q}_2 A, M(t) \leq \xi A, \) and \( N(t) \leq \bar{p} A; \)
(iii) \( e(0,t) \leq R^2 + \beta A^2 \) and \( i(0,t) \leq \xi A, \) where \( \beta = \beta_1 \bar{q}_1 + \beta_2 \bar{q}_2. \)

By Proposition \[2.2\] Assumption \[1.1\] and \[10\] Proposition 4.1, we can obtain the following basic properties of the functions \( P(t), Q(t), M(t), \) and \( N(t) \).

**Proposition 2.3.** Let \( A \geq \max \left\{ \frac{h}{\mu_0}, \frac{\bar{p}h}{\mu_0 c} \right\} \) be given. Then, for any solution of (1.4) with initial condition in \( \Xi \), the associated functions \( P(t), Q(t), M(t), \) and \( N(t) \) are Lipschitz continuous on \( \mathbb{R}_+ \) with Lipschitz constants
\[
L_P = (\bar{q}_1 \beta A + \bar{q}_1 \theta_1 + M_{q_1})A, \quad L_Q = (\bar{q}_2 \xi + \bar{q}_2 \theta_2 + M_{q_2})A,
\]
\[
L_M = (\bar{p} \xi + \bar{p} \theta_1 + M_{\xi})A, \quad L_N = (\bar{p} \xi + \bar{p} \theta_2 + M_{\xi})A,
\]
respectively.
2.2. The existence of equilibria. System \(1.4\) always has an infection-free equilibrium \(P^0 = (T^0, e^0, i^0, V^0) := (\frac{K}{h}, 0, 0, 0)\).

Generally, an equilibrium \((T^*, e^*, i^*, V^*) \in \mathcal{Y}\) of \(1.4\) satisfies

\[
\begin{aligned}
    &h -dT^* - \beta T^*V^* - \beta_1 T^* \int_0^\infty q_1(a)e^*(a)da - \beta_2 T^* \int_0^\infty q_2(b)i^*(b)db = 0, \\
    \frac{d}{dt}e^*(a) = -\theta_1(a)e^*(a), \\
    \frac{d}{dt}i^*(b) = -\theta_2(b)i^*(b), \\
    \int_0^\infty p(b)i^*(b)db = cV^*, \\
    e^*(0) = \beta T^*V^* + \beta_1 T^* \int_0^\infty q_1(a)e^*(a)da + \beta_2 T^* \int_0^\infty q_2(b)i^*(b)db, \\
    i^*(0) = \int_0^\infty \xi(a)e^*(a)da.
\end{aligned}
\]

(2.5)

It follows that if one of \(e^*, i^*, \text{ and } V^*\) is not zero then the others are not either, that is, an equilibrium must be an infection equilibrium if it is not the infection-free equilibrium. Denote

\[
\begin{aligned}
    H &= \int_0^\infty q_1(a)\Omega(a)da, & L &= \int_0^\infty q_2(b)\Gamma(b)db, \\
    K &= \int_0^\infty \xi(a)\Omega(a)da, & J &= \int_0^\infty p(b)\Gamma(b)db.
\end{aligned}
\]

(2.6)

Note that \(K > 0\) and \(J > 0\) by Assumption 1.1(iii). After a simple calculation, we see that \(1.4\) has infection equilibria if and only if \(R_0 > 1\) and in this case it only has a unique infection equilibrium \(P^* = (T^*, e^*, i^*, V^*)\) with

\[
T^* = \frac{h}{\beta \theta_0}, \quad e^*(\cdot) = h \left(1 - \frac{1}{R_0}\right) \Omega(\cdot), \\
i^*(\cdot) = h \left(1 - \frac{1}{R_0}\right) K \Gamma(\cdot), \quad V^* = \frac{hK}{c} \left(1 - \frac{1}{R_0}\right) \int_0^\infty p(b)\Gamma(b)db,
\]

(2.7)

where

\[
R_0 = \frac{\beta T^0 KL}{c} + \beta_1 T^0 H + \beta_2 T^0 KL.
\]

\(R_0\) is called the basic reproduction number of \(1.4\).

Biologically, \(\frac{\beta T^0 KL}{c}\) accounts for the total number of newly infected cells resulted from the cell-free infection mode, which is the basic reproduction number for the corresponding model with cell-free infection only. Similarly, \(\beta_1 T^0 H\) and \(\beta_2 T^0 KL\) denote the total numbers of newly infected cells that arise from any one latently infected cell and from the cell-to-cell transmission, respectively. \(\beta_2 T^0 KL\) is also the basic reproduction number for the corresponding model with the cell-to-cell transmission only. As we will see later, \(R_0\) serves as a sharp threshold parameter for \(1.4\), which completely determines the global behavior of \(1.4\).

In summary, we have shown the following result.

**Theorem 2.1.**

(i) If \(R_0 \leq 1\), then \(1.4\) only has the infection-free equilibrium \(P^0\).

(ii) If \(R_0 > 1\), then besides \(P^0\), \(1.4\) also has a unique infection equilibrium \(P^* = (T^*, e^*, i^*, V^*)\) defined by (2.7).

3. Asymptotic smoothness of \(\Phi(t, X_0)\). To give the proof of the global attractivity of equilibria, we will use the Lyapunov functional technique combined with the invariance principle. To this end, according to [35] Theorem 4.2 of Chapter IV, we have to ensure the relative compactness of the orbit \(\{\Phi(t, X_0) \mid t \in \mathbb{R}_+\}\) in \(\mathcal{Y}\).  


as our problem is an infinite dimensional dynamical system. To achieve this, we decompose \( \Phi: \mathbb{R}_+ \times \mathcal{Y} \to \mathcal{Y} \) into the following two operators \( \Theta, \Psi: \mathbb{R}_+ \times \mathcal{Y} \to \mathcal{Y} \),

\[
\begin{align*}
\Theta(t, X_0) &:= (0, \tilde{\varphi}_e(\cdot, t), \tilde{\varphi}_i(\cdot, t), 0), \\
\Psi(t, X_0) &:= (T(t), \tilde{\epsilon}(\cdot, t), \tilde{i}(\cdot, t), V(t)),
\end{align*}
\]

where

\[
\begin{align*}
\tilde{\varphi}_e(a, t) &= \begin{cases} 
0 & \text{if } t > a \geq 0, \\
e_0(a-t) \frac{\Omega(a)}{\Omega(a-t)} & \text{if } a \geq t \geq 0;
\end{cases} \\
\tilde{\varphi}_i(b, t) &= \begin{cases} 
0 & \text{if } t > b \geq 0, \\
i(b, t) & \text{if } b \geq t \geq 0;
\end{cases}
\end{align*}
\]

\[
\begin{align*}
\tilde{\epsilon}(a, t) &= \begin{cases} 
e(a, t) & \text{if } t > a \geq 0, \\
0 & \text{if } a \geq t \geq 0;
\end{cases} \\
i(b, t) &= \begin{cases} i(b, t) & \text{if } t > b \geq 0, \\
0 & \text{if } b \geq t \geq 0.
\end{cases}
\end{align*}
\]

Then \( \Phi(t, X_0) = \Theta(t, X_0) + \Psi(t, X_0) \) for \( t \in \mathbb{R}_+ \). Following the proof of [51, Proposition 3.13], we can arrive at the following main result of this section with the help of Lemma 3.1 and Lemma 3.2.

**Theorem 3.1.** For \( X_0 \in \mathcal{Y} \), the orbit \( \{\Phi(t, X_0) \mid t \in \mathbb{R}_+\} \) has a compact closure in \( \mathcal{Y} \).

**Lemma 3.1.** For \( r > 0 \), let \( \Delta(t, r) = e^{-\mu t} r \). Then \( \lim_{t \to \infty} \Delta(t, r) = 0 \) and if \( X_0 \in \mathcal{Y} \) with \( \|X_0\| \leq r \) then \( \|\Theta(t, X_0)\| \leq \Delta(t, r) \) for \( t \in \mathbb{R}_+ \).

**Proof.** Obviously, \( \lim_{t \to \infty} \Delta(t, r) = 0 \). By (2.2) and (2.3),

\[
\begin{align*}
\tilde{\varphi}_e(a, t) &= \begin{cases} 
0 & \text{if } t > a \geq 0, \\
e_0(a-t) \frac{\Omega(a)}{\Omega(a-t)} & \text{if } a \geq t \geq 0;
\end{cases} \\
\tilde{\varphi}_i(b, t) &= \begin{cases} 
0 & \text{if } t > b \geq 0, \\
i(b, t) & \text{if } b \geq t \geq 0;
\end{cases}
\end{align*}
\]

Then, for \( X_0 \in \mathcal{Y} \) satisfying \( \|X_0\| \leq r \) and for \( t \in \mathbb{R}_+ \), we have

\[
\|\Theta(t, X_0)\| = |0| + \|\tilde{\varphi}_e(\cdot, t)\|_{L^1} + \|\tilde{\varphi}_i(\cdot, t)\|_{L^1} + |0|
= \int_t^\infty \left| e_0(a-t) \frac{\Omega(a)}{\Omega(a-t)} \right| da + \int_t^\infty \left| i_0(b-t) \frac{\Gamma(b)}{\Gamma(b-t)} \right| db
\]

\[
= \int_0^\infty \left| e_0(\sigma) \frac{\Omega(\sigma+t)}{\Omega(\sigma)} \right| d\sigma + \int_0^\infty \left| i_0(\sigma) \frac{\Gamma(\sigma+t)}{\Gamma(\sigma)} \right| d\sigma
\]

\[
= \int_0^\infty \left| e_0(\sigma)e^{-\int_{\sigma}^{\infty} \theta_1(\tau)d\tau} \right| d\sigma + \int_0^\infty \left| i_0(\sigma)e^{-\int_{\sigma}^{\infty} \theta_2(\tau)d\tau} \right| d\sigma
\]

\[
\leq e^{-\mu t} \left| e_0 \right|_{L^1} + e^{-\mu t} \left| i_0 \right|_{L^1}
\]

\[
\leq e^{-\mu t} \left\| X_0 \right\|
\leq e^{-\mu t} r
= \Delta(t, r).
\]

This completes the proof.

**Lemma 3.2.** For \( t \in \mathbb{R}_+ \), \( \Phi(t, \cdot) \) maps any bounded set of \( \mathbb{R} \) into a set with compact closure in \( \mathcal{Y} \).

**Proof.** From Proposition 2.11, it is easily seen that \( T(t) \) and \( V(t) \) remain in the compact sets \( [0, \frac{A}{\mu_0}] \subset [0, A] \) and \( [0, \frac{1}{\mu_0 c}] \subset [0, A] \), respectively. Thus it suffices to show that \( \tilde{\epsilon}(\cdot, t) \) and \( \tilde{i}(\cdot, t) \) remain in precompact subsets of \( L^1(0, \infty) \), which
is independent of \( X_0 \in \Xi \). To achieve it, we only need to verify the following conditions for \( \tilde{e}(a, t) \) and similar ones for \( i(b, t) \) whose proofs are omitted (see, for example, \([30]\) Theorem B.2).

(i) The supremum of \( \| \tilde{e}(\cdot, t) \|_{L^1} \) with respect to \( X_0 \in \Xi \) is finite;
(ii) \( \lim_{h \to \infty} \int_0^h \tilde{e}(a, t) \, da = 0 \) uniformly with respect to \( X_0 \in \Xi \);
(iii) \( \lim_{h \to 0^+} \int_0^h |\tilde{e}(a+h, t) - \tilde{e}(a, t)| \, da = 0 \) uniformly with respect to \( X_0 \in \Xi \);
(iv) \( \lim_{h \to 0^+} \int_0^h \tilde{e}(a, t) \, da = 0 \) uniformly with respect to \( X_0 \in \Xi \).

It follows from \([22]\) and \([23]\) that

\[
0 \leq \tilde{e}(a, t) = \begin{cases} \tilde{e}(0, t-a)\Omega(a) & \text{if } 0 \leq a \leq t, \\ 0 & \text{if } 0 \leq t < a. \end{cases}
\]

This, together with Proposition \([22]\) and \([24]\), gives

\( \tilde{e}(a, t) \leq (\beta + \beta_1 q_1 + \beta_2 q_2) A^2 e^{-\mu_0 a} \),

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

Now, we are in a position to verify condition (iii). For sufficiently small \( h \in (0, t) \), we have

\[
\int_0^\infty |\tilde{e}(a+h, t) - \tilde{e}(a, t)| \, da = \int_0^{t-h} |e(a+h, t) - e(a, t)| \, da + \int_{t-h}^t |0 - e(a, t)| \, da
\]

\[
= \int_0^{t-h} |e(0, t-a-h)\Omega(a+h) - e(0, t-a)\Omega(a)| \, da
\]

\[
+ \int_{t-h}^t |e(0, t-a)\Omega(a)| \, da
\]

\[
\leq \Delta_1 + \Delta_2 + \tilde{\beta}A^2 h,
\]

where

\[
\Delta_1 = \int_0^{t-h} e(0, t-a-h)|\Omega(a+h) - \Omega(a)| \, da
\]

and

\[
\Delta_2 = \int_0^{t-h} e(0, t-a-h) - e(0, t-a)|\Omega(a)| \, da.
\]

Due to the fact that \( 0 \leq \Omega(a) \leq 1 \) and \( \Omega \) is a non-increasing function, we have

\[
\int_0^{t-h} |\Omega(a+h) - \Omega(a)| \, da = \int_0^{t-h} (\Omega(a) - \Omega(a+h)) \, da
\]

\[
= \int_0^{t-h} \Omega(a) \, da - \int_h^{t} \Omega(a) \, da
\]

\[
= \int_0^{t-h} \Omega(a) \, da - \int_h^{t-h} \Omega(a) \, da - \int_{t-h}^{t} \Omega(a) \, da
\]

\[
= \int_0^{h} \Omega(a) \, da - \int_{t-h}^{t} \Omega(a) \, da
\]

\[
\leq h.
\]

Hence, from Proposition \([22]\) we can conclude that

\[
\Delta_1 \leq \tilde{\beta}A^2 h.
\]
Next we estimate $\Delta_2$. Firstly, we have

$$\Delta_2 = \int_0^{t-h} \left| \beta V(t-a-h) + \beta_1 P(t-a-h) + \beta_2 Q(t-a-h) \right| T(t-a-h) \, da$$

$$= \int_0^{t-h} \left| \beta V(t-a) + \beta_1 P(t-a) + \beta_2 Q(t-a) \right| T(t-a) \, da$$

$$\leq \int_0^{t-h} \left| \beta T(t-a-h) V(t-a-h) - \beta T(t-a) V(t-a) \right| \Omega(a) \, da$$

$$+ \int_0^{t-h} \left| \beta_1 T(t-a-h) P(t-a-h) - \beta_1 T(t-a) P(t-a) \right| \Omega(a) \, da$$

$$+ \int_0^{t-h} \left| \beta_2 T(t-a-h) Q(t-a-h) - \beta_2 T(t-a) Q(t-a) \right| \Omega(a) \, da.$$

It follows from Proposition 2.2 and the first and fourth equations of (1.4) that follows from the above estimate that

$$\Delta_2 \leq Mh \int_0^{t-h} e^{-\mu_0 a} \, da \leq \frac{Mh}{\mu_0}.$$

Hence

$$\int_0^{t-h} \left| \tilde{e}(a+h,t) - \tilde{e}(a,t) \right| \, da \leq \left( \beta A^2 + \frac{M}{\mu_0} + \beta A^2 \right) h$$

and condition (iii) directly follows. This completes the proof.

From Proposition 2.1 and Theorem 3.1, we have the following result for the semi-flow \{\Phi(t)\}_{t \geq 0} as a consequence of the results on the existence of global attractors in Hale [7] and Smith and Thieme [50].

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

4. The uniform persistence. The aim of this section is to show that (1.3) is uniformly persistent under the condition that \(\mathcal{R}_0 > 1\).

Define a function \(\rho : \mathcal{Y} \to \mathbb{R}_+\) on \(\mathcal{Y}\) by

$$\rho(x, \varphi, \psi, y) = \beta xy + \beta_1 x \int_0^\infty q_1(a) \varphi(a) \, da + \beta_2 x \int_0^\infty q_2(b) \psi(b) \, db, \quad (x, \varphi, \psi, y) \in \mathcal{Y}.$$

Let

$$\mathcal{Y}_0 = \{X_0 \in \mathcal{Y} | \rho(\Phi(t_0, X_0)) > 0\}$$

for some \(t_0 \in \mathbb{R}_+\).

Then one can easily see that \(\Phi(t, X_0) \to \mathcal{P}^0\) as \(t \to \infty\) if \(X_0 \in \mathcal{Y} \setminus \mathcal{Y}_0\).

**Definition 4.1 ([50] pp. 61]).** System (1.3) is uniformly weakly \(\rho\)-persistent (respectively, uniformly strongly \(\rho\)-persistent) if there exists an \(\epsilon > 0\), independent of the initial conditions, such that

$$\limsup_{t \to \infty} \rho(\Phi(t, X_0)) > \epsilon$$

(respectively, \(\liminf_{t \to \infty} \rho(\Phi(t, X_0)) > \epsilon\))
for $X_0 \in Y_0$.

**Theorem 4.2.** Suppose $R_0 > 1$. Then (4.1) is uniformly weakly $\rho$-persistent.

**Proof.** By way of contradiction, for any $\varepsilon > 0$, there exists $X_0^\varepsilon \in Y_0$ such that

$$\lim_{t \to \infty} \rho(\Phi(t, X_0^\varepsilon)) \leq \varepsilon.$$  

Since $R_0 > 1$, there exists a sufficiently small $\varepsilon_0 > 0$ such that

$$1 < \frac{\beta}{c} \left( \frac{h-\varepsilon_0}{d} - \varepsilon_0 \right) \int_0^\infty p(b) \Gamma(b) db \int_0^\infty \xi(a) \Omega(a) da$$

\begin{equation}
+ \beta_1 \left( \frac{h-\varepsilon_0}{d} - \varepsilon_0 \right) \int_0^\infty q_1(a) \Omega(a) da
+ \beta_2 \left( \frac{h-\varepsilon_0}{d} - \varepsilon_0 \right) \int_0^\infty q_2(b) \Gamma(b) db \int_0^\infty \xi(a) \Omega(a) da. \tag{4.1}
\end{equation}

Then there exists $X_0^{2\varepsilon} \in Y_0$ (for simplicity, denoted by $X_0$ in the remaining of the proof) such that

$$\lim_{t \to \infty} \rho(\Phi(t, X_0)) \leq \frac{\varepsilon_0}{2}.$$  

Without loss of generality (with possible replacing of the initial condition), we can assume that

$$\rho(\Phi(t, X_0)) \leq \varepsilon_0, \quad t \in \mathbb{R}_+.$$  

We shall obtain a contradiction as follows.

It follows from the first equation of (4.1) that

$$\frac{d}{dt} \geq h - d T(t) - \varepsilon_0 \quad \text{for } t \in \mathbb{R}_+,$$

which implies that $\liminf_{t \to \infty} T(t) \geq \frac{h-\varepsilon_0}{d}$. As before, we can assume that

$$T(t) \geq \frac{h-\varepsilon_0}{d} - \varepsilon_0, \quad t \in \mathbb{R}_+.$$  

By the fourth equation of (4.1), we have

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

$$= \int_0^t e^{-c(t-\tau)} \int_0^\tau p(b) \Gamma(b) i(0, \tau - b) db d\tau$$

$$\geq \int_0^t e^{-c(t-\tau)} \int_0^\tau p(b) \Gamma(b) \int_0^{\tau-b} \xi(a) \Omega(a) e(0, \tau - b - a) da db d\tau.$$  

Then

$$e(0, t)$$

$$\geq \beta T(t) V(t) + \beta_1 T(t) \int_0^t q_1(a) e(a, t) da + \beta_2 T(t) \int_0^t q_2(b) i(b, t) db$$

$$\geq \beta \left( \frac{h-\varepsilon_0}{d} - \varepsilon_0 \right) \int_0^t e^{-c(t-\tau)} \int_0^\tau p(b) \Gamma(b) \int_0^{\tau-b} \xi(a) \Omega(a) e(0, \tau - b - a) da db d\tau$$

$$+ \beta_1 \left( \frac{h-\varepsilon_0}{d} - \varepsilon_0 \right) \int_0^t q_1(a) \Omega(a) e(0, t - a) da$$

$$+ \beta_2 \left( \frac{h-\varepsilon_0}{d} - \varepsilon_0 \right) \int_0^t q_2(b) \Gamma(b) \int_0^{t-b} \xi(a) \Omega(a) e(0, t - b - a) da db$$

for all $t \in \mathbb{R}_+$. Taking the Laplace transforms of the above inequality gives us

$$\mathcal{L}[e(0, \cdot)]$$

$$\geq \beta \left( \frac{h-\varepsilon_0}{d} - \varepsilon_0 \right) \int_0^\infty e^{-st} \int_0^t e^{-c(t-\tau)} \int_0^\tau p(b) \Gamma(b) \int_0^{\tau-b} \xi(a) \Omega(a) e(0, \tau - b - a) da db d\tau dt$$
Corollary 4.1. Suppose \( \Phi \) is a function \( \Phi: \mathbb{R} \to \mathcal{Y} \) such that \( \Phi(t, \mathcal{X}(r)) = \Phi(t + r) \) for all \( t, r \in \mathbb{R} \). Letting \( \lambda \) be a total trajectory passing through \( \mathcal{X}(0) \) such that it must be invariant. For a total trajectory \( \mathcal{X}(t) = (T(t), e(\cdot, t), i(\cdot, t), V(t)) \),

\[
e(a, r) = e(0, r - a) \Omega(a) \quad \text{for} \quad r \in \mathbb{R} \quad \text{and} \quad a \in \mathbb{R}_+,
\]

\[
i(b, r) = i(0, r - b) \Gamma(b) \quad \text{for} \quad r \in \mathbb{R} \quad \text{and} \quad b \in \mathbb{R}_+.
\]

The alpha limit of a total trajectory \( \mathcal{X} \) passing through \( \mathcal{X}(0) = X_0 \) is

\[
\alpha(X_0) = \bigcap_{t \leq 0} \bigcup_{s \leq t} \{X(s)\} \subseteq \mathcal{A}.
\]

Corollary 4.1. Suppose \( \mathcal{R}_0 > 1 \). Let \( \mathcal{X}(t) = (T(t), e(\cdot,t), i(\cdot, t), V(t)) \) be a total trajectory of \( \Phi \) in \( \mathcal{A} \cap \mathcal{Y}_0 \). Then there exists \( \varepsilon > 0 \) such that

\[
S(t), e(0, t), i(0, t), V(t) \geq \varepsilon \quad \text{for all} \quad t \in \mathbb{R}.
\]
Proof. On the one hand, by the first equation of (1.4) and Proposition 2.1,
\[ \frac{dT(t)}{dt} \geq h - \left( d + \frac{\beta \phi_h}{\mu_0 c} + \max\{\beta_1 \bar{q}_1, \beta_2 \bar{q}_2\} \frac{h}{\mu_0} \right) T(t) \quad \text{for } t \in \mathbb{R}, \]
which implies that
\[ \liminf_{t \to \infty} T(t) \geq \frac{h}{d + \frac{\beta \phi_h}{\mu_0 c} + \max\{\beta_1 \bar{q}_1, \beta_2 \bar{q}_2\} \frac{h}{\mu_0}} \triangleq \varepsilon_1. \]
This provides a lower bound \( \varepsilon_1 \) for the \( T \)-coordinate for any point in \( A \cap Y_0 \). On the other hand, by Theorem 4.3, there exists \( \varepsilon_2 > 0 \) such that \( e(0, t) \geq \varepsilon_2 \) for all \( t \in \mathbb{R} \). Then, for \( t \in \mathbb{R} \),
\[ i(0, t) = \int_0^\infty \xi(a)e(a, t) da = \int_0^\infty \xi(a) e(0, t-a) \Omega(a) da \geq \varepsilon_2 K \]
and hence
\[ \frac{dV(t)}{dt} = \int_0^\infty p(b)i(b, t)db - cV(t) = \int_0^\infty p(b)\Gamma(b)i(0, t-b)db - cV(t) \geq \varepsilon_2 K J - cV(t), \]
which implies that \( \liminf_{t \to \infty} V(t) \geq \varepsilon_2 K J \triangleq \varepsilon_3 \). This gives a lower bound \( \varepsilon_3 \) for the \( V \)-coordinate for any point in \( A \cap Y_0 \). Letting \( \varepsilon = \min\{\varepsilon_1, \varepsilon_2, \varepsilon_2 K, \varepsilon_3\} \) completes the proof. \( \square \)

5. The local stability of equilibria. We first investigate the local stability of the infection-free equilibrium \( P^0 \).

**Theorem 5.1.** The infection-free equilibrium \( P^0 \) is locally asymptotically stable if \( R_0 < 1 \) and it is unstable if \( R_0 > 1 \).

**Proof.** Linearizing (1.4) around the disease-free equilibrium \( P^0 \), we get the associated characteristic equation,
\[ C_0(\lambda) = 1, \quad (5.1) \]
where
\[ C_0(\lambda) = \frac{h\beta}{\lambda + c} \int_0^\infty \xi(a)e^{-\lambda a - \int_0^a \theta_1(s)ds} da \int_0^\infty p(b)e^{-\lambda b - \int_0^b \theta_2(s)ds} db + \frac{h\beta_1}{d} \int_0^\infty q_1(a)e^{-\lambda a - \int_0^a \theta_1(s)ds} da \int_0^\infty q_2(b)e^{-\lambda b - \int_0^b \theta_2(s)ds} db. \]
Since \( C_0 \) is a continuously differentiable function with \( \lim_{\lambda \to \infty} C_0(\lambda) = 0 \), \( \lim_{\lambda \to -\infty} C_0(\lambda) = \infty \), and \( C_0(0) = R_0 \), we know that (5.1) has a unique real root, say \( \lambda^* \). Moreover, noting \( C_0(0) = R_0 \), we have \( \lambda^* < 0 \) if \( R_0 < 1 \) and \( \lambda^* > 0 \) if \( R_0 > 1 \), which implies that \( P^0 \) is unstable if \( R_0 > 1 \). Now suppose that \( R_0 < 1 \). Let \( \lambda = \mu + \nu i \) be an arbitrary complex root of (5.1). Then
\[ 1 = |C_0(\lambda)| = |C_0(\mu + \nu i)| \leq C_0(\mu), \]
which implies that \( 0 > \lambda^* \geq \mu \). In other words, all roots of (5.1) have negative real parts and hence \( P^0 \) is locally asymptotically stable if \( R_0 < 1 \). This completes the proof. \( \square \)

**Theorem 5.2.** The unique infection equilibrium \( P^* \) of (1.4) is locally asymptotically stable when \( R_0 > 1 \).
Proof. This time, the characteristic equation at $P^*$ is
\[ C^*(\lambda) = (\lambda + d)C_1(\lambda) - \lambda - dR_0 = 0, \tag{5.2} \]
where
\[
C_1(\lambda) = \frac{\beta T^*}{\lambda} \int_0^\infty \xi(a) e^{-\lambda a - \int_0^a \theta_1(s) ds} da \int_0^\infty p(b) e^{-\lambda b - \int_0^b \theta_2(s) ds} db
+ \beta_1 T^* \int_0^\infty q_1(a) e^{-\lambda a - \int_0^a \theta_1(s) ds} da
+ \beta_2 T^* \int_0^\infty q_2(a) e^{-\lambda a - \int_0^a \theta_1(s) ds} da \int_0^\infty p(b) e^{-\lambda b - \int_0^b \theta_2(s) ds} db.
\]
It is sufficient to show that (5.2) has no roots with non-negative real parts. By way of contradiction, suppose that it has a root $\lambda = \mu + \nu i$ with $\mu \geq 0$. Then we have
\[
(\mu + \nu i + d)C_1(\mu + \nu i) - \mu - i\nu - dR_0 = 0.
\]
Separating the real parts of the above equality gives
\[
\Re C_1(\mu + \nu i) = \frac{(\mu + dR_0)(\mu + d) + \nu^2}{(\mu + d)^2 + \nu^2} > 1. \tag{5.3}
\]
Noticing that $C_1(0) = T^* \frac{\beta}{c_0} = 1$ and $C_1$ is a decreasing function, we have
\[
\Re C_1(\mu + \nu i) \leq |C_1(\mu)| = C_1(\mu) \leq C_1(0) = 1,
\]
which contradicts with (5.3). This completes the proof. \qed

6. Global stability of the infection-free equilibrium. In this section, we study the global stability of the infection-free equilibrium $P^0$. In the discussion, we need the important function $g$ on $(0, \infty)$ defined by $g(x) = x - 1 - \ln x$ for $x \in (0, \infty)$. This function is continuous and concave up. Moreover, it only attains its global minimum at $x = 1$ with $g(1) = 0$.

**Theorem 6.1.** The infection-free equilibrium $P^0$ of (1.1) is globally attractive if $R_0 \leq 1$.

**Proof.** Consider a candidate Lyapunov functional defined by
\[
\mathcal{L}_{IFE}(t) = \mathcal{L}_1(t) + \mathcal{L}_2(t) + \mathcal{L}_3(t) + \mathcal{L}_4(t),
\]
where $\mathcal{L}_1(t) = T^0 g \left( \frac{T^0(t)}{T} \right)$, $\mathcal{L}_2(t) = \int_0^\infty \phi(a) e(a, t) da$, $\mathcal{L}_3(t) = \int_0^\infty \psi(b) i(b, t) db$, and $\mathcal{L}_4(t) = \frac{\beta T^0}{c} V(t)$. Here the nonnegative kernel functions $\phi$ and $\psi$ will be determined later. By Proposition 2.1, without loss of generality, we can assume that $T_0 > 0$ and hence $\mathcal{L}_{IFE}$ is well defined. The derivative of $\mathcal{L}_1$ along the solutions of (1.1) is calculated as follows,
\[
\frac{d\mathcal{L}_1(t)}{dt} = \left( 1 - \frac{T^0}{T} \right) \left( h - dT - \beta TV - \beta_1 T \int_0^\infty q_1(a) e(a, t) da \right.
- \beta_2 T \int_0^\infty q_2(b) i(b, t) db \bigg)
\]
\[
= \left( 1 - \frac{T^0}{T} \right) \left( dT^0 - dT - \beta TV - \beta_1 T \int_0^\infty q_1(a) e(a, t) da \right.
- \beta_2 T \int_0^\infty q_2(b) i(b, t) db \bigg)
\]
Using integration by parts, we have
\[ \frac{dL_2(t)}{dt} = \int_0^\infty \phi(a) \frac{\partial e(a,t)}{\partial t} da \]
\[ = -\int_0^\infty \phi(a) \left[ \theta_1(a)e(a,t) + \frac{\partial e(a,t)}{\partial a} \right] da \]
\[ = -\phi(a)e(a,t) \bigg|_0^\infty + \int_0^\infty \phi'(a)e(a,t) da - \int_0^\infty \phi(a)\theta_1(a)e(a,t) da \]
\[ = \phi(0)e(0,t) + \int_0^\infty \left( \phi'(a) - \phi(a)\theta_1(a) \right) e(a,t) da. \]

Similarly,
\[ \frac{dL_3(t)}{dt} = \psi(0)i(0,t) + \int_0^\infty \left( \psi'(b) - \psi(b)\theta_2(b) \right) i(b,t) db. \]

It is easy to see that
\[ \frac{dL_4(t)}{dt} = \frac{\beta T^0}{c} \left( \int_0^\infty p(b)i(b,t) db - c V \right) = \frac{\beta T^0}{c} \int_0^\infty p(b)i(b,t) db - \beta T^0 V. \]

Therefore, we have
\[ \frac{dL(t)}{dt} = -dT_0 \left( 2 - \frac{T^0}{T} - \frac{T}{T_0} \right) - e(0,t) + \phi(0)e(0,t) \]
\[ + \int_0^\infty \left( \phi'(a) - \phi(a)\theta_1(a) + \beta_1 T^0 q_1(a) + \psi(0)\xi(a) \right) e(a,t) da \]
\[ + \int_0^\infty \left( \psi'(b) - \psi(b)\theta_2(b) + \beta_2 T^0 q_2(b) + \frac{\beta T^0}{c} p(b) \right) i(b,t) db. \]

Now we choose
\[ \psi(b) = \int_b^\infty \left( \frac{\beta T^0}{c} p(u) + \beta_2 T^0 q_2(u) \right) e^{-\int_u^\infty \theta_2(\omega) d\omega} du \]
and
\[ \phi(a) = \int_a^\infty \left( \beta_1 T^0 q_1(u) + \psi(0)\xi(u) \right) e^{-\int_u^\infty \theta_1(\omega) d\omega} du. \]

Then \( \psi(0) = \frac{\beta T^0}{c} + \beta_2 T^0 L, \phi(0) = \Re_0, \) and \( \psi \) and \( \phi \) satisfy
\[ \psi'(b) - \psi(b)\theta_2(b) + \beta_2 T^0 q_2(b) + \frac{\beta T^0}{c} p(b) = 0, \]
and
\[ \phi'(a) - \phi(a)\theta_1(a) + \beta_1 T^d q_1(a) + \psi(0)\xi(a) = 0, \]
respectively. It follows that the derivative of \( \mathcal{L}_{IF} \) along solutions of (1.4) is
\[ \frac{d\mathcal{L}_{IF}(t)}{dt} = -dT_0 \left( 2 - \frac{T^0}{T} - \frac{T}{T_0} \right) + (\Re_0 - 1)e(0, t) \leq 0. \]
Notice that \( \frac{d\mathcal{L}_{IF}(t)}{dt} = 0 \) implies that \( T = T^0 \). It can be verified that the largest invariant set where \( \frac{d\mathcal{L}_{IF}(t)}{dt} = 0 \) is the singleton \( \{ P^0 \} \). Therefore, by the invariance principle, \( P^0 \) is globally attractive when \( \Re_0 \leq 1 \).

The following result immediately follows from Theorem 5.1 and Theorem 6.1.

Theorem 6.2. If \( \Re_0 < 1 \) then the infection-free equilibrium \( P^0 \) of (1.4) is globally asymptotically stable.

7. Global stability of the infection equilibrium. To establish the global stability of the infection equilibrium, we need the following properties of solutions to (1.4).

Lemma 7.1. Suppose that \( \Re_0 > 1 \). Then, for any solution \((T(t), e(\cdot, t), i(\cdot, t), V(t))\) of (1.4) with \((T_0, e_0, i_0, V_0) \in \mathcal{Y}_0 \), the following equalities hold.

\[ 0 = \int_0^\infty \beta T^* J\xi(a) c e^*(a) \left[ 1 - \frac{e(a, t)i^*(0)}{e^*(a)i(0, t)} \right] da, \]  
(7.1)

\[ 0 = \int_0^\infty \beta_2 T^* \xi(a) Le^*(a) \left[ 1 - \frac{e(a, t)i^*(a)}{e^*(a)i(a, t)} \right] da, \]  
(7.2)

\[ 0 = \int_0^\infty \beta T^* p(b) c i^*(b) \left[ 1 - \frac{e^*(0)TV}{e(0, t)T^*V^*} \right] \left. \right|_a \]  
\[ + \int_0^\infty \beta_1 T^* q_1(a) e^*(a) \left[ 1 - \frac{Te^*(0)e(a, t)}{Te^*(0)e^*(a)} \right] da \]  
\[ + \int_0^\infty \beta_2 T^* q_2(b) i^*(b) \left[ 1 - \frac{Te^*(0)i(b, t)}{Te^*(0)i^*(b)} \right] db. \]  
(7.3)

Proof. The proofs of (7.1)–(7.3) are quite similar and we only give that for (7.1) as an illustration. In fact,
\[ \int_0^\infty \beta T^* J\xi(a) c e^*(a) \left[ 1 - \frac{e(a, t)i^*(0)}{e^*(a)i(0, t)} \right] da \]  
\[ = \frac{\beta T^* J}{c} \int_0^\infty e^*(a)\xi(a) da - \frac{i^*(0)}{i(0, t)} \int_0^\infty e^*(a)\xi(a) \frac{da}{i(0, t)} \]  

This, combined with (1.5) and (2.5), immediately gives (7.1).

Theorem 7.1. Assume that \( \Re_0 > 1 \). Then the unique infection equilibrium \( P^* = (T^*, e^*, i^*, V^*) \) of (1.4) defined by (2.4) is globally asymptotically stable in \( \mathcal{Y}_0 \).

Proof. By Theorem 6.2 it suffices to show that \( \mathcal{A} \cap \mathcal{Y}_0 = \{ P^* \} \). We show this by applying the Lyapunov functional technique again. Define
\[ G(x, y) = x - y - x \ln \frac{x}{y} \quad \text{for } x, y > 0. \]
It is easy to see that $G$ is non-negative on $(0, \infty) \times (0, \infty)$ with the minimum value 0 only when $x = y$. Furthermore, it is easy to verify that $xG_x[x, y] + yG_y[x, y] = G[x, y]$. Let $X(t) = (T(t), e(\cdot, t), i(\cdot, t), V(t))$ be a total trajectory in $A \cap Y_0$. Consider a candidate Lyapunov functional defined as follows,

$$L_{EE}(t) = H_1(t) + H_2(t) + H_3(t) + H_4(t),$$

where

$$H_1(t) = G[T, T^*],$$
$$H_2(t) = \int_0^\infty \phi_1(a)G[e(a, t), e^*(a)] da,$$
$$H_3(t) = \int_0^\infty \psi_1(b)G[i(b, t), i^*(b)] db,$$
$$H_4(t) = \frac{\beta T^*}{e} G[V, V^*]$$

with

$$\phi_1(a) = \int_a^\infty \left( \beta_1 T^* q_1(u) + \psi(0) \xi(u) \right) e^{-\int_u^\infty \beta_1(\omega) da} du$$

and

$$\psi_1(b) = \int_b^\infty \left( \frac{\beta T^*}{c} p(u) + \beta_2 T^* q_2(u) \right) e^{-\int_u^\infty \beta_2(\omega) da} du$$

(This reason of this choice is similar to that in the Proof of Theorem 6.1). One can easily see that $\phi_1(0) = 1$, $\psi_1(0) = \frac{\beta T^*}{c} + \beta_2 T^*$, and

$$\psi'_1(b) - \phi_1(b) \theta_2(b) = - \left( \frac{\beta T^*}{c} p(b) + \beta_2 T^* q_2(b) \right),$$
$$\phi'_1(a) - \phi_1(a) \theta_1(a) = - \left( \beta_1 T^* q_1(a) + \psi(0) \xi(a) \right). \quad (7.4)$$

Note that $T(t)$, $e(0, t)$, $i(0, t)$, and $V(t)$ are bounded. Moreover, they are also bounded away from 0 by Corollary 4.1. Hence $L_{EE}(t)$ is well-defined and is bounded on $X(t)$.

Now, we show that $\frac{dL_{EE}(t)}{dt}$ is non-positive. Firstly,

$$\frac{dH_1(t)}{dt} = \left( 1 - \frac{T^*}{T} \right) \left( h - dT - \beta T V - \beta_1 T \int_0^\infty q_1(a) e(a, t) da \right)$$
$$\quad - \beta_2 T \int_0^\infty q_2(b) i(b, t) db$$
$$= \left( 1 - \frac{T^*}{T} \right) \left( h - dT - e(0, t) \right)$$
$$= \left( 1 - \frac{T^*}{T} \right) \left( dT^* - dT + e^*(0) - e(0, t) \right)$$
$$= -dT^* \left( 2 - \frac{T}{T^*} - \frac{T^*}{T} \right) + e^*(0) - e(0, t) - e^*(0) \frac{T^*}{T} + e(0, t) \frac{T^*}{T}.$$

Secondly, using (2.2) we have

$$H_2(t) = \int_0^t \phi(a) G[e(0, t - a) \Omega(a), e^*(a)] da$$

...
The second last equality follows from (2.2) and the fact that \( xG = dt \). Similarly, we have
\[
+ \int_{t}^{\infty} \phi(a)G[e_{0}(a-t)e^{-\int_{0}^{a-t} \theta_{1}(\omega)d\omega}, e^{*}(a)]da
\]
\[
= \int_{0}^{t} \phi(t-r)G[e(0,r)\Omega(t-r), e^{*}(t-r)]dr
\]
\[
+ \int_{0}^{\infty} \phi(t+r)G[e_{0}(r)e^{-\int_{0}^{t+r} \theta_{1}(\omega)d\omega}, e^{*}(t+r)]dr.
\]
Differentiating and using \( e^{*}(a) = e^{*}(0)e^{-\int_{0}^{a} \theta_{1}(\omega)d\omega} \) and \( e(0, t) \), produce
\[
\frac{dH_{2}(t)}{dt} = G[e(0, t), e^{*}(0)] + \int_{0}^{t} \phi'(t-r)G[e(0, r)e^{-\int_{0}^{t-r} \theta_{1}(\omega)d\omega}, e^{*}(t-r)]dr
\]
\[
- \int_{0}^{t} \phi(t-r)\theta_{1}(t-r)[e(0, r)e^{-\int_{0}^{t-r} \theta_{1}(\omega)d\omega}]G[e(0, r)e^{-\int_{0}^{t-r} \theta_{1}(\omega)d\omega}, e^{*}(t-r)]
\]
\[
+ e^{*}(t-r)Gy[e(0, r)e^{-\int_{0}^{t-r} \theta_{1}(\omega)d\omega}, e^{*}(t-r)]
\]
\[
+ \int_{0}^{\infty} \phi'(t+r)G[e_{0}(r)e^{-\int_{0}^{t+r} \theta_{1}(\omega)d\omega}, e^{*}(t+r)]dr
\]
\[
- \int_{0}^{\infty} \phi(t+r)\theta_{1}(t+r)[e_{0}(r)e^{-\int_{0}^{t+r} \theta_{1}(\omega)d\omega}]G[e_{0}(r)e^{-\int_{0}^{t+r} \theta_{1}(\omega)d\omega}, e^{*}(t+r)]
\]
\[
+ e^{*}(t+r)Gy[e_{0}(r)e^{-\int_{0}^{t+r} \theta_{1}(\omega)d\omega}, e^{*}(t+r)]
\]
\[
= G[e(0, t), e^{*}(0)] + \int_{0}^{\infty} \left[ \phi'(a) - \phi(a)\theta_{1}(a) \right]G[e(a, t), e^{*}(a)]da
\]
\[
= \int_{0}^{\infty} \left[ \beta_{2}T^{*}q_{1}(a) + \psi_{1}(0)\xi(a) \right] e^{*}(a) - e(a, t) + e^{*}(a) \ln \frac{e(a, t)}{e^{*}(a)} \right) da
\]
\[
+ e(0, t) - e^{*}(0) - e^{*}(0) \ln \frac{e(0, t)}{e^{*}(0)}.
\]

The second last equality follows from (2.2) and the fact that \( xG_{2}[x, y] + yG_{y}[x, y] = G[x, y] \). Similarly, we have
\[
\frac{dH_{3}(t)}{dt} = \psi(0)G[i(0, t), i^{*}(0)] + \int_{0}^{\infty} \left[ \psi'(b) - \psi(b)\theta_{2}(b) \right]G[i(b, t), i^{*}(b)]db
\]
\[
= \int_{0}^{\infty} \left[ \frac{\beta T^{*}}{c}p(b) + \beta_{2}T^{*}q_{2}(b) \right] \left( i^{*}(b) - i(b, t) + i^{*}(b) \ln \frac{i(b, t)}{i^{*}(b)} \right) db
\]
\[
+ \left( \frac{\beta T^{*}J}{c} + \beta_{2}T^{*}L \right) \left( i(0, t) - i^{*}(0) - i^{*}(0) \ln \frac{i(0, t)}{i^{*}(0)} \right).
\]

Finally,
\[
\frac{dH_{4}(t)}{dt} = \frac{\beta T^{*}}{c} \left( 1 - \frac{V^{*}}{V} \right) \frac{dV(t)}{dt}
\]
\[
= \frac{\beta T^{*}}{c} \left( 1 - \frac{V^{*}}{V} \right) \left( \int_{0}^{\infty} p(b)i(b, t)db - cV(t) \right)
\]
\[
= \frac{\beta T^{*}}{c} \int_{0}^{\infty} p(b)i(b, t)db - \beta T^{*}V + \beta T^{*}V^{*} - \frac{\beta T^{*}V^{*}}{cV} \int_{0}^{\infty} p(b)i(b, t)db.
\]
If follows from $\psi_1(0) = \frac{\beta T^*}{c} + \beta_2 T^* L$ that
\[
\frac{dL_{EE}}{dt} = -dT^* \left( 2 - \frac{T}{T^*} - \frac{T^*}{T} \right) - e^*(0) \frac{T^*}{T} + e(0, t) \frac{T^*}{T} - e^*(0) \ln \frac{e(0, t)}{e^*(0)}
\]
\[+ \int_0^\infty \beta_1 T^* q_1(a) \left( e^*(a) - e(a, t) + e^*(a) \ln \frac{e(a, t)}{e^*(a)} \right) da
\]
\[+ \int_0^\infty \left( \frac{\beta T^* J}{c} + \beta_2 T^* L \right) \xi(a) \left( e^*(a) - e(a, t) + e^*(a) \ln \frac{e(a, t)}{e^*(a)} \right) da
\]
\[+ \int_0^\infty \left[ \frac{\beta T^* J}{c} p(b) + \beta_2 T^* q_2(b) \right] \left( t^*(b) - i(b, t) + i^*(b) \ln \frac{i(b, t)}{i^*(b)} \right) db (7.5)
\]
\[+ \int_0^\infty \left[ \frac{\beta T^* J}{c} p(b) + \beta_2 T^* q_2(b) \right] \left( t^*(b) - i(b, t) + i^*(b) \ln \frac{i(b, t)}{i^*(b)} \right) db
\]
From the second equation of (1.5) and the sixth equation of (2.5), we have
\[\int_0^\infty \left( \frac{\beta T^* J}{c} + \beta_2 T^* L \right) \xi(a) \left( e^*(a) - e(a, t) \right) da = \left( \frac{\beta T^* J}{c} + \beta_2 T^* L \right) t^*(0, t) - i^*(0, t)
\]
Thus (7.5) reduces to
\[
\frac{dL_{EE}}{dt} = -dT^* \left( 2 - \frac{T}{T^*} - \frac{T^*}{T} \right) - e^*(0) \frac{T^*}{T} + e(0, t) \frac{T^*}{T} - e^*(0) \ln \frac{e(0, t)}{e^*(0)}
\]
\[+ \int_0^\infty \beta_1 T^* q_1(a) \left( e^*(a) - e(a, t) + e^*(a) \ln \frac{e(a, t)}{e^*(a)} \right) da
\]
\[+ \int_0^\infty \left( \frac{\beta T^* J}{c} + \beta_2 T^* L \right) \xi(a) e^*(a) \ln \frac{e(a, t)}{e^*(a)} i(0, t) da
\]
\[+ \int_0^\infty \left[ \frac{\beta T^* J}{c} p(b) + \beta_2 T^* q_2(b) \right] \left( t^*(b) - i(b, t) + i^*(b) \ln \frac{i(b, t)}{i^*(b)} \right) db
\]
\[+ \int_0^\infty \left[ \frac{\beta T^* J}{c} p(b) + \beta_2 T^* q_2(b) \right] \left( t^*(b) - i(b, t) + i^*(b) \ln \frac{i(b, t)}{i^*(b)} \right) db
\]
With the help of the first equation of (1.5) and the fifth equation of (2.5), we see
\[
\frac{dL_{EE}(t)}{dt} = -dT^* \left( 2 - \frac{T}{T^*} - \frac{T^*}{T} \right) - \left( \int_0^\infty \frac{\beta T^* p(b)}{c} i^*(b) db \right)
\]
\[+ \int_0^\infty \beta_1 T^* q_1(a) e^*(a) da + \int_0^\infty \beta_2 T^* q_2(b) i^*(b) db \left( \frac{T^*}{T} + \ln \frac{e(0, t)}{e^*(0)} \right)
\]
\[+ \beta T^* V + \int_0^\infty \beta_1 T^* q_1(a) e(a, t) da + \int_0^\infty \beta_2 T^* q_2(b) i(b, t) db
\]
\[+ \int_0^\infty \beta_1 T^* q_1(a) \left( e^*(a) - e(a, t) + e^*(a) \ln \frac{e(a, t)}{e^*(a)} \right) da
\]
\[+ \int_0^\infty \left( \frac{\beta T^* J}{c} + \beta_2 T^* L \right) \xi(a) e^*(a) \ln \frac{e(a, t)}{e^*(a)} i(0, t) da
\]
\[+ \int_0^\infty \left[ \frac{\beta T^* J}{c} p(b) + \beta_2 T^* q_2(b) \right] \left( t^*(b) - i(b, t) + i^*(b) \ln \frac{i(b, t)}{i^*(b)} \right) db
\]
With the help of (7.1)–(7.3), we obtain

\[
\int_0^\infty \frac{\beta T^*}{c} p(b)i(b,t)db - \beta T^*V + \beta T^*V^* - \frac{V^*}{V} \int_0^\infty \frac{\beta T^*}{c} p(b)i(b,t)db.
\]

Collecting the terms of (7.4) yields

\[
d\mathcal{L}_{EE}(t) = -dT^*\left(2 - \frac{T}{T^*} - \frac{T^*}{T}\right)
\]

\[
+ \int_0^\infty \left(\frac{\beta T^*J}{c} + \beta_2 T^*L\right) \xi(a) e^*(a) \ln \frac{e^*(a)i(0)}{e^*(a)i(0,t)} da
\]

\[
+ \int_0^\infty \beta_1 T^* q_1(a) e^*(a) \left(1 + \ln \frac{e^*(a)}{e^*(a)i(0,t)} - \ln \frac{e^*(0)}{e^*(0)}\right) da
\]

\[
+ \int_0^\infty \beta_2 T^* q_2(b)i^*(b) \left(1 + \ln \frac{i(b)}{i^*(b)} - \ln \frac{e^*(0)}{e^*(0)}\right) db
\]

\[
+ \int_0^\infty \frac{\beta T^*}{c} p(b)i^*(b) \left(2 + \ln \frac{i(b)}{i^*(b)} - \frac{T^*}{T} - \ln \frac{V^*i(b,t)}{V^*i^*(b)}\right) db,
\]

or

\[
d\mathcal{L}_{EE}(t) = -dT^*\left(2 - \frac{T}{T^*} - \frac{T^*}{T}\right)
\]

\[
+ \int_0^\infty \left(\frac{\beta T^*J}{c} + \beta_2 T^*L\right) \xi(a) e^*(a) \left(1 - \frac{e^*(a)i(0)}{e^*(a)i(0,t)} + \ln \frac{e^*(a)i(0,t)}{e^*(a)i(0)}\right) da
\]

\[
- \int_0^\infty \left(\frac{\beta T^*J}{c} + \beta_2 T^*L\right) \xi(a) e^*(a) \left(1 - \frac{e^*(a)i(0)}{e^*(a)i(0,t)} - \ln \frac{e^*(0)}{e^*(0)}\right) da
\]

\[
+ \int_0^\infty \frac{\beta T^*p(b)}{c} i^*(b) \left(1 - \frac{T^*}{T} + \ln \frac{T^*}{T} + 1 - \frac{V^*i(b,t)}{V^*i^*(b)} + \ln \frac{V^*i(b,t)}{V^*i^*(b)}\right)
\]

\[
+ 1 - \frac{TV e^*(0)}{T^*V^*e(0,t)} + \ln \frac{TV e^*(0)}{T^*V^*e(0,t)}\right) db + \int_0^\infty \beta_1 T^* q_1(a) e^*(a) \left(1 - \frac{T^*}{T}\right) da
\]

\[
+ \ln \frac{T^*}{T} + 1 - \frac{T c^*(0)e(a,t)}{T^*e(0,t)e^*(a)} + \ln \frac{T c^*(0)e(a,t)}{T^*e(0,t)e^*(a)}\right) da
\]

\[
+ \int_0^\infty \beta_2 T^* q_2(b)i^*(b) \left(1 - \frac{T^*}{T} + \ln \frac{T^*}{T} + 1 - \frac{T e^*(0)i(b,t)}{T^*e(0,t)i^*(b)}\right)
\]

\[
+ \ln \frac{T e^*(0)i(b,t)}{T^*e(0,t)i^*(b)} db - \left\{ \int_0^\infty \frac{\beta T^*p(b)}{c} i^*(b) \left[1 - \frac{e^*(0)TV}{e(0,t)T^*V^*}\right] db
\]

\[
+ \int_0^\infty \beta_1 T^* q_1(a) e^*(a) \left[1 - \frac{T e^*(0)e(a,t)}{T^*e(0,t)e^*(a)}\right] da
\]

\[
+ \int_0^\infty \beta_2 T^* q_2(b)i^*(b) \left[1 - \frac{T e^*(0)i(b,t)}{T^*e(0,t)i^*(b)}\right] db\right\}.
\]

With the help of (7.1)–(7.3), we obtain

\[
d\mathcal{L}_{EE}(t) \leq -dT^*\left(2 - \frac{T}{T^*} - \frac{T^*}{T}\right)
\]
The basic reproduction number of (8.1) is given by the symbols for parameters in order to be consistent with (1.4)). Cells are not included, model (1.4) reduces to model (1.3) (here we have changed the latent cells changes when the latency cells are included. Note that if latency and 7.1 by performing numerical simulations. Further, we show how the distribution

Therefore, \( \mathcal{L}_{EE} \) is a non-increasing function. Since \( \mathcal{L}_{EE} \) is bounded on \( X(t) \), \( \alpha(X_0) \) must be contained in the largest invariant subset \( \mathcal{M} \) in \( \{ \mathcal{L}_{EE} = 0 \} \). Clearly, \( \frac{d\mathcal{L}_{EE}(t)}{dt} = 0 \) implies that \( T = T^* \) and

\[
\frac{i(b,t)}{i^*(b)} = \frac{i(0,t)}{i^*(0)} = \frac{V(0,t)}{V^*} = \frac{e(0,t)}{e^*(0)} = \frac{e(a,t)}{e^*(a)} \text{ for all } a, b \in \mathbb{R}_+.
\]

Then it is not difficult to check that \( \mathcal{M} = \{ P^* \} \).

From the above discussion, we see that \( \alpha(X_0) = \{ P^* \} \) and hence \( \mathcal{L}_{EE}(X(t)) \leq \mathcal{L}_{EE} \{ P^* \} \) for all \( t \in \mathbb{R} \). It follows that \( X(t) \equiv P^* \) and so \( \mathcal{A} \cap \mathcal{Y}_0 = \{ P^* \} \). This completes the proof.

8. Numerical examples. In this section, we illustrate the validity of Theorems 6.2 and 7.1 by performing numerical simulations. Further, we show how the distribution of infected cells changes when the latency cells are included. Note that if latency cells are not included, model (1.4) reduces to model (1.3) (here we have changed the symbols for parameters in order to be consistent with (1.4)),

\[
\begin{align*}
\frac{dT}{dt} &= h - dT(t) - \beta T(t)V(t) - \beta_2 T(t) \int_0^{\infty} q_2(b,i(b,t))db, \\
\frac{dV}{dt} &= \frac{a}{d} i(b,t) = -\theta_2(b)i(b,t), \\
\frac{d}{dt} \int_0^{\infty} p(b)i(b,t)db &\leq -cV(t),
\end{align*}
\]

with boundary conditions

\[
i(0,t) = \beta T(t)V(t) + \beta_2 T(t) \int_0^{\infty} q_2(b)i(b,t)db,
\]

and initial conditions

\[
T(0) = T_0 \in \mathbb{R}_+, \quad i(\cdot,0) = i_0 \in L^1_+(0,\infty), \quad V(0) = V_0 \in \mathbb{R}_+.
\]

The basic reproduction number of (8.1) is given by

\[
\Re_0^{8.1} = \frac{\beta_1 T_0 J}{c} + \beta_2 T_0 L,
\]

where \( J \) and \( L \) are defined in (2.6). According to Theorem 1.1 in [37], \( \Re_0^{8.1} \) serves as the sharp threshold parameter of model (8.1). We artificially choose some functions in (8.1) as follows,

\[
g(a) = 1 + \sin \left( \frac{(a - 5)\pi}{200} \right), \quad p(a) = q_1(a) = 0.1g(a),
\]
\[ q_2(a) = 0.6g(a), \]
\[ \theta_1(a) = 0.4g(a), \]
\[ \theta_2(a) = 0.5g(a), \]
\[ \xi(a) = 0.25g(a). \]

First, with the following parameter values,
\[ h = 0.5, \ d = 0.001, \ \beta = 0.00007, \ \beta_1 = 0.00001, \ \beta_2 = 0.00005, \ c = 0.01, \quad (8.3) \]
\[ R_0 = 0.445771 < 1 \text{ and } R_0^{8.1} = 0.724973. \] Hence, from Theorem 6.2 we see that the infection-free equilibrium is globally asymptotically stable. In fact, in Figure 2 the numbers of infected cells of (8.1) and (1.4), and the number of latent cells of (1.4)

![Figure 2](image)

**Figure 2.** The distributions of infected cells and latent cells with parameter (8.3) of (1.4) will converge to zero. In Figure 2(d), we also depicted the time evolution of infected cells of both models at infection age 0.

Now, we keep the parameter values in (8.3) except changing \( h \) into 1. In this case, \( R_0 = 0.891543 < 1 \) and \( R_0^{8.1} = 1.449946 > 1. \) Hence, from Theorem 6.2 we see that the infection-free equilibrium of (1.4) is globally asymptotically stable, which is supported by Figure 3(a). However, the infected cells of (8.1) will converge to positive distribution according to Theorem 1.1 in [37]. Again, Figure 3(d) shows the difference of time evolution of \( i(t, 0) \) for both models.

Finally, we choose the following epidemic parameter values,
\[ h = 1, \ d = 0.001, \ \beta = 0.0002, \ \beta_1 = 0.00001, \ \beta_2 = 0.00005, \ c = 0.01. \quad (8.4) \]
Then we have $\mathcal{R}_0 = 2.474853 > 1$ and $\mathcal{R}_0^{(8.1)} = 4.03204 > 1$. Hence the infection equilibria for both models are globally asymptotically stable. Figure 4 has illustrated this for the infected cells and latent cells.

Figures 2, 3, and 4 tell us that incorporating latency-age structured cells can significantly decrease the distribution of infected cells. This can be easily seen from (d) of the Figures. Moreover, on the one hand, compared to the basic reproduction number $\mathcal{R}_0^{(8.1)}$, $\mathcal{R}_0$ does not altered the global dynamics qualitatively. On the other hand, from the examples of parameter values, if latency-age structured cells are ignored, then the basic reproduction number will be over-estimated. In practice, this would lead to wrong diagnosis.

9. Summary. In this paper, an age-structured HIV infection model incorporating latency and cell-to-cell transmission is proposed. We focus on the mathematical analysis of the model, which is formulated as a hybrid system consisting of coupled ordinary differential equations and partial differential equations. After addressing the relative compactness and persistence of the solution semi-flow and the existence of a global attractor, we establish a threshold dynamics completely determined by the basic reproduction number $\mathcal{R}_0$. Namely, if $\mathcal{R}_0 < 1$ then the infection-free equilibrium is globally asymptotically stable, which means that the virus can be cleared; if $\mathcal{R}_0 > 1$ then the infection equilibrium is globally attractive to solutions with initial effective infection and hence the virus is persistent.
The threshold dynamics is supported with numerical simulations, which also indicate how the inclusion of latent cells affects the distribution of infected cells. On the one hand, including latent cells will decrease the basic reproduction number corresponding with the case without it and hence it can make the infection less persistent. On the other hand, when the infection is persistent, the inclusion of latent cells can significantly decrease the level of infected cells at the infection equilibrium. In other words, without considering latent cells will overestimate the infection. From the perspective of therapy, this may lead to overdose.

However due to the virus persistence in cellular compartments or reservoirs, how to design and solve the situation of long-term low viral load persistence in patients with antiretroviral therapy remains an interesting question to address in the future.

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E-mail address: jinliangwang@hlju.edu.cn
E-mail address: jiyinlingang@aliyun.com
E-mail address: ychen@wlu.ca