HOPF BIFURCATION OF AN AGE-STRUCTURED VIRUS INFECTION MODEL

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Abstract. In this paper, we introduce and analyze a mathematical model of a viral infection with explicit age-since infection structure for infected cells. We extend previous age-structured within-host virus models by including logistic growth of target cells and allowing for absorption of multiple virus particles by infected cells. The persistence of the virus is shown to depend on the basic reproduction number $R_0$. In particular, when $R_0 \leq 1$, the infection free equilibrium is globally asymptotically stable, and conversely if $R_0 > 1$, then the infection free equilibrium is unstable, the system is uniformly persistent and there exists a unique positive equilibrium. We show that our system undergoes a Hopf bifurcation through which the infection equilibrium loses the stability and periodic solutions appear.

1. Introduction. Within-host virus dynamics has been studied by many authors using differential equations to model the coupled changes in target cell, infected cell and virus populations; e.g. Perelson and Nelson [23], De Leenheer and Smith [8], Nowak and May [21], Culshaw and Ruan [7]. In particular, age-structured virus models have been of recent interest in the literature. Nelson et. al. [20], proposed an age structured model for HIV-1 infection, which generalizes the standard delay differential equation models by allowing for infected cell death rate and viral production to vary with age since infection of an infected cell. Rong et. al. [25] considered two age-structured models to study HIV-1 infection dynamics which extend the existing age-structured models by Nelson et. al. [20] and Kirschner and Webb [17] by incorporating combination therapies. The age related models are normally in the form of partial differential equations (PDEs). Rong et. al. [25] proved the local stability of the positive equilibrium when the basic reproduction number is

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greater than unity, and global stability results for a general age-structured model of intra-individual HIV dynamics are proved by Huang et. al. [15]. Recently the global dynamical properties of PDEs have also attracted interest in the literature, e.g. Browne and Pilyugin [6], McCluskey [19], Yang et. al. [31].

In virus models, the stability of the positive equilibrium is of interest, since researchers investigate whether certain factors may lead to sustained oscillations in the viral concentration. De Leenheer and Smith found that the infection equilibrium can be destabilized via a Hopf bifurcation when the underlying growth rate has logistic form, rather than the simpler linear form often assumed in virus models [8]. Previous studies have shown that target cell growth may be density dependent and follow a logistic-like growth equation [2]. In recent work on virus models with distributed delays, sustained oscillations were found to be induced by logistic growth of uninfected cells, showing the importance of the nonlinear target cell growth rate in causing oscillatory dynamics [14].

In modeling virus dynamics, the interaction between the virus and uninfected cells is usually described by a linear mass action function [21]. In many studies the (mass-action) loss of virus due to entrance into uninfected and infected cells are often neglected because the uninfected and infected cells are considered to change on a much slower time scale than the free virus [23]. This simplification may be valid in HIV-1 infection, but not in other infections such as Polio infection [3]. Even when modeling HIV, explicit inclusion of viral absorption into target cells can affect the dynamics [29]. Additionally, the proportion of infected cells co-infected by multiple instances of viral absorption may be rather large, and is important to quantify for estimating the viral recombination rate [9, 16]. Recombination within co-infected cells can play a large role in viral diversity and evolution within a host. Some recent works have extended the standard HIV model to include viral absorption by infected cells [9, 10, 24]. Based on these points, we think that it is reasonable to consider virus dynamics with consideration of depletion of viruses due to entrance into the uninfected and infected cells.

In this paper, we extend previous models to study the behavior of viral infection with explicit cell infection-age structure, logistic target cell growth rate, and viral absorption by infected cells. We consider the following system:

\[
\frac{dT(t)}{dt} = sT(t)(1 - \frac{T(t)}{T_0}) - kT(t)V(t),
\]

\[
\frac{dV(t)}{dt} = \int_0^\infty p(a)T^*(t, a)da - dV(t) - kV(t)T(t) - \gamma V(t) \int_0^\infty T^*(t, a)da,
\]

\[
\frac{\partial T^*}{\partial t} + \frac{\partial T^*}{\partial a} = -\delta(a)T^*(t, a),
\]

\[
T^*(t, 0) = kV(t)T(t), \quad T^*(0, a) = T^*(a) \in \mathcal{L}_+^1(0, \infty),
\]

\[
T(0) = T_0 \in \mathbb{R}_+, \quad V(0) = V_0 \in \mathbb{R}_+.
\]

Here \(T(t)\) and \(V(t)\) denote the concentrations of healthy cells and free virus particles at time \(t\), respectively. \(T^*(t, a)\) denotes the density of infected cell concentration with respect to age \(a\) since infection at time \(t\) and \(\mathcal{L}_+^1(0, \infty)\) is the non-negative cone of \(\mathcal{L}^1(0, \infty)\) and \(\mathbb{R}_+\) is non-negative real numbers. In this model it is assumed that \(T\) cells are only created by proliferation of existing \(T\) cells as \textit{in vitro}. We present the proliferation by a logistic function in which \(s = e - g\) where \(e\) is the proliferation rate and \(g\) is natural death rate of uninfected cells. Moreover \(\frac{e}{T_{max}} = \frac{s}{T_0}\), where \(T_{max}\)
The function $\delta(a)$ represents the age dependent death rate of infected cells and $p(a)$ is the virion production rate of an infected cell of age $a$. Both, $\delta(a)$ and $p(a)$ are assumed to be in the non-negative cone of $\mathcal{L}^\infty(0,\infty)$, moreover $0 < b \leq \delta(a)$ and $p(a) \leq \kappa$ a.e. for some constants $b$ and $\kappa$. Free virus can re-infect the previously infected cells, described by the mass action term $\gamma V(t) \int_0^\infty T^*(t,a) da$ inserted into the right hand side of $V(t)$ equation, where $\gamma$ is re-infection rate and $\int_0^\infty T^*(t,a) da$ is the total population of infected cells.

The paper is organized as follows. In section 2, the reproduction number as a threshold is obtained and the local stability of disease-free equilibrium and infection equilibrium are studied. Section 3 is devoted to persistent analysis of the system (1)-(4). In section 4, by constructing the suitable Lyapunov function, the global stability of uninfected equilibrium for $R_0 \leq 1$ is established. In section 5, special cases of system (1)-(4) showing Hopf bifurcation are studied, along with quantification of viral re-infection and recombination rates. Finally section 6 is devoted to a brief discussion.

2. Local stability. By integrating along characteristics and applying boundary condition, the PDE in (3) will be in the following form:

$$T^*(t,a) = \begin{cases} kV(t-a)T(t-a)\phi(a), & t > a, \\ \frac{\phi(a)}{\phi(a-t)}T^*(0,a-t), & t \leq a, \end{cases}$$

(5)

where $\phi(a) = e^{-\int_a^\infty \delta(s)ds}$, is the probability that an infected cell survives till age $a$.

By (5), the system (1)-(4) is equivalent to the following system:

$$\frac{dT(t)}{dt} = sT(t)(1 - \frac{T(t)}{T_0}) - kT(t)V(t),$$

(6)

$$\frac{dV(t)}{dt} = \int_0^\infty p(a)T^*(t,a)da - dV(t) - kV(t)T(t) - \gamma V(t) \int_0^\infty T^*(t,a) da,$$

(7)

$$T^*(t,a) = 1_{\{t > a\}} kV(t-a)T(t-a)\phi(a) + 1_{\{a > t\}} \frac{\phi(a)}{\phi(a-t)} T^*(0,a-t),$$

(8)

where $1_{\{\}}$ is the indicator function.

Preliminary results. In the following, we give two theorems about existence, uniqueness, boundedness and nonnegativity of solutions of system (6)-(8). Due to similarity of system (6)-(8) and system (3) in [6], our proofs are almost similar to the related proofs in [6] in some cases.

**Theorem 2.1.** Let $x_0 = (T(0),V(0),T^*(0,a) \in \mathbb{R}_+^2 \times \mathcal{L}_+^1(0,\infty)$. Then there exists $\epsilon > 0$ and a neighborhood $B_0 \subset \mathbb{R}_+^2 \times \mathcal{L}_+^1(0,\infty)$, with $x_0 \in B_0$ such that there exists a unique continuous function, $\psi : [0,\epsilon] \times B_0 \to \mathbb{R}^2 \times \mathcal{L}_+^1(0,\infty)$ where $\psi(t,x)$ is the solution to system (6)-(8).
Proof. Solutions to the system (6)-(8) must satisfy the following equation:

\[
\begin{align*}
T(t) &= T(0) + \int_0^t sT(\eta)(1 - \frac{T(\eta)}{T_0}) - kT(\eta)V(\eta)d\eta, \\
V(t) &= V(0) + \int_0^t \left( \int_0^\infty p(a)T^*(\eta,a)da - dV(\eta) - kV(\eta)T(\eta) - \gamma V(\eta) \int_0^\infty T^*(\eta,a)da \right) d\eta, \\
T^*(t,a) &= 1_{\{t>a\}} kV(t-a)T(t-a)\phi(a) + 1_{\{a>t\}} \frac{\phi(a)}{\phi(a-t)} T^*(0,a-t).
\end{align*}
\]

Let \( Y \) be the set of continuous functions from \([0,\epsilon] \times B_0 \) to \( \mathbb{R}^2 \times L^1_1(0,\infty) \), where \( \epsilon > 0 \) and \( B_0 \subset \mathbb{R}^2 \times L^1_1(0,\infty) \), a neighborhood containing \( x_0 \), are to be determined. Let \( \mathcal{D} \subset Y \), contain functions whose range is contained in ball \( B = B((T(0),V(0),T^*(0,a)),r) \), for some radius \( r \). Note that \( \mathcal{D} \) is complete metric space. At the following, we define operator \( \Gamma \) on \( \mathcal{D} \) and show that:

i) \( \Gamma(\eta)(t,x) \in Y \) and \( \Gamma(\eta) : \mathcal{D} \to \mathcal{D} \).

ii) \( \Gamma(\eta) \) is a contraction map on complete metric space \( \mathcal{D} \), whose fixed point is the unique solution of the system (6)-(8) with initial point \( x_0 \).

Now let \( x = (x_1,x_2,l(a)) \in B_0 \) and \( g(t,x) = (g_1(t,x),g_2(t,x),g_3(t,x)) \in \mathcal{D} \), and define operator \( \Gamma \) as follows:

\[
\Gamma(g)(t,x) = \begin{pmatrix}
\Gamma_1(g)(t,x) \\
\Gamma_2(g)(t,x) \\
\Gamma_3(g)(t,x)
\end{pmatrix},
\]

where

\[
\begin{align*}
\Gamma_1(g)(t,x) &= x_1 + \int_0^t s g_1(\eta,x)(1 - \frac{g_1(\eta,x)}{T_0}) - k g_1(\eta,x)g_2(\eta,x)d\eta, \\
\Gamma_2(g)(t,x) &= x_2 + \int_0^t \left( \int_0^\infty p(a)g_3(\eta,x)da - dg_2(\eta,x) - kg_2(\eta,x)g_1(\eta,x) - \gamma g_2(\eta,x) \int_0^\infty g_3(\eta,x)da \right) d\eta, \\
\Gamma_3(g)(t,x) &= 1_{\{t\geq a\}} k g_2(t-a,x)g_1(t-a,x)\phi(a) + 1_{\{a\geq t\}} \frac{\phi(a)}{\phi(a-t)} l(a-t).
\end{align*}
\]

To prove the first part of (i), it is clear that \( \Gamma_1(\eta)(t,x) \in \mathbb{R} \) and from the assumption \( p(a) \leq \kappa \), a.e. on \([0,\infty)\), where \( \kappa \) is a constant, \( \Gamma_2(\eta)(t,x) \in \mathbb{R} \). Now it is sufficient to prove \( \Gamma_3(\eta)(t,x) \in L_1(0,\infty) \).

\[
\begin{align*}
\int_0^\infty \left| \frac{1_{\{t\geq a\}} k g_2(t-a,x)g_1(t-a,x)\phi(a) + 1_{\{a\geq t\}} \frac{\phi(a)}{\phi(a-t)} l(a-t)}{da} \right| & \leq \int_0^t \left| k g_2(t-a,x)g_1(t-a,x)\phi(a) \right| da + \int_t^\infty \left| \frac{\phi(a)}{\phi(a-t)} l(a-t) \right| da \\
& \leq \frac{1}{b} (1 - e^{-bt})k|T(0)| + r||V(0)|| + r|+||l|| < \infty,
\end{align*}
\]

where, \( 0 < b \leq \delta(a) \) on \([0,\infty)\) for some constant \( b \). To prove the second part of (i), take \( B_0 = B((T(0),V(0),T^*(0,a)),r/2) \). Then
\[ \| \Gamma(g)(t,x) - x_0 \| = \left| x_1 - T(0) + \int_{0}^{t} s g_1(\eta, x)(1 - \frac{g_1(\eta, x)}{T_0}) - kg_1(\eta, x).g_2(\eta, x)d\eta \right| \\
+ |x_2 - V(0) + \int_{0}^{2} \left( \int_{0}^{\infty} p(a)g_3(\eta, x)da - dg_2(\eta, x) - kg_2(\eta, x)g_1(\eta, x) - \gamma g_2(\eta, x) \right) d\eta| \\
+ \int_{0}^{\infty} \left| 1_{\{t \geq a\}}kg_2(t - a, x)g_1(t - a, x)\phi(a) + 1_{\{a \geq t\}} \frac{\phi(a)}{\phi(a - t)} l(a - t) - T^*(0, a) \right| da \\
\leq |x_1 - T(0)| + \frac{\epsilon T_0}{2} + \epsilon k |T(0) + r| |V(0) + r| + \\
|x_2 - V(0)| + \epsilon \kappa(|T^*(0, a)| + r) + \epsilon d |V(0) + r| + \epsilon k |T(0) + r| |V(0) + r| \\
+ \epsilon \gamma |V(0) + r|(|T^*(0, a)| + r) + \frac{1}{b} (1 - e^{-bk}) k |T(0) + r| |V(0) + r| \\
+ \int_{0}^{\infty} 1_{\{a \geq t\}} \frac{\phi(a)}{\phi(a - t)} |l(a - t) - T^*(0, a - t)| da + \\
+ \int_{0}^{\infty} 1_{\{a \geq t\}} \frac{\phi(a)}{\phi(a - t)} T^*(0, a - t) - T^*(0, a) da \\
\leq \| x - x_0 \| + \epsilon M_1 + (1 - e^{-bk}) M_2 \\
+ \int_{0}^{\infty} 1_{\{a \geq t\}} \frac{\phi(a)}{\phi(a - t)} T^*(0, a - t) - T^*(0, a) da.
\]

Notice that

\[ \int_{0}^{\infty} \left| 1_{\{a \geq t\}} \frac{\phi(a)}{\phi(a - t)} T^*(0, a - t) - T^*(0, a) \right| da \]
\[ \leq \int_{0}^{\infty} 1_{\{a \geq t\}} T^*(0, a - t) \left| \frac{\phi(a)}{\phi(a - t)} - 1 \right| da + \int_{0}^{\infty} 1_{\{a \geq t\}} T^*(0, a - t) - T^*(0, a) da \]
\[ := J_1 + J_2. \]

By Dominated Convergence Theorem (DCT), \( J_1 \to 0 \) as \( t \to 0 \). Hence \( J_1 \leq \frac{r}{16} \) for all \( t \in [0, \epsilon] \) provided that \( \epsilon \) sufficiently small. We note that, set of continuous functions with compact support is dense in \( L^1 \). Now let \( \zeta \) be continuous function with compact support in \([0, \infty]\) such that \( \| T^*(0, .) - \zeta \| < \frac{r}{32} \). Then

\[ J_2 = \int_{0}^{t} |T^*(0, a)| da \\
+ \int_{t}^{\infty} |T^*(0, a - t) - \zeta(a - t) + \zeta(a) - \zeta(a) + \zeta(a) - T^*(0, a)| da \\
\leq \int_{0}^{t} |T^*(0, a)| da + \int_{0}^{\infty} |T^*(0, a) - \zeta(a)| da + \int_{0}^{\infty} |\zeta(a) - \zeta(a + t)| da + \\
\int_{t}^{\infty} |\zeta(a) - T^*(0, a)| da \\
\leq \int_{0}^{t} |T^*(0, a)| da + 2 \int_{0}^{\infty} |T^*(0, a) - \zeta(a)| da + \int_{0}^{\infty} |\zeta(a) - \zeta(a + t)| da. \]
Hence
\[
\frac{r}{32} + \frac{r}{8} + \frac{r}{8} \text{ for } \epsilon, \text{ sufficiently small.}
\]

Hence
\[
\|\Gamma(g)(t, x) - x_0\| \leq \frac{r}{2} + \frac{r}{4} + \frac{r}{4} = r,
\]
for constants \(M_1, M_2\) and \(\epsilon\) sufficiently small. Therefore \(\Gamma(\eta) : \mathcal{D} \to \mathcal{D}\). To prove (ii), let \(g, h \in \mathcal{D}\). Then
\[
\|\Gamma(g)(t, x) - \Gamma(h)(t, x)\| \\
\leq s \int_0^t \left| g_1(\eta, x)(1 - \frac{g_1(\eta, x)}{T_0}) - h_1(\eta, x)(1 - \frac{h_1(\eta, x)}{T_0}) \right| d\eta \\
+ 2k \int_0^t \left| g_1(\eta, x)g_2(\eta, x) - h_1(\eta, x)h_2(\eta, x) \right| d\eta \\
+ \int_0^t \int_0^\infty p(a) \left| g_3(\eta, x) - h_3(\eta, x) \right| da d\eta + d \int_0^t \left| g_2(\eta, x) - h_2(\eta, x) \right| d\eta \\
+ \gamma \int_0^t \left( \int_0^t g_2(\eta, x) \int_0^\infty g_3(\eta, x) da - h_2(\eta, x) \int_0^\infty h_3(\eta, x) da \right) d\eta \\
+ \int_0^t e^{\eta a} \left| g_2(t - a, x)g_1(t - a) - h_2(t - a, x)h_1(t - a, x) \right| da
\]
\[
\leq c s \frac{1 + (T(0) + r)(V(0) + r)}{T_0} \| g_1 - h_1 \| \\
+ c 2k(T(0) + r) \| g_2 - h_2 \| + c 2k(V(0) + r) \| g_1 - h_1 \| \\
+ c \kappa \| g_3 - h_3 \| + c d \| g_2 - h_2 \| \\
+ c \gamma \| T^*(0, a) \| + r) \| g_2 - h_2 \| + c \gamma (V(0) + r) \| g_3 - h_3 \| \\
+ c k(T(0) + r) \| g_2 - h_2 \| + c k(V(0) + r) \| g_1 - h_1 \| \\
\leq c M \| g - h \|,
\]
where \(M\) is a constant. Therefore \(\Gamma\) is a contraction mapping on \(\mathcal{D}\) for \(\epsilon\) sufficiently small. By the Contraction Mapping Theorem there exists a unique fixed point of \(\Gamma\) in \(\mathcal{D}\) that we denote this function by \(\psi(t, x)\), which solves the initial value problem and is continuous on \([0, \epsilon] \times B_0\). \(\square\)

**Theorem 2.2.** Solution to the system (6)-(8) remain nonnegative for almost every \(a \geq 0\) and bounded in forward time.

**Proof.** Let \(T(t), V(t)\) and \(T^*(t, a)\) be a particular solution to the system (6)-(8) on the interval \([0, \alpha]\), where \(\alpha < \rho\) and \([0, \rho]\) is the maximal interval of existence, which \(\rho\) is allowed to be \(\infty\). Suppose by way of contradiction that this is not true. Let \(T(0) > 0\) and \(\tau = \inf\{t \in [0, \alpha] : T(t) = 0\}\). From (6) we have \(T'(\tau) = 0\) and by induction it is easy to prove \(\frac{d^n T(t)}{dt^n}|_{t=\tau} = 0\) for any \(n \in \mathbb{N}\). Hence \(T(t) = 0\), which is a contradiction. Therefore we can suppose \(T(t) > 0\). Now let \(\tau = \min\{\inf\{t \in [0, \alpha] : V(t) < 0\}, \inf\{t \in [0, \alpha] : T^*(t, \cdot) \notin L_1(0, \infty)\}\}\). First, suppose \(\tau = \inf\{t \in [0, \alpha] : T^*(t, \cdot) \notin L_1(0, \infty)\}\). Then \(t_n \downarrow \tau\) and \(T^*(t_n, \cdot) \notin L_1(0, \infty)\), for all \(n\). Moreover, \(T^*(t_n, \cdot) \in L_1(0, \infty)\) and (5) imply
\[
\{a \in [0, \infty) : T^*(t_n, a) < 0\} = \{a \in [0, t_n) : \phi(a)kV(t_n - a)T(t_n - a) < 0\} = \{a \in [0, t_n) : V(t_n - a) < 0\}.
\]
Therefore for all $n$, $\forall t \in [0, t_n)$, such that $V(t) < 0$. Since $t_n \downarrow \tau$, we find that $\inf\{t \in [0, \alpha] : V(t) < 0\} \leq \tau$. Hence, it suffices to consider $\tau = \inf\{t \in [0, \alpha] : V(t) < 0\}$. Then $V(\tau) = 0$ and $T^*(\tau, a) \in C^1([0, \alpha])$.

That means $V(t) < 0$ for $t \in (\tau - \epsilon, \tau)$, where $\epsilon$ is some positive constant. This leads to a contradiction with definition of $\tau$. Hence the solution to system (6)-(8) must remain nonnegative on $[0, \alpha]$. Since $\alpha < \rho$ is arbitrary, we conclude that the solution remains nonnegative on its maximal interval of existence $[0, \rho]$.

To prove the boundedness of solutions, we note that our assumption on the parameters imply that $0 \leq p(a) \leq \kappa$ a.e., and $0 < b \leq \delta(a)$ a.e., $\forall a \in [0, \infty)$. Also, from the nonnegativity of solutions of system (6)-(8), $T(t) \leq \max(T(0), T_0) := M$ for all $t \geq 0$ in the interval of its existence. Now, consider the following:

$$\frac{d}{dt}(T(t) + \int_0^\infty T^*(t, a)da + \frac{b}{2\kappa}V(t)) =$$

$$sT(t)(1 - \frac{T(t)}{T_0}) - kTV(t) + \int_0^\infty (\frac{\partial T^*(t, a)}{\partial a} + \frac{\partial T^*(t, a)}{\partial t})da$$

$$+ \frac{b}{2\kappa}(\int_0^\infty p(a)T^*(t, a)da - dV(t) - kV(t)T^*(t, a) - \gamma V(t)T^*(t, a)da)$$

$$\leq sM - \frac{sM}{T_0}T(t) - b \int_0^\infty T^*(t, a)da + \frac{b}{2\kappa} \int_0^\infty T^*(t, a)da - \frac{b}{2\kappa}dV(t)$$

$$= sM - \frac{sM}{T_0}T(t) - \frac{b}{2} \int_0^\infty T^*(t, a)da - \frac{b}{2\kappa}dV(t)$$

$$\leq sM - m(T(t) + \int_0^\infty T^*(t, a)da + \frac{b}{2\kappa}V(t)),$$

where, $m = \min\{\frac{sM}{T_0}, \frac{b}{2}, d\}$. This implies that

$$\limsup_{t \to \infty} \left(T(t) + \int_0^\infty T^*(t, a)da + \frac{b}{2\kappa}V(t)\right) \leq \frac{sM}{m}.$$

Now, boundedness follow from nonnegativity of solutions. □

**Local analysis.** System (6)-(8) has an infection free equilibrium $E^0 = (T_0, 0, 0)$, and if $V(0) + \int_0^\infty T^*(a)da > 0$, then there exist an infection equilibrium $\bar{E} = (\bar{T}, \bar{V}, T^*(a))$ satisfying the following equations,

$$sT(1 - \frac{T}{T_0}) - k\bar{T} \bar{V} = 0, \quad (9)$$

$$\int_0^\infty p(a)T^*(a)da - d\bar{V} - k\bar{V}T - \gamma \bar{V} \int_0^\infty T^*(a)da = 0, \quad (10)$$

$$T^*(a) = T^*(0)\phi(a), \quad (11)$$

where $T^*(0) = k\bar{V}T$. Substituting (11) into (10), we get

$$k\bar{V}T \int_0^\infty p(a)\phi(a)da - d\bar{V} - k\bar{V}T - k\gamma \bar{V}^2T \int_0^\infty \phi(a)da = 0, \quad (12)$$
solving (9) in $\mathcal{T}$,
\[
\mathcal{T} = \frac{T_0}{s}(s - k\mathcal{V}),
\] (13)
and substituting into (12), we have
\[
k\gamma A\mathcal{V}^2 + (k(1 - N) - s\gamma A)\mathcal{V} + (N - 1)s - \frac{sd}{kT_0} = 0,
\] (14)
where $A := \int_{0}^{\infty} \phi(a) da$ and $N = \int_{0}^{\infty} p(a)\phi(a) da$. Solving (14) in $\mathcal{V}$, we have the following:
\[
\mathcal{V} = \frac{k(N - 1) + s\gamma A \pm \sqrt{\Delta}}{2k\gamma A},
\]
in which
\[
\Delta := [k(1 - N) + s\gamma A]^2 + 4s\gamma AdT_0 > 0.
\]
Now we define the basic reproduction numbers which governs the stability of infection free equilibrium and the existence of infection equilibrium,
\[
R_0 := \frac{NkT_0}{d + kT_0}.
\] (15)
The above quantity, $R_0$, can be interpreted as the average number of infected cells produced by a single infected cell in a $T$ cell population at infection-free level $T_0$. The following cases are established:

i) If $R_0 < 1$, then the positive root for the equation (14) is
\[
\mathcal{V}_1 = \frac{k(N - 1) + s\gamma A + \sqrt{\Delta}}{2k\gamma A},
\]
from (13), the related $\mathcal{T}$ must satisfy the next relation as follows:
\[
s\mathcal{T}_1 = \left(\frac{s}{2} - \frac{k(N - 1)}{2\gamma A}\right) - \sqrt{\left(\frac{s}{2} - \frac{k(N - 1)}{2\gamma A}\right)^2 + \frac{sd}{T_0\gamma A}} < 0,
\]
in this case, there is not infection equilibrium.

ii) If $R_0 > 1$, we have two positive roots for (14) but only smaller root leads to non-negative $\mathcal{T}$ with,
\[
\mathcal{V}_2 = \frac{k(N - 1) + s\gamma A - \sqrt{\Delta}}{2k\gamma A},
\] (16)
and
\[
s\mathcal{T}_2 = \left(\frac{s}{2} - \frac{k(N - 1)}{2\gamma A}\right) + \sqrt{\left(\frac{s}{2} - \frac{k(N - 1)}{2\gamma A}\right)^2 + \frac{sd}{T_0\gamma A}}.
\] (17)
In this case also, the system (1)-(5) has a unique infection equilibrium $\mathcal{E} = (\mathcal{T}_2, \mathcal{V}_2, \mathcal{T}^*_2(a))$, that we simply denote by $\mathcal{E} = (\mathcal{T}, \mathcal{V}, \mathcal{T}^*(a))$, where $\mathcal{T}^*(a)$ is given by (11).

iii) If $R_0 = 1$, which implies that $N > 1$, then one root of the above equation is $\mathcal{V}_3 = 0$, whose related equilibrium is $E^0 = (T_0, 0, 0)$ and the other root is
\[
\mathcal{V}_4 = \frac{k(N - 1) + s\gamma A}{k\gamma A},
\]
and the related $T_4$ must satisfy the condition (13). Then we have:

$$T_4 = -\frac{k(N-1)T_0}{\gamma sA},$$

hence the necessary condition for the admissibility of $T_4$ is $N \leq 1$ which is a contradiction. Therefore $(T, \nabla, T^\tau(a)) = (T_0, 0, 0)$ and the only equilibrium point in this condition is $E^0 = (T_0, 0, 0)$.

**Theorem 2.3.** If $R_0 \leq 1$, then the infection free equilibrium $E^0$ of the system (6)-(8) is locally asymptotically stable and if $R_0 > 1$, then $E^0$ is unstable.

**Proof.** First, we study the local stability of $E^0$. Linearizing system (1)-(5) about $E^0$, we obtain:

$$
\begin{align*}
\frac{dT_1(t)}{dt} &= -sT_1 - kT_0 V_1, \\
\frac{dV_1(t)}{dt} &= (-d - kT_0)V_1 + \int_0^\infty p(a)T_1^*(t,a)da, \\
\frac{\partial T_1^*}{\partial t} + \frac{\partial T_1^*}{\partial a} &= -\delta(a)T_1^*(t,a), \\
T_1^*(t,0) &= kT_0 V_1(t),
\end{align*}
\tag{18}
$$

where $T_1(t) = T(t) - T_0$, $V_1(t) = V(t)$ and $T_1^*(t,a) = T^*(t,a)$. Consider the exponential solutions $T_1(t) = T_1 e^{\lambda t}$, $V_1(t) = V_1 e^{\lambda t}$ and $T_1^*(t,a) = T_1^*(a)e^{\lambda t}$ of the system (18). Then we have:

$$
\begin{align*}
(\lambda + s)T_1 &= -kT_0 V_1, \\
(\lambda + d + kT_0)V_1 &= \int_0^\infty p(a)T_1^*(a)da, \\
T_1^*(a) &= T_1^*(0)e^{-\lambda a - \int_0^a \delta(\omega)d\omega}, \\
T_1^*(0) &= kT_0 V_1.
\end{align*}
\tag{19-22}
$$

With substituting (22) into (21), we have

$$
T_1^*(a) = kT_0 V_1 e^{-\lambda a - \int_0^a \delta(\omega)d\omega}.
\tag{23}
$$

Then, by substituting (23) in (20), and letting $\lambda = u + iv$ as a complex number, the next follows as below:

$$
\begin{align*}
(\lambda + d)V_1 &= kT_0 V_1(\int_0^\infty p(a)\phi(a)e^{-\lambda a}da - 1), \\
\lambda &= kT_0 \int_0^\infty p(a)\phi(a)e^{-\lambda a}da - kT_0 - d \\
&= kT_0 \int_0^\infty p(a)\phi(a)e^{-\lambda a}da - \frac{NkT_0}{R_0} \\
&= \frac{kT_0}{R_0} \left( R_0 \int_0^\infty p(a)\phi(a)e^{-\lambda a}da - \int_0^\infty p(a)\phi(a)da \right) \\
&= \frac{kT_0}{R_0} \left( \int_0^\infty p(a)\phi(a)(R_0e^{-\lambda a} - 1)da \right).
\end{align*}
\tag{24-27}
$$
Now let $\lambda = u + iv$, then the real-part of the above equation is
\[ \Rightarrow u = \frac{kT_0}{R_0} \left( \int_0^\infty p(a)\phi(a)(R_0e^{-ua}\cos(ua) - 1)da \right), \] (24)
then if $u > 0$, the righthand side of the above equation is negative that is a contradiction. Now define $H(u)$ as follows:
\[ H(u) := \frac{kT_0}{R_0} \left( \int_0^\infty p(a)\phi(a)(R_0e^{-ua}\cos(ua) - 1)da \right) - u. \]
It is clear that $H(u) \to -\infty$ as $u \to +\infty$, and $H(0) > 0$ if $R_0 > 1$. This implies that equation (24) has at least one positive root. Hence, $E^0$ is unstable. \hfill \Box

**Proposition 2.4.** Let $R = \frac{T_0}{T}$, then $R > 1$ is equivalent to $R_0 > 1$.

**Proof.** Suppose that $\gamma \neq 0$. The proof is similar and simpler for the case $\gamma = 0$. If $\gamma \neq 0$, from (17),
\[ R = \frac{T_0}{T} > 1, \]
\[ \Leftrightarrow \frac{s}{\left( \frac{s}{2} - \frac{k(N - 1)}{2\gamma A} \right) + \sqrt{\left( \frac{s}{2} - \frac{k(N - 1)}{2\gamma A} \right)^2 + \frac{sd}{T_0\gamma A}} > 1, \]
\[ \Leftrightarrow s^2 - 2s \left( \frac{s}{2} - \frac{k(N - 1)}{2\gamma A} \right) > \frac{sd}{T_0\gamma A}, \]
\[ \Leftrightarrow \frac{k(N - 1)T_0}{d} > 1 \Leftrightarrow R_0 > 1. \] (25)
\hfill \Box

Now we investigate the local stability of $\overline{E}$ when $R_0 > 1$. We show that unique infection equilibrium $\overline{E}$ of system (6)-(8) can be stable or unstable depending on parameter values.

In order to investigate the local stability of $\overline{E}$, let $T_1(t) = T(t) - \overline{T}$, $V_1(t) = V(t) - \overline{V}$ and $T_1^*(t,a) = T^*(t,a) - \overline{T}^*(a)$. Then the exponential solution of linearized system about $\overline{E}$ in the form of $T_1(t) = T_1e^{\lambda t}$, $V_1(t) = V_1e^{\lambda t}$ and $T_1^*(t,a) = T_1^*(a)e^{\lambda t}$, satisfies the following equations:
\[ \lambda T_1 = (s - \frac{2sT}{T_0} - k\overline{V})T_1 - k\overline{V}V_1, \]
\[ \lambda V_1 = \int_0^\infty p(a)T_1^*(a)da - dV_1 - k\overline{V}T_1 - k\overline{V}V_1 - \gamma \int_0^\infty T_1^*(a)daV_1 - \gamma \int_0^\infty V_1^*(a)daV_1, \]
\[ T_1^*(t,0) = k\overline{V}T_1(t) + k\overline{V}V_1(t) \Rightarrow T_1^*(0) = k\overline{V}T_1 + k\overline{V}V_1, \]
\[ T_1^*(a) = T_1^*(a)e^{-\lambda a - \int_0^a \delta(\omega)d\omega}. \]
Doing some simplification, we have the following:
\[ (\lambda - s + \frac{2sT}{T_0} + k\overline{V})T_1 = -k\overline{V}V_1, \] (26)
\[(\lambda + d + kT + \gamma \int_0^\infty T^*(a)da)V_1\]
\[= \int_0^\infty p(a)T_1^*(a)da - \gamma V \int_0^\infty T_1^*(a)da - kVT_1, \quad \text{(27)}\]
\[T_1^*(a) = (kVT_1 + kTV_1)\phi(a)e^{-\lambda a}. \quad \text{(28)}\]

Substituting (26) and (28) into (27), the next follows as below:
\[\left(\lambda + d + kT + \gamma \int_0^\infty T^*(a)da\right)V_1\]
\[= \left(-\lambda + s - \frac{2sT}{T_0}\right) \left[\int_0^\infty p(a)\phi(a)e^{-\lambda a}da - \gamma V \int_0^\infty \phi(a)e^{-\lambda a}da\right] - kVT_1. \quad \text{(29)}\]

From (9), \(\Sigma := \lambda - s + \frac{2sT}{T_0} + kV = \lambda - s + \frac{2s}{R} + s(1 - \frac{1}{R}) = \lambda + \frac{s}{R} \). So the above equation simplifies to the following:
\[\Rightarrow \left(\lambda + \gamma \int_0^\infty T^*(a)da\right) \left(\lambda + \frac{s}{R}\right) + dkV + (\lambda - s + \frac{2s}{R})(d + kT)\]
\[= (\lambda - s + \frac{2s}{R})kT \left[\int_0^\infty \left(p(a) - \gamma V\right)\phi(a)e^{-\lambda a}da\right]. \quad \text{(30)}\]

We note that \(E = (\bar{T}, \bar{V}, \bar{T}^*(a)) = (\bar{T}_2, \bar{V}_2, \bar{T}^*_2(a))\) whose amounts are given by (16), (17) and (11). From (10) we have:
\[kT \int_0^\infty (p(a) - \gamma V)\phi(a)da = d + kT. \quad \text{(31)}\]

Clearly from (30) and (29), \(\lambda = 0\) cannot be a solution of (29). Therefore, in the case that the equation (29) has solution where the real part of \(\lambda\) changes sign by changing parameter values, then Hopf bifurcation occurs. To compute Hopf critical point, let complex number \(\lambda = ic\) be the solution of (29). Therefore from (29), we have:
\[\Rightarrow \left(ic + \gamma \int_0^\infty T^*(a)da\right) (ic + \frac{s}{R}) + dkV + (ic - s + \frac{2s}{R})(d + kT)\]
\[= (ic - s + \frac{2s}{R})kT \left[\int_0^\infty \left(p(a) - \gamma V\right)\phi(a)e^{-ic a}da\right]. \quad \text{(32)}\]

The real part and imaginary part of the above equation is as follows respectively:

**Real part:** \(-c^2 + \frac{\gamma s}{R} \int_0^\infty T^*(a)da + dkV + (-s + \frac{2s}{R})(d + kT)\)
\[-= (-s + \frac{2s}{R})kT \left[\int_0^\infty \left(p(a) - \gamma V\right)\phi(a)\cos(\omega a)da\right] + c kT \left[\int_0^\infty \left(p(a) - \gamma V\right)\phi(a)\sin(\omega a)da\right]. \quad \text{(32)}\]

**Imaginary part:** \(c \left[\gamma \int_0^\infty T^*(a)da + \frac{s}{R} + d + kT\right] \]
\[= (c)kT \left[\int_0^\infty \left(p(a) - \gamma V\right)\phi(a)\cos(\omega a)da\right] \]
whether a species will ultimately persist or extinct in a dynamical system.

3. Respectively.

\[ \psi \leq R \]

solution of \( \frac{c}{d} \) real part for different values of parameters. Therefore, \( E \) be the Hopf critical point.

\[ \Rightarrow (-s + \frac{2a}{R}) \int_0^\infty \left( p(a) - \psi \right) \phi(a) \sin(\phi) \, da \].

Using (33) in (32), we have the following rough equation where existence of real solution of \( c \) is equivalent to with \( E \) be the Hopf critical point.

\[ -(s + \frac{2a}{R}) \left( c^2 + \frac{2s}{R} \int_0^\infty T^*(a) \, da + dk\psi \right) + \left( s + \frac{2a}{R} \right)^2 (d + kT) \]

\[ = \left( -s + \frac{2a}{R} \right)^2 k\psi + c^2 kT \left( \int_0^\infty \left( p(a) - \psi \right) \phi(a) \cos(\phi) \, da \right) \]

\[ - c^2 \left( \int_0^\infty T^*(a) \, da + \frac{s}{R} + d + kT \right). \] (34)

In the numerical section, Section 5, for the case \( 1 < R_0 \), we have chosen the parameter values in such ways that (29) has solutions with negative or non-negative real part for different values of parameters. Therefore, \( E \) will be stable or unstable, respectively.

3. Uniform persistence. Persistent theory provides a tool for determining whether a species will ultimately persist or extinct in a dynamical system.

Define \( X = \mathbb{R}^+_0 \times L^1_0 (0, \infty) \), which is a complete metric space. Let \( S(t)x = \psi(t, x) \) be the solution to system (6)-(8), where \( \psi(t, x) = (T(t), V(t), T^*(t, \cdot)) \). It can be verified that \( S(t) \) is a \( C^0 \) semigroup on \( X \); that is, \( S(0)x = x \), \( S(t+s)x = S(t)S(s)x \) for \( t, s \geq 0 \), and \( S(t)x \) is continuous in \( t, x \). For \( \epsilon \in \mathbb{R}_+ \), let \( S(-\epsilon)y = x \), then we define \( S(t)x = y \).

We first give some preliminary definitions from [13] and [11] as follows:

The semigroup \( S(t) \) is said to be uniformly persistent (with respect to \( X^0 \) and \( \partial X^0 \)) if there exists \( \eta > 0 \), such that for any \( x \in X^0 \), \( \liminf_{t \to \infty} d(S(t)x, \partial X^0) \geq \eta \), where \( d(A, B) = \sup_{x \in A} \inf_{y \in B} \| x - y \| \).

The semigroup \( S(x) \) is said to be asymptotically smooth, if for any bounded subset \( B \subset X \), for which \( S(t)B \subset B \) for \( t \geq 0 \), there exists a compact set \( K \) such that \( d(S(t)B, K) \to 0 \) as \( t \to \infty \).

The semigroup \( S(t) \) is said to be point dissipative in \( X \) if there is a bounded nonempty set \( B \) in \( X \) such that, for any \( x \in X \), there is a \( t_0 = t_0(x, B) \) such that \( S(t)x \in B \) for \( t \geq t_0 \).

A set \( A \) in \( X \) is said to be global attractor if it is compact, invariant and for any bounded set in \( X, d(S(t)B, A) \to 0 \) as \( t \to \infty \). Let \( U \subset X \) be bounded in \( X \), then we define \( \gamma^+(U) = \{ y \in X | y = \psi(t, x), t \geq 0, x \in U \} \). Define \( \mathcal{A}_0 = \cup_{x \in \mathcal{A}} \omega(x) \), where \( \mathcal{A}_0 \) is global attractor in \( \partial X \), and \( \omega(x) = \{ y \in X : \exists n \uparrow \infty \text{ such that } S(t_n)x \to y \} \) is omega limit set of \( x \). Also, a set \( A \) in \( X \) is said to be a global attractor if it is compact, invariant and for any bounded set \( B \) in \( X \), \( d(S(t)B, A) \to 0 \) as \( t \to 0 \). A set \( A \) in \( X \) is said to be invariant if \( S(t)A = A \) for \( t \geq 0 \) if \( S(t)A \subset A \), it is said to be forward invariant. The stable (or attracting) set of a compact invariant set \( A \) is denoted by \( W^s(A) = \{ x | x \in X, \omega(x) \neq \emptyset, \omega(x) \subset A \} \). The unstable (or repelling) set of a compact invariant set \( A \), \( W^u \) is defined by \( W^u(A) = \{ x | x \in X, \exists x \to \infty, \text{ such that } S(t_n)x \to y \} \) is alpha limit of \( x \). It should be noted that, there is no backward uniqueness, hence the definitions will possibly consider multiple backward orbits from a point.

To consider uniform persistence of \( S(t) \) and existence of global attractor in \( X_0 \), we will use the following theorems, from Hale and Waltman[13].
Theorem 3.1 (Theorem 4.2 [13]). Suppose metric space $X$ is a closure of an open set $X^0$; that is $X = X^0 \cup \partial X^0$, and $S(t)$ satisfies condition:
\[
\begin{aligned}
S : X^0 \rightarrow X^0, \\
S : \partial X^0 \rightarrow \partial X^0,
\end{aligned}
\]
and we have the following:

i) $S(t)$ is asymptotically smooth,

ii) $S(t)$ is point dissipative in $X$,

iii) $\gamma^+(U)$ is bounded in $X$ if $U$ is bounded in $X$.

Then, there are global attractors $A$ in $X$ and $A_0$ in $\partial X^0$ and a global attractor $A_0$ in $X^0$ relative to strongly bounded sets. Furthermore, $A = A_0 \cup W^u(A_0)$.

To verify the asymptotically smoothness of semigroup generated by system (6)-(8), we use the following lemma:

Lemma 3.3 ([12]). For each $t \geq 0$, suppose $R(t) = U(t) + C(t) : X \rightarrow X$ has the property that $C(t)$ is completely continuous function and there is a continuous function $k : \mathbb{R}_+ \times \mathbb{R}_+ \rightarrow \mathbb{R}_+$ such that $k(t, r) \rightarrow 0$ as $t \rightarrow 0$ and $\| U(t)x \| \leq k(t, r)$ if $\| x \| \leq r$. Then $R(t)$, $t \geq 0$, is asymptotically smooth.

We note that, a continuous mapping $S : X \rightarrow X$ is said to be compact (completely continuous) if $S$ maps any bounded set to a precompact set in $M$ (i.e., $\overline{M}$ is compact). A semigroup $C(t)$ is completely continuous if for each $t \geq 0$ and each bounded set $B \subset X$, we have, $\{ C(s)B, 0 \leq s \leq t \}$ is bounded and $C(t)B$ is precompact. Since one of the components of $S(t)$ is $L_1^q(0, \infty)$, which is infinite dimensional space, boundedness does not imply precompactness. Therefore, we use the following lemma:

Lemma 3.4 ([1]). Let $K \subset L^p(0, \infty)$ be closed and bounded where $p \geq 1$. Then $K$ is compact if and only if the following holds:

i) $\lim_{h \rightarrow 0} \int_0^\infty |u(z + h) - u(z)|^p dz = 0$ uniformly for $u \in K$. ($u(z + h) = 0$ if $z + h < 0$).

ii) $\lim_{h \rightarrow 0} \int_0^\infty |u(z)|^p dz = 0$ uniformly for $u \in K$.

Proposition 3.5. The semigroup $S(t)$, generated by system (6)-(8), is asymptotically smooth.

Proof. Let $S(t) = U(t) + C(t)$ where,
\[
U(t) = \begin{pmatrix} 0 \\ U_2(t) \end{pmatrix}, \quad C(t) = \begin{pmatrix} \pi_1 S(t) \\ C_2(t) \end{pmatrix},
\]
wherein
\[
(U_2(t)x)(a) = \frac{\phi(a)}{\phi(a - t)} T^*(0, a - t)1_{\{a > t\}},
\]
\[
(C_2(t)x)(a) = \phi(a)kV(t - a)T(t - a)1_{\{a \leq t\}},
\]
\( X = \mathbb{R}_+^2 \times L^1_+(0, \infty) \) and \( x = (T(0), V(0), T^*(0, .)) \) \( \in X \). Moreover \( \pi_1 S(t) \) is projection of \( S(t) \) on \( \mathbb{R}_+^2 \). Let \( B \subset X \) be a bounded set. Then from the theorem (2.2), \( \pi_1 S(t)B \) is bounded in \( \mathbb{R}_+^2 \), therefore is precompact. The projection of \( S(t) \) on \( L^1_+(0, \infty) \) is given by \( \pi_2 S(t) = U_2(t) + C_2(t) \).

Let \( \| x \| \leq r \), then we have:

\[
\| U_2(t)x \| \leq \int_0^\infty \frac{\phi(a)}{\phi(a-t)} T^*(0, a-t)da \leq e^{-bt} \int_0^\infty T^*(0, a-t)da \leq e^{-bt} \| T^*(0,.) \| \leq k(t, r),
\]

where \( k(t, r) = re^{-bt} \). Clearly, \( \| U(t)x \| \leq k(t, r) \to 0 \) as \( t \to 0 \). To show that \( C_2(t)B \) satisfies compactness condition, we apply lemma (3.4).

Let \( B \subset X \) be closed and bounded, and \( \| x \| \leq r \) for all \( x \in B \). Now we check the first condition of lemma (3.4). We have:

\[
\int_0^\infty |(C_2(t)x)(a) - (C_2(t)x)(a+h)|da
\]

\[
= \int_0^t |(\phi(a)kV(t-a)T(t-a) - \phi(a+h)kV(t-a-h)T(t-a-h)|da
\]

\[
= \int_0^t |(\phi(a)kV(t-a)T(t-a) - \phi(a+h)kV(t-a-h)T(t-a-h)|da
\]

\[
\leq \int_0^t e^{-ba}|kV(t-a)T(t-a) - \phi(a+h)kV(t-a-h)T(t-a-h)|da
\]

\[
+ \int_0^t e^{-ba} \phi(a+h)|kV(t-a)T(t-a) - kV(t-a-h)T(t-a-h)|da
\]

\[
\leq M_1 \int_0^t e^{-ba}|1 - \phi(a+h)\phi(a)|da
\]

\[
+ k \sup_{\tau \in [0, t]} |V(\tau)T(\tau) - V(\tau-h)T(\tau-h)| \int_0^t e^{-ba}da
\]

\[
\leq M_1 \int_0^t e^{-ba}|1 - \phi(a+h)\phi(a)|da + k \sup_{\tau \in [0, t]} (|V(\tau)||T(\tau) - T(\tau-h)|
\]

\[
+ |T(\tau)||V(\tau) - V(\tau-h)| \int_0^t e^{-ba}da,
\]

where \( M_1 \) is a constant. Existence of such a constant \( M_1 \), follows from Theorem (2.2). By integral formation of solutions and Theorem (2.2), there exist constants \( M_2 \) and \( M_3 \) such that:

\[
|T(\tau) - T(\tau-h)| \leq \int_{\tau-h}^\tau |sT(\tau)(1 - \frac{T(\tau)}{T_0}) - kT(\tau)V(\tau)|d\tau
\]

\[
\leq h \left( \frac{T_0}{2} + k \| T \| \| V \| \right)
\]

\[
\leq hM_2,
\]

(37)

\[
|V(\tau) - V(\tau-h)| \leq \int_{\tau-h}^\tau \left| \int_0^\infty p(a)T^*(\tau, a)da - dV(\tau) - kV(\tau)T(\tau)
\]

\[
- \gamma V(\tau) \int_0^\infty T^*(\tau, a)da \right|d\tau
\]
Define $$S$$ where,

$$\triangledown X$$

Hence

$$E$$

Proof. First we show that the infection free equilibrium $$E$$ is globally asymptotically stable for the semiflow generated by system (1)-(4) on $$X$$. Moreover, the infection free equilibrium $$E_0 = (T_0, 0, 0)$$ is globally asymptotically stable for the semiflow $$(S(t))_{t \geq 0}$$ restricted to $$\partial X^0$$.

Lemma 3.6. Let $$X^0$$ and $$\partial X^0$$ be as defined above. Then, both sets are forward invariant under the semiflow $$(S(t))_{t \geq 0}$$ generated by system (1)-(4) on $$X$$. Moreover, the infection free equilibrium $$E_0 = (T_0, 0, 0)$$ is globally asymptotically stable for the semiflow $$(S(t))_{t \geq 0}$$.

Proof. First we show that $$S(t) : \partial X^0 \rightarrow \partial X^0$$. Let $$x \in \partial X^0$$ and $$\tau = \inf \{t > 0 : S(t)x \in X^0\}$$. By continuity of $$S(t)$$, we obtain that $$S(\tau)x \in \partial X^0$$. Then we have:

$$\frac{dV(\tau)}{dt} = \int_0^\tau p(a)T^*(\tau, a)da - dV(\tau) - kV(\tau)T(\tau) - \gamma V(\tau)\int_0^\tau T^*(\tau, a)da = 0,$$

$$T^*(\tau, a) = \phi(a)kV(\tau - a)T(\tau - a)1_{\{a \leq \tau\}} + \frac{\phi(a)}{\phi(a - \tau)}T^*(0, a - \tau)1_{\{a > \tau\}}$$

Define

$$\eta(t) = (T_1(t), V_1(t), T_1^*(t, a)) = (T(t + \tau), 0, \frac{\phi(a)}{\phi(a - \tau)}T^*(0, a - \tau - t)1_{\{a > \tau + t\}})$$

Moreover, $$\eta(t)$$ is a solution to system (6)-(8) with the initial condition $$(S(\tau)x$$. Then by forward uniqueness of solutions, Theorem (2.1), $$S(t)x \in \partial X^0$$, $$\forall t \geq 0$$. From the equation (6), it is clear that for any solution in $$\partial X^0$$, $$T(t) \rightarrow T_0$$ as $$t \rightarrow \infty$$. Hence $$E_0 = (T_0, 0, 0)$$ is globally asymptotically stable for the semiflow $$(S(t))_{t \geq 0}$$.
restricted to $\partial X^0$. Now let $x = (T(0), V(0), T^*(0, a)) \in X_0$ be the initial point of $(T(t), V(t), T^*(t, a))$, then
\[
\frac{d}{dt}(V(t) + \int_0^\infty T^*(t, a)da)
\geq -dV(t) - \gamma V(t) \int_0^\infty T^*(t, a)da - \delta_{\max} \int_0^\infty T^*(t, a)da
\geq -\max\{\delta_{\max}, d\}(V(t) + \int_0^\infty T^*(t, a)da) - \frac{\gamma}{2}(V(t) + \int_0^\infty T^*(t, a)da)^2,
\]
where $\delta_{\max} = \text{ess sup}_{a \in (0, \infty)} \delta(a)$. Then $(V(t) + \int_0^\infty T^*(t, a)da) > y(t)$ that $y(t)$ is the solution of the following equation:
\[
\frac{dy(t)}{dt} = -Ay(t) - By(t)^2,
\]
with initial condition $y(0) = V(0) + \int_0^\infty T^*(0, a)da$ where $A = \max\{\delta_{\max}, d\}$ and $B = \frac{\gamma}{2}$, which leads to
\[
y(t) = \frac{1}{B(e^{At} - 1) + \frac{1}{y_0}} > 0, \quad \forall t \geq 0.
\]
This implies that $X^0$ is forward invariant. \hfill \Box

We will need the following result about linear Volterra integro-differential equations.

**Lemma 3.7** ([6]). Consider the following scalar integro-differential equation:
\[
\dot{y}(t) = \int_0^\infty h(a)y(t - a)da - cy, \quad y(0) > 0,
\]
where $h(\cdot) \in L_2((0, \infty], c > 0$, and $\int_0^\infty h(a)da > c$. There is a unique solution $y(t)$, which is unbounded.

Now we are ready to state and prove the uniform persistence of system (6)-(8).

**Theorem 3.8.** Assume $R_0 > 1$, the semiflow $\{S(t)\}_{t \geq 0}$ generated by system (1)-(4) is uniformly persistent with respect to the sets $\partial X_0, X_0$; that is, there exists $\epsilon > 0$, such that for each $x \in X_0$,
\[
\lim_{t \to +\infty} d(S(t)x, \partial X_0) \geq \epsilon,
\]
where $X^0$ and $\partial X^0$ are as in Lemma (3.6). Furthermore, there exists a compact subset $A_0 \subset X_0$ which is global attractor for $\{S(t)\}_{t \geq 0}$ in $X_0$.

**Proof.** To prove the uniform persistence and the existence of compact attractor, we will apply Theorem (3.1), and Theorem (3.2) or Theorem 3.7 in [18]. We will use the same argument as in the proof of theorem 3.6 in [6].

From the Proposition (3.5) and from the proof of Theorem (2.2), the semigroup $S(t)$ is asymptotically smooth and point dissipative (i.e. there exists a bounded set $B \subset X$ which attracts all points of $X$) respectively, and boundedness of $\gamma^+(U)$ for bounded $U \subset X$, is immediate from Theorem (2.2). The global attractor in $\partial X$, $A_0$, is the fixed point $\{E^0\} = \{(T_0, 0, 0)\}$, hence $\tilde{A}_0 = A_0$. We will show that $\{E^0\}$ is acyclic. Clearly, we have $\partial X^0 \subset W_s(\{E^0\})$. Also, $\partial X^0 \setminus \{E^0\} \cap W_u(\{E^0\}) = \emptyset$. Indeed, let $x = (T(0), 0, T^*(0, a)) \in \partial X^0 \setminus \{E^0\}$. Since $\partial X^0$ is
forward invariant, it is sufficient to show that any backward orbit of \( x \) stay in \( \partial X^0 \). To this end, if \( T^* (0, a) = 0 \), then system (6)-(8), become a scaler ODE with a unique positive equilibrium \( E^0 \), and \( \lim_{t \to -\infty} T(t) = 0 \) or \( \infty \). Suppose \( \int_0^\infty T^* (0, a) da > 0 \). Since \( x \in \partial X^0 \), \( \int_0^\infty T^* (0, a) da = 0 \). Suppose further, \( \exists \tau > 0 \), \( x_1 = (T(-\tau), 0, l_1(a)) \) to \( \partial X^0 \), such that \( S(\tau) x_1 = x \). Then, \( \int_0^\infty T^* (0, a) da = \int_{\bar{a} + \tau}^\infty e^{-\int_{\bar{a}}^a T^* (0, a - \tau) da} < \int_{\bar{a} + \tau}^\infty l_1(a) da \). Therefore, the norm of \( L^1 \)-component is strictly increasing on backward orbits and hence \( x_0 \) cannot be an \( \alpha \)-limit point of \( x \).

To complete the prove that \( x_0 \) is acyclic, we need only to prove \( W_s(\{ x_0 \}) \cap X^0 = \emptyset \).

Suppose by the way of contradiction, that there exists \( x \in X^0 \), such that \( x \in W_s(\{ x_0 \}) \). Then \( S(t)x \to x_0 \) as \( t \to 0 \). Indeed, if \( S(t) \to x_0 \), then \( \exists \epsilon > 0 \) and \( t_n \to \infty \) such that \( \| S(t_n)x - x_0 \| < \epsilon \). From Proposition (3.5), \( S(t) = U(t) + C(t) \). Since \( \{ C(t_n) \} \) is precompact, there exists a convergent subsequent \( \{ t_n \} \), such that \( C(t_{n_k}) \to x \neq x_0 \). Then \( S(t_{n_k})x \to x_1 \) because \( \| U(t_{n_k}) \to 0 \| \), which contradicts the assumption that \( x \in W_s(\{ x_0 \}) \). Hence \( S(t)x \to x_0 \) as \( t \to \infty \). It follows that we can find a sequence \( \{ x_n \} \subset X_0 \) such that \( \| S(t)x_n - x_0 \| < \frac{1}{n}, \forall t \geq 0 \).

Let \( S(t)x_n = (T_n(t), V_n(t), T_n^*(t, a)) \) and \( x_n = (T_n(0), V_n(0), T_n^*(0, a)) \). Then we have:

\[
|T_n(t) - T_0| < \frac{1}{n}, \quad \| T_n^*(t, a) \| < \frac{1}{n}, \quad \forall t \geq 0.
\]

Then, from equations (7) and (8), and comparison principle, we have:

\[
\frac{dV(t)}{dt} \geq \frac{dy_n(t)}{dt} = \int_0^t kp(a) \phi(a)(T_0 - \frac{1}{n})y_n(t - a) da - \left( d + k(T_0 + \frac{1}{n}) + \frac{\gamma}{n} \right) y_n(t),
\]

\[
y_n(0) = V(0).
\]

Without lose of generality, we can take \( V_n(t) > 0 \). Indeed, if \( V_n(0) = 0 \) then \( \int_0^a T_n^*(0, a) da > 0 \), and then \( \dot{V}(0) = 0 \). We claim that when \( \mathcal{R}_0 > 1 \), for \( n \) sufficiently large, \( y_n \) is unbounded. The assumption \( \mathcal{R}_0 > 1 \) is equivalent to \( kT_0 \int_0^\infty p(a) \phi(a) da - (d + kT_0) > 0 \). Therefore, for \( N \in \mathbb{N} \) sufficiently large, we have \( k(T_0 - \frac{1}{N}) \int_0^\infty p(a) \phi(a) da - (d + kT_0) > 0 \). Then by Lemma (3.7), \( y_N \) is unbounded. Since \( V_N \geq y_N \), hence, \( S(t)x_N \) is unbounded, which is a contradiction. Therefore, \( W_s(\{ x_0 \}) \cap X^0 = \emptyset \). Then by Theorem (3.1), \( S(t) \) is uniformly persistent, and by Theorem (3.2), there exists a compact set \( A_0 \subset X^0 \) which is global attractor for \( \{ S(t) \}, t \geq 0 \) in \( X^0 \).

\[
4. \text{Global analysis.} \text{ In this section, we construct suitable Lyapunov function to investigate the global stability of the infection free equilibrium for system } (1)-(5).
\]

**Theorem 4.1.** If \( \mathcal{R}_0 := \frac{NkT_0}{d + kT_0} \leq 1 \), then the infection free equilibrium \( E^0 \) of the system (1)-(5) is globally asymptotically stable.

**Proof.** Define a Lyapunov function on \( X \) as follows:

\[
W(t) = \int_0^\infty \alpha(a)T^*(t, a) da + V(t),
\]

that \( \alpha(a) = \int_0^\infty p(\theta)e^{-\int_0^a \delta(s)ds}d\theta \), \( \alpha(0) = N \) and \( \alpha'(a) = \delta(a)\alpha(a) - p(a), \forall a \geq 0 \).
Then, we have:

\[
\frac{dW(t)}{dt} = \int_0^\infty \alpha(a) \frac{\partial T^*(t, a)}{\partial t} da + \frac{dV(t)}{dt}
\]

\[
= - \int_0^\infty \alpha(a) \left( \frac{\partial T^*(t, a)}{\partial a} + \delta(a) T^*(t, a) \right) + 
\]

\[
+ \int_0^\infty p(a) T^*(t, a) da - dV(t) - kT(t) V(t) - \gamma V(t) \int_0^\infty T^*(t, a) da
\]

\[
= - \int_0^\infty \alpha(a) \frac{\partial T^*(t, a)}{\partial a} da + \int_0^\infty (p(a) - \alpha(a) \delta(a)) T^*(t, a) da
\]

\[
- dV(t) - kT(t) V(t) - \gamma V(t) \int_0^\infty T^*(t, a) da
\]

\[
= - \alpha(a) T^*(t, a) |_{a}^\infty + \int_0^\infty (\alpha(a) \delta(a) - p(a)) T^*(t, a) da
\]

\[
+ \int_0^\infty (p(a) - \alpha(a) \delta(a)) T^*(t, a) da
\]

\[
- dV(t) - kT(t) V(t) - \gamma V(t) \int_0^\infty p(a) T^*(t, a) da
\]

\[
= k(N - 1) V(t) T(t) - dV(t) - \gamma V(t) \int_0^\infty T^*(t, a) da
\]

\[
\leq dV(t) \left( \frac{k(N - 1) T_0}{d} - 1 - \frac{\gamma}{d} \int_0^\infty T^*(t, a) da \right)
\]

\[
= dV(t) \left( (R_0 - 1)(1 + \frac{k T_0}{d} - \frac{\gamma}{d} \int_0^\infty T^*(t, a) da) \right).
\]

Note that the last inequalities follow from the fact that $R_0 \leq 1$ and $\frac{dT}{dt} \leq sT - \frac{sT^2}{T_0}$.

The latter implies $\lim_{t \to \infty} T(t) \leq \lim_{t \to \infty} y(t) = T_0$, where $\dot{y} = sy - \frac{sy^2}{T_0}$ is a Bernoulli equation with $\lim_{t \to \infty} y(t) = T_0$. Therefore $\frac{dW(t)}{dt} = 0$, implies that $V(t) = 0$ or $R_0 = 1$ and $T(t) = y(t)$. It is easy to show that the largest invariant set where $\frac{dW(t)}{dt} = 0$ is the singleton $\{E^0\}$. Thus, when $R_0 \leq 1$, by Liapunov-LaSalle asymptotic stability theorem, $\{E^0\}$ is globally asymptotically stable for system (1)-(5).

\[\Box\]

5. Numerical results and Hopf bifurcation. In this section we study numerical examples, and apply the results obtained in the previous sections to two special cases. The parameter values for some infectious models in literatures are listed in Table 1, in which $s = e - g$ where $e$ is the proliferation rate and $g$ is natural death rate of uninfected cells, and $\frac{e}{T_{\text{max}}} = \frac{s}{T_0}$, where $T_{\text{max}}$ is the T cell population density at which proliferation shuts off as noted in introduction. In order to check our computation in this paper, we choose arbitrary values for certain parameters in some cases.

**Example 1.** Suppose that $\delta(a) = \delta, p(a) = p$ and $I(t) := T^*(t) = \int_0^\infty T^*(t, a) da$, then the system (1)-(4) becomes similar to the system (1) in [24] with $k_2 = 0$ as
follows:

\[ \begin{align*}
\frac{dT(t)}{dt} &= sT(t)(1 - \frac{T(t)}{T_0}) - kT(t)V(t), \\
\frac{dV(t)}{dt} &= \rho I(t) - dV(t) - kV(t)T(t) - \gamma V(t)I(t), \\
\frac{dI(t)}{dt} &= kT(t)V(t) - \delta I(t).
\end{align*} \]  

(40)

**Example 2 (DDE).** Now we consider infected cell death rates \( \delta(a) \) and viral production rates \( \rho(a) \) of the following piecewise form:

\[ \delta(a) = \begin{cases} 
\mu & 0 \leq a < \tau \\
\nu & \tau < a
\end{cases}, \quad \rho(a) = \begin{cases} 
0 & 0 \leq a < \tau \\
\rho & \tau < a
\end{cases} \]

Note that by defining \( J(t) = \int_T^a T^*(t, a) da \) and \( I(t) = \int_T^\infty T^*(t, a) da \), then (1)-(4) turn to the following delay differential equations

\[ \begin{align*}
\frac{dT(t)}{dt} &= sT(t)(1 - \frac{T(t)}{T_0}) - kT(t)V(t), \\
\frac{dV(t)}{dt} &= \rho I(t) - dV(t) - kV(t)T(t) - \gamma V(t)(J(t) + I(t)),
\end{align*} \]

(41), (42)
Figure 2. A numerical solution of system (40) approaches to $\bar{E}$, as time tends to infinity, and $\bar{E}$ is stable, wherein parameter values are $[s, k, T_0, p, d, \gamma, \delta] = [0.03285, 0.01, 4.6137, 1.3, 0.045, 0.1, 0.0351]$. In this case $R_0 = 16.0999$, $\bar{E} = (\bar{T}, \bar{V}, \bar{I}) = [0.2212, 3.1275, 0.1971]$. (A) Time series of $T$, $T^*$ and $V$. (B) An orbit in the $TVT^*$ space.

Figure 3. A numerical solution of system (40) tends to the limit cycle, as time tends to infinity, and $\bar{E}$ is unstable, wherein parameter values are $[s, k, T_0, p, d, \gamma, \delta] = [0.03285, 0.01, 4.6137, 1.3, 0.03, 0.1, 0.0351]$. In this case $R_0 = 22.4437$, $\bar{E} = (\bar{T}, \bar{V}, \bar{I}) = [0.1115, 3.2056, 0.1018]$. (A) Time series of $T$, $T^*$ and $V$. (B) An orbit in the $TVT^*$ space. Eigenvalues of linearized matrix about $\bar{E}$ are $\lambda_1 = -0.0779 + 0.0009i$, $\lambda_2 = 0.0004 - 0.0209i$, $\lambda_3 = 0.0004 + 0.0209i$.

As in [4, 25], we think of $\tau$ as the intracellular delay between cell infection and viral production. Experimental results have shown that for HIV infection this delay $\tau$ is between 1 and 2 days, we utilize $\tau = 2$ days in our simulations of this model. The defined variables $J(t)$ and $I(t)$ represent infected cells in their eclipse phase and productive phase, respectively.

Figure 1, 2 and 3 show simulations of system (40) and Figure 4, 5 and 6 show simulations of system (41)-(44). In figures 1 and 4, the parameter values are chosen such that $R_0 < 1$. In this cases, $E_0$ is globally asymptotically stable. In other figures $R_0 > 1$ and $E_0$ is unstable. In Figures 2 and 5 , $\bar{E}$ is stable and in Figures 3 and 6, $\bar{E}$ is unstable and solutions approach to a periodic solution. We note that in both examples the Hopf bifurcation occurs when we increase $R_0$ by altering a couple of the parameters.
parameter values (see captions for details). While the condition for Hopf bifurcation, Eq. (36), is too complicated to formally analyze, we can conjecture that the logistic growth of target cells is necessary for the observed oscillatory dynamics. Indeed, the model analyzed in [24] is similar to system (38), except without logistic growth rate, and did not display periodic solutions. Additionally, Shu et al. found that a similar delay model to (41)-(44) (without cell re-infection) only displayed oscillations when logistic growth was used for uninfected cells [14] In further simulations (not shown), we varied re-infection rate $\gamma$ and did not find it to be a critical parameter for Hopf bifurcation. Thus, evidence suggests that the logistic growth of uninfected cells is the factor which can induce sustained oscillations.

Figure 4. A numerical solution of system (41)-(44) tends to the DFE, as time tends to infinity, wherein parameter values are $[s, T_0, k, \rho, d, \gamma, \tau, \mu, v] = [1, 100000, 0.0000005, 200, 13, 0.000003, 2, 0.05, 0.7]$. In this case $R_0 = 0.9905$ and $(\bar{T}, \bar{V}, \bar{I}) = [10^5, 0, 0]$. (A) Time series of $T$, $T^* = J + I$ and $V$. (B) An orbit in the $TVT^*$ space.

In addition, we quantify the probability of an infected cell being re-infected before infection-age $\sigma \leq \tau$, where $\sigma$ is the cell infection-age when reverse transcription is complete. The interest in this quantity lies in the fact that viral recombination within a co-infected cell can only occur before completion of the reverse transcription, and the recombination rate is of significance for within-host HIV evolution [16]. In general, the probability of an infected cell being re-infected before infection-age $\sigma \leq \tau$ at the positive equilibrium, similar to calculations in [30], is given by

$$
\pi(\sigma) = \gamma \bar{V} \int_0^\sigma \phi(a) e^{-\gamma \bar{V} a} da.
$$

For the piecewise function in this example, $\pi(\sigma) = \frac{\gamma \bar{V}}{\mu + \gamma \bar{V}} \left( 1 - e^{-(\mu + \gamma \bar{V})\sigma} \right)$. In general, the number of infected cells which have been re-infected before age $\sigma$ at any time $t$, denoted by $R(t, \sigma)$, is given by the following expression:

$$
R(t, \sigma) = \int_0^\infty \phi(a) \int_0^a \frac{\gamma}{\phi(s)} V(t - a + s) T^* (t - a + s) e^{-\gamma \int_a^s V(t-a+u)du} 1_{\{s \leq \sigma\}} dsda
$$

The above formula is similar to equations derived when the age-structured model includes explicit immune response in [5]. At the positive equilibrium, it can be shown
Figure 5. A numerical solution of system (41)-(44) tends to the \( \bar{E} \), as time tends to infinity, and \( \bar{E} \) is stable, wherein parameter values are \([s, T0, k, p, d, \gamma, \tau, \mu, \nu] = [1, 100000, 0.0000008, 200, 13, 0.000003, 2, 0.05, 0.7]\). In this case \( R_0 \) = 1.5812, \((\bar{T}, \bar{V}, \bar{J} + \bar{I}) = [6.3209 \times 10^4, 4.5989 \times 10^4, 7.4321 \times 10^3]\). The probability of re-infection of infected cells during eclipse phase (during age \( 0 \leq a \leq \tau \)) calculated at \( \bar{E} \) is \( \pi(\tau) = 0.23 \). (A) Time series of \( T, T^* = J + I \) and \( V \). (B) An orbit in the \( TVT^* \) space.

Figure 6. A numerical solution of system (41)-(44) tends to the limit cycle, as time tends to infinity, and \( \bar{E} \) is unstable, wherein parameter values are \([s, T0, k, p, d, \gamma, \tau, \mu, \nu] = [1, 100000, 0.000005, 200, 13, 0.000001, 2, 0.05, 0.7]\). In this case \( R_0 \) = 9.5750, \((\bar{T}, \bar{V}, \bar{J} + \bar{I}) = [1.0119 \times 10^5, 1.7976 \times 10^5, 2.9066 \times 10^4]\). The probability of re-infection of infected cells during eclipse phase calculated at \( \bar{E} \) is \( \pi(\tau) = 0.2882 \). (A) Time series of \( T, T^* = J + I \) and \( V \). (B) An orbit in the \( TVT^* \) space.

that the above equations are related as probability of reinfection is equal to the proportion of re-infected cells (re-infected at age \( a \leq \sigma \)): \( \pi(\sigma) = \bar{R}(\sigma)/\int_0^\infty \bar{T}^*(a)da \). For each of the cells re-infected before reverse transcription (before age \( \sigma \)), there
is a probability that recombination can occur. Experimental estimates of the proportion of re-infected cells have recently been measured to be 10-30\% of infected cells in for HIV [16, 10]. For the parameters in Figures 5 and 6, we calculate the probability of re-infection of an infected cell during the eclipse phase (calculated at the positive equilibrium) to be $\pi(\tau) = 0.23$ and $\pi(\tau) = 0.2882$, respectively. A fraction of re-infected cells will undergo recombination during reverse transcription.

6. Discussion. The global analysis of age-structured within-host virus model was studied by many authors such as [31] and [6]. To study the global stability of infection equilibrium, Browne and Pilyugin [6] assumed the “sector” condition, which does not hold for our model that incorporates proliferation of healthy cells. Also, they assumed that the proportion of viruses which entered into the cells are small in comparison to the free viruses or can be absorbed into the viral death rate, a common assumption for HIV models. However, this model does not work for all infections, such as poliovirus, where the amount of virus entered into the cells is notable to consider. In addition, for HIV infection, the re-infection of already infected cells is important to consider for quantifying viral recombination which may contribute significantly to in-host evolution [10]. In this paper, we introduced a model which accounts for viral entry into infected cells, which amplifies the complexity of analysis of the model.

In this paper, we find reproduction number and analyzed the model for $R_0 \leq 1$ and $1 < R_0$. For $R_0 \leq 1$, we proved that the infection-free equilibrium is globally asymptotically stable. Conversely, we showed that in the case $1 < R_0$, the infection free equilibrium, there exists a unique infection equilibrium, and the system is uniformly persistent. By choosing different parameters values the unique infection equilibrium can destabilize through a Hopf bifurcation. In this unstable case, we demonstrate sustained oscillations in numerical examples, along with quantifying the amount of viral re-infection.

There are several limitations to our study which should be noted. Although the model predicts clearance of the virus when $R_0 \leq 1$, current treatment for HIV cannot eradicate the virus due to latently infected cells which are not targeted by antiviral therapy. Recent studies have modeled HIV persistence and the latent reservoir [26], which provides motivation for future work on extending our model to include latency. Our model also neglects virus mutations, which occur very frequently for HIV. This is particularly relevant for viral resistance to host immune response or drug treatment, and viral recombination in co-infected cells may effect the evolution of resistance. Finally, we note that the Hopf bifurcation condition (36) was too complex for rigorous analysis at this point. Future work will further analyze the observed oscillatory behavior and determine how cell re-infection affects viral dynamics.

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