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GLOBAL ANALYSIS OF AGE-STRUCTURED WITHIN-HOST VIRUS MODEL

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Abstract. A mathematical model of a within-host viral infection with explicit age-since-infection structure for infected cells is presented. A global analysis of the model is conducted. It is shown that when the basic reproductive number falls below unity, the infection dies out. On the contrary, when the basic reproductive number exceeds unity, there exists a unique positive equilibrium that attracts all positive solutions of the model. The global stability analysis combines the existence of a compact global attractor and a Lyapunov function.

1. **Introduction.** In this paper, we present a global analysis of an age-structured within-host virus model. Modeling within-host virus dynamics has been an extensive area of research over the past couple of decades. Much of the work on this topic builds upon the standard virus model: a nonlinear system of three ordinary differential equations incorporating target cells, infected cells, and free virus particles as the state variables [12]. To account for the time lag between viral entry of a target cell and subsequent viral production from the newly infected cell, Perelson et al. included discrete and distributed delays in the standard model [11]. Nelson et al. considered a model with age structure in the infected cell compartment, which generalizes the delay standard virus model by allowing for infected cell death rate and viral production to vary with age since infection of an infected cell [10].

This age-structured within-host virus model has been of recent interest in the literature [2, 4, 7, 13]. Gilchrist et al. investigated viral production strategies which optimize viral fitness under various assumptions on the infected cell life history [2]. Althaus et al. estimated HIV parameters in the age-structured model using viral decline data from patients undergoing drug therapy [4]. Rong et al. incorporated treatment with three different classes of drugs into the age-structured model in order to assess the effect of different combination therapies on viral dynamics. They proved the local stability of the positive equilibrium in the case when the derived basic reproduction number is greater than unity, but left the global behavior as an open question [13]. Huang et al. (2012), independently of our research, studied the global behavior under more restrictive conditions than the present work [7].

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The model considered in this paper has the following form:

$$\begin{aligned} \frac{dT(t)}{dt} &= f(T(t)) - kV(t)T(t), \\ \frac{\partial T^*(t,a)}{\partial t} + \frac{\partial T^*(t,a)}{\partial a} &= -\delta(a)T^*(t,a), \\ \frac{dV(t)}{dt} &= \int_0^\infty p(a)T^*(t,a)\,da - \gamma V(t), \\ T^*(t,0) &= kV(t)T(t) \quad T^*(0,a) \in L^1_+(0,\infty), \\ T(0) &= T_0 \in \mathbb{R}_+, \quad V(0) = V_0 \in \mathbb{R}_+, \end{aligned} \tag{1}$$

where $T(t)$ and $V(t)$ denote the concentrations of healthy cells and free virus particles, respectively. $T^*(t,a)$ denotes the density of infected cell concentration with respect to age since infection. Note that $T^*(0,a)$ is assumed to belong to the set $L^1_+(0,\infty)$, the non-negative cone of $L^1(0,\infty)$. The parameters k and γ are assumed to be positive. The parameter γ is the decay rate of virus particles. The infection of healthy cells is modeled by a mass action term kVT. The function $\delta(a)$ represents the age-dependent death rate of the infected cells. The function $p(a)$ 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 $L^\infty(0,\infty)$. We also make the assumption that $\delta(a) \geq b > 0$ for some constant b. The homeostatically regulated growth rate of the uninfected cell population is given by the smooth function $f : \mathbb{R} \to \mathbb{R}$, which is assumed to satisfy the following:

$$\exists\ T_0 > 0 : f(T)(T - T_0) < 0 \quad \text{ for all } T \neq T_0 \text{ and } f'(T_0) < 0.$$

The class of admissible functions $f(T)$ is chosen to be quite large, but we will impose an additional condition to prove the global stability of the infection equilibrium of (1).

Various approaches have been developed for analyzing age structured models. The general idea is to study the nonlinear semigroup generated by the family of solutions. One approach is to use the theory of integrated semigroups [8, 14]. We employ another method, namely integrating solutions along the characteristics to obtain an equivalent integral equation. This approach was developed by Webb for age dependent models [15], but the setting there is somewhat different from our hybrid ODE-PDE system. Hence, we use fundamental principles, results from Hale on asymptotic smoothness [5], and a compactness condition for L^p spaces to rigorously prove existence, uniqueness and eventual compactness of the nonlinear semigroup associated with the solutions to (1).

In order to study the global behavior when the basic reproduction number, $\mathcal{R}_0$, exceeds 1, we follow a similar approach to [8]. We use results from Hale and Waltman [6] to prove uniform persistence and use results from Magal and Zhao [9] to establish existence of a compact global attractor, $\mathcal{A}_0$, contained inside the uniformly persistent set. We subsequently define a Lyapunov functional on $\mathcal{A}_0$ which relies on the uniform persistence and invariance in order to be well-defined and bounded. Then, by using compactness of $\mathcal{A}_0$, we prove convergence of backward orbits to $\overline{x}$ via the Lyapunov function. This will then imply $\mathcal{A}_0 = \{\overline{x}\}$ and global stability follows.

This paper is organized as follows: In Section 2 we prove the existence and uniqueness of solutions of an equivalent integral formulation of (1) using the contraction mapping theorem and also prove boundedness of solutions. In Section 3, we study the global dynamics of the semiflow associated with the solutions of (1). We define the basic reproductive number, $\mathcal{R}_0$, and prove the global extinction when $\mathcal{R}_0 \leq 1$ and the global asymptotic stability of the unique infection equilibrium when $\mathcal{R}_0 > 1$.

2. **Volterra formulation and the existence of solutions.** We note that the PDE in (1) is a linear transport equation with decay. Hence it can be solved, at least formally, by integrating along the characteristics and incorporating the boundary condition:

$$T^*(t,a) = \begin{cases} \phi(a)kV(t-a)T(t-a), & \text{if } t > a \\ \\ \frac{\phi(a)}{\phi(a-t)}T^*(0,a-t), & \text{if } t \leq a, \end{cases} \tag{2}$$

where $\phi(a) = \exp\left(-\int_0^a \delta(s)\,ds\right)$. The function $\phi(a)$ is typically interpreted as the probability that an infected cell survives till age a. The equivalent integral formulation of (1) is the following system of integro-differential equations:

$$\begin{aligned} \frac{dT(t)}{dt} &= f(T(t)) - kV(t)T(t), \\ \frac{dV(t)}{dt} &= \int_0^\infty p(a)T^*(t,a)\,da - \gamma V(t), \\ T^*(t,a) &= \phi(a)kV(t-a)T(t-a)\mathbf{1}_{\{t>a\}} + \frac{\phi(a)}{\phi(a-t)}T^*(0,a-t)\mathbf{1}_{\{a>t\}}. \end{aligned} \tag{3}$$

We now prove local existence and uniqueness of solutions to (3) and hence to (1).

Theorem 2.1. *Let $x_0 = ((T(0), V(0), T^*(0,a)) \in \mathbb{R}^2_+ \times L^1_+(0,\infty)$. Then there exists $\epsilon > 0$ and neighborhood $B_0 \subset \mathbb{R}^2_+ \times L^1_+(0,\infty)$ with $x_0 \in B_0$ such that there exists a unique continuous function, $\psi : [0,\epsilon] \times B_0 \to \mathbb{R}^2 \times L^1_+(0,\infty)$ where $\psi(t,x)$ is the solution to (3) with $\psi(0,x) = x$.*

Proof. Any solution to (3) must satisfy the following integral equation:

$$\begin{aligned} T(t) &= T(0) + \int_0^t f(T(s)) - kV(s)T(s)\,ds, \\ V(t) &= V(0) + \int_0^t \int_0^\infty p(a)T^*(s,a)\,da\,ds - \gamma \int_0^t V(s)\,ds, \\ T^*(t,a) &= \phi(a)kV(t-a)T(t-a)\mathbf{1}_{\{t>a\}} + \frac{\phi(a)}{\phi(a-t)}T^*(0,a-t)\mathbf{1}_{\{a>t\}}. \end{aligned} \tag{4}$$

Let $Y := \mathcal{C}([0,\epsilon]\times B_0, \mathbb{R}^2 \times L^1(0,\infty))$, the set of continuous functions from $[0,\epsilon]\times B_0$ to $\mathbb{R}^2 \times L^1(0,\infty)$, where $\epsilon > 0$ and $B_0 \subset \mathbb{R}^2_+ \times L^1_+(0,\infty)$, a neighborhood containing x_0, are to be determined. Let $\mathcal{B} \subset Y$ contain functions whose range is contained in $B \subset \mathbb{R}^2 \times L^1(0,\infty)$ where $B = \overline{B}((T(0), V(0), T^*(0,a)), r)$ is the closed ball of radius r centered around the initial condition, for some $r > 0$. Now define the operator Λ on $\mathcal{B}$ as follows: Let $x = (x_1, x_2, \ell(a)) \in B_0$ and the vector valued function $\eta = (\eta_1, \eta_2, \eta_3) \in \mathcal{B}$. Define

$$\Lambda(\eta)\,(t,x) = \begin{pmatrix} x_1 + \int_0^t [f(\eta_1(s,x)) - k\eta_2(s,x)\eta_1(s,x)]\,ds \\ x_2 + \int_0^t \left[\int_0^\infty p(a)\eta_3(s,x)(a)\,da - \gamma\eta_2(s,x)\right]\,ds \\ \phi(a)k\eta_1(t-a,x)\eta_2(t-a,x)\mathbf{1}_{\{t>a\}} + \frac{\phi(a)}{\phi(a-t)}\ell(a-t)\mathbf{1}_{\{a>t\}} \end{pmatrix}.$$

We have that $\Lambda(\eta) \in Y$, indeed since

$$\begin{aligned}
&\int_0^\infty \left|\phi(a)k\eta_1(t-a,x)\eta_2(t-a,x)\mathbf{1}_{\{t>a\}} + \frac{\phi(a)}{\phi(a-t)}\ell(a-t)\mathbf{1}_{\{a>t\}}\right| da \\
\leq\ & \int_0^t \phi(a)k|\eta_1(t-a,x)\eta_2(t-a,x)|\, da + \int_t^\infty \frac{\phi(a)}{\phi(a-t)}\ell(a-t)\, da \\
&\leq t\frac{1}{b}(1-e^{-bt})\kappa k|T(0)+r|\cdot|V(0)+r| + \|\ell\| < \infty
\end{aligned}$$

where $\kappa > 0$ is a constant such that $p(a) \leq \kappa$ a.e. on $[0,\infty)$.

Take $B_0 = B((T(0), V(0), T^*(0,a)), r/2)$. Then

$$\begin{aligned}
\|\Lambda(\eta)(t,x) - x_0\| &= |x_1 - T(0) + \int_0^t f(\eta_1(s,x)) - k\eta_2(s,x)\eta_1(s,x)\, ds| \\
&\quad + |x_2 - V(0) + \int_0^t \int_0^\infty p(a)\eta_3(s,x)(a)\, da\, ds - \gamma \int_0^t \eta_2(s)\, ds| \\
&\quad + \int_0^\infty \Big|\phi(a)k\eta_1(t-a,x)\eta_2(t-a,x)\mathbf{1}_{\{t>a\}} \\
&\qquad\qquad + \frac{\phi(a)}{\phi(a-t)}\ell(a-t)\mathbf{1}_{\{a\geq t\}} - T^*(0,a)\Big|\, da \\
&\leq |x_1 - T(0)| + \epsilon \max_{z\in B(T(0),r)} |f(z)| + \epsilon k|T(0)+r|\cdot|V(0)+r| \\
&\quad + |x_2 - V(0)| + \epsilon\kappa(\|T^*(0,a)\| + r) + \epsilon\gamma|V(0)+r| \\
&\quad + \frac{1}{b}(1-e^{-b\epsilon})k|T(0)+r|\cdot|V(0)+r| \\
&\quad + \int_0^\infty \frac{\phi(a)}{\phi(a-t)}\mathbf{1}_{\{a\geq t\}}\, |\ell(a-t) - T^*(0,a-t)|\, da \\
&\quad + \int_0^\infty \left|\frac{\phi(a)}{\phi(a-t)}\mathbf{1}_{\{a\geq t\}}T^*(0,a-t) - T^*(0,a)\right| da.
\end{aligned}$$

Notice that

$$\int_0^\infty \frac{\phi(a)}{\phi(a-t)}\mathbf{1}_{\{a\geq t\}}\, |\ell(a-t) - T^*(0,a-t)|\, da \leq \|\ell - T^*(0,\cdot)\|\,.$$

Also,

$$\begin{aligned}
&\int_0^\infty \left|\frac{\phi(a)}{\phi(a-t)}\mathbf{1}_{\{a\geq t\}}T^*(0,a-t) - T^*(0,a)\right| da \\
&\qquad \leq \int_0^\infty \mathbf{1}_{\{a\geq t\}}T^*(0,a-t)\left|\frac{\phi(a)}{\phi(a-t)} - 1\right| da \qquad \text{(J1)} \\
&\qquad\qquad + \int_0^\infty \left|\mathbf{1}_{\{a\geq t\}}T^*(0,a-t) - T^*(0,a)\right| da. \qquad \text{(J2)}
\end{aligned}$$

By the Dominated Convergence Theorem, (J1)$\to 0$ as $t \to 0$. Hence $(J1) < \frac{r}{16}$ for all $t \in [0,\epsilon]$ provided that ϵ sufficiently small. Let ξ be a continuous function with compact support in $[0,\infty)$ such that $\|T^*(0,\cdot) - \xi\| < \frac{r}{32}$. We note that the existence of ξ follows from the fact that the set of all continous functions with compact support is dense in L^1. Then

$$\begin{aligned}(J2) &\leq \int_0^t |T^*(0,a)|\, da + \int_0^\infty |T^*(0,a) - \xi(a)|\, da + \int_0^\infty |\xi(a) - \xi(a+t)|\, da \\ &\qquad + \int_t^\infty |T^*(a) - \xi(a)|\, da \\ &\leq 2\int_0^\infty |T^*(0,a) - \xi(a)|\, da + \int_0^t |T^*(0,a)|\, da + \int_0^\infty |\xi(a) - \xi(a+t)|\, da \\ &\leq \frac{r}{8} + \frac{r}{32} + \frac{r}{32} \quad \text{for } \epsilon \text{ sufficiently small.}\end{aligned}$$

Therefore $(J1) + (J2) < \frac{r}{4}$ and hence

$$\begin{aligned}\|\Lambda(\eta)(t,x) - x_0\| &\leq \|x - x_0\| + \epsilon M_1 + (1 - e^{-b\epsilon})M_2 + \frac{r}{4} \\ &< \frac{r}{2} + \frac{r}{4} + \frac{r}{4}\end{aligned}$$

for constants $M_1, M_2 > 0$ and $\epsilon > 0$ sufficiently small. Therefore $\Lambda : \mathcal{B} \to \mathcal{B}$. Note that $\mathcal{B}$ is a complete metric space. We will now show that Λ is a contraction on $\mathcal{B}$ for ϵ sufficiently small. Let $\eta, \zeta \in \mathcal{B}$. Then

$$\begin{aligned}&\|\Lambda(\eta)(t,x) - \Lambda(\zeta)(t,x)\| \\ &\leq \int_0^t |f(\eta_1(s,x)) - f(\zeta_1(s,x))|\, ds + k\int_0^t |\zeta_2(s,x)\zeta_1(s,x) - \eta_2(s,x)\eta_1(s,x)|\, ds \\ &\quad + \int_0^t \int_0^\infty p(a)|\eta_3(s,x)(a) - \zeta_3(s,x)(a)|\, da\, ds + \int_0^t \gamma|\zeta_2(s,x) - \eta_2(s,x)|\, ds \\ &\quad + \int_0^t e^{-ba} k|\eta_2(t-a,x)\eta_1(t-a,x) - \zeta_2(t-a,x)\zeta_1(t-a,x)|\, da \\ &\leq \epsilon\lambda_{\mathcal{A}} \|\eta_1 - \zeta_1\| + \epsilon k(T(0)+r)\|\eta_2 - \zeta_2\| + \epsilon k(V(0)+r)\|\eta_1 - \zeta_1\| \\ &\quad + \epsilon\kappa\|\eta_3 - \zeta_3\| + \epsilon\gamma\|\eta_2 - \zeta_2\| + \epsilon k(T(0)+r)\|\eta_2 - \zeta_2\| + \epsilon k(V(0)+r)\|\eta_1 - \zeta_1\| \\ &\leq \epsilon M \|\eta - \zeta\|.\end{aligned}$$

where $M > 0$ is a constant. Therefore Λ is a contraction mapping on $\mathcal{B}$ for ϵ sufficiently small. By the Contraction Mapping Theorem there exists a unique fixed point of Λ in $\mathcal{B}$, denote this function by ψ. Then $\psi(t,x)$ solves the initial value problem and is continuous on $[0,\epsilon] \times B_0$. $\square$

Lemma 2.2. *Solutions to (3) remain non-negative for almost every $a \geq 0$ and bounded in forward time.*

Proof. Upon inspection of the integral equations for $T(t)$ and $V(t)$, notice that $T(t)$ and $V(t)$ are differentiable by the fundamental theorem of calculus. Also, $\int_0^\infty T^*(t,a)\, da$ is differentiable in t by the smoothing properties of convolution.

Let $T(t)$, $T^*(t,a)$, and $V(t)$ be a particular solution to (3) and hence the (possibly weak) solution to (1) on the interval $[0,\beta]$, where $\beta < \rho$ and $[0,\rho)$ is the maximal interval of existence guaranteed to exist from Theorem 2.1 (ρ is allowed to be ∞). First, we show solutions remain non-negative on $[0,\beta]$. Suppose by way of contradiction that this is not true. Notice that $T(t) > 0\ \forall t \in (0,\beta)$ by the continuity of $T(t)$ and the assumption that $f(0) > 0$ and f is smooth. Define

$$\tau = \min\left(\inf\{t \in [0,\beta] : V(t) < 0\}, \inf\left\{t \in [0,\beta] : T^*(t,\cdot) \notin L^1_+(0,\infty)\right\}\right).$$

Then, $0 \leq \tau \leq \beta$. First, suppose that $\tau = \inf\left\{t \in [0,\beta] : T^*(t,\cdot) \notin L^1_+(0,\infty)\right\}$. Then $\exists (t_n)$ such that $t_n \downarrow \tau$ and for all n, $T^*(t_n,\cdot) \notin L^1_+(0,\infty)$. Also, $T^*(0,\cdot) \in L^1_+(0,\infty)$ and (2) imply

$$\begin{aligned}\{a \in [0,\infty) : T^*(t_n,a) < 0\} &= \{a \in [0,t_n) : \phi(a)kV(t_n-a)T(t_n-a) < 0\}\\ &= \{a \in [0,t_n) : V(t_n-a) < 0\}.\end{aligned}$$

Therefore for all n, $\exists t \in [0,t_n)$, such that $V(t) < 0$. Since $t_n \downarrow \tau$, we find that $\inf\{t \in [0,\beta] : V(t) < 0\} \leq \tau$. Hence, it suffices to consider the case where $\tau = \inf\{t \in [0,\beta] : V(t) < 0\}$. By the semigroup property, it suffices to consider $\tau = 0$. Then $V(0) = 0$.

$$\begin{aligned}\dot{V}(t) &= \int_0^\infty p(a)T^*(t,a)\,da - \gamma V(t)\\ &= \int_0^t p(a)\phi(a)kV(t-a)T(t-a)\,da\\ &\qquad + \int_t^\infty p(a)\frac{\phi(a)}{\phi(a-t)}T^*(0,a-t)\,da - \gamma V(t)\\ (\dot{V}(t)+\gamma V(t))e^{\gamma t} &= \int_0^t e^{\gamma(t-a)}p(t-a)\phi(t-a)kT(a)e^{\gamma a}V(a)\,da\\ &\qquad + e^{\gamma t}\int_t^\infty p(a)\frac{\phi(a)}{\phi(a-t)}T^*(0,a-t)\,da.\end{aligned}$$

Let $\widetilde{V}(t) = V(t)e^{\gamma t}$ and $g(t,a) = e^{\gamma(t-a)}p(t-a)\phi(t-a)kT(a)$. Note $g(t,a) \geq 0$. Then we have the following differential equation:

$$\frac{d}{dt}\widetilde{V}(t) = \int_0^t g(t,a)\widetilde{V}(a)\,da + e^{\gamma t}\int_t^\infty p(a)\frac{\phi(a)}{\phi(a-t)}T^*(0,a-t)\,da, \qquad \widetilde{V}(0) = 0.$$

For this equation, we claim that there exists a non-negative solution on a sufficiently small interval of time. Indeed, let $\widetilde{Y} = \mathcal{C}\left([0,\epsilon],\mathbb{R}_+\right)$ and $\widetilde{\mathcal{B}} \subset \widetilde{Y}$ be the set of functions whose range is contained in $[0,1]$, i.e. $\widetilde{\mathcal{B}} = \mathcal{C}\left([0,\epsilon],[0,1]\right)$. Define $\widetilde{\Lambda}$ on $\widetilde{\mathcal{B}}$ as

$$\widetilde{\Lambda}(\eta)(t) = \int_0^t\int_0^s g(s,a)\eta(a)\,da\,ds + \int_0^t e^{\gamma t}\int_s^\infty p(a)\frac{\phi(a)}{\phi(a-s)}T^*(0,a-s)\,da,\,ds.$$

For $\epsilon > 0$ sufficiently small, we can show, similar to the proof of Theorem 2.1, the following: $\widetilde{\Lambda} : \widetilde{\mathcal{B}} \to \widetilde{\mathcal{B}}$ and $\widetilde{\Lambda}$ is a contraction mapping on the complete metric space $\widetilde{\mathcal{B}}$. Upon application of the contraction mapping theorem, the claim follows. But then this either contradicts the definition of τ or the uniqueness of solutions to (3). Hence the solution to (3) must remain non-negative on $[0,\beta]$. Since $\beta < \rho$ is arbitrary, we conclude that the solution remains non-negative on its maximal interval of existence $[0,\rho)$.

Our assumptions on the parameters imply that $\delta(a) \geq b > 0$ $\forall a \in [0,\infty)$ and $0 \leq p(a) \leq \kappa$. Also, we note that for all nonnegative solutions of (1), $T(t) \leq \max(T(0),T_0) := M$ for all $t \geq 0$ in the interval of its existence. Since $f(T)$ is bounded on $[0,M]$, there exist $A > 0$ and $B > 0$ such that $f(T) \leq A - BT$ for all

$T \in [0, M]$. Consider $T + \int_0^\infty T^* \, da + \frac{b}{2\kappa} V$. Then

$$\begin{aligned}\frac{d}{dt}(T + \int_0^\infty T^* \, da + \frac{b}{2\kappa} V) &= f(T) - \int_0^\infty \delta(a) T^* \, da + \frac{b}{2\kappa}(\int_0^\infty p(a) T^*(t,a) \, da - \gamma V) \\ &\le A - BT - b \int_0^\infty T^* \, da + \frac{b}{2\kappa} \kappa \int_0^\infty T^* \, da - \frac{b}{2\kappa} \gamma V \\ &= A - BT - \frac{b}{2} \int_0^\infty T^* \, da - \frac{b}{2\kappa} \gamma V \\ &\le A - \alpha(T + \int_0^\infty T^* \, da + \frac{b}{2\kappa} V)\end{aligned}$$

where $\alpha = \min(B, \frac{b}{2}, \gamma)$. This implies that

$$\limsup_{t \to \infty} \left(T + \int_0^\infty T^* \, da + \frac{b}{2\kappa} V) \right) \le \frac{A}{\alpha}.$$

Boundedness follows from nonnegativity of solutions. □

3. **Dynamics of solutions.** We will now define a reproduction number, $\mathcal{R}_0$, for the system, along with describing the equilibria. Notice, there exists an infection free equilibrium, $x_0 = (T_0, 0, 0)$, of (3). Let

$$\mathcal{R}_0 := \frac{kT_0}{\gamma} \int_0^\infty p(a) \phi(a) \, da.$$

If $\mathcal{R}_0 > 1$, then observe that there exist a unique positive equilibrium x_1:

$$\overline{T} = \frac{T_0}{\mathcal{R}_0}, \quad \overline{V} = \frac{f(\overline{T})}{k\overline{T}}, \quad \overline{T}^*(a) = k\overline{V}\,\overline{T}\phi(a). \tag{5}$$

Now define $X = \mathbb{R}_+^2 \times L_+^1(0, \infty)$. Note that X is a complete metric space. Let $x = (x_1, x_2, \ell(a)) \in X$. Let $\psi(t, x)$ be the solution to (3) as in Theorem 2.1, which we know from Lemma 2.2 is bounded and forward complete. For $t \ge 0$ define the flow, $S(t) : X \to X$ as $S(t)x = \psi(t, x)$. We claim that the family of functions $\{S(t)\}_{t \ge 0}$ is a C^0 semigroup on X. Clearly $S(0)x = x$. Now to show the semigroup property, by standard arguments $\forall t \ge 0, s \ge 0 \quad \psi(t, \psi(s, x)) = \psi(t + s, x)$. Indeed, define $\eta(t) = \psi(t + s, x)$, then $\eta(t)$ is a solution to (3) with initial condition $\psi(s, x)$, and then invoke forward uniqueness from Theorem 2.1. Also the continuity follows from Theorem 2.1. In the following, we will often let $S(t)x = (T(t), V(t), T^*(t, a))$ with $x = (T(0), V(0), T^*(0, a))$.

3.1. **Asymptotic smoothness.** In order to obtain global properties of the dynamics of the flow, it is important to prove that the semigroup $S(t)$ is asymptotically smooth. A C^0 semigroup $R(t) : X \to X$ is said to be asymptotically smooth, if, for any nonempty, closed bounded set $B \subset X$ for which $R(t)B \subset B$, there is a compact set $J \subset B$ such that J attracts B [5]. A definition which is useful in proving asymptotic smoothness is the following: A semigroup $R(t)$ is completely continuous if for each $t > 0$ and each bounded set $B \subset X$, we have $\{R(s)B, 0 \le s \le t\}$ is bounded and $R(t)B$ is precompact. We will apply the following lemma:

Lemma 3.1 ([5]). *For each $t \ge 0$, suppose $R(t) = U(t) + C(t) : X \to X$ has the property that $C(t)$ is completely continuous and there is a continuous function $k : \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}^+$ such that $k(t, r) \to 0$ as $t \to \infty$ and $\|U(t)x\| \le k(t, r)$ if $\|x\| \le r$. Then $R(t), t \ge 0$, is asymptotically smooth.*

Also, since $L^1_+(0,\infty)$ is a component of our state space X, we need a notion of compactness in L^1. Being an infinite dimensional space, boundedness does not imply precompactness. We use the following result.

Lemma 3.2 ([1])**.** *Let $K \subset L^p(0,\infty)$ be closed and bounded where $p \geq 1$. Then K is compact iff the following hold:*

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

Proposition 1. *The semigroup, $S(t)$, generated by (3), is asymptotically smooth.*

Proof. In our case, it is clear that if for any bounded set $B \subset X$, we project $S(t)B$ on to $\mathbb{R}^2$, $\pi_1 S(t)B$, we have that $\pi_1 S(t)B$ is precompact because solutions remain bounded. Suppose we show that the projection of $S(t)$ on to $L^1(0,\infty)$, $\pi_2 S(t)$, can be written as $\pi_2 S(t) = U(t) + C(t)$, where there exists $k(t,r) \to 0$ as $t \to \infty$ with $\|U(t)x\| \leq k(t,r)$ if $\|x\| \leq r$, and for any $B \subset X$ which is closed and bounded, we have $C(t)B$ is compact. Then we can apply Lemma 3.1 for $S(t) = \widetilde{U}(t) + \widetilde{C}(t)$ where

$$\widetilde{U}(t) = \begin{pmatrix} 0 \\ U(t) \end{pmatrix}, \quad \widetilde{C}(t) = \begin{pmatrix} \pi_1 S(t) \\ C(t) \end{pmatrix}$$

Indeed, if $B \subset X$ is closed and bounded, then $\widetilde{C}(t)B \subset \pi_1 S(t)B \times C(t)B$ is a closed subset of a compact set, and hence is compact. Also, the decaying requirement for $\widetilde{U}(t)$ is certainly satistfied. In order to follow this plan of action, let $\pi_2 S(t) = U(t) + C(t)$ where

$$\begin{aligned}
(U(t)x)(a) &= \phi(a)T^*(0,a-t)\mathbf{1}_{\{a>t\}}, \\
(C(t)x)(a) &= \frac{\phi(a)}{\phi(a-t)}kV(t-a)T(t-a)\mathbf{1}_{\{t>a\}}
\end{aligned}$$

for $x = (T(0), V(0), T^*(0,\cdot))$ and $(T(t), V(t), T^*(t,\cdot)) = \psi(t,x)$, the solution to (1). Then

$$\|U(t)x\|_{L^1} = \int_t^\infty \frac{\phi(a)}{\phi(a-t)}T^*(0,a-t)\,da \leq e^{-bt}\int_t^\infty T^*(0,a-t)\,da \leq e^{-bt}\,\|T^*(0,\cdot)\|\,.$$

Hence, if we let $k(t,r) = re^{-bt}$, then certainly $k(t,r) \to 0$ as $t \to \infty$ and $\|U(t)x\| \leq k(t,r)$ if $\|x\| \leq r$. To show that $C(t)$ satisfies the compactness condition, we apply Lemma 3.2.

Let $B \subset X$ be closed and bounded. Suppose $r > 0$ such that $\|x\| \leq r$ for all $x \in B$. Notice that for all $x \in B$, $\int_h^\infty |(C(t)x)(a)|\,da = 0 \quad \forall h \geq t$. Therefore (ii) is satisfied for the set $C(t)B \subset L^1(0,\infty)$. To check condition (ii), observe:

$$\begin{aligned}
&\int_0^\infty |(C(t)x)(a) - (C(t)x)(a+h)|\, da \\
&\quad = \int_0^t |\phi(a)kV(t-a)T(t-a) - \phi(a+h)kV(t-a-h)T(t-a-h)|\, da \\
&\quad = \int_0^t \phi(a) \left| kV(t-a)T(t-a) - \frac{\phi(a+h)}{\phi(a)} kV(t-a-h)T(t-a-h) \right| da \\
&\quad \le \int_0^t e^{-ba} \left| kV(t-a)T(t-a) - \frac{\phi(a+h)}{\phi(a)} kV(t-a)T(t-a) \right| da \\
&\qquad + \int_0^t e^{-ba} \frac{\phi(a+h)}{\phi(a)} |kV(t-a)T(t-a) - kV(t-a-h)T(t-a-h)|\, da \quad (6)
\end{aligned}$$

Let $M = \max(r, \frac{2\kappa A}{b\alpha})$ where A, α are defined in Lemma 2.2. Notice that

$$\begin{aligned}
&\int_0^t e^{-ba} \left| kV(t-a)T(t-a) - \frac{\phi(a+h)}{\phi(a)} kV(t-a)T(t-a) \right| da \\
&\qquad = \int_0^t e^{-ba} kV(t-a)T(t-a) \left(1 - \frac{\phi(a+h)}{\phi(a)}\right) da \\
&\qquad \le M \int_0^\infty e^{-ba} \left(1 - \frac{\phi(a+h)}{\phi(a)}\right) da,
\end{aligned}$$

$$\lim_{h\to 0} \int_0^\infty e^{-ba} \left(1 - \frac{\phi(a+h)}{\phi(a)}\right) da = \int_0^\infty e^{-ba} \left(1 - \lim_{h\to 0} \frac{\phi(a+h)}{\phi(a)}\right) da = 0,$$

where we applied Dominated Convergence Theorem. Also,

$$\begin{aligned}
&\int_0^t e^{-ba} \left| \frac{\phi(a+h)}{\phi(a)} kV(t-a)T(t-a) - \frac{\phi(a+h)}{\phi(a)} kV(t-a-h)T(t-a-h) \right| da \\
&\quad \le k \sup_{\tau\in[0,t]} |V(\tau)T(\tau) - V(\tau-h)T(\tau-h)| \int_0^\infty e^{-ba}\, da \\
&\quad \le k \sup_{\tau\in[0,t]} (|V(\tau)| \cdot |T(\tau) - T(\tau-h)| \\
&\qquad\qquad + |T(\tau-h)| \cdot |V(\tau) - V(\tau-h)|) \int_0^\infty e^{-ba}\, da \quad (7)
\end{aligned}$$

By our integral formation, we find that

$$\begin{aligned}
|V(\tau) - V(\tau-h)| &= \left| \int_{\tau-h}^\tau \int_0^\infty p(a)T^*(s,a)\, da\, ds - \gamma \int_{\tau-h}^\tau V(s)\, ds \right| \\
&\le h(\kappa \|T^*\| + \gamma \|V\|) \\
&\le h(\kappa + \gamma) r
\end{aligned}$$

$$\begin{aligned}
|T(\tau) - T(\tau-h)| &\le \int_{\tau-h}^\tau |f(T(s)) - kV(s)T(s)|\, ds \\
&\le \left(\max_{s\in[0,r]} |f(s)| + r^2 \right) h
\end{aligned}$$

Hence, by (7)

$$\int_0^t e^{-ba}\frac{\phi(a+h)}{\phi(a)}\left|kV(t-a)T(t-a)-kV(t-a-h)T(t-a-h)\right|da \leq h\cdot M$$

where $M = r(\kappa+\gamma+\max_{s\in[0,r]}|f(s)|+r^2)\int_0^\infty e^{-ba}\,da$. This converges uniformly to 0 as $h\to 0$. Therefore (6) converges uniformly to 0 as $h\to 0$ and condition (ii) is proved for $C(t)B$. Hence, by Lemma 3.2, $C(t)B$ is compact. By the aforementioned argument we can apply Lemma 3.1 and conclude that $S(t)$ is asymptotically smooth. □

3.2. **Preliminary definitions and transformation.** The following definitions will be important in our analysis. A set $B\subset X$ is defined to be *forward invariant* if $S(t)B\subset B$ $\forall t\geq 0$. A set $B\subset X$ is defined to be *invariant* if $S(t)B = B$ $\forall t\geq 0$.

We use the following definitions concerning attractors from Magal and Zhao [9]: A set $A\subset X$ *attracts* a set $B\subset X$ if, $\mathrm{dist}(S(t)B,A)\to 0$ as $t\to\infty$, where $\mathrm{dist}(B,A)$ is the distance from set B to set A, i.e.

$$\mathrm{dist}(B,A) := \sup_{y\in B}\inf_{x\in A}\|y-x\|.$$

A set A in X is defined to be an *attractor* if A is non-empty, compact and invariant, and there exists some open neighborhood U of A in X such that A attracts U.

A *global attractor* is defined to be an attractor which attracts every point in X.

From the proof of Lemma 2.2, we determine that the semigroup $S(t)$ is point dissipative, i.e. there exists a bounded set $B\subset X$ which attracts all points of X. Also, by the proof of Lemma 2.2, positive orbits of compact sets are bounded in X. Then, we can apply Theorem 2.6 in [9] to conclude that there exists a global attractor $\mathcal{A}$ contained in X.

Let $x\in\mathcal{A}$. Because $\mathcal{A}$ is invariant, we can find a complete orbit through x which is contained in $\mathcal{A}$. This means we can find $\{z(t)\}_{t\in\mathbb{R}}\subset\mathcal{A}$ such that $\forall t,s\in\mathbb{R}$, $z(t)=S(t-s)z(s)$ whenever $t\geq s$. Here, we just let $z(t)=S(t)x$ for $t\geq 0$, and for $t<0$, we let $z(t)=S(t)y$ where $y\in\mathcal{A}$ and $S(t)y=x$. Note, that this is possible because $S(t)$ is invariant, i.e. $S(t)\mathcal{A}=\mathcal{A}$ $\forall t\geq 0$.

Consider $x=(T(0),V(0),T^*(0,a))\in\mathcal{A}$. Extend $T(t),V(t),T^*(t,a)$ so that $t\in\mathbb{R}$, i.e. $z(t)=(T(t),V(t),T^*(t,a))$ $\forall t\in\mathbb{R}$ is a complete orbit through x. Here $z(t)$ must satisfy the system:

$$\begin{aligned}\frac{dT(t)}{dt} &= f(T(t))-kV(t)T(t),\\ \frac{dV(t)}{dt} &= \int_0^\infty p(a)T^*(t,a)\,da-\gamma V(t),\\ T^*(t,a) &= \phi(a)kV(t-a)T(t-a)\\ (T(0),V(0),T^*(0,a)) &\in \mathcal{A}\subset\mathbb{R}_+^2\times L_+^1\end{aligned}\tag{8}$$

We introduce a transformation which will make certain calculations simpler. For $y=(T,V,T^*(a))\in\mathcal{A}$, define the transformation, $h(y)$ as:

$$h(y)=\left(T,V,\frac{1}{\phi(a)}T^*(a)\right)\tag{9}$$

Then $h(z(t))$ satisfies the following system:

$$\begin{aligned}\frac{dT(t)}{dt} &= f(T(t)) - kV(t)T(t),\\ \frac{dV(t)}{dt} &= \int_0^\infty q(a)u(t,a)\,da - \gamma V(t),\\ u(t,a) &= kV(t-a)T(t-a)\\ (T(0),V(0),\phi(a)u(0,a)) &\in \mathcal{A}\subset \mathbb{R}_+^2\times L_+^1\end{aligned}\tag{10}$$

where

$$\begin{aligned}u(t,a) &= \frac{1}{\phi(a)}T^*(t,a) \quad\text{and}\\ q(a) &= \phi(a)p(a).\end{aligned}$$

There exists $M>0$ such that $\|y\|<M$ for all $y\in\mathcal{A}$. Hence,

$$u(t,a) = kV(t-a)T(t-a) < kM^2\ \forall a\in[0,\infty), t\in\mathbb{R}.$$

Note that this bound is independent of the choice of an orbit in $\mathcal{A}$.

In what follows, we will define Lyapunov functionals on the global attractor $\mathcal{A}$. We will use the following function in our Lyapunov functionals:

$$g(r) = r - \log r - 1 \quad \text{where } r\in(0,\infty)\tag{11}$$

Note that $g(r)$ is is non-negative and continuous on $(0,\infty)$ with a unique root at $r=1$. Also, define the following function on $[0,\infty)$:

$$\alpha(a) = \int_a^\infty q(\ell)\,d\ell.\tag{12}$$

By Lebesgue Differentiation Theorem, the function $\alpha(a)$ is differentiable a.e. for $a\geq 0$ and $\alpha'(a) = -q(a)$.

3.3. Global extinction when $\mathcal{R}_0\leq 1$.

Theorem 3.3. *If $\mathcal{R}_0\leq 1$, then x_0 is globally asymptotically stable in X.*

Proof. Define the following Lyapunov functional on $h(\mathcal{A})$:

$$\Psi : (T,V,u(a)) \mapsto T_0 g\left(\frac{T}{T_0}\right) + \frac{1}{\alpha(0)}\left(\int_0^\infty \alpha(a)u(a)\,da + V\right)$$

For any $h(x) = (T,V,u)\in h(\mathcal{A})$, the following is true:

$$\begin{aligned}\int_0^\infty \alpha(a)u(a)\,da \leq kM^2\int_0^\infty \alpha(a)\,da &= kM^2\int_0^\infty\int_a^\infty \phi(\ell)p(\ell)\,d\ell\,da\\ &\leq k\kappa M^2\int_0^\infty\int_a^\infty e^{-b\ell}\,d\ell\,da\\ &= \frac{k\kappa M^2}{b^2}\end{aligned}$$

Hence Ψ is bounded on $h(\mathcal{A})$. We consider a transformed complete orbit $h(z(t)) = (T(t),V(t),u(t,a))$ in $h(\mathcal{A})$. For convenience we let T and V denote $T(t)$ and $V(t)$, respectively. Also, note that $\int_0^\infty \alpha(a)u(t,a)\,da$ is differentiable in t since this term is really a convolution which we can differentiate, as we will see below.

$$\begin{aligned}
&\frac{d}{dt}\Psi(h(z(t)))\\
&\quad= T_0 g'\left(\frac{T}{T_0}\right)\frac{\dot{T}}{T_0} + \frac{1}{\alpha(0)}\left(\frac{d}{dt}\int_0^\infty \alpha(a)u(t,a)\,da + \dot{V}\right)\\
&\quad= T_0 g'\left(\frac{T}{T_0}\right)\frac{\dot{T}}{T_0} + \frac{1}{\alpha(0)}\left(\frac{d}{dt}\int_0^\infty \alpha(a)u(t-a,0)\,da + \dot{V}\right)\\
&\quad= T_0 g'\left(\frac{T}{T_0}\right)\frac{\dot{T}}{T_0} + \frac{1}{\alpha(0)}\left(\frac{d}{dt}\int_{-\infty}^t \alpha(a)u(s,0)\,ds + \dot{V}\right)\\
&\quad= \left(1-\frac{T_0}{T}\right)(f(T)-kVT)\\
&\qquad+\frac{1}{\alpha(0)}\left(\alpha(0)u(t,0)+\int_{-\infty}^t \alpha'(t-s)u(s,0)\,ds + \int_0^\infty q(a)u(t,a)\,da - \gamma V\right)\\
&\quad= f(T)-kVT-\frac{T_0}{T}f(T)-kVT_0+kVT\\
&\qquad+\frac{1}{\alpha(0)}\left(\int_0^\infty \alpha'(a)u(t,a)\,da + \int_0^\infty q(a)u(t,a)\,da - \gamma V\right)\\
&\quad= f(T)\left(1-\frac{T_0}{T}\right)+V\left(kT_0-\frac{\gamma}{\alpha(0)}\right)\\
&\qquad+\frac{1}{\alpha(0)}\left(-\int_0^\infty q(a)u(t,a)\,da + \int_0^\infty q(a)u(t,a)\,da\right)\\
&\quad= f(T)\left(1-\frac{T_0}{T}\right)+kT_0V\left(1-\frac{1}{\mathcal{R}_0}\right)\\
&\quad\le 0 \quad \text{when } \mathcal{R}_0\le 1
\end{aligned}$$

Note that $\frac{d}{dt}\Psi\circ h = 0 \Rightarrow T = T_0$. The largest invariant set inside $\{(y_1, y_2, y_3(a)) \in X : y_1 = T_0\}$ is $\{x_0\}$. Hence, the largest invariant set with the property that $\frac{d}{dt}\Psi\circ h = 0$ is $\{x_0\}$. Let $x \in \mathcal{A}$, with complete orbit $z(t)$ through x. We consider the alpha limit set corresponding to the complete orbit, $\alpha_z(x)$. Since $\mathcal{A}$ is compact, $\alpha_z(x)$ is nonempty, invariant and contained in $\mathcal{A}$. Note that if $z(t_n) \to \widetilde{x} \in \alpha_z(x)$ as $t_n \downarrow -\infty$, then $\Psi(h(z(t_n))) \to \Psi(h(\widetilde{x}))$. Indeed, if $T^*(t_n, a) \to \widetilde{T}^*(a)$ in L^1, then

$$\begin{aligned}
&\left|\int_0^\infty \alpha(a)u(t_n,a)\,da - \int_0^\infty \alpha(a)\widetilde{u}(a)\,da\right|\\
&\qquad\le \int_0^\infty\int_a^\infty \phi(\ell)p(\ell)\,d\ell\frac{1}{\phi(a)}\left|T^*(t_n,a)-\widetilde{T}^*(a)\right|\,da\\
&\qquad= \kappa\int_0^\infty\int_a^\infty e^{-\int_a^\ell \delta(s)\,ds}\,d\ell\left|T^*(t_n,a)-\widetilde{T}^*(a)\right|\,da\\
&\qquad\le \kappa\int_0^\infty\int_a^\infty e^{-b(\ell-a)}\,d\ell\left|T^*(t_n,a)-\widetilde{T}^*(a)\right|\,da\\
&\qquad= \frac{\kappa}{b}\int_0^\infty\left|T^*(t_n,a)-\widetilde{T}^*(a)\right|\,da \quad\to 0 \quad \text{as } t_n\downarrow -\infty.
\end{aligned}$$

The other parts of $\Psi(h(z(t_n)))$ converge by continuity of $g(T(t))$ and $V(t)$. Since $\Psi\circ h(z(t))$ is non-increasing and bounded, $\Psi(h(z(t_n))) \uparrow c < \infty$ as $t \downarrow -\infty$ for some constant c. Thus, $\Psi \circ h = c$ on $\alpha_z(x)$. Since $\alpha_z(x)$ is invariant, $\frac{d}{dt}\Psi \circ h(S(t)\alpha_z(x)) = 0$. Again by invariance of $\alpha_z(x)$, we conclude that $\alpha_z(x) = \{x_0\}$. Thus, $\Psi(h(z(t))) \leq \Psi(h(x_0))\ \forall t \in \mathbb{R}$. Since x_0 is the unique minimizer of $\Psi \circ h$, we obtain that $z(t) = x_0\ \forall t \in \mathbb{R}$. Hence, $\mathcal{A} = \{x_0\}$. This proves that x_0 is globally asymptotically stable. $\square$

3.4. **Uniform persistence.** In this section, we prove the uniform persistence and the existence of compact attractor by using results of Hale and Waltman [6]. We need to partition X as $X = X^0 \cup \partial X^0$, where X^0 is going to be a repeller.

Let $\overline{a} = \sup\{a \in (0,\infty) : p(a) > 0\}$. Note that, possibly, $\overline{a} = +\infty$. Let $M^0 = \left\{\eta(a) \in L^1_+(0,\infty) : \int_0^{\overline{a}} \eta(a)\, da > 0\right\}$. Let $\partial M^0 = L^1_+(0,\infty) \setminus M^0$. Let $X^0 = \{\mathbb{R}_+ \times (0,\infty) \times L^1_+(0,\infty)\} \cup \{\mathbb{R}^2_+ \times M^0\}$. Here $X^0 \subset X$. Let $\partial X^0 = \mathbb{R}_+ \times \{0\} \times \partial M^0$. Then $X = X^0 \cup \partial X^0$. Also define $X^0_+ = \mathbb{R}_+ \times (0,\infty) \times M^0$.

Lemma 3.4. *The sets X^0 and ∂X^0 are forward invariant under the semigroup $S(t)$. Also, $\forall x \in \partial X^0$, we have $S(t)x \to x_0$ as $t \to \infty$ where $x_0 = (T_0, 0, 0)$. In addition, $S(t)X^0 \subset X^0_+\ \forall t > 0$.*

Proof. First we show the conclusions for ∂X^0. Suppose by way of contradiction that there exists $x \in \partial X^0$ and $t_1 > 0$ such that $S(t_1)x \in X^0$. Let $\tau = \inf\left\{t > 0 : S(t)x \in X^0\right\}$. Since X^0 is an open set in X and by the continuity of the semigroup $S(t)$, we obtain that $S(\tau)x \notin X^0$ and, hence, $S(\tau)x \in \partial X^0$. Then $\dot{V}(\tau) = \int_0^{\overline{a}} p(a)T^*(\tau,a)\, da - \gamma V(\tau) = 0$ and $T^*(\tau,a) = \phi(a)kV(\tau-a)T(\tau-a)\mathbf{1}_{\{\tau>a\}} + \frac{\phi(a)}{\phi(a-\tau)}T^*(0,a-\tau)\mathbf{1}_{\{a>\tau\}} = \frac{\phi(a)}{\phi(a-\tau)}T^*(0,a-\tau)\mathbf{1}_{\{a>\tau\}} \in \partial M^0$. For $t \geq 0$, define $x_2(t) = 0$, $x_3(t,a) = \frac{\phi(a)}{\phi(a-t)}T^*(0,a-t)\mathbf{1}_{\{a>\tau+t\}}$. Then, $\xi(t) := (T(t+\tau), x_2(t), x_3(t,a))$ is a solution to (3) with initial condition $\xi(0) = S(\tau)x$ and $\xi(t) \in \partial X^0\ \forall t \geq 0$. Then, by forward uniqueness of solutions, $S(t)x \in \partial X^0\ \forall t \geq 0$, which contradicts our assumption that $S(t_1)x \in X^0$. Thus ∂X^0 is forward invariant. In view of our system and the properties of $f(T)$, it is clear that for any solution in ∂X^0, $T(t) \to T_0$, hence we have $S(t)x \to x_0$ as $t \to \infty$ where $x_0 = (T_0, 0, 0)$.

Now to show X^0 is forward invariant. Notice that $\dot{V} \geq -\gamma V$. Hence $V(t) \geq V(0)e^{-\gamma t}$ for all $t \geq 0$. If $V(0) > 0$, then the result follows. If $V(0) = 0$, then $\int_0^\infty p(a)T^*(0,a)\, da > 0$ (since $x(0) \in X^0$). Then $\dot{V}(0) > 0$, so that $\exists \tau > 0$ such that $\forall t \in (0,\tau]$, we have $V(t) > 0$. Note that in this case, we can choose τ such that $\int_0^\infty p(a)T^*(t,a)\, da > 0$ for all $t \in [0,\tau]$. Then, the same argument applies with $V(t) \geq V(\tau)e^{-\gamma t}$ for $t \geq \tau$. Hence $V(t) > 0\ \forall t > 0$. Then, since $T(t) > 0\ \forall t > 0$, we have that $T^*(t,a) \geq kV(t-a)T(t-a)\phi(a) > 0$ for all $t > 0$. Therefore, $S(t)X^0 \subset X^0_+$ for all $t > 0$. $\square$

We will use the following definition of the stable manifold of a compact invariant set $A \subset X$:

$$W_s(A) = \{x \in X : \omega(x) \neq \emptyset \text{ and } \omega(x) \subset A\}.$$

The alpha limit set of x, $\alpha(x)$, and unstable manifold of a compact invariant set A, $W_u(A)$, can be similarly defined with the added caveat that there is no backward uniqueness hence the definitions will possibly consider multiple backward orbits from a point. We will need the following result about linear scalar Voterra integro-differential equations.

Lemma 3.5. *Consider the following scalar integro-differential equation:*

$$\dot{y}(t) = \int_0^t h(a)y(t-a)\,da - cy(t), \qquad y(0) > 0, \tag{13}$$

where $h(\cdot) \in L^1_+(0,\infty)$, $c > 0$, and $\int_0^\infty h(a)\,da > c$. There is a unique solution, $y(t)$, which is unbounded.

Proof. From similar arguments to Theorem 2.1 and Lemma 2.2, we can get existence, uniqueness, differentiability, and positivity of a solution, $y(t)$, to the integro-differential equation (13). Positivity of $y(t)$ is clear, since $y(t) \geq y(0)e^{-ct}$. Suppose, for the sake of contradiction, that $y(t)$ is bounded. Then, since $y(t)$ is continuous and bounded, the Laplace transform of $y(t)$, $\mathcal{L}[y](s) := \int_0^\infty e^{-st}y(t)\,dt$ is defined for all $s > 0$. Then using properties of the Laplace transform, the solution must satisfy:

$$\mathcal{L}[y](s) = \frac{y(0)}{s + c - \mathcal{L}[h](s)}$$

where $\mathcal{L}[h](s)$ is defined $\forall s \geq 0$ since $h \in L^1_+(0,\infty)$. Now, $\mathcal{L}[h](s) \to \mathcal{L}[h](0)$ as $s \to 0$ by the Dominated Convergence Theorem. Since $\mathcal{L}[h](0) = \int_0^\infty h(a)\,da > c$, there exists $\delta > 0$ such that $c - \mathcal{L}[h](s) < -\delta$ for all $s \in [0,\delta)$. Hence, $\mathcal{L}[y](s) < 0$ for all $s \in [0,\delta)$. But this contradicts the positivity of $y(t)$. ☐

Theorem 3.6. *Suppose that $\mathcal{R}_0 > 1$. Then $S(t)$ is uniformly persistent, i.e. $\exists \mu > 0$ such that for any $x \in X^0$, $\liminf_{t\to\infty} d(S(t)x, \partial X^0) \geq \mu$. Moreover, there exists a compact set $\mathcal{A}_0 \subset X^0$ which is a global attractor for $\{S(t)\}_{t\geq 0}$ in X^0.*

Proof. We will apply Theorem 4.2 in [6] to prove uniform persistence. Observe that $\partial X^0 \subset W_s(\{x_0\})$. Also $\left(\partial X^0 \setminus \{x_0\}\right) \cap W_u(\{x_0\}) = \emptyset$. Indeed, let $x \in \partial X^0 \setminus \{x_0\}$. Any backward orbit of x must stay in ∂X^0 since X^0 (the complement of ∂X^0) is forward invariant. Suppose $x = (T(0), 0, \ell(a))$. If $\ell(a) = 0$ (in L^1), then we have a scalar ODE with a unique positive equilibrium and $\lim_{t\to-\infty} T(t) = 0$ or ∞. Suppose $\int_0^\infty \ell(a)\,da > 0$. Since $x \in \partial X^0$, $\int_0^{\overline{a}} \ell(a)\,da = 0$. Suppose $\exists \tau > 0, x_1 = (T(-\tau), 0, \ell_1(a)) \in \partial X^0$ such that $S(\tau)x_1 = x$. Then, $\int_{\overline{a}}^\infty \ell(a)\,da = \int_{\overline{a}+\tau}^\infty e^{-\int_{a-\tau}^a \delta(s)\,ds}\ell(a-\tau)\,da < \int_{\overline{a}+\tau}^\infty \ell_1(a)\,da$. Hence, the norm of the L^1-component is strictly increasing on backward orbits and hence x_0 cannot be an α-limit point of x. Therefore, in order for $\{x_0\}$ to be acyclic (which would satisfy the assumptions of Theorem 4.2 [6]), and to satisfy the equivalent condition for uniform persistence given in the conclusion of the same theorem, we need only to prove $W_s(\{x_0\}) \cap X^0 = \emptyset$.

Suppose by way of contradiction that there exists $x \in X^0$ such that $x \in W_s(\{x_0\})$. Then, we claim that $S(t)x \to x_0$ as $t \to \infty$. Indeed, if $S(t) \not\to x_0$, then $\exists \epsilon > 0, t_n \uparrow \infty$ such that $\|S(t_n)x - x_0\| \geq \epsilon$. From Proposition 1, the semigroup $S(t)$ can be written as $S(t) = C(t) + U(t)$. Since $\{C(t_n)x\}$ is pre-compact, there exists a convergent subsequence: $C(t_{n_k}) \to x^*$. Then $S(t_{n_k}) \to x^*$ because $\|U(t_{n_k})\| \to 0$. But then $x^* \in \omega(x)$, but $x^* \neq x_0$, 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

$$\|S(t)x_n - x_0\| < \frac{1}{n} \quad \forall t \geq 0.$$

Let $S(t)x_n = (T_n(t), V_n(t), T_n^*(t,a))$ and $x_n = (T_n(0), V_n(0), T_n^*(0,a))$. The following is true:

$$|T_n(t) - T_0| \leq \frac{1}{n}, \quad \forall t \geq 0.$$

Then, by inserting equation (2) into the $\dot{V}$ equation and applying a simple comparison principle, we deduce that $V_n(t) \geq y_n(t)$ where $y_n(t)$ is a solution of

$$\frac{dy_n(t)}{dt} = \int_0^t kp(a)\phi(a)(T_0 - \frac{1}{n})y_n(t-a)\,da - \gamma y_n(t), \quad y_n(0) = V_n(0).$$

Note that if $V_n(0) = 0$, then clearly $T_n^*(0,a) \in M^0$ and hence $\dot{y}_n(0) > 0$, so without loss of generality we can take $V_n(0) > 0$. We claim that for n sufficiently large, y_n is unbounded. The assumption $\mathcal{R}_0 > 1$ is equivalent to $-\gamma + kT_0 \int_0^\infty p(a)\phi(a)\,da > 0$. Hence $\exists N \in \mathbb{N}$ such that $-\gamma + k\left(T_0 - \frac{1}{N}\right)\int_0^\infty p(a)\phi(a)\,da > 0$. Then by Lemma 3.5, y_N is unbounded. Since $V_N \geq y_N$, we get that V_N is unbounded and, hence, $S(t)x_N$ is unbounded, which is certainly a contradiction. Therefore $W_s(\{x_0\}) \cap X^0 = \emptyset$. By Theorem 4.2 [6], we get that $S(t)$ is uniformly persistent. Then by Theorem 3.7 in [9], we can conclude for our case that there exists a compact set $\mathcal{A}_0 \subset X^0$ which is a global attractor for $\{S(t)\}_{t\geq 0}$ in X^0. $\square$

Because $S(t)X^0 \subset X^0_+$, the global attractor, $\mathcal{A}_0$, is actually contained in X^0_+. Therefore, there exists $\mu > 0$ such that

$$\liminf_{t\to\infty} V(t) \geq \mu, \quad \text{and} \quad \liminf_{t\to\infty} d(T^*(t,a), \partial M^0) \geq \mu.$$

3.5. **Lyapunov functional and global stability. Assumption:** In the following, we assume that $f(T)$ satisfies the following "sector" condition, first introduced in [3]:

$$(\mathbf{C}) \quad \left(f(T) - f(\overline{T})\right)\left(1 - \frac{\overline{T}}{T}\right) \leq 0.$$

Note that this condition is satisfied when $f(T)$ is a decreasing function, independently of the value of $\overline{T}$, for example $f(T) = s - \mu T$. In the case of $f(T) = s + rT(1 - T/T_{max})$, (**C**) is satisfied when $s \geq f(\overline{T})$.

For $x \in \mathcal{A}_0$, let $x = (T(0), V(0), T^*(0,a)) \in \mathcal{A}_0$. Since $\mathcal{A}_0$ is invariant, there exists a complete orbit through x, call it $z(t)$. Extend $T(t), V(t), T^*(t,a)$ so that $t \in \mathbb{R}$, i.e. $z(t) = (T(t), V(t), T^*(t,a))\ \forall t \in \mathbb{R}$. Recall that under the change of variables (9), $h(z(t))$ satisfies the following system:

$$\begin{aligned}
\frac{dT(t)}{dt} &= f(T(t)) - kV(t)T(t),\\
\frac{dV(t)}{dt} &= \int_0^\infty q(a)u(t,a)\,da - \gamma V(t),\\
u(t,a) &= kV(t-a)T(t-a),\\
(T(0), V(0), \phi(a)u(0,a)) &\in \mathcal{A}_0 \subset \mathbb{R}^2_+ \times L^1_+,
\end{aligned}$$

with $u(t,a) = \frac{1}{\phi(a)}T^*(t,a)$ and $q(a) = p(a)\phi(a)$. Notice there is a positive equilibrium to the above system, with $\overline{u}(a) = \frac{1}{\phi(a)}\overline{T^*}(a) = k\overline{VT}$, which is constant in a, so let $\overline{u}(a) = \overline{u} > 0$. Then we have the following conditions:

$$\gamma = k\overline{T}\int_0^\infty q(a)\,da \quad f(\overline{T}) = k\overline{VT} = \overline{u}$$

Since Theorem 3.6 implies the compactness of $\mathcal{A}_0$, there exist $\epsilon, M > 0$ such that for any solution in $\mathcal{A}_0$ for all $t \in \mathbb{R}$, it holds that

$$\begin{aligned} \epsilon \leq T(t) &\leq M, \\ k\epsilon^2 \leq u(t,a) &\leq kM^2, \quad \forall a \in [0,\infty), \\ \epsilon \leq V(t) &\leq M. \end{aligned}$$

Previously, we defined: $g(r) = r - \log(r) - 1$ and $\alpha(a) = \int_a^\infty q(\ell)\, d\ell$. We define the following function on $h(\mathcal{A}_0)$:

$$W : (T, V, u(a)) \mapsto W_T + W_V + W_u,$$

where

$$W_T = \frac{\overline{T}}{\overline{u}} g\left(\frac{T}{\overline{T}}\right), \quad W_V = \frac{k\overline{T}\overline{V}}{\gamma \overline{u}} g\left(\frac{V}{\overline{V}}\right), \quad W_u = \frac{k\overline{T}}{\gamma} \int_0^\infty \alpha(a) g\left(\frac{u(a)}{\overline{u}}\right) da.$$

Since $k\epsilon^2 \leq u(t,a) \leq kM^2$ for all $a \in [0,\infty)$ and $t \in \mathbb{R}$ for any complete orbit in $\mathcal{A}_0$, we have that $\exists M_1 > 0$ such that

$$0 \leq g\left(\frac{u(a)}{\overline{u}}\right) \leq M_1, \quad \forall a \in (0,\infty),$$

where M_1 is a uniform bound for $\mathcal{A}_0$. Then,

$$\int_0^\infty \alpha(a) g\left(\frac{u(a)}{\overline{u}}\right) da \leq M_1 \int_0^\infty \alpha(a)\, da = \frac{\kappa M_1}{b^2} < \infty.$$

Therefore it follows that $W = W_T + W_u + W_V$ is well-defined and bounded on $h(\mathcal{A}_0)$. For convenience, $W_T(T(t))$ is denoted by W_T, and likewise for the other two components. Differentiating W along a solution in $\mathcal{A}_0$, we find that

$$\begin{aligned} \frac{d}{dt} W_u &= \frac{d}{dt} \frac{k\overline{T}}{\gamma} \int_0^\infty \alpha(a) g\left(\frac{u(t,a)}{\overline{u}}\right) da \\ &= \frac{k\overline{T}}{\gamma} \frac{d}{dt} \int_0^\infty \alpha(a) g\left(\frac{u(t-a,0)}{\overline{u}}\right) da \\ &= \frac{k\overline{T}}{\gamma} \frac{d}{dt} \int_{-\infty}^t \alpha(t-s) g\left(\frac{u(s,0)}{\overline{u}}\right) ds \\ &= \frac{k\overline{T}}{\gamma} \left[\alpha(0) g\left(\frac{u(t,0)}{\overline{u}}\right) + \int_{-\infty}^t \alpha'(t-s) g\left(\frac{u(s,0)}{\overline{u}}\right) ds\right] \\ &= \frac{k\overline{T}}{\gamma} \left[\alpha(0) g\left(\frac{u(t,0)}{\overline{u}}\right) + \int_0^\infty \alpha'(a) g\left(\frac{u(t,a)}{\overline{u}}\right) da\right] \\ &= \frac{k\overline{T}}{\gamma} \left[\int_0^\infty q(a) \left(\frac{u(t,0)}{\overline{u}} - 1 - \log\frac{u(t,0)}{\overline{u}} - \frac{u(t,a)}{\overline{u}} + 1 + \log\frac{u(t,a)}{\overline{u}}\right) da\right] \\ &= \frac{k\overline{T}}{\gamma} \left[\int_0^\infty q(a) \left(\frac{u(t,0)}{\overline{u}} - \frac{u(t,a)}{\overline{u}} + \log\frac{u(t,a)}{u(t,0)}\right) da\right] \end{aligned}$$

Recalling that

$$f(\overline{T}) = k\overline{T}\overline{V} = \overline{u}, \quad \frac{\overline{V}}{V} = \frac{T\overline{u}}{\overline{T}u(t,0)}, \quad \frac{\gamma}{k\overline{T}} = \int_0^\infty q(a)\, da,$$

we obtain the following:

$$
\begin{aligned}
&\frac{d}{dt}\left(W_T+W_V\right)\\
&\quad=\frac{d}{dt}\left[\frac{\overline{T}}{\overline{u}}g\left(\frac{T}{\overline{T}}\right)+\frac{k\overline{T}\overline{V}}{\overline{u}\gamma}g\left(\frac{V}{\overline{V}}\right)\right]\\
&\quad=\frac{1}{\overline{u}}\left[\overline{T}\cdot g'\left(\frac{T}{\overline{T}}\right)\cdot\frac{\dot{T}}{\overline{T}}+\frac{k\overline{T}\overline{V}}{\gamma}g'\left(\frac{V}{\overline{V}}\right)\frac{\dot{V}}{\overline{V}}\right]\\
&\quad=\frac{1}{\overline{u}}\left[\left(1-\frac{\overline{T}}{T}\right)\left(f(T)-kVT\right)+\frac{k\overline{T}}{\gamma}\left(1-\frac{\overline{V}}{V}\right)\left(\int_0^\infty q(a)u(t,a)\,da-\gamma V\right)\right]\\
&\quad=\frac{1}{\overline{u}}\left[\left(f(T)-f(\overline{T})\right)\left(1-\frac{\overline{T}}{T}\right)+f(\overline{T})\left(1-\frac{\overline{T}}{T}\right)-kVT+kV\overline{T}\right.\\
&\qquad\quad\left.+\frac{k\overline{T}}{\gamma}\int_0^\infty q(a)u(t,a)\left(1-\frac{\overline{V}}{V}\right)da-kV\overline{T}+\frac{k\overline{T}}{\gamma}\gamma\overline{V}\right]\\
&\quad=\frac{1}{\overline{u}}\left(f(T)-f(\overline{T})\right)\left(1-\frac{\overline{T}}{T}\right)+\frac{1}{\overline{u}}\frac{k\overline{T}}{\gamma}\left[\frac{\gamma}{k\overline{T}}\left(f(\overline{T})-f(\overline{T})\frac{\overline{T}}{T}-kVT\right)\right]\\
&\qquad+\frac{1}{\overline{u}}\frac{k\overline{T}}{\gamma}\left[\int_0^\infty q(a)u(t,a)\left(1-\frac{\overline{V}}{V}\right)da+\frac{\gamma}{k\overline{T}}k\overline{T}\overline{V}\right]\\
&\quad=\frac{1}{\overline{u}}\left(f(T)-f(\overline{T})\right)\left(1-\frac{\overline{T}}{T}\right)\\
&\qquad+\frac{k\overline{T}}{\gamma}\int_0^\infty q(a)\left(\frac{-u(t,0)}{\overline{u}}-\frac{\overline{T}}{T}+\frac{u(t,a)}{\overline{u}}-\frac{Tu(t,a)}{\overline{T}u(t,0)}+2\right)da
\end{aligned}
$$

$$
\begin{aligned}
\text{Thus, }\ &\frac{d}{dt}\left(W_T+W_V+W_u\right)\\
&\quad=\frac{1}{\overline{u}}\left(f(T)-f(\overline{T})\right)\left(1-\frac{\overline{T}}{T}\right)\\
&\qquad\quad+\frac{k\overline{T}}{\gamma}\int_0^\infty q(a)\left(2-\frac{\overline{T}}{T}-\frac{Tu(t,a)}{\overline{T}u(t,0)}+\log\frac{u(t,a)}{u(t,0)}\right)da\\
&\quad\le\frac{k\overline{T}}{\gamma}\int_0^\infty q(a)\left(2-2\sqrt{\frac{u(t,a)}{u(t,0)}}+\log\frac{u(t,a)}{u(t,0)}\right)da\\
&\quad=2\frac{k\overline{T}}{\gamma}\int_0^\infty q(a)\left(1-\sqrt{\frac{u(t,a)}{u(t,0)}}+\log\sqrt{\frac{u(t,a)}{u(t,0)}}\right)da\\
&\quad=-2\frac{k\overline{T}}{\gamma}\int_0^\infty q(a)g\left(\sqrt{\frac{u(t,a)}{u(t,0)}}\right)da\\
&\quad\le 0,
\end{aligned}
$$

where we have used the sector condition (Condition 3.5), the arithmetic/geometric mean inequality, and the positivity of g. We conclude that

$$\frac{dW}{dt}=0\quad\Leftrightarrow\quad u(t,a)\equiv u(t,0)\text{ and }T=\overline{T}\quad\Leftrightarrow\quad (T,V,u(a))=\left(\overline{T},\overline{V},\overline{u}\right).$$

Now we are ready to prove global asymptotic stability of the interior equilibrium, $\overline{x}$, when $\mathcal{R}_0 > 1$ and $f(T)$ satisfies the sector condition.

Theorem 3.7. *Let $\mathcal{R}_0 > 1$ and suppose that Condition 3.5 holds. Then $\overline{x} := (\overline{T}, \overline{V}, \overline{T}^*(a))$ is globally asymptotically stable in X^0.*

Proof. We prove that $\mathcal{A}_0 = \{\overline{x}\}$. Consider some $x \in \mathcal{A}_0$ and a complete orbit through x, $\{z(t)\}_{t\in\mathbb{R}}$, contained in $\mathcal{A}_0$. Consider the alpha limit set on this specific orbit, $\alpha_z(x)$. Since $\mathcal{A}_0$ is compact, we conclude that $\alpha_z(x)$ is non-empty, compact, invariant, and belongs to $\mathcal{A}_0$. We claim that $\alpha_z(x) = \{\overline{x}\}$. Let $\widetilde{x} \in \alpha_z(x)$. Let $z(t) = (T(t), V(t), T^*(t,a))$. Then $\exists t_n \downarrow -\infty$ such that $x_n := z(t_n) \to \widetilde{x} \in \mathcal{A}_0$. In particular $T^*(t_n, a) \to \widetilde{T}^*(a)$ in L^1 as $t_n \downarrow -\infty$. Then, we claim $W_u(\frac{1}{\phi(a)}T^*(t_n,a)) \to W_u(\frac{1}{\phi(a)}\widetilde{T}^*(a))$ as $t_n \downarrow -\infty$. Because $x_n, \widetilde{x} \in \mathcal{A}_0$, we obtain that

$$k\epsilon^2 \le \frac{1}{\phi(a)}T^*(t_n,a) \le kM^2$$
$$k\epsilon^2 \le \frac{1}{\phi(a)}\widetilde{T}^*(a) \le kM^2$$

Let $u(t,a) = \frac{1}{\phi(a)}T^*(t,a)$ and $\widetilde{u}(a) = \frac{1}{\phi(a)}\widetilde{T}^*(a)$ as before. Then

$$\begin{aligned}
&|W_u(u(t_n,a) - W_u(\widetilde{u}(t,a)| \\
&= \left| \int_0^\infty \int_a^\infty \phi(\ell)p(\ell)\,d\ell \left(g\left(\frac{u(t_n,a)}{\overline{u}}\right) - g\left(\frac{\widetilde{u}(a)}{\overline{u}}\right)\right) da \right| \\
&\le \kappa \int_0^\infty \int_a^\infty \phi(\ell)\,d\ell \left| g\left(\frac{u(t_n,a)}{\overline{u}}\right) - g\left(\frac{\widetilde{u}(a)}{\overline{u}}\right)\right| da \\
&\le \kappa \int_0^\infty \int_a^\infty \phi(\ell)\,d\ell \max_{k\epsilon^2 \le s \le kM^2} |g'(s)| \cdot \left| \frac{u(t_n,a)}{\overline{u}} - \frac{\widetilde{u}(a)}{\overline{u}} \right| da \\
&= \frac{\kappa M_1}{\overline{u}} \int_0^\infty \int_a^\infty \phi(\ell)\,d\ell \frac{1}{\phi(a)} \left| T^*(t_n,a) - \widetilde{T}^*(a)\right| da \\
&\le \frac{\kappa M_1}{b\overline{u}} \int_0^\infty \left| T^*(t_n,a) - \widetilde{T}^*(a)\right| da \\
&\to 0 \quad \text{as } t_n \downarrow -\infty
\end{aligned}$$

The convergence of the other components of W is a consequence of the continuity of g. Then, $W(h(z(t_n))) \to W(h(\widetilde{x}))$ as $t_n \downarrow -\infty$. Since $W(h(z(t)))$ is a non-increasing map, which is bounded above, we conclude that $W(h(z(t))) \uparrow c < \infty$ as $t \downarrow -\infty$. Therefore, $W(h(\hat{x})) = c$ for all $\hat{x} \in \alpha_z(x)$. Combining this with the fact that $\alpha_z(x)$ is invariant, we get that $W(h(\zeta(t))) = c$ for all $t \in \mathbb{R}$, where $\zeta(t)$ is a complete orbit through $\widetilde{x}$ (with $\zeta(0) = \widetilde{x}$). Hence, $\frac{d}{dt}(W(h(\zeta(t))) = 0$ for all $t \in \mathbb{R}$. Therefore, $h(\zeta(t)) = h(\overline{x})$ for all t, in particular when $t = 0$. So, $\widetilde{x} = \overline{x}$. This shows that $\alpha_z(x) = \{\overline{x}\}$. Thus, $W(h(z(t)) \le W(h(\overline{x}))$ for all $t \in \mathbb{R}$. Note that $W \circ h(\overline{x}) = 0$ and $W \circ h > 0 \;\; \forall y \in \mathcal{A}_0 \setminus \{\overline{x}\}$. It follows that $z(t) = \overline{x}$ for all $t \in \mathbb{R}$ and, hence, $\mathcal{A}_0 = \{\overline{x}\}$. This proves the result. ☐

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