MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **13**, Number **5**, October **2016**

doi:10.3934/mbe.2016022

pp. **887–909**

IMMUNE RESPONSE IN VIRUS MODEL STRUCTURED BY CELL INFECTION-AGE

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(Communicated by Yang Kuang)

Abstract. This paper concerns modeling the coupled within-host population dynamics of virus and CTL (Cytotoxic T Lymphocyte) immune response. There is substantial evidence that the CTL immune response plays a crucial role in controlling HIV in infected patients. Recent experimental studies have demonstrated that certain CTL variants can recognize HIV infected cells early in the infected cell lifecycle before viral production, while other CTLs only detect viral proteins (epitopes) presented on the surface of infected cells after viral production. The kinetics of epitope presentation and immune recognition can impact the efficacy of the immune response. We extend previous virus models to include cell infection-age structure in the infected cell compartment and immune response killing/activation rates of a PDE-ODE system. We characterize solutions to our system utilizing semigroup theory, determine equilibria and reproduction numbers, and prove stability and persistence results. Numerical simulations show that "early immune recognition" precipitates *both* enhanced viral control and sustained oscillations via a Hopf bifurcation. In addition to inducing oscillatory dynamics, considering immune process rates to be functions of cell infection-age can also lead to coexistence of multiple distinct immune effector populations.

1. **Introduction.** Mathematical modeling of within-host virus dynamics has been an extensive subject of research over the past two decades. Many of the models have been related to a differential equation system often referred to as the standard virus model [31]. This standard model describes the coupled changes in target cells, infected cells, and free virus particles through time in an infected individual. The model has been very useful in quantifying certain parameters, especially for HIV, and providing insights for viral infections.

The standard virus model neglects certain features that may be important to consider for HIV, such as the host immune response. There is substantial evidence that the CD8+ T cell, also known as CTL (Cytotoxic T Lymphocyte), immune response plays a crucial role in controlling HIV and disease progression in infected patients [42]. CTL immune effectors recognize pathogen-derived proteins (epitopes) presented on the surface of infected cells to mediate their killing [19]. The CTL immune response has been included in various extensions of the standard virus model. Nowak and Bangham considered an immune effector population which kills

2010 *Mathematics Subject Classification.* Primary: 92C60; Secondary: 35B40.

Key words and phrases. Mathematical model, virus dynamics, HIV, immune response, age-structured, partial differential equation, stability, oscillations, Hopf bifurcation.

and is activated by infected cells according to a "mass-action" (bilinear) rate [27]. In subsequent work, e.g. [28, 44], the most popular functional forms for the killing and proliferation rates of immune effectors are this mass-action kinetics, although other forms have been utilized and can offer certain advantages [12].

Additionally, the standard virus model does not include details of infected cell lifecycle, in particular, the time lag between viral entry of a target cell and subsequent viral production from the newly infected cell. To account for this intracellular delay, many authors have studied virus models with discrete or distributed delays [11, 26, 5, 21, 35]. Nelson et al. considered a model with age structure in the infected cell component, which generalizes the delay standard virus model by allowing for infected cell death and viral production rates to vary with age since infection of an infected cell [25]. This model has appeared often in the literature [3, 15, 17, 32, 13, 6, 20] and the global dynamics were analyzed in [7].

Intracellular delays and immune response, along with delays in immune activation process have been considered together in the virus model, e.g. [21, 38, 43, 35]. Delays in the immune activation have been found to induce oscillations via Hopf bifurcation [38, 43, 35]. Even with no immune activation delays (or immune response in the model), it is known that some target-cell dynamics can cause sustained oscillations [37]. In the absence of immune activation delay and with certain restrictions on the target cell growth rate, in a general viral model with distributed intracellular delays and immune response, Shu et al. proved the global stability of the system equilibria [35]. In their model, along with others in the literature, the immune activation and killing rates are assumed to be functions of the total amount of virus-producing infected cells. However, it may be important for immune effector activation and killing processes to be more general functions of cellular infection-age since different epitopes can be presented at distinct stages in the infected cell life, in particular prior to viral production, as discussed in the next paragraph.

Recent experimental studies [34, 29, 19, 8, 10, 4] have demonstrated the importance and heterogeneity of epitope presentation timing with respect to the infected cell lifecycle for subsequent clearance of the infected cells. Certain immune effector populations have shown the ability to recognize and kill infected cells early in the infected cell lifecycle before viral production. The kinetics of antigen presentation may be a crucial determinant of the effectiveness of certain HIV-specific CTL clones, as the earlier the recognition, the more likely it is that the cell will be killed before the release of new virions and the less likely that the CTLs will be affected by Nef-mediated class I downregulation [10, 19, 4]. Also CTLs which attack early in the infected cell life cycle could reduce the amount of latently infected cells [8].

In this article, motivated by the aforementioned HIV research, we generalize the standard virus model to include immune effector processes dependent upon cellular infection age by considering the following PDE-ODE system:

$$\begin{aligned}
\frac{dT(t)}{dt} &= s - cT - kV(t)T(t),\\
\frac{\partial T^*(t,a)}{\partial t} + \frac{\partial T^*(t,a)}{\partial a} &= -\delta(a)T^*(t,a) - r(a)E(t)T^*(t,a), \qquad (1)\\
T^*(t,0) &= kV(t)T(t),\\
\frac{dV(t)}{dt} &= \int_0^\infty p(a)T^*(t,a)\,da - \gamma V(t),
\end{aligned}$$

$$\frac{dE(t)}{dt} = qE(t)\int_0^\infty r(a)T^*(t,a)\,da - \mu E(t),$$

$$T(0), V(0), E(0) \in \mathbb{R}^+, \quad T^*(0,\cdot) \in L^1_+(0,\infty).$$

The variables $T(t)$ and $V(t)$ denote the concentration of uninfected target cells and free virus particles, respectively. $T^*(t,a)$ denotes the density, with respect to age since infection, of infected cells. $E(t)$ is the concentration of a population of immune effector cells. Here $L^1_+(0,\infty)$ is the non-negative cone of $L^1(0,\infty)$ and $\mathbb{R}_+ = [0,\infty)$. The function $f(T) = s - cT$ represents the net growth rate of the uninfected cell population. The parameters k and γ are the infection rate and clearance rate for the virus. The functions $\delta(a)$ and $p(a)$ are the infection-age dependent (per-capita) rates of infected cell death and virion production for infected cells, respectively. The age dependent parameter $r(a)$ describes the killing rate of the immune cell population E (with respect to relevant epitopes presented on infected cell surface) as a function of time-since infection of the infected cells. The activation rate of immune cells E responding to epitopes presented on the infected cell is assumed to be proportional to $r(a)$ with proportionality factor q. Note the mass-action forms of the immune killing and activation rates are representative of actions that occur proportionally to the strength of interaction, denoted $\sigma(a)$, between immune cells and epitopes on the surface of infected cells (of age a). Thus it is reasonable to assume that the (cell infection-age dependent) killing and activation rate functions are of the form $r(a) = r\sigma(a)$ and $q(a) = qr\sigma(a)$, respectively, which gives the respective rates $r(a)$ and $qr(a)$. Finally, the parameter μ denotes the death rate of the immune effector cells.

Mathematical analysis of continuous age-structured models such as system (1) are complicated by the infinite-dimensionality of the underlying state space. A general approach is to study the nonlinear semigroup generated by solutions through recasting the system utilizing integrated semigroup theory or integrating along characteristic curves. We utilize both of these methods, along with prior results, in order to prove existence and uniqueness of solutions and asymptotic smoothness of the generated semigroup. In addition, we find two threshold quantities, $\mathcal{R}_0$ and $\mathcal{R}_1$, which yield conditions for uniform persistence of the virus and immune effector solution components, respectively, along with existence and stability results for the virus-free equilibrium, immune-free virus equilibrium and positive immune-controlled virus equilibrium.

Numerical simulations corroborate the basic kinetic advantage of immune effector cells which recognize epitopes early in the infected cell life, however we interestingly find that this "early immune recognition" can destabilize the positive equilibrium and induce sustained oscillations via Hopf bifurcation. Thus early immune recognition can be a fundamental mechanism for oscillatory dynamics in the virus model. As an extension of model (1), we also consider the case of two distinct immune effector populations competing for an infected cell population. Here we find another consequence of cell-infection age dependent immune processes; namely, coexistence of the effector populations can occur whereas the analogous ODE model produces competitive exclusion of immune responses.

The paper is organized as follows: In Section 2, we reformulate the model (1) and prove existence of a dissipative, asymptotically smooth semigroup generated by its solutions. In Section 3, equilibria and reproduction numbers are determine,

along with associated threshold properties consisting of local stability and persistence results. In Section 4, we conduct numerical simulations of model (1) and study an associated stage-structured ODE system, in order to explore enhanced control and oscillatory dynamics induced by early immune recognition. In Section 5, we extend the age-structured PDE model (1) to include multiple immune effector populations and find coexistence of immune responses. Finally in Section 6, we provide a discussion of our results and outline future work.

2. Existence of solutions and semigroup properties.

Various approaches have been developed for formulating solutions of age structured models. One approach is to use the theory of integrated semigroups [22, 41]. Another approach is integrating solutions along the characteristics to obtain an equivalent integral equation, referred to as the Volterra formulation [45]. We will use both methods to represent solutions. First, we state a few assumptions on the parameters of model (1). Each age-dependent parameter function $(\delta(a), p(a), r(a))$ is assumed to be in $L^\infty_+(0,\infty)$, the non-negative cone of $L^\infty(0,\infty)$. In addition, it is reasonable to assume that $\delta(a) \geq c \ \forall a \in (0,\infty)$. We also note that the term $-kVT$ associated with the loss of free virus particles due to absorption in target cell upon infection have been ignored in the $\frac{dV}{dt}$ equations. This is a common assumption in HIV models since the loss terms are considered relatively small and can be absorbed into the virus clearance rate γ [30].

2.1. Volterra formulation.

We find the Volterra formulation of system (1). Define the following functions:

$$\phi(a) = e^{-\int_0^a \delta(s)\,ds}, \qquad \psi(a, E(t)) = e^{-\int_0^a r(s)E(t-a+s)\,ds} \tag{2}$$

The function $\psi(a, E(t))$ represents the probability of infected cells (infected at time $t-a$) surviving the immune response to age a. The product $\phi(a)\psi(a, E(t))$ gives the probability of the infected cells surviving (both immune response and death by other causes) to age a. Also, denote $\mathbb{1}_{\{t>a\}}$ as the indicator function for the set $\{a \in (0,\infty) : t > a\}$. Integrating along the characteristics, we can reformulate system (1) as:

$$\begin{aligned}
\frac{dT(t)}{dt} &= s - cT - kV(t)T(t),\\
T^*(t,a) &= \phi(a)\psi(a,E(t))kV(t-a)T(t-a)\mathbb{1}_{\{t>a\}}\\
&\qquad + \frac{\phi(a)}{\phi(a-t)}\frac{\psi(a,E(t))}{\psi(a-t,E(t))}T^*(0,a-t)\mathbb{1}_{\{a>t\}},\\
\frac{dV(t)}{dt} &= \int_0^\infty p(a)T^*(t,a)\,da - \gamma V(t),\\
\frac{dE(t)}{dt} &= qE(t)\int_0^\infty r(a)T^*(t,a)\,da - \mu E(t)
\end{aligned} \tag{3}$$

2.2. Integrated semigroup formulation.

We introduce the Banach space $\hat{X} = \mathbb{R} \times L^1(0,\infty)$, its positive cone $\hat{X}_+ = \mathbb{R}_+ \times L^1_+(0,\infty)$ and the linear operator $\hat{A} : D(\hat{A}) \subset \hat{X} \to \hat{X}$ defined by

$$D(\hat{A}) = \{0\} \times W^{1,1}(0,\infty), \qquad \hat{A}\begin{pmatrix} 0 \\ \phi \end{pmatrix} = \begin{pmatrix} -\phi(0) \\ -\phi' - \delta\phi \end{pmatrix}.$$

Next consider the Banach space $\tilde{X}$ and its positive cone $\tilde{X}_+$ defined by

$$\tilde{X} = \mathbb{R} \times \hat{X} \times \mathbb{R}^2, \qquad \tilde{X}_+ = \mathbb{R}_+ \times \hat{X}_+ \times \mathbb{R}^2_+,$$

endowed with the product norm. Let $A : D(A) \subset \tilde{X} \to \tilde{X}$ be the linear operator defined by

$$D(A) = \mathbb{R} \times D(\hat{A}) \times \mathbb{R}^2, \qquad A = \operatorname{diag}\left(-c, \hat{A}, -\gamma, -\mu\right).$$

Then we define the nonlinear map $F : \overline{D(A)} \to \tilde{X}$ defined by

$$F\big(\,(T,(0,T^*(a)),V,E)\,\big) \;=\; \left(s - kVT,\ (0,-r(a)T^*(a)E),\ \int_0^\infty p(a)T^*(a)da,\ qE\int_0^\infty r(a)T^*(a)da\right).$$

Now set $X_0 = \overline{D(A)} \cap \tilde{X}_+$. Then the system (1) can be rewritten as the following non-densely defined Cauchy problem:

$$\frac{du(t)}{dt} = Au(t) + F(u(t)), \quad t \geq 0, \quad u(0) = u_0 \in X_0 \tag{4}$$

We can now derive that the above abstract Cauchy problem generates a unique globally defined, positive and point dissipative, strongly continuous semigroup.

Theorem 2.1. *Consider the assumptions put on the parameters of system (1). Then there exists a unique strongly continuous semigroup $(U(t))_{t\geq 0}$ on X_0 such that for each $u_0 \in X_0$, the map $u \in C([0,\infty), X_0)$ defined by $u(t) = U(t)u_0$ is a mild solution of (4), i.e. it satisfies*

$$\int_0^t u(s)ds \in D(A), \quad u(t) = u_0 + A\int_0^t u(s)ds + \int_0^t F(u(s))ds, \ \forall t \geq 0.$$

Furthermore $(U(t))_{t\geq 0}$ satisfies the following properties:

- *(i) Let $U(t)u_0 = \big(\,(T(t),(0,T^*(t,a)),V(t),E(t))\,\big)$. Then $S(t)x = \big(\,(T(t),T^*(t,a),V(t),E(t))\,\big)$ defines a strongly continuous semigroup $(S(t))_{t\geq 0}$ on $X := \mathbb{R}_+ \times L^1_+(0,\infty) \times \mathbb{R}^2_+$, where $x \in X$ and the components satisfy the equations in (3).*
- *(ii) The semigroup $S(t)$ is point dissipative in X.*
- *(iii) The semigroup $S(t)$ is asymptotically smooth.*

Proof. The proof of existence and uniqueness of mild solution is relatively standard. Indeed, it is easy to show that the operator A satisfies the Hille-Yosida property. Also, the non-linearities are Lipschitz continuous on bounded sets. Existence of solution and semigroup $U(t)$ follows by results from any of [23, 39]. Then integrating along the characteristics to obtain the Volterra formulation [45], we establish (i). Next, we show (ii), i.e. the dissipativity of the semigroup $S(t)$. Define $I(t) = \int_0^\infty T^*(t,a)\,da$. Note that it can be ascertained that $I(t)$ is differentiable in t by the smoothing properties of convolution which defines the Volterra formulation (3). Consider the time-derivative of $M(t) := T(t) + I(t) + \frac{c}{2\|p\|}V(t) + \frac{1}{2q}E(t)$:

$$\frac{d}{dt}M(t) = s - cT - \int_0^\infty \delta(a)T^*(t,a)\,da - E(t)\int_0^\infty r(a)T^*(t,a)\,da$$
$$\frac{c}{2\,\|p\|}\left(\int_0^\infty p(a)T^*(t,a)\,da - \gamma V\right)$$

$$
\begin{aligned}
&\qquad + \frac{1}{2q} qE(t) \left(\int_0^\infty r(a) T^*(t,a)\, da - \mu \right) \\
&\leq s - cT - c\int_0^\infty T^*\, da + \frac{c}{2}\int_0^\infty T^*\, da - \frac{c}{2\,\|p\|}\gamma V \\
&\qquad - \frac{1}{2}E(t)\int_0^\infty r(a)T^*(t,a)\, da - \frac{\mu}{2q}E(t) \\
&\leq s - \alpha M(t)
\end{aligned}
$$

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

$$\limsup_{t\to\infty} M(t) \leq \frac{s}{\alpha}.$$

Boundedness follows from positivity of solutions.

Finally, to show asymptotic smoothness, we simply note that the proof is almost identical to the proof of Proposition 1 in [7]. □

3. **Threshold dynamics.**

3.1. **Equilibria and reproduction numbers.** First, we can readily obtain the virus-free equilibrium $\overline{x}_0 := \left(\frac{s}{c}, 0, 0, 0\right)$. Define the basic reproduction number, $\mathcal{R}_0$:

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

If $\mathcal{R}_0 > 1$, then there exists the immune-free virus equilibrium, $\overline{x}_1 = (\overline{T}_1, \overline{T}_1^*(a), \overline{V}_1, 0)$, where

$$\overline{T}_1 = \frac{s}{c\mathcal{R}_0}, \quad \overline{V}_i = \frac{s - c\overline{T}_1}{k\overline{T}_1}, \quad \overline{T}_1^*(a) = k\overline{V}_1\overline{T}_1\phi(a).$$

In order to determine existence of a positive immune-controlled virus equilibrium, let $\overline{x}_2 = (\overline{T}, \overline{T}^*(a), \overline{V}, \overline{E})$ denote such an equilibrium. Thus, we find that $\overline{T}^*(a) = k\overline{V}\overline{T}\phi(a)\exp\left(-\overline{E}\int_0^a r(\ell)\, d\ell\right)$. Inserting this expression into the RHS of the $\dot{V}$ equation and equating to zero, we find

$$\overline{T} = \frac{\gamma}{k\int_0^\infty p(a)\phi(a)\exp\left(-\overline{E}\int_0^a r(\ell)\, d\ell\right)\, da}.$$

Then, utilizing the fact that $k\overline{V}\overline{T} = s - c\overline{T}$ and inserting $\overline{T}^*(a)$ into the RHS of the $\dot{E}$ equation and setting equal to zero, we obtain the equation:

$$s - \frac{c\gamma}{k\int_0^\infty p(a)\phi(a)\exp\left(-\overline{E}\int_0^a r(\ell)\, d\ell\right)\, da} = \frac{\mu}{q\int_0^\infty r(a)\phi(a)\exp\left(-\overline{E}\int_0^a r(\ell)\, d\ell\right)\, da}.$$

Denote the LHS of the above equation as $g(E)$ and the RHS as $h(E)$. Observe that $g(E)$ is decreasing and $h(E)$ is increasing. Thus there exists the positive equilibrium $\overline{x}_2$, which is always unique, if and only if:

$$
\begin{aligned}
g(0) > h(0) &\Leftrightarrow s - \frac{c\gamma}{k\int_0^\infty p(a)\phi(a)\, da} = \frac{\mu}{q\int_0^\infty r(a)\phi(a)\, da} \\
&\Leftrightarrow 1 < \left(1 - \frac{1}{\mathcal{R}_0}\right)\mathcal{R}_E, \\
&\text{where} \quad \mathcal{R}_E := \frac{sq}{\mu}\int_0^\infty r(a)\phi(a)\, da.
\end{aligned}
$$

Thus, we define

$$\mathcal{R}_1 = \left(1 - \frac{1}{\mathcal{R}_0}\right)\mathcal{R}_E. \tag{6}$$

The unique positive equilibrium $\overline{x}_2$ exists if and only if $\mathcal{R}_1 > 1$. Note that $\mathcal{R}_0 > 1$ is required for this condition to hold.

3.2. **Stability analysis.** In the following, we will conduct stability analysis of the equilibria $\overline{x}_0$ and $\overline{x}_1$ (the characteristic equation corresponding to $\overline{x}_2$ is too complex for any analytical results). For local stability, the strategy is to linearize about the equilibrium $\overline{x}_i$, where $i = 0, 1, 2$:

$$\frac{du(t)}{dt} = Au(t) + DF(\overline{x}_i)(u(t)) \tag{7}$$

We first show that the point spectrum is the relevant subset of the spectrum to look at for stability.

Lemma 3.1. *Let* $\Omega = \{\lambda \in \mathbb{C} : \mathrm{Re}(\lambda) > \min(-c, -\gamma, -\mu)\}$. *Then the spectrum* $\sigma\left(A + DF(\overline{x}_i)\right) \cap \Omega$ *only consists of the point spectrum.*

Proof. Define A_0 as the part of A in $\overline{D(A)}$. It is the infinitesimal generator of a C_0-semigroup on $\overline{D(A)}$, denoted by $(S_{A_0}(t))_{t\geq 0}$. It is not hard to show that the exponential growth rate of this semigroup satisfies $\omega_{ess}(A_0) \leq \min(-c, -\gamma, -\mu)$. Clearly $DF(\overline{x}_i)$ is a bounded linear operator and since the semigroup $(S(t))$ is asymptotically smooth, it is not hard to show that $DF(\overline{x}_i)$ is also compact. Denote $\left(S_{A_0+DF(\overline{x}_i)}(t)\right)_{t\geq 0}$ as the linear C_0-semigroup generated by $(A_0 + DF(\overline{x}_i))_0$, the part of $A_0 + DF(\overline{x}_i)$ in $\overline{D(A)}$. It follows that $\omega_{ess}\left((A_0 + DF(\overline{x}_i))_0\right) \leq \min(-c, -\gamma, -\mu)$. Applying results in [40, 14], we find that the spectrum $\sigma\left(A + DF(\overline{x}_i)\right) \cap \Omega$ only consists of the point spectrum. □

Proposition 1. *Consider the system (3). If* $\mathcal{R}_0 < 1$, *then the infection-free equilibrium* $\overline{x}_0$ *is globally asymptotically stable in the state space* X. *Conversely, if* $\mathcal{R}_0 > 1$, *then* $\overline{x}_0$ *is unstable.*

Proof. We first determine local stability by considering the linear system (7) about $\overline{x}_0$. In order to linearize around $\overline{x}_0$, consider perturbations around $\overline{x}_0$: $x(t) = T(t) - \frac{s}{c}$, $y(t, a) = T^*(t, a)$, $v(t) = V(t)$ and $u(t) = E(t)$. After simplification and neglecting nonlinear terms, we obtain the following equations:

$$\begin{aligned}
\frac{dx(t)}{dt} &= -cx(t) - k\frac{s}{c}v(t) \\
\frac{\partial y(t,a)}{\partial t} + \frac{\partial y(t,a)}{\partial a} &= -\delta(a)y(t,a), \qquad y(t,0) = kv(t)\frac{s}{c} \\
\frac{dv(t)}{dt} &= \int_0^\infty p(a)y(t,a)\,da - \gamma v(t) \\
\frac{du(t)}{dt} &= -\mu u(t).
\end{aligned}$$

By Lemma 3.1, we only need to consider exponential solutions to the above system of the form $x(t) = x_0e^{\lambda t}$, $y(t, a) = y_0(a)e^{\lambda t}$, $v(t) = v_0e^{\lambda t}$, and $u(t) = u_0e^{\lambda t}$. The below linear system follows:

$$\lambda x_0 = -cx_0 - k\frac{s}{c}v_0$$

$$\lambda y_0(a) + y_0'(a) = -\delta(a)y_0(a), \qquad y_0(0) = kv_0\frac{s}{c}$$
$$\lambda v_0 = \int_0^\infty p(a)y_0(a)\,da - \gamma v_0$$
$$\lambda u_0 = -\mu u_0$$

Thus $y_0(a) = kv_0\frac{s}{c}\phi(a)e^{-\lambda a}$. Inserting this into the third equation above and canceling out v_0, the characteristic equation for λ is obtained:

$$\lambda + \gamma = k\frac{s}{c}\int_0^\infty p(a)\phi(a)e^{-\lambda a}\,da$$

First, suppose that $\mathcal{R}_0 < 1$. We will show that any eigenvalue λ of the characteristic equation has negative real part. Suppose by way of contradiction that $\mathrm{Re}(\lambda) \geq 0$. Then

$$1 \leq \frac{|\lambda+\gamma|}{\gamma} = \frac{k\frac{s}{c}\int_0^\infty p(a)\phi(a)|e^{-\lambda a}|\,da}{\gamma} \leq \frac{k\frac{s}{c}\int_0^\infty p(a)\phi(a)\,da}{\gamma} = \mathcal{R}_0.$$

This implies that $\mathcal{R}_0 \geq 1$, which is a contradiction. Hence, $\mathrm{Re}(\lambda) < 0$ and $\overline{x}_0$ is locally asymptotically stable when $\mathcal{R}_0 < 1$. On the other hand if $\mathcal{R}_0 > 1$, then $\gamma < k\frac{s}{c}\int_0^\infty p(a)\phi(a)\,da$, which implies there is a positive eigenvalue λ. Thus, $\overline{x}_0$ is unstable.

Furthermore, it can be proved that $\overline{x}_0$ is globally asymptotically stable when $\mathcal{R}_0 < 1$. Indeed, since $E(t)$ is non-negative for all t, we find that

$$\frac{dV(t)}{dt} \leq \int_0^t kp(a)\phi(a)V(t-a)T(t-a)\,da + \int_t^\infty \frac{\phi(a)}{\phi(a-t)}T^*(0,a-t)\,da - \gamma V(t)$$

Then using a simple comparison principle and Theorem 3.3 in [7], we find that $V(t) \to 0$ as $t \to \infty$. With the same argument contained in the proof of Proposition 4.1 in [6], we also conclude that $T^*(t,a) \to 0$ in $L^1_+(0,\infty)$ as $t \to \infty$. □

Proposition 2. *If $\mathcal{R}_1 < 1 < \mathcal{R}_0$, then $\overline{x}_1$ is locally asymptotically stable. However, if $\mathcal{R}_1 > 1$, then $\overline{x}_1$ is unstable.*

Proof. Linearizing around $\overline{x}_1$ produces the following system:

$$\frac{dx(t)}{dt} = -cx(t) - k\overline{T}_1 v(t) - k\overline{V}_1 x(t)$$
$$\frac{\partial y(t,a)}{\partial t} + \frac{\partial y(t,a)}{\partial a} = -\delta(a)y(t,a) - r(a)\overline{T}^*(a)u(t), \quad y(t,0) = kv(t)\overline{T}_1 + k\overline{V}_1 x(t)$$
$$\frac{dv(t)}{dt} = \int_0^\infty p(a)y(t,a)\,da - \gamma v(t)$$
$$\frac{du(t)}{dt} = u(t)\int_0^\infty q(a)\overline{T}^*(a)\,da - \mu u(t).$$

Assuming solutions of the exponential form as previously, we obtain the following system:

$$\lambda x_0 = -cx_0 - k\overline{T}_1 v_0 - k\overline{V}_1 x_0$$
$$\lambda y_0(a) + y_0'(a) = -\delta(a)y_0(a) - r(a)\overline{T}^*(a)u_0, \quad y_0(0) = kv_0\overline{T}_1 + k\overline{V}_1 x_0$$
$$\lambda v_0 = \int_0^\infty p(a)y_0(a)\,da - \gamma v_0$$
$$\lambda u_0 = u_0 q\int_0^\infty r(a)\overline{T}^*(a)\,da - \mu u_0. \tag{8}$$

If $u_0 \neq 0$ and $x_0 = v_0 = 0$, $y_0(a) \equiv 0$, then the equation (8) gives the eigenvalue:

$$\begin{aligned}\lambda &= q\int_0^\infty r(a)\overline{T}^*(a)\,da - \mu\\ &= k\overline{V}_1\overline{T}_1 q\int_0^\infty r(a)\phi(a)\,da - \mu\\ &= (s - c\overline{T}_1)q\int_0^\infty r(a)\phi(a)\,da - \mu\\ &= \mu\left[\left(1-\frac{1}{\mathcal{R}_0}\right)\frac{sq}{\mu}\int_0^\infty r(a)\phi(a)\,da - 1\right]\\ &= \mu(\mathcal{R}_1 - 1)\end{aligned}$$

Thus $\lambda > 0$ when $\mathcal{R}_1 > 1$. Therefore $\overline{x}_1$ is unstable when $\mathcal{R}_1 > 1$. If $\mathcal{R}_1 < 1$, then this eigenvalue λ is negative. In this case, the other equations need to be checked. Hence, we assume that $u_0 = 0$. Then, $y_0(a) = k(v_0\overline{T}_1 + x_0\overline{V}_1)\phi(a)e^{-\lambda a}$. Also, $x_0 = \frac{-kv_0\overline{T}_1}{\lambda + c + k\overline{V}_1}$. Then:

$$\begin{aligned}\lambda v_0 &= k\left[v_0\overline{T}_1 - \left(\frac{kv_0\overline{T}_1}{\lambda + c + k\overline{V}_1}\right)\overline{V}_1\right]\int_0^\infty p(a)\phi(a)e^{-\lambda a}\,da - \gamma v_0\\ \Rightarrow &\frac{\left(\lambda + c + k\overline{V}_1\right)(\lambda+\gamma)}{\lambda + c} = k\overline{T}_1\int_0^\infty p(a)\phi(a)e^{-\lambda a}\,da\end{aligned}$$

Now suppose by way of contradiction that $\mathrm{Re}(\lambda) \geq 0$. Then:

$$\begin{aligned}1 < \left|\frac{\left(\lambda + c + k\overline{V}_1\right)(\lambda+\gamma)}{(\lambda+c)\gamma}\right| &= \frac{k\overline{T}_1}{\gamma}\int_0^\infty p(a)\phi(a)|e^{-\lambda a}|\,da\\ &\leq \frac{ks}{\gamma c\mathcal{R}_0}\int_0^\infty p(a)\phi(a)\,da = \frac{\mathcal{R}_0}{\mathcal{R}_0} = 1\end{aligned}$$

Thus we obtain $1 < 1$, a contradiction. Hence $\mathrm{Re}(\lambda) < 0$ for this eigenvalue. This implies that $\overline{x}_1$ is locally asymptotically stable when $\mathcal{R}_1 < 1$ and $\mathcal{R}_0 > 1$. □

We conjecture that $\overline{x}_1$ is globally asymptotically stable when $\mathcal{R}_1 < 1 < \mathcal{R}_0$. However, a comparison argument does not work in this case and a Lyapunov functional seems difficult to find. We also remark that Lemma 3.1 applies to the positive equilibrium $\overline{x}_2$, so that the point spectrum determines the stability. Linearizing about $\overline{x}_2$ and looking for exponential solutions, we find the characteristic equation $G(\lambda) = 1$ where

$$G(\lambda) = \frac{q\overline{E}}{\lambda}\left[\frac{(\lambda+c)k\overline{T}\int_0^\infty r(a)\phi(a)\psi(a,\overline{E})e^{-\lambda a}\,da\int_0^\infty p(a)\int_0^a r(b)\overline{T}^*(b)\frac{\phi(a)}{\phi(b)}\frac{\psi(a,\overline{E})}{\psi(b,\overline{E})}e^{-\lambda(a-b)}\,db\,da}{(\lambda+c+k\overline{V})(\lambda+\gamma) - (\lambda+c)k\overline{T}\int_0^\infty p(a)\phi(a)\psi(a,\overline{E})e^{-\lambda a}\,da}\right.$$
$$\left. + \int_0^\infty r(a)\int_0^a r(b)\overline{T}^*(b)\frac{\phi(a)}{\phi(b)}\frac{\psi(a,\overline{E})}{\psi(b,\overline{E})}e^{-\lambda(a-b)}\,db\,da\right]. \tag{9}$$

This characteristic equation is too difficult to analyze, and in Section 4, numerical simulations suggest that $\overline{x}_2$ can be destabilized when $\mathcal{R}_1 > 1$, undergoing a Hopf bifurcation.

3.3. **Uniform persistence.** In this section, we consider uniform persistence of the system by utilizing results of Hale and Waltman [16].

Let $\bar{a}_1 = \sup\{a \in (0,\infty) : p(a) > 0\}$ and $\bar{a}_2 = \sup\{a \in (0,\infty) : q(a) > 0\}$. Note that, possibly, $\bar{a}_i = +\infty$. Define the following sets:

$$\partial M_1 = \left\{\eta(a) \in L^1_+(0,\infty) : \int_0^{\bar{a}_1} \eta(a)\,da = 0\right\}, \quad M_1 = L^1_+(0,\infty) \setminus \partial M_1$$

$$\partial M = \left\{\eta(a) \in L^1_+(0,\infty) : \int_0^{\bar{a}_1 \vee \bar{a}_2} \eta(a)\,da = 0\right\}, \quad M = L^1_+(0,\infty) \setminus \partial M$$

$$\partial X_1 = \mathbb{R}_+ \times \partial M_1 \times \{0\} \times \mathbb{R}_+, \quad X_1 = X \setminus \partial X_1, \quad X_1^+ = \mathbb{R}_+ \times M_1 \times (0,\infty) \times \mathbb{R}_+$$

$$\partial X_2 = \left(\mathbb{R}_+ \times L^1_+(0,\infty) \times \mathbb{R}_+ \times \{0\}\right) \bigcup \left(\mathbb{R}_+ \times \partial M \times \{0\} \times \mathbb{R}_+\right), \quad X_2 = X \setminus \partial X_2$$

Lemma 3.2. *The sets X_1, X_2, ∂X_1 and ∂X_2 are forward invariant under the semigroup $S(t)$. Also, $\forall x \in \partial X_1$, we have $S(t)x \to \overline{x}_0$ as $t \to \infty$; and $\forall x \in \partial X_2 \cap X_1$, we have $S(t)x \to \overline{x}_1$ as $t \to \infty$. In addition, $S(t)X_1 \subset X_1^+$ $\forall t > 0$.*

Proof. First we show the conclusions for ∂X_1. Suppose by way of contradiction that there exists $x \in \partial X_1$ and $t_1 > 0$ such that $S(t_1)x \in X_1$. Let $\tau = \inf\{t > 0 : S(t)x \in X_1\}$. Since X_1 is an open set in X and by the continuity of the semigroup $S(t)$, we obtain that $S(\tau)x \notin X_1$ and, hence, $S(\tau)x \in \partial X_1$. For $t \geq 0$, define $x_3(t) = 0$, $x_4(t) = E(t)$, $x_2(t,a) = \frac{\phi(a)}{\phi(a-t)} \frac{\psi(a,E(t))}{\psi(a-t,E(t))} T^*(0,a-t)\mathbb{1}_{\{a>\tau+t\}}$. Then, $\xi(t) := (T(t+\tau), x_2(t,a), x_3(t), x_4(t+\tau))$ is a solution to the system with initial condition $\xi(0) = S(\tau)x$ and $\xi(t) \in \partial X_1$ $\forall t \geq 0$. Then, by forward uniqueness of solutions, $S(t)x \in \partial X_1$ $\forall t \geq 0$, which contradicts our assumption that $S(t_1)x \in X_1$. Thus ∂X_1 is forward invariant. It is clear that for any solution in ∂X_1, $T(t) \to T_0$, hence we have $S(t)x \to \overline{x}_0$ as $t \to \infty$.

Now we show X_1 is forward invariant. Notice that $V(t) \geq V(0)e^{-\gamma t}$ 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 $x \in X_1$), which implies 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, $S(t)X_1 \subset X_1^+$ for all $t > 0$ and $S(t)X_1^+ \subset X_1^+$ for all $t \geq 0$. With a simple argument, this implies that ∂X_2 is forward invariant. By Theorem 3.7 in [7], $\forall x \in \partial X_2 \cap X_1$, we have $S(t)x \to \overline{x}_1$ as $t \to \infty$. Finally, $E(t) \geq E(0)e^{-\mu t}$ implies that X_2 is forward invariant. □

We will use the following definitions. The *omega limit set* of $x \in X$, $\omega(x)$, is defined as

$$\omega(x) := \{y \in X : \exists\ t_n \uparrow \infty \text{ such that } S(t_n)x \to y\}.$$

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.

Theorem 3.3. *Suppose that $\mathcal{R}_0 > 1$. Then $S(t)$ is uniformly persistent with respect to X_1, i.e. $\exists \epsilon > 0$ such that for any $x \in X_1$, $\liminf_{t\to\infty} d(S(t)x, \partial X_1) \geq \epsilon$.*

Proof. We will apply Theorem 4.2 in [16] to prove uniform persistence. Observe that $\partial X_1 \subset W_s(\{\overline{x}_0\})$. Also $(\partial X_1 \setminus \{\overline{x}_0\}) \cap W_u(\{\overline{x}_0\}) = \emptyset$. Indeed, let $x \in \partial X_1 \setminus \{\overline{x}_0\}$.

Any backward orbit of x must stay in ∂X_1 since X_1 is forward invariant. Suppose $x = (T(0), \ell(a), 0, E(0))$. If $\ell(a) = 0$ (in L^1), then we have an ODE with a unique equilibrium and $\lim_{t\to-\infty} T(t) = 0$ or ∞. Thus in this case $\overline{x}_0$ cannot be an α-limit point of x. Also such an x cannot be contained on a complete orbit. With this, we conclude that $\{\overline{x}_0\}$ is isolated in ∂X_1. Now suppose $\int_0^\infty \ell(a)\,da > 0$. Since $x \in \partial X_1$, $\int_0^{\overline{a}_1} \ell(a)\,da = 0$. Suppose $\exists \tau > 0, x_1 = (T(-\tau), \ell_1(a), 0, E(-\tau)) \in \partial X_1$ such that $S(\tau)x_1 = x$. Then, $\int_{\overline{a}_1}^\infty \ell(a)\,da = \int_{\overline{a}_1+\tau}^\infty e^{-\int_{a-\tau}^a \delta(s)\,ds}\ell(a-\tau)\,da < \int_{\overline{a}+\tau}^\infty \ell_1(a)\,da$. Hence, the norm of the L^1-component is strictly increasing on backward orbits and hence $\overline{x}_0$ cannot be an α-limit point of x. Therefore, in order for $\{\overline{x}_0\}$ to be acyclic and isolated (which would satisfy the assumptions of Theorem 4.2 in [16]), and to satisfy the equivalent condition for uniform persistence given in the conclusion of the same theorem, we need only to prove $W_s(\{\overline{x}_0\}) \cap X_1 = \emptyset$.

Suppose by way of contradiction that there exists $x \in X_1$ such that $x \in W_s(\{\overline{x}_0\})$. Then, utilizing arguments contained in the proof of Theorem 3.6 in [7] and the asymptotic smoothness of $S(t)$, we can establish $S(t)x \to \overline{x}_0$ as $t \to \infty$. It follows that we can find a sequence $(x_n) \subset X_1$ such that

$$\|S(t)x_n - \overline{x}_0\| < \frac{1}{n} \quad \forall t \geq 0.$$

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

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

Then, by inserting the integrated formal solution of $T^*(t,a)$ 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

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

Note that if $V_n(0) = 0$, then clearly $T_n^*(0,a) \in M_1$ 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 $-\gamma + k\left(T_0 - \frac{1}{N}\right)\int_0^\infty p(a)\phi(a)\exp\left(\frac{-a\|r\|_\infty}{n}\right)da > 0$. Then by Lemma 3.5 in [7], 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 $W_s(\{\overline{x}_0\}) \cap X_1 = \emptyset$. By Theorem 4.2 [16], we get that $S(t)$ is uniformly persistent with respect to X_1. Then by Theorem 3.7 in [24], we can conclude for our case that there exists a compact set $\mathcal{A}_0 \subset X_1$ which is a global attractor for $\{S(t)\}_{t\geq 0}$ in X_1. □

Because $S(t)X_1 \subset X_1^+$, the global attractor, $\mathcal{A}_0$, is actually contained in X_1^+. Therefore, there exists $\epsilon > 0$ such that

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

Theorem 3.4. *Suppose that $\mathcal{R}_1 > 1$. Then $S(t)$ is uniformly persistent with respect to X_2, i.e. $\exists \epsilon > 0$ such that for any $x \in X_2$, $\liminf_{t\to\infty} d(S(t)x, \partial X_2) \geq \epsilon$.*

Proof. Again, we will apply Theorem 4.2 in [16] to prove uniform persistence. Let A_δ be the (strong) global attractor of ∂X_2. Partition ∂X_2 as $Y_1 \bigcup Y_2$ where $Y_1 =$

$(\mathbb{R}_+ \times \partial M \times \{0\} \times \mathbb{R}_+)$ and $Y_2 = \partial X_2 \setminus Y_1$. Observe that Y_2 is forward invariant. Observe that $Y_1 \subset W_s(\{\overline{x}_0\})$. Also $(W_s(\{\overline{x}_0\}) \cap \partial X_2) = Y_1$. In addition, $Y_2 = \partial X_2 \cap X_1$, and utilizing Lemma 3.2, we can obtain $(W_s(\{\overline{x}_1\}) \cap \partial X_2) = Y_2$. Also, consider $\widetilde{A}_\delta := \cup_{A_\delta} \omega(x)$. We obtain that $\widetilde{A}_\delta = \{\overline{x}_0, \overline{x}_1\}$. We claim that $\{\overline{x}_0\}$ and $\{\overline{x}_1\}$ are isolated invariant sets. Clearly $\{\overline{x}_0\}$ is isolated by the same argument contained in Theorem 3.3. Next, let $B := B_r(\overline{x}_1)$ be an open ball of sufficiently small radius r around $\overline{x}_1$. We claim that B is an isolating neighborhood. Suppose by way of contradiction that $\{\overline{x}_1\}$ is not a maximal invariant set. Then, let $M \subset B$ be an invariant set with $M \neq \{\overline{x}_1\}$. There exists a complete orbit $\gamma(x) \subset M$ for $x \in M \setminus \{\overline{x}_1\} \subset X \setminus Y_1$. If $x \in Y_2$, then Theorem 3.7 in [7] implies $x = \overline{x}_1$, a contradiction. If $x \in M \cap X_2$, then, using Proposition 2, the instability of $\overline{x}_1$ implies that $S(t)x \notin M$ for some t, contradicting the invariance of M. Therefore, $\widetilde{A}_\delta$ is isolated.

The next condition to check is for $\widetilde{A}_\delta$ to be acyclic. Consider the semigroup restricted to the boundary, i.e. $S(t)|_{\partial X_2}$ and first suppose there is a cycle of length 2. If this is the case, then there exists $x \in \partial X_2$ such that $x \in W_u(\{\overline{x}_1\}) \cap W_s(\{\overline{x}_0\})$. Then $S(0)x \in Y_1$, i.e. $V(0) = 0$ and $T^*(0, a) \in \partial M$. Note that $Y_1 \subset \partial X_1$. The forward invariance of X_1 implies that $V(t) = 0$ and $T^*(t, a) \in \partial M_1$ for any negative t on a backward orbit through x. Thus $\alpha(x) \subset \partial X_1$. So $x \notin W_u(\{\overline{x}_1\})$. Next, consider the possibility of a cycle of length 1. We can use similar arguments to those contained in Theorem 5.1 (Lemma 2) of [6] to show that there can not be $x \in W_u(\{\overline{x}_i\}) \cap W_s(\{\overline{x}_i\})$ for $x \neq \overline{x}_i$, $i = 1, 2$, and $x \in \partial X_2$. It remains only to prove that $W_s(\{\overline{x}_1\}) \cap X_2 = \emptyset$.

Suppose by way of contradiction that there exists $x \in X_2$ such that $x \in W_s(\{\overline{x}_1\})$. Then, as before $S(t)x \to \overline{x}_1$ as $t \to \infty$. It follows that we can find a sequence $(x_n) \subset X_2$ such that

$$\|S(t)x_n - \overline{x}_0\| < \frac{1}{n} \quad \forall t \geq 0.$$

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

$$|T_n(t) - \overline{T}_1| \leq \frac{1}{n}, \ |V_n(t) - \overline{V}_1| \leq \frac{1}{n}, \ E_n(t) \leq \frac{1}{n} \quad \forall t \geq 0.$$

Then, by inserting $T^*(t, a)$ into the $\dot{E}$ equation and applying a simple comparison principle as before, we deduce that $E_n(t) \geq y_n(t)$ where $y_n(t)$ is a solution of

$$\frac{dy_n(t)}{dt} = \left((\overline{T}_1 - \frac{1}{n})(\overline{V}_1 - \frac{1}{n}) \int_0^t kq(a)\phi(a) e^{\frac{-a}{n}\|r\|_\infty} \, da - \mu \right) y_n(t),$$

where $y_n(0) = E_n(0) > 0$. We claim that for n sufficiently large, y_n is unbounded. The assumption $\mathcal{R}_1 > 1$ is equivalent to

$$k\overline{V}_1\overline{T}_1 \int_0^\infty q(a)\phi(a)da - \mu > 0.$$

Then for sufficiently large n, there exists τ_n such that $\frac{dy_n(t)}{dt} \geq Ay_n(t)$ for all $t \geq \tau_n$ for some positive constant A. Thus y_n is unbounded and, since $E_n(t) \geq y_n(t)$, E_n is unbounded, which is a contradiction. Therefore $W_s(\{\overline{x}_1\}) \cap X_2 = \emptyset$. By Theorem 4.2 [16], we get that $S(t)$ is uniformly persistent with respect to X_2. Then by Theorem 3.7 in [24], we can conclude for our case that there exists a compact set $\mathcal{A}_0 \subset X_2$ which is a global attractor for $\{S(t)\}_{t \geq 0}$ in X_2. □

Analogous to the case $\mathcal{R}_0 > 1$, this result implies that if $\mathcal{R}_1 > 1$, then there exists $\epsilon > 0$ such that

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

Summarizing the results of this subsection, we found that: (i) if $\mathcal{R}_0 > 1$, then the viral components of the solution to (1) are uniformly persistent; and (ii) if $\mathcal{R}_1 > 1$, then *both* the viral components and the immune effector population are uniformly persistent.

4. **Numerical simulations and oscillatory dynamics.** In this section, we first conduct numerical simulations of solutions to model (1). Suppose τ is the intracellular delay between viral entry of an infected cell and viral production, i.e. $\tau = \inf\{a : p(a) > 0\}$. Also, suppose that the immune recognition is of the form $r(a) = r\mathbb{1}_{\{a>\sigma\}}$, i.e. the immune cells can recognize infected cells σ units of time after cell infection. If $\sigma = \tau$, i.e. immune recognition occurs when viral production starts, then the system can be rewritten with distributed delays and Shu et al. proved that the positive equilibrium $\overline{x}_2$ is globally stable in such a model [35]. In the following simulations, we consider the piecewise constant viral production rate $p(a) = p\mathbb{1}_{\{a>\tau\}}$ and infected cell death rate $\delta(a) = c\mathbb{1}_{\{a<\tau\}} + \nu\mathbb{1}_{\{a>\tau\}}$. As σ decreases from values larger than τ, the healthy cell equilibrium, $\overline{T}$, increases since the immune response can recognize and kill the infected cell at earlier infection-ages (see Figure 1(a)).

Interestingly we find that the equilibrium $\overline{x}_2$ can go from local stability to instability as the age of immune recognition σ decreases. Indeed simulations show that when σ decreases past a critical value $\sigma^* < \tau$, a bifurcation occurs in which the numerical solutions produce sustained oscillations for $\sigma < \sigma^*$ (see Figure 1). For the chosen parameters (note that $\tau = 2$ d (days)), $\sigma^* \approx 1.57$ d. We hypothesize that this value σ^* corresponds to a Hopf bifurcation, but given the complexity of the characteristic equation for the eigenvalues corresponding to the equilibrium $\overline{x}_2$, it is difficult to directly confirm this. Despite the fact that the ability of the immune effectors to recognize infected cells before viral production can induce oscillations, early immune recognition still likely confers an advantage for the host. Indeed, Figure 1 shows that the amount of healthy T-cells is substantially increased for $\sigma = 0.5$ d and, to a lesser extent, $\sigma = 1.5$ d, compared with $\sigma = 1.8$ d. However, at the trough of the periodic solution, the T-cell count for $\sigma = 1.5$ d becomes lower than the stable equilibrium for $\sigma = 1.8$ d, and the large amplitude in $V(t)$ for $\sigma = 0.5$ d and $\sigma = 1.5$ d pushes the peak viral load well above the steady state value for V when $\sigma = 1.8$ d.

Numerical simulations indicate that the system can undergo a Hopf bifurcation and have sustained oscillations when the "early immune recognition" is sufficient, but further evidence is needed to support this assertion. Unfortunately, the characteristic equation (9) is too complicated to find the eigenvalues. Additionally, oscillations are often found to occur in age-structured and delay differential equation models. Thus it would be informative to isolate the effect of "early killing" inducing oscillations in an ordinary differential equation model in which the eigenvalues corresponding to the positive equilibrium can be calculated. Indeed, we will show that oscillatory dynamics are produced by an ODE which is motivated from a special case of a slightly generalized version of model (12). The ODE also provides a simple means of modeling CTL "early killing" or "late killing" of infected

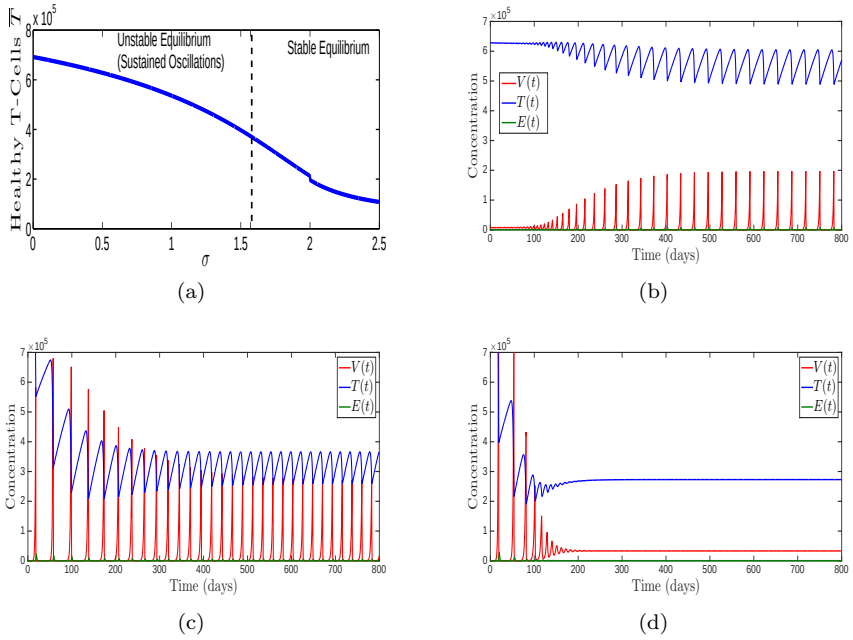


FIGURE 1. *Effect of early immune recognition on dynamics.* Simulations of (1) in the case of piecewise constant parameters: $p(a) = p\mathbb{1}_{\{a>\tau\}}$, $r(a) = r\mathbb{1}_{\{a>\sigma\}}$ and $\delta(a) = c\mathbb{1}_{\{a<\tau\}} + \nu\mathbb{1}_{\{a>\tau\}}$. (a) The equilibrium number of healthy cells, $\overline{T}$, increases as the time of immune recognition after cell infection, σ, decreases. However smaller values of σ also lead to instability of the equilibrium and sustained oscillations of virus (red), healthy cells (blue) and immune effectors (green). The bifurcation from stable equilibrium to sustained oscillations occurs as σ decreases below $\sigma^* \approx 1.57$ d. In the simulations, σ is varied as follows: (b) $\sigma = 0.5$ d, (c) $\sigma = 1.5$ d, (d) $\sigma = 1.8$ d. Note that in (b), the initial condition for the simulation is set as the (unstable) positive equilibrium, whereas in (c) and (d) the initial condition is set as an initial unit of virus in an otherwise healthy individual ($T(0) = 10^6$ ml^{-1}, $T^*(0,a) \equiv 0$ ml^{-1}, $V(0) = 1$ ml^{-1}, $E(0) = 1$ ml^{-1}). Also, note that the cell infection age when viral production begins is assumed $\tau = 2$ d. The other parameters are $s = 10^4$ ml^{-1} d^{-1}, $c = 0.01$ d^{-1}, $k = 8\times10^{-7}$ ml d^{-1}, $\nu = 0.7$ d^{-1}, $p = 200$ d^{-1}, $r = 0.003$ ml d^{-1}, $q = 0.1$ and $\mu = 1$ d^{-1}.

cells. To derive an ODE from the aforementioned age-structured model, we use the linear chain trick [36]. For simplicity let $T^*(0,a) \equiv 0$. Also, we assume the age-independent rates $\delta(a) \equiv \alpha$ and $r(a) \equiv r$. Define $Y(t) := \int_0^\infty T^*(t,a)\,da$.

$$\begin{aligned} Y(t) &= \int_0^t T^*(t,a)\,da \\ &= \int_0^t kV(t-a)T(t-a)e^{-\alpha a}e^{-r\int_0^a E(t-a+\ell)\,d\ell}\,da \end{aligned}$$

$$= \int_0^t kV(u)T(u)e^{-(\alpha(t-u)+r\int_0^{t-u} E(u+\ell)\,d\ell)}\,du$$

Therefore,

$$\begin{aligned}\frac{dY(t)}{dt} &= kV(t)T(t) - (\alpha + rE(t))\int_0^t kV(u)T(u)e^{-(\alpha(t-u)+r\int_0^{t-u} E(u+\ell)\,d\ell)}\,du \\ &= kV(t)T(t) - \alpha Y(t) - rE(t)Y(t).\end{aligned}$$

Now define $I(t) = \int_0^\infty \alpha a T^*(t,a)\,da$. Thus

$$\begin{aligned}\frac{dI(t)}{dt} &= \frac{d}{dt}\int_0^t \alpha(t-u)kV(u)T(u)e^{-(\alpha(t-u)+r\int_0^{t-u} E(u+\ell)\,d\ell)}\,du \\ &= \int_0^t kV(u)T(u)e^{-(\alpha(t-u)+r\int_0^{t-u} E(u+\ell)\,d\ell)}\left[\alpha - (\alpha + rE(t))\alpha(t-u)\right]\,du \\ &= \alpha Y(t) - \alpha I(t) - rE(t)I(t).\end{aligned}$$

For this case, we remove the assumption that $p(a) \in L^\infty$, and let $p(a) = p\alpha a$. Also, we generalize the constant parameter q to the age-dependent function $q(a) = q_1 + q_2\alpha a$. Then,

$$\begin{aligned}\frac{dV(t)}{dt} &= p\int_0^\infty \alpha a T^*(t,a)\,da - \gamma V(t) = pI(t) - \gamma V(t), \\ \frac{dE(t)}{dt} &= rE(t)\int_0^\infty (q_1 + q_2\alpha a)T^*(t,a)da - \mu E(t) = rE(t)(q_1Y(t) + q_2I(t)) - \mu E(t)\end{aligned}$$

Now to reduce the dimension of the system we make the quasi-steady state approximation $V(t) \approx \frac{p}{\gamma}I(t)$, a common assumption for within-host virus models. Let $\beta := k\frac{p}{\gamma}$ and then the following ODE system is obtained:

$$\begin{aligned}\frac{dT}{dt} &= s - cT - \beta IT \\ \frac{dY}{dt} &= \beta IT - \alpha Y - rEY \\ \frac{dI}{dt} &= \alpha Y - \alpha I - rEI \\ \frac{dE}{dt} &= rE(q_1Y + q_2I) - \mu E\end{aligned}$$

This is a special case of the following ODE model:

$$\begin{aligned}\frac{dT}{dt} &= s - cT - \beta IT \\ \frac{dY}{dt} &= \beta IT - \alpha Y - \eta Y - r_1EY \\ \frac{dI}{dt} &= \alpha Y - \nu I - r_2EI \\ \frac{dE}{dt} &= E(q_1r_1Y + q_2r_2I) - \mu E.\end{aligned} \tag{10}$$

Here $Y(t)$ can be thought of as infected cells in the eclipse (non-productive) phase and $I(t)$ are the infected cells in the productive stage. The immune effector cells can recognize infected cells in both phases with r_1 being the killing rate during the eclipse phase and r_2 the killing rate during the productive phase of the infected cell. Inclusion of an eclipse phase in the standard ODE virus model has been considered in various works [9, 2, 33, 47]. In particular, Zhou et al. [47] studied system

(10) without immune recognition of infected cells in eclipse phase ($r_1 = 0$) and an additional term allowing infected cells to transition back to healthy cells from the eclipse stage. They classified the global dynamics in such a system and found that the positive equilibrium is globally asymptotically stable under the appropriate conditions. Specifically, if we consider system (10) with $r_1 = 0$, then the unique positive equilibrium $\overline{y_2} = (\overline{T}, \overline{Y}, \overline{I}, \overline{E})$ is globally stable whenever it exists (in the positive orthant). We will show that letting $r_1 > 0$ can destabilize this equilibrium through a Hopf bifurcation. We also remark that Althaus et al. [2] considered the standard virus model with eclipse phase and *implicit* inclusion of "early" and "late" killing by immune effectors, i.e. they did not consider an E variable and assumed that the immune response simply alters η or ν.

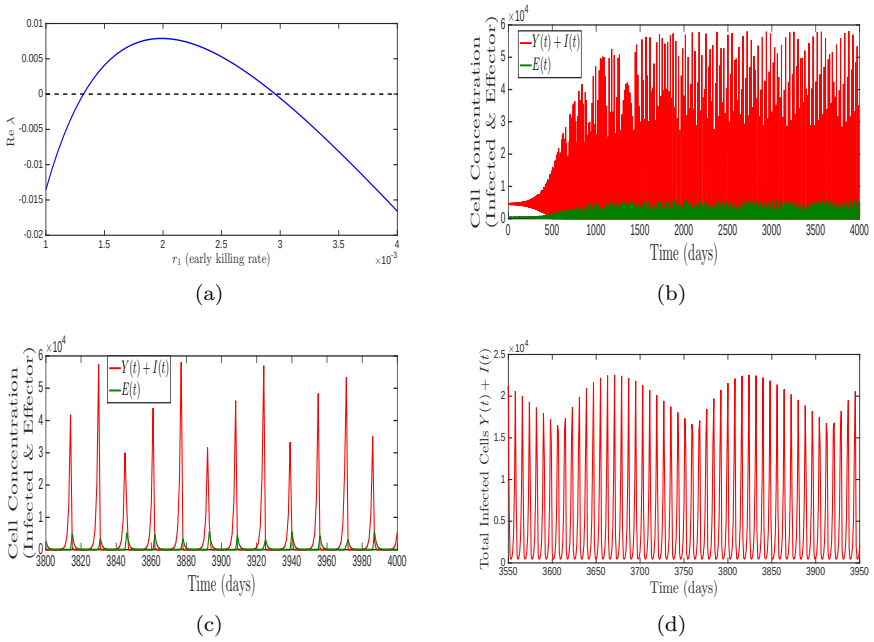


FIGURE 2. *Sustained oscillations in ODE model of "early immune recognition and killing" (system (10)).* (a) The real part of the pair of complex eigenvalues $\lambda = a \pm bi$ with maximal real part, Reλ, of the Jacobian (11) corresponding to the positive equilibrium $\overline{x}_2$ as r_1 varies. A Hopf bifurcation occurs at $r_1 \approx 0.0014$ ml d^{-1} and Re$\lambda > 0$ for $r_1 \in [0.0014, 0.003]$. (b,c) Simulation of the solution to (10) when $r_1 = 0.002$ ml d^{-1}. (d) Asymptotic periodic solution in the case $r_1 = 0.0015$ ml d^{-1}. In all simulations, the remaining parameters are: $s = 10^4$ ml^{-1} d^{-1}, $c = \eta = 0.01$ d^{-1}, $\nu = 0.7$ d^{-1}, $\alpha = 0.5$ d^{-1}, $\beta = 1.29 \times 10^{-5}$ ml d^{-1}, $q_1 = q_2 = 0.1$, $r_2 = 0.003$ ml d^{-1}.

Analogous to the general age-structured model (1), we can define the following reproductive numbers for the ODE system (10) (which are consistent with findings

in [33, 47]):

$$\mathcal{R}_0 = \frac{s\beta\alpha}{c(\alpha+\eta)\nu}, \qquad \text{where } \beta = \frac{kp}{\gamma},$$
$$\mathcal{R}_E = \frac{sq_1r_1}{\mu(\alpha+\eta)}\left(1+\frac{\alpha}{\nu}\frac{q_2r_2}{q_1r_1}\right),$$
$$\mathcal{R}_1 = \left(1-\frac{1}{\mathcal{R}_0}\right)\mathcal{R}_E.$$

Then it can be shown that there exists a immune-free infection steady state $\overline{x}_1 = \left(\bar{T}_1, \bar{Y}_1, \bar{I}_1, 0\right)$ (with $\bar{T}_1, \bar{Y}_1, \bar{I}_1 > 0$) when $\mathcal{R}_0 > 1$. And there exists a positive steady state $\overline{x}_2 = \left(\bar{T}, \bar{Y}, \bar{I}, \bar{E}\right)$ (with $\bar{T}, \bar{Y}, \bar{I}, \bar{E} > 0$) when $\mathcal{R}_1 > 1$. The Jacobian of the system (10) at the equilibrium $\overline{x}_2$ is:

$$J = \begin{pmatrix} -c-\beta\bar{I} & 0 & -\beta\bar{T} & 0 \\ \beta\bar{I} & -\eta-\alpha-r_1\bar{E} & \beta\bar{T} & -r_1\bar{Y} \\ 0 & \alpha & -\nu-r_2\bar{E} & -r_2\bar{I} \\ 0 & q_1r_1\bar{E} & q_2r_2\bar{E} & 0 \end{pmatrix} \tag{11}$$

The characteristic polynomial of J, $\det(\lambda I - J)$, is generally a quartic polynomial in λ where some coefficients are complicated expressions of the model parameters. Thus it seems too difficult to analytically prove whether or not a Hopf bifurcation occurs with respect to the parameter r_1. However, we numerically calculate the equilibrium $\overline{x}_2$, along with the eigenvalues of (11), while varying r_1 and find that a Hopf bifurcation occurs. In particular, for the chosen parameters in Figure 2(a), as r_1 increases past approximately 0.0014, the real part of the pair of complex eigenvalues with maximal real part goes from negative to positive, and then becomes negative again after $r_1 \approx 0.003$. This signals that a Hopf bifurcation occurs at $r_1 \approx 0.0014$, with oscillatory dynamics in the parameter range $r_1 \in [0.0014, 0.003]$, as opposed to a stable attractive equilibrium for values of r_1 outside this range. The sustained oscillations are illustrated in Figure 2.

5. **Extension to multiple immune effector populations.** In this section, we extend the age-structured model (1) to include multiple distinct immune effector populations. Consider the following general model for the interaction of multiple variants of immune effector cells and a virus population, with age-since-infection structure in the infected cell compartment:

$$\begin{aligned} \frac{dT(t)}{dt} &= s - cT - kV(t)T(t), \\ \frac{\partial T^*(t,a)}{\partial t} + \frac{\partial T^*(t,a)}{\partial a} &= -\delta(a)T^*(t,a) - T^*(t,a)\sum_{j=1}^{m} r_j(a)E_j(t), \\ T^*(t,0) &= kV(t)T(t), \\ \frac{dV(t)}{dt} &= \int_0^\infty p(a)T^*(t,a)\,da - \gamma V(t), \\ \frac{dE_j(t)}{dt} &= q_jE_j(t)\int_0^\infty r_j(a)T^*(t,a)\,da - \mu_jE_j(t), \quad j = 1,\dots,n. \end{aligned} \tag{12}$$

This is a generalization of the ODE model:

$$\frac{dT(t)}{dt} = s - cT - kV(t)T(t),$$

$$\begin{aligned}
\frac{dT^*(t)}{dt} &= kV(t)T(t) - \delta T^*(t) - T^*(t)\sum_{j=1}^{m} r_j E_j(t), \qquad (13)\\
\frac{dV(t)}{dt} &= pT^*(t) - \gamma V(t),\\
\frac{dE_j(t)}{dt} &= q_j r_j T^*(t) E_j(t) - \mu_j E_j(t), \quad j = 1, \dots, n.
\end{aligned}$$

Assume, without loss of generality that

$$\frac{q_1 r_1}{\mu_1} \geq \frac{q_2 r_2}{\mu_2} \geq \cdots \geq \frac{q_n r_n}{\mu_n}.$$

In system (13), multiple variants of immune response can not coexist in the asymptotic dynamics, except in the degenerate case where $\frac{q_1 r_1}{\mu_1} = \frac{q_2 r_2}{\mu_2}$. Indeed, consider the function $W_j(t) := E_j^{q_1 r_1}/E_1^{q_j r_j}$ for each $j = 2, \dots, n$. Calculating the time derivative, we find:

$$\begin{aligned}
\frac{dW_j(t)}{dt} &= \frac{E_j(t)^{q_1 r_1}}{E_1(t)^{q_j r_j}} \left(q_1 r_1 \frac{\dot{E}_j(t)}{E_j(t)} - q_j r_j \frac{\dot{E}_1(t)}{E_1} \right)\\
&= W_j(t) \left(q_1 r_1 (q_j r_j T^*(t) - \mu_j) - q_j r_j (q_1 r_1 T^*(t) - \mu_1) \right)\\
&= W_j(t) \left(q_j r_j \mu_1 - q_1 r_1 \mu_j \right)
\end{aligned}$$

Since in the non-degenerate case $\frac{q_1 r_1}{\mu_1} > \frac{q_j r_j}{\mu_j}$, we obtain that $W_j(t) \to 0$ exponentially which implies $E_j(t) \to 0$ for $j = 2, \dots, n$. Thus coexistence can not occur in this model. Note that it is not hard to prove that E_1 persists if the reproduction number, $\mathcal{R}_1$, is larger than 1 (where $\mathcal{R}_1$ is defined as before, here with respect to E_1) and, hence, E_1 competitively excludes the other variants.

We will show that the addition of cell infection-age a and immune recognition rates $r_i(a)$ which are functions of a can induce coexistence of multiple variants. For simplicity, consider the case of two immune variants. Let $\overline{E}_1$, $\overline{E}_2$ be positive components corresponding to distinct immune variants in a coexistence equilibrium $\overline{x}_2 = \left(\overline{T}, \overline{T}^*(a), \overline{V}, \overline{E}_1, \overline{E}_2\right)$. The following relations are obtained by setting the LHS of (12) equal to zero:

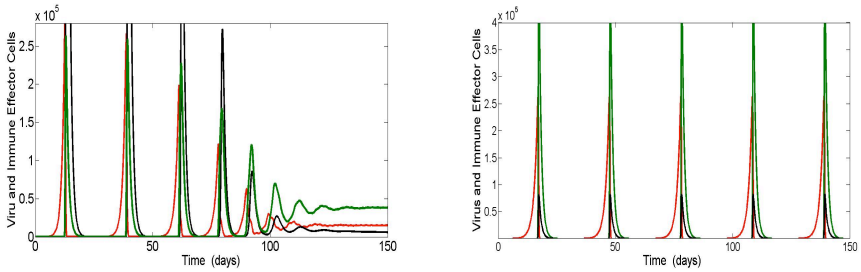
$$\begin{aligned}
\int_0^\infty r_i(a)\overline{T}^*(a)\, da &= \frac{\mu_i}{q_i}, \quad i = 1, 2\\
k\overline{T}\int_0^\infty p(a)\overline{T}^*(a)\, da &= \gamma,\\
\overline{T}^*(a) &= k\overline{V}\overline{T}\phi(a)\exp\left(-\int_0^a \sum r_i(\ell)\overline{E}_i\, d\ell \right)\\
k\overline{V}\overline{T} &= s - c\overline{T}.
\end{aligned}$$

Utilizing these relations, we arrive at the following system of two equations for $\overline{E}_1$, $\overline{E}_2$:

$$s - \frac{c\gamma}{k\int_0^\infty p(a)\phi(a)e^{-\int_0^a \sum r_i(\ell)\overline{E}_i d\ell}\, da} = \frac{\mu_i}{q_i \int_0^\infty r_i(a)\phi(a)e^{-\int_0^a \sum r_i(\ell)\overline{E}_i d\ell}\, da} \qquad (14)$$

Subtracting the two equations and rearranging, we can obtain the following formula:

$$\int_0^\infty \phi(a)\exp\left(-\int_0^a \sum r_i(\ell)\overline{E}_i\, d\ell \right)\left[\frac{\mu_1}{q_1} r_2(a) - \frac{\mu_2}{q_2} r_1(a) \right] da = 0 \qquad (15)$$



(a) (b)

FIGURE 3. With two immune effector variants (green and black), the cell infection age-structure can lead to co-existence as stable equilibrium (a) or sustained oscillations (b).

Clearly, if $\frac{q_1 r_1(a)}{\mu_1} < (>) \frac{q_2 r_2(a)}{\mu_2}$ for all $a \in [0, \infty)$, then the coexistence equilibrium is not possible.

Now we consider the special case where $\delta(a) = \delta_1 \mathbb{1}_{(0,\tau)} + \delta_2 \mathbb{1}_{(\tau,\infty)}$, $p(a) = p\mathbb{1}_{(\tau,\infty)}$, $r_1(a) = r_1 \mathbb{1}_{(\sigma,\tau)}$ and $r_2(a) = r_2 \mathbb{1}_{(\tau,\infty)}$. Inserting these functional forms into (15) and simplifying yields:

$$\delta_2 + r_2 \overline{E}_2 = \frac{\mu_1 q_2 r_2 (\delta_1 + r_1 \overline{E}_1)}{\mu_2 q_1 r_1 \left(e^{(\delta_1 + r_1 \overline{E}_1)(\tau - \sigma)} - 1 \right)} \tag{16}$$

Now by the first equation in (14), we find that:

$$s - \frac{c\gamma \mu_1 q_2 r_2 (\delta_1 + r_1 \overline{E}_1)}{pk\mu_2 q_1 r_1 e^{-\delta_1 \sigma} \left(1 - e^{-(\delta_1 + r_1 \overline{E}_1)(\tau - \sigma)} \right)} = \frac{\mu_1 (\delta_1 + r_1 \overline{E}_1)}{q_1 r_1 \left(1 - e^{-(\delta_1 + r_1 \overline{E}_1)(\tau - \sigma)} \right)}$$

Define $f(z) = s - \frac{c\gamma \mu_1 q_2 r_2}{pk\mu_2 q_1 r_1} h(z)$ and $g(z) = \frac{\mu_1}{q_1 r_1} h(z)$ where $h(z) = \frac{z}{1 - e^{-(\tau - \sigma) z}}$. Thus the equilibrium condition is $f(\delta_1 + r_1 \overline{E}_1) = g(\delta_1 + r_1 \overline{E}_1)$. It can be shown that $h'(z) > 0$ for $z > 0$. Therefore $f'(z) < 0$ and $g'(z) > 0$ for $z > 0$. Hence, a positive equilibrium component $\overline{E}_1$ exists (and is unique) if and only if:

$$\begin{aligned} \overline{E}_1 > 0 &\Leftrightarrow f(\delta_1) > g(\delta_1) \\ &\Leftrightarrow s - \frac{c\gamma \mu_1 q_2 r_2 \delta_1}{pk\mu_2 q_1 r_1 e^{-\delta_1 \sigma} (1 - e^{-(\tau - \sigma)\delta_1})} > \frac{\mu_1 \delta_1}{q_1 r_1 (1 - e^{-(\tau - \sigma)\delta_1})} \\ &\Leftrightarrow \frac{1 - e^{-(\tau - \sigma)\delta_1}}{\delta_1} > \frac{\mu_1}{s q_1 r_1} \left(\frac{c\gamma q_2 r_2}{pk\mu_2 e^{-\delta_1 \sigma}} + 1 \right) \end{aligned} \tag{17}$$

By (16), we have that

$$\overline{E}_2 = \frac{\mu_1 q_2 (\delta_1 + r_1 \overline{E}_1)}{\mu_2 q_1 r_1 \left(e^{(\delta_1 + r_1 \overline{E}_1)(\tau - \sigma)} - 1 \right)} - \frac{\delta_2}{r_2} \tag{18}$$

Thus if (17) is satisfied and (18) is positive, then there is a coexistence equilibrium. Notice that if (17) is satisfied, then for δ_2 sufficiently small, (18) is positive and a coexistence equilibrium will exist.

The ODE version of this extended model, system (13), has been discussed as a pitfall for assuming mass-action killing and proliferation when explicitly modeling immune response [12, 46], since there is competitive exclusion by the dominant immune

effector population which conflicts with the observed presence of sub-dominant responses [1, 18]. The preceding argument shows the existence of a (immune effector) coexistence equilibrium for certain parameters in the age-structured PDE model (12). Thus, by adding the biologically motivated infected cell age-structure, we can obtain coexistence of different CTL clones responding to distinct epitopes, which is observed in reality. The result can be interpreted in ecological terms. Two species can not occupy the same niche, but by including the infected cell age-structure, the two immune cell populations can specialize in attacking different parts of the infected cell lifecycle. Numerical simulations confirm the coexistence equilibrium, and also show that this equilibrium can either be stable or unstable with sustained oscillations, as displayed in Figure 3.

6. **Discussion.** In this article we have considered a within-host virus model with cellular infection-age structure and immune effectors. The infection-age structure allows for general intracellular delays and the immune effector population dynamics can describe the CTL immune response upon interaction with epitopes presented on the surface of infected cells. Both features have often been included in virus models, but the general dependence of immune epitope recognition on cellular infection age in our model ($r(a)$) is novel and motivated by recent experiments. In particular, recent research [19] has shown that certain CTL populations can recognize infected cells early within a few hours of infection well before viral production, whereas other epitopes are only effective after viral production. The experiments show "early recognition" CTLs to be especially effective immune responders.

In our general model (1), we find three types of equilibria: virus-free equilibrium $\overline{x}_0$, immune-free virus equilibrium $\overline{x}_1$, and immune-controlled virus equilibrium $\overline{x}_2$. Two reproduction numbers determine threshold dynamics: basic reproduction number $\mathcal{R}_0$ and immune reproduction number (at viral steady state) $\mathcal{R}_1$. We proved: (i) if $\mathcal{R}_0 < 1$, then the virus-free equilibrium $\overline{x}_0$ is globally asymptotically stable; (ii) if $\mathcal{R}_1 < 1 < \mathcal{R}_0$, then $\overline{x}_0$ is unstable, and the immune-free virus equilibrium $\overline{x}_1$ exists and is locally asymptotically stable; (iii) if $\mathcal{R}_1 > 1$, then $\overline{x}_1$ (and $\overline{x}_0$) is unstable and the immune-controlled virus equilibrium $\overline{x}_2$ exists. Furthermore, we establish the following persistence results: (iv) if $\mathcal{R}_0 > 1$, then the virus is uniformly persistent; (v) if $\mathcal{R}_1 > 1$, then the entire system (virus and immune response) is uniformly persistent.

In the particular case of piecewise constant age-dependent parameters, numerical simulations show that decreasing σ, the infection-age when epitopes are first recognized, causes an increase in the healthy cell population for the equilibrium $\overline{x}_2$. This is in agreement with experimental results showing the importance of early-presented viral epitopes for rapid elimination of HIV-1-infected cells [19]. Interestingly, in the numerical simulations, decreasing σ past a critical value $\sigma^* < \tau$, where τ is the intracellular delay in viral production, causes $\overline{x}_2$ to undergo a Hopf bifurcation and sustained oscillations occur for $\sigma < \sigma^*$. In addition, we numerically show that this Hopf bifurcation also occurs in a simpler stage-structured ODE model with respect to the rate of immune killing of infected cells in their eclipse phase. In contrast, previous works assume immune recognition exclusively of virus producing infected cells and have found globally stable equilibria [35, 47]. Thus, early immune recognition of epitopes is a fundamental mechanism causing sustained oscillations in within-host virus models. We also find that extending our model to multiple cellular infection-age dependent immune responses can induce coexistence of immune effector populations.

There are several directions for future research related to our work in this paper. Data indicates a dose-response dependency between the levels of "early recognition" CTL activation and the amount of virus inoculum involved in HIV cell infection [4, 19]. Thus, we may consider the immune recognition rate to be a function of cellular infection-age and viral load at infection, i.e. $r(a, V(t-a))$. In addition, latently infected cells remain the largest barrier to eradication of HIV and there is experimental evidence that "early recognition" CTLs can reduce the latent reservoir [8]. We will include latently infected cells in our model to assess this effect. Finally, an extended version of model (12) with, both, multiple immune and viral variants would be difficult to analyze, but may offer insights into an optimal immune response in a diverse, evolving host immune-virus system.

REFERENCES

[1] A. Akram and R. D. Inman, Immunodominance: A pivotal principle in host response to viral infections, *Clinical Immunology*, **143** (2012), 99–115.

[2] C. L. Althaus and R. J. De Boer, Implications of ctl-mediated killing of hiv-infected cells during the non-productive stage of infection, *PLoS One*, **6** (2011), e16468–e16468.

[3] C. L. Althaus, A. S. De Vos and R. J. De Boer, Reassessing the human immunodeficiency virus type 1 life cycle through age-structured modeling: life span of infected cells, viral generation time, and basic reproductive number, r0, *Journal of Virology*, **83** (2009), 7659–7667.

[4] A. Balamurugan, A. Ali, J. Boucau, S. Le Gall, H. L. Ng and O. O. Yang, Hiv-1 gag cytotoxic t lymphocyte epitopes vary in presentation kinetics relative to hla class i downregulation, *Journal of Virology*, **87** (2013), 8726–8734.

[5] H. T. Banks, D. M. Bortz and S. E. Holte, Incorporation of variability into the modeling of viral delays in hiv infection dynamics, *Mathematical Biosciences*, **183** (2003), 63–91.

[6] C. J. Browne, A multi-strain virus model with infected cell age structure: Application to hiv, *Nonlinear Analysis: Real World Applications*, **22** (2015), 354–372.

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

[8] R. W. Buckheit III, R. F. Siliciano and J. N. Blankson, Primary cd8+ t cells from elite suppressors effectively eliminate non-productively hiv-1 infected resting and activated cd4+ t cells, *Retrovirology*, **10** (2013), 1–12.

[9] B. Buonomo and C. Vargas-De-León, Global stability for an hiv-1 infection model including an eclipse stage of infected cells, *Journal of Mathematical Analysis and Applications*, **385** (2012), 709–720.

[10] D. Y. Chen, A. Balamurugan, H. L. Ng, W. G. Cumberland and O. O. Yang, Epitope targeting and viral inoculum are determinants of nef-mediated immune evasion of hiv-1 from cytotoxic t lymphocytes, *Blood*, **120** (2012), 100–111.

[11] R. V Culshaw and S. Ruan, A delay-differential equation model of hiv infection of cd4+ t-cells, *Mathematical Biosciences*, **165** (2000), 27–39.

[12] R. J. De Boer, Which of our modeling predictions are robust, *PLoS Comput. Biol.*, **8** (2012), e1002593, 5pp.

[13] R. D. Demasse and A. Ducrot, An age-structured within-host model for multistrain malaria infections, *SIAM Journal on Applied Mathematics*, **73** (2013), 572–593.

[14] A. Ducrot, Z. Liu and P. Magal, Essential growth rate for bounded linear perturbation of non-densely defined cauchy problems, *Journal of Mathematical Analysis and applications*, **341** (2008), 501–518.

[15] M. A. Gilchrist, D. Coombs and A. S. Perelson, Optimizing within-host viral fitness: Infected cell lifespan and virion production rate, *Journal of Theoretical Biology*, **229** (2004), 281–288.

[16] J. K. Hale and P. Waltman, Persistence in infinite-dimensional systems, *SIAM Journal on Mathematical Analysis*, **20** (1989), 388–395.

[17] G. Huang, X. Liu and Y. Takeuchi, Lyapunov functions and global stability for age-structured hiv infection model, *SIAM Journal on Applied Mathematics*, **72** (2012), 25–38.

[18] W. Kastenmuller, G. Gasteiger, J. H. Gronau, R. Baier, R. Ljapoci, D. H. Busch and I. Drexler, Cross-competition of cd8+ t cells shapes the immunodominance hierarchy during boost vaccination, *The Journal of Experimental Medicine*, **204** (2007), 2187–2198.

[19] H. N. Kløverpris, R. P. Payne, J. B. Sacha, J. T. Rasaiyaah, F. Chen, M. Takiguchi, O. O. Yang, G. J. Towers, P. Goulder and J. G. Prado, Early antigen presentation of protective hiv-1 kf11gag and kk10gag epitopes from incoming viral particles facilitates rapid recognition of infected cells by specific cd8+ t cells, *Journal of Virology*, **87** (2013), 2628–2638.

[20] X. Lai and X. Zou, Dynamics of evolutionary competition between budding and lytic viral release strategies, *Mathematical Biosciences and Engineering: MBE*, **11** (2014), 1091–1113.

[21] M. Y. Li and H. Shu, Global dynamics of an in-host viral model with intracellular delay, *Bulletin of Mathematical Biology*, **72** (2010), 1492–1505.

[22] P. Magal, C. C. McCluskey and G. F. Webb, Lyapunov functional and global asymptotic stability for an infection-age model, *Applicable Analysis*, **89** (2010), 1109–1140.

[23] P. Magal, Compact attractors for time periodic age-structured population models, *Electronic Journal of Differential Equations*, **2001** (2001), 1–35.

[24] P. Magal and X.-Q. Zhao, Global attractors and steady states for uniformly persistent dynamical systems, *SIAM Journal on Mathematical Analysis*, **37** (2005), 251–275.

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

[26] P. W. Nelson and A. S. Perelson, Mathematical analysis of delay differential equation models of hiv-1 infection, *Mathematical Biosciences*, **179** (2002), 73–94.

[27] M. A. Nowak and C. R. M. Bangham, Population dynamics of immune responses to persistent viruses, *Science*, **272** (1996), 74–79.

[28] M. A. Nowak, R. M. May and K. Sigmund, Immune responses against multiple epitopes, *Journal of Theoretical Biology*, **175** (1995), 325–353.

[29] R. P. Payne, H. Kløverpris, J. B. Sacha, Z. Brumme, C. Brumme, S. Buus, S. Sims, S. Hickling, L. Riddell, F. Chen, et al, Efficacious early antiviral activity of hiv gag-and pol-specific hla-b* 2705-restricted cd8+ t cells, *Journal of Virology*, **84** (2010), 10543–10557.

[30] A. S. Perelson and P. W. Nelson, Mathematical analysis of hiv-1 dynamics in vivo, *SIAM Review*, **41** (1999), 3–44.

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

[32] L. Rong, Z. Feng and A. S. Perelson, Mathematical analysis of age-structured hiv-1 dynamics with combination antiretroviral therapy, *SIAM Journal on Applied Mathematics*, **67** (2007), 731–756.

[33] L. Rong, M. A. Gilchrist, Z. Feng and A. S. Perelson, Modeling within-host hiv-1 dynamics and the evolution of drug resistance: Trade-offs between viral enzyme function and drug susceptibility, *Journal of Theoretical Biology*, **247** (2007), 804–818.

[34] J. B. Sacha, C. Chung, E. G. Rakasz, S. P. Spencer, A. K. Jonas, A. T. Bean, W. Lee, B. J. Burwitz, J. J. Stephany, J. T. Loffredo, et al, Gag-specific cd8+ t lymphocytes recognize infected cells before aids-virus integration and viral protein expression, *The Journal of Immunology*, **178** (2007), 2746–2754.

[35] H. Shu, L. Wang and J. Watmough, Global stability of a nonlinear viral infection model with infinitely distributed intracellular delays and ctl immune responses, *SIAM Journal on Applied Mathematics*, **73** (2013), 1280–1302.

[36] H. Smith, *An Introduction to Delay Differential Equations with Applications to the Life Sciences*, volume 57. Springer Science & Business Media, 2011.

[37] H. L. Smith and P. De Leenheer, Virus dynamics: A global analysis, *SIAM Journal on Applied Mathematics*, **63** (2003), 1313–1327.

[38] X. Song, S. Wang and J. Dong, Stability properties and hopf bifurcation of a delayed viral infection model with lytic immune response, *Journal of Mathematical Analysis and Applications*, **373** (2011), 345–355.

[39] H. R. Thieme, Integrated semigroups and integrated solutions to abstract cauchy problems, *Journal of Mathematical Analysis and Applications*, **152** (1990), 416–447.

[40] H. R. Thieme, Quasi-compact semigroups via bounded perturbation, *Advances in Mathematical Population Dynamics-Molecules, Cells and Man., Volume 6, Worlds Scientific*, pages 691–711, 1997.

[41] H. R. Thieme et al, Semiflows generated by lipschitz perturbations of non-densely defined operators, *Differential and Integral Equations*, **3** (1990), 1035–1066.

[42] B. D. Walker and G. Y. Xu, Unravelling the mechanisms of durable control of hiv-1, *Nature Reviews Immunology*, **13** (2013), 487–498.
[43] K. Wang, W. Wang, H. Pang and X. Liu, Complex dynamic behavior in a viral model with delayed immune response, *Physica D: Nonlinear Phenomena*, **226** (2007), 197–208.
[44] Y. Wang, Y. Zhou, F. Brauer and J. M. Heffernan, Viral dynamics model with ctl immune response incorporating antiretroviral therapy, *Journal of Mathematical Biology*, **67** (2013), 901–934.
[45] G. F. Webb, *Theory of Nonlinear Age-Dependent Population Dynamics*, CRC Press, 1985.
[46] D. Wodarz, Ecological and evolutionary principles in immunology, *Ecology Letters*, **9** (2006), 694–705.
[47] S. Zhou, Z. Hu, W. Ma and F. Liao, Dynamics analysis of an hiv infection model including infected cells in an eclipse stage, *Journal of Applied Mathematics*, (2013), Art. ID 419593, 12 pp.

Received October 22, 2015; Accepted April 09, 2016.

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