

GLOBAL ANALYSIS OF WITHIN HOST VIRUS MODELS WITH CELL-TO-CELL VIRAL TRANSMISSION

ABSTRACT. Recent experimental studies have shown that HIV can be transmitted directly from cell to cell when structures called virological synapses form during interactions between T cells. In this article, we describe a new within-host model of HIV infection that incorporates two mechanisms: infection by free virions and the direct cell-to-cell transmission. We conduct the local and global stability analysis of the model. We show that if the basic reproduction number $\mathcal{R}_0 \leq 1$, the virus is cleared and the disease dies out; if $\mathcal{R}_0 > 1$, the virus persists in the host. We also prove that the unique positive equilibrium attracts all positive solutions under additional assumptions on the parameters. Finally, a multi strain model incorporating cell-to-cell viral transmission is proposed and shown to exhibit a competitive exclusion principle.

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This paper is dedicated to Chris Cosner, on the occasion of his 60th birthday.

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1. Introduction. Mathematical modeling of within host virus models has flourished over the past few decades. These models have been used to describe the dynamics inside the host of various infectious diseases such as HIV, HCV, HTLV, as well as the flu or even the malaria parasite. Testing specific hypotheses based on clinical data is often difficult since samples cannot always be taken too frequently from patients, or because detection techniques of the virus may not be accurate. This justifies the central role played by mathematical models in this area of research.

One of the early models, known as the standard model and reviewed in the next section, was used by Nowak and May [16], and by Perelson and Nelson [17] to model HIV. It was successful in numerically reproducing the dynamics of the early stages of HIV and its target, the $CD4^+$ T cells, following an infection event. The global behavior of the standard model was first investigated analytically in [2]. Here, the global stability of the disease steady state was proved using the powerful second compound matrix methods developed by Muldowney [15] and by Li and Muldowney [10]. Among the first successes of this geometrical method was the long

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sought-after proof of global stability in the classical epidemiological SEIR model [11]. Since epidemic models and within host virus models are structurally similar, it should not come as a surprise that the geometrical methods of [10, 15] are at the basis of the global stability proof of the standard model in [2].

It is well-known from the converse Lyapunov theorem [7], that whenever a non-linear system of ODEs has a globally stable steady state, that then there exists a global Lyapunov function. Korobeinikov in [8] was the first to discover a Lyapunov function in the context of SEIR and SEIS models. Korobeinikov's Lyapunov function was exploited further in [3] to establish global stability for the standard model under relaxed conditions for the model parameters, as well as for within host virus models with multiple, possibly mutating, strains.

Although our discussion so far was focused on the global stability of certain steady states, it has been demonstrated that more complex dynamical behavior, in particular taking the form of sustained oscillations, may arise in the standard model for specific proliferation rates of healthy cells [2, 24], or under the assumption that infected cells proliferate as well [23], a feature which is not encoded in the standard model.

Based on more recent findings about additional infection processes, it is the main goal of this paper to extend the standard model in two ways:

1. In the standard model it is assumed that healthy cells can only be infected by viruses. However, recent work shows that cell-to-cell transmission of viruses also occurs when a healthy cell comes into contact with an infected cell [18]. In fact, in vitro experiments reported in [21] have shown that in shaken cultures, viral transfer via cell-to-cell contact is much more rapid and efficient than infection by free virus because it avoids several biophysical and kinetic barriers. In vivo, direct cell-to-cell transmission is also more potent and more efficient according to [14]. The details of the infection mechanism via cell-to-cell contact are described in [13, 14, 19] and have been attributed to the formation of virological synapses (VSs), filopodia and nanotubes. The model proposed here deviates from, and in fact, expands the standard model, by including the additional cell-to-cell infection mechanism.
2. According to the standard model, viruses do not enter previously infected cells, although most HIV infected splenocytes for example, are found to be multiply infected [4]. Moreover, the loss of virus upon entry of a healthy cell, has often been neglected in the literature. The model we propose here, accounts for both processes.

2. The mathematical model. The standard model of a within-host virus infection [16, 17] is

$$\begin{cases} \dot{T} = f(T) - kVT, \\ \dot{T}^* = kVT - \beta T^*, \\ \dot{V} = N\beta T^* - \gamma V \quad (-kVT), \end{cases}$$

where the term in the parentheses may or may not be present.

Our mathematical model has the following form:

$$\begin{cases} \dot{T} = f(T) - k_1VT - k_2TT^*, \\ \dot{T}^* = k_1VT + k_2TT^* - \beta T^*, \\ \dot{V} = N\beta T^* - \gamma V - k_3VT - k_4VT^*. \end{cases} \quad (1)$$

where T, T^* and V denote the concentrations of uninfected host cells, infected host cells and free virus particles, respectively. Parameters k_1, k_2, β, N and γ are all positive constants. k_1 is the contact rate between uninfected cells and viruses. k_2 is the contact rate between uninfected cells and infected cells. The parameters β and γ represent the death rate of infected cells and virus particles, respectively. In the case of budding viruses, N is the average number of virus particles produced by an infected cell during its lifetime; in case of lytic viruses, N represents the average burst size of an infected cell. The parameter k_3 models the rate of absorption of free virions into healthy cells during the infection process. In some instances, this term has been neglected [16, 17]. The parameter k_4 models the absorption of free virions into already infected cells, a process which may be biologically relevant for some viruses, yet in each case it will be determined by the specific mechanism of the viral cell entry [4].

The growth rate of the uninfected cell population is modeled by the smooth function $f : \mathbb{R}_+ \rightarrow \mathbb{R}$, which is assumed to satisfy the following:

$$\exists T_0 > 0 : f(T)(T - T_0) < 0, \quad \forall T \neq T_0, \quad \text{and} \quad f'(T) < 0 \quad \forall T \in [0, T_0]. \quad (2)$$

The continuity of f implies that $f(T_0) = 0$, and hence $E_0 = (T_0, 0, 0)$ is an equilibrium point of system (1). Biologically, E_0 represents the disease-free equilibrium.

The Jacobian matrix of (1) at E_0 is

$$J_0 = \begin{bmatrix} f'(T_0) & -k_2 T_0 & -k_1 T_0 \\ 0 & k_2 T_0 - \beta & k_1 T_0 \\ 0 & N\beta & -\gamma - k_3 T_0 \end{bmatrix}.$$

The submatrix of J_0 corresponding to the infectious compartments can be split as follows:

$$J_{01} = \begin{bmatrix} k_2 T_0 - \beta & k_1 T_0 \\ N\beta & -\gamma - k_3 T_0 \end{bmatrix} = \begin{bmatrix} k_2 T_0 & k_1 T_0 \\ 0 & 0 \end{bmatrix} - \begin{bmatrix} \beta & 0 \\ -N\beta & \gamma + k_3 T_0 \end{bmatrix} =: F - V.$$

A quick calculation shows that the next generation matrix is given by

$$FV^{-1} = \begin{bmatrix} \frac{k_2 T_0}{\beta} + \frac{Nk_1 T_0}{\gamma + k_3 T_0} & \frac{k_1 T_0}{\gamma + k_3 T_0} \\ 0 & 0 \end{bmatrix}.$$

The basic reproductive number, \mathcal{R}_0 , is defined as the spectral radius of FV^{-1} [22], hence

$$\mathcal{R}_0 := \rho(FV^{-1}) = \frac{k_2 T_0}{\beta} + \frac{Nk_1 T_0}{\gamma + k_3 T_0}. \quad (3)$$

One eigenvalue of J_0 is given by $f'(T_0) < 0$, and the remaining two are also eigenvalues of J_{01} . The determinant of J_{01} is given by

$$\begin{aligned} \det J_{01} &= (\beta - k_2 T_0)(\gamma + k_3 T_0) - N\beta k_1 T_0 \\ &= \beta(\gamma + k_3 T_0) \left(1 - \frac{k_2 T_0}{\beta} - \frac{Nk_1 T_0}{\gamma + k_3 T_0} \right) \\ &= \beta(\gamma + k_3 T_0)(1 - \mathcal{R}_0). \end{aligned}$$

Consequently, if $\mathcal{R}_0 > 1$, then $\det J_{01} < 0$, and J_0 has a positive eigenvalue. If $\mathcal{R}_0 < 1$, then $\det J_{01} > 0$, and $k_2 T_0 < \beta$ which implies that $\text{tr} J_{01} < 0$, so that all eigenvalues of J_0 have negative real parts. We obtain our first result.

Theorem 2.1. *If $\mathcal{R}_0 < 1$, then E_0 is locally asymptotically stable; if $\mathcal{R}_0 > 1$, E_0 is unstable.*

A positive equilibrium $E = (\bar{T}, \bar{T}^*, \bar{V})$ must satisfy the following relations:

$$\beta \bar{T}^* = f(\bar{T}), \quad \bar{V} = \frac{Nf(\bar{T})}{\gamma + k_3\bar{T} + k_4\bar{T}^*}, \quad 1 = \frac{k_2\bar{T}}{\beta} + \frac{Nk_1\bar{T}}{\gamma + k_3\bar{T} + \frac{k_4f(\bar{T})}{\beta}} := G(\bar{T}).$$

The function G is monotonically increasing, since the first term is linear in \bar{T} , and the reciprocal of the second term

$$\frac{\gamma}{Nk_1\bar{T}} + \frac{k_3}{Nk_1} + \frac{k_4f(\bar{T})}{Nk_1\beta\bar{T}}$$

is strictly decreasing in \bar{T} when \bar{T} is in $(0, T_0)$, by (2). A positive equilibrium corresponds to a solution of $G(\bar{T}) = 1$ with $0 < \bar{T} < T_0$. Since $G(0) = 0$ and $G(T_0) = \mathcal{R}_0$, we conclude that a unique positive equilibrium exists if and only if $\mathcal{R}_0 > 1$.

Lemma 2.2. *If $\mathcal{R}_0 \leq 1$ the equilibrium E_0 is the only equilibrium of (1), and if $\mathcal{R}_0 > 1$ then E_0 and $E = (\bar{T}, \bar{T}^*, \bar{V})$ are the only two equilibria of (1).*

3. Preliminary results for the general model.

Lemma 3.1. *Every forward solution of (1) starting in \mathbb{R}_+^3 , is defined in \mathbb{R}_+^3 for all $t \geq 0$, and bounded. Furthermore, system (1) is uniformly dissipative in \mathbb{R}_+^3 .*

Proof. Positive invariance of \mathbb{R}_+^3 follows from the standard argument that the vector field of system (1) is inward pointing on the boundary of \mathbb{R}_+^3 . To show boundedness, fix a forward solution in \mathbb{R}_+^3 . Observe that the T -equation in (1) implies that $T(t) \leq M := \max(T_0, T(0))$ for all $t \geq 0$ as long as the solution is defined. Since $f(T)$ is bounded on $[0, M]$, there exist $A, B > 0$ such that $f(T) \leq A - BT$ for all $T \in [0, M]$. Choose a constant $0 < \alpha_1 < 1/N$ and consider an auxiliary function $U = T + T^* + \alpha_1 V$. Due to (1), we have

$$\dot{U} \leq f(T) - \beta(1 - \alpha_1 N)T^* - \alpha_1 \gamma V \leq A - BT - \beta(1 - \alpha_1 N)T^* - \alpha_1 \gamma V \leq A - \alpha_2 U,$$

where $\alpha_2 = \min(B, \beta(1 - \alpha_1 N), \gamma) > 0$. Hence, $U(t) \leq \max\left(U(0), \frac{A}{\alpha_2}\right)$ for all $t \geq 0$. This implies that the corresponding forward solution of (1) is bounded in \mathbb{R}_+^3 and exists for all $t \geq 0$.

From the above argument, it is clear that any solution of (1) in \mathbb{R}_+^3 eventually satisfies $T(t) \leq M_0 := T_0 + 1$, and therefore one can choose uniform constants $A_0, B_0 > 0$ so that the function $U(t)$ eventually satisfies the inequality $\dot{U} \leq A_0 - \alpha_0 U$ where $\alpha_0 = \min(B_0, \beta(1 - \alpha_1 N), \gamma) > 0$. Hence, any solution of (1) in \mathbb{R}_+^3 eventually enters a forward invariant simplex

$$D = \left\{ (T, T^*, V) \in \mathbb{R}_+^3 : T + T^* + \alpha_1 V \leq \frac{A_0}{\alpha_0} + 1 \right\}. \quad (4)$$

Hence, system (1) is uniformly dissipative in \mathbb{R}_+^3 . \square

At this point, we make the following (possibly trivial) remark: Consider any solution of (1) in \mathbb{R}_+^3 . If there exists a t_0 such that $T(t_0) < T_0$ then $T(t) < T_0$ for all $t \geq t_0$. Our next result provides the necessary and sufficient condition for the global stability of E_0 .

Theorem 3.2. *If $\mathcal{R}_0 \leq 1$ then the infection free equilibrium E_0 attracts all solutions in \mathbb{R}_+^3 .*

Proof. If $T(0) = 0$, then $\dot{T}(0) > 0$, so $T(t) > 0$ for all sufficiently small $t > 0$. If $T^*(t) = V(t) = 0$, then it is clear that $T(t) \rightarrow T_0$ as $t \rightarrow \infty$. If exactly one of $T^*(0)$ or $V(0)$ is zero, then its derivative at $t = 0$ is positive, and hence this variable is positive for all small $t > 0$. Furthermore, none of $T(t)$, $T^*(t)$ or $V(t)$ can decrease to zero in finite time, hence it suffices to consider only solutions with both $T^*(t)$ and $V(t)$ positive for all $t \geq 0$. We previously remarked that either $T(t) \geq T_0$ for all $t \geq 0$, or there exists a $t_0 \geq 0$ such that $T(t) < T_0$ for all $t > t_0$.

Consider the former case, that is, $T(t) \geq T_0$ for all $t \geq 0$. Then $\dot{T}(t) \leq 0$ for all $t \geq 0$, and $T(t) \rightarrow T_\infty \geq T_0$ as $t \rightarrow \infty$. Barbalat's Lemma implies that $\lim_{t \rightarrow \infty} \dot{T}(t) = 0$. Noticing that by (2), $f(T_\infty) \leq f(T_0) = 0$, we use the T -equation in (1), to conclude that $T_\infty = T_0$, and $\lim_{t \rightarrow \infty} T^*(t) = \lim_{t \rightarrow \infty} V(t) = 0$.

Now, suppose that there exists a $t_0 \geq 0$ such that $T(t) < T_0$ for all $t > t_0$. Without loss of generality, we may assume that $T(t) < T_0$ for all $t \geq 0$. We introduce an auxiliary function:

$$W = (\gamma + k_3 T_0) T^* + k_1 T_0 V, \quad (5)$$

and evaluate \dot{W} along a solution of (1):

$$\begin{aligned} \dot{W} &= (\gamma + k_3 T_0) \dot{T}^* + k_1 T_0 \dot{V} \\ &= (\gamma + k_3 T_0) (k_1 V T + k_2 T T^* - \beta T^*) + k_1 T_0 (N \beta T^* - \gamma V - k_3 V T - k_4 V T^*) \\ &= T^* (k_1 T_0 N \beta + (\gamma + k_3 T_0) (k_2 T - \beta)) \\ &\quad + V (k_1 T (\gamma + k_3 T_0) - k_1 T_0 (\gamma + k_3 T) - k_1 T_0 k_4 T^*) \\ &\leq \beta (\gamma + k_3 T_0) T^* (\mathcal{R}_0 - 1) + k_1 \gamma V (T - T_0) - k_1 k_4 T_0 V T^* \leq 0, \end{aligned}$$

where all three terms are non-positive. Therefore, there exists $\lim_{t \rightarrow \infty} W(t) = W_\infty \geq 0$. Barbalat's Lemma then implies that $\lim_{t \rightarrow \infty} \dot{W}(t) = 0$.

If $W_\infty = 0$, it is clear that $\lim_{t \rightarrow \infty} T^*(t) = \lim_{t \rightarrow \infty} V(t) = 0$ and $\lim_{t \rightarrow \infty} T(t) = T_0$.

If $W_\infty > 0$, then there exists $\Delta_1 > 0$ such that $k_1 V + k_2 T^* \geq \Delta_1 > 0$ for all sufficiently large t . The T -equation in (1) implies that $\dot{T} \leq f(T) - \Delta_1 T$, and thus there exists $\Delta_2 > 0$ such that $T(t) \leq T_0 - \Delta_2$ for all sufficiently large t . Since $\dot{W} \leq k_1 \gamma V (T - T_0) \leq -k_1 \gamma \Delta_2 V$, $\lim_{t \rightarrow \infty} \dot{W}(t) = 0$ implies that $\lim_{t \rightarrow \infty} V(t) = 0$, and by Barbalat's Lemma, we have that $\lim_{t \rightarrow \infty} \dot{V}(t) = 0$, and the V -equation in (1) implies $\lim_{t \rightarrow \infty} T^*(t) = 0$, hence $W_\infty = 0$, a contradiction. Therefore, $W_\infty = 0$, and the proof is complete. \square

The next Theorem shows that the positive equilibrium E is locally stable whenever it exists.

Theorem 3.3. *If $\mathcal{R}_0 > 1$, then E is locally asymptotically stable.*

Proof. If $\mathcal{R}_0 > 1$, a unique positive equilibrium E exists by Lemma 2.2. For notational convenience, we will drop all bars so that all variables are at their equilibrium values. The following relations hold at E :

$$\beta T^* = f(T), \quad k_1 V + k_2 T^* = f(T)/T, \quad \gamma + k_3 T + k_4 T^* = \frac{N \beta T^*}{V} = \frac{N f(T)}{V},$$

and

$$\beta - k_2 T = \frac{k_1 V T}{T^*}.$$

The Jacobian at E has the form

$$J(E) = \begin{bmatrix} f'(T) - k_1V - k_2T^* & -k_2T & -k_1T \\ k_1V + k_2T^* & k_2T - \beta & k_1T \\ -k_3V & N\beta - k_4V & -\gamma - k_3T - k_4T^* \end{bmatrix}.$$

Using the equilibrium relations, $J(E)$ simplifies to

$$J(E) = \begin{bmatrix} f' - f/T & -k_2T & -k_1T \\ f/T & -\frac{k_1VT}{T^*} & k_1T \\ -k_3V & (\gamma + k_3T)\frac{V}{T^*} & -\frac{Nf}{V} \end{bmatrix},$$

where we have suppressed the arguments of f and f' . The characteristic polynomial $p(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$ is given by

$$p(\lambda) = \det \begin{bmatrix} \lambda - f' + f/T & k_2T & k_1T \\ -f/T & \lambda + \frac{k_1VT}{T^*} & -k_1T \\ k_3V & -(\gamma + k_3T)\frac{V}{T^*} & \lambda + \frac{Nf}{V} \end{bmatrix}.$$

A direct computation using the equilibrium relations above to simplify a_2 and a_3 , we obtain

$$a_1 = f/T - f' + \frac{k_1VT}{T^*} + \frac{Nf}{V} > (f/T - f') + \frac{Nf}{V} > 0,$$

$$a_2 = k_1k_4VT + (-f' + f/T) \left(\frac{k_1VT}{T^*} + \frac{Nf}{V} \right) + k_2f - k_1k_3VT,$$

$$a_3 = (-f' + f/T)k_1k_4VT + f/T \left(k_2T\frac{Nf}{V} + k_1T(\gamma + k_3T)\frac{V}{T^*} \right) - k_1k_3\beta VT.$$

Since $-f' > 0$, we have that

$$a_2 > k_1k_4VT + \frac{k_1Vf}{T^*} + \frac{Nf^2}{VT} + k_2f - k_1k_3VT.$$

Since $\frac{k_1Vf}{T^*} = k_1\beta V$, $\frac{Nf}{V} > k_3T$, and $f/T > k_1V$, we have that

$$a_2 > k_1k_4VT + k_1\beta V + k_2f > 0.$$

Simplifying a_3 in a similar fashion, we find that

$$a_3 = (-f' + f/T)k_1k_4VT + \frac{k_2Nf^2}{V} + k_1\beta\gamma V > 0.$$

Finally, since $\frac{Nf}{V} > \gamma$, we have that $a_1a_2 > a_3$, and $J(E)$ satisfies the Routh-Hurwitz stability conditions. \square

Lemma 3.4. *System (1) is uniformly persistent in $\overset{\circ}{D}$, the interior of D , if and only if $\mathcal{R}_0 > 1$. Here, the set D is defined in (4).*

Proof. If $\mathcal{R}_0 \leq 1$, then by Theorem 3.2, E_0 attracts all positive solutions. Hence $\mathcal{R}_0 > 1$ is necessary for persistence. The sufficiency of the condition $\mathcal{R}_0 > 1$ follows from a uniform persistence result, Theorem 4.3 in [6]. To demonstrate that system (1) satisfies all the conditions of Theorem 4.3 in [6] when $\mathcal{R}_0 > 1$, choose $X = \mathbb{R}_+^3$ and $E = D$. The maximal invariant set N on the boundary ∂D is the singleton $\{E_0\}$ and it is isolated. Thus, the hypothesis (H) of [6] holds for (1). We conclude the proof by observing that, in the setting of (1), the necessary and sufficient condition for uniform persistence in Theorem 4.3 of [6] is equivalent to E_0 being unstable. \square

In the remainder of this paper, we prove that the positive equilibrium E is globally asymptotically stable in several special cases of system (1).

4. **The case $k_4 = 0$.** We begin this section by introducing the method of demonstrating global stability through the use of compound matrices; see [10, 15].

Let Ω be an open subset of \mathbb{R}^n , and let $f : \Omega \rightarrow \mathbb{R}^n$ be a vector field that generates the flow $\phi(t, x)$. That is, for a given $x \in \Omega$, $z(t) = \phi(t, x)$ is the unique solution of the system

$$\dot{z} = f(z) \tag{6}$$

with $z(0) = x$. A compact set $K \subset \Omega$ is called absorbing if for each compact set $F \subset \Omega$ there exists a $T > 0$ such that $\phi(t, F) \subset K$ for all $t \geq T$. It is clear that an absorbing set must contain all equilibria of f in Ω . We say that an open set $\Omega \subset \mathbb{R}^n$ is simply connected if each closed curve in Ω can be contracted to a singleton within Ω .

Let \wedge denote the exterior product on $\mathbb{R}^n \times \mathbb{R}^n$, that is, a surjective antisymmetric bilinear transformation $\wedge : \mathbb{R}^n \times \mathbb{R}^n \rightarrow \mathbb{R}^d$, where $d = \binom{n}{2}$. Consider the basis of \mathbb{R}^d consisting of pairwise products $e_i \wedge e_j$, $1 \leq i < j \leq n$ ordered lexicographically, where the vectors e_i , $1 \leq i \leq n$ are the elements of the canonical basis of \mathbb{R}^n . For a real $n \times n$ matrix M , its second additive compound matrix, denoted by $M^{[2]}$, is defined by its action on the chosen basis as follows:

$$M^{[2]}(e_i \wedge e_j) := (Me_i) \wedge e_j + e_i \wedge (Me_j), \quad 1 \leq i < j \leq n.$$

According to this definition, $M^{[2]}$ is a $d \times d$ matrix. For instance, if $M = (m_{ij})$ is a 3×3 matrix, then its second additive compound is given by

$$M^{[2]} = \begin{pmatrix} m_{11} + m_{22} & m_{23} & -m_{13} \\ m_{32} & m_{11} + m_{33} & m_{12} \\ -m_{31} & m_{21} & m_{22} + m_{33} \end{pmatrix}. \tag{7}$$

For more details on compound matrices, we refer the reader to [5, 15].

Let $|\cdot|$ denote a vector norm on \mathbb{R}^d and let $\|\cdot\|$ be the induced matrix norm on $\mathbb{R}^{d \times d}$, the space of all real $d \times d$ matrices. For a given matrix $A \in \mathbb{R}^{d \times d}$, we define its Lozinskii measure with respect to the norm $\|\cdot\|$ as

$$\mu(A) = \lim_{h \rightarrow 0^+} \frac{\|I + hA\| - 1}{h}.$$

More details on the properties of Lozinskii measures can be found in [1]. For future reference we recall without proof the Lozinskii measure, associated to the l_1 vector norm:

Lemma 4.1. *The Lozinskii measure of a real $n \times n$ matrix M with respect to the matrix norm induced by the l_1 vector norm, is given by*

$$\mu_1(M) = \max_i \left(m_{ii} + \sum_{j \neq i} |m_{ji}| \right)$$

Let the map $A : \Omega \rightarrow \mathbb{R}^{d \times d}$ be continuously differentiable and nonsingular for all $x \in \Omega$, and let μ be a Lozinskii measure on $\mathbb{R}^{d \times d}$, where $d = \binom{n}{2}$. Let K be a compact absorbing set for the flow $\phi(t, x)$ in Ω . Define a quantity \bar{q}_2 as

$$\bar{q}_2 = \limsup_{t \rightarrow \infty} \sup_{x \in K} \frac{1}{t} \int_0^t \mu(M(\phi(s, x))) ds, \tag{8}$$

where

$$M(x) = A_f(x)A^{-1}(x) + A(x)J^{[2]}(x)A^{-1}(x), \tag{9}$$

with

$$A_f(x) := \frac{d}{dt}A(\phi(t, x)), \quad J(x) := \frac{\partial f}{\partial x}(x).$$

We have the following result [10, 24].

Theorem 4.2. *Consider system (6), and suppose that Ω is simply connected and contains a compact absorbing set K . Let (6) have a unique equilibrium point $\bar{x} \in K$. If $A : \Omega \rightarrow \mathbb{R}^{d \times d}$ is C^1 and everywhere nonsingular, and if μ is a Lozinskii measure such that $\bar{q}_2 < 0$, then \bar{x} is globally asymptotically stable in Ω .*

For the proof of the global stability of E , we will need the following Lemma.

Lemma 4.3. *Every forward solution of (1) in \mathbb{R}_+^3 satisfies*

$$\limsup_{t \rightarrow \infty} V(t) \leq \frac{N\beta}{\gamma} \left(\frac{f(0)}{\beta} + T_0 \right) =: V_{\max}.$$

Proof. Consider a nonnegative forward solution of (1) and let $\epsilon > 0$. The T-equation in (1) implies that $T(t) \leq T_0 + \epsilon$ for all sufficiently large t . Hence, since $f'(T) < 0$ on $[0, T_0]$ by (2), the total number of cells, $T_{tot} := T + T^*$, for all large t satisfies:

$$\dot{T}_{tot} = f(T) - \beta T^* \leq f(0) + \beta T - \beta T_{tot} \leq f(0) + \beta(T_0 + \epsilon) - \beta T_{tot}.$$

It follows that $T^*(t) \leq T_{tot}(t) \leq \frac{f(0)}{\beta} + T_0 + 2\epsilon$ for all sufficiently large t . The V-equation in (1) now implies that

$$\dot{V} \leq N\beta \left(\frac{f(0)}{\beta} + T_0 + 2\epsilon \right) - \gamma V$$

for all sufficiently large t , thus

$$V(t) \leq \frac{N\beta}{\gamma} \left(\frac{f(0)}{\beta} + T_0 + 3\epsilon \right)$$

for all sufficiently large t . Since $\epsilon > 0$ is arbitrary, the claim follows. \square

Theorem 4.4. *Suppose that $k_4 = 0$ and $k_3 \geq 0$. Let D be the set defined in (4), and let $\Omega = \mathring{D}$. Suppose that $\mathcal{R}_0 > 1$, $2k_2T_0 < \beta$, and $k_3(f(0) + \beta T_0) < \beta\gamma$, then E is globally asymptotically stable for system (1) in Ω .*

Proof. Consider a positive solution of (1). As in the proof of Theorem 3.2, any solution with $T(t) \geq T_0$ for all $t \geq 0$ converges to E_0 . Since $\mathcal{R}_0 > 1$, Lemma 3.4 implies persistence, hence any positive solution must satisfy $T(t) < T_0$ for all sufficiently large t . In addition, Lemma 4.3 implies that $\limsup_{t \rightarrow \infty} V(t) \leq V_{\max}$. The condition $k_3(f(0) + \beta T_0) < \beta\gamma$ implies that $k_3V_{\max} < N\beta$, hence $k_3V(t) < N\beta$ for all sufficiently large t . By shifting time (which does not affect the value of the quantity \bar{q}_2), if necessary, we will assume that $T(t) < T_0$ and $k_3V(t) < N\beta$ for all $t \geq 0$.

Now, consider the Jacobian matrix of system (1):

$$J = \begin{bmatrix} f'(T) - k_1V - k_2T^* & -k_2T & -k_1T \\ k_1V + k_2T^* & k_2T - \beta & k_1T \\ -k_3V & N\beta & -\gamma - k_3T \end{bmatrix}. \quad (10)$$

The second compound matrix corresponding to J is given by

$$J^{[2]} = \begin{bmatrix} a - \beta & k_1T & k_1T \\ N\beta & b - \gamma & -k_2T \\ k_3V & k_1V + k_2T^* & c - \beta - \gamma \end{bmatrix}, \quad (11)$$

where

$$\begin{aligned} a &= f'(T) - k_1V - k_2T^* + k_2T, \\ b &= f'(T) - k_1V - k_2T^* - k_3T, \\ c &= k_2T - k_3T. \end{aligned} \tag{12}$$

Define an auxiliary matrix function A on Ω as

$$A := \text{diag} \left(\frac{1}{T^*}, \frac{1}{V}, \frac{1}{V} \right).$$

Since $T^*, V > 0$ everywhere in Ω , A is smooth and nonsingular. Furthermore, we find that

$$\begin{aligned} A_f &= \text{diag} \left(-\frac{\dot{T}^*}{(T^*)^2}, -\frac{\dot{V}}{V^2}, -\frac{\dot{V}}{V^2} \right), \\ A_f A^{-1} &= \text{diag} \left(-\frac{\dot{T}^*}{T^*}, -\frac{\dot{V}}{V}, -\frac{\dot{V}}{V} \right), \end{aligned}$$

$$AJ^{[2]}A^{-1} = \begin{bmatrix} a - \beta & \frac{k_1TV}{T^*} & \frac{k_1TV}{T^*} \\ \frac{N\beta T^*}{V} & b - \gamma & -k_2T \\ k_3T^* & k_1V + k_2T^* & c - \beta - \gamma \end{bmatrix}, \tag{13}$$

hence

$$\begin{aligned} M = A_f A^{-1} + AJ^{[2]}A^{-1} &= \begin{bmatrix} a - \beta - \frac{\dot{T}^*}{T^*} & \frac{k_1TV}{T^*} & \frac{k_1TV}{T^*} \\ \frac{N\beta T^*}{V} & b - \gamma - \frac{\dot{V}}{V} & -k_2T \\ k_3T^* & k_1V + k_2T^* & c - \beta - \gamma - \frac{\dot{V}}{V} \end{bmatrix} \\ &= \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix}, \end{aligned} \tag{14}$$

where

$$M_{11} = \left[a - \beta - \frac{\dot{T}^*}{T^*} \right], \quad M_{12} = \left[\frac{k_1TV}{T^*} \quad \frac{k_1TV}{T^*} \right], \quad M_{21} = \left[\frac{N\beta T^*}{V} \right],$$

$$M_{22} = \begin{bmatrix} b - \gamma - \frac{\dot{V}}{V} & -k_2T \\ k_1V + k_2T^* & c - \beta - \gamma - \frac{\dot{V}}{V} \end{bmatrix}.$$

Let (u, v, w) denote a vector in \mathbb{R}^3 , and define a vector norm on \mathbb{R}^3 as $|(u, v, w)| = \max(|u|, |v| + |w|)$ and let μ be the corresponding Lozinskii measure. Then from [11, 12], we have that

$$\mu(M) \leq \max(g_1, g_2), \tag{15}$$

where

$$g_1 = \mu_1(M_{11}) + \|M_{12}\|, \quad g_2 = \mu_1(M_{22}) + \|M_{21}\|.$$

$\|M_{12}\|, \|M_{21}\|$ are the operator norms associated to the linear mappings $M_{12} : \mathbb{R}^2 \rightarrow \mathbb{R}$, and $M_{21} : \mathbb{R} \rightarrow \mathbb{R}^2$ respectively, where \mathbb{R}^2 is endowed with the l_1 vector norm in both cases.

We have the following

$$\mu_1(M_{11}) = a - \beta - \frac{\dot{T}^*}{T^*}, \quad \|M_{12}\| = \frac{k_1TV}{T^*}, \quad \|M_{21}\| = \max\left(\frac{N\beta T^*}{V}, k_3T^*\right),$$

$$\mu_1(M_{22}) = -\gamma - \frac{\dot{V}}{V} + \max(k_1V + k_2T^* + b, k_2T + c - \beta),$$

where Lemma 4.1 has been used to calculate $\mu_1(M_{22})$. Since $k_3V < N\beta$, it follows that $\frac{N\beta T^*}{V} \geq k_3T^*$, and $\|M_{21}\| = \frac{N\beta T^*}{V}$. Using (1), we find that

$$\frac{\dot{T}^*}{T^*} = \frac{k_1VT}{T^*} + k_2T - \beta, \quad (16)$$

$$\frac{\dot{V}}{V} = \frac{N\beta T^*}{V} - \gamma - k_3T. \quad (17)$$

Recalling the expressions for a, b and c in (12), we have that

$$\mu_1(M_{22}) = -\frac{N\beta T^*}{V} + \max(f'(T), 2k_2T - \beta),$$

and therefore that

$$\begin{aligned} g_1 &= a - \beta - \frac{\dot{T}^*}{T^*} + \frac{k_1TV}{T^*} = f'(T) - k_1V - k_2T^*, \\ g_2 &= \max(f'(T), 2k_2T - \beta). \end{aligned}$$

Since $f'(T) - k_1V - k_2T^* \leq \max(f'(T), 2k_2T - \beta)$, we find that $g_1 \leq g_2$, and then (15) implies that $\mu(M) \leq g_2$. Let

$$p_1 = \max_{[0, T_0]} f'(T), \quad \text{and} \quad p_2 = 2k_2T_0 - \beta.$$

The assumptions in 2 imply that $p_1 < 0$, and the assumptions of this Theorem imply that $p_2 < 0$. Hence,

$$\mu(M) \leq p, \quad p := \max(p_1, p_2) < 0.$$

Integrating the above inequality, we find that

$$\frac{1}{t} \int_0^t \mu(M) ds \leq p.$$

Therefore,

$$\limsup_{t \rightarrow \infty} \frac{1}{t} \int_0^t \mu(M) ds \leq p < 0.$$

This clearly holds for all solutions in Ω , thus $\bar{q}_2 \leq p < 0$. The uniform persistence established in Lemma 3.4 implies the existence of a compact absorbing set $K \subset \Omega$. Observing that Ω is simply connected, we apply Theorem 4.2 to complete the proof. \square

5. **The case $k_3 = 0$.** Although this case is biologically relevant only if $k_4 = 0$, the following global stability result holds for all $k_4 \geq 0$.

Theorem 5.1. *Suppose that $k_3 = 0$ and $k_4 \geq 0$. Let D and Ω be as defined in Theorem 4.4. If $\mathcal{R}_0 > 1$, then the equilibrium E is globally asymptotically stable for system (1) in Ω .*

Proof. Local stability of E follows from Theorem 3.3. Recall that the following equilibrium relations hold:

$$k_1\bar{V}\bar{T} + k_2\bar{T}\bar{T}^* = \beta\bar{T}^*, \quad (18)$$

$$\bar{T}^* = \frac{k_1\bar{V}\bar{T}}{\beta - k_2\bar{T}}, \quad (19)$$

$$N\beta\bar{T}^* = \gamma\bar{V} + k_4\bar{V}\bar{T}^*. \quad (20)$$

Combining (19) and (20), we find that

$$N\beta k_1\bar{T} = \gamma\beta - k_2\gamma\bar{T} + k_1k_4\bar{V}\bar{T}. \quad (21)$$

Consider the following function on $\mathring{\mathbb{R}}_+^3$:

$$W = \int_{\bar{T}}^T \left(1 - \frac{\bar{T}}{\tau}\right) d\tau + \int_{\bar{T}^*}^{T^*} \left(1 - \frac{\bar{T}^*}{\tau}\right) d\tau + \frac{k_1\bar{T}}{\gamma} \int_{\bar{V}}^V \left(1 - \frac{\bar{V}}{\tau}\right) d\tau.$$

So,

$$\frac{dW}{dt} = \left(1 - \frac{\bar{T}}{T}\right) \frac{dT}{dt} + \left(1 - \frac{\bar{T}^*}{T^*}\right) \frac{dT^*}{dt} + \frac{k_1\bar{T}}{\gamma} \left(1 - \frac{\bar{V}}{V}\right) \frac{dV}{dt} := A_1 + A_2 + A_3.$$

The first term, A_1 , in \dot{W} can be rewritten as

$$\begin{aligned} A_1 &= \left(1 - \frac{\bar{T}}{T}\right) (f(T) - k_1VT - k_2TT^*) \\ &= \left(1 - \frac{\bar{T}}{T}\right) (f(T) - f(\bar{T})) + \left(1 - \frac{\bar{T}}{T}\right) f(\bar{T}) - T(k_1V + k_2T^*) + \bar{T}(k_1V + k_2T^*) \\ &= \left(1 - \frac{\bar{T}}{T}\right) (f(T) - f(\bar{T})) + \left(1 - \frac{\bar{T}}{T}\right) \bar{T}(k_1\bar{V} + k_2\bar{T}^*) - T(k_1V + k_2T^*) \\ &\quad + \bar{T}(k_1V + k_2T^*) \\ &= \left(1 - \frac{\bar{T}}{T}\right) (f(T) - f(\bar{T})) + \bar{T}(k_1\bar{V} + k_2\bar{T}^*) - \frac{\bar{T}^2}{T}(k_1\bar{V} + k_2\bar{T}^*) \\ &\quad - T(k_1V + k_2T^*) + \bar{T}(k_1V + k_2T^*). \end{aligned}$$

Due to (18), the second term, A_2 , in \dot{W} takes the form

$$\begin{aligned} A_2 &= \left(1 - \frac{\bar{T}^*}{T^*}\right) (k_1VT + k_2TT^* - \beta T^*) = \\ &= k_1VT + k_2TT^* - \beta T^* - k_1VT \frac{\bar{T}^*}{T^*} - k_2T\bar{T}^* + k_1\bar{V}\bar{T} + k_2\bar{T}\bar{T}^*. \end{aligned}$$

The third term, A_3 , in \dot{W} is

$$\begin{aligned} A_3 &= \frac{k_1\bar{T}}{\gamma} \left(1 - \frac{\bar{V}}{V}\right) (N\beta T^* - \gamma V - k_4VT^*) = \\ &= \frac{k_1N\beta}{\gamma} \bar{T}T^* - k_1\bar{T}V - \frac{k_1k_4}{\gamma} \bar{T}VT^* - \frac{k_1N\beta}{\gamma} \bar{T}T^* \frac{\bar{V}}{V} + k_1\bar{T}\bar{V} + \frac{k_1k_4}{\gamma} \bar{T}T^*\bar{V}. \end{aligned}$$

Using (21), A_3 can be written as

$$\begin{aligned} A_3 &= \beta T^* - k_2\bar{T}T^* + \frac{k_1k_4}{\gamma} \bar{V}\bar{T}T^* - k_1\bar{T}V - \frac{k_1k_4}{\gamma} \bar{T}VT^* - \beta T^* \frac{\bar{V}}{V} \\ &\quad + k_2\bar{T}T^* \frac{\bar{V}}{V} - \frac{k_1k_4}{\gamma} \bar{T}T^* \frac{\bar{V}^2}{V} + k_1\bar{T}\bar{V} + \frac{k_1k_4}{\gamma} \bar{T}T^*\bar{V}. \end{aligned}$$

Adding $A_1 + A_2 + A_3$, and using (18), we obtain

$$\begin{aligned} \dot{W} &= \left(1 - \frac{\bar{T}}{T}\right) (f(T) - f(\bar{T})) + k_1 \bar{V} \bar{T} \left(3 - \frac{\bar{T}}{T} - \frac{V T \bar{T}^*}{\bar{V} \bar{T} T^*} - \frac{T^* \bar{V}}{\bar{T}^* \bar{V}}\right) \\ &\quad + k_2 \bar{T} \bar{T}^* \left(2 - \frac{\bar{T}}{T} - \frac{T}{\bar{T}}\right) + \frac{k_1 k_4}{\gamma} \bar{V} \bar{T} T^* \left(2 - \frac{V}{\bar{V}} - \frac{\bar{V}}{V}\right). \end{aligned}$$

The first term is always non-positive due to our assumptions on f . The second, third and fourth terms are non-positive as well due to the arithmetic-geometric mean (AM-GM) inequality. Hence, $\dot{W} \leq 0$ in $\mathring{\mathbb{R}}_+^3$. To characterize the subset of $\mathring{\mathbb{R}}_+^3$ where \dot{W} equals zero, we distinguish two cases: $k_4 > 0$ and $k_4 = 0$. If $k_4 > 0$, then \dot{W} equals zero if and only if $(T, T^*, V) = E$. Since W is a proper Lyapunov function in $\mathring{\mathbb{R}}_+^3$, it follows that E is globally asymptotically stable in $\mathring{\mathbb{R}}_+^3$. If $k_4 = 0$, then $\dot{W} = 0$ if and only if $T = \bar{T}$ and $\bar{T}^* V = T^* \bar{V}$. Since all solutions of (1) in $\mathring{\mathbb{R}}_+^3$ are bounded by Lemma 3.1, the LaSalle's invariance principle implies that any ω -limit set in $\mathring{\mathbb{R}}_+^3$ is a subset of the largest invariant set in

$$M = \{(T, T^*, V) \in \mathring{\mathbb{R}}_+^3 \mid T = \bar{T}, \bar{T}^* V = T^* \bar{V}\}.$$

Any such invariant set in M must satisfy $\dot{T} = 0$, hence

$$0 = f(\bar{T}) - \bar{T} \frac{V}{\bar{V}} (k_1 \bar{V} + k_2 \bar{T}^*) = f(\bar{T}) \left(1 - \frac{V}{\bar{V}}\right),$$

which implies that $V = \bar{V}$ and $T^* = \bar{T}^*$. Therefore, the largest invariant set in M is the singleton $\{E\}$, and since W is a proper function in $\mathring{\mathbb{R}}_+^3$, E attracts all solutions in $\mathring{\mathbb{R}}_+^3$. \square

5.1. Competitive exclusion. The global stability result of Theorem 5.1 can be readily extended to the model with several viral strains competing for the same pool of susceptible cells. The multistrain competition model takes the form

$$\begin{cases} \dot{T} &= f(T) - \sum_i k_1^i V_i T - \sum_i k_2^i T_i^* T, \\ \dot{T}_i^* &= k_1^i V_i T + k_2^i T_i^* T - \beta_i T_i^*, \quad i = 1, \dots, n, \\ \dot{V}_i &= N_i \beta_i T_i^* - \gamma_i V_i, \quad i = 1, \dots, n, \end{cases} \quad (22)$$

on \mathbb{R}_+^{2n+1} , where we neglect the loss of virions due to cellular absorption. For each strain, we define the quantities

$$\mathcal{T}_0^i = \frac{k_2^i T_0}{\beta_i} + \frac{N_i k_1^i T_0}{\gamma_i}, \quad \bar{T}_i = \frac{\gamma_i \beta_i}{k_2^i \gamma_i + N_i k_1^i \beta_i} = \frac{T_0}{\mathcal{T}_0^i}.$$

We have the following extinction result.

Theorem 5.2. *Suppose that $\mathcal{T}_0^1 > \max\{1, \mathcal{T}_0^2, \dots, \mathcal{T}_0^n\}$. Then the equilibrium $E_1 = (\bar{T}_1, \bar{T}_1^*, \bar{V}_1, 0, \dots, 0)$ attracts all solutions of (22) with $T_1^*(0) + V_1(0) > 0$. Here, $\bar{T}_1^* := f(\bar{T}_1)/\beta_1$ and $\bar{V}_1 := N_1 f(\bar{T}_1)/\gamma_1$.*

Proof. We begin by observing that $\mathcal{T}_0^1 > \mathcal{T}_0^i$ is equivalent to $\bar{T}_1 < \bar{T}_i$ for $i = 2, \dots, n$. It is also easy to check that E_1 is indeed an equilibrium of (22). Define W as follows

$$\begin{aligned} W &= \int_{\bar{T}_1}^T \left(1 - \frac{\bar{T}_1}{\tau}\right) d\tau + \int_{\bar{T}_1^*}^{T_1^*} \left(1 - \frac{\bar{T}_1}{\tau}\right) d\tau + \frac{k_1^1 \bar{T}_1}{\gamma} \int_{\bar{V}_1}^{V_1} \left(1 - \frac{\bar{V}_1}{\tau}\right) d\tau \\ &\quad + \sum_{i \geq 2} (T_i^* + B_i V_i), \end{aligned}$$

where $B_i = \frac{k_1^i \bar{T}_1}{\gamma_i}$ for $i = 2, \dots, n$. Evaluating \dot{W} , we find that $\dot{W} = A_1 + A_2 + \dots + A_n$, where

$$\begin{aligned} A_1 &= \frac{(T - \bar{T}_1)(f(T) - f(\bar{T}_1))}{T} + k_1^1 \bar{V}_1 \bar{T}_1 \left(3 - \frac{\bar{T}_1}{T} - \frac{V_1 T \bar{T}_1^*}{V_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} \right) \\ &\quad + k_2^1 \bar{T}_1 \bar{T}_1^* \left(2 - \frac{\bar{T}_1}{T} - \frac{T}{\bar{T}_1} \right) \end{aligned}$$

is the same as \dot{W} in the proof of Theorem 5.1, and

$$\begin{aligned} A_i &= \bar{T}_1 (k_1^i V_i + k_2^i T_i^*) - \beta_i T_i^* + B_i (N_i \beta_i T_i^* - \gamma V_i) \\ &= T_i^* (\bar{T}_1 k_2^i - \beta_i + B_i N_i \beta_i) + V_i (\bar{T}_1 k_1^i - B_i \gamma_i) \\ &= T_i^* \left(\bar{T}_1 k_2^i - \beta_i + \frac{k_1^i N_i \beta_i \bar{T}_1}{\gamma_i} \right) \\ &= \frac{k_2^i \gamma_i + N_i k_1^i \beta_i}{\gamma_i} T_i^* (\bar{T}_1 - \bar{T}_i) = \frac{\beta_i \mathcal{T}_0^i}{T_0} T_i^* (\bar{T}_1 - \bar{T}_i). \end{aligned}$$

Clearly, all A_i 's are non-positive, hence $\dot{W} \leq 0$. Furthermore, the set M where $\dot{W} = 0$ is given by

$$M = \{T = \bar{T}_1, T_1^* \bar{V}_1 = \bar{T}_1^* V_1, T_2^* = \dots = T_n^* = 0\},$$

thus the largest invariant set of (22) in M is E_1 . An application of the LaSalle's invariance principle concludes the proof. \square

6. The case $0 < k_3 \ll k_4$. In this section, we use a global perturbation result [20] to show that the positive equilibrium E is globally asymptotically stable for system (1) in \mathbb{R}_+^3 , provided that $k_i > 0$ for $i = 1, \dots, 4$, and k_3 is sufficiently small. We begin with the following result.

Lemma 6.1. *Suppose that $k_1, k_2, k_4 > 0$, $k_3 = 0$, and $\mathcal{R}_0 > 1$. Let W be the Lyapunov function defined in the proof of Theorem 5.1. Then there exist $\epsilon_1, \epsilon_2 > 0$ such that $\dot{W}(x) \leq -\epsilon_1$ for all $x \in \mathbb{R}_+^3$ such that $|x - E| \geq \epsilon_2$. In other words, \dot{W} is bounded away from zero outside of any compact neighborhood of E in \mathbb{R}_+^3 .*

Proof. From the proof of Theorem 5.1, we have that

$$\begin{aligned} \dot{W} &\leq k_1 \bar{V} \bar{T} \left(3 - \frac{\bar{T}}{T} - \frac{V T \bar{T}^*}{\bar{V} \bar{T} T^*} - \frac{T^* \bar{V}}{\bar{T}^* V} \right) + k_2 \bar{T} \bar{T}^* \left(2 - \frac{\bar{T}}{T} - \frac{T}{\bar{T}} \right) \\ &\quad + \frac{k_1 k_4}{\gamma} \bar{V} \bar{T} \bar{T}^* \frac{T^*}{T^*} \left(2 - \frac{V}{\bar{V}} - \frac{\bar{V}}{V} \right). \end{aligned}$$

To simplify the notation, let

$$A_1 = k_1 \bar{V} \bar{T}, \quad A_2 = k_2 \bar{T} \bar{T}^*, \quad A_3 = \frac{k_1 k_4}{\gamma} \bar{V} \bar{T} \bar{T}^*, \quad u = \frac{T}{\bar{T}}, \quad v = \frac{T^* \bar{V}}{\bar{T}^* V}, \quad w = \frac{V}{\bar{V}},$$

so that

$$\dot{W} \leq A_1 \left(3 - \frac{1}{u} - \frac{u}{v} - v \right) - A_2 \frac{(u-1)^2}{u} - A_3 v (w-1)^2.$$

For each $v > 0$, the first term is maximized when $u = \sqrt{v}$, hence

$$3 - \frac{1}{u} - \frac{u}{v} - v \leq 3 - \frac{2}{\sqrt{v}} - v = -\frac{2 + \sqrt{v}}{\sqrt{v}} (\sqrt{v} - 1)^2 = -\frac{2 + \sqrt{v}}{\sqrt{v}(\sqrt{v} + 1)^2} (v - 1)^2.$$

Therefore,

$$\dot{W} \leq -A_1 \frac{2 + \sqrt{v}}{\sqrt{v}(\sqrt{v} + 1)^2} (v - 1)^2 - A_2 \frac{(u - 1)^2}{u} - A_3 v (w - 1)^2.$$

Now, let $\epsilon > 0$ be sufficiently small, and suppose that $\dot{W} \in (-\epsilon^2, 0)$. Then we have

$$A_2 \frac{(u - 1)^2}{u} < \epsilon^2 \Rightarrow |u - 1| < \kappa_1 \epsilon \Rightarrow |T - \bar{T}| < \kappa_1 \bar{T} \epsilon,$$

for some $\kappa_1 > 0$ which is independent of ϵ . Similarly,

$$A_1 \frac{2 + \sqrt{v}}{\sqrt{v}(\sqrt{v} + 1)^2} (v - 1)^2 < \epsilon^2 \Rightarrow |v - 1| < \kappa_2 \epsilon,$$

for some $\kappa_2 > 0$ which is independent of ϵ . This implies that

$$|w - 1| \leq \frac{\epsilon}{A_3(1 - \sqrt{\kappa_2 \epsilon})} < \kappa_3 \epsilon \Rightarrow |V - \bar{V}| < \kappa_3 \bar{V} \epsilon,$$

for an appropriate $\kappa_3 > 0$. Lastly, we have that

$$|T^* - \bar{T}^*| = \frac{\bar{T}^*}{w} |w - v| \leq \frac{\bar{T}^*(\kappa_2 + \kappa_3)\epsilon}{1 - \kappa_3 \epsilon} < \kappa_4 \bar{T}^* \epsilon,$$

for some $\kappa_4 > 0$. Combining the above inequalities, we conclude that there exists $\kappa_0 > 0$ such that for all sufficiently small $\epsilon > 0$, the inequality $-\epsilon^2 < \dot{W}(x) < 0$ implies that $|x - E| < \kappa_0 \epsilon$, and the claim follows. \square

Theorem 6.2. *Suppose that $k_1, k_2, k_4 > 0$, $k_3 = 0$, and $\mathcal{R}_0 > 1$. Then there exist $\delta > 0$ and a smooth mapping $E : [0, \delta) \rightarrow \mathbb{R}_+^3$, such that for every $k_3 \in [0, \delta)$ the point $E(k_3)$ is a globally asymptotically stable equilibrium of (1) in \mathbb{R}_+^3 .*

Proof. First, we observe that \mathcal{R}_0 is a continuous function of k_3 and for $k_3 = 0$, $\mathcal{R}_0 > 1$. Hence, there exists $\delta_1 > 0$ such that $\mathcal{R}_0 > 1$ as long as $k_3 \in [0, \delta_1)$. By Lemma 2.2, for each $k_3 \in [0, \delta_1)$ there exists a unique positive equilibrium $E(k_3)$ of (1) which is locally asymptotically stable by Theorem 3.3. By the Implicit Function Theorem, the mapping $E : [0, \delta_1) \rightarrow \mathbb{R}_+^3$ is smooth.

Now, let $\epsilon_1, \epsilon_2 > 0$ be as defined in Lemma 6.1. Let W be the Lyapunov function defined in the proof of Theorem 5.1. Since W is a proper Lyapunov function, there exists a sufficiently small $\epsilon_0 > 0$ such that $W(x) \leq \epsilon_0$ implies $|x - E(0)| \leq \epsilon_2$. Define the compact set $K = W^{-1}([0, \epsilon_0])$. Let

$$\delta_2 := \frac{\gamma \epsilon_1}{2k_1 \bar{T} \bar{V} (T_0 + 1)},$$

and suppose that $k_3 \in [0, \delta_2)$. Then for any solution of (1) in \mathbb{R}_+^3 it holds that $T(t) < T_0 + 1$ for all sufficiently large t . We have that

$$\begin{aligned} \dot{W} &= \left(1 - \frac{\bar{T}}{T}\right) (f(T) - f(\bar{T})) + k_1 \bar{V} \bar{T} \left(3 - \frac{\bar{T}}{T} - \frac{V T \bar{T}^*}{\bar{V} \bar{T} T^*} - \frac{T^* \bar{V}}{\bar{T}^* V}\right) \\ &\quad + k_2 \bar{T} \bar{T}^* \left(2 - \frac{\bar{T}}{T} - \frac{T}{\bar{T}}\right) + \frac{k_1 k_4}{\gamma} \bar{V} \bar{T} T^* \left(2 - \frac{V}{\bar{V}} - \frac{\bar{V}}{V}\right) - \frac{k_1 k_3 \bar{T} T}{\gamma} (V - \bar{V}). \end{aligned}$$

As long as $x \notin K$ and $T(t) < T_0 + 1$, Lemma 6.1 implies that

$$\dot{W} \leq -\epsilon_1 + \frac{k_1 \delta_2 \bar{T} (T_0 + 1) \bar{V}}{\gamma} \leq -\frac{\epsilon_1}{2} < 0,$$

hence every positive solution enters the set K in finite time, so that K is an absorbing forward invariant compact set for (1) for all $k_3 \in [0, \delta_2)$. Now, letting

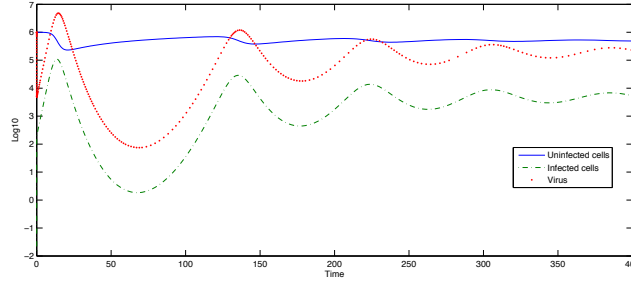


FIGURE 1. Time series of a solution $(T(t), T^*(t), V(t))$ of system (1) with parameter values as described in Example 1 in the text.

$\delta = \min(\delta_1, \delta_2)$, we apply the global perturbation result (Proposition 2.3 in [20]) to conclude that $E(k_3)$ is globally stable under (1) for all $k_3 \in [0, \delta)$. \square

7. Numerical examples. In this Section we numerically explore the behavior of our model when some of the conditions of the main results, Theorem 4.4 and Theorem 6.2, fail. In both cases, it appears that the disease steady state attracts the simulated solution, providing evidence for the conjecture that this steady state is globally stable when it exists.

Example 1: In this example, we set $k_4 = 0$ and we have chosen the parameters such that both $2k_2T_0 > \beta$ and $k_3(f(0) + \beta T_0) > \beta\gamma$, which implies that Theorem 4.4 is not applicable.

We used $f(T) = a - bT$ with $a = 10^4 ml^{-1} day^{-1}$ and $b = 0.01 day^{-1}$ (which implies that $T_0 = 10^6 ml^{-1}$), $k_1 = 2.4 \times 10^{-8} ml day^{-1}$, $k_2 = 10^{-6} ml day^{-1}$, $k_3 = 10^{-4} ml day^{-1}$, $N = 3000$, $\gamma = 23 day^{-1}$, $\beta = 1 day^{-1}$.

Notice that with these assignments we have that $\mathcal{R}_0 = 1.414 > 1$, $2k_2T_0 - \beta = 1 > 0$, and $k_3(f(0) + \beta T_0) - \beta\gamma = 78 > 0$. The time series of the components of a simulated solution with initial condition $(T(0), T^*(0), V(0)) = (10^6, 0, 10^6)$ are displayed in Figure 1. They suggest convergence to a positive steady state.

Example 2: In this example, we have chosen $k_3 \gg k_4 > 0$ (in fact, $k_3 = 10k_4$), which implies that Theorem 6.2 may not be applicable.

Once again, we have set $f(T) = a - bT$, and for $a, b, k_1, k_2, k_3, N, \gamma$ and β we used the same values as in Example 1. On the other hand, here, $k_4 = 10^{-5} ml day^{-1}$. Notice that these assignments yield the same value for $\mathcal{R}_0 = 1.414$ as in Example 1 because this value is independent of k_4 ; see (3).

The time series of the components of a simulated solution with the same initial condition as in Example 1 are displayed in Figure 2, and they suggest convergence to a positive steady state as before.

8. Conclusions. In this paper, we have analyzed a within-host virus model which incorporated the mechanisms of direct cell-to-cell viral transmission and the viral coinfection (absorption of free virions into already infected cells). We obtained a complete analytic description of equilibria and their local stability. We presented the basic reproductive number \mathcal{R}_0 and proved that the infection persists when $\mathcal{R}_0 > 1$ and becomes extinct when $\mathcal{R}_0 \leq 1$. We also obtained sufficient conditions for the global stability of the endemic equilibrium in several particular cases. We were unable to establish the global stability in the most general cases where all coefficients

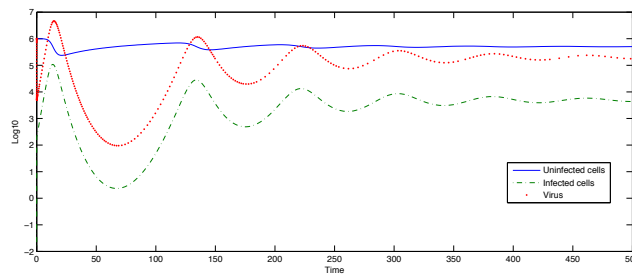


FIGURE 2. Time series of a solution $(T(t), T^*(t), V(t))$ of system (1) with parameter values as described in Example 2 in the text.

are positive. In one instance, namely when the absorption of free virions into infected cells can be neglected (the case $k_3 = 0$), we used the geometric approach developed by Li and Muldowney to prove the global stability [10]. In another instance, when the absorption of free virions into uninfected cells can be neglected (admittedly, not a biologically plausible scenario), we employed a Lyapunov function approach with a specific function similar to that used by Li *et al* in [9]. If both $k_3 = k_4 = 0$, we extended the global stability result to include a competition of several viral strains, and proved that the competitive exclusion is the typical outcome. Moreover, as it is common in competition models, it turns out that the fittest competitor is determined by the highest value of the basic reproduction number, \mathcal{R}_0 . Another implication of this result is that a direct cell-to-cell viral transmission cannot induce coexistence of viral strains. Using the same Lyapunov function, we were able to invoke a global perturbation result of Smith and Waltman [20] to prove the global stability of the endemic equilibrium when $k_3 > 0$ is a small parameter. Finally, we presented two numerical examples to illustrate the global stability of the endemic equilibrium. We conjecture that such equilibrium is globally stable whenever it exists, but the proof of this general result remains an open question.

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