SIAM J. APPL. MATH.
Vol. 63, No. 4, pp. 1313–1327
© 2003 Society for Industrial and Applied Mathematics

# VIRUS DYNAMICS: A GLOBAL ANALYSIS*

PATRICK DE LEENHEER† AND HAL L. SMITH†

**Abstract.** Exploiting the fact that standard models of within-host viral infections of target cell populations by HIV, developed by Perelson and Nelson [*SIAM Rev.*, 41 (1999), pp. 3–44] and Nowak and May [*Virus Dynamics*, Oxford University Press, New York, 2000], give rise to competitive three dimensional dynamical systems, we provide a global analysis of their dynamics. If the basic reproduction number $R_0 < 1$, the virus is cleared and the disease dies out; if $R_0 > 1$, then the virus persists in the host, solutions approaching either a chronic disease steady state or a periodic orbit. The latter can be ruled out in some cases but not in general.

**Key words.** virus dynamics, global stability, oscillations, HIV

**AMS subject classifications.** 34D23, 34A34

**PII.** S0036139902406905

## 1. Introduction.

Recently there has been a substantial effort in the mathematical modeling of virus dynamics, primarily motivated by the AIDS epidemic and HIV; see, e.g., [9, 11, 15]. Perelson and Nelson [14] and Nowak and May [12] provide excellent reviews and many more citations. The latter has a somewhat broader focus, also treating SIV (the simian version of HIV) and the hepatitis B viral infections. These models focus on the disease dynamics within an infected individual and contrast with an earlier parallel literature on the dynamics within the human population. Simple HIV models have played a significant role in the development of a better understanding of the disease and the various drug therapy strategies used against it. For example, they provided a quantitative understanding of the level of virus production during the long asymptomatic stage of HIV infection; see [13, 14, 12].

We focus primarily on HIV models here but note, following [12], that the basic model applies to many other viral infections. Moreover, similar models exist which describe infections of marine bacteria by bacteriophages; see [1].

A brief review of the salient features of the role of HIV in the disease will be useful. The course of an HIV infection is as follows. First, HIV enters its target, a T cell. Inside this cell it makes a DNA copy of its viral RNA; hence it falls into the class of so-called retroviruses. In this process it needs the enzyme reverse transcriptase (RT). The viral DNA is then inserted into the DNA of the T cell, which will henceforth produce viral particles that can bud off the cell to infect other uninfected T cells. Before leaving the host cell, the virus particle is equipped with protease, an enzyme used to cleave a long protein chain. If this feature is lost, the virus particle is not capable of successfully infecting other T cells.

The models considered in [14, 12] have three state variables: $T$, the concentration of uninfected $T$ cells; $T^*$, the concentration of productively infected $T$ cells; and $V$, the concentration of free virus particles in the blood. In chemical reaction notation, the model can be written

$$T + V \to T^* \to NV,$$

*Received by the editors May 1, 2002; accepted for publication (in revised form) September 30, 2002; published electronically April 23, 2003.
http://www.siam.org/journals/siap/63-4/40690.html
†Department of Mathematics and Statistics, Arizona State University, Tempe, AZ 85287 (leenheer@math.la.asu.edu, halsmith@asu.edu). The research of the second author was supported by NSF grant DMS 9700910.

because mass action reaction terms are used and each infected T cell is assumed to produce $N$ viral particles over its lifespan. The interaction between these cells and virus particles is then given by the following equations:

$$\begin{aligned} \dot{T} &= f(T) - kVT, \\ \dot{T}^* &= -\beta T^* + kVT, \\ \dot{V} &= -\gamma V + N\beta T^*, \end{aligned} \tag{1}$$

where we have relabeled many of the parameters used in [14, 12]. The functional form of $f$ is defined differently by different authors:

1. Perelson and Nelson [14]: $f(T) = f_1(T) \equiv \delta - \alpha T + pT(1 - \frac{T}{T_{max}})$.
2. Nowak and May [12]: $f(T) = f_2(T) \equiv \delta - \alpha T$.

The parameters $\alpha$, $\beta$, $\gamma$, $\delta$, $k$, $N$, $p$, and $T_{\max}$ are positive.

We briefly summarize the interpretation of the different parameters in the model. Parameters $\alpha$, $\beta$, and $\gamma$ are the death rates of the uninfected T cells, the infected T cells, and the virus particles, respectively. $k$ is the contact rate between uninfected T cells and virus particles. $\delta$ represents a constant production of $T$ cells in the thymus. In the literature this process is not assumed to be constant, but to depend on virus loads. Usually $\delta$ is then replaced by a decreasing function of the concentration of virus particles; see, e.g., [15]. $N$ is the average number of virus particles produced by an infected T cell. In the case $f = f_1$, healthy $T$ cells are assumed to proliferate logistically, although the control mechanisms for $T$ cell proliferation are largely unknown. The $p$ and $T_{\max}$ are the growth rate (respectively, carrying capacity) associated with a logistic growth of uninfected T cells in the absence of virus particles, infected $T$-cells, and natural body sources such as the thymus. Note that simplification of the logistic term $pT(1 - (T + T^*)/T_{\max})$ to $pT(1 - T/T_{\max})$ is not always performed; see, e.g., [15]. From a mathematical point of view, this simplification leads to a competitive system, which opens up a whole arsenal of tools in the subsequent analysis. We will elaborate on this below. Another simplification, found in all models in the literature, is that (logistic) proliferation of $T^*$ cells has been neglected.

Both Perelson and Nelson and Nowak and May ignore the loss term $-kVT$, which should appear in the $V$ equation, i.e.,

$$\dot{V} = -\gamma V + N\beta T^* - kVT, \tag{2}$$

representing the loss of a free virus particle once it enters the target cell, arguing that this small term can be absorbed into the loss term $-\gamma V$. We will consider (1) with and without this added term.

An important feature of this model is that it ignores the reaction of the immune system, and therefore the model describes a worst-case scenario in some sense; see [12, 11] for models which include an immune response to the virus. More realistic models also include a compartment for latently infected T cells [14, 12, 15], which are capable of but not actively producing virus. A related modeling approach consists of incorporating a delay term describing the delay between the time of infection of a T cell and the time of emission of virus particles from this cell [3]. Our model also neglects virus mutations, which occur very frequently and on a fast time-scale. Some of these mutations cause drug resistance, which makes effective treatment very difficult.

System (1), with or without the $-kVT$ term in the $V$ equation, is competitive with respect to the cone $K := \{(X, Y, Z) \in R^3 | \, X, Z \geq 0, Y \leq 0\}$—see p. 49 in [16]—and thus solutions with initial states ordered according to the order of $K$ (i.e., their

difference is a vector in $K$) remain ordered for backward time. Indeed, the Jacobian matrix of system (1) (respectively of system (1) with the $V$-equation replaced by (2)) at an arbitrary point of $R^3_+$ possesses the following structures:

$$\begin{pmatrix} * & 0 & - \\ + & * & + \\ 0 & + & * \end{pmatrix}, \quad \begin{pmatrix} * & 0 & - \\ + & * & + \\ - & + & * \end{pmatrix}, \tag{3}$$

where some of the + and − signs can actually be zero for points on the boundary of $R^3_+$. Note that these matrices are sign-symmetric; i.e., for every $i \neq j$, the product of the $(i, j)$th and the $(j, i)$th entry of these matrices is nonnegative. The incidence graph associated with this matrix, where edges between the nodes are furnished with a + or a − sign, depending on the sign of one of the corresponding entries in the above Jacobian matrix, satisfies the following property: Every closed loop in this graph possesses an odd number of edges with − signs. This property implies that the system is competitive. Alternatively, the change of variables $T^* \to -T^*$ results in a system the Jacobian for which has nonpositive off-diagonal terms on the relevant domain and hence is competitive in the usual sense. The theory of competitive (and cooperative) systems was initiated by Hirsch in a series of six well-known papers, of which we list [5, 6, 7, 8]. Contributions to this theory were also made by Smith, e.g., [17, 18, 20]; see [16] for a review. A particular consequence of the theory of competitive systems is a generalization of the Poincaré–Bendixson theorem to dimension 3; see, e.g., [5, 6] or Theorem 4.1 in [16]: A compact limit set of a competitive system in $R^3$ which contains no steady states is a periodic orbit. Furthermore, a periodic orbit of a competitive system in $R^3$ must contain a steady state inside a certain topological closed ball on the surface of which lies the periodic orbit; see Theorem 2.4 in [17]. These results will play a major role in our analysis.

We will also exploit the "isomorphism" between system (1) with $f = f_2$ and the standard SEIR model with constant population size, analyzed by Li and Muldowney in their well-known paper [10]. Although this isomorphism breaks down when $f \neq f_2$ or when the $-kVT$ term is included in the $V$ equation, the method used by Li and Muldowney to prove orbital asymptotic stability of any periodic orbit, and thereby to derive a contradiction to their existence, extends under suitable restrictions.

We identify a basic reproduction number $R_0$ for the model, which gives the number of infected T cells produced by a single infected T cell in a healthy individual. Our main results are formulated in terms of this number and extend the existing ones in the following five directions:

1. If $R_0 < 1$, we show that the virus is cleared.
2. If $R_0 > 1$, then a chronic disease steady state exists which is globally asymptotically stable under certain conditions. In particular, these conditions are satisfied for the special case $f = f_2$ using parameter values appropriate for HIV.
3. For $f = f_1$, orbitally asymptotically stable periodic orbits are shown to exist and to attract almost all solutions under suitable conditions if $R_0 > 1$. These conditions are apparently not satisfied for HIV. We note that sustained oscillations were observed from numerical simulations by Perelson, Kirschner, and de Boer [15] in a four dimensional model including a compartment of latently infected T cells.
4. Since the function $f$, which models healthy $T$ cell dynamics, is poorly understood, we start analyzing our model with only minimal assumptions on $f$. We

show that particular choices for $f$ may lead to different qualitative behavior. For example, for $f = f_2$ the chronic disease steady state, if it exists, is always locally asymptotically stable, while for $f = f_1$ this steady state may be unstable and sustained oscillations may occur. This sensitivity of the behavior to $f$, in particular, calls for a better understanding of the mechanisms of $T$ cell proliferation.

5. Applications are made to drug therapy following Perelson and Nelson's treatment in [14].

**2. Main results.** We consider a model of a virus infecting a target cell population. Denoting by $T$ the target cell and using the same symbol for its concentration in the appropriate bodily fluid, we assume that the target cell population is regulated in a healthy individual according to some dynamics given by

$$\dot{T} = f(T),$$

where $f$ is a smooth function. We expect homeostasis to be maintained in a healthy individual with $T$ cell levels at some positive steady state $\bar{T} > 0$. Therefore, assume that $f$ satisfies

$$f(T) > 0,\ 0 \le T < \bar{T}, \quad f(\bar{T}) = 0, \quad f'(\bar{T}) < 0, \quad \text{and} \quad f(T) < 0,\ T > \bar{T}. \tag{4}$$

Consider an individual infected with a virus $V$ which attacks target cells, producing productively infected cells $T^*$, which, in turn, produce on average $N$ virus particles during their life spans. Following [14, 12], we obtain the following system for the dynamics of $T, T^*, V$:

$$\begin{aligned} \dot{T} &= f(T) - kVT, \\ \dot{T}^* &= -\beta T^* + kVT, \\ \dot{V} &= -\gamma V + N\beta T^* - ikVT, \end{aligned} \tag{5}$$

where $i = 0$ if we choose, following [14, 12], to ignore the loss of a viral particle when it enters a target cell, or $i = 1$ when we do not.

The basic reproduction number for the model is intuitively determined by considering the fate of a single productively infected cell in an otherwise healthy individual with normal target cell level $T = \bar{T}$. This infected cell produces $N$ virions, each with life span $\gamma^{-1}$, which will infect $k\bar{T}N\gamma^{-1}$ healthy target cells. Thus we expect the amplification factor to be $k\bar{T}N\gamma^{-1}$. In fact, a local stability calculation, carried out in the proof of Lemma 3.2 below, leads to

$$R_0 = \frac{k\bar{T}(N - i)}{\gamma}, \tag{6}$$

reflecting the loss of the original productively infected cell if $i = 1$. In any case, as $N$ is typically large, this is a minor point.

Our main result, proved in a series of results in the next section, shows that the global dynamics is largely determined by $R_0$.

THEOREM 2.1.

1. *For $R_0 < 1$ the only steady state is the disease-free state $E_0 \equiv (\bar{T}, 0, 0)$, and it is globally attracting; the virus is cleared.*

2. *For $R_0 > 1$, in addition to the disease-free state, which is unstable, there is a "chronic disease" steady state $E_e \equiv (T_e, T_e^*, V_e)$ given by*

$$T_e = \frac{\gamma}{k(N-i)}(\equiv \bar{T}/R_0), \quad T_e^* = \frac{\gamma V_e}{(N-i)\beta}, \quad V_e = \frac{f(T_e)}{kT_e}, \tag{7}$$

*which is locally attracting if $f'(T_e) \le 0$, e.g., when $f = f_2$.*
*In particular, with $R_0$ as a bifurcation parameter, $E_0$ exchanges its local stability properties with $E_e$ when $R_0$ passes through 1, making $E_e$ locally attracting if $R_0 > 1$ and $R_0 - 1$ small.*
*The disease persists in the sense that there exist $\epsilon > 0$ and $M > 0$, independent of initial data $(T_0, T_0^*, V_0)$ satisfying $T_0^* + V_0 > 0$, such that*

$$\epsilon < T(t), T^*(t), V(t) < M$$

*for all large $t$.*
*The omega limit set of every solution with initial conditions as restricted above either contains $E_e$ or is a nontrivial periodic orbit.*
*If $f'(T) < 0$ for $T \in [0, \bar{T}]$, and denoting $0 < \alpha^* = -\max_{T\in[0,\bar{T}]} f'(T)$, $E_e$ is a globally asymptotically stable steady state for system (5) with respect to initial conditions not on the $T$ axis in case $i = 0$ or in case $i = 1$ and $kf(0) - \min(\alpha^*, \beta)\beta < 0$.*
*In the special case $f = f_1$, for both $i = 0, 1$ there exist parameter values for which $E_e$ is unstable with a two dimensional unstable manifold (see Lemma 3.4). In this case, there exists an orbitally asymptotically stable periodic orbit; every solution except those with initial data on the one dimensional stable manifold of $E_e$ or on the $T$ axis converges to a nontrivial periodic orbit.*

Observe that, as $f(T) > 0$ only if $T < \bar{T}$, the positivity of $V_e$ requires that $T_e < \bar{T}$, or equivalently, $R_0 > 1$.

Our main result says that if a typical productively infected target cell, introduced into an otherwise healthy individual where $T = \bar{T}$, cannot replace itself by producing virus that infects at least one healthy target cell, then the virus is eventually cleared and the individual returns to the disease-free state. However, if the infected cell can replace itself, then the disease persists indefinitely into the future in the sense that the viral load is ultimately bounded from below by an initial-condition-independent value. Moreover, the omega limit set either contains the chronic disease state $E_e$, coinciding with it in case it is locally attracting, or is a nontrivial periodic orbit. In the latter case, the viral load and the target cell populations cycle periodically.

If $f = f_2$ and $R_0 > 1$, then $f' = -\alpha < 0$ is automatically satisfied and therefore $E_e$ is globally asymptotically stable if $i = 0$ or if $i = 1$ and $kf_2(0) - \min(\alpha^*, \beta)\beta = k\delta - \min(\alpha, \beta)\beta < 0$. In case of HIV, $\alpha \le \beta$ is expected to hold, reflecting the fact that removal rates for healthy target cells are lower than those for infected target cells, and thus the last condition reduces to $k\delta - \alpha\beta < 0$, which is easily verified for the (biologically plausible) numerical data for HIV in [15].

In the special case $f = f_1$, $E_e$ is asymptotically stable when $R_0 > 1$ and $R_0 - 1$ is small, but this stability can be lost for certain parameter values. In Figure 1 below, we show that periodic oscillations in the viral load and T cell populations are possible. The parameter values are not chosen to match those for a particular viral infection; they are chosen simply to establish the possibility for oscillations. As in [15], time is measured in days and $T, T^*, V$ have units $\text{mm}^{-3}$. See Lemma 3.4 for more information about parameter ranges for which periodic solutions are expected.

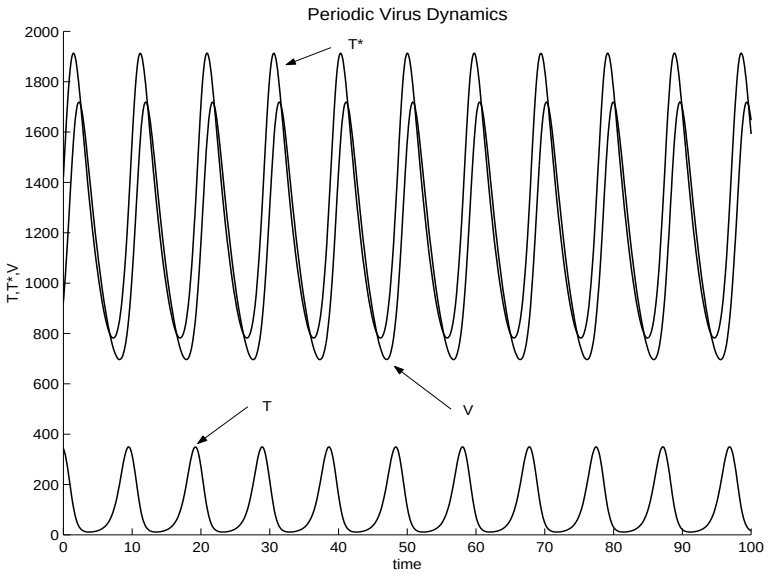


FIG. 1. *Periodic solution for* $f = f_1$. *Parameters:* $\delta = 10day^{-1}mm^{-3}, \alpha = 0.02day^{-1}$, $p = 3day^{-1}$, $T_{max} = 1500mm^{-3}$, $\beta = 0.24day^{-1}$, $\gamma = 2.4day^{-1}$, $k = 0.0027mm^3day^{-1}$, $N = 10$, *and* $i = 1$.

Our results can be used to give a mathematically rigorous justification for the plausible approximation arguments employed by Perelson and Nelson [14] to show that combination drug therapy can be effective in clearing the virus. Currently, the main drugs are RT inhibitors and protease inhibitors, and in practice, cocktails of several of these drugs have been most successful. The first type inhibits the copying of viral RNA to DNA and results in unsuccessful infection of the T cell by the virus. The second type results in virus particles that are noninfectious. Following [14], the short-term behavior after infection is given by the following system describing uninfected and infected T cells, infectious virus $V_I$, and noninfectious virus $V_{NI}$:

$$\begin{aligned} \dot{T} &= f(T) - k(1-\eta_{RT})V_I T, \\ \dot{T}^* &= -\beta T^* + k(1-\eta_{RT})V_I T, \\ \dot{V}_I &= -\gamma V_I + N\beta(1-\eta_{PI})T^* - ikV_I T, \\ \dot{V}_{NI} &= -\gamma V_{NI} + N\beta\eta_{PI}T^*, \end{aligned} \tag{8}$$

where, again, $i = 0$ corresponds to the system treated in [14], and $i = 1$ takes account of the loss of a virus particle when it enters a target cell (whether or not the virus is able to convert its RNA to DNA and insert itself in the host genome). The "effectiveness" coefficients $\eta_{RT}$ for RT inhibitor and $\eta_{PI}$ for protease inhibitor are assumed to lie somewhere between zero, meaning totally ineffective, and one, which represents 100% effectiveness.

Of course, the primary focus of drug therapy is on the possibility of clearing the virus. Observing that the first three equations are decoupled from the last one and that this subsystem is essentially similar to (5), we can calculate the basic reproduction number $R_0^c$ under combination therapy by linearizing about the disease-free state $E_0$

to obtain

$$R_0^c = \frac{k\bar{T}[N(1-\eta_{RT})(1-\eta_{PI}) - i]}{\gamma}. \tag{9}$$

Comparing this with (6), we see that, in essence, $N$ has been reduced to $N(1-\eta_{RT})(1-\eta_{PI})$. As $i$ is typically much smaller than $N$ and can be neglected, we see that the two inhibitors act in concert to reduce $R_0$ in (6) by the factor $(1-\eta_{RT})(1-\eta_{PI})$. If $R_0^c < 1$, the virus is cleared.

COROLLARY 2.2. *If $R_0^c < 1$, then the disease-free steady state $E_0$ is globally attracting. If $R_0^c > 1$, then $E_0$ is unstable.*

Assuming that current treatment does not allow for HIV eradication in an individual, this result implies one of the following: The efficiency of drugs is never high enough to make $R_o^c < 1$, or model (8) is not appropriate to describe HIV dynamics in a treated individual. It is argued in the recent paper by Callaway and Perelson that the first explanation is not viable. The second is adopted instead, and modified models are proposed to bring reality and theory closer to each other; see [2] for details.

## 3. Proofs.

**3.1. Boundedness and stability of the disease-free steady state.** First we show that solutions of model (5) are bounded.

LEMMA 3.1. *The closed positive orthant is positively invariant for* (5) *and there exists $M > 0$ such that all solutions satisfy $T(t), T^*(t), V(t) < M$ for all large $t$.*

*Proof.* The positive invariance of the positive orthant is trivial; we sketch the ultimate boundedness argument. Since $\dot{T} < f(T)$, we see that $T(t) < \bar{T} + 1$ for all large $t$, say $t > t_0$. Let $S = \max_{T \geq 0} f(T)$. Adding the first two equations gives $\dot{T} + \dot{T}^* = f(T) - \beta T^* \leq S - \beta T^*$. Let $A > 0$ be such that $\beta A > S + 1$. Then, so long as $T(t) + T^*(t) \geq A + \bar{T} + 1$ and $t > t_0$, we have $\dot{T} + \dot{T}^* < -1$. Clearly, there must exist $t_1 > t_0$ such that $T(t) + T^*(t) < A + \bar{T} + 1$ for all $t > t_1$.

The asymptotic bound for $T^*(t)$, namely, $T(t)^* \leq A + \bar{T} + 1$, together with the differential inequality $\dot{V} \leq -\gamma V + N\beta[A + \bar{T} + 1]$, which holds for large $t$, leads immediately to the asymptotic bound $V(t) \leq \gamma^{-1} N\beta[A + \bar{T} + 1]$. ∎

Next we consider the local stability behavior of (5) at the disease-free steady state $E_0$.

LEMMA 3.2. *If $R_0 < 1$, then the disease-free state $E_0$ is a locally asymptotically stable steady state of system* (5)*; if $R_0 > 1$, then it is unstable.*

*Proof.* The Jacobian matrix of the vector field corresponding to system (5), evaluated at $E_0$, is

$$J_0 := \begin{pmatrix} f'(\bar{T}) & 0 & -k\bar{T} \\ 0 & -\beta & k\bar{T} \\ 0 & N\beta & -\gamma - ik\bar{T} \end{pmatrix}. \tag{10}$$

Here $f'(\bar{T}) < 0$ is an eigenvalue, and the remaining eigenvalues derive from the two-by-two lower right submatrix, whose trace is negative and determinant is $\beta\gamma[1 - R_0]$. The result follows immediately. ∎

We remark that the same result holds for (8) with drug therapy, where $R_0^c$ replaces $R_0$.

The following result deals with the global stability behavior of the disease-free steady state $E_0$.

LEMMA 3.3. *If $R_0 < 1$, then all solutions approach the disease-free state $E_0$.*

*Proof.* On consideration of the competitive vector field given by (5) on the three faces of the positive orthant, we see that any nontrivial periodic orbit must lie entirely in the interior of the positive orthant. If $P$ denotes such a nontrivial periodic orbit, then it follows that the smallest box $B$ containing $P$ whose sides are parallel to the coordinate planes must also lie interior to the positive orthant. We can express $B$ as $B = [p, q]_K$, where $K$ denotes the cone $K \equiv \{(T, T^*, V) : T, V \geq 0, T^* \leq 0\}$. Indeed, if $X^P$ (respectively, $X_P$) denotes the maximum (respectively, minimum) of coordinate $X = T, T^*, V$ on the periodic orbit $P$, then $p = (T_P, T^{*P}, V_P)$ and $q = (T^P, T^*_P, V^P)$. By Proposition 4.3 of [16], $B$ must contain a steady state of (5). However, $E_0$ is the only steady state and $E_0 \notin B$. We conclude that no nontrivial periodic orbit exists. By the Poincaré–Bendixson theory for three dimensional competitive systems and the local stability of $E_0$, all solutions must approach $E_0$ in the limit. ∎

The same result holds for (8), with $R_0^c$ in place of $R_0$. The entirely similar argument uses the fact that an endemic steady state exists only when the disease-free state is unstable ($R_0^c > 1$).

**3.2. Local stability of the disease steady state.** The local stability of the disease steady state is discussed next.

LEMMA 3.4. *Let $R_0 > 1$ and $f'(T_e) \leq 0$; then the nontrivial steady state $E_e \in \mathrm{int}(R^3_+)$ is locally asymptotically stable for system (5), for $i = 0, 1$. If $R_0 > 1$ and $f = f_1$, then $E_e$ is unstable with a two dimensional unstable manifold under each of the following conditions:*

(a) *$i = 0$ with $T_{max}$ large enough and (19) holds.*

(b) *$i = 1$ with $kT_{max}$ large (see (20)) and $p$ large enough.*

*Proof.* A calculation shows that the Jacobian matrix of the vector field corresponding to system (5), evaluated at $E_e$, takes the following form:

$$J_1 := \begin{pmatrix} -a & 0 & -kT_e \\ kV_e & -\beta & kT_e \\ -ikV_e & N\beta & -c \end{pmatrix}, \tag{11}$$

where

$$a := -f'(T_e) + kV_e \quad \text{and} \quad c := \gamma + ikT_e. \tag{12}$$

The characteristic equation associated with $J_1$ is given by

$$\lambda^3 + (a + \beta + c)\lambda^2 + [a(\beta + \gamma) - ikT_e f'(T_e)]\lambda + k\beta\gamma V_e = 0, \tag{13}$$

where we have used the expressions (6), (7) to simplify the coefficient of first and zeroth order. If $f'(T_e) \leq 0$, then it is easy to see that all coefficients are positive.

To finish the proof by means of the Routh–Hurwitz criterion, we need to show that

$$\Delta \equiv (a + \beta + c)(a(\beta + \gamma) - ikT_e f'(T_e)) - k\beta\gamma V_e \tag{14}$$

is positive. Using (12), it follows that

$$\begin{aligned} \Delta &= (-f'(T_e) + kV_e + \beta + \gamma + ikT_e)[(-f'(T_e) + kV_e)(\beta + \gamma) - ikT_e f'(T_e)] - k\beta\gamma V_e \\ &= (\beta + \gamma)^2(kV_e - f'(T_e)) - (\beta + \gamma)ikT_e f'(T_e) + (\beta + \gamma)ikT_e(kV_e - f'(T_e)) \\ &\quad - (ikT_e)^2 f'(T_e) + (\beta + \gamma)(kV_e - f'(T_e))^2 - ikT_e f'(T_e)(kV_e - f'(T_e)) \\ &\quad - k\beta\gamma V_e. \end{aligned} \tag{15}$$

If $f'(T_e) \leq 0$, then all terms in (15) are nonnegative except the last. However, the very first term $(\beta+\gamma)^2(kV_e - f'(T_e))$ can be expanded, yielding a term $2\beta\gamma kV_e$, which exceeds the last term $-k\beta\gamma V_e$. This implies that $\Delta$ is positive.

Hereafter, we consider the case in which $f = f_1$. A calculation yields

$$a = \frac{\delta}{T_e} + \frac{pT_e}{T_{max}} > 0, \tag{16}$$

and thus the coefficients of the zero and second powers of $\lambda$ in the characteristic polynomial are positive. Together with the claim (which is proved below) that the Jacobian matrix has a real eigenvalue which is strictly less than the real parts of any other eigenvalue, it follows that if the Jacobian is hyperbolic and unstable, then there can be only one eigenvalue with negative real part (in fact it is negative) and two with positive real part. Further, hyperbolicity can only fail by a pair of pure imaginary eigenvalues and one negative eigenvalue.

*Proof of claim.* We prove that the Jacobian matrix possesses a real eigenvalue which is strictly less than the real part of the other eigenvalues. This follows from an application of the Perron–Frobenius theorem. Recall that the Perron–Frobenius theorem holds for nonnegative matrices and states that these matrices possess a real eigenvalue which is nonnegative. In addition, the modulus of every eigenvalue is not larger than this real eigenvalue. Now notice that the linear transformation $(x, y, z) \to (x, -y, z)$ puts $J_1$ in the following form:

$$\tilde{J}_1 := \begin{pmatrix} -a & 0 & -kT_e \\ -kV_e & -\beta & -kT_e \\ -ikV_e & -N\beta & -c \end{pmatrix}. \tag{17}$$

Of course, the eigenvalues of $J_1$ and $\tilde{J}_1$ are the same. Finally, observe that $-\tilde{J}_1$ is a nonnegative matrix for which the Perron–Frobenius theorem holds. The claim then follows immediately since the eigenvalues of $-\tilde{J}_1$ are the opposites of the eigenvalues of $J_1$.

If $i = 0$ and $f = f_1$, then all coefficients of (13) are positive as noted above. Inserting (16) and the values of $V_e, T_e$ into (15) leads to

$$\begin{aligned} \Delta &= (\beta+\gamma)^2 a + (\beta+\gamma)a^2 - k\beta\gamma V_e \\ &= m\left(\frac{p}{T_{max}}\right)^2 + n\frac{p}{T_{max}} + q, \end{aligned} \tag{18}$$

where

$$\begin{aligned} m &= \frac{(\beta+\gamma)\gamma^2}{(Nk)^2}, \\ n &= \frac{(\beta+\gamma)^2\gamma}{Nk} + 2\delta(\beta+\gamma) - \beta\gamma T_{max} + \frac{\beta\gamma^2}{Nk}, \\ q &= (\beta+\gamma)^2\frac{Nk\delta}{\gamma} + (\beta+\gamma)\frac{(Nk\delta)^2}{\gamma^2} - \beta\delta Nk + \beta\gamma\alpha. \end{aligned}$$

Clearly, $m > 0$ and, less obviously, $q > 0$ since the first term exceeds the third in absolute value. By choosing $T_{max}$ large, we may make $n < 0$ and as large in absolute value as we desire. In particular, if $n < 0$ and $n^2 > 4om$, then the quadratic (18) in

$p/T_{max}$ is negative for an interval of values of $p/T_{max}$ centered on

$$\frac{p}{T_{max}} = \frac{-n}{2m}, \tag{19}$$

ensuring that $\Delta < 0$. It follows that $E_e$ is hyperbolic and unstable with a two dimensional unstable manifold.

If $i = 1$ and $f = f_1$, then a straightforward calculation shows that the coefficient of $\lambda$ in (13) is given by

$$a_2 \equiv \frac{\gamma p}{N-1}\left[\frac{\beta+\gamma}{kT_{max}} + \frac{2\gamma}{k(N-1)T_{max}} - 1\right] + \frac{\gamma\alpha}{N-1} + \frac{(\beta+\gamma)\delta(N-1)k}{\gamma},$$

which can be negative when the term in brackets is negative, provided that $p$ is large enough. Fixing $kT_{max}$ so large that

$$kT_{max} > \beta + \gamma + \frac{2\gamma}{N-1} \tag{20}$$

ensures that the term in brackets is negative. Then, provided that $p$ is large enough, it follows that $E_e$ is hyperbolic and unstable with a two dimensional unstable manifold. □

**3.3. Disease persistence.** We discuss persistence of the disease next.

LEMMA 3.5. *If $R_0 > 1$, then there exists $\epsilon > 0$, independent of initial conditions satisfying $T^*(0) + V(0) > 0$, such that $\liminf_{t\to\infty} X(t) > \epsilon$ for $X = T, T^*, V$.*

*Proof.* The result follows from an application of Theorem 4.6 in [19], with $X_1 = \text{int}(R^3_+)$ and $X_2 = \text{bd}(R^3_+)$. This choice is in accordance with the conditions stated in this theorem. Furthermore, note that by virtue of Lemma 3.1 there exists a compact set $B$ in which all solutions of system (5) initiated in $R^3_+$ ultimately enter and remain forever after. The compactness condition $(C_{4.2})$ is easily verified for this set $B$. Denoting the omega limit set of the solution $x(t, x_0)$ of system (5) starting in $x_0 \in R^3_+$ by $\omega(x_0)$ (which exists by Lemma 3.1), we need to determine the following set:

$$\Omega_2 = \cup_{y\in Y_2}\omega(y), \quad \text{where } Y_2 = \{x_0 \in X_2 |\, x(t, x_0) \in X_2, \forall t > 0\}. \tag{21}$$

From the system equations (5) it follows that all solutions starting in $\text{bd}(R^3_+)$ but not on the $T$ axis leave $\text{bd}(R^3_+)$ and that the $T$ axis is an invariant set, implying that $Y_2 = \{(T, T^*, V)^T \in \text{bd}(R^3_+) |\ T^* = V = 0\}$. Furthermore, it is easy to see that $\Omega_2 = \{E_0\}$ as all solutions initiated on the $T$ axis converge to $E_0$. Then $E_0$ is a covering of $\Omega_2$, which is isolated (since $E_0$ is a hyperbolic steady state under the assumption of the theorem) and acyclic (because there is no nontrivial solution in $\text{bd}(R^3_+)$ which links $E_0$ to itself). Finally, if it is shown that $E_0$ is a weak repeller for $X_1$, the proof will be done.

By definition, $E_0$ is a weak repeller for $X_1$ if for every solution starting in $x_0 \in X_1$

$$\limsup_{t\to+\infty} d(x(t, x_0), E_0) > 0. \tag{22}$$

We claim that (22) is satisfied if the following holds:

$$W^s(E_0) \cap \text{int}(R^3_+) = \emptyset, \tag{23}$$

where $W^s(E_0)$ denotes the stable manifold of $E_0$. To see this, suppose that (22) does not hold for some solution $x(t, x_0)$ starting in $x_0 \in X_1$. In view of the fact that the closed positive orthant is positively invariant for system (5) (recall Lemma 3.1), it follows that $\liminf_{t\to+\infty} d(x(t, x_0), E_0) = \limsup_{t\to+\infty} d(x(t, x_0), E_0) = 0$ and thus that $\lim_{t\to+\infty} x(t, x_0) = E_0$, which is clearly impossible if (23) holds.

What remains to be shown is that (23) holds. To that end, recall that the Jacobian matrix of system (5) at $E_0$, given in (10), is unstable if $R_0 > 1$. In particular, $J_0$ possesses one eigenvalue with positive real part, which we denote as $\lambda_+$, and two eigenvalues with negative real part, $f'(\bar{T})$, and an eigenvalue which we denote as $\lambda_-$. (Note that $\lambda_-$ may be equal to $f'(\bar{T})$.) We proceed by determining the location of $E^s(E_0)$, the stable eigenspace of $E_0$. Clearly $(1, 0, 0)^T$ is an eigenvector of $J_0$ associated to $f'(\bar{T})$. If $\lambda_- \neq f'(\bar{T})$, then the eigenvector associated to $\lambda_-$ has the following structure: $(0, p_2, p_3)^T$, where $p_2$ and $p_3$ satisfy the eigenvector equation

$$\begin{pmatrix} -\beta & k\bar{T} \\ N\beta & -\gamma - ik\bar{T} \end{pmatrix} \begin{pmatrix} p_2 \\ p_3 \end{pmatrix} = \lambda_- \begin{pmatrix} p_2 \\ p_3 \end{pmatrix}. \tag{24}$$

If $\lambda_- = f'(\bar{T})$, then $\lambda_-$ is a repeated eigenvalue, and an associated generalized eigenvector will possess the following structure: $(*, p_2, p_3)^T$, where the value of $*$ is irrelevant for what follows and $p_2$ and $p_3$ also satisfy (24).

We claim that in both cases (i.e., $\lambda_- \neq f'(\bar{T})$ and $\lambda_- = f'(\bar{T})$) the vector $(p_2, p_3)^T \notin R^2_+$. The matrix in (24) is an irreducible Metzler matrix. A Metzler matrix is a matrix with nonnegative off-diagonal entries. For the definition of an irreducible matrix, see [4]. Observe that adding a sufficiently large positive multiple of the identity matrix to the matrix in (24) results in a nonnegative irreducible matrix for which the Perron–Frobenius theorem [4] holds. Consequently, the matrix in (24) possesses a simple real eigenvalue which is larger than the real part of any other eigenvalue, also called the *dominant eigenvalue*. Clearly, the dominant eigenvalue here is $\lambda_+$. But the Perron–Frobenius theorem also implies that every eigenvector that is not associated with the dominant eigenvalue does not belong to the closed positive orthant. Applied here, this means that $(p_2, p_3) \notin R^2_+$. Consequently, $E_s(E_0) \cap \mathrm{int}(R^3_+) = \emptyset$, and therefore also $W^s(E_0) \cap \mathrm{int}(R^3_+) = \emptyset$, which concludes the proof. □

**3.4. Oscillations.** Lemma 3.4 provides sufficient conditions for the Jacobian at $E_e$ to have two eigenvalues with positive real part and one negative eigenvalue. The dynamical consequences of this are described in the following result.

LEMMA 3.6. *If $R_0 > 1$, the omega limit set of a solution which is not initiated on the $T$ axis either contains $E_e$ or is a nontrivial periodic orbit. If $R_0 > 1$ and if the Jacobian matrix at $E_e$ has two eigenvalues with positive real part and one negative eigenvalue, then there exists an orbitally asymptotically stable periodic orbit. Every solution except those with initial data on the one dimensional stable manifold of $E_e$ or on the $T$ axis approaches a nontrivial periodic orbit.*

*Proof.* For $R_0 > 1$ it follows from the persistence result in Lemma 3.5 that the omega limit set of a solution which is not initiated on the $T$ axis cannot contain a point on the $T$ axis. Since there is only one steady state $E^e$ which does not belong to the $T$ axis, the first statement of the theorem follows from the generalized Poincaré–Bendixson theorem for competitive systems in dimension 3.

The assertions regarding the existence of an orbitally asymptotically stable periodic orbit follow from Theorem 1.2 in [20] and the fact that nonlinearities in (5) are analytic. In order to apply that result, we take the domain for (5) to be the interior of the positive orthant, in which the only steady state is $E_e$. Lemmas 3.1 and 3.5

imply that the dissipativity hypothesis of Theorem 1.2 is satisfied. The negativity of the Jacobian determinant, also required for Theorem 1.2, follows from our hypotheses concerning the eigenvalues. The assertion that suitably restricted forward orbits approach a periodic orbit follows from Theorem 4.2 in [16]. That result is stated for systems which are competitive in the traditional sense and so it applies to (5) since it can be transformed to a system which is competitive in the traditional sense. See also the remarks following Theorem 4.2, where it is noted that the second hypothesis of Theorem 4.2 holds if the Jacobian matrix is irreducible. □

**3.5. Global asymptotic stability of the disease steady state.** Finally we provide sufficient conditions preventing oscillations and leading to a globally asymptotically stable disease steady state.

LEMMA 3.7. *Suppose that* $R_0 > 1$, $f'(T) < 0$ *for* $T \in [0, \bar{T}]$, *and denote* $0 < \alpha^* = -\max_{T\in[0,\bar{T}]} f'(T)$. *If* $i = 0$ *or if* $i = 1$ *and* $kf(0) - \min(\alpha^*, \beta)\beta < 0$, *then* $E_e$ *is a globally asymptotically stable steady state for system* (5) *with respect to initial conditions not on the* $T$ *axis.*

*Proof.* The proof is based on an extension of the Poincaré–Bendixson theorem for the class of three dimensional competitive systems [16] and a powerful theory of second compound equations to prove asymptotic orbital stability of periodic solutions; see [10] and references cited therein. We do not wish to repeat the details of a precise proof here, because many of the arguments are the same as in [10], where a global stability result for a related epidemiological model is proved. Instead we provide only a sketch of the proof and go into details only where our proof is different. Under the assumptions of this lemma, system (5) possesses a steady state $E_e \in \text{int}(R^3_+)$, which is unique in $\text{int}(R^3_+)$. Moreover, from the proof of Lemma 3.5 it follows that the omega limit sets of solutions not initiated on the $T$ axis are in $\text{int}(R^3_+)$. We claim that the only possible omega limit sets of solutions of system (5) are $E_e$ or nontrivial periodic orbits. Indeed, if an omega limit set of a solution does not possess $E_e$, then it cannot contain another steady state ($E_e$ is the unique steady state in $\text{int}(R^3_+)$), and thus it must be a nontrivial periodic orbit according to the extension of the Poincaré–Bendixson theorem for competitive systems. On the other hand, if an omega limit set does contain $E_e$, it *is* $\{E_e\}$, because $E_e$ is a locally asymptotically stable steady state of system (5) according to Lemma 3.4 (notice that the condition needed to apply this Lemma, $f'(T_e) \le 0$, is satisfied here because $T_e = \bar{T}/R_0 < \bar{T}$ and $f' < 0$ in $[0, \bar{T}]$ by assumption), which establishes the claim. Finally we will show below that if system (5) possesses a nontrivial periodic solution, then this solution must be asymptotically orbitally stable. This fact will imply that $E_e$ is a globally asymptotically stable steady state of system (5) with respect to initial conditions not on the $T$ axis, which concludes the proof of this theorem. A proof of this implication can be found in [10]. The argument is that if $E_e$ would not be globally asymptotically stable, then there would have to be a nontrivial periodic solution in $\text{int}(R^3_+)$. But it can then be shown that the region of attraction of $E_e$ would have nonempty intersection with the region of attraction of the periodic solution, a contradiction. We prove the following: If system (5) possesses a nontrivial period solution, then this solution is asymptotically orbitally stable. Denote the periodic solution by $p(t) \equiv (p_1(t), p_2(t), p_3(t))^T$ and suppose that its minimal period is $\omega > 0$. Recall that from the proof of Lemma 3.1

$$0 \le p_1(t) \le \bar{T} \qquad \forall t \in [0, \omega]. \tag{25}$$

To establish asymptotic orbital stability of a periodic solution, we resort to the so-called method of the second compound equation; see [10] and references cited therein.

The second compound equation is the following periodic linear system:

$$\dot{z} = \frac{\partial f^{[2]}}{\partial x}(p(t))z, \tag{26}$$

where $z = (z_1, z_2, z_3)^T$ and $\frac{\partial f^{[2]}}{\partial x}$ is derived from the Jacobian matrix of system (5) and defined as follows:

$$\begin{aligned}\frac{\partial f^{[2]}}{\partial x} &:= \begin{pmatrix} j_{11}+j_{22} & j_{23} & -j_{13} \\ j_{32} & j_{11}+j_{33} & j_{12} \\ -j_{31} & j_{21} & j_{22}+j_{33} \end{pmatrix} \\ &= \begin{pmatrix} f'(T)-\beta-kV & kT & kT \\ N\beta & f'(T)-\gamma-k(iT+V) & 0 \\ ikV & kV & -\beta-\gamma-ikT \end{pmatrix}, \end{aligned} \tag{27}$$

where $j_{kl}$ is the $(k, l)$th entry of the Jacobian matrix associated with system (5). The importance of the second compound equation is that if system (26) is asymptotically stable, then the periodic solution $p(t)$ is asymptotically orbitally stable for system (5); see [10]. We will show that the function

$$V(z_1, z_2, z_3; p(t)) := \sup\left\{|z_1|, \frac{p_2(t)}{p_3(t)}(|z_2|+|z_3|)\right\} \tag{28}$$

is a Lyapunov function for system (26). This function is positive, but not differentiable everywhere. Fortunately, this lack of differentiability can be remedied by using the right derivative of $V$, denoted as $D_+V(t)$. We have

$$D_+(|z_1(t)|) \le -(-f'(p_1(t)) + \beta + kp_3(t)).|z_1(t)| + k\frac{p_1(t)p_3(t)}{p_2(t)}.\frac{p_2(t)}{p_3(t)}(|z_2(t)|+|z_3(t)|) \tag{29}$$

and

$$\begin{aligned} D_+\left(\frac{p_2(t)}{p_3(t)}(|z_2(t)|+|z_3(t)|)\right) &= \left(\frac{\dot{p}_2(t)}{p_2(t)} - \frac{\dot{p}_3(t)}{p_3(t)}\right).\frac{p_2(t)}{p_3(t)}(|z_2(t)|+|z_3(t)|) \\ &\quad + \frac{p_2(t)}{p_3(t)}D_+(|z_2(t)|+|z_3(t)|) \\ &\le \left(\frac{p_2(t)}{p_3(t)}(N\beta + ikp_3(t))\right).|z_1(t)| \\ &\quad + \left(\frac{\dot{p}_2(t)}{p_2(t)} - \frac{\dot{p}_3(t)}{p_3(t)} - \gamma - ikp_1(t)\right).\frac{p_2(t)}{p_3(t)}(|z_2(t)|+|z_3(t)|) \\ &\quad - \frac{p_2(t)}{p_3(t)}(-f'(p_1(t))|z_2(t)| + \beta|z_3(t)|) \\ &\le \left(\frac{p_2(t)}{p_3(t)}(N\beta + ikp_3(t))\right).|z_1(t)| \\ &\quad + \left(\frac{\dot{p}_2(t)}{p_2(t)} - \frac{\dot{p}_3(t)}{p_3(t)} - \gamma - ikp_1(t) \right. \\ &\qquad \left. - \min(\alpha^*, \beta)\right).\frac{p_2(t)}{p_3(t)}(|z_2(t)|+|z_3(t)|), \end{aligned}$$

where the last inequality was obtained using the definition of $\alpha^*$ and (25).

Defining the following functions,

$$g_1(t) = -(-f'(p_1(t)) + \beta + kp_3(t)) + k\frac{p_1(t)p_3(t)}{p_2(t)}$$

$$= -(-f'(p_1(t)) + kp_3(t)) + \frac{\dot{p}_2(t)}{p_2(t)}, \tag{30}$$

$$g_2(t) = \frac{p_2(t)}{p_3(t)}(N\beta + ikp_3(t)) + \frac{\dot{p}_2(t)}{p_2(t)} - \frac{\dot{p}_3(t)}{p_3(t)} - \gamma - ikp_1(t) - \min(\alpha^*, \beta)$$

$$= ikp_2(t) + \frac{\dot{p}_2(t)}{p_2(t)} - \min(\alpha^*, \beta), \tag{31}$$

where the second equalities in (30) and (31) stem from the fact that $p(t)$ satisfies the system equations (5), we obtain that

$$D_+V(t) \le \sup(g_1(t), g_2(t))V(t). \tag{32}$$

Using the definition of $\alpha^*$ and (25), it follows from (30) that $g_1(t) \le -\alpha^* + \dot{p}_2(t)/p_2(t)$, and thus that $g_1(t) \le g_2(t)$. Then (32) can be rewritten as

$$D_+V(t) \le g_2(t)V(t). \tag{33}$$

We claim that the following holds:

$$\int_0^\omega g_2(t)dt < 0. \tag{34}$$

If this is established, it will follow from (33) that $V$ is a Lyapunov function for system (26), and this will conclude the proof of the theorem.

(a) When $i = 0$, (34) is immediate from (31).

(b) When $i = 1$, using the fact that $p(t)$ is a periodic solution of (5), we see that

$$\int_0^\omega \beta p_2(t)dt = \int_0^\omega kp_3(t)p_1(t)dt = \int_0^\omega f(p_1(t))dt \le f(0)\omega$$

because, by assumption, $f'(T) < 0$ for all $T \in [0, \bar{T}]$ and since (25) holds. Consequently,

$$\int_0^\omega g_2(t)dt = \int_0^\omega [kp_2(t) - \min(\alpha^*, \beta)]dt \le \left[k\frac{f(0)}{\beta} - \min(\alpha^*, \beta)\right]\omega, \tag{35}$$

and it follows, under the assumption that $kf(0) - \min(\alpha^*, \beta)\beta < 0$, that (34) holds as claimed. □

## REFERENCES


[1] E. Beretta and Y. Kuang, *Modeling and analysis of a marine bacteriophage infection*, Math. Biosci., 149 (1998), pp. 57–76.

[2] D.S. Callaway and A.S. Perelson, *HIV-1 infection and low steady state viral loads*, Bull. Math. Biol., 64 (2002), pp. 29–64.

[3] R.V. Culshaw and S. Ruan, *A delay-differential equation model of HIV infection of CD4$^+$ T-cells*, Math. Biosci., 165 (2000), pp. 27–39.

[4] F.R. Gantmacher, *The Theory of Matrices*, Chelsea, New York, 1959.

[5] M.W. Hirsch, *Systems of differential equations which are competitive or cooperative.* I: *Limit sets*, SIAM J. Math. Anal., 13 (1982), pp. 167–179.
[6] M.W. Hirsch, *Systems of differential equations that are competitive or cooperative* II: *Convergence almost everywhere*, SIAM J. Math. Anal., 16 (1985), pp. 423–439.
[7] M.W. Hirsch, *Systems of differential equations which are competitive or cooperative* III: *Competing species*, Nonlinearity, 1 (1988), pp. 51–71.
[8] M.W. Hirsch, *Systems of differential equations that are competitive or cooperative.* IV: *Structural stability in three-dimensional systems*, SIAM J. Math. Anal., 21 (1990), pp. 1225–1234.
[9] S. Merrill, *Modeling the interaction of HIV with the cells of the immune system*, in Mathematical and Statistical Approaches to AIDS Epidemiology, Lecture Notes in Biomath. 83, Springer-Verlag, New York, 1989.
[10] M.Y. Li and J.S. Muldowney, *Global stability for the SEIR model in epidemiology*, Math. Biosci., 125 (1995), pp. 155–164.
[11] M.A. Nowak and C.R.M. Bangham, *Population dynamics of immune responses to persistent viruses*, Science, 272 (1996), pp. 74–79.
[12] M.A. Nowak and R.M. May, *Virus Dynamics*, Oxford University Press, New York, 2000.
[13] 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), pp. 1582–1585.
[14] A.S. Perelson and P.W. Nelson, *Mathematical analysis of HIV-1 dynamics in vivo*, SIAM Rev., 41 (1999), pp. 3–44.
[15] A.S. Perelson, D.E. Kirschner, and R. de Boer, *Dynamics of HIV infection of $CD4^+$ T cells*, Math. Biosci., 114 (1993), pp. 81–125.
[16] H.L. Smith, *Monotone Dynamical Systems*, AMS, Providence, RI, 1995.
[17] H.L. Smith, *Periodic orbits of competitive and cooperative systems*, J. Differential Equations, 65 (1986), pp. 361–373.
[18] H.L. Smith, *Systems of ordinary differential equations which generate an order preserving flow. A survey of results*, SIAM Rev., 30 (1988), pp. 87–113.
[19] H.R. Thieme, *Persistence under relaxed point-dissipativity (with application to an endemic model)*, SIAM J. Math. Anal., 24 (1993), pp. 407–435.
[20] H.R. Zhu and H.L. Smith, *Stable periodic orbits for a class of three dimensional competitive system*, J. Differential Equations, 110 (1994), pp. 143–156.