GLOBAL ANALYSIS OF HIV MODELS

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Abstract

Exploiting the fact that standard models of within-host viral infections of target cell populations by HIV of Perelson et al and Nowak and May give rise to competitive three dimensional dynamical systems, we provide a global analysis of their dynamics. If the basic reproductive 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 either approaching a chronic disease steady state or a periodic orbit. The latter can be ruled out in some cases but not in general. Also simple drug treatment schemes are investigated.

1 Introduction

Recently there has been a substantial effort in the mathematical modeling of HIV dynamics see e.g. [9]. Perelson and Nelson [12] and Nowak and May [10] provide excellent reviews. 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 toward 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 [11, 12, 10].

We focus on the HIV models here but note, following [10], that the basic model applies to many other viral infections. A brief review of the salient features of the role of HIV in the disease will be useful. The mechanism of an HIV infection is as follows: First, the HIV virus 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 [12, 10] 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

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

because mass action reaction terms are used and each infected T cell is assumed to produce N viral particles over its life span. 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 [12, 10]. The functional form of f differs by author:

1. (Perelson et al [12]): $f(T) = f_1(T) \equiv \delta - \alpha T + pT(1 - \frac{T}{T_{max}})$.
2. (Nowak-May [10]): $f(T) = f_2(T) \equiv \delta - \alpha T$.

Parameters α, β, γ, δ, k, N, p and $T_{\max}$ are positive.

We briefly summarize the interpretation of the different parameters in the model. Parameters α, β and γ 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. δ represents a constant production of T cells in the thymus. In the literature this process is not always assumed to be constant, but to depend on virus loads. Usually δ is then replaced by a decreasing function of the concentration of virus particles. N is the average number of virus particles produced by an infected T cell. In case $f = f_1$, healthy T-cells are assumed to proliferate logistically, although the mechanisms for T-cell proliferation are largely unknown. The p and $T_{\max}$ are the growth rate, respectively carrying capacity associated to 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 simplifying the logistic term $pT(1-(T+T^*)/T_{\max})$ to $pT(1-T/T_{\max})$ is not always performed. 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 et al and Nowak and May ignore the loss term $-kVT$ which should appear in the V equation, i.e.,

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

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 term added on.

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 [10, 9] for models which include an immune response to the virus. More realistic models also include a compartment for latently infected T cells [12, 10] which are capable of but not actively producing virus. A related modeling approach consists in 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 [2]. 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 a very difficult task.

System (1), with or without the $-kVT$ term in the V equation, is competitive with respect to the cone $K := \{(T,\, T^*,\, V) \in \mathbb{R}^3 |\, T,\, V \geq 0,\, T^* \leq 0\}$, see [13]. Indeed, the Jacobian matrix of system (1) at an arbitrary point of $\mathbb{R}^3_+$ possesses the following structure (where a 0 can be replaced by either a $+$ or a $-$):

$$\begin{pmatrix} * & + & - \\ + & * & + \\ - & + & * \end{pmatrix} \tag{2}$$

which is sign-symmetric. The incidence graph associated to this matrix, where edges between the nodes are furnished with a $+$ or a $-$sign, depending on the sign of both 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 non-positive 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 M. Hirsch in a series of six well-known papers, of which we list [4, 5, 6, 7]. For a more recent review, see [13].

A particular consequence of the theory of competitive systems is a generalization of the Poincaré-Bendixson Theorem to dimension 3, see e.g. [4, 5] or Theorem 4.1 in [13]: A compact limit set of a competitive system in $\mathbb{R}^3$ which contains no steady states is a periodic orbit. Furthermore, a periodic orbit of a competitive system in $\mathbb{R}^3$ must contain a steady state inside a certain topological closed ball on the surface of which lies the periodic orbit [13]. 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 [8]. 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 reproductive 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 $f = f_1$ and both $i = 0, 1$, 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.
4. Part of the analysis of our model holds for rather general functions f which model healthy T cell dynamics, because this function is poorly known. We will show that particular choices for f may result in 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 mechanisms of T cell proliferation.
5. Applications are made to drug therapy following Perelson and Nelson's treatment in [12].

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

$$f(T) > 0 \text{ if } 0 \leq T < \bar{T},\; f(T) < 0 \text{ if } T > \bar{T},\; f'(\bar{T}) < 0, \tag{3}$$

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 its life span. Following [12, 10], we obtain the following system for the dynamics of T, T^*, V.

$$\begin{aligned} \dot{T} &= f(T) - kVT \\ \dot{T}^* &= -\beta T^* + kVT \\ \dot{V} &= -\gamma V + N\beta T^* - ikVT \end{aligned} \tag{4}$$

where $i = 0$ if we choose, following [12, 10], to ignore the loss of a viral particle when it enters a target cell, or $i = 1$ when we do not.

The basic reproductive number for the model is easily 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 γ^{-1}, which will infect $k\bar{T}N\gamma^{-1}$ healthy target cells. Thus we expect that the amplification factor to be $k\bar{T}N\gamma^{-1}$. In fact,

$$R_0 = \frac{k\bar{T}(N-i)}{\gamma} \tag{5}$$

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 is the following one which shows that the global dynamics is largely determined by R_0.

Theorem 1. *1. For $R_0 < 1$ the only steady state is the virus-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

$$T_e = \bar{T}/R_0, \quad T_e^* = \gamma V_e/(N-i)\beta, \quad V_e = f(T_e)/kT_e. \tag{6}$$

which is locally attracting if $f'(T_e) \leq 0$, 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 exists $\epsilon > 0$ 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 non-trivial 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 (4) 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 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 non-trivial 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 infect at least one healthy target cell, then the virus is eventually cleared and the individual returns to the virus-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, $\alpha \leq \beta$ is expected to hold, expressing that removal rates for healthy target cells is less than that 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 the special case $f = f_1$, E_e is asymptotically stable when $R_0 > 1$ and $R_0 - 1$ small but this stability can be lost for certain parameter values. Periodic oscillations in the viral load and T cell populations are possible, see [3]. The parameter values are not chosen to match those for a particular viral infection; they are chosen simply to establish the possibility for oscillations. See Lemma 4 for more information about parameter ranges for which periodic solutions are expected.

Our results can be used to give a mathematically rigorous justification for the plausible approximation arguments employed by Perelson and Nelson [12] 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 non-infectious. Following [12], the system describing uninfected and infected T cells, infectious virus V_I and noninfectious virus V_{NI} is given by

$$\begin{aligned} \dot{T} &= f(T) - k(1-\eta_{RT})V_I T \\ \dot{T}^* &= -\beta T^* + k(1-\eta_{RT})V_I T \\ \dot{V}_I &= -\gamma V_I + N\beta(1-\eta_{PI})T^* - ikV_I T \\ \dot{V}_{NI} &= -\gamma V_{NI} + N\beta\eta_{PI}T^* \end{aligned} \tag{7}$$

where, again, $i = 0$ corresponds to the system treated in [12] 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 η_{RT} for RT inhibitor and η_{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 (4), we can calculate the basic reproductive number, R_0^c, under combination therapy by linearizing about the virus-free state E_0 to obtain

$$R_0^c = \frac{k\bar{T}[N(1-\eta_{RT})(1-\eta_{PI})-i]}{\gamma} \tag{8}$$

Comparing with (5), 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 (5) by the factor $(1-\eta_{RT})(1-\eta_{PI})$. If $R_0^c < 1$, the virus is cleared.

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

In view of the fact that current treatment does not allow for HIV eradication in an individual, this result implies either one of the following: The efficiency of drugs is never high enough to make $R_o^c < 1$ or model (7) 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 [1] for details.

3 Sketches of proofs

Due to space constraints we cannot include all proofs. For details we refer to [3].

Lemma 1. *The closed positive orthant is positively invariant for (4) 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 $V(t) \leq \gamma^{-1} N\beta[A + \bar{T} + 1]$. □

Lemma 2. *If $R_0 < 1$ then the virus-free state E_0 is a locally asymptotically stable steady state of system (4); if $R_0 > 1$ then it is unstable.*

This is based on a simple linearization argument. The same result holds for (7) with R_0^c replaced by R_0.

Lemma 3. *If $R_0 < 1$, then all solutions approach the virus-free state E_0.*

Proof. On consideration of the competitive vector field given by (4) 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 [13], B must contain a steady state of (4). 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 (7) 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 virus-free state is unstable ($R_0^c > 1$).

Next we deal with the stability properties of the nontrivial equilibrium point E_e.

Lemma 4. *Let $R_0 > 1$ and $f'(T_e) \leq 0$, then the nontrivial steady state $E_e \in \mathrm{int}(\mathbb{R}^3_+)$ is locally asymptotically stable for system (4), 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

$$p/T_{max} = -n/2m, \tag{9}$$

holds.

(b) $i = 1$ with kT_{max} large enough:

$$kT_{max} > \beta + \gamma + \frac{2\gamma}{N-1} \tag{10}$$

and p large enough.

Lemma 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 [14] with $X_1 = \mathrm{int}(\mathbb{R}^3_+)$ and $X_2 = \mathrm{bd}(\mathbb{R}^3_+)$. This choice is in accordance with the conditions stated in this Theorem. Furthermore, note that by virtue of Lemma 1 there exists a compact set B in which all solutions of system (4) initiated in $\mathbb{R}^3_+$, ultimately enter and remain for ever after. The compactness condition $(\mathbf{C_{4.2}})$ is easily verified for this set B. Denoting the omega limit set of the solution $x(t, x_0)$ of system (4) starting

in $x_0 \in \mathbb{R}^3_+$ by $\omega(x_0)$ (which exists by Lemma 1), we need to determine the set $\Omega_2 = \cup_{y\in Y_2}\omega(y)$ where $Y_2 = \{x_0 \in X_2 | \, x(t, x_0) \in X_2, \forall t > 0\}$. From the system equations (4) follows that all solutions starting in $\mathrm{bd}(\mathbb{R}^3_+)$ but not on the T axis leave $\mathrm{bd}(\mathbb{R}^3_+)$ and that the T axis is an invariant set, implying that $Y_2 = \{(T, T^*, V)^T \in \mathrm{bd}(\mathbb{R}^3_+) | \; T^* = V = 0\}$. 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 Ω_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 $\mathrm{bd}(\mathbb{R}^3_+)$ 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 $x_0 \in X_1$

$$\limsup_{t\to+\infty} d(x(t, x_0), E_0) > 0 \tag{11}$$

We claim that (11) is satisfied if the following holds:

$$W^s(E_0) \cap \mathrm{int}(\mathbb{R}^3_+) = \emptyset \tag{12}$$

where $W^s(E_0)$ denotes the stable manifold of E_0. To see this, suppose that (11) 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 (4) (recall Lemma 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 (12) holds.
What remains to be shown is that (12) holds. To that end, recall that the Jacobian matrix of system (4) at E_0, is unstable if $R_0 > 1$. In particular, J_0 possesses one eigenvalue with positive real part, which we denote as λ_+ and two eigenvalues with negative real part, $f'(\bar{T})$ and an eigenvalue which we denote as λ_- (Note that λ_- 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 λ_- has the following structure: $(0, p_2, p_3)^T$, where p_2 and p_3 satisfy the following eigenvector equation:

$$\begin{pmatrix} -\beta & k\bar{T} \\ N\beta & -\gamma - ik\bar{T} \end{pmatrix} \begin{pmatrix} p_2 \\ p_3 \end{pmatrix} = \lambda_- \begin{pmatrix} p_2 \\ p_3 \end{pmatrix} \tag{13}$$

If $\lambda_- = f'(\bar{T})$, then λ_- 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 the sequel and p_2 and p_3 also satisfy (13).
We claim that in both cases (i.e. $\lambda_- \neq f'(\bar{T})$ and $\lambda_- = f'(\bar{T})$) the vector $(p_2, p_3)^T \notin \mathbb{R}^2_+$. The matrix in (13) is an irreducible Metzler matrix, which -by an immediate consequence of the Perron-Frobenius Theorem- possesses a simple, real and dominant eigenvalue[1]. Clearly, this dominant eigenvalue is λ_+. But the Perron-Frobenius Theorem also implies that every eigenvector which is associated to an eigenvalue, different from this dominant eigenvalue, does not belong to the closed positive orthant. Applied here, this means that $(p_2, p_3) \notin \mathbb{R}^2_+$. Consequently, $E_s(E_0) \cap \mathrm{int}(\mathbb{R}^3_+) = \emptyset$ and therefore also $W^s(E_0) \cap \mathrm{int}(\mathbb{R}^3_+) = \emptyset$, which concludes the proof. □

[1] *Dominant* should be interpreted in the sense that the real part of any other eigenvalue is strictly smaller than this real eigenvalue.

Lemma 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.

Proposition 1. *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 non-trivial periodic orbit.*

Proof. For $R_0 > 1$ it follows from the persistence result in Lemma 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 [15] and the fact that nonlinearities in (4) are analytic. In order to apply that result, we take the domain for (4) to be the interior of the positive orthant, in which the only steady state is E_e. Lemma 1 and Lemma 5 imply 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 follow from Theorem 4.2 in [13]. That result is stated for systems which are competitive in the traditional sense and so it applies to (4) 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. □

Next is one of the main results of this paper.

Theorem 2. *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 (4) 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 3-dimensional competitive systems [13], and a powerful theory of second compound equations to prove asymptotic orbital stability of periodic solutions, see [8] and cited references therein. Under the assumptions of the Theorem, system (4) possesses an steady state

$E_e \in \text{int}(\mathbb{R}^3_+)$, which is unique in $\text{int}(\mathbb{R}^3_+)$. Moreover, from the proof of Lemma 5 follows that the omega limit sets of solutions not initiated on the T axis are in $\text{int}(\mathbb{R}^3_+)$. We claim that the only possible omega limit sets of solutions of system (4) 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 $\text{int}(\mathbb{R}^3_+)$), so 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 (4) according to Lemma 4 (notice that the condition needed to apply this Lemma, $f'(T_e) \leq 0$, 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 (4) 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 (4) with respect to initial conditions not on the T axis, which concludes the proof of this Theorem, see [8]. We prove the following: If system (4) 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 1

$$0 \leq p_1(t) \leq \bar{T},\ \forall t \in [0,\, \omega] \tag{14}$$

To establish asymptotic orbital stability of a periodic solution, we resort to the so-called method of the second compound equation, see [8] and cited references therein. The second compound equation is the following periodic linear system:

$$\dot{z} = \frac{\partial f^{[2]}}{\partial x}(p(t))z \tag{15}$$

where $z = (z_1,\, z_2,\, z_3)^T$ and $\frac{\partial f^{[2]}}{\partial x}$ is derived from the Jacobian matrix of system (4) and defined as follows:

$$\frac{\partial f^{[2]}}{\partial x} := \begin{pmatrix} j_{11} + j_{22} & j_{23} & -j_{13} \\ j_{32} & j_{11} + j_{33} & j_{12} \\ -j_{31} & j_{21} & j_{22} + j_{33} \end{pmatrix}$$

where j_{kl} is the $(k,\, l)$-th entry of the Jacobian matrix associated to system (4). The importance of the second compound equation is that if system (15) is asymptotically stable, then the periodic solution $p(t)$ is asymptotically orbitally stable for system (4), see [8]. It can be shown that given the assumptions of this theorem, the function

$$V(z_1,\, z_2,\, z_3;\, p(t)) := \sup\{|z_1|,\, \frac{p_2(t)}{p_3(t)}(|z_2| + |z_3|)\} \tag{16}$$

is a Lyapunov function for system (15), see [3] for details. □

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