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GLOBAL STABILITY FOR A VIRUS DYNAMICS MODEL WITH NONLINEAR INCIDENCE OF INFECTION AND REMOVAL*

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Abstract. Global dynamics of a compartmental model which describes virus propagation in vivo is studied using the direct Lyapunov method, where the incidence rate of the infection and the removal rate of the virus are assumed to be nonlinear. In the case where the functional quotient between the force of infection and the removal rate of the virus is a nonincreasing function of the virus concentration, the existence of a threshold parameter, i.e., the basic reproduction number or basic reproductive ratio, is established and the global stability of the equilibria is discussed. Moreover, in the absence of the above-mentioned monotonicity property, estimations for the sizes of the domains of attraction are given. Biological significance of the results and possible extensions of the model are also discussed.

Key words. virus propagation, compartmental model, global stability, Lyapunov functional, endemic equilibrium, basic reproduction number

AMS subject classifications. 92D25, 92D30, 34D20, 34D23, 93D20

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1. Introduction.

We consider a compartmental model for the propagation of a virus in vivo, in the form

$$\text{(S)} \qquad \begin{cases} S' = n(S) - c(S)f(V), \\ E' = c(S)f(V) - c_1 i(E), \\ I' = c_2 i(E) - c_3 p(I), \\ V' = c_4 p(I) - r(V). \end{cases}$$

Here, S denotes the concentration of the cells in the susceptible (i.e., uninfected) class, E denotes the concentration of cells in the exposed (i.e., latent) class, I denotes the concentration of cells in the infected class, and V denotes the concentration of the virus itself.

The intrinsic growth rate of the susceptible class, which includes both production of new cells and natural mortality of cells, is given by $n(S)$ with all the newly produced cells assumed to be susceptible. The movement of cells from the exposed class into the infected class and the production of free virus from infected cells are given by $c_2 i(E)$ and $c_4 p(I)$, respectively. By $c_1 i(E)$ and $c_3 p(I)$, we denote the removal of the exposed and infected classes, respectively, which include the mortality of cells in the above-mentioned classes.

It is assumed that the infection process is characterized by the incidence rate $c(S)f(V)$, where $c(S)$ denotes the contact function at concentration S and $f(V)$ denotes the force of infection by virus at concentration V. We note that our incidence

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rate is sufficiently general to encompass many forms of commonly used incidence rate, including simple mass action. The removal rate of the virus is denoted by $r(V)$. All functions c, f, i, p, r, n are allowed to be nonlinear and all constants c_1, c_2, c_3, c_4 are assumed to be positive.

We thereby assume that the major infection pathway is virus-to-cell, since the cell-to-cell pathway is sometimes less documented and therefore less considered, particularly in diseases such as AIDS (see Perelson and Nelson [18]).

While this model has been studied in Bonhoeffer et al. [1], Korobeinikov [7], Nowak and May [14], and Perelson and Nelson [18], among others, for linear c, f, i, p, r, n, it is perhaps important to account for a number of nonlinear features of the biological phenomena which are involved, especially for the nonlinearity of the incidence rate, which is influenced by the availability of susceptible cells and by the force of infection of viral cells. As the concentration of viral cells becomes higher, the simple mass action law βSV may not necessarily suffice. Moreover, the rate at which an infected cell or virus will die as a function of their concentrations is generally not known, and hence we make a further generalization by assuming that the removal rate is also nonlinear. For a detailed discussion on the virus dynamics of HIV, readers are referred to Perelson and Nelson [18].

We note that in (S), for $i(x) = x$ and $p(x) = x$, the constant $1/c_1$ represents the average time spent by a cell in the latent state, while $1/c_3$ represents the average lifetime of an infected cell. Also, $c_1 \geq c_2$ and $c_1 - c_2$ represents the mortality rate of the exposed cells, while c_4 relates to the production of virus from infected cells.

As noted by Korobeinikov in [7], if there is no exposed class E and consequently $c(S)f(V)$ represents the movement of cells from the susceptible class directly into the infected class, the (reduced three-dimensional) system (S) is equivalent to a SEIR model with a constant population assumption. It is therefore expected that the dynamics of our model will share some features with the dynamics of a SEIR model. Some perspectives and results from the global stability theory for SEIR models would also be relevant for our discussion. See Korobeinikov and Maini [8], Li et al. [11], Li and Muldowney [12], and Li, Muldowney, and van den Driessche [13] for global stability results for SEIR models. However, in [11, 12, 13] the approach is essentially geometrical, using a stability criteria which extends the Poincaré–Bendixson theorem and ruling out periodic orbits, rather than constructing a Lyapunov functional.

A related investigation pertaining to the dynamics of infectious disease models which incorporated nonlinear incidence rates of a very general form has recently been performed by Korobeinikov and Maini in [9] by using the Lyapunov method. In [9], the local stability of the equilibria for SIRS and SEIRS models has been considered assuming that the incidence rate is given by an arbitrary function $f(S, I, N)$, while the global stability of the equilibria for SIR and SEIR models has been considered assuming that the incidence rate is of the form $f(I)g(S)$. However, apart from the incidence rate, the other functions which appear in the models considered in [9] are linear and a constant population assumption is used, while for our model full nonlinearity is assured and a constant population assumption would not be an option. Moreover, the analysis performed in [9] is done in a somewhat different manner, with a focus on the role of the concavity of the nonlinear incidence rate in the existence and stability of the endemic equilibrium.

Substantial results regarding the global dynamics of a three-dimensional HIV model have been obtained by De Leenheer and Smith [3] using a different approach; their result distinguishes whether or not the term $-kVT$, which models the loss of a free virus particle once it enters the target cell, can be absorbed into the general loss

term $-\gamma V$. In [3], V is the concentration of free virus particles in the blood and T is the concentration of T cells. De Leenheer and Smith start with general assumptions on the function f which models T cell dynamics in a healthy individual and then specialize their results for two particular functions: $f_1(T) = \delta - \alpha T + pT(1 - T/T_{max})$ as used by Perelson and Nelson in [18] and $f_2(T) = \delta - \alpha T$ as used by Nowak and May in [14]. Certain linearity assumptions on some other functions appearing in the model are also made.

In the particular case in which the term $-kVT$ is absorbed into the general loss term (as done in [18] and [14])) and $f = f_2$, the model used in [3] can be thought of as a reduced version of our model, with no exposed class and extra linearity assumptions. However, the proof of our global stability result uses in an unavoidable manner the monotonicity assumption on n, which corresponds to f in [3], and therefore it can accommodate the case $f = f_2$ only and not the case $f = f_1$. In particular, our model does not admit orbitally asymptotically stable periodic solutions, which are obtained in [3] for $f = f_1$; see [3, Theorem 1] for details.

The paper is organized in the following manner. We propose the model to be studied in section 2 and discuss its well-posedness. In section 3 we give results on the stability of the disease-free equilibrium and persistence of the system, while sections 4 and 5 contain discussions on the existence, uniqueness, and global stability of the endemic equilibrium. Finally, in section 6, we give some remarks on the biological interpretation of our results, as well as some further extensions of the model one can make.

2. The model and its well-posedness. We assume that c, f, i, p, r are real locally Lipschitz functions defined at least on $[0, \infty)$ which satisfy

$$\begin{aligned} c(0) = f(0) = i(0) = p(0) = r(0) = 0, \\ c(t), f(t), i(t), p(t), r(t) > 0 \quad \text{for } t > 0 \end{aligned}$$

and that n is a real locally Lipschitz function defined at least on $[0, \infty)$ with $n(0) > 0$ such that the equation $n(S) = 0$ has a single solution S_0. We also assume that

$$\begin{aligned} (n(S) - n(S_0))(S - S_0) < 0 \quad \text{for } S \neq S_0, \\ (c(S) - c(S_0))(S - S_0) > 0 \quad \text{for } S \neq S_0 \end{aligned} \tag{2.1}$$

together with

$$\int_{0+}^{1} \frac{1}{\varphi(\tau)} d\tau = +\infty \quad \text{for all } \varphi \in \{c, f, i, p\}. \tag{D}$$

Note that (2.1) is satisfied if, for instance, n is strictly decreasing and c is strictly increasing. We also suppose that there are k_n, k_i, k_p, k_v, $\tilde{k}_n > 0$ such that

$$\begin{aligned} &n(S) \leq \tilde{k}_n - k_n S \text{ for } S \geq 0, \quad i(E) \geq k_i E \text{ for } E \geq 0, \quad p(I) \geq k_p I \text{ for } I \geq 0, \\ &r(V) \geq k_r V \text{ for } V \geq 0. \end{aligned} \tag{G}$$

The set of growth conditions (G) will be used to establish, in our general setting, the global existence of the solution for the Cauchy problem associated with the system (S). We note that these conditions may be dropped if the global existence property is known or the a priori boundedness of the solutions may be established by other methods. We shall indicate in section 6 how to remove conditions (G) at the expense

of other conditions on the behavior of c, f, i, p near $+\infty$ if f/r is nonincreasing on $(0, \infty)$.

First, it can be easily shown that a solution of the system (S) which starts in $[0, \infty)^4$ remains there on its whole interval of existence. To this purpose, we note that the vector (R_1, R_2, R_3, R_4) points inside $Q = [0, \infty)^4$ at all points of ∂Q, where R_1, R_2, R_3, and R_4 are the right-hand sides appearing in (S), and hence Nagumo's tangency conditions are satisfied. See [15] for details.

From our assumptions, it is clear that the system (S) has a unique saturated (i.e., nonextendable) solution for any initial data $(S(0), E(0), I(0), V(0))$. Using (G), it is possible to prove that all saturated solutions are global. To this aim, note that

$$\left(S + E + \frac{c_1}{2c_2} I + \frac{c_1 c_3}{4c_2 c_4} V\right)' \leq \tilde{k}_n - k_n S - \frac{c_1 k_i}{2} E - \frac{c_1 c_3}{4c_2} k_p I - \frac{c_1 c_3}{4c_2 c_4} k_r V,$$

it follows that there is $\delta = \delta(k_n, k_i, k_p, k_r, c_1, c_2, c_3, c_4) > 0$ small enough such that

$$\left(S + E + \frac{c_1}{2c_2} I + \frac{c_1 c_3}{4c_2 c_4} V\right)' + \delta \left(S + E + \frac{c_1}{2c_2} I + \frac{c_1 c_3}{4c_2 c_4} V\right) \leq \tilde{k}_n,$$

which implies that

$$\begin{aligned} &S + E + \frac{c_1}{2c_2} I + \frac{c_1 c_3}{4c_2 c_4} V - \frac{\tilde{k}_n}{\delta} \\ &\quad \leq \left(S(0) + E(0) + \frac{c_1}{2c_2} I(0) + \frac{c_1 c_3}{4c_2 c_4} V(0) - \frac{\tilde{k}_n}{\delta}\right) e^{-\delta t} \quad \text{for } t \geq 0, \end{aligned}$$

and therefore S, E, I, V are bounded on their maximal interval of existence. It follows that the functions $S(t)$, $E(t)$, $I(t)$, $V(t)$ are defined on $[0, \infty)$, and so the Cauchy problem with nonnegative initial data is well-posed for the system (S). Moreover, if we denote

$$F = \left\{(S, E, I, V) \in [0, \infty)^4; S + E + \frac{c_1}{2c_2} I + \frac{c_1 c_3}{4c_2 c_4} V \leq \frac{\tilde{k}_n}{\delta}\right\},$$

it follows that F is a feasible region for the system (S). Of course, the feasible region determined above is neither minimal nor unique, and the parameter δ above is obviously not uniquely determined. We shall simply choose

$$\delta = \min\left(k_n, \frac{c_1}{2} k_i, \frac{c_3}{2} k_p, k_r\right). \tag{2.2}$$

If S is small, then $S' = n(S) - c(S)F(V) > 0$ if V stays in a bounded set, since $n(0) > 0$ and $\lim_{S \to 0} c(S) = 0$, and we may infer that for any $S(0) > 0$ there is $\varepsilon_{S(0)} > 0$ such that $S(t) \geq \varepsilon_{S(0)}$ for all $t > 0$. This means that all solutions which start with positive $S(0)$ do not reach any point with $S = 0$ in future time. If $S(0) = 0$, then $S' > 0$ in a vicinity of 0 and, again, $S(t)$ raises over a certain minimum value (of course, the case in which $S(0) = 0$ does not make much biological sense). Also, it can be seen that the only w-limit point of (S) on the boundary of F is the disease-free equilibrium $(S_0, 0, 0, 0)$ and the only points on the boundary of $[0, \infty)^4$ which can be attained in finite time are situated on $[OS$, the positive S-semiaxis containing the origin.

3. Stability of disease-free equilibrium. Since the equation $n(S) = 0$ has a single solution S_0 and $f(0) = i(0) = p(0) = r(0) = 0$, it is easy to see that the system (S) admits a unique disease-free equilibrium $(S_0, 0, 0, 0)$. We now turn our attention to the study of its stability.

Consider the Lyapunov functional

$$U_1(S, E, I, V) = \int_{S_0}^{S} \frac{c(\tau) - c(S_0)}{c(\tau)} d\tau + E + \frac{c_1}{c_2} I + \frac{c_1 c_3}{c_2 c_4} V.$$

Since $(c(S) - c(S_0))(S - S_0) > 0$ for $S \neq S_0$, it is seen that U_1 increases whenever any of $|S - S_0|$, E, I, V increases and $U_1(S, E, I, V) \geq 0$ for all $S, E, I, V \geq 0$, while $U_1(S, E, I, V) = 0$ if and only if $(S, E, I, V) = (S_0, 0, 0, 0)$.

We now compute the time derivative of U_1 along the solutions of (S). It is seen that

$$\begin{aligned} \dot{U_1} = \left(1 - \frac{c(S_0)}{c(S)}\right)(n(S) - c(S)f(V)) + (c(S)f(V) - c_1 i(E)) \\ + \frac{c_1}{c_2}(c_2 i(E) - c_3 p(I)) + \frac{c_1 c_3}{c_2 c_4}(c_4 p(I) - r(V)), \end{aligned}$$

and since $n(S_0) = 0$, we can deduce that

$$\dot{U_1}(S, E, I, V) = \left(1 - \frac{c(S_0)}{c(S)}\right)(n(S) - n(S_0)) + \left[c(S_0)f(V) - \frac{c_1 c_3}{c_2 c_4} r(V)\right]. \tag{3.1}$$

Due to (2.1), it is easily seen that

$$\left(1 - \frac{c(S_0)}{c(S)}\right)(n(S) - n(S_0)) < 0 \quad \text{for } S \neq S_0, \tag{3.2}$$

and the first term in the right-hand side of (3.1) is negative. It is then seen that the stability of the disease-free equilibrium is related to the sign of the remaining term in the right-hand side of (3.1).

THEOREM 3.1. *Suppose that there is a number $V_R > 0$ such that*

$$c(S_0)\frac{f(V)}{r(V)}\frac{c_2 c_4}{c_1 c_3} \leq 1 \quad \textit{for } V \in (0, V_R), \tag{3.3}$$

and let $m = U_1(S_0, 0, 0, V_R)$. Then the disease-free equilibrium $(S_0, 0, 0, 0)$ is locally asymptotically stable and its domain of attraction includes the set

$$M_m = \left\{(S, E, I, V) \in (0, \infty) \times [0, \infty)^3; U_1(S, E, I, V) < m\right\}.$$

Proof. From (3.1), (3.2), and (3.3), it is seen that $\dot{U_1}(S, E, I, V) \leq 0$ for $0 \leq V < V_R$, with equality if and only if $S = S_0$ and either $V = 0$ or the equality in (3.3) holds.

Let us denote $\tilde{M} = \left\{(S, E, I, V) \in (0, \infty) \times [0, \infty)^3, 0 \leq V < V_R\right\}$ and take $k < m$ arbitrary. Since for all $V \geq V_R$ one has $U_1(S, E, I, V) \geq U_1(S_0, 0, 0, V_R)$, it is seen that $M_k \subset \tilde{M}$. Consequently, $U_1(S, E, I, V) \leq 0$ on M_k, with equality if and only if $S = S_0$ and the equality in (3.3) holds.

We now find the invariant subsets $\tilde{P}$ within the set

$$P = \left\{(S, E, I, V) \in M_k; \dot{U_1}(S, E, I, V) = 0\right\}.$$

Since $S = S_0$ on $\tilde{P}$ and consequently $S' = -c(S_0)f(V)$, it is seen that $V = 0$ and one similarly deduces that $E = I = 0$; that is, the only invariant subset of P is the singleton $\tilde{P} = \{(S_0, 0, 0, 0)\}$. From LaSalle's invariance principle (see LaSalle [10]) and the fact that $k < m$ was arbitrary, the conclusion follows. □

To complement Theorem 3.1, we further consider the case in which the disease-free equilibrium is unstable and give some remarks related to the persistence of the system. The system (S) is said to be *uniformly persistent* on F if there is a constant $\varepsilon_0 > 0$ such that any solution of (S) which starts in $(S(0), E(0), I(0), E(0)) \in \overset{\circ}{F}$ satisfies

$$\liminf_{t\to\infty} S(t) \geq \varepsilon_0, \quad \liminf_{t\to\infty} E(t) \geq \varepsilon_0, \quad \liminf_{t\to\infty} I(t) \geq \varepsilon_0, \quad \liminf_{t\to\infty} V(t) \geq \varepsilon_0.$$

See also Butler, Freedman, and Waltman [2] or Hofbauer and So [6].

Consider the Lyapunov function

$$U_2(S, E, I, V) = E + \frac{c_1}{c_2} I + \frac{c_1 c_3}{c_2 c_4} V.$$

Similar to the derivation of (3.1), the time derivative of U_2 along the solutions of (S) is given by

$$\dot{U}_2(S, E, I, V) = c(S)f(V) - \frac{c_1 c_3}{c_2 c_4} r(V). \tag{3.4}$$

Obviously, if (S) is uniformly persistent, then the disease remains endemic and stability for the disease-free equilibrium is excluded. In this regard, we have already observed that if (3.3) is satisfied on some interval $(0, V_R)$, then the disease-free equilibrium is locally asymptotically stable. If, on the other hand, the opposite of (3.3) is satisfied on some interval $(0, V_R)$, then the system (S) is uniformly persistent in the sense mentioned above.

THEOREM 3.2. *Assume that there is a number $V_R > 0$ such that*

$$c(S^0)\frac{f(V)}{r(V)}\frac{c_2 c_4}{c_1 c_3} > 1 \quad \text{for } V \in (0, V_R). \tag{3.5}$$

Then (S) *is uniformly persistent and the disease-free equilibrium* $(S_0, 0, 0, 0)$ *is unstable, with the positive semiaxis* $[OS$ *as its stable variety.*

Proof. From (3.4), (3.5), and the continuity of the function c at S_0, it follows that $\dot{U}_2 > 0$ on a small vicinity of $(S_0, 0, 0, 0)$, except for the points with $V = 0$. It then follows that any solution which starts in that vicinity remains away from $(S_0, 0, 0, 0)$, except for those starting on the positive semiaxis $[OS$, which tend to $(S_0, 0, 0, 0)$ while remaining on $[OS$. It may now be obtained, as in Proposition 3.3 in Li et al. [11], that the system (S) is uniformly persistent. This amounts to observing that $(S_0, 0, 0, 0)$ is the unique compact invariant set on the boundary of our feasible domain (so it is isolated) and its stable variety is the positive semiaxis $[OS$, which is contained in the boundary of the feasible domain. Then the use of Theorem 4.1 in Hofbauer and So [6], together with the remark that a flow and its time one map have the same maximal compact invariant set and the same stable set in a region, concludes the proof. □

It now remains to indicate some situations in which (3.3) or (3.5) are satisfied. Suppose for the moment that f/r is nonincreasing on $(0, \infty)$ and define a basic reproduction number R_0 of the system (S) by

$$R_0 = c(S_0)\frac{c_2 c_4}{c_1 c_3}\lim_{V\to 0}\frac{f(V)}{r(V)} \tag{3.6}$$

(note that the limit $\lim_{V\to 0}\frac{f(V)}{r(V)}$ does indeed exist, since f/r is monotone on $(0, \infty)$).

If $R_0 \leq 1$, then (3.3) is satisfied on $[0,\infty)$, while if $R_0 > 1$, then (3.5) is satisfied for V in a vicinity of 0. Also, it may be seen that $\lim_{V_R\to\infty} U_1(S_0,0,0,V_R) = +\infty$. One then obtains the following result, which establishes that R_0 is the threshold parameter for the stability of the disease-free equilibrium.

THEOREM 3.3. *Suppose that f/r is nonincreasing on $(0,\infty)$.*

1. *If $R_0 \leq 1$, then the disease-free equilibrium $(S_0,0,0,0)$ is globally asymptotically stable.*
2. *If $R_0 > 1$, then* (S) *is uniformly persistent and the disease-free equilibrium $(S_0,0,0,0)$ is unstable, with the positive semiaxis $[OS$ as its stable variety.*

In fact, if f/r is nonincreasing on $(0,\infty)$, more can be said for the case $R_0 > 1$, and it will be shown in sections 4 and 5 that, in this situation, the system (S) admits a positive endemic equilibrium, which is globally asymptotically stable.

We also note that if the functions f and r are of class C^1 and the limit $\lim_{V\to 0} \frac{f'(V)}{r'(V)}$ exists, then by the L'Hôpital theorem

$$R_0 = c(S_0)\frac{c_2c_4}{c_1c_3}\lim_{V\to 0}\frac{f'(V)}{r'(V)},$$

which is in agreement with the definition of the basic reproduction number given by van den Driessche and Watmough in [19] for a large class of compartmental models, including the present model. We do not need, however, to assume C^1 regularity for the functional coefficients throughout our proofs. We also note that, since no C^1 regularity is assumed, local stability analysis based on Jacobian matrices would fail.

4. Existence of endemic equilibrium. We now try to establish some sufficient conditions for the existence of the endemic equilibrium (S^*,E^*,I^*,V^*). Since it would be somehow unrealistic to attempt to solve the system (EQ) in its greatest generality, we impose some additional conditions on our functional coefficients. Let us suppose the following:

(4.1)
f/r is nonincreasing on $(0,\infty)$,

(4.2)
c, f, i, p are strictly increasing on $[0,\infty)$ and n is strictly decreasing on $[0,\infty)$,

(4.3)
$$\lim_{x\to\infty} i(x) = \lim_{x\to\infty} p(x) = +\infty.$$

Necessarily, $S^*,E^*,I^*,V^* > 0$, and the following equilibrium relations are satisfied:

$$\text{(EQ)}\qquad \begin{aligned} &n(S^*) = c(S^*)f(V^*), \quad c(S^*)f(V^*) = c_1 i(E^*), \quad c_2 i(E^*) = c_3 p(I^*),\\ &c_4 p(I^*) = r(V^*). \end{aligned}$$

To solve the equilibrium system (EQ), note first that from the last three equalities in (EQ) one obtains

$$c(S^*)f(V^*) = \frac{c_1c_3}{c_2c_4}r(V^*).$$

Let us define

$$F_1(S,V) = n(S) - c(S)f(V), \quad F_2(S,V) = c(S)f(V) - \frac{c_1c_3}{c_2c_4}r(V).$$

Since $S \mapsto F_1(S,V)$ is strictly decreasing and $F_1(0,V) \cdot F_1(S_0,V) < 0$ for all V, the equation $F_1(S,V) = 0$ can be uniquely solved with respect to S as a function of V for all V. That is, there is a function $S = \psi_1(V)$ which satisfies

$$\frac{n(\psi_1(V))}{c(\psi_1(V))} = f(V). \tag{4.4}$$

Since n/c is strictly decreasing and f is strictly increasing, it follows that ψ_1 is strictly decreasing. Note also that due to (4.4), $\lim_{V\to\infty} \psi_1(V) = 0$.

Similarly, $S \mapsto F_2(S,V)$ is strictly increasing and $F_2(0,V) < 0$ for all V. However, in this instance it is not necessarily true that $F_2(S_0,V) > 0$, and hence the same approach we used to solve the equation $F_2(S,V) = 0$ would not work. However, for our purpose we do not actually need the global solvability of the equation $F_2(S,V) = 0$, since we are searching for a unique endemic equilibrium and consequently for a single V^*. In some situations, local solvability may suffice.

To gain insight, suppose for the moment that the equation $F_2(S,V) = 0$ may also be uniquely solved with respect to S as a function of V (locally for V). That is, there is a function $S = \psi_2(V)$ which satisfies

$$c(\psi_2(V)) = \frac{c_1c_3}{c_2c_4}\frac{r(V)}{f(V)}.$$

Since c is strictly increasing, it follows that ψ_2 is strictly increasing.

Since ψ_1 is strictly decreasing, ψ_2 is strictly increasing and $\lim_{V\to\infty} \psi_1(V) = 0$, the curves defined by $S = \psi_1(V)$ and $S = \psi_2(V)$ have a common point (S^*, V^*) with $S^* > 0$ and $V^* > 0$ if and only if $\psi_1(0) > \psi_2(0)$, or equivalently, $c(\psi_1(0)) > c(\psi_2(0))$. Since $\psi_1(0) = S_0$ and $c(\psi_2(0)) = \frac{c_1c_3}{c_2c_4} \lim_{V\to 0} \frac{r(V)}{f(V)}$, the existence condition is $c(S_0) > \frac{c_1c_3}{c_2c_4} \lim_{V\to 0} \frac{r(V)}{f(V)}$. Using the basic reproduction number of the system (S) as defined in (3.6) (note again that f/r is monotone), this condition may be rewritten as $R_0 > 1$.

Up to now, we have shown that if the equation $F_2(S,V) = 0$ is solvable with respect to S as a function of V, then the necessary and sufficient condition for the existence of positive (S^*, V^*) is that $R_0 > 1$. In this case, we have

$$F_2(S,V) = \frac{c_1c_3}{c_2c_4} r(V) \left[c(S) \frac{c_2c_4}{c_1c_3} \frac{f(V)}{r(V)} - 1 \right];$$

and $F_2(S_0,V)$ is positive for V in a vicinity of 0. Since we have already noted that $F_2(0,V) < 0$ for all V, it follows that the equation $F_2(S,V) = 0$ is solvable with respect to S as a function of V (locally for V) if $R_0 > 1$, which is precisely what we needed. That is, we have shown that the existence of positive (S^*, V^*) is equivalent to the validity of condition $R_0 > 1$.

Also, if i, p are strictly increasing on $[0,\infty)$ and $\lim_{x\to\infty} i(x) = \lim_{x\to\infty} p(x) = +\infty$, then the equations $i(E) = \frac{1}{c_1} n(S^*)$ and $p(I) = \frac{c_2}{c_3c_1} n(S^*)$ will have unique positive solutions E^*, I^*, respectively. In view of the above, we can summarize our discussion with the following result.

THEOREM 4.1. *Assume that conditions* (4.1), (4.2), *and* (4.3) *are satisfied. Then there is a unique positive endemic equilibrium* (S^*, E^*, I^*, V^*) *of* (S) *if and only if* $R_0 > 1$, *where* R_0 *is the basic reproduction number for the system* (S), *as defined in* (3.6).

We note that conditions (4.1), (4.2), and (4.3) (combined with $R_0 > 1$) are sufficient for the existence of the endemic equilibrium but not necessary. Actually, if

one assumes that the removal rate $r(V)$ of the virus is influenced by treatment which is administered if an increase of the virus load over a certain value is observed, while the force of infection $f(V)$ is not, it is easy to think of a function f/r which is not monotone, for instance. In this situation, the disease-free equilibrium may coexist with multiple positive endemic equilibria. It is perhaps also worth noting that the stability of the equilibria depends essentially on the behavior of the function f/r and depends on the contact function c only through the basic reproduction number R_0.

5. Stability of endemic equilibrium. In this section we assume that the system (S) admits a positive endemic equilibrium (S^*, E^*, I^*, V^*) and study its stability. However, we do not assume that (4.1), (4.2), and (4.3) are satisfied and establish our results under somewhat weaker hypotheses. This is consistent with the remark that conditions (4.1), (4.2), and (4.3) are sufficient for the existence of the endemic equilibrium but not necessary. For our purpose, apart from the existence of the endemic equilibrium, we assume that

$$\text{(P)}\qquad \begin{aligned} (c(S)-c(S^*))\,(S-S^*) &> 0 \quad \text{for } S\neq S^*, S\geq 0,\\ (f(V)-f(V^*))\,(V-V^*) &> 0 \quad \text{for } V\neq V^*, V\geq 0,\\ (i(E)-i(E^*))\,(E-E^*) &> 0 \quad \text{for } E\neq E^*, E\geq 0,\\ (p(I)-p(I^*))\,(I-I^*) &> 0 \quad \text{for } I\neq I^*, I\geq 0 \end{aligned}$$

and

$$\text{(N)}\qquad (n(S)-n(S^*))\,(S-S^*)\leq 0 \quad \text{for all } S\geq 0.$$

Note that conditions (P) and (N) are satisfied if (4.2) holds. However, nonmonotone functions c, f, i, p, n can also satisfy (P) and (N).

We consider the Lyapunov function

$$\begin{aligned} U_3(S,E,I,V) = &\int_{S^*}^{S}\frac{c(\tau)-c(S^*)}{c(\tau)}d\tau + \int_{E^*}^{E}\frac{i(\tau)-i(E^*)}{i(\tau)}d\tau\\ &+\frac{c_1}{c_2}\int_{I^*}^{I}\frac{p(\tau)-p(I^*)}{p(\tau)}d\tau + \frac{c_1c_3}{c_2c_4}\int_{V^*}^{V}\frac{f(\tau)-f(V^*)}{f(\tau)}d\tau. \end{aligned}$$

Due to the sign conditions (P), it is seen that U_3 increases whenever any of $|S-S^*|$, $|E-E^*|$, $|I-I^*|$, $|V-V^*|$ increases and $U_3(S,E,I,V)\geq 0$ for all $S,E,I,V\geq 0$, while $U_3(S,E,I,V)=0$ if and only if $(S,E,I,V)=(S^*,E^*,I^*,V^*)$. We note that if any of S,E,I,V tends to 0, then $U_3(S,E,I,V)$ tends to ∞ due to the divergence condition (D). It then follows that all level sets of U_3 have no limit points on the boundary of $(0,\infty)^4$.

We now compute the time derivative of U_3 along the solutions of (S).

LEMMA 5.1. *The time derivative of U_3 with respect to the solutions of* (S) *is*

$$\begin{aligned} \dot{U_3}&(S,E,I,V)\\ &= (n(S)-n(S^*))\left(1-\frac{c(S^*)}{c(S)}\right) + c(S^*)r(V)\left(\frac{f(V^*)}{f(V)}-1\right)\left(\frac{f(V^*)}{r(V^*)}-\frac{f(V)}{r(V)}\right)\\ &\quad - c_1 i(E^*)\left[\frac{c(S^*)}{c(S)}+\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+\frac{i(E)}{i(E^*)}\frac{p(I^*)}{p(I)}+\frac{f(V^*)}{f(V)}\frac{p(I)}{p(I^*)}-4\right]. \end{aligned}$$

If the inequality

$$c(S^*)r(V)\left(\frac{f(V^*)}{f(V)}-1\right)\left(\frac{f(V^*)}{r(V^*)}-\frac{f(V)}{r(V)}\right)\leq 0 \tag{5.1}$$

holds true for V in some given interval (V_L,V_R), then $\dot{U}_3(S,E,I,V)\leq 0$ for $V\in(V_L,V_R)$, with equality if and only if

$$S=S^* \quad \textit{and} \quad \frac{i(E)}{i(E^*)}=\frac{f(V)}{f(V^*)}=\frac{p(I)}{p(I^*)}.$$

Proof. It is seen that

$$\begin{aligned}
\dot{U}_3 &= \left(1-\frac{c(S^*)}{c(S)}\right)(n(S)-c(S)f(V))+\left(1-\frac{i(E^*)}{i(E)}\right)(c(S)f(V)-c_1i(E))\\
&\quad+\frac{c_1}{c_2}\left(1-\frac{p(I^*)}{p(I)}\right)(c_2i(E)-c_3p(I))+\frac{c_1c_3}{c_2c_4}\left(1-\frac{f(V^*)}{f(V)}\right)(c_4p(I)-r(V))\\
&= n(S)\left(1-\frac{c(S^*)}{c(S)}\right)+c(S^*)f(V)-\frac{i(E^*)}{i(E)}c(S)f(V)+c_1i(E^*)-c_1\frac{p(I^*)}{p(I)}i(E)\\
&\quad+\frac{c_1c_3}{c_2}p(I^*)-\frac{c_1c_3}{c_2c_4}r(V)-\frac{c_1c_3}{c_2}\frac{f(V^*)}{f(V)}p(I)+\frac{c_1c_3}{c_2c_4}\frac{f(V^*)}{f(V)}r(V).
\end{aligned}$$

Using the equilibrium relations (EQ), it follows that

$$\begin{aligned}
\dot{U}_3 &= n(S)\left(1-\frac{c(S^*)}{c(S)}\right)+c(S^*)f(V)-c_1i(E^*)\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+c_1i(E^*)\\
&\quad-c_1i(E^*)\frac{i(E)}{i(E^*)}\frac{p(I^*)}{p(I)}+c_1i(E^*)-c_1i(E^*)\frac{r(V)}{r(V^*)}-c_1i(E^*)\frac{f(V^*)}{f(V)}\frac{p(I)}{p(I^*)}\\
&\quad+c_1i(E^*)\frac{f(V^*)}{f(V)}\frac{r(V)}{r(V^*)}\\
&= n(S)\left(1-\frac{c(S^*)}{c(S)}\right)+c(S^*)f(V)+c_1i(E^*)\left(\frac{f(V^*)}{f(V)}\frac{r(V)}{r(V^*)}-\frac{r(V^*)}{r(V)}\right)\\
&\quad-c_1i(E^*)\left[\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+\frac{i(E)}{i(E^*)}\frac{p(I^*)}{p(I)}+\frac{f(V^*)}{f(V)}\frac{p(I)}{p(I^*)}-2\right]\\
&= n(S)\left(1-\frac{c(S^*)}{c(S)}\right)+c_1i(E^*)\frac{f(V)}{f(V^*)}+c_1i(E^*)\left(\frac{f(V^*)}{f(V)}\frac{r(V)}{r(V^*)}-\frac{r(V)}{r(V^*)}\right)\\
&\quad-c_1i(E^*)\left[\frac{c(S^*)}{c(S)}+\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+\frac{i(E)}{i(E^*)}\frac{p(I^*)}{p(I)}+\frac{f(V^*)}{f(V)}\frac{p(I)}{p(I^*)}-4\right]\\
&\quad+c_1i(E^*)\frac{c(S^*)}{c(S)}-2c_1i(E^*).
\end{aligned}$$

This implies that

$$\begin{aligned}
\dot{U}_3 &= (n(S)-c_1i(E^*))\left(1-\frac{c(S^*)}{c(S)}\right)\\
&\quad+c_1i(E^*)\left(\frac{f(V^*)}{f(V)}\frac{r(V)}{r(V^*)}-\frac{r(V)}{r(V^*)}+\frac{f(V)}{f(V^*)}-1\right)\\
&\quad-c_1i(E^*)\left[\frac{c(S^*)}{c(S)}+\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+\frac{i(E)}{i(E^*)}\frac{p(I^*)}{p(I)}+\frac{f(V^*)}{f(V)}\frac{p(I)}{p(I^*)}-4\right],
\end{aligned}$$

and since $c_1 i(E^*) = n(S^*)$, it follows that

$$\begin{aligned}\dot{U_3}&(S,E,I,V)\\ &= (n(S)-n(S^*))\left(1-\frac{c(S^*)}{c(S)}\right)+c_1 i(E^*)\left(\frac{f(V^*)}{f(V)}-1\right)\left(\frac{r(V)}{r(V^*)}-\frac{f(V)}{f(V^*)}\right)\\ &\quad - c_1 i(E^*)\left[\frac{c(S^*)}{c(S)}+\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+\frac{i(E)}{i(E^*)}\frac{p(I^*)}{p(I)}+\frac{f(V^*)}{f(V)}\frac{p(I)}{p(I^*)}-4\right].\end{aligned}$$

Using the relation $c_1 i(E^*) = c(S^*)f(V^*)$, one gets the required conclusion. Now, from the sign condition (N) it is seen that

$$(n(S)-n(S^*))\left(1-\frac{c(S^*)}{c(S)}\right)\le 0 \quad \text{for } S\ge 0,$$

with equality if and only if $S = S^*$, and from the *AM-GM* inequality (which says that the algebraic mean is not smaller than the geometric mean) it is seen that

$$\frac{c(S^*)}{c(S)}+\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+\frac{i(E)}{i(E^*)}\frac{p(I^*)}{p(I)}+\frac{f(V^*)}{f(V)}\frac{p(I)}{p(I^*)}\ge 4,$$

with equality if and only if

$$\frac{c(S^*)}{c(S)}=\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}=\frac{i(E)}{i(E^*)}\frac{p(I^*)}{p(I)}=\frac{f(V^*)}{f(V)}\frac{p(I)}{p(I^*)}=1. \tag{5.2}$$

It then follows that if the inequality

$$c(S^*)r(V)\left(\frac{f(V^*)}{f(V)}-1\right)\left(\frac{f(V^*)}{r(V^*)}-\frac{f(V)}{r(V)}\right)\le 0$$

holds true for $v\in(V_L,V_R)$, then $\dot{U_3}(S,E,I,V)\le 0$. For the equality case, we note that $c(S^*) = c(S)$ if and only if $S = S^*$, and substituting this into (5.2) one obtains that

$$\frac{i(E)}{i(E^*)}=\frac{f(V)}{f(V^*)}=\frac{p(I)}{p(I^*)}. \qquad \square$$

It is now obvious that the stability of the endemic equilibrium (S^*,E^*,I^*,V^*) is related to the validity of the inequality (5.1). Subsequently, we estimate the size of the domain of attraction associated with (S^*,E^*,I^*,V^*).

THEOREM 5.2. *Assume that the sign conditions* (P) *and* (N) *are satisfied and there are V_L and V_R such that*

$$\begin{aligned}&\frac{f(V)}{r(V)}\le\frac{f(V^*)}{r(V^*)} \quad \textit{for } V^*\le V<V_R,\\ &\frac{f(V)}{r(V)}\ge\frac{f(V^*)}{r(V^*)} \quad \textit{for } V_L<V\le V^*.\end{aligned} \tag{5.3}$$

Define $m = \min\left(U_3(S^*,E^*,I^*,V_L), U_3(S^*,E^*,I^*,V_R)\right)$. Then (S^*,E^*,I^*,V^*) is locally asymptotically stable and its domain of attraction includes the set

$$M_m=\left\{(S,E,I,V)\in(0,\infty)^4; U_3(S,E,I,V)<m\right\}.$$

Proof. Denote

$$\tilde{M} = \left\{(S, E, I, V) \in (0, \infty)^4; V_L < V < V_R\right\}.$$

From (5.3) it follows that (5.1) is satisfied for $V \in (V_L, V_R)$, and using Lemma 5.1 one may infer that $\dot{U}_3(S, E, I, V) \leq 0$ on $\tilde{M}$, with equality if and only if

$$S = S^* \quad \text{and} \quad \frac{i(E)}{i(E^*)} = \frac{f(V)}{f(V^*)} = \frac{p(I)}{p(I^*)}.$$

Take an arbitrary $k < m$. Since U_3 increases whenever any of $|S - S^*|$, $|E - E^*|$, $|I - I^*|$, $|V - V^*|$ increases, it follows easily that, for all V outside (V_L, V_R), one has $U_3(S, E, I, V) \geq m$ for all $S, E, I > 0$. Consequently $M_k \subset \tilde{M}$. Moreover, as noted previously, M_k is a bounded set which has no limit points on the boundary of $\tilde{M}$.

We now find the invariant subsets $\tilde{N}$ within the set

$$N = \left\{(S, E, I, V) \in M_k; \dot{U}_3(S, E, I, V) \leq 0\right\}.$$

Since $S = S^*$ on $\tilde{N}$ and consequently $S' = n(S^*) - c(S^*)f(V)$, it follows that $S' = c(S^*)(f(V^*) - f(V))$, and so $S' = 0$ if and only if $V = V^*$. From $\frac{i(E)}{i(E^*)} = \frac{p(I)}{p(I^*)} = 1$ we then deduce that $E = E^*$ and $I = I^*$ by using the sign condition (P).

Therefore, using LaSalle's invariance principle (see LaSalle [10]) one obtains that any trajectory which starts in M_k tends to (S^*, E^*, I^*, V^*) as $t \to \infty$. Then the endemic equilibrium (S^*, E^*, I^*, V^*) is locally asymptotically stable and the set M_k belongs to its domain of attraction. Since k was arbitrary and less than m, one obtains the required conclusion. □

We now continue with a few considerations on the inequalities (5.3). Since

$$\lim_{V_L \to 0} U_3(S^*, E^*, I^*, V_L) = \lim_{V_R \to \infty} U_3(S^*, E^*, I^*, V_R) = +\infty,$$

one obtains that if the following inequalities are satisfied,

$$\begin{aligned} &\frac{f(V)}{r(V)} \leq \frac{f(V^*)}{r(V^*)} \quad \text{for } V^* \leq V, \\ &\frac{f(V)}{r(V)} \geq \frac{f(V^*)}{r(V^*)} \quad \text{for } 0 < V \leq V^*, \end{aligned} \tag{5.4}$$

then (S^*, E^*, I^*, V^*) is globally asymptotically stable in $(0, \infty)^4$.

Regarding the inequalities (5.4) (or (5.3)), it is easy to see that they are verified if the function f/r is nonincreasing on $(0, \infty)$ (or on (V_L, V_R)); however, this monotonicity property is only sufficient and not necessary. If $r(V) = kV$, for some k, then the above monotonicity property is satisfied for three common incidence rates, namely $c_1(S)f_1(V) = \beta_1 SV$, $c_2(S)f_2(V) = \beta_2 S^p V^q$, where $0 < q \leq 1$, and $c_3(S)f_3(V) = \beta_3 SV/(1 + a_1 V)$.

We also remark that the inequalities (5.4) alone imply the uniqueness of the endemic equilibrium (S^*, E^*, I^*, V^*). To show this, suppose that there is another endemic equilibrium $(S_1^*, E_1^*, I_1^*, V_1^*)$. Apart from (EQ), one then has

$$\begin{aligned} (\text{EQ}') \qquad & n(S_1^*) = c(S_1^*)f(V_1^*), \quad c(S_1^*)f(V_1^*) = c_1 i(E_1^*), \quad c_2 i(E_1^*) = c_3 p(I_1^*), \\ & c_4 p(I_1^*) = r(V_1^*). \end{aligned}$$

It follows that

$$c(S^*) - c(S_1^*) = \frac{c_1 c_3}{c_2 c_4}\left(\frac{r(V^*)}{f(V^*)} - \frac{r(V_1^*)}{f(V_1^*)}\right), \tag{5.5}$$

$$n(S^*) - n(S_1^*) = \frac{c_1 c_3}{c_2 c_4}\left(r(V^*) - r(V_1^*)\right) \tag{5.6}$$

and therefore

$$\left(c(S^*) - c(S_1^*)\right)\left(V^* - V_1^*\right) \geq 0.$$

If $V^* > V_1^*$, then, from (5.5), $c(S^*) \geq c(S_1^*)$, $S^* \geq S_1^*$, which implies $n(S^*) \leq n(S_1^*)$ and consequently from (5.6), $r(V^*) \leq r(V_1^*)$, which is a contradiction. The case $V^* < V_1^*$ is dismissed in a similar manner, subsequently $V^* = V_1^*$ and from (5.5), $S = S_1^*$. Substituting these equalities into (EQ) and (EQ′) we obtain that $i(E^*) = i(E_1^*)$ and $p(I^*) = p(I_1^*)$, and hence $E^* = E_1^*$ and $I^* = I_1^*$; that is, the endemic equilibrium is uniquely determined. However, we should point out that inequalities (5.4) ensure the uniqueness of the endemic equilibrium only and not necessarily its existence.

6. Discussions and concluding remarks. The earlier analysis clearly indicates the importance of the quantity

$$c(S_0)\frac{f(V)}{r(V)}\frac{c_2 c_4}{c_1 c_3}$$

in the discussion on local stability of the disease-free equilibrium and persistence for the system. Moreover, under the monotonicity condition on $f(V)/r(V)$, we obtain the basic reproduction number

$$R_0 = c(S_0)\frac{c_2 c_4}{c_1 c_3}\lim_{V\to 0}\frac{f(V)}{r(V)}. \tag{6.1}$$

We will now give a biological interpretation of this result. From (S), it is obvious that the terms in the numerator denote the growth in the concentrations of the infected cells, E and I, and of the virus V. The terms in the denominator, on the other hand, denote the removal (or decrease in concentration) of these three same classes. Therefore, the ratio of the two can be considered as a measurement of the combined "productivity," perhaps more aptly, the *basic reproductive ratio* of the infected classes in the system. The fact that the stability of the disease-free equilibrium and the persistence of the system depend on whether this quantity is less than one or not (Theorems 3.1 and 3.2) further confirms our assertion.

The quantity $f(V)/r(V)$ is also important for our results. It can be interpreted as the efficiency of the virus, that is, the ratio of its infectivity to its removal, as a function of the virus concentration. Theorems 3.3, 4.1, and 5.2 require $f(V)/r(V)$ to be a nonincreasing function of V. Some recent studies (see, e.g., [16, 17]) let $f(V) = r(V) = V$, an assumption which is supported by some clinical data. We note that in this case $f(V)/r(V) = 1$, and hence our condition of nonincreasing ratio $f(V)/r(V)$, which generalizes to the models with nonlinear $f(V)$ and $r(V)$, is satisfied. For HIV, it has been observed that the productivity of the virus, $f(V)$, increases as the virus concentration increases. Our analysis is valid if the increase in removal of the virus $r(V)$ as virus concentration increases is at least to the same level as the increase in $f(V)$. Further studies are needed to verify whether our assertion holds.

On the other hand, if the function f/r is indeed increasing on $(0,\infty)$, then U_1 and U_3 are not necessarily global Lyapunov functionals and therefore do not create their own boundedness structure for the solutions of (S). For the global existence of the solutions, growth conditions (G) (see section 2) need to be imposed. If f/r is nonincreasing on $(0,\infty)$, however, the boundedness structures created by the level sets of U_1 and U_3 render the growth conditions unnecessary.

Suppose that f/r is nonincreasing on $(0,\infty)$ and $R_0 > 1$. Assume that the following conditions are satisfied:

$$\text{(B)} \qquad \lim_{y\to\infty}\left(y-\varphi(x)\int_x^y \frac{1}{\varphi(\tau)}d\tau\right)=+\infty \quad \text{for all } x>0 \text{ and } \varphi\in\{c,f,i,p\}\,.$$

Note that (B) is satisfied for a function φ such that $\lim_{y\to\infty}\varphi(y)=+\infty$, since in this situation

$$\lim_{y\to\infty}\frac{\int_x^y \frac{1}{\varphi(\tau)}d\tau}{y}=\lim_{y\to\infty}\frac{1}{\varphi(y)}=0 \quad \text{for } \varphi\in\{c,f,i,p\}\,.$$

However, condition (B) is also satisfied for $\varphi(x)=x^p/(1+ax^p), 0<p\le 1$ (this is, for instance, the case when $\varphi(V)=f(V)=V^p/(1+aV^p)$ is a nonlinear force of infection with saturation), which does not tend to $+\infty$ as $x\to+\infty$.

Regarding conditions (D), since the only points on the boundary of $[0,\infty)^4$ which can be reached in finite time are situated on $[OS$ and the only w-limit point of (S) on the boundary of $[0,\infty)^4$ is the disease-free equilibrium $(S_0,0,0,0)$, a less restrictive condition than (D) would suffice to avoid these situations, namely

$$\text{(D}')\qquad \int_{0+}^1 \frac{1}{\varphi(\tau)}d\tau=+\infty \quad \text{for some } \varphi\in\{f,i,p\}\,.$$

Then, by the results in the previous section, there is a unique positive endemic equilibrium which verifies relations (EQ). Take $(S(0),E(0),I(0),V(0))\in(0,\infty)^4$. Then $U_3\le 0$ for all t, and it follows that $(S(t),E(t),I(t),V(t))$ stays in a level set of U_3 on its whole interval of existence. Since the level sets of U_3 are bounded due to (B), it follows that the saturated solution which starts in $(S(0),E(0),I(0),V(0))$ exists on $[0,\infty)$. The growth conditions (G), which were used to obtain global existence, therefore become unnecessary and the proof proceeds in the same manner. Then, as in section 3, all solutions which start in $[0,\infty)^4$ tend to (S^*,E^*,I^*,V^*), except for those which start on $[OS$ and tend to $(S_0,0,0,0)$ as $t\to\infty$. The growth conditions become unnecessary for the proof of the uniform persistence result as well, since the system (S) admits an endemic equilibrium and it is obviously uniformly persistent.

If $R_0\le 1$, the reasoning is quite similar, with U_1 in place of U_3, and it is obtained again that all the saturated solutions are global and the stability result remains valid. We then summarize our discussion in the following result.

THEOREM 6.1. *Suppose that f/r is nonincreasing on $(0,\infty)$ and conditions* (4.2), (4.3), (B), *and* (D′) *are satisfied.*

1. *If $R_0\le 1$, then the disease-free equilibrium $(S_0,0,0,0)$ is globally asymptotically stable.*
2. *If $R_0>1$, then the system* (S) *admits a unique positive endemic equilibrium which is globally asymptotically stable. The disease-free equilibrium $(S_0,0,0,0)$ is unstable, with the positive semiaxis $[OS$ as its stable variety.*

Obviously, in statement 2 the stable variety of the endemic equilibrium actually excludes $[OS$.

As an example to illustrate the usefulness of our results, it is easy to see that a system which fits into our framework is

$$\text{(RS)} \qquad \begin{cases} S' = b - mS - \beta S \dfrac{V^p}{1 + aV^p}, \\ E' = \beta S \dfrac{V^p}{1 + a_1 V^p} - c_1 E, \\ I' = c_2 E - c_3 I, \\ V' = c_4 I - kV^\gamma \end{cases}$$

for $b, m, \beta, k > 0$, $a \geq 0$, and $0 < p \leq \gamma \leq 1$. In this situation, $c(S) = \beta S$, $f(V) = V^p/(1 + aV^p)$, $i(E) = E$, $p(I) = I$, $r(V) = V^\gamma$, $n(S) = b - mS$.

It follows that $f/r = 1/((1 + a_1 V^p)V^{\gamma - p})$ is nonincreasing on $(0, \infty)$,

$$\lim_{E \to \infty} E = \lim_{I \to \infty} I = \lim_{V \to \infty} kV^\gamma = +\infty,$$

and $\lim_{V \to \infty} V^p/(1 + aV^p) = +\infty$ if $a = 0$, while if $a > 0$, then

$$\lim_{V \to \infty} \left(V - \frac{x^p}{1 + ax^p} \int_x^V \frac{1 + a\tau^p}{\tau^p} d\tau \right) = +\infty \quad \text{for all } x > 0.$$

Also, $\int_{0+}^1 \frac{1}{E} dE = +\infty$. Note that if $a = 0$ and $p \in (0, 1)$, then $f(V) = V^p$ is not Lipschitzian on $[0, \infty)$ due to its behavior near 0. However, our solutions which start with $V > 0$ do not reach points for which $V = 0$ in finite time. Hence the uniqueness property is not impaired. The same remark applies to the function r. We can therefore apply the results in the previous sections and obtain the following result.

THEOREM 6.2.

1. *If $p < \gamma$, the basic reproduction number R_0 of the system* (RS) *is $+\infty$. The system* (RS) *admits a positive endemic equilibrium which is globally asymptotically stable. The disease-free equilibrium $(S_0, 0, 0, 0)$ is unstable, with the positive semiaxis $[OS$ as its stable variety.*
2. *If $p = \gamma$, the basic reproduction number R_0 of the system* (RS) *is*

$$R_0 = \frac{\beta b}{m} \frac{c_2 c_4}{c_1 c_3} \frac{1}{k}.$$

In this case, if $R_0 \leq 1$, then the disease-free equilibrium $(S_0, 0, 0, 0)$ is globally asymptotically stable, while if $R_0 > 1$, the system (RS) *admits a positive endemic equilibrium which is globally asymptotically stable. The disease-free equilibrium $(S_0, 0, 0, 0)$ is unstable, with the positive semiaxis $[OS$ as its stable variety.*

Again, the "global" stable variety of the endemic equilibrium is understood to exclude $[OS$. Note that for $p = \gamma = 1$ and $a = 0$ we obtain the results given in Korobeinikov [7].

As a final remark, we note that similar analysis can be extended to a system of the form

$$\text{(SE)}\qquad \begin{cases} S' = n(S) - c(S)f(V), \\ E' = c(S)f(V) - c_1 i(E), \\ I_1' = c_2 i(E) - k_1 p_1(I_1), \\ I_j' = \tilde{k}_{j-1} p_{j-1}(I_{j-1}) - k_j p_j(I_j), \quad 2 \le j \le n, \\ V' = \tilde{k}_n p_n(I_n) - r(V). \end{cases}$$

The associated Lyapunov functionals are in this case

$$U_1(S, E, I_1, \dots, I_n) = \int_{S_0}^{S} \frac{c(\tau) - c(S_0)}{c(\tau)} d\tau + E + \frac{c_1}{c_2} \sum_{i=1}^{n} \left(\prod_{j=1}^{i-1} \frac{k_j}{\tilde{k}_j} \right) I_i + \frac{c_1}{c_2} \prod_{j=1}^{n} \frac{k_j}{\tilde{k}_j} V,$$

$$U_2(S, E, I_1, \dots, I_n) = E + \frac{c_1}{c_2} \sum_{i=1}^{n} \left(\prod_{j=1}^{i-1} \frac{k_j}{\tilde{k}_j} \right) I_i + \frac{c_1}{c_2} \prod_{j=1}^{n} \frac{k_j}{\tilde{k}_j} V,$$

and

$$\begin{aligned} U_3(S, E, I_1, \dots, I_n) = {} & \int_{S^*}^{S} \frac{c(\tau) - c(S^*)}{c(\tau)} d\tau + \int_{E^*}^{E} \frac{i(\tau) - i(E^*)}{i(\tau)} d\tau \\ & + \frac{c_1}{c_2} \sum_{i=1}^{n} \left(\prod_{j=1}^{i-1} \frac{k_j}{\tilde{k}_j} \right) \int_{I_i^*}^{I_i} \frac{p_i(\tau) - p_i(I_i^*)}{p_i(\tau)} d\tau \\ & + \frac{c_1}{c_2} \left(\prod_{j=1}^{n} \frac{k_j}{\tilde{k}_j} \right) \int_{V^*}^{V} \frac{c(\tau) - c(V^*)}{c(\tau)} d\tau, \end{aligned}$$

with the convention $\prod_{j=1}^{0} \frac{k_j}{\tilde{k}_j} = 1$.

Again, related asymptotic stability can be obtained as in previous sections, and the size of the domain of attraction depends essentially on the behavior of the function f/r. If the function f/r is nonincreasing on $(0, \infty)$, the threshold parameter R_0 is given by

$$R_0 = c(S_0) \frac{c_2}{c_1} \left(\prod_{j=1}^{n} \frac{\tilde{k}_j}{k_j} \right) \lim_{V \to 0} \frac{f(V)}{r(V)}.$$

The first Lyapunov functional of type $\sum_{i=1}^{n} d_i \big(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*} \big)$, to which our functional U_3 reduces when c, f, i, p are linear functions, has been used by Volterra in [20] to treat a two-dimensional predator-prey model which describes the interaction between sharks and predated fish in the Mediterranean Sea. (See also Goh [4].) In [5], Harrison constructed a Lyapunov functional of this type for a two-dimensional predator-prey model which accounted for very general numerical and functional responses of the predator. The computation of the derivatives is straightforward and hence omitted for brevity.

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