GLOBAL PROPERTIES FOR A VIRUS PROPAGATION MODEL WITH STAGED PROGRESSION

Paul Georgescu[1]

Abstract. We consider the global dynamics of a virus propagation model in which infective cells pass through several successive stages, assuming that the incidence of infection and the removal rate of the virus are nonlinear functions given in an abstract, unspecified form. Suitable Lyapunov functionals are constructed to establish the existence of a threshold parameter, the basic reproduction number R_0 of the system. It is shown that if $R_0 > 1$, then the disease-free equilibrium is unstable and the endemic equilibrium is globally asymptotically stable (the disease remains endemic, that is), while if $R_0 \leq 1$ then there is no endemic equilibrium and the disease-free equilibrium is globally asymptotically stable (the disease dies out, that is).

2000 *Mathematics Subject Classification*: 92D30, 34D20.

1. Introduction

We consider a compartmental model for the propagation of a virus in vivo with staged progression of the infective cells through several stages with distinct infectivity. This model is understood to be appropriate especially for diseases with slow progression such as tuberculosis, where the latent period ranges from months to decades and the average infectious period is comparatively short (usually a few months), some infective individuals never progressing to the infectious state. See Okuonghae and Korobeinikov [19] for a model for the transmission of tuberculosis in Nigeria. In this regard, it is assumed that the infection pathway is virus-to-cell (as opposed to an infected cell-to-cell pathway) and that new viruses are produced by infected cells only in the last

[1]Research supported by the project ID 342/2008, CNCSIS, Romania

infectious stage. We denote by S the concentration of cells in the susceptible (uninfected) stage, by E the concentration of cells in the exposed (latent, incubating) stage, by I_1, I_2, ..., I_n the concentration of cells in the successive infection stages from the first through the last and by V the concentration of viral cells.

Motivated by these considerations, we introduce the compartmental model to be studied in the form

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

In the above model, $g(S)$ denotes the intrinsic growth rate of the susceptible class, which includes both the production of new cells and their removal due to natural causes, all newly produced cells being susceptible. The movement of exposed cells into the infected class and the removal of exposed cells are denoted by $c_2 i(E)$ and $c_1 i(E)$, respectively. By $k_j p_j(I_j)$, $1 \leq j \leq n$, we denote the removal of the infective cells in the j-th stage, while $\tilde{k}_j$, $1 \leq j \leq n-1$, describes the progression of infective cells from the j-th stage to the $j+1$-th stage. The production of free virus cells from infected cells in the n-th stage is denoted by $\tilde{k}_n p_n(I_n)$ and the removal rate of viral cells is denoted by $r(V)$. It is also assumed that the disease transmission is characterized by the infection 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. All functions g, c, f, r, p_j, $1 \leq j \leq n$, are assumed to be nonlinear and all constants k_j, $\tilde{k}_j$, $1 \leq j \leq n$, are assumed to be positive.

The stability of many disease transmission models depends in a decisive fashion upon the so-called basic reproduction number R_0, defined as the average number of new infections caused by a single carrier (infective individual or viral cell) when introduced in a totally susceptible population at equilibrium. In this regard, it is often the case that if $R_0 < 1$ then the disease dies out and the disease-free equilibrium is globally asymptotically stable.

If $R_0 > 1$, then any carrier causes, in average, more than one infection and the disease is expected to remain endemic. However, proving the global stability of the endemic equilibrium in the case in which $R_0 > 1$, whenever this is feasible, is a comparatively more difficult task. It is perhaps worth

mentioning that the global stability of the so-called SEIR (susceptible-exposed-infective-removed) model for the case in which $R_0 > 1$ has been obtained as late as 1995 by Li and Muldowney in [18], their approach being essentially geometrical, relying on the fact that three-dimensional competitive systems satisfy Poincaré-Bendixson property. For the case in which the system is not competitive, another approach, due also to Li and Muldowney [17], is to show that the system satisfies a Poincaré-Bendixson property which is robust under C^1-perturbations.

A different (and simpler) path towards proving global stability results for mathematical epidemiology models has been taken by Korobeinikov and Maini [14,15] (see also Korobeinikov [11,12,13]), who used Lyapunov functionals of type $\sum_i A_i(X_i(t) - X_i^* \ln X_i(t))$, where A_i are properly selected constants, X_i is the population size of the i-th compartment and X_i^* is its equilibrium level. The first Lyapunov functional of this type has actually been used by Volterra in [21], but for the analysis of a two-dimensional predator-prey model, the celebrated Lotka-Volterra model. See also Goh [6], who uses a related functional to study the stability of a n-dimensional Lotka-Volterra model and Harrison [8], for the study of a two-dimensional predator-prey system which vastly generalizes Lotka-Volterra model, also by Lyapunov's method.

Similarly, Lyapunov's method is used in Georgescu and Hsieh [3] to study the global dynamics of a SEIV model with nonlinear incidence of infection and removal rate and in Georgescu and Hsieh [2] to discuss the global properties of a stage-structured predator-prey model with stage structure for the predator. See also Guo, Li and Shuai [7], Yuan and Wang [22] for recent results in this area which establish the global stability of certain classes of multigroup models. This paper attempts to enlarge the results obtained in [3], where the case of a single infective stage has been discussed.

2. Basic assumptions and the well-posedness of the model

We assume that c, f, r, p_j, $1 \leq j \leq n$, are real functions of class C^1 defined at least on $[0, \infty)$ such that

$$c(0) = f(0) = r(0) = i(0) = 0; \quad p_j(0) = 0, 1 \leq j \leq n,$$

and that g is a real function of class C^1 defined at least on $[0, \infty)$ with $g(0) > 0$ such that the equation $g(S) = 0$ has a single strictly positive solution S_0. We also assume that the following hypotheses hold.

(M) $\frac{f}{r}$ is nonincreasing, g is strictly decreasing, c, i, p_j, $1 \leq j \leq n$, are strictly increasing.

(L) $\lim_{x\to\infty} g(x) < 0$, $\lim_{x\to\infty} i(x) = \lim_{j\to\infty} p_j(x) = +\infty$, $1 \leq j \leq n$.

(D) $\int_{0+}^{1} \frac{1}{\varphi(\tau)} d\tau = +\infty$ for $\varphi \in \{c, f, i, p_j,\ 1 \leq j \leq n\}$.

(G) $g(S) \leq a_1 - a_2 S$ for $s \geq 0$, $i(E) \geq a_i E$ for $E \geq 0$, $p_j(I) \geq a_p I$ for $I \geq 0$ and $1 \leq j \leq n$, $r(V) \geq a_r V$ for $V \geq 0$; a_1, a_2, a_i, a_p, $a_r > 0$.

From the above, it follows that the system (1) admits a single disease-free equilibrium $(S_0, 0, 0, \ldots, 0, 0)$, which we shall denote in the following by $\mathbf{E_0}$. We shall also denote $(I_1, I_2, \ldots, I_n)$ by $\mathbf{I}$.

It can be easily seen that (1) has a unique saturated solution for any given initial data and that $Q_1 = [0, \infty)^{n+3}$ is an invariant set for (1), that is, a solution which starts in Q_1 remains there on its whole interval of existence, by noting that the vector $(R_1, R_2, \ldots, R_{n+3})$ of the right-hand sides of (1) points inside Q_1 at all points of ∂Q_1.

One also sees that

$$\left(S + E + \frac{c_1}{2c_2} I_1 + \frac{c_1}{2c_2} \sum_{j=2}^{n} \left(\prod_{i=1}^{j-1} \frac{\tilde{k}_i}{2k_i}\right) I_j + \frac{c_1}{2c_2} \left(\prod_{i=1}^{n} \frac{\tilde{k}_i}{2k_i}\right) V)\right)'$$
$$\leq \tilde{K} - \tilde{\delta} \left(S + E + \frac{c_1}{2c_2} I_1 + \frac{c_1}{2c_2} \sum_{j=2}^{n} \left(\prod_{i=1}^{j-1} \frac{\tilde{k}_i}{2k_i}\right) I_j + \frac{c_1}{2c_2} \left(\prod_{i=1}^{n} \frac{\tilde{k}_i}{2k_i}\right) V\right)$$

for suitable $\tilde{K}, \tilde{\delta}$, from which we deduce that

$$F = \left\{(S, E, \mathbf{I}, V) \in Q_1, S + E + \tfrac{c_1}{2c_2} I_1 + \tfrac{c_1}{2c_2} \textstyle\sum_{j=2}^{n} \left(\prod_{i=1}^{j-1} \frac{\tilde{k}_i}{2k_i}\right) I_j \right.$$
$$\left. + \tfrac{c_1}{2c_2} \left(\textstyle\prod_{i=1}^{n} \frac{\tilde{k}_i}{2k_i}\right) V \leq \frac{\tilde{K}}{\tilde{\delta}}\right\}$$

is a feasible region (obviously, neither minimal nor unique) for (1). In the following, we shall assume without further notice that all admissible initial data belong to F.

It is also possible to prove, as done in Georgescu, Hsieh and Zhang [4], that if we denote $Q_2 = (0, \infty)^{n+3}$, then $F \cap Q_2$ is also a feasible region for (1). Regarding the behavior of solutions which start on the boundary of Q_2, it is seen that all solutions which start on $[OS$ tend to S_0 remaining on $[OS$, while they enter Q_2 (and stay there) otherwise.

Let us define the basic reproduction number of the virus by

$$R_0 = c(S_0)\frac{c_2}{c_1}\left(\prod_{j=1}^{n}\frac{\tilde{k}_j}{k_j}\right)\frac{f'(0)}{r'(0)}. \tag{2}$$

In this regard, a derivation of R_0 can be performed as in van den Driessche and Watmough [20]. We rearrange the system as

$$\begin{pmatrix} E' \\ I' \\ \vdots \\ I'_n \\ V' \\ S' \end{pmatrix} = \begin{pmatrix} c(S)f(V) \\ 0 \\ \vdots \\ 0 \\ 0 \\ 0 \end{pmatrix} - \begin{pmatrix} c_1 i(E) \\ -c_2 i(E) + k_1 p_1(I_1) \\ \vdots \\ -\tilde{k}_{n-1}p_{n-1}(I_{n-1}) + k_n p_n(I_n) \\ -\tilde{k}_n p_n(I_n) + r(V) \\ -g(S) + c(S)f(V) \end{pmatrix} = \mathcal{F} - \mathcal{V}.$$

At the disease-free equilibrium $\mathbf{E_0}$, the Jacobi matrices of $\mathcal{F}$ and $\mathcal{V}$ are

$$D\mathcal{F}(\mathbf{E_0}) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad D\mathcal{V}(\mathbf{E_0}) = \begin{pmatrix} V & 0 \\ J_1 & J_2 \end{pmatrix},$$

where the infection matrix F and the transition matrix V are given by

$$F = \begin{pmatrix} 0 & 0 & \dots & 0 & c(S_0)f'(0) \\ 0 & 0 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \dots & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} c_1 i'(0) & 0 & \dots & 0 & 0 \\ -c_2 i'(0) & k_1 p'_1(0) & \dots & 0 & 0 \\ 0 & -\tilde{k}_1 p'_1(0) & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & -\tilde{k}_{n-1}p'_{n-1}(0) & k_n p'_n(0) \end{pmatrix}.$$

Then, as derived in [20], R_0 is the largest eigenvalue of the next generation matrix FV^{-1}, from which (2) follows.

3. The stability of the disease-free equilibrium

We have previously seen that the system (1) admits a single disease-free equilibrium $\mathbf{E_0}$ regardless of the value of R_0. We now turn our attention to the study of its stability. To this purpose, let us consider the following Lyapunov functional

$$U_1(S,E,\mathbf{I},V)=\int_{S_0}^{S}\frac{c(\tau)-c(S_0)}{c(\tau)}d\tau+E+\frac{c_1}{c_2}\sum_{j=1}^{n}\left(\prod_{i=1}^{j-1}\frac{k_i}{\tilde{k}_i}\right)I_j+\frac{c_1}{c_2}\left(\prod_{i=1}^{n}\frac{k_i}{\tilde{k}_i}\right)V, \tag{3}$$

with the convention that $\prod_{i=1}^{0}\frac{k_i}{\tilde{k}_i}=1$. Since c is strictly increasing, it is seen that U_1 increases whenever any of $|S-S_0|$, E, I_j, $1\leq j\leq n$, V increases and $U_1\geq 0$, with equality if and only if $(S,E,\mathbf{I},V)=\mathbf{E_0}$. We now compute the derivative of U_1 along the solutions of (1). It is seen that

$$\begin{aligned}
&\dot{U_1}\,(S,E,\mathbf{I},V)\\
&=\left(1-\frac{c(S_0)}{c(S)}\right)(g(S)-c(S)f(V))+(c(S)f(V)-c_1i(E))\\
&\quad+\frac{c_1}{c_2}(c_2i(E)-k_1p_1(I_1))+\frac{c_1}{c_2}\sum_{j=2}^{n}\left(\prod_{i=1}^{j-1}\frac{k_i}{\tilde{k}_i}\right)(\tilde{k}_{j-1}p_{j-1}(I_{j-1})-k_jp_j(I_j))\\
&\quad+\frac{c_1}{c_2}\left(\prod_{i=1}^{n}\frac{k_i}{\tilde{k}_i}\right)(\tilde{k}_np_n(I_n)-r(V))\\
&=\left(1-\frac{c(S_0)}{c(S)}g(S)\right)+c(S_0)f(V)-\frac{c_1}{c_2}\left(\prod_{i=1}^{n}\frac{k_i}{\tilde{k}_i}\right)r(V).
\end{aligned}$$

Since $g(S_0)=0$, we may deduce that

$$\begin{aligned}
\dot{U_1}\,(S,E,\mathbf{I},V) &= \left(1-\frac{c(S_0)}{c(S)}\right)(g(S)-g(S_0)) \\
&\quad+\frac{c_1}{c_2}\left(\prod_{i=1}^{n}\frac{k_i}{\tilde{k}_i}\right)r(V)\left[c(S_0)\frac{c_2}{c_1}\frac{f(V)}{r(V)}\left(\prod_{i=1}^{n}\frac{\tilde{k}_i}{k_i}\right)-1\right].
\end{aligned} \tag{4}$$

We may now obtain the following global stability result.

Theorem 1 *Suppose that $R_0\leq 1$. Then the disease-free equilibrium $\mathbf{E_0}$ is globally asymptotically stable in Q_1.*

Proof. From (4) and the monotonicity conditions (**M**), it is seen that $\dot{U_1}\leq 0$ on Q_2, with equality if and only if $S=S_0$ and $R_0=1$. Since the only invariant

set within the set of points for which $S = S_0$ is $\mathbf{E_0}$, it follows that $\mathbf{E_0}$ is globally asymptotically stable in Q_2, by LaSalle's invariance principle (see LaSalle [16] or Khalil [10]). The remarks regarding the behavior of the solutions starting on the boundary of ∂Q_2 complete the proof. ■

We now further consider the case in which $R_0 > 1$. Under this assumption, it will be shown that the disease-free equilibrium $\mathbf{E_0}$ is unstable.

In this regard, it is said that (1) is uniformly persistent (or permanent) in D if there is $\varepsilon_0 > 0$ (not depending on the initial data) such that any solution of (1) which starts in int$D$ satisfies

$$\liminf_{t\to\infty} S(t) \geq \varepsilon_0, \quad \liminf_{t\to\infty} E(t) \geq \varepsilon_0, \quad \liminf_{t\to\infty} I_j(t) \geq \varepsilon_0,\ 1 \leq j \leq n,$$
$$\liminf_{t\to\infty} V(t) \geq \varepsilon_0.$$

The biological significance of the notion of persistence is that the disease remains endemic in the long term. In mathematical terms, all solutions with strictly positive initial data are eventually uniformly bounded away from the boundary. Of course, this mutually excludes any sort of stability of the disease-free equilibrium. See also Butler, Freedman and Waltman [1] for weaker notions of persistence.

Let us consider the following the quasi-Lyapunov function

$$U_2(S, E, \mathbf{I}, V) = E + \frac{c_1}{c_2} \sum_{j=1}^{n} \left(\prod_{i=1}^{j-1} \frac{k_i}{\tilde{k}_i} \right) I_j + \frac{c_1}{c_2} \left(\prod_{i=1}^{n} \frac{k_i}{\tilde{k}_i} \right) V.$$

In a way similar to the derivation of (4), it is seen that

$$\dot{U}_2\,(S, E, \mathbf{I}, V) = c(S)f(V) - \frac{c_1}{c_2} \left(\prod_{i=1}^{n} \frac{k_i}{\tilde{k}_i} \right) r(V). \tag{5}$$

We may now obtain the following persistence result

Theorem 2 *Suppose that $R_0 > 1$. Then (1) is uniformly persistent.*

Proof. From (5), we note that

$$\dot{U}_2\,(S, E, \mathbf{I}, V) = \frac{c_1}{c_2} \left(\prod_{i=1}^{n} \frac{k_i}{\tilde{k}_i} \right) r(V) \left[c(S_0) \frac{c_2}{c_1} \frac{f(V)}{r(V)} \left(\prod_{i=1}^{n} \frac{\tilde{k}_i}{k_i} \right) - 1 \right]$$

and consequently $\dot{U}_2 > 0$ on a small vicinity of $\mathbf{E_0}$. It is also seen that $\mathbf{E_0}$ is the unique (and therefore isolated) compact invariant set on the boundary of

the feasible domain, its stable manifold being included in the boundary of Q_2. The conclusion now follows from Theorem 4.1 of Hofbauer and So [9]. See also Georgescu and Moroşanu [5] for a different approach to the persistence of a related system. ■

4. The existence and stability of the endemic equilibrium

We now try to find a necessary and sufficient condition for the existence of a positive (endemic) equilibrium $\mathbf{E}^* = (S^*, E^*, \mathbf{I}^*, V^*)$, where $\mathbf{I}^* = (I_1^*, I_2^*, \ldots, I_n^*)$, prior to studying its stability. To this purpose, let us observe that $S^*, E^*, \mathbf{I}^*, V^*$ should satisfy the following system of equilibrium conditions

$$\begin{aligned} &g(S^*) = c(S^*)f(V^*), \quad c(S^*)f(V^*) = c_1 i(E^*), \quad c_2 i(E^*) = k_1 p_1 i(I_1^*), \\ &\tilde{k}_{j-1} p_{j-1}^*(I_{j-1}^*) = k_j p_j^*(I_j^*),\ 2 \le j \le n, \quad \tilde{k}_n p_n(I_n^*) = r(V^*). \end{aligned} \tag{6}$$

To solve (6), let us define

$$\begin{aligned} F_1(S,V) &= g(S) - c(S)f(V), \\ F_2(S,V) &= c(S)f(V) - \frac{c_1}{c_2}\left(\prod_{i=1}^n \frac{k_i}{\tilde{k}_i}\right) r(V). \end{aligned}$$

Since $S \to F_1(S,V)$ is strictly decreasing and $F_1(0,V)F_1(S_0,V) < 0$ for all $V > 0$, it follows that the equation $F_1(S,V) = 0$ can be uniquely solved with respect to S as a function of V for all $V \ge 0$, that is, there is $\psi_1 : [0,\infty) \to (0,\infty)$ (which is strictly decreasing, with $\lim_{x\to\infty} \psi_1(x) = 0$ and $\psi_1(0) = S_0$) such that $S = \psi_1(V)$ and $F_1(\psi_1(V), V) = 0$.

Then

$$\begin{aligned} F_2(V, \psi_1(V)) &= c(\psi_1(V))f(V) - \frac{c_1}{c_2}\left(\prod_{i=1}^n \frac{k_i}{\tilde{k}_i}\right) r(V) \\ &= \frac{c_1}{c_2}\left(\prod_{i=1}^n \frac{k_i}{\tilde{k}_i}\right) r(V) \left[c(\psi_1(V))\frac{c_2}{c_1}\frac{f(V)}{r(V)}\left(\prod_{i=1}^n \frac{\tilde{k}_i}{k_i}\right) - 1\right]. \end{aligned}$$

Since ψ_1 is strictly decreasing and $\frac{f}{r}$ is nonincreasing, it follows that a necessary and sufficient condition for the existence of V^* is that

$$\lim_{V\to 0} c(\psi_1(V))\frac{c_2}{c_1}\frac{f(V)}{r(V)}\left(\prod_{i=1}^n \frac{\tilde{k}_i}{k_i}\right) - 1 > 0,$$

that is, $R_0 > 1$. Note that in this situation V^* is unique.

Also, due to the strict monotonicity of i and p_j, $1 \leq j \leq n$, and to the conditions (**L**) and (**M**), it follows that E^* and I_j^*, $1 \leq j \leq n$, exist and are also unique, while the existence and uniqueness of S^* follows from the unique solvability of the equation $F_1(S, V^*) = 0$ with respect to S. In view of the above, we obtain the following existence result.

Theorem 3 *There is an endemic equilibrium* $\mathbf{E}^*$ *of (1) if and only if* $R_0 > 1$. *The endemic equilibrium* $\mathbf{E}^*$ *is unique if it exists.*

We continue our analysis with a discussion on the stability of the endemic equilibrium, assuming that $R_0 > 1$. Let us consider the following Lyapunov functional

$$\begin{aligned} U_3(S, E, \mathbf{I}, V) &= \int_{S^*}^{S} \frac{c(\tau) - c(S^*)}{c(\tau)} d\tau + \int_{E^*}^{E} \frac{i(\tau) - i(E^*)}{i(\tau)} d\tau \\ &+ \frac{c_1}{c_2} \sum_{j=1}^{n} \left(\prod_{i=1}^{j-1} \frac{k_i}{\tilde{k}_i} \right) \int_{I_j^*}^{I_j} \frac{p_j(\tau) - p_j(I_j^*)}{p_j(\tau)} d\tau \\ &+ \frac{c_1}{c_2} \left(\prod_{i=1}^{n} \frac{k_i}{\tilde{k}_i} \right) \int_{V^*}^{V} \frac{f(\tau) - f(V^*)}{f(\tau)} d\tau. \end{aligned} \tag{7}$$

It is seen that U_3 increases whenever any of $|S - S^*|$, E, I_j, $1 \leq j \leq n$, V increases and that $U_3 \geq 0$, with equality if and only if $(S, E, I, V) = \mathbf{E}^*$. Also, due to the divergence conditions (**D**), $U_3(S, E, \mathbf{I}, V)$ tends to $+\infty$ if any of S, E, I_j, $1 \leq j \leq n$, V tends to 0.

We now compute the derivative of (7) along the solutions of (1). It is seen that

$$\begin{aligned} &\dot{U}_3\,(S, E, \mathbf{I}, V) \\ &= \left(1 - \frac{c(S^*)}{c(S)}\right)(g(S) - c(S)f(V)) + \left(1 - \frac{i(E^*)}{i(E)}\right)(c(S)f(V) - c_1 i(E)) \\ &+ \frac{c_1}{c_2}\left(1 - \frac{p_1(I_1^*)}{p_1(I_1)}\right)(c_2 i(E) - k_1 p_1(I_1)) \\ &+ \frac{c_1}{c_2} \sum_{j=2}^{n} \left(\prod_{i=1}^{j-1} \frac{k_j}{\tilde{k}_j} \right) \left(1 - \frac{p_j(I_j^*)}{p_j(I_j)}\right)(\tilde{k}_{j-1} p_{j-1}(I_{j-1}) - k_j p_j(I_j)) \\ &+ \frac{c_1}{c_2} \left(\prod_{i=1}^{n} \frac{k_i}{\tilde{k}_i} \right) \left(1 - \frac{f(V^*)}{f(V)}\right)(\tilde{k}_n p_n(I_n) - r(V)). \end{aligned}$$

Using the equilibrium relations (6), it follows that

$$\begin{aligned}\dot{U_3} &= \left(1-\frac{c(S^*)}{c(S)}\right)g(S)+c(S^*)f(V)-c_1i(E^*)\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+c_1i(E^*)\\ &\quad -c_1i(E^*)\frac{p_1(I_1^*)}{p_1(I_1)}\frac{i(E)}{i(E^*)}+c_1i(E^*)\\ &\quad -c_1i(E^*)\sum_{j=2}^{n}\frac{p_j(I_j^*)}{p_j(I_j)}\frac{p_{j-1}(I_{j-1})}{p_j(I_j)}+(n-1)c_ii(E^*)\\ &\quad -c_1i(E^*)\frac{r(V)}{r(V^*)}-c_1i(E^*)\frac{f(V^*)}{f(V)}\frac{p_n(I_n)}{p_n(I_n^*)}+c_1i(E)\frac{f(V^*)}{f(V)}\frac{r(V)}{r(V^*)}.\end{aligned}$$

It is then seen that

$$\begin{aligned}\dot{U_3} &= \left(1-\frac{c(S^*)}{c(S)}\right)(g(S)-g(S^*))+c_1i(E^*)\left(\frac{f(V^*)}{f(V)}-1\right)\left(\frac{f(V^*)}{r(V^*)}-\frac{f(V)}{r(V)}\right)\\ &\quad -c_1i(E^*)\left[\frac{c(S^*)}{c(S)}+\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+\frac{i(E)}{i(E^*)}\frac{p_1(I_1^*)}{p_1(I_1)}\right.\\ &\qquad \left.+\sum_{j=2}^{n}\frac{p_j(I_j^*)}{p_j(I_j)}\frac{p_{j-1}(I_{j-1})}{p_j(I_j)}+\frac{p_n(I_n)}{p_n(I_n^*)}\frac{f(V^*)}{f(V)}-(n+2)\right].\end{aligned}$$

We are now ready to establish the global stability of the endemic equilibrium.

Theorem 4 *Suppose that $R_0>1$. Then the endemic equilibrium E^* is globally asymptotically stable in Q_2.*

Proof. From the monotonicity conditions (**M**), it follows that

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

with equality if and only if $S=S^*$ and that

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

Also, from the $AM-GM$ inequality, which says that the arithmetic mean is at least equal to the geometric mean, it follows that

$$\begin{aligned}&\frac{c(S^*)}{c(S)}+\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}+\frac{i(E)}{i(E^*)}\frac{p_1(I_1^*)}{p_1(I_1)}+\sum_{j=2}^{n}\frac{p_j(I_j^*)}{p_j(I_j)}\frac{p_{j-1}(I_{j-1})}{p_j(I_j)}\\ &+\frac{p_n(I_n)}{p_n(I_n^*)}\frac{f(V^*)}{f(V)}-(n+2)\ge 0\end{aligned}$$

with equality if and only if

$$\frac{c(S^*)}{c(S)}=\frac{i(E^*)}{i(E)}\frac{c(S)}{c(S^*)}\frac{f(V)}{f(V^*)}=\frac{i(E)}{i(E^*)}\frac{p_1(I_1^*)}{p_1(I_1)}=\frac{p_j(I_j^*)}{p_j(I_j)}\frac{p_{j-1}(I_{j-1})}{p_j(I_j)},\ 2\le j\le n,$$
$$=\frac{p_n(I_n)}{p_n(I_n^*)}\frac{f(V^*)}{f(V)}=1.$$

Consequently, $\dot{U}_3=0$ if and only if $S=S^*$ and

$$\frac{i(E}{i(E^*)}=\frac{f(V)}{f(V^*)}=\frac{p_j(I_j)}{p_j(I_j^*)},\ 1\le j\le n,=\frac{f(V)}{f(V^*)}. \tag{8}$$

We now try to find the invariant subsets within the set of points which satisfy the conditions above. Since $S'=g(S^*)-c(S^*)f(V)$ on these subsets, it follows that

$$S'=c(S^*)(f(V^*)-f(V))$$

and consequently $S'=0$ if and only if $V=V^*$. From (8), we then deduce that $E=E^*$ and $I_j=I_j^*$ for $1\le j\le n$. Consequently, the endemic equilibrium $\mathbf{E}^*$ is the unique such invariant set and consequently it is globally asymptotically stable on Q_2, by LaSalle's invariance principle. ■

5. Concluding remarks

Our mathematical findings can be summarized in the following result.

Theorem 5 *1. If $R_0>1$, then the disease-free equilibrium $\mathbf{E_0}$ is unstable and the system is permanent. There is a single endemic equilibrium $\mathbf{E}^*$, which is globally asymptotically stable in Q_2.*

2. If $R_0\le 1$, then the disease-free equilibrium $\mathbf{E_0}$ is globally asymptotically stable in Q_1 and there is no endemic equilibrium.

From Theorem 5, it is seen that the basic reproduction number R_0 is a threshold parameter, governing the stability of both the disease-free and the endemic equilibrium, not to mention the very existence of the latter. Comparing our Theorem 5 with the results obtained in Georgescu and Hsieh [2], it is seen that the SEIV model has a robust structural stability, in the sense that its stability properties are not affected by the number of stages in the infective

period. Directions for further research include considering whether or not these properties are affected by multiple contagion pathways (to allow for infected cell-to-cell infection pathways of for multiple infective parallel stages) or by increased viral cell production (to suppose that viral cells are produced in each infective stage).

References

[1] G. Butler, H. I. Freedman, P. Waltman, *Uniformly persistent systems*, Proc. Amer. Math. Soc., 96 (1986), 425–430.

[2] P. Georgescu, Y.-H. Hsieh, *Global dynamics of a predator-prey model with stage structure for predator*, SIAM J. Appl. Math., 67 (2006), 1379–1395.

[3] P. Georgescu, Y.-H. Hsieh, *Global stability for a virus dynamics model with nonlinear incidence of infection and removal*, SIAM J. Appl. Math., 67 (2006), 337–353.

[4] P. Georgescu, Y.-H. Hsieh, H. Zhang, *A Lyapunov functional for a stage-structured predator-prey model with nonlinear predation rate*, preprint.

[5] P. Georgescu, G. Moroşanu, *Global stability for a stage-structured predator-prey model*, Math. Sci. Res. J., 10 (2006), 214–226.

[6] B. S. Goh, *Global stability in many species systems*, Am. Naturalist, 111 (1977), 135–143.

[7] H. Guo, M. Y. Li, Z. Shuai, *A graph-theoretic approach to the method of Lyapunov functions*, Proc. Amer. Math. Soc., 136 (2008), 2793–2802.

[8] G. W. Harrison, *Global stability of predator-prey interactions*, J. Math. Biol., 8 (1979), 159–171.

[9] J. Hofbauer, J. W. H. So, *Uniform persistence and repellors for maps*, Proc. Amer. Math. Soc., 107 (1989), 1137–1142.

[10] H. Khalil, *Nonlinear systems*, Prentice Hall, 2002.

[11] A. Korobeinikov, *Global properties of basic virus dynamics models*, Bull. Math. Biol., 66 (2004), 879–883.

[12] A. Korobeinikov, *Lyapunov functions and global properties for SEIR and SEIS epidemic models*, Math. Med. Biol, 21 (2004), 75–83.

[13] A. Korobeinikov, *Lyapunov functions and global stability for SIR and SIRS epidemiological models with non-linear transmission*, Bull. Math. Biol., 30 (2006), 615–626.

[14] A. Korobeinikov, P. K. Maini, *A Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence*, Math. Biosci. Eng., 1 (2004), 57–60.

[15] A. Korobeinikov, P. K. Maini, *Non-linear incidence and stability of infectious disease models*, Math. Med. Biol., 22 (2005), 113–128.

[16] J. P. LaSalle, *The stability of dynamical systems*, SIAM Regional Conference Series in Applied Mathematics, 1976.

[17] M. Y. Li and J. S. Muldowney, *A geometric approach to global stability problems*, SIAM J. Math. Appl., 27 (1996), 1070–1083.

[18] M. Y. Li and J. S. Muldowney, *Global stability for the SEIR model in epidemiology*, Math. Biosci., 125 (1995), 155–164.

[19] D. Okuonghae, A. Korobeinikov, *Dynamics of tuberculosis: the effect of direct observation therapy strategy (DOTS) in Nigeria*, Math. Model. Nat. Phenom. Epidemiol. 2 (2006), 99-111.

[20] P. van den Driessche, J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci., 180 (2002), 29–48.

[21] V. Volterra, *Leçons sur la Theorie Mathematique de la Lutte pour la Vie*, Gauthier-Villars, 1931.

[22] Z. Yuan, L. Wang, *Global stability of epidemiological models with group mixing and nonlinear incidence rates*, to appear in Nonlinear Anal., Real World Appl..

Paul Georgescu
Department of Mathematics
Technical University of Iaşi
Bd. Copou 11, 700506 Iaşi, Romania
email:*v.p.georgescu@gmail.com*