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GLOBAL STABILITY OF SEIRS MODELS IN EPIDEMIOLOGY

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ABSTRACT. SEIRS epidemiological models with general nonlinear incidence in a constant population are studied. Under the restriction that the rate of loss of immunity is either sufficiently small or sufficiently large, global asymptotic stability of the endemic equilibrium when it is unique is proved using a geometric approach to global stability for nonlinear autonomous systems. For the special case of bilinear incidence, this global result completes determination of a sharp threshold for the classical SEIRS model under the above restriction.

1. Introduction. In [5], Hethcote and van den Driessche studied an epidemic model of SEIRS type that is described by the following system of ordinary differential equations

$$\begin{aligned} S' &= -\beta g(I)S + \nu - \nu S + \delta R \\ E' &= \beta g(I)S - (\varepsilon + \nu)E \\ I' &= \varepsilon E - (\gamma + \nu)I \\ R' &= \gamma I - (\delta + \nu)R, \end{aligned} \tag{1.1}$$

where $S(t), E(t), I(t)$ and $R(t)$ denote the fractions of the population that are susceptible, exposed (not yet infectious), infectious, and recovered with temporary immunity at time t, respectively. The nonlinear incidence rate is given by $\beta g(I)S$, where the transmission coefficient $\beta > 0$ and $g(I)$ is such that $g(0) = 0$, $g(I) > 0$ for $I \in (0, 1]$ and $g \in C^1(0, 1]$. The birth rate constant and the natural death rate constant are assumed to be equal and denoted by $\nu > 0$ and in consequence

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the total population is constant; thus, $S + E + I + R = 1$. All newborns are assumed to be susceptible. Individuals are susceptible, then exposed, then infectious, and then recovered with the possibility of becoming susceptible again with the rate constant of loss of immunity equal to $\delta \geq 0$. The parameter $\varepsilon > 0$ is the rate constant at which exposed individuals become infectious, and $\gamma > 0$ is the rate constant that infectious individuals become recovered; thus, $1/\varepsilon$ and $1/\gamma$ are the mean latent and infectious periods, respectively. If the immunity is assumed to be permanent, that is, $\delta = 0$, then this model becomes an SEIR model. In this case individuals, once infected and recovered, will not become susceptible again. This is an appropriate model for diseases such as measles and varicella. In the limiting case $\delta \to \infty$, this model reduces to an SEIS model, appropriate for diseases that confer no immunity. Other limiting cases yield models that have been widely studied; for example, the limit $\varepsilon \to \infty$ yields an SIRS model, which might be appropriate for diseases such as influenza.

Standard epidemiological models use a bilinear incidence rate βIS based on the law of mass action. This works well when there are a large number of susceptibles. If the population is saturated with infectives, the incidence rate may have a nonlinear dependence on I. A variety of nonlinear incidence forms has been used in the literature. The incidence $\beta I^p S^q$, where p and q are positive parameters, is used by Liu, Hethcote and Levin [**15**]. They show that the qualitative behavior is not affected by changing q from 1, but is affected significantly by changing p from 1. Another common nonlinear incidence form that incorporates the saturation of infectives is $\beta IS/(1 + aI)$ with a some positive parameter (see [**1**]). These three different forms are included in $g(I) = I^p/(1 + aI^p)$. Note that $g'(0)$ does not exist when $p < 1$, whereas $g'(0) = 1$ when $p = 1$. The general incidence form $\beta g(I)S$ allows a unified treatment for all these biologically important cases.

It is demonstrated in [**5**], [**15**] that, in SEIRS models with nonlinear incidence, multiple endemic equilibria can exist and periodic oscillations may occur. It is also generally believed that when the endemic equilibrium is unique, it is globally asymptotically stable in the feasible region. The global stability of the endemic equilibrium when it is unique is conjectured in [**15**], but is left unresolved in both [**5**] and [**15**]. In fact, this has been an outstanding open question even in the bilinear incidence cases. The main purpose of the present paper is to resolve

this global stability question, under the restriction that δ is either sufficiently small or sufficient large, for a general class of functions $g(I)$ that includes the three biologically important cases mentioned above.

For the case $\delta = 0$ (i.e., an SEIR model) and incidence $\beta I^p S^q$, $0 < p \leq 1$, this global stability question was resolved in Li and Muldowney [**12**]. The proof in [**12**] depends crucially on the fact that the corresponding SEIR model can be reduced to a three-dimensional competitive system and that such a system satisfies the Poincare-Bendixson property (see [**6**] and [**19**]). A similar approach was also used in [**10**] to resolve the global stability problem in an SEIR model with varying population size. Since the monotonicity property no longer holds for the SEIRS model (1.1), its treatment calls for a completely different approach. To establish our results we apply a novel method for proving global stability that first appeared in Smith [**20**] and was further developed in Li and Muldowney [**11**], [**13**], [**14**], and Li [**8**], [**9**]. To our knowledge, no Lyapunov function has been constructed in the literature to show the global stability of the endemic equilibrium for SEIRS type models; the approach illustrated in the present paper offers a useful and practical solution.

In the next section we present our main result in Theorem 2.3, after we have given a local stability analysis of the disease-free equilibrium P_0 and proved that (1.1) is uniformly persistent whenever P_0 is unstable. In Section 3, we illustrate our approach to proving global stability and present the proof of Theorem 2.3.

2. Preliminaries and the statement of main results. The feasible region for (1.1) is the nonnegative cone $\mathbf{R}^4_+$, which can be shown to be positively invariant with respect to (1.1). Given nonnegative initial data, solutions exist and have nonnegative components for all $t \geq 0$, and thus the model is well posed. Adding the equations in (1.1) implies that the three-dimensional simplex

$$\Gamma = \{(S, E, I, R) \in \mathbf{R}^4_+ : S + E + I + R = 1\} \tag{2.1}$$

is positively invariant and globally attracting in $\mathbf{R}^4_+$. It thus suffices to study the dynamics of (1.1) on Γ.

The system (1.1) always has a disease-free equilibrium $P_0 = (1, 0, 0, 0)$. Since $g(I)$ in (1.1) is not assumed to be C^1 at P_0, linear stability analysis does not apply. A local Lyapunov function needs to be constructed

to investigate the Lyapunov stability of P_0. In the rest of this paper we make the following basic assumption on the force of infection function $g(I)$:

(H)
$$(1)\quad g \in C^1(0,1], \quad g(0) = 0, \quad g(I) > 0 \quad \text{for } I \in (0,1].$$
$$(2)\quad c = \lim_{I \to 0^+} \frac{g(I)}{I} \leq +\infty; \quad \text{when } 0 < c < +\infty,$$
$$g(I) \leq cI \quad \text{for sufficiently small } I.$$

Set

$$\mathcal{R}_0 = \frac{c\beta\varepsilon}{(\varepsilon+\nu)(\gamma+\nu)}.$$

When $0 < c < +\infty$, $\mathcal{R}_0$ can be interpreted as the basic reproduction number, namely the average number of secondary infections generated by an infectious individual introduced into a fully susceptible population. When $g(I) = I$ or $g(I) = I/(1+\alpha I)$, then $c = g'(0) = 1$ and $\mathcal{R}_0$ takes the familiar form $\beta\varepsilon/(\varepsilon+\nu)(\gamma+\nu)$, which is the product of the transmission coefficient β, the fraction surviving the exposed class $\varepsilon/(\varepsilon+\nu)$ and the average infectious period $1/(\gamma+\nu)$.

The following proposition shows that the parameter $\mathcal{R}_0$ satisfies a threshold property with threshold value 1.

Proposition 2.1. *Assume that $g(I)$ satisfies* (H). *Then for system* (1.1),

(i) $P_0 = (1,0,0,0)$ *is locally asymptotically stable if* $\mathcal{R}_0 \leq 1$;

(ii) P_0 *is unstable if* $\mathcal{R}_0 > 1$; *in this case, all trajectories starting in a sufficiently small neighborhood of* P_0 *in* Γ *move away from* P_0, *except those on the* $S-R$ *coordinate plane (the case of no infection), which converge to* P_0 *in this plane.*

Proof. Using $S + E + I + R = 1$ we can reduce (1.1) to a three-dimensional system. The equilibrium P_0 now corresponds to $(0,0,0)$ in the (E,I,R) space, and the feasible region is

$$T = \{(E,I,R) \in \mathbf{R}^3_+ : E + I + R \leq 1\}. \tag{2.2}$$

Considering a Lyapunov function

$$L = E + \frac{\varepsilon+\nu}{\varepsilon} I, \tag{2.3}$$

we find

$$L' = \frac{\beta I}{\sigma}\left(\frac{\beta\varepsilon}{(\varepsilon+\nu)(\gamma+\nu)}\frac{g(I)}{I}(1-E-I-R)-1\right),$$

where $\sigma = \beta\varepsilon/(\varepsilon+\nu)(\gamma+\nu)$. If $\mathcal{R}_0 \leq 1$, then $L' \leq 0$ for $(E,I,R) \in T$ sufficiently close to $(0,0,0)$, and $L' = 0$ holds only when $I = 0$. Since $\{(0,0,0)\}$ is the largest invariant set in the subset of T where $L' = 0$, its asymptotic stability follows from LaSalle's invariance principle [**7**, Chapter 2, Theorem 6.4]. If $\mathcal{R}_0 > 1$, then $L' > 0$ for (E,I,R) sufficiently close to $(0,0,0)$ in T except when $I = 0$. Thus any solution of the three-dimensional system starting sufficiently close to (0,0,0) and not on the R-axis moves away from (0,0,0). The corresponding claims for trajectories of (1.1) follow from the above analysis and the fact that the $S-R$ coordinate plane is invariant with respect to (1.1). □

Remarks. (1) If g is C^1 at 0, then $c = g'(0)$. Linearization of (1.1) near P_0 shows that P_0 is hyperbolic when $\mathcal{R}_0 < 1$, and thus its asymptotic stability can be obtained by showing that real parts of all the eigenvalues of the first approximation are negative. However, P_0 is not hyperbolic when $\mathcal{R}_0 = 1$ so the linear analysis breaks down. Also, as we noted earlier, linear stability analysis is not applicable if $g(I) = I^p/(1+aI^p)$ and $p < 1$.

(2) The Lyapunov function in the proof of Proposition 2.1 can also be used to discuss the global asymptotic stability of P_0 (see [**5**], [**15**]). If the assumption (H) is strengthened so that, when $c > 0$, $g(I) \leq cI$ for all $I \in (0,1]$, then $L' \leq 0$ holds for all $(E,I,R) \in T$ when $\mathcal{R}_0 \leq 1$. The same proof then shows that P_0 is globally asymptotically stable in Γ if $\mathcal{R}_0 \leq 1$. This stronger assumption is satisfied by $g(I) = I^p/(1+aI^p)$ for $p \leq 1$, $a \geq 0$. Thus the global dynamics of (1.1) with such an incidence form is completely determined when $\mathcal{R}_0 \leq 1$; namely, the disease always dies out if $\mathcal{R}_0 \leq 1$.

In what follows we study the global dynamics of (1.1) in $\overset{\circ}{\Gamma}$, the interior of Γ, when $\mathcal{R}_0 > 1$. System (1.1) is said to be *uniformly persistent* (see [**2**], [**4**], [**21**]) if there exists a constant $0 < \varepsilon_0 < 1$ such that, any solution $(S(t),E(t),I(t),R(t))$ of (1.1) with $(S(0),E(0),I(0),R(0)) \in \overset{\circ}{\Gamma}$ satisfies

$$\begin{aligned} &\liminf_{t\to\infty} S(t) > \varepsilon_0, \qquad \liminf_{t\to\infty} E(T) > \varepsilon_0, \\ &\liminf_{t\to\infty} I(t) > \varepsilon_0, \qquad \liminf_{t\to\infty} R(t) > \varepsilon_0. \end{aligned} \tag{2.4}$$

The disease is endemic if (1.1) is uniformly persistent. In this case both the infective and the latent fractions persist above a certain positive level. Weaker notions of persistence have been defined and used in the literature of population dynamics (see [2], [4], [21]). One may choose to define endemicity of the disease using one of the weaker notions of persistence. However, as the following result shows, persistence of (1.1) in any reasonable sense is equivalent to the uniform persistence defined above.

Proposition 2.2. *Under the assumption that $g(I)$ satisfies* (H), *system* (1.1) *is uniformly persistent if and only if $\mathcal{R}_0 > 1$.*

Proof. The necessity of $\mathcal{R}_0 > 1$ follows from Proposition 2.1 and the fact that the asymptotic stability of P_0 precludes any kind of persistence. The sufficiency of the condition $\mathcal{R}_0 > 1$ follows from a uniform persistence result, Theorem 4.3, in [4]. To demonstrate that (1.1) satisfies all the conditions of Theorem 4.3 in [4] when $\mathcal{R}_0 > 1$, choose $X = \mathbf{R}^3$ and the set $E = \Gamma$. The maximal invariant set N on the boundary $\partial\Gamma$ is the singleton $\{P_0\}$ and is isolated. Thus, the hypothesis (H) of [4] holds for (1.1). The proposition is proved by observing that, in the setting of (1.1), the necessary and sufficient condition for uniform persistence in Theorem 4.3 of [4] is equivalent to P_0 being unstable. □

Let ε_0 be a uniform persistence constant in (2.4) associated with system (1.1) when $\mathcal{R}_0 > 1$. Set

$$\eta_0 = \min_{I \in [\varepsilon_0, 1]} g(I) > 0. \tag{2.5}$$

In the rest of the paper, we make the following restriction on the parameters in the system (1.1): either

$$\gamma\delta < \varepsilon_0(\beta\eta_0 + \gamma + \nu)(\beta\eta_0 + \delta + \nu) \tag{2.6}$$

or

$$\varepsilon - \gamma - \nu < \delta. \tag{2.7}$$

The condition (2.6) holds when $\delta = 0$ and thus also holds when $0 \leq \delta < \delta^*$ for some $\delta^* > 0$. Also note in (2.6) that δ and γ can

be exchanged, so (2.6) is satisfied for all δ if $0 \leq \gamma < \gamma^*$ for some $\gamma^* < 0$. The relation (2.7) holds for sufficiently large δ, and for all $\delta \geq 0$ if $\varepsilon < \gamma + \nu$.

Let $T \subset \mathbf{R}^2$ be the unit circle. A *rectifiable* closed curve in Γ is a mapping $\psi \in \mathrm{Lip}\,(T \to \Gamma)$. It is said to be *simple* if it is one to one. A closed curve ψ is said to be *invariant* with respect to (1.1) if $\psi(T)$ is an invariant set for (1.1). For instance, a periodic trajectory gives rise to a simple closed rectifiable curve that is invariant with respect to (1.1). The following theorem is a convergence result for system (1.1). Its proof will be postponed to Section 3.

Theorem 2.3. *Suppose that $g(I)$ satisfies* (H) *and*

$$|g'(I)|I \leq g(I) \quad \text{for } I \in (0,1]. \tag{2.8}$$

Assume that $\mathcal{R}_0 > 1$. Then no simple closed rectifiable curve can be invariant with respect to (1.1) *provided that one of the conditions* (2.6) *or* (2.7) *is satisfied. Moreover, each semi-trajectory of* (1.1) *in* Γ *converges to an equilibrium.*

Remarks. (1) Theorem 2.3 rules out the existence of the following type of trajectories: a periodic trajectory; a homoclinic trajectory; and a heteroclinic cycle, since each case gives rise to an invariant simple closed curve.

(2) Theorem 2.3 implies each positive (negative) semi-trajectory in Γ converges to an equilibrium as $t \to +\infty$ ($t \to -\infty$).

(3) Propositions 2.1 and 2.2 imply that the disease becomes endemic if $\mathcal{R}_0 > 1$. Theorem 2.3 implies that, if g satisfies (2.8) and one of (2.6) or (2.7) holds, the disease tends to persist at a constant equilibrium level, rather than in a periodic or other recurrent fashion. In particular, Theorem 2.3 implies the existence of endemic (interior) equilibria.

Suppose (1.1) has a unique interior equilibrium P^*. Then Theorem 2.3 implies that all positive semi-trajectories in the interior of Γ converge to P^*, and thus P^* attracts all interior points of Γ. Moreover, this implies that P^* is locally stable, since otherwise P^* is both the alpha and omega limit point of a homoclinic trajectory. As a consequence, P^* is globally asymptotically stable in $\overset{\circ}{\Gamma}$. We thus have the following result.

Corollary 2.4. *Assume that $g(I)$ satisfies* (H) *and* (2.8), *and that $\mathcal{R}_0 > 1$. Suppose that one of the conditions* (2.6) *or* (2.7) *holds and that* (1.1) *has a unique endemic equilibrium P^*. Then P^* is globally asymptotically stable in $\overset{\circ}{\Gamma}$.*

The proof of Theorem 2.3 will be given in Section 3. In the rest of this section, we consider the following specific form of the force of infection function considered in [5],

$$g(I) = \frac{I^p}{1 + aI^p}, \quad p > 0, a \geq 0. \tag{2.9}$$

As remarked earlier, when $a = 0$, $g(I)$ gives the nonlinear incidence considered in [15], which includes the bilinear incidence; when $p = 1$ and $a > 0$, it gives the saturated mass action used in [1]. Observe that $g(I)$ satisfies (2.8) when $p \leq 1$. It is shown in [5], Tables 1 and 2, that for $g(I)$ given in (2.9) and $p \leq 1$ the system (1.1) has a unique endemic equilibrium P^* whenever the disease-free equilibrium P_0 is unstable. We thus have the following result on the global stability of P^* for this particular form of $g(I)$.

Theorem 2.5. *Assume that $g(I)$ is given in* (2.9) *and $p \leq 1$. Suppose that one of the conditions* (2.6) *or* (2.7) *holds. Then, if $\mathcal{R}_0 > 1$,* (1.1) *has a unique endemic equilibrium P^* that is globally asymptotically stable in $\overset{\circ}{\Gamma}$.*

Under the restriction (2.6) or (2.7), Theorem 2.5 answers the question of the global stability of an endemic equilibrium in the case when it is unique, which was left unresolved in [5]. In the special case $g(I) = I^p$, it gives an affirmative answer to a conjecture of Liu, Hethcote and Levin [15], namely, that for this force of infection with $0 < p < 1$, or $p = 1$ and $\mathcal{R}_0 > 1$, the endemic equilibrium is globally asymptotically stable in $\overset{\circ}{\Gamma}$. In the case of classical bilinear incidence (mass action), this result completes the determination of a sharp threshold in the dynamical behavior of the model provided that (2.6) or (2.7) holds; if $\mathcal{R}_0 \leq 1$, then the disease dies out, whereas if $\mathcal{R}_0 > 1$, then (in $\overset{\circ}{\Gamma}$) the infectious fraction approaches a constant endemic value. Restriction (2.6) or (2.7)

is needed by our choices of Lyapunov functions which imply the equi-uniform asymptotic stability of a certain set of linear systems (see (3.14) and (3.15), see also (3.3) and (3.4)). We expect that other choices are possible so that no such restriction is needed; but this remains open. Our results hold in the limit $\delta \to 0$ ((2.6) holds) or $\delta \to \infty$ ((2.7) holds), for the SEIR or SEIS model, respectively, and extend to δ sufficiently small or sufficiently large. The global stability result in [**12**] is a special case of our Theorem 2.5 ($\delta = 0$) for a specific incidence form ($g(I) = I^p$). The global stability of (1.1) with bilinear incidence also has been considered by Rinaldi [**18**]. However, the global stability proof there (Theorem 3.1) in constructing a Lyapunov function appears to use a constant matrix result applied to a nonconstant matrix.

3. A new approach to global stability and the proof of Theorem 2.3. System (1.1) and other epidemic models are notorious for the fact that global Lyapunov functions have rarely been constructed to establish global stability of the unique endemic equilibrium. To establish our main result, Theorem 2.3, we apply a novel approach for proving convergence of trajectories and, in particular, global stability of an equilibrium. The general theory, which has been developed in Smith [**20**], Li and Muldowney [**11**], [**13**], and Li [**8**], [**9**] is formulated for general autonomous systems in $\mathbf{R}^n$. In this section, these general results will be interpreted in the context of our particular system (1.1), followed by a proof of Theorem 2.3. The presentation will follow that in [**8**], [**9**].

At each $(S, E, I, R) \in \overset{\circ}{\Gamma}$, the Jacobian matrix $J = J(S, E, I, R)$ of (1.1) can be written as

$$J = -\nu I_{4\times 4} + \Phi, \tag{3.1}$$

where $I_{4\times 4}$ is the 4×4 identity matrix and

$$\Phi = \begin{bmatrix} -\beta g(I) & 0 & -\beta g'(I)S & \delta \\ \beta g(I) & -\varepsilon & \beta g'(I)S & 0 \\ 0 & \varepsilon & -\gamma & 0 \\ 0 & 0 & \gamma & -\delta \end{bmatrix},$$

which satisfies

$$(1, 1, 1, 1)\Phi = (0, 0, 0, 0). \tag{3.2}$$

Following the formulation in [9], (1.1) satisfies the hypothesis (H_1) and (H_2) in [9] with $n = 4$, $r = 1$ and $B = (1, 1, 1, 1)$. The hypothesis (H_1) requires that the system possesses an invariant affine manifold of dimension $(n-r)$, which in our case is the three-dimensional simplex Γ defined in (2.1) with $\bar{x}$ chosen as any point in the simplex. Identities (3.1) and (3.2) verify the conditions (1.3) and (1.4) of [9], respectively. Thus (1.1) is an example of a system, in $\mathbf{R}^4$, having a (three-dimensional) affine invariant manifold as studied in [9].

For an $n \times n$ matrix F, and an integer $1 \leq k \leq n$, the kth *additive compound matrix* of F is denoted by $F^{[k]}$. This is an $\binom{n}{k} \times \binom{n}{k}$ matrix whose entries are linear expressions of those of F. Among the useful properties of additive compound matrices are $(F_1 + F_2)^{[k]} = F_1^{[k]} + F_2^{[k]}$ and their spectral properties, namely, if $\sigma(F) = \{\lambda_1, \ldots, \lambda_n\}$ is the spectrum of F, then $\sigma(F^{[k]}) = \{\lambda_{i_1} + \cdots + \lambda_{i_k} : 1 \leq i_1 < \cdots < i_k \leq n\}$ is the spectrum of $F^{[k]}$. For a detailed study of compound matrices and their relations to differential equations, we refer the reader to [17]. The compound matrix that is relevant to our system (1.1) $(n = 4, r = 1)$, according to [9], is the third compound matrix of a 4×4 matrix, which itself is a 4×4 matrix ($r + 2 = 3$ and $\binom{4}{3} = 4$). See the Appendix for its formula.

Let $\mathcal{F}$ denote a set of $N \times N$ matrix-valued functions $t \mapsto A(t)$, $t \in \mathbf{R}_+$. The set of linear differential systems

$$z'(t) = A(t)z(t), \quad A \in \mathcal{F} \tag{3.3}$$

is *equi-uniformly asymptotically stable* if constants $M, m > 0$ exist such that

$$|z(t)| \leq M|z(s)|e^{-m(t-s)}, \quad 0 \leq s \leq t < \infty \tag{3.4}$$

whenever $z(t)$ is a solution to one of the systems (3.3). The equi-uniformity in the above definition requires that the constants M, m in (3.4) are independent of $A \in \mathcal{F}$. It is easy to see from the definition that if the set of systems (3.3) is equi-uniformly asymptotically stable, then each linear system in the set is uniformly asymptotically stable. If $\mathcal{F}$ contains only one function $A(t)$, then (3.3) is equi-uniformly asymptotically stable if and only if it is uniformly asymptotically stable (see [3, p. 54]).

When $\mathcal{R}_0 > 1$, the disease-free equilibrium P_0 is unstable and (1.1) is uniformly persistent in Γ. A compact set $K \subset \overset{\circ}{\Gamma}$ exists such that $x(t) = (S(t), E(t), I(t), R(t)) \in K$ for $t > T$ and $x(0) = (S(0), E(0), I(0), R(0)) \in \overset{\circ}{\Gamma}$. Moreover, T can be chosen uniformly for $x(0)$ in any compact subset of $\overset{\circ}{\Gamma}$. Such a K is usually called an *absorbing* set. We consider the following set of 4×4 linear systems associated with (1.1),

$$z'(t) = [\nu I_{4\times 4} + J^{[3]}(x(t))]z(t), \quad x(0) \in K \tag{3.5}$$

where $J^{[3]}(x(t))$ is the third additive compound matrix of $J(x(t))$ in (3.1).

It is shown in [**9**, Theorem 2.3] that the equi-uniform stability of the set of linear systems (3.5) implies that no simple closed invariant curve exists in $\overset{\circ}{\Gamma}$. The autonomous convergence principle of Smith states that (see [**9**], [**13**], [**20**]) if such an equi-uniform stability still holds under small smooth perturbations of the vector field of (1.1) that also preserve the affine invariant manifold Γ, then every semi-trajectory in $\overset{\circ}{\Gamma}$ converges to an equilibrium. To be more precise, define a subset $\mathcal{S}_\Gamma$ of $C^1(\mathbf{R}^4_+ \to \mathbf{R}^4)$ by

$$\mathcal{S}_\Gamma = \{h \in C^1(\mathbf{R}^4_+ \longrightarrow \mathbf{R}^4) : \Gamma \text{ is invariant for } x' = h(x)\}.$$

The distance between two functions f, h in $\mathcal{S}_\Gamma$ such that $f - h$ has compact support is in the usual C^1 sense

$$|f - h|_{C^1} = \sup\left\{|f(x) - h(x)| + \left|\frac{\partial f}{\partial x}(x) - \frac{\partial h}{\partial x}(x)\right| : x \in \mathbf{R}^4_+\right\}.$$

Let $f, h \in \mathcal{S}_\Gamma$. For $x_0 \in \Gamma$ and $\bar{\varepsilon} > 0$, h is said to be a *local $\bar{\varepsilon}$-perturbation of* f if there is a neighborhood G of x_0 in $\mathbf{R}^4_+$ such that the support $\operatorname{supp}(f - h) \subset G$ and $|f - h|_{C^1} < \bar{\varepsilon}$. In the following, a property $\mathcal{P}$ which is satisfied by $f \in \mathcal{S}_\Gamma$ is said to be *robust under local perturbations in $\mathcal{S}_\Gamma$ at x_0* if, for each sufficiently small neighborhood G of x_0 and $\bar{\varepsilon} > 0$, $\mathcal{P}$ is also satisfied by $\bar{\varepsilon}$-perturbations h in $\mathcal{S}_\Gamma$ such that $\operatorname{supp}(f - h) \subset G$.

Proposition 3.1. *Suppose*

(a) *The system* (1.1) *is uniformly persistent with K a compact absorbing set in* $\overset{\circ}{\Gamma}$.

(b) *The systems* (3.5) *are equi-uniformly asymptotically stable.*

(c) *The condition* (b) *is robust under local perturbations of f in $\mathcal{S}_\Gamma$ at all nonequilibrium points in* $\overset{\circ}{\Gamma}$.

Then no simple closed rectifiable curve in $\overset{\circ}{\Gamma}$ *can be invariant with respect to* (1.1) *and every semi-trajectory in* $\overset{\circ}{\Gamma}$ *converges to an equilibrium.*

This proposition combines the results in Theorems 2.3 and 3.4 in [9] for the case $n = 4$, $r = 1$. The condition (a) is the hypothesis (H_3) in [9]. The condition (2.7) in [9] for $r = 1$, namely, $\bar{q}_3 < 0$, is a sufficient condition for the equi-uniform asymptotic stability of (3.5) that is required in (b). It is this stability condition (b) that is used in [9, Theorem 2.3] to show that no simple closed rectifiable curve can be an invariant set for (1.1) in $\mathcal{S}_\Gamma$. Then, by condition (c), which is equivalent to Proposition 3.1 in [9], and using the autonomous convergence principle of Smith, one can conclude as in [9, Theorem 3.4] that every omega limit set is a singleton and hence an equilibrium. While the terminology 'equi-uniform asymptotic stability' is not used in [9], this is the central idea in the proofs of the results cited from this paper.

To implement Proposition 3.1 in a proof of Theorem 2.3 we use the direct method of Lyapunov to establish the equi-uniform asymptotic stability of the set of linear systems (3.5). For $(x, z) \in \mathbf{R}^4_+ \times \mathbf{R}^4$, let $(x, z) \mapsto V(x, z)$ be a real-valued locally Lipschitzian function, and let

$$\dot{V}(x, z) = \limsup_{h \to 0^+} \frac{1}{h}[V(x + hf(x), z + h(\nu I_{4\times 4} + J^{[3]}(x))z) - V(x, z)].$$

If $x(t)$ is a solution of (1.1) and $z(t)$ a solution of the corresponding equation (3.5), then

$$D_+ V(x(t), z(t)) = \dot{V}(x, z)$$

whenever the righthand time derivative $D_+ V(x(t), z(t))$ exists.

Corollary 3.2. *Assume that the condition* (a) *of Proposition* 3.1 *is satisfied. Suppose that positive numbers* $a_1, a_2, b > 0$ *exist such that*

(i) $a_1|z| \le V(x,z) \le a_2|z|$,

(ii) $\dot{V}(x,z) \le -bV(x,z)$,

for all $(x,z) \in K \times \mathbf{R}^4$. *Then the conclusions of Proposition* 3.1 *hold.*

For $\varepsilon_1 > 0$, the local Lipschitz condition satisfied by V together with (i) implies that the condition (ii) of Corollary 3.2 is satisfied by C^1 small local perturbations of f in $\mathcal{S}_\Gamma$ when $|z| \ge \varepsilon_1$ and b is replaced by $m \in (0,b)$. Then a standard argument shows that $|z(t)| \le (a_2/a_1)|z(s)|\exp\{-m(t-s)\}$, when $z(t)$ is a corresponding solution of (3.5), as long as $|z(\tau)| \ge \varepsilon_1, s \le \tau \le t$; see Yoshizawa [**22**, Theorem 11.6]. The positive homogeneity of (3.4) and (3.5) in z then implies that (3.4) is satisfied with $M = a_2/a_1$.

Proof of Theorem 2.3. We now use Proposition 3.1, via Corollary 3.2, to prove Theorem 2.3. It has been established in Proposition 2.2 that system (1.1) is uniformly persistent if $\mathcal{R}_0 > 1$. We need to choose a Lyapunov function V for the set of linear systems (3.5) so that conditions (i) and (ii) of Corollary 3.2 are satisfied. Let $z(t) = (X(t), Y(t), Z(t), W(t))$ denote a solution to linear system (3.5) associated with a solution $x(t) = (S(t), E(t), I(t), R(t))$ of (1.1) such that $x(0) \in K$, the compact absorbing set. From (3.5) and direct calculation (cf. [**3**] and [**16**]) it follows that the vector-valued function $((\alpha/E)|X|, (1/E)|Y|, (1/I)(|Z| + |W|))$, where α is a positive number, satisfies the following system of differential inequalities,

$$
\begin{aligned}
D_+\frac{\alpha|X|}{E} &\le -\left(\frac{E'}{E} + \beta g(I) + \varepsilon + \gamma + 2\nu\right)\frac{\alpha|X|}{E} \\
&\quad + \frac{\alpha\delta I}{E}\frac{|Z|+|W|}{I}, \\
D_+\frac{|Y|}{E} &\le \frac{\gamma}{\alpha}\frac{\alpha|X|}{E} - \left(\frac{E'}{E} + \beta g(I) + \varepsilon + \delta + 2\nu\right)\frac{|Y|}{E} \\
&\quad + \frac{\beta|g'(I)|IS}{E}\frac{|Z|+|W|}{I}, \\
D_+\frac{|Z|+|W|}{I} &\le \frac{\varepsilon E}{I}\frac{|Y|}{E} - \left(\frac{I'}{I} + \gamma + \delta + 2\nu\right)\frac{|Z|+|W|}{I},
\end{aligned}
$$

where D_+ denotes the righthand derivative with respect to t.

From (1.1),

$$\frac{E'}{E} = \frac{\beta g(I)S}{E} - \varepsilon - \nu \tag{3.6}$$

$$\frac{I'}{I} = \frac{\varepsilon E}{I} - \gamma - \nu \tag{3.7}$$

and in particular

$$\frac{E'}{E} + \varepsilon + \nu = \frac{\beta g(I)S}{E} \geq 0. \tag{3.8}$$

By the uniform persistence assumption on (1.1) and relation (2.5), $T > 0$ exists such that $t > T$ implies

$$|(S(t), E(t), I(t), R(t))| > \varepsilon_0 \tag{3.9}$$

and

$$g(I(t)) \geq \eta_0 \tag{3.10}$$

for all $(S(0), E(0), I(0), R(0))$ in the compact absorbing set K. Relations (3.6)–(3.10) and (2.8) imply

$$D_+\frac{\alpha|X|}{E} \leq -(\beta\eta_0 + \gamma + \nu)\frac{\alpha|X|}{E} + \frac{\alpha\delta}{\varepsilon_0}\frac{|Z| + |W|}{I}, \tag{3.11}$$

$$D_+\frac{|Y|}{E} \leq \frac{\gamma}{\alpha}\frac{\alpha|X|}{E} - \left(\frac{\beta g(I)S}{E} + \beta\eta_0 + \delta + \nu\right)\frac{|Y|}{E} + \frac{\beta g(I)S}{E}\frac{|Z| + |W|}{I}, \tag{3.12}$$

$$D_+\frac{|Z| + |W|}{I} \leq \frac{\varepsilon E}{I}\frac{|Y|}{E} - \left(\frac{\varepsilon E}{I} + \delta + \nu\right)\frac{|Z| + |W|}{I}. \tag{3.13}$$

We choose a Lyapunov function $V_1 = V_1(S, E, I, R, X, Y, Z, W)$ defined by

$$V_1 = \max\left\{\frac{\alpha|X|}{E}, \frac{|Y|}{E}, \frac{|Z| + |W|}{I}\right\}, \tag{3.14}$$

where α is to be specified later. Using (3.9) and the fact that each of $S(t), E(t), I(t)$ and $R(t)$ is bounded above by 1, we conclude that there are constants $a_1, a_2 > 0$ independent of $(S(0), E(0), I(0), R(0)) \in K$ such that

$$a_1|(X, Y, Z, W)| \leq |V_1| \leq a_2|(X, Y, Z, W)|$$

where the norm $|(X, Y, Z, W)|$ may be chosen as $|X| + |Y| + |Z| + |W|$. Thus V_1 satisfies condition (i) of Corollary 3.2. Differential inequalities (3.11)–(3.13) imply (cf. [**3**] and [**16**]) $D_+V_1 \leq -bV_1$ where

$$-b = \max\left\{-(\beta\eta_0 + \gamma + \nu) + \frac{\alpha\delta}{\varepsilon_0},\ -(\beta\eta_0 + \delta + \nu) + \frac{\gamma}{\alpha},\ -(\delta + \nu)\right\}.$$

By Corollary 3.2 the conclusion of Theorem 2.3 holds if α can be chosen so that $b > 0$. This is possible when

$$\gamma\delta < \varepsilon_0(\beta\eta_0 + \gamma + \nu)(\beta\eta_0 + \delta + \nu),$$

in which case we may choose any $\alpha \in (\gamma/(\beta\eta_0+\delta+\nu), \varepsilon_0(\beta\eta_0+\gamma+\nu)/\delta)$ in the definition (3.14) of V_1. This proves Theorem 2.3 under the condition (2.6).

In the same way, let

$$(3.15)\quad V_2 = \max\left\{\frac{1}{E}\left(|X| + |Y| + \frac{\delta}{\varepsilon}|Z| + \frac{\delta}{\varepsilon}|W|\right),\ \frac{1}{I}(|Z| + |W|)\right\}.$$

Then V_2 is also a Lyapunov function for the equi-uniform asymptotic stability of the set of linear systems (3.5) provided

$$\varepsilon - \gamma - \nu < \delta.$$

This proves Theorem 2.3 under the condition (2.7), completing the proof.

APPENDIX

The third additive compound matrix $A^{[3]}$ for a 4×4 matrix $A = (a_{ij})$ is

$$A^{[3]} = \begin{bmatrix} a_{11}+a_{22}+a_{33} & a_{34} & -a_{24} & a_{14} \\ a_{43} & a_{11}+a_{22}+a_{44} & a_{23} & -a_{13} \\ -a_{42} & a_{32} & a_{11}+a_{33}+a_{44} & a_{12} \\ a_{41} & -a_{31} & a_{21} & a_{22}+a_{33}+a_{44} \end{bmatrix}.$$

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