

# GLOBAL STABILITY IN SOME SEIR EPIDEMIC MODELS

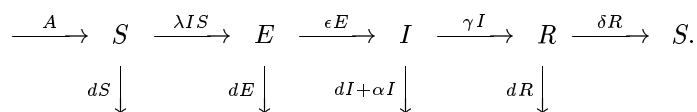
MICHAEL Y. LI\* AND LIANCHENG WANG†

**Abstract.** The dynamics of many epidemic models for infectious diseases that spread in a single host population demonstrate a threshold phenomenon. If the basic reproduction number  $R_0$  is below unity, the disease-free equilibrium  $P_0$  is globally stable in the feasible region and the disease always dies out. If  $R_0 > 1$ , a unique endemic equilibrium  $P^*$  is globally asymptotically stable in the interior of the feasible region and the disease will persist at the endemic equilibrium if it is initially present. In this paper, this threshold phenomenon is established for two epidemic models of SEIR type using two recent approaches to the global-stability problem.

**Key words.** Epidemic models, endemic equilibrium, latent period, global stability, compound matrices.

**AMS(MOS) subject classifications.** Primary 92D30.

**1. Introduction.** Epidemic models study the transmission dynamics of infectious diseases in host populations. In this paper, we deal with diseases that spread in a single host population through direct contact among hosts. Typically after the initial infection, a host stays in a latent period before becoming infectious. At the infectious stage a host may die from the disease or may recover with acquired immunity. The population can be partitioned into four compartments: susceptible, latent or exposed, infectious, and recovered, with sizes denoted by  $S$ ,  $E$ ,  $I$ , and  $R$ , respectively. The total population  $N = S + E + I + R$ . The dynamical transfer of hosts among compartments can be demonstrated in a diagram



The resulting model is of SEIRS type. The term  $A$  denotes the influx or recruitment of susceptibles. The constants  $d$  and  $\alpha$  denote the rates of natural and disease-caused death, respectively. The parameters  $\epsilon$ ,  $\gamma$ , and  $\delta$  denote the transfer rates between the corresponding compartments. Heuristically,  $1/\epsilon$  can be regarded as the mean latent period,  $1/\gamma$  the mean infectious period, and  $1/\delta$  the mean immune period. In the special case when  $\delta = 0$ , the immunity is permanent and there is no return from the  $R$  class to the  $S$  class, the resulting model is an SEIR model. Other special cases include SIRS ( $\epsilon \rightarrow \infty$ ) and SEIS ( $\delta \rightarrow \infty$ ) models, see [2, 3, 8, 12, 29, 32, 39]

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\*Department of Mathematics and Statistics, Mississippi State University, Mississippi State, MS 39762.

†Current address: Department of Mathematics and Computer Science, Georgia Southern University, Statesboro, GA 30460-8093.

for detailed discussions. The bilinear incidence form  $\lambda IS$  assumes that the disease incidence is in proportion to the sizes of  $S$  and  $I$  classes ([1, 2]). Other incidence forms include the proportionate mixing incidence  $\beta IS/N$  ([2, 6]), nonlinear incidence  $\lambda I^p S^q$  ([16, 29]), and saturation incidences  $\lambda IS/(1 + aI)$  ([4, 16]) or  $\lambda IS/(1 + aS)$  ([2, 31]).

Using the transfer diagram, the following system of differential equations can be derived

$$(1.1) \quad \begin{aligned} S' &= A - dS - \lambda IS + \delta R \\ E' &= \lambda IS - (\epsilon + d)E \\ I' &= \epsilon E - (\gamma + \alpha + d)I \\ R' &= \gamma I - (\delta + d)R. \end{aligned}$$

From (1.1) and  $N(t) = S(t) + E(t) + I(t) + R(t)$  we have

$$(1.2) \quad N' = A - dN - \alpha I.$$

If  $A$  is a constant, the feasible region for (1.1) is

$$(1.3) \quad \Gamma = \{(S, E, I, R) \in \mathbf{R}_+^4 : S + E + I + R \leq A/d\},$$

since by (1.2),  $\limsup_{t \rightarrow \infty} N(t) \leq A/d$ , and thus the global attractor of (1.1) is contained in  $\Gamma$ . The dynamical behavior of (1.1) in  $\Gamma$  and the fate of the disease is determined by the basic reproduction number

$$(1.4) \quad R_0 = \frac{A\lambda\epsilon}{d(d + \epsilon)(\gamma + d + \alpha)}.$$

If  $R_0 \leq 1$ , (1.1) has only the disease-free equilibrium  $P_0 = (A/d, 0, 0, 0)$  and  $P_0$  is globally asymptotically stable in  $\Gamma$ . If  $R_0 > 1$ ,  $P_0$  becomes unstable and endemic equilibria  $P^* = (S^*, E^*, I^*, R^*)$  exist in  $\overset{\circ}{\Gamma}$ , the interior of  $\Gamma$ . Typically, if the endemic equilibrium is unique, it is globally asymptotically stable in  $\overset{\circ}{\Gamma}$ . Because of the high dimensionality of (1.1), it is highly non-trivial to prove the global stability of the unique endemic equilibrium  $P^*$ , and establish rigorously the threshold phenomena. Some earlier work deal with models that can be reduced to a 2-dimensional system. The global stability of  $P^*$  is proved using the classical Poincaré-Bendixson Theorem and periodic solutions are ruled out using Bendixson-Dulac conditions or a condition of Busenberg and van den Driessche [5], see [12, 14, 15, 32] for surveys of these results. In some recent work ([22, 25]), for SEIR models that can be reduced to a 3-dimensional monotone system, the global stability of  $P^*$  is proved using a Poincaré-Bendixson property due to Hirsch [17] and Smith [36], and periodic solutions are ruled out using a stability criterion of Muldowney [33] for periodic solutions in higher dimensions. This method is also used in a Dengue fever model by Esteva and Vargas [10]. In [26], the global stability of  $P^*$  is resolved for  $\delta$  small or  $\delta$  large in an SEIRS model with a constant population, in which the monotonicity is not

present. The proof uses a geometric approach to global-stability problems developed in Li and Muldowney [23] and Li [21], also see Smith [38] and Leonov *et al* [20]. This approach is also used in [28] to resolve the global stability of  $P^*$  for an SEIR model with vertical transmission.

In the present paper, we apply these two aforementioned approaches to prove the global stability of  $P^*$  in two SEIR models. The first model is (1.1) with  $\delta = 0$  and a constant recruitment  $A$ . The global stability of a unique  $P^*$  is proved using monotonicity and Muldowney's stability criterion. The second model is an SEIR model with a constant total population and  $A = bN$ . It also incorporates vertical transmission and vaccination. The proof of global stability of  $P^*$  in the second model uses the geometric approach of Li and Muldowney. These global-stability results have not been obtained before. Our main purpose is to demonstrate these new methods. We do not strive for the most generality in modeling considerations. The geometric approach of Li and Muldowney may be applied as in [26] to resolve the global stability of  $P^*$  when the immune period is sufficiently long ( $\delta$  small) or sufficiently short ( $\delta$  large).

Using a Lyapunov function, Mena-Lorca and Hethcote [32] prove the global stability of a unique endemic equilibrium for SIRS models with a varying size and constant recruitment when the disease does not cause fatality. Thieme and van den Driessche [40] consider SIRS models where the recovered class  $R$  has distributed stages. A unique endemic equilibrium is shown to be globally stable whenever it exists using techniques from differential-integral equations and a Lyapunov function.

Our paper is organized as follows, in the next section, we outline two general mathematical frameworks for resolving global-stability problems. The two SEIR models are analyzed in Sections 3 and 4. The paper ends with a brief discussion in Section 5.

**2. Mathematical frameworks.** In this section we outline two general mathematical frameworks for proving global-stability, and they will be applied to two SEIR models in Sections 3 and 4.

Let  $A$  be a linear operator on  $\mathbf{R}^n$  and also denote its matrix representation with respect to the standard basis of  $\mathbf{R}^n$ . Let  $\wedge^2 \mathbf{R}^n$  denote the exterior product of  $\mathbf{R}^n$ .  $A$  induces canonically a linear operator  $A^{[2]}$  on  $\wedge^2 \mathbf{R}^n$ : for  $u_1, u_2 \in \mathbf{R}^n$ , define

$$A^{[2]}(u_1 \wedge u_2) := A(u_1) \wedge u_2 + u_1 \wedge A(u_2)$$

and extend the definition over  $\wedge^2 \mathbf{R}^n$  by linearity. The matrix representation of  $A^{[2]}$  with respect to the canonical basis in  $\wedge^2 \mathbf{R}^n$  is called the *second additive compound matrix* of  $A$ . This is an  $\binom{n}{2} \times \binom{n}{2}$  matrix and satisfies the property  $(A + B)^{[2]} = A^{[2]} + B^{[2]}$ . In the special case when  $n = 2$ , we have  $A_{2 \times 2}^{[2]} = \text{tr}A$ . In general, each entry of  $A^{[2]}$  is a linear expression of those of  $A$ . For instance, when  $n = 3$ , the second additive compound matrix of  $A = (a_{ij})$  is

$$(2.1) \quad A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}.$$

Let  $\sigma(A) = \{\lambda_1, \dots, \lambda_n\}$  be the spectrum of  $A$ . Then,  $\sigma(A^{[2]}) = \{\lambda_i + \lambda_j : 1 \leq i < j \leq n\}$  is the spectrum of  $A^{[2]}$ . For detailed discussions of general compound matrices and their properties we refer the reader to [11, 33]. A comprehensive survey on compound matrices and their relations to differential equations is given in [33].

Let  $x \mapsto f(x) \in \mathbf{R}^n$  be a  $C^1$  function for  $x$  in an open set  $D \subset \mathbf{R}^n$ . Consider the differential equation

$$(2.2) \quad x' = f(x).$$

Denote by  $x(t, x_0)$  the solution to (2.2) such that  $x(0, x_0) = x_0$ . A set  $K$  is said to be *absorbing* in  $D$  for (2.2) if  $x(t, K_1) \subset K$  for each compact  $K_1 \subset D$  and  $t$  sufficiently large. We make the following two basic assumptions:

( $H_1$ ) There exists a compact absorbing set  $K \subset D$ .

( $H_2$ ) Equation (2.2) has a unique equilibrium  $\bar{x}$  in  $D$ .

The equilibrium  $\bar{x}$  is said to be *globally stable* in  $D$  if it is locally stable and all trajectories in  $D$  converge to  $\bar{x}$ . The assumptions ( $H_1$ ) and ( $H_2$ ) are satisfied if  $\bar{x}$  is globally stable in  $D$ . For epidemic models and many other biological models where the feasible region is a bounded cone, ( $H_1$ ) is equivalent to the uniform persistence of (2.2) (see [7, 41]). The following global-stability problem is formulated in [23].

*Global-Stability Problem.* Under assumptions ( $H_1$ ) and ( $H_2$ ), find conditions on the vector field of (2.2) such that the local stability of  $\bar{x}$  implies its global stability in  $D$ .

When  $n = 2$ , the classical Poincaré-Bendixson theory allows the following two approaches to solve the global-stability problem. Approach I: if all periodic orbits  $\Omega$  of (2.2) in  $D$  can be shown to be orbitally asymptotically stable, using Poincaré's stability condition  $\int_{\Omega} \operatorname{div} f dt < 0$  ([13]) for instance, then the local asymptotic stability of  $\bar{x}$  also implies its global stability in  $D$ . Approach II: if  $D \subset \mathbf{R}^2$  is simply connected and that the Bendixson's criterion  $\operatorname{div} f < 0$  holds in  $D$ , then (2.2) has no nontrivial periodic orbits and  $\bar{x}$  is globally stable in  $D$ . Recent developments in the qualitative theory make it possible to use similar approaches in higher dimensions. We give a brief outline in the following two subsections.

**2.1. Proving global stability using the Poincaré-Bendixson property.** System (2.2) is said to satisfy the *Poincaré-Bendixson Property* if any nonempty compact omega limit set of (2.2) that contains no equilibria is a closed orbit.

Any autonomous system (2.2) in the plane satisfies the Poincaré-Bendixson Property by the classical Poincaré-Bendixson theory ([13]). It

is also known that a three-dimensional competitive system satisfies the Poincaré-Bendixson Property in a convex region, as shown by Hirsch [17] and Smith [36]. See [37] for a general definition of competitive systems.

**THEOREM 2.1.** *Assume that  $n = 3$  and  $D$  is convex. Suppose that (2.2) is competitive in  $D$ . Then it satisfies the Poincaré-Bendixson Property. (cf. [37, Chapter 3, Theorem 4.1.] )*

For higher dimensional systems that satisfy the Poincaré-Bendixson Property, we prove the following global stability result.

**THEOREM 2.2.** *Assume that*

- (1) *assumptions  $(H_1)$  and  $(H_2)$  hold;*
- (2)  *$\bar{x}$  is locally asymptotically stable;*
- (3) *system (2.2) satisfies the Poincaré-Bendixson Property;*
- (4) *each periodic orbit of (2.2) in  $D$  is orbitally asymptotically stable.*

*Then the unique equilibrium  $\bar{x}$  is globally asymptotically stable in  $D$ .*

*Proof.* It suffices to show that  $\bar{x}$  attracts all points in  $D$ . Let  $U$  be the basin of attraction of  $\bar{x}$ , the set of all  $x_0$  such that  $x(t, x_0)$  converges to  $\bar{x}$ . Then  $U$  is nonempty and open by the asymptotic stability of  $\bar{x}$ . The theorem is proved if we establish that  $D \subset U$ . Assume the contrary; then the boundary  $\partial U$  of  $U$  has a nonempty intersection  $\mathcal{I}$  with  $D$ . Since both  $U$  and its closure  $\bar{U}$  are invariant and  $U$  is open,  $\partial U = \bar{U} - U$  is also invariant, and thus  $\mathcal{I}$  is positively invariant. Therefore  $\mathcal{I}$  contains a nonempty compact omega limit set  $\Omega$ . By the assumption  $(H_1)$ , we must have  $\Omega \cap \partial D = \emptyset$ . Since it contains no equilibria,  $\Omega$  is a closed orbit by the Poincaré-Bendixson Property, and is asymptotically orbitally stable by the assumption (4) of Theorem 2.2. We thus obtain a contradiction since  $\Omega$  belongs to the alpha limit set of a trajectory in  $U$ . This completes the proof.  $\square$

*Remark.* A similar proof was used in [25] in the context of epidemic models. We reproduce it here in a more general setting for the convenience of the reader.

The assumption (3) is satisfied if  $D$  is a convex region in  $\mathbf{R}^3$  and (2.2) is a competitive system in  $D$ . The orbital stability of periodic solutions in  $\mathbf{R}^n$  ( $n \geq 2$ ) can be verified using the following result of Muldowney [33], which generalizes a 2d condition of Poincaré.

**THEOREM 2.3.** *A periodic orbit  $\Omega = \{p(t) : 0 \leq t < \omega\}$  of (2.2) is orbitally asymptotically stable with asymptotic phase if the linear system*

$$(2.3) \quad z'(t) = \frac{\partial f^{[2]}}{\partial x}(p(t)) z(t)$$

*is asymptotically stable, where  $\frac{\partial f^{[2]}}{\partial x}$  is the second additive compound matrix of the Jacobian matrix  $\frac{\partial f}{\partial x}$  of  $f$ . (cf. [33, Theorem 4.2.] )*

A matrix is *stable* if all its eigenvalues have negative real parts. The next result gives a criterion for the stability of matrices. A proof can be found in [27].

**THEOREM 2.4.** *An  $n \times n$  real matrix  $A$  is stable if and only if  $A^{[2]}$  is stable and  $(-1)^n \det(A) > 0$ .*

Using Theorems 2.2-2.4, we prove the following result.

**THEOREM 2.5.** *Assume that*

- (1) *assumptions  $(H_1)$  and  $(H_2)$  hold;*
- (2) *system (2.2) satisfies the Poincaré-Bendixson Property;*
- (3) *For each periodic solution  $x = p(t)$  to (2.2) with  $p(0) \in D$ , system (2.3) is asymptotically stable,*
- (4)  $(-1)^n \det \left( \frac{\partial f}{\partial x}(\bar{x}) \right) > 0$ .

*Then the unique equilibrium  $\bar{x}$  is globally asymptotically stable in  $D$ .*

*Proof.* It suffices to show that  $\bar{x}$  is locally asymptotically stable. Regard the equilibrium solution  $x = \bar{x}$  as a constant periodic solution. Then assumption (3) of the theorem implies that the matrix  $\frac{\partial f}{\partial x}^{[2]}(\bar{x})$  is stable. This and the assumption (4) of the theorem imply that the Jacobian matrix  $\frac{\partial f}{\partial x}(\bar{x})$  is stable, by Theorem 2.4. Therefore,  $\bar{x}$  is locally asymptotically stable, and thus Theorem 2.5 follows from Theorem 2.2.  $\square$

**2.2. Proving global stability using autonomous convergence theorems.** When a Poincaré-Bendixson Property is not known to exist for a system, a type of results known as autonomous convergence theorems (see [24, 38]) can be used to prove global stability.

For  $n \geq 2$ , by a *Bendixson criterion* we mean a condition satisfied by  $f$  which precludes the existence of nonconstant periodic solutions of (2.2). A Bendixson criterion is said to be *robust under  $C^1$  local perturbations of  $f$  at  $x_1 \in D$*  if, for sufficiently small  $\epsilon > 0$  and neighborhood  $U$  of  $x_1$ , it is also satisfied by  $g \in C^1(D \rightarrow \mathbf{R}^n)$  such that the support  $\text{supp}(f - g) \subset U$  and  $|f - g|_{C^1} < \epsilon$ , where

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

Such  $g$  will be called *local  $\epsilon$ -perturbations of  $f$  at  $x_1$* . It is easy to see that the classical Bendixson's condition  $\text{div} f(x) < 0$  for  $n = 2$  is robust under  $C^1$  local perturbations of  $f$  at each  $x_1 \in \mathbf{R}^2$ . Bendixson criterion for higher dimensional systems that are  $C^1$  robust are discussed in [21, 23, 24, 38].

A point  $x_0 \in D$  is *wandering* for (2.2) if there exists a neighborhood  $U$  of  $x_0$  and  $T > 0$  such that  $U \cap x(t, U)$  is empty for all  $t > T$ . Thus, for example, all equilibria and limit points are nonwandering. The following is a version of the local  $C^1$  Closing Lemma of Pugh (see [34, 35]) as stated in [18].

LEMMA 2.1. *Let  $f \in C^1(D \rightarrow \mathbf{R}^n)$ . Suppose that  $x_0$  is a nonwandering point of (2.2) and that  $f(x_0) \neq 0$ . Then, for each neighborhood  $U$  of  $x_0$  and  $\epsilon > 0$ , there exists a  $C^1$  local  $\epsilon$ -perturbation  $g$  of  $f$  at  $x_0$  such that*

- (1)  *$\text{supp}(f - g) \subset U$ , and*
- (2) *the perturbed system  $x' = g(x)$  has a nonconstant periodic solution whose trajectory passes through  $x_0$ .*

The following global-stability principle is established in Li and Muldowney [23] for autonomous systems in any finite dimension.

THEOREM 2.6. *Suppose that assumptions  $(H_1)$  and  $(H_2)$  hold. Assume that (2.2) satisfies a Bendixson criterion that is robust under  $C^1$  local perturbations of  $f$  at all nonequilibrium nonwandering points for (2.2). Then  $\bar{x}$  is globally stable in  $D$  provided it is stable. (cf. [23, Theorem 2.3.] )*

The main idea of the proof in [23] for Theorem 2.6 is as follows. Suppose that system (2.2) satisfies a Bendixson criterion. Then it does not have any nonconstant periodic solutions. Moreover, the robustness of the Bendixson criterion implies that all nearby differential equations have no nonconstant periodic solutions. Thus by Lemma 2.1, all nonwandering points of (2.2) in  $D$  must be equilibria. In particular, each omega limit point in  $D$  must be an equilibrium. Therefore  $\omega(x_0) = \{\bar{x}\}$  for all  $x_0 \in D$  since  $\bar{x}$  is the only equilibrium in  $D$ .

The following Bendixson criterion is given in [23] and shown to have the robustness required by Theorem 2.6. Let  $x \mapsto P(x)$  be an  $\binom{n}{2} \times \binom{n}{2}$  matrix-valued function that is  $C^1$  for  $x \in D$ . Assume that  $P^{-1}(x)$  exists and is continuous for  $x \in K$ , the compact absorbing set. A quantity  $\bar{q}_2$  is defined as

$$(2.4) \quad \bar{q}_2 = \limsup_{t \rightarrow \infty} \sup_{x_0 \in K} \frac{1}{t} \int_0^t \mu(B(x(s, x_0))) ds$$

where

$$(2.5) \quad B = P_f P^{-1} + P \frac{\partial f^{[2]}}{\partial x} P^{-1},$$

the matrix  $P_f$  is obtained by replacing each entry  $p$  of  $P$  by its derivative in the direction of  $f$ ,  $p_{ijf}$ , and  $\mu(B)$  is the *Lozinskiĭ measure* of  $B$  with respect to a vector norm  $|\cdot|$  in  $\mathbf{R}^N$ ,  $N = \binom{n}{2}$ , defined by (see [9], p.41)

$$\mu(B) = \lim_{h \rightarrow 0^+} \frac{|I + hB| - 1}{h}.$$

It is easy to see that  $\bar{q}_2$  is well defined. It is shown in [23] that, if  $D$  is simply connected, the condition  $\bar{q}_2 < 0$  rules out the presence of any orbit that gives rise to a simple closed rectifiable curve that is invariant for (2.2), such as periodic orbits, homoclinic orbits, and heteroclinic cycles. Moreover, it is robust under  $C^1$  local perturbations of  $f$  near any nonequilibrium point

that is nonwandering. In particular, the following global-stability result is proved in Li and Muldowney [23].

**THEOREM 2.7.** *Assume that  $D$  is simply connected and that the assumptions  $(H_1)$ ,  $(H_2)$  hold. Then the unique equilibrium  $\bar{x}$  of (2.2) is globally stable in  $D$  if  $\bar{q}_2 < 0$ . (cf. [23, Theorem 3.5.] )*

**3. Global dynamics of an SEIR model with constant recruitment.** Let  $\delta = 0$  in (1.1). Then the first three equations in (1.1) contain no  $R$  terms. This allows the reduction of (1.1) to

$$(3.1) \quad \begin{aligned} S' &= A - dS - \lambda IS \\ E' &= \lambda IS - (\epsilon + d)E \\ I' &= \epsilon E - (\gamma + \alpha + d)I, \end{aligned}$$

and  $N, R$  can be obtained from  $N' = A - dN - \alpha I$  and  $R = N - S - E - I$ . The feasible region of (3.1) is  $\Delta = \{(S, E, I) \in \mathbf{R}_+^3 : S + E + I \leq A/d\}$ , which is positively invariant for (3.1). Let  $R_0$  be defined as in (1.4). Straightforward calculations show that the disease-free equilibrium  $P_0 = (A/d, 0, 0)$  exists for all values of parameters. It is the only equilibrium in  $\Delta$  if  $R_0 \leq 1$ . If  $R_0 > 1$ , a unique endemic equilibrium  $P^* = (S^*, E^*, I^*) \in \overset{\circ}{\Delta}$  exists with

$$S^* = \frac{A}{dR_0}, \quad E^* = \frac{d}{\lambda}(R_0 - 1), \quad I^* = \frac{\epsilon}{(\gamma + d + \alpha)}E^*.$$

**THEOREM 3.1.** *The disease-free equilibrium  $P_0 = (A/d, 0, 0)$  of (3.1) is globally asymptotically stable in  $\Delta$  if  $R_0 \leq 1$ ; it is unstable if  $R_0 > 1$ , and the solutions of (3.1) starting sufficiently close to  $P_0$  in  $\Delta$  move away from  $P_0$  except that those starting on the invariant  $S$ -axis approach  $P_0$  along this axis.*

*Proof.* Set  $L = \epsilon E + (\epsilon + d)I$ . Then, if  $R_0 \leq 1$ ,

$$L' = I [\lambda \epsilon S - (\epsilon + d)(\gamma + d + \alpha)] = \frac{\lambda \epsilon AI}{d} \left( \frac{d}{A} S - \frac{1}{R_0} \right) \leq 0,$$

and  $L' = 0$  if and only if  $I = 0$ . The largest compact invariant set in  $\{(S, E, I) \in \Delta : L' = 0\}$  is the singleton  $\{P_0\}$ . The global stability of  $P_0$  then follows from LaSalle's Invariance Principle ([19, Chapter 2, Theorem 6.4]). If  $R_0 > 1$ , then  $L' > 0$  for  $S$  sufficiently close to  $A/d$  except when  $E = I = 0$ . Solutions starting sufficiently close to  $P_0$  leave a neighborhood of  $P_0$  except those on the invariant  $S$ -axis, on which (3.1) reduces to  $S' = A - dS$  and thus  $S(t) \rightarrow A/d$ , as  $t \rightarrow \infty$ . This establishes the theorem.  $\square$

Theorem 3.1 completely determines the global dynamics of (3.1) in  $\Delta$  for the case  $R_0 \leq 1$ . Its epidemiological implication is that the infected

population (the sum of the latent and the infectious population) vanish in time so the disease dies out. When  $R_0 > 1$ , the local behavior of (3.1) near  $P_0$  as described in Theorem 3.1 allows us to use a similar argument as in the proof of Proposition 3.3 in [22] and show that system (3.1) is uniformly persistent, namely, there exists constant  $0 < c < 1$  such that any solution  $(S(t), E(t), I(t))$  with  $(S(0), E(0), I(0)) \in \overset{\circ}{\Delta}$  satisfies

$$(3.2) \quad \min \left\{ \liminf_{t \rightarrow \infty} S(t), \liminf_{t \rightarrow \infty} E(t), \liminf_{t \rightarrow \infty} I(t) \right\} > c.$$

The boundedness of  $\Delta$  and condition (3.2) imply that (3.1) has a compact absorbing set  $K \subset \overset{\circ}{\Delta}$  (see [7, 41]).

**THEOREM 3.2.** *If  $R_0 > 1$ , then the unique endemic equilibrium  $P^*$  is globally asymptotically stable in  $\overset{\circ}{\Delta}$ .*

*Proof.* By examining the Jacobian matrix of (3.1), it can be verified that (3.1) is competitive in the convex region  $\overset{\circ}{\Delta}$ , with respect to the partial ordering defined by the orthant  $\{(S, E, I) \in \mathbf{R}^3 : S \leq 0, E \geq 0, I \leq 0\}$  (see [37]). By Theorem 2.1, (3.1) satisfies the Poincaré-Bendixson Property, and thus conditions (1) and (2) of Theorem 2.5 hold. The second compound system of (3.1) along a periodic solution  $(S(t), E(t), I(t))$  is

$$(3.3) \quad \begin{aligned} X' &= -(2d + \lambda I + \epsilon)X + \lambda S Y + \lambda S Z \\ Y' &= \epsilon X - (2d + \lambda I + \gamma + \alpha)Y \\ Z' &= \lambda I Y - (2d + \epsilon + \gamma + \alpha)Z. \end{aligned}$$

To show that (3.3) is asymptotically stable, consider a Lyapunov function

$$(3.4) \quad V(X, Y, Z; S, E, I) = \sup \left\{ |X|, \frac{E}{I} (|Y| + |Z|) \right\}.$$

The orbit  $\mathcal{O}$  of the periodic solution  $(S(t), E(t), I(t))$  is at a positive distance from the boundary  $\partial\Delta$  by the uniform persistence. Thus there exists a constant  $c_1 > 0$  such that

$$(3.5) \quad V(X, Y, Z; S, E, I) \geq c_1 \sup\{|X|, |Y|, |Z|\}$$

for all  $(X, Y, Z) \in \mathbf{R}^3$  and  $(S, E, I) \in \mathcal{O}$ . The right derivative of  $V$  along a solution  $(X(t), Y(t), Z(t))$  to (3.3) and  $(S(t), E(t), I(t))$  can be estimated as follows.

$$(3.6) \quad \begin{aligned} D_+ |X(t)| &\leq -(2d + \lambda I + \epsilon) |X(t)| + \lambda S (|Y(t)| + |Z(t)|) \\ &= -(2d + \lambda I + \epsilon) |X(t)| + \frac{\lambda I S E}{E I} (|Y(t)| + |Z(t)|), \end{aligned}$$

and

$$(3.7) \quad \begin{aligned} D_+ |Y(t)| &\leq \epsilon |X(t)| - (2d + \lambda I + \gamma + \alpha) |Y(t)| \\ D_+ |Z(t)| &\leq \lambda I |Y(t)| - (2d + \epsilon + \gamma + \alpha) |Z(t)|. \end{aligned}$$

Therefore

$$\begin{aligned}
& D_+ \frac{E}{I} (|Y(t)| + |Z(t)|) \\
&= \left( \frac{E'}{E} - \frac{I'}{I} \right) \frac{E}{I} (|Y(t)| + |Z(t)|) + \frac{E}{I} D_+ (|Y(t)| + |Z(t)|) \\
&\leq \frac{\epsilon E}{I} |X(t)| + \left( \frac{E'}{E} - \frac{I'}{I} - 2d - \gamma - \alpha \right) \frac{E}{I} (|Y(t)| + |Z(t)|).
\end{aligned}$$

Relations (3.6) and (3.7) lead to

$$(3.8) \quad D_+ V(t) \leq \max\{g_1(t), g_2(t)\} V(t),$$

where

$$(3.9) \quad g_1(t) = -2d - \lambda I - \epsilon + \frac{\lambda IS}{E},$$

$$(3.10) \quad g_2(t) = \frac{E'}{E} - \frac{I'}{I} - 2d - \gamma - \alpha + \frac{\epsilon E}{I}.$$

Rewriting (3.1), we find that

$$(3.11) \quad \frac{\lambda IS}{E} = \frac{E'}{E} + \epsilon + d, \quad \frac{\epsilon E}{I} = \frac{I'}{I} + \gamma + d + \alpha.$$

From (3.9)–(3.11),  $\max\{g_1(t), g_2(t)\} \leq \frac{E'(t)}{E(t)} - d$ , and thus

$$\int_0^\omega \max\{g_1(t), g_2(t)\} dt \leq \log E(t) \Big|_0^\omega - d = -d,$$

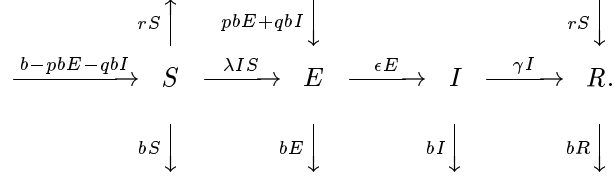
since  $E(t)$  is periodic of minimal period  $\omega$ . This relation and (3.8) imply that  $V(t) \rightarrow 0$  as  $t \rightarrow \infty$ , and in turn that  $(X(t), Y(t), Z(t)) \rightarrow 0$  as  $t \rightarrow \infty$  by (3.5). As a result, the second compound system (3.3) is asymptotically stable if the minimal period  $\omega > 0$ . The same estimates also hold when  $\omega \rightarrow 0$ . This verifies the condition (3) of Theorem 2.5. Let  $J(P^*)$  be the Jacobian matrix of (3.1) at  $P^*$ . Then

$$\begin{aligned}
\det(J(P^*)) &= \begin{vmatrix} -\lambda I^* - d & 0 & -\lambda S^* \\ \lambda I^* & -\epsilon - d & \lambda S^* \\ 0 & \epsilon & -\gamma - \alpha - d \end{vmatrix} \\
&= -(\lambda I^* + d)(\epsilon + d)(\gamma + \alpha + d) + \lambda \epsilon S^* d.
\end{aligned}$$

Using the equilibril equations for  $P^* = (S^*, E^*, I^*)$  we can derive that  $\lambda \epsilon S^* = (\epsilon + d)(\gamma + \alpha + d)$ . Therefore,  $\det(J(P^*)) = -\lambda I^* (\epsilon + d)(\gamma + \alpha + d) < 0$ . This verifies the condition (4) of Theorem 2.5. Hence  $P^*$  is globally stable in  $\overset{\circ}{\Delta}$  by Theorem 2.5.  $\square$

#### 4. An SEIR model with vertical transmission and vaccination.

In this section, we consider an SEIR model that has an exponential birth. We assume that the disease spreads through both horizontal and vertical transmission. The transfer diagram for the model is



We assume that the disease is not fatal ( $\alpha = 0$ ) and that the birth and death rates are equal and denoted by  $b$ . Hence the total population is constant;  $N = S + E + I + R = 1$ , and thus the natural birth recruitment  $A = bN = b$ . For the vertical transmission, we assume that a fraction  $p$  and a fraction  $q$  of the offspring from the exposed and the infectious classes, respectively, are born into the exposed class  $E$ . Consequently, the birth flux into the exposed class is given by  $pbE + qbI$  and the birth flux into the susceptible class is given by  $b - pbE - qbI$ . Naturally,  $0 \leq p \leq 1$  and  $0 \leq q \leq 1$ . For the vaccination, we assume that all susceptible individuals are vaccinated at a constant per capita rate  $r$  and that the vaccination has no effect on infected individuals. When  $r = 0$ , no vaccination is considered, and the model reduces to that considered in [28]. The transfer diagram leads to the following system of differential equations

$$\begin{aligned}
 S' &= b - \lambda IS - pbE - qbI - bS - rS \\
 E' &= \lambda IS + pbE + qbI - (\epsilon + b)E \\
 I' &= \epsilon E - (\gamma + b)I \\
 R' &= \gamma I - bR + rS.
 \end{aligned}
 \tag{4.1}$$

As in Section 3, we study the reduced 3d system

$$\begin{aligned}
 S' &= b - \lambda IS - pbE - qbI - bS - rS \\
 E' &= \lambda IS + pbE + qbI - (\epsilon + b)E \\
 I' &= \epsilon E - (\gamma + b)I
 \end{aligned}
 \tag{4.2}$$

in its feasible region  $\Sigma = \{(S, E, I) \in \mathbf{R}_+^3 : S + E + I \leq 1\}$ . The dynamics of (4.2) is determined by the following vaccination modified basic reproduction number

$$R_0 = \frac{\lambda \epsilon}{(b + \epsilon)(b + \gamma) - bp(b + \gamma) - bq\epsilon} \frac{b}{b + r}.
 \tag{4.3}$$

If  $R_0 \leq 1$ , the disease-free equilibrium  $P_0 = (b/(b+r), 0, 0)$  is the only equilibrium. If  $R_0 > 1$ , there is a unique endemic equilibrium  $P^* = (S^*, E^*, I^*)$  with  $S^* = 1/R_0$ . The following result can be proved as Proposition 3.1 by using a global Lyapunov function  $L = \epsilon E + (\epsilon + b - pb)I$ .

**THEOREM 4.1.** (a) If  $R_0 \leq 1$ , then  $P_0$  is the only equilibrium in  $\Sigma$  and it is globally stable in  $\Sigma$ . (b) If  $R_0 > 1$ , then  $P_0$  is unstable and there exists a unique endemic equilibrium  $P^*$ . Furthermore, the system (4.2) is uniformly persistent in  $\Sigma$  if  $R_0 > 1$ .

From Theorem 4.1, we know that system (4.2) satisfies the assumptions  $(H_1)$  and  $(H_2)$ . Using Theorem 2.7, we can prove that  $P^*$  is globally stable in  $\overset{\circ}{\Sigma}$  if  $R_0 > 1$ .

**THEOREM 4.2.** Assume that  $R_0 > 1$ . Then the unique endemic equilibrium  $P^*$  is globally stable in  $\overset{\circ}{\Sigma}$ .

*Proof.* The Jacobian matrix  $J = \frac{\partial f}{\partial x}$  associated with a general solution  $(S(t), E(t), I(t))$  to (4.2) is

$$J = \begin{bmatrix} -\lambda I - b - r & -pb & -\lambda S - qb \\ \lambda I & pb - b - \epsilon & \lambda S + qb \\ 0 & \epsilon & -b - \gamma \end{bmatrix}$$

and its second additive compound matrix  $J^{[2]}$  is, by (2.1),

$$(4.4) \quad \begin{bmatrix} -\lambda I - \epsilon - 2b - r + pb & \lambda S + qb & \lambda S + qb \\ \epsilon & -\lambda I - \gamma - 2b - r & -pb \\ 0 & \lambda I & -\epsilon - \gamma - 2b + pb \end{bmatrix}.$$

Set the function  $P(x) = P(S, E, I)$  in (2.5) as

$$P(S, E, I) = \begin{bmatrix} a_1 & 0 & 0 \\ 0 & (1 - a_2)\frac{E}{I} & 0 \\ 0 & a_2\frac{E}{I} & \frac{E}{I} \end{bmatrix}$$

where  $1 < a_1 < 1 + \lambda c^2/(\lambda + b)$ ,  $c$  is a uniform persistence constant and

$$(4.5) \quad a_2 = \begin{cases} 0, & \text{if } \epsilon \geq pb, \\ 1 - \frac{\epsilon}{pb}, & \text{if } \epsilon < pb. \end{cases}$$

Then  $P_f P^{-1} = \text{diag}(0, E'/E - I'/I, E'/E - I'/I)$ , and the matrix  $B = P_f P^{-1} + P J^{[2]} P^{-1}$  in (2.5) can be written in block form  $B = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix}$  with  $B_{11} = -\lambda I - \epsilon - 2b - r + pb$ ,

$$B_{12} = a_1 \left[ (\lambda S + qb)\frac{I}{E}, \quad (\lambda S + qb)\frac{I}{E} \right], \quad B_{21} = \frac{1}{a_1} \begin{bmatrix} (1 - a_2)\frac{\epsilon E}{I} \\ a_2\frac{\epsilon E}{I} \end{bmatrix},$$

and  $B_{22}$  being the following

$$\left[ \begin{array}{cc} \frac{E'}{E} - \frac{I'}{I} - \lambda I - \gamma - 2b - r + a_2 pb & -(1 - a_2)pb \\ \lambda I + \frac{a_2 [\epsilon - (1 - a_2)pb]}{1 - a_2} & \frac{E'}{E} - \frac{I'}{I} - \epsilon - \gamma - 2b + (1 - a_2)pb \end{array} \right],$$

which simplifies to

$$\left[ \begin{array}{cc} \frac{E'}{E} - \frac{I'}{I} - \lambda I - \gamma - 2b - r + a_2 pb & -(1 - a_2)pb \\ \lambda I & \frac{E'}{E} - \frac{I'}{I} - \epsilon - \gamma - 2b + (1 - a_2)pb \end{array} \right],$$

since  $a_2[\epsilon - (1 - a_2)pb] = 0$  by (4.5). Let  $(u, v, w)$  denote the vectors in  $\mathbf{R}^3 \cong \mathbf{R}^{(3)}$ , we select a norm in  $\mathbf{R}^3$  as  $|(u, v, w)| = \max\{|u|, |v| + |w|\}$  and let  $\mu$  denote the Lozinskiĭ measure with respect to this norm. Following the method in [30], we have the estimate  $\mu(B) \leq \sup\{g_1, g_2\}$ , where

$$g_1 = \mu_1(B_{11}) + |B_{12}|, \quad \text{and} \quad g_2 = |B_{21}| + \mu_1(B_{22}),$$

$|B_{12}|$ ,  $|B_{21}|$  are matrix norms with respect to the  $l_1$  vector norm, and  $\mu_1$  denotes the Lozinskiĭ measure with respect to the  $l_1$  norm, see [9, p.41]. More specifically,  $\mu_1(B_{11}) = -\lambda I - \epsilon - 2b - r + pb$ ,  $|B_{12}| = a_1(\lambda S + qb)I/E$ ,  $|B_{21}| = \epsilon E/(a_1 I)$ . To calculate  $\mu_1(B_{22})$ , add the absolute value of the off-diagonal elements to the diagonal one in each column of  $B_{22}$ , and then take the maximum of two sums, see [9, p.50]. We thus obtain

$$\begin{aligned} \mu_1(B_{22}) &= \frac{E'}{E} - \frac{I'}{I} - \gamma - 2b \\ &\quad + \max\{a_2 pb - r, \quad (1 - a_2)pb - \epsilon + (1 - a_2)pb\} \\ &\leq \frac{E'}{E} - \frac{I'}{I} - \gamma - 2b + pb, \end{aligned}$$

since  $0 \leq a_2 < 1$  and  $(1 - a_2)pb - \epsilon \leq 0$  from (4.5). Therefore

$$(4.6) \quad g_1 = -\lambda I - \epsilon - 2b - r + pb + a_1(\lambda S + qb)\frac{I}{E},$$

$$(4.7) \quad g_2 \leq \frac{E'}{E} - \frac{I'}{I} - \gamma - 2b + pb + \frac{1}{a_1} \frac{\epsilon E}{I}.$$

Rewriting (4.2), we have

$$(4.8) \quad \frac{E'}{E} + b + \epsilon - pb = (\lambda S + qb)\frac{I}{E}, \quad \frac{I'}{I} + b + \gamma = \frac{\epsilon E}{I}.$$

The uniform persistence constant  $c$  can be adjusted so that there exists  $T > 0$  independent of  $(S(0), E(0), I(0)) \in K$ , the compact absorbing set, such that

$$(4.9) \quad I(t) > c \quad \text{and} \quad E(t) > c \quad \text{for} \quad t > T.$$

Substituting (4.8) into (4.6) and (4.7) and using (4.9), we obtain, for  $t > T$ ,

$$(4.10) \quad \begin{aligned} g_1 &\leq -\lambda I - b + \frac{E'}{E} + (a_1 - 1)(\lambda S + qb) \frac{I}{E} \\ &\leq \frac{E'}{E} - \lambda c - b + (a_1 - 1) \frac{\lambda + b}{c} \leq \frac{E'}{E} - b \end{aligned}$$

and

$$(4.11) \quad \begin{aligned} g_2 &\leq \frac{E'}{E} - b + pb + \left( \frac{1}{a_1} - 1 \right) \frac{\epsilon E}{I} \\ &\leq \frac{E'}{E} - b + pb + \frac{(1 - a_1)\epsilon c}{a_1} \leq \frac{E'}{E} - \frac{(a_1 - 1)\epsilon c}{a_1}, \end{aligned}$$

since  $0 \leq p \leq 1$ . Therefore  $\mu(B) \leq E'/E - \bar{b}$  for  $t > T$  by (4.10) and (4.11), where  $\bar{b} = \min\{b, (a_1 - 1)\epsilon c/a_1\} > 0$ . Along each solution  $(S(t), E(t), I(t))$  to (4.2) such that  $(S(0), E(0), I(0)) \in K$  and for  $t > T$ , we have

$$\frac{1}{t} \int_0^t \mu(B) ds \leq \frac{1}{t} \int_0^T \mu(B) ds + \frac{1}{t} \log \frac{E(t)}{E(T)} - \bar{b} \frac{t - T}{t},$$

which implies  $\bar{q}_2 \leq -\bar{b}/2 < 0$  from (2.4), proving Theorem 4.2.  $\square$

If  $r = 0$ , then  $R_0$  reduces to the threshold parameter  $R_0(p, q)$  in [28] for an SEIR model with no vaccination. In fact,  $R_0 = \frac{b}{b+r} R_0(p, q)$ . This relation clearly shows that vaccination lowers the basic reproduction number. When  $r = p = q = 0$ , then  $R_0 = \frac{\lambda \epsilon}{(\epsilon + b)(\gamma + b)}$ , which is the basic reproduction number (see [2, 12]) or the contact number (see [15, 29]) for the SEIR or SEIRS models with only horizontal transmission. In the limiting case when  $\epsilon \rightarrow \infty$ ,  $R_0$  gives the basic reproduction number in [4] for a SIR model.

Theorem 4.2 contains a global stability result in [28] for an SEIR model with vertical transmission but with no vaccination ( $r = 0$ ). It also contains a global result in [25], in which no vertical transmission and vaccination are assumed ( $r = p = q = 0$ ). Since our model contains SIR models as special cases ( $\epsilon \rightarrow \infty$ ), Theorem 4.1 also generalizes some earlier results on SIR models with vertical transmission and a constant population, see [4] and the references therein.

**5. Discussion.** In this paper, two recent mathematical approaches are used to establish the global stability of the unique endemic equilibrium in two epidemic models of SEIR type. One model has constant recruitment and exponential natural and disease-caused death. The total population size varies in time. The incidence is of bilinear form. In the second model, a balanced exponential birth and natural death is assumed and the disease causes no fatality so that the total population is constant. Both horizontal

and vertical transmission modes are considered. The horizontal transmission has a bilinear incidence. For the vertical transmission, we assume that a fraction  $p$  and a fraction  $q$  of the offspring from the exposed and the infectious classes, respectively, are born into the exposed class  $E$ . We have also considered the effects of vaccination in the second model.

In both models, the basic reproduction number  $R_0$  is identified and is established as a sharp threshold parameter. If  $R_0 \leq 1$ , the disease-free equilibrium  $P_0$  is globally stable in the feasible region and the disease always dies out. If  $R_0 > 1$ , a unique endemic equilibrium  $P^*$  exists and is globally stable in the interior of the feasible region, and once the disease appears, it eventually persists at the unique endemic equilibrium level. The global stability of  $P_0$  when  $R_0 \leq 1$  is proved using a Lyapunov function that has been widely used in the literature of epidemic models (see [29]). The mathematical difficulty lies in the proof of the global stability of  $P^*$  when  $R_0 > 1$ , since both models reduce to nonlinear ordinary differential equations in  $\mathbf{R}^3$ .

The global stability of  $P^*$  in the first model is proved using the approach of Li and Muldowney in [25], which takes the advantage of the monotonicity property that is present in the model and a Poincaré-Bendixson Property for 3-dimensional monotone systems due to Hirsch [17] and Smith [36]. Periodic solutions are ruled out using a stability criterion of Muldowney [33] for periodic orbits in higher dimensions. In the second model, the monotonicity is no longer present. The global stability of  $P^*$  is proved using a geometrical approach of Li and Muldowney in [23]. We expect that these approaches can be applied to solve global-stability problems in many other models.

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## REFERENCES

- [1] R.M. ANDERSON AND R.M. MAY, *Population biology of infectious diseases I*, Nature, **180** (1979), pp. 361–367.
- [2] R.M. ANDERSON AND R.M. MAY, *Infectious Diseases of Humans, Dynamics and Control*, Oxford University Press, Oxford, 1992.
- [3] F. BRAUER, *Models for the spread of universally fatal diseases*, J. Math. Biol. **28** (1990), pp. 451–462.
- [4] S. BUSENBERG AND K. COOKE, *Vertically Transmitted Diseases*, Biomathematics, vol. 23, Springer-Verlag, Berlin, 1993.
- [5] S.N. BUSENBERG AND P. VAN DEN DRIESSCHE, *A method for proving the non-existence of limit cycles*, J. Math. Anal. Appl. **172** (1993), pp. 463–479.

- [6] S.N. BUSENBERG AND P. VAN DEN DRIESSCHE, *Analysis of a disease transmission model in a population with varying size*, J. Math. Biol. **28** (1990), pp. 257–270.
- [7] G.J. BUTLER AND P. WALTMAN, *Persistence in dynamical systems*, Proc. Amer. Math. Soc. **96** (1986), pp. 425–430.
- [8] K.L. COOK AND P. VAN DEN DRIESSCHE, *Analysis of an SEIRS epidemic model with two delays*, J. Math. Biol. **35** (1996), pp. 240–260.
- [9] W.A. COPPEL, *Stability and Asymptotic Behavior of Differential Equations*, Health, Boston, 1965.
- [10] L. ESTEVA AND C. VARGAS, *A model for dengue disease with variable human population*, J. Math. Biol. **38** (1999), pp. 220–240.
- [11] M. FIEDLER, *Additive compound matrices and inequality for eigenvalues of stochastic matrices*, Czech. Math. J. **99** (1974), pp. 392–402.
- [12] D. GREENHALGH, *Hopf bifurcation in epidemic models with a latent period and nonpermanent immunity*, Math. Comput. Modelling **25** (1997), pp. 85–107.
- [13] J.K. HALE, *Ordinary Differential Equations*, John Wiley & Sons, New York, 1969.
- [14] H.W. HETHCOTE AND S.A. LEVIN, *Periodicity in epidemiological models*, in Applied Mathematical Ecology, L. Gross and S.A. Levin (eds.), Springer, New York, 1989, pp. 193–211.
- [15] H.W. HETHCOTE, H.W. STECH, AND P. VAN DEN DRIESSCHE, *Periodicity and stability in epidemic models: a survey*, in Differential Equations and Applications in Ecology, Epidemics, and Population Problems, K. L. Cook (ed.), Academic Press, New York, 1981, pp. 65–85.
- [16] H.W. HETHCOTE AND P. VAN DEN DRIESSCHE, *Some epidemiological models with nonlinear incidence*, J. Math. Biol. **29** (1991), pp. 271–287.
- [17] M.W. HIRSCH, *Systems of differential equations which are competitive or cooperative IV: Structural stability in three dimensional systems*, SIAM J. Math. Anal. **21** (1990), pp. 1225–1234.
- [18] M.W. HIRSCH, *Systems of differential equations that are competitive or cooperative. VI: A local  $C^r$  closing lemma for 3-dimensional systems*, Ergod. Th. & Dynam. Sys. **11** (1991), pp. 443–454.
- [19] J.P. LASALLE, *The Stability of Dynamical Systems*, Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, 1976.
- [20] G.A. LEONOV, D.V. PONOMARENKO, AND V.B. SMIRNOVA, *Frequency-Domain Methods for Nonlinear Analysis, Theory and Applications*, World Scientific, Singapore, 1996.
- [21] M.Y. LI, *Dulac criteria for autonomous systems having an invariant affine manifold*, J. Math. Anal. Appl. **199** (1996), pp. 374–390.
- [22] M.Y. LI, J.R. GRAEF, L.C. WANG, AND J. KARSAI, *Global dynamics of a SEIR model with a varying total population size*, Math. Biosci. **160** (1999), pp. 191–213.
- [23] M.Y. LI AND J.S. MULDOWNNEY, *A geometric approach to the global-stability problems*, SIAM J. Math. Anal. **27** (1996), pp. 1070–1083.
- [24] M.Y. LI AND J.S. MULDOWNNEY, *On R.A. Smith’s autonomous convergence theorem*, Rocky Mount. J. Math. **25** (1995), pp. 365–379.
- [25] M.Y. LI AND J.S. MULDOWNNEY, *Global stability for the SEIR model in epidemiology*, Math. Biosci. **125** (1995), pp. 155–164.
- [26] M.Y. LI, J.S. MULDOWNNEY, AND P. VAN DEN DRIESSCHE, *Global stability for SEIRS models in epidemiology*, Canadian Appl. Math. Quart., to appear.
- [27] M.Y. LI AND L. WANG, *A criterion for stability of matrices*, J. Math. Anal. Appl. **225** (1998), pp. 249–264.
- [28] M.Y. LI, H.L. SMITH, AND L. WANG, *Global stability of an SEIR model with vertical transmission*, SIAM J. Appl. Math., to appear.
- [29] W.-M. LIU, H.W. HETHCOTE AND S.A. LEVIN, *Dynamical behavior of epidemiological models with nonlinear incidence rate*, J. Math. Biol. **25** (1987), pp. 359–380.

- [30] R.H. MARTIN, JR., *Logarithmic norms and projections applied to linear differential systems*, J. Math. Anal. Appl. **45** (1974), pp. 432–454.
- [31] R.M. MAY AND R.M. ANDERSON, *Regulation and stability of host-parasite population interactions. II. Destabilizing process*, J. Anim. Ecol. **47** (1978), pp. 219–267.
- [32] J. MENA-LORCA AND H.W. HETHCOTE, *Dynamic models of infectious diseases as regulator of population sizes*, J. Math. Biol. **30** (1992), pp. 693–716.
- [33] J.S. MULDOWNY, *Compound matrices and ordinary differential equations*, Rocky Mount. J. Math. **20** (1990), pp. 857–872.
- [34] C.C. PUGH, *An improved closing lemma and the general density theorem*, Amer. J. Math. **89** (1967), pp. 1010–1021.
- [35] C.C. PUGH AND C. ROBINSON, *The  $C^1$  closing lemma including Hamiltonians*, Ergod. Th. & Dynam. Sys. **3** (1983), pp. 261–313.
- [36] H.L. SMITH, *Periodic orbits of competitive and cooperative systems*, J. Differential Equations **65** (1986), pp. 361–373.
- [37] H.L. SMITH, *Monotone Dynamical Systems, An Introduction to the Theory of Competitive and Cooperative Systems*, Amer. Math. Soc., Providence, 1995.
- [38] R.A. SMITH, *Some applications of Hausdorff dimension inequalities for ordinary differential equations*, Proc. Roy. Soc. Edinburgh **104A** (1986), pp. 235–259.
- [39] H. THIEME, *Epidemic and demographic interaction in the spread of potentially fatal diseases in growing populations*, Math. Biosci. **111** (1992), pp. 99–130.
- [40] H.R. THIEME AND P. VAN DEN DRIESSCHE, *Global stability in cyclic epidemic models with disease fatalities*, in Differential Equations with Applications to Biology (Halifax, NS, 1997), pp. 459–472, Fields Inst. Commun., vol. 21, Amer. Math. Soc., Providence, 1999.
- [41] P. WALTMAN, *A brief survey of persistence*, in Delay Differential Equations and Dynamical Systems, S. Busenberg and M. Martelli (eds.), Springer-Verlag, New York, 1991, pp. 31–40.