1-1-2013

Global Stability of Infectious Disease Models Using Lyapunov Functions

Zhisheng Shuai
University of Central Florida

P. Van Den Driessche

SIAM J. APPL. MATH.
Vol. 73, No. 4, pp. 1513–1532

GLOBAL STABILITY OF INFECTIOUS DISEASE MODELS USING LYAPUNOV FUNCTIONS*

ZHISHENG SHUAI† AND P. VAN DEN DRIESSCHE‡

Abstract. Two systematic methods are presented to guide the construction of Lyapunov functions for general infectious disease models and are thus applicable to establish their global dynamics. Specifically, a matrix-theoretic method using the Perron eigenvector is applied to prove the global stability of the disease-free equilibrium, while a graph-theoretic method based on Kirchhoff's matrix tree theorem and two new combinatorial identities are used to prove the global stability of the endemic equilibrium. Several disease models in the literature and two new cholera models are used to demonstrate the applications of these methods.

Key words. disease model, global stability, Lyapunov function, graph-theoretic method

AMS subject classifications. 34D23, 92D30

DOI. 10.1137/120876642

1. Introduction.

In compartmental models for infectious disease transmission, individuals are categorized into several compartments: some are called disease compartments if the individuals therein are infected, while others are called nondisease compartments. Suppose that there are $n > 0$ disease compartments and $m > 0$ nondisease compartments. Then a general compartmental disease transmission model can be written as

$$x' = \mathcal{F}(x, y) - \mathcal{V}(x, y), \qquad y' = g(x, y), \tag{1.1}$$

with $g = (g_1, \ldots, g_m)^T$. Here $'$ denotes differentiation with respect to time; $x = (x_1, \ldots, x_n)^T \in \mathbb{R}^n$ and $y = (y_1, \ldots, y_m)^T \in \mathbb{R}^m$ represent the populations in disease compartments and nondisease compartments, respectively; $\mathcal{F} = (\mathcal{F}_1, \ldots, \mathcal{F}_n)^T$ and $\mathcal{V} = (\mathcal{V}_1, \ldots, \mathcal{V}_n)^T$, where $\mathcal{F}_i$ represents the rate of new infections in the ith disease compartment; and $\mathcal{V}_i$ represents the transition terms, for example, death and recovery in the ith disease compartment.

The following assumptions follow those in [37] and are made to ensure the well-posedness of the model and the existence of a disease-free equilibrium (DFE). Assume that $\mathcal{F}_i(0, y) = 0$, $\mathcal{V}_i(0, y) = 0$, $\mathcal{F}_i(x, y) \geq 0$, $\mathcal{V}_i(x, y) \leq 0$ whenever $x_i = 0$, and $\sum_{i=1}^{n} \mathcal{V}_i(x, y) \geq 0$ for all $x, y \geq 0$, $i = 1, \ldots, n$. Also assume that the disease-free system $y' = g(0, y)$ has a unique equilibrium $y = y_0 > 0$ that is locally asymptotically stable within the disease-free space. See [36, 37] for a detailed discussion and interpretation of these assumptions.

*Received by the editors May 10, 2012; accepted for publication (in revised form) May 1, 2013; published electronically July 16, 2013. This research was supported in part by grants from the Natural Science and Engineering Research Council of Canada (NSERC) and Mprime project "Transmission Dynamics and Spatial Spread of Infectious Diseases: Modelling, Prediction and Control."
http://www.siam.org/journals/siap/73-4/87664.html

†Department of Mathematics and Statistics, University of Victoria, Victoria, BC, V8W 3R4, Canada. Current address: Department of Mathematics, University of Central Florida, Orlando, FL 32816 (shuai@ucf.edu). This author acknowledges the support of an NSERC postdoctoral fellowship.

‡Department of Mathematics and Statistics, University of Victoria, Victoria, BC, V8W 3R4, Canada (pvdd@math.uvic.ca).

Following [36, 37], define two $n \times n$ matrices

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(0, y_0)\right] \qquad \text{and} \qquad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(0, y_0)\right]. \tag{1.2}$$

Assume that $F \geq 0$ and $V^{-1} \geq 0$, which are biologically reasonable. Then the next-generation matrix is $K = FV^{-1}$, and the basic reproduction number $\mathcal{R}_0$ can be defined as the spectral radius of K (see [6, 36]), that is,

$$\mathcal{R}_0 = \rho(FV^{-1}). \tag{1.3}$$

By Theorem 2 in [36], the DFE $P_0 = (0, y_0)$ is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable otherwise. Customarily, this approach determining the basic reproduction number is called the Next Generation Matrix (NGM) approach.

Furthermore, for many disease models, the basic reproduction number $\mathcal{R}_0$ gives a sharp threshold that completely determines their global dynamics; thus the following property is stated.

Sharp threshold property. Model (1.1) has the sharp threshold property if $\mathcal{R}_0$ given by (1.3) is such that

- the DFE P_0 is global asymptotically stable for $\mathcal{R}_0 \leq 1$, and
- there is a unique endemic equilibrium (EE) P^* that is globally asymptotically stable in the interior of the feasible region for $\mathcal{R}_0 > 1$.

This property hold for the models in this paper and others in the literature. Biologically, the sharp threshold property shows that the disease will eventually die out if the basic reproduction number $\mathcal{R}_0 \leq 1$, while the disease persists at a positive level if $\mathcal{R}_0 > 1$. However, the rigorous proofs of these global stability results are nontrivial for many disease models. In particular, the global stability of the EE normally becomes a challenging mathematical problem due to the complexity and high dimension of disease models. For example, cholera and other waterborne diseases can be transmitted directly to humans by person-to-person contact or indirectly to humans via contaminated water. As a consequence, it is important to incorporate pathogens in the environment (water) into the disease models. Thus the existing compartmental models for the transmission of waterborne diseases such as cholera normally have higher dimension than only directly transmitted diseases; see, for example, a basic cholera model in [5] consisting of four ordinary differential equations (ODEs). The effect of differential infectivity or spatial heterogeneity on the spread of infectious diseases also requires complex disease models. For example, a hyperinfectivity model consisting of five ODEs is proposed in [17] to study the effect of hyperinfectivity of freshly shed pathogen on the transmission of cholera, while a multistage model is used in [33] to model waterborne diseases with multiple infection stages. A more general cholera model proposed in [31] incorporates simultaneously multiple infection stages of individuals and multiple infectious states of a pathogen. Spatial heterogeneity is incorporated into a multigroup cholera model in [34] to explain the spatial spread of cholera in Haiti. These cholera models all consist of many nonlinear differential equations, and an understanding of their dynamics is mathematically challenging; for example, only [31] contains results like the sharp threshold property.

The method of Lyapunov functions is commonly used to establish global stability results for biological models; see, for example, [15, 23] for general theory of Lyapunov functions and [8, 20, 21] for applications in mathematical biology. (Recall that D is called a Lyapunov function for system (1.1) if D is continuous and

is nonincreasing along every solution of (1.1).) However, it is often difficult to construct such Lyapunov functions and no general method is available. For example, a general form of Lyapunov functions used in the literature of mathematical biology is $D = \sum_{i=1}^{n} c_i(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*})$, originally from the first integral of a Lotka–Volterra system. When applied to disease models, suitable coefficients c_i have to be determined such that the derivative of D along solutions of the model is nonpositive, and such a determination becomes very challenging for models with high dimension such as the cholera models cited above. A graph-theoretic method based on Kirchhoff's matrix tree theorem was recently developed in [26] to guide the construction of Lyapunov functions for coupled systems on networks. When the disease model provides a network structure and can be regarded as a coupled system where each subsystem has a Lyapunov function, then the graph-theoretic method can be used to construct a Lyapunov function for the coupled system. This method has been applied successfully to establish the global stability of the EE for several complex disease models; see, for example, [11, 12, 26]. Nevertheless, a systematic approach is lacking to guide the construction of Lyapunov functions for each subsystem when the disease model has a network structure, and also for disease models that do not have an explicit network structure.

In this paper, two methods are presented to guide the construction of Lyapunov functions for disease models and thus establish the global asymptotic stability (GAS) of the DFE and EE: a matrix-theoretic method based on the Perron eigenvector is used to prove the GAS of the DFE (see section 2), while the graph-theoretic method and new combinatorial relations are used to prove the GAS of the EE (see section 3). Several disease models in the literature (sections 4–6) and new models for cholera (sections 7–8) are used to demonstrate different applications of these methods.

2. Global stability of the DFE: A matrix-theoretic method. To address the first statement of the sharp threshold property, a systematic method is presented to guide the construction of a Lyapunov function.

Following [4, 37], set

$$f(x,y) := (F-V)x - \mathcal{F}(x,y) + \mathcal{V}(x,y). \tag{2.1}$$

Then (1.1) for the disease compartments can be written as

$$x' = (F-V)x - f(x,y). \tag{2.2}$$

Note that from the previous assumptions, $f(0,y) = 0$. Let $\omega^T \geq 0$ be the left eigenvector of the nonnegative matrix $V^{-1}F$ corresponding to the eigenvalue $\rho(V^{-1}F) = \rho(FV^{-1}) = \mathcal{R}_0$. The following result provides a general method to construct a Lyapunov function for (1.1). Note that this type of Lyapunov function involving the Perron eigenvector has previously been used to study the global dynamics for several specific disease models; see, for example, [11, 13, 31]. Here it is used for a general disease model.

THEOREM 2.1. *Let F, V and $f(x,y)$ be defined as in* (1.2) *and* (2.1)*, respectively. If $f(x,y) \geq 0$ in $\Gamma \subset \mathbb{R}_+^{n+m}$, $F \geq 0$, $V^{-1} \geq 0$, and $\mathcal{R}_0 \leq 1$, then the function $Q = \omega^T V^{-1} x$ is a Lyapunov function for model* (1.1) *on* Γ.

Proof. Differentiating Q along solutions of (1.1) gives

$$\begin{aligned} Q' = Q'|_{(1.1)} &= \omega^T V^{-1} x' = \omega^T V^{-1}(F-V)x - \omega^T V^{-1} f(x,y) \\ &= (\mathcal{R}_0 - 1)\omega^T x - \omega^T V^{-1} f(x,y). \end{aligned} \tag{2.3}$$

Since $\omega^T \geq 0$, $V^{-1} \geq 0$, and $f(x,y) \geq 0$ in Γ, the last term is nonpositive. If $\mathcal{R}_0 \leq 1$, then $Q' \leq 0$ in Γ, and thus Q is a Lyapunov function for system (1.1). ∎

In applications to infectious disease models, the set Γ in Theorem 2.1 is normally chosen as a compact subset of $\mathbb{R}^{n+m}_+$ such that $(0, y_0) \in \Gamma$ and Γ is positively invariant with respect to (1.1). Hence, the Lyapunov function constructed in Theorem 2.1 can be used to prove not only the global stability of the DFE but also uniform persistence and thus establish the existence of an EE. The following result provides a scenario in which assumptions can be conveniently checked for disease models.

THEOREM 2.2. *Let F, V and $f(x,y)$ be defined as in* (1.2) *and* (2.1)*, respectively, and let $\Gamma \subset \mathbb{R}^{n+m}_+$ be compact such that $(0, y_0) \in \Gamma$ and Γ is positively invariant with respect to* (1.1)*. Suppose that $f(x,y) \geq 0$ with $f(x, y_0) = 0$ in Γ, $F \geq 0$, $V^{-1} \geq 0$, and $V^{-1}F$ is irreducible. Assume that the disease-free system $y' = g(0,y)$ has a unique equilibrium $y = y_0 > 0$ that is GAS in $\mathbb{R}^m_+$. Then the following results hold for* (1.1)*:*

1. *If $\mathcal{R}_0 < 1$, then the DFE P_0 is GAS in Γ.*
2. *If $\mathcal{R}_0 > 1$, then P_0 is unstable and system* (1.1) *is uniformly persistent and there exists at least one EE.*

Proof. By Theorem 2.1, $Q = \omega^T V^{-1} x$ is a Lyapunov function for (1.1) provided $\mathcal{R}_0 < 1$. Since $V^{-1}F$ is irreducible and nonnegative, it follows by Perron–Frobenius theory that $\omega > 0$. Hence, by (2.3), $Q' = 0$ implies that $\omega^T x = 0$ and thus $x = 0$. Using the global stability assumption for the disease-free system and the fact that $f(0,y) = 0$, the only invariant set in $\mathbb{R}^{n+m}_+$ where $x = 0$ is the singleton $\{P_0\}$. By LaSalle's invariance principle [23], P_0 is GAS in Γ.

If $\mathcal{R}_0 > 1$, then by (2.3), $Q' = (\mathcal{R}_0 - 1)\omega^T x > 0$ provided $x > 0$ and $y = y_0$. By continuity $Q' > 0$ in a neighborhood of P_0. Solutions in the positive cone sufficiently close to P_0 move away from P_0, implying that P_0 is unstable. Using a uniform persistence result from [9] and an argument as in the proof of Proposition 3.3 of [24], it can be shown that when $R_0 > 1$, instability of P_0 implies uniform persistence of (1.1). Uniform persistence and the positive invariance of the compact set Γ imply the existence of an EE of (1.1). (See Theorem D.3 in [32] or Theorem 2.8.6 in [2].) ∎

Other general global stability results for the DFE proved by comparison arguments can be found in [4, section 3] and [37, section 6.6] but cannot be used directly to establish results for the persistence of the model or existence of the EE.

We remark that for the case $\mathcal{R}_0 = 1$, the global stability of the DFE can be proved by using LaSalle's invariant principle and analyzing the largest invariant set where $Q' = \omega^T V^{-1} f(x,y) = 0$; see, for example, sections 4–8. For some disease models, the irreducibility assumption in Theorem 2.2 may fail; however, arguments for the case $Q' = 0$ can be applied (see, for example, section 5).

3. Global stability of the EE: A graph-theoretic method.

3.1. Graph-theoretical results. We begin by recalling some definitions and results from graph theory; as general references see, for example, [16] or [40].

A *directed graph* (*digraph*) $\mathcal{G}$ consists of a set of *vertices* and a set of ordered pairs (i,j) of (not necessarily distinct) vertices; each such pair (i,j) is called an *arc* from its *initial vertex* i to its *terminal vertex* j. The in-degree of a vertex i, denoted as $d^-(i)$, is the number of arcs in $\mathcal{G}$ whose terminal vertex is i, and the out-degree $d^+(i)$ is the number of arcs whose initial vertex is i. A subdigraph $\mathcal{H}$ of $\mathcal{G}$ is *spanning* if $\mathcal{H}$ and $\mathcal{G}$ have the same vertex sets. A digraph $\mathcal{G}$ is *weighted* if each arc is assigned a positive weight. The weight $w(\mathcal{H})$ of a subdigraph $\mathcal{H}$ is the product of the weights on all its arcs.

A (*rooted*) *tree* is a subdigraph $\mathcal{T}$ of $\mathcal{G}$ that is a single connected component and in which the in-degree of one vertex, the root, is zero, but each of the remaining vertices has in-degree 1. A (*directed*) path $\mathcal{P}$ is a subdigraph with distinct vertices labeled $i_1, i_2, \ldots, i_m$ so that its arcs are of the form (i_k, i_{k+1}) for $k = 1, 2, \ldots, m-1$; a (*directed*) *cycle* $\mathcal{C}$ is the subdigraph obtained from such a path $\mathcal{P}$ by adding the arc (i_m, i_1). If $m = 1$, the cycle consisting of a single vertex i_1 and a single arc (i_1, i_1) is called a *loop*. A *unicyclic graph* is a subdigraph $\mathcal{Q}$ consisting of a collection of disjoint rooted trees whose roots are the vertices of a directed cycle; notice that the in-degree of every vertex of such a graph equals 1.

Given a weighted digraph $\mathcal{G}$ with n vertices, define the $n \times n$ weight matrix $A = [a_{ij}]$ with entry $a_{ij} > 0$ equal to the weight of arc (j, i) if it exists and 0 otherwise. We denote such a weighted digraph by $(\mathcal{G}, A)$. A digraph $\mathcal{G}$ is strongly connected if for any pair of distinct vertices i, j, there exists a directed path from i to j (and also from j to i). A weighted digraph $(\mathcal{G}, A)$ is strongly connected if and only if the weight matrix A is irreducible [1]. The Laplacian matrix $L = [\ell_{ij}]$ of $(\mathcal{G}, A)$ is defined as

$$\ell_{ij} = \begin{cases} -a_{ij} & \text{for } i \neq j, \\ \sum_{k \neq i} a_{ik} & \text{for } i = j. \end{cases} \tag{3.1}$$

The following result gives a graph-theoretic description of the cofactors of the diagonal entries of L.

PROPOSITION 3.1 (Kirchhoff's matrix tree theorem). *Assume $n \geq 2$ and let c_i be the cofactor of ℓ_{ii} in L. Then*

$$c_i = \sum_{\mathcal{T} \in \mathbb{T}_i} w(\mathcal{T}), \qquad i = 1, 2, \ldots, n, \tag{3.2}$$

where $\mathbb{T}_i$ is the set of all spanning trees $\mathcal{T}$ of $(\mathcal{G}, A)$ that are rooted at vertex i, and $w(\mathcal{T})$ is the weight of $\mathcal{T}$. If $(\mathcal{G}, A)$ is strongly connected, then $c_i > 0$ for $1 \leq i \leq n$.

The next identity is similar to the one in [26, Theorem 2.3], following directly from the tree cycle identity [26, Theorem 2.2].

THEOREM 3.2. *Let c_i be as given in the Kirchhoff's matrix tree theorem, and let $\{H_i(z)\}_{i=1}^n$ be any family of functions with $z = (z_1, \ldots, z_m)^T \in \mathbb{R}^m$. Then*

$$\sum_{i,j=1}^{n} c_i \, a_{ij} \, H_i(z) = \sum_{i,j=1}^{n} c_i \, a_{ij} \, H_j(z). \tag{3.3}$$

When the weighted digraph $(\mathcal{G}, A)$ has a certain structure, two new relations among the c_i can be established via combinatorial identities.

THEOREM 3.3. *Let c_i be as given in Proposition 3.1. If $a_{ij} > 0$ and $d^+(j) = 1$ for some i, j, then*

$$c_i a_{ij} = \sum_{k=1}^{n} c_j a_{jk}. \tag{3.4}$$

Proof. For every spanning tree $\mathcal{T}$ rooted at vertex i, $w(\mathcal{T}) a_{ij} = w(\mathcal{Q})$, where $\mathcal{Q}$ is the unicyclic graph obtained from $\mathcal{T}$ by adding arc (j, i); see [26, Figure 2]. By Proposition 3.1, $c_i = \sum_{\mathcal{T} \in \mathbb{T}_i} w(\mathcal{T})$; hence, the left-hand side of (3.4) is the sum of the weight of all spanning unicyclic graphs of $(\mathcal{G}, A)$ whose cycle includes the arc (j, i). The right-hand side of (3.4) is the sum of the weights of all spanning unicyclic graphs

of $(\mathcal{G}, A)$ whose cycle includes the vertex j and thus includes the arc (j, i) that is the only arc leaving vertex j. Therefore, the identity (3.4) holds. ∎

THEOREM 3.4. *Let c_i be as given in Proposition* 3.1. *If $a_{ij} > 0$ and $d^-(i) = 1$ for some i, j, then*

$$c_i a_{ij} = \sum_{k=1}^{n} c_k a_{ki}. \tag{3.5}$$

Proof. As in the proof of Theorem 3.3, both sides of (3.5) are equal to the sum of the weights of all spanning unicyclic graphs whose cycle includes the arc (j, i). ∎

3.2. Lyapunov functions. Let U be an open set in $\mathbb{R}^m$. Consider a differential equation system

$$z_k' = f_k(z_1, z_2, \ldots, z_m), \qquad k = 1, 2, \ldots, m, \tag{3.6}$$

with $z = (z_1, z_2, \ldots, z_m) \in U$. The following new result is similar to Theorem 3.1 in [26] but is more general and useful in applications.

THEOREM 3.5. *Suppose that the following assumptions are satisfied:*

(1) *There exist functions $D_i : U \to \mathbb{R}, G_{ij} : U \to \mathbb{R}$ and constants $a_{ij} \geq 0$ such that for every $1 \leq i \leq n$, $D_i' = D_i'|_{(3.6)} \leq \sum_{j=1}^{n} a_{ij} G_{ij}(z)$ for $z \in U$.*

(2) *For $A = [a_{ij}]$, each directed cycle $\mathcal{C}$ of $(\mathcal{G}, A)$ has $\sum_{(s,r)\in\mathcal{E}(\mathcal{C})} G_{rs}(z) \leq 0$ for $z \in U$, where $\mathcal{E}(\mathcal{C})$ denotes the arc set of the directed cycle $\mathcal{C}$.*

Then, the function $D(z) = \sum_{i=1}^{n} c_i D_i(z)$, with constants $c_i \geq 0$ as given in Proposition 3.1, *satisfies $D' = D'|_{(3.6)} \leq 0$; that is, D is a Lyapunov function for* (3.6).

Proof. Direct calculation and using assumption (1) give $D' = \sum_{i=1}^{n} c_i D_i' \leq \sum_{i,j=1}^{n} c_i a_{ij} G_{ij}(z)$. Applying the tree cycle identity [26, Theorem 2.2] to the right-hand side of this inequality gives $\sum_{i,j=1}^{n} c_i a_{ij} G_{ij}(z) = \sum_{\mathcal{Q}} w(Q) \sum_{(s,r)\in\mathcal{E}(\mathcal{C}_\mathcal{Q})} G_{rs}(z)$, where the first sum on the right-hand side has terms corresponding to each unicyclic graph $\mathcal{Q}$ of $(\mathcal{G}, A)$, and $\mathcal{C}_\mathcal{Q}$ denotes the directed cycle of $\mathcal{Q}$ with arc set $\mathcal{E}(\mathcal{C}_\mathcal{Q})$. By assumption (2), $\sum_{(s,r)\in\mathcal{E}(\mathcal{C}_\mathcal{Q})} G_{rs}(z) \leq 0$. Hence $D' \leq 0$, namely, D is a Lyapunov function for (3.6). ∎

Theorem 3.5 can be used to guide the construction of Lyapunov functions for not only models that can be regarded as coupled systems on networks (e.g., see [26]) but also models that do not have an explicit network structure. In the applications to disease models considered here, the D_i are chosen from functions commonly used in population models. The calculation of D_i' follows from the disease model under consideration and upper bounds for these derivatives are determined. The functions G_{ij} and constants a_{ij} are chosen so that assumptions (1) and (2) in Theorem 3.5 hold simultaneously. A weighted digraph is constructed corresponding to the weight matrix $A = [a_{ij}]$ determined from assumption (1), depending on the choice of $D_i, i = 1, \ldots, n$, and estimates of D_i'. Different numbers and/or types of functions D_i can be used for a particular disease model, giving different weighted digraphs; see, for example, section 4. The function G_{ij} does not necessarily depend only on z_i and z_j; see, for example, G_{21} in section 5. With knowledge of a specific graph structure, the new combinatorial identities (Theorems 3.3 and 3.4) can further be applied to derive explicitly the coefficients c_i in a constructed Lyapunov function; see, for example, sections 4–5 and 7–8.

4. Application to a classical susceptible-infectious-removed disease model. In this section and the following sections the systematic methods developed in sections 2 and 3 are applied to various disease models to illustrate several aspects of these methods.

The first model is used to demonstrate that the graph-theoretic method is applicable to different types of Lyapunov functions, such as quadratic and Volterra type functions as commonly used in ecological models. Consider the following susceptible-infectious-removed (SIR) model:

$$\begin{aligned} S' &= \Lambda - \beta SI - dS, \\ I' &= \beta SI - (d+\gamma+\alpha)I, \\ R' &= \gamma I - dR \end{aligned} \tag{4.1}$$

with nonnegative initial conditions $S(0), I(0), R(0)$. Here S, I, R represent the numbers of individuals in susceptible, infectious, and removed compartments, respectively. These letters are also used to identify the compartment. Among the parameters in (4.1), $\Lambda > 0$ represents the constant input, $d > 0$ represents the natural mortality rate, $\alpha \geq 0$ represents the mortality rate due to disease, $\gamma > 0$ represents the recovery rate, and $\beta > 0$ represents the disease transmission rate per individual. Model (4.1) can be regarded as a basic framework for the dynamics of many viral diseases, e.g., measles, influenza.

The feasible region $\Gamma = \{(S, I, R) \in \mathbb{R}^3_+ \mid S + I + R \leq \frac{\Lambda}{d}\}$ is positively invariant with respect to (4.1). Model (4.1) always admits a DFE $P_0 = (S_0, 0, 0) \in \Gamma$ with $S_0 = \frac{\Lambda}{d}$. An EE $P^* = (S^*, I^*, R^*) \in \text{int}(\Gamma)$ exists if and only if the basic reproduction number $\mathcal{R}_0 = \frac{\beta\Lambda}{d(d+\gamma+\alpha)} > 1$ with $S^* = \frac{\Lambda}{d\mathcal{R}_0}, I^* = \frac{d(\mathcal{R}_0-1)}{\beta}$ and $R^* = \frac{\gamma I^*}{d}$. The following result is one of the classical global stability results of mathematical epidemiology.

THEOREM 4.1. *Let* $\mathcal{R}_0 = \frac{\beta\Lambda}{d(d+\gamma+\alpha)}$. *Then the sharp threshold property holds for model* (4.1).

Proof. Since the disease compartment has dimension 1, $Q = I$ is a Lyapunov function that can be used to prove the global stability of the DFE. In fact, $Q' = I' = \beta S_0 I - (d+\gamma+\alpha)I - f(S, I) = (\mathcal{R}_0 - 1)(d+\gamma+\alpha)I - f(S, I)$ with $f(S, I) := \beta(S_0 - S)I \geq 0$ in Γ. By Theorem 2.2, P_0 is GAS in Γ provided $\mathcal{R}_0 < 1$.

When $\mathcal{R}_0 = 1$, $Q' = 0$ implies $f(S, I) = 0$. Notice that $f(S, I) = 0$ if and only if $S = S_0$ or $I = 0$. For either case, it can be verified that the largest invariant set for (4.1) is the singleton $\{P_0\}$. Hence, by LaSalle's invariance principle [23], P_0 is also GAS in Γ when $\mathcal{R}_0 = 1$.

Using the graph-theoretic method developed in section 3, several Lyapunov functions $\tilde{D}$ are constructed below to prove the GAS of P^* if $\mathcal{R}_0 > 1$. For each of these Lyapunov functions, the largest invariant set for (4.1) where $\tilde{D}' = 0$ is the singleton $\{P^*\}$. Therefore, by LaSalle's invariance principle [23], P^* is GAS in int(Γ). ∎

Construction 1. Let $D_1 = S - S^* - S^* \ln \frac{S}{S^*}$ and $D_2 = I - I^* - I^* \ln \frac{I}{I^*}$. Using the inequality $1 - x + \ln x \leq 0$ for $x > 0$ with equality holding if and only if $x = 1$, differentiation and use of the EE values give

$$\begin{aligned} D_1' &= \frac{S - S^*}{S} S' = \frac{S - S^*}{S}(\beta S^* I^* + dS^* - \beta SI - dS) \\ &= -d\frac{(S - S^*)^2}{S} + \beta S^* I^* \left(1 - \frac{S^*}{S} - \frac{SI}{S^* I^*} + \frac{I}{I^*}\right) \\ &\leq \beta S^* I^* \left(\frac{I}{I^*} - \ln \frac{I}{I^*} - \frac{SI}{S^* I^*} + \ln \frac{SI}{S^* I^*}\right) =: a_{12} G_{12} \end{aligned}$$

and similarly

$$D_2' = \beta S^* I^* \left(\frac{SI}{S^* I^*} - \frac{S}{S^*} - \frac{I}{I^*} + 1\right) \leq \beta S^* I^* \left(\frac{SI}{S^* I^*} - \ln \frac{SI}{S^* I^*} - \frac{I}{I^*} + \ln \frac{I}{I^*}\right) =: a_{21} G_{21}$$

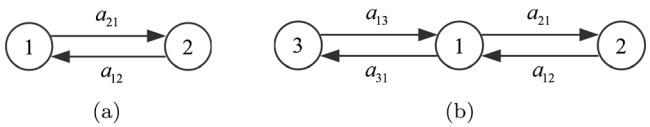

FIG. 4.1. *Two weighted digraphs* $(\mathcal{G}, A)$ *constructed for the SIR model* (5.1)*:* (a) *for Constructions* 1 *and* 2*;* (b) *for Construction* 3.

with $a_{12} = a_{21} = \beta S^* I^*$ and $G_{12} = -G_{21} = \frac{I}{I^*} - \ln \frac{I}{I^*} - \frac{SI}{S^*I^*} + \ln \frac{SI}{S^*I^*}$. Construct a weighted digraph with two vertices and two arcs; see Figure 4.1(a). Along the only cycle, $G_{12}+G_{21} = 0$. By Theorem 3.5, there exist c_1 and c_2 such that $D = c_1D_1+c_2D_2$ is a Lyapunov function for (4.1). Since $d^+(1) = 1$, $c_1a_{12} = c_2a_{21}$ by Theorem 3.3, and thus $c_1 = c_2$. Therefore, a Lyapunov function $\tilde{D} = D_1 + D_2$ can be used to prove the GAS of P^*. Notice that Lyapunov function $\tilde{D}$ agrees with the one constructed in [21], where coefficients c_1, c_2 are just stated.

Construction 2. Let $D_1 = \frac{1}{2}(S - S^*)^2$ and $D_2 = I - I^* - I^* \ln \frac{I}{I^*}$. Differentiation gives

$$D_1' = (S - S^*)(\beta S^* I^* + dS^* - \beta SI - dS) \le \beta S^*(S - S^*)(I^* - I) =: a_{12}G_{12}$$

and

$$D_2' = \frac{I - I^*}{I}(\beta SI - \beta S^* I) = \beta(S - S^*)(I - I^*) =: a_{21}G_{21}$$

with $a_{12} = \beta S^*$, $a_{21} = \beta$, and $G_{12} = -G_{21} = (S - S^*)(I^* - I)$. Construct a weighted digraph as in Construction 1. Similarly, the assumptions of Theorem 3.5 hold, and by Theorem 3.3, $c_2 = S^*c_1$. Thus a Lyapunov function $\tilde{D} = D_1 + S^*D_2$ can be used to prove the GAS of P^*. The same kind of Lyapunov function consisting of quadratic and Volterra type function has previously been used in [28] to study the global stability of the EE of the SIRS model.

Construction 3. Let $D_1 = \frac{1}{2}(S - S^* + I - I^* + R - R^*)^2$, $D_2 = I - I^* - I^* \ln \frac{I}{I^*}$ and $D_3 = \frac{1}{2}(R - R^*)^2$. Differentiation gives

$$\begin{aligned} D_1' &= ((S - S^* + R - R^*) + (I - I^*))(d(S^* - S + R^* - R) + (d + \alpha)(I^* - I)) \\ &\le (2d + \alpha)(S - S^*)(I^* - I) + (2d + \alpha)(I^* - I)(R - R^*) \\ &=: a_{12}G_{12} + a_{13}G_{13}, \\ D_2' &= \beta(S - S^*)(I - I^*) =: a_{21}G_{21}, \end{aligned}$$

and

$$D_3' = (R - R^*)(\gamma I - \gamma I^* + dR^* - dR) \le \gamma(I - I^*)(R - R^*) =: a_{31}G_{31}$$

with $a_{12} = a_{13} = 2d + \alpha$, $a_{21} = \beta$, $a_{31} = \gamma$, and other $a_{ij} = 0$. Functions G_{ij} can be defined accordingly. Notice that G_{13} is a function of variables I and R, rather than the variable S. Construct a weighted digraph with three vertices and four arcs; see Figure 4.1(b). Along each cycle, $G_{12}+G_{21} = 0$ and $G_{13}+G_{31} = 0$, so by Theorem 3.5 there exist $c_i, i = 1, 2, 3$, such that $D = c_1D_1 + c_2D_2 + c_3D_3$ is a Lyapunov function for (4.1). Since $d^+(2) = 1$ and $d^+(3) = 1$, Theorem 3.3 implies that $c_2 = \frac{2d+\alpha}{\beta}c_1$ and $c_3 = \frac{2d+\alpha}{\gamma}c_1$. Therefore, a Lyapunov function $\tilde{D} = D_1 + \frac{2d+\alpha}{\beta}D_2 + \frac{2d+\alpha}{\gamma}D_3$ can be used to prove the global stability of P^*. Note that the Lyapunov function $\tilde{D}$ is the same as the one used in [38, section 3.2].

Three different Lyapunov functions for (4.1) are constructed above that consist of Volterra type functions and/or quadratics. For each construction, the graph-theoretic method provides a systematic approach to determine their coefficients. We comment that such a general method can also be applied to guide the construction of other Lyapunov functions for different choices of D_i, probably giving different weighted digraphs. The Lyapunov function in Construction 1 can be used as a building block to construct a Lyapunov function for a multigroup/multipatch SIR model (see [11, 25]), while the same process as in Construction 2 or 3 can be applied to construct a Lyapunov function for a SIRS/SIS model, which is basically the same as in [38].

5. Application to a susceptible-exposed-infectious-recovered disease model with relapse. In this section we consider a susceptible-exposed-infectious-recovered (SEIR) model with relapse, as the ODE version of the model proposed in [35]:

$$\begin{aligned} S' &= \Lambda - \beta SI - dS, \\ E' &= \beta SI - (d+\epsilon)E, \\ I' &= \epsilon E - (d+\gamma+\alpha)I + \eta R, \\ R' &= \gamma I - (d+\eta)R \end{aligned} \tag{5.1}$$

with nonnegative initial conditions. Here E represents the number of latent (exposed) individuals, $\epsilon > 0$ represents the rate that exposed individuals become infectious (i.e., $1/\epsilon$ represents the average latent period), and $\eta \geq 0$ represents the rate that recovered individuals relapse and regain infectiousness. Other parameters and variables are interpreted in the same way as those in model (4.1). This relapse model is motivated by the spread of herpes; individuals recovered from infection can experience relapse of the disease [3].

The feasible region $\Gamma = \{(S, E, I, R) \in \mathbb{R}^4_+ \mid S + E + I + R \leq \frac{\Lambda}{d}\}$ is positively invariant with respect to (5.1). The DFE has the form $P_0 = (S_0, 0, 0, 0)$ with $S_0 = \frac{\Lambda}{d}$. There are three disease compartments: E, I, R. Following the NGM approach, let

$$F = \begin{bmatrix} 0 & \beta S_0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} d+\epsilon & 0 & 0 \\ -\epsilon & d+\gamma+\alpha & -\eta \\ 0 & -\gamma & d+\eta \end{bmatrix}.$$

Thus the basic reproduction number can be calculated as

$$\mathcal{R}_0 = \rho(FV^{-1}) = \beta S_0 \frac{\epsilon(d+\eta)}{(d+\epsilon)((d+\alpha)(d+\eta)+d\gamma)}. \tag{5.2}$$

THEOREM 5.1. *Let $\mathcal{R}_0$ be as defined in* (5.2)*. Then the sharp threshold property holds for* (5.1)*.*

Proof. Since matrix $V^{-1}F$ is reducible (the second column is the only nonzero column), the condition of Theorem 2.2 fails. Instead, the Lyapunov function constructed in Theorem 2.1 can be used to establish the GAS of P_0. Let $x = (E, I, R)^T$, then $x' = (F - V)x - f(x, S)$ with $f(x, S) := \beta I(S_0 - S) \geq 0$ in Γ. By Theorem 2.1, $Q = \omega^T V^{-1} x$ is a Lyapunov function, where $\omega^T = (0, 1, 0)$ is the left eigenvector of matrix $V^{-1}F$. Straightforward calculation gives $Q = \frac{\mathcal{R}_0}{\beta S_0}(E + \frac{d+\epsilon}{\epsilon} I + \frac{(d+\epsilon)\eta}{(d+\eta)\epsilon} R)$ and $Q' = (\mathcal{R}_0 - 1)I - \frac{\mathcal{R}_0}{S_0} I(S_0 - S) \leq 0$ provided $\mathcal{R}_0 \leq 1$. Furthermore, $Q' = 0$ implies that $I = 0$ or $S = S_0$. It can be verified that the only invariant set where $I = 0$ or $S = S_0$ is the singleton $\{P_0\}$. Therefore, by LaSalle's invariance principle,

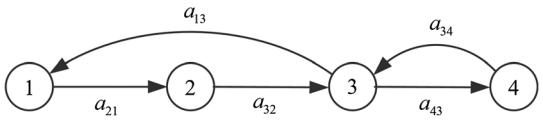

FIG. 5.1. *The weighted digraph* $(\mathcal{G}, A)$ *constructed for the relapse model* (5.1).

P_0 is GAS in Γ. The same arguments as those in the proof of Theorem 2.2 can be used to prove the instability of P_0 and the persistence and the existence of an EE $P^* = (S^*, E^*, I^*, R^*) \in \text{int}(\Gamma)$, where S^*, E^*, I^*, R^* satisfy (5.1) with each right-hand side equal to 0.

To establish the uniqueness and global stability of P^*, set $D_1 = S - S^* - S^* \ln \frac{S}{S^*}$, $D_2 = E - E^* - E^* \ln \frac{E}{E^*}$, $D_3 = I - I^* - I^* \ln \frac{I}{I^*}$, and $D_4 = R - R^* - R^* \ln \frac{R}{R^*}$. Differentiation gives

$$
\begin{aligned}
D_1' &\le \beta S^* I^* \left(\frac{I}{I^*} - \ln \frac{I}{I^*} - \frac{SI}{S^* I^*} + \ln \frac{SI}{S^* I^*} \right) =: a_{13} G_{13}, \\
D_2' &\le \beta S^* I^* \left(\frac{SI}{S^* I^*} - \ln \frac{SI}{S^* I^*} - \frac{E}{E^*} + \ln \frac{E}{E^*} \right) =: a_{21} G_{21}, \\
D_3' &\le \epsilon E^* \left(\frac{E}{E^*} - \ln \frac{E}{E^*} - \frac{I}{I^*} + \ln \frac{I}{I^*} \right) \\
&\quad + \eta R^* \left(\frac{R}{R^*} - \ln \frac{R}{R^*} - \frac{I}{I^*} + \ln \frac{I}{I^*} \right) =: a_{32} G_{32} + a_{34} G_{34},
\end{aligned}
$$

and

$$
D_4' \le \gamma I^* \left(\frac{I}{I^*} - \ln \frac{I}{I^*} - \frac{R}{R^*} + \ln \frac{R}{R^*} \right) =: a_{43} G_{43}
$$

with $a_{13} = a_{21} = \beta S^* I^*$, $a_{32} = \epsilon E^*$, $a_{34} = \eta R^*$, $a_{43} = \gamma I^*$, and all other $a_{ij} = 0$. The associated weighted digraph $(\mathcal{G}, A)$ has four vertices and two cycles; see Figure 5.1. Along each cycle, $G_{13} + G_{32} + G_{21} = 0$ and $G_{34} + G_{43} = 0$. By Theorem 3.5, there exists $c_i, 1 \le i \le 4$, such that $V = \sum_{i=1}^{n} c_i V_i$ is a Lyapunov function for (5.1). The relations between c_i's can be derived from Theorems 3.3 and 3.4: $d^+(1) = 1$ implies $c_2 a_{21} = c_1 a_{13}$, $d^+(2) = 1$ implies $c_3 a_{32} = c_2 a_{21}$, and $d^-(4) = 1$ implies $c_4 a_{43} = c_3 a_{34}$. Hence, $c_2 = c_1$, $c_3 = \frac{\beta S^* I^*}{\epsilon E^*} c_1$, $c_4 = \frac{\eta R^*}{\gamma I^*} c_3$. Therefore, $\tilde{D} = D_1 + D_2 + \frac{\beta S^* I^*}{\epsilon E^*} D_3 + \frac{\eta R^* \beta S^*}{\gamma \epsilon E^*} D_4$ is a Lyapunov function for (5.1), which is basically the same as the one for the ODE model in [35]. It can be verified that $\{P^*\}$ is the only invariant set in $\text{int}(\Gamma)$ where $\tilde{D}' = 0$; therefore, P^* is GAS in $\text{int}(\Gamma)$ and thus unique. ∎

6. Application to a heterogeneous SIS disease model. Consider a multigroup SIS model:

$$
\begin{aligned}
S_i' &= \Lambda_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j - d_i S_i + \gamma_i I_i, \\
I_i' &= \sum_{j=1}^{n} \beta_{ij} S_i I_j - (d_i + \gamma_i) I_i, \quad i = 1, \ldots, n.
\end{aligned} \tag{6.1}
$$

Let $N_i = S_i + I_i$ denote the total population in the ith group. It follows that $N_i' = \Lambda_i - d_i N_i$, and thus $\lim_{t \to \infty} N_i(t) = \frac{\Lambda_i}{d_i}$. Model (6.1) was first proposed by Lajmanovich and Yorke in [22] as a model for the spread of gonorrhea. Model (6.1) also agrees

with the mean-field reaction rate equations of the SIS disease model proposed by Pastor-Satorras and Vespignani for epidemic spreading in scale-free networks [29, 30].

The feasible region $\Gamma = \{(S_1, I_1, \ldots, S_n, I_n) \in \mathbb{R}^{2n}_+ \mid S_i + I_i \le \frac{\Lambda_i}{d_i}\}$ is positively invariant with respect to (6.1). The DFE $P_0 = (S_1^0, 0, \ldots, S_n^0, 0)$ with $S_i^0 = \frac{\Lambda_i}{d_i}$ always exists in Γ. Following the NGM approach with disease compartments $x = (I_1, \ldots, I_n)^T$ and nondisease compartments $y = (S_1, \ldots, S_n)^T$, define two $n \times n$ matrices $F = [\beta_{ij} S_i^0]$ and $V = \mathrm{diag}\{d_1 + \gamma_1, \ldots, d_n + \gamma_n\}$. Then $\mathcal{R}_0 = \rho(FV^{-1}) = \rho([\frac{\beta_{ij} S_i^0}{d_j + \gamma_j}])$.

THEOREM 6.1. *Assume that contact matrix $[\beta_{ij}]$ is irreducible. Then the sharp threshold property holds for* (6.1).

Proof. It follows from (2.1) and the definition of Γ that

$$f(x, y) = \left(\sum_{j=1}^{n} \beta_{1j} I_j (S_1^0 - S_1), \ldots, \sum_{j=1}^{n} \beta_{nj} I_j (S_n^0 - S_n) \right) \ge 0, \qquad (x, y) \in \Gamma.$$

By Theorem 2.1, $Q = \omega^T V^{-1} x$ is a Lyapunov function for (6.1), where $\omega^T \ge 0$ is the left eigenvector of $V^{-1}F$ corresponding to $\mathcal{R}_0 = \rho(V^{-1}F)$. Since $[\beta_{ij}]$ is irreducible, $V^{-1}F$ is also irreducible. Thus the condition of Theorem 2.2 holds and $\omega^T > 0$. Hence, by Theorem 2.2, P_0 is GAS in Γ if $\mathcal{R}_0 < 1$; if $\mathcal{R}_0 > 1$, then P_0 is unstable and there exists an EE $P^* = (S_1^*, I_1^*, \ldots, S_n^*, I_n^*)$ with coordinates satisfying (6.1) with right-hand sides equal to zero. When $\mathcal{R}_0 = 1$, it can be verified that the largest invariant set in Γ where $Q' = 0$ is the singleton $\{P_0\}$; thus by LaSalle's invariant principle, P_0 is GAS in Γ.

To study the global dynamics of (6.1) when $\mathcal{R}_0 > 1$, it is sufficient to study the global dynamics of the model as $\lim_{t\to\infty} N_i(t) = \frac{\Lambda_i}{d_i}$, namely,

$$I_i' = \sum_{j=1}^{n} \beta_{ij} \left(\frac{\Lambda_i}{d_i} - I_i \right) I_j - (d_i + \gamma_i) I_i, \quad i = 1, \ldots, n. \tag{6.2}$$

Let $D_i = I_i - I_i^* - I_i^* \ln \frac{I_i}{I_i^*}$. Differentiating and using the equilibrium equations give

$$\begin{aligned} D_i' &= -\sum_{j=1}^{n} \beta_{ij} I_j \frac{(I_i - I_i^*)^2}{I_i} + \sum_{j=1}^{n} \beta_{ij} \left(\frac{\Lambda_i}{d_i} - I_i^* \right) I_j^* \left(1 - \frac{I_i}{I_i^*} + \frac{I_j}{I_j^*} - \frac{I_i^* I_j}{I_i I_j^*} \right) \\ &\le \sum_{j=1}^{n} \beta_{ij} \left(\frac{\Lambda_i}{d_i} - I_i^* \right) I_j^* \left(\frac{I_j}{I_j^*} - \ln \frac{I_j}{I_j^*} - \frac{I_i}{I_i^*} + \ln \frac{I_i}{I_i^*} \right) := \sum_{j=1}^{n} a_{ij} G_{ij} \end{aligned}$$

with $a_{ij} = \beta_{ij} (\frac{\Lambda_i}{d_i} - I_i^*) I_j^* \ge 0$ and $G_{ij} = \frac{I_j}{I_j^*} - \ln \frac{I_j}{I_j^*} - \frac{I_i}{I_i^*} + \ln \frac{I_i}{I_i^*}$. Let $H_i = \frac{I_i}{I_i^*} - \ln \frac{I_i}{I_i^*}$; then $G_{ij} = H_j - H_i$. A weighted digraph $\mathcal{G}$ can be constructed to associate with the weight matrix $A = [a_{ij}]$. Notice that along any directed cycle $\mathcal{C}$ of $(\mathcal{G}, A)$,

$$\sum_{(s,r) \in \mathcal{E}(\mathcal{C})} G_{rs} = \sum_{(s,r) \in \mathcal{E}(\mathcal{C})} (H_s - H_r) = 0.$$

Since all assumptions of Theorem 3.5 hold, let c_i be as given in Proposition 3.1; then by Theorem 3.5, $D = \sum_{i=1}^{n} c_i D_i$ is a Lyapunov function for (6.2). Using this Lyapunov function, the irreducibility of $[\beta_{ij}]$, and LaSalle's invariance principle, it can be proved that $\{(I_1^*, \ldots, I_n^*)\}$ is the largest invariant set for (6.2), and thus if $\mathcal{R}_0 > 1$, then the positive equilibrium $(I_1^*, \ldots, I_n^*)$ is GAS for (6.2). As a consequence, P^* is GAS in $\mathrm{int}(\Gamma)$ for (6.1). ∎

The application of the Lyapunov method used here is different from the one used in [22]. For the proof in [22], two Lyapunov functions are constructed, while the graph-theoretic method allows us to construct a single Lyapunov function and simplify verification of the nonincreasing property. Knowledge of which β_{ij} are nonzero would enable explicit calculation of c_i in a particular example. Note that Lyapunov functions have been previously constructed in [11, 12] using the graph-theoretic method for multigroup SIR/SEIR epidemic models, but (to the best of our knowledge) this is the first time this method has been used for a multigroup SIS model. Comparison arguments can also be used to prove the global stability of the EE for (6.1); see [39] for more details. We refer the readers to the survey paper [18] for general methods in proving global stability of disease models.

7. Application to a multistage cholera model. In this section we apply our two methods to investigate the global dynamics of a new multistage cholera model. Our new model generalizes the multistage model for waterborne diseases in [33, model (A.1)] by including different pathogen compartments to distinguish the infectivity and removal rate of the pathogen shed from different infected stages. See section 1 for background on cholera disease and other cholera models. Let $S, I_i, 1 \le i \le n, R$ denote the number of individuals that are in the susceptible compartment, the ith infected compartment, and the removed compartment, respectively. Let W_i denote the number of pathogen shed by individuals in I_i. Susceptible individuals can be infected either by contacting infectious individuals (direct transmission) or by ingesting contaminated water (indirect transmission). All newly infected individuals first enter the stage I_1, then enter I_2 and so on; see Figure 7.1 for the flow diagram of this model. As in [33, (A.1)], mass action incidence is assumed; that is, transmission is given by

$$\sum_{i=1}^{n} \beta_i S I_i + \sum_{i=1}^{n} \lambda_i S W_i = \sum_{i=1}^{n} S(\beta_i I_i + \lambda_i W_i),$$

where $\beta_i, \lambda_i > 0$ are the direct and indirect transmission contact rate per individual, respectively. A multistage cholera model can be formulated as the following system of $2n+1$ ODEs:

$$\begin{aligned} S' &= \Lambda - dS - \sum_{i=1}^{n} S(\beta_i I_i + \lambda_i W_i), \\ I_1' &= \sum_{i=1}^{n} S(\beta_i I_i + \lambda_i W_i) - \mu_1 I_1, \\ I_j' &= \gamma_{j-1} I_{j-1} - \mu_j I_j, \quad j = 2, \dots, n, \\ W_i' &= \xi_i I_i - \delta_i W_i, \quad i = 1, \dots, n, \end{aligned} \tag{7.1}$$

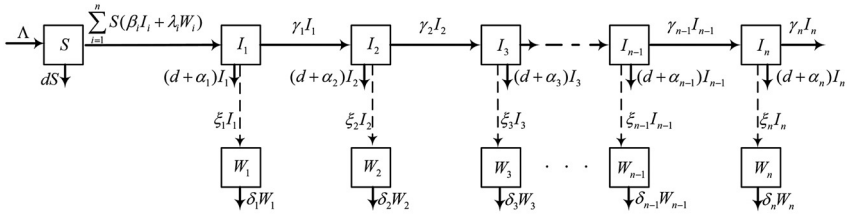

FIG. 7.1. *The flow diagram for the multistage cholera model* (7.1).

with nonnegative initial conditions $S(0), I_i(0), W_i(0)$ for all $1 \le i \le n$. The removed individuals satisfy $R' = \gamma_n I_n - dR$ with $R(0) \ge 0$. Here $\mu_i = d + \gamma_i + \alpha_i$ with $d > 0, \gamma_i > 0, \alpha_i \ge 0$ representing the natural mortality rate, progression rate to the next infection stage of individuals in the ith infection stage, and mortality rate due to the disease, respectively; $\xi_i > 0$ represents the shedding rate of I_i individuals, and $\delta_i > 0$ represents the removal rate of W_i. Note that ξ_i is assumed to be positive; otherwise W_i will decrease exponentially to zero and thus not contribute to the dynamics of (7.1). Model (7.1) becomes the model $(A.1)$ in [33] when all pathogens have the same removal rates δ_i and the same indirect transmission coefficients λ_i.

The feasible region $\Gamma = \{(S, I_1, \dots, I_n, W_1, \dots, W_n) \in \mathbb{R}_+^{2n+1} | \, S + I_1 + \cdots + I_n \le \frac{\Lambda}{d}, W_i \le \frac{\Lambda \xi_i}{d\delta_i}, i = 1, \dots, n\}$ is positively invariant with respect to (7.1). Model (7.1) always admits the DFE $P_0 = (S_0, 0, \dots, 0) \in \Gamma$ with $S_0 = \frac{\Lambda}{d}$, and may admit an EE $P^* = (S^*, I_1^*, \dots, I_n^*, W_1^*, \dots, W_n^*) \in \text{int}(\Gamma)$ with $S^*, I_1^*, \dots, I_n^*, W_1^*, \dots, W_n^*$ satisfying the equilibrium equations given by (7.1) with zero right-hand sides.

Assuming that new infections occur only in the I_1 compartment, the NGM method implies that $F = S_0 e_1[\beta_1, \dots, \beta_n \lambda_1, \dots, \lambda_n]$, where e_1 is the $2n$-vector with first entry equal to 1 and all other entries 0, and

$$V = \begin{bmatrix} V_1 & 0 \\ -V_2 & V_3 \end{bmatrix} \qquad \text{with } V_1 = \begin{bmatrix} \mu_1 & & & & \\ -\gamma_1 & \mu_2 & & & \\ & -\gamma_2 & \ddots & & \\ & & \ddots & \mu_{n-1} & \\ & & & -\gamma_{n-1} & \mu_n \end{bmatrix},$$

$V_2 = \text{diag}\{\xi_1, \dots, \xi_n\}$, and $V_3 = \text{diag}\{\delta_1, \dots, \delta_n\}$. Note that V_1 is a nonsingular M-matrix [1, p. 137], and thus $V_1^{-1} \ge 0$. In fact, the (i, j) entries of V_1^{-1} are given by

$$V_{1,ij}^{-1} = \begin{cases} \frac{1}{\mu_i} & 1 \le i = j \le n, \\ 0 & 1 \le i \le n, 1 \le i < j \le n, \\ \frac{\prod_{k=j}^{i-1} \gamma_k}{\prod_{k=j}^{i} \mu_k} & 1 \le i \le n, 1 \le j < i \le n. \end{cases}$$

As a consequence, $V^{-1} = \begin{bmatrix} V_1^{-1} & 0 \\ V_3^{-1} V_2 V_1^{-1} & V_3^{-1} \end{bmatrix} \ge 0$, and thus V is a nonsingular M-matrix. The basic reproduction number $\mathcal{R}_0$ can be calculated as $\mathcal{R}_0 = \rho(FV^{-1})$. Since F has rank 1,

$$\mathcal{R}_0 = \frac{S_0}{\mu_1}\left(\beta_1 + \frac{\lambda_1 \xi_1}{\delta}\right) + \frac{S_0 \gamma_1}{\mu_1 \mu_2}\left(\beta_2 + \frac{\lambda_2 \xi_2}{\delta_2}\right) + \cdots + \frac{S_0 \gamma_1 \cdots \gamma_{n-1}}{\mu_1 \cdots \mu_n}\left(\beta_n + \frac{\lambda_n \xi_n}{\delta_n}\right). \tag{7.2}$$

The first term inside each bracket represents the contribution from direct transmission, whereas the second term represents the contribution from indirect transmission.

THEOREM 7.1. *Let $\mathcal{R}_0$ be as defined in* (7.2). *Then the sharp threshold property holds for model* (7.1).

Proof. Let $x = (I_1, \dots, I_n, W_1, \dots, W_n)^T$ be the vector whose entries correspond to disease compartments in model (7.1); then it follows that $x' = (F - V)x - f(x, S)$ with $f(x, S) = (\sum_{i=1}^n (S_0 - S)(\beta_i I_i + \lambda_i W_i), 0, \dots, 0) \ge 0$. Since $V^{-1}F$ is irreducible, then by Theorem 2.2, P_0 is GAS in Γ if $\mathcal{R}_0 < 1$, whereas if $\mathcal{R}_0 > 1$, then P_0 is unstable and there exists at least one EE P^* whose coordinates satisfy the equilibrium equations of (7.1). When $\mathcal{R}_0 = 1$, it can be shown as in the proof of Theorem 4.1 that P_0 is GAS in Γ.

To prove the global stability of P^*, set $D_1 = S - S^* - S^* \ln \frac{S}{S^*} + I_1 - I_1^* - I_1^* \ln \frac{I_1}{I_1^*}$, $D_j = I_j - I_j^* - I_j^* \ln \frac{I_j}{I_j^*}$ for $j = 2, \ldots, n$, and $D_{n+i} = W_i - W_i^* - W_i^* \ln \frac{W_i}{W_i^*}$ for $i = 1, \ldots, n$. Differentiating along (7.1) and using the equilibrium equations give

$$\begin{aligned}
D_1' &= \frac{S - S^*}{S}\left(dS^* + \sum_{i=1}^n S^*(\beta_i I_i^* + \lambda_i W_i^*) - dS - \sum_{i=1}^n S(\beta_i I_i + \lambda_i W_i)\right) \\
&\quad + \frac{I_1 - I_1^*}{I_1}\left(\sum_{i=1}^n S(\beta_i I_i + \lambda_i W_i) - \sum_{i=1}^n \frac{S^* I_1}{I_1^*}(\beta_i I_i^* + \lambda_i W_i^*)\right) \\
&= -d\frac{(S - S^*)^2}{S} + \sum_{i=1}^n \beta_i S^* I_i^* \left(2 - \frac{S^*}{S} + \frac{I_i}{I_i^*} - \frac{S I_i I_1^*}{S^* I_i^* I_1} - \frac{I_1}{I_1^*}\right) \\
&\quad + \sum_{i=1}^n \lambda_i S^* W_i^* \left(2 - \frac{S^*}{S} + \frac{W_i}{W_i^*} - \frac{S W_i I_1^*}{S^* W_i^* I_1} - \frac{I_1}{I_1^*}\right) \\
&\le \sum_{i=1}^n \beta_i S^* I_i^* \left(\frac{I_i}{I_i^*} - \frac{I_1}{I_1^*} - \ln\frac{I_i}{I_i^*} + \ln\frac{I_1}{I_1^*}\right) \\
&\quad + \sum_{i=1}^n \lambda_i S^* W_i^* \left(\frac{W_i}{W_i^*} - \frac{I_1}{I_1^*} - \ln\frac{W_i}{W_i^*} + \ln\frac{I_1}{I_1^*}\right) \\
&=: \sum_{k=2}^{2n+1} a_{1k} G_{1k} \qquad \text{with } a_{1,i} = \beta_i S^* I_i^*,\ a_{1,n+i} = \lambda S^* W_i^*,\ i = 1, \ldots, n, \\
D_j' &= \frac{I_j - I_j^*}{I_j}\left(\gamma_{j-1} I_{j-1} - \gamma_{j-1} I_{j-1}^* \frac{I_j}{I_j^*}\right) \\
&= \gamma_{j-1} I_{j-1}^* \left(\frac{I_{j-1}}{I_{j-1}^*} - \frac{I_j^* I_{j-1}}{I_j I_{j-1}^*} - \frac{I_j}{I_j^*} + 1\right) \\
&\le \gamma_{j-1} I_{j-1}^* \left(\frac{I_{j-1}}{I_{j-1}^*} - \ln\frac{I_{j-1}}{I_{j-1}^*} - \frac{I_j}{I_j^*} + \ln\frac{I_j}{I_j^*}\right) \\
&=: a_{j,j-1} G_{j,j-1} \qquad \text{with } a_{j,j-1} = \gamma_{j-1} I_{j-1}^*,\ j = 2, \ldots, n,
\end{aligned}$$

and

$$\begin{aligned}
D_{n+i}' &= \xi_i I_i^* \left(\frac{I_i}{I_i^*} - \frac{I_i W_i^*}{I_i^* W_i} - \frac{W_i}{W_i^*} + 1\right) \\
&\le \xi_i I_i^* \left(\frac{I_i}{I_i^*} - \ln\frac{I_i}{I_i^*} - \frac{W_i}{W_i^*} + \ln\frac{W_i}{W_i^*}\right) \\
&=: a_{n+i,i} G_{n+i,i} \qquad \text{with } a_{n+i,i} = \xi_i I_i^*,\ i = 1, \ldots, n.
\end{aligned}$$

Hence assumption (1) of Theorem 3.5 holds. To verify assumption (2) of the theorem, define the weighted digraph $(\mathcal{G}, A)$ associated with the weight matrix $A = [a_{ij}]$ with $a_{ij} > 0$ as defined above and all other $a_{ij} = 0$; see Figure 7.2. In $(\mathcal{G}, A)$, there are two kinds of cycles: cycles involving direct transmission and cycles involving indirect transmission. For each cycle, assumption (2) of Theorem 3.5 can be verified. Therefore, by Theorem 3.5, $D = \sum_{i=1}^n c_i D_i$ is a Lyapunov function for (7.1). Specifically, Theorems 3.3 and 3.4 give $c_{n+i} a_{n+i,i} = c_1 a_{1,n+i}$ and $c_j a_{j,j-1} = c_{n+j} a_{n+j,j} + c_1 a_{1j}$

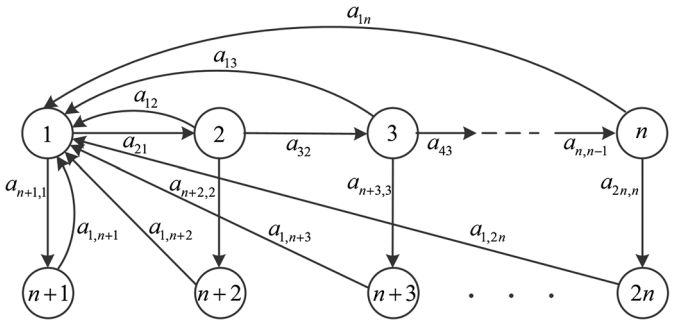

FIG. 7.2. *The weighted digraph* $(\mathcal{G}, A)$ *constructed for the multistage model* (7.1).

for $1 \le i \le n$ and $2 \le j \le n$. Using this Lyapunov function and LaSalle's invariance principle, it follows that P^* is GAS in int(Γ). □

Theorem 7.1 provides a complete global dynamics result for model (7.1) and also for the model (A.1) in [33], which has only one pathogen compartment. This global stability result also extends earlier results in [10] from directly transmitted diseases to waterborne diseases with both direct and indirect transmission.

8. Application to a multigroup cholera model. To incorporate spatial effects, a population can be divided into subpopulations; see, for example, [27]. Each subpopulation is further partitioned into three compartments: susceptible (S_i), infectious (I_i), and removed (R_i). Let W_i denote the number of pathogen shed by individuals in I_i. Then the following multigroup model incorporates both within-group and inter-group direct/indirect transmission and is suitable for investigating the spatial spread of waterborne diseases such as cholera:

$$
\begin{aligned}
S_i' &= \Lambda_i - \sum_{j=1}^{n} \beta_{ij}\phi_i(S_i)\varphi_j(I_j) - \sum_{j=1}^{n} \lambda_{ij}\phi_i(S_i)\psi_j(W_j) - d_i S_i,\\
I_i' &= \sum_{j=1}^{n} \beta_{ij}\phi_i(S_i)\varphi_j(I_j) + \sum_{j=1}^{n} \lambda_{ij}\phi_i(S_i)\psi_j(W_j) - \mu_i I_i,\\
W_i' &= h_i(I_i) - \delta_i W_i, \qquad i = 1, \dots, n,
\end{aligned}
\tag{8.1}
$$

with $\Lambda_i > 0$, $d_i > 0$, $\mu_i = d_i + \gamma_i + \alpha_i > 0$, and $\delta_i > 0$. Model (8.1) includes and provides a proof of the global dynamics for the cholera model in [34], which incorporates 10 groups of host populations corresponding to populations in 10 departments in Haiti and gives numerical simulations for control strategies including vaccination and provision of clean water. Here nonnegative functions $\phi_i, \varphi_i, \psi_i$, and h_i are assumed to be differentiable, and thus solutions to (8.1) with nonnegative initial conditions exist and are unique. Throughout we also assume the following properties of functions $\phi_i, \varphi_i, \psi_i$, h_i, which are biologically reasonable:

(H_1) (nonnegativity) All nonnegative functions $\phi_i, \varphi_i, \psi_i$, h_i only vanish at 0.

(H_2) (monotone) ϕ_i, φ_i, ψ_i, and h_i are monotone nondecreasing.

(H_3) (concavity) $\varphi_i(I_i)/I_i$, $\psi_i(W_i)/W_i$, and $h_i(I_i)/I_i$ are monotone nonincreasing.

Notice that incidence functions and shedding functions that are commonly used in the literature satisfy assumptions (H_1)–(H_3), for example, mass action incidence $\beta_{ij} S_i I_j$ for the direct transmission, saturating incidence $\lambda_{ij} \frac{S_i W_j}{\kappa_j + W_j}$ for the indirect transmission, and linear shedding function $h_i(I_i) = \xi_i I_i$.

Adding the first two equations of (8.1) gives $\frac{d}{dt}(S_i+I_i) \le \Lambda_i - d_i(S_i+I_i)$, which implies that $\limsup_{t\to\infty}(S_i(t)+I_i(t)) \le \frac{\Lambda_i}{d_i}$. Let $H_i = \max_{I_i\in[0,\frac{\Lambda_i}{d_i}]} h_i(I_i)$. It follows from the last equation of (8.1) that $\frac{dW_i}{dt} \le H_i - \delta_i W_i$ and thus $\limsup_{t\to\infty} W_i(t) \le \frac{H_i}{\delta_i}$. Therefore, the feasible region $\Gamma = \{(S_1, I_1, W_1 \ldots, S_n, I_n, W_n) \in \mathbb{R}^{3n}_+ | \, S_i + I_i \le \frac{\Lambda_i}{d_i}, W_i \le \frac{H_i}{\delta_i}, i = 1, \ldots, n\}$ is positively invariant with respect to model (8.1). From assumption (H_1), model (8.1) always admits the DFE $P_0 = (S_1^0, 0, 0, \ldots, S_n^0, 0, 0)$ in Γ, where $S_i^0 = \frac{\Lambda_i}{d_i}$, and P_0 is the unique equilibrium that lies on the boundary of Γ. An EE of (8.1), if one exists, is denoted by $P^* = (S_1^*, I_1^*, W_1^* \ldots, S_n^*, I_n^*, W_n^*)$. Here $S^*, I_1^*, \ldots, I_n^*, W_1^*, W_m^* > 0$ satisfy (8.1) with right-hand sides zero.

Set $p_{ij} = \beta_{ij}\phi_i(S_i^0)\varphi_j'(0)$, $q_{ij} = \lambda_{ij}\phi_i(S_i^0)\psi_j'(0)$, and $r_i = h_i'(0)$. Without loss of generality, assume $r_i > 0$ for all i (otherwise, W_i will decrease exponentially to zero and thus not contribute to the dynamics of (8.1)). Following the NGM approach, define two $2n \times 2n$ matrices $F = \begin{bmatrix} F_1 & F_2 \\ 0 & 0 \end{bmatrix}$ and $V = \begin{bmatrix} V_1 & 0 \\ -V_2 & V_3 \end{bmatrix}$ with $n \times n$ matrices $F_1 = [p_{ij}]$, $F_2 = [q_{ij}]$, $V_1 = \mathrm{diag}\{\mu_1, \ldots, \mu_n\}$, $V_2 = \mathrm{diag}\{\delta_1, \ldots, \delta_n\}$, and $V_3 = \mathrm{diag}\{r_1, \ldots, r_n\}$. Using the NGM approach, the basic reproduction number is defined as $\mathcal{R}_0 = \rho(FV^{-1}) = \rho(F_1V_1^{-1} + F_2V_3^{-1}V_2V_1^{-1})$. Here matrix $F_1V_1^{-1}$ gives the contribution from direct transmission, whereas matrix $F_2V_3^{-1}V_2V_1^{-1}$ gives the contribution from indirect transmission via water.

THEOREM 8.1. *Suppose that assumptions* (H_1)–(H_3) *hold. Assume that matrices* $[\beta_{ij}]$ *and* $[\lambda_{ij}]$ *are irreducible. Then the sharp threshold property holds for* (8.1).

Proof. Let $x = (I_1, \ldots, I_n, W_1, \ldots, W_n)^T$ and $y = (S_1, \ldots, S_n)^T$ be the disease compartment and nondisease compartment vector, respectively. It follows that $x' = (F-V)x - f(x,y)$ with $f(x,y) = (\sum_{j=1}^n (p_{1j}I_1 + q_{1j}W_1 - \beta_{1j}\phi_1(S_1)\varphi_j(I_j) - \lambda_{1j}\phi_1(S_1)\psi_j(W_j)), \ldots, \sum_{j=1}^n (p_{nj}I_n + q_{nj}W_n - \beta_{nj}\phi_n(S_n)\varphi_j(I_j) - \lambda_{nj}\phi_n(S_n)\psi_j(W_j)), 0, \ldots, 0)^T \ge 0$ in Γ due to assumptions (H_2)–(H_3). Since both $[\beta_{ij}]$ and $[\lambda_{ij}]$ are irreducible, the matrix $V^{-1}F$ is also irreducible. By Theorem 2.2, P_0 is GAS in Γ when $\mathcal{R}_0 < 1$, whereas if $\mathcal{R}_0 > 1$, then P_0 is unstable and there exists at least one EE P^*. When $\mathcal{R}_0 = 1$, the largest invariant set where $Q' = 0$ is the singleton $\{P_0\}$; therefore, P_0 is GAS in Γ.

To study the global stability of P^* when $\mathcal{R}_0 > 1$, let $D_i = \int_{S_i^*}^{S_i} \frac{\phi_i(z) - \phi_i(S_i^*)}{\phi_i(z)} dz + I_i - I_i^* - I_i^* \ln \frac{I_i}{I_i^*}$ and $D_{n+i} = W_i - W_i^* - W_i^* \ln \frac{W_i}{W_i^*}$. For $i = 1, \ldots, n$, differentiating and using the equilibrium equations give

$$
\begin{aligned}
D_i' = {} & \left(1 - \frac{\phi_i(S_i^*)}{\phi_i(S_i)}\right)\left\{ d_i(S_i^* - S_i) + \sum_{j=1}^n \beta_{ij}\left(\phi_i(S_i^*)\varphi_j(I_j^*) - \phi_i(S_i)\varphi_j(I_j)\right)\right. \\
& \left. + \sum_{j=1}^n \lambda_{ij}\left(\phi_i(S_i^*)\psi_j(W_j^*) - \phi_i(S_i)\psi_j(W_j)\right)\right\} \\
& + \left(1 - \frac{I_i^*}{I_i}\right)\left\{ \sum_{j=1}^n \beta_{ij}\left(\phi_i(S_i)\varphi_j(I_j) - \phi_i(S_i^*)\varphi_j(I_j^*)\frac{I_i}{I_i^*}\right)\right. \\
& \left. + \sum_{j=1}^n \lambda_{ij}\left(\phi_i(S_i)\psi_j(W_j) - \phi_i(S_i^*)\psi_j(W_j^*)\frac{I_i}{I_i^*}\right)\right\} \\
\le {} & \sum_{j=1}^n \beta_{ij}\phi_i(S_i^*)\varphi_j(I_j^*)\left(2 - \frac{I_i}{I_i^*} - \frac{\phi_i(S_i^*)}{\phi_i(S_i)} - \frac{\phi_i(S_i)\varphi_j(I_j)I_i^*}{\phi_i(S_i^*)\varphi_j(I_j^*)I_i} + \frac{\varphi_j(I_j)}{\varphi_j(I_j^*)}\right)
\end{aligned}
$$

$$
\begin{aligned}
&+\sum_{j=1}^{n}\lambda_{ij}\phi_i(S_i^*)\psi_j(W_j^*)\left(2-\frac{I_i}{I_i^*}-\frac{\phi_i(S_i^*)}{\phi_i(S_i)}-\frac{\phi_i(S_i)\psi_j(W_j)I_i^*}{\phi_i(S_i^*)\psi_j(W_j^*)I_i}+\frac{\psi_j(W_j)}{\psi_j(W_j^*)}\right)\\
&\le \sum_{j=1}^{n}\beta_{ij}\phi_i(S_i^*)\varphi_j(I_j^*)\left\{\left(\frac{\varphi_j(I_j)}{\varphi_j(I_j^*)}-1\right)\left(1-\frac{\varphi_j(I_j^*)I_j}{\varphi_j(I_j)I_j^*}\right)\right.\\
&\quad\left.+\left(\frac{I_j}{I_j^*}-\ln\frac{I_j}{I_j^*}-\frac{I_i}{I_i^*}+\ln\frac{I_i}{I_i^*}\right)\right\}\\
&\quad+\sum_{j=1}^{n}\lambda_{ij}\phi_i(S_i^*)\psi_j(W_j^*)\left\{\left(\frac{\psi_j(W_j)}{\psi_j(W_j^*)}-1\right)\left(1-\frac{\psi_j(W_j^*)W_j}{\psi_j(W_j)W_j^*}\right)\right.\\
&\quad\left.+\left(\frac{W_j}{W_j^*}-\ln\frac{W_j}{W_j^*}-\frac{I_i}{I_i^*}+\ln\frac{I_i}{I_i^*}\right)\right\}\\
&\le \sum_{j=1}^{n}\beta_{ij}\phi_i(S_i^*)\varphi_j(I_j^*)\left(\frac{I_j}{I_j^*}-\ln\frac{I_j}{I_j^*}-\frac{I_i}{I_i^*}+\ln\frac{I_i}{I_i^*}\right)\\
&\quad+\sum_{j=1}^{n}\lambda_{ij}\phi_i(S_i^*)\psi_j(W_j^*)\left(\frac{W_j}{W_j^*}-\ln\frac{W_j}{W_j^*}-\frac{I_i}{I_i^*}+\ln\frac{I_i}{I_i^*}\right)\\
&=:\sum_{j=1}^{2n}a_{ij}G_{ij}\qquad\text{with}\quad a_{ij}=\begin{cases}\beta_{ij}\phi_i(S_i^*)\varphi_j(I_j^*) & 1\le j\le n,\\ \lambda_{ij}\phi_i(S_i^*)\psi_j(W_j^*) & n+1\le j\le 2n.\end{cases}
\end{aligned}
$$

The first and third inequalities follow from assumptions (H_2)–(H_3), respectively, and the second inequality uses the technique in Construction 1 of section 4. Similarly,

$$
\begin{aligned}
D'_{n+i}&=h_i(I_i^*)\left(1-\frac{W_i}{W_i^*}+\frac{h_i(I_i)}{h_i(I_i^*)}-\frac{h_i(I_i)W_i^*}{h_i(I_i^*)W_i}\right)\\
&\le h_i(I_i^*)\left\{\left(\frac{h_i(I_i)}{h_i(I_i^*)}-1\right)\left(1-\frac{h_i(I_i^*)I_i}{h_i(I_i)I_i^*}\right)+\left(\frac{I_i}{I_i^*}-\ln\frac{I_i}{I_i^*}-\frac{W_i}{W_i^*}+\ln\frac{W_i}{W_i^*}\right)\right\}\\
&\le h_i(I_i^*)\left(\frac{I_i}{I_i^*}-\ln\frac{I_i}{I_i^*}-\frac{W_i}{W_i^*}+\ln\frac{W_i}{W_i^*}\right)=:a_{n+i,i}G_{n+i,i}
\end{aligned}
$$

with $a_{n+i,i}=h_i(I_i^*)$. Let $A=[a_{ij}]$ with $a_{ij}>0$ as defined above and otherwise zero. A weighted digraph $(\mathcal{G},A)$ can be constructed such that A is the weight matrix; see Figure 8.1. Let c_i be as given in Proposition 3.1 with $(\mathcal{G},A)$. Since $d^-(n+i)=1$ for each i (see Figure 8.1), by Theorem 3.4, $c_{n+i}=\sum_{j=1}^{n}c_ja_{j,n+i}/a_{n+i,i}$. Thus,

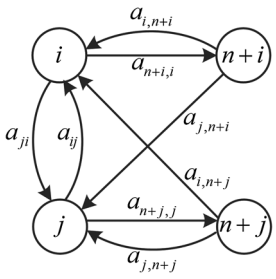

FIG. 8.1. *The weighted digraph* $(\mathcal{G},A)$ *constructed for model* (8.1) *with two groups.*

$$D = \sum_{i=1}^{n} c_i D_i + \sum_{i=1}^{n}\sum_{j=1}^{n} c_j a_{j,n+i} \frac{D_{n+i}}{a_{n+i,i}}.$$

Since $G_{i,n+j} + G_{n+j,j} = \frac{I_j}{I_j^*} - \ln \frac{I_j}{I_j^*} - \frac{I_i}{I_i^*} + \ln \frac{I_i}{I_i^*} = G_{ij}$, it follows that

$$\begin{aligned} D' &\le \sum_{i=1}^{n}\sum_{j=1}^{n} c_i a_{ij} G_{ij} + \sum_{i=1}^{n}\sum_{j=1}^{n} c_i a_{i,n+j} G_{i,n+j} + \sum_{i=1}^{n}\sum_{j=1}^{n} c_j a_{j,n+i} G_{n+i,i} \\ &= \sum_{i=1}^{n}\sum_{j=1}^{n} c_i a_{ij} G_{ij} + \sum_{i=1}^{n}\sum_{j=1}^{n} c_i a_{i,n+j} (G_{i,n+j} + G_{n+j,j}) \\ &= \sum_{i=1}^{n}\sum_{j=1}^{n} c_i (a_{ij} + a_{i,n+j}) \left(\frac{I_j}{I_j^*} - \ln \frac{I_j}{I_j^*} - \frac{I_i}{I_i^*} + \ln \frac{I_i}{I_i^*} \right). \end{aligned} \tag{8.2}$$

Let $\tilde{c}_i, i = 1, \ldots, n$, be as given in Proposition 3.1 with $(\tilde{\mathcal{G}}, \tilde{A})$, where the entry of the $n \times n$ matrix $\tilde{A} = [\tilde{a}_{ij}]$ is defined as $\tilde{a}_{ij} = a_{ij} + a_{i,n+j}$. Let $\tilde{c}_{n+i} = \sum_{j=1}^{n} \tilde{c}_j \frac{a_{j,n+i}}{a_{n+i,i}}$. Now we claim that $\tilde{D} = \sum_{i=1}^{n} \tilde{c}_i D_i + \sum_{i=1}^{n} \tilde{c}_{n+i} D_{n+i}$ is a Lyapunov function for (8.1). In fact, replacing all c_i by $\tilde{c}_i$ in the calculation of (8.2) yields

$$\tilde{D}' \le \sum_{i=1}^{n}\sum_{j=1}^{n} c_i \tilde{a}_{ij} \left(\frac{I_j}{I_j^*} - \ln \frac{I_j}{I_j^*} - \frac{I_i}{I_i^*} + \ln \frac{I_i}{I_i^*} \right) = 0.$$

Here the last equality follows from Theorem 3.3. It can be verified that the largest invariant set where $\tilde{D}' = 0$ is the singleton $\{P^*\}$. Therefore, by LaSalle's invariance principle, P^* is GAS in int(Γ) and thus unique. ∎

Theorem 8.1 provides a complete global dynamic analysis for (8.1) and uses the graph-theoretic method in a different way from that in the proof of Theorem 7.1. Here the construction of the Lyapunov function $\tilde{D}$ relies on the application of the new combinatorial identity established in section 3.

9. Discussion. Two systematic methods (the matrix-theoretic method and the graph-theoretic method) of construction for Lyapunov functions were developed to investigate the global stability of the disease-free and endemic equilibria for disease models and were applied to several examples. These include models in which homogeneous mixing is assumed, such as the SIR model (section 4) and the SEIR model with relapse (section 5), and those incorporating different kinds of heterogeneity, such as multigroup models (sections 6 and 8) and the multistage model (section 7). For all these examples, the sharp threshold property was completely established using these two methods, showing that the basic reproduction number $\mathcal{R}_0$ is a sharp threshold.

Although the sharp threshold property holds for many disease models including those in this paper, there are disease models for which such a result does not hold. For example, the first part of the result fails when backward bifurcation happens; see, for example, [7, 14]. Specifically, when $\mathcal{R}_0 < 1$, there may exist two EEs: one is stable, while the other is unstable. In this situation, the DFE is only locally asymptotically stable but not globally asymptotically stable. On the other hand, when $\mathcal{R}_0 > 1$, the EE may lose its stability due to Hopf bifurcation, and disease oscillations occur; see, for example, [19].

For models in which the sharp threshold property holds, including those considered in sections 4–8, sensitivity analysis of $\mathcal{R}_0$ can be used with knowledge of disease data to quantify the effects of control strategies. For example, for the multigroup

cholera model (section 8), vaccination would reduce the transmission coefficients (i.e., β_{ij}, λ_{ij}), and sanitation and/or provision of clean water would reduce indirect transmission (λ_{ij}) and shedding $h_i(I_i)$. We expect that our two methods can also be applied to models for other infectious diseases that incorporate control and intervention strategies.

Acknowledgments. Both authors thank Dr. Michael Y. Li for helpful discussions. Dr. Junling Ma for providing a preprint of [34], and the anonymous reviewers for helpful suggestions.

REFERENCES

[1] A. Berman and R. J. Plemmons, *Nonnegative Matrices in the Mathematical Sciences*, Academic Press, New York, 1979.
[2] N. P. Bhatia and G. P. Szegö, *Dynamical Systems: Stability Theory and Applications*, Lecture Notes in Math. 35, Springer, Berlin, 1967.
[3] S. Blower, T. C. Porco, and G. Darby, *Predicting and preventing the emergence of antiviral drug resistance in HSV-2*, Nat. Med., 4 (1998), pp. 673–678.
[4] C. Castillo-Chavez, Z. Feng, and W. Huang, *On the computation of R_0 and its role on global stability*, in Mathematical Approaches for Emerging and Reemerging Infectious Diseases: Models, Methods and Theory, C. Castillo-Chavez, S. Blower, P. van den Driessche, D. Kirschner, and A.-A. Yakubu, eds., Springer, Berlin, 2002, pp. 229–250.
[5] C. T. Codeço, *Endemic and epidemic dynamics of cholera: The role of the aquatic reservoir*, BMC Infectious Diseases, 1 (2001).
[6] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*, J. Math. Biol., 28 (1990), pp. 365–382.
[7] J. Dushoff, W. Huang, and C. Castillo-Chavez, *Backwards bifurcations and catastrophe in simple models of fatal diseases*, J. Math. Biol., 36 (1998), pp. 227–248.
[8] A. Fall, A. Iggidr, G. Sallet, and J. J. Tewa, *Epidemiological models and Lyapunov functions*, Math. Model. Nat. Phenom., 2 (2007), pp. 55–73.
[9] H. I. Freedman, S. Ruan, and M. Tang, *Uniform persistence and flows near a closed positively invariant set*, J. Dynam. Differential Equations, 6 (1994), pp. 583–600.
[10] H. Guo and M. Y. Li, *Global dynamics of a staged progression model for infectious diseases*, Math. Biosci. Eng., 3 (2006), pp. 513–525.
[11] H. Guo, M. Y. Li, and Z. Shuai, *Global stability of the endemic equilibrium of multigroup SIR epidemic models*, Canad. Appl. Math. Quart., 14 (2006), pp. 259–284.
[12] H. Guo, M. Y. Li, and Z. Shuai, *A graph-theoretic approach to the method of global Lyapunov functions*, Proc. Amer. Math. Soc., 136 (2008), pp. 2793–2802.
[13] H. Guo, M. Y. Li, and Z. Shuai, *Global dynamics of a general class of multistage models for infectious diseases*, SIAM J. Appl. Math., 72 (2012), pp. 261–279.
[14] K. P. Hadeler and P. van den Driessche, *Backward bifurcation in epidemic control*, Math. Biosci., 146 (1997), pp. 15–35.
[15] J. K. Hale, *Ordinary Differential Equations*, 2nd ed., Krieger, Malabar, FL, 1980.
[16] F. Harary, *Graph Theory*, Addison-Wesley, Reading, MA, 1969.
[17] D. M. Hartley, J. G. Morris, Jr., and D. L. Smith, *Hyperinfectivity: A critical element in the ability of V. cholerae to cause epidemics?* PLOS Med., 3 (2006), pp. 63–69.
[18] H. W. Hethcote, *The mathematics of infectious diseases*, SIAM Rev., 42 (2000), pp. 599–653.
[19] H. W. Hethcote, H. W. Stech, and P. van den Driessche, *Nonlinear oscillations in epidemic models*, SIAM J. Appl. Math., 40 (1981), pp. 1–9.
[20] S.-B. Hsu, *A survey of constructing Lyapunov functions for mathematical models in population biology*, Taiwanese J. Math., 9 (2005), pp. 151–173.
[21] A. Korobeinikov and P. K. Maini, *A Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence*, Math. Biosci. Eng., 1 (2004), pp. 57–60.
[22] A. Lajmanovich and J. A. Yorke, *A deterministic model for gonorrhea in a nonhomogeneous population*, Math. Biosci., 28 (1976), pp. 221–236.
[23] J. P. LaSalle, *The Stability of Dynamical Systems*, Regional Conf. Ser. Appl. Math., SIAM, Philadelphia, 1976.

[24] M. Y. Li, J. R. Graef, L. Wang, and J. Karsai, *Global dynamics of a SEIR model with varying total population size*, Math. Biosci., 160 (1999), pp. 191–213.
[25] M. Y. Li and Z. Shuai, *Global stability of an epidemic model in a patchy environment*, Canad. Appl. Math. Quart., 17 (2009), pp. 175–187.
[26] M. Y. Li and Z. Shuai, *Global-stability problems for coupled systems of differential equations on networks*, J. Differential Equations, 248 (2010), pp. 1–20.
[27] A. L. Lloyd and R. M. May, *Spatial heterogeneity in epidemic models*, J. Theoret. Biol., 179 (1996), pp. 1–11.
[28] J. Mena-Lorca, H. W. Hethcote, *Dynamic models of infectious diseases as regulators of population sizes*, J. Math. Biol., 30 (1992), pp. 693–716.
[29] R. Pastor-Satorras and A. Vespignani, *Epidemic spreading in scale-free networks*, Phys. Rev. Lett., 86 (2001), pp. 3200–3203.
[30] R. Pastor-Satorras and A. Vespignani, *Epidemic dynamics in finite size scale-free networks*, Phys. Rev. E, 65 (2002), 035108.
[31] Z. Shuai and P. van den Driessche, *Global dynamics of cholera models with differential infectivity*, Math. Biosci., 234 (2011), pp. 118–126.
[32] H. L. Smith and P. Waltman, *The Theory of the Chemostat: Dynamics of Microbial Competition*, Cambridge University Press, Cambridge, UK, 1995.
[33] J. H. Tien and D. J. D. Earn, *Multiple transmission pathways and disease dynamics in a waterborne pathogen model*, Bull. Math. Biol., 72 (2010), pp. 1506–1533.
[34] A. R. Tuite, J. H. Tien, M. Eisenberg, D. J. D. Earn, J. Ma, and D. N. Fisman, *Cholera epidemic in Haiti,* 2010*: Using a transmission model to explain spatial spread of disease and identify optimal control interventions*, Ann. Internal Med., 154 (2011), pp. 593–601.
[35] P. van den Driessche, L. Wang, and X. Zou, *Modeling diseases with latency and relapse*, Math. Biosci. Eng., 4 (2007), pp. 205–219.
[36] P. van den Driessche and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartments models of disease transmission*, Math. Biosci., 180 (2002), pp. 29–48.
[37] P. van den Driessche and J. Watmough, *Further notes on the basic reproduction number*, in Mathematical Epidemiology, F. Brauer, P. van den Driessche, and J. Wu, eds., Lecture Notes in Math. 1945, Springer, Berlin, 2008, pp. 159–178.
[38] C. Vargas De León, *Constructions of Lyapunov functions for classics SIS, SIR and SIRS epidemic model with variable population size*, Rev. Electrón. Foro Red Mat., 26 (2009), pp. 1–12.
[39] L. Wang and G.-Z. Dai, *Global stability of virus spreading in complex heterogeneous networks*, SIAM J. Appl. Math., 68 (2008), pp. 1495–1502.
[40] D. B. West, *Introduction to Graph Theory*, Prentice-Hall, Upper Saddle River, NJ, 1996.