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IMPACT OF HETEROGENEITY ON THE DYNAMICS OF AN SEIR EPIDEMIC MODEL

Zhisheng Shuai and P. van den Driessche

Department of Mathematics and Statistics, University of Victoria
Victoria, B.C., V8W 3R4, Canada

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Abstract. An SEIR epidemic model with an arbitrarily distributed exposed stage is revisited to study the impact of heterogeneity on the spread of infectious diseases. The heterogeneity may come from age or behavior and disease stages, resulting in multi-group and multi-stage models, respectively. For each model, Lyapunov functionals are used to show that the basic reproduction number $\mathcal{R}_0$ gives a sharp threshold. If $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable and the disease dies out from all groups or stages. If $\mathcal{R}_0 > 1$, then the disease persists in all groups or stages, and the endemic equilibrium is globally asymptotically stable.

1. **Introduction.** Heterogeneity exists in many aspects of disease transmission processes [1, 2, 12, 33], for example, heterogeneous spatial distribution of host populations, heterogeneous susceptibility among age groups, heterogeneous social behavior among groups for sexually transmitted diseases, and multi-hosts for many diseases such as West Nile virus and Avian influenza. Different types of heterogeneous epidemic models and attempts to understand the impact of heterogeneity on the disease transmission have appeared in the literature; see, for example, [19, 22, 33, 37]. It has been found that heterogeneity sometimes does not alter the dynamical structure of epidemic models, while sometimes it produces more complicated dynamical behavior than found in homogeneous models. For example, if the basic reproduction number $\mathcal{R}_0$ completely determines the dynamics of homogeneous epidemic models in which the disease eventually either dies out or persists at a positive level, then the associated heterogeneous models might have the same dichotomy: there exists either a globally attracting disease-free equilibrium or a globally attracting endemic equilibrium. On the other hand, if the original homogeneous model has rich dynamical behavior such as oscillations, then the associated heterogeneous models have much richer dynamics such as a switch of oscillations from one group to the other [41].

In Section 2, we formulate a basic susceptible-exposed-infectious-removed (SEIR) epidemic model in which an arbitrarily distributed exposed stage is assumed. Using this basic model as a building block, we consider two different heterogeneous models: multi-group models for heterogeneity in a host population (Section 3) and multi-stage models for heterogeneity of infectious individuals (Section 4). For both

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models, we establish their global dynamics and demonstrate that the heterogeneity does not alter the dynamical structure of the SEIR model with an arbitrarily distributed exposed stage.

Our proof for the global stability of endemic equilibria utilizes global Lyapunov functionals that are motivated by the work in [20, 21, 34, 35] and the graph-theoretic approach for large-scale systems developed in [10, 11, 29]. This graph-theoretic approach, based on Kirchhoff's Matrix Tree Theorem, has previously only been applied to one study of delay epidemic models, namely, the multi-group model in [30]. We demonstrate that, for the two types of heterogeneous delay epidemic models considered, this graph-theoretic approach can be successfully applied by choosing an appropriate weight matrix.

2. **Basic model.** Since our main goal is to investigate the impact of heterogeneity on dynamics of epidemic models, we start with a relatively simple model and then build on this to formulate and analyze different heterogeneous models. We now formulate a simple epidemic model for a homogeneous population that includes an arbitrarily distributed exposed stage, while two different heterogeneous models will be formulated in Sections 3 and 4. Let $S(t), E(t), I(t)$, and $R(t)$ be the numbers of individuals in the susceptible, exposed, infectious, and removed compartments, respectively, with the total population $N(t) = S(t) + E(t) + I(t) + R(t)$. Suppose that $A > 0$ represents the constant recruitment, $m > 0$ represents the natural mortality rate, and $\alpha \geq 0$ represents the mortality rate due to the disease. The rate of change of $N(t)$ is

$$N'(t) = A - mN(t) - \alpha I(t). \tag{2.1}$$

Assuming mass action for the disease transmission and letting $\beta > 0$ denote the effective contact rate, the rate of change of $S(t)$ is

$$S'(t) = A - \beta S(t)I(t) - mS(t). \tag{2.2}$$

Let $P(t)$ denote the fraction of exposed individuals remaining in the exposed class t units after entering the exposed class. Throughout we assume the following properties of $P(t)$, which are biologically reasonable.

(*H*) $P(t)$ is nonincreasing, piecewise continuous with possibly finitely many jumps, satisfies $P(0) = 1$ and $\lim_{t\to\infty} P(t) = 0$, and the mean latent period $\omega = \int_0^\infty P(u)du$ is finite.

The number of exposed individuals can be expressed by the integral

$$E(t) = E(0)e^{-mt} + \int_0^t \beta S(u)I(u)e^{-m(t-u)}P(t-u)\,du, \tag{2.3}$$

where $E(0)$ is the number exposed at $t = 0$. Differentiating (2.3) gives

$$E'(t) = \beta S(t)I(t) - mE(t) + \int_0^t \beta S(u)I(u)e^{-m(t-u)}d_tP(t-u)\,du. \tag{2.4}$$

Here the integral is in the Riemann-Stieltjes sense, and $d_tP(t-u) = \frac{dP(t-u)}{dt}$ whenever the derivative exists. It can be verified that $E(t)$ given in (2.3) is the unique solution of (2.4) with the initial condition $E(0)$. Assuming that the recovery rate is γ, $\gamma \geq 0$, the rate of change of $I(t)$ is

$$I'(t) = -\int_0^t \beta S(u)I(u)e^{-m(t-u)}d_tP(t-u)\,du - (m+\alpha+\gamma)I(t). \tag{2.5}$$

If $\gamma > 0$, then $1/\gamma$ is the average infectious period; whereas if $\gamma = 0$, then there is no removed compartment. Substituting (2.1), (2.2), (2.4), and (2.5) into $R'(t) = N'(t) - S'(t) - E'(t) - I'(t)$ leads to

$$R'(t) = \gamma I(t) - mR(t).$$

Therefore, the epidemic model can be written as the system

$$\begin{aligned} S'(t) &= A - \beta S(t)I(t) - mS(t), \\ E'(t) &= \beta S(t)I(t) - mE(t) + \int_0^t \beta S(u)I(u)e^{-m(t-u)}d_tP(t-u)\,du, \\ I'(t) &= -\int_0^t \beta S(u)I(u)e^{-m(t-u)}d_tP(t-u)\,du - (m+\alpha+\gamma)I(t), \\ R'(t) &= \gamma I(t) - mR(t), \end{aligned} \tag{2.6}$$

with nonnegative initial conditions. Model (2.6) includes as special cases several earlier models, such as the standard SEIR ordinary differential equation (ODE) model [21, 24] and the SEIR model with a discrete delay [17, 39]. Epidemic models such as (2.6) with an arbitrarily distributed exposed stage have been studied in the literature; see, for example, [8, 14, 15]. Recently, a model of this type, but including the possibility of disease relapse, has been proposed in [40, 43] to study the transmission and spread of some infectious disease such as herpes, and its global dynamics have been completely investigated in [31, 40]. The model in [31, 40, 43] can be regarded as a generalization of our model (2.6), and thus the stability results there can be immediately applied to our model (2.6) by setting the relapse rate to zero. We outline some of their results in the following; their proofs and more detailed study can be found in [31, 40].

The existence, uniqueness, and continuity of solutions of system (2.6) follow from the standard theory of Volterra integro-differential equations, see, for example, [36, p.338]. The feasible region

$$D = \left\{(S,E,I,R) \in \mathbb{R}^4 \;\middle|\; S,E,I,R \geq 0,\ S+E+I+R \leq \frac{A}{m}\right\}$$

is positively invariant with respect to (2.6). Let $\overset{\circ}{D}$ denote the interior of D. System (2.6) always has a *disease-free equilibrium* (DFE) $P_0 = (S^0, 0, 0, 0)$ in D, where $S^0 = \frac{A}{m}$.

Let

$$Q = -\int_0^\infty e^{-mu}d_uP(u)\,du, \tag{2.7}$$

and note that with a positive mean latent period,

$$0 < Q = 1 - \int_0^\infty mP(u)e^{-mu}\,du < 1.$$

Define the basic reproduction number as

$$\mathcal{R}_0 = \frac{\beta Q S^0}{m+\alpha+\gamma},$$

which completely determines the stability of the DFE. We refer the reader to [3, 7, 40, 42, 43] for biological interpretation of $\mathcal{R}_0$.

Proposition 2.1 (van den Driessche et al. [40], Liu et al. [31]). *The following results hold for system* (2.6).

(1) *If* $\mathcal{R}_0 \leq 1$, *then the DFE is globally asymptotically stable in* D.
(2) *If* $\mathcal{R}_0 > 1$, *then the DFE is unstable.*

In order to study the dynamical behavior of (2.6) when $\mathcal{R}_0 > 1$, the following limiting system (see [36, p.176]) has been studied as a special case in [31]:

$$\begin{aligned} S'(t) &= A - \beta S(t)I(t) - mS(t), \\ E'(t) &= \beta S(t)I(t) - mE(t) + \int_{-\infty}^{t} \beta S(u)I(u)e^{-m(t-u)} d_t P(t-u)\, du, \\ I'(t) &= -\int_{-\infty}^{t} \beta S(u)I(u)e^{-m(t-u)} d_t P(t-u)\, du - (m+\alpha+\gamma)I(t), \\ R'(t) &= \gamma I(t) - mR(t). \end{aligned} \tag{2.8}$$

For any $\kappa \in (0, m)$, define a Banach space of fading memory type (e.g., see [4] and references therein)

$$C_\kappa = \Big\{ \phi \in ((-\infty, 0], \mathbb{R}) \;\Big|\; \phi(s)e^{\kappa s} \text{ is uniformly continuous on } (-\infty, 0], \text{ and } \sup_{s\leq 0} |\phi(s)|e^{\kappa s} < \infty \Big\} \tag{2.9}$$

with norm $||\phi||_\kappa = \sup_{s\leq 0} |\phi(s)|e^{\kappa s}$. For $\psi \in C(\mathbb{R}, \mathbb{R})$ and $t > 0$, let $\psi_t \in C_\kappa$ be such that $\psi_t(s) = \psi(t+s)$, $s \in (-\infty, 0]$. Consider system (2.8) in the phase space

$$X = C_\kappa \times \mathbb{R} \times C_\kappa \times \mathbb{R}. \tag{2.10}$$

Let $E(0), R(0) \geq 0$ and $\phi, \psi \in C_\kappa$ such that $\phi(s) \geq 0, \psi(s) \geq 0$ for all $s \in (-\infty, 0]$. For any solution $(S_t, E(t), I_t, R(t))$ of system (2.8) with initial conditions $(\phi, E(0), \psi, R(0))$, standard theory of functional differential equations [16] implies that $S_t, I_t \in C_\kappa$ for all $t > 0$. The set

$$\Delta = \Big\{ (S(\cdot), E, I(\cdot), R) \in X \;\Big|\; S(s) \geq 0, I(s) \geq 0, s \in (-\infty, 0], E, R \geq 0, S(0) + E + I(0) + R \leq \frac{A}{m} \Big\} \tag{2.11}$$

is positively invariant for system (2.8). Let $\overset{\circ}{\Delta}$ be the interior of Δ.

When $\mathcal{R}_0 > 1$, the limiting system (2.8) has a unique *endemic equilibrium* (EE) $P^* = (S^*, E^*, I^*, R^*)$ in $\overset{\circ}{\Delta}$. Here, $S^* = \frac{S^0}{\mathcal{R}_0} = \frac{m+\alpha+\gamma}{\beta Q} > 0, E^* = (1-Q)(\frac{A}{m} - S^*) > 0$ provided $Q < 1$, $I^* = \frac{m}{\beta}(\mathcal{R}_0 - 1) > 0$, and $R^* = \frac{\gamma}{\beta}(\mathcal{R}_0 - 1) > 0$. The global stability of the EE is established by constructing a Lyapunov functional, giving the following result.

Proposition 2.2 (Liu et al. [31]). *If* $\mathcal{R}_0 > 1$, *then the EE of system* (2.8) *is globally asymptotically stable in* $\overset{\circ}{\Delta}$. *As a consequence, all solutions of system* (2.6) *starting in* $\overset{\circ}{D}$ *approach the EE of* (2.8) *if* $\mathcal{R}_0 > 1$.

When $P(t) = e^{-\epsilon t}$ with $\epsilon > 0$, system (2.6) becomes an ODE model, for which the global dynamics have been established by Li and Muldowney [24] using the theory of compound matrices and by Korobeinikov and Maini [21] using the method of Lyapunov functions. When $P(t)$ is a step function, system (2.6) becomes a

delay differential equation model [39]. Propositions 2.1 and 2.2 establish the global dynamics of the model (2.6) with an arbitrarily exposed stage.

3. **Multi-group model.** System (2.6) assumes homogeneous mixing of individuals in the host population, and this is certainly unrealistically simple. Heterogeneity in the host population can result from different contact patterns such as those among children and adults for childhood diseases (e.g., measles and mumps), or different behavior (e.g., numbers of sexual partners for some sexually transmitted infections). In this section, we extend model (2.6) to the situation in which the population is divided into n groups according to different contact patterns or differential infectivity. Each group is further partitioned into four compartments: S_i, E_i, I_i, and R_i, denoting the number of susceptible, exposed, infectious, and removed individuals in group i, respectively. For $1 \le i, j \le n$, the disease effective contact rate between compartments S_i and I_j is denoted by β_{ij}, so that the new infection occurring in the i-th group is given by

$$\sum_{j=1}^{n} \beta_{ij} S_i(t) I_j(t).$$

Hence, the n-group model associated with (2.6) can be written as the following system with the stated assumptions:

$$\begin{aligned}
S_i'(t) &= A_i - \sum_{j=1}^{n} \beta_{ij} S_i(t) I_j(t) - m_i S_i(t),\\
E_i'(t) &= \sum_{j=1}^{n} \beta_{ij} S_i(t) I_j(t) - m_i E_i(t) + \sum_{j=1}^{n} \int_0^t \beta_{ij} S_i(u) I_j(u) e^{-m_i(t-u)} d_t P_i(t-u)\, du,\\
I_i'(t) &= -\sum_{j=1}^{n} \int_0^t \beta_{ij} S_i(u) I_j(u) e^{-m_i(t-u)} d_t P_i(t-u)\, du - (m_i + \alpha_i + \gamma_i) I_i(t),\\
R_i'(t) &= \gamma_i I_i(t) - m_i R_i(t), \qquad i = 1, 2, \ldots, n.
\end{aligned} \tag{3.1}$$

Assume that $A_i > 0, m_i > 0, \gamma_i \ge 0, \alpha_i \ge 0$, and each P_i satisfies assumption (H) in Section 2. The contact matrix $B = (\beta_{ij})$ is assumed to be nonnegative and irreducible; thus any two groups i and j have a direct or indirect route of transmission.

Model (3.1) has been previously seen in [44]. In the special case when $P_i, 1 \le i \le n$, are gamma distributions, the global dynamics have been established in [44] by using a linear chain trick. However, the linear chain trick fails to apply to model (3.1) with general distributions P_i. In this section we demonstrate that the graph-theoretic approach developed in [10, 11, 29] can be successfully applied to construct suitable Lyapunov functionals, and thus prove the global stability of the endemic equilibrium for model (3.1) with general distributions P_i. This model differs from the multi-group delay epidemic model in [30] in the delay terms: arbitrarily distributed exposed stages are modeled in (3.1) while age structure is modeled in [30]. Model (3.1) can also be applied to study heterogeneous spatial distribution of the host population with implicit migration among groups; see, for example, [33].

For model (3.1) and the other heterogeneous model in Section 4, the existence, uniqueness, and continuity of solutions follow as for the basic model (2.6) from [36, p.338]. It can be easily verified that every solution of (3.1) with nonnegative initial conditions remain nonnegative. From the first equation of (3.1), it follows that

$S_i'(t) \le A_i - m_i S_i(t)$, and thus $\limsup_{t\to\infty} S_i(t) \le \frac{A_i}{m_i}$ for all i. Adding the four equations of (3.1) together yields

$$(S_i(t) + E_i(t) + I_i(t) + R_i(t))' \le A_i - m_i(S_i(t) + E_i(t) + I_i(t) + R_i(t)),$$

which implies that, for each i, $\limsup_{t\to\infty}(S_i(t) + E_i(t) + I_i(t) + R_i(t)) \le \frac{A_i}{m_i}$. Therefore, the feasible region

$$D_g = \Big\{(S_1, E_1, I_1, R_1, \dots, S_n, E_n, I_n, R_n) \in \mathbb{R}^{4n} \;\Big|\; S_i + E_i + I_i + R_i \le \frac{A_i}{m_i}, \\ S_i, E_i, I_i, R_i \ge 0,\ 1 \le i \le n\Big\}$$

is positively invariant with respect to system (3.1). Let $\overset{\circ}{D}_g$ denote the interior of D_g.

System (3.1) always admits a disease-free equilibrium $P_0 = (S_1^0, 0, 0, 0, \dots, S_n^0, 0, 0, 0)$ with $S_i^0 = \frac{A_i}{m_i}$ in D_g. Let

$$Q_i = -\int_0^\infty e^{-m_i u} d_u P_i(u)\, du. \tag{3.2}$$

It can be verified that $0 < Q_i < 1$ for all i. With ρ denoting the spectral radius, define the basic reproduction number as the spectral radius of the $n \times n$ matrix $Y = \Big(\frac{\beta_{ij} Q_i S_i^0}{m_i + \alpha_i + \gamma_i}\Big)$, that is,

$$\mathcal{R}_0 = \rho(Y) = \rho\Big(\Big(\frac{\beta_{ij} Q_i S_i^0}{m_i + \alpha_i + \gamma_i}\Big)\Big). \tag{3.3}$$

The following result establishes that $\mathcal{R}_0$ is a threshold value for the DFE.

Theorem 3.1. *The following results hold for system (3.1) with $\mathcal{R}_0$ given by (3.3).*

(1) *If $\mathcal{R}_0 \le 1$, then the DFE is globally asymptotically stable in D_g.*
(2) *If $\mathcal{R}_0 > 1$, then the DFE is unstable.*

Proof. Since the variables E_i and R_i do not appear in the equations of S_i and I_i of (3.1), we can first study the following reduced system consisting of variables S_i and I_i

$$\begin{aligned} S_i'(t) &= A_i - \sum_{j=1}^n \beta_{ij} S_i(t) I_j(t) - m_i S_i(t), \\ I_i'(t) &= -\sum_{j=1}^n \int_0^t \beta_{ij} S_i(u) I_j(u) e^{-m_i(t-u)} d_t P_i(t-u)\, du - (m_i + \alpha_i + \gamma_i) I_i(t), \\ &\qquad i = 1, 2, \dots, n. \end{aligned} \tag{3.4}$$

We prove that the equilibrium $(S_1^0, 0, S_2^0, 0, \dots, S_n^0, 0)$ of system (3.4) is globally asymptotically stable by the method of Lyapunov functions. Then our stability results for the reduced system (3.4) can be extended to system (3.1) by the theory of asymptotically autonomous systems.

Since $B = (\beta_{ij})$ is irreducible, the nonnegative matrix $Y = (\frac{\beta_{ij} Q_i S_i^0}{m_i + \alpha_i + \gamma_i})$ is also irreducible, and Y has a positive left eigenvector $(w_1, w_2, \dots, w_n)$ corresponding to the spectral radius $\rho(Y) = \mathcal{R}_0 > 0$. Motivated by [10], let

$$c_i = \frac{w_i}{m_i + \alpha_i + \gamma_i} > 0,$$

and define

$$Q_i(r) = -\int_r^\infty e^{-m_i u} d_u P_i(u)\, du. \tag{3.5}$$

From (3.2), it follows that $Q_i(0) = Q_i$. Consider a Lyapunov functional for system (3.4)

$$L = \sum_{i=1}^n c_i \Big[Q_i \Big(S_i - S_i^0 - S_i^0 \ln \frac{S_i}{S_i^0} \Big) + I_i + \sum_{j=1}^n \int_0^t \beta_{ij} Q_i(r) S_i(t-r) I_j(t-r)\, dr \Big].$$

Observe that $L \geq 0$, and $L = 0$ if and only if $S_i = S_i^0, I_i(r) = 0$ for all i and $0 \leq r \leq t$. Before we differentiate L along the solution of system (3.4), we follow the idea in [34, 35] and using integration by parts obtain

$$\begin{aligned}
&\frac{\partial}{\partial t}\Big(\int_0^t Q_i(r) S_i(t-r) I_j(t-r)\, dr \Big) \\
&= Q_i(t) S_i(0) I_j(0) + \int_0^t Q_i(r) \frac{\partial}{\partial t} (S_i(t-r) I_j(t-r))\, dr \\
&= Q_i(t) S_i(0) I_j(0) + \int_0^t Q_i(r)(-1) \frac{\partial}{\partial r} (S_i(t-r) I_j(t-r))\, dr \\
&= Q_i(t) S_i(0) I_j(0) - Q_i(r) S_i(t-r) I_j(t-r)\Big|_{r=0}^t \\
&\quad + \int_0^t S_i(t-r) I_j(t-r) e^{-m_i r} d_r P_i(r)\, dr \\
&= Q_i S_i(t) I_j(t) + \int_0^t S_i(t-r) I_j(t-r) e^{-m_i r} d_r P_i(r)\, dr.
\end{aligned} \tag{3.6}$$

Now differentiating L along the solution of system (3.4), using (3.6) and the non-increasing property of P_i (see assumption (H)), and setting $I = (I_1, I_2, \ldots, I_n)^T$ give

$$\begin{aligned}
L'|_{(3.4)} &= \sum_{i=1}^n c_i \Big[Q_i \Big(A_i - \sum_{j=1}^n \beta_{ij} S_i(t) I_j(t) - m_i S_i(t) - A_i \frac{S_i^0}{S_i(t)} + m_i S_i^0 \\
&\quad + \sum_{j=1}^n \beta_{ij} S_i^0 I_j(t) \Big) - \sum_{j=1}^n \int_0^t \beta_{ij} S_i(u) I_j(u) e^{-m_i(t-u)} d_t P_i(t-u)\, du \\
&\quad - (m_i + \alpha_i + \gamma_i) I_i(t) + \sum_{j=1}^n \beta_{ij} Q_i S_i(t) I_j(t) \\
&\quad + \sum_{j=1}^n \int_0^t \beta_{ij} S_i(t-r) I_j(t-r) e^{-m_i r} d_r P_i(r)\, dr \Big] \\
&= \sum_{i=1}^n c_i Q_i A_i \Big(2 - \frac{S_i(t)}{S_i^0} - \frac{S_i^0}{S_i(t)} \Big) + \sum_{i=1}^n c_i \Big(\sum_{j=1}^n \beta_{ij} Q_i S_i^0 I_j(t) \\
&\quad - (m_i + \alpha_i + \gamma_i) I_i(t) \Big)
\end{aligned}$$

$$
\begin{aligned}
&= \sum_{i=1}^{n} c_i Q_i A_i \Big(2 - \frac{S_i(t)}{S_i^0} - \frac{S_i^0}{S_i(t)}\Big) \\
&\quad + \sum_{i=1}^{n} \frac{w_i}{m_i + \alpha_i + \gamma_i} \Big(\sum_{j=1}^{n} \beta_{ij} Q_i S_i^0 I_j(t) - (m_i + \alpha_i + \gamma_i) I_i(t) \Big) \\
&= \sum_{i=1}^{n} c_i Q_i A_i \Big(2 - \frac{S_i(t)}{S_i^0} - \frac{S_i^0}{S_i(t)}\Big) + (w_1, w_2, \ldots, w_n)(YI - I) \\
&= \sum_{i=1}^{n} c_i Q_i A_i \Big(2 - \frac{S_i(t)}{S_i^0} - \frac{S_i^0}{S_i(t)}\Big) + (\rho(Y) - 1)(w_1, w_2, \ldots, w_n) I \\
&\le 0, \quad \text{if } \mathcal{R}_0 \le 1. \qquad (3.7)
\end{aligned}
$$

Let

$$K = \{(S_1, I_1, \ldots, S_n, I_n) \mid L'|_{(3.4)} = 0\},$$

and $\mathit{\Gamma}$ be the largest invariant set in K. We now show $\mathit{\Gamma} = \{(S_1^0, 0, \ldots, S_n^0, 0)\}$. From (3.7) and $c_i > 0$, $L'|_{(3.4)} = 0$ implies that $2 - \frac{S_i(t)}{S_i^0} - \frac{S_i^0}{S_i(t)} = 0$ for all $1 \le i \le n$ and $t \ge 0$, and thus $S_i(t) \equiv S_i^0 = \frac{A_i}{m_i}$. Hence, the first equation of (3.4) gives $\sum_{j=1}^{n} \beta_{ij} S_i^0 I_j(t) = 0$ for all $t \ge 0$ and $1 \le i \le n$. By the irreducibility of B, for each j, there exists $i \ne j$ such that $\beta_{ij} \ne 0$, and thus $I_j(t) = 0$ for all $t \ge 0$. Therefore, $\mathit{\Gamma} = \{(S_1^0, 0, \ldots, S_n^0, 0)\}$. Using the LaSalle-Lyapunov Theorem (see [23, Theorem 3.4.7] or [13, Theorem 5.3.1]), it follows that $(S_1^0, 0, \ldots, S_n^0, 0)$ attracts all solutions of system (3.4) whose initial conditions satisfy $0 \le S_i(0) + I_i(0) \le \frac{A_i}{m_i}$. By Lemma A.1 in Appendix A, it follows that $(S_1^0, 0, \ldots, S_n^0, 0)$ is locally stable for system (3.4) since there exists a nonnegative monotone increasing function $a(r)$ such that (A.2) holds. Therefore, for the reduced system (3.4), the equilibrium $(S_1^0, 0, \ldots, S_n^0, 0)$ is globally asymptotically stable when $\mathcal{R}_0 \le 1$. Using the fact that $S_i(t) \to S_i^0$ and $I_i(t) \to 0$ as $t \to \infty$ along with the theory of asymptotically autonomous systems, $E_i(t) \to 0$ and $R_i(t) \to 0$ as $t \to \infty$. Therefore, the DFE P_0 for system (3.1) is globally asymptotically stable in D_g when $\mathcal{R}_0 \le 1$.

If $\mathcal{R}_0 > 1$ and $I \ne 0$, it follows that

$$(\rho(Y) - 1)(w_1, w_2, \ldots, w_n) I > 0,$$

which implies that by continuity $L'|_{(3.4)} > 0$ in a small enough neighborhood of P_0 in $\overset{\circ}{D}_g$. Therefore, P_0 is unstable when $\mathcal{R}_0 > 1$. □

To analyze the dynamical behavior of (3.1) when $\mathcal{R}_0 > 1$, we consider the limiting system of (3.1)

$$
\begin{aligned}
S_i'(t) &= A_i - \sum_{j=1}^{n} \beta_{ij} S_i(t) I_j(t) - m_i S_i(t), \\
E_i'(t) &= \sum_{j=1}^{n} \beta_{ij} S_i(t) I_j(t) - m_i E_i(t) + \sum_{j=1}^{n} \int_{-\infty}^{t} \beta_{ij} S_i(u) I_j(u) e^{-m_i(t-u)} d_t P_i(t-u)\, du, \\
I_i'(t) &= -\sum_{j=1}^{n} \int_{-\infty}^{t} \beta_{ij} S_i(u) I_j(u) e^{-m_i(t-u)} d_t P_i(t-u)\, du - (m_i + \alpha_i + \gamma_i) I_i(t), \\
R_i'(t) &= \gamma_i I_i(t) - m_i R_i(t), \qquad i = 1, 2, \ldots, n. \qquad (3.8)
\end{aligned}
$$

For any $\kappa_i \in (0, m_i)$, the Banach space of fading memory type C_{κ_i} can be defined similarly as given in (2.9). We study system (3.8) in the phase space

$$X_g = \prod_{i=1}^{n} (C_{\kappa_i} \times \mathbb{R} \times C_{\kappa_i} \times \mathbb{R}).$$

It can be easily verified that

$$\Delta_g = \Big\{ (S_1(\cdot), E_1, I_1(\cdot), R_1, \ldots, S_n(\cdot), E_n, I_n(\cdot), R_n) \in X_g \;\Big|\; E_i, R_i \geq 0, \\ S_i(s), I_i(s) \geq 0, s \in (-\infty, 0], S_i(0) + E_i + I_i(0) + R_i \leq \frac{A_i}{m_i},\ 1 \leq i \leq n \Big\}$$

is positively invariant with respect to system (3.8). Let $\overset{\circ}{\Delta}_g$ be the interior of Δ_g.

The following result establishes the existence and uniqueness of an endemic equilibrium for system (3.8).

Lemma 3.2. *If $\mathcal{R}_0 > 1$, then system (3.8) has a unique endemic equilibrium $P^* = (S_1^*, E_1^*, I_1^*, R_1^*, \ldots, S_n^*, E_n^*, I_n^*, R_n^*)$ in $\overset{\circ}{\Delta}_g$.*

Proof. From the equilibrium equations of (3.8),

$$A_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j - m_i S_i = 0, \tag{3.9}$$

and

$$\sum_{j=1}^{n} \beta_{ij} S_i I_j - \frac{m_i + \alpha_i + \gamma_i}{Q_i} I_i = 0. \tag{3.10}$$

Consider the auxiliary system

$$\begin{aligned} S_i' &= A_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j - m_i S_i, \\ I_i' &= \sum_{j=1}^{n} \beta_{ij} S_i I_j - \frac{m_i + \alpha_i + \gamma_i}{Q_i} I_i. \end{aligned} \tag{3.11}$$

The global dynamics of system (3.11) have been studied in [10], where it is shown that if $\mathcal{R}_0 = \rho(Y) = \rho\Big(\frac{\beta_{ij} Q_i S_i^0}{m_i + \alpha_i + \gamma_i}\Big) > 1$, then a unique endemic equilibrium $(S_1^*, I_1^*, \ldots, S_n^*, I_n^*)$ exists. This is, there exists a unique positive solution $(S_1^*, I_1^*, \ldots, S_n^*, I_n^*)$ solving the equations (3.9) and (3.10) if $\mathcal{R}_0 > 1$. Using the equilibrium equations of E_i and R_i in (3.8), it follows that $E_i^* = \frac{\sum_{j=1}^{n} \beta_{ij} S_i^* I_j^* (1 - Q_i)}{m_i}$ and $R_i^* = \frac{\gamma_i I_i^*}{m_i}$ for each i. Therefore, if $\mathcal{R}_0 > 1$, then $P^* = (S_1^*, E_1^*, I_1^*, R_1^*, \ldots, S_n^*, E_n^*, I_n^*, R_n^*)$ is a unique endemic equilibrium for system (3.8). □

Using the graph-theoretic approach recently developed in [10, 11, 29], we prove the global stability of the EE for (3.8).

Theorem 3.3. *If $\mathcal{R}_0 > 1$, then the unique EE of system (3.8) is globally asymptotically stable in $\overset{\circ}{\Delta}_g$. As a consequence, all solutions of (3.1) starting in $\overset{\circ}{D}_g$ approach the EE of (3.8) if $\mathcal{R}_0 > 1$.*

Proof. As in the proof of Theorem 3.1, we first study the reduced system

$$\begin{aligned} S_i'(t) &= A_i - \sum_{j=1}^{n} \beta_{ij} S_i(t) I_j(t) - m_i S_i(t), \\ I_i'(t) &= -\sum_{j=1}^{n} \int_{-\infty}^{t} \beta_{ij} S_i(u) I_j(u) e^{-m_i(t-u)} d_t P_i(t-u)\, du - (m_i + \alpha_i + \gamma_i) I_i(t), \\ & \qquad i = 1, 2, \ldots, n, \end{aligned} \tag{3.12}$$

which is the limiting system of (3.4). In the following, we prove that the equilibrium $(S_1^*, I_1^*, S_2^*, I_2^*, \ldots, S_n^*, I_n^*)$ of (3.12) is globally asymptotically stable by constructing a suitable Lyapunov functional. Set

$$U_i = Q_i\Big(S_i - S_i^* - S_i^* \ln \frac{S_i}{S_i^*}\Big) + I_i - I_i^* - I_i^* \ln \frac{I_i}{I_i^*},$$

$$W_i = \sum_{j=1}^{n} \int_0^{\infty} \beta_{ij} Q_i(r) \Big(S_i(t-r) I_j(t-r) - S_i^* I_j^* - S_i^* I_j^* \ln \frac{S_i(t-r) I_j(t-r)}{S_i^* I_j^*} \Big)\, dr,$$

and

$$V_i = U_i + W_i.$$

Here Q_i and $Q_i(r)$ are defined in (3.2) and (3.5), respectively, and $Q_i(0) = Q_i$. Lyapunov functions as U_i have been successfully applied to epidemic models since the work in [20, 21], while Lyapunov functionals as W_i have been shown to be powerful for delay epidemic models [34, 35]. Functional W_i is different from those in [30, 34, 35] because of different delay terms in model (3.1), but is motivated by those in [17, 18, 27, 28]. Differentiating U_i along the solution of (3.12) and using the equilibrium equations (3.9) and (3.10) yield

$$\begin{aligned} U_i'|_{(3.12)} =& Q_i\Big(A_i - \sum_{j=1}^{n} \beta_{ij} S_i(t) I_j(t) - m_i S_i(t) - A_i \frac{S_i^*}{S_i(t)} + \sum_{j=1}^{n} \beta_{ij} S_i^* I_j(t) + m_i S_i^*\Big) \\ & - \sum_{j=1}^{n} \int_{-\infty}^{t} \beta_{ij} S_i(u) I_j(u) e^{-m_i(t-u)} d_t P_i(t-u)\, du - (m_i + \alpha_i + \gamma_i) I_i(t) \\ & + \sum_{j=1}^{n} \int_{-\infty}^{t} \beta_{ij} S_i(u) I_j(u) \frac{I_i^*}{I_i(t)} e^{-m_i(t-u)} d_t P_i(t-u)\, du + (m_i + \alpha_i + \gamma_i) I_i^* \\ =& Q_i m_i S_i^* \Big(2 - \frac{S_i(t)}{S_i^*} - \frac{S_i^*}{S_i(t)}\Big) \\ & + \sum_{j=1}^{n} \beta_{ij} Q_i S_i^* I_j^* \Big(2 - \frac{S_i(t) I_j(t)}{S_i^* I_j^*} - \frac{S_i^*}{S_i(t)} + \frac{I_j(t)}{I_j^*} - \frac{I_i(t)}{I_i^*}\Big) \\ & - \sum_{j=1}^{n} \int_{-\infty}^{t} \beta_{ij} S_i(u) I_j(u) \Big(1 - \frac{I_i^*}{I_i(t)}\Big) e^{-m_i(t-u)} d_t P_i(t-u)\, du. \end{aligned} \tag{3.13}$$

For the integral in W_i, integration by parts gives

$$\begin{aligned}&\int_0^\infty Q_i(r)\frac{\partial}{\partial t}\Big(S_i(t-r)I_j(t-r)-S_i^*I_j^*-S_i^*I_j^*\ln\frac{S_i(t-r)I_j(t-r)}{S_i^*I_j^*}\Big)\,dr\\&=Q_iS_i(t)I_j(t)+\int_0^\infty\Big(S_i(t-r)I_j(t-r)+S_i^*I_j^*\ln\frac{S_i(t)I_j(t)}{S_i(t-r)I_j(t-r)}\Big)\\&\quad\cdot e^{-m_ir}d_rP_i(r)\,dr.\end{aligned}$$

It follows that

$$\begin{aligned}W_i'|_{(3.12)}\;=\;&\sum_{j=1}^n\beta_{ij}\Big[Q_iS_i(t)I_j(t)+\int_0^\infty\Big(S_i(t-r)I_j(t-r)\\&+S_i^*I_j^*\ln\frac{S_i(t)I_j(t)}{S_i(t-r)I_j(t-r)}\Big)e^{-m_ir}d_rP_i(r)\,dr\Big].\end{aligned}\tag{3.14}$$

Adding equations (3.13) and (3.14) yields

$$\begin{aligned}V_i'|_{(3.12)}=&Q_im_iS_i^*\Big(2-\frac{S_i(t)}{S_i^*}-\frac{S_i^*}{S_i(t)}\Big)+\sum_{j=1}^n\beta_{ij}S_i^*I_j^*\Big[Q_i\Big(2-\frac{S_i^*}{S_i(t)}+\frac{I_j(t)}{I_j^*}\\&-\frac{I_i(t)}{I_i^*}\Big)+\int_0^\infty\Big(\frac{S_i(t-r)I_j(t-r)I_i^*}{S_i^*I_j^*I_i(t)}+\ln\frac{S_i(t)I_j(t)}{S_i(t-r)I_j(t-r)}\Big)\\&\cdot e^{-m_ir}d_rP_i(r)\,dr\Big]\\\le&\sum_{j=1}^n\beta_{ij}S_i^*I_j^*\Big[Q_i\Big(1-\frac{S_i^*}{S_i(t)}+\ln\frac{S_i^*}{S_i(t)}\Big)+Q_i\Big(\frac{I_j(t)}{I_j^*}-\frac{I_i(t)}{I_i^*}-\ln\frac{I_j(t)}{I_j^*}\\&+\ln\frac{I_i(t)}{I_i^*}\Big)-\int_0^\infty\Big(1-\frac{S_i(t-r)I_j(t-r)I_i^*}{S_i^*I_j^*I_i(t)}+\ln\frac{S_i(t-r)I_j(t-r)I_i^*}{S_i^*I_j^*I_i(t)}\Big)\\&\cdot e^{-m_ir}d_rP_i(r)\,dr\Big]\\\le&\sum_{j=1}^n\beta_{ij}Q_iS_i^*I_j^*\Big(\frac{I_j(t)}{I_j^*}-\frac{I_i(t)}{I_i^*}-\ln\frac{I_j(t)}{I_j^*}+\ln\frac{I_i(t)}{I_i^*}\Big),\end{aligned}\tag{3.15}$$

where the following inequalities have been used:

$$\begin{aligned}&2-\frac{S_i(t)}{S_i^*}-\frac{S_i^*}{S_i(t)}\le0,\qquad 1-\frac{S_i^*}{S_i(t)}+\ln\frac{S_i^*}{S_i(t)}\le0,\\&1-\frac{S_i(t-r)I_j(t-r)I_i^*}{S_i^*I_j^*I_i(t)}+\ln\frac{S_i(t-r)I_j(t-r)I_i^*}{S_i^*I_j^*I_i(t)}\le0.\end{aligned}$$

Considering (3.15), take the weight matrix $W=(w_{ij})$ with constant entry $w_{ij}=\beta_{ij}Q_iS_i^*I_j^*\ge0$ and denote the corresponding weighted digraph as $(\mathcal{G},W)$. Let $c_i=\sum_{\mathcal{T}\in\mathbb{T}_i}w(T)\ge0$ be as given in (B.1) in Appendix B with $(\mathcal{G},W)$. Then, by (B.2), the following identity holds

$$\sum_{i,j=1}^n c_i\beta_{ij}Q_iS_i^*I_j^*\Big(\frac{I_i(t)}{I_i^*}-\ln\frac{I_i(t)}{I_i^*}\Big)=\sum_{i,j=1}^n c_i\beta_{ij}Q_iS_i^*I_j^*\Big(\frac{I_j(t)}{I_j^*}-\ln\frac{I_j(t)}{I_j^*}\Big).\tag{3.16}$$

Set

$$V=\sum_{i=1}^n c_iV_i.$$

Using (3.15) and (3.16) gives

$$V'|_{(3.12)} = \sum_{i=1}^{n} c_i V_i' \le \sum_{i,j=1}^{n} c_i \beta_{ij} Q_i S_i^* I_j^* \Big(\frac{I_j(t)}{I_j^*} - \frac{I_i(t)}{I_i^*} - \ln \frac{I_j(t)}{I_j^*} + \ln \frac{I_i(t)}{I_i^*} \Big) = 0.$$

Therefore, V is a Lyapunov functional for system (3.12). This rules out the possibility that solutions of (3.12) approach the boundary $S_i = 0$ or $I_i = 0$ in Δ_g since $V \to \infty$ if $S_i \to 0$ or $I_i \to 0$. Since B is irreducible, $c_i > 0$ for all i (see Appendix B), and thus $V'|_{(3.12)} = 0$ implies that $S_i = S_i^*$ for all i. It can be verified that as in the proof of Theorem 3.1 the largest invariant set where $V'|_{(3.12)} = 0$ is the singleton $\{(S_1^*, I_1^*, \dots, S_n^*, I_n^*)\}$. Therefore, by the LaSalle-Lyapunov Theorem and a similar argument as in the proof of Theorem 3.1, it follows that $(S_1^*, I_1^*, \dots, S_n^*, I_n^*)$ is globally asymptotically stable for system (3.12). Thus for the limiting system (3.8) if $\mathcal{R}_0 > 1$, then the EE P^* is globally asymptotically stable in $\overset{\circ}{\Delta}_g$. An immediate consequence of Theorem 7.2 in [36] is that P^* attracts all solutions of (3.1) in $\overset{\circ}{D}_g$. □

Theorems 3.1 and 3.3 completely determine the dynamical behavior of the multi-group model (3.1) under the stated assumptions: if the basic reproduction number $\mathcal{R}_0 \le 1$, then the disease dies out from all groups; if $\mathcal{R}_0 > 1$, the disease persists at a positive level in all groups. It follows that the multi-group structure does not alter the qualitative behavior of the SEIR model (2.6) with an arbitrarily distributed exposed stage.

4. **Multi-stage model.** Multi-stage models has been proposed in the literature to describe the progression of infectious diseases with a long infectious period, for example, HIV/AIDS. Individuals infected with HIV are highly infectious in the first few weeks after infection, then remain in an asymptotic stage of low infectiousness for many years, and become gradually more infectious as their immune systems become compromised and they progress to AIDS [9, 19, 38]. So infectious individuals can be categorized into n different stages according to the age of infection. We include such stage structure into our model (2.6) and arrive at the following system in which $I_i(t)$ denotes the number of individuals in infection stage i with effective contact rate $\beta_i \ge 0$, $\gamma_i > 0$ is the rate of transferring from stage I_i to I_{i+1} (or to compartment R when $i = n$), $\delta_i \ge 0$ is the rate of transferring from stage I_i to I_{i-1} when $i \ge 2$, and $\alpha_{n+1} \ge 0$ is the mortality due to disease in the removed (AIDS) compartment:

$$\begin{aligned}
S'(t) &= A - \sum_{j=1}^{n} \beta_j S(t) I_j(t) - mS(t),\\
E'(t) &= \sum_{j=1}^{n} \beta_j S(t) I_j(t) - mE(t) + \sum_{j=1}^{n} \int_0^t \beta_j S(u) I_j(u) e^{-m(t-u)} d_t P(t-u)\, du,\\
I_1'(t) &= -\sum_{j=1}^{n} \int_0^t \beta_j S(u) I_j(u) e^{-m(t-u)} d_t P(t-u)\, du - (m + \alpha_1 + \gamma_1) I_1(t) + \delta_2 I_2(t),\\
I_i'(t) &= \gamma_{i-1} I_{i-1}(t) - (m + \alpha_i + \delta_i + \gamma_i) I_i(t) + \delta_{i+1} I_{i+1}(t), \quad i = 2, 3, \dots, n-1,\\
I_n'(t) &= \gamma_{n-1} I_{n-1}(t) - (m + \alpha_n + \delta_n + \gamma_n) I_n(t),\\
R'(t) &= \gamma_n I_n(t) - (m + \alpha_{n+1}) R(t).
\end{aligned} \tag{4.1}$$

Without loss of generality, assume that there exists $k \geq 1$ such that $\beta_k > 0$, $\beta_j = 0$, and $\delta_j > 0$ for all $k < j \leq n$. In fact, if $\beta_j = 0$ and $\delta_j = 0$ for all $k < j \leq n$, then the variables $I_j, k < j \leq n$, do not appear in the first $k+2$ equations and play the same role as the removed compartment R. In the case when $k = n-1$, that is, $\beta_{n-1} > 0$, $\beta_n = 0$, and $\delta_n > 0$, the compartment I_n can be treated as a temporally removed compartment and $\delta_n I_n$ represents the relapse of diseases, so the models with disease relapse in [40, 43] become special cases of (4.1). To the best of our knowledge, model (4.1) is the first multi-stage model in the literature with an arbitrarily distributed exposed stage.

With assumptions as in the previous sections, it can be verified that

$$D_s = \Big\{(S, E, I_1, \ldots, I_n, R) \in \mathbb{R}^{n+3} \;\Big|\; S, E, R, I_i \geq 0,\ 1 \leq i \leq n, \\ S + E + R + \sum_{i=1}^{n} I_i \leq \frac{A}{m}\Big\}$$

is positively invariant with respect to system (4.1). Let $\overset{\circ}{D}_s$ denote the interior of D_s. For system (4.1), there always exists a disease-free equilibrium $P_0 = (S^0, 0, 0, \ldots, 0, 0)$ with $S^0 = \frac{A}{m}$ in D_s.

Writing $\eta_1 = m + \alpha_1 + \gamma_1$ and $\eta_i = m + \alpha_i + \gamma_i + \delta_i, 2 \leq i \leq n$, define the basic reproduction number

$$\mathcal{R}_0 = QS^0(\beta_1, \beta_2, \ldots, \beta_n)M^{-1}(1, 0, \ldots, 0)^T, \tag{4.2}$$

where Q is defined as in (2.7) and tridiagonal

$$M = \begin{pmatrix} \eta_1 & -\delta_2 & & & \\ -\gamma_1 & \eta_2 & & & \\ & \ddots & \ddots & \ddots & \\ & & & \eta_{n-1} & -\delta_n \\ & & & -\gamma_{n-1} & \eta_n \end{pmatrix}.$$

The following result establishes that $\mathcal{R}_0$ is a threshold value for the DFE.

Theorem 4.1. *The following results hold for system* (4.1).

(1) *If* $\mathcal{R}_0 \leq 1$, *then the DFE is globally asymptotically stable in* D_s.
(2) *If* $\mathcal{R}_0 > 1$, *then the DFE is unstable.*

Proof. Since all off-diagonal entries of M are nonpositive and the sum of the entries in each column of M is positive, M is a nonsingular M-matrix and $M^{-1} \geq 0$ [5, p.137]. Following [9], let $(w_1, w_2, \ldots, w_n) = (\beta_1, \beta_2, \ldots, \beta_n)M^{-1}$, giving $w_1 = (\beta_1, \beta_2, \ldots, \beta_n)M^{-1}(1, 0, \ldots, 0)^T$ and $\mathcal{R}_0 = w_1 QS^0$. As in the proof of Theorem 3.1, we construct a Lyapunov functional for the reduced system of (4.1)

$$L = w_1 Q\Big(S - S^0 - S^0 \ln \frac{S}{S^0}\Big) + \sum_{i=1}^{n} w_i I_i + w_1 \sum_{i=1}^{n} \int_0^t \beta_i Q(r) S(t-r) I_i(t-r)\, dr,$$

where $Q(r) = -\int_r^\infty e^{-mu} d_u P(u)\, du$. Differentiating L along the reduced system of (4.1) and using a result as in (3.6) give

$$\begin{aligned} L'|_{(4.1)} =& w_1 Qm S^0\Big(2 - \frac{S_i(t)}{S_i^0} - \frac{S_i^0}{S_i(t)}\Big) + w_1 QS^0(\beta_1, \ldots, \beta_n)I - (w_1, \ldots, w_n)MI \\ \leq& (w_1 QS^0 - 1)(\beta_1, \ldots, \beta_n)I \leq 0, \qquad \text{if } \mathcal{R}_0 \leq 1. \end{aligned}$$

Here $I = (I_1(t), I_2(t), \dots, I_n(t))^T$. It can be verified that the largest invariant set where $L'|_{(4.1)} = 0$ is the singleton of the DFE. Therefore, the DFE is globally asymptotically stable in D_s if $\mathcal{R}_0 \le 1$, and unstable if $\mathcal{R}_0 > 1$ (using similar arguments as in the proof of Theorem 3.1). □

To study the dynamical behavior of (4.1) when $\mathcal{R}_0 > 1$, we consider the limiting system of (4.1)

$$\begin{aligned}
S'(t) &= A - \sum_{j=1}^{n} \beta_j S(t) I_j(t) - mS(t),\\
E'(t) &= \sum_{j=1}^{n} \beta_j S(t) I_j(t) - mE(t) + \sum_{j=1}^{n} \int_{-\infty}^{t} \beta_j S(u) I_j(u) e^{-m(t-u)} d_t P(t-u)\, du,\\
I_1'(t) &= -\sum_{j=1}^{n} \int_{-\infty}^{t} \beta_j S(u) I_j(u) e^{-m(t-u)} d_t P(t-u)\, du - \eta_1 I_1(t) + \delta_2 I_2(t),\\
I_i'(t) &= \gamma_{i-1} I_{i-1}(t) - \eta_i I_i(t) + \delta_{i+1} I_{i+1}(t), \quad i = 2, 3, \dots, n-1,\\
I_n'(t) &= \gamma_{n-1} I_{n-1}(t) - \eta_n I_n(t),\\
R'(t) &= \gamma_n I_n(t) - (m + \alpha_{n+1}) R(t).
\end{aligned} \tag{4.3}$$

We consider system (4.3) in the phase space

$$X_s = C_\kappa \times \mathbb{R} \times (C_\kappa)^n \times \mathbb{R},$$

where $\kappa \in (0, m)$ and C_κ is given in (2.9). It can be verified that

$$\Delta_s = \Big\{ (S(\cdot), E, I_1(\cdot), \dots, I_n(\cdot), R) \in X_s \;\Big|\; S(s), I_i(s) \ge 0, 1 \le i \le n, s \in (-\infty, 0], \\ E, R \ge 0,\ S(0) + E + I_1(0) + \cdots + I_n(0) + R \le \frac{A}{m} \Big\}$$

is positively invariant with respect to system (4.3). Let $\overset{\circ}{\Delta}_s$ be the interior of Δ_s. The existence and uniqueness of an endemic equilibrium for (4.3) can be established using an argument as in the proof of Lemma 3.2 and a result for the multi-stage ODE model in [9, Theorem 3.1].

Lemma 4.2. *If $\mathcal{R}_0 > 1$, then system (4.3) has a unique endemic equilibrium $P^* = (S^*, E^*, I_1^*, \dots, I_n^*, R^*)$ in $\overset{\circ}{\Delta}_s$.*

The global stability of the EE can be established by choosing an appropriate weight matrix as in Section 3.

Theorem 4.3. *If $\mathcal{R}_0 > 1$, then the EE of system (4.3) is globally asymptotically stable in $\overset{\circ}{\Delta}_s$. As a consequence, all solutions of (4.1) starting in $\overset{\circ}{D}_s$ approach the EE of (4.3) if $\mathcal{R}_0 > 1$.*

Proof. Choose the weight matrix $W = (w_{ij})$ as given by

$$w_{ij} = \begin{cases} \beta_2 Q S^* I_2^* + \delta_2 I_2^* & \text{if } i = 1, j = 2\\ \beta_j Q S^* I_j^* & \text{if } i = 1, j \ne 2\\ \gamma_{i-1} I_{i-1}^* & \text{if } i \ge 2, j = i-1\\ \delta_{i+1} I_{i+1}^* & \text{if } 2 \le i \le n-1, j = i+1\\ 0 & \text{otherwise.} \end{cases}$$

Let $c_i = \sum_{\mathcal{T}\in\mathbb{T}_i} w(T)$ be as given in (B.1) in Appendix B with the weighted digraph $(\mathcal{G}, W)$. Since $\beta_k > 0$, $\beta_j = 0$, $\delta_j > 0$, and $\gamma_i > 0$ for some $k \geq 1$, all $1 \leq i \leq n$, and all $k < j \leq n$, it follows that W is irreducible. As a consequence, $c_i > 0$ for all i (see Appendix B). A Lyapunov functional

$$V = c_1 Q\Big(S - S^* - S^* \ln\frac{S^*}{S}\Big) + \sum_{i=1}^{n} c_i\Big(I_i - I_i^* - I_i^* \ln\frac{I_i}{I_i^*}\Big)$$
$$+ c_1 \sum_{i=1}^{n}\int_0^\infty \beta_i Q(r)\Big(S(t-r)I_i(t-r) - S^* I_i^* - S^* I_i^* \ln\frac{S(t-r)I_i(t-r)}{S^* I_i^*}\Big)\, dr.$$

can be constructed for system (4.3). Using similar derivations as in the proof of Theorem 3.3 and identity (B.2), differentiating V along the limiting system (4.3) gives

$$\begin{aligned}
V' =& c_1 Q m S^*\Big(2 - \frac{S(t)}{S^*} - \frac{S^*}{S(t)}\Big) + c_1 Q\sum_{j=1}^{n}\beta_j S^* I_j^*\Big(1 - \frac{S^*}{S(t)} - \frac{S(t)}{S^*}\Big)\\
&- \sum_{j=1}^{n} c_1\beta_j S^* I_j^* \int_0^\infty \Big(1 - \frac{S(t-r)I_j(t-r)I_1^*}{S^* I_j^* I_1(t)} + \ln\frac{S(t-r)I_j(t-r)I_1^*}{S^* I_j^* I_1(t)}\Big)\\
&\cdot e^{-m_i r} d_r P_i(r)\, dr + \sum_{j=1}^{n} c_1 Q\beta_j S^* I_j^*\Big(\frac{I_j(t)}{I_j^*} - \frac{I_1(t)}{I_1^*} - \ln\frac{I_j(t)}{I_j^*} + \ln\frac{I_1(t)}{I_1^*}\Big)\\
&+ \sum_{i=2}^{n} c_i\gamma_{i-1} I_{i-1}^*\Big(\frac{I_{i-1}(t)}{I_{i-1}^*} - \frac{I_i(t)}{I_i^*} + 1 - \frac{I_{i-1}(t)I_i^*}{I_{i-1}^* I_i(t)}\Big)\\
&+ \sum_{i=1}^{n-1} c_i\delta_{i+1} I_{i+1}^*\Big(\frac{I_{i+1}(t)}{I_{i+1}^*} - \frac{I_i(t)}{I_i^*} + 1 - \frac{I_{i+1}(t)I_i^*}{I_{i+1}^* I_i(t)}\Big)\\
\leq& \sum_{j=1}^{n} c_1 Q\beta_j S^* I_j^*\Big(\frac{I_j(t)}{I_j^*} - \frac{I_1(t)}{I_1^*} - \ln\frac{I_j(t)}{I_j^*} + \ln\frac{I_1(t)}{I_1^*}\Big)\\
&+ \sum_{i=2}^{n} c_i\gamma_{i-1} I_{i-1}^*\Big(\frac{I_{i-1}(t)}{I_{i-1}^*} - \frac{I_i(t)}{I_i^*} - \ln\frac{I_{i-1}(t)}{I_{i-1}^*} + \ln\frac{I_i(t)}{I_i^*}\Big)\\
&+ \sum_{i=1}^{n-1} c_i\delta_{i+1} I_{i+1}^*\Big(\frac{I_{i+1}(t)}{I_{i+1}^*} - \frac{I_i(t)}{I_i^*} - \ln\frac{I_{i+1}(t)}{I_{i+1}^*} + \ln\frac{I_i(t)}{I_i^*}\Big)\\
=& \sum_{i,j=1}^{n} c_i w_{ij}\Big(\frac{I_j(t)}{I_j^*} - \frac{I_i(t)}{I_i^*} - \ln\frac{I_j(t)}{I_j^*} + \ln\frac{I_i(t)}{I_i^*}\Big)\\
=& 0.
\end{aligned}$$

By similar arguments as in the proof of Theorem 3.3, it follows that for system (4.3) P^* is globally asymptotically stable in $\overset{\circ}{\Delta}_s$. As a consequence, all solutions of (4.1) starting in $\overset{\circ}{D}_s$ approach P^* as the time goes to infinity. □

The global dynamics of (4.1) are completely determined by Theorems 4.1 and 4.3. Biologically, if the basic reproduction number $\mathcal{R}_0 \leq 1$, then the disease dies out eventually. If $\mathcal{R}_0 > 1$, then the disease persists in all stages of infection. As

a consequence, the stage structure in the long infection period does not alter the dynamics of the SEIR model (2.6).

5. **Summary and discussion.** We have investigated the impact of heterogeneity, which comes from age, behavior, or disease stages, on the dynamics of the SEIR epidemic model (2.6) with an arbitrarily distributed exposed stage. The resulting models are the multi-group model (3.1) and the multi-stage model (4.1), respectively. Both models are analyzed by determining the basic reproduction number $\mathcal{R}_0$ (i.e., (3.3) or (4.2)) and proving that it determines a sharp threshold as for the basic model (2.6). That is, if $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium is globally asymptotically stable and the disease dies out from all groups or stages; if $\mathcal{R}_0 > 1$, then the endemic equilibrium is globally asymptotically stable and the disease persists in all groups or stages. Thus heterogeneity that arises from age or behavior and disease stages does not alter the qualitative behavior of the basic SEIR model (2.6), although the value of $\mathcal{R}_0$ depends on the heterogeneity and the distribution of the exposed stage; see (3.3) and (4.2).

In the special case of the multi-group model (3.1) when $P_i(t), 1 \leq i \leq n$, are gamma distributions, the global stability of the DFE and EE has been established in [44]. When $P_i(t), 1 \leq i \leq n$, are negatively exponentially distributions, system (3.1) becomes the multi-group SEIR ODE model for which the global dynamics have been established in [10, 11]. Theorems 3.1 and 3.3 extend these stability results to the case with general distributions $P_i(t)$.

In the special case of the multi-stage model when $n = 2$, $\beta_1 > 0, \beta_2 = 0$, and $\delta_2 > 0$, system (4.1) becomes model (3) in [40] with relabeling I_2 by R and dropping the R equation in (4.1). Theorems 4.1 and 4.3 extend the stability results in [31, 40, 43] to system (4.1) with multiple infection stages. In another special case when $P_i(t), 1 \leq i \leq n$, are negatively exponentially distributions, system (4.1) includes the multi-stage ODE model studied in [9], and Theorem 4.3 generalizes Theorem 6.1 in [9].

Our models in this paper are of SEIR type as individuals recovering from disease are assumed to obtain permanent immunity. Epidemic models of SEIRS type have been used in the literature modeling infectious diseases with only temporary immunity, for example, see [6, 25, 26, 32]. Our SEIR models can be easily modified to include temporary immunity and become SEIRS epidemic models. For the SEIRS model, the basic reproduction number $\mathcal{R}_0$ has the same expression as for the corresponding SEIR model, and the global stability of the disease-free equilibrium can be proved in the same way as the proof of Theorems 3.1 and 4.1. However, the uniqueness and global stability of the endemic equilibrium for the SEIRS models remain open, even for the ODE models. Disease control strategies (e.g., isolation, quarantine and vaccination) can also be incorporated into our models. Our methods can sometimes be applied to analyze global dynamics of these resulting models and thus may assist public health planning to control disease.

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Appendix A. A local stability lemma

Consider a functional differential equation

$$x'(t) = f(x_t), \tag{A.1}$$

where $f : C \to \mathbb{R}^n$ is continuous. Assume that solutions of (A.1) are unique and continuously dependence on the initial data $x_0 \in C$. The following result can be proved similarly as Corollary 5.3.1 in [13].

Lemma A.1. *Assume that $a(\cdot)$ is nonnegative, monotone increasing, and that $V : C \to \mathbb{R}$ is continuous, $V(0) = 0$, and satisfies*

$$V(\phi) \geq a(|\phi(0)|), \tag{A.2}$$

$$V'\big|_{(A.1)} \leq 0. \tag{A.3}$$

Then the solution $x = 0$ of (A.1) is locally stable.

Proof. Since V is continuous and $V(0) = 0$, for any given $\epsilon > 0$, there exists $\delta > 0$ such that $V(x_0) \leq a(\epsilon)$ holds as long as $|x_0| < \delta$. It follows that

$$a(|x(t)|) \leq V(x_t) \leq V(x_0) \leq a(\epsilon).$$

This implies $|x(t)| < \epsilon$ and thus the result holds. □

Appendix B. A combinatorial identity

Let $(\mathcal{G}, W)$ be a weighted digraph with $n \geq 2$ vertices, where $W = (w_{ij})$ is the weight matrix. Weight w_{ij} is positive if the directed arc (j, i) from vertex j to vertex i exists, otherwise $w_{ij} = 0$. Let c_i be the cofactor of the (i, i) entry of the Laplacian matrix of W [29], and let $\mathbb{T}_i$ be the set of all spanning trees of $(\mathcal{G}, W)$ rooted at vertex i. By Kirchhoff's Matrix Tree Theorem,

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

where $w(T)$ is the product of weights on all arcs of $\mathcal{T} \in \mathbb{T}_i$. Then $c_i \geq 0$, and for any family of functions $\{G_i(x_i)\}_{i=1}^n$, the following identity holds

$$\sum_{i,j=1}^{n} c_i\, w_{ij}\, G_i(x_i) = \sum_{i,j=1}^{n} c_i\, w_{ij}\, G_j(x_j). \tag{B.2}$$

If $W = (w_{ij})$ is irreducible, then $c_i > 0$ for $i = 1, 2, \ldots, n$. We refer the reader to [29] for the proof of (B.2).

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E-mail address: zshuai@uvic.ca
E-mail address: pvdd@math.uvic.ca