GLOBAL DYNAMICS OF A STAGED PROGRESSION MODEL FOR INFECTIOUS DISEASES

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Abstract. We analyze a mathematical model for infectious diseases that progress through distinct stages within infected hosts. An example of such a disease is AIDS, which results from HIV infection. For a general n-stage stage-progression (SP) model with bilinear incidences, we prove that the global dynamics are completely determined by the basic reproduction number R_0. If $R_0 \leq 1$, then the disease-free equilibrium P_0 is globally asymptotically stable and the disease always dies out. If $R_0 > 1$, P_0 is unstable, and a unique endemic equilibrium P^* is globally asymptotically stable, and the disease persists at the endemic equilibrium. The basic reproduction numbers for the SP model with density dependent incidence forms are also discussed.

1. **Introduction.** For diseases that progress through a long infectious period, infectivity or infectiousness can vary greatly in time. The progression of a typical HIV infection can take eight to ten years before the clinical syndrome (AIDS) occurs, and the progression goes through several distinct stages, marked by drastically different $CD4^+$ T-cell counts and viral RNA levels. HIV-infected individuals 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 the immune system becomes compromised and they progress to AIDS. Variability of infectiousness in time has been modelled in the literature by Markov chain models or staged-progression (SP) models (see, e.g. [1]-[10]). A deterministic SP model was proposed and analyzed in [4]. To formulate an SP model, the total host population is partitioned into the following compartments: the susceptible compartment S; the infectious compartment I_i, whose members are in the i-th stage of the disease progression, where $i = 1, 2, \cdots, n$; and the terminal compartment A. Let δ_i be the mean progression rate from the i-th stage to the $(i+1)$-th stage, for $i = 1, 2, \cdots, n-1$, and δ_n the mean progression rate from the n-th stage to the terminal stage of the disease. We assume that hosts in the terminal compartment are non-infectious due to inactivity. In the case of AIDS, the terminal compartment consists of people with active AIDS. AIDS patients typically either become sexually inactive or isolated from the infection process, and their infectivity is negligible. We also assume that there is no recovery from the disease, and thus the only exit from compartment A is death. Let λ_i be the transmission coefficient for the infection of a susceptible from an infectious in the class I_i, which takes into account average number of contact and probability of infection for each contact; then the total
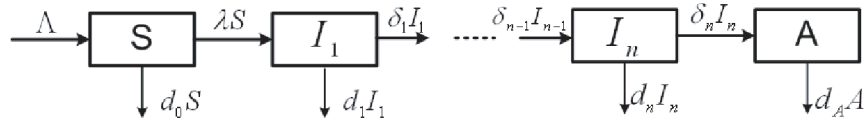

FIGURE 1. The transfer diagram for model (1).

incidence is given by $\sum_{i=1}^{n} \lambda_i I_i S f(N)$, where $N = S + I_1 + \cdots + I_n$ is the total active population. Here we assume that the density dependence of the incidence is given by a function $f(N)$, which will be specified later. A class of special interest is $f(N) = N^{-\alpha}$, $0 \le \alpha \le 1$, the resulting incidence term includes two of the most common incidence forms: the standard incidence form ($\alpha = 1$) and the bilinear incidence ($\alpha = 0$). The average death rate for the susceptible compartment is d_0; for the compartment I_i it is d_i, which may include death due to infection; and for the terminal compartment it is d_A. We assume the inflow of susceptibles is a constant Λ. The population transfer among compartments is schematically depicted in the transfer diagram in Figure 1. All parameters in the model are assumed to be positive.

Based on our assumptions and the transfer diagram, the following system of differential equations can be derived for the n-stage SP model:

$$
\begin{aligned}
S^{'} &= \Lambda - d_0 S - \lambda S, \\
I_1^{'} &= \lambda S - (d_1 + \delta_1)I_1, \\
I_i^{'} &= \delta_{i-1}I_{i-1} - (d_i + \delta_i)I_i, \quad i = 2, \ldots, n,
\end{aligned}
\tag{1}
$$

and

$$
A^{'} = \delta_n I_n - d_A A.
$$

The incidence form is λS, where the force of infection

$$
\lambda = f(N) \sum_{i=1}^{n} \lambda_i I_i
\tag{2}
$$

is density dependent. We assume that the function $f(N)$ satisfies the following assumptions, for $N > 0$,

(**H**) $f(N) > 0$, $f^{'}(N) \le 0$, $|Nf^{'}(N)| \le f(N)$, and $Nf(N)$ is monotonically increasing.

The assumptions that $f(N) > 0$ and $f'(N) \le 0$ are biologically motivated. As the total population N increases, the probability of a contact with a susceptible decreases, and thus the force of infection is expected to be a decreasing function of N. The other two conditions we impose on f are needed for our analysis. It can be verified that the class $f(N) = N^{-\alpha}$, $0 \le \alpha \le 1$, satisfies (**H**). This class contains the standard incidence ($\alpha = 1$) and the bilinear incidence ($\alpha = 0$).

Adding the equations in (1) we obtain

$$
N^{'} = \Lambda - d_0 S - d_1 I_1 - \cdots - d_n I_n - \delta_n I_n \le \Lambda - dN,
$$

where $d = \min\{d_0, d_1, \cdots d_n\}$. It follows that $\limsup\limits_{t \to \infty} N(t) \le \dfrac{\Lambda}{d}$. Similarly, from the first equation of (1) we obtain $S^{'} \le \Lambda - d_0 S$, and thus $\limsup\limits_{t \to \infty} S(t) \le \dfrac{\Lambda}{d_0}$. The

feasible region for (1) can be chosen as the closed set

$$\Gamma = \{(S, I_1, \cdots, I_n) \in \mathbb{R}_+^{n+1} \; : \; 0 \leq S \leq \frac{\Lambda}{d_0}, \; 0 \leq S + I_1 + \cdots + I_n \leq \frac{\Lambda}{d}\},$$

which can be verified to be positively invariant with respect to (1).

We show in Section 4 that the basic reproduction number for model (1) is given by

$$R_0 = \Big[\frac{\lambda_1}{d_1 + \delta_1} + \frac{\lambda_2}{d_1 + \delta_1} \frac{\delta_1}{d_2 + \delta_2} + \cdots + \frac{\lambda_n}{d_1 + \delta_1} \frac{\delta_1}{d_2 + \delta_2} \cdots \frac{\delta_{n-1}}{d_n + \delta_n} \Big] \frac{\Lambda}{d_0} f\Big(\frac{\Lambda}{d_0}\Big). \quad (3)$$

We prove that the global dynamics of model (1) are completely determined by the basic reproduction number R_0. If $R_0 \leq 1$, then the disease-free equilibrium $P_0 = (\Lambda/d_0, 0, \cdots, 0)$ is globally asymptotically stable in the feasible region Γ, and the disease always dies out. If $R_0 > 1$, then P_0 becomes unstable, and system (1) is uniformly persistent. Moreover, a unique endemic equilibrium $P^* = (S^*, I_1^*, \cdots, I_n^*)$ exists in the interior of Γ. For the case of bilinear incidence, namely, when $f(N) = 1$, we prove that P^* is globally asymptotically stable in the interior of Γ if $R_0 > 1$.

In the next section, we prove the uniqueness of the endemic equilibrium when $R_0 > 1$. In Section 3, global stability of P_0 is established for $R_0 \leq 1$. Concrete expressions of R_0 are derived in Section 4. The global stability of P^* for the case $f(N) = 1$ is proved in Section 5.

2. **Equilibria.** An equilibrium $(S, I_1, \cdots, I_n)$ of (1) satisfies

$$\begin{aligned}
0 &= \Lambda - d_0 S - \lambda S, \\
0 &= \lambda S - (d_1 + \delta_1) I_1, \\
0 &= \delta_{i-1} I_{i-1} - (d_i + \delta_i) I_i, \quad i = 2, \cdots, n,
\end{aligned} \quad (4)$$

where λ is given in (2). The disease-free equilibrium $P_0 = (\Lambda/d_0, 0, \cdots, 0)$ exists for all positive parameter values. Next we consider the existence of endemic equilibria $P^* = (S^*, I_1^*, \cdots, I_n^*)$, $S^* > 0$, $I_i^* > 0$, $i = 1, \cdots, n$.

Let

$$A = \begin{bmatrix}
-d_1 - \delta_1 & & & & \\
\delta_1 & -d_2 - \delta_2 & & & \\
& \delta_2 & -d_3 - \delta_3 & & \\
& & \ddots & \ddots & \\
& & & \delta_{n-1} & -d_n - \delta_n
\end{bmatrix}. \quad (5)$$

Then the following properties of the matrix A follow from the definition and properties of M-matrices given in the Appendix.

PROPOSITION 2.1. *The following holds for the matrix A defined above.*
  (1) $-A$ *is a M-matrix.*
  (2) $-A^{-1}$ *exists and is a non-negative matrix.*
  (3) *There exists $\alpha > 0$ such that $-A^{-1}x \geq \alpha\, x$ for $x \geq 0$.*

By Proposition 2.1, we know that

$$\beta = -(\lambda_1, \cdots, \lambda_n) A^{-1} \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} > 0. \quad (6)$$

Define the basic reproduction number of (1) as

$$R_0 = \beta \frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right). \tag{7}$$

In Section 4, we will derive the explicit expression of R_0 and give its justification. We have the following result on the number of equilibria.

THEOREM 2.1. *Assume that f satisfies (**H**). If $R_0 \leq 1$, then P_0 is the only equilibrium in Γ. If $R_0 > 1$, then a unique endemic equilibrium P^* exists in the interior of Γ.*

Proof. The last n equations of (4) can be written in the form

$$A \begin{bmatrix} I_1 \\ I_2 \\ \vdots \\ I_n \end{bmatrix} = \begin{bmatrix} -\lambda S \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \text{ or } \begin{bmatrix} I_1 \\ I_2 \\ \vdots \\ I_n \end{bmatrix} = A^{-1} \begin{bmatrix} -\lambda S \\ 0 \\ \vdots \\ 0 \end{bmatrix}. \tag{8}$$

Multiplying the row vector $(\lambda_1, \cdots, \lambda_n)$ to (8), we have

$$\sum_{i=1}^{n} \lambda_i I_i = (\lambda_1, \cdots, \lambda_n) \begin{bmatrix} I_1 \\ I_2 \\ \vdots \\ I_n \end{bmatrix} = (\lambda_1, \cdots, \lambda_n) A^{-1} \begin{bmatrix} -\lambda S \\ 0 \\ \vdots \\ 0 \end{bmatrix}.$$

Using $\lambda = f(N) \sum_{i=1}^{n} \lambda_i I_i$ we have

$$\sum_{i=1}^{n} \lambda_i I_i = (\lambda_1, \cdots, \lambda_n) A^{-1} \begin{bmatrix} -\lambda S \\ 0 \\ \vdots \\ 0 \end{bmatrix} = (\lambda_1, \cdots, \lambda_n) A^{-1} \begin{bmatrix} -f(N)S \\ 0 \\ \vdots \\ 0 \end{bmatrix} \sum_{i=1}^{n} \lambda_i I_i.$$

Since $\sum_{i=1}^{n} \lambda_i I_i \neq 0$, we obtain

$$1 = (\lambda_1, \cdots, \lambda_n) A^{-1} \begin{bmatrix} -f(N)S \\ 0 \\ \vdots \\ 0 \end{bmatrix} = -Sf(N)(\lambda_1, \cdots, \lambda_n) A^{-1} \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = \beta S f(N). \tag{9}$$

Also, by (8),

$$(1, \cdots, 1) \begin{bmatrix} I_1 \\ I_2 \\ \vdots \\ I_n \end{bmatrix} = (1, \cdots, 1) A^{-1} \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} \left(\sum_{i=1}^{n} \lambda_i I_i\right)(-f(N)S) = pSf(N) \sum_{i=1}^{n} \lambda_i I_i, \tag{10}$$

where, by Proposition 2.1,

$$p \doteq -(1, \cdots, 1)A^{-1} \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} > 0. \tag{11}$$

From the first equation of (4) we get

$$f(N)S \sum_{i=1}^{n} \lambda_i I_i = \Lambda - d_0 S,$$

which, together with (10), implies

$$\sum_{i=1}^{n} I_i = p(\Lambda - d_0 S),$$

and thus

$$N = S + \sum_{i=1}^{n} I_i = S + p(\Lambda - d_0 S) = p\Lambda + (1 - pd_0)S. \tag{12}$$

Substitute (12) into (9), and we obtain the equation for an endemic equilibrium $(S, I_1, \cdots, I_n)$

$$Sf(p\Lambda + (1 - pd_0)S) = \frac{1}{\beta}. \tag{13}$$

We will show that equation (13) has a unique positive solution in the interval $(0, \Lambda/d_0)$ when $R_0 > 1$. Let

$$g(S) = S f(p\Lambda + (1 - pd_0)S).$$

Then $g(0) = 0$, and

$$g\left(\frac{\Lambda}{d_0}\right) = \frac{\Lambda}{d_0} f\left(p\Lambda + (1 - pd_0)\frac{\Lambda}{d_0}\right) = \frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right) = \frac{R_0}{\beta}.$$

Furthermore, by our assumption (**H**) on function $f(N)$,

$$g'(S) = f(p\Lambda + (1 - pd_0)S) + (1 - pd_0)Sf'(p\Lambda + (1 - pd_0)S)$$
$$= f(N) + N f'(N) - p\Lambda f'(N) > 0,$$

where $N = p\Lambda + (1 - pd_0)S$. Thus the function $y = g(S)$ is strictly monotonically increasing, and its graph has at most one intersection with the line $y = 1/\beta$. Such an intersection exists for $S \in (0, \Lambda/d_0)$ if and only if $g(\Lambda/d_0) > 1/\beta$, namely, $R_0 > 1$. This completes the proof of Theorem 2.1. $\square$

3. **Stability of the disease-free equilibrium P_0.** The following stability result can be derived from a more general result in [14] for a model with arbitrarily distributed infectious stages. The proof we presented here provides a motivation for our definition of R_0.

THEOREM 3.1. *Assume that f satisfies (**H**). If $R_0 \leq 1$, then P_0 is globally asymptotically stable in Γ. If $R_0 > 1$, then P_0 is unstable, and system (1) is uniformly persistent with respect to Γ.*

Proof. The last n equations in (1) can be rewritten as

$$\begin{bmatrix} I_1' \\ I_2' \\ \vdots \\ I_n' \end{bmatrix} = \begin{bmatrix} \lambda S \\ 0 \\ \vdots \\ 0 \end{bmatrix} + A \begin{bmatrix} I_1 \\ I_2 \\ \vdots \\ I_n \end{bmatrix},$$

where A is given as in (5). Multiplying a row vector $(c_1, c_2, \cdots, c_n)$ to the above equation, we obtain

$$(c_1, c_2, \cdots, c_n) \begin{bmatrix} I_1' \\ I_2' \\ \vdots \\ I_n' \end{bmatrix} = (c_1, c_2, \cdots, c_n) \begin{bmatrix} \lambda S \\ 0 \\ \vdots \\ 0 \end{bmatrix} + (c_1, c_2, \cdots, c_n) A \begin{bmatrix} I_1 \\ I_2 \\ \vdots \\ I_n \end{bmatrix}.$$

Choose

$$(c_1, c_2, \cdots, c_n) = -(\lambda_1, \lambda_2, \cdots, \lambda_n) A^{-1}. \tag{14}$$

Since $-A^{-1}$ is nonnegative, we know $c_k \geq 0$, $k = 1, \cdots, n$. In particular,

$$c_1 = -(\lambda_1, \lambda_2, \cdots, \lambda_n) A^{-1} \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} = \beta > 0.$$

For the choice of c_i in (14), define a Lyapunov function

$$L = \sum_{k=1}^{n} c_k I_k.$$

Then, using assumption (**H**) we obtain, along a solution of (1),

$$L' = c_1 f(N) S \sum_{i=1}^{n} \lambda_i I_i - \sum_{i=1}^{n} \lambda_i I_i = (c_1 f(N) S - 1) \sum_{i=1}^{n} \lambda_i I_i$$

$$= (\beta f(N) S - 1) \sum_{i=1}^{n} \lambda_i I_i \leq (\beta f(S) S - 1) \sum_{i=1}^{n} \lambda_i I_i$$

$$\leq \left[\beta f\left(\frac{\Lambda}{d_0}\right) \frac{\Lambda}{d_0} - 1 \right] \sum_{i=1}^{n} \lambda_i I_i = (R_0 - 1) \sum_{i=1}^{n} \lambda_i I_i \leq 0, \quad \text{if } R_0 \leq 1.$$

Furthermore, $L' = 0$ if and only if either (a) $I_1 = I_2 = \cdots = I_n = 0$ or (b) $R_0 = 1$ and $S = \Lambda/d_0$ are satisfied. In either case, the largest compact invariant subset of the set

$$G = \{(S, I_1, \cdots, I_n) \in \Gamma \ : \ L' = 0\}$$

is the singleton $\{P_0\}$. To see this, let K be the largest compact invariant subset of G. In case (a), each solution in K satisfies equation $S'(t) = \Lambda - d_0 S$, and the only solution that is bounded for $t \in (-\infty, \infty)$ is $S = \Lambda/d_0$. In case (b), $S = \Lambda/d_0$ satisfies equation

$$S' = \Lambda - d_0 S - [f(N) \sum_{k=1}^{n} \lambda_k I_k] S,$$

which implies $\sum_{k=1}^{n} \lambda_k I_k = 0$, i.e., $I_1 = \cdots = I_n = 0$. Therefore, all solutions in Γ converge to P_0, by LaSalle's Invariance Principle (see [11]). The global attractivity

of P_0 and the Lyapunov function L imply that P_0 is also locally stable, since otherwise P_0 will have a homoclinic orbit that is entirely contained in G, contradicting that the largest compact invariant set in G is $\{P_0\}$. This establishes the global stability of P_0 when $R_0 \leq 1$.

If $R_0 > 1$, $L' > 0$ for S sufficiently close to Λ/d_0, and thus solutions in Γ sufficiently close to P_0 move away from P_0, except those on the invariant S-axis, along which solutions converge to P_0. Therefore, P_0 is unstable. Furthermore, $\{P_0\}$ is the only compact invariant set on the boundary of Γ and is isolated. The local dynamics near P_0 and the boundary of Γ imply that system (1) is uniformly persistent (see [12]) with respect to Γ, when $R_0 > 1$. The proof of uniform persistence of (1) is similar to that of Proposition 3.3 in [13]. $\qquad\square$

4. **The basic reproduction number R_0.** Theorems 2.1 and 3.1 establish R_0 as a sharp threshold parameter. If $R_0 \leq 1$, the disease dies out irrespective of the initial number of cases. If $R_0 > 1$, then the disease persists in the feasible region and there is a unique endemic equilibrium. Such a role of threshold parameter is expected of the basic reproduction number, the average number of infections caused by a single infective in a population at the disease-free equilibrium ([15, 16, 17, 18, 19, 20]). It is then reasonable to regard the parameter R_0 defined in (7) as the basic reproduction number.

Our derivation of R_0 is based on the stability analysis of the disease-free equilibrium P_0 using a Lyapunov function, as in [19]. Other methods of deriving R_0 exist in the literature; among them are the method of second generation matrix in [17], which was later modified in [20], and the derivation based on the linear stability analysis of P_0 (see [18]). In the following, we show that the method of next generation matrix as formulated in [20] for deriving the basic reproduction number leads to the same R_0 as given in (7).

Set $y = (I_1, \cdots, I_n, S)^T$. Then model (1) can be written as

$$y' = \mathcal{F}(y) + \mathcal{V}(y),$$

where

$$\mathcal{F}(y) = \begin{bmatrix} \lambda S \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \quad \mathcal{V}(y) = \begin{bmatrix} -(d_1 + \delta_1)I_1 \\ \delta_1 I_1 - (d_2 + \delta_2)I_2 \\ \vdots \\ \delta_{n-1}I_{n-1} - (d_n + \delta_n)I_n \\ \Lambda - d_0 S - \lambda S \end{bmatrix}.$$

At the disease-free equilibrium in the new coordinates, $\tilde{P}_0 = (0, 0, \cdots, 0, \Lambda/d_0)$,

$$\frac{\partial \mathcal{F}}{\partial y}(\tilde{P}_0) = \begin{bmatrix} F_{n \times n} & 0 \\ 0 & 0 \end{bmatrix},$$

where

$$F_{n \times n} = \begin{bmatrix} -\lambda_1 & -\lambda_2 & \cdots & -\lambda_n \\ 0 & \cdots & \cdots & 0 \\ \vdots & & & \vdots \\ 0 & \cdots & \cdots & 0 \end{bmatrix} g\left(\frac{\Lambda}{d_0}\right),$$

and $g(N) = Nf(N)$. Moreover,

$$\frac{\partial \mathcal{V}}{\partial y}(\tilde{P}_0) = \begin{bmatrix} & & & 0 \\ & V_{n \times n} & & \vdots \\ & & & 0 \\ -\lambda_1 g\left(\frac{\Lambda}{d_0}\right) & \cdots & -\lambda_n g\left(\frac{\Lambda}{d_0}\right) & -d_0 \end{bmatrix}.$$

Here $V_{n \times n} = A$, where A is defined in (5). Hence, the next generation matrix (see [20])

$$FV^{-1} = \begin{bmatrix} c_1 & c_2 & \cdots & c_n \\ 0 & \cdots & \cdots & 0 \\ \vdots & & & \vdots \\ 0 & \cdots & \cdots & 0 \end{bmatrix} g\left(\frac{\Lambda}{d_0}\right),$$

where c_i are defined in (14), and thus $c_1 = \beta$. The basic reproduction number is defined in [20] as the spectral radius, $\rho(FV^{-1})$, of the matrix FV^{-1}. It is easy to see that

$$\rho(FV^{-1}) = c_1 \, g\left(\frac{\Lambda}{d_0}\right) = \beta \, \frac{\Lambda}{d_0} \, f\left(\frac{\Lambda}{d_0}\right),$$

which gives the same R_0 as in (7).

Next, we derive the explicit expression of β defined in (6) and then derive R_0 according to (7). Let $I_{n \times n}$ be the identity matrix. Solving the matrix equation $-AX = I_{n \times n}$, we obtain that $X = -A^{-1}$ is a lower triangular matrix

$$-A^{-1} = \begin{bmatrix} c_{11} & & & 0 \\ c_{21} & c_{22} & & \\ \vdots & \vdots & \ddots & \\ c_{n1} & c_{n2} & \cdots & c_{nn} \end{bmatrix}, \tag{15}$$

where c_{ij}'s are determined by the following iterative relations:

$$c_{ii} = \frac{1}{d_i + \delta_i}, \quad i = 1, \cdots, n,$$

$$c_{ki} = \frac{\delta_{k-1}}{d_k + \delta_k} c_{(k-1)i}, \quad i = 1, \cdots, n, \quad k = 2, \cdots, n, \; k \neq i.$$

Therefore

$$R_0 = \left[\frac{\lambda_1}{d_1 + \delta_1} + \frac{\lambda_2}{d_1 + \delta_1} \frac{\delta_1}{d_2 + \delta_2} + \cdots + \frac{\lambda_n}{d_1 + \delta_1} \frac{\delta_1}{d_2 + \delta_2} \cdots \frac{\delta_{n-1}}{d_n + \delta_n} \right] \frac{\Lambda}{d_0} f\left(\frac{\Lambda}{d_0}\right). \tag{16}$$

For the class $f(N) = N^{-\alpha}$, $0 \leq \alpha \leq 1$, we have the corresponding basic reproduction number

$$R_{0,\alpha} = \left[\frac{\lambda_1}{d_1 + \delta_1} + \frac{\lambda_2}{d_1 + \delta_1} \frac{\delta_1}{d_2 + \delta_2} + \cdots + \frac{\lambda_n}{d_1 + \delta_1} \frac{\delta_1}{d_2 + \delta_2} \cdots \frac{\delta_{n-1}}{d_n + \delta_n} \right] \left(\frac{\Lambda}{d_0}\right)^{1-\alpha}. \tag{17}$$

If $\alpha = 1$, then $R_{0,1}$ gives the same expression for the basic reproduction number for the standard incidence as in [4, 20], while if $\alpha = 0$, $R_{0,0}$ gives the basic reproduction number for the bilinear incidence. We also note from (17) that $R_{0,\alpha}$ decreases as α increases, if $\Lambda/d_0 > 1$; the bilinear incidence gives the largest value of $R_{0,\alpha}$ while the standard incidence gives the smallest value (see Figure 2).
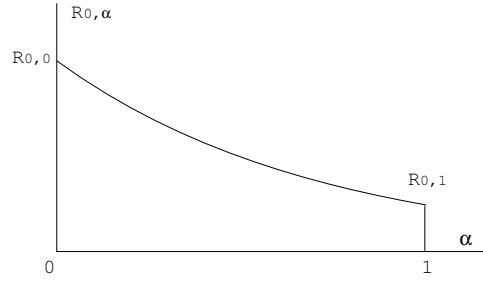
FIGURE 2. Dependence of $R_{0,\alpha}$ on α.

5. **Stability of the endemic equilibrium P^*.** In this section, for $f(N) \equiv 1$, we prove the global stability of the endemic equilibrium P^* when $R_0 > 1$.

THEOREM 5.1. *Assume that $f(N) \equiv 1$ and $R_0 > 1$. Then the endemic equilibrium P^* is asymptotically stable. Furthermore, all solutions in the interior of Γ converge to P^*.*

Proof. Rewrite the equilibrium equations (4) for $P^* = (S^*, I_1^*, \cdots, I_n^*)$ as

$$\Lambda = d_0 S^* + (\sum_{i=1}^{n} \lambda_i I_i^*) S^*,$$

$$\sum_{i=1}^{n} \lambda_i I_i^* S^* = (d_1 + \delta_1) I_1^*, \tag{18}$$

$$\delta_{i-1} I_{i-1}^* = (d_i + \delta_i) I_i^*, \quad i = 2, \ldots, n,$$

which leads to

$$S^* = \frac{(d_1 + \delta_1) I_1^*}{\sum\limits_{i=1}^{n} \lambda_i I_i^*}, \tag{19}$$

and

$$\frac{\delta_{i-1} I_{i-1}^*}{d_i + \delta_i} = I_i^*, \quad i = 2, \cdots, n. \tag{20}$$

Set $x = (S, I_1, I_2, \cdots, I_n) \in \Gamma \subset \mathbb{R}_{n+1}^{+}$. Consider a Lyapunov function

$$W = W(x) = \left(S - S^* - S^* \ln \frac{S}{S^*}\right) + \left(I_1 - I_1^* - I_1^* \ln \frac{I_1}{I_1^*}\right) + \sum_{i=2}^{n} b_i \left(I_i - I_i^* - I_i^* \ln \frac{I_i}{I_i^*}\right),$$

where $x^* = P^* = (S^*, I_1^*, \cdots, I_n^*)$, and $b_i > 0$ is defined inductively in the following way:

$$b_i = \frac{b_{i+1}\delta_i + \lambda_i S^*}{d_i + \delta_i}, \quad i = 2, \cdots, n-1, \quad \text{and} \quad b_n = \frac{\lambda_n S^*}{d_n + \delta_n}. \tag{21}$$

We note that $W(x) \geq 0$, for $x \in \text{Int}\,\Gamma$, the interior of Γ, and $W(x) = 0 \iff x = x^*$. So function W is positive definite with respect to the endemic equilibrium $x^* = P^*$. Solving the inductive relation (21), we obtain

$$b_i = \frac{\sum\limits_{k=i}^{n} \lambda_k I_k^* S^*}{(d_i + \delta_i) I_i^*}, \quad i = 2, \cdots, n, \tag{22}$$

or equivalently

$$b_i(d_i + \delta_i)I_i^* = \sum_{k=i}^{n} \lambda_k I_k^* S^*, \quad i = 2, \cdots, n. \tag{23}$$

Computing the derivative of W along solutions of system (1), we obtain

$$\frac{dW}{dt} = (1 - \frac{S^*}{S})S' + (1 - \frac{I_1^*}{I_1})I_1' + \sum_{i=2}^{n} b_i(1 - \frac{I_i^*}{I_i})I_i'. \tag{24}$$

Using (1) we have

$$(1 - \frac{S^*}{S})S'$$

$$= \Lambda - d_0 S - \sum_{i=1}^{n} \lambda_i I_i S - \frac{\Lambda S^*}{S} + d_0 S^* + \sum_{i=1}^{n} \lambda_i I_i S^*$$

$$= 2d_0 S^* + \sum_{i=1}^{n} \lambda_i I_i^* S^* - d_0 S - \sum_{i=1}^{n} \lambda_i I_i S - \frac{d_0 S^{*2}}{S} - \sum_{i=1}^{n} \lambda_i I_i^* \frac{S^{*2}}{S} + \sum_{i=1}^{n} \lambda_i I_i S^*$$

$$= \left(2d_0 S^* - d_0 S - \frac{d_0 S^{*2}}{S}\right) - \sum_{i=1}^{n} \lambda_i I_i S + \sum_{i=1}^{n} \lambda_i I_i S^* + \sum_{i=1}^{n} \lambda_i I_i^* S^* - \sum_{i=1}^{n} \lambda_i I_i^* \frac{S^{*2}}{S}$$

$$\leq -\sum_{i=1}^{n} \lambda_i I_i S + \sum_{i=1}^{n} \lambda_i I_i S^* + \sum_{i=1}^{n} \lambda_i I_i^* S^* - \sum_{i=1}^{n} \lambda_i I_i^* \frac{S^{*2}}{S}, \tag{25}$$

since

$$\left(2d_0 S^* - d_0 S - \frac{d_0 S^{*2}}{S}\right) = d_0 S^* \left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) \leq 0.$$

In the second step of the above derivation, we substituted Λ by the right-hand side of the first equation of (18). Similarly, using (1) and (18), we obtain

$$(1 - \frac{I_1^*}{I_1})I_1' = \sum_{i=1}^{n} \lambda_i I_i S - (d_1 + \delta_1)I_1 - \sum_{i=1}^{n} \lambda_i I_i S \frac{I_1^*}{I_1} + (d_1 + \delta_1)I_1^*$$

$$= \sum_{i=1}^{n} \lambda_i I_i S - (d_1 + \delta_1)I_1 - \sum_{i=1}^{n} \lambda_i I_i S \frac{I_1^*}{I_1} + \sum_{i=1}^{n} \lambda_i I_i^* S^*. \tag{26}$$

For $i = 2, 3, \cdots, n$, using (1),

$$b_i(1 - \frac{I_i^*}{I_i})I_i' = b_i \delta_{i-1} I_{i-1} - b_i(d_i + \delta_i)I_i - \frac{b_i \delta_{i-1} I_{i-1} I_i^*}{I_i} + b_i(d_i + \delta_i)I_i^*. \tag{27}$$

Notice that

$$\sum_{i=1}^{n} \lambda_i I_i S^* - (d_1 + \delta_1)I_1 + \sum_{i=2}^{n} [b_i \delta_{i-1} I_{i-1} - b_i(d_i + \delta_i)I_i]$$

$$= \lambda_1 I_1 S^* - (d_1 + \delta_1)I_1 + \sum_{i=2}^{n} (\lambda_i I_i S^* + b_i \delta_{i-1} I_{i-1} - b_i(d_i + \delta_i)I_i)$$

$$= (\lambda_1 S^* - (d_1 + \delta_1) + b_2 \delta_1)I_1 + \sum_{i=2}^{n-1} (\lambda_i S^* + b_{i+1}\delta_i - b_i(d_i + \delta_i))I_i$$

$$\quad + (\lambda_n S^* - b_n(d_n + \delta_n))I_n$$

$$= 0. \tag{28}$$

It is straightforward to verify that the last two terms of the above expression are 0, using the inductive relation (21) of b_i, $i = 2, \cdots, n$. To see that the first term is zero, we observe

$$\lambda_1 S^* - (d_1 + \delta_1) + b_2 \delta_1$$

$$= \lambda_1 S^* + \frac{\sum_{k=2}^n \lambda_k I_k^* S^*}{(d_2 + \delta_2) I_2^*} \delta_1 - (d_1 + \delta_1) = \lambda_1 S^* + \sum_{k=2}^n \lambda_k I_k^* S^* \frac{\delta_1}{\delta_1 I_1^*} - (d_1 + \delta_1)$$

$$= \lambda_1 S^* + \sum_{k=2}^n \lambda_k I_k^* S^* \frac{1}{I_1^*} - (d_1 + \delta_1) = \frac{1}{I_1^*} \left[\sum_{k=1}^n \lambda_k I_k^* S^* - (d_1 + \delta_1) I_1^* \right] = 0$$

by (19). Using (25)-(28), we can calculate and simplify (24) as

$$\frac{dW}{dt} \leq \left(-\sum_{i=1}^n \lambda_i I_i^* \frac{S^{*2}}{S} - \sum_{i=1}^n \lambda_i I_i S \frac{I_1^*}{I_1} - \sum_{i=2}^n \frac{b_i \delta_{i-1} I_{i-1} I_i^*}{I_i} \right)$$

$$+ \left(\sum_{i=2}^n b_i (d_i + \delta_i) I_i^* + 2 \sum_{i=1}^n \lambda_i I_i^* S^* \right) \tag{29}$$

$$\doteq A + B.$$

From (23) we have

$$B = \sum_{i=2}^n b_i (d_i + \delta_i) I_i^* + 2 \sum_{i=1}^n \lambda_i I_i^* S^*$$

$$= \sum_{i=1}^n (i+1) \lambda_i I_i^* S^*. \tag{30}$$

By (22), (20), and exchange of order of summation, we have

$$\sum_{i=2}^n \frac{b_i \delta_{i-1} I_{i-1} I_i^*}{I_i} = \sum_{i=2}^n \frac{\sum_{k=i}^n \lambda_k I_k^* S^*}{(d_i + \delta_i) I_i^*} \frac{\delta_{i-1} I_{i-1} I_i^*}{I_i} = \sum_{i=2}^n \sum_{k=i}^n \lambda_k I_k^* S^* \frac{\delta_{i-1} I_{i-1}}{(d_i + \delta_i) I_i}$$

$$= \sum_{i=2}^n \sum_{k=i}^n \lambda_k I_k^* S^* \frac{I_i^* I_{i-1}}{I_{i-1}^* I_i} = \sum_{i=2}^n \lambda_i I_i^* S^* \sum_{k=2}^i \frac{I_k^* I_{k-1}}{I_k I_{k-1}^*}. \tag{31}$$

Therefore, from (29) - (31), we have

$$\frac{dW}{dt} \leq \sum_{i=2}^n \left[(i+1) \lambda_i I_i^* S^* - \lambda_i I_i^* \frac{S^{*2}}{S} - \lambda_i I_i S \frac{I_1^*}{I_1} - \lambda_i I_i^* S^* \sum_{k=2}^i \frac{I_k^* I_{k-1}}{I_k I_{k-1}^*} \right]$$

$$= \sum_{i=2}^n \lambda_i I_i^* S^* \left[(i+1) - \frac{S^*}{S} - \frac{S I_i I_1^*}{S^* I_i^* I_1} - \sum_{k=2}^i \frac{I_k^* I_{k-1}}{I_k I_{k-1}^*} \right]. \tag{32}$$

For each i, we have

$$-\frac{S^*}{S} - \frac{S I_i I_1^*}{S^* I_i^* I_1} - \sum_{k=2}^i \frac{I_k^* I_{k-1}}{I_k I_{k-1}^*} \leq -(i+1), \tag{33}$$

by the inequality

$$a_1 + a_2 + \cdots + a_n \geq n \sqrt[n]{a_1 \cdot a_2 \cdots a_n}, \quad \text{for} \quad a_i \geq 0, \quad i = 1, \cdots, n.$$

Therefore, along any solution $(S(t), I_1(t), I_2(t), \cdots, I_n(t))$ in $\operatorname{Int}\Gamma$, we conclude from (32) and (33) that $\dfrac{dW}{dt} \leq 0$. Furthermore, $\dfrac{dW}{dt} = 0$, if and only if equalities hold in (25), (29), (32), and (33), and if and only if $(S(t), I_1(t), I_2(t), \cdots, I_n(t))$ is the endemic equilibrium P^*. Therefore the directional derivative of W in the direction of the vector field of (1) is negative definite in $\operatorname{Int}\Gamma$ with respect to the endemic equilibrium P^*. This implies that the basin of attraction of P^* contains $\operatorname{Int}\Gamma$. The positive definiteness of $W(x)$ with respect to P^* implies that P^* is also locally stable. This completes the proof of Theorem 5.1. $\qquad\square$

REMARK 1. *Lyapunov functions of the type used in the proof of Theorem 5.1 have been used in the literature, for ecological models (e.g., see [21]) and more recently for epidemic models (e.g., see [22]).*

6. **Appendix.** The following definition and properties of M-matrices are used in our analysis. They can be found in most of the texts on matrix theory; see, e.g., [23].

DEFINITION 6.1. *$B_{n \times n}$ is a M-matrix if*

(1) *Off-diagonal entries of B are non-positive, and*
(2) *B is positively stable, namely, all eigenvalues of B have positive real parts.*

PROPOSITION 6.1. *Properties of M-matrices*

(1) *$B = \alpha I - P$, $P \geq 0$, $\alpha > \rho(P)$, the spectral radius of P.*
(2) *B is nonsingular and $B^{-1} \geq 0$.*
(3) *There exists $\beta > 0$ such that $B^{-1}x \geq \beta\,x$ for $x \geq 0$.*

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