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A multi-species epidemic model with spatial dynamics

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A model is formulated that describes the spatial propagation of a disease that can be transmitted between multiple species. The spatial component consists, for each species, of a certain number of patches that make up the vertices of a digraph, the arcs of which represent the movement of the various species between the patches. In each of the patches and for each species, a susceptible-exposed-infectious-recovered (SEIR) epidemic model describes the evolution of the disease status of individuals. Also in each patch, there is transmission of the disease from species to species. An analysis of the system is given, beginning with results on the mobility component. A formula is derived for the computation of the basic reproduction number $\mathcal{R}_0$ for s species and n patches, which then determines the global stability properties of the disease free equilibrium. Simulations for the spread of a disease in one species and two patches are presented.

Keywords: spatial epidemic; multiple species; basic reproduction number; global stability.

1. Introduction

The spatial and temporal spread of infectious disesases is of considerable practical importance. The world has observed the efficient spatial spread of infection following the introduction of agents at discrete locations and times; plague in Europe in the 1300s, smallpox in the New World in the 1500s (Zinsser, 1935), West Nile virus in North America in the 1990s (Petersen & Roehrig, 2001) and SARS

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in Asia in 2003 (World Health Organization, 2003) are but a few examples. Concern over potential biological terrorism (Henderson, 1999) further highlights the need to understand the dynamics of disease outbreaks. To the extent that population and geographic heterogeneities play key roles in the infection-spread process, epidemiology models must include them, in order to capture the necessary character of the epidemic and endemic states. Population heterogeneities, such as age structure, multiple risk groups and the existence of vector species are routinely handled in models, see, e.g. Grenfell & Dobson (1995), Isham & Medley (1996) and Mollison (1995). However, much of classical mathematical epidemiology tends to minimize geographic heterogeneity and related spatial aspects of deterministic epidemic models.

One notable example of a deterministic disease model that includes spatial heterogeneity is provided by the work of Baroyan *et al.*, which is applied to the spatial spread of influenza between cities in the Soviet Union (Baroyan & Rvachev, 1967; Baroyan *et al.*, 1971). In their approach, a large geographic region (country) is partitioned into smaller sub-regions (cities). Migration and transportation between these sub-regions are explicitly incorporated. Within a given sub-region, transmission is handled according to a discrete deterministic compartmental susceptible-infectious-recovered (SIR) model. The spread of infection from city to city could be modeled, given appropriate transportation data. Such an approach is appealing because it allows infection to be modeled on single-patch, as well as multi-patch, scales, preserving patch-to-patch heterogeneity. A general compartmental model can be formulated and applied on a patch-by-patch basis, allowing for variations in population and immunological attributes. If information on the flow of individuals between patches is known, or if reasonable estimates can be made, then the spread of contagion between patches can be investigated.

Theoretical analysis of such migration models has until recently been confined to limiting cases, wherein the model reduced to the more familiar reaction–diffusion formulation (Murray, 1993). Models with a multi-patch formulation have recently been considered by Sattenspiel & Dietz (1995), Arino & van den Driessche (2003) and Wang & Zhao (2004). The desirability of having analytic, as opposed to purely numerical, tools to analyze this class of multi-patch models is evident: such tools should allow for valuable predictions and analysis of the behavior of solutions for the model. For example, it is desirable to be able to determine the linear stability of the disease free equilibrium (DFE) (i.e. compute the basic reproduction number $\mathcal{R}_0$) explicitly in terms of model parameters. Similarly, a detailed theoretical analysis can be expected to suggest whether migration between arbitrary patches tends to have a stabilizing or a destabilizing effect.

We undertake such a theoretical analysis of a general multi-species, multi-patch model with four disease status compartments (an SEIR model). In Section 2, the model is described, in Section 3 it is analyzed and a general formula for $\mathcal{R}_0$ is derived; a proof of the global stability of the DFE in the case $\mathcal{R}_0 < 1$ is given. In Section 4, we consider the case of a single species on multiple patches, including numerical simulations of the spread of disease concentrating on the case of two patches.

2. The model

An SEIR epidemic model with spatial dynamics is considered for a population consisting of s species and occupying n spatial patches. The numbers of susceptible, exposed (latent), infective (infectious) and recovered individuals of species i in patch p at time t are denoted by S_{ip}, E_{ip}, I_{ip} and R_{ip}, respectively, with the total number of individuals of species i in patch p denoted by N_{ip}. Note that, unlike the single-species models introduced by Sattenspiel & Dietz (1995) and further analyzed by Arino & van den Driessche (2003), we do not keep track of where an individual usually resides, but only where an individual is at time t. The dynamics for species $i = 1, \ldots, s$ in patch $p = 1, \ldots, n$ is given by the

following system of $4sn$ equations;

$$\frac{\mathrm{d}S_{ip}}{\mathrm{d}t} = d_{ip}(N_{ip} - S_{ip}) - \sum_{j=1}^{s} \beta_{ijp} S_{ip} \frac{I_{jp}}{N_{jp}} + \sum_{q=1}^{n} m_{ipq} S_{iq} - \sum_{q=1}^{n} m_{iqp} S_{ip}, \tag{2.1a}$$

$$\frac{\mathrm{d}E_{ip}}{\mathrm{d}t} = \sum_{j=1}^{s} \beta_{ijp} S_{ip} \frac{I_{jp}}{N_{jp}} - (d_{ip} + \varepsilon_{ip}) E_{ip} + \sum_{q=1}^{n} m_{ipq} E_{iq} - \sum_{q=1}^{n} m_{iqp} E_{ip}, \tag{2.1b}$$

$$\frac{\mathrm{d}I_{ip}}{\mathrm{d}t} = \varepsilon_{ip} E_{ip} - (d_{ip} + \gamma_{ip}) I_{ip} + \sum_{q=1}^{n} m_{ipq} I_{iq} - \sum_{q=1}^{n} m_{iqp} I_{ip}, \tag{2.1c}$$

$$\frac{\mathrm{d}R_{ip}}{\mathrm{d}t} = \gamma_{ip} I_{ip} - d_{ip} R_{ip} + \sum_{q=1}^{n} m_{ipq} R_{iq} - \sum_{q=1}^{n} m_{iqp} R_{ip}, \tag{2.1d}$$

where $N_{ip} = S_{ip} + E_{ip} + I_{ip} + R_{ip}$. Here $1/d_{ip} > 0$, $1/\varepsilon_{ip} > 0$, $1/\gamma_{ip} > 0$ are the average lifetime, latent period and infectious period for species i in patch p, respectively. All newborns are assumed to be susceptible with birth term $d_{ip}N_{ip}$, and disease related mortality is neglected. The disease is assumed to be horizontally transmitted within and between species according to standard incidence (see, e.g. Hethcote, 2000; McCallum *et al.*, 2001) with $\beta_{ijp} \geqslant 0$ the rate of disease transfer from species j to species i in patch p. The rate of travel, for species i, from patch q to patch p, is given by m_{ipq} with $m_{ipq} \geqslant 0$ and is assumed to be the same for each type of individual of species i. We set $m_{ipp} = 0$, but note that the m_{ipp} terms cancel in each equation. We use the terms movement, travel, migration and mobility interchangeably throughout the text. The population of species i in patch p is N_{ip}, and the total population for species i is $\sum_{p=1}^{n} N_{ip} = N_i^0$, a fixed constant. The initial value problem is given by (2.1) together with initial conditions $N_{ip} > 0$ and S_{ip}, E_{ip}, I_{ip}, $R_{ip} \geqslant 0$ at time $t = 0$. The system (2.1) is well posed, with all variables remaining non-negative and N_{ip} positive for $t \geqslant 0$.

By adding the equations in (2.1), the mobility equation for the population of species i in patch p is

$$\frac{\mathrm{d}N_{ip}}{\mathrm{d}t} = \sum_{q=1}^{n} m_{ipq} N_{iq} - \sum_{q=1}^{n} m_{iqp} N_{ip}. \tag{2.2}$$

With $N_i = [N_{i1}, \ldots, N_{in}]^t$, this can be written as the linear system

$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = M_i N_i, \tag{2.3}$$

with mobility matrix for species i

$$M_i = \begin{bmatrix} -\sum_{q=1}^{n} m_{iq1} & m_{i12} & \cdots & m_{i1n} \\ \vdots & & \ddots & \\ m_{in1} & m_{in2} & \cdots & -\sum_{q=1}^{n} m_{iqn} \end{bmatrix}. \tag{2.4}$$

Note that $(-M_i)$ has the Z-sign pattern and (since there is no birth and death during travel) each column sum of M_i is zero, i.e. $\mathbb{1}_n^t(-M_i) = 0$ for all i, where the $1 \times n$ vector $\mathbb{1}_n^t = [1, \ldots, 1]$. Thus, $(-M_i)$ is a singular M-matrix (see, e.g. Fiedler, 1986, Theorem 5.11).

The zero/non-zero structure of the mobility matrix M_i specifies the arcs of a directed graph (digraph) describing how the patches as vertices are connected. For species i, a patch q has direct access to patch

p (Berman & Plemmons, 1979, p. 39) if $m_{ipq} > 0$ (i.e. qp is an arc in the digraph). Patch q has an access to patch p if there exists a path in the digraph from q to p. Patch q has an access to patch p for all p, q if and only if M_i is irreducible.

3. Analysis of the general model

System (2.1) is at an equilibrium if all time derivatives are zero. There is no disease in species i if $E_{ip} = I_{ip} = 0$ for $p = 1, \ldots, n$. Similarly there is no disease in patch p if $E_{ip} = I_{ip} = 0$ for $i = 1, \ldots, s$. If patch p is at an equilibrium and has no disease, then it is at the DFE. The system is at the DFE if $E_{ip} = I_{ip} = 0$ for all i, p. From (2.1d) with $I_{ip} = 0$ and $R_i = (R_{i1}, \ldots, R_{in})^t$, it follows that $\mathrm{d}R_i/\mathrm{d}t = (M_i - \mathrm{diag}(d_{i1}, \ldots, d_{in}))R_i$. The matrix $M_i - \mathrm{diag}(d_{i1}, \ldots, d_{in})$ is non-singular, implying that at the DFE, $R_i = 0$, and so $\hat{S}_{ip} = N^*_{ip}$, where N^*_{ip} is a constant. The disease in patch p is at an endemic equilibrium in species i if $E_{ip} + I_{ip} > 0$ for some i.

The graph theoretic ideas introduced above are used in the following two results; in particular, to determine where the endemic equilibrium in one patch propagates by mobility.

THEOREM 3.1 Suppose that system (2.1) is at an equilibrium and that there is no disease in patch p. Then for a given species i, $E_{ij} = I_{ij} = 0$ for each patch j that has an access to patch p. In particular, if the matrices M_i are irreducible, then the system is at the DFE.

Proof. Fix the species index at i. For simplicity suppose that $p = 1$, i.e. that there is no disease in patch 1, thus $E_{i1} = I_{i1} = 0$. Then for $p = 1$, (2.1c) is

$$0 = \frac{\mathrm{d}I_{i1}}{\mathrm{d}t} = \sum_{r=2}^{n} m_{i1r} I_{ir}.$$

For a given patch r define

$$\mathcal{I}^r_{\mathrm{da}} = \{q : m_{irq} > 0\},$$

as the subset of patches with a direct access to patch r, and

$$\mathcal{I}^r_{\mathrm{nda}} = \{q \neq r : m_{irq} = 0\},$$

as the subset of patches with no direct access to r. Using these subsets of indices for patch 1, it follows from the non-negativity of I_{ir} and

$$\sum_{r=2}^{n} m_{i1r} I_{ir} = \sum_{r \in \mathcal{I}^1_{\mathrm{da}}} m_{i1r} I_{ir} + \sum_{r \in \mathcal{I}^1_{\mathrm{nda}}} m_{i1r} I_{ir} = 0$$

that $I_{ir} = 0$ for $r \in \mathcal{I}^1_{\mathrm{da}}$. Similarly, setting $p = 1$ in (2.1b) and using $\mathcal{I}^1_{\mathrm{da}}$ it follows that $E_{ir} = 0$ for $r \in \mathcal{I}^1_{\mathrm{da}}$. Thus, all patches r with a direct access to patch 1 have no disease, i.e. are such that $E_{ir} = I_{ir} = 0$.

Now consider a patch r in $\mathcal{I}^1_{\mathrm{da}}$. Using the same argument as previously, it follows that $E_{iw} = I_{iw} = 0$ for all $w \in \mathcal{I}^r_{\mathrm{da}}$. Patches that are in $\mathcal{I}^r_{\mathrm{da}} \setminus \mathcal{I}^1_{\mathrm{da}}$ have a length 2 access to patch 1. By induction, all patches belonging to the same strongly connected component of the digraph as patch 1 are at the DFE if patch 1 is at the DFE.

A sufficient condition for all patches to be disease free (if one patch is disease free) is for M_i to be irreducible. If M_i is reducible, then all patches belonging to the strongly connected component of patch 1 are at the DFE. □

THEOREM 3.2 Suppose that system (2.1) is at an equilibrium. If the disease in patch p is at an endemic equilibrium in species i, then the disease is also at an endemic equilibrium in species i in all patches to which patch p has an access. In particular, if matrix M_i is irreducible, then the disease is at an endemic equilibrium in species i in all patches.

Proof. Fix the species index i. For simplicity suppose that $p = 1$, i.e. $E_{i1} + I_{i1} > 0$. From (2.1b) and (2.1c) with $q \neq 1$,

$$0 = \frac{\mathrm{d}}{\mathrm{d}t}(E_{iq} + I_{iq}) = \sum_{j=1}^{s} \beta_{ijq} S_{ij} \frac{I_{iq}}{N_{iq}} - d_{iq}(E_{iq} + I_{iq}) - \gamma_{iq} I_{iq} + \sum_{r=1}^{n} m_{iqr}(E_{ir} + I_{ir}) - \sum_{r=1}^{n} m_{irq}(E_{iq} + I_{iq}).$$

Assume that $E_{iq} + I_{iq} = 0$ (i.e. $E_{iq} = I_{iq} = 0$) and $m_{iq1} > 0$, i.e. patch 1 has access to patch q. Then the above equation reduces to

$$0 = \sum_{r=1}^{n} m_{iqr}(E_{ir} + I_{ir}),$$

and implies that $E_{i1} + I_{i1} = 0$, giving a contradiction. Thus, the disease in patch q is at an endemic equilibrium. The remainder of the proof follows as in the proof of Theorem 3.1. □

We now assume that matrix M_i is irreducible for each species i; i.e. there exists a path in the digraph from patch q to patch p for all p, q.

THEOREM 3.3 The mobility equation (2.3) subject to the constraint of constant total population for species i has a positive equilibrium, which is asymptotically stable.

Proof. Without loss of generality, the species index i can be dropped. Finding the equilibrium amounts to solving the $n + 1$ linear equations in n variables

$$\begin{bmatrix} \mathbb{1}_n^t \\ \cdots\cdots \\ M \end{bmatrix} \begin{bmatrix} N_1 \\ N_2 \\ \vdots \\ N_n \end{bmatrix} = \begin{bmatrix} N^0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}. \tag{3.1}$$

All column sums of the last n rows are zero, thus the second equation (e.g.) can be eliminated. Now perform column operations $c_r \leftarrow c_r - c_1$ for $r = 2, \ldots, n$ on the determinant of the resulting coefficient matrix, reducing it to the $n-1$ determinant $\det(M(1) + T_1)$, where $M(1)$ denotes matrix M with its first row and column deleted, thus

$$M(1) = \begin{bmatrix} -\sum_{q=1}^{n} m_{q2} & m_{23} & \cdots & m_{2n} \\ \vdots & & \ddots & \\ m_{n2} & m_{n3} & \cdots & -\sum_{q=1}^{n} m_{qn} \end{bmatrix},$$

and $T_1 = m_1 \mathbb{1}_{n-1}^t = [-m_{21}, \ldots, -m_{n1}]^t[1, \ldots, 1]$, where m_1 is the vector formed from the first column of M by omitting the first entry.

By Berman & Plemmons (1979, M_{35}, p. 127) since $m_{pq} \geqslant 0$, $-M(1)$ is a non-singular M-matrix (it has the Z-sign pattern and $\mathbb{1}_{n-1}^t(-M(1)) \geqslant 0$ and is not the zero vector by the assumption that M is irreducible). Thus, $\det(-M(1)) > 0$ and so $\det M(1)$ has sign $(-1)^{n+1}$. Since T_1 has rank 1, it follows from the linearity of the determinant subject to rank 1 perturbations (see, e.g. Rump, 1997, Corollary 4.2), that $\det(M(1) + T_1) = \det M(1)(1 + \mathbb{1}_{n-1}^t M(1)^{-1} m_1)$. As $-M(1)$ is an M-matrix, $(-M(1)^{-1}) \geqslant 0$, thus $M(1)^{-1} \leqslant 0$. But $m_1 \leqslant 0$, thus $1 + \mathbb{1}_{n-1}^t M(1)^{-1} m_1$ is positive and so $\det(M(1) + T_1)$ has the sign of $\det M(1)$, namely $(-1)^{n+1}$.

By Cramer's Rule,

$$N_1 = \frac{\det M(1) N^0}{\det(M(1) + T_1)} = \frac{N^0}{1 + \mathbb{1}_{n-1}^t (M(1))^{-1} m_1} > 0.$$

Similarly, by deleting the $(p+1)$-st equation in (3.1),

$$N_p = \frac{\det M(p) N^0}{\det(M(p) + T_p)} = \frac{N^0}{1 + \mathbb{1}_{n-1}^t (M(p))^{-1} m_p} > 0,$$

where $T_p = m_p \mathbb{1}_{n-1}^t = [-m_{1p}, \ldots, -m_{p-1,p}, -m_{p+1,p}, \ldots, -m_{np}]^t \mathbb{1}_{n-1}^t$ for $p = 1, \ldots, n$. Here m_p is the vector formed from the p-th column of M by omitting the p-th entry. Thus, given a value of N^0, there is a unique positive solution $N_p = N_p^*$ for $p = 1, \ldots, n$.

Since $(-M)$ is an irreducible singular M-matrix, 0 is a simple eigenvalue and all the non-zero eigenvalues of M have negative real parts. The zero eigenvalue occurs as a consequence of the constant population constraint. Thus, the population N_p in each patch tends to N_p^*. □

From the above result, the DFE for species i in patch p exists with $\hat{S}_{ip} = N_{ip}^*$. Note that $N_i^* = (N_{i1}^*, \ldots, N_{in}^*)^t$ is a right null vector of M_i. An example for three species on two patches is given below in Section 3.1.

The local stability of the DFE of system (2.1) is governed by the basic reproduction number $\mathcal{R}_0$, which depends in general on the demographic, disease and mobility parameters. A formula for the basic reproduction number $\mathcal{R}_0$ for system (2.1) is derived using the next generation matrix (Diekmann & Heesterbeek, 2000; van den Driessche & Watmough, 2002) and can be used to determine numerically the value of $\mathcal{R}_0$ for a given set of parameter values. This method involves writing the flows of individuals between the different compartments as two vectors $\mathcal{F}$ and $\mathcal{V}$. The former describes the inflow of new infected individuals, hence here corresponds to the infection terms for each exposed class. The vector $\mathcal{V}$ then summarizes all other flows occuring in the system. Differentiating with respect to the state variables, keeping only those parts of $D\mathcal{F}$ and $D\mathcal{V}$ relative to the infected classes (i.e. E_{ip} and I_{ip} here), and evaluating at the DFE gives matrices F and V. The value of $\mathcal{R}_0$ can be deduced as $\mathcal{R}_0 = \rho(FV^{-1})$, where ρ is the spectral radius. The basic reproduction number acts as a threshold for stability of the DFE; if $\mathcal{R}_0 < 1$ then the DFE is locally asymptotically stable (all eigenvalues of $F - V$ have negative real parts), whereas it is unstable if $\mathcal{R}_0 > 1$ (van den Driessche & Watmough, 2002, Theorem 2).

To determine the matrices F and V, order the infected variables by type, then by patch, i.e.

$$E_{11}, E_{21}, \ldots, E_{s1}, E_{12}, \ldots, E_{sn}, I_{11}, I_{21}, \ldots, I_{s1}, I_{12}, \ldots, I_{sn}.$$

Then the non-negative matrix F has the form

$$F = \left[\begin{array}{c:c} 0 & G \\ \hdashline 0 & 0 \end{array}\right] = \left[\begin{array}{c:c} 0 & \bigoplus_{k=1}^{n} G_k \\ \hdashline 0 & 0 \end{array}\right],$$

and the matrix V is the block matrix

$$V = \left[\begin{array}{c:c} A & 0 \\ \hdashline -C & B \end{array}\right] = \left[\begin{array}{ccc:ccc} A_{11} & \cdots & A_{1n} & & & \\ \vdots & \ddots & \vdots & & 0 & \\ A_{n1} & \cdots & A_{nn} & & & \\ \hdashline & & & B_{11} & \cdots & B_{1n} \\ & -\bigoplus_{k=1}^{n} C_k & & \vdots & \ddots & \vdots \\ & & & B_{n1} & \cdots & B_{nn} \end{array}\right].$$

Here G_k is an $s \times s$ matrix with (i, j) entry equal to $\beta_{ijk} N_{ik}^*/N_{jk}^*$. Matrix A is the block matrix $A = A_{jk}$, with each A_{jk} block an $s \times s$ diagonal matrix. The (i, i) entry of A_{kk} is equal to $d_{ik} + \varepsilon_{ik} + \sum_{l=1}^{n} m_{ilk}$, whereas for $j \neq k$ the (i, i) entry of A_{jk} is $-m_{ijk}$. Matrix B is the same as A but with ε_{ik} replaced by γ_{ik}. Finally, C_k is an $s \times s$ diagonal matrix with (i, i) entry equal to ε_{ik}.

Matrices G, A, B and C are $sn \times sn$ matrices. Matrices A and B are non-singular M-matrices since they have the Z-sign pattern and are diagonally dominant by columns (Berman & Plemmons, 1979, M_{35}, p. 127). Thus, A^{-1} and B^{-1} are non-negative.

THEOREM 3.4 For model (2.1) with s species and n patches,

$$\mathcal{R}_0 = \rho\,(GB^{-1}CA^{-1})$$

If $\mathcal{R}_0 < 1$, then the DFE is globally asymptotically stable, if $\mathcal{R}_0 > 1$ then the DFE is unstable.

Proof. Due to the particular structure of F and V, the computation of $\rho\,(FV^{-1})$ is greatly simplified. Indeed, the inverse V^{-1} of V keeps its block triangular structure

$$V^{-1} = \left[\begin{array}{c:c} A^{-1} & 0 \\ \hdashline B^{-1}CA^{-1} & B^{-1} \end{array}\right],$$

and

$$FV^{-1} = \left[\begin{array}{c:c} 0 & G \\ \hdashline 0 & 0 \end{array}\right]\left[\begin{array}{c:c} A^{-1} & 0 \\ \hdashline B^{-1}CA^{-1} & B^{-1} \end{array}\right] = \left[\begin{array}{c:c} GB^{-1}CA^{-1} & GB^{-1} \\ \hdashline 0 & 0 \end{array}\right].$$

Thus,

$$\mathcal{R}_0 = \rho\,(GB^{-1}CA^{-1}).$$

Since $GB^{-1}CA^{-1}$ is a non-negative matrix, its spectral radius is attained at the largest real eigenvalue. If $\mathcal{R}_0 < 1$, then the DFE is locally stable, whereas if $\mathcal{R}_0 > 1$, then the DFE is unstable (van den Driessche & Watmough, 2002, Theorem 2).

To establish the global stability of the DFE, consider the non-autonomous system consisting of (2.1b), (2.1c) and (2.1d) written in the form

$$\begin{aligned}\frac{\mathrm{d}E_{ip}}{\mathrm{d}t} &= \sum_{j=1}^{s} \beta_{ijp}(N_{ip} - E_{ip} - I_{ip} - R_{ip})\frac{I_{jp}}{N_{jp}} \\ &\quad - (d_{ip} + \varepsilon_{ip})E_{ip} + \sum_{q=1}^{n} m_{ipq}E_{iq} - \sum_{q=1}^{n} m_{iqp}E_{ip},\end{aligned} \tag{3.2}$$

in which S_{ip} has been replaced by $N_{ip} - E_{ip} - I_{ip} - R_{ip}$, and N_{ip} is a solution of (2.2). Write this system as

$$x' = f(t, x), \tag{3.3}$$

where x is the $3sn$-dimensional vector consisting of the E_{ip}, I_{ip} and R_{ip}. The DFE of (2.1) corresponds to the equilibrium $x = 0$ in (3.3). System (2.2), i.e. (2.3) and (2.4), can be solved for $N_{ip}(t)$ independently of the epidemic variables, and Theorem 3.3 implies that the time dependent functions $N_{ip}(t) \to N_{ip}^*$ as $t \to \infty$. Substituting this large time limit value N_{ip}^* for N_{ip} in (3.2) gives

$$\begin{aligned}\frac{\mathrm{d}E_{ip}}{\mathrm{d}t} &= \sum_{j=1}^{s} \beta_{ijp}(N_{ip}^* - E_{ip} - I_{ip} - R_{ip})\frac{I_{jp}}{N_{jp}^*} \\ &\quad - (d_{ip} + \varepsilon_{ip})E_{ip} + \sum_{q=1}^{n} m_{ipq}E_{iq} - \sum_{q=1}^{n} m_{iqp}E_{ip}.\end{aligned} \tag{3.4}$$

Therefore, system (3.3) is asymptotically autonomous, with limit equation

$$x' = g(x). \tag{3.5}$$

To show that 0 is a globally asymptotically stable equilibrium for the limit system (3.5), consider the linear system

$$x' = Lx, \tag{3.6}$$

where x is the $3sn$-dimensional vector consisting of the E_{ip}, I_{ip} and R_{ip}. In L, we replace S_{ip}/N_{jp} with N_{ip}^*/N_{jp}^*. Equations (2.1c) and (2.1d) are not affected by this transformation, whereas (2.1b) takes the form

$$\frac{\mathrm{d}E_{ip}}{\mathrm{d}t} = \sum_{j=1}^{s} \beta_{ijp}\frac{N_{ip}^*}{N_{jp}^*}I_{jp} - (d_{ip} + \varepsilon_{ip})E_{ip} + \sum_{q=1}^{n} m_{ipq}E_{iq} - \sum_{q=1}^{n} m_{iqp}E_{ip}. \tag{3.7}$$

Comparing (3.4) and (3.7), we note that $g(x) \leqslant Lx$ for all $x \in \mathbb{R}_+^{3sn}$. In system (3.6), the equations for E_{ip} and I_{ip} do not involve R_{ip}. Let $\tilde{x}$ be the part of the vector x corresponding to the variables E_{ip} and I_{ip}, and $\tilde{L}$ be the corresponding sub-matrix of L. The method of van den Driessche & Watmough (2002) as used to prove local stability can also be applied to study the stability of the $\tilde{x} = 0$ equilibrium

of the sub-system $\tilde{x}' = \widetilde{L}\tilde{x}$, with $\widetilde{L} = F - V$. Therefore, if $\mathcal{R}_0 < 1$, then the equilibrium $\tilde{x} = 0$ of the sub-system $\tilde{x}' = \widetilde{L}\tilde{x}$ is stable. When $\tilde{x} = 0$, (2.1d) takes the form

$$\frac{\mathrm{d}R_i}{\mathrm{d}t} = (M_i - D_i)R_i,$$

with $R_i = (R_{i1}, \ldots, R_{in})^t$ and D_i is the diagonal matrix with p-th diagonal entry equal to d_{ip}. It was shown in the proof of Theorem 3.3 that $(-M_i)$ is a singular M-matrix. Using the result (Berman & Plemmons, 1979, A_3, p. 149), it follows that $-M_i + D_i$ is a non-singular M-matrix for each D_i. Thus, the equilibrium $R_i = 0$ of this linear system in R_i is stable. As a consequence, the equilibrium $x = 0$ of (3.6) is stable when $\mathcal{R}_0 < 1$. Using a standard comparison theorem (see, e.g. Lakshmikantham *et al.*, 1989, Theorem 1.5.4), it follows that 0 is a globally asymptotically stable equilibrium of (3.5).

For $\mathcal{R}_0 < 1$, the linear system (3.7) and (2.1c) has a unique equilibrium (the DFE) since its coefficient matrix $F - V$ is non-singular. The proof of global stability is completed using results on asymptotically autonomous equations; see, e.g. Thieme (1992, Theorem 4.1) and Castillo-Chavez & Thieme (1995). □

3.1 *Example of three species on two patches*

Consider a special case of three species on two patches, which might model, e.g. the spread of bubonic plague between an urban area (patch 1) and the surrounding suburbs (patch 2), the species being fleas, rodents and humans. Likewise, the dynamics of many vector-borne diseases could be modeled this way.

For each species $i = 1, 2, 3$, the null vector of the mobility matrix M_i under the constraint of total population N_i^0 is

$$(N_{i1}^*, N_{i2}^*) = \left(\frac{m_{i12}}{m_{i12} + m_{i21}} N_i^0, \frac{m_{i21}}{m_{i12} + m_{i21}} N_i^0\right).$$

The matrices G, A, B and C are as follows.

$$G = \left[\begin{array}{ccc:ccc} \beta_{111} & \beta_{121}\frac{\hat{S}_{11}}{N_{21}^*} & \beta_{131}\frac{\hat{S}_{11}}{N_{31}^*} & & & \\ \beta_{211}\frac{\hat{S}_{21}}{N_{11}^*} & \beta_{221} & \beta_{231}\frac{\hat{S}_{21}}{N_{31}^*} & & 0 & \\ \beta_{311}\frac{\hat{S}_{31}}{N_{11}^*} & \beta_{321}\frac{\hat{S}_{31}}{N_{21}^*} & \beta_{331} & & & \\ \hdashline & & & \beta_{112} & \beta_{122}\frac{\hat{S}_{12}}{N_{22}^*} & \beta_{132}\frac{\hat{S}_{12}}{N_{32}^*} \\ & 0 & & \beta_{212}\frac{\hat{S}_{22}}{N_{12}^*} & \beta_{222} & \beta_{232}\frac{\hat{S}_{22}}{N_{32}^*} \\ & & & \beta_{312}\frac{\hat{S}_{32}}{N_{12}^*} & \beta_{322}\frac{\hat{S}_{32}}{N_{22}^*} & \beta_{332} \end{array}\right].$$

Let

$$\widetilde{M} = \left[\begin{array}{ccc:ccc} -m_{121} & 0 & 0 & m_{112} & 0 & 0 \\ 0 & -m_{221} & 0 & 0 & m_{212} & 0 \\ 0 & 0 & -m_{321} & 0 & 0 & m_{312} \\ \hdashline m_{121} & 0 & 0 & -m_{112} & 0 & 0 \\ 0 & m_{221} & 0 & 0 & -m_{212} & 0 \\ 0 & 0 & m_{321} & 0 & 0 & -m_{312} \end{array}\right]$$

Then

$$A = \left[\begin{array}{ccc:ccc} d_{11}+\varepsilon_{11} & 0 & 0 & & & \\ 0 & d_{21}+\varepsilon_{21} & 0 & & 0 & \\ 0 & 0 & d_{31}+\varepsilon_{31} & & & \\ \hdashline & & & d_{12}+\varepsilon_{12} & 0 & 0 \\ & 0 & & 0 & d_{22}+\varepsilon_{22} & 0 \\ & & & 0 & 0 & d_{32}+\varepsilon_{32} \end{array}\right] - \widetilde{M},$$

$$B = \left[\begin{array}{ccc:ccc} d_{11}+\gamma_{11} & 0 & 0 & & & \\ 0 & d_{21}+\gamma_{21} & 0 & & 0 & \\ 0 & 0 & d_{31}+\gamma_{31} & & & \\ \hdashline & & & d_{12}+\gamma_{12} & 0 & 0 \\ & 0 & & 0 & d_{22}+\gamma_{22} & 0 \\ & & & 0 & 0 & d_{32}+\gamma_{32} \end{array}\right] - \widetilde{M}$$

and $C = \text{diag}\ (\varepsilon_{11}, \varepsilon_{21}, \varepsilon_{31}, \varepsilon_{12}, \varepsilon_{22}, \varepsilon_{32})$.

To obtain $\mathcal{R}_0$ for a given set of parameter values, we compute the spectral radius of the 6×6 matrix $GB^{-1}CA^{-1}$ (see Theorem 3.4).

4. Case of one species

System (2.1), specialized to one species on n patches could model, e.g. the spread of pneumonic plague, measles or influenza between distinct cities or blocks within a single city. For convenience, drop the species index, thus β_p is the disease transmission rate in patch p.

THEOREM 4.1 For model (2.1), in the case of one species on n patches,

$$\mathcal{R}_0 = \rho\ (\text{diag}\ (\beta_p)B^{-1}\text{diag}\ (\varepsilon_p)A^{-1}).$$

Furthermore, if $\mathcal{R}_0 < 1$, then the DFE is globally asymptotically stable, if $\mathcal{R}_0 > 1$, then the DFE is unstable.

Proof. In the notation of Section 3, $G = \text{diag}\ (\beta_p)$, M is given by (2.4) with the species index i dropped, $A = \text{diag}(d_p + \varepsilon_p) - M$, $B = \text{diag}(d_p + \gamma_p) - M$ and $C = \text{diag}\ (\varepsilon_p)$ where the matrices are $n \times n$. Thus, the results of Theorem 3.4 apply, with

$$\mathcal{R}_0 = \rho\ (\text{diag}\ (\beta_p)B^{-1}\text{diag}\ (\varepsilon_p)A^{-1}). \qquad \square$$

In the special case of isotropic mobility, i.e. $m_{pq} = m > 0$ for all $p, q \neq p$, matrix $M = -nmI_n + mJ_n$, where I_n is the $n \times n$ identity matrix and J_n is the $n \times n$ matrix of all ones. If, in addition, all parameters are equal in each patch, then the model behavior reduces to that of a one-species SEIR epidemic model with no spatial dynamics.

THEOREM 4.2 Consider the case of model (2.1) with one species, isotropic mobility and equal parameters in each patch. Then $\mathcal{R}_0 = \frac{\beta\varepsilon}{(d+\varepsilon)(d+\gamma)}$. For $\mathcal{R}_0 < 1$, the DFE is globally asymptotically

stable. For $\mathcal{R}_0 > 1$, there is a unique endemic equilibrium $(S_p^*, E_p^*, I_p^*, R_p^*)$ given by $S_p^* = \frac{N^0}{n\mathcal{R}_0}$, $I_p^* = \frac{\varepsilon d N^0}{n(d+\varepsilon)(d+\gamma)}(1 - \frac{1}{\mathcal{R}_0})$, $E_p^* = \frac{d+\gamma}{\varepsilon} I_p^*$ and $R_p^* = \frac{\gamma}{d} I_p^*$ for $p = 1, \ldots, n$.

Proof. Since parameters are equal in each patch, let $\beta_p = \beta$, $\varepsilon_p = \varepsilon$, $\gamma_p = \gamma$ and $d_p = d$ for $p = 1, \ldots, n$. For isotropic mobility the matrices in the proof of Theorem 4.1 are $A = (d+\varepsilon+nm)I_n - mJ_n$, $B = (d + \gamma + nm)I_n - mJ_n$ and $C = \varepsilon I_n$. Since these matrices commute and the smallest eigenvalues of A and B are $(d + \varepsilon)$ and $(d + \gamma)$ respectively, Theorem 4.1 gives $\mathcal{R}_0 = \frac{\beta\varepsilon}{(d+\varepsilon)(d+\gamma)}$ and global asymptotic stability when $\mathcal{R}_0 < 1$. For $\mathcal{R}_0 > 1$, system (2.1) can be solved to give the unique endemic equilibrium as stated so that $\sum_{p=1}^n N_p = N^0$. □

Numerical simulations in the special case of Theorem 4.2 indicate that, if $\mathcal{R}_0 > 1$, then solutions tend to this unique endemic equilibrium. Numerical simulations for the general case of one species and n patches with $\mathcal{R}_0$ as given by Theorem 4.1, indicate that for $\mathcal{R}_0 > 1$ this model also tends to a unique endemic equilibrium with disease present in each patch (recall that M is assumed to be irreducible).

4.1 *Two patches case*

In this case, the null vector of the mobility matrix M is

$$(N_1^*, N_2^*) = \left(\frac{m_{12}}{m_{12} + m_{21}} N^0, \frac{m_{21}}{m_{12} + m_{21}} N^0\right)$$

from Theorem 3.3. The basic reproduction number $\mathcal{R}_0$ can then be obtained by Theorem 4.1 as the largest root of a quadratic equation.

The influence of small migration on the reproduction number can be found by neglecting terms of second order in m_{pq}. Provided parameter values are not all equal in the two patches, then small mobility can help to stabilize the DFE. Let $\mathcal{R}_0^p = \frac{\beta_p \varepsilon_p}{(d_p+\varepsilon_p)(d_p+\gamma_p)}$ be the basic reproduction number in patch p.

Consider the case of model (2.1) with one species, two patches and small rates of travel, i.e. $m_{12}, m_{21} \ll 1$, with not all parameters equal in the two patches.

Then $\mathcal{R}_0$ is approximated by the spectral radius of $\mathrm{diag}(h_1, h_2)/(\det A \det B)$, where

$$h_r = \beta_r \varepsilon_r \prod_{\substack{p=1 \\ p \neq r}}^{2} \left\{ \left(d_p + \varepsilon_p + \sum_{q=1}^{2} m_{qp} \right) \left(d_p + \gamma_p + \sum_{q=1}^{2} m_{qp} \right) \right\}.$$

But $(\det A \det B)$ is approximately equal to

$$\prod_{p=1}^{2} \left\{ \left(d_p + \varepsilon_p + \sum_{q=1}^{2} m_{qp} \right) \left(d_p + \gamma_p + \sum_{q=1}^{2} m_{qp} \right) \right\}.$$

Neglecting terms in m_{pq}^2, this gives $\mathcal{R}_0$ approximately equal to

$$\begin{aligned} &\max_{p=1,2} \left\{ \frac{\beta_p \varepsilon_p}{(d_p + \varepsilon_p + \sum_{q=1}^{2} m_{qp})(d_p + \gamma_p + \sum_{q=1}^{n} m_{qp})} \right\} \\ &\quad = \max_{p=1,2} \left\{ \mathcal{R}_0^p \left(1 - \frac{\sum_{q=1}^{2} m_{qp}}{d_p + \varepsilon_p} \right) \left(1 - \frac{\sum_{q=1}^{2} m_{qp}}{d_p + \gamma_p} \right) \right\} \end{aligned}$$

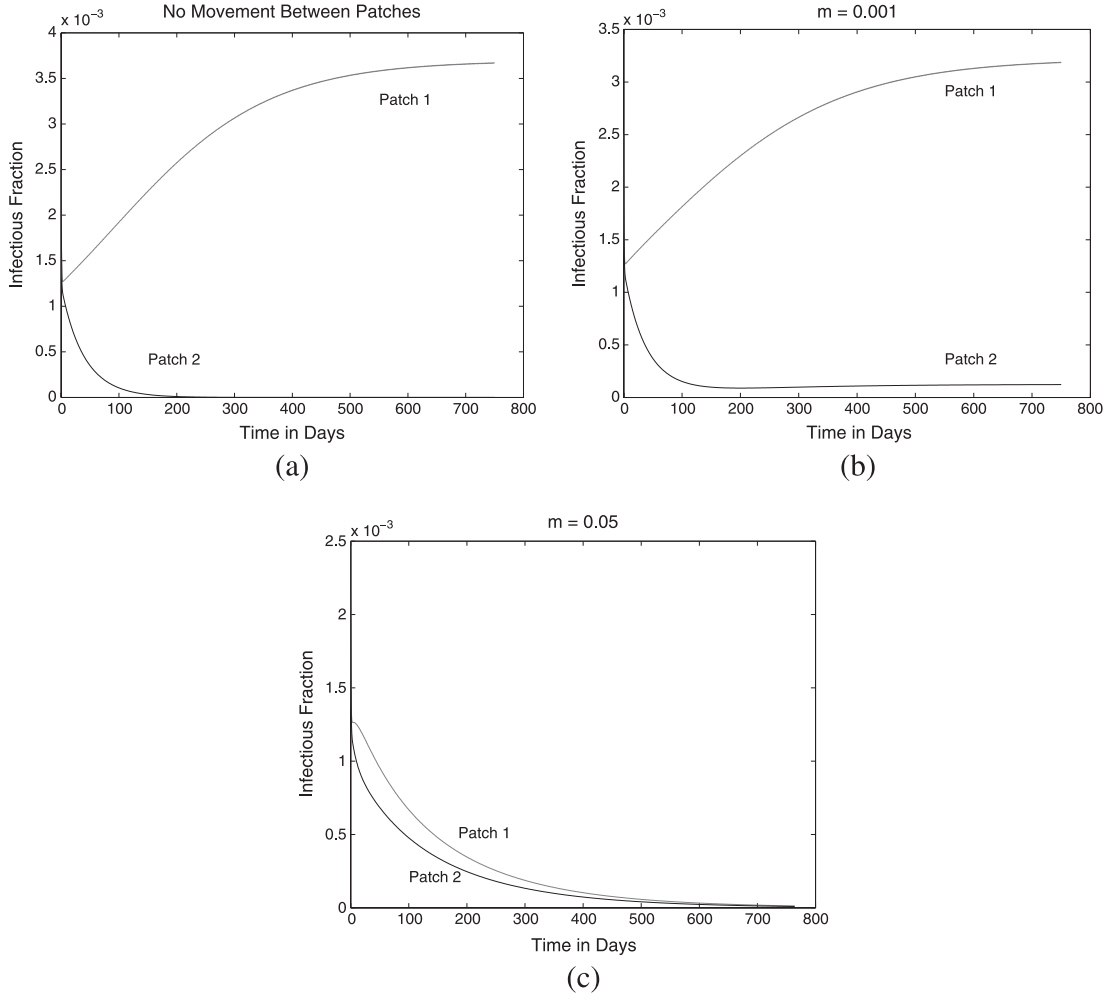

FIG. 1. Effect of small migration on a two-patch, one-species system. The initial population is of 20,000 individuals per patch, including 50 infectives. Parameters as in the text. Displayed are the infectious fractions in each patch, I_1/N_1 and I_2/N_2, as functions of time. (a) No migration; (b) very small migration ($m_{12} = m_{21} = 0.001$) and (c) small migration ($m_{12} = m_{21} = 0.05$).

$$= \max_{p=1,2} \left\{ \mathcal{R}_0^p \left(1 - \sum_{q=1}^{2} m_{qp} \frac{2d_p + \varepsilon_p + \gamma_p}{(d_p + \varepsilon_p)(d_p + \gamma_p)} \right) \right\}$$
$$< \max_{p=1,2} \mathcal{R}_0^p$$

by the irreducibility assumption.

To illustrate the above results, we have carried out numerical simulations for a single species on two spatial patches. We have chosen parameter values compatible with influenza, and such that $\mathcal{R}_0^1$ is slightly larger than 1 and $\mathcal{R}_0^2$ is slightly less than 1. Specifically, $1/\gamma_1 = 1/\gamma_2 = 2$ days, $1/d_1 = 1/d_2 = 77$

years, $1/\varepsilon_1 = 1/\varepsilon_2 = 4$ days. Using $\beta_1 = 0.5076$, $\beta_2 = 0.4761$ gives $\mathcal{R}_0^1 = 1.015$ and $\mathcal{R}_0^2 \approx 0.952$. The initial population in each patch is 20,000, with 19,950 susceptible and 50 infectious individuals. When there is no movement between patches, an endemic equilibrium is reached in patch 1, while in patch 2 the disease dies out (Fig. 1(a)). If mobility is introduced, but is sufficiently small, as in Fig. 1(b), where $m_{12} = m_{21} = 0.001$, $\mathcal{R}_0$ is greater than 1 ($\mathcal{R}_0 \approx 1.0095$ from Theorem 4.1) and the system approaches an endemic equilibrium in both patches. As mobility is increased, $\mathcal{R}_0$ becomes less than 1 ($\mathcal{R}_0 \approx 0.985$ from Theorem 4.1) and a disease free state is approached in both patches. This is illustrated in Fig. 1(c), in which $m_{12} = m_{21} = 0.05$.

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