A MULTI-CITY EPIDEMIC MODEL

Julien Arino [*†‡] P. van den Driessche [*†]

Abstract

Some analytical results are given for a model that describes the propagation of a disease in a population of individuals who travel between n cities. The model is formulated as a system of $2n^2$ ordinary differential equations with terms accounting for disease transmission, recovery, birth, death, and travel between cities. The mobility component is represented as a directed graph with cities as vertices and arcs determined by outgoing (or return) travel. An explicit formula that can be used to compute the basic reproduction number $\mathcal{R}_0$ is obtained, and explicit bounds on $\mathcal{R}_0$ are determined in the case of homogeneous contacts between individuals within each city. Numerical simulations indicate that $\mathcal{R}_0$ is a sharp threshold, with the disease dying out if $\mathcal{R}_0 < 1$ and reaching an endemic level in all connected cities if $\mathcal{R}_0 > 1$.

INTRODUCTION

The spatial spread of infectious diseases is a phenomenon that involves many different components. Modeling this spread is a complex task. Spatial heterogeneity can be incorporated by formulating small household models; a recent overview of such stochastic models with references is given by Ball and Lyne (2002). A more general model that allows for larger households was formulated by Arrigoni and Pugliese (2002) as a continuous time Markov chain. Another typical approach introducing spatial variation in epidemic models involves the use of partial differential equations (see, *e.g.*, Bailey (1980)). There are however cases where the latter type of spatial approach may not be appropriate. Consider a human specific disease that is spread by person to person contact in the context of a large country with a small number of potentially large cities, a

[*]Department of Mathematics and Statistics, University of Victoria, Victoria, B.C., Canada. pvdd@math.uvic.ca

[†]Research sponsored in part by MITACS and NSERC

[‡]Present address: Department of Mathematics and Statistics, McMaster University, Hamilton, ON, Canada. arino@math.mcmaster.ca

Acknowledgements: We thank L. Sattenspiel for introducing us to her papers, and O.Arino and C. Connell McCluskey for helpful discussions about the model.

This is "J. Arino and P. van den Driessche. A multi-city epidemic model. Mathematical Population Studies, 10(3):175-193, 2003", with publisher's typos corrected.

very sparse or even nonexistant rural population and a good transportation system. Then the movements from one city to another are fast, and the (eventual) propagation of an epidemic takes place only at the destination location. In this setting, travel of individuals between discrete geographical regions (cities) must play some role in the spreading of the disease. The situation is then that of a directed graph, with the vertices representing the cities (or discrete geographical regions or patches) and the arcs representing the links between these cities.

Most spatial models with this latter approach originate from mathematical ecology, and concern the behavior of competing and/or predator-prey metapopulations living in various patches (Hanski and Gilpin 1997, Levin, Powell and Steele 1993). The main disadvantage of this approach is the high dimensionality of the resulting models. For example a model for n cities and p different classes of individuals can have pn^2 equations. Thus, such models are often studied by computer simulations.

In mathematical epidemiology a few models have been studied that incorporate discrete geographical regions. Discrete time difference equations in a continuous state space were used by Rvachev and Longini (Longini 1988, Rvachev and Longini 1985) to study the global spread of influenza taking into account the airline network. Sattenspiel and Dietz (1995) introduced a model with travel between populations. They proceeded to an identification of the parameters in the case of the transmission of measles in the Caribbean island of Dominica, and numerically studied the behavior of the model. Sattenspiel and Herring (1998) considered the same type of model but applied to travel between populations in the Canadian subartic, which can be thought of as a closed population where travel is easily quantified. Recently, the same authors (Sattenspiel and Herring 2003) formulated a model that includes quarantine, and applied it to data of the 1918-19 influenza epidemic in central Canada. Fulford et al (Fulford, Roberts and Heesterbeek 2002) and Wang and Zhao (Wang and Zhao 2002) have also recently formulated and discussed other models for the spread of a disease among patches.

We first formulate a mobility model for residents of n cities (or discrete geographical regions) who may travel between them. The demographic model formulated here is adapted from (Sattenspiel and Dietz 1995). Although the justification for our approach is here geographical, it should be noted that there is an obvious connection to the modeling of heterogeneous populations (Sattenspiel and Simon 1988). Then we consider the time evolution of a disease that confers no immunity upon recovery superimposed on this demographic structure. We give a rigorous derivation of the basic reproduction number $\mathcal{R}_0$, which is the average number of new infectives produced by one infective introduced into a susceptible population; see, *e.g.*, (Diekmann and Heesterbeek 2000). We also give some bounds on $\mathcal{R}_0$, as well as some numerical simulations indicating that $\mathcal{R}_0 = 1$ acts as a sharp threshold between the disease dying out ($\mathcal{R}_0 < 1$) and endemic disease ($\mathcal{R}_0 > 1$).

THE MOBILITY MODEL

In the model introduced in (Sattenspiel and Dietz 1995) there is no intracity demography (no birth or natural death of individuals), only intercity travel. To make the model a little more realistic, but in order to work with a constant overall population, we suppose that birth and death occur with the same rate. In addition, we suppose that individuals who are out of their home city do not give birth, and so birth occurs in the home city at a per capita rate $d > 0$, and death takes place anywhere with a per capita rate d.

Suppose that the total number of cities is n. In the following, we call *residents* of a city i the individuals who were born in and normally live in that city, and *travelers* the individuals who at the time they are considered, are not in the city they reside in. We denote the number of residents of city i who are present in city j at time t by N_{ij}. Letting N_i^r be the resident population of city i at time t, then

$$N_i^r = \sum_{j=1}^{n} N_{ij} \tag{1}$$

Also, letting N_i^p be the population of city i at time t, *i.e.*, the number of individuals who are physically present in city i, both residents and travellers, then

$$N_i^p = \sum_{j=1}^{n} N_{ji} \tag{2}$$

As in (Sattenspiel and Dietz 1995) residents of city i leave the city at a per capita rate $g_i \geq 0$ per unit time. A fraction $m_{ji} \geq 0$ of these outgoing individuals go to city j. Thus if $g_i > 0$, then $\sum_{j=1}^{n} m_{ji} = 1$, with $m_{ii} = 0$, and $g_i m_{ji}$ is the travel rate from city i to city j. Residents of city i who are in city j return to i with a per capita rate of $r_{ij} \geq 0$, with $r_{ii} = 0$. Obviously with these assumptions, an individual resident in a given city, say city i, who is present in some city j, must first return to city i before travelling to another city k, where i, j, k are distinct. The different processes taking place are summarized in Figure 1, in which only the movements between two cities i and j are detailed.

Taking the previous assumptions into account, and assuming that population numbers are sufficiently large for a deterministic formulation, ordinary differential equations can be derived for the dynamics of the population. Firstly, the evolution of the number of residents of city i present in city i is given by

$$\frac{dN_{ii}}{dt} = d(N_i^r - N_{ii}) + \sum_{j=1}^{n} r_{ij} N_{ij} - g_i N_{ii} \tag{3a}$$

The evolution of the number of residents of city i who are present in city $j \neq i$ is

$$\frac{dN_{ij}}{dt} = g_i m_{ji} N_{ii} - r_{ij} N_{ij} - d N_{ij} \tag{3b}$$

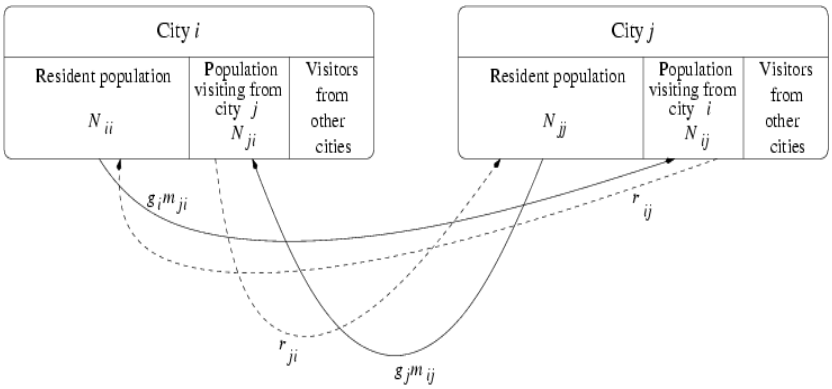


Figure 1: Travel component of the model.

Two composite quantities obtained from the previous equations are the evolution of the resident population of city i

$$\begin{aligned}
\frac{dN_i^r}{dt} &= \frac{d}{dt}\sum_{j=1}^{n} N_{ij} = \frac{d}{dt}N_{ii} + \sum_{\substack{j=1\\ j\neq i}}^{n} \frac{d}{dt}N_{ij} \\
&= d(N_i^r - N_{ii}) + \sum_{j=1}^{n} r_{ij}N_{ij} - g_i N_{ii} + \sum_{\substack{j=1\\ j\neq i}}^{n} [g_i m_{ji} N_{ii} - r_{ij}N_{ij} - dN_{ij}] \\
&= 0, \qquad (4)
\end{aligned}$$

and the change of the population of city i

$$\begin{aligned}
\frac{dN_i^p}{dt} &= d(N_i^r - N_{ii}) + \sum_{j=1}^{n} r_{ij}N_{ij} - g_i N_{ii} + \sum_{\substack{j=1\\ j\neq i}}^{n} [g_j m_{ij} N_{jj} - r_{ji}N_{ji} - dN_{ji}] \\
&= d(N_i^r - N_i^p) + \sum_{j=1}^{n} r_{ij}N_{ij} - \sum_{\substack{j=1\\ j\neq i}}^{n} r_{ji}N_{ji} + \sum_{\substack{j=1\\ j\neq i}}^{n} g_j m_{ij} N_{jj} - g_i N_{ii} \\
&= d(N_i^r - N_i^p) + \sum_{\substack{j=1\\ j\neq i}}^{n} (r_{ij}N_{ij} - r_{ji}N_{ji}) + \sum_{\substack{j=1\\ j\neq i}}^{n} g_j m_{ij} N_{jj} - g_i N_{ii} \qquad (5)
\end{aligned}$$

From (4), it follows that the number of residents of city i is a fixed quantity, but from (5), the number of individuals present in city i is in general a variable quantity. Finally an important observation is that the total population in the n-city system is given by

$$N = \sum_{i=1}^{n} N_i^r = \sum_{i=1}^{n} N_i^p = \sum_{i=1}^{n}\sum_{j=1}^{n} N_{ij} \qquad (6)$$

Since from (4) the resident population of each city is constant, it follows that N is constant.

The outgoing travel rates as well as the rates of returning to the home city define two digraphs with cities as vertices and arcs between these vertices where the coefficients are nonzero. As the model describes travels, it is natural to assume that if individuals travel between one city and another, then at least some of these travelers return home. Thus the outgoing matrix $M^T = [g_i m_{ji}]$ and the return matrix $R = [r_{ij}]$, which represent the outgoing travel from i to j and the return to i from j, respectively, have the same zero/nonzero pattern. Either matrix then determines the arcs for the mobility digraph. Note that the distance between cities i and j is not explicitly taken into account, but is implicitly in the terms m_{ji} and r_{ij}.

Consider a given city i, and define the following subsets of indices (or vertices). First, the indices of cities that can be *accessed directly* from city i

$$\mathcal{V}_{i\rightarrow} = \{k \neq i : g_i m_{ki} > 0\}$$

Because of the above assumption on M^T and R, the union of the return digraph and the outgoing digraph is a symmetric digraph (Bang-Jensen and Gutin 2001), and thus $\mathcal{V}_{i\rightarrow} = \{k \neq i : r_{ik} > 0\}$. Consider also the converse relation, cities that have a *direct travel access* to city i,

$$\mathcal{V}_{\rightarrow i} = \{k \neq i : g_k m_{ik} > 0\}$$

As for $\mathcal{V}_{i\rightarrow}$, the assumptions on M^T and R imply that $\mathcal{V}_{\rightarrow i} = \{k \neq i : r_{ki} > 0\}$. By continuing the definition of $\mathcal{V}_{i\rightarrow}$

$$\mathcal{A}_{i\rightarrow} = \{k \neq i : \exists \text{ distinct } (k_1, \ldots, k_q),\ m_{k_1 i} m_{k_2 k_1} \cdots m_{k k_q} > 0 \text{ and } g_i g_{k_1} \cdots g_{k_q} > 0\}$$

is the set of cities that can be *accessed* from city i. Similarly

$$\mathcal{A}_{\rightarrow i} = \{k \neq i : \exists \text{ distinct } (k_1, \ldots, k_q),\ m_{k_1 k} m_{k_2 k_1} \cdots m_{i k_q} > 0 \text{ and } g_k g_{k_1} \cdots g_{k_q} > 0\}$$

is the set of cities that have an *access* to city i.

Equilibrium of the Mobility Model

Equations (3) subject to the initial values $N_{ij} \geq 0$ at $t = 0$ with fixed $N_i^r > 0$ constitute the mobility model, which is linear. Since $d > 0$, this model has a unique equilibrium as given in the following result.

Theorem 1 *The mobility model (3) has the (globally) asymptotically stable equilibrium*

$$\hat{N}_{ii} = \left(\frac{1}{1 + g_i C_i}\right) N_i^r \tag{7}$$

and, for $j \neq i$

$$\hat{N}_{ij} = g_i \frac{m_{ji}}{d + r_{ij}} \left(\frac{1}{1 + g_i C_i}\right) N_i^r \tag{8}$$

where $C_i = \sum_{k=1}^{n} \frac{m_{ki}}{d + r_{ik}}$ for $i = 1, \ldots, n$.

Proof It follows from equation (3b) that at the equilibrium, for $j \neq i$,

$$N_{ij} = \frac{g_i m_{ji}}{d + r_{ij}} N_{ii}$$

Summing for $j \neq i$ gives

$$\sum_{\substack{j=1 \\ j \neq i}}^{n} N_{ij} = g_i N_{ii} \sum_{\substack{j=1 \\ j \neq i}}^{n} \frac{m_{ji}}{d + r_{ij}} = g_i C_i N_{ii}$$

since $m_{ii} = 0$. Now using (1)

$$\begin{aligned} N_i^r &= \sum_{j=1}^{n} N_{ij} = \sum_{\substack{j=1 \\ j \neq i}}^{n} N_{ij} + N_{ii} \\ &= (1 + g_i C_i) N_{ii} \end{aligned}$$

from which (7) follows, which in turns implies (8) for $j \neq i$. For given $N_i^r > 0$, these determine the unique equilibrium for the distribution of the residents of city i. Note that $\hat{N}_{ij} = 0$ iff $g_i m_{ji} = 0$.

Now ordering the state variables as $N = (N_{11}, \ldots, N_{1n}, N_{21}, \ldots, N_{nn})^T$, the mobility model (3) can be written as the linear cooperative system

$$\frac{d}{dt} N = \mathcal{M} N$$

where $\mathcal{M} = \text{diag}(\mathcal{M}_{ii})$ is the block-diagonal mobility matrix with birth and death, with each block $\mathcal{M}_{ii}$ given by

$$\mathcal{M}_{ii} = \begin{bmatrix} -g_i & r_{i2} + d & r_{i3} + d & \cdots & r_{in} + d \\ g_i m_{2i} & -r_{i2} - d & 0 & \cdots & 0 \\ g_i m_{3i} & 0 & -r_{i3} - d & \cdots & 0 \\ & & & & \\ g_i m_{ni} & 0 & \cdots & 0 & -r_{in} - d \end{bmatrix}$$

Thus if $N_i = (N_{i1}, \ldots, N_{in})^T$ the behavior of $dN_i/dt = \mathcal{M}_{ii} N_i$ can be considered independently for each $i = 1, \ldots, n$.

Let $v_i = \text{Card}(\mathcal{V}_{i\rightarrow})$ be the number of cities that can be accessed directly from city i. Then, by reordering if necessary, each of the $\mathcal{M}_{ii}$ matrices can be partitioned as

$$\mathcal{M}_{ii} = \left[\begin{array}{c:c} P_{i11} & P_{i12} \\ \hdashline 0 & P_{i22} \end{array}\right]$$

Two cases must then be distinguished. In the degenerate case $g_i = 0$ (*i.e.*, no residents leave city i), P_{i11} is the zero scalar, and P_{i22} is a diagonal matrix with every entry negative. For $g_i > 0$, P_{i11} is an irreducible $v_i \times v_i$-matrix, P_{i12} has nonzero d entries only on the first row and $P_{i22} = \text{diag}(-d)$ is a $(n - v_i) \times (n - v_i)$-matrix. If $v_i = n$, then P_{i22} is vacuous. If $v_i < n$ then P_{i22} has the eigenvalue

$-d$ of multiplicity v_i. By Gerschgorin's theorem (see, *e.g.*, (Horn and Johnson 1990, Th. 6.1.1)) and the fact that it is diagonally similar to a symmetric matrix, P_{i11} has all eigenvalues real and nonpositive. Each column sum of P_{i11} is zero, thus P_{i11} has a simple zero eigenvalue. The zero eigenvalue comes from the fact that the system is overdetermined since N_i^r is constant. Thus $\hat{N}_i$ is (globally) asymptotically stable. ■

Note that, if the return rate is equal in all cities, *i.e.*, $r_{ij} = r$, then $\hat{N}_{ii} = (d+r)N_i^r/(d+r+g_i)$ and for $j \neq i$, $\hat{N}_{ij} = g_i m_{ji} N_i^r/(d+r+g_i)$.

THE EPIDEMIC MODEL

In each of the n cities, an epidemic model can be constructed. In (Sattenspiel and Dietz 1995), an SIR model is formulated in each city (called region), with two types of mobility (infants and adults) in each region. In (Sattenspiel and Herring 1998), each region has an SIR model. For a disease that confers no immunity (*e.g.*, gonnorhea), we construct an SIS model and superimpose this on the demographic model formulated in the previous section.

The SIS Model

Let S_{ij} and I_{ij} denote the number of susceptible and infective individuals resident in city i who are present in city j at time t; thus $N_{ij} = S_{ij} + I_{ij}$ for all $i, j = 1, \ldots, n$. Disease transmission is modelled using standard incidence, which, for human diseases, is considered more accurate than mass action (see, *e.g.*, (Hethcote 2000, McCallum, Barlow and Hone 2001)). In city j, this gives

$$\sum_{j=1}^{n} \sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{S_{ij} I_{kj}}{N_j^p} \tag{9}$$

where the disease transmission coefficient $\beta_{ikj} > 0$ is the proportion of adequate contacts in city j between a susceptible from city i and an infective from city k that actually results in transmission of the disease and $\kappa_j > 0$ is the average number of such contacts in city j per unit time. Let $\gamma > 0$ denote the recovery rate of infectives, thus $1/\gamma$ is the average infective period. Note that γ is assumed to be the same for all cities.

In each city, there are $2n$ equations. The first n equations describe the dynamics of the susceptibles, and the n others describe the dynamics of the infectives. Since there are n cities, there is a total of $2n^2$ equations for n cities. The dynamics of the number of susceptibles and infectives originating from city i (with $i = 1, \ldots, n$) is given by the following system.

$$\frac{dS_{ii}}{dt} = \sum_{k=1}^{n} r_{ik} S_{ik} - g_i S_{ii} - \sum_{k=1}^{n} \kappa_i \beta_{iki} \frac{S_{ii} I_{ki}}{N_i^p} + d(N_i^r - S_{ii}) + \gamma I_{ii} \tag{10a}$$

$$\frac{dI_{ii}}{dt} = \sum_{k=1}^{n} r_{ik} I_{ik} - g_i I_{ii} + \sum_{k=1}^{n} \kappa_i \beta_{iki} \frac{S_{ii} I_{ki}}{N_i^p} - (\gamma + d) I_{ii} \tag{10b}$$

and, for $j \neq i$,

$$\frac{dS_{ij}}{dt} = g_i m_{ji} S_{ii} - r_{ij} S_{ij} - \sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{S_{ij} I_{kj}}{N_j^p} - d S_{ij} + \gamma I_{ij} \tag{10c}$$

$$\frac{dI_{ij}}{dt} = g_i m_{ji} I_{ii} - r_{ij} I_{ij} + \sum_{k=1}^{n} \kappa_j \beta_{ikj} \frac{S_{ij} I_{kj}}{N_j^p} - (\gamma + d) I_{ij} \tag{10d}$$

Equations (10a) and (10b) describe the evolution of the number of susceptibles and infectives, residents of city i who are present in city i, while equations (10c) and (10d) describe the residents of city i who are currently present in city j. These equations, together with nonnegative initial conditions, constitute the SIS epidemic model.

Proposition 2 *The nonnegative orthant $\mathbb{R}_+^{2n^2}$ is positively invariant under the flow of (10), and for all $t > 0$, $S_{ii} > 0$ and $S_{ij} > 0$ provided that $g_i m_{ji} > 0$. Furthermore, solutions of (10) are bounded.*

Proof The fact that solutions remain nonnegative follows naturally from (10). From (10a), if $S_{ii} = 0$ at $t = 0$, then $dS_{ii}/dt > 0$ and thus $S_{ii} > 0$ for $t > 0$. This, together with (10c), implies that for all $t > 0$, $S_{ij} > 0$ for $j \neq i$. Since there is no disease specific mortality, the constant population property of the mobility model still holds. The boundedness then follows from the positive invariance of $\mathbb{R}_+^{2n^2}$ and the constant population property. ■

For parameters relevant to a specific disease, system (10) can be solved numerically. Before reporting on numerical results, we consider the case where the system is at equilibrium. The system is at an equilibrium if the time derivatives in (10) are zero. City i is at the disease free equilibrium (DFE) if $I_{ji} = 0$ and $S_{ji} = \hat{N}_{ji}$ given by (7) and (8) for all $j = 1, \ldots, n$. The n-city model given by (10) is at the DFE if every city is at the DFE, *i.e.*, $I_{ji} = 0$ and $S_{ji} = \hat{N}_{ji}$ for all $i, j = 1, \ldots, n$. The DFE of (10) always exists, and in the case in which the disease is absent in all cities, the metapopulation model reduces to that of the previous section.

Theorem 3 *Suppose that system (10) is at an equilibrium, and that a given city i is at the DFE. Then all cities that can be accessed from city i and all cities that have an access to city i are at the DFE. In particular, if the outgoing matrix M^T is irreducible, then all cities are at the DFE.*

Proof For simplicity, suppose that city 1 is at the DFE, *i.e.*, $I_{k1} = 0$ for all $k = 1, \ldots, n$. Consider (10b) with $i = 1$, namely

$$\frac{dI_{11}}{dt} = \sum_{k=1}^{n} r_{1k} I_{1k}$$

As city 1 is at the DFE, $dI_{11}/dt = 0$, and thus, since $r_{1v} > 0$ for all $v \in \mathcal{V}_{1\rightarrow}$, it follows that $I_{1v} = 0$ for all $v \in \mathcal{V}_{1\rightarrow}$. Now consider (10d) with $i = 1$ and

$v \in \mathcal{V}_{1\rightarrow}$, giving

$$\frac{dI_{1v}}{dt} = \sum_{k=1}^{n} \kappa_v \beta_{1kv} \frac{S_{1v} I_{kv}}{N_v^p}$$

Since $\kappa_v \beta_{1kv} > 0$, and from Proposition 2, $S_{1j} > 0$ for $t > 0$, this implies that if $v \in \mathcal{V}_{1\rightarrow}$, then $I_{kv} = 0$ for all k. Hence a city that can be accessed directly from city 1 is at the DFE. By induction, all cities in $\mathcal{A}_{1\rightarrow}$ are at the DFE.

Consider (10d) with $j = 1$,

$$\frac{dI_{i1}}{dt} = g_i m_{1i} I_{ii}$$

Thus, since the system is at an equilibrium, $I_{ii} = 0$ for $i \in \mathcal{V}_{\rightarrow 1}$. So consider a city $v \in \mathcal{V}_{\rightarrow 1}$ and use (10b) with $i = v$

$$\frac{dI_{vv}}{dt} = \sum_{k=1}^{n} r_{vk} I_{vk} + \sum_{k=1}^{n} \kappa_v \beta_{vkv} \frac{S_{vv} I_{kv}}{N_v^p}$$

As the system is at an equilibrium, this implies in particular that $S_{vv} I_{kv} = 0$ for all $k \in \mathcal{V}_{\rightarrow v}$. From Proposition 2, $S_{vv} > 0$ for $t > 0$, and therefore $I_{kv} = 0$ for all $k \in \mathcal{V}_{\rightarrow v}$. If $v \neq k$ and $g_k m_{vk} = 0$ (*i.e.*, $k \notin \mathcal{V}_{\rightarrow v}$), then $I_{kv} = 0$, thus $I_{kv} = 0$ for all k, and cities $v \in \mathcal{V}_{\rightarrow 1}$ are at the DFE. By induction, all cities in $\mathcal{A}_{\rightarrow 1}$ are at the DFE.

A sufficient condition for city 1 to have an access to all cities is for the outgoing matrix to be irreducible. ■

The disease is *endemic* in a population if the number of infectives is positive in this population. The disease is endemic in city i if there is a population in city i in which the disease is endemic, *i.e.*, there exists $k \in \{1, \ldots, n\}$ such that $I_{ki} > 0$.

Theorem 4 *Suppose that system (10) is at an equilibrium, and that the disease is endemic in city i. Then the disease is endemic in all cities that can be accessed from city i. In particular, if the mobility matrix M^T is irreducible, then the disease is endemic in all cities.*

Proof Assume that the disease is endemic in city 1, *i.e.*, there exists q such that $I_{q1} > 0$. For the second part of the proof, we need to show that if the disease is endemic in city 1, then necessarily $I_{11} > 0$.

If $q = 1$ then we can proceed. So suppose $q \neq 1$, and assume that $I_{11} = 0$. Since the system is at an equilibrium, from (10b)

$$0 = \frac{dI_{11}}{dt} = \sum_{k=1}^{n} r_{1k} I_{1k} + \sum_{k=1}^{n} \kappa_1 \beta_{1k1} \frac{S_{11} I_{k1}}{N_1^p}$$

Since $\kappa_1 \beta_{1k1} > 0$ and $S_{11} > 0$ for $t > 0$, it follows that $I_{k1} = 0$ for all k, which is a contradiction (since $I_{q1} > 0$). Therefore $I_{11} > 0$ if the disease is endemic in city 1, which we now assume.

Now consider (10d) with $i = 1$ and $j \neq i$. Further assume that $I_{1j} = 0$. Since the system is at an equilibrium,

$$0 = \frac{dI_{1j}}{dt} = g_1 m_{j1} I_{11} + \sum_{k=1}^{n} \kappa_j \beta_{1kj} \frac{S_{1j} I_{kj}}{N_j^p}$$

If $j \in \mathcal{V}_{1\rightarrow}$, this implies that $I_{11} = 0$, which is a contradiction. Thus $I_{1j} > 0$ (*i.e.*, the disease is endemic) for all $j \in \mathcal{V}_{1\rightarrow}$, and in particular $I_{jj} > 0$ from the first part of the proof. Continuing the argument, the disease is endemic in all cities $j \in \mathcal{A}_{1\rightarrow}$. ■

The above two results rule out certain types of equilibria. In particular, they imply that it is not possible, in a connected component, to have one city without any disease with related cities with an endemic disease. In most practical situations, interest is focussed on cities belonging to one connected component.

The Basic Reproduction Number

Firstly, note that if a city i is isolated from the others, *i.e.*, that $\mathcal{A}_{i\rightarrow} = \mathcal{A}_{\rightarrow i} = \emptyset$, then the basic reproduction number in city i is

$$\mathcal{R}_0^i = \frac{\kappa_i \beta_{iii}}{d + \gamma} \tag{11}$$

For city i, this is the average number of new infections produced by one infective introduced into a susceptible population. To discuss local stability of the DFE in the n-city model given by (10), we use the next generation matrix (Diekmann and Heesterbeek 2000) and the method of (van den Driessche and Watmough 2002). Ordering the infective variables as

$$I_{11}, \ldots, I_{1n}, I_{21}, I_{22}, \ldots I_{2n}, \ldots I_{nn}$$

gives the diagonal block matrix $V = \mathrm{diag}(V_{ii})$, where for $i = 1, \ldots n$, V_{ii} is an $n \times n$ matrix with

$$V_{ii} = \begin{bmatrix} r_{i1} + \gamma + d & 0 & \cdots & 0 & -g_i m_{1i} & 0 & \cdots & 0 \\ 0 & r_{i2} + \gamma + d & & & -g_i m_{2i} & 0 & \cdots & 0 \\ & & & & & & & \\ -r_{i1} & -r_{i2} & & & g_i + \gamma + d & & & -r_{in} \\ & & & & & & & \\ 0 & \cdots & & & -g_i m_{ni} & 0 & & r_{in} + \gamma + d \end{bmatrix}$$

For a fixed i, and $k \neq i$, the (i,k) entry of V_{ii} is $-r_{ik}$, the (k,i) entry is $-g_i m_{ki}$, the k^{th} diagonal entry is $r_{ik} + \gamma + d$, the (i,i) entry is $g_i + \gamma + d$, and other entries are zero. Since V_{ii} has the Z-sign pattern and has all positive column sums, V_{ii} is a nonsingular M-matrix (Berman and Plemmons 1979, p. 136). The inverse of V is then easily computed as a nonnegative matrix $V^{-1} = \mathrm{diag}(V_{ii}^{-1})$. Matrix

F is a block matrix with n^2 blocks, where each block F_{ij} is $n \times n$ diagonal and has the form $F_{ij} = \text{diag}(f_{ijq})$, where

$$f_{ijq} = \kappa_q \beta_{ijq} \frac{\hat{N}_{iq}}{\hat{N}_q^p} \tag{12}$$

for $q = 1, \ldots, n$.

Since V^{-1} is block diagonal, FV^{-1} can be given by blocks, where the i, j block is $F_{ij}V_{jj}^{-1}$. By (van den Driessche and Watmough 2002, Theorem 2), the basic reproduction number for system (10) is

$$\mathcal{R}_0 = \rho(FV^{-1}) \tag{13}$$

where $\rho(\cdot)$ is the spectral radius, and the DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

To summarize, we have the following result.

Theorem 5 *Let $\mathcal{R}_0$ be defined as in (13). If $\mathcal{R}_0 < 1$, then the DFE of (10) is locally asymptotically stable. If $\mathcal{R}_0 > 1$, then the DFE of (10) is unstable.*

In the case of disease transmission coefficients equal for all populations present in a city, *i.e.*, $\beta_{ijk} = \beta_k$ for all i, j, giving $\mathcal{R}_0^i = \kappa_i \beta_i/(d + \gamma)$, the following bounds hold for $\mathcal{R}_0$.

Theorem 6 *Suppose that $\beta_{ijk} = \beta_k$ for all $i, j = 1, \ldots, n$. Then*

$$\min_{i=1,\ldots,n} \mathcal{R}_0^i \leq \mathcal{R}_0 \leq \max_{i=1,\ldots,n} \mathcal{R}_0^i$$

Proof Suppose that $\beta_{ijk} = \beta_k$ for all i, j. Then

$$f_{ijq} = \kappa_q \beta_q \frac{\hat{N}_{iq}}{\hat{N}_q^p}$$

thus $F_{ij} = F_{i1}$ for all i, j, and the i, j block of FV^{-1} is $F_{i1}V_{jj}^{-1}$ for all i, j. As F_{i1} is diagonal, left multiplication with V_{jj}^{-1} amounts to multiplying row q of V_{jj}^{-1} by $\kappa_q \beta_q \hat{N}_{iq}/\hat{N}_q^p$ for $q = 1, \ldots, n$. Let $v_{kl}^{-1}(j)$ denote the (k, l) entry of V_{jj}^{-1}, for $k, l = 1, \ldots, n$. Consider the first column of $F_{i1}V_{11}^{-1}$, and let $[\mathbb{1}^T F_{i1}V_{11}^{-1}]_1$ denote the sum of the entries in the first column of $F_{i1}V_{11}^{-1}$, with $\mathbb{1}^T = (1, \ldots, 1)$. Then

$$\begin{aligned}
[\mathbb{1}^T F_{i1}V_{11}^{-1}]_1 &= \kappa_1\beta_1 \frac{\hat{N}_{11}}{\hat{N}_1^p} v_{11}^{-1}(1) + \kappa_2\beta_2 \frac{\hat{N}_{12}}{\hat{N}_2^p} v_{21}^{-1}(1) + \cdots + \kappa_n\beta_n \frac{\hat{N}_{1n}}{\hat{N}_n^p} v_{n1}^{-1}(1) \\
&\quad + \kappa_1\beta_1 \frac{\hat{N}_{21}}{\hat{N}_1^p} v_{11}^{-1}(1) + \kappa_2\beta_2 \frac{\hat{N}_{22}}{\hat{N}_2^p} v_{21}^{-1}(1) + \cdots + \kappa_n\beta_n \frac{\hat{N}_{2n}}{\hat{N}_n^p} v_{n1}^{-1}(1) \\
&\quad + \cdots \\
&\quad + \kappa_1\beta_1 \frac{\hat{N}_{n1}}{\hat{N}_1^p} v_{11}^{-1}(1) + \kappa_2\beta_2 \frac{\hat{N}_{n2}}{\hat{N}_2^p} v_{21}^{-1}(1) + \cdots + \kappa_n\beta_n \frac{\hat{N}_{nn}}{\hat{N}_n^p} v_{n1}^{-1}(1) \\
&= \kappa_1\beta_1 v_{11}^{-1}(1) + \cdots + \kappa_n\beta_n v_{n1}^{-1}(1) \qquad (14)
\end{aligned}$$

in which the last equality follows from (2). Without loss of generality, suppose that

$$\min_{i=1,\ldots,n} \mathcal{R}_0^i = \mathcal{R}_0^1 \leq \mathcal{R}_0^2 \leq \ldots \leq \mathcal{R}_0^n = \max_{i=1,\ldots,n} \mathcal{R}_0^i$$

Then

$$\kappa_1\beta_1 \leq \kappa_2\beta_2 \leq \ldots \leq \kappa_n\beta_n$$

Using these inequalities in (14),

$$\kappa_1\beta_1 \left(v_{11}^{-1}(1) + \cdots + v_{n1}^{-1}(1)\right) \leq [\mathbb{1}^T F_{i1} V_{11}^{-1}]_1 \leq \kappa_n\beta_n \left(v_{11}^{-1}(1) + \cdots + v_{n1}^{-1}(1)\right)$$

Each diagonal block V_{ii} of V has column sum $\gamma + d$, *i.e.*, $\mathbb{1}^T V = (\gamma + d)\mathbb{1}^T$. Hence $\mathbb{1}^T V^{-1} = 1/(\gamma + d)\mathbb{1}^T$. Therefore,

$$\mathcal{R}_0^1 = \frac{\kappa_1\beta_1}{d+\gamma} \leq [\mathbb{1}^T F_{i1} V_{11}^{-1}]_1 \leq \frac{\kappa_n\beta_n}{d+\gamma} = \mathcal{R}_0^n$$

The same argument shows that this inequality remains true for every column of FV^{-1}. A standard result on the localization of the dominant eigenvalue of a nonnegative matrix (see, *e.g.*, (Minc 1988, Theorem 1.1)) then implies that $\min_{i=1,\ldots,n} \mathcal{R}_0^i \leq \rho(FV^{-1}) \leq \max_{i=1,\ldots,n} \mathcal{R}_0^i$, and the result follows from (13). ■

Note that if $\mathcal{R}_0^i < 1$ for all i, then $\mathcal{R}_0 < 1$, thus the DFE is locally asymptotically stable. Similarly, if $\mathcal{R}_0^i > 1$ for all i, then $\mathcal{R}_0 > 1$, thus the DFE is unstable. In these cases, mobility does not induce a bifurcation. Note also that if the disease transmission coefficients are identical in all cities, then $\mathcal{R}_0$ is $\kappa\beta/(d+\gamma)$, as in a classical SIS model. Indeed, we have the following corollary, in which mobility plays no role.

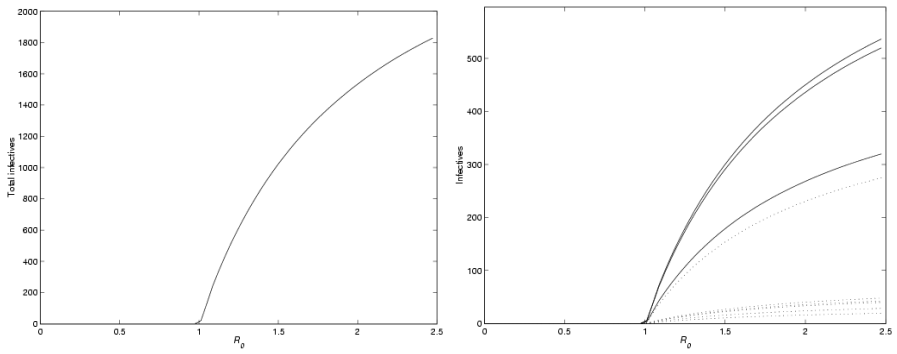
Corollary 7 *Suppose that for all i, j, k, $\beta_{ijk} = \beta$ and $\kappa_i = \kappa$. Then the basic reproduction number of (10) is*

$$\mathcal{R}_0 = \frac{\kappa\beta}{d+\gamma}$$

Proof The result follows from Theorem 6 since under the current hypotheses, $\mathcal{R}_0^i = \kappa\beta/(d+\gamma)$ for all $i = 1, \ldots, n$. ■

Numerical Simulations

Consider the case of three cities and the computation of $\mathcal{R}_0$ using the method of the previous section, namely the one leading to (13). Parameters are chosen to be relevant for a disease like gonorrhea (Hethcote and Yorke 1984): recovery takes 25 days on average, *i.e.*, $\gamma = 1/25$ with the time unit taken as 1 day. Initially, $S_{ij} > 0$ for all i, j and the disease is only present in city 1, *i.e.*, $I_{11} > 0$ and all other $I_{ij} = 0$. We use $\kappa_i = \kappa = 1$ for $i = 1, 2, 3$ and taking the average life time as 75 years, $d = 1/(75 \times 365)$. Values in the vector g and the matrix R are random numbers chosen from $(0, 0.05)$ and $[0.01, 0.11)$, respectively. Finally,



(a) (b)

Figure 2: Birth of an endemic equilibrium point through a forward bifurcation at the point $\mathcal{R}_0 = 1$. Parameters as given in the text. (a) Total number of infectives in the population. (b) Number of infectives in each subpopulation (plain lines show resident populations, dotted lines show travelling populations).

for $i \neq j$, $m_{ji} = 1/2$. Transmission coefficients are chosen equal for all contact types (*i.e.*, $\beta_{ijk} = \beta$ for all $i, j, k = 1, 2$), thus $\mathcal{R}_0 = \kappa\beta/(d+\gamma)$ from Corollary 7. All the parameters are then fixed, except for β, which is varied in such a way that $0 \leq \mathcal{R}_0 \leq 2.5$. Numerical simulation of system (10) with $n = 3$ is carried out, and the equilibrium numbers of infectives in the different subpopulations as a function of $\mathcal{R}_0$ are shown in Figure 2. These numerical simulations show that (for these parameter values) when $\mathcal{R}_0 > 1$, the total number of infectives $\sum_{i=1}^{3}\sum_{j=1}^{3} I_{ij}$ goes to a unique endemic equilibrium. This is also the case for each of the 9 subpopulations I_{ij}, as can be inferred from Figure 2(b). At $\mathcal{R}_0 = 1$, there is a forward bifurcation, with the disease dying out if $\mathcal{R}_0 < 1$, but present in each city and each subpopulation if $\mathcal{R}_0 > 1$.

CASE OF TWO CITIES

As can be inferred from the previous section, the high dimensionality of the model makes it difficult to give analytical results. Even running numerical simulations is slow. In order to gain more understanding of some of the processes involved, we consider the case of two cities.

The SIS model in two cities, with $g_1, g_2 > 0$ has $m_{12} = m_{21} = 1$. From Theorems 3 and 4, the DFE exists in each city, and if both cities are at an equilibrium with the DFE in one of the cities, then the other city is at the DFE. Similarly, if both cities are at an equilibrium with one of the two cities at an endemic equilibrium, then the disease is endemic in the other city.

Suppose that the disease transmission coefficients are equal in each city for all contact types (*i.e.*, $\beta_{ijk} = \beta_k$, $i, j = 1, 2$). Then using the notation as in the previous section,

$$F = \frac{1}{\hat{N}_1^p \hat{N}_2^p} \left[\begin{array}{cc:cc} \kappa_1\beta_1\hat{N}_{11}\hat{N}_2^p & 0 & \kappa_1\beta_1\hat{N}_{11}\hat{N}_2^p & 0 \\ 0 & \kappa_2\beta_2\hat{N}_{12}\hat{N}_1^p & 0 & \kappa_2\beta_2\hat{N}_{12}\hat{N}_1^p \\ \hdashline \kappa_1\beta_1\hat{N}_{21}\hat{N}_2^p & 0 & \kappa_1\beta_1\hat{N}_{21}\hat{N}_2^p & 0 \\ 0 & \kappa_2\beta_2\hat{N}_{22}\hat{N}_1^p & 0 & \kappa_2\beta_2\hat{N}_{22}\hat{N}_1^p \end{array}\right]$$

$$= \frac{1}{\hat{N}_1^p \hat{N}_2^p} \left[\begin{array}{c:c} \tilde{F}_{11} & \tilde{F}_{11} \\ \hdashline \tilde{F}_{22} & \tilde{F}_{22} \end{array}\right]$$

which has rank 2, and

$$V = \begin{bmatrix} g_1+\gamma+d & -r_{12} & 0 & 0 \\ -g_1 & r_{12}+\gamma+d & 0 & 0 \\ 0 & 0 & r_{21}+\gamma+d & -g_2 \\ 0 & 0 & -r_{21} & g_2+\gamma+d \end{bmatrix} = \left[\begin{array}{c:c} V_{11} & 0 \\ \hdashline 0 & V_{22} \end{array}\right]$$

Here

$$V_{11}^{-1} = \frac{1}{\Delta_1} \begin{bmatrix} r_{12}+\gamma+d & r_{12} \\ g_1 & g_1+\gamma+d \end{bmatrix} = \frac{1}{\Delta_1}\tilde{V}_{11}^{-1}$$

and

$$V_{22}^{-1} = \frac{1}{\Delta_2} \begin{bmatrix} g_2+\gamma+d & g_2 \\ r_{21} & r_{21}+\gamma+d \end{bmatrix} = \frac{1}{\Delta_2}\tilde{V}_{22}^{-1}$$

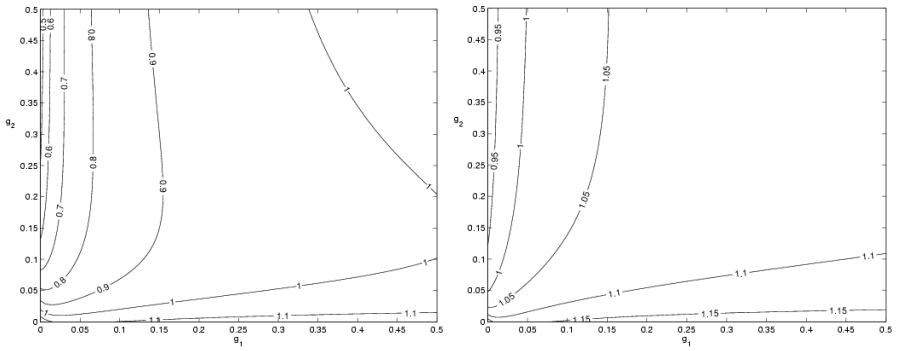
with $\Delta_1 = (\gamma+d)(\gamma+d+g_1+r_{12})$ and $\Delta_2 = (\gamma+d)(\gamma+d+g_2+r_{21})$. Note that each column sum of V^{-1} is $1/(\gamma+d)$. Thus,

$$FV^{-1} = \frac{1}{\Delta_1\Delta_2\hat{N}_1^p\hat{N}_2^p} \left[\begin{array}{c:c} \Delta_2\tilde{F}_{11}\tilde{V}_{11}^{-1} & \Delta_1\tilde{F}_{11}\tilde{V}_{22}^{-1} \\ \hdashline \Delta_2\tilde{F}_{22}\tilde{V}_{11}^{-1} & \Delta_1\tilde{F}_{22}\tilde{V}_{22}^{-1} \end{array}\right] \tag{15}$$

and the basic reproduction number $\mathcal{R}_0 = \rho(FV^{-1})$ from (13) is the largest eigenvalue of FV^{-1}, since this positive matrix has rank 2. This is easy to compute from (15) for a given set of parameter values.

Numerical Simulations for Two Cities

The following simulations give some insight into the effect of the mobility on the propagation of the epidemic. Suppose initially that cities 1 and 2 are disconnected (zero mobility), and that city 1 is such that the disease is absent, while city 2 is such that the disease is endemic, *i.e.*, $\mathcal{R}_0^1 < 1$ while $\mathcal{R}_0^2 > 1$. Then the cities become connected. If all parameters are equal in the two cities except for β_i, then varying the value of the migration rate g_i, $i = 1, 2$, results in a change of the value of $\mathcal{R}_0$ as computed from (15). From Theorem 6, $\mathcal{R}_0 \in [\mathcal{R}_0^1, \mathcal{R}_0^2]$.



(a) (b)

Figure 3: Level curves of $\mathcal{R}_0$ in the (g_1, g_2)-plane, for two cities. (a) Case $\mathcal{R}_0^1 = 0.4$ and $\mathcal{R}_0^2 = 1.2$. (b) Case $\mathcal{R}_0^1 = 0.9$ and $\mathcal{R}_0^2 = 1.2$.

Suppose that $N_1^r = N_2^r = 1500$, $d = 1/(75 \times 365)$, $\gamma = 1/25$, $\kappa_1 = \kappa_2 = 1$ and $r_{12} = r_{21} = 0.05$. We then obtain Figure 3, which shows the level curves of $\mathcal{R}_0$ in the (g_1, g_2)-plane, in the two cities case when $\beta_{ijk} = \beta_k$. In the case of Figure 3(a), parameters are such that $\mathcal{R}_0^1 = 0.4$, *i.e.*, $\beta_1 \simeq 0.016$, whereas in Figure 3(b), $\mathcal{R}_0^1 = 0.9$ (*i.e.*, $\beta_1 \simeq 0.036$). In both cases, $\mathcal{R}_0^2 = 1.2$, *i.e.*, $\beta_2 \simeq 0.048$.

From the numerics, as $\mathcal{R}_0^1$ becomes closer to 1, the region in the (g_1, g_2)-plane where $\mathcal{R}_0 < 1$ becomes smaller. For small g_1 and large g_2, $\mathcal{R}_0 \approx \mathcal{R}_0^1$ since the population of city 2 spends most time in city 1. Similarly, for small g_2 and large g_1, $\mathcal{R}_0 \approx \mathcal{R}_0^2$. A change in mobility can induce a bifurcation from $\mathcal{R}_0 < 1$ to $\mathcal{R}_0 > 1$ or vice versa. Thus mobility can stabilize or destabilize the DFE. The same possibilities were observed in the 2-patch model of (Wang and Zhao 2002) that assumes mass action incidence and nonlinear birth. Furthermore, for the $\mathcal{R}_0^i$ values of Figure 3(a), if $g_1 = 0.4$ and g_2 is increased, then there are two successive bifurcations. For small g_2, there is a unique endemic equilibrium; for intermediate g_2, there is no endemic equilibrium and the disease dies out; for large g_2 a unique endemic equilibrium is again present. Also from Figure 3(a) if the rate of leaving is the same in each city ($g_1 = g_2$), then two bifurcations are also observed, with an endemic equilibrium present for large g_i. For Figure 3(b), the $\mathcal{R}_0^1$ value is larger, and for most of the (g_1, g_2)-plane there is a unique endemic equilibrium. These figures illustrate the complexity of behavior possible when intercity travel is present.

DISCUSSION

The SIS epidemic model formulated in (10) describes the travels of individuals between discrete geographical regions as incorporated in a model by Sattenspiel and Dietz (Sattenspiel and Dietz 1995). The mobility (travel) component of the system, namely (3), has a unique stable equilibrium, with population numbers given by (7) and (8). These numbers serve as the disease free equilibrium of the epidemic model (10). If the system is at an equilibrium and one city is at the disease free equilibrium, then all cities that can be accessed from or have an access to this city are also at the disease free equilibrium. When the system is at an equilibrium and one city has an endemic disease level then all cities that can be accessed from this city are also at an endemic level. These results assume that the system is at a steady state. At the start of a disease outbreak in a certain city (or cities), the number of infectives in each city as a function of time can be determined by numerically solving system (10). An explicit formula for the computation of the basic reproduction number $\mathcal{R}_0$ is derived; the DFE of (10) is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$. Numerical simulations indicate that $\mathcal{R}_0$ acts as a threshold between the extinction and the invasion of the disease. They also indicate that the endemic equilibrium is unique with infective numbers tending to this equilibrium whenever $\mathcal{R}_0 > 1$. Thus to control the disease, measures should be taken to reduce $\mathcal{R}_0$ below 1. Note that $\mathcal{R}_0 = \rho(FV^{-1})$, in which both F and V depend on the migration and return matrices. Thus more analysis is needed to quantify the effect of travel between cities on $\mathcal{R}_0$, and consequently on control strategies. To strive for greater realism, stochastic effects (as for example in (Arrigoni and Pugliese 2002, Ball and Lyne 2002)) should also be included.

References

Arrigoni, F. and Pugliese, A. (2002). Limits of a multi-patch SIS epidemic model, *J. Math. Biol.* **45**: 419–440.

Bailey, N. T. J. (1980). Spatial models in the epidemiology of infectious diseases, *Biological Growth and Spread*, Vol. 38 of *Lecture Notes in Biomathematics*, Springer-Verlag, pp. 233–261.

Ball, F. and Lyne, O. (2002). Epidemics among a population of households, *in* C. Castillo-Chavez, with S. Blower, P. van den Driessche, D. Kirschner and A.-A. Yakubu (eds), *Mathematical Approaches for Emerging and Reemerging Infectious Diseases: Models, Methods, and Theory*, Vol. 126 of *IMA Volumes in Mathematics and its Applications*, pp. 115–142.

Bang-Jensen, J. and Gutin, G. (2001). *Digraphs: Theory, Algorithms and Applications*, Springer-Verlag.

Berman, A. and Plemmons, R. J. (1979). *Nonnegative Matrices in the Mathematical Sciences*, Academic Press.

Diekmann, O. and Heesterbeek, J. A. P. (2000). *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*, Wiley.

Fulford, G. R., Roberts, M. G. and Heesterbeek, J. A. P. (2002). The metapopulation dynamics of an infectious disease: tuberculosis in possums, *Theoretical Population Biology* **61**: 15–29.

Hanski, I. A. and Gilpin, M. E. (1997). *Metapopulation Biology: Ecology, Genetics, and Evolution*, Academic Press.

Hethcote, H. W. (2000). The mathematics of infectious diseases, *SIAM Review* **42**(4): 599–653.

Hethcote, H. W. and Yorke, J. A. (1984). *Gonorrhea Transmission Dynamics and Control*, Vol. 56 of *Lecture Notes in Biomathematics*, Springer-Verlag.

Horn, R. and Johnson, C. (1990). *Matrix Analysis*, Cambridge University Press.

Levin, S. A., Powell, T. M. and Steele, J. H. (eds) (1993). *Patch Dynamics*, Vol. 96 of *Lecture Notes in Biomathematics*, Springer-Verlag.

Longini, I. (1988). A mathematical model for predicting the geographic spread of new infectious agents, *Math. Biosci.* **90**: 367–383.

McCallum, H., Barlow, N. and Hone, J. (2001). How should pathogen transmission be modelled?, *Trends Ecol. Evol.* **16**: 295–300.

Minc, H. (1988). *Nonnegative Matrices*, Wiley Interscience.

Rvachev, L. and Longini, I. (1985). A mathematical model for the global spread of influenza, *Math. Biosci.* **75**: 3:22.

Sattenspiel, L. and Dietz, K. (1995). A structured epidemic model incorporating geographic mobility among regions, *Math. Biosci.* **128**: 71–91.

Sattenspiel, L. and Herring, D. (2003). Simulating the effect of quarantine on the spread of the 1918-19 flu in central Canada, *Bull. Math. Biol.* **65**: 1–26.

Sattenspiel, L. and Herring, D. A. (1998). Structured epidemic models and the spread of influenza in the central Canadian subartic, *Human Biology* **70**: 91–115.

Sattenspiel, L. and Simon, C. (1988). The spread and persistence of infectious diseases in structured populations, *Math. Biosci.* **90**: 341–366.

van den Driessche, P. and Watmough, J. (2002). Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.* **180**: 29–48.

Wang, W. and Zhao, X.-Q. (2002). An epidemic model in a patchy environment, Submitted.