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Disease Spread in Metapopulations

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Abstract. Some continuous time, discrete space, metapopulation models that have been formulated for disease spread are presented. Motivation for such a formulation with travel between discrete patches is presented. A system of $4p$ ordinary differential equations describes disease spread in an environment divided into p patches. The basic reproduction number $\mathcal{R}_0$ is calculated, with the disease dying out in each patch if $\mathcal{R}_0 < 1$. If travel is assumed to be independent of disease status, then numerical results are cited that indicate that for $\mathcal{R}_0 > 1$ solutions tend to an endemic equilibrium with the disease present in each patch. The system is extended to include cross infection between several species. A second extension involves keeping track of both the current patch and the patch in which an individual usually resides. Travel can change disease spread in a complicated way; it may help the disease to persist or may aid disease extinction. Complexity that can be built into metapopulation models is illustrated by three case-study examples from the literature.

1 Motivation for Spatial Epidemic Models

Classical deterministic epidemic models implicitly assume that space is homogeneous, and so do not include spatial variation. There are, however, many reasons why epidemic models should include spatial variation. Firstly, initial conditions of disease are often heterogeneous, with disease spreading geographically with time. For example, plague (black death) spread east to west and south to north along the trade routes of Europe between 1347 and 1350, and fox rabies spread west from the Russian-Polish border in 1940 to reach France by 1968. More recently, West Nile virus arrived in New York in 1999 and spread to the west coast of North American by 2004. Secondly, the environment is heterogeneous both in a geographical sense and in a human sense with birth rates, death rates and health care facilities

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varying with location. Thirdly, different species have different travel rates, a factor that is especially important for diseases involving many species (for example, the foot-and-mouth disease outbreak in the UK in 2001) and for vector transmitted diseases. For bubonic plague, the vectors, which are fleas, travel quickly over short distances; whereas the reservoir mammals, which are rodents, travel more slowly but over longer distances. Mosquitoes and birds, the vectors and reservoirs for West Nile virus, respectively, have different flight patterns that also depend on season, topography, and geographic conditions. In the case of rabies, foxes have different travel patterns when infective. Fourthly, for human diseases, social groupings and mixing patterns vary with geography and age. This can be illustrated by comparing humans in a hospital setting with those in isolated communities in Canada's North and with children in schools. Currently most humans live in cities and travel along defined routes. These influence the spatial spread of disease, for example, HIV spread along highways in the USA during the latter part of the twentieth century, and SARS in 2003 was spread by air travellers.

Continuous spatial models with continuous time yield partial differential equations of reaction-diffusion type. For example, such models have been formulated and analyzed for rabies by Murray and coauthors, see [21], and for West Nile virus in [18]. Discrete spatial models with continuous time yield systems of ordinary differential equations, which are *metapopulation* models involving movement of individuals between discrete spatial patches. This movement is captured by a digraph (or a multi-digraph) with the patches as vertices. Such compartmental models have been discussed for influenza spread due to air travel between cities by Hyman and LaForce [15] using a model with structure similar to that developed by Rvachev and Longini [23]. Such models have also been formulated for measles and influenza by Sattenspiel and coauthors [25, 26], further analyzed by Arino and coauthors [2, 3, 4, 5], and Wang and coauthors [16, 22, 30, 31, 32]. Here we review some of these models and survey other metapopulation models in the literature. We focus in particular on the basic reproduction number, $\mathcal{R}_0$, which is the average number of secondary cases produced by a single infected introduced into a totally susceptible population. This parameter $\mathcal{R}_0$ is a key concept in the study of infectious diseases and can aid in guiding measures to control disease. If $\mathcal{R}_0 < 1$, then the disease should die out if introduced at a low level, whereas if $\mathcal{R}_0 > 1$, then the disease is able to invade the population. To calculate $\mathcal{R}_0$, the next generation matrix method is used, details are given in [10, 29].

We remark that other types of spatial models have also been formulated in the literature; see, for example, [19, Part 2]. Included there are papers by Cliff [8] on geographic mapping methods to trace spatial disease spread, Metz and van den Bosch [20] on velocities of epidemic spread and Durrett [11] on disease spread on a lattice. Epidemics among a population partitioned into households are considered by Ball and Lyne [6], disease dynamics in discrete-time patchy environments are formulated by Castillo-Chavez and Yakubu [9], the rate of spread of endemic infections using integrodifference equations is investigated by Allen and Ernest [1], and urban social networks using a bipartite graph are explored by Eubank et al [12].

Due in part to increasing capacities of computers and to advances in mathematical analysis, there has been a recent surge of interest in metapopulation models. We hope that this review, although personal and not exhaustive, will encourage readers to delve further into the literature and to formulate new metapopulation models for disease spread.

2 Metapopulation Model on p Patches

We begin with the formulation of a general metapopulation SEIRS epidemic model. The structure of our model is based on that of Arino *et al.* [4], in which a multi-species epidemic model is constructed with the assumption that travel rates are independent of disease status. However, our model here is for disease transmission in one species, but allows for travel rates to depend on disease status. To formulate the deterministic model, assume that the environment under consideration is divided into p patches, which may be cities, geographic regions or communities. Within each patch conditions are assumed to be homogeneous. The population in patch i, is divided into compartments of susceptible, exposed (latent), infective and recovered individuals with the number in each compartment denoted by $S_i(t)$, $E_i(t)$, $I_i(t)$ and $R_i(t)$, respectively, for $i = 1, \ldots, p$. The total number of individuals in patch i is $N_i(t) = S_i(t) + E_i(t) + I_i(t) + R_i(t)$. The rates of travel of individuals between patches are assumed to depend on disease status, and individuals do not change disease status during travel. Let m_{ij}^S, m_{ij}^E, m_{ij}^I, m_{ij}^R denote the rate of travel from patch j to patch i of susceptible, exposed, infective, recovered individuals, respectively, where $m_{ii}^S = m_{ii}^E = m_{ii}^I = m_{ii}^R = 0$. This structure defines a multi-digraph with patches as vertices and arcs given by the travel rates, which can be represented by the nonnegative matrices $M^S = \left[m_{ij}^S\right]$, $M^E = \left[m_{ij}^E\right]$, $M^I = \left[m_{ij}^I\right]$ and $M^R = \left[m_{ij}^R\right]$. It is assumed that these matrices are irreducible.

Birth (or input) in patch i is assumed to be into the susceptible class at a rate $A_i(N_i) > 0$ individuals per unit time, and natural death is assumed to be independent of disease status with rate constant $d_i > 0$. The disease is assumed to be transmitted by horizontal incidence $\beta_i(N_i) S_i I_i$, thus an average individual makes $\beta_i(N_i) N_i$ contacts per unit time. It is reasonable to take $\beta_i(N_i)$ as a nonnegative nonincreasing function of N_i. Once infected, a susceptible individual harbors an agent of disease and moves to the exposed compartment, then into the infective compartment as the individual becomes able to transmit the disease. On recovering from the disease, an individual moves to the recovered compartment, and then back to the susceptible compartment as disease immunity fades. The period in the exposed, infective and recovered compartment is taken to be exponentially distributed with rate constant α_i, γ_i, δ_i, respectively. Thus $1/\alpha_i$, $1/\gamma_i$, $1/\delta_i$ is the average period (without accounting for death) of latency, infection, immunity, respectively. For a disease that causes mortality, the death rate constant for infectives is denoted by ε_i. The epidemic parameters are assumed to be nonnegative, with limiting cases giving simpler models. For example, if a disease confers permanent immunity, then $\delta_i = 0$ and an SEIR model results. If a disease has a very short latent period that can be ignored, then $\alpha_i \to \infty$ (an SIRS model); and if in addition the period of immunity is so short that it can be ignored, then $\delta_i \to \infty$ and an SIS model results. Such a model is appropriate for gonorrhea.

The above assumptions lead to a system of $4p$ ordinary differential equations (ODEs) describing the disease dynamics. For $i = 1, \ldots, p$ these equations are

$$\frac{dS_i}{dt} = A_i(N_i) - \beta_i(N_i) S_i I_i - d_i S_i + \delta_i R_i + \sum_{j=1}^{p} m_{ij}^S S_j - \sum_{j=1}^{p} m_{ji}^S S_i \quad (2.1)$$

$$\frac{dE_i}{dt} = \beta_i(N_i) S_i I_i - (\alpha_i + d_i) E_i + \sum_{j=1}^{p} m_{ij}^E E_j - \sum_{j=1}^{p} m_{ji}^E E_i \quad (2.2)$$

$$\frac{dI_i}{dt} = \alpha_i E_i - (\varepsilon_i + \gamma_i + d_i) I_i + \sum_{j=1}^{p} m_{ij}^I I_j - \sum_{j=1}^{p} m_{ji}^I I_i \quad (2.3)$$

$$\frac{dR_i}{dt} = \gamma_i I_i - (d_i + \delta_i) R_i + \sum_{j=1}^{p} m_{ij}^R R_j - \sum_{j=1}^{p} m_{ji}^R R_i \quad (2.4)$$

with initial conditions $S_i(0) > 0, E_i(0), I_i(0), R_i(0) \geq 0, \sum_{i=1}^{p} E_i(0) + I_i(0) > 0$.

The population of patch i, namely N_i, evolves according to the sum of equations (2.1)-(2.4). Solutions of (2.1)-(2.4) remain nonnegative with N_i positive for all $t \geq 0$. The total population in all patches $N = N_1 + N_2 + \ldots + N_p$ satisfies

$$\frac{dN}{dt} = \sum_{i=1}^{p} (A_i(N_i) - \varepsilon_i I_i - d_i N_i) \quad (2.5)$$

The metapopulation model is at equilibrium if the time derivatives in (2.1)-(2.4) are zero. Patch i is at a disease free equilibrium (DFE) if $E_i = I_i = 0$, and the p-patch model is at a DFE if $E_i = I_i = 0$ for all $i = 1, \ldots, p$. Thus at a DFE, for all $i = 1, \ldots, p, S_i = N_i$ and satisfies

$$A_i(N_i) - d_i N_i + \sum_{j=1}^{p} m_{ij}^S N_j - \sum_{j=1}^{p} m_{ji}^S N_i = 0 \quad (2.6)$$

Assume that (2.6) has a solution that gives the DFE $S_i^* = N_i^*$, which is unique This is certainly true if $A_i(N_i) = d_i N_i$ (i.e., birth rate equal to the death rate) and $\varepsilon_i = 0$ (i.e., no disease related death) giving a constant total population from (2.5). Arino *et al* [4] make these assumptions for a multi-species epidemic model. It is also true if $A_i(N_i) = A_i$ as assumed in [24].

Linear stability of the disease free equilibrium can be investigated by using the next generation matrix [10, 29]. Using the notation of [29], and ordering the infected variables as $E_1, \ldots, E_p, I_1, \ldots, I_p$ the matrix of new infections F and the matrix of transfer between compartments V are given in partitioned form by

$$F = \begin{bmatrix} 0 & F_{12} \\ 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} V_{11} & 0 \\ -V_{21} & V_{22} \end{bmatrix} \quad (2.7)$$

Here $F_{12} = \operatorname{diag}(\beta_i(N_i^*) N_i^*)$, $V_{11} = -M^E + \operatorname{diag}\left(\alpha_i + d_i + \sum_{j=1}^{p} m_{ji}^E\right)$, $V_{21} = \operatorname{diag}(\alpha_i)$, $V_{22} = -M^I + \operatorname{diag}\left(\varepsilon_i + \gamma_i + d_i + \sum_{j=1}^{p} m_{ji}^I\right)$.

Matrices V_{11} and V_{22} are $p \times p$ irreducible M-matrices [7] and thus have positive inverses. The next generation matrix

$$FV^{-1} = \begin{bmatrix} F_{12}V_{22}^{-1}V_{21}V_{11}^{-1} & F_{12}V_{22}^{-1} \\ 0 & 0 \end{bmatrix}$$

has spectral radius, denoted by ρ, given by $\rho\left(FV^{-1}\right) = \rho\left(F_{12}V_{22}^{-1}V_{21}V_{11}^{-1}\right)$. As shown in [29], the Jacobian matrix of the infected compartments at the DFE, which is given by $F - V$, has all eigenvalues with negative real parts if and only if $\rho\left(FV^{-1}\right) < 1$. The number $\rho\left(FV^{-1}\right)$ is the basic reproduction number $\mathcal{R}_0$ for the disease transmission model, thus

$$\mathcal{R}_0 = \rho\left(F_{12}V_{22}^{-1}V_{21}V_{11}^{-1}\right), \tag{2.8}$$

and the DFE is linearly stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$. If $A_i\left(N_i\right) = A_i$ and $\beta_i\left(N_i\right) = \beta_i/N_i$ (standard incidence), then a comparison theorem argument can be used to show that if $\mathcal{R}_0 < 1$, then the DFE is globally asymptotically stable [24]. This extends the results for 2 patches given by [30, Theorem 2.1] for a constant population. Wang and Zhao [31] assume mass action incidence and show that population travel in an SIS model can either intensify or reduce the spread of disease in a metapopulation. Moreover, for this SIS model, the disease persists for $\mathcal{R}_0 > 1$, and if susceptible and infective individuals have the same travel rates, then there exists a unique, globally attracting endemic equilibrium [16, Theorem 3.1].

3 Travel Rates Independent of Disease Status

For mild diseases it may be reasonable to simplify the model of the previous section by assuming that individuals do not die from disease ($\varepsilon_i = 0$) and travel rates are independent of disease status, thus $M^S = M^E = M^I = M^R = M = [m_{ij}]$ (irreducible). Travel rates are thus specified on a digraph. These assumptions are made in the multi-species model formulated by Arino *et al.* [4], in which it is also assumed that $A_i(N_i) = d_i N_i$ and $\beta_i(N_i) = \beta_i/N_i$ (i.e., standard incidence). With these assumptions the one species given by model equations (2.1)-(2.4) becomes for $i = 1, \ldots, p$

$$\frac{dS_i}{dt} = d_i\left(N_i - S_i\right) - \beta_i\frac{S_iI_i}{N_i} + \delta_iR_i + \sum_{j=1}^{p} m_{ij}S_j - \sum_{j=1}^{p} m_{ji}S_i \tag{3.1}$$

$$\frac{dE_i}{dt} = \beta_i\frac{S_iI_i}{N_i} - \left(\alpha_i + d_i\right)E_i + \sum_{j=1}^{p} m_{ij}E_j - \sum_{j=1}^{p} m_{ji}E_i \tag{3.2}$$

$$\frac{dI_i}{dt} = \alpha_iE_i - \left(\gamma_i + d_i\right)I_i + \sum_{j=1}^{p} m_{ij}I_j - \sum_{j=1}^{p} m_{ji}I_i \tag{3.3}$$

$$\frac{dR_i}{dt} = \gamma_iI_i - \left(d_i + \delta_i\right)R_i + \sum_{j=1}^{p} m_{ij}R_j - \sum_{j=1}^{p} m_{ji}R_i \tag{3.4}$$

Summing (3.1)-(3.4) gives

$$\frac{dN_i}{dt} = \sum_{i=1}^{p} m_{ij}N_j - \sum_{j=1}^{p} m_{ji}N_i \tag{3.5}$$

Thus the N_i equation uncouples from the epidemic variables. This linear system of equations has coefficient matrix $M - \text{diag}\left(\sum_{j=1}^{p} m_{ji}\right)$ which is the negative of a singular M-matrix (since each column sum is zero). From (3.5), see also (2.5), the total population N is constant. Subject to this constraint, it can be shown that (3.5) has a unique positive equilibrium $N_i = N_i^*$ that is asymptotically stable [4, Theorem 3.3]. Thus the disease free equilibrium of (3.1)-(3.4) is given by $(S_i, E_i, I_i, R_i) = (N_i^*, 0, 0, 0)$ and is unique.

The basic reproduction number $\mathcal{R}_0$ is calculated as in Section 2 with $F_{12} = \text{diag}\,(\beta_i)$ and $M^E = M^I = M$. The linear stability result for $\mathcal{R}_0 < 1$ can be strengthened to a global result as follows. Since $S_i \leq N_i$, equation (3.2) gives the inequality

$$\frac{dE_i}{dt} \leq \beta_i I_i - (\alpha_i + d_i)\, E_i + \sum_{j=1}^{p} m_{ij} E_j - \sum_{j=1}^{p} m_{ji} E_i \tag{3.6}$$

For comparison, define a linear system given by (3.6) with equality, namely

$$\frac{dE_i}{dt} = \beta_i I_i - (\alpha_i + d_i)\, E_i + \sum_{j=1}^{p} m_{ij} E_j - \sum_{j=1}^{p} m_j E_i$$

and by equation (3.3). This system has coefficient matrix $F - V$, and so by the argument in Section 2, satisfies $\lim_{t\to\infty} E_i = 0$ and $\lim_{t\to\infty} I_i = 0$ for $\mathcal{R}_0 = \rho(FV^{-1}) < 1$. Using a comparison theorem [17, Theorem 1.5.4], [28, Theorem B.1] and noting (3.6), it follows that these limits also hold for the nonlinear system (3.2) and (3.3). That $\lim_{t\to\infty} R_i = 0$ and $\lim_{t\to\infty} S_i = N_i^*$ follow from (3.4) and (3.1). Thus for $\mathcal{R}_0 < 1$, the disease free equilibrium is globally asymptotically stable and the disease dies out.

The existence and stability of endemic equilibria if $\mathcal{R}_0 > 1$ are open analytical questions. As in many high dimensional epidemic models, these are hard problems. It is sometimes possible to prove that the disease is globally uniformly persistent by appealing to the techniques of persistence theory; see [33].

Arino *et al* [4, Section 4] state that numerical simulations of (3.1)-(3.4) indicate that solutions of their metapopulation model specialized to one species on p patches with $\mathcal{R}_0 > 1$ tend to a unique endemic equilibrium with disease present in each patch. They display [4, Figure 1] solutions in the case of $p = 2$ patches with parameter values compatible with influenza that give $\mathcal{R}_0^{(1)} = 1.015$ and $\mathcal{R}_0^{(2)} = 0.952$. With no travel between patches, disease is endemic in patch 1, but dies out in patch 2. With small travel rates $m_{12} = m_{21} = 0.001$, equation (2.8) gives $\mathcal{R}_0 \approx 1.0095 > 1$, and the system approaches an epidemic equilibrium in both patches. However if travel rates are increased to $m_{12} = m_{21} = 0.05$, then $\mathcal{R}_0 \approx 0.985 < 1$ and the system approaches the DFE in both patches. Thus small travel rates help the disease to persist, whereas slightly higher travel rates stabilize the DFE. For a single species, the effect of quarantine where the patches are arranged in a ring is numerically investigated in [5].

4 Multi-Species Model

Spatial spread is all the more important for diseases that involve several species, for example, bubonic plague and West Nile virus. In [4] an SEIR epidemic model for a population consisting of s species and occupying p spatial patches is considered. This is extended in [5] to allow for temporary immunity, giving an SEIRS model. Here, we also allow rates of travel between patches to depend on disease status. With assumptions as in Section 2 and using standard incidence, the dynamics for species $j = 1, \dots, s$ in patch $i = 1, \dots, p$ is given by the following system of $4sp$ equations

$$\begin{aligned}
\frac{dS_{ji}}{dt} &= A_{ji}(N_{ji}) - \sum_{k=1}^{s} \beta_{jki} S_{ji} \frac{I_{ki}}{N_{ki}} - d_{ji} S_{ji} + \delta_{ji} R_{ji} + \\
&\quad \sum_{q=1}^{p} m^S_{jiq} S_{jq} - \sum_{q=1}^{p} m^S_{jqi} S_{ji} && (4.1)\\
\frac{dE_{ji}}{dt} &= \sum_{k=1}^{s} \beta_{jki} S_{ji} \frac{I_{ki}}{N_{ki}} - (\alpha_{ji} + d_{ji}) E_{ji} + \sum_{q=1}^{p} m^E_{jiq} E_{jq} - \sum_{q=1}^{p} m^E_{jqi} E_{ji} && (4.2)\\
\frac{dI_{ji}}{dt} &= \alpha_{ji} E_{ji} - (\varepsilon_{ji} + \gamma_{ji} + d_{ji}) I_{ji} + \sum_{q=1}^{p} m^I_{jiq} I_{jq} - \sum_{q=1}^{p} m^I_{jqi} I_{ji} && (4.3)\\
\frac{dR_{ji}}{dt} &= \gamma_{ji} I_{ji} - (d_{ji} + \delta_{ji}) R_{ji} + \sum_{q=1}^{p} m^R_{jiq} R_{jq} - \sum_{q=1}^{p} m^R_{jqi} R_{ji} && (4.4)
\end{aligned}$$

where the total population of species j in patch i is denoted by $N_{ji} = S_{ji} + E_{ji} + I_{ji} + R_{ji}$. The parameters are defined similarly to those in Section 2, but now the first subscript denotes the species, for example, $1/\gamma_{ji}$ is the average period of infection for species j in patch i and β_{jki} is the rate of disease transfer from species k to species j in patch i. Each species has its own travel matrices, for example $M^I_j = [m^I_{jiq}]$ where m^I_{jiq} denotes the rate of travel of an infective individual of species j from patch q to patch i. With nonnegative initial conditions having $N_{ji}(0) > 0$ the solutions remain nonnegative with $N_{ji}(t) > 0$ for all $t \geq 0$.

For a simplified version of (4.1)-(4.4) in which the birth (input) term $A_{ji}(N_{ji}) = d_{ji} N_{ji}$, recovered individuals have permanent immunity ($\delta_{ji} = 0$) and travel is independent of disease status, there is a unique DFE; see [4, Theorem 3.3]. Assume this is true for (4.1)-(4.4) with $S^*_{ji} = N^*_{ji}$ at the DFE. Then the basic reproduction number, $\mathcal{R}_0$, can be calculated by the method used in Section 2. This is illustrated for the case of two species on three patches. The infected variables are ordered as $E_{11}, E_{21}, E_{12}, E_{22}, E_{13}, E_{23}, I_{11}, I_{21}, I_{12}, I_{22}, I_{13}, I_{23}$. The nonnegative matrix F has the form given by (2.7) with $F_{12} = G_1 \oplus G_2 \oplus G_3$ where for $r = 1, 2, 3$,

$$G_r = \begin{bmatrix} \beta_{11r} & \beta_{12r} \frac{N^*_{1r}}{N^*_{2r}} \\ \beta_{21r} \frac{N^*_{2r}}{N^*_{1r}} & \beta_{22r} \end{bmatrix}$$

Matrices V_{11}, V_{21} and V_{22} in V given by (2.7) are now block matrices with each block being a 2×2 diagonal matrix. Writing

$$V_{11} = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{bmatrix}$$

the (i,i) entry of A_{kk} is $\alpha_{ik} + d_{ik} + \sum_{q=1}^{3} m_{iqk}^E$, and the (i,i) entry of A_{jk} for $j \neq k$ is $-m_{ijk}^E$. Similarly writing V_{22} as the block matrix B_{jk} , the (i,i) entry of B_{kk} is $\varepsilon_{ik} + \gamma_{ik} + d_{ik} + \sum_{q=1}^{3} m_{iqk}^I$ and for $j \neq k$, the (i,i) entry of B_{jk} is $-m_{ijk}^I$. The matrix $V_{21} = C_1 \oplus C_2 \oplus C_3$ with C_r having (i,i) entry equal to α_{ir}.

In terms of the above matrices, the basic reproduction number $\mathcal{R}_0$ is given by (2.8). The block structure enables $\mathcal{R}_0$ to be easily calculated for a given set of disease parameters. Note that $\mathcal{R}_0$ depends explicitly on the travel rates of exposed and infective individuals, and implicitly (through N_{jr}^*) on the travel rates of susceptible individuals. In the case in which travel is independent of disease status and there is no disease death, a comparison theorem argument can be used as in Section 3 to show that if $\mathcal{R}_0 < 1$, then the DFE is globally asymptotically stable; whereas if $\mathcal{R}_0 > 1$, then the DFE is unstable. A ring of patches with one-way travel is used to model low pathogenecity avian influenza in birds and humans [5].

5 Model Including Residency Patch

Sattenspiel and Dietz [26] introduced a single species, multi-patch model that describes the travel of individuals, and keeps track of the patch where an individual is born and usually resides as well as the patch where an individual is at a given time. This model has subsequently been studied numerically in various contexts, including the effects of quarantining [27]. We studied this model [2, 3] giving some analytical results and calculating the basic reproduction number. In this model, if a resident from patch i travels to patch j then they are assumed to return home to patch i before traveling to another patch k, i.e., such an individual does not travel directly from patch j to patch k (for j, $k \neq i$). We now extend the SIR model in [26] by removing this restriction and allowing for such an individual to travel between two patches that are not their residency patch. The assumption of [26] may be appropriate for travel between isolated communities; see [25] and references therein for situations linked to the spread of influenza in the Canadian subarctic. However, our formulation allows for a wider range of travel patterns.

To formulate our model, let $N_{ij}(t)$ be the number of residents of patch i who are present in patch j at time t, with $S_{ij}(t)$, $I_{ij}(t)$ and $R_{ij}(t)$ being the number that are susceptible, infective and recovered, respectively. Matrix $M_i^S = [m_{ijk}^S]$ gives the travel rates of susceptible individuals resident in patch i from patch k to patch j. Similarly $M_i^I = [m_{ijk}^I]$ and $M_i^R = [m_{ijk}^R]$ give these rates for infective and recovered individuals. Taking standard incidence as in previous models, β_{ikj} denotes the proportion of adequate contacts in patch j between a susceptible from patch i and an infective from patch k that results in disease transmission and κ_j denotes the average number of such contacts in patch j. For all patches, the recovery rate of infectives is denoted by γ, the loss of immunity rate by δ, birth is

assumed to occur in the residency patch at rate d and natural death to occur (in all disease states) at the same rate d. For p patches, the model takes the following form for $i, j = 1, \ldots, p$.

$$\begin{aligned}
\frac{dS_{ii}}{dt} &= d\sum_{k=1}^{p} N_{ik} - \sum_{k=1}^{p}\kappa_i\beta_{iki}S_{ii}\frac{I_{ki}}{\mathbf{N}_i} - dS_{ii} + \delta R_{ji} + \sum_{k=1}^{p} m^S_{iik}S_{ik} - \sum_{k=1}^{p} m^S_{iki}S_{ii} \\
\frac{dI_{ii}}{dt} &= \sum_{k=1}^{p}\kappa_i\beta_{iki}S_{ii}\frac{I_{ki}}{\mathbf{N}_i} - (d+\gamma)I_{ii} + \sum_{k=1}^{p} m^I_{iik}I_{ik} - \sum_{k=1}^{p} m^I_{iki}I_{ii} \\
\frac{dR_{ii}}{dt} &= \gamma I_{ii} - (d+\delta)R_{ii} + \sum_{k=1}^{p} m^R_{iik}R_{ik} - \sum_{k=1}^{p} m^R_{iki}R_{ii}
\end{aligned}$$

and for $i \neq j$

$$\begin{aligned}
\frac{dS_{ij}}{dt} &= -\sum_{k=1}^{p}\kappa_j\beta_{ikj}S_{ij}\frac{I_{kj}}{\mathbf{N}_i} - dS_{ij} + \delta R_{ij} + \sum_{k=1}^{p} m^S_{ijk}S_{ik} - \sum_{k=1}^{p} m^S_{ikj}S_{ij} \\
\frac{dI_{ij}}{dt} &= \sum_{k=1}^{p}\kappa_j\beta_{ikj}S_{ij}\frac{I_{kj}}{\mathbf{N}_j} - (d+\gamma)I_{ij} + \sum_{k=1}^{p} m^I_{ijk}I_{ik} - \sum_{k=1}^{p} m^I_{ijk}I_{ij} \\
\frac{dR_{ij}}{dt} &= \gamma I_{ij} - (d+\delta)R_{ij} + \sum_{k=1}^{p} m^R_{ijk}R_{ik} - \sum_{k=1}^{p} m^R_{ijk}R_{ij}
\end{aligned}$$

where $\mathbf{N}_i = \sum_{j=1}^{p} N_{ji}$, the number present in patch i. Properties of this model remain to be explored.

For the simpler case formulated in [26] in which travel is independent of disease status and individuals return to their residency patch after traveling to another patch, some analysis is given in [2, 3] for corresponding SIS and SEIRS models. These models have a unique DFE and the basic reproduction number is calculated by the method used in Section 2 with F and V being block matrices. Numerical simulations show that a change in travel rates can lead to a bifurcation at $\mathcal{R}_0 = 1$; thus travel can stabilize or destabilize the disease free equilibrium.

6 Other Discrete Spatial Models

We end this survey with a brief description of three other metapopulation models from the recent literature and we emphasize their novel features. The first is for a human disease, whereas the last two model specific animal diseases. Together they illustrate the possible complexity that can be built into patch models. We hope that these descriptions encourage readers to consult the original papers as well as to formulate and analyze other metapopulation models that are applicable to disease spread.

6.1 Spread of Influenza. Hyman and LaForce [15] formulate a multi-city transmission model for the spread of influenza between cities (patches) with the assumption that people continue to travel when they are infectious and there is no death due to influenza. Because influenza is more likely to spread in the winter than in the summer, they assume that the infection rate has a periodic component. In addition, they introduce a new disease state P in which people have partial

immunity to the current strain of influenza. Thus they have an SIRPS model in which both susceptible and partially immune individuals can be infected, but this is more likely for susceptibles. A symmetric travel matrix $M = [m_{ij}]$ with $m_{ij} = m_{ji}$ is assumed, thus the population of each city remains constant. Their model for p cities is formulated as a $4p$ system of non autonomous ODEs.

The authors take epidemic parameters appropriate for influenza virus, in particular for strains of H3N2 in the 1996-2001 influenza seasons with an infectious period of $1/\alpha = 4.1$ days in all cities. Parameters modeling the number of adequate contacts per person per day and the seasonal change of infectivity are estimated by a least squares fit to data. The populations of the largest 33 cities in the US are taken from 2000 census data, and migration between cities is approximated by airline flight data. A sensitivity analysis reveals that the parameter α is the most single important parameter. From numerical simulations on the network of 33 cities, the authors find that the peak of the epidemic lags behind the seasonal peak in infectivity. A comparison of model results with data is given for several cities, and the model is seen to capture the essential features of the yearly influenza epidemics.

6.2 Tuberculosis in Possums. The spread of bovine tuberculosis amongst the common brushtail possum in New Zealand, is modeled by Fulford *et al* [14]. Since only maturing possums (1 to 2 year old males) travel large distances, the authors formulate a two-age class metapopulation model with juvenile and adult possums. As this disease is fatal, an SEI model is appropriate. In addition to horizontal transmission between both age-classes, pseudo-vertical transmission is included since juveniles may become infected by their mothers. Susceptible and exposed juveniles (but not infective juveniles) travel between patches as they mature. For p patches, the authors formulate a system of $6p$ ODEs to describe the disease dynamics. Using the next generation matrix method [10, 29], the authors explicitly calculate $\mathcal{R}_0$ for $p = 1$ and for $p = 2$, and give the structures of the next generation matrices for $p = 4$ and three spatial topologies, namely a spider, chain and loop.

Fulford *et al* [14] give numerical results and compute $\mathcal{R}_0$ with appropriate parameters [14, Table 1] for $p = 2$ and for $p = 4$ with the above topologies. The design of control strategies (culling) based on these three spatial topologies is considered. The critical culling rates are calculated and the spatial aspects are shown to be important.

6.3 Feline Leukemia Virus. Fromont *et al* [13] derive a model appropriate for Feline Leukemia Virus among a population of domestic cats. There are p patches called farms or villages depending on the magnitude of the patch carrying capacity. Dispersal (which depends on disease state) can take place between any pair of patches or into/out of non-specified populations surrounding the patches (representing transient feral males). Infected cats become either infectious or immune and remain so for life, thus the model is of SIR type, but a proportion of cats go directly from the susceptible to the immune state. A density dependent mortality function is assumed, as well as different incidence functions depending on the population density (mass action for cats on farms, but standard incidence for cats in villages).

The model consists of $3p$ ODEs and is analyzed for the case $p = 2$. Fromont *et al* [13] take data appropriate for the virus with one patch being a village and one patch being a farm, or both patches being farms. For a set of parameters such that

in isolation the virus develops in the village but goes extinct on the farm, travel between the patches of either susceptible and immune cats or of infective cats can result in the virus persisting in both patches. Thus results show that, in general for this model, spatial heterogeneity promotes disease persistence.

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