Diseases in metapopulations*

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Abstract

Metapopulation models consist of graphs, with systems of differential equations at each vertex. This modeling paradigm is appropriate for the description of the spatio-temporal spread of infectious diseases. In this document, I present the setting of these models, and some of the mathematical techniques that can be used to study them. I conclude with a brief review of some models using this approach.

1 Foreword – Notation

These lecture notes attempt to give a relatively exhaustive overview of methodological aspects of ordinary differential equations metapopulation models in the context of the spatial spread of diseases. They are based on work carried out with Pauline van den Driessche (in particular [5, 6, 7, 8]) and extensions of this work, and the work of all the authors cited.

It is assumed that basic mathematical epidemiology is known. A certain number of reference works can be consulted, if such is not the case. Some of the most significative are the books of Anderson and May [3], Diekmann and Heesterbeek [21], Brauer and Castillo-Chavez [14] and Thieme [59]. Hethcote also gave a good review that focuses on vaccination aspects [30]. There are also reference works concerning specific diseases. The book of Hethcote and Yorke on gonorrhea [32] or the one of Busenberg and Cooke on vertically transmitted diseases [15] are but two examples. See also the papers in [17, 18, 27, 35, 43].

We adopt the convention that roman letters represent demographic parameters, whereas greek letters denote disease related parameters. Notation has been adjusted, where possible, to abide to this rule. The SEIRS model, and its subcases (SI, SIS, SEI, SEIS, SIR and SIRS, to cite the most commonly used), will appear throughout this document, it is therefore detailed here with the parameters used in the manuscript. The flow diagram of the model is as follows:

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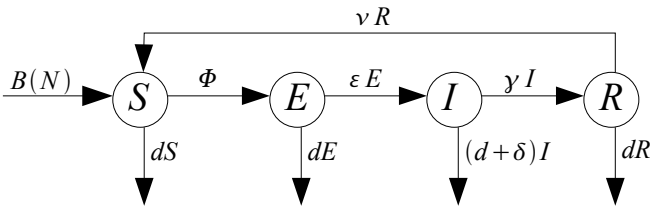


The SEIRS system then takes the form

$$S' = \mathcal{B}(N) + \nu R - \Phi - dS \tag{1.1a}$$
$$E' = \Phi - (\varepsilon + d)E \tag{1.1b}$$
$$I' = \varepsilon E - (\gamma + d + \delta)I \tag{1.1c}$$
$$R' = \gamma I - (\nu + d)R, \tag{1.1d}$$

It is assumed that there is no *vertical transmission* of the disease, so that all birth occurs into the susceptible class, at the rate $\mathcal{B}(N) > 0$, where $N = S + E + I + R$. Individuals in all epidemiological classes are subject to natural death, at the per capita rate d. If the birth rate is supposed equal to the death rate, as is done frequently, then the letter d is used for both. The force of infection is denoted Φ. It describes the rate of apparition of new infections. The most commonly used forms are mass action incidence

$$\Phi = \beta SI,$$

and proportional (or standard) incidence,

$$\Phi = \beta \frac{SI}{N},$$

where β is the transmission parameter. When a generic form is needed, it will be assumed that the force of infection can be written as

$$\Phi = \beta(N)SI$$

where the function β operates a scaling of the contacts by the population size. It is assumed throughout that β is a nonnegative nonincreasing function of N. Note that β might depend additionally on individual components of N, such as S and I, although this is not indicated for clarity of notations.

Upon infection, individuals move to the exposed (or latent) phase, where they are not yet infectious. The time of sojourn in the E class is exponentially distributed with mean $1/\varepsilon$, giving the rate of movement out of the E class ε. From the E class, individuals move to the infective (I) class, where they can infect susceptible individuals. When infective, individuals are subject to additional death due to infection, at the rate

δ. The average duration of infection is $1/\gamma$, after which time individuals move to the recovered (R) class. In the recovered class, individuals are immune to the disease. They lose immunity after a mean time period of $1/\nu$.

The epidemic parameters are assumed to be nonnegative, with limiting cases giving simpler models. For example, if a disease confers permanent immunity, then $\nu = 0$ and an SEIR model results. If a disease has a very short latent period that can be ignored, then $\varepsilon \to \infty$ (an SIRS model); and if in addition the period of immunity is so short that it can be ignored, then $\nu \to \infty$ and an SIS model results.

Because of space limitations, and of the focus that is put here on mathematical aspects, I will assume that the reader knows the reasons that lead to the use of a metapopulation-type framework in models of the spread of an infectious disease. If this is not the case, I recommend reading the lengthy introduction in [5], which provides some explanations as well as references.

This document is organized as follows. Section 2 details the general framework of metapopulations, and in particular, graph theoretic aspects. Disease models set in the context of metapopulations are presented in Section 3. Specific questions are addressed, and steps of a general method to study these problems are outlined using three specific models. Equiped with this knowledge, the reader should then refer to Section 4 to see what the current state of the art is on the topic.

2 Metapopulations

This section deals with metapopulation dynamics in the most general setting, i.e., when seen as large systems of differential equations coupled together within a graph. We give here the graph theoretic and dynamical systems context in which metapopulation models are formulated.

2.1 Introduction

The subject of metapopulations dynamics is relatively recent in the mathematical biology field, although it has been used in ecology for a longer time. A reference work on mathematical models is the book of Levin, Powell and Steele [39], whereas Hanski and Gilpin [28] give a more ecological account of the subject.

The simplest type of metapopulation models derive from the same type of models that led to discrete cellular automatons. In this setting,

often referred to as *patch occupancy* models, a patch (generally, a domain in space) is *occupied* or *unoccupied* by individuals of a given species. Typically, one considers the evolution of the number of occupied patches in a network, where the occupancy of a given patch depends on the occupancy of neighboring or connected patches. This type of system will not be discussed here. The type of systems that *will* be discussed here can be defined, loosely, as follows.

> **Practical definition:** A metapopulation model involves explicit movements of the individuals between distinct locations.

Movement can correspond to an actual physical movement of individuals, but can also represent the evolution of a trait.

To summarize, in the context of this document, a *metapopulation* is a graph with vertices (in metapopulation terminology, *patches*) containing a certain number of subpopulations, linked by migration as arcs, with explicit, non trivial dynamics for the subpopulations in each patch. To construct such models, several components must be defined, that are detailed in the remainder of this section.

2.2 The connection graph

Suppose that there are $\bar{p}$ patches. The set of patches is denoted $\mathcal{P}$, with $\bar{p} = |\mathcal{P}|$. Each patch $p \in \mathcal{P}$ contains a certain number of species belonging to a common set $\mathcal{S}$ of species. We denote $\bar{s} = |\mathcal{S}|$ the total number of species in the system. Note that at this point in our exposition, "species" is employed in a loose sense: two different epidemiological states represent two species. Each patch is a vertex in a graph $\mathcal{G}$. The edges of $\mathcal{G}$ represent the possibility for a given species to move between two patches; as a consequence, any two patches are connected by a maximum of $\bar{s}$ edges. The edges are then given an orientation (they are *arcs*, in graph terminology), to take into account that movement is not always symmetric.

Thus, the graph is a multi-digraph $\mathcal{G} = (\mathcal{P}, \mathcal{A})$, where $\mathcal{A}$ is the set of arcs, i.e., an ordered multiset of pairs of elements of $\mathcal{P}$. Any two vertices $X, Y \in \mathcal{P}$ are connected by at most $\bar{s}$ arcs from X to Y and at most $\bar{s}$ arcs from Y to X.

The formalism of graphs is helpful to characterize some of the properties of metapopulation models, and so a few further definitions are given, in which $X, Y \in \mathcal{P}$ are patches.

Direct access. Define the binary relation R^s by

$R^s(X,Y)$ if, for species $s \in \mathcal{S}$, there exists an arc $A \in \mathcal{A}$ from X to Y.

In this case, we say that *species s has direct access to patch Y from patch X*. We write $R(X,Y)$, and say that patch X has direct access to patch Y or that *patch Y can be accessed directly from patch X*, if there exists $s \in \mathcal{S}$ such that $R^s(X,Y)$. We write $\overline{R}(X,Y)$ and say that patch X has *full direct access* to patch Y if $R^s(X,Y)$ for all $s \in \mathcal{S}$.

The converse properties are also defined: species $s \in \mathcal{S}$ has no direct access to patch Y from patch X if $R^s(X,Y)$ does not hold, which we write **not** $R^s(X,Y)$; patch X has no direct access to patch Y if there is no $s \in \mathcal{S}$ such that $R^s(X,Y)$, i.e., $\forall s \in \mathcal{S}$, **not** $R^s(X,Y)$.

For a given patch X, define

$$\mathcal{P}^s_{X\rightarrow} = \{Y \in \mathcal{P} : R^s(X,Y)\}$$

and

$$\mathcal{P}_{X\rightarrow} = \{Y \in \mathcal{P} : \exists s \in \mathcal{S} \text{ such that } R^s(X,Y)\},$$

the sets of patches that can be directly accessed from patch X, and

$$\mathcal{P}^s_{\rightarrow X} = \{Y \in \mathcal{P} : R^s(Y,X)\}$$

and

$$\mathcal{P}_{\rightarrow X} = \{Y \in \mathcal{P} : \exists s \in \mathcal{S} \text{ such that } R^s(Y,X)\},$$

sets of patches that have direct access to patch X.

Connection matrix For a given species $s \in \mathcal{S}$, a *connection matrix* can be associated to the multi-digraph $\mathcal{G}$. Choosing an ordering $P_1, \ldots, P_{\bar{p}}$ for the elements of $\mathcal{P}$, the (j,i) entry of the $\bar{p} \times \bar{p}$-matrix $\mathcal{C}_s$ is one if $R^s(P_i, P_j)$ and zero otherwise, that is, if P_i has no direct access to P_j. Note that this gives the transpose matrix of the adjacency matrix obtained with the usual convention in graph theory that entry (i,j) be 1 if P_i has direct access to P_j. For convenience, the ordering of the patches is generally assumed the same for all species.

Indirect access. A given species $s \in \mathcal{S}$ has *indirect access* to patch Y from patch X if, for species $s \in \mathcal{S}$, there exists a path from X to Y in $\mathcal{G}$ but species s does not have direct access from X to Y. In other words, there exists $X_1 \in \mathcal{P}$ such that

$$R^s(X,X_1)R^s(X_1,Y),$$

but

$$\textbf{not } R^s(X,Y).$$

Indirect access can be defined on longer chains, by assuming that there exists $X_1, \ldots, X_n \in \mathcal{P}$, with $n \leq \bar{p}$, such that

$$R^s(X, X_1)R^s(X_1, X_2)\ldots R^s(X_n, Y),$$

but

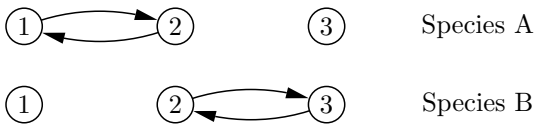
$$\textbf{not } R^s(X, Y), \textbf{not } R^s(X_1, Y), \ldots, \textbf{not } R^s(X_{n-1}, Y).$$

For problems involving disease propagation, the notion of *species-independent indirect access* from one patch to another is also very important. Patch X has species-independent indirect access to patch Y if there exists two species s_1 and s_2 in $\mathcal{S}$ and a patch $X_1 \in \mathcal{P}$ such that

$$R^{s_1}(X, X_1)R^{s_2}(X_2, Y),$$

with **not** $\bar{R}(X, Y)$. As for indirect access, species-independent indirect access can also be defined on longer chains.

For disease models, indirect access (in all forms) is particularly relevant for animals. If space is discretized in patches, humans typically have direct access from one patch to another, although some exceptions do occur if, for example, patches cover a very small surface area or in the case of some political restrictions of travel. Migrating animals, on the other hand, will typically follow a route involving sequences of patches that are connected two-by-two. The following graph illustrates the importance of species-independent indirect access. Suppose the top graph shows the connections for species A, while the bottom graph represents connections for species B.



Then, despite the absence of species-specific connection between patches 1 and 3, there exists a link between patches 1 and 3. If a disease is transmitted between species A and B, this means that the disease can move to patch 3 from patch 1.

For a given species, indirect access can be read in the connection matrix $\mathcal{C}_s$. Indeed, entries of $\mathcal{C}_s^2$ give the paths of length exactly 2 in $\mathcal{G}$ for species s, and by induction, entries of $\mathcal{C}_s^k$ give the paths of length exactly k in $\mathcal{G}$.

Access is the combination of direct and indirect access. Species $s \in \mathcal{S}$ in patch X has access to patch Y if species s has direct or indirect access to patch Y from patch X, and patch X has access to patch Y if it has direct or indirect access to patch Y from patch X. Two patches X and Y are *connected* if X can be accessed from Y and/or Y can be accessed from X.

For a given patch X, the sets $\overline{\mathcal{P}}^s_{X\rightarrow}$, $\overline{\mathcal{P}}_{X\rightarrow}$, $\overline{\mathcal{P}}^s_{\rightarrow X}$ and $\overline{\mathcal{P}}_{\rightarrow X}$ of patches that species s in X has access to, X has access to, for which species s has access to X and that have access to patch X, respectively, are defined as were the related sets for direct access, but considering the more general notion of access.

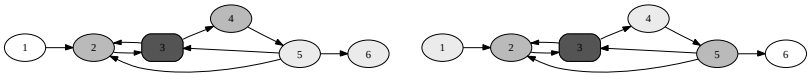


Figure 2.1: The sets $\overline{\mathcal{P}}_{3\rightarrow}$ (left) and $\overline{\mathcal{P}}_{\rightarrow 3}$ (right) for an example connection graph. Patches directly connected to 3 appear in darker gray, indirectly connected patches appear in lighter gray. Patches with no access to 3 or that cannot be accessed from 3 are white.

Symmetric multi-digraph. The multi-digraph $\mathcal{G}$ is *symmetric* for species s if for all $X, Y \in \mathcal{P}$, $R^s(X,Y)$ implies $R^s(Y,X)$, that is, if the binary relation R^s is symmetric. It is *fully symmetric* if, for all $X, Y \in \mathcal{P}$, $\overline{R}(X,Y)$ implies $\overline{R}(Y,X)$. Note that this implies that the associated connection matrices are symmetric.

Movement is similar for all species if, in the multi-digraph $\mathcal{G}$, the existence of an $s \in \mathcal{S}$ such that $R^s(X,Y)$ implies that $R^s(X,Y)$ for all $s \in \mathcal{S}$.

Strongly connected multi-digraph. The last property we consider is strong connectedness. For a given species s, the *strongly connected components* (or *strong components*, for short) are such that, for all patches X, Y in a strong component, species s in X has access to Y. The multi-digraph is strongly connected for species s if all patches belong to the same connected component. Strong connectedness is equivalent to *irreducibility* of the connection matrix $\mathcal{C}_s$, which is defined as follows. The matrix A is irreducible if for all $i, j = 1, \ldots, \bar{p}$, there exists k such that $a^k_{ij} > 0$, where a^k_{ij} is the (i,j)-entry in A^k. A matrix that is not irreducible is *reducible*.

A characterization of reducible matrices that is useful is the following. A matrix A is reducible if there exists a permutation matrix P such that P^TAP is block triangular,

$$P^TAP = \begin{pmatrix} A_{11} & 0 & & 0 \\ A_{21} & A_{22} & & 0 \\ & & \ddots & 0 \\ A_{n1} & A_{n2} & & A_{nn} \end{pmatrix},$$

with every block A_{ii} square and either irreducible or a 1×1 null matrix (an irreducible matrix A has block $(1,1)$ equal to A).

2.3 Dynamics between the patches

The dynamics of the system combines the dynamics in each patch resulting from the interactions of the various species that are present, with an operator describing the movements of individuals between the patches. The models that are considered in the rest of this document are time autonomous with linear movement operators, so the exposition is now specialized to this case.

Let N_s^p be the number of individuals of species $s \in \mathcal{S}$ in patch $p \in \mathcal{P}$ at time t, $N_s = (N_s^1, \ldots, N_s^{\bar{p}})^T$ be the vector of distribution of the individuals of a given species s among the different patches and $N^p = (N_1^p, \ldots, N_{\bar{s}}^p)^T$ be the vector of composition of the population of a given patch p. There are several ways of describing the evolution of the populations. The most obvious is to write the evolution of each individual component of the system; for all $s = 1, \ldots, \bar{s}$ and $p = 1, \ldots, \bar{p}$,

$$\frac{d}{dt}N_s^p = f_s^p(N^p) + \sum_{i=1}^{\bar{p}} m_{pi}^s N_s^i - \sum_{i=1}^{\bar{p}} m_{ip}^s N_s^p, \tag{2.1}$$

with $f_s^p : \mathbb{R}^{\bar{s}} \to \mathbb{R}$ a function describing the dynamics within patch p of individuals of species s. This function might involve all individuals that are present in the patch, regardless of their species, hence its dependence on N^p; we suppose that there are no between-patch interactions, though, so that f_s^p only involves individuals from patch p. The term $\sum_{i=1}^{\bar{p}} m_{pi}^s N_s^i$ describes the inflow of individuals of species s into patch p, from all patches in $\mathcal{P}_{\to p}$. The term $-\sum_{i=1}^{\bar{p}} m_{ip}^s N_s^p$ is the outflow of individuals of species s towards all patches in $\mathcal{P}_{p\to}$.

Note that it is assumed here that $m_{ii}^s = 0$ for all s. Another way to deal with linear movement operators is to suppose that

$$m_{ii}^s = -\sum_{\substack{j=1 \\ j\neq i}}^{\bar{p}} m_{ji}^s,$$

which allows us to write (2.1) in the form $\frac{d}{dt}N_s^p = f_s^p(N^p) + \sum_{i=1}^{\bar{p}} m_{pi}^s N_s^i$. For the clarity of the exposition, we use here the convention $m_{ii}^s = 0$.

Although a painstaking approach, the use of the form (2.1) is sometimes required to establish properties such as the positive invariance of the positive orthant under the flow of the system. It is also the most straightforward way to formulate models.

However, because of the notational burden, vector notations are often used. The most common of these vector notations (and the only one we detail here) proceeds species by species, using a vector equation for each successive species. For all $s = 1, \ldots, \bar{s}$,

$$\frac{d}{dt}N_s = f^p(N^p) + \mathcal{M}_s N_s, \tag{2.2}$$

with $f^p : \mathbb{R}^{\bar{s}} \to \mathbb{R}^{\bar{p}}$ and $\mathcal{M}_s$ a $\bar{p} \times \bar{p}$ matrix representing the movement terms. For a given species s, it takes the form,

$$\mathcal{M}_s = \begin{pmatrix} -\sum_{k=1}^{\bar{p}} m_{k1}^s & m_{12}^s & \cdots & m_{1\bar{p}}^s \\ m_{21}^s & -\sum_{k=1}^{\bar{p}} m_{k2}^s & \cdots & m_{2\bar{p}}^s \\ \vdots & & \ddots & \vdots \\ m_{\bar{p}1}^s & m_{\bar{p}2}^s & \cdots & -\sum_{k=1}^{\bar{p}} m_{k\bar{p}}^s \end{pmatrix}. \tag{2.3}$$

Note that the matrix $\mathcal{M}_s$ combines the connection matrix deduced from the graph of patches, and a description of the intensity of the connections. The connection matrix of the graph is thus easily reconstructed from $\mathcal{M}_s$ by setting diagonal entries in $\mathcal{M}_s$ to zero, and nonzero offdiagonal entries to 1.

Throughout this text, the following notations and names are used for matrices. Let A, B be two $n \times n$-matrices, with $A = [a_{ij}]$ and $B = [b_{ij}]$. Then

- $A \geq 0$ is a *nonnegative* matrix if $a_{ij} \geq 0$ for all i, j, and $A \geq B$ if $A - B \geq 0$.
- $A > 0$ is a *positive* matrix if additionally, there exists i, j such that $a_{ij} > 0$, and $A > B$ if $A - B > 0$.
- $A \gg 0$ is *strongly positive* if $a_{ij} > 0$ for all i, j, and $A \gg B$ if $A - B \gg 0$.

The same notation and names are used for vectors. Note that this terminology is not standard. Many authors in linear algebra say that a matrix $A \gg 0$ is positive, and use no specific name for a matrix $A > 0$. Here, it is however important to distinguish between, for example, a vector that is positive and one that is strongly positive.

2.3.1 Properties of the movement matrix

Matrix $\mathcal{M}_s$ is used extensively in the remainder of this document. Its main properties are summarized in the following result.

Theorem 2.1. *Consider a species $s \in \mathcal{S}$. Then $(-\mathcal{M}_s)$ is a singular M-matrix. All eigenvalues of $\mathcal{M}_s$ have nonpositive real parts. 0 is an eigenvalue of $\mathcal{M}_s$, and one of the eigenvectors associated to the eigenvalue 0 is the vector $\mathbb{1}_{\bar{p}}^T = (1, \ldots, 1)$. In the case that $\mathcal{M}_s$ is irreducible, then 0 is an eigenvalue with multiplicity 1, $\mathbb{1}_{\bar{p}}^T$ is (to a multiple) the only strongly positive left eigenvector associated with $\mathcal{M}_s$, and all other eigenvalues have negative real parts.*

Proof. Matrix $(-\mathcal{M}_s)$ has the Z-sign pattern, that is, has nonnegative diagonal and nonpositive offdiagonal entries. Each column sum of $\mathcal{M}_s$ is zero, *i.e.*, $\mathbb{1}_{\bar{p}}^T(-\mathcal{M}_s) = 0$ for all $s \in \mathcal{S}$, where the $1 \times \bar{p}$ vector $\mathbb{1}_{\bar{p}}^T = (1, \ldots, 1)$. (The index on $\mathbb{1}^T$ is dropped in the sequel if unambiguous). It follows that $(-\mathcal{M}_s)$ is a singular M-matrix; see, *e.g.*, [12] or [23, Th. 5.11].

Because the column sums of $\mathcal{M}_s$ are all zero with nonpositive diagonal entries, Gershgorin's circle theorem [41, 61] implies that all eigenvalues λ of $\mathcal{M}_s$ have nonpositive real parts. Indeed, defining

$$\bar{d} = \max_{i=1,\ldots,\bar{p}} \sum_{k=1}^{\bar{p}} m_{ki}^s,$$

all Gershgorin disks are contained in the disk centered at $-\bar{d}$ and with radius $\bar{d}$. Also, from the singularity of $\mathcal{M}_s$, 0 is an eigenvalue. Since $\mathbb{1}^T\mathcal{M}_s = 0$, it also follows that $\mathbb{1}^T$ is a (left) eigenvector of $\mathcal{M}_s$ associated to the eigenvalue 0.

To show that the eigenvector $\mathbb{1}^T$ is, to a multiple, the only strongly positive (left) eigenvector of $\mathcal{M}_s$, we proceed as follows. The matrix

$$\mathcal{M}_s + \overline{d}\mathbb{I}$$

is nonnegative, with $\mathbb{I}$ the identity matrix, and therefore, the Perron-Frobenius theorem for nonnegative matrices ([12, Theorem 2.1.4], [61, Theorem C.2]) implies that the spectral radius

$$\rho(\mathcal{M}_s + \overline{d}\mathbb{I}) = \max\{|\lambda| : \lambda \in \mathrm{Sp}(\mathcal{M}_s + \overline{d}\mathbb{I})\},$$

where $\mathrm{Sp}(A)$ is the spectrum of the matrix A, is an eigenvalue associated to a strongly positive eigenvector v. Another conclusion of [12, Theorem 2.1.4] is that any other eigenvalue $\lambda \in \mathrm{Sp}(\mathcal{M}_s + \overline{d}\mathbb{I})$ such that $|\lambda| = \rho(\mathcal{M}_s + \overline{d}\mathbb{I})$ is also simple, and that any other nonnegative eigenvector of $\mathcal{M}_s + \overline{d}\mathbb{I}$ is a multiple of v.

Using a left eigenvector, we have

$$v^T(\mathcal{M}_s + \overline{d}\mathbb{I}) = \rho(\mathcal{M}_s + \overline{d}\mathbb{I})v^T$$

for $v^T \gg 0$ unique to a multiple. Since $\mathbb{1}^T(\mathcal{M}_s + \bar{d}\mathbb{I}) = \mathbb{1}^T\mathcal{M}_s + \bar{d}\mathbb{1}^T = \bar{d}\mathbb{1}^T$, it follows that $\rho(\mathcal{M}_s + \overline{d}\mathbb{I}) = \overline{d}$ and $v^T = \mathbb{1}^T$ is the eigenvector associated to the spectral radius $\overline{d}$ of $\mathcal{M}_s + \overline{d}\mathbb{I}$.

Now note that the spectra of $\mathcal{M}_s$ and $\mathcal{M}_s + \overline{d}\mathbb{I}$ are translated of $\bar{d}$, which implies that $\mathbb{1}^T$ is the only strongly positive (left) eigenvector of $\mathcal{M}_s$, and is associated to the eigenvalue 0.

In the case that $\mathcal{M}_s$ is irreducible, $\mathcal{M}_s + \overline{d}\mathbb{I}$ is also irreducible (the irreducibility of $\mathcal{M}_s$ is not affected by modifying its diagonal entries; think of the associated connection graph). The Perron-Frobenius theorem in the irreducible case can be used (see, e.g., [61, Theorem C.1] or [56, Theorem I]), implying that, additionally to the formerly given properties, the spectral radius $\rho(\mathcal{M}_s + \overline{d}I)$ of $\mathcal{M}_s + \overline{d}\mathbb{I}$ is positive, is an eigenvalue of multiplicity one, and is such that for all other $\lambda \in \mathrm{Sp}(\mathcal{M}_s + \overline{d}\mathbb{I})$, $|\lambda| < \rho(\mathcal{M}_s + \overline{d}\mathbb{I})$.

As a consequence, since the spectra of $\mathcal{M}_s$ and $\mathcal{M}_s + \bar{d}\mathbb{I}$ are translated of $\bar{d}$, 0 is the dominant eigenvalue of $\mathcal{M}_s$ and is of multiplicity one, and all other eigenvalues of $\mathcal{M}_s$ have negative real parts. □

Note that for matrix $\mathcal{M}_s$, the difference between the reducible and the irreducible case is not as important as it is in general, because the nature of $\mathcal{M}_s$ implies that the conclusions we can draw in the reducible case are stronger than they typically are.

Also, in the irreducible case, a shorter proof that 0 is the spectral radius is given by using [12, Theorem 2.2.35] with the zero column sum property. Similarly, the Perron-Frobenius theorem has been formulated directly for matrices such as $\mathcal{M}_s$, which are called *essentially nonnegative* (or *essentially positive* in the irreducible case). However, it seemed of interest to show how to obtain these results here.

Lastly, all diagonal entries of $\mathcal{M}_s + \overline{d}\mathbb{I}$ are positive, except the entries corresponding to $\bar{d}$ in $\mathcal{M}_s$ which is zero, the matrix $\mathcal{M}_s$ is primitive, from [12, Corollary 2.4.8]. (In the case that $\mathcal{M}_s$ has only $\overline{d}$ on the diagonal, then it suffices to consider $\mathcal{M}_s + (\overline{d} + e)\mathbb{I}$, for $e > 0$, instead of $\mathcal{M}_s + \overline{d}\mathbb{I}$ to obtain positive terms on the main diagonal). Therefore, the strongest version of the Perron-Frobenius theorem could also have been used, which applies to primitive matrices. But, again, because of the nature of $\mathcal{M}_s$, the conclusions drawn are not stronger than those obtained in the irreducible case.

2.3.2 Case of an irreducible movement matrix

The following theorem describes the dynamics for one species, in the case where there is no internal patch dynamics or that this dynamics simplifies, and that the movement matrix is irreducible. It is used frequently in Section 4.

Theorem 2.2. *For a given species $s \in \mathcal{S}$, suppose that the movement matrix $\mathcal{M}_s$ is irreducible, and that the within-patch dynamics simplifies, that is,* $\lim_{t\to\infty} f^p(N^p(t)) = 0$. *Then the migration component of* (2.2) *satisfies*

$$\lim_{t\to\infty} N_s(t) = N_s^* \gg 0.$$

Proof. Since $\lim_{t\to\infty} f^p(N^p(t)) = 0$, we can suppose that $f^p(N^p) = 0$.

The existence part is adapted from [4]. Remark that system (2.2) with $f^p(N^p) = 0$ is overdetermined, in the sense that the total population $\mathbb{1}^T N_s = \sum_{p\in\mathcal{P}} N_s^p$ is constant. To find the equilibrium value N_s^*, the system

$$\mathcal{M}_s N_s = 0$$

must be solved, with $\mathcal{M}_s$ a singular matrix. This is achieved by considering the augmented system of $\bar{p}+1$ equations in $\bar{p}$ unknowns,

$$\begin{pmatrix} \mathbb{1}^T \\ \hdashline \mathcal{M}_s \end{pmatrix} N_s = \begin{pmatrix} N^0 \\ \hdashline 0 \\ \vdots \\ 0 \end{pmatrix}, \tag{2.4}$$

where $N^0 = \sum_{p=1}^{\bar{p}} N_s^p(0)$. All column sums of the last $\bar{p}$ rows are zero, thus the second equation (for example) can be eliminated. Now perform column operations $c_r \leftarrow c_r - c_1$ for $r = 2, \ldots, \bar{p}$ on the determinant of the resulting coefficient matrix, reducing it to the $\bar{p}-1$ determinant $\det(M(1) + T_1)$, where $M(1)$ denotes matrix $\mathcal{M}_s$ with its first row and column deleted, thus

$$M(1) = \begin{pmatrix} -\sum_{q=1}^{\bar{p}} m_{q2} & m_{23} & \cdots & m_{2\bar{p}} \\ \vdots & & \ddots & \\ m_{\bar{p}2} & m_{\bar{p}3} & \cdots & -\sum_{q=1}^{\bar{p}} m_{q\bar{p}} \end{pmatrix}$$

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

By [12, M_{35}, p. 137] since $m_{pq} \geq 0$, $-M(1)$ is a nonsingular M-matrix (it has the Z-sign pattern and $\mathbb{1}_{\bar{p}-1}^T(-M(1)) \geq 0$ and is not the zero vector by the assumption that $\mathcal{M}_s$ is irreducible). Thus $\det(-M(1)) > 0$ and so $\det M(1)$ has sign $(-1)^{\bar{p}+1}$. Since T_1 has rank 1, it follows from

the linearity of the determinant subject to rank 1 perturbations, see, *e.g.*, [46, Corollary 4.2], that $\det(M(1)+T_1) = \det M(1)(1+\mathbb{1}_{\bar{p}-1}^T M(1)^{-1} m_1)$. As $-M(1)$ is an M-matrix, $(-M(1)^{-1}) \geq 0$, thus $M(1)^{-1} \leq 0$. But $m_1 \leq 0$, thus $1 + \mathbb{1}_{\bar{p}-1}^T M(1)^{-1} m_1$ is positive and so $\det(M(1) + T_1)$ has the sign of $\det M(1)$, namely $(-1)^{\bar{p}+1}$.

By Cramer's Rule,

$$N_1 = \frac{\det M(1) N^0}{\det(M(1) + T_1)} = \frac{N^0}{1 + \mathbb{1}_{\bar{p}-1}^T (M(1))^{-1} m_1} > 0$$

Similarly by deleting the $(p+1)^{\text{st}}$ equation in (2.4),

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

where $T_p = m_p \mathbb{1}_{\bar{p}-1}^T = [-m_{1p}, \ldots, -m_{p-1,p}, -m_{p+1,p}, \ldots, -m_{\bar{p}p}]^T \mathbb{1}_{\bar{p}-1}^T$ for $p = 1, \ldots, \bar{p}$. 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 $p = 1, \ldots, \bar{p}$.

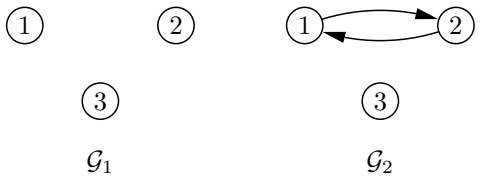
We now consider the stability of N^*. □

2.3.3 Case of a reducible movement matrix

In most of Section 3, it is assumed that the movement matrices are irreducible, for each species. It is however possible to assume that the movement matrices are reducible, but this changes the approach: results such as Theorem 2.2, which could be obtained in full generality in the irreducible situation, have to be treated on a case by case basis, depending on the precise nature of the movement matrices. Although the results of this section are not used elsewhere in the text, it seemed worth including them here, in order to show the additional problems arising in the reducible case.

Rather than attempt a systematic treatment of the reducible case, which would require a rather lengthy development, I discuss here the main differences with the irreducible situation, by presenting the possible cases for 3 patches, which can easily be extended to cover the general case.

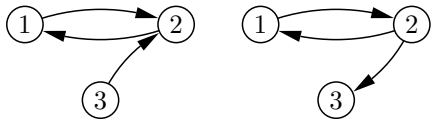
Generically, with 3 patches, the reducible situation corresponds to one of the following graphs (operating a relabelling of patches if need be). There can be no graph with only one strong connected component, as it corresponds to the irreducible case. There are two graphs with only isolated strong components: graphs $\mathcal{G}_1$ and $\mathcal{G}_2$:



$\mathcal{G}_1$ $\mathcal{G}_2$

Theorem 2.2 can be applied to the study of each of the isolated strong components in $\mathcal{G}_1$ and $\mathcal{G}_2$. So, in practice, this is an irreducible configuration, which corresponds to the reduced form of $\mathcal{M}_s$ being block diagonal, that is, direct sum of irreducible blocks.

In the case where the system does not separate, there can be two or three strong components. First, in the case of 2 strong components, we have the following two graphs, $\mathcal{G}_3$ and $\mathcal{G}_4$:

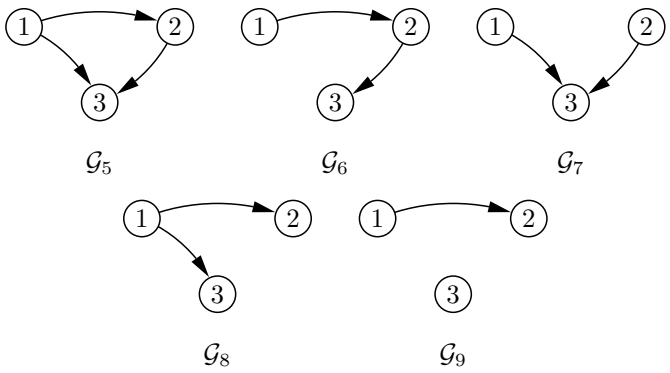


$\mathcal{G}_3$ $\mathcal{G}_4$

with associated movement matrices

$$\mathcal{M}_3 = \begin{bmatrix} -m_{21} & m_{12} & 0 \\ m_{21} & -m_{12} & m_{23} \\ 0 & 0 & -m_{23} \end{bmatrix} \quad \text{and} \quad \mathcal{M}_4 = \begin{bmatrix} -m_{21} & m_{12} & 0 \\ m_{21} & -(m_{12}+m_{32}) & 0 \\ 0 & m_{32} & 0 \end{bmatrix}.$$

The remaining cases, graphs $\mathcal{G}_5$, $\mathcal{G}_6$, $\mathcal{G}_7$, $\mathcal{G}_8$ and $\mathcal{G}_9$, have 3 strong components:



$\mathcal{G}_5$ $\mathcal{G}_6$ $\mathcal{G}_7$

$\mathcal{G}_8$ $\mathcal{G}_9$

Associated to these graphs are the movement matrices

$$\mathcal{M}_5 = \begin{bmatrix} -(m_{21}+m_{31}) & 0 & 0 \\ m_{21} & -m_{32} & 0 \\ m_{31} & m_{32} & 0 \end{bmatrix}, \quad \mathcal{M}_6 = \begin{bmatrix} -m_{21} & 0 & 0 \\ m_{21} & -m_{32} & 0 \\ 0 & m_{32} & 0 \end{bmatrix},$$

$$\mathcal{M}_7 = \begin{bmatrix} -m_{31} & 0 & 0 \\ 0 & -m_{32} & 0 \\ m_{31} & m_{32} & 0 \end{bmatrix}, \quad \mathcal{M}_8 = \begin{bmatrix} -(m_{21}+m_{31}) & 0 & 0 \\ m_{21} & 0 & 0 \\ m_{31} & 0 & 0 \end{bmatrix}$$

and

$$\mathcal{M}_9 = \begin{bmatrix} -m_{21} & 0 & 0 \\ m_{21} & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

The main distinction between the cases is not the number of strong components, but rather the number of sinks and/or isolated strong components in the decomposition into strongly connected components. If, by abuse of language, we call *sink* a patch that is a sink, or a strong component that is a sink in the condensed graph, or an isolated strong component, then we observe that the multiplicity of the dominant eigenvalue 0 is equal to the number of sinks in the graph.This is summarized in the following table

Case	# Sinks	Eigenvalues
$\mathcal{G}_1$	3	$0, 0, 0$
$\mathcal{G}_2$	2	$0, 0, -(m_{12}+m_{21})$
$\mathcal{G}_3$	1	$0, -m_{23}, -(m_{12}+m_{21})$
$\mathcal{G}_4$	1	$0, \lambda_2, \lambda_3$
$\mathcal{G}_5$	1	$0, -m_{32}, -(m_{21}+m_{31})$
$\mathcal{G}_6$	1	$0, -m_{21}, -m_{32}$
$\mathcal{G}_7$	1	$0, -m_{31}, -m_{32}$
$\mathcal{G}_8$	2	$0, 0, -(m_{21}+m_{31})$
$\mathcal{G}_9$	2	$0, 0, -m_{21}$

where λ_2 and λ_3 are two negative eigenvalues with slightly more complicated expressions than those presented in the table.

Studying (2.1), it is clear that the population vanishes in a source that is reduced to one patch. Intuition indicates that this is also the case for sources not reduced to a single patch. Solving, as in the irreducible case, the augmented system

$$\begin{pmatrix} \mathbb{1}^T \\ \cdots \\ \mathcal{M}_i \end{pmatrix} \begin{pmatrix} N_1 \\ N_2 \\ N_3 \end{pmatrix} = \begin{pmatrix} N(0) \\ \cdots \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

with $N(0) = N_1(0) + N_2(0) + N_3(0)$, confirms this intuition. Cases $\mathcal{G}_1$ and $\mathcal{G}_2$ have equilibria given by the following table.

Case	N_1^*	N_2^*	N_3^*
$\mathcal{G}_1$	$N_1(0)$	$N_2(0)$	$N_3(0)$
$\mathcal{G}_2$	$\dfrac{m_{12}(N_1(0)+N_2(0))}{m_{12}+m_{21}}$	$\dfrac{m_{21}(N_1(0)+N_2(0))}{m_{12}+m_{21}}$	$N_3(0)$

In the case of $\mathcal{G}_3$, patch 3 is a source and the strong component $\{1,2\}$ is a sink, and the equilibrium is given by

Case	N_1^*	N_2^*	N_3^*
$\mathcal{G}_3$	$N_1(0) + \frac{m_{21}N_3(0)}{m_{21}+m_{31}}$	$N_2(0) + \frac{m_{31}N_3(0)}{m_{21}+m_{31}}$	0

Cases $\mathcal{G}_4$ to $\mathcal{G}_7$, all the individuals migrate to patch 3, which is the only sink in the graphs, and equilibria take the form

Case	N_1^*	N_2^*	N_3^*
$\mathcal{G}_4$	0	0	$N_1(0)+N_2(0)+N_3(0)$
$\mathcal{G}_5$	0	0	$N_1(0)+N_2(0)+N_3(0)$
$\mathcal{G}_6$	0	0	$N_1(0)+N_2(0)+N_3(0)$
$\mathcal{G}_7$	0	0	$N_1(0)+N_2(0)+N_3(0)$

Finally, $\mathcal{G}_8$ and $\mathcal{G}_9$ have two sinks, and equilibria given by

Case	N_1^*	N_2^*	N_3^*
$\mathcal{G}_8$	0	$N_2(0) + \frac{m_{21}N_1(0)}{m_{21}+m_{31}}$	$N_3(0) + \frac{m_{31}N_1(0)}{m_{21}+m_{31}}$
$\mathcal{G}_9$	0	$N_1(0)+N_2(0)$	$N_3(0)$

Note that this gives a different interpretation of the discussion in [12, pp 38-45], where a different vocabulary is used.

3 Methodological aspects

A certain number of objectives or steps can be isolated, when studying a metapopulation disease model. They are not very different from the steps that are carried out when lower dimensional systems are studied, but the high dimensionality of the systems makes them somewhat specific. This programme typically should involve at least the following steps, to take place once a satisfactory model is formulated.

1. Establish the well-posedness of the system.
2. Study the existence of disease free equilibria.
3. Compute a reproduction number for the system, and consider the local asymptotic stability of the disease free equilibria.

The steps above provide a basic understanding of the behavior of metapopulation disease models. Additionally to these steps, other questions worth addressing are the following.

4. If the disease free equilibrium is unique, prove that it is globally asymptotically stable when $\mathcal{R}_0 < 1$.

5. Step 2 above addresses the existence of an equilibrium without disease for the whole system. Of importance in the context of epidemic spread is also the possibility for the system to have *mixed* equilibria, with some patches disease free and others with disease.
6. The expression obtained for $\mathcal{R}_0$ is typically very complicated, so obtaining some bounds on the value of $\mathcal{R}_0$ can be helpful.

This programme is illustrated in the following sections, with examples chosen from the author's work.

3.1 The models under consideration

The models used here are formulated in a very general setting. Three types of models are considered, that are SEIRS-type models of the form of system (1.1), set in a patch setting. The population in each patch is divided into compartments of susceptible, exposed (latent), infective and recovered individuals with the number in each compartment denoted by $S_\bullet(t)$, $E_\bullet(t)$, $I_\bullet(t)$ and $R_\bullet(t)$, respectively. The symbol $\bullet$ is used to indicate that a variable or parameter might have one or several indices. The following system summarizes their common aspects, and will be used when genericity is needed.

$$\frac{d}{dt}S_\bullet = \mathcal{B}(N_\bullet) - \Phi_\bullet - d_\bullet S_\bullet + \nu_\bullet R_\bullet + \Omega^S(S_\bullet) \tag{3.1a}$$

$$\frac{d}{dt}E_\bullet = \Phi_\bullet - (\varepsilon_\bullet + d_\bullet)E_\bullet + \Omega^E(E_\bullet) \tag{3.1b}$$

$$\frac{d}{dt}I_\bullet = \varepsilon_\bullet E_\bullet - (\gamma_\bullet + d_\bullet + \delta_\bullet)I_\bullet + \Omega^I(I_\bullet) \tag{3.1c}$$

$$\frac{d}{dt}R_\bullet = \gamma_\bullet I_\bullet - (\nu_\bullet + d_\bullet)R_\bullet + \Omega^R(R_\bullet). \tag{3.1d}$$

The operators $\Omega^X(X_\bullet)$, for $X \in \{S, E, I, R\}$, are the movement operators; they potentially involve all components of a given state X. As discussed in Section 2.3, it is assumed that they are linear. Also, unless otherwise stated, it is assumed throughout that for a given state/species combination $X \in \{S, E, I, R\}$, Ω^X induces a graph that is strongly connected for that state/species combination. Finally, note that since travel is instantaneous, there is no change of epidemiological status during travel.

We consider three types of models. The first is a particular case of the second, but it is useful for illustrating the type of computations needed without overburdenning the reader with notations. The other two serve the converse purpose of showing that even though they are complex, the computations can be carried out.

3.1.1 Simple SEIRS

The model here is for disease transmission in one species, but allows for movement rates to depend on disease status.

Within each patch conditions are assumed to be homogeneous. The total number of individuals in patch $p = 1, \ldots, \bar{p}$ is $N_p(t) = S_p(t) + E_p(t) + I_p(t) + R_p(t)$. The rates of movement of individuals between patches are assumed to depend on disease status, and individuals do not change disease status during movement. Let m^S_{pq}, m^E_{pq}, m^I_{pq}, m^R_{pq} denote the rate of movement from patch q to patch p of susceptible, exposed, infective, recovered individuals, respectively, where $m^S_{pp} = m^E_{pp} = m^I_{pp} = m^R_{pp} = 0$. This defines the nonnegative matrices $M^S = \left[m^S_{pq}\right]$, $M^E = \left[m^E_{pq}\right]$, $M^I = \left[m^I_{pq}\right]$ and $M^R = \left[m^R_{pq}\right]$. The movement matrices are deduced from these matrices by setting, for $X \in \{S, E, I, R\}$,

$$\mathcal{M}^X = M^X - \text{diag}\left(\mathbb{1}^T M^X\right).$$

Unless otherwise indicated, it is assumed that these matrices are irreducible.

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

$$\frac{d}{dt}S_p = \mathcal{B}_p\left(N_p\right) - \Phi_p - d_p S_p + \nu_p R_p + \sum_{q=1}^{\bar{p}} m^S_{pq} S_q - \sum_{q=1}^{\bar{p}} m^S_{qp} S_p \quad (3.2a)$$

$$\frac{d}{dt}E_p = \Phi_p - \left(\varepsilon_p + d_p\right) E_p + \sum_{q=1}^{\bar{p}} m^E_{pq} E_q - \sum_{q=1}^{\bar{p}} m^E_{qp} E_p \quad (3.2b)$$

$$\frac{d}{dt}I_p = \varepsilon_p E_p - (\gamma_p + d_p + \delta_p) I_p + \sum_{q=1}^{\bar{p}} m^I_{pq} I_q - \sum_{q=1}^{\bar{p}} m^I_{qp} I_p \quad (3.2c)$$

$$\frac{d}{dt}R_p = \gamma_p I_p - \left(\nu_p + d_p\right) R_p + \sum_{q=1}^{\bar{p}} m^R_{pq} R_q - \sum_{q=1}^{\bar{p}} m^R_{qp} R_p \quad (3.2d)$$

with initial conditions $S_p(0) > 0$ and $E_p(0), I_p(0), R_p(0) \geq 0$ such that $\sum_{p=1}^{\bar{p}} \{E_p(0) + I_p(0)\} > 0$, so that there are initially infected individuals in the system. The force of infection Φ_p takes into account contacts between susceptibles and infectious in patch p. It takes the general form

$$\Phi_p = \beta_p(N_p) S_p I_p, \quad (3.3)$$

with assumptions on β_p as in Section 1. In some specific cases, proportional incidence will be considered, with

$$\Phi_i = \beta_i S_i \frac{I_i}{N_i}. \quad (3.4)$$

3.1.2 SEIRS for multiple species

The model here is the generalization of system (3.2) to $\bar{s}$ species (where we use the term species *stricto sensu*, not for epidemiological states). The dynamics for species $s = 1, \ldots, \bar{s}$ in patch $p = 1, \ldots, \bar{p}$ is given by the following system of $4\bar{s}\bar{p}$ equations,

$$\frac{d}{dt}S_{sp} = \mathcal{B}_{sp}(N_{sp}) - \Phi_{sp} - d_{sp}S_{sp} + \nu_{sp}R_{sp} + \sum_{q=1}^{\bar{p}} m^S_{spq}S_{sq} - \sum_{q=1}^{\bar{p}} m^S_{sqp}S_{sp} \tag{3.5a}$$

$$\frac{d}{dt}E_{sp} = \Phi_{sp} - (\varepsilon_{sp} + d_{sp})E_{sp} + \sum_{q=1}^{\bar{p}} m^E_{spq}E_{sq} - \sum_{q=1}^{\bar{p}} m^E_{sqp}E_{sp} \tag{3.5b}$$

$$\frac{d}{dt}I_{sp} = \varepsilon_{sp}E_{sp} - (\gamma_{sp} + d_{sp} + \delta_{sp})I_{sp} + \sum_{q=1}^{\bar{p}} m^I_{spq}I_{sq} - \sum_{q=1}^{\bar{p}} m^I_{sqp}I_{sp} \tag{3.5c}$$

$$\frac{d}{dt}R_{sp} = \gamma_{sp}I_{sp} - (\nu_{sp} + d_{sp})R_{sp} + \sum_{q=1}^{\bar{p}} m^R_{spq}R_{sq} - \sum_{q=1}^{\bar{p}} m^R_{sqp}R_{sp}. \tag{3.5d}$$

The parameters are defined similarly to those of system (3.2), but now the first subscript denotes the species; for example, $1/\gamma_{sp}$ is the average period of infection for species s in patch p. Each species has its own movement matrices, for example $\mathcal{M}^I_s$ for infectious individuals of species s, obtained from the nonnegative matrix $M^I_s = [m^I_{spq}]$ where m^I_{spq} denotes the rate of movement of an infective individual of species s from patch q to patch p, by setting

$$\mathcal{M}^I_s = M^I_s - \text{diag}\,\left(\mathbb{1}^T M^I_s\right).$$

Denoting the total population of species s in patch p by $N_{sp} = S_{sp} + E_{sp} + I_{sp} + R_{sp}$, the force of infection takes the form

$$\Phi_{sp} = \sum_{k=1}^{\bar{s}} \beta_{skp}S_{sp}\frac{I_{kp}}{N_{kp}}, \tag{3.6}$$

in [4], but more generally, it can be assumed to take the form

$$\Phi_{sp} = \sum_{k=1}^{\bar{s}} \beta_{kp}(N_{kp})S_{sp}I_{kp}, \tag{3.7}$$

with assumptions on $\beta_{kp}(N_{kp})$ as in Section 1. Thus, infection in patch p for susceptibles of species s involves contacts with infectives from all species that are present in the patch.

This model is considered together with nonnegative initial conditions having, for all $s = 1, \ldots, \bar{s}$ and all $p = 1, \ldots, \bar{p}$, $S_{sp}(0) > 0$ and $E_{sp}(0), I_{sp}(0), R_{sp}(0) \geq 0$ such that

$$\sum_{s=1}^{\bar{s}} \sum_{p=1}^{\bar{p}} \{E_{sp}(0) + I_{sp}(0)\} > 0.$$

3.1.3 SEIRS model with residency patch

The main difference in the following model compared to (3.2) and (3.5) is that it tracks the place of residence of individuals: they can move between patches, but are always identified by the patch in which they were born. In this sense, this model is more adequate to describe the short term travels of humans, rather than migrations.

Let $N_{pq}(t)$ be the number of residents of patch p who are present in patch q at time t, with $S_{pq}(t)$, E_{pq}, $I_{pq}(t)$ and $R_{pq}(t)$ being the number that are susceptible, exposed, infective and recovered, respectively. The nonnegative matrix $M_p^S = [m_{pqr}^S]$ gives the movement rates of susceptible individuals resident in patch p from patch r to patch q. Similarly $M_p^E = [m_{pqr}^E]$, $M_p^I = [m_{pqr}^I]$ and $M_p^R = [m_{pqr}^R]$ give these rates for exposed, infective and recovered individuals. From these matrices, the movement matrices $\mathcal{M}_p^X$ for residents of patch p in epidemiological state X are constructed, using

$$\mathcal{M}_p^X = M_p^X - \text{diag } \left(\mathbb{1}^T M_p^X\right).$$

For simplicity, denote

$$N_p^r = \sum_{q=1}^{\bar{p}} N_{pq}, \tag{3.8}$$

the population of individuals born in patch $p \in \mathcal{P}$ (called the *residents* of patch p), and

$$N_p^c = \sum_{q=1}^{\bar{p}} N_{qp}, \tag{3.9}$$

the number of individuals currently in patch p. Birth is assumed to occur in the residency patch at rate $\mathcal{B}_{pp}(N_p^r)$ and natural death occurs (in all disease states) in all patches at the rate d_{pq}. For $\bar{p}$ patches, the model takes the following form for $p, q = 1, \ldots, \bar{p}$.

$$\frac{d}{dt}S_{pq} = \mathcal{B}_{pq}\left(N_p^r\right) + \nu_{pq}R_{pq} - d_{pq}S_{pq} - \Phi_{pq} + \sum_{r=1}^{\bar{p}} m_{pqr}^S S_{pr} - \sum_{r=1}^{\bar{p}} m_{prq}^S S_{pq} \tag{3.10a}$$

$$\frac{d}{dt}E_{pq} = \Phi_{pq} - (\varepsilon_{pq} + d_{pq})E_{pq} + \sum_{r=1}^{\bar{p}} m_{pqr}^E E_{pr} - \sum_{r=1}^{\bar{p}} m_{prq}^E E_{pq} \tag{3.10b}$$

$$\frac{d}{dt}I_{pq} = \varepsilon_{pq}E_{pq} - (\gamma_{pq} + d_{pq} + \delta_{pq})I_{pq} + \sum_{r=1}^{\bar{p}} m_{pqr}^I I_{pr} - \sum_{r=1}^{\bar{p}} m_{prq}^I I_{pq} \tag{3.10c}$$

$$\frac{d}{dt}R_{pq} = \gamma_{pq}I_{pq} - (\nu_{pq} + d_{pq})R_{pq} + \sum_{r=1}^{\bar{p}} m_{pqr}^R R_{pr} - \sum_{r=1}^{\bar{p}} m_{prq}^R R_{pq}. \tag{3.10d}$$

The force of infection for residents of patch p that are susceptible and currently in patch q, Φ_{pq}, takes the form

$$\Phi_{pq} = \sum_{r=1}^{\bar{p}} \beta_{rq}(N_q^c) S_{pq} I_{rq}, \tag{3.11}$$

that is, it describes the contacts, in patch q, between susceptibles residents of patch p who are currently in patch q, and infectives residents of all patches who are currently in patch q, related to the total current population in the patch. Assumptions on β_{rq} are as in Section 1.

If standard incidence is used as in the previous models, giving

$$\Phi_{pq} = \sum_{r=1}^{\bar{p}} \beta_{prq} S_{pq} \frac{I_{rq}}{N_q^c}, \tag{3.12}$$

then β_{prq} denotes the rate of transmission of the disease for a contact in patch q between a susceptible from patch p and an infective from patch r that results in disease transmission (it is the product of the proportion of such adequate contacts and the average number of such contacts). Here, the residents of each patch can be thought of as a species in the sense of Section 2.

Note that models (3.5) and (3.10) are more complicated than (3.2). System (3.5) has $4\bar{s}\bar{p}$ equations, (3.10) has $4\bar{p}^2$ equations, whereas (3.2) "only" has $4\bar{p}$ equations. Also, where (3.2) has at most 4 arcs in each direction between any two given patches, (3.5) and (3.10) have a maximum of $4\bar{s}$ and $4\bar{p}$ arcs between any two given patches, respectively. (Typically, $\bar{p} > \bar{s}$).

3.1.4 Types of movement matrices

In the context of the models considered here, movement similar for all states takes the following form.

Definition 3.1. *Movement in system* (3.2) *is similar for all states if, for all* $p, q = 1, \ldots, \bar{p}$*, there holds that either*

$$m^S_{pq} m^E_{pq} m^I_{pq} m^R_{pq} > 0$$

or

$$m^S_{pq} = m^E_{pq} = m^I_{pq} = m^R_{pq} = 0.$$

Movement in system (3.5) *is similar for all states if, for all* $p, q = 1, \ldots, \bar{p}$ *and a given species* $s \in \mathcal{S}$*, there holds that either*

$$m^S_{spq} m^E_{spq} m^I_{spq} m^R_{spq} > 0$$

or

$$m^S_{spq} = m^E_{spq} = m^I_{spq} = m^R_{spq} = 0.$$

If this is true for all states and all species, then movement in (3.5) *is similar for all states and all species. Movement in system* (3.10) *is similar for all states if, for all* $p, q, r = 1, \ldots, \bar{p}$*, there holds that either*

$$m^S_{pqr} m^E_{pqr} m^I_{pqr} m^R_{pqr} > 0$$

or

$$m^S_{pqr} = m^E_{pqr} = m^I_{pqr} = m^R_{pqr} = 0.$$

Unless otherwise specified, it is assumed throughout that movement is similar for all epidemiological states. Results shown for similar movement rates are of course valid in the particular case of identical movement, which here takes the form $m^X_\bullet \equiv m_\bullet$ for all $X = \{S, E, I, R\}$.

When movement is similar for all states, we drop the superscript indicating the disease state in

$$\mathcal{P}^X_{p\rightarrow}, \overline{\mathcal{P}}^X_{p\rightarrow}, \mathcal{P}^X_{\rightarrow p}, \overline{\mathcal{P}}^X_{\rightarrow p}, \mathcal{P}^{sX}_{p\rightarrow}, \overline{\mathcal{P}}^{sX}_{p\rightarrow}, \mathcal{P}^{sX}_{\rightarrow p} \text{ and } \overline{\mathcal{P}}^{sX}_{\rightarrow p}$$

and thus denote by

$$\mathcal{P}_{p\rightarrow}, \overline{\mathcal{P}}_{p\rightarrow}, \mathcal{P}_{\rightarrow p}, \overline{\mathcal{P}}_{\rightarrow p}, \mathcal{P}^s_{p\rightarrow}, \overline{\mathcal{P}}^s_{p\rightarrow}, \mathcal{P}^s_{\rightarrow p} \text{ and } \overline{\mathcal{P}}^s_{\rightarrow p}$$

the sets of patches that can be accessed directly from p, can be accessed from p, have access to p directly, have access to p, can be accessed directly from p by species s, can be accessed from p by species s, to which species s has direct access from p, and to which species s has access from p, respectively.

3.2 Well-posedness

A system is well-posed if its solutions exist for all positive times, are unique, exhibit sensitive dependence on parameters and initial data. For systems describing populations, reasonable additional conditions of well-posedness are that solutions remain nonnegative for nonnegative initial conditions, as negative population values have no interpretable meaning, and that they remain bounded. To study the well-posedness and in particular, the boundedness of solutions, it is convenient to consider the demographic component, that is, the total population in each patch or in the whole system.

3.2.1 Existence and uniqueness of solutions

With systems such as (3.1), the existence and uniqueness of solutions, as well as continuous dependence on parameters and initial data, is assured by a proper choice of birth and force of infection functions, since the other processes are described by constant or linear terms. In the cases treated later, the birth function is either constant or a linear combination of state variables. There may exist problems at the origin, if the force of infection is not defined there, but this problem is solved by mollifying the functions if need be. Therefore, it is assumed from now on that solutions exist and are unique, and depend continuously on initial data and parameters.

3.2.2 Nonnegativity and/or positivity of solutions

Take for example (3.2). To show the positive invariance of the positive orthant $\mathbb{R}^{4\bar{p}}_+$ under the flow of system (3.2), it suffices to show that each of the faces of the positive orthant cannot be crossed, that is, that the vector field points inward on these faces. Assume that initially, all variables are nonnegative. Setting $S_p = 0$ in (3.2a) gives

$$\frac{d}{dt}S_p = \mathcal{B}_p(N_p) + \nu_p R_p + \sum_{q=1}^{\bar{p}} m^S_{pq} S_q \geq 0,$$

implying that $S_p = 0$ cannot be crossed from positive to negative S_p. Similarly, setting $E_p = 0$ in (3.2b) gives

$$\frac{d}{dt}E_p = \Phi_p + \sum_{q=1}^{\bar{p}} m^E_{pq} E_q \geq 0,$$

and $E_p = 0$ cannot be crossed. The same argument shows that neither I_p nor R_p can be crossed. Hence solutions remain nonnegative for nonnegative initial conditions.

The result can be in fact strengthened, by noting that for positive N_p, $\mathcal{B}_p(N_p) > 0$, and for $q \in \mathcal{P}^S_{\to p}$, $m^S_{pq} > 0$, implying that $dS_p/dt > 0$, in turn implying that for positive initial conditions, S_p remains positive. The same type of reasoning can be applied to systems (3.5) and (3.10).

To summarize, in all cases above, it has been assumed that initial conditions are such that $S_\bullet(0) > 0$ and $E_\bullet(0), I_\bullet(0), R_\bullet(0) \geq 0$, with $\sum_\bullet \{E_\bullet(0) + I_\bullet(0)\} > 0$ (so that there are exposed and/or infectives at initial time). This implies that $S_\bullet > 0$ for all times. The following generic result can be stated.

Theorem 3.2. *If a given movement rate $m_\bullet > 0$, then the linked $S_\bullet > 0$ provided that $S_\bullet(0) > 0$.*

3.2.3 Boundedness of solutions

Establishing that solutions are bounded can be more difficult, and requires that the behavior of the total population in each patch or the total population in the system be studied.

We make the following hypotheses on the birth functions. For system (3.5), we assume that

$$\mathcal{B}_{sp}(N_{sp}) = A_{sp} + b_{sp}N_{sp}, \tag{3.13}$$

with the species index s dropped in the case of (3.2), while for system (3.10), we suppose that

$$\mathcal{B}_{pq}(N^r_p) = \begin{cases} A_p + b_p N^r_p & \text{if } p = q \\ 0 & \text{if } p \neq q, \end{cases} \tag{3.14}$$

where for each p, one of the following two conditions holds:

H1 $A_\bullet > 0$, $d_\bullet > b_\bullet$.

H2 $A_\bullet = 0$, $d_\bullet = b_\bullet$.

Theorem 3.3. *Provided that the birth functions satisfy* **H1** *or* **H2**, *solutions to system* (3.2), (3.5) *and* (3.10) *are bounded.*

Proof. Consider system (3.5). When the behavior of the demographic component is considered, the fact that movement depends on the state implies that the dynamics of the total population N_{sp} in patch p for species s takes the form

$$\begin{aligned} \frac{d}{dt}N_{sp} &= \mathcal{B}_{sp}(N_{sp}) - d_{sp}N_{sp} - \delta_{sp}I_{sp} \\ &\quad + \sum_{X\in\{S,E,I,R\}} \left(\sum_{q=1}^{\bar{p}} m^X_{spq}X_{sq} - \sum_{q=1}^{\bar{p}} m^X_{sqp}X_{sp} \right), \end{aligned} \tag{3.15}$$

which cannot be evaluated independently of the dynamics of (3.5). However, the total population in the system for species s, $\mathbf{N}_s$, satisfies

$$\begin{aligned}\frac{d}{dt}\mathbf{N}_s &= \sum_{p=1}^{\bar{p}} \left(\mathcal{B}_{sp}(N_{sp}) - d_{sp}N_{sp} - \delta_{sp}I_{sp}\right) \\ &\quad + \sum_{p=1}^{\bar{p}} \left(\sum_{X\in\{S,E,I,R\}} \left(\sum_{q=1}^{\bar{p}} m^X_{spq}X_{sq} - \sum_{q=1}^{\bar{p}} m^X_{sqp}X_{sp} \right) \right) \\ &= \sum_{p=1}^{\bar{p}} \left(\mathcal{B}_{sp}(N_{sp}) - d_{sp}N_{sp} - \delta_{sp}I_{sp}\right) \\ &\quad + \sum_{X\in\{S,E,I,R\}} \left(\sum_{p=1}^{\bar{p}} \left(\sum_{q=1}^{\bar{p}} m^X_{spq}X_{sq} - \sum_{q=1}^{\bar{p}} m^X_{sqp}X_{sp} \right) \right) \\ &= \sum_{p=1}^{\bar{p}} \left(\mathcal{B}_{sp}(N_{sp}) - d_{sp}N_{sp} - \delta_{sp}I_{sp}\right). \end{aligned} \tag{3.16}$$

The last equality results from the fact that for each state $X \in \{S, E, I, R\}$, the sums

$$\sum_{p=1}^{\bar{p}}\sum_{q=1}^{\bar{p}} m^X_{spq}X_{sq} - \sum_{p=1}^{\bar{p}}\sum_{q=1}^{\bar{p}} m^X_{sqp}X_{sp}$$

cancel. This is readily established by noticing that in these sums, each term appears exactly once with a positive sign and once with a negative sign. That solutions to (3.2) are bounded is deduced directly from the boundedness of solutions to (3.5) in the case $\bar{s} = 1$.

Similarly, in the case of system (3.10), the variation of the number N^r_p of residents in patch p is given by

$$\begin{aligned}\frac{d}{dt}N^r_p &= \mathcal{B}_{pp}(N^r_p) - \sum_{q=1}^{\bar{p}} \left(d_{pq}N_{pq} - \delta_{pq}I_{pq}\right) \\ &\quad + \sum_{X\in\{S,E,I,R\}} \left(\sum_{q=1}^{\bar{p}} \left[\sum_{r=1}^{\bar{p}} m^X_{pqr}X_{pr} - \sum_{r=1}^{\bar{p}} m^X_{prq}X_{pq} \right] \right). \end{aligned} \tag{3.17}$$

As in the case of (3.16) for system (3.5), the movement terms cancel when considering the total population for system (3.10), $\mathbf{N} = \sum_{p=1}^{\bar{p}} N^r_p$, which implies that $\mathbf{N}$ satisfies the equation

$$\frac{d}{dt}\mathbf{N} = \sum_{p=1}^{\bar{p}} \left(\mathcal{B}_{pp}(N^r_p) - \sum_{q=1}^{\bar{p}} \left(d_{pq}N_{pq} - \delta_{pq}I_{pq}\right) \right). \tag{3.18}$$

Therefore the total population for system (3.5) is nonincreasing if

$$\sum_{p=1}^{\bar{p}} \mathcal{B}_{sp}(N_{sp}) \leq \sum_{p=1}^{\bar{p}} \left(d_{sp}N_{sp} - \delta_{sp}I_{sp}\right),$$

or increasing if

$$\sum_{p=1}^{\bar{p}} \mathcal{B}_{sp}(N_{sp}) > \sum_{p=1}^{\bar{p}} \left(d_{sp}N_{sp} - \delta_{sp}I_{sp}\right),$$

and that of system (3.10) depends on the sign of

$$\sum_{p=1}^{\bar{p}} \left(\mathcal{B}_{pp}(N_p^r) - \sum_{j=1}^{\bar{p}} \left(d_{pq}N_{pq} - \delta_{pq}I_{pq}\right) \right).$$

If **H1** holds, as was assumed in [50], then the population in patch p is bounded above by $\max\{A_p/(d_p - b_p), N_p^r(0)\}$. If **H2** holds, as was assumed in [6, 7] with $d_p = d$, then the resident population of patch i is constant with $N_p^r = N_p^r(0)$, and if this is true for all patches, then the total population in the system is constant. □

3.3 Behavior of the demographic component

Consider system (3.2). In the case of mild diseases it may be reasonable to assume that movement rates are independent of disease status, thus $\mathcal{M}^S = \mathcal{M}^E = \mathcal{M}^I = \mathcal{M}^R =: \mathcal{M}$. In this case, the behavior of the demographic component can be linked to the behavior of the underlying metapopulation model without disease. The total population N_p in patch p, evolves following the equation

$$\frac{d}{dt}N_p = \mathcal{B}_p(N_p) - d_pN_p - \delta_pI_p + \sum_{q=1}^{\bar{p}} m_{pq}N_q - \sum_{q=1}^{\bar{p}} m_{qp}N_p. \qquad (3.19)$$

First, consider a particular case, with assumptions made in the multispecies model of [4].

Theorem 3.4. *Suppose that in system* (3.2)*, there is no disease induced death ($\delta_p = 0$ for all p), movement is identical for all epidemiological states, that in each patch, birth compensates natural death, that is, $\mathcal{B}_p(N_p) = d_pN_p$, and that the movement matrix is irreducible. Then for every patch $p = 1, \ldots, \bar{p}$, there holds*

$$\lim_{t\to\infty} N_p(t) = N_p^* > 0.$$

Proof. Under the assumptions of the theorem, the system is linear and decouples from the epidemic variables, and takes the form, for $p = 1, \ldots, \bar{p}$,

$$\frac{d}{dt}N_p = \sum_{q=1}^{\bar{p}} m_{pq}N_q - \sum_{q=1}^{\bar{p}} m_{qp}N_p$$

The result follows from Theorem 2.2. □

The same type of result holds for systems (3.5) and (3.10), that are given here without proof.

Theorem 3.5. *Suppose that, in system* (3.5)*, there is no disease induced death, movement is identical for all epidemiological states and that in each patch, birth compensates natural death, that is,* $\mathcal{B}_{sp}(N_{sp}) = d_{sp}N_{sp}$*. Then the movement model is given, for all* $s = 1, \ldots, \bar{s}$ *and all* $p = 1, \ldots, \bar{p}$*, by*

$$\frac{d}{dt}N_{sp} = \sum_{q=1}^{\bar{p}} m_{spq}N_{sq} - \sum_{q=1}^{\bar{p}} m_{sqp}N_{sp}, \tag{3.20}$$

and there holds

$$\lim_{t\to\infty} N_{sp}(t) = N^*_{sp} > 0.$$

Theorem 3.6. *Suppose that, in system* (3.10)*, there is no disease induced death, movement is identical for all epidemiological states and yields an irreducible movement matrix, and that in each patch, birth compensates natural death, that is,*

$$\mathcal{B}_{pq}(N^r_p) = \begin{cases} d_{pq} \sum\limits_{r=1}^{\bar{p}} N_{pr} & \text{if } p = q, \\ 0 & \text{if } p \neq q. \end{cases}$$

Then for every patch $p = 1, \ldots, \bar{p}$ *and subpopulation* $q = 1, \ldots, \bar{p}$*, there holds*

$$\lim_{t\to\infty} N_{pq}(t) = N^*_{pq} > 0.$$

Theorems 3.4, 3.5 and 3.6 establish that if movement is identical for all classes and there is no disease induced mortality, then the behavior of the total population is independent of the disease characteristics. In the general case, the demography is not independent of the disease, and it is not possible to characterize the behavior of the former independently of the latter.

It is clear, however, that the convergence of N can still be established, provided that I converges to some value I^*. For example, for system (3.2), it is established in Section 3.6 that $I \to 0$ when the basic reproduction number, $\mathcal{R}_0$, is less than 1, and this is done with no assumption on N.

3.4 Existence of a disease free equilibrium (DFE)

The metapopulation model is at equilibrium if the time derivatives are zero. In the case of system (3.2), patch p is at a disease free equilibrium (DFE) if $E_p = I_p = 0$, and the $\bar{p}$-patch model is at a DFE if $E_p = I_p = 0$ for all $p = 1, \ldots, \bar{p}$. System (3.5) is at a DFE if $E_{sp} = I_{sp} = 0$ for all $s = 1, \ldots, \bar{s}$ and all $p = 1, \ldots, \bar{p}$. System (3.10) is at a DFE if $E_{pq} = I_{pq} = 0$ for all $p, q = 1, \ldots, \bar{p}$.

At this point, the objective is to find the DFE for the $\bar{p}$-patch model. In Section 3.7, the existence of *mixed* equilibria, with some patches at the DFE and others at an endemic equilibrium, is considered.

First, it must be shown that at a DFE, $R_\bullet = 0$. We have the following result.

Theorem 3.7. *Suppose that, in system* (3.2)*,* $E_p = I_p = 0$ *for all* $p = 1, \ldots, \bar{p}$*. Then for all* $p = 1, \ldots, \bar{p}$*,*

$$\lim_{t \to \infty} R_p(t) = 0.$$

Suppose that, in system (3.5)*,* $E_{sp} = I_{sp} = 0$ *for all* $p = 1, \ldots, \bar{p}$ *and all species* $s = 1, \ldots, \bar{s}$*. Then, for all* $p = 1, \ldots, \bar{p}$ *and all* $s = 1, \ldots, \bar{s}$*, there holds,*

$$\lim_{t \to \infty} R_{sp}(t) = 0.$$

Suppose that, in system (3.10)*, there holds that* $E_{pq} = I_{pq}$ *for all* $p, q = 1, \ldots, \bar{p}$*. Then, for all* $p, q = 1, \ldots, \bar{p}$*,*

$$\lim_{t \to \infty} R_{pq}(t) = 0.$$

Proof. Substituting $I_p = 0$ in (3.2d), there holds that at the DFE, using the vector form of the equation,

$$\left(\mathcal{M}^R - \text{diag } (\nu_p + d_p)\right) R = 0.$$

From Theorem 2.1, the matrix $(-\mathcal{M}^R)$ is a singular M-matrix. It follows that $\mathcal{M}^R - \text{diag } (\nu_p + d_p)$ is nonsingular, and at a DFE, $R = 0$. To show the result for (3.5), it suffices to proceed species by species, while for (3.10), proceeding resident patch by resident patch leads to the same result. □

Thus at a DFE, system (3.2) is such that, for all $p = 1, \ldots, \bar{p}$, $S_p = N_p$ and satisfies

$$\mathcal{B}_p\left(N_p\right) - d_p N_p + \sum_{q=1}^{\bar{p}} m_{pq}^S N_q - \sum_{q=1}^{\bar{p}} m_{qp}^S N_p = 0 \tag{3.21}$$

Assume that (3.21) has a solution that gives the DFE $S_p^* = N_p^*$, which is unique. This is certainly true if $\mathcal{B}_p(N_p) = d_p N_p$ (i.e., birth rate equal to the death rate) and $\delta_p = 0$ (i.e., no disease related death) giving a constant total population as in [4]. It is also true if $\mathcal{B}_p(N_p) = b_p$ as assumed in [49, 50].

At the DFE, system (3.5) takes the form

$$\mathcal{B}_{sp}(N_{sp}) - d_{sp}S_{sp} + \sum_{q=1}^{\bar{p}} m_{spq}^S S_{sq} - \sum_{q=1}^{\bar{p}} m_{sqp}^S S_{sp} = 0, \tag{3.22}$$

while (3.10) takes the form

$$\mathcal{B}_{pq}(N_p^r) - d_{pq}S_{pq} + \sum_{r=1}^{\bar{p}} m_{pqr}^S S_{pr} - \sum_{r=1}^{\bar{p}} m_{prq}^S S_{pq} = 0. \tag{3.23}$$

Let us return to (3.2) and (3.21). Letting $\vec{d} = (d_1, \ldots, d_{\bar{p}})^T$, then if $\mathcal{B}(S) \neq \vec{d}\, I$, the problem (3.21) can be written as a fixed point problem,

$$\left(\vec{d}\, I - \mathcal{M}^S\right)^{-1} \mathcal{B}(S) = S.$$

Since $-\mathcal{M}^S$ is a singular M-matrix, $\vec{d}\, I - \mathcal{M}^S$ is a nonsingular M-matrix. As a consequence, $(\vec{d}\, I - \mathcal{M}^S)^{-1}$ is a nonnegative matrix that leaves the positive cone $\mathbb{R}_+^n$ invariant. If $\mathcal{B}$ has the required property, then the contraction mapping principle can be used and there is a unique solution to the fixed point problem. Otherwise, provided $\mathcal{B}$ is a continuous mapping such that the total population is bounded, fixed point results ensure that there exist solutions to the problem, although uniqueness is not guaranteed.

3.5 Reproduction number and local stability of DFE

In this part, we assume that a DFE exists. Linear stability of the disease free equilibrium can be investigated by using the next generation matrix [21, 60]. Note that, in general, $\mathcal{R}_0$ depends on the demographic, disease and mobility parameters.

3.5.1 Simple SEIRS

To derive the basic reproduction number in the most general context, system (3.2) with a generic force of infection (3.3) is first considered. Using the notation of [60], and ordering the infected variables as $E_1, \ldots, E_{\bar{p}}$, $I_1, \ldots, I_{\bar{p}}$, form the vectors

$$\mathcal{F} = (\Phi_1, \ldots, \Phi_{\bar{p}}, 0, \ldots, 0)^T,$$

representing new infections into the infected classes $E_1, \ldots, E_{\bar{p}}, I_1, \ldots, I_{\bar{p}}$, and

$$\mathcal{V} = - \begin{pmatrix} -(\varepsilon_1 + d_1)E_1 + \sum_{j=1}^{\bar{p}} m_{1j}^E E_j - \sum_{j=1}^{\bar{p}} m_{j1}^E E_1 \\ \vdots \\ -(\varepsilon_{\bar{p}} + d_{\bar{p}})E_{\bar{p}} + \sum_{j=1}^{\bar{p}} m_{\bar{p}j}^E E_j - \sum_{j=1}^{\bar{p}} m_{j\bar{p}}^E E_{\bar{p}} \\ \varepsilon_1 E_1 - (\gamma_1 + d_1 + \delta_1)I_1 + \sum_{j=1}^{\bar{p}} m_{1j}^I I_j - \sum_{j=1}^{\bar{p}} m_{j1}^I I_1 \\ \vdots \\ \varepsilon_{\bar{p}} E_{\bar{p}} - (\gamma_{\bar{p}} + d_{\bar{p}} + \delta_{\bar{p}})I_{\bar{p}} + \sum_{j=1}^{\bar{p}} m_{\bar{p}j}^I I_j - \sum_{j=1}^{\bar{p}} m_{j\bar{p}}^I I_{\bar{p}} \end{pmatrix},$$

representing other flows within and out of the infected classes $E_1, \ldots, E_{\bar{p}}$, $I_1, \ldots, I_{\bar{p}}$ (note that $\mathcal{V}$ has a minus sign). The matrix of new infections F and the matrix of transfer between compartments V are then the Jacobian matrices obtained by differentiating $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected variables, evaluated at the disease free equilibrium (DFE). Note that

$$\frac{\partial \Phi_p}{\partial E_p} = \frac{\partial}{\partial E_p} \beta_p(N_p) S_p I_p,$$

and therefore it follows that $\partial \Phi_p / \partial E_p = 0$ at the DFE. Therefore, the matrices F and V are given in partitioned form by

$$F = \begin{bmatrix} 0 & F_{12} \\ 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} V_{11} & 0 \\ -V_{21} & V_{22} \end{bmatrix} \tag{3.24}$$

with

$$F_{12} = \text{diag } \left(\left. \frac{\partial \Phi_p}{\partial I_p} \right|_{DFE} \right),$$

and

$$V_{11} = -\mathcal{M}^E + \text{diag } (\varepsilon_i + d_i), \quad V_{21} = \text{diag } (\varepsilon_i),$$
$$V_{22} = -\mathcal{M}^I + \text{diag } (\gamma_i + d_i + \delta_i).$$

Matrices V_{11} and V_{22} are $\bar{p} \times \bar{p}$ irreducible M-matrices [12] 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 [60], 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 $\rho\left(FV^{-1}\right) < 1$. Note that the conditions of application of Theorem 2 in [60] are satisfied, and in particular, condition (A5) holds if $\mathcal{B}$ is such that the demographic component without disease converges. This is summarized in the following theorem.

Theorem 3.8. *Define the basic reproduction number $\mathcal{R}_0$ for system* (3.2) *with force of infection* (3.3) *by*

$$\mathcal{R}_0 = \rho\left(FV^{-1}\right) = \rho\left(F_{12}V_{22}^{-1}V_{21}V_{11}^{-1}\right), \tag{3.25}$$

with matrices F and V defined by (3.24)*. Then the DFE is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

With force of infection (3.4), i.e., using standard incidence, the matrix V still takes the value computed above, as it does not involve incidence, whereas

$$\left.\frac{\partial \Phi_p}{\partial I_p}\right|_{DFE} = \beta_p \frac{S_p^*}{N_p^*} = \beta_p,$$

so $F_{12} = \text{diag}\,(\beta_1, \ldots, \beta_{\bar{p}})$ provided that $\mathcal{B}_p(N_p)$ is such that $S_p^* = N_p^*$ (as is the case for example if $\mathcal{B}_p(N_p) = d_p N_p$).

3.5.2 SEIRS with multiple species

We turn to the case of system (3.5). Suppose that the functions $\mathcal{B}_{sp}$ are such that for all $s = 1, \ldots, \bar{s}$ and $p = 1, \ldots, \bar{p}$, $\lim_{t\to\infty} N_{sp}(t) = N_{sp}^* > 0$. The method for multiple species is essentially the same as for a single species. To determine the matrices F and V, order the state variables by species, then by patch, *i.e.*,

$$E_{11}, E_{21}, \ldots, E_{\bar{s}1}, E_{12}, \ldots, E_{\bar{s}\bar{p}}, I_{11}, I_{21}, \ldots, I_{\bar{s}1}, I_{12}, \ldots, I_{\bar{s}\bar{p}}.$$

The vector $\mathcal{F}$ then takes the form

$$\mathcal{F} = (\Phi_{11}, \Phi_{21}, \ldots, \Phi_{\bar{s}1}, \Phi_{21}, \ldots, \Phi_{\bar{s}\bar{p}}, 0, \ldots, 0),$$

with $\bar{s}\bar{p}$ zeros corresponding to the I variables. As for the single species case, there holds that, at the DFE, $\partial\Phi_{sp}/\partial E_{ij} = 0$, for all $s, i = 1, \ldots, \bar{s}$ and $p, j = 1, \ldots, \bar{p}$. Also, $\partial\Phi_{sp}/\partial I_{ij} = 0$ for all $s, i = 1, \ldots, \bar{s}$ and $p, j = 1, \ldots, \bar{p}$, whenever $p \neq i$, since there are no contacts outside of the patch. Then the nonnegative matrix F takes the form

$$F = \begin{bmatrix} 0 & G \\ 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 & \bigoplus_{p=1}^{\bar{p}} G_p \\ 0 & 0 \end{bmatrix},$$

where $\oplus G_p$ denotes the direct sum of the G_p's, with G_p an $\bar{s} \times \bar{s}$-matrix with (r, s) entry equal to

$$[G_p]_{rs} = \left.\frac{\partial \Phi_{rp}}{\partial I_{sp}}\right|_{DFE},$$

and representing the contacts between species r and s in patch p. The matrix V is the block matrix

$$V = \left[\begin{array}{c:c} A & 0 \\ \hdashline -C & B \end{array}\right] = \left[\begin{array}{ccc:ccc} A_{11} & \cdots & A_{1\bar{p}} & & & \\ \vdots & \ddots & \vdots & & 0 & \\ A_{\bar{p}1} & \cdots & A_{\bar{p}\bar{p}} & & & \\ \hdashline & & & B_{11} & \cdots & B_{1\bar{p}} \\ & -\bigoplus_{p=1}^{\bar{p}} C_p & & \vdots & \ddots & \vdots \\ & & & B_{\bar{p}1} & \cdots & B_{\bar{p}\bar{p}} \end{array}\right]$$

Matrix A is a block matrix, with each block A_{pq} a $\bar{s} \times \bar{s}$ diagonal matrix. The (r, r) entry of A_{pp} is equal to $d_{rp} + \varepsilon_{rp} + \sum_{l=1}^{\bar{p}} m^E_{rlp}$, whereas for $p \neq q$ the (r, r) entry of A_{pq} is $-m^E_{rpq}$. The (p, p) entry of B_{pp} is equal to $d_{rp} + \gamma_{rp} + \sum_{l=1}^{\bar{p}} m^I_{rlp}$, whereas for $p \neq q$ the (r, r) entry of B_{pq} is $-m^I_{rpq}$. Finally, C_p is an $\bar{s} \times \bar{s}$ diagonal matrix with (r, r) entry equal to ε_{rp}.

Matrices G, A, B and C are $\bar{s}\bar{p} \times \bar{s}\bar{p}$-matrices. Matrices A and B are nonsingular M-matrices since they have the Z-sign pattern and are diagonally dominant by columns [12, M_{35} p. 137]. Thus A^{-1} and B^{-1} are nonnegative.

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 it follows that

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

Thus

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

Since $GB^{-1}CA^{-1}$ is a nonnegative 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 [60, Theorem 2]. The following result has been proved.

Theorem 3.9. *For system* (3.5) *with* $\bar{s}$ *species and* $\bar{n}$ *patches,*

$$\mathcal{R}_0 = \rho(GB^{-1}CA^{-1}) \tag{3.26}$$

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

In the case of a force of infection with proportional incidence such as (3.6), the (r, s) entry of G_p takes the form $\beta_{rsp}\hat{S}_{rp}/N^*_{sp}$.

3.5.3 SEIRS with residency patch

In the case of system (3.10), we order the infected variables (exposed and infectives) as

$$E_{11}, \ldots, E_{1\bar{p}}, E_{21}, \ldots E_{2\bar{p}}, \ldots E_{\bar{p}\bar{p}}, I_{11}, \ldots, I_{1\bar{p}}, I_{21}, \ldots I_{2\bar{p}}, \ldots, I_{\bar{p}\bar{p}}.$$

Since Φ_{pq} describes the infection of susceptible residents of patch p who are currently in patch q, there holds that $\partial\Phi_{pq}/\partial I_{ij} = 0$ if $q \neq j$, for all $i, j, p, q = 1, \ldots, \bar{p}$, since contacts only involve individuals that are in the same patch. This gives the block matrix F,

$$F = \left[\begin{array}{c:c} 0 & G \\ \hdashline 0 & 0 \end{array}\right]$$

where G is an $\bar{p}^2 \times \bar{p}^2$ matrix having $\bar{p}^2$ blocks, with each block G_{pq} a $\bar{p} \times \bar{p}$ diagonal matrix of the form

$$G_{pq} = \text{diag}\left(\left.\frac{\partial\Phi_{p1}}{\partial I_{q1}}\right|_{DFE}, \left.\frac{\partial\Phi_{p2}}{\partial I_{q2}}\right|_{DFE}, \ldots, \left.\frac{\partial\Phi_{p\bar{p}}}{\partial I_{q\bar{p}}}\right|_{DFE}\right).$$

Also, V is a lower triangular block matrix,

$$V = \left[\begin{array}{c:c} A & 0 \\ \hdashline C & B \end{array}\right] = \left[\begin{array}{c:c} \displaystyle\bigoplus_{p=1}^{\bar{p}} A_p & 0 \\ \hdashline -\displaystyle\bigoplus_{p=1}^{\bar{p}} C_p & \displaystyle\bigoplus_{p=1}^{\bar{p}} B_p \end{array}\right]$$

where each block A, B and C is $\bar{p}^2 \times \bar{p}^2$. For $p = 1, \ldots \bar{p}$, A_p is an $\bar{p} \times \bar{p}$ matrix with

$$A_p = \begin{bmatrix} \varepsilon_{p1} + d_{p1} + \sum_{k=1}^{\bar{p}} m^E_{pk1} & \cdots & -m^E_{p1\bar{p}} \\ -m^E_{p21} & \cdots & -m^E_{p2\bar{p}} \\ & & \\ -m^E_{p\bar{p}1} & \cdots & \varepsilon_{p\bar{p}} + d_{p\bar{p}} + \sum_{k=1}^{\bar{p}} m^E_{pk\bar{p}} \end{bmatrix},$$

B_p is an $\bar{p} \times \bar{p}$-matrix with

$$B_p = \begin{bmatrix} \gamma_{p1} + d_{p1} + \sum_{k=1}^{\bar{p}} m_{pk1}^I & \cdots & -m_{p1\bar{p}}^I \\ -m_{p21}^I & \cdots & -m_{p2\bar{p}}^I \\ & & \\ -m_{p\bar{p}1}^I & \cdots & \gamma_{p\bar{p}} + d_{p\bar{p}} + \sum_{k=1}^{\bar{p}} m_{pk\bar{p}}^I \end{bmatrix},$$

and C_p is a $\bar{p} \times \bar{p}$ diagonal matrix with $C_p = \text{diag}\,(\varepsilon_{p1}, \ldots, \varepsilon_{p\bar{p}})$.

Since A_k and B_k have the Z-sign pattern and have all positive column sums, A_k and B_k are nonsingular M-matrices [12]. Note that

$$\left(\bigoplus_{p=1}^{\bar{p}} B_p^{-1}\right)\left(\bigoplus_{p=1}^{\bar{p}} C_p\right)\left(\bigoplus_{p=1}^{\bar{p}} A_p^{-1}\right) = \bigoplus_{p=1}^{\bar{p}} \left(A_p C_p^{-1} B_p\right)^{-1}.$$

Therefore, the inverse of V is the nonnegative matrix

$$V^{-1} = \left[\begin{array}{c:c} \displaystyle\bigoplus_{p=1}^{\bar{p}} A_p^{-1} & 0 \\ \hdashline \displaystyle\bigoplus_{p=1}^{\bar{p}} \left(A_p C_p^{-1} B_p\right)^{-1} & \displaystyle\bigoplus_{p=1}^{\bar{p}} B_p^{-1} \end{array}\right]. \tag{3.27}$$

Since V^{-1} is lower triangular by blocks, FV^{-1} can be given by blocks. By [60, Theorem 2], the basic reproduction number for system (3.10) is

$$\mathcal{R}_0 = \rho\left(G\left(\bigoplus_{p=1}^{\bar{p}} A_p C_p^{-1} B_p\right)^{-1}\right), \tag{3.28}$$

and the following result holds.

Theorem 3.10. *Let $\mathcal{R}_0$ be defined as in (3.28). If $\mathcal{R}_0 < 1$, then the DFE of (3.10) is locally asymptotically stable. If $\mathcal{R}_0 > 1$, then the DFE of (3.10) is unstable.*

3.6 Global stability of the disease free equilibrium

In the case of proportional incidence, a comparison theorem argument can be used to show that if $\mathcal{R}_0 < 1$, then the DFE is globally asymptotically stable.

3.6.1 Simple SEIRS

In the case of system (3.2), the local asymptotic stability result for $\mathcal{R}_0 < 1$ is readily strengthened to a global result.

Theorem 3.11. *Consider system* (3.2) *with standard incidence* (3.4)*, and assume that the birth function* $\mathcal{B}_p$ *is such that* (3.2) *has a unique DFE. Let* $\mathcal{R}_0$ *be defined by* (3.25)*. If* $\mathcal{R}_0 < 1$*, then the DFE is globally asymptotically stable.*

Proof. Since $S_p \leq N_p$, it follows that $\Phi_p \leq \beta_p N_p I_p / N_p = \beta_p I_p$, and equation (3.2b) gives the inequality

$$\frac{d}{dt}E_p \leq \beta_p I_p - (\varepsilon_p + d_p)E_p + \sum_{q=1}^{\bar{p}} m^E_{pq} E_q - \sum_{q=1}^{\bar{p}} m^E_{qp} E_p. \tag{3.29}$$

For comparison, define a linear system given by (3.29) with equality and equation (3.2c), namely

$$\begin{aligned}
\frac{d}{dt}E_p &= \beta_p I_p - (\varepsilon_p + d_p)E_p + \sum_{q=1}^{\bar{p}} m^E_{pq} E_q - \sum_{q=1}^{\bar{p}} m^E_{qp} E_p \\
\frac{d}{dt}I_p &= \varepsilon_p E_p - (\gamma_p + d_p + \delta_p)I_p + \sum_{q=1}^{\bar{p}} m^I_{pq} I_q - \sum_{q=1}^{\bar{p}} m^I_{qp} I_p.
\end{aligned}$$

This linear system has coefficient matrix $F - V$, and so by the argument in the proof of Theorem 3.8, satisfies $\lim_{t\to\infty} E_p = 0$ and $\lim_{t\to\infty} I_p = 0$ for $\mathcal{R}_0 = \rho(FV^{-1}) < 1$. Using a comparison theorem (e.g, [38, Theorem 1.5.4] or [57, Theorem 13.1]) and noting (3.29), it follows that these limits also hold for the nonlinear system (3.2b) and (3.2c). That $\lim_{t\to\infty} R_p = 0$ follows from Theorem 3.7, and $\lim_{t\to\infty} S_p = S_p^*$ follows from (3.2a) and the assumption that a unique DFE exists. Thus for $\mathcal{R}_0 < 1$, the disease free equilibrium is globally asymptotically stable and the disease dies out. □

Note that it is clear from this proof that any incidence function Φ_p such that

$$\Phi_p \leq \left.\frac{\partial \Phi_p}{\partial I_p}\right|_{DFE} I_p$$

would lead to the same conclusion.

3.6.2 SEIRS with multiple species

A comparison theorem argument can be used as in Theorem 3.11 to show that if $\mathcal{R}_0 < 1$, then the DFE of the multiple species system (3.5) is globally asymptotically stable. Note, however, that the proof requires here the use of the theory of asymptotically autonomous differential equations.

Theorem 3.12. *For system* (3.5) *with* $\bar{s}$ *species and* $\bar{p}$ *patches, birth rate of the form* (3.13)*, no disease induced mortality and proportional incidence* (3.6)*, define* $\mathcal{R}_0$ *as in* (3.26)*. If* $\mathcal{R}_0 < 1$*, then the DFE is globally asymptotically stable.*

Proof. To establish the global stability of the DFE, consider the nonautonomous system consisting of (3.5b)-(3.5d), with (3.5b) written in the form

$$\begin{aligned}\frac{d}{dt}E_{sp} = &\sum_{j=1}^{\bar{s}} \beta_{sjp}(N_{sp} - E_{sp} - I_{sp} - R_{sp})\frac{I_{jp}}{N_{jp}} \\ &- (d_{sp} + \varepsilon_{sp})E_{sp} + \sum_{q=1}^{\bar{p}} m^E_{spq}E_{sq} - \sum_{q=1}^{\bar{p}} m^E_{sqp}E_{sp},\end{aligned} \tag{3.30}$$

in which S_{sp} has been replaced by $N_{sp} - E_{sp} - I_{sp} - R_{sp}$, and N_{sp} is a solution of (3.20). Write this system as

$$x' = f(t, x), \tag{3.31}$$

where x is the $3\bar{s}\bar{p}$ dimensional vector consisting of the E_{sp}, I_{sp} and R_{sp}. The DFE of (3.5) corresponds to the equilibrium $x = 0$ in (3.31). Since $\delta_{sp} = 0$, system (3.20) can be solved for $N_{sp}(t)$ independently of the epidemic variables, and Theorem 3.5 implies that the time dependent functions $N_{sp}(t) \to N^*_{sp}$ as $t \to \infty$. Substituting this large time limit value N^*_{sp} for N_{sp} in (3.30) gives

$$\begin{aligned}\frac{d}{dt}E_{sp} = &\sum_{j=1}^{s} \beta_{sjp}(N^*_{sp} - E_{sp} - I_{sp} - R_{sp})\frac{I_{jp}}{N^*_{jp}} \\ &- (d_{sp} + \varepsilon_{sp})E_{sp} + \sum_{q=1}^{n} m^E_{spq}E_{sq} - \sum_{q=1}^{n} m^E_{sqp}E_{sp}.\end{aligned} \tag{3.32}$$

Therefore, system (3.31) is asymptotically autonomous, with limit equation

$$x' = g(x). \tag{3.33}$$

To show that 0 is a globally asymptotically stable equilibrium for the limit system (3.33), remark that the linear system

$$x' = Lx, \tag{3.34}$$

where x is the $3\bar{s}\bar{p}$ dimensional vector consisting of the E_{sp}, I_{sp} and R_{sp},

but with the equation for E_{sp} taking the form

$$\begin{aligned}\frac{d}{dt}E_{sp} = \sum_{j=1}^{\bar{s}} \beta_{sjp}\frac{N^*_{sp}}{N^*_{jp}}I_{jp} - (d_{sp}+\varepsilon_{sp})E_{sp} \\ + \sum_{q=1}^{\bar{p}} m^E_{spq}E_{sq} - \sum_{q=1}^{\bar{p}} m^E_{sqp}E_{sp}\end{aligned} \tag{3.35}$$

is such that $g(x) \leq Lx$ for all $x \in \mathbb{R}^{3\bar{s}\bar{n}}_+$. In system (3.34), the equations for E_{sp} and I_{sp} do not involve R_{sp}, and can thus be considered independently from the latter.

Let $\tilde{x}$ be the part of the vector x corresponding to the variables E_{sp} and I_{sp}, and $\tilde{L}$ be the corresponding submatrix of L. The term $\beta_{sjp}N^*_{sp}/N^*_{jp}$ corresponds to the (s,j) entry of the matrix G_p used in Theorem 3.9, since $S_{sp} \to N^*_{sp}$ under the current assumptions. (See the remark following Theorem 3.9.) Therefore, the method used in Section 3.5 to prove local stability can also be applied to study the stability of the $\tilde{x} = 0$ equilibrium of the subsystem $\tilde{x}' = \tilde{L}\tilde{x}$, with $\tilde{L} = F - V$. Therefore, if $\mathcal{R}_0 < 1$, then the equilibrium $\tilde{x} = 0$ of the subsystem $\tilde{x}' = \tilde{L}\tilde{x}$ is stable. When $\tilde{x} = 0$, the conclusion of Theorem 3.7 holds, and $\lim_{t\to\infty} R_s(t) = 0$, with $R_s = (R_{s1}, \ldots, R_{s\bar{p}})^T$. Thus the equilibrium $R_s = 0$ of this linear system in R_s is stable. As a consequence, the equilibrium $x = 0$ of (3.34) is stable when $\mathcal{R}_0 < 1$. Using a standard comparison theorem (see, e.g., [38, Theorem 1.5.4]), it follows that 0 is a globally asymptotically stable equilibrium of (3.33).

For $\mathcal{R}_0 < 1$, the linear system (3.35) and (3.5c) has a unique equilibrium (the DFE) since its coefficient matrix $F - V$ is nonsingular. The proof of global stability is completed using results on asymptotically autonomous equations; see, *e.g.*, [58, Thm. 4.1] and [19]. □

As in the simple SEIRS case (Theorem 3.11), any incidence function Φ_{sp} such that

$$\Phi_{sp} \leq \left.\frac{\partial \Phi_{sp}}{\partial I_{sp}}\right|_{DFE} I_{sp}$$

would lead to the same conclusion. Also, the assumption that there is no disease induced mortality can be relaxed, provided that it can be shown that N_{sp} converges for all s, p.

3.6.3 SEIRS with residence patch

Theorem 3.13. *For system* (3.10) *with* $\bar{p}$ *patches, birth rate* $\mathcal{B}_{pq}$ *such that* $\lim_{t\to\infty} S_{pq} = N^*_{pq}$*, and proportional incidence* (3.12)*, define* $\mathcal{R}_0$ *as in* (3.28)*. If* $\mathcal{R}_0 < 1$*, then the DFE is globally asymptotically stable.*

The proof proceeds exactly as the proof of Theorem 3.12, except that the incidence function takes the form

$$\Phi_{pq} = \sum_{r=1}^{\bar{p}} \beta_{prq} S_{pq} \frac{I_{rq}}{\sum_{k=1}^{\bar{p}} N_{kq}},$$

and thus we obtain an upper bound by noting that

$$\Phi_{pq} \leq \sum_{r=1}^{\bar{p}} \beta_{prq} S_{pq} \frac{I_{rq}}{N_{rq}}.$$

As in the proof of Theorem 3.12, letting $S_{pq} \to N_{pq}^*$ we obtain the terms that appear in the matrix F used in Theorem 3.10 when considering proportional incidence (3.12).

The same remark about incidence holds as in the simple and the multiple species cases above. Note however that the formulation of Theorem 3.13 assumes the convergence of S, which is obtained by assuming no disease induced mortality, but also with properly chosen birth functions.

3.7 Existence of mixed equilibria

A *mixed equilibrium* is an equilibrium for the whole system with some patches at a disease free equilibrium and others at an endemic equilibrium. The assumption of strongly connected movement graphs is here relaxed.

To summarize the results established in this section, if movement is similar for all states, then the type of equilibria is fixed for each strongly connected component in the movement graph $\mathcal{G}$. If movement is dissimilar, the situation is unresolved.

3.7.1 Model with classic movement

The situation is discussed in the case of the system with multiple species (3.5). Specialization to the case of a single species is trivial.

Theorem 3.14. *Suppose that* (3.5) *with movement similar for all states is at an equilibrium. If a given patch p is at a DFE, then all patches that have an access to patch p for a given species s, i.e., patches $q \in \overline{\mathcal{P}}^s_{\to p}$, are also at a DFE.*

Proof. Fix the species index at s. For simplicity suppose that $p = 1$, i.e., there is no disease in patch 1. Thus $E_{s1} = I_{s1} = 0$. Then for $p = 1$, (3.5c) is

$$0 = \frac{d}{dt} I_{s1} = \sum_{r=2}^{\bar{p}} m^I_{s1r} I_{sr}.$$

Since $I_{sr} \geq 0$ and

$$\sum_{r=2}^{\bar{p}} m^I_{s1r} I_{sr} = \sum_{r \in \mathcal{P}_{\to 1}} m^I_{s1r} I_{sr} + \sum_{r \notin \mathcal{P}_{\to 1}} m_{s1r} I_{sr} = 0,$$

it follows that $I_{sr} = 0$ for $r \in \mathcal{P}_{\to 1}$. Similarly, setting $p = 1$ in (3.5b) and using $\mathcal{P}_{\to 1}$, it follows that $E_{sr} = 0$ for $r \in \mathcal{P}_{\to 1}$. Thus, all patches r with a direct access to patch 1 have no disease, i.e., are such that $E_{sr} = I_{sr} = 0$.

Now consider a patch r in $\mathcal{P}_{\to 1}$. Using the same argument as previously, it follows that $E_{sw} = I_{sw} = 0$ for all $w \in \mathcal{P}_{\to r}$. Patches that are in $\mathcal{P}_{\to r} \setminus \mathcal{P}_{\to 1}$ have a length 2 access to patch 1. By induction, all patches in $\overline{\mathcal{P}}_{\to 1}$ are at the DFE if patch 1 is at the DFE. □

Note that this result is independent of the nature of the birth function $\mathcal{B}_{sp}$. Also, conclusions have not been derived on the nature of R_p for those patches that are at the DFE, nor has it been shown that $S_p \to N^*_p$. In fact, with a little additional work and using the same type of argument used in Theorem 3.7, it can be shown that $\lim_{t\to\infty} R_k(t) = 0$ for $k \in \overline{\mathcal{P}}_{\to p}$. In this case, $S_p \to N^*_p$, with the precise value of N^*_p undetermined until a birth function has been chosen.

Theorem 3.15. *Suppose that* (3.5) *with movement similar for all states is at an equilibrium. If a given patch p is at an endemic equilibrium, then all patches that can be accessed from patch p for a given species s, i.e., patches* $q \in \overline{\mathcal{P}}^s_{p\to}$*, are also at an endemic equilibrium.*

Proof. Fix the species index s. For simplicity suppose that $p = 1$, i.e., $E_{s1} + I_{s1} > 0$. From (3.5b) and (3.5c) with $q \neq 1$,

$$0 = \frac{d}{dt}(E_{sq} + I_{sq}) = \Phi_{sq} - d_{sq}(E_{sq} + I_{sq}) - \gamma_{sq} I_{sq} + \sum_{r=1}^{\bar{p}} m_{sqr}(E_{sr} + I_{sr}) - \sum_{r=1}^{\bar{p}} m_{srq}(E_{sq} + I_{sq}).$$

Assume that $E_{sq} + I_{sq} = 0$ and $m_{sq1} > 0$, i.e., patch 1 has access to patch q. Then the above equation reduces to

$$0 = \sum_{r=1}^{\bar{p}} m_{sqr}(E_{sr} + I_{sr}),$$

and implies that $E_{s1} + I_{s1} = 0$, 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 3.14. □

3.7.2 Model with residency patch

Theorem 3.16. *Suppose that system* (3.10) *with movement similar for all states is at an equilibrium, and that a given patch p is at the DFE. Then all patches that can be accessed from patch p, and all patches that have an access to patch p, are at the DFE.*

Proof. Suppose for simplicity and without loss of generality that patch 1 is at the DFE, i.e., $I_{k1} = E_{k1} = 0$ for all $k = 1, \ldots, \bar{p}$. Then consider (3.10b) and (3.10c) with $i = 1$. Since $I_{11} = 0$, it follows that $\Phi_{11} = 0$ and thus

$$\frac{d}{dt}E_{11} = \sum_{k=1}^{\bar{p}} m^E_{11k}E_{1k}$$
$$\frac{d}{dt}I_{11} = \sum_{k=1}^{\bar{p}} m^I_{11k}I_{1k}.$$

Recall that variables remain nonnegative. It follows that, since the system is at equilibrium, $E_{1k} = 0$ for all patches in $\mathcal{P}^E_{\to 1}$, and $I_{1k} = 0$ for all patches k in $\mathcal{P}^I_{\to 1}$. Since movement is similar for all states, $\mathcal{P}^E_{\to 1} = \mathcal{P}^I_{\to 1} =: \mathcal{P}_{\to 1}$.

In summary, if patch 1 is at the DFE, then there holds that for all patches j in $\mathcal{P}_{\to 1}$, $E_{1j} = I_{1j} = 0$, i.e., there is no disease in visitors from patch 1 visiting patches that have direct access to patch 1. Consider now (3.10b) for one of these patches, i.e., for $j \in \mathcal{P}_{\to 1}$. There holds, for visitors to j from patch 1,

$$\frac{d}{dt}E_{1j} = \Phi_{1j}.$$

Since the system is at an equilibrium, $E_{1j} = 0$, that is

$$0 = \Phi_{1j} = \sum_{r=1}^{\bar{p}} \beta_{rj}(N^c_j)S_{1j}I_{rj}.$$

It was shown (Theorem 3.2) that $S_{pq} > 0$ for all positive times, provided that $m^S_{pqr} > 0$. Since the S_{pq} are positive, there holds that for all $j \in \mathcal{P}_{\to 1}$ such that $m^S_{1jk} > 0$, $I_{kj} = 0$. Using the same type of argument that was used to show that $R = 0$ in the proof of Theorem 3.12, it follows that for these patches, there also holds that $E_{kj} = 0$.

To summarize, if patch 1 is at the DFE, then patches $j \in \mathcal{P}_{\to 1}$ are also at the DFE. By induction, all patches that are in $\overline{\mathcal{P}}_{\to 1}$ are at the DFE. □

3.8 Bounds on $\mathcal{R}_0$

The expression obtained for $\mathcal{R}_0$ in all three models is complicated. Therefore, it is useful to derive some bounds on the value of $\mathcal{R}_0$. We do so in the most complicated case, that of the SEIRS model with residency patch. The results are also formulated in the simpler cases, but no proofs are provided.

3.8.1 SEIRS with residency patch

For convenience, write

$$\frac{\partial \Phi^D_{pr}}{\partial I_{jk}} := \left.\frac{\partial \Phi_{pr}}{\partial I_{jk}}\right|_{DFE}.$$

Theorem 3.17. *Let v_m^{-1} and v_M^{-1} be the minimum and maximum column sums of the (2,1) block $\bigoplus_{p=1}^{\bar{p}}(A_pC_p^{-1}B_p)$ in matrix V^{-1} defined by* (3.27)*. Then there holds that*

$$\bar{p}\left(\min_{i,j,k=1,\ldots,\bar{p}} \frac{\partial \Phi^D_{ik}}{\partial I_{jk}}\right) v_m^{-1} \leq \mathcal{R}_0 \leq \bar{p}\left(\max_{i,j,k=1,\ldots,\bar{p}} \frac{\partial \Phi^D_{ik}}{\partial I_{jk}}\right) v_M^{-1}. \qquad (3.36)$$

Proof. We denote $G(\oplus(A_\bullet C_\bullet^{-1}B_\bullet)^{-1}) := G\left(\oplus_k(A_kC_k^{-1}B_k)^{-1}\right)$ for simplicity. The (p,q) block of $G\left(\oplus(A_\bullet C_\bullet^{-1}B_\bullet)^{-1}\right)$ is $G_{pq}(A_qC_q^{-1}B_q)^{-1}$ for all p,q. As G_{pq} is diagonal, multiplication with $(A_qC_q^{-1}B_q)^{-1}$ amounts to multiplying row $k=1,\ldots,\bar{p}$ of $(A_qC_q^{-1}B_q)^{-1}$ by the k^{th} diagonal entry of G_{pq}, that is, $\partial\Phi^D_{pk}/\partial I_{qk}$. Let $v_{kl}^{-1}(q)$ denote the (k,l) entry of $(A_qC_q^{-1}B_q)^{-1}$, for $k,l=1,\ldots,\bar{p}$. Then a given block $G_{pq}(A_qC_q^{-1}B_q)^{-1}$ takes the form

$$G_{pq}(A_qC_q^{-1}B_q)^{-1} = \begin{pmatrix} \frac{\partial \Phi^D_{p1}}{\partial I_{q1}} v_{11}^{-1}(q) & \cdots & \frac{\partial \Phi^D_{p1}}{\partial I_{q1}} v_{1\bar{p}}^{-1}(q) \\ \vdots & & \vdots \\ \frac{\partial \Phi^D_{p\bar{p}}}{\partial I_{q\bar{p}}} v_{\bar{p}1}^{-1}(q) & \cdots & \frac{\partial \Phi^D_{p\bar{p}}}{\partial I_{q\bar{p}}} v_{\bar{p}\bar{p}}^{-1}(q) \end{pmatrix}$$

It follows that

$$\mathbb{1}^T G_{pq}(A_qC_q^{-1}B_q)^{-1} = \left(\sum_{k=1}^{\bar{p}} \frac{\partial \Phi^D_{pk}}{\partial I_{qk}} v_{k1}^{-1}(q), \ldots, \sum_{k=1}^{\bar{p}} \frac{\partial \Phi^D_{pr}}{\partial I_{qk}} v_{k\bar{p}}^{-1}(q)\right)$$

Summing for $p=1,\ldots,\bar{p}$ gives the column sums in the q^{th} block of

columns as

$$\left[\mathbb{1}^T G\left(\oplus(A_\bullet C_\bullet^{-1} B_\bullet)^{-1}\right)\right]_{[q]} = \left(\sum_{p,k=1}^{\bar{p}} \frac{\partial \Phi_{pk}^D}{\partial I_{qk}} v_{k1}^{-1}(q), \ldots, \sum_{p,k=1}^{\bar{p}} \frac{\partial \Phi_{pk}^D}{\partial I_{qk}} v_{k\bar{p}}^{-1}(q)\right),$$

where we denote

$$\sum_{p,k=1}^{\bar{p}} := \sum_{p=1}^{\bar{p}} \sum_{k=1}^{\bar{p}}$$

in order to simplify notations. Thus, for the whole matrix,

$$\mathbb{1}^T G\left(\oplus(A_\bullet C_\bullet^{-1} B_\bullet)^{-1}\right) = \left(\sum_{p,k=1}^{\bar{p}} \frac{\partial \Phi_{pk}^D}{\partial I_{1k}} v_{k1}^{-1}(1), \ldots, \sum_{p,k=1}^{\bar{p}} \frac{\partial \Phi_{pk}^D}{\partial I_{\bar{p}k}} v_{k\bar{p}}^{-1}(\bar{p})\right). \quad (3.37)$$

Define

$$\frac{\partial \Phi_{i_m k_m}^D}{\partial I_{j_m k_m}} = \min_{i,j,k=1,\ldots,\bar{p}} \frac{\partial \Phi_{ik}^D}{\partial I_{jk}}$$

and

$$\frac{\partial \Phi_{i_M k_M}^D}{\partial I_{j_M k_M}} = \max_{i,j,k=1,\ldots,\bar{p}} \frac{\partial \Phi_{ik}^D}{\partial I_{jk}}.$$

Then, for any column c in the j^{th} block of columns, there holds

$$\begin{aligned}
&\sum_{i,k=1}^{\bar{p}} \frac{\partial \Phi_{i_m k_m}^D}{\partial I_{j_m k_m}} v_{kc}^{-1}(j) \leq \sum_{i,k=1}^{\bar{p}} \frac{\partial \Phi_{pr}^D}{\partial I_{jk}} v_{kc}^{-1}(j) \leq \sum_{i,k=1}^{\bar{p}} \frac{\partial \Phi_{i_M k_M}^D}{\partial I_{j_M k_M}} v_{kc}^{-1}(j) \\
\Leftrightarrow\ &\frac{\partial \Phi_{i_m k_m}^D}{\partial I_{j_m k_m}} \sum_{i,k=1}^{\bar{p}} v_{kc}^{-1}(j) \leq \sum_{i,k=1}^{\bar{p}} \frac{\partial \Phi_{pr}^D}{\partial I_{jk}} v_{kc}^{-1}(j) \leq \frac{\partial \Phi_{i_M k_M}^D}{\partial I_{j_M k_M}} \sum_{i,k=1}^{\bar{p}} v_{kc}^{-1}(j) \\
\Leftrightarrow\ &\bar{p} \frac{\partial \Phi_{i_m k_m}^D}{\partial I_{j_m k_m}} \sum_{k=1}^{\bar{p}} v_{kc}^{-1}(j) \leq \sum_{i,k=1}^{\bar{p}} \frac{\partial \Phi_{pr}^D}{\partial I_{jk}} v_{kc}^{-1}(j) \leq \bar{p} \frac{\partial \Phi_{i_M k_M}^D}{\partial I_{j_M k_M}} \sum_{k=1}^{\bar{p}} v_{kc}^{-1}(j).
\end{aligned} \quad (3.38)$$

Defining v_m^{-1} and v_M^{-1} as in the theorem, it follows that for all $c, j = 1, \ldots, \bar{p}$,

$$\bar{p} \frac{\partial \Phi_{i_m k_m}^D}{\partial I_{j_m k_m}} v_m^{-1} \leq \sum_{i,k=1}^{\bar{p}} \frac{\partial \Phi_{pr}^D}{\partial I_{jk}} v_{kc}^{-1}(j) \leq \bar{p} \frac{\partial \Phi_{i_M k_M}^D}{\partial I_{j_M k_M}} v_M^{-1},$$

and thus

$$\bar{p}\frac{\partial\Phi^D_{i_m k_m}}{\partial I_{j_m k_m}}v_m^{-1} \le \mathbb{1}^T G\left(\oplus(A_\bullet C_\bullet^{-1}B_\bullet)^{-1}\right) \le \bar{p}\frac{\partial\Phi^D_{i_M k_M}}{\partial I_{j_M k_M}}v_M^{-1}.$$

Using a standard result on the localization of the dominant eigenvalue of a nonnegative matrix (see, *e.g.*, [42, Theorem 1.1]), which states that the dominant eigenvalue of a nonnegative matrix is bounded below and above by the minimum and maximum of its column sums, the result then follows. □

Consider patch p isolated from the other patches (with movement rates into and out of the patch set to zero). In this case, all nonresident populations tend to zero. The basic reproduction number in patch p, $\mathcal{R}_0^p$, is given by

$$\mathcal{R}_0^p = \frac{\varepsilon_{pp}}{(\varepsilon_{pp}+d_{pp})(\gamma_{pp}+d_{pp})}\,\frac{\partial\Phi^D_{pp}}{\partial I_{pp}}$$

Corollary 3.18. *Suppose that $\Phi_{pq} = \Phi_q$ for all $p, q = 1, \ldots, \bar{p}$, i.e., infection occurs at the same rate for all individuals in a given patch q. Then*

$$\min_{p=1,\ldots,\bar{p}} \mathcal{R}_0^p \le \mathcal{R}_0 \le \max_{p=1,\ldots,\bar{p}} \mathcal{R}_0^p$$

Proof. Note that G_{pq} represents infections in patch q of susceptibles from patch p. The assumptions of the corollary imply that $G_{pq} = G_q$ for all $p = 1, \ldots, \bar{p}$. □

In the particular case where parameters except the force of infection are equal in each patch, the bounds in Theorem 3.17 take an easier form.

Theorem 3.19. *Suppose that for system (3.10), parameters are the same in all patches, i.e., $\varepsilon_{pq} = \varepsilon$, $\gamma_{pq} = \gamma$ and $d_{pq} = d$ for all $p, q = 1, \ldots, \bar{p}$. Then*

$$\left(\min_{i,j,k}\frac{\partial\Phi^D_{pr}}{\partial I_{jk}}\right)\frac{\bar{p}\varepsilon}{(\gamma+d)(\varepsilon+d)} \le \mathcal{R}_0 \le \left(\max_{i,j,k}\frac{\partial\Phi^D_{pr}}{\partial I_{jk}}\right)\frac{\bar{p}\varepsilon}{(\gamma+d)(\varepsilon+d)} \quad (3.39)$$

Proof. Under the assumptions of the theorem, the following holds true:

$$\mathbb{1}^T A_p = (\varepsilon+d)\mathbb{1}^T \Rightarrow \mathbb{1}^T A_p C_p^{-1} = \frac{\varepsilon+d}{\varepsilon}\mathbb{1}^T$$
$$\Rightarrow \mathbb{1}^T A_p C_p^{-1} B_p = \frac{(\varepsilon+d)(\gamma+d)}{\varepsilon}\mathbb{1}^T.$$

Consider an invertible matrix M such that $\mathbb{1}^T M = c\mathbb{1}^T$. Then there holds that $\mathbb{1}^T M M^{-1} = c\mathbb{1}^T M^{-1}$, and thus $\mathbb{1}^T M^{-1} = 1/c$. This implies that

$$\mathbb{1}^T (A_p C^{-1} B_p)^{-1} = \frac{\varepsilon}{(\varepsilon + d)(\gamma + d)}.$$

Substituting this value for $\sum_{p=1}^{\bar{p}} v_{pc}^{-1}(j)$ in (3.38), and using in (3.37) gives the result. □

So, in the case that disease characteristics are identical for all individuals, and that transmission is identical for all individuals in a given patch, there are easily computable bounds for $\mathcal{R}_0$. In particular, if $\mathcal{R}_0^p < 1$ for all $p = 1, \ldots, \bar{p}$, then the DFE is locally asymptotically stable, or globally asymptotically stable if the stronger hypotheses needed for this are satisfied; if $\mathcal{R}_0^p > 1$ for all $p = 1, \ldots, \bar{p}$, then the DFE is unstable.

If, additionally, $\Phi_{pq} = \Phi$ for all patches, then $\mathcal{R}_0$ for the whole system is equal to $\mathcal{R}_0$ as obtained with the 4-dimensional system (1.1). Although this seems obvious, it seems interesting to point out that this is obtained while the $4\bar{p}^2$-dimensional system (3.10) does not aggregate to (1.1), in the sense that the nonlinearities do not cancel. For example, for system (3.10), letting $\mathbf{E} = E_{11} + \cdots + E_{\bar{p}\bar{p}}$, we have, under the assumption of equal parameters in all patches and all subpopulations,

$$\mathbf{E}' = \sum_{p,q=1}^{\bar{p}} \Phi - (d + \varepsilon)\mathbf{E},$$

but it is not possible to simplify $\sum_{pq=1}^{\bar{p}} \Phi$ to obtain an expression of the form $\mathbf{E}' = \Phi - (d + \varepsilon)\mathbf{E}$.

3.9 Further problems

I mention briefly here other problems that could and should be considered. They are not detailed here, but references are provided in Section 4.

3.9.1 Existence of endemic equilibria

The existence of endemic equilibria, that is, equilibria with positive numbers of infectives, has barely been discussed here. In Section 3.7, it was established that endemic equilibria, if they exist, populate whole strongly connected components. However, no method was given to prove their existence. Numerical simulations seem to indicate that, for the systems presented here, there is a unique, globally asymptotically stable equilibrium point, when $\mathcal{R}_0 > 1$.

Clearly, establishing properties of persistence of the system when $\mathcal{R}_0 > 1$ would be interesting steps in that direction.

3.9.2 Understand the effect of movement

Theorem 3.17 establishes that in the case of a relatively homogeneous system, the movement matrix plays a role only insofar as it determines the value at the DFE. If disease transmission is also homogeneous within each patch, then Corollary 3.18 proves that the situation is even more constrained. In particular, in that case, it is impossible, for example, for movement to stabilize an unstable situation, or to destabilize a stable situation. Indeed, consider a system consisting of two connected patches, and suppose that both are such that their $\mathcal{R}_0^p < 1$ when taken in isolation. If the conditions of Corollary 3.18 hold, then movement cannot change this situation. The same holds true if both patches are such that $\mathcal{R}_0^p > 1$: movement cannot stabilize such a situation.

In a less restrictive setting, movement can either stabilize an unstable situation, or destabilize a stable one. This has been investigated, for example, in [1, 49, 50].

4 Diseases in metapopulations – A review

4.1 Focus of the review

Our definition of metapopulations *de facto* excludes pure group models, that consider strict interactions between groups. Such models have been considered for about the same amount of time as metapopulation models. The first such models are due to Rushton and Mautner [47] and Haskey [29]. Other well known examples are due to Lajmanovich and Yorke [37], Hethcote [33], Hethcote and Thieme [31]. While these models are conceptually quite similar to metapopulation models, they make the assumption that there is no exchange of individuals between the subpopulations. Their analysis can be quite similar to the analysis of metapopulation models, and much can be gained by comparing the two types of approaches. Also, our emphasis is on deterministic models that have been mathematically analyzed. Finally, we focus on time continuous models. There are some very interesting works that are formulated in discrete time (see, e.g., [2, 16]), but the theory is quite different.

In summary, the review that follows concerns the analysis of deterministic models with explicit movement of individuals between patches.

4.2 Early works

Bartlett, 1956 The first work that we are aware of that uses a patch approach is due to Bartlett [11]. He considers the following model on

two patches,

$$S_1' = -(\beta_1 I_1 + \beta_2 I_2)S_1 + b + m_S(S_2 - S_1) \tag{4.1a}$$
$$I_1' = (\beta_1 I_1 + \beta_2 I_2)S_1 - (d+\rho)\mu I_1 + m_I(I_2 - I_1) \tag{4.1b}$$
$$S_2' = -(\beta_1 I_1 + \beta_2 I_2)S_2 + b + m_S(S_1 - S_2) \tag{4.1c}$$
$$I_2' = (\beta_1 I_1 + \beta_2 I_2)S_2 - (d+\rho)I_2 + m_I(I_1 - I_2) \tag{4.1d}$$

The rate $d + \rho$ incorporates the natural death rate d as well as the rate ρ of occurence of any other event leading to an individual leaving the infected class (disease specific death, recovery, etc.). b is the birth rate. Note that this model is a hybrid of metapopulation and group models. Indeed, there is an exchange of individuals between patches through migration, but there is also cross patch infection.

Baroyan and Rvachev, late 60s, and directly related articles Following the work of Bartlett comes works by Baroyan, Rvachev and collaborators [9, 10]. They consider the spatial spread of influenza between cities in the Soviet Union. In their approach, a large geographic region (country) is partitioned into smaller sub-regions (cities). Migration and transportation between these cities are explicitly incorporated, and within a given city, transmission is modeled by a discrete deterministic compartmental SIR model. In [48], the parameters of the model are estimated using Hong Kong as a reference; the model is then used to simulate the spread of the Hong Kong influenza pandemic between 52 world cities. In [40], an epidemic threshold theorem is obtained. An SEIR version of this model was used recently [26].

Using the framework of Rvachev and Longini, Hyman and LaForce [34] formulate a multy-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. Epidemic parameters appropriate for influenza virus are used, 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 $1/\alpha$, the average duration of infection, is the most important parameter.

4.3 Kermack-McKendrick-type models

The model known as the Kermack-McKendrick (KMK) model takes the form [36]

$$\begin{aligned}\frac{d}{dt}S &= -\beta SI\\ \frac{d}{dt}I &= \beta SI - \gamma I\\ \frac{d}{dt}R &= \gamma I,\end{aligned}$$

that is, an SIR model without demography. The parameter γ represents here the rate of removal from the I class, it aggregating disease induced death and recovery from the disease. This system has the advantage that an explicit solution can be found (see, e.g., [13]). Several authors have used KMK-type models in a metapopulation context.

Faddy, 1986 In a short note, Faddy [22] introduces a KMK-type SI model

$$S_i' = -S_i \sum_{j=1}^{n} \beta_{ji} I_j \tag{4.2a}$$

$$I_i' = S_i \sum_{j=1}^{n} \beta_{ji} I_j - \gamma_i I_i + \sum_{j\neq i} m_{ij} I_j - \sum_{j\neq i} m_{ji} I_i, \tag{4.2b}$$

where γ_i represents the sum of all removals from the I class. As in the case of system (4.1), this system mixes group models with migration. An interesting remark made by Faddy is that there exists a sort of conservation law, since the quantity

$$S_i + I_i - \frac{\sum\limits_{j\neq i} m_{ij} + \gamma_i}{\beta_{ii}} \log S_i - \left(m_{ji} + \frac{\left(\sum\limits_{j\neq i} m_{ij} + \gamma_i \right) \beta_{ji}}{\beta_{ii}} \right) \sum_{j\neq i} \int I_j dt$$

does not change over time. The interest here is on the final size of the epidemic, for which an expression is obtained.

In the spatially homogeneous case where $S_i(0) = S(0)$, a given value in all patches, $m_i = \sum_{j \neq i} m_{ij} = m$, $\beta_{ij} = \beta$ and $\gamma_i = \gamma$, he obtains that

$$\frac{S_i(0) - S_i(\infty)}{S(0)} = 1 - \exp\left(-\beta \frac{S_i(0) - S_i(\infty)}{\gamma}\right),$$

where $S_i(\infty)$ is the final number of susceptibles remaining uninfected in patch i.

Clancy, 1996 Clancy [20] introduces a Kermack-McKendrick type model on patches, but that describes the dynamics of a very simple epidemic with carriers, whose numbers is denoted C. The carriers are subject to specific removal (either through treatment of death), at a rate γ. The system includes a removed class, that we do not show here as it bears no influence on the dynamics of the system. The latter takes the form

$$S_i' = -\frac{\beta}{N_i} S_i C_i + \sum_{j=1}^{n} m_{ji}^S S_j \tag{4.3a}$$

$$C_i' = -\gamma C_i + \sum_{j=1}^{n} m_{ji}^C C_j. \tag{4.3b}$$

He also introduces a corresponding stochastic version. The focus here is on the ultimate size of the epidemic; more precisely, estimates of S_i as $t \to \infty$ are sought.

Rodríguez and Torres-Sorando, 2001, consider in [44] a direct transmission model and a model of malaria. The malaria model tracks the evolution of the numbers I_i and Y_i of infectious humans and infectious mosquitoes, respectively, on patch i. The total population of both species is assumed constant on each patch, and denoted N_i and M_i, respectively, for humans and mosquitoes. Thus, the numbers of susceptibles are obtained by $S_i = N_i - I_i$ and $Z_i = M_i - Y_i$. The system takes the form

$$I_i' = \beta S_i Y_i - \gamma I_i + \beta S_i \sum_{j \neq i} m_{ij} Y_j \tag{4.4a}$$

$$Y_i' = \beta Z_i I_i - d_M Y_i + \beta Z_i \sum_{j \neq i} m_{ji} I_j. \tag{4.4b}$$

β is the rate of transmission of the disease when a contact occurs. They consider the effect of different migration patterns and of the environment heterogeneity on the dynamics of the system, and in particular

on the possibility of the disease becoming established. To study this, they consider the jacobian matrix at the DFE, and study the sign of the dominant eigenvalue.

4.4 Migration models

Wang and Mulone, 2003 Wang and Mulone [63] consider the following model in the case $\bar{p} = 2$ patches,

$$S_i' = d_i(N_i - S_i) - \beta_i S_i \frac{I_i}{N_i} + \gamma_i I_i + \sum_{j=1}^{\bar{p}} m_{ij}^S S_j \tag{4.5a}$$

$$I_i' = \beta_i S_i \frac{I_i}{N_i} - (d_i + \gamma_i) I_i + \sum_{j=1}^{\bar{p}} m_{ij}^I I_j. \tag{4.5b}$$

They establish a series of interesting results concerning the conditions under which the disease is persistent in the system. One particular conclusion that they draw is that, provided they are positive, the migration rates of susceptibles m_{12}^S, m_{21}^S do not play a role in the permanence conditions.

Wang and Zhao, 2004 Wang and Zhao [64] consider a model of the form

$$S_i' = B_i(N_i)N_i - \mu_i S_i - \beta_i S_i I_i + \gamma_i I_i + \sum_{j=1}^{n} m_{ij}^S S_j \tag{4.6a}$$

$$I_1' = \beta_i S_i I_i - (\mu_i + \gamma_i) I_i + \sum_{j=1}^{n} m_{ij}^I I_j. \tag{4.6b}$$

With this more general birth function B_i, even finding a disease free equilibrium is a difficult task. It is shown that, in this case, population movement can either intensify or reduce the spread of disease.

Salmani and van den Driessche, 2006 Salmani and van den Driessche introduce in [50] a single species SEIRS model with status dependent movement and disease induced death, from which (3.2) is derived. In a first part, following the approach of [6, 7], they establish a basic reproduction number for the system, and as in [4], the global stability of the DFE when $\mathcal{R}_0 < 1$. They then proceed to a more detailed study of an SIS particular case in two patches. They establish that with different movement rates, different situations can prevail, with for example a global $\mathcal{R}_0 < 1$ and individual $\mathcal{R}_0^p$ in the patches less than 1.

Fulford, Roberts and Heesterbeek, 2002 The spread of bovine tuberculosis amongst the common brushtail possum in New Zealand, is modeled by Fulford *et al* [25]. Since only maturing possums (1 to 2 year old males) travel large distances, a two-age class metapopulation model is formulated, with juvenile and adult possums. As this disease is fatal, a 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 $\bar{p}$ patches, the authors formulate a system of $6\bar{p}$ ODEs to describe the disease dynamics. Using the next generation matrix method [21], the authors explicitly calculate $\mathcal{R}_0$ for $\bar{p} = 1$ and for $\bar{p} = 2$, and give the structures of the next generation matrices for $\bar{p} = 4$ and three spatial topologies, namely a spider, chain and loop. The design of control strategies (culling) based on these three spatial topologies is considered. The critical culling rates (where $\mathcal{R}_0 = 1$) are calculated and the spatial aspects are shown to be important.

4.5 Model including residency patch

Sattenspiel and coauthors In [55], Sattenspiel and Simon introduced a model for the interaction between individuals in $\bar{p}$ neighborhoods, taking into account that some individuals only have contacts in their neighborhoods. Although this is a strict group model, since individuals do not move explicitly between neighborhoods, it is mentioned here because it is an obvious basis to the models with residency patch. Also, it contains some interesting matrix-based analysis.

Sattenspiel and Dietz [51] 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. Hence this type of model describes human travel rather than migration.

This framework was subsequently used numerically by Sattenspiel and others to describe various situations linked to the spread of influenza in the Canadian subartic [52], the effect of quarantining [53] and the influence of the mobility patterns [54].

Arino and van den Driessche We studied the model of [51] in [6, 7], giving some analytical results and calculating the basic reproduction number in the SIS [7] and SEIRS [6] cases, giving the first example of application of the method of [60] to such high dimensional models. These models have a unique DFE. 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. This model is the basis for

[8], which extends the model of [51] by allowing individuals to travel between two patches that are not their residency patch. The resulting model is system (3.10), analyzed in detail in Section 3.

Ruan, Wang and Levin, 2006 Using the framework of [51], Ruan, Wang and Levin [45] study the global spread of SARS. The system takes the form of an SEIRS model with an additional class for quarantined individuals, denoted Q, that do not travel. They study the existence of a DFE, and establish the basic reproduction number $\mathcal{R}_0$, deducing the local asymptotic stability of the DFE when $\mathcal{R}_0 < 1$ using the result of [60], as detailed in the SEIRS case in Section 3.5. The basic reproduction number depends explicitly on quarantining parameters. A particular case for two cities (Honk Kong and Toronto) is then considered.

4.6 New directions

To conclude this brief review of diseases in metapopulations, a few directions that appear promising to the author are now listed. It is hoped that, although necessarily biased by the author's opinions, this will encourage readers to study more in detail some of the aspects.

4.6.1 True patch heterogeneity

Metapopulations have been introduced in the context of epidemic diseases to take into account spatial heterogeneities. However, in all the models discussed so far, the spatial heterogeneity is not 'true'. Indeed, it is assumed that in the different patches, parameters are different, but that the incidence function is similar. The effect of the contact structure (the nature of the incidence function) on the dynamics is determinant. A model of Fromont, Pontier and Langlais [24] is the first we know that breaks this homogeneity. They consider a model appropriate for Feline Leukemia Virus among a population of domestic cats. There are $\bar{p}$ 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, standard incidence for cats in villages).

The model consists of $3\bar{p}$ ODEs and is analyzed for the case $\bar{p} = 2$, taking 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, spatial heterogeneity promotes disease persistence.

4.6.2 Models with infinite dimensional aspects

Wang, Fergola and Tenneriello, 2003 Wang, Fergola and Tennierello [62] study a model for the diffusion of innovation in a two patch environment. Although not strictly an epidemic model, the spread of innovation can easily be reread in terms of disease propagation. They first formulate the model in ODE and show that it has a globally asymptotically stable equilibrium (note that this is different from classical epidemic models, in the sense that there is no bifurcation from a disease free equilibrium to an endemic equilibrium). They then incorporate delay, in the form of product duration. Written in epidemiological terms, the model then takes the form

$$\begin{aligned}\frac{d}{dt}S_1 &= \Pi_1 - (\alpha_1 + \beta_1 I_1)S_1 - d_1 S_1 + m_2(S_2 + (1-k_2)I_2) - m_1 S_1 \\ &\quad + e^{-d_1\tau_1}(\gamma_1 S_1(t-\tau_1) + \beta_1 S_1(t-\tau_1)I(t-\tau_1)) \qquad (4.7a)\\ \frac{d}{dt}I_1 &= (\alpha_1 + \beta_1 I_1)S_1 - d_1 I_1 - m_1 I_1 + k_2 m_2 I_2 \\ &\quad - e^{-d_1\tau_1}(\gamma_1 S_1(t-\tau_1) + \beta_1 S(t-\tau_1)I(t-\tau_1)) \qquad (4.7b)\\ \frac{d}{dt}S_2 &= \Pi_2 - (\alpha_2 + \beta_2 I_2)S_2 - d_2 S_2 + m_1(S_1 + (1-k_1)I_1) - m_2 S_2 \\ &\quad + e^{-d_2\tau_2}(\gamma_2 S_2(t-\tau_2) + \beta_2 S_2(t-\tau_2)I(t-\tau_2)) \qquad (4.7c)\\ \frac{d}{dt}I_2 &= (\alpha_2 + \beta_2 I_2)S_2 - d_2 I_2 - m_2 I_2 + k_1 m_1 I_1 \\ &\quad - e^{-d_2\tau_2}(\gamma_2 S_2(t-\tau_2) + \beta_2 S(t-\tau_2)I(t-\tau_2)). \qquad (4.7d)\end{aligned}$$

In each patch $i = 1, 2$, besides the usual parameters, Π_i is the birth rate (a constant), α_i is the intensity of advertisement for the products (this additional recruitment term is the main difference from classical epidemic models) and τ_i is the duration of the product (that is, of infection) in each patch. The migration is slightly different from the other models seen so far, in the sense that individuals can change status when they move from one patch to the other: m_1 is the rate of movement from 1 to 2, m_2 is the rate of movement from 2 to 1, k_1 is the fraction of infected from patch 1 that remain infected when moving to 2 and k_2 is the fraction of infected from patch 2 that remain infected when moving to patch 1.

Here again, there is a unique positive equilibrium, which is shown to be globally asymptotically stable under some conditions on parameter values. The paper concludes with a study of periodic solutions in the case where advertisement, i.e., α_i, is periodic (in the delayed case). It is shown that there exists parameter values for which a periodic solution exists and is globally stable.

Wang and Zhao, 2005 Wang and Zhao [65] formulated a model for an SIS model on patches, with a class of juveniles (denoted by J). On each patch $p = 1, \ldots, \bar{p}$,

$$\frac{d}{dt}J_p = \mathcal{B}_p(A_p)A_p - d_p^J J_p - R_p(t) + \sum_{k=1}^{\bar{p}} m_{pk}^J J_k \tag{4.8a}$$

$$\frac{d}{dt}S_p = R_p(t) - d_p S_p - \beta_p S_p I_p + \gamma_p I_p + \sum_{k=1}^{\bar{p}} m_{pj}^S S_j \tag{4.8b}$$

$$\frac{d}{dt}I_p = \beta_p S_p I_p - (d_p + \gamma_p)I_p + \sum_{k=1}^{\bar{p}} m_{pj}^I I_j, \tag{4.8c}$$

where $A_p = S_p + I_p$ (the population of adults), d_p^J is the death rate of juveniles and d_p is the death rate of adults, and $R_p(t)$ is rate of recruitment of juveniles into the susceptible adult class. It is assumed that $\mathcal{B}(A_p) > 0$ for $A_p > 0$, $\mathcal{B}_p$ continuously differentiable for $A_p > 0$ and $\mathcal{B}_p'(A_p) < 0$ for all $A_p > 0$.

Recruitment into the adult class has to take into account that juveniles can be born in a given patch, and become adults in another patch. Let r be the age of recruitment into the adult class (assumed the same in each patch), and $J(t,a) := (J_1(t,a), \ldots, J_{\bar{p}}(t,a))^T$, with $J_p(t,a)$ the number of juveniles in patch p at time t that are of age a. The recruitment $R(t)$ then satisfies $R(t) := (R_1(t), \ldots, R_{\bar{p}}(t))^T = J(t,r)$. The age-space dynamics is described by

$$\begin{aligned}(\partial_t + \partial_a)J_p(t,a) &= \sum_{k=1}^{\bar{p}} m_{pk}^J J_k(t,a) - \left(\sum_{k=1}^{\bar{p}} m_{kp}^J + d_p^J\right) J_p(t,a) \\ &= \sum_{k=1}^{\bar{p}} m_{pk}^J J_k(t,a) - d_p^J J_p(t,a),\end{aligned}$$

with $J(t,0) = \mathcal{B}(A(t)) := (\mathcal{B}_1(A_1(t))A_1(t), \ldots, \mathcal{B}_{\bar{p}}(A_{\bar{p}}(t))A_{\bar{p}}(t))^T$. Then, after some computations,

$$R(t) = J(t,r) = \exp(C_J r)B(A(t-r)),$$

where

$$C_J = \begin{pmatrix} -d_1^J + m_{11}^J & c_{12} & \cdots & m_{1\bar{p}}^J \\ m_{21}^J & -d_2^J + m_{22}^J & \cdots & m_{2\bar{p}}^J \\ \cdots & \cdots & \cdots & \cdots \\ m_{\bar{p}1}^J & m_{\bar{p}2}^J & \cdots & -d_{\bar{p}}^J + m_{\bar{p}\bar{p}}^J \end{pmatrix}.$$

Using $R(t)$, the equations for S and I decouple from the equations for J, giving a system of $2\bar{p}$ delay differential equations.

The authors then establish the existence of a unique disease free equilibrium under a certain number of assumptions. They then derive a basic reproduction number for the system, and consider the global stability of the disease free equilibrium, as well as the persistence of the system when this equilibrium is unstable, and the existence of an endemic equilibrium. The paper concludes with a study of a two patch particular case.

5 Conclusion

My aim here was to show that metapopulation models are usable in the context of epidemiology, to provide an extensive overview of the mathematical problems that arise when studying such models, and to illustrate some of the solutions that can be given to these problems. This was done through two classes of models that van den Driessche and I have considered, with a simple single population SEIRS also used to illustrate the most simple properties.

I hope to have convinced the reader, at the cost of maybe a little too much detail, that the mathematical complications arising in these models can be dealt with, and that there is a pattern to these solutions that allows a general theory of metapopulation models in epidemiology to be envisioned. This theory is barely sketched here.

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