# Adding space to FMD and AI models

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- ▶ We now consider spatial spread

# What are metapopulations?

Metapopulations are *populations* of *populations*.

Two main types of metapopulation models:

- ▶ *patch occupancy models*. Describe whether a location is *occupied* by a species or not. Depends on the occupancy of neighboring or connected locations. Dynamics describes the number of occupied locations

- ▶ Models with *explicit movement*. Movement between locations is described explicitly. In each location, a set of differential equations describes the dynamics of the populations present

# What is a location?

A *location* is a unit (typically geographical) within which the population is considered homogeneous

- ▶ city
- ▶ region
- ▶ country
- ▶ but also, location where a given species lives (for example, forest, swamp, etc.)

Locations may or may not overlap

# A model of Richard Levins (1969)

R. Levins. Some Demographic and Genetic Consequences of Environmental Heterogeneity for Biological Control. Bulletin of the Entomological Society of America **15**(3): 237-240 (1969)

Cited 4,400+ times, numerous higher order "offspring"

Quickly evolved to include prey-predators or competition systems

# The Levins model

Rate of change of # of local populations $P$:

$$P' = \beta P \left(1 - \frac{P}{T}\right) - \mu P \qquad (1)$$

$\beta$ immigration rate between *locations*, $T$ total number of locations and $\mu$ extinction rate of local populations

Ecologists & mathematicians think of patches differently. For mathematicians, typically, one place in space. To be clear, in the remainder of these slides, I will speak of *locations*

# Metapopulations with implicit movement

Same philosophy as the Levins model

- There is a set $\mathcal{P}$ of locations called *locations*
- Each location $p \in \mathcal{P}$ has an internal dynamics $x_p = f_p(x_p)$, where $x_p \in \mathbb{R}_+^{n_p}$ and $f_p : \mathbb{R}^{n_p} \to \mathbb{R}^{n_p}$
- No flow of individuals between locations
- The influence of location $q \neq p$ on $p$ is described through a function $g_{qp}(x_p, x_q)$, where $x_q \in \mathbb{R}^{n_q}$ and $g_p : \mathbb{R}^{n_p} \times \mathbb{R}^{n_q} \to \mathbb{R}^{n_p}$

So the population in location $p \in \mathcal{P}$ has dynamics

$$x_p' = f_p(x_p) + \sum_{\substack{q \in \mathcal{P} \\ q \neq p}} g_{qp}(x_p, x_q) \tag{2}$$

# Levins-type vs Explicit movement

Levins model and its offspring: movement is implicit

$$P' = \beta P \left( 1 - \frac{P}{T} \right) - \mu P$$

$\beta$ immigration rate between locations incorporates geography

Sometimes we have explicit movement information or want to incorporate known spatial information $\implies$ models with explicit movement

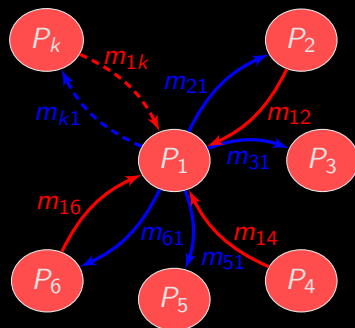Levin (1974)

# Metapopulations with explicit movement

Split continuous space into $N$ discrete geographical locations (*ptatches*)

Each location contains **compartments** (homogeneous groups of individuals). E.g., preys, predators, etc.

Here, we consider a single compartment, the *species of interest*, with no further compartmentalisation

Individuals *may* move between locations; $m_{qp} \geq 0$ rate of movement of individuals from location $p = 1, \ldots, N$ to location $q = 1, \ldots, N$

# Explicit movement (focus on $P_1$)



$$P_1' = \sum_{\substack{j=1 \\ j \neq 1}}^{N} m_{1j}P_j - P_1 \sum_{\substack{j=1 \\ j \neq 1}}^{N} m_{j1}$$

or

$$P_1' = \sum_{j=1}^{N} m_{1j}P_j \text{ assuming } m_{11} = -\sum_{\substack{j=1 \\ j \neq 1}}^{N} m_{j1}$$

# Graph setting

Suppose

- ▶ $|\mathcal{P}|$ locations, vertices in a (directed) graph $\mathcal{G}$
- ▶ Each location contains a certain number of compartments belonging to a common set $\mathcal{C}$ of compartments
- ▶ Arcs of $\mathcal{G}$ represent the possibility for a given compartment to move between two locations; any two locations are connected by a maximum of $|\mathcal{C}|$ edges

Graph is a digraph: movement is not always symmetric

$\mathcal{G} = (\mathcal{P}, \mathcal{A})$ is multi-digraph, where

- ▶ $\mathcal{P}$ is the set of vertices (locations)
- ▶ $\mathcal{A}$ 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 $|\mathcal{C}|$ arcs from $X$ to $Y$ and at most $|\mathcal{C}|$ arcs from $Y$ to $X$

Because there are $|\mathcal{C}|$ compartments and movements are compartment-specific, we also define, for all $c \in \mathcal{C}$, $\mathcal{P}_c$ and $\mathcal{A}_c$ as well as the compartment-specific digraphs $\mathcal{G}^c = (\mathcal{P}_c, \mathcal{A}_c)$

# Connection matrix

For a given compartment $c \in \mathcal{C}$, a *connection matrix* can be associated to the digraph $\mathcal{G}_c$

This is the **adjacency matrix** of $\mathcal{G}_c$, but we emphasize the reason why we use $\mathcal{G}_c$ by using the term *connection*

Choosing an ordering of elements of $\mathcal{P}$, the $(i,j)$ entry of the $|\mathcal{P}| \times |\mathcal{P}|$-matrix $\mathcal{N}_c = \mathcal{N}_c(\mathcal{G}_c)$ is one if $R^c(P_i, P_j)$ and zero otherwise, i.e., if $P_i$ has no direct access to $P_j$

For convenience, the ordering of the locations is generally assumed the same for all compartments

# Strongly connected multi-digraph

### Definition 1 (Strongly connected components)

For a given compartment $s$, the **strongly connected components** (or **strong components**, for short) are such that, for all locations $X, Y$ in a strong component, compartment $s$ in $X$ has access to $Y$

### Definition 2 (Strong connectedness for a compartment)

The multi-digraph is strongly connected for compartment $c$ if all locations belong to the same strong component of $\mathcal{G}_c$

# Srong connectedness and irreducibility

## Definition 3 (Reducible/irreducible matrix)

A matrix $A$ is **reducible** if there exists a permutation matrix $P$ such that $P^T A P$ is block upper triangular. A matrix that is not reducible is **irreducible**

Matrix $A \in \mathbb{F}^{n \times n}$ is irreducible if for all $i, j = 1, \ldots, n$, there exists $k$ such that $a_{ij}^k > 0$, where $a_{ij}^k$ is the $(i, j)$-entry in $A^k$

## Theorem 4

*Strong connectedness $\Leftrightarrow$* **irreducibility** *of the connection matrix* $\mathcal{C}_c$

# Notation

- $N_{cp}(t)$ number of individuals of compartment $c$ in location $p$ at time $t$

- $N_c = \left(N_{c1}, \ldots, N_{c|\mathcal{P}|}\right)^T$ distribution of individuals of compartment $c \in \mathcal{C}$ among the different locations

- $N^p = \left(N_1^p, \ldots, N_{|\mathcal{P}|}^p\right)^T$ composition of the population in location $p \in \mathcal{P}$

# Metapopulation models with linear movement

Use a linear autonomous movement operator

Then, for a given compartment $c \in \mathcal{C}$ and in a given location $p \in \mathcal{P}$

$$N'_{cp} = f_{cp}(N^p) + \sum_{\substack{q \in \mathcal{P} \\ q \neq p}} m_{cpq} N_{cq} - \left( \sum_{\substack{q \in \mathcal{P} \\ q \neq p}} m_{cqp} \right) N_{cp}$$

where $m_{cpq}$ rate of movement of individuals in compartment $c \in \mathcal{C}$ from location $q \in \mathcal{P}$ to location $p \in \mathcal{P}$

# A more compact notation

To make

$$N'_{cp} = f_{cp}(N^p) + \sum_{\substack{q \in \mathcal{P} \\ q \neq p}} m_{cpq} N_{cq} - \left( \sum_{\substack{q \in \mathcal{P} \\ q \neq p}} m_{cqp} \right) N_{cp}$$

more compact, denote the rate of leaving location $p$ as

$$m_{cpp} = - \sum_{\substack{q \in \mathcal{P} \\ q \neq p}} m_{cqp} \tag{3}$$

Then

$$N'_s = f_{cp}(N^p) + \sum_{q \in \mathcal{P}} m_{cpq} N_{cq} \tag{4}$$

## Vector form of the system

For compartment $c \in \mathcal{C}$,

$$N_c' = f(N) + \mathcal{M}_c N_c \tag{5}$$

with

$$\mathcal{M}_c = \begin{pmatrix} -\sum\limits_{k \in \mathcal{P}} m_{ck1} & m_{c12} & \cdots & m_{c1|\mathcal{P}|} \\ \\ m_{c|\mathcal{P}|1} & m_{c|\mathcal{P}|2} & \cdots & -\sum\limits_{k \in \mathcal{P}} m_{ck|\mathcal{P}|} \end{pmatrix} \tag{6}$$

A brief history of metapopulations

The general context
    The graph setting
    Generic model
    The movement matrix
    Behaviour of the mobility component

Diseases in metapopulations

Computational considerations

A few FMD models

# Definitions and notation for matrices

- $M \in \mathbb{R}^{n \times n}$ a square matrix with entries denoted $m_{ij}$

- $M \geq \mathbf{0}$ if $m_{ij} \geq 0$ for all $i, j$ (could be the zero matrix); $M > \mathbf{0}$ if $M \geq \mathbf{0}$ and $\exists i, j$ with $m_{ij} > 0$; $M \gg \mathbf{0}$ if $m_{ij} > 0$ $\forall i, j = 1, \ldots, n$. Same notation for vectors

- $\sigma(M) = \{\lambda \in \mathbf{C}; M\lambda = \lambda\mathbf{v}, \mathbf{v} \neq \mathbf{0}\}$ **spectrum** of $M$

- $\rho(M) = \max_{\lambda \in \sigma(M)}\{|\lambda|\}$ **spectral radius**

- $s(M) = \max_{\lambda \in \sigma(M)}\{\mathrm{Re}\,(\lambda)\}$ **spectral abscissa** (or **stability modulus**)

- $M$ is an **M-matrix** if it is a **Z-matrix** ($m_{ij} \leq 0$ for $i \neq j$) and $M = s\mathbb{I} - A$, with $A \geq 0$ and $s \geq \rho(A)$

# The movement matrix

The matrix

$$\mathcal{M}_c = \begin{pmatrix} -\sum\limits_{k\in\mathcal{P}} m_{ck1} & m_{c12} & \cdots & m_{c1|\mathcal{P}|} \\ \\ m_{c|\mathcal{P}|1} & m_{c|\mathcal{P}|2} & \cdots & -\sum\limits_{k\in\mathcal{P}} m_{ck|\mathcal{P}|} \end{pmatrix} \quad (6)$$

is the **movement matrix**

It plays an extremely important role in the analysis of metapopulation systems, so we'll spend some time discussing its properties

$\mathcal{M}_c$ describes

- ▶ existence of connections
- ▶ when they exist, their "intensity"

# Properties of the movement matrix $\mathcal{M}$

First, remark $-\mathcal{M}_c$ is a Laplacian matrix (cf. Michael's course)

## Lemma 5

1. $0 \in \sigma(\mathcal{M})$ *corresponding to left e.v.* $\mathbb{1}^T$       *[$\sigma$ spectrum]*
2. $-\mathcal{M}$ *is a singular M-matrix*
3. $0 = s(\mathcal{M}) \in \sigma(\mathcal{M})$       *[s spectral abscissa]*
4. *If $\mathcal{M}$ irreducible, then $s(\mathcal{M})$ has multiplicity 1*

For complete proof of Lemma 5 and Proposition 6 (next page), see Arino, Bajeux & Kirkland, BMB 2019

## Proposition 6 ($D$ a diagonal matrix)

1. $s(\mathcal{M} + d\mathbb{I}) = d$, $\forall d \in \mathbb{R}$
2. $s(\mathcal{M} + D) \in \sigma(\mathcal{M} + D)$ associated to $\mathbf{v} > \mathbf{0}$. If $\mathcal{M}$ irreducible, $s(\mathcal{M} + D)$ has multiplicity 1 and is associated to $\mathbf{v} \gg \mathbf{0}$
3. If $\text{diag}(D) \gg \mathbf{0}$, then $D - \mathcal{M}$ invertible M-matrix and $(D - \mathcal{M})^{-1} > \mathbf{0}$
4. $\mathcal{M}$ irreducible and $\text{diag}(D) > \mathbf{0} \implies D - \mathcal{M}$ nonsingular irreducible M-matrix and $(D - \mathcal{M})^{-1} \gg \mathbf{0}$

# Behaviour of the mobility component

Assume no within-location dynamics, just movement. Then (5) takes the form

$$N'_c = \mathcal{M}_c N_c \tag{7}$$

## Theorem 7

*For a given compartment $c \in \mathcal{C}$, suppose that the movement matrix $\mathcal{M}_c$ is irreducible. Then for any $N_c(0) > 0$, (7) satisfies*

$$\lim_{t \to \infty} N_c(t) = N_c^\star \gg 0$$

Note that $N_c^\star$ depends on $\mathbb{1}^T N_c(0)$

# Reduction to total population per location

Let

$$T_p = \sum_{c \in \mathcal{C}} N_{cp}$$

be the total population in location $p$

It is often posssible to obtain, in each location $p \in \mathcal{P}$, an equation for the evolution of the total population that takes the form

$$T_p' = D_p(T_p) + \sum_{c \in \mathcal{C}} \sum_{q \in \mathcal{P}} m_{cpq} N_{cq} \tag{8}$$

where $D_p(T_p)$ describes the demography in location $p$

# Nature of the demography

Most common types of demographic functions
- ▶ $D_p(T_p) = b_p - d_p T_p$ (asymptotically constant population)
- ▶ $D_p(T_p) = b_p T_p - d_p T_p$
- ▶ $D_p(T_p) = d_p T_p - d_p T_p = 0$ (constant population)
- ▶ $D_p(T_p) = r_p T_p(1 - T_p/K_p)$ (logistic demography)

In what follows, assume

$$D_p(T_p) = b_p - d_p T_p \tag{9}$$

# Vector / matrix form of the equation

Assuming demography is of the form (9), write (8) in vector form

$$\mathbf{T}' = \mathbf{b} - \mathbf{d}\mathbf{T} + \sum_{c \in \mathcal{C}} \mathcal{M}_c \mathbf{N}_c \qquad (10)$$

where

- $\mathbf{b} = (b_1, \ldots, b_{|\mathcal{P}|})^T \in \mathbb{R}^{|\mathcal{P}|}$
- $\mathbf{T} = (T_1, \ldots, T_{|\mathcal{P}|})^T \in \mathbb{R}^{|\mathcal{P}|}$
- $\mathbf{N} = (N_{c1}, \ldots, N_{c|\mathcal{P}|})^T \in \mathbb{R}^{|\mathcal{P}|}$
- $\mathbf{d} = \mathrm{diag}\left(d_1, \ldots, d_{|\mathcal{P}|}\right) \in \mathbb{R}^{|\mathcal{P}| \times |\mathcal{P}|}$
- $\mathcal{M}_c \in \mathbb{R}^{|\mathcal{P}| \times |\mathcal{P}|}$

# The nice case

Suppose movement rates **equal for all compartments**, i.e.,

$$\mathcal{M}_c \equiv \mathcal{M}$$

(stronger than Definition **??**, which only requires zero/nonzero patterns in all $\mathcal{M}_c$, $c \in \mathcal{C}$, to be the same)

Then

$$\mathbf{T}' = \mathbf{b} - \mathbf{d}\mathbf{T} + \mathcal{M} \sum_{c \in \mathcal{C}} \mathbf{N}_c$$
$$= \mathbf{b} - \mathbf{d}\mathbf{T} + \mathcal{M}\mathbf{T} \qquad (11)$$

## Equilibria

$$\mathbf{T}' = \mathbf{0} \Leftrightarrow \mathbf{b} - \mathbf{d}\mathbf{T} + \mathcal{M}\mathbf{T} = \mathbf{0}$$
$$\Leftrightarrow (\mathbf{d} - \mathcal{M})\mathbf{T} = \mathbf{b}$$
$$\Leftrightarrow \mathbf{T}^\star = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$$

given, of course, that $\mathbf{d} - \mathcal{M}$ (or, equivalently, $\mathcal{M} - \mathbf{d}$) is invertible..

Is it?

# Nonsingularity of $\mathcal{M} - \mathbf{d}$

Using the spectrum shift of Theorem 6(1)

$$s\left(\mathcal{M} - \min_{p \in \mathcal{P}} d_p\right) = -\min_{p \in \mathcal{P}} d_p$$

This gives a constraint: for total population to behave well (in general, we want this), we *must assume all death rates are positive*

Assume they are (in other words, assume $\mathbf{d}$ nonsingular). Then $\mathcal{M} - \mathbf{d}$ is nonsingular and $\mathbf{T}^\star = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$ unique

# Behaviour of the total population

Equal irreducible movement case

$\mathbf{T}^\star = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$ attracts solutions of

$$\mathbf{T}' = \mathbf{b} - \mathbf{d}\mathbf{T} + \mathcal{M}\mathbf{T} =: f(\mathbf{T})$$

Indeed, we have

$$Df = \mathcal{M} - \mathbf{d}$$

Since we now assume that $\mathbf{d}$ is nonsingular, we have by Theorem 6(1) that $s(\mathcal{M} - \min_{p \in \mathcal{P}} d_p) = -\min_{p \in \mathcal{P}} d_p < 0$

$\mathcal{M}$ irreducible $\to \mathbf{T}^\star \gg 0$ (provided $\mathbf{b} > \mathbf{0}$, of course)

A brief history of metapopulations

The general context

Diseases in metapopulations
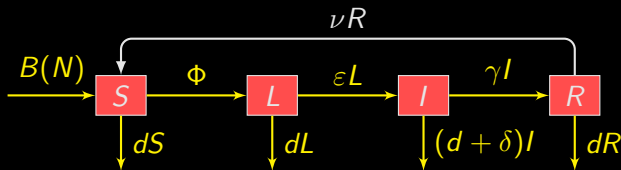    A few sample models
    Existence of a DFE
    Computation of a reproduction number
    Global stability of the DFE when $\mathcal{R}_0 < 1$

Computational considerations

A few FMD models

# The toy SLIRS model in patches



$$S' = \mathcal{B}(N) + \nu R - \Phi - dS \tag{12a}$$

$$L' = \Phi - (\varepsilon + d)L \tag{12b}$$

$$I' = \varepsilon L - (\gamma + d + \delta)I \tag{12c}$$

$$R' = \gamma I - (\nu + d)R \tag{12d}$$

$\Phi$ force of infection. Depends on $S, I$, possibly $N$. In general

$$\Phi = \beta(N)\phi(S, I)$$

Mass action, $\Phi = \beta S I$, proportional incidence, $\Phi = \beta S I / N$

# $|\mathcal{P}|$-SLIRS model

$$S'_p = \mathcal{B}_p(N_p) + \nu_p R_p - \Phi_p - d_p S_p + \sum_{q \in \mathcal{P}} m_{Spq} S_q \tag{13a}$$

$$L'_p = \Phi_p - (\varepsilon_p + d_p) L_p + \sum_{q \in \mathcal{P}} m_{Lpq} L_q \tag{13b}$$

$$I'_p = \varepsilon_p L_p - (\gamma_p + d_p) I_p + \sum_{q \in \mathcal{P}} m_{Ipq} I_q \tag{13c}$$

$$R'_p = \gamma_p I_p - (\nu_p + d_p) R_p + \sum_{q \in \mathcal{P}} m_{Rpq} R_q \tag{13d}$$

with incidence

$$\Phi_p = \beta_p \frac{S_p I_p}{N_p^{q_p}}, \qquad q_p \in \{0, 1\} \tag{13e}$$

# $|\mathcal{S}|$ $|\mathcal{P}|$-**SLIRS (multiple species)**

$p \in \mathcal{P}$ and $s \in \mathcal{S}$ (a set of species)

$$S'_{sp} = \mathcal{B}_{sp}(N_{sp}) + \nu_{sp}R_{sp} - \Phi_{sp} - d_{sp}S_{sp} + \sum_{q \in \mathcal{P}} m_{Sspq}S_{sq} \quad \text{(14a)}$$

$$L'_{sp} = \Phi_{sp} - (\varepsilon_{sp} + d_{sp})L_{sp} + \sum_{q \in \mathcal{P}} m_{Lspq}L_{sq} \quad \text{(14b)}$$

$$I'_{sp} = \varepsilon_{sp}L_{sp} - (\gamma_{sp} + d_{sp})I_{sp} + \sum_{q \in \mathcal{P}} m_{Ispq}I_{sq} \quad \text{(14c)}$$

$$R_{sp} = \gamma_{sp}I_{sp} - (\nu_{sp} + d_{sp})R_{sp} + \sum_{q \in \mathcal{P}} m_{Rspq}R_{sq} \quad \text{(14d)}$$

with incidence

$$\Phi_{sp} = \sum_{k \in \mathcal{S}} \beta_{skp} \frac{S_{sp}I_{kp}}{N_p^{q_p}}, \qquad q_p \in \{0, 1\} \quad \text{(14e)}$$

▶ JA, Davis, Hartley, Jordan, Miller & PvdD. A multi-species epidemic model with spatial dynamics. *Mathematical Medicine and Biology* **22**(2):129-142 (2005)

▶ JA, Jordan & PvdD. Quarantine in a multi-species epidemic model with spatial dynamics. *Mathematical Biosciences* **206**(1):46-60 (2007)

# $|\mathcal{P}|^2$-SLIRS (residents-travellers)

$$S'_{pq} = \mathcal{B}_{pq}\left(N_p^r\right) + \nu_{pq}R_{pq} - \Phi_{pq} - d_{pq}S_{pq} + \sum_{k\in\mathcal{P}} m_{Spqk}S_{pk} \tag{15a}$$

$$L'_{pq} = \Phi_{pq} - (\varepsilon_{pq} + d_{pq})L_{pq} + \sum_{k\in\mathcal{P}} m_{Lpqk}L_{pk} \tag{15b}$$

$$I'_{pq} = \varepsilon_{pq}L_{pq} - (\gamma_{pq} + d_{pq})I_{pq} + \sum_{k\in\mathcal{P}} m_{Ipqk}I_{pk} \tag{15c}$$

$$R'_{pq} = \gamma_{pq}I_{pq} - (\nu_{pq} + d_{pq})R_{pq} + \sum_{k\in\mathcal{P}} m_{Rpqk}R_{pk} \tag{15d}$$

with incidence

$$\Phi_{pq} = \sum_{k\in\mathcal{P}} \beta_{pqk} \frac{S_{pq}I_{kq}}{N_p^{q_q}}, \qquad q_q = \{0, 1\} \tag{15e}$$

► Sattenspiel & Dietz. A structured epidemic model incorporating geographic mobility among regions (1995)

► JA & PvdD. A multi-city epidemic model. *Mathematical Population Studies* **10**(3):175-193 (2003)

► JA & PvdD. The basic reproduction number in a multi-city compartmental epidemic model. In *Positive Systems* (2003)

# Steps for an analysis

**Basic steps**

1. Well-posedness of the system
2. Existence of disease free equilibria (DFE)
3. Computation of a reproduction number $\mathcal{R}_0$, study local asymptotic stability of DFE
4. If DFE unique, prove global asymptotic stability when $\mathcal{R}_0 < 1$

**Additional steps**

5. Existence of *mixed* equilibria, with some locations at DFE and others with disease
6. Computation of some bounds on $\mathcal{R}_0$
7. EEP and its LAS & GAS properties

. . .

## Analysis – Toy system

For simplicity, consider $|\mathcal{P}|$-SLIRS with $\mathcal{B}_p(N_p) = \mathcal{B}_p$

$$S_p' = \mathcal{B}_p - \Phi_p - d_p S_p + \nu_p R_p + \sum_{q \in \mathcal{P}} m_{Spq} S_q \qquad (16a)$$

$$L_p' = \Phi_p - (\varepsilon_p + d_p) L_p + \sum_{q \in \mathcal{P}} m_{Lpq} L_q \qquad (16b)$$

$$I_p' = \varepsilon_p L_p - (\gamma_p + d_p) I_p + \sum_{q \in \mathcal{P}} m_{Ipq} I_q \qquad (16c)$$

$$R_p' = \gamma_p I_p - (\nu_p + d_p) R_p + \sum_{q \in \mathcal{P}} m_{Rpq} R_q \qquad (16d)$$

with incidence

$$\Phi_p = \beta_p \frac{S_p I_p}{N_p^{q_p}}, \qquad q_p \in \{0, 1\} \qquad (16e)$$

System of $4|\mathcal{P}|$ equations

# Don't panic: size is not that bad..

System of $4|\mathcal{P}|$ equations !!!

However, a lot of structure:

- ▶ $|\mathcal{P}|$ *copies* of individual units, each comprising 4 equations
- ▶ Dynamics of individual units well understood
- ▶ Coupling is linear

$\implies$ Good case of large-scale system

(matrix analysis is your friend)

# Existence and uniqueness

▶ Existence and uniqueness of solutions classic, assured by good choice of birth and force of infection functions

▶ In the cases treated later, the birth function is either constant or a linear combination of state variables

▶ May exist problems at the origin, if the force of infection is not defined there

▶ Assumption form now on: existence and uniqueness

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# Disease free equilibrium

The model is at equilibrium if the time derivatives are zero

### Definition 8 (Metapopulation DFE)

In the case of system (16), location $p \in \mathcal{P}$ is at a disease-free equilibrium (DFE) if $L_p = I_p = 0$, and the $|\mathcal{P}|$-location model is at a **metapopulation DFE** if $L_p = I_p = 0$ for all $p \in \mathcal{P}$

Here, we want to find the DFE for the $|\mathcal{P}|$-location model. Later, the existence of mixed equilibria, with some locations at the DFE and others at an endemic equilibrium, is considered

(For (14), replace $L_p$ with $L_{sp}$ and $I_p$ with $I_{sp}$, for (15), replace $L_p$ by $L_{pp}$ and $I_p$ by $I_{pp}$. To simplify notation, we could write $L_\bullet$ and $I_\bullet$)

Assume (16) at metapopulation DFE. Then $\Phi_p = 0$ and

$$0 = \mathcal{B}_p - d_p S_p + \nu_p R_p + \sum_{q \in \mathcal{P}} m_{Spq} S_q$$
$$0 = -\left(\nu_p + d_p\right) R_p + \sum_{q \in \mathcal{P}} m_{Rpq} R_q$$

Want to solve for $S_p, R_p$. Here, it is best (crucial in fact) to remember some linear algebra. Write system in vector form:

$$\mathbf{0} = \mathbf{b} - \mathbf{d}\mathbf{S} + \nu\mathbf{R} + \mathcal{M}^S\mathbf{S}$$
$$\mathbf{0} = -\left(\nu + \mathbf{d}\right)\mathbf{R} + \mathcal{M}^R\mathbf{R}$$

where $\mathbf{S}, \mathbf{R}, \mathbf{b} \in \mathbb{R}^{|\mathcal{P}|}$, $\mathbf{d}, \nu, \mathcal{M}^S, \mathcal{M}^R$ $|\mathcal{P}| \times |\mathcal{P}|$-matrices ($\mathbf{d}, \nu$ diagonal)

# R at DFE

Recall second equation:

$$0 = -(\nu + \mathbf{d})\,\mathbf{R} + \mathcal{M}^R\mathbf{R} \Leftrightarrow (\mathcal{M}^R - \nu - \mathbf{d})\mathbf{R} = \mathbf{0}$$

So unique solution $\mathbf{R} = \mathbf{0}$ if $\mathcal{M}^R - \nu - \mathbf{d}$ invertible Is it?

We have been here before!

From spectrum shift, $s(\mathcal{M}^R - \nu - \mathbf{d}) = -\min_{p \in \mathcal{P}}(\nu_p + d_p) < 0$

So, given $\mathbf{L} = \mathbf{I} = \mathbf{0}$, $\mathbf{R} = \mathbf{0}$ is the unique equilibrium and

$$\lim_{t \to \infty} \mathbf{R}(t) = \mathbf{0}$$

$\implies$ DFE has $\mathbf{L} = \mathbf{I} = \mathbf{R} = \mathbf{0}$

# S at the DFE

DFE has $\mathbf{L} = \mathbf{I} = \mathbf{R} = \mathbf{0}$ and $\mathbf{b} - \mathbf{dS} + \mathcal{M}^S \mathbf{S} = \mathbf{0}$, i.e.,

$$\mathbf{S} = (\mathbf{d} - \mathcal{M}^S)^{-1}\mathbf{b}$$

Recall: $-\mathcal{M}^S$ singular M-matrix. From previous reasoning, $\mathbf{d} - \mathcal{M}^S$ has **instability modulus** shifted *right* by $\min_{p \in \mathcal{P}} d_p$. So:

- $\mathbf{d} - \mathcal{M}^S$ invertible
- $\mathbf{d} - \mathcal{M}^S$ nonsingular M-matrix

Second point $\implies (\mathbf{d} - \mathcal{M}^S)^{-1} > \mathbf{0} \implies (\mathbf{d} - \mathcal{M}^S)^{-1}\mathbf{b} > \mathbf{0}$ (would have $\gg \mathbf{0}$ if $\mathcal{M}^S$ irreducible)

So DFE makes sense with

$$(\mathbf{S}, \mathbf{L}, \mathbf{I}, \mathbf{R}) = \left((\mathbf{d} - \mathcal{M}^S)^{-1}\mathbf{b}, \mathbf{0}, \mathbf{0}, \mathbf{0}\right)$$

# Computing the basic reproduction number $\mathcal{R}_0$

Use next generation method with $\Xi = \{L_1, \ldots, L_{|\mathcal{P}|}, I_1, \ldots, I_{|\mathcal{P}|}\}$,
$\Xi' = \mathcal{F} - \mathcal{V}$

$$\mathcal{F} = \left( \Phi_1, \ldots, \Phi_{|\mathcal{P}|}, 0, \ldots, 0 \right)^T$$

$$\mathcal{V} = \begin{pmatrix} (\varepsilon_1 + d_1) L_1 - \sum_{q \in \mathcal{P}} m_{L1q} L_q \\ \vdots \\ (\varepsilon_{|\mathcal{P}|} + d_{|\mathcal{P}|}) L_{|\mathcal{P}|} - \sum_{q \in \mathcal{P}} m_{L|\mathcal{P}|q} L_q \\ -\varepsilon_1 L_1 + (\gamma_1 + d_1) I_1 - \sum_{q \in \mathcal{P}} m_{I1q} I_q \\ \vdots \\ -\varepsilon_{|\mathcal{P}|} L_{|\mathcal{P}|} + (\gamma_{|\mathcal{P}|} + d_{|\mathcal{P}|}) I_{|\mathcal{P}|} - \sum_{q \in \mathcal{P}} m_{I|\mathcal{P}|q} I_q \end{pmatrix}$$

Differentiate w.r.t. $\Xi$:

$$D\mathcal{F} = \begin{pmatrix} \dfrac{\partial \Phi_1}{\partial L_1} & \cdots & \dfrac{\partial \Phi_1}{\partial L_{|\mathcal{P}|}} & \dfrac{\partial \Phi_1}{\partial I_1} & \cdots & \dfrac{\partial \Phi_1}{\partial I_{|\mathcal{P}|}} \\ \vdots & & \vdots & \vdots & & \vdots \\ \dfrac{\partial \Phi_{|\mathcal{P}|}}{\partial L_1} & \cdots & \dfrac{\partial \Phi_{|\mathcal{P}|}}{\partial L_{|\mathcal{P}|}} & \dfrac{\partial \Phi_{|\mathcal{P}|}}{\partial I_1} & \cdots & \dfrac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}} \\ 0 & \cdots & 0 & 0 & \cdots & 0 \\ \vdots & & \vdots & \vdots & & \vdots \\ 0 & \cdots & 0 & 0 & \cdots & 0 \end{pmatrix}$$

Note that
$$\frac{\partial \Phi_p}{\partial L_k} = \frac{\partial \Phi_p}{\partial I_k} = 0$$
whenever $k \neq p$, so

$$D\mathcal{F} = \begin{pmatrix} \text{diag}\left(\frac{\partial \Phi_1}{\partial L_1}, \ldots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial L_{|\mathcal{P}|}}\right) & \text{diag}\left(\frac{\partial \Phi_1}{\partial I_1}, \ldots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}}\right) \\ \mathbf{0} & \mathbf{0} \end{pmatrix}$$

# Evaluate $D\mathcal{F}$ at DFE

If $\Phi_p = \beta_p S_p I_p$, then

▶ $\dfrac{\partial \Phi_p}{\partial L_p} = 0$

▶ $\dfrac{\partial \Phi_p}{\partial I_p} = \beta_p S_p$

If $\Phi_p = \beta_p \dfrac{S_p I_p}{N_p}$, then

▶ $\dfrac{\partial \Phi_p}{\partial L_p} = \beta_p \dfrac{S_p I_p}{N_p^2} = 0$ at DFE

▶ $\dfrac{\partial \Phi_p}{\partial I_p} = \beta_p \dfrac{S_p}{N_p}$ at DFE

In both cases, $\partial/\partial L$ block is zero so

$$F = D\mathcal{F}(DFE) = \begin{pmatrix} \mathbf{0} & \mathrm{diag}\left(\frac{\partial \Phi_1}{\partial I_1}, \ldots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}}\right) \\ \mathbf{0} & \mathbf{0} \end{pmatrix}$$

# Compute $D\mathcal{V}$ and evaluate at DFE

$$V = \begin{pmatrix} \mathrm{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L & \mathbf{0} \\ -\mathrm{diag}_p(\varepsilon_p) & \mathrm{diag}_p(\gamma_p + d_p) - \mathcal{M}^I \end{pmatrix}$$

where $\mathrm{diag}_p(z_p) := \mathrm{diag}(z_1, \ldots, z_{|\mathcal{P}|})$

Inverse of $V$ easy ($2 \times 2$ block lower triangular):

$$V^{-1} = \begin{pmatrix} \left(\mathrm{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L\right)^{-1} & \mathbf{0} \\ \tilde{V}_{21}^{-1} & \left(\mathrm{diag}_p(\gamma_p + d_p) - \mathcal{M}^I\right)^{-1} \end{pmatrix}$$

where

$$\tilde{V}_{21}^{-1} = \left(\mathrm{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L\right)^{-1}$$
$$\mathrm{diag}_p(\varepsilon_p) \left(\mathrm{diag}_p(\gamma_p + d_p) - \mathcal{M}^I\right)^{-1}$$

# $\mathcal{R}_0$ as $\rho(FV^{-1})$

Next generation matrix

$$FV^{-1} = \begin{pmatrix} \mathbf{0} & F_{12} \\ \mathbf{0} & \mathbf{0} \end{pmatrix} \begin{pmatrix} \tilde{V}_{11}^{-1} & \mathbf{0} \\ \tilde{V}_{21}^{-1} & \tilde{V}_{22}^{-1} \end{pmatrix} = \begin{pmatrix} F_{12}\tilde{V}_{21}^{-1} & F_{12}\tilde{V}_{22}^{-1} \\ \mathbf{0} & \mathbf{0} \end{pmatrix}$$

where $\tilde{V}_{ij}^{-1}$ is block $ij$ in $V^{-1}$. So

$$\mathcal{R}_0 = \rho\left(F_{12}\tilde{V}_{21}^{-1}\right)$$

i.e.,

$$\mathcal{R}_0 = \rho\Bigg(\mathsf{diag}\left(\frac{\partial \Phi_1}{\partial I_1}, \ldots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}}\right)\left(\mathsf{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L\right)^{-1}$$

$$\mathsf{diag}_p(\varepsilon_p)\left(\mathsf{diag}_p(\gamma_p + d_p) - \mathcal{M}^I\right)^{-1}\Bigg)$$

# Local asymptotic stability of the DFE

## Theorem 9

*Define $\mathcal{R}_0$ for the $|\mathcal{P}|$-SLIRS as*

$$\mathcal{R}_0 = \rho\Bigg(\text{diag}\left(\frac{\partial\Phi_1}{\partial I_1},\ldots,\frac{\partial\Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}}\right)\left(\text{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L\right)^{-1}$$

$$\text{diag}_p(\varepsilon_p)\left(\text{diag}_p(\gamma_p + d_p) - \mathcal{M}^I\right)^{-1}\Bigg)$$

*Then the DFE*

$$(\mathbf{S}, \mathbf{L}, \mathbf{I}, \mathbf{R}) = \left((\mathbf{d} - \mathcal{M}^S)^{-1}\mathbf{b}, \mathbf{0}, \mathbf{0}, \mathbf{0}\right)$$

*is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$*

From PvdD & Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Bulletin of Mathematical Biology* **180**(1-2): 29-48 (2002)

# Some remarks about $\mathcal{R}_0$

The expression for $\mathcal{R}_0$ in Theorem 9 is exact

However, unless you consider a very small set of locations, you will not get a closed form expression

Indeed, by Theorem 6(3) and more importantly (often $\mathcal{M}$ is irreducible), Theorem 6(4), the two inverses in $\mathcal{R}_0$ are likely crowded ($\gg 0$ in the irreducible case)

However, numerically, this works easy unless conditioning is bad

# The toy $|\mathcal{P}|$-SLIRS

LAS results for $\mathcal{R}_0 < 1$ can sometimes be strengthened to GAS. One class of models where this works often is when the population is either constant or asymptotically constant and incidence is *standard*

## Theorem 10

*Let $\mathcal{R}_0$ be defined as in Theorem 9 and use proportional incidence $\Phi_p = \beta_p S_p I_p / N_p$. If $\mathcal{R}_0 < 1$, then the DFE of system (16) is globally asymptotically stable*

# $|\mathcal{S}|\,|\mathcal{P}|$-**SLIRS with multiple species**

In the case in which movement is equal for all compartments and there is no disease death, a comparison theorem argument can be used as in Theorem 10 to show that if $\mathcal{R}_0 < 1$, then the DFE of the $|\mathcal{S}|\,|\mathcal{P}|$-SLIRS (14) is globally asymptotically stable.

## Theorem 11

*For system* (14) *with* $|\mathcal{S}|$ *species and* $|\mathcal{P}|$ *locations, with movement equal for all compartments, define* $\mathcal{R}_0$ *appropriately and use proportional incidence. If* $\mathcal{R}_0 < 1$, *then the DFE is globally asymptotically stable*

# Set up parameters

```
pop = c(34.017, 1348.932, 1224.614, 173.593, 93.261) * 1e+06
countries = c("Canada", "China", "India", "Pakistan", "
    Philippines")
T = matrix(data =
              c(0, 1268, 900, 489, 200,
              1274, 0, 678, 859, 150,
              985, 703, 0, 148, 58,
              515, 893, 144, 0, 9,
              209, 174, 90, 2, 0),
          nrow = 5, ncol = 5, byrow = TRUE)
```

# Work out movement matrix

```
p = list()
# Use the approximation explained in Arino & Portet (JMB 2015)
p$M = mat.or.vec(nr = dim(T)[1], nc = dim(T)[2])
for (from in 1:5) {
    for (to in 1:5) {
    p$M[to, from] = -log(1 - T[from, to]/pop[from])
    }
    p$M[from, from] = 0
}
p$M = p$M - diag(colSums(p$M))
```

```
p$P = dim(p$M)[1]
p$eta = rep(0.3, p$P)
p$epsilon = rep((1/1.5), p$P)
p$pi = rep(0.7, p$P)
p$gammaI = rep((1/5), p$P)
p$gammaA = rep((1/3), p$P)
# The desired values for R_0
R_0 = rep(1.5, p$P)
```

# Write down indices of the different state variable types

Save index of state variable types in state variables vector (we have to use a vector and thus, for instance, the name "S" needs to be defined)

```
p$idx_S = 1:p$P
p$idx_L = (p$P+1):(2*p$P)
p$idx_I = (2*p$P+1):(3*p$P)
p$idx_A = (3*p$P+1):(4*p$P)
p$idx_R = (4*p$P+1):(5*p$P)
```

# Set up IC and time

```r
# Set initial conditions. For example, we start with 2
# infectious individuals in Canada.
L0 = mat.or.vec(p$P, 1)
I0 = mat.or.vec(p$P, 1)
A0 = mat.or.vec(p$P, 1)
R0 = mat.or.vec(p$P, 1)
I0[1] = 2
S0 = pop - (L0 + I0 + A0 + R0)
# Vector of initial conditions to be passed to ODE solver.
IC = c(S = S0, L = L0, I = I0, A = A0, R = R0)
# Time span of the simulation (5 years here)
tspan = seq(from = 0, to = 5 * 365.25, by = 0.1)
```

# Set up $\beta$ to avoid blow up

Let us take $\mathcal{R}_0 = 1.5$ for patches in isolation. Solve $\mathcal{R}_0$ for $\beta$

$$\beta = \frac{\mathcal{R}_0}{S(0)} \left( \frac{1 - \pi_p}{\gamma_{Ip}} + \frac{\pi_p \eta_p}{\gamma_{Ap}} \right)^{-1}$$

```
for (i in 1:p$P) {
    p$beta[i] =
        R_0[i] / S0[i] * 1/((1 - p$pi[i])/p$gammaI[i] + p$pi[i] *
    p$eta[i]/p$gammaA[i])
}
```

# Define the vector field

```r
SLIAR_metapop_rhs <- function(t, x, p) {
    with(as.list(p), {
        S = x[idx_S]
        L = x[idx_L]
        I = x[idx_I]
        A = x[idx_A]
        R = x[idx_R]
        N = S + L + I + A + R
        Phi = beta * S * (I + eta * A) / N
        dS = - Phi + MS %*% S
        dL = Phi - epsilon * L + p$ML %*% L
        dI = (1 - pi) * epsilon * L - gammaI * I + MI %*% I
        dA = pi * epsilon * L - gammaA * A + MA %*% A
        dR = gammaI * I + gammaA * A + MR %*% R
        dx = list(c(dS, dL, dI, dA, dR))
        return(dx)
    })
}
```

# And now call the solver

```
# Call the ODE solver
sol <- ode(y = IC,
           times = tspan,
           func = SLIAR_metapop_rhs,
           parms = p,
           method = "ode45")
```

## One little trick (case with demography)

Suppose demographic EP is $\mathbf{N}^\star = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$

Want to maintain $\mathbf{N}(t) = \mathbf{N}^\star$ for all $t$ to ignore convergence to demographic EP. Think in terms of $\mathbf{b}$:

$$\mathbf{N}' = 0 \iff \mathbf{b} - \mathbf{d}\mathbf{N} + \mathcal{M}\mathbf{N} = 0 \iff \mathbf{b} = (\mathbf{d} - \mathcal{M})\mathbf{N}$$

So take $\mathbf{b} = (\mathbf{d} - \mathcal{M})\mathbf{N}^\star$

Then

$$\mathbf{N}' = (\mathbf{d} - \mathcal{M})\mathbf{N}^\star - \mathbf{d}\mathbf{N} + \mathcal{M}\mathbf{N}$$

and thus if $\mathbf{N}(0) = \mathbf{N}^\star$, then $\mathbf{N}'(0) = 0$ and thus $\mathbf{N}' = 0$ for all $t \geq 0$, i.e., $\mathbf{N}(t) = \mathbf{N}^\star$ for all $t \geq 0$

# Word of warning about that trick, though..

$$\mathbf{b} = (\mathbf{d} - \mathcal{M})\mathbf{N}^\star$$

$\mathbf{d} - \mathcal{M}$ has nonnegative (typically positive) diagonal entries and nonpositive off-diagonal entries

Easy to think of situations where the diagonal will be dominated by the off-diagonal, so $\mathbf{b}$ could have negative entries

$\implies$ use this for numerics, not for the mathematical analysis

A brief history of metapopulations

The general context

Diseases in metapopulations

Computational considerations

A few FMD models
   Ringa & Bauch

CrossMark

# Dynamics and control of foot-and-mouth disease in endemic countries: A pair approximation model

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HIGHLIGHTS

- Traditional models of FMD focus on control and dynamics in disease-free settings.
- We analyze long-term dynamics and control of FMD in endemic countries.
- Success of vaccination depends on rates of vaccine and natural immunity waning.
- Prophylactic vaccination performs better that ring vaccination.
- More mathematical models applicable to FMD-endemic countries need to be developed.

# An analysis of foot-and-mouth-disease epidemics in the UK

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# A model à la Levin

Space is implicit: count infected herds

# Chapter 13

# Mathematical Models of the Epidemiology and Control of Foot-and-Mouth Disease

Mark E. J. Woolhouse

ELSEVIER

# Highly pathogenic avian influenza H5N8 in south-west France 2016–2017: A modeling study of control strategies

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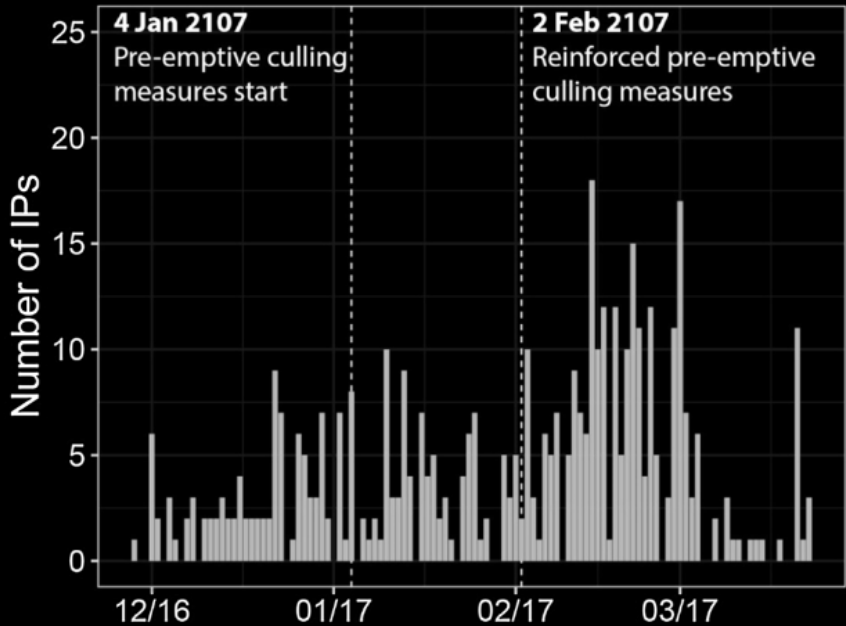[e] *IHAP, Université de Toulouse, INRA, ENVT, Toulouse, France*

Fig. 1. Epidemic curve. Daily number of IPs by date of suspicion.

# Conclusion