

# Adding space to FMD and AI models

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April 2023

- ▶ We now consider spatial spread

A brief history of metapopulations

Metapopulations à la Levins

Metapopulations with explicit movement

The general context

Diseases in metapopulations

Computational considerations

A few FMD models

# 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

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# 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  $P$ :

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

$\beta$  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  $\dot{x}_p = f_p(x_p)$ , where  $x_p \in \mathbb{R}_+^{n_p}$  and  $f_p : \mathbb{R}_+^{n_p} \rightarrow \mathbb{R}_+^{n_p}$
- ▶ 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  $g_p : \mathbb{R}^{n_p} \times \mathbb{R}^{n_q} \rightarrow \mathbb{R}^{n_p}$

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

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

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# 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

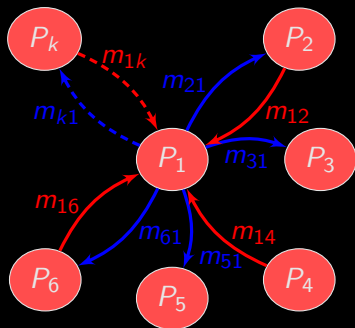
Split continuous space into  $N$  discrete geographical locations (*patches*)

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  $p = 1, \dots, N$  to location  $q = 1, \dots, N$

# 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

$$P'_1 = \sum_{j=1}^N m_{1j} P_j \text{ assuming } m_{11} = - \sum_{\substack{j=1 \\ j \neq 1}}^N m_{j1}$$

## 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

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# 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  $\mathcal{G}_c$

# Strong 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  $i, j = 1, \dots, n$ , 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  $\mathcal{C}_c$

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# Notation

- ▶  $N_{cp}(t)$  number of individuals of compartment  $c$  in location  $p$  at time  $t$
- ▶  $N_c = (N_{c1}, \dots, N_{c|\mathcal{P}|})^T$  distribution of individuals of compartment  $c \in \mathcal{C}$  among the different locations
- ▶  $N^p = (N_1^p, \dots, N_{|\mathcal{P}|}^p)^T$  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

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

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

$$m_{cpp} = - \sum_{\substack{q \in \mathcal{P} \\ q \neq p}} m_{cq p} \quad (3)$$

Then

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



# Vector form of the system

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

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

with

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

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# 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  $m_{ij} > 0 \forall i, j = 1, \dots, n$ . 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**
- ▶  $s(M) = \max_{\lambda \in \sigma(M)} \{\operatorname{Re}(\lambda)\}$  **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

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

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  $(D - \mathcal{M})^{-1} \gg \mathbf{0}$

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# Behaviour of the mobility component

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

$$N'_c = \mathcal{M}_c N_c \quad (7)$$

## 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*

$$\lim_{t \rightarrow \infty} N_c(t) = N_c^* \gg 0$$

Note that  $N_c^*$  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 possible to obtain, in each location  $p \in \mathcal{P}$ , an equation for the evolution of the total population that takes the form

$$T'_p = D_p(T_p) + \sum_{c \in \mathcal{C}} \sum_{q \in \mathcal{P}} m_{cpq} N_{cq} \quad (8)$$

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

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

where

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

# 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

$$\begin{aligned}\mathbf{T}' &= \mathbf{b} - \mathbf{d}\mathbf{T} + \mathcal{M} \sum_{c \in \mathcal{C}} \mathbf{N}_c \\ &= \mathbf{b} - \mathbf{d}\mathbf{T} + \mathcal{M}\mathbf{T}\end{aligned}\tag{11}$$

# Equilibria

$$\mathbf{T}' = \mathbf{0} \Leftrightarrow \mathbf{b} - \mathbf{d}\mathbf{T} + \mathcal{M}\mathbf{T} = \mathbf{0}$$

$$\Leftrightarrow (\mathbf{d} - \mathcal{M})\mathbf{T} = \mathbf{b}$$

$$\Leftrightarrow \mathbf{T}^* = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$$

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  $\mathbf{T}^* = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$  unique

# Behaviour of the total population

Equal irreducible movement case

$\mathbf{T}^* = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$  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  $\rightarrow \mathbf{T}^* \gg 0$  (provided  $\mathbf{b} > \mathbf{0}$ , of course)

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- A few sample models

- Existence of a DFE

- Computation of a reproduction number

- Global stability of the DFE when  $\mathcal{R}_0 < 1$

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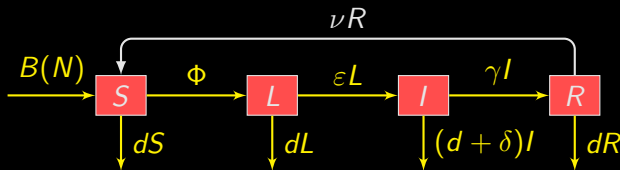
Computation of a reproduction number

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# The toy SLIRS model in patches



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

$$L' = \Phi - (\varepsilon + d)L \quad (12b)$$

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

$$R' = \gamma I - (\nu + d)R \quad (12d)$$

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

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

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

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

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

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

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

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

with incidence

$$\Phi_p = \beta_p \frac{S_p I_p}{N_p^{q_p}}, \quad q_p \in \{0, 1\} \quad (13e)$$

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

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

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

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

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

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

with incidence

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

- ▶ 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)

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

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

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

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

with incidence

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

- ▶ 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  $\mathcal{B}_p(N_p) = \mathcal{B}_p$

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

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

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

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

with incidence

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

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 from now on: existence and uniqueness

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A few FMD models

# 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

$$0 = \mathcal{B}_p - d_p S_p + \nu_p R_p + \sum_{q \in \mathcal{P}} m_{Spq} S_q$$

$$0 = -(\nu_p + d_p) R_p + \sum_{q \in \mathcal{P}} m_{Rpq} R_q$$

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:

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

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

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:

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

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

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

$\implies$  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  $\mathbf{b} - \mathbf{d}\mathbf{S} + \mathcal{M}^S\mathbf{S} = \mathbf{0}$ , 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

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

## 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

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

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

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

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



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

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

Note that

$$\frac{\partial \Phi_p}{\partial L_k} = \frac{\partial \Phi_p}{\partial I_k} = 0$$

whenever  $k \neq p$ , so

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

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

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

- ▶  $\frac{\partial \Phi_p}{\partial L_p} = 0$
- ▶  $\frac{\partial \Phi_p}{\partial I_p} = \beta_p S_p$

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

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

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

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

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

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

where  $\text{diag}_p(z_p) := \text{diag}(z_1, \dots, z_{|P|})$

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

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

where

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

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

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.,

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

# Local asymptotic stability of the DFE

## Theorem 9

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

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

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

A brief history of metapopulations

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# 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*

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# 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

```
# 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

```
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  $\mathbf{N}^* = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$

Want to maintain  $\mathbf{N}(t) = \mathbf{N}^*$  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  $\mathbf{b} = (\mathbf{d} - \mathcal{M})\mathbf{N}^*$

Then

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

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

# Word of warning about that trick, though..

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

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

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# 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 than ring vaccination.
- More mathematical models applicable to FMD-endemic countries need to be developed.



*IMA Journal of Mathematics Applied in Medicine & Biology* (1997) **14**, 1–9

## **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

From: Foot-and-Mouth Disease: Current Perspectives. Edited by: Francisco Sobrino and Esteban Domingo

## **Chapter 13**

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

Mark E. J. Woolhouse

# Conclusion