Metapopulation models and a few advanced models

Populate Summer School – Course 02

Julien Arino
Department of Mathematics @ University of Manitoba
Maud Menten Institute @ PIMS
julien.arino@umanitoba.ca

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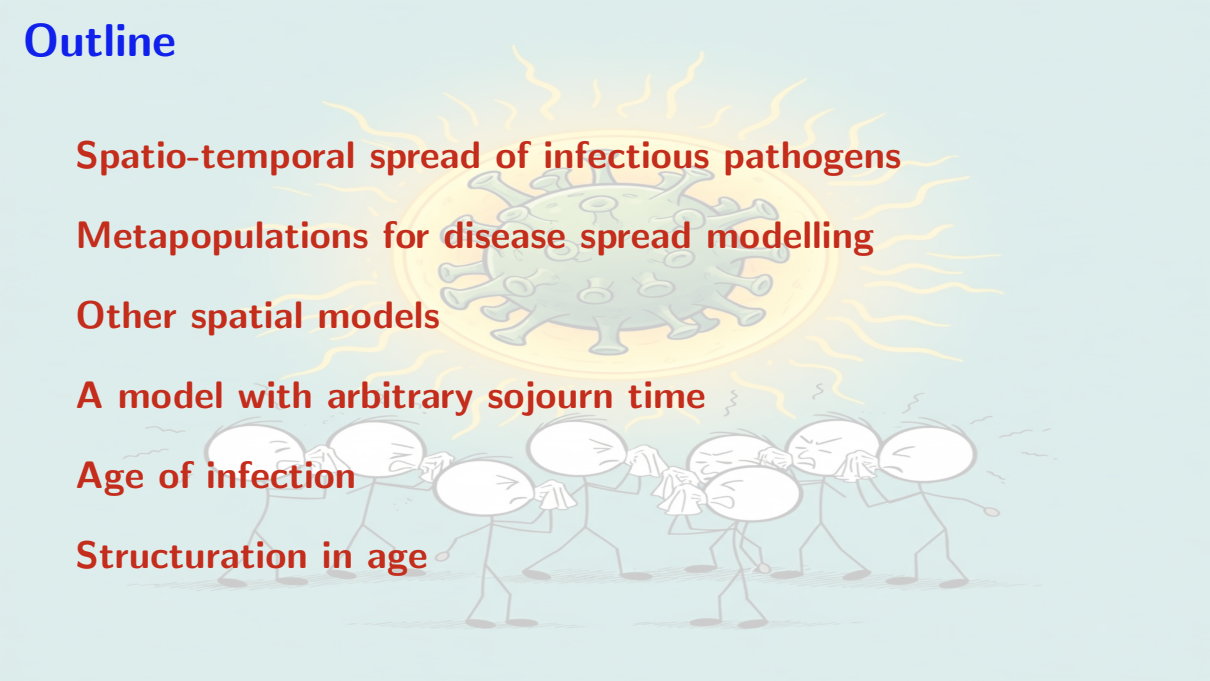
The University of Manitoba campuses are located on original lands of Anishinaabeg, Ininew, Anisininew, Dakota and Dene peoples, and on the National Homeland of the Red River Métis.
We respect the Treaties that were made on these territories, we acknowledge the harms and mistakes of the past, and we dedicate ourselves to move forward in partnership with Indigenous communities in a spirit of Reconciliation and collaboration.

Outline



Spatio-temporal spread of infectious pathogens

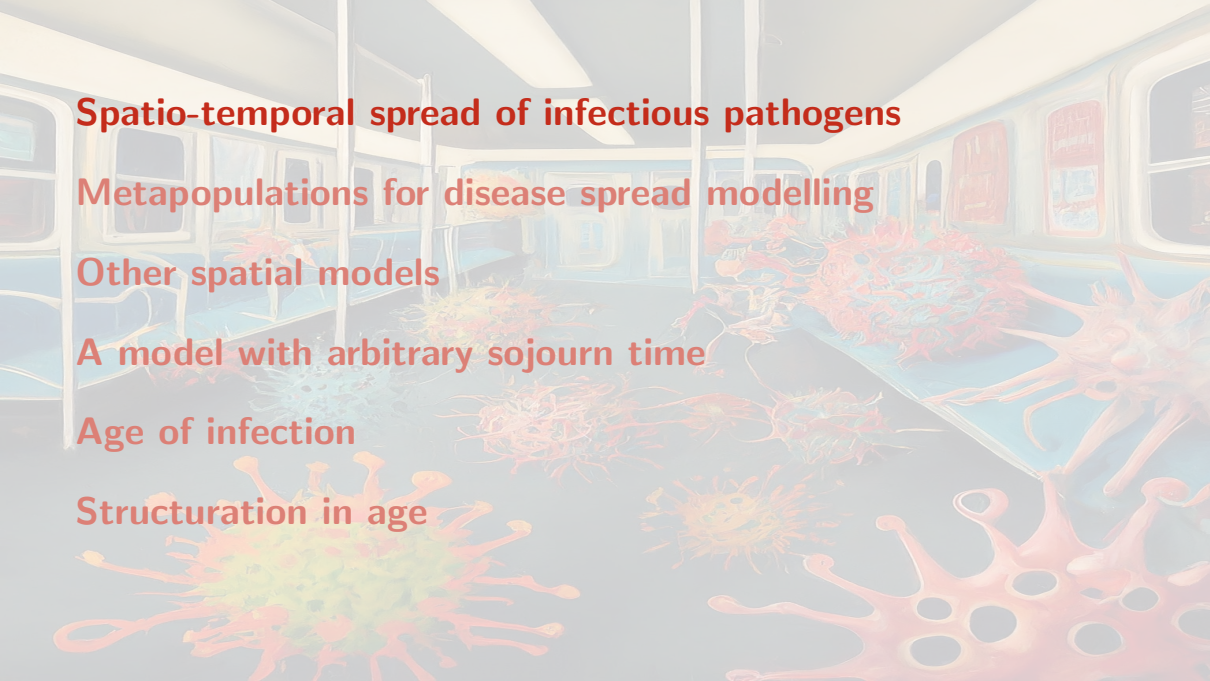
Metapopulations for disease spread modelling

Other spatial models

A model with arbitrary sojourn time

Age of infection

Structuration in age



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Diseases have been known to be mobile for a while

The plague of Athens of 430 BCE

It first began, it is said, in the parts of Ethiopia above Egypt, and thence descended into Egypt and Libya and into most of the [Persian] King's country. Suddenly falling upon Athens, it first attacked the population in Piraeus [..] and afterwards appeared in the upper city, when the deaths became much more frequent.

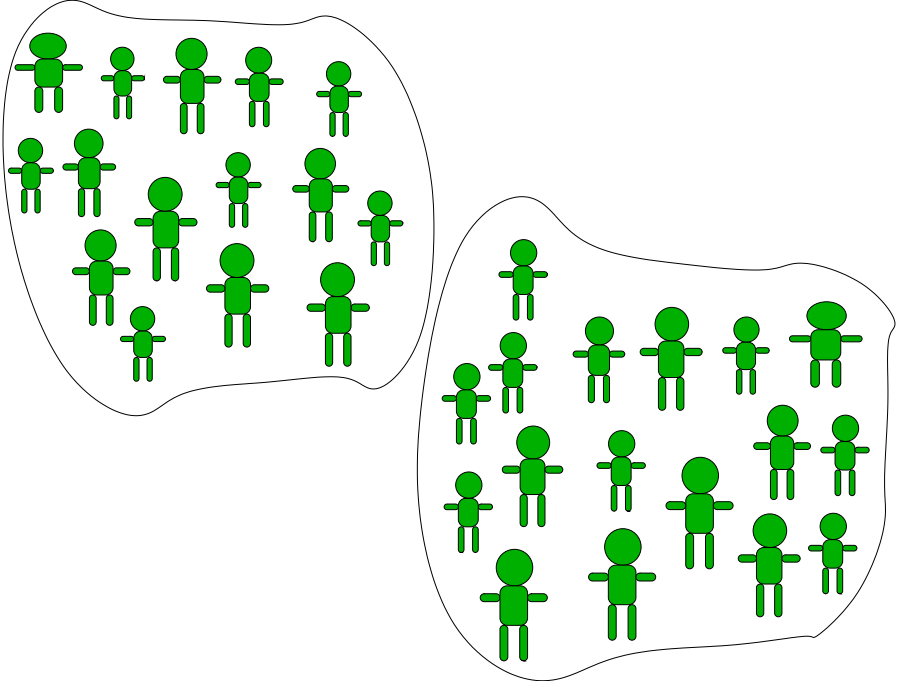
Thucydides (c. 460 BCE - c. 395 BCE)
History of the Peloponnesian War

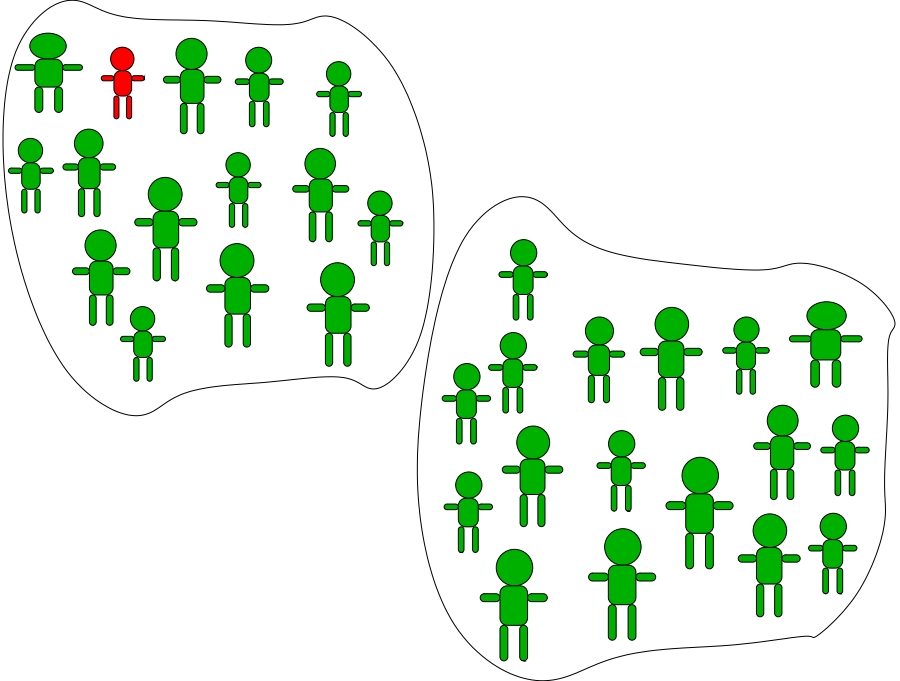
How infectious pathogens become mobile

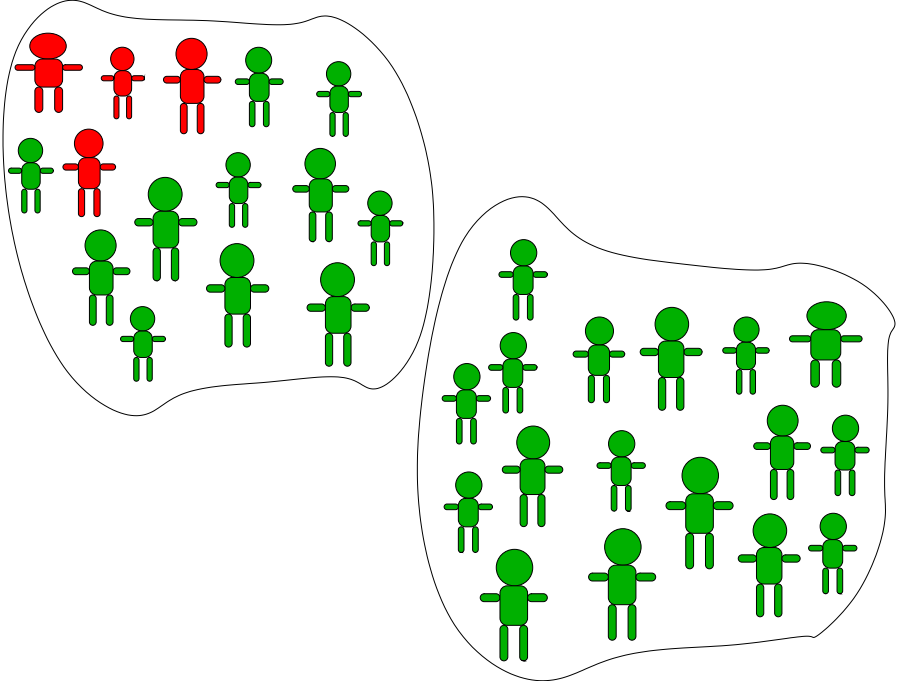
- I used to show the following set of figures to illustrate the spatialisation of spread

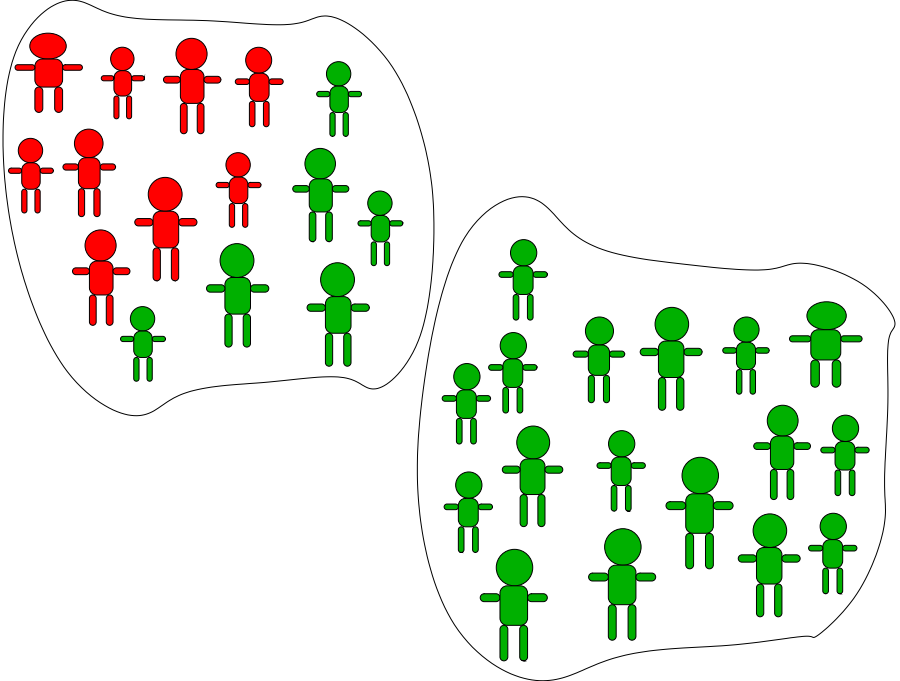
- I tried to get Gemini to do the same but the "returning home" part was not working at all

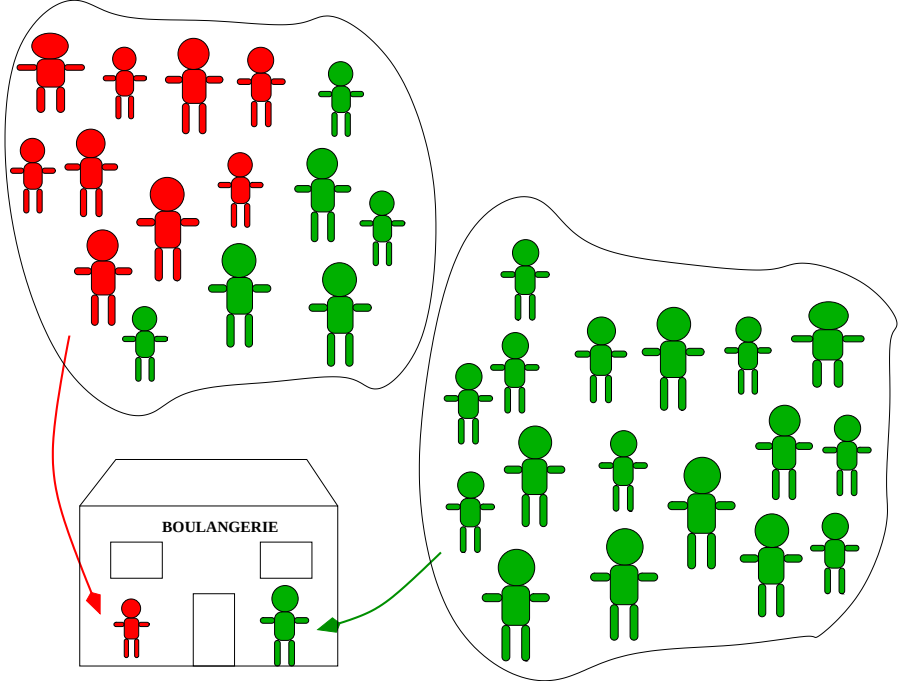
- So enjoy my fantastic skills instead







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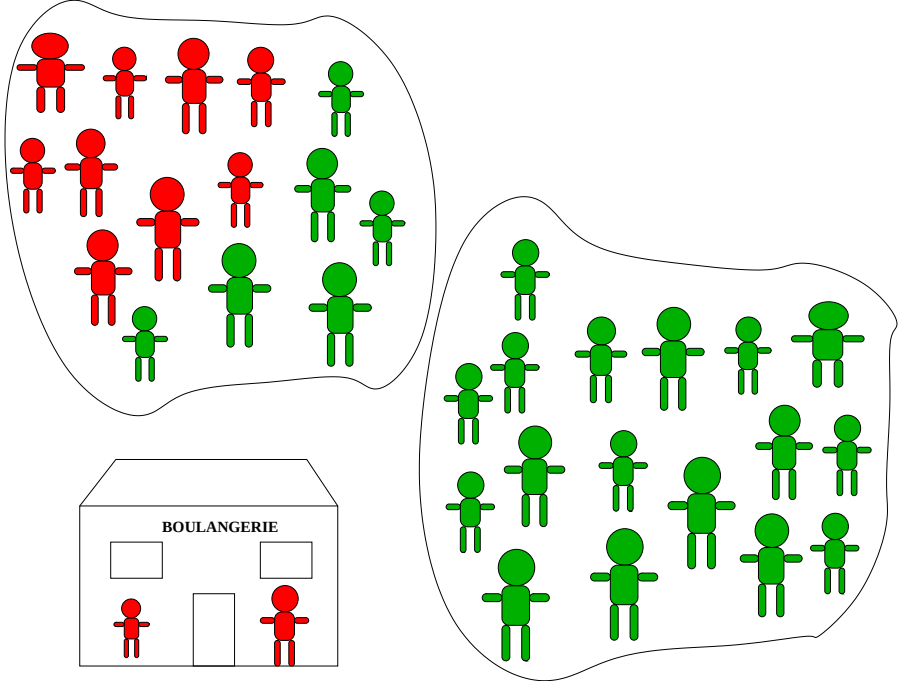
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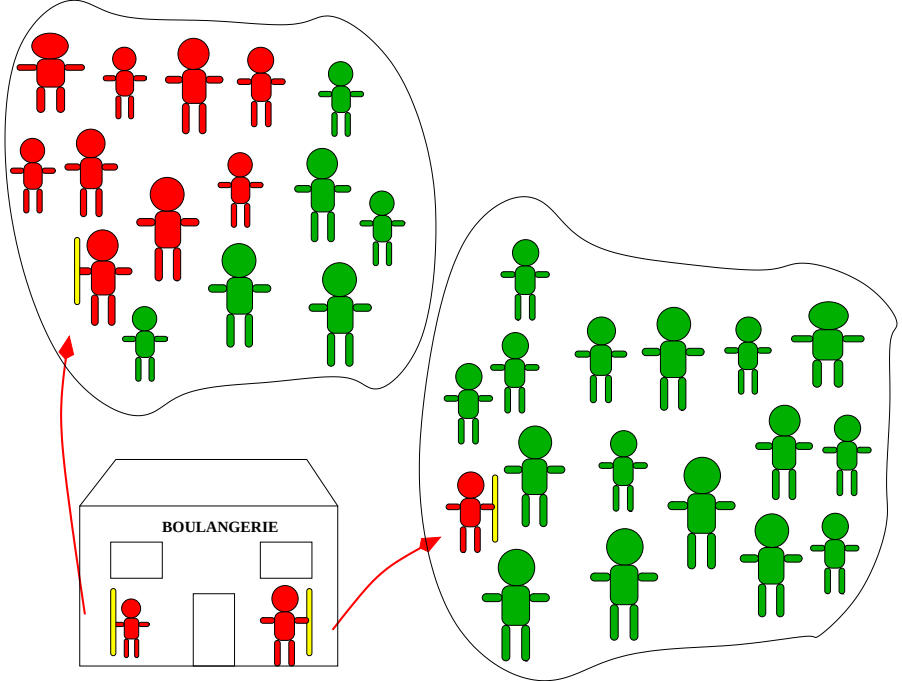
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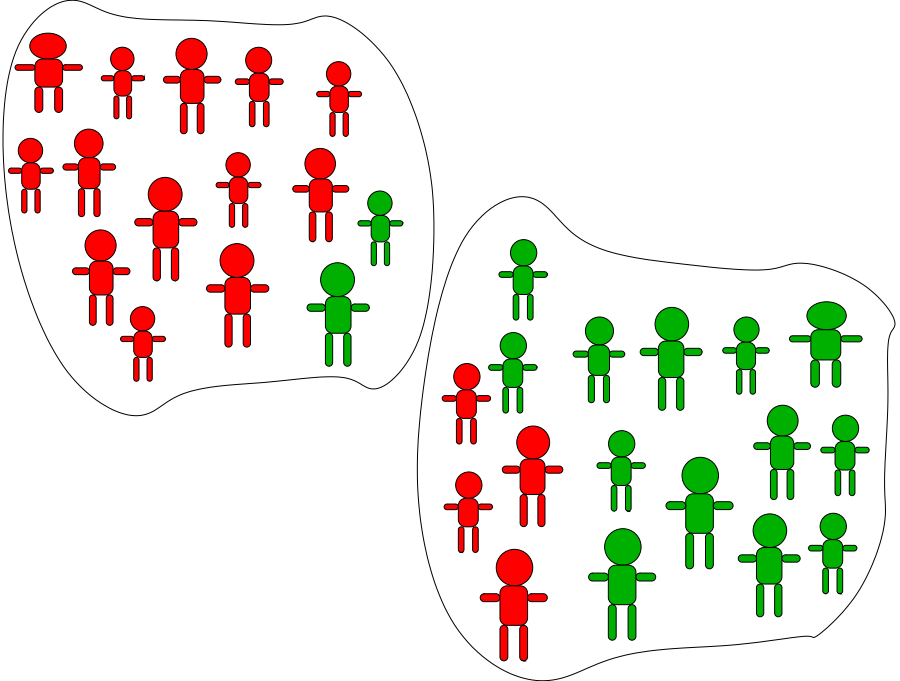
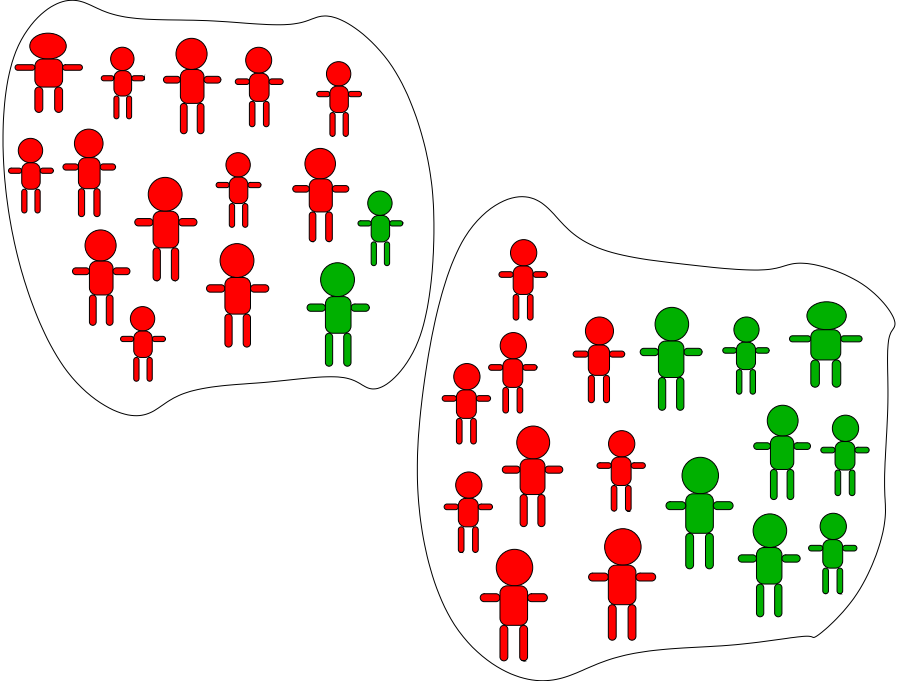
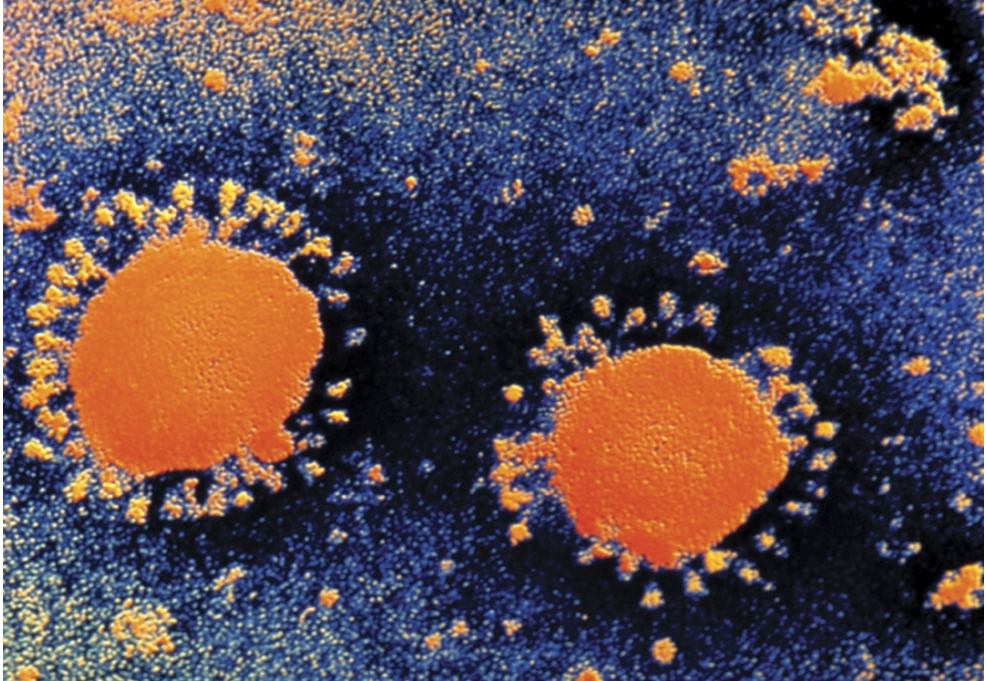




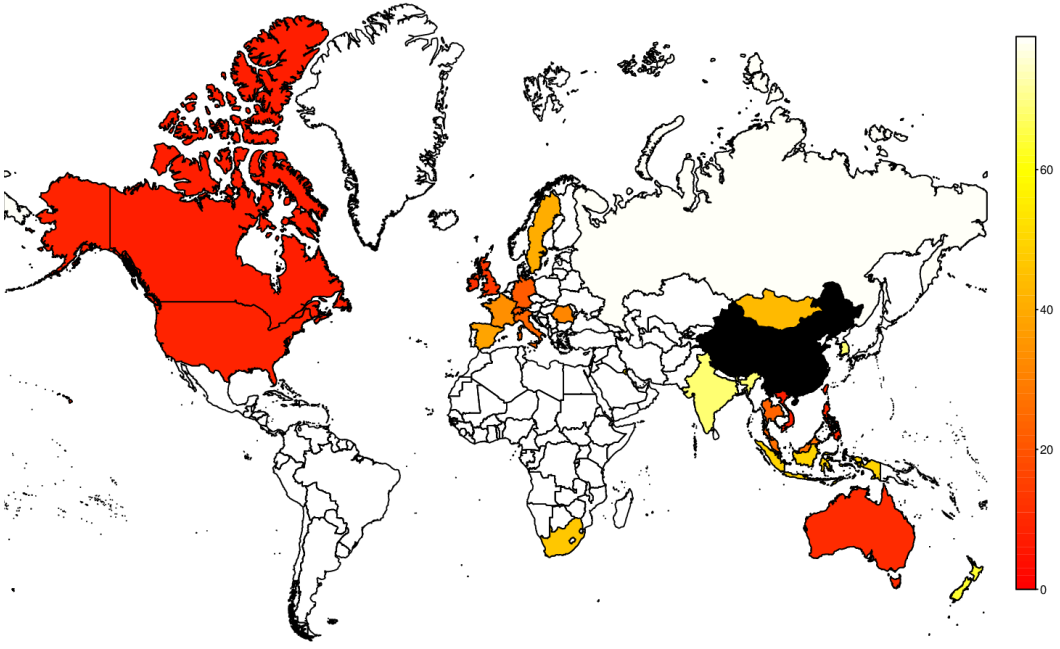
So...

- Bakery-driven pathogen spread

- Joke aside, let's consider two examples



Countries with SARS cases (WHO/Dec 2003)

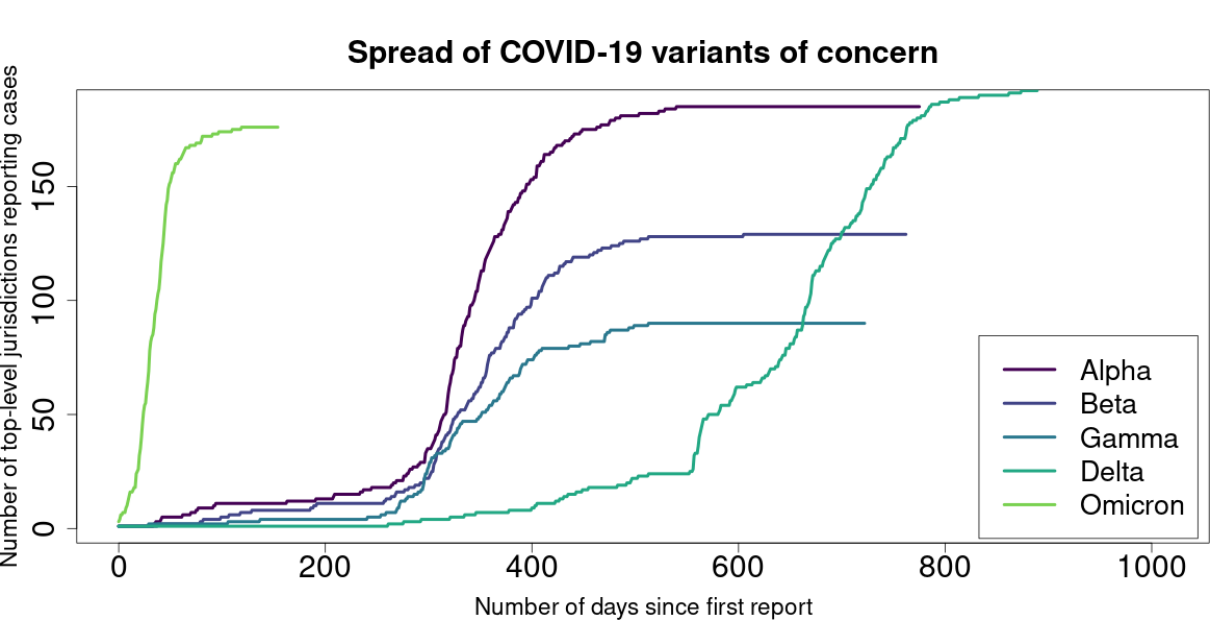


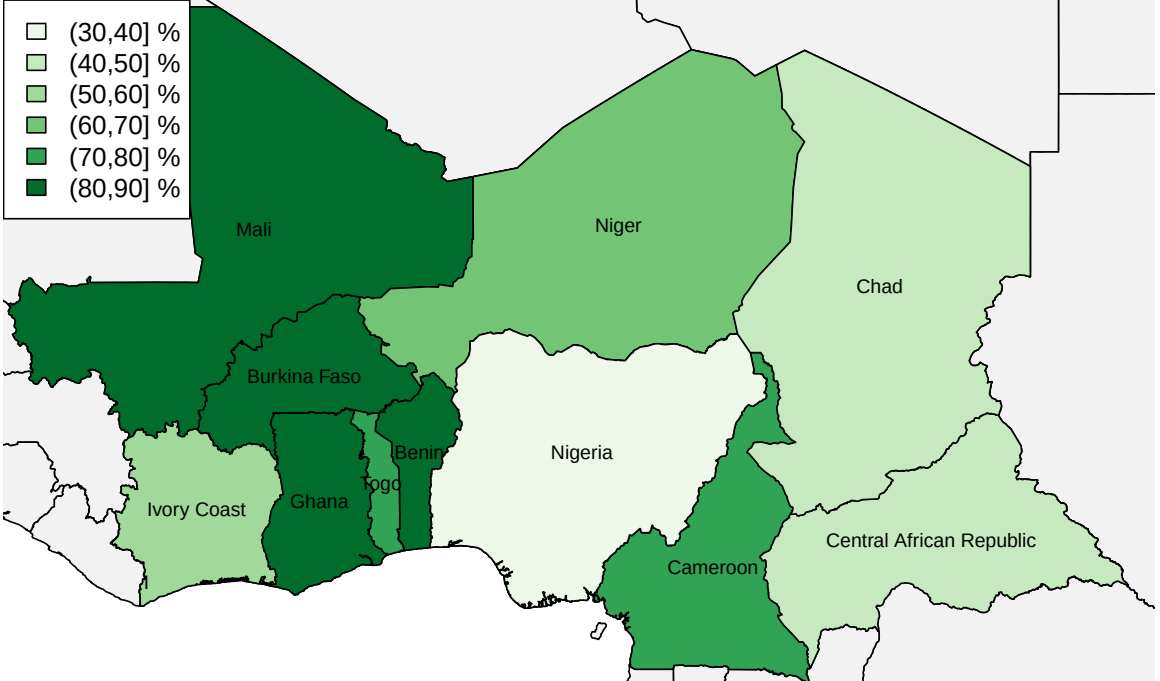
Spatial spread of pH1N1 in 2009

In March and April 2008 (used as surrogate for 2009 data),

- 2.35 million passengers flew from MX to 1018 cities in 164 countries
- 80.7% flew to US and Canada, 8.8% South and Central America, 8.7% Europe
- of 20 countries with highest volumes of passengers arriving from MX, 16 had confirmed importations from MX on 5/25
- ROC curve of relationship between international air-traffic flows and H1N1 importation: countries receiving more than 1400 passengers from MX at significantly elevated risk for importation
- Use this passenger threshold: international air-traffic volume $>$ 92% sensitive and $>$ 92% specific in predicting importation (area under ROC curve 0.97)

Khan, JA, Hu et al, New England Journal of Medicine, 2009


Spread of COVID-19 variants of concern
Number of top-level jurisdictions reporting cases
0
50
100
150
0
200
400
600
800
1000
Number of days since first report
Alpha
Beta
Gamma
Delta
Omicron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Ghana
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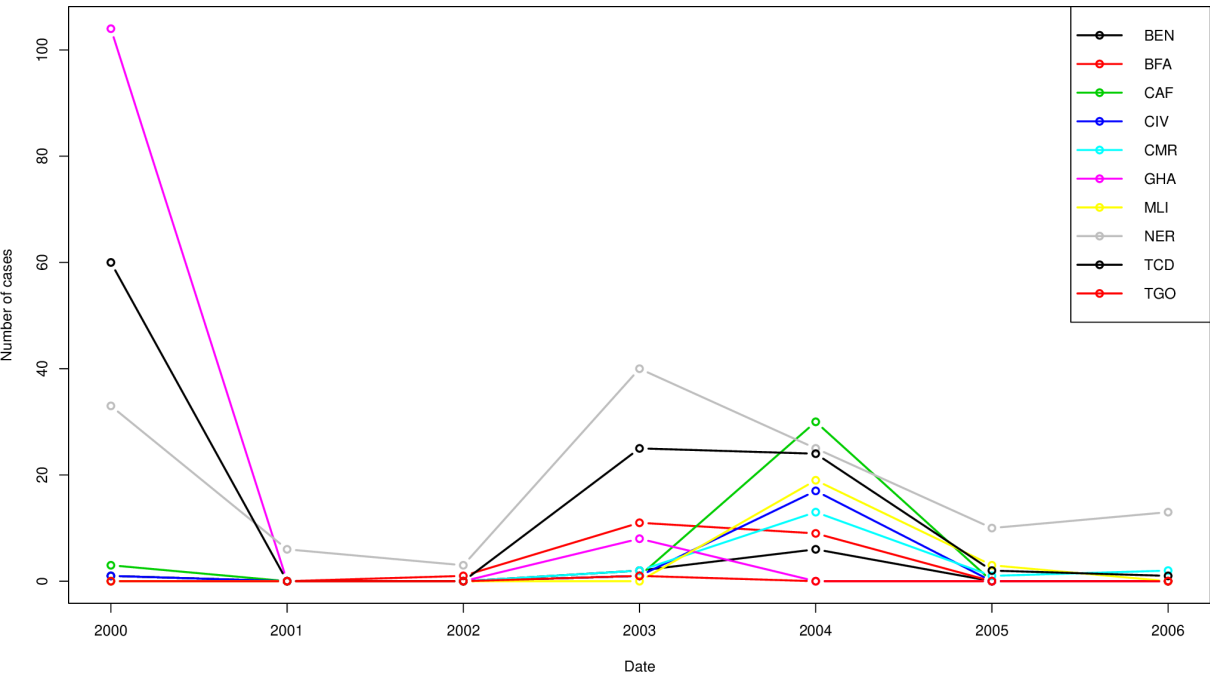
Cameroon
Central African Republic


BEN
BFA
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CIV
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GHA
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Number of cases
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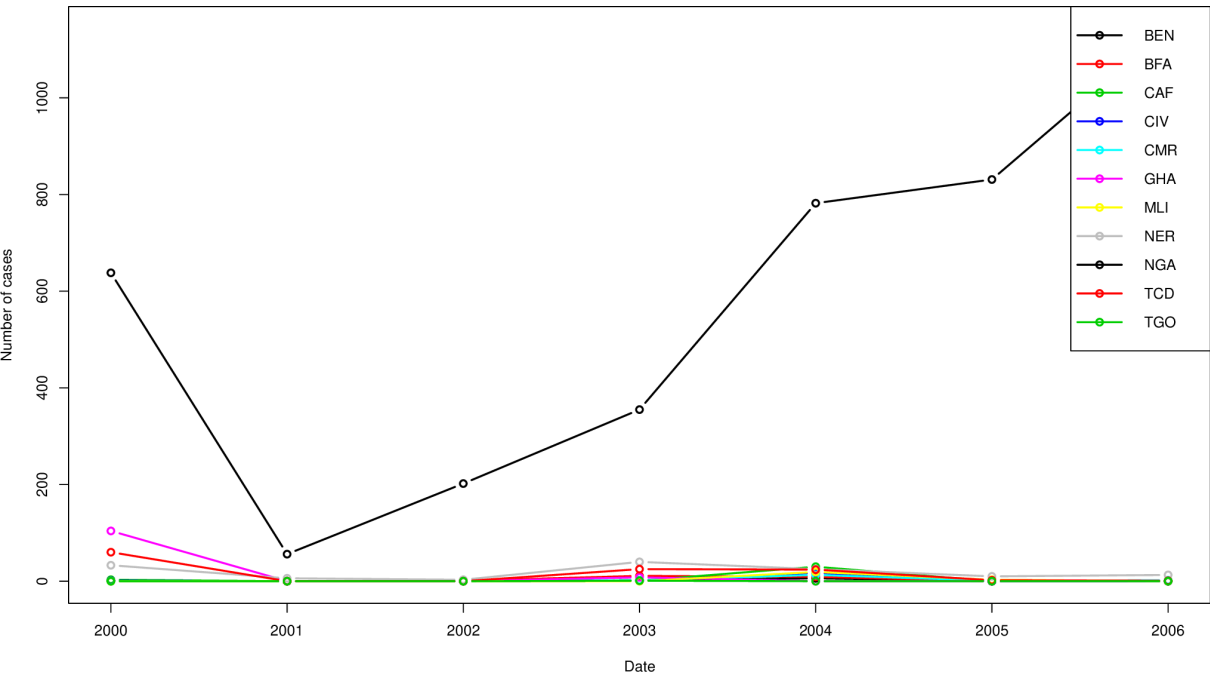
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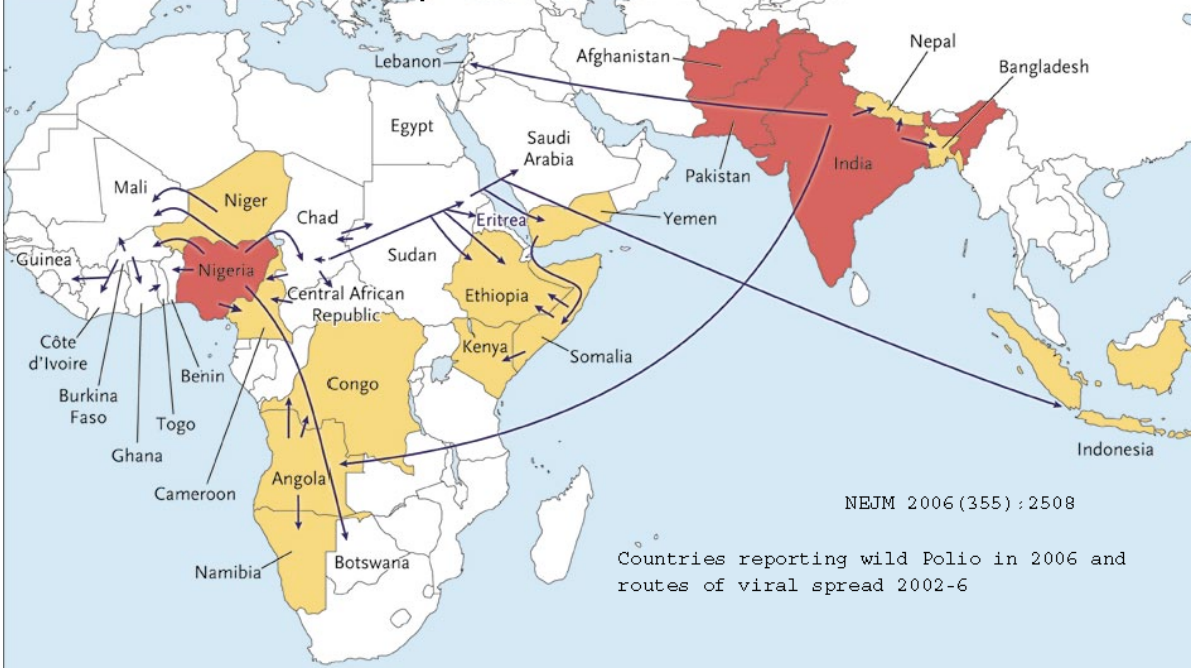
Lebanon
Afghanistan
Nepal
Bangladesh
Egypt
Saudi Arabia
Pakistan
India
Mali
Niger
Chad
Eritrea
Yemen
Guinea
Nigeria
Sudan
Central African Republic
Ethiopia
Kenya
Somalia
Côte d'Ivoire
Burkina Faso
Benin
Togo
Ghana
Congo
Cameroon
Angola
Namibia
Botswana
Indonesia
NEJM 2006(355):2508
Countries reporting wild Polio in 2006 and routes of viral spread 2002-6

In a globalised world

- Public health policy decisions are taken at the jurisdictional level, typically national (ISO 3166-1) or first-level sub-national (ISO 3166-2) – extremely rarely supra-nationally

(International Health Regulations (IHR) define processes regarding reporting of disease outbreaks, make recommendations about handling of travellers, etc. See COVID-19: even those of the rules that were somewhat prescriptive were not followed)

- Individuals are mobile and thus so are the pathogens they harbour

- Policy decisions have consequences outside the jurisdictions where they are taken!

- COVID-19 was a single outbreak, not one outbreak per country it affected

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Metapopulations for disease spread modelling

Why use metapopulation models?

Metapopulations with explicit movement

The graph setting

The models considered

Going to vector form

The movement matrix

Behaviour of the mobility component

Existence of a DFE

Computation of a reproduction number

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

Metapopulation-specific problems

Computational aspects of metapopulation models

Why use metapopulations for disease models?

- Appropriate for the description of spatial spread of some diseases
- Ease of simulation
- Aggregation of data by governments is most often done at the jurisdictional level, very easy to reconcile with locations in metapopulations

A few pointers

- JA & PvdD. Disease spread in metapopulations. *Fields Institute Communications* **48**:1-13 (2006)
- JA. Diseases in metapopulations. In *Modeling and Dynamics of Infectious Diseases*, World Scientific (2009)
- JA. Spatio-temporal spread of infectious pathogens of humans. *Infectious Disease Modelling* **2**(2):218-228 (2017)
- JA, Bajeux & Kirkland. Number of source patches required for population persistence in a source-sink metapopulation. *Bulletin of Mathematical Biology* **81**: 1916–1942 (2019)

Metapopulations for disease spread modelling

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- **Metapopulations with explicit movement**
- The graph setting
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Metapopulations with explicit movement

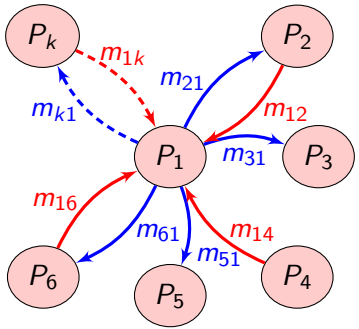
Split continuous space into N discrete geographical locations (*ptatches*)

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

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

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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

Srong connectedness and irreducibility

Definition 1 (Reducible/irreducible matrix)

A matrix A is **reducible** if there exists a permutation matrix P such that $P^T AP$ 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 2

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

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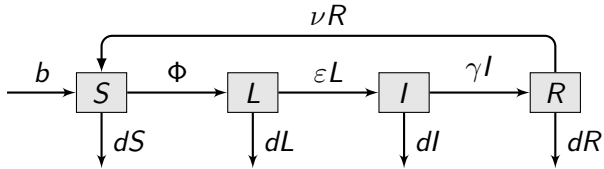
The prototype SLIRS used in patches



$$S' = b + \nu R - \Phi - dS \tag{1a}$$
$$L' = \Phi - (\varepsilon + d)L \tag{1b}$$
$$I' = \varepsilon L - (\gamma + d)I \tag{1c}$$
$$R' = \gamma I - (\nu + d)R \tag{1d}$$

Φ 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

$$S'_p = b_p + \nu_p R_p - \Phi_p - d_p S_p + \sum_{q\in\mathcal{P}} m_{Spq} S_q \tag{2a}$$

$$L'_p = \Phi_p - (\varepsilon_p + d_p)\, L_p + \sum_{q\in\mathcal{P}} m_{Lpq} L_q \tag{2b}$$

$$I'_p = \varepsilon_p L_p - (\gamma_p + d_p) I_p + \sum_{q\in\mathcal{P}} m_{Ipq} I_q \tag{2c}$$

$$R'_p = \gamma_p I_p - (\nu_p + d_p)\, R_p + \sum_{q\in\mathcal{P}} m_{Rpq} R_q \tag{2d}$$

with incidence

$$\Phi_p = \beta_p \frac{S_p I_p}{N_p^{q_p}}, \qquad q_p \in \{0, 1\} \tag{2e}$$

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

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

$$S'_{sp} = b_p + \nu_{sp} R_{sp} - \Phi_{sp} - d_{sp} S_{sp} + \sum_{q \in \mathcal{P}} m_{Sspq} S_{sq} \tag{3a}$$

$$L'_{sp} = \Phi_{sp} - (\varepsilon_{sp} + d_{sp}) L_{sp} + \sum_{q \in \mathcal{P}} m_{Lspq} L_{sq} \tag{3b}$$

$$I'_{sp} = \varepsilon_{sp} L_{sp} - (\gamma_{sp} + d_{sp}) I_{sp} + \sum_{q \in \mathcal{P}} m_{Ispq} I_{sq} \tag{3c}$$

$$R_{sp} = \gamma_{sp} I_{sp} - (\nu_{sp} + d_{sp}) R_{sp} + \sum_{q \in \mathcal{P}} m_{Rspq} R_{sq} \tag{3d}$$

with incidence

$$\Phi_{sp} = \sum_{k \in \mathcal{S}} \beta_{skp} \frac{S_{sp} I_{kp}}{N_p^{q_p}}, \qquad q_p \in \{0, 1\} \tag{3e}$$

- 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) [Arino et al., 2007]

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

$$S'_{pq} = b_p + \nu_{pq} R_{pq} - \Phi_{pq} - d_{pq} S_{pq} + \sum_{k \in \mathcal{P}} m_{Spqk} S_{pk} \tag{4a}$$

$$L'_{pq} = \Phi_{pq} - (\varepsilon_{pq} + d_{pq}) L_{pq} + \sum_{k \in \mathcal{P}} m_{Lpqk} L_{pk} \tag{4b}$$

$$I'_{pq} = \varepsilon_{pq} L_{pq} - (\gamma_{pq} + d_{pq}) I_{pq} + \sum_{k \in \mathcal{P}} m_{Ipqk} I_{pk} \tag{4c}$$

$$R'_{pq} = \gamma_{pq} I_{pq} - (\nu_{pq} + d_{pq}) R_{pq} + \sum_{k \in \mathcal{P}} m_{Rpqk} R_{pk} \tag{4d}$$

with incidence

$$\Phi_{pq} = \sum_{k \in \mathcal{P}} \beta_{pqk} \frac{S_{pq} I_{kq}}{N_p^{q_q}}, \qquad q_q = \{0, 1\} \tag{4e}$$

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

$$S'_p = b_p - \Phi_p - d_p S_p + \nu_p R_p + \sum_{q\in\mathcal{P}} m_{Spq} S_q \tag{5a}$$
$$L'_p = \Phi_p - (\varepsilon_p + d_p)\, L_p + \sum_{q\in\mathcal{P}} m_{Lpq} L_q \tag{5b}$$
$$I'_p = \varepsilon_p L_p - (\gamma_p + d_p) I_p + \sum_{q\in\mathcal{P}} m_{Ipq} I_q \tag{5c}$$
$$R'_p = \gamma_p I_p - (\nu_p + d_p)\, R_p + \sum_{q\in\mathcal{P}} m_{Rpq} R_q \tag{5d}$$

with incidence

$$\Phi_p = \beta_p S_p I_p \tag{5e}$$

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

$\Longrightarrow$ Good case of large-scale system

(matrix analysis is your friend)

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Notation

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

  (Here and elsewhere: omit dependence on t unless it causes confusion)

- $\boldsymbol{X}_c = \left(X_{c1}, \ldots, X_{c|\mathcal{P}|}\right)^T$ distribution of individuals of compartment $c \in \mathcal{C}$ among the different locations
  [E.g., for (5), $\boldsymbol{X}_S = (S_1, \ldots, S_{|\mathcal{P}|})^T$]

- $\boldsymbol{X}^p = \left(X_1^p, \ldots, X_{|\mathcal{P}|}^p\right)^T$ composition of the population in location $p \in \mathcal{P}$
  [E.g., for (5), $\boldsymbol{X}^p = (S_p, L_p, I_p, R_p)^T$]

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 $p \in \mathcal{P}$

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

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

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

more compact, denote the rate of leaving location p as

$$m_{cpp} = - \sum_{\substack{q \in \mathcal{P} \\ q \neq p}} m_{cqp} \tag{6}$$

Then

$$X'_{cp} = f_{cp}(\boldsymbol{X}^p) + \sum_{q \in \mathcal{P}} m_{cpq} X_{cq} \tag{7}$$

Vector form of the system

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

$$\boldsymbol{X}_c' = f(\boldsymbol{X}) + \mathcal{M}_c \boldsymbol{X}_c \tag{8}$$

with

$$\mathcal{M}_c = \begin{pmatrix} -\sum_{k \in \mathcal{P}} m_{ck1} & m_{c12} & \cdots & m_{c1|\mathcal{P}|} \\ & & & \\ m_{c|\mathcal{P}|1} & m_{c|\mathcal{P}|2} & \cdots & -\sum_{k \in \mathcal{P}} m_{ck|\mathcal{P}|} \end{pmatrix} \tag{9}$$

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- **The movement matrix**
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- Existence of a DFE
- Computation of a reproduction number
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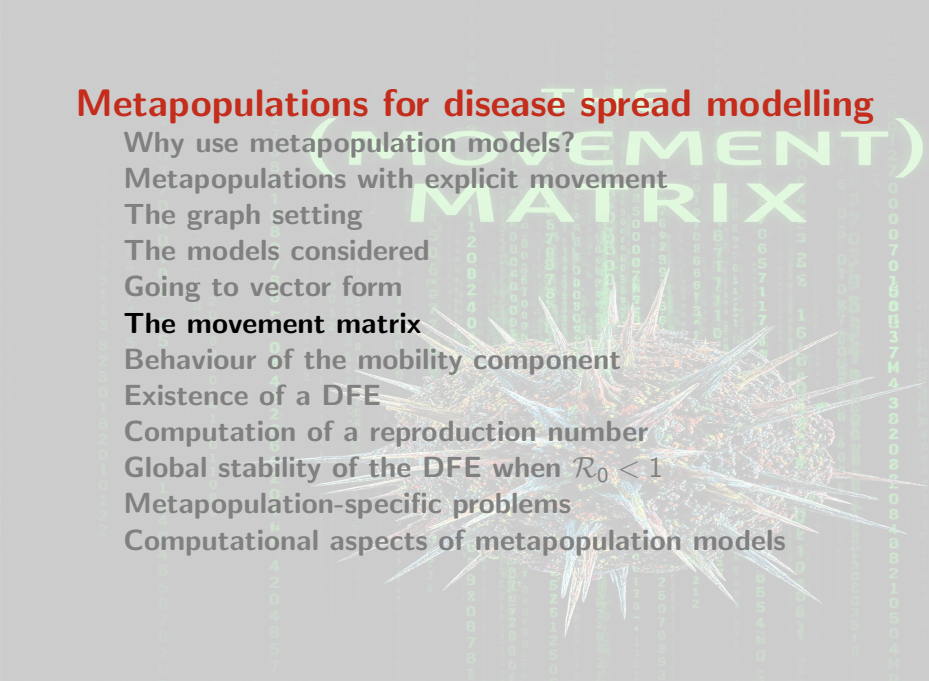

Definitions and notation for matrices

- $M \in \mathbb{R}^{n \times n}$ 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 $m_{ij} > 0$ $\forall i, j = 1, \ldots, n$. 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

$$\mathcal{M}_c = \begin{pmatrix} -\sum_{k\in\mathcal{P}} m_{ck1} & m_{c12} & \cdots & m_{c1|\mathcal{P}|} \\ & & & \\ m_{c|\mathcal{P}|1} & m_{c|\mathcal{P}|2} & \cdots & -\sum_{k\in\mathcal{P}} m_{ck|\mathcal{P}|} \end{pmatrix} \tag{9}$$

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 weighted Laplacian matrix (using out-degrees)

Lemma 3

1. $0 \in \sigma(\mathcal{M})$ *corresponding to left e.v.* $\mathbb{1}^T$ *[σ 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 3 and Proposition 4 (next page), see Arino, Bajeux & Kirkland, BMB 2019

Proposition 4 (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* $\boldsymbol{v} > \mathbf{0}$. *If* $\mathcal{M}$ *irreducible,* $s(\mathcal{M} + D)$ *has multiplicity 1 and is associated to* $\boldsymbol{v} \gg \mathbf{0}$
3. *If* $\mathrm{diag}(D) \gg \mathbf{0}$, *then* $D - \mathcal{M}$ *invertible M-matrix and* $(D - \mathcal{M})^{-1} > \mathbf{0}$
4. $\mathcal{M}$ *irreducible and* $\mathrm{diag}(D) > \mathbf{0} \Longrightarrow D - \mathcal{M}$ *nonsingular irreducible M-matrix and* $(D - \mathcal{M})^{-1} \gg \mathbf{0}$

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Behaviour of the mobility component – No demography

Assume no within-location dynamics, just movement. Then (8) takes the form

$$\boldsymbol{X}_c' = \mathcal{M}_c \boldsymbol{X}_c \tag{10}$$

Theorem 5

For a given compartment $c \in \mathcal{C}$, suppose that the movement matrix $\mathcal{M}_c$ is irreducible. Then for any $\boldsymbol{X}_c(0) > 0$, (10) satisfies

$$\lim_{t \to \infty} \boldsymbol{X}_c(t) = \boldsymbol{X}_c^\star \gg 0$$

Note that $\boldsymbol{X}_c^\star$ depends on $\langle \mathbb{1}, \boldsymbol{X}_c(0) \rangle$

Reduction to total population per location – Demography

Let

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

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

$$T_p' = D_p(T_p) + \sum_{c \in \mathcal{C}} \sum_{q \in \mathcal{P}} m_{cpq} X_{cq} \tag{11}$$

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)

We have assumed (since birth term is b_p)

$$D_p(T_p) = b_p - d_p T_p \tag{12}$$

Vector / matrix form of the equation

Assuming demography is of the form (12), write (11) in vector form

$$\mathbf{T}' = \mathbf{b} - \boldsymbol{d}\boldsymbol{T} + \sum_{c \in \mathcal{C}} \mathcal{M}_c \boldsymbol{X}_c \tag{13}$$

where

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

The nice case

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

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

(stronger than the property of movement being *similar for all compartments*, which only requires zero/nonzero patterns in all $\mathcal{M}_c$, $c \in \mathcal{C}$, to be the same)

Then

$$\begin{aligned} \boldsymbol{T}' &= \boldsymbol{b} - \boldsymbol{d}\boldsymbol{T} + \mathcal{M} \sum_{c \in \mathcal{C}} \boldsymbol{N}_c \\ &= \boldsymbol{b} - \boldsymbol{d}\boldsymbol{T} + \mathcal{M}\boldsymbol{T} \end{aligned} \tag{14}$$

Equilibria

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

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

Is it?

Nonsingularity of $\mathcal{M} - \boldsymbol{d}$

Using the spectrum shift of Theorem 4(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 $\boldsymbol{d}$ nonsingular). Then $\mathcal{M} - \boldsymbol{d}$ is nonsingular and $\boldsymbol{T}^\star = (\boldsymbol{d} - \mathcal{M})^{-1}\mathbf{b}$ unique

Behaviour of the total population

Equal irreducible movement case

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

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

Indeed, we have

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

Since we now assume that $\boldsymbol{d}$ is nonsingular, we have by Theorem 4(1) that $s(\mathcal{M} - \min_{p\in\mathcal{P}} d_p) = -\min_{p\in\mathcal{P}} d_p < 0$

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

Behaviour of total population (equal *reducible* movement)

Theorem 6

Assume $\mathcal{M}$ reducible. Let a be the number of minimal absorbing sets in the corresponding connection graph $\mathcal{G}(\mathcal{M})$. Then

1. *The spectral abscissa $s(\mathcal{M}) = 0$ has multiplicity a*
2. *Associated to $s(\mathcal{M})$ is a nonnegative eigenvector $\mathbf{v}$ s.t.*
   - *$v_i > 0$ if i is a vertex in a minimal absorbing set*
   - *$v_i = 0$ if i is a transient vertex*

From Foster and Jacquez, Multiple zeros for eigenvalues and the multiplicity of traps of a linear compartmental system, *Mathematical Biosciences* (1975)

The not-so-nice case

Recall that

$$\boldsymbol{T}' = \mathbf{b} - \boldsymbol{d}\boldsymbol{T} + \sum_{c \in \mathcal{C}} \mathcal{M}_c \boldsymbol{X}_c$$

Suppose movement rates **similar for all compartments**, i.e., the zero/nonzero patterns in all matrices are the same but not the entries

Let

$$\underline{\mathcal{M}} = \left[\min_{c \in \mathcal{C}} m_{cpq} \right]_{pq, p \neq q} \qquad \underline{\mathcal{M}} = \left[\max_{c \in \mathcal{C}} m_{cpq} \right]_{pq, p = q}$$

and

$$\overline{\mathcal{M}} = \left[\max_{c \in \mathcal{C}} m_{cpq} \right]_{pq, p \neq q} \qquad \overline{\mathcal{M}} = \left[\min_{c \in \mathcal{C}} m_{cpq} \right]_{pq, p = q}$$

Cool, no? No!

Then we have

$$\mathbf{b} - \boldsymbol{d}\mathbf{T} + \underline{\mathcal{M}}\mathbf{T} \leq \mathbf{T}' \leq \mathbf{b} - \boldsymbol{d}\mathbf{T} + \overline{\mathcal{M}}\mathbf{T}$$

Me, roughly every 6 months: *Oooh, coooool, a linear differential inclusion!*

Me, roughly 10 minutes after making that previous statement: *Quel con!*

Indeed $\underline{\mathcal{M}}$ and $\overline{\mathcal{M}}$ are **are not** movement matrices (in particular, their column sums are not all zero)

So no luck there..

We can still do stuff, however more on a case-by-case basis

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Disease free equilibrium

The model is at equilibrium if the time derivatives are zero

Definition 7 (Metapopulation DFE)

In the case of system (5), 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 (3), replace L_p with L_{sp} and I_p with I_{sp}, for (4), replace L_p by L_{pp} and I_p by I_{pp}. To simplify notation, we could write $L_\bullet$ and $I_\bullet$)

Assume (5) at metapopulation DFE. Then $\Phi_p = 0$ and

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

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:

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

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

$\boldsymbol{R}$ at DFE

Recall second equation:

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

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

We have been here before!

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

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

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

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

$\mathbf{S}$ at the DFE

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

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

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

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

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

So DFE makes sense with

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

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- Linear stability of the disease free equilibrium can be investigated by using the next generation matrix method of [van den Driessche and Watmough, 2002]

- In general, $\mathcal{R}_0$ depends on the demographic, disease and mobility parameters

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

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

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

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

Differentiate w.r.t. Ξ:

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

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

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

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 (2×2 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

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

$\mathcal{R}_0$ 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.,

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

Local asymptotic stability of the DFE

Theorem 8

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

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

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 8 is exact

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

Indeed, by Theorem 4(3) and more importantly (often $\mathcal{M}$ is irreducible), Theorem 4(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

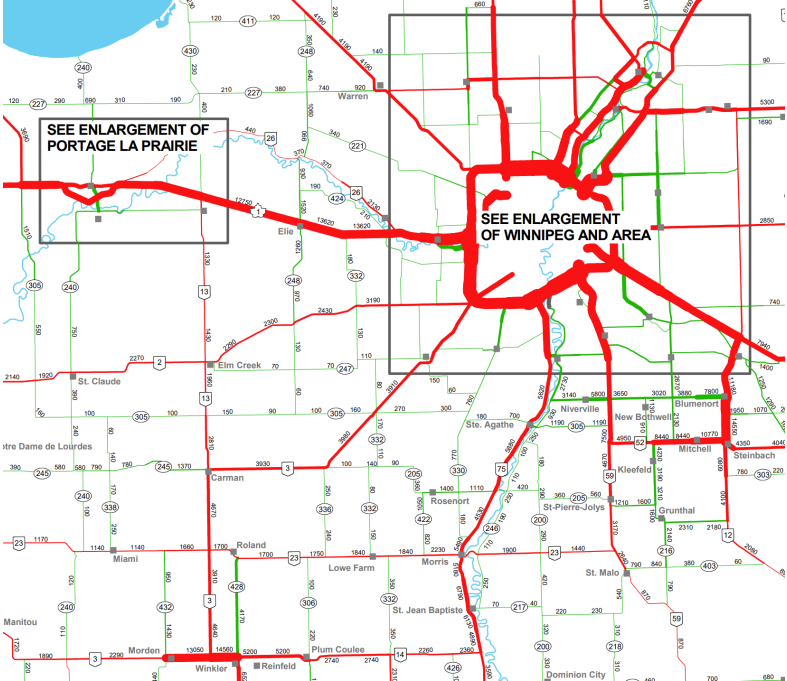
Do not in $\mathcal{R}_0$ put all your .. interpretation?

An urban centre and satellite cities

Winnipeg as urban centre and 3 smaller satellite cities: Portage la Prairie, Selkirk and Steinbach

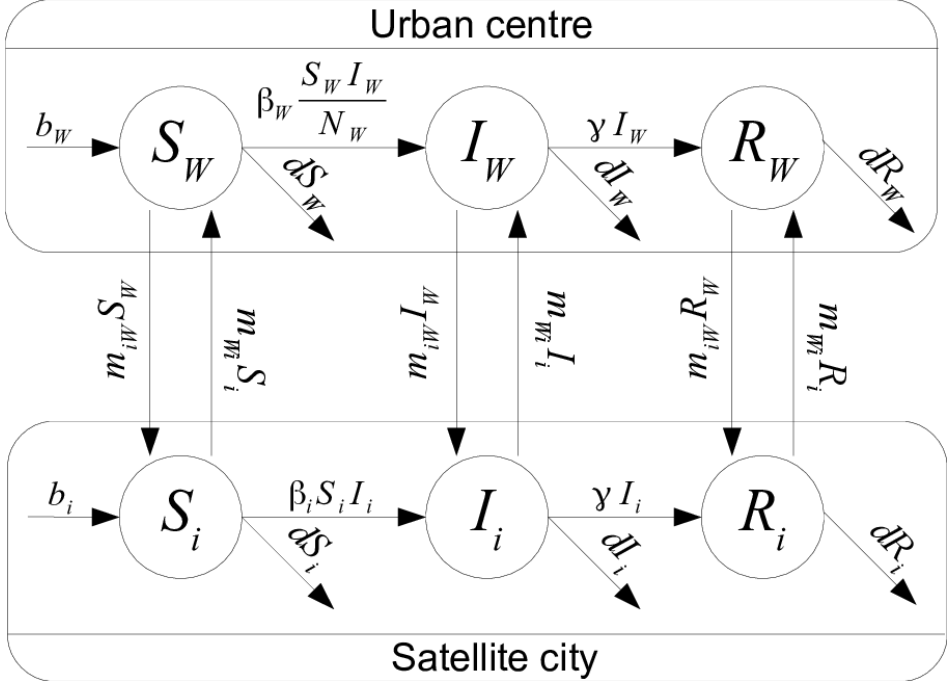
- population density low to very low outside of Winnipeg
- MB road network well studied by MB Infrastructure Traffic Engineering Branch

JA & S Portet. Epidemiological implications of mobility between a large urban centre and smaller satellite cities. *Journal of Mathematical Biology* **71**(5):1243-1265 (2015)


SEE ENLARGEMENT OF PORTAGE LA PRAIRIE
SEE ENLARGEMENT OF WINNIPEG AND AREA
Warren
Elie
Elm Creek
St. Claude
Carman
Roland
Miami
Lowe Farm
Morris
Rosenort
Ste. Agathe
Nivervile
New Bothwell
Blumenort
Mitchell
Steinbach
Kleefeld
St-Pierre-Jolys
Grunthal
St. Malo
St. Jean Baptiste
Plum Coulee
Reinfeld
Winkler
Morden
Manitou
Dominion City

Known and estimated quantities

City	Pop. (2014)	Pop. (now)	Dist.	Avg. trips/day
Winnipeg (W)	663,617	749,607	-	-
Portage la Prairie (1)	12,996	13,270	88	4,115
Selkirk (2)	9,834	10,504	34	7,983
Steinbach (3)	13,524	17,806	66	7,505


Urban centre
b_W
S_W
$\beta_W \frac{S_W I_W}{N_W}$
I_W
γI_W
R_W
dS_W
dI_W
dR_W
$m_{iW} S_W$
$m_{Wi} S_i$
$m_{iW} I_W$
$m_{Wi} I_i$
$m_{iW} R_W$
$m_{Wi} R_i$
b_i
S_i
$\beta_i S_i I_i$
I_i
γI_i
R_i
dS_i
dI_i
dR_i
Satellite city

Estimating movement rates

Assume m_{yx} movement rate from city x to city y. *Ceteris paribus*, $N_x' = -m_{yx}N_x$, so $N_x(t) = N_x(0)e^{-m_{yx}t}$. Therefore, after one day, $N_x(1) = N_x(0)e^{-m_{yx}}$, i.e.,

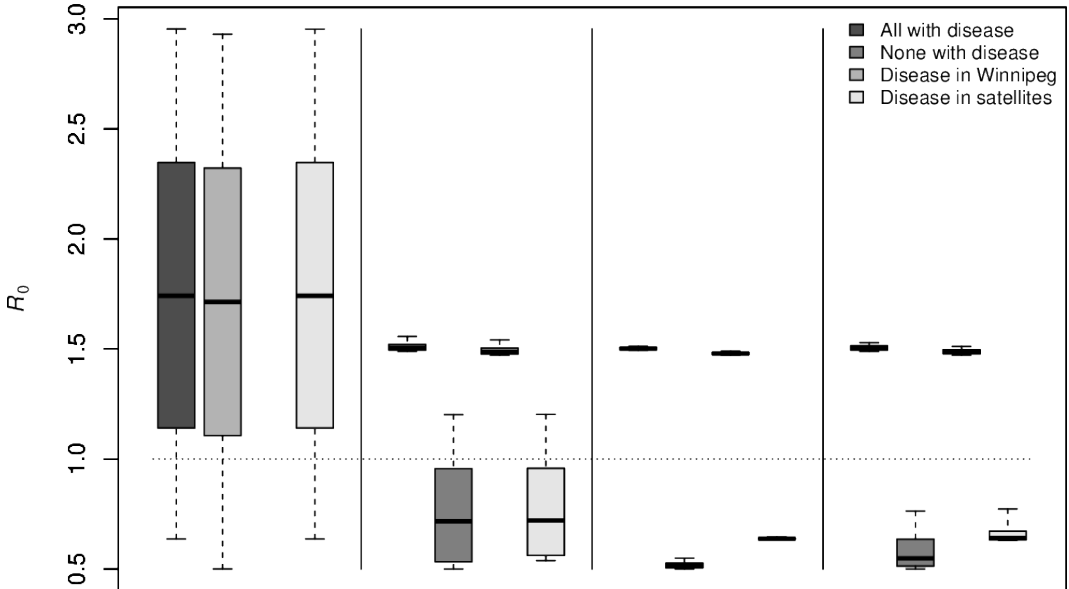
$$m_{yx} = -\ln\left(\frac{N_x(1)}{N_x(0)}\right)$$

Now, $N_x(1) = N_x(0) - T_{yx}$, where T_{yx} number of individuals going from x to y / day. So

$$m_{yx} = -\ln\left(1 - \frac{T_{yx}}{N_x(0)}\right)$$

Computed for all pairs (W, i) and (i, W) of cities

Sensitivity of $\mathcal{R}_0$ to variations of $\mathcal{R}_0^x \in [0.5, 3]$



Lower connectivity can drive $\mathcal{R}_0$

PLP and Steinbach have comparable populations but with parameters used, only PLP can cause the general $\mathcal{R}_0$ to take values larger than 1 when $\mathcal{R}_0^W < 1$

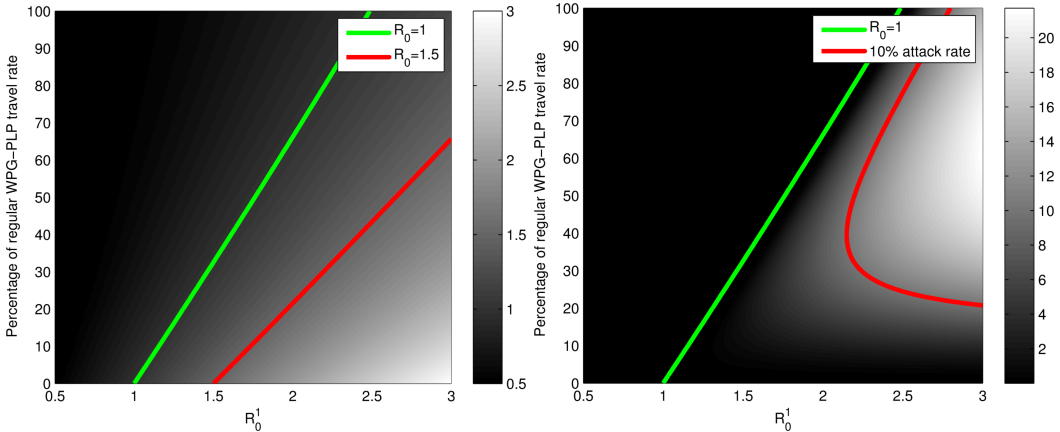
This is due to the movement rate: if $\mathcal{M} = 0$, then

$$\mathcal{R}_0 = \max\{\mathcal{R}_0^W, \mathcal{R}_0^1, \mathcal{R}_0^2, \mathcal{R}_0^3\},$$

since FV^{-1} is then block diagonal

Movement rates to and from PLP are lower $\rightarrow$ situation closer to uncoupled case and $\mathcal{R}_0^1$ has more impact on the general $\mathcal{R}_0$

$\mathcal{R}_0$ does not tell the whole story!



Plots as functions of $\mathcal{R}_0^1$ in PLP and the reduction of movement between Winnipeg and PLP. Left: general $\mathcal{R}_0$. Right: Attack rate in Winnipeg

Metapopulations for disease spread modelling

Why use metapopulation models?
Metapopulations with explicit movement
The graph setting
The models considered
Going to vector form
The movement matrix
Behaviour of the mobility component
Existence of a DFE
Computation of a reproduction number
Global stability of the DFE when $\mathcal{R}_0 < 1$
Metapopulation-specific problems
Computational aspects of metapopulation models

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 9

Let $\mathcal{R}_0$ be defined as in Theorem 8 and use proportional incidence $\Phi_p = \beta_p S_p I_p / N_p$. If $\mathcal{R}_0 < 1$, then the DFE of system (5) 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 9 to show that if $\mathcal{R}_0 < 1$, then the DFE of the $|\mathcal{S}|$ $|\mathcal{P}|$-SLIRS (3) is globally asymptotically stable.

Theorem 10

For system (3) *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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- **Metapopulation-specific problems**
- Computational aspects of metapopulation models

Metapopulation-specific problems – Two main types

- **Inheritance problems** – Which of the properties of the constituting units are inherited by the metapopulation?

- **Metapopulation-specific behaviours** – Are there dynamic behaviours observed in a metapopulation not observed in the constituting units?

Inherited dynamical properties (a.k.a. I am lazy)

Given

$$s'_{kp} = f_{kp}(S_p, I_p) \tag{15a}$$
$$i'_{\ell p} = g_{\ell p}(S_p, I_p) \tag{15b}$$

with known properties, what is known of

$$s'_{kp} = f_{kp}(S_p, I_p) + \sum_{q\in\mathcal{P}} m_{kpq} s_{kq} \tag{16a}$$
$$i'_{\ell p} = g_{\ell p}(S_p, I_p) + \sum_{q\in\mathcal{P}} m_{\ell pq} i_{\ell q} \tag{16b}$$

- Existence and uniqueness ✓
- Invariance of $\mathbb{R}^{\bullet}_{+}$ under the flow ✓
- Boundedness ✓
- Location of individual $\mathcal{R}_{0i}$ and general $\mathcal{R}_0$?
- GAS ?

-

An inheritance problem – Backward bifurcations

- Suppose a model that, isolated in a single patch, undergoes so-called backward bifurcations
- This means the model admits subthreshold endemic equilibria
- What happens when you couple many such consistuting units?

YES, coupling together backward bifurcating units can lead to a system-level backward bifurcation

JA, Ducrot & Zongo. A metapopulation model for malaria with transmission-blocking partial immunity in hosts. *Journal of Mathematical Biology* **64**(3):423-448 (2012)

Metapopulation-induced behaviours ?

"Converse" problem to inheritance problem. Given

$$s'_{kp} = f_{kp}(S_p, I_p) \tag{9a}$$
$$i'_{\ell p} = g_{\ell p}(S_p, I_p) \tag{9b}$$

with known properties, does

$$s'_{kp} = f_{kp}(S_p, I_p) + \sum_{q\in\mathcal{P}} m_{kpq} s_{kq} \tag{10a}$$
$$i'_{\ell p} = g_{\ell p}(S_p, I_p) + \sum_{q\in\mathcal{P}} m_{\ell pq} i_{\ell q} \tag{10b}$$

exhibit some behaviours not observed in the uncoupled system?
E.g.: units have $\{\mathcal{R}_0 < 1 \implies$ DFE GAS, $\mathcal{R}_0 > 1 \implies$ 1 GAS EEP$\}$ behaviour, metapopulation has periodic solutions

Mixed equilibria

Can there be situations where some locations are at the DFE and others at an EEP?

This is the problem of **mixed equilibria**

This is a metapopulation-specific problem, not one of inheritance of dynamical properties!

Types of equilibria

Definition 11 (Location level EP)

Location $p \in \mathcal{P}$ at equilibrium is **empty** if $X_p^\star = 0$, at the **disease-free equilibrium** if $X_p^\star = (s_{k_1 p}^\star, \ldots, s_{k_u p}^\star, 0, \ldots, 0)$, where $k_1, \ldots, k_u$ are some indices with $1 \leq u \leq |\mathcal{U}|$ and $s_{k_1 p}^\star, \ldots, s_{k_u p}^\star$ are positive, and at an **endemic equilibrium** if $X_p \gg 0$

Definition 12 (Metapopulation level EP)

A **population-free equilibrium** has all locations empty. A **metapopulation disease-free equilibrium** has all locations at the disease-free equilibrium for the same compartments. A **metapopulation endemic equilibrium** has all locations at an endemic equilibrium

Mixed equilibria

Definition 13

A **mixed equilibrium** is an equilibrium such that

- all locations are at a disease-free equilibrium but the system is not at a metapopulation disease-free equilibrium
- or, there are at least two locations that have different types of location-level equilibrium (empty, disease-free or endemic)

E.g.,

$$((S_1, I_1, R_1), (S_2, I_2, R_2)) = ((+, 0, 0), (+, +, +))$$

is mixed and so is

$$((S_1, I_1, R_1), (S_2, I_2, R_2)) = ((+, 0, 0), (+, 0, +))$$

Notation is specific here: $p \in \mathcal{P}$, $\mathcal{A}(p)$ and $\mathcal{D}(p)$ are the ancestry and descendents of p in the movement digraph

Theorem 14

Suppose that movement is similar for all compartments (MSAC) and that the system is at equilibrium

- *If patch $p \in \mathcal{P}$ is empty, then all patches in $\mathcal{A}(p)$ are empty*
- *If patch $p \in \mathcal{P}$ is at a disease free equilibrium, then the subsystem consisting of all patches in $\{p, \mathcal{A}(p)\}$ is at a metapopulation disease free equilibrium*
- *If patch $p \in \mathcal{P}$ is at an endemic equilibrium, then all patches in $\mathcal{D}(p)$ are also at an endemic equilibrium*
- *If $\mathcal{G}^c$ is strongly connected for some compartment $c \in \mathcal{C}$, then there does not exist mixed equilibria*

Note that MSAC $\implies$ $\mathcal{A}^c = \mathcal{A}$ and $\mathcal{D}^c = \mathcal{D}$ for all $c \in \mathcal{C}$

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- Computation of a reproduction number
- Global stability of the DFE when $\mathcal{R}_0 < 1$
- Metapopulation-specific problems
- **Computational aspects of metapopulation models**

- JA. Spatio-temporal spread of infectious pathogens of humans. *Infectious Disease Modelling* **2**(2):218-228 (2017)
- JA. Mathematical epidemiology in a data-rich world. *Infectious Disease Modelling* **5**:161-188 (2020)
- github repo modelling-with-data

Not very difficult

As for the mathematical analysis: if you do things carefully and think about things a bit, numerics are not hard. Well: not harder than numerics in low-D

Exploit vector structure

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)
```

Computing birth and death rates

Average life expectancy at birth (years): 81.30, 78.59, 67.74, 66.43, 72.19

```
pop = c(34.017, 1348.932, 1224.614, 173.593, 93.261) * 1e+06
countries = c("Canada", "China", "India", "Pakistan", "Philippines")
death_rates = 1/(365.25*c(81.30, 78.59, 67.74, 66.43, 72.19))
birth_rates = pop*death_rates
```

Work out movement matrix

Use the approximation explained in Arino & Portet (JMB 2015)

```
p = list()
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))
```

For simplicity, let's assume all movement rates are equal

```
p$P = dim(p$M)[1]
p$epsilon = rep((1/1.5), p$P)
p$gamma = rep((1/5), p$P)
p$nu = rep((1/365.25), p$P)
p$b = birth_rates
p$d = death_rates
# 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$idx_R = (3*p$P+1):(4*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)
R0 = mat.or.vec(p$P, 1)
I0[1] = 2
S0 = pop - (L0 + I0 + R0)
# Vector of initial conditions to be passed to ODE solver.
IC = c(S = S0, L = L0, I = I0, R = R0)
# Time span of the simulation (5 years here)
tspan = seq(from = 0, to = 100, by = 0.1)
```

Computing $\mathcal{R}_0$ in patches in isolation to set up β

Useful to know $\mathcal{R}_{0p}$, basic reproduction numnber for patch $p \in \mathcal{P}$ disconnected from the network

In the absence of movement, system in $p \in \mathcal{P}$ is

$$S_p' = b_p - \beta_p S_p I_p - d_p S_p + \nu_p R_p \tag{17a}$$
$$L_p' = \beta_p S_p I_p - (\varepsilon_p + d_p) L_p \tag{17b}$$
$$I_p' = \varepsilon_p L_p - (\gamma_p + d_p) I_p \tag{17c}$$
$$R_p' = \gamma_p I_p - (\nu_p + d_p) R_p \tag{17d}$$

DFE is clearly $(S_p, L_p, I_p, R_p) = (b_p/d_p, 0, 0, 0)$

Infected variables are $\mathcal{I} = \{L, I\}$

$$\mathcal{F} = (\beta_p S_p I_p, 0)^T \text{ and } \mathcal{V} = ((\varepsilon_p + d_p)L_p, -\varepsilon_p L_p + (\gamma_p + d_p)I_p)$$

so

$$F = \begin{pmatrix} 0 & \beta_p \frac{b_p}{d_p} \\ 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} \varepsilon_p + d_p & 0 \\ -\varepsilon_p & \gamma_p + d_p \end{pmatrix}$$

Thus

$$\mathcal{R}_{0p} = \rho(FV^{-1}) = \rho\left(\begin{pmatrix} 0 & \beta_p \frac{b_p}{d_p} \\ 0 & 0 \end{pmatrix} \frac{1}{(\varepsilon_p + d_p)(\gamma_p + d_p)} \begin{pmatrix} \gamma_p + d_p & 0 \\ \varepsilon_p & \varepsilon_p + d_p \end{pmatrix}\right)$$

and it follows that

$$\mathcal{R}_{0p} = \frac{\beta_p}{\gamma_p + d_p} \frac{\varepsilon_p}{\varepsilon_p + d_p} \frac{b_p}{d_p} \tag{18}$$

Set up β to avoid blow up

Let us take $\mathcal{R}_{0p} = 1.5$ for patches in isolation. Solve (18) for β_p:

$$\beta_p = \frac{\mathcal{R}_{0p}(\gamma_p + d_p)(\varepsilon_p + d_p)d_p}{\varepsilon_p b_p}$$

```
for (i in 1:p$P) {
  p$beta[i] =
    R_0[i] *(p$gamma[i]+p$d[i]) * (p$epsilon[i]+p$d[i]) * p$d[i] /
    (p$epsilon[i]*p$d[i])
}
```

Define the vector field

```
SLIRS_metapop_rhs <- function(t, x, p) {
        with(as.list(p), {
                S = x[idx_S]
                L = x[idx_L]
                I = x[idx_I]
                R = x[idx_R]
                Phi = beta*S*I
                dS = b - d*S - Phi + M%*%S
                dL = Phi - (epsilon+d)*L + M%*%L
                dI = epsilon*L - (gamma+d)*I + M%*%I
                dR = gamma*I + - (nu+d)*R + M%*%R
                return(list(c(dS, dL, dI, dR)))
        })
}
```

And now call the solver

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

One little trick (case with demography)

Suppose demographic EP is $\mathbf{N}^\star = (\boldsymbol{d} - \mathcal{M})^{-1}\mathbf{b}$
Want to maintain $\mathbf{N}(t) = \mathbf{N}^\star$ for all t to ignore convergence to demographic EP.
Think in terms of $\mathbf{b}$:

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

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

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

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..

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

$\boldsymbol{d} - \mathcal{M}$ 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 $\boldsymbol{b}$ could have negative entries

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

Spatio-temporal spread of infectious pathogens

Metapopulations for disease spread modelling

Other spatial models

A model with arbitrary sojourn time

Age of infection

Structuration in age

Other spatial models

- **Spatial propagation on a “road”**
- **A diffusion spatial spread model**

PERGAMON Mathematical and Computer Modelling 29 (1999) 55–69

MATHEMATICAL AND COMPUTER MODELLING

Modelling the Spread of Infections When the Contact Rate Among Individuals is Short Ranged: Propagation of Epidemic Waves

L. F. LOPEZ, F. A. B. COUTINHO, M. N. BURATTINI AND E. MASSAD
Discipline of Medical Informatics
School of Medicine, The University of Sao Paulo
Av. Dr. Arnaldo, 455, Sao Paulo 01246-903 SP, Brazil
lopez@dns2.fm.usp.br

(Received and accepted July 1998)

Spatial spread of an epidemic on a "road"

- SIS and SIR models
- Consider a road of length L
- $S(x,t)$, $I(x,t)$ and (when relevant) $R(x,t)$ are the densities of individuals in the different compartments at location $x \in [0, L]$ at time t
- For simplicity, denote

$$\frac{\partial}{\partial t} X(x,t) = X_t(x,t)$$

The SIR model on the road

$$S_t(x,t) = -\beta(x,t)S(x,t) - dS(x,t) + dN(x) + \lambda_1 I(x,t) \tag{19a}$$
$$I_t(x,t) = \lambda(x,t)S(x,t) - dI(x,t) - (\gamma_1 + \gamma_2)I(x,t) \tag{19b}$$
$$R_t(x,t) = \gamma_2 I(x,t) - dR(x,t) \tag{19c}$$

where the force of infection is

$$\lambda(x,t) = \frac{1}{N}\int_0^L \beta(x,x')I(x,x')dx' \tag{19d}$$

and the total population along the road is

$$N = \int_0^L N(x')dx' \tag{19e}$$

Take the SIS model as an example ($\gamma_2 = 0, \gamma_1 = \gamma$). Solve (19b) in terms of λ:

$$
\begin{aligned}
I(x,t) = & \exp\left(-\int_0^t \lambda(x,s) - (d+\gamma)tds\right) \\
& \times \int_0^t \lambda(x,t')N(x)e^{\int_0^{t'} \lambda(x,s)+(d+\gamma)t'ds} dt' \\
& + I(x,0)\exp\left(-\int_0^t \lambda(x,s) - (d+\gamma)tds\right)
\end{aligned} \tag{20}
$$

Substitute (20) into (19d)

$$\lambda(x,t) = \int_0^L \beta(x,x')n(x') \int_0^t \lambda(x',t')e^{-\int_{t'}^t \lambda(x',s)-(d+\gamma)(t-t')ds} dt'dx'$$
$$+ \int_0^L \beta(x,x')i(x',0)e^{-\int_0^t \lambda(x',s)-(d+\gamma)tds} dx'$$

where $n(x) = N(x)/N$ and $i(x,t) = I(x,t)/N$. Without demography ($d = 0$):

$$\lambda(x,t) = \int_0^L \beta(x,x')n(x') \int_0^t \lambda(x',t')e^{-\int_{t'}^t \lambda(x',s)-\gamma(t-t')ds} dt'dx'$$
$$+ \int_0^L \beta(x,x')i(x',0)e^{-\int_0^t \lambda(x',s)-\gamma tds} dx'$$

Thus the problem is in the form

$$\boldsymbol{B}\lambda(x,t) = \lambda(x,t)$$

In both cases, $\boldsymbol{B}$ is a Hammerstein-type operator in x

- SIR case: $\boldsymbol{B}$ is a nonlinear Volterra operator in t $\Rightarrow$existence and uniqueness of solutions
- SIS case: $\boldsymbol{B}$ is not a nonlinear Volterra operator in t. However, it resembles one and the authors establish existence and uniqueness of solutions

In both cases, there is a travelling wave front then convergence to a steady state

In the SIS case

$$\lambda(x) = \lim_{t\to\infty} \boldsymbol{B}\lambda(x,t) = \boldsymbol{B}_\infty\lambda(x) = \int_0^L \beta(x,x')n(x')\frac{\lambda(x',\infty)}{\lambda(x',\infty)+\gamma}$$

which does not depend on t

They then discuss conditions s.t. this limit $\neq 0$, by looking for values of z s.t. $\boldsymbol{B}_\infty\lambda(x) = z\lambda(x)$ has a positive solution

Show there exists a threshold $z_{\text{threshold}} = \mathcal{R}_0$ s.t. $\lambda(x) \equiv 0$ if $\mathcal{R}_0 < 1$ and a positive solution if $\mathcal{R}_0 > 1$

Other spatial models

Spatial propagation on a “road”

A diffusion spatial spread model

J. theor. Biol. (1992) **156,** 327–348

On the Spatial Spread of Rabies Among Foxes with Immunity

J. D. MURRAY† AND W. L. SEWARD‡

† *Applied Mathematics FS-20, University of Washington, Seattle, WA* 98195, *U.S.A. and* ‡ *Department of Computer Science, University of Waterloo, Waterloo, Ontario N2L* 3G1, *Canada*

(*Received on* 10 *December* 1990, *Accepted in revised form on* 10 *December* 1991)

Spatial spread of rabies with immunity

$$\frac{\partial S}{\partial t} = (a-b)\left(1-\frac{N}{K}\right)S + a^{\star}R - \beta SI \tag{21a}$$

$$\frac{\partial L}{\partial t} = \beta SI - \sigma L - \left(b + (a-b)\frac{N}{K}\right)L \tag{21b}$$

$$\frac{\partial I}{\partial t} = \sigma L - \alpha I - \gamma I - \left(b + (a-b)\frac{N}{K}\right)I + D_I\frac{\partial^2 I}{\partial x^2} \tag{21c}$$

$$\frac{\partial R}{\partial t} = \gamma I + (a-a^{\star})R + \left(b + (a-b)\frac{N}{K}\right)R \tag{21d}$$

where $N = S + L + I + R$

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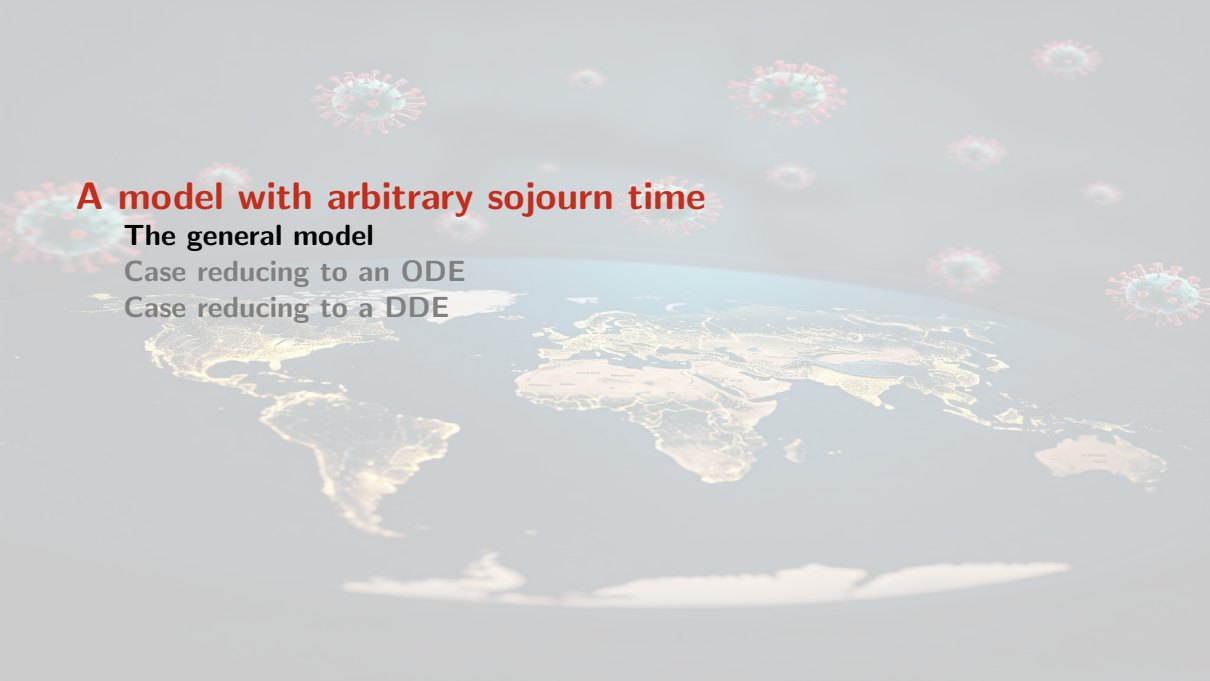


A model with arbitrary sojourn time

- **The general model**
- Case reducing to an ODE
- Case reducing to a DDE

DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS–SERIES B
Volume **4**, Number **2**, May **2004**

Website: http://AIMsciences.org

pp. **479–495**

AN EPIDEMIOLOGY MODEL THAT INCLUDES A LEAKY VACCINE WITH A GENERAL WANING FUNCTION

Julien Arino
Department of Mathematics and Statistics
University of Victoria, Victoria B.C., Canada V8W 3P4

K.L. Cooke
Department of Mathematics
Pomona College, Claremont, CA 91711-6348 USA

P. van den Driessche
Department of Mathematics and Statistics
University of Victoria, Victoria B.C., Canada V8W 3P4

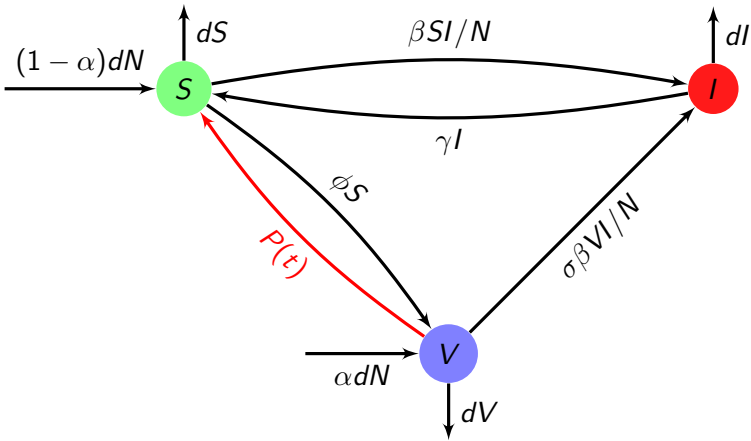
J. Velasco-Hernández
Programa de Matemáticas Aplicadas y Computación
Instituto Mexicano del Petróleo, Eje Central Lázaro Cárdenas 152
San Bartolo Atepehuacan, D.F. 07730, Mexico

(Communicated by Linda Allen)

A model with vaccine efficacy and waning

- Exponential distribution of recovery times (rate γ)
- Susceptible individuals are vaccinated (number of vaccinated at time t is denoted $V(t)$)
- Vaccination wanes, a fraction $P(t)$ of the vaccinated at time $t = 0$ remain protected by the vaccine
- Vaccination is imperfect, $0 \leq 1 - \sigma \leq 1$ is the vaccine **efficacy**

Model structure



Parametres

- $d > 0$: mortality rate
- $\gamma \geq 0$: recovery rate
- $\beta > 0$: infectiousness of the disease
- $\phi \geq 0$: vaccination rate of susceptible individuals
- $\alpha \in [0, 1)$: fraction of newborns vaccinates
- $0 \leq 1 - \sigma \leq 1$: efficacy of the vaccine. From now on, assume $0 \leq \sigma < 1$

- Disease transmission: standard incidence

- Vaccination of newborns

- Birth and death rate equal ($\Rightarrow$constant total population)

Assumptions on P: $P(t)$ is a nonnegative and nonincreasing function with $P(0^+) = 1$, and such that $\int_0^\infty P(u)du$ is positive and finite

Constant total population $\Rightarrow S(t) = N - I(t) - V(t)$; further, we switch to **proportions**: S, I and V represent the proportions in the population, and $N = 1$ (S used in equations for conciseness)

The SIS model with vaccination

$$\frac{dI(t)}{dt} = \beta(S(t) + \sigma V(t))I(t) - (d + \gamma)I(t) \tag{22a}$$

$$V(t) = V_0(t) + \int_0^t (\phi S(u) + \alpha d)P(t-u)e^{-d(t-u)}e^{-\sigma\beta\int_u^t I(x)dx}du \tag{22b}$$

- αd proportion of vaccinated newborns,
- $\phi S(u)$ proportion of vaccinated susceptibles,
- $P(t-u)$ fraction of the proportion vaccinated still in the V class $t-u$ time units after going in,
- $e^{-d(t-u)}$ fraction of the proportion vaccinated not dead due to natural causes,
- $e^{-\sigma\beta\int_u^t I(x)dx}$ fraction of the proportion vaccinated not gone to the infective class.

Obtaining the initial condition

Let $v(t,\tau)$ be the (density) proportion of individuals in vaccination class-age τ still vaccinated at time t, then

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial \tau}\right) v(t,\tau) = -(\sigma\beta I(t) + d + \eta(\tau))v(t,\tau) \tag{23}$$

where $V(t) = \int_0^\infty v(t,\tau)d\tau$. $\eta(\tau)$ is the vaccine waning rate coefficient, with proportion still in the vaccination class-age τ being $P(\tau) = \exp\left(-\int_0^\tau \eta(q)dq\right)$. It is assumed that P is a survival function

Inflow in class-age zero is

$$v(t,0) = \phi S(t) + \alpha d$$

and $v(0,\tau) \geq 0$ is assumed

Integrating (23) along characteristics, dividing the integral for $V(t)$ at t, substituting in the solutions, and changing integration variables, we get

$$V_0(t) = e^{-\int_0^t (\sigma\beta I(x)+d)dx} \int_0^\infty v(0,u)\frac{P(t+u)}{P(u)}du \tag{24}$$

The ratio $P(t+u)/P(u) = \exp\left(\int_u^{t+u} \eta(q)dq\right)$ is well defined for $t+u \geq u \geq 0$ and bounded above by 1.

Since $V(0)$ is finite, the integral in $V_0(t)$ converges, and thus $V_0(t)$ is nonnegative, nonincreasing and $\lim_{t\to\infty} V_0(t) = 0$

Let

$$\mathcal{D} = \{(S, I, V); S \geq 0, I \geq 0, V \geq 0, S + I + V = 1\}$$

Theorem 15

The set $\mathcal{D}$ is positively invariant under the flow of (22) with $I(0) > 0, S(0) > 0$

With the assumed initial conditions in $\mathcal{D}$, it can be shown that the system defined by (22a) and (22b) is equivalent to the system defined by (22a) and

$$\frac{d}{dt}V(t) = \frac{d}{dt}V_0(t) + \phi S(t) + \alpha d - (d + \sigma\beta I(t))(V(t) - V_0(t)) + Q(t) \tag{25}$$

where to simplify notation, we denote

$$Q(t) = \int_0^t (\phi S(u) + \alpha d) d_t(P(t-u)) e^{-d(t-u)} e^{-\sigma\beta \int_u^t I(x)dx} du$$

The system defined by (22a) and (25) is of standard form, therefore results of Hale [Hale and Verduyn-Lunel, 2013] ensure the local existence, uniqueness and continuation of solutions of model (22)

$\mathcal{R}_0$

Define $\mathcal{R}_0$ with vaccination as

$$\mathcal{R}_v = \mathcal{R}_0 \left[\frac{1 + \sigma\phi\tilde{P} - (1-\sigma)\alpha d\tilde{P}}{1 + \phi\tilde{P}} \right] \tag{26}$$

where $\mathcal{R}_0 = \frac{\beta}{d+\gamma}$ is the reproduction number in the absence of vaccination and

$$\tilde{P} = \lim_{t\to\infty} \int_0^t P(v) e^{-dv} dv$$

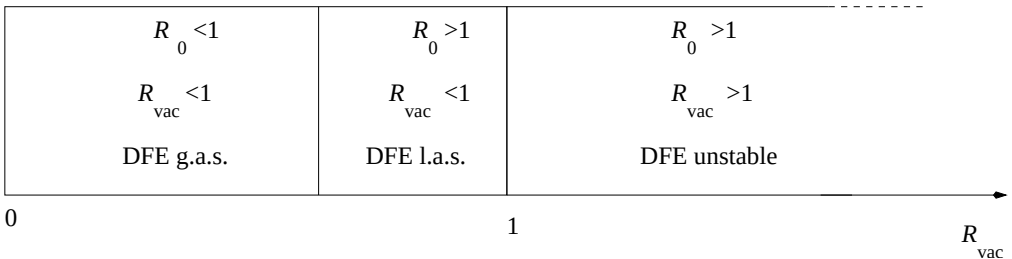
in such a way that $\tilde{P} < 1/d$

- $\mathcal{R}_v \leq \mathcal{R}_0$ and, in absence of vaccination, $\mathcal{R}_v = \mathcal{R}_0$

Theorem 16

System (22) *with an arbitrary loss of vaccination function* $P(t)$ *always admits the disease-free equilibrium*

- *If* $\mathcal{R}_0 < 1$*, then the DFE is the only equilibrium of the system and the disease goes extinct*
- *If* $\mathcal{R}_v < 1$*, the DFE is LAS; if* $\mathcal{R}_v > 1$*, the DFE is unstable*



A model with arbitrary sojourn time

- The general model
- **Case reducing to an ODE**
- Case reducing to a DDE

Reduction of the system using specific $P(t)$ functions

As before, two examples

- The distribution of waning times is exponential, which leads to an ODE system. Treated briefly here, just so as to emphasize the presence of a so-called *backward bifurcation*, a rather uncommon phenomenon in epidemiological models

- The waning time is a constant, which leads to a DDE model. We show that the backward bifurcation is also present

Case reducing to an ODE system

Assume $P(v) = e^{-\theta v}$, $\theta > 0$. $V_0(t) = V_0(0)e^{-(d+\theta)t}e^{-\int_0^t \sigma\beta I(x)dx}$ from (24). Then (22a) and (25) give the ODE system

$$\frac{dI}{dt} = \beta(1 - I - (1-\sigma)V)I - (d+\gamma)I \tag{27a}$$

$$\frac{dV}{dt} = \phi(1 - I - V) - \sigma\beta IV - (d+\theta)V + \alpha d \tag{27b}$$

which with no newborn vaccination ($\alpha = 0$) is the model studied in Kribs-Zaletta & Velasco-Hernandez, 2000 (extended to SIR with vaccination: Arino, McCluskey and van den Driessche).

From Theorem 16 the DFE always exists, with

$$I_{DFE} = 0, S_{DFE} = \frac{\theta + d(1-\alpha)}{d+\theta+\phi}, V_{DFE} = \frac{\phi + \alpha d}{d+\theta+\phi}$$

Backward bifurcation

Assume that $\mathcal{R}_0 > 1$, then endemic equilibria (positive I equilibria, denoted by $I^\star$) can be obtained analytically from the quadratic equation

$$\mathcal{P}(I) = AI^2 + BI + C = 0$$

where

$$\begin{aligned} A &= -\sigma\beta \\ B &= \sigma(\beta - (d+\gamma)) - (d+\theta+\sigma\phi) \\ C &= (d+\gamma)(d+\theta+\phi)(\mathcal{R}_v - 1)/\beta \end{aligned}$$

with

$$\mathcal{R}_v = \mathcal{R}_0 \frac{d+\theta+\sigma\phi-\alpha(1-\sigma)d}{d+\theta+\phi}$$

from (26).

Backward bifurcation leading to two endemic equilibria occurs for $\sigma > 0$ if $\mathcal{P}'(0) = B > 0$, $\mathcal{P}(0) = C < 0$ and $B^2 > 4AC$ (we always have $\mathcal{P}(1) < 0$)

- On an $(\mathcal{R}_v, I)$ bifurcation diagram, this occurs for $\mathcal{R}_c < \mathcal{R}_v < 1$, where $\mathcal{R}_c$ is the value of $\mathcal{R}_v$ at the saddle node bifurcation point where the two values of I coincide, *i.e.*, $I = I_c = B/(-2A)$

- For $\mathcal{R}_v < \mathcal{R}_c$, there is no endemic equilibrium (EEP). For $\mathcal{R}_v > 1$, the constant term $C > 0$, and there is a unique EEP

- In the case of forward bifurcation, $\mathcal{R}_c = 1$; this is the case in particular if the vaccine is totally effective ($\sigma = 0$)

By standard planar ODE arguments the following can be shown

Theorem 17

For the ODE system (27) with $V(0) \geq 0$, $I(0) > 0$, and $\mathcal{R}_0 > 1$

(i) if $\mathcal{R}_v < \mathcal{R}_c$, then the disease dies out,

(ii) if $\mathcal{R}_c < \mathcal{R}_v < 1$, then the EEP with larger I is l.a.s., and the EEP with smaller I is unstable

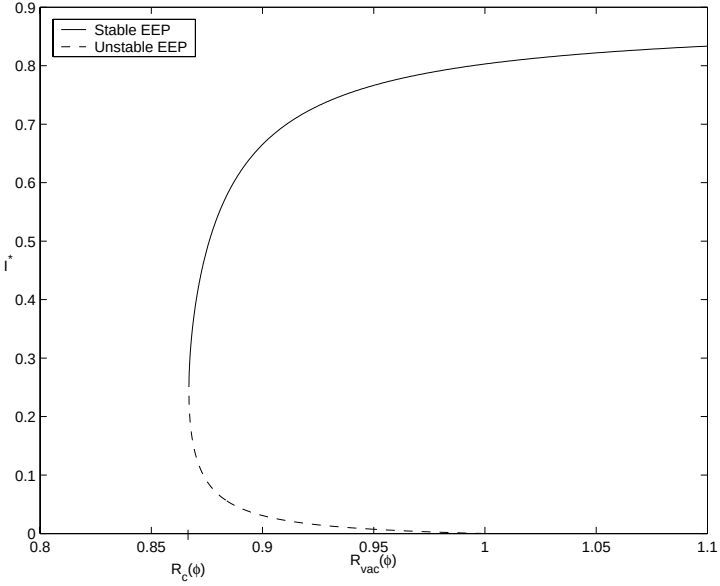
(iii) if $\mathcal{R}_v > 1$, then the unique EEP is globally asymptotically stable in $\mathcal{D} - \{I = 0\}$

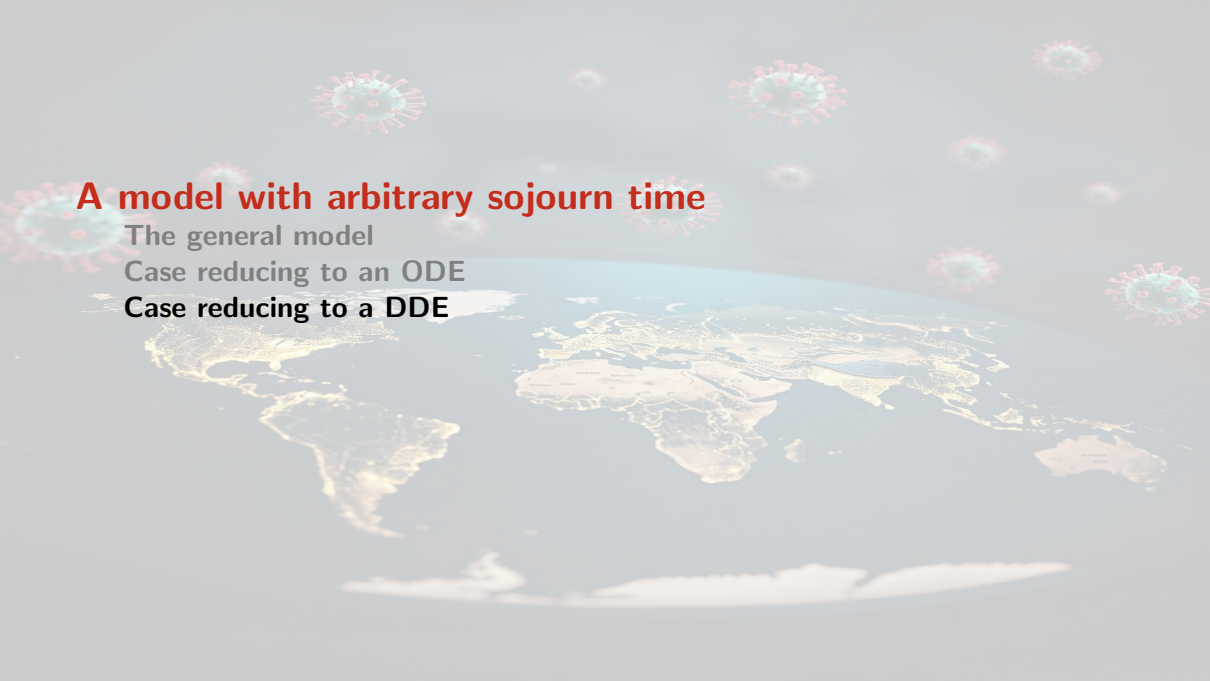
Pertussis:

- 3 week average disease duration ($\gamma = 0.04762$)
- Average lifetime 75 years ($d = 3.6530E - 05$)
- Average number of adequate contacts per infective per day is estimated at 0.4 ($\beta = 0.4$)
- Most newborns are vaccinated in the first few months of life ($\alpha = 0.9$)
- Vaccine is effective, $\sigma = 0.1$ (90% effective vaccine).
- Pertussis vaccine begins to wane after about 3 years and the average waning time of the vaccine $1/\theta$ is assumed to be 5 years, giving $\theta = 5.4794E - 04$

With these parameter values, there is backward bifurcation for a range of ϕ values given by $0.0254 \leq \phi \leq 0.1506$

With the above parameter values, $\mathcal{R}_0 = 8.3936$ and $\mathcal{R}_v(\phi) = 0.8807$ for $\phi = 0.1$, which is in the range of backward bifurcation since the critical value $\mathcal{R}_c(\phi) = 0.8669 < \mathcal{R}_v(\phi) < 1$





A model with arbitrary sojourn time

- The general model
- Case reducing to an ODE
- **Case reducing to a DDE**

Step function case: a delay integral model

Suppose that

$$P(v) = \begin{cases} 1 \text{ if } v \in [0, \omega] \\ 0 \text{ otherwise} \end{cases}$$

Since $V_0(t) = 0$ for $t > \omega$, with $S = 1 - I - V$ the integral equation (22b) becomes, for $t > \omega$

$$V(t) = \int_{t-\omega}^{t} (\phi(1 - I(u) - V(u)) + \alpha d) e^{-d(t-u)} e^{-\sigma\beta \int_u^t I(x)dx} du \tag{28}$$

Differentiating (28) (see equation (25)) gives the model as the two dimensional system, for $t > \omega$

$$\frac{d}{dt}I(t) = \beta(1 - I(t) - (1-\sigma)V(t))I(t) - (d+\gamma)I(t) \tag{29a}$$

$$\begin{aligned}\frac{d}{dt}V(t) = {} & \phi(1 - I(t) - V(t)) \\ & - \phi(1 - I(t-\omega) - V(t-\omega))e^{-d\omega}e^{-\sigma\beta\int_{t-\omega}^{t} I(x)dx} \\ & - \sigma\beta IV - dV + \alpha d\left(1 - e^{-d\omega}e^{-\sigma\beta\int_{t-\omega}^{t} I(x)dx}\right)\end{aligned} \tag{29b}$$

Hereafter, shift time by ω so that these equations hold for $t > 0$

The well posedness of the problem follows from Theorem 15 and from the fact that solutions of (22) exist and are unique. For a constant waning period, the basic reproduction number from (26) is

$$\mathcal{R}_v = \mathcal{R}_0 \frac{d + (\sigma\phi - \alpha(1-\sigma)d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \tag{30}$$

With $I_{DF} = 0$, from Theorem 16

$$V_{DF} = \frac{(\phi + \alpha d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})}, \; S_{DF} = \frac{d - \alpha d(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \tag{31}$$

Finding the EEP's

From nullclines, there exists one (or more) endemic equilbria (EEP) iff there exists $0 < I^\star \leq 1$ such that

$$V^\star = f(I^\star) = g(I^\star) \tag{32}$$

where

$$f(I) = \frac{1 - 1/\mathcal{R}_0 - I}{1 - \sigma} \tag{33}$$

for $\sigma < 1$, and

$$g(I) = \frac{(\phi(1 - I) + \alpha d)(1 - e^{-d\omega - \sigma\beta\omega I})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I}) + d + \sigma\beta I} \tag{34}$$

Visualising and locating the bifurcation

From the nullcline equations, an EEP exists iff there exists an $I^\star \in (0,1]$ such that equations (32)-(34) hold. So we study the zeros of

$$H(I) = \frac{1 - 1/\mathcal{R}_0 - I}{1-\sigma} - \frac{(\phi(1-I) + \alpha d)(1 - e^{-d\omega - \sigma\beta\omega I})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I}) + d + \sigma\beta I}$$

To state the problem in a formal way, let $\mathcal{A} = \{\alpha, \beta, \gamma, \omega, \phi, \sigma\}$ be the set of parameters of interest, and denote

$$H(I, \mathcal{A}) = f(I) - g(I) \tag{35}$$

to show the dependence on these parameters.

We proceed as follows.

1. Choose a parameter $a_i \in \mathcal{A}$.
2. Fix all other a_j's ($j \neq i$).
3. Choose $a_{i,min}$, $a_{i,max}$ and Δa_i for a_i.
4. For all $a_{i,k} = a_{i,min} + k\Delta a_i$ (k such that $a_{i,k} \leq a_{i,max}$), compute $I^\star$ such that $H(I^\star, a_{i,k}) = 0$.

Step 4 is carried out using the MatLab `fzero` function.
Further precision can be gained by showing that

$$H(0) = \frac{\mathcal{R}_v - 1}{(1-\sigma)\mathcal{R}_0}$$

and that, for $\sigma < 1$

$$H(1) = -\frac{1}{(1-\sigma)\mathcal{R}_0} - \frac{\alpha d(1 - e^{-d\omega - \sigma\beta\omega})}{\phi(1 - e^{-d\omega-\sigma\beta\omega}) + d + \sigma\beta} < 0$$

Define $\mathcal{R}_c$ as previously. For $\mathcal{R}_0 > 1$ and $\mathcal{R}_v < 1$, there are several possibilities.

- If $\mathcal{R}_v < \mathcal{R}_c$, then there is no EEP. $H(0)$ and $H(1)$ are strictly negative, and numerical simulations seem to indicate that H has no roots in $(0, 1]$ (*i.e.*, that $H < 0$ on this interval).
- If $\mathcal{R}_c < \mathcal{R}_v < 1$, then there are endemic equilibria. Here, since $H(0)$ and $H(1)$ are strictly negative, the only possibility is thus to have an even number of zeros of H. Numerical simulations appear to indicate that the number of endemic equilibria is 2.

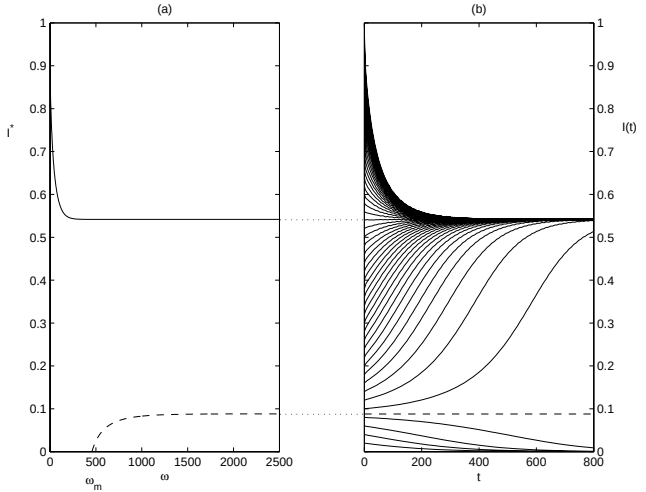
In between these two situations $\mathcal{R}_v = \mathcal{R}_c$ and there is one endemic equilibrium $I^\star$. Using the same procedure as for the visualisation of the bifurcation, it is possible to compute $\mathcal{R}_c$ by finding the value $I^\star$ such that $H(I^\star, \mathcal{A}) = 0$ and $H'(I^\star, \mathcal{A}) = 0$, for a given parameter $a_i \in \mathcal{A}$.
If $\mathcal{R}_v > 1$ then $H(0) > 0$ and so there is an odd number of endemic equilibria. Numerical simulations indicate that there is a unique EEP.

Numerical bifurcation analysis

Same parameter values as in ODE case, except that the constant waning time (the delay) ω has to be substituted for θ. We take $\omega = 1825$, *i.e.*, corresponding to a 5 years waning time

These parameters give $\mathcal{R}_0 = 8.3936$ and $\mathcal{R}_v(\phi) = 0.8819$, which is in the range of the backward bifurcation since (using the above method) $\mathcal{R}_c(\phi) = 0.8675$

The bifurcation diagram is very like that depicted in earlier for the ODE. Numerical simulations of the DDE model (using `dde23`) indicate that there are no additional bifurcations; solutions either go to the DFE or to the (larger) EEP



(a) Values of $I^\star$ as a function of ω by solving $H(I, \mathcal{A}) = 0$ with $a_i = \omega$. (b) Value of $I(t)$ versus time, obtained by numerical integration of system (29) with initial data $I(t) = c$, for $t \in [-\omega, 0]$, $\omega = 1825$, c varying from 0 to 1 by steps of 0.02

Spatio-temporal spread of infectious pathogens

Metapopulations for disease spread modelling

Other spatial models

A model with arbitrary sojourn time

Age of infection

Structuration in age

Age of infection

We have seen that infinite dimensionality could result from a detailed description (or an unspecified one) of the sojourn time in compartments

Originally, age of infection was introduced to account for differences in infectivity depending on the time since an individual became infected

For instance, it is known that infectiousness of HIV positive patients vary as a function of time since infection


Age of infection
Age of vaccination

Age of vaccination

We used age of vaccination to find the initial condition of (22)

Here we take a closer look at this type of model

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EVALUATION OF VACCINATION STRATEGIES DURING PANDEMIC OUTBREAKS

Christopher S. Bowman

Institute for Biodiagnostics
National Research Council Canada
435 Ellice Avenue, Winnipeg, MB, R3B 1Y6, Canada

Julien Arino

Department of Mathematics
University of Manitoba
Winnipeg, Manitoba, R3T 2N2, Canada

Seyed M. Moghadas

Institute for Biodiagnostics
National Research Council Canada
435 Ellice Avenue, Winnipeg, MB, R3B 1Y6, Canada
and
Department of Mathematics and Statistics
University of Winnipeg
Winnipeg, MB, R3B 2E9, Canada

How to model time between vaccine doses

$$S' = -fS - V_1(t,0) \tag{36a}$$

$$A' = \Big((1-p)S + (1-p_1)\delta_1\tilde{V}_1 + (1-p_2)\delta_2 V_2\Big) f - \mu_A A \tag{36b}$$

$$I' = (pS + p_1\delta_1\tilde{V}_1 + p_2\delta_2 V_2)f - \mu I \tag{36c}$$

$$V_2{}' = V_1(t,a^\star) - \delta_2 f V_2(t) \tag{36d}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) V_1(t,a) = -\delta_1 f V_1(t,a), \quad 0 \le a \le a^\star \tag{36e}$$

and boundary condition

$$V_1(t,0) = \begin{cases} \gamma S_0\left(\frac{S(t)}{S(t)+A(t)}\right) & \text{if } T \le t \le T_e \text{ and } S > 0 \\ 0 & \text{otherwise} \end{cases} \tag{36f}$$

where $f = \beta(\delta_A A + I)$ and $\tilde{V}_1(t) = \int_0^{a^\star} V_1(t,a)da$

Simplifying a bit

Integrate (36e) using characteristics along lines $a = s$ and $t = T + s$, with s as a new variable

$$V_1(t, a) = V_1(t - a, 0) \exp\left(\int_{t-a}^{t} -\delta_1 f(\xi)\ d\xi\right) \tag{37}$$

Define

$$\zeta(t) = \int_0^t \delta_1 f(\xi) d\xi$$

and substitute into (37), giving

$$V_1(t, a) = V_1(t - a, 0) \exp\left(\zeta(t - a)\zeta(t)\right)$$

So the distributed delay is now discrete

Simplifying a bit more

Let

$$\nu(t) = \int_0^t V_1(s,0)e^{\zeta(s)}ds$$

Then the total number of individuals having been vaccinated with a single dose is

$$\tilde{V}_1(t) = e^{-\zeta(t)}\left(\nu(t) - \nu(t-a^\star)\right)$$

$$S' = -fS - V_1(t,0) \tag{38a}$$

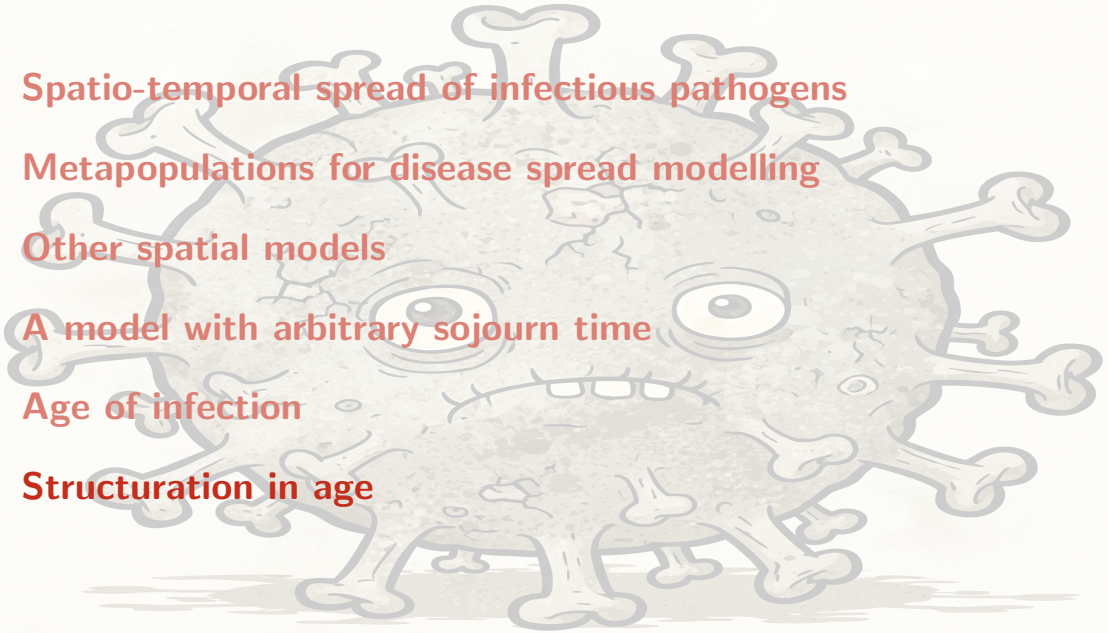
$$A' = \left((1-p)S + (1-p_1)\delta_1\tilde{V}_1 + (1-p_2)\delta_2 V_2\right)f - \mu_A A \tag{38b}$$

$$I' = (pS + p_1\delta_1\tilde{V}_1 + p_2\delta_2 V_2)f - \mu I \tag{38c}$$

$$V_2{}' = V_1(t-a^\star,0)e^{\zeta(t-a^\star)} - \delta_2 f V_2(t) \tag{38d}$$

$$\zeta' = \delta_1 f \tag{38e}$$

$$\nu' = V_1(t,0)e^{\zeta(t)} \tag{38f}$$



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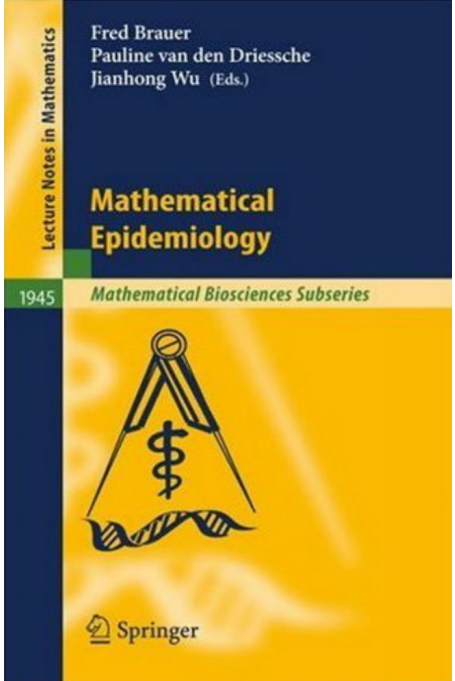
Age structure

Taking into account age can be important in some cases

- Demographic characteristics vary with age
- Interactions are in general more frequent between people of a similar age. They are also more frequent in younger individuals
- Some diseases attack preferentially younger individuals
- The immunity of individuals changes with age, so for instance, older people may be more susceptible to some diseases than younger people

This is based on courses given by Jia Li during a Banff summer school in 2004


Lecture Notes in Mathematics
Fred Brauer
Pauline van den Driessche
Jianhong Wu (Eds.)
Mathematical Epidemiology
1945
Mathematical Biosciences Subseries
Springer

Note on age

Chronological age, as a structuring variable, is "easier" than other structuring variables

Indeed, if a is (chronological) age, then

$$\frac{d}{dt}a = 1$$

Formulation of an SIR model

Let a be the age. Assume that natural death and recovery occur at the rates μ and γ, respectively, both dependent on a

When an individual is sick, they are subject to disease-induced death at the rate $\delta(a)$

Governing equations are

$$(\partial_t + \partial_a)S(t,a) = \Lambda(a) - (\mu(a) + \lambda(t,a))S(t,a) \tag{39a}$$
$$(\partial_t + \partial_a)I(t,a) = -(\mu(a) + \gamma(a) + \delta(a))I(t,a) + \lambda(t,a)S(t,a) \tag{39b}$$
$$(\partial_t + \partial_a)R(t,a) = \gamma(a)I(t,a) \tag{39c}$$

Boundary conditions are

$$S(t, a_0) = B \tag{39d}$$
$$I(t, a_0) = 0 \tag{39e}$$
$$R(t, a_0) = 0 \tag{39f}$$

while initial conditions take the form

$$S(0, a) = \Phi(a) \tag{39g}$$
$$I(0, a) = \Psi(a) \tag{39h}$$
$$R(0, a) = 0 \tag{39i}$$

Force of infection

Transmission $\lambda(t, a)$ of the disease takes the form

$$\lambda(t, a) = r(a) \int_{a_0}^{\infty} \beta(a, s)\rho(a, s)\frac{I(t, s)}{N(t, s)} ds$$

where

- $r(a)$ is the number of contacts by individuals of age a per unit time
- $\beta(a, s)$ is the probability of disease transmission to a susceptible of age a by an infectious of age s
- $\rho(a, s)$ is the meeting rate between people of age a and people of age s
- $N(t, a) = S(t, a) + I(t, a) + R(t, a)$ is the distribution of total population

To simplify, assume that $\beta(a, s)$ is separable

$$\beta(a, s) = f(a)g(s)$$

where $f(a)$ is the susceptibility of individuals aged a and $g(s)$ is the force of infection of individuals aged s

Then

$$\lambda(t, a) = r(a)f(a) \int_{a_0}^{\infty} g(s)\rho(a, s) \frac{I(t, s)}{N(t, s)} ds \tag{40}$$

Analysis of the SIR model

We seek the DFE by setting $I = 0$

We find $(S, I, R) = (S^0(a), 0, 0)$ with

$$S^0(a) = Be^{-M(a)} + e^{-M(a)} \int_{a_0}^{a} e^{M(x)} \Lambda(x) dx$$

where

$$M(a) = \int_{a_0}^{a} \mu(s) ds$$

Consider the perturbed solution $u(t,a) = S(t,a) - S^0(a)$. Assume that the meeting rate ρ is also separable,

$$\rho(a,s) = p_1(a)p_2(s)$$

Then

$$\tilde{\lambda}(t,a) := r(a)f(a)p_1(a)\int_{a_0}^{\infty} \frac{g(s)p_2(s)}{S^0(s)} I(t,s)ds \simeq \lambda(t,a)$$

and we obtain the linearisation

$$\begin{aligned}
(\partial_t + \partial_a)u &= -\mu(a)u - \tilde{\lambda}(t,a)S^0(a) \\
(\partial_t + \partial_a)I &= -(\mu(a) + \gamma(a) + \delta(a))I + \tilde{\lambda}(t,a)S^0(a) \\
(\partial_t + \partial_a)R &= \gamma(a)I
\end{aligned}$$

Let

$$u(t,a) = \tilde{u}(a)e^{c(t-a)} \qquad I(t,a) = \tilde{I}(a)e^{c(t-a)}$$

and denote

$$b(a) = S^0(a)r(a)f(a)p_1(a) \qquad W = \int_{a_0}^{\infty} \frac{g(s)p_2(s)}{S^0(s)} e^{-cs}\tilde{I}(s)ds$$

Then

$$\frac{d\tilde{u}(a)}{da} = -\mu(a)\tilde{u}(a) - b(a)e^{ca}W$$
$$\frac{d\tilde{I}(a)}{da} = -(\mu(a) + \gamma(a))\tilde{I}(a) + b(a)e^{ca}W$$

$$\tilde{I}(a) = We^{-M(a)-\Gamma(a)} \int_{a_0}^{\infty} e^{M(s)+\Gamma(s)} b(s)e^{cs} ds$$

where $\Gamma(a) = \int_{a_0}^{a} \gamma(s)ds$

Therefore

$$W = W \int_{a_0}^{\infty} \frac{g(s)p_2(s)}{S^0(s)} e^{-M(s)-\Gamma(s)} \int_{a_0}^{s} e^{M(v)+\Gamma(v)} b(v)e^{-c(s-v)} dvds$$

Let then

$$H(c) := \int_{a_0}^{\infty} \frac{g(s)p_2(s)}{S^0(s)} e^{-M(s)-\Gamma(s)} \int_{a_0}^{s} e^{M(v)+\Gamma(v)} b(v) e^{-c(s-v)} dvds$$

We seek roots of the characteristic equation $H(c) = 1$

We have

$$\frac{dH(c)}{dc} = -\int_{a_0}^{\infty} \frac{g(s)p_2(s)}{S^0(s)} e^{-M(s)-\Gamma(s)} \int_{a_0}^{s} (s-v) e^{M(v)+\Gamma(v)} b(v) e^{-c(s-v)} dvds < 0$$

implying that $H(c)$ is a decreasing function

- Let $c^\star$ be a real solution to $H(c) = 1$. If $H(0) > 1$, then $c > 0$, whereas if $H(0) < 1$, $c < 0$

- Suppose that $c^\star = \alpha + i\beta$ is a complex root of $H(c) = 1$. Then

$$\mathrm{Re}\ H(c) = \int_{a_0}^{\infty} \frac{g(s)p_2(s)}{S^0(s)} e^{-M(s)-\Gamma(s)} \int_{a_0}^{s} e^{M(v)+\Gamma(v)} b(v) e^{-\alpha(s-v)} \cos\beta(s-v) dv ds$$

As a consequence, $H(0) < 1 \implies \alpha < 0$

So $H(0) = 1$ is a threshold and we take $\mathcal{R}_0 = H(0)$

Analysis using semigroups: SIA model

To illustrate the use of the semigroup method in this context, we consider an SIA model describing the evolution of HIV/AIDS

The model is almost equivalent to (39), with a few differences

The I compartment contains inviduals bearing HIV, but not yet in the AIDS stage

The rate $\gamma(a)$ represents the progression towards the AIDS stage

The AIDS stage is represented by compartment A, where individuals are subject to a specific mortality rate

$$(\partial_t + \partial_a)S(t,a) = \Lambda(a) - (d(a) + \lambda(t,a))S(t,a) \tag{41a}$$
$$(\partial_t + \partial_a)I(t,a) = -(d(a) + \gamma(a))I(t,a) + \lambda(t,a)S(t,a) \tag{41b}$$
$$(\partial_t + \partial_a)A(t,a) = \gamma(a)A(t,a) - (d(a) + \delta(a))A(t,a) \tag{41c}$$

Assume

$$\lambda(t,a) = h(a)\int_{a_0}^{\infty} \rho(a,a')\frac{I(t,a')}{T(t,a')}da' \tag{41d}$$

where $T(t,a') = S(t,a') + I(t,a')$

An individual in AIDS stage no longer has contacts. Therefore the dynamics of S and I do not depend on the dynamics of A, and we consider the system consisting of the first two variables

Let ω be the maximum age. The system in proportions takes the form

$$x := \frac{S}{T} \qquad y := \frac{I}{T}$$

As we are only considering S and I, we have $x + y = 1$ and the system reads

$$(\partial_t + \partial_a) y(t,a) = (1-y)(-\gamma(a) y + \lambda(t,a)) \tag{42a}$$

$$\lambda(t,a) = h(a) \int_0^\omega p(a,a') y(t,a') da' \tag{42b}$$

Let $X = \{f \in L^1(0,\omega)\}$. Define

$$(Af)(a) := -\frac{d}{da}f(a), \quad f \in D(A)$$

with $D(a) = \{f \in X,\ f \text{ is absolutely continuous, } f(0) = 0\}$, and

$$F(f)(a) \equiv (1 - f(a))\left(-\gamma(a)f(a) + h(a)\int_0^\omega p(a,a')f(a')da'\right)$$

an operator from $X \to X$

Let $\Omega = \{f \in X,\ 0 \le f \le 1 \text{ a.e.}\}$. Then (42) takes the form

$$\frac{dy}{dt} = Ay + F(y)$$
$$y(0) = y_0 \in \Omega$$

Let

$$(\mathcal{B}f)(a) = -\frac{df(a)}{da} - \gamma(a)f(a) \qquad (\mathcal{P}f)(a) = h(a)\int_0^\omega p(a,a')f(a')da'$$

We have

$$(\partial_t + \partial_a)y = -\gamma(a)y + h(a)\int_0^\omega \rho(a,a')y(t,a')da' \Leftrightarrow \frac{dy}{dt} = (\mathcal{B}+\mathcal{P})y$$

$\mathcal{B}+\mathcal{P}$ generates a C_0-semigroup $T(t)$, $t \geq 0$, which is eventually uniformly continuous

The resolvant of $\mathcal{B}+\mathcal{P}$ is

$$R(\lambda;\mathcal{B}+\mathcal{P}) = (S_\lambda - I)^{-1} G$$

with

$$(Gf)(a) = \int_0^a e^{-\lambda(a-\sigma)} \frac{\Gamma(a)}{\Gamma(\sigma)} f(\sigma) d\sigma$$

$$(S_\lambda f)(a) = \int_0^\omega \int_0^a e^{-\lambda(a-\sigma)} \frac{\Gamma(a)}{\Gamma(\sigma)} \rho(\sigma,\xi) d\sigma f(\xi) d\xi$$

where we denoted

$$\Gamma(a) = \exp\left(-\int_0^a \gamma(a')da'\right)$$

$\mathcal{R}_0$

$\mathcal{R}_0$ is the spectral radius of the operator

$$(Sf)(a) = \int_0^\omega \int_0^a \frac{\Gamma(a)}{\Gamma(\sigma)} h(\sigma) p(\sigma, \xi) d\sigma f(\xi) d\xi$$

Pair formation

$\rho(t, a, a')$ proportion of partners of an individual aged a who are aged a'

$r(t, a)$ mean number of partners of an individual aged a

$T(t, a)$ total number of individuals aged a

The following conditions must hold

- $0 \leq \rho \leq 1$
- $\int_0^\infty \rho(t, a, a')da' = 1$
- $\rho(t, a, a')r(t, a)T(t, a) = \rho(t, a', a)r(t, a')T(t, a')$
- $r(t, a)T(t, a)r(t, a')T(t, a') = 0 \Rightarrow \rho(t, a, a') = 0$

```r
# From https://stackoverflow.com/questions/36868287/purl-within-knit-dupli
rmd_chunks_to_r_temp <- function(file){
  callr::r(function(file, temp){
    out_file = sprintf("../CODE/%s", gsub(".Rnw", ".R", file))
    knitr::purl(file, output = out_file, documentation = 1)
  }, args = list(file))
}
rmd_chunks_to_r_temp("course-02-metapopulations-and-advanced-models.Rnw")

## [1] "../CODE/course-02-metapopulations-and-advanced-models.R"
```

Bibliography I

- Arino, J. (2009). Diseases in metapopulations. In Ma, Z., Zhou, Y., and Wu, J., editors, *Modeling and Dynamics of Infectious Diseases*, volume 11 of *Series in Contemporary Applied Mathematics*, pages 65–123. World Scientific.
- Arino, J. (2017). Spatio-temporal spread of infectious pathogens of humans. *Infectious Disease Modelling*, 2(2):218–228.
- Arino, J., Bajeux, N., and Kirkland, S. (2019). Number of source patches required for population persistence in a source-sink metapopulation. *Bulletin of Mathematical Biology*, 81(6):1916–1942.
- Arino, J., Cooke, K., van den Driessche, P., and Velasco-Hernández, J. (2004). An epidemiology model that includes a leaky vaccine with a general waning function. *DCDS-B*, 4(2):479–495.

Bibliography II

- Arino, J., Davis, J., Hartley, D., Jordan, R., Miller, J., and van den Driessche, P. (2005). A multi-species epidemic model with spatial migration. *Mathematical Medicine and Biology*, 22(2):129–142.
- Arino, J., Jordan, R., and van den Driessche, P. (2007). Quarantine in a multi-species epidemic model with spatial dynamics. *Mathematical Biosciences*, 206(1):46–60.
- Arino, J. and van den Driessche, P. (2003a). The basic reproduction number in a multi-city compartmental epidemic model. *Lecture Notes in Control and Information Science*, 294:135–142.
- Arino, J. and van den Driessche, P. (2003b). A multi-city epidemic model. *Mathematical Population Studies*, 10(3):175–193.
- Arino, J. and van den Driessche, P. (2006). Metapopulations epidemic models. A survey. *Fields Institute Communications*, 48:1–12.

Bibliography III

- Brauer, F., Van den Driessche, P., Wu, J., and Allen, L. (2008). *Mathematical epidemiology*, volume 1945 of *Lecture Notes in Mathematics*. Springer.
- Foster, D. and Jacquez, J. (1975). Multiple zeros for eigenvalues and the multiplicity of traps of a linear compartmental system. *Mathematical Biosciences*, 26(1-2):89–97.
- Hale, J. and Verduyn-Lunel, S. (2013). *Introduction to functional differential equations*, volume 99. Springer Science & Business Media.
- Khan, K., Arino, J., Hu, W., Raposo, P., Sears, J., Calderon, F., Heidebrecht, C., Macdonald, M., Liauw, J., Chan, A., and Gardam, M. (2009). Spread of a novel influenza A (H1N1) virus via global airline transportation. *New England Journal of Medicine*, 361(2):212–214.

Bibliography IV

- Li, J. and Brauer, F. (2008). Continuous-time age-structured models in population dynamics and epidemiology. In *Mathematical Epidemiology*, pages 205–227. Springer.
- Lopez, L., Coutinho, F., Burattini, M., and Massad, E. (1999). Modelling the spread of infections when the contact rate among individuals is short ranged: Propagation of epidemic waves. *Mathematical and Computer Modelling*, 29(7):55–69.
- Murray, J. and Seward, W. (1992). On the spatial spread of rabies among foxes with immunity. *Journal of Theoretical Biology*, 156(3):327–348.
- Sattenspiel, L. and Dietz, K. (1995). A structured epidemic model incorporating geographic mobility among regions. *Mathematical Biosciences*, 128(1-2):71–91.

Bibliography V

 van den Driessche, P. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180(1-2):29–48.