



University
of Manitoba

Metapopulation models and a few advanced models

Populate Summer School – Course 02

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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

Introductions

Probability of introductions

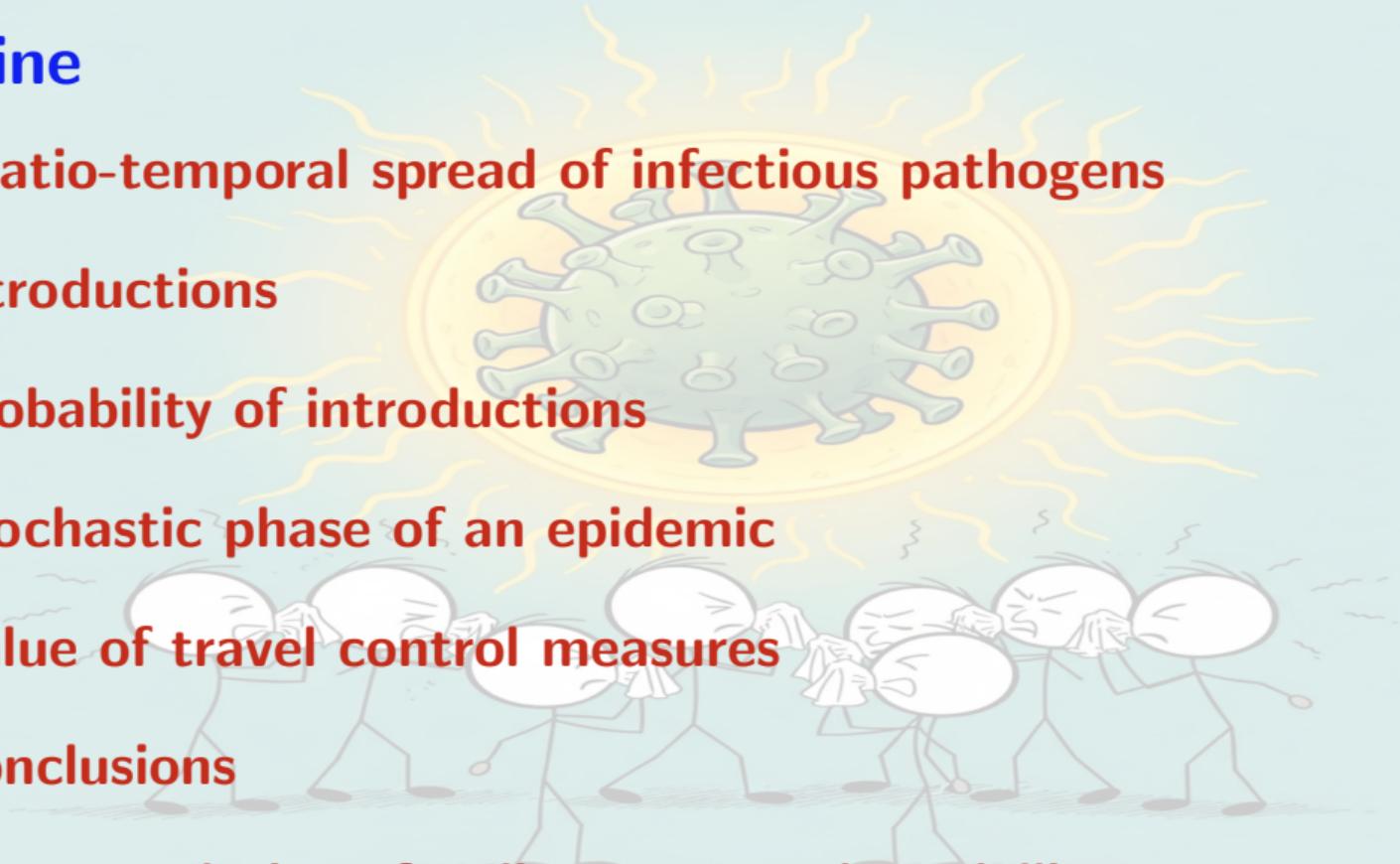
Stochastic phase of an epidemic

Value of travel control measures

Conclusions

Metapopulations for disease spread modelling

Other spatial models



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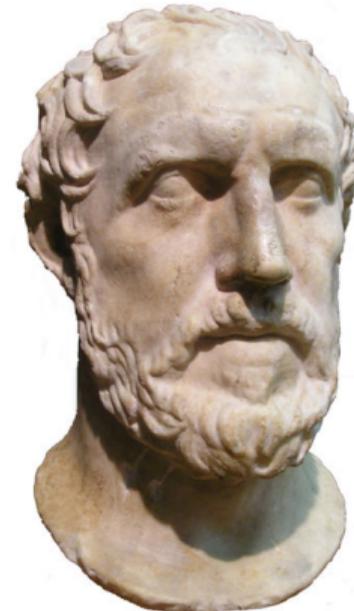
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Diseases have been known to be mobile for a while

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



Scale of mobility difficult to apprehend ... but mobility is critical

Working definition

Mobility is the collection of processes through which individuals change their current location

All migrants/travellers carry with them their “health history”

Pathogens ignore borders and politics

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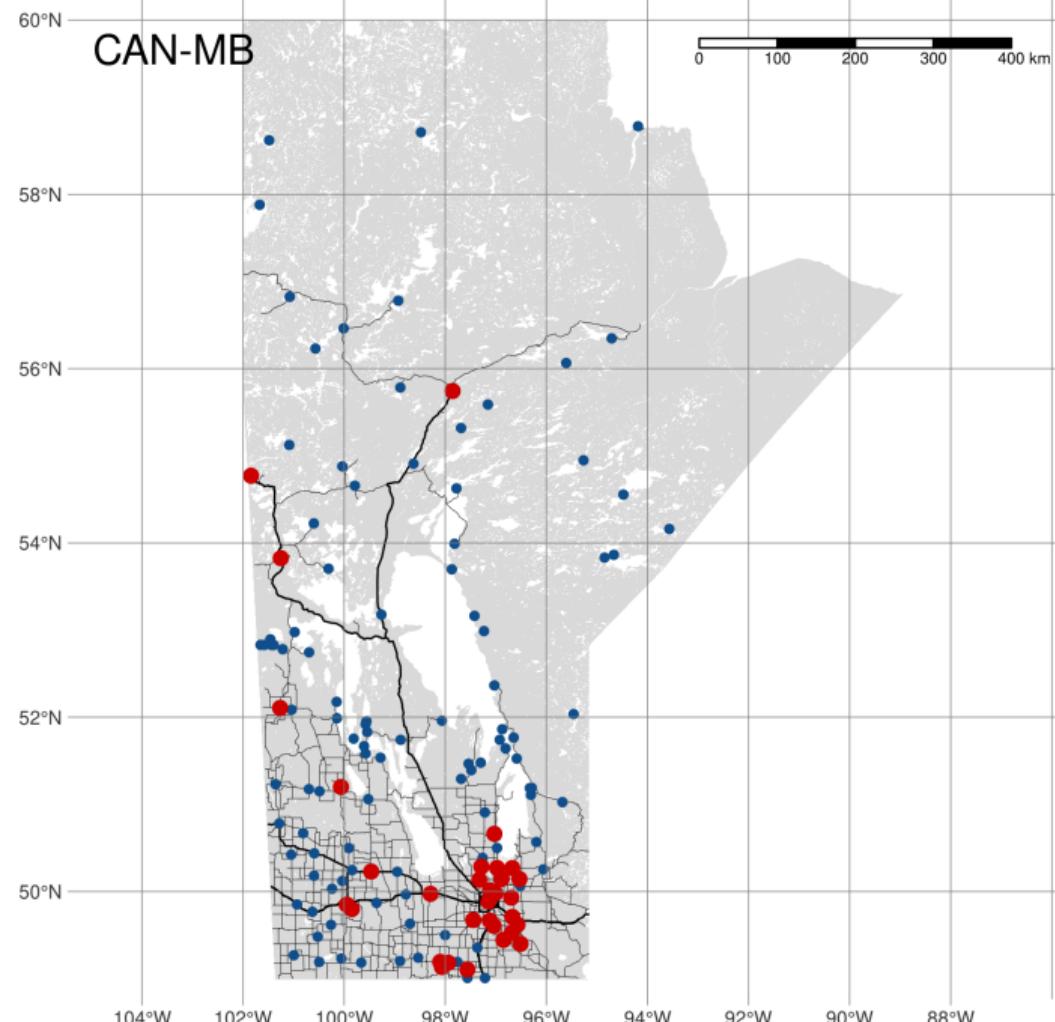
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Summary and discussion

Why small jurisdictions?

MB is very unbalanced, population-wise

Province	Largest	Second Largest	Ratio
AB	Calgary (CMA)	Edmonton (CMA)	1.04
NB	Moncton (CMA)	Saint John (CMA)	1.2
SK	Saskatoon (CMA)	Regina (CMA)	1.27
ON	Toronto (CMA)	Ottawa-Gatineau (CMA)	4.17
PE	Charlottetown (CA)	Summerside (CA)	4.75
NS	Halifax (CMA)	Cape Breton (CA)	4.97
QC	Montréal (CMA)	Québec City (CMA)	5.11
BC	Vancouver (CMA)	Victoria (CMA)	6.66
NL	St. John's (CMA)	Corner Brook (CA)	7.14
MB	Winnipeg (CMA)	Brandon (CA)	8.76



Northern Manitoba chiefs call for immediate federal action on health-care crisis

Recent deaths linked to inadequate medical care include mother of 5 from Manto Sipi Cree Nation, chief says

CBC News · Posted: Apr 03, 2023 3:20 PM CDT | Last Updated: April 3, 2023



A group of Manitoba chiefs is calling for immediate action from the federal government to address what they call a health-care crisis causing preventable deaths on northern First Nations in the province.

That action needs to start with ensuring nursing stations in remote communities are staffed adequately with nurses and have a full-time doctor available, said Michael Yellowback, chief of Manto Sipi Cree Nation (previously known as God's River).

Right now, the community only has two of the three nurses it's supposed to, and doctors only visit every two weeks, he said.



'It's not working'

With a nursing shortage and no hospital,
Island Lake First Nations communities
face health-care struggle

'A lengthy process to get help here'

Wasagamack is one of four First Nations communities that make up Island Lake, an area in northeastern Manitoba dotted with hundreds of small islands.

Island Lake has a population of at least 15,000, according to Scott Harper, the grand chief of Anisininew Okimawin, which represents the four communities.

Despite having a population roughly the size of Thompson, and having diabetes and hospitalization rates well above provincial averages, Island Lake has no hospital of its own. The region is accessible only by air, boat and an unreliable winter road.

The nursing station in Wasagamack First Nation, which has about 2,300 people, according to federal government data, typically operates short-staffed, with only two or three of five registered nurses working on any given rotation and a fly-in doctor who comes weekly.

For First Nation and Métis Communities

Remote describes a **geographical area** where a community is **located over 350 km** from the **nearest service centre having year-round access** by land and/or water routes normally used in all weather conditions

Isolated means a **geographical area** that has **scheduled flights** and good telephone service, but is **without year-round access** by land and/or water normally used in all weather conditions

Remote-Isolated means a **geographic area** that has **neither scheduled flights nor year-round access** by land and/or water routes normally that can be used in all weather conditions, irrespective of the level of telephone and radio service available

For Inuit communities

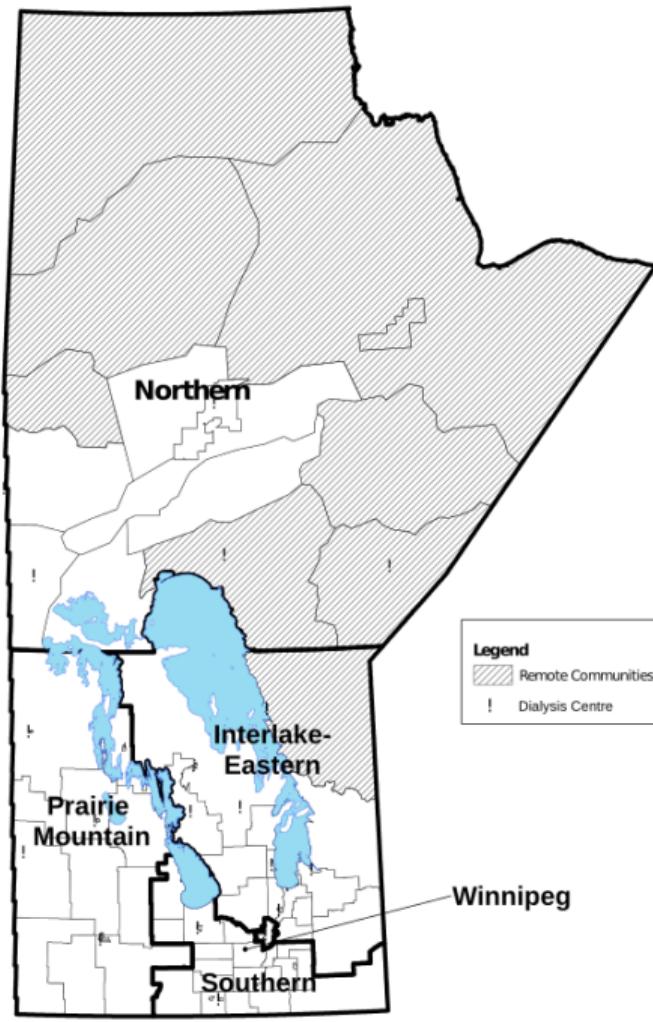
Inuit Communities to be referred to as **Inuit Nunangat**, not remote and isolated communities to respect the unique language and culture of Inuit regions, as well as the common challenges in social determinants of health, access to care, and infrastructure found across all Inuit communities

MB remote communities

Remote communities are communities in Manitoba that **do not have permanent road access** (i.e., no all-weather road), are **more than a four-hour drive from a major rural hospital (and a dialysis unit)**, or **have rail or fly-in access only**. This includes Norway House, Lynn Lake, Leaf Rapids, Gillam, and Cross Lake. If most communities in a health district are designated as "remote", the entire district is designated as "remote". In Manitoba, remote districts include:

- ▶ Northern Health Region: NO23, NO13, NO25, NO16, NO22, NO26, NO28, NO31, and
- ▶ Interlake-Eastern Health Region: IE61.

Chartier M, Dart A, Tangri N, Komenda P, Walld R, Bogdanovic B, Burchill C, Koseva I, McGowan K, Rajotte L. Care of Manitobans Living with Chronic Kidney Disease. Winnipeg, MB. Manitoba Centre for Health Policy, December 2015



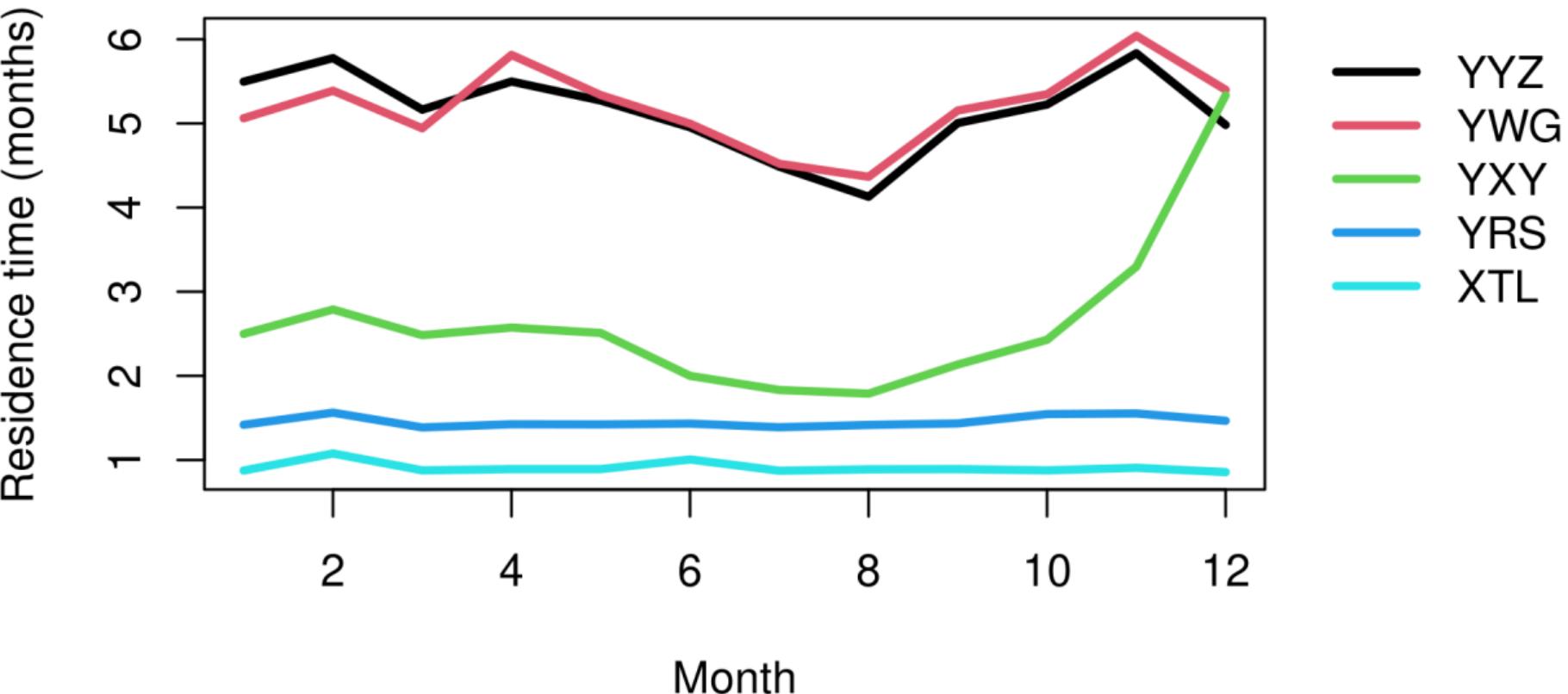
One interesting paradox

Think about travel to/from remote or isolated communities..

How do you think this compares to travel in non-remote/isolated communities ?

Residence time (the lake ecology version): theoretic time an average water or comparable molecule spends in a lake, considering inflow into and outflow from the lake

Residence times in months



The paradox of travel to/from remote/isolated communities

Travel volumes small but movement rates high

ICs are highly connected to the urban centre(s) they are subordinated to

Further reinforced in Winnipeg by urban indigenous population (102,075 or 12.45% of metro population), meaning many family connections exist

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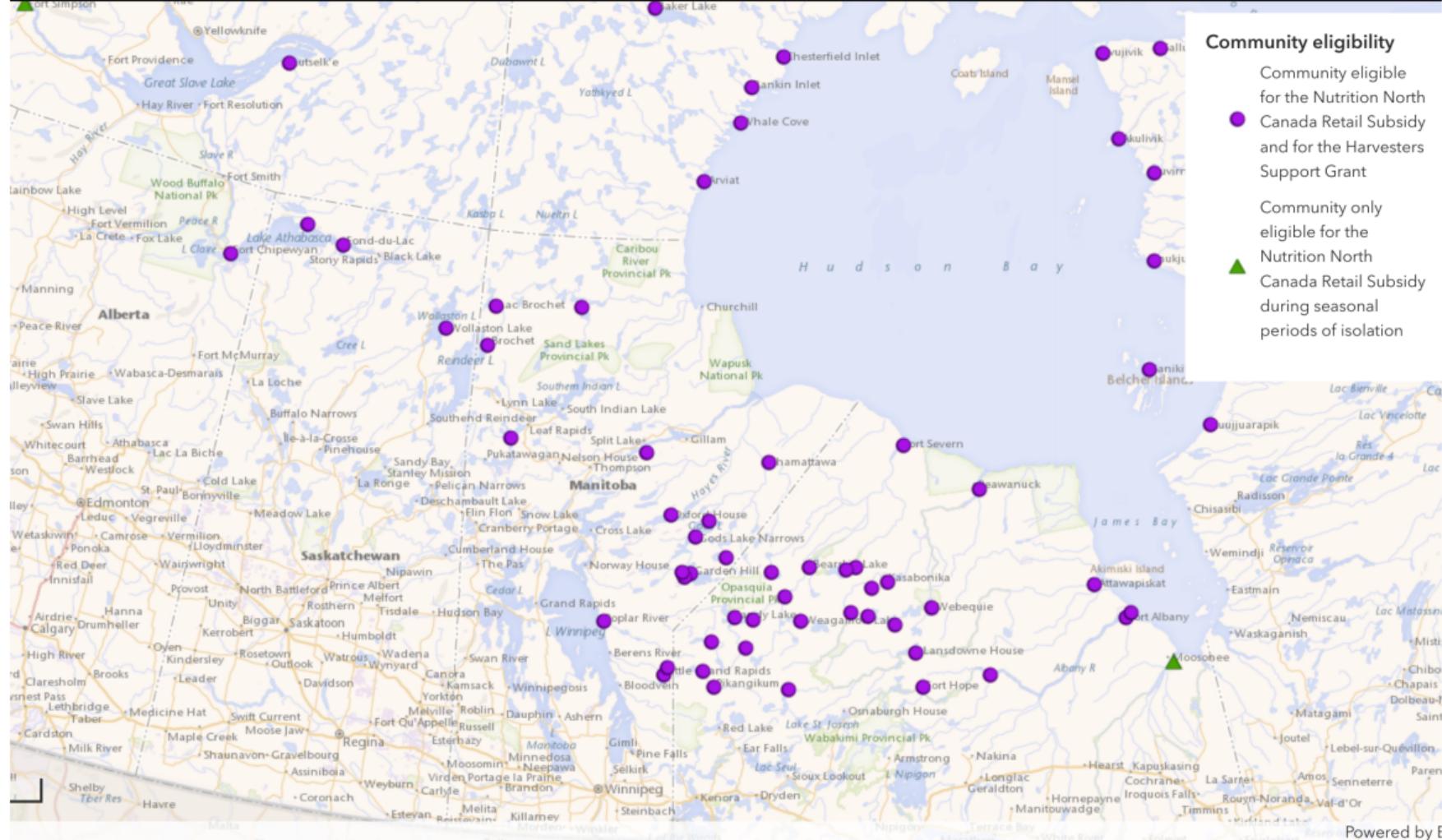
Community eligibility

Community eligible
for the Nutrition North

● Canada Retail Subsidy
and for the Harvesters
Support Grant

Community only
eligible for the
Nutrition North

▲ Canada Retail Subsidy
during seasonal
periods of isolation



As the Kivalliq Inuit Centre struggled to keep up with the ever-increasing needs for medical travellers, Sakku Investments Corporation has now purchased the Clarion Hotel in Winnipeg to become its new medical boarding facility.

The facility hosts 139 rooms, 40,000 square feet of commercial office space, event areas, a pool, spa and much more.

"There are a lot of amenities that are available throughout the building that we currently don't have with the existing location," said David Kakuktinniq, president and CEO of Sakku Investments Corporation.

The Kivalliq Inuit Centre, the previous location for medical travellers, is a 44-room facility with 120 beds, but with the arrangement of three beds per room, there were often challenges making use of the space and housing everyone who needed it.

Kakuktinniq said 200 people per day are being processed for medical, which meant some would be sent to overflow facilities when the Kivalliq Inuit Centre became full. That, in turn, led to significant stresses for medical travellers, their escorts and the staff charged with getting them to appointments and making sure their needs were taken care of.

Travel restrictions/interruptions

During COVID, travelling above 53 north in MB was forbidden for anyone not resident above 53 north

If you wanted to fly to Nunavut, you needed to spend two weeks in quarantine in a hotel in Edmonton, Ottawa or Winnipeg

Canada implemented two weeks quarantine when IB from abroad (with exceptions)

Canada interrupted travel from a variety of places

Questions

- ▶ What is the probability that an introduction is successful?
(note: I am judging things from the perspective of the pathogen)

- ▶ How long is the stochastic phase following an introduction?
(what Amy called the “stuttering period”)

- ▶ What do the different control measures do, how good are they?

Spatio-temporal spread of infectious pathogens

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Stochastic phase of an epidemic

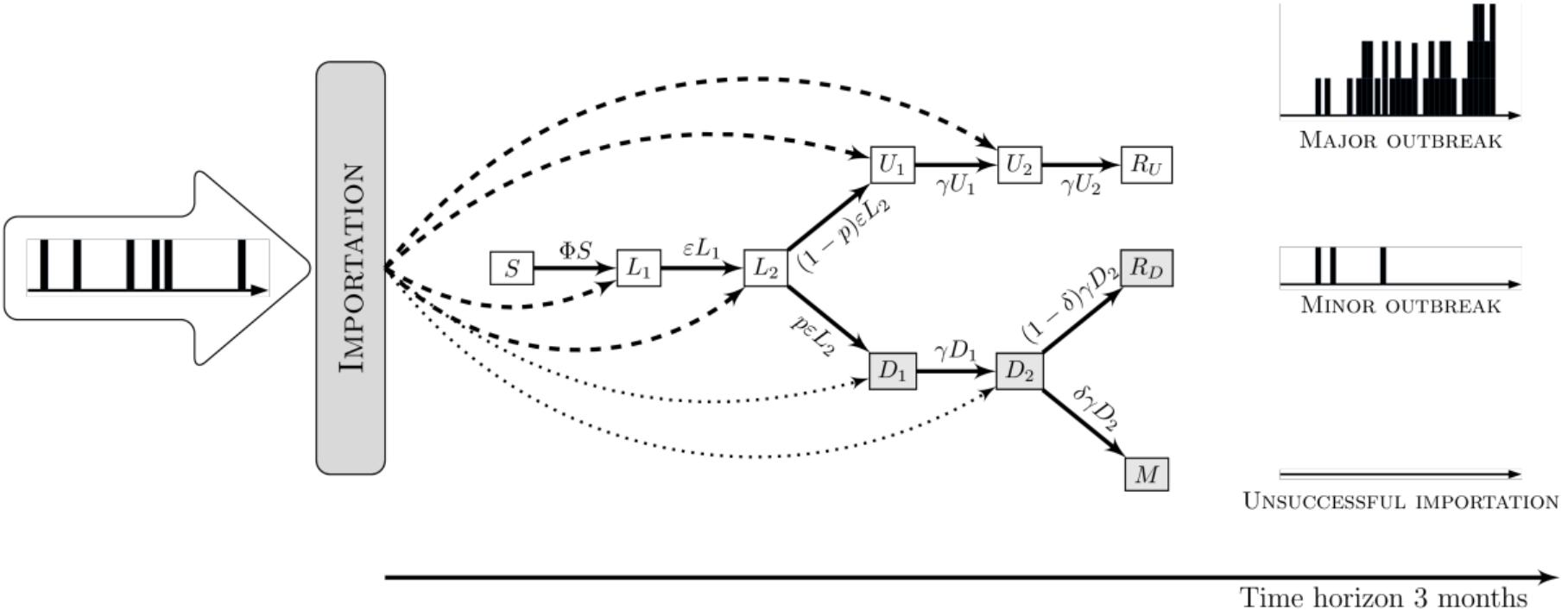
Value of travel control measures

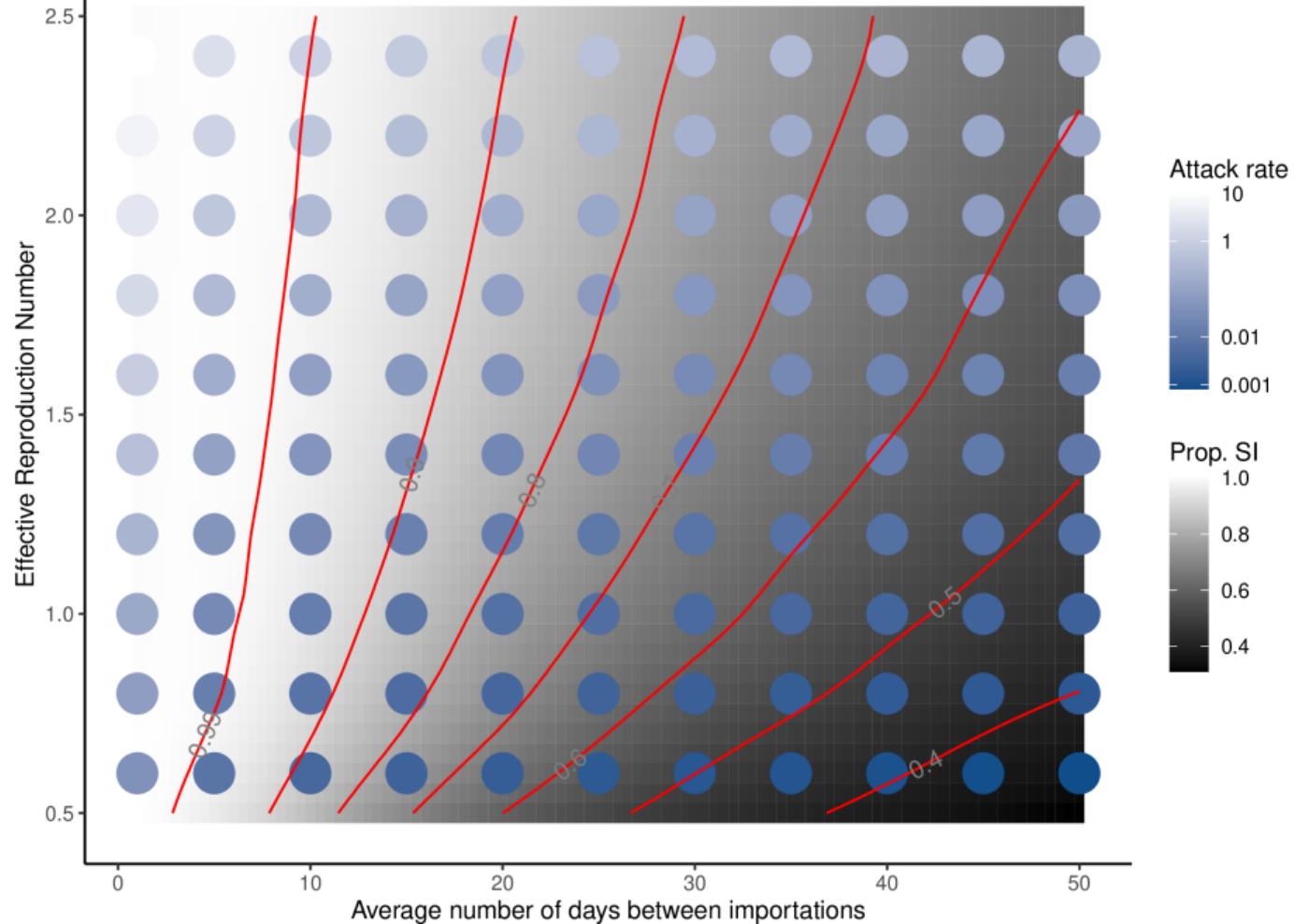
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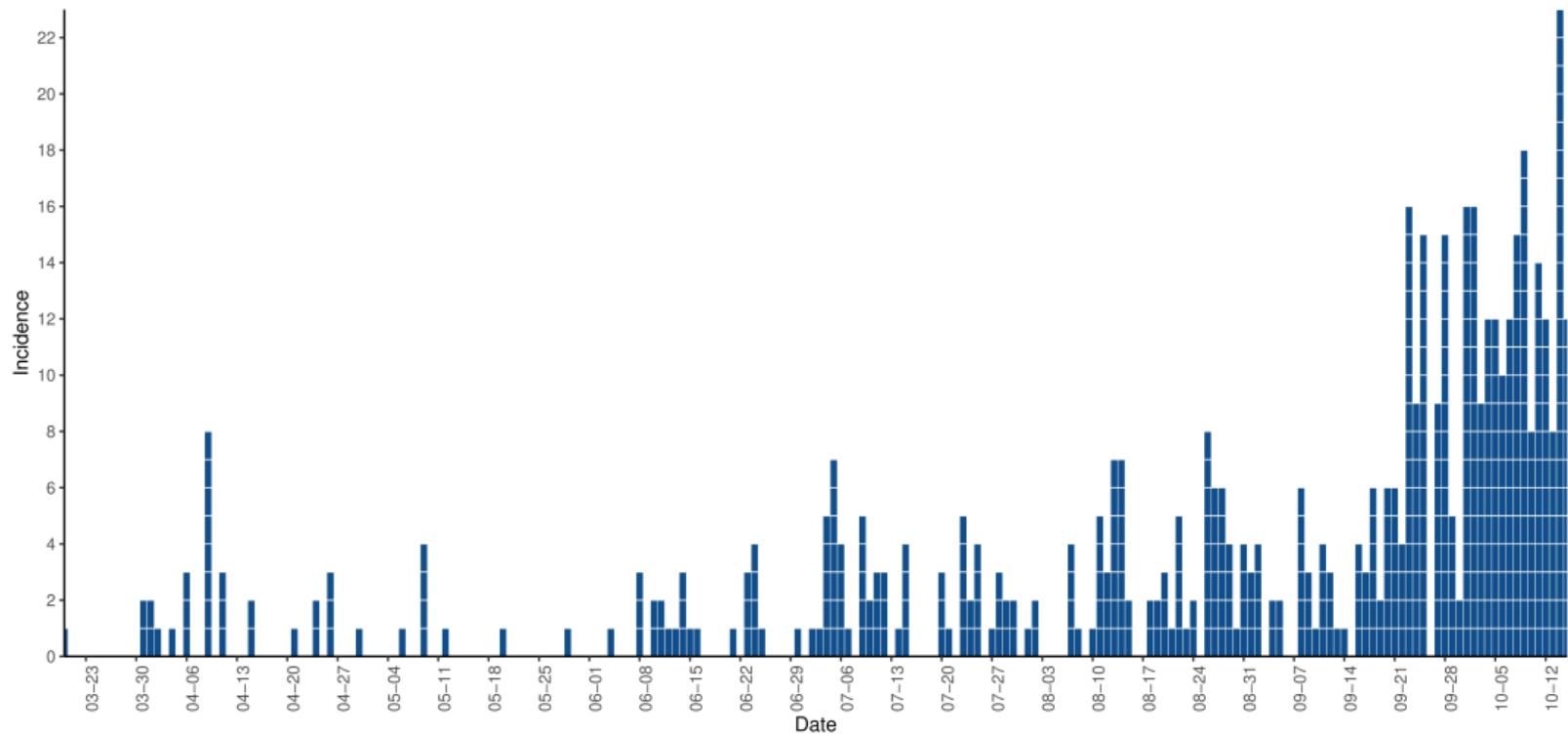
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Campbell county, Wyoming



Investigating outbreak types using a simple CTMC SIS

$$\mathbf{X}(t) = (S^A(t), I^A(t))$$

CTMC $\mathbf{X}(t)$ characterized by transitions

Description	Transition	Rate
Infection	$(S^A, I^A) \rightarrow (S^A - 1, I^A + 1)$	$\beta^A S^A I^A$
Recovery	$(S^A, I^A) \rightarrow (S^A + 1, I^A - 1)$	$\gamma^A I^A$

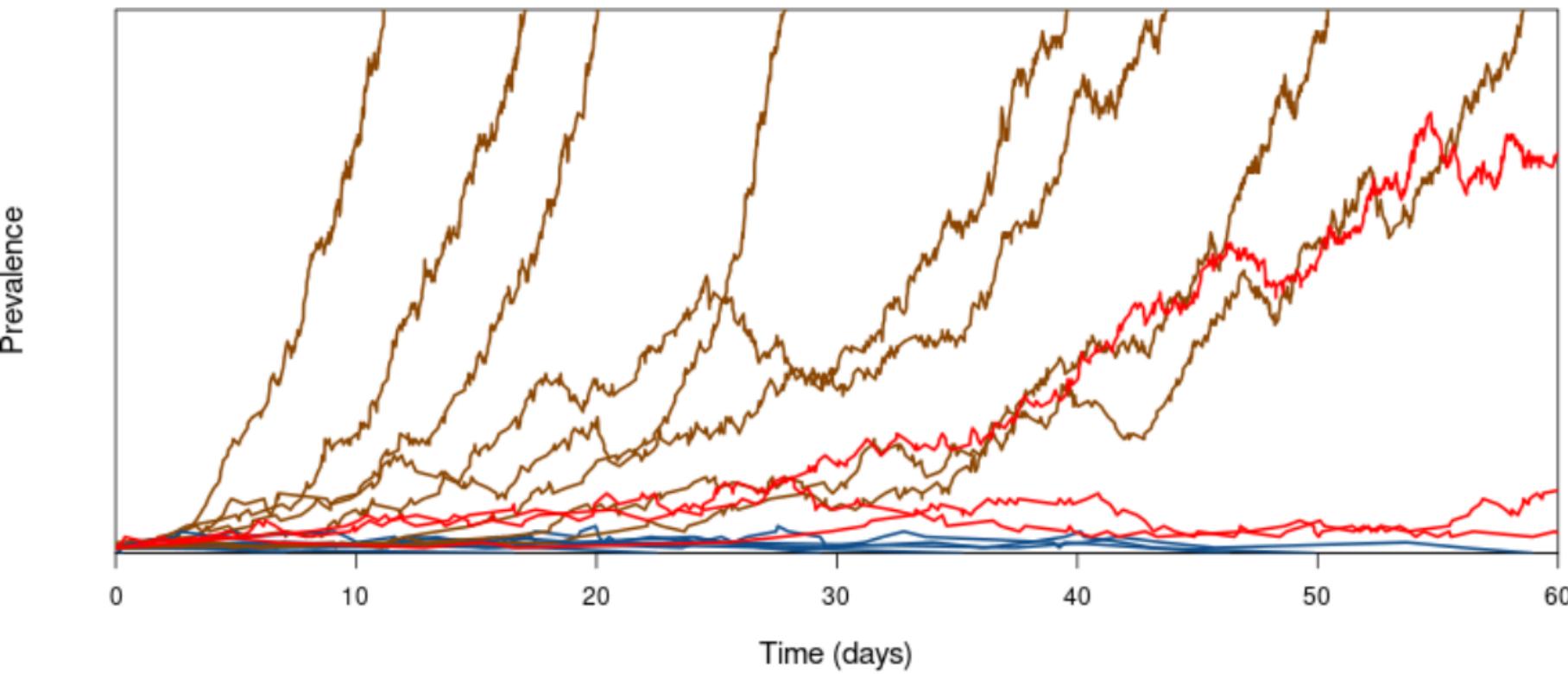
Investigating outbreak types using a simple CTMC SIS *with a twist*

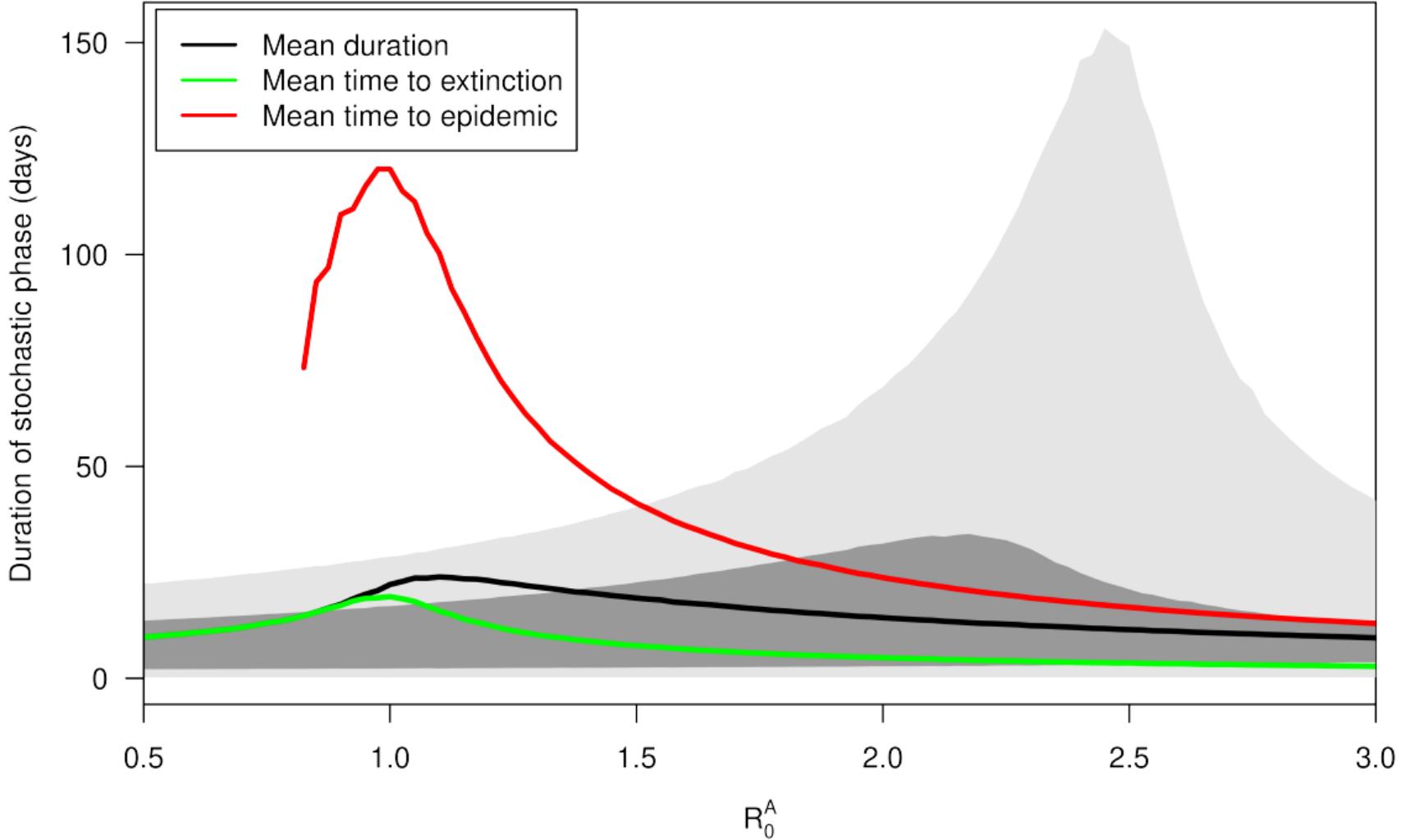
Regular chain of this type has $I = 0$ as sole absorbing state

We add another absorbing state: if $I = \hat{I}$, then the chain has *left* the stochastic phase and is in a quasi-deterministic phase with exponential growth

Doing this, time to absorption measures become usable additionally to first passage time ones

And the question becomes: how long does the chain “linger on” (“stutter”) before it is absorbed? We define the inter-absorption trajectory as the stochastic phase





Problem of the value of the upper bound \hat{I}

- ▶ Choose \hat{I} too small and the stochastic phase will not last long
- ▶ Choose \hat{I} too large and absorption will only be at the DFE
- ▶ So, how does one choose \hat{I} ?
 - ▶ A formula of Whittle (1955)
 - ▶ Multitype branching process (MTBP)

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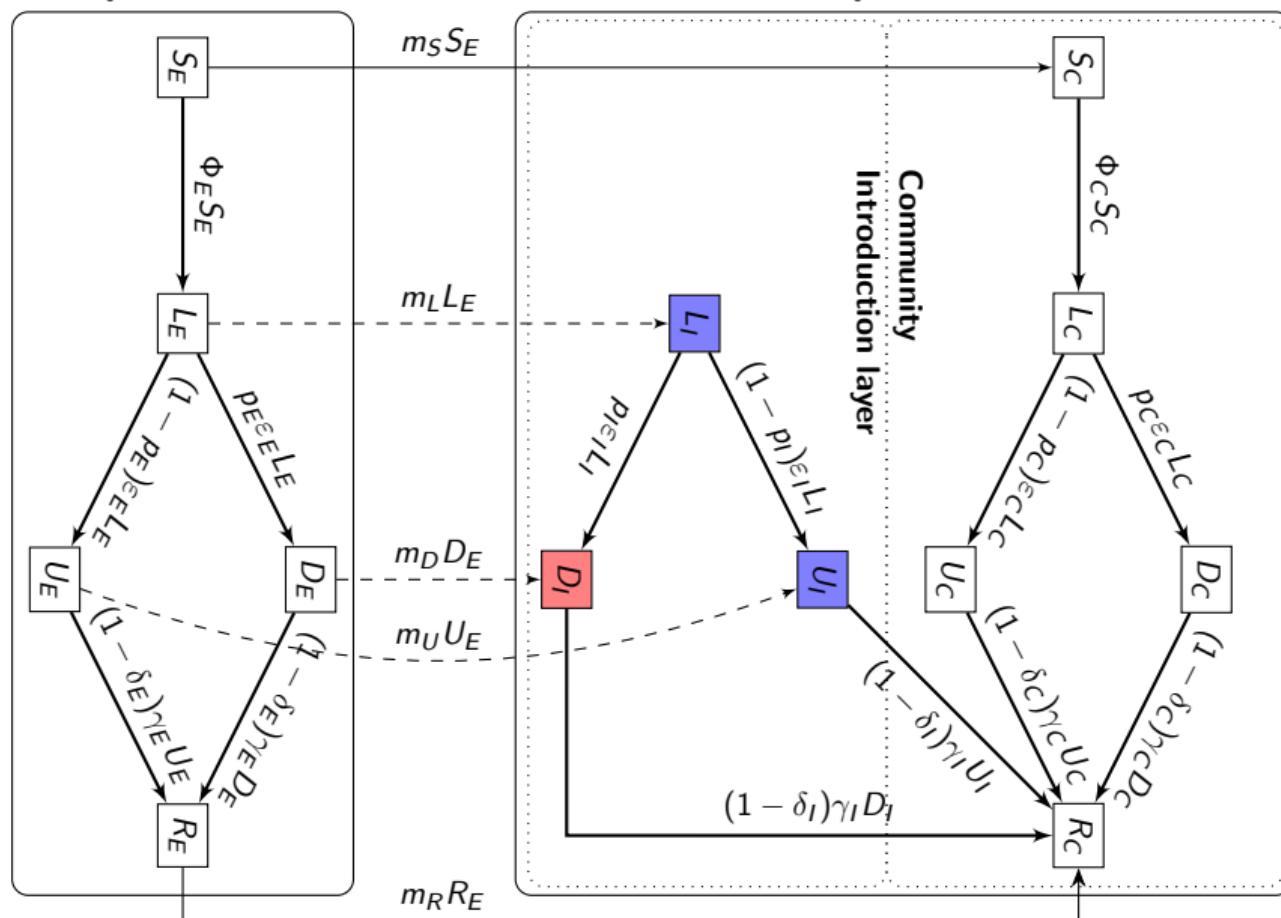
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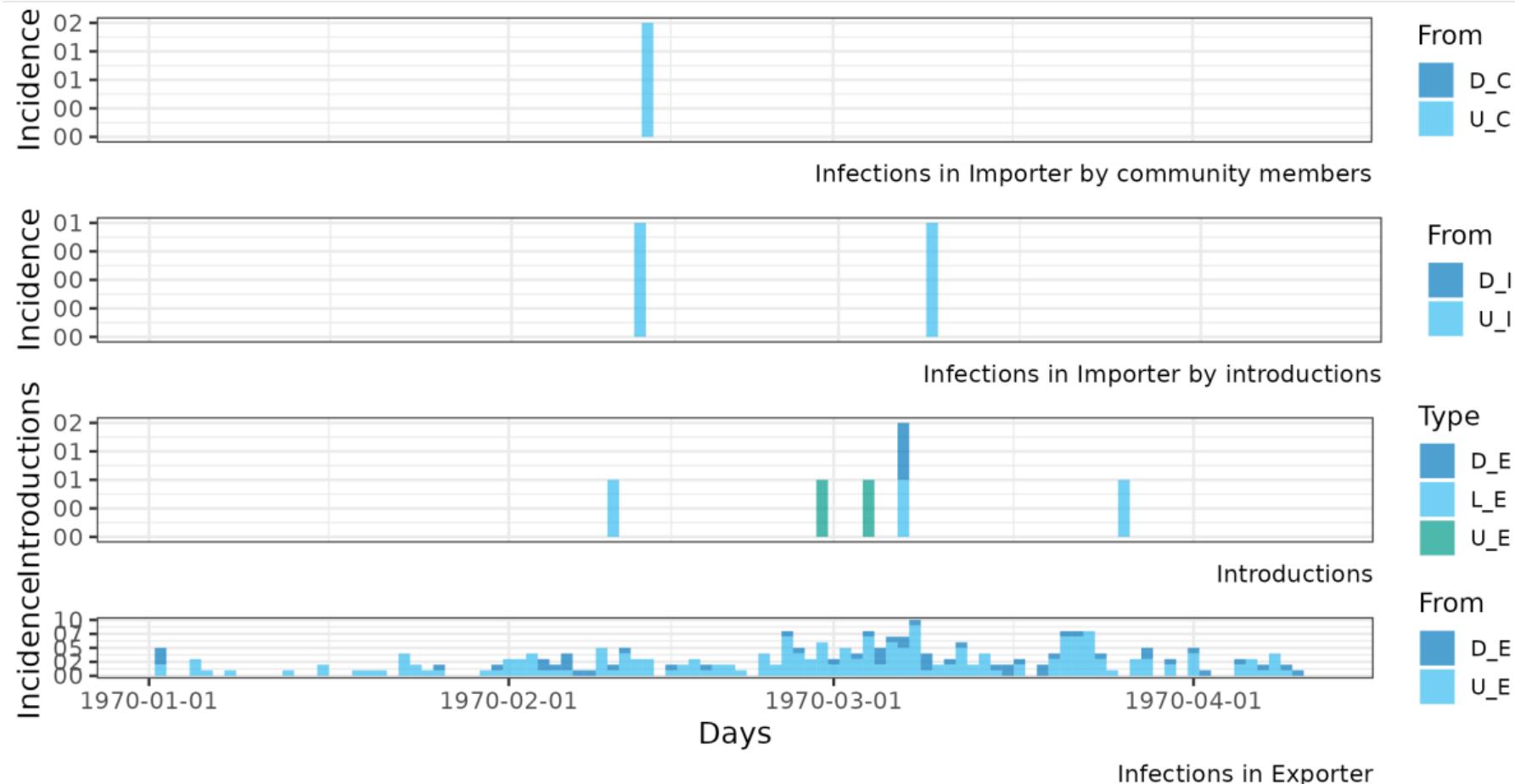
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Exporter

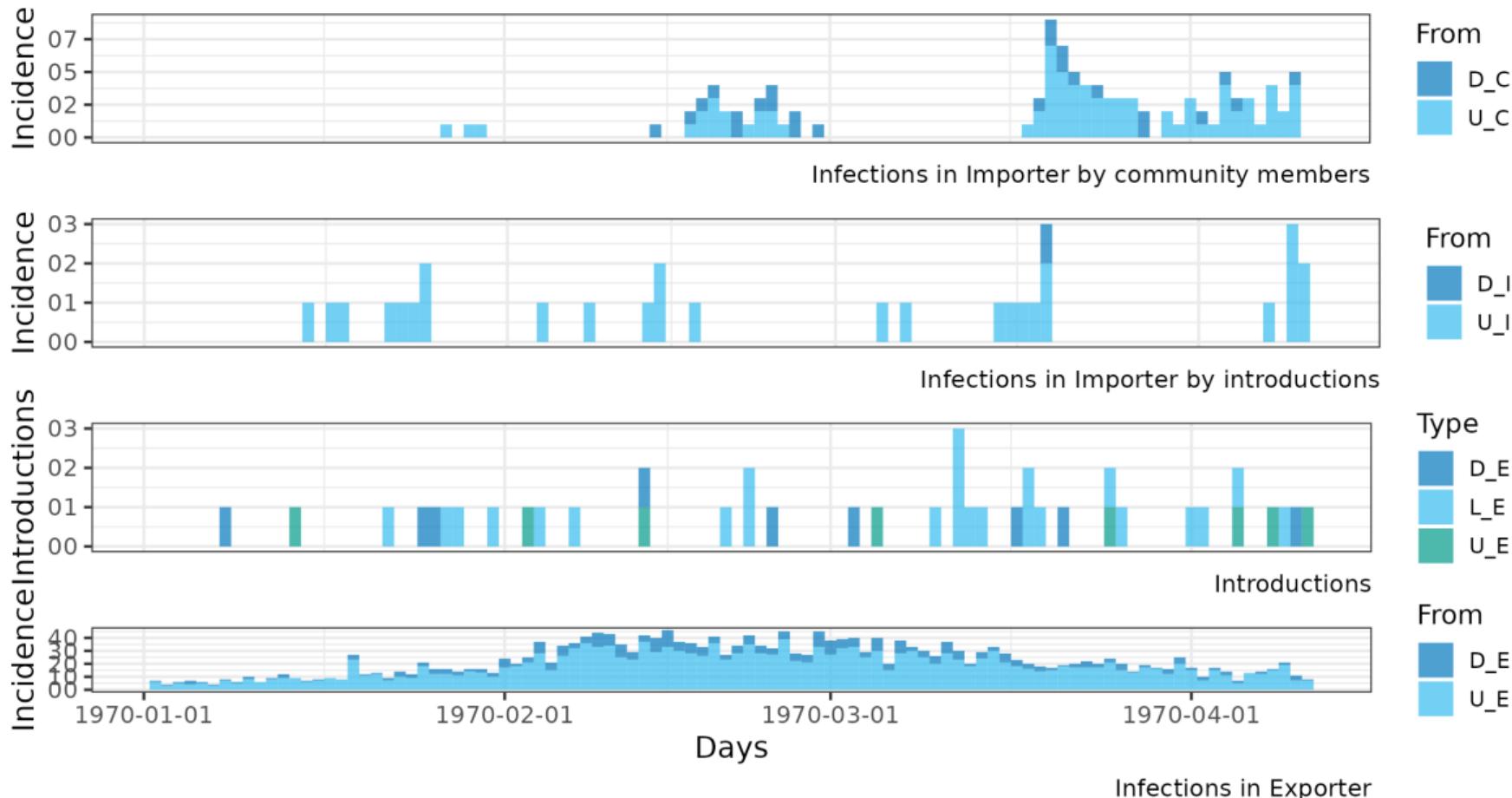
Importer



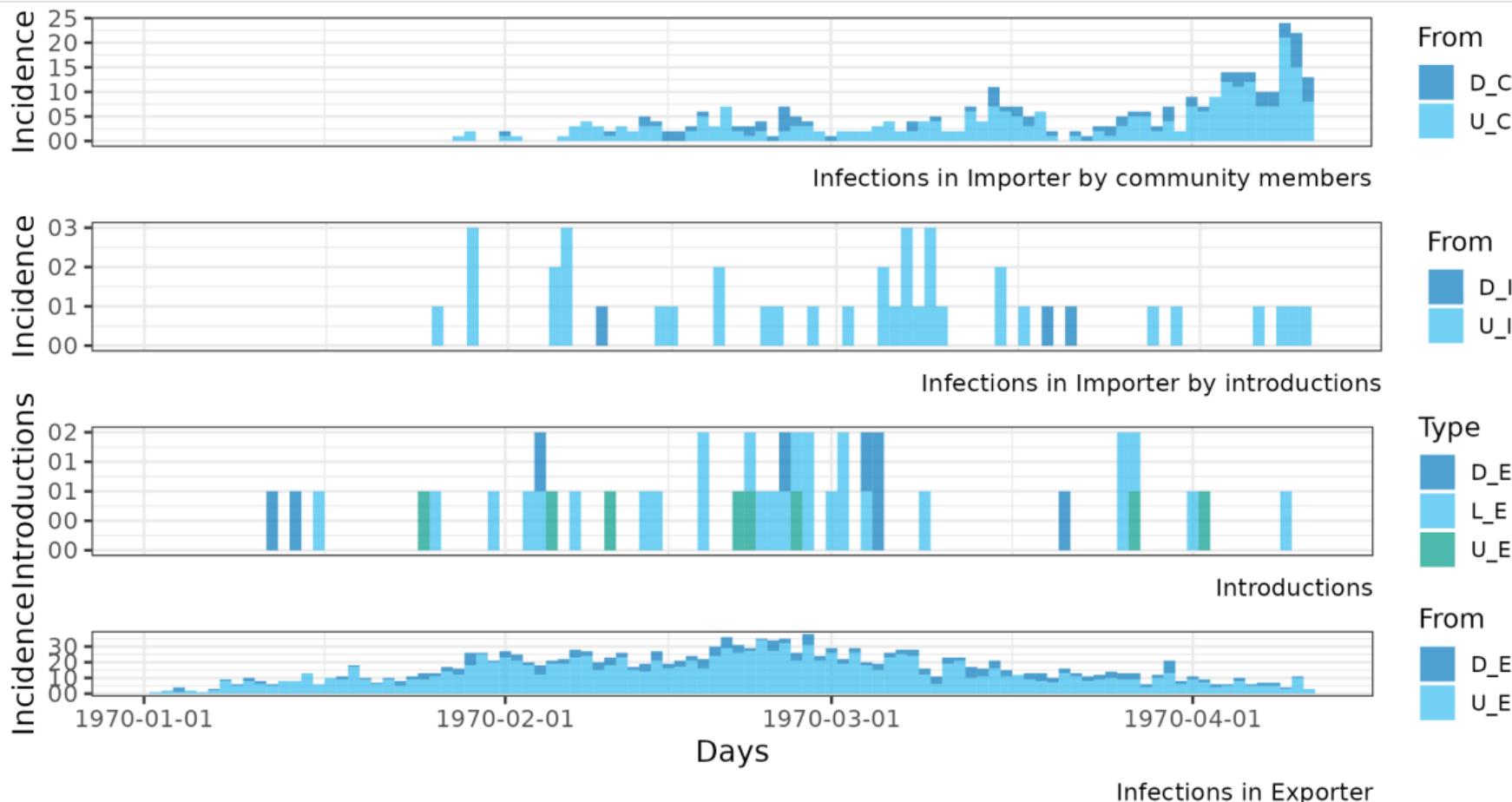
$$R_0^E = 1.5, R_0^C = 0.8, \text{pop}_E = 10000, \text{pop}_I = 10000$$



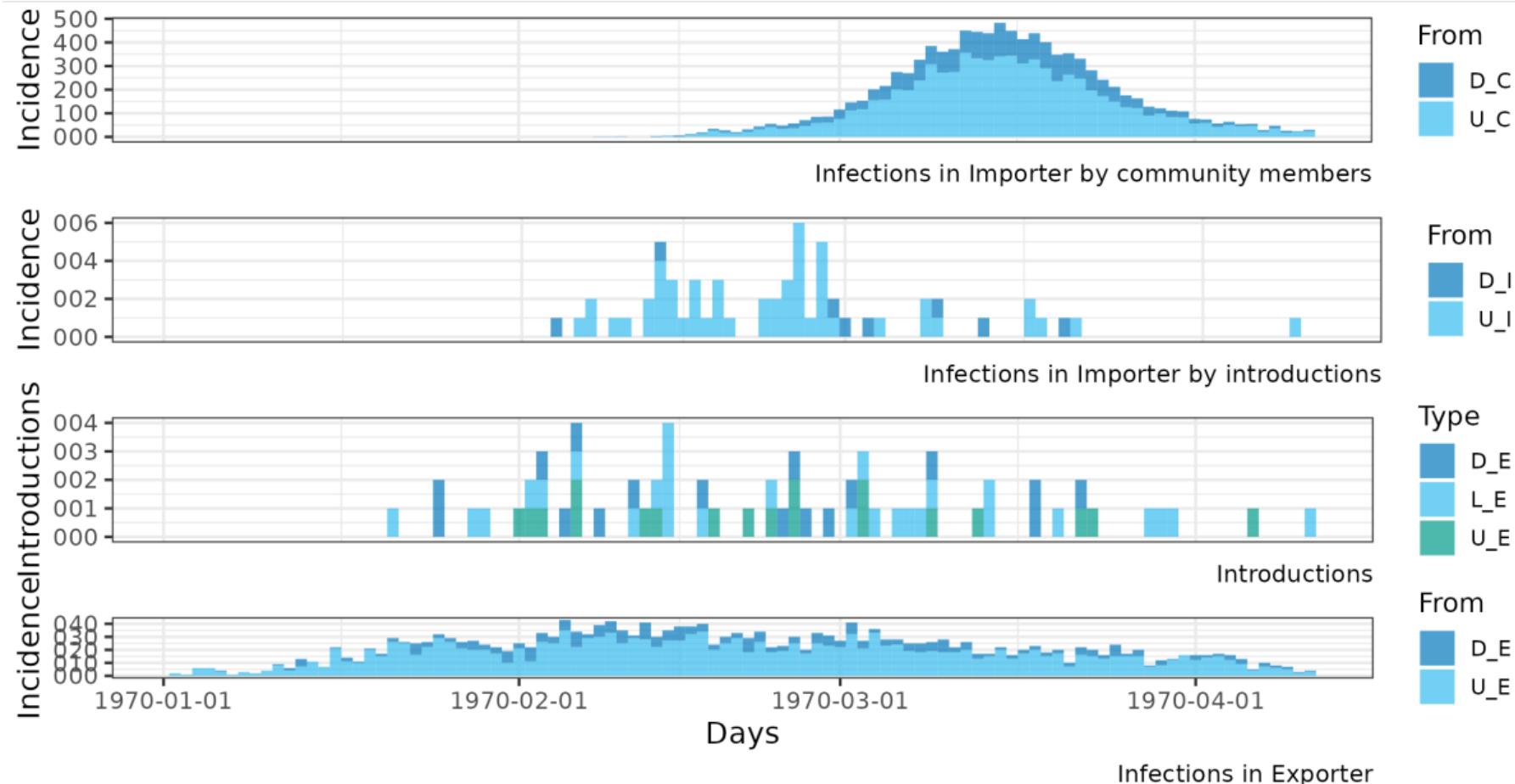
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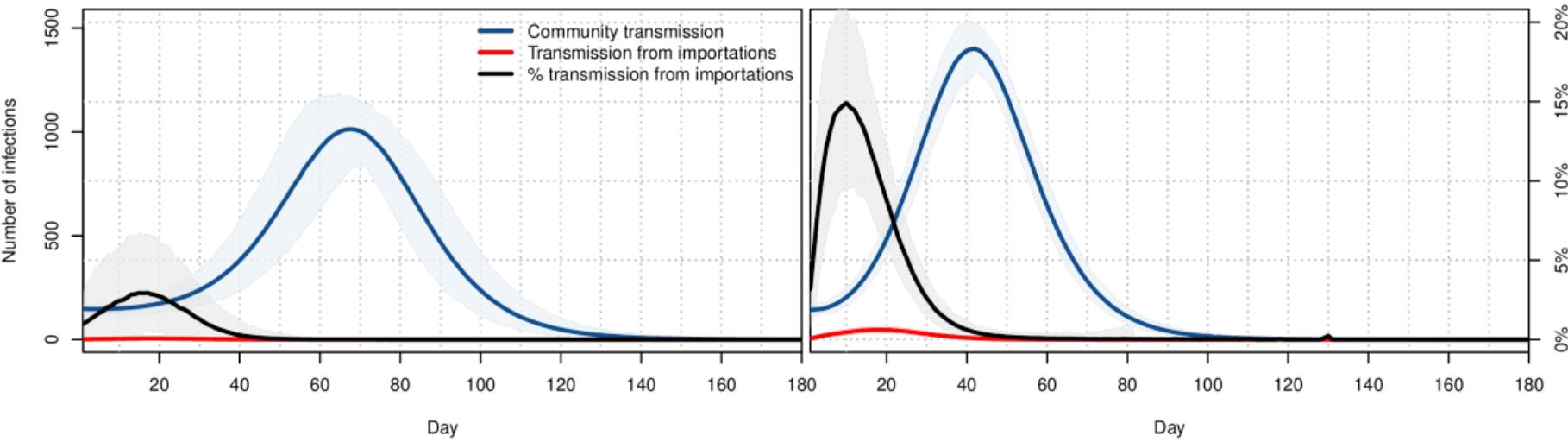


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To do

- ▶ Try to work quarantine into the model in a “non-cohorty” manner
- ▶ MBPA to compute probability of an outbreak
- ▶ Detailed computational analysis of the CTMC

One last thought for the road

V. Chetail. Crisis without borders: What does international law say about border closure in the context of Covid-19? *Frontiers in Political Science*, 2 (12) (2020)

[..] a powerful expression of state's sovereignty, immigration control provides a typical avenue for governments to reassure their citizens and bolster a national sense of belonging, while providing an ideal scapegoat for their own failure or negligence.

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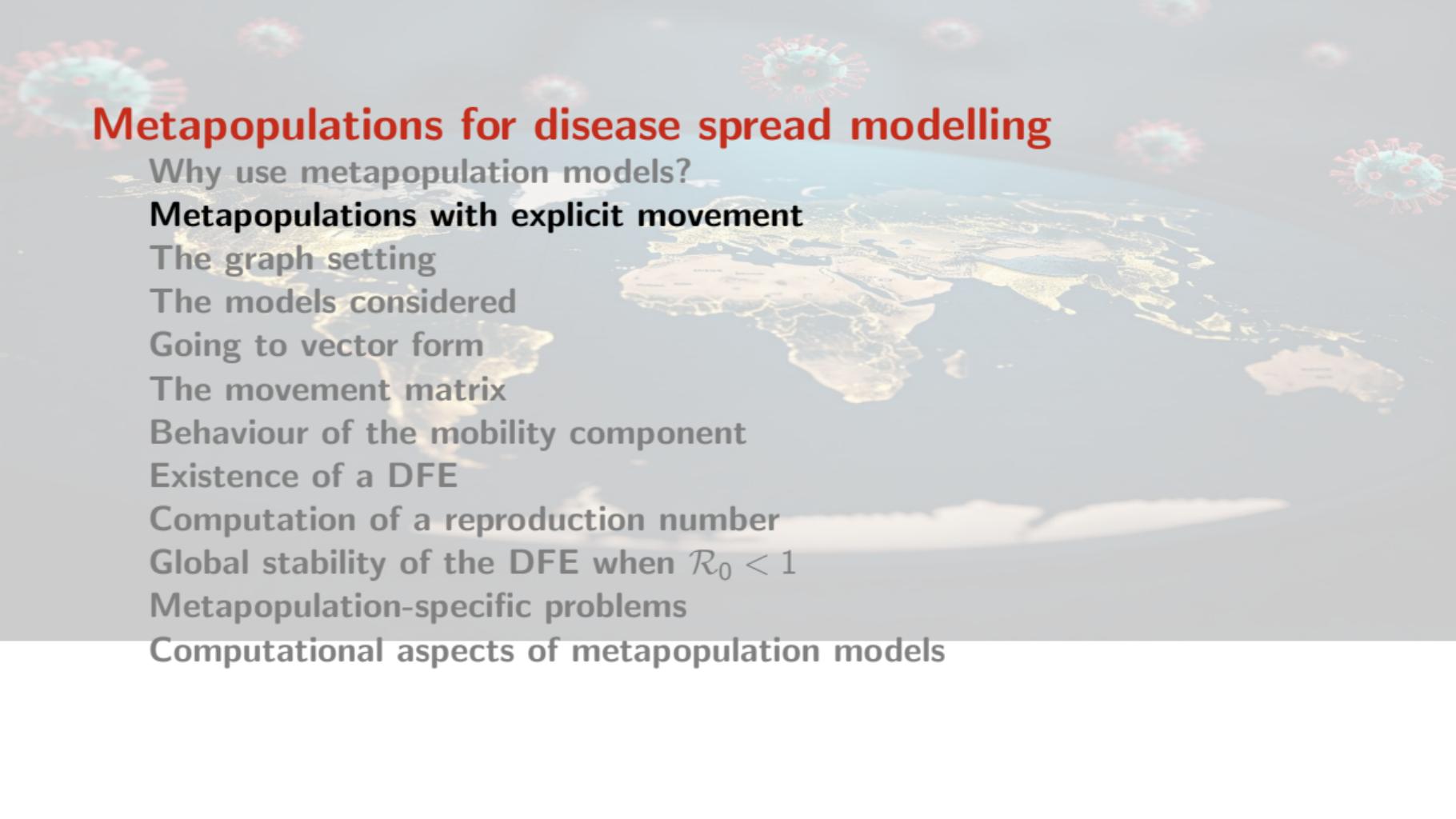
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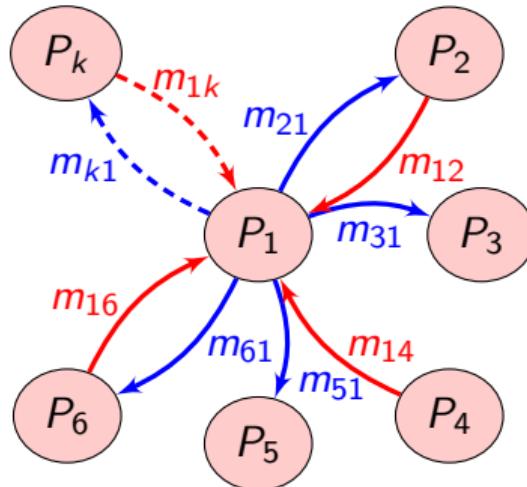
Split continuous space into N discrete geographical locations (*ptatches*)

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 $p = 1, \dots, N$ 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

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

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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

Strong connectedness and irreducibility

Definition 1 (Reducible/irreducible matrix)

A matrix A is **reducible** if there exists a permutation matrix P such that P^TAP 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 2

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

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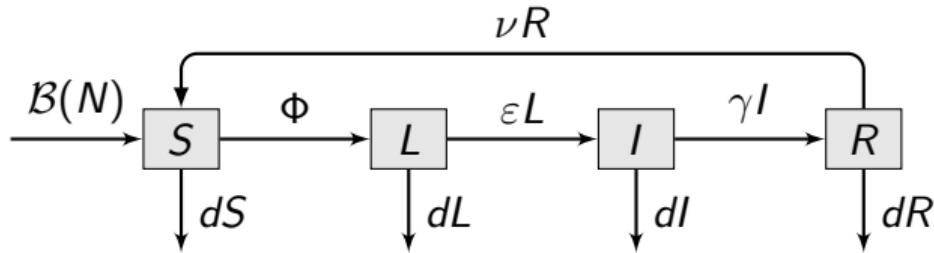
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Computational aspects of metapopulation models

The prototype SLIRS used in patches



$$S' = \mathcal{B}(N) + \nu R - \Phi - dS \quad (1a)$$

$$L' = \Phi - (\varepsilon + d)L \quad (1b)$$

$$I' = \varepsilon L - (\gamma + d)I \quad (1c)$$

$$R' = \gamma I - (\nu + d)R \quad (1d)$$

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

$$S'_p = \mathcal{B}(N_p) + \nu_p R_p - \Phi_p - d_p S_p + \sum_{q \in \mathcal{P}} m_{Spq} S_q \quad (2a)$$

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

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

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

with incidence

$$\Phi_p = \beta_p \frac{S_p I_p}{N_p^{q_p}}, \quad q_p \in \{0, 1\} \quad (2e)$$

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

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

$$S'_{sp} = \mathcal{B}_{sp}(N_{sp}) + \nu_{sp}R_{sp} - \Phi_{sp} - d_{sp}S_{sp} + \sum_{q \in \mathcal{P}} m_{Sspq}S_{sq} \quad (3a)$$

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

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

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

with incidence

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

- ▶ JA, Davis, Hartley, Jordan, Miller & PvD. A multi-species epidemic model with spatial dynamics. *Mathematical Medicine and Biology* 22(2):129-142 (2005)
- ▶ JA, Jordan & PvD. Quarantine in a multi-species epidemic model with spatial dynamics. *Mathematical Biosciences* 206(1):46-60 (2007)

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

$$S'_{pq} = \mathcal{B}_{pq}(N_p^r) + \nu_{pq}R_{pq} - \Phi_{pq} - d_{pq}S_{pq} + \sum_{k \in \mathcal{P}} m_{Spqk}S_{pk} \quad (4a)$$

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

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

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

with incidence

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

- ▶ 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 $\mathcal{B}_p(N_p) = b_p$

$$S'_p = b_p - \Phi_p - d_p S_p + \nu_p R_p + \sum_{q \in \mathcal{P}} m_{Spq} S_q \quad (5a)$$

$$L'_p = \Phi_p - (\varepsilon_p + d_p) L_p + \sum_{q \in \mathcal{P}} m_{Lpq} L_q \quad (5b)$$

$$I'_p = \varepsilon_p L_p - (\gamma_p + d_p) I_p + \sum_{q \in \mathcal{P}} m_{Ipq} I_q \quad (5c)$$

$$R'_p = \gamma_p I_p - (\nu_p + d_p) R_p + \sum_{q \in \mathcal{P}} m_{Rpq} R_q \quad (5d)$$

with incidence

$$\Phi_p = \beta_p S_p I_p \quad (5e)$$

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

⇒ Good case of large-scale system

(matrix analysis is your friend)

Metapopulations for disease spread modelling

Why use metapopulation models?

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The models considered

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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

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)
- ▶ $\mathbf{X}_c = (X_{c1}, \dots, X_{c|\mathcal{P}|})^T$ distribution of individuals of compartment $c \in \mathcal{C}$ among the different locations
[E.g., for (5), $\mathbf{X}_S = (S_1, \dots, S_{|\mathcal{P}|})^T$]
- ▶ $\mathbf{X}^p = (X_1^p, \dots, X_{|\mathcal{P}|}^p)^T$ composition of the population in location $p \in \mathcal{P}$
[E.g., for (5), $\mathbf{X}^p = (S_p, L_p, I_p, R_p)^T$]

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 $p \in \mathcal{P}$

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

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

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

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

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

Vector form of the system

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

$$\mathbf{X}'_c = f(\mathbf{X}) + \mathcal{M}_c \mathbf{X}_c \quad (8)$$

with

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

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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
- ▶ $\sigma(M) = \{\lambda \in \mathbb{C}; M\lambda = \lambda\mathbf{v}, \mathbf{v} \neq \mathbf{0}\}$ **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 $A \geq \mathbf{0}$ and $s \geq \rho(A)$

The movement matrix

The matrix

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

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 Laplacian matrix

Lemma 3

1. $0 \in \sigma(\mathcal{M})$ corresponding to left e.v. $\mathbf{1}^T$ [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 $\mathbf{v} > \mathbf{0}$. 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 – No demography

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

$$\mathbf{X}'_c = \mathcal{M}_c \mathbf{X}_c \quad (10)$$

Theorem 5

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

$$\lim_{t \rightarrow \infty} \mathbf{X}_c(t) = \mathbf{X}_c^* \gg 0$$

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

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

$$T'_p = D_p(T_p) + \sum_{c \in \mathcal{C}} \sum_{q \in \mathcal{P}} m_{cpq} X_{cq} \quad (11)$$

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)
- ▶ $D_p(T_p) = b_p T_p - d_p T_p$
- ▶ $D_p(T_p) = d_p T_p - b_p T_p = 0$ (constant population)
- ▶ $D_p(T_p) = r_p T_p(1 - T_p/K_p)$ (logistic demography)

In what follows, assume

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

Vector / matrix form of the equation

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

$$\mathbf{T}' = \mathbf{b} - \mathbf{dT} + \sum_{c \in C} \mathcal{M}_c \mathbf{X}_c \quad (13)$$

where

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

The nice case

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

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

(stronger than 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

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

Equilibria

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

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 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 \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

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

Indeed, we have

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

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

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

Behaviour of total population

Equal reducible movement case

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

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

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

Let

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

and

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

Cool, no? No!

Then we have

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

Me, roughly every 6 months: *Oooh, cooooool, 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..

However, we can still do stuff, but more on a case-by-case basis

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

Other basic stuff

Skipped until I homogeneise notation

Not complicated but sometimes tedious

Easy if it has been proved for the constituting units

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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

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

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:

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

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}, ν 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 $\mathbf{b} - \mathbf{dS} + \mathcal{M}^S \mathbf{S} = \mathbf{0}$, i.e.,

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

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

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

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

So DFE makes sense with

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

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- ▶ Linear stability of the disease free equilibrium can be investigated by using the next generation matrix
- ▶ 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 $\Xi = \{L_1, \dots, L_{|\mathcal{P}|}, I_1, \dots, I_{|\mathcal{P}|}\}$, $\Xi' = \mathcal{F} - \mathcal{V}$

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

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

Differentiate w.r.t. Ξ :

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

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

Inverse of V easy (2×2 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 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

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

i.e.,

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

Local asymptotic stability of the DFE

Theorem 8

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

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

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

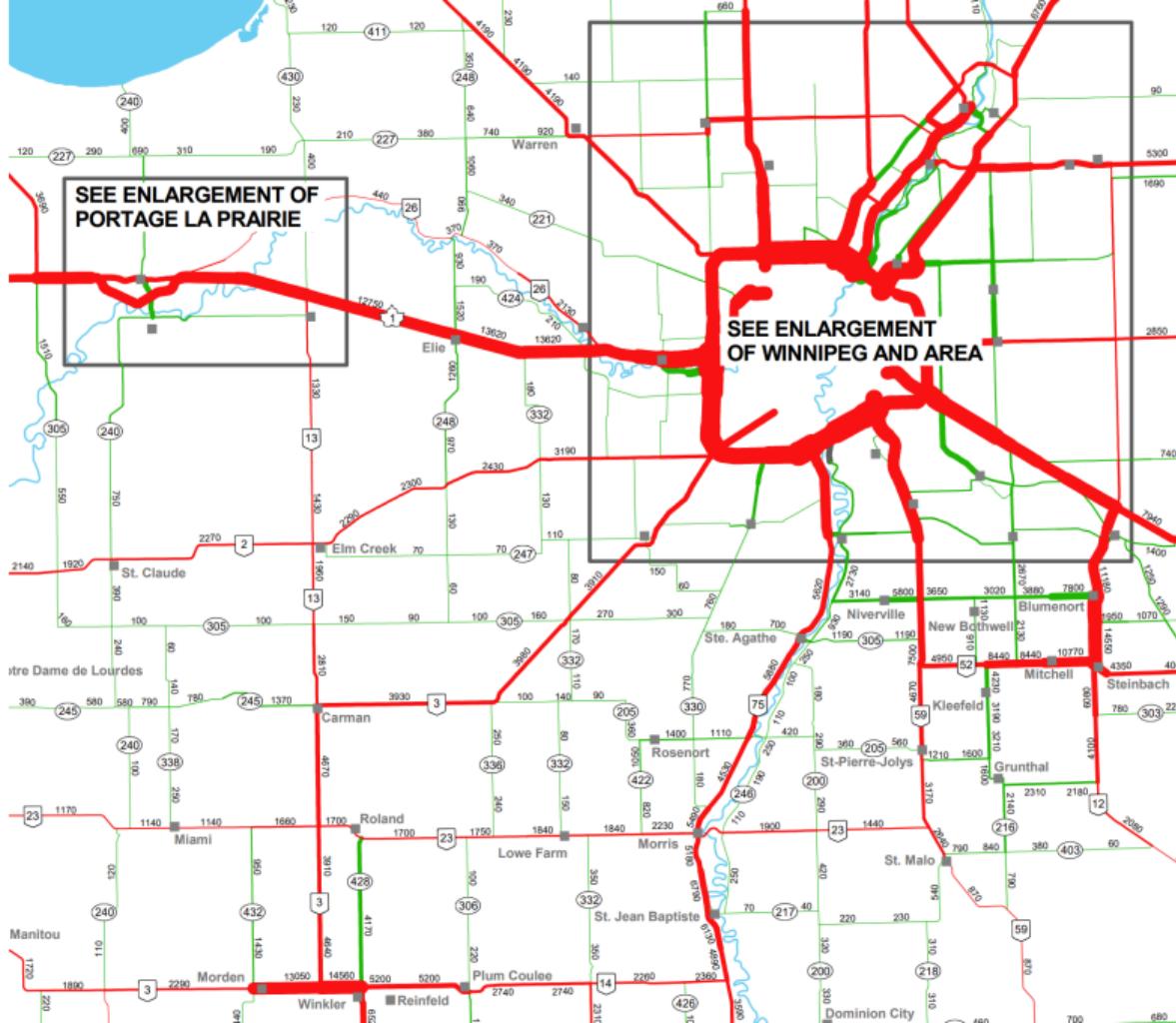
Do not in \mathcal{R}_0 put all your .. interpretation?

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

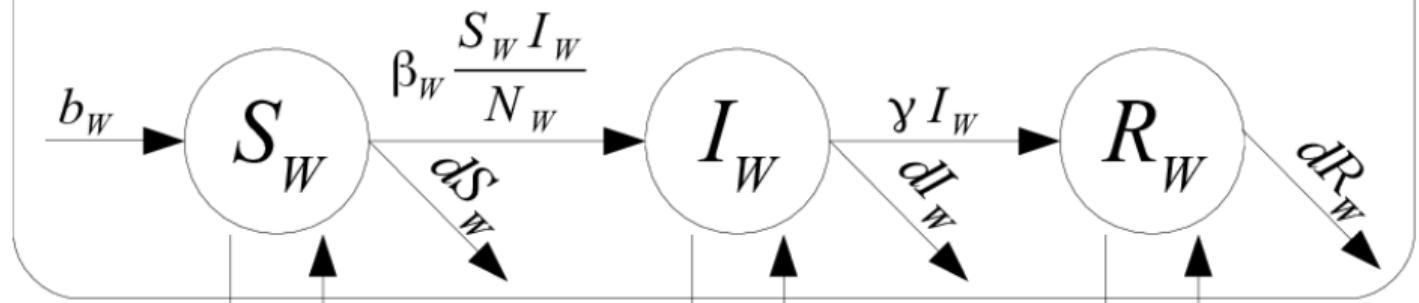
JA & S Portet. Epidemiological implications of mobility between a large urban centre and smaller satellite cities. *Journal of Mathematical Biology* **71**(5):1243-1265 (2015)



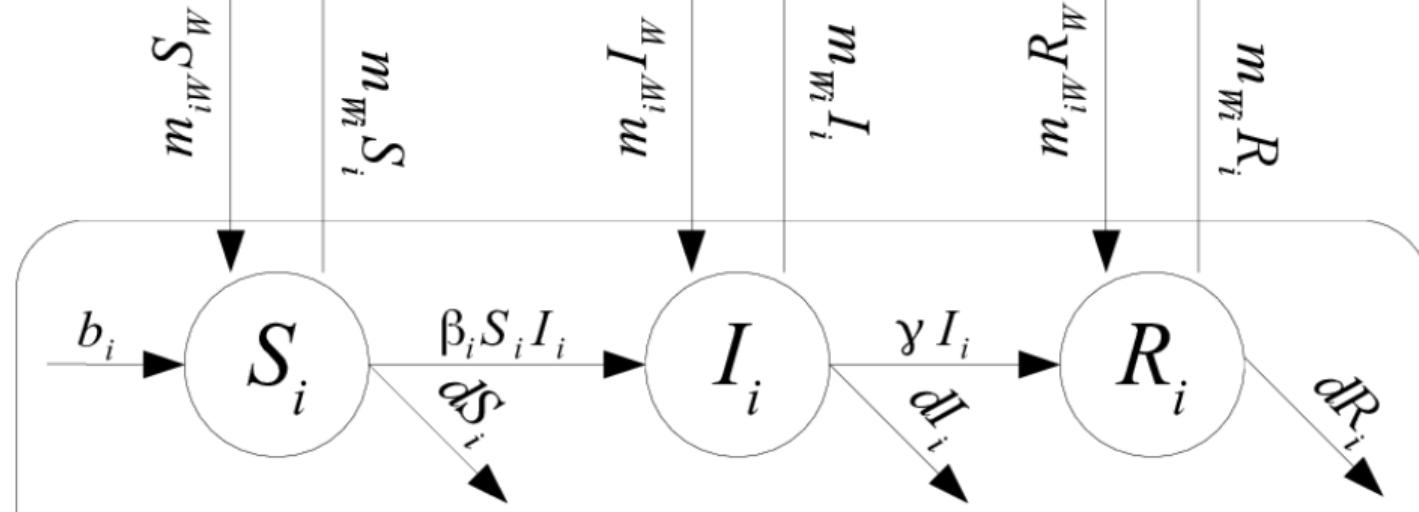
Known and estimated quantities

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



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.,

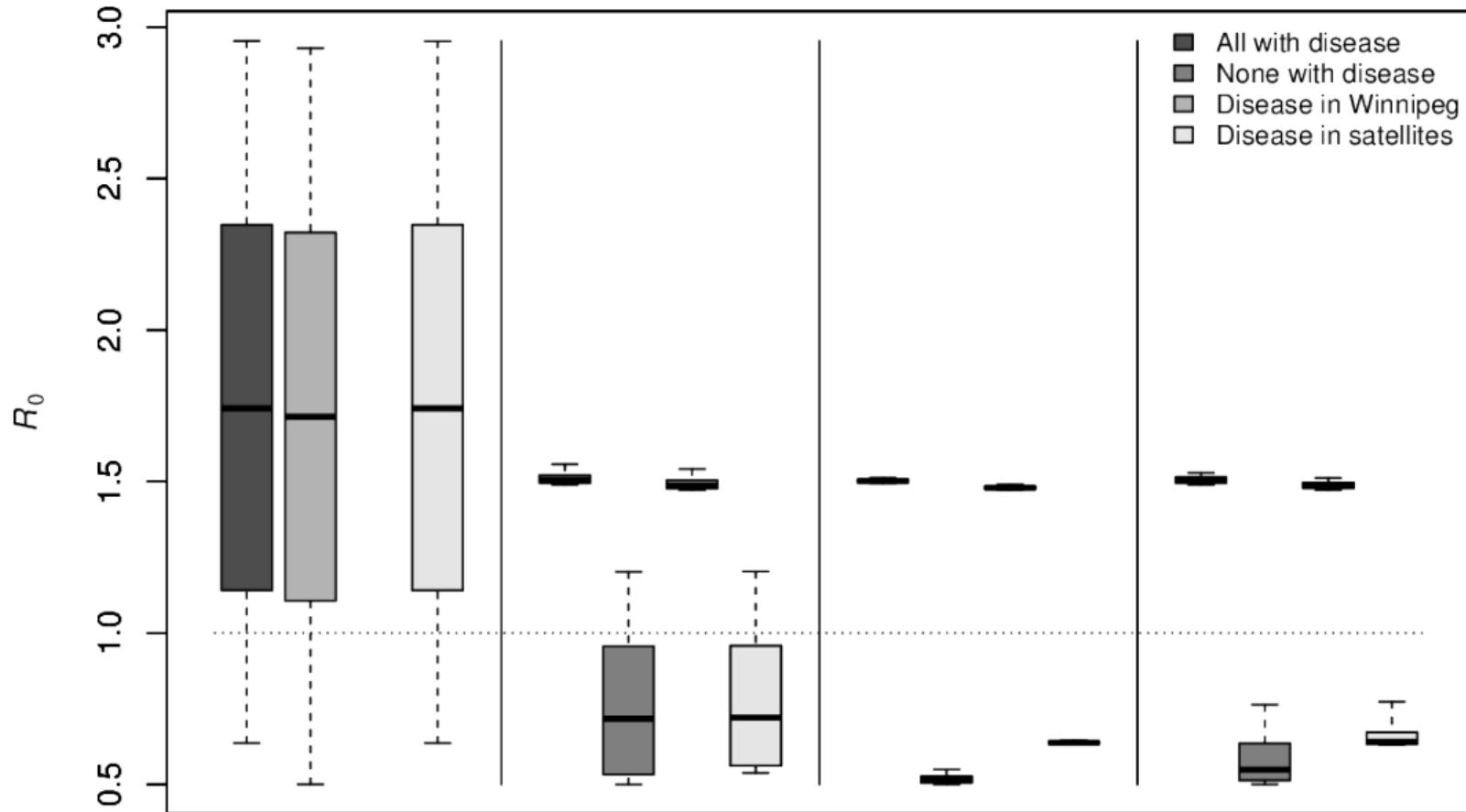
$$m_{yx} = -\ln \left(\frac{N_x(1)}{N_x(0)} \right)$$

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 $\mathcal{R}_0^W < 1$

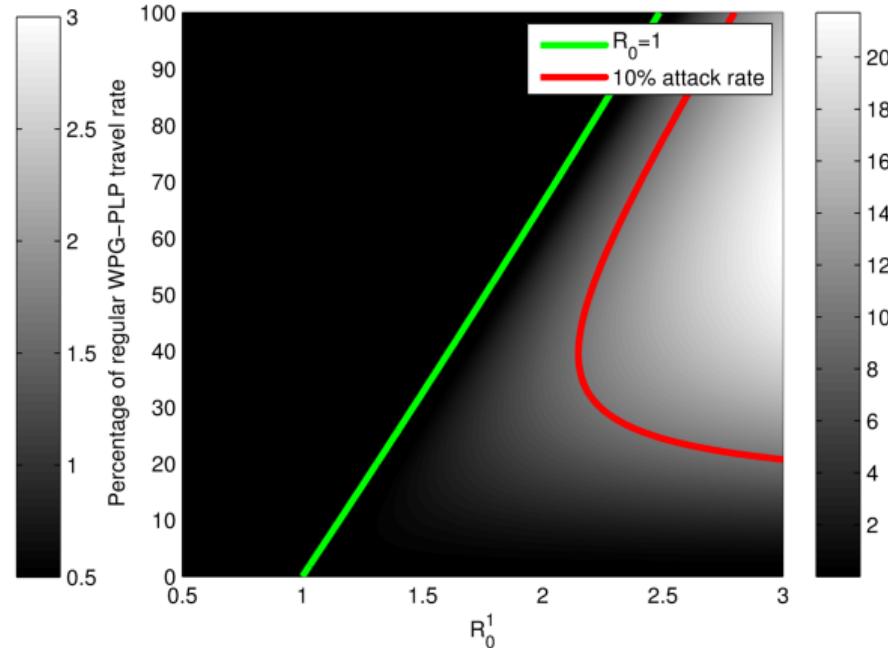
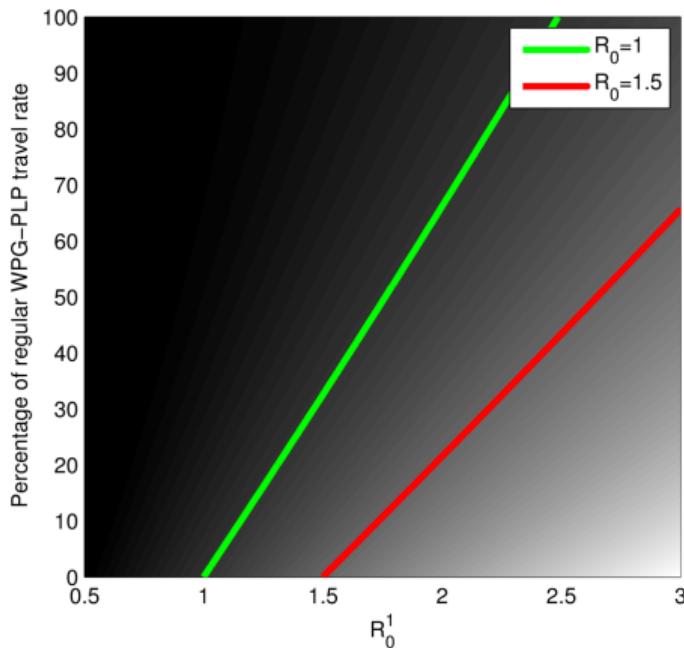
This is due to the movement rate: if $\mathcal{M} = 0$, then

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

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 – 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

$$s'_{kp} = f_{kp}(S_p, I_p) \quad (15a)$$

$$i'_{\ell p} = g_{\ell p}(S_p, I_p) \quad (15b)$$

with known properties, what is known of

$$s'_{kp} = f_{kp}(S_p, I_p) + \sum_{q \in \mathcal{P}} m_{kpq} s_{kq} \quad (16a)$$

$$i'_{\ell p} = g_{\ell p}(S_p, I_p) + \sum_{q \in \mathcal{P}} m_{\ell pq} i_{\ell q} \quad (16b)$$

- ▶ 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 constituting 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

$$s'_{kp} = f_{kp}(S_p, I_p) \quad (9a)$$

$$i'_{\ell p} = g_{\ell p}(S_p, I_p) \quad (9b)$$

with known properties, does

$$s'_{kp} = f_{kp}(S_p, I_p) + \sum_{q \in \mathcal{P}} m_{kpq} s_{kq} \quad (10a)$$

$$i'_{\ell p} = g_{\ell p}(S_p, I_p) + \sum_{q \in \mathcal{P}} m_{\ell pq} i_{\ell q} \quad (10b)$$

exhibit some behaviours not observed in the uncoupled system?

E.g.: units have $\{\mathcal{R}_0 < 1 \implies \text{DFE GAS}, \mathcal{R}_0 > 1 \implies \text{1 GAS EEP}\}$ 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 $X_p^* = 0$, at the **disease-free equilibrium** if $X_p^* = (s_{k_1 p}^*, \dots, s_{k_u p}^*, 0, \dots, 0)$, where k_1, \dots, k_u are some indices with $1 \leq u \leq |\mathcal{U}|$ and $s_{k_1 p}^*, \dots, s_{k_u p}^*$ 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

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

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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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 = 5 * 365.25, by = 0.1)
```

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

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

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

$$S'_p = b_p - \beta_p S_p I_p - d_p S_p + \nu_p R_p \quad (17a)$$

$$L'_p = \beta_p S_p I_p - (\varepsilon_p + d_p) L_p \quad (17b)$$

$$I'_p = \varepsilon_p L_p - (\gamma_p + d_p) I_p \quad (17c)$$

$$R'_p = \gamma_p I_p - (\nu_p + d_p) R_p \quad (17d)$$

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

```
SLIAR_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")

## Error: object 'SLIRS_metapop_rhs' not found
```

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

⇒ use this for numerics, not for the mathematical analysis

Spatio-temporal spread of infectious pathogens

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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

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(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

$$S_t(x, t) = -\beta(x, t)S(x, t) - dS(x, t) + dN(x) + \lambda_1 I(x, t) \quad (19a)$$

$$I_t(x, t) = \lambda(x, t)S(x, t) - dI(x, t) - (\gamma_1 + \gamma_2)I(x, t) \quad (19b)$$

$$R_t(x, t) = \gamma_2 I(x, t) - dR(x, t) \quad (19c)$$

where the force of infection is

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

and the total population along the road is

$$N = \int_0^L N(x') dx' \quad (19e)$$

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

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

Substitute (20) into (19d)

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

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

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

Thus the problem is in the form

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

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

- ▶ SIR case: \mathcal{B} is a nonlinear Volterra operator in $t \Rightarrow$ existence and uniqueness of solutions
- ▶ SIS case: \mathcal{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

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

which does not depend on t

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

On the Spatial Spread of Rabies Among Foxes with Immunity

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

Spatial spread of rabies with immunity

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

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

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

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

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

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See the work of Horst Thieme

If one considers time of sojourn in compartments from a more detailed perspective, one obtains integro-differential models

We use here continuous random variables. See chapters 12 and 13 in Thieme's book for arbitrary distributions

Sojourn times-related models

Two “extreme” distributions

A simple cohort model with death

Sojourn times in an SIS disease transmission model

A model with vaccination

The exponential distribution

The random variable T has an **exponential** distribution if its probability density function takes the form

$$f(t) = \begin{cases} 0 & \text{if } t < 0, \\ \theta e^{-\theta t} & \text{if } t \geq 0, \end{cases} \quad (22)$$

with $\theta > 0$. Then the survival function for state S_1 is of the form $S(t) = e^{-\theta t}$, for $t \geq 0$, and the average sojourn time in state S_1 is

$$\tau = \int_0^\infty e^{-\theta t} dt = \frac{1}{\theta}$$

Particularities of the exponential distribution

The standard deviation of an exponential distribution is also $1/\theta$. When estimating θ , it is impossible to distinguish the mean and the standard deviation

The exponential distribution is **memoryless**: its conditional probability obeys

$$P(T > s + t \mid T > s) = P(T > t), \quad \forall s, t \geq 0$$

The exponential and geometric distributions are the only memoryless probability distributions

The exponential distribution has a constant hazard function

The Dirac delta distribution

If for some constant $\omega > 0$,

$$S(t) = \begin{cases} 1, & 0 \leq t \leq \omega \\ 0, & \omega < t \end{cases}$$

meaning that T has a Dirac delta distribution $\delta_\omega(t)$, then the average sojourn time is

$$\tau = \int_0^\omega dt = \omega$$

Sojourn times-related models

Two “extreme” distributions

A simple cohort model with death

Sojourn times in an SIS disease transmission model

A model with vaccination

A model for a cohort with one cause of death

Consider a **cohort** of individuals born at the same time, e.g., the same year

- ▶ At time $t = 0$, there are initially $N_0 > 0$ individuals
- ▶ All causes of death are compounded together
- ▶ The time until death, for a given individual, is a random variable T , with continuous probability density distribution $f(t)$ and survival function $P(t)$

$N(t)$ the cohort population at time $t \geq 0$

$$N(t) = N_0 P(t) \tag{23}$$

$N_0 P(t)$ proportion of initial population still alive at time t

Case where T is exponentially distributed

Suppose that T has an exponential distribution with mean $1/d$ (or parameter d), $f(t) = de^{-dt}$. Then the survival function is $P(t) = e^{-dt}$, and (23) takes the form

$$N(t) = N_0 e^{-dt} \tag{24}$$

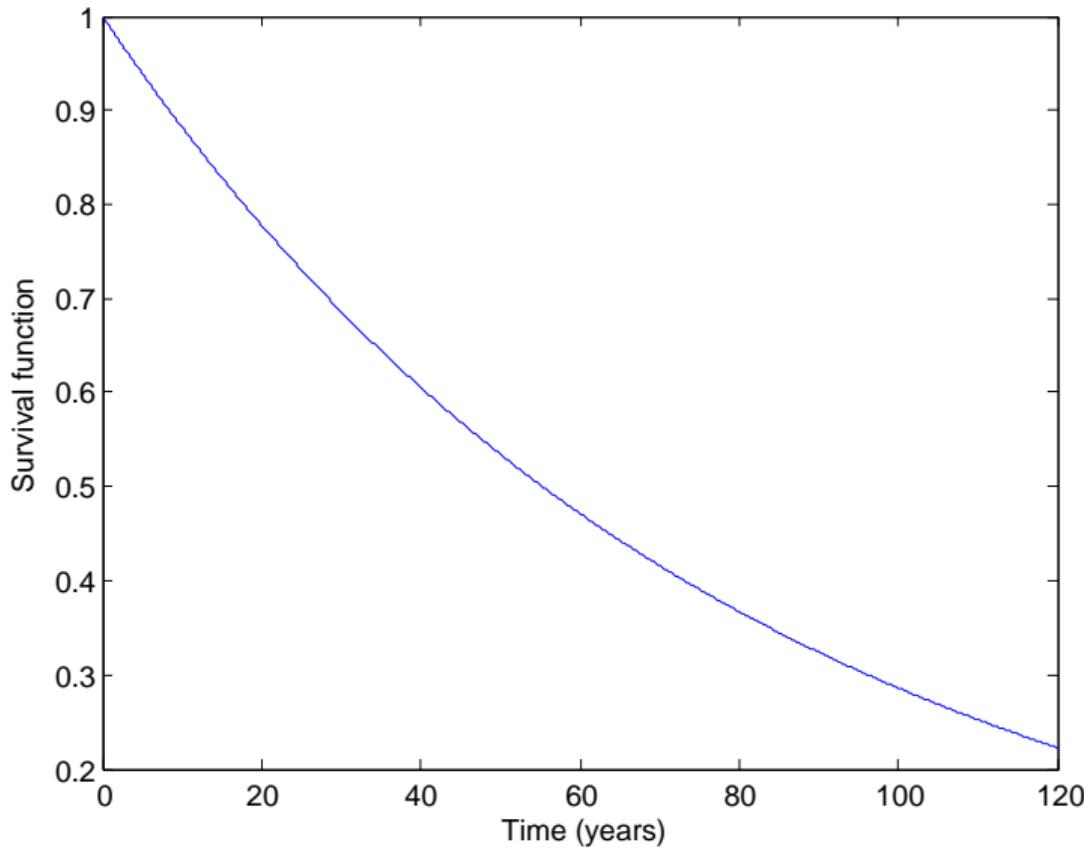
Now note that

$$\begin{aligned}\frac{d}{dt}N(t) &= -dN_0 e^{-dt} \\ &= -dN(t)\end{aligned}$$

with $N(0) = N_0$.

⇒ The ODE $N' = -dN$ makes the assumption that the life expectancy at birth is exponentially distributed

Survival function, $S(t) = \mathbb{P}(T > t)$, for an exponential distribution with mean 80 years



Case where T has a Dirac delta distribution

Suppose that T has a Dirac delta distribution at $t = \omega$, giving the survival function

$$P(t) = \begin{cases} 1, & 0 \leq t \leq \omega, \\ 0, & t > \omega. \end{cases}$$

Then (23) takes the form

$$N(t) = \begin{cases} N_0, & 0 \leq t \leq \omega, \\ 0, & t > \omega. \end{cases} \quad (25)$$

All individuals survive until time ω , then they all die at time ω .

Here, we have $N' = 0$ everywhere except at $t = \omega$, where it is undefined.

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An SIS model

Hypotheses

- ▶ Individuals typically recover from the disease
- ▶ The disease does not confer immunity
- ▶ There is no birth or death (from the disease or natural)
⇒ Constant total population $N \equiv N(t) = S(t) + I(t)$
- ▶ Infection is of **standard incidence** type

Recovery

- ▶ Traditional models suppose that recovery occurs with rate constant γ
- ▶ Here, of the individuals that become infective at time t_0 , a fraction $P(t - t_0)$ remain infective at time $t \geq t_0$
- ▶ \Rightarrow For $t \geq 0$, $P(t)$ is a survival function. As such, it verifies $P(0) = 1$ and P is nonnegative and nonincreasing

Model for infectious individuals

Since N is constant, $S(t) = N - I(t)$ and we need only consider the following equation (where S is used for clarity)

$$I(t) = I_0(t) + \int_0^t \beta \frac{S(u)I(u)}{N} P(t-u) du \quad (26)$$

- ▶ $I_0(t)$ number of individuals who were infective at time $t = 0$ and still are at time t .
 - ▶ $I_0(t)$ is nonnegative, nonincreasing, and such that $\lim_{t \rightarrow \infty} I_0(t) = 0$.
- ▶ $P(t-u)$ proportion of individuals who became infective at time u and who still are at time t .

Expression under the integral

Integral equation for the number of infective individuals:

$$I(t) = I_0(t) + \int_0^t \beta \frac{(N - I(u))I(u)}{N} P(t - u) du \quad (26)$$

The term

$$\beta \frac{(N - I(u))I(u)}{N} P(t - u)$$

- ▶ $\beta(N - I(u))I(u)/N$ is the rate at which new infectives are created, at time u ,
- ▶ multiplying by $P(t - u)$ gives the proportion of those who became infectives at time u and who still are at time t .

Summing over $[0, t]$ gives the number of infective individuals at time t .

Case of an exponentially distributed time to recovery

Suppose $P(t)$ such that sojourn time in the infective state has exponential distribution with mean $1/\gamma$, i.e., $P(t) = e^{-\gamma t}$.

Initial condition function $I_0(t)$ takes the form

$$I_0(t) = I_0(0)e^{-\gamma t},$$

with $I_0(0)$ the number of infective individuals at time $t = 0$. Obtained by considering the cohort of initially infectious individuals, giving a model such as (23).

Equation (26) becomes

$$I(t) = I_0(0)e^{-\gamma t} + \int_0^t \beta \frac{(N - I(u))I(u)}{N} e^{-\gamma(t-u)} du. \quad (27)$$

Taking the time derivative of (27) yields

$$\begin{aligned}I'(t) &= -\gamma I_0(0)e^{-\gamma t} - \gamma \int_0^t \beta \frac{(N - I(u))I(u)}{N} e^{-\gamma(t-u)} du \\&\quad + \beta \frac{(N - I(t))I(t)}{N} \\&= -\gamma \left(I_0(0)e^{-\gamma t} + \int_0^t \beta \frac{(N - I(u))I(u)}{N} e^{-\gamma(t-u)} du \right) \\&\quad + \beta \frac{(N - I(t))I(t)}{N} \\&= \beta \frac{(N - I(t))I(t)}{N} - \gamma I(t),\end{aligned}$$

which is the classical logistic type ordinary differential equation (ODE) for I in an SIS model without vital dynamics (no birth or death).

Case of a step function survival function

Consider case where the time spent infected has survival function

$$P(t) = \begin{cases} 1, & 0 \leq t \leq \omega, \\ 0, & t > \omega. \end{cases}$$

i.e., the sojourn time in the infective state is a constant $\omega > 0$.

In this case (26) becomes

$$I(t) = I_0(t) + \int_{t-\omega}^t \beta \frac{(N - I(u))I(u)}{N} du. \quad (28)$$

Here, it is more difficult to obtain an expression for $I_0(t)$. It is however assumed that $I_0(t)$ vanishes for $t > \omega$.

When differentiated, (28) gives, for $t \geq \omega$,

$$I'(t) = I'_0(t) + \beta \frac{(N - I(t))I(t)}{N} - \beta \frac{(N - I(t - \omega))I(t - \omega)}{N}.$$

Since $I_0(t)$ vanishes for $t > \omega$, this gives the delay differential equation (DDE)

$$I'(t) = \beta \frac{(N - I(t))I(t)}{N} - \beta \frac{(N - I(t - \omega))I(t - \omega)}{N}.$$

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

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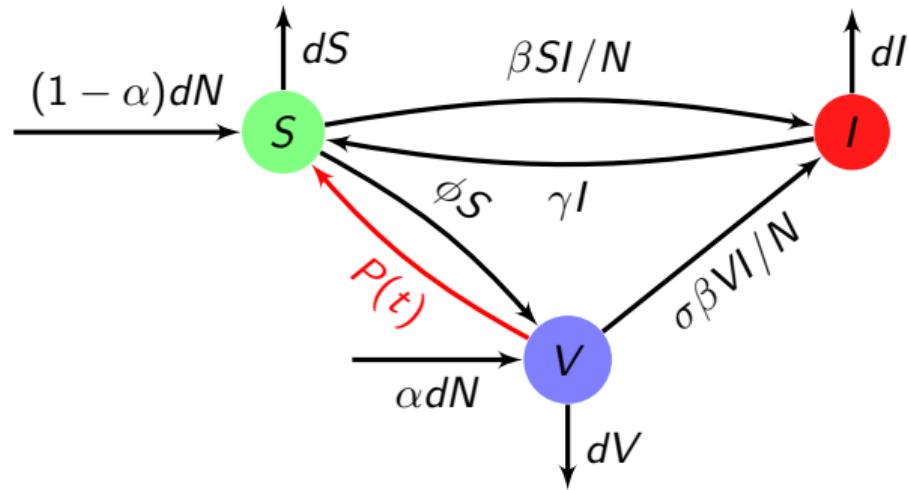
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(Communicated by Linda Allen)

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

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

$$V(t) = V_0(t) \quad (29b)$$

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

- ▶ 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

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau} \right) v(t, \tau) = -(\sigma \beta I(t) + d + \eta(\tau))v(t, \tau) \quad (30)$$

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 $P(\tau) = \exp(-\int_0^\tau \eta(q) dq)$. 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 (30) along characteristics, dividing the integral for $V(t)$ at t , substituting in the solutions, and changing integration variables, we get

$$V_0(t) = e^{-\int_0^t (\sigma \beta I(x) + d) dx} \int_0^\infty v(0, u) \frac{P(t+u)}{P(u)} du \quad (31)$$

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 $\lim_{t \rightarrow \infty} V_0(t) = 0$

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 (29) with $I(0) > 0, S(0) > 0$

With the assumed initial conditions in \mathcal{D} , it can be shown that the system defined by (29a) and (29b) is equivalent to the system defined by (29a) and

$$\begin{aligned}\frac{d}{dt}V(t) &= \frac{d}{dt}V_0(t) + \phi S(t) + \alpha d \\ &\quad - (d + \sigma\beta I(t))(V(t) - V_0(t)) + Q(t)\end{aligned}\tag{32}$$

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 (29a) and (32) is of standard form, therefore results of Hale (see Hale & Verduyn-Lunel) ensure the local existence, uniqueness and continuation of solutions of model (29)

\mathcal{R}_0

Define \mathcal{R}_0 with vaccination as

$$\mathcal{R}_v = \mathcal{R}_0 \left[\frac{1 + \sigma\phi\tilde{P} - (1 - \sigma)\alpha d\tilde{P}}{1 + \phi\tilde{P}} \right] \quad (33)$$

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

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

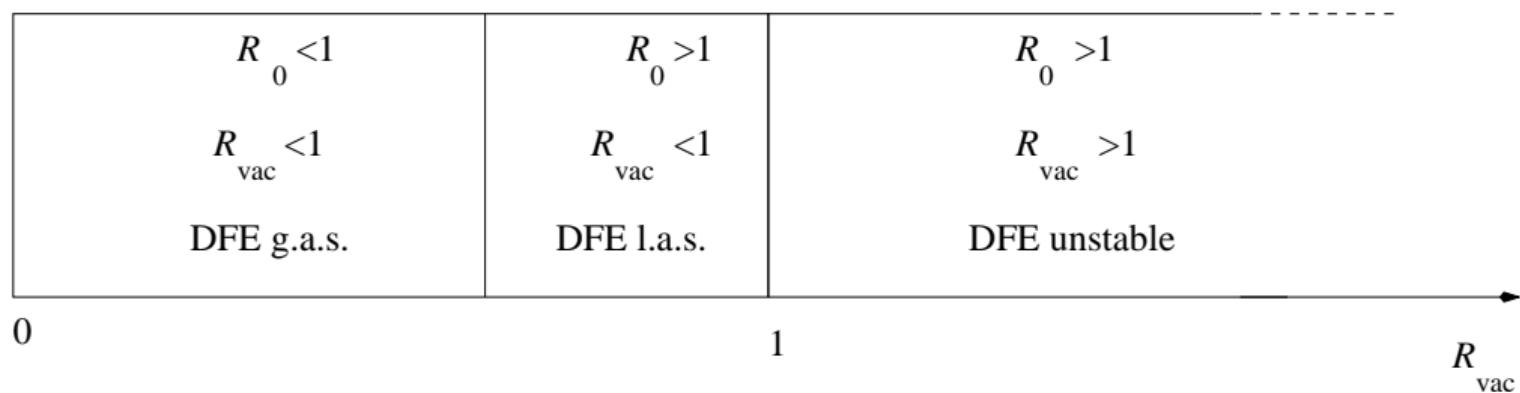
in such a way that $\tilde{P} < 1/d$

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

Theorem 16

System (29) 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



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 (31). Then (29a) and (32) give the ODE system

$$\frac{dI}{dt} = \beta(1 - I - (1 - \sigma)V)I - (d + \gamma)I \quad (34a)$$

$$\frac{dV}{dt} = \phi(1 - I - V) - \sigma \beta I V - (d + \theta)V + \alpha d \quad (34b)$$

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^*) can be obtained analytically from the quadratic equation

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

where

$$A = -\sigma\beta$$

$$B = \sigma(\beta - (d + \gamma)) - (d + \theta + \sigma\phi)$$

$$C = (d + \gamma)(d + \theta + \phi)(\mathcal{R}_v - 1)/\beta$$

with

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

from (33).

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

- ▶ 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 (34) 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 $\mathcal{D} - \{I = 0\}$

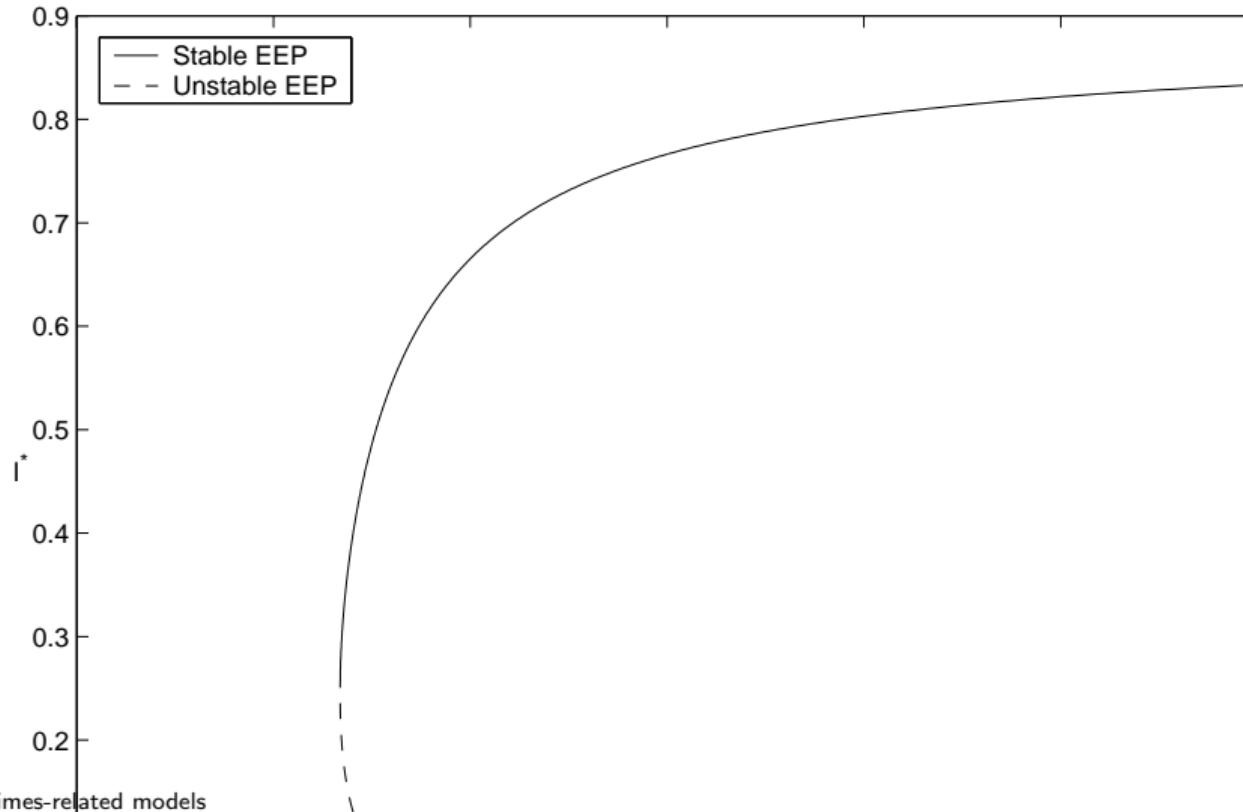
Pertussis:

- ▶ 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

$$\mathcal{R}_c(\phi) = 0.8669 < \mathcal{R}_v(\phi) < 1$$



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 (29b) becomes, for $t > \omega$

$$V(t) = \int_{t-\omega}^t (\phi(1 - I(u) - V(u)) + \alpha d) e^{-d(t-u)} e^{-\sigma \beta \int_u^t I(x) dx} du \quad (35)$$

Differentiating (35) (see equation (32)) gives the model as the two dimensional system, for $t > \omega$

$$\frac{d}{dt}I(t) = \beta(1 - I(t) - (1 - \sigma)V(t))I(t) - (d + \gamma)I(t) \quad (36a)$$

$$\frac{d}{dt}V(t) = \phi(1 - I(t) - V(t)) \quad (36b)$$

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

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 (29) exist and are unique. For a constant waning period, the basic reproduction number from (33) is

$$\mathcal{R}_v = \mathcal{R}_0 \frac{d + (\sigma\phi - \alpha(1 - \sigma)d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \quad (37)$$

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

$$V_{DF} = \frac{(\phi + \alpha d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})}, \quad S_{DF} = \frac{d - \alpha d(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \quad (38)$$

Finding the EEP's

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

$$V^* = f(I^*) = g(I^*) \quad (39)$$

where

$$f(I) = \frac{1 - 1/\mathcal{R}_0 - I}{1 - \sigma} \quad (40)$$

for $\sigma < 1$, and

$$g(I) = \frac{(\phi(1 - I) + \alpha d)(1 - e^{-d\omega - \sigma\beta\omega I})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I}) + d + \sigma\beta I} \quad (41)$$

Visualising and locating the bifurcation

From the nullcline equations, an EEP exists iff there exists an $I^* \in (0, 1]$ such that equations (39)-(41) 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

$$H(I, \mathcal{A}) = f(I) - g(I) \tag{42}$$

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^* such that $H(I^*, a_{i,k}) = 0$.

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^* . Using the same procedure as for the visualisation of the bifurcation, it is possible to compute \mathcal{R}_c by finding the value I^* such that $H(I^*, \mathcal{A}) = 0$ and $H'(I^*, \mathcal{A}) = 0$, for a given parameter $a_i \in \mathcal{A}$.

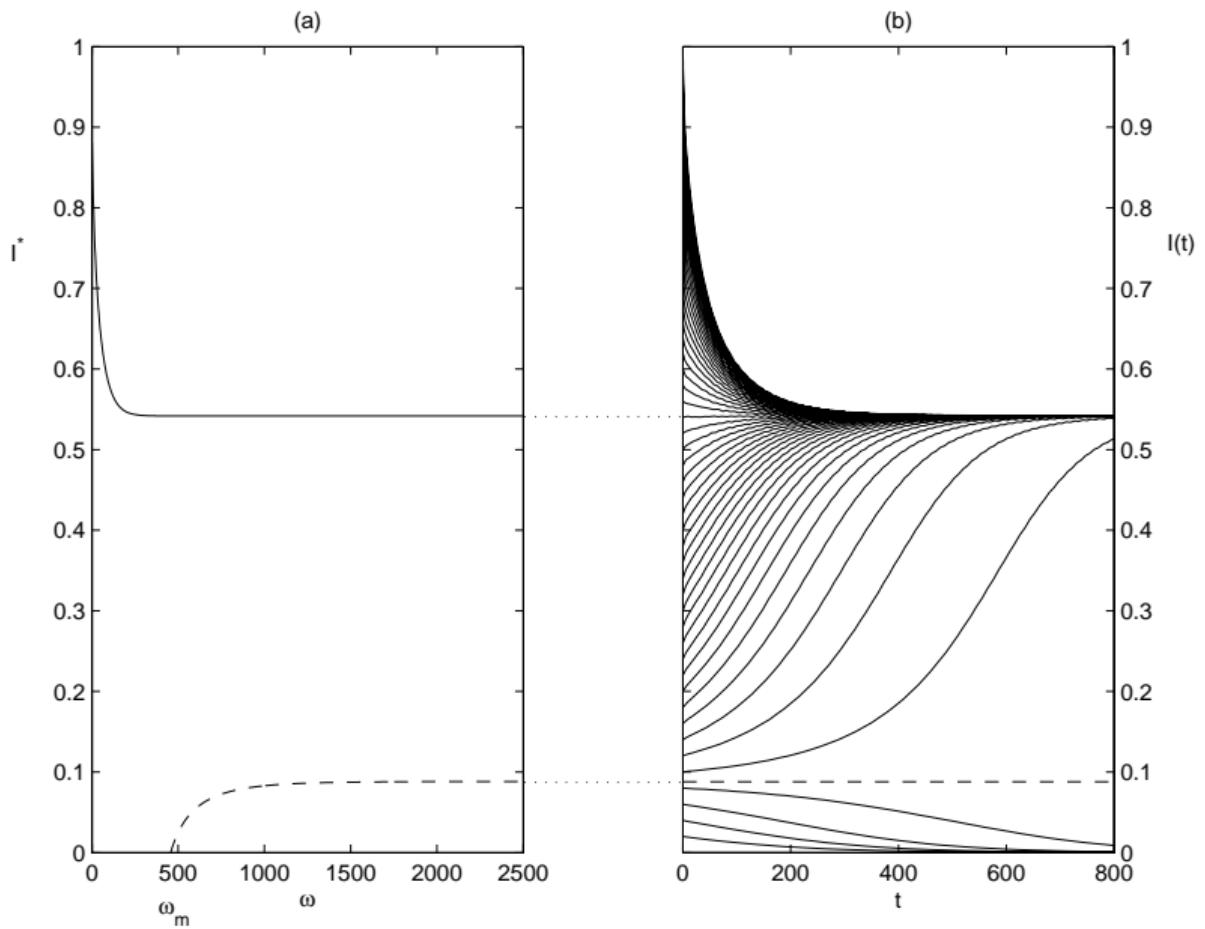
If $\mathcal{R}_v > 1$ then $H(0) > 0$ and so there is an odd number of endemic equilibria. Numerical simulations indicate that there is a unique EEP.

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



p. 171 (a) Values of I^* as a function of ω by solving $H(I, \mathcal{A}) = 0$ with $a_i = \omega$. (b) Value of

Spatio-temporal spread of infectious pathogens

Introductions

Probability of introductions

Stochastic phase of an epidemic

Value of travel control measures

Conclusions

Metapopulations for disease spread modelling

Other spatial models

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

We used age of vaccination to find the initial condition of system (29)

Here we take a closer look at this type of model

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

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Pierre Magal
(1967-10-24 – 2024-02-20)



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

$$(\partial_t + \partial_a)S(t, a) = \Lambda(a) - (\mu(a) + \lambda(t, a))S(t, a) \quad (43a)$$

$$(\partial_t + \partial_a)I(t, a) = -(\mu(a) + \gamma(a) + \delta(a))I(t, a) + \lambda(t, a)S(t, a) \quad (43b)$$

$$(\partial_t + \partial_a)R(t, a) = \gamma(a)I(t, a) \quad (43c)$$

Boundary conditions are

$$S(t, a_0) = B \quad (43d)$$

$$I(t, a_0) = 0 \quad (43e)$$

$$R(t, a_0) = 0 \quad (43f)$$

while initial conditions take the form

$$S(0, a) = \Phi(a) \quad (43g)$$

$$I(0, a) = \Psi(a) \quad (43h)$$

$$R(0, a) = 0 \quad (43i)$$

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

$$\lambda(t, a) = r(a)f(a) \int_{a_0}^{\infty} g(s)\rho(a, s) \frac{I(t, s)}{N(t, s)} ds \quad (44)$$

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

$$(\partial_t + \partial_a)u = -\mu(a)u - \tilde{\lambda}(t, a)S^0(a)$$

$$(\partial_t + \partial_a)I = -(\mu(a) + \gamma(a) + \delta(a))I + \tilde{\lambda}(t, a)S^0(a)$$

$$(\partial_t + \partial_a)R = \gamma(a)I$$

Let

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

and denote

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

Then

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

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

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

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

Therefore

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

Let then

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

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

We have

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

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

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

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

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

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 (43), with a few differences

The I compartment contains individuals 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

$$(\partial_t + \partial_a)S(t, a) = \Lambda(a) - (d(a) + \lambda(t, a))S(t, a) \quad (45a)$$

$$(\partial_t + \partial_a)I(t, a) = -(d(a) + \gamma(a))I(t, a) + \lambda(t, a)S(t, a) \quad (45b)$$

$$(\partial_t + \partial_a)A(t, a) = \gamma(a)A(t, a) - (d(a) + \delta(a))A(t, a) \quad (45c)$$

Assume

$$\lambda(t, a) = h(a) \int_{a_0}^{\infty} \rho(a, a') \frac{I(t, a')}{T(t, a')} da' \quad (45d)$$

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

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

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

$$(\partial_t + \partial_a)y(t, a) = (1 - y)(-\gamma(a)y + \lambda(t, a)) \quad (46a)$$

$$\lambda(t, a) = h(a) \int_0^\omega p(a, a')y(t, a')da' \quad (46b)$$

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 $X \rightarrow X$

Let $\Omega = \{f \in X, 0 \leq f \leq 1 \text{ a.e.}\}$. Then (46) takes the form

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

Let

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

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 resolvent 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

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

```
# 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"
```