

Stochastic and non-ODE epidemiological models

Populate Summer School – Course 03

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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

Sojourn times in compartments

Continuous time Markov chains

Structuration in age



A landscape painting featuring a winding blue river in the foreground, dotted with small red flowers. The river flows from the bottom left towards the center. In the background, there are rolling green hills under a light blue sky with white clouds.

Sojourn times in compartments

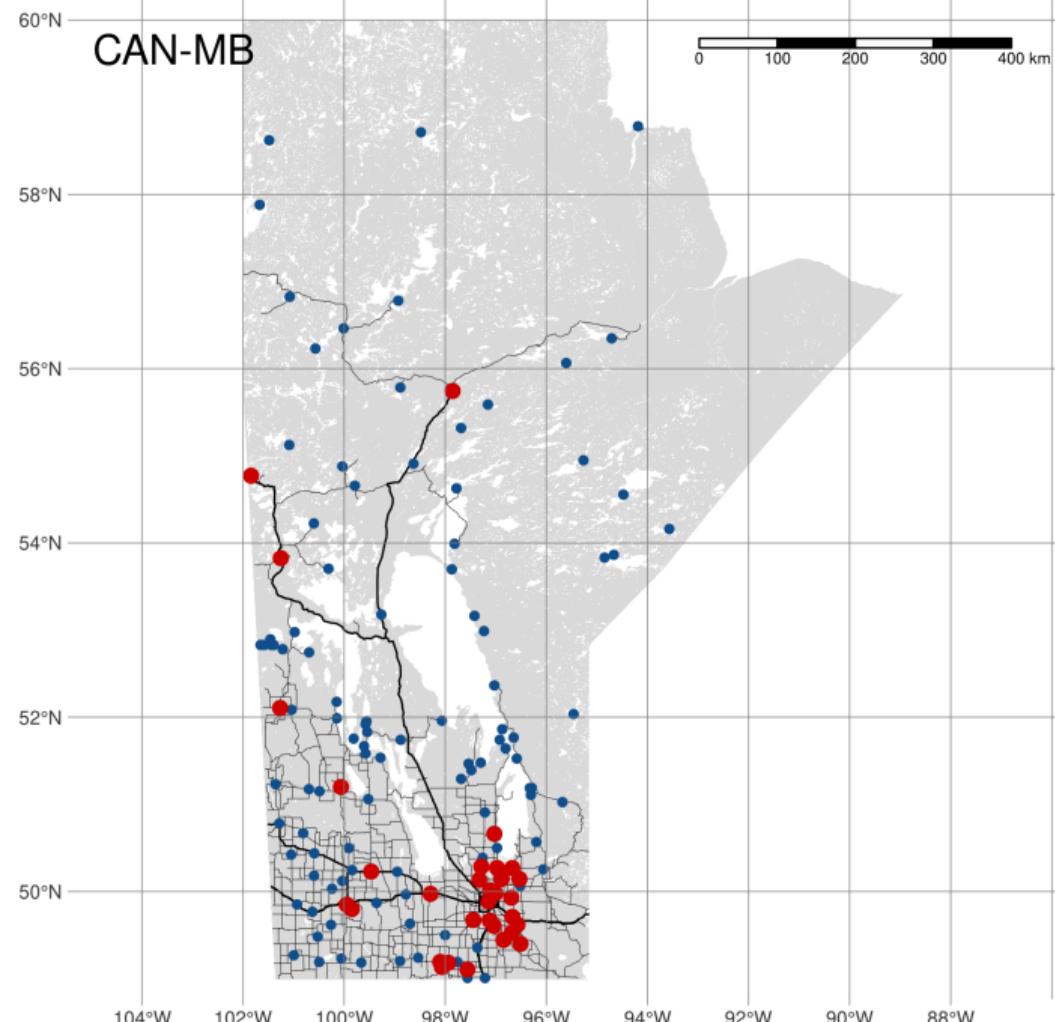
Continuous time Markov chains

Structuration in age

At the beginning of COVID-19

- ▶ I was working under contract with the Public Health Agency of Canada on *COVID-19 importation risk assessment*
- ▶ Produced daily report with list of countries most likely to next report cases of COVID-19
- ▶ Used ensemble runs of a fitted global deterministic metapopulation model





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

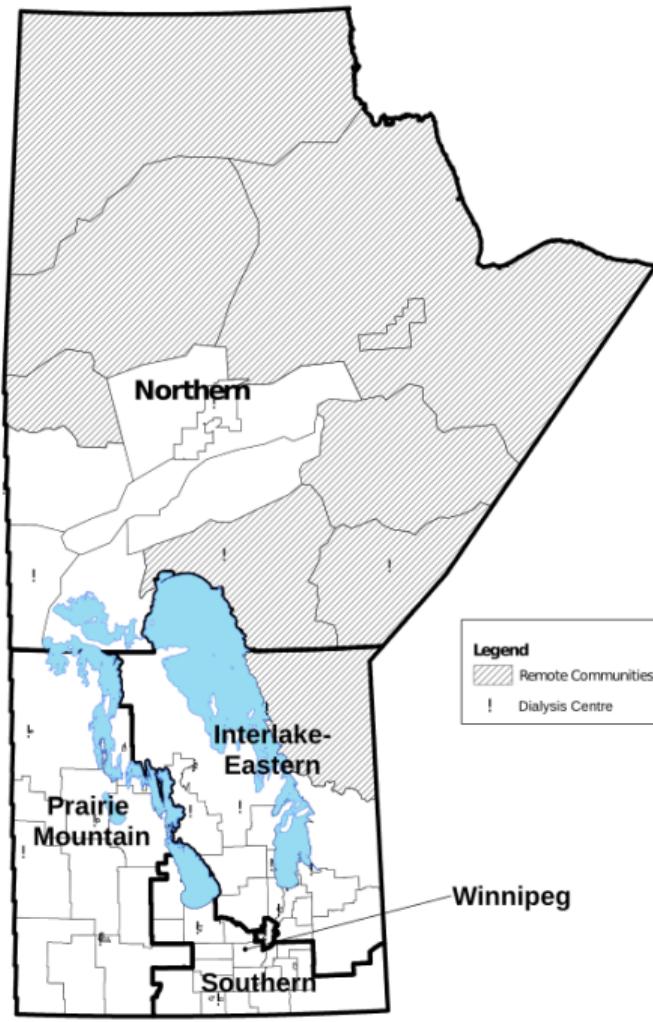
Inuit Communities to be referred to as **Inuit Nunangat**, not remote and isolated communities to respect the unique language and culture of Inuit regions, as well as the common challenges in social determinants of health, access to care, and infrastructure found across all Inuit communities

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



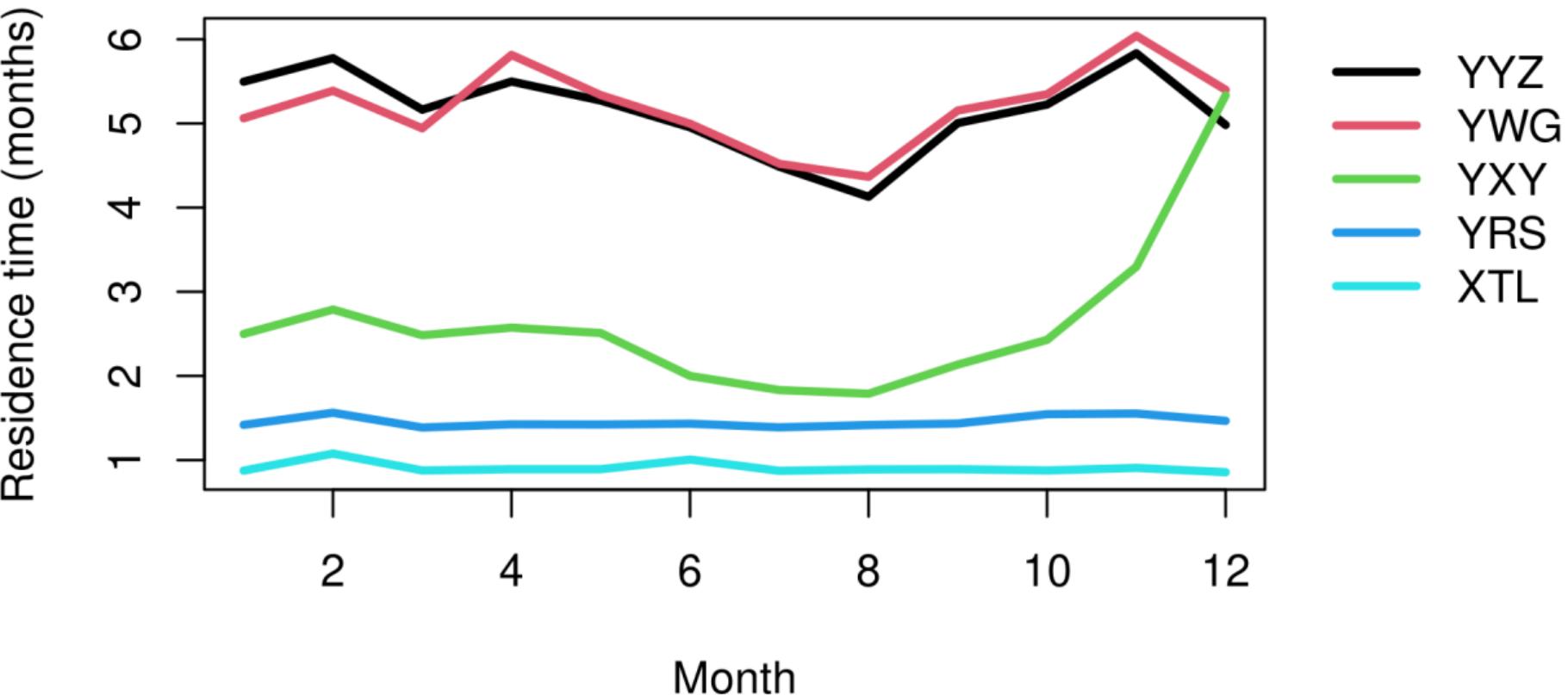
One interesting paradox

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

FIGS/Screenshot from 2024-06-27 00-33-22.png

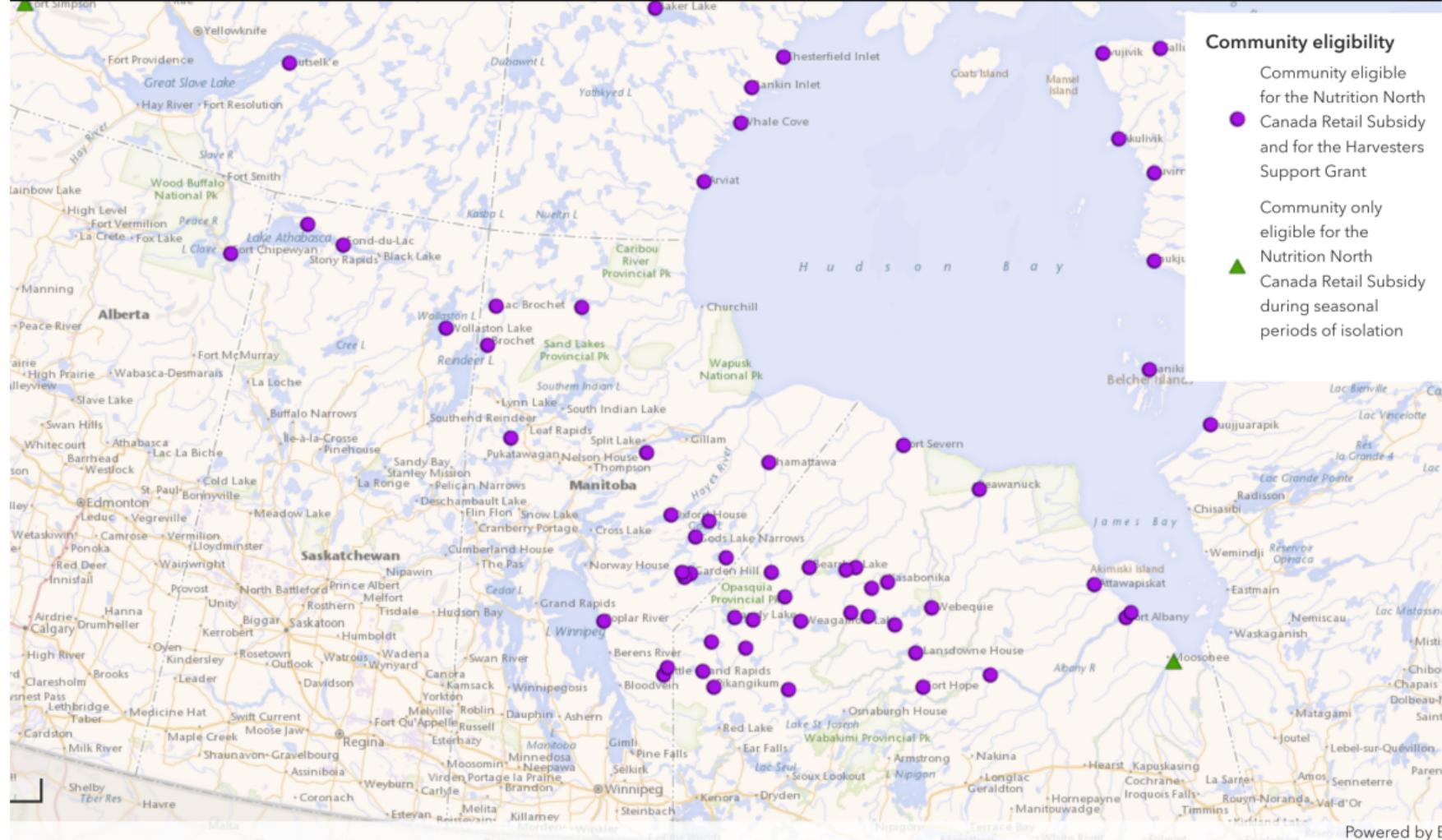
Community eligibility

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”)

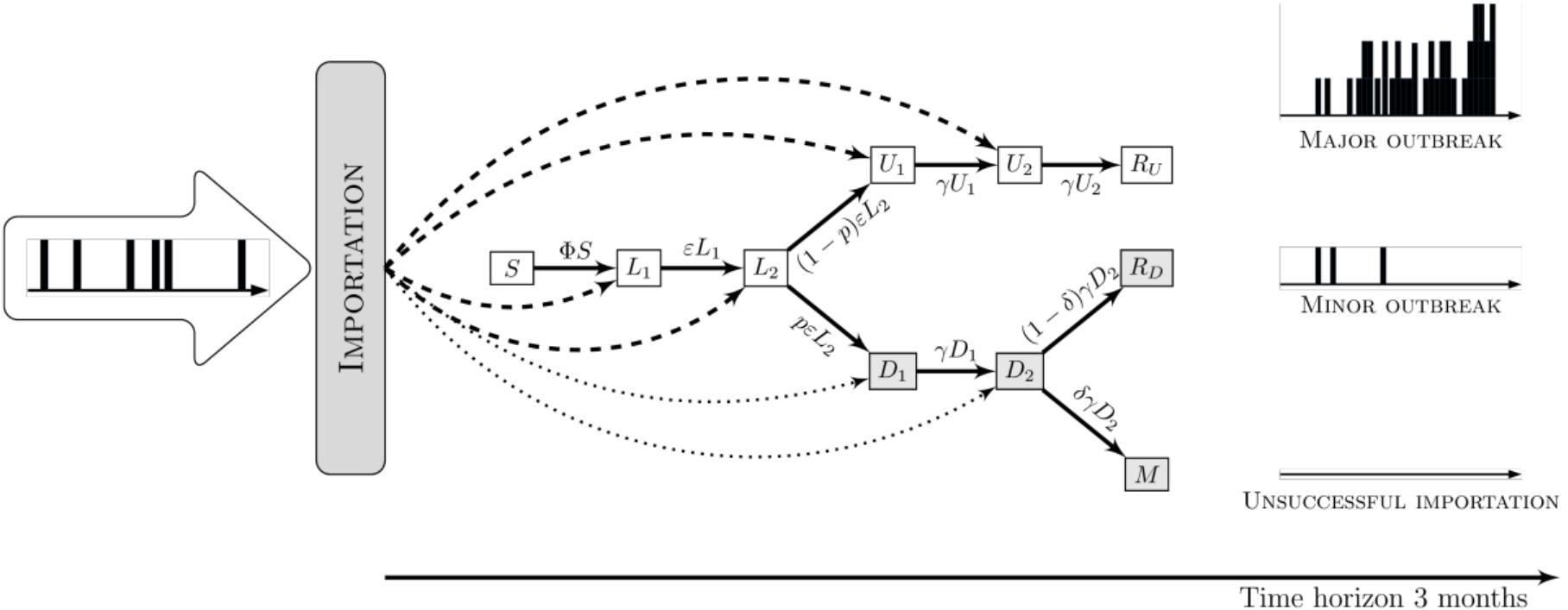
- ▶ What do the different control measures do, how good are they?

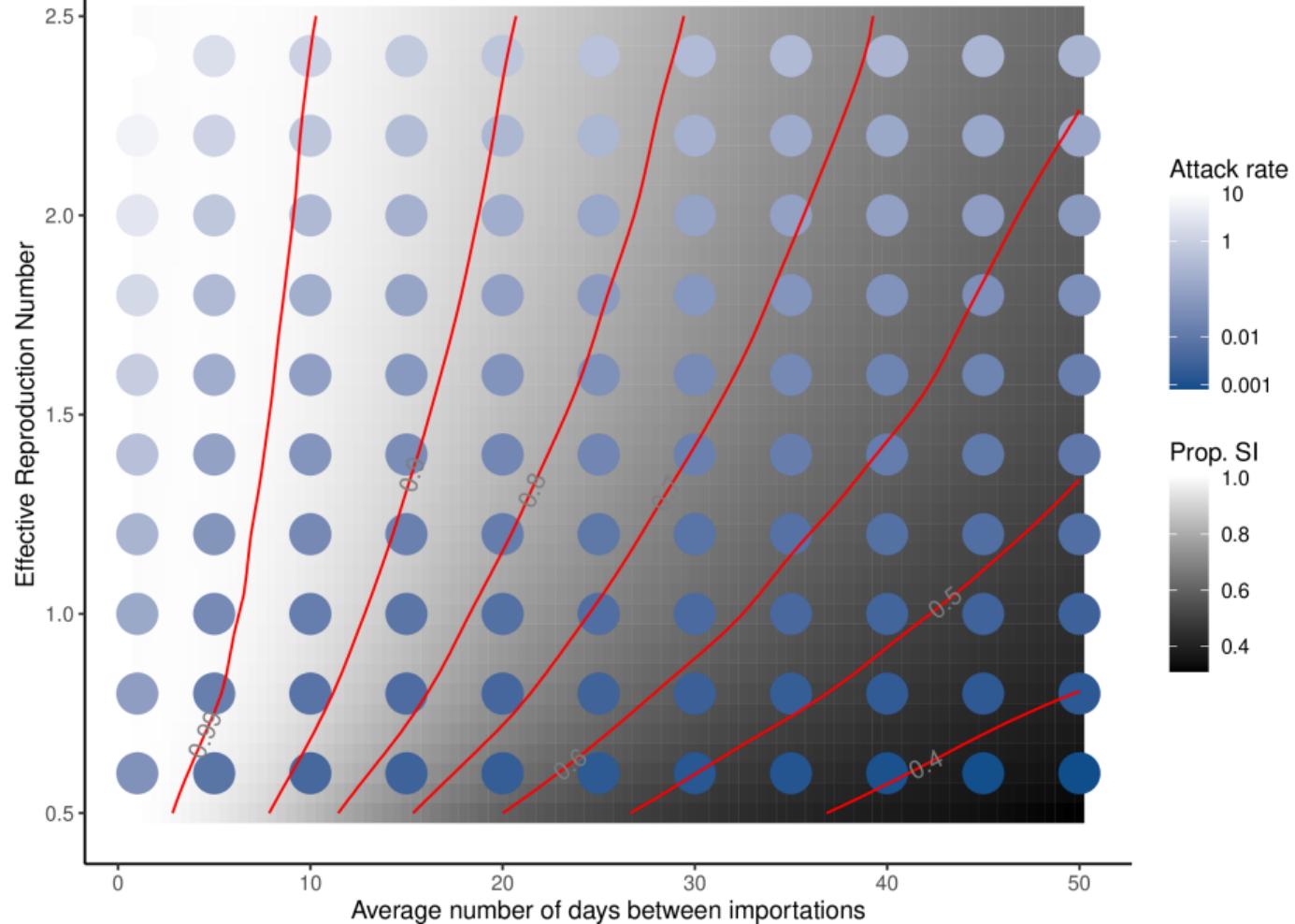


Sojourn times in compartments

Continuous time Markov chains

Structuration in age





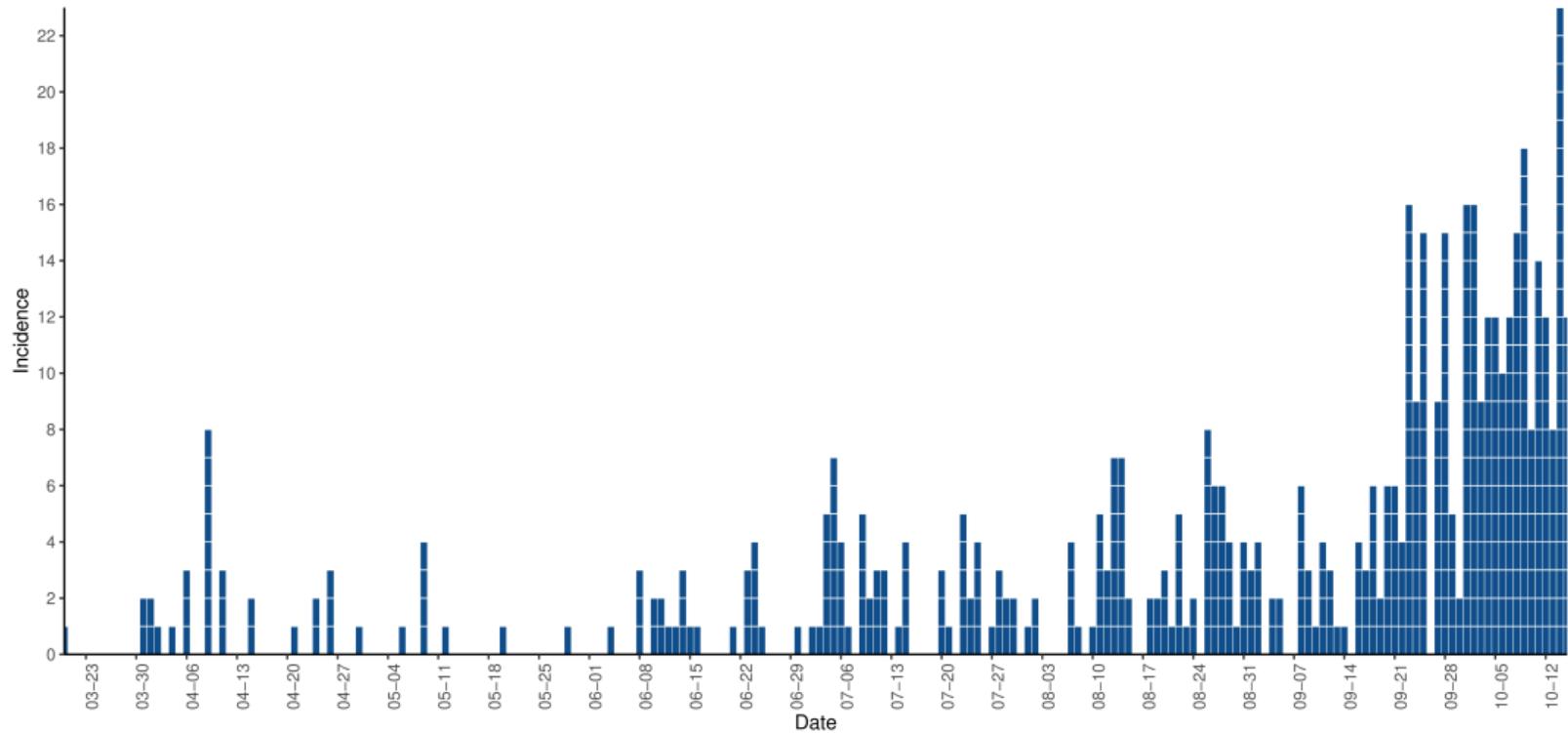


Sojourn times in compartments

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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	$(S^A, I^A) \rightarrow (S^A + 1, I^A - 1)$	$\gamma^A I^A$

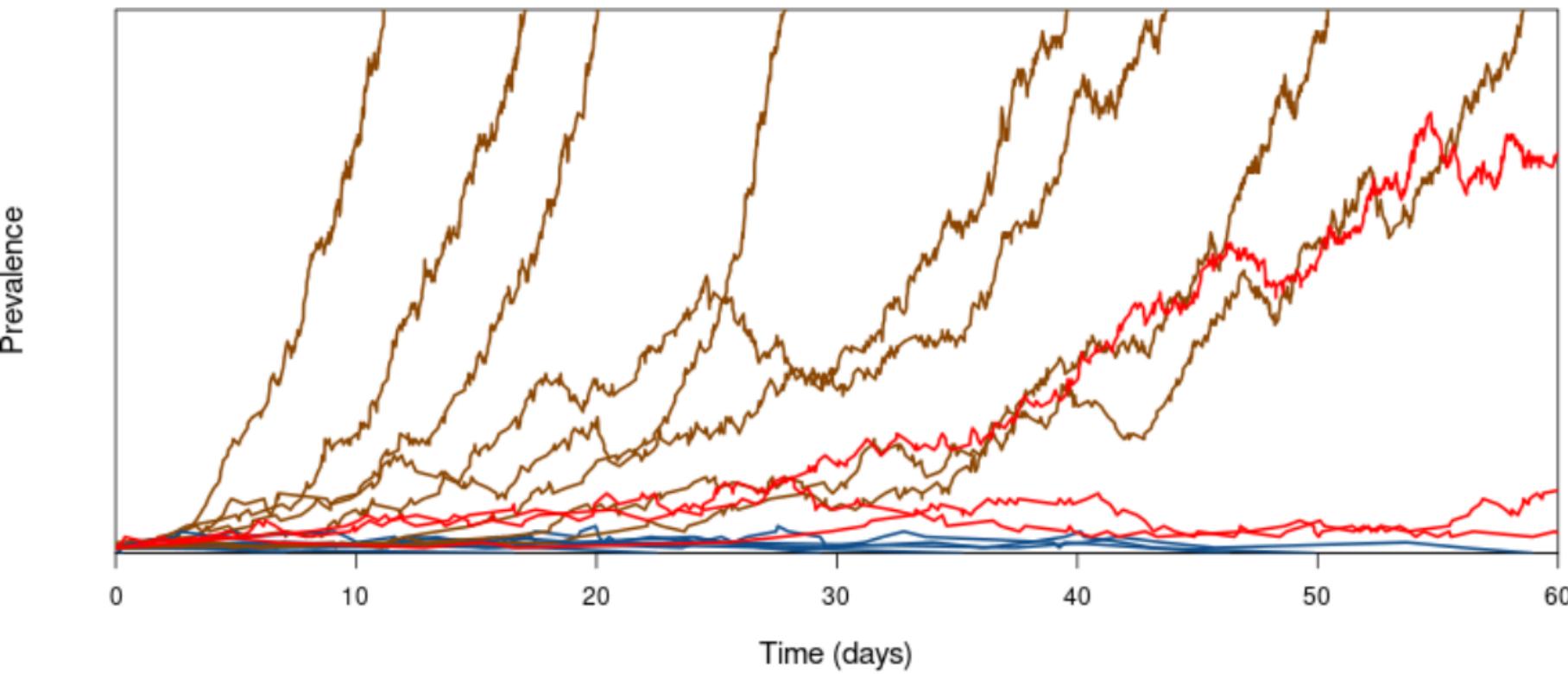
Investigating outbreak types using a simple CTMC SIS *with a twist*

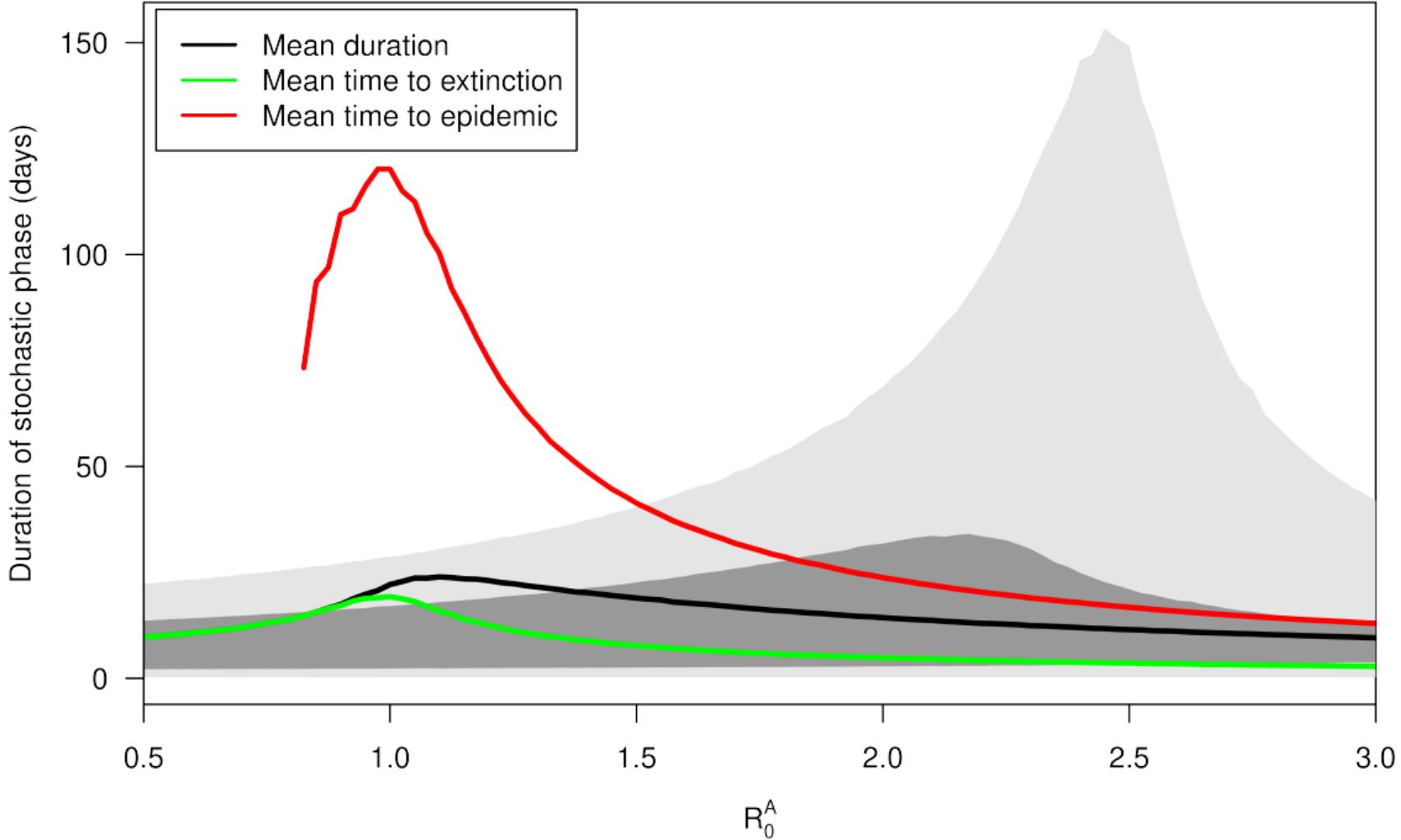
Regular chain of this type has $I = 0$ as sole absorbing state

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)



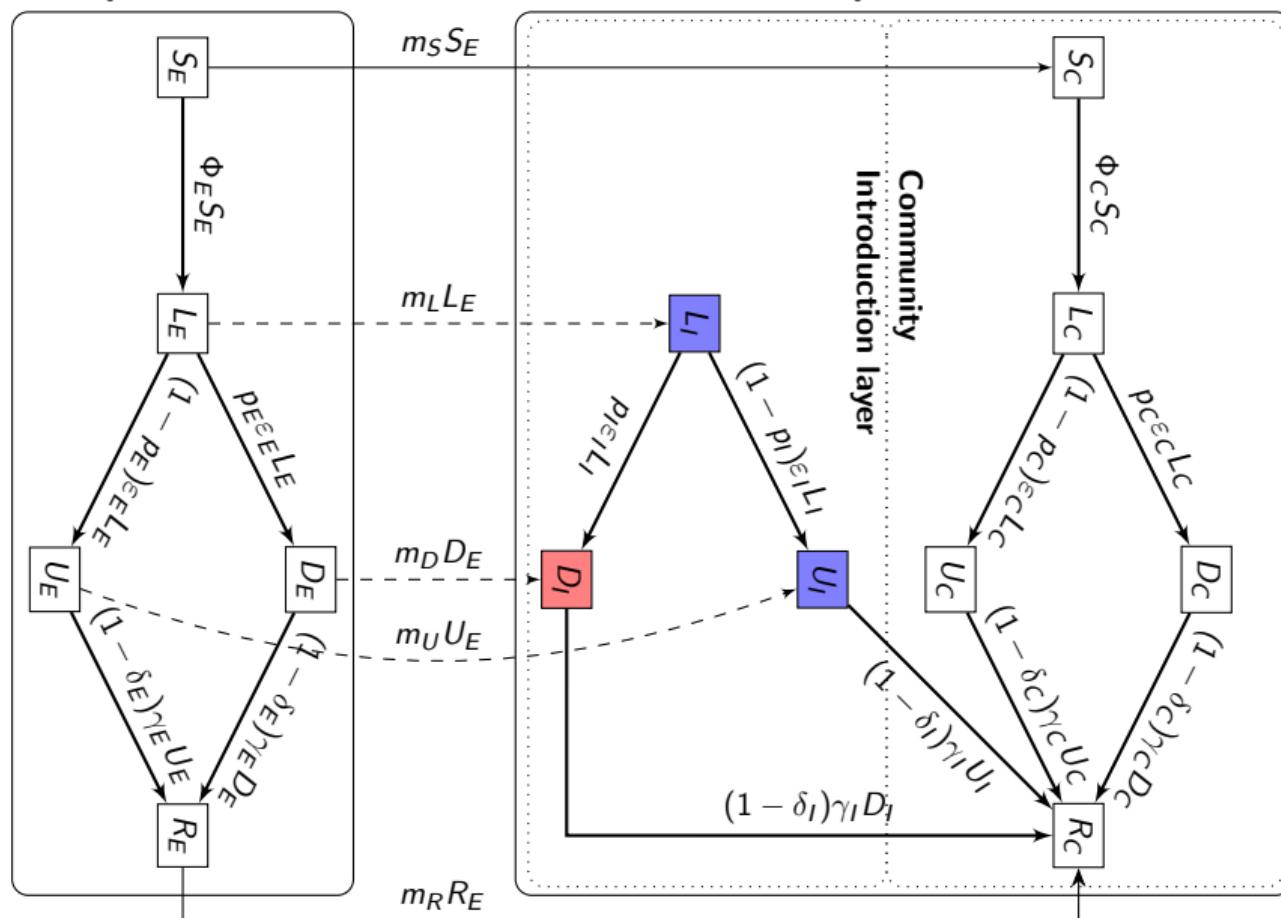
Sojourn times in compartments

Continuous time Markov chains

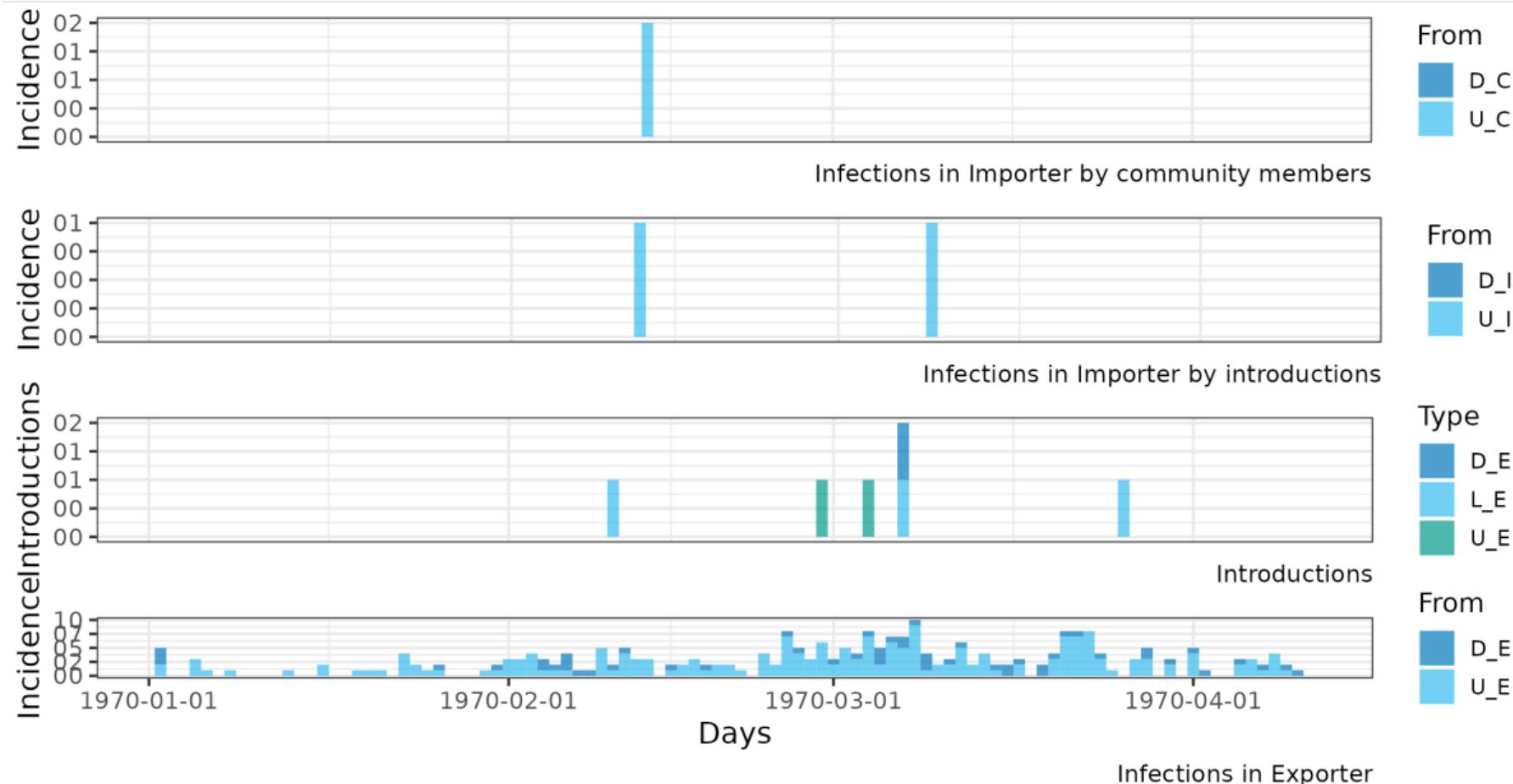
Structuration in age

Exporter

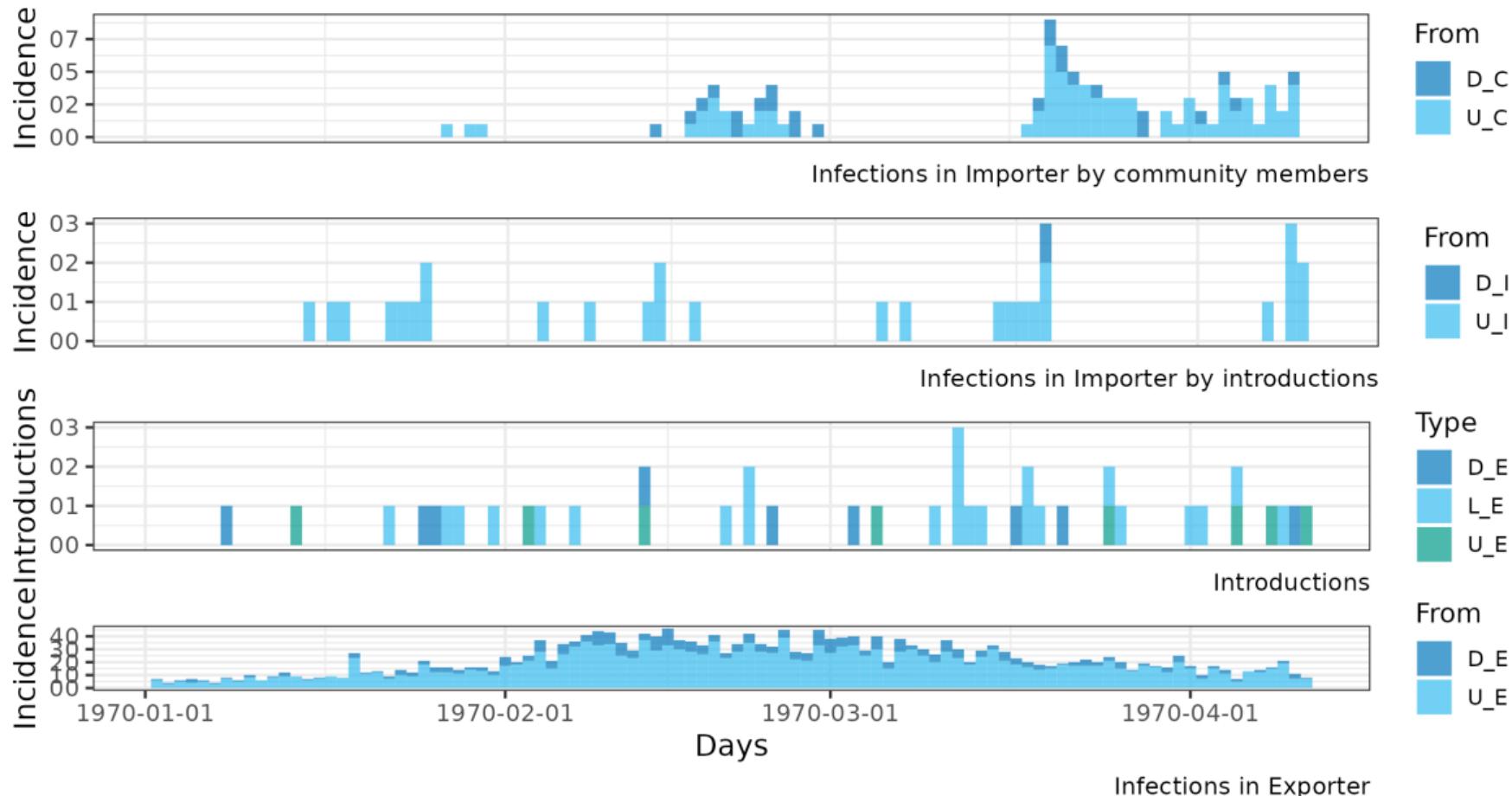
Importer



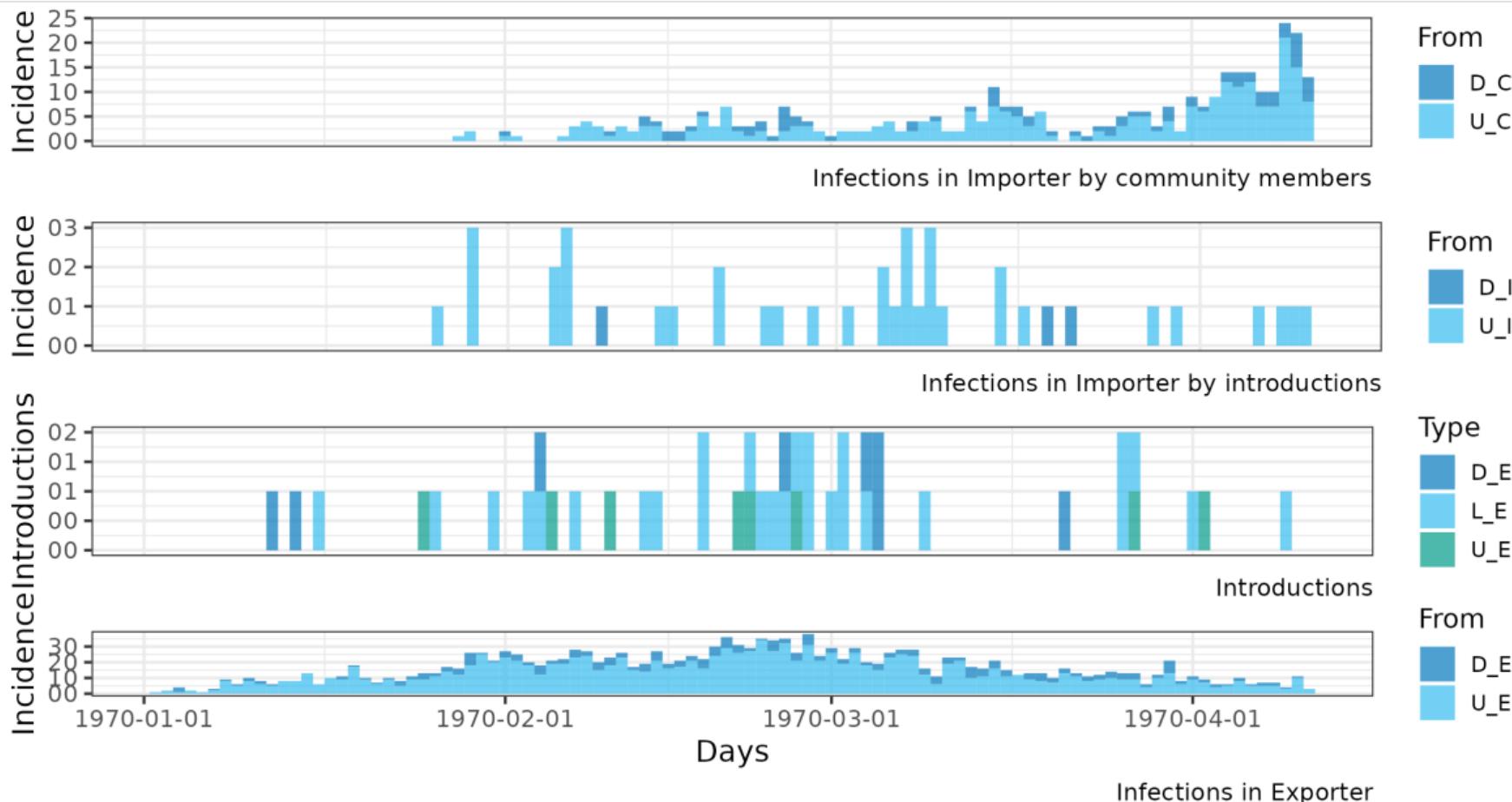
$$R_0^E = 1.5, R_0^C = 0.8, \text{pop}_E = 10000, \text{pop}_I = 10000$$



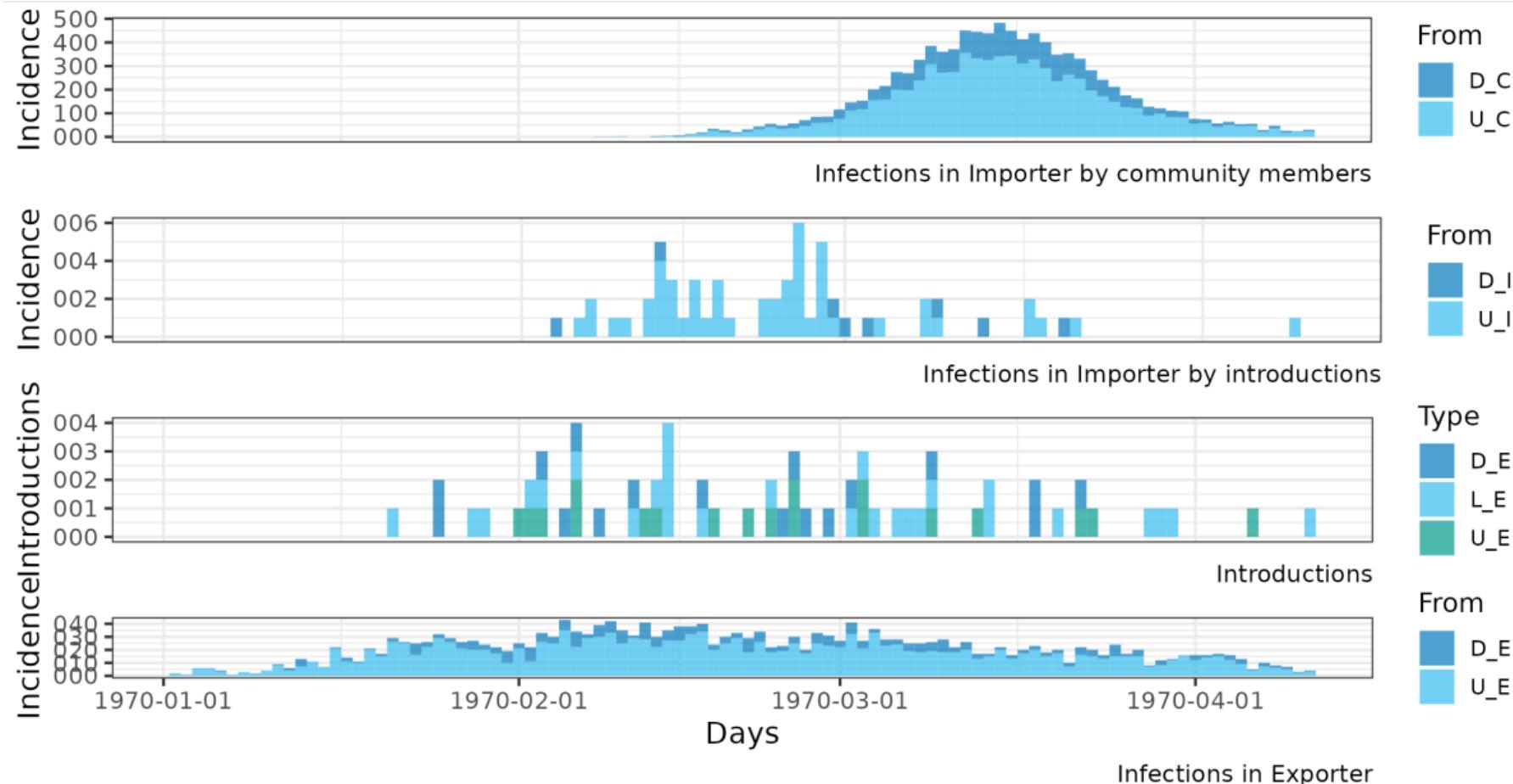
$$R_0^E = 1.5, R_0^C = 0.8, \text{pop}_E = 10000, \text{pop}_I = 10000$$

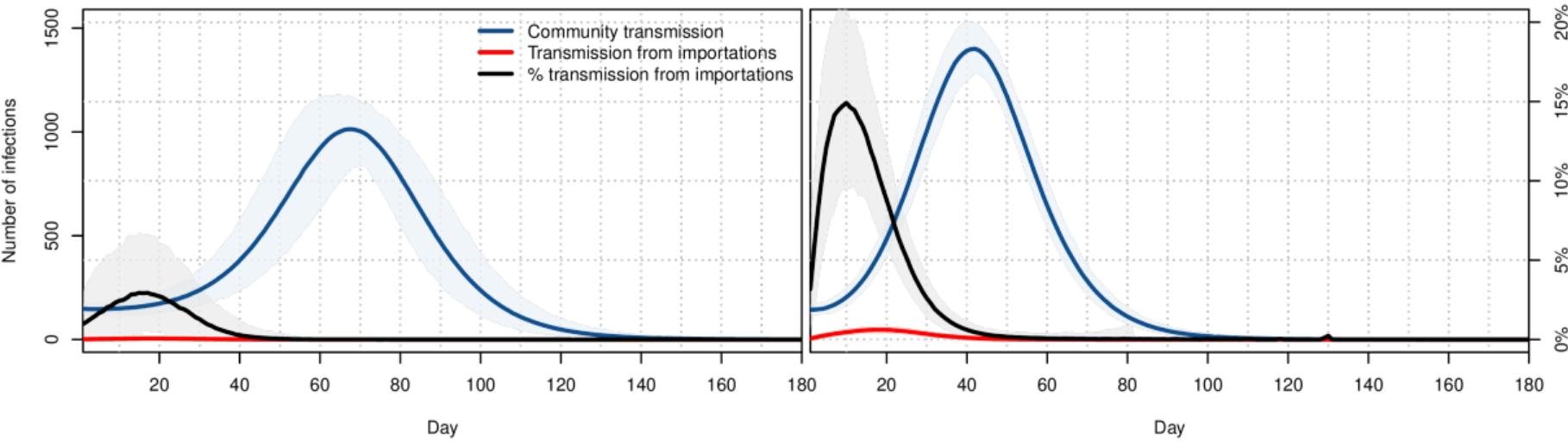


$$R_0^E = 1.5, R_0^C = 0.8, \text{pop}_E = 10000, \text{pop}_I = 10000$$



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





Sojourn times in compartments

Continuous time Markov chains

Structuration in age

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.

See in particular 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

Time to events

We suppose that a system can be in two states, S_0 and S_2

- ▶ At time $t = 0$, the system is in state S_0
- ▶ An event happens at some time $t = \tau$, which triggers the switch from state S_0 to state S_1

Let us call T the random variable

"time spent in state S_0 before switching into state S_1 "

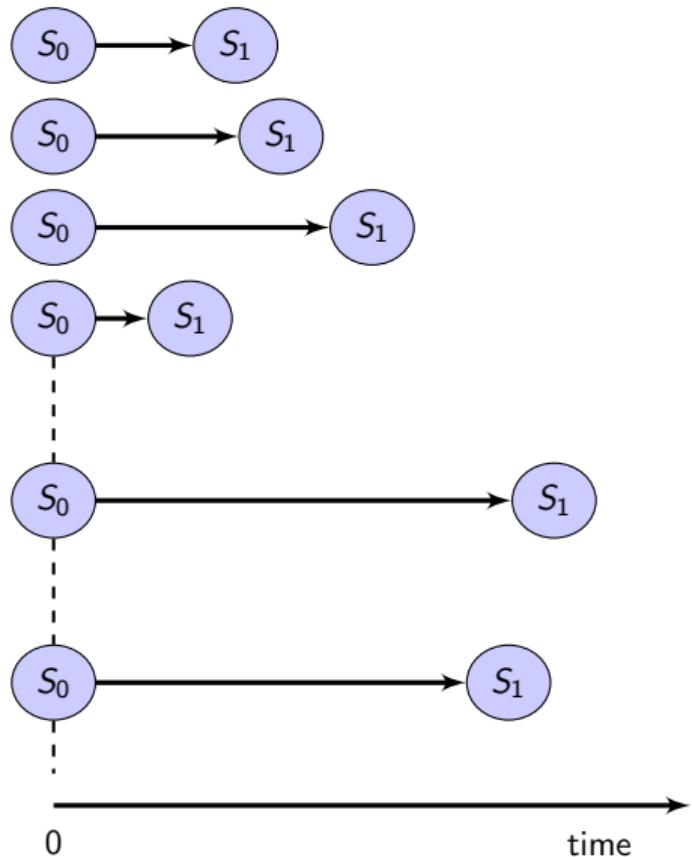
The states can be anything:

- ▶ S_0 : working, S_1 : broken
- ▶ S_0 : infected, S_1 : recovered
- ▶ S_0 : alive, S_1 : dead
- ▶ ...

We take a collection of objects or individuals that are in state S_0 and want some law for the **distribution** of the times spent in S_0 , i.e., a law for T

For example, we make light bulbs and would like to tell our customers that on average, our light bulbs last 200 years...

We conduct an **infinite** number of experiments, and observe the time that it takes, in every experiment, to switch from S_0 to S_1



A distribution of probability is a model

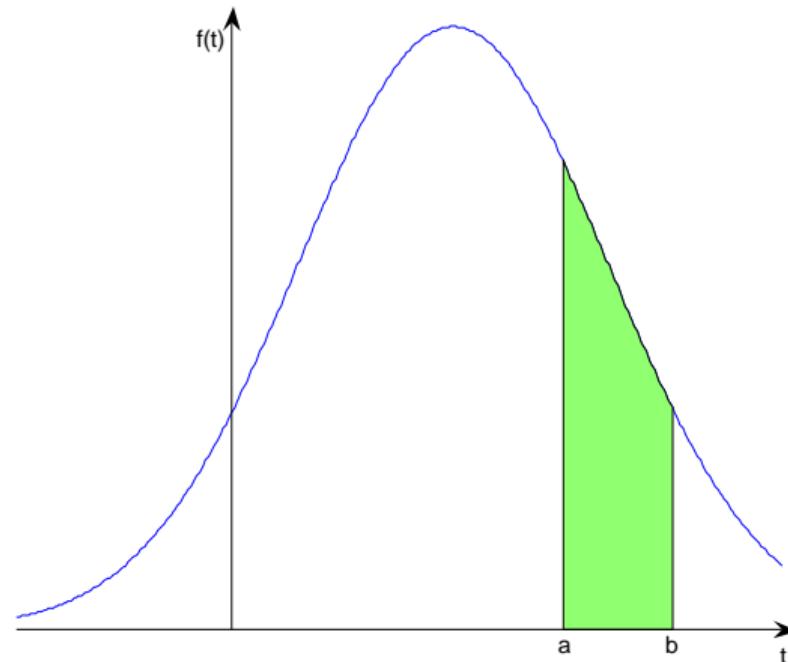
From the sequence of experiments, we deduce a model, which in this context is called a **probability distribution**

We assume that T is a **continuous** random variable

Probability density function

Since T is continuous, it has a continuous **probability density function** f

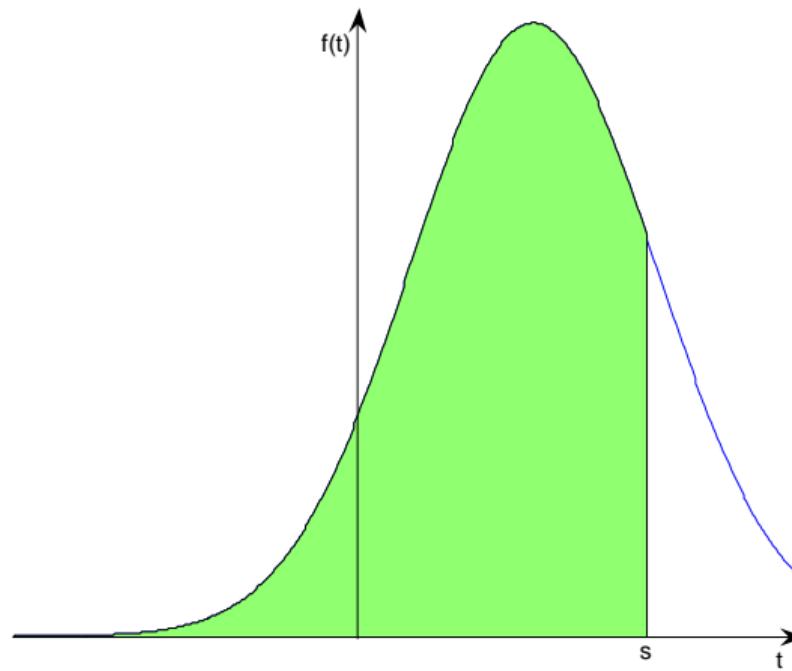
- ▶ $f \geq 0$
- ▶ $\int_{-\infty}^{+\infty} f(s)ds = 1$
- ▶ $\mathbb{P}(a \leq T \leq b) = \int_a^b f(t)dt$



Cumulative distribution function

The cumulative distribution function (c.d.f.) is a function $F(t)$ that characterizes the distribution of T , and defined by

$$F(s) = \mathbb{P}(T \leq s) = \int_{-\infty}^s f(x)dx$$



Survival function

Another characterization of the distribution of the random variable T is through the **survival** (or **sojourn**) function

The survival function of state S_0 is given by

$$S(t) = 1 - F(t) = \mathbb{P}(T > t) \quad (1)$$

This gives a description of the **sojourn time** of a system in a particular state (the time spent in the state)

S is a nonincreasing function (since $S = 1 - F$ with F a c.d.f.), and $S(0) = 1$ (since T is a nonnegative random variable)

The **average sojourn time** τ in state S_0 is given by

$$\tau = E(T) = \int_0^\infty t f(t) dt$$

Since $\lim_{t \rightarrow \infty} t S(t) = 0$, it follows that

$$\tau = \int_0^\infty S(t) dt$$

Expected future lifetime:

$$\frac{1}{S(t_0)} \int_0^\infty t f(t + t_0) dt$$

$$\begin{aligned} S(t) - S(a) &= \mathbb{P}\{\text{survive during } (a, t) \text{ having survived until } a\} \\ &= \exp\left(-\int_a^t h(u) du\right) \end{aligned}$$

Hazard rate

The **hazard rate** (or **failure rate**) is

$$\begin{aligned} h(t) &= \lim_{\Delta t \rightarrow 0} \frac{\mathcal{S}(t) - \mathcal{S}(t + \Delta t)}{\Delta t} \\ &= \lim_{\Delta t \rightarrow 0} \frac{\mathbb{P} T < t + \Delta t | T \geq t}{\Delta t} \\ &= \frac{f(t)}{\mathcal{S}(t)} \end{aligned}$$

It gives probability of failure between t and Δt , given survival to t .

We have

$$h(t) = -\frac{d}{dt} \ln \mathcal{S}(t)$$

Competing risks

Suppose now that the system starts in state A at time $t = 0$ and that depending on which of the two events \mathcal{E}_1 or \mathcal{E}_2 takes place first, it switches to state B_1 or B_2 , respectively

Consider the random variables T_A , *time spent in state A* (or sojourn time in A), T_{AB_1} , *time before switch to B_1* and T_{AB_2} , *time before switch to B_2*

If we consider state A , we cannot observe the variables T_{AB_1} or T_{AB_2} . What is observable is the sojourn time in A

$$T_A^* = \min(T_{AB_1}, T_{AB_2})$$

(where * indicates that a quantity is observable)

Failure rate by type of event

We have two (or more) types of events whose individual failure rates have to be accounted for

$$h_j(t) = \lim_{\Delta t \rightarrow 0} \frac{\mathbb{P}(T < t + \Delta t, S = S_j | T \geq t)}{\Delta t}$$

where $\mathbb{P}(T < t + \Delta t, S = S_j | T \geq t)$ is the probability of failure due to cause S_j ($j = 1, 2$ ici), i.e., S is a discrete r.v. representing the event that is taking place

By the law of total probability, since only one of the event can take place, if there are n risks, then

$$h(t) = \sum_{i=1}^n h_j(t)$$

or, identically,

$$\mathcal{S}(t) = \exp \left(- \int_0^t \sum_{j=1}^n h_j(s) \, ds \right)$$

As a consequence, suppose a process is subject to two competing exponential risks with respective distributions with parameters θ_1 and θ_2

Then the mean sojourn time in the initial state before being affected by one of the two risks is

$$\frac{1}{\theta_1 + \theta_2}$$

The exponential distribution

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

$$f(t) = \begin{cases} 0 & \text{if } t < 0, \\ \theta e^{-\theta t} & \text{if } t \geq 0, \end{cases} \quad (2)$$

with $\theta > 0$. Then the survival function for state S_0 is of the form $S(t) = e^{-\theta t}$, for $t \geq 0$, and the average sojourn time in state S_0 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

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

with standard deviation $\sigma = 0$

The Gamma distribution

R.v. X is **Gamma** distributed ($X \sim \Gamma(k, \theta)$) with **shape parameter** k and **scale parameter** θ (or **rate** $\beta = 1/\theta$) (all positive) if its probability density function takes the form

$$f(x; k, \theta) = \frac{x^{k-1} e^{-\frac{x}{\theta}}}{\Gamma(k)\theta^k} \quad (3)$$

where $x > 0$ and Γ is the Euler Gamma function, defined for all $z \in \mathbb{C}$ s.t. $\operatorname{Re}(z) > 0$ by

$$\Gamma : z \mapsto \int_0^{+\infty} t^{z-1} e^{-t} dt$$

Properties of the Gamma distribution

Mean $k\theta$, variance $k\theta^2$

Survival function

$$S(t) = 1 - \frac{1}{\Gamma(k)} \gamma\left(k, \frac{t}{\theta}\right) = 1 - \frac{1}{\Gamma(k)} \gamma(k, \beta t)$$

where

$$\gamma(a, x) = \int_0^x t^{a-1} e^{-t} dt$$

is an incomplete Gamma function

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 $t \geq 0$

$$N(t) = N_0 P(t) \tag{4}$$

$P(t)$ proportion of initial population still alive at time t , so $N_0 P(t)$ number in the cohort 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 (4) takes the form

$$N(t) = N_0 e^{-dt} \tag{5}$$

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, $\mathcal{S}(t) = \mathbb{P}(T > t)$, 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 (4) takes the form

$$N(t) = \begin{cases} N_0, & 0 \leq t \leq \omega \\ 0, & t > \omega \end{cases} \quad (6)$$

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

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

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

Survival for the exponential distribution

Issues with the exponential distribution

- ▶ Survival drops quickly
- ▶ Survival continues way beyond the mean

Acceptable if what matters is the average duration of sojourn in a compartment (e.g., long term dynamics)

More iffy if one is interested in short-term dynamics

- ▶ Exponential distribution with parameter θ has same mean and standard deviation $1/\theta$, i.e., a single parameter controls mean and dispersion about the mean

Exponential distributions are bad but also cool

X_1 and X_2 2 i.i.d. (independent and identically distributed) r.v. with parameters θ_1 and θ_2 . Then the probability density function of the r.v. $Z = X_1 + X_2$ is given by the convolution

$$\begin{aligned} f_Z(z) &= \int_{-\infty}^{\infty} f_{X_1}(x_1) f_{X_2}(z - x_1) dx_1 \\ &= \int_0^z \theta_1 e^{-\theta_1 x_1} \theta_2 e^{-\theta_2(z-x_1)} dx_1 \\ &= \theta_1 \theta_2 e^{-\theta_2 z} \int_0^z e^{(\theta_2 - \theta_1)x_1} dx_1 \\ &= \begin{cases} \frac{\theta_1 \theta_2}{\theta_2 - \theta_1} (e^{-\theta_1 z} - e^{-\theta_2 z}) & \text{if } \theta_1 \neq \theta_2 \\ \theta^2 z e^{-\theta z} & \text{if } \theta_1 = \theta_2 =: \theta \end{cases} \end{aligned} \tag{7}$$

The tool we use

Theorem 1

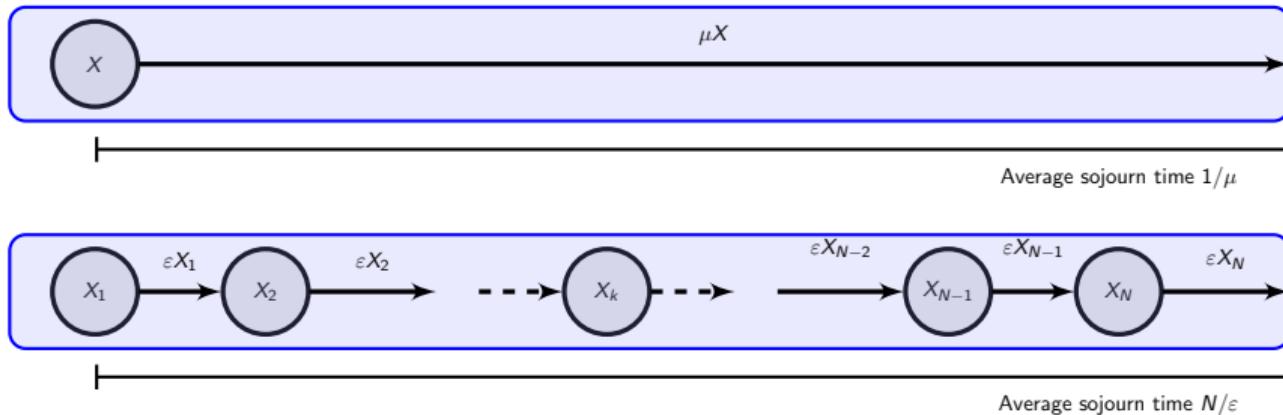
Let X_i be independent exponentially distributed random variables with parameter ξ and $Y = \sum_{i=1}^n X_i$

Then the random variable $Y \rightsquigarrow E(n, \xi)$, an Erlang distribution with shape parameter n and scale parameter ξ

(Erlang distribution: Gamma distribution with integer shape parameter)

Consequences for compartmental models

If n compartments are traversed successively by individuals, with each compartment having an outflow rate of $1/\xi$ (or a mean sojourn time of ξ), then the time of sojourn from entry into the first compartment to exit from the last is Erlang distributed with mean $E(Y) = n\xi$ and variance $\text{Var}(Y) = n\xi^2$



I have a Shiny app for this :)

Example: EVD incubation periods

Consider the incubation period for Ebola Virus Disease. During the 2014 EVD crisis in Western Africa, the WHO Ebola Response Team estimated incubation periods in a 2015 paper

Table S2 in the Supplementary Information in that paper gives the best fit for the distribution of incubation periods for EVD as a Gamma distribution with mean 10.3 days and standard deviation 8.2, i.e., $n\varepsilon = 10.3$ and $\varepsilon\sqrt{n} = 8.2$

From this, $\varepsilon = 8.2^2/10.3 \simeq 6.53$ and $n = 10.3^2/8.2^2 \simeq 1.57$. However, that is a Gamma distribution

Switching to a compartmental model approach

To use multiple compartments to better fit residence times, we need to find the closest possible Erlang distribution to this Gamma distribution

⇒ compute RSS errors between data points generated from the given Gamma distribution and an Erlang

```
error_Gamma <- function(theta,shape,t,d) {  
  test_points <- dgamma(t, shape = shape, scale = theta)  
  ls_error <- sum((d-test_points)^2)  
  return(ls_error)  
}
```

```
optimize_gamma <- function(t,d) {  
  max_shape <- 10  
  error_vector <- mat.or.vec(max_shape,1)  
  scale_vector <- mat.or.vec(max_shape,1)  
  for (i in 1:max_shape) {  
    result_optim <- try(optim(par = 3,  
                               fn = error_Gamma,  
                               lower = 0,  
                               method = "L-BFGS-B",  
                               shape = i,  
                               t = t,  
                               d = d),  
                           TRUE)  
    if (!inherits(result_optim,"try-error")) {  
      error_vector[i] <- result_optim$value  
      scale_vector[i] <- result_optim$par  
    } else {  
      error_vector[i] <- NaN  
    }  
  }  
}
```

```
time_points <- seq(0,60)
data_points <- dgamma(time_points, shape = 1.57,
                      scale = 6.53)
# Run the minimization
optim_fits <- optimize_gamma(time_points,data_points)
# Which is the best Erlang to fit the data
idx_best <- which.min(optim_fits$error)
```

Now plot the result as well as the original curve (code chunk not shown)

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)

$$I(t) = I_0(t) + \int_0^t \beta \frac{S(u)I(u)}{N} P(t-u) du \quad (8)$$

- ▶ $I_0(t)$ 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:

$$I(t) = I_0(t) + \int_0^t \beta \frac{(N - I(u))I(u)}{N} P(t - u) du \quad (8)$$

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 (4)

Equation (8) becomes

$$I(t) = I_0(0)e^{-\gamma t} + \int_0^t \beta \frac{(N - I(u))I(u)}{N} e^{-\gamma(t-u)} du \quad (9)$$

Taking the time derivative of (9) yields

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

This 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 (8) becomes

$$I(t) = I_0(t) + \int_{t-\omega}^t \beta \frac{(N - I(u))I(u)}{N} du. \quad (10)$$

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, (10) 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)

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

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

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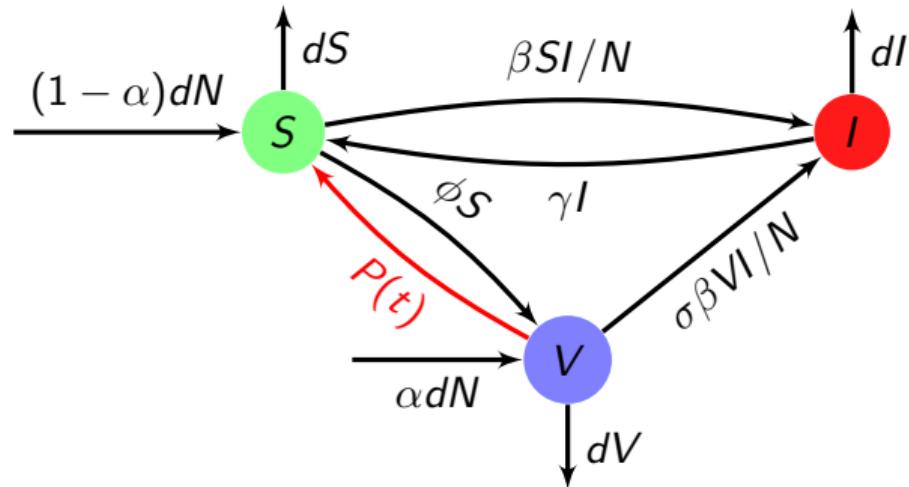
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(Communicated by Linda Allen)

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

$$\frac{dI(t)}{dt} = \beta(S(t) + \sigma V(t))I(t) - (d + \gamma)I(t) \quad (11a)$$

$$V(t) = V_0(t) \quad (11b)$$

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

- ▶ 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

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau} \right) v(t, \tau) = -(\sigma \beta I(t) + d + \eta(\tau))v(t, \tau) \quad (12)$$

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

$$V_0(t) = e^{-\int_0^t (\sigma \beta I(x) + d) dx} \int_0^\infty v(0, u) \frac{P(t+u)}{P(u)} du \quad (13)$$

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 2

The set \mathcal{D} is positively invariant under the flow of (11) with $I(0) > 0, S(0) > 0$

With the assumed initial conditions in \mathcal{D} , it can be shown that the system defined by (11a) and (11b) is equivalent to the system defined by (11a) and

$$\begin{aligned} \frac{d}{dt} V(t) &= \frac{d}{dt} V_0(t) + \phi S(t) + \alpha d \\ &\quad - (d + \sigma \beta I(t))(V(t) - V_0(t)) + Q(t) \end{aligned} \tag{14}$$

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 (11a) and (14) is of standard form, therefore results of Hale (see Hale & Verduyn-Lunel) ensure the local existence, uniqueness and continuation of solutions of model (11)

\mathcal{R}_0

Define \mathcal{R}_0 with vaccination as

$$\mathcal{R}_v = \mathcal{R}_0 \left[\frac{1 + \sigma\phi\tilde{P} - (1 - \sigma)\alpha d\tilde{P}}{1 + \phi\tilde{P}} \right] \quad (15)$$

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

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

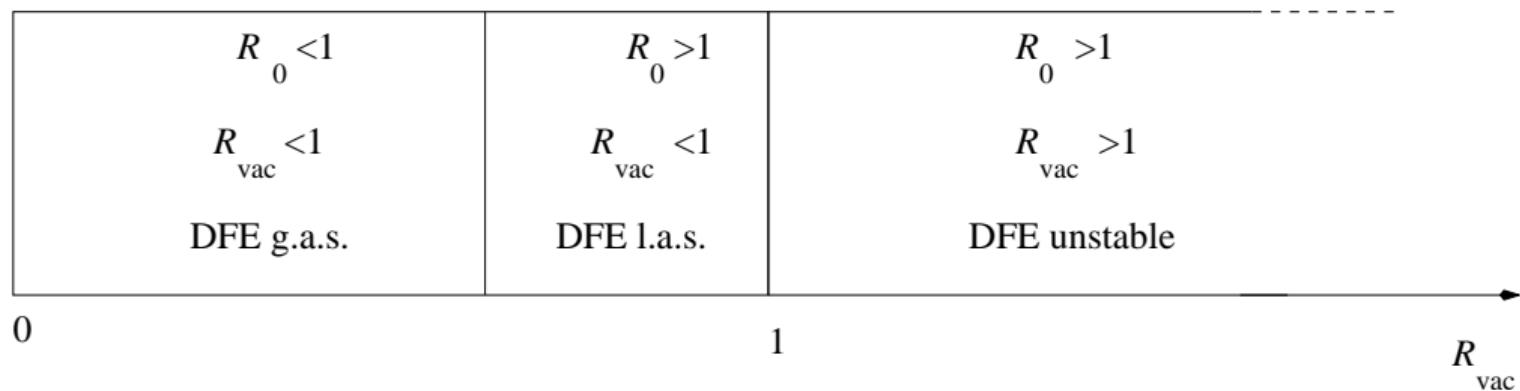
in such a way that $\tilde{P} < 1/d$

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

Theorem 3

System (11) 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 (13). Then (11a) and (14) give the ODE system

$$\frac{dI}{dt} = \beta(1 - I - (1 - \sigma)V)I - (d + \gamma)I \quad (16a)$$

$$\frac{dV}{dt} = \phi(1 - I - V) - \sigma\beta I V - (d + \theta)V + \alpha d \quad (16b)$$

which with no newborn vaccination ($\alpha = 0$) is the model studied in Kribs-Zaletta & Velasco-Hernandez, 2000

From Theorem 3 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 (15).

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 4

For the ODE system (16) 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 $\mathcal{D} \setminus \{I = 0\}$

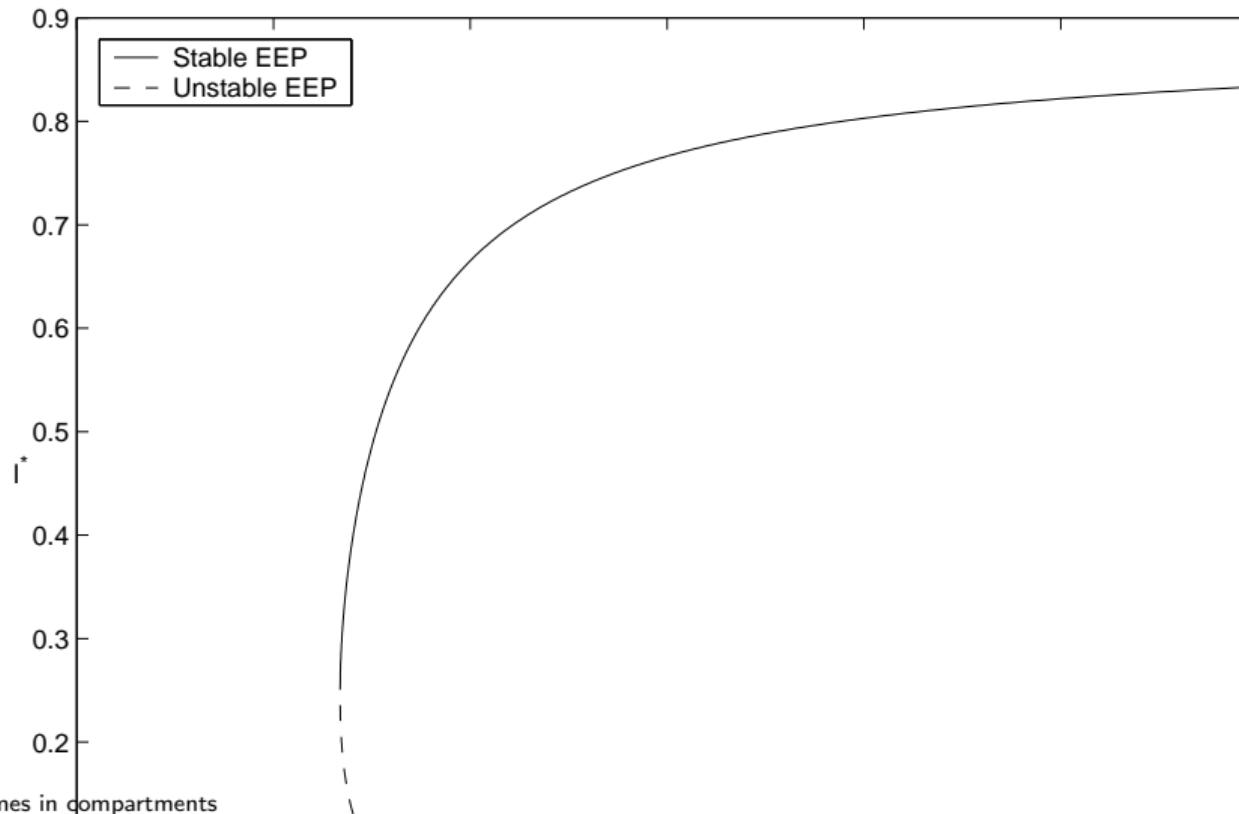
Pertussis:

- ▶ 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 (11b) becomes, for $t > \omega$

$$V(t) = \int_{t-\omega}^t (\phi(1 - I(u) - V(u)) + \alpha d) e^{-d(t-u)} e^{-\sigma \beta \int_u^t I(x) dx} du \quad (17)$$

Differentiating (17) (see equation (14)) gives the model as the two dimensional system, for $t > \omega$

$$\frac{d}{dt}I(t) = \beta(1 - I(t) - (1 - \sigma)V(t))I(t) - (d + \gamma)I(t) \quad (18a)$$

$$\frac{d}{dt}V(t) = \phi(1 - I(t) - V(t)) \quad (18b)$$

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

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

The well posedness of the problem follows from Theorem 2 and from the fact that solutions of (11) exist and are unique. For a constant waning period, the basic reproduction number from (15) is

$$\mathcal{R}_v = \mathcal{R}_0 \frac{d + (\sigma\phi - \alpha(1 - \sigma)d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \quad (19)$$

With $I_{DF} = 0$, from Theorem 3

$$V_{DF} = \frac{(\phi + \alpha d)(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})}, \quad S_{DF} = \frac{d - \alpha d(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \quad (20)$$

Finding the EEP's

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

$$V^* = f(I^*) = g(I^*) \quad (21)$$

where

$$f(I) = \frac{1 - 1/\mathcal{R}_0 - I}{1 - \sigma} \quad (22)$$

for $\sigma < 1$, and

$$g(I) = \frac{(\phi(1 - I) + \alpha d)(1 - e^{-d\omega - \sigma\beta\omega I})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I}) + d + \sigma\beta I} \quad (23)$$

Visualising and locating the bifurcation

From the nullcline equations, an EEP exists iff there exists an $I^* \in (0, 1]$ such that equations (21)-(23) 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

$$H(I, \mathcal{A}) = f(I) - g(I) \tag{24}$$

to show the dependence on these parameters.

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 $a_i \in \mathcal{A}$

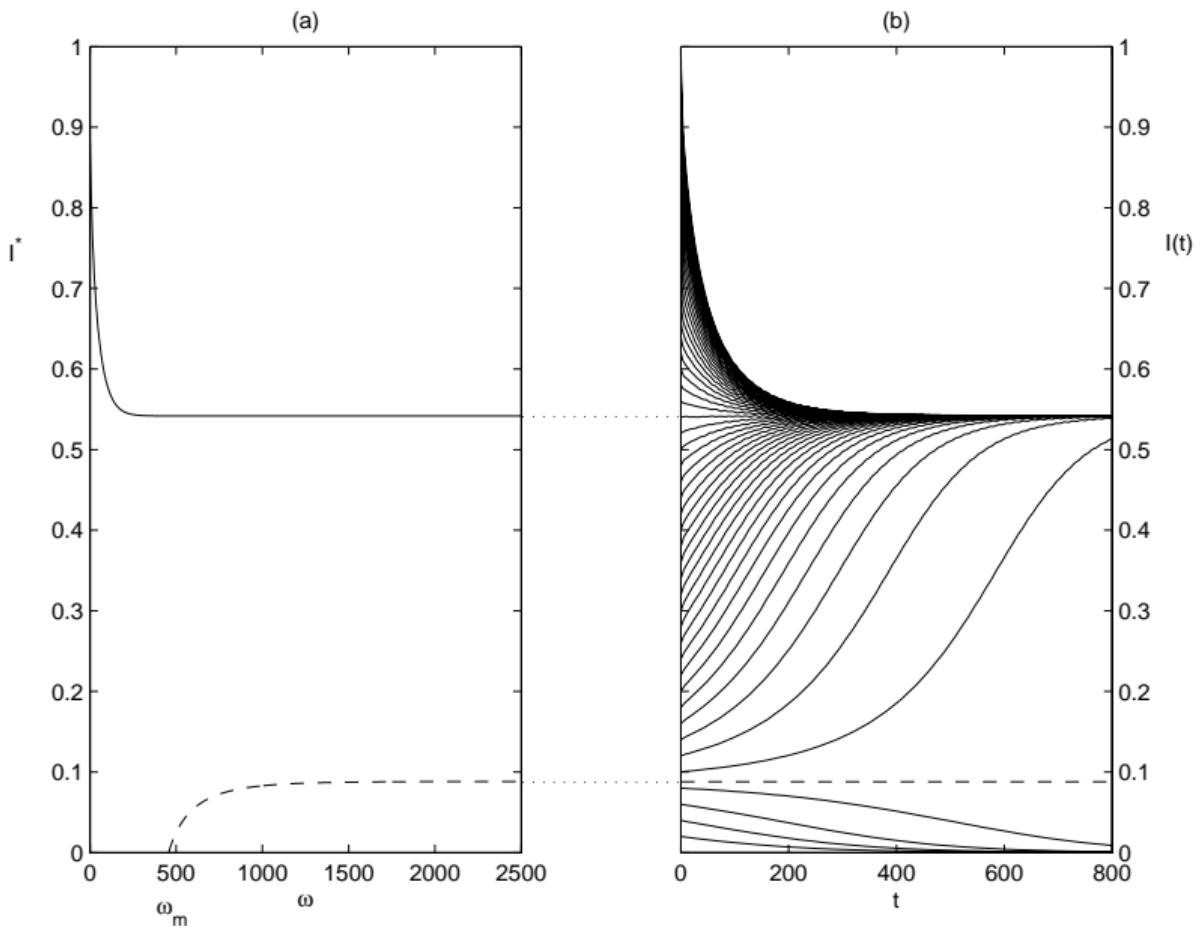
If $\mathcal{R}_v > 1$ then $H(0) > 0$ and so there is an odd number of endemic equilibria. Numerical simulations indicate that there is a unique EEP

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

Age of vaccination

We have seen that infinite dimensionality can 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 (11)

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

FIGS/BowmanArinoMoghadas-2011-cover.png

How to model time between vaccine doses

$$S' = -fS - V_1(t, 0) \quad (25a)$$

$$A' = \left((1-p)S + (1-p_1)\delta_1 \tilde{V}_1 + (1-p_2)\delta_2 V_2 \right) f - \mu_A A \quad (25b)$$

$$I' = (pS + p_1\delta_1 \tilde{V}_1 + p_2\delta_2 V_2)f - \mu I \quad (25c)$$

$$V_2' = V_1(t, a^*) - \delta_2 f V_2(t) \quad (25d)$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a} \right) V_1(t, a) = -\delta_1 f V_1(t, a), \quad 0 \leq a \leq a^* \quad (25e)$$

and boundary condition

$$V_1(t, 0) = \begin{cases} \gamma S_0 \left(\frac{S(t)}{S(t)+A(t)} \right) & \text{if } T \leq t \leq T_e \text{ and } S > 0 \\ 0 & \text{otherwise} \end{cases} \quad (25f)$$

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

Simplifying a bit

Integrate (25e) using characteristics along lines $a = s$ and $t = T + s$, with s as a new variable

$$V_1(t, a) = V_1(t - a, 0) \exp \left(\int_{t-a}^t -\delta_1 f(\xi) d\xi \right) \quad (26)$$

Define

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

and substitute into (26), giving

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

So the distributed delay is now discrete

Simplifying a bit more

Let

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

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

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

$$S' = -fS - V_1(t, 0) \tag{27a}$$

$$A' = \left((1-p)S + (1-p_1)\delta_1 \tilde{V}_1 + (1-p_2)\delta_2 V_2 \right) f - \mu_A A \tag{27b}$$

$$I' = (pS + p_1\delta_1 \tilde{V}_1 + p_2\delta_2 V_2)f - \mu I \tag{27c}$$

$$V_2' = V_1(t - a^*, 0) e^{\zeta(t-a^*)} - \delta_2 f V_2(t) \tag{27d}$$

$$\zeta' = \delta_1 f \tag{27e}$$

$$\nu' = V_1(t, 0) e^{\zeta(t)} \tag{27f}$$

Conclusions on sojourn times

- ▶ The time of sojourn in compartments plays an important role in determining the type of model that we deal with
- ▶ All ODE models, when they use terms of the form κX , make the assumption that the time of sojourn in compartments is exponentially distributed with parameter κ
- ▶ At the other end of the spectrum, delay differential with discrete delay make the assumption of a constant sojourn time, equal for all individuals
- ▶ Both can be true sometimes... but reality is more likely somewhere in between

Continuous-time Markov chains

CTMC similar to DTMC except in way they handle time between events (transitions)

DTMC: transitions occur each Δt

CTMC: $\Delta t \rightarrow 0$ and transition times follow an exponential distribution parametrised by the state of the system

CTMC are roughly equivalent to ODE

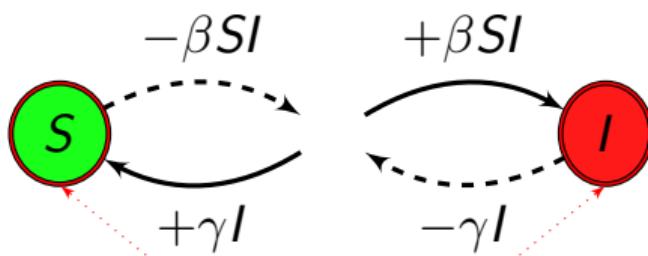
Converting your compartmental ODE model to CTMC

Easy as π :)

- ▶ Compartmental ODE model focuses on flows into and out of compartments
- ▶ ODE model has as many equations as there are compartments
- ▶ Compartmental CTMC model focuses on transitions
- ▶ CTMC model has as many transitions as there are arrows between (or into or out of) compartments

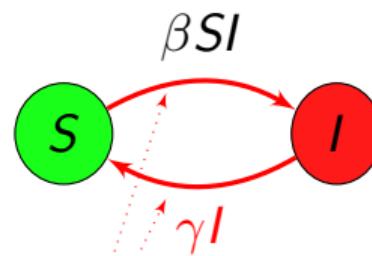
ODE to CTMC : focus on different components

ODE



focus

CTMC



focus

SIS without demography

Transition	Effect	Weight	Probability
$S \rightarrow S - 1, I \rightarrow I + 1$	new infection	βSI	$\frac{\beta SI}{\beta SI + \gamma I}$
$S \rightarrow S + 1, I \rightarrow I - 1$	recovery of an infectious	γI	$\frac{\gamma I}{\beta SI + \gamma I}$

States are S, I

SIS with demography

Transition	Effect	Weight	Probability
$S \rightarrow S + 1$	birth of a susceptible	b	$\frac{b}{b+d(S+I)+\beta SI+\gamma I}$
$S \rightarrow S - 1$	death of a susceptible	dS	$\frac{dS}{b+d(S+I)+\beta SI+\gamma I}$
$S \rightarrow S - 1, I \rightarrow I + 1$	new infection	βSI	$\frac{\beta SI}{b+d(S+I)+\beta SI+\gamma I}$
$I \rightarrow I - 1$	death of an infectious	dI	$\frac{dI}{b+d(S+I)+\beta SI+\gamma I}$
$S \rightarrow S + 1, I \rightarrow I - 1$	recovery of an infectious	γI	$\frac{\gamma I}{b+d(S+I)+\beta SI+\gamma I}$

States are S, I

Kermack & McKendrick model

Transition	Effect	Weight	Probability
$S \rightarrow S - 1, I \rightarrow I + 1$	new infection	βSI	$\frac{\beta SI}{\beta SI + \gamma I}$
$I \rightarrow I - 1, R \rightarrow R + 1$	recovery of an infectious	γI	$\frac{\gamma I}{\beta SI + \gamma I}$

States are S, I, R

Gillespie's algorithm

- ▶ A.k.a. the stochastic simulation algorithm (SSA)
- ▶ Derived in 1976 by Daniel Gillespie
- ▶ Generates possible solutions for CTMC
- ▶ Extremely simple, so worth learning how to implement; there are however packages that you can use (see later)

Gillespie's algorithm

Suppose system has state $\mathbf{x}(t)$ with initial condition $\mathbf{x}(t_0) = \mathbf{x}_0$ and *propensity functions* a_i of elementary reactions

set $t \leftarrow t_0$ and $\mathbf{x}(t) \leftarrow \mathbf{x}_0$

while $t \leq t_f$

- $\xi_t \leftarrow \sum_j a_j(\mathbf{x}(t))$
- Draw τ_t from $T \sim \mathcal{E}(\xi_t)$
- Draw ζ_t from $\mathcal{U}([0, 1])$
- Find r , smallest integer s.t. $\sum_{k=1}^r a_k(\mathbf{x}(t)) > \zeta_t \sum_j a_j(\mathbf{x}(t)) = \zeta_t \xi_t$
- Effect the next reaction (the one indexed r)
- $t \leftarrow t + \tau_t$

Drawing at random from an exponential distribution

If you do not have an exponential distribution random number generator.. We want τ_t from $T \sim \mathcal{E}(\xi_t)$, i.e., T has probability density function

$$f(x, \xi_t) = \xi_t e^{-\xi_t x} \mathbf{1}_{x \geq 0}$$

Use cumulative distribution function $F(x, \xi_t) = \int_{-\infty}^x f(s, \xi_t) ds$

$$F(x, \xi_t) = (1 - e^{-\xi_t x}) \mathbf{1}_{x \geq 0}$$

which has values in $[0, 1]$. So draw ζ from $\mathcal{U}([0, 1])$ and solve $F(x, \xi_t) = \zeta$ for x

$$\begin{aligned} F(x, \xi_t) = \zeta &\Leftrightarrow 1 - e^{-\xi_t x} = \zeta \\ &\Leftrightarrow e^{-\xi_t x} = 1 - \zeta \\ &\Leftrightarrow \xi_t x = -\ln(1 - \zeta) \\ &\Leftrightarrow x = \boxed{\frac{-\ln(1 - \zeta)}{\xi_t}} \end{aligned}$$

Gillespie's algorithm (SIS model with only 1 eq.)

set $t \leftarrow t_0$ and $I(t) \leftarrow I(t_0)$

while $t \leq t_f$

- $\xi_t \leftarrow \beta(P^* - i)i + \gamma i$
- Draw τ_t from $T \sim \mathcal{E}(\xi_t)$
- $v \leftarrow [\beta(P^* - i)i, \xi_t] / \xi_t$
- Draw ζ_t from $\mathcal{U}(0, 1)$
- Find pos such that $v_{pos-1} \leq \zeta_t \leq v_{pos}$
- switch pos
 - 1: New infection, $I(t + \tau_t) = I(t) + 1$
 - 2: End of infectious period, $I(t + \tau_t) = I(t) - 1$
- $t \leftarrow t + \tau_t$

Sometimes Gillespie goes bad

- ▶ Recall that the inter-event time is exponentially distributed
- ▶ Critical step of the Gillespie algorithm:
 - ▶ $\xi_t \leftarrow$ weight of all possible events (*propensity*)
 - ▶ Draw τ_t from $T \sim \mathcal{E}(\xi_t)$
- ▶ So the inter-event time $\tau_t \rightarrow 0$ if ξ_t becomes very large for some t
- ▶ This can cause the simulation to grind to a halt

Example: a birth and death process

- ▶ Individuals born at *per capita* rate b
- ▶ Individuals die at *per capita* rate d
- ▶ Let's implement this using classic Gillespie

(See `simulate_birth_death_CTMC.R` on course GitHub repo)

Gillespie's algorithm (birth-death model)

```
set  $t \leftarrow t_0$  and  $N(t) \leftarrow N(t_0)$ 
while  $t \leq t_f$ 
    -  $\xi_t \leftarrow (b + d)N(t)$ 
    - Draw  $\tau_t$  from  $T \sim \mathcal{E}(\xi_t)$ 
    -  $v \leftarrow [bN(t), \xi_t] / \xi_t$ 
    - Draw  $\zeta_t$  from  $\mathcal{U}(0, 1)$ 
    - Find  $pos$  such that  $v_{pos-1} \leq \zeta_t \leq v_{pos}$ 
    - switch  $pos$ 
        - 1: Birth,  $N(t + \tau_t) = N(t) + 1$ 
        - 2: Death,  $N(t + \tau_t) = N(t) - 1$ 
    -  $t \leftarrow t + \tau_t$ 
```

```
b = 0.01 # Birth rate
d = 0.01 # Death rate
t_0 = 0 # Initial time
N_0 = 100 # Initial population

# Vectors to store time and state. Initialise with initial condition.
t = t_0
N = N_0

t_f = 1000 # Final time

# We'll track the current time and state (could also just check last entry in t
# and N, but will take more operations)
t_curr = t_0
N_curr = N_0
```

```

while (t_curr<=t_f) {
  xi_t = (b+d)*N_curr
  # The exponential number generator does not like a rate of 0 (when the
  # population crashes), so we check if we need to quit
  if (N_curr == 0) {
    break
  }
  tau_t = rexp(1, rate = xi_t)
  t_curr = t_curr+tau_t
  v = c(b*N_curr, xi_t)/xi_t
  zeta_t = runif(n = 1)
  pos = findInterval(zeta_t, v)+1
  switch(pos,
    {
      N_curr = N_curr+1 # Birth
    },
    {
      N_curr = N_curr-1 # Death
    })
  N = c(N, N_curr)
  t = c(t, t_curr)
}

```


Last one did not go well

- ▶ Wanted 1000 time units (days?)
- ▶ Interrupted at $t = 344.4432$ because I lost patience
(Penultimate slide: sim stopped because the population went extinct, I did not stop it!)
- ▶ At stop time
 - ▶ $N = 103,646$
 - ▶ $|N| = 208,217$ (and $|t|$ as well, of course!)
 - ▶ time was moving slowly

```
> tail(diff(t))
[1] 1.282040e-05 5.386999e-04 5.468540e-04 1.779985e-04 6.737294e-05 2.618084e-04
```


Tau-leaping (and packages) to the rescue!

- ▶ *Approximation* method (compared to classic Gillespie, which is exact)
- ▶ Roughly: consider "groups" of events instead of individual events
- ▶ Good news: GillespieSSA2 and adaptivetau, two standard packages for SSA in R, implement tau leaping

Simulating a CTMC

```
library(GillespieSSA2)
IC <- c(S = (Pop-I_0), I = I_0)
params <- c(gamma = gamma, beta = beta)
reactions <- list(
    reaction("beta*S*I", c(S=-1,I=+1), "new_infection"),
    reaction("gamma*I", c(S=+1,I=-1), "recovery")
)
set.seed(NULL)
sol <- ssa(
    initial_state = IC,
    reactions = reactions,
    params = params,
    method = ssa_exact(),
    final_time = t_f,
)
plot(sol$time, sol$state[, "I"], type = "l",
     xlab = "Time (days)", ylab = "Number infectious")
```


Parallelisation

To see multiple realisations: good idea to parallelise, then interpolate results. Write a function, e.g., `run_one_sim` that .. runs one simulation

On the GitHub repo for the course, see

- ▶ `SIS-CTMC-parallel.R`
- ▶ `SIS-CTMC-parallel-multiple-R0.R`

```
run_one_sim = function(params) {
  IC <- c(S = (params$Pop - params$I_0), I = params$I_0)
  params_local <- c(gamma = params$gamma, beta = params$beta)
  reactions <- list(
    # propensity function effects name for reaction
    reaction("beta*S*I", c(S=-1, I=+1), "new_infection"),
    reaction("gamma*I", c(S=+1, I=-1), "recovery")
  )
  set.seed(NULL)
  sol <- ssa(
    initial_state = IC,
    reactions = reactions,
    params = params_local,
    method = ssa_exact(),
    final_time = params$t_f,
    log_firings = TRUE      # This way we keep track of events
  )
```

```
# Interpolate result (just I will do)
wanted_t = seq(from = 0, to = params$t_f, by = 0.01)
sol$interp_I = approx(x = sol$time, y = sol$state[, "I"], xout = wanted_t)
names(sol$interp_I) = c("time", "I")
# Return result
return(sol)
}
```

```
nb_cores <- detectCores()
if (nb_cores > 124) {
  nb_cores = 124
}
cl <- makeCluster(nb_cores)
clusterEvalQ(cl,{
  library(GillespieSSA2)
})
clusterExport(cl,
  c("params",
    "run_one_sim"),
  envir = .GlobalEnv)
SIMS = parLapply(cl = cl,
  X = 1:params$number_sims,
  fun =  function(x) run_one_sim(params))
stopCluster(cl)
```


Benefit of parallelisation

Run the parallel code for 100 sims between ‘tictoc::tic()’ and ‘tictoc::toc()’, giving ‘66.958 sec elapsed’, then the sequential version

```
tictoc::tic()  
SIMS = lapply(X = 1:params$number_sims,  
              FUN = function(x) run_one_sim(params))  
tictoc::toc()
```

which gives ‘318.141 sec elapsed’ on a 6C/12T Intel(R) Core(TM) i9-8950HK CPU @ 2.90GHz ($4.75\times$ faster) or ‘12.067 sec elapsed’ versus ‘258.985 sec elapsed’ on a 32C/64T AMD Ryzen Threadripper 3970X 32-Core Processor ($21.46\times$ faster !)

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

$$(\partial_t + \partial_a)S(t, a) = \Lambda(a) - (\mu(a) + \lambda(t, a))S(t, a) \quad (28a)$$

$$(\partial_t + \partial_a)I(t, a) = -(\mu(a) + \gamma(a) + \delta(a))I(t, a) + \lambda(t, a)S(t, a) \quad (28b)$$

$$(\partial_t + \partial_a)R(t, a) = \gamma(a)I(t, a) \quad (28c)$$

Boundary conditions are

$$S(t, a_0) = B \quad (28d)$$

$$I(t, a_0) = 0 \quad (28e)$$

$$R(t, a_0) = 0 \quad (28f)$$

while initial conditions take the form

$$S(0, a) = \Phi(a) \quad (28g)$$

$$I(0, a) = \Psi(a) \quad (28h)$$

$$R(0, a) = 0 \quad (28i)$$

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

$$\lambda(t, a) = r(a)f(a) \int_{a_0}^{\infty} g(s)\rho(a, s) \frac{I(t, s)}{N(t, s)} ds \quad (29)$$

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 (28), 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

$$(\partial_t + \partial_a)S(t, a) = \Lambda(a) - (d(a) + \lambda(t, a))S(t, a) \quad (30a)$$

$$(\partial_t + \partial_a)I(t, a) = -(d(a) + \gamma(a))I(t, a) + \lambda(t, a)S(t, a) \quad (30b)$$

$$(\partial_t + \partial_a)A(t, a) = \gamma(a)A(t, a) - (d(a) + \delta(a))A(t, a) \quad (30c)$$

Assume

$$\lambda(t, a) = h(a) \int_{a_0}^{\infty} \rho(a, a') \frac{I(t, a')}{T(t, a')} da' \quad (30d)$$

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

$$(\partial_t + \partial_a)y(t, a) = (1 - y)(-\gamma(a)y + \lambda(t, a)) \quad (31a)$$

$$\lambda(t, a) = h(a) \int_0^\omega p(a, a')y(t, a')da' \quad (31b)$$

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 (31) 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

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