



University
of Manitoba

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

Why incorporate stochasticity?

Stochasticity in deterministic models

Continuous time Markov chains

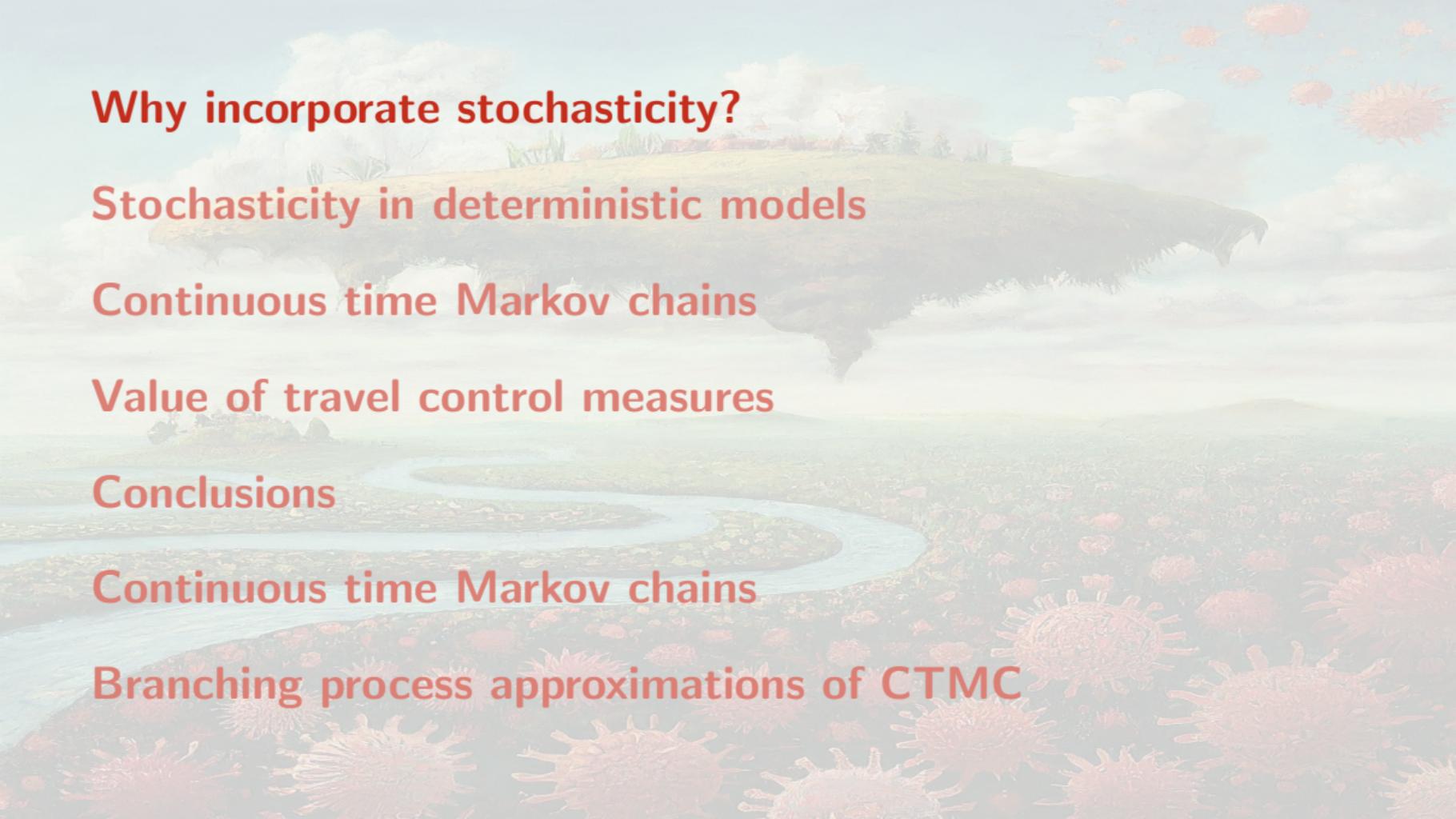
Value of travel control measures

Conclusions

Continuous time Markov chains

Branching process approximations of CTMC



The background of the slide features a detailed landscape illustration. It includes a winding blue river, green fields, a forested hillside, and a large, dark bird of prey, possibly a hawk or eagle, flying in the upper right. The sky is light blue with soft, white clouds.

Why incorporate stochasticity?

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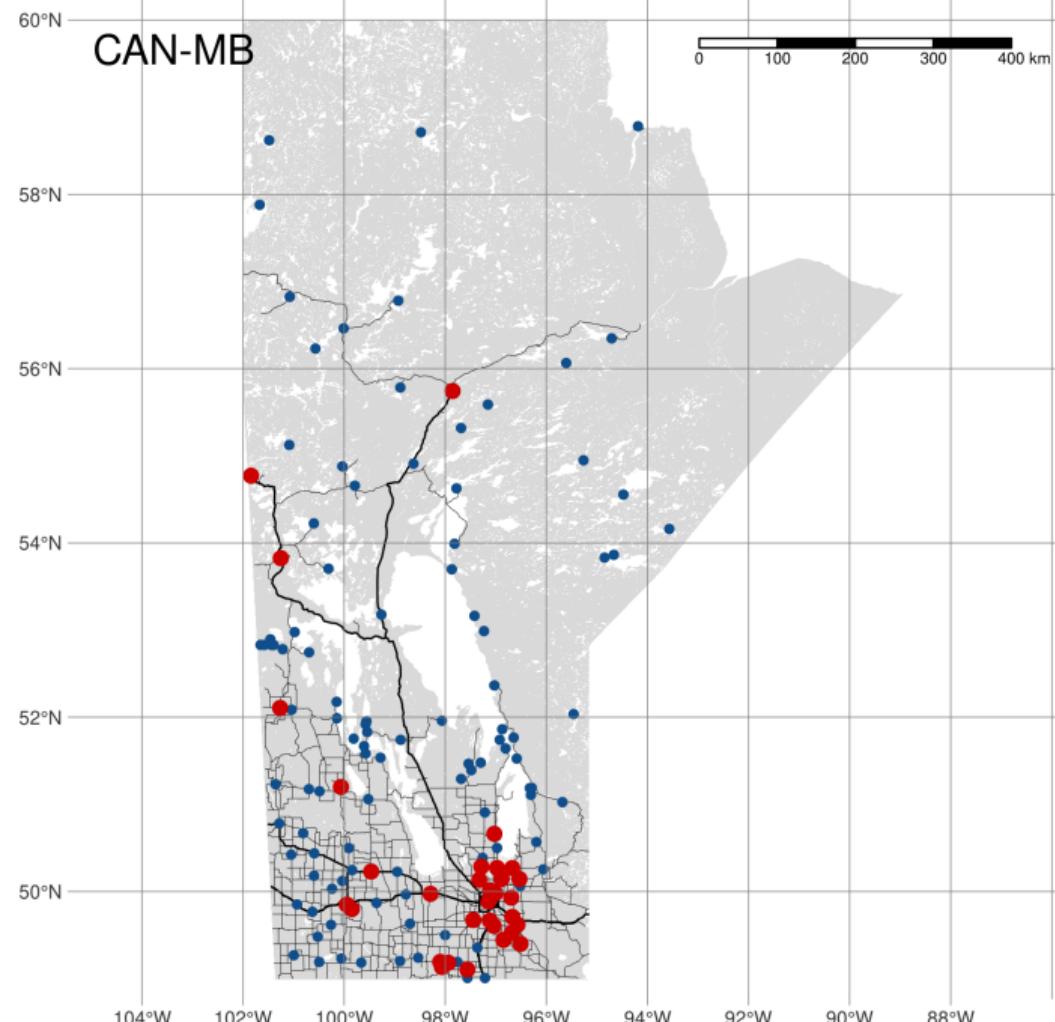
Branching process approximations of CTMC

At the beginning of the COVID-19 crisis

- ▶ 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



- ▶ Very very long days (18-20 hours, 7 days a week)
 - ▶ including a lot of time waiting for the “cluster” to finish
- ⇒ PHAC gave me money for a cluster (yay Threadrippers!!!)
- ⇒ Also thought about whether my model was really adequate as our focus switched from thinking about movement on a planetary scale to movement within Canadian provinces



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

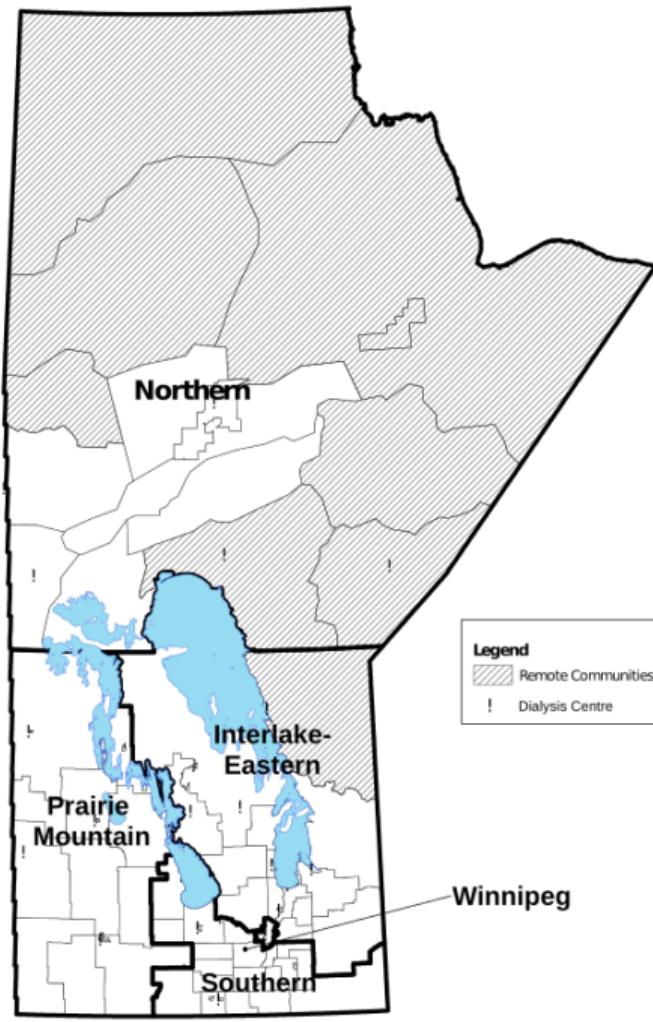
Inuit Communities to be referred to as **Inuit Nunangat**, not remote and isolated communities to respect the unique language and culture of Inuit regions, as well as the common challenges in social determinants of health, access to care, and infrastructure found across all Inuit communities

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



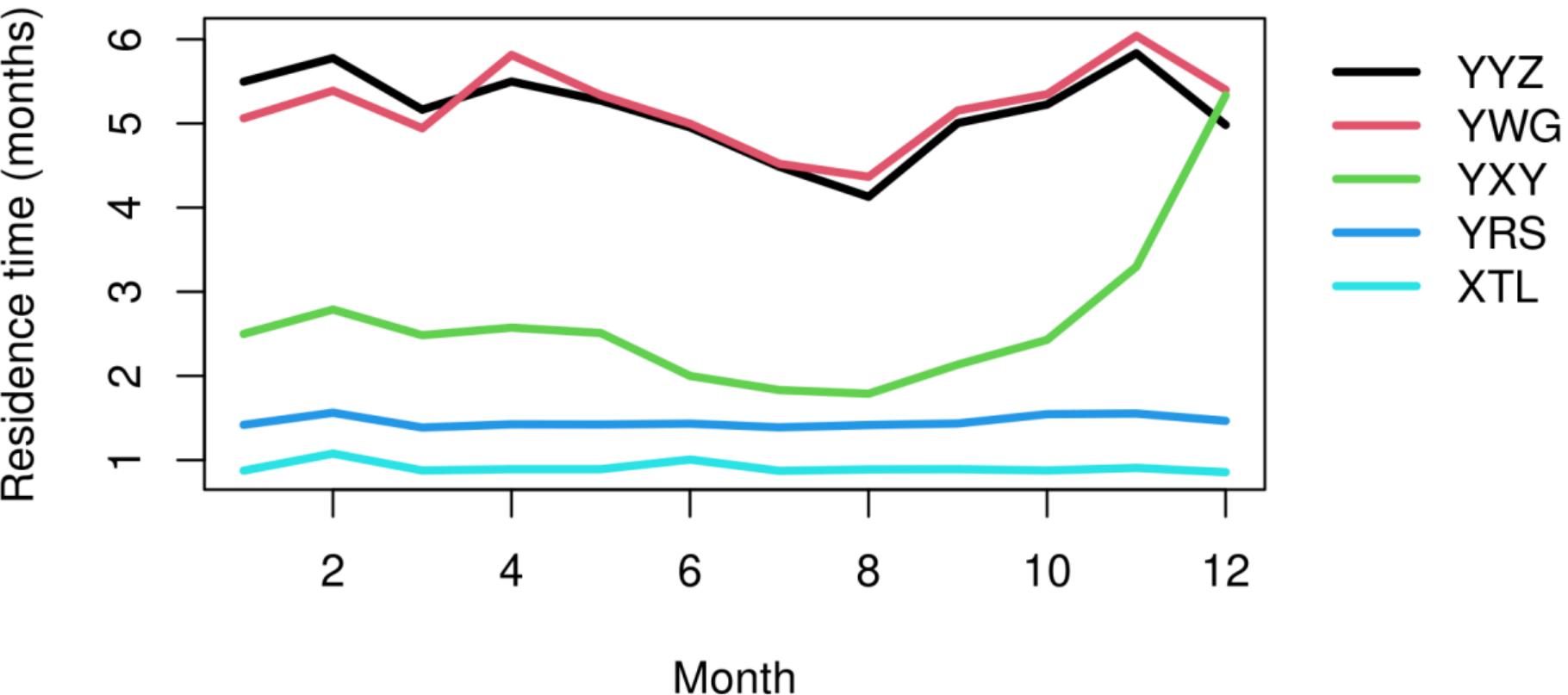
One interesting paradox

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



[Home](#) » About

About the WRHA

The WRHA serves residents of the city of Winnipeg, as well as the northern community of Churchill and the rural municipalities of East and West St. Paul, representing a total population of more than 750,000. The WRHA also provides health-care support and specialty referral services to nearly half a million Manitobans who live beyond these boundaries, as well as residents of northwestern Ontario and Nunavut, who often require the services and expertise available within the WRHA.

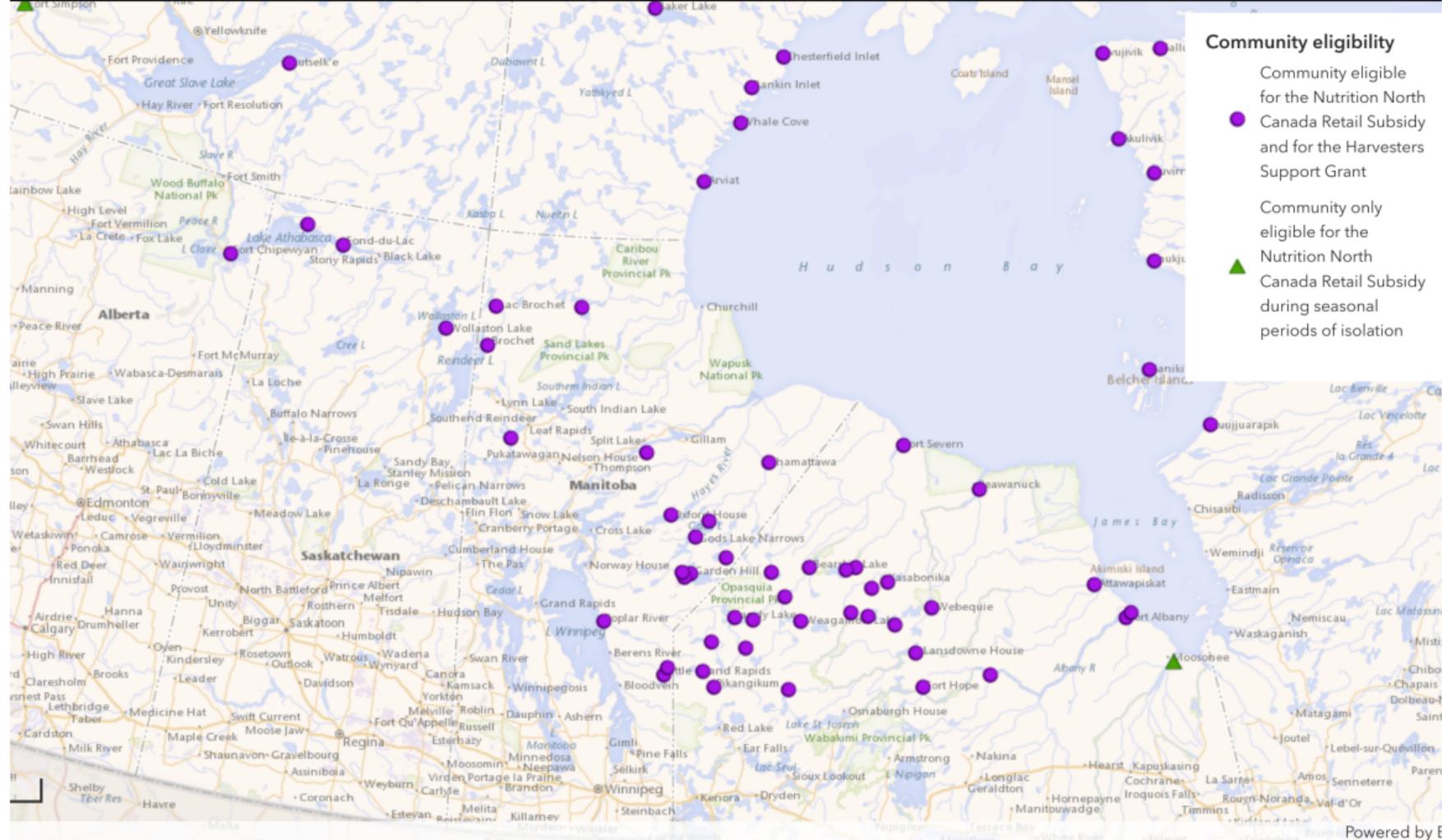
Community eligibility

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?

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 "

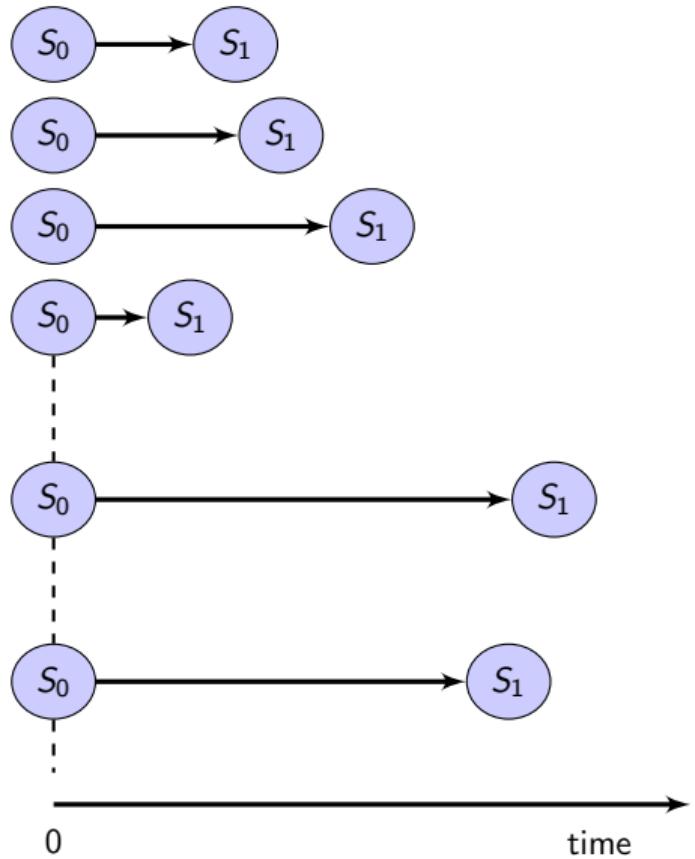
The states can be anything:

- ▶ 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

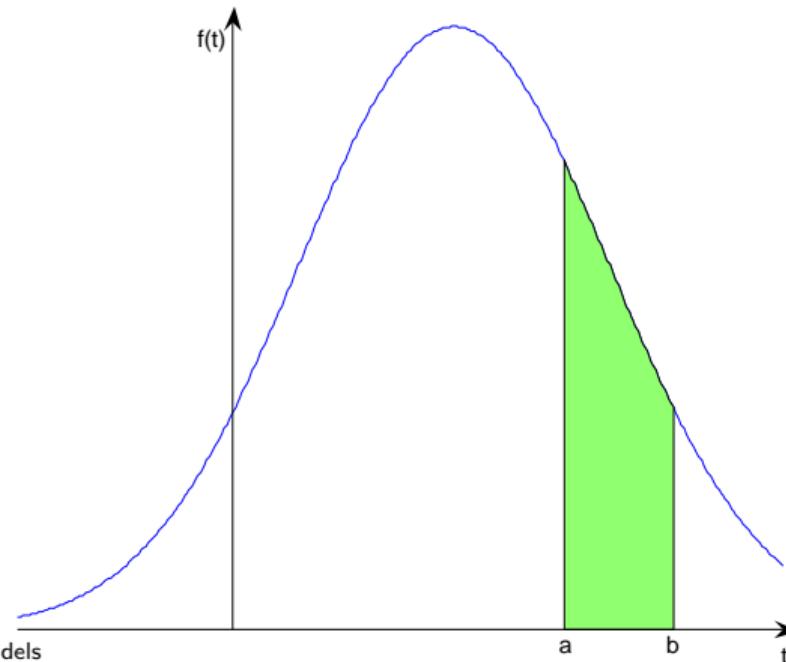
From the sequence of experiments, we deduce a model, which in this context is called a **probability distribution**

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

Probability density function

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

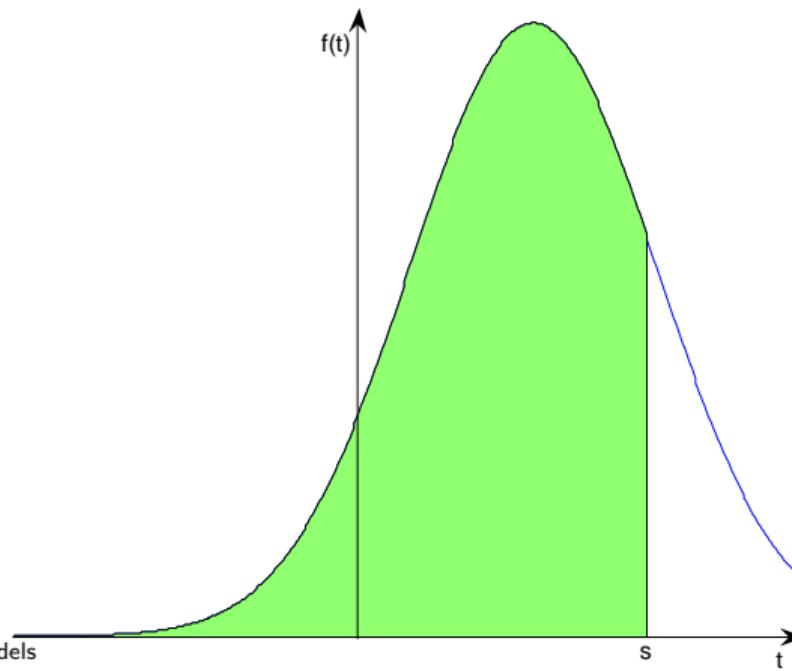
- ▶ $f \geq 0$
- ▶ $\int_{-\infty}^{+\infty} f(s)ds = 1$
- ▶ $\mathbb{P}(a \leq T \leq b) = \int_a^b f(t)dt$



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

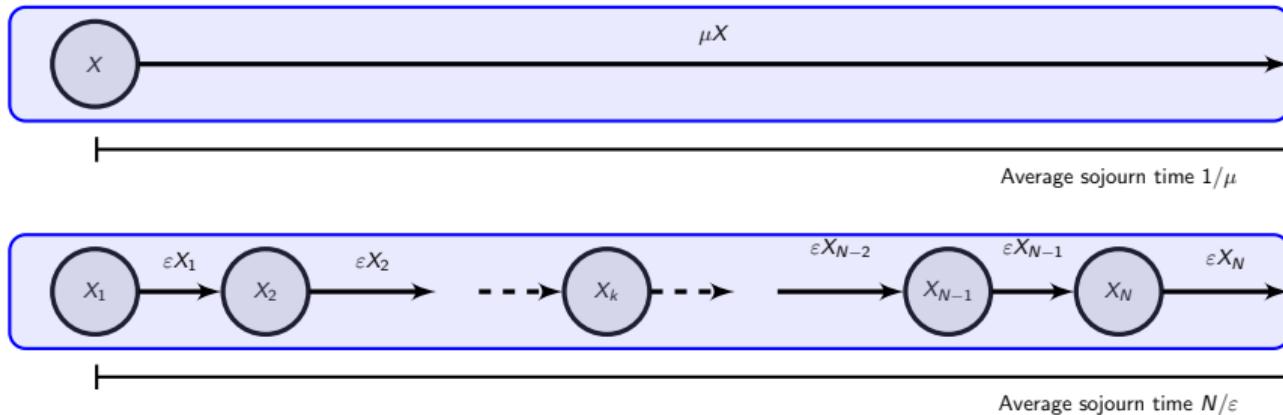
Let X_i be independent exponentially distributed random variables with parameter ξ and $Y = \sum_{i=1}^n X_i$

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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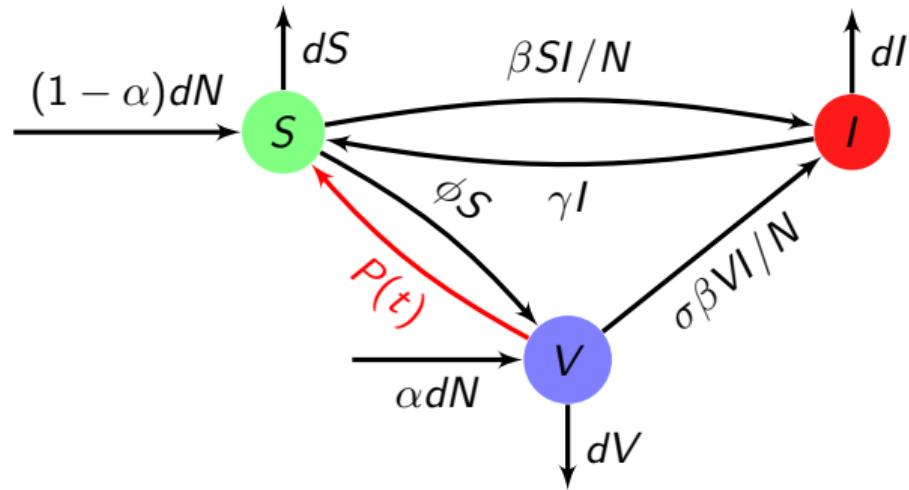
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(Communicated by Linda Allen)

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

\mathcal{R}_0

Define \mathcal{R}_0 with vaccination as

$$\mathcal{R}_v = \mathcal{R}_0 \left[\frac{1 + \sigma\phi\tilde{P} - (1 - \sigma)\alpha d\tilde{P}}{1 + \phi\tilde{P}} \right] \quad (14)$$

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

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

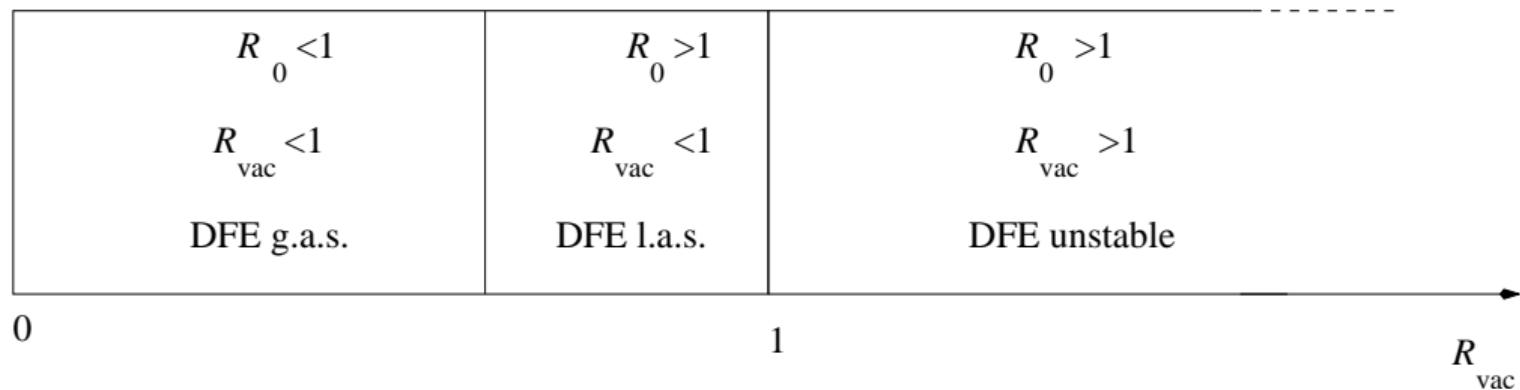
in such a way that $\tilde{P} < 1/d$

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

Theorem 2

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
- ▶ The waning time is a constant, i.e., $P(t)$ is Diract distributed, which leads to a discrete DDE model

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 (??) give the ODE system

$$\frac{dI}{dt} = \beta(1 - I - (1 - \sigma)V)I - (d + \gamma)I \quad (15a)$$

$$\frac{dV}{dt} = \phi(1 - I - V) - \sigma\beta I V - (d + \theta)V + \alpha d \quad (15b)$$

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

From Theorem 2 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 (14).

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 3

For the ODE system (15) 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 $\mathcal{D} \setminus \{I = 0\}$

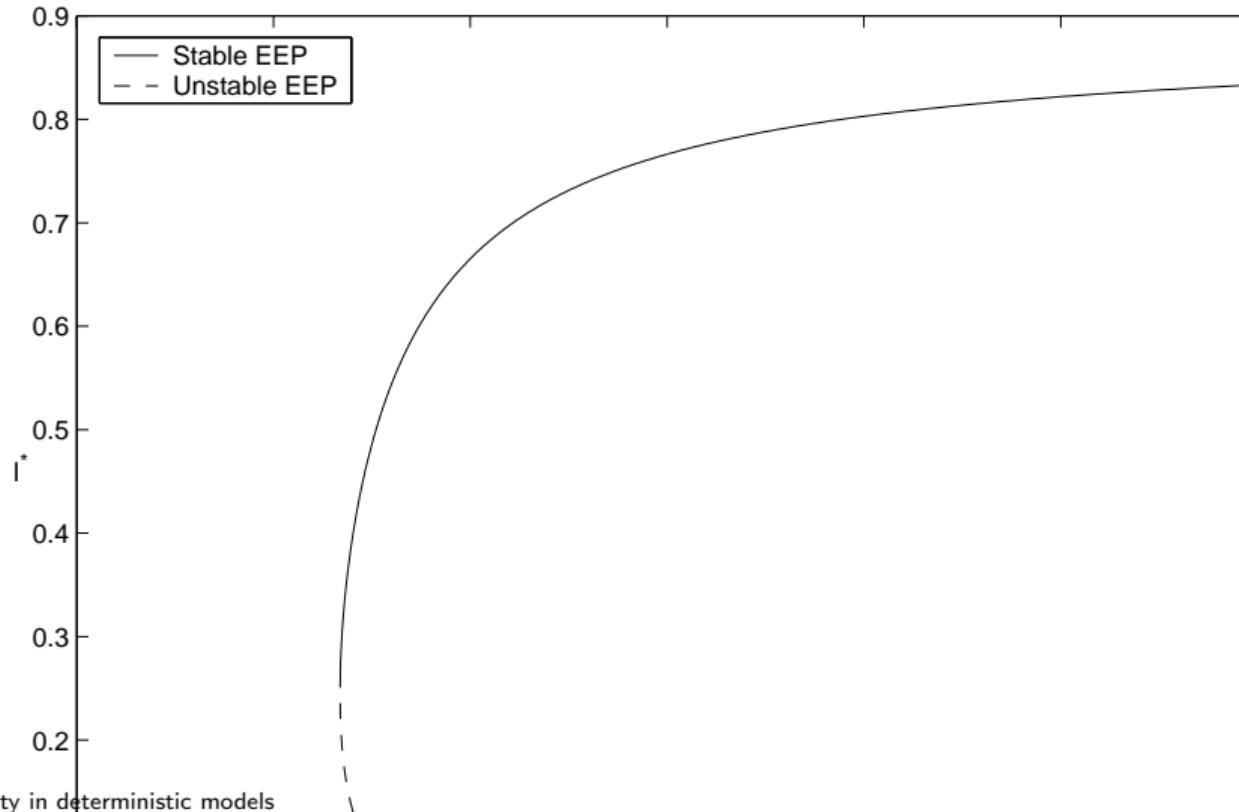
Pertussis:

- ▶ 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 $t > \omega$

$$V(t) = \int_{t-\omega}^t (\phi(1 - I(u) - V(u)) + \alpha d) e^{-d(t-u)} e^{-\sigma \beta \int_u^t I(x) dx} du \quad (16)$$

Differentiating (16) (see equation (??)) gives the model as the two dimensional system, for $t > \omega$

$$\frac{d}{dt}I(t) = \beta(1 - I(t) - (1 - \sigma)V(t))I(t) - (d + \gamma)I(t) \quad (17a)$$

$$\frac{d}{dt}V(t) = \phi(1 - I(t) - V(t)) \quad (17b)$$

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

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

Finding the EEP's

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

$$V^* = f(I^*) = g(I^*) \quad (18)$$

where

$$f(I) = \frac{1 - 1/\mathcal{R}_0 - I}{1 - \sigma} \quad (19)$$

for $\sigma < 1$, and

$$g(I) = \frac{(\phi(1 - I) + \alpha d)(1 - e^{-d\omega - \sigma\beta\omega I})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I}) + d + \sigma\beta I} \quad (20)$$

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

$$S' = -fS - V_1(t, 0) \quad (21a)$$

$$A' = \left((1-p)S + (1-p_1)\delta_1 \tilde{V}_1 + (1-p_2)\delta_2 V_2 \right) f - \mu_A A \quad (21b)$$

$$I' = (pS + p_1\delta_1 \tilde{V}_1 + p_2\delta_2 V_2)f - \mu I \quad (21c)$$

$$V_2' = V_1(t, a^*) - \delta_2 f V_2(t) \quad (21d)$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a} \right) V_1(t, a) = -\delta_1 f V_1(t, a), \quad 0 \leq a \leq a^* \quad (21e)$$

and boundary condition

$$V_1(t, 0) = \begin{cases} \gamma S_0 \left(\frac{S(t)}{S(t)+A(t)} \right) & \text{if } T \leq t \leq T_e \text{ and } S > 0 \\ 0 & \text{otherwise} \end{cases} \quad (21f)$$

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

Simplifying a bit

Integrate (21e) using characteristics along lines $a = s$ and $t = T + s$, with s as a new variable

$$V_1(t, a) = V_1(t - a, 0) \exp \left(\int_{t-a}^t -\delta_1 f(\xi) d\xi \right) \quad (22)$$

Define

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

and substitute into (22), 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

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

$$S' = -fS - V_1(t, 0) \tag{23a}$$

$$A' = \left((1-p)S + (1-p_1)\delta_1 \tilde{V}_1 + (1-p_2)\delta_2 V_2 \right) f - \mu_A A \tag{23b}$$

$$I' = (pS + p_1\delta_1 \tilde{V}_1 + p_2\delta_2 V_2)f - \mu I \tag{23c}$$

$$V_2' = V_1(t - a^*, 0) e^{\zeta(t-a^*)} - \delta_2 f V_2(t) \tag{23d}$$

$$\zeta' = \delta_1 f \tag{23e}$$

$$\nu' = V_1(t, 0) e^{\zeta(t)} \tag{23f}$$

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



Why incorporate stochasticity?

Stochasticity in deterministic models

Continuous time Markov chains

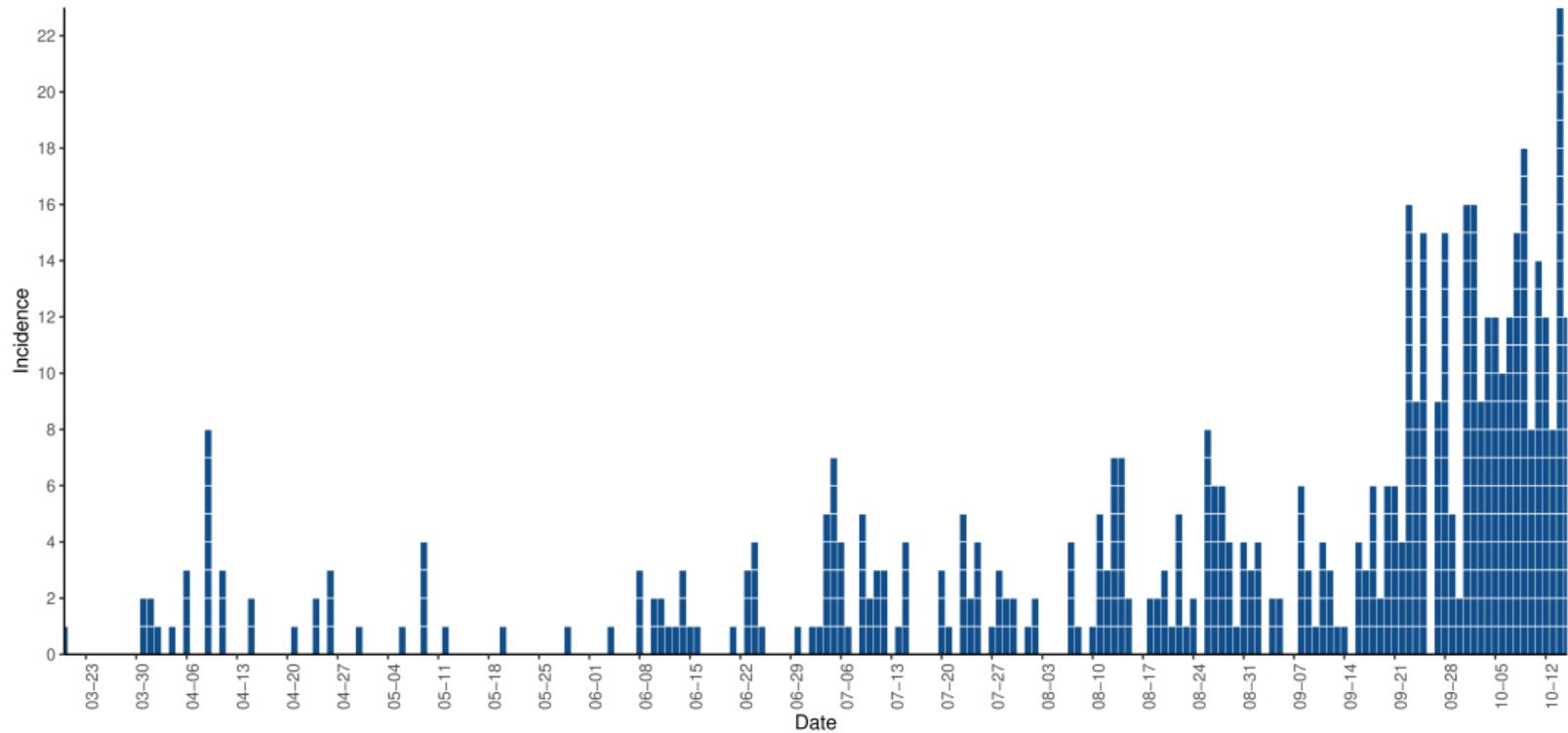
Value of travel control measures

Conclusions

Continuous time Markov chains

Branching process approximations of CTMC

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

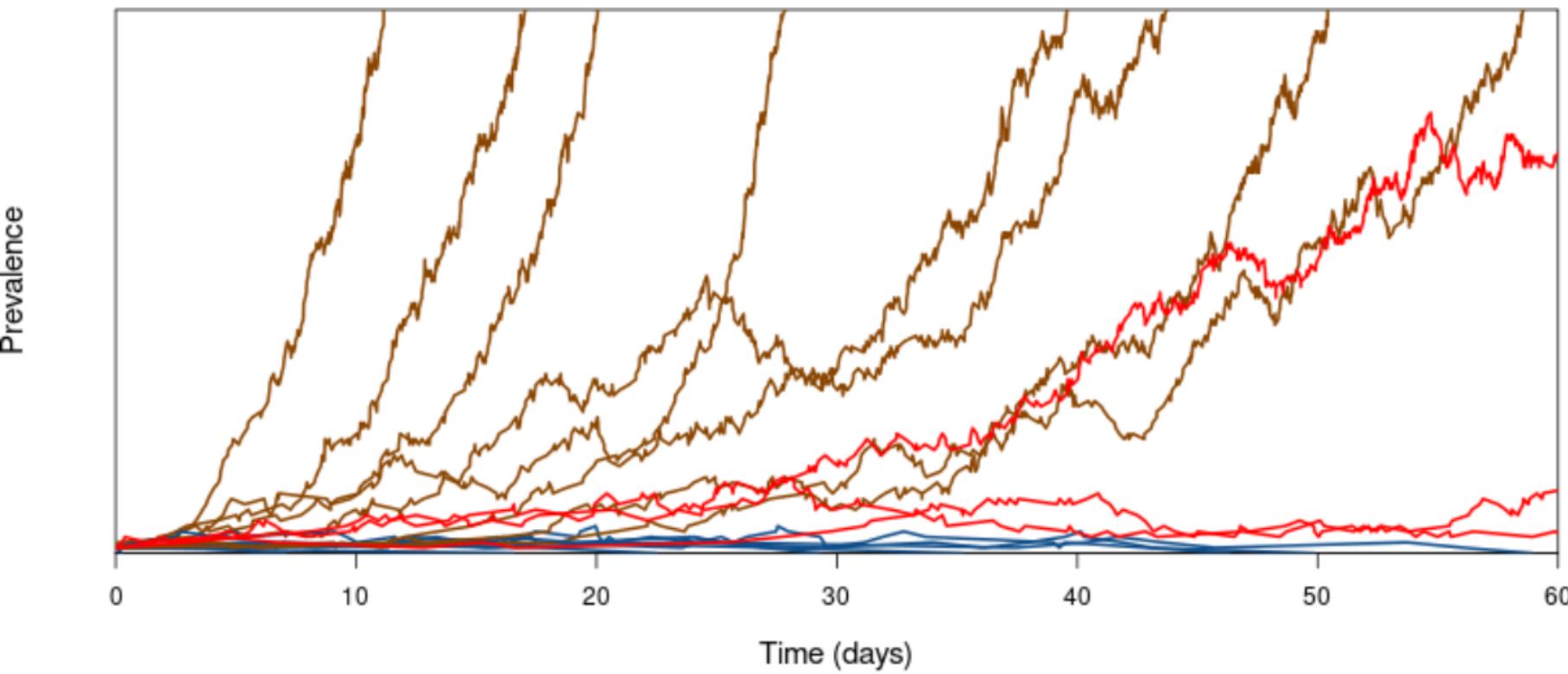
Investigating outbreak types using a simple CTMC SIS *with a twist*

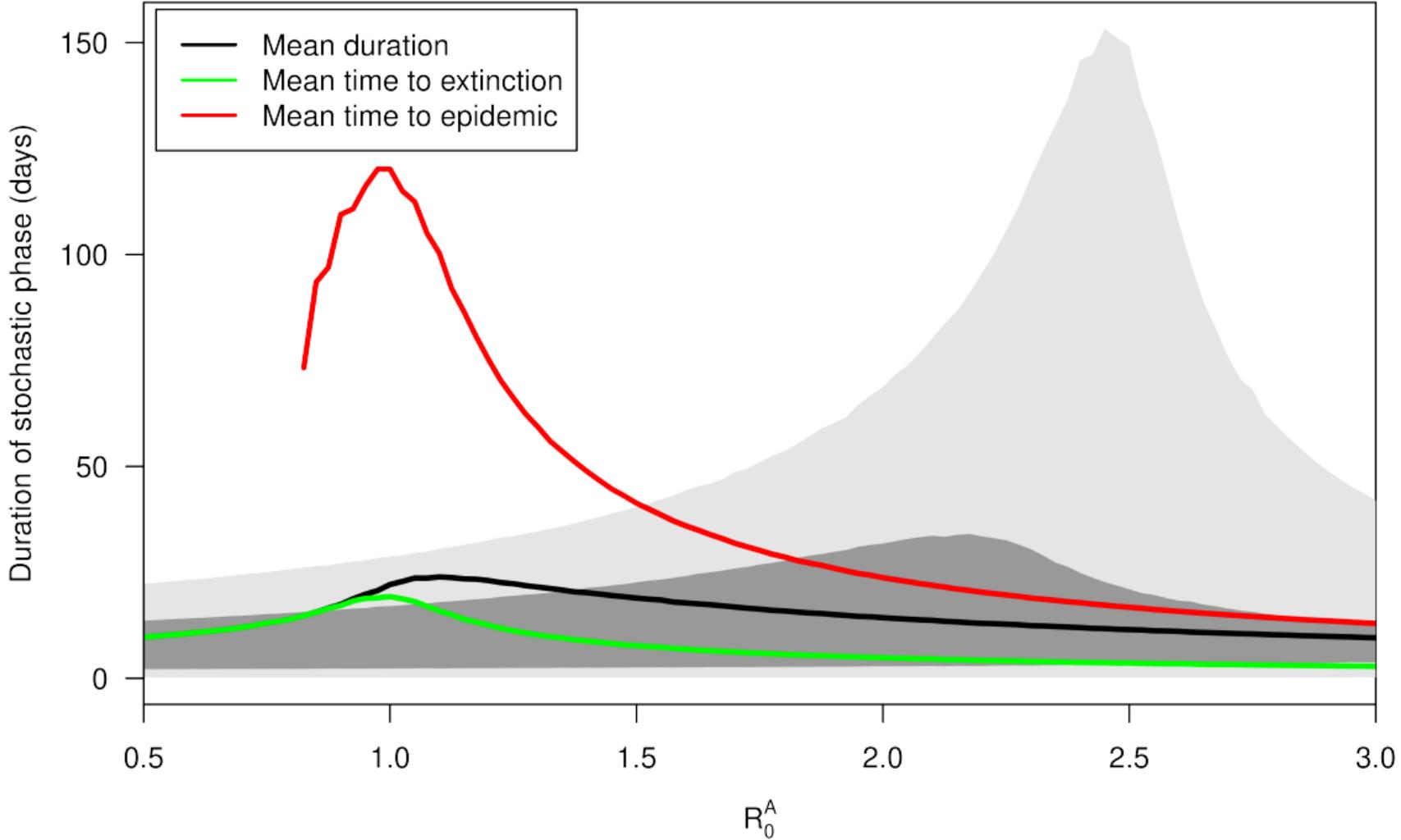
Regular chain of this type has $I = 0$ as sole absorbing state

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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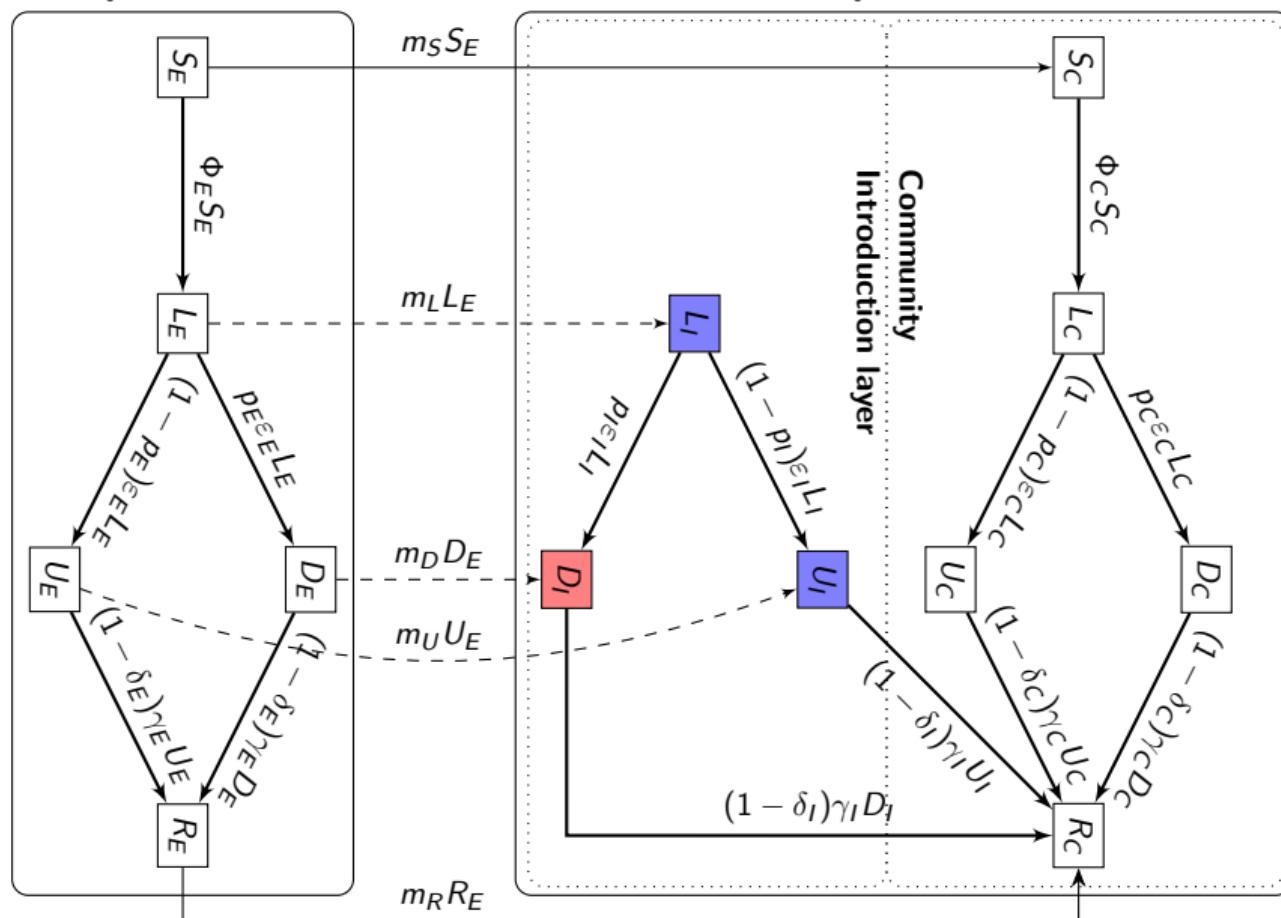
Conclusions

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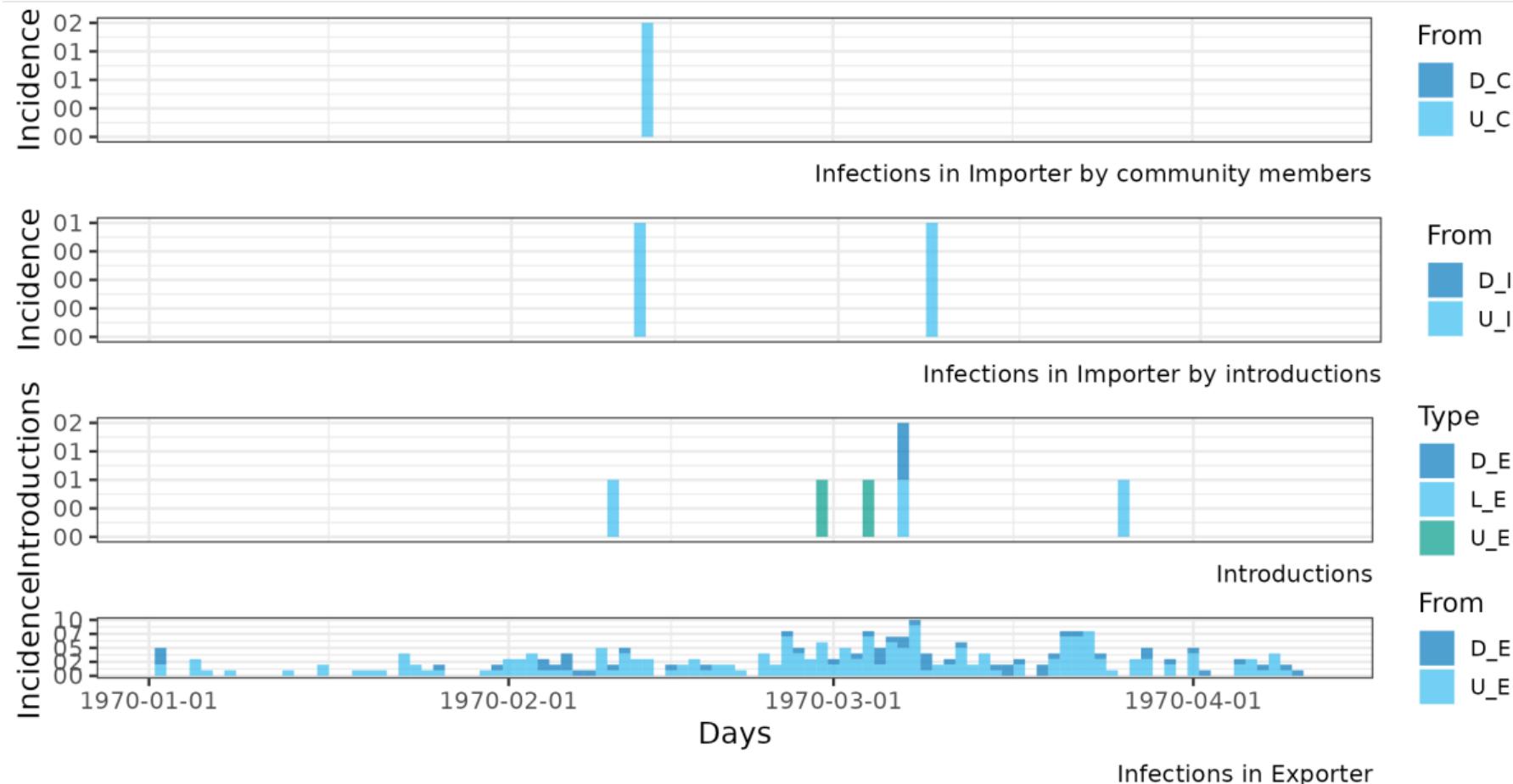
Branching process approximations of CTMC

Exporter

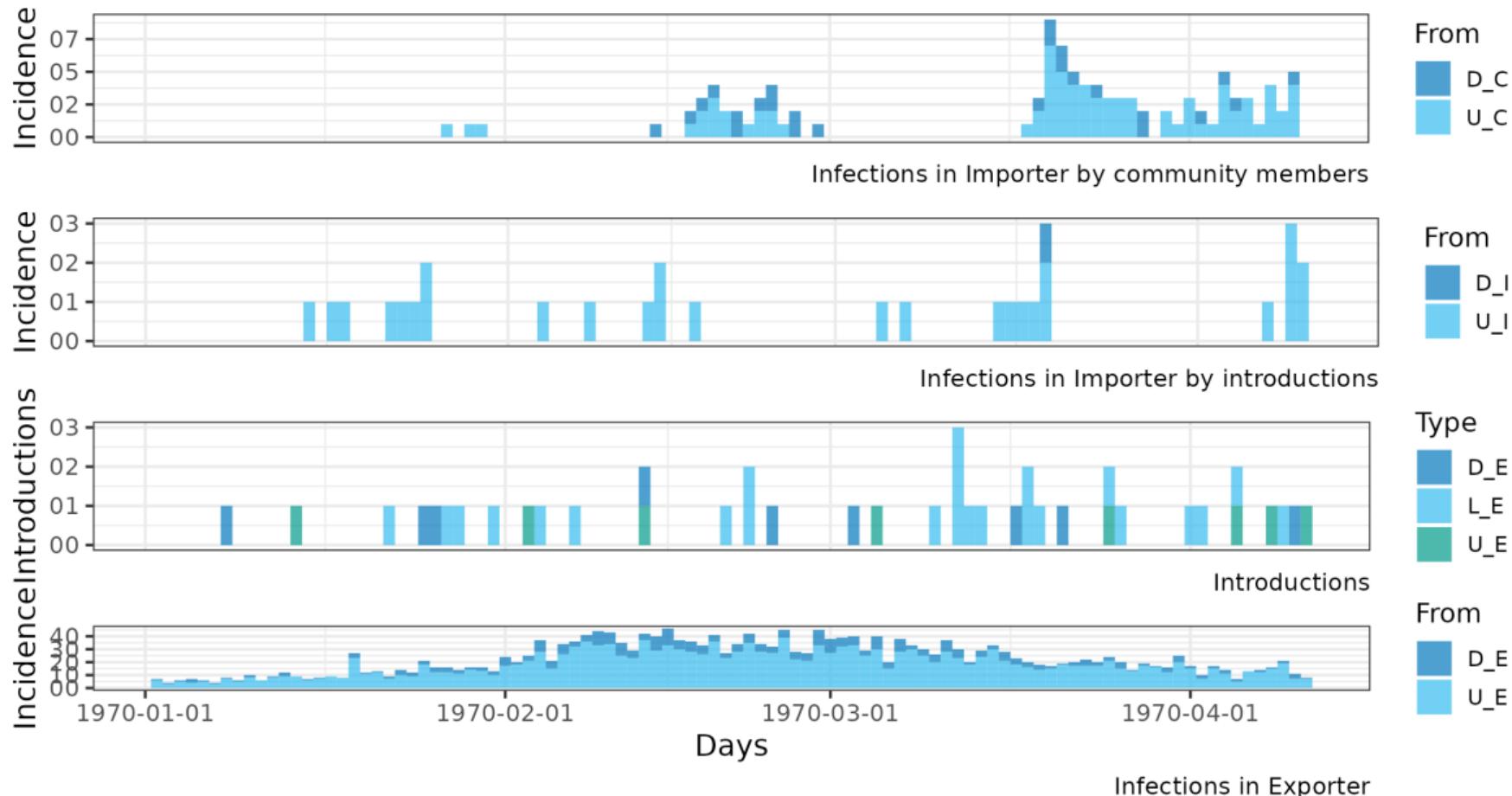
Importer



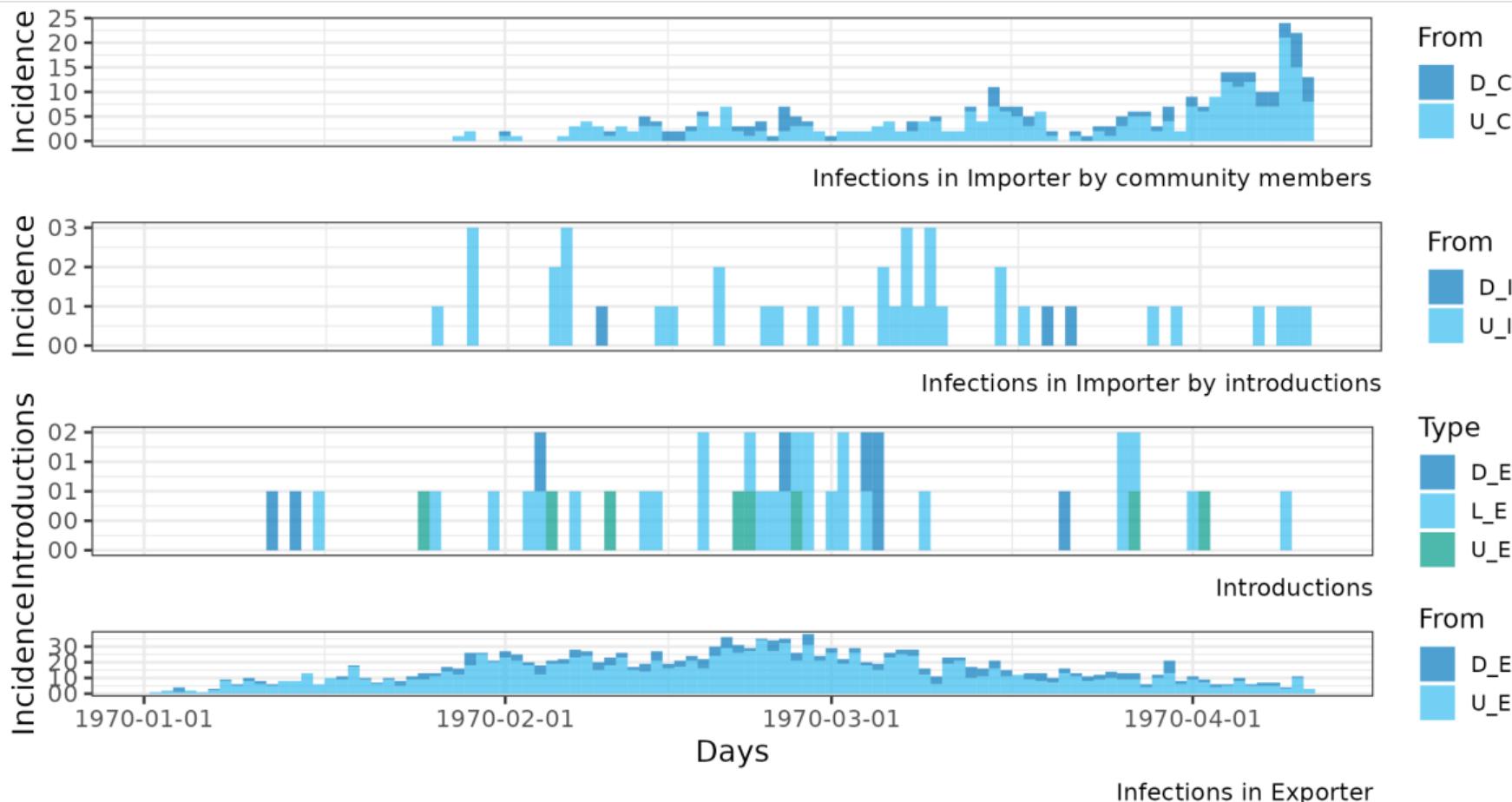
$$R_0^E = 1.5, R_0^C = 0.8, \text{pop}_E = 10000, \text{pop}_I = 10000$$



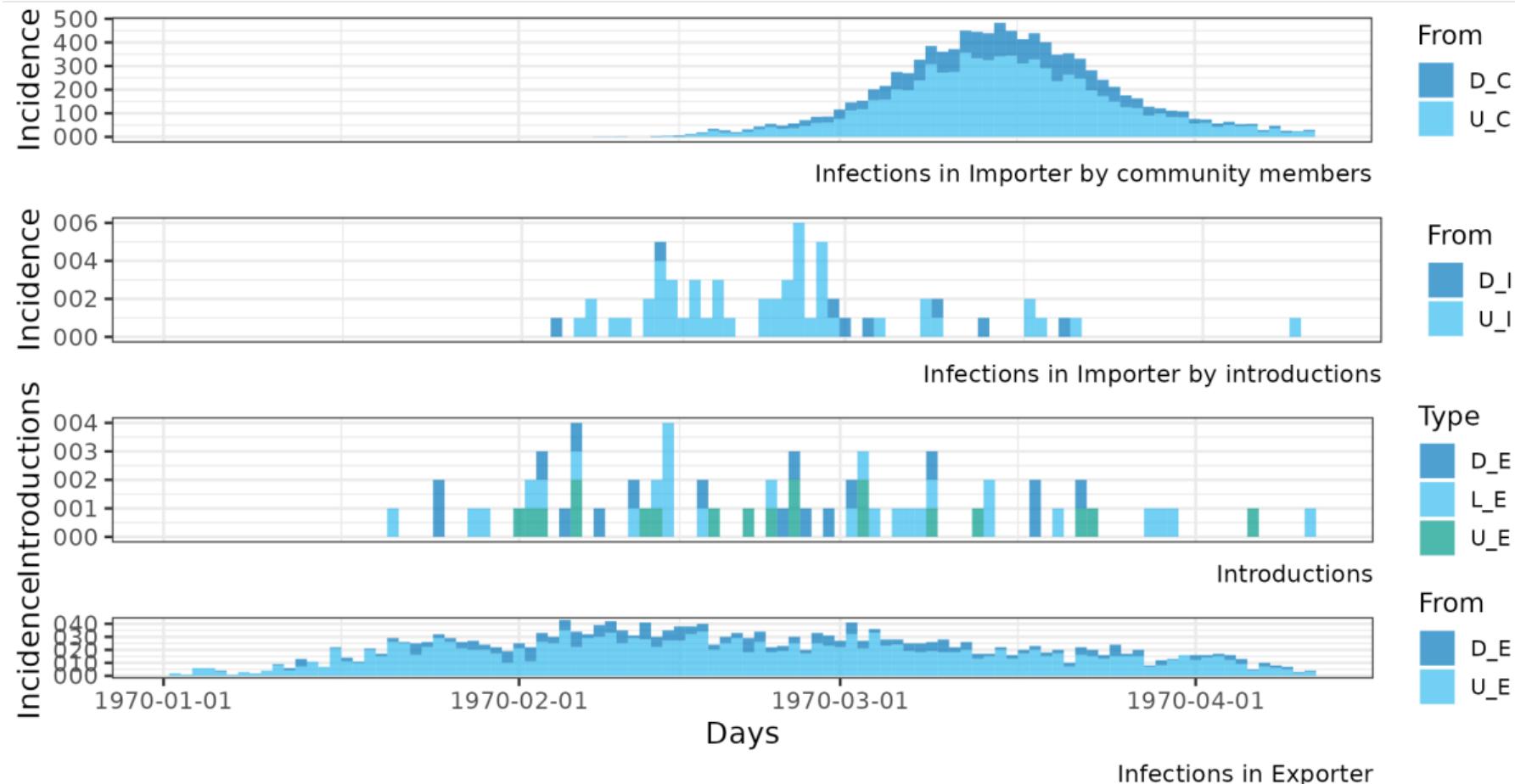
$$R_0^E = 1.5, R_0^C = 0.8, \text{pop}_E = 10000, \text{pop}_I = 10000$$

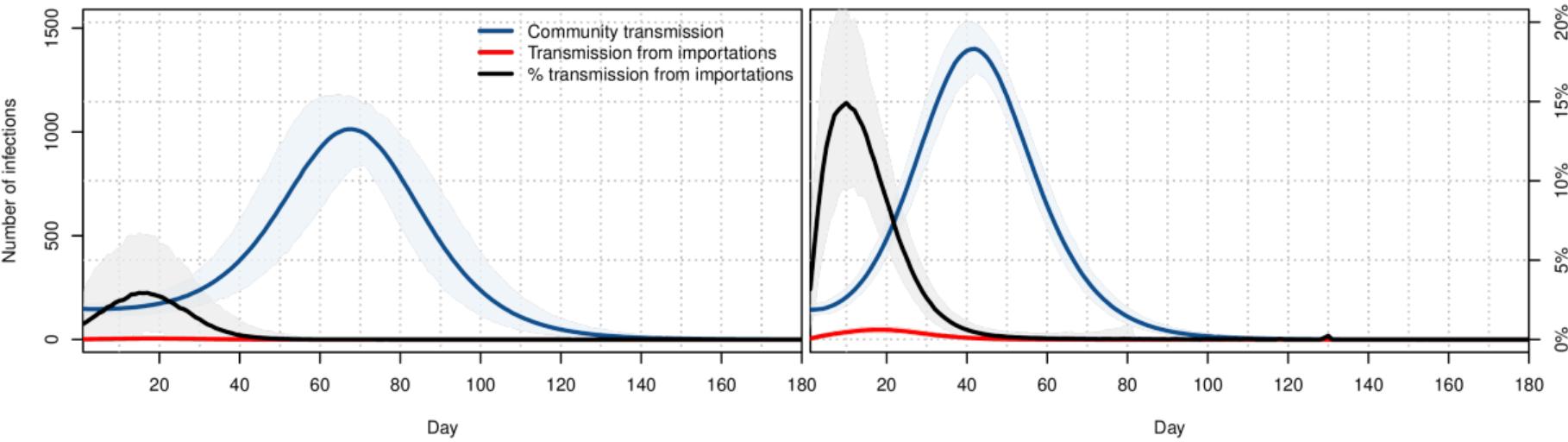


$$R_0^E = 1.5, R_0^C = 0.8, \text{pop}_E = 10000, \text{pop}_I = 10000$$



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





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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.

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

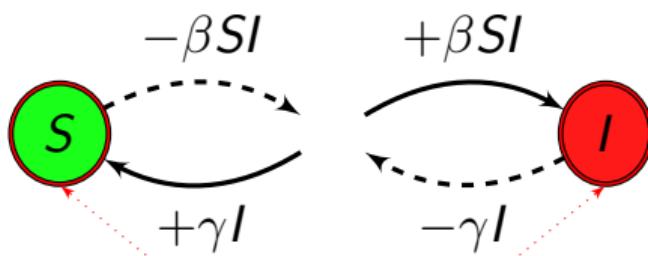
Converting your compartmental ODE model to CTMC

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

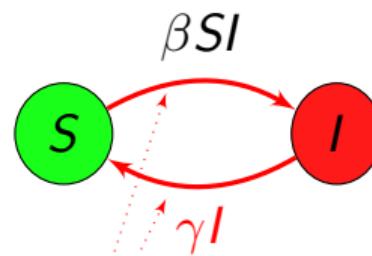
ODE to CTMC : focus on different components

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,  $N(t + \tau_t) = N(t) - 1$ 
    -  $t \leftarrow t + \tau_t$ 
```

A Long Function Definition I

```
birth_death_CTMC = function(b = 0.01, d = 0.01) {  
  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  
  
  # Track the current time and state (could just check last entry in t  
  # and N, but will take more operations)  
  t_curr = t_0  
  N_curr = N_0
```

A Long Function Definition II

```
while (t_curr<=t_f) {  
  xi_t = (b+d)*N_curr  
  if (N_curr == 0) {  
    break # Avoid error with rexp when xi_t = 0  
  }  
  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)
```

A Long Function Definition III

```
    }  
}
```


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

```
library(GillespieSSA2)
Pop <- 1000
I_0 <- 2
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,
)
```

```
## Error:  params is not a numeric or integer vector
```



```
plot(sol$time, sol$state[, "I"], type = "l",
      xlab = "Time (days)", ylab = "Number infectious")
```

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


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`

```
library(parallel)
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)
})
## [[1]]
## [1] "GillespieSSA2" "stats"           "graphics"        "grDevices"
```

```
## [5] "utils"           "datasets"        "methods"        "base"
##
## [[2]]
## [1] "GillespieSSA2" "stats"          "graphics"       "grDevices"
## [5] "utils"           "datasets"        "methods"        "base"
##
## [[3]]
## [1] "GillespieSSA2" "stats"          "graphics"       "grDevices"
## [5] "utils"           "datasets"        "methods"        "base"
##
## [[4]]
## [1] "GillespieSSA2" "stats"          "graphics"       "grDevices"
## [5] "utils"           "datasets"        "methods"        "base"
##
## [[5]]
## [1] "GillespieSSA2" "stats"          "graphics"       "grDevices"
## [5] "utils"           "datasets"        "methods"        "base"
```

```
## [[6]]
## [1] "GillespieSSA2" "stats"           "graphics"      "grDevices"
## [5] "utils"          "datasets"        "methods"       "base"
##
## [[7]]
## [1] "GillespieSSA2" "stats"           "graphics"      "grDevices"
## [5] "utils"          "datasets"        "methods"       "base"
##
## [[8]]
## [1] "GillespieSSA2" "stats"           "graphics"      "grDevices"
## [5] "utils"          "datasets"        "methods"       "base"

clusterExport(cl,
              c("params",
                "run_one_sim"),
              envir = .GlobalEnv)
SIMS = parLapply(cl = cl,
                  X = 1:params$number_sims,
```

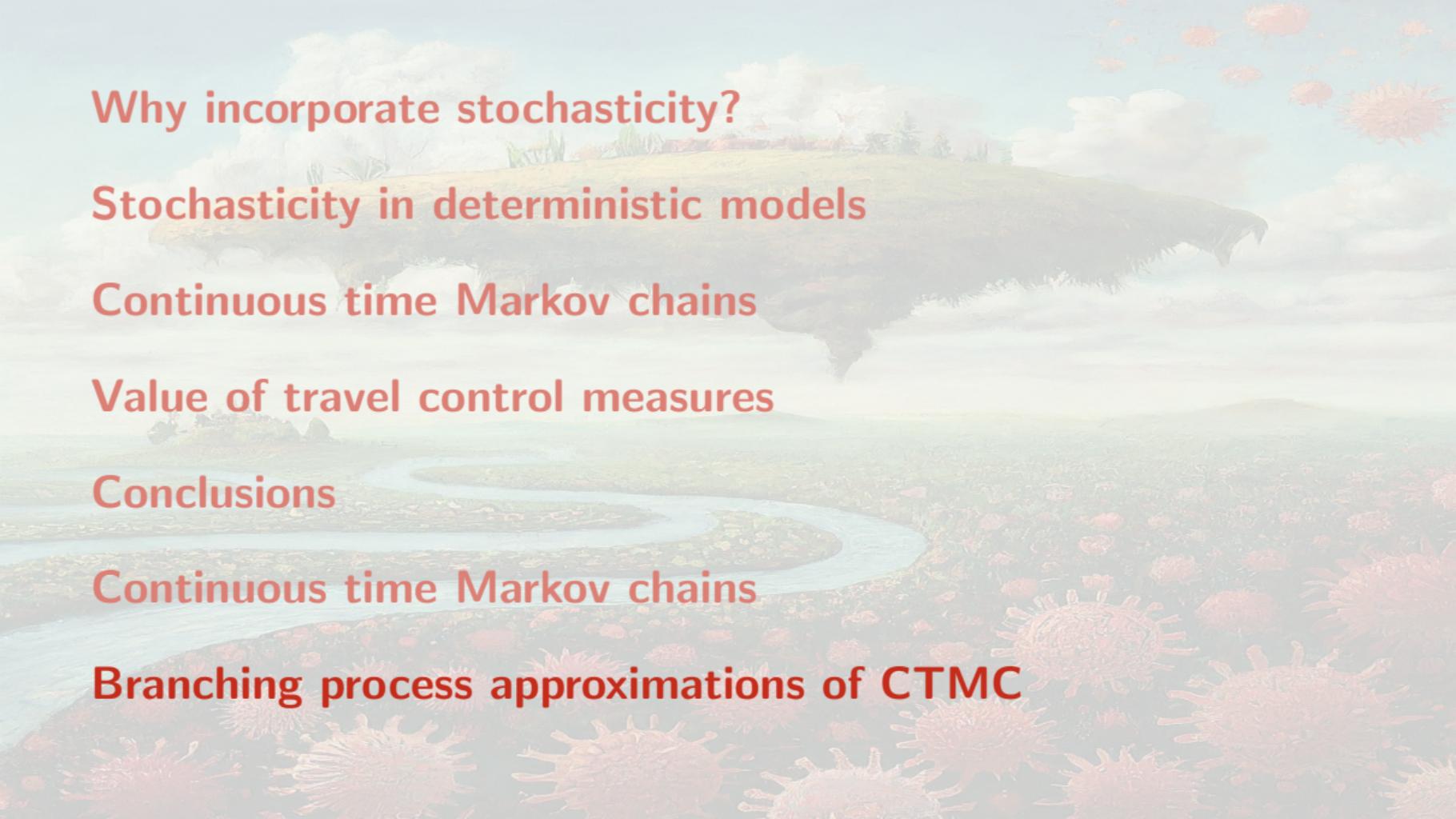
```
fun = function(x) run_one_sim(params))  
  
## Error in 1:params$number_sims: argument of length 0  
  
stopCluster(cl)
```


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 !)

The background of the slide features a soft-focus landscape illustration. It depicts a winding river flowing through a valley, with green hills and a blue sky above. A large, dark bird of prey, possibly a hawk or eagle, is captured in mid-flight in the upper right quadrant. The overall aesthetic is painterly and serves as a backdrop for the text.

Why incorporate stochasticity?

Stochasticity in deterministic models

Continuous time Markov chains

Value of travel control measures

Conclusions

Continuous time Markov chains

Branching process approximations of CTMC

What is a Branching Process?

The Core Idea

A branching process is a mathematical model for a population where individuals produce a random number of offspring and then die.

- ▶ Think of bacteria splitting, a virus spreading, or even the survival of family surnames.
- ▶ We start with an initial population, Z_0 .
- ▶ Each individual in generation n produces a number of offspring for generation $n + 1$.
- ▶ This "number of offspring" is a random variable. All individuals produce offspring according to the same probability distribution, independently of each other.

A simple population tree.

The Galton-Watson Process: A Formal View

Let Z_n be the size of the population in generation n . We typically start with $Z_0 = 1$.

The Galton-Watson Process: A Formal View

Let Z_n be the size of the population in generation n . We typically start with $Z_0 = 1$. The population evolves according to the rule:

$$Z_{n+1} = \sum_{i=1}^{Z_n} X_{n,i}$$

- ▶ The term $X_{n,i}$ represents the number of offspring produced by the i -th individual in generation n .
- ▶ The variables $\{X_{n,i}\}$ are assumed to be **independent and identically distributed (i.i.d.)** integer-valued random variables.
- ▶ We call their common distribution $\{p_k\}_{k=0}^{\infty}$ the **offspring distribution**, where $p_k = P(X = k)$.

The Fundamental Questions

1. What is the long-term expected size of the population?
2. What is the probability that the population eventually dies out?

The Most Important Number: Mean Offspring

The entire fate of the population hinges on a single parameter: the mean of the offspring distribution.

$$\mu = E[X] = \sum_{k=0}^{\infty} k \cdot p_k$$

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Expected Population Size

Using the law of total expectation, we can find the expected size of the next generation:

$$E[Z_{n+1}|Z_n] = E\left[\sum_{i=1}^{Z_n} X_{n,i} \middle| Z_n\right] = Z_n E[X] = Z_n \mu$$

Taking the expectation again, we get a simple recurrence:

$$E[Z_{n+1}] = \mu E[Z_n]$$

This implies:

The Three Regimes of Population Growth

The behavior of $E[Z_n] = Z_0\mu^n$ suggests three distinct cases:

Subcritical ($\mu < 1$)

$E[Z_n] \rightarrow 0$. The population is expected to shrink. It goes extinct with probability 1.

Critical ($\mu = 1$)

$E[Z_n] = Z_0$. The population is expected to remain stable. Surprisingly, it still goes extinct with probability 1.

Supercritical ($\mu > 1$)

$E[Z_n] \rightarrow \infty$. The population is expected to grow exponentially. It has a non-zero probability of surviving forever.

Tool: The Probability Generating Function

To find the extinction probability, we need a powerful tool: the **probability generating function (PGF)** of the offspring distribution X .

$$G(s) = E[s^X] = \sum_{k=0}^{\infty} p_k s^k \quad \text{for } |s| \leq 1$$

Key Properties

- ▶ $G(1) = \sum p_k = 1$
- ▶ The mean can be found from the derivative: $G'(1) = \sum kp_k = \mu$.
- ▶ The PGF of Z_n is the n -th iterate of $G(s)$ with itself. If $G_n(s)$ is the PGF of Z_n , then $G_{n+1}(s) = G(G_n(s))$.

The Extinction Probability Equation

Let π_0 be the probability of eventual extinction, starting with $Z_0 = 1$.

$$\pi_0 = P(\text{population dies out}) = \lim_{n \rightarrow \infty} P(Z_n = 0)$$

Since $P(Z_n = 0) = G_n(0)$, and $G_{n+1}(0) = G(G_n(0))$, in the limit the extinction probability π_0 must satisfy the equation:

$$\pi_0 = G(\pi_0)$$

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Theorem 4

*The extinction probability π_0 is the **smallest non-negative solution** to the equation $s = G(s)$.*

- ▶ If $\mu \leq 1$, the only solution in $[0, 1]$ is $s = 1$. So $\pi_0 = 1$.
- ▶ If $\mu > 1$, there is a unique solution in $[0, 1)$, which is the extinction probability $\pi_0 < 1$.

From Discrete to Continuous Time

Limitation of Galton-Watson

Generations don't happen in synchronized steps in the real world. Individuals give birth and die at random times.

This leads us to **Continuous-Time Markov Chains (CTMCs)**.

- ▶ The state of the system is the population size, $k \in \{0, 1, 2, \dots\}$.
- ▶ Instead of generations, we have transition rates:
 - ▶ λ_k : rate of birth when population is size k (moves to $k + 1$).
 - ▶ δ_k : rate of death when population is size k (moves to $k - 1$).
- ▶ Often, we assume these rates are linear: $\lambda_k = k\lambda$ and $\delta_k = k\delta$. This means individuals act independently.

Branching Process Approximation of a CTMC

The Key Insight

At the beginning of an outbreak (or for a very large population), the dynamics caused by a single individual are largely independent of others.

This allows us to approximate the start of a CTMC population process with a branching process.

Example: A Simple Epidemic (SIR Model)

- ▶ S : Susceptible, I : Infected, R : Recovered.
- ▶ An infected person meets others at a certain rate. If they meet a susceptible, a new infection may occur (an "offspring").
- ▶ The infected person recovers (or dies) at another rate, ending their infectious period.
- ▶ **Question:** How many new infections does a single infected person cause on average?

Case Study: The Basic Reproduction Number \mathcal{R}_0

Consider a single infected individual in a large population of susceptibles.

- ▶ Let β be the infection rate (rate of producing "offspring").
- ▶ Let γ be the recovery rate (rate of "dying").

The individual's infectious lifetime is an exponential random variable with mean $1/\gamma$.

Case Study: The Basic Reproduction Number \mathcal{R}_0

Consider a single infected individual in a large population of susceptibles.

- ▶ Let β be the infection rate (rate of producing "offspring").
- ▶ Let γ be the recovery rate (rate of "dying").

The individual's infectious lifetime is an exponential random variable with mean $1/\gamma$.
The average number of secondary infections they cause is:

$$\mathcal{R}_0 = (\text{rate of infection}) \times (\text{average infectious period}) = \beta \times \frac{1}{\gamma} = \frac{\beta}{\gamma}$$

The Connection

\mathcal{R}_0 is precisely the **mean offspring number** μ for the embedded branching process that approximates the start of the epidemic.

Applying Branching Theory to Epidemics

The fate of the epidemic's initial phase is determined by \mathcal{R}_0 :

- ▶ If $\mathcal{R}_0 \leq 1$ ($\mu \leq 1$): The number of infected individuals is a subcritical or critical process. The epidemic will die out with probability 1.
- ▶ If $\mathcal{R}_0 > 1$ ($\mu > 1$): The process is supercritical. There is a positive probability that the epidemic takes off and causes a major outbreak.

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- ▶ If $\mathcal{R}_0 > 1$ ($\mu > 1$): The process is supercritical. There is a positive probability that the epidemic takes off and causes a major outbreak.

We can even calculate the probability of a major outbreak! It is $1 - \pi_0$, where π_0 is the extinction probability.

For this simple birth-death infection process, the PGF is $G(s) = \frac{\gamma}{\beta+\gamma} + \frac{\beta}{\beta+\gamma}s$. Solving $s = G(s)$ gives the extinction probability:

$$\pi_0 = \frac{\gamma}{\beta} = \frac{1}{\mathcal{R}_0}$$

The probability of a major outbreak is $1 - 1/\mathcal{R}_0$.

Summary

- ▶ **Branching Processes** model populations with i.i.d. offspring generation.
- ▶ The fate of the population is determined by the **mean offspring number** μ . Extinction is certain if $\mu \leq 1$.
- ▶ The **extinction probability** π_0 can be calculated as the smallest non-negative fixed point of the probability generating function $G(s)$.
- ▶ The initial stages of many large-scale **Continuous-Time Markov Chains** can be approximated by a branching process.
- ▶ This allows us to apply the theory to real-world problems, like calculating an epidemic's **basic reproduction number** \mathcal{R}_0 and its probability of causing a major outbreak.