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

Branching process approximations of CTMC

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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

msi
ASUS
ASUS
ThinkPad

- Very very long days (18-20 hours, 7 days a week)

- including a lot of time waiting for the “cluster” to finish

$\Longrightarrow$ PHAC gave me money for a cluster (yay Threadrippers!!!)

$\Longrightarrow$ 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

What is wrong with deterministic models?

- I pointed out yesterday that SARS-CoV-2 is one *single* realisation of a stochastic process
- Deterministic models "operate on averages" over a large ($\to \infty$) number of realisations
- If we want to get a better sense of what could happen, not only on average, then we need to see what can indeed happen

My new focus – Introductions

- I started thinking in particular about **introductions** (or importations) of pathogens into new populations

- Indeed, introductions are an obligatory step in spatial spread

First piece of evidence

In real life, introductions of pathogens does not always follow the patter

$$\{\mathcal{R}_0 < 1 \implies \to \text{DFE} \text{ — } \mathcal{R}_0 > 1 \implies \text{ epidemic or } \to \text{EEP}\}$$

Aging and Disease
www.aginganddisease.org
Early access date: October 28, 2022
http://dx.doi.org/10.14336/AD.2022.0820

Short Communication

SARS-CoV-2 in Nursing Homes: Analysis of Routine Surveillance Data in Four European Countries

Tristan Delory[1,2*], Julien Arino[3], Paul-Emile Haÿ[4], Vincent Klotz[4], Pierre-Yves Boëlle[1]

[1] Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, IPLESP, F-75012, Paris, France. [2]Centre Hospitalier Annecy Genevois, France. [3]Department of Mathematics, University of Manitoba, Winnipeg, Manitoba, Canada. [4]Groupe Colisee.

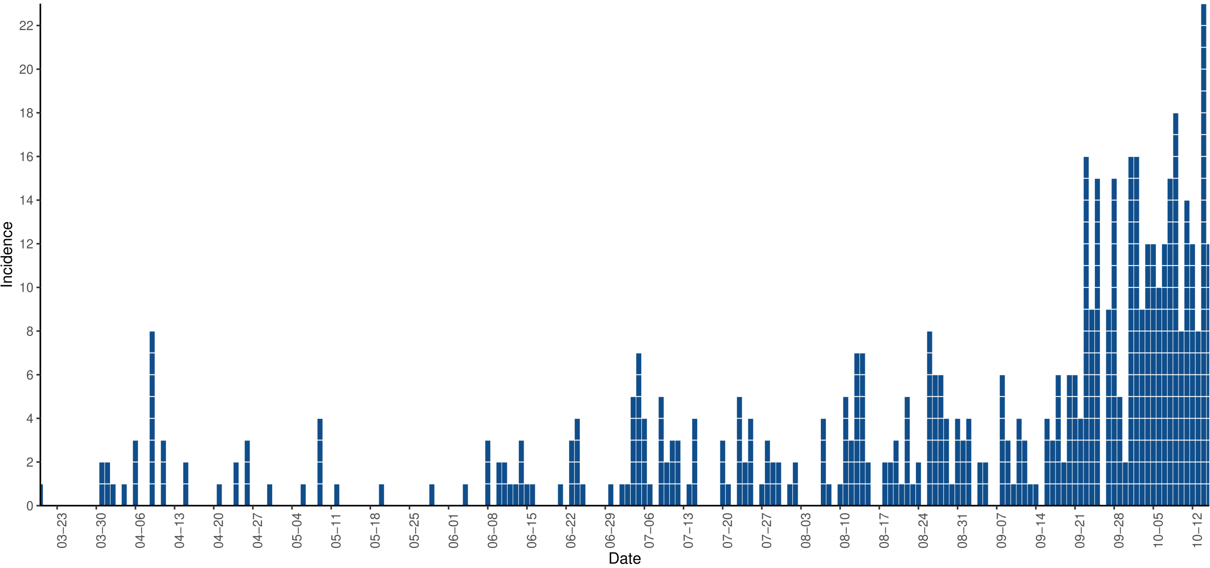
Table 1. Effect of vaccination scaling-up on the probability of successful viral introduction.

Period	Failed N = 136	Successful N = 366	aOR*	95%CI	P-value
Before vaccination	94 (69.1%)	311 (85.0%)	Ref		
January 15 to January 31	12 (8.8%)	37 (10.1%)	0.89	0.42 – 1.92	0.770
February 01 to February 15	17 (12.5%)	14 (3.8%)	0.23	0.10 – 0.52	<0.001
February 16 to February 28	13 (9.6%)	4 (1.1%)	0.08	0.02 - 0.29	<0.001

* Adjusted on study period, country, staffing ratio, cumulative attack rate at onset of introduction, and number of PCR per 1000-residents or 1000-staff members, at onset of introduction, and nursing home maximal capacity.

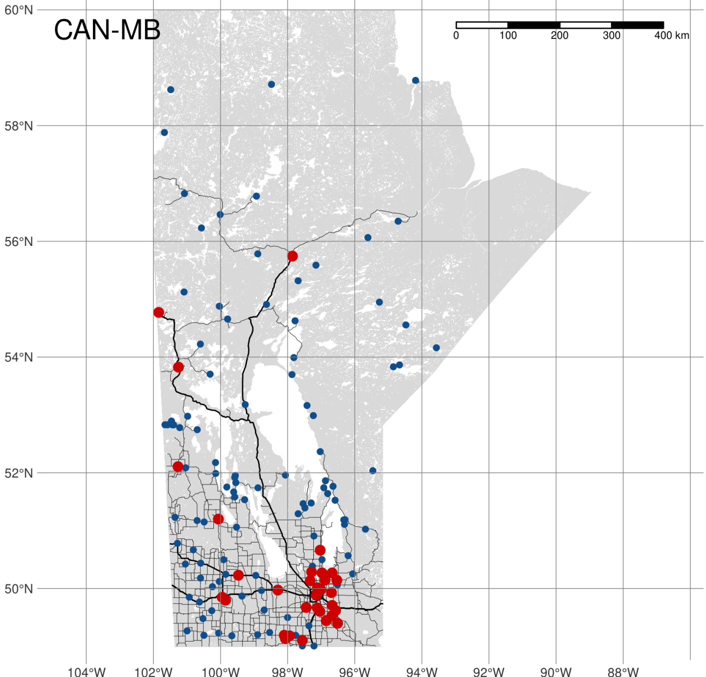
Second piece of evidence

The start of an outbreak can be extremely slow, with very few cases for quite a while

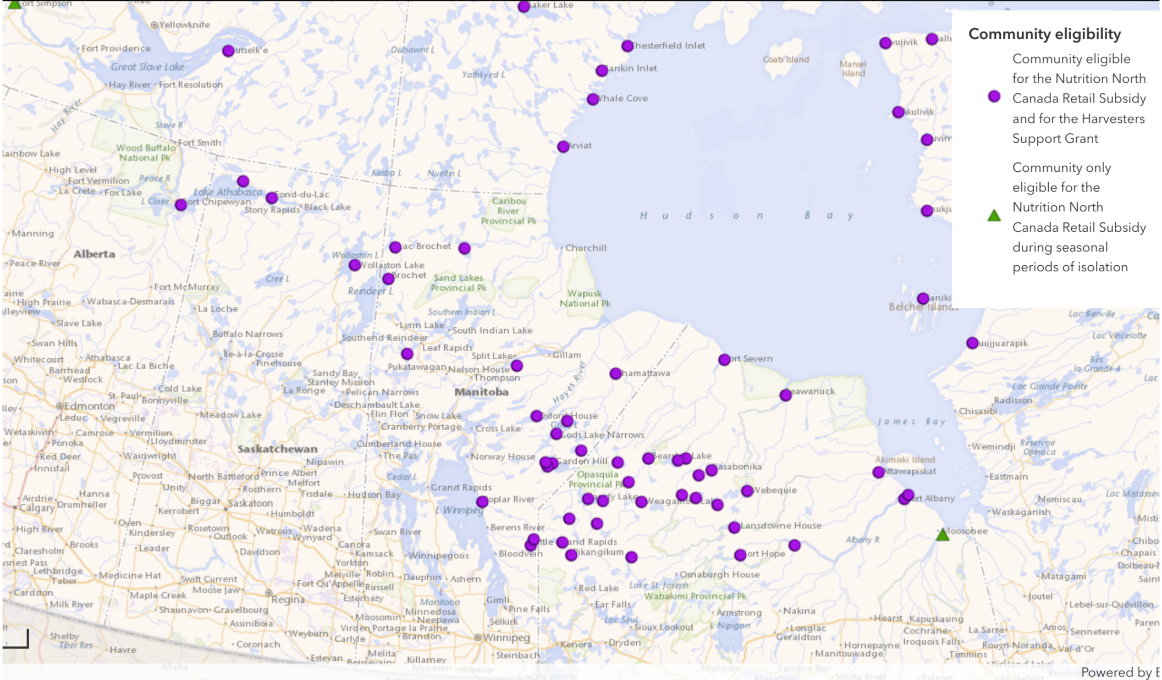

Incidence
0
2
4
6
8
10
12
14
16
18
20
22
03−23
03−30
04−06
04−13
04−20
04−27
05−04
05−11
05−18
05−25
06−01
06−08
06−15
06−22
06−29
07−06
07−13
07−20
07−27
08−03
08−10
08−17
08−24
08−31
09−07
09−14
09−21
09−28
10−05
10−12
Date

Why this is relevant

Far from the only reason, but as an example: Canada has remote/isolated communities that are vulnerable to introductions of pathogens



CAN-MB
0
100
200
300
400 km
60°N
58°N
56°N
54°N
52°N
50°N
104°W
102°W
100°W
98°W
96°W
94°W
92°W
90°W
88°W


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
Hudson Bay
James Bay
Alberta
Saskatchewan
Manitoba
Great Slave Lake
Lake Athabasca
Yellowknife
Fort Providence
Hay River
Fort Resolution
Fort Smith
Fort Chipewyan
Fond-du-Lac
Stony Rapids
Black Lake
Wollaston Lake
Churchill
Arviat
Whale Cove
Rankin Inlet
Chesterfield Inlet
Baker Lake
Coats Island
Mansel Island
Belcher Islands
Kuujjuarapik
Fort Severn
Peawanuck
Attawapiskat
Fort Albany
Moosonee
Lansdowne House
Fort Hope
Webequie
Kasabonika
Bearskin Lake
Garden Hill
Gods Lake Narrows
Oxford House
Shamattawa
Pukatawagan
Nelson House
Thompson
Lac Brochet
Brochet
Poplar River
Little Grand Rapids
Pikangikum
Fort McMurray
Edmonton
Calgary
Regina
Saskatoon
Winnipeg
Prince Albert
The Pas
Flin Flon
Norway House
Cross Lake
Berens River
Bloodvein
Red Lake
Sioux Lookout
Kenora
Dryden
Timmins
Cochrane
Radisson
Chisasibi
Wemindji
Eastmain
Waskaganish
Nemiscau
Powered by

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 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

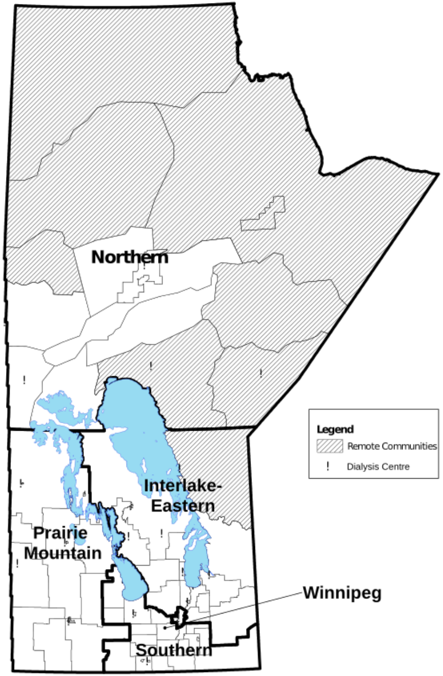
Inuit Communities to be referred to as **Inuit Nunangat**, not remote and isolated communities to respect the unique language and culture of Inuit regions, as well as the common challenges in social determinants of health, access to care, and infrastructure found across all Inuit communities

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


Northern
Interlake-
Eastern
Prairie
Mountain
Winnipeg
Southern
Legend
Remote Communities
Dialysis Centre

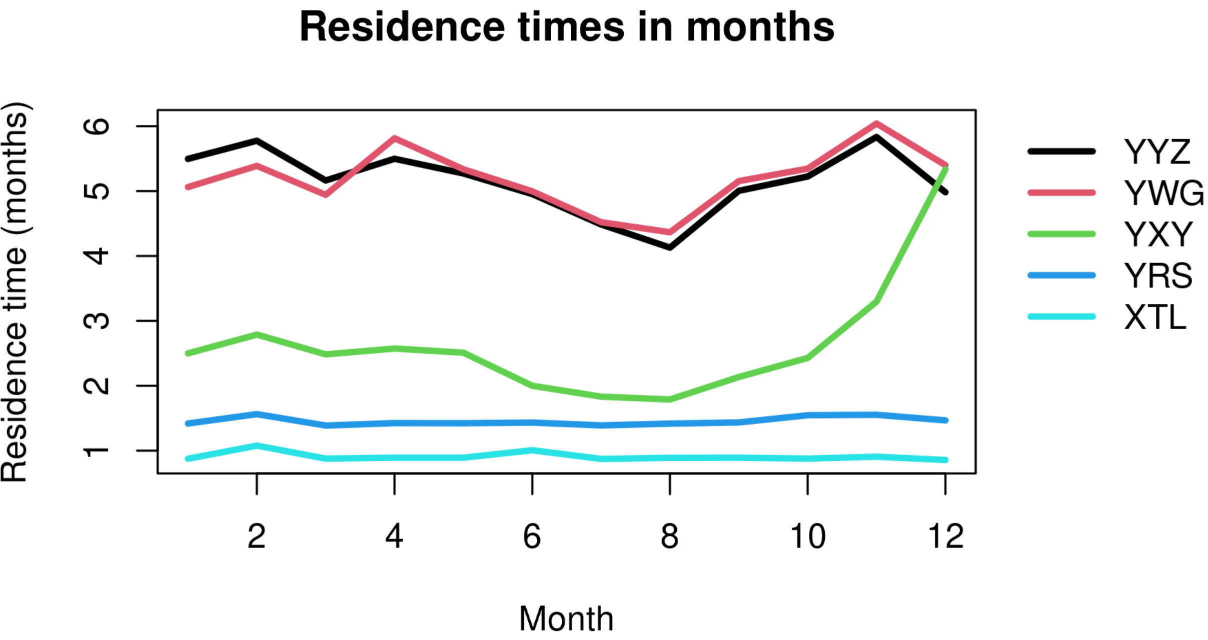
Travel to/from remote or isolated communities

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

Think of residence times in these communities: what is the average time a person spends in a remote or isolated community before leaving it?

The **residence time in a location** is the total number of trips inbound into and outbound from location over a duration of time (1 month here) divided by the normal population in the location

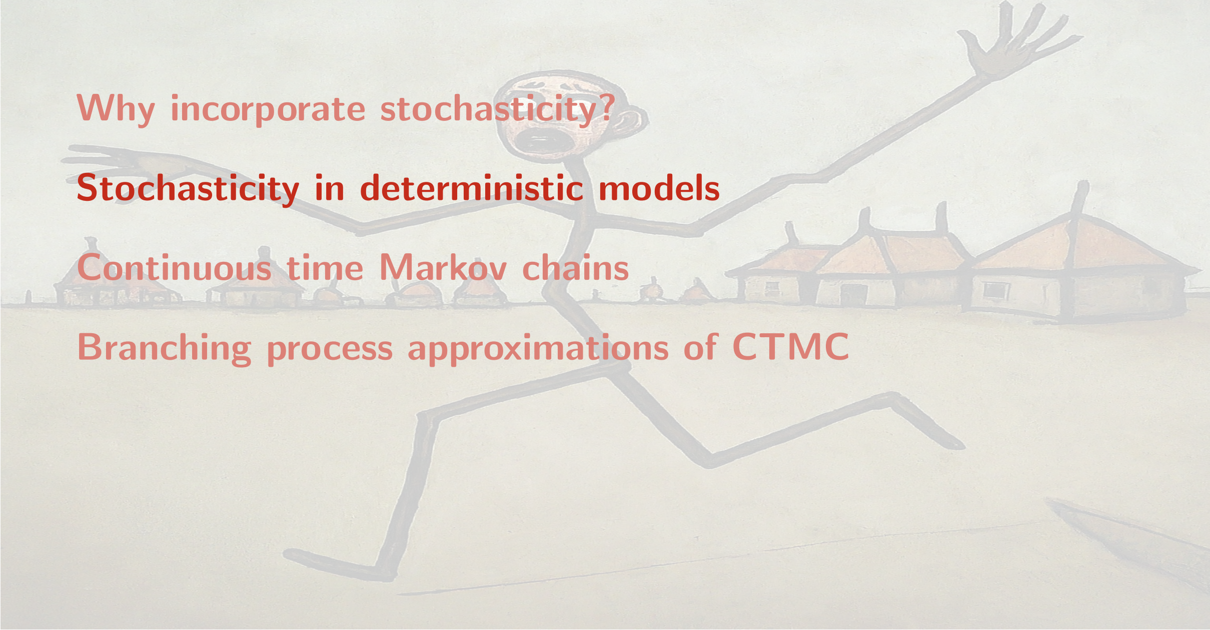

Residence times in months
Residence time (months)
1
2
3
4
5
6
2
4
6
8
10
12
Month
YYZ
YWG
YXY
YRS
XTL

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



Why incorporate stochasticity?

Stochasticity in deterministic models

Continuous time Markov chains

Branching process approximations of CTMC

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

Stochasticity in deterministic models

Distributions of times to events

Two “extreme” distributions and a nicer one

A simple cohort model with death

A possible fix to the exponential distribution issue

Sojourn times in an SIS disease transmission model

A model with vaccination

Time to events

We suppose that a system can be in two states, A and B

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

Let us call T the random variable

"time spent in state A before switching into state B"

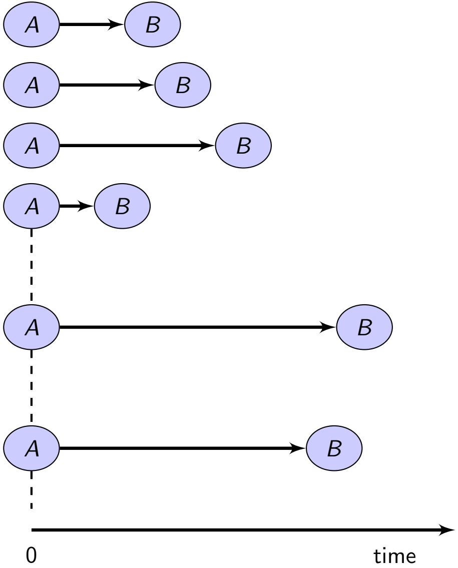
The states can be anything:

- A: working, B: broken
- A: infected, B: recovered
- A: alive, B: dead
- $\dots$

We take a collection of objects or individuals that are in state A and want some law for the **distribution** of the times spent in A, 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 A to B


A
B
A
B
A
B
A
B
A
B
A
B
0
time

A distribution of probability is a model

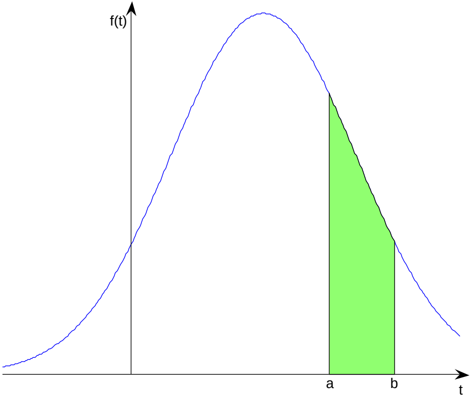
From the sequence of experiments, we deduce a model, which in this context is called a **probability distribution**

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

Probability density function

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

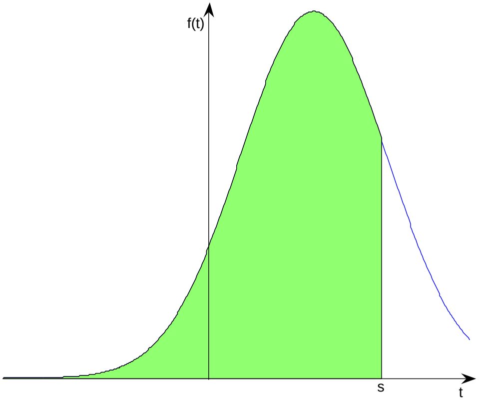
- $f \geq 0$
- $\int_{-\infty}^{+\infty} f(s)ds = 1$
- $\mathbb{P}(a \leq T \leq b) = \int_a^b f(t)dt$



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 A is given by

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

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

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

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

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

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

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

Expected future lifetime:

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

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

Hazard rate

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

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

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

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

(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

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

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

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

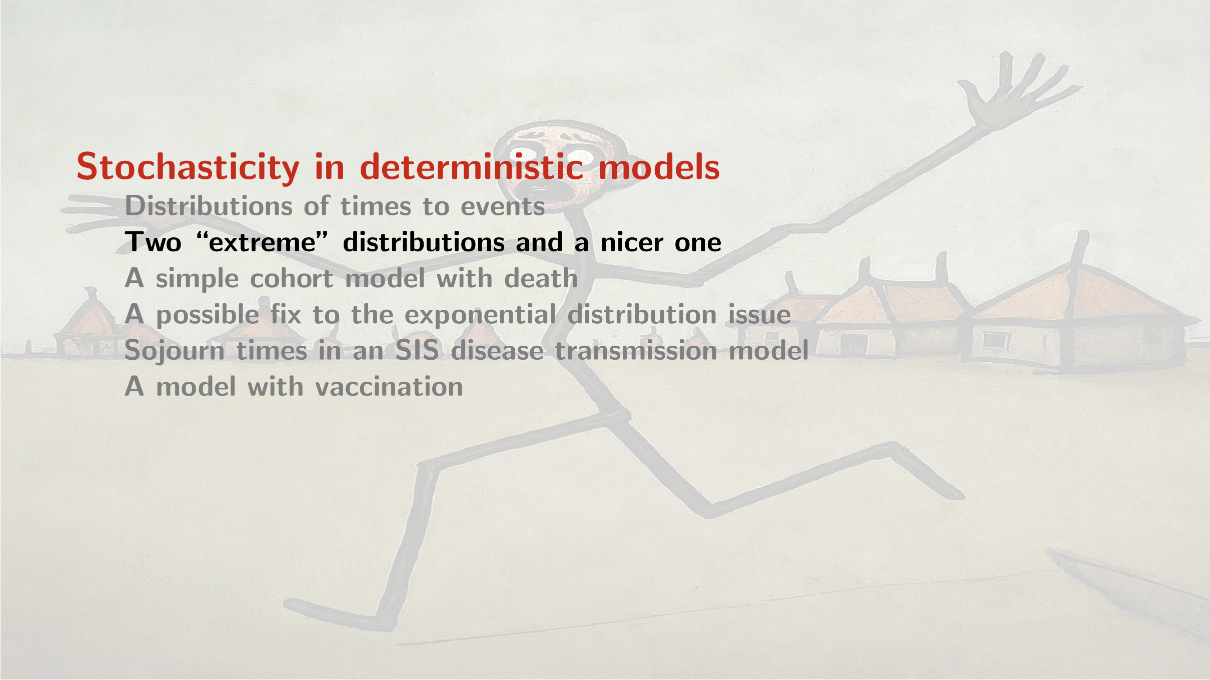
or, identically,

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

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

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



Stochasticity in deterministic models

- Distributions of times to events
- **Two "extreme" distributions and a nicer one**
- A simple cohort model with death
- A possible fix to the exponential distribution issue
- Sojourn times in an SIS disease transmission model
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The exponential distribution

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

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

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

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

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

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

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

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

Properties of the Gamma distribution

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

Survival function

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

where

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

is an incomplete Gamma function

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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

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

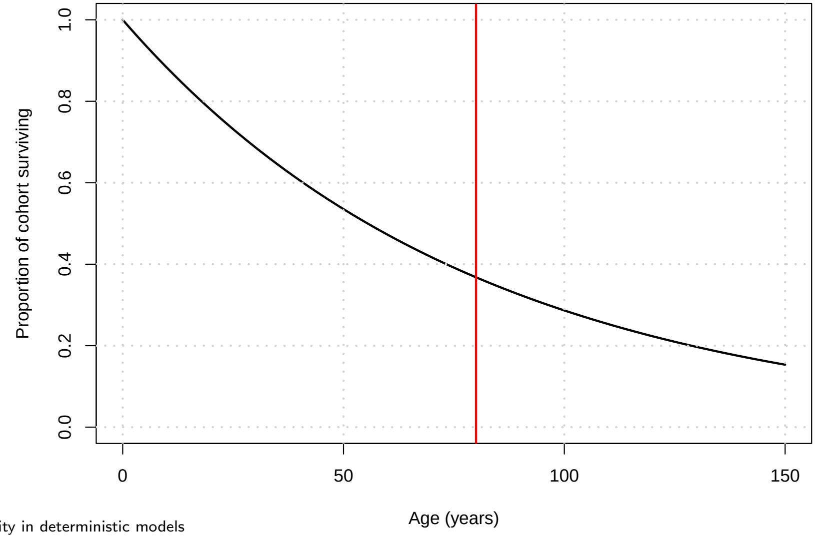
Now note that

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

with $N(0) = N_0$.

$\Rightarrow$ 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

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

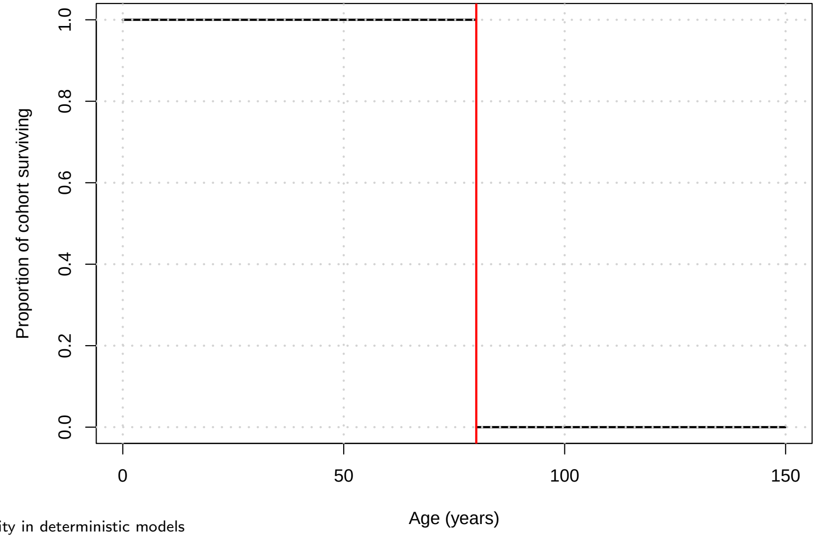
Then (4) takes the form

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

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



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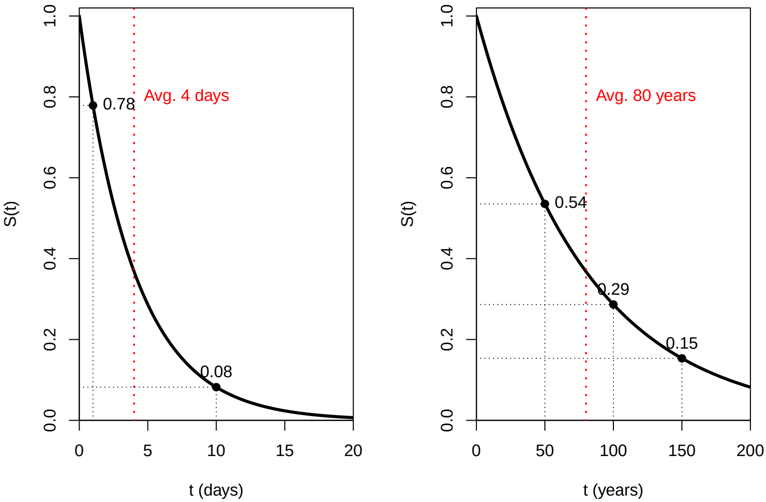
Survival for the exponential distribution



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 parametres θ_1 and θ_2. Then the probability density function of the r.v. $Z = X_1 + X_2$ is given by the convolution

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

The tool we use

Theorem 1

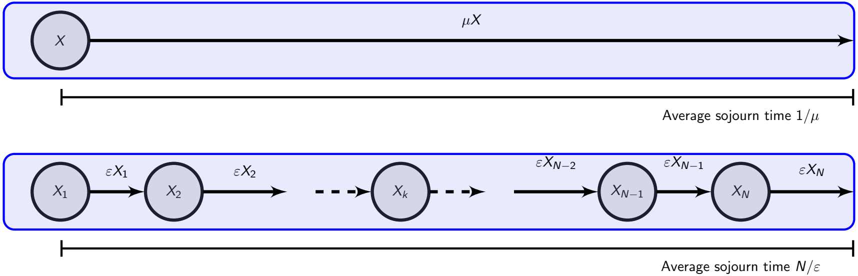
Let X_i be independent exponentially distributed random variables with parameter ξ and $Y = \sum_{i=1}^{n} X_i$

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 $\mathrm{Var}(Y) = n\xi^2$



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

$\Longrightarrow$ compute RSS errors between data points generated from the given Gamma distribution and an Erlang

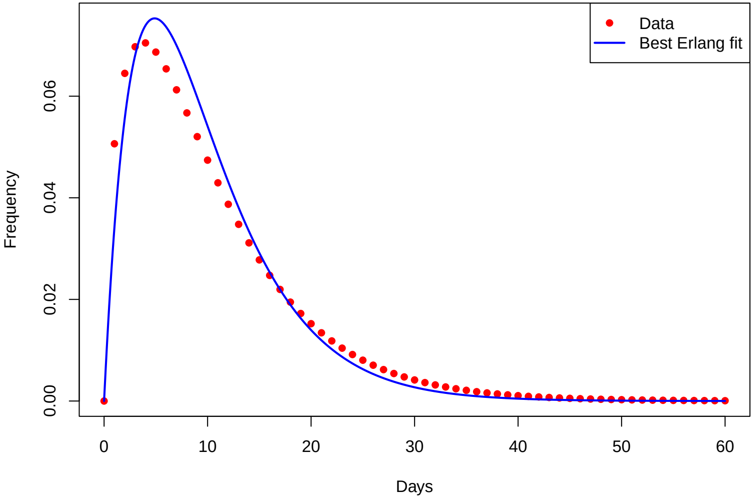
```
error_Gamma <- function(theta,shape,t,d) {
  test_points <- dgamma(t, shape = shape, scale = theta)
  ls_error <- sum((d-test_points)^2)
  return(ls_error)
}
```

```
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
      scale_vector[i] <- NaN
    }
  }
  result_optim <- data.frame(seq(1,max_shape),
                             scale_vector,
                             error_vector)
  colnames(result_optim) <- c("shape","scale","error")
  result_optim <- result_optim[complete.cases(result_optim),]
  return(result_optim)
}
```

```r
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)



Stochasticity in deterministic models

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)
  $\Rightarrow$ 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 $\mathcal{S}(t - t_0)$ remain infective at time $t \geq t_0$
- $\Rightarrow$ For $t \geq 0$, $\mathcal{S}(t)$ is a survival function. As such, it verifies $\mathcal{S}(0) = 1$ and $\mathcal{S}$ 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)

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

- $I_0(t)$ 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 $\lim_{t\to\infty} I_0(t) = 0$
- $\mathcal{S}(t-u)$ 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:

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

The term

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

- $\beta(N - I(u))I(u)/N$ is the rate at which new infectives are created, at time u
- multiplying by $\mathcal{S}(t-u)$ 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 $\mathcal{S}(t)$ such that sojourn time in the infective state has exponential distribution with mean $1/\gamma$, *i.e.*, $\mathcal{S}(t) = e^{-\gamma t}$

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

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

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

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

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

In this case (8) becomes

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

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)

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

Stochasticity in deterministic models

Distributions of times to events

Two “extreme” distributions and a nicer one

A simple cohort model with death

A possible fix to the exponential distribution issue

Sojourn times in an SIS disease transmission model

A model with vaccination

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

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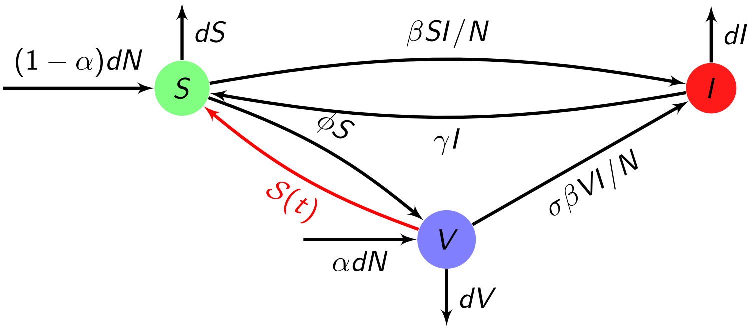
(Communicated by Linda Allen)

Model structure



Assumptions on $\mathcal{S}$

$\mathcal{S}(t)$ is a nonnegative and nonincreasing function with $\mathcal{S}(0^+) = 1$, and such that $\int_0^\infty \mathcal{S}(u)du$ is positive and finite

So $\mathcal{S}(t)$ is a survival function

The SIS model with vaccination

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

$$V(t) = V_0(t) + \int_0^t (\phi S(u) + \alpha d)\mathcal{S}(t-u)e^{-d(t-u)}e^{-\sigma\beta\int_u^t I(x)dx}du \tag{11b}$$

- αd proportion of vaccinated newborns
- $\phi S(u)$ proportion of vaccinated susceptibles
- $\mathcal{S}(t-u)$ 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

Reduction of the system using specific $\mathcal{S}(t)$ functions

- The distribution of waning times being exponential leads to an ODE system
- $\mathcal{S}(t)$ originating in a Dirac distribution leads to a discrete DDE model

- Why incorporate stochasticity?
- Stochasticity in deterministic models
- **Continuous time Markov chains**
- Branching process approximations of CTMC

Continuous-time Markov chains

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

DTMC: transitions occur each Δt

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

CTMC are roughly equivalent to ODE

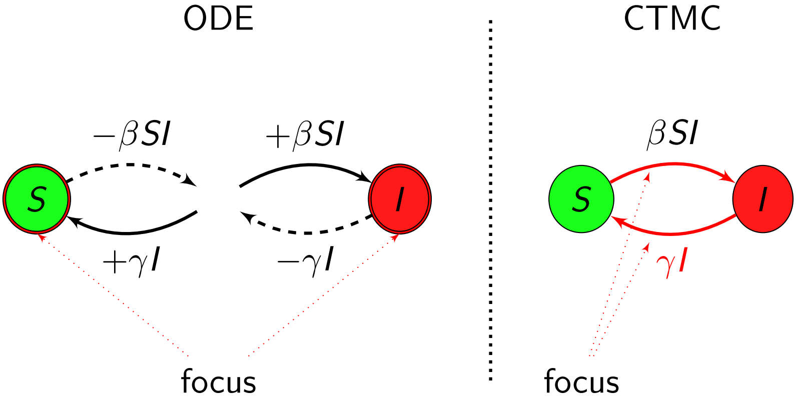
Continuous time Markov chains

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



SIS without demography

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

States are S, I

SIS with demography

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

States are S, I, R

Continuous time Markov chains

ODE and CTMC

Simulating CTMC (in theory)

Value of travel control measures

Conclusions

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. $\sum_{k=1}^{j} a_k(\mathbf{x}(t)) > \zeta_t \sum_j a_j(\mathbf{x}(t)) = \zeta_t \xi_t$
- 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

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

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

set $t \leftarrow t_0$ and $I(t) \leftarrow I(t_0)$
while $t \leq t_f$
- $\xi_t \leftarrow \beta(P^\star - i)i + \gamma i$
- Draw τ_t from $T \sim \mathcal{E}(\xi_t)$
- $v \leftarrow [\beta(P^\star - i)i, \xi_t] / \xi_t$
- 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 $\tau_t \to 0$ 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)

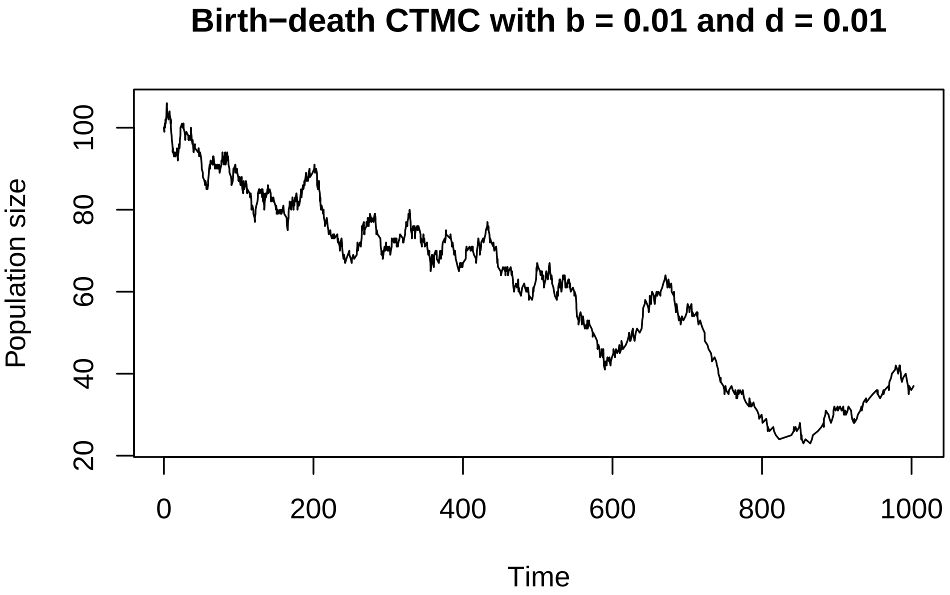
Gillespie's algorithm (birth-death model)

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 τ_t from $T \sim \mathcal{E}(\xi_t)$
- $v \leftarrow [bN(t), \xi_t] / \xi_t$
- Draw ζ_t from $\mathcal{U}([0,1])$
- Find *pos* such that $v_{pos-1} \leq \zeta_t \leq v_{pos}$
- switch *pos*
    - 1: Birth, $N(t+\tau_t) = N(t) + 1$
    - 2: Death, $N(t+\tau_t) = N(t) - 1$
- $t \leftarrow t + \tau_t$

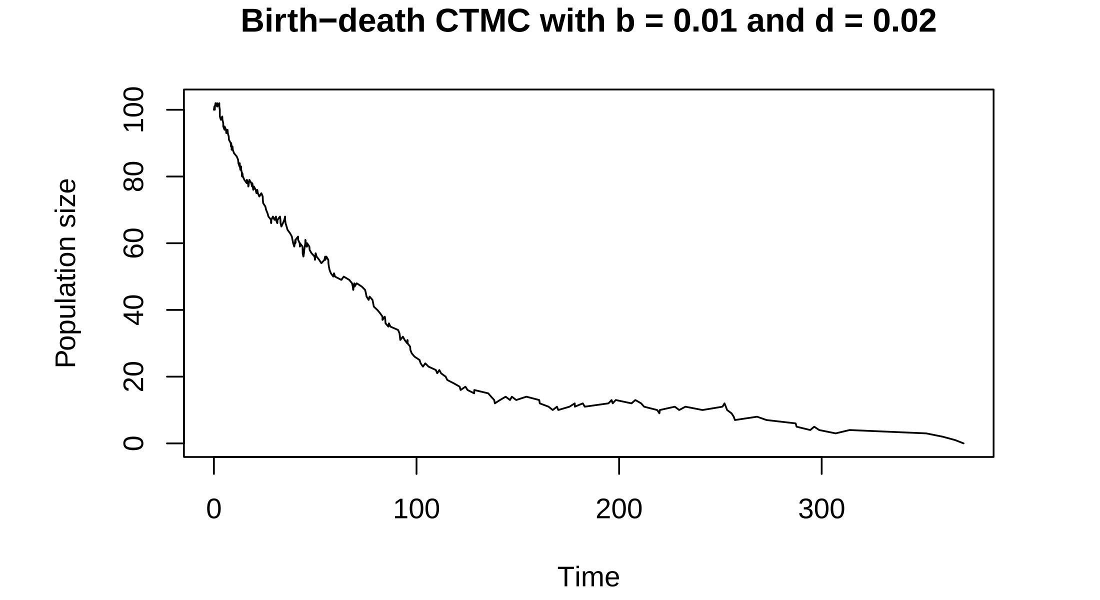
```
birth_death_CTMC = function(b = 0.01, d = 0.01) {
  t_0 = 0     # Initial time
  N_0 = 100   # Initial population

  # 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
  while (t_curr<=t_f) {
    xi_t = (b+d)*N_curr
```

```r
    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)
  }
  plot(t, N, type = "l",
       xlab = "Time", ylab = "Population size",
       main = paste("Birth-death CTMC with b =", b, "and d =", d))
```

}



Birth−death CTMC with b = 0.01 and d = 0.01
Population size
20
40
60
80
100
0
200
400
600
800
1000
Time



Birth−death CTMC with b = 0.01 and d = 0.02
Population size
0
20
40
60
80
100
0
100
200
300
Time

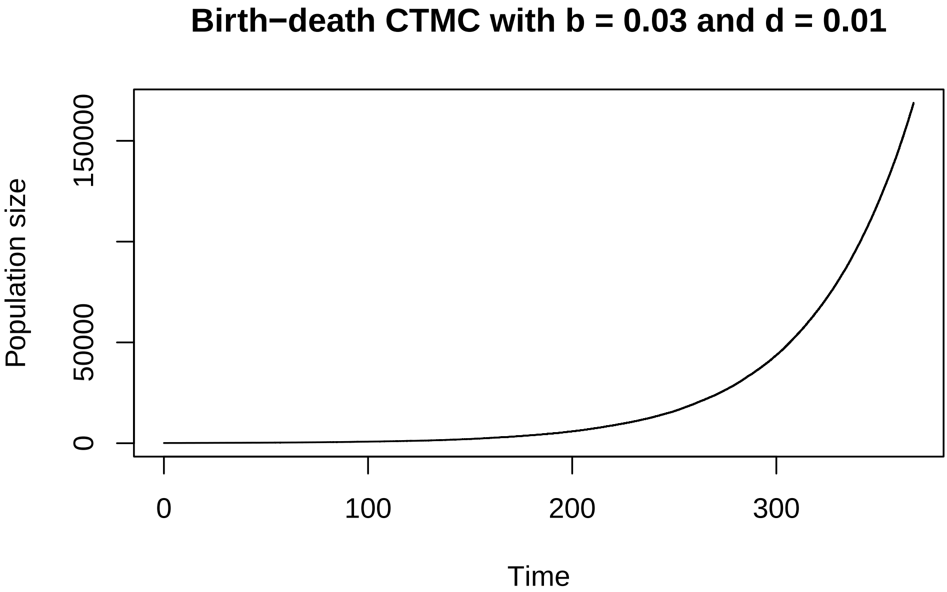
$b = 0.03$ & $d = 0.01$...

We want to run the function with these parameter values but I know in advance this will not work well, so let's tweak the function a bit...

```r
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
  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)
if (t[length(t)]-t[(length(t)-1)] < 1e-9) {
  # If the time step is too small, stop the simulation
  message("Stopping simulation because time step is too small")
  break
```

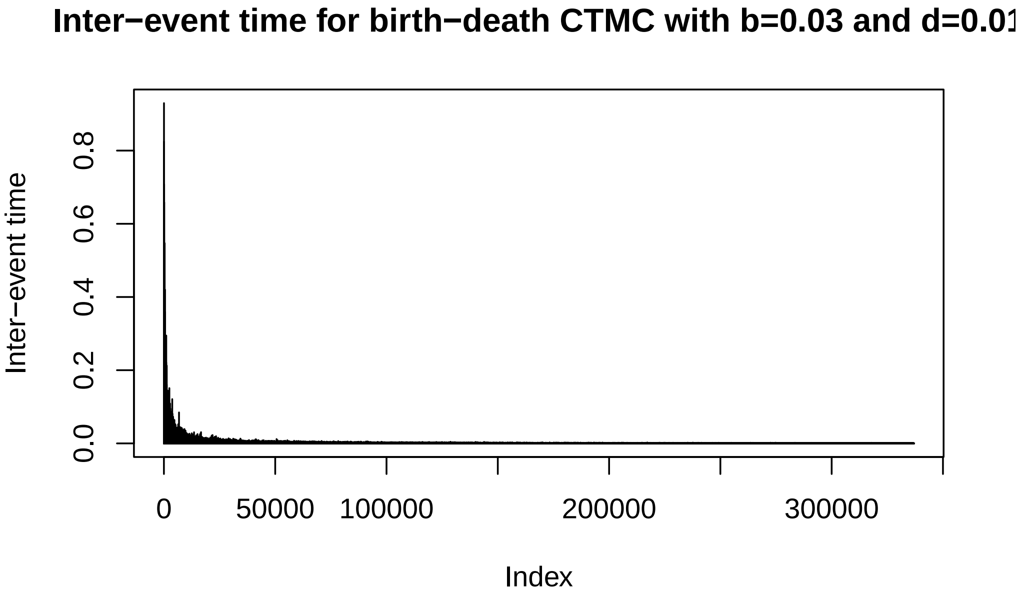
```
    }
  }
  plot(t, N, type = "l",
       xlab = "Time", ylab = "Population size",
       main = paste("Birth-death CTMC with b =", b, "and d =", d))
  return(list(t = t, N = N))
}
```


Birth−death CTMC with b = 0.03 and d = 0.01
Population size
0
50000
150000
0
100
200
300
Time

Last one did not go well

- Wanted 1000 time units (days?)
- Interrupted at 367.2470966 because of the test
  (Penultimate slide: sim stopped because the population went extinct, I did not stop it!)
- At stop time
  - $N = 1.6875 \times 10^5$
  - $|N| = 336813$ (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
```


Inter−event time for birth−death CTMC with b=0.03 and d=0.01
Inter−event time
0.0
0.2
0.4
0.6
0.8
0
50000
100000
200000
300000
Index

Investigating outbreak types using a simple CTMC SIS

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

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

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

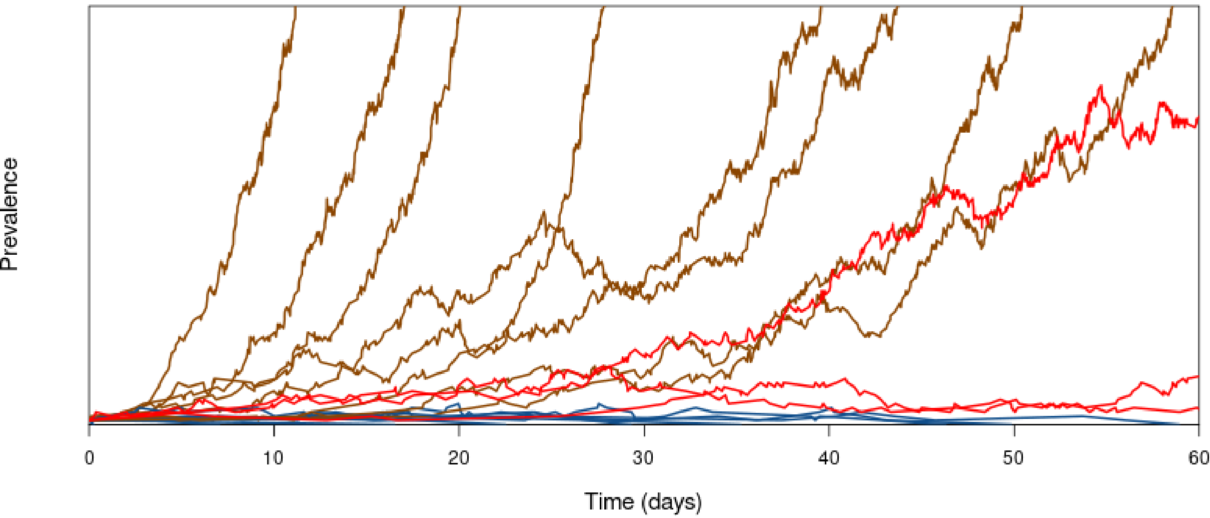
Investigating outbreak types using a simple CTMC SIS *with a twist*

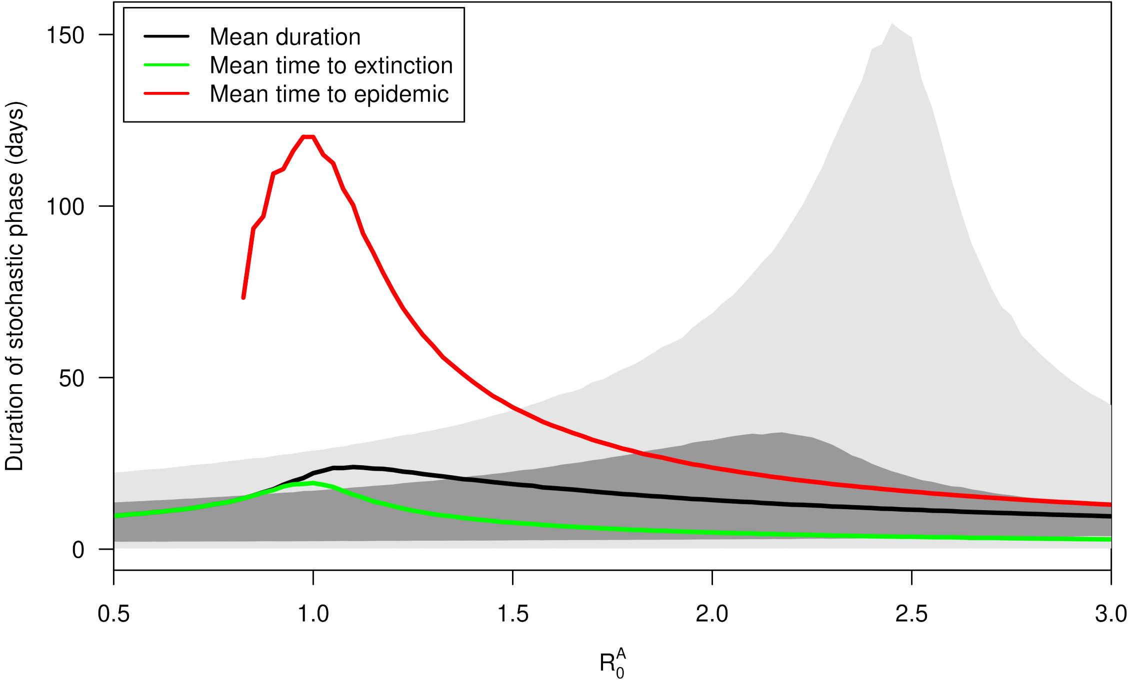
Regular chain of this type has $I = 0$ as sole absorbing state

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


Prevalence
0
10
20
30
40
50
60
Time (days)



Mean duration
Mean time to extinction
Mean time to epidemic
Duration of stochastic phase (days)
150
100
50
0
0.5
1.0
1.5
2.0
2.5
3.0
R_0^A

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

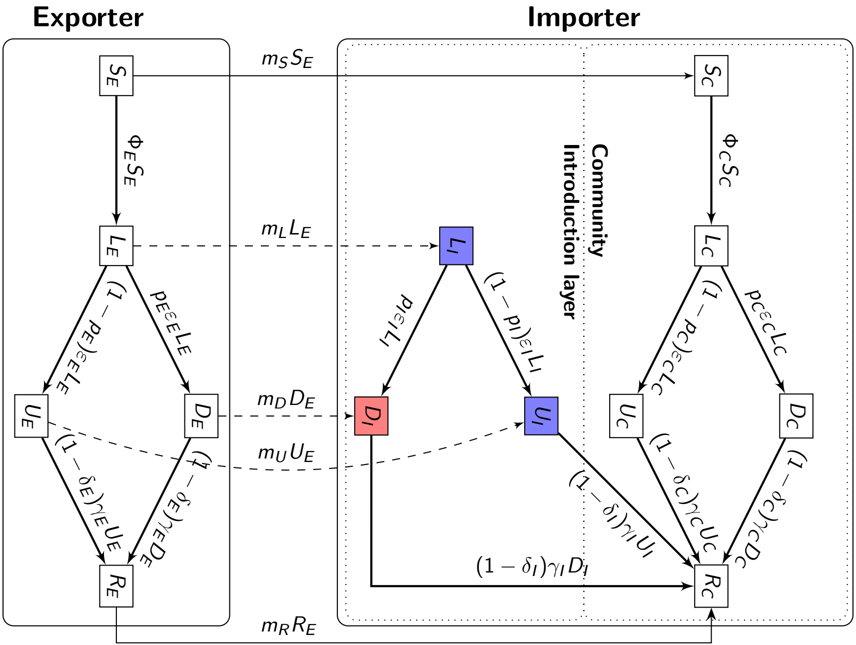
- Choose $\hat{I}$ too small and the stochastic phase will not last long

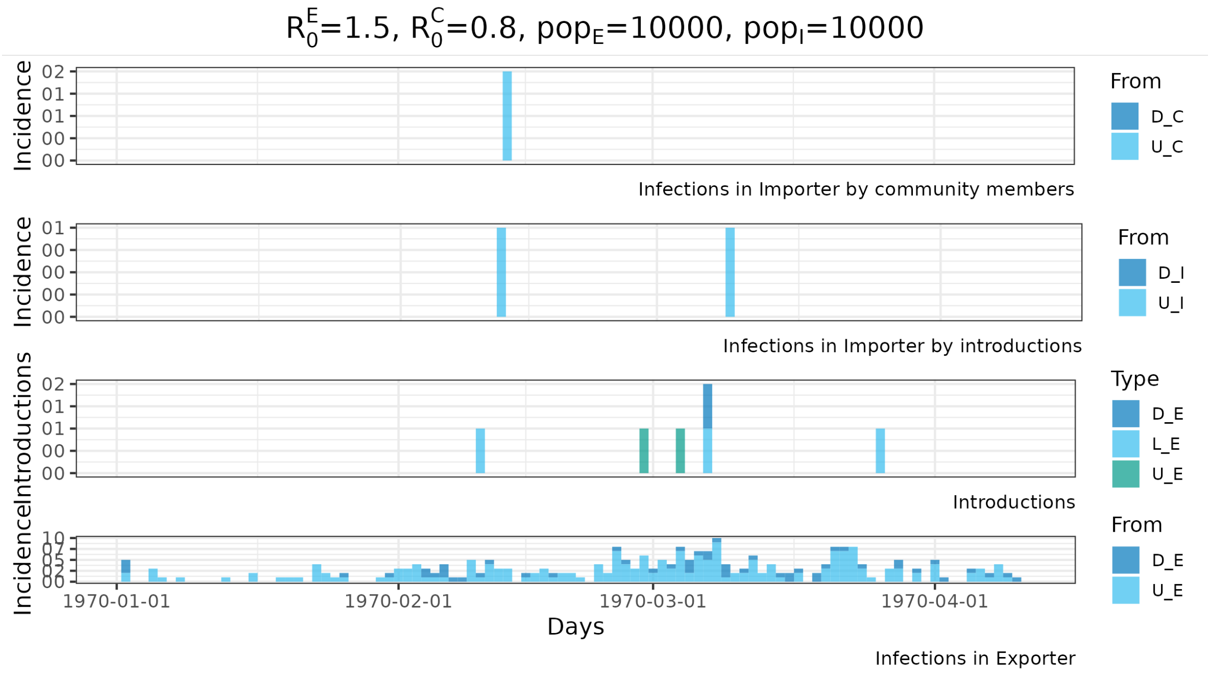
- Choose $\hat{I}$ too large and absorption will only be at the DFE

- So, how does one choose $\hat{I}$?
  - A formula of Whittle (1955)
  - Multitype branching process (MTBP)

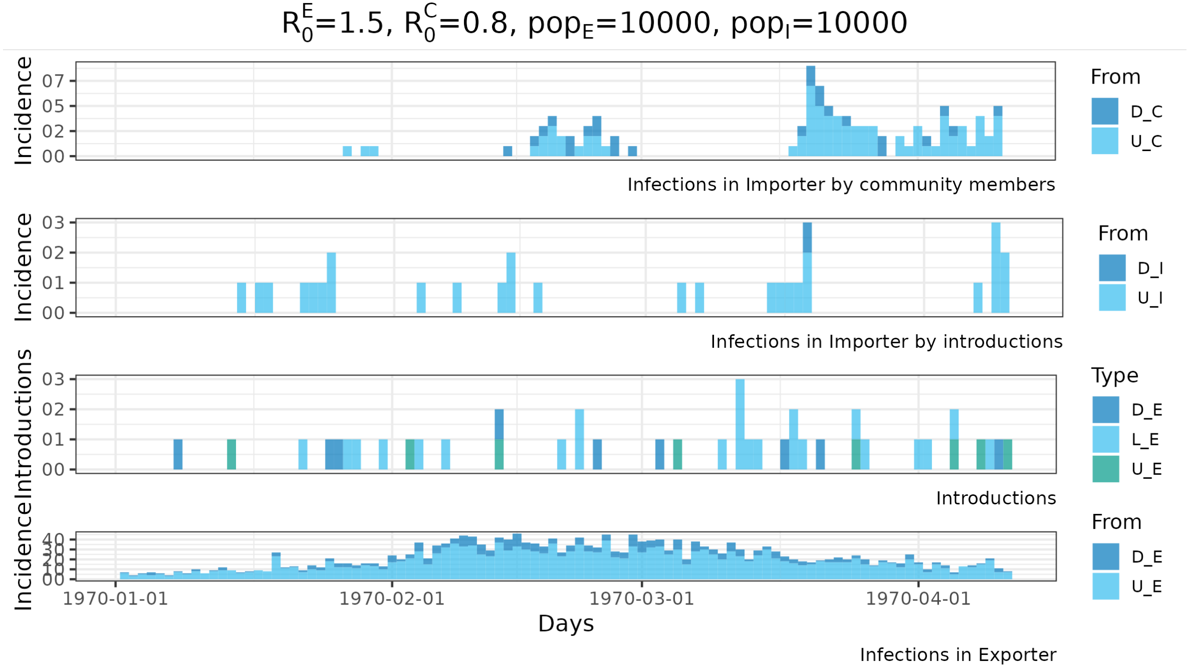
Continuous time Markov chains

- ODE and CTMC
- Simulating CTMC (in theory)
- **Value of travel control measures**
- Conclusions

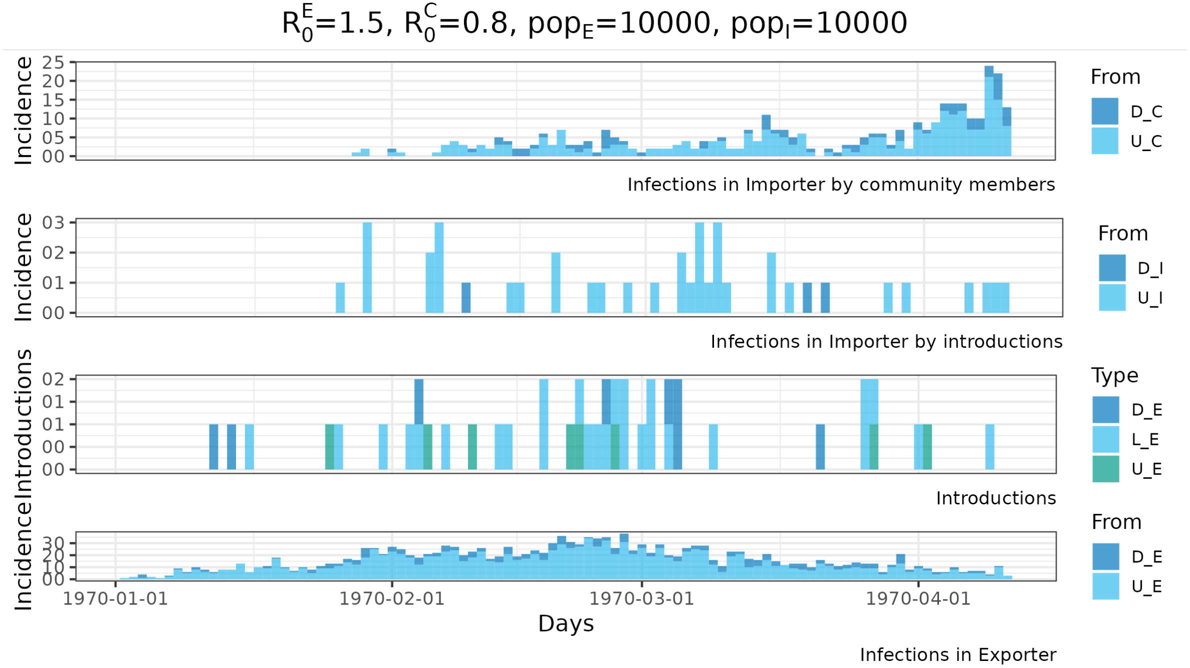

Exporter
Importer
S_E
L_E
U_E
D_E
R_E
$\Phi_E S_E$
$(1-p_E)\varepsilon_E L_E$
$p_E \varepsilon_E L_E$
$(1-\delta_E)\gamma_E U_E$
$(1-\delta_E)\gamma_E D_E$
$m_S S_E$
$m_L L_E$
$m_D D_E$
$m_U U_E$
$m_R R_E$
Introduction layer
Community
L_I
D_I
U_I
$p_I \varepsilon_I L_I$
$(1-p_I)\varepsilon_I L_I$
$(1-\delta_I)\gamma_I U_I$
$(1-\delta_I)\gamma_I D_I$
S_C
L_C
U_C
D_C
R_C
$\Phi_C S_C$
$(1-p_C)\varepsilon_C L_C$
$p_C \varepsilon_C L_C$
$(1-\delta_C)\gamma_C U_C$
$(1-\delta_C)\gamma_C D_C$



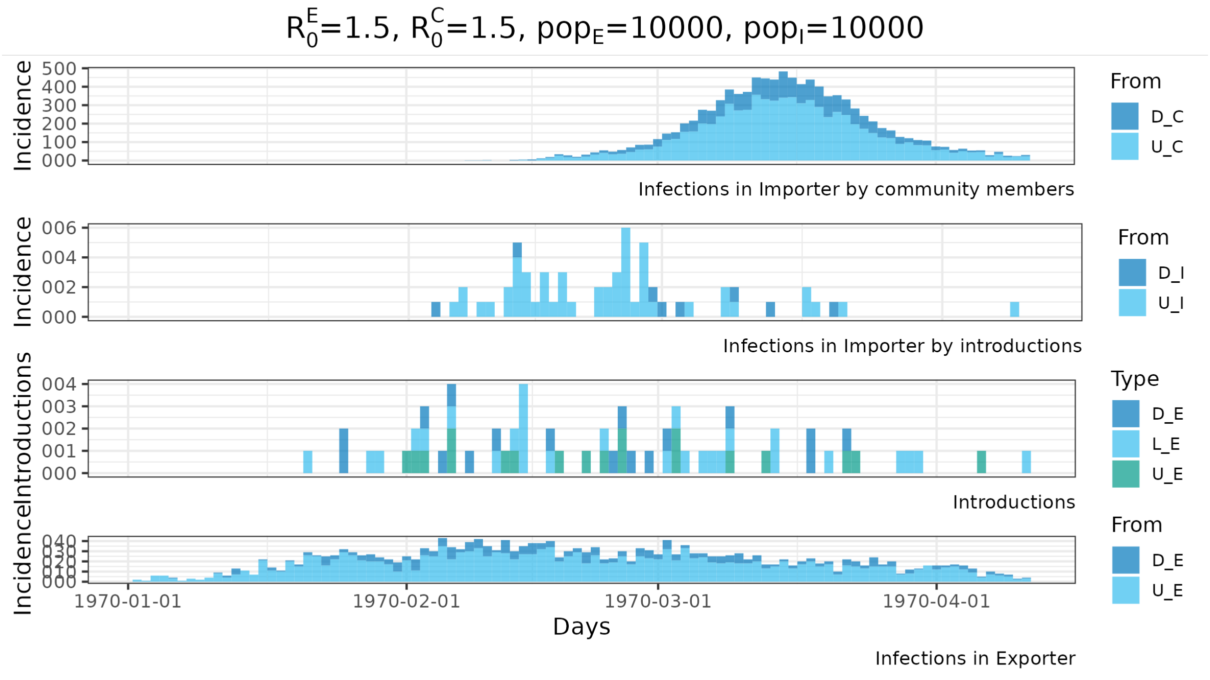
R_0^E=1.5, R_0^C=0.8, pop_E=10000, pop_I=10000
Incidence
02
01
01
00
00
From
D_C
U_C
Infections in Importer by community members
Incidence
01
00
00
00
00
From
D_I
U_I
Infections in Importer by introductions
Introductions
02
01
01
00
00
Type
D_E
L_E
U_E
Introductions
Incidence
10
07
05
02
00
From
D_E
U_E
1970-01-01
1970-02-01
1970-03-01
1970-04-01
Days
Infections in Exporter



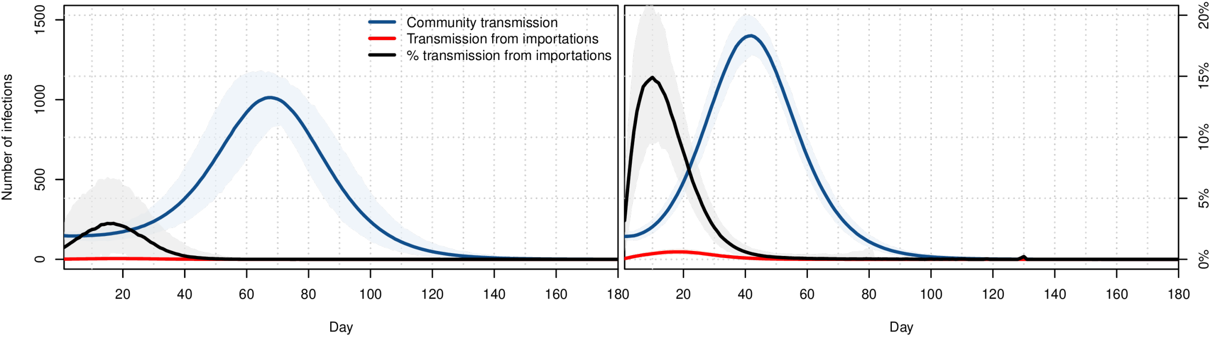
R_0^E=1.5, R_0^C=0.8, pop_E=10000, pop_I=10000
Incidence
07
05
02
00
From
D_C
U_C
Infections in Importer by community members
Incidence
03
02
01
00
From
D_I
U_I
Infections in Importer by introductions
Introductions
03
02
01
00
Type
D_E
L_E
U_E
Introductions
Incidence
40
30
20
10
00
From
D_E
U_E
1970-01-01
1970-02-01
1970-03-01
1970-04-01
Days
Infections in Exporter



R_0^E=1.5, R_0^C=0.8, pop_E=10000, pop_I=10000
Incidence
From
D_C
U_C
Infections in Importer by community members
Incidence
From
D_I
U_I
Infections in Importer by introductions
Introductions
Type
D_E
L_E
U_E
Introductions
Incidence
From
D_E
U_E
1970-01-01
1970-02-01
1970-03-01
1970-04-01
Days
Infections in Exporter



R_0^E=1.5, R_0^C=1.5, pop_E=10000, pop_I=10000
Incidence
500
400
300
200
100
000
From
D_C
U_C
Infections in Importer by community members
Incidence
006
004
002
000
From
D_I
U_I
Infections in Importer by introductions
Introductions
004
003
002
001
000
Type
D_E
L_E
U_E
Introductions
Incidence
040
030
020
010
000
From
D_E
U_E
1970-01-01
1970-02-01
1970-03-01
1970-04-01
Days
Infections in Exporter



Community transmission
Transmission from importations
% transmission from importations
Number of infections
0
500
1000
1500
20
40
60
80
100
120
140
160
180
Day
0%
5%
10%
15%
20%

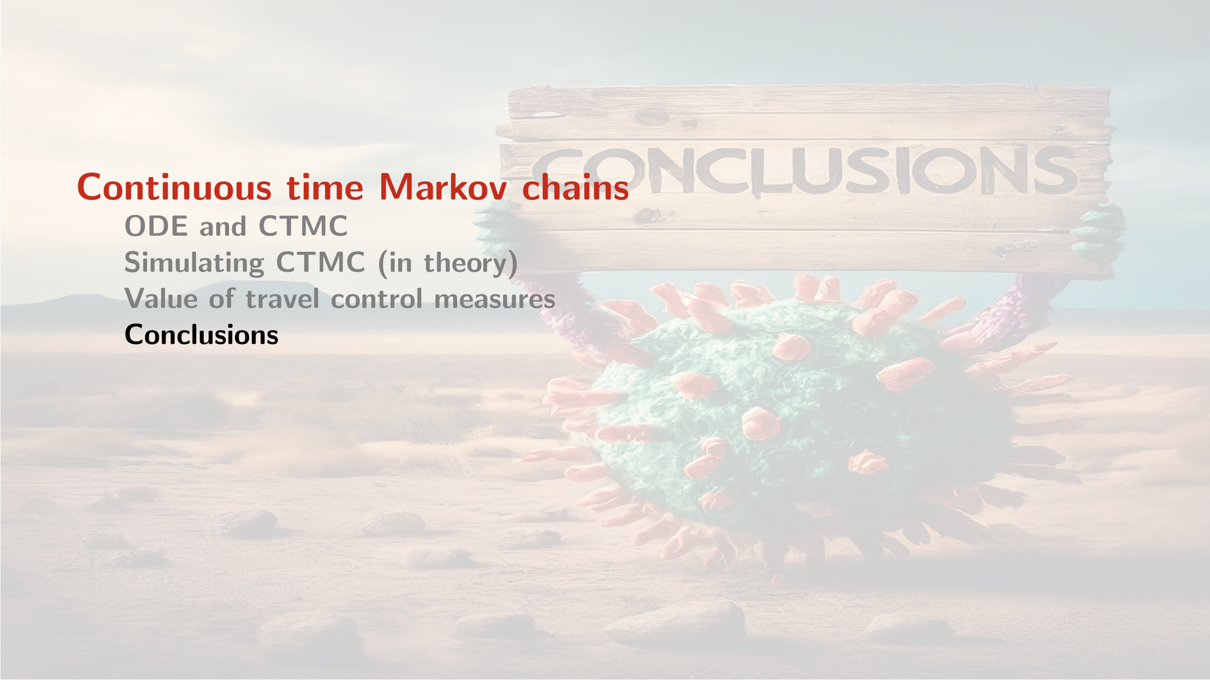
Continuous time Markov chains

ODE and CTMC

Simulating CTMC (in theory)

Value of travel control measures

Conclusions



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.*

Why incorporate stochasticity?

Stochasticity in deterministic models

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.

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?

Mean Offspring

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

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

Expected Population Size

Using the law of total expectation, we 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: