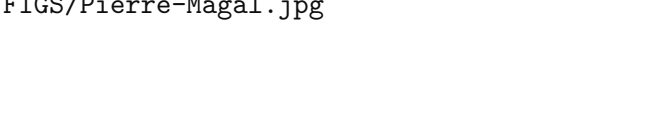
Pierre Magal
(1968 – 2024-02-20)



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"

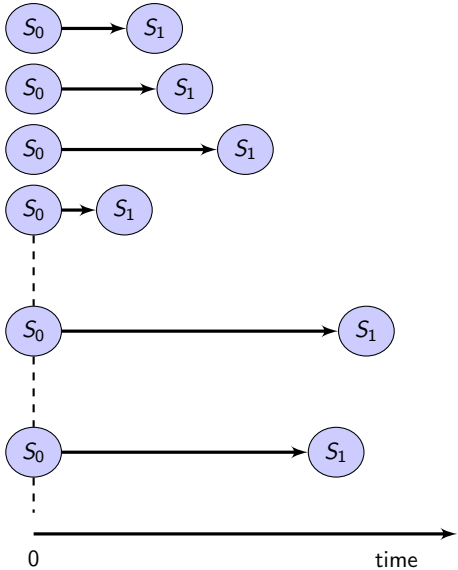
The states can be anything:

- 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


S_0
S_1
S_0
S_1
S_0
S_1
S_0
S_1
S_0
S_1
S_0
S_1
0
time

A distribution of probability is a model

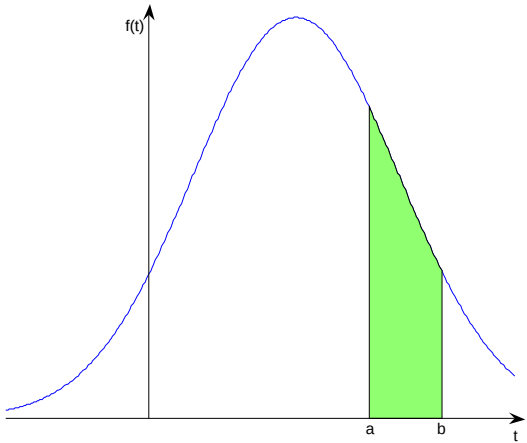
From the sequence of experiments, we deduce a model, which in this context is called a **probability distribution**

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

Probability density function

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

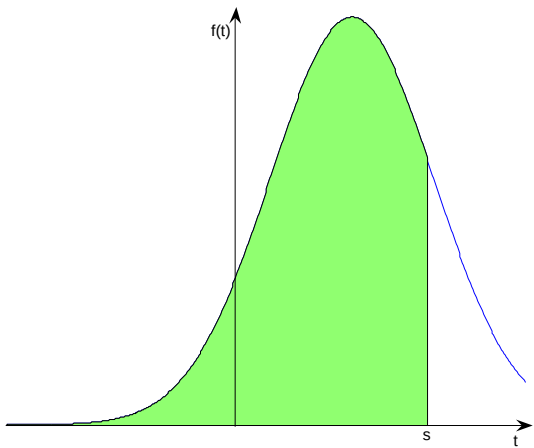
- $f \geq 0$
- $\int_{-\infty}^{+\infty} f(s)ds = 1$
- $\mathbb{P}(a \leq T \leq b) = \int_a^b f(t)dt$



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 S_0 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 S_0 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:

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

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

Hazard rate

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

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

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

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

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 S_0 is of the form $\mathcal{S}(t) = e^{-\theta t}$, 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 $\omega > 0$,

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

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

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

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

Then (4) takes the form

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

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

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

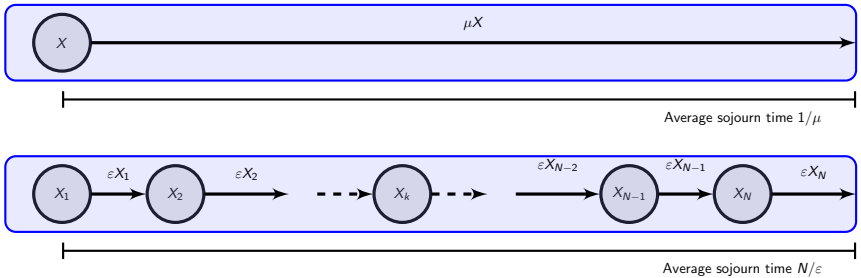
Let X_i be independent exponentially distributed random variables with parameter ξ and $Y = \sum_{i=1}^{n} X_i$

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)
}
```

```r
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
```

```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)

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 $P(t - t_0)$ 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)

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

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

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

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

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

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

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

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

In this case (8) becomes

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

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)

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

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

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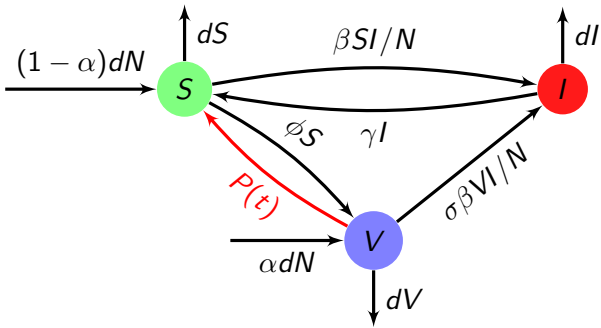
(Communicated by Linda Allen)

A model with vaccine efficacy and waning

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

Model structure



Parametres

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

- Disease transmission: standard incidence
- Vaccination of newborns
- Birth and death rate equal ($\Rightarrow$constant total population)

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

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

The SIS model with vaccination

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

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

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

Obtaining the initial condition

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

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

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 $P(\tau) = \exp\left(-\int_0^\tau \eta(q)dq\right)$. It is assumed that P is a survival function

Inflow in class-age zero is

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

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

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

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

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

Let

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

Theorem 2

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

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

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

where to simplify notation, we denote

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

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

$\mathcal{R}_0$

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

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

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

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

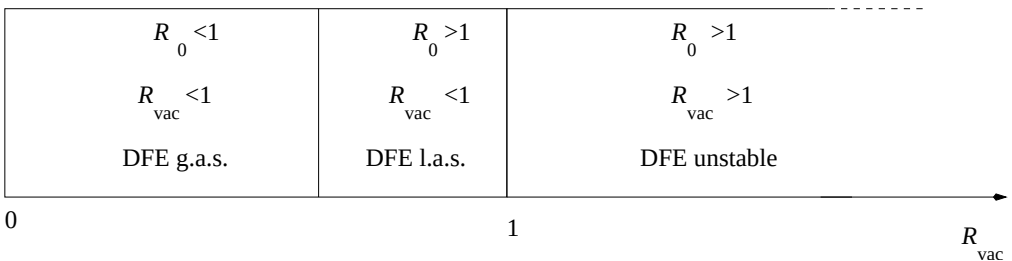
in such a way that $\tilde{P} < 1/d$

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

Theorem 3

System (11) *with an arbitrary loss of vaccination function* $P(t)$ *always admits the disease-free equilibrium*

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



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

As before, two examples

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

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

Case reducing to an ODE system

Assume $P(v) = e^{-\theta v}$, $\theta > 0$. $V_0(t) = V_0(0)e^{-(d+\theta)t}e^{-\int_0^t \sigma\beta I(x)dx}$ from (13). Then (11a) and (14) give the ODE system

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

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

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

From Theorem 3 the DFE always exists, with

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

Backward bifurcation

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

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

where

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

with

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

from (15).

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

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

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

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

By standard planar ODE arguments the following can be shown

Theorem 4

For the ODE system (16) with $V(0) \geq 0$, $I(0) > 0$, and $\mathcal{R}_0 > 1$

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

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

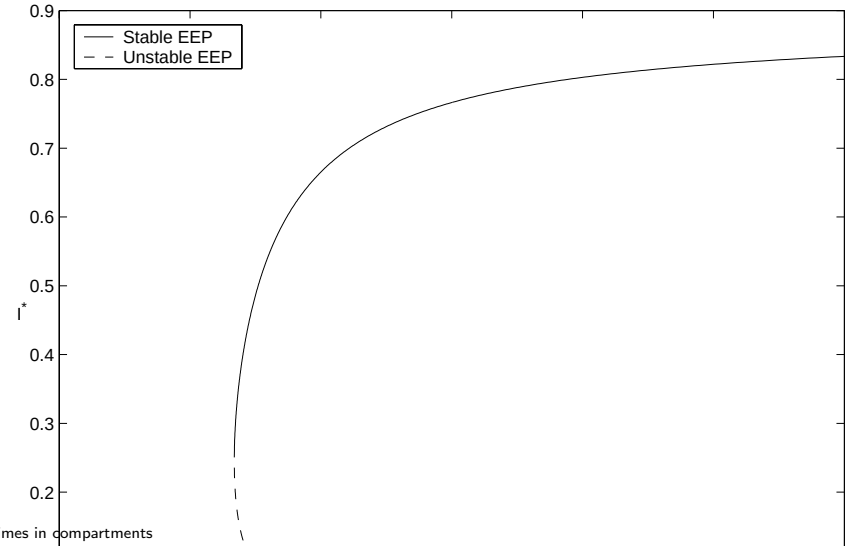
(iii) if $\mathcal{R}_v > 1$, then the unique EEP is globally asymptotically stable in $\mathcal{D} \setminus \{I = 0\}$

Pertussis:

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

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

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



Step function case: a delay integral model

Suppose that

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

Since $V_0(t) = 0$ for $t > \omega$, with $S = 1 - I - V$ the integral equation (11b) becomes, for $t > \omega$

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

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

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

$$\begin{aligned}\frac{d}{dt}V(t) = {} & \phi(1 - I(t) - V(t)) \\ & - \phi(1 - I(t-\omega) - V(t-\omega))e^{-d\omega}e^{-\sigma\beta\int_{t-\omega}^{t} I(x)dx} \\ & - \sigma\beta IV - dV + \alpha d\left(1 - e^{-d\omega}e^{-\sigma\beta\int_{t-\omega}^{t} I(x)dx}\right)\end{aligned} \tag{18b}$$

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

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

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

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

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

Finding the EEP's

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

$$V^\star = f(I^\star) = g(I^\star) \tag{21}$$

where

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

for $\sigma < 1$, and

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

Visualising and locating the bifurcation

From the nullcline equations, an EEP exists iff there exists an $I^\star \in (0, 1]$ such that equations (21)-(23) hold. So we study the zeros of

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

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

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

to show the dependence on these parameters.

Proceed as follows

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

Step 4 is carried out using the MatLab `fzero` function

Further precision can be gained by showing that

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

and that, for $\sigma < 1$

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

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

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

In between these two situations $\mathcal{R}_v = \mathcal{R}_c$ and there is one endemic equilibrium $I^\star$. Using the same procedure as for the visualisation of the bifurcation, it is possible to compute $\mathcal{R}_c$ by finding the value $I^\star$ such that $H(I^\star, \mathcal{A}) = 0$ and $H'(I^\star, \mathcal{A}) = 0$, for a given parameter $a_i \in \mathcal{A}$

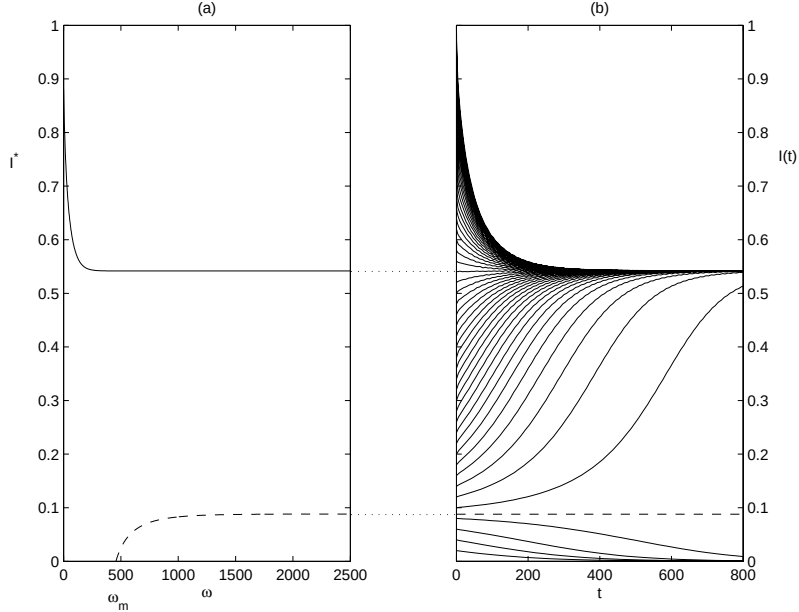
If $\mathcal{R}_v > 1$ then $H(0) > 0$ and so there is an odd number of endemic equilibria. Numerical simulations indicate that there is a unique EEP

Numerical bifurcation analysis

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

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

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



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

Age of vaccination

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

We used age of vaccination to find the initial condition of (11)

Here we take a closer look at this type of model

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

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


FIGS/BowmanArinoMoghadas-2011-cover.png

How to model time between vaccine doses

$$S' = -fS - V_1(t,0) \tag{25a}$$

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

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

$$V_2{}' = V_1(t,a^\star) - \delta_2 f V_2(t) \tag{25d}$$

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

and boundary condition

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

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

Simplifying a bit

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

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

Define

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

and substitute into (26), giving

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

So the distributed delay is now discrete

Simplifying a bit more

Let

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

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

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

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

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

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

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

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

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

Conclusions on sojourn times

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

Continuous-time Markov chains

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

DTMC: transitions occur each Δt

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

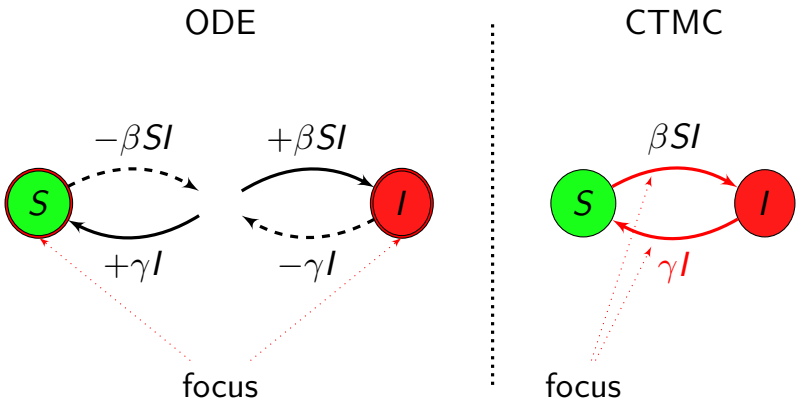
CTMC are roughly equivalent to ODE

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



SIS without demography

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

States are S, I

SIS with demography

Transition	Effect	Weight	Probability
$S \to S+1$	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	$\frac{\beta SI}{\beta SI + \gamma I}$
$I \to I-1,\ R \to R+1$	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. $\sum_{k=1}^{j} a_k(\mathbf{x}(t)) > \zeta_t \sum_j a_j(\mathbf{x}(t)) = \zeta_t \xi_t$
- 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, $N(t+\tau_t) = N(t) - 1$
- $t \leftarrow t + \tau_t$

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

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

t_f = 1000  # Final time

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

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

Last one did not go well

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

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

Tau-leaping (and packages) to the rescue!

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

Simulating a CTMC

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

Parallelisation

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

On the GitHub repo for the course, see

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

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

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

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

Benefit of parallelisation

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

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

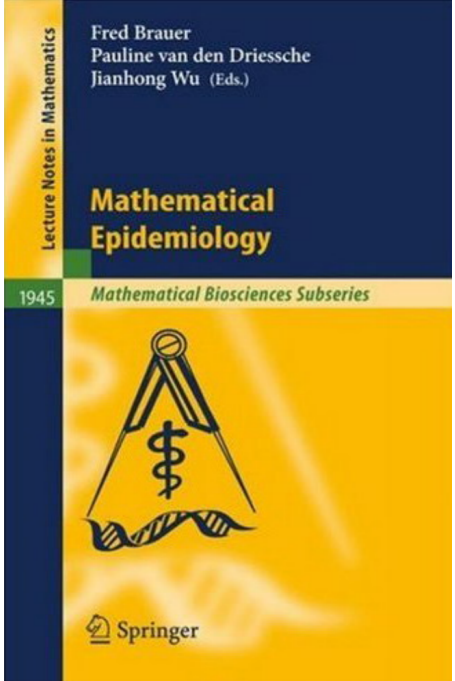
which gives ‘318.141 sec elapsed‘ on a 6C/12T Intel(R) Core(TM) i9-8950HK CPU @ 2.90GHz (4.75× faster) or ‘12.067 sec elapsed‘ versus ‘258.985 sec elapsed‘ on a 32C/64T AMD Ryzen Threadripper 3970X 32-Core Processor (21.46× faster !)

Age structure

Taking into account age can be important in some cases

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

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


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

Note on age

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

Indeed, if a is (chronological) age, then

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

Formulation of an SIR model

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

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

Governing equations are

$$(\partial_t + \partial_a)S(t,a) = \Lambda(a) - (\mu(a) + \lambda(t,a))S(t,a) \tag{28a}$$
$$(\partial_t + \partial_a)I(t,a) = -(\mu(a) + \gamma(a) + \delta(a))I(t,a) + \lambda(t,a)S(t,a) \tag{28b}$$
$$(\partial_t + \partial_a)R(t,a) = \gamma(a)I(t,a) \tag{28c}$$

Boundary conditions are

$$S(t, a_0) = B \tag{28d}$$
$$I(t, a_0) = 0 \tag{28e}$$
$$R(t, a_0) = 0 \tag{28f}$$

while initial conditions take the form

$$S(0, a) = \Phi(a) \tag{28g}$$
$$I(0, a) = \Psi(a) \tag{28h}$$
$$R(0, a) = 0 \tag{28i}$$

Force of infection

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

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

where

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

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

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

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

Then

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

Analysis of the SIR model

We seek the DFE by setting $I = 0$

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

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

where

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

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

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

Then

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

and we obtain the linearisation

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

Let

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

and denote

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

Then

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

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

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

Therefore

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

Let then

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

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

We have

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

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

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

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

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

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

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

Analysis using semigroups: SIA model

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

The model is almost equivalent to (28), with a few differences

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

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

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

$$(\partial_t + \partial_a)S(t,a) = \Lambda(a) - (d(a) + \lambda(t,a))S(t,a) \tag{30a}$$
$$(\partial_t + \partial_a)I(t,a) = -(d(a) + \gamma(a))I(t,a) + \lambda(t,a)S(t,a) \tag{30b}$$
$$(\partial_t + \partial_a)A(t,a) = \gamma(a)A(t,a) - (d(a) + \delta(a))A(t,a) \tag{30c}$$

Assume

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

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

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

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

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

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

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

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

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

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

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

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

an operator from $X \to X$

Let $\Omega = \{f \in X,\ 0 \le f \le 1 \text{ a.e.}\}$. Then (31) takes the form

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

Let

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

We have

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

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

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

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

with

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

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

where we denoted

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

$\mathcal{R}_0$

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

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

Pair formation

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

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

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

The following conditions must hold

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