Modelling Infectious Diseases

Mathematical Models of Infectious Diseases

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Introduction

- There are countless of infectious agents that can infect human, animal and plant hosts.
- They can be transmitted directly between hosts via respiratory air droplets or bodily fluids.
- They can also be transmitted indirectly through an intermediary source, for instance via mosquitoes, ticks, rodents, environmental particles or contaminated blood products.
- Infectious agents evolve and transform while new agents emerge regularly, implying their supply can be considered infinite.

Introduction

- Microscopically small infectious agents with relatively short life spans, which replicate within their hosts are called microparasites such as viruses, bacteria and fungi.
- Larger infectious agents with relatively longer life spans called macroparasites such as parasitic worms.
- Many infectious agents live inside or on the surface of their hosts' bodies without causing illness or even discomfort. In fact, hosts even depend for their survival on infectious agents (e.g., bacteria in the human gut).
- Infectious agents causing disease in their hosts are often referred to as pathogens.
- Infectious diseases are caused by pathogens, which are transmissible between hosts, either directly or indirectly.

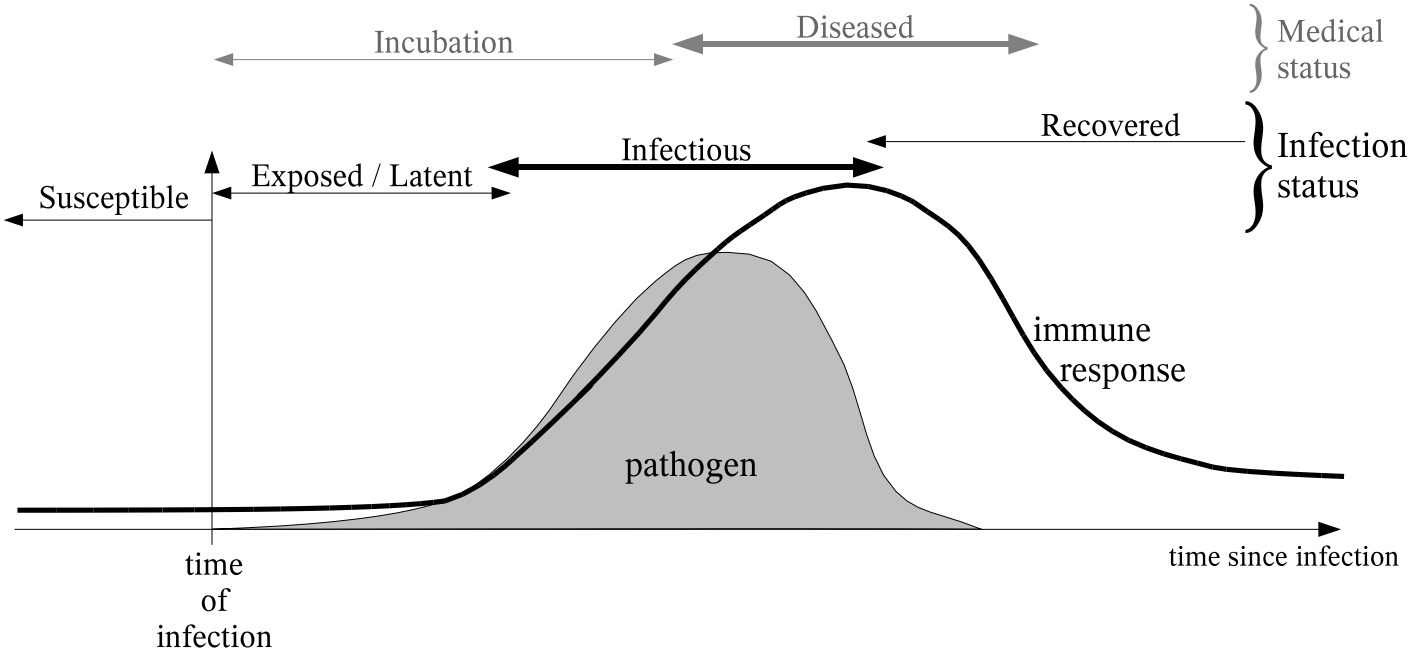
Introduction

An infectious disease is often characterized by its

- transmission route
- transmission potential
- natural history
  - incubation time
  - latent or pre-infectious period
  - infectious period
- acquired immunity
- symptomatic/asymptomatic

Natural history

The Infectious Disease Process:



Keeling and Rohani (2008)

Transmission routes

- Close contacts transmission (Varicella, Influenza, Mumps, Tuberculosis, Measles, ...)
- Sexual transmission (Hepatitis B, HIV, HPV, ...)
- Parenteral transmission (Hepatitis B and C, HIV, ...)
- Orofecal transmission (Hepatitis A, Cholera, Rotavirus, ...)
- Vertical transmission (Hepatitis B and C, HIV, Syphilis, ...)
- Vectorborne transmission (Malaria, Dengue, Leishmaniasis, ...)
- ...

Historic pandemics

- Plague of Justinian, from 541 to 750, killed between 50% and 60% of Europe's population
- The Black Death of 1347 to 1352 killed 25 million in Europe over 5 years (estimated to be between 25 and 50% of the populations of Europe, Asia, and Africa - the world population at the time was 500 million)
- The introduction of smallpox, measles, and typhus to the areas of Central and South America by European explorers during the 15th and 16th centuries caused pandemics among the native inhabitants
- Between 1518 and 1568 disease pandemics are said to have caused the population of Mexico to fall from 20 million to 3 million

Historic pandemics

- The first European influenza epidemic occurred between 1556 and 1560, with an estimated mortality rate of 20%
- Smallpox killed an estimated 60 million Europeans during the 18th century
- In the 19th century, tuberculosis killed an estimated one-quarter of the adult population of Europe; by 1918 one in six deaths in France were still caused by TB.
- The Influenza Pandemic of 1918 (or the Spanish Flu) killed 25-50 million people
- UNAIDS estimates that in 2013, 35 million people live with HIV and 1.5 million people died due to AIDS worldwide

Part I

Mathematical Models of Infectious Diseases

Outline

2 Introduction

3 Compartmental Models

- Discrete time models
- A mathematical intermezzo
- Kermack and McKendrick's Model
  - The SIR model with vital dynamics
  - The SIR model with vital dynamics and vaccination
- Building your own model
- Transmission within multiple subpopulations
- Who Acquires Infection From Whom?

4 Epilogue

Mathematical modelling of infectious diseases

- Purposes:
  - prediction: requires the inclusion of known complexities and population-level heterogeneity
  - understanding: investigating the factors that drive dynamics
- Building a model presents a trade-off:
  - accuracy: reproduce what is observed and predict future dynamics
  - transparency: ability to understand how model components influence the dynamics and interact
  - flexibility: ease of adapting the model to new situations

Mathematical modelling of infectious diseases

- Limitations:
  - models present a simplification of reality
  - chance events of infectious disease transmission hinder perfect prediction
- A good model:
  - suited to its purpose: simple as possible, but no simpler
  - balance accuracy, transparency, flexibility
  - parametrisable from available data

Mathematical modelling of infectious diseases

- Daniel Bernoulli was the first to present a mathematical model for smallpox in 1760
- Since then many people have developed models to describe infectious disease dynamics, see e.g. Bailey (1975); Anderson and May (1991); Grenfell and Dobson (1995); Daley and Gani (1999); Hethcote (2000)
- see e.g. historical perspectives by Klaus Dietz.
- Several textbooks are available; amongst which Vynnycky and White (2010) provides an excellent introduction to mathematical modelling

Contact between individuals

- Predicting the number of infections at time $t+1$ based on the circumstance at time t
- The force of infection λ
  - the per capita rate at which a susceptible individual contracts infection
  - it is assumed proportional to the number of infectious persons at time t and depending on how the contact structure is assumed to change with population size N it is given by:

$$\lambda_t = \beta I_t$$
$$\lambda_t = \beta I_t / N_t$$

Contact between individuals

- The number of new infections at time $t+1$ is given by $\lambda_t S_t$ and thus:

$$I_{t+1} = \beta S_t I_t$$
$$I_{t+1} = \beta S_t I_t / N_t$$

  This is referred to as the mass action principle

- density-dependent transmission: $I_{t+1} = \beta S_t I_t$:
  - as the population size increases, so does the contact rate
  - mostly applicable to plant and animal diseases (homogeneity)
- frequency-dependent transmission: $I_{t+1} = \beta S_t I_t / N_t$:
  - the contact rate is assumed constant regardless of a change in population size
  - mostly applicable to human and vectorborne diseases (heterogeneity)

Contact between individuals

- Note that when in a constant population, both density- and frequency-dependent are equivalent

$$I_{t+1} = \beta S_t I_t / N_t = \beta S_t I_t / N = \tilde{\beta} S_t I_t$$

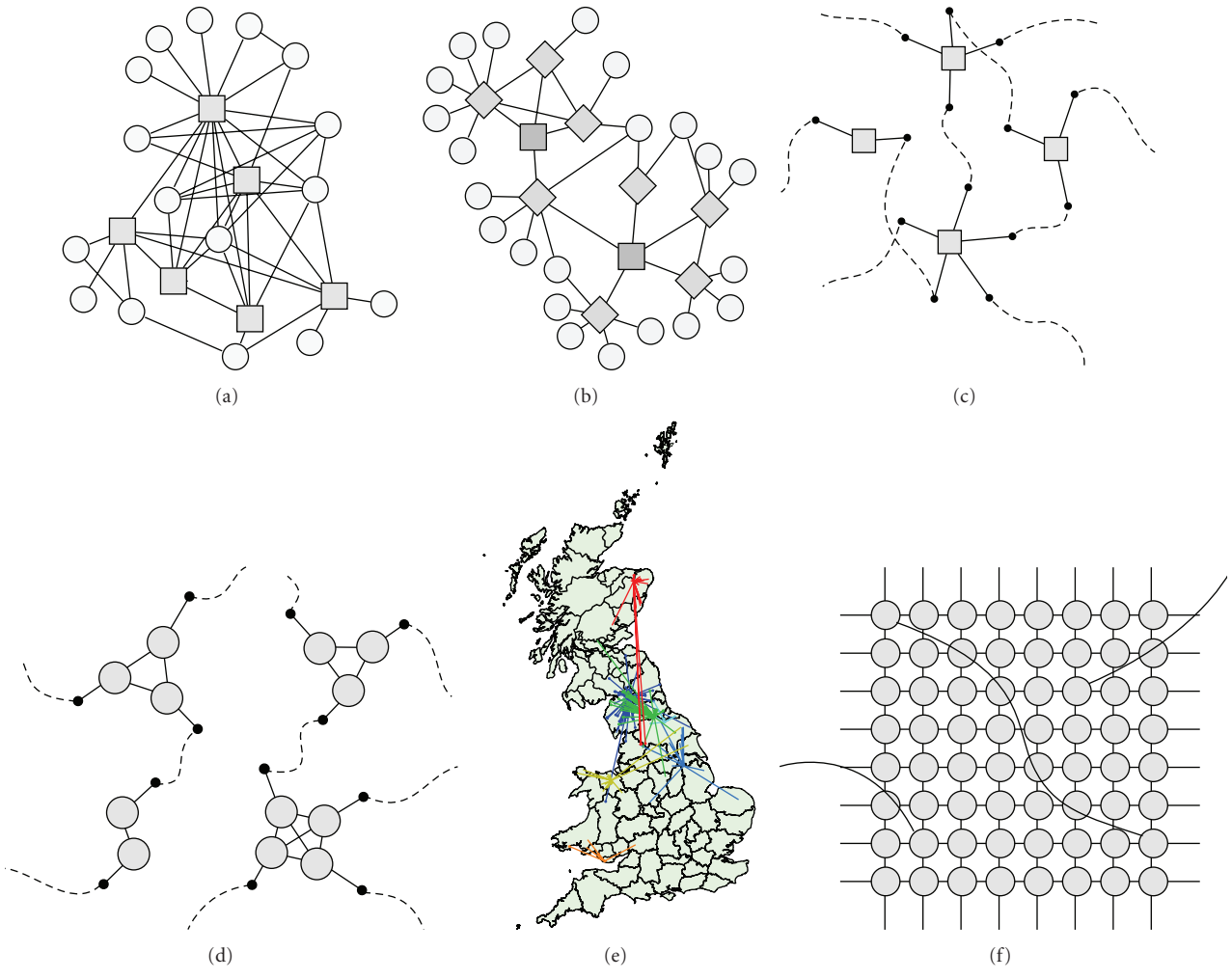
- In what follows I will use $I_{t+1} = \beta S_t I_t$ without loss of generality unless specified differently.

Contact between individuals

Heterogeneity

- airborne infections: age - example: children at school have more contacts with children of the same age
- sexually transmitted infections: age and sexual behavior
- temporal heterogeneity
  - seasonality,
  - week vs weekend,
  - holiday vs non-holiday, ...
- ...

Contact between individuals, plants, herds, . . .



Modeling frameworks

- compartmental models
  - the population is subdivided into broad subgroups (compartments)
  - individuals are tracked collectively
  - roughly either deterministic or stochastic (probabilistic)
    - deterministic models describe what happens 'on average' in a population
    - stochastic models allow the number of individuals who move between compartments to vary through chance
  - transmission dynamic or static models
- metapopulation models
- network models
- microsimulation or agent-based models

Rules of engagement

Entity	Symbol 1	Symbol 2
maternal immune	M (number)	m_{pi} (proportion)
susceptibles	S (number)	s (proportion)
exposed/latent*	E (number)	e (proportion)
infected	I (number)	i (proportion)
recovered	R (number)	r (proportion)
total population size	N (number)	-
age-stratified pop. size	$N(a)$ (number)	-
life expectancy	L (dec. number)	-
survivor function	-	m (proportion)
recovery rate	ν (rate)	-
force of infection	λ (rate)	-
transmission parameter	β (rate)	-
basic reproduction number	R_0 (dec. number)	-

*depending on the context e refers to $\exp(1) = 2.71828\ldots$

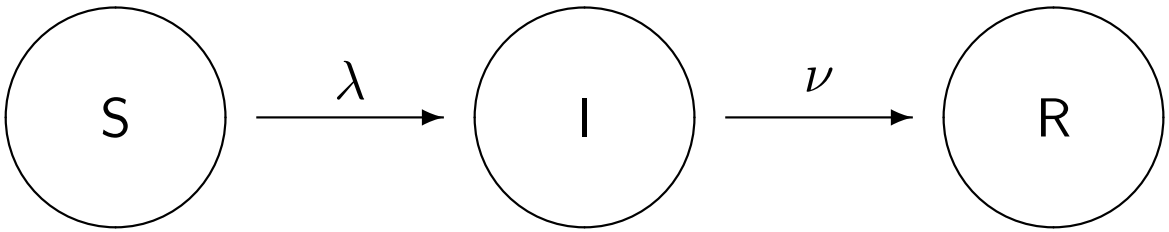
Table: Glossary of the most important symbols in this section.

The basic SIR compartmental model

- State variables
  S: susceptible individuals
  I: infectious individuals (able to transmit the infectious agent)
  R: removed/recovered ind. (not transmitting the infectious agent)
  $N = S + I + R$: total and constant population size
- Parameters
  β: transmission rate
  ν: recovery rate
- Force of infection
  follows the law of mass action: $\lambda_t = \beta I_t$
- $\rightarrow$ lifelong immunity after infection

Model formulation

- SIR model:



- Extensions
  - maternal immunity/passive immunity: MSIR
  - exposed or latent infection (pre-infectious): SEIR
  - waning of immunity: SIRS
  - susceptible upon recovery: SIS
  - infected for life: SI

The discrete time deterministic SIR model

- SIR compartmental model
- Equations:

$$\begin{aligned} S_{t+1} &= S_t - \lambda_t S_t \\ I_{t+1} &= I_t + \lambda_t S_t - \nu I_t \\ R_{t+1} &= R_t + \nu I_t \end{aligned}$$

with $N_{t+1} = S_{t+1} + I_{t+1} + R_{t+1} = S_t + I_t + R_t = N_t$.

- $\lambda_t = \beta I_t$ and ν are risks
- risks are related to rates as follows:

$$\text{risk} = 1 - e^{-\text{rate}}$$

- if the 'rate' is small:

$$\text{risk} \approx \text{rate}$$

The discrete time stochastic SIR model

- The number of newly infected cases arises from a stochastic process with mean $\beta I_t S_t$
- The number of newly recovered individuals arises from a stochastic process with mean $\nu_t I_t$
- What distribution would you assume for both these quantities?

The discrete time stochastic SIR model

- The number of newly infected cases arises from a stochastic process with mean $\beta I_t S_t$
- The number of newly recovered individuals arises from a stochastic process with mean $\nu_t I_t$
- What distribution would you assume for both these quantities?
  - a Poisson distribution
  - a binomial distribution
- What are the (dis)advantages for both distributions?

The discrete time deterministic SIR model

- When do you expect the number of new infections to decrease?
- Focus on the second equation:

$$I_{t+1} = I_t + \beta I_t S_t - \nu I_t$$

  clearly $I_{t+1} = I_t$ if $\beta S_t = \nu$
- The epidemic will
  - decrease if $S_t < \nu/\beta$
  - increase if $S_t > \nu/\beta$
- $\nu/(\beta N)$ is called the relative removal rate
- $N\beta/\nu = N\beta D$ is called the basic reproduction number R_0

  Here D denotes the average infectious period
- Consequently $\beta = R_0/(ND)$

R-code for the discrete stochastic SIR model

```
# R website : http://cran.r-project.org
# Initial parameters
N = 1E6 # Total population
I = 1 # Number of Infectious at time 0
S = N-1 # Number of Susceptibles at time 0
R = 0 # Number of Recovered at time 0

# Transmission parameters
R0 = 2.48 # Basic Reproduction number
nu = 1/6 # Recovery rate (in days)
b = nu*R0/N # Infection rate (in days)

# Initial states
Sold = S # Number of Susceptibles at time t=0
Iold = I # Number of Infectious at time t=0
Rold = R # Number of Recovered at time t=0
```

R-code discrete stochastic SIR model: option 1: Poisson

```
# Placeholders
Svec =Sold; Ivec = Iold; Rvec = Rold
stop = FALSE
# Loop - continue until stop = TRUE
while (!stop){
        Ih = rpois(1,b*Iold*Sold); print(Ih)
        Rh = rpois(1,nu*Iold)
        if ((Iold+Ih-Rh)<=0) break
        Sold = Sold-Ih
        if (Sold<=0){Rold=N; break}
        Iold = Iold+Ih-Rh
        Rold = Rold+Rh
        Svec = c(Svec,Sold)
        Ivec = c(Ivec,Iold)
        Rvec = c(Rvec,Rold)
        if (Iold==0){stop=T}
}
```

R-code discrete stochastic SIR model: option 2: Binomial

```
# Placeholders
Svec =Sold; Ivec = Iold; Rvec = Rold
stop = FALSE
# Loop - continue until stop=TRUE
while (!stop){
        Ih = rbinom(1,Sold,(1-exp(-b*Iold)))
        print(Ih)
        Rh = rbinom(1,Iold,(1-exp(-nu)))
        Sold = Sold-Ih
        Iold = Iold+Ih-Rh
        Rold = Rold+Rh
        Svec = c(Svec,Sold)
        Ivec = c(Ivec,Iold)
        Rvec = c(Rvec,Rold)
        if (Iold==0){stop=T}
}
```

Class exercise

- Run the discrete SIR model 100,000 times
- Keep track of the final size
- Study the distribution of final sizes. What do you observe?
- How does this distribution change with increasing R_0?
- What happens if R_0 decreases below 1?

The basic reproduction number

- Recall $R_0 = N\beta D$, the basic reproduction number
- What does R_0 represent?
- Consider the total number of new infections in the population between time t and $t+1$:

$$\beta I_t S_t$$

- At the start of an epidemic, say $t = 0$: $I_0 = 1$ and $S_0 = N$ and thus the total number of new infections between $t = 0$ and $t = 1$ equals

$$\beta N$$

- By the end of the infectious period of duration D time units, the infectious person would have infected βND individuals
- Therefore R_0 is the number of secondary cases caused by a single infective introduced into a wholly susceptible population of size N during the infective's infectious period.

The basic reproduction number

- R_0 constitutes a threshold:
  - if $R_0 > 1$ then the epidemic can grow
  - if $R_0 \leq 1$ then the epidemic will die out
- Using R_0, one defines the number of effective contacts by each person per unit time by

$$c_e = R_0/D.$$

- Therefore $\beta = c_e/N$ is the "per capita number of effective contacts made by a given individual per unit time", or equivalently "the per capita rate at which two specific individuals come into effective contact per unit time"
- For a given pathogen, it is difficult to define an effective contact
- More on this later on

Discrete time models: an alternative notation

- Other notation:

$$\begin{aligned} S_{t+\delta t} &= S_t - \lambda_t S_t \delta t \\ I_{t+\delta t} &= I_t + \lambda_t S_t \delta t - \nu I_t \delta t \\ R_{t+\delta t} &= R_t + \nu I_t \delta t \end{aligned}$$

  with δt symbolizing the size of a small time step.

- The time step in a discrete time model could be very important. Why?

- Next:

  $\rightarrow$ consider continuous time models

  $\rightarrow$ focus on deterministic continuous time models

From discrete to continuous time models

- Reordering the equation:

$$\begin{aligned}
\frac{S_{t+\delta t} - S_t}{\delta t} &= -\lambda_t S_t \\
\frac{I_{t+\delta t} - I_t}{\delta t} &= \lambda_t S_t - \nu I_t \\
\frac{R_{t+\delta t} - R_t}{\delta t} &= \nu I_t
\end{aligned}$$

From discrete to continuous time models

- Limit for $\delta t \to 0$:

$$\begin{aligned}
\lim_{\delta t \to 0} \frac{S_{t+\delta t} - S_t}{\delta t} &= -\lambda_t S_t \\
\lim_{\delta t \to 0} \frac{I_{t+\delta t} - I_t}{\delta t} &= \lambda_t S_t - \nu I_t \\
\lim_{\delta t \to 0} \frac{R_{t+\delta t} - R_t}{\delta t} &= \nu I_t
\end{aligned}$$

From discrete to continuous time models

- Using derivatives:

$$\begin{aligned}
\frac{dS_t}{dt} &= -\lambda_t S_t \\
\frac{dI_t}{dt} &= \lambda_t S_t - \nu I_t \\
\frac{dR_t}{dt} &= \nu I_t
\end{aligned}$$

Population dynamics: Malthus (1798)

Evolution is determined by the balance between births and deaths:

$$\frac{dx}{dt} = bx - mx = (b - m)x \equiv rx.$$

- For $r = 0$, steady population:

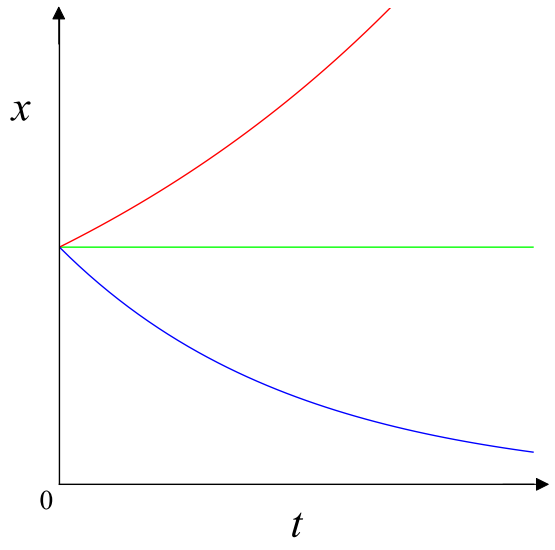
$$x(t) = x(0).$$

- For $r > 0$, exponential growth:

$$x(t) = x(0)\, e^{|r|t}.$$

- For $r < 0$, exponential decay:

$$x(t) = x(0)\, e^{-|r|t}.$$



Population dynamics: Verhulst (1836)

Some limiting factor must prevent the population to grow indefinitely:

$$\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right).$$

- All solutions scale to one:

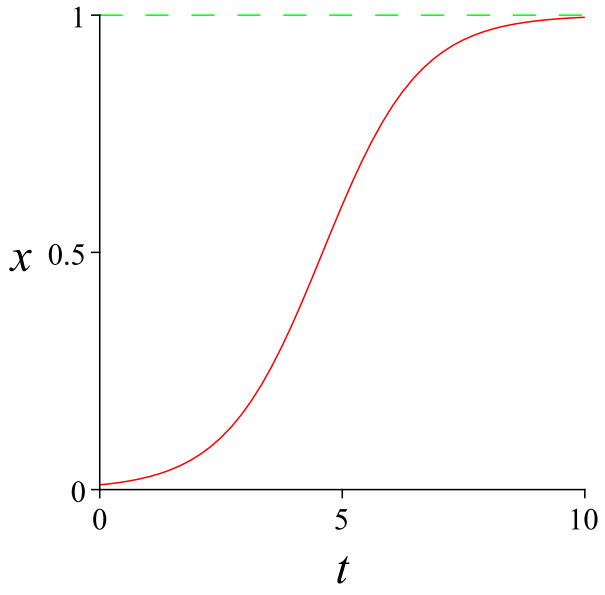
$$t \to r^{-1}t, \quad x \to Kx.$$

- Analytical solution:

$$x(t) = \frac{x(0)\,e^t}{1 + x(0)(e^t - 1)}.$$

- Horizontal asymptote:

$$\lim_{t\to+\infty} x(t) = 1.$$



Linear stability analysis

Steady states are points where evolution stops:

$$\frac{dx}{dt} = F(x) = x(1-x) = 0 \quad \longrightarrow \quad x = 0, 1.$$

- Small deviation from 0 increases:

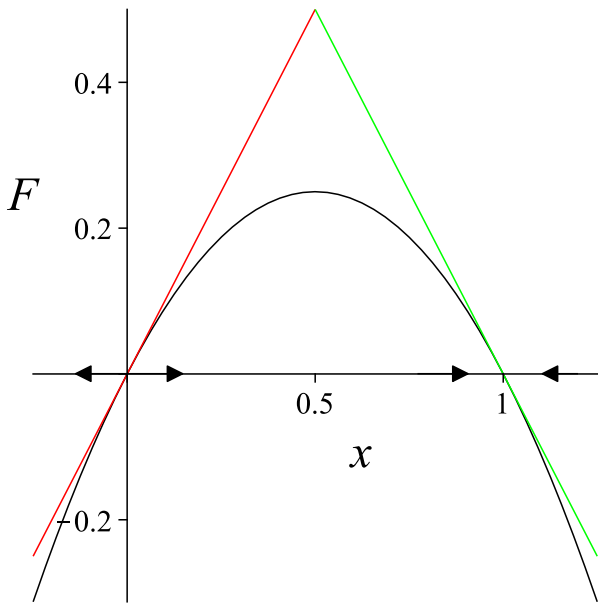
  $$x(t) = \delta x(t) \to \delta x(t) \propto e^{t},$$

  the steady state is unstable.

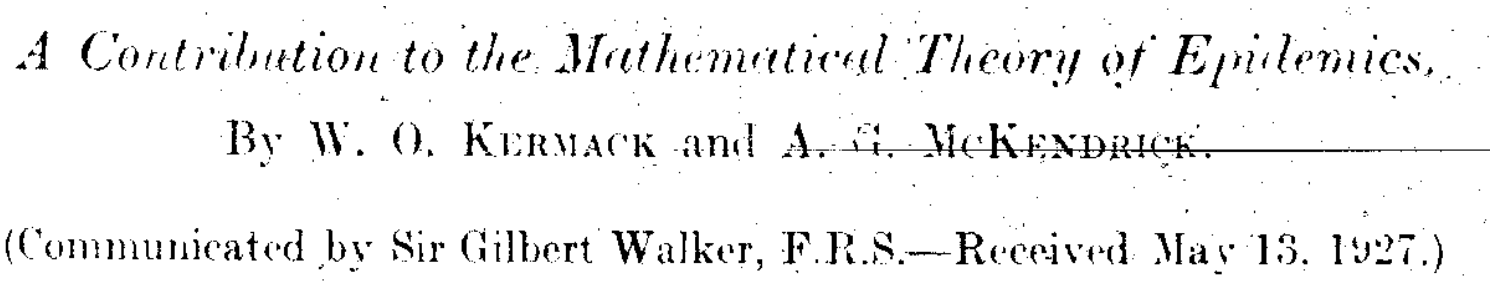
- Small deviation from 1 decreases:

  $$x(t) = 1 - \delta x(t) \to \delta x(t) \propto e^{-t},$$

  the steady state is stable.



A Contribution to the Mathematical Theory of Epidemics



A Contribution to the Mathematical Theory of Epidemics.

By W. O. Kermack and A. G. McKendrick.

(Communicated by Sir Gilbert Walker, F.R.S.—Received May 13, 1927.)

more than a contribution, a basis...

"Reference may here be made to the work of Ross and Hudson (1915-17) in which the same problem is attacked. The problem is here carried to a further stage, and it is considered from a point of view which is in one sense more general.[...]"

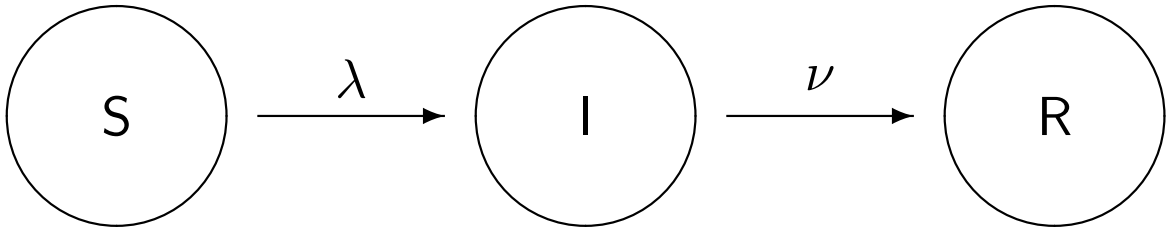
Kermack and McKendrick (1927)

Kermack-McKendrick's model

The SIR model without vital dynamics
(and without a general infectious period distribution)

- State variables
  S: Susceptible individuals
  I: Infectious individuals (able to transmit the infectious agent)
  R: Removed/Recovered ind. (not transmitting the infectious agent)
  $N = S + I + R$: Total (and constant) population
- Parameters
  β: transmission rate
  ν: recovery rate
- Force of infection (frequency dependent mass action)
  follows the law of mass action: $\lambda(t) = \beta \frac{I(t)}{N}$

The SIR model



$$\begin{aligned}
\frac{dS(t)}{dt} &= -\beta S \frac{I}{N}, \\
\frac{dI(t)}{dt} &= \beta S \frac{I}{N} - \nu I, \\
\frac{dR(t)}{dt} &= \nu I,
\end{aligned}$$

with $N = S + I + R$.

Note that the time dependence is not always made explicit in the notation; here in the right-hand side (RHS) of the equation.

Analytic approximation of the incidence

- Let s, i, r denote the proportion of population in the susceptible, infectious and removed classes, respectively:

$$s = \frac{S}{N}, \; i = \frac{I}{N}, \; r = \frac{R}{N},$$

$\tau = \nu t$, $\sigma = \frac{\beta}{\nu}$.

- The equations for the SIR model can be written as

$$\begin{aligned} \frac{ds(\tau)}{d\tau} &= -\sigma si, \\ \frac{di(\tau)}{d\tau} &= \sigma si - i, \\ \frac{dr(\tau)}{d\tau} &= i, \end{aligned}$$

with $s + i + r = 1$.

Analogy with ecology

- For very slow recovery, $\sigma >> 1$, the system reduces to

$$\begin{aligned} \frac{ds}{d\tau} &= -\sigma si, \\ \frac{di}{d\tau} &= \sigma si, \end{aligned}$$

  with $s + i = 1$.

- It is equivalent to two logistic equations

$$\begin{aligned} \frac{ds}{d\tau} &= -\sigma s(1-s), \\ \frac{di}{d\tau} &= \sigma(1-i)i. \end{aligned}$$

Analytic approximation of the incidence

- Substituting $i = 1 - s - r$ in 1st and 3rd equation of system our SIR model:

$$\begin{aligned} \frac{dr}{d\tau} &= 1 - s - r \\ \frac{ds}{dr} &= -\sigma s \end{aligned}$$

with initial values $s(0) = s_0$ and $r(0) = 0$, one obtains

$$\frac{dr}{d\tau} = 1 - s_0 e^{-\sigma r} - r.$$

- Assuming $\sigma r \ll 1$ and developing the exponential term

$$\frac{dr}{d\tau} \approx 1 - s_0 + (s_0\sigma - 1)(r) + \frac{1}{2} s_0 \sigma^2 r^2 := F(r).$$

Analytic approximation of the incidence

- Analytic solution

$$r(t) = \frac{1}{\sigma^2 s_0}\left(\sigma s_0 - 1 + \sqrt{-q}\tanh(\frac{\sqrt{-q}}{2}t - \varphi)\right)$$

where

$$\sqrt{-q} = \sqrt{(\sigma s_0 - 1)^2 + 2 s_0 i_0 \sigma^2}$$

and

$$\varphi = \tanh^{-1}\left(\frac{\sigma s_0 - 1}{\sqrt{-q}}\right)$$

Analytic approximation of the incidence

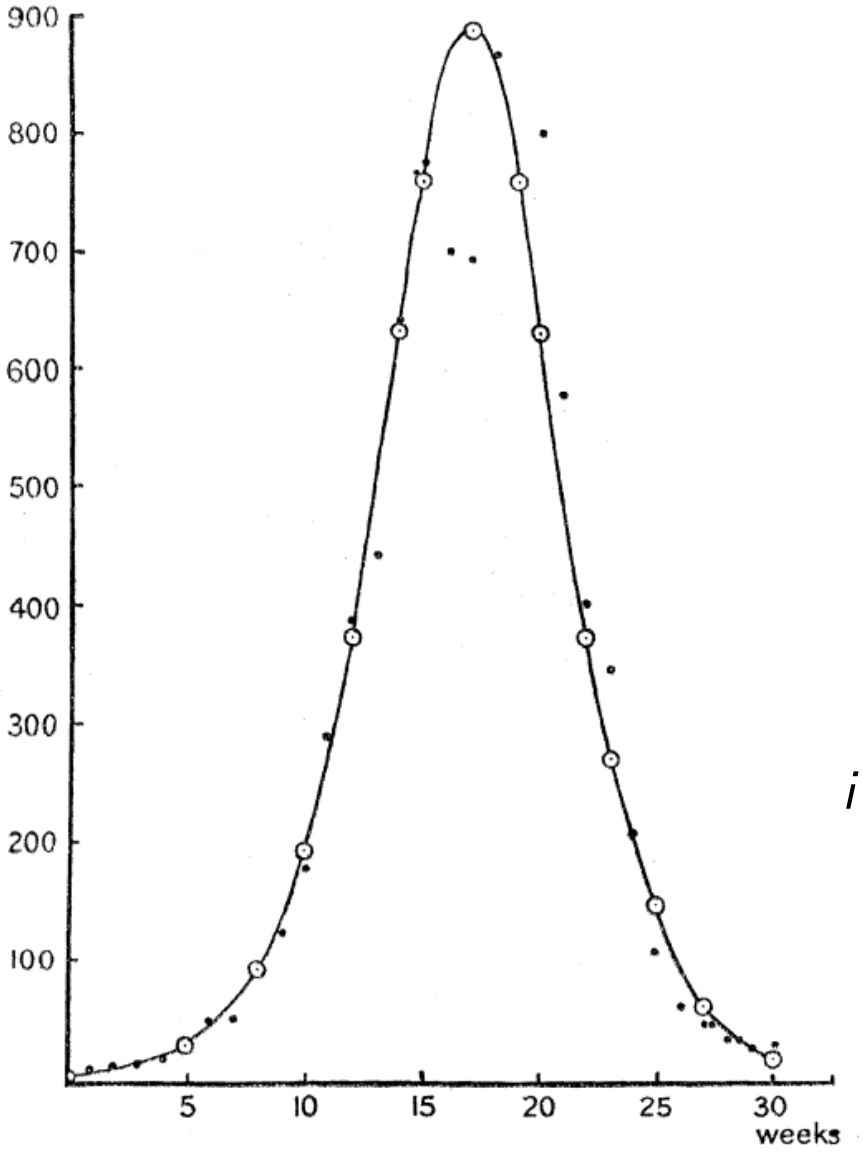
- Finally, since

$$i(t) = \frac{dr}{dt}$$

$$i(t) = \frac{1}{2s_0\sigma^2}\sqrt{-q}\cosh^{-2}\left(\frac{\sqrt{-q}}{2}t - \varphi\right)$$

- Application: Plague-related deaths in Bombay (1905-1906)

Kermack and McKendrick: theory of epidemics



$$i(t) = 890 \cosh^{-2}(0.2t - 3.4)$$

Kermack and McKendrick: the threshold phenomenon

- Let's focus now on the second equation:

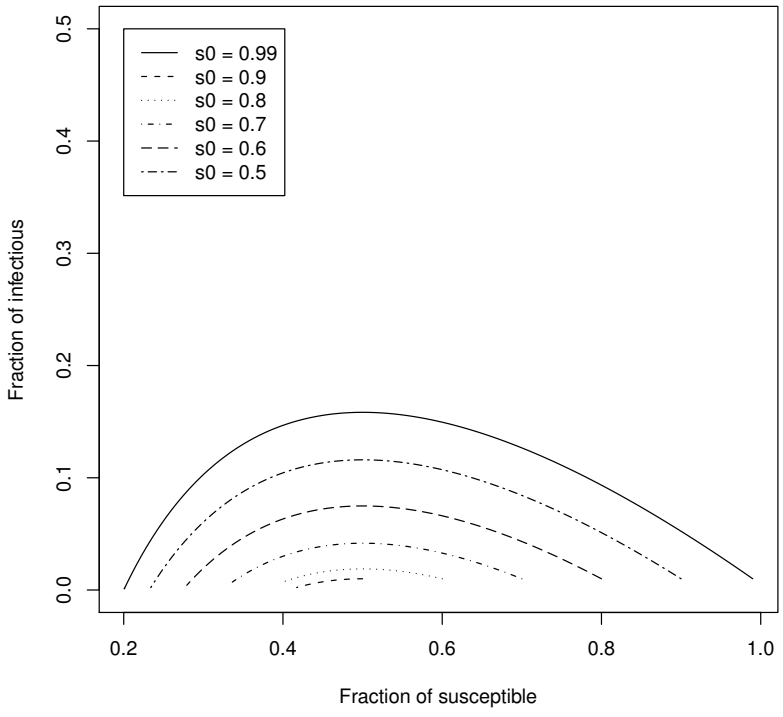
$$\begin{aligned} \frac{di(t)}{dt} &= \beta si - \nu i, \\ &= (\beta s - \nu) i. \end{aligned}$$

- If the initial fraction of the susceptible population is less than ν/β then we have $\frac{di(t)}{dt} < 0$ and the epidemic dies out:
  - ν/β is called the relative removal rate
  - The inverse of the relative removal rate is called the basic reproduction number

A pathogen will invade if and only if $R_0 > 1$.

Kermack and McKendrick: phase-plot

$$\beta = 0.2856, \nu = 1/7, R_0 = 2$$



- Application: Vaccination can be used to reduce the proportion of susceptible population below $1/R_0$ for disease eradication.

  This matter will be discussed later.

Kermack and McKendrick: the threshold phenomenon

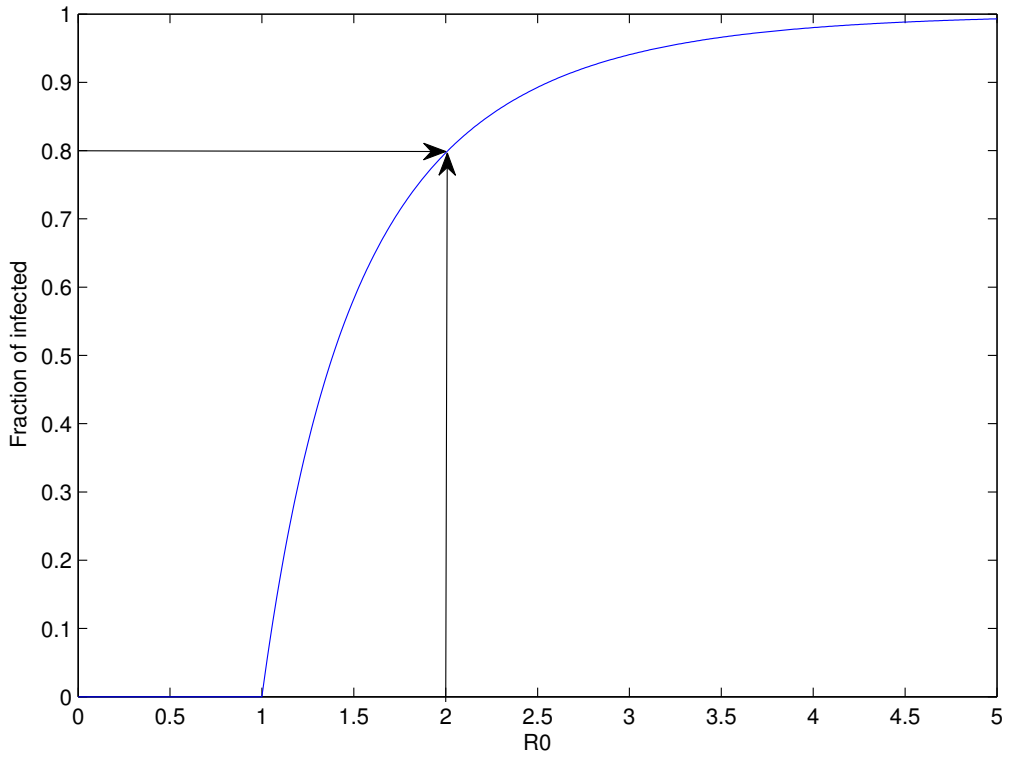
- Having defined R_0,
- assuming an entirely susceptible population $s_0 \approx 1$, the threshold phenomenon can be re-expressed as:

  A pathogen will invade if and only if $R_0 > 1$.

- Note that in a stochastic model this is not true: 'can invade'

Kermack and McKendrick: final size and R_0

Total fraction of infected population according to R_0



Some first conclusions

- Assumption:

  the time course of the epidemic is sufficiently fast not to be influenced by population demography.

- Conclusion:

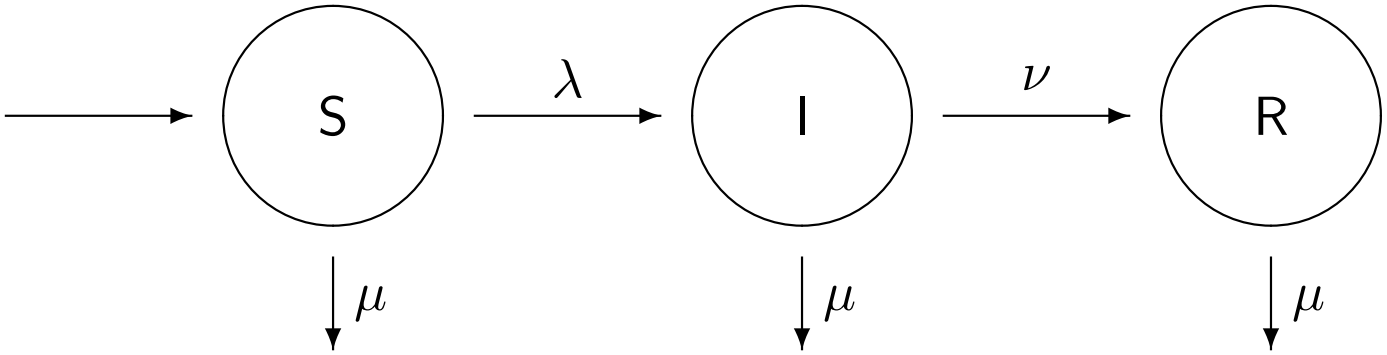
  extinction of the pathogen

- Question:

  How to explore the long-term persistence and endemic dynamics of an infectious disease?

Inclusion of demographic processes

SIR model with demography: model formulation



$$\begin{aligned}
\frac{dS(t)}{dt} &= B - \beta S\frac{I}{N} - \mu S, \\
\frac{dI(t)}{dt} &= \beta S\frac{I}{N} - \nu I - \mu I, \\
\frac{dR(t)}{dt} &= \nu I - \mu R.
\end{aligned}$$

SIR model with demography: model formulation

- Working with constant population:

$$S + I + R = N \Rightarrow B = \mu N$$

- Let s, i, r denote the proportion of population in the susceptible, infectious and removed classes, respectively.

$$\begin{aligned}
\frac{ds(t)}{dt} &= \mu - \beta si - \mu s, \\
\frac{di(t)}{dt} &= \beta si - \nu i - \mu i, \\
\frac{dr(t)}{dt} &= \nu i - \mu r.
\end{aligned}$$

Equilibrium values

- Setting the right-hand side of the system to 0:

$$\begin{aligned} \mu - \beta si - \mu s &= 0, \\ \beta si - \nu i - \mu i &= 0, \\ \nu i - \mu r &= 0. \end{aligned}$$

- Existence of two equilibria:
  - The trivial equilibrium (disease free equilibrium):

$$E_0 = (1, 0, 0)$$

  - The endemic equilibrium:

$$\begin{aligned} E_1 &= (s_1, i_1, r_1) \\ &= \left(\frac{\mu + \nu}{\beta}, \frac{\mu}{\beta} \left(\frac{\beta}{\mu + \nu} - 1 \right), 1 - s_1 - i_1 \right). \end{aligned}$$

$$E_1 \text{ is positive} \Leftrightarrow \frac{\beta}{\mu + \nu} > 1.$$

Threshold value

- Focus on the second equation of the system:

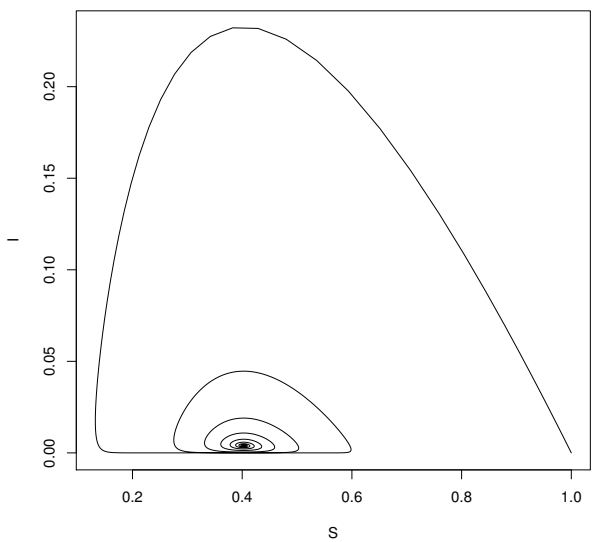
$$\frac{di(t)}{dt} = \beta si - \nu i - \mu i$$

$\beta = 5, \mu = 1/75, \nu = 2 \Rightarrow R_0 = 2.49$

- We have

$$\frac{di(t)}{dt} > 0 \Leftrightarrow \beta s - (\nu + \mu) > 0$$

$$\frac{di(t)}{dt} > 0 \Leftrightarrow s > \frac{\nu + \mu}{\beta}$$



Threshold value: the basic reproduction number

- Intuitively:
  - β: the transmission rate

    the mean number of new cases produced by an infectious individual per time unit.
  - An infected individual remains infectious for $1/(\mu+\nu)$ time unit
  - During that time period, a typical infectious individual produces $\frac{\beta}{\mu+\nu}$ infections in a totally susceptible population. Thus,

$$R_0 = \frac{\beta}{\mu+\nu}.$$

Threshold value: the basic reproduction number

- If $R_0 > 1$, an epidemic occurs and the solution of the system approaches the endemic equilibrium:

$$E_1 = \left(\frac{1}{R_0}, \frac{\mu}{\mu + \nu} \left(1 - \frac{1}{R_0} \right), 1 - s_1 - i_1 \right).$$

R code for solving dynamical systems

- R package desolve (Soetaert et al, 2010)
  Solving Initial value differential equations in R
- Calling the library

```
library(deSolve)
```

- Function *ode* in R, general call:

```
ode(y=vector containing state variables,
    times=vector containing the time units for integration,
    func=function containing the model equations,
    parms=vector containing the model parameters)
```

The SIR model in R

- Definition of the ODE system:
  - Derivatives of state variables are expressed as a list

```
SIR<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
N=S+I+R
dS = mu*N-beta*I*S/N - mu*S
dI = beta*I*S/N - nu*I - mu*I
dR = nu*I -mu*R
list(c(dS, dI, dR))
})
}
```

The SIR model in R

- Parameter definition/initialisation

```
N=50000
R0=2; mu0=1/75; nu0=1/(1/24)
beta0=R0*(mu0+nu0)
parameters = c(mu=mu0,beta=beta0,nu=nu0)
```

- Initial values

```
state = c(S=N-1,I=1,R=0)
```

- Time range:

  from $T_0 = 0$ to $T_{\max} = 1000$ by step of 0.01

```
times<-seq(0,1000,by=0.01)
```

- Solution of Initial value differential equations

```
out<-as.data.frame(
ode(y=state,times=times,func=SIR,parms=parameters)
)
```

Summary

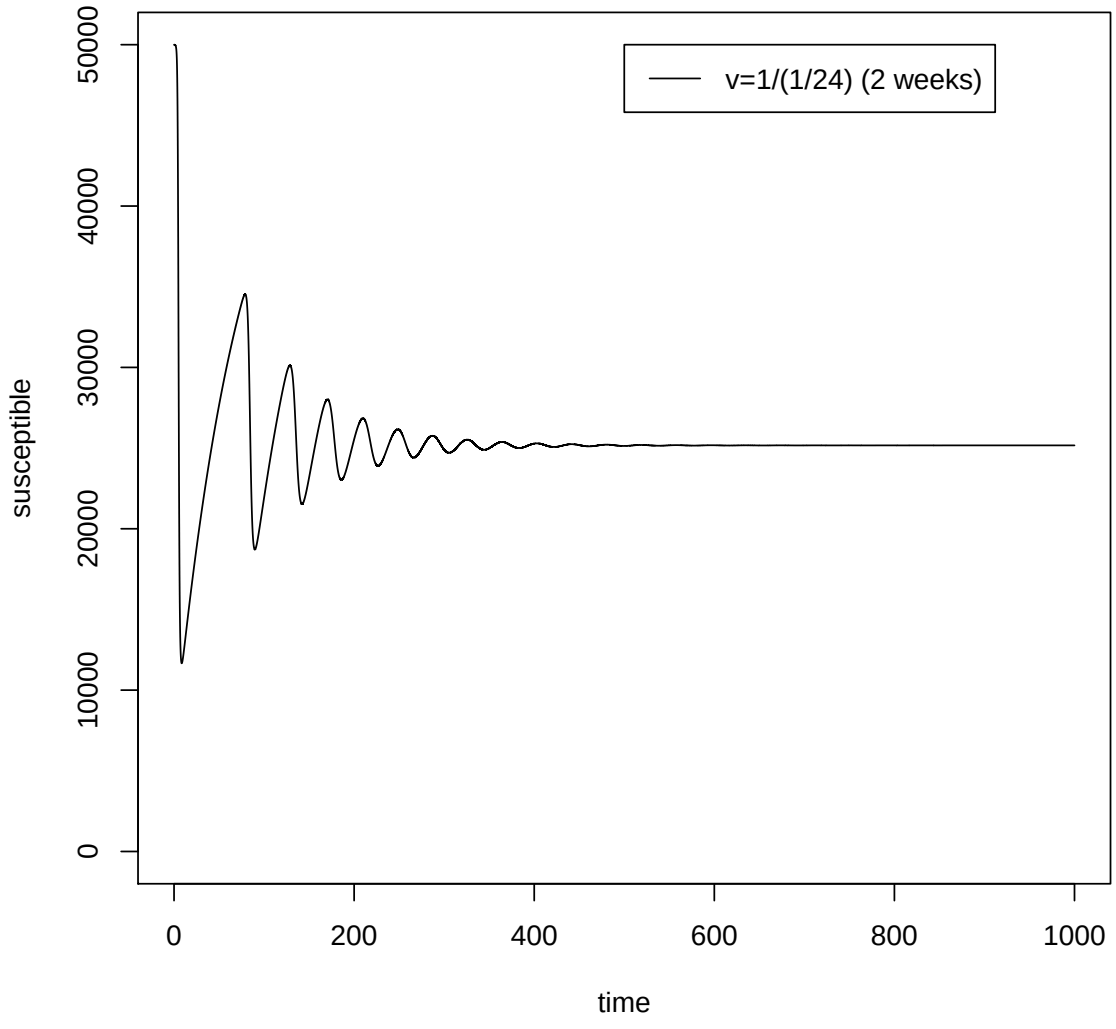
```
library(deSolve)
N=50000;R0=2; mu0=1/75; nu0=1/(1/24)
beta0=R0*(mu0+nu0)
parameters = c(mu=mu0,beta=beta0,nu=nu0)
state = c(S=N-1,I=1,R=0)
times = seq(0,1000,by=0.01)
SIR<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
N=S+I+R
dS <- mu*N-beta*I*S/N - mu*S
dI <- beta*I*S/N - nu*I - mu*I
dR <- nu*I -mu*R
list(c(dS, dI, dR))
})
}
require(deSolve)
out<-as.data.frame(ode(y=state,times=times,func=SIR,parms=parameters))
```

Number of susceptible individuals

```
tail(out)
        time          S            I         R
99996   999.95 25166.63 164.4616 24668.91
99997   999.96 25166.63 164.4615 24668.91
99998   999.97 25166.63 164.4615 24668.91
99999   999.98 25166.63 164.4615 24668.91
100000  999.99 25166.63 164.4615 24668.91
100001 1000.00 25166.63 164.4615 24668.91
```

- Thus, for $R_0 = 2$, the proportion of susceptible individuals at equilibrium is around 50%.

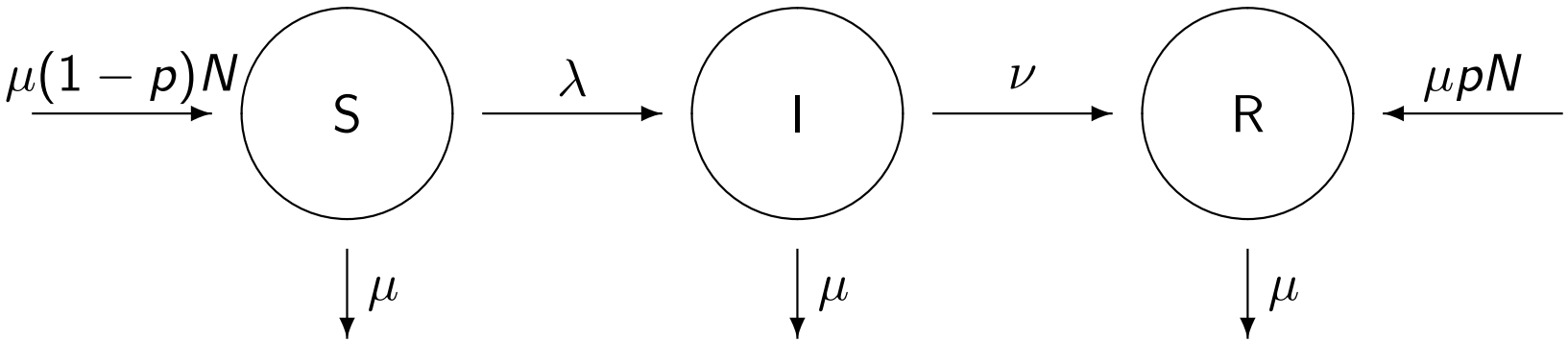
Number of infected individuals



The basic reproduction number and vaccination programs

- Assumptions
  - SIR model with demography
  - a proportion p of each cohort of new-born is vaccinated immediately at birth
- Model representation

Model formulation



$$\begin{aligned}
\frac{dS(t)}{dt} &= \mu(1-p)N - \beta S\frac{I}{N} - \mu S, \\
\frac{dI(t)}{dt} &= \beta S\frac{I}{N} - \nu I - \mu I, \\
\frac{dR(t)}{dt} &= \mu pN + \nu I - \mu R.
\end{aligned}$$

Model formulation

- Working with constant population:

$$S + I + R = N \Rightarrow B = \mu N.$$

- Let s, i, r denote the proportion of population in the susceptible, infectious and removed classes, respectively.

$$\begin{aligned}
\frac{ds(t)}{dt} &= \mu(1-p) - \beta si - \mu s, \\
\frac{di(t)}{dt} &= \beta si - \nu i - \mu i, \\
\frac{dr(t)}{dt} &= \mu p + \nu i - \mu r.
\end{aligned}$$

Equilibrium Values

- Setting the right-hand side of the system to 0:

$$\begin{aligned} \mu(1-p) - \beta si - \mu s &= 0, \\ \beta si - \nu i - \mu i &= 0, \\ \mu p + \nu i - \mu r &= 0. \end{aligned}$$

- Existence of two equilibria
  - The trivial equilibrium (disease free equilibrium):

$$E_0 = (1-p, 0, p)$$

  - The endemic equilibrium:

$$\begin{aligned} E_1 &= (s_1, i_1, r_1) \\ &= \left(\frac{\mu+\nu}{\beta}, \frac{\mu}{\beta}\left((1-p)R_0 - 1\right), 1 - s_1 - i_1 \right). \end{aligned}$$

E_1 is positive $\Leftrightarrow (1-p)R_0 > 1$

Threshold value

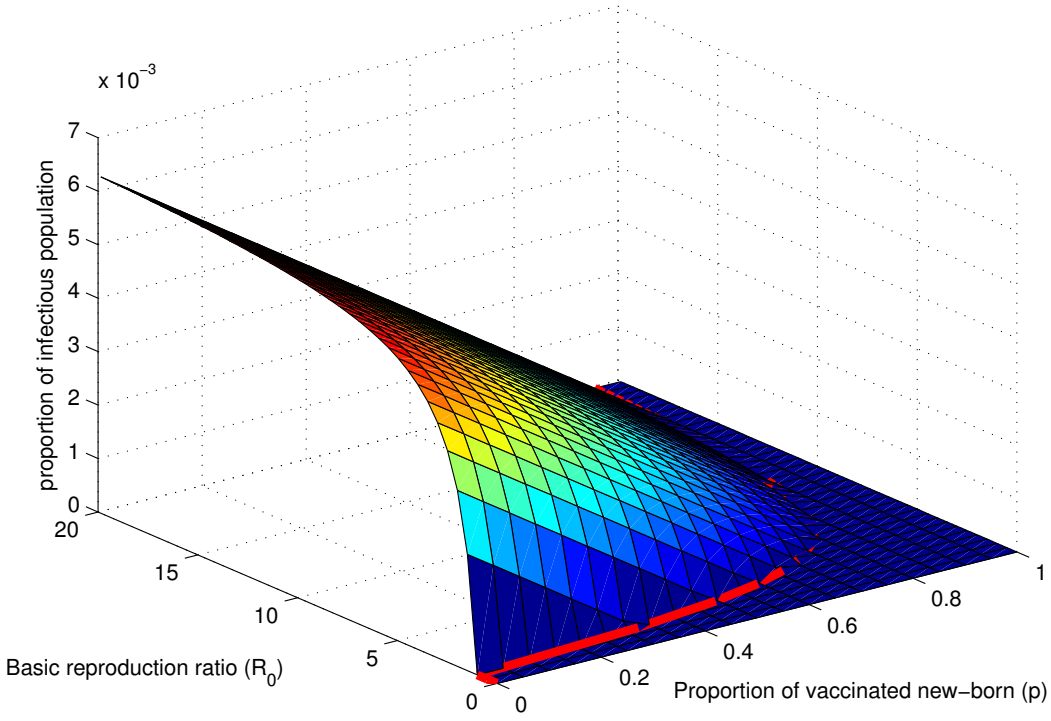
- Vaccination efficacy:
  The efficacy of vaccination programs is governed by the relationship between vaccination coverage and the basic reproduction number.

- The proportion of vaccinated new-born population should attain the critical value
$$p_c = 1 - \frac{1}{R_0}$$
for disease eradication. This quantity is also know as the herd immunity threshold

- Herd immunity refers to the indirect protection experienced by unvaccinated individuals resulting from immune individuals in the population

- This leads us to the definition of the effective reproduction number
$$R_e = p_s R_0,$$
where p_s is the proportion susceptible to infection

Threshold value

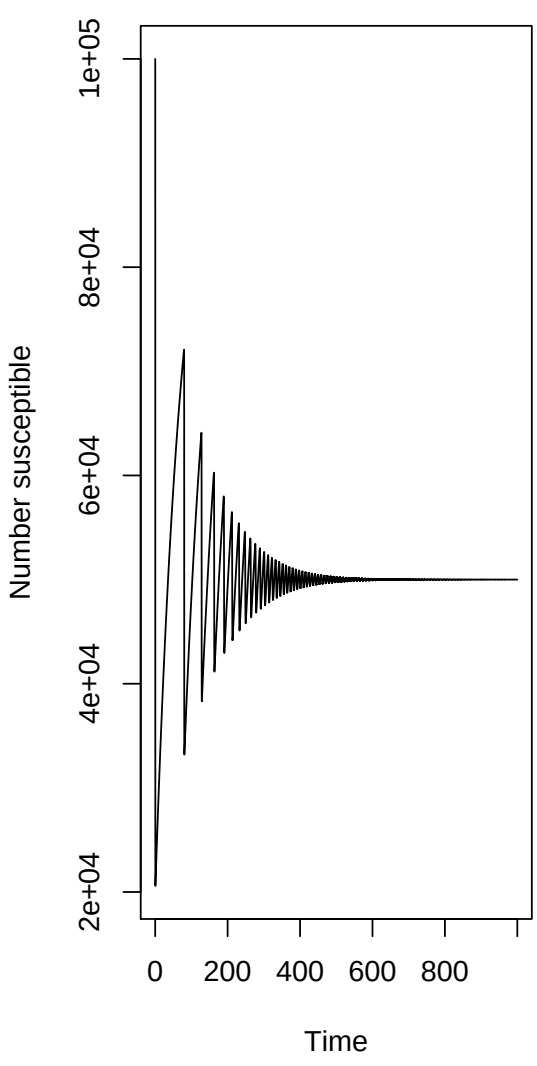


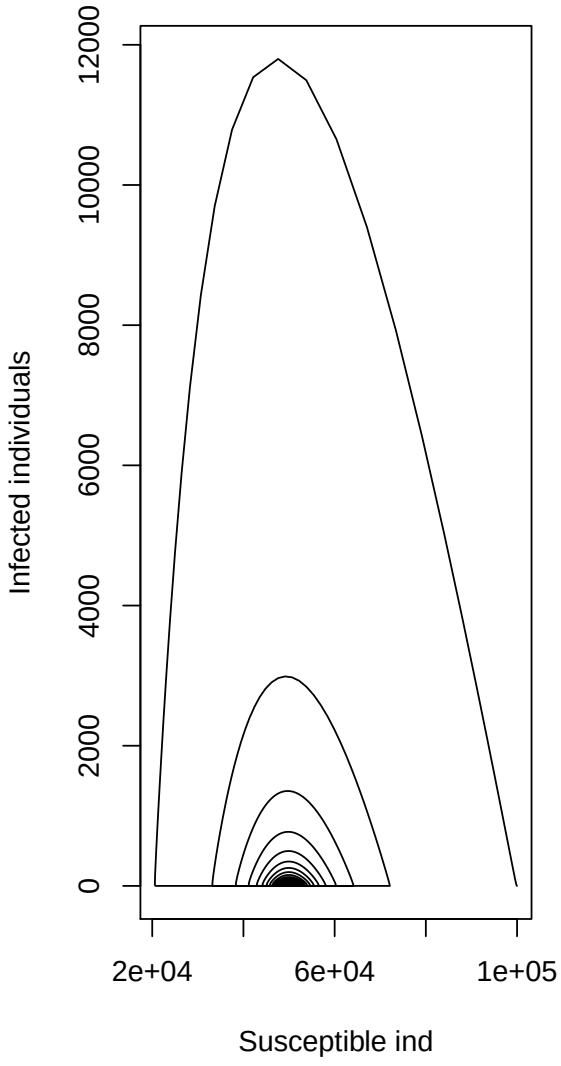
Proportion of infected population regarding different values of R_0 and the proportion of vaccinated population.

SIR model with vaccination in R

```
N=50000
R0=2; mu0=1/75; nu0=1/(1/24); p0=0.4
beta0=R0*(mu0+nu0)
parameters = c(mu=mu0,beta=beta0,nu=nu0,p=p0)
state = c(S=N-1,I=1,R=0)
times = seq(0,1000,by=0.01)
SIRv=function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
N=S+I+R
dS = mu*(1-p)*N-beta*I*S/N - mu*S
dI = beta*I*S/N - nu*I - mu*I
dR = nu*I -mu*R+mu*p*N
list(c(dS, dI, dR))
})
}
out = as.data.frame(ode(y=state,times=times,func=SIRv,parms=parameters)
```

Results


Number susceptible
2e+04
4e+04
6e+04
8e+04
1e+05
0
200
400
600
800
Time


Infected individuals
0
2000
4000
6000
8000
10000
12000
2e+04
6e+04
1e+05
Susceptible ind

Building your own model

Consider a constant population and an infectious agent with the following characteristics:

- New-born individuals are passively immune (maternal antibodies) for time period $1/\gamma$ after which they are susceptible to infection
- Force of infection: mass action principle
- Newly infected individuals enter into a latent phase (duration $1/\kappa$): these individuals are infected but not infectious; they were Exposed to the infectious agent.
- Life-long immunity

What does the flow diagram look like?

Building your own model: an MSEIR example

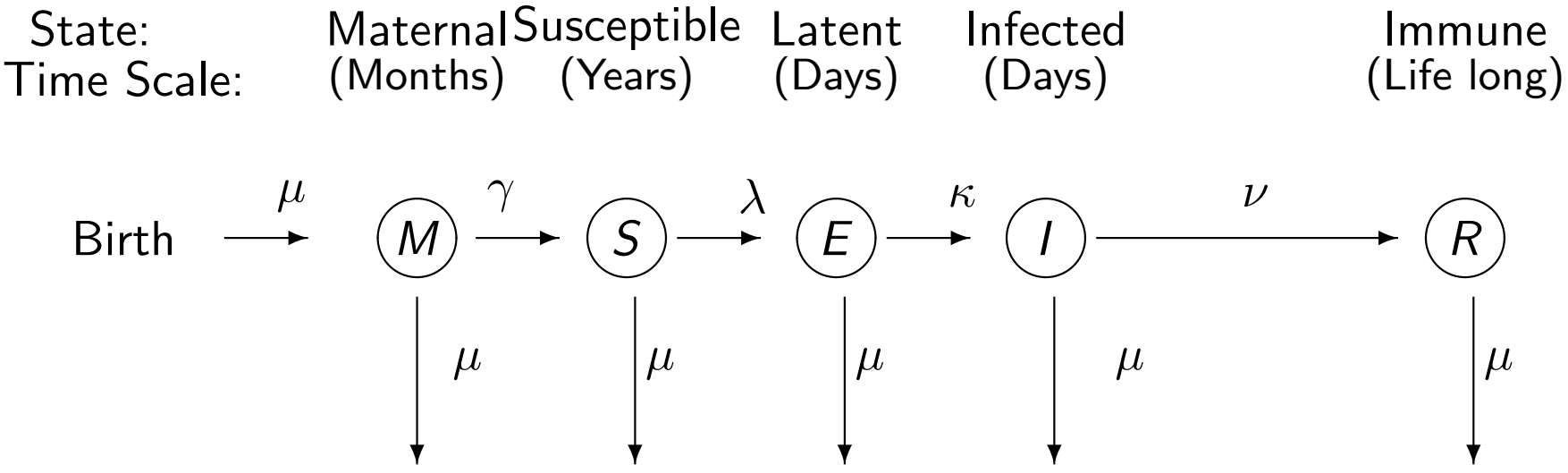


Figure: Illustration of the MSEIR model. The individuals enter to the population protected by maternal antibodies after loosing those they move into the susceptible class, after infection to the exposed class (infected but not infectious), after a latent period to the infectious class and after recovering to the immune class.

ODE system?

MSEIR example: ODE System

$$\begin{aligned}
\frac{dM(t)}{dt} &= \mu N - (\gamma + \mu)M \\
\frac{dS(t)}{dt} &= \gamma M - (\lambda + \mu)S \\
\frac{dE(t)}{dt} &= \lambda S - (\mu + \kappa)E \\
\frac{dI(t)}{dt} &= \kappa E - (\mu + \nu)I \\
\frac{dR(t)}{dt} &= \nu I - \mu R.
\end{aligned}$$

where $\lambda = \beta \frac{I}{N}$.

In this case the basic reproductive number is given by:

$$R_0 = \frac{\kappa\beta}{(\kappa + \mu)(\nu + \mu)}.$$

MSEIR example

- Basic reproduction number: $R_0=2$
- Duration of maternal immunity: 3 months
- Duration of the latent period: 2 days
- Duration of the infectious period: 1 week

MSEIR example

- Basic reproduction number: R_0=2
- Duration of maternal immunity: 3 months
- Duration of the latent period: 2 days
- Duration of the infectious period: 1 week
- Parameters:
  - $\beta = \frac{R_0(\kappa+\mu)(\nu+\mu)}{\kappa}$
  - $\gamma = 1/(3/12); \mu = 1/75; \nu = 52; \kappa = 1/(2/365)$
- Work with numbers:

Implementation in R?

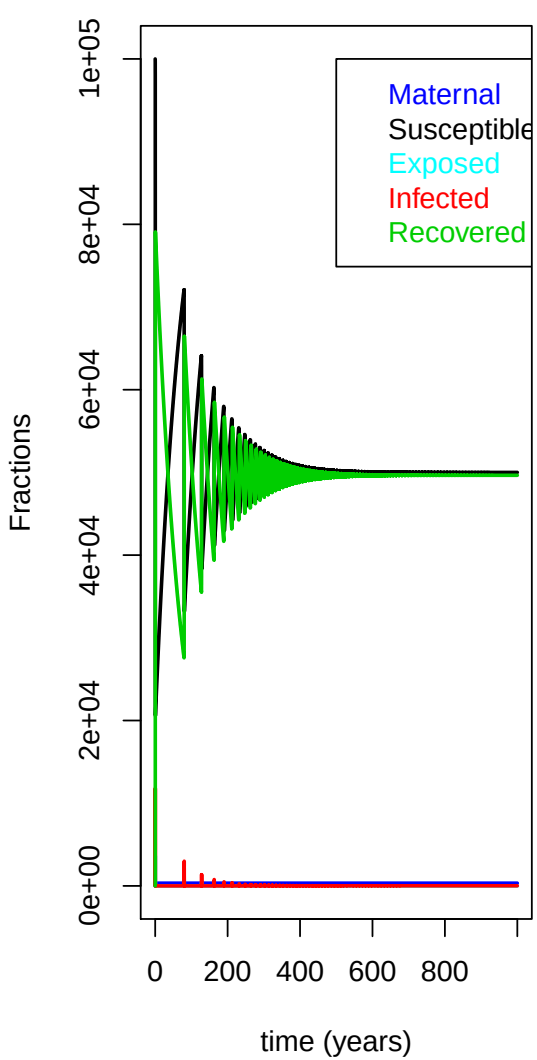
Summary

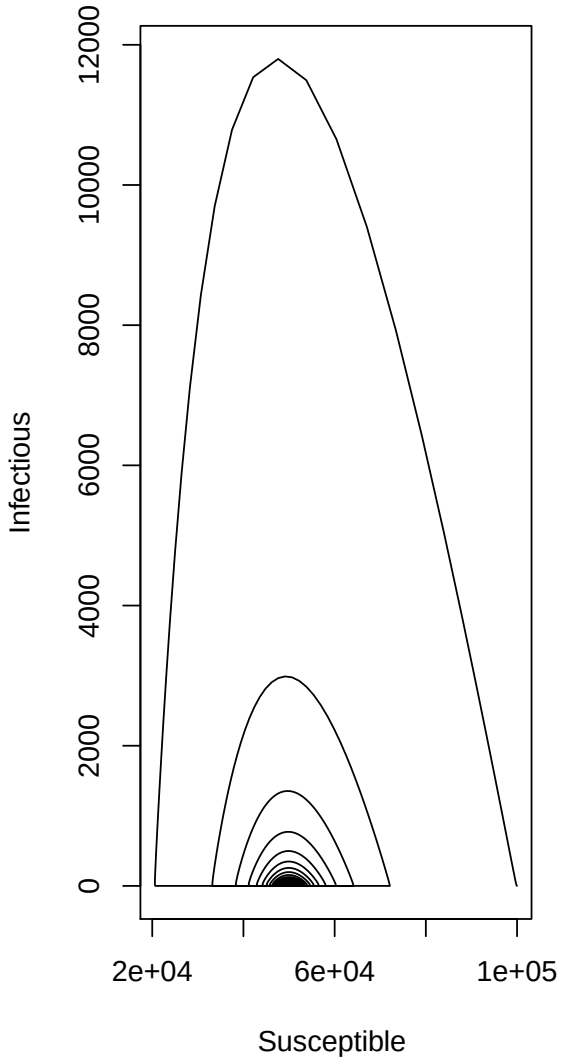
```
N=1E5
mu0=1/75; sigma0=1/(3/12);kappa0=1/(2/365);nu0=1/(7/365);
          beta0=R0*(kappa0+mu0)*(nu0+mu0)/kappa0
parameters = c(mu=mu0, sigma=sigma0,kappa=kappa0,nu=nu0,beta=beta0)
state = c(M=1, S=N-2,E=0, I=1,R=0)
times=seq(0,1000,by=0.01)

MSEIR=function(t,state,parameters)
{
  with(as.list(c(state, parameters)),
       {
         N=M+S+E+I+R
         dM= mu*N-(mu+sigma)*M
         dS = sigma*M-beta*I*S/N - mu*S
         dE = beta*I*S/N-(kappa+mu)*E
         dI = kappa*E - nu*I - mu*I
         dR = nu*I -mu*R
         list(c(dM, dS, dE, dI, dR))
       })
}
```

Summary

```
out=as.data.frame(ode(y=state,times=times,func=MSEIR,parms=parameters))

par(mfrow=c(1,2))
#### Time series plot
plot(range(times),c(0,N),xlab="time (years)",
     ylab="Fractions",type="n",ylim=c(0,N))
lines(out$time,out$M,lwd=2,col=4)
lines(out$time,out$S,lwd=2,col=1)
lines(out$time,out$E,lwd=2,col=5)
lines(out$time,out$I,lwd=2,col=2)
lines(out$time,out$R,lwd=2,col=3)
legend(mean(times),N,c("Maternal","Susceptible","Exposed",
                       "Infected","Recovered"),text.col=c(4,1,5,2:3))
##### Phase plan
plot(out$S,out$I ,type="l",main=" ", xlab="Susceptible ", ylab="Infecti
```

The MSEIR model results





Class exercise

- Implement vaccinating children in the MSEIR model
- Code the model using proportions rather than numbers
- Code an extension of the model in which recovered individuals become susceptible again: MSEIRS
- What would happen if one switches to a resolution of days for the time scale?

Transmission within multiple subpopulations

The law of mass action as stated before relies on the hypothesis that infected and susceptible individuals mix homogeneously.
β is thus considered as age and time independent.

- Objective Taking into account the social structures in the population.
- Assumptions
  - The population is constructed from multiple subpopulations.
  - the transmission process is governed by the mixing patterns in the population

Who Acquires Infection From Whom?

The transmission process is governed by the mixing pattern commonly represented by the WAIFW 'Who Acquires Infection From Whom' matrix.

- A first example

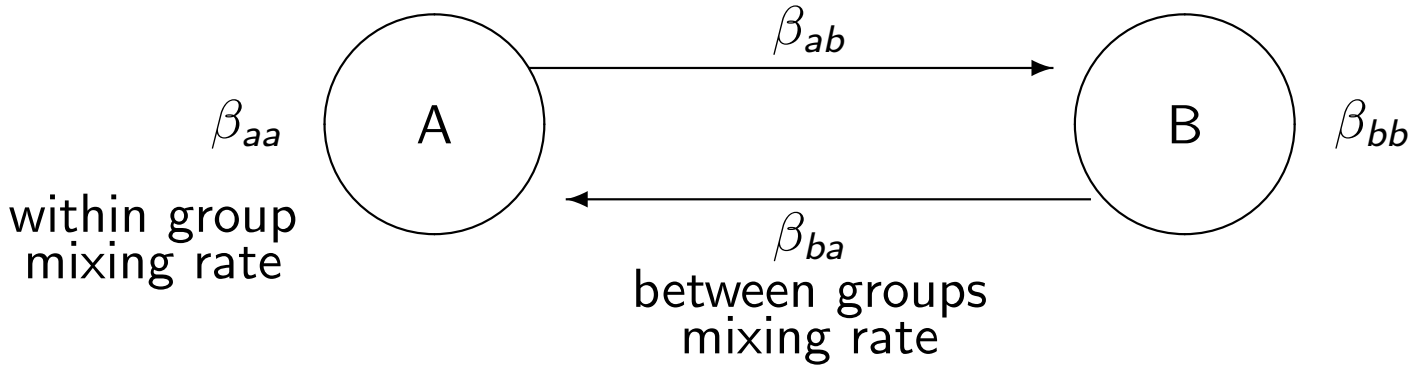


Figure: *Mixing patterns between two subpopulations: β_{aa} is the mixing rate within group A, β_{bb} is the mixing rate within group B. β_{ab} and β_{ba} are the mixing rates between the two groups.*

The WAIFW matrix:

$$C = \begin{pmatrix} \beta_{aa} & \beta_{ab} \\ \beta_{ba} & \beta_{bb} \end{pmatrix}.$$

Application 1: The SIS transmission model for Gonorrhea

- Gonorrhea is a disease transmitted through the population by heterosexual contacts.
- Immunity to reinfection does not exist.
- The two subpopulations, males and females, interact according to the following mixing matrix

$$C = \begin{pmatrix} 0 & \beta_{fm} \\ \beta_{mf} & 0 \end{pmatrix}.$$

Application 1: The SIS transmission model for Gonorrhea

- The SIS transmission model for Gonorrhea (Capasso, 2008):

$$\begin{aligned}
\frac{dS_f}{dt} &= -\beta_{fm} S_f(t) I_m(t) + \nu_f I_f(t) \\
\frac{dI_f}{dt} &= \beta_{fm} S_f(t) I_m(t) - \nu_f I_f(t) \\
\frac{dS_m}{dt} &= -\beta_{mf} S_m(t) I_f(t) + \nu_m I_m(t) \\
\frac{dI_m}{dt} &= \beta_{mf} S_m(t) I_f(t) - \nu_m I_m(t).
\end{aligned}$$

- Assuming $N_f = S_f + I_f$ and $N_m = S_m + I_m$

$$\begin{aligned}
\frac{dI_f}{dt} &= \beta_{fm}(N_f - I_f(t)) I_m(t) - \nu_f I_f(t), \\
\frac{dI_m}{dt} &= \beta_{mf}(N_m - I_m(t)) I_f(t) - \nu_m I_m(t).
\end{aligned}$$

SIS model for Gonorrhea: endemic equilibrium

- System:

$$\begin{aligned} \beta_{fm}(N_f - I_f(t))I_m(t) - \nu_f I_f(t) &= 0, \\ \beta_{mf}(N_m - I_m(t))I_f(t) - \nu_m I_m(t) &= 0. \end{aligned}$$

- After some calculations, and noting the relative removal rates as $\rho_f = \nu_f/\beta_f, \rho_m = \nu_m/\beta_m$

$$I_f(\infty) = \frac{N_f N_m - \rho_f \rho_m}{\rho_f + N + N_m} \text{ and } I_m(\infty) = \frac{N_f N_m - \rho_f \rho_m}{\rho_m + N + N_f}.$$

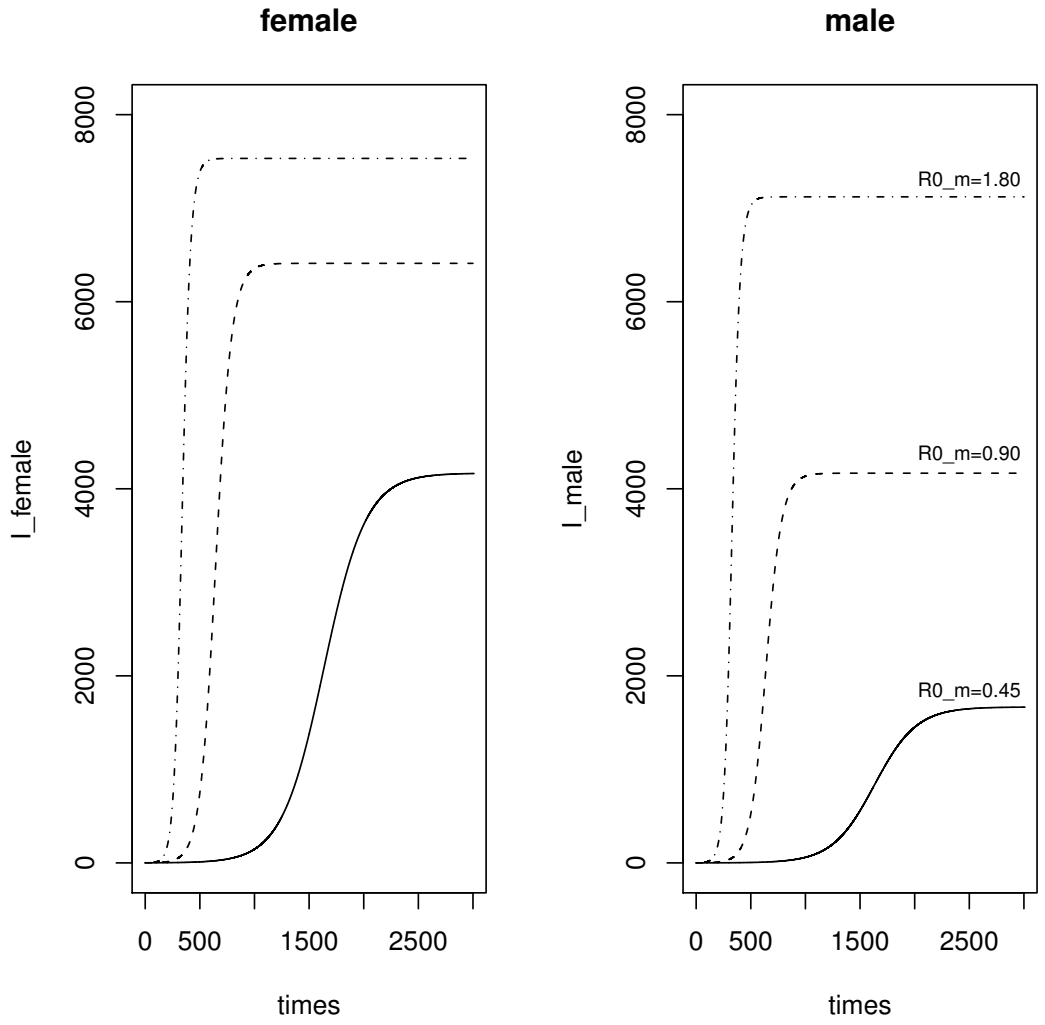
- This equilibrium is positive $\Leftrightarrow N_f N_m - \rho_f \rho_m > 0$ or

$$\left(\frac{N_f \beta_f}{\nu_f} \times \frac{N_m \beta_m}{\nu_m}\right) = R_{0,f} \times R_{0,m} > 1.$$

SIS Model for Gonorrhea in R

```
parameters <- c(beta1=0.000003,beta2=0.000006,v1=0.007,v2=0.05,N1=10000,N2=15000)
state <- c(IF=1,IM=0)
Gonorrhea<-function(t,state,parameters){
with(as.list(c(state, parameters)),{
dIF <- beta1*(N1-IF)*IM-v1*IF
dIM <- beta2*(N2-IM)*IF-v2*IM
list(c(dIF,dIM))})
}
times<-seq(0,3000,by=0.1)

beta2.i<-0.000006*c(0.25,0.5,1)
beta2.i
y1mat<-y2mat<-matrix(0,length(times),length(beta2.i))
for(i in 1:length(beta2.i)){
parameters <- c(beta1=0.000003,beta2=beta2.i[i],v1=0.007,v2=0.05,N1=10000,N2=15000)
require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=Gonorrhea,parms=parameters))
y1mat[,i]<-out$IF
y2mat[,i]<-out$IM}
```

SIS Model for Gonorrhea: results



Application 2: SIR - 2 interacting subpopulations

- Model structure: Conversely to gonorrhea model, the out-diagonal elements of the WAIFW matrix are positive

$$C = \begin{pmatrix} \beta_{11} & \beta_{12} \\ \beta_{21} & \beta_{22} \end{pmatrix}.$$

representing contacts within and across subpopulations.

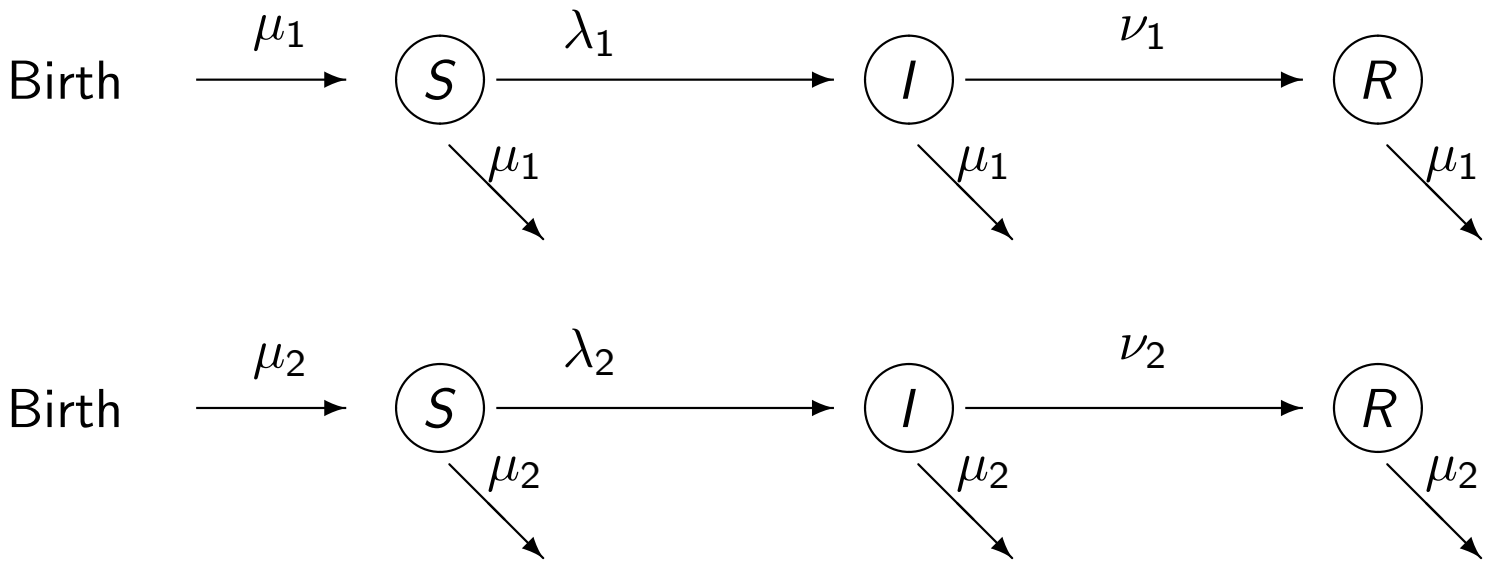


Figure: *Illustration of a SIR model with two subpopulations.*

Application 2: SIR - 2 interacting subpopulations

- Force of infection

$$\left(\Sigma_{j=1}^{2}\beta_{ij}I_j\right)S_i = \lambda_i S_i.$$

- ODE system

$$\begin{aligned}
\frac{dS_i(t)}{dt} &= -\left(\Sigma_{j=1}^{2}\beta_{ij}I_j\right)S_i + N_i\mu_i - \mu_i S_i \\
\frac{dI_i(t)}{dt} &= \left(\Sigma_{j=1}^{2}\beta_{ij}I_j\right)S_i - (\mu_i + \nu_i)I_i \\
\frac{dR_i(t)}{dt} &= \nu_i I_i - \mu_i R_i.
\end{aligned}$$

- We will now consider the symmetric case setting $\beta_{12} = \beta_{21} = \alpha$.

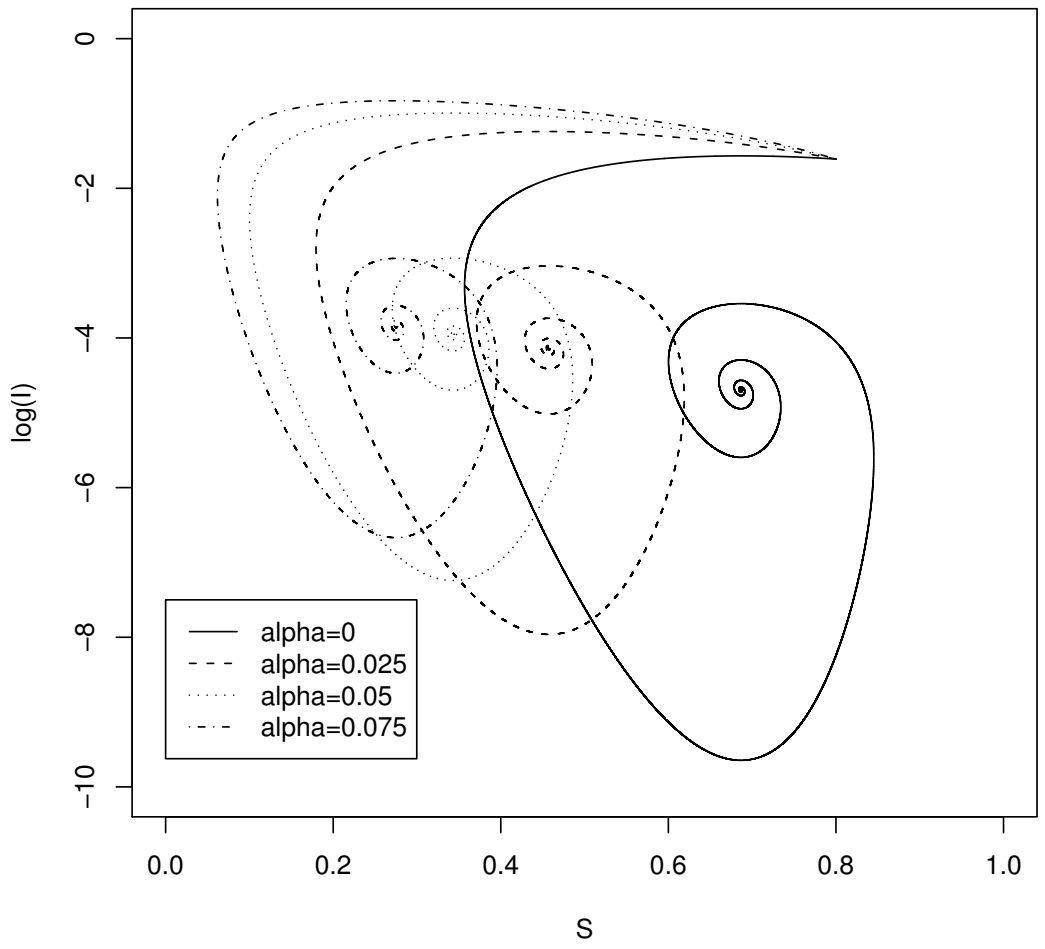
Application 2: implementation in R

```
alpha<-0
parameters <- c(beta11=0.05,beta12=alpha,beta21=alpha,beta22=0.05,
                nu1=1/30,nu2=1/30,mu=0.001)
state <- c(S1=0.8,I1=0.2,R1=0,S2=0.8,I2=0.2,R2=0)
times<-seq(0,10000,by=0.01)

SIRtwo<-function(t,state,parameters)
{
with(as.list(c(state, parameters)),
{
dS1 <- -(beta11*I1+beta12*I2)*S1+mu-mu*S1
dI1 <- (beta11*I1+beta12*I2)*S1-nu1*I1-mu*I1
dR1 <- nu1*I1 - mu*R1
dS2 <- -(beta21*I1+beta22*I2)*S2+mu-mu*S2
dI2 <-  (beta21*I1+beta22*I2)*S2-nu2*I2-mu*I2
dR2 <- nu2*I2 - mu*R2
list(c(dS1,dI1,dR1,dS2,dI2,dR2))
})
}
```

Application 2: implementation in R

```
times<-seq(0,10000,by=0.01)
require(deSolve)
out <- as.data.frame(ode(y=state,times=times,func=SIRtwo,
                parms=parameters))

par(mfrow=c(1,1))
plot(out$S1,log(out$I1),type="l",main=" ",
     xlab="S",ylab="log(I)",ylim=c(-10,0),xlim=c(0,1))
legend(0,-7.5,c("alpha=0"),lty=c(1:4))
```

Application 2: results



Transmission over age and time in the SIR model

- The model with interacting subpopulations can be seen as an age-time dependent SIR model or age-structured SIR model
- The population is divided into a finite number of age groups interacting with each other

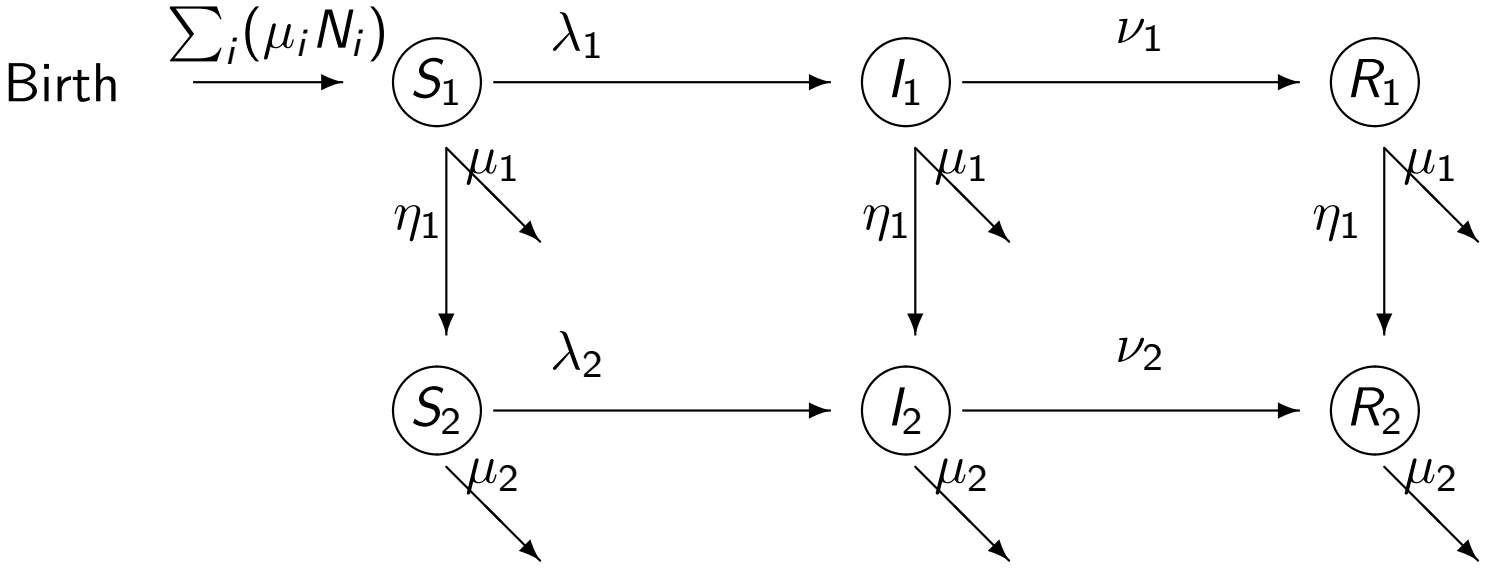


Figure: *Illustration of age structured SIR model with two age groups.*

Transmission over age and time in the SIR model

- A general approach: partial differential equations
- Each differential equation represent the change (over time and age) in the compartment.

$$\begin{cases} \frac{\partial S(a,t)}{\partial a} + \frac{\partial S(a,t)}{\partial t} = -(\lambda(a,t) + \mu(a))S(a,t), \\ \frac{\partial I(a,t)}{\partial a} + \frac{\partial I(a,t)}{\partial t} = \lambda(a,t)S(a,t) - (\nu + \alpha + \mu(a))I(a,t), \\ \frac{\partial R(a,t)}{\partial a} + \frac{\partial R(a,t)}{\partial t} = \nu I(a,t) - \mu(a)R(a,t), \end{cases}$$

  where $N(a,t) = S(a,t) + I(a,t) + R(a,t)$ and $S(0,T) = B(t)$, the number of births all susceptible to infection.

- Quite complicated to solve

The Cohort Age Structured model

- For a population with K age groups, the system of ordinary differential equations for the first age group ($i = 1$) in an age-structured SIR model is given by

$$\begin{aligned}
\frac{dS_1(t)}{dt} &= -\left(\Sigma_{j=1}^{K}\beta_{1j}I_j\right)S_1 + \sum_i(\mu_i N_i) - \mu_1 S_1 - \eta_1 S_1, \\
\frac{dI_1(t)}{dt} &= \left(\Sigma_{j=1}^{K}\beta_{1j}I_j\right)S_1 - \nu_1 I_1 - \eta_1 I_1, \\
\frac{dR_1(t)}{dt} &= \nu_1 I_1 - \mu_1 R_1 - \eta_1 R_1.
\end{aligned}$$

The Cohort Age Structured model

- Denoting η_i is the rate at which individuals of age-class i pass from S_i, I_i, R_i to $S_{i+1}, I_{i+1}, R_{i+1}$, we have for $i = 2$ to K

$$\begin{aligned}
\frac{dS_i(t)}{dt} &= -\left(\Sigma_{j=1}^{K}\beta_{ij}I_j\right)S_i + \eta_{i-1}S_{i-1} - \mu_i S_i - \eta_i S_i, \\
\frac{dI_i(t)}{dt} &= \left(\Sigma_{j=1}^{K}\beta_{ij}I_j\right)S_i + \eta_{i-1}I_{i-1} - (\nu_i + \mu_i)I_i - \eta_i I_i, \\
\frac{dR_i(t)}{dt} &= \nu_i I_i - \mu_i R_i + \eta_{i-1}R_{i-1} - \eta_i R_i.
\end{aligned}$$

- This model is a cohort age-structured model (CAS-model) with the disadvantage that people can instantaneously grow older.

The Realistic Age Structured model

- A better alternative to the CAS-model is the RAS-model: Realistic Age-structured Model
- In the RAS-model the SIR model is applied to each age-class of one year and after one year people instantaneously move to the next age-class
- The model resembles the educational system were children move to another class after one year
- The RAS-model consists of the following two-step iteration: Assuming one-year age-groups, let $\{S_i(t), I_i(t), R_i(t)\}$ denote the number of susceptible, infected and recovered individuals of age $i = 0, \ldots K-1$ at time t (in years).

The Realistic Age Structured model

Step 1: Given initial values $\{S_i(t), I_i(t), R_i(t)\} = \{S_i(t_0), I_i(t_0), R_i(t_0)\}, i = 0, \ldots K-1$ we solve the following set of ODEs:

$$\begin{cases} \frac{dS_i(t)}{dt} &= -(\lambda_i(t) + \mu_i)S_i(t), \\ \frac{dI_i(t)}{dt} &= \lambda_i(t)S_i(t) - (\nu + \mu_i)I_i(t), \\ \frac{dR_i(t)}{dt} &= \nu I_i(t) - \mu_i R_i(t), \end{cases}$$

to obtain $\{S_i(t+1), I_i(t+1), R_i(t+1)\}, i = 0, \ldots K-1$ after one year.

The Realistic Age Structured model

Step 2: Individuals are then shifted by one year:

- $\{S_i(t+1), I_i(t+1), R_i(t+1)\} \rightarrow$
  $\{S_{i+1}(t+1), I_{i+1}(t+1), R_{i+1}(t+1)\}, i = 0, \ldots, K-2$
- all newborns B are assumed susceptible to infection:
  $\{S_0(t+1), I_0(t+1), R_0(t+1)\} = \{B, 0, 0\}$.

This process is iterated throughout the time period of interest.

Two examples (PDE and RAS)

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METHODOLOGY ARTICLE Open Access

Heterogeneous computing for epidemiological model fitting and simulation

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Epidemics

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Estimating dynamic transmission model parameters for seasonal influenza by fitting to age and season-specific influenza-like illness incidence

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Goeyvaerts et al. (2015); Kovac et al. (2018)

Summary

- We have introduced the basic building blocks of mathematical models of infectious diseases
- Models are a simplification of reality and model assumptions are crucial in the development of mathematical models
- However, several questions still remain:
  - How do we inform models using empirical data?
  - How can models be compared?
  - ...

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More in:

Hens, N., Shkedy, Z., Aerts, M., Faes, C., Van Damme, P. and Beutels, P. "Modeling Infectious Disease Parameters Based on Serological and Social Contact Data: A Modern Statistical Perspective" Springer-Verlag New York. 2012

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