L01 Compartmental Models[1]

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Statistical Methods in Infectious Disease Epidemiology
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Outline

Overview

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The Reed-Frost epidemic model

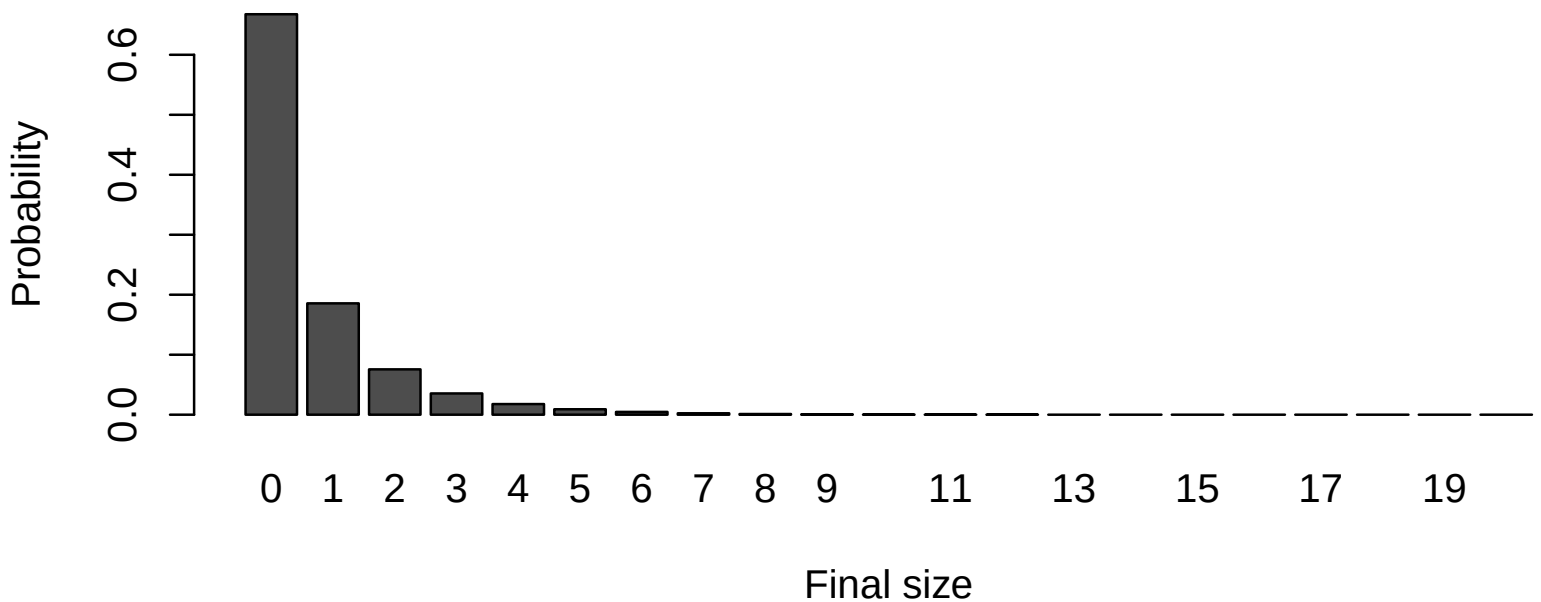
- Discrete-time SIR model, where individuals are either
  - *S*usceptible,
  - *I*nfectious or
  - *R*ecovered / *R*emoved (dead, isolated or immune)
- Closed population with initially
  - $x_0 = n$ susceptible and
  - $y_0 = m$ infectious individuals
- Dynamics are described by a discrete-time Markov chain

$$Y_{t+1}|x_t, y_t \sim \text{Bin}(x_t, 1 - (1 - w)^{y_t}),$$
$$X_{t+1} = x_t - Y_{t+1},$$

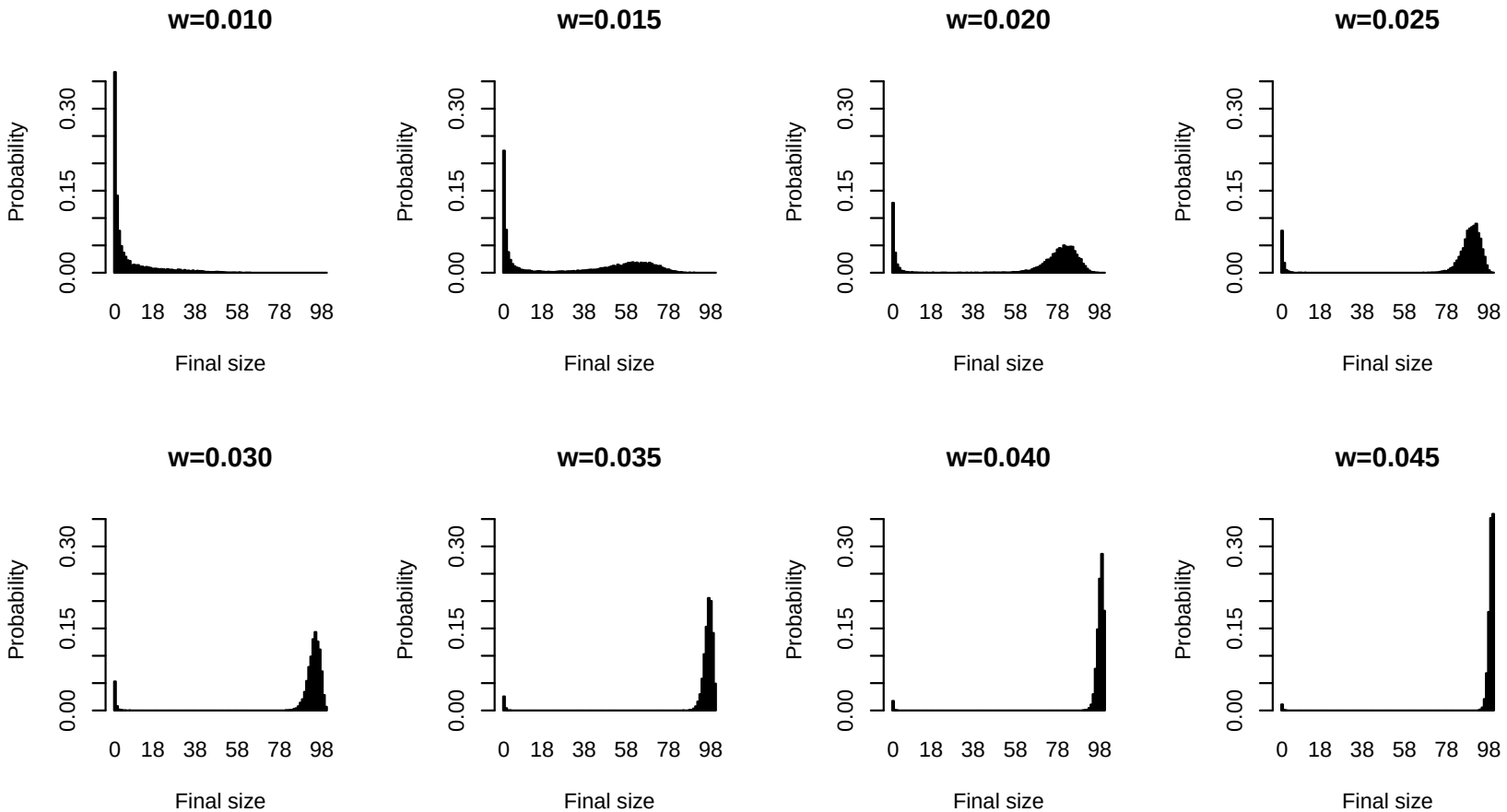
where w is the probability of an infectious contact between an infectious and a susceptible during one unit of time.

Final size distribution

- The *final size* of the epidemic is $Z = Y_1 + Y_2 + Y_3 + \ldots$
- Final size distribution can be computed exactly for small n, say $n \leq 30$.
- Final size distribution for $n = 20$, $m = 1$ and $w = 0.02$:



Simulated final size distribution for $n = 100$ and $m = 1$



R Code for Simulation of the Reed-Frost Model

```
fsize.RF <-
function(n, m, w, samples) {
  #Initial susceptible
  xj <- matrix(data=n,nrow=samples,ncol=1)
  #Initial infectives
  yj <- matrix(data=m,nrow=samples,ncol=1)

  #Loop over all (samples) simulations until they all are ceased.
  while (sum(yj>0) & sum(xj>0)) {
    #Sample from all processes concurrently
    yj <- ifelse(xj > 0, rbinom(samples, xj, 1-(1-w)^yj), 0)
    #Update all xj
    xj <- xj - yj
  }
  #Done
  return(n-xj)
}
```

Mathematical challenges

- Mathematical abstractions of real world phenomena $\rightarrow$ **equations**
- No outbreaks are similar $\rightarrow$ **stochasticity**
- Different modes of transmission: person-to-person, air-borne, water-borne, food-borne and vector-borne $\rightarrow$ **direct and indirect transmission**
- Population heterogeneity (e.g. different places of residence, contact behaviour, susceptibility) needs to be taken into account
- Conflict between observation frequency and speed of the epidemic $\rightarrow$ **time scale of a model**
- Not all relevant events for the course of the epidemic are observable $\rightarrow$ **partial observability**

Outline

The SIR model

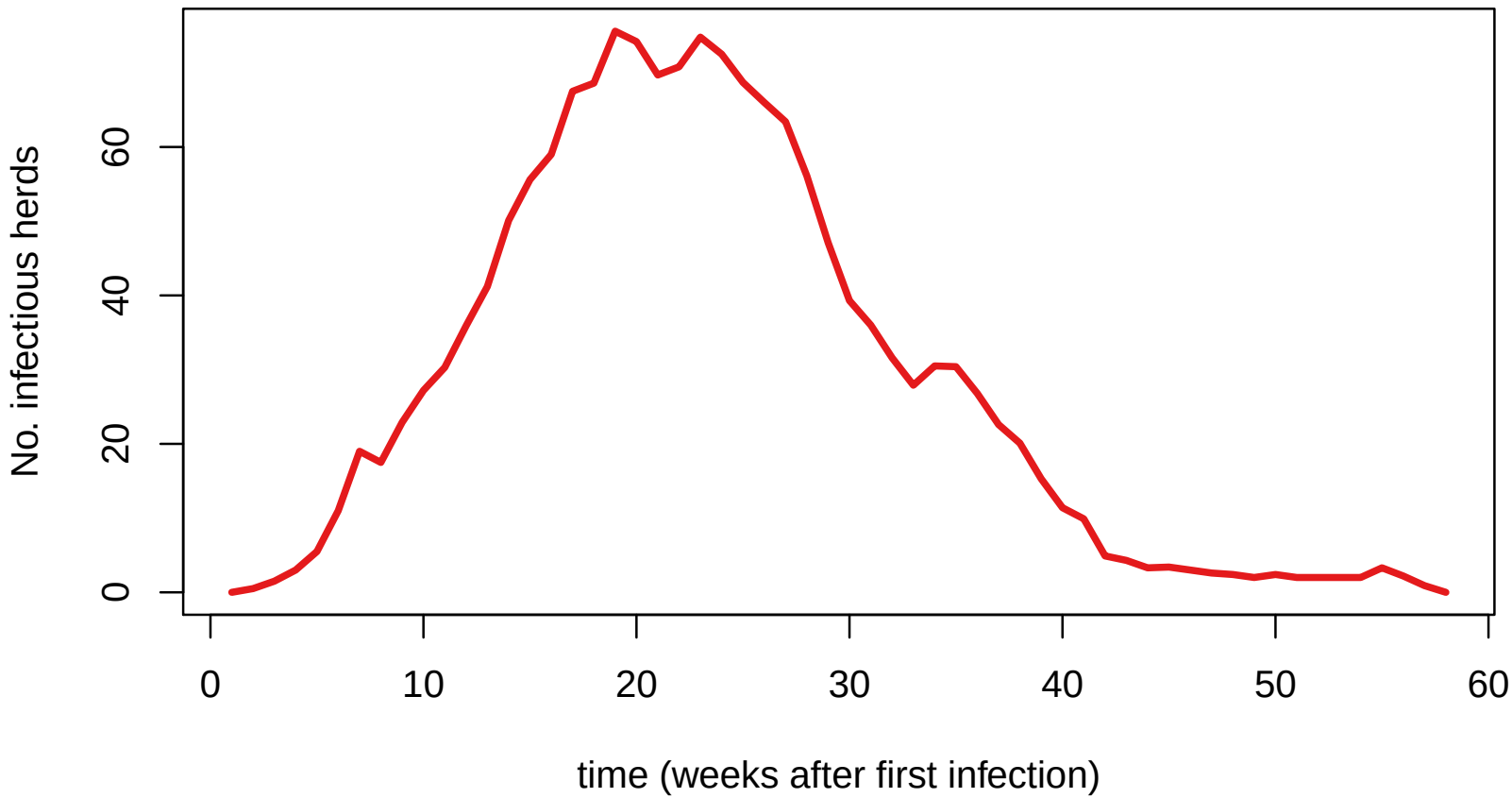
- When the population considered is large, it can be sufficient to disregard the stochasticity of the epidemic process and use deterministic models.
- Can formulate a continuous-time deterministic **SIR model** by using ordinary differential equations (ODEs).
- The deterministic system intends to model the mean behaviour of the underlying stochastic system.
- We assume a closed population (i.e. no demographics turnover) of size N.

Example: CSFV in The Netherlands (1)

- Classical swine fever virus (CSFV) is a highly contagious disease of pigs and wild boar.
- Characteristics of the disease are
  - Symptoms after infection: dullness and anorexia.
  - Acute form: rapid mortality often without clinical symptoms.
  - Secondary symptoms: diarrhea or respiratory problems.
- A huge outbreak in the Netherlands took place between February 1997 and May 1998.
  - 429 infected herds detected and stamped out ($\sim$ 700,000 pigs)
  - 1286 herds pre-emptively slaughtered ($\sim$ 1.1 million pigs)
  - Note: Netherlands has approximately 21,500 pig herds

Example: CSFV in the Netherlands (2)

- Stegeman, Elbers, Smak, and de Jong (1999) provide estimates on the weekly number of infectious herds from contact tracing and serological analysis:



SIR differential equation system

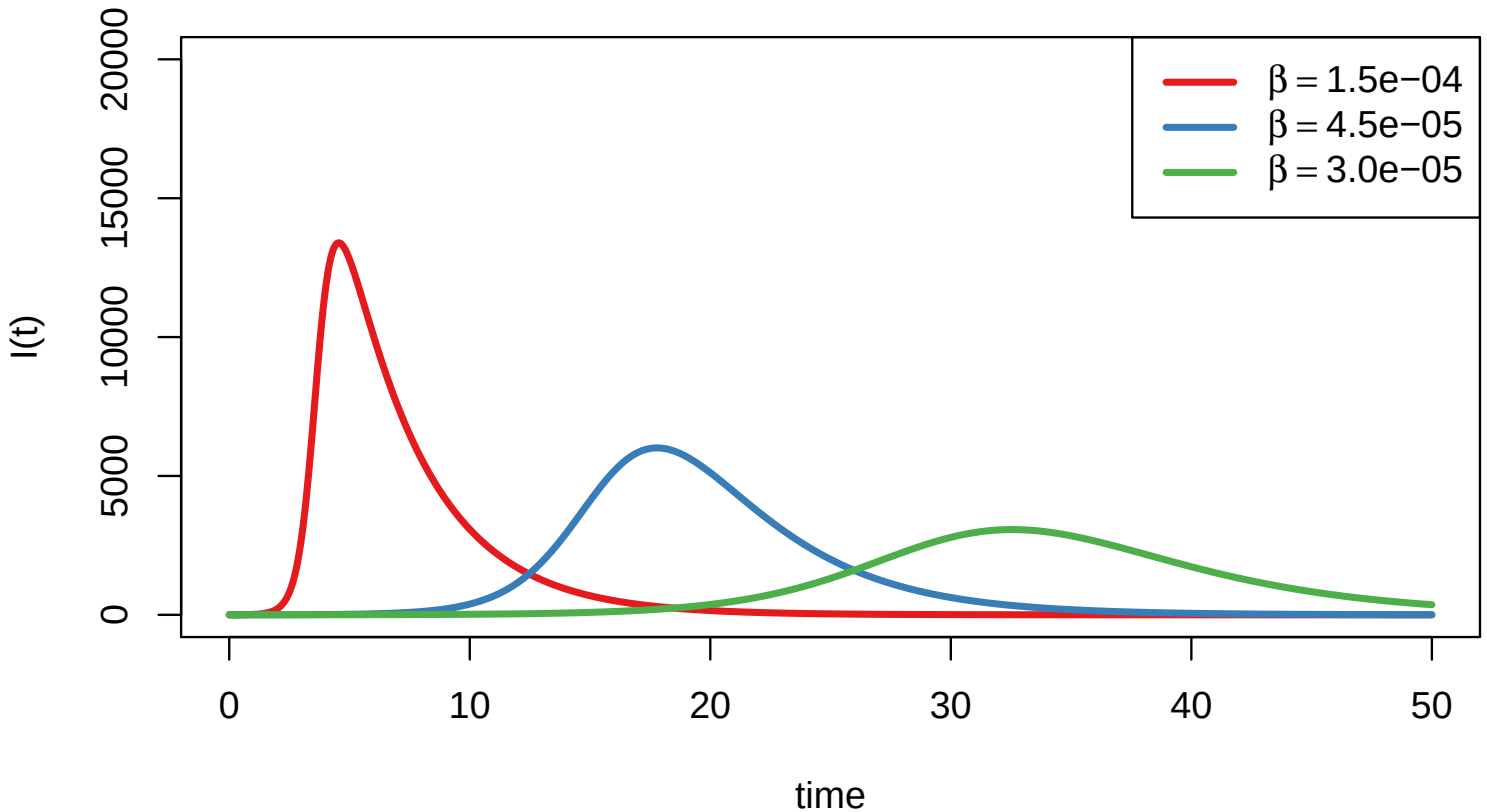
- As before, divide population into three groups
  - *S*usceptible,
  - *I*nfectious or
  - *R*ecovered / *R*emoved
- At all times $S(t) + I(t) + R(t) = N$, so $S(0) + I(0) = N$.
- Describe dynamics using an ordinary differential equation system

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

  where β, $\gamma > 0$.
- Solve ODE with initial condition $(S(0), I(0), 0)$ using numerical routines (`R` package `deSolve`).

Example

- Number of infected $I(t)$ for $\gamma = 0.3$, $N = 2 \times 10^4$, $I(0) = 1$ and different values of β.



Numerical Solution of the SIR ODE

- Defining the vector of derivatives for the SIR ODE

```
#####################################################################
# Function to compute the derivative of the ODE system
#
#  t - time
#  y - current state vector of the ODE at time t
#  parms - Parameter vector used by the ODE system
#
# Returns:
#  list containing dS(t)/dt and dI(t)/dt
#####################################################################

sir <- function(t,y, parms) {
  beta <- parms[1]
  gamma <- parms[2]
  S <- y[1]
  I <- y[2]
  return(list(c(S=-beta*S*I,I=beta*S*I-gamma*I)))
}
```

- Use `deSolve::lsoda`

```
sim <- lsoda(y=c(N-1,1), times=times, func=sir,parms=c(beta.grid[1],gamma))
head(sim, n=3)
##             time        1        2
## [1,] 0.00000000 19999.00 1.000000
## [2,] 0.05005005 19998.84 1.144682
## [3,] 0.10010010 19998.66 1.310297
```

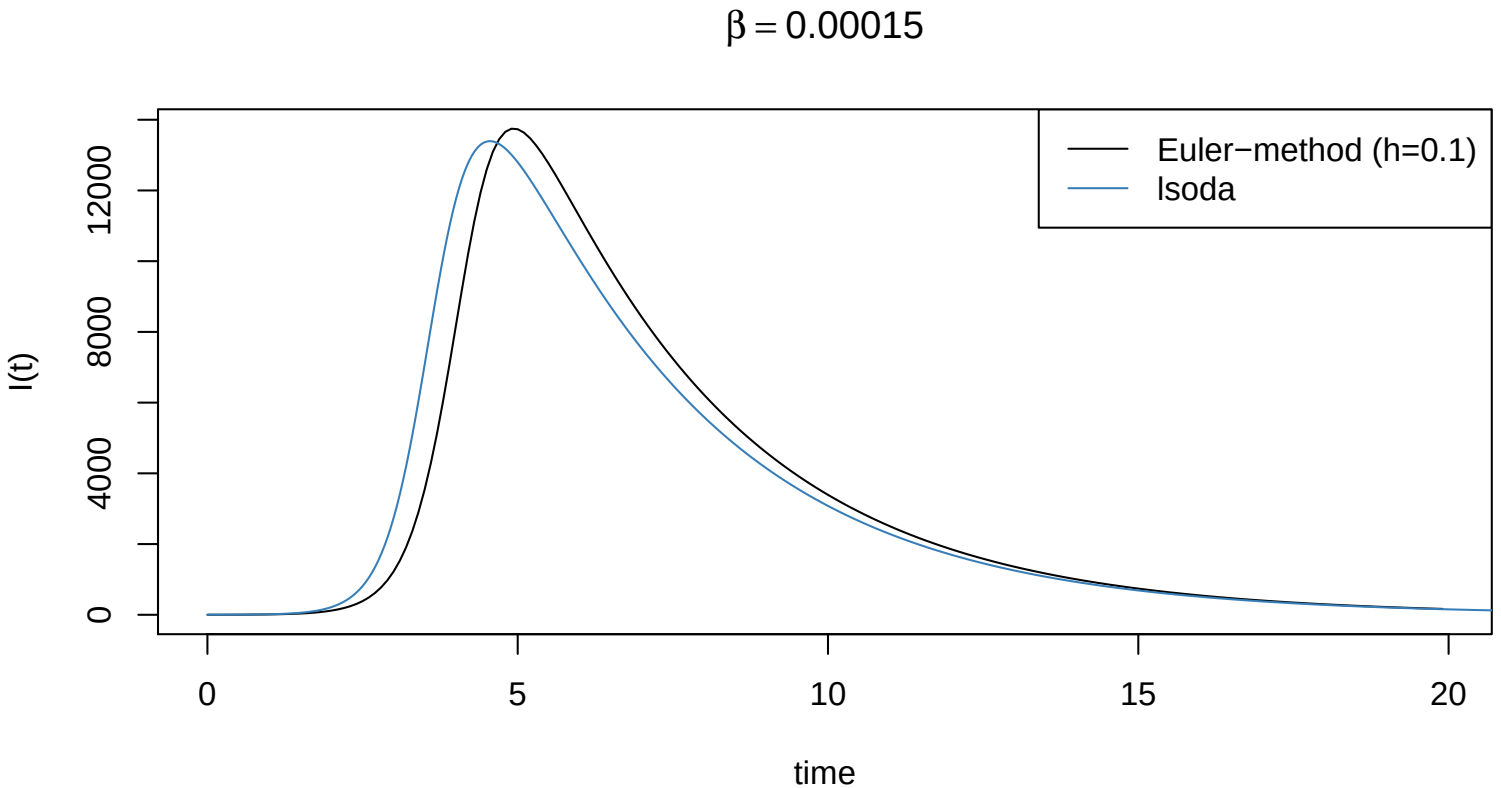
Aside: Numerical Solution of ODEs (1)

- Simple method to solve an ODE system numerically given the initial condition: Euler-Method
- Example in R: Stepwidth h and initial value is $S(0) = N - 1$ and $I(0) = 1$

```
# Step width of the Euler method
h <- 0.1
y <- matrix(NA, nrow=ceiling(20/h), ncol=3, dimnames=list(NULL, c("t","S","I")))
# Initial value
y[1,] <- c(0,N-1,1)
# Loop
for (i in 2:nrow(y)){
  y[i,] <- c(y[i-1,"t"]+h, y[i-1,c("S","I")] +
          h * sir(y[i-1,"t"], y[i-1,c("S","I")], parms=c(beta.grid[1],gamma))[[1]])
}
```

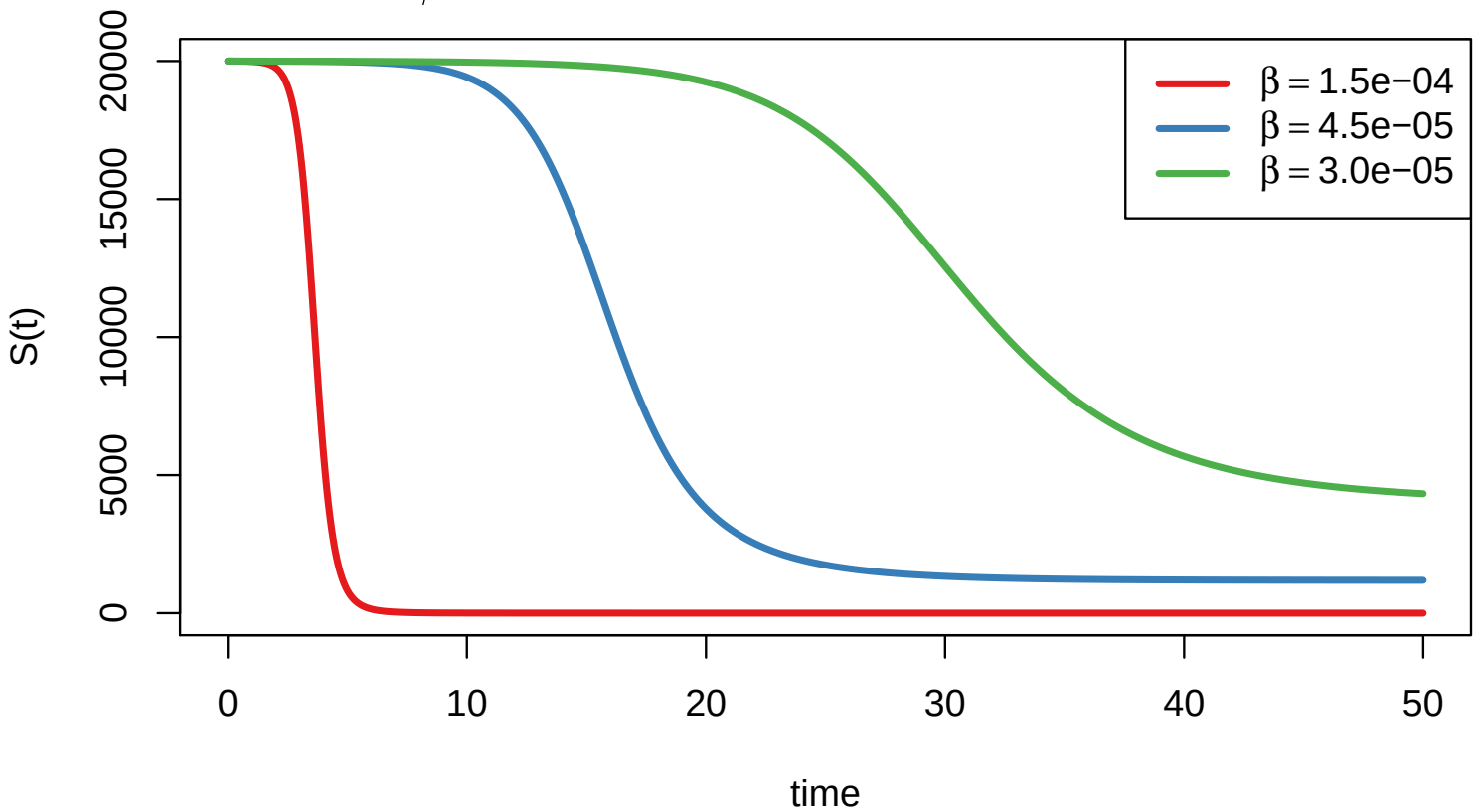
Aside: Numerical Solution of ODEs (2)

- Plot for Euler solve for SIR system



Example cont.

- Number of susceptibles $S(t)$ for $\gamma = 0.3$, $N = 2 \times 10^4$, $I(0) = 1$ and different values of β.



The basic reproduction number R_0

Basic reproduction number R_0

R_0 is the number of new infections produced by one infected in a fully susceptible population

- If $R_0 < 1$ the number of infected is expected to fade out right after introduction. If $R_0 > 1$ an epidemic will result.
- In a simple SIR model
$$R_0 = \frac{\beta N}{\gamma}.$$
- In the previous example we thus have $R_0 = 10$, 3 and 2.

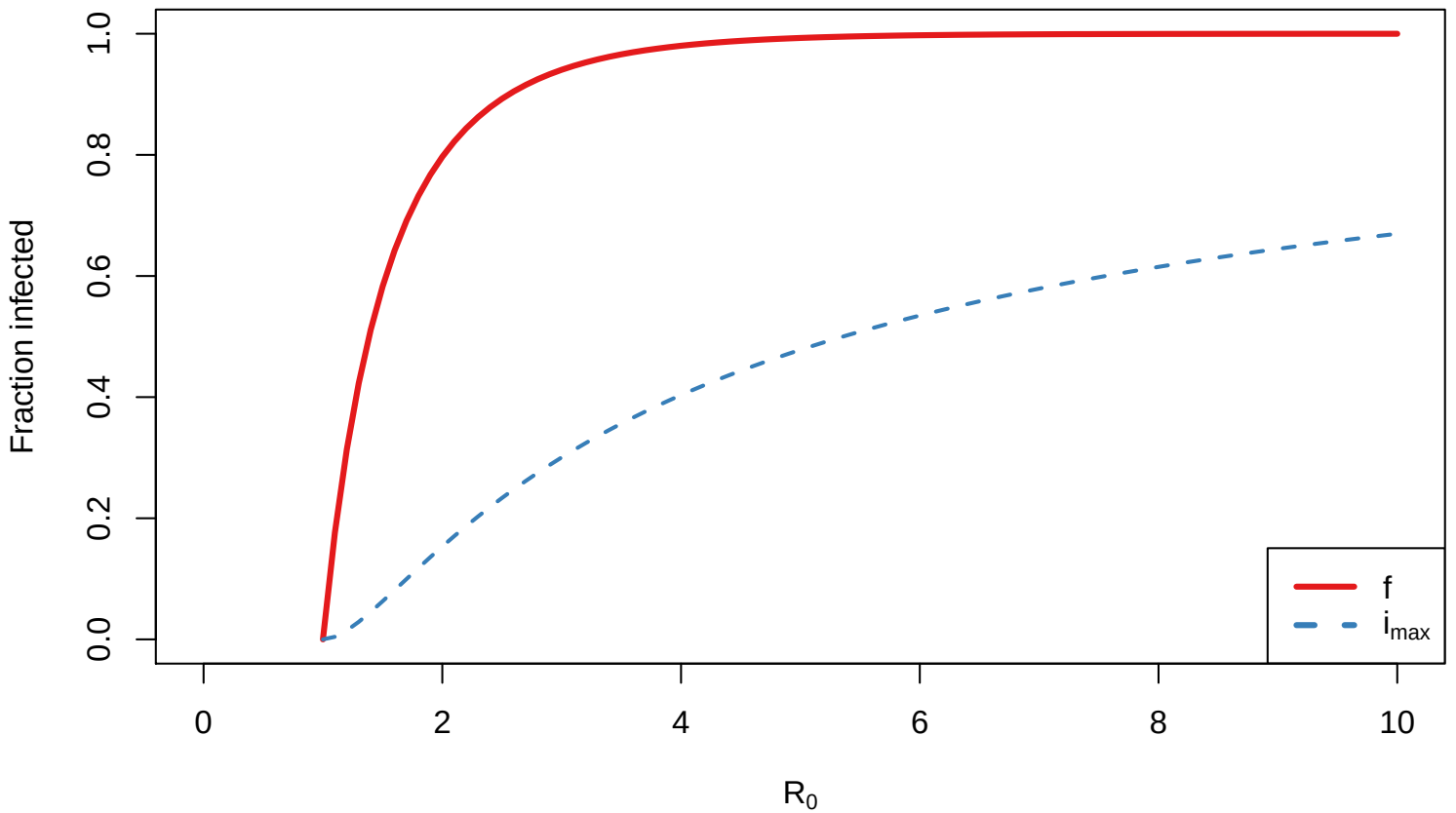
The final size of an epidemic (1)

- In a closed population the number of susceptibles can only decrease, hence it must have a limit for $t \to \infty$.
- Is the limit zero? Or will some fraction of the population escape from ever getting infected?
- Let f be the fraction of the (initially susceptible) population that got infected. This is also called the *final size* of the epidemic.
- It can be found as the solution to the equation

$$1 - f = \exp(-R_0 f).$$

The final size of an epidemic (2)

- For fixed R_0 the final size equation can be solved numerically
- Plot of f as a function of R_0 together with $i_{\max} = \max_{0 \le t \le \infty} (I(t)/N)$:



- In the example we thus have $f = 1$, 0.94 and 0.8.

Outline

Stochastic SIR model in continuous time (1)

- If the population under study is large enough, deterministic approximations are reasonably valid to obtain an understanding of the disease.
- In small populations, however, stochasticity plays an important role for extinction, which cannot be ignored.
- Stochastic epidemic modeling is described in Becker (1989), Daley and Gani (1999) and Andersson and Britton (2000), who all rely heavily on the theory of stochastic processes.

Stochastic SIR model in continuous time (2)

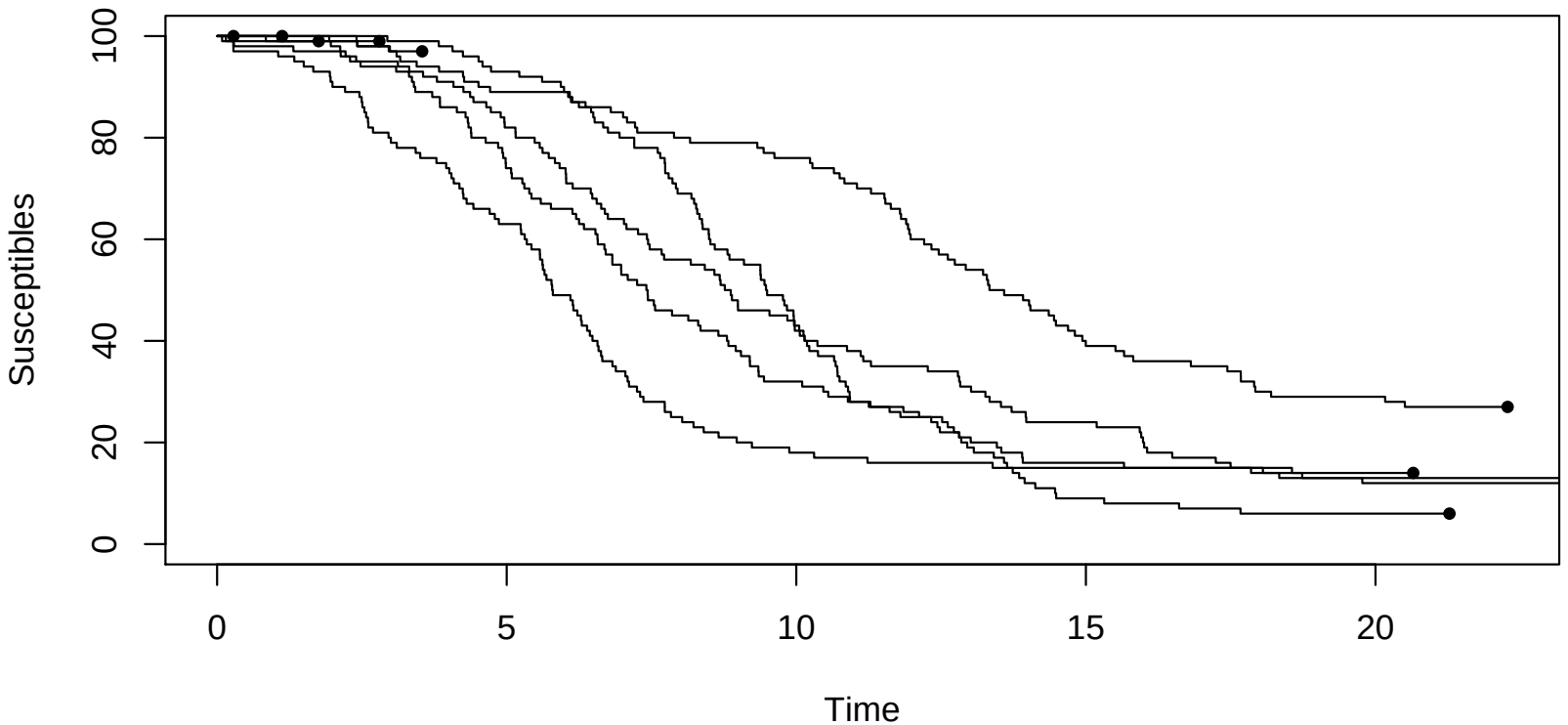
- The *stochastic SIR model* can be described as a continuous-time Markov process, where the event rates for infection and removal are:

Event		Transition	Rate
Infection:	$(S(t), I(t))$	$\to (S(t)-1, I(t)+1)$	$\beta \cdot S(t) \cdot I(t)$
Removal:		$\to (S(t), I(t)-1)$	$\gamma \cdot I(t)$

- Again, $R(t)$ is implicitly given, because a fixed population of size $S(0) + I(0)$ is assumed.
- The integer size of the population is now taken into account: Once $I(t) = 0$, the epidemic ceases.
- Point process viewpoint: piecewise constant rates, while the length of the infective period is exponentially distributed.

Stochastic SIR model in continuous time (3)

10 SIR simulations with $S(0) = 100$, $I(0) = 1$, $\beta = 0.01$ and $\gamma = 0.5$:



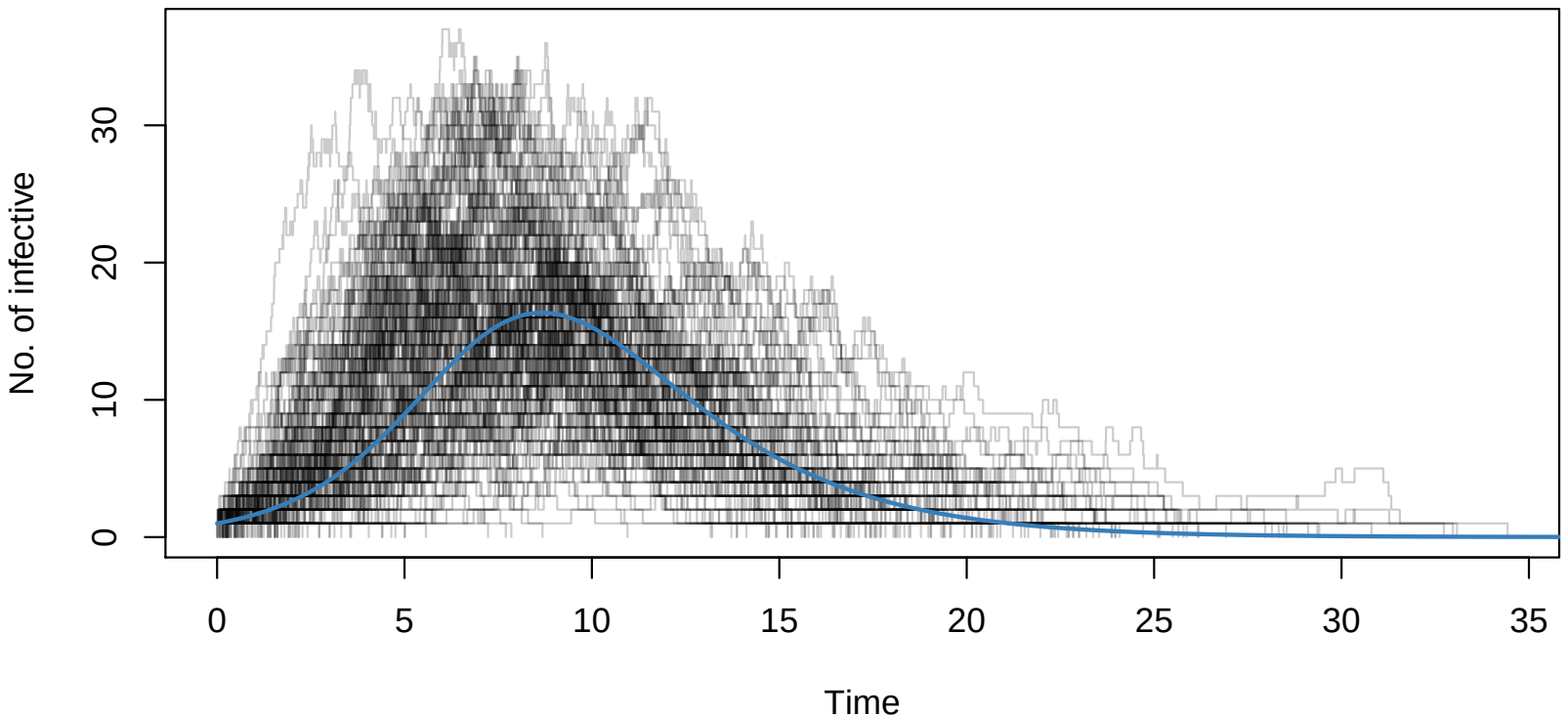
R Code for Simulation of the Stochastic SIR Model

```
rSIR <-
function(T, beta, gamma, n, m) {
  #Initialize (x= number of susceptibles)
  t <- 0
  x <- n
  y <- m

  #Possible events
  eventLevels <- c("S->I","I->R")
  #Initialize result
  events <- data.frame(t=t,x=x,y=y,event=NA)
  #Loop until we are past time T
  while (t < T & (y>0)) {
      #Draw the waiting type for each possible event
      wait <-  rexp(2,c("S->I"=beta*x*y,"I->R"=gamma*y))
      #Which event occurs first
      i <- which.min(wait)
      #Advance Time
      t <- t+wait[i]
      #Update population according to the eventy type
      if (eventLevels[i]=="S->I") { x <- x-1 ; y <- y+1}
      if (eventLevels[i]=="I->R") { y <- y-1 }
      #Store result
      events <- rbind(events,c(t,x,y,i))
  }
  #Recode event type and return
  events$event <- factor(eventLevels[events$event], levels=eventLevels)
  return(events)
}
```

Stochastic SIR vs. determinstic SIR model

Same parameters as previously - 250 trajectories vs. the ODE solution:



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