Bayesian workflow for disease transmission modeling in Stan

Eustat – XXXIII International Statistical Seminar

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Preface

- Objective: fit transmission models in Stan
- Based on Grinsztajn et al., 2020 (link)
- Prerequisites:
  - general understanding of Bayesian inference
  - basic programming with `R` and `Stan`
- All material is available on
  `https://github.com/jriou/bayesian_workflow`

Outline

- **Introduction**
- (Quick notice: Bayesian inference with Stan)
- Fitting a simple SIR
- Simulations to understand the model
- Scaling up ODE-based models
- Extensions

Introduction

Models of disease transmission:

- Interpretability: mechanistic, phenomenological
- Scale: agent-based, population-based
- Framework: deterministic, stochastic
- Data-generating mechanisms: incubation, contagion, immunity...

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Mechanistic + population-based + deterministic

$\rightarrow$ ordinary differential equations (ODE)-based compartmental model

Introduction

ODE-based compartmental model:

- Divide the population into homogeneous groups (compartments)
- Define the flows between compartments with ODEs
- Define initial conditions (at t_0)
- Solve for the time-dependent volume in each compartment

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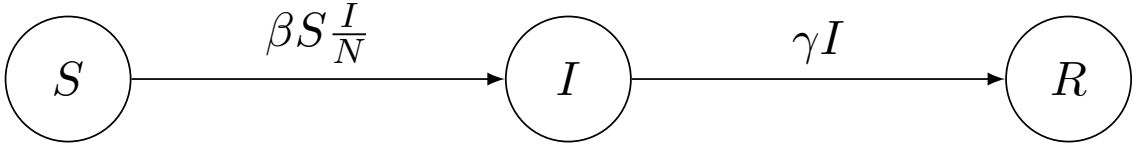
The susceptible-infectious-recovered (SIR) model:

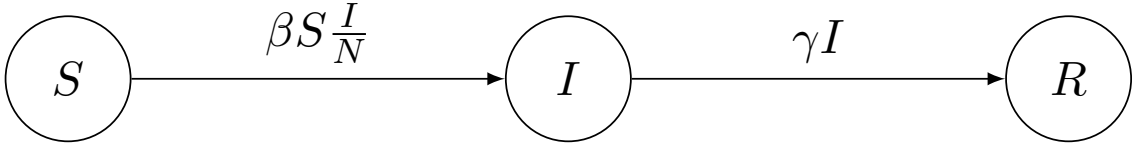


$$\frac{dS}{dt} = -\beta S \frac{I}{N}$$

$$\frac{dI}{dt} = \beta S \frac{I}{N} - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

Introduction



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$$\frac{dI}{dt} = \beta S \frac{I}{N} - \gamma I$$

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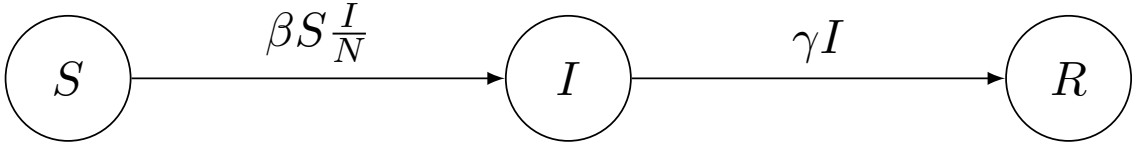
Where:

- $S(t)$ is the number of people susceptible to infection
- $I(t)$ is the number of people infected (i.e. the prevalence)
- $R(t)$ is the number of people recovered (lifelong immunity)
- N is the population size ($S(t) + I(t) + R(t) = N$ for any t)
- β is the infectious contact rate (per day per person)
- γ is the recovery rate (1/infectious period)

Introduction



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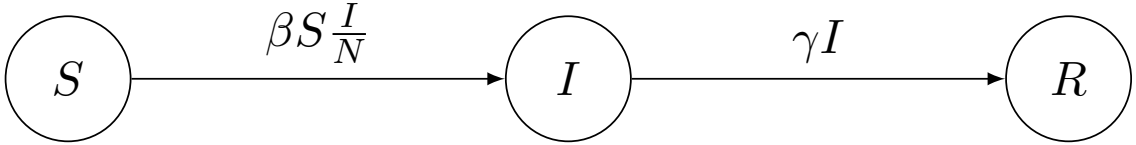
Intuition behind the SIR model:

- $I(t)/N$ is the proportion of infected (and infectious)
- $\beta I(t)/N$ is the daily number of contacts with infectious people
- hence each day, $\beta S I(t)/N$ people become infected (the force of infection)

Introduction



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Assumptions behind the SIR model:

- homogeneous mixing
- β and γ constant over time
- all infections are observed
- no incubation, exponentially-distributed recovery
- lifelong immunity
- stable population

Introduction

Simulate in `R` with package `deSolve`:

- set compartments and differential equations

```
> ## Set model ----
> seir = function(t, x, parms, ...) {
+   with(as.list(c(parms, x)), {
+     dS = - beta*S*I/(S+I+R)
+     dI = beta*S*I/(S+I+R) - gamma*I
+     dR = gamma*I
+     list(c(dS, dI, dR))
+   })
+ }
```

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+ }
```

- set (fixed) values for $\beta = 0.8$; $\rho = 1/7$; $S_0 = 100,000 - 50$; $I_0 = 50$ and $R_0 = 0$

```
> ## Set parameters ----
> pars = c(beta = 0.8,
+          gamma = 1/7
+ )
```

```
> ## Set initial values ----
> N_0 = 100000
> I_0 = 50
> inits = c(
+   S = N_0 - I_0,
+   I = I_0,
+   R = 0
+ )
```

Introduction

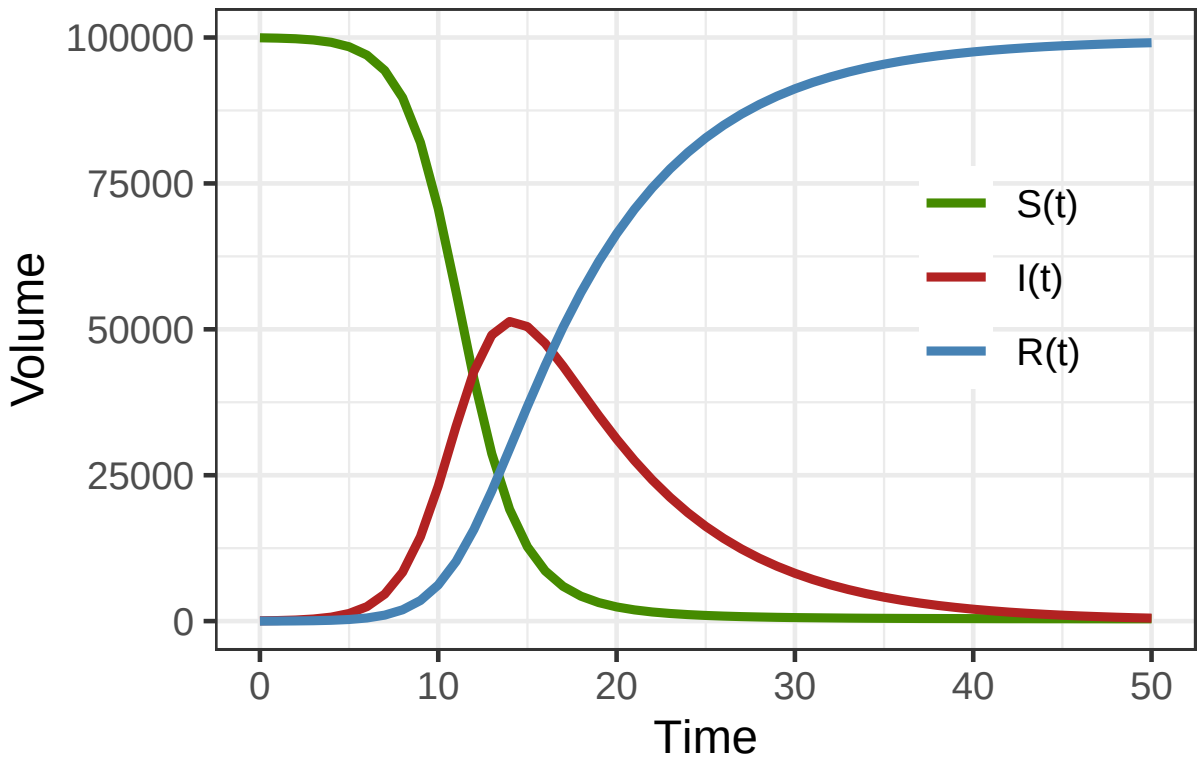
- solve the ODE system numerically (Runge-Kutta 4th order) to obtain unique solutions for $S(t)$, $I(t)$ and $R(t)$

$$f(\beta, \gamma, S_0, I_0, R_0) = \{S(t), I(t), R(t)\}$$

```
> ## Simulate ----
> times = seq(0,50,by=1)
> sim_data = ode(inits, times, seir, pars,method="rk4")
> tibble(sim_data)
# A tibble: 51 x 1
   sim_data[,"time"] [,"S"]  [,"I"] [,"R"]
               <dbl>  <dbl>   <dbl>  <dbl>
 1                 0 99950     50      0
 2                 1 99894.    96.3   10.1
 3                 2 99785.   186.    29.5
 4                 3 99576.   357.    66.9
 5                 4 99176.   685.   139.
 6                 5 98415.  1308.   276.
 7                 6 96984.  2478.   538.
 8                 7 94350.  4621.  1030.
 9                 8 89692.  8374.  1934.
10                 9 82009. 14457.  3533.
# … with 41 more rows
```

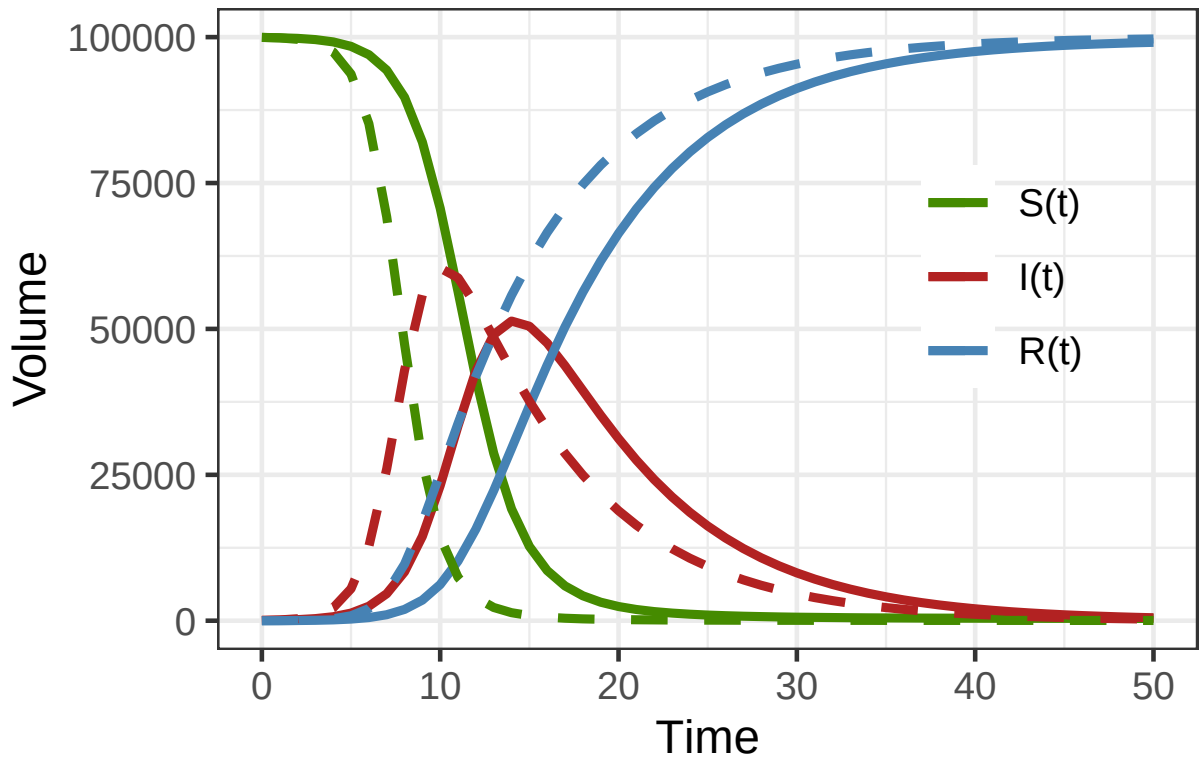
Introduction

with $\beta = 0.8$; $\rho = 1/7$; $S_0 = 100000 - 50$; $I_0 = 50$ and $R_0 = 0$



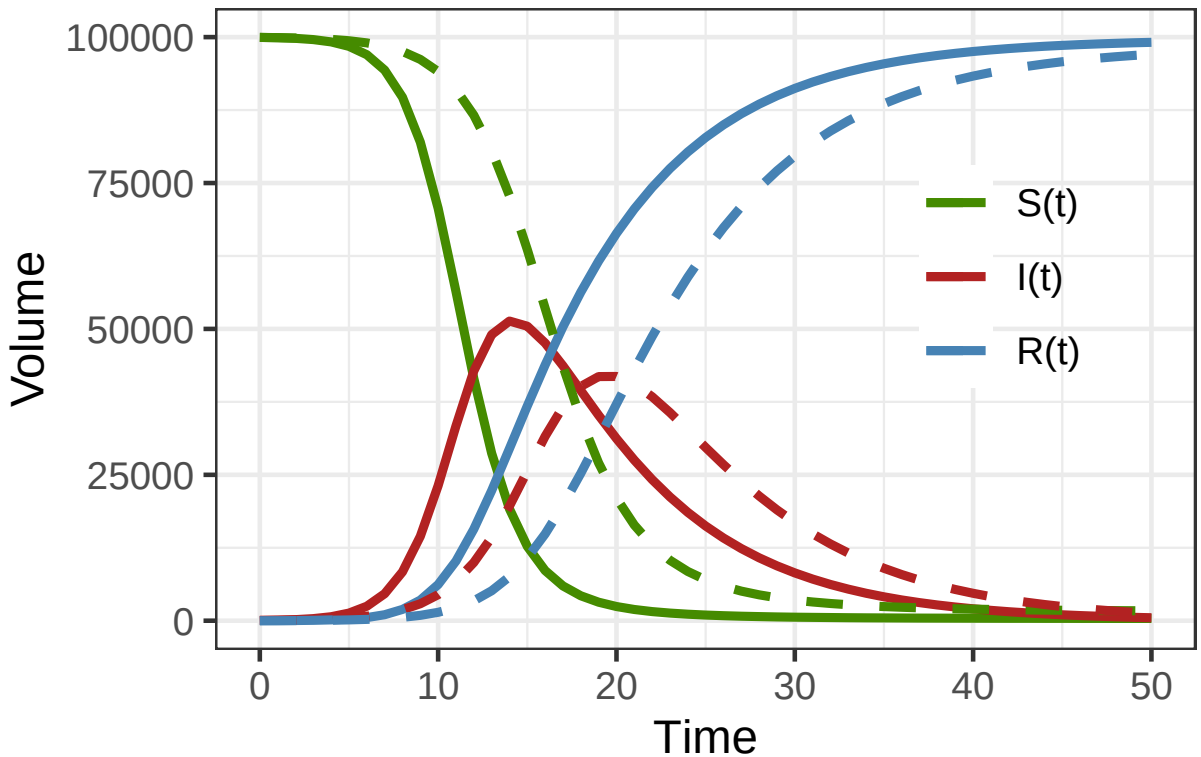
Introduction

with $\beta = 1.1$ instead of 0.8, we get



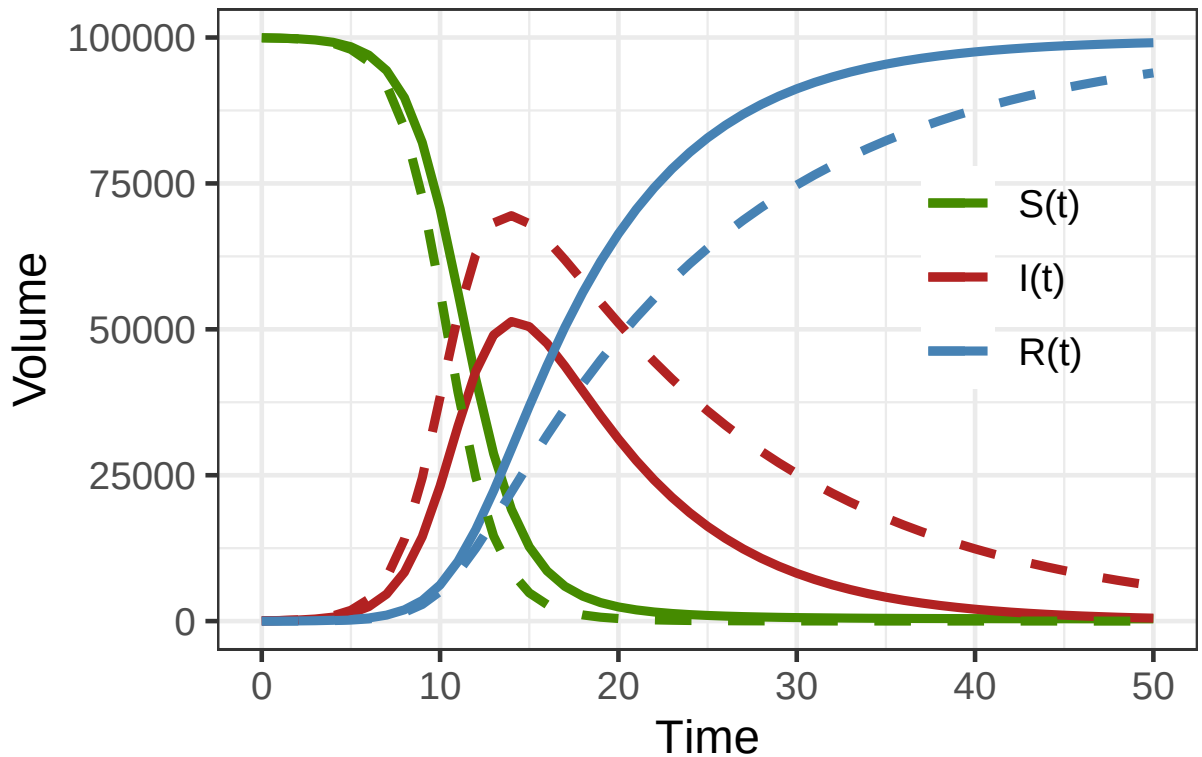
Introduction

with $\beta = 0.6$ instead of 0.8, we get



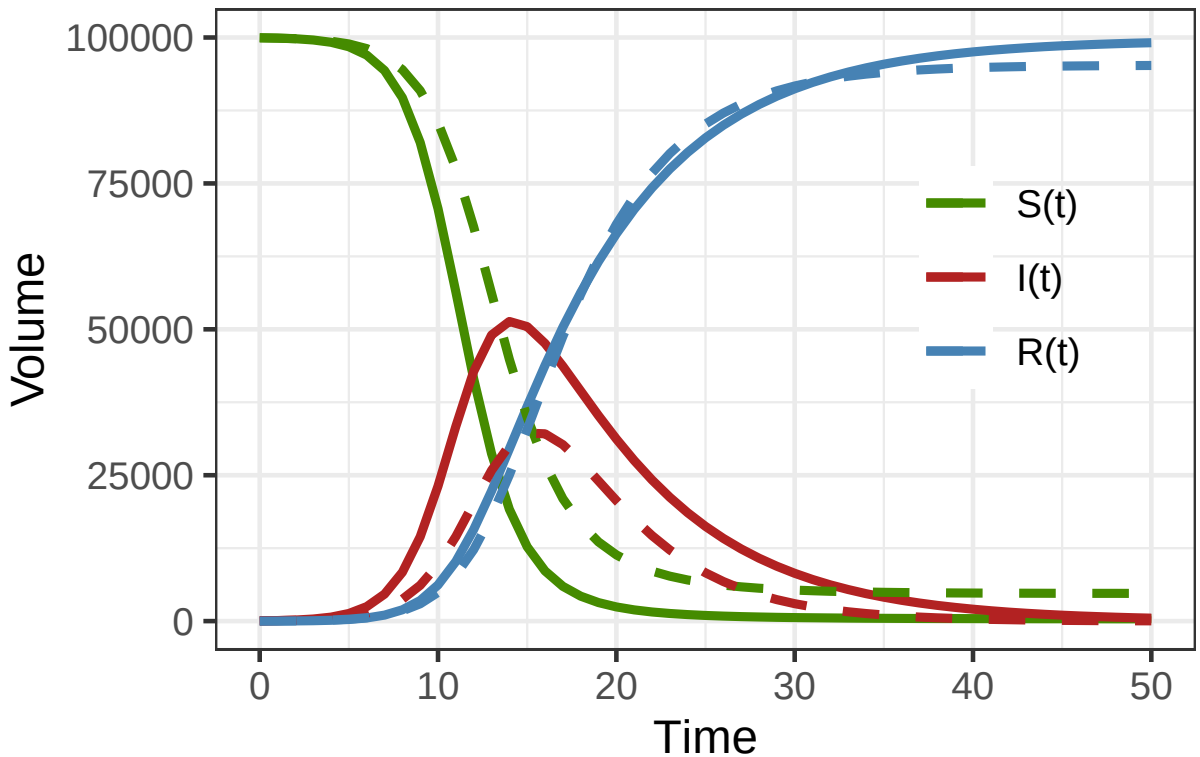
Introduction

with $\gamma = 1/14$ instead of $1/7$, we get



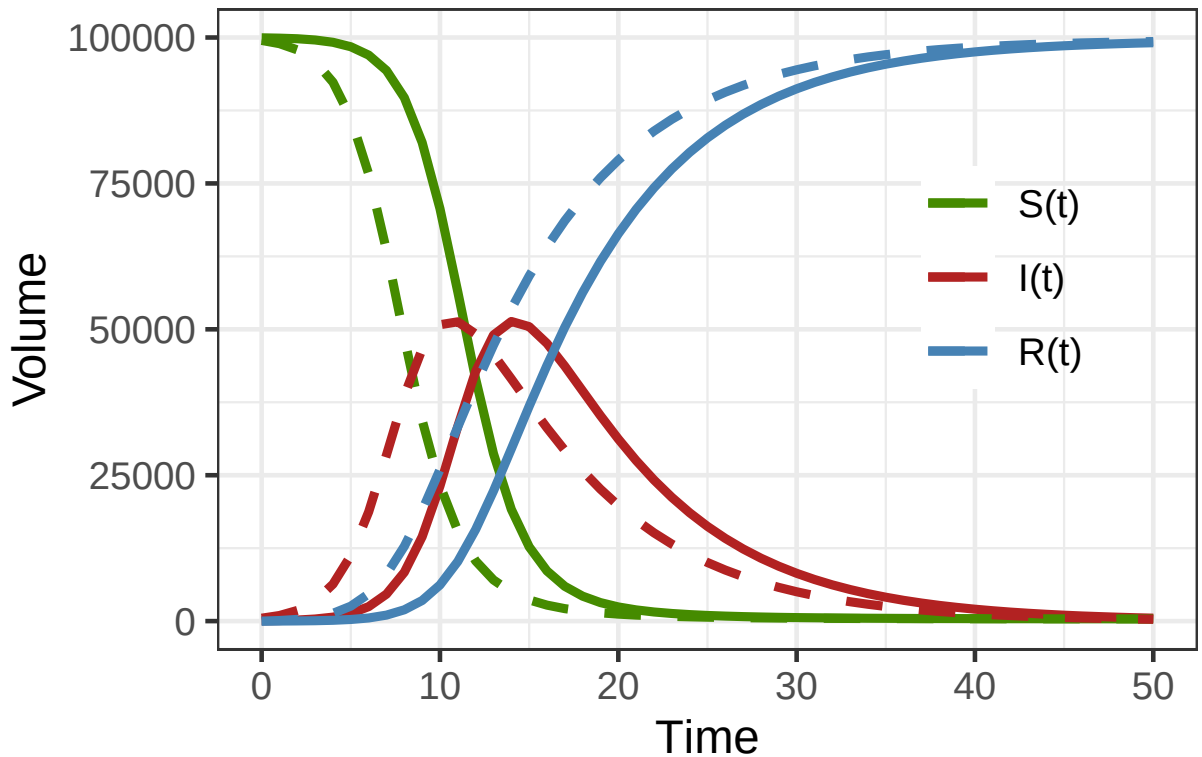
Introduction

with $\gamma = 1/4$ instead of $1/7$, we get



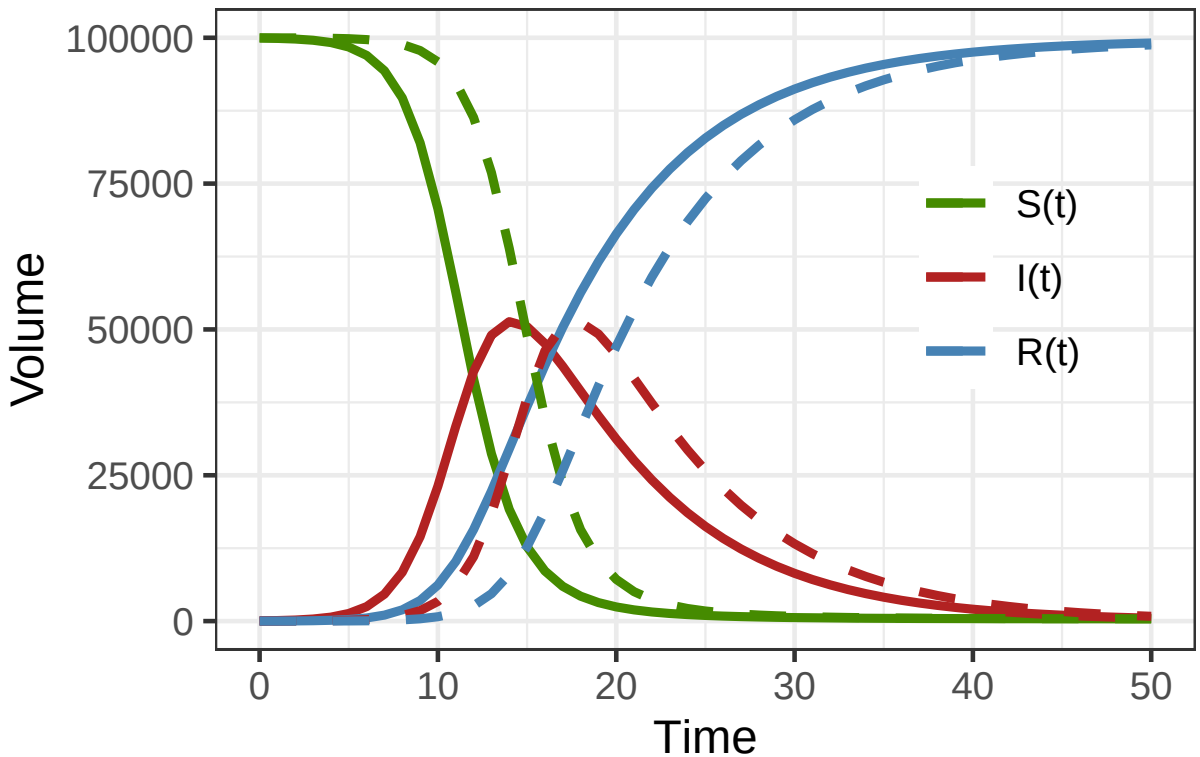
Introduction

with $I(0) = 500$ instead of 50, we get



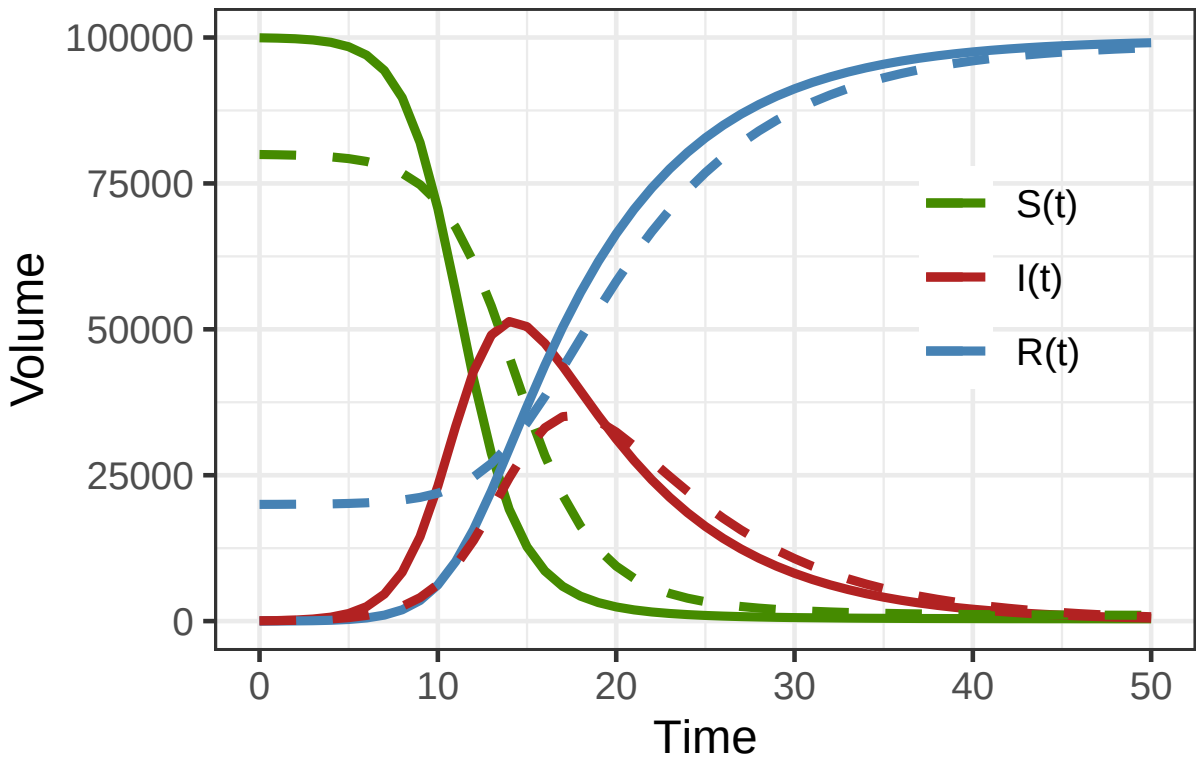
Introduction

with $I(0) = 5$ instead of 50, we get



Introduction

with $R(0) = 20,000$ instead of 0, we get



Introduction

Compartmental models have many uses:

- formalize and put numerical values on general concepts (herd immunity, vaccination threshold...)
- get mechanistic insight about an epidemic (transmissibility levels, drivers of transmission)

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

- produce precise forecasts (based on mechanisms)

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- produce precise forecasts (based on mechanisms)

$\rightarrow$ all these uses are based on numerical values for β, ρ and the initial conditions and their uncertainty

Introduction

Enters Bayesian inference:

- infer parameter values by integrating data and domain knowledge
- more efficient for complex models (high dimensionality)
- rigorously quantify and propagate uncertainty in parameter estimates and forecast

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$\rightarrow$ Markov Chain Monte Carlo (MCMC) methods and Stan

Outline

- Introduction
- **(Quick notice: Bayesian inference with Stan)**
- Fitting a simple SIR
- Simulations to understand the model
- Scaling up ODE-based models
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(Bayesian inference with Stan)

General principle of Bayesian inference:

- specify a complete Bayesian model
  - consider data $y = \{y_1, ..., y_n\}$ and parameter θ
  - specify an observation model

$$\Pr(y|\theta) = \prod_n \text{normal}(y_n|\theta, 1)$$

  - complete the model with a prior distribution

$$\Pr(\theta) = \text{normal}(0, 1)$$

- sample the posterior distribution of the parameter

(Bayesian inference with Stan)

Stan is a probabilistic programming framework for Bayesian inference

- it is designed to let the user focus on modeling while inference happens under the hood
- object-oriented language (based on `C++`) that supports many operations, probability densities and ODE solvers
- extremely efficient MCMC algorithm (Hamiltonian Monte Carlo)
- diagnostic tools to evaluate the inference
- interfaces in `R` (package `rstan`), `python`, `julia`...

(Bayesian inference with Stan)

Programming in Stan is structured in blocks:

- the `data` block defines data variables

```
data {
  int N;
  real y[N];
}
```

- the `parameters` block defines parameters

```
parameters {
  real theta;
}
```

- the `model` block defines the target log probability density function

```
model {
  theta ~ normal(0,1);
  y ~ normal(theta,1);
}
```

- save in `model_linear.stan`

(Bayesian inference with Stan)

We then explore the target with Stan's MCMC sampler:

- load `rstan` package

```
## Setup ----
library(rstan)
options(mc.cores = parallel::detectCores())
```

- simulate $N = 50$ data points with $\theta = 0.7$

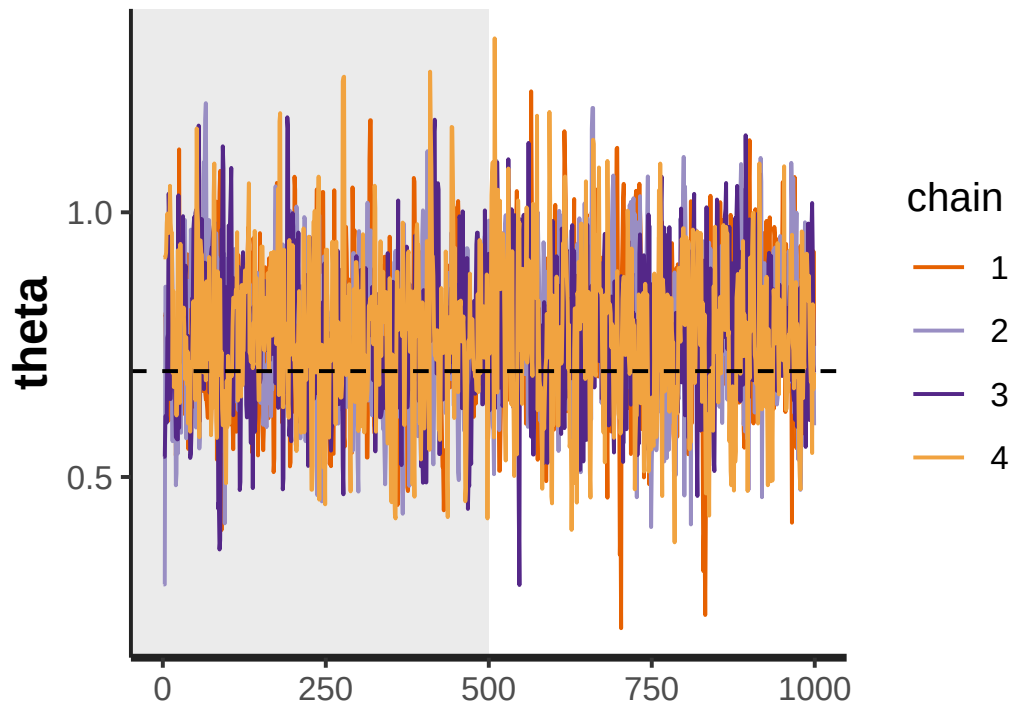
```
## Simulate data ----
N = 50
theta = 0.7
y = rnorm(N,theta,1)
input_data = list(N=N,y=y)
```

- run MCMC sampling

```
## Sample ----
fit = stan(file='model_linear.stan',
           data=input_data,
           chains=4,
           iter=1000)
```

(Bayesian inference with Stan)

We use multiple chains that should converge after warm-up



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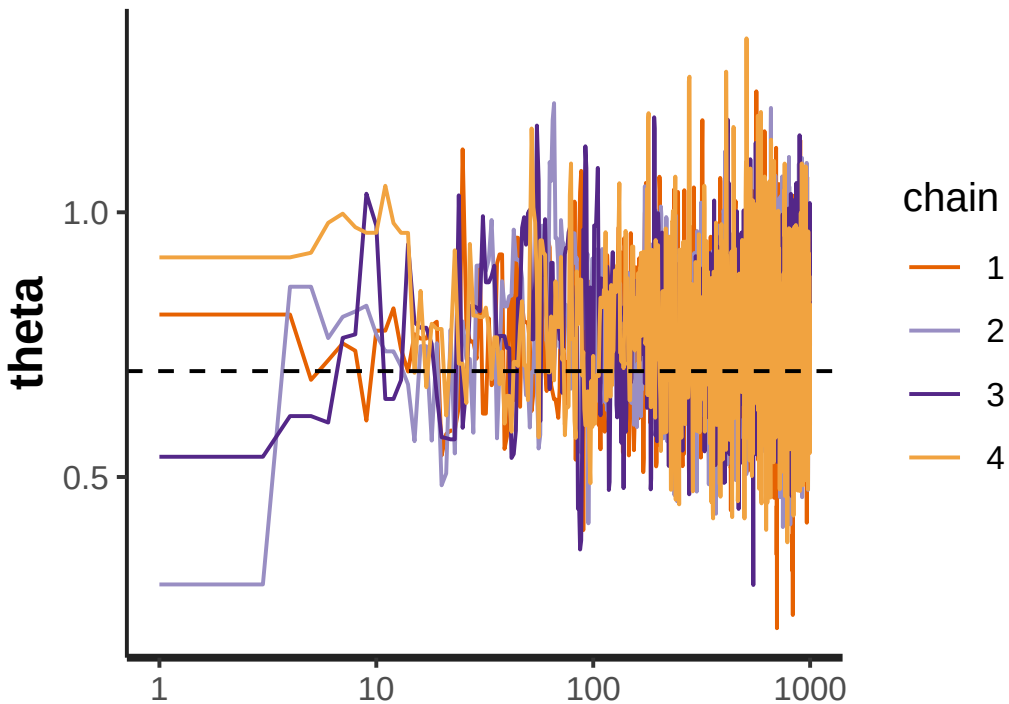
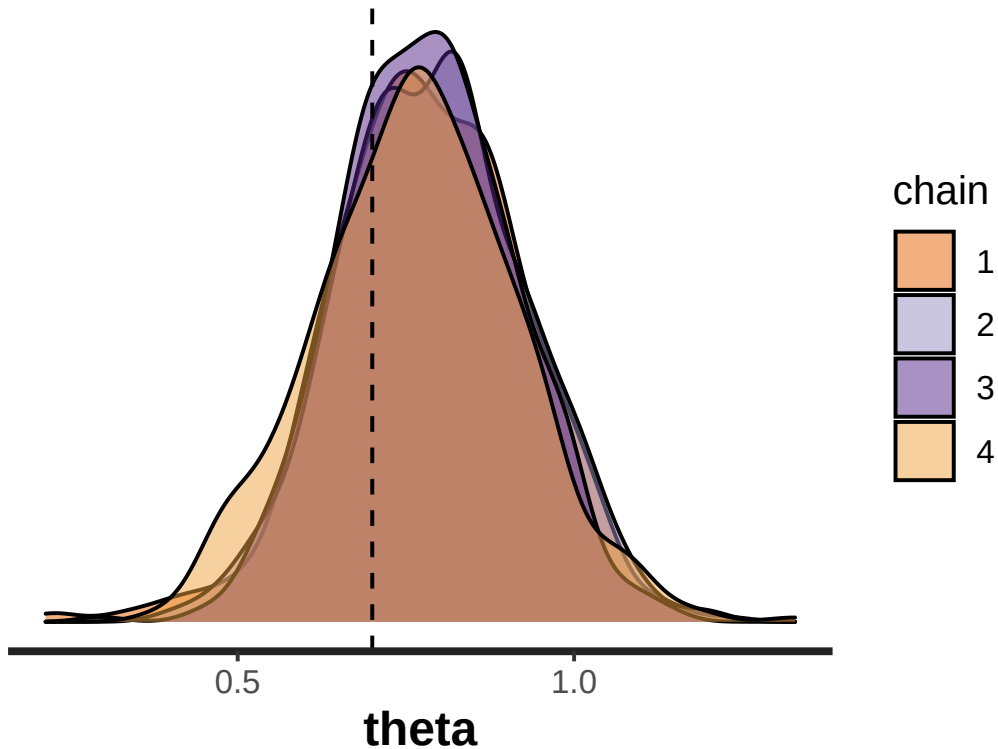


(Bayesian inference with Stan)

The post-warm-up samples of θ approximate its posterior distribution



(Bayesian inference with Stan)

We run basic diagnosis tools: divergences, tree depth, energy

```
> check_hmc_diagnostics(fit)

Divergences:
0 of 2000 iterations ended with a divergence.

Tree depth:
0 of 2000 iterations saturated the maximum tree depth of 10.

Energy:
E-BFMI indicated no pathological behavior.
```

(Bayesian inference with Stan)

Printing the object gives:

- diagnostics: effective sample size, Gelman-Rubin $\hat{R}$
- inference: full posterior distribution of θ

```
> print(fit)
Inference for Stan model: model_linear.
4 chains, each with iter=1000; warmup=500; thin=1;
post-warmup draws per chain=500, total post-warmup draws=2000.

        mean se_mean   sd   2.5%    25%    50%    75%  97.5% n_eff Rhat
theta   0.78    0.01 0.14   0.51   0.69   0.78   0.87   1.05   760    1
lp__  -18.30    0.03 0.73 -20.28 -18.44 -18.03 -17.86 -17.81   799    1

Samples were drawn using NUTS(diag_e) at Thu Nov 12 19:15:33 2020.
For each parameter, n_eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor on split chains (at
convergence, Rhat=1).
```

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- Introduction
- (Quick notice: Bayesian inference with Stan)
- **Fitting a simple SIR**
- Simulations to understand the model
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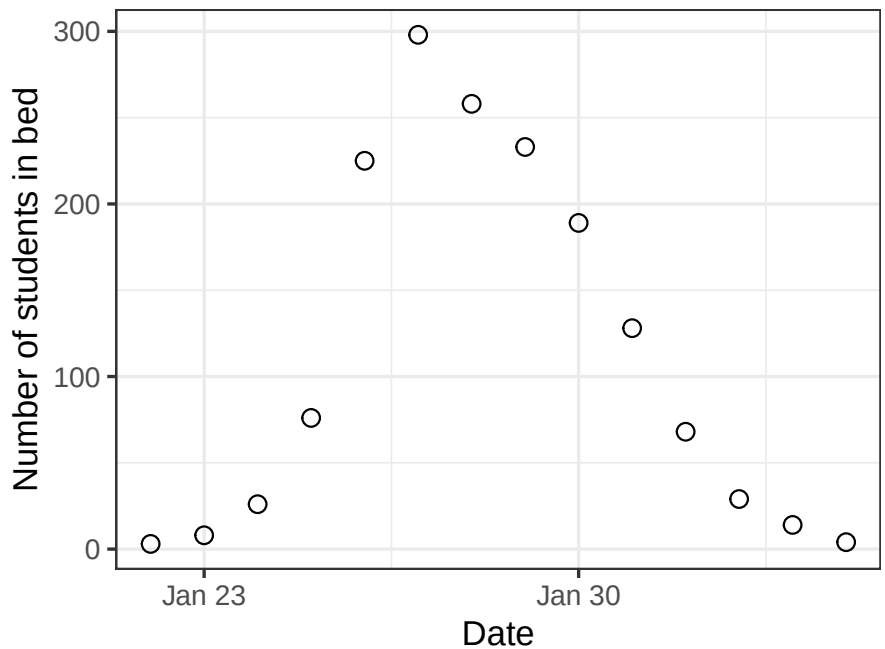
Fitting a simple SIR

Example data: outbreak of influenza A (H1N1) at a British boarding school in 1978 (available in `R` package `outbreaks`)

- 763 students, 512 had symptoms
- daily number of students in bed over 14 days (prevalence data)



Fitting a simple SIR

Specifying the model:

- prevalence data: $\mathbb{I}_t$ with $t \in \{1, \ldots, 14\}$
- parameters to estimate: $\theta = \{\beta, \gamma, \phi\}$
- parameters that will remain fixed: $\{S_0 = 762, I_0 = 1, R_0 = 0\}$
- map data $\mathbb{I}_t$ to SIR model output $I(t)$ using an observation model with an appropriate probability distribution:

$$\Pr(\mathbb{I}|\theta) = \prod_{t=1}^{14} \text{neg-bin}(\mathbb{I}_t|I(t), \phi)$$

- prior distributions

$$\Pr(\beta) = \text{exponential}(1)$$

$$\Pr(1/\gamma) = \text{normal}(2, 0.5)$$

$$\Pr(1/\phi) = \text{exponential}(5)$$

Fitting a simple SIR

We define the ODE system in the `function` block

```
functions {
  real[] sir(real t, real[] y, real[] theta, real[] x_r, int[] x_i) {

    real S = y[1];
    real I = y[2];
    real R = y[3];
    real N = x_i[1];

    real beta = theta[1];
    real gamma = theta[2];

    real dS_dt = -beta * I * S / N;
    real dI_dt =  beta * I * S / N - gamma * I;
    real dR_dt =  gamma * I;

    return {dS_dt, dI_dt, dR_dt};
  }
}
```

⚠ Be careful of the signature and formats!

Fitting a simple SIR

We declare the data variables in the `data` block

```
data {
  int<lower=1> T;
  real y0[3];
  real t0;
  real ts[T];
  int N;
  int cases[T];
}
```

Fitting a simple SIR

We declare the data variables in the `data` block

```
data {
  int<lower=1> T;
  real y0[3];
  real t0;
  real ts[T];
  int N;
  int cases[T];
}
```

and define additional data variables in `transformed data`

```
transformed data {
  real x_r[0];
  int x_i[1];
  x_i[1]=N;
}
```

Fitting a simple SIR

Similarly, parameters are declared in the `parameters` block

```
parameters {
  real<lower=0> beta;
  real<lower=0> recovery_time;
  real<lower=0> phi_inv;
}
```

⚠ It sometimes makes more sense to transform some parameters (e.g., recovery rate γ and overdispersion ϕ) to improve interpretability

Fitting a simple SIR

In `transformed parameters`, we define additional parameters and solve the ODE system

```
transformed parameters{
  real y[T,3];
  real phi = 1. / phi_inv;
  real gamma = 1. / recovery_time;
  real theta[2];
  theta[1] = beta;
  theta[2] = gamma;

  y = integrate_ode_rk45(sir, y0, t0, ts, theta, x_r, x_i);
}
```

Fitting a simple SIR

```
y = integrate_ode_rk45(sir, y0, t0, ts, theta, x_r, x_i);
```

Two crucial points:

- be careful about the formats and signatures
  - the ODE output `y` is an array of size `T`$\times$3 (number of time steps and number of compartments)
  - `sir` is the name of the function defined in the `function` block
  - `y0` is an array of size 3 defined in the `data` block
  - `ts` is an array of size `T` defined in the `data` block
  - `theta` is an array of size 2 storing the parameters
  - `x_r` is defined as empty in `transformed data`, but can be used to store fixed real values
  - `x_i` is an array of size 1 storing the population size `N` (can also be used to store fixed integer values)

Fitting a simple SIR

```
y = integrate_ode_rk45(sir, y0, t0, ts, theta, x_r, x_i);
```

Two crucial points:

- two ODE solvers are available:
  - `integrate_ode_rk45` uses the Runge-Kutta method (quicker but non-adapted to stiff systems)
  - `integrate_ode_bdf` uses the backward differentiation method (slower but adapted to stiff systems)

Fitting a simple SIR

In the `model` block, we write the priors and the observation model

```
model {
  // priors
  beta ~ exponential(1);
  recovery_time ~ normal(2,0.5);
  phi_inv ~ exponential(5);

  // observation model
  cases ~ neg_binomial_2(col(to_matrix(y),2), phi);
}
```

⚠ It's important that the chosen distributions correspond with the boundaries set in the `parameters` block (`<lower=0>`)

⚠ `col(to_to_matrix(y))` extracts the 2nd column of `y`

Fitting a simple SIR

Last, we add a `generated quantities` block that does not influence sampling and can be used for "post-processing":

- reproduction number $\mathcal{R}_0 = \beta/\gamma$
- model predictions of prevalence from the negative binomial

```
generated quantities {
  real R0 = beta/gamma;
  real pred_cases[T];
  pred_cases = neg_binomial_2_rng(col(to_matrix(y),2), phi);
}
```

Fitting a simple SIR

In summary:

- `functions`: define the ODE system (⚠ signature and formats)
- `data`: declare data variables that will be provided
- `tranformed data`: additional quantities that can be computed internally or from `data` variables
- `parameters`: declare parameters (⚠ boundaries)
- `transformed parameters`: quantities that can be computed internally or from `data` or `parameters` variables, including the ODE output (⚠ signature and format)
- `model`: priors and observation model
- `generated quantities`: additional quantities that can be computed without influencing the sampling

Fitting a simple SIR

As before, we conduct the inference from `R` with the package `rstan`:

```r
## Format input ----
# prevalence data
cases = influenza_england_1978_school$in_bed
N = 763
n_days = 14
t0 = 0
t = 1:n_days

# initial conditions
i0 = 1
s0 = N - i0
r0 = 0
y0 = c(s0, i0, r0)

# put into list
input_data = list(T = n_days, y0 = y0, t0 = t0, ts = t, N = N, cases = cases)
```

⚠ data is put in a list with names matching the `data` block in Stan

Fitting a simple SIR

Hit the inference button!

```
## Sample ----
fit = stan(file='sir_negbin.stan',
           data=input_data,
           chains=4,
           iter=1000)
```

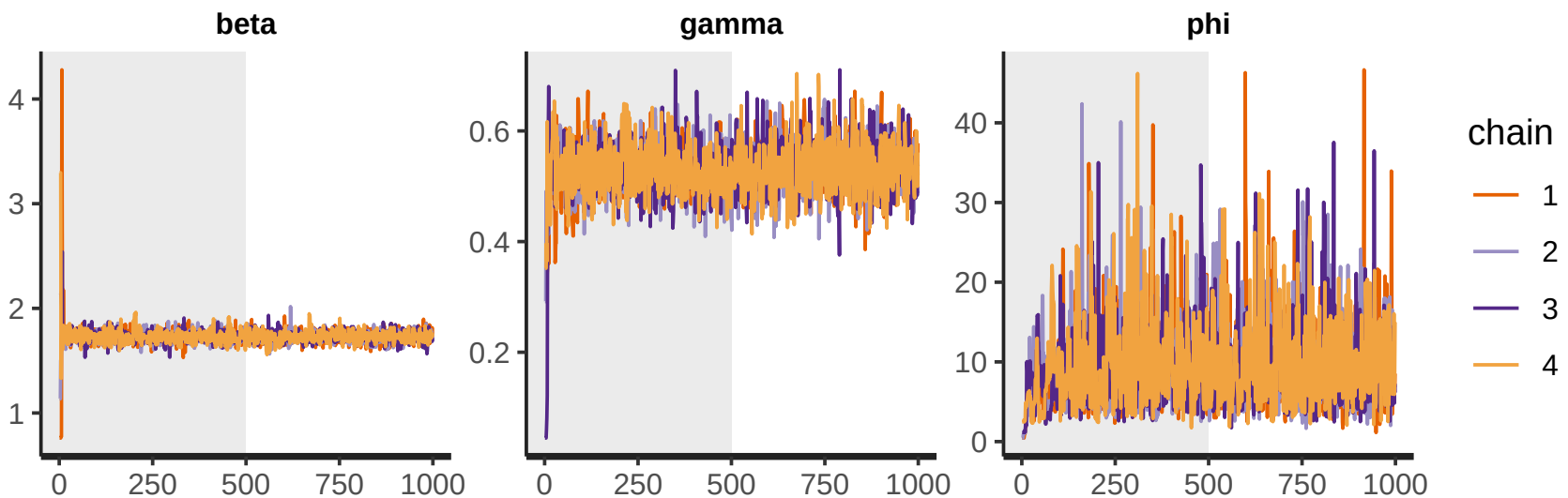
Fitting a simple SIR

Run basic diagnosis tools:

```
> check_hmc_diagnostics(fit)

Divergences:
0 of 2000 iterations ended with a divergence.

Tree depth:
0 of 2000 iterations saturated the maximum tree depth of 10.

Energy:
E-BFMI indicated no pathological behavior.
```

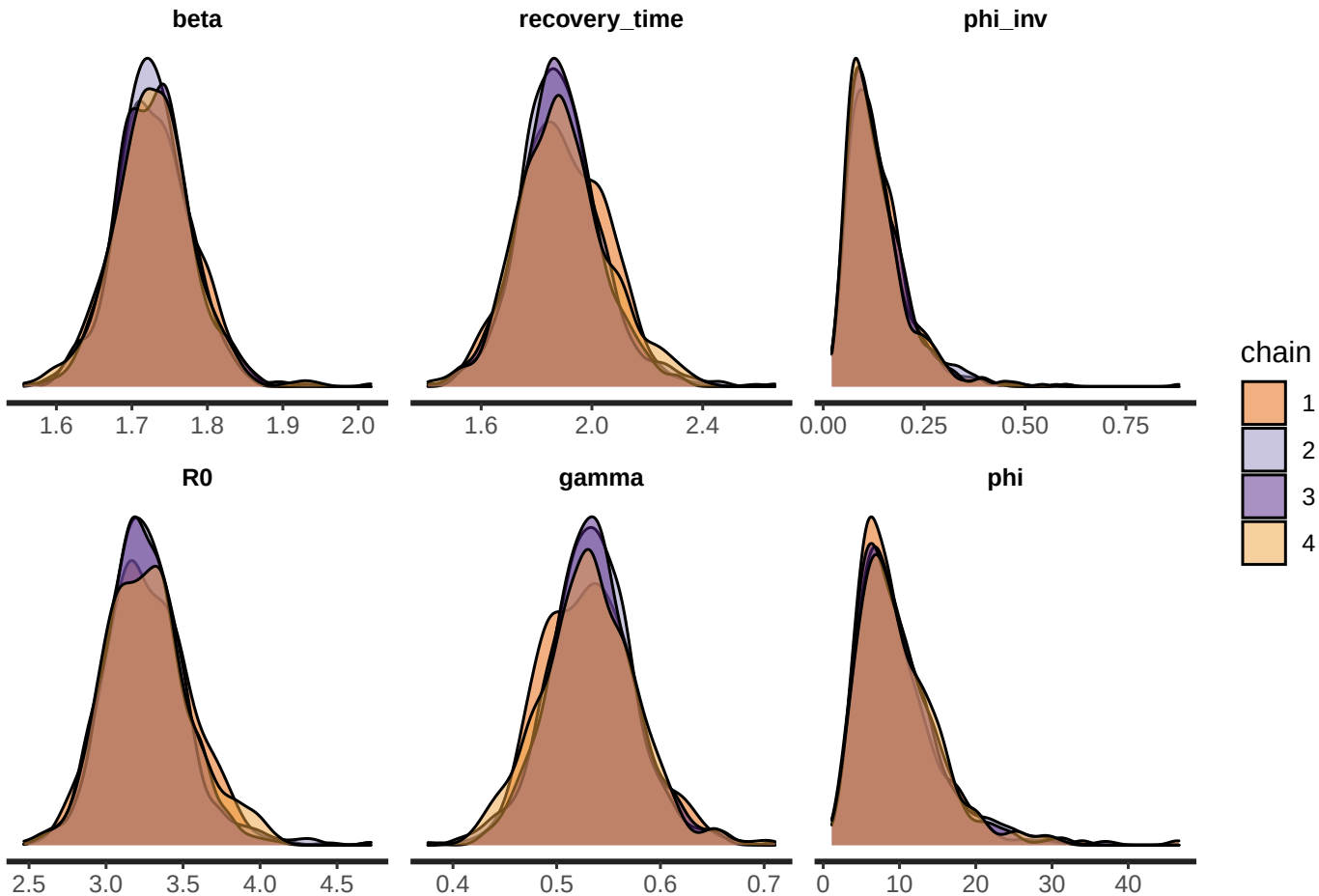
Fitting a simple SIR

Examine trace plots:



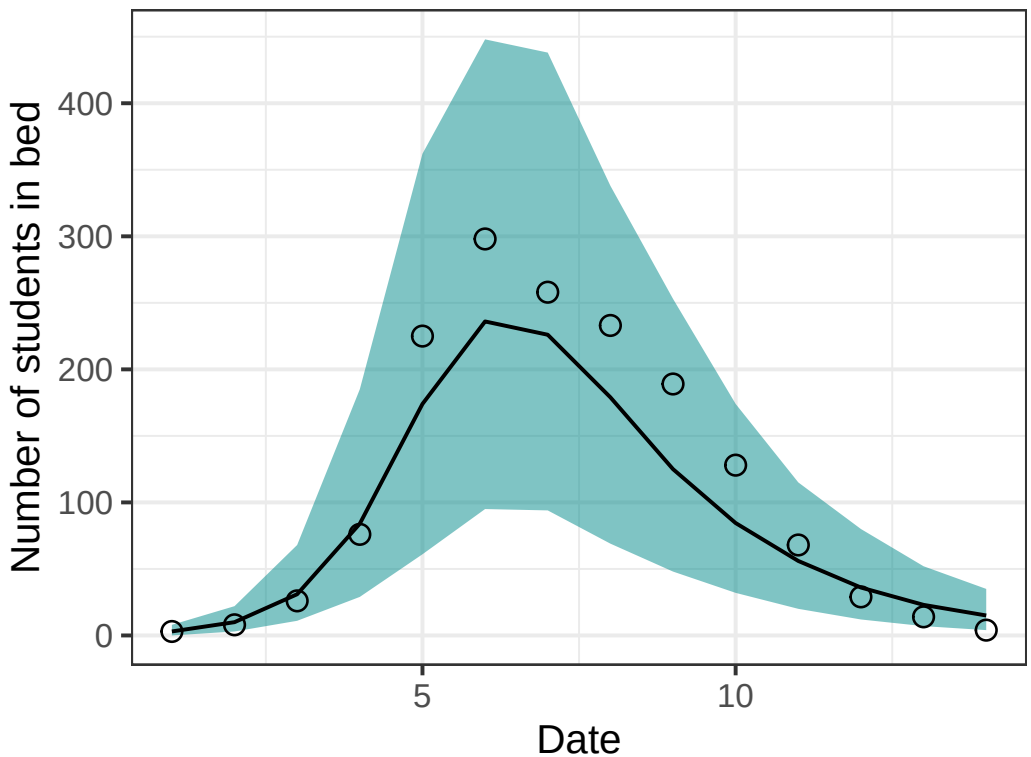
Fitting a simple SIR

Examine chain mixing:



Fitting a simple SIR

Posterior predictive checking:



Fitting a simple SIR

Print the results:

```
> print(fit,pars=c("beta","gamma","phi","R0","recovery_time"))
Inference for Stan model: sir_negbin.
4 chains, each with iter=1000; warmup=500; thin=1;
post-warmup draws per chain=500, total post-warmup draws=2000.

               mean se_mean   sd 2.5%  25%  50%   75% 97.5% n_eff Rhat
beta           1.73    0.00 0.06 1.61 1.70 1.73  1.76  1.85  1049    1
gamma          0.53    0.00 0.04 0.44 0.50 0.53  0.56  0.63  1382    1
phi            9.61    0.22 6.13 2.94 5.72 8.31 11.80 23.40   743    1
R0             3.27    0.01 0.29 2.79 3.09 3.25  3.42  3.96  1403    1
recovery_time 1.89    0.00 0.16 1.59 1.79 1.88  1.98  2.25  1410    1

Samples were drawn using NUTS(diag_e) at Thu Nov 12 19:10:02 2020.
For each parameter, n_eff is a crude measure of effective sample size,
and Rhat is the potential scale reduction factor on split chains (at
convergence, Rhat=1).
```

Fitting a simple SIR

Conclusions:

- we estimate $\mathcal{R}_0$ to 3.3 (95% credible interval: 2.8 to 4.0)
- this corresponds to the direct estimation from the final size of the epidemic $q = 512/763 = 0.67$

$$\mathcal{R}_0 = 1/(1-q) = 3.03$$

- based on many assumptions:
  - common to all SIRs (homogeneous mixing, no incubation...)
  - prior distributions (especially on the recovery period)
  - complete ascertainment, no asymptomatics
  - no initial immunity

Outline

- Introduction
- (Quick notice: Bayesian inference with Stan)
- Fitting a simple SIR
- **Simulations to understand the model**
- Scaling up ODE-based models
- Extensions

Simulations to understand the model

In practice, the situation is often less clear than in the boarding school example:

- incomplete data, insufficient domain knowledge
- uncertainty on necessary model features

Fake data can be used to probe the model and better understand its behaviour:

- prior predictive checking
- model reliability checking

Simulations to understand the model

Prior predictive checking consists in simulating data from the priors:

- visualize priors (especially after transformation)
- this shows the range of data compatible with the model
- it helps understand the adequacy of the chosen priors, as it is often easier to elicit expert knowledge on measureable quantities of interest rather than abstract parameter values

Simulations to understand the model

Prior predictive checking consists in simulating data from the priors:

- visualize priors (especially after transformation)
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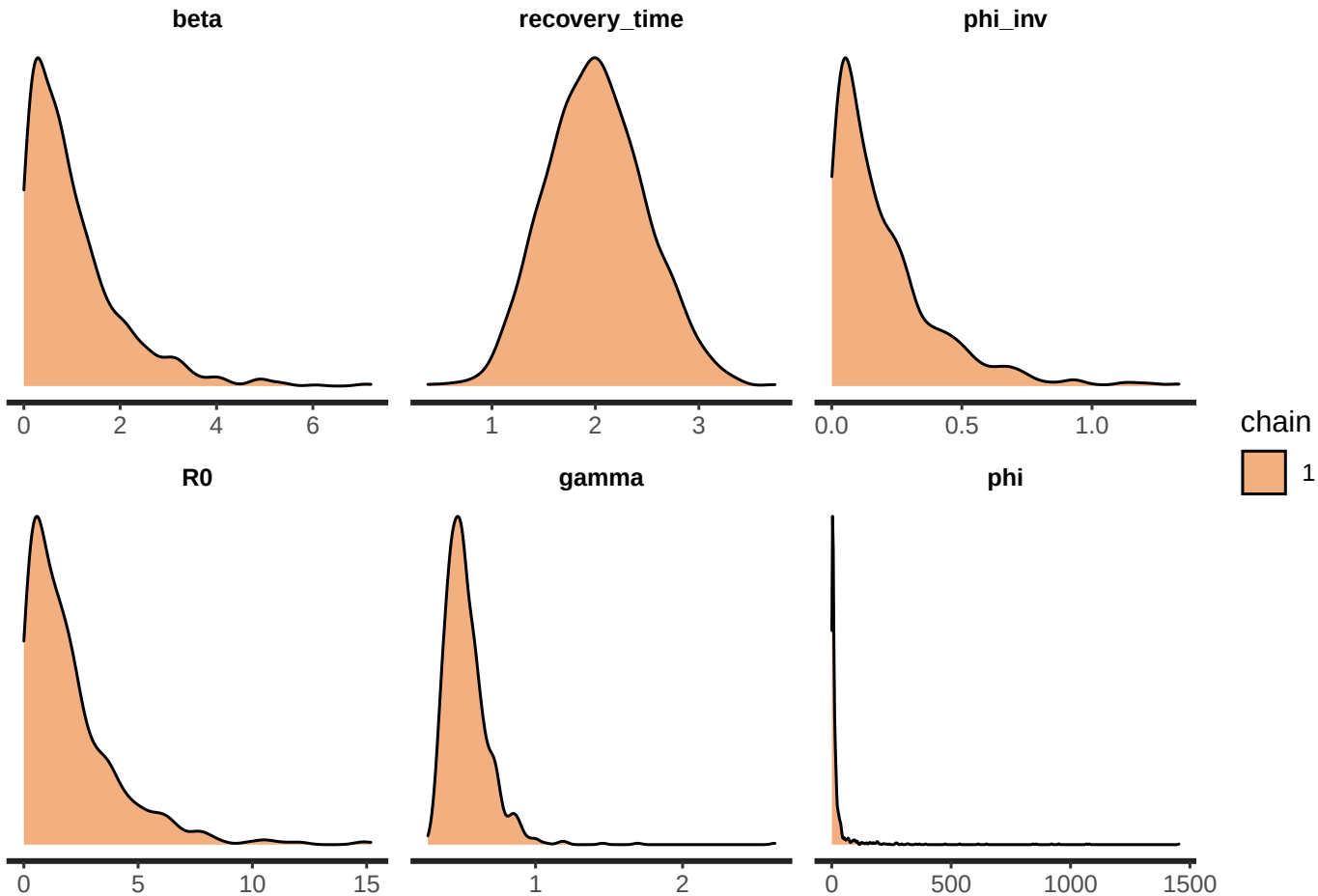
- remove (or switch off) the likelihood from the `model` block

```
// observation model
if(switch_likelihood==1) cases ~ neg_binomial_2(col(to_matrix(y),2), phi);
```

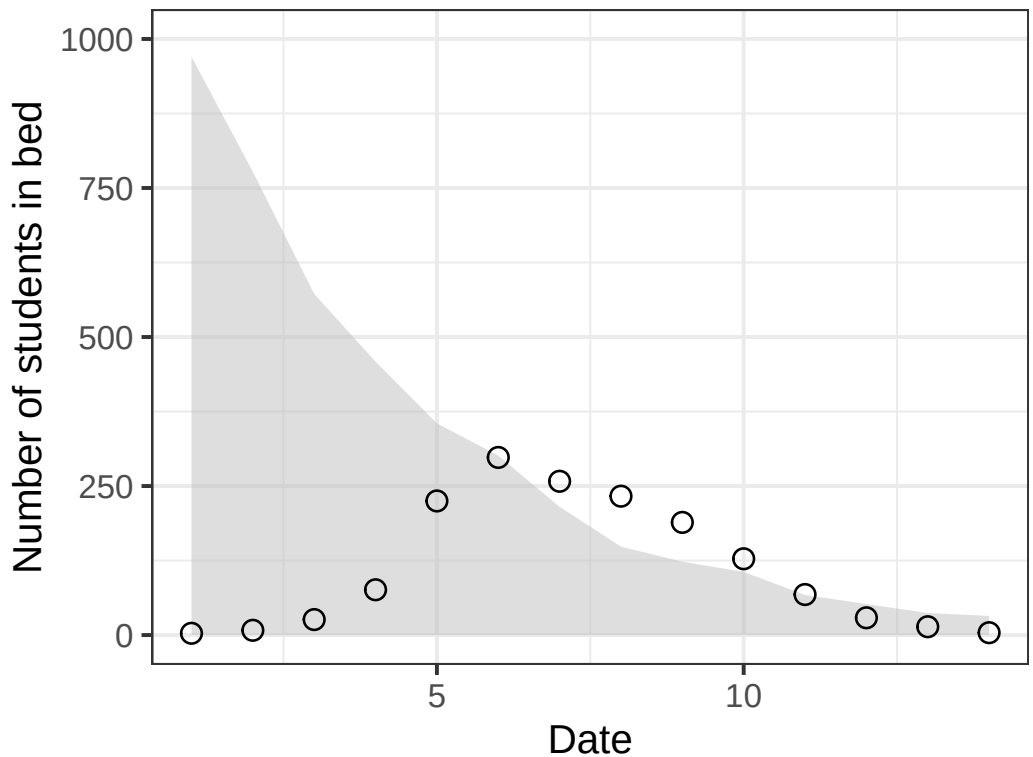
Simulations to understand the model

Simulating priors in the boarding school example:



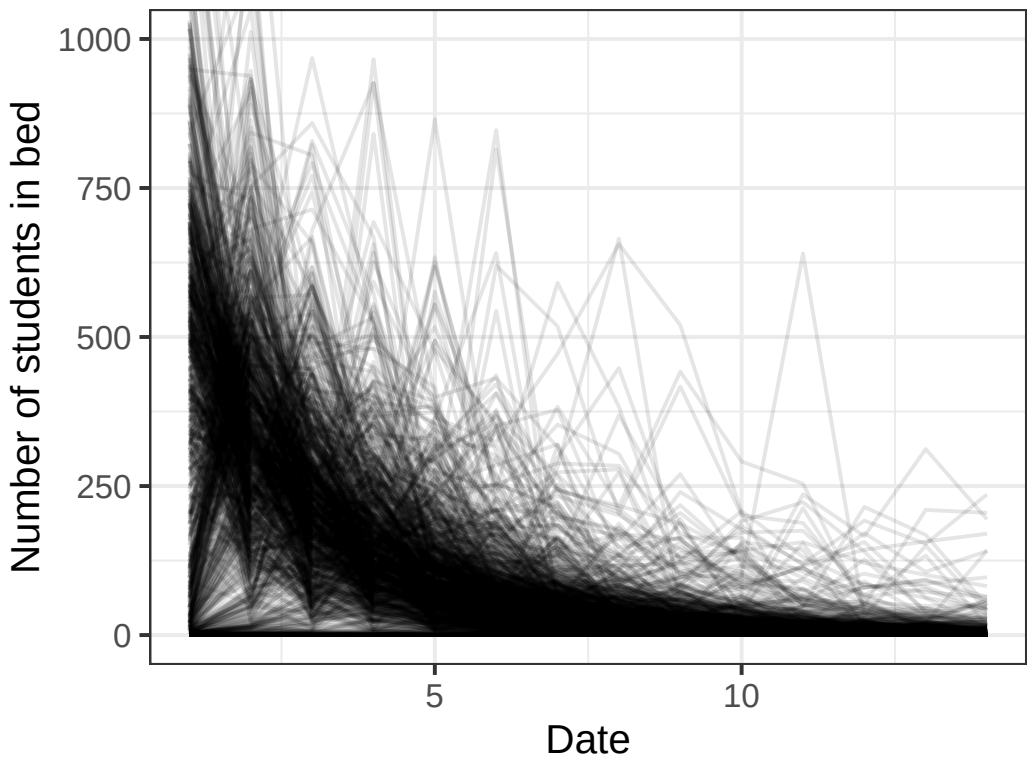
Simulations to understand the model

Prior predictive checking: simulating epidemic trajectories



Simulations to understand the model

Prior predictive checking: simulating epidemic trajectories



Simulations to understand the model

Prior predictive checking brings insight about non-obvious features:

- while the priors seem large and weakly informative, there is actually not a lot of leeway
- highly constrained model:
  - if β is high, the epidemic will stop rapidly by lack of susceptibles
  - if β is small, the epidemic will be small
- the negative binomial might lead to problems in extreme situations, e.g. more cases (>1000) than the overall number of students

Simulations to understand the model

Model reliability checking consists in attempting to recover chosen parameter values with the model: identifiability issues

Acknowledgements & ressources

- Michael Betancourt, *Introduction to Stan*
  `https://betanalpha.github.io/assets/case_studies/stan_intro.html`
- Andrew Gelman et al., *Bayesian workflow*
  `https://arxiv.org/abs/2011.01808`
- Chi Feng, *MCMC interactive gallery*
  `https://chi-feng.github.io/mcmc-demo/app.html`
- Daniel Lee, *ODEs in Stan*
  `https://youtu.be/hJ34_xJhYeY`
- Richard McElreath, *Statistical rethinking*
  `https://youtu.be/4WVelCswXo4`