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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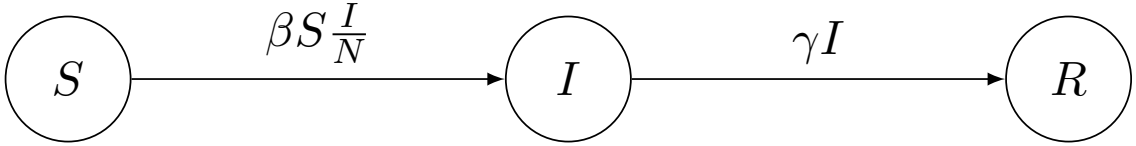
The susceptible-infectious-recovered (SIR) model:

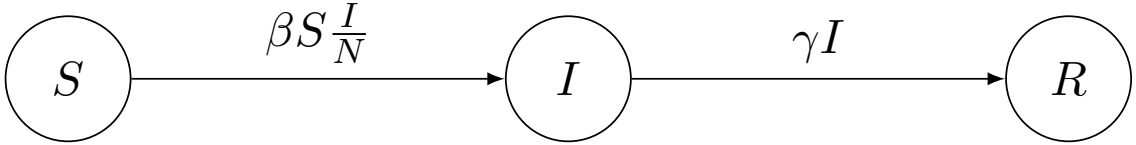


$$\frac{dS}{dt} = -\beta S \frac{I}{N}$$

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

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

Introduction



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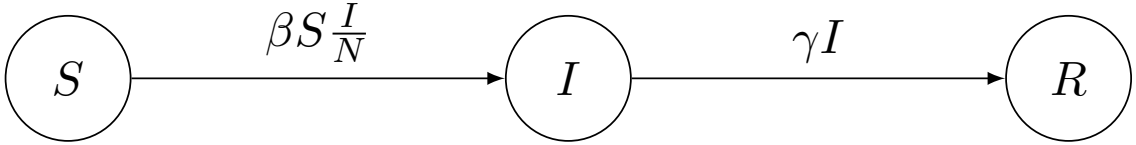
$$\frac{dR}{dt} = \gamma I$$

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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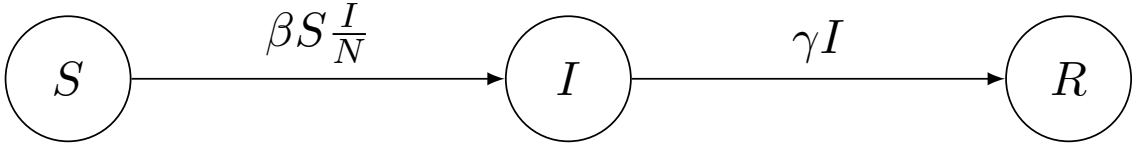
Intuition behind the SIR model:

- $I(t)/N$ 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



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

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

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

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))
+   })
+ }
```

Introduction

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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

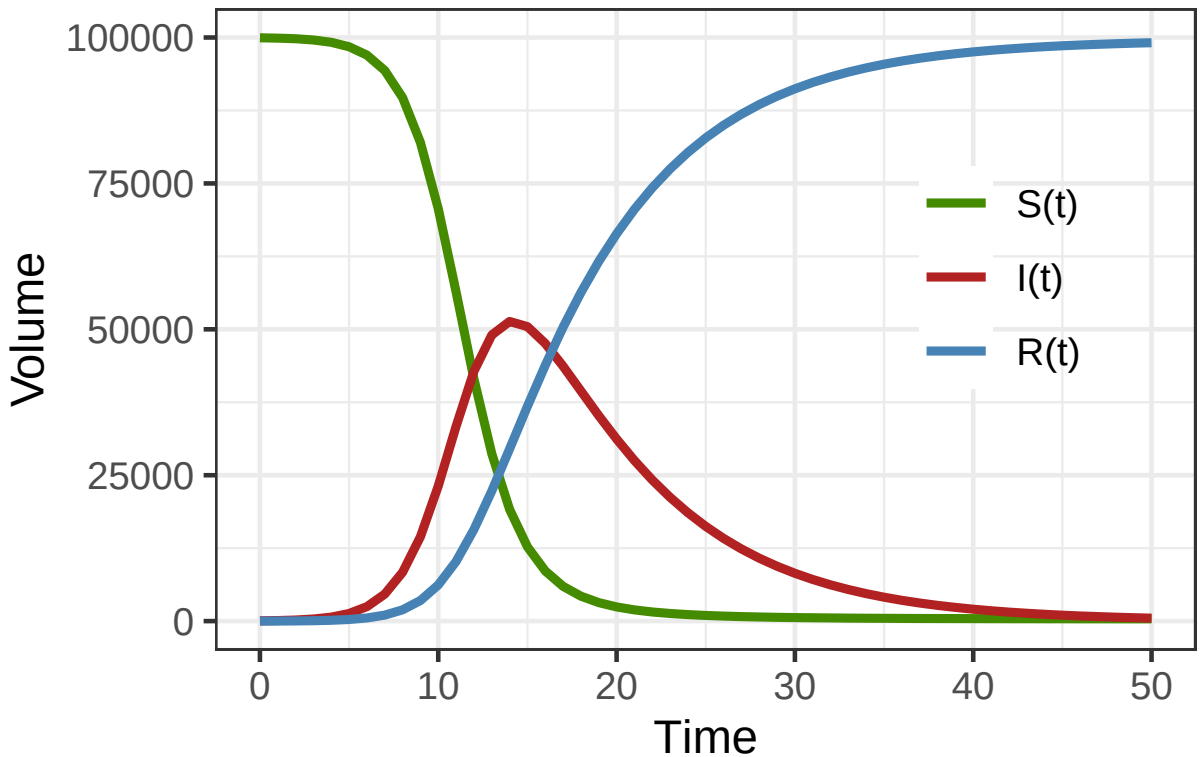
- solve the ODE system numerically (Runge-Kutta 4th order) to obtain unique solutions for $S(t)$, $I(t)$ and $R(t)$

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

```
> ## 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
```

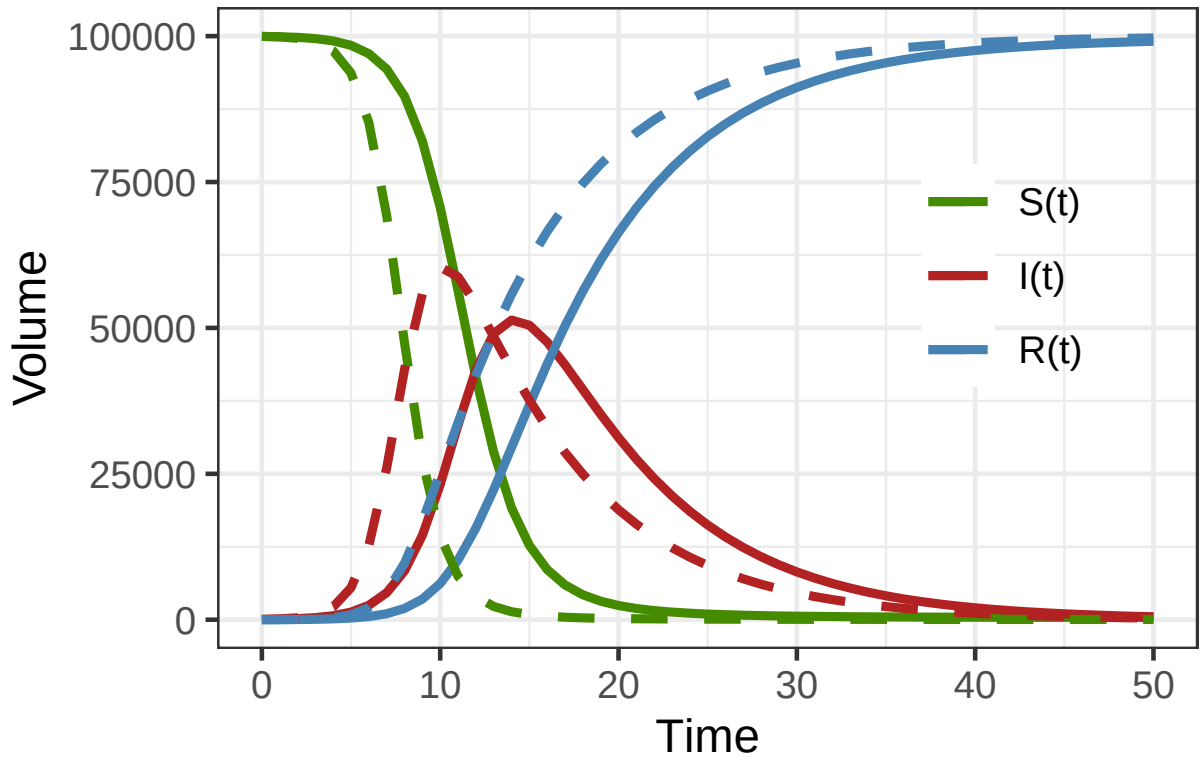
Introduction

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



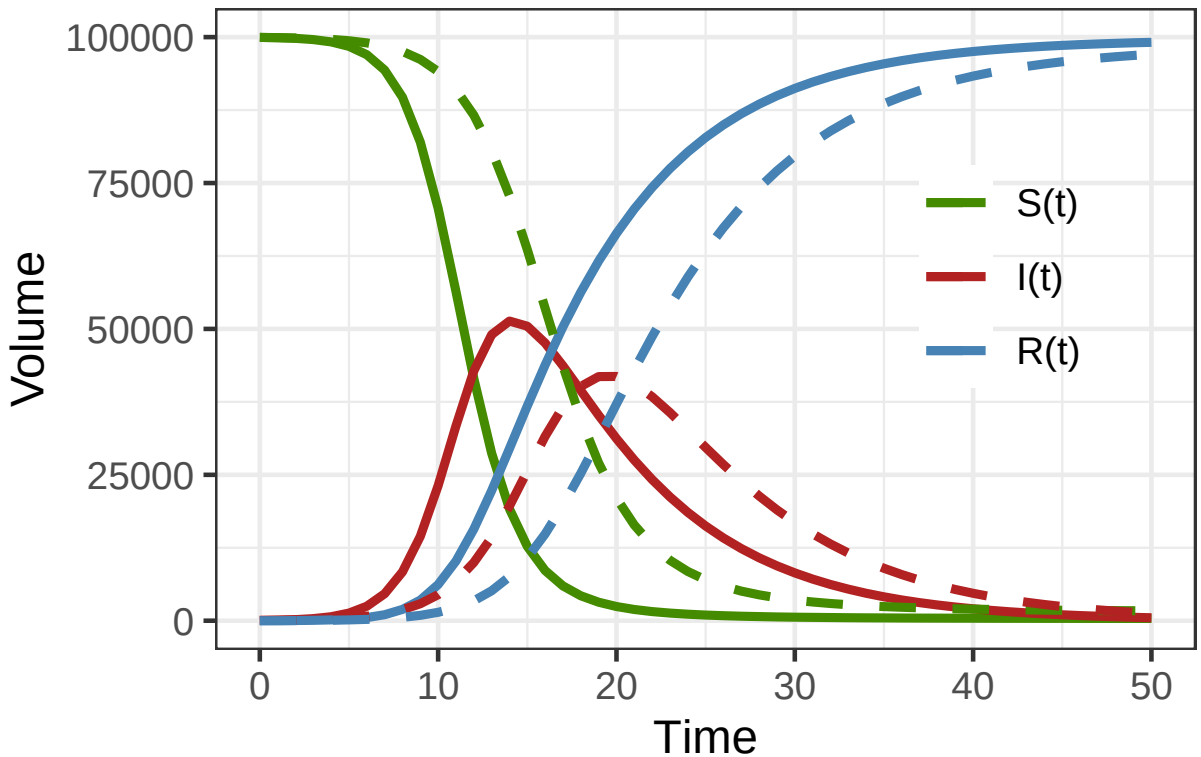
Introduction

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



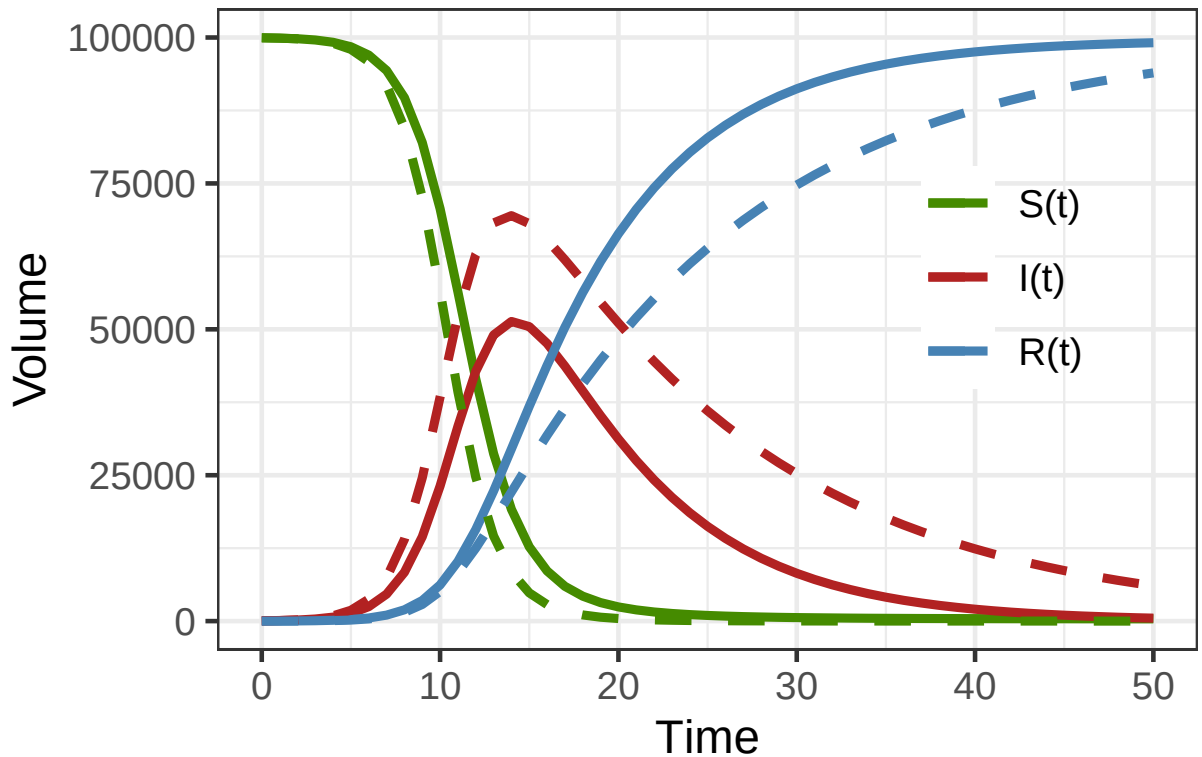
Introduction

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



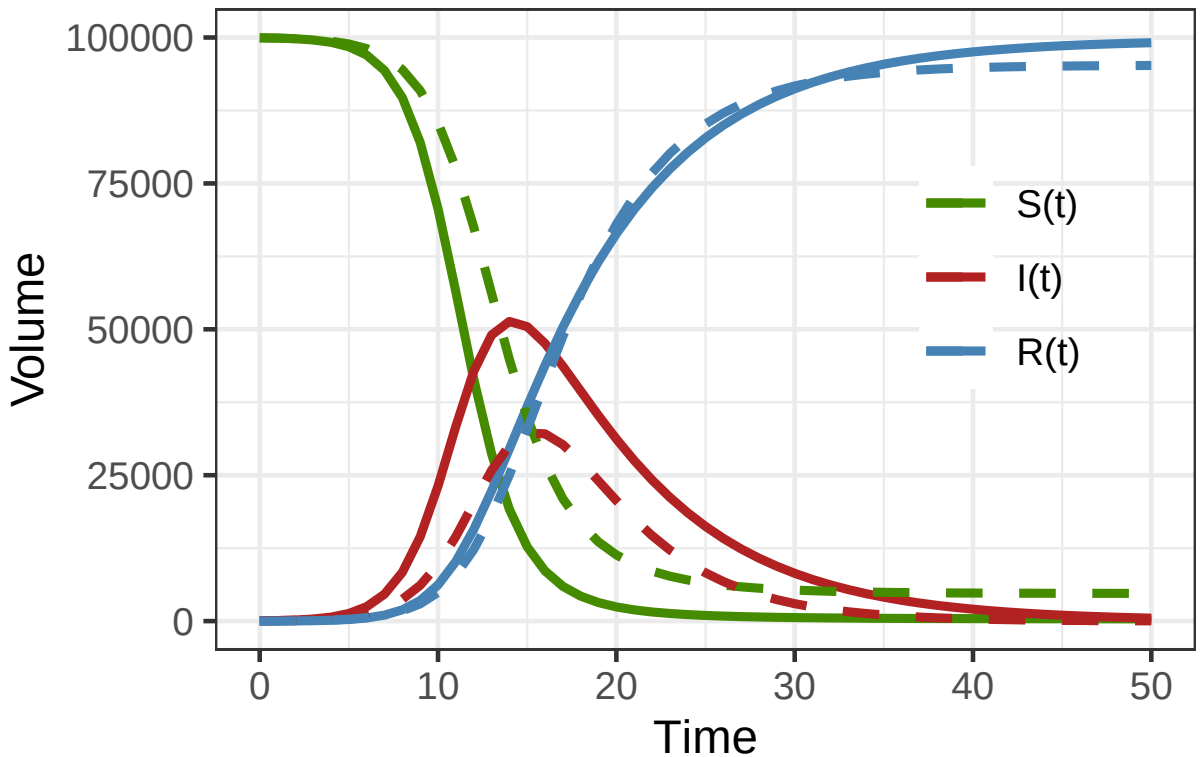
Introduction

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



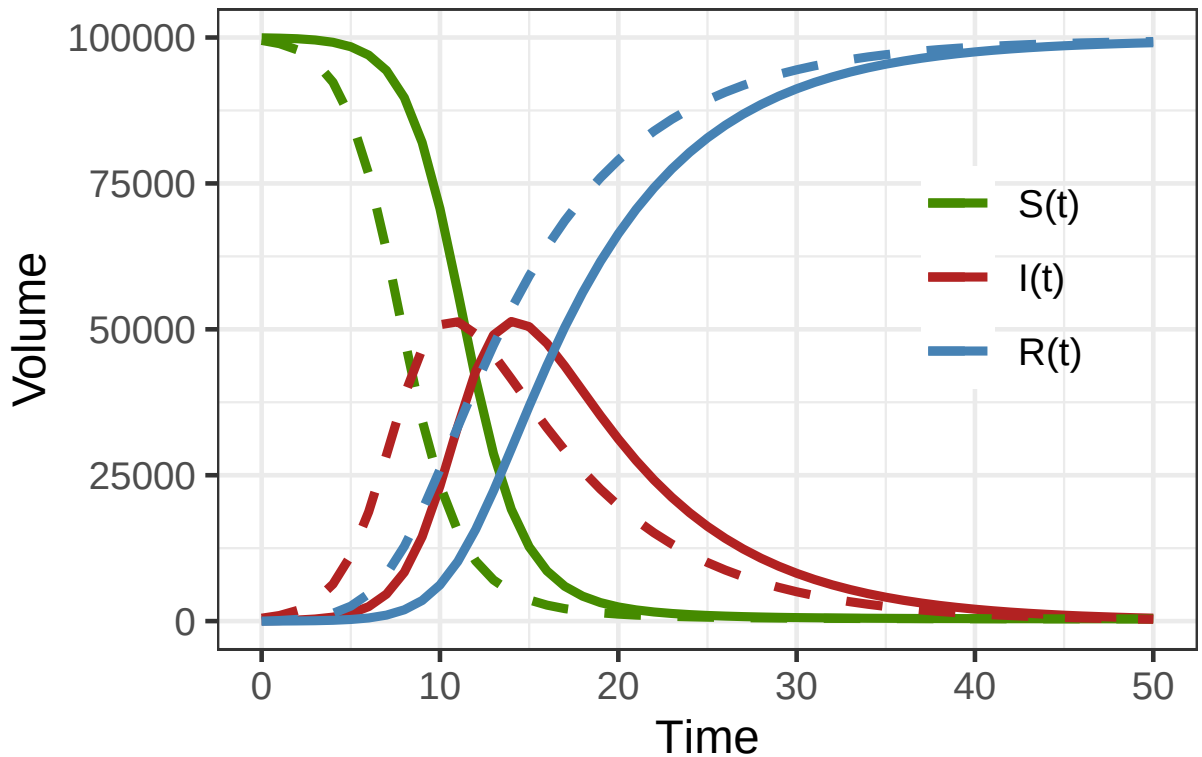
Introduction

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



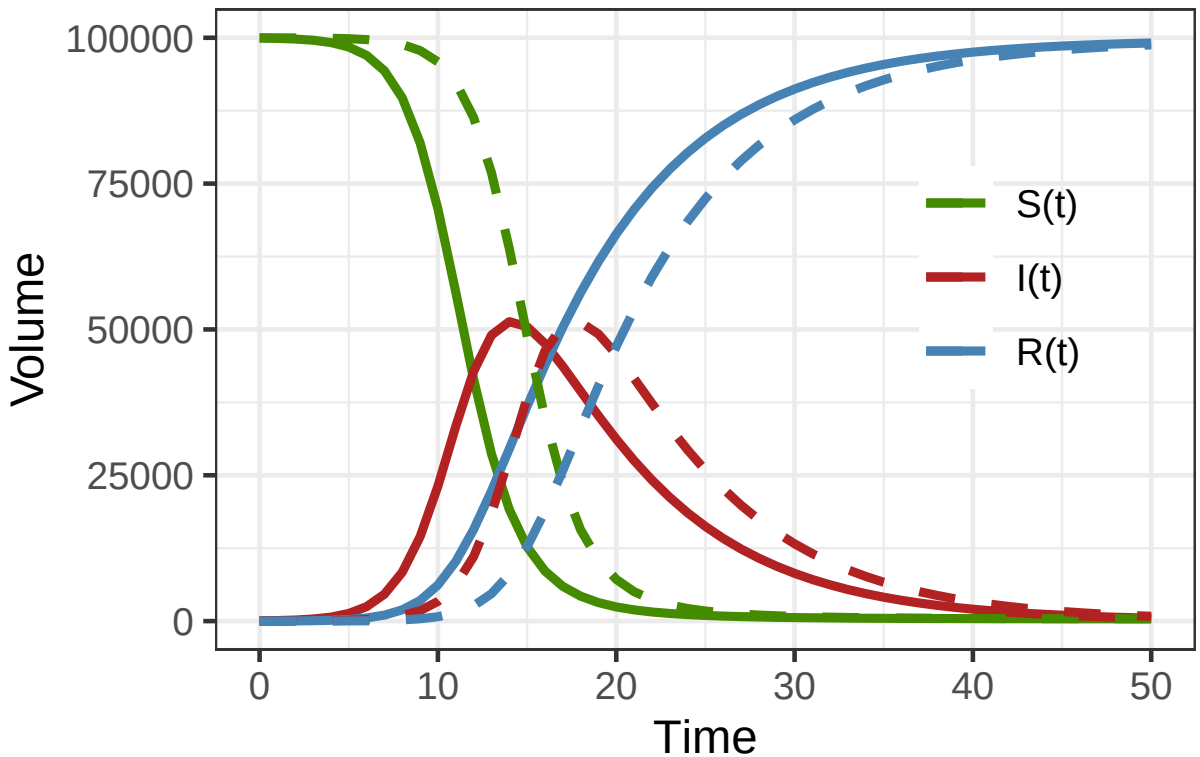
Introduction

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



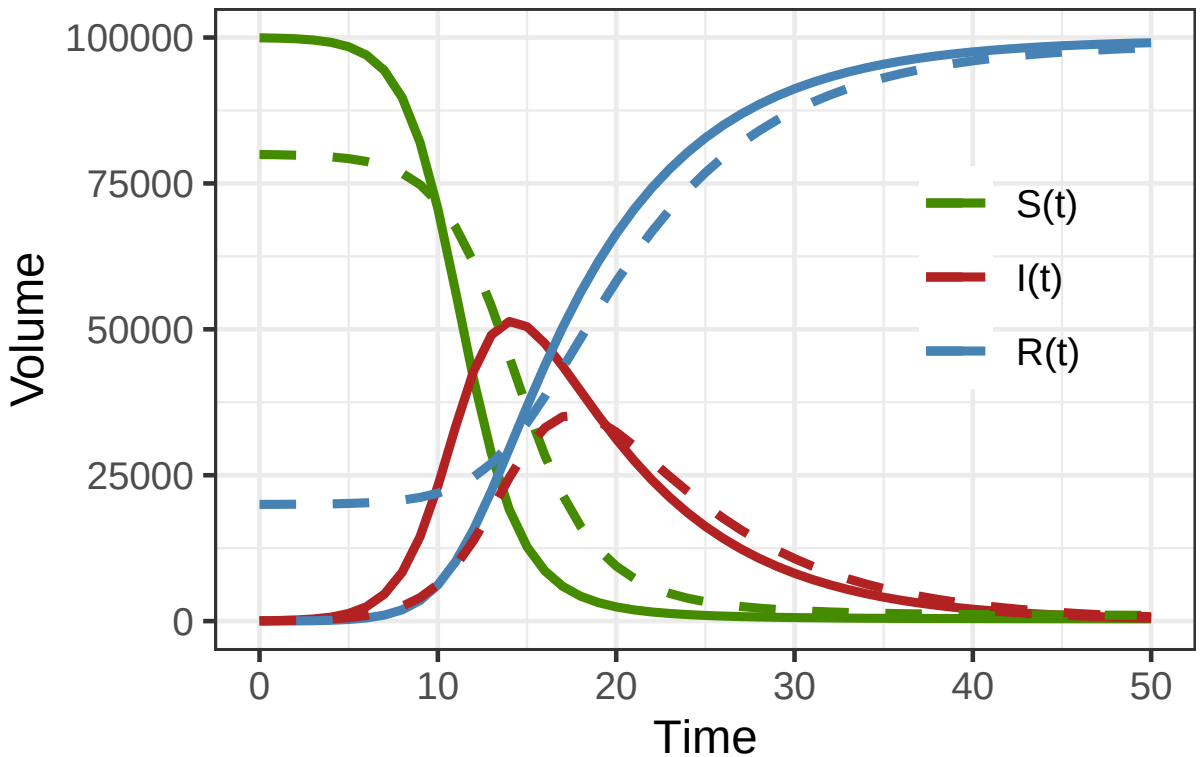
Introduction

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

- 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 prior 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

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- **(Quick notice: Bayesian inference with Stan)**
- Fitting a simple SIR
- Simulations to understand the model
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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 $\theta = 0.7$

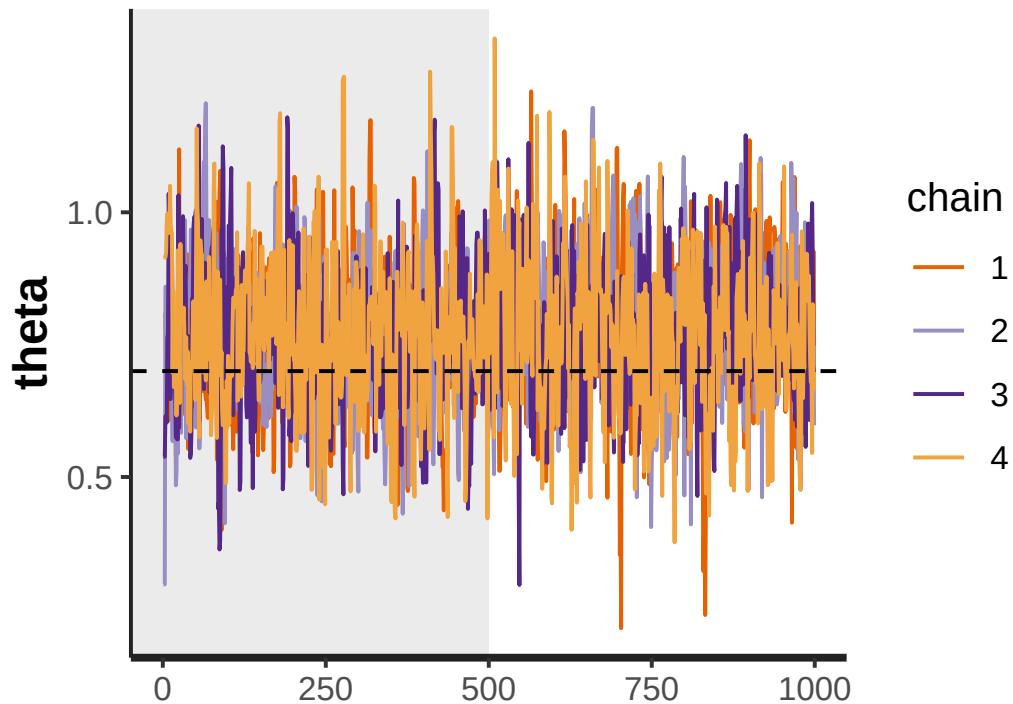
```
## Simulate data ----
N = 50
theta = 0.7
y = rnorm(N,theta,1)
input_data = list(N=N,y=y)
```

- 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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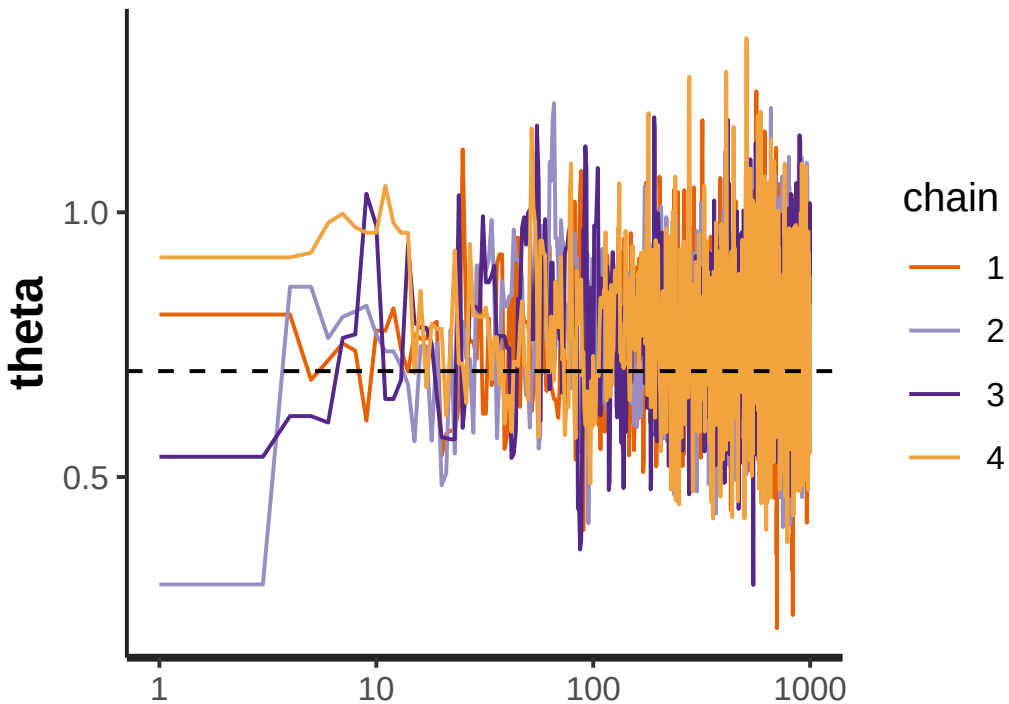
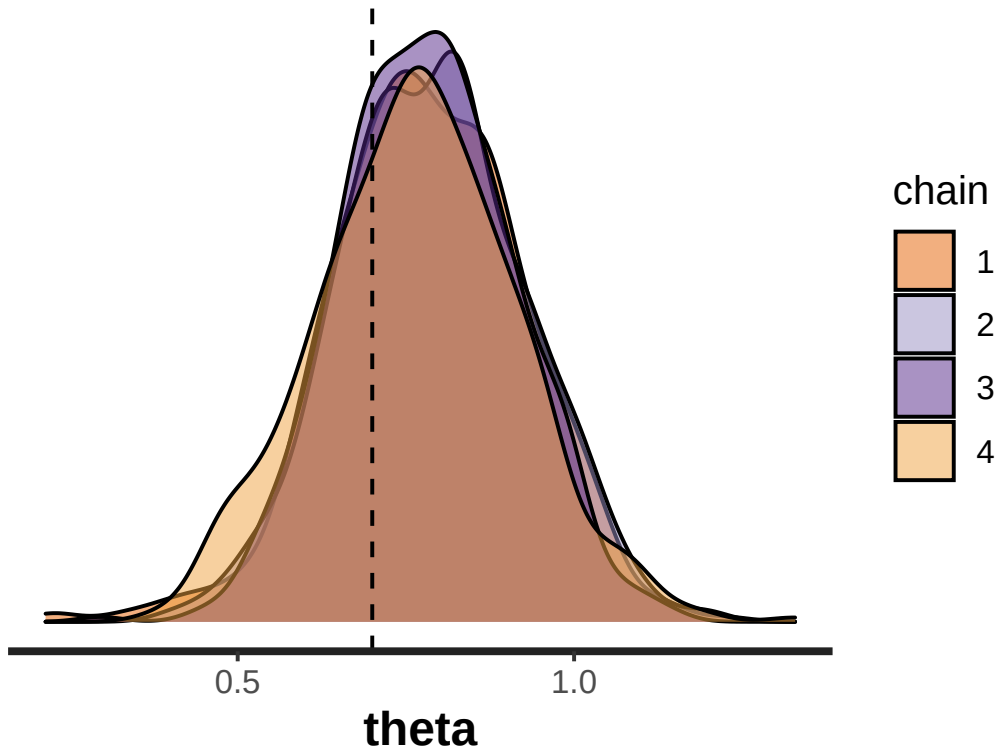


(Bayesian inference with Stan)

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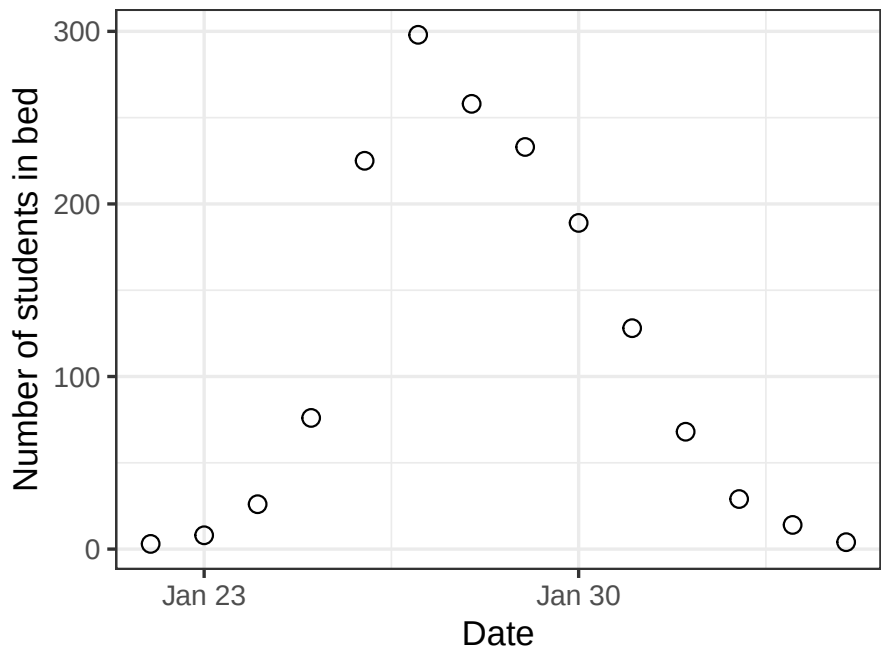
Fitting a simple SIR

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.

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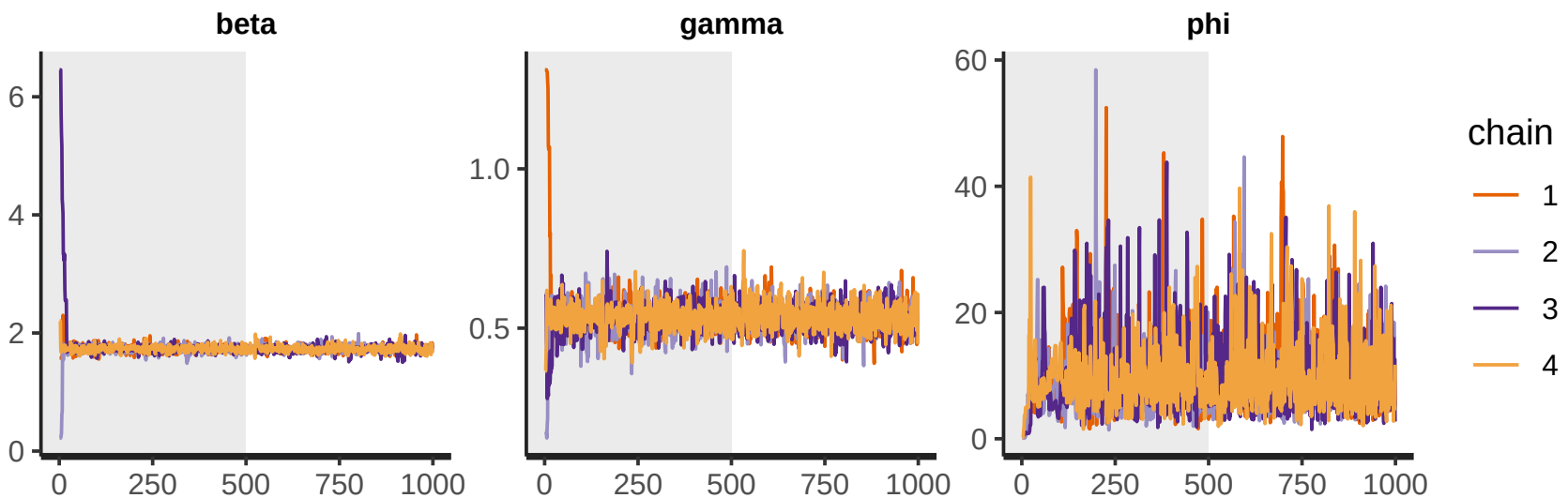
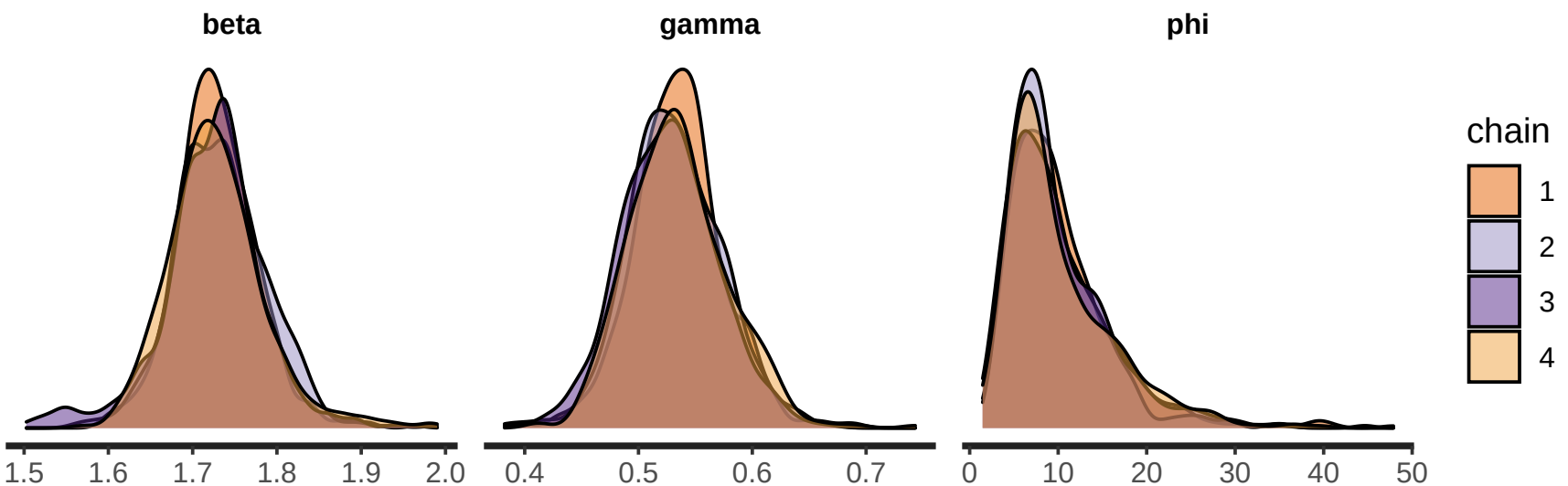
Fitting a simple SIR

Examine trace plots:



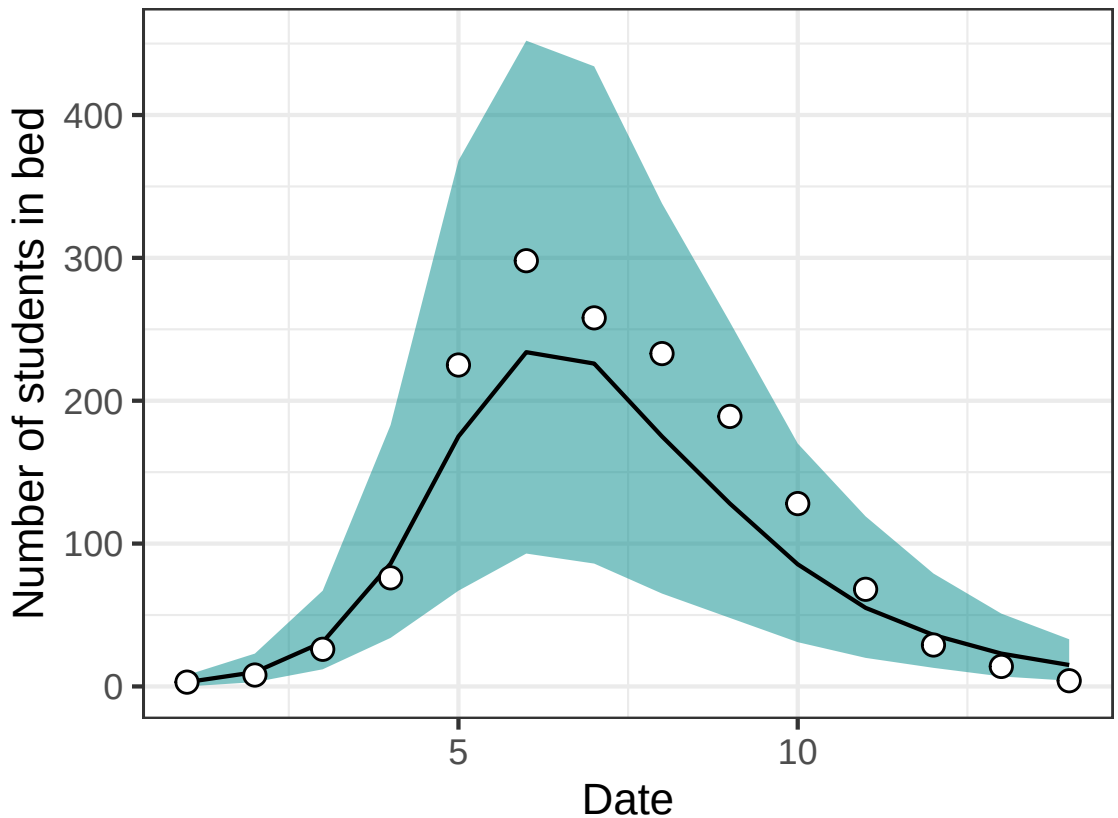
Fitting a simple SIR

Examine chain mixing:



Fitting a simple SIR

Posterior predictive check:



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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).
```

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

Acknowledgements & ressources

- Michael Betancourt's *Introduction to Stan*
  `https://betanalpha.github.io/assets/case_studies/stan_intro.html`
- Daniel Lee's *ODEs in Stan*
  `https://youtu.be/hJ34_xJhYeY`
- Richard McElreath's *Statistical rethinking*
  `https://youtu.be/4WVelCswXo4`