# Bayesian workflow for disease transmission modeling in Stan

Léo Grinsztajn, Charles Margossian, Elizaveta Semenova, Julien Riou

> MfPH Next Generation talk 2 November 2022

## Preface

- Objective: fit simple transmission models in Stan
- Based on Grinsztajn et al., 2021 (link)
- Prerequisites:
  - basic programming with R
  - general understanding of Bayesian inference
- All material is available on github (<u>link</u>)

# Outline

#### Models of disease transmission

Bayesian inference with Stan

Fitting a simple SIR

Bayesian workflow

Using simulations to understand the model

Conclusions

Bonus



#### Models of disease transmission:

- Interpretability: phenomenological, mechanistic
- Scale: compartmental, agent-based
- ► Framework: deterministic, stochastic
- Data-generating mechanisms: incubation, contagion, immunity, vaccination, mobility...
- Objectives: simulation, inference

#### Models of disease transmission:

- Interpretability: phenomenological, mechanistic
- Scale: compartmental, agent-based
- Framework: deterministic, stochastic
- Data-generating mechanisms: incubation, contagion, immunity, vaccination, mobility...
- Objectives: simulation, inference

## Mechanistic + population-based + deterministic

ightarrow ordinary differential equations-based compartmental model



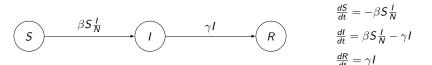
## ODE-based compartmental model:

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

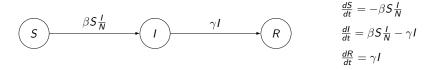
### ODE-based compartmental model:

- 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

The susceptible-infectious-recovered (SIR) model:



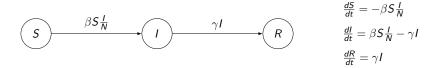
## The SIR model



#### Where:

- $\triangleright$  S(t) is the number of people susceptible to infection
- ightharpoonup I(t) is the number of people infected (i.e. the prevalence)
- ightharpoonup 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)
- $\triangleright$   $\beta$  is the infectious contact rate (per day per person)
- $ightharpoonup \gamma$  is the recovery rate (1/infectious period)

# The SIR model

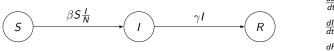


#### Intuition behind the SIR model:

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



# The SIR model



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

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

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

### Assumptions behind the SIR model:

- homogeneous mixing
- ightharpoonup eta and  $\gamma$  constant over time
- all infections are observed
- no incubation, exponentially-distributed recovery
- lifelong immunity
- stable population

- load library deSolve (and tidyverse)
- set compartments and differential equations

```
sir = function(t, x, pars, ...) {
  with(as.list(c(x, pars)), {
    dS = - beta*S*I/(S*I+R)
    dI = beta*S*I/(S*I+R) - gamma*I
    dR = gamma*I
    list(c(dS, dI, dR))
  })
}
```

- load library deSolve (and tidyverse)
- set compartments and differential equations

```
sir = function(t, x, pars, ...) {
  with(as.list(c(x, pars)), {
    dS = - beta*S*I/(S+I+R)
    dI = beta*S*I/(S+I+R) - gamma*I
    dR = gamma*I
    list(c(dS, dI, dR))
})
}
```

• set (fixed) values for parameters:  $\beta = 0.8$ ;  $\gamma = 1/7$ 

```
pars = c(beta = 0.8, gamma = 1/7)
```

- load library deSolve (and tidyverse)
- set compartments and differential equations

```
sir = function(t, x, pars, ...) {
  with(as.list(c(x, pars)), {
    dS = - beta*S*I/(S+I+R)
    dI = beta*S*I/(S+I+R) - gamma*I
    dR = gamma*I
    list(c(dS, dI, dR))
})
}
```

• set (fixed) values for parameters:  $\beta = 0.8$ ;  $\gamma = 1/7$ 

```
pars = c(beta = 0.8, gamma = 1/7)
```

set (fixed) values for initial values

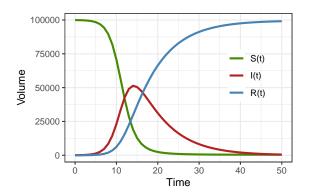
```
N_0 = 100000
I_0 = 50
inits = c(S = N_0 - I_0,
I = I_0,
R = 0)
```

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

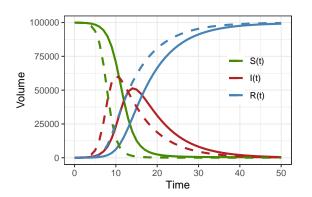
$$f(\beta, \gamma, S_0, I_0, R_0) = \{S(t), I(t), R(t)\}$$

```
times = seq(0,50,by=1)
sim_data = ode(inits, times, sir, pars, method="rk4")
```

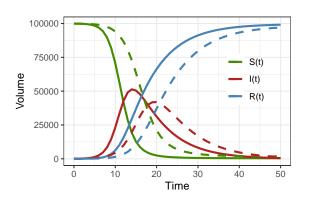
with  $\beta=$  0.8;  $\gamma=1/7;$   $\emph{S}_{0}=100000-50;$   $\emph{I}_{0}=50$  and  $\emph{R}_{0}=0$ 



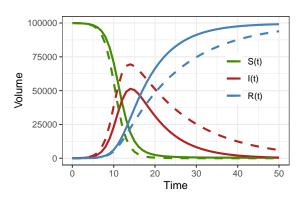
with  $\beta = 1.1$  instead of 0.8, we get

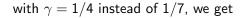


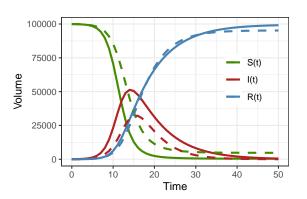
with  $\beta = 0.6$  instead of 0.8, we get

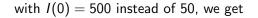


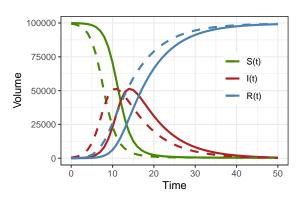


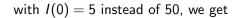


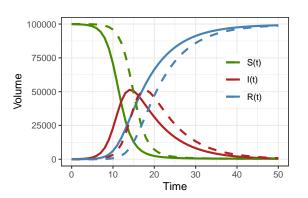


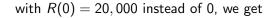


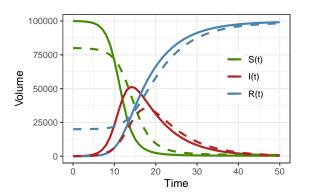












### Compartmental models have many uses:

 get mechanistic insight about an epidemic (transmissibility levels, drivers of transmission)

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

 formalize and put numerical values on general concepts (herd immunity threshold...)

$$V_c = \frac{1}{\mathcal{R}_0}$$

produce (short-term) forecasts accounting for contagion and immunity

### Compartmental models have many uses:

 get mechanistic insight about an epidemic (transmissibility levels, drivers of transmission)

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

 formalize and put numerical values on general concepts (herd immunity threshold...)

$$V_c = \frac{1}{\mathcal{R}_0}$$

produce (short-term) forecasts accounting for contagion and immunity

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



### 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

## 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

→ Markov Chain Monte Carlo (MCMC) methods and Stan

# Outline

Models of disease transmission

Bayesian inference with Stan

Fitting a simple SIR

Bayesian workflow

Using simulations to understand the model

Conclusions

Bonus

# Bayesian inference

$$\underbrace{p(\theta|y)}_{\text{posterior}} \propto \underbrace{p(y|\theta)}_{\text{likelihood}} \underbrace{p(\theta)}_{\text{prior}}$$

# General principle

### General principle of Bayesian inference:

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

$$p(y|\theta) = \prod_{n} \mathsf{normal}(y_n|\theta,1)$$

- complete the model with a prior distribution, e.g.

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

sample the posterior distribution of the parameter

## 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...

# Stan program structure

### A Stan program is structured in blocks:

- ▶ functions
- data
- transformed data
- parameters
- transformed parameters
- ▶ model
- generated quantities

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

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

▶ load rstan package

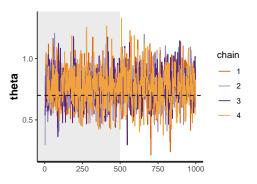
```
## Setup ----
library(rstan)
options(mc.cores = parallel::detectCores())
```

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

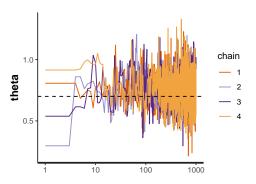
```
## Simulate data ----
N = 50
theta = 0.7
y = rnorm(N,theta,1)
input_data = list(N=N,y=y)
```

run MCMC sampling

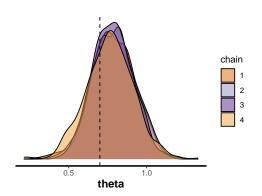
We use multiple chains and inspect convergence after warm-up



We use multiple chains and inspect convergence after warm-up



The post-warm-up samples of  $\theta$  approximate its posterior distribution



## Stan example

#### Printing the object gives:

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

```
> 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).
```

### Outline

Models of disease transmission

Bayesian inference with Stan

Fitting a simple SIR

Bayesian workflow

Using simulations to understand the model

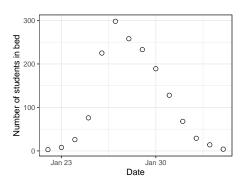
Conclusions

Bonus

# Example dataset

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)



## Specify the model

#### Points to consider:

- ▶ prevalence data:  $\mathbb{I}_t$  with  $t \in \{1, ..., 14\}$
- ▶ inputs 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:

$$p(\mathbb{I}| heta) = \prod_{t=1}^{14} \mathsf{NegBinomial}(\mathbb{I}_t|I(t),\phi)$$

- **parameters** to estimate:  $\theta = \{\beta, \gamma, \phi\}$
- prior distributions

$$p(eta) = \mathsf{Exponential}(1)$$
  $p(1/\gamma) = \mathsf{Normal}^+(2, 0.5)$   $p(1/\phi) = \mathsf{Exponential}(5)$ 

A Note that further we are using ODE signature as presented in the paper. Since then a new interface has become available.

We define the ODE system in the function block

```
real[] sir(real t, real[] y, real[] theta, real[] x_r, int[] x_i) {
 real S = v[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!

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];
}
```

We declare the data variables in the data block

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

and define additional data variables in transformed data block

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

Similarly, parameters are declared in the parameters block

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

f A It sometimes makes more sense to transform some parameters (e.g., recovery rate  $\gamma$  and overdispersion  $\phi$ ) to improve interpretability

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);
}
```

#### y = integrate\_ode\_rk45(sir, y0, t0, ts, theta, x\_r, x\_i);

- ▶ 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)

#### y = integrate\_ode\_rk45(sir, y0, t0, ts, theta, x\_r, x\_i);

- Chose an ODE solver. In the previous interface:
  - 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)
- ► In the new interface:
  - ode\_bdf, ode\_adams, ode\_rk45,
  - ode\_bdf\_tol,ode\_adams\_tol, ode\_rk45\_tol

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);
}
```

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

▲ col(to\_matrix(y)) extracts the 2nd column of y

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);
}
```

#### 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

#### Inference

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

```
## 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)
```

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

#### Inference

#### Hit the inference button!

#### Use the basic diagnostics tools:

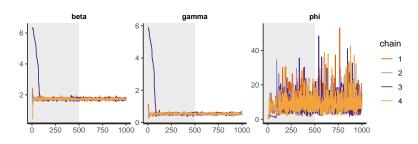
```
> check_hmc_diagnostics(fit)

Divergences:
0 of 2000 iterations ended with a divergence.

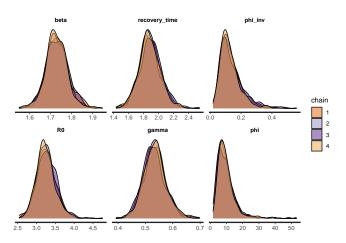
Tree depth:
0 of 2000 iterations saturated the maximum tree depth of 10.

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

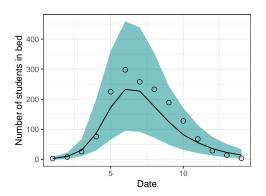
#### Examine trace plots:



#### Examine chain mixing:



### Posterior predictive checking:



#### Results

#### 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.
                           sd 2.5% 25% 50% 75% 97.5% n eff Rhat
             mean se mean
             1.73 0.00 0.06 1.61 1.70 1.73 1.76 1.85 1049
beta
gamma
             0.53 0.00 0.04 0.44 0.50 0.53 0.56 0.63 1382
phi
             9.61 0.22 6.13 2.94 5.72 8.31 11.80 23.40 743
RO
             3.27 0.01 0.29 2.79 3.09 3.25 3.42 3.96 1403
recovery time 1.89 0.00 0.16 1.59 1.79 1.88 1.98 2.25 1410
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).
```

#### Results

- we estimate  $\mathcal{R}_0$  to 3.3 (95% credible interval: 2.8 to 4.0)
- 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

Models of disease transmission

Bayesian inference with Stan

Fitting a simple SIR

Bayesian workflow

Using simulations to understand the model

Conclusions

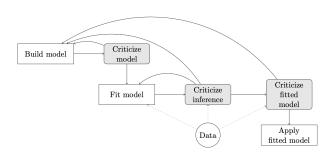
Bonus

# Box's loop

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

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

# Box's loop



# Model development

#### Model development is an iterative procedure:

- troubleshoot the model before fitting it,
- criticize the inference after attempting a fit,
- criticize the fitted model.

### Outline

Models of disease transmission

Bayesian inference with Stan

Fitting a simple SIR

Bayesian workflow

Using simulations to understand the model

Conclusions

Bonus

# Model development

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

- prior predictive checks
- simulation study

Prior predictive checking consists in simulating data from the priors:

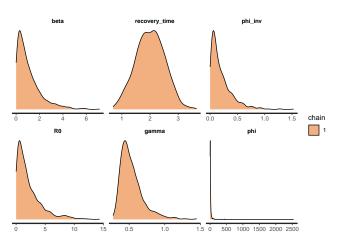
- visualize priors (especially after transformation)
- this shows the range of data compatible with the model
- ▶ it helps understand the adequacy of the chosen priors, as it is often easier to elicit expert knowledge on measureable quantities of interest rather than abstract parameter values

Prior predictive checking consists in simulating data from the priors:

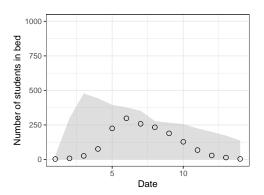
- visualize priors (especially after transformation)
- this shows the range of data compatible with the model
- ▶ it helps understand the adequacy of the chosen priors, as it is often easier to elicit expert knowledge on measureable quantities of interest rather than abstract parameter values
- remove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

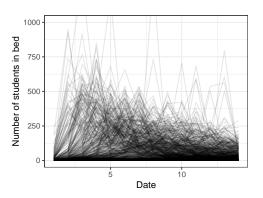
Simulating priors in the boarding school example:



Prior predictive check: simulating potential epidemic trajectories



Prior predictive check: simulating potential epidemic trajectories



Prior predictive checks bring insight about non-obvious features:

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

#### Simulation-based checks

#### A simulation study consists out of two steps:

- simulate data with specified parameter values
- measure the capacity of the model to recover the chosen parameter values

#### A simulation study consists out of two steps:

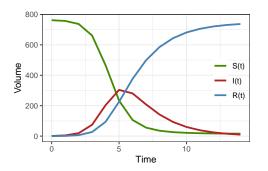
- simulate data with specified parameter values
- measure the capacity of the model to recover the chosen parameter values

#### Many advantages:

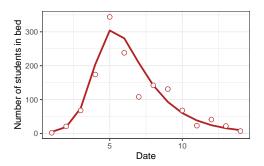
- check for bugs and coding mistakes
- check for identifiability issues
- compare different versions of a model
- understand in what situations a model works or not

Let's go back to the simple SIR example from the beginning:

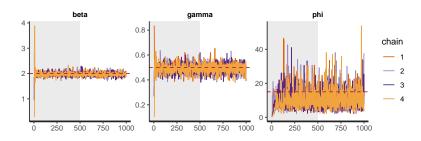
- ightharpoonup set  $\beta=2$  and  $\gamma=0.5$  (so that  $\mathcal{R}_0=4$ )
- ightharpoonup simulate in a susceptible population of size N=763 with  $I_0=1$



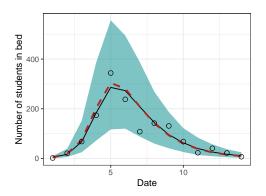
Add noise with a negative binomial distribution with  $\phi=15$ 



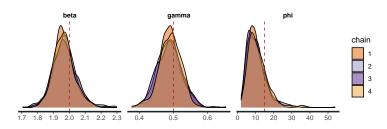
#### Fit the same model as for the boarding school example



#### Posterior predictive checking



Compare the posterior distributions of the parameters with the "truth"



- no identifiability issue
- ightharpoonup eta and  $\gamma$  are well estimated, but  $\phi$  is not
- try with other values to understand when does the model break

## Outline

Models of disease transmission

Bayesian inference with Stan

Fitting a simple SIR

Bayesian workflow

Using simulations to understand the mode

Conclusions

Bonus



#### Conclusions

#### General comments:

- develop models that correspond to the data-generating mechanisms
- use Bayesian inference to propagate uncertainty from the data (and priors) into the results (and forecasts)
- carefully examine the modelling process (Bayesian workflow)
- be transparent about assumptions (open code)

#### Try by yourself!

- https://github.com/charlesm93/disease\_ transmission\_workflow
- ▶ julien.riou@ispm.unibe.ch

# 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
- ▶ Ben Bales, Sebastian Weber , Upgrading to the new ODE interface
  - https://mc-stan.org/users/documentation/case-studies/convert\_odes.html

## Outline

Models of disease transmission

Bayesian inference with Stan

Fitting a simple SIR

Bayesian workflow

Using simulations to understand the model

Conclusions

Bonus

Example with SARS-CoV-2 from Hauser et al. (2020):

# PLOS MEDICINE

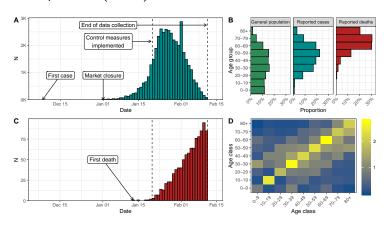
⑥ OPEN ACCESS № PEER-REVIEWED RESEARCH ARTICLE

Estimation of SARS-CoV-2 mortality during the early stages of an epidemic: A modeling study in Hubei, China, and six regions in Europe

Anthony Hauser, Michel J. Counotte, Charles C. Margossian, Garyfallos Konstantinoudis, Nicola Low, Christian L. Althaus, Julien Riou

Published: July 28, 2020 • https://doi.org/10.1371/journal.pmed.1003189

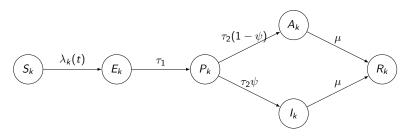
#### In Hubei province (China):



Specific features and natural history of SARS-CoV-2 infection:

- ► Incubation period of 5 days (SEIR)
- Pre-symptomatic transmission accounting for 44-48% (SEPIR)
- Symptoms in 81% (95%Crl 71%–89%) of cases (SEPIAR)
- Respiratory virus transmitted through contacts (age stratification)
- ▶ Effect of control measures (time-dependent force of infection)
- lacktriangle Mortality is delayed by  $20.2 \pm 11.6$  days (fit to mortality data)

#### Final model:



$S_k$	Susceptible (for age group $k$ )	$\lambda_k(t)$	Force of infection (time-dependent)
$E_k$	Exposed	$1/ au_1 + 1/ au_2$	Incubation period (split in two)
$P_k$	Presymptomatic	$\psi$	Proportion of symptomatic
$A_k$	Infected asymptomatic	$1/ au_2$	Presymptomatic infectious period
$I_k$	Infected symptomatic	$1/\mu$	Symptomatic infectious period
Rı.	Removed	, .	

## Posterior predictive check (Hubei):

