Bayesian workflow for disease transmission modeling in Stan

Eustat – XXXIII International Statistical Seminar

Julien Riou, MD PhD
Institute of Social and Preventive Medicine, University of Bern, Switzerland

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 2.21`
- 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:

$$\begin{tikzcd} S \arrow[r, "\beta S \frac{I}{N}"] & I \arrow[r, "\gamma I"] & R \end{tikzcd}$$

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

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

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

Introduction

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

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

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

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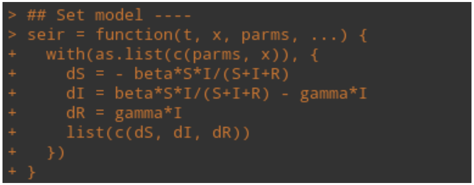
Assumptions behind the SIR model:

- 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))
+   })
+ }
```

Introduction

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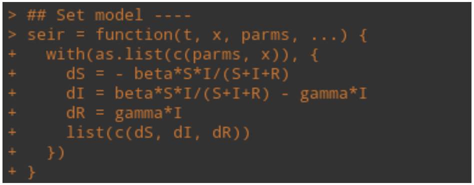

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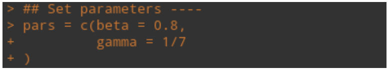
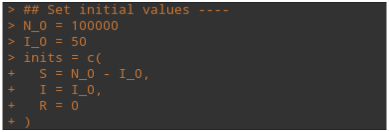
+   })
+ }
```

- 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
+ )
```

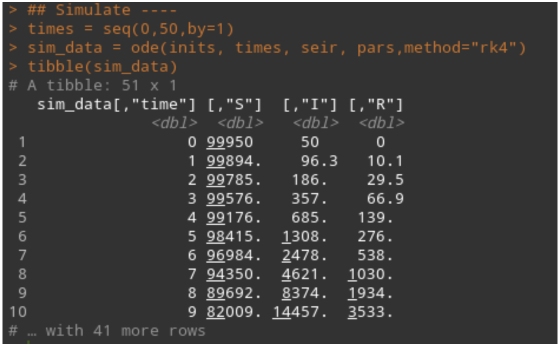


```
> ## Set initial values ----
> N_0 = 100000
> I_0 = 50
> inits = c(
+   S = N_0 - I_0,
+   I = I_0,
+   R = 0
+ )
```

Introduction

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

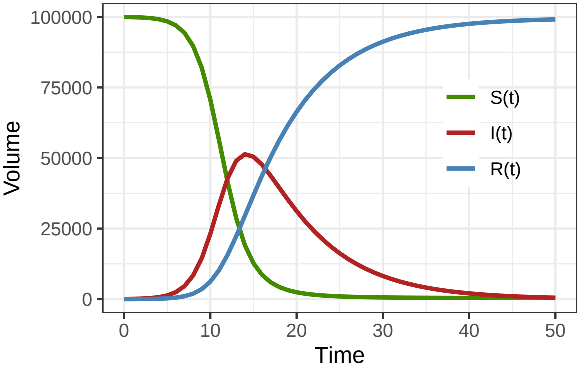
$$f(\beta, \gamma, S_0, I_0, R_0) = \{S(t), I(t), R(t)\}$$



```
> ## 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
```

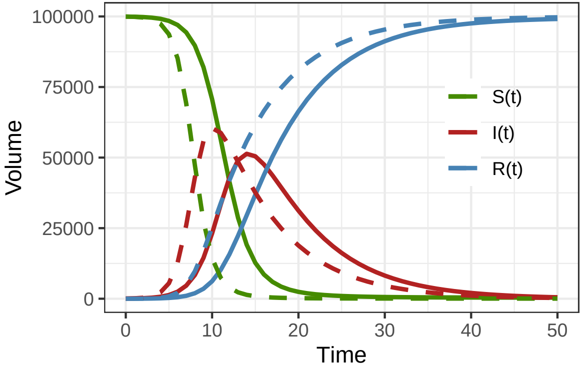
Introduction

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



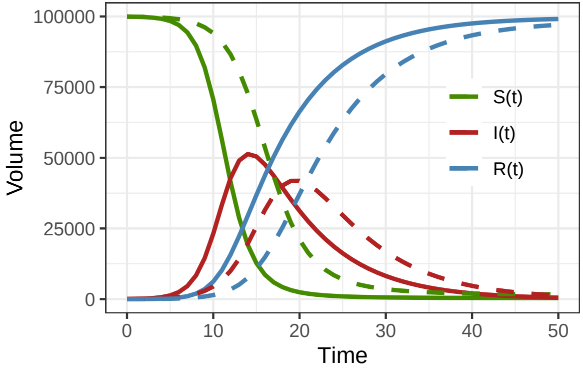
Introduction

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



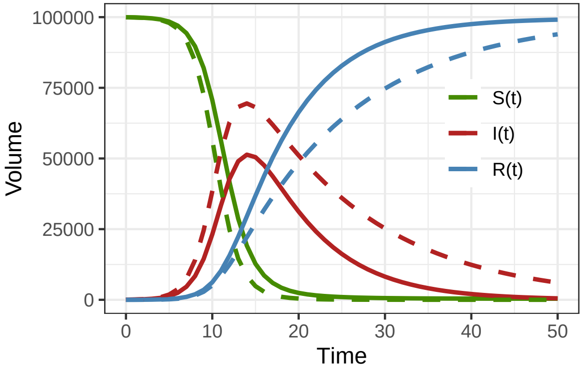
Introduction

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



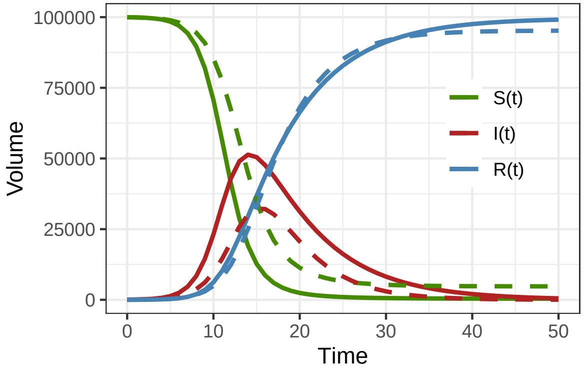
Introduction

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



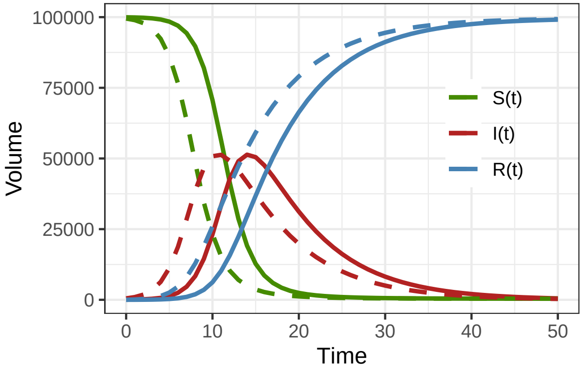
Introduction

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



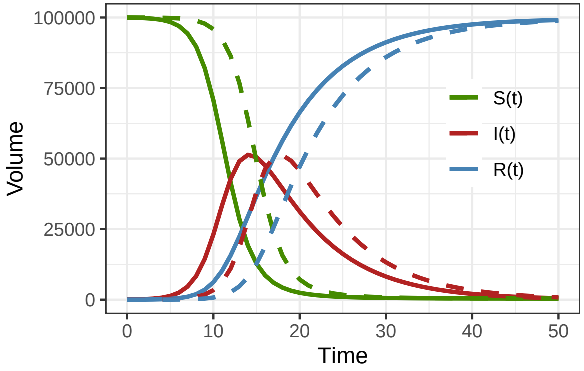
Introduction

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



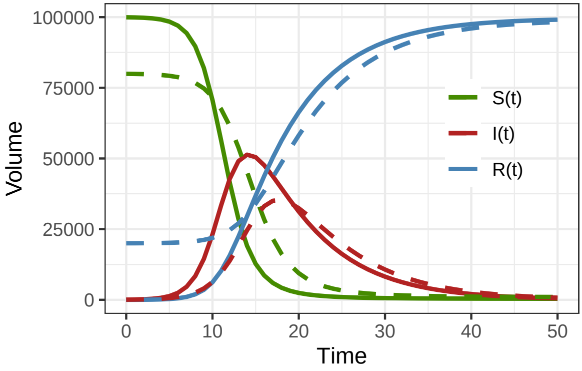
Introduction

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

(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)

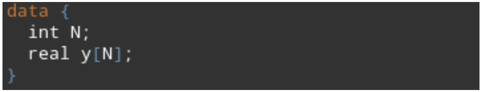
Stan is a probabilistic programming framework for Bayesian inference

- 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)

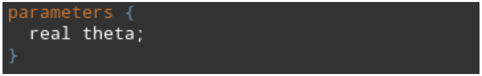
Programming in Stan is structured in blocks:

- the `data` block defines data variables



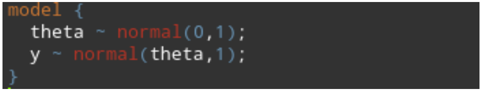
```
data {
  int N;
  real y[N];
}
```

- 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

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

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

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

- run MCMC sampling

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

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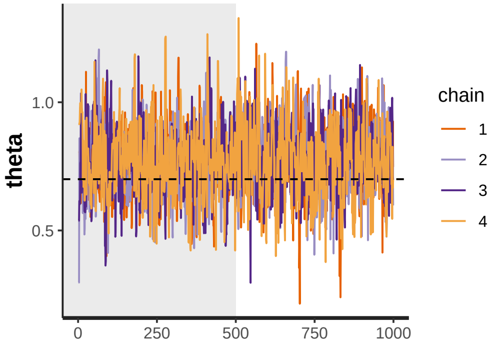
(Bayesian inference with Stan)

We use multiple chains that should converge after warm-up



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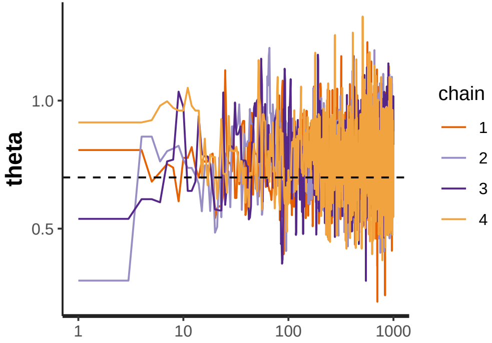
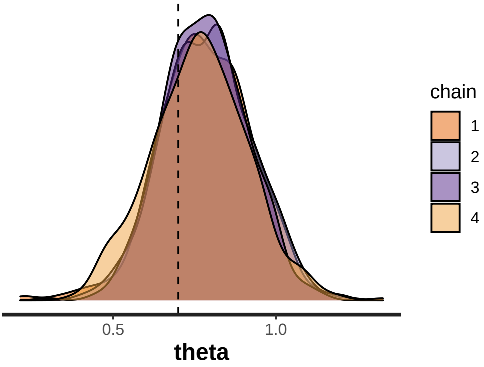


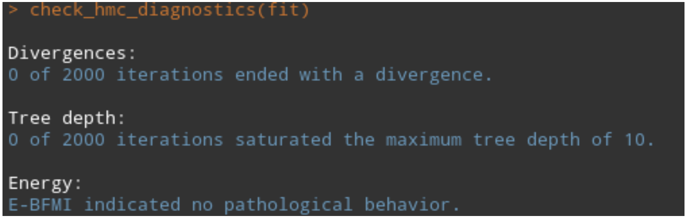
(Bayesian inference with Stan)

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



(Bayesian inference with Stan)

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

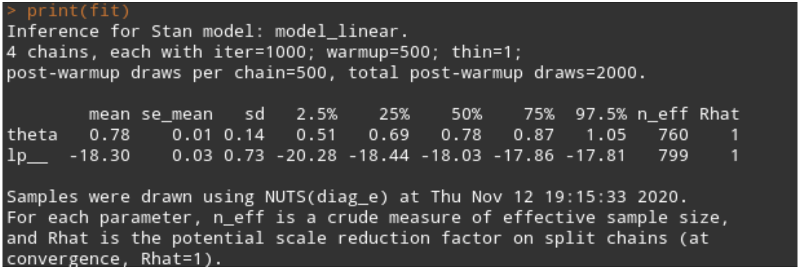


```
> check_hmc_diagnostics(fit)

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



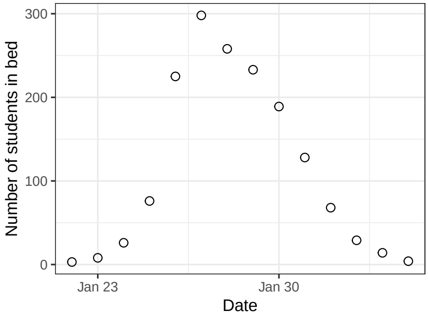
```
> print(fit)
Inference for Stan model: model_linear.
4 chains, each with iter=1000; warmup=500; thin=1;
post-warmup draws per chain=500, total post-warmup draws=2000.

        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).
```

Outline

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 $t \in \{1, \dots, 14\}$
- 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

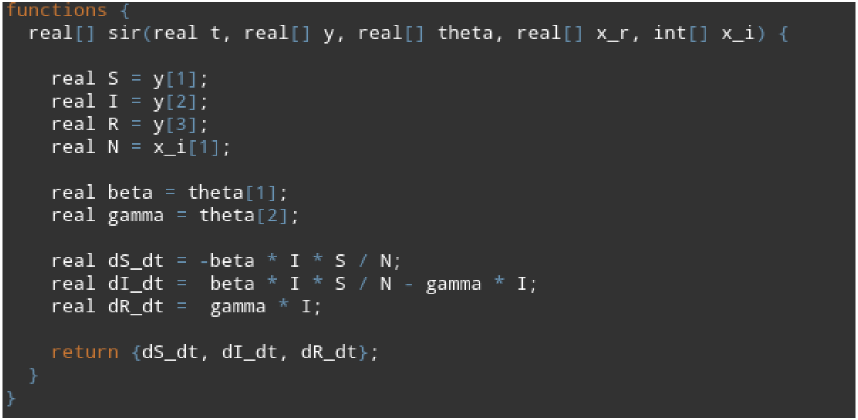
$$\Pr(\beta) = \text{exponential}(1)$$

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

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

Fitting a simple SIR

We define the ODE system in the `function` block

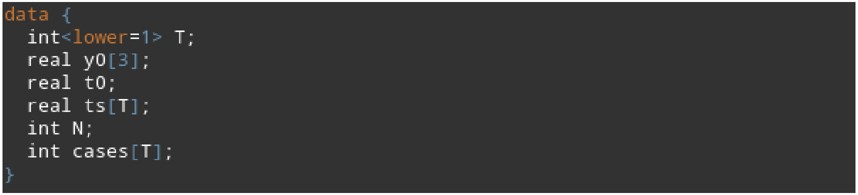


```
functions {
  real[] sir(real t, real[] y, real[] theta, real[] x_r, int[] x_i) {

    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

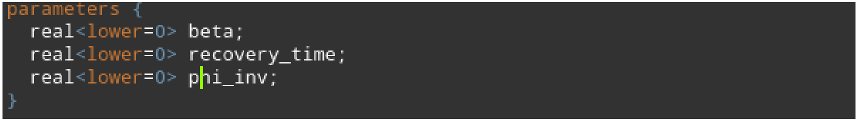
```
data {
  int<lower=1> T;
  real y0[3];
  real t0;
  real ts[T];
  int N;
  int cases[T];
}
```

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

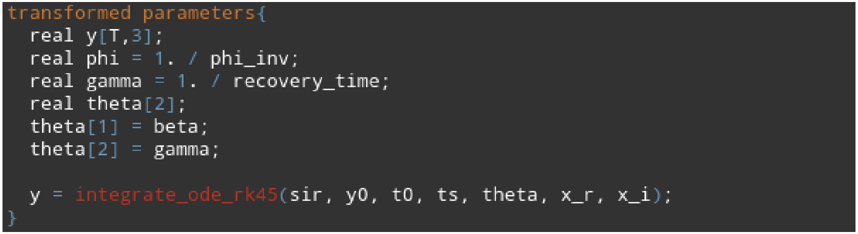


```
parameters {
  real<lower=0> beta;
  real<lower=0> recovery_time;
  real<lower=0> phi_inv;
}
```

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

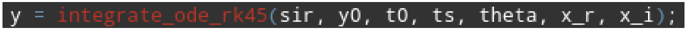
Fitting a simple SIR

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

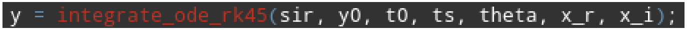


```
y = integrate_ode_rk45(sir, y0, t0, ts, theta, x_r, x_i);
```

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



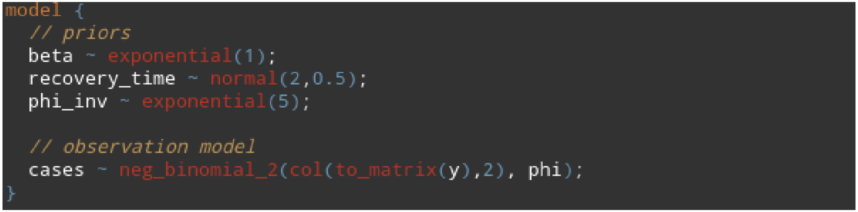
```
y = integrate_ode_rk45(sir, y0, t0, ts, theta, x_r, x_i);
```

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`

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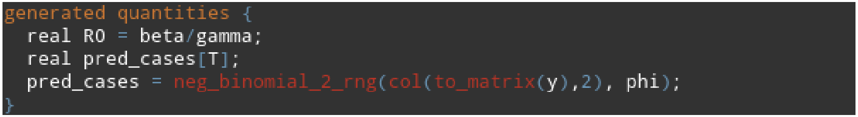
Fitting a simple SIR

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);
}
```

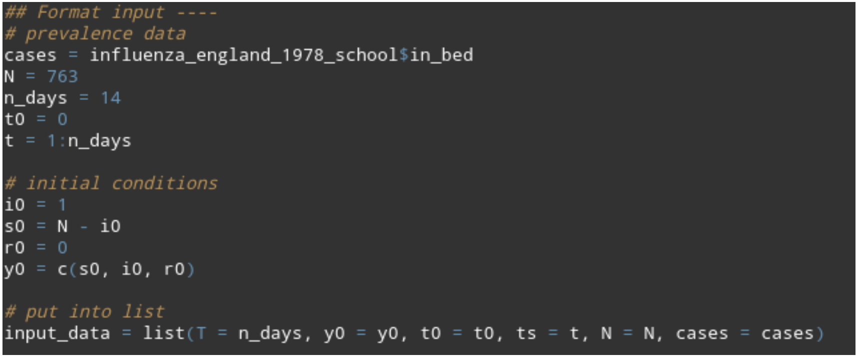
Fitting a simple SIR

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`:

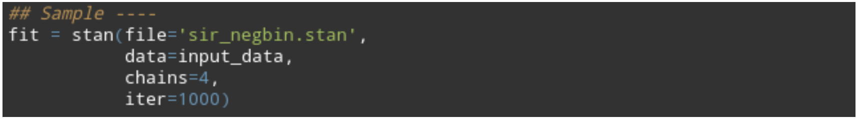


```
## Format input ----
# prevalence data
cases = influenza_england_1978_school$in_bed
N = 763
n_days = 14
t0 = 0
t = 1:n_days

# 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

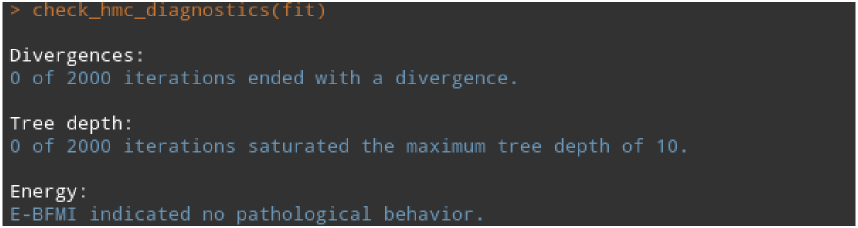
Hit the inference button!



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

Fitting a simple SIR

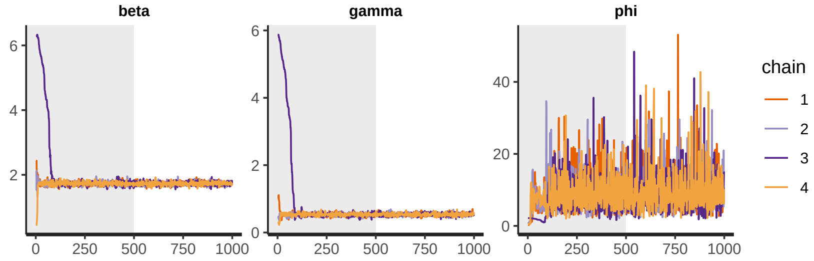
Run basic diagnosis tools:



```
> 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.
```

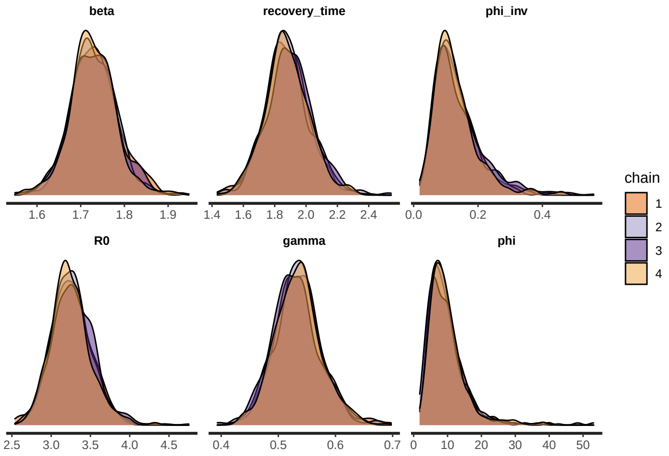
Fitting a simple SIR

Examine trace plots:



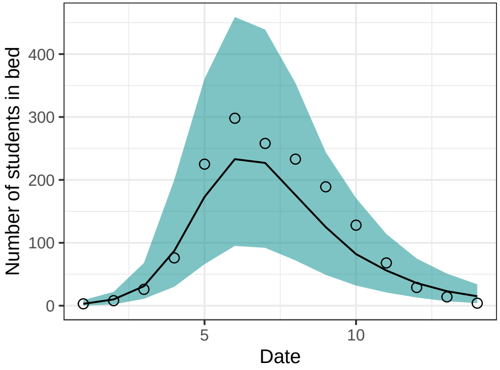
Fitting a simple SIR

Examine chain mixing:



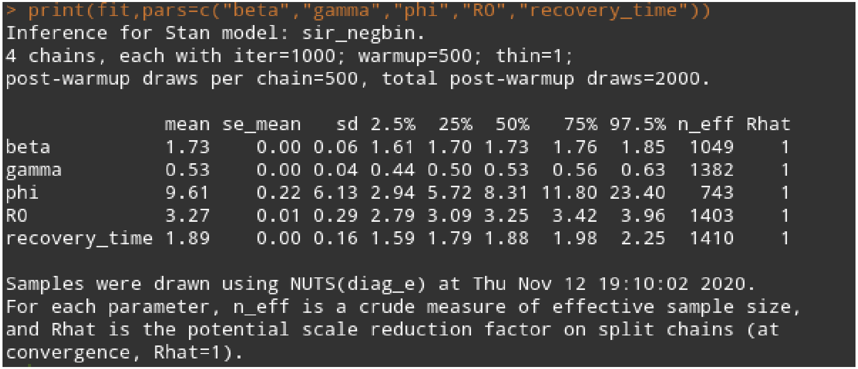
Fitting a simple SIR

Posterior predictive checking (always show!):



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
- simulation study

Simulations to understand the model

Prior predictive checking consists in simulating data from the priors:

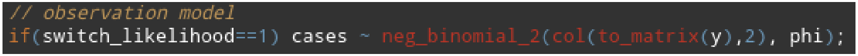
- visualize priors (especially after transformation)
- this shows the range of data compatible with the model
- it helps understand the adequacy of the chosen priors, as it is often easier to elicit expert knowledge on measureable quantities of interest rather than abstract parameter values

Simulations to understand the model

Prior predictive checking consists in simulating data from the priors:

- visualize priors (especially after transformation)
- 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);
```

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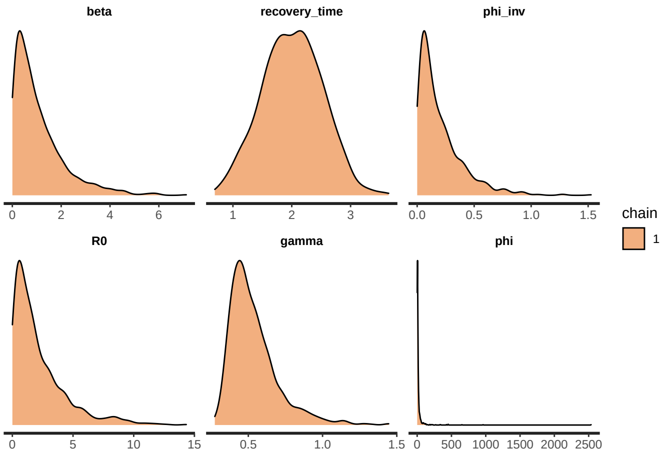
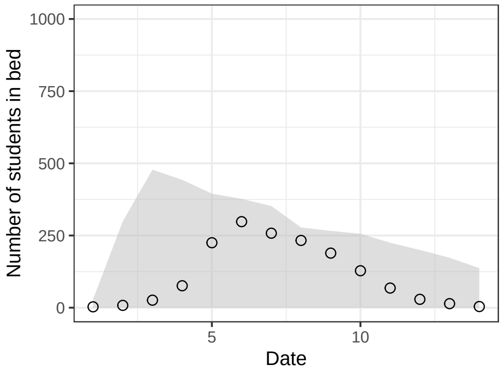
Simulations to understand the model

Simulating priors in the boarding school example:



Simulations to understand the model

Prior predictive checking: simulating epidemic trajectories



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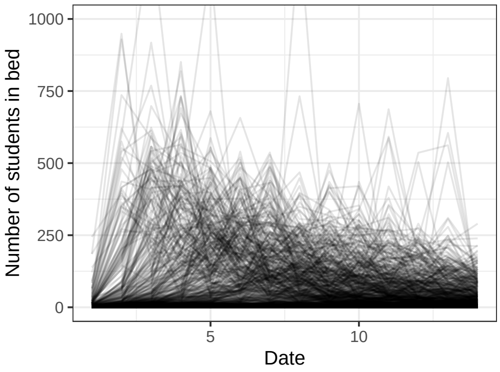
Simulations to understand the model

Prior predictive checking: simulating epidemic trajectories



Simulations to understand the model

Prior predictive checking brings insight about non-obvious features:

- even if the priors seem 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

A simulation study consists in two steps:

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

Simulations to understand the model

A simulation study consists in two steps:

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

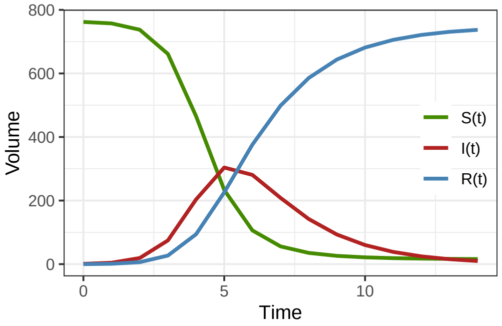
Many advantages:

- 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

Simulations to understand the model

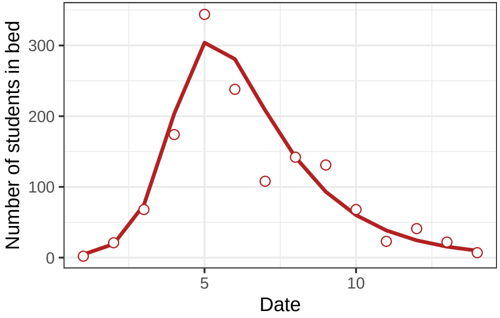
Let's go back to the simple SIR example from the beginning:

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



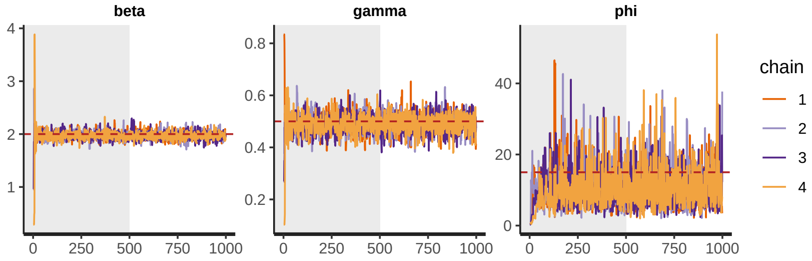
Simulations to understand the model

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



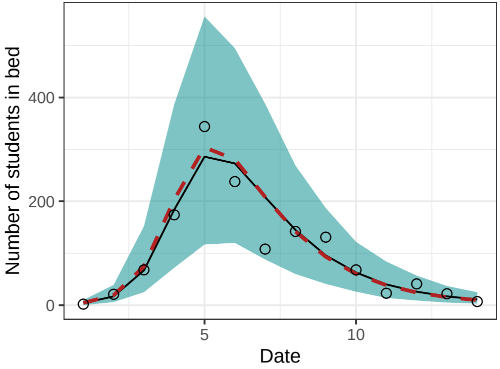
Simulations to understand the model

Fit the same model as for the boarding school example



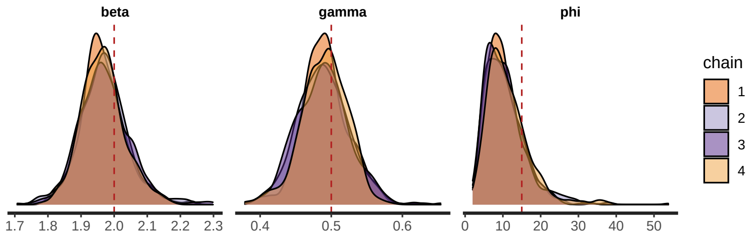
Simulations to understand the model

Posterior predictive checking



Simulations to understand the model

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



- no identifiability issue
- β and γ are well estimated, but ϕ is not
- try with other values to understand when does the model break

Outline

- Introduction
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- **Scaling up ODE-based models**
- Extensions

Scaling up ODE-based models

Inference with ODE-based models is computationally intensive

Be attentive to the model structure:

- HMC requires to compute the gradient of the log joint density multiple times for each iteration

$$\nabla_\theta \log \Pr(y, \theta)$$

- each block is treated differently
  - `transformed data` and `generated quantities` are evaluated once per iteration
  - `parameters`, `transformed parameters` and `model` are evaluated multiple times for each iteration

  $\rightarrow$ put everything that does not influence the inference (e.g. $\mathcal{R}_0$ or predicted values) in `generated quantities`

Scaling up ODE-based models

Limiting the load of the ODE solver:

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

- the computational cost of solving the ODEs scales with $N + NK$
  - N: the number of compartments
  - K: the number of parameters in `y0` and `theta`

$\rightarrow$ remove unnecessary compartments (e.g. $R(t)$)

$\rightarrow$ reparametrize initial conditions

Scaling up ODE-based models

Picking the right ODE solver:

- two 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)
- there is no formal definition of stiffness
- intuitively, it occurs when the time step of the integrator needs to be very small to keep the solution stable (e.g. large variations in magnitude in time)

→ start with `rk45`, move to `bdf` if there are problems (*folk theorem of statistical computing*)

Scaling up ODE-based models

Tuning the ODE solver:

- additional options in the solver function

```
y_hat = integrate_ode_bdf(sho, y0, t0, ts, theta, x_r, x_i,
                          rel_tol, abs_tol, max_steps);
```

  - `rel_tol` is the relative tolerance
  - `abs_tol` is the absolute tolerance
  - `max_steps` is the maximum number of steps
- can be adjusted depending on the level of precision needed

⚠ be cause of the tolerance, the ODE solver may sometimes give negative values when too close to zero, causing issues

$\rightarrow$ this can be solved by adding 5-10 times the absolute tolerance to the ODE output

Outline

- Introduction
- (Quick notice: Bayesian inference with Stan)
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- **Extensions**

Extensions

In practice, the boarding school example quickly reaches its limits:

- epidemics are not often observed in such a controlled environment (under-ascertainment)
- epidemics are not always left uncontrolled
- data generally consist of daily counts of new cases (incidence) rather than counts of currently sick people (prevalence)
- most infectious diseases have an incubation period (SEIR instead of SIR)
- transmission is generally not homogeneous in the full population (stratification by age, sex...)
- ...

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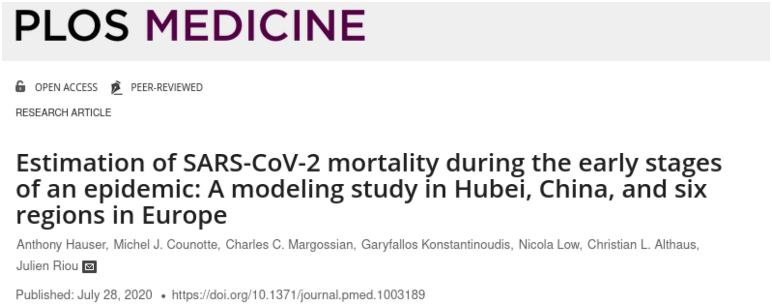
Extensions

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



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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

Background

The case fatality ratio (CFR) is computed as the number of deaths divided by the number of reported cases at time t.

Estimated in real time, the CFR is a misleading indicator of mortality due to SARS-CoV-2 because of two opposing biases:

- preferential ascertainment of severe cases: severe cases are both more likely to die and more likely to be diagnosed and reported

$\rightarrow$ overestimates mortality

- right-censoring of deaths: there is a long delay between infection and deaths, so that part of the cases at time t will die in the future

$\rightarrow$ underestimates mortality

Background

This limits the interpretability of the CFR:

- varies in time (ascending or descending phase)
- varies across countries (depending on surveillance system)

$\rightarrow$ April 2020: from 2.4% in Wuhan to 17.8% in Lombardy)

- the real indicator of interest is the infection fatality ratio, i.e. the total number of deaths that occur among people infected with SARS-CoV-2

Objectives

(1) Simulate the dynamics of transmission and mortality of SARS-CoV-2 using publicly available surveillance data

(2) Provide overall and age-stratified estimates of IFR for SARS-CoV-2 infection adjusted for right-censoring and preferential ascertainment

in seven different geographic locations with available data on:

- reported cases by date of disease onset
- deaths linked to SARS-CoV-2 infection by date of death
- age distribution of cases
- age distribution of deaths

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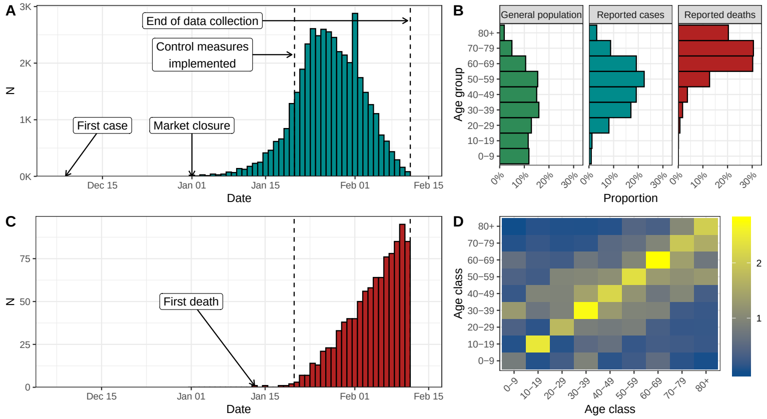
Data

In Hubei province (China):



Model development

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%CrI 71%–89%) of cases (SEPIAR)
- Respiratory virus transmitted through contacts (age stratification)
- Effect of control measures (time-dependent force of infection)
- Mortality is delayed by 20.2 ± 11.6 days (fit to mortality data)

Model development

Final model:

$$\begin{tikzcd}
 & & & A_k \arrow[dr, "\mu"] & \\
S_k \arrow[r, "\lambda_k(t)"] & E_k \arrow[r, "\tau_1"] & P_k \arrow[ur, "\tau_2(1-\psi)"] \arrow[dr, "\tau_2\psi"] & & R_k \\
 & & & I_k \arrow[ur, "\mu"] &
\end{tikzcd}$$

S_k	Susceptible (for age group k)	$\lambda_k(t)$	Force of infection (time-dependent)
E_k	Exposed	$1/\tau_1 + 1/\tau_2$	Incubation period (split in two)
P_k	Presymptomatic	ψ	Proportion of symptomatic
A_k	Infected asymptomatic	$1/\tau_2$	Presymptomatic infectious period
I_k	Infected symptomatic	$1/\mu$	Symptomatic infectious period
R_k	Removed		

Model development

Incubation:

- SEIR: adding a compartment E for exposed, i.e. infected but not yet symptomatic

$$\begin{tikzcd} S \arrow[r, "\lambda"] & E \arrow[r, "\tau"] & I \arrow[r, "\mu"] & R \end{tikzcd}$$

  - τ is the inverse of the incubation period
  - individuals are infectious from symptom onset (when entering I)

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

Model development

Pre-symptomatic transmission:

- SEPIR: adding a compartment P for pre-symptomatic, i.e. not yet symptomatic but already infectious

$$\begin{tikzcd} S \arrow[r, "\lambda"] & E \arrow[r, "\tau_1"] & P \arrow[r, "\tau_2"] & I \arrow[r, "\mu"] & R \end{tikzcd}$$

  - the incubation period is split in two phases with rates τ_1 and τ_2
  - individuals are infectious before symptom onset (entering P)

$$\lambda = \beta \frac{P + I}{N}$$

  - we can introduce reduced transmissibility before symptom onset

$$\lambda = \beta \frac{\kappa P + I}{N}$$

Model development

Asymptomatic infections:

- SEPIAR: adding a compartment A for asymptomatic

$$\begin{tikzcd}
 & & & A \arrow[dr, "\mu"] & \\
S \arrow[r, "\lambda"] & E \arrow[r, "\tau_1"] & P \arrow[ur, "(1-\phi)\tau_2"] \arrow[dr, "\phi\tau_2"] & & R \\
 & & & I \arrow[ur, "\mu"] &
\end{tikzcd}$$

  - we introduce the proportion of symptomatics ϕ
  - we can introduce reduced transmissibility for asymptomatics

$$\lambda = \beta \frac{\kappa P + I + \kappa A}{N}$$

Model development

Age stratification:

- the transmission of respiratory viruses (influenza virus, rhinovirus...) is highly dependent on age
- the mortality of respiratory infections (even more so for SARS-CoV-2) is highly dependent on age

$\rightarrow$ stratification in nine age groups $k \in \{1, \ldots, 9\}$ for (0-9, . . . , 80+)

$$\begin{tikzcd}
 & & & A_k \arrow[dr, "\mu"] & \\
S_k \arrow[r, "\lambda_k"] & E_k \arrow[r, "\tau_1"] & P_k \arrow[ur, "(1-\phi)\tau_2"] \arrow[dr, "\phi\tau_2"] & & R_k \\
 & & & I_k \arrow[ur, "\mu"'] &
\end{tikzcd}$$

Model development

Characterizing the force of infection:

- in the simple SIR, the force of infection is defined as the rate at which susceptible individuals acquire infection

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

- the transmission rate β can be split in a contact rate c times a probability of transmission upon contact β, so that

$$\lambda = \beta c \frac{I}{N}$$

⚠ the same symbol β is used for the transmission rate and the probability of transmission upon contact depending on context

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Model development

- time-dependent force of infection using a forcing function

$$\lambda = f(t)\beta c\frac{I}{N}$$

  - to model the effect of control measures, we want a downward function that maps onto the interval $[0, 1]$, e.g. a logistic function:

$$f(t) = \eta + \frac{1-\eta}{1+\exp(\xi(t-t_c-\nu))}$$

  - η is the relative reduction in transmission after control measures
  - ξ is the slope of implementation of the control measures
  - ν is the delay until the control measures are 50% effective (in days after t_c, the date of introduction of control measures).

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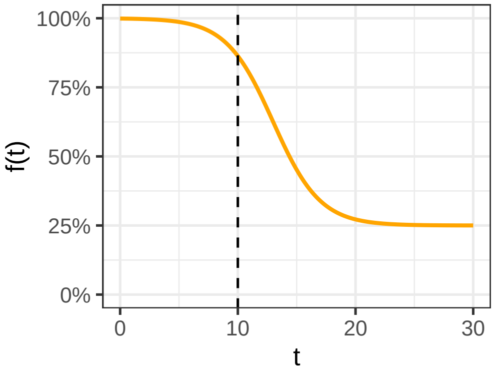
Model development

with $t_c = 10; \eta = 0.25; \nu = 3$ and $\xi = 0.5$



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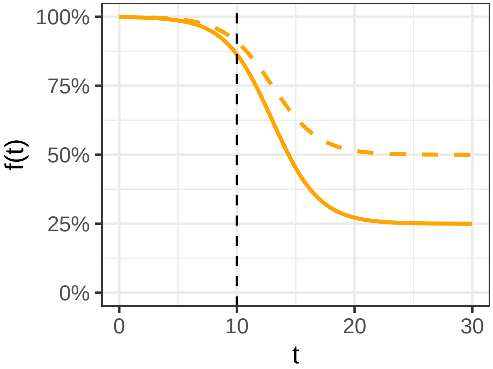
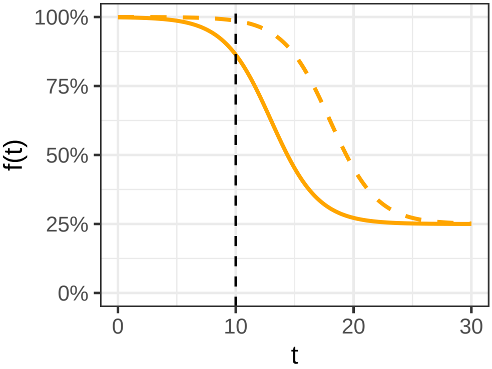
Model development

with $\eta = 0.5$ instead of 0.25, we get



Model development

with $\nu = 8$ instead of 3, we get



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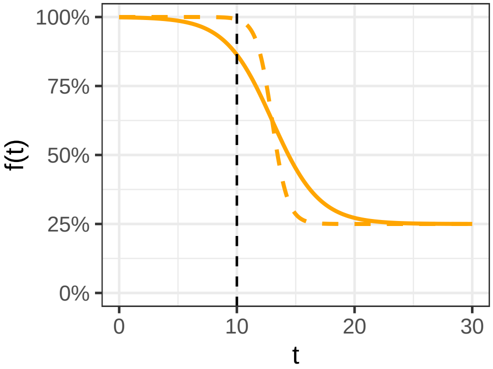
Model development

with $\xi = 1.5$ instead of 0.5, we get



Model development

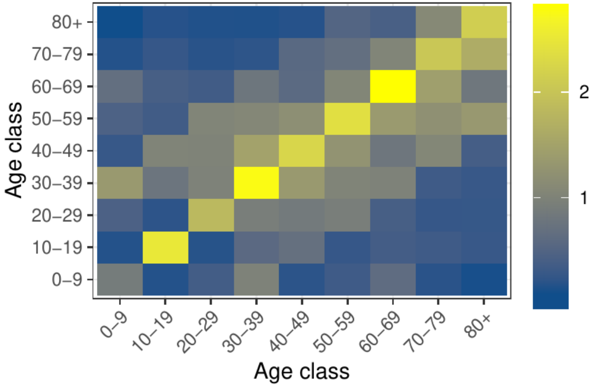
- we account for behaviour differences across age groups:

$$\lambda_k(t) = f(t)\beta \sum_{l=1}^{9} \mathbb{F}_{k,l} \frac{I_l}{N_l}$$

  - one force of infection for each age group k
  - includes a specific contact rate between age group k and each age group l (corresponding to one cell of the contact matrix $\mathbb{F}_{k,l}$)
  - includes the prevalence in age group l (I_l/N_l)

Model development

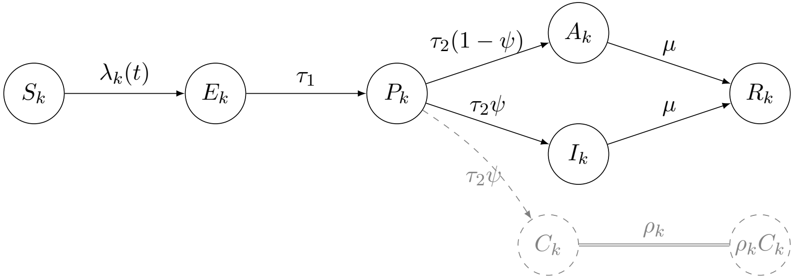
Age-specific contact matrix in China



Model development

Model fit to reported cases:

- obtaining incidence from the ODE output:



  - dummy compartment $C_k(t)$ records the cumulative incidence of symptomatic infections for each age group k

$$\frac{dC_k}{dt} = \tau_2 \psi P_k$$

Model development

- new symptomatic infections by day of symptom onset by age:

$$\Delta C_{k,t} = C_k(t) - C_k(t-1)$$

- new reported infections per day of symptom onset, introducing the age-specific ascertainment proportion ρ_k:

$$A_t = \sum_{k}^{9} \rho_k \Delta C^I_{k,t}$$

- the age distribution of all reported cases up to t_{max} :

$$B_k = \frac{\rho_k C^I_k(t_{\text{max}})}{\sum_k^9 \rho_k C^I_k(t_{\text{max}})}$$

Model development

- A_t can be mapped to reported incidence data $\mathbb{A}$ using a negative binomial likelihood:

$$\Pr(\theta|\mathbb{A}) = \prod_{t=t_1}^{t_{\text{max}}} \text{Neg-Bin}(\mathbb{A}_t|A_t, \phi_1)$$

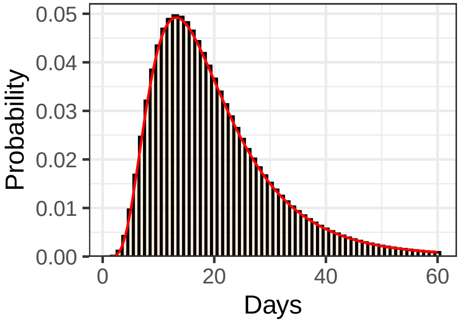
- B_k can be mapped to the age distribution of reported cases $\mathbb{B}$ using a multinomial likelihood:

$$\Pr(\theta|\mathbb{B}) = \text{Multinomial}(\mathbb{B}_1, \dots, \mathbb{B}_9|B_1, \dots, B_9)$$

Model development

Model fit to deaths:

- mortality is considered outside of the system of ODEs, using an age-specific mortality parameter ε_k (probability of death given *symptomatic* infection)
- we account for the delay with a discretized log-normal distribution of time from symptom onset to death $\mathbb{I}$ of length 60



Model development

- deaths in age group k at time t $(1 \leq t \leq t_{\text{max}} + 60)$ among people infected up to t_{max}:

$$M_{k,t} = \varepsilon_k \sum_{d}^{60} \Delta C_{k,t-d} \mathbb{I}_d$$

- deaths summed over age groups, assuming that all deaths are reported:

$$M_t = \sum_{k}^{9} M_{k,t}$$

- the age distribution of all deaths occurring up to t_{max}:

$$D_k = \frac{\sum_{t=1}^{t_{\text{max}}} M_{k,t}}{\sum_{t=1}^{t_{\text{max}}} M_t}$$

Model development

- M_t can be mapped to daily death data $\mathbb{C}$ using a negative binomial likelihood:

$$\Pr(\theta|\mathbb{C}) = \prod_{t=t_1}^{t_{\text{max}}} \text{Neg-Bin}(\mathbb{C}_t|M_t, \phi_2)$$

- D_k can be mapped to the age distribution of deaths $\mathbb{D}$ using a multinomial likelihood:

$$\Pr(\theta|\mathbb{D}) = \text{Multinomial}(\mathbb{D}_1, \ldots, \mathbb{D}_9|D_1, \ldots, D_9)$$

This leads to the following joint likelihood:

$$\Pr(\theta|\mathbb{A}, \mathbb{B}, \mathbb{C}, \mathbb{D}) = \Pr(\theta|\mathbb{A}) \cdot \Pr(\theta|\mathbb{B}) \cdot \Pr(\theta|\mathbb{C}) \cdot \Pr(\theta|\mathbb{D})$$

with $\theta = \{\beta, \eta, \xi, \nu, \psi, \pi, \rho_k, \varepsilon_k, \phi_1, \phi_2\}$.

Model development

Last bits:

- there is an identifiability issue with ρ

$\rightarrow$ fix ρ_9 (for 80+) to 100%, assuming that all symptomatic infections among very high risk persons will be reported

- some remaining unknowns (data correction in China, role of children, lower ρ_9...)

$\rightarrow$ sensitivity analyses

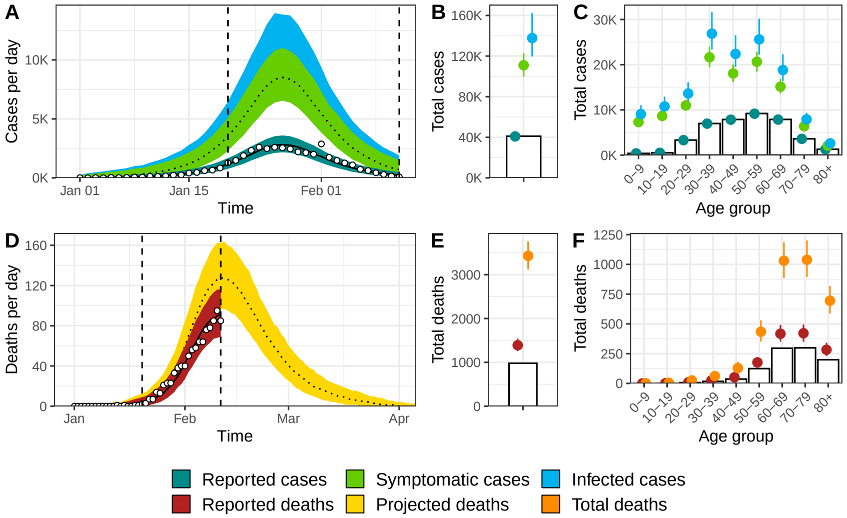
Inference

You know the drill:

- set priors
- prior predictive check
- sampling (on high performance computing cluster $\sim$ 2h)
- basic diagnostic tests
- examine trace plots and chains
- posterior predictive check

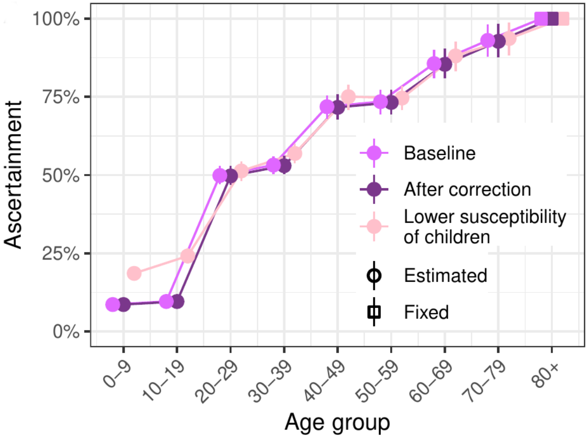
Results in Hubei

Posterior predictive check (Hubei):



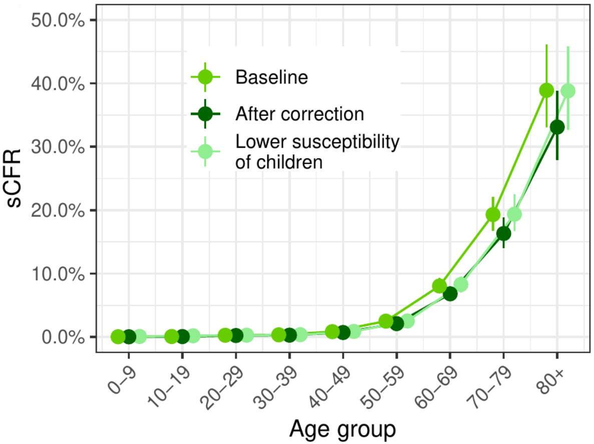
Results in Hubei

Ascertainment (posteriors of ρ_k):



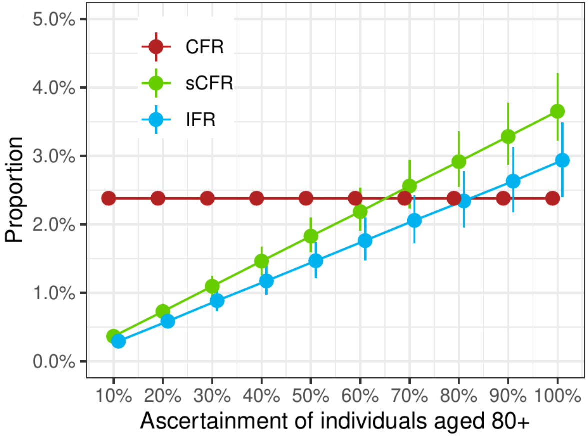
Results in Hubei

Mortality among symptomatics or sCFR (posteriors of ε_k):



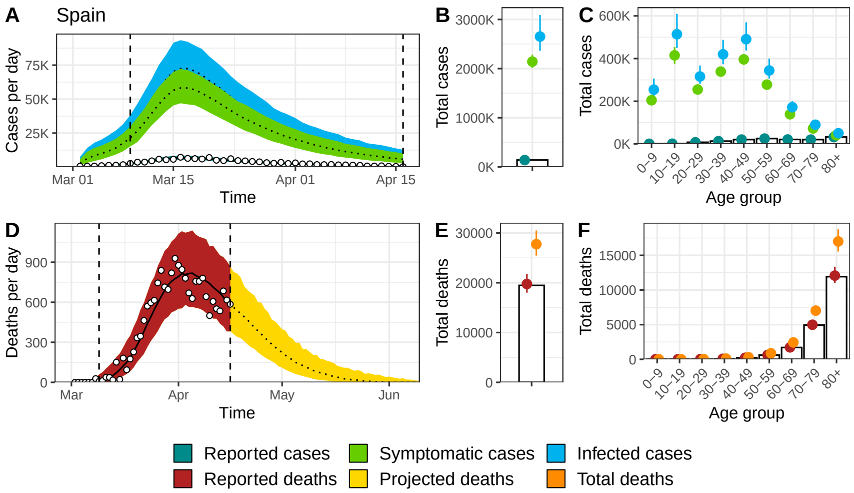
Results in Hubei

Effect on the assumption on ρ_9 on IFR estimate:



Results in all regions

Posterior predictive check (Spain):



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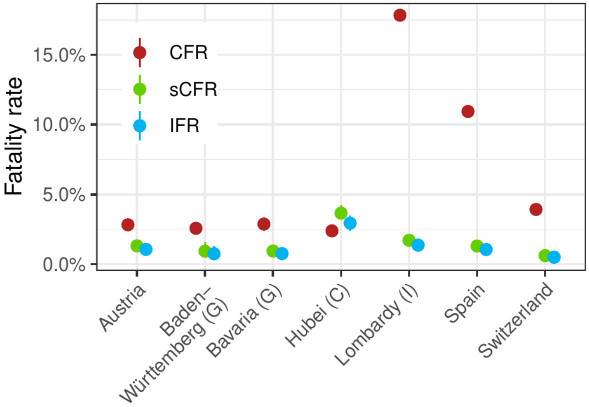
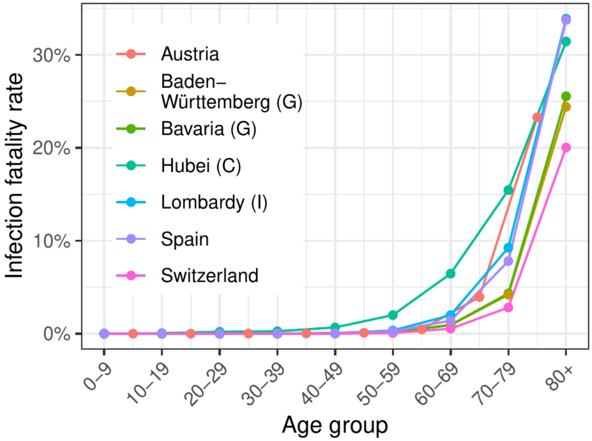
Results in all regions

IFR estimates (compared to CFR and sCFR)



Results in all regions

IFR estimates by age



Conclusions

Location (limit date)	Estimated attack rate	CFR	sCFR	IFR
Hubei, China (11 February)	0.2% (0.2-0.3)	2.0%	3.1% (2.7-3.5)	2.5% (2.1-2.9)
Austria (14 April)	0.8% (0.6-0.9)	2.8%	1.3% (1.1-1.6)	1.1% (0.8-1.3)
Baden-Württemberg, Germany (16 April)	1.9% (1.7-2.2)	2.6%	0.9% (0.6-1.6)	0.7% (0.5-1.3)
Bavaria, Germany (16 April)	2.0% (1.7-2.3)	2.9%	0.9% (0.7-1.3)	0.8% (0.5-1.1)
Lombardy, Italy (25 April)	11.5% (10.1-13.4)	17.8%	1.7% (1.5-2.0)	1.4% (1.1-1.6)
Spain (16 April)	5.7% (5.0-6.6)	10.9%	1.3% (1.2-1.5)	1.0% (0.9-1.2)
Switzerland (23 April)	3.6% (2.9-4.5)	3.9%	0.6% (0.5-0.8)	0.5% (0.4-0.6)

- IFR estimates adjusted for under-ascertainment and right-censoring are more similar across countries than CFR
- still some degree of heterogeneity
- clear increase of mortality with age

Conclusions

General comments:

- knowing the data-generating mechanisms to avoid misinterpretation
- this knowledge can be used to build a model to adjust for known biases
- estimates of IFR obtained early in the epidemic, mostly confirmed in later seroprevalence studies

Acknowledgements & ressources

- Stan forums
  `https://discourse.mc-stan.org/`
- 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`