L03 Reproduction numbers and their estimation[1]

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Outline

Overview

Outline

Basic Reproduction Number

- In a previous lecture we considered the **basic reproduction number** R_0, which was given as[2]

$$R_0 = \beta/\gamma S(0)$$

- R_0 is the mean number of direct offspring one infectious case generates in a *completely susceptible population without intervention measures*
- However, once an epidemic unfolds susceptibles are depleted. Furthermore, interventions or behavioral changes aim at reducing β, γ or the amount of susceptibles ($\rightarrow$ vaccination).
- In order to assess public health interventions the basic reproduction number is not useful (Delamater, Street, Leslie, Yang, and Jacobsen 2019).

[2] β was the infectious contact rate, γ the mean duration of the infectious period and $S(0)$ is the number of susceptibles at time zero ($S(0) \approx N$).

Effective Reproduction Number (1)

- We define the time-varying effective reproduction number $R(t)$ as a time varying quantity denoting the average number of secondary cases generated by one case at calendar time t
- If contact and recovery rates do not vary with time we get

$$R(t) = R_0 \times \frac{S(t)}{S(0)}$$

- Interventions could be reflected by extending this to

$$R(t) = (1 - c(t)) \times R_0 \times \frac{S(t)}{S(0)}$$

Effective Reproduction Number (2)

- The derivations in this lecture will follow Fraser (2007), who does not explicitly consider depletion of susceptibles
- Let the **transmissibility** function $\beta(t, \tau)$ be a function of calendar time t and time since infection τ
- Dependence on τ could, e.g., be due to time-dependence of viral shedding in the host, but also changes in contact behaviour after infection, depletion of susceptibles
- Renewal equation

$$I(t) = \int_0^\infty \beta(t, \tau) I(t - \tau) d\tau \tag{1}$$

Effective Reproduction Number (3)

- Case reproduction number

$$R_c(t) = \int_0^\infty \beta(t+\tau, \tau) d\tau$$

  Interpretation: Average number of individuals an infected at time t can expect to infect

- Instantaneous reproduction number

$$R(t) = \int_0^\infty \beta(t, \tau) d\tau$$

  Interpretation: Average number of individuals an infected at time t is expected to infect should conditions remain unchanged

Effective Reproduction Number (4)

- Assuming the factorization

$$\beta(t, \tau) = \phi_1(t)\phi_2(\tau),$$

Fraser (2007) shows that by assuming $\int_0^\infty \phi_2(\tau)d\tau = 1$ we get

$$\beta(t, \tau) = R(t)w(\tau) \tag{2}$$

- Here $w(\tau)$ denotes the distribution of the new infections as a function of time since infection, i.e. the generation time distribution.

Effective Reproduction Number (5)

Inserting (2) into (1) yields:

- Instantaneous reproduction number

$$R(t) = \frac{I(t)}{\int_0^\infty I(t-\tau)w(\tau)d\tau}$$

- Case reproduction number

$$R_c(t) = \int_0^\infty R(t+\tau)w(\tau)d\tau$$

Discretised Instantaneous Reproduction Number (1)

- If only discrete observations for time intervals $t_i \equiv [t_i, t_{i+1})$ are available, then one would use a discretized version of the instantaneous reproduction number

$$R(t_i) = \frac{I_i}{\sum_{j=0}^{n} w_j I_{i-j}}$$

- Note: the $0 \leq w_i \leq 1$ now denote the probability mass function of a discretized version of the generation time, i.e. $\sum_{i=0}^{n} w_i = 1$.

Discretised Instantaneous Reproduction Number (2)

- Casting this into a distributional framework, e.g.,

$$I_i | I_{i-1}, I_{i-1}, \ldots \sim Po\left(R(t_i) \times \sum_{j=0}^{n} w_j I_{i-j}\right)$$

  allows the consideration of $R(t_i)$ as a parameter to be estimated in a statistical model
- This also allows the construction of confidence intervals or credibility regions for $R(t_i)$.

Smoothed Instantaneous Reproduction Number

- Estimate $R(t)$ using discrete data is subject to fluctuations and it is therefore in general not recommended to just use one time point (Cori, Ferguson, Fraser, and Cauchemez 2013)
- Suggested improvement: Compute instantaneous reproduction number over an interval of τ days as follows

$$R_\tau(t_i) = \frac{\sum_{k=i-\tau+1}^{i} I_k}{\sum_{k=i-\tau+1}^{i} \sum_{j=0}^{n} w_j I_{k-j}}$$

- Note that this is slightly different from just using the mean of the τ computed $R(t)$ values, i.e.

$$\overline{R}_\tau(t) = \frac{1}{\tau} \sum_{k=i-\tau+1}^{i} R(t_{i-k})$$

Superspreading

- So far we have considered the *mean* number of offspring one infectious case generates
- This view ignores the variability in the offspring distribution, e.g., the larger the variation, the greater the probability of extinction
- Lloyd-Smith, Schreiber, Kopp, and Getz (2005) analysed that the 2002-2004 SARS-CoV-1 epidemic was driven by a small number of events where one case directly infected a large number of secondary cases, whereas many other cases did not infect any secondary cases
- If we can identify settings where super-spreading occurs, one can reduce the mean number of offspring substantially

Outline

Outbreak simulation (1)

- Consider a growth model and denote by y_t the expected number of new symptom onsets we observe on day t.
- Let $(w_1, \ldots, w_M)'$, denote the probability mass function of the generation time distribution, i.e. $P(GT = i) = w_i$ for $i = 1, 2, \ldots, M$.
- Assume that the expected number of cases can be described by the homogeneous linear difference equation

$$y_t = \sum_{i=1}^{M} R_c(t-i) w_i y_{t-i}, \quad t = 2, 3, \ldots$$

- Note: We use the case reproduction number and ignore terms on the RHS when $t - M \leq 0$.

Outbreak simulation (2)

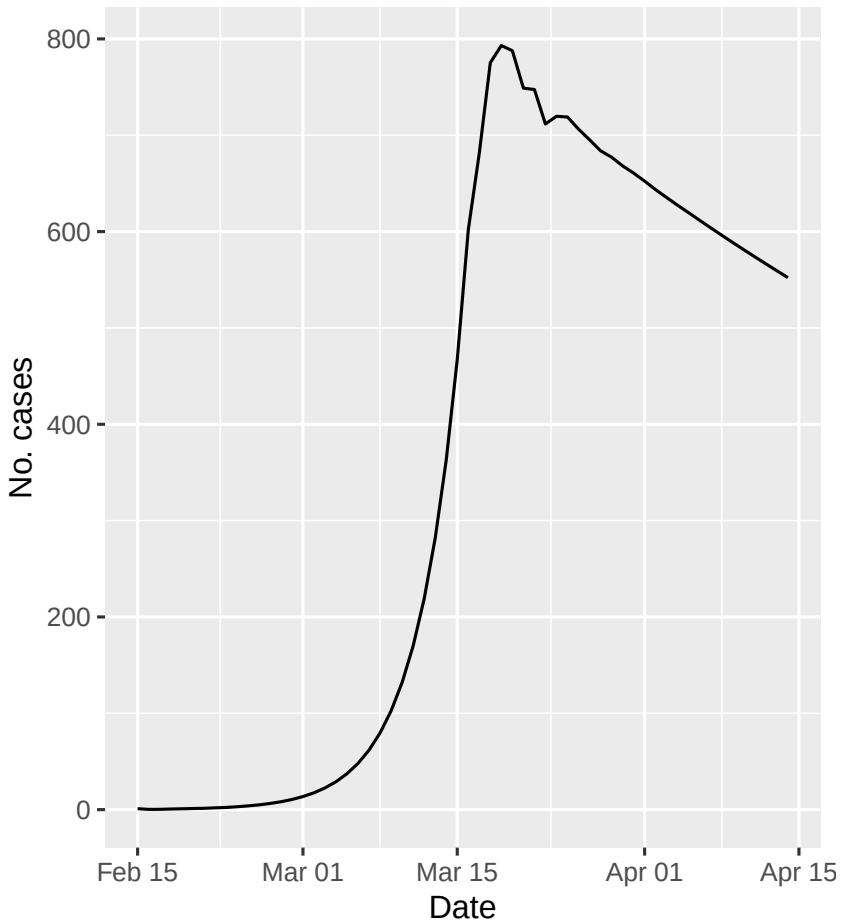
- Somewhat arbitrarily we fix $y_1 = 1$ and conceptually denote by $t = 1$ the 15th of February 2020 in calendar time.
- To simulate a COVID-19 like outbreak with lockdown type intervention we use

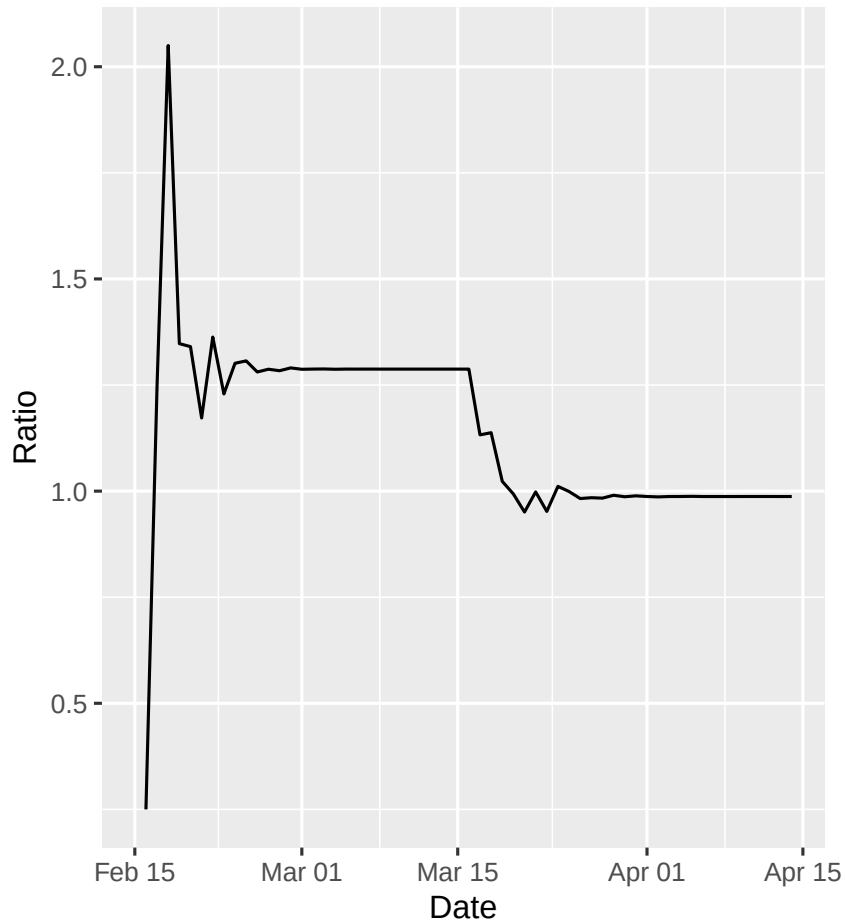
$$R_e(t) = \begin{cases} 2.5 & \text{if } t \leq \text{2020-03-15} \\ 0.95 & \text{otherwise} \end{cases}$$

- We use the following generation time distribution

```
##   0   1   2   3   4   5   6   7
## 0.0 0.1 0.1 0.2 0.2 0.2 0.1 0.1
```

Outbreak simulation (3)





EpiEstim (1)

- An implementation of the instantaneous reproduction estimate is available in the R package `EpiEstim` (Cori, Ferguson, Fraser, and Cauchemez 2013)
- Input is a ‘data.frame‘ containing the column ‘dates‘ and ‘I‘ (for the incidence each day)
- It also computes credibility regions for $R(t)$ and allows one to address uncertainty in the estimation of the generation time distribution

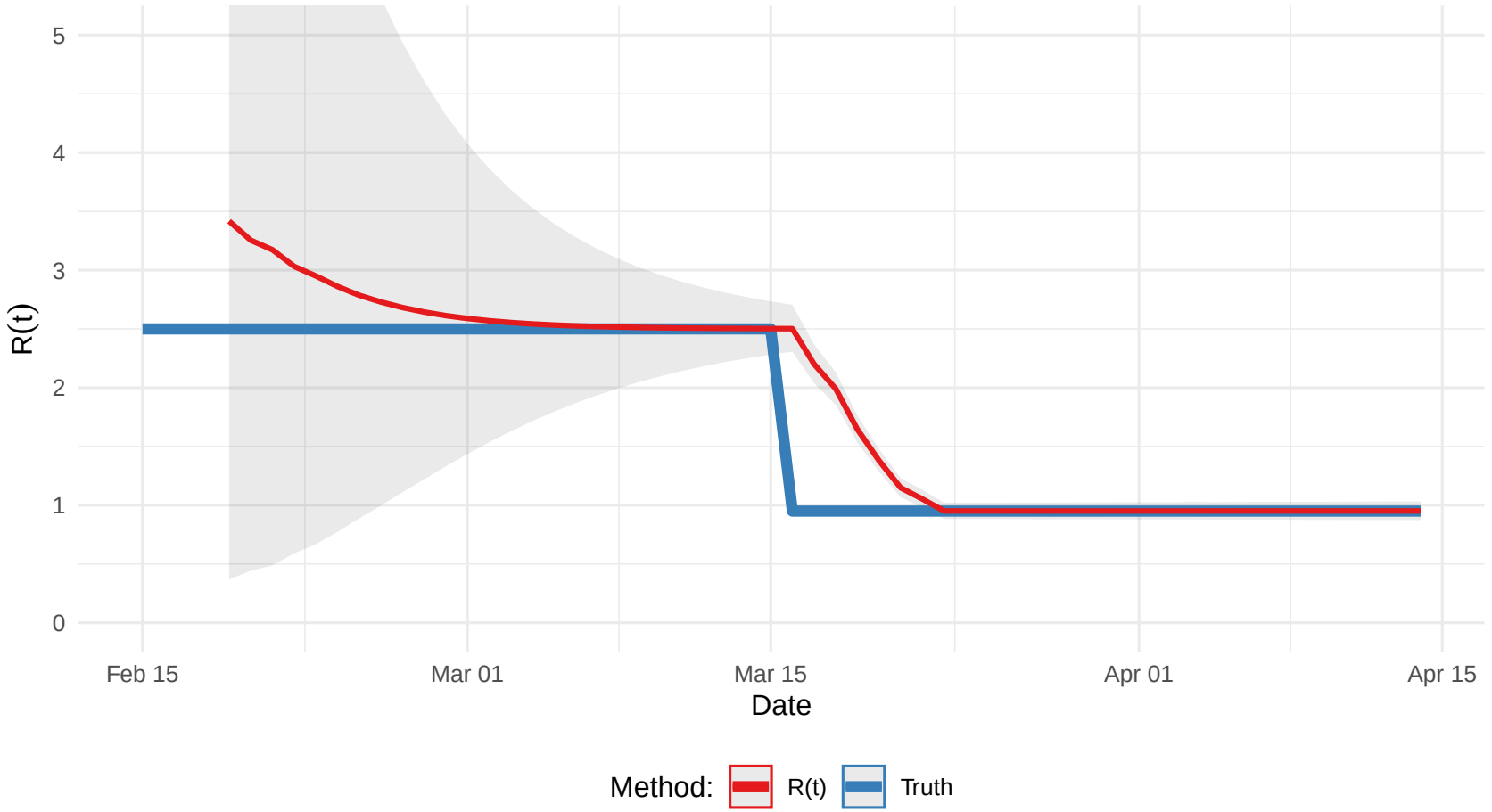
EpiEstim (2)

```
library(EpiEstim)
# Rename data.frame columns to names handled by the EpiEstim pkg.
out_epiestim <- out %>% rename(I = y, dates = Date) %>% select(dates, I)

# Estimate the instantaneous reproduction number
res <- EpiEstim::estimate_R(out_epiestim, method = "non_parametric_si",
                            config=make_config(si_distr=GT_obj$GT,
                                               t_start=2:nrow(out_epiestim),
                                               t_end=2:nrow(out_epiestim))
)

# Convert result to a data.frame
rt_irt_df <- data.frame(Date=res$dates[res$R$t_end],
                        R_hat=res$R$`Mean(R)`,
                        lower=res$R$`Quantile.0.025`,
                        upper=res$R$`Quantile.0.975`,
                        Method="R(t)")
```

EpiEstim (3)

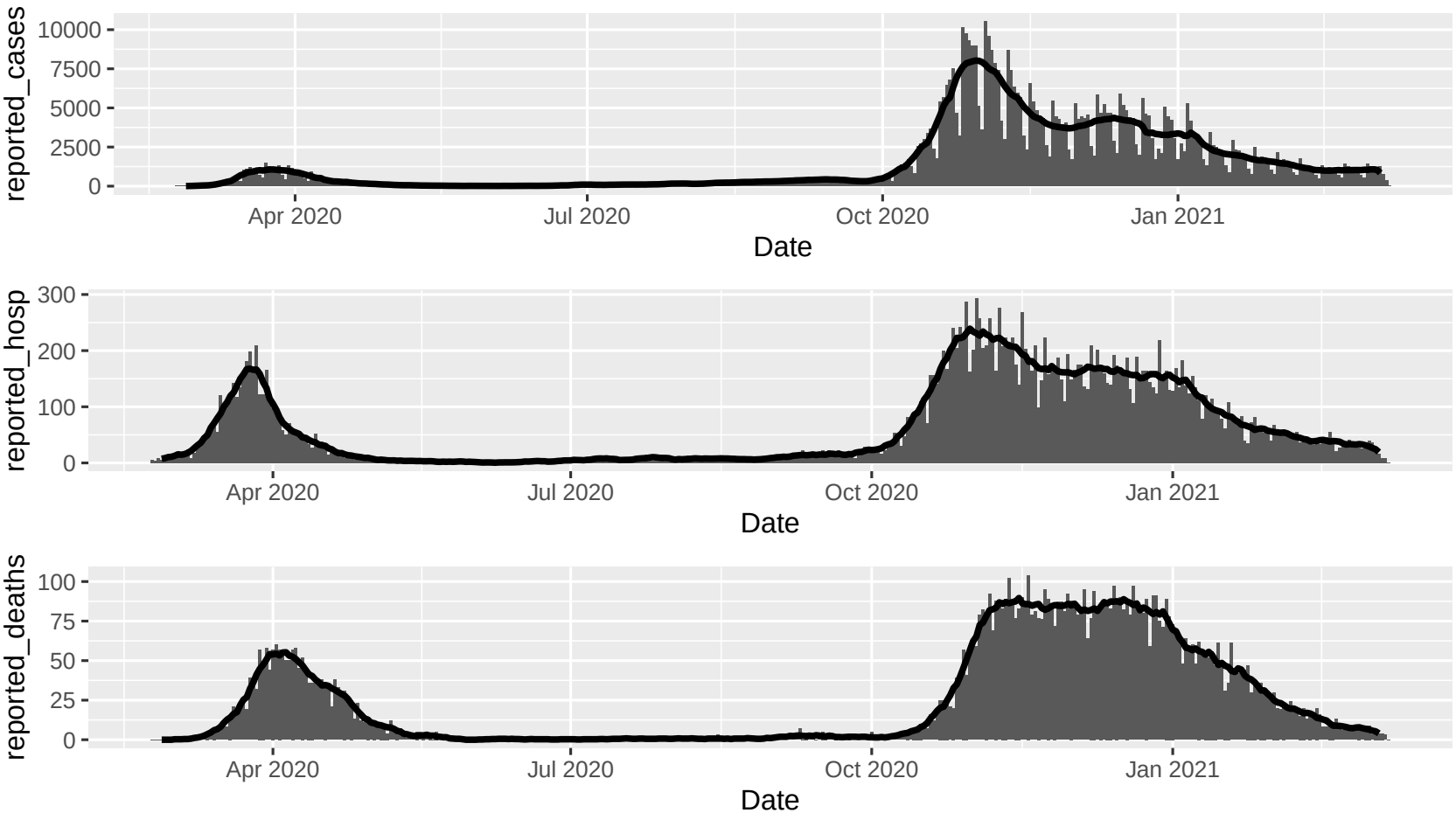

5
4
3
2
1
0
R(t)
Feb 15
Mar 01
Mar 15
Apr 01
Apr 15
Date
Method:
R(t)
Truth

R(t) for Switzerland

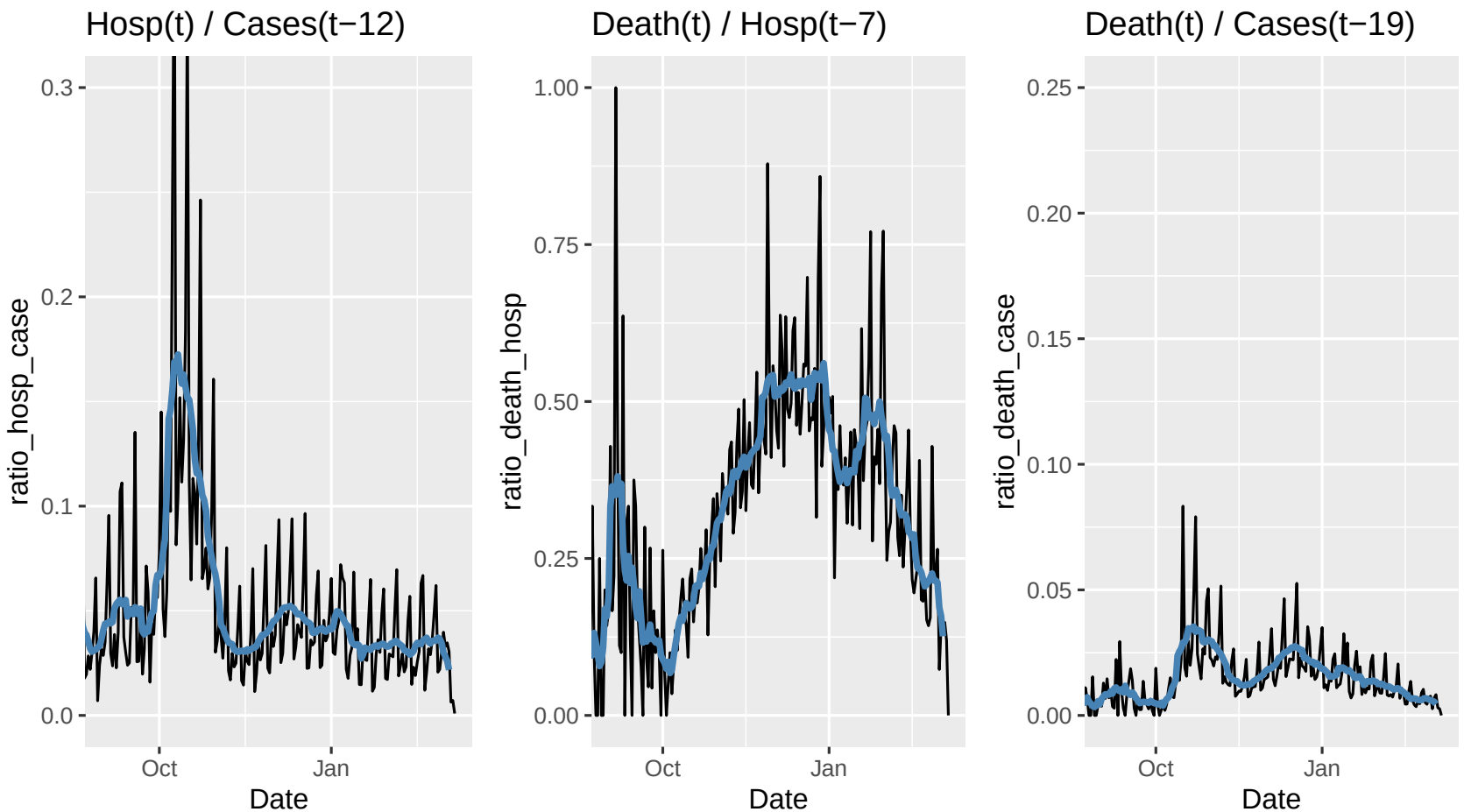
- Aim: Produce a crude $R(t)$ for Switzerland based on the daily number of new cases as reported by the Swiss Federal Office of Public Health (FOPH)
- In order to do so, we first look a bit closer at the data as of 2021-03-10 available from `https://www.covid19.admin.ch/`

reported_cases	reported_hosp	reported_deaths
562364	23665	9294

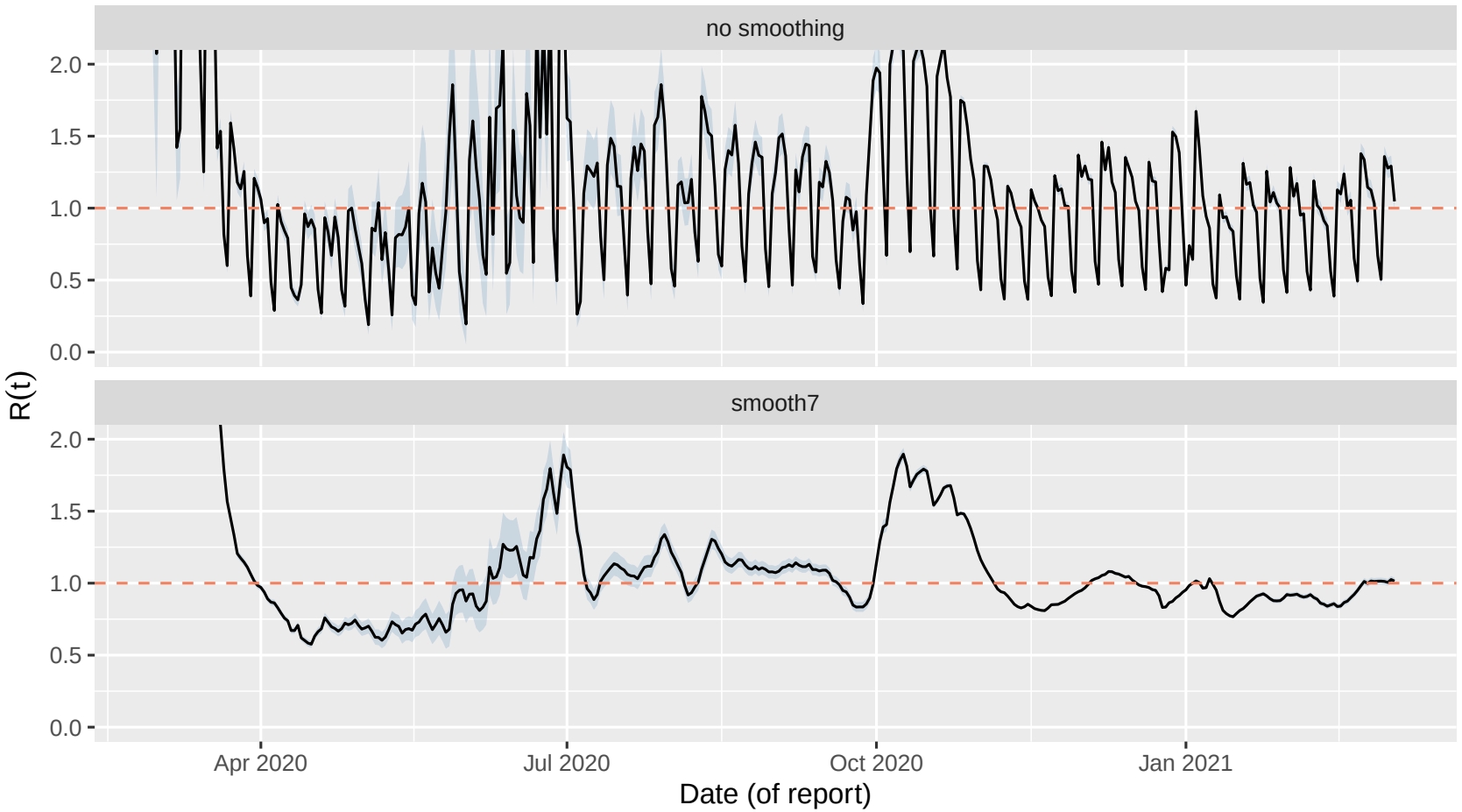
COVID-19 Time Series for Switzerland (1)



COVID-19 Time Series for Switzerland (2)



Coarse $R(t)$ Estimate (1)



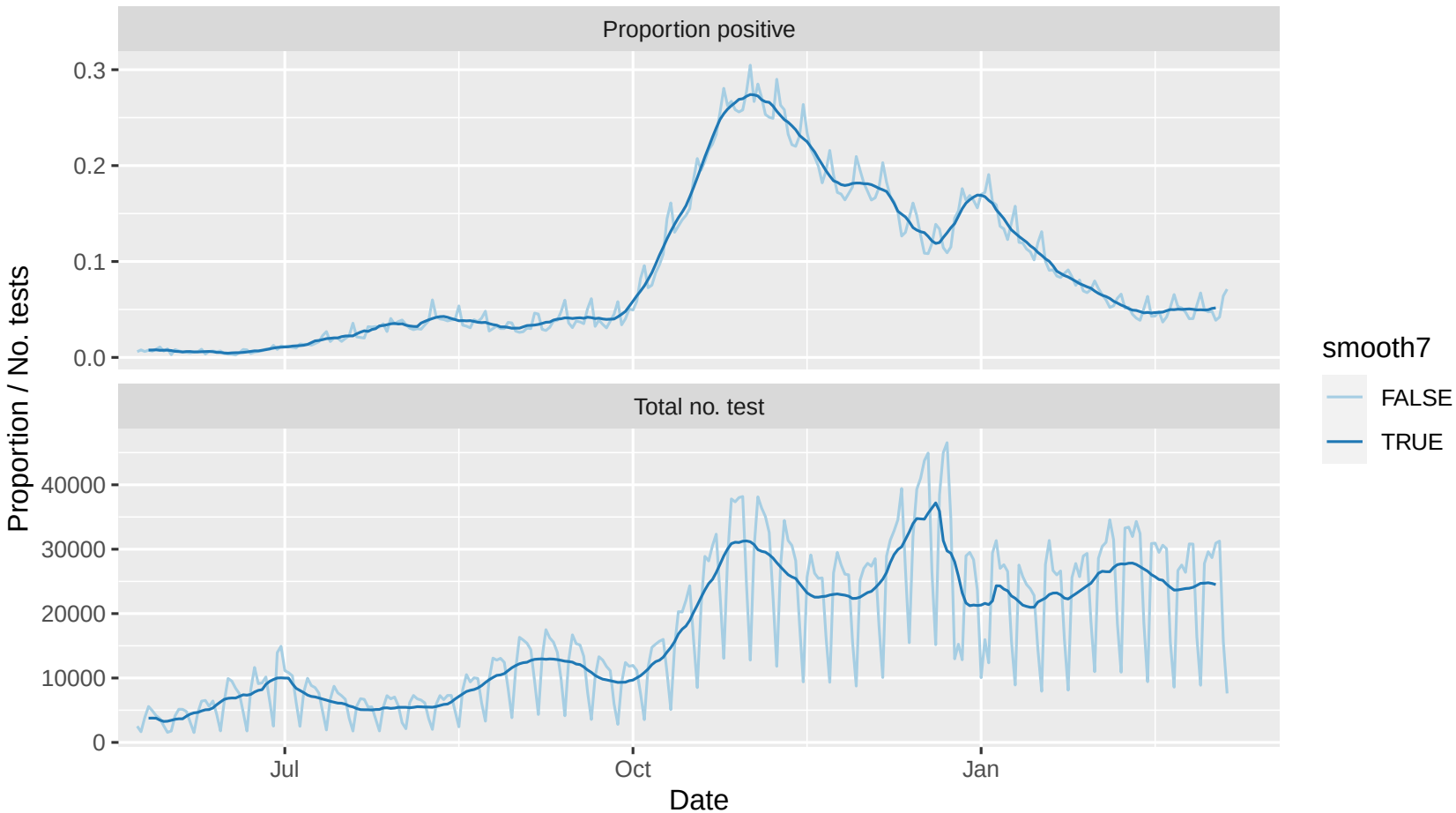
Coarse $R(t)$ Estimate (2)

Limitations:

- All cases are considered as community transmissions, but
  - there is an increase in the overall number of tests
  - some settings are tested more pro-actively than others (e.g. hospital staff)
  - imported cases are ignored (negligible from mid March)
- Serial interval
  - The analysis used an estimate from Nishiura, Linton, and Akhmetzhanov (2020) with mean 4.8 days and a standard deviation of 2.3 days
  - Difference between generation time and serial interval (infection vs. symptom onset - see Svensson (2007))
  - However, in this coarse analysis the event is actually "Day of report".
  - No specific Swiss serial interval was available to me and no estimation uncertainty is considered

Coarse $R(t)$ Estimate (3)

- Total number of tests and prroportion of positive tests over time in Switzerland



Coarse $R(t)$ Estimate (4)

- $R(t)$ always needs context, e.g., the absolute number of (reported) cases.
- The implication of $R(t) = 1.3$ is very different when you have 10,000 cases or when you have 100.
- Especially when the case number is low, spikes due to outbreaks can lead to large $R(t)$ fluctuations
- Be very careful when using $R(t)$ graphs to assess interventions!

Outline

Outlook

- Good overview preprint about pitfalls when estimating R(t) by Gostic et al. (2020)
- Site estimating COVID-19 R(t) for countries around the world:

  `https://epiforecasts.io/covid`

Literature I


Cori, Anne, et al. 2013. "A New Framework and Software to Estimate Time-Varying Reproduction Numbers During Epidemics". American Journal of Epidemiology 178 (9): 1505–1512. doi:10.1093/aje/kwt133. eprint: http://aje.oxfordjournals.org/content/178/9/1505.full.pdf+html. http://aje.oxfordjournals.org/content/178/9/1505.abstract.


Delamater, P. L., et al. 2019. "Complexity of the Basic Reproduction Number (R_0)". 25 (1): 1. doi:10.3201/eid2501.171901.


Fraser, Christophe. 2007. "Estimating Individual and Household Reproduction Numbers in an Emerging Epidemic". PLOS ONE 2, no. 8 (): e758.


Gostic, Katelyn M, et al. 2020. "Practical considerations for measuring the effective reproductive number, Rt." PLoS Computational Biology 16, no. 12 (): e1008409. doi:10.1371/journal.pcbi.1008409.

Literature II


Lloyd-Smith, J. O., et al. 2005. "Superspreading and the effect of individual variation on disease emergence". Nature 438 (7066): 355–359. doi:10.1038/nature04153.


Nishiura, Hiroshi, Natalie M. Linton, and Andrei R. Akhmetzhanov. 2020. "Serial interval of novel coronavirus (COVID-19) infections". International Journal of Infectious Diseases 93 (): 284–286. ISSN: 1201-9712, visited on 04/12/2020. doi:10.1016/j.ijid.2020.02.060.


Svensson, Å. 2007. "A note on generation times in epidemic models". Math Biosci 208, no. 1 (): 300–311. doi:10.1016/j.mbs.2006.10.010.