Likelihood-based estimation and prediction for misspecified epidemic models: an application to measles in Samoa

SMB 2021

David Wu[1]
with Helen Petousis-Harris[2], Janine Paynter[2], Vinod Suresh[1,3], and Oliver J. Maclaren[1]

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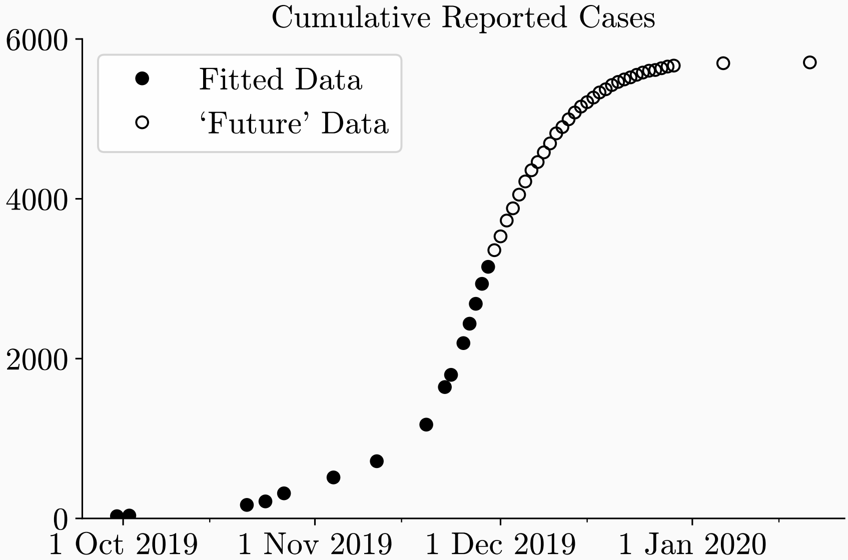
[1]Dept. Engineering Science, University of Auckland
[2]Dept. of General Practice and Primary Health Care, University of Auckland
[3]Auckland Bioengineering Institute, University of Auckland

2019 Samoan Measles Outbreak

Measles outbreak in the small South Pacific island nation of Samoa

- September 2019 – January 2020
- Over 5700 cases (pop. 200 000)
- 83 deaths
- Anomalously low vaccination coverage in infants
    - 40% MCV1
    - 28% MCV2

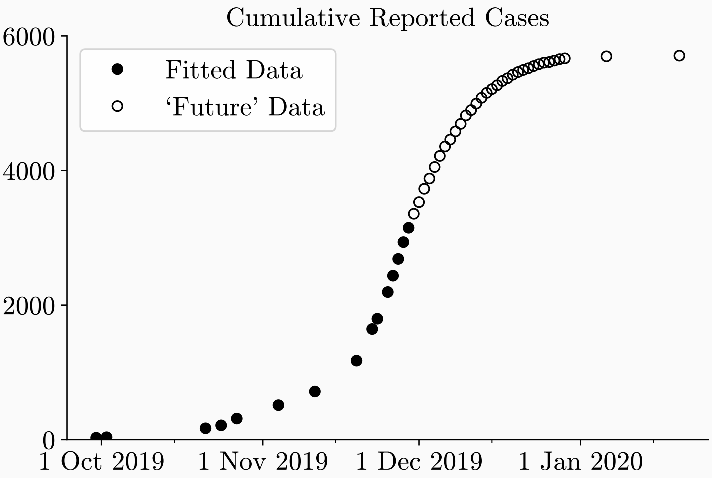
2019 Samoan Measles Outbreak



Core Questions

- How many cases in total?
- How many deaths in total?

Data collected is usually *noisy* and *incomplete*. Our models are only *partially observed*.



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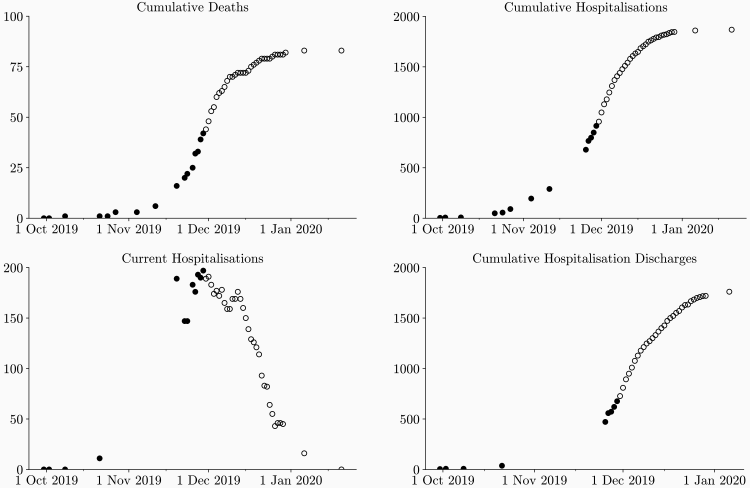

Epidemic models are often modelled using *differential equations*.

$$\frac{dx}{dt} = f(x, \theta)$$

Some Problems: Models

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$$\dot{S} = -\beta S I$$
$$\dot{I} = \beta S I - \alpha I$$

Some Problems: Models

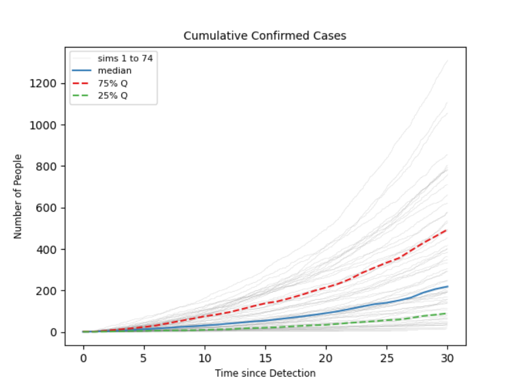
Epidemic models are often modelled using *differential equations*.

$$\frac{dx}{dt} = f(x, \theta)$$

These models are *idealised* and may not correctly reflect realistic processes.

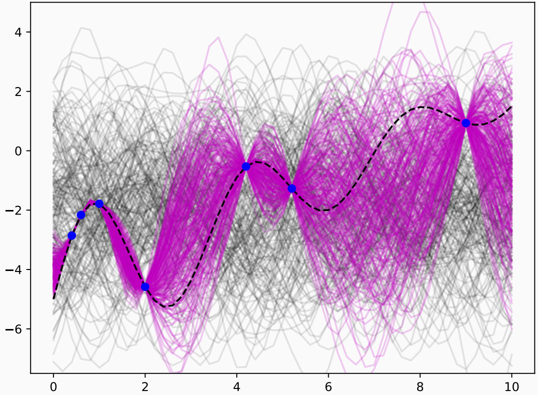
Dealing with Model Misfit

Our model may not correctly reflect reality – we can recover some of this by allowing for misfit as a random effect e.g. with a stochastic differential equation.



But this means we have to marginalise over the realisations!

A less expensive way is to use Gaussian processes to model the discrepancy*.



*Brynjarsdóttir and O'Hagan 2014, "Learning about physical parameters: the importance of model discrepancy".

Typical approach is to use nonlinear least-squares:

$$l(\theta) = \left\| y(t) - g\left(\int_{t_0}^{t} f(\tau, \theta) d\tau\right) \right\|^2$$

Can then pass to other algorithms to get estimators and uncertainties.

Standard Approaches

Typical approach is to use nonlinear least-squares:

$$l(\theta) = \left\| y(t) - g\left(\int_{t_0}^{t} f(\tau, \theta) d\tau \right) \right\|^2$$

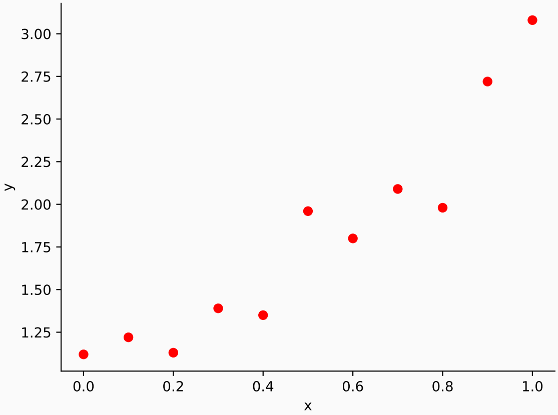
Can then pass to other algorithms to get estimators and uncertainties.

Lots of numerical integration!

Enforces the model exactly!

Avoiding Integration: Two-Stage LS

Fit the derivatives to the ODE model directly!



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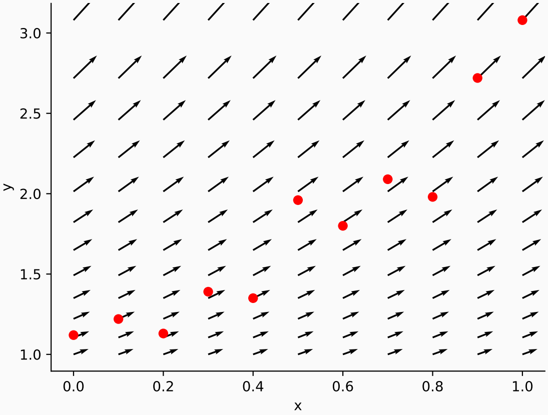

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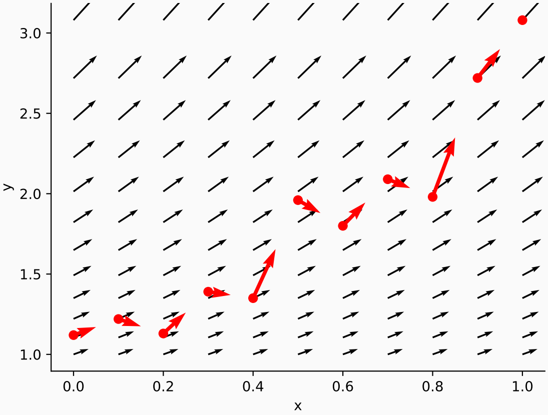

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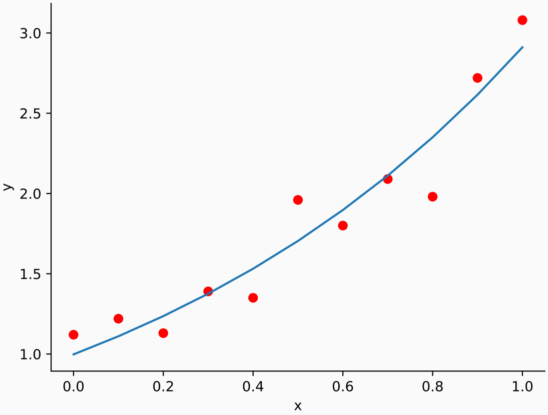

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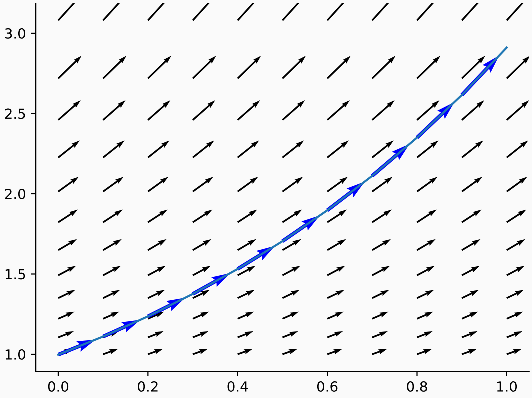


Avoiding Integration: Two-Stage LS

Fit the derivatives to the ODE model directly!

$$s(t) = \sum_{i}^{K} \varphi_i(t) c_i$$

$$\hat{s}(t) = \arg\min_{s} \left\{ \|y(t) - g(s(t))\|^2 + \lambda \left\| \frac{d^2 s}{dt^2} \right\|^2 \right\}$$

$$l(\theta) = \left\| \frac{d\hat{s}}{dt} - f(\hat{s}, \theta) \right\|^2$$

- Need to tune hyperparameter
- Breaks down if we only have partially observed models (can't compute f)

Generalised profiling: Penalise the smooth using the model!

$$s(t) = \sum_{i}^{K} \varphi_i(t) c_i$$

$$\hat{s}_\theta(t) = \arg\min_{s} \left\{ \|y(t) - g(s(t))\|^2 + \lambda \left\| \frac{ds}{dt} - f(s(t), \theta) \right\|^2 \right\}$$

$$l(\theta) = \|y - g(\hat{s}_\theta)\|^2$$

first by Ramsay et al.[†], in the field of functional data analysis.

† Ramsay et al. 2007, "Parameter estimation for differential equations: a generalized smoothing approach".

GP Likelihood: Formulation

Reframe as likelihoods by assuming additive Gaussian noise model, and modelling the process as an SDE.

$$s(t) = \sum_{i}^{K} \varphi_i(t) c_i$$

$$l(\theta) = \|L(y - g(s))\|^2 + \left\| W \left(\frac{ds}{dt} - f(s, \theta) \right) \right\|^2$$

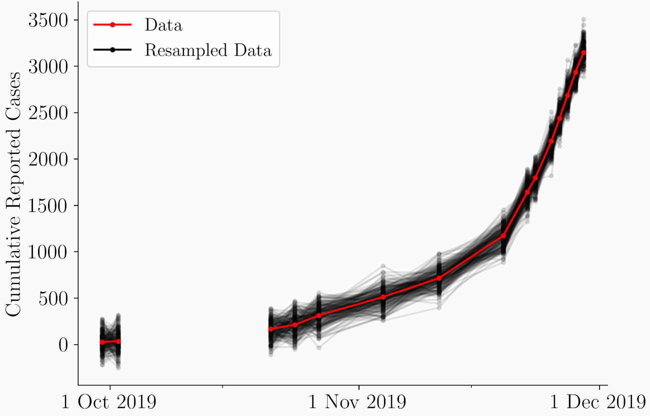
L and W come out as the whitening matrices of the covariance matrices of the associated noise.

GP Likelihood: Benefits

- Can add regularisation naturally by stacking terms
- Can use generalised least squares to automatically find L, W
- Allows for natural state estimation into the future
- Incorporates a model misfit
- No numerical integration

Can now just use frequentist methods to quantify uncertainty.

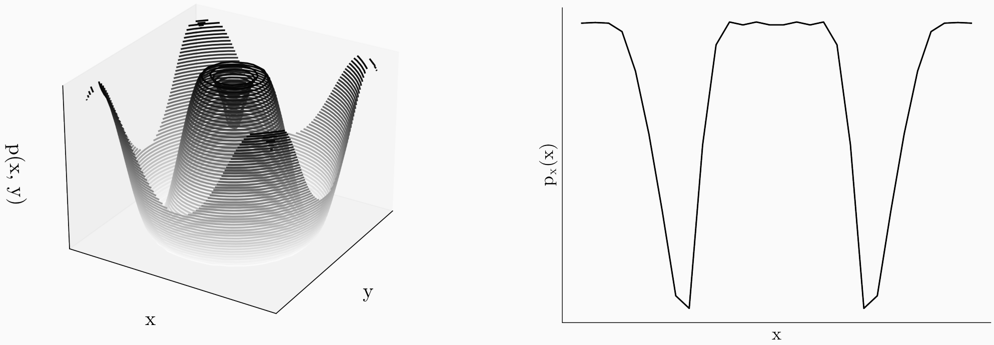
→ Bootstrap by resampling "data error" and "model error".



Uncertainty

Can now just use frequentist methods to quantify uncertainty.

$\rightarrow$ Compute profile likelihoods using constrained optimisation.



Back to the Case Study...

On 29th November 2019:

- over 3000 cases
- nearly 200 cases in hospital
- 42 deaths

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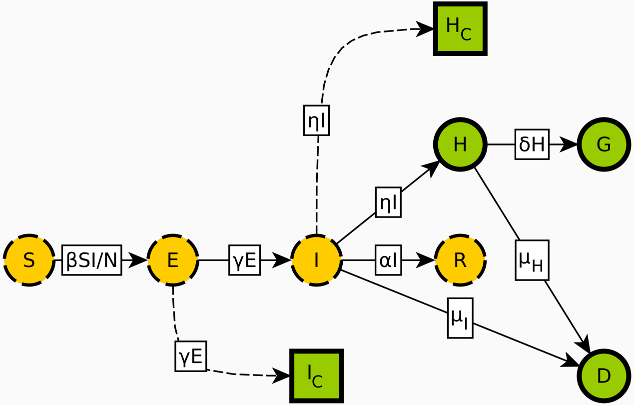
At the time, we made a prediction of between 4500 and 6500 cases, and around 70 deaths, most of the cases within a month.

Model

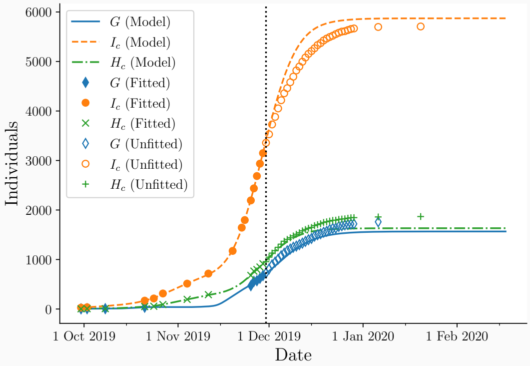
Use an SEIR model with hospitalisation.

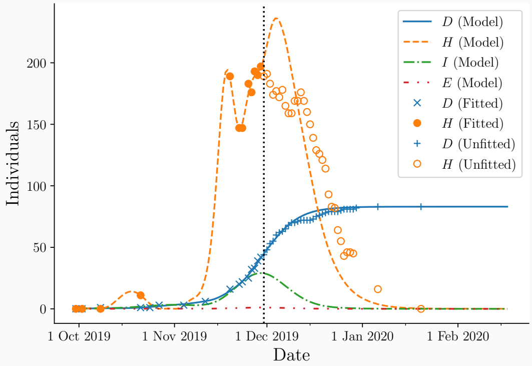


Only green, solid-bordered states are available in publicly available data.

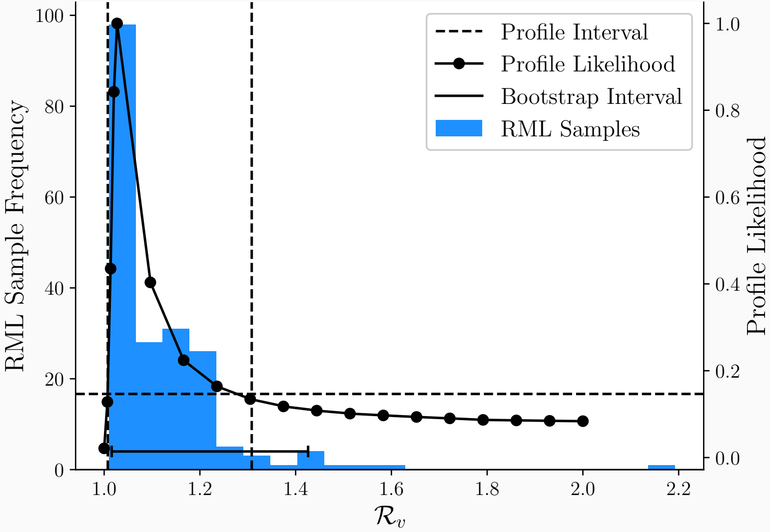
Maximum Likelihood Estimate

We fit to data from 30 Sept. 2020 to 29 Nov. 2020

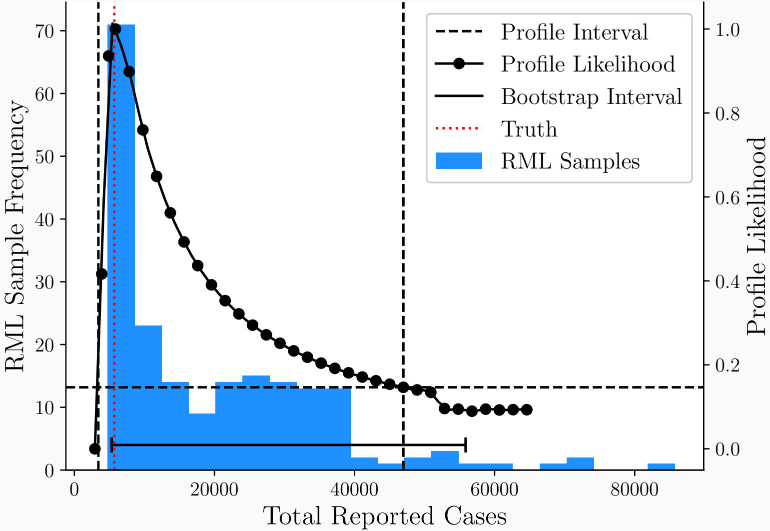




Quantifying Uncertainty: $\mathcal{R}_v$



Quantifying Uncertainty: Total Cases



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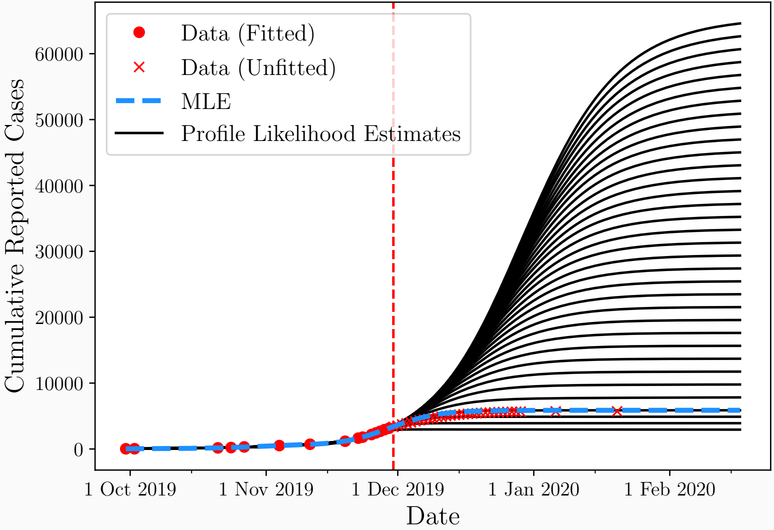

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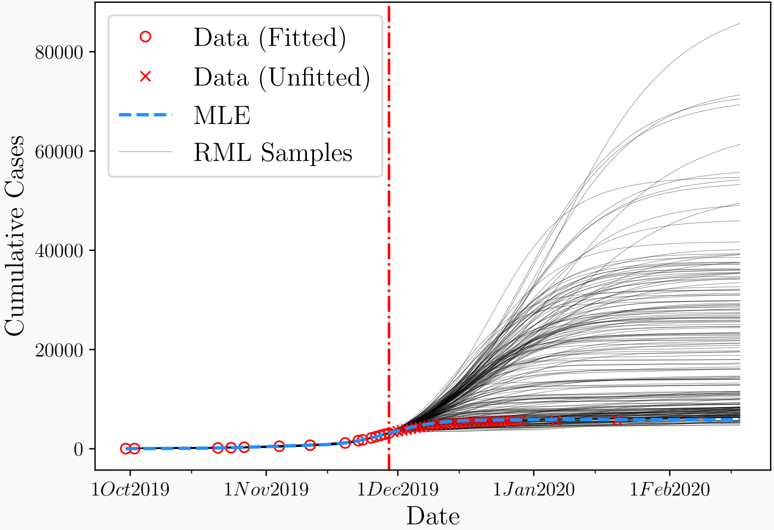
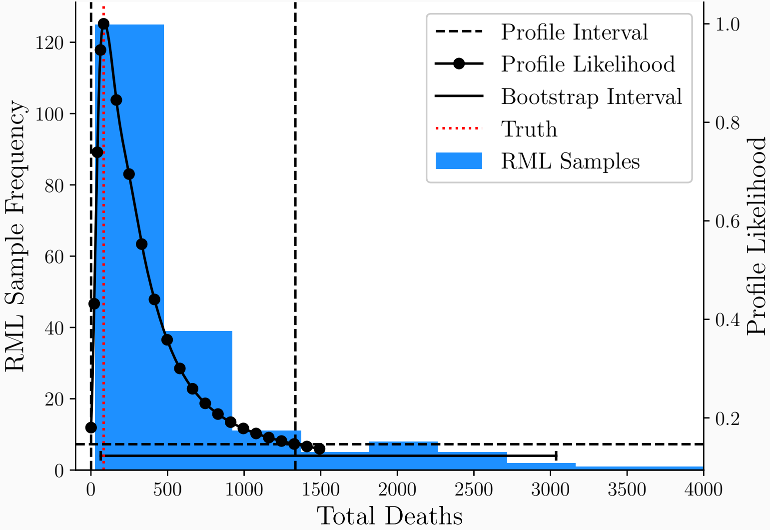


Quantifying Uncertainty: Total Deaths



Inference Takeaways

- Outbreak was likely to be around 6000 cases, and under 100 deaths.
- *but* the tail of the CI extends to horrifically high numbers.

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- *but* the tail of the CI extends to horrifically high numbers.

The Government of Samoa implemented a curfew system on the 2nd Dec. 2019, and began a mass-vaccination campaign, and mitigated the likelihood of severe outcomes.

Recap

- We can avoid integration by using collocation methods like generalised profiling, which naturally gives us model misfit.
- Formulating it in a likelihood framework allows for natural uncertainty quantification and hyperparameter tuning.
- It works well (for a certain definition of "well") for the Samoan measles outbreak case study.

Thanks

Oliver Maclaren

Vinod Suresh

Helen Petousis-Harris

Janine Paynter

THE UNIVERSITY OF AUCKLAND NEW ZEALAND

samoaobserver

Thanks for coming!

Questions?

arXiv: 2103.16058

References

Brynjarsdóttir, Jenný and Anthony O'Hagan (Nov. 2014). "Learning about physical parameters: the importance of model discrepancy". In: *Inverse Problems* 30.11, p. 114007. ISSN: 0266-5611. DOI: *10.1088/0266-5611/30/11/114007*.

Ramsay, J. O. et al. (Nov. 2007). "Parameter estimation for differential equations: a generalized smoothing approach". In: *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 69.5, pp. 741–796. ISSN: 13697412. DOI: *10.1111/j.1467-9868.2007.00610.x*.

Mathematical Formulation

Formulation

Model:

$$y = g(x) + \epsilon$$
$$dx = f(x, \theta)dt + \Sigma dW_t$$
$$\epsilon \sim \mathcal{N}(0, \Gamma)$$

Log-Likelihood function:

$$-2 \log \mathcal{L}(x, \theta) = \frac{1}{n} \|L(y - g(x))\|^2 + \frac{1}{m} \left\| W \left(\frac{dx}{dt} - f(x, \theta) \right) \right\|^2 + 2 \log |L| + 2 \log |W|$$
$$x = \Phi c, \quad L^T L = \Gamma^{-1}, \quad W^T W = \Sigma^{-1}$$
$$y \in \mathbb{R}^n, \quad \Phi \in \mathbb{R}^{m \times k}, \quad c \in \mathbb{R}^k$$

Regularisation as stacking

Have a regularisation term or additional data:

$$r(x,\theta) \sim \mathcal{N}(0,(R^T R)^{-1})$$

Can stack more terms to add regularisation:

$$\begin{aligned}-2\log\mathcal{L}(x,\theta) = &\frac{1}{n}\left\|L(y-g(x))\right\|^2 + \frac{1}{m}\left\|W\left(\frac{dx}{dt}-f(x,\theta)\right)\right\|^2 + \left\|Rr(\theta,x)\right\|^2 \\ &+ 2\log|L| + 2\log|W| + 2\log|R|\end{aligned}$$

Similar to Bayesian framing of priors and posteriors, except we are *maximising* over the distributions, instead of *marginalising*.

GLS/IRLS

$$-2\log\mathcal{L}(x,\theta)=\frac{1}{n}\left\|L(y-g(x))\right\|^2+\frac{1}{m}\left\|W\left(\frac{dx}{dt}-f(x,\theta)\right)\right\|^2+2\log|L|+2\log|W|$$

IRLS is repeated iterations of:

$$\hat{x}^{(i)},\hat{\theta}^{(i)}=\underset{x,\theta}{\arg\min}\left\{-2\log\mathcal{L}(x,\theta|\hat{L}^{(i)},\hat{W}^{(i)})\right\}$$

$$\hat{L}^{(i+1)},\hat{W}^{(i+1)}=\underset{L,W}{\arg\min}\left\{-2\log\mathcal{L}(L,W|\hat{x}^{(i)},\hat{\theta}^{(i)})\right\}$$

RML bootstrapping

$$
\begin{aligned}
-2\log\mathcal{L}(x,\theta) &= \frac{1}{n}\|L(y-g(x))\|^2 + \frac{1}{m}\left\|W\left(\frac{dx}{dt}-f(x,\theta)\right)\right\|^2 + 2\log|L| + 2\log|W| \\
&= \frac{1}{n}\|L(y-g(x))\|^2 + \frac{1}{m}\left\|W\left(r-\left(\frac{dx}{dt}-f(x,\theta)\right)\right)\right\|^2 + 2\log|L| + 2\log|W| \\
&\text{where } r = 0
\end{aligned}
$$

Resampled data is:

$$
\begin{aligned}
y^* &\sim \mathcal{N}(y,(L^TL)^{-1}) \\
r^* &\sim \mathcal{N}(r,(W^TW)^{-1})
\end{aligned}
$$

Profile Likelihood

The profile likelihood of a likelihood $\mathcal{L}(x, \theta)$ over function $\Omega(x, \theta)$ is:

$$\mathcal{L}_{\Omega(x,\theta)}(\omega) = \max_{x,\theta} \mathcal{L}(x, \theta | \Omega(x, \theta) = \omega)$$

Typically we see this used when profiling over a particular parameter:

$$\theta = (\theta^*, \tilde{\theta})$$

$$\mathcal{L}_{\theta^*}(\omega) = \max_{x,\tilde{\theta}} \mathcal{L}(x, \theta | \theta^* = \omega)$$

We also typically normalise the profile likelihood:

$$\mathcal{L}^*_{\Omega(x,\theta)}(\omega) = \frac{\mathcal{L}_{\Omega(x,\theta)}(\omega)}{\max_\omega \mathcal{L}_{\Omega(x,\theta)}(\omega)}$$

Nonlinear least squares

Model:

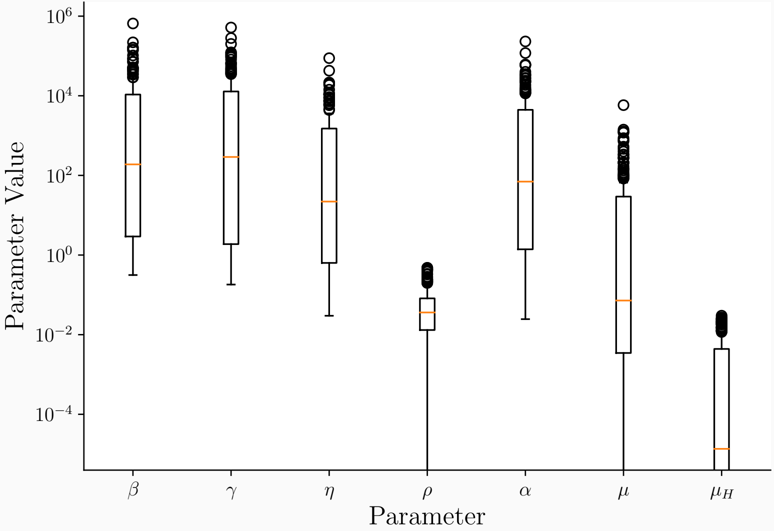
$$y = g(x) + \epsilon$$
$$\frac{dx}{dt} = f(x, \theta)$$
$$\epsilon \sim \mathcal{N}(0, \Gamma)$$

NLS is an optimisation problem with an embedded integration task.

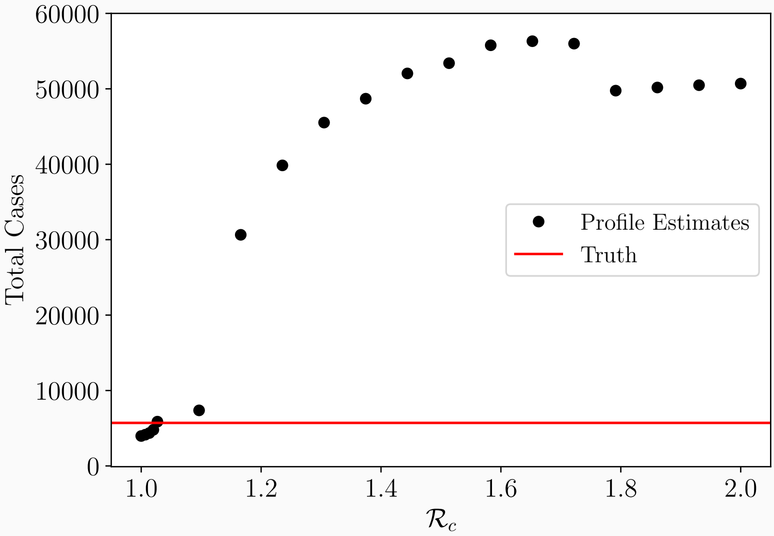
$$\min_{\theta, x_0} -2 \log \mathcal{L}(\theta, x_0) = \min_{\theta, x_0} \left\{ r^T \Gamma^{-1} r \right\}$$
$$r = y(t) - g\left(x(t)\right)$$
$$x(t) = \int_{t_0}^{t} f(\tau, \theta) d\tau$$
$$x(t_0) = x_0$$

Additional Results

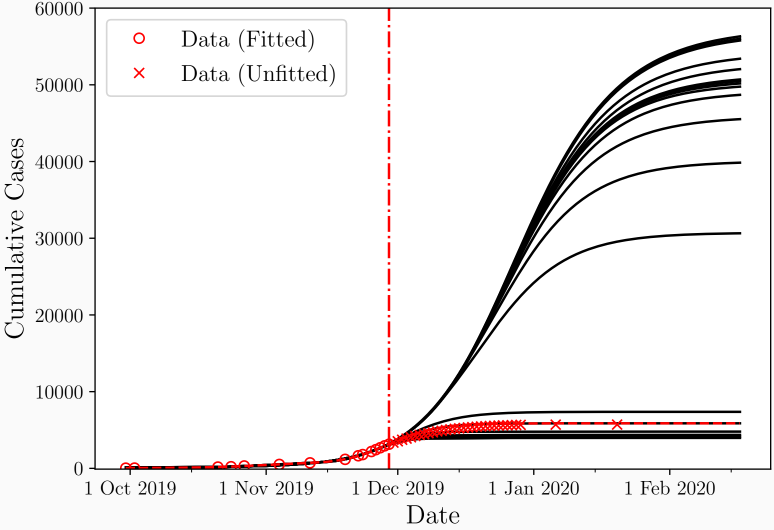
RML bootstrap parameter estimates



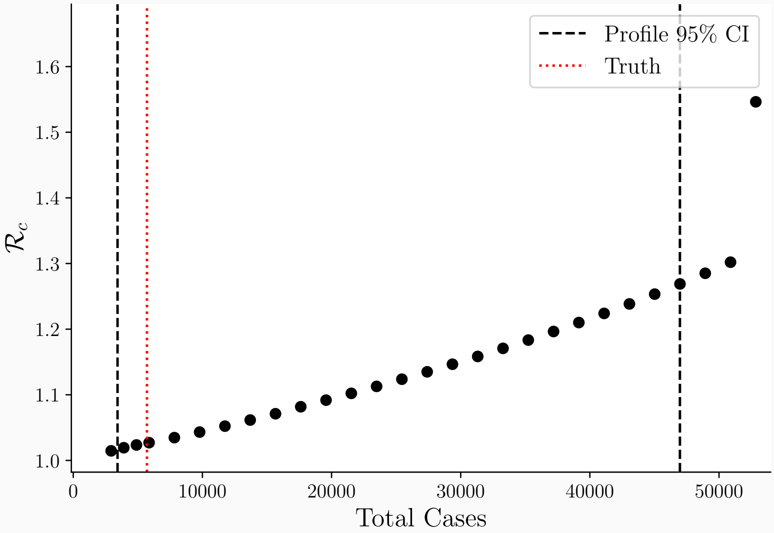
Total Cases along $\mathcal{R}_c$ profile



Cumulative Case Trajectory along $\mathcal{R}_c$ profile



$\mathcal{R}_c$ along Total Cases profile



Synthetic SEIR experiment

Observation Window Experiment

Have SEIR model

$$\dot{S} = -\beta SI/N \qquad \dot{E} = \beta SI/N - \gamma E$$

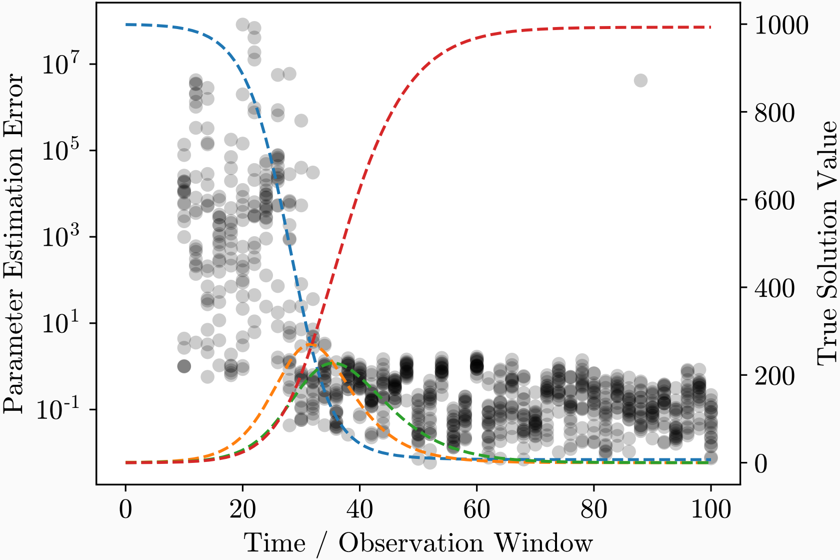
$$\dot{I} = \gamma E - \alpha I \qquad \dot{R} = \alpha I$$

Generate data y:

$$y_i \sim \text{Poisson}([S(t_i), R(t_i)]) \qquad t_i \in [0, 1, \ldots, T]$$

for $T \in [10, 11, \ldots, 100]$.

Observation Window Effects (SEIR model, synthetic data)



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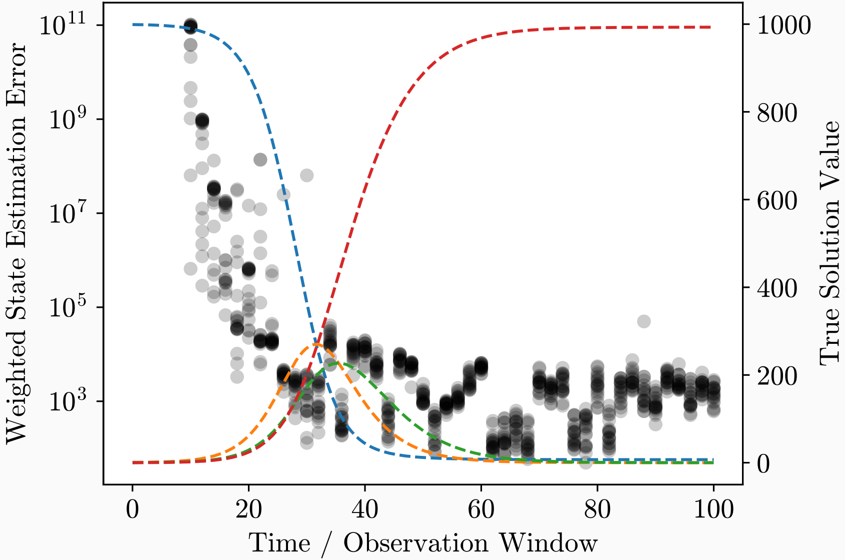

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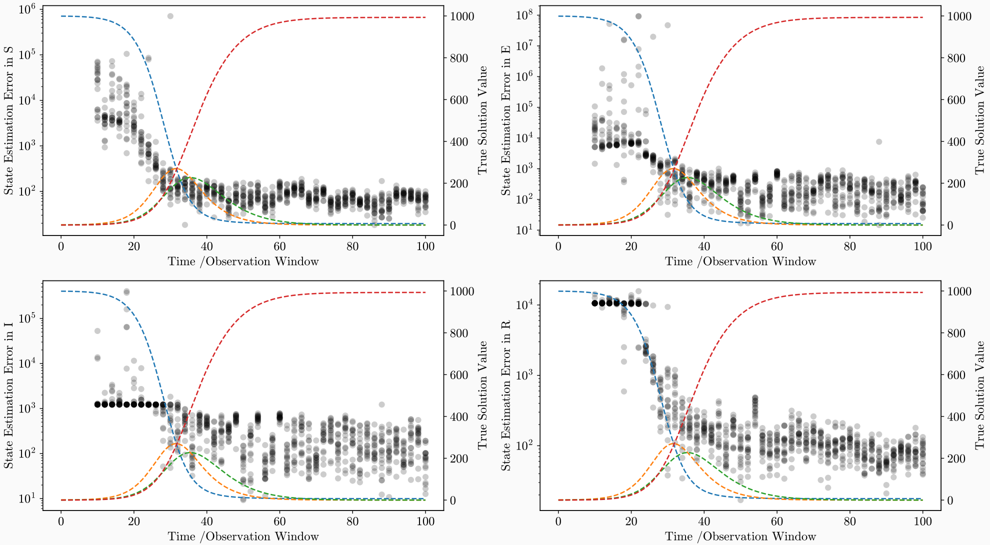


Synthetic SIR experiment

SIR Synthetic Data Validation

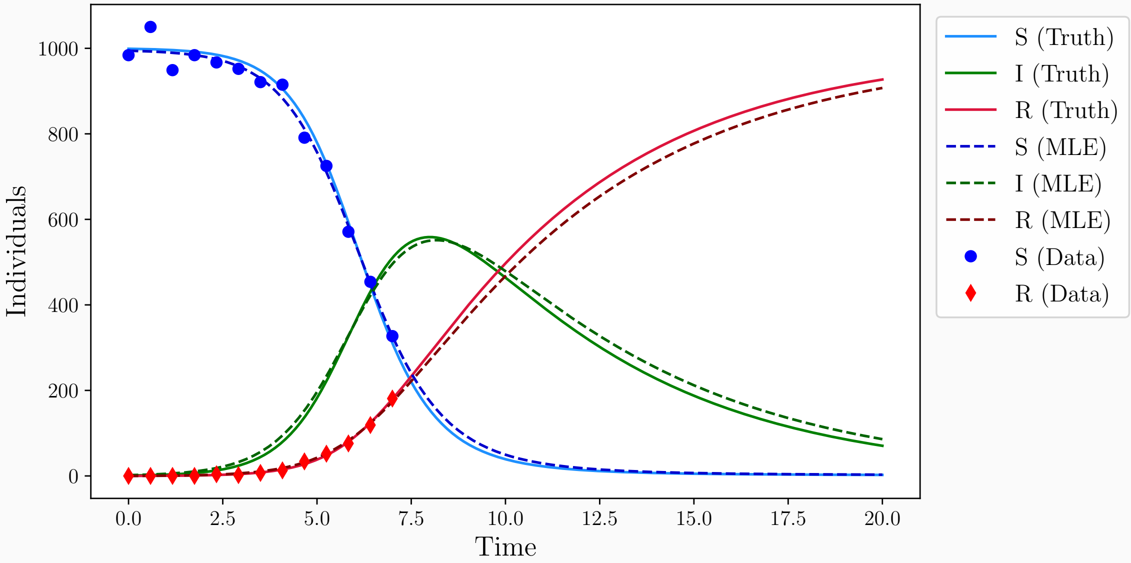
Have SIR model

$$\dot{S} = -\beta SI/N$$
$$\dot{I} = \beta SI/N - \alpha I$$
$$\dot{R} = \alpha I$$

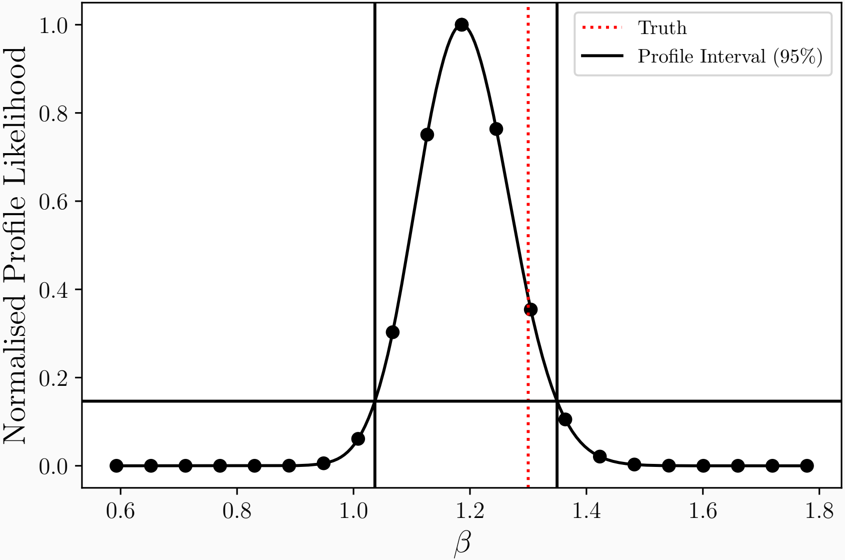
Generate data y

$$y_i \sim \text{Poisson}([S(t_i), R(t_i)])$$
$$t_i \in [0, \ldots, 7]$$

Fit with SIR model



Profiles (SIR)



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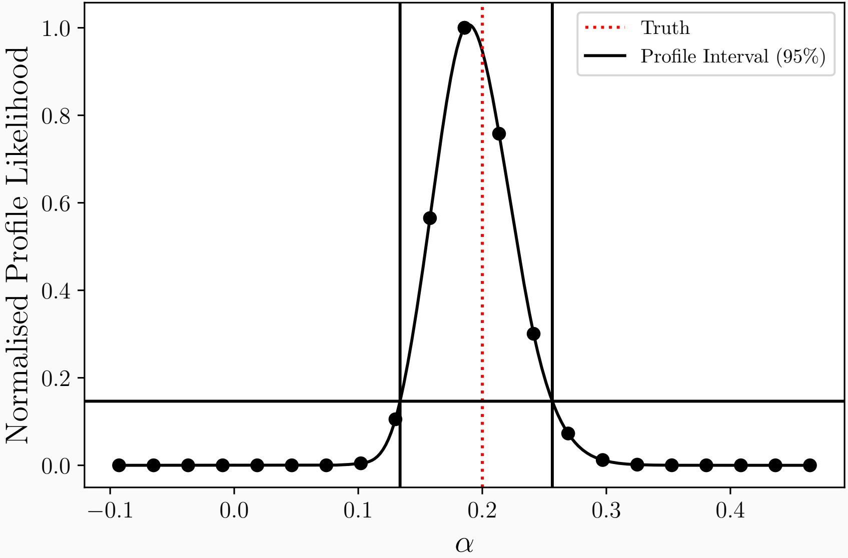

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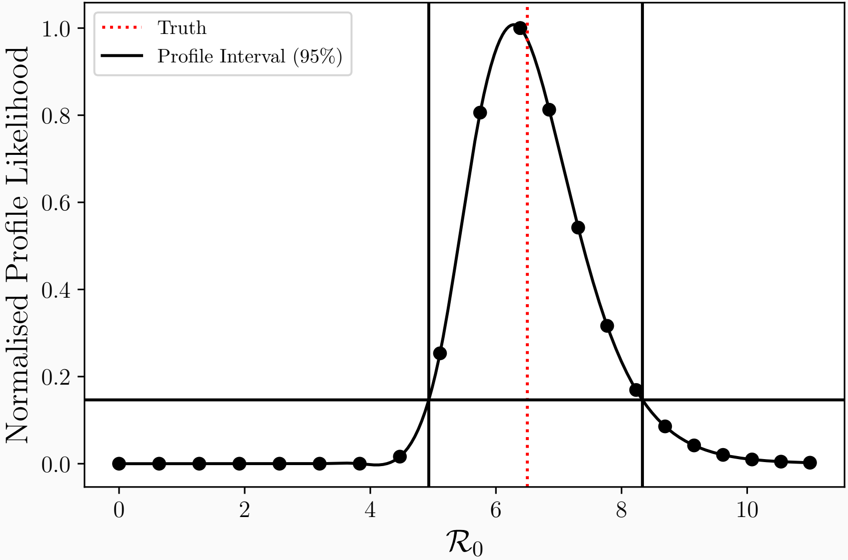

RML Bootstrap