So what did happen on Tristan da Cunha?

Anton Camacho

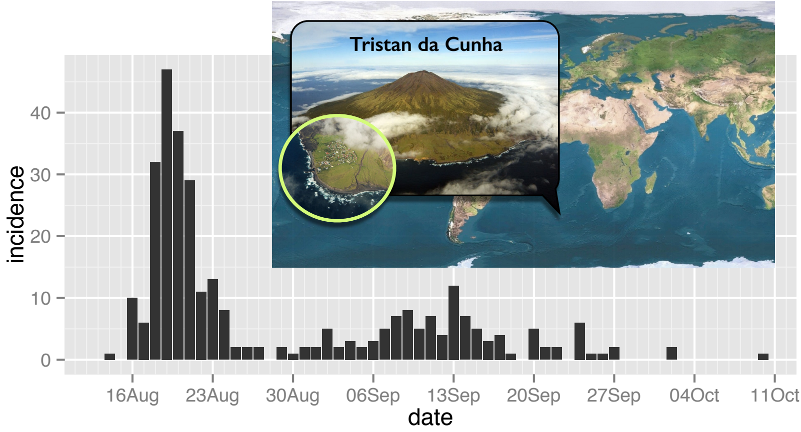
Thesis: Stochastic modelling in epidemiology
with applications to human influenza

UMR 7625 PARIS

Under the supervision of
Bernard Cazelles and Amaury Lambert

Contents

1971 influenza epidemic on Tristan da Cunha



Two waves, 96% infected, 32% reinfected

Mantle and Tyrrell (1973)

Broader context

- Influenza usually spreads through the human population in multiple-wave outbreaks.
- Successive reinfection of individuals over a short time interval has been explicitly reported during past pandemics.

Cross-Protection between Successive Waves of the 1918–1919 Influenza Pandemic: Epidemiological Evidence from US Army Camps and from Britain

John M. Barry,[1] Cécile Viboud,[2] and Lone Simonsen[3]

2008 *J Infect Dis*

Pandemic (H1N1) 2009 Reinfection, Chile

Carlos M. Perez, Marcela Ferres, and Jaime A. Labarca

2010 *Emerg Infect Dis*

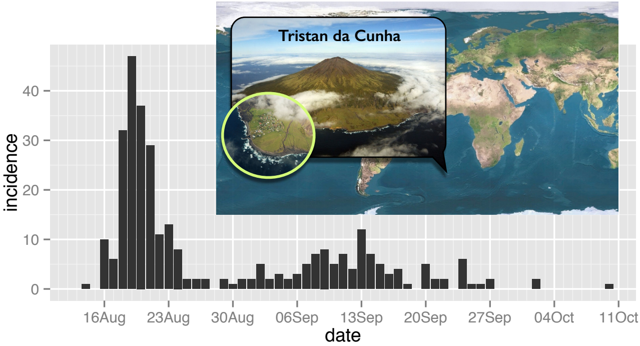
Broader context

- Influenza usually spreads through the human population in multiple-wave outbreaks.
- Successive reinfection of individuals over a short time interval has been explicitly reported during past pandemics.

Problematic

The *causes* of rapid reinfection and the *role* of reinfection in driving multiple-wave outbreaks remain poorly understood.

Case study

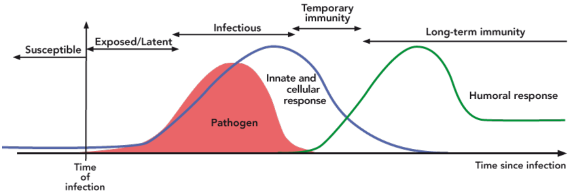


Objectives

- Disentangling between 5 biological mechanisms that could explain rapid reinfection of the islanders
- Assess how well the most likely mechanism can reproduce the data

Contents

Mechanistic modelling of reinfection hypotheses



Primary immune response to influenza

Mut	the virus Mutated during the first wave
2Vi	2 Viruses since the beginning of the epidemic
InH	Intra-Host reinfection
PPI	Partially Protective Immunity
AoN	All or Nothing (the SEITL model in the practical)
Win	Window of reinfection

Camacho et al. (2011) *Proc. Roy. Soc. B*

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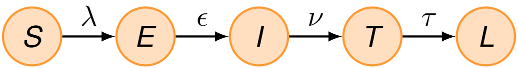

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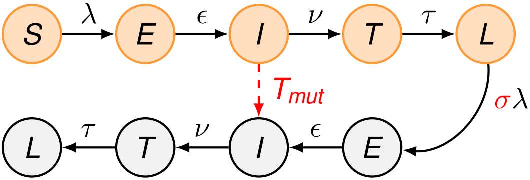

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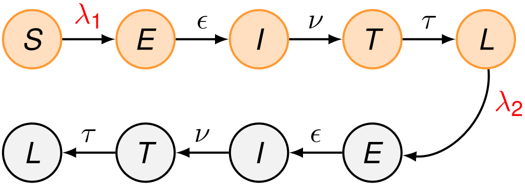

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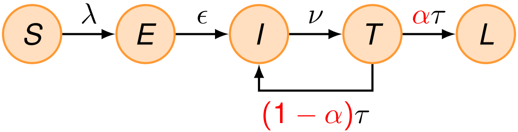

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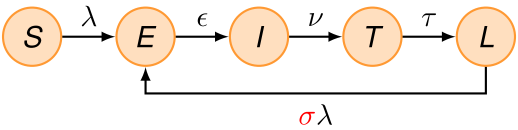

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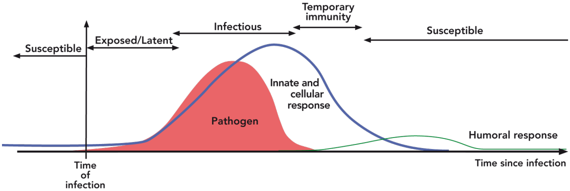

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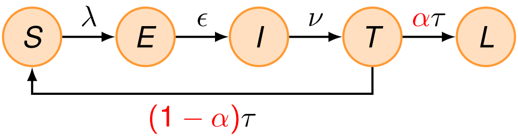

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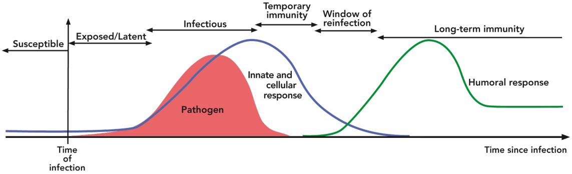

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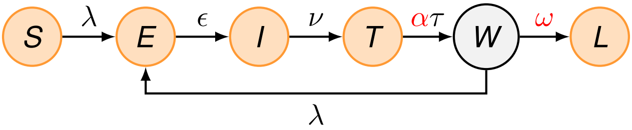

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Likelihood approach

For a given time series: $y_{1:T} = (y_1, y_2, ..., y_T)$ and a state space model completely specified by:

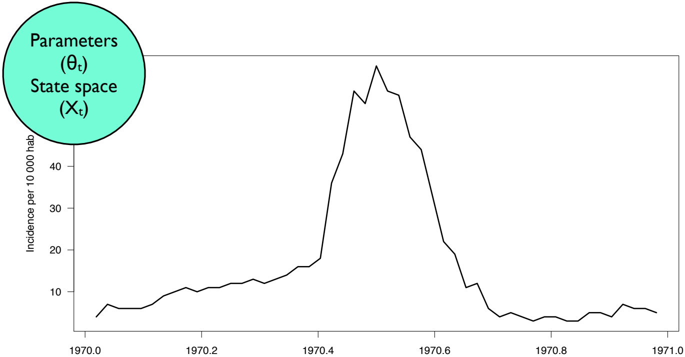
$$M : \begin{cases} p(x_t|x_{t-1}, \theta) & \text{fitmodel\$simulate} \\ p(y_t|x_t, \theta) & \text{fitmodel\$pointLogLike} \\ p(x_0|\theta) & \text{init.state now depends on } \theta \end{cases}$$

the likelihood is given by the identity:

$$p(y_{1:T}|\theta) = \prod_{t=1}^{T} p(y_t|y_{1:t-1}, \theta)$$

How can we find θ_{MLE} that maximises the likelihood?

Iterated Filtering (Ionides et al., 2006)



$$M \begin{cases} f(x_t|x_{t-1},\theta) \\ f(y_t|x_t,\theta) \\ f(x_0|\theta) \end{cases} \Rightarrow M' \begin{cases} f(x_t|x_{t-1},\theta_t) \\ f(y_t|x_t,\theta_t) \\ f(x_0|\theta_t) \end{cases}$$

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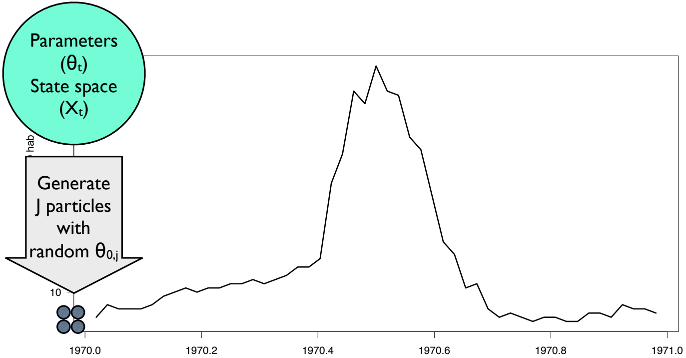

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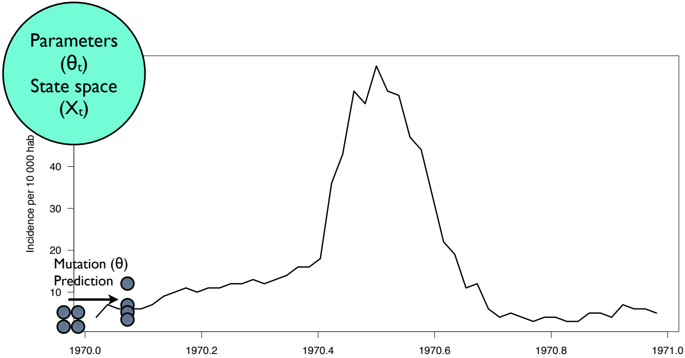

$$\text{For each particle } j : \begin{cases} X_{1,j} & \text{is drawn from} \quad f(x_1 | x_0 = X_{0,j}, \theta_{0,j}) \\ \theta_{1,j} & \text{is drawn from} \quad \mathcal{N}(\theta_{0,j}, \sigma) \\ w_{1,j} & \text{is equal to} \quad f(y_1 | x_1 = X_{1,j}, \theta_{1,j}) \end{cases}$$

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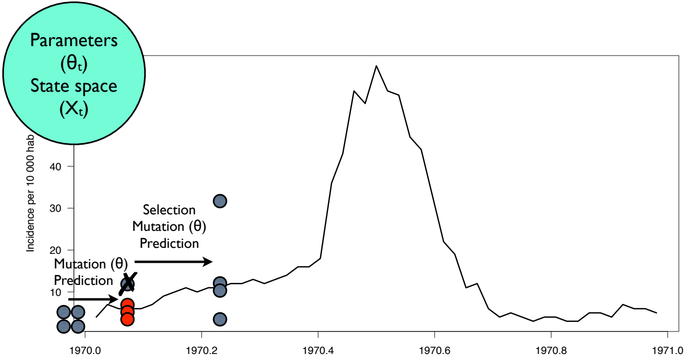
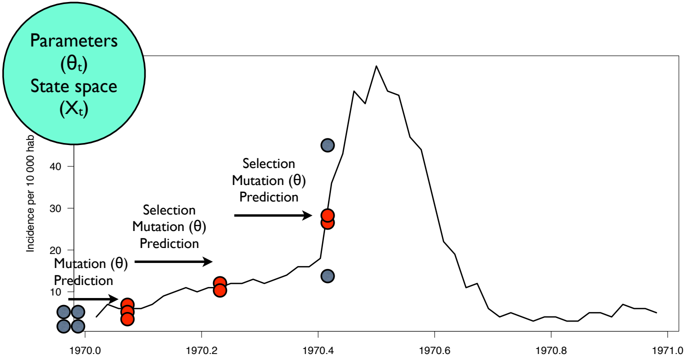


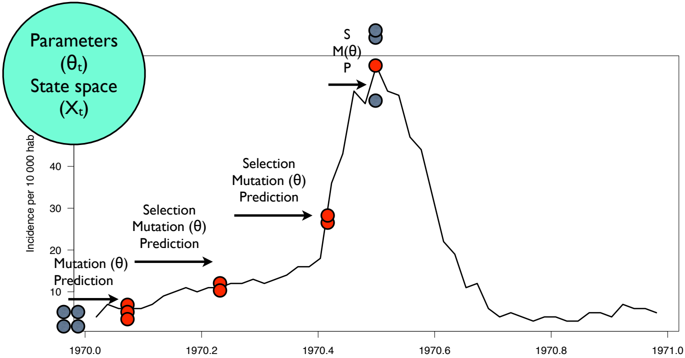
Darwinian selection: particles reproduce proportionally to their weight w_j

Iterated Filtering (Ionides et al., 2006)



Selection + Mutation + Prediction

Iterated Filtering (Ionides et al., 2006)



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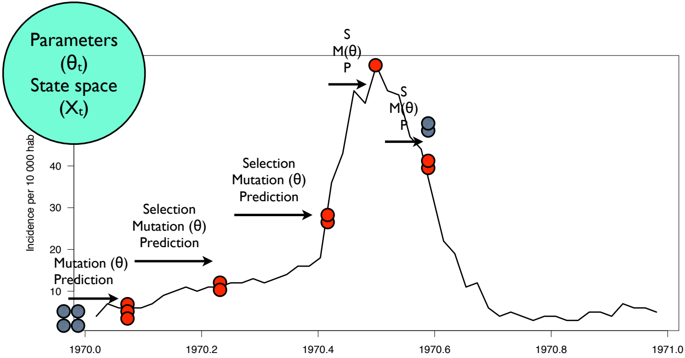

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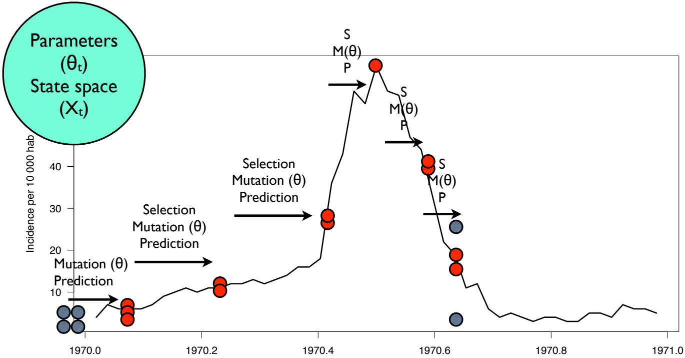

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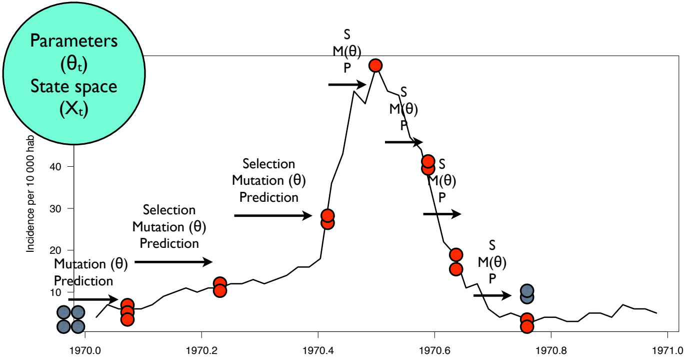

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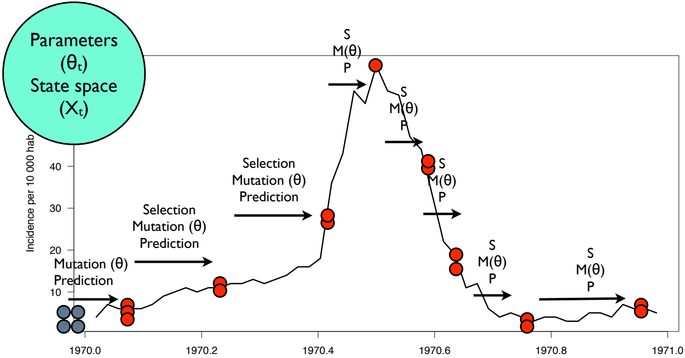
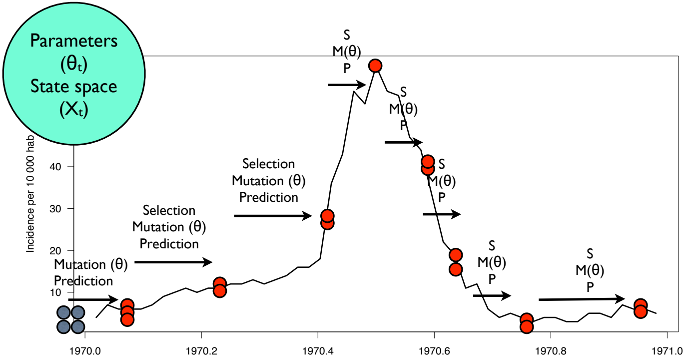


$$\text{Punctual estimates for each time } t \text{ from } \{(\theta_{t,j}, w_{t,j})\}_J \left\{ \begin{array}{rcl} E[\theta_t|y_{1:t}] & \text{by} & \hat{\theta}_t \\ Var(\theta_t|y_{1:t-1}) & \text{by} & V_t \\ f(y_t|y_{1:t-1}, \theta) & \text{by} & l_t(\theta) = \frac{1}{J}\sum_J w_{t,j} \end{array} \right.$$

Iterated Filtering (Ionides et al., 2006)



$$\text{Global estimate: } \hat{\theta} = \hat{\theta}_0 + V_1 \sum_{t=1}^{T} \frac{\hat{\theta}_t - \hat{\theta}_{t-1}}{V_t}$$

$$\text{Log-likelihood: } \mathcal{L}(\hat{\theta}) = \log(\prod_T l_t(\theta))$$

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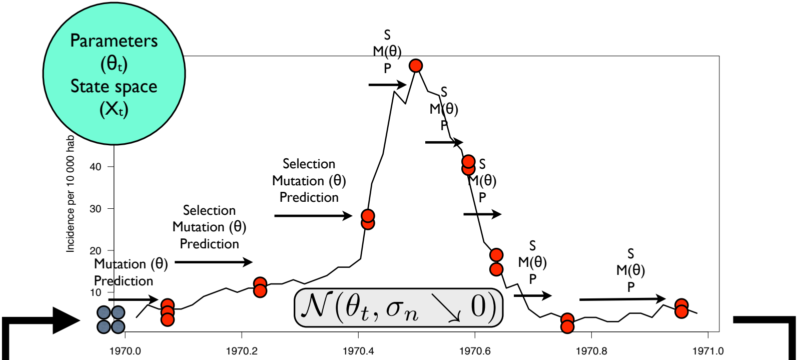


Global estimate: $\hat{\theta}^{(n)} = \hat{\theta}^{(n-1)} + V_1^{(n)} \sum_{t=1}^{T} \frac{\hat{\theta}_t^{(n)} - \hat{\theta}_{t-1}^{(n)}}{V_t^{(n)}}$

Log-likelihood: $\mathcal{L}(\hat{\theta}^{(n)}) = \log(\prod_T l_t^{(n)}(\theta))$

Convergence of global estimator

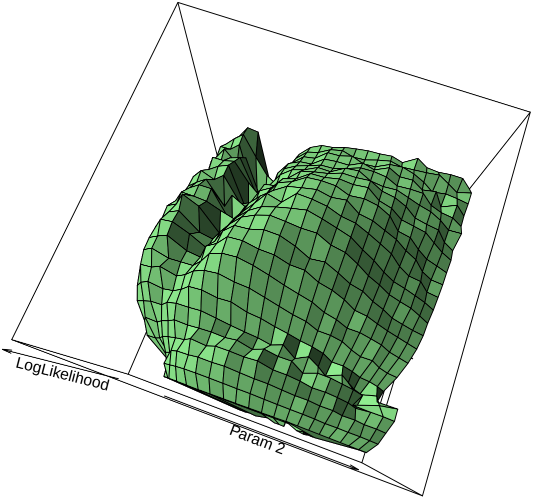
$$\hat{\theta}^{(n)} = \hat{\theta}^{(n-1)} + V_1^{(n)} \sum_{t=1}^{T} \frac{\hat{\theta}_t^{(n)} - \hat{\theta}_{t-1}^{(n)}}{V_t^{(n)}}$$

As shown by Ionides *et al.* (2006), under rather mild assumptions,

$$\lim_{\sigma \to 0} \sum_{t=1}^{T} \frac{\hat{\theta}_t - \hat{\theta}_{t-1}}{V_t} = \nabla \log f(y_{1:T} | \theta, \sigma = 0)$$

so that, for a sufficiently small σ_n, the algorithm iteratively updates $\hat{\theta}^{(n)}$ in the direction of increasing likelihood, with a fixed point at a local maximum of the likelihood surface.

Exploring the likelihood surface



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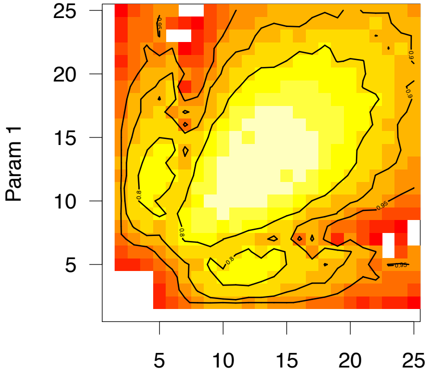

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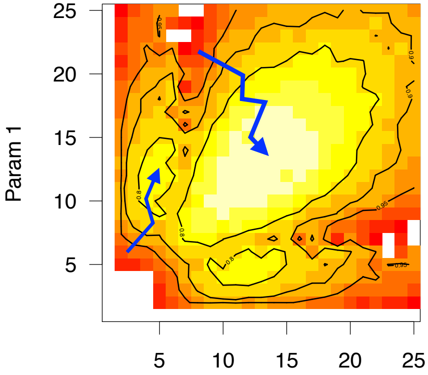

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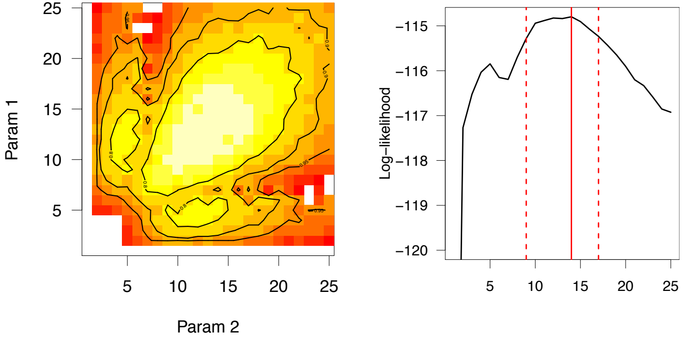
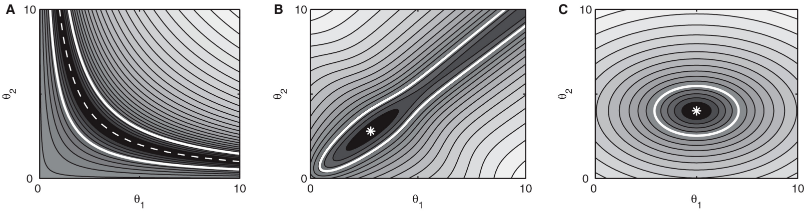


Log-likelihood profiles allows us to compute 95% *confidence* intervals.

Identifiability issues

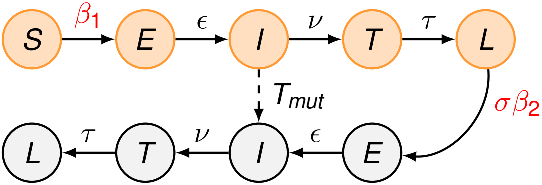


Structural non-identifiability

Practical non-identifiability

Identifiability

Identifiability issues



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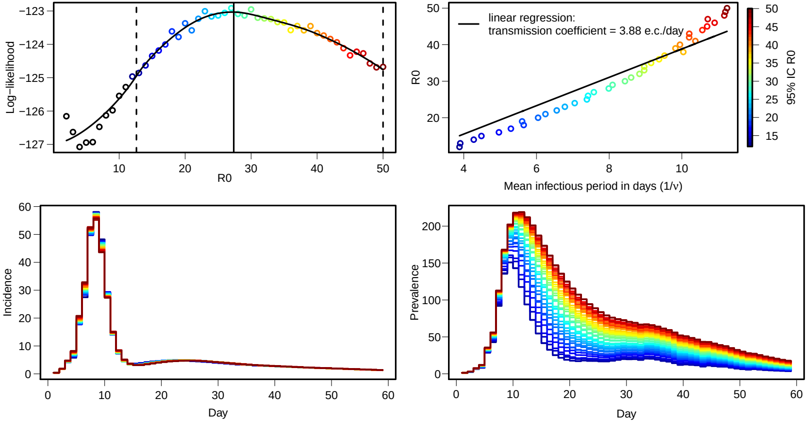

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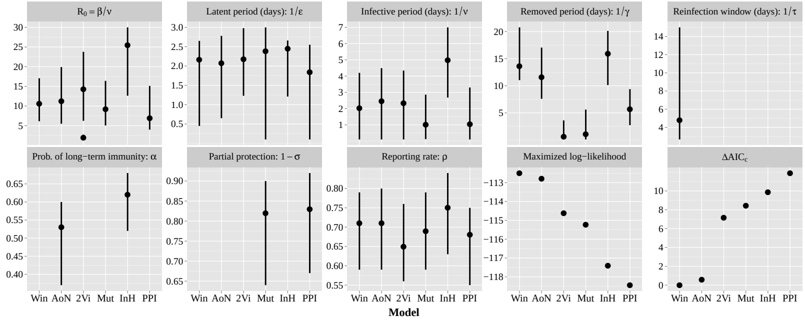
Parameter inference



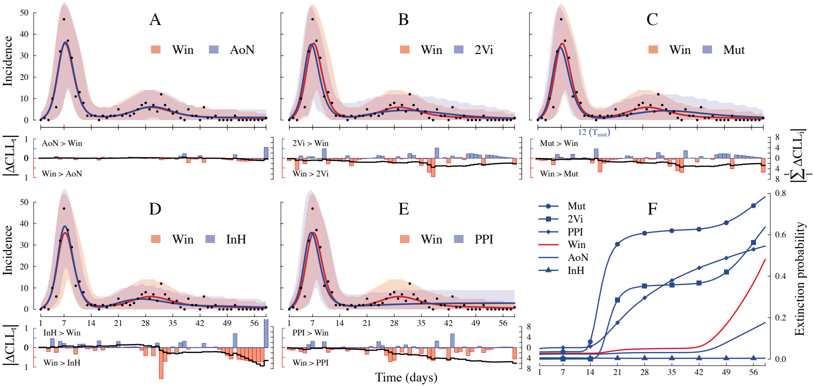
Model selection

- We used the corrected Akaike Information Criterion (AIC_c) to select the best model

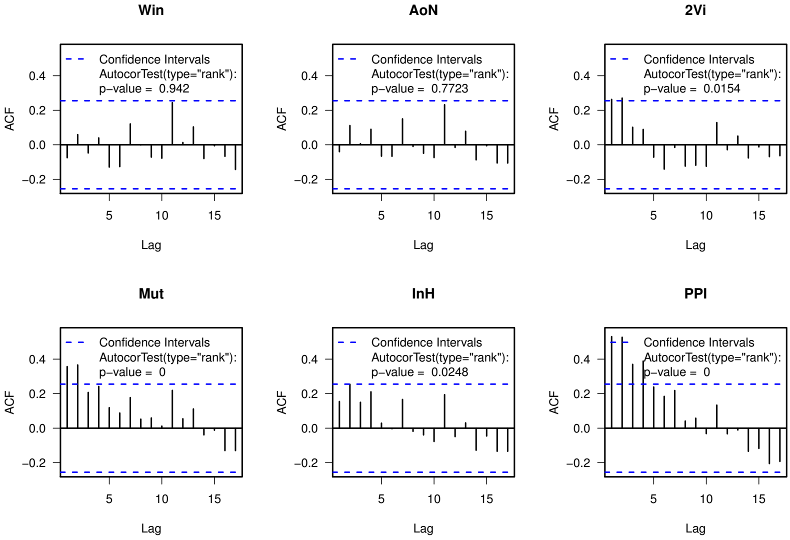
$$\mathrm{AIC}_c = -2\mathcal{L}(\theta_{MLE}) + 2k + \frac{2k(k+1)}{T-k-1} \text{ with } k = ||\theta||$$

- The best model corresponds to the Windows of reinfection hypothesis.
- The AoN (SEITL in the practical) model has substantial support ($\Delta\mathrm{AIC}_c < 2$).
- The other models have considerably less support ($\Delta\mathrm{AIC}_c > 7$)

Assess the fit



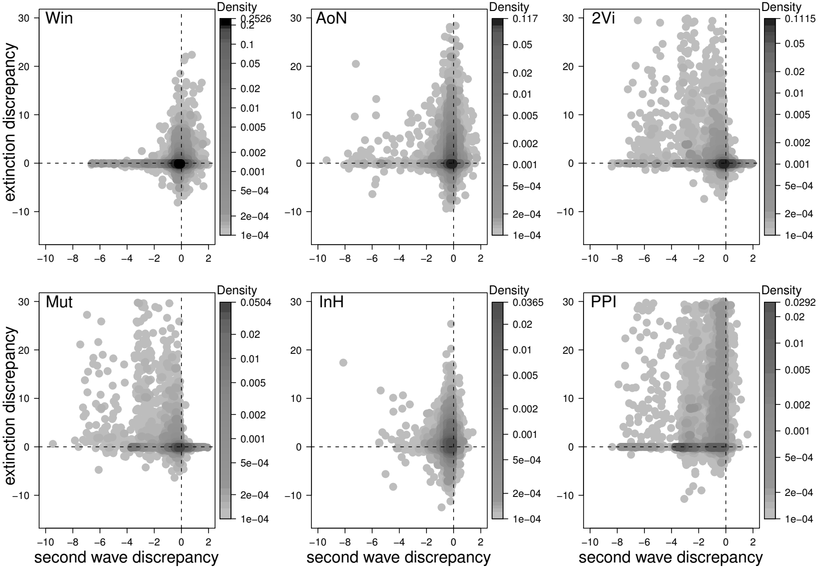
Autocorrelation of the residuals



Posterior predictive checks

- Pick one or more summary-statistics of the time-series
- Compute their distances between model and data
- Do it for 10000 replicates of the model under $\theta_M LE$

Posterior predictive checks



Posterior predictive checks

Proportion of points within a radius R from $(0, 0)$:

Model	$R = 0.25$	$R = 0.5$	$R = 1$	$R = 2$
Win	0.26	0.5	0.7	0.81
AoN	0.12	0.26	0.43	0.60
2Vi	0.14	0.31	0.42	0.50
Mut	0.06	0.14	0.20	0.24
InH	0.02	0.14	0.40	0.65
PPI	0.01	0.05	0.11	0.18

Conclusion; fitting stochastic models

- Bayesian (pMCMC) or Frequentist (MIF)?
- Sampling from the posterior vs Exploring the likelihood surface?
- For both methods, a particle filter is required to evaluate the likelihood of stochastic models.

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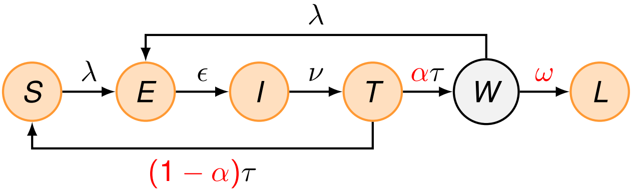
Win + AoN = WoN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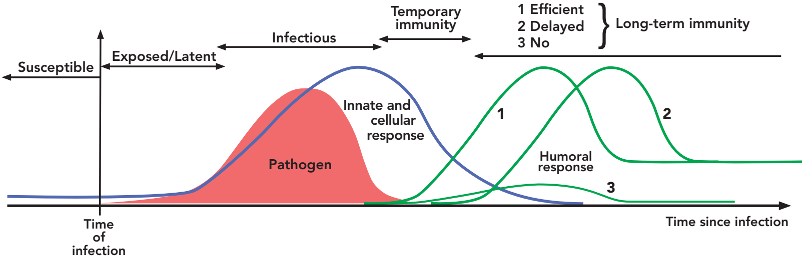
Temporary immunity
1 Efficient
2 Delayed
3 No
Long-term immunity
Infectious
Exposed/Latent
Susceptible
Innate and cellular response
Pathogen
1
2
Humoral response
3
Time of infection
Time since infection

Thanks! Merci! Danke!