Disentangling between different mechanisms for explaining observed two waves influenza epidemics.

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CNRS - UMR 7625 Ecologie et Evolution
Equipe Eco-Evolution Mathematique
ENS Ulm - UPMC

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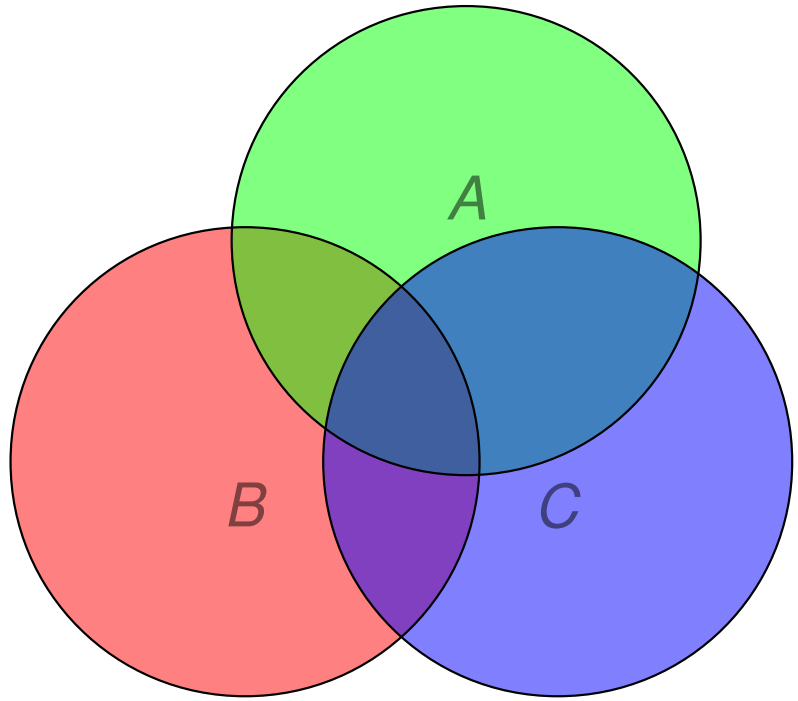
General context

Three main componants:

A Host immune response

B Virus evolution

C Structured host population



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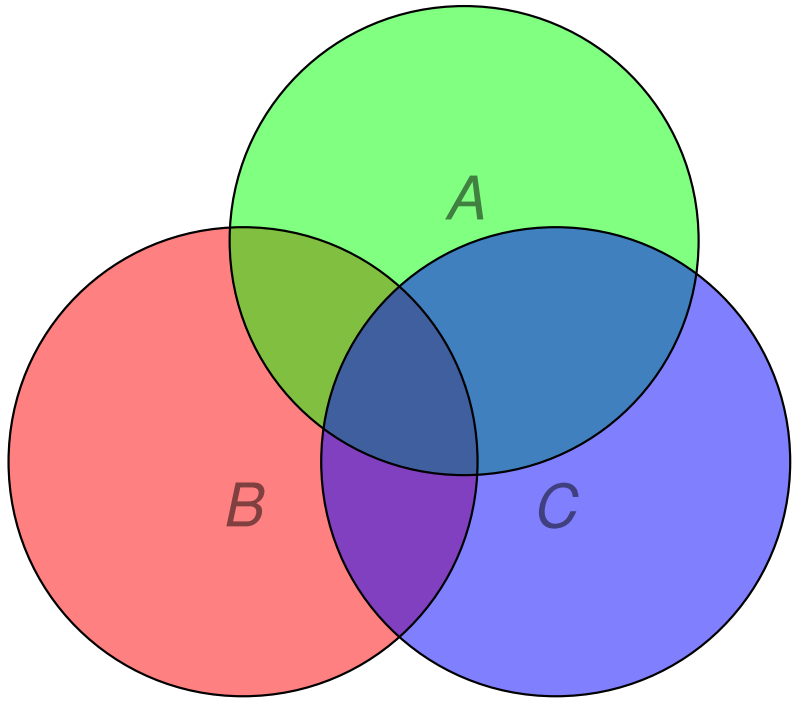
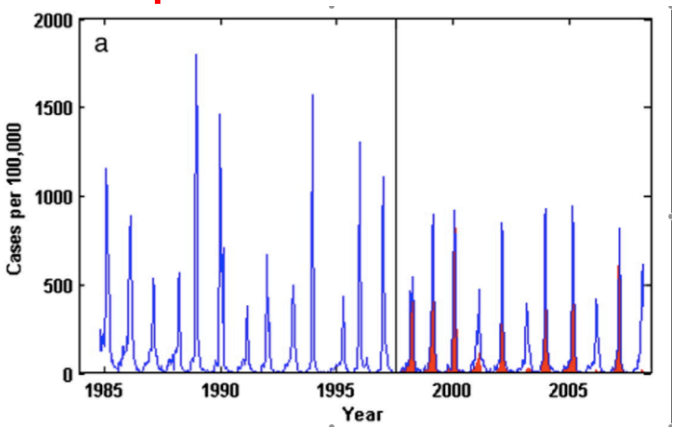


To explain:



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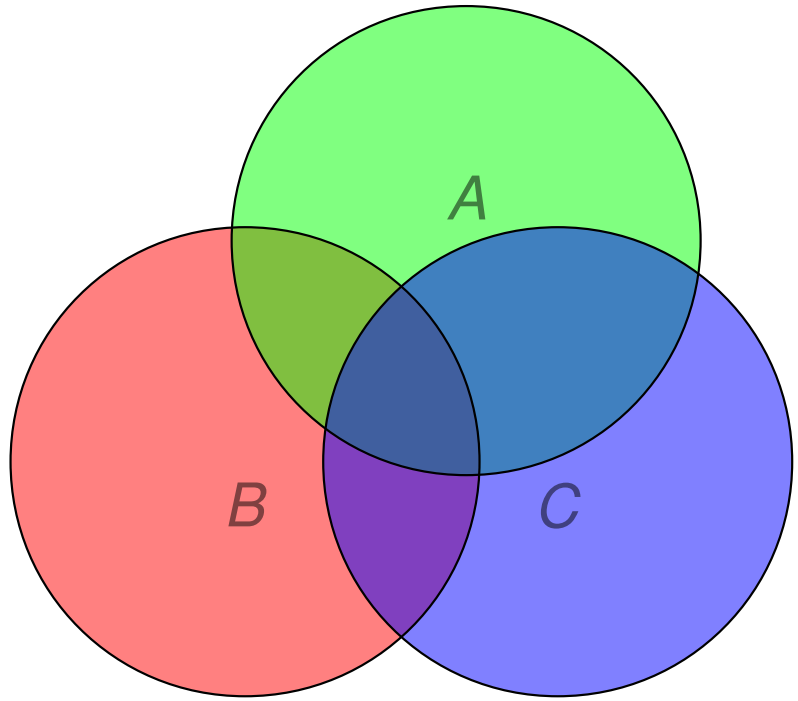

State of the art

- Different models with different mechanisms
- Qualitative validation

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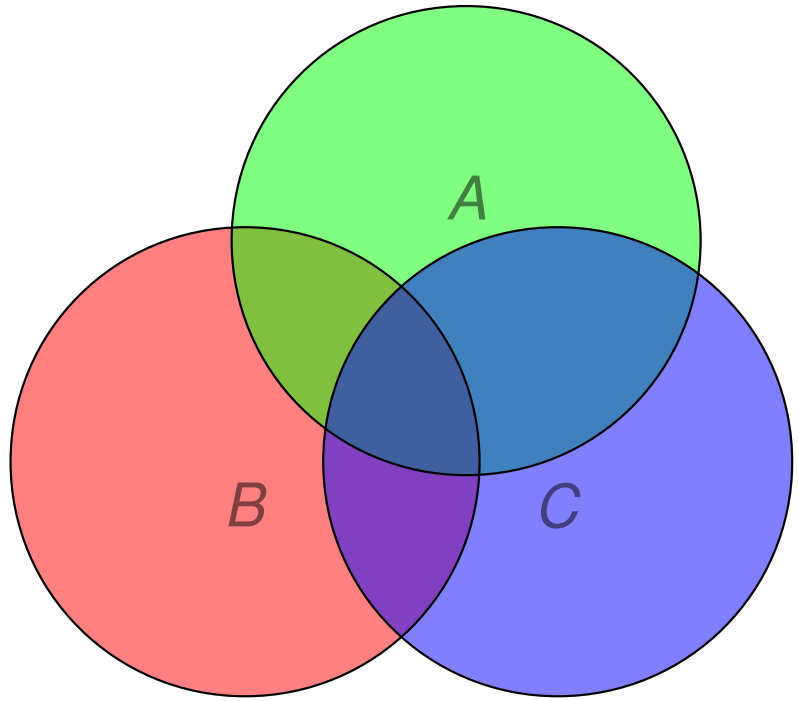


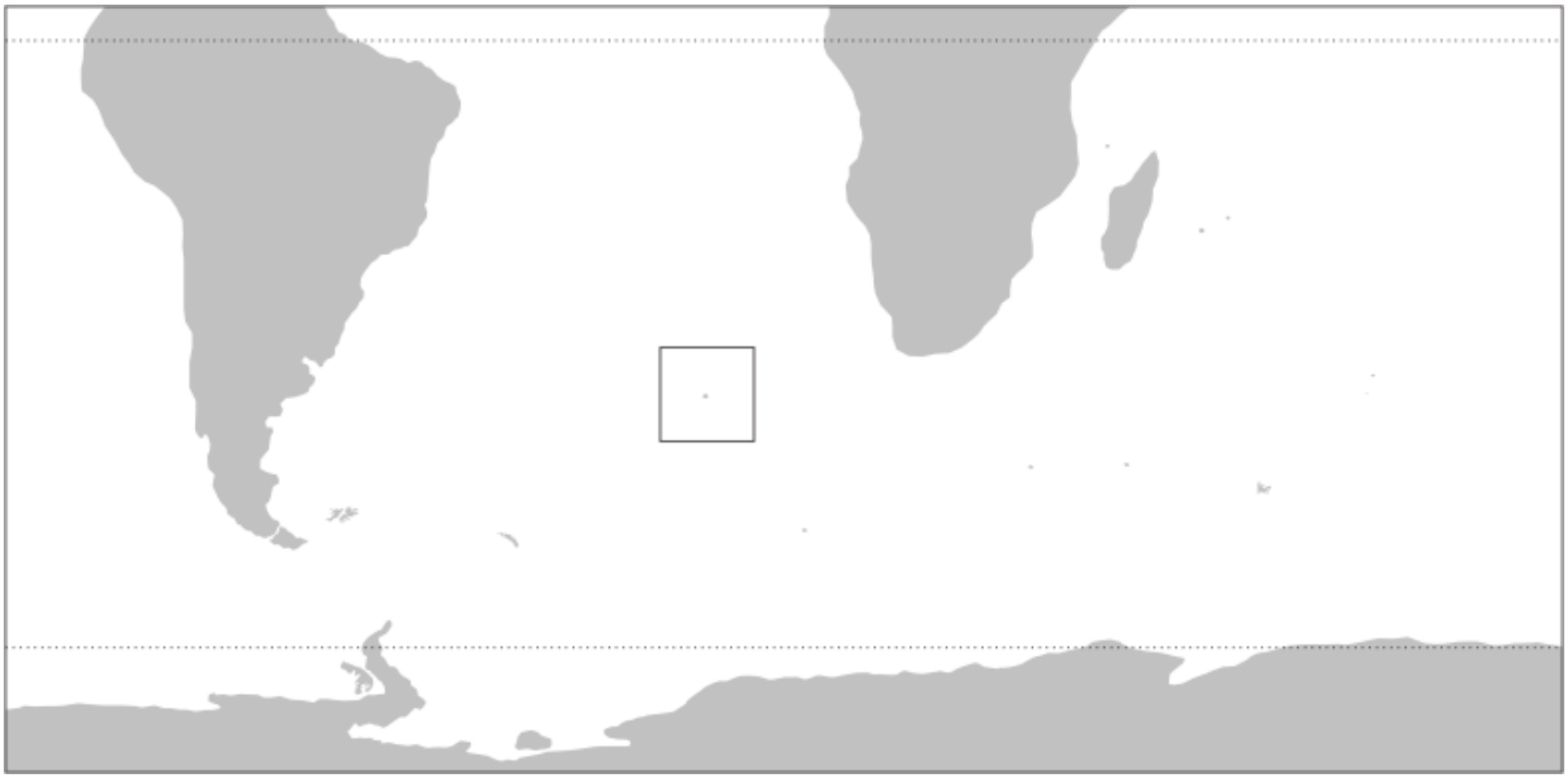
Needs

- Quantitative validation
- Model vs Data via statistical frameworks

Overview of the talk

Contents

Tristan da Cunha?



Epidemiological context

- 284 islanders in 1971.
- Free of influenza for at least 9 years.
- 1968: emergence of *H3N2* influenza.

August 13th, 1971: ship arrival from Cape Town

2 passengers presented influenza symptoms immediately after landing.

A welcome home, *homogeneous mixing*, dance was given!

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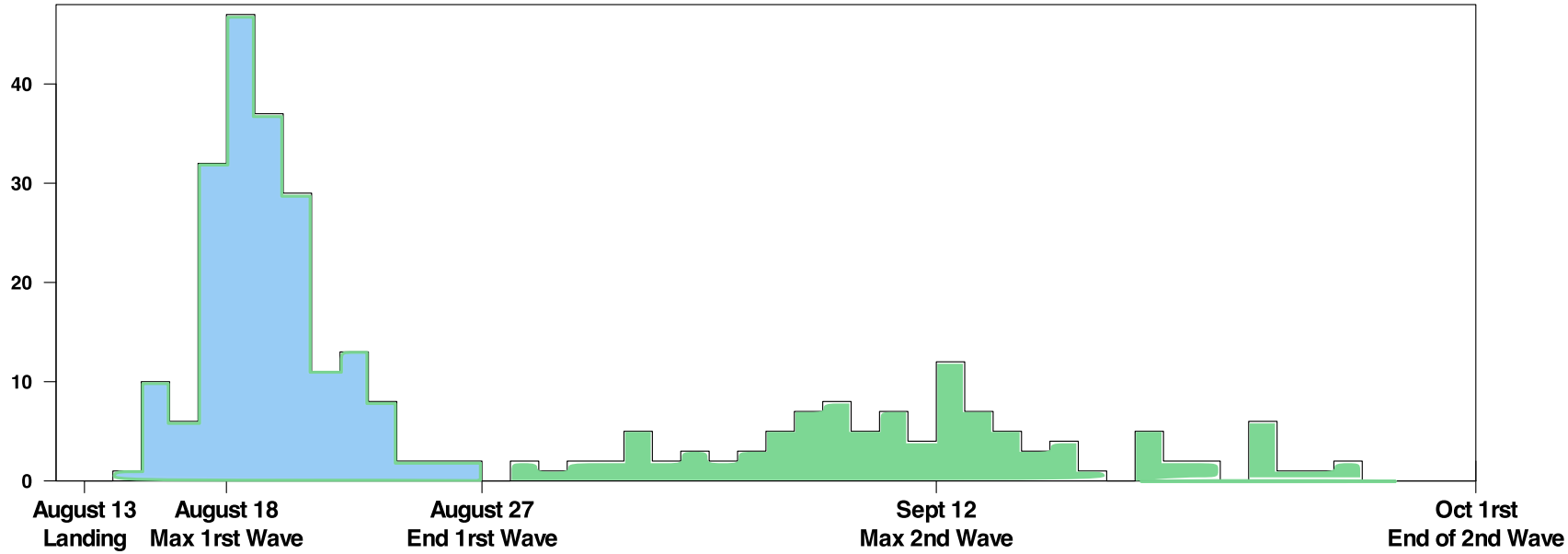
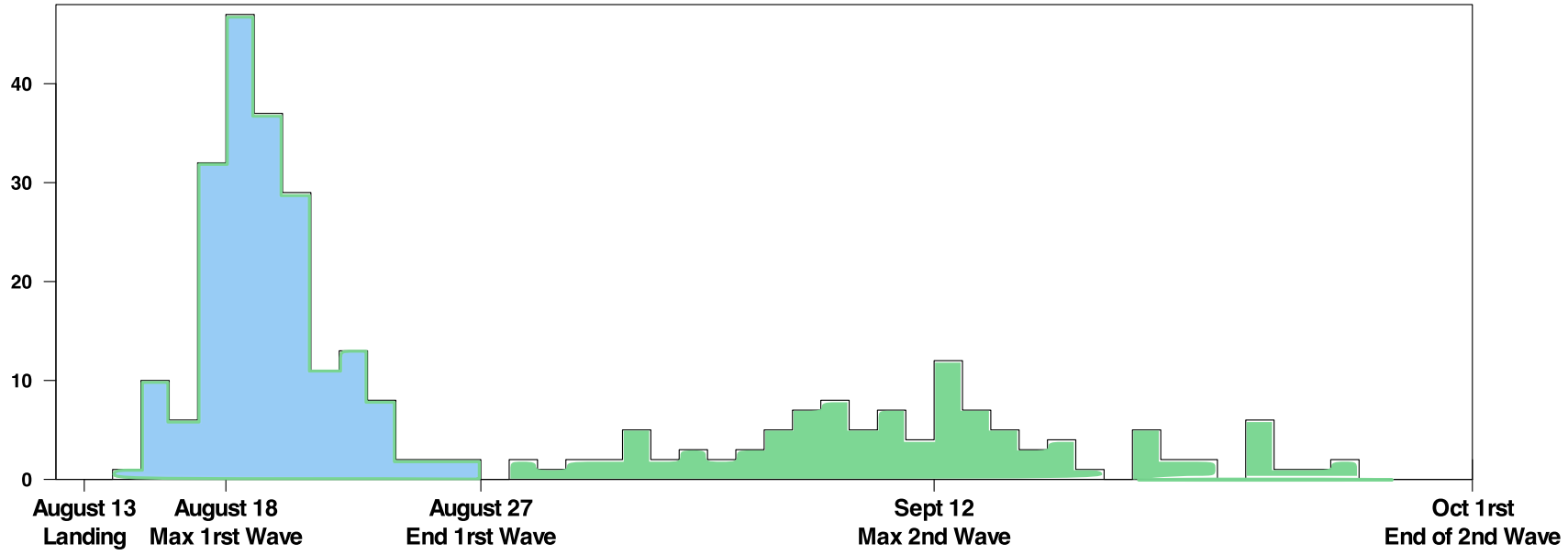
A two waves epidemic



365 attacks for 284 islanders

- 273/284 experienced a first attack (96%).
- 92/284 experienced a second attack (32%).
- Most second attacks coincided with the second wave.

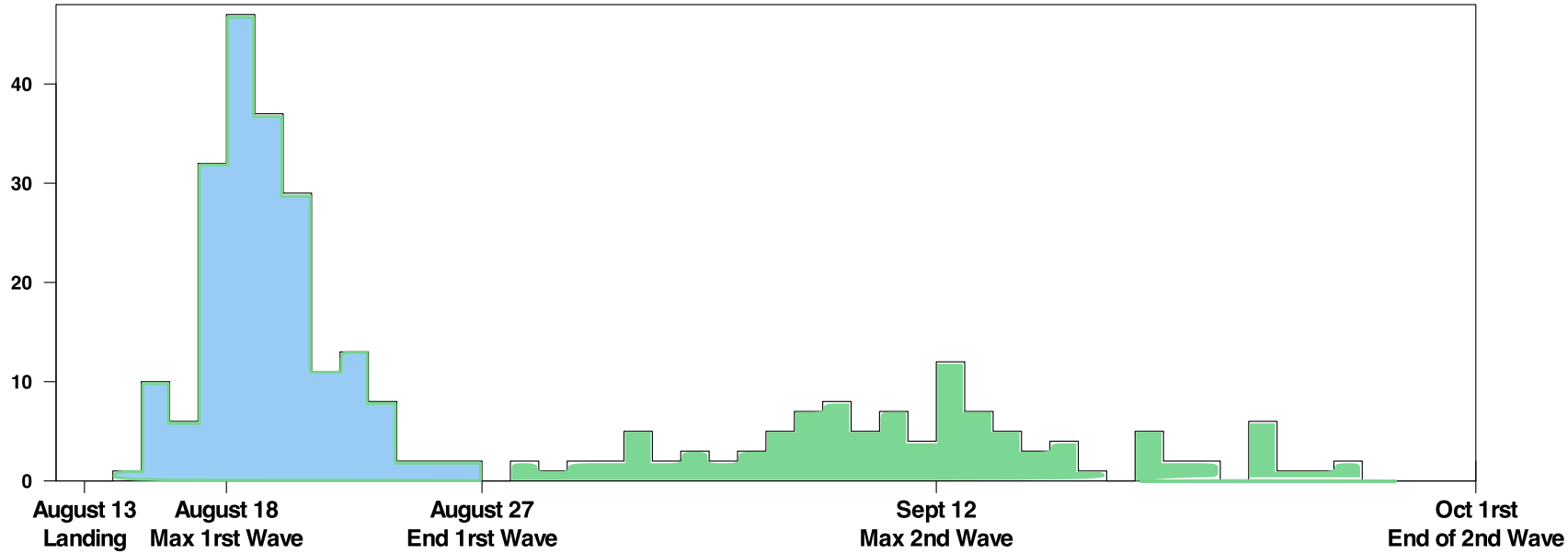
A two waves epidemic



Reporting rate

- Data: daily symptom onset available only for 310/365 attacks (85%)

A two waves epidemic



Objectives of the talk

- Disentangling between different biological hypothesis that could explain this two waves epidemic with multiple infection.
- Model selection based on Maximum Likelihood and AIC.

Contents

Biological hypothesis

Multiple infection could be due to:

- Multiple contacts before acquiring long-term immunity.
- Partial immune protection.
- Virus mutation.
- Unless second attacks were not due to flu!
  (Influenza-like symptoms)

Epidemiological issues:

- A better understanding of the host-immune response.

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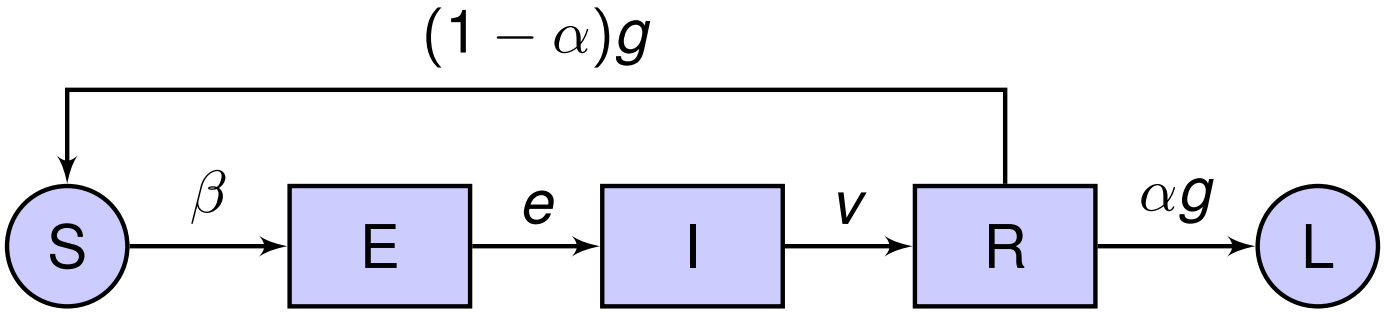
Multiple-contacts model



Epidemiological status:

- S : Susceptible.
- E : Exposed (latent state).
- I : Infected.
- R : short-term Resistance.
- L : Long-term immunity.

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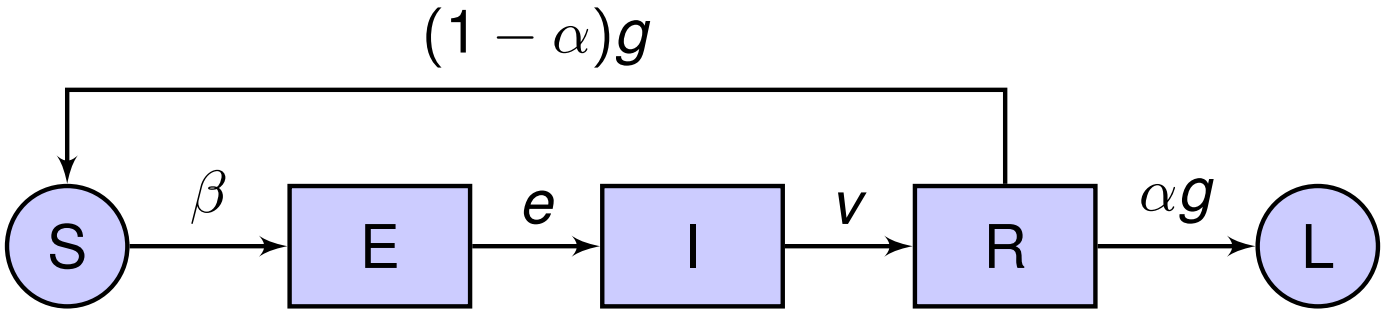

Parameters:

- $\beta =$ effective contact rate.
- $1/e =$ mean time in state of latent infection.
- $1/v =$ mean time as Infective.
- $1/g =$ mean time in Resistant state.
- $\alpha =$ proportion of Resistant developing Long-term immunity.

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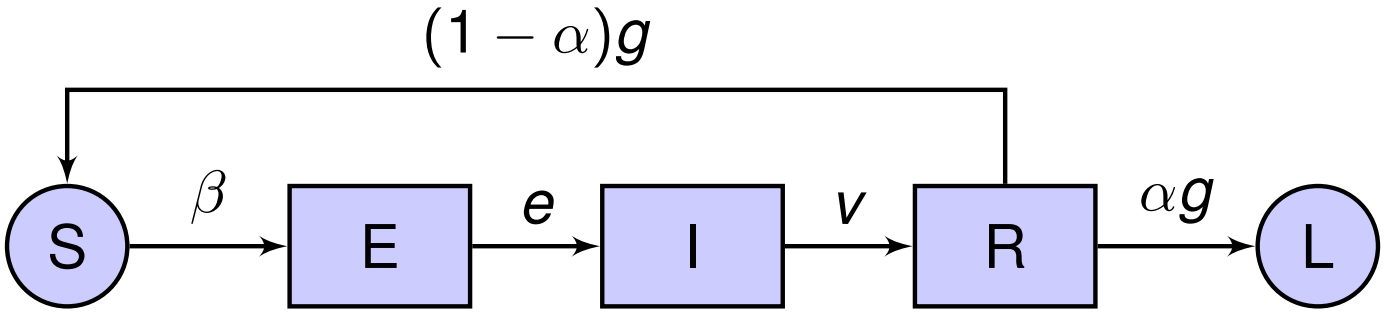
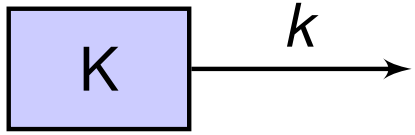
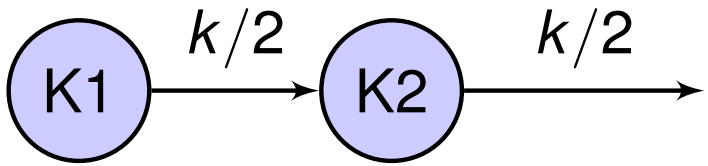
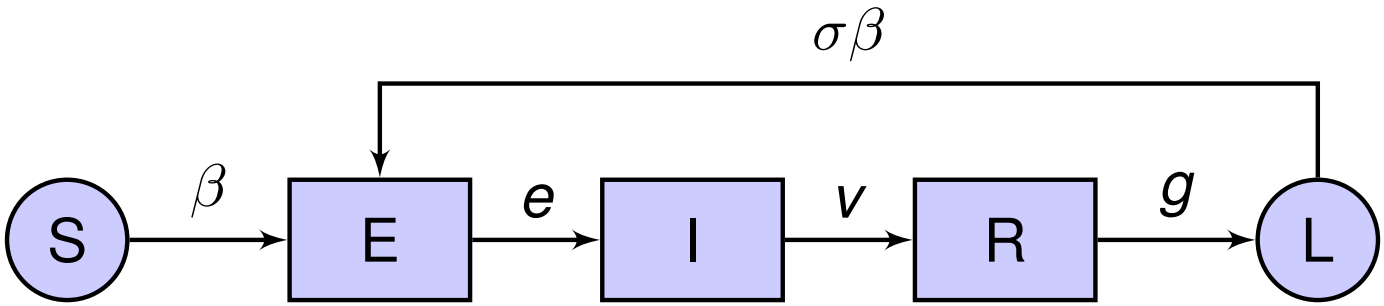


Erlang distribution for residence time:





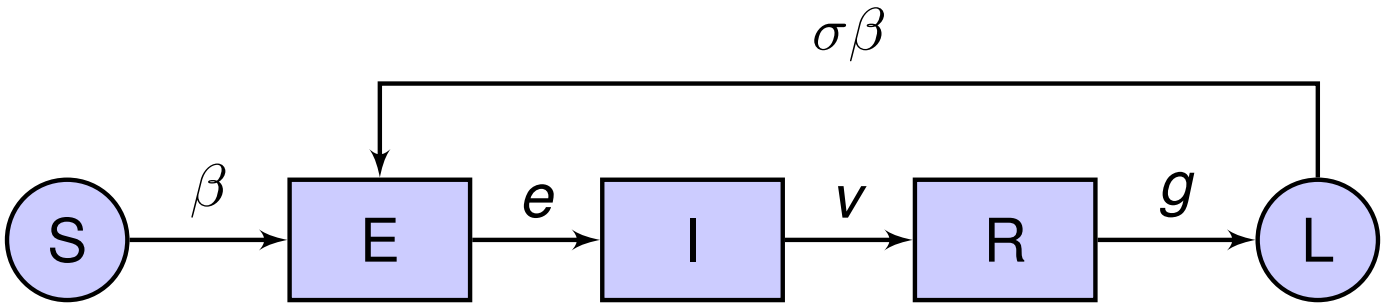
Partial-immunity model



Parameter $\sigma \in [0, 1]$

- Partial immunity induced by a previous infection.
- Reinfection treshold $\sigma = 1/R_0$
- Transition between *SIR*-like and *SIS*-like dynamics.

Partial-immunity model



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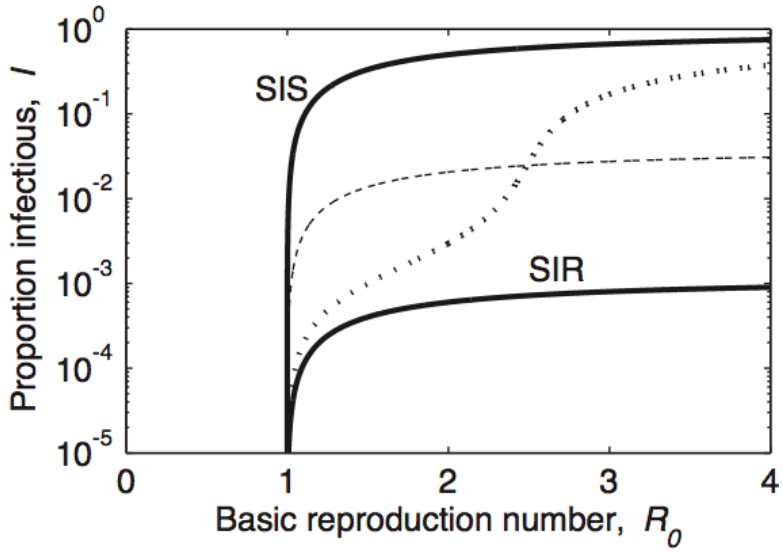
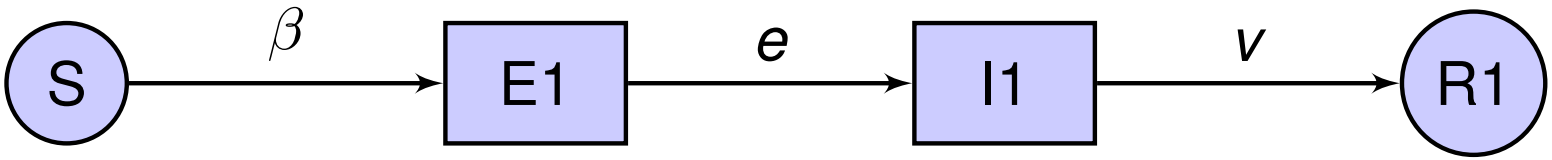


Gomes *et al.*, 2004

Mutation model



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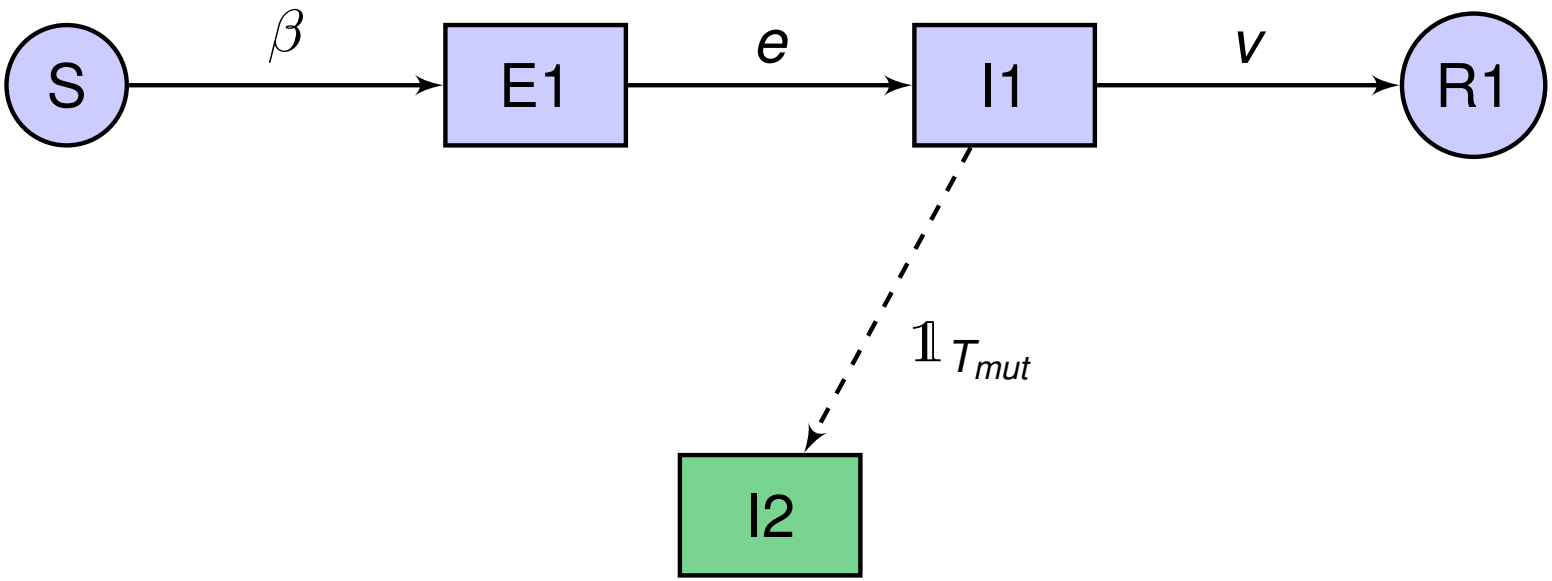

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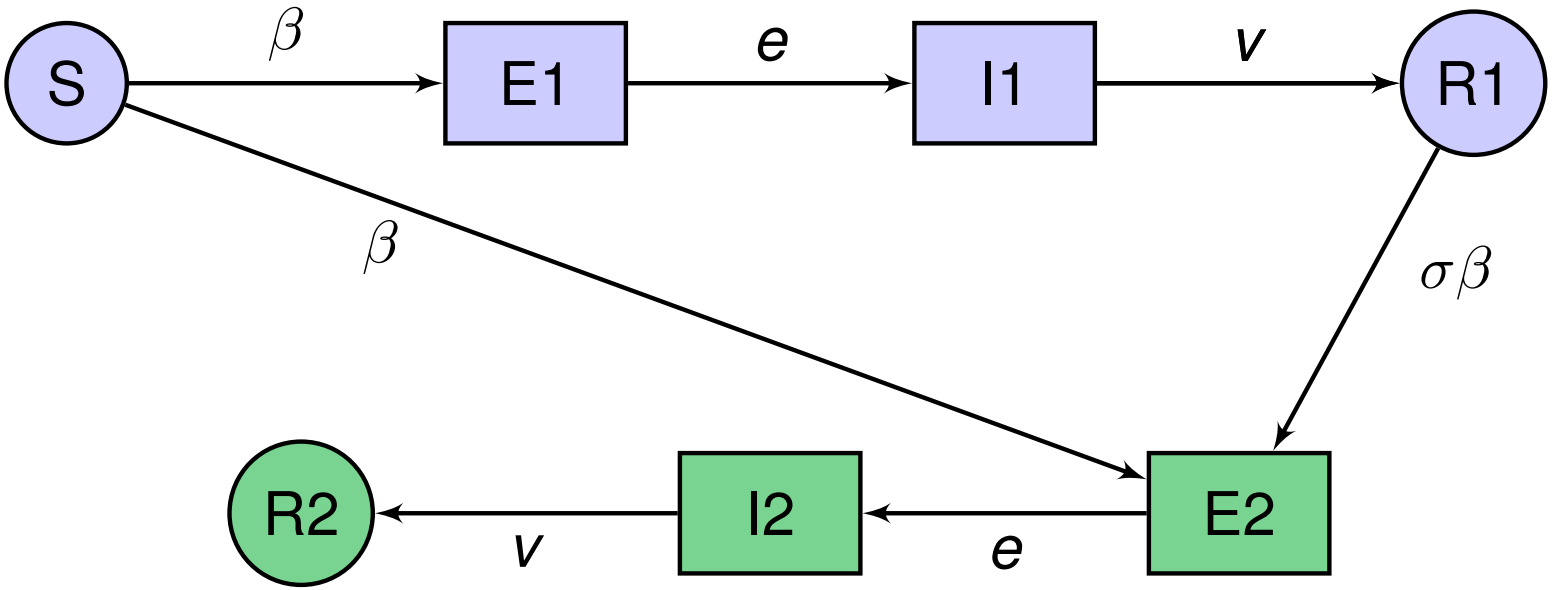

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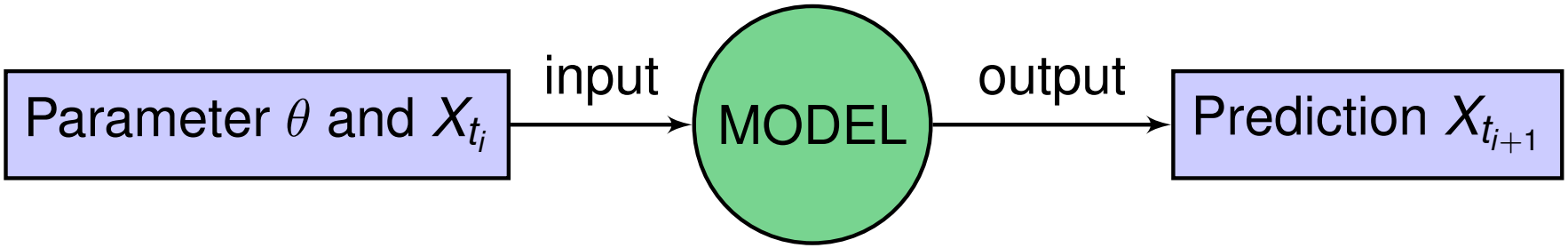
Inference Framework

Model as black box



Data

Daily symptom onset: $Y_{t_{1:N}}$

Observation process

We used a Poisson counting with reporting rate ρ to be infered ($\rho \in \theta$).

Likelihood

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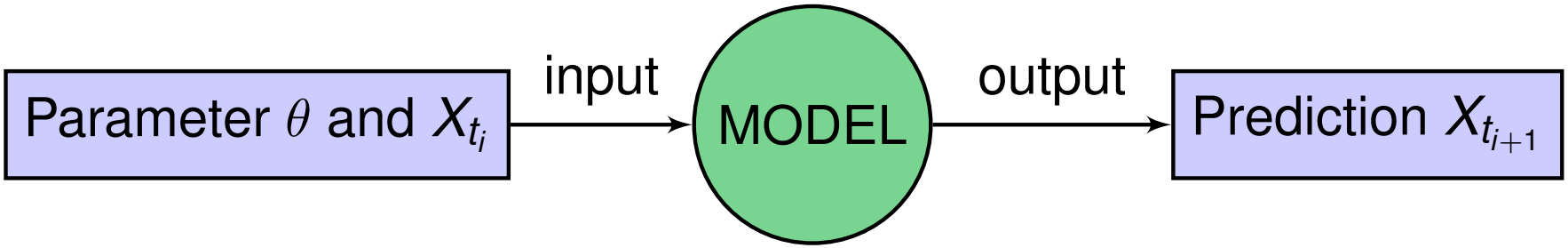

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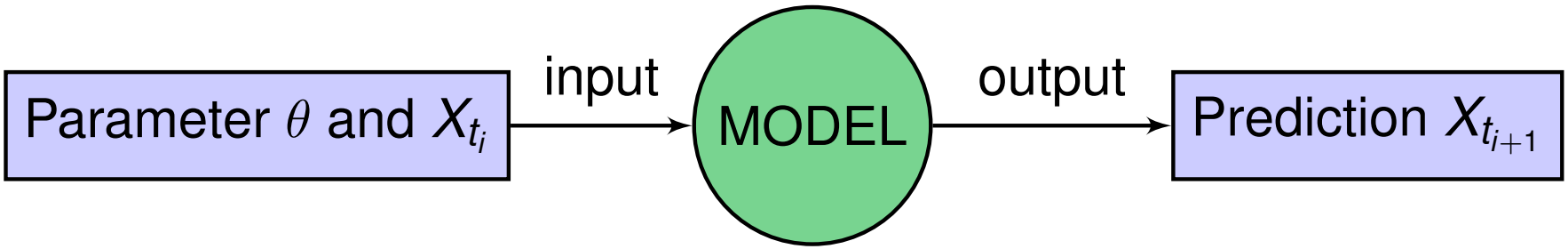

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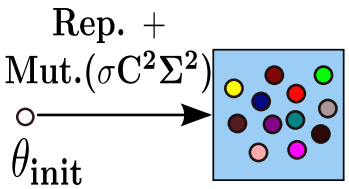

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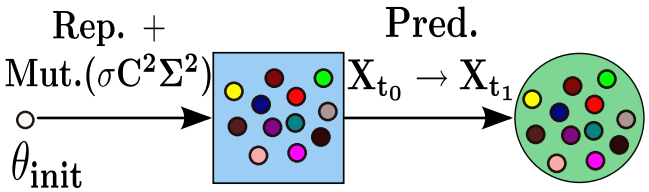

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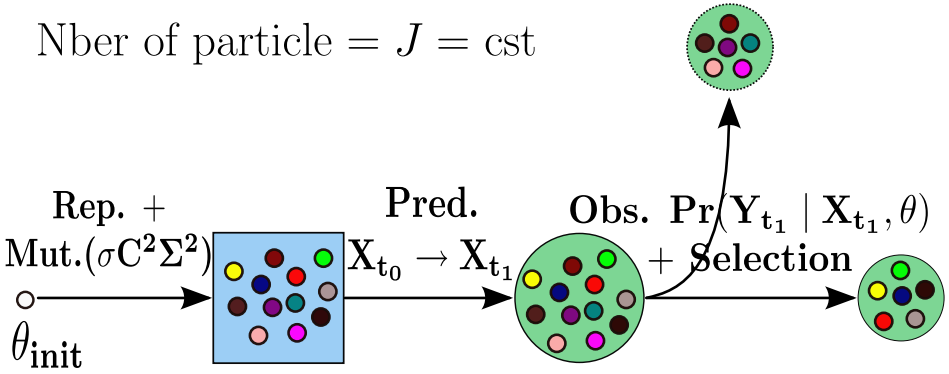

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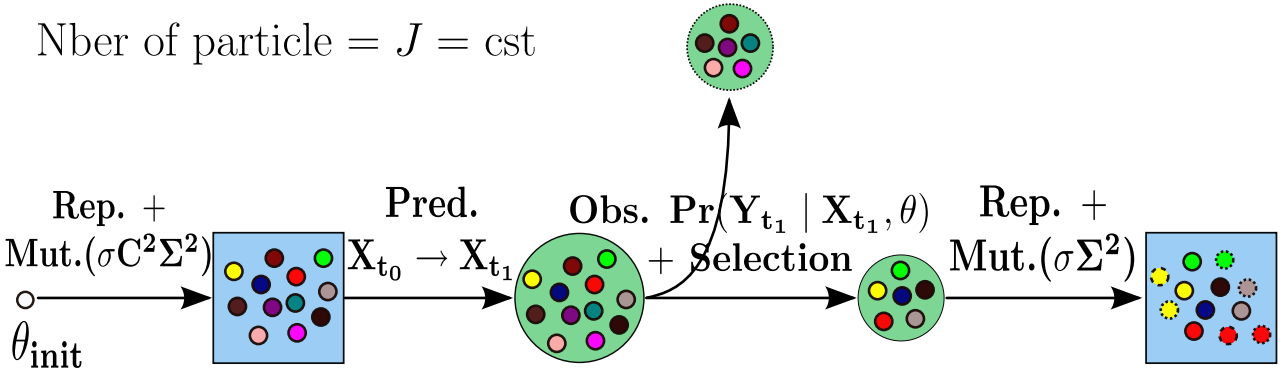

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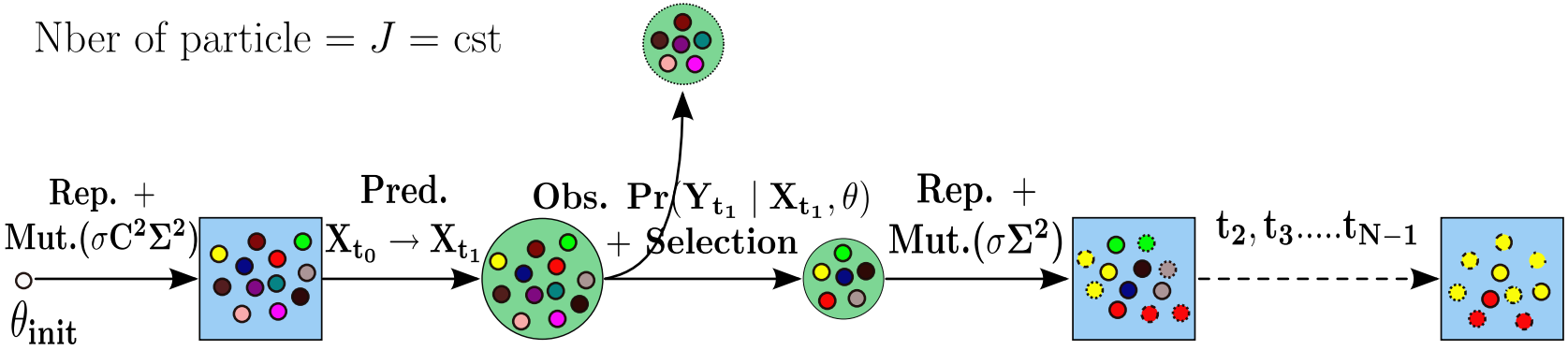

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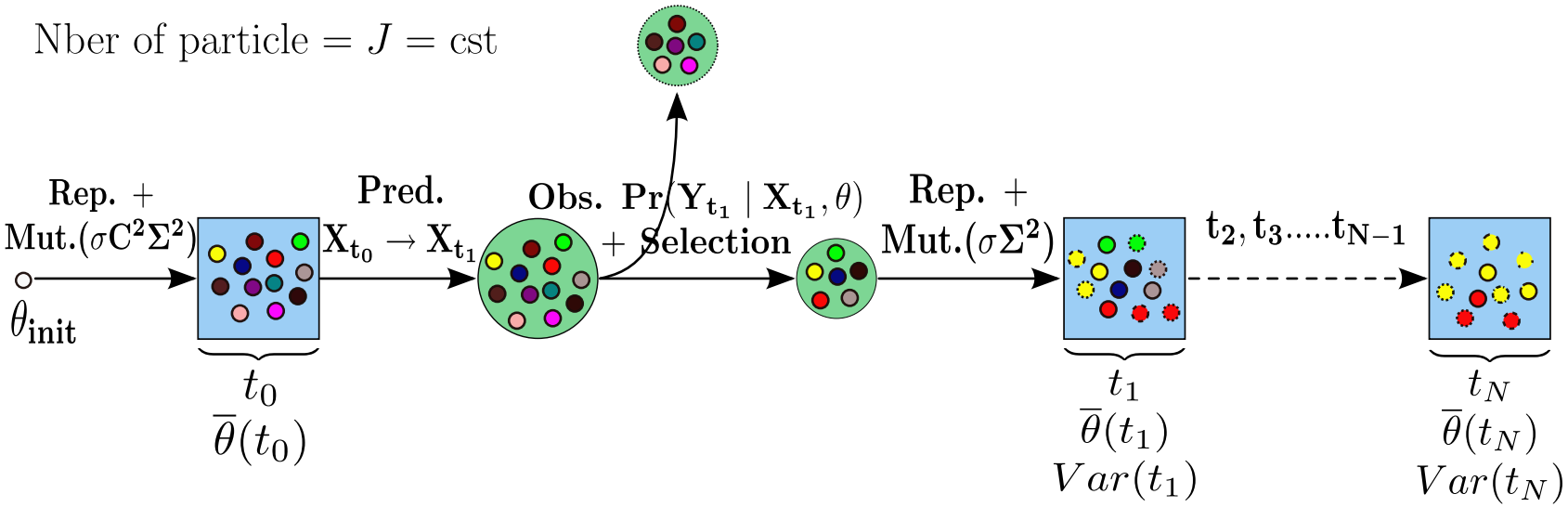

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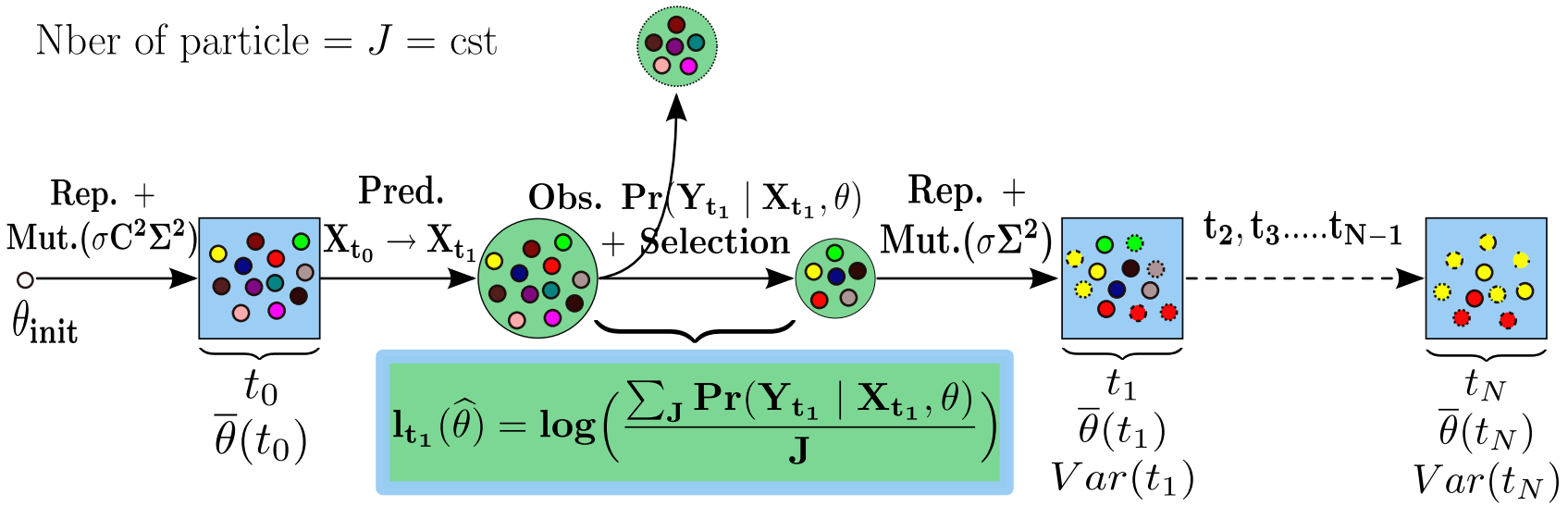

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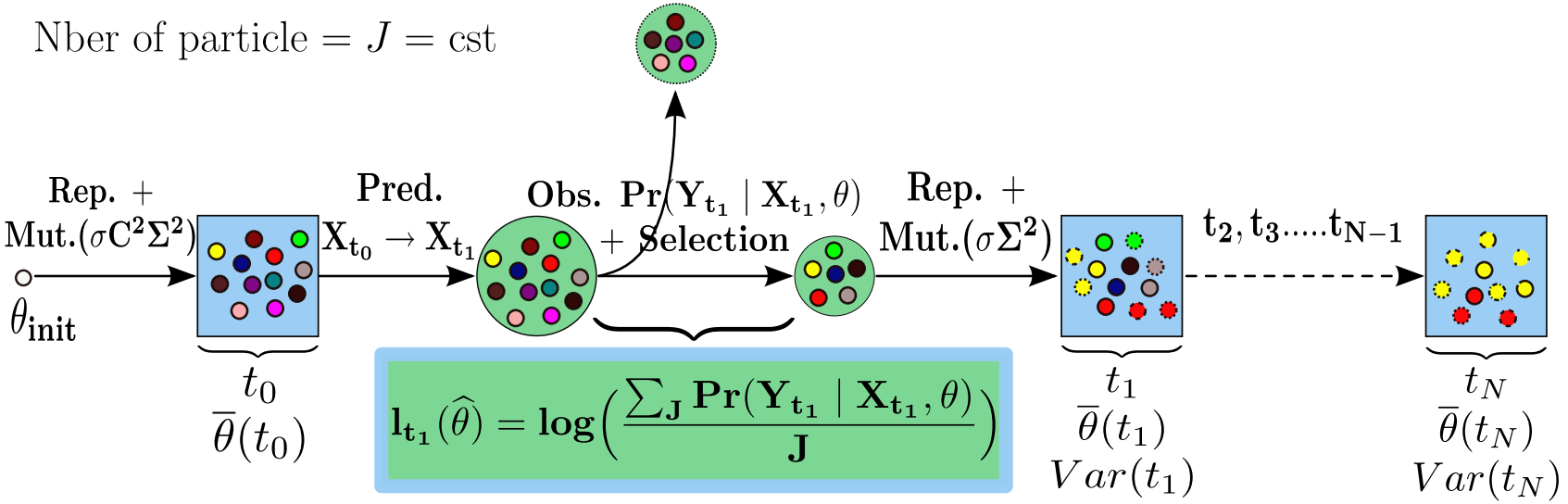

$$\widehat{\theta} = \overline{\theta}(\mathbf{t_0}) + \mathbf{Var(t_1)} \sum_{\mathbf{n=1}}^{\mathbf{N}} \frac{\overline{\theta}(\mathbf{t_n}) - \overline{\theta}(\mathbf{t_{n-1}})}{\mathbf{Var(t_n)}} \text{ and } \mathbf{L}(\widehat{\theta}) = \sum_{\mathbf{i=1}}^{\mathbf{N}} \mathbf{l_{t_i}}(\widehat{\theta}))$$

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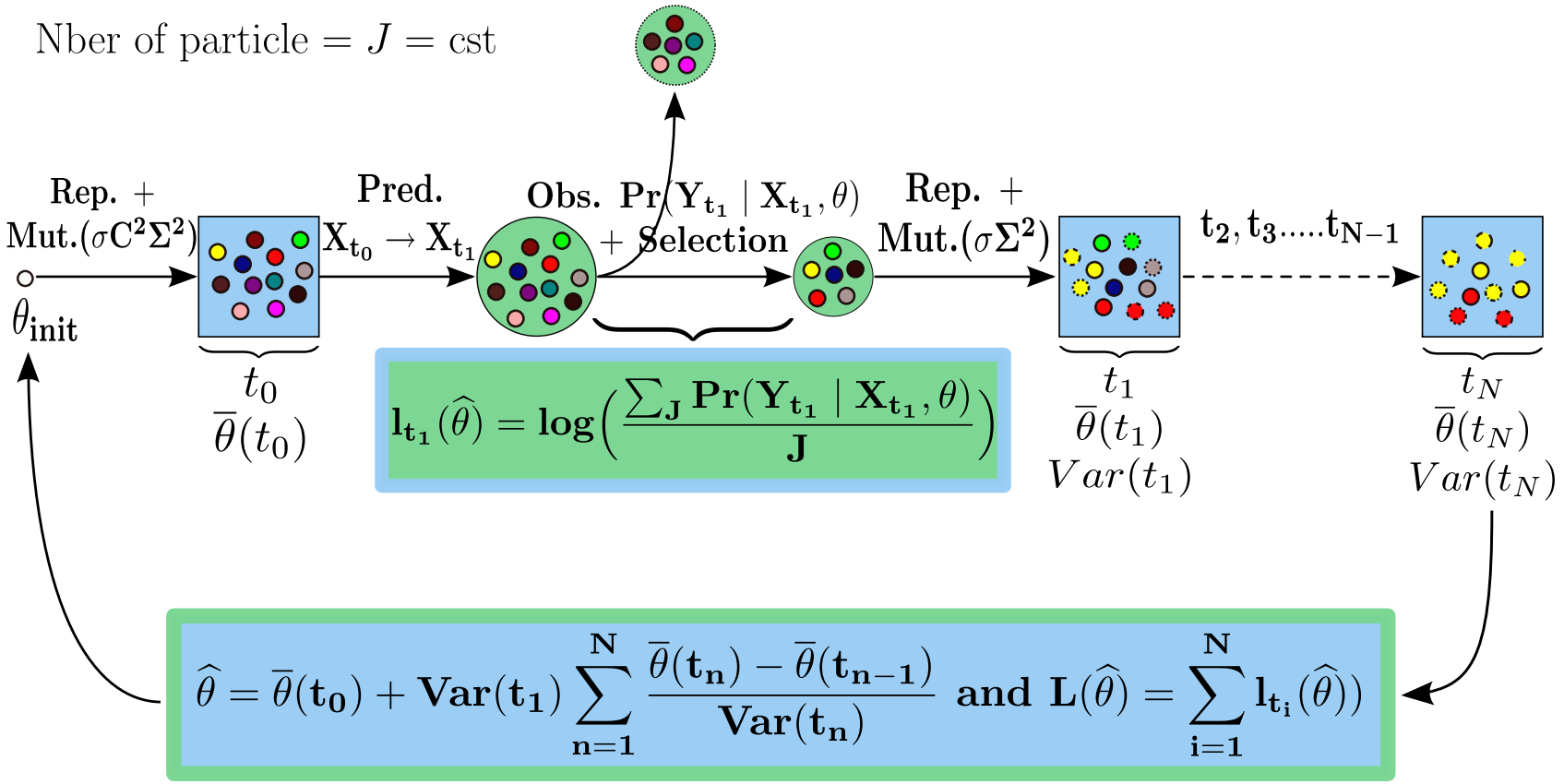

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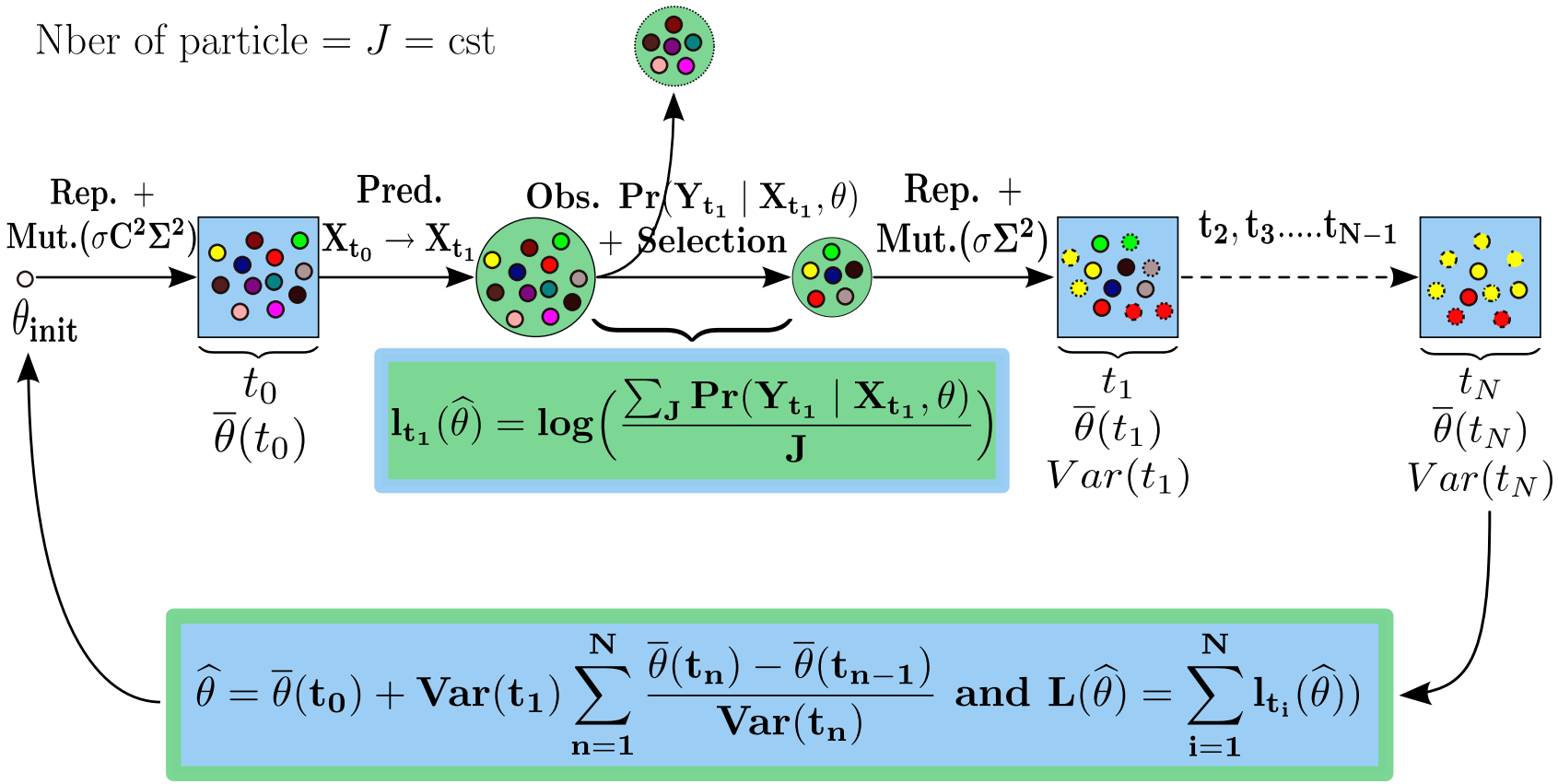

$\lim_{\sigma \to 0} \widehat{\theta} = \theta_{\mathbf{MLE}}$ **(Maximum Likelihood Estimate for parameters) [Ionides, 2006]**

Model selection and parameters estimation

Stochastic simulations

- Demographic stochasticity must be taken into account for small population size (stochastic extinction).
- Continuous time Markov process simulated by exact algorithm [Gillespie ,1977]

Model selection

$AIC_c = -2L(\widehat{\theta}) + 2k + \frac{2k(k+1)}{n-k-1}$

$k =$ number of parameters

$n =$ number of observations.

Parameter estimation and 95% I.C.

Smoothed profile: $2|L(\theta_{MLE}) - L(\widehat{\theta})| < \chi^2_{dl=1}(0.95) = 3.84$

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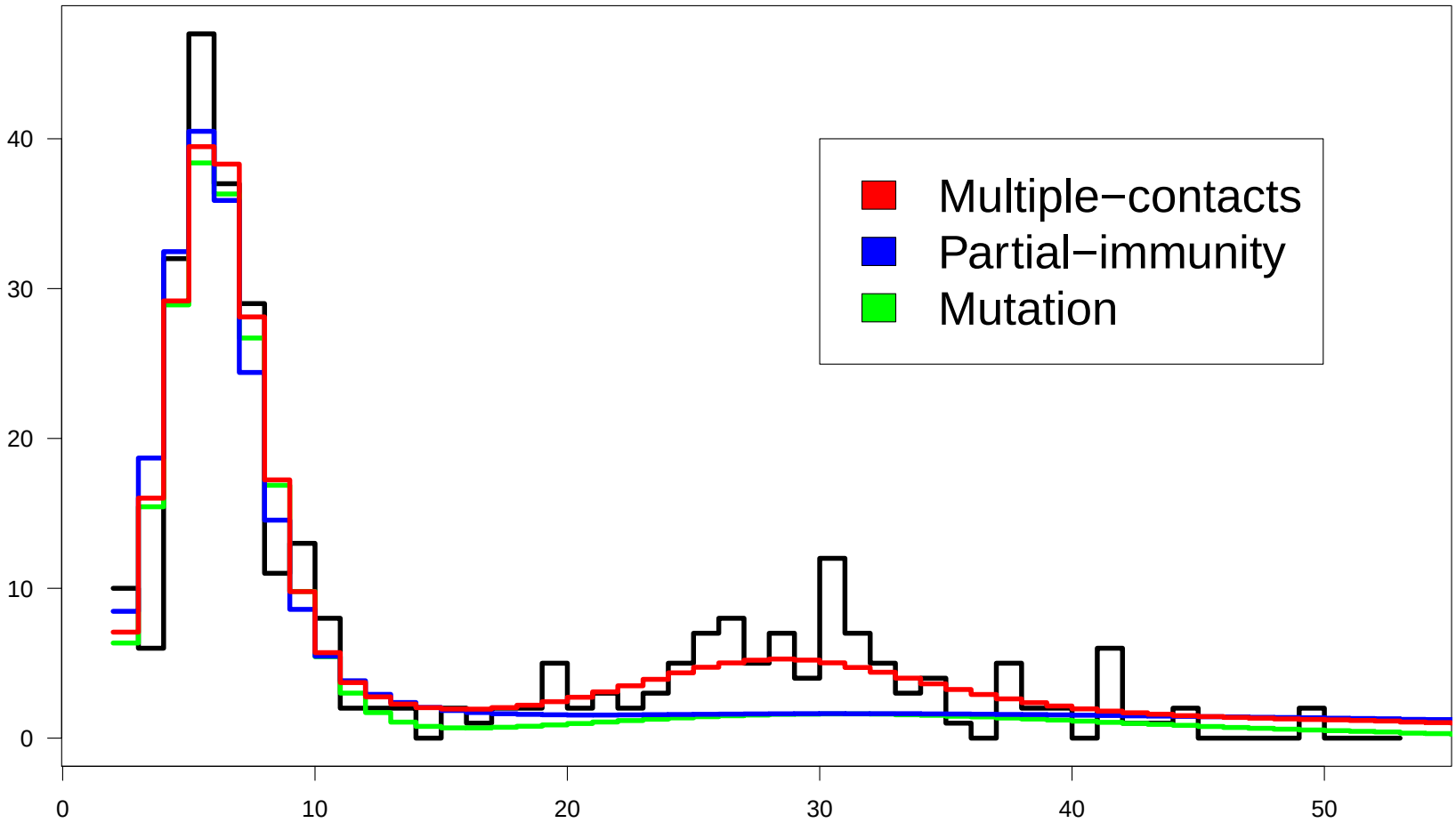

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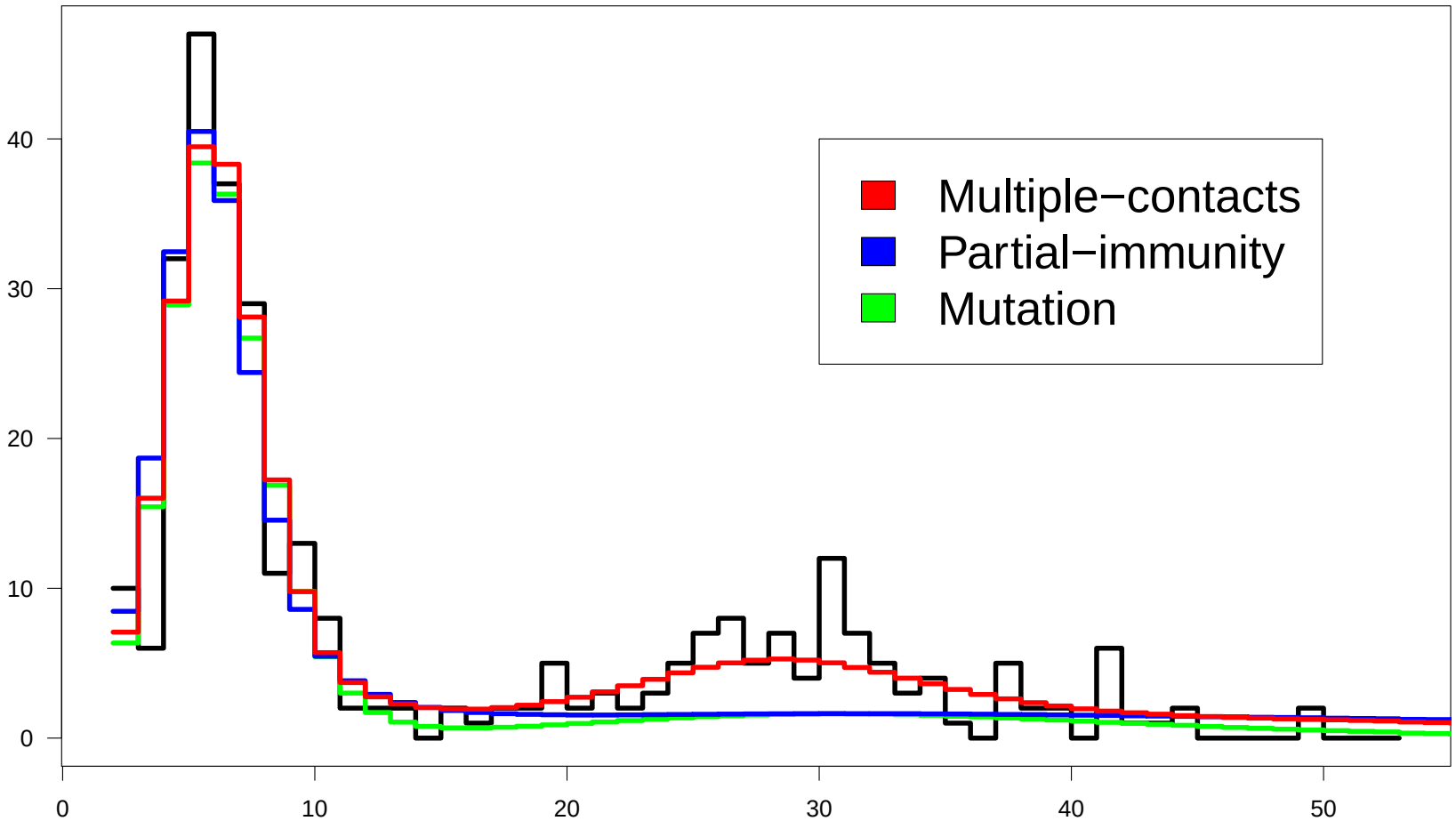
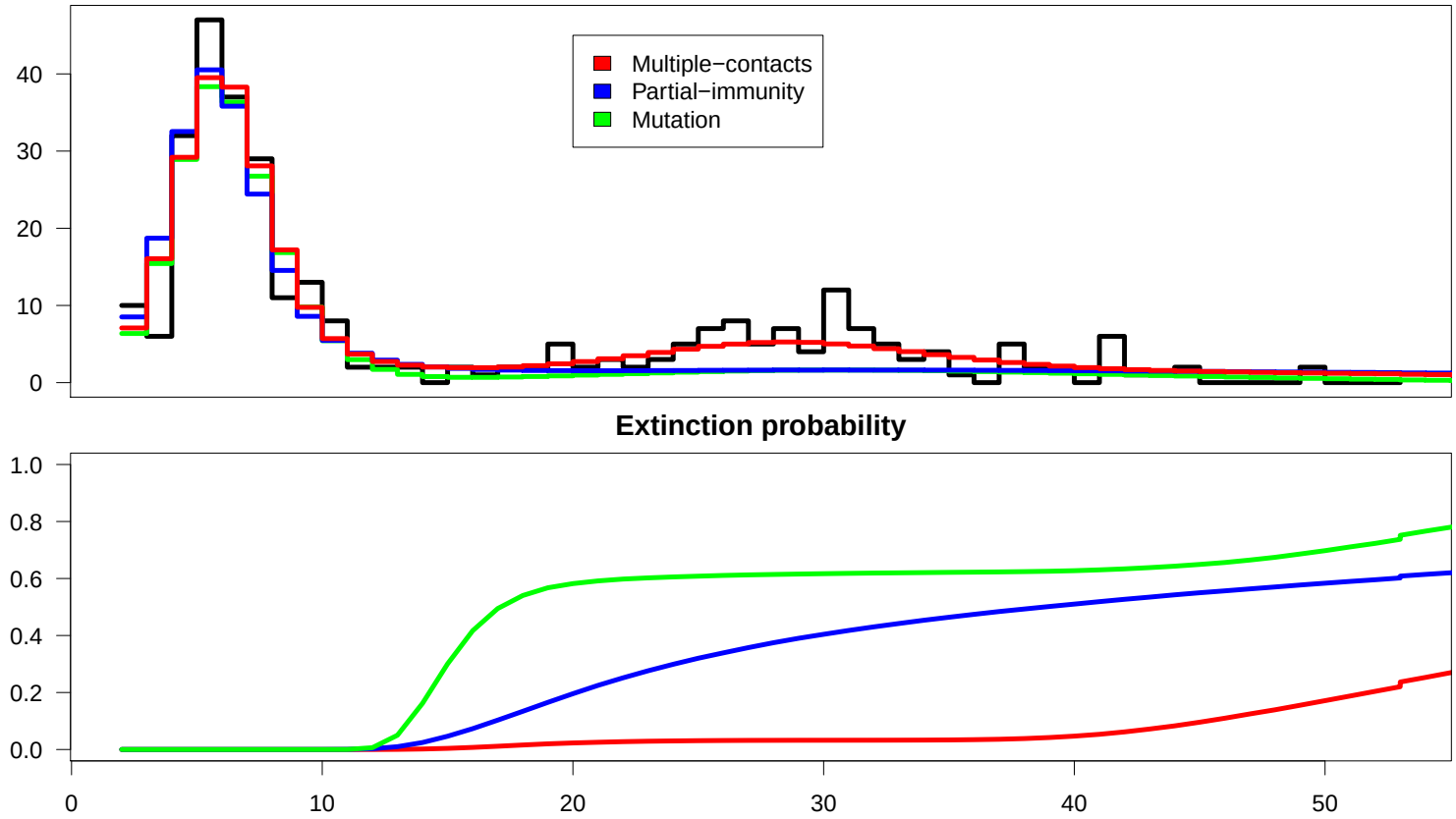


Model	Multiple-Contacts	Partial-Immunity	Mutation
$L(\theta_{MLE})$	-106.13	-124.11	-130.03
AIC_c	231.61	267.57	279.41

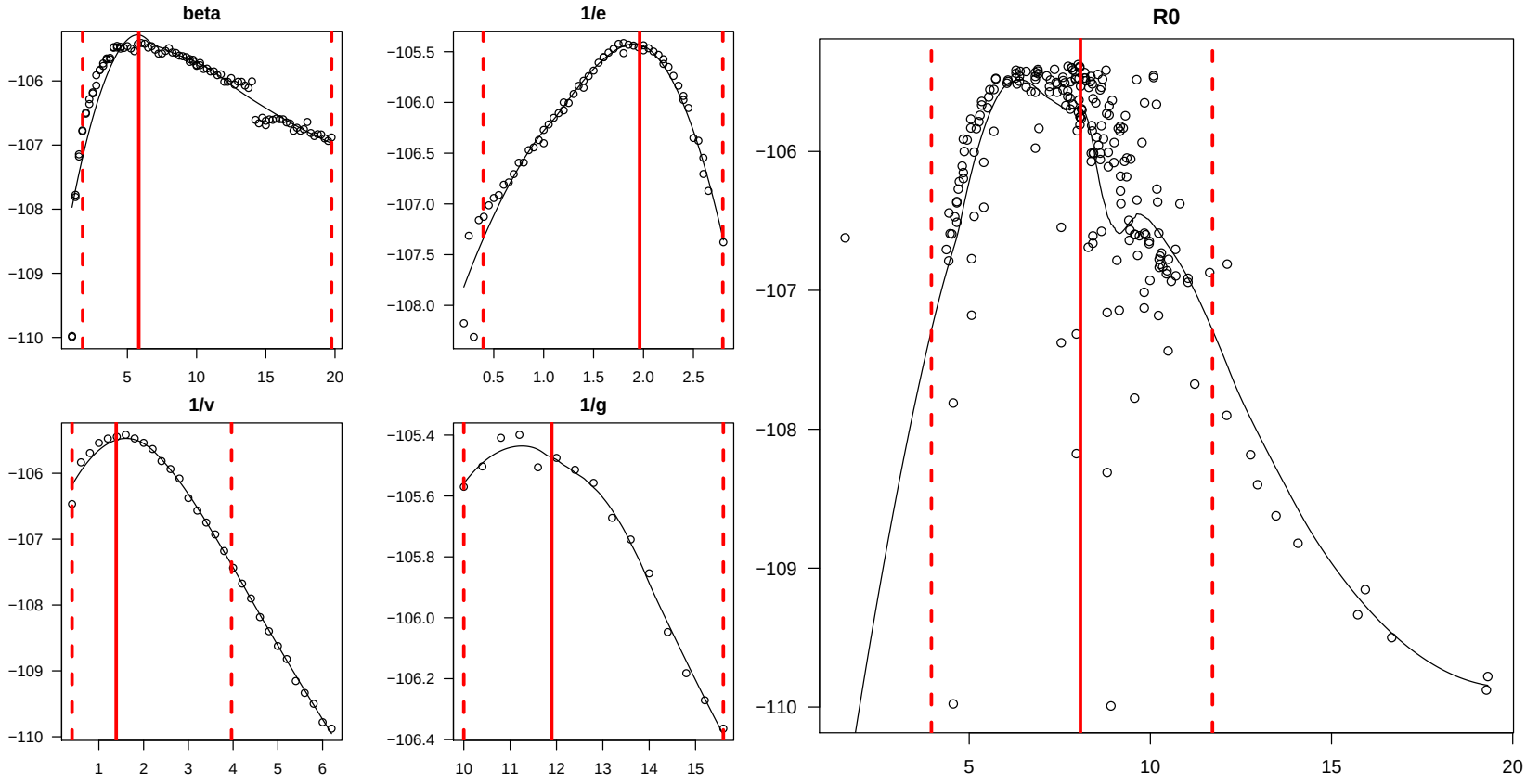
Stochastic extinctions



Chance for second wave to occur

Multiple-contacts model is more robust to stochastic extinctions between the two waves.

Profile for multiple-contacts model



	Latent	Infectious	Resistant	R_0	α
Stochastic	2 days	1.4 days	12 days	8	0.48
Deterministic*	1.36 days	0.98 days	12 days	6.44	0.49

*Mathews *et al.* 2007

Contents

Conclusion

- We tested 3 biological mechanisms to explain two waves epidemic.
- Multiple-contacts before acquiring long-term immunity appears the most probable.
- Demographic stochasticity between the two waves must be taken into account.
- But maybe the second infection was not due to influenza?
- Parameter estimation has been confirmed by another bayesian method (not shown).

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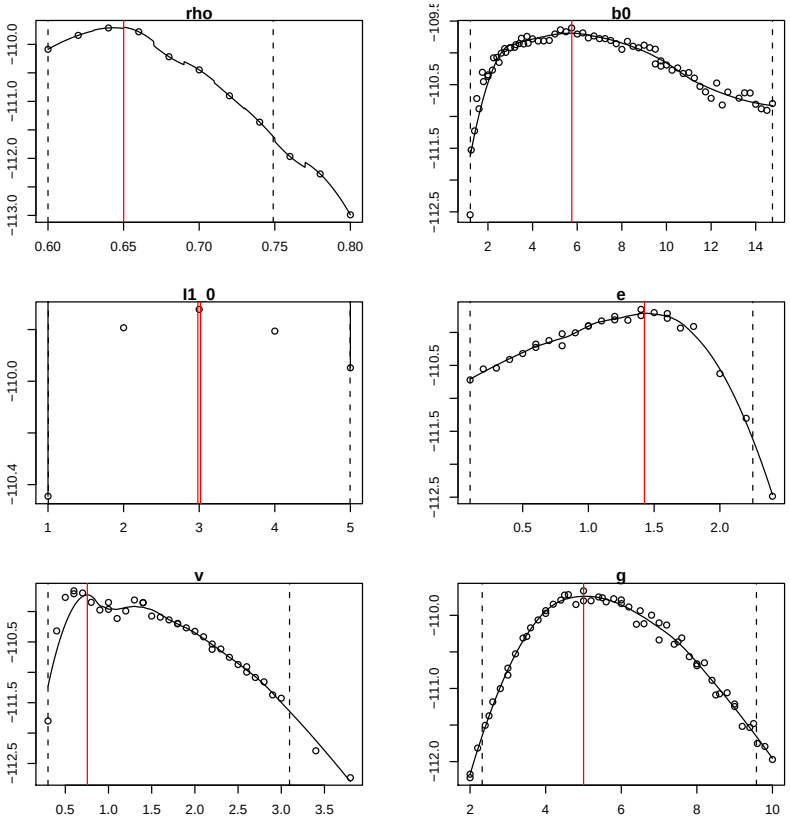
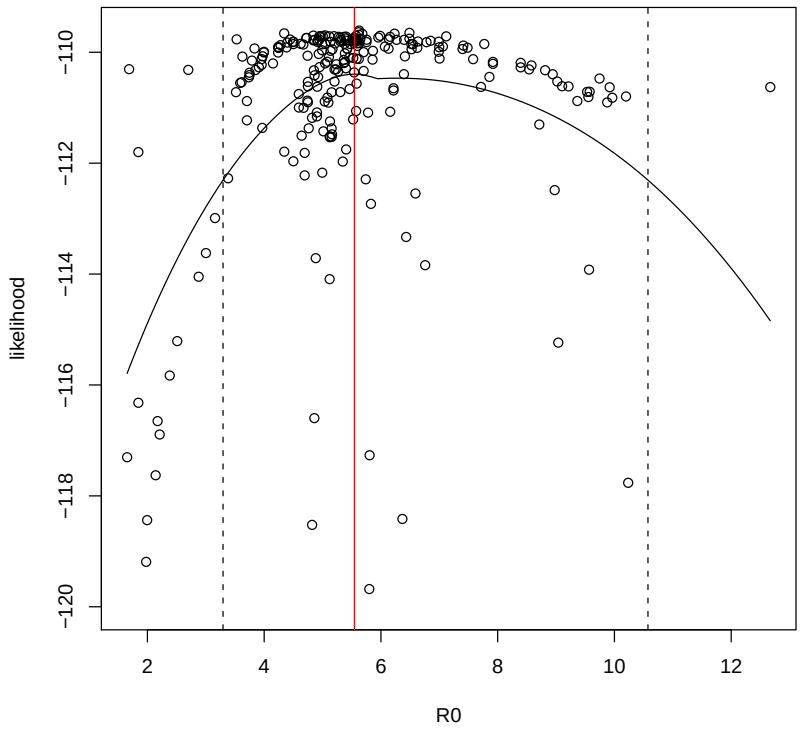
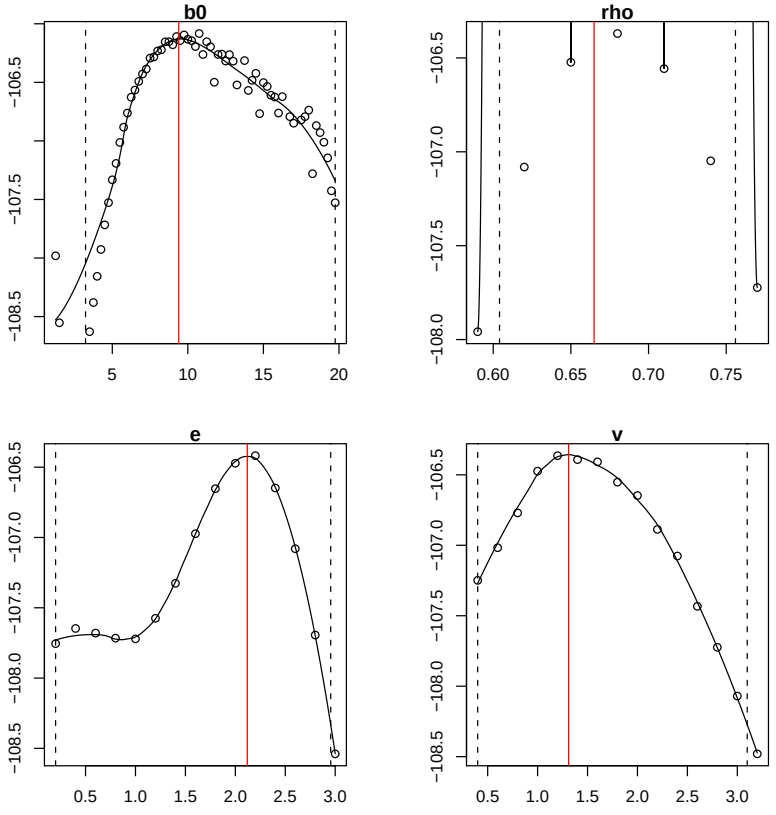
...see you next wave!

Profile for partial-immunity model

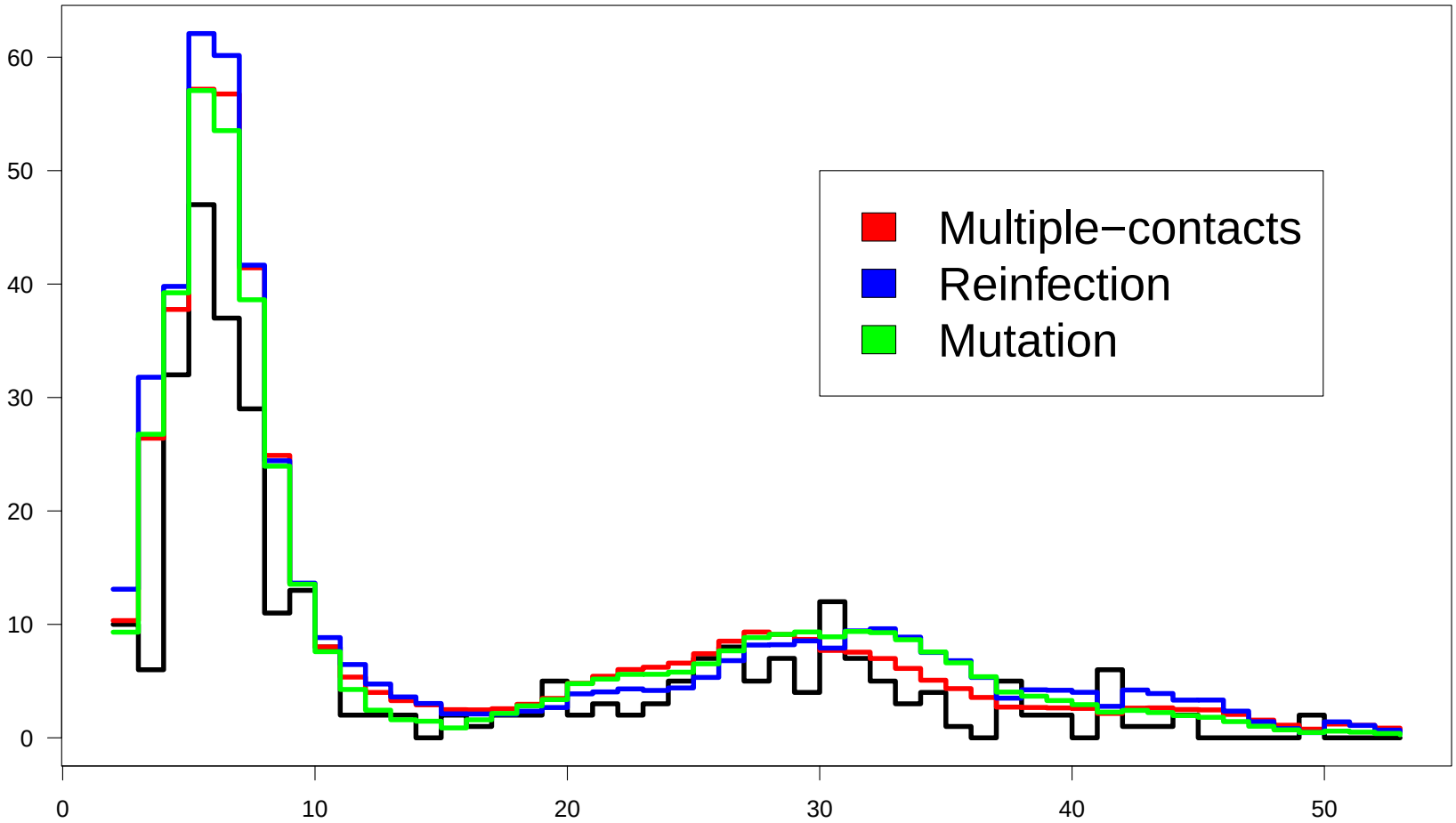




Profile for mutation model



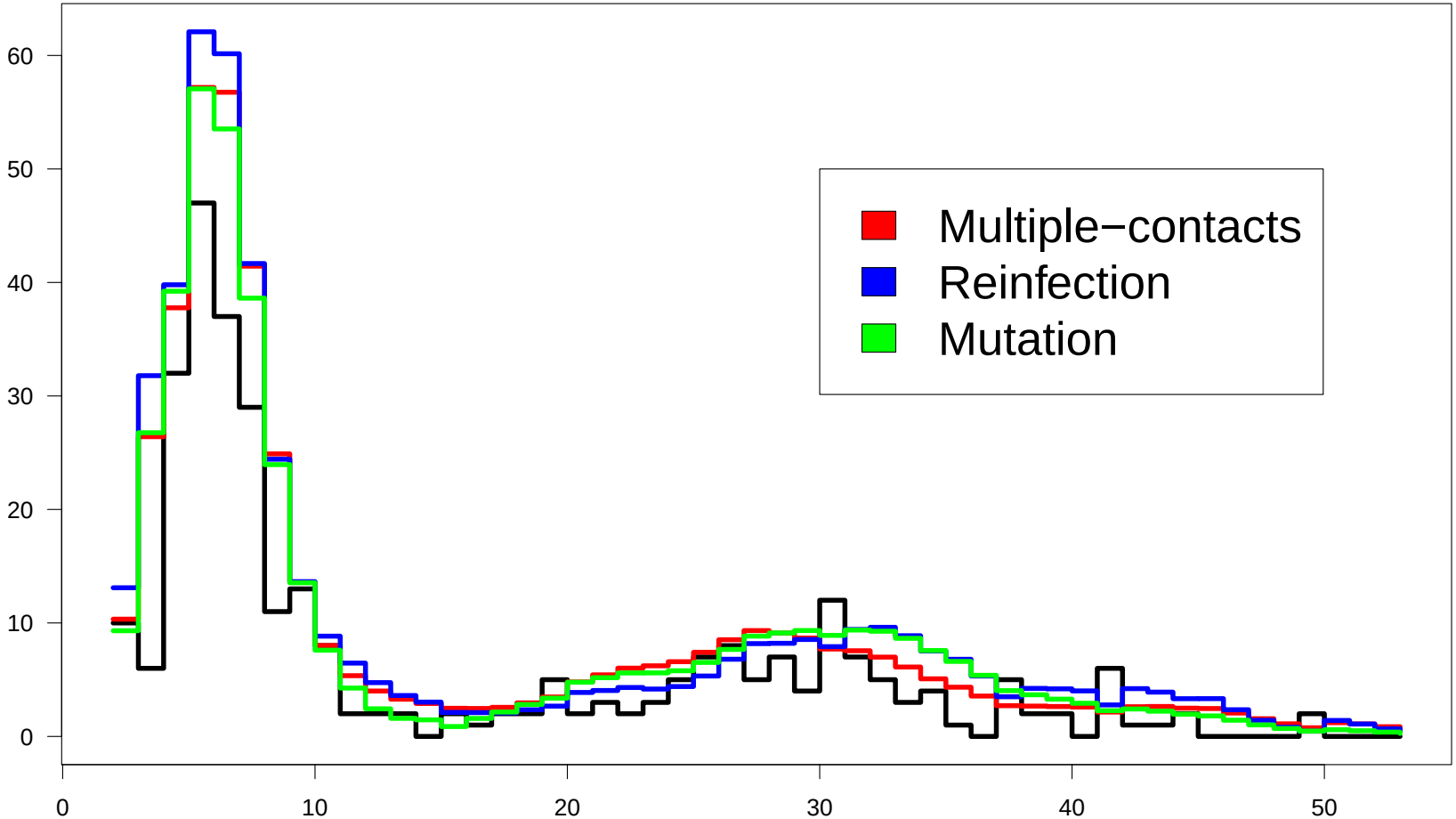
Mean Incidence Filtered



Mean trajectory but conditioned on no extinction

Filtering implicitely selects the surviving particles that escape stochastic extinction.

Mean Incidence Filtered



Model	M-C	P-I	Mu
L	-105.36	-109.70	-106.05
AIC	230.08	238.766	231.448