Gradual & Punctuated antigenic drift for influenza evolution

A quantitative approach based on time series analysis

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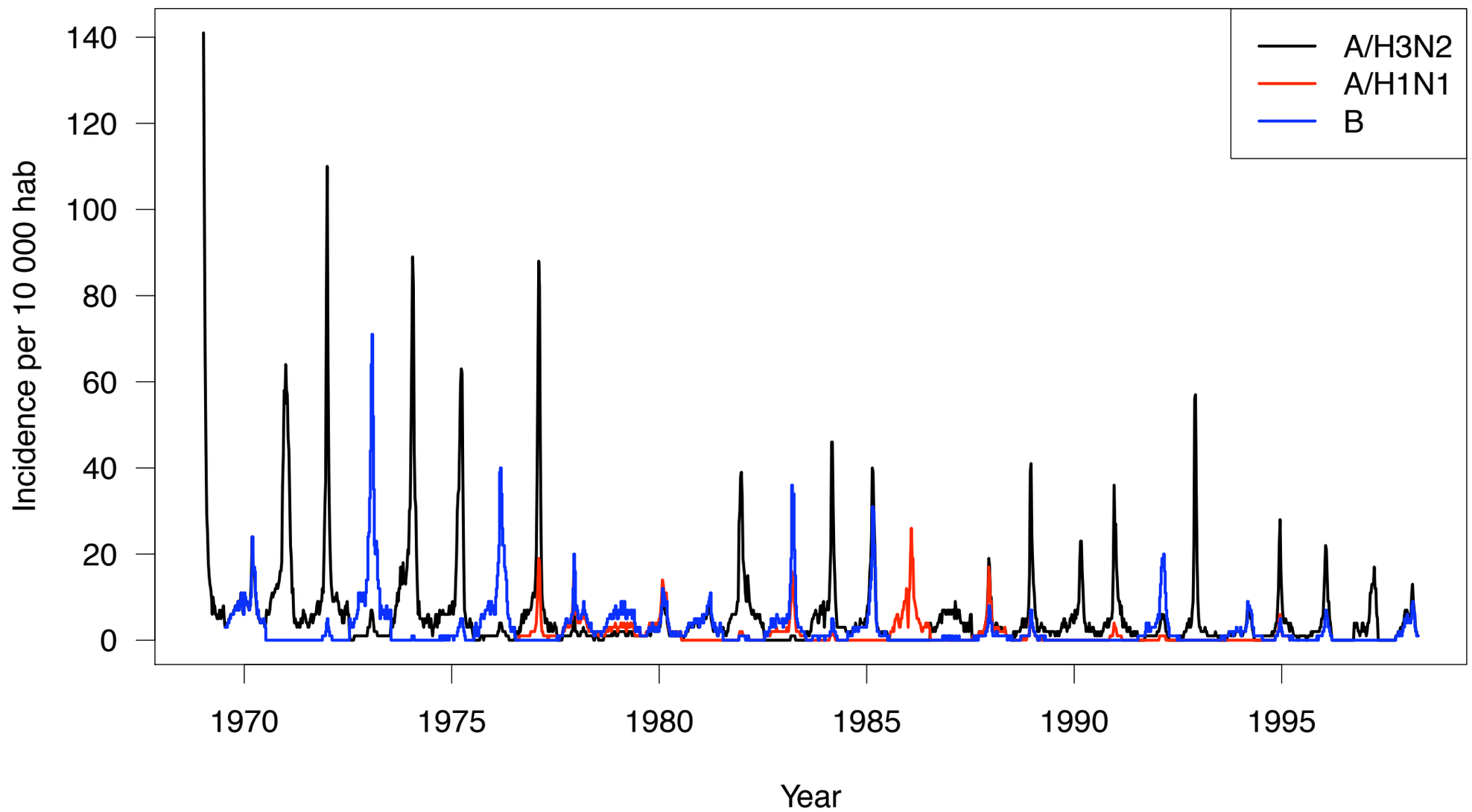
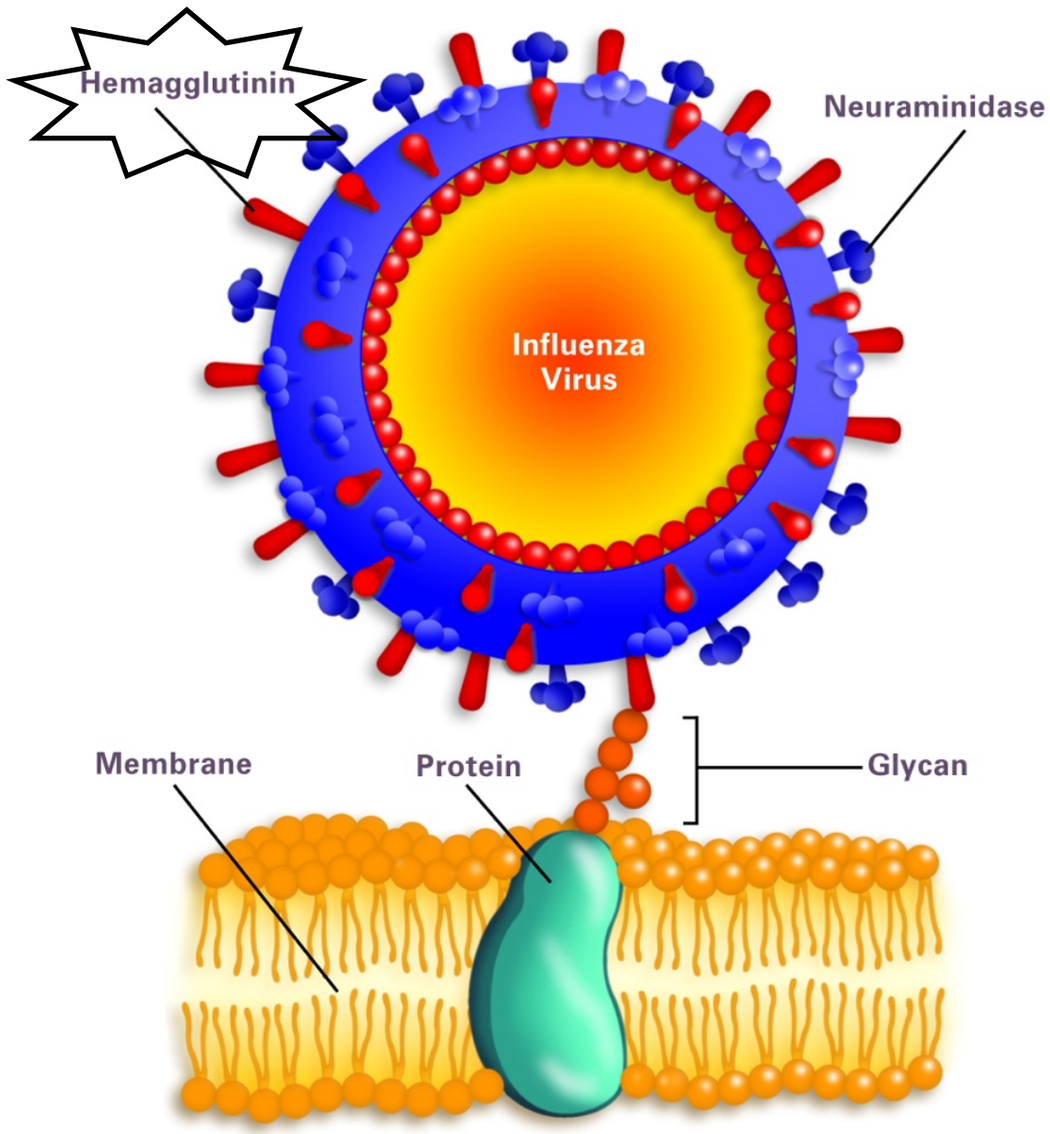
Influenza incidence time series in the Netherlands from 1970 to 2000

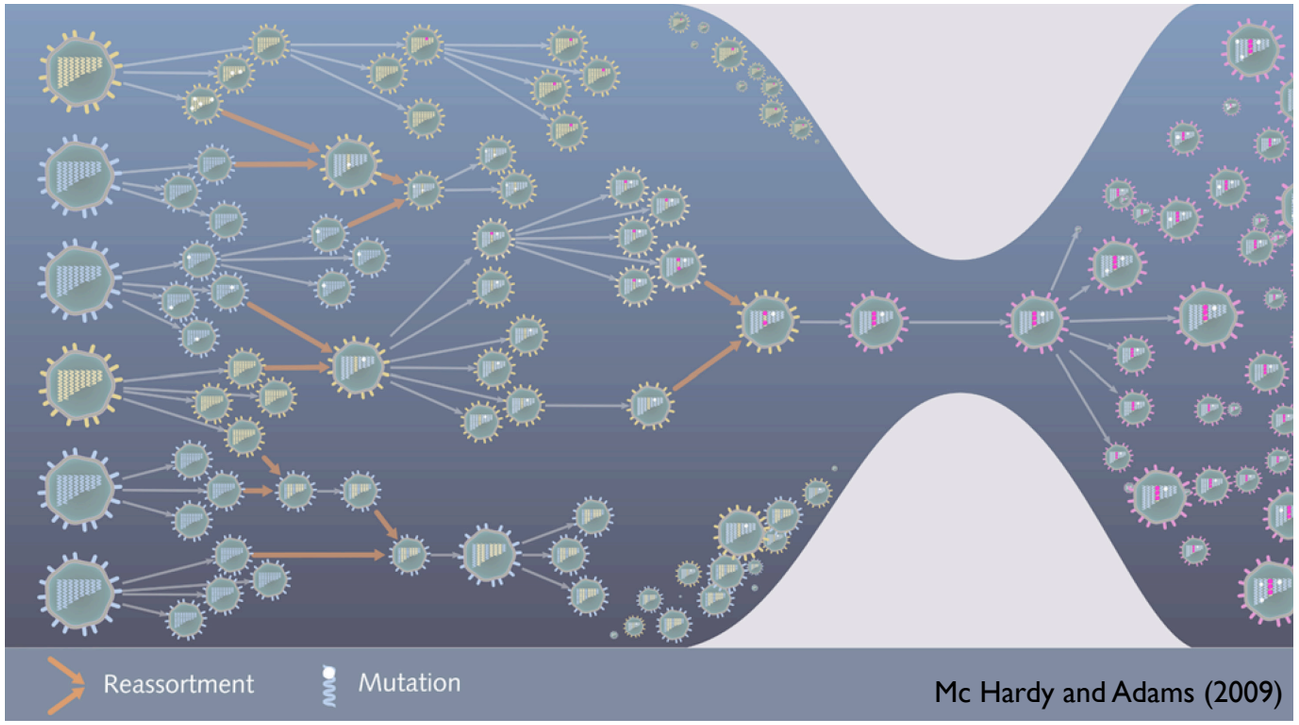
Thanks to Yingcun Xia



- One epidemic each year with variable amplitude
- Type/subtype alternate

Infection/Replication/Selection

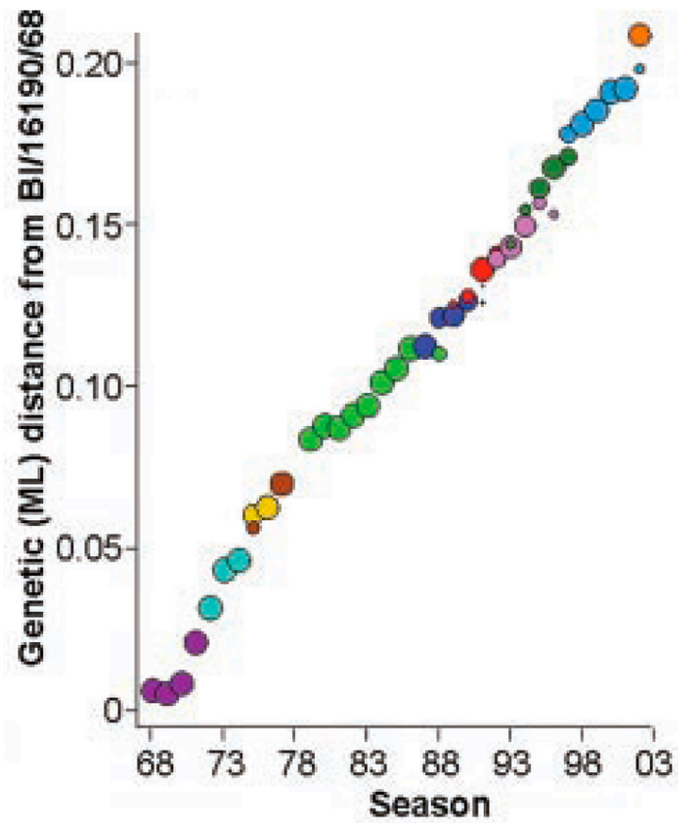




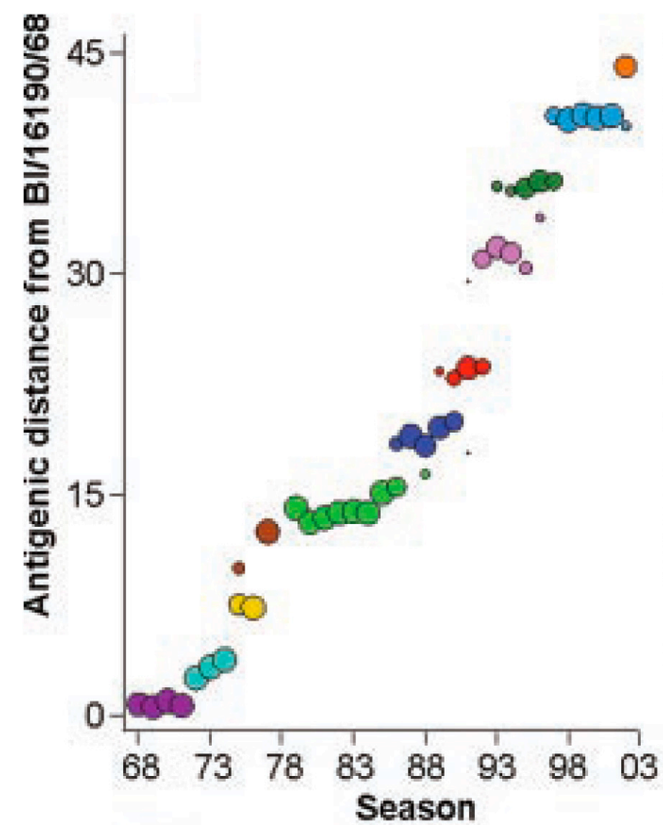
High selective pressure on hemagglutinin (HA) to escape immune recognition

Epochal evolution of A/H3N2's HA

Genetic evolution

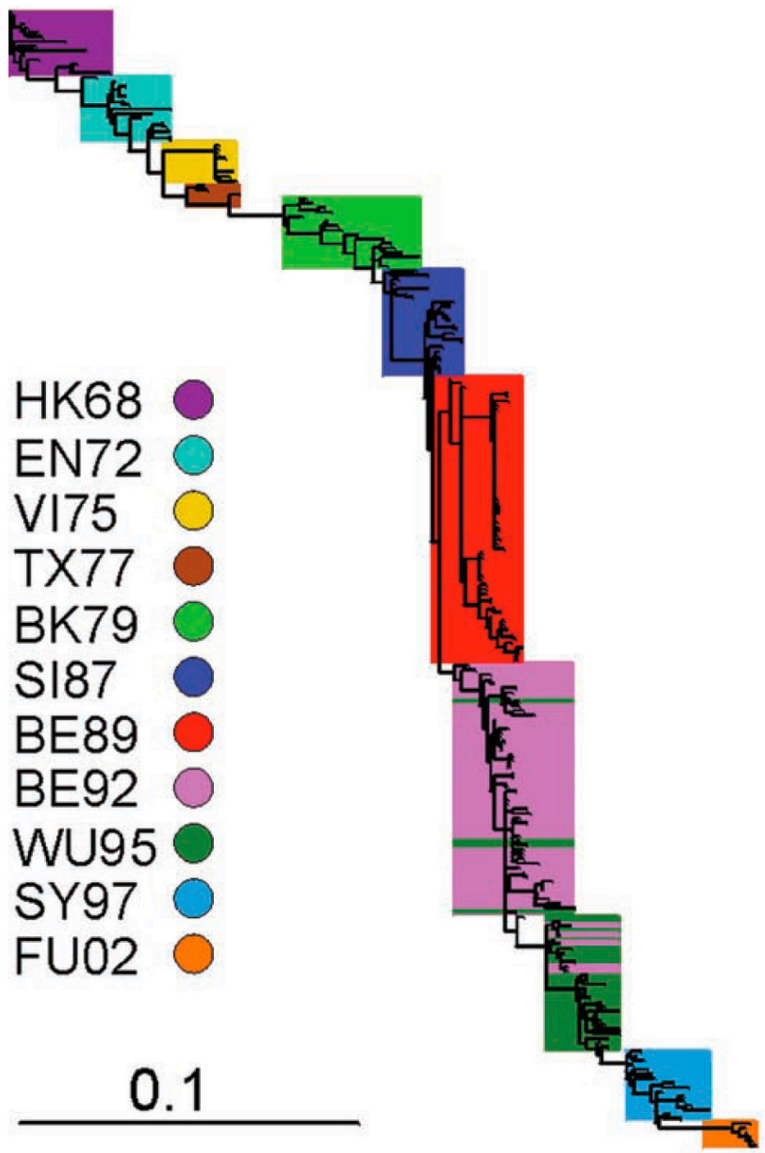


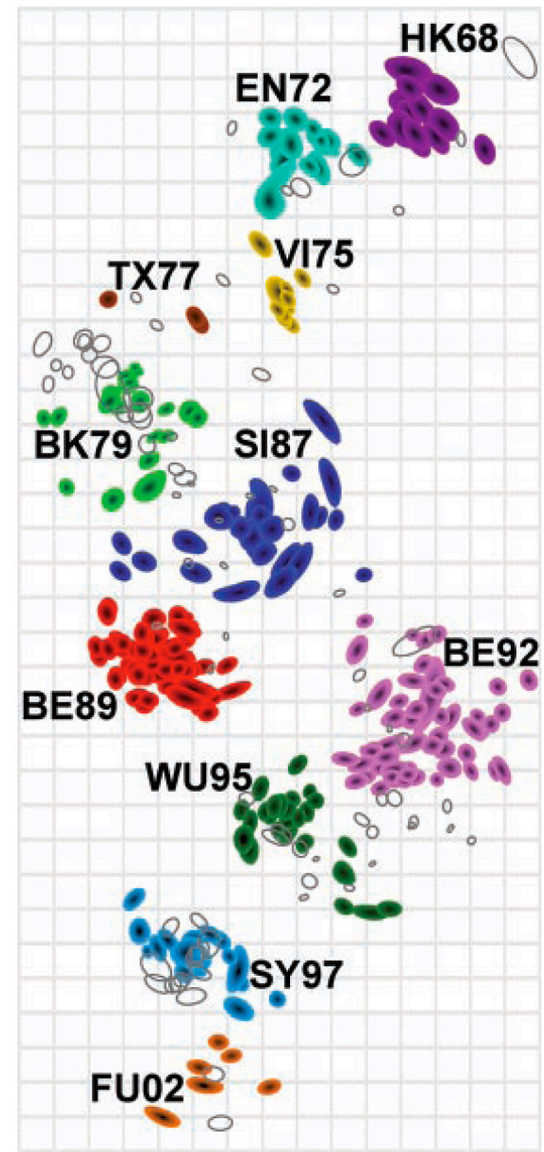
Antigenic evolution



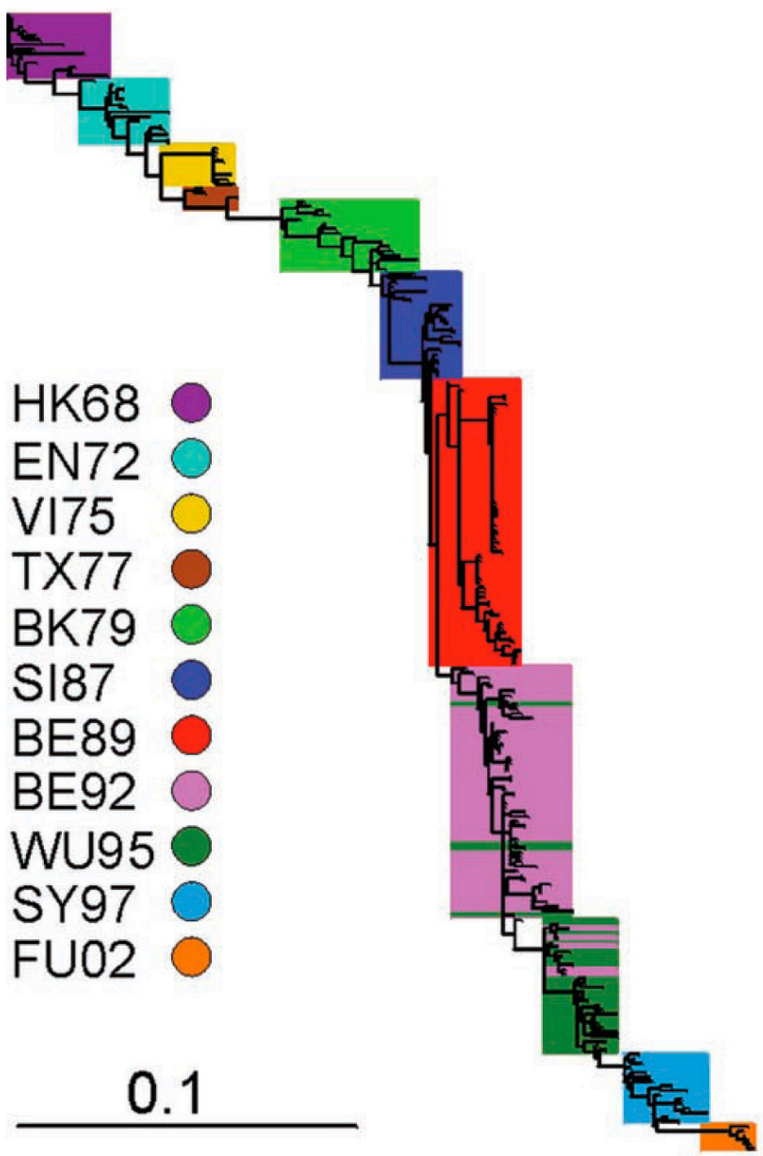
Gradual genetic evolution
but punctuated antigenic evolution (Smith et al. 2004)

Antigenic clusters replace one another



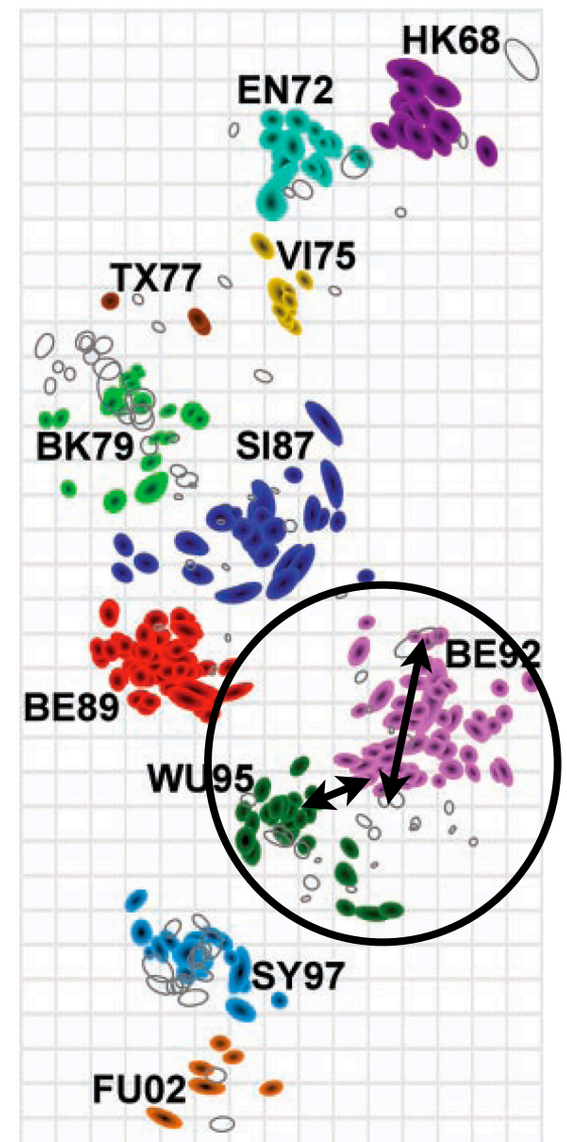


Antigenic clusters replace one another



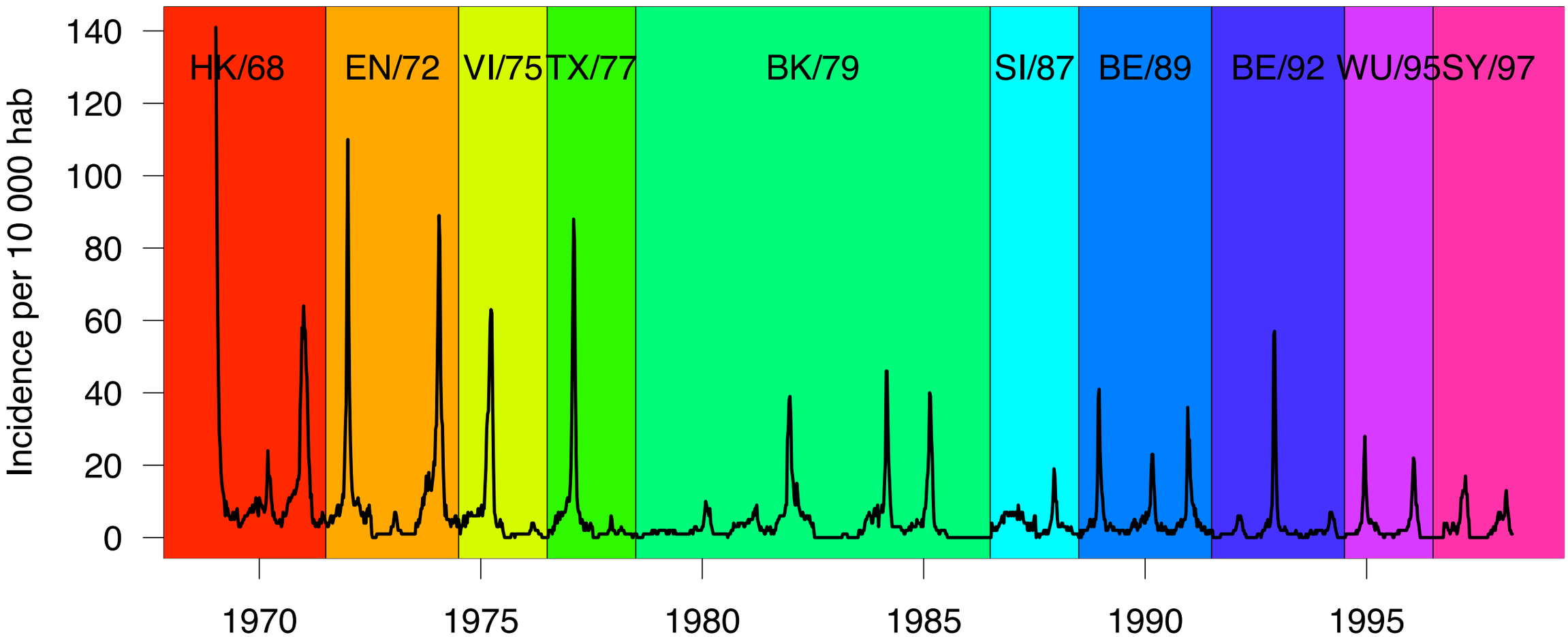
Positive selection has been ongoing most of the time (Shih et al. 2007)

"Antigenic change accumulates most of the time with occasional large changes"



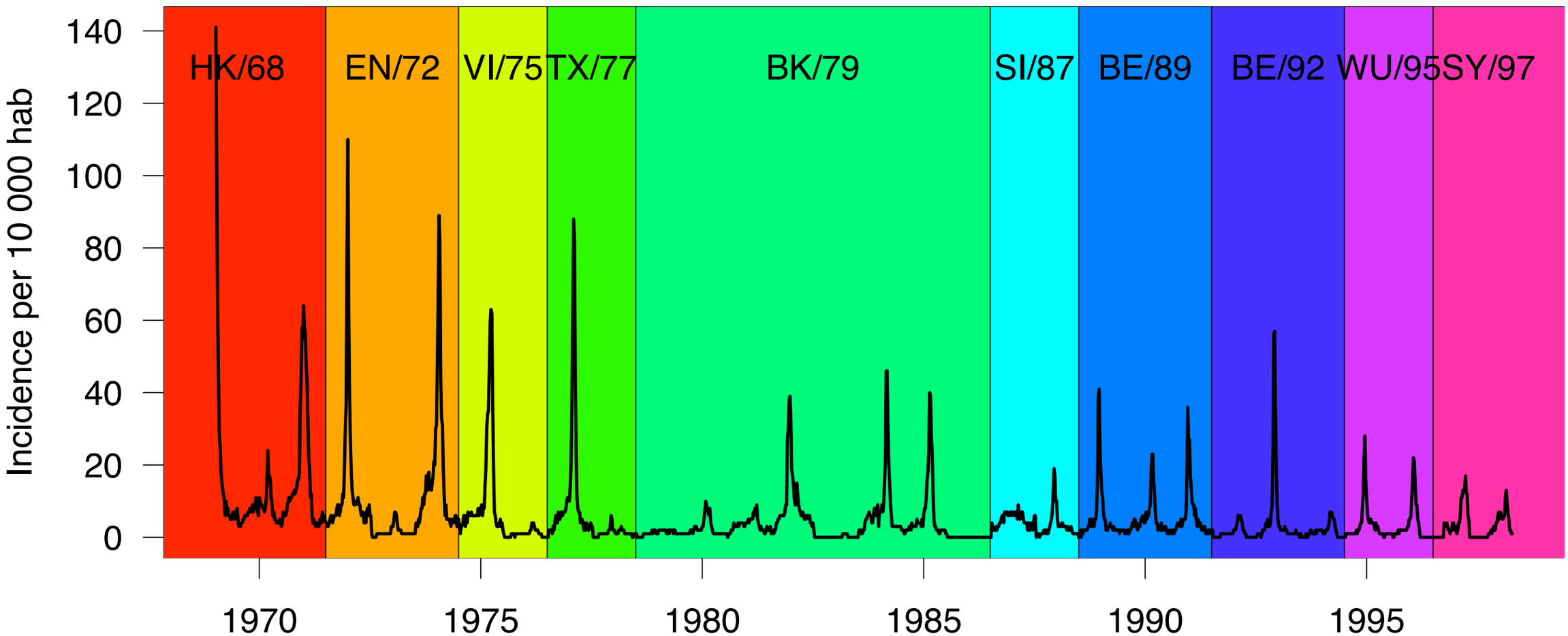
Implication for vaccination strategies

A/H3N2 time series



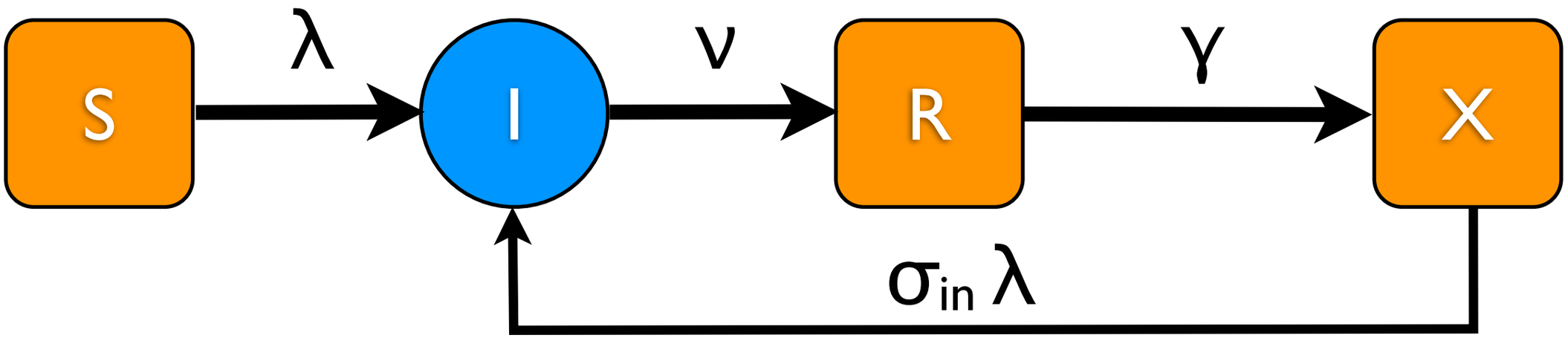
- High epidemics correlate with cluster transitions (at least at the beginning) and are followed by refractory periods
- High epidemics occur also between two transitions
- Epidemic sizes (seem to) disminish with time

A/H3N2 time series



- Can we reproduce these patterns with a simple model including both gradual and punctual antigenic drift?
- Can we assess the relative importance of gradual/punctual antigenic drift by fitting this time series?

The SIRX model: 1 cluster



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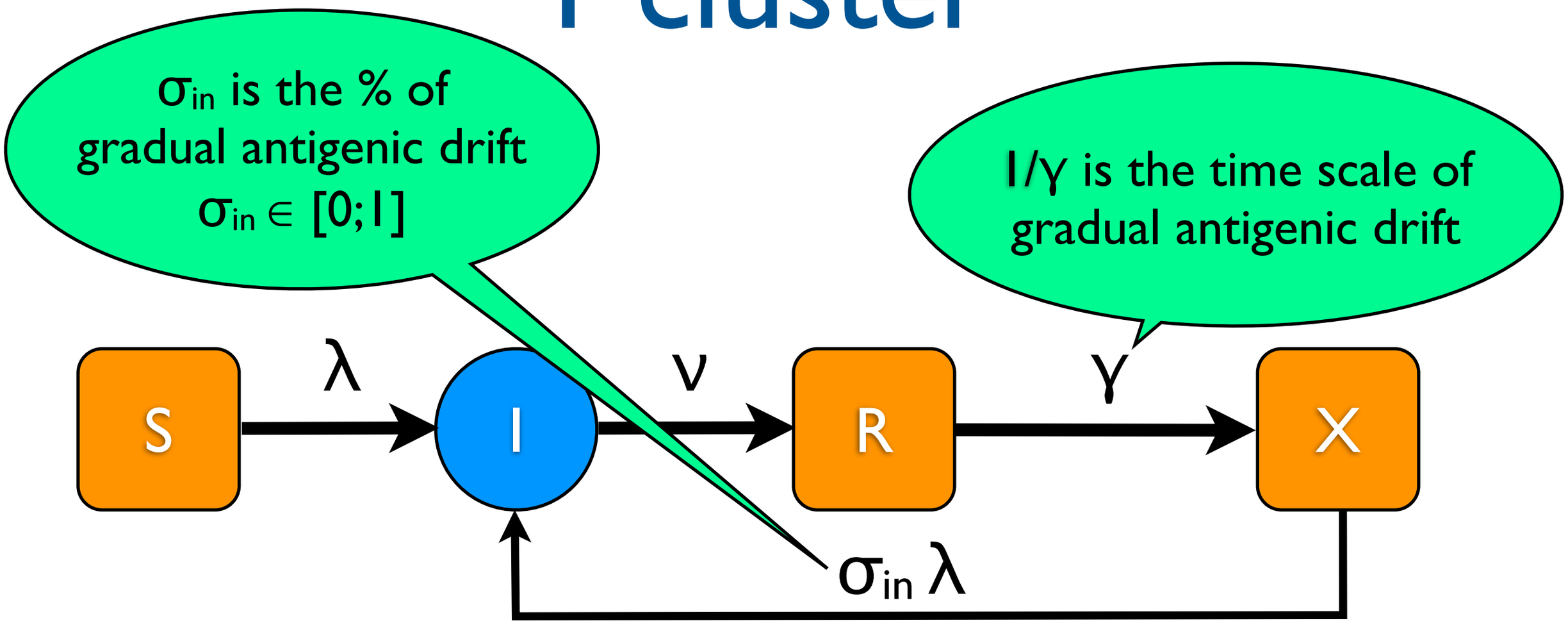

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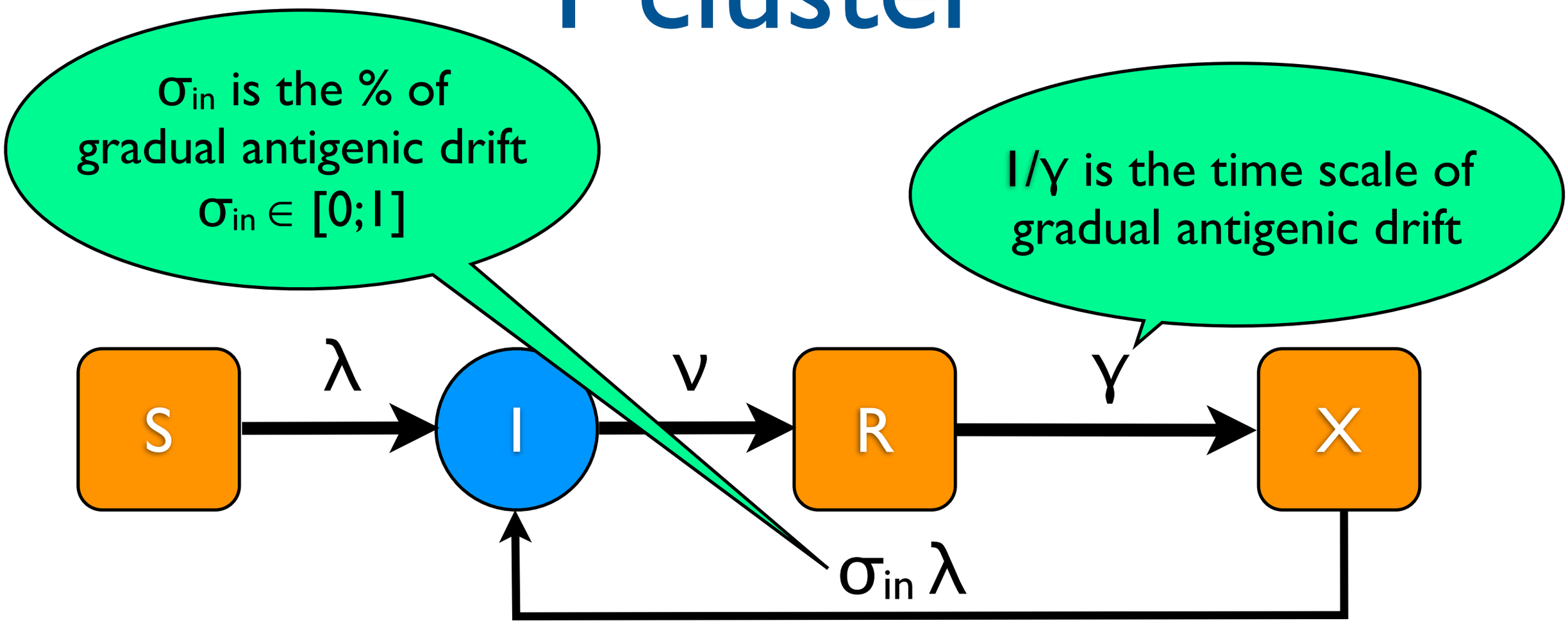
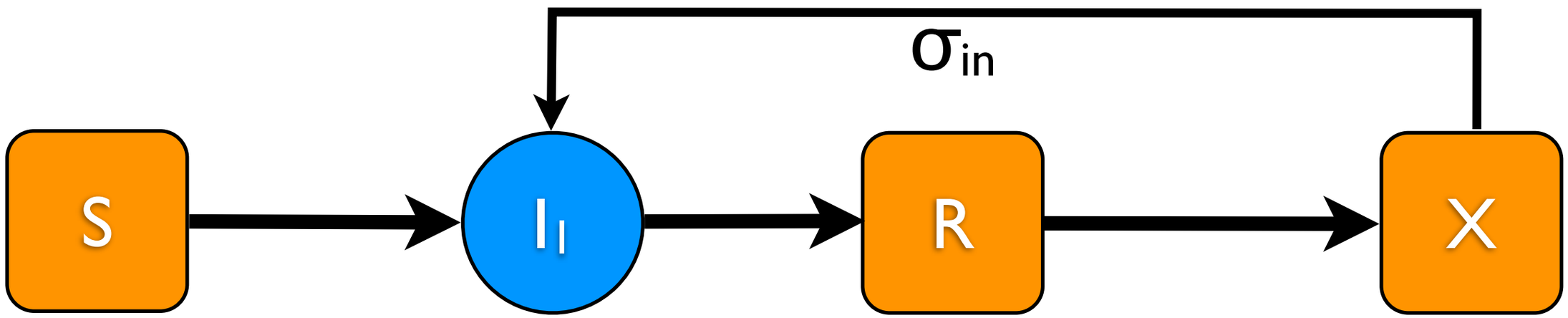


The SIRX model: 2 clusters



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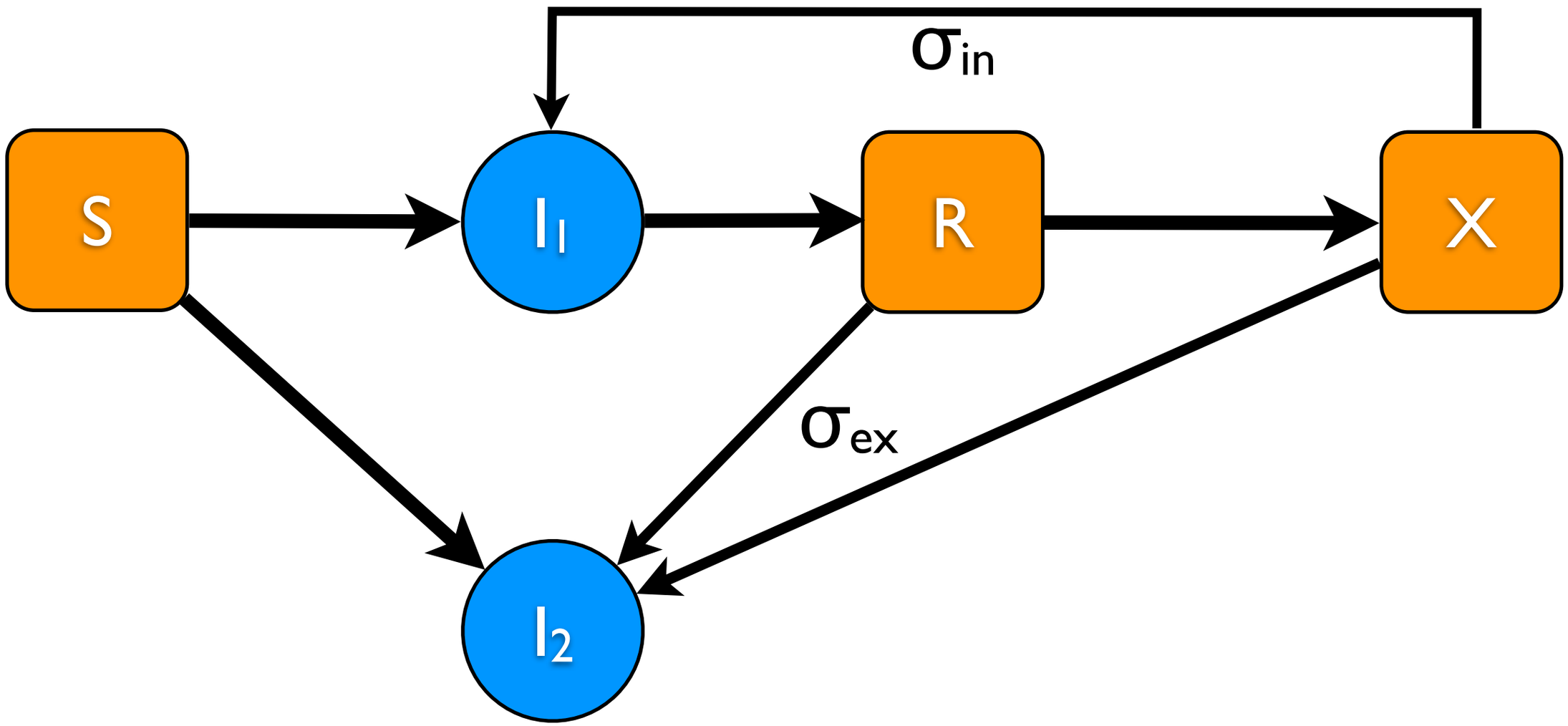

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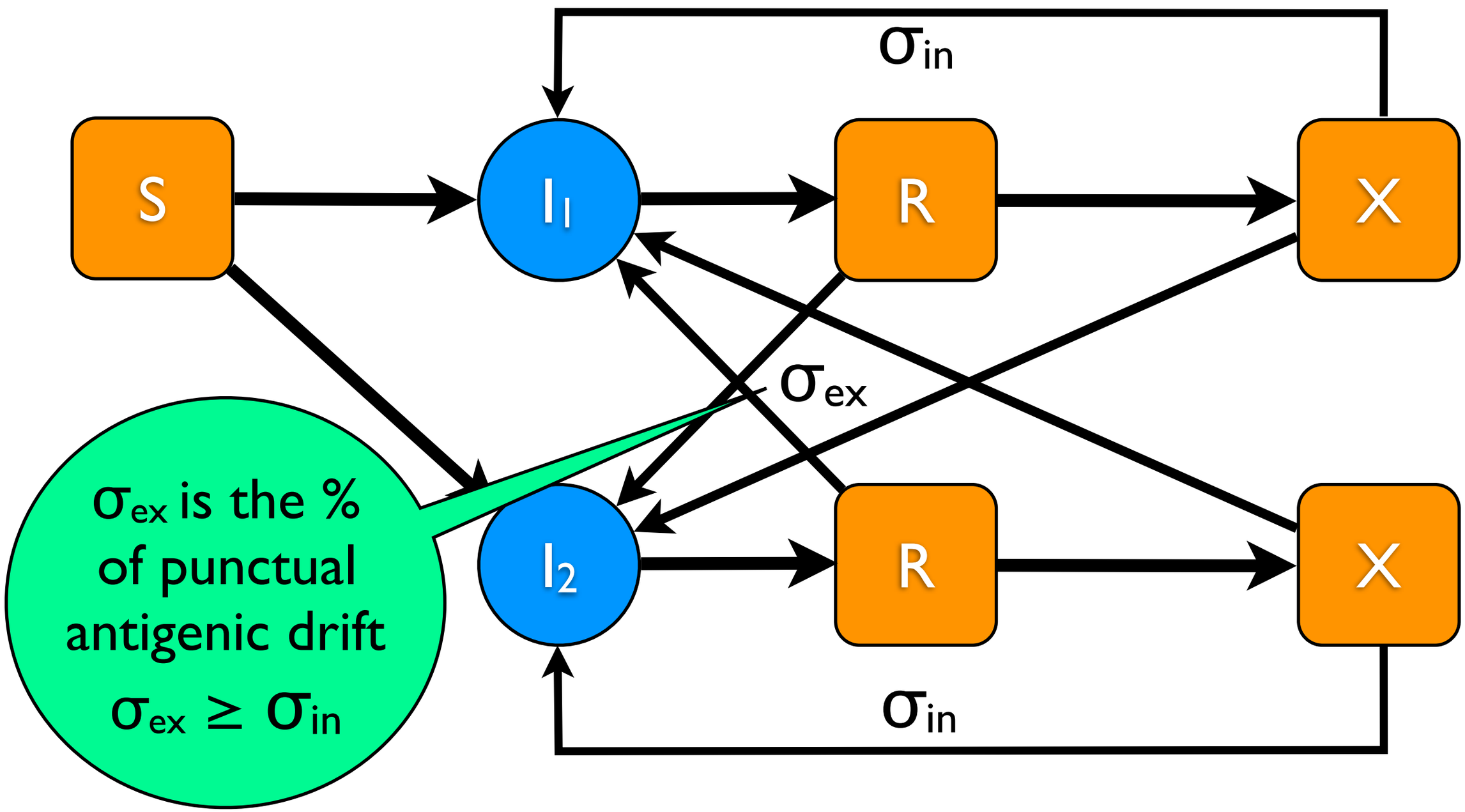
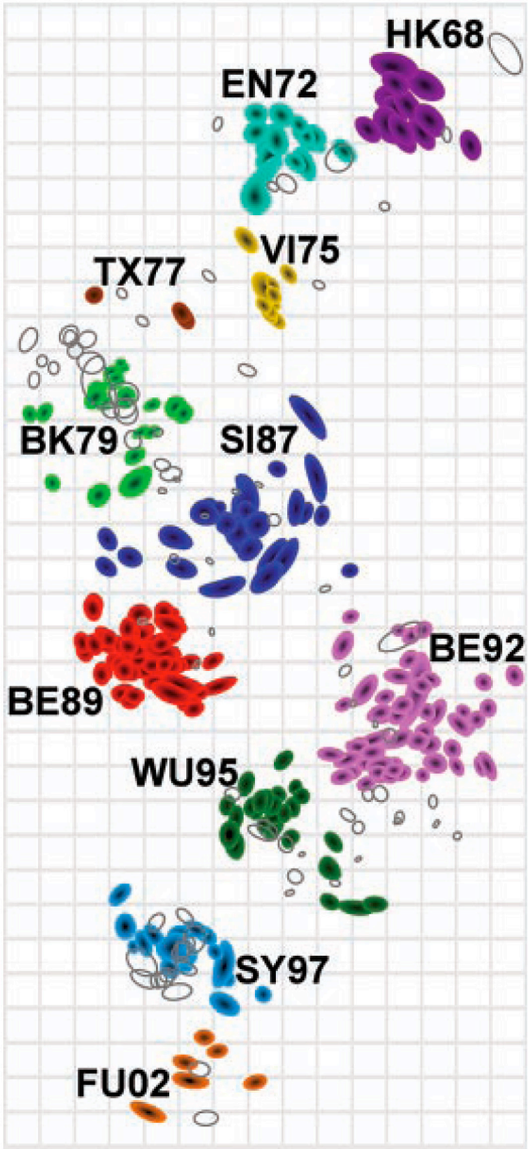


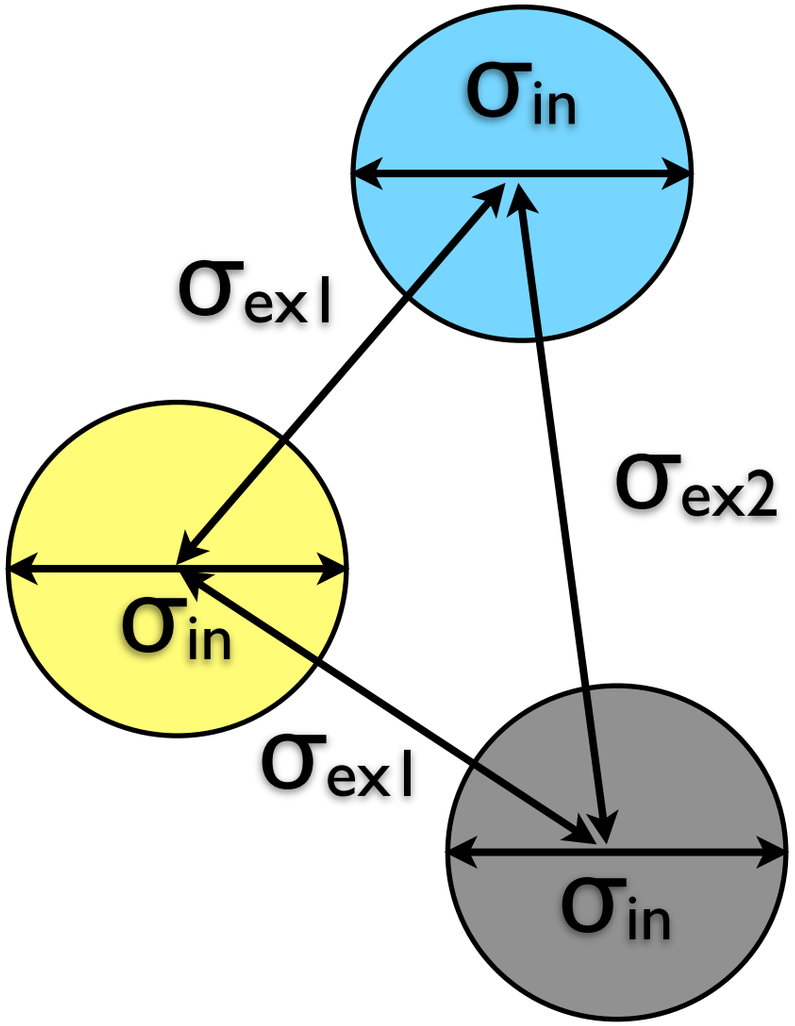
The SIRX model: N clusters

- History based model with two levels of immunity (intra & extra cluster) $\Rightarrow O(N3^N)$ for complexity (in practice $N < 10$)
- Stochastic framework via Euler multinomial scheme ($\delta t = 6$ hrs)
- With or without coinfection
- Circulating clusters give rise to new ones according to a Weibull hazard function (Koelle et al. 2010)
- Extra-cluster cross-immunity between i & j:
  $C_{ij} = f(K_{ij})$, K_{ij} is the kinship level between i & j
- Cross-protection conferred by an immune repertoire R against infection by a cluster i: $C_{Ri} = g(\{C_{ki}\}_{k \in R}) \Rightarrow \sigma_{Ri} = 1 - C_{Ri}$
- Cross-protection can act by: reduced susceptibility, reduced infectiosity, polarised infectiosity

Biological interpretation

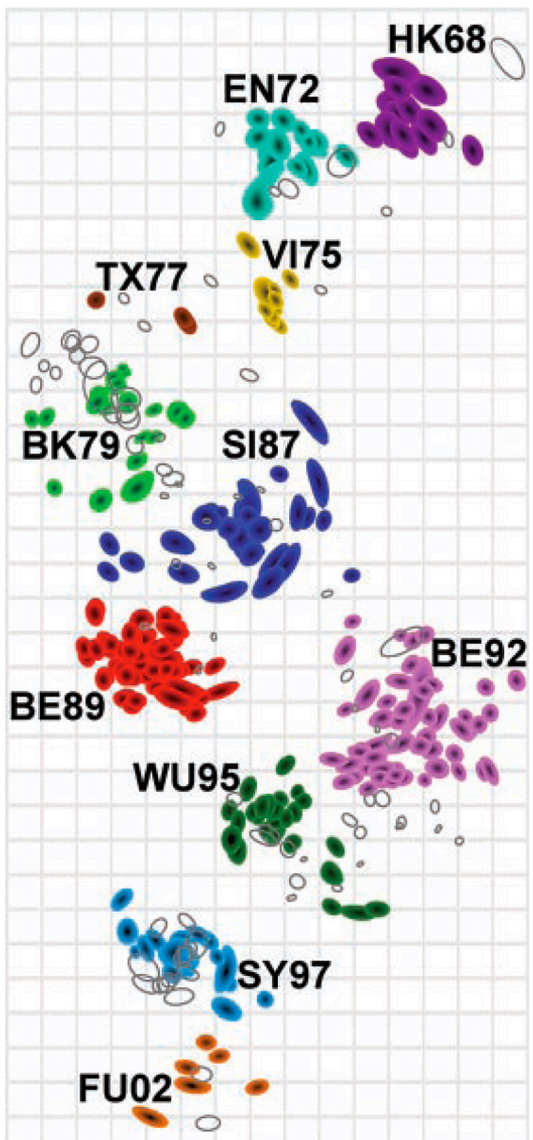
$\sigma_{in}>0$ & $\sigma_{ex}>>\sigma_{in}$ $\Longrightarrow$ gradual & punctuated antigenic drift

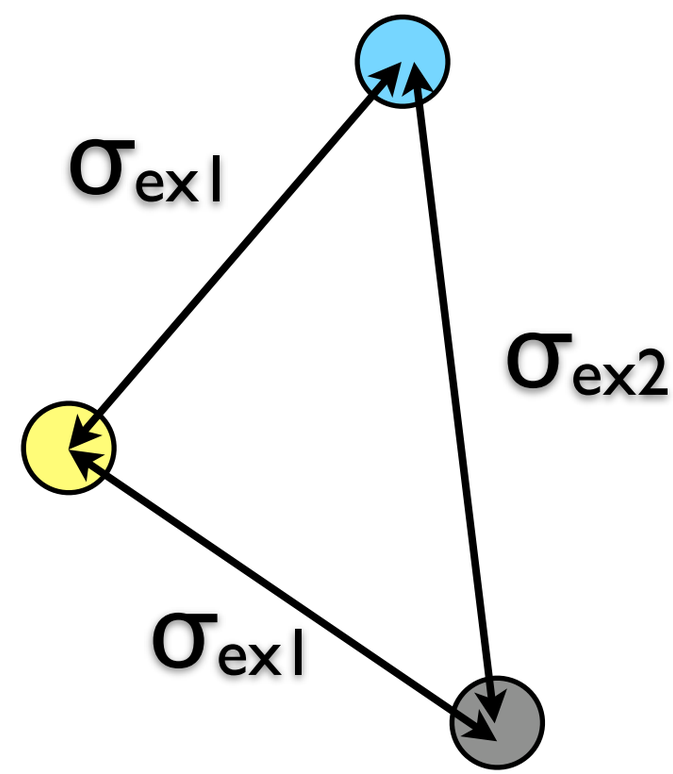




Biological interpretation

$\sigma_{in} = 0 \implies$ punctuated antigenic drift

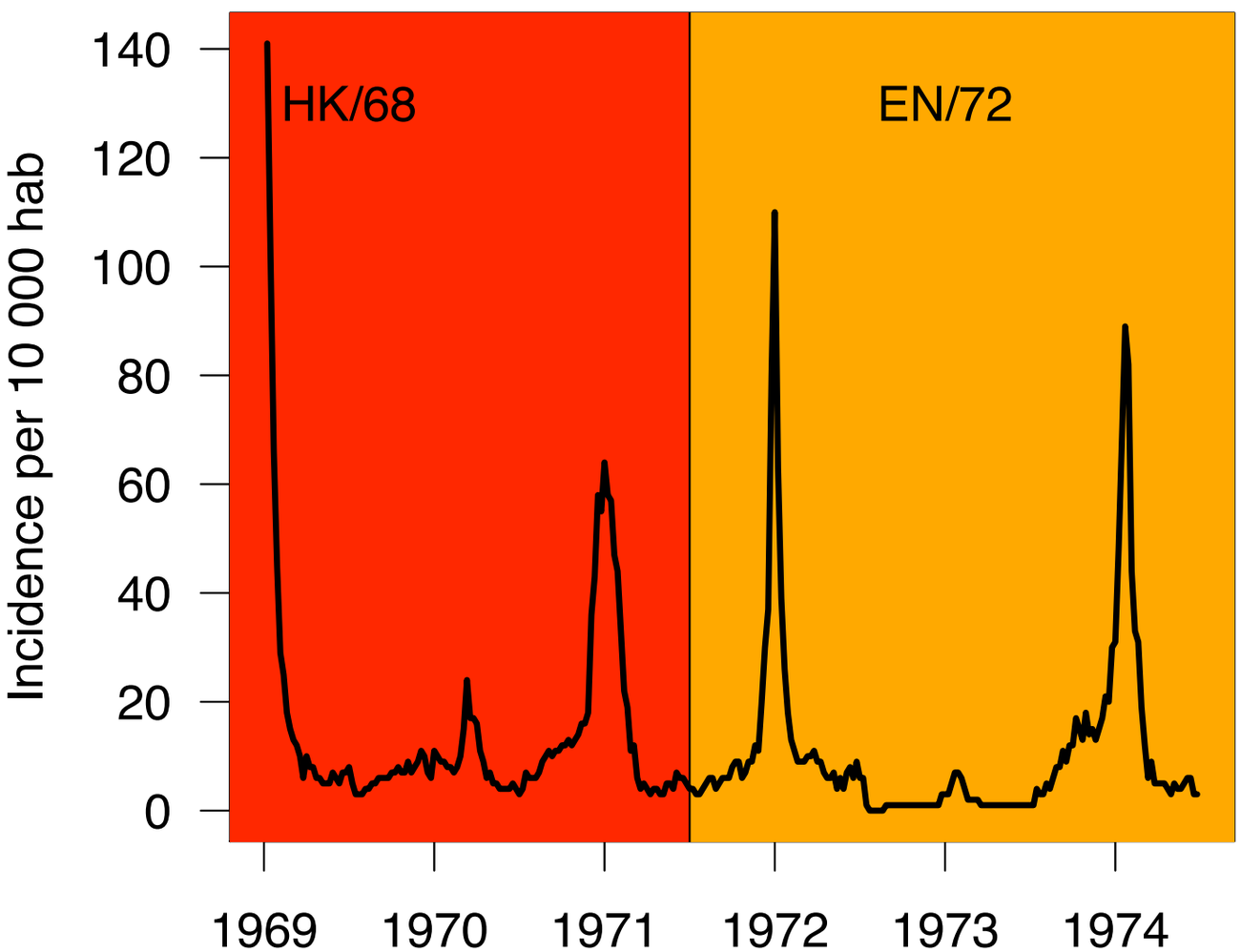




Previous works

- Koelle et al. 2006: model the genetic-antigenic map and find cluster replacement
- Gökaydin et al. 2007: SIRI limit of the SIRX model ($\gamma = 0$) and N=2. Cluster replacement occurs below the reinfection threshold ($R_0=1/\sigma_{in}$) for $\sigma_{ex}>>\sigma_{in}$ (numerical study)
- Koelle et al. 2010: SIRS limit of the SIRX model ($\sigma_{in} = 1$) within a status-based framework. Both gradual and punctuated antigenic drift are necessary to reproduce influenza time-series (not fitted)

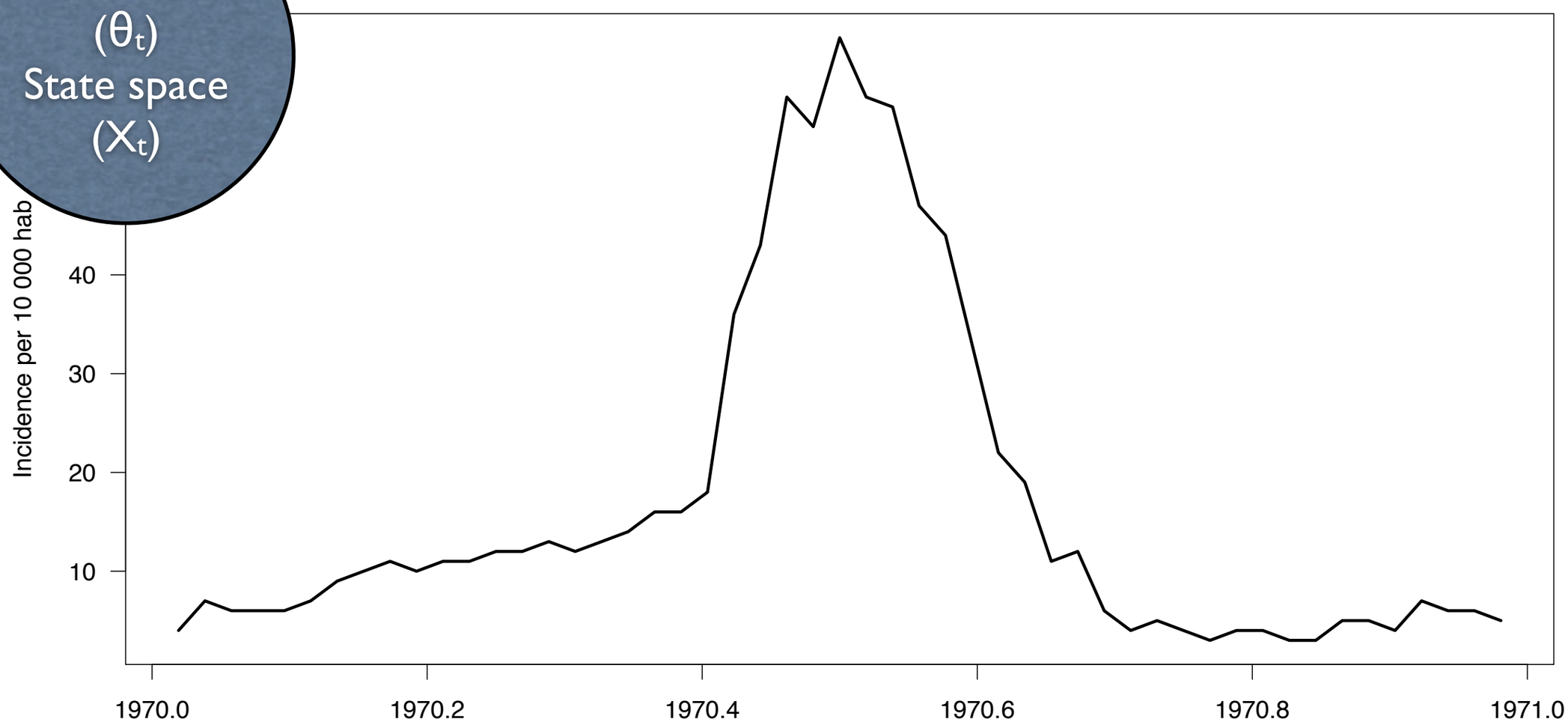
Preliminary study



- Replacement of HK/68 by EN/72
- Can we reproduce this non-trivial dynamics?
- Fit the SIRX model with N=2 clusters, protection acts by reducing susceptibility
- Seasonal forcing: simple sinusoidal
- Simplification: the second cluster is introduced in october 1972 by 1 individual

Maximum likelihood via Iterated Filtering (Ionides 2006)

Parameters
(θ_t)
State space
(X_t)



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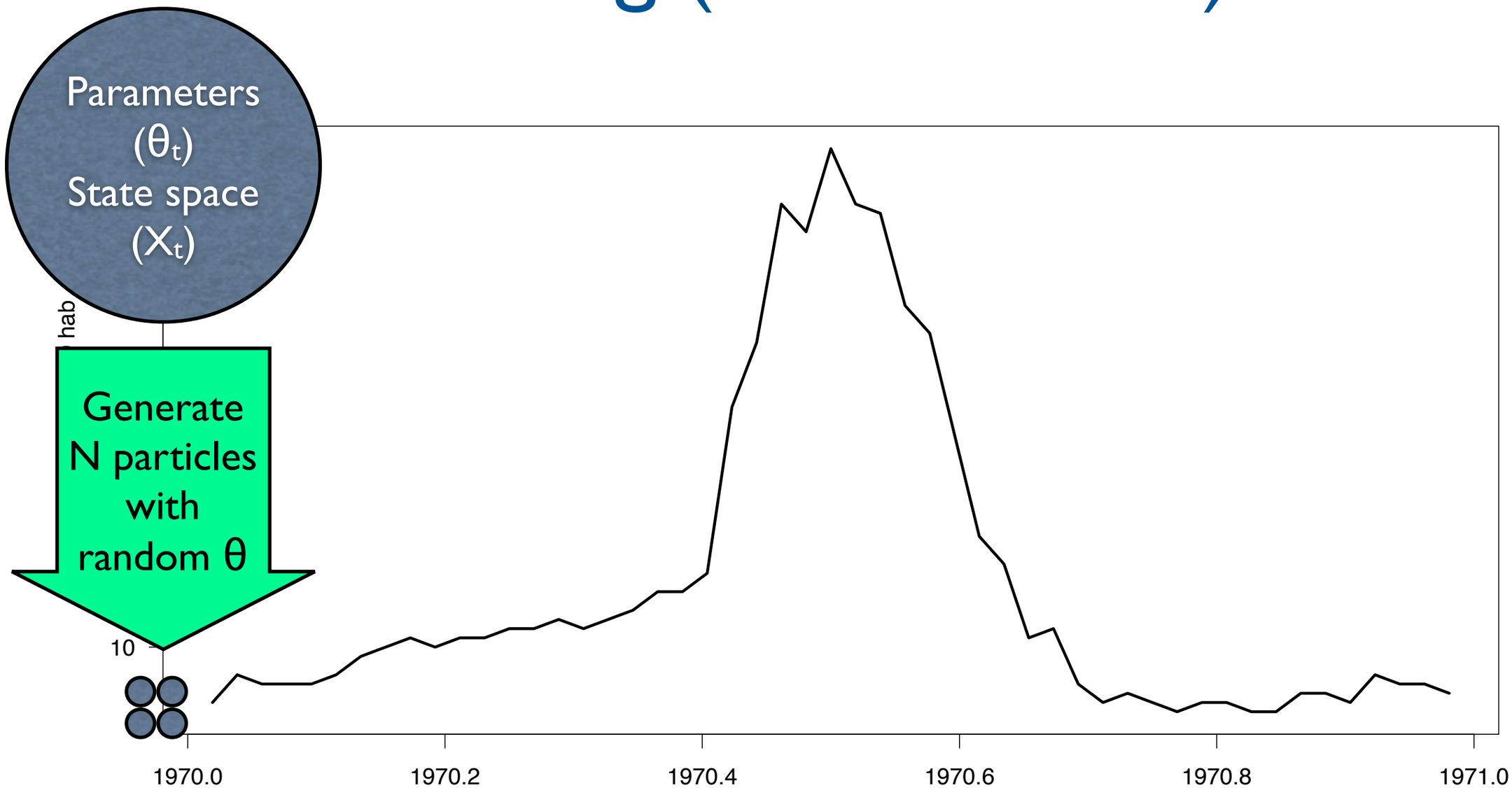

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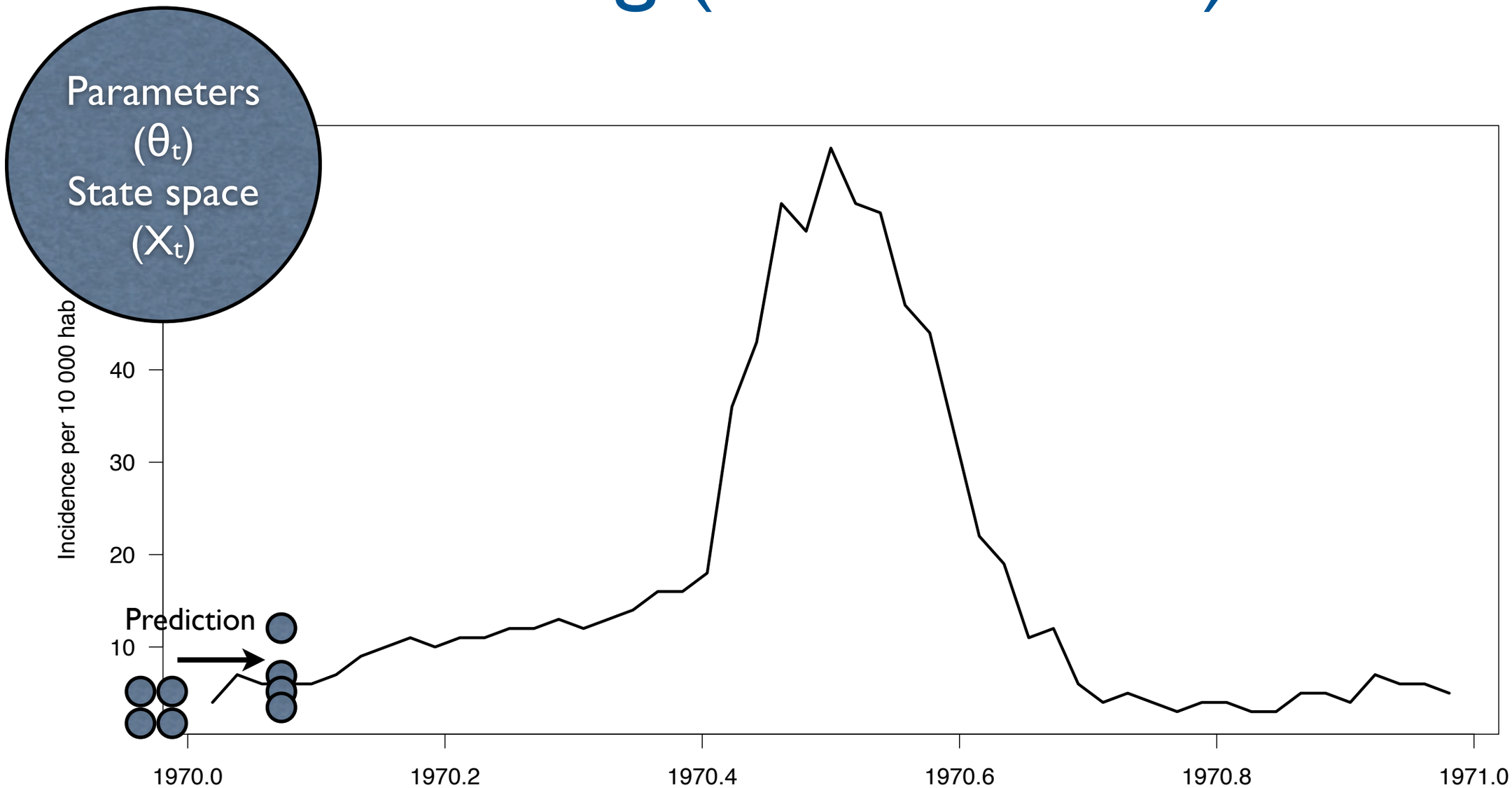

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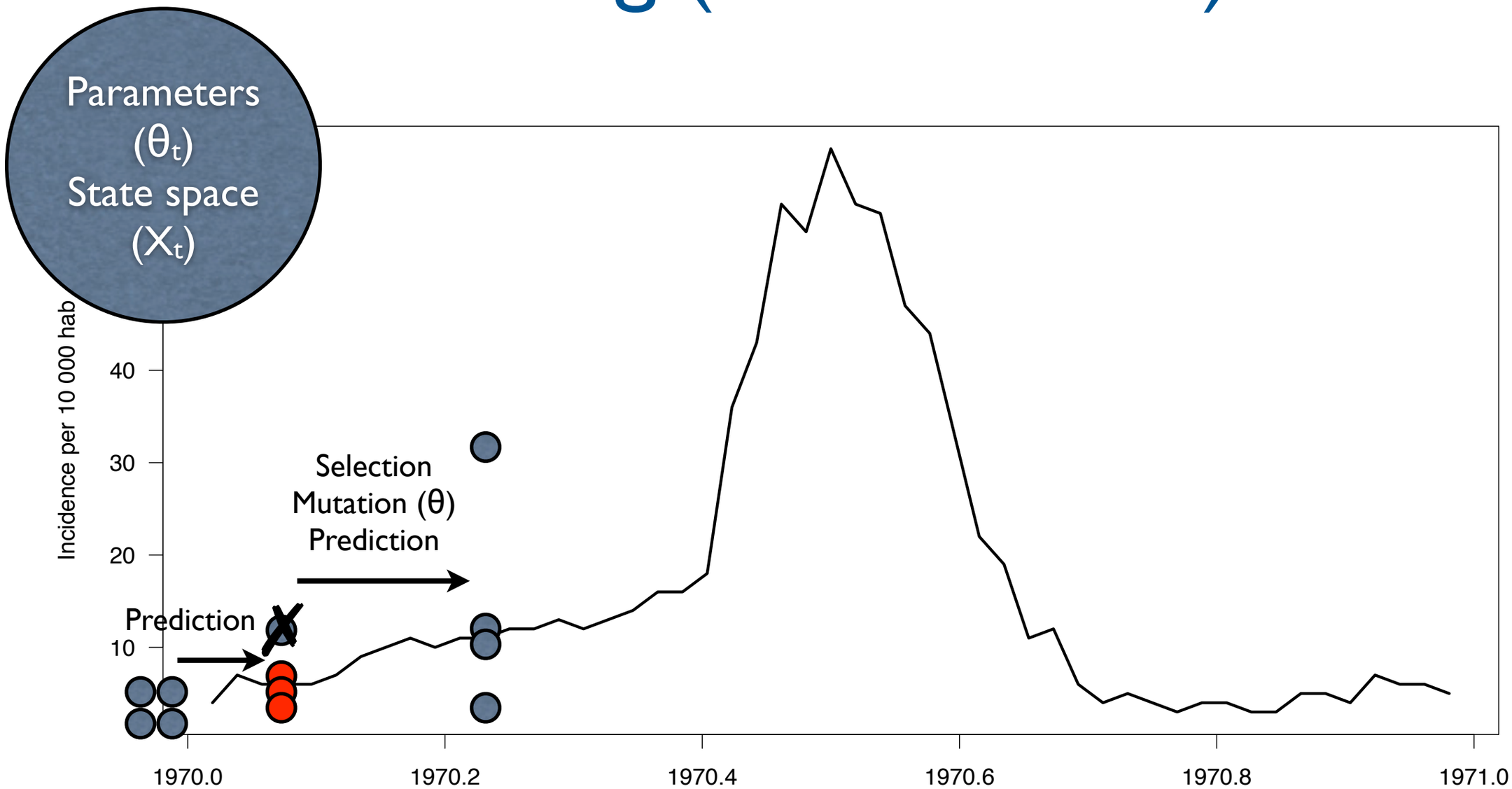

- Selection: particles reproduce proportionally to their likelihood

Prob(data | prediction) i.e. negative binomial observation process

- Mutation: $\theta_{t+1} \rightarrow N(\theta_t, m)$

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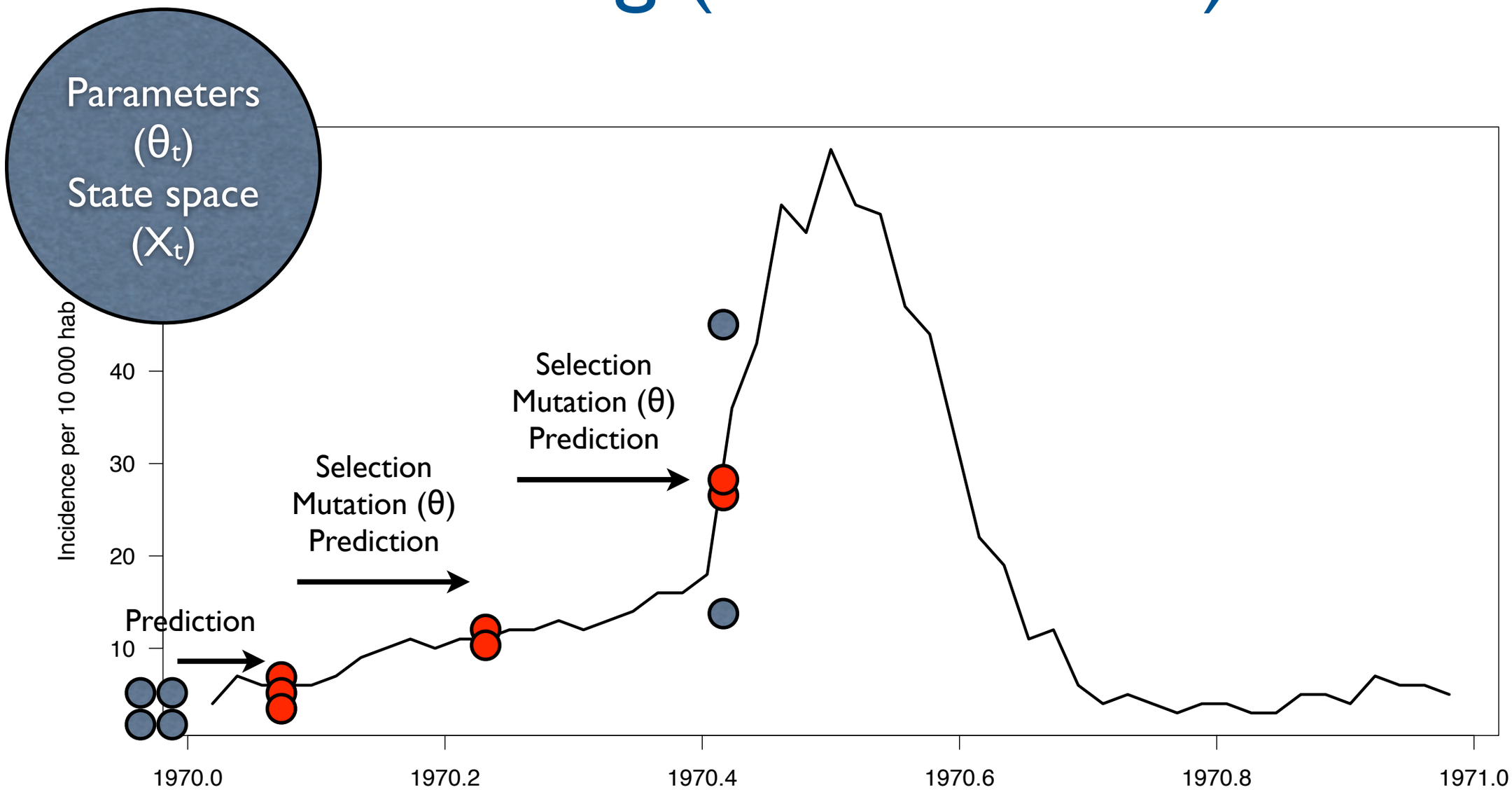

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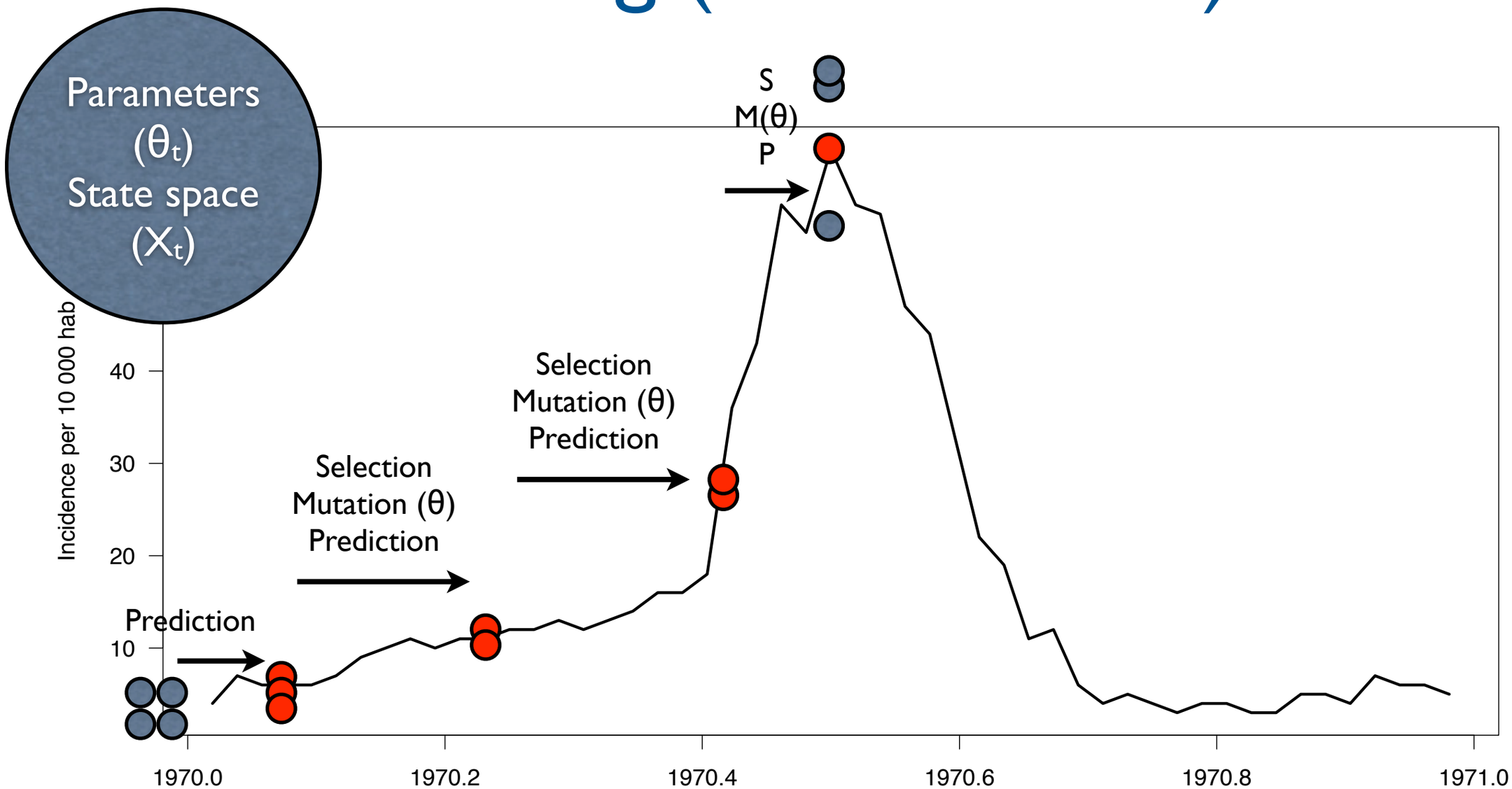

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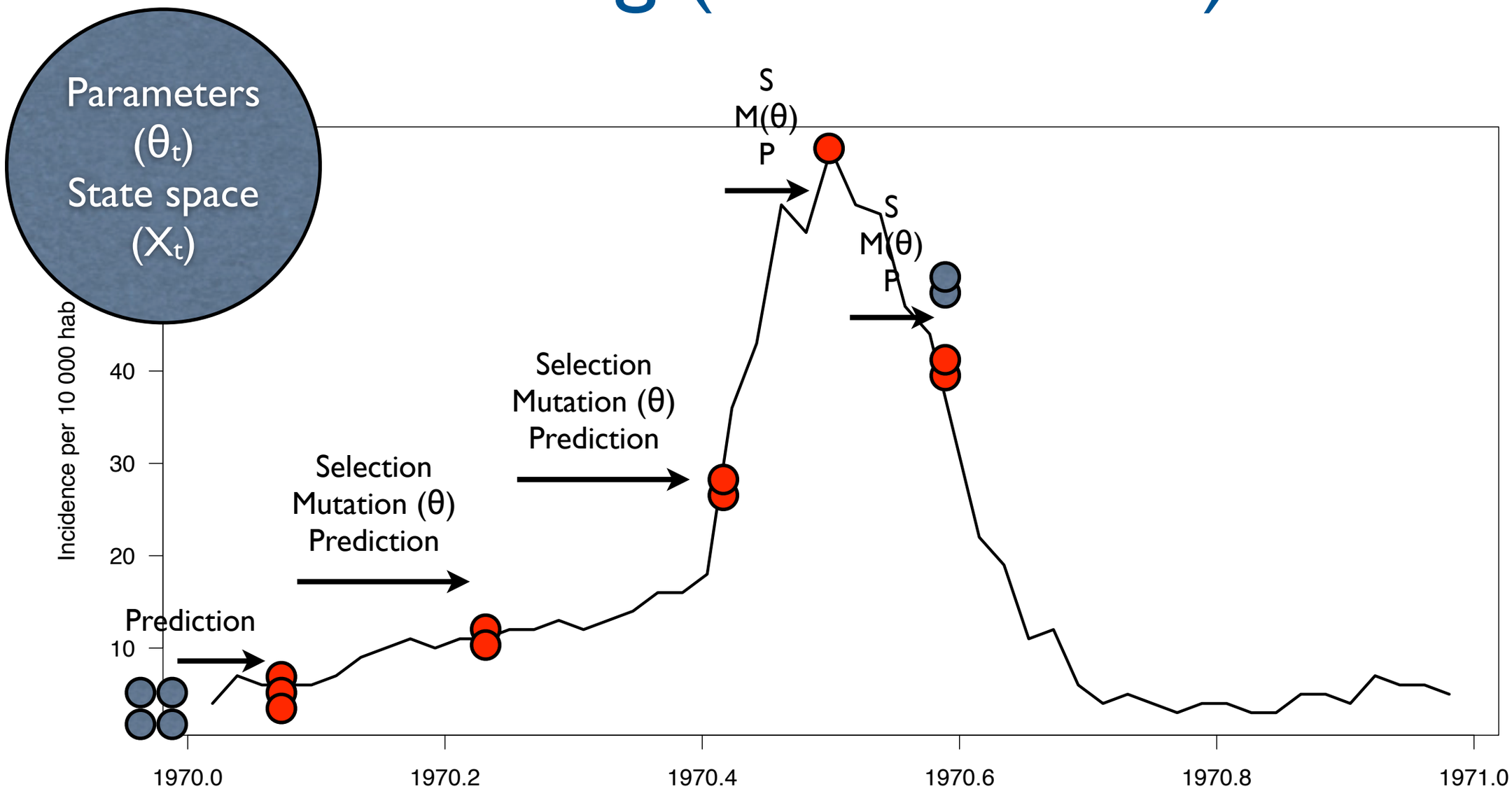

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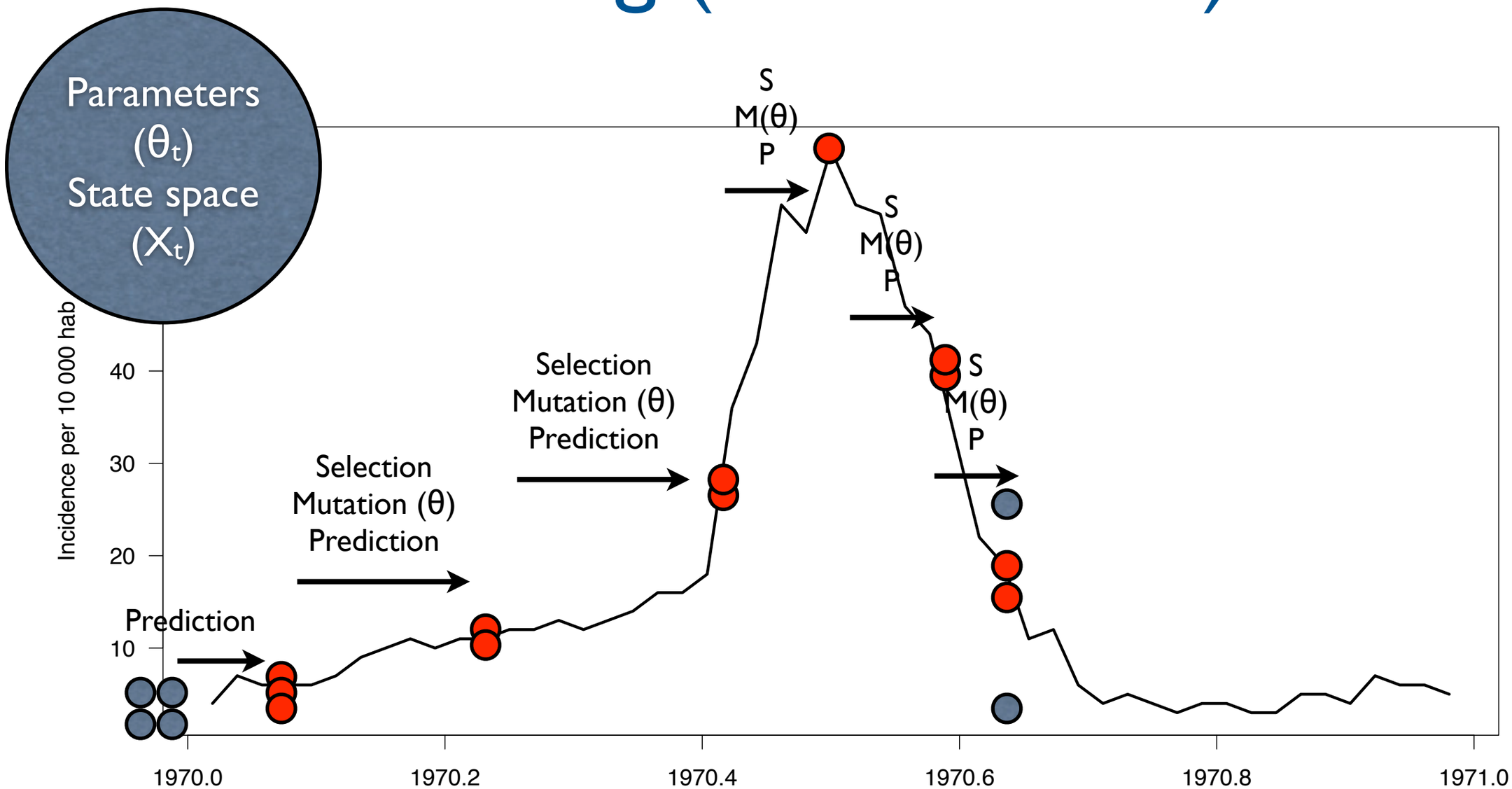

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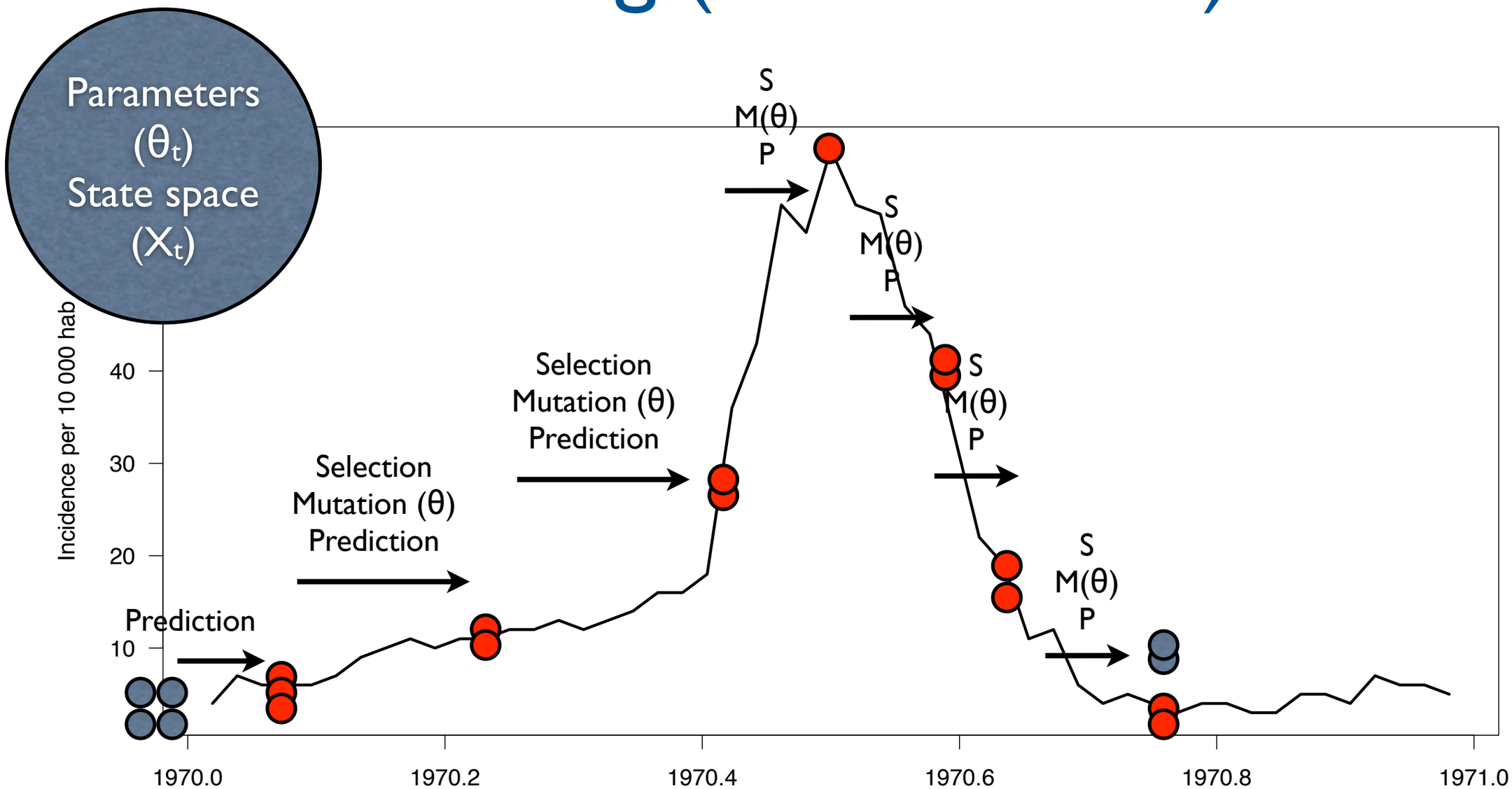

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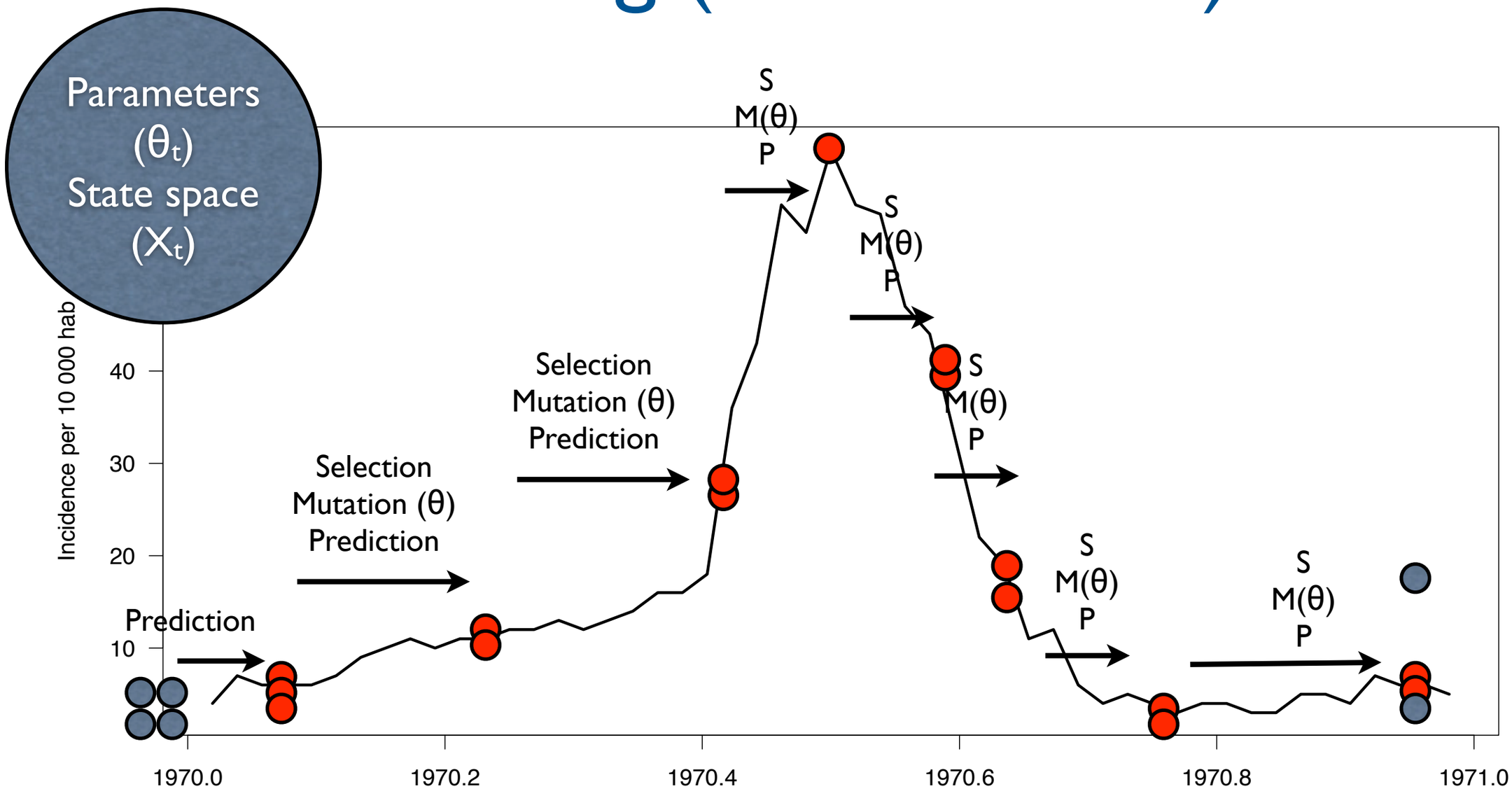

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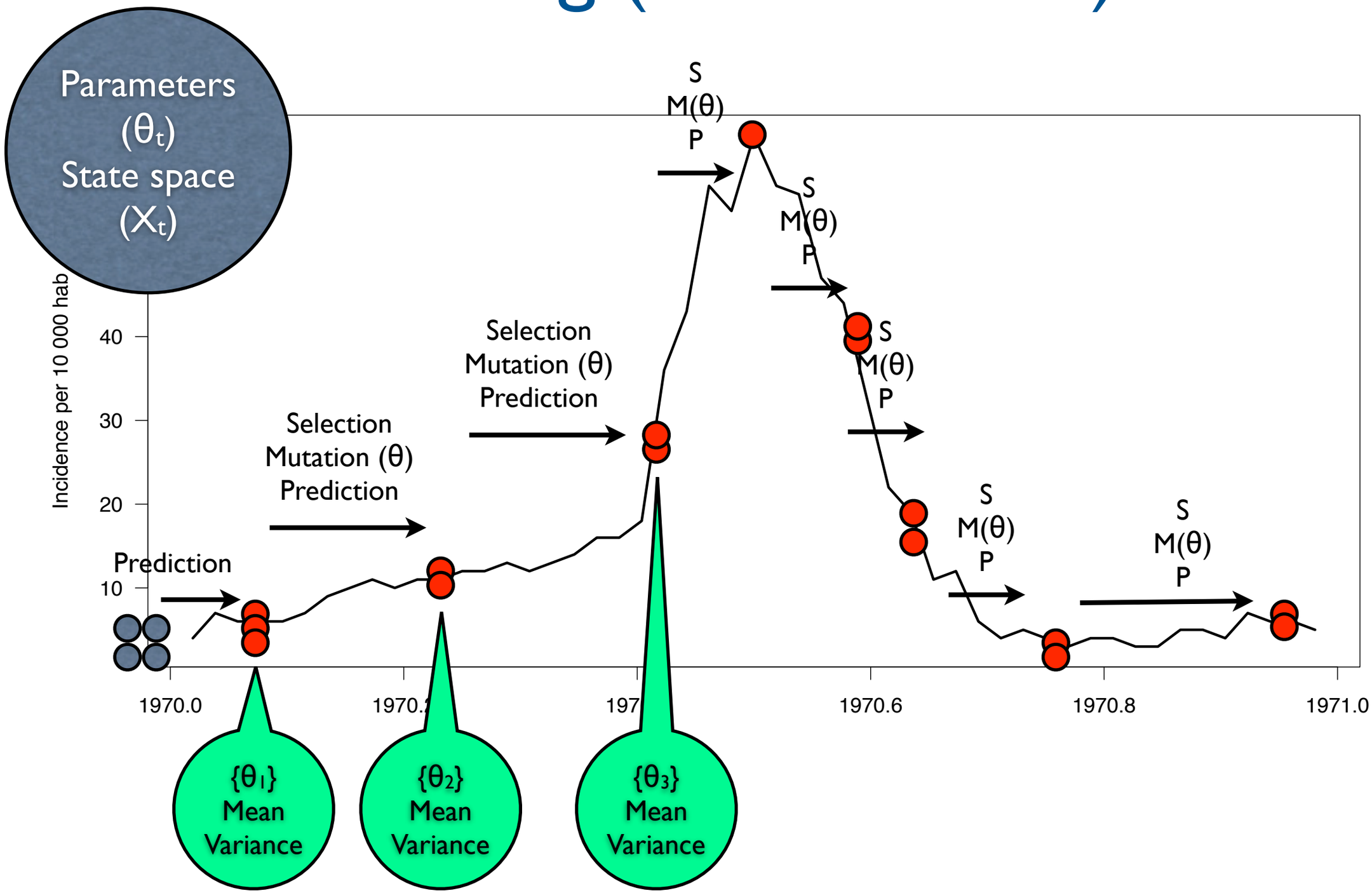

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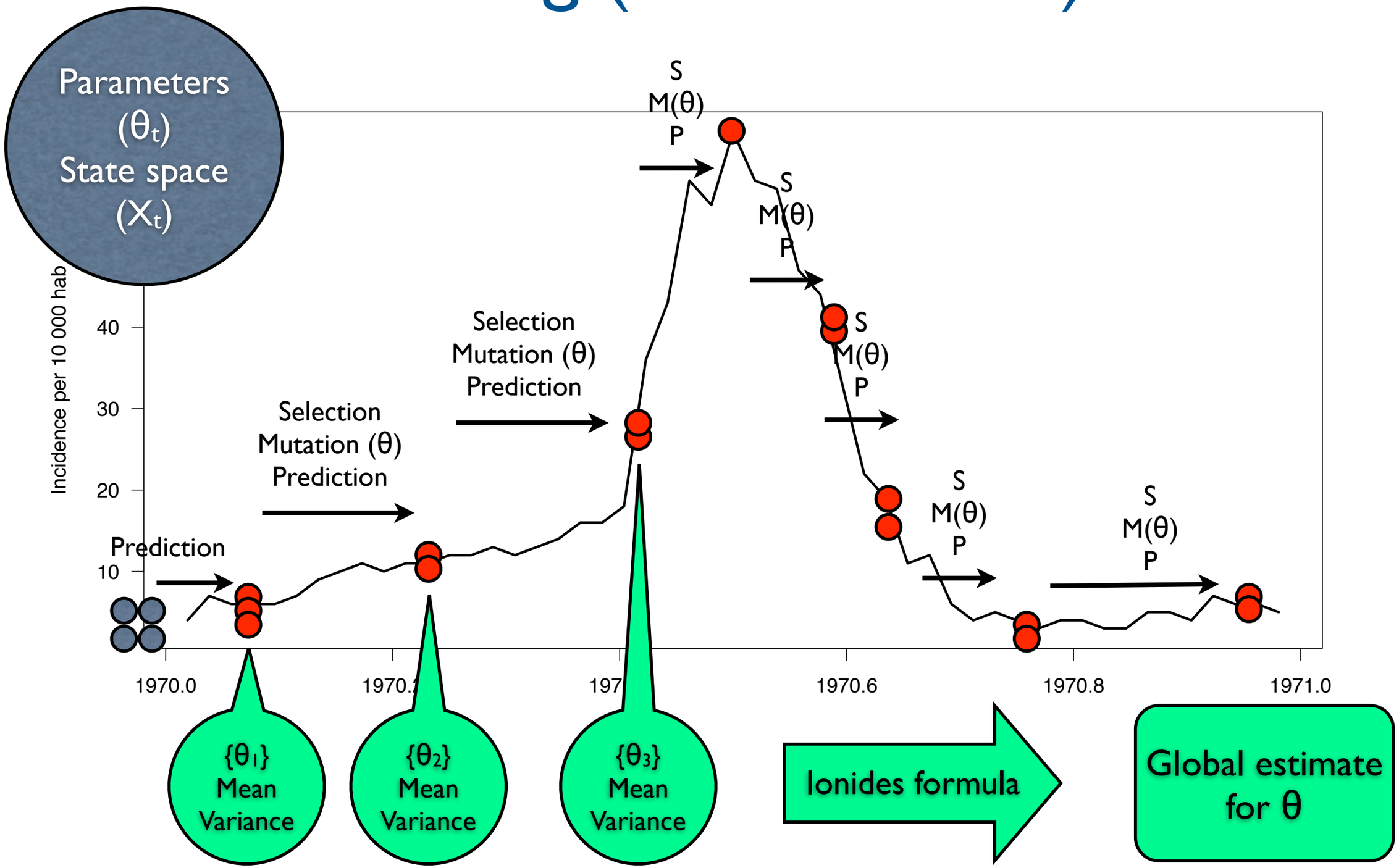

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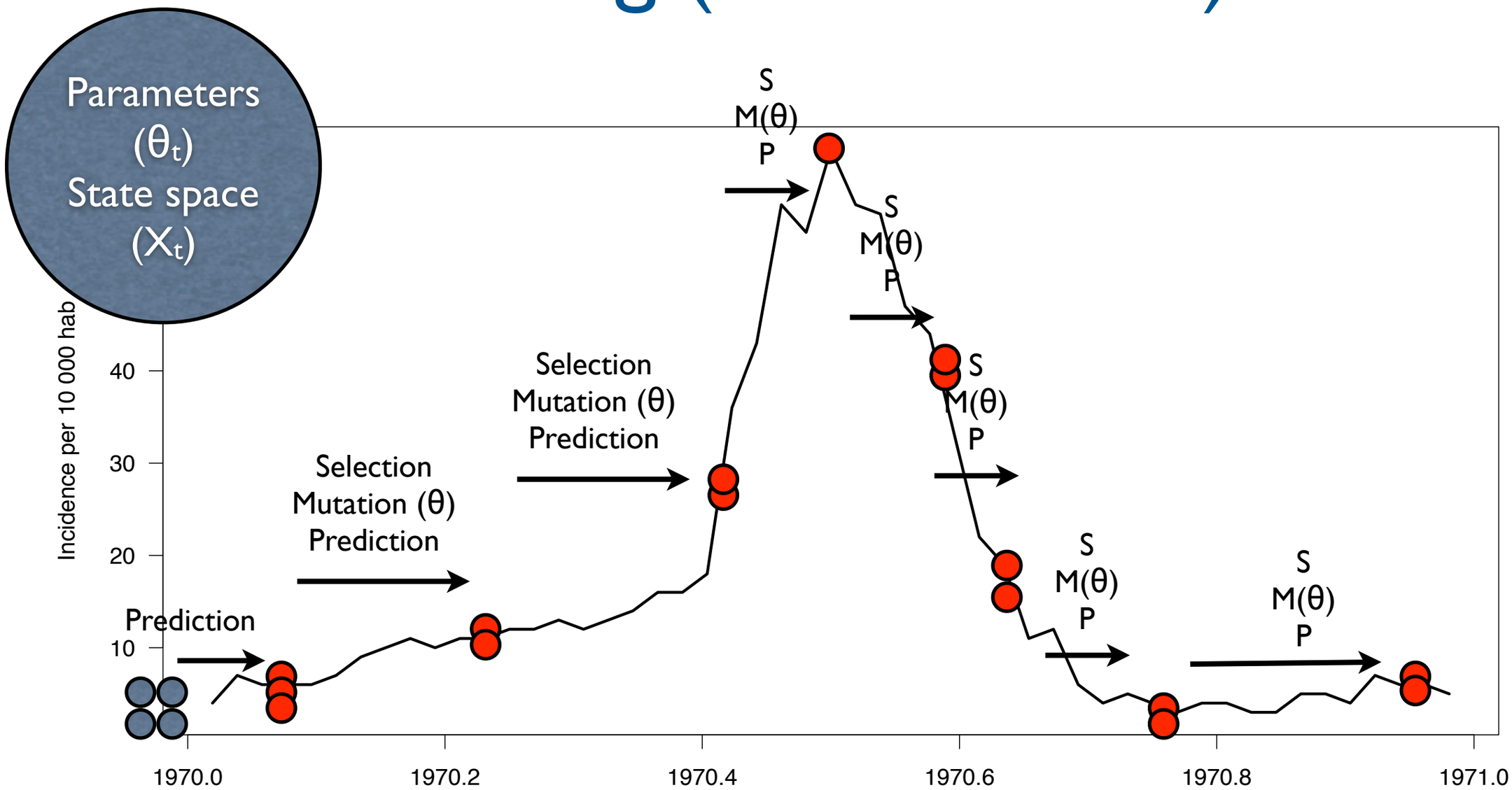
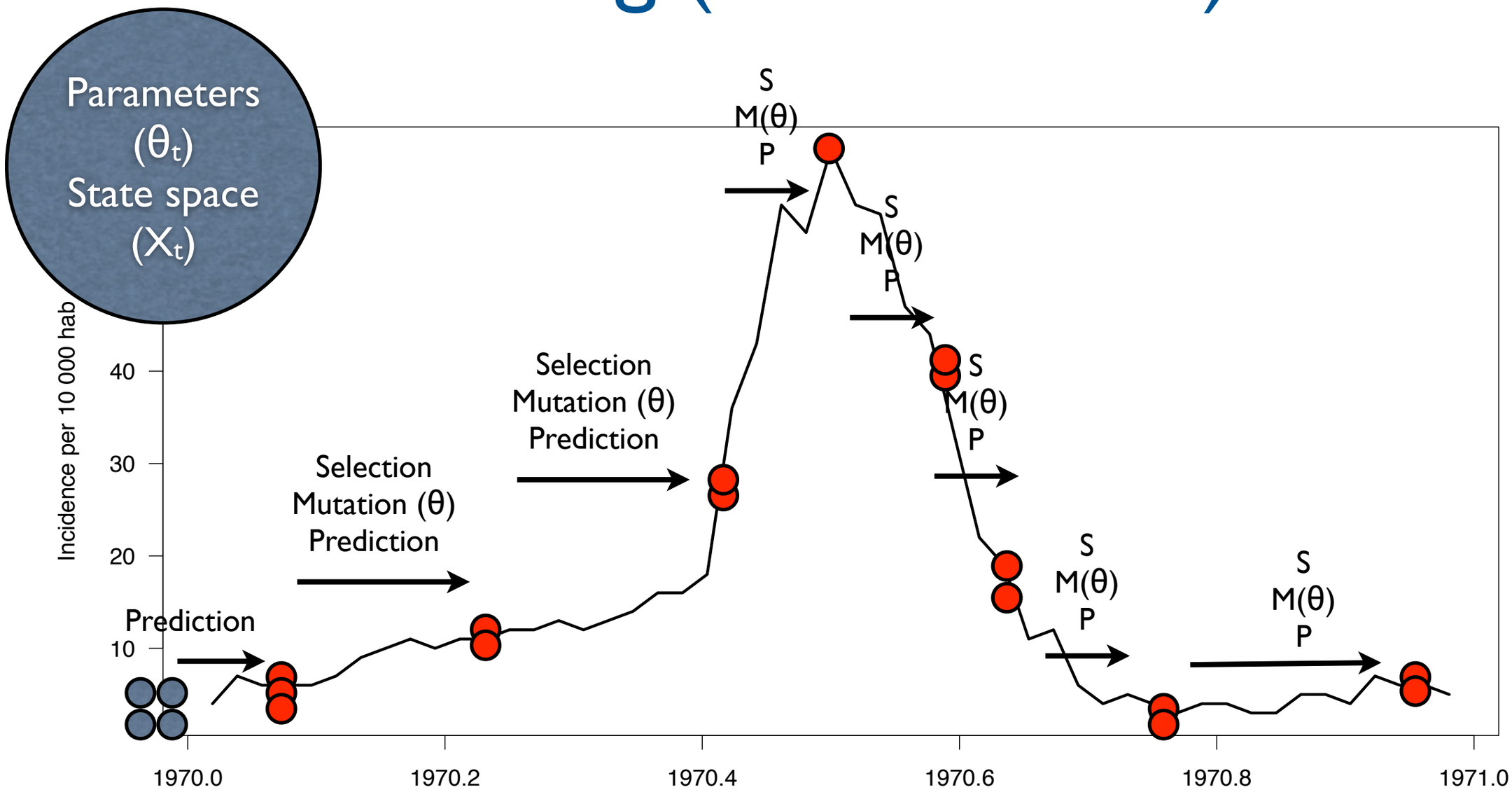


Generate N new particles and iterate filtering

Global estimate for θ

Maximum likelihood via Iterated Filtering (Ionides 2006)



Mutations $N(\theta, m \rightarrow 0)$ decrease at each iteration

$\theta \rightarrow$ Maximum Likelihood Estimate

Exploring the likelihood surface

- High dimensional (11) parameter space

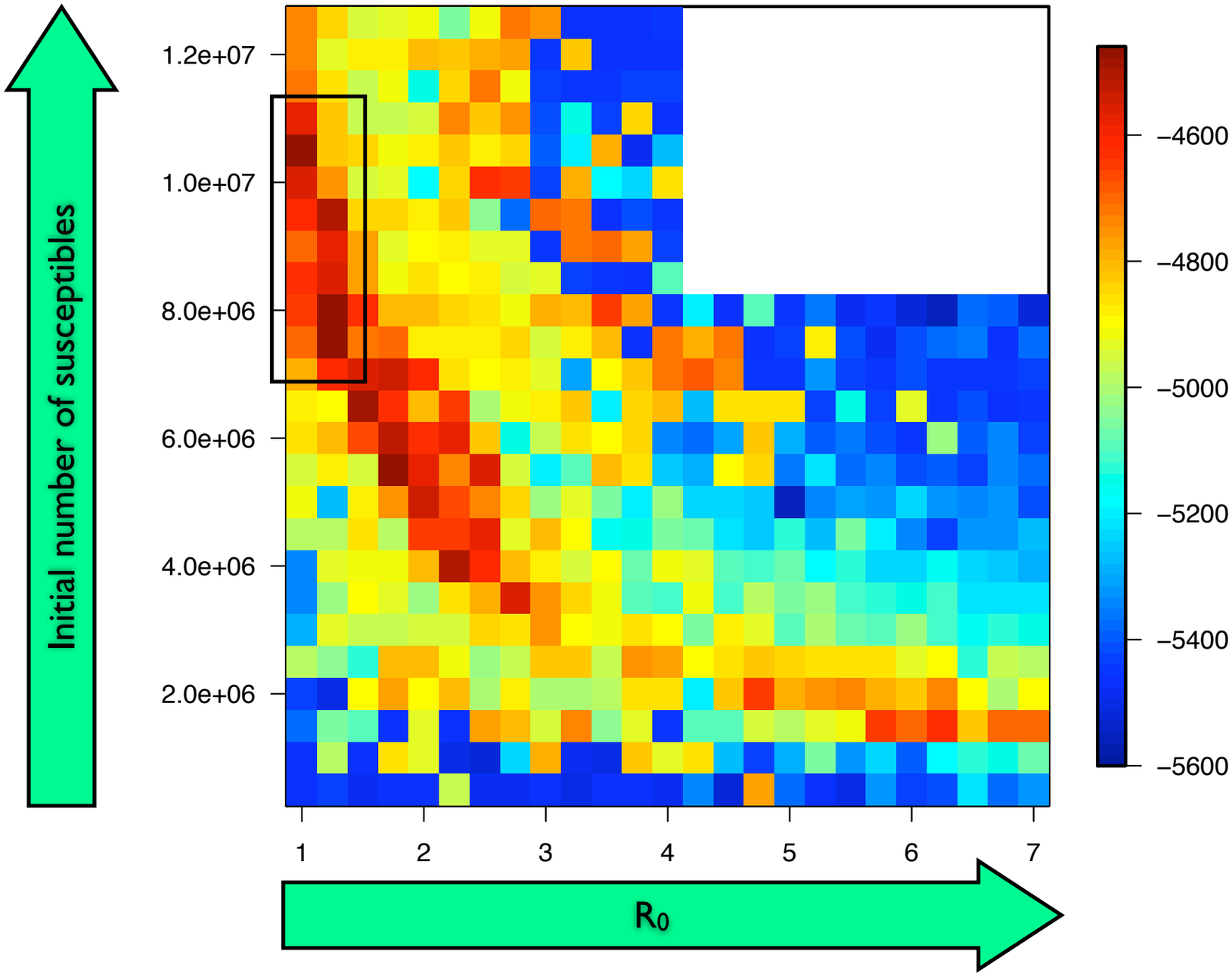
➽ bound the parameter space within biologically realistic values

1. $\sigma_{in} \in [0;0.2]$ (intra-cluster cross-immunity > 80%)
2. $\sigma_{ex} \in [0;0.5]$ (extra-cluster cross-immunity > 50%)
3. $\sigma_{in} \leq \sigma_{ex}$

- Structural (model) and practical (data) identifiability analysis

➽ 2 dimensional profile likelihood

Purely punctuated antigenic drift model ($\sigma_{in} = 0$)



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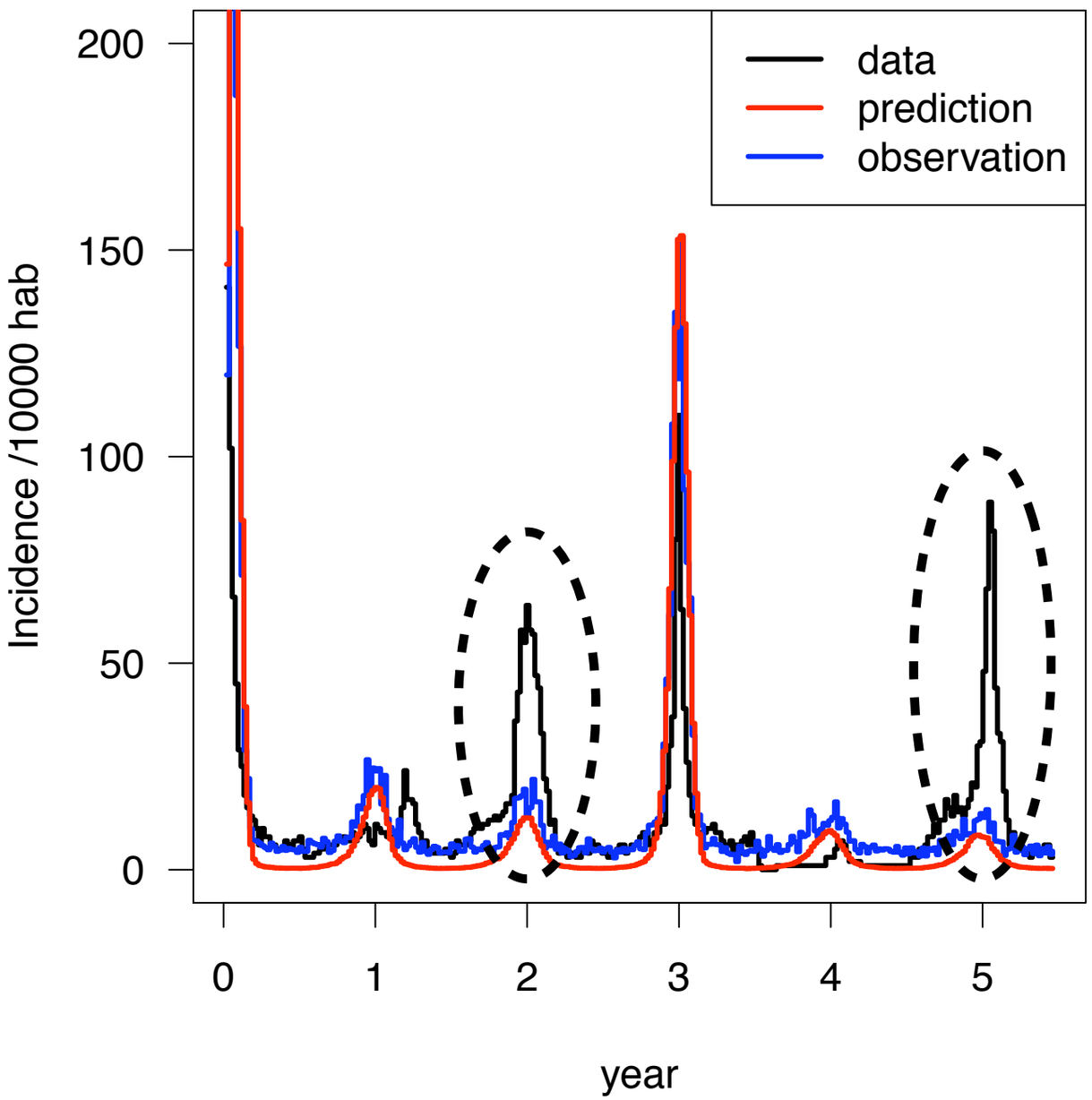
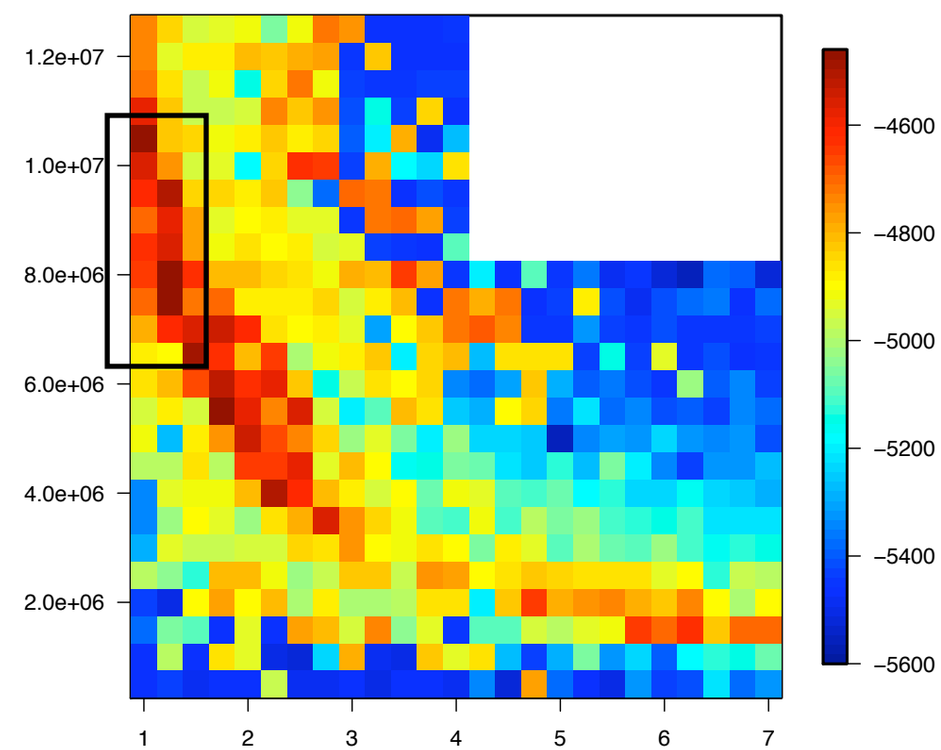
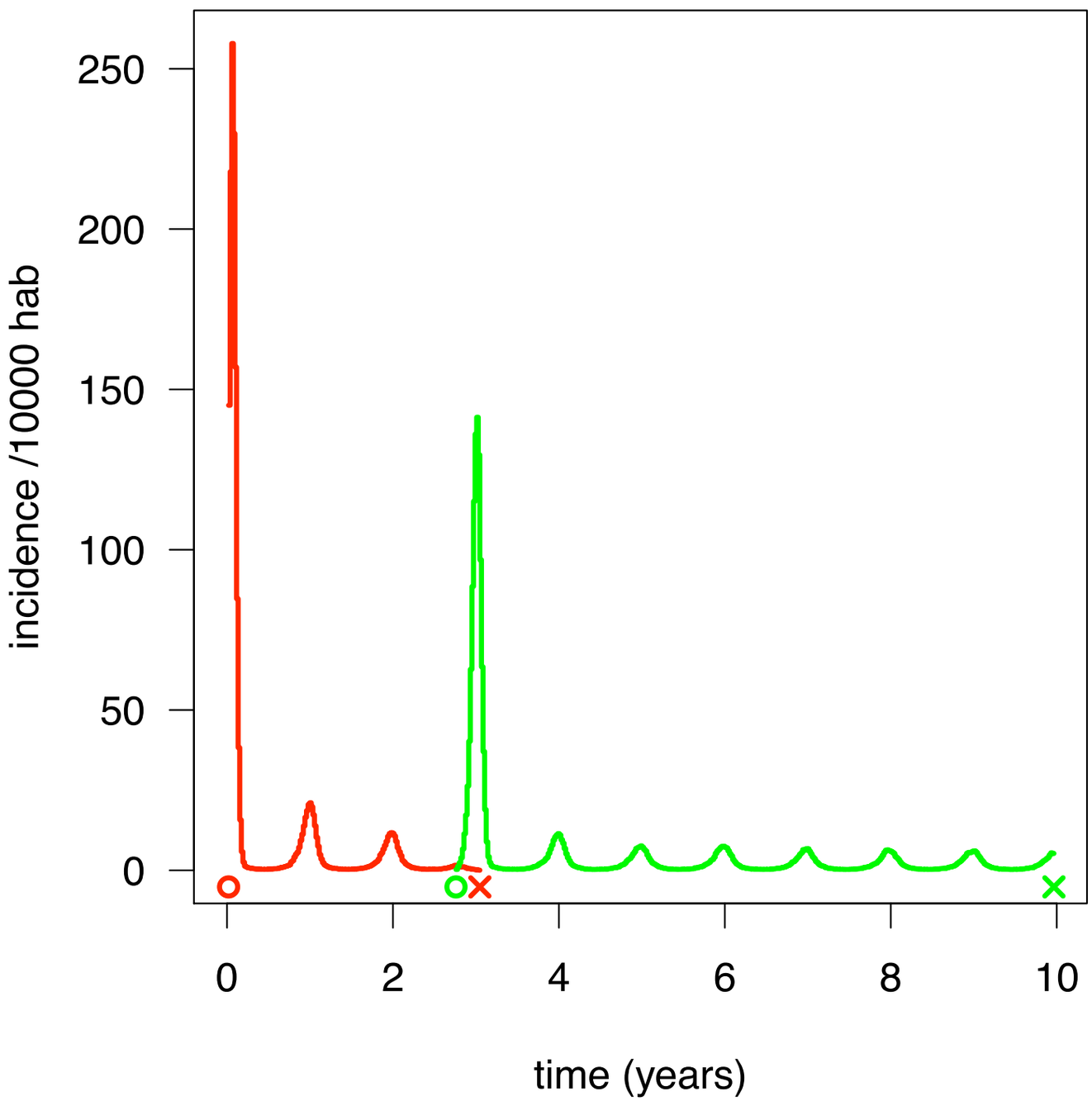
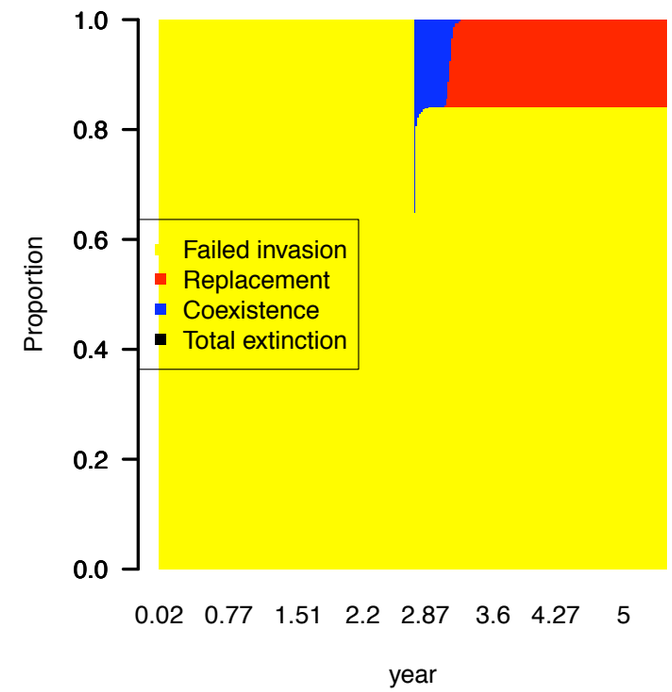




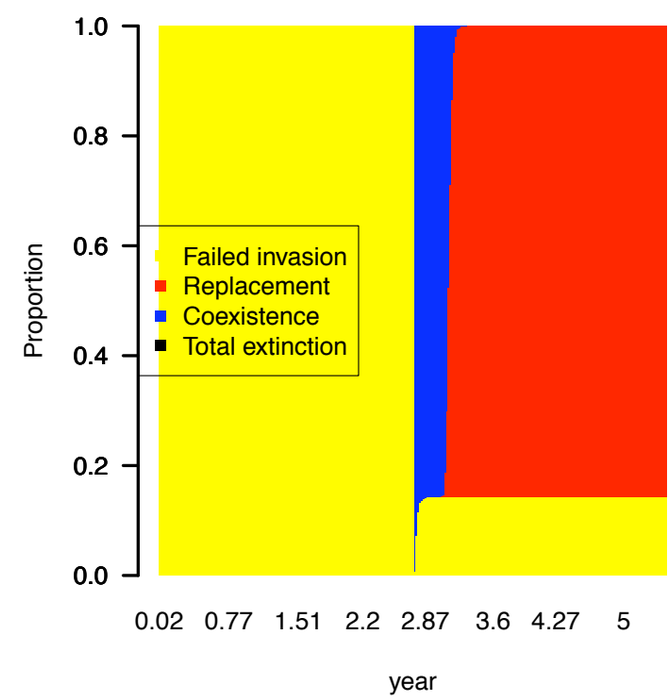
- R_0 = 1±0.5 (seasonality)
- Punctual immune escape σ_{ex} = 20% to 30%
- Initial proportion of susceptibles: 75%

Purely punctuated antigenic drift model ($\sigma_{in} = 0$)



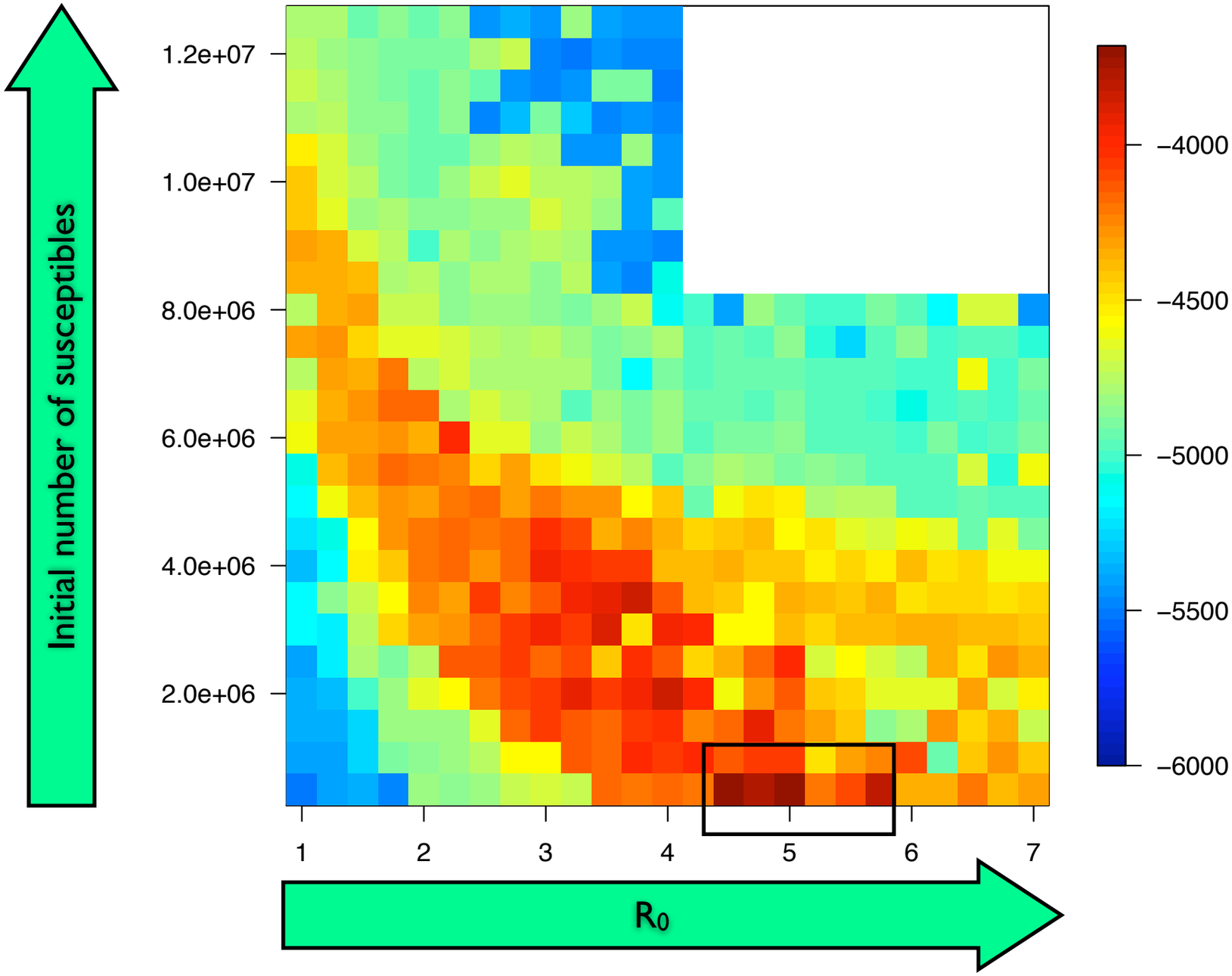


1 ind with cluster 2



10 ind with cluster 2

Gradual & punctuated antigenic drift model



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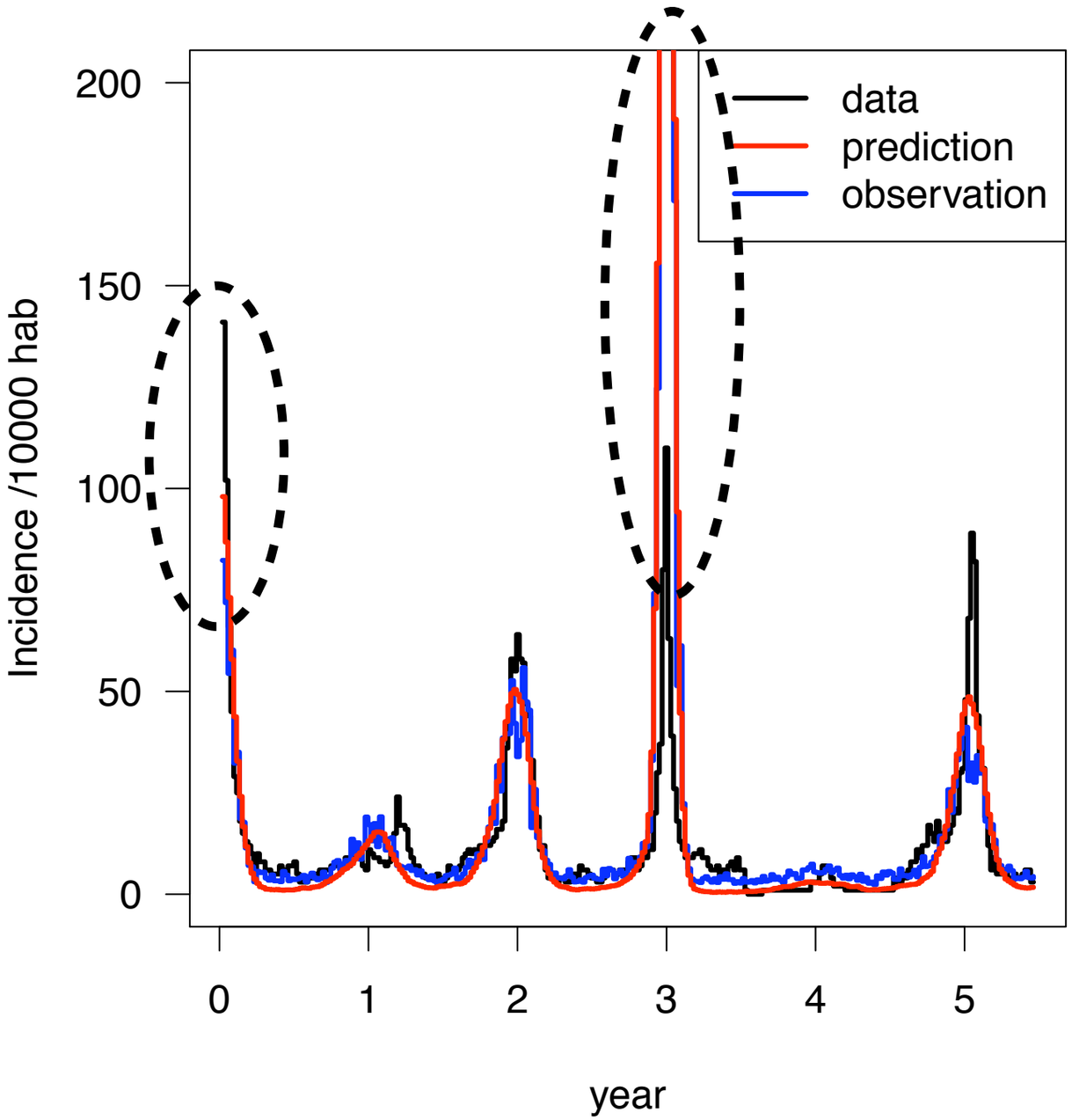
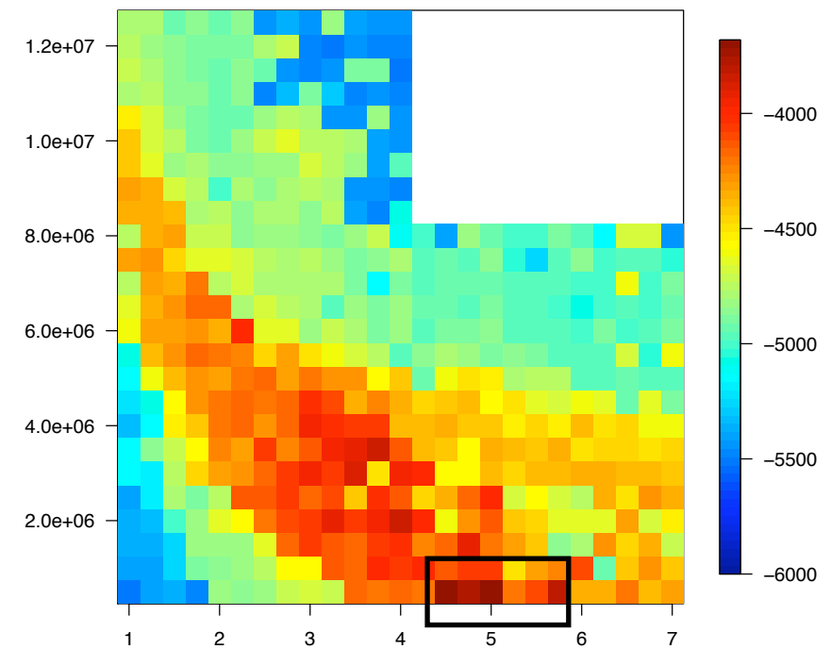
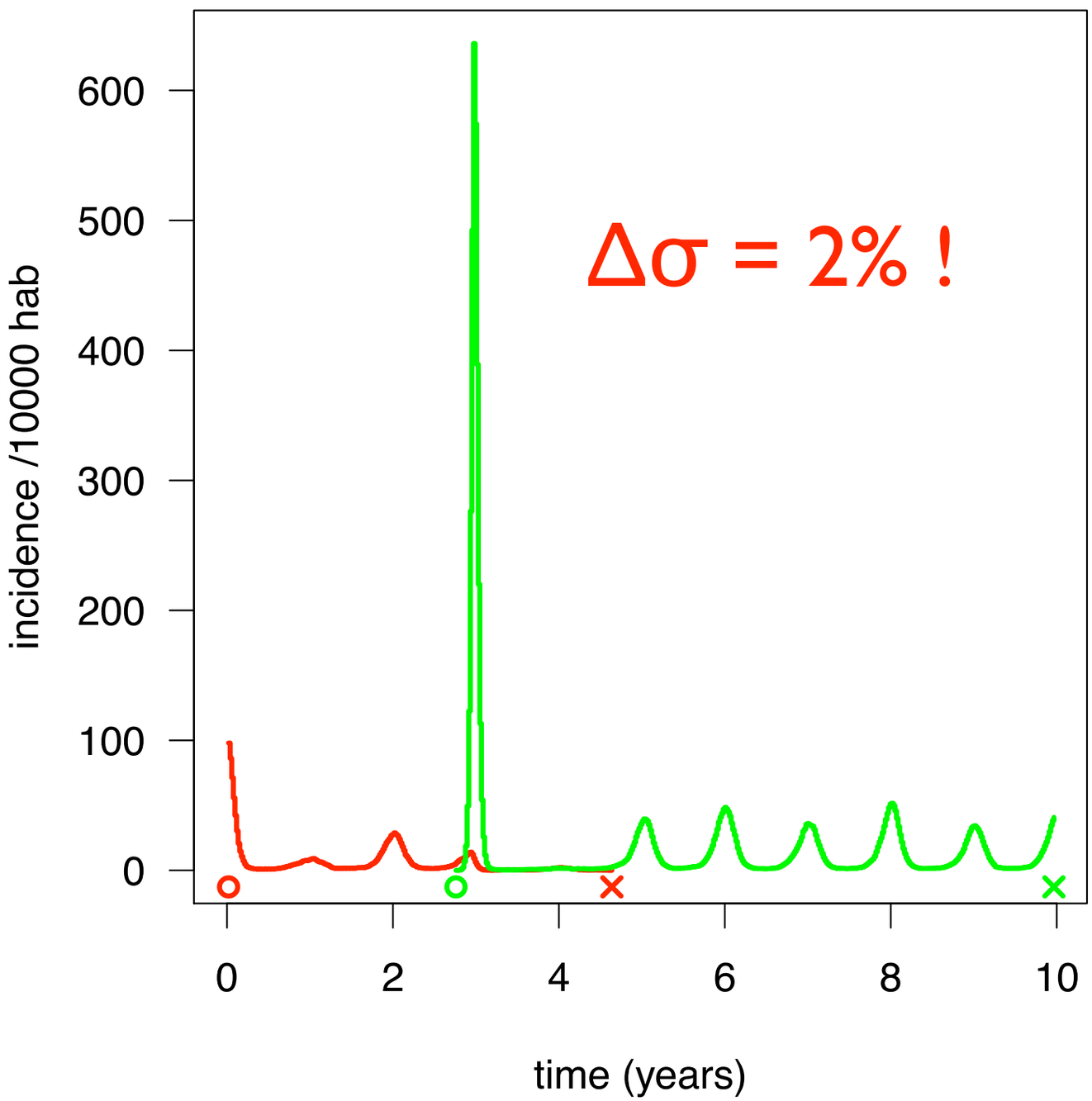
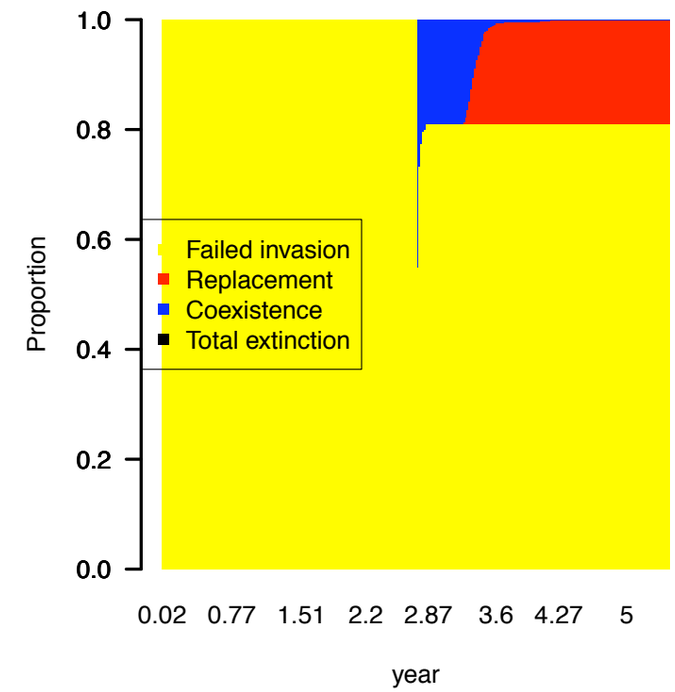




- R_0 = 5±0.2 (seasonality)
- Punctual immune escape: σ_{ex} = 19%
- Gradual immune escape: σ_{in} = 17% & $1/\gamma$ = 2 years
- Initial proportion of fully susceptibles (S): 4%
- Initial proportion of partially susceptibles (X): 94%

Gradual & punctuated antigenic drift model





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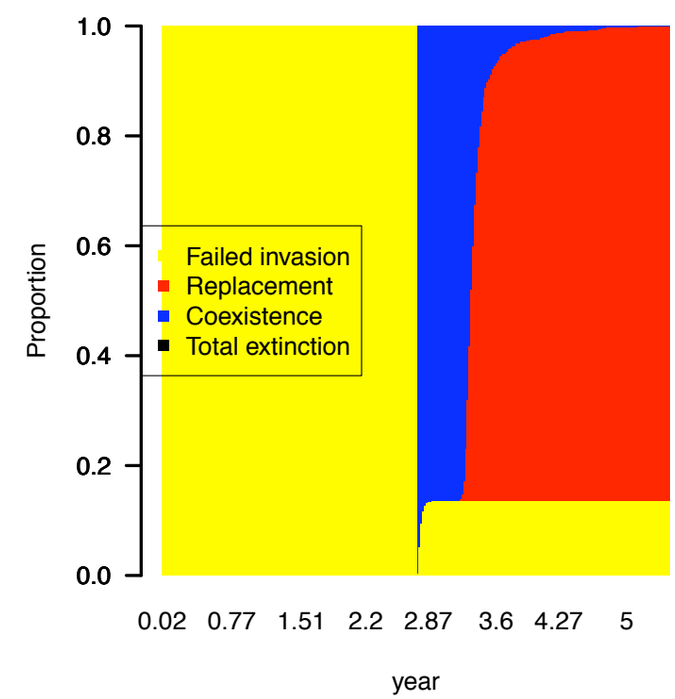
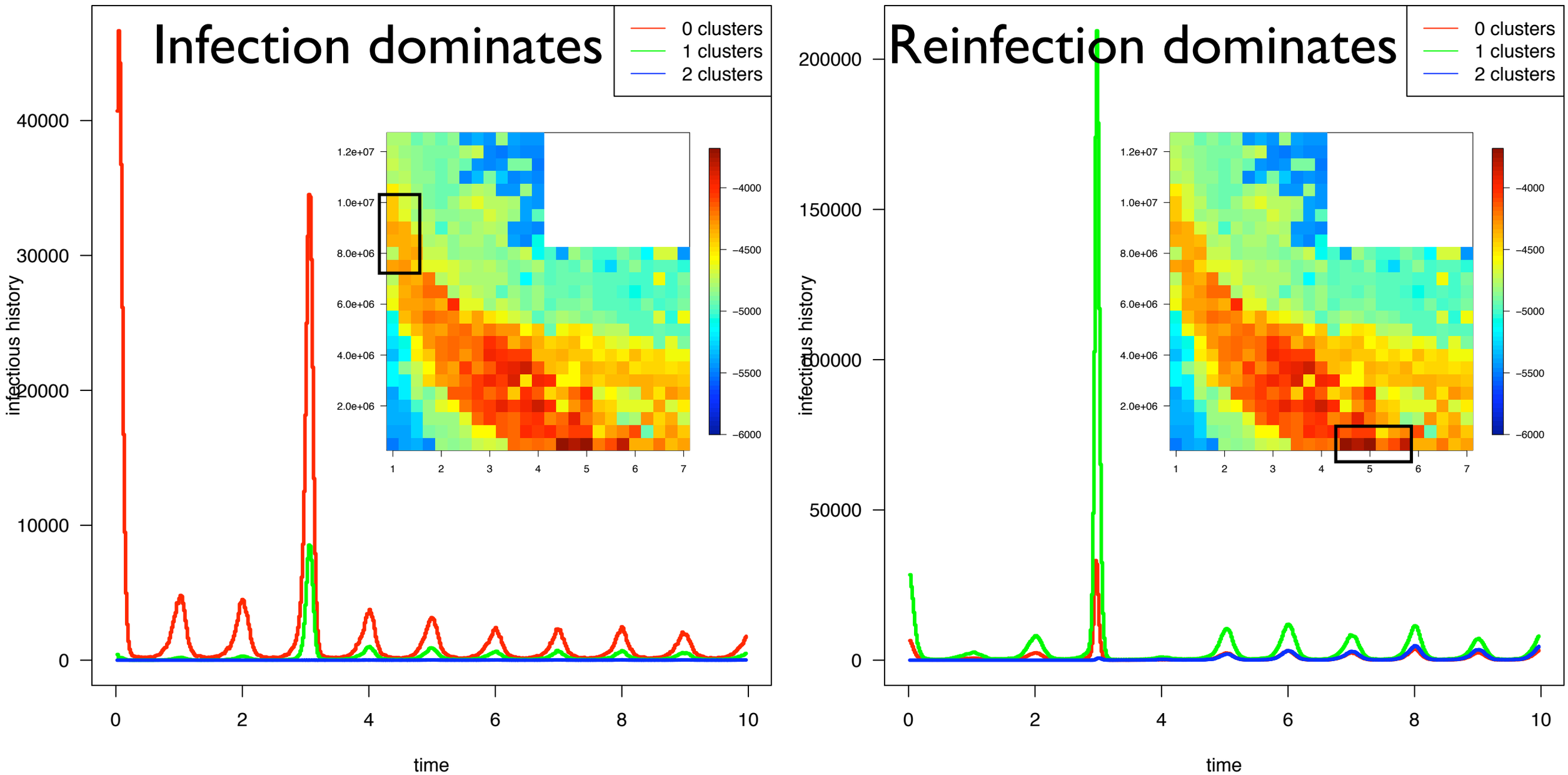


10 ind with cluster 2

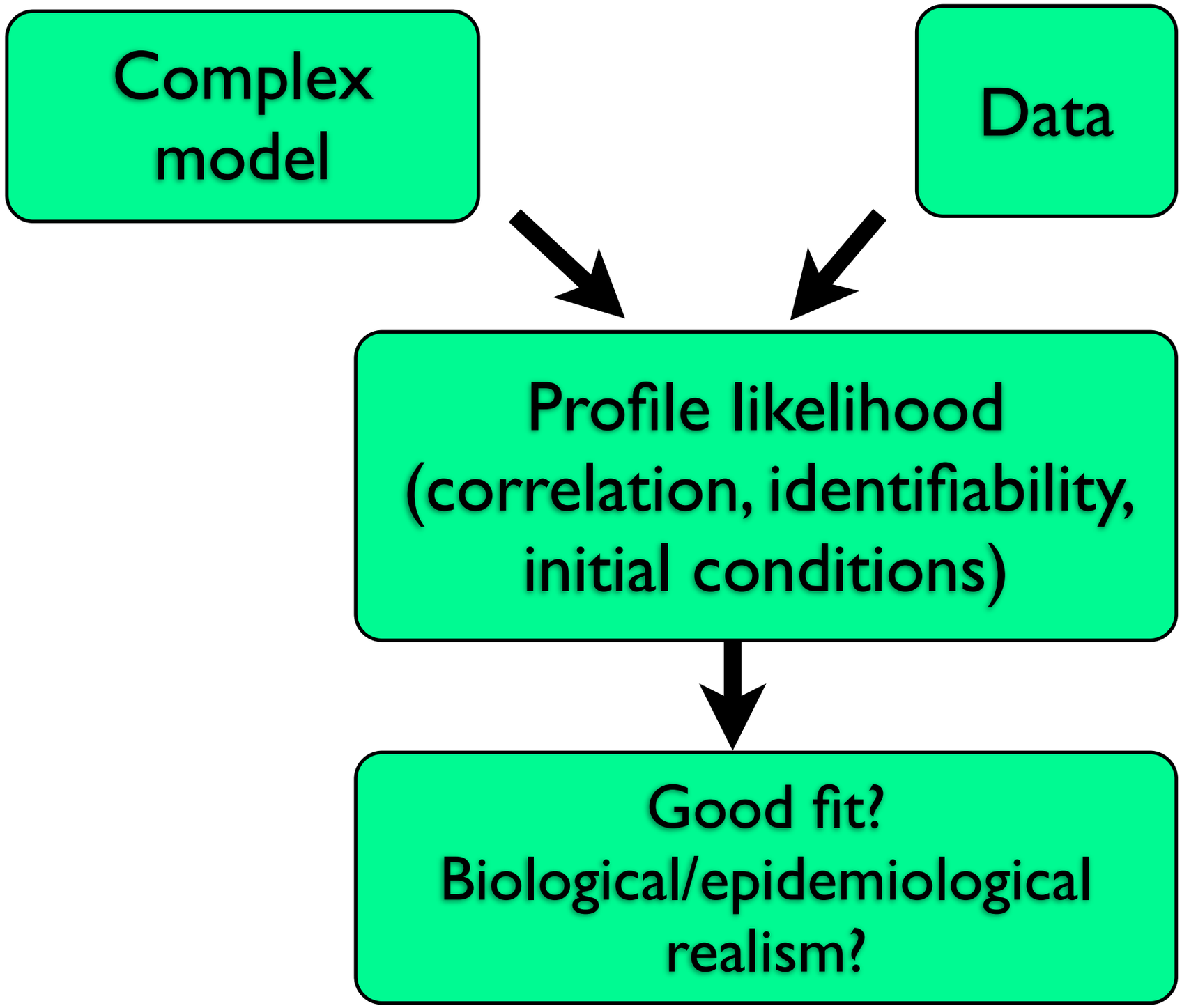
Gradual & punctuated antigenic drift model



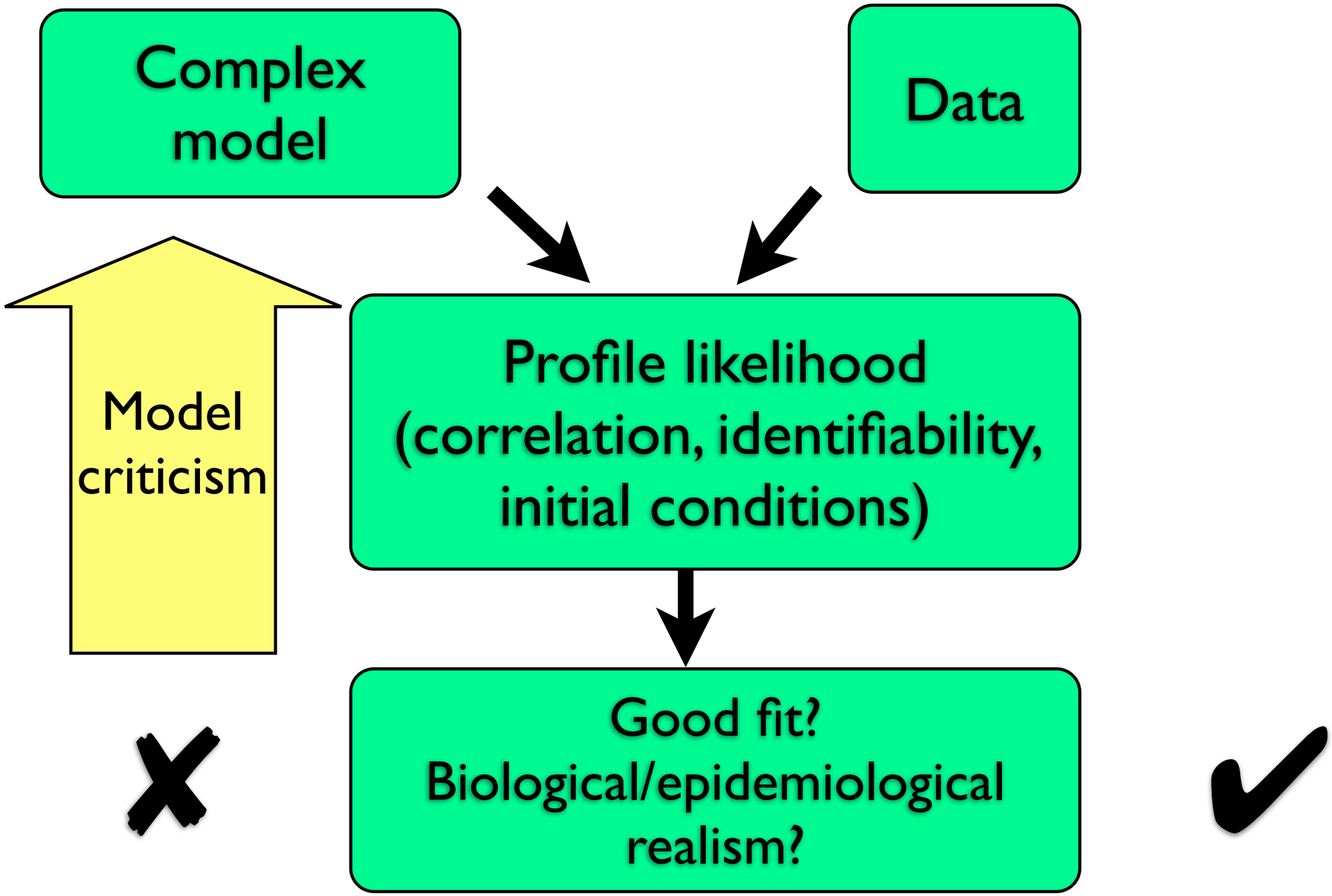
Summary

- Punctual antigenic drift alone is sufficient to reproduce cluster replacement but not the between-cluster dynamics. Parameter estimates are realistic.
- Adding gradual antigenic drift shift the MLE near the reinfection threshold and the between-cluster dynamics is reproduced. However, epidemics are too high at cluster transition whereas immune escape and initial conditions are biologically and epidemiologically unrealistic.

Systematic analysis



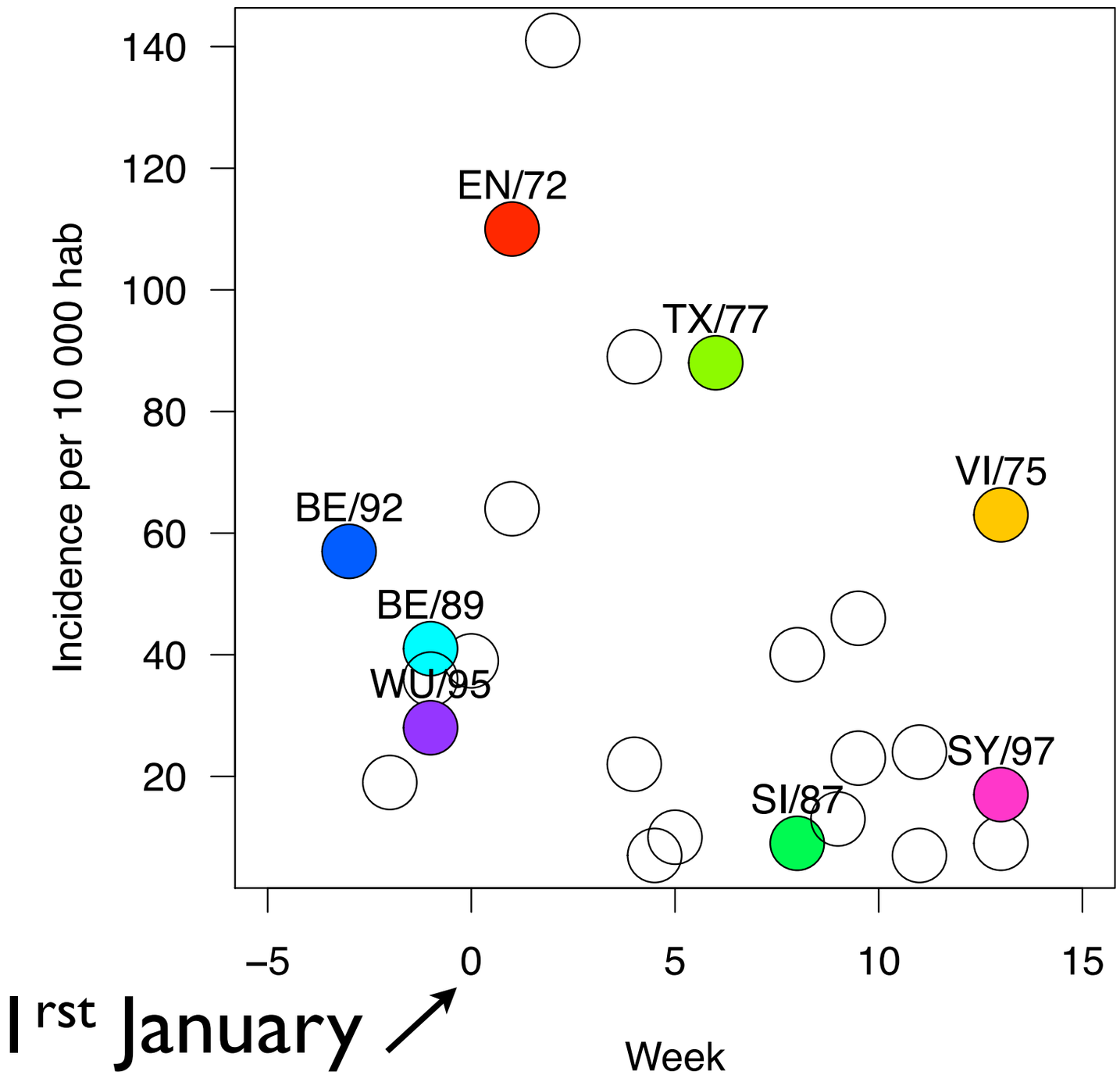
Systematic analysis

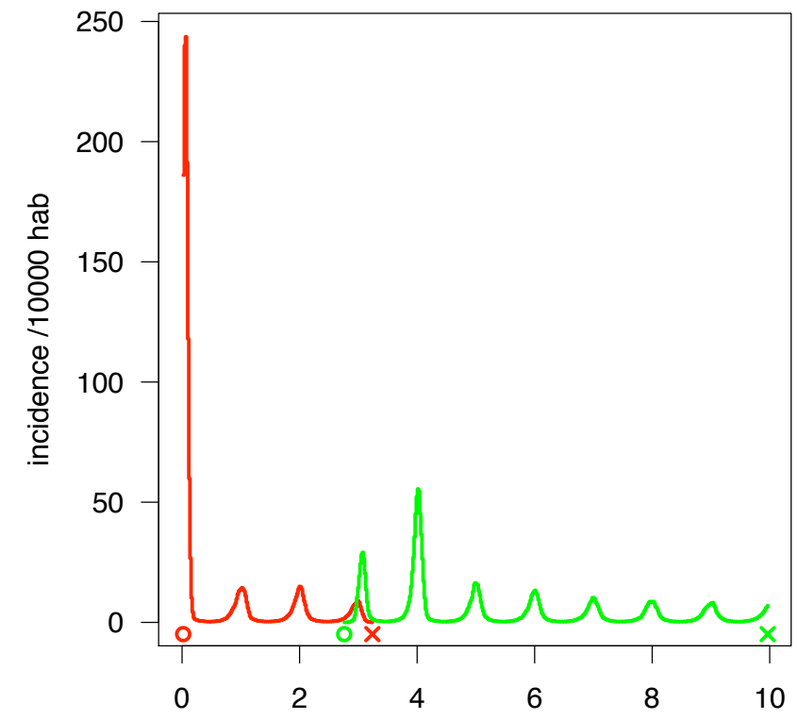


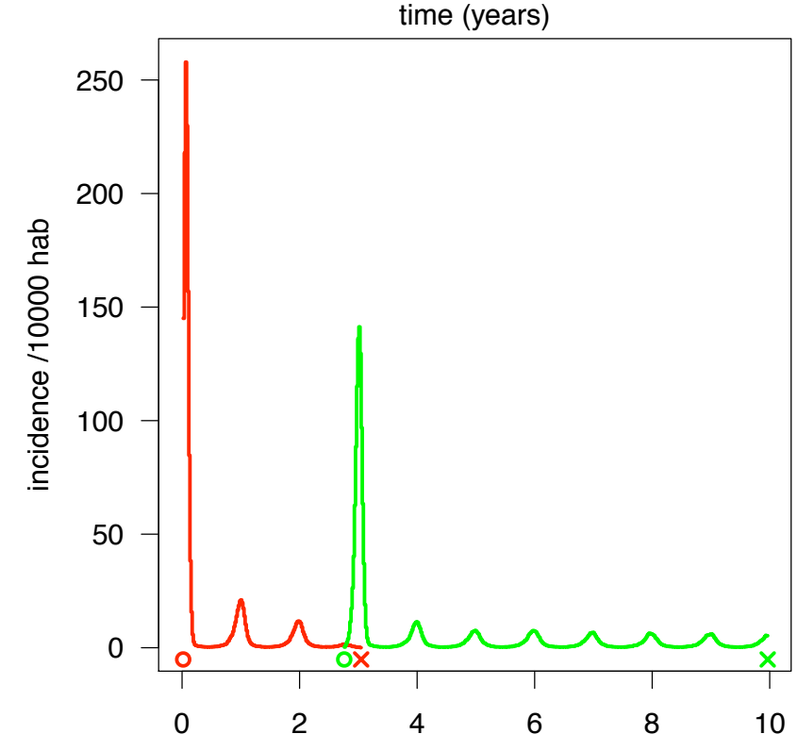
Discussion

- Neither of these 2 simple model can reproduce the whole complex dynamics of H3N2 for the considered period (1970 - 1975). Confidence in data could be assessed by fitting other data sets.
- For small R_0 the gradual antigenic drift does not play a major role in the dynamics because σ_{in} is well below the reinfection threshold ($1/R_0$). How to explain the high epidemics after the refractory periods? infection of susceptible or reinfection? maybe the SIRX model or temperate time series are not suitable to detect gradual antigenic drift?
- Gradual vs Punctuated antigenic drift is maybe a false debate, other mechanisms seem necessary to understand influenza dynamics in temperate area: environmental stochasticity on the transmission, more realistic seasonal forcing, variation in the introduction time of new clusters... work in progress!

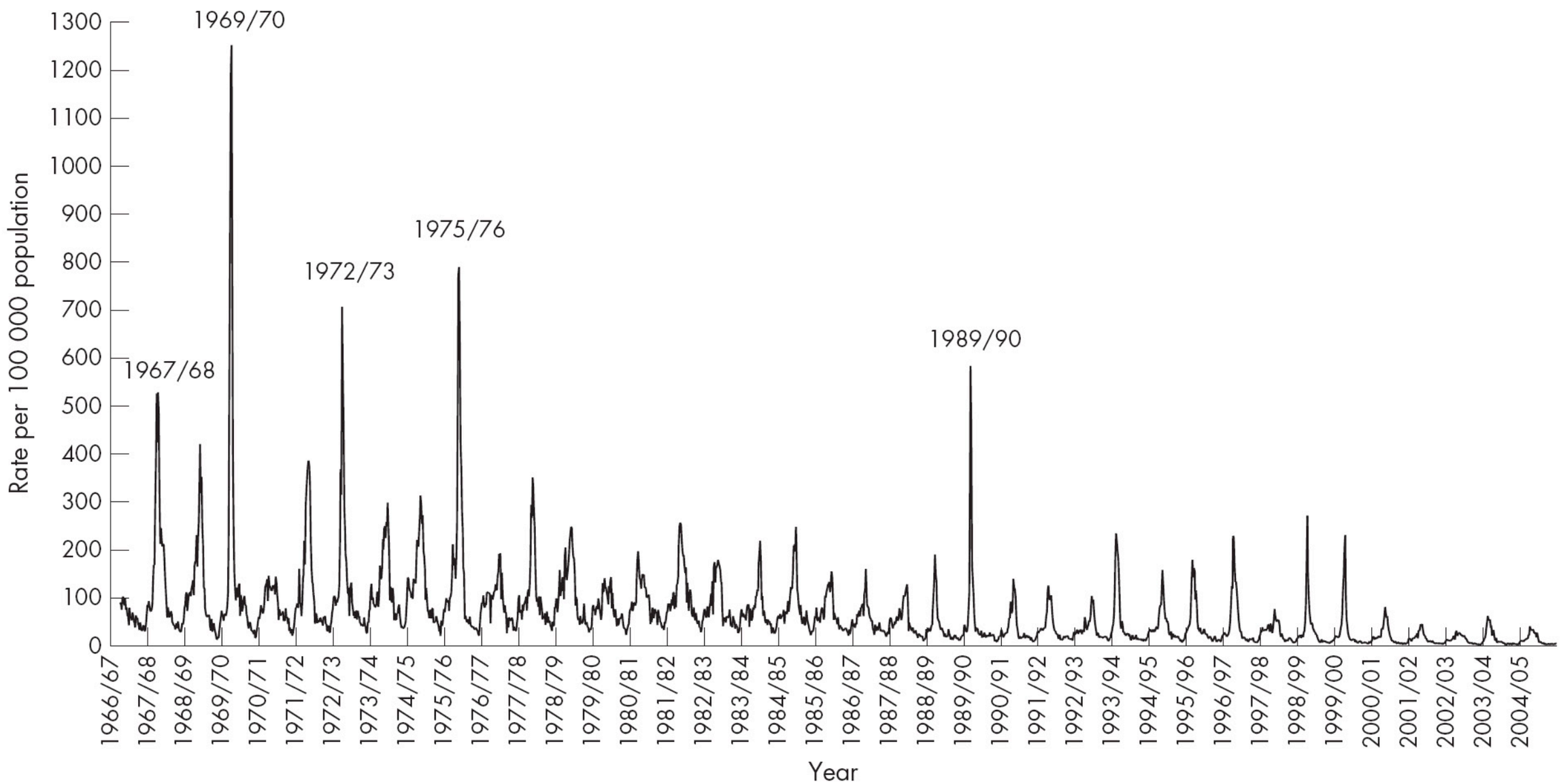
Peak time


Incidence per 10 000 hab
140
120
100
80
60
40
20
EN/72
TX/77
VI/75
BE/92
BE/89
WU/95
SY/97
SI/87
−5
0
5
10
15
Week
1rst January

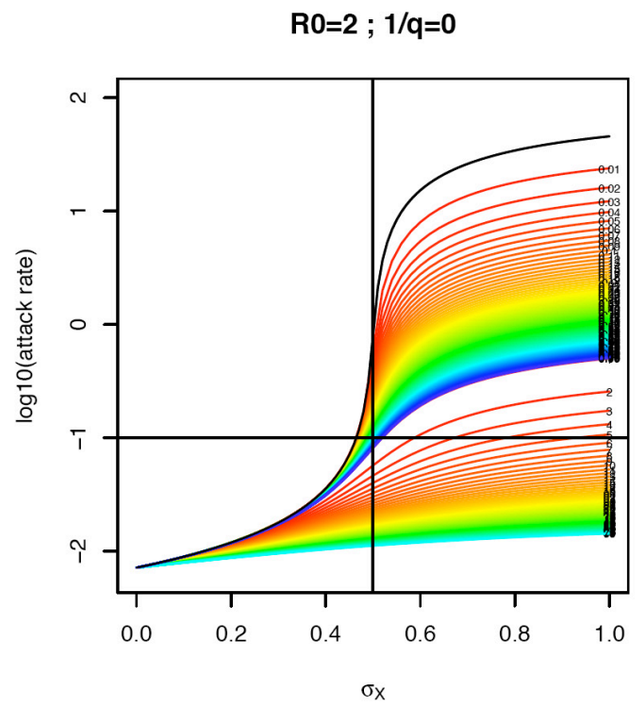

incidence /10000 hab
250
200
150
100
50
0
0
2
4
6
8
10
time (years)

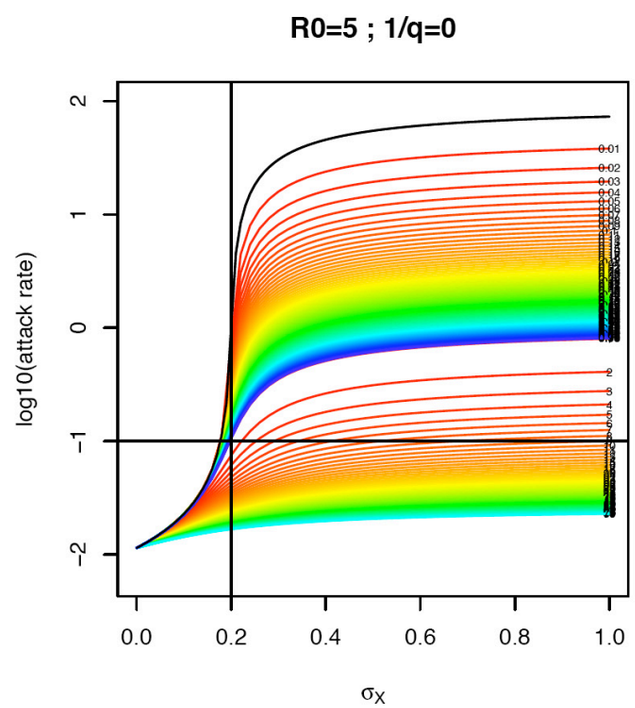

incidence /10000 hab
250
200
150
100
50
0
0
2
4
6
8
10

Influenza time series England



Reinfection threshold





Invasion outcomes