SAMPLING-AWARE **PHYLODYNAMICS** WITH THE **BAYESIAN EPOCH SAMPLING SKYLINE PLOT**

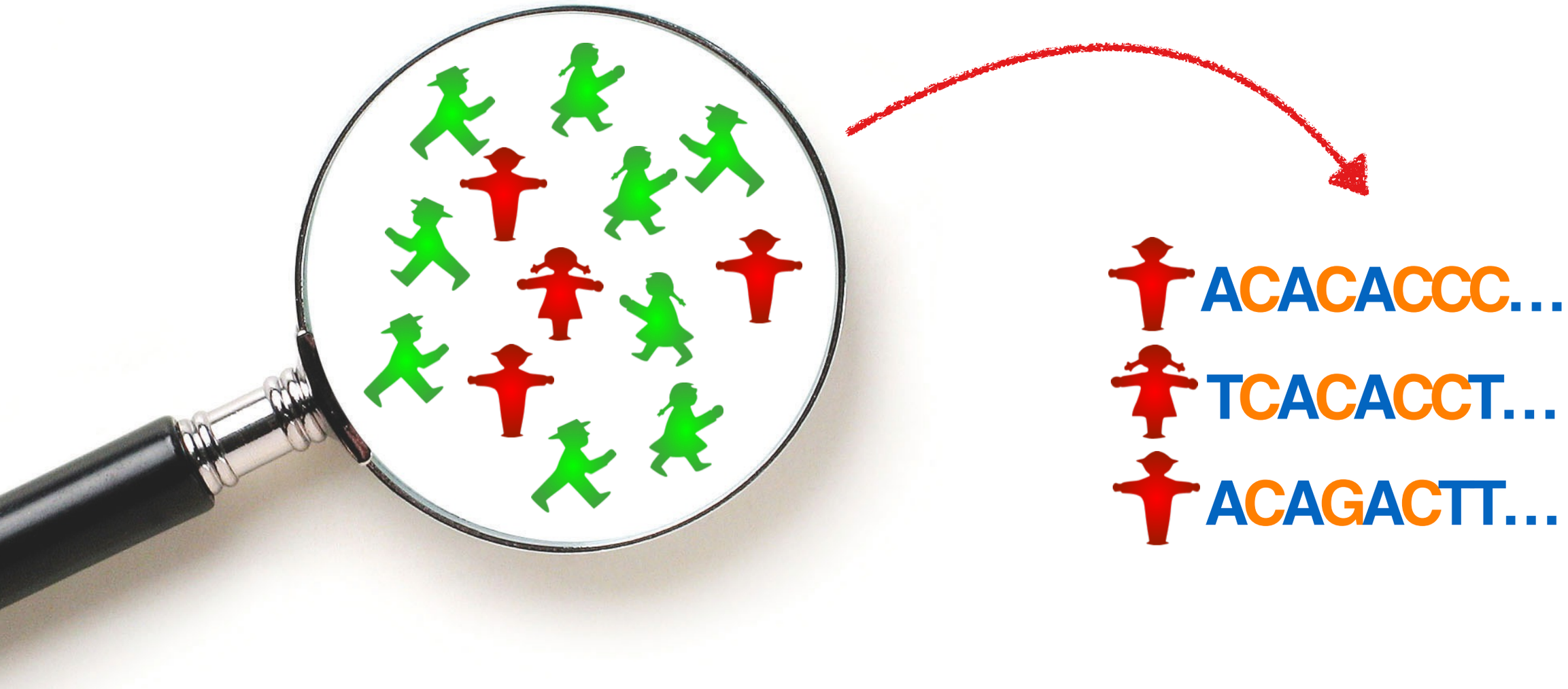
LOUIS DU PLESSIS, KRIS PARAG AND OLIVER PYBUS

PHYLODYNAMIQUE

EN PRENANT EN COMPTE L'ÉCHANTILLONNAGE AVEC LE

BAYESIAN EPOCH SAMPLING SKYLINE PLOT

LOUIS DU PLESSIS, KRIS PARAG AND OLIVER PYBUS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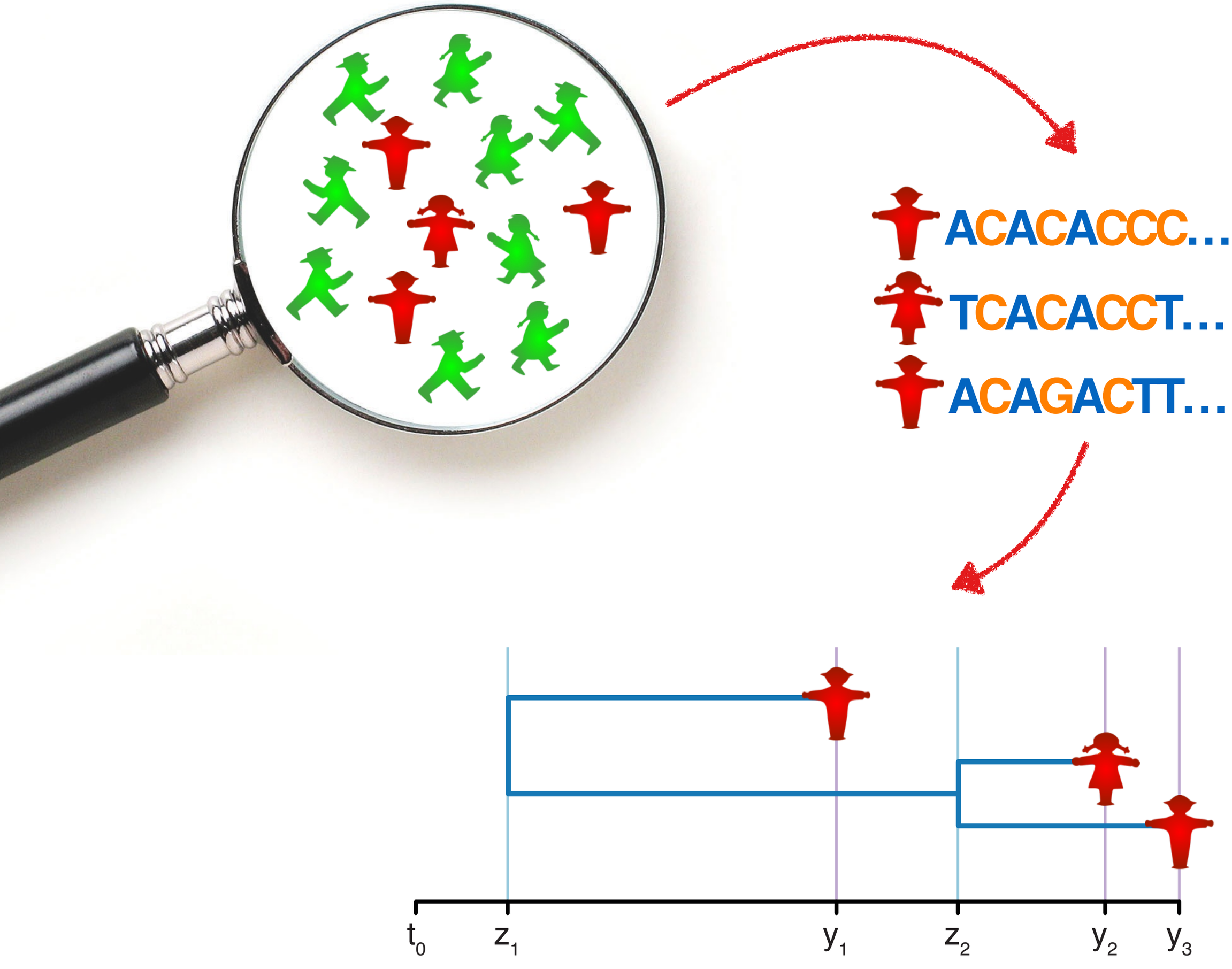
TCACACCT…
ACAGACTT…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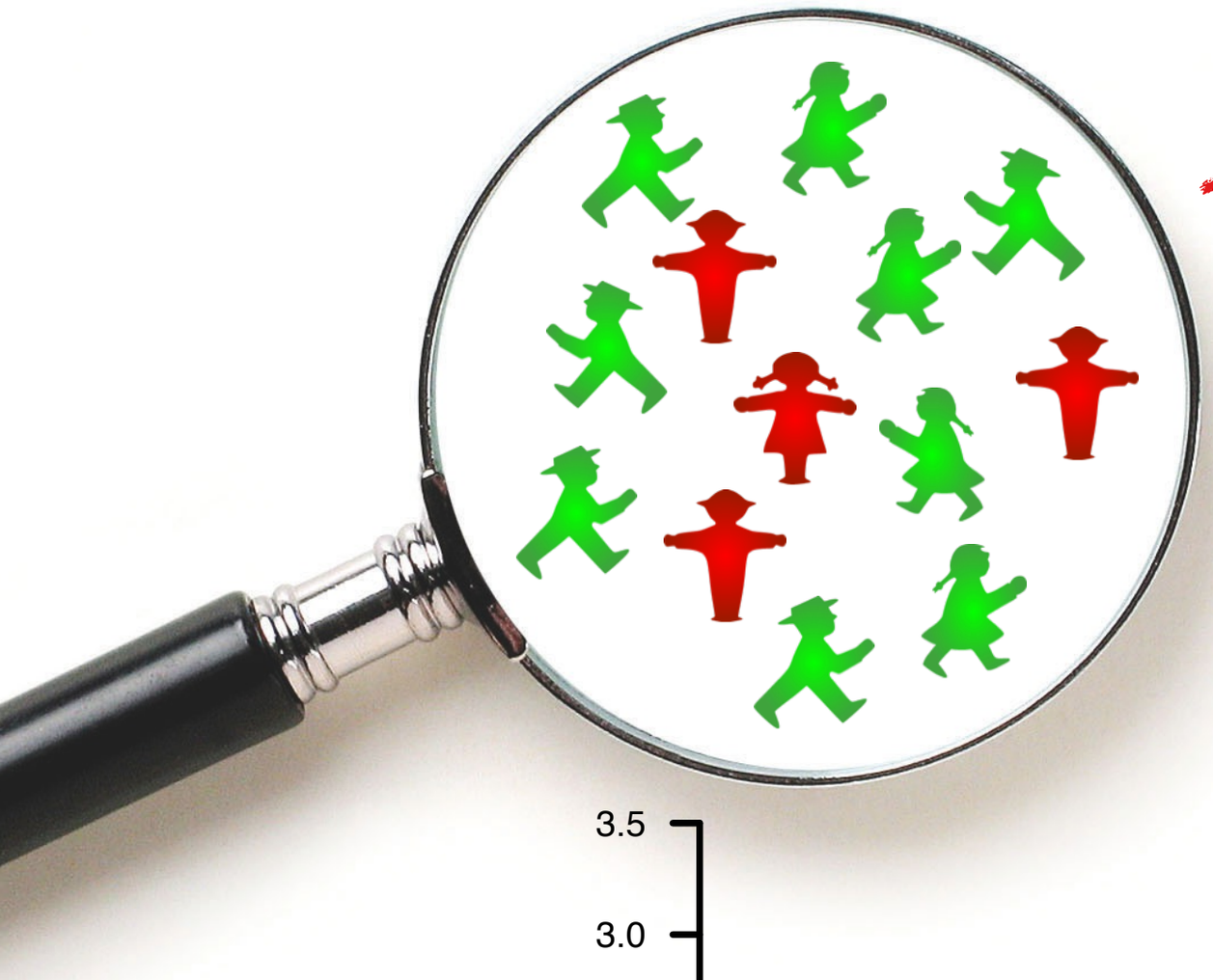
TCACACCT…
ACAGACTT…
t0
z1
y1
z2
y2
y3

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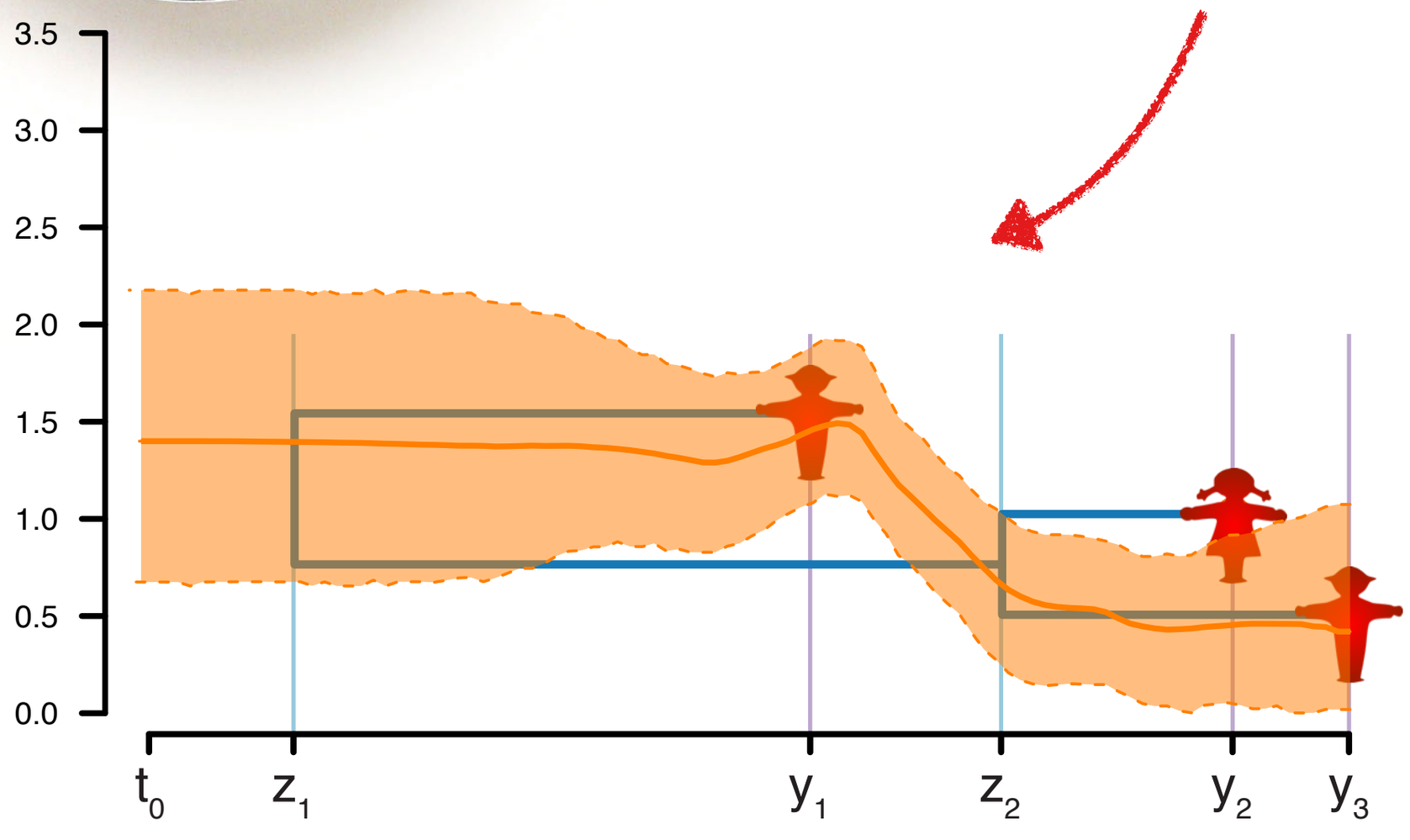
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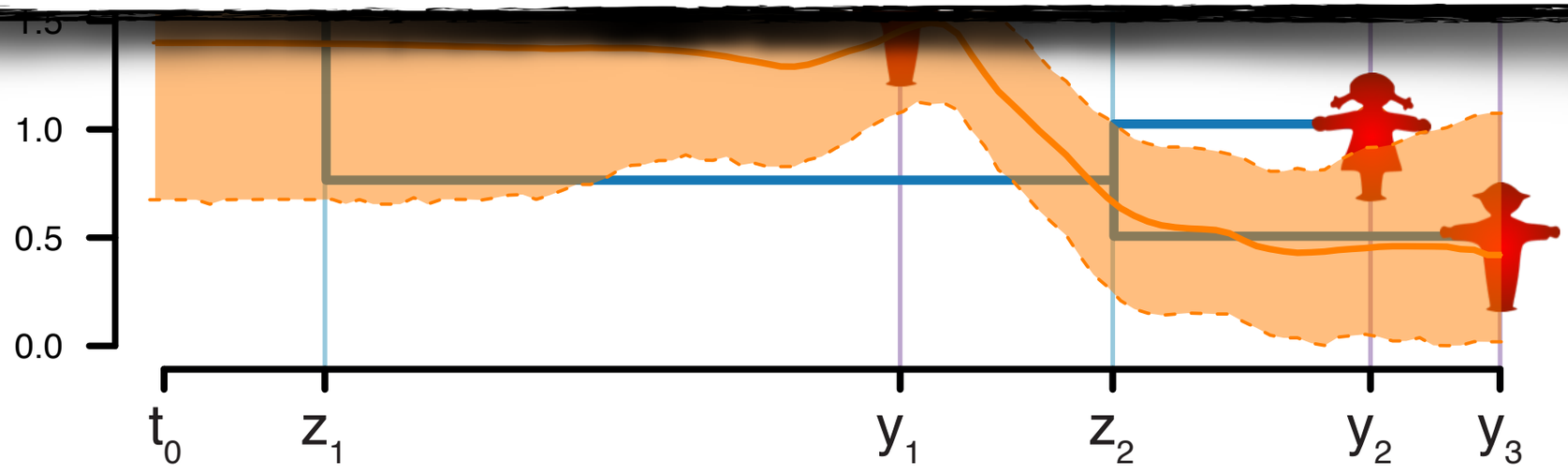
3.0
2.5
2.0
1.5
1.0
0.5
0.0
t_0
z_1
y_1
z_2
y_2
y_3

Tree
Realisation of a stochastic process

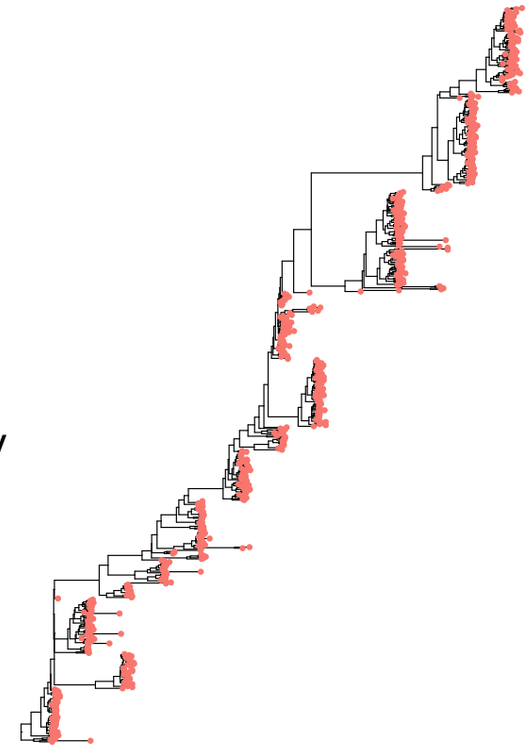
$P(\text{tree} \mid \text{demography})$

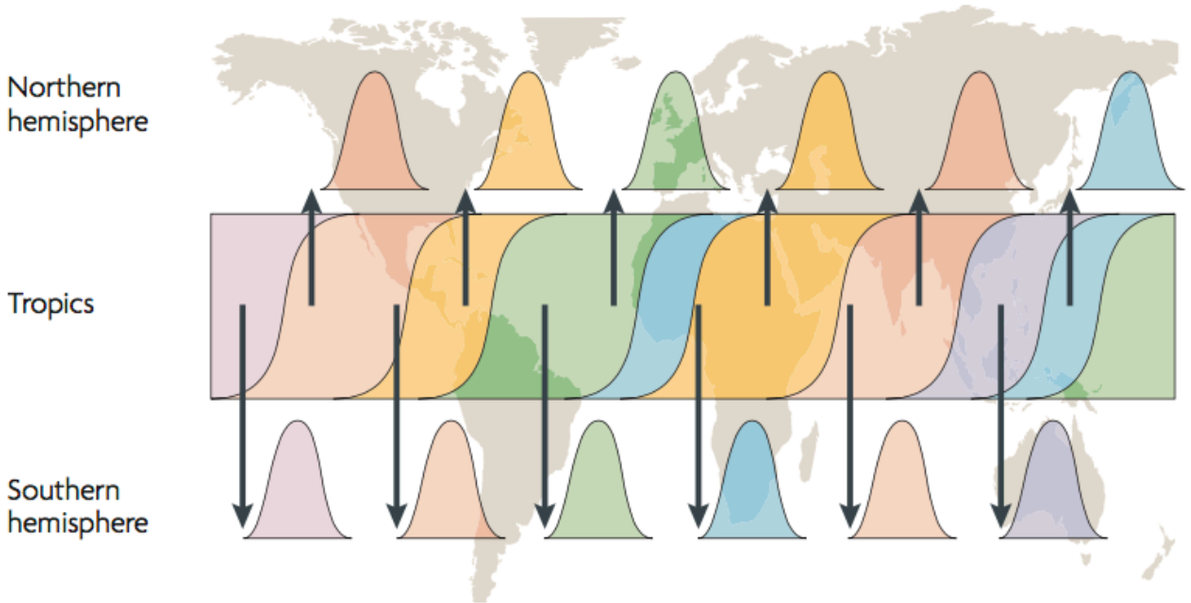
Demographic model
Describes the growth of the tree (spread of epidemic)

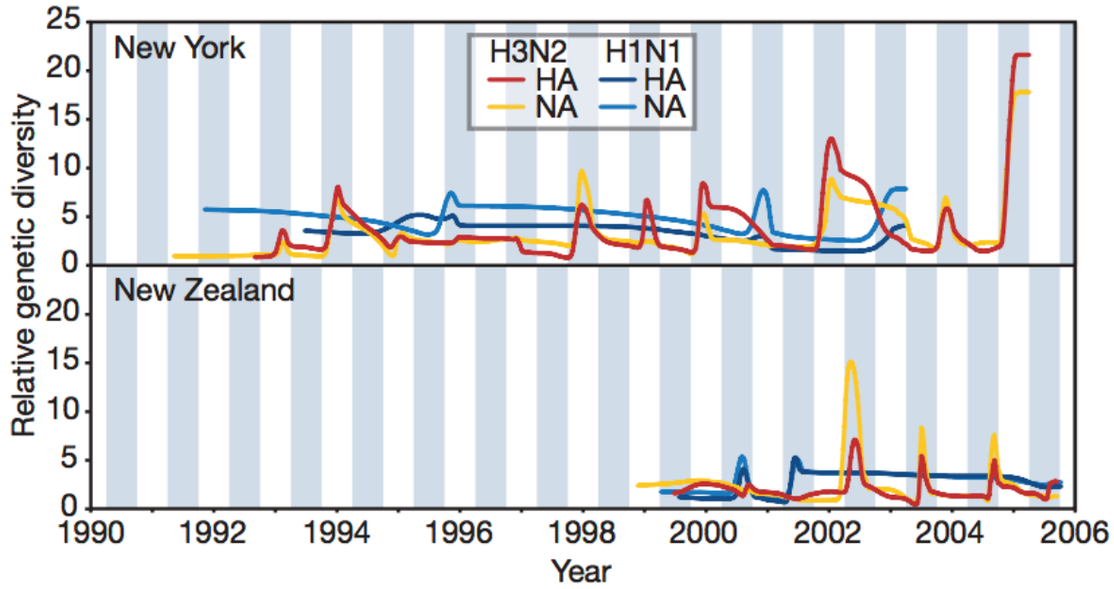


Seasonal influenza

- Yearly winter outbreaks in temperate regions
- Influenza **A/H3N2** is the dominant subtype
- Tropical source population seeds yearly epidemics in temperate sinks
- Strong directional selection maintains limited genetic diversity (most visible in HA gene)







Rambaut *et al.* **Nature 2008**
Pybus and Rambaut **Nature Reviews Genetics 2009**

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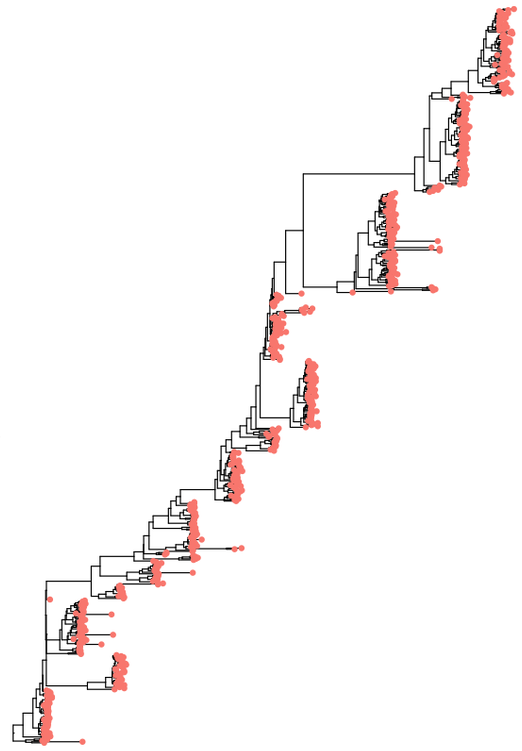
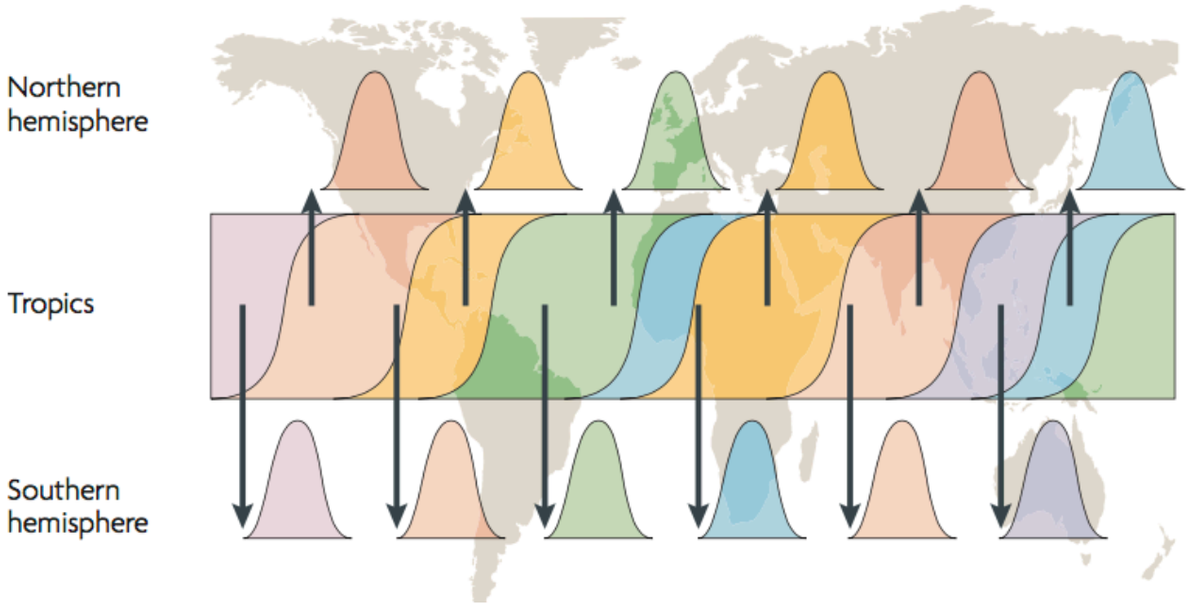
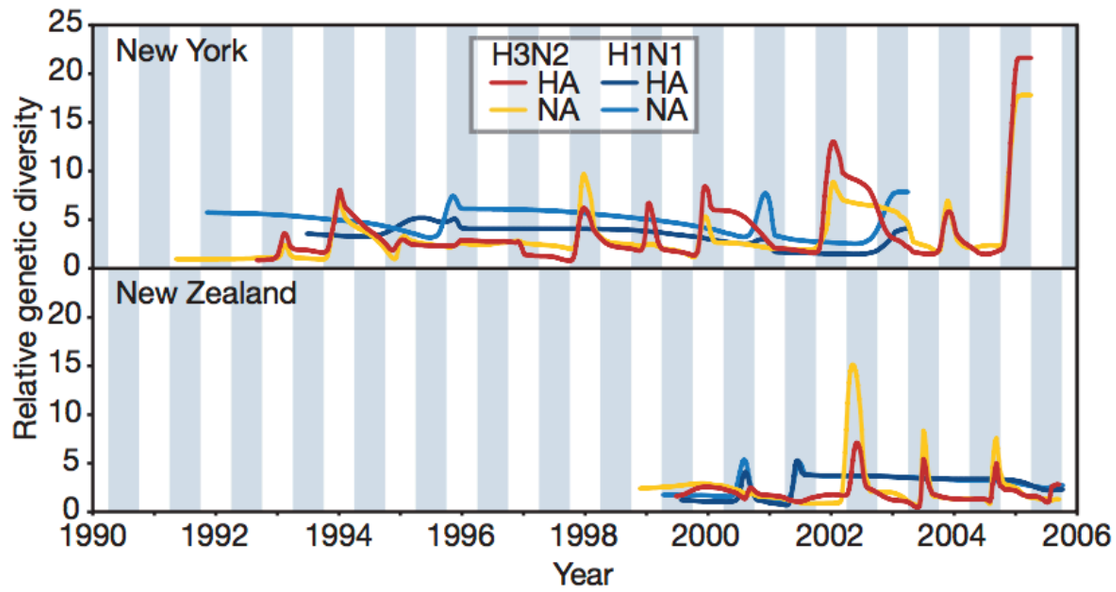


Bayesian Skyline Plot

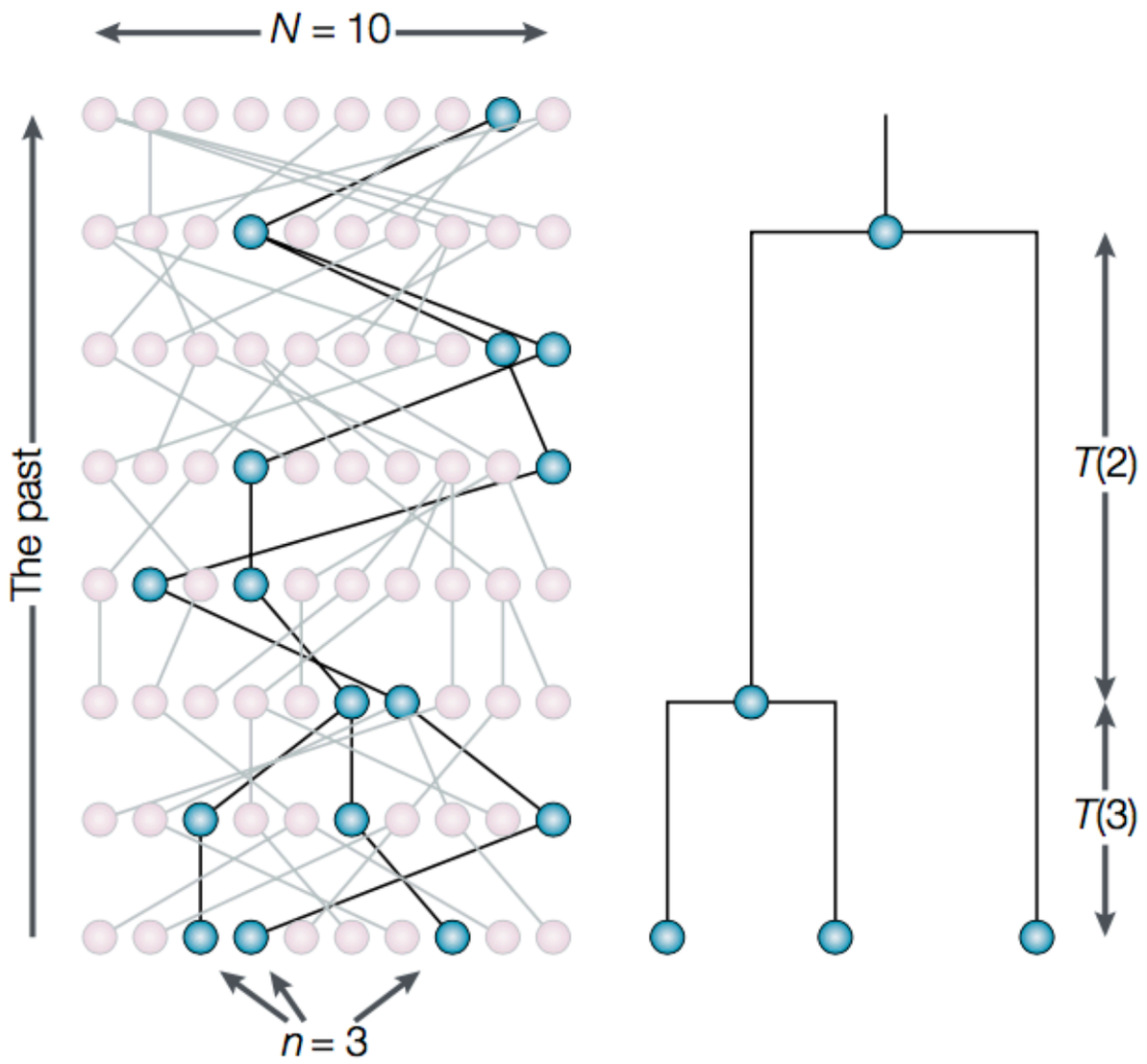




Rambaut *et al.* **Nature 2008**
Pybus and Rambaut **Nature Reviews Genetics 2009**

Kingman coalescent

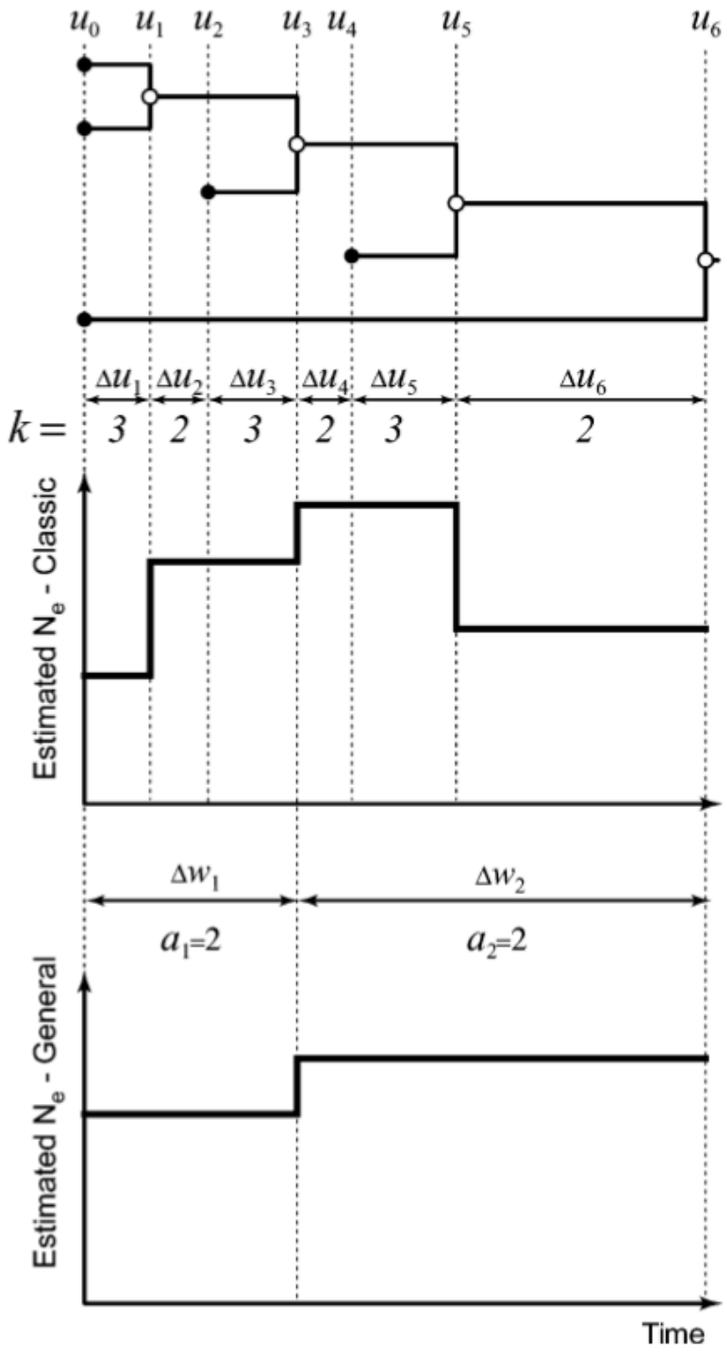
Full population **Sampled tree**



- Approximation to Wright-Fisher population dynamics (with large **N**)
- Trace ancestry of **n** samples in a population of size **N**
- Given **N** it is easy to calculate the probability for **2** nodes to coalesce in time **t**
- Calculate the probability of observing a given **tree** for a particular **N**
  → estimate **N**
  (**N_e** or relative genetic diversity in practice)
- Easy to extend to time changing **N(t)**

Rosenberg and Nordborg **Nature Reviews Genetics 2002**

Skyline plots



Classic skyline plot

- Piecewise constant N_e
- Change-points at coalescent times
- Noisy estimate

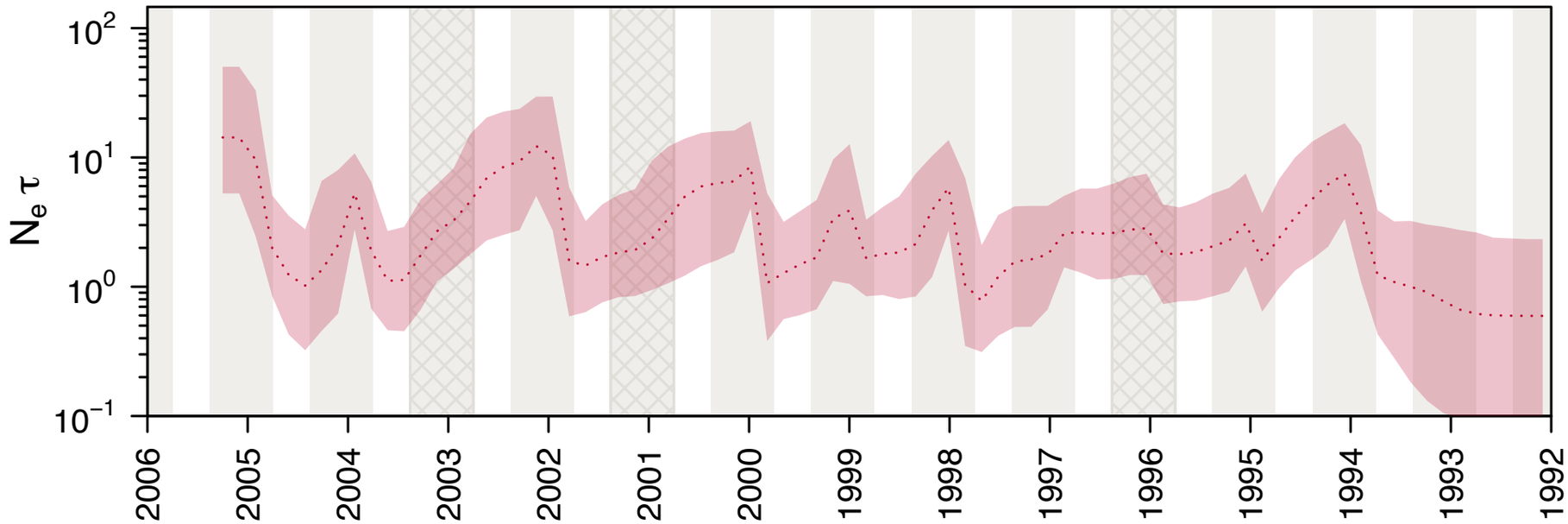
Generalised skyline plot

- Group neighbouring segments
- Smoother estimate

Drummond *et al.* **MBE 2005**

Bayesian Skyline Plot **(BSP)**

637 New York Influenza A/H3N2 HA sequences across 12 seasons



$$P(\text{genealogy}, \text{demographic}, \text{site}, \text{clock} \mid \text{ACAC}\ldots/\text{TCAC}\ldots/\text{ACAG}\ldots) = \frac{P(\text{ACAC}\ldots/\text{TCAC}\ldots/\text{ACAG}\ldots \mid \text{genealogy}, \text{site}, \text{clock})\, P(\text{genealogy} \mid \text{demographic})\, P(\text{demographic})\, P(\text{site})\, P(\text{clock})}{P(\text{ACAC}\ldots/\text{TCAC}\ldots/\text{ACAG}\ldots)}$$

ACAC…
TCAC…
ACAG…
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genealogy

demographic model

site model

molecular clock model

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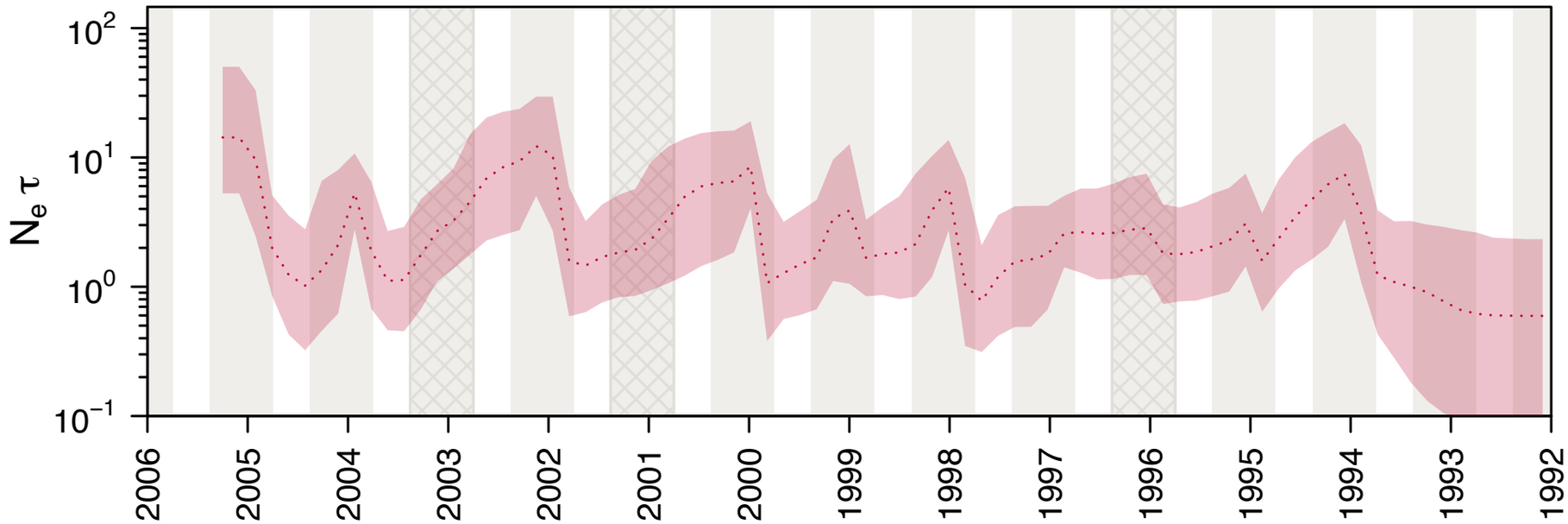

Bayesian Skyline Plot
(Tree prior)

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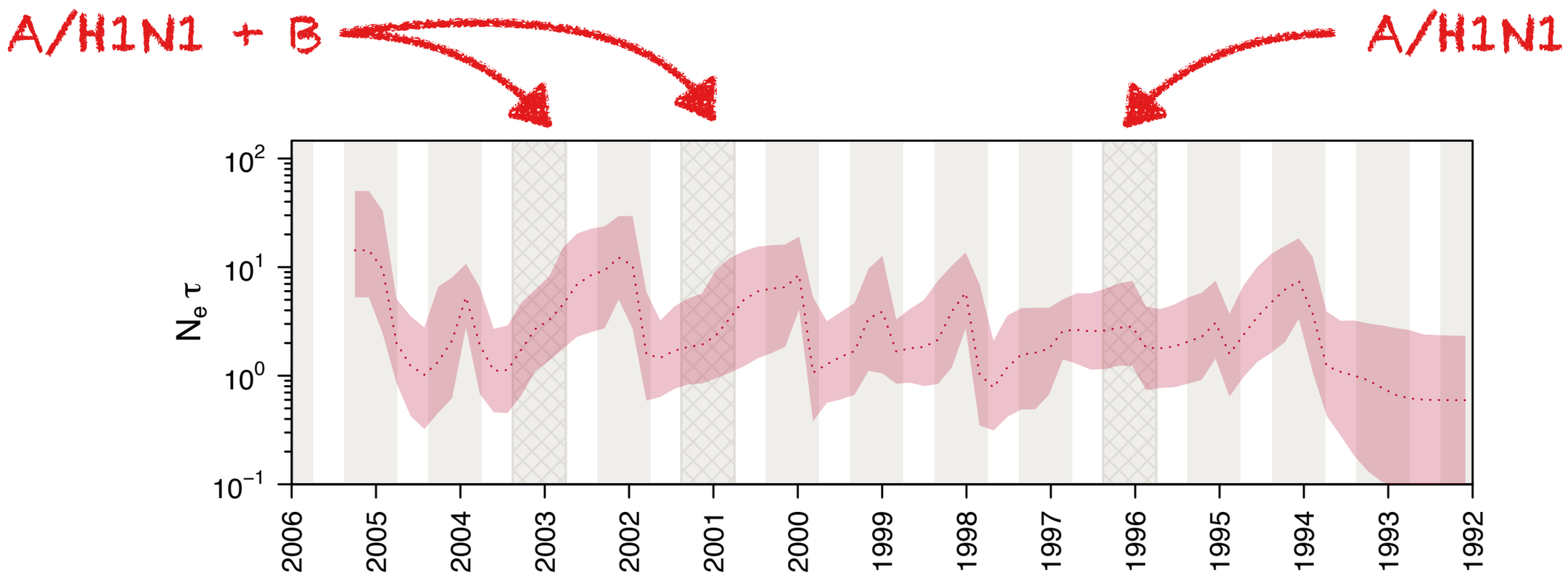

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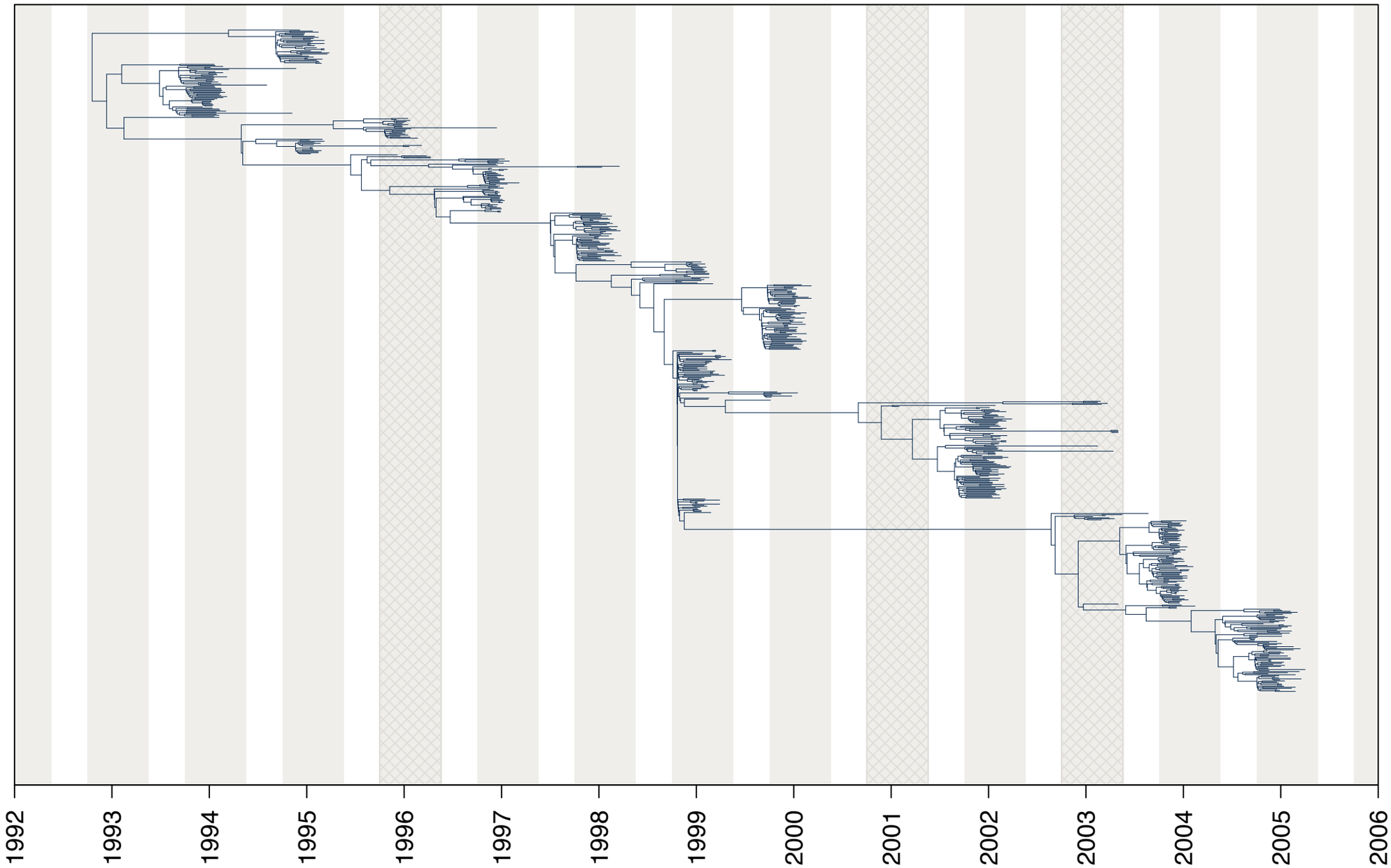

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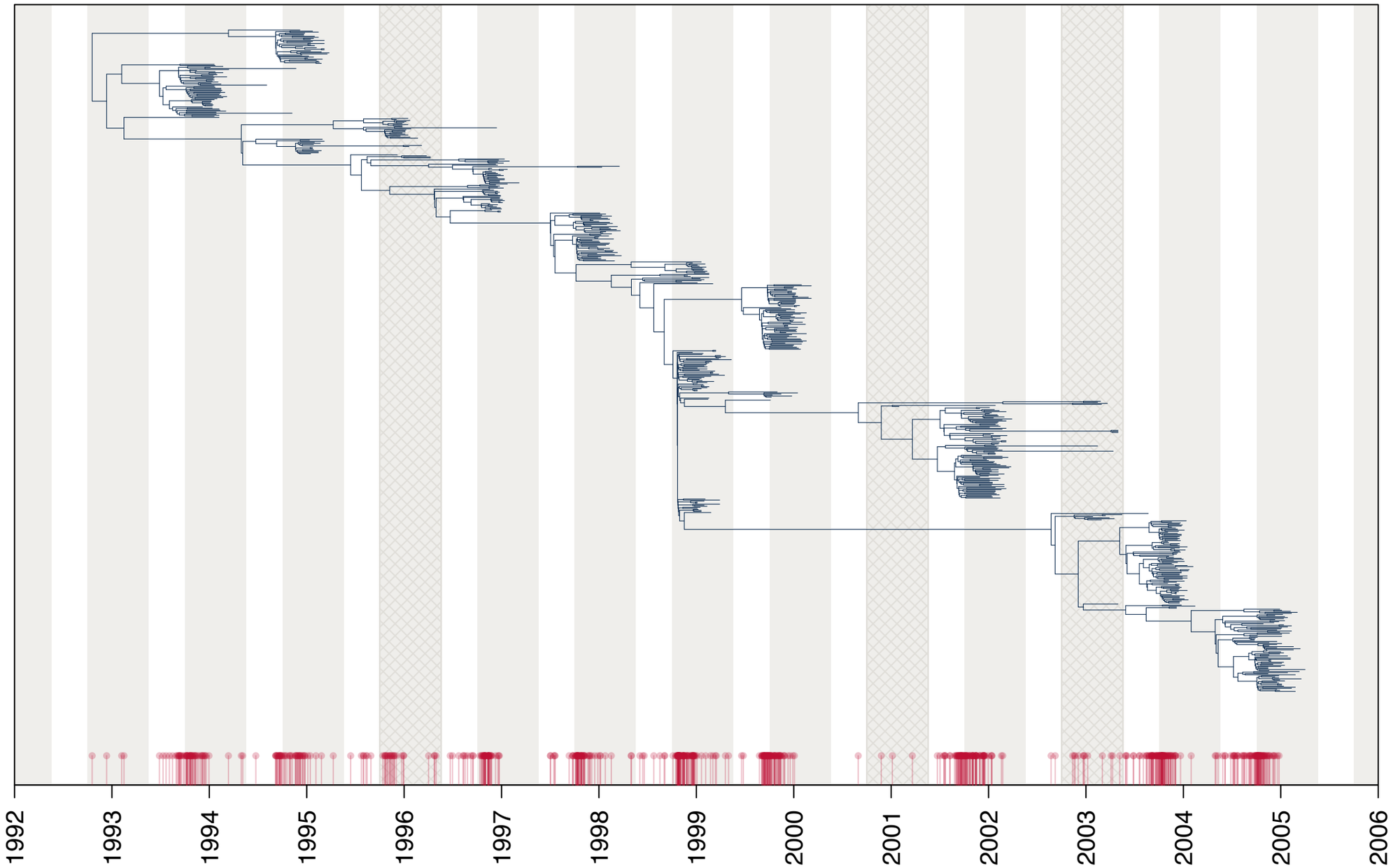
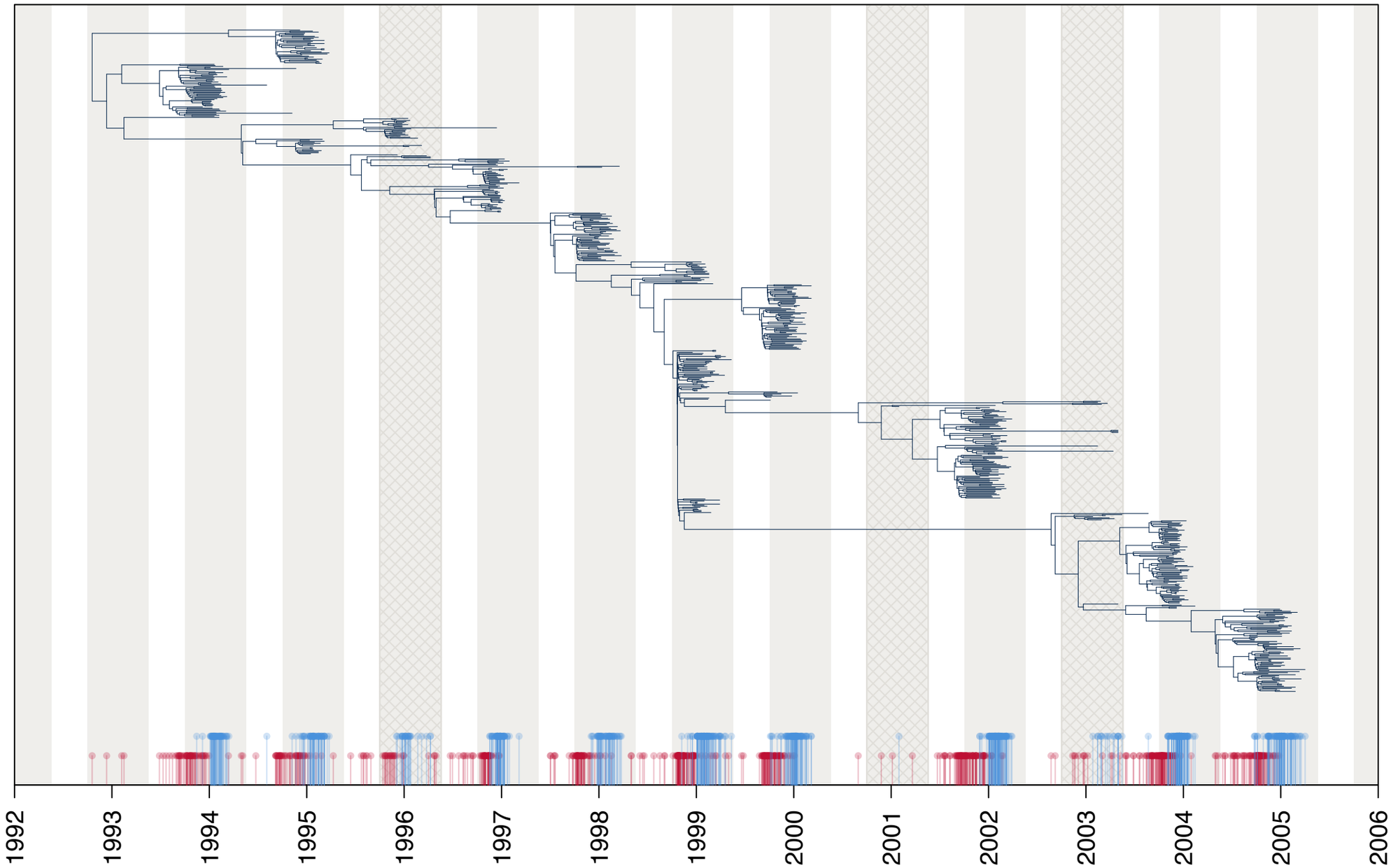


Only coalescent times are informative to the Bayesian Skyline Plot!

Bayesian Skyline Plot **(BSP)**

637 New York Influenza A/H3N2 HA sequences across 12 seasons



What about the sampling times?

Bayesian Skyline Plot **(BSP)**

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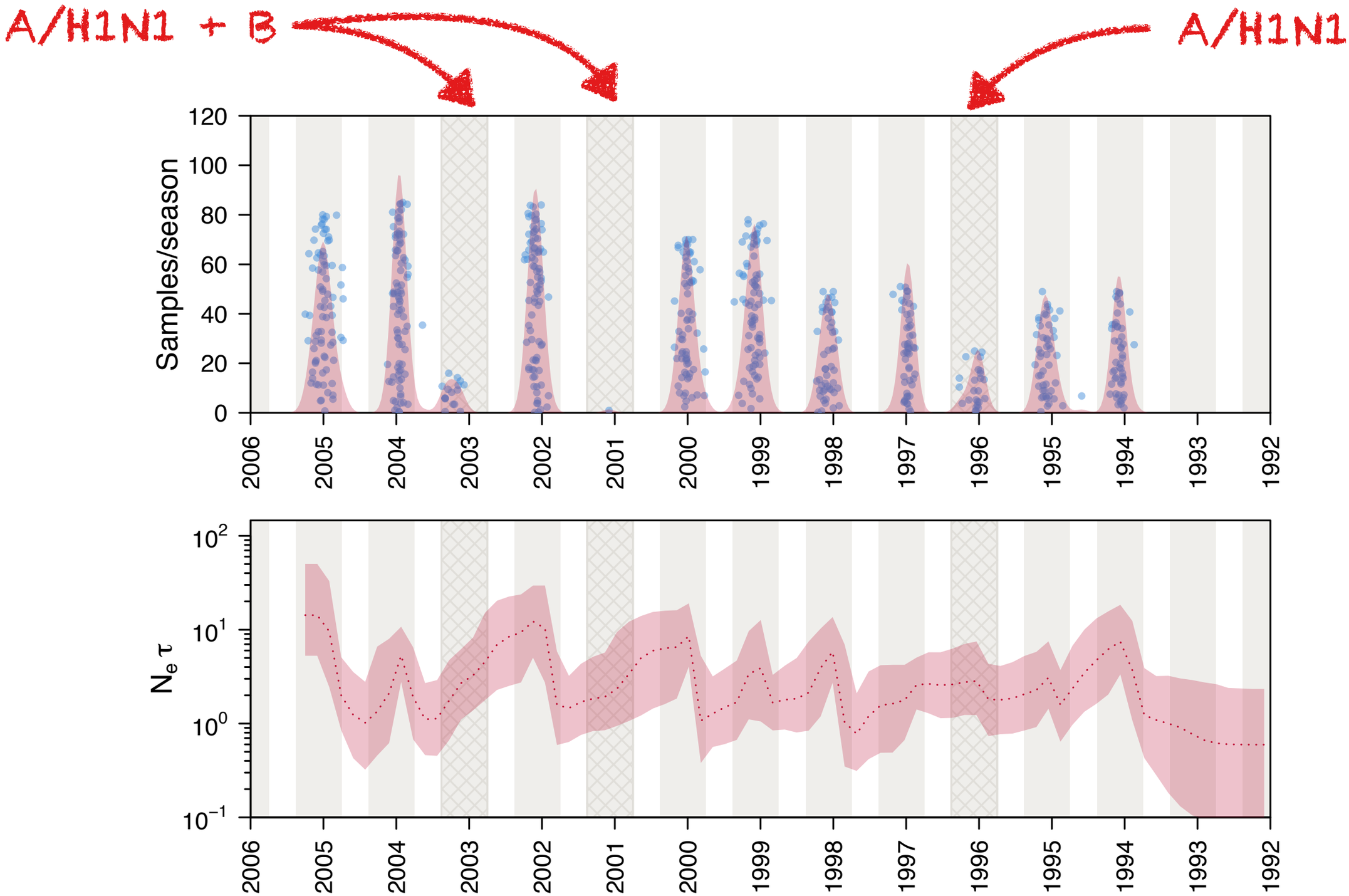

Coalescent with sampling

- Sampling events follow a Poisson process
- Sampling is proportional to population size with intensity β

Sampling rate: $\psi = \beta \cdot N(t)$

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Sampling through time and phylodynamic inference with coalescent and birth–death models

Erik M. Volz[1] and Simon D. W. Frost[2]

- Added to exponential growth coalescent

PLOS | COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Quantifying and Mitigating the Effect of Preferential Sampling on Phylodynamic Inference

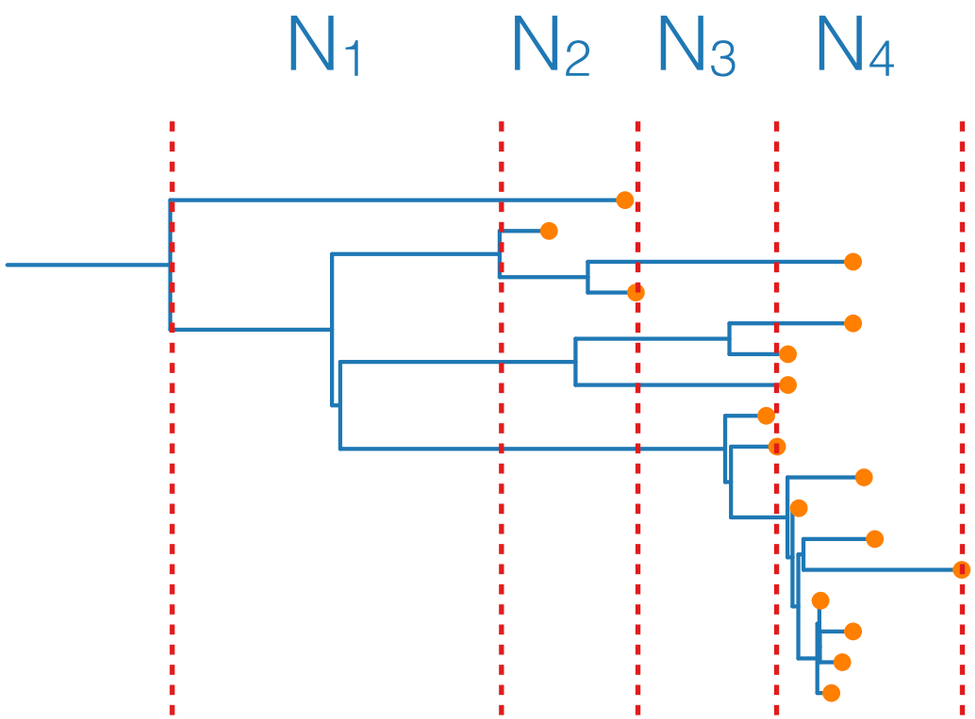
Michael D. Karcher[1], Julia A. Palacios[2,3,4], Trevor Bedford[5], Marc A. Suchard[6,7,8], Vladimir N. Minin[1,9]*

- Added to a Skygrid model
- Non-linear dependence on population size (preferential sampling)

Bayesian Epoch Sampling Skyline plot **(BESP)**

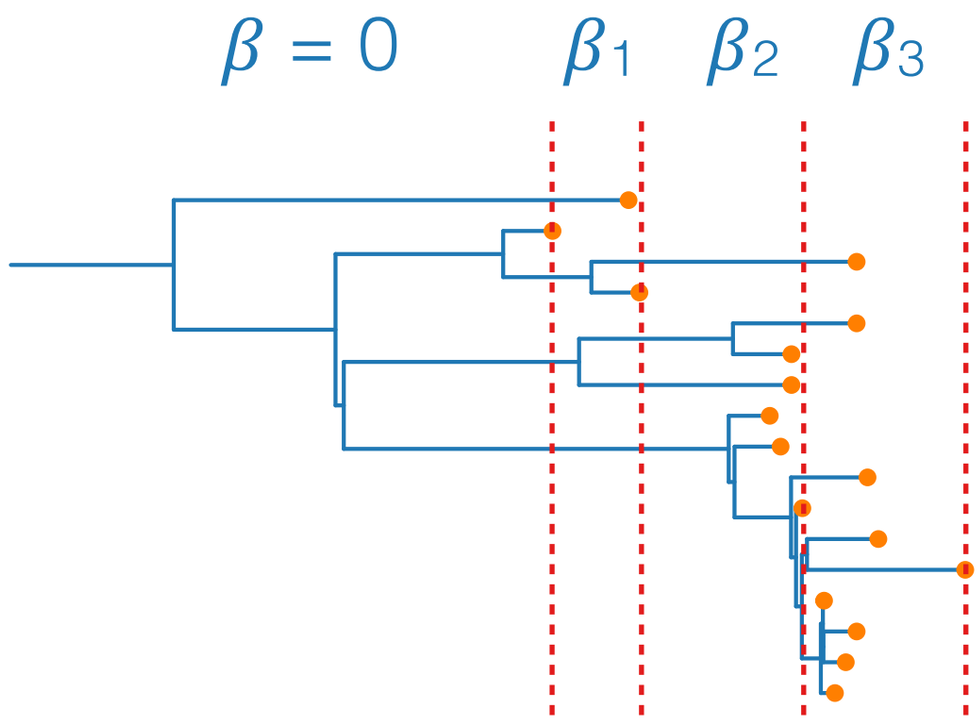
Allow for flexible nonparametric sampling model while ensuring identifiability

Population size



- Group into segments between TMRCA and present
- Change-point times can fall on coalescent or sampling events
- ≥ 2 events / segment

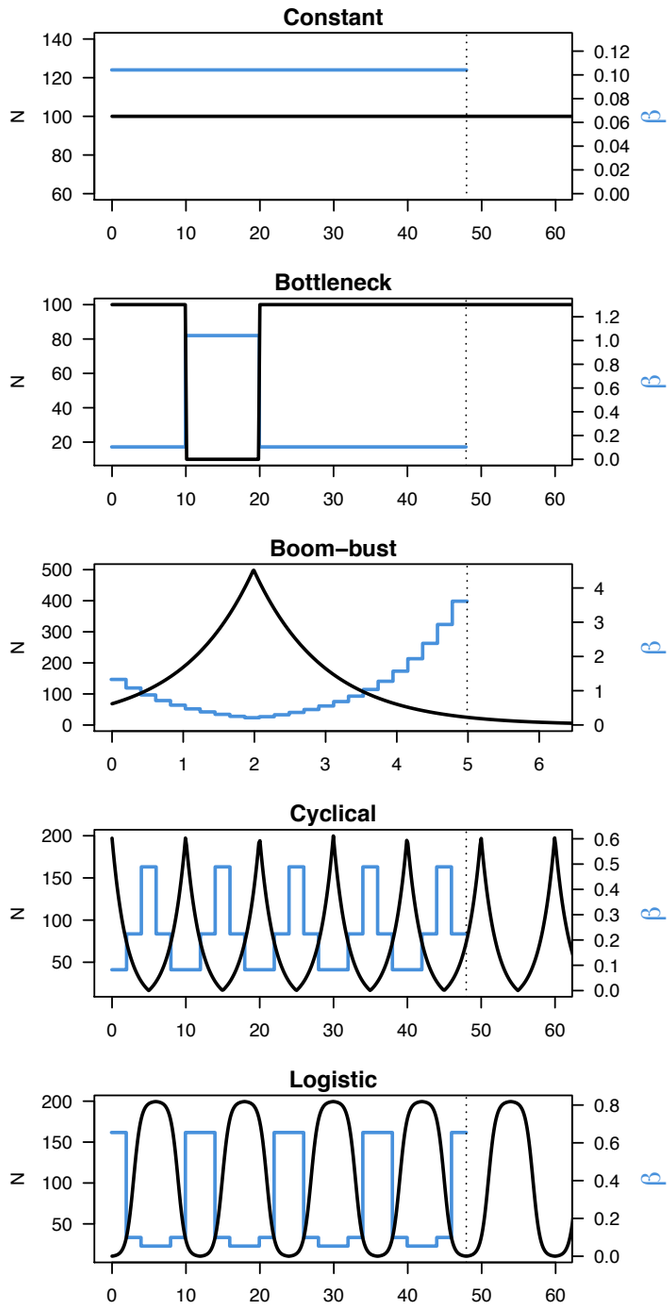
Sampling intensity



- Group into epochs between oldest and most recent samples
- Change-point times fall on sampling events
- ≥ 2 events / epoch

Simulation study **(BEAST2 implementation)**

100 replicates / population trajectory simulated with **24 sampling epochs**



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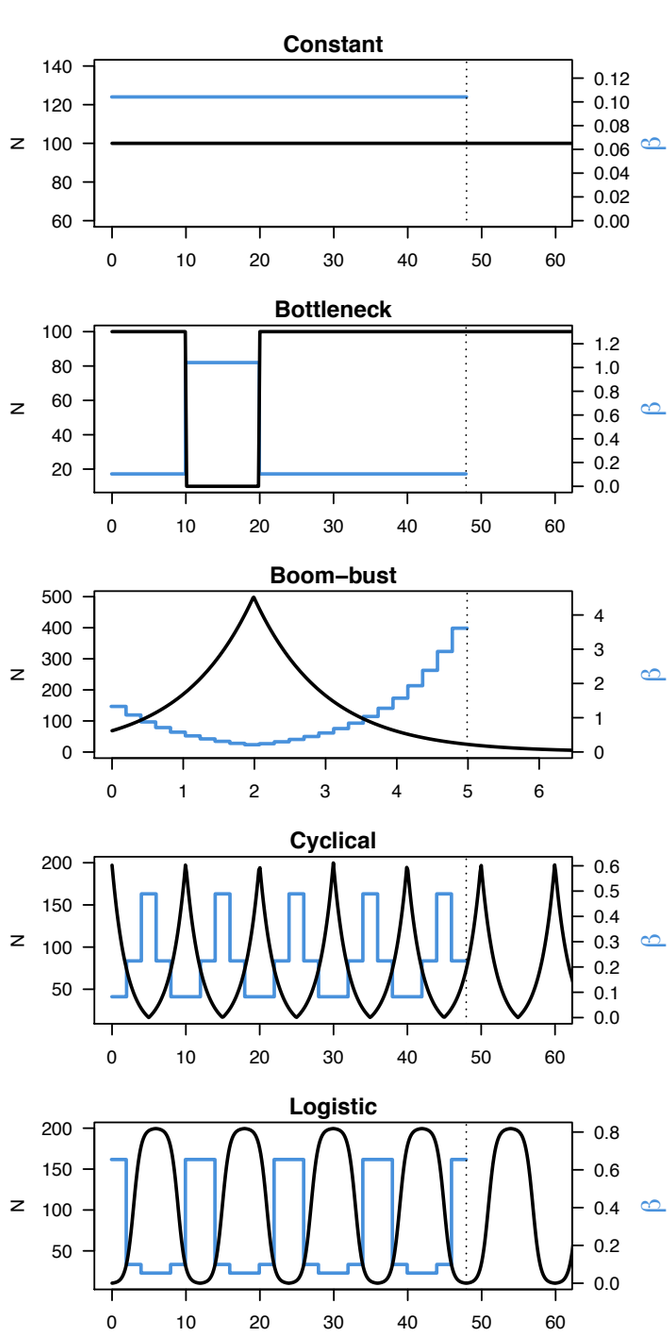

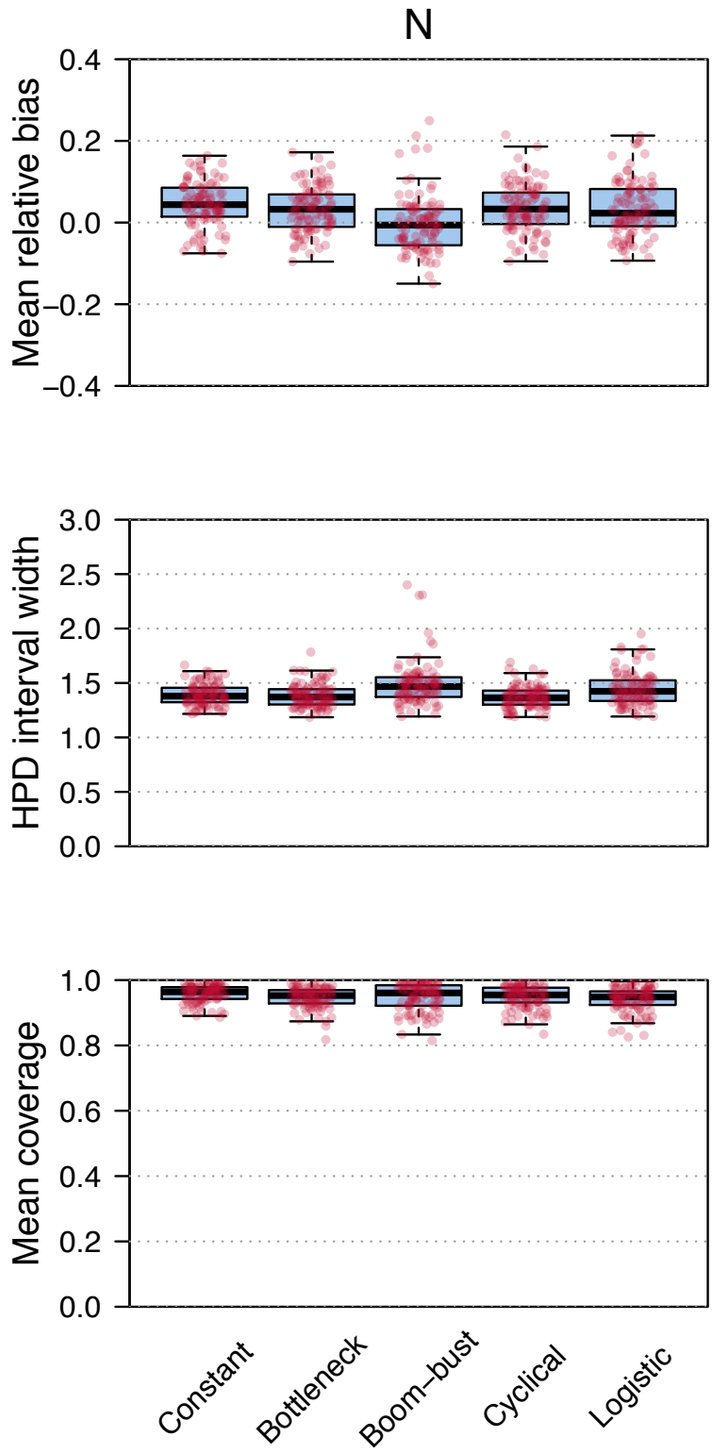

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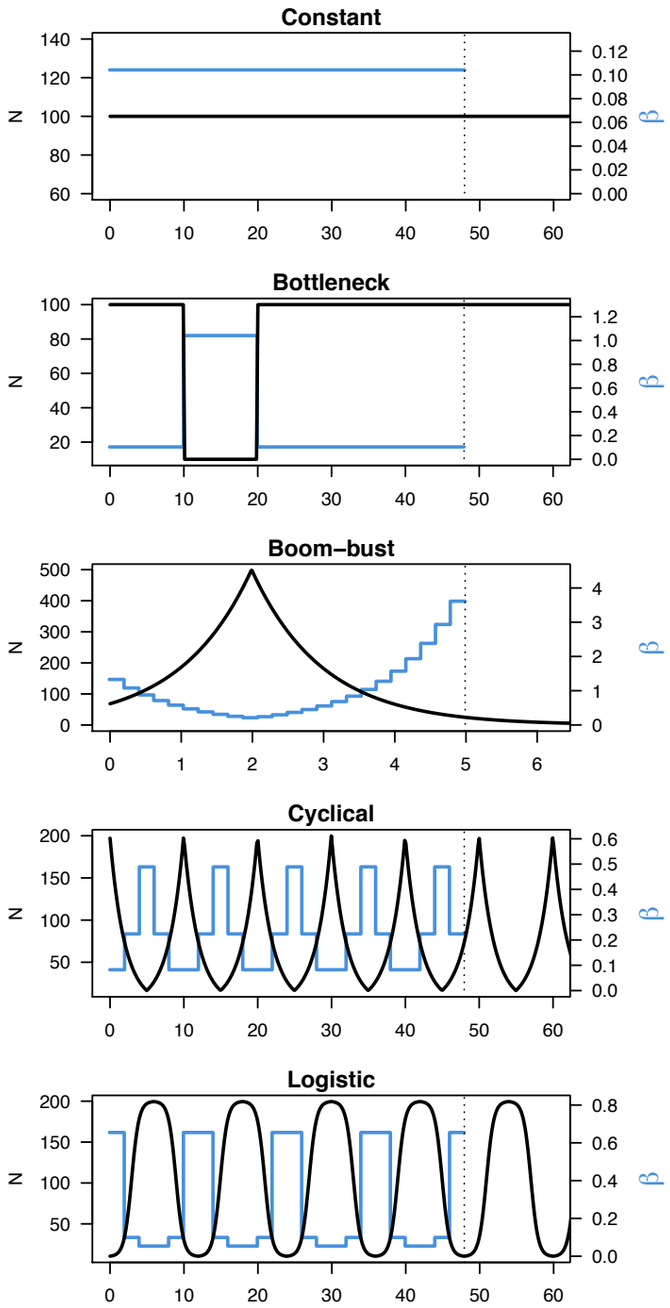
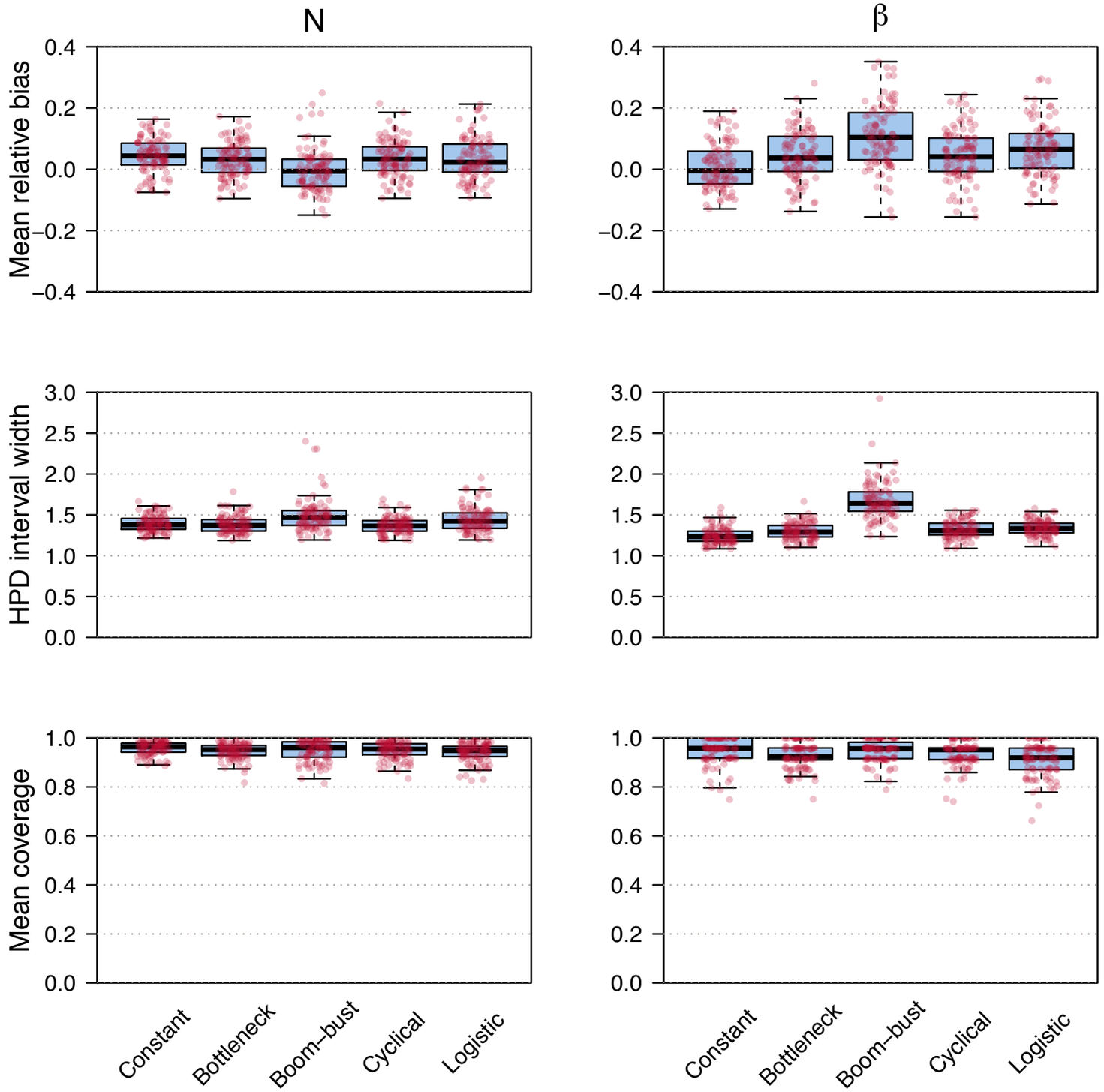
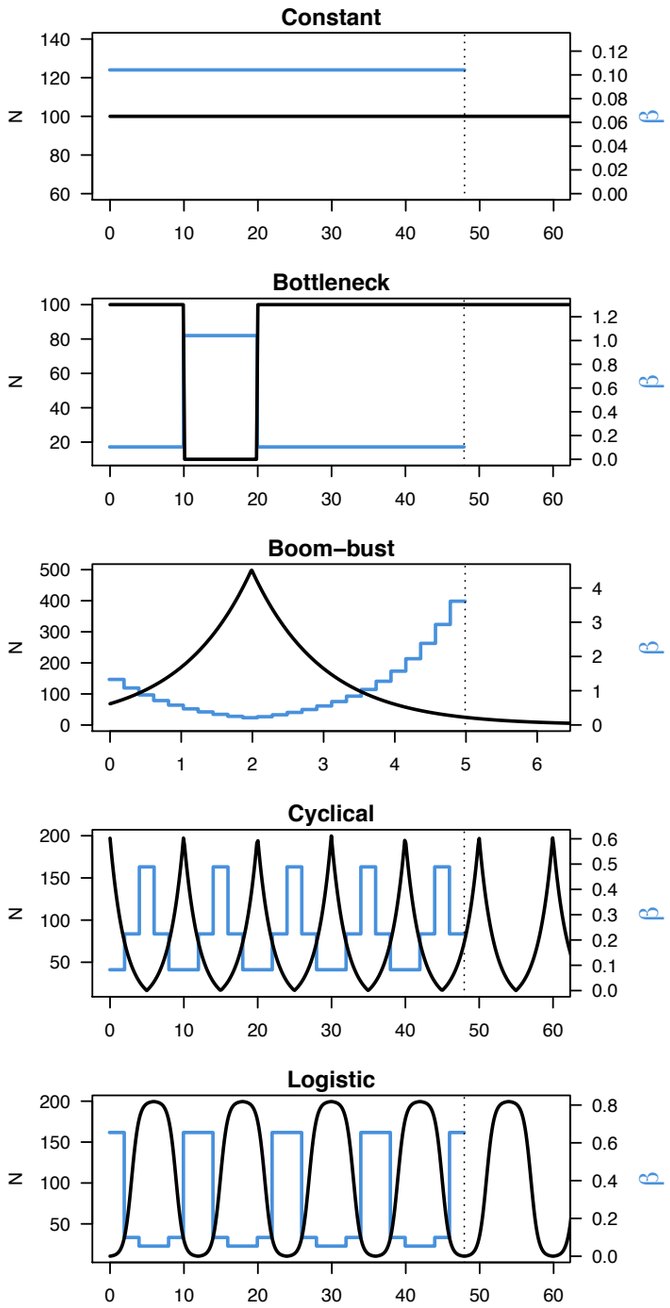
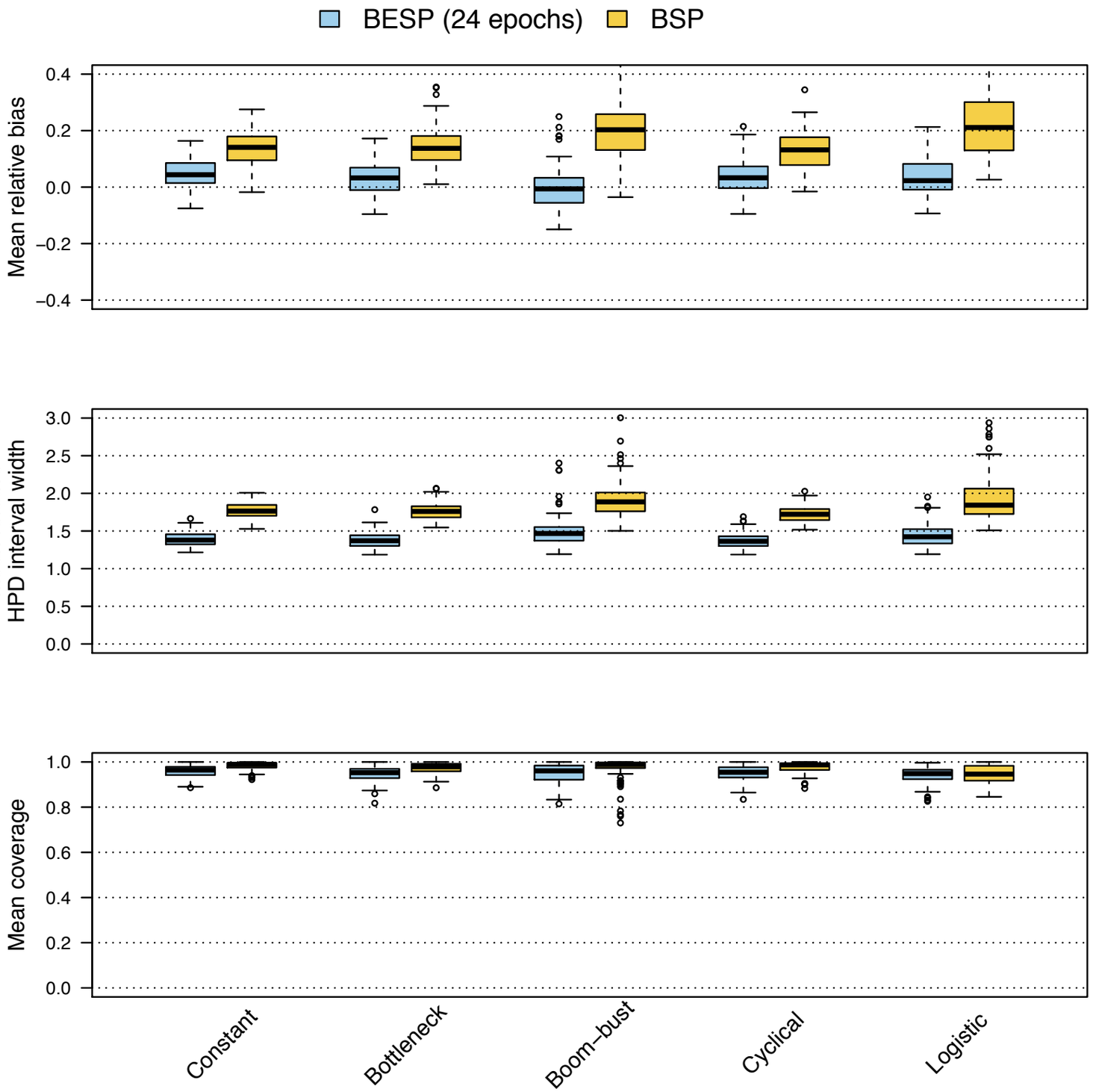




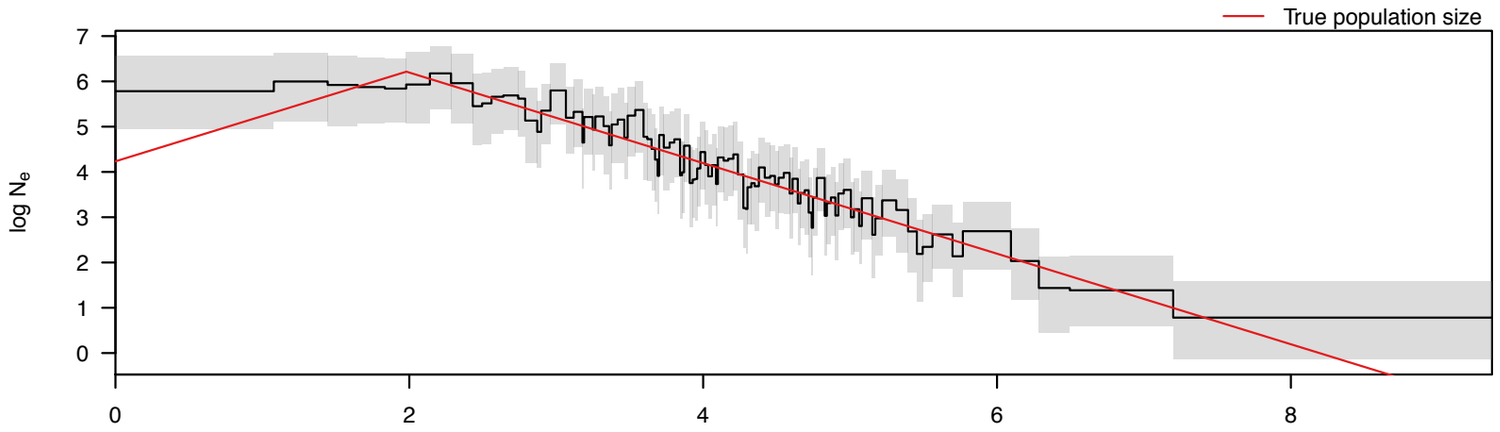
Simulation study **(population size — N)**

100 replicates / population trajectory simulated with **24 sampling epochs**

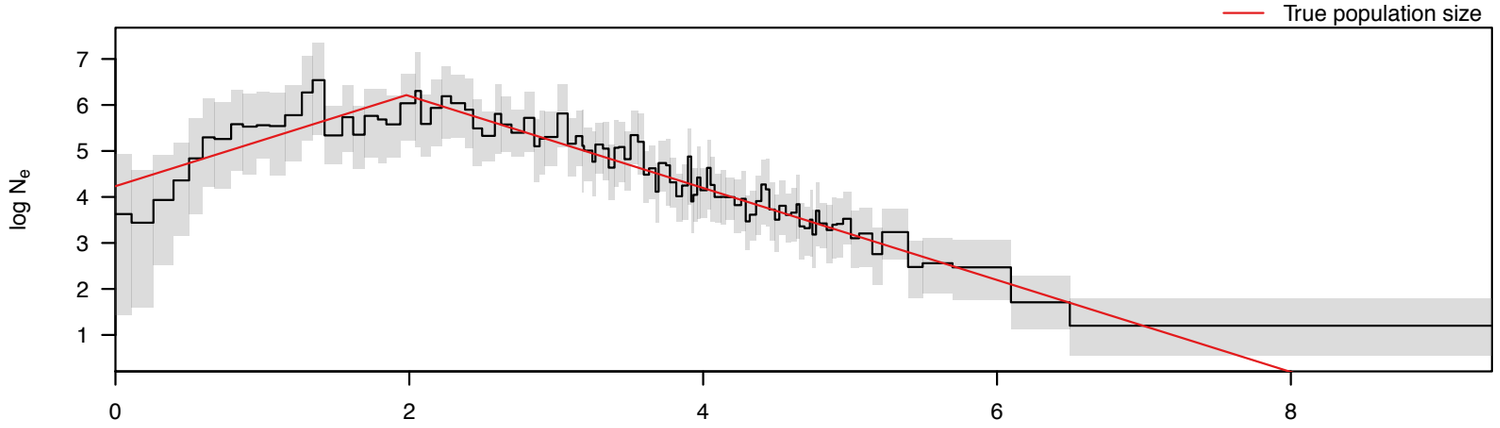




Boom-bust example

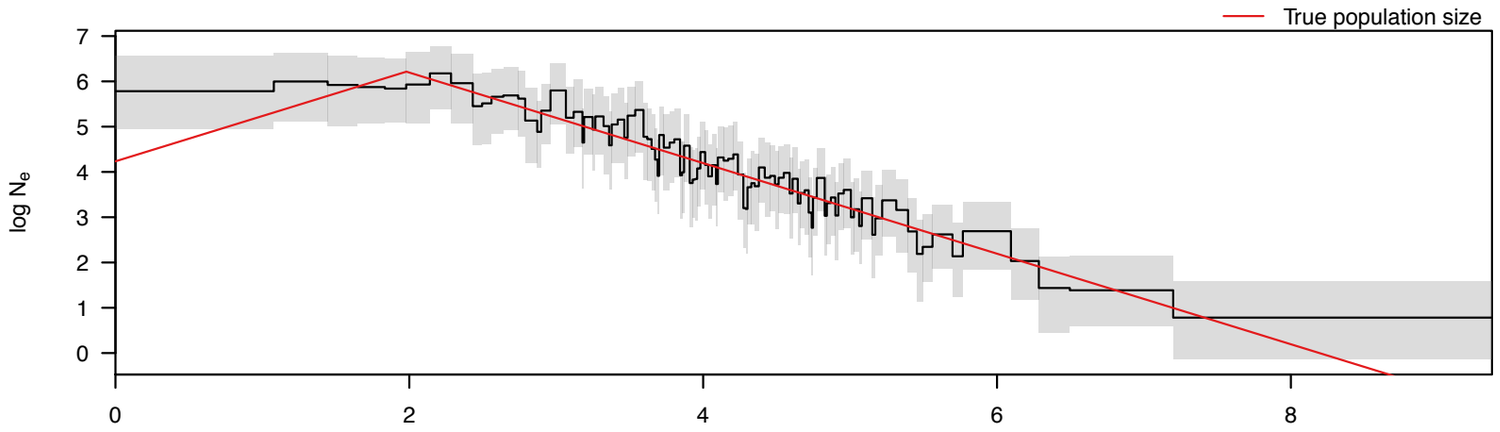


Bayesian Skyline plot



Bayesian Epoch Sampling Skyline plot

Boom-bust example



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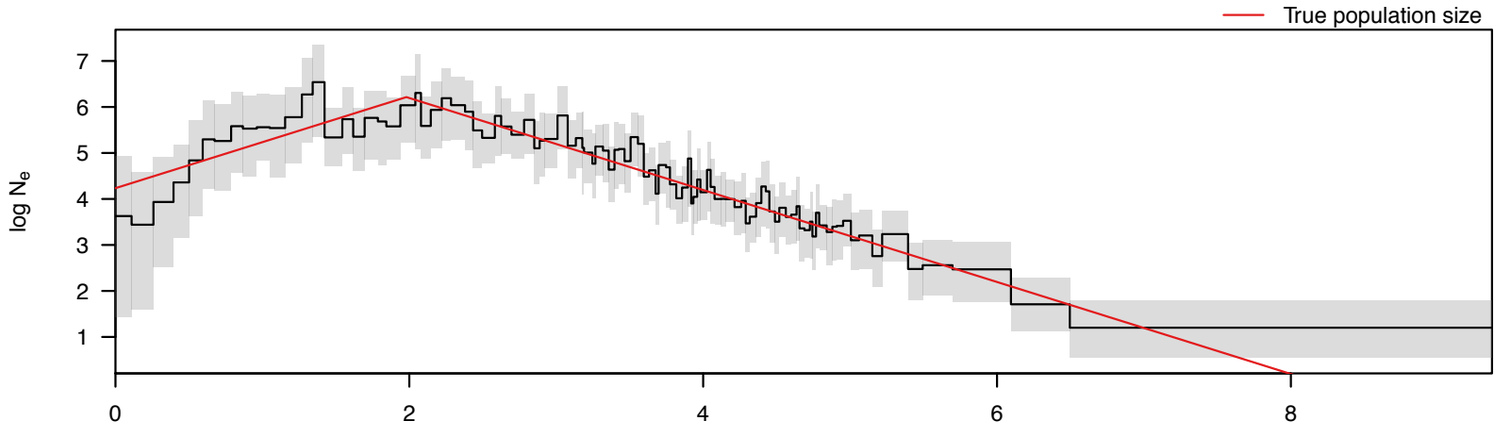

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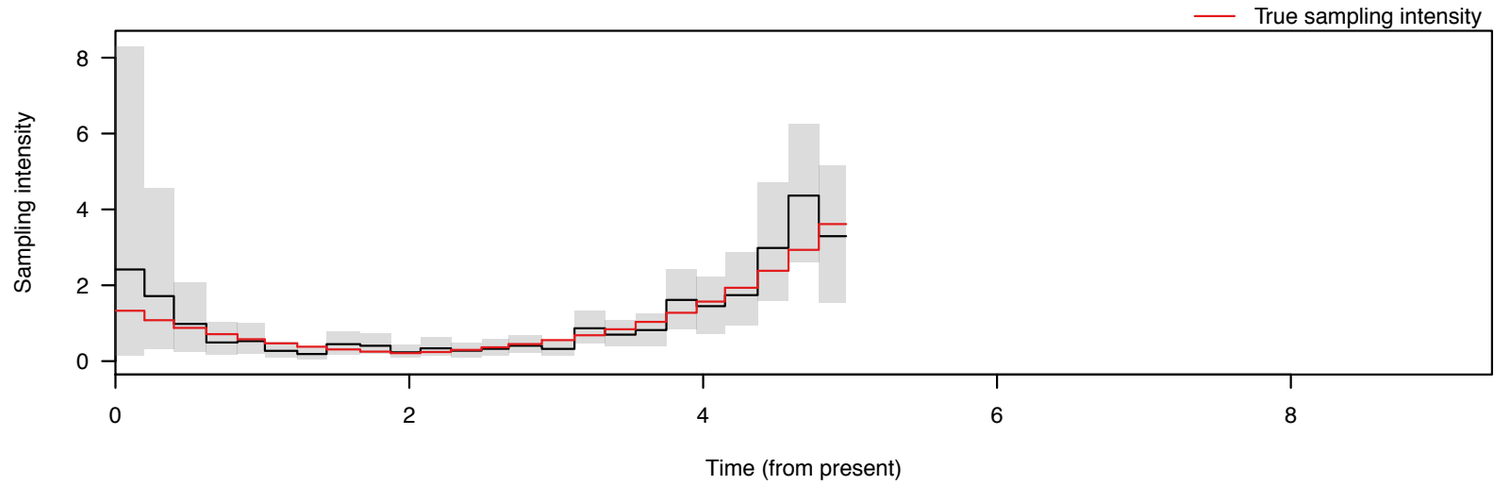
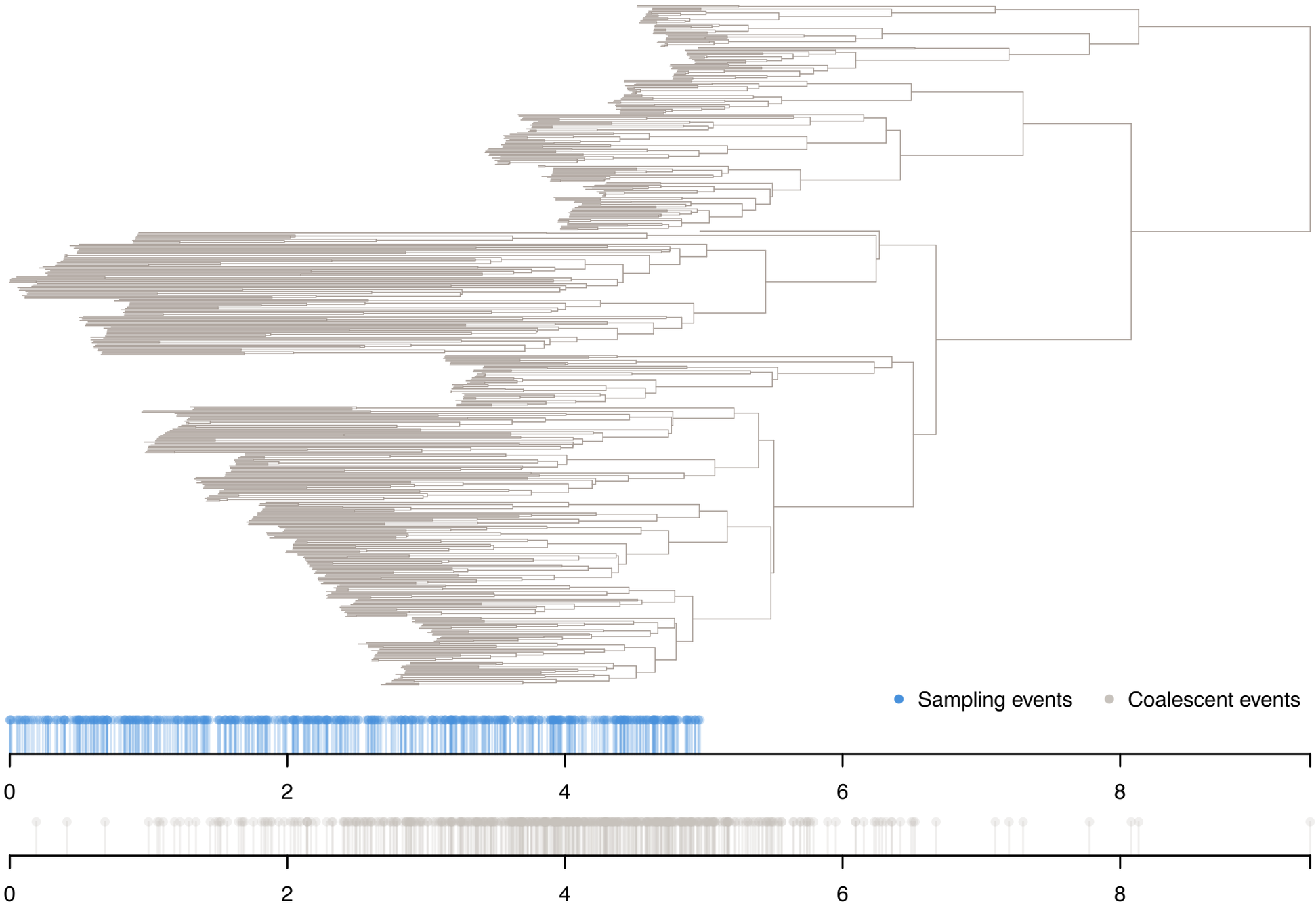
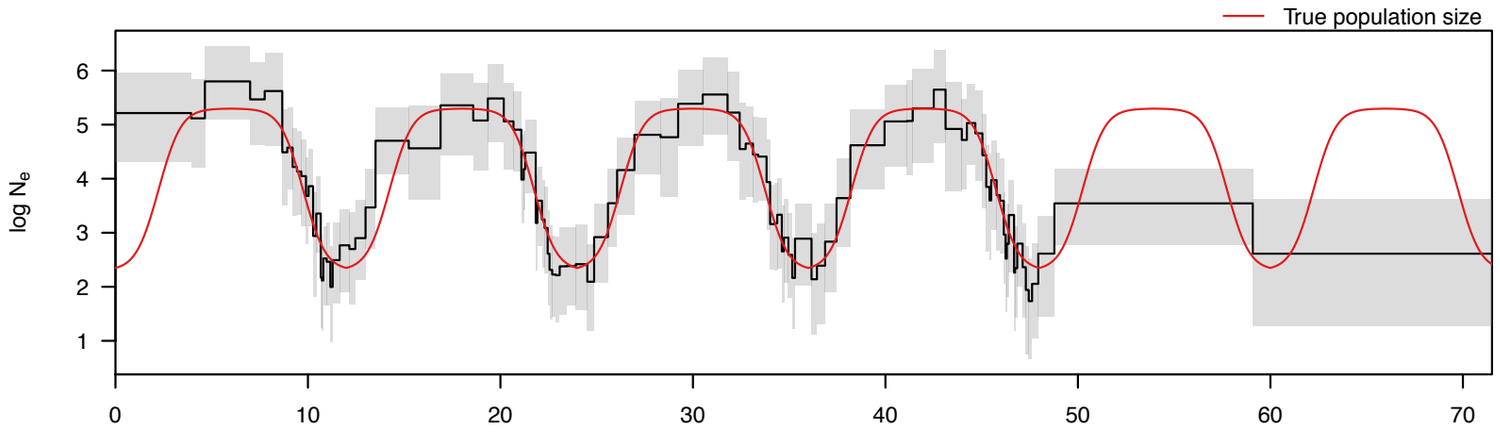


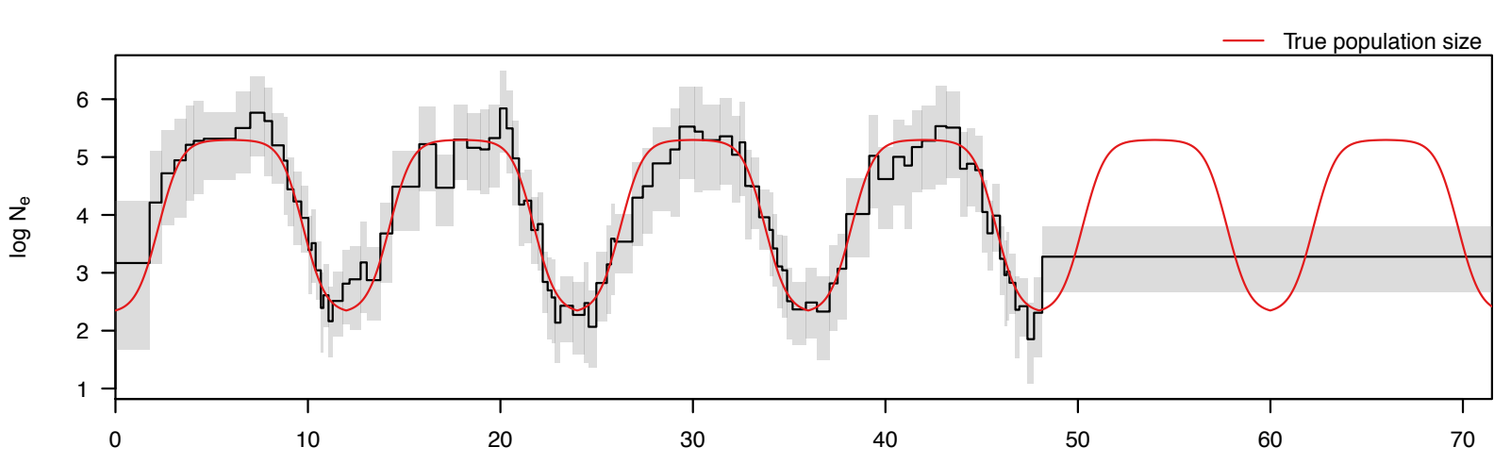


- Not many coalescences during population decline…
- Using sampling time information **doubles** the number of informative data points

Logistic growth and decline example



Bayesian Skyline plot



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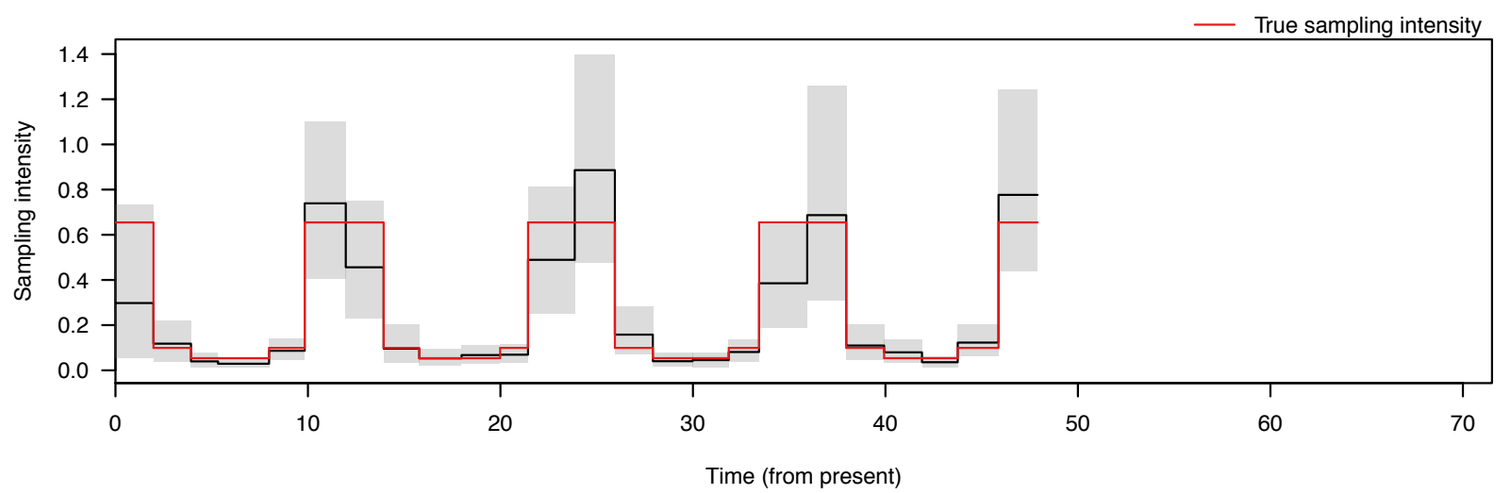

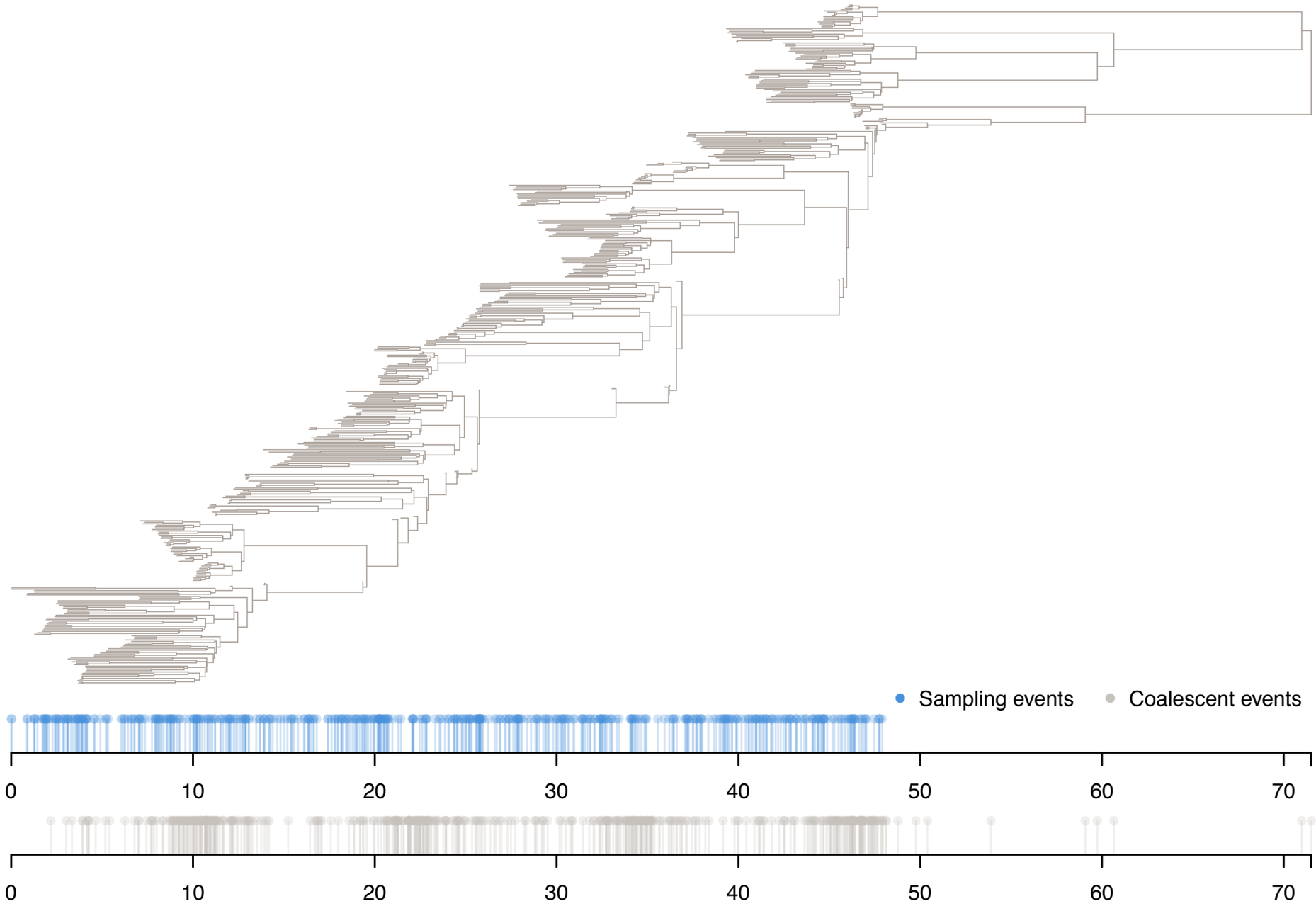

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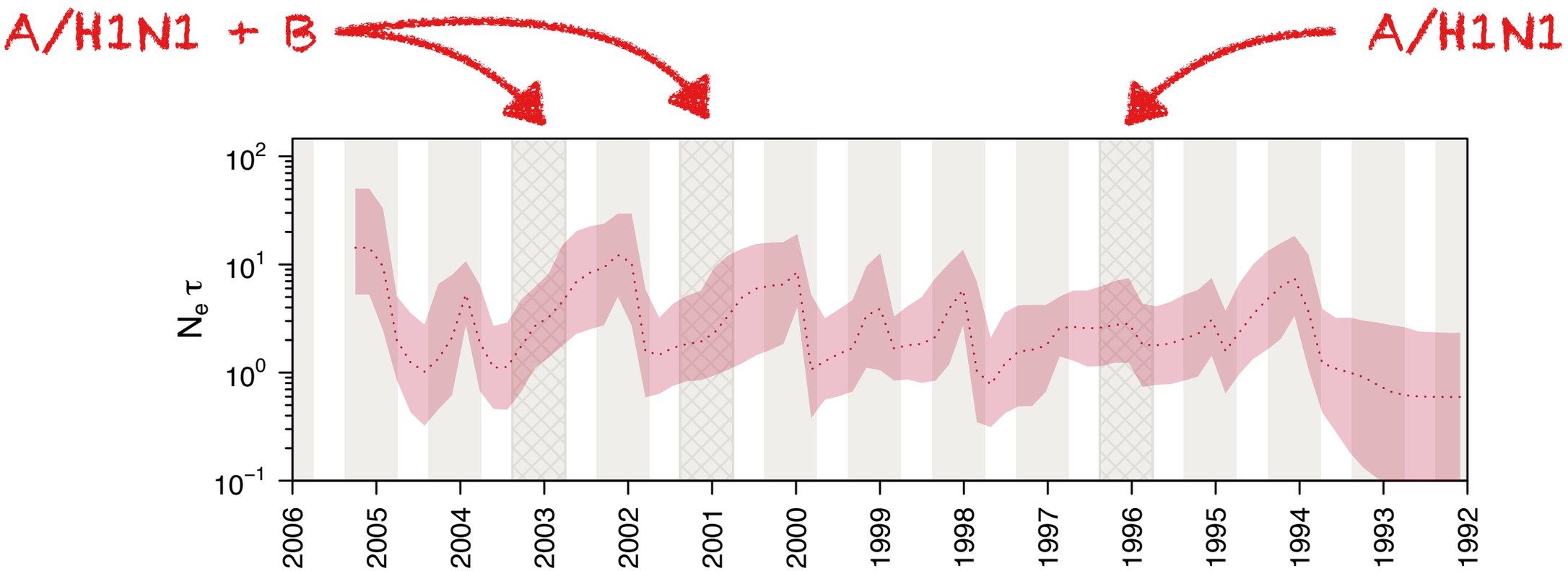

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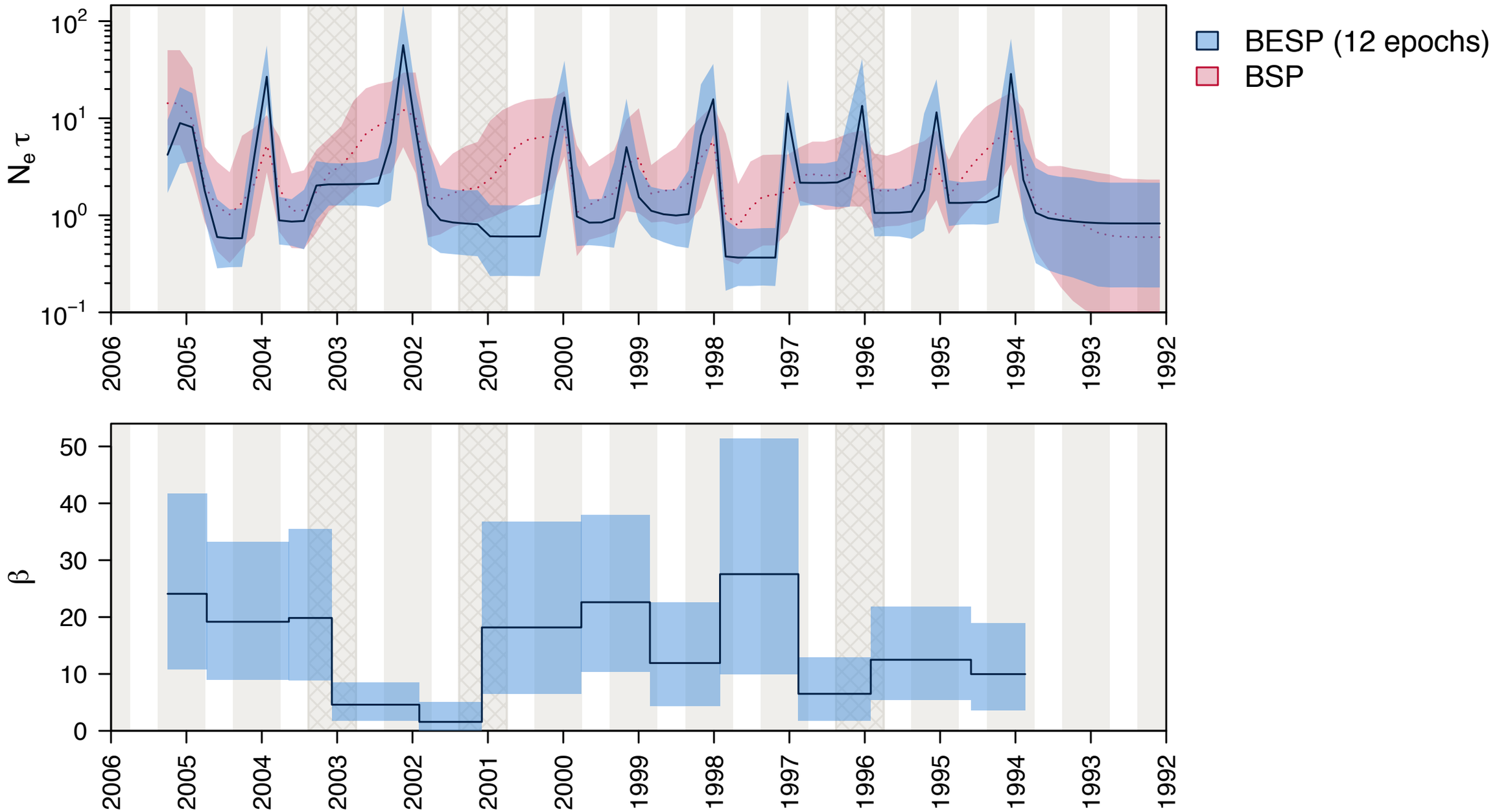
A/H1N1 + B

A/H1N1



New Results

Jointly inferring the dynamics of population size and sampling intensity from molecular sequences

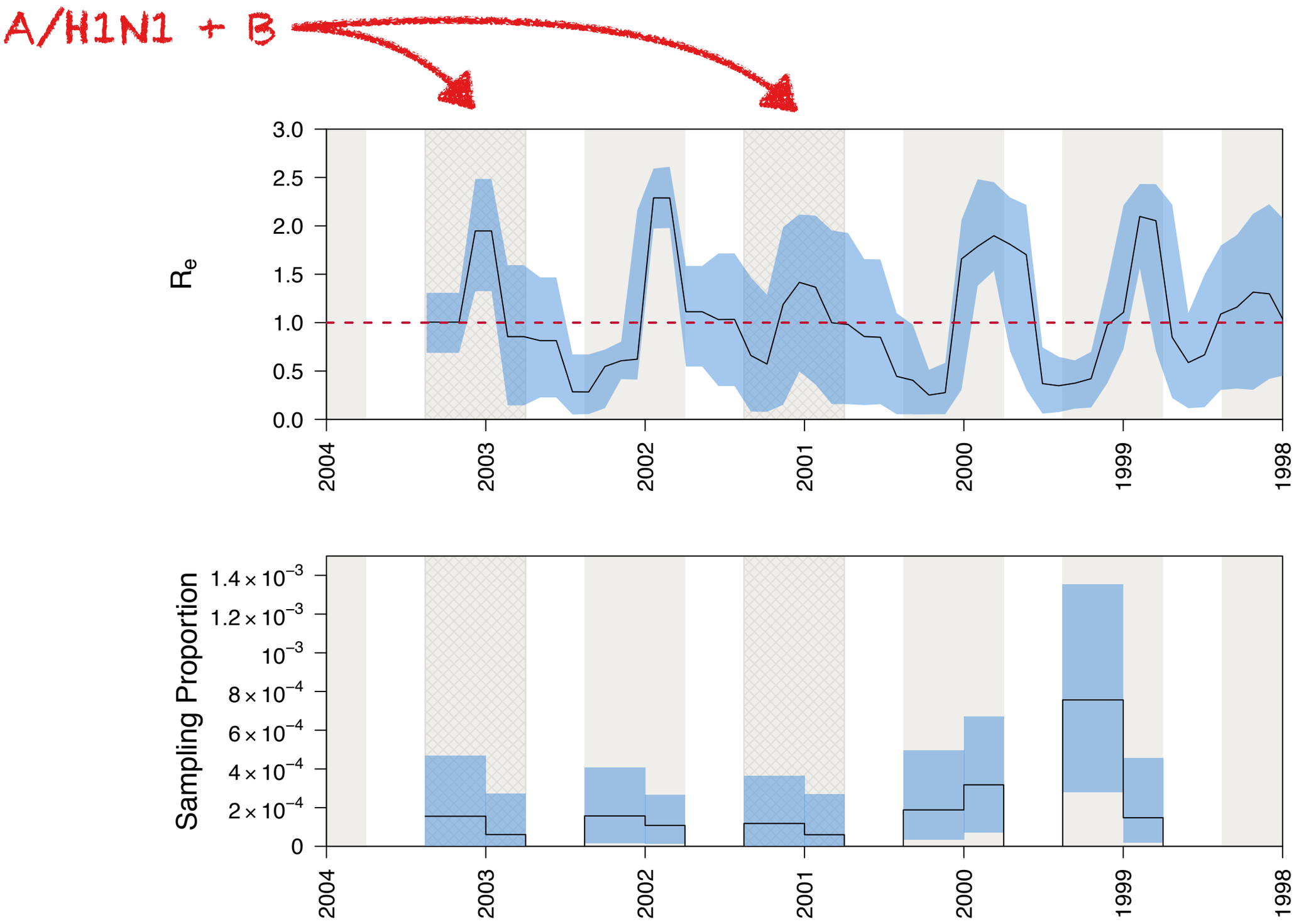
KV Parag, L du Plessis, OG Pybus

doi: https://doi.org/10.1101/686378

BEAST2 package:
github.com/laduplessis/besp/

Birth-death skyline digression

249 New York Influenza A/H3N2 HA sequences across 5 seasons



Birth-death skyline digression

249 New York Influenza A/H3N2 HA sequences across 5 seasons

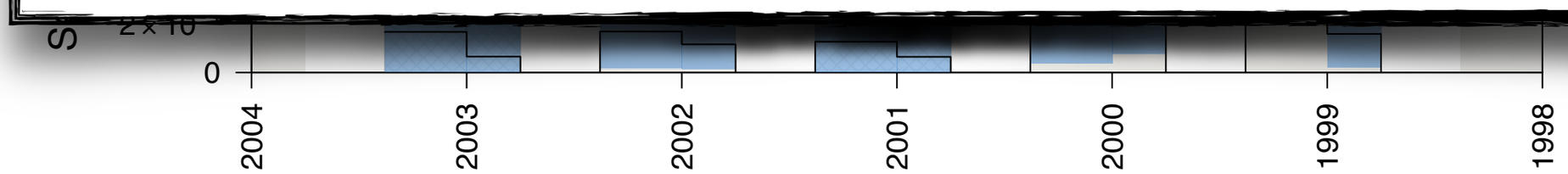
A/H1N

Caveats:

- Parameter-rich models
- To ensure identifiability need to fix parameters *a priori* or use very strong priors

Personal experience:

- When the fraction of sampled cases is **small** the sampling proportion is **not identifiable** (Zika, Influenza, Dengue, Chikungunya etc.)
- Only relative changes are identifiable



Summary

- **Sampling times are informative about population dynamics** (if they are non-random)
- **BESP** is a **flexible nonparametric** method for the **demographic history** and the **sampling process**
- **BEAST2** package

Things I left out

- Fast **maximum-likelihood solution**
- Accounting for sampling at least **doubles the precision**
- **Model is identifiable** and not overly reliant on strong priors

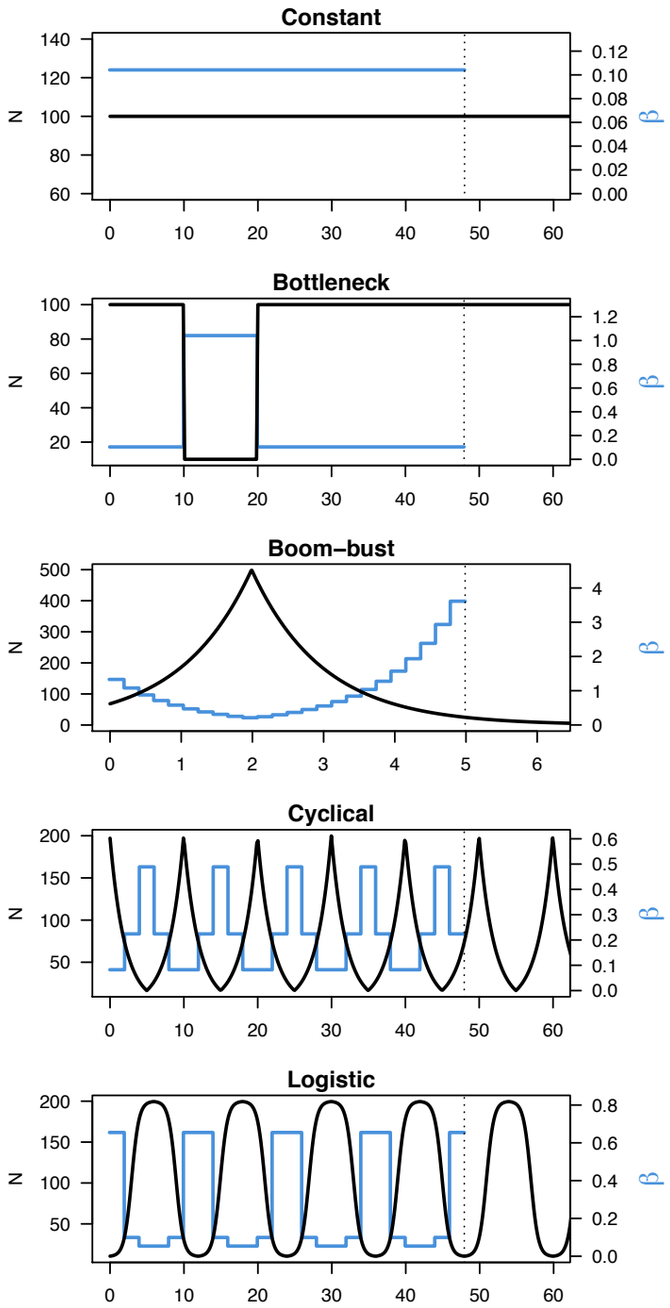
Thanks to:

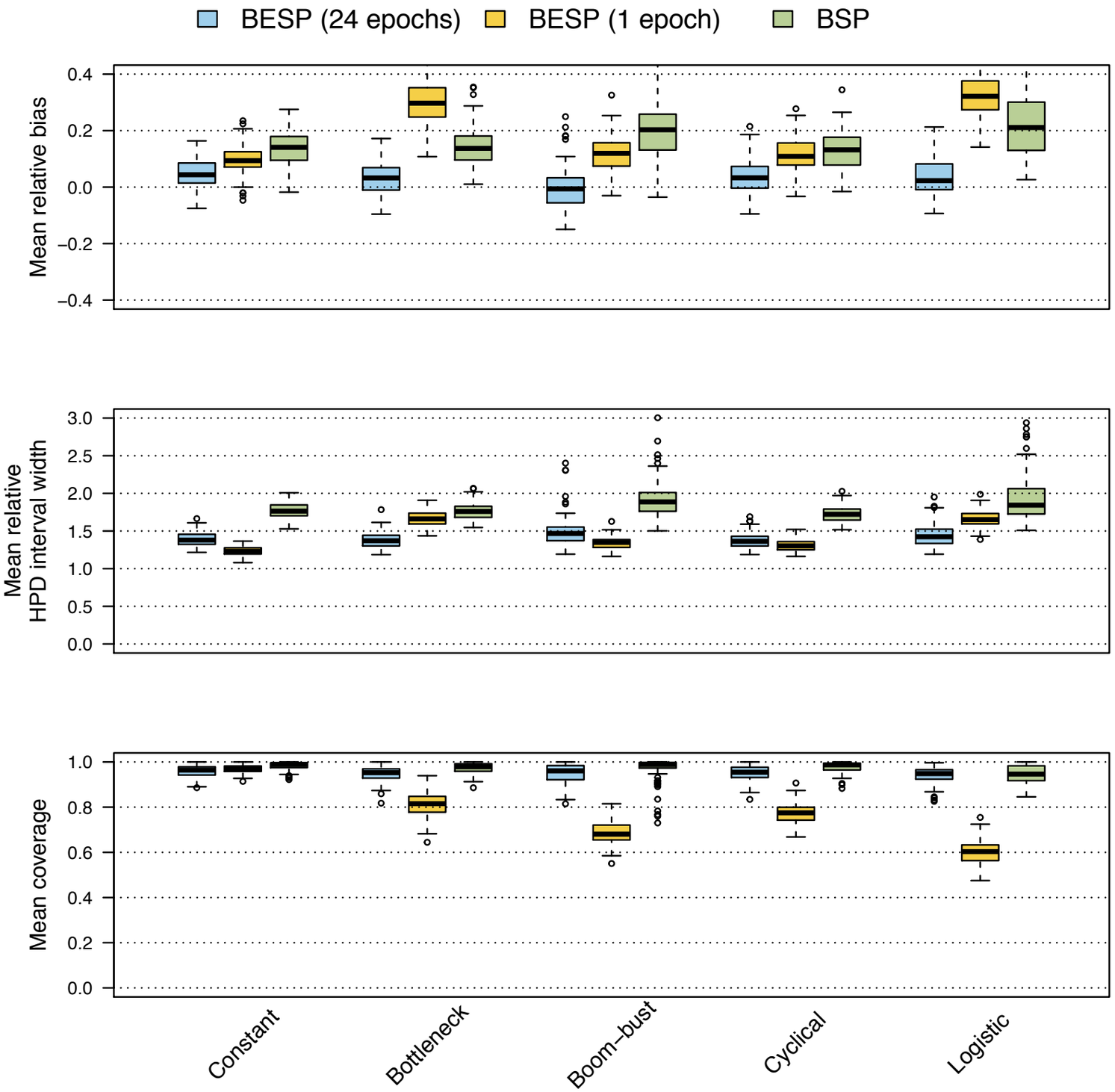
Kris Parag and Oliver Pybus

Edward Holmes, Beth Shapiro, Cécile Viboud, Amanda Perofsky

Simulation study **(population size — N)**

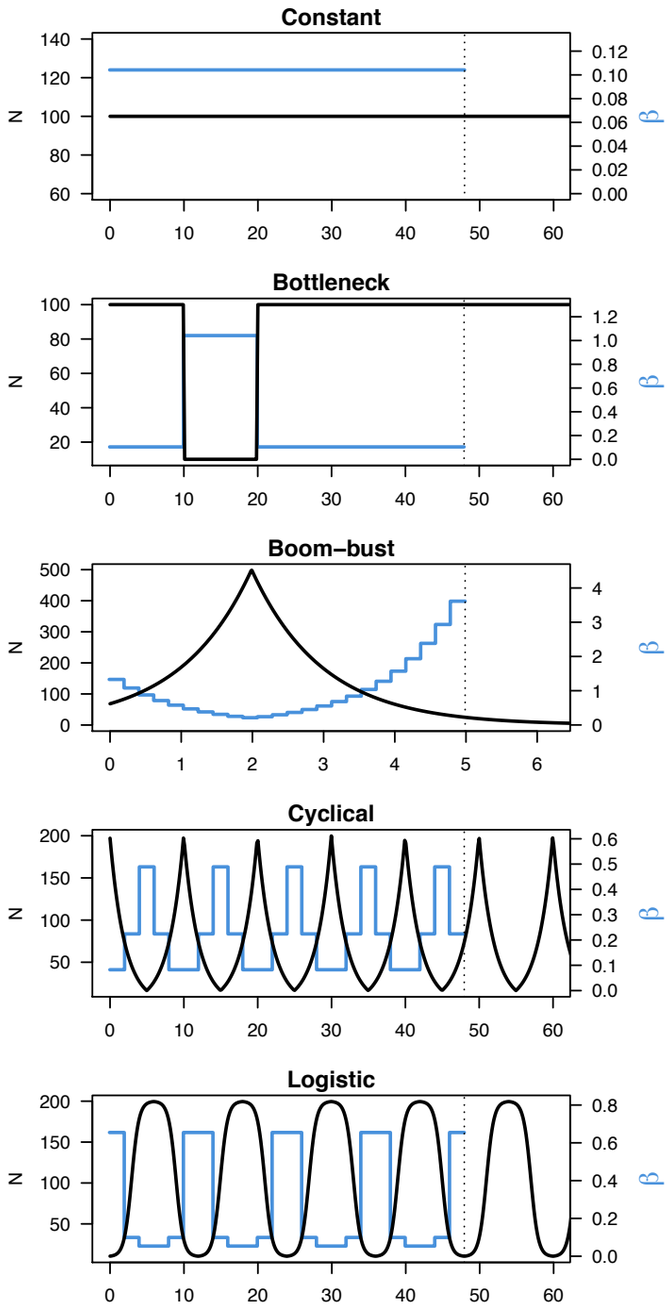
100 replicates / population trajectory using BEAST2 implementation

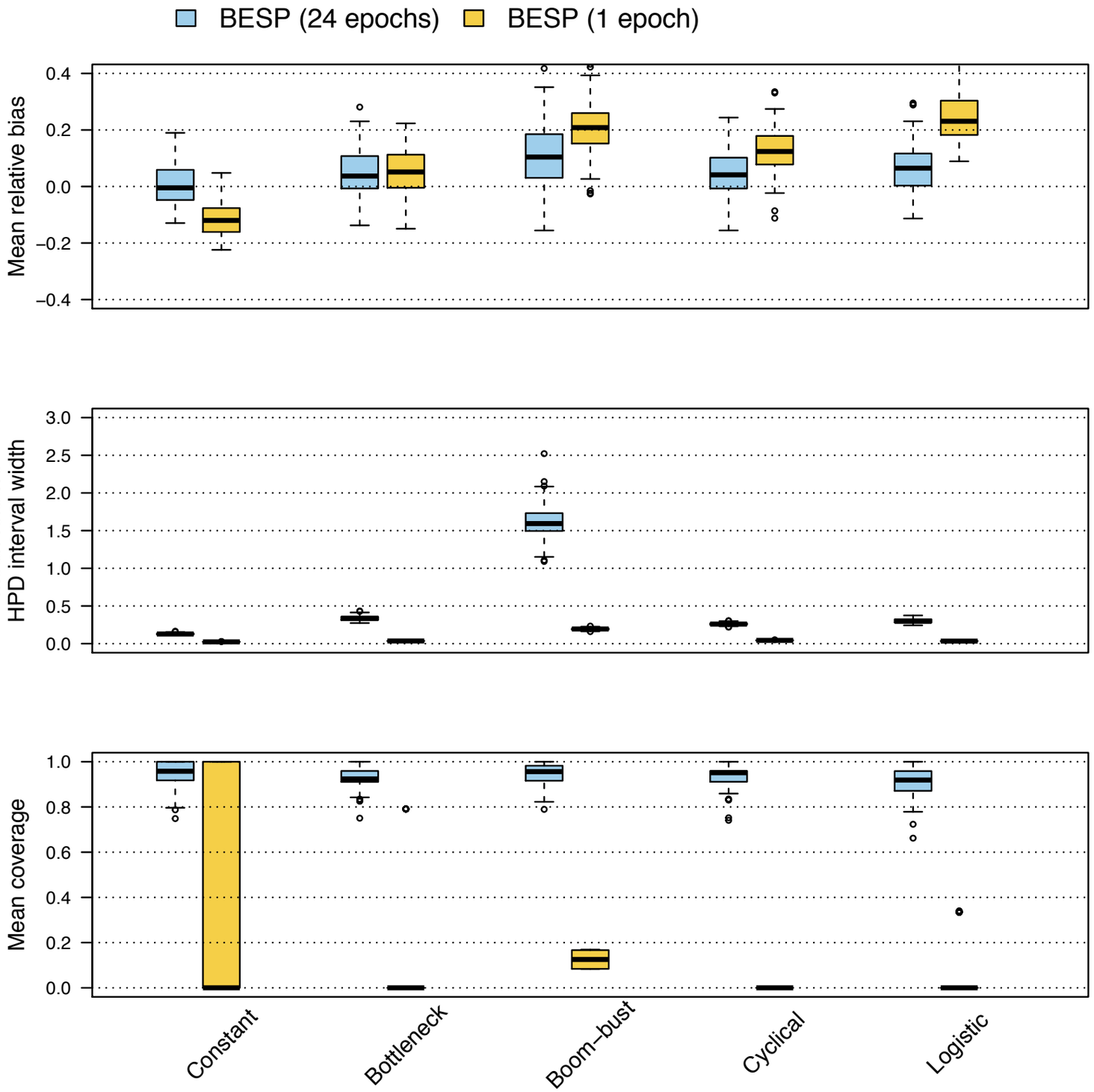




Simulation study **(sampling intensity — β)**

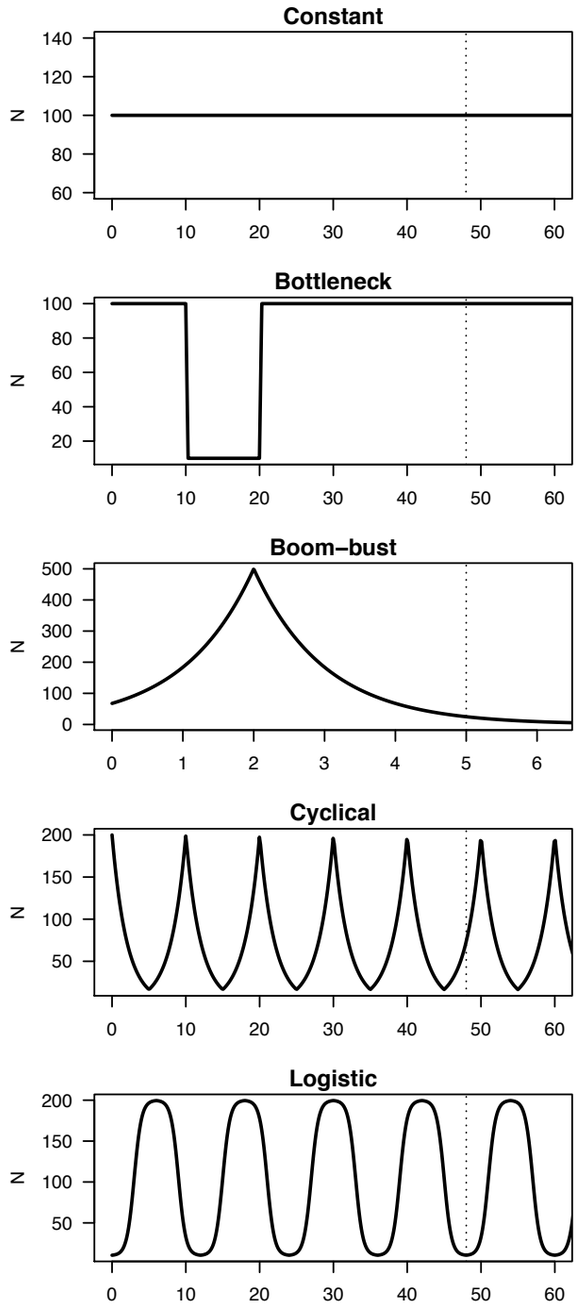
100 replicates / population trajectory using BEAST2 implementation

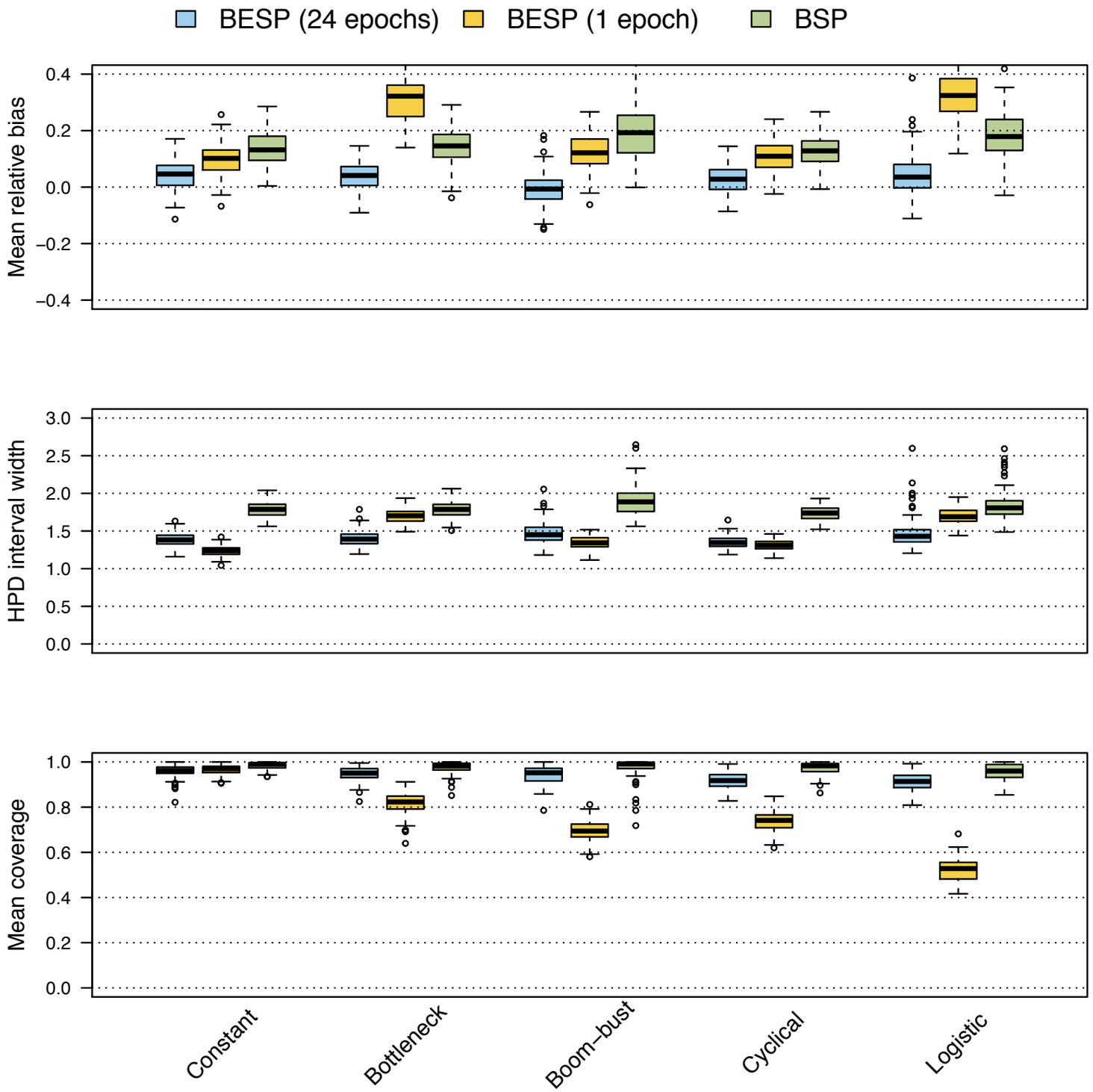




Simulation study **(population size — N)**

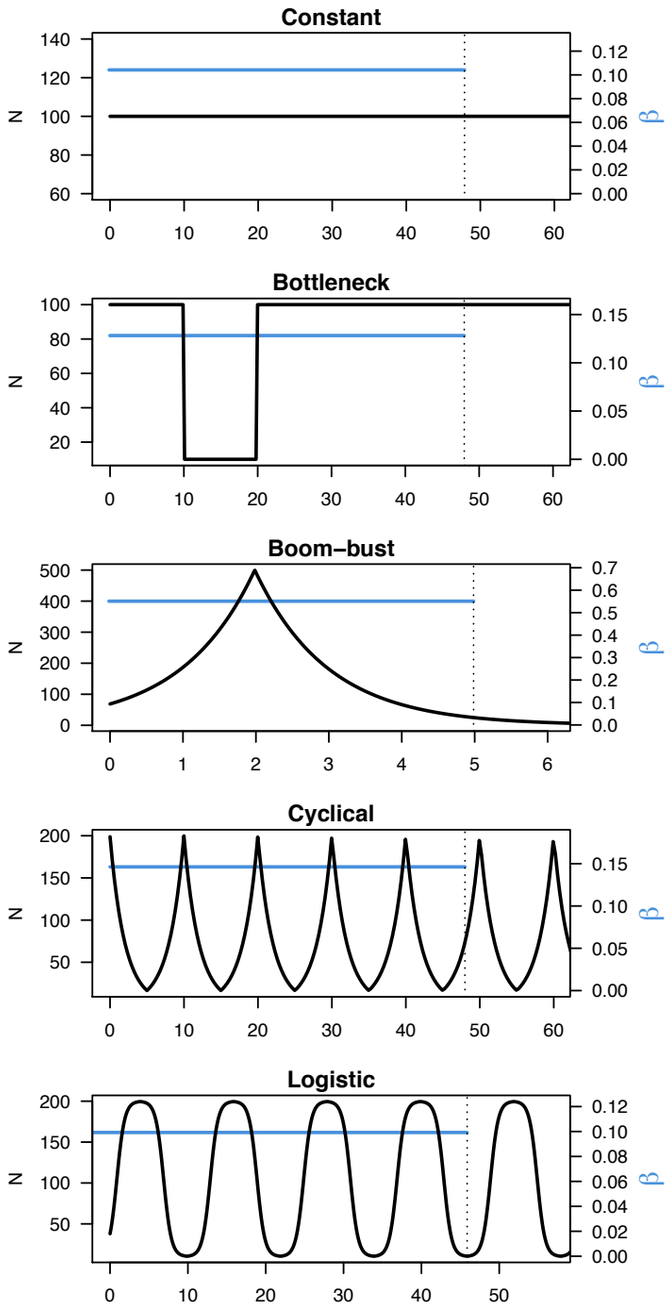
Simulated with **uninformative** sampling times

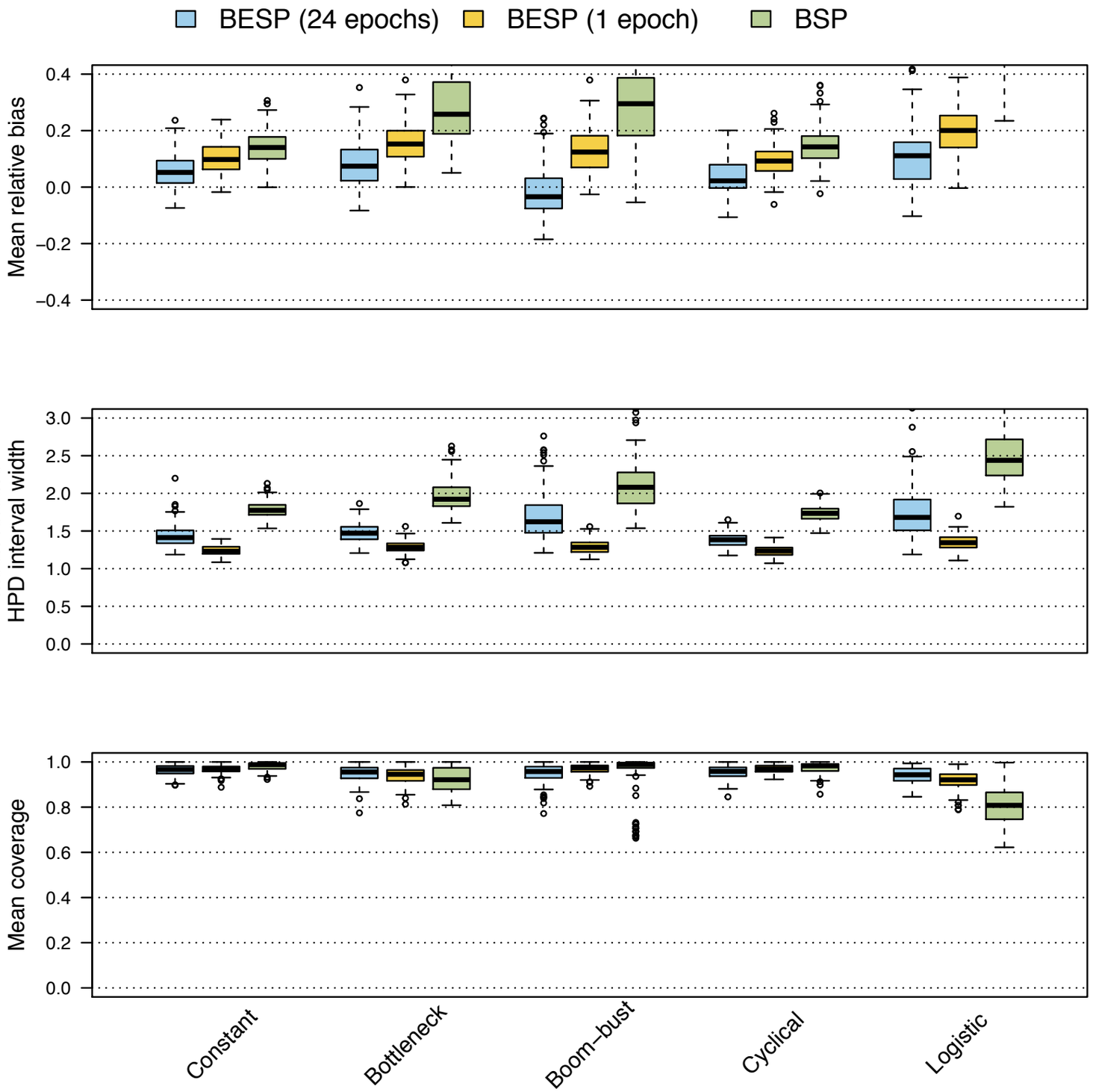




Simulation study **(population size — N)**

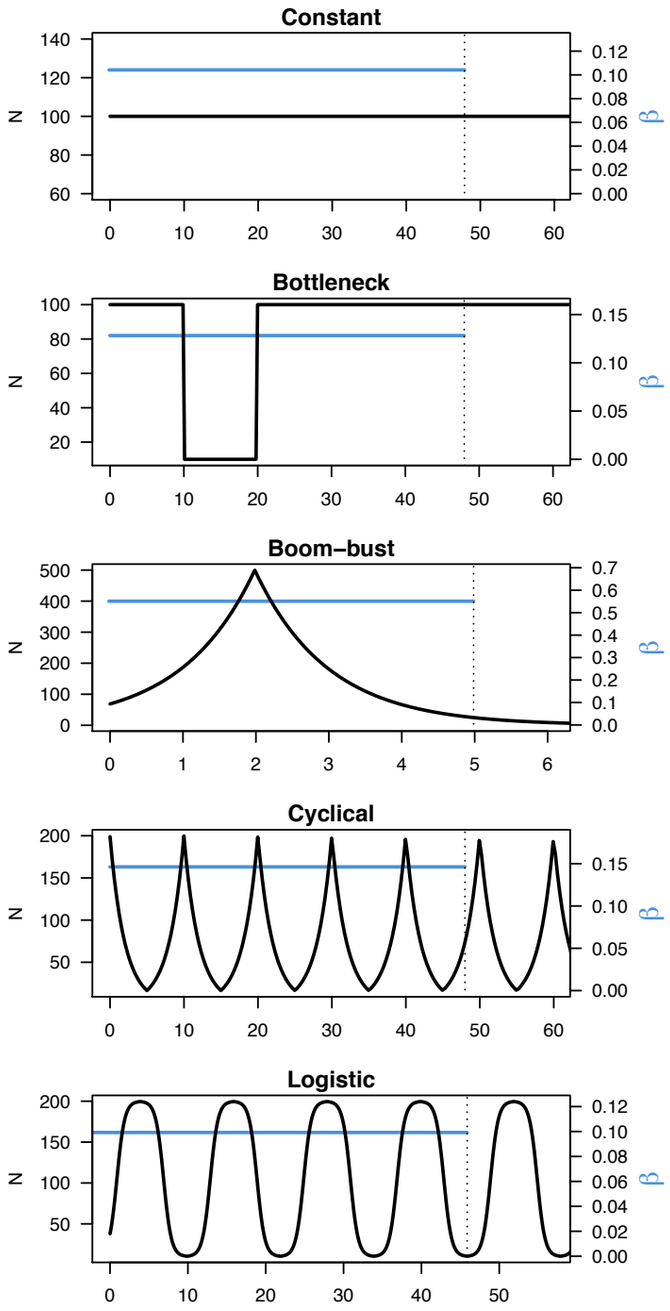
Simulated with **constant** sampling intensity

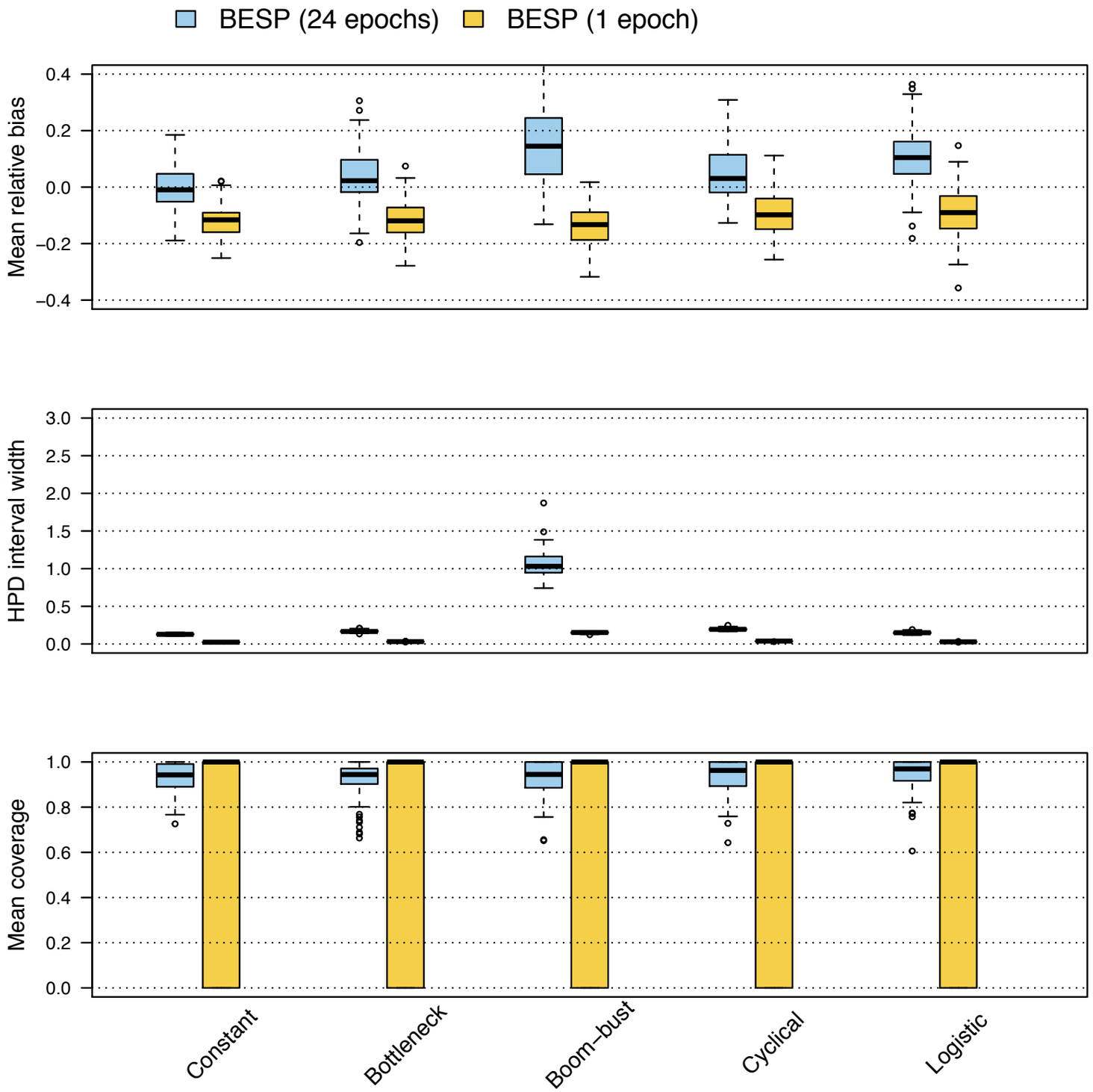




Simulation study **(sampling intensity — β)**

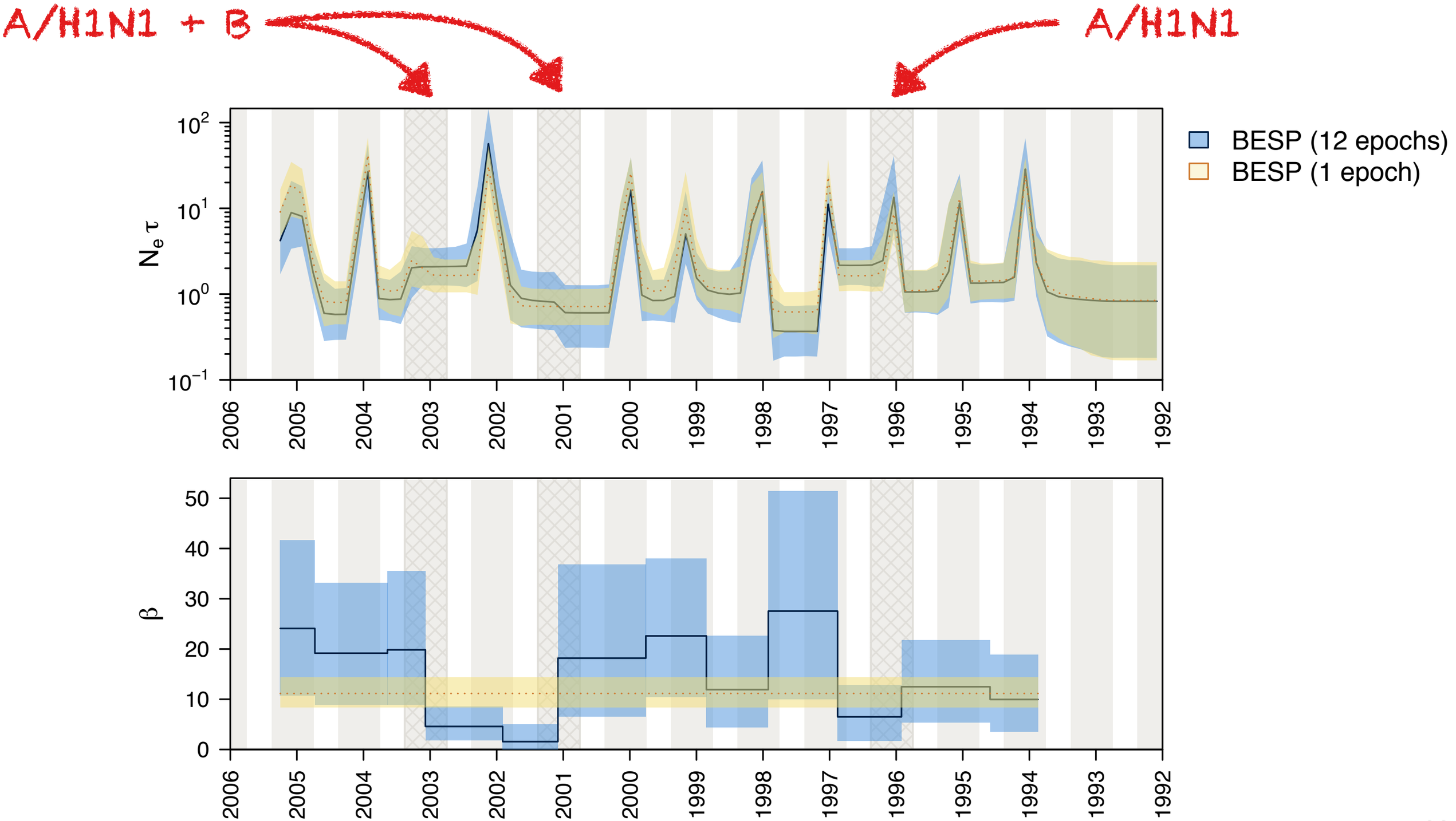
Simulated with **constant** sampling intensity





Bayesian Epoch Sampling Skyline Plot

637 New York Influenza A/H3N2 HA sequences across 12 seasons



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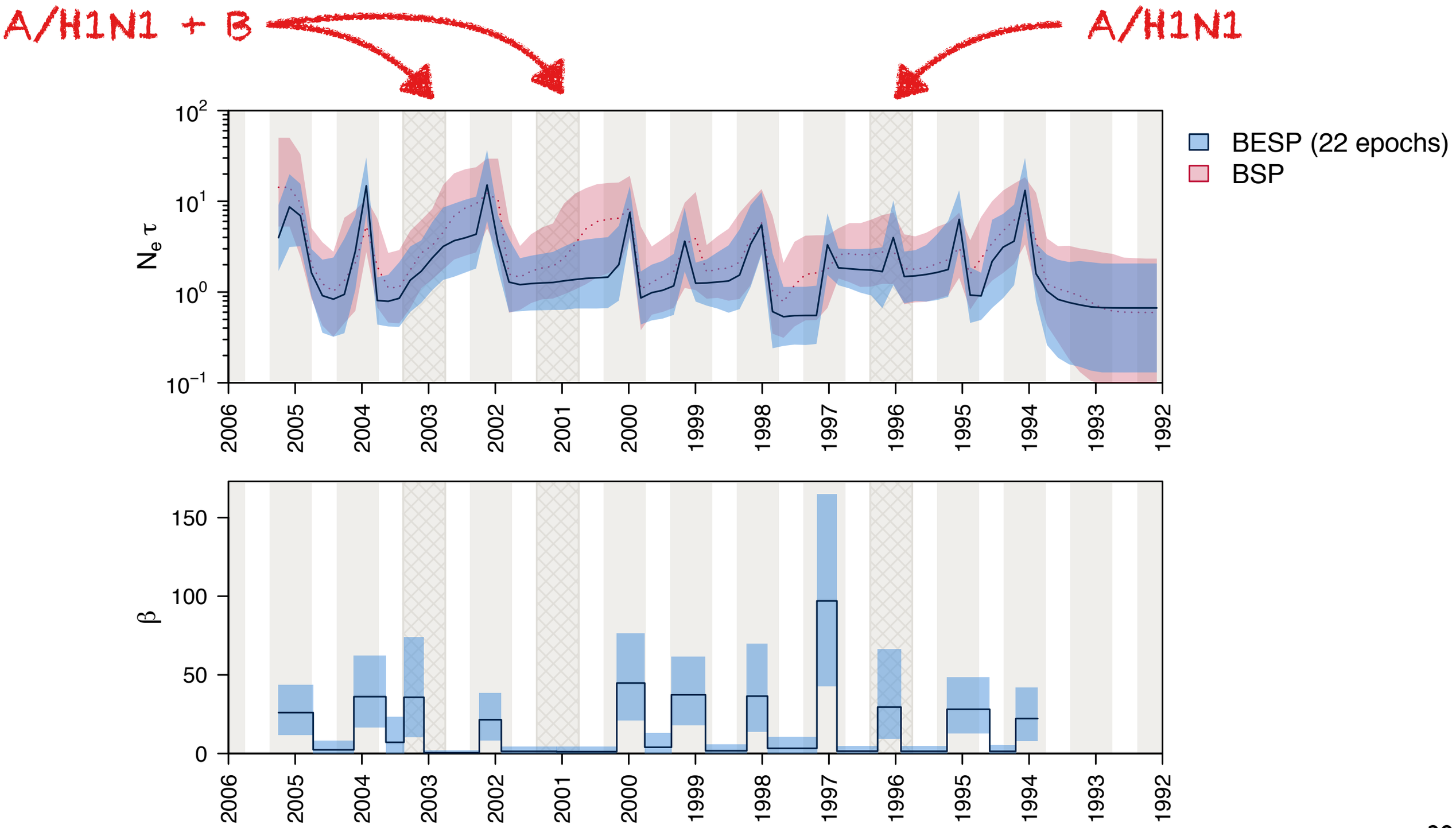

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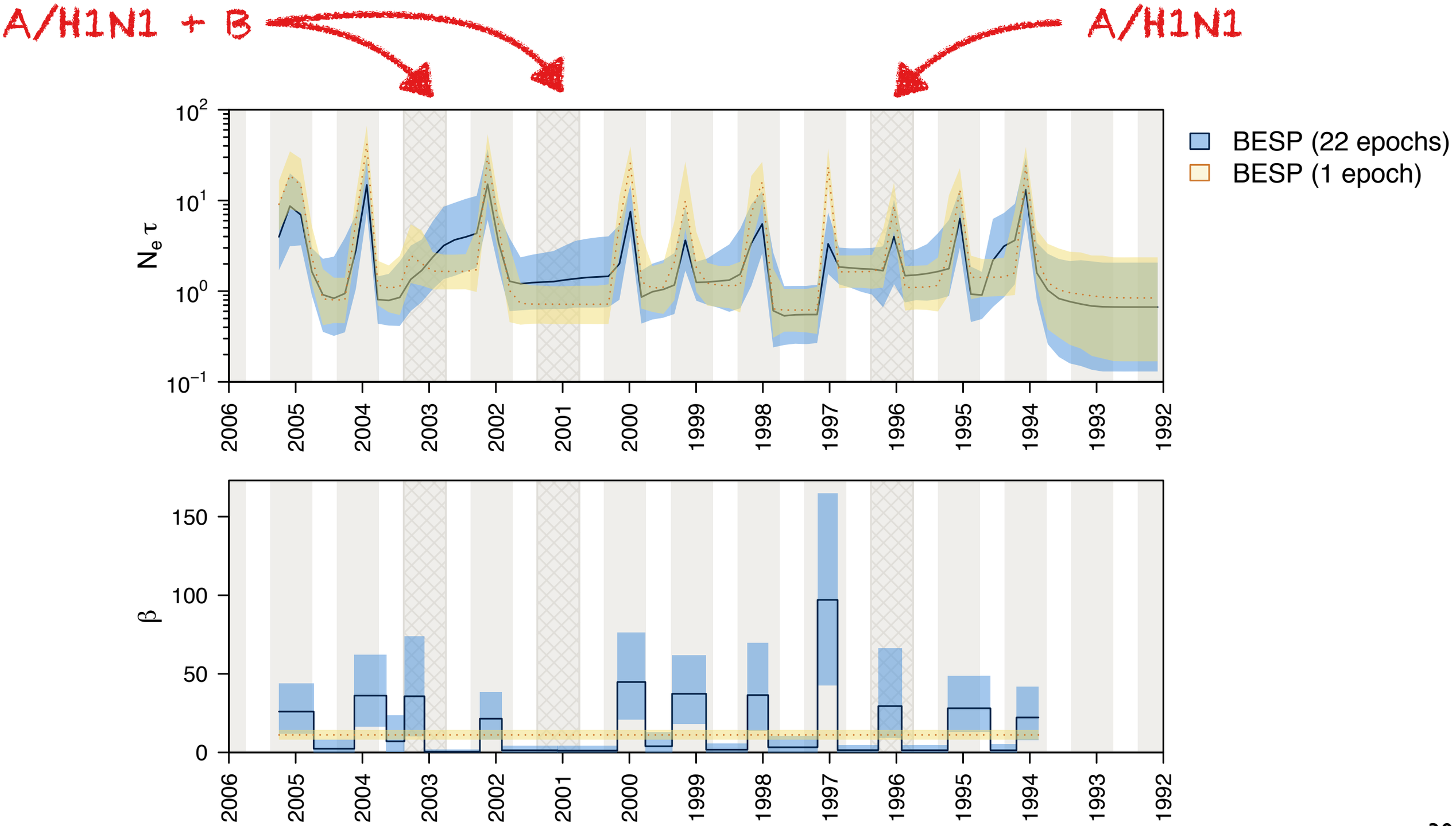
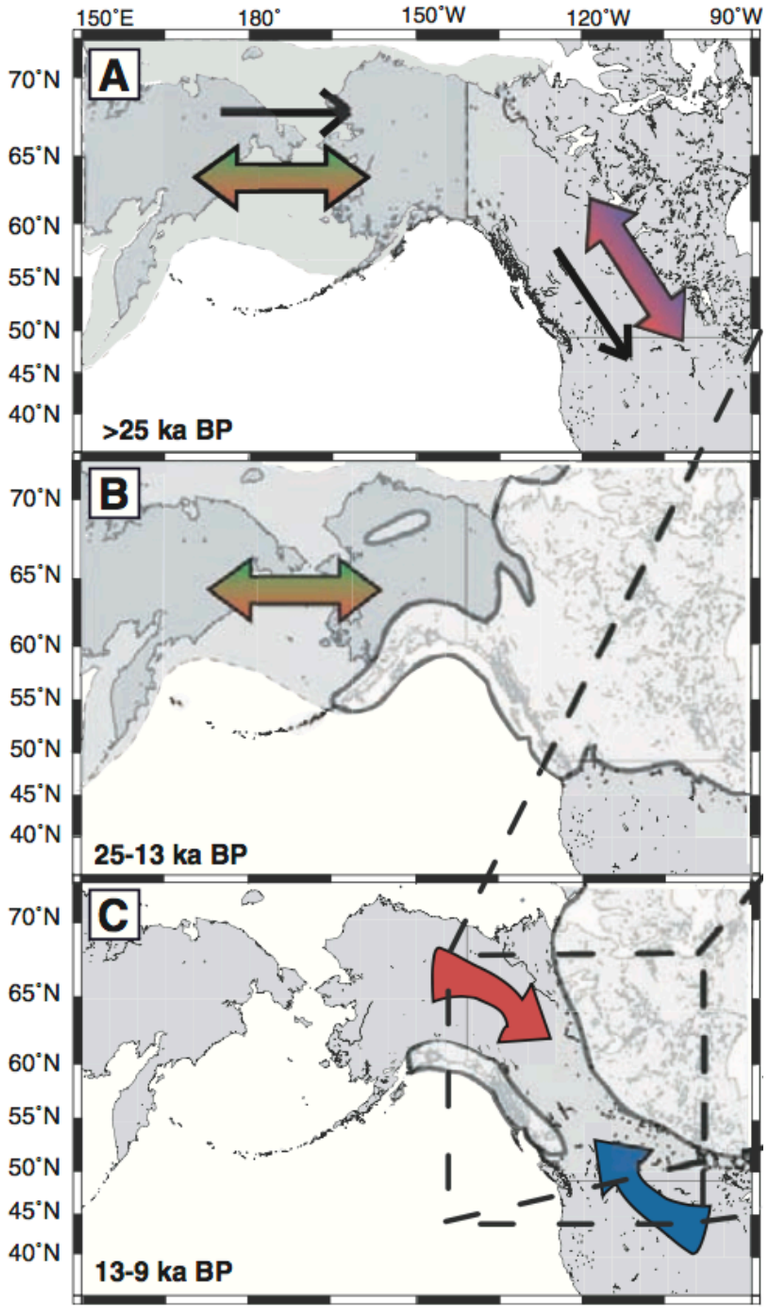
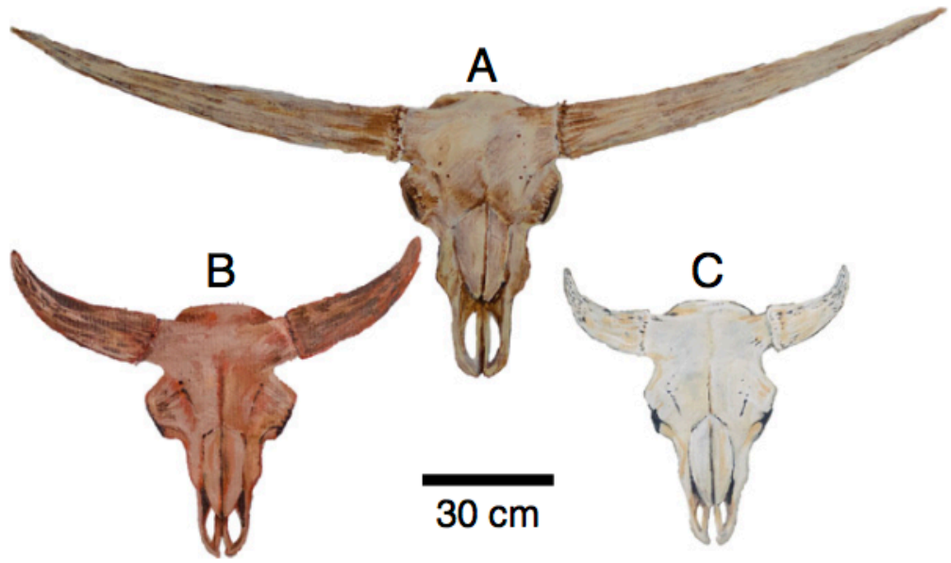


Bison in Beringia



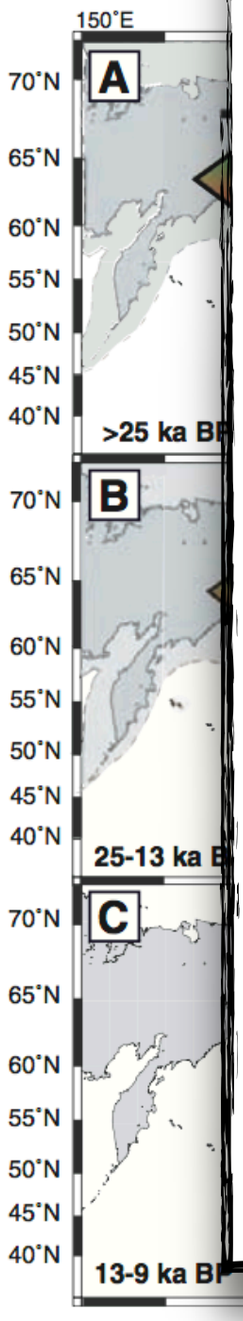


- Some of the most abundant megafauna in Beringia
- Colonised North America from Eurasia
- Big population bottleneck after the Late Quaternary Extinction event
- Extinct in Eurasia but survived in North America

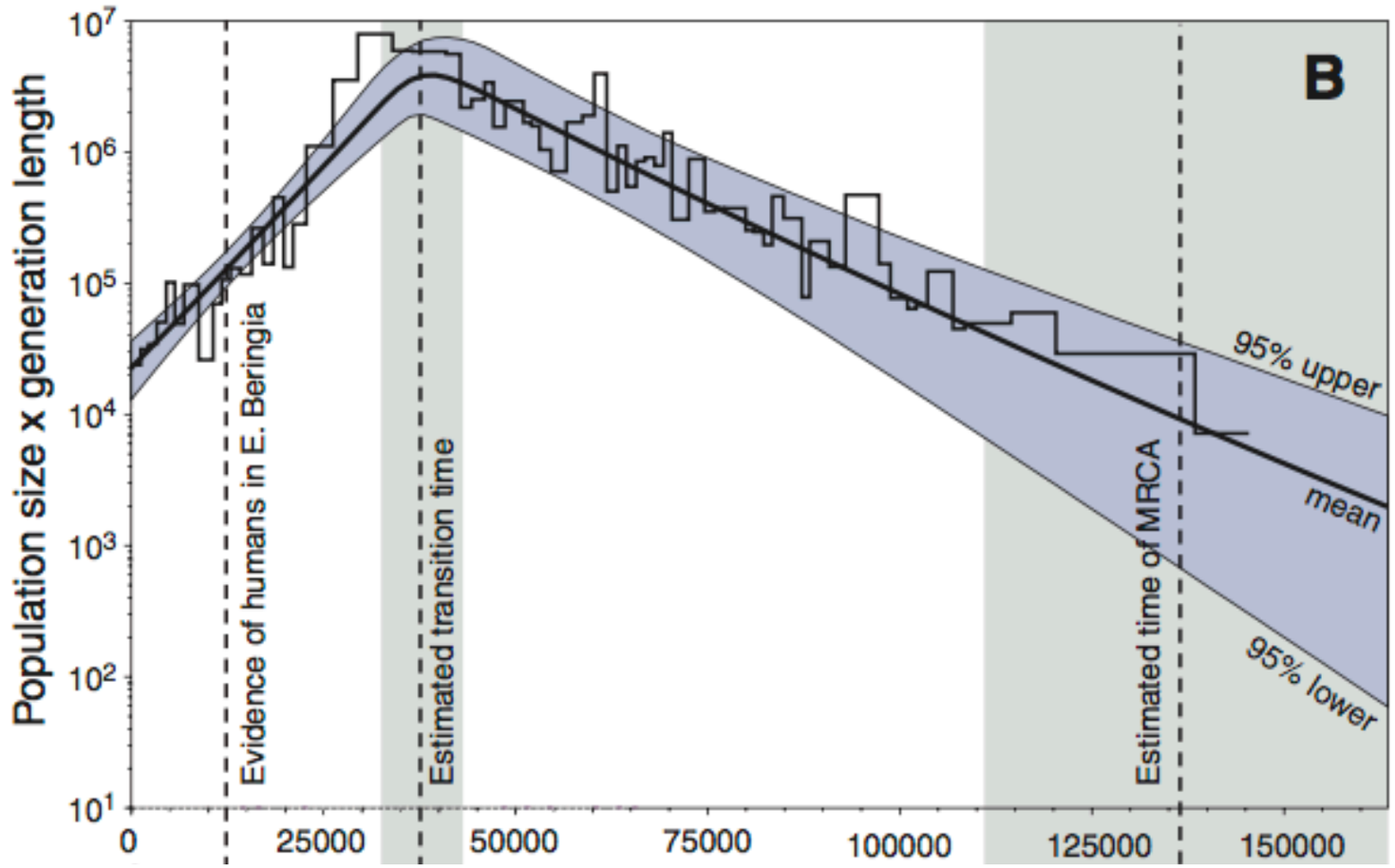
Shapiro *et al.* **Science 2004**

Froese *et al.* **PNAS 2017**

Bison in Beringia



Demographic history



Parametric boom-bust coalescent model

urasia

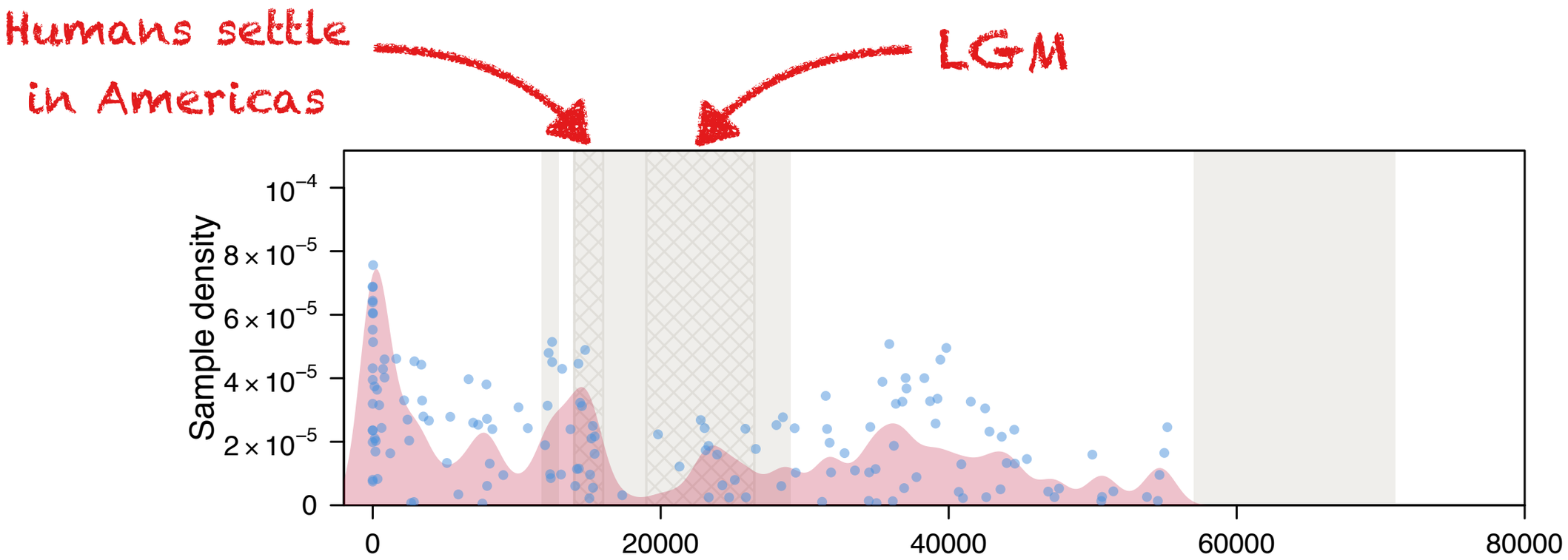
he

Shapiro *et al.* **Science 2004**

Froese *et al.* **PNAS 2017**

Bison in Beringia

152 mtDNA sequences across 55,000 years



Bison in Beringia

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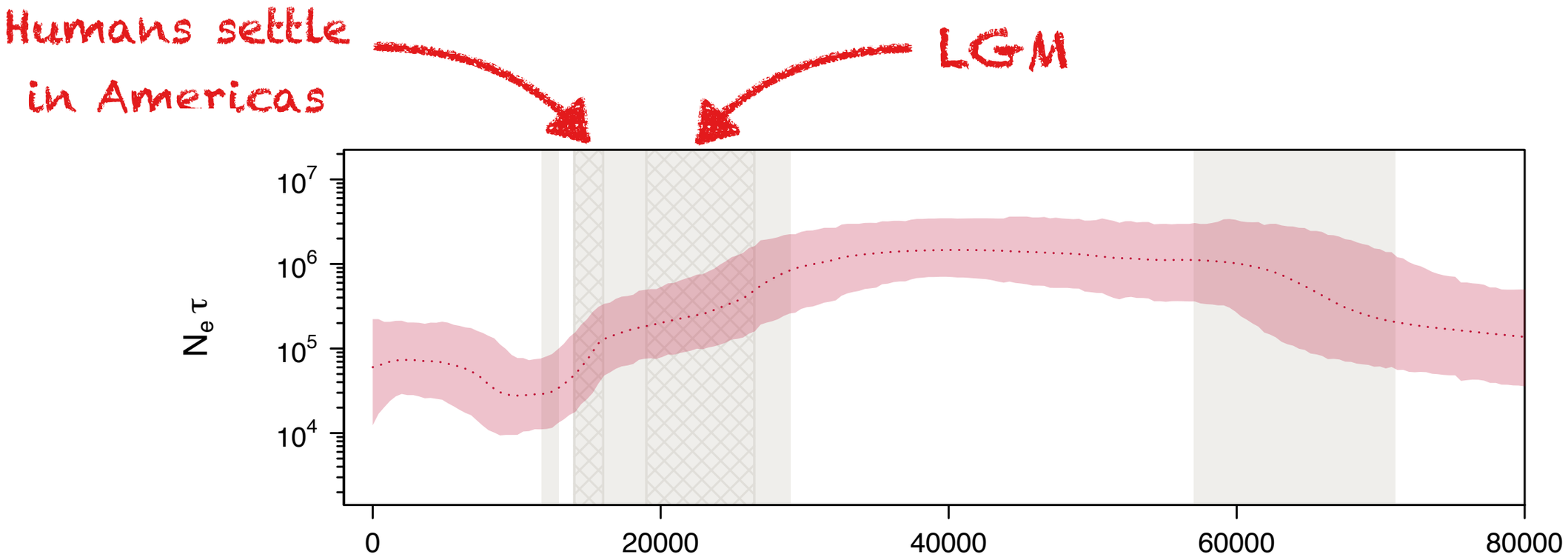

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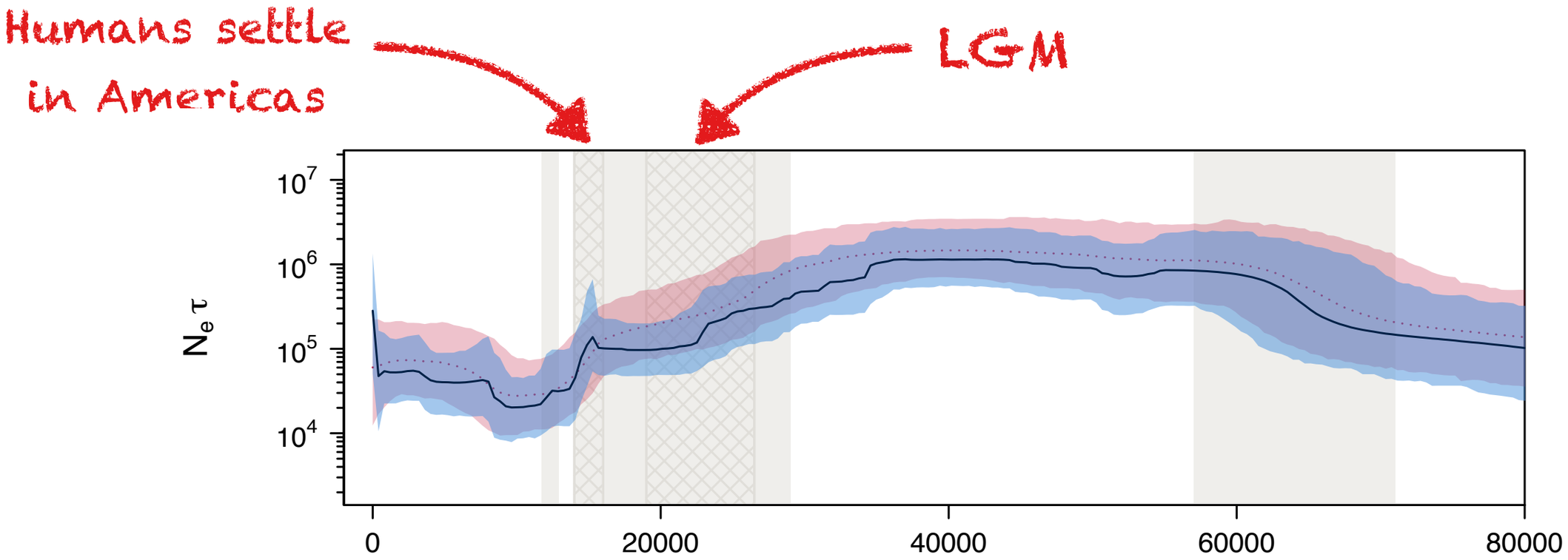

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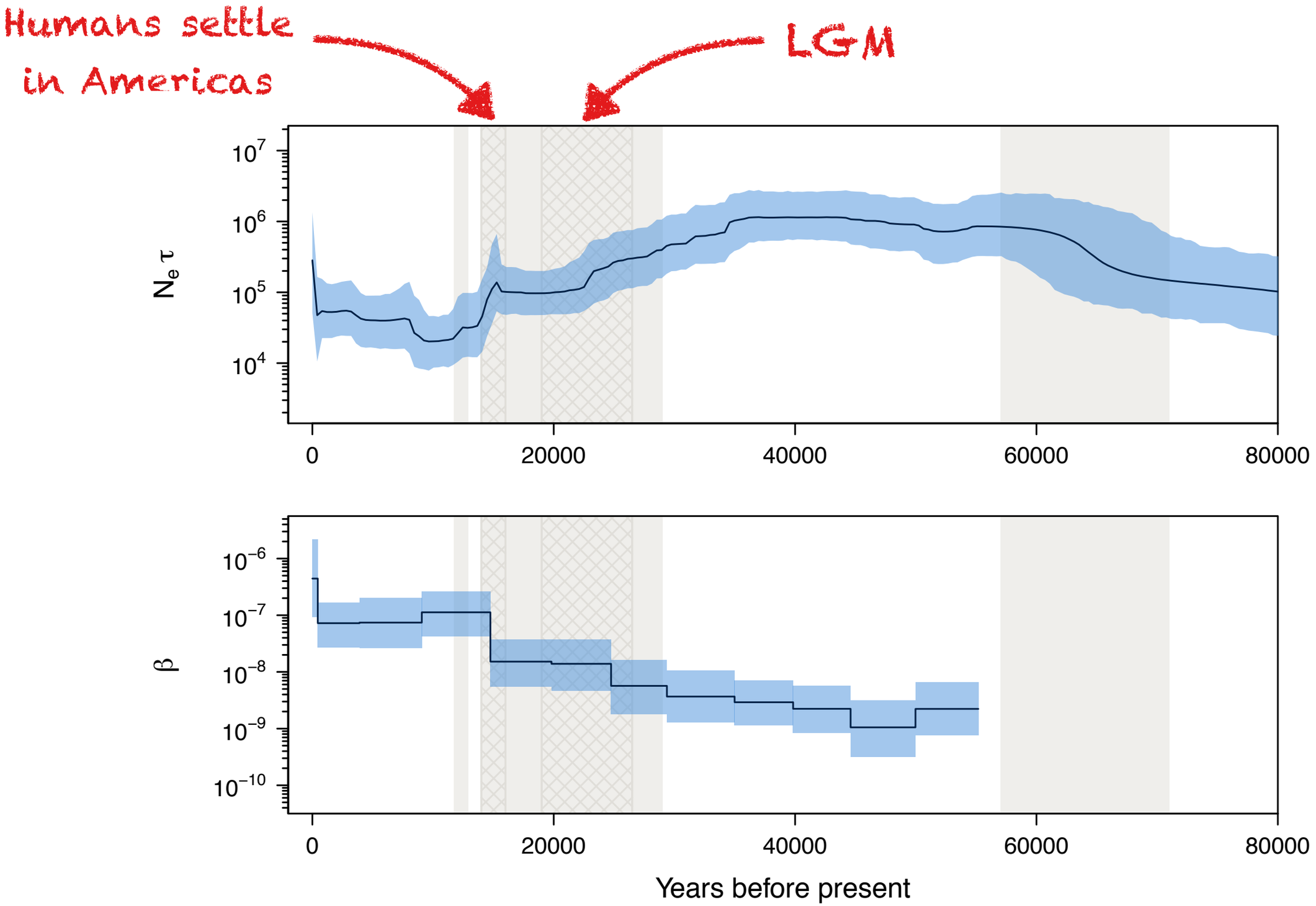

Not accounting for changes in sampling intensity gives biased results!