

Inferring epidemic, population, and species trajectories

Tim Vaughan

Taming the BEAST 2021 Online



Overview

Setting the Scene

Background theory

Coalescent theory

Birth-death tree probabilities

Approximate birth-death trajectories

Exact birth-death trajectories

Applications

SARS-CoV-2

Dinosaurs

Extensions

Non-linear models

Multi-type models

BEAST Packages

PhyDyn

Epilnf

BDMM-Prime

Alternative approach

Summary

Inferring epidemic,
population, and
species trajectories

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

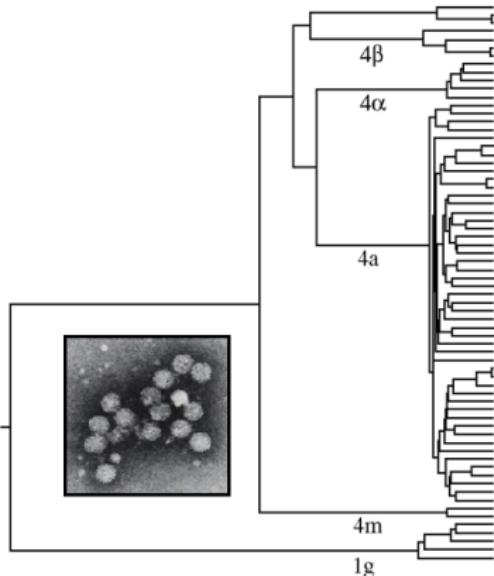
References



Inference of HCV dynamics Egypt

Inferring epidemic,
population, and
species trajectories

- ▶ Return again to Egyptian HCV epidemic.
- ▶ Different phylodynamic analyses presented of the same 63 sequences from samples isolated in the 1990s (Ray et al., 2000).
- ▶ Coalescent-based methods showed an increase in N_e .
- ▶ Birth-death methods show an increase in R_e .



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References



Bayesian Skyline Plot reconstruction of N_e

Inferring epidemic,
population, and
species trajectories

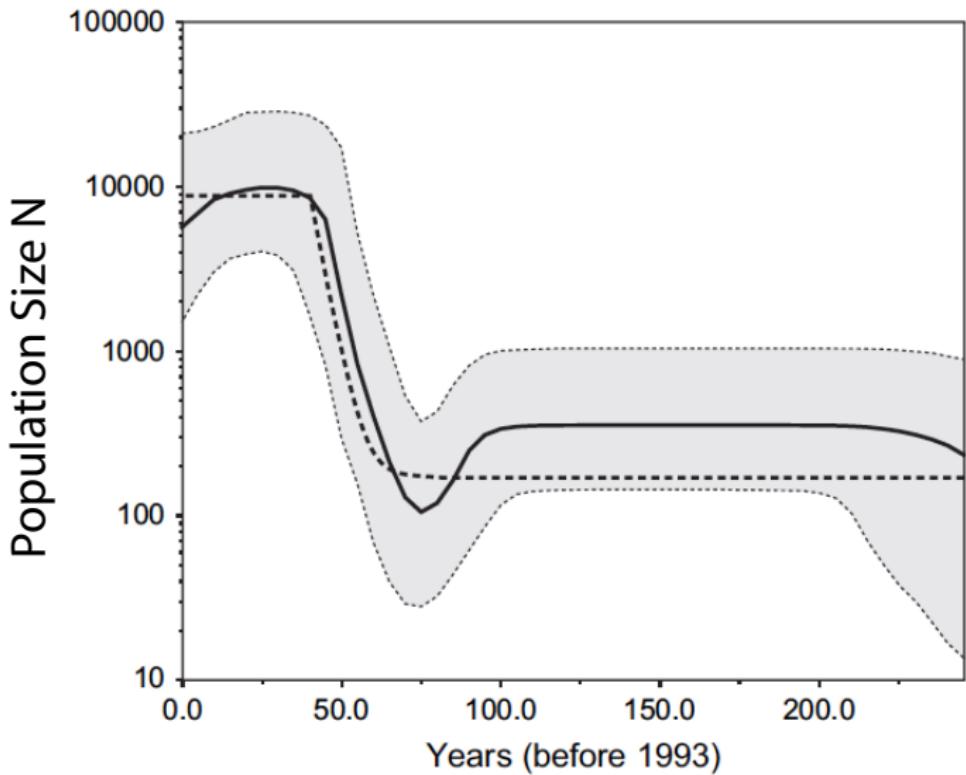


Figure from Drummond (2005).



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References

Birth-death Skyline reconstruction of R_e

Inferring epidemic,
population, and
species trajectories

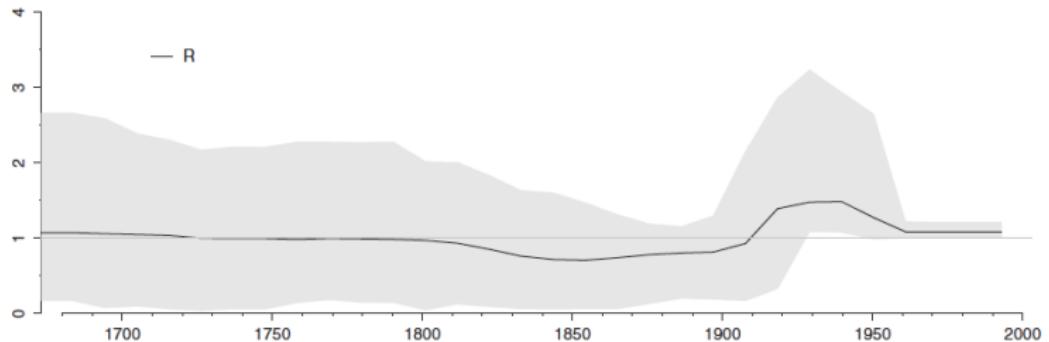


Figure from Stadler et al. (2012).



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References

Comparison of R_e , δ and N_e reconstructions

Inferring epidemic,
population, and
species trajectories

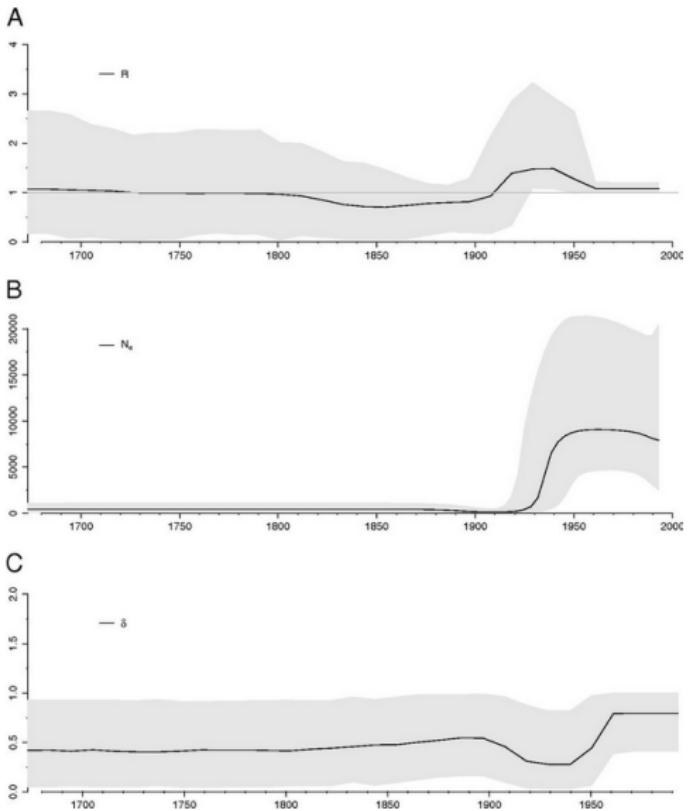


Figure from Stadler et al. (2012).



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References

Differences between Birth-Death and Coalescent inference

Question

What are the main differences between Birth-Death and Coalescent phylodynamic inference methods, as usually used?

Inferring epidemic,
population, and
species trajectories

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References



Differences between Birth-Death and Coalescent inference

Inferring epidemic,
population, and
species trajectories

Question

What are the main differences between Birth-Death and Coalescent phylodynamic inference methods, as usually used?

- ▶ Deterministic vs stochastic population size.
- ▶ Birth-death model includes explicit sampling model.
- ▶ Expressed as backwards vs forwards in time.



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References

Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Wright-Fisher model:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Wright-Fisher model:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

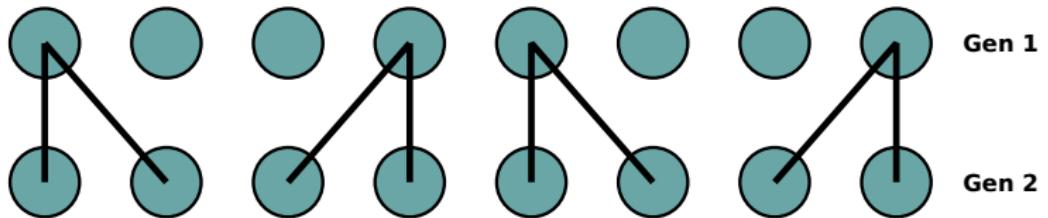
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Wright-Fisher model:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

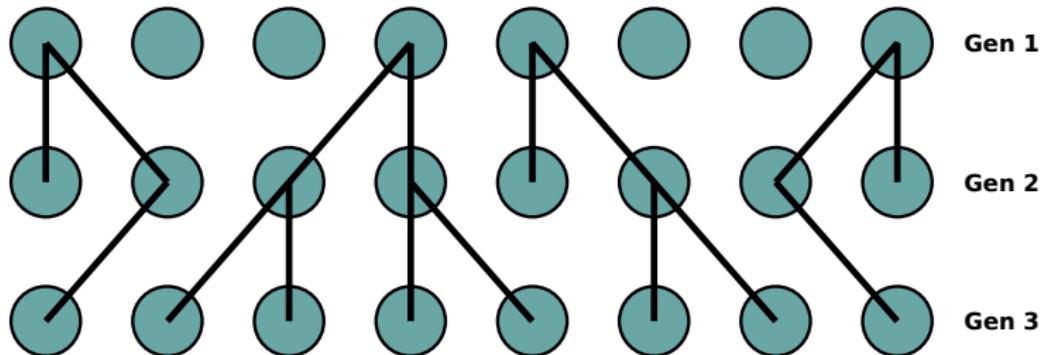
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Wright-Fisher model:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

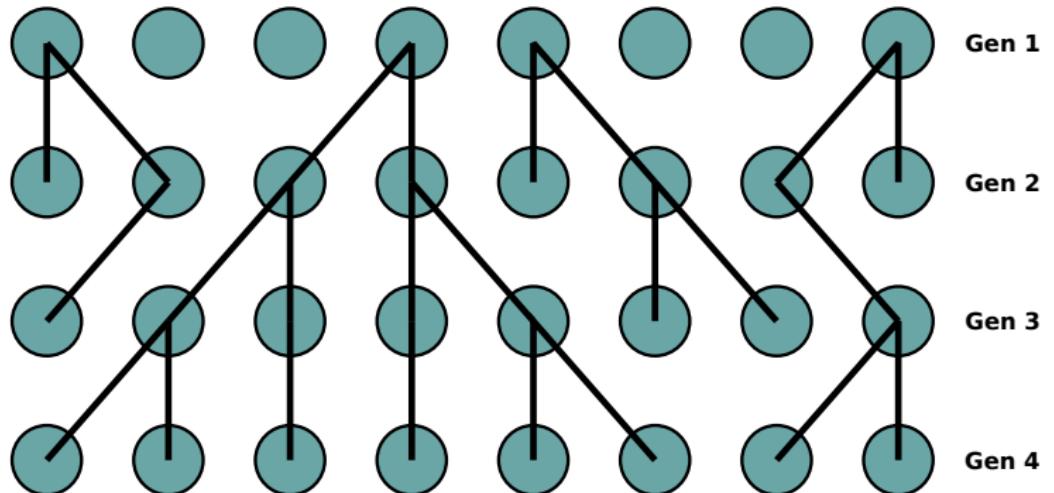
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Wright-Fisher model:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

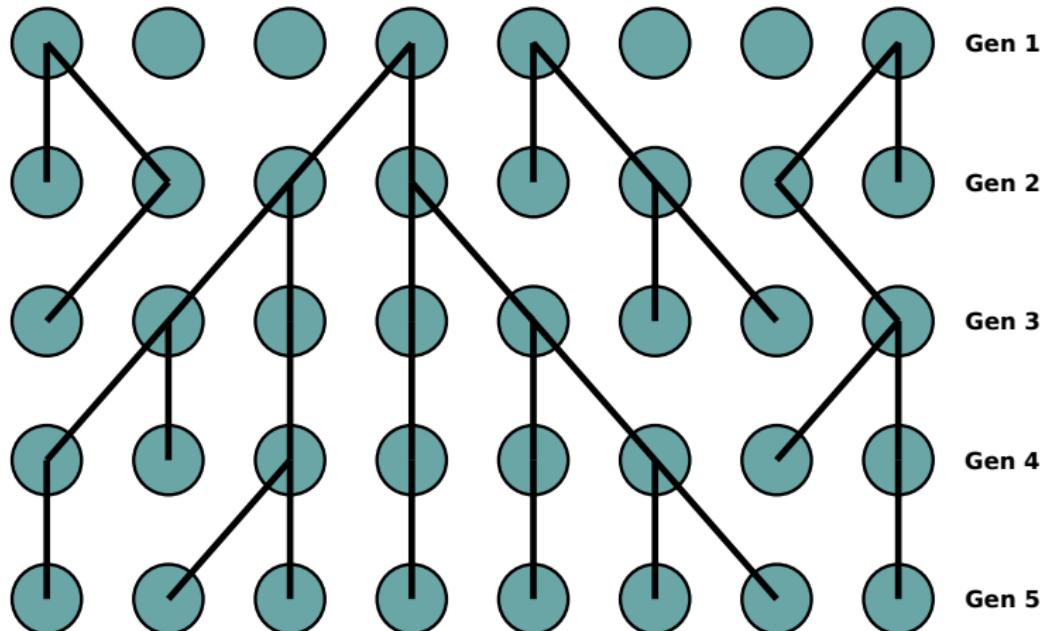
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Wright-Fisher model:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

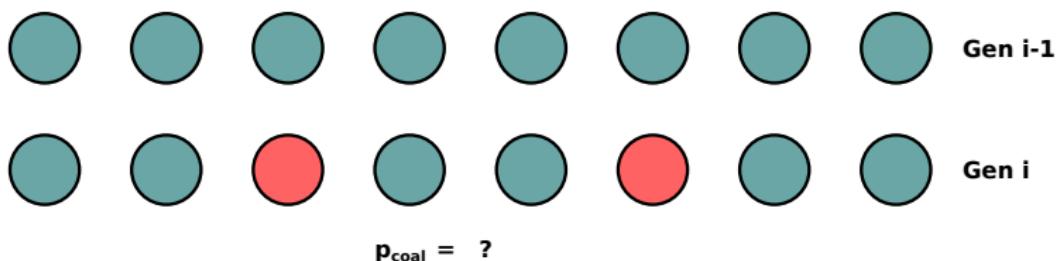
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

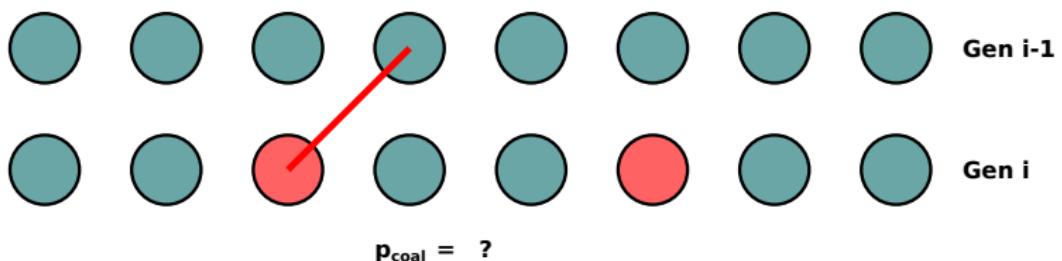
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

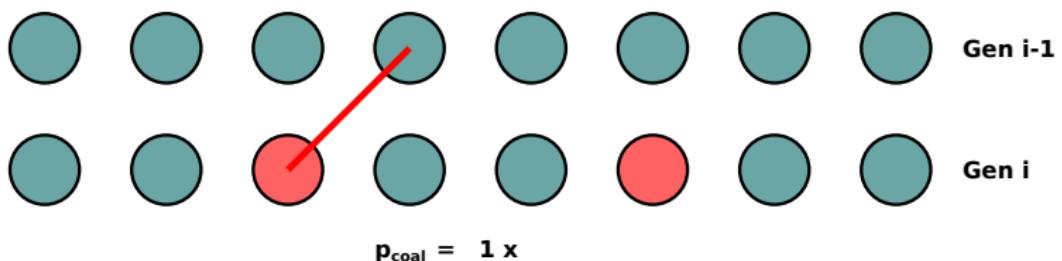
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

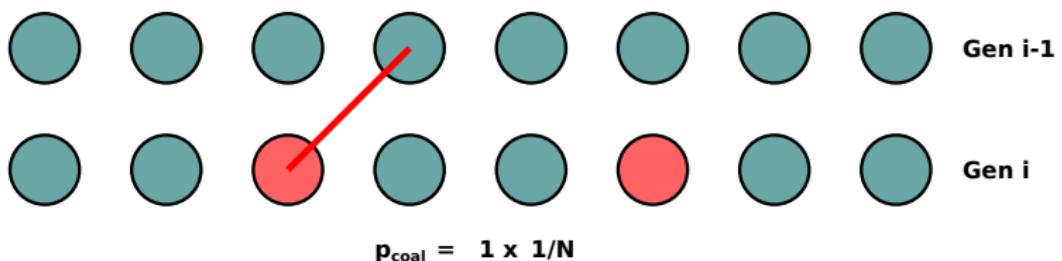
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

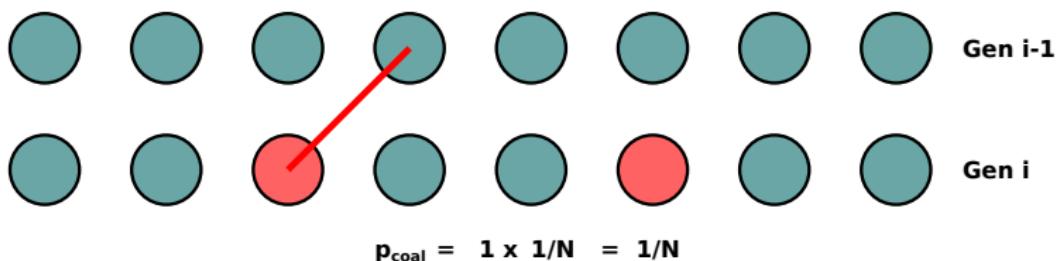
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

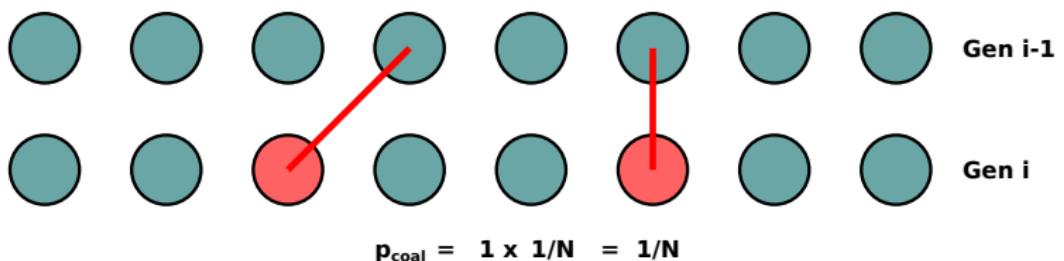
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

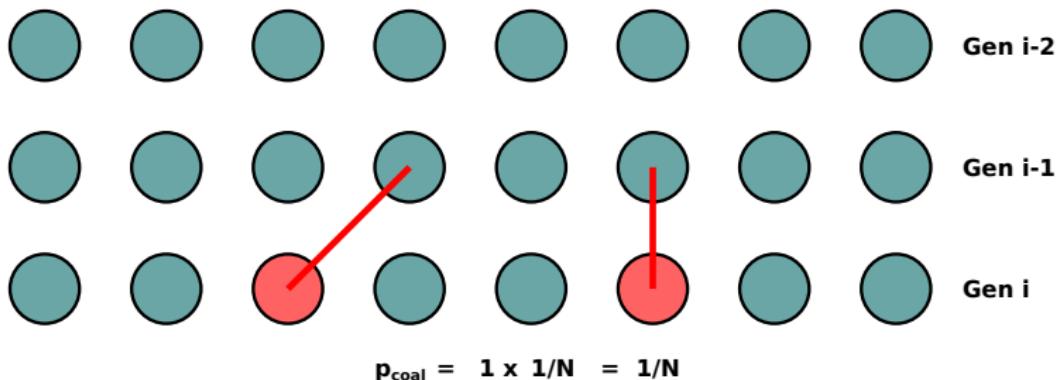
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

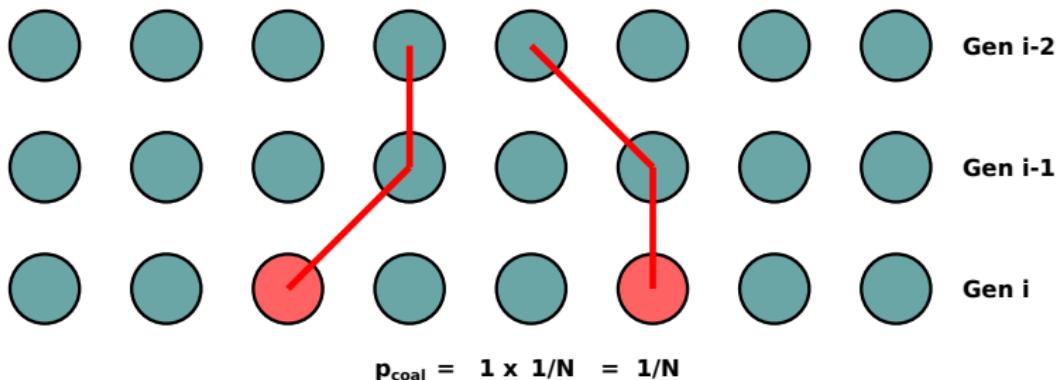
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

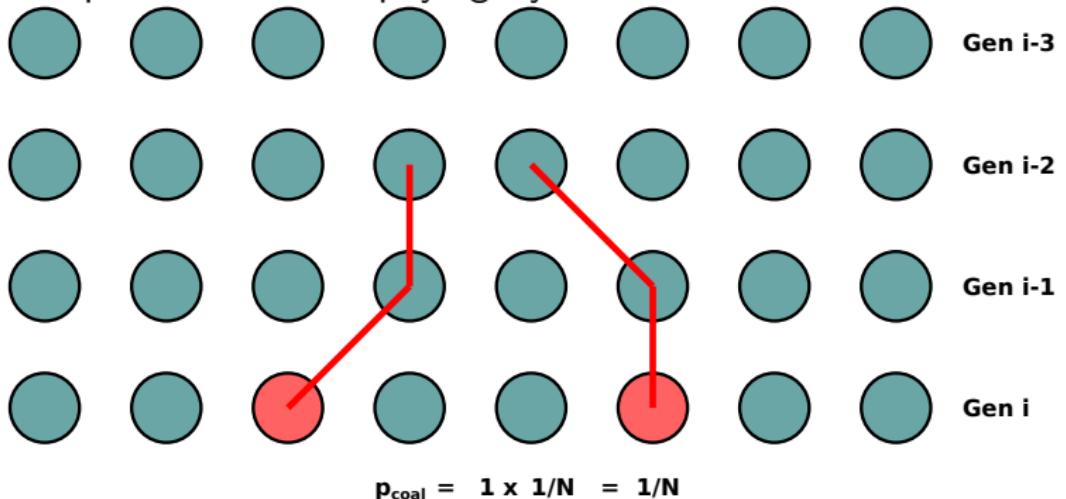
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

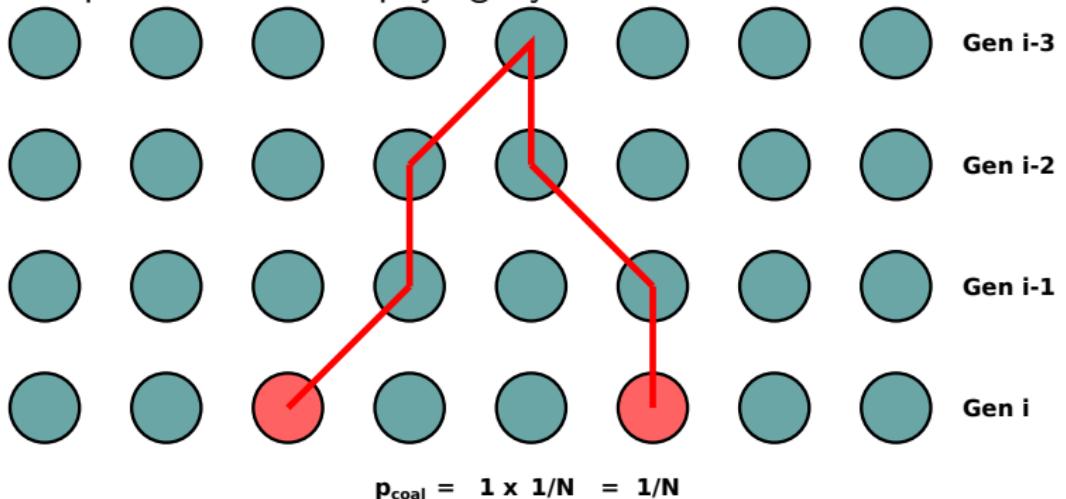
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

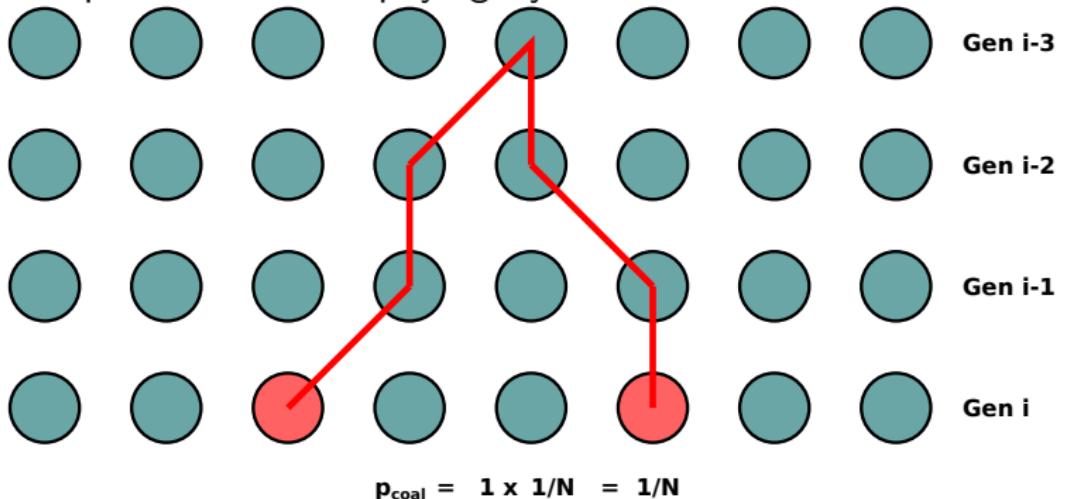
References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:



- ▶ **Question** How can this be generalized to k samples?



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

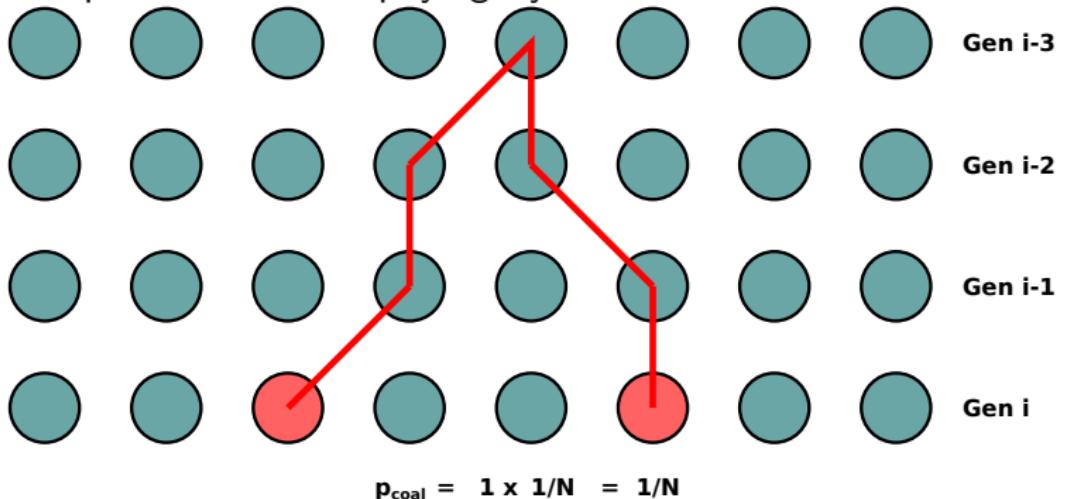
Summary

References

Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories

Sampled 2-individual phylogeny:

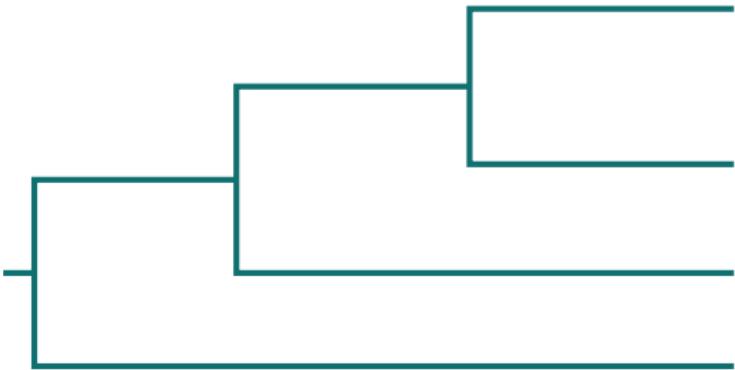


- ▶ **Question** How can this be generalized to k samples?
- ▶ **Answer** $p_{coal} \simeq \binom{k}{2} \frac{1}{N}$



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

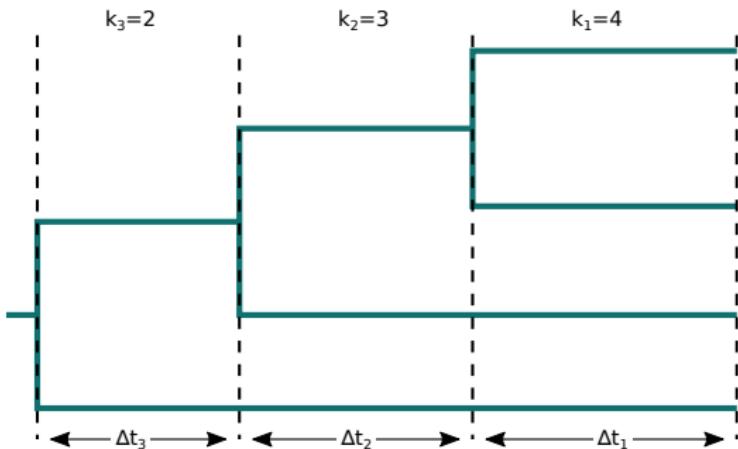
Alternative
approach

Summary

References



Recap: Coalescent tree probabilities



Inferring epidemic,
population, and
species trajectories

Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

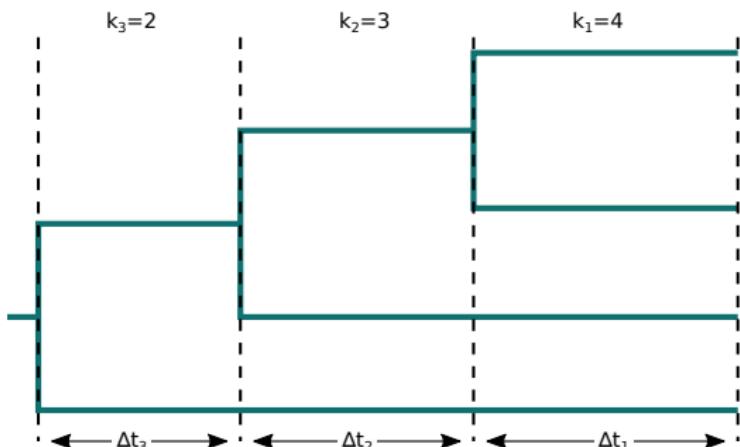
Summary

References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories



$$P(\mathcal{T}|Ng) = e^{-\Delta t_1 \binom{4}{2} \frac{1}{Ng}} \times \frac{1}{Ng} \times e^{-\Delta t_2 \binom{3}{2} \frac{1}{Ng}} \times \frac{1}{Ng} \times e^{-\Delta t_3 \binom{2}{2} \frac{1}{Ng}}$$
$$= \prod_{i=1}^{n-1} \left(\exp \left[-\Delta t_i \binom{k_i}{2} \frac{1}{Ng} \right] \frac{1}{Ng} \right)$$

$$\times \frac{1}{Ng}$$

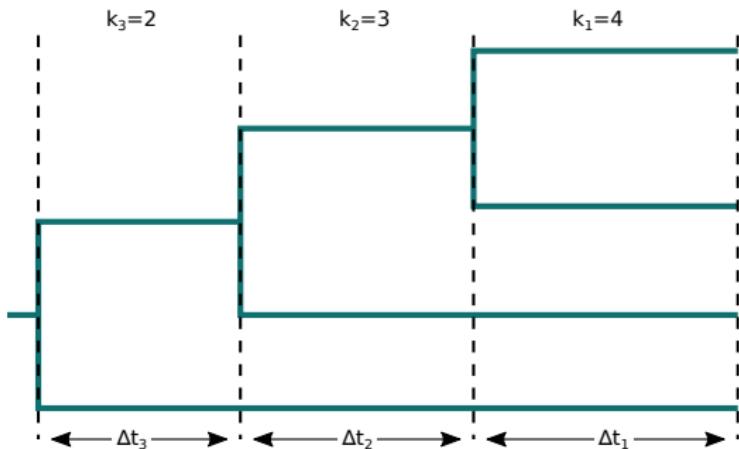
Summary

References



Recap: Coalescent tree probabilities

Inferring epidemic,
population, and
species trajectories



$$\begin{aligned} P(\mathcal{T}|Ng) &= e^{-\Delta t_1 \binom{4}{2} \frac{1}{Ng}} \times \frac{1}{Ng} \times e^{-\Delta t_2 \binom{3}{2} \frac{1}{Ng}} \times \frac{1}{Ng} \times e^{-\Delta t_3 \binom{2}{2} \frac{1}{Ng}} \\ &= \prod_{i=1}^{n-1} \left(\exp \left[-\Delta t_i \binom{k_i}{2} \frac{1}{Ng} \right] \frac{1}{Ng} \right) \end{aligned}$$

The exponentials give the probability of nothing happening in interval Δt_i , and the $1/gN$ factors are probability densities of the particular coalescent events. (Note the units!)

Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

$\times \frac{1}{Ng}$
Alternative
approach

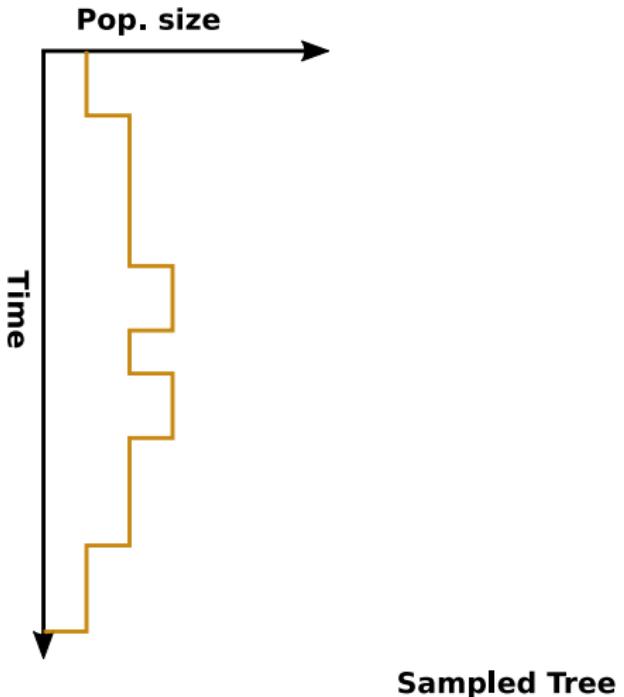
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

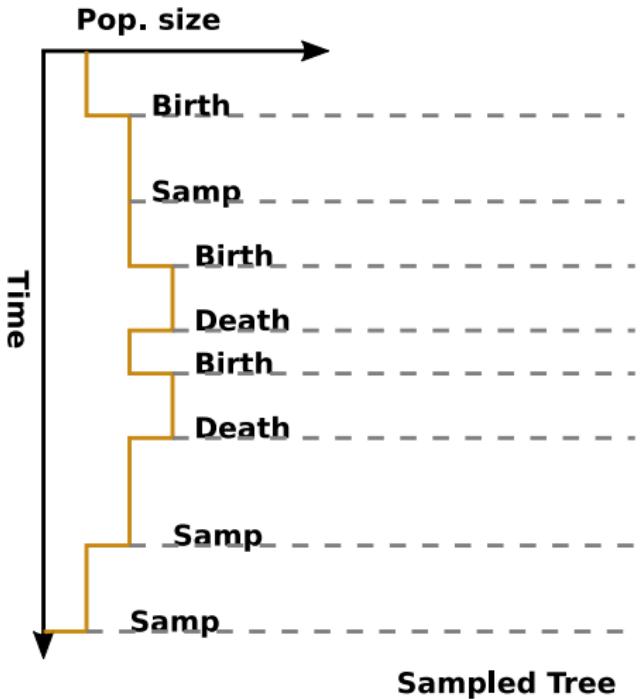
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

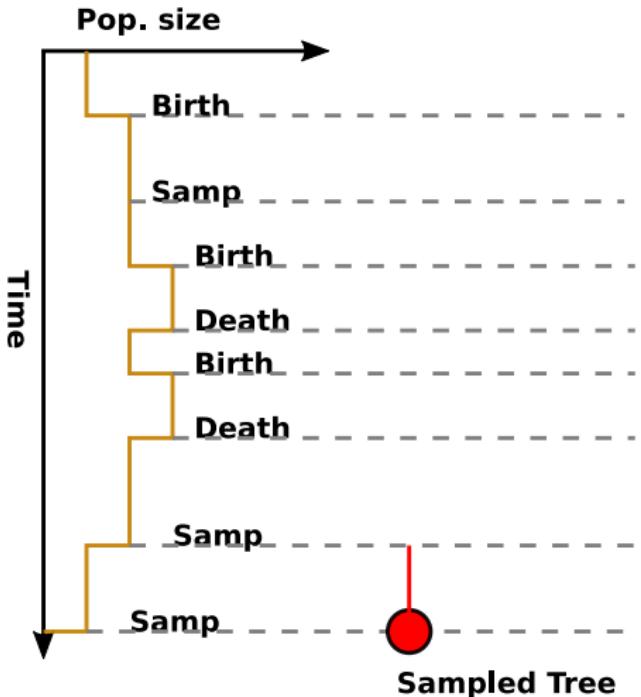
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

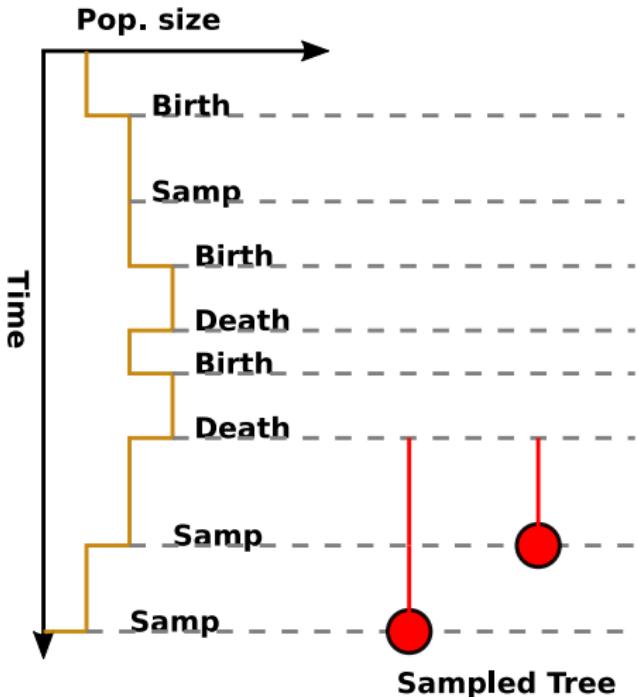
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

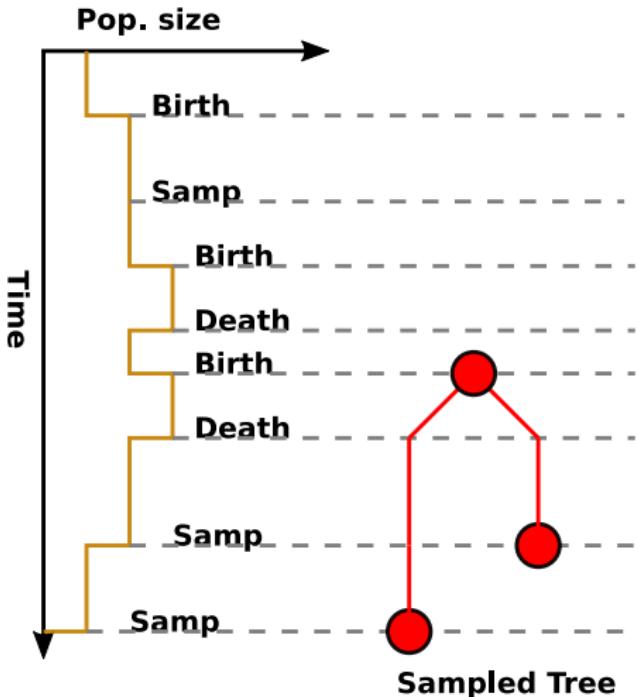
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

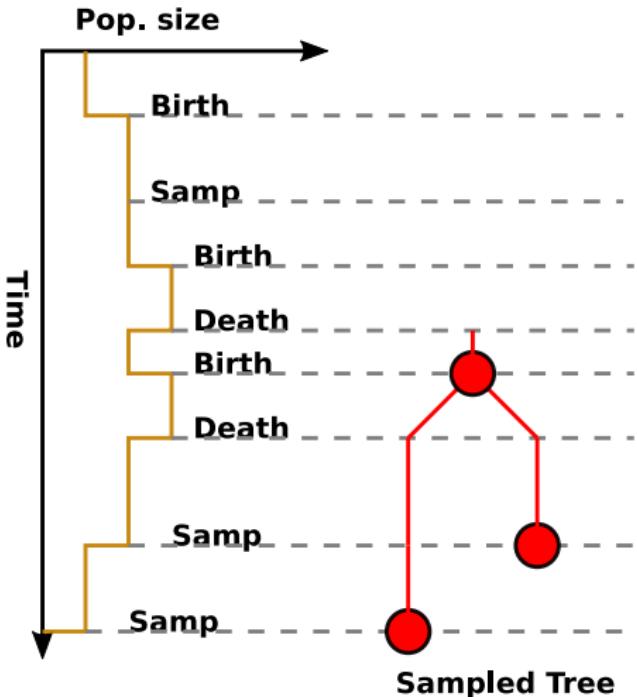
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

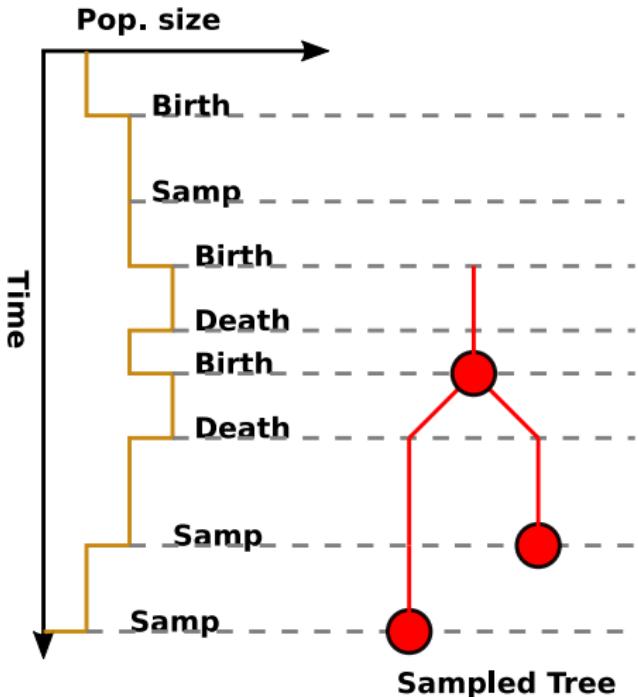
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

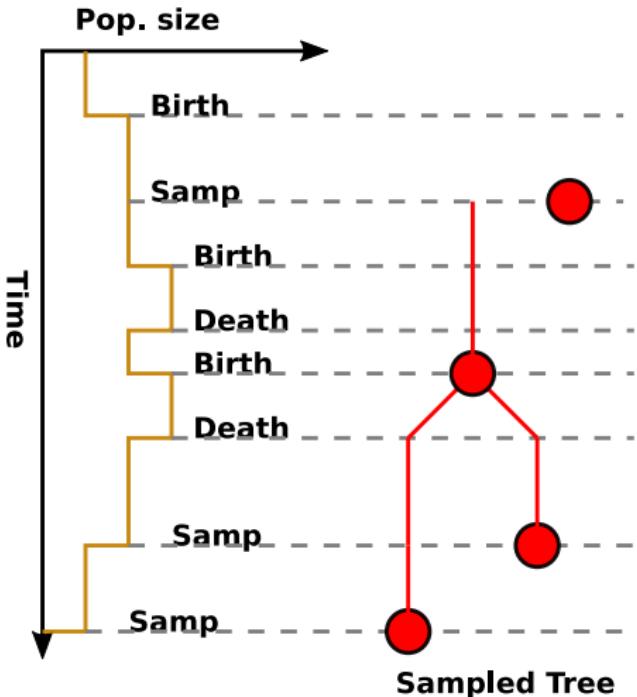
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

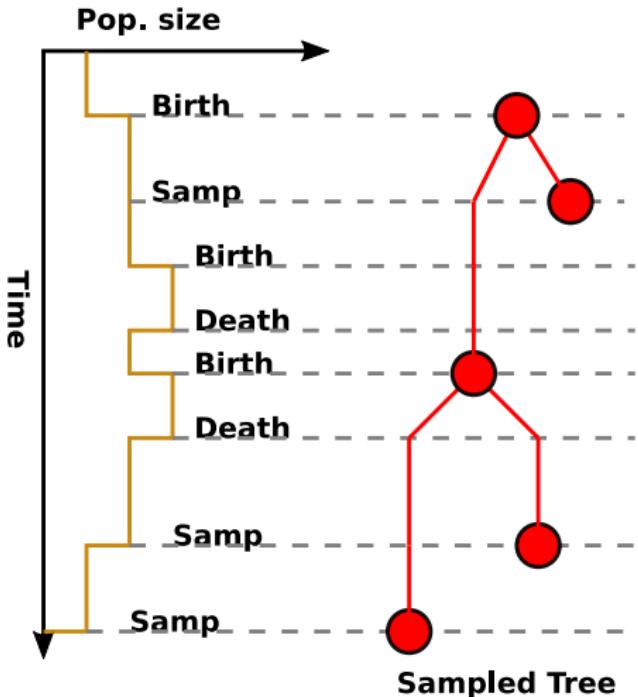
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

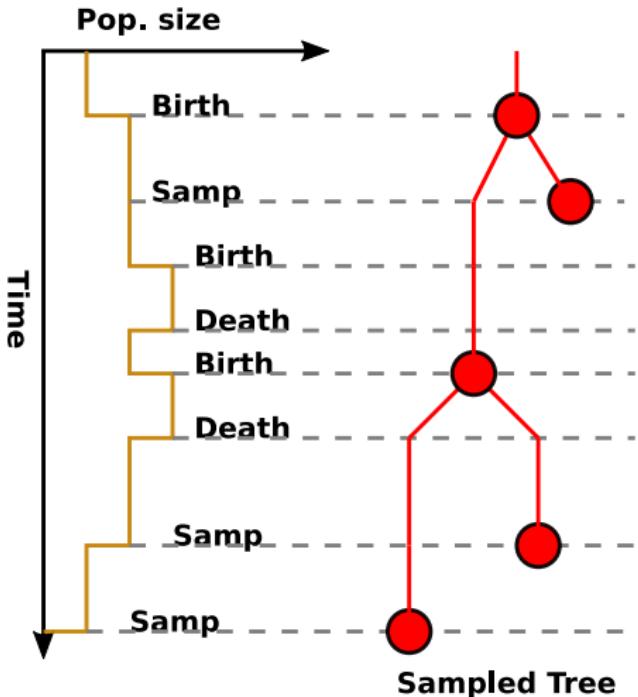
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

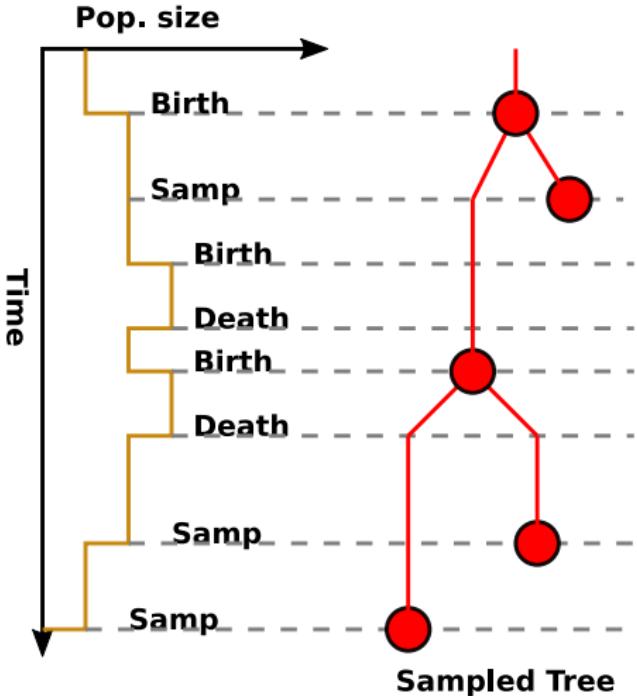
Summary

References



Another way of thinking about Birth-death trees

Inferring epidemic,
population, and
species trajectories



Probability of coalescence at birth: $\binom{k}{2} / \binom{N}{2}$.



Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References

Question

How can we use this?

Setting the Scene

Background theory

Coalescent theory

Birth-death tree
probabilities

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

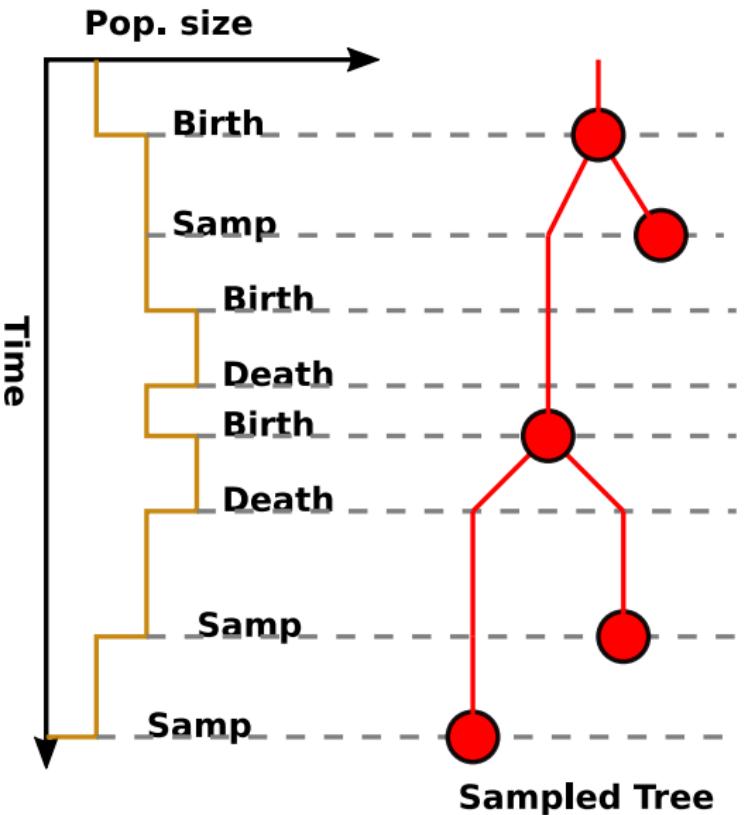
Alternative
approach

Summary

References



Idea 1: Coalescent approximation for Birth-death models (Volz et al., 2009)



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

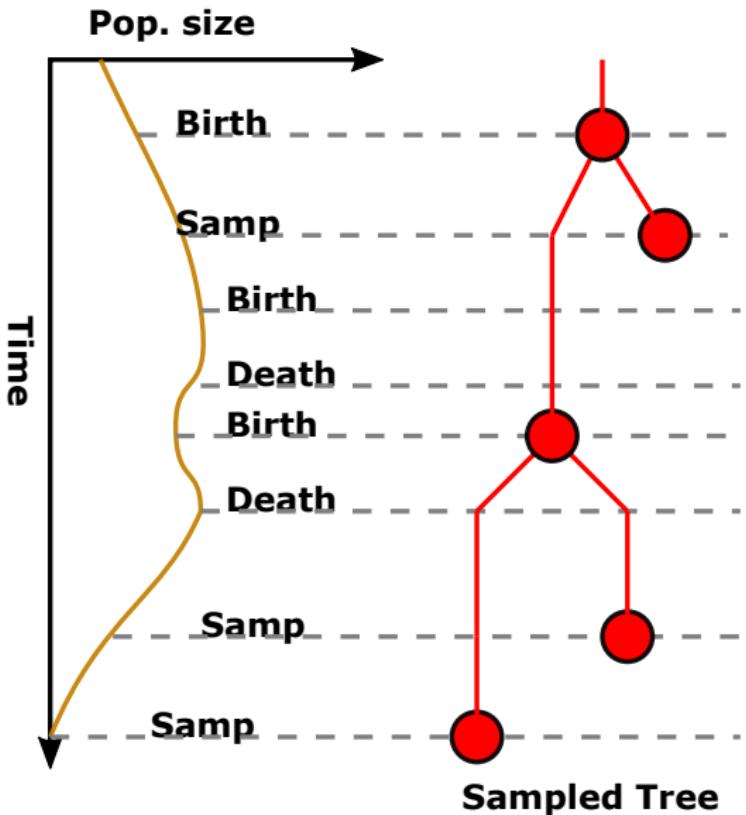
Summary

References



Idea 1: Coalescent approximation for Birth-death models (Volz et al., 2009)

Inferring epidemic, population, and species trajectories



Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Extensions

BEAST Packages

Alternative approach

Summary

References



Idea 1: Coalescent approximation for Birth-death models (Volz et al., 2009)

- ▶ Coalescent distributions can approximate the probability density of sampled phylogenies generated by birth-death processes.

Inferring epidemic, population, and species trajectories

Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Extensions

BEAST Packages

Alternative approach

Summary

References



Idea 1: Coalescent approximation for Birth-death models (Volz et al., 2009)

- ▶ Coalescent distributions can approximate the probability density of sampled phylogenies generated by birth-death processes.
- ▶ Assume the approximate ODE solution $I(t) = I(T)e^{(\beta-\delta)(T-t)}$ is correct.

Inferring epidemic, population, and species trajectories

Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Extensions

BEAST Packages

Alternative approach

Summary

References



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- ▶ Coalescent distributions can approximate the probability density of sampled phylogenies generated by birth-death processes.
- ▶ Assume the approximate ODE solution $I(t) = I(T)e^{(\beta-\delta)(T-t)}$ is correct.
- ▶ Birth events occur at time t with the rate of $\beta I(t)$.

Inferring epidemic, population, and species trajectories

Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Extensions

BEAST Packages

Alternative approach

Summary

References



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- ▶ Every birth is a potential coalescence.

Inferring epidemic, population, and species trajectories

Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Extensions

BEAST Packages

Alternative approach

Summary

References



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- ▶ Every birth is a potential coalescence.
- ▶ Probability of choosing a sampled lineage pair is $\binom{k}{2} / \binom{I(t)}{2}$.

Inferring epidemic, population, and species trajectories

Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Extensions

BEAST Packages

Alternative approach

Summary

References



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- ▶ Birth events occur at time t with the rate of $\beta I(t)$.
- ▶ Every birth is a potential coalescence.
- ▶ Probability of choosing a sampled lineage pair is $\binom{k}{2} / \binom{I(t)}{2}$.
- ▶ Approximate coalescence rate is

$$\beta I(t) \frac{k(k-1)}{I(t)(I(t)-1)} \simeq \binom{k}{2} \frac{2\beta}{I(t)}$$

Setting the Scene
Background theory
Approximate birth-death trajectories
Exact birth-death trajectories
Extensions
BEAST Packages
Alternative approach
Summary
References



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- ▶ Probability of choosing a sampled lineage pair is $\binom{k}{2} / \binom{I(t)}{2}$.
- ▶ Approximate coalescence rate is

$$\beta I(t) \frac{k(k-1)}{I(t)(I(t)-1)} \simeq \binom{k}{2} \frac{2\beta}{I(t)}$$

- ▶ One can use this coalescence rate to compute an approximation to $P(\mathcal{T}|\beta, \delta, T)$.

Setting the Scene

Background theory

Approximate
birth-death
trajectoriesExact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

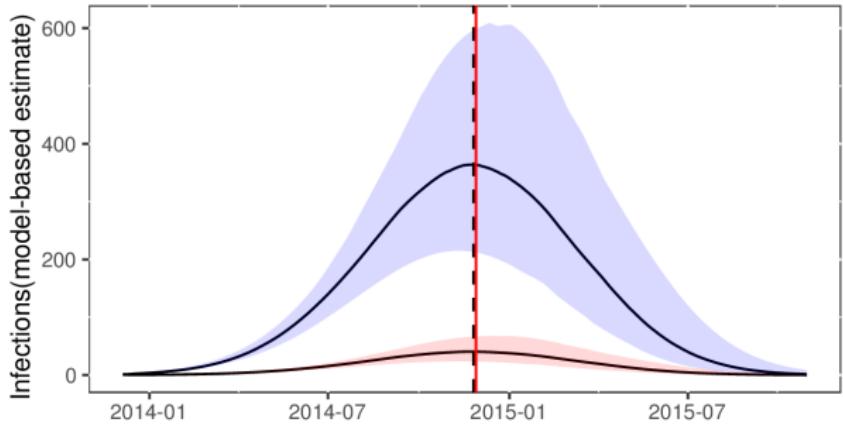
Summary

References

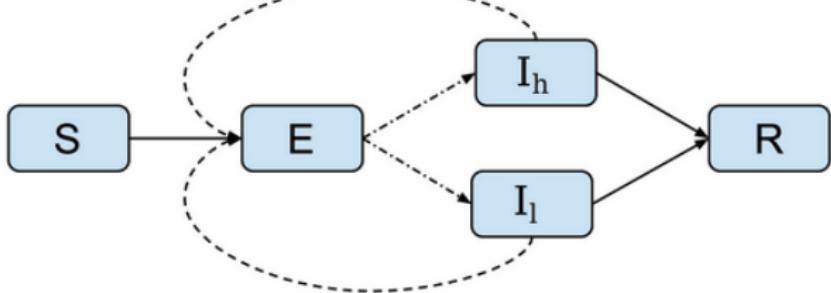


Coalescent inference of Ebola dynamics

Inferring epidemic,
population, and
species trajectories



B



Figures from Volz and Siveroni (2018). BEAST 2 package:
PhyDyn.



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References

Limitations of this approximation

- ▶ Quality of approximation depends heavily on how well birth-death population dynamics are approximated by deterministic ODE solution.

Inferring epidemic,
population, and
species trajectories

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

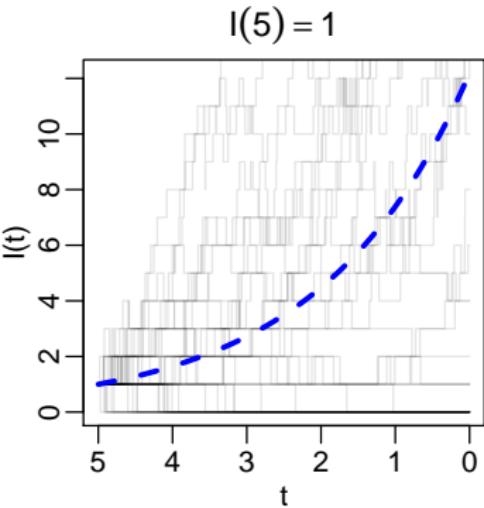
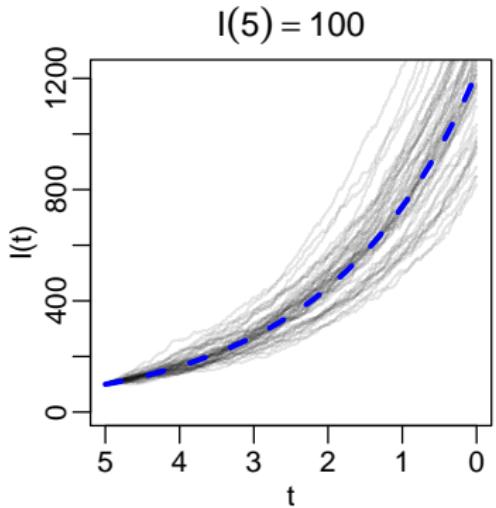
References



Limitations of this approximation

Inferring epidemic,
population, and
species trajectories

- Quality of approximation depends heavily on how well birth-death population dynamics are approximated by deterministic ODE solution.



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

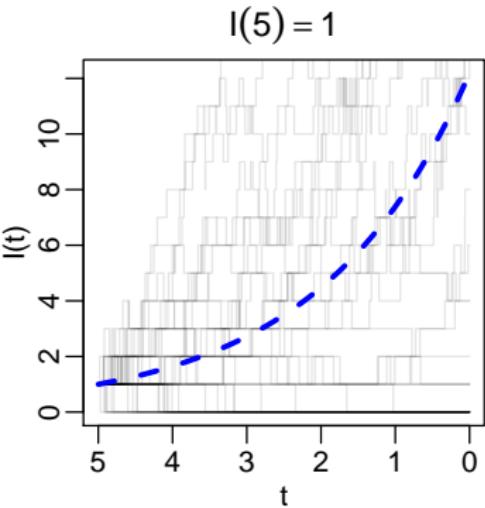
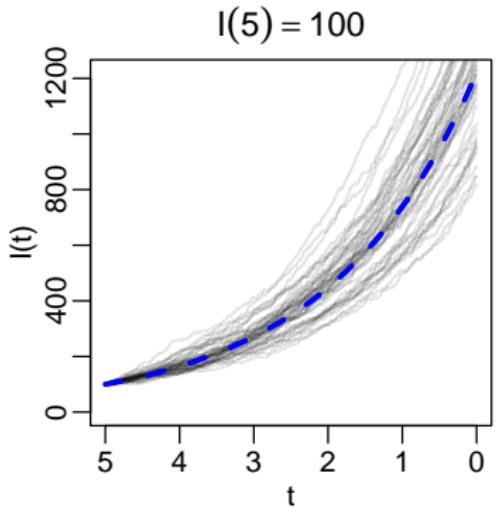
Summary

References



Limitations of this approximation

- Quality of approximation depends heavily on how well birth-death population dynamics are approximated by deterministic ODE solution.



- This approximation can perform very poorly when population size is small, *as it always is at the start of an epidemic.*



Setting the Scene

Background theory

Approximate
birth-death
trajectoriesExact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

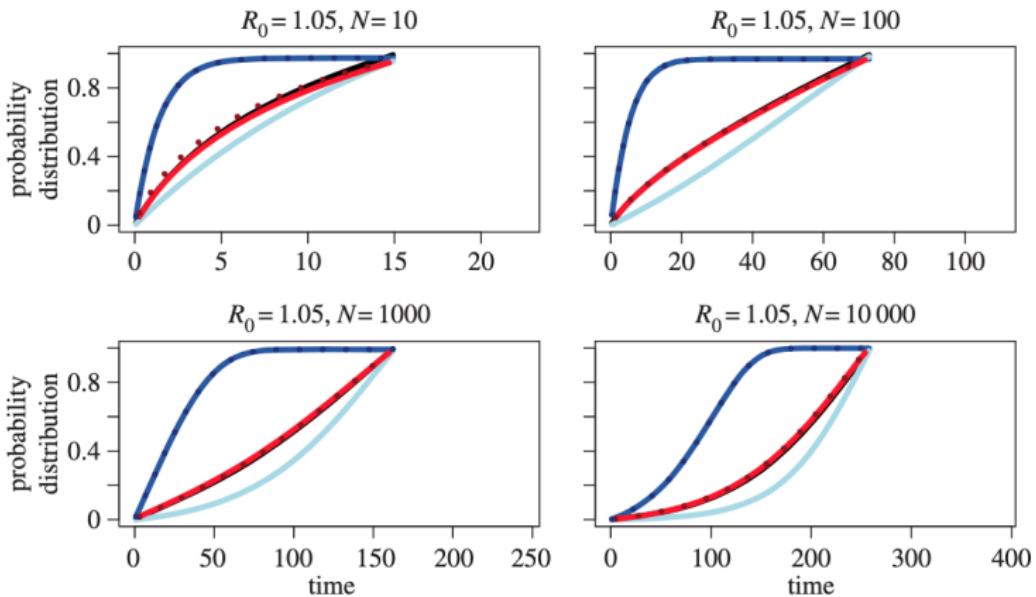
Summary

References

Limitations of this approximation

Inferring epidemic,
population, and
species trajectories

Coalescent time comparisons between BD and Coalescent models:



Stadler et al. (2015)



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References

Idea 2: Use stochastic simulation to infer trajectories

Inferring epidemic, population, and species trajectories

Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Applications

SARS-CoV-2

Dinosaurs

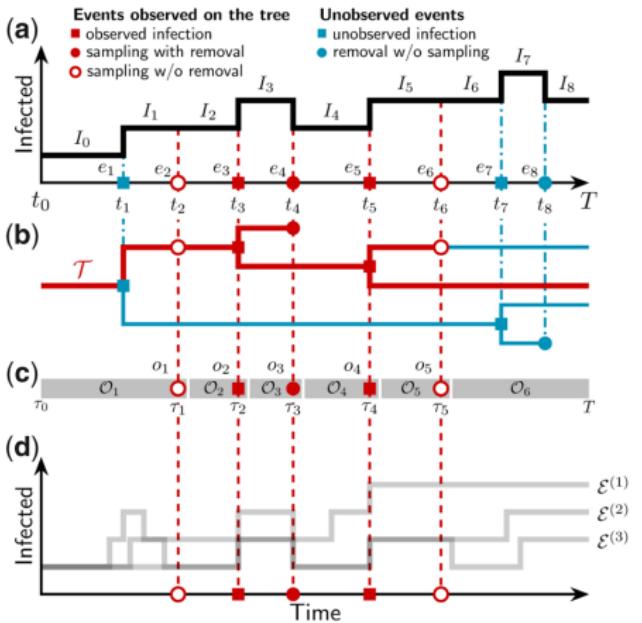
Extensions

BEAST Packages

Alternative approach

Summary

References



Vaughan et al. (2019)

Particle filtering introduction

Inferring epidemic,
population, and
species trajectories

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

Summary

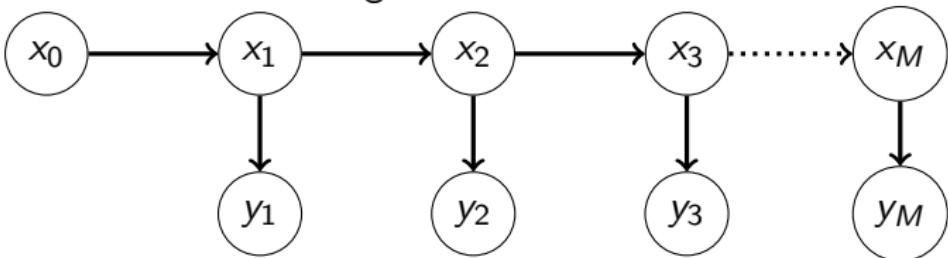
References



Particle filtering introduction

Inferring epidemic,
population, and
species trajectories

- ▶ Consider the following hidden Markov model:



with transition probabilities $P(x_{t+1}|x_t)$ and emission probabilities $P(y_t|x_t)$.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

Summary

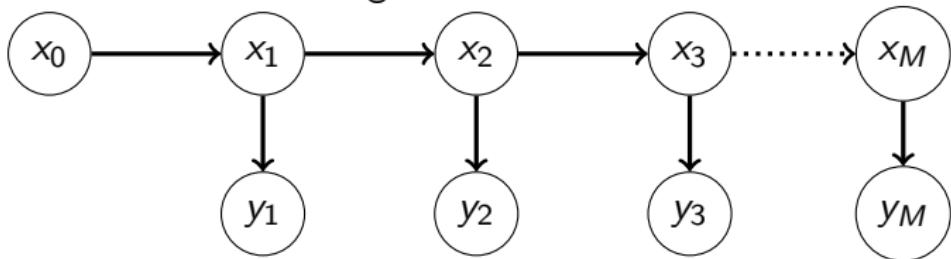
References



Particle filtering introduction

Inferring epidemic,
population, and
species trajectories

- ▶ Consider the following hidden Markov model:



with transition probabilities $P(x_{t+1}|x_t)$ and emission probabilities $P(y_t|x_t)$.

- ▶ BPF is a simple algorithm for sampling from $P(x_{1:M}|y_{1:M})$ and providing Monte Carlo estimates of the marginal likelihood $P(y_{1:M})$.



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

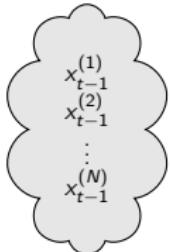
Alternative
approach

Summary

References

Bootstrap Particle Filtering

Inferring epidemic,
population, and
species trajectories



1. Set $t \leftarrow 1$ and draw a set of N initial (particle) states
- $x_0^{(i)} \sim P(x_0)$.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

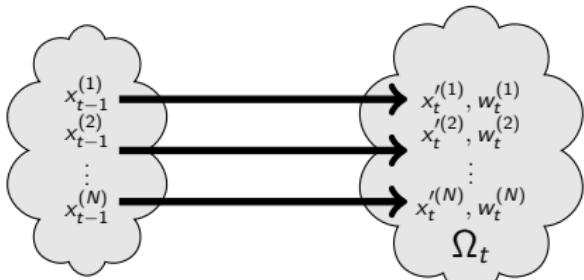
Summary

References



Bootstrap Particle Filtering

Inferring epidemic,
population, and
species trajectories



1. Set $t \leftarrow 1$ and draw a set of N initial (particle) states $x_0^{(i)} \sim P(x_0)$.
2. Propagate each particle state by generating a new set of N states $x_t'^{(i)} \sim P(x_t | x_{t-1}^{(i)})$.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications

SARS-CoV-2

Dinosaurs

Extensions

BEAST Packages

Alternative
approach

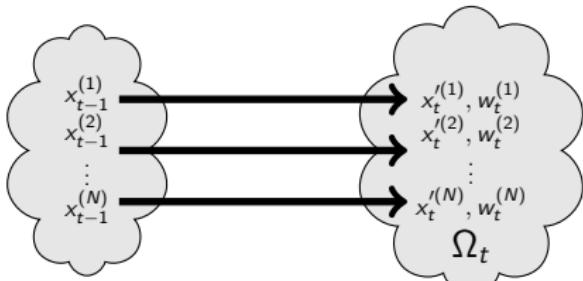
Summary

References



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Inferring epidemic,
population, and
species trajectories



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Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications

SARS-CoV-2

Dinosaurs

Extensions

BEAST Packages

Alternative
approach

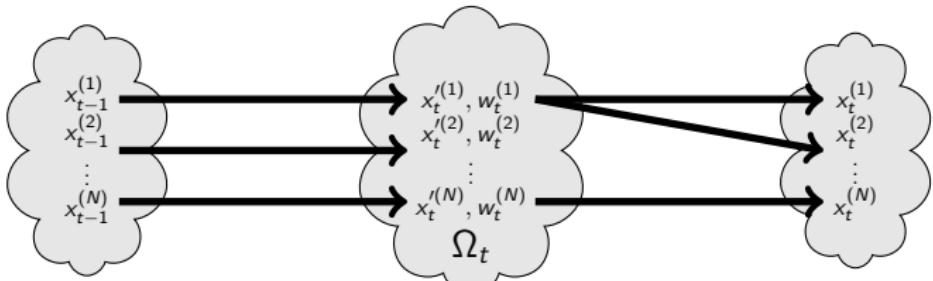
Summary

References



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Inferring epidemic,
population, and
species trajectories



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Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

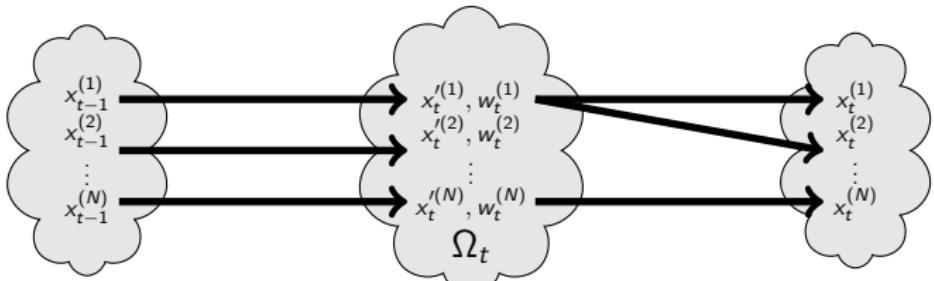
Summary

References



Bootstrap Particle Filtering

Inferring epidemic,
population, and
species trajectories



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4. Sample N new $x_t^{(i)}$ from weighted states $\{x_t'^{(i)}\}$.
5. If $t < M$, set $t \leftarrow t + 1$ and return to step 2.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

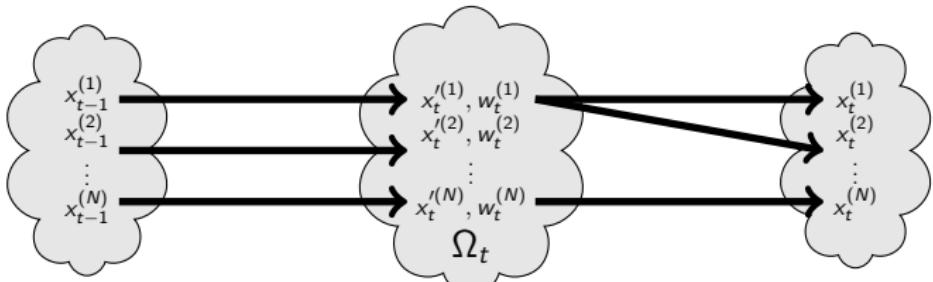
Summary

References



Bootstrap Particle Filtering

Inferring epidemic,
population, and
species trajectories



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4. Sample N new $x_t^{(i)}$ from weighted states $\{x_t'^{(i)}\}$.
5. If $t < M$, set $t \leftarrow t + 1$ and return to step 2.

The product $\prod_{t=1}^M \Omega_t$ gives an *unbiased* estimate for $P(y_{1:M})$, and a particle trajectory gives an approximate draw from $P(x_{1:M} | y_{1:M})$.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

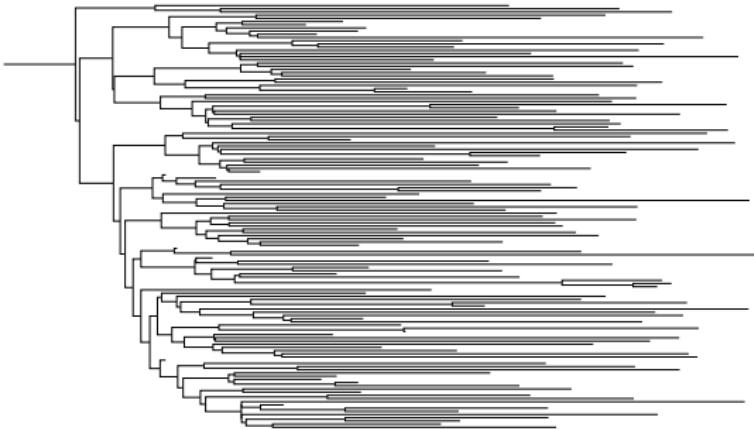
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications

SARS-CoV-2

Dinosaurs

Extensions

BEAST Packages

Alternative
approach

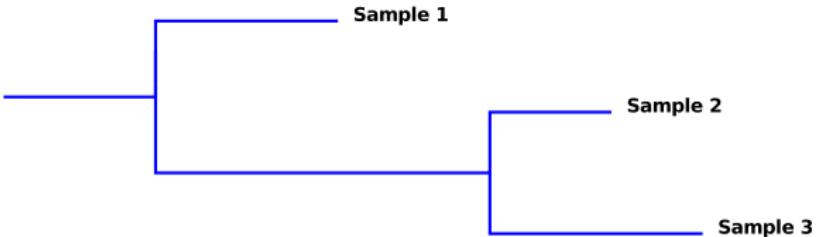
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

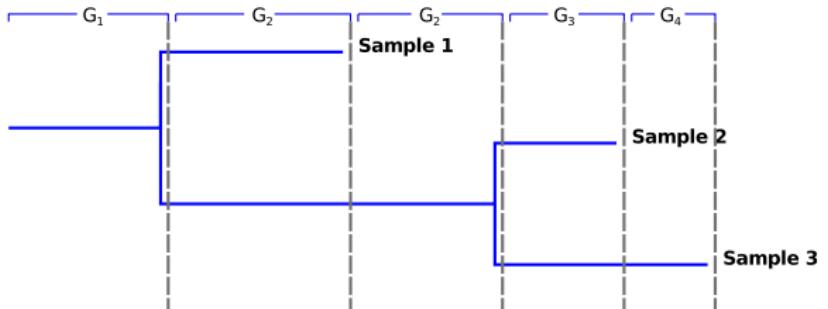
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

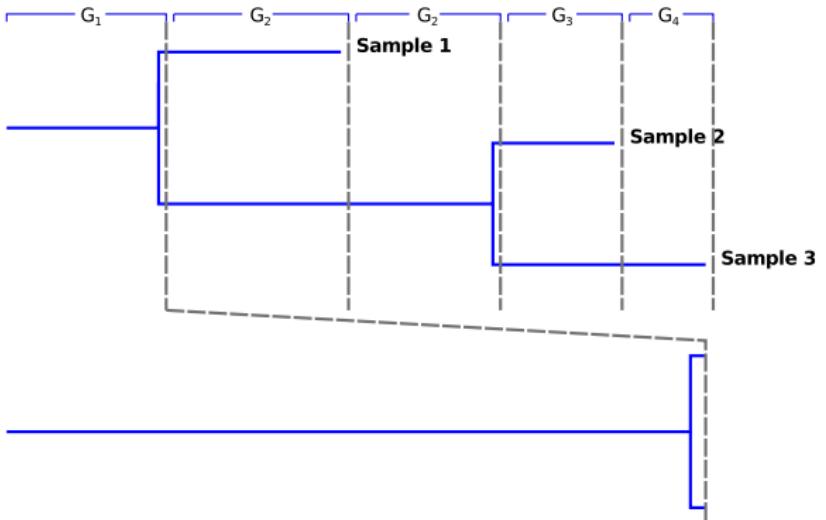
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

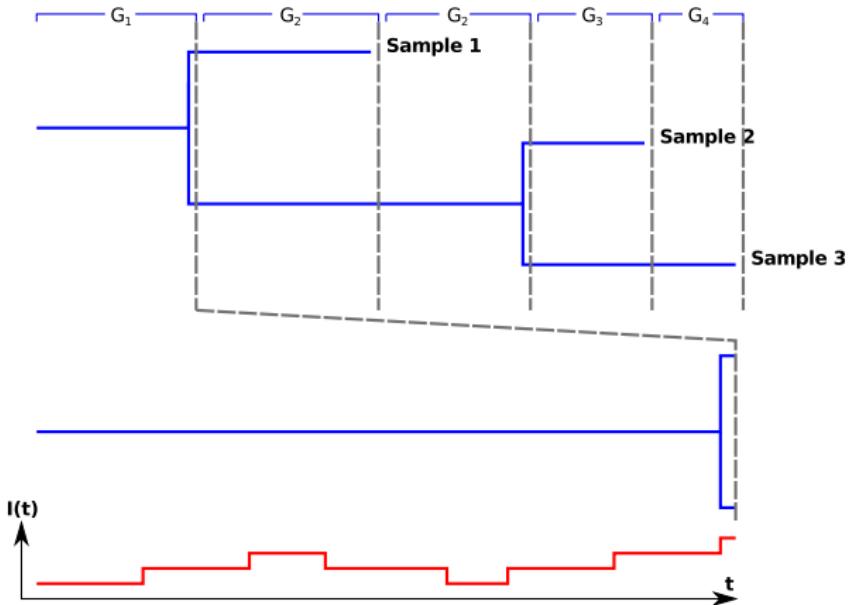
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

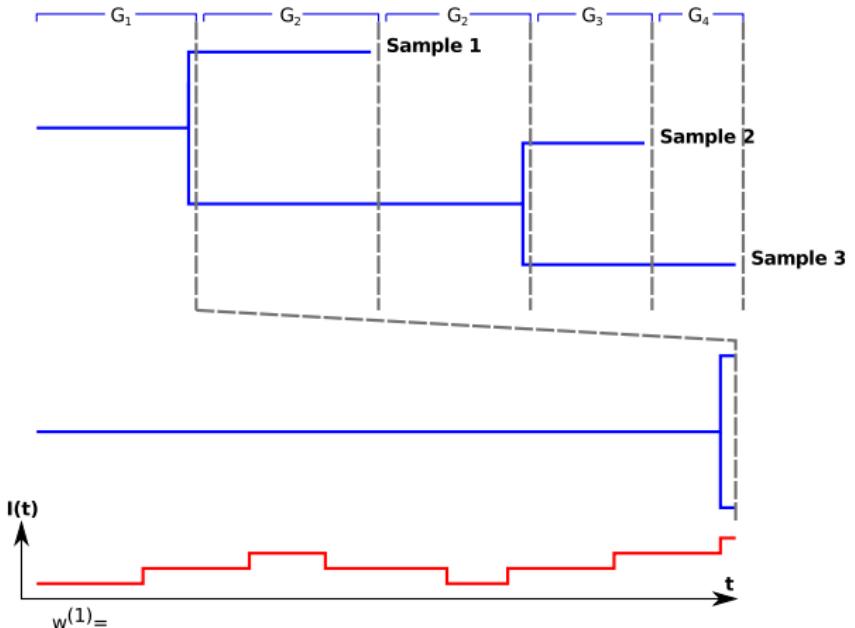
Summary

References



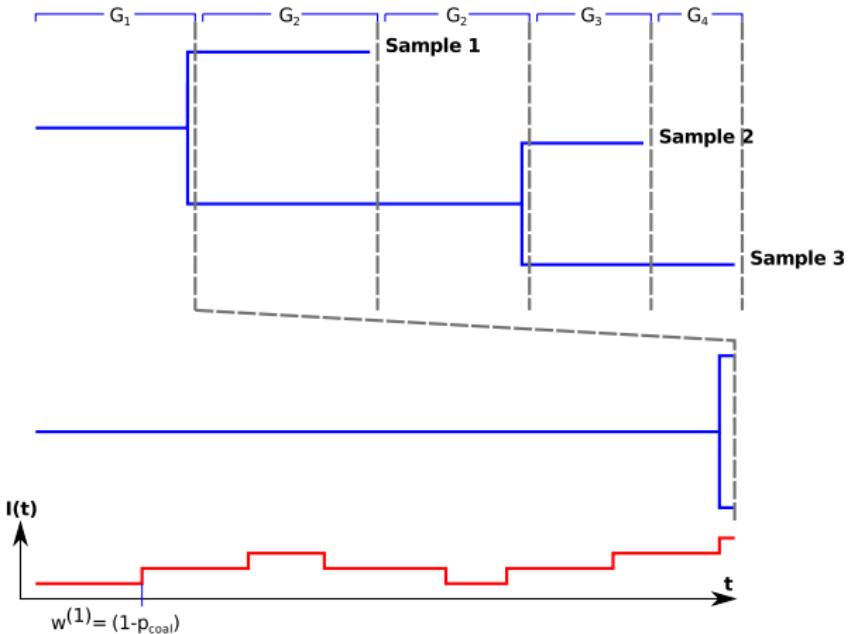
Particle filtering for inferring trajectories from trees

Inferring epidemic, population, and species trajectories



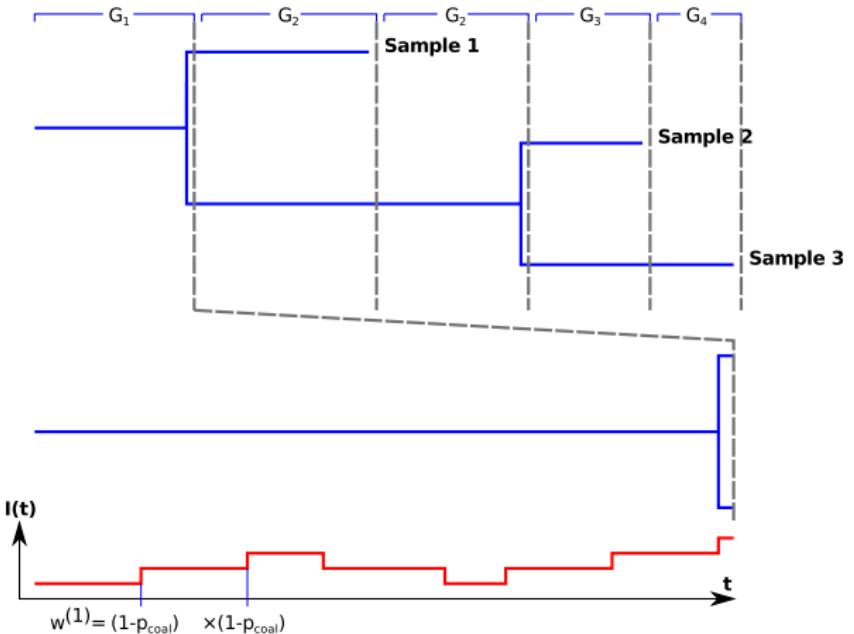
Particle filtering for inferring trajectories from trees

Inferring epidemic, population, and species trajectories



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

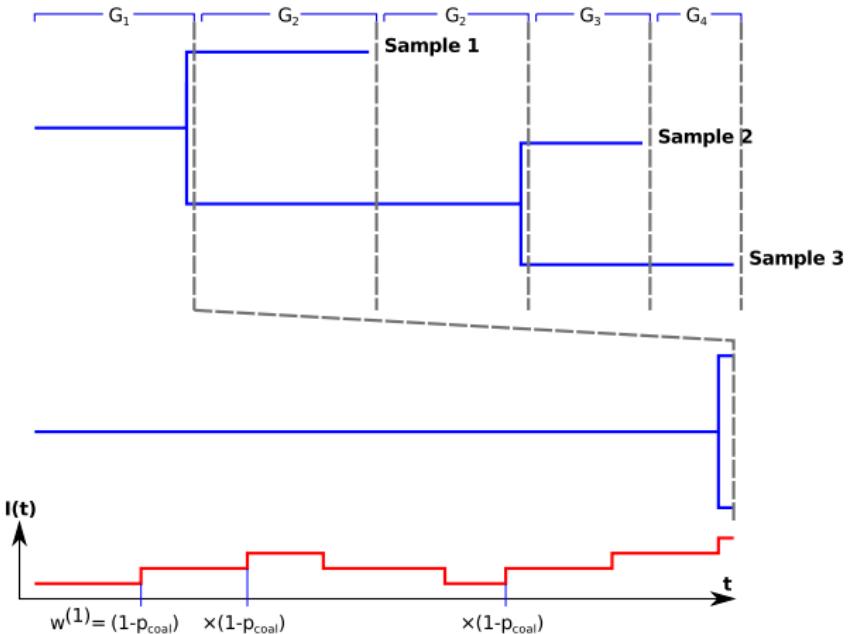
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

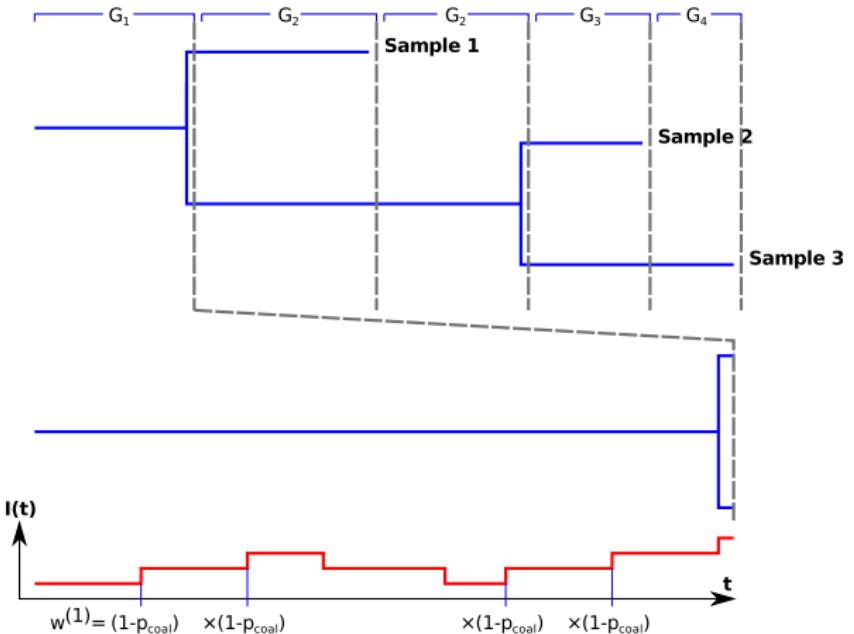
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

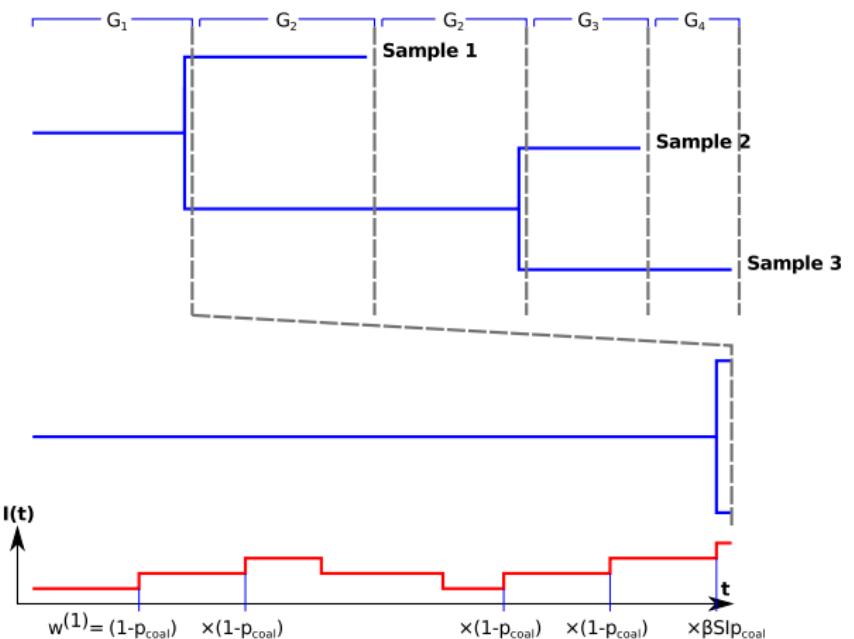
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

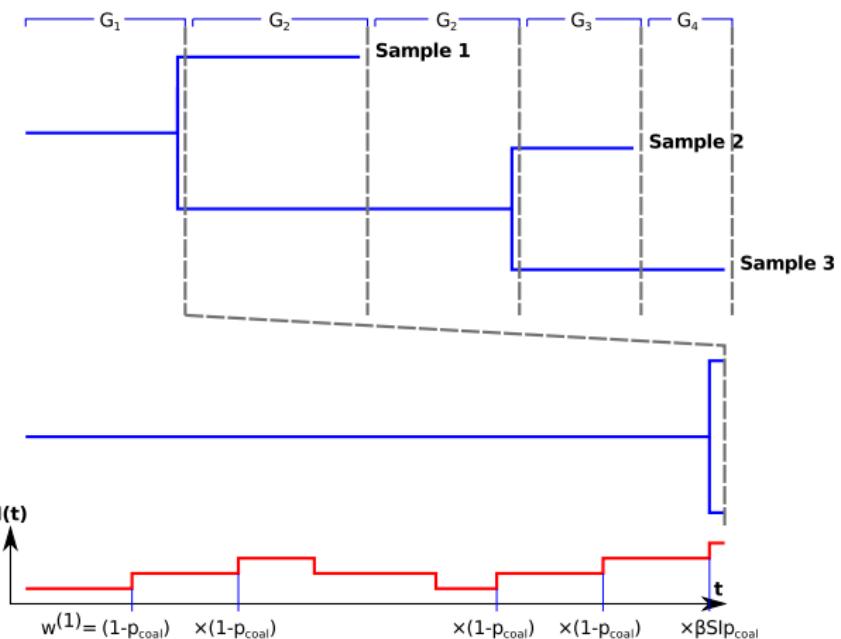
Summary

References



Particle filtering for inferring trajectories from trees

Inferring epidemic,
population, and
species trajectories



Here $p_{coal} = \frac{k(t)(k(t)-1)}{I(t)(I(t)-1)}$ with $k(t)$ being the number of lineages extant at time t immediately following the event.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

Summary

References



Application to SARS-CoV-2 trajectories

Inferring epidemic,
population, and
species trajectories

- ▶ Early in 2020, the nascent SARS-CoV-2 pandemic was beginning to rage in several countries.
- ▶ Sequencing data rapidly became available due to sequencing efforts in many of these countries.
- ▶ Sarah Nadeau and others assembled and curated several high-quality alignments, ideally containing only sequences produced by transmission clusters local to specific countries.
- ▶ BDSKY analyses allowed us to infer R_0 for each of these outbreaks.
- ▶ Particle filtering allowed us to further infer outbreak prevalence trajectories.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

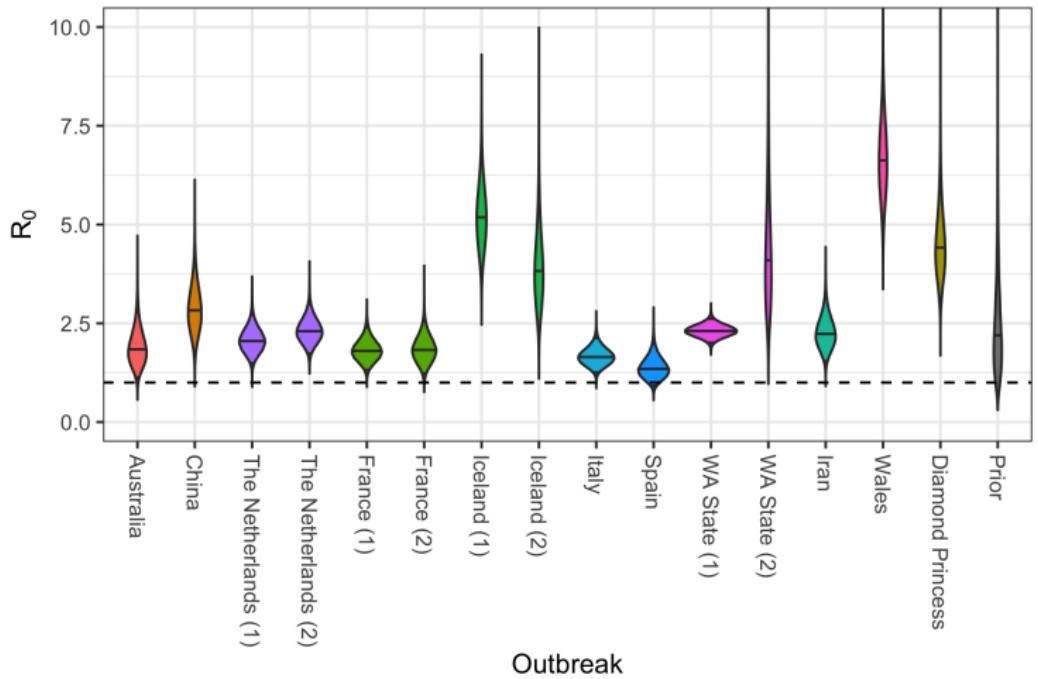
Summary

References



Outbreak-specific R_0 estimates

Inferring epidemic,
population, and
species trajectories



Vaughan et al. (2020) (preprint)



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

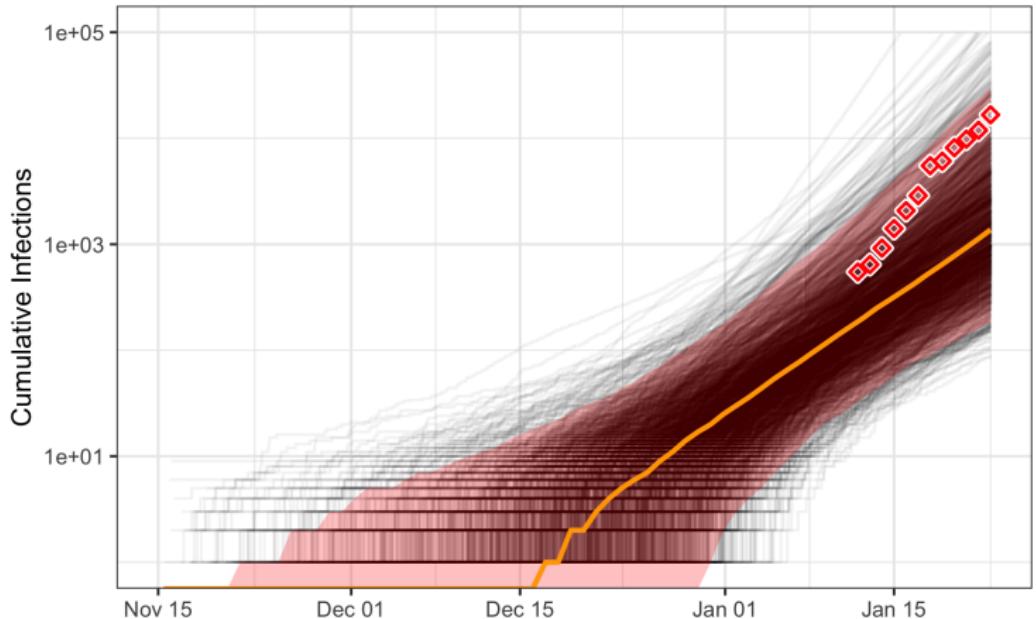
Summary

References

Country-specific prevalence trajectories

Inferring epidemic,
population, and
species trajectories

China



Vaughan et al. (2020) (preprint)

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

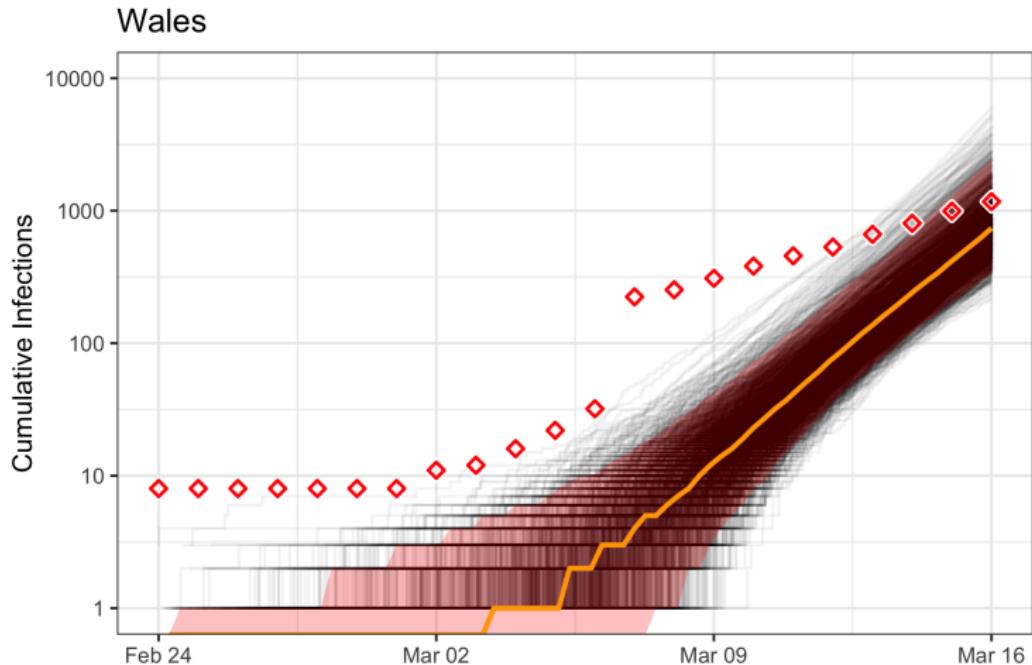
Summary

References



Country-specific prevalence trajectories

Inferring epidemic,
population, and
species trajectories



Vaughan et al. (2020) (preprint)



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications

SARS-CoV-2

Dinosaurs

Extensions

BEAST Packages

Alternative
approach

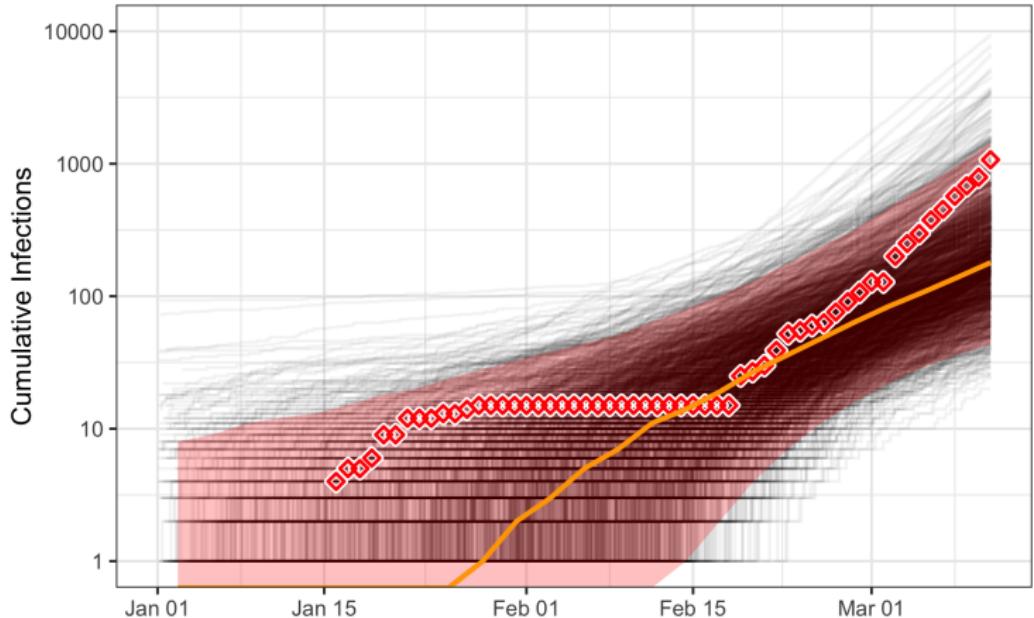
Summary

References

Country-specific prevalence trajectories

Inferring epidemic,
population, and
species trajectories

Australia



Vaughan et al. (2020) (preprint)

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

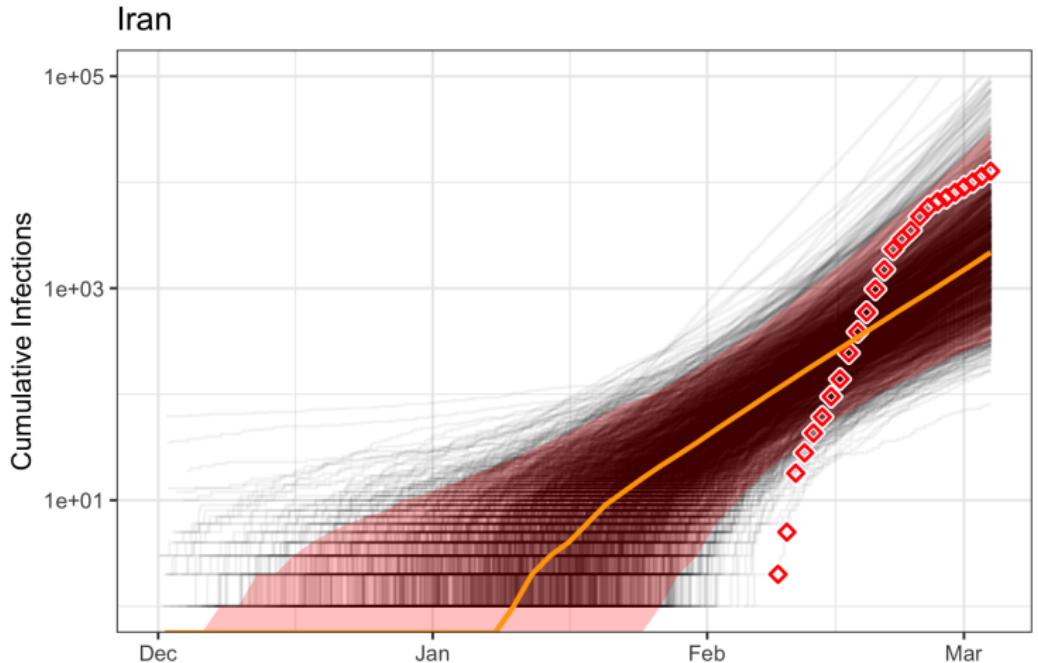
Summary

References



Country-specific prevalence trajectories

Inferring epidemic,
population, and
species trajectories



Vaughan et al. (2020) (preprint)

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

Summary

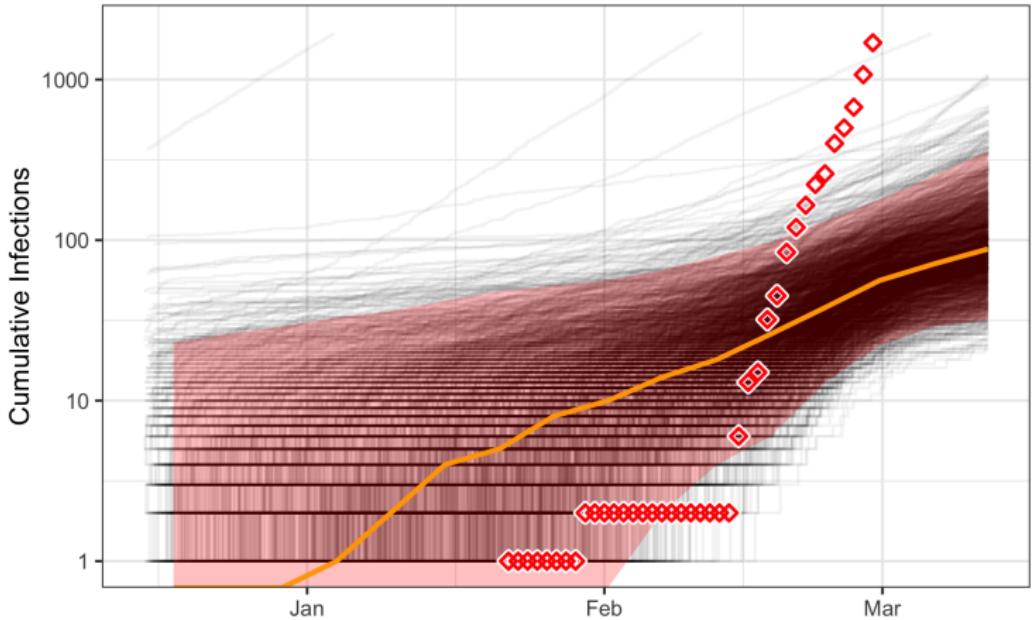
References



Country-specific prevalence trajectories

Inferring epidemic,
population, and
species trajectories

Spain



Vaughan et al. (2020) (preprint)



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

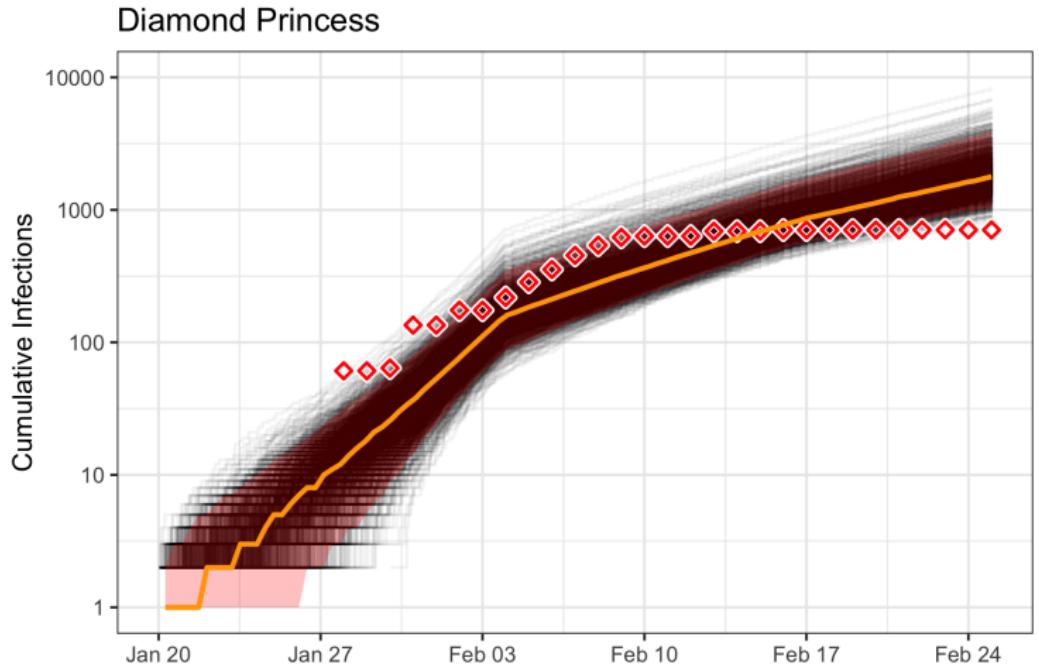
Alternative
approach

Summary

References

Country-specific prevalence trajectories

Inferring epidemic,
population, and
species trajectories



Vaughan et al. (2020) (preprint)

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

Summary

References

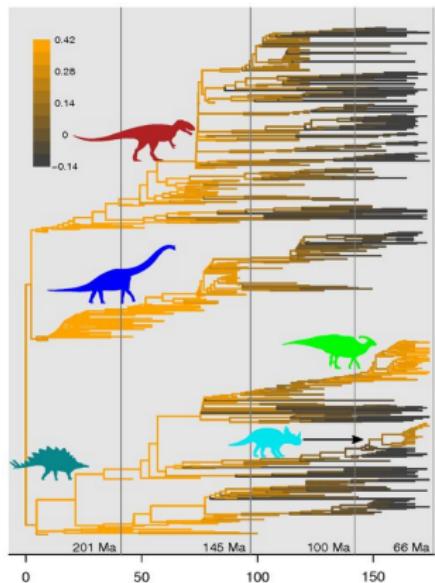


Application to Dinosaur species richness

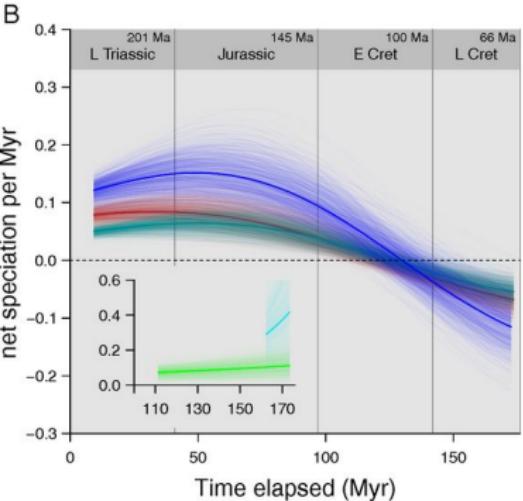
Inferring epidemic, population, and species trajectories

While the effect of the K-Pg extinction event on dinosaurs is well-known, evidence exists for a decline in species richness prior to this point, e.g. the work of Sakamoto et al. (2016):

A



B



Sakamoto et al. (2016)

What does a birth-death phylodynamic analysis say?

Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Applications

SARS-CoV-2

Dinosaurs

Extensions

BEAST Packages

Alternative approach

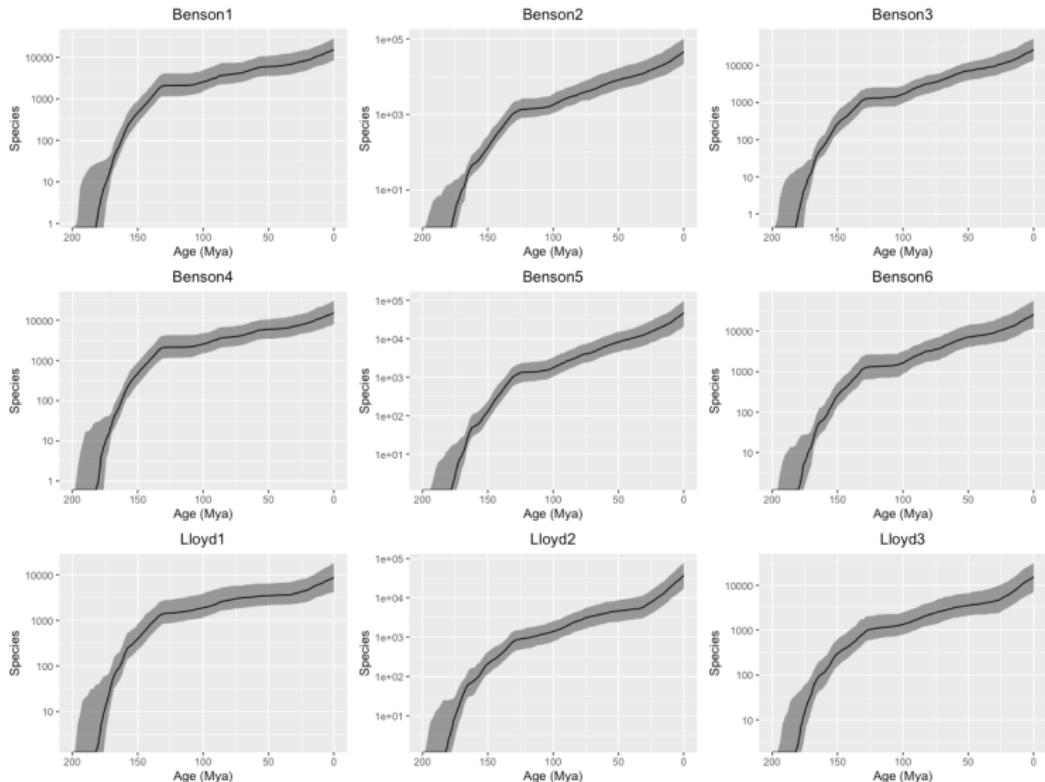
Summary

References



Application to Dinosaur species richness

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications

SARS-CoV-2

Dinosaurs

Extensions

BEAST Packages

Alternative
approach

Summary

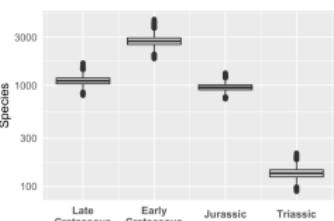
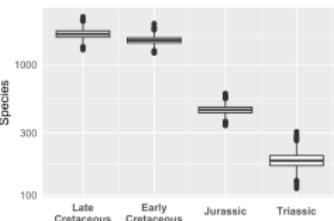
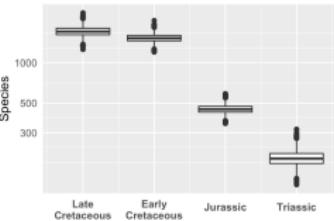
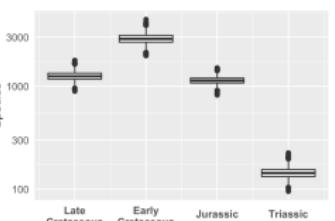
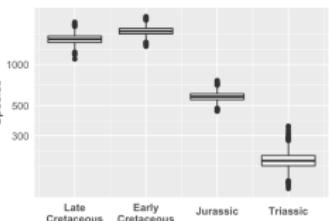
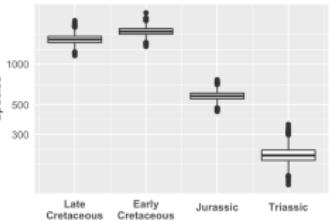
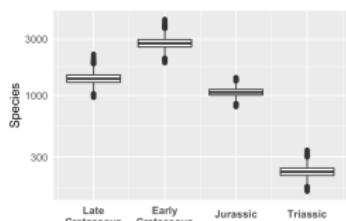
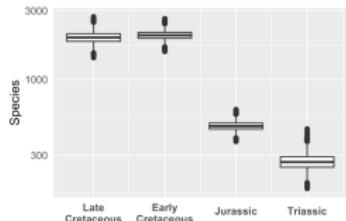
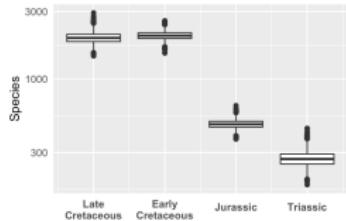
References



(Volkova et al., in preparation)

Application to Dinosaur species richness

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Applications
SARS-CoV-2
Dinosaurs

Extensions

BEAST Packages

Alternative
approach

Summary

References



(Volkova et al., in preparation)

Extension: non-linear models

Inferring epidemic,
population, and
species trajectories

- ▶ All of the (non-approximate) methods above have involved only linear birth-death processes.
- ▶ That is, the rate at which births, deaths, and samples occur is assumed to be linearly proportional to the population size.
- ▶ This assumption is violated for many interesting epidemiological models:
 - ▶ SIR, SIS, etc.
- ▶ However, this is the assumption that allows us to infer trajectories separately to the MCMC.

What can we do?

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

Alternative
approach

Summary

References



Extension: non-linear models

Inferring epidemic,
population, and
species trajectories

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- ▶ This assumption is violated for many interesting epidemiological models:
 - ▶ SIR, SIS, etc.
- ▶ However, this is the assumption that allows us to infer trajectories separately to the MCMC.

What can we do?

- ▶ Use our particle filter to jointly estimate the tree prior probability!



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

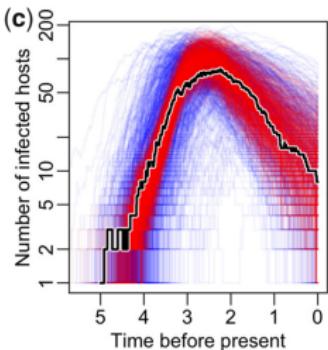
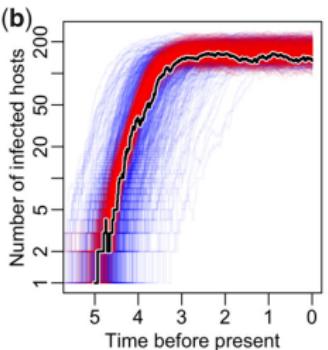
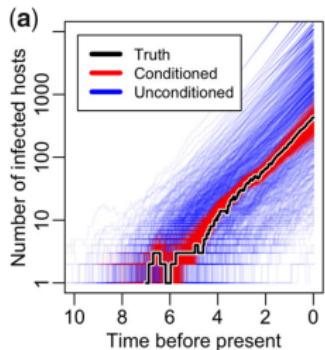
Alternative
approach

Summary

References

Extension: non-linear models

Inferring epidemic,
population, and
species trajectories



Vaughan et al. (2019)



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

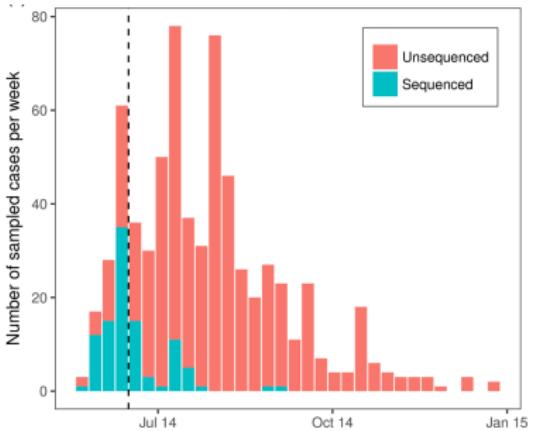
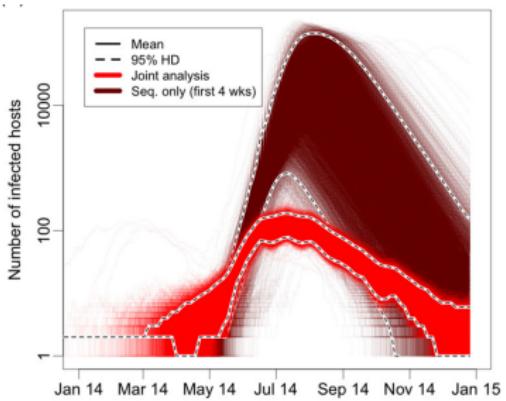
Alternative
approach

Summary

References

Application to 2014-2016 West African Ebola epidemic

Inferring epidemic,
population, and
species trajectories



Vaughan et al. (2019)

Simulation-based approach also enables joint inference of sequence and case data.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

Alternative
approach

Summary

References



Extension: multi-type models

Inferring epidemic,
population, and
species trajectories

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

Alternative
approach

Summary

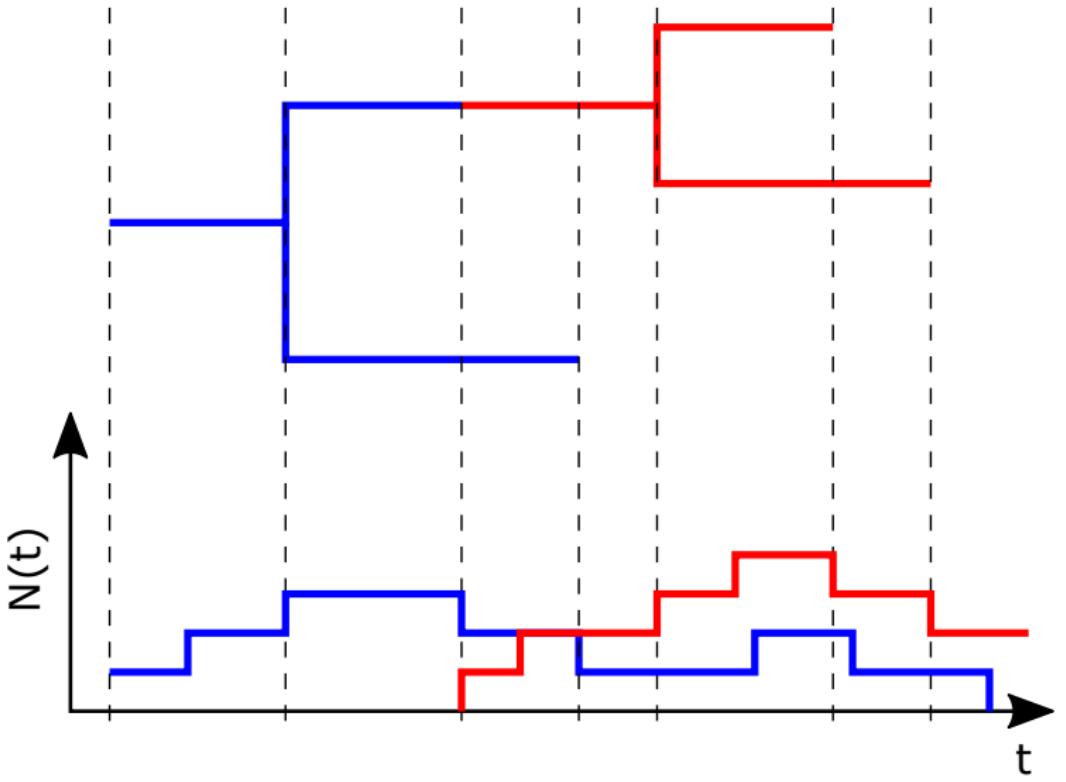
References

- ▶ All of the (non-approximate) methods above have involved only single-type trajectories.
- ▶ How can we deal with structured populations?
- ▶ For linear multi-type birth-death models, we can use particle filtering to sample *multi-type trajectories* compatible with coloured (multi-type) trees.
- ▶ Even better: we can use simulation approaches to add the ancestral types to trees generated by methods which do not sample these types.



Extension: multi-type models

Inferring epidemic,
population, and
species trajectories



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

Alternative
approach

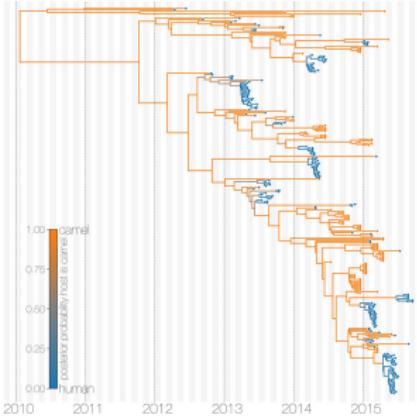
Summary

References



Application: MERS-CoV

Inferring epidemic,
population, and
species trajectories



- Dudas et al. (2018) analyzed 274 MERS-CoV genomes sampled from Camels and Humans and used these to study spillover events from Camels into the Human population using a structured coalescent model.



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models

Multi-type models

BEAST Packages

Alternative
approach

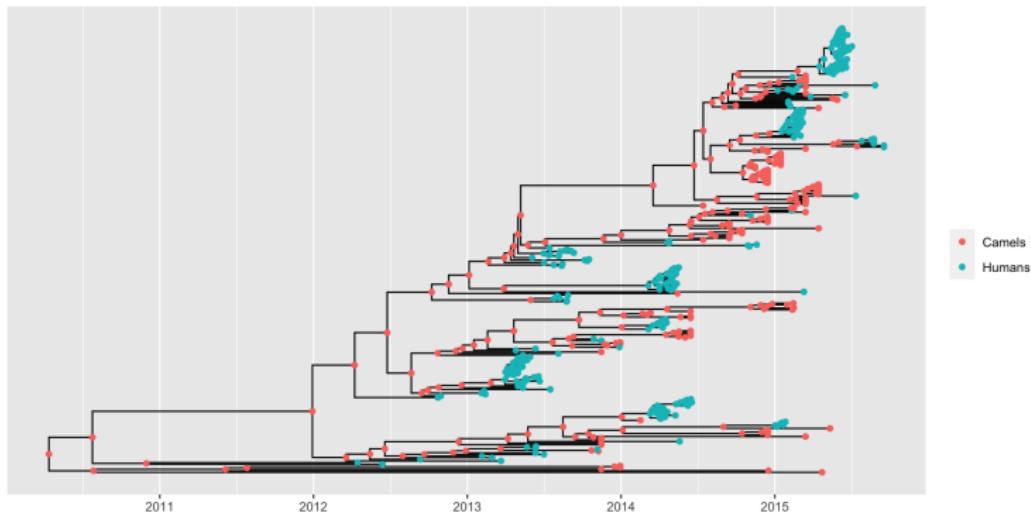
Summary

References

Application: MERS-CoV

Inferring epidemic,
population, and
species trajectories

- ▶ What can we learn using a multi-type BD model?



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

Alternative
approach

Summary

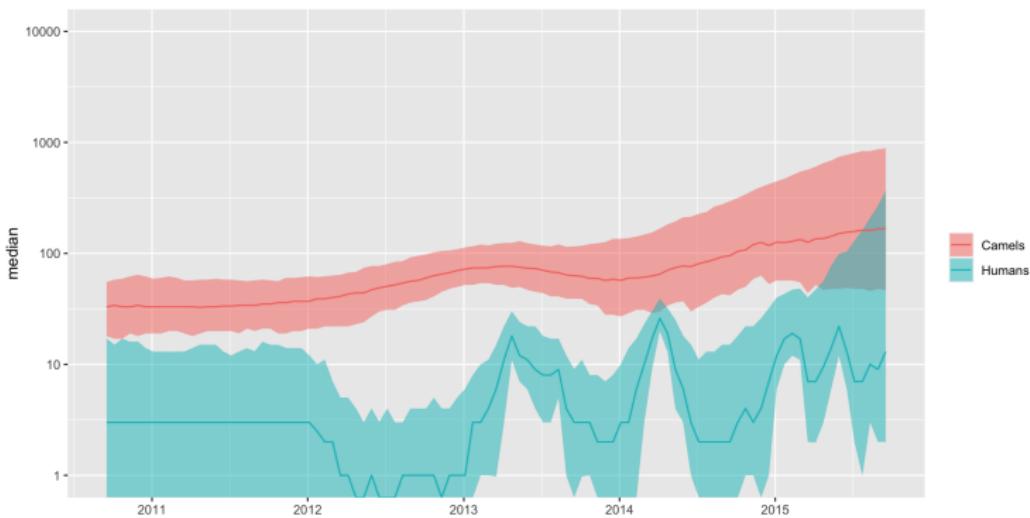
References



Application: MERS-CoV

Inferring epidemic,
population, and
species trajectories

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Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

Alternative
approach

Summary

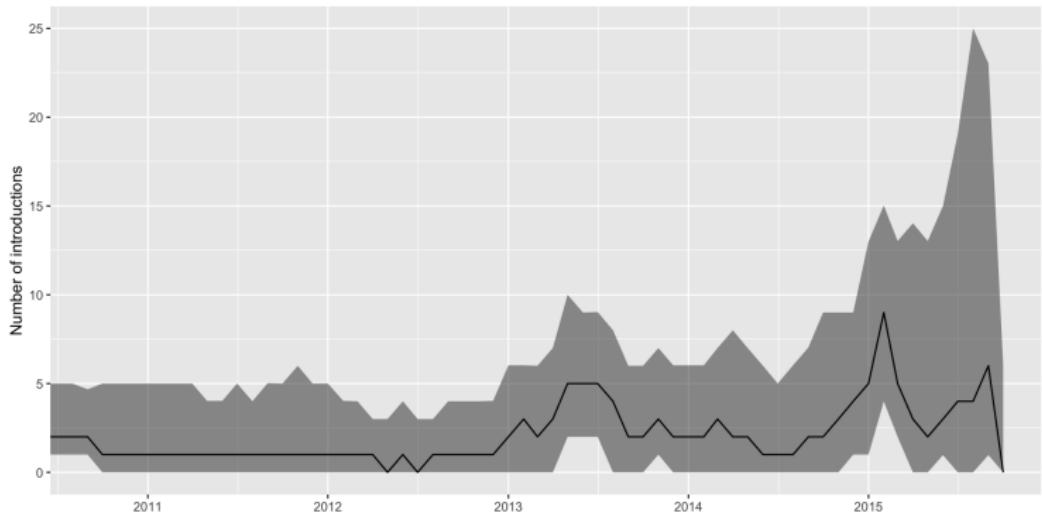
References



Application: MERS-CoV

Inferring epidemic,
population, and
species trajectories

- ▶ What can we learn using a multi-type BD model?



Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

Non-linear models
Multi-type models

BEAST Packages

Alternative
approach

Summary

References



PhyDyn: Epidemiological modelling in BEAST.

Igor Siveroni and Erik Volz. Department of Infectious Disease Epidemiology, Imperial College London.

- ▶ Due to Igor Siveroni and Erik Volz. (Volz and Siveroni, 2018)
- ▶ Flexible syntax for specifying nonlinear multi-type compartmental models.
- ▶ Trajectory inference is done under the deterministic coalescent approximation described above.
- ▶ Install via BEAUTi. Documentation at <https://github.com/mrc-ide/PhyDyn>.

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

PhyDyn

EpilInf

BDMM-Prime

Alternative
approach

Summary

References



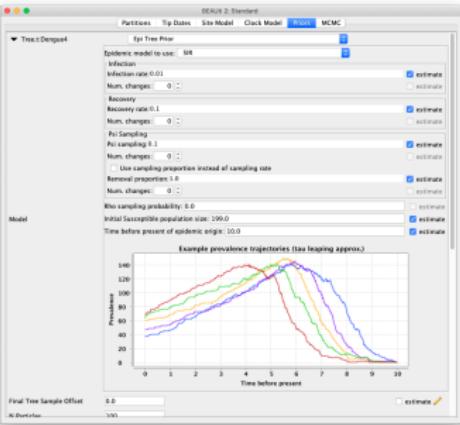
BEAST Package: EpiInf

EpiInf

Documentation

Source Code

EpiInf is a BEAST 2 package for performing exact inference of stochastic compartmental epidemiological model parameters using particle filtering to compute the prior probability density of a tree. Joint inference of prevalence trajectories is also performed.



- ▶ Uses particle filtering to jointly infer trees and trajectories using sequence and prevalence data.
(Vaughan et al., 2019)
- ▶ Single-type linear/nonlinear models.
- ▶ Can be computationally demanding.
- ▶ Install via BEAUTi. Documentation at
<https://tgvaughan.github.com/EpiInf>.



Inferring epidemic,
population, and
species trajectories

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

PhyDyn

EpiInf

BDMM-Prime

Alternative
approach

Summary

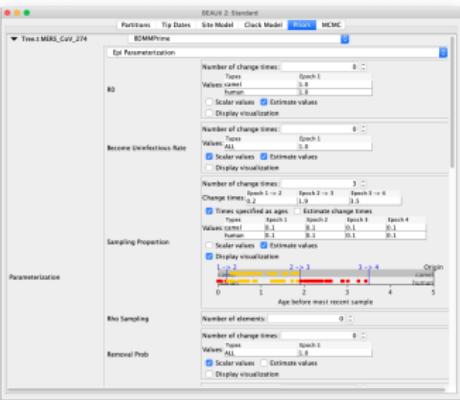
References

BEAST Package: BDMM-Prime

BDMM-Prime

Unit/integration tests passing

The BDMM-Prime project provides a BEAST 2 package for performing phylodynamic inference under both structured and unstructured birth-death models.



- ▶ Recent fork of BDMM Kühnert et al. (2016) which integrates over ancestral types during MCMC but uses simulation methods to produce coloured trees and trajectories.
- ▶ Limited to linear models.
- ▶ Computationally efficient (due to work of Jérémie Sciré).
- ▶ Still in development, but can be installed from <https://github.com/tgvaughan/BDMM-Prime>.

Inferring epidemic,
population, and
species trajectories

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

PhyDyn
Epilinf
BDMM-Prime

Alternative
approach

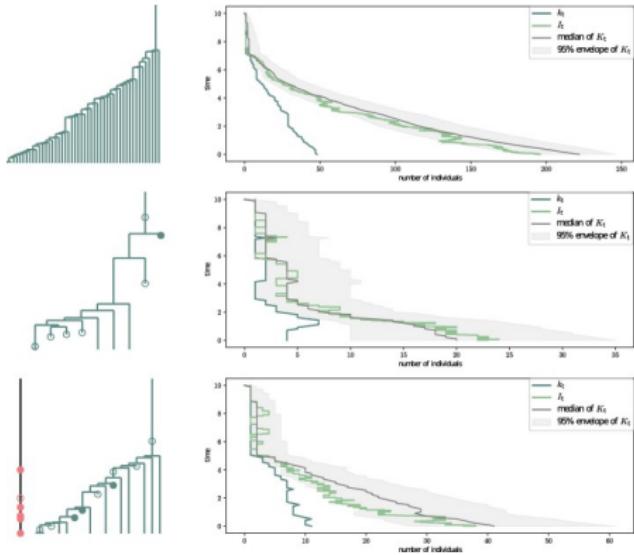
Summary

References



Alternative approach (Manceau et al., 2021)

Inferring epidemic,
population, and
species trajectories



- ▶ Directly computes probability distribution of population sizes conditional on the tree and prevalence data.
- ▶ Potentially more efficient than simulation-based approaches for single-typed models.
- ▶ BEAST implementations in progress.



Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Extensions

BEAST Packages

Alternative approach

Summary

References

Summary

Inferring epidemic,
population, and
species trajectories

- ▶ There are deep connections between coalescent and birth-death models.
- ▶ These connections help motivate methods to infer population trajectories both approximately and exactly.
- ▶ All of these methods have limitations, are some are still experimental, but most can already be used in BEAST.
- ▶ Expect to see more of these approaches in the future!

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References



Acknowledgements

Inferring epidemic,
population, and
species trajectories

Much of the work presented here is due to, or done in collaboration with, others:

- ▶ Alexei Drummond, David Welch, and others at the Department of Computer Science at The University of Auckland,
- ▶ Jérémie Sciré, Tanja Stadler, and other members of the Stadler group,
- ▶ Gabriel Leventhal (PharmaBiome AG)
- ▶ David Rasmussen (Dept. of Entomology and Plant Pathology, North Carolina State University)

Setting the Scene

Background theory

Approximate
birth-death
trajectories

Exact birth-death
trajectories

Extensions

BEAST Packages

Alternative
approach

Summary

References



References

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Inferring epidemic, population, and species trajectories

Setting the Scene

Background theory

Approximate birth-death trajectories

Exact birth-death trajectories

Extensions

BEAST Packages

Alternative approach

Summary

References

