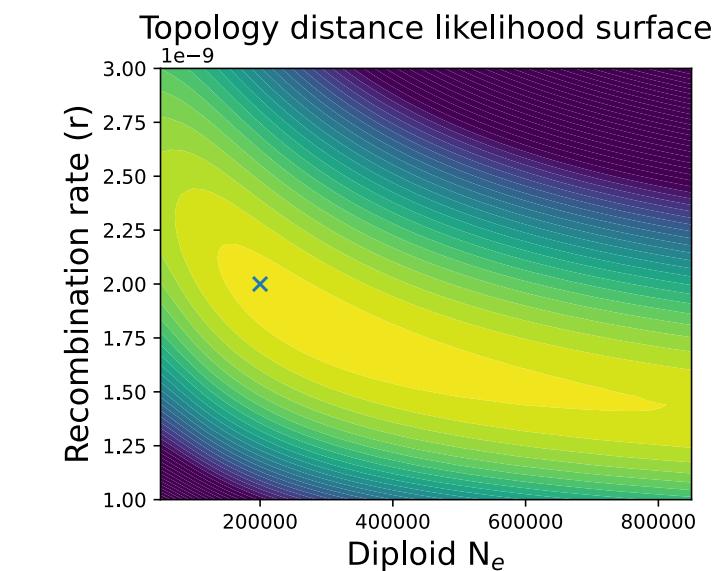
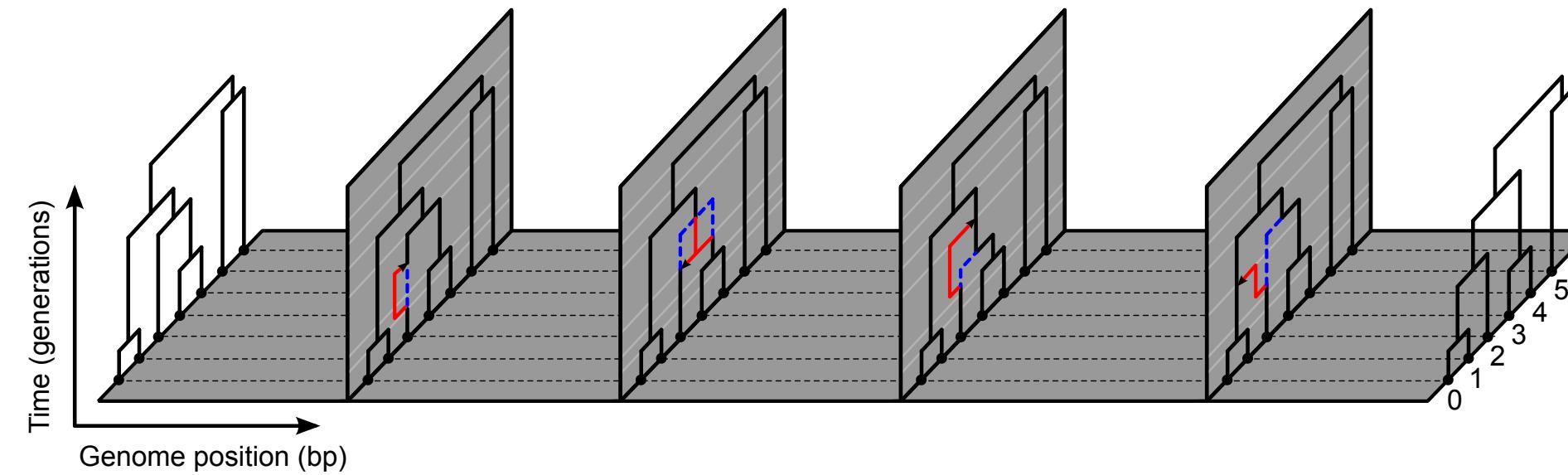


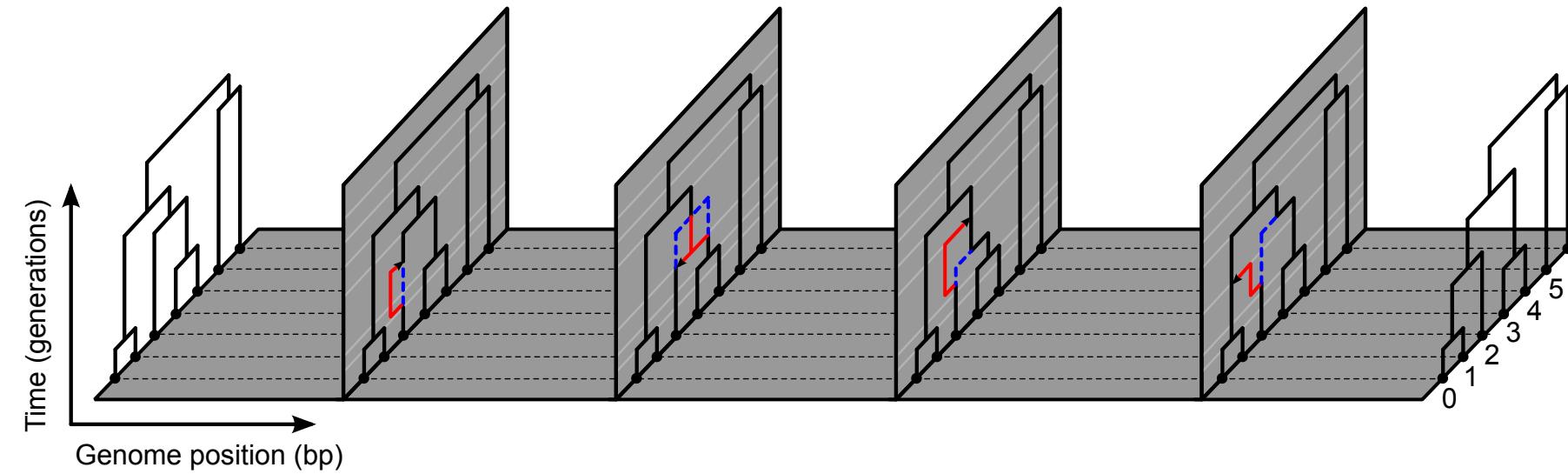
Linking Phylogenetic Inference at Genome-wide and Genealogical Scales



Deren Eaton and Patrick McKenzie
Ecology, Evolution, and Environmental Biology, Columbia University

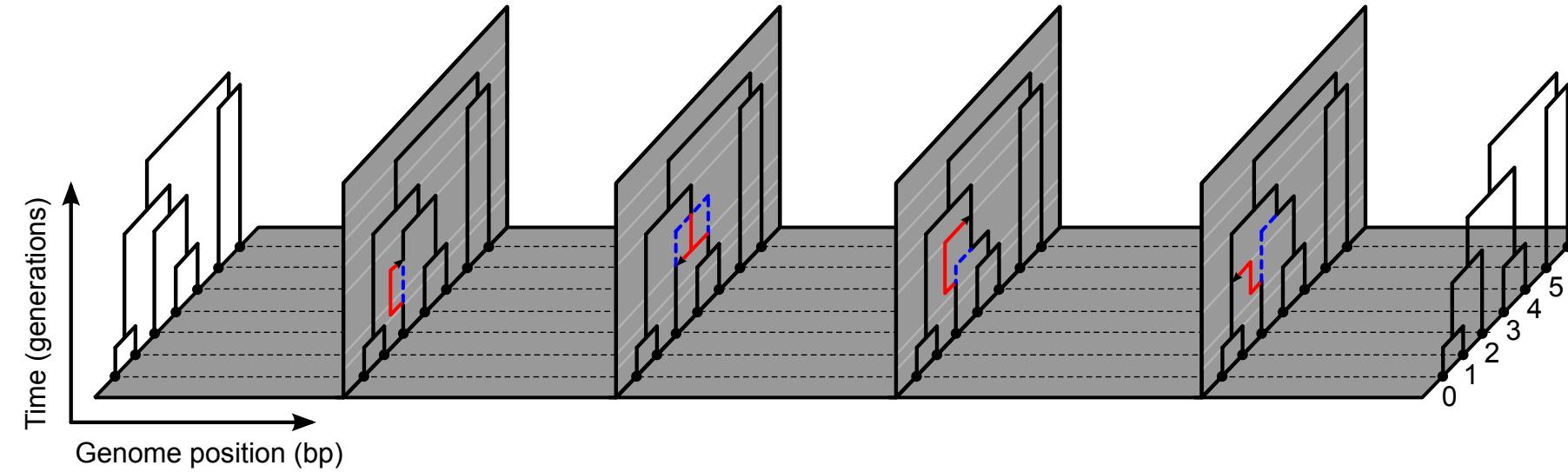
Genealogical variation

Genomes are composed of a mosaic of segments inherited from different ancestors, each separated by past recombination events.



Genealogical variation

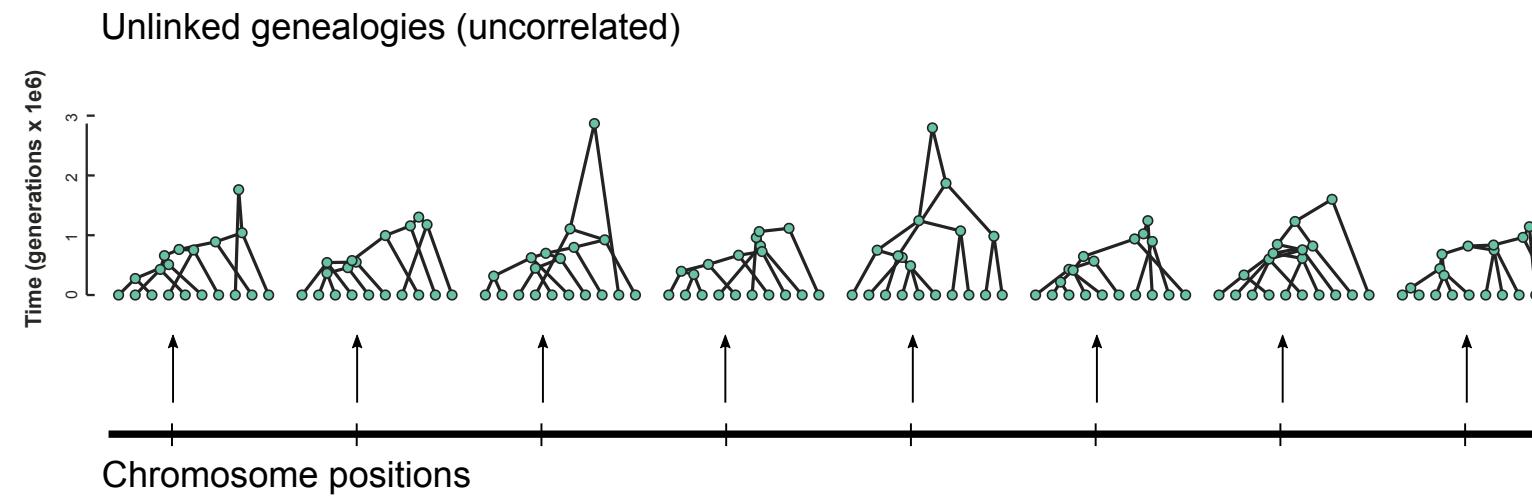
Genomes are composed of a mosaic of segments inherited from different ancestors, each separated by past recombination events.



Consequently, genealogical relationships vary spatially across genomes.

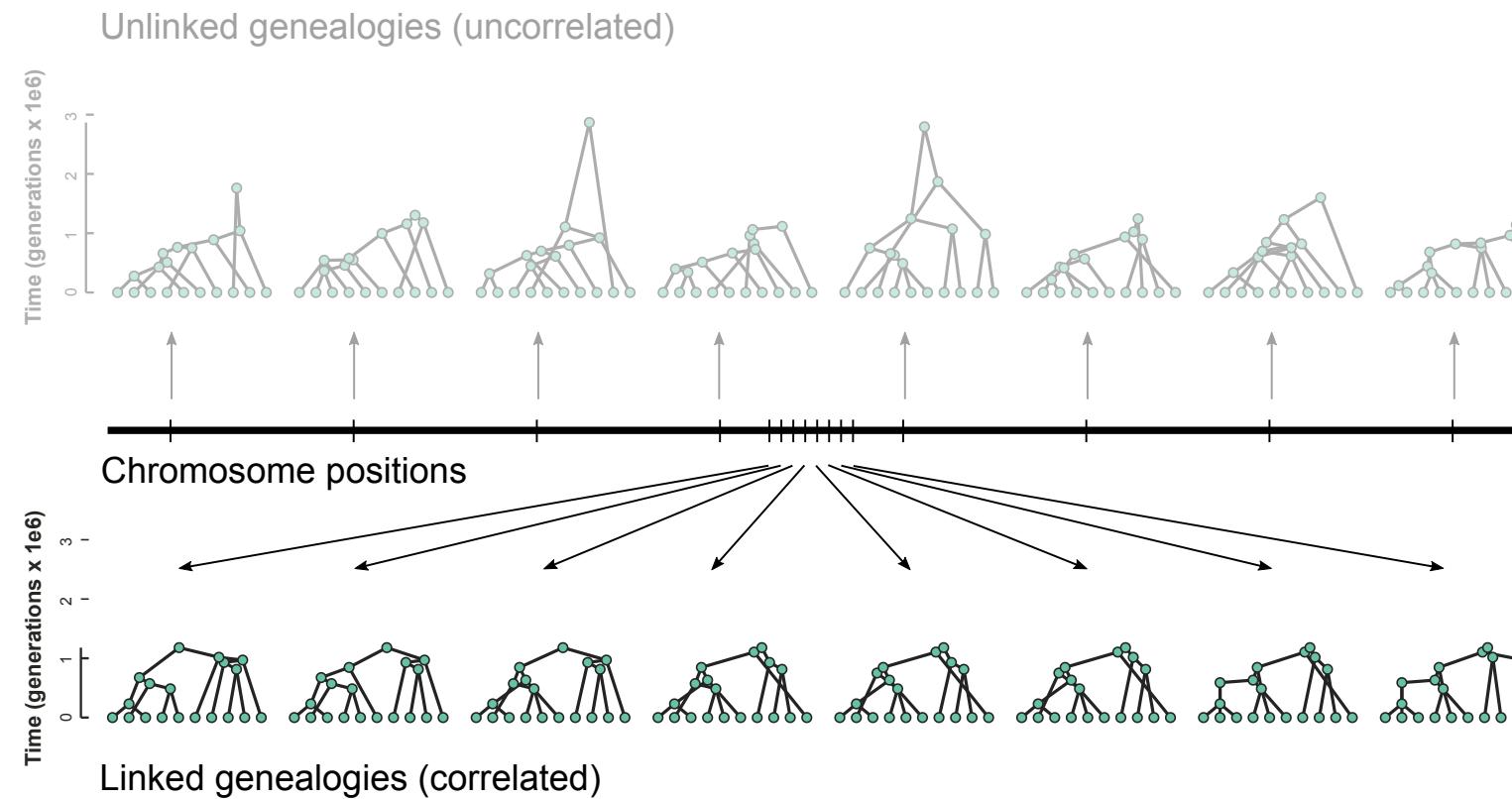
Multispecies coalescent assumptions

The multispecies coalescent (MSC) describes the expected distribution of *unlinked* genealogies, as a function of demographic model parameters (N_e , τ , topology).



Multispecies coalescent assumptions

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The expected distribution of *linked* genealogical variation is poorly characterized.

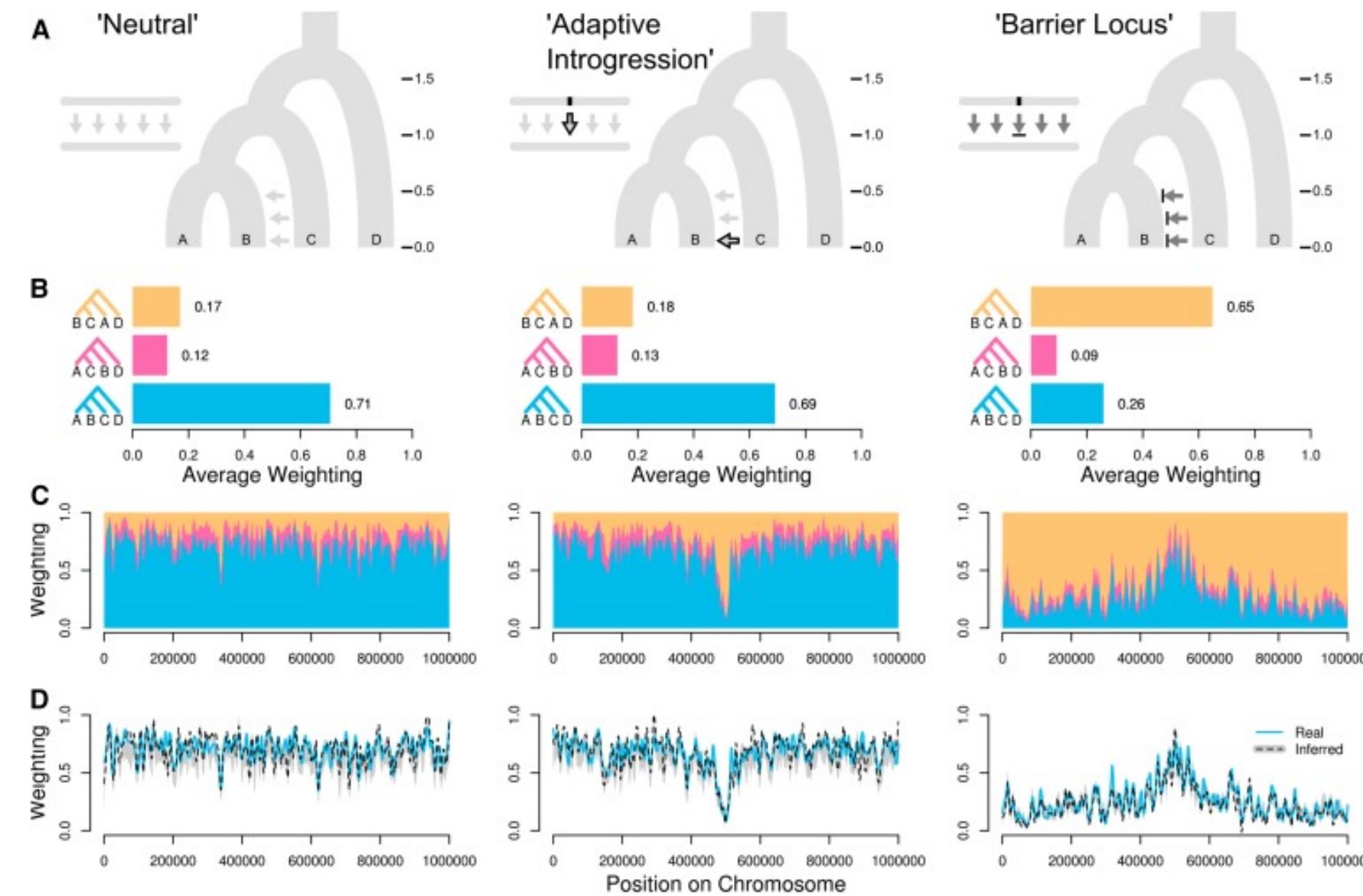
What is the expectation for the distribution of
linked genealogical variation?

How does it relate to demographic model parameters?

Why care about local genealogical variation?

- Subsampling unlinked loci effectively discards >99% genomic info.
- Ignoring linkage introduces bias (*concatalescence*; Gatesy 2013).
- Local ancestry is informative about selection and introgression.

Why care about local genealogical variation?



(Martin & Belleghem 2017)

Why care about local genealogical variation?

- Subsampling unlinked loci effectively discards >99% genomic info.
- Ignoring linkage introduces bias (*concatalescence*; Gatesy 2013).
- Local ancestry is informative about selection and introgression.
- **We lack a null expectation for spatial genealogical variation.**

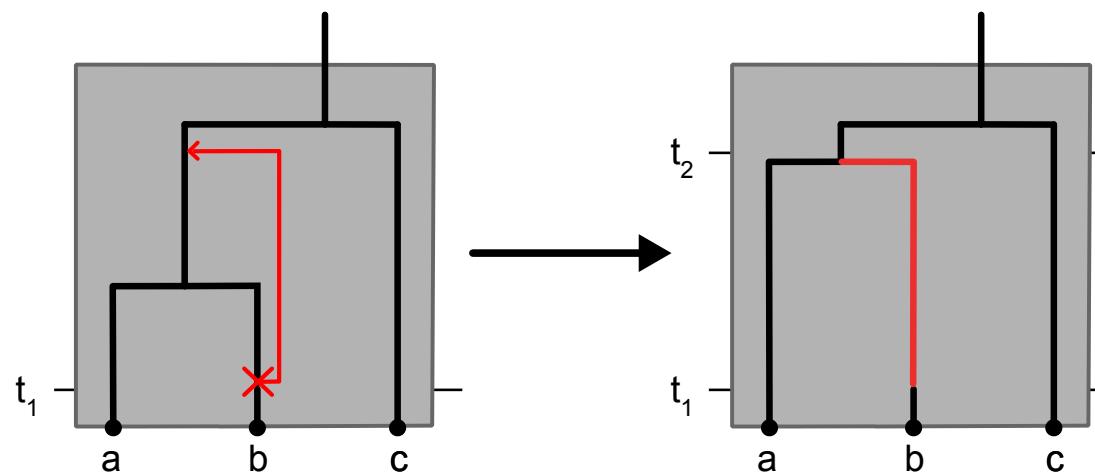
Outline: Multispecies Sequentially Markov Coalescent

- Background: SMC' model.
- SMC' waiting distances (Deng et al. 2021) in a single population.
- Introduce our new model for MS-SMC' waiting distances.
- Validate solutions against stochastic coalescent simulations.
- Demonstrate likelihood framework to use waiting distances to fit models.

Sequentially Markov Coalescent (McVean and Cardin, 2005)

An approximation of the coalescent with recombination

Given a starting genealogy a change to the next genealogy is modeled as a Markov process
– a single transition – which enables a tractable likelihood framework.

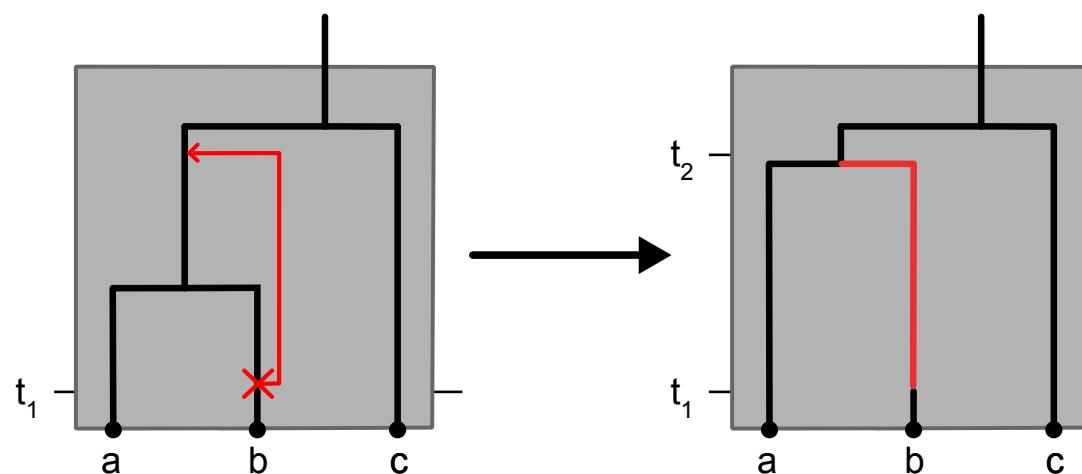


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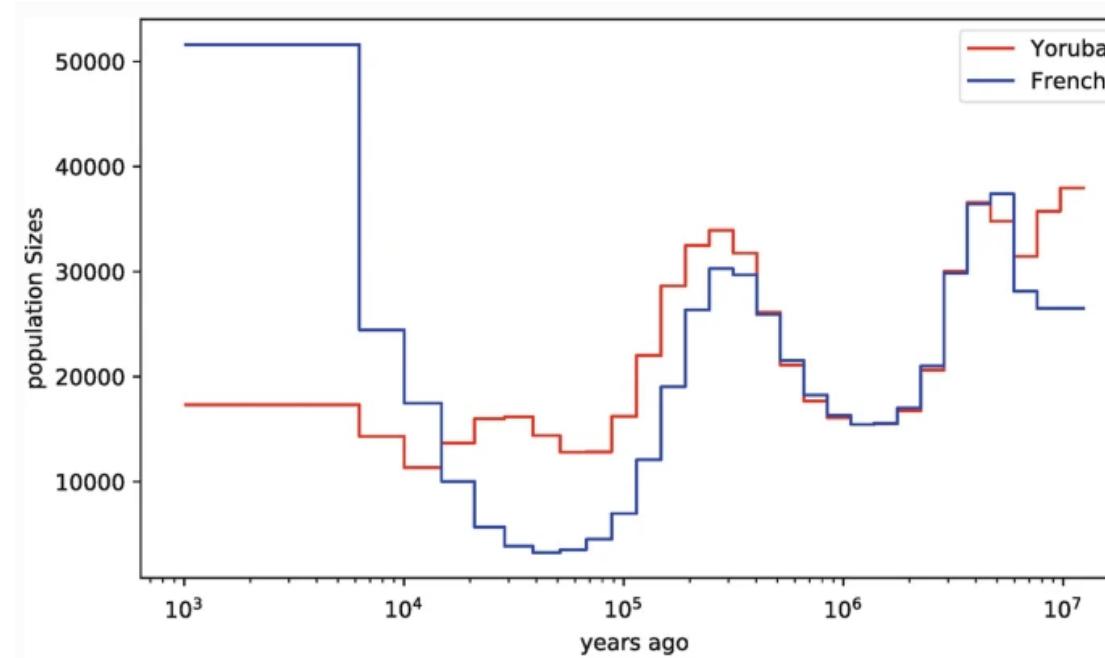
Given a starting genealogy a change to the next genealogy is modeled as a Markov process
– a single transition – which enables a tractable likelihood framework.

Process: recombination occurs w/ uniform probability anywhere on a tree (t_1), creating a detached subtree, which re-coalesces above t_1 with an ancestral lineage.



SMC' is widely used in HMM methods

PSMC (Li & Durbin 2011), MSMC (Schiffels & Durbin 2014), use pairwise coalescent times between sequential genealogies to infer changes in N_e through time.

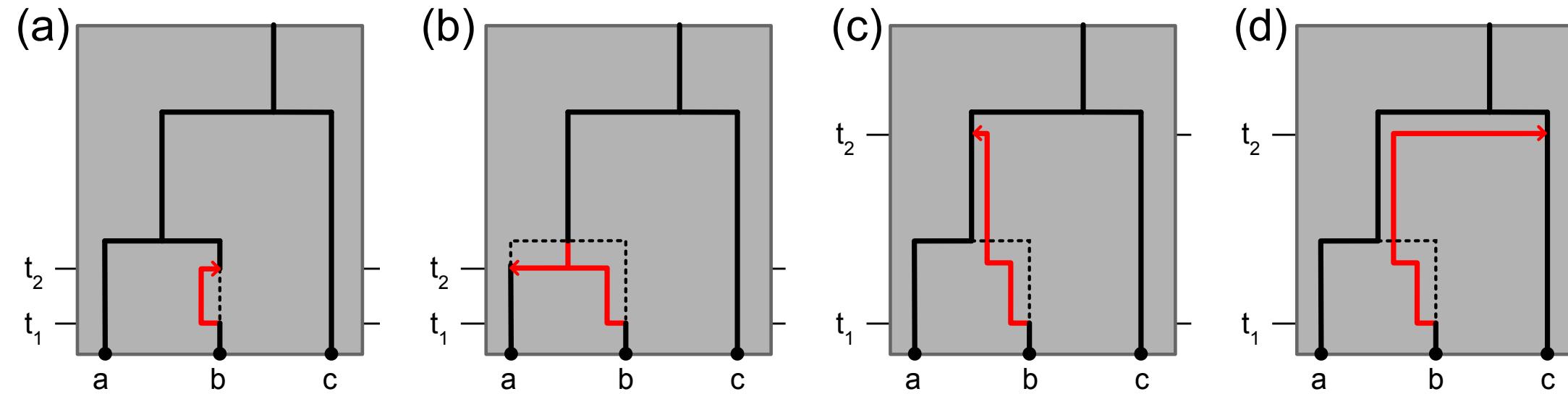


ARGweaver (Rasmussen et al. 2014) and ARGweaver-D (Hubisz & Siepel 2020) use an SMC'-based conditional sampling method to infer ARGs from sequence data.

Currently, we extract a fairly limited amount of spatial information from genomes.

Categorical event outcomes under the SMC'

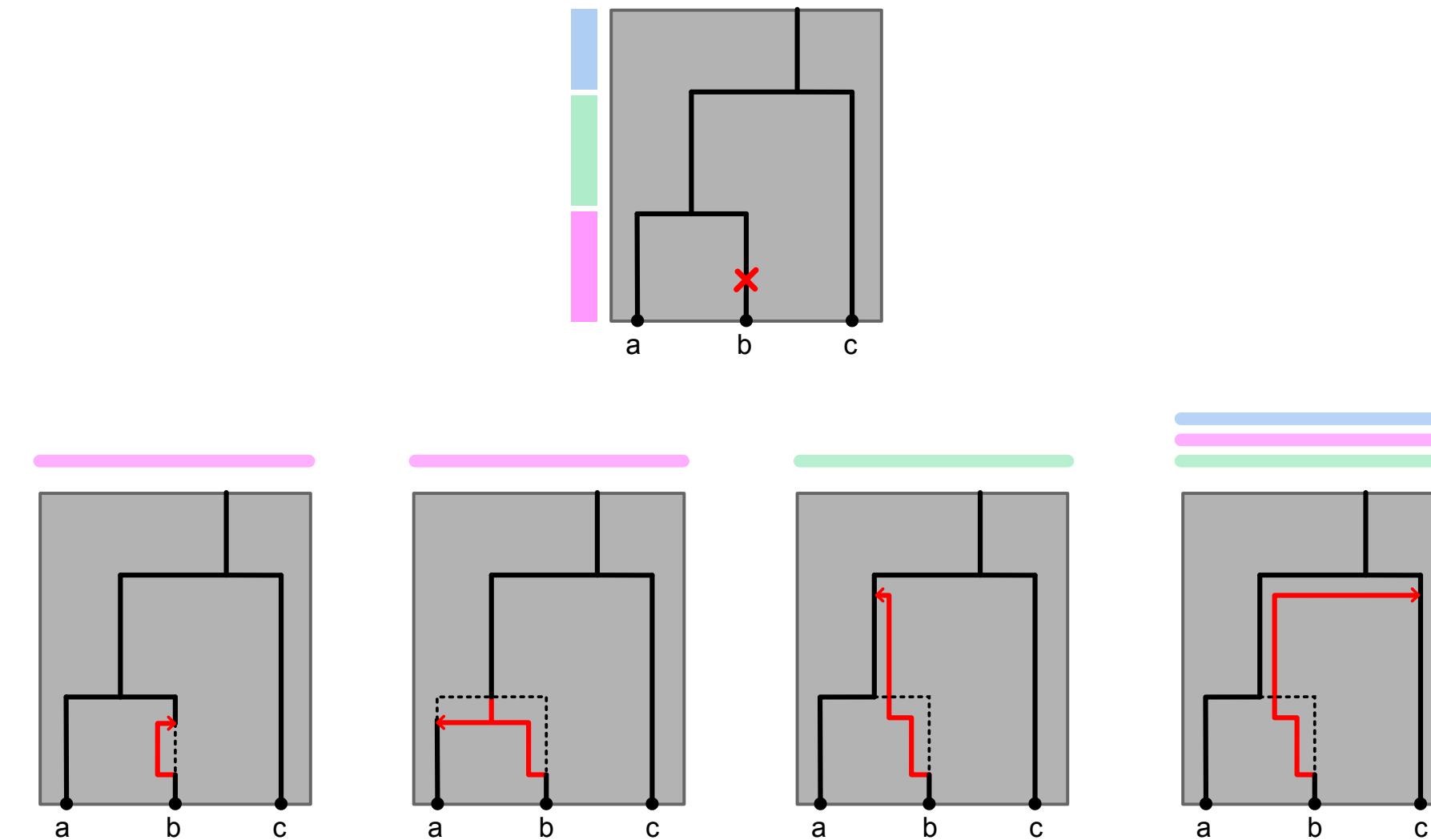
(a) no-change; (b-c) tree-change; and (d) topology-change.



(Deng et al. 2021)

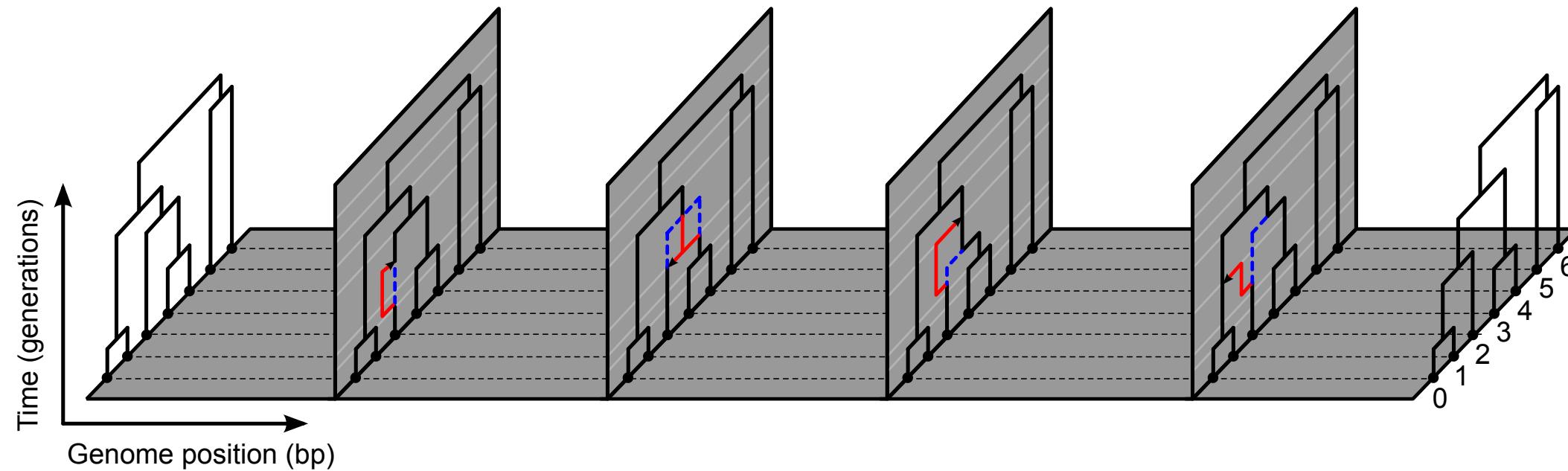
The distribution of waiting distances in ancestral recombination graphs

Yun Deng^{a,*}, Yun S. Song^{b,c,d}, Rasmus Nielsen^{b,e}



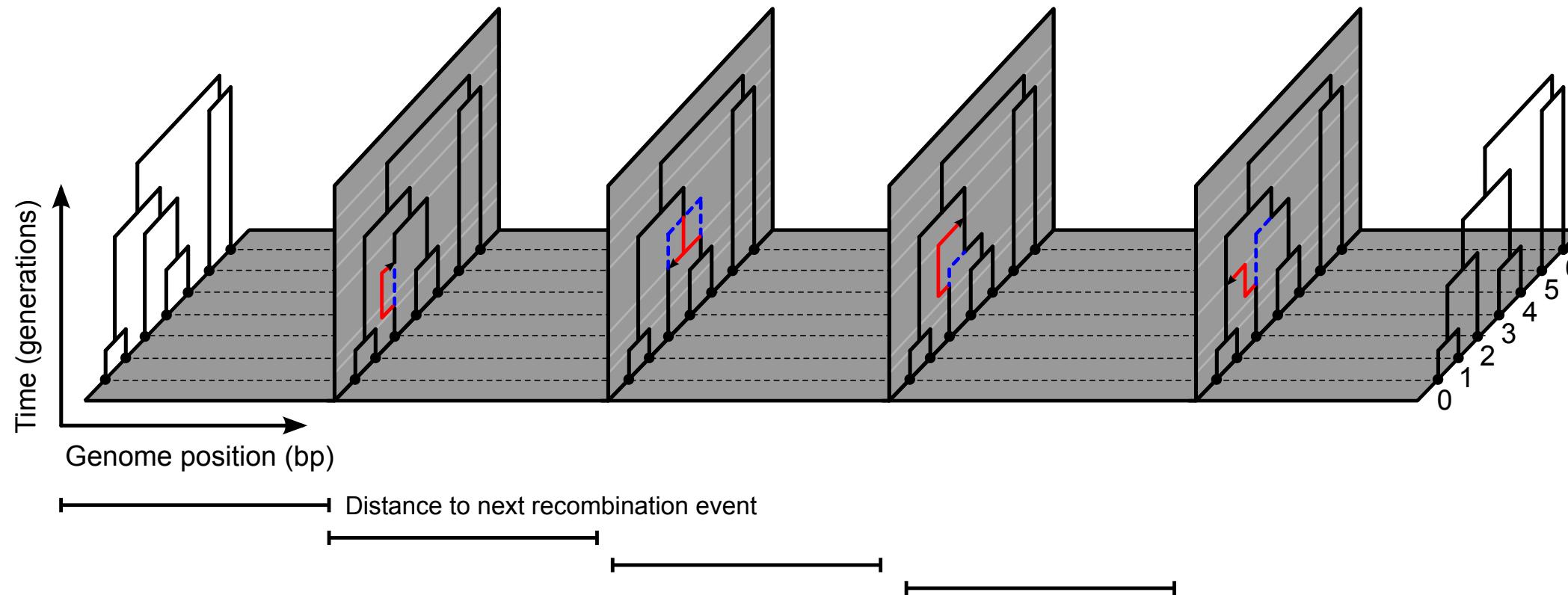
Estimating waiting distances under the SMC'

Expected Tree and Topology Distances represent new spatial genetic information.



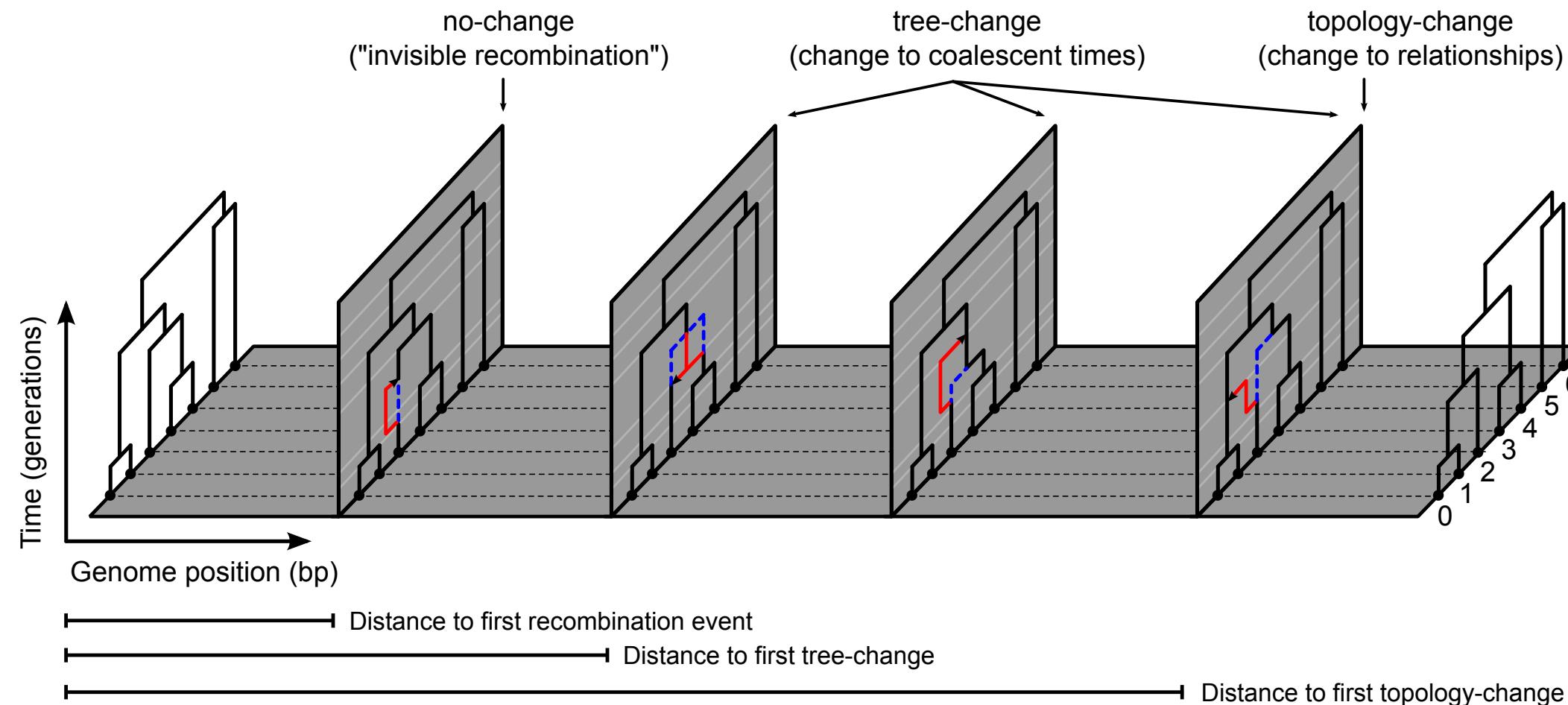
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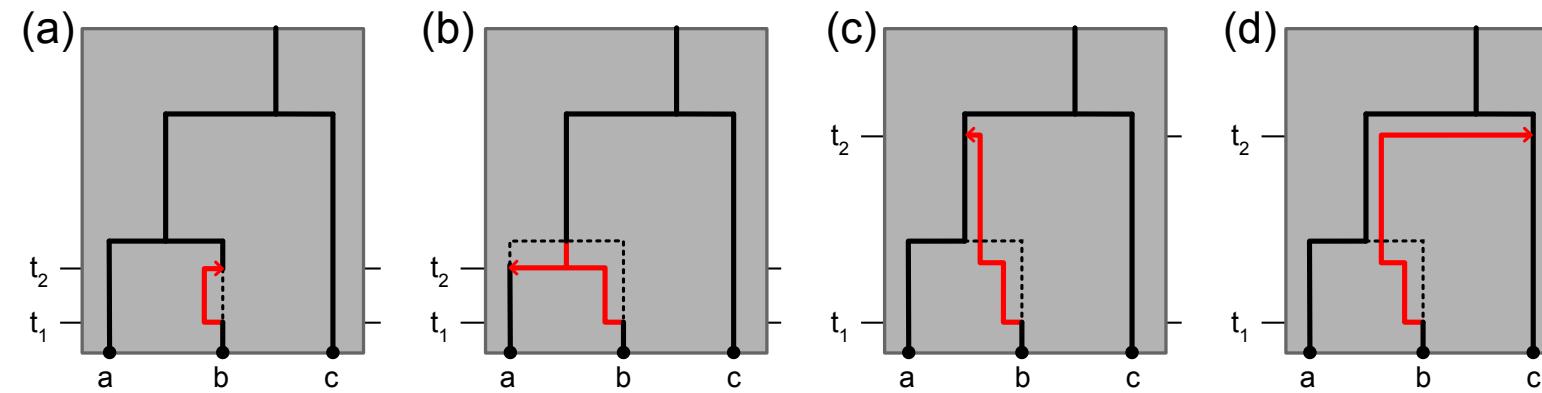
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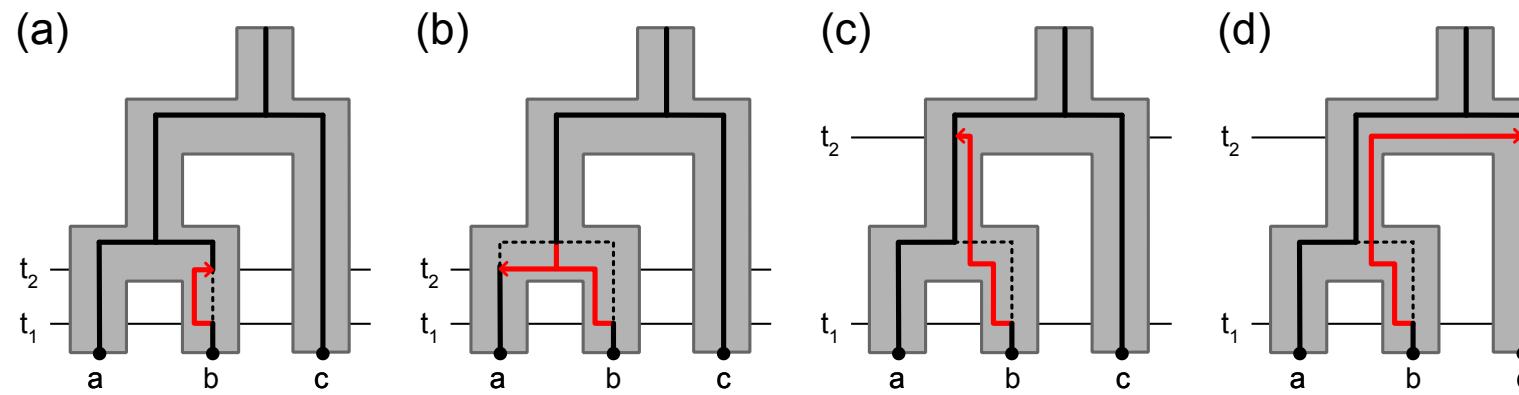
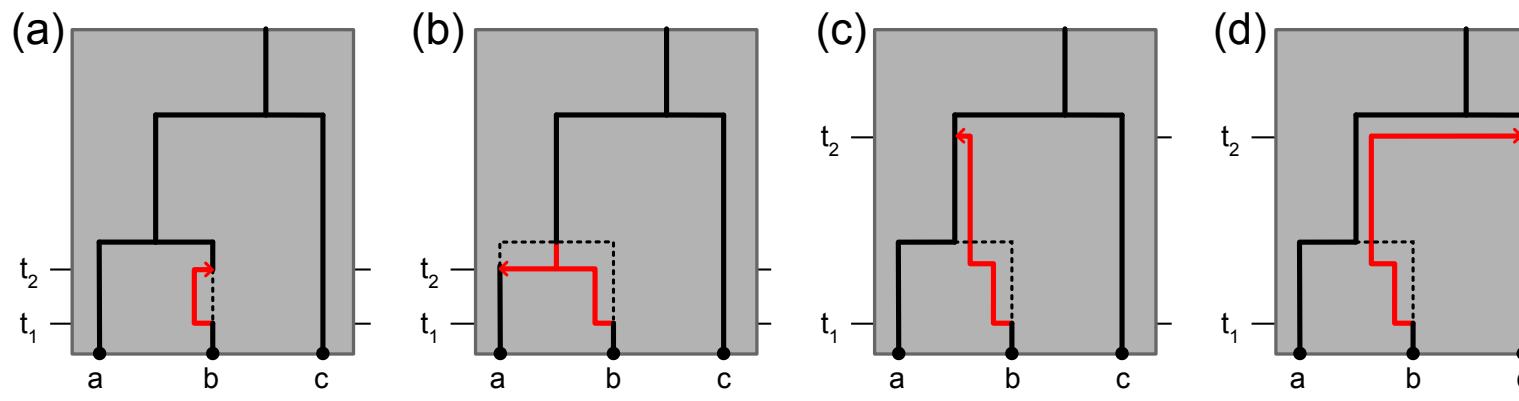
A multispecies extension to estimating waiting distances

Barriers to coalescence and variable N_e among species tree intervals.



A multispecies extension to estimating waiting distances

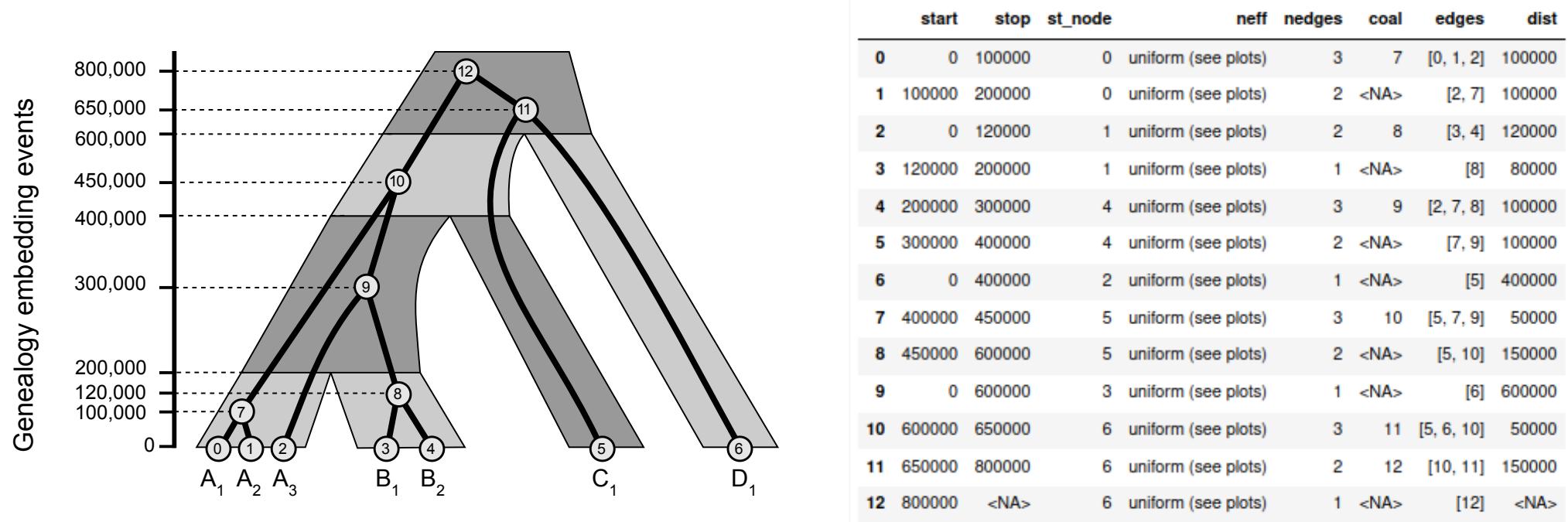
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Patrick McKenzie
PhD student

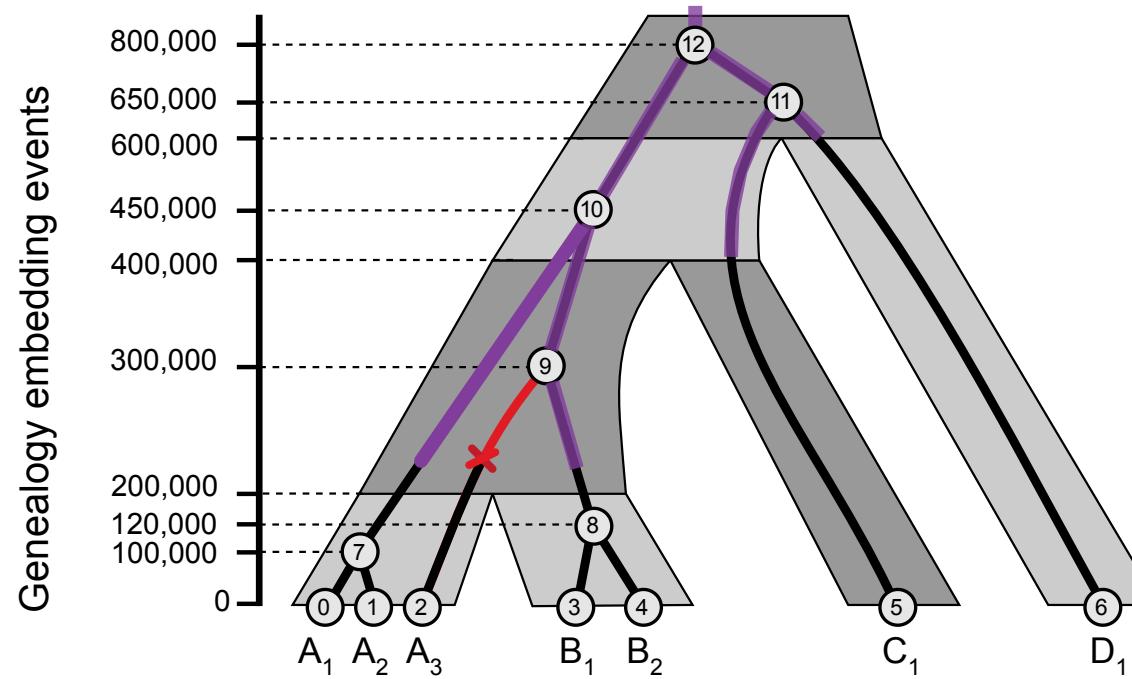
Extending SMC' waiting distance estimation

Genealogy embedding table with piecewise constant coal rates in
all intervals between coal events or population intervals.



MS-SMC' analytical solutions

$$P(\text{tree-unchanged} | \mathcal{S}, \mathcal{G}, b, t_r) = \int_{t_r}^{t_b^u} \frac{1}{2N(\tau)} e^{-\int_{t_r}^{\tau} \frac{A(s)}{2N(s)} ds} d\tau$$



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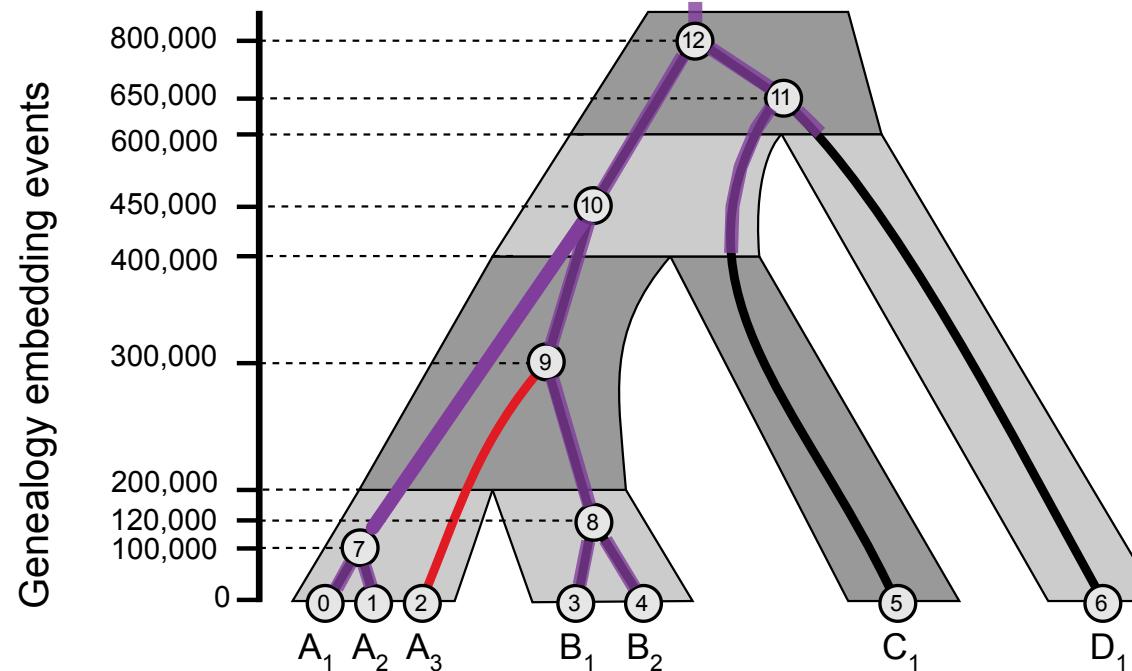
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$$\mathbb{P}(\text{tree-unchanged}|\mathcal{S}, \mathcal{G}) = \sum_{b \in \mathcal{G}} \left[\frac{t_b^u - t_b^l}{L(\mathcal{G})} \right] \mathbb{P}(\text{tree-unchanged}|\mathcal{S}, \mathcal{G}, b)$$

Exponentially distributed waiting distances

Expected number of sites until a recombination event is observed.

$$\lambda_r = L(\mathcal{G}) \times r$$

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Exponentially distributed waiting distances

Expected number of sites until a recombination event is observed.

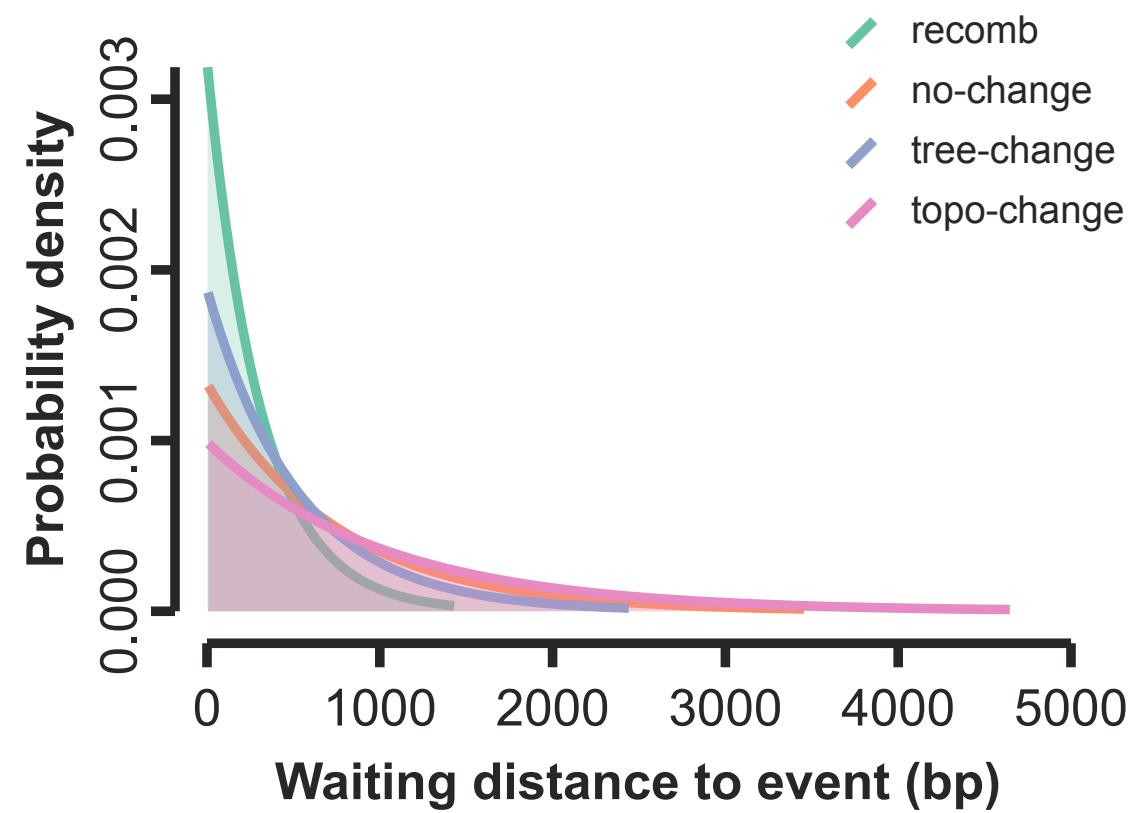
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$$\lambda_n = L(\mathcal{G}) \times r \times P(\text{tree-unchanged}|\mathcal{S}, \mathcal{G})$$

$$\lambda_g = L(\mathcal{G}) \times r \times P(\text{tree-changed}|\mathcal{S}, \mathcal{G})$$

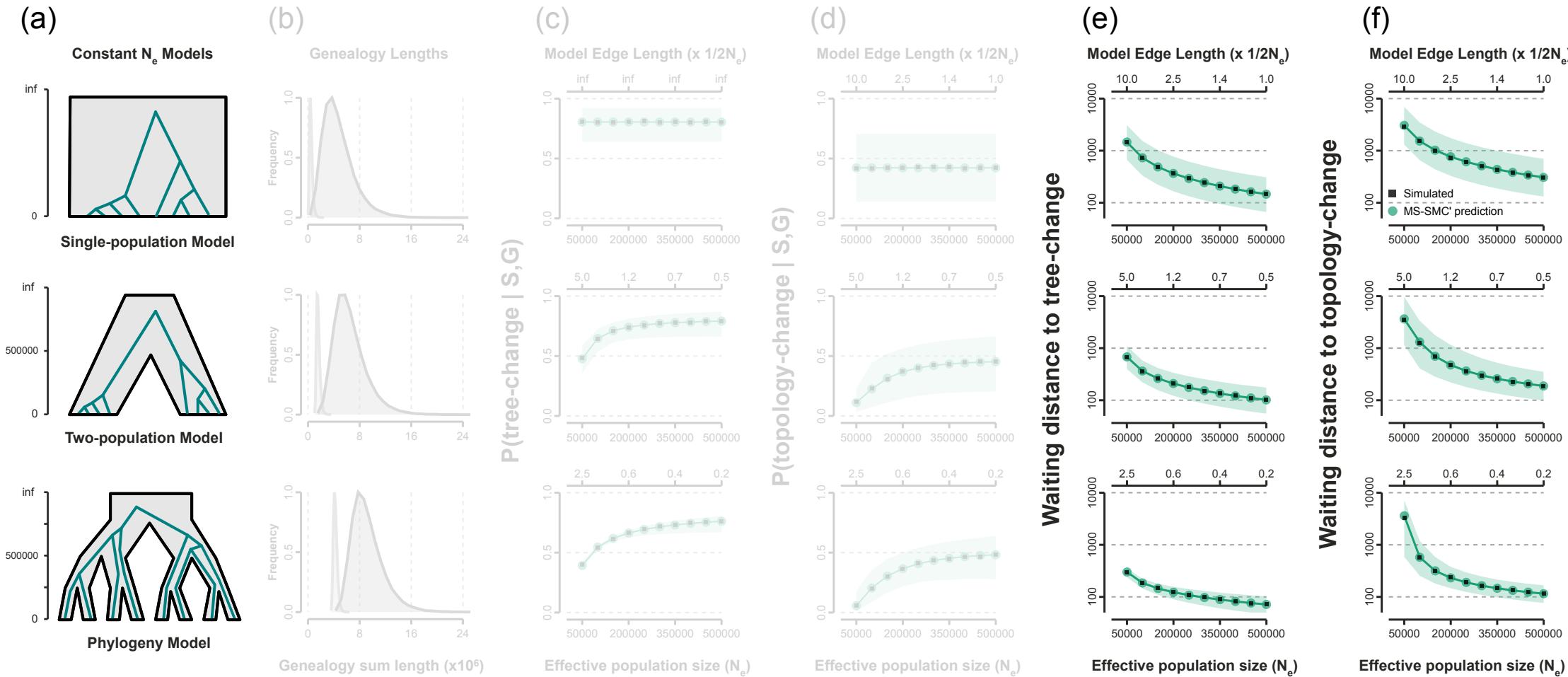
$$\lambda_t = L(\mathcal{G}) \times r \times P(\text{topology-changed}|\mathcal{S}, \mathcal{G})$$

Exponentially distributed waiting distances



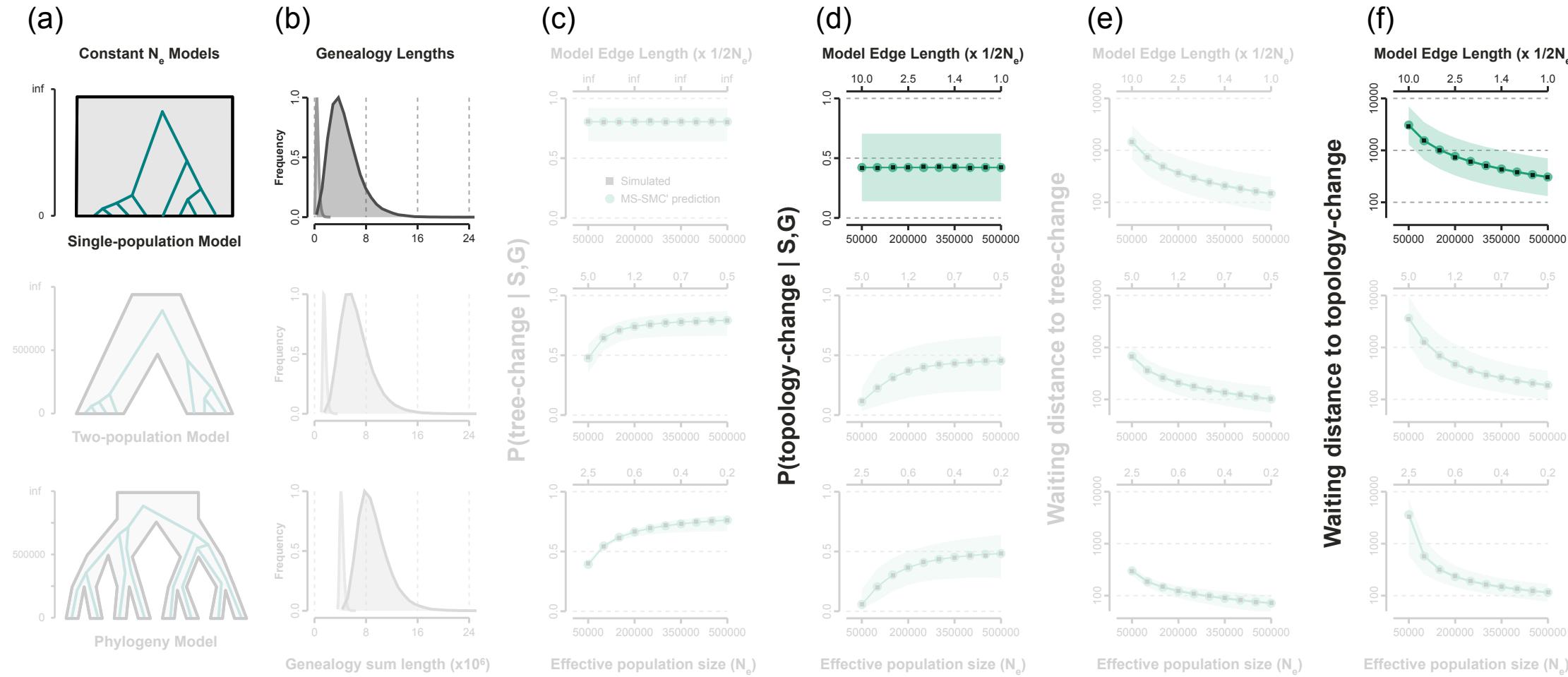
Validation:

Analytical results match expectation of stochastic coalescent simulations.



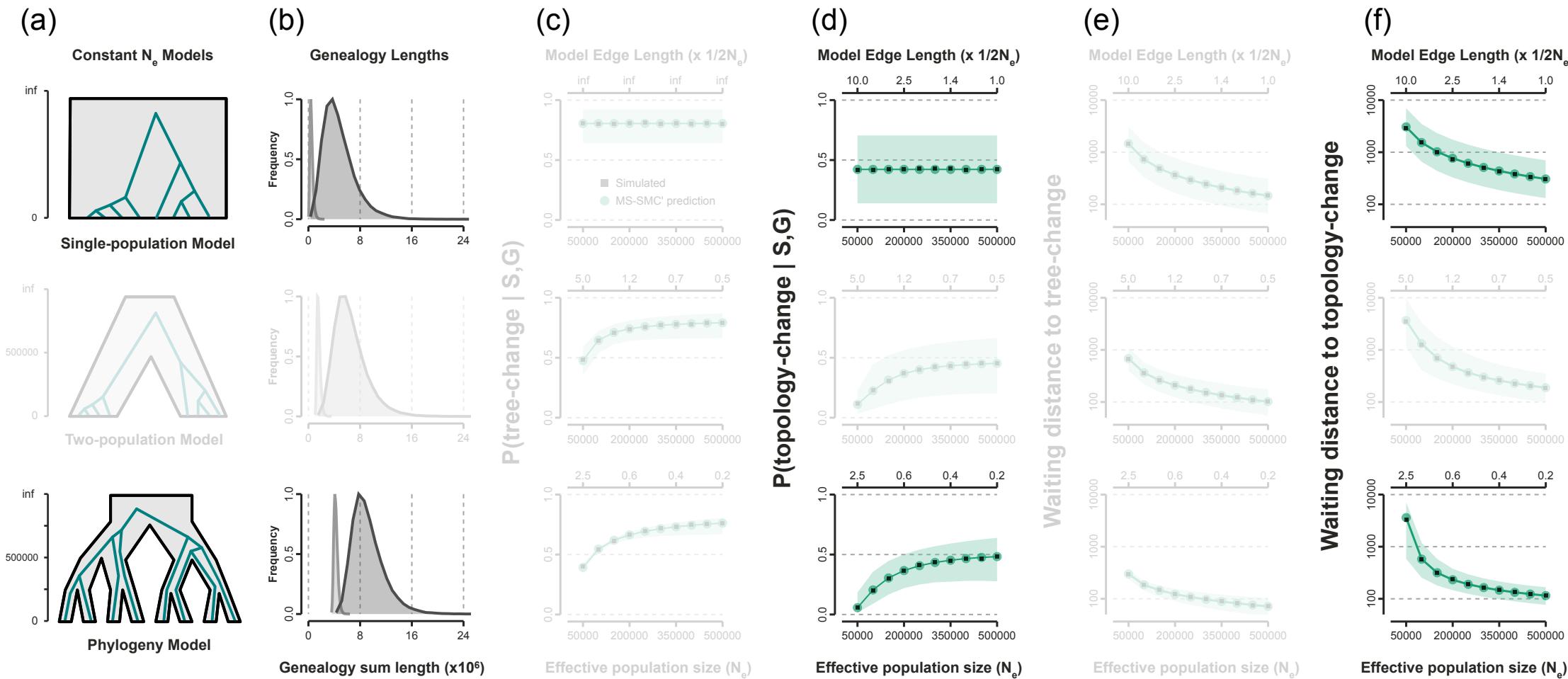
Validation:

In single population model (Deng et al.) N_e only affects edge lengths.



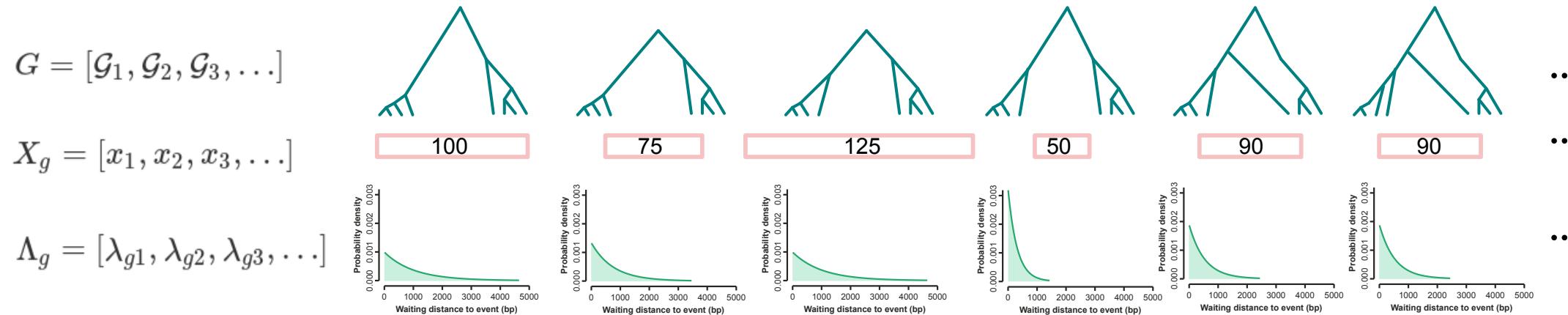
Validation:

In an MSC model N_e affects probability of tree/topology change as well as edge lengths.



Likelihood framework

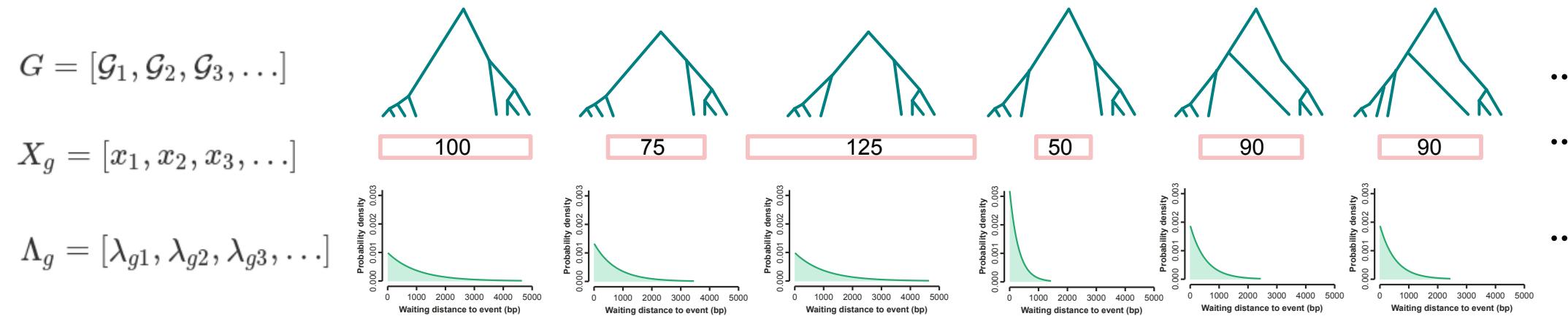
Given an observed/proposed ARG (genealogies and interval lengths)
get expected waiting distance for each (λ_i)...



where: $\lambda_g = L(\mathcal{G}) \times r \times \mathbb{P}(\text{tree-unchanged} | \mathcal{S}, \mathcal{G})$

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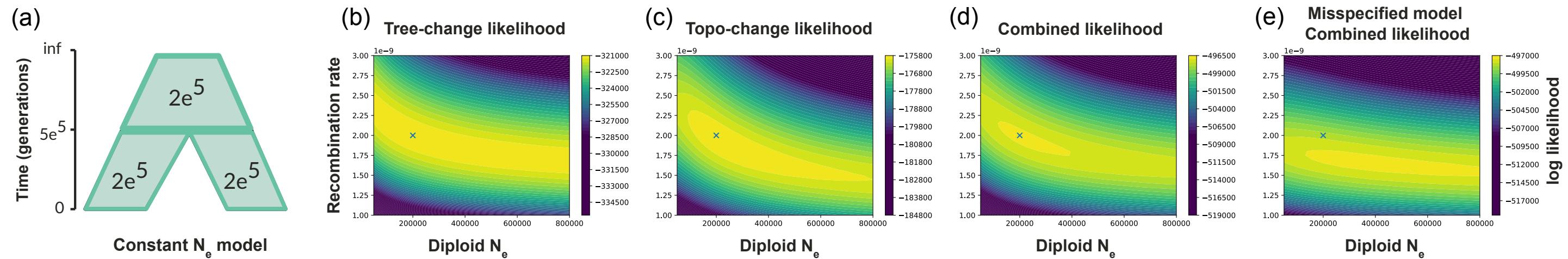
... and calculate likelihood of MSC model (\mathcal{S}) from exponential probability densities.

$$\mathcal{L}(\mathcal{S}|\Lambda_g, X_g) = \sum_i \log(\lambda_i e^{-\lambda_i x_i})$$

Likelihood surface: single N_e

Topology-changes are more informative than tree-changes; optima at true sim. values.

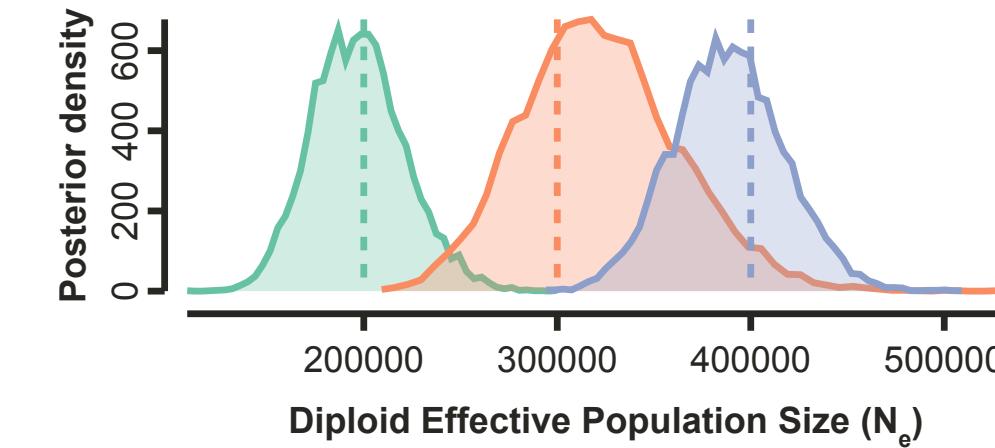
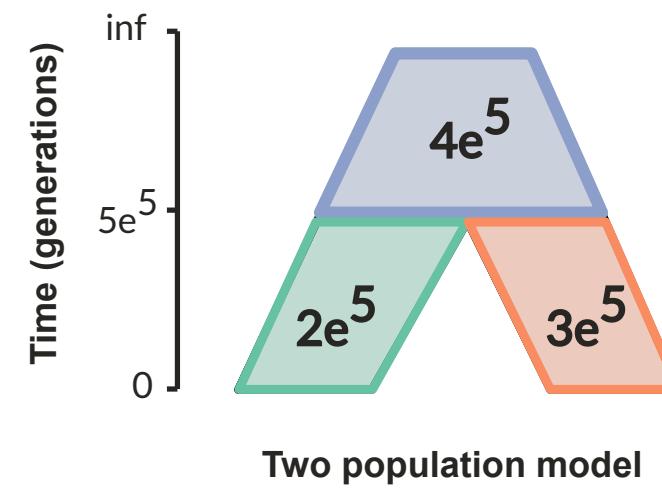
Example: loci=50, length=0.1Mb, recomb=2e-9, samples-per-lineage=4.



Joint inference of multiple MSC model parameters

Metropolis Hastings MCMC converges on correct w/ increasing data.

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Summary: Multispecies Sequentially Markov Coalescent

- We extended method of Deng et al. (2021) to MSC models
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- We can estimate MSC model parameters from *linked genome data!*
- Topology-changes are easily detectable in sequence data.

Future directions

- Manuscript on biorxiv (hopefully soon also in print)
- Implemented at <https://github.com/eaton-lab/ipcoal/>
- Software to analyze real genetic data is a future development
- Extensions to Multispecies Network Coalescent.
- and more...

Acknowledgements

Thanks to the symposium organizers and to:



Patrick McKenzie
PhD student



[Eaton lab at Columbia University in New York City.](#)

Contact us: [@dereneaton](https://twitter.com/dereneaton)



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