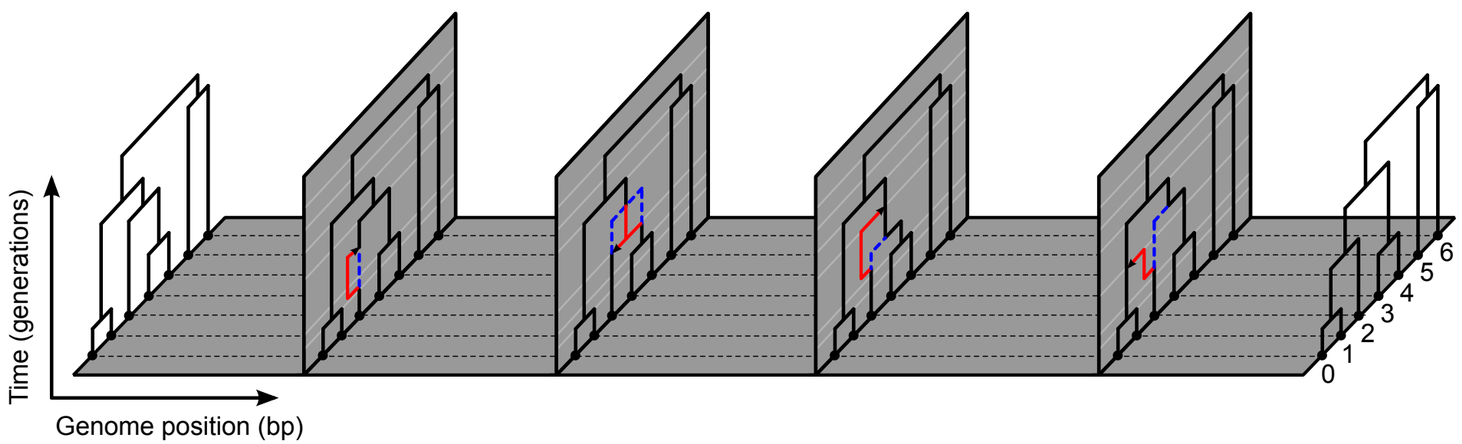
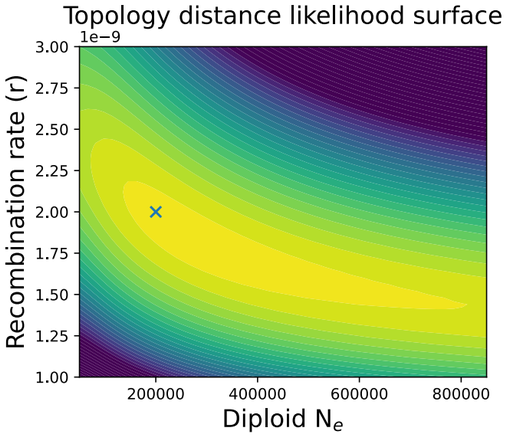
Linking Phylogenetic Inference at Genome-wide and Genealogical Scales



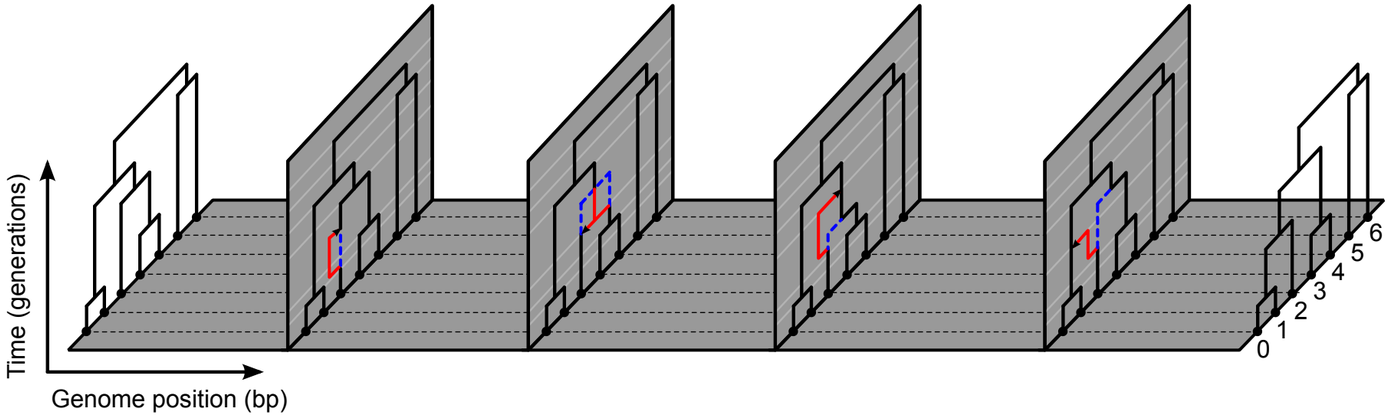


Deren Eaton and Patrick McKenzie

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.



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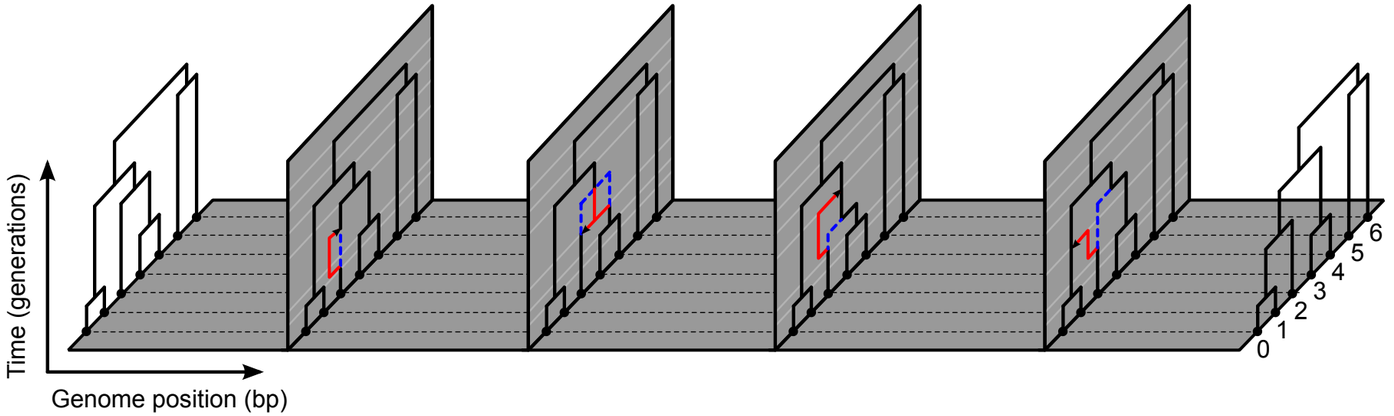
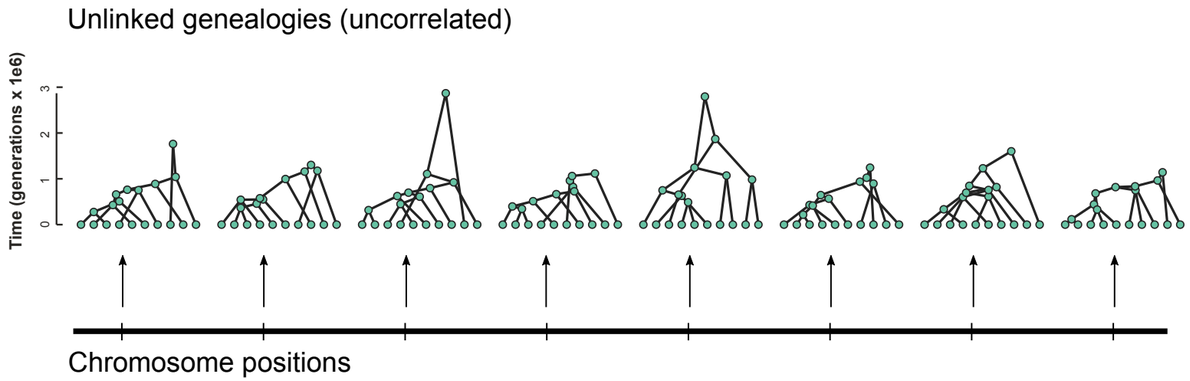


Consequently, genealogical relationships vary spatially across genomes.

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).



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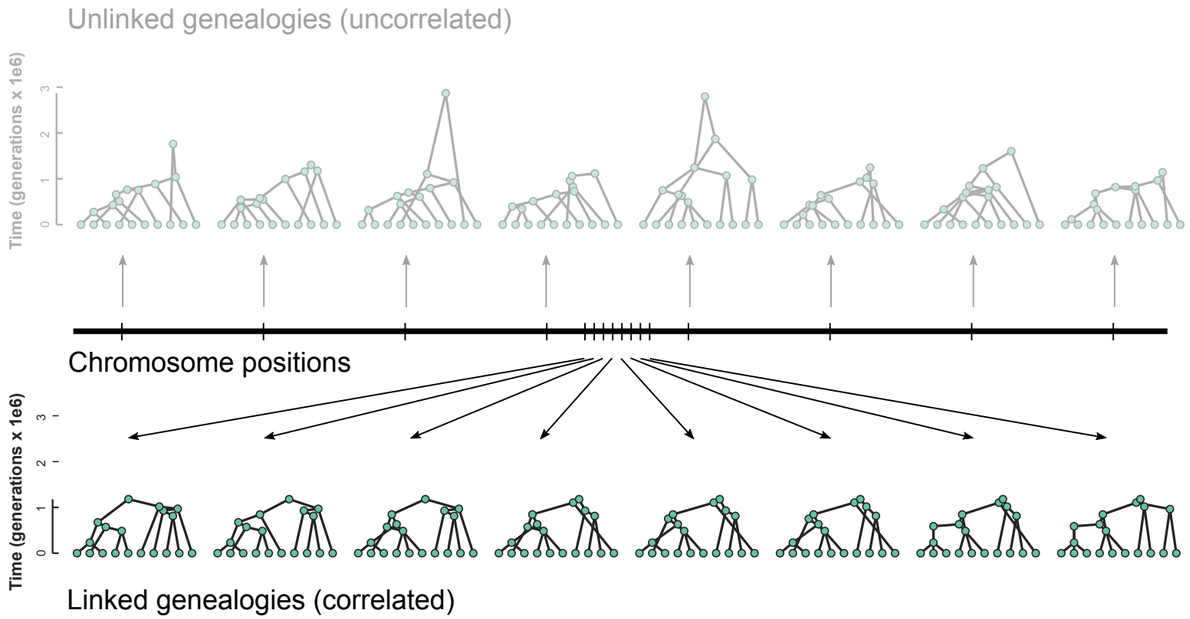

The expected distribution of ***linked*** genealogical variation is poorly characterized.

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.

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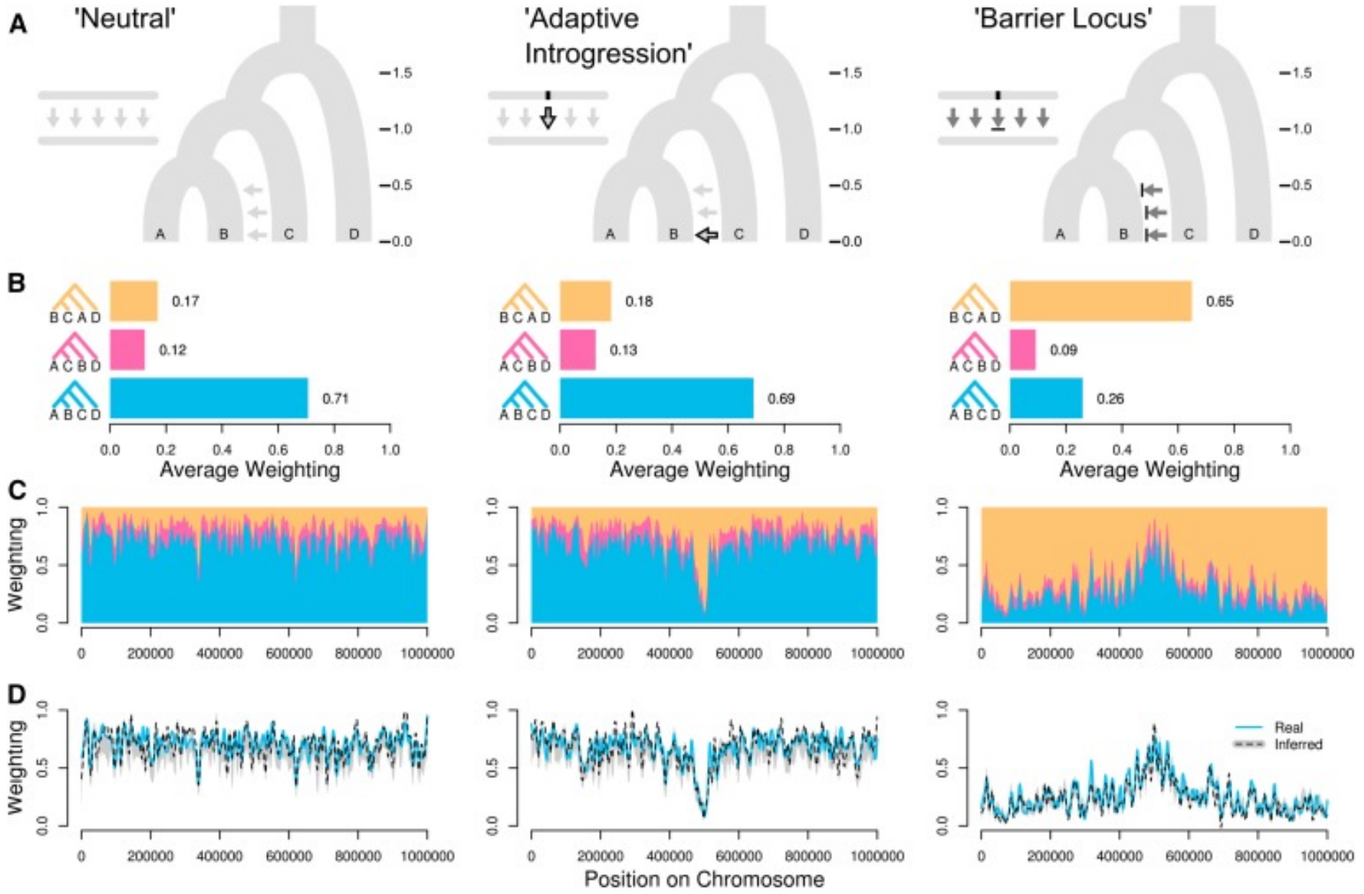

(Martin & Belleghem 2017)

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- 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.**

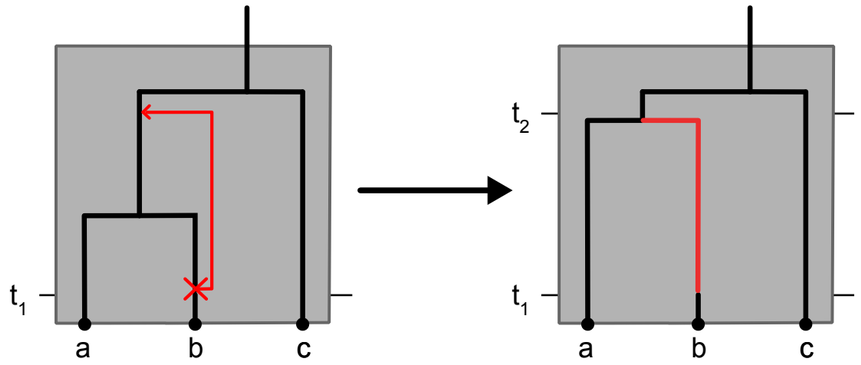
Outline: *Multispecies Sequentially Markov Coalescent*

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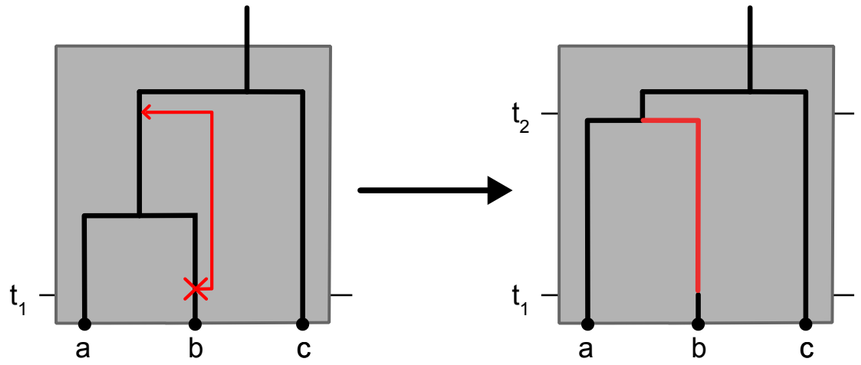
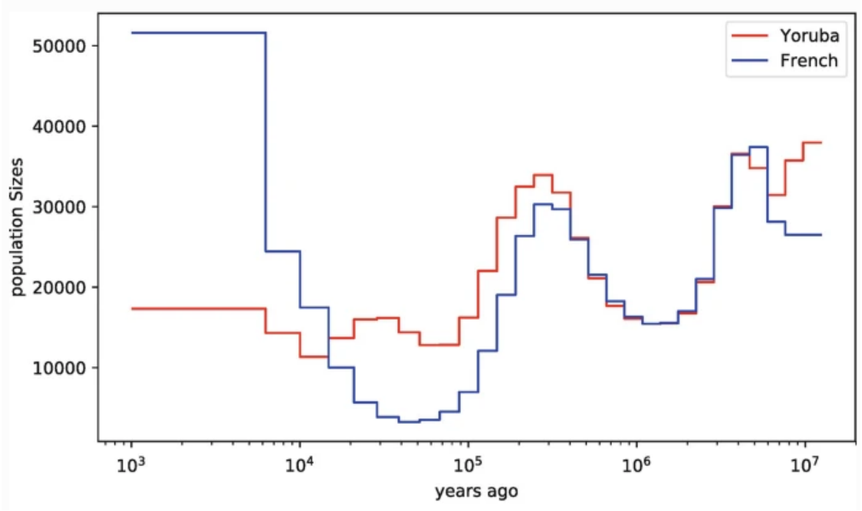
Process: recombination occurs w/ uniform probability anywhere on a tree (t_1), creating a detached subtree, which re-coalesces above t_1 with an ancestral lineage.



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.

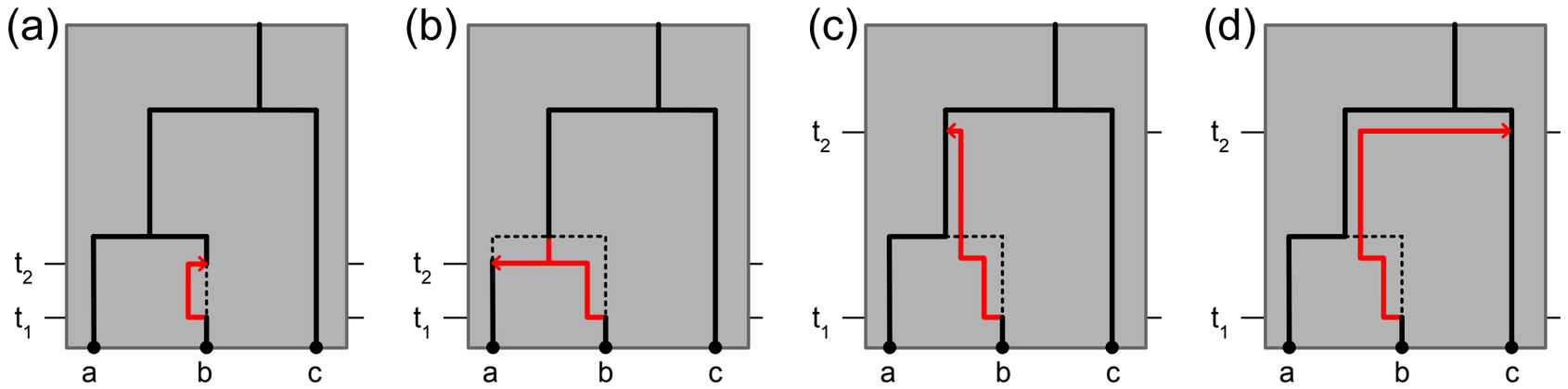


ARGweaver (Rasmussen et al. 2014) and ARGweaver-D (Hubisz & Siepel 2020) use an SMC'-based conditional sampling method to infer ARGs from sequence data.

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

Categorical event outcomes under the SMC'

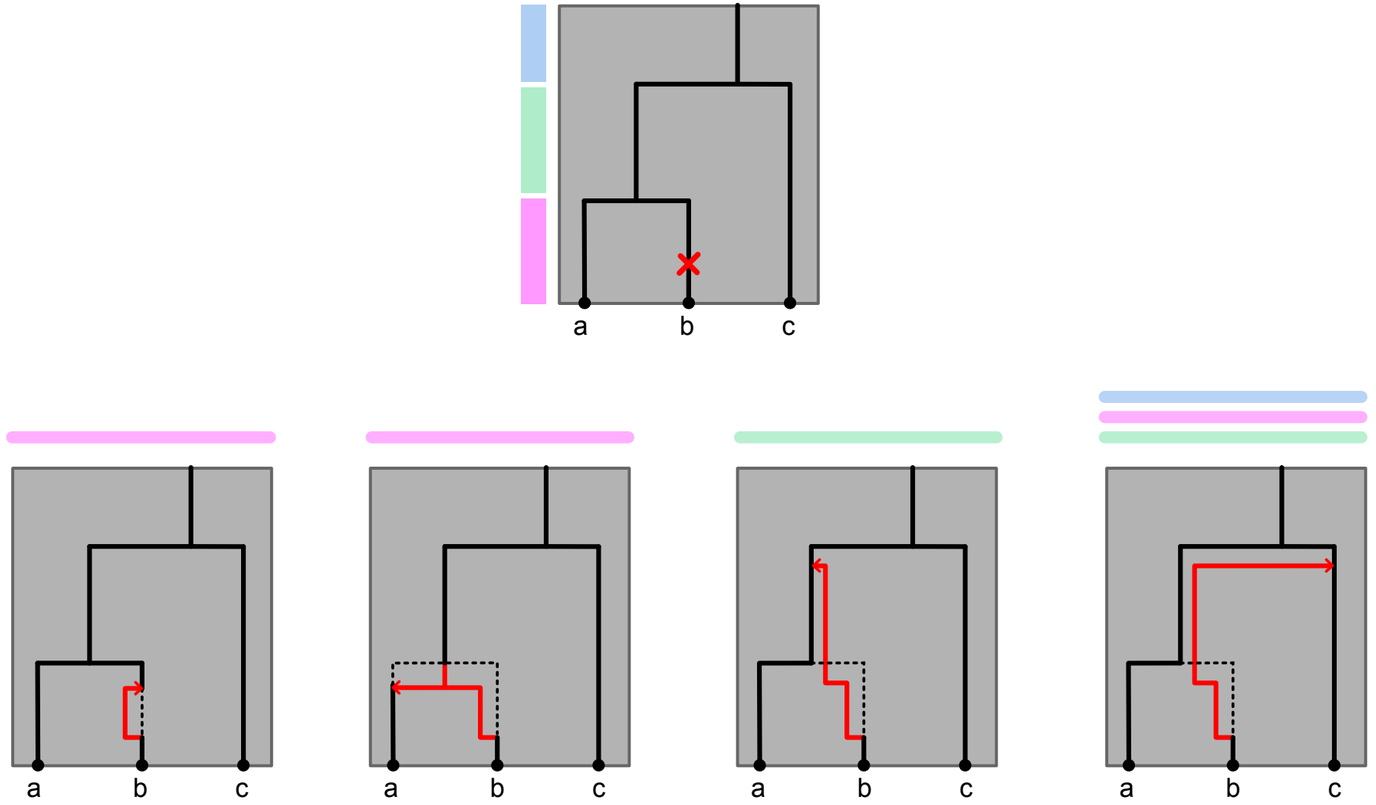
(a) no-change; (b-c) tree-change; and (d) topology-change.



(Deng et al. 2021)

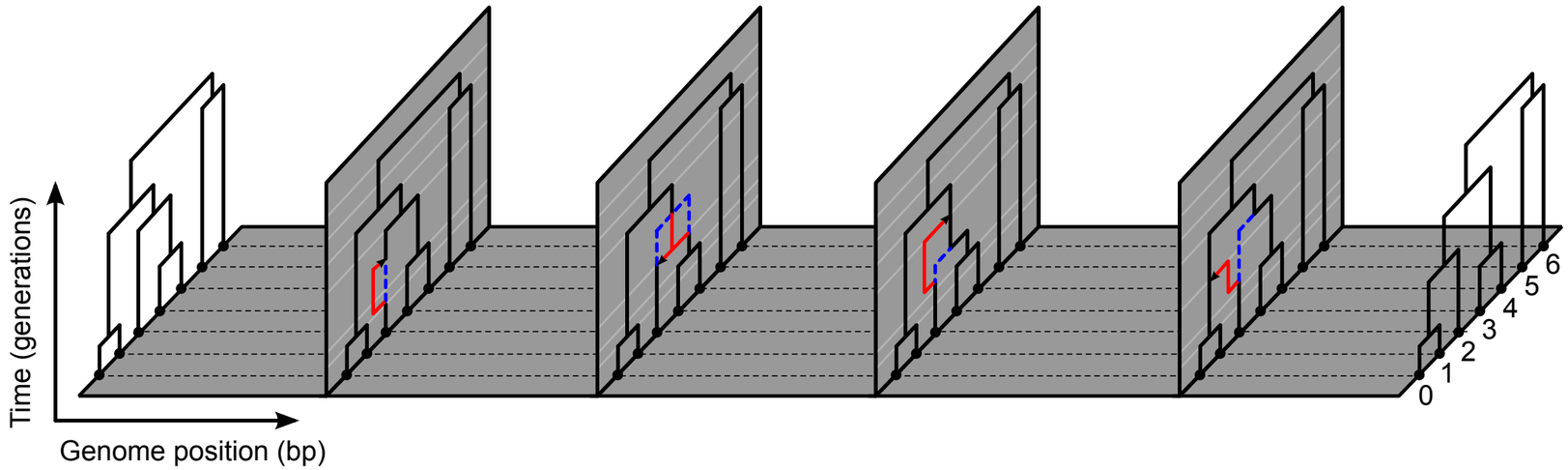
The distribution of waiting distances in ancestral recombination graphs

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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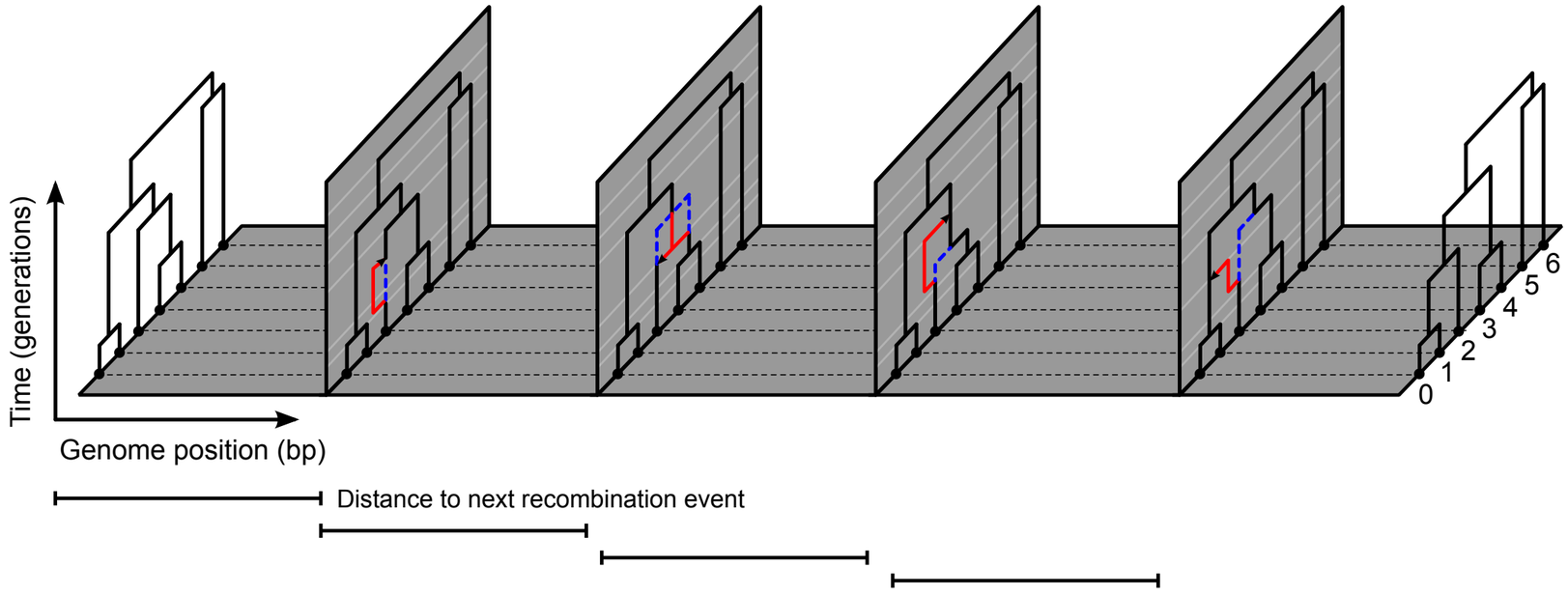

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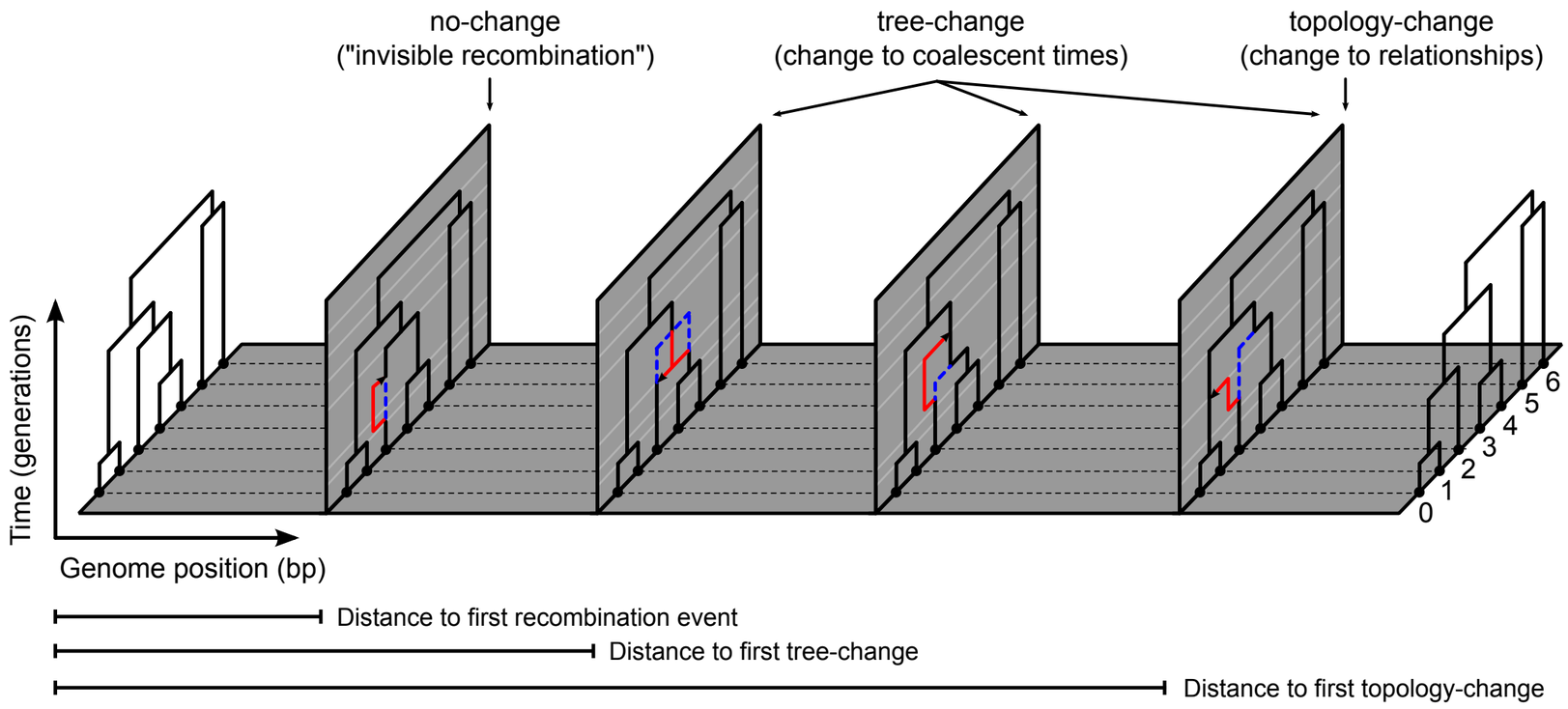
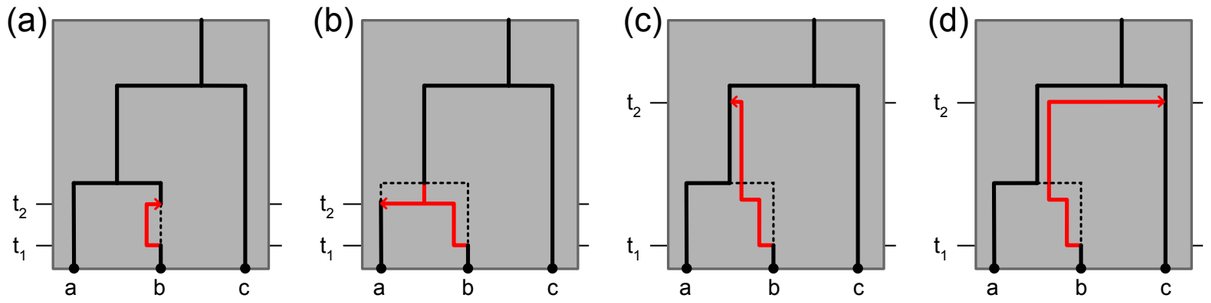


A multispecies extension to estimating waiting distances

Barriers to coalescence and variable N_e among species tree intervals.



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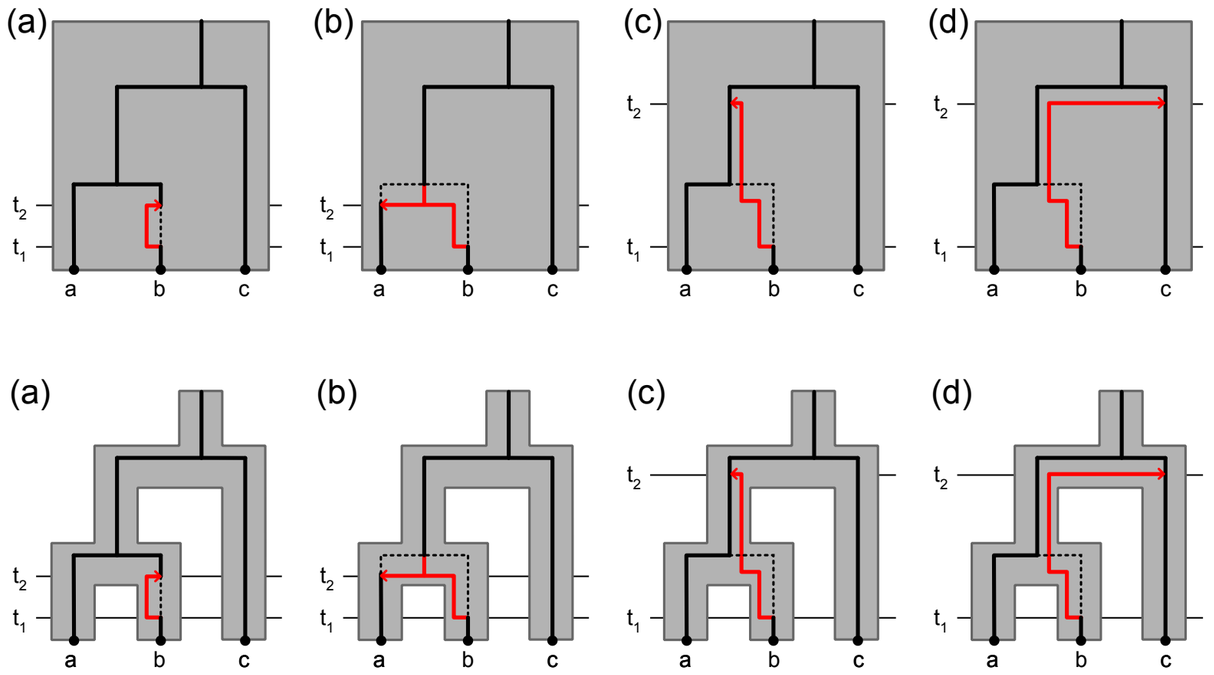
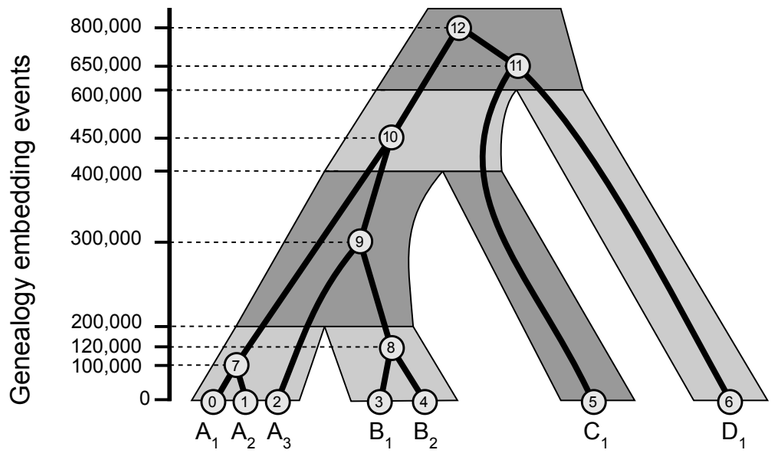


Patrick McKenzie

PhD student

Extending SMC' waiting distance estimation

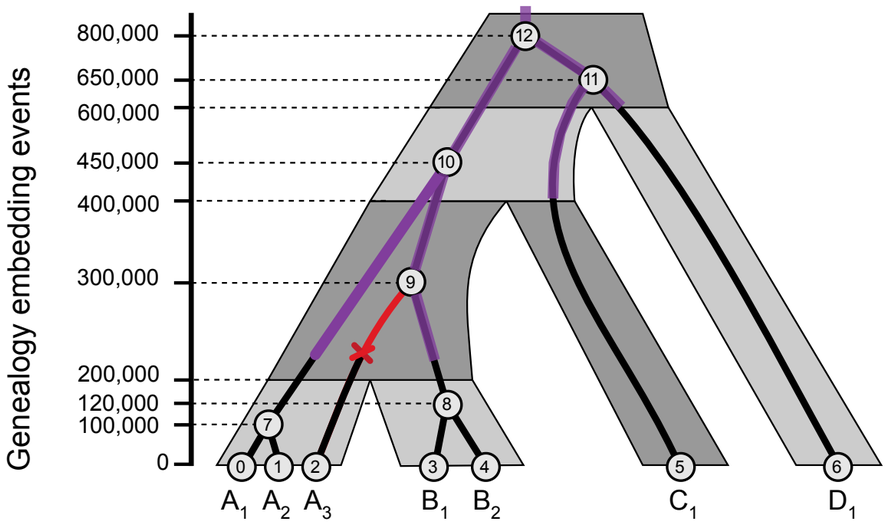
Genealogy embedding table with piecewise constant coal rates in all intervals between coal events or population intervals.



	start	stop	st_node	neff	nedges	coal	edges	dist
0	0	100000	0	uniform (see plots)	3	7	[0, 1, 2]	100000
1	100000	200000	0	uniform (see plots)	2	<NA>	[2, 7]	100000
2	0	120000	1	uniform (see plots)	2	8	[3, 4]	120000
3	120000	200000	1	uniform (see plots)	1	<NA>	[8]	80000
4	200000	300000	4	uniform (see plots)	3	9	[2, 7, 8]	100000
5	300000	400000	4	uniform (see plots)	2	<NA>	[7, 9]	100000
6	0	400000	2	uniform (see plots)	1	<NA>	[5]	400000
7	400000	450000	5	uniform (see plots)	3	10	[5, 7, 9]	50000
8	450000	600000	5	uniform (see plots)	2	<NA>	[5, 10]	150000
9	0	600000	3	uniform (see plots)	1	<NA>	[6]	600000
10	600000	650000	6	uniform (see plots)	3	11	[5, 6, 10]	50000
11	650000	800000	6	uniform (see plots)	2	12	[10, 11]	150000
12	800000	<NA>	6	uniform (see plots)	1	<NA>	[12]	<NA>

MS-SMC' analytical solutions

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



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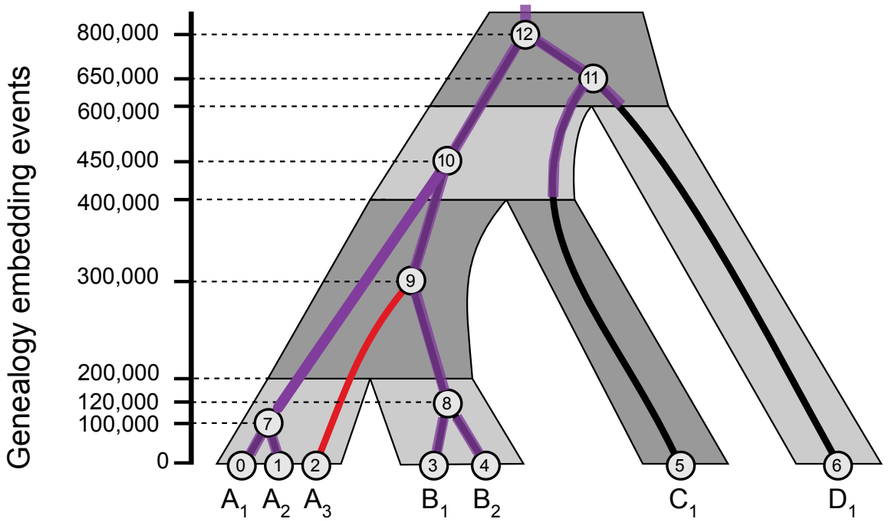

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$$\mathbb{P}(\textit{tree-unchanged}|\mathcal{S},\mathcal{G}) = \sum_{b \in \mathcal{G}} \left\lceil \frac{t_b^u - t_b^l}{L(\mathcal{G})} \right\rceil \mathbb{P}(\textit{tree-unchanged}|\mathcal{S},\mathcal{G},b)$$

Exponentially distributed waiting distances

Expected number of sites until a recombination event is observed.

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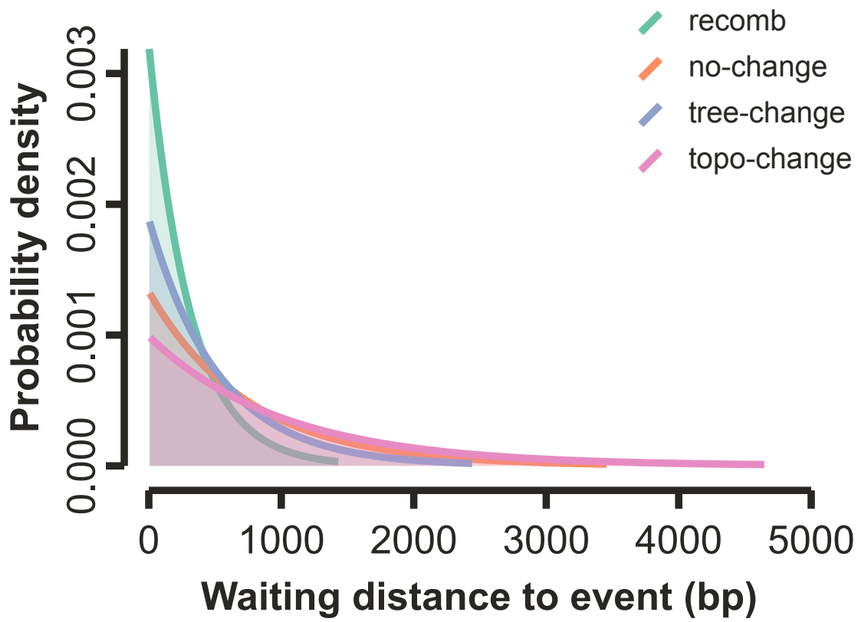
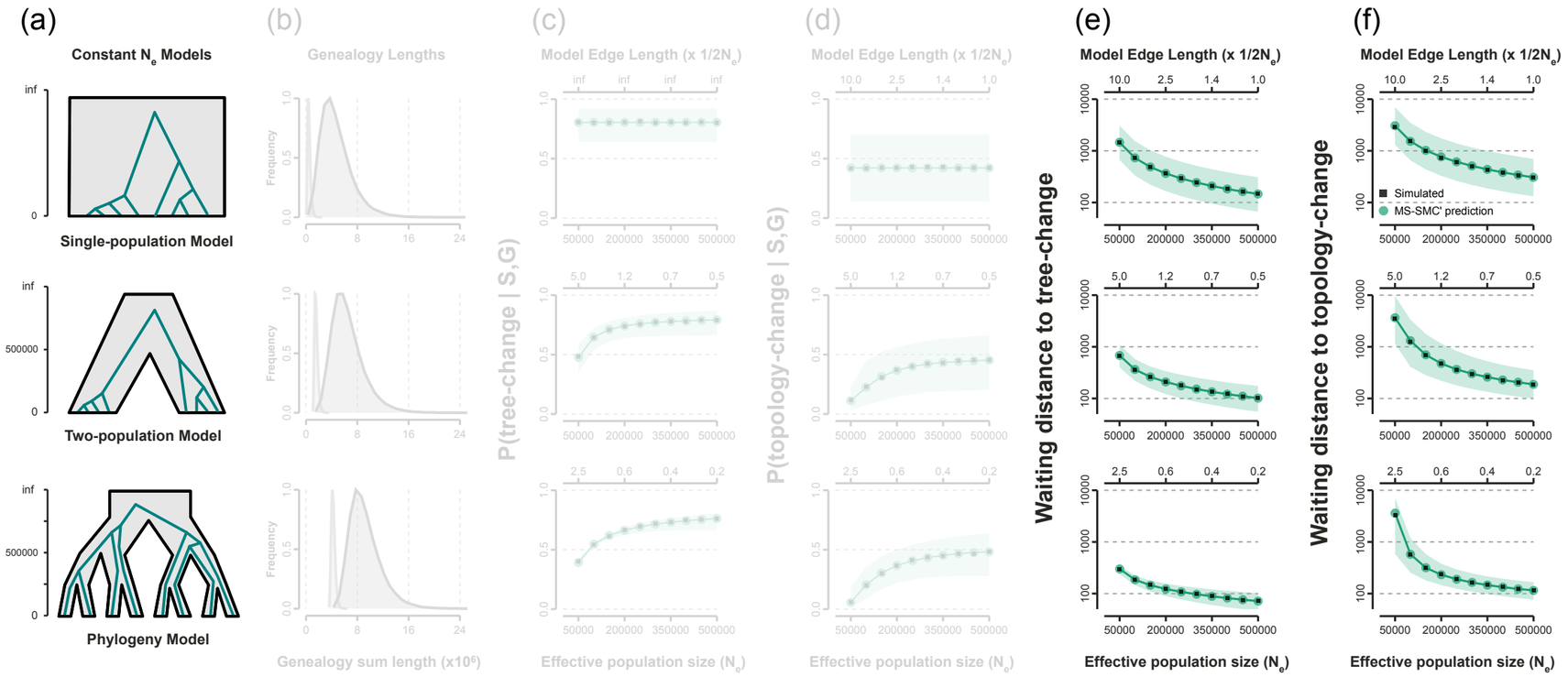
$$\lambda_t = L(\mathcal{G}) \times r \times \mathbb{P}(\textit{topology-changed}|\mathcal{S}, \mathcal{G})$$

Exponentially distributed waiting distances



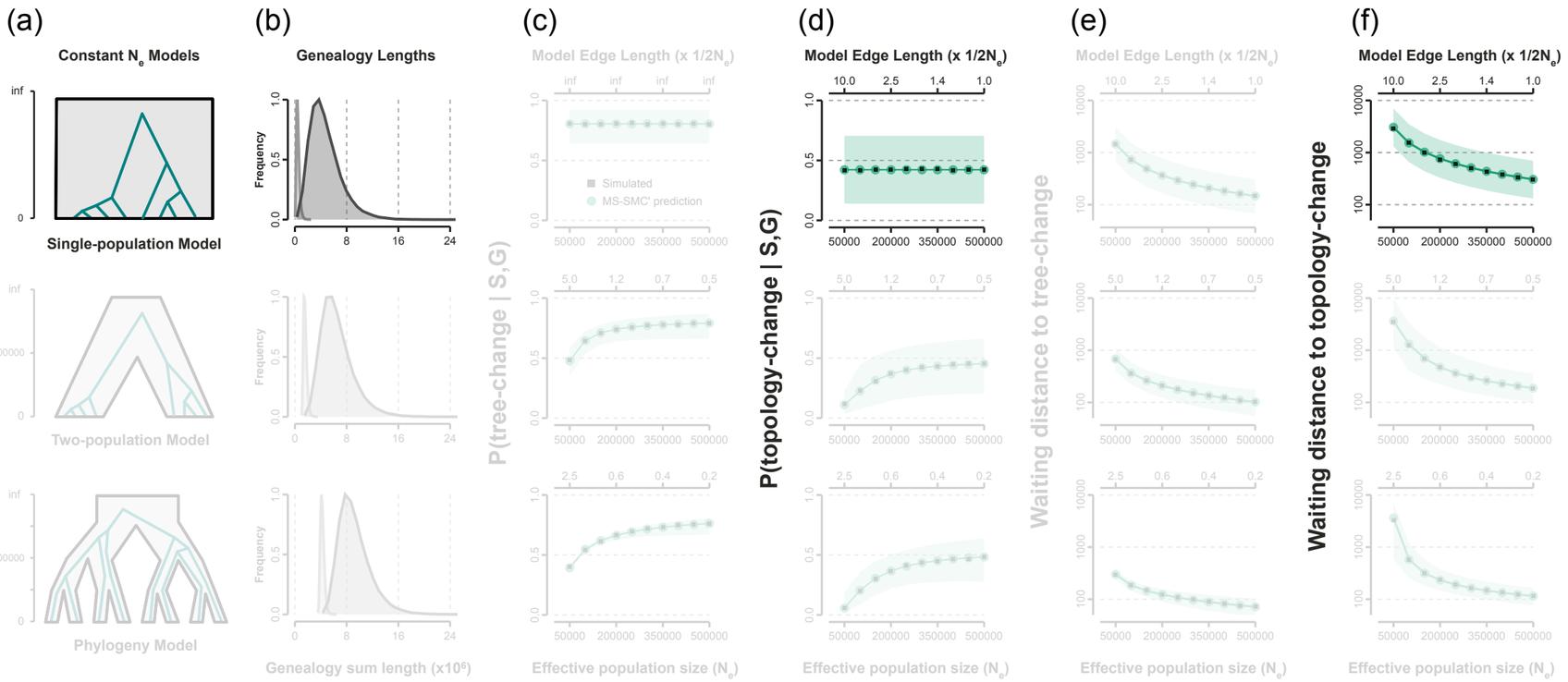
Validation:

Analytical results match expectation of stochastic coalescent simulations.



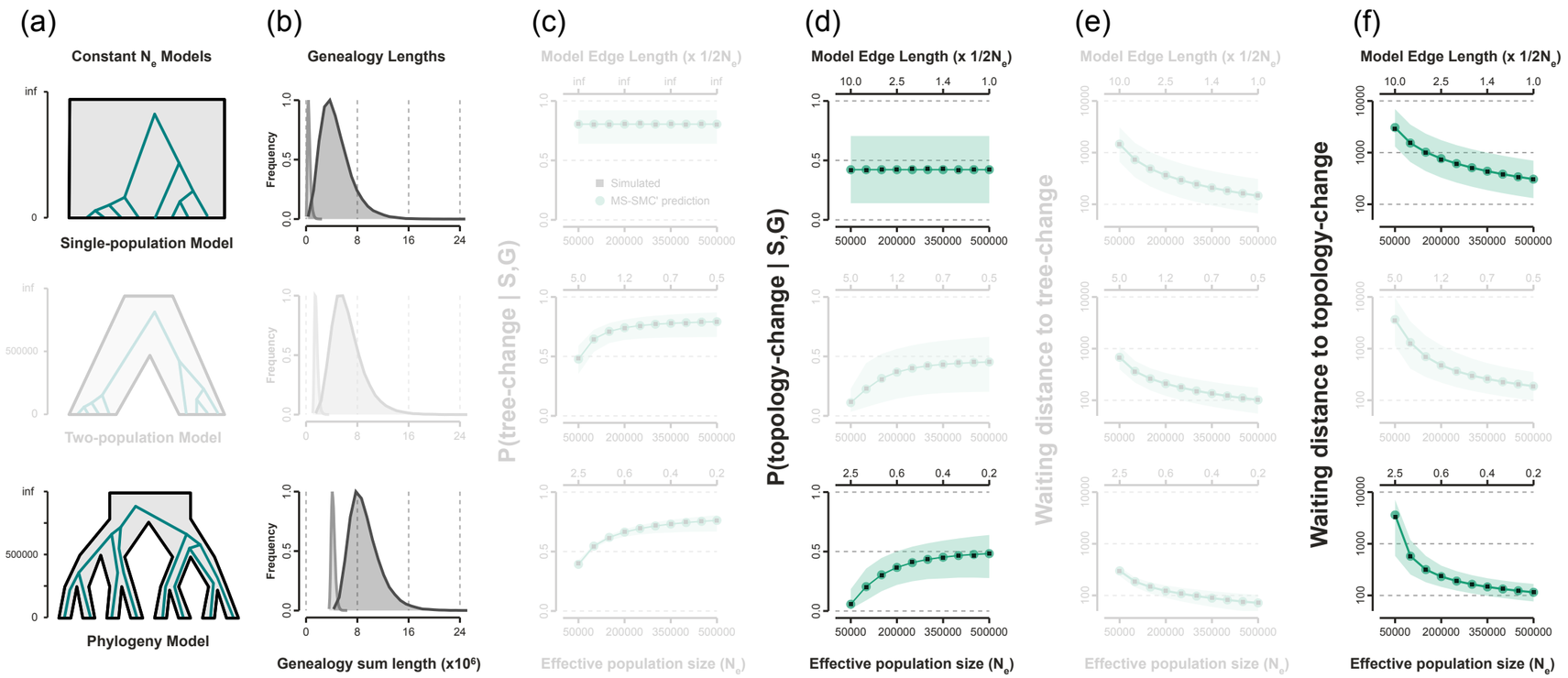
Validation:

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

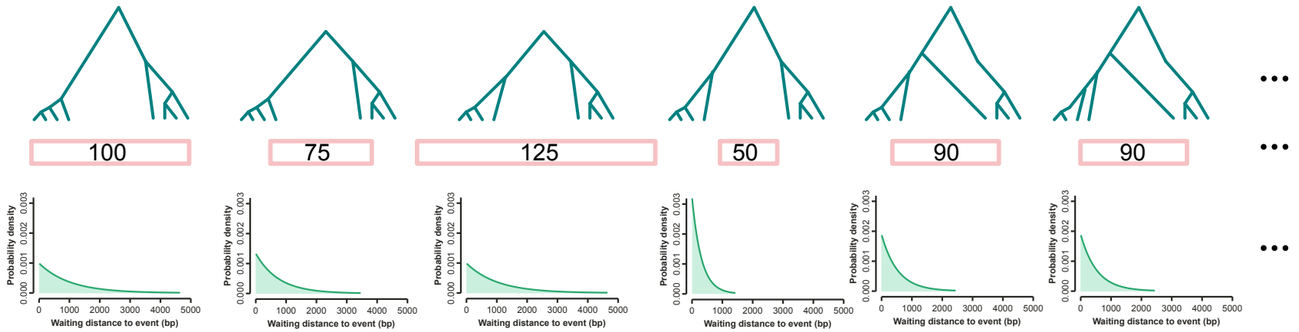
Given an observed/proposed ARG (genealogies and interval lengths)

get expected waiting distance for each (λ_i)...

$G = [\mathcal{G}_1, \mathcal{G}_2, \mathcal{G}_3, \ldots]$

$X_g = [x_1, x_2, x_3, \ldots]$

$\Lambda_g = [\lambda_{g1}, \lambda_{g2}, \lambda_{g3}, \ldots]$



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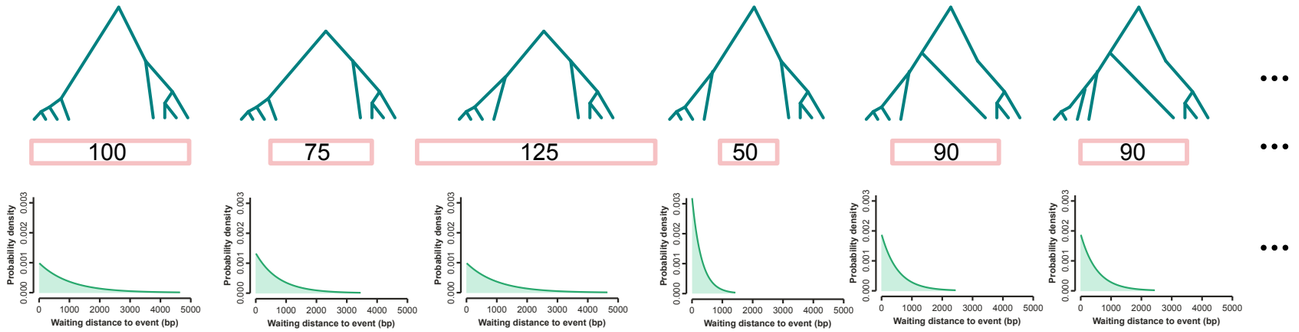

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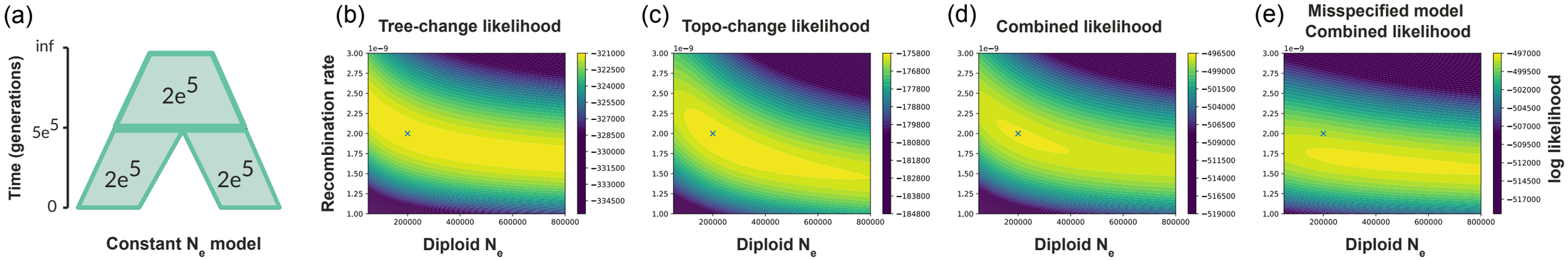
... and calculate likelihood of MSC model ($\mathcal{S}$) from exponential probability densities.

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

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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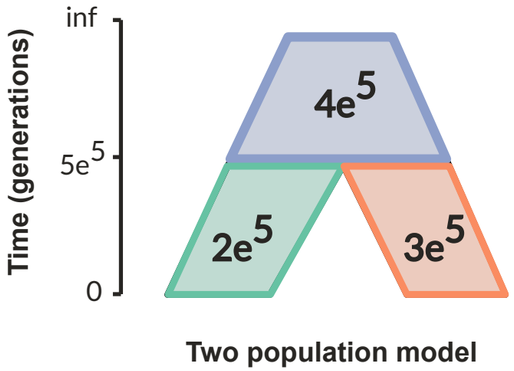

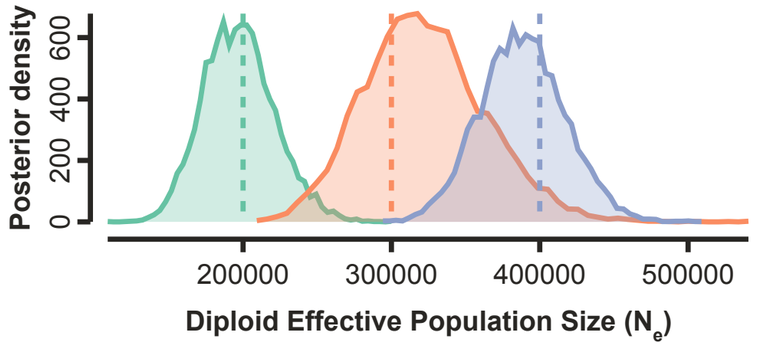

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- A big step towards estimating MSC models from *linked genome data!*
- Topology-changes are easily detactable in sequence data.

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

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PhD student

Eaton lab at Columbia University in New York City.
Contact us: @dereneaton

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