Efficient simulation of introgression, admixture and local ancestry

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Talk outline

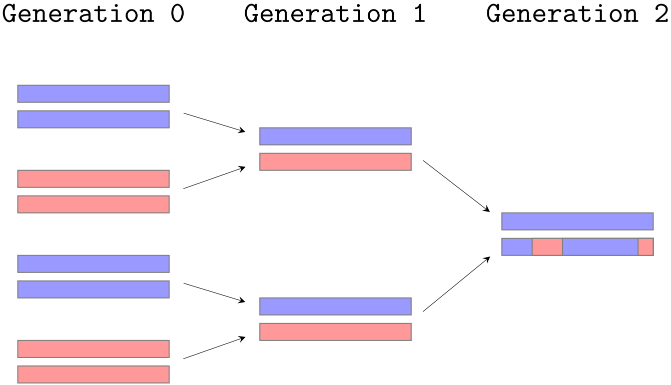
1. Introduction to admixture and local ancestry
2. Tree sequences
3. Simulating tree sequences
4. Simulating local ancestry
5. A new method for simulating local ancestry
6. Why this work matters

Intro to admixture and local ancestry

What's admixture?

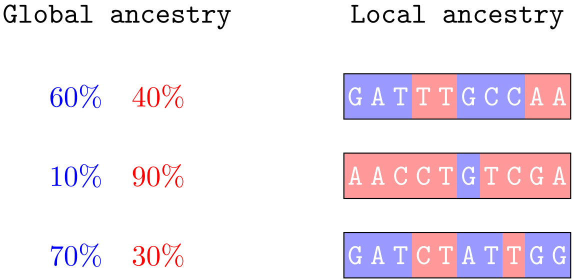
- A person has ancestry with a given population if they have inherited some genetic material from ancestors who belonged to that population.
- Any person with > 1 ancestry is admixed.
- Introgression is admixture between different species.

What is admixture?



Generation 0 Generation 1 Generation 2

Reporting ancestry



Global ancestry		Local ancestry
60%	40%	G A T T T G C C A A
10%	90%	A A C C T G T C G A
70%	30%	G A T C T A T T G G

My PhD work is about simulating and inferring local ancestry.

Why is understanding admixture and ancestry important?

- **Demography and history**
  Inference about the dates and composition of historical migrations and admixture events.

- **Medicine**
  GWAS and risk prediction studies, admixture mapping studies.

- **Genetic pipelines**
  Phasing and imputation.

Storing genomes with history using tree sequences

Context - genetic data is BIG and REPETITIVE

```
...GTAACGCGATAAGAGATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGAGATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGTAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGTAATAGCGTA...
```

$\leftarrow 5 \times 10^7$ bases for small human chromosome $\rightarrow$

Storing $n = 1 \times 10^5$ chromosomes in a compressed VCF requires $\approx$ 50 GB.

Shared haplotypes are often due to shared history

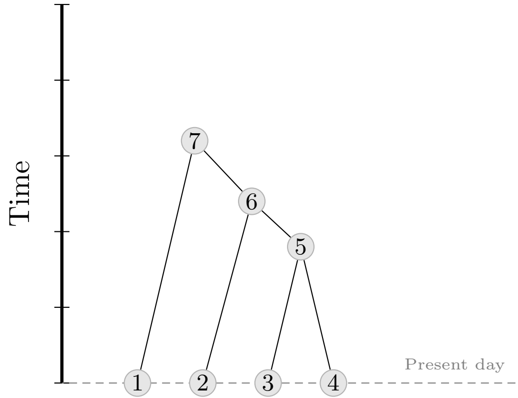
```
...GTAACGCGATAAGAGATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGAGATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGAAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGTAATAGCGTA...
...GTAACGCGATAAGATATTAGCCCAAAAACACAGACATGGTAATAGCGTA...
```

Q. Can we use this history to store DNA more compactly?

Tree sequences are the future!

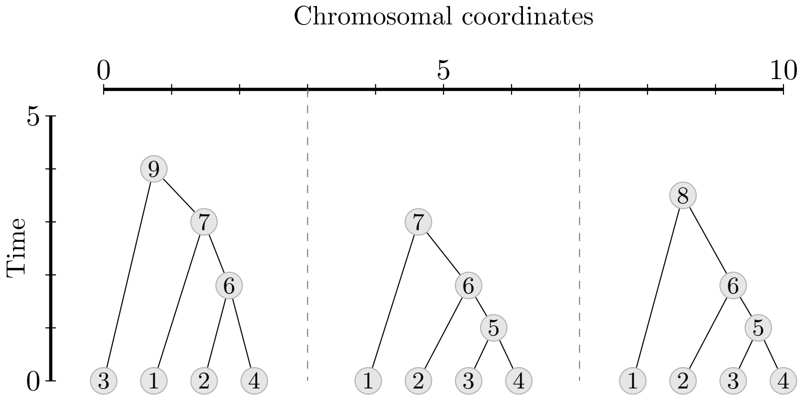
- Tree sequences contain rich information about the history of a sample, not just the genotypes.
- We can simulate this data structure using well-established software (`msprime`, `SLiM`). (With some caveats...)
- We can infer this data structure with some success (`tsinfer`).

Trees show genealogy at a single allele



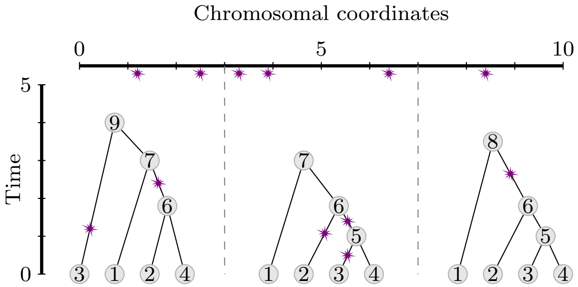
- Nodes = haplotypes
- Edge lengths = time

Tree sequences show genealogy over an interval of alleles

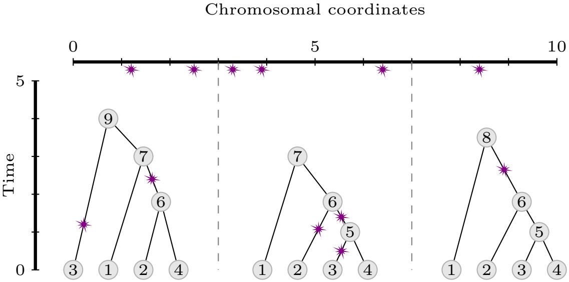


Tree sequences can encode haplotypes

Node 1	0	0	0	0	0	0
Node 2	1	0	1	0	0	1
Node 3	0	1	0	1	1	1
Node 4	1	0	0	0	1	1



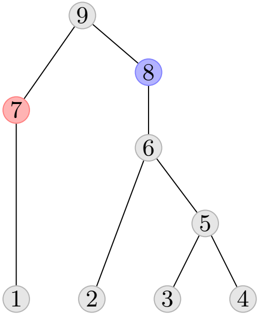
Tree sequences can be stored in tables



Nodes		Edges			
id	time	left	right	parent	child
1	0.0	0.0	7.0	5	3
2	0.0	0.0	7.0	5	4
3	0.0	0.0	10.0	6	2
4	0.0	0.0	3.0	6	4
5	1.1	3.0	10.0	6	5
6	1.8	0.0	7.0	7	1
7	3.0	0.0	7.0	7	6
8	3.5	1.0	10.0	8	1
9	4.0	7.0	10.0	8	6
		0.0	3.0	9	3
		0.0	3.0	9	7

Mutations		
location	time	nearest node
1.2	2.5	6
2.5	1.2	3
3.3	1.3	2
3.9	0.4	3
6.4	1.4	5
8.4	2.7	6

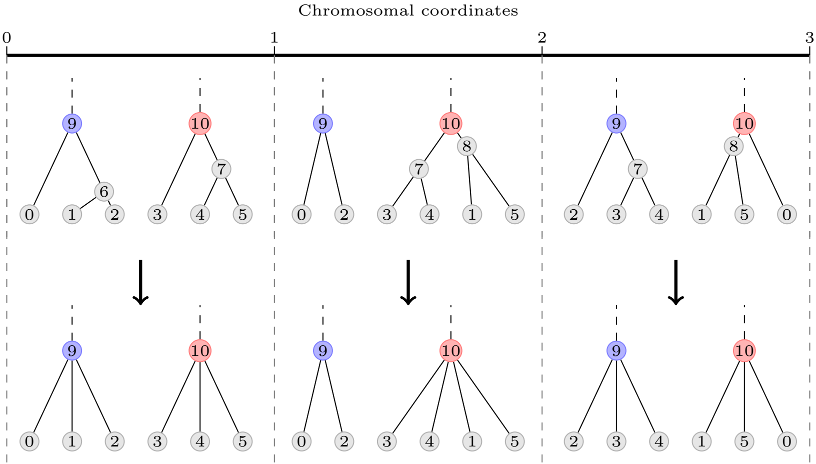
Tree sequences can hold info on population structure



Nodes may be assigned to populations.

The branch joining a sample node to an ancestral node shows the sample's ancestry.

Local ancestry can be extracted from tree sequences



But doing this efficiently is hard...

- There are substiantial correlations in genealogy between individual nodes, and across genomes.
- Requires clever operations for altering tree sequences by ‘simplifying’ the tables that represent them.
- More detail in an upcoming paper by Georgia, Damjan, Stephen, Jerome Kelleher (Oxford) & Peter Ralph (Oregon).

Simulating tree sequences

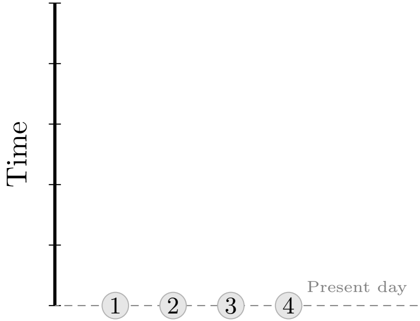
Realistic simulations are important

- **Exploration**
  Simulations allow us to explore the influence of various historical scenarios on observed patterns of genetic variation and inheritance.

- **Benchmarking and evaluating method performance**
  To assess the accuracy of inferential methods, we need test datasets for which the true values of important parameters are known.

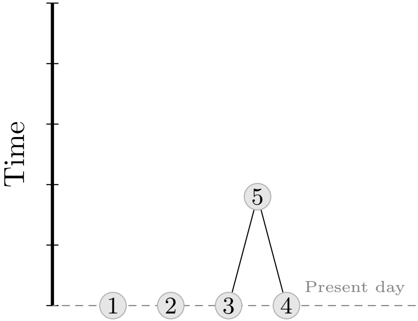
- **Model training**
  Some methods for ancestry inference are trained on simulated data.

`msprime` simulates a sample backwards-in-time



- Simulates tree sequences under an implementation of the coalescent model.

`msprime` simulates a sample backwards-in-time



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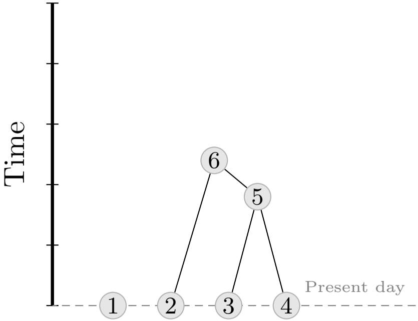
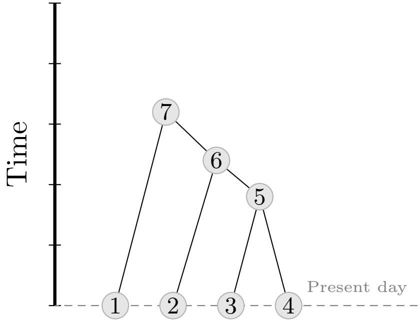


- Simulates tree sequences under an implementation of the coalescent model.

msprime simulates a sample backwards-in-time



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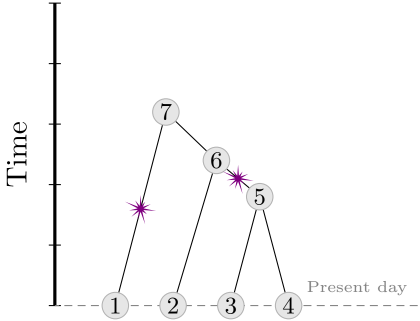


- Mutations are assumed to be neutral and can be generated independently of the tree topologies and edge lengths.

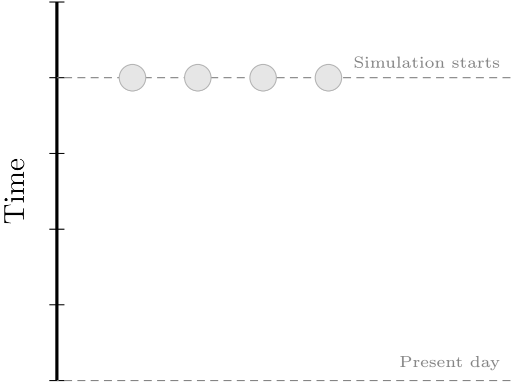
- `msprime` simulates the sparsest set of haplotypes that are needed to represent the relative genealogical history of the samples.

- This sparsity makes it quick and memory-efficient to run.

- Limited by the assumptions of the coalescent model: infinite sites, no selection or deviations from random mating, small sample size relative to effective population size...

- See (Kelleher et al., 2016) for more details.

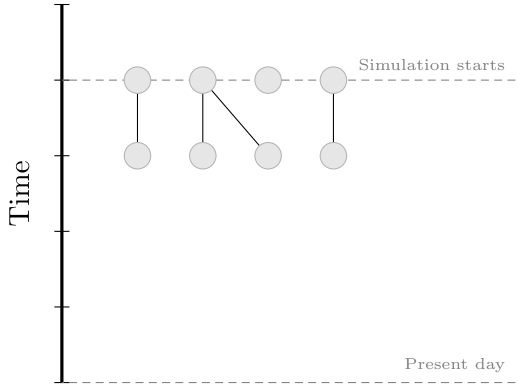
SLiM simulates an entire population forward-in-time



Alternates between

1. forward simulation
2. pruning of irrelevant history.

SLiM simulates an entire population forward-in-time



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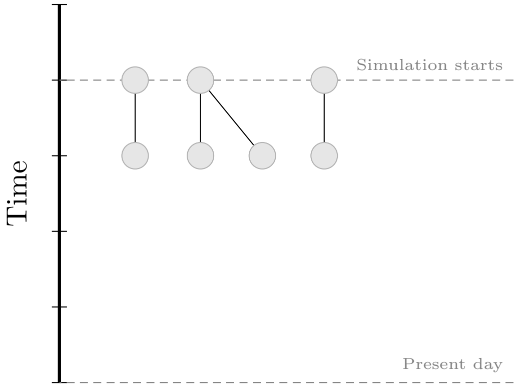

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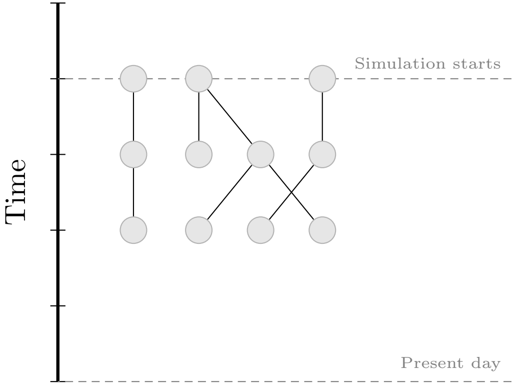

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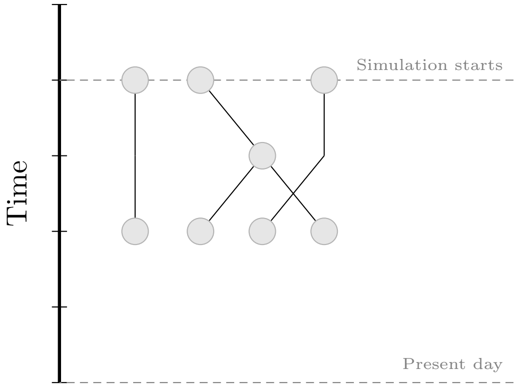

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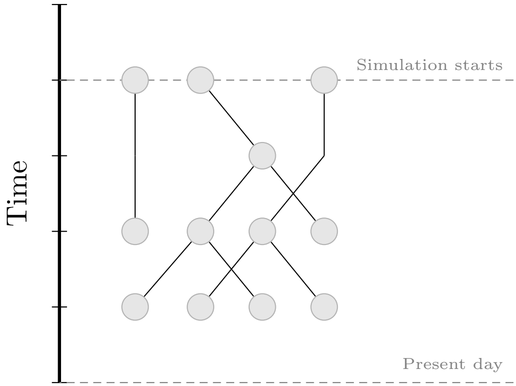

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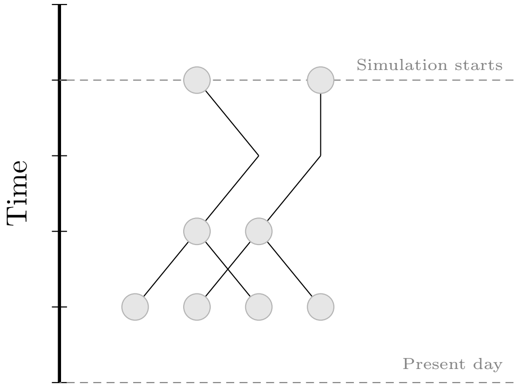

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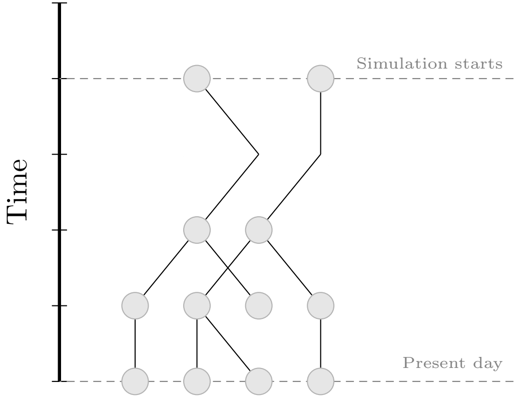

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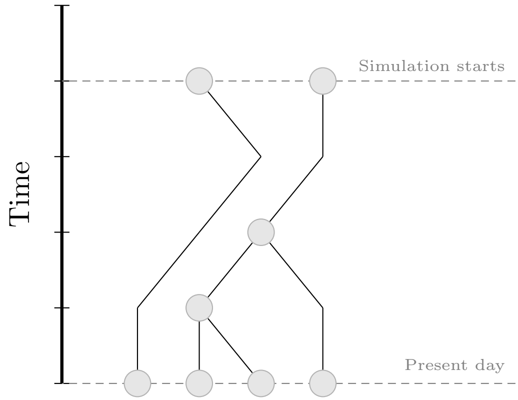

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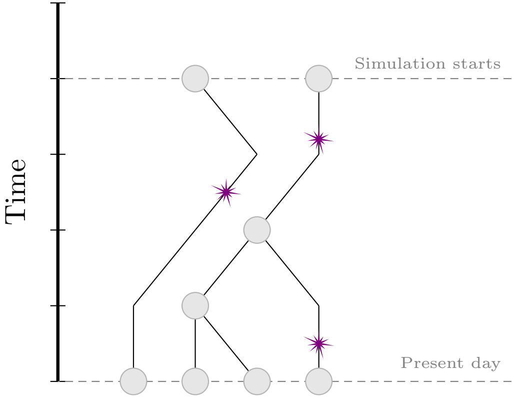


Mutations can be added during the simulation of the tree topologies, or generated independently and added afterwards.

- Can accomodate complex and more ecologically realistic demographic scenarios including selection, overlapping generations, spatially-based survival and mating patterns, density-dependent population regulation...

- Simulates entire population in every generation, so much slower than `msprime`.

- See (Haller et al., 2018) and (Haller & Messer, 2019) for details about `SLiM`, and (Kelleher et al., 2018) for details of the tree sequence pruning/simplification technique.

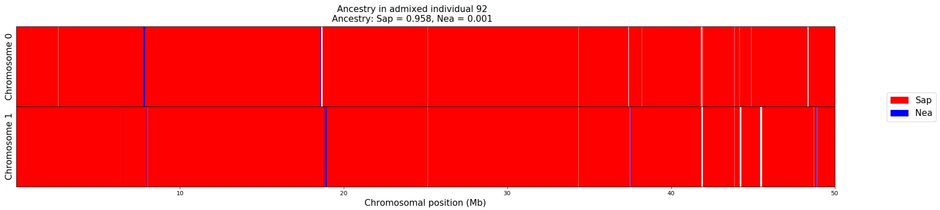
Q. Can these methods simulate local ancestry?

A simplified toy example: Neanderthal introgression

Generations	**Event**
≈ 240 000	Common ancestor of all modern Eurasians and Neanderthals at all loci.
20 000	Divergence of Eurasians and Neanderthals.
2 500	2% introgression of Neanderthals into Eurasians.
0	Samples from 100 Eurasian individuals obtained.

Chromosome of 50 000 000 base pairs, constant effective population sizes of 5000 individuals, uniform recombination rate 1×10^{-8} bp/generation, uniform mutation rate 1×10^{-8} bp/generation, all variation is neutral.

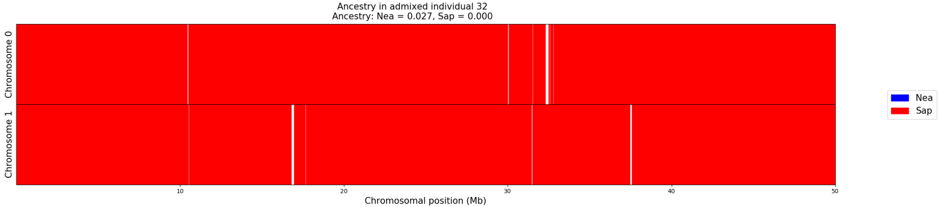
msprime results



Global ancestry averaged over all of the simulated samples was

- 96.0% Sapiens
- $<$ 0.05% Neanderthal
- 4.0% unassigned.

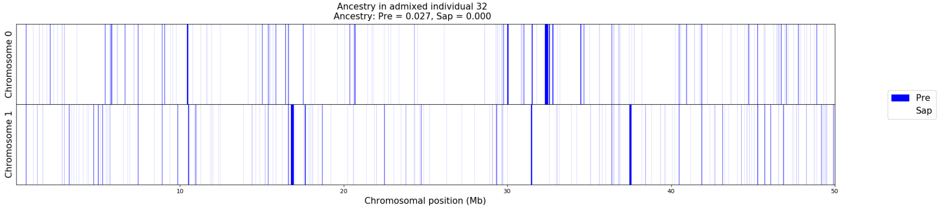
SLiM results



Global ancestry averaged over all of the simulated samples was

- 96.2% Sapiens
- $< 0.05\%$ Neanderthal
- 3.8% unassigned.

SLiM results - missing ancestry



Global ancestry averaged over all of the simulated samples was

- 96.2% Sapiens
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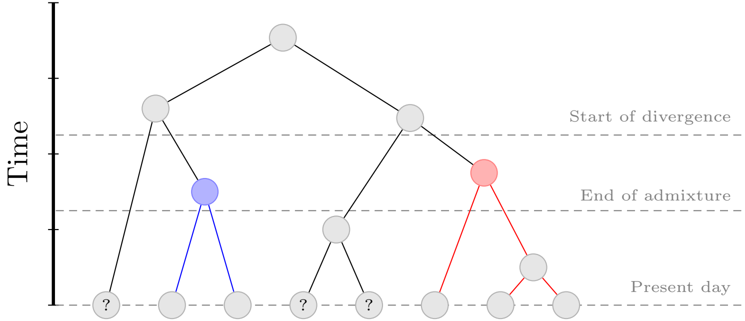
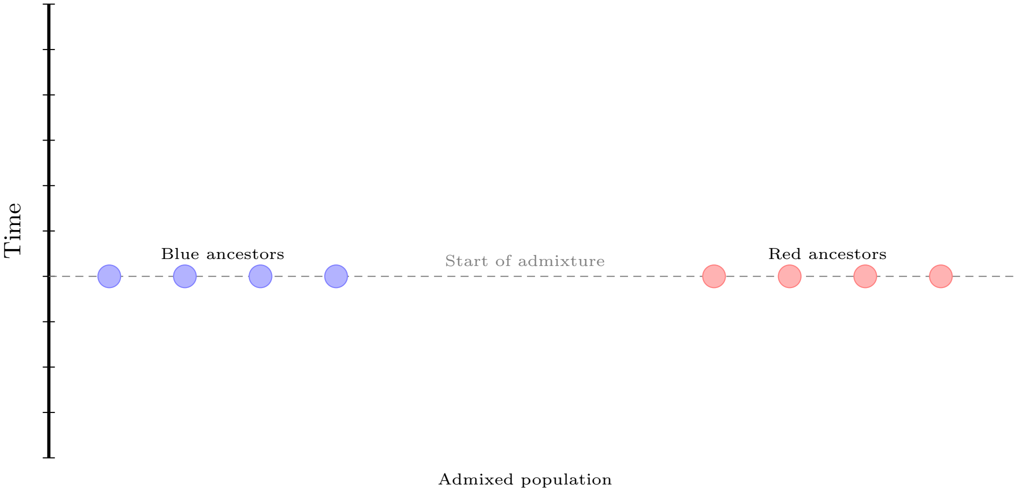
- 3.8% unassigned.

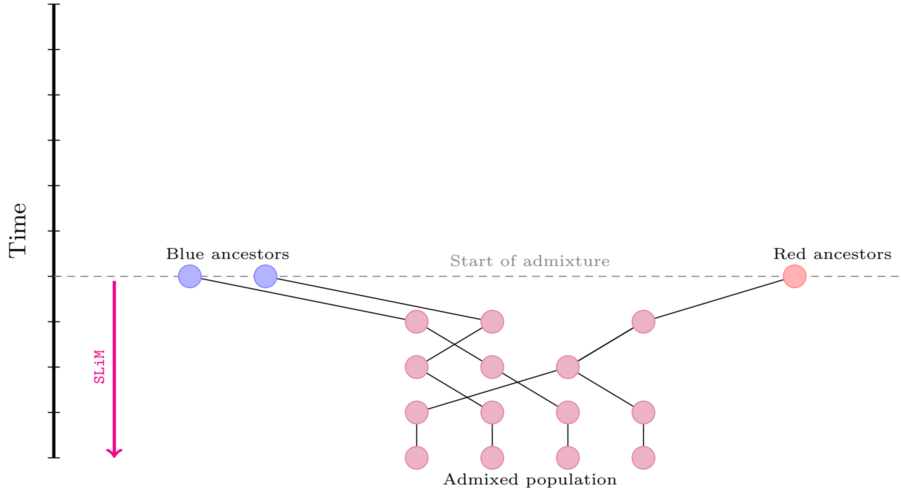
The problem is incomplete lineage sorting

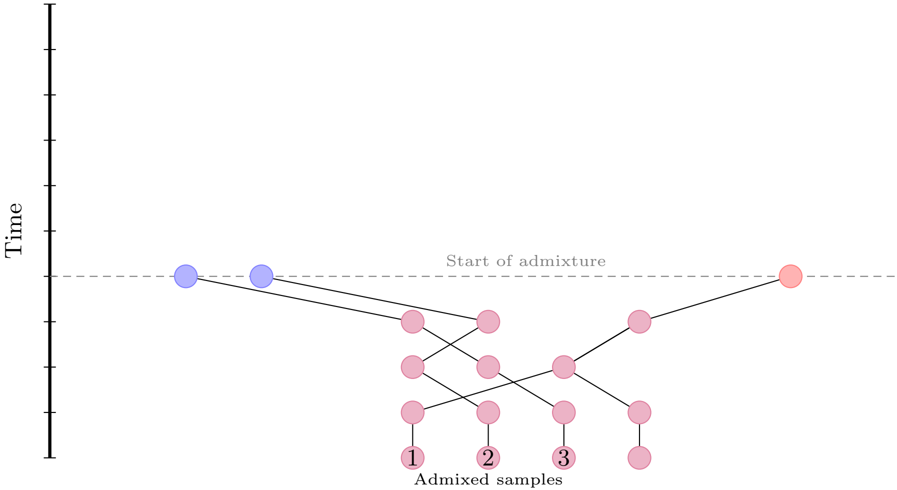


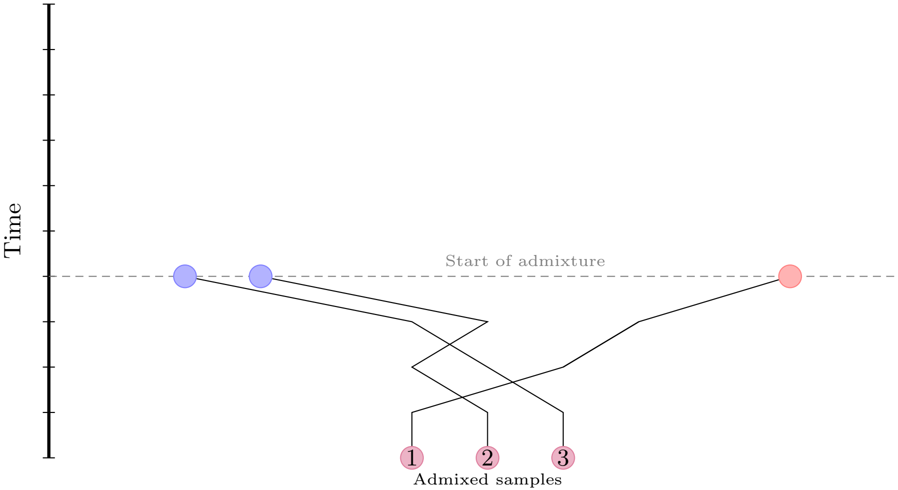
Some samples do not have simulated ancestors in the given populations.

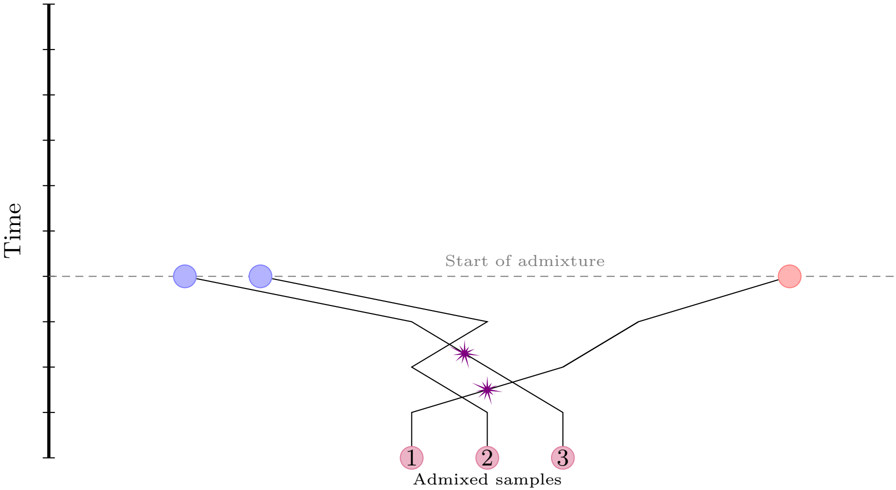
A new method for simulating admixture

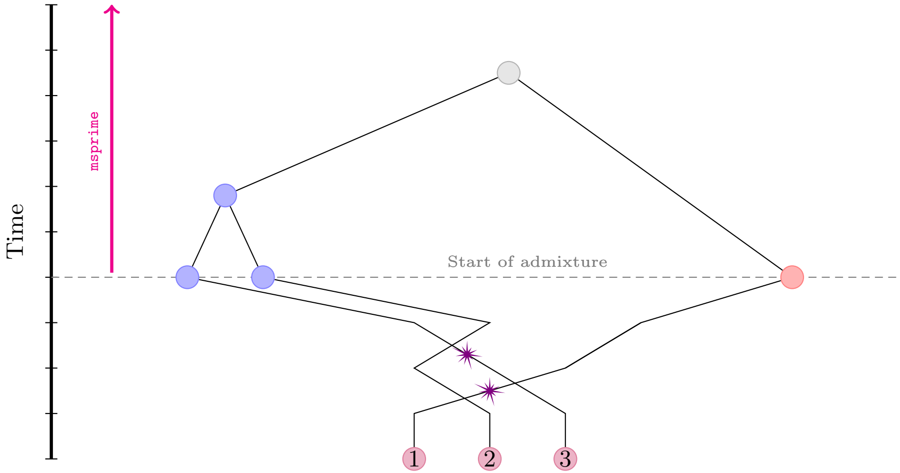

Time
Blue ancestors
Start of admixture
Red ancestors
Admixed population

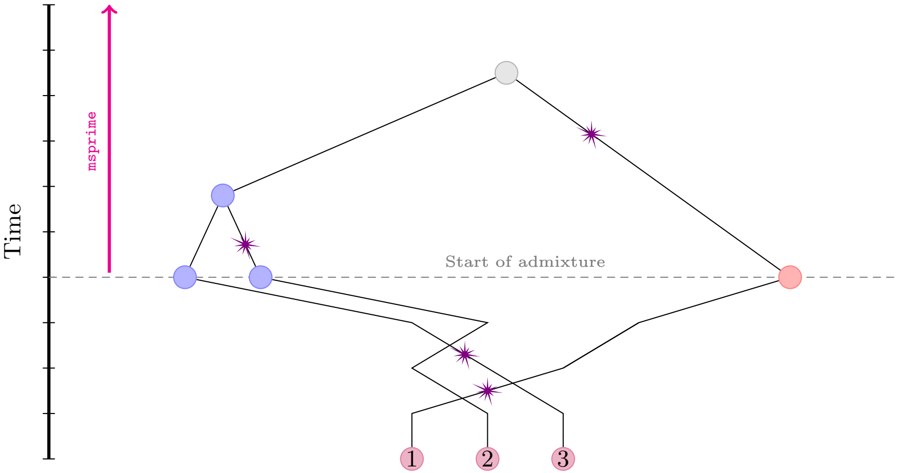

Time
Blue ancestors
Start of admixture
Red ancestors
SLiM
Admixed population


Time
Start of admixture
1
2
3
Admixed samples

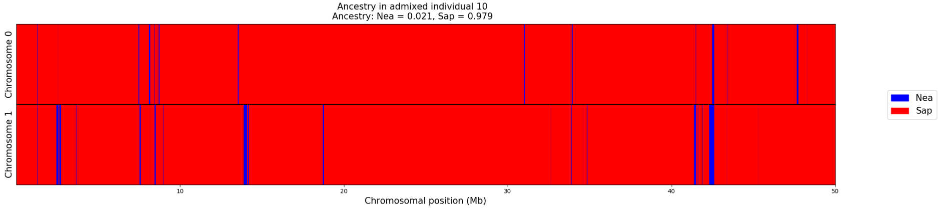

Time
Start of admixture
1
2
3
Admixed samples


Time
Start of admixture
1
2
3
Admixed samples


Time
msprime
Start of admixture
1
2
3


Time
msprime
Start of admixture
1
2
3

Results



Global ancestry averaged over all of the simulated samples was

- 98.0% Sapiens
- 2.0% Neanderthal
- 0.0% unassigned.

Why this work matters

	Global ancestry		
	Sapiens	Neanderthal	Missing
msprime	96.0%	≈ 0.0%	4.0%
SLiM	96.2%	≈ 0.0%	3.8%
Georgia	98.0%	2.0%	0.0%
Expected	98.0%	2.0%	0.0%

Affects the computation of ancestral tract lengths, population-specific frequency spectra, ancestry-informative markers...

Summary

- It is useful to keep track of local ancestry in genetic simulations.
- Standard tree sequence simulators are able to do this with the help of efficient ancestry-extraction algorithms.
- However, they do not retain the ancestry of all segments due to incomplete lineage sorting.
- A new simulation method overcomes this problem.

Thanks to...

My supervisors	Damjan Vukcevic Stephen Leslie
My collaborators	Peter Ralph (University of Oregon) Jerome Kelleher (BDI, University of Oxford)
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