Efficient simulation of introgression, admixture and local ancestry

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MELBOURNE

Talk outline

1. Introduction to admixture and local ancestry

2. Tree sequences

3. Simulating local ancestry with tree sequences - existing ways

4. Simulating local ancestry with tree sequences - new way
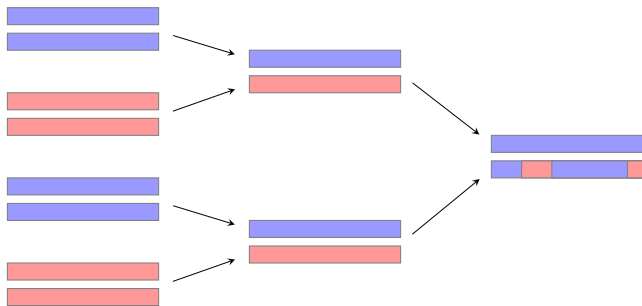
Intro to admixture and local ancestry

What is admixture?

- An organism has ancestry with a given population if they have inherited some genetic material from ancestors who belonged to that population.

- Any organism with > 1 ancestry is admixed.

- Introgression is admixture between different species.

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.

Being able to simulate genetic ancestry is useful!

- **Benchmarking and evaluating method performance**
  To assess the accuracy of methods that infer ancestry, we need test datasets for which true local ancestry is known.

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

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

Tree sequences: the data format

Context - genetic data is BIG and REPETITIVE

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

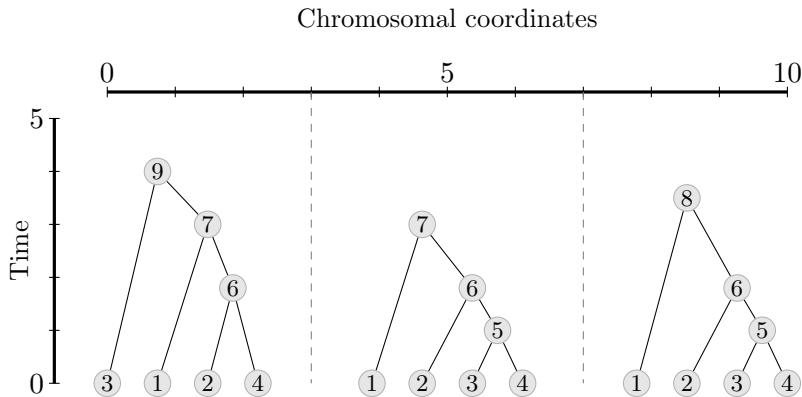$\leftarrow 5 \times 10^7$ bases for small human chromosome $\rightarrow$

Repeated haplotypes are often just a consequence of shared history.

Q. Can we use this history to represent DNA sequences more compactly?
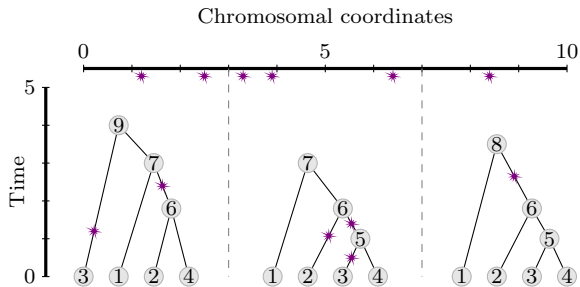
Trees show genealogy at a single allele

- Nodes = haplotypes

- Edge heights = time
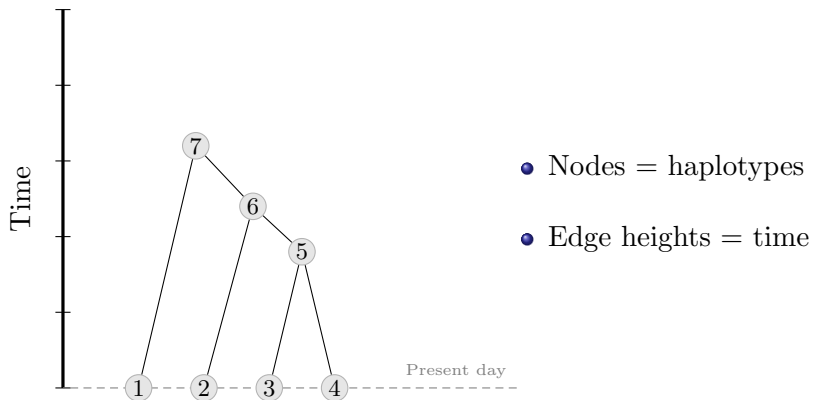
Tree sequences show genealogy over an interval of alleles

Tree sequences can encode haplotypes

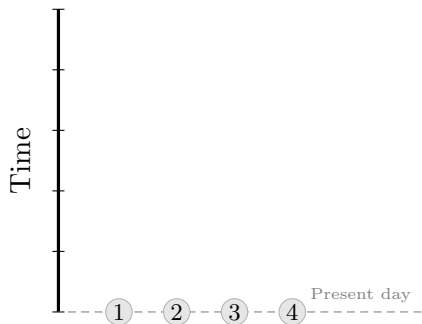|						
Node 1	0	0	0	0	0	0
Node 2	1	0	1	0	0	1
Node 3	0	1	0	1	1	1
Node 4	1	0	0	0	1	1

Chromosomal coordinates

Tree sequences can hold info on local ancestry
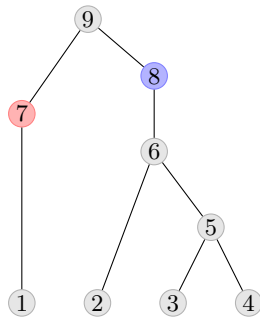
Nodes may be assigned to populations. The branch joining a sample node to an ancestral node shows the sample's ancestry.
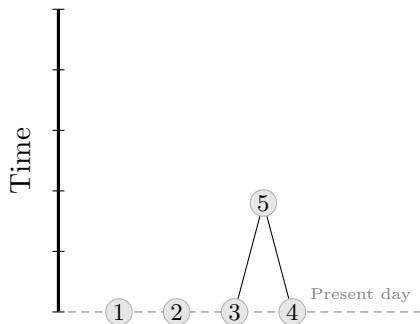
Simulating admixture - old methods

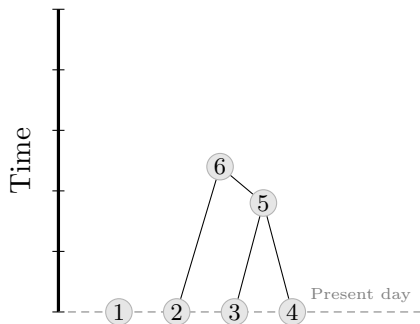# msprime simulates a sample backwards-in-time

Simulates tree sequences under the coalescent model.

msprime simulates a sample backwards-in-time

Simulates tree sequences under the coalescent model.

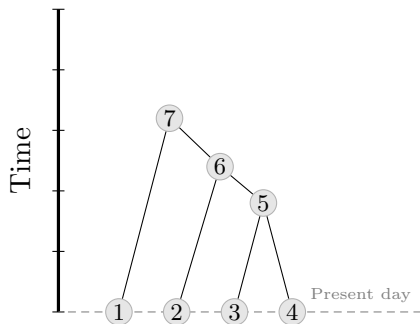# `msprime` simulates a sample backwards-in-time

Simulates tree sequences under the coalescent model.

`msprime` simulates a sample backwards-in-time

Simulates tree sequences under the coalescent model.

A simplified toy example: Neanderthal introgression

Generations	Event
$\approx 240\,000$	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.
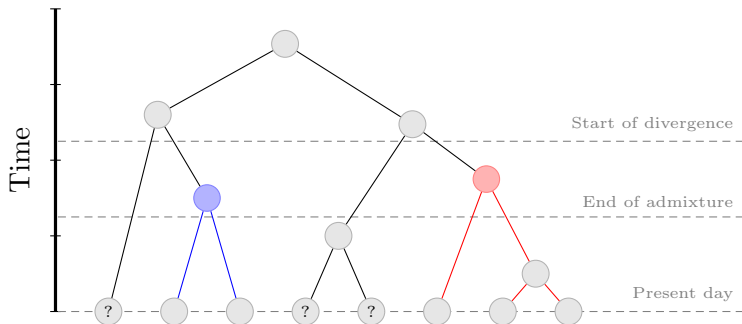
`msprime` results - missing ancestry data
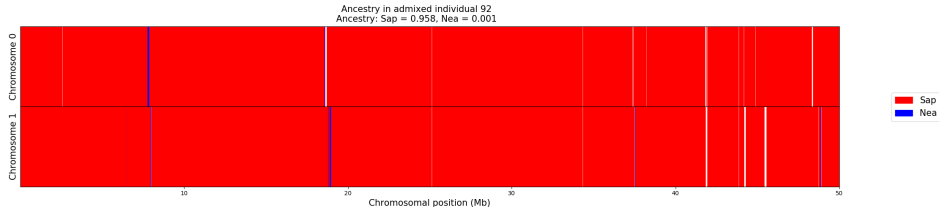
Global ancestry averaged over all of the simulated samples was

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

# Missing ancestry is due to incomplete lineage sorting

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

msprime performance

	Missing data	Run time	File size	Realism
default	4.0%	6 sec	9 Mb	✗
+ all ancestors	0.0%	53 sec	1700 Mb	✗

Restricted by the limitations of the coalescent model: no selection, random mating, small sample sizes, no more than 1 mutation at any location . . .
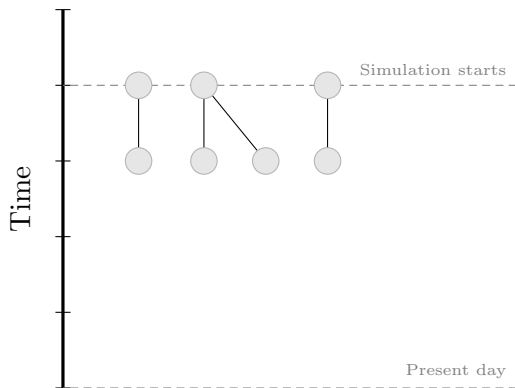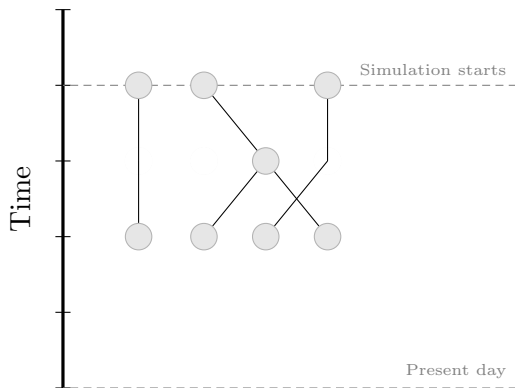
SLiM simulates an entire population forward-in-time
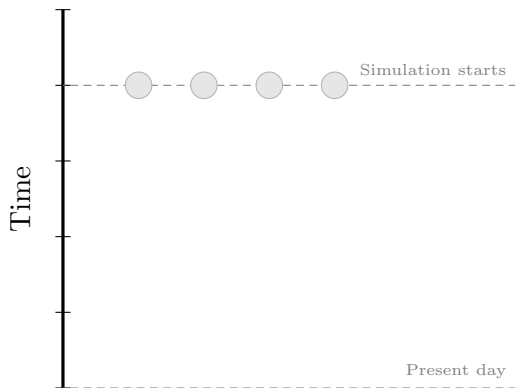
Alternates between

1. forward simulation
2. pruning of irrelevant history.

SLiM simulates an entire population forward-in-time

Alternates between

1. forward simulation
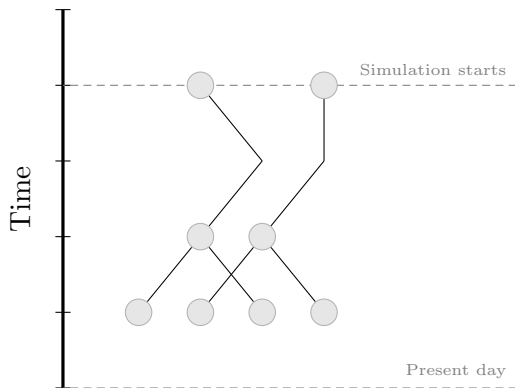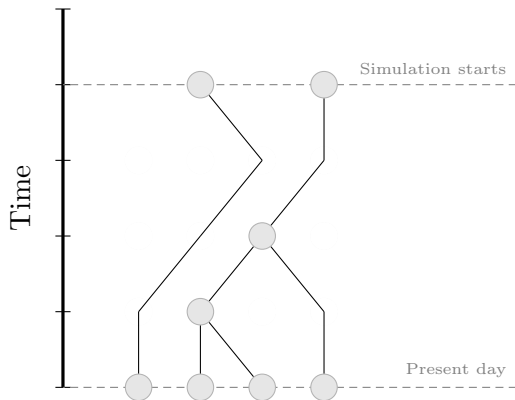2. pruning of irrelevant history.

SLiM simulates an entire population forward-in-time

Alternates between

1. forward simulation
2. pruning of irrelevant history.

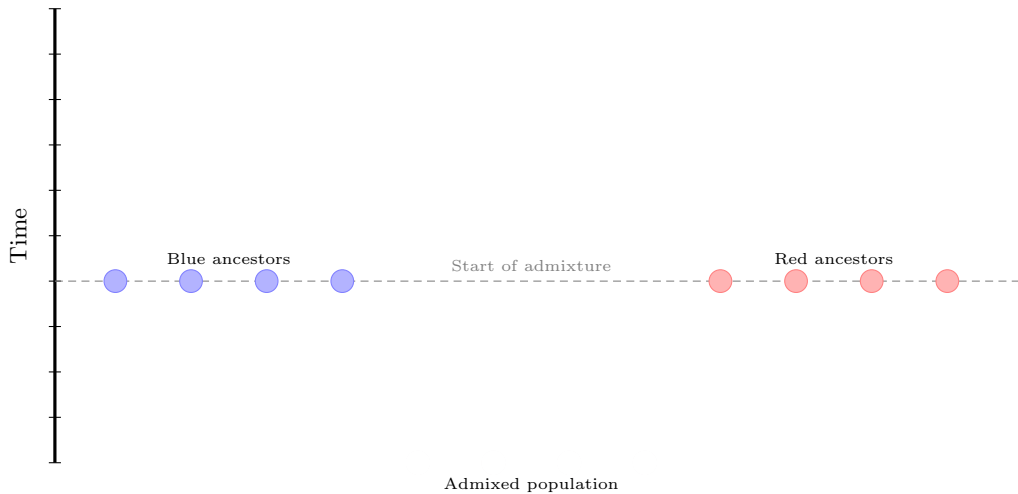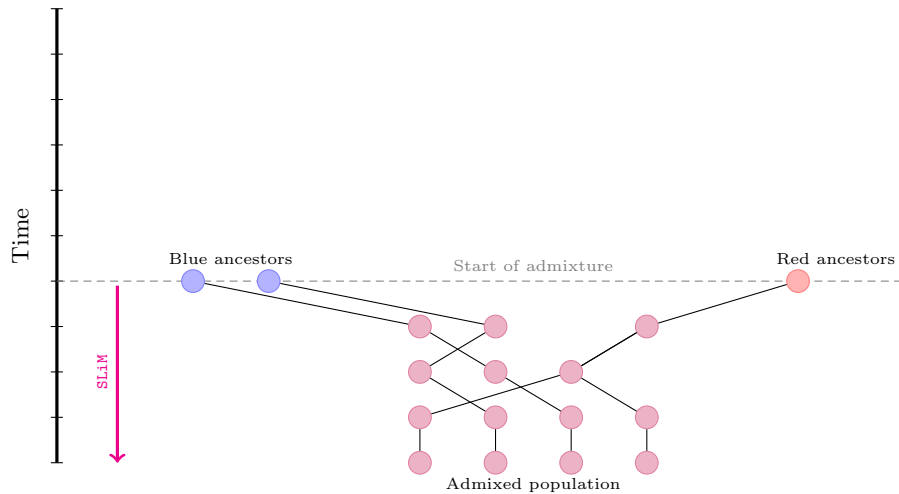# SLiM simulates an entire population forward-in-time

Alternates between

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SLiM simulates an entire population forward-in-time

Alternates between

1. forward simulation
2. pruning of irrelevant history.

SLiM performance

	Missing data	Run time	File size	Realism
msprime	0.0%	53 sec	1700 Mb	✗
SLiM	0.0%	> 1 hr	41 Mb	✓

Simulating tree sequences - new method

Time

Blue ancestors   Start of admixture   Red ancestors

Admixed population

Admixed population

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
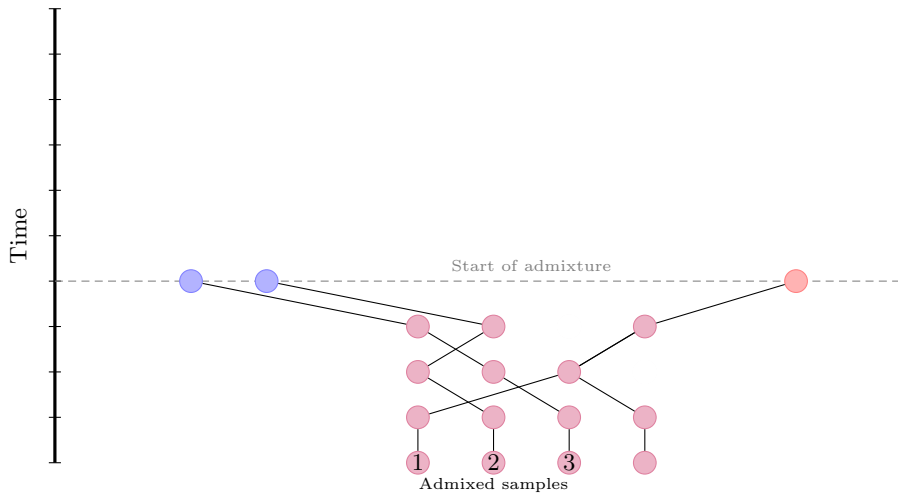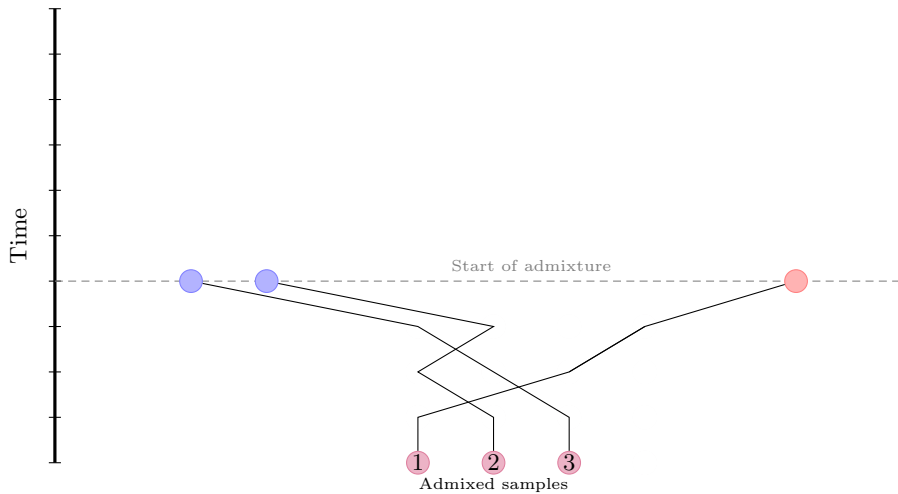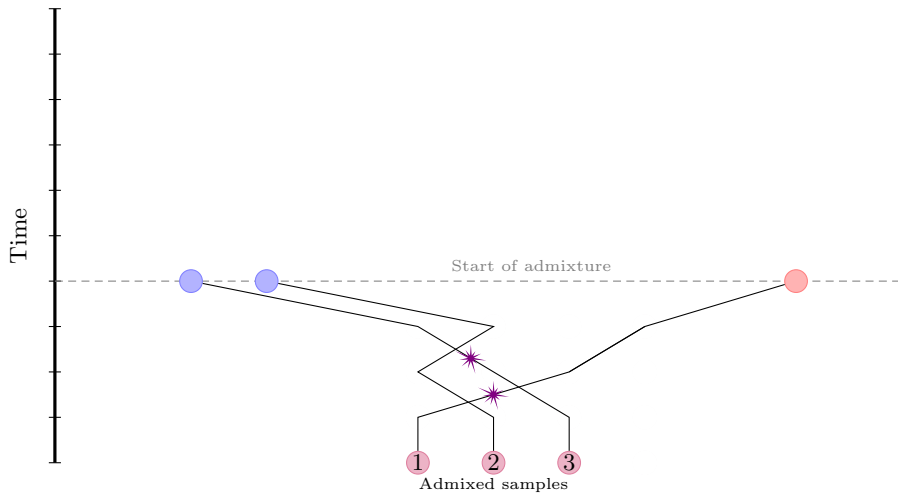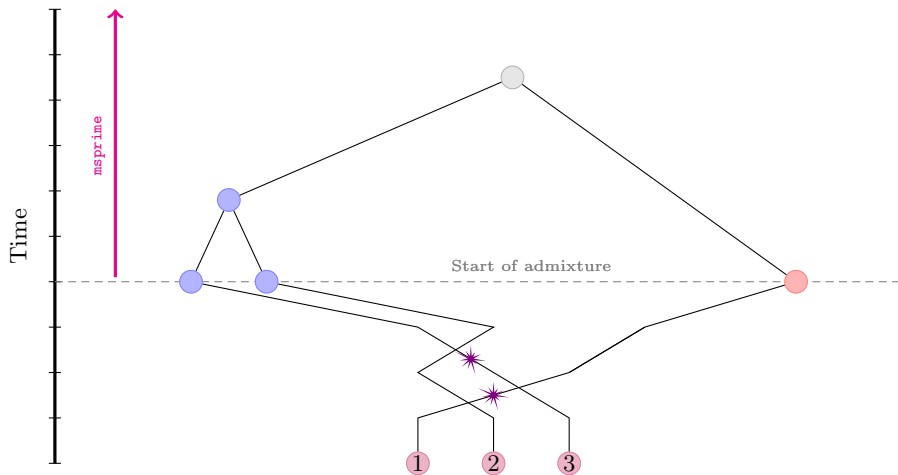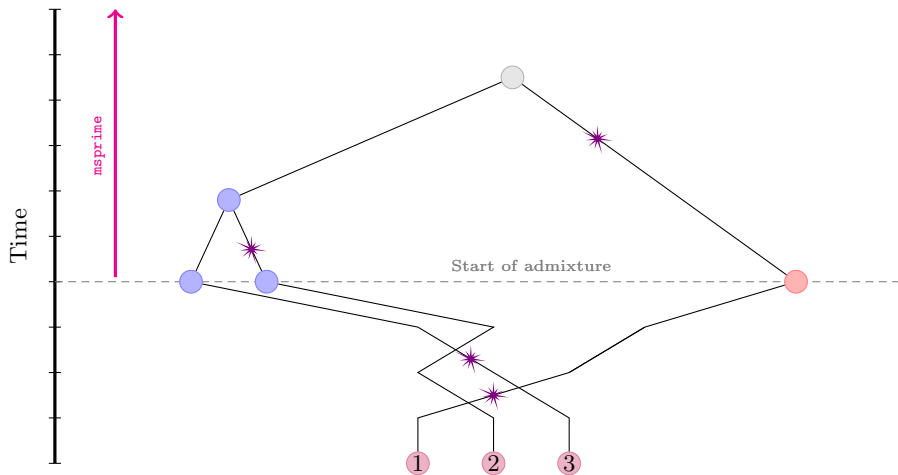
New method performance

	Missing data	Run time	File size	Realism
`msprime`	0.0%	53 sec	1700 Mb	✗
`SLiM`	0.0%	> 1 hr	41 Mb	✓
Georgia	0.0%	86 sec	39 Mb	✓

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.

- A new simulation method can do this quickly while also allowing the user to model complex admixture scenarios.

Thanks to...

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My collaborators $\begin{cases} \text{Peter Ralph (University of Oregon)} \\ \text{Jerome Kelleher (BDI, University of Oxford)} \end{cases}$

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References

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SLiM:
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Ecology Resources, (November 2018), 552–566.