Efficient simulation of identity-by-descent and ancestry in large datasets

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0. Introduction

To assess the performance of methods in population genetics, we often wish to simulate realistic genetic datasets while retaining detailed information about the history of the simulated genomes. This poster briefly describes how we can efficiently simulate genetic information with full information about the common ancestry of particular genomic segments, as well as information about the populations that these segments have been inherited from. Although the software is still under development in `tskit` [1], our progress to date suggests that our methods are scaleable and fast enough to be useful in high-powered studies of subtle demographic questions.

1. The data structure: tree sequences

Genetic sequence data is BIG and REPETITIVE:

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

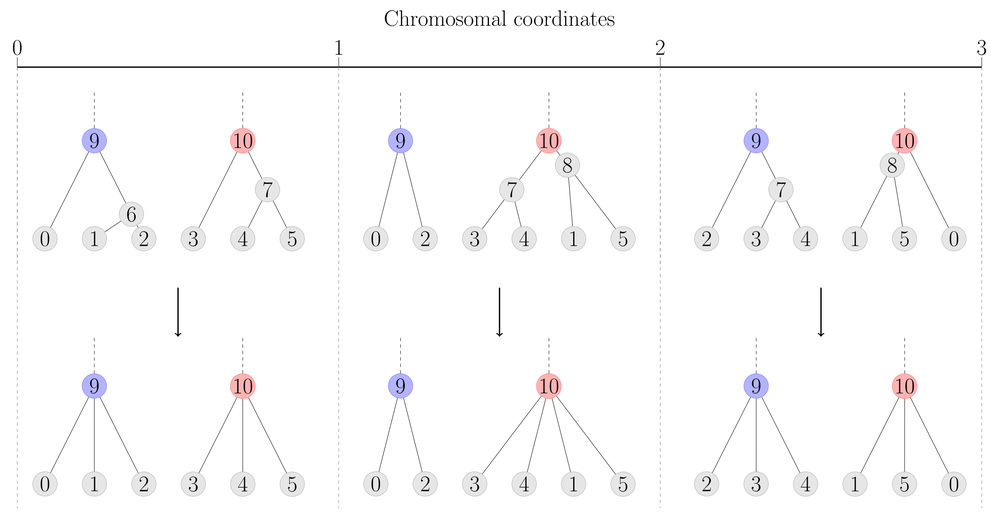
$\leftarrow 5 \times 10^7$ bases for small human chromosome $\rightarrow$

However, common haplotypes in a sample are often simply a consequence of some common history. So if we know this history (as we always do in simulations!), storing it directly is often more convenient and efficient than storing the raw haplotypes. This is the key idea behind the tree sequence data structure [1], which encodes a complete genealogy for a sample of chromosomes in a succinct set of tables.

Tree sequences offer a few benefits to population geneticists compared with traditional sequence-based file formats:

- They can store large simulated datasets extremely compactly.
- As they hold rich detail about the history of the sample, many important processes can be observed directly from the tree structure.
- They can be queried and modified extremely quickly.

2. IBD and ancestry in tree sequences

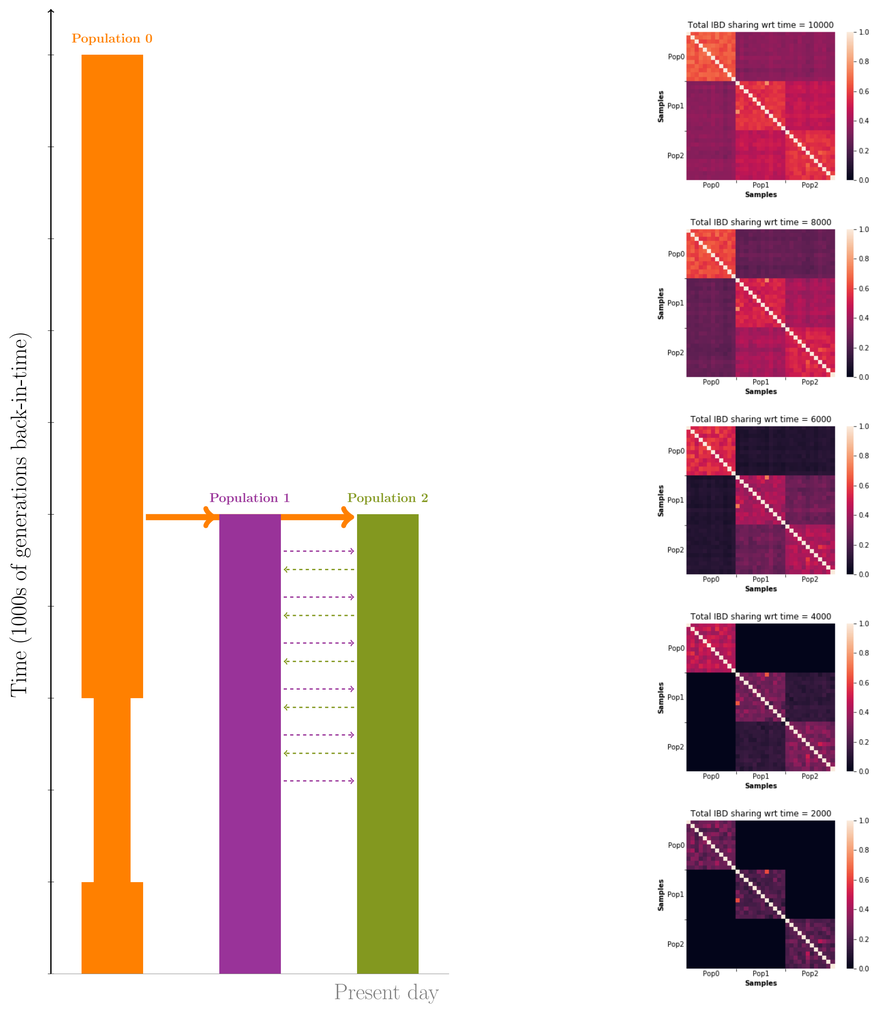


Questions about inheritance and ancestry can be reframed as questions about the underlying tree sequence that represent our datasets:

- *Identity-by-descent: which samples share a common ancestor?*
- *Local ancestry: which ancestors have what population labels, and which samples descend from them?*

Extracting this information efficiently is challenging due to correlations in genealogical structure between samples, and across chromosomes; in an upcoming paper, we will describe algorithms that allow us to do this.

3. Example: total IBD sharing over time



4. Application: demography inference

To explore the power of our method, we attempted to recreate some of the important findings from a recent study of Ashkenazi Jewish (AJ) demographic history [2]. This work provided evidence for a recent divergence event between Eastern and Western communities of AJ people. It was estimated that this happened about 15 generations ago.

Using `msprime` [1], we performed 50 000 simulations of each demographic scenario hypothesised in [2], and 20 simulations with fixed demographic parameter values that we took as the "truth". Each replicate contained 240 samples of a 100Mb chromosome with a recombination rate of 1.25×10^{-7} base/gen. For each simulation, we calculated moments of IBD segment lengths at multiple time points.

We used the `abcrf` package to infer the most plausible demographic scenario, and the `abc` package with neural-net regression to estimate parameter values.

Results: inference of demographic scenario

Posterior probability	Votes for correct model	Prior error rate
$93.36\% \pm 4.69\%$	0.9633 ± 0.0268	0.0993 ± 0.0008

Results: inference of divergence time

Mode	True value	Prior	95% HPDI
13.59	14.93	$(11.22, 19.90)$	$(11.22, 19.90)$

All simulations and analyses were completed on a standard desktop in under 12 hours.

5. Acknowledgements, references and further information

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[1] `https://tskit.readthedocs.io/en/latest/`

[2] Kelleher, J., et al. (2016). Efficient Coalescent Simulation and Genealogical Analysis for Large Sample Sizes. PLOS Computational Biology, 12(5).

[3] Gladstein, A and Hammer, M. (2019). Substructured Population Growth in the Ashkenazi Jews Inferred with Approximate Bayesian Computation. Molecular Biology and Evolution, 36(6), 1162-1171.

[4] Raynal, L., et al. (2019). ABC random forests for Bayesian parameter inference. Bioinformatics, 35(10), 1720 - 1728.

[5] Csillery, K., et al. (2012). Abc: An R package for approximate Bayesian computation (ABC). Methods in Ecology and Evolution, 3(3), 475 - 479.

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