Efficient forwards-time simulation with ancestral recombination graphs

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Abstract

To use genomic data for inference and prediction it is often necessary to obtain whole-genome information from individual-based simulations, but the computational burden of tracking the genome of each simulated individual can be substantial. In this note we describe how to both (a) dramatically reduce this burden and (b) efficiently record the entire history of the population. We do this by simulating only those loci that may affect reproduction (those having non-neutral variants), and recording the entire history of genetic inheritance in an efficient representation of the ancestral recombination graph, on which neutral mutations can be quickly placed afterwards. *make more clear data structure was already developed? refer to 'tree sequence' by name?* The algorithm is implemented in python, and is designed to be easily used by any forwards-time simulation software.

Coalescent simulations are very helpful but require random mating and neutrality. For continuous space, polygenic selection, or detailed dissection of life history, we must use forwards-time, individual-based simulation. These are much slower due in part to carrying around neutral genotypes irrelevant to the process. Here we show how to efficiently produce and store the entire history of ancestry and recombination from an individual-based simulation, on which neutral mutations can be placed afterwards. This has the promise of making large-scale, whole-genome simulations with realistic geography and selection finally possible.

OUTLINE

1. motivate need for whole-genome fwd-time simulations; point out that we only recently have the computing power to do this
2. explain ARG: explain that for forwards-time only need selected loci as by defn all others can be put on afterwards
3. review something about msprime methods for storing/traversing tree sequence
4. describe tables and write out conditions to have valid tables
5. write down algorithm used to do simple WF simulation
6. describe simplify algorithm
7. back-of-the-envelope calculation to compare cost of tracking whole genomes versus putting mutations on ARG
8. comparison of speed with simupop, fwdpp

Introduction

perhaps some of this veers into methods rather than introduction

Since the 1980's, coalescent theory has enabled computer simulation of the results of population genetics models identical to that which would be produced by large, randomly mating populations over long periods of time without actually requiring simulation of so many generations or meioses. Coalescent theory thus had three transformative effects on population genetics: first, giving researchers better conceptual tools to describe *gene trees* and thus bringing within-population trees into better focus; second, producing analytical methods to estimate parameters of interest from genetic data (e.g. $\theta = 4N_e\mu$); and finally, providing a computationally feasible method to produce computer simulations of population genetics processes. However, these powerful advances came with substantial caveats: the backwards-in-time processes that are described by coalescent theory are only *Markovian*, and thus feasible to work with, thanks to the important assumptions of (a) random mating, and (b) neutrality. *Brief statement why this is. Also include stationarity?* Both assumptions can be side-stepped to a limited extent, and so coalescent methods are now commonly used to simulate the results of population dynamics of a collection of randomly mating populations exchanging migrants, having a small number of loci under selection. Mapping results of such models onto real species can be challenging, as these are often distributed across geographical space and may have large numbers of loci under various sorts of selection. Furthermore, the relationship between the life history of a species – fecundity and mortality schedules, allee effects, and demographic fluctuations – are all absorbed into a single compound parameter, the coalescence rate. These considerations, and increasing computational power, have led to a resurgence of interest in forwards-time, individual-based simulations.

Another critical assumption of the coalescent is that the sample size n is much smaller than the effective population size N_e. With the very large sample sizes becoming common in human genetics, this is no longer a safe assumption. For example, a recent study [Martin et al., 2017] simulated 600,000 samples of human chromosome 20 to assess the impact of European biased reference panels in genome wide association studies. While many results of the coalescent are surprisingly robust to violations of the assumption that $n \ll N$, there are instances where genealogical properties are distorted and coalescent simulations may be misleading [Wakeley and Takahashi, 2003, Maruvka et al., 2011, Bhaskar et al., 2014]. A hybrid approach, in which the recent history of a large sample of individuals is simulated under a detailed forwards-in-time model and the deep history under the coalescent, is an attractive prospect. *Not sure where this should go; perhaps in the discussion? We can make the point that by keeping track of the genealogies forwards in time we can easily combine these with the deep history simulated by msprime*

With modern computing power, pure demographic calculations are not a barrier, even though biological population sizes are often above 10^6, and coalescent theory tells us that a population of size N must be run for a multiple of N generations to produce stable genetic patterns. However, if our interest lies in the resulting genetic patterns of variation – and often, the point of such simulations is to compare to real data – then such simulations must somehow produce at the end data for each individual on a genomic scale. As samples of most species genomes harbor tens or hundreds of millions of variant sites, naively carrying full genotypes for even modest numbers of individuals through a simulation becomes quickly prohibitive.

However, it is thought that much of that variation is selectively neutral (or nearly so). By definition, the alleles carried by individuals in a population at neutral sites do not affect the population process. For this reason, if one records the entire genealogical history of a population over the course of a simulation, one can lay down neutral mutations on top of that history afterwards, without loss of generality. Precisely, we would need to know the genealogical tree relating all sampled individuals at each position along the genome. In this paper, we show how to use algorithmic tools and data structures developed for the coalescent simulator `msprime` to efficiently record, and later process, this history.

In so doing we record the *population pedigree* – the entire history of parent-offspring relationships of an entire population going back to a remote time – as well as information encoding the genetic outcomes of each ancestral meiosis – who inherited which parts of which parental chromosomes. This embellished pedigree contains all the information necessary to construct the genealogical tree that relates each individual to each other at each position on the genome, i.e., the *tree sequence*. Combined with ancestral genotypes and the origins of new mutations, it also completely specifies the genomic sequence of any individual in the

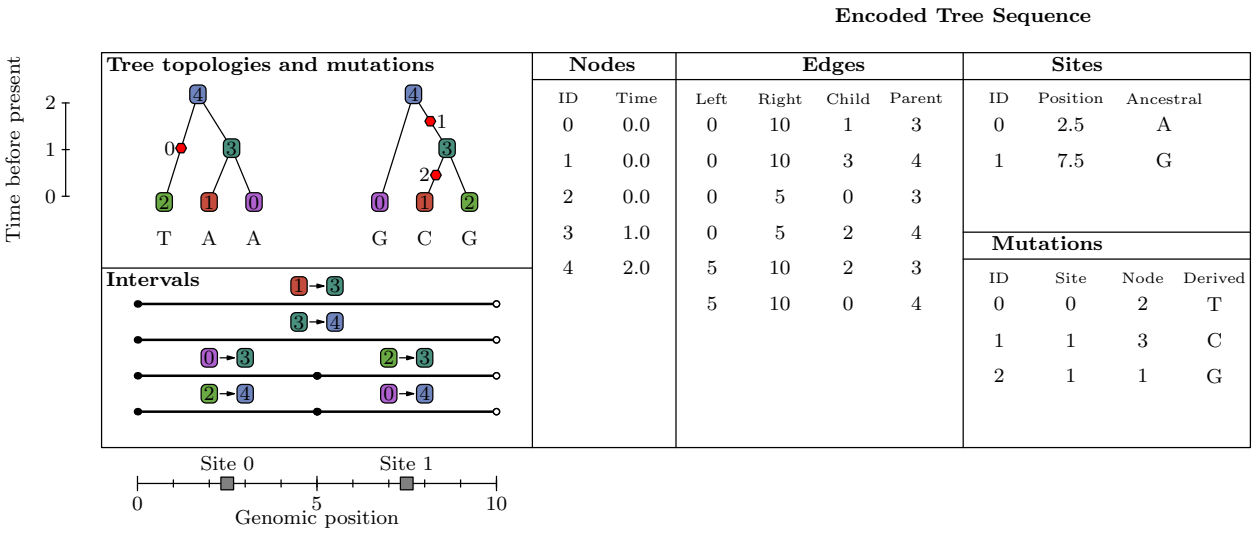


Figure 1: An example tree sequence with three samples over a chromosome of length 10. In the left-most panel we show the tree sequence pictorially in two different ways: in the top are the tree topologies and the bottom shows the spatial extent of the edges that define these topologies. The right-hand panels show the specific encoding of this tree sequence in the four tables (nodes, edges, sites and mutations) defined by `msprime`. *Some minor alignment issues present here.*

population at any time. This is much more than we need to know, however, so we discard all information irrelevant to the genetic history of the *sampled* individuals, which results in considerable savings.

Another way of representing this same information is known as the *ancestral recombination graph*, or ARG [Griffiths and Marjoram, 1997], which has been the subject of substantial study under the assumptions of coalescent theory [Wiuf and Hein, 1997, 1999, Marjoram and Wall, 2006, Wilton et al., 2015].

Methods

Reminder of what we need to know in the end (the trees), and quick review of `msprime` *methods: sparse trees, tree differences.*

Tree sequences

A tree sequence is an efficient encoding for a sequence of correlated trees such as is produced by recombination. The encoding is efficient because branches that are shared by adjacent trees are stored once, rather than repeatedly for each tree. The topology of a tree sequence is defined via a set of *nodes* and *edges*. A node in a tree sequence refers to a distinct ancestor and corresponds to the vertices in the individual genealogies along the sequence. Since each node represents a specific ancestor, it has a unique "time", thought of as her birth time, which determines the height of any vertices she is associated with. In the example of Figure 1 we have a total of five nodes. Nodes 0, 1 and 2 occur at time 0 and are our samples. Nodes 3 and 4 represent the ancestors of these samples, and were born at time 1.5 and 2.5 respectively.

The topology of a tree sequence is defined by the *edges* which define how nodes relate to each other over specific genomic intervals. Each edge is a tuple (ℓ, r, p, c), where $[\ell, r)$ is a half-open genomic interval defining the spatial extend of the edge; p and c are the parent and child nodes specifying a single branch in the tree over this interval. The spatial extent of the edges defining the topology of Figure 1 in the bottom left panel. For example, the branch joining nodes 1 to 3 is shared in both trees, and is recorded in a single

edge extending over the whole chromosome. It is this method of capturing the shared structure between adjacent trees that makes the tree sequence encoding very compact and algorithmically efficient.

Recovering the sequence of trees from a collection of edges is straightforward: each point along the genome that the tree topology changes is accompanied by the end of some *edges* and the beginning of others. Since each *edge* records the genomic interval over which a given node inherits from a particular ancestor, to construct the tree at a certain point in the genome we need only retrieve all edges overlapping that point and construct the corresponding edges. To construct the tree at a nearby location, we need only remove those edges whose intervals do not overlap that location, and add those new edges whose intervals do. Incidentally, this property that edges naturally encode *differences* between nearby trees (e.g., as "subtree prune and regraft" moves) allows for efficient algorithms that take advantage of the highly correlated nature of nearby trees.

Given the topology defined by the nodes and edges, *sites* and *mutations* encode the sequence information for each sample in an efficient way. Each site is associated with a position on the genome and an ancestral state. For example, in Figure 1 we have two sites, one at position 2 and ancestral state 'A' and the other at position 7 with ancestral state 'G'. If no mutations occur, all samples inherit the ancestral state at a given site. A mutation occurs over a specific node at a given site, and results in a specific derived state. Thus, all samples below the mutation node in the tree will inherit this state (unless further mutations are encountered). Three mutations are shown in Figure 1, illustrated by red hexagons. The first mutation occurs at site zero (which is in the left-hand tree), which is a simple mutation resulting in node 2 inheriting the state 'T'. The second side (in the right hand tree) has two mutations: one occurring over node 3 changing the state to 'C' and a back mutation over node 1 changing the state to 'G'.

This encoding of a sequence of trees and accompanying mutational information is very concise. To illustrate this, we ran a simulation of $500,000$ samples of a 200 megabase human-like chromosome ($N_e = 10^4$ and per-base mutation and recombination rates of 10^{-8} per generation) using `msprime`. This resulted in about 1 million distinct marginal trees and 1.1 million infinite-sites mutations. The HDF5 file encoding the nodes, edges, sites and mutations (as described above) for this simulation consumed 157MiB of storage space. Using the `msprime` Python API, the time required to load this file into memory was around 1.5 seconds, and the time required to iterate over all 1 million tree was 2.7 seconds. In contrast, recording the topological information in Newick format would require around 20 TiB and storing the genotype information in VCF would require about 1 TiB. Working with either the Newick or VCF encoding of this dataset would be exceedingly cumbersome, likely requiring several days of CPU time simply to read the information info memory.

Recording the pedigree in forwards time

To record the genealogical history of a forwards in time simulation we need to record two things for each new chromosome: the birth time, and the endpoints and parental IDs of each distinctly inherited segment. For concreteness, here we write out in pseudocode how to run a neutral Wright–Fisher simulation with overlapping generations that records genealogical history in this way. The simulation will run for T generations, and has N haploid individuals, each carrying a single chromosome of length L. For simplicity we assume there is exactly one crossover per generation. The probability of death per individual each generation is δ.

Let $\mathcal{R}_U(A)$ to be an element of the set A chosen uniformly at random (note that each instance of $\mathcal{R}_U(A)$ within an algorithm listing represents an independent draw from the set A).

Algorithm W. (*Forwards-time tree sequence*). Runs a forwards time Wright–Fisher simulation of a populations with N individuals with a probability of death per generation δ and a chromosome of length L for T generations. On termination, there will be n nodes with times recorded in the vector τ, and E will contain a set of (ℓ, r, p, c) tuples describing the recorded edges.

W1. [Initialisation.] For $0 \leq j < N$, set $P_j \leftarrow j$ and $\tau_j \leftarrow T$. Set $E \leftarrow \emptyset$, $t \leftarrow T$ and $n \leftarrow N$.

W2. [Generation loop.] If $t = 0$ terminate. Set $P'_j \leftarrow P_j$ for $0 \leq j < N$ and then set $t \leftarrow t - 1$ and $j \leftarrow 0$.

W3. [Individual loop.] If $j = N$ set $P \leftarrow P'$ and go to W2.

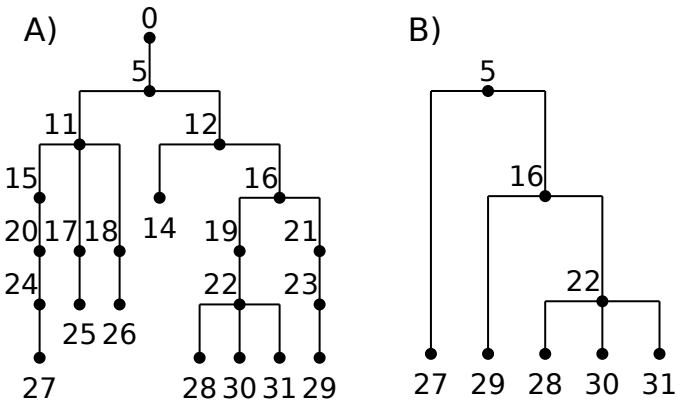


Figure 2: An example of a marginal genealogy from a Wright-Fisher simulation with $N = 5$. On the left we have the original tree including all intermediate nodes and dead-ends. On the right we have the minimal tree relating all of the currently-alive individuals (27–31). *This figure needs a little tidying up. We should combine the two SVGs into a single image with some (a) (b) annotations. Also the node labels are poorly aligned. The SVGs are generated by the sims/wf-figures.py.*

W4. [Mortality.] If $\mathcal{R}_U([0,1)) \geq \delta$ go to W8.

W5. [New node.] Set $P'_j \leftarrow n$ and $\tau_n \leftarrow t$.

W6. [Choose parents.] Set $a \leftarrow \mathcal{R}_U(\{0,\ldots,N-1\})$, $b \leftarrow \mathcal{R}_U(\{0,\ldots,N-1\})$ and $x \leftarrow \mathcal{R}_U([0,L))$.

W7. [Record edges] Set $E \leftarrow E \cup \{(0,x,P_a,n),(x,L,P_b,n)\}$ and $n \leftarrow n+1$.

W8. [Loop tail] Set $j \leftarrow j+1$ and go to W3.

I haven't checked this carefully. If we used 1-based indexes it might make things a bit simpler.

Algorithm W is a very simple implementation of a Wright–Fisher model intended to illustrate how we can record the nodes and edges of a tree sequence forwards in time. We begin in W1 by allocating our initial population P and creating N nodes with birth time T generations ago, recorded in the vector τ. The set E is used to store the edges that we output during the simulation, and n is the number of nodes created so far (and so, the ID of the next node we create). Steps W2 and W3 simply loop over the generation clock t and individual index j. In W4 we check if an individual P_j has died in this generation. If it has, we replace it in steps W5–W7; if not, we proceed immediately to the next individual. When an individual in the population dies, we first allocate a new node with ID n in W5 and record its birth time. Then, in step W6 we choose two indexes a and b uniformly (giving us parents P_a and P_b) and choose a breakpoint x. We record the effects of this event by storing two new edges: one recording that the parent of node n from 0 to x is P_a, and another recording that the parent of n from x to L is P_b. We then complete the replacement event by incrementing n, ready to represent the next new node.

This algorithm records only the topological information resulting from the forwards in time Wright-Fisher process, but it is straightforward to add mutational information. This can be done in two different ways. We can record mutations that occur during the simulation quite simply. For example, in Algorithm W we would generate mutations after we have recorded the edges joining the new node n to its parents P_a and P_b in step W7. For example, if we assume that infinite sites mutations occur at rate μ per generation then there are Poisson $((r-\ell)(\tau_p - \tau_c))$ mutations on each edge (ℓ, r, p, c). Each of these mutations will occur on a distinct site x drawn uniformly from $(\ell, r]$ and be over node c. It is straightforward to record this information during the simulation, but it is significantly simpler and more efficient to generate these mutations after the simulation has completed. In the case of infinite sites mutations there is no difference between generating these mutations during the forwards in time simulation and after it has completed. We are using precisely the same information.

It is significantly more efficient to generate mutations as a separate process after the topological simulation has completed because we will generate many mutations that will be lost in the population. Figure 2 shows an example of a marginal genealogy produced by a forwards-time Wright-Fisher process like Algorithm W. There are two different trees in this figure: one shows all the edges output by the simulation and the other is the minimal tree representing the ancestry of the currently alive population. Clearly there is a great deal of redundancy in the topological information output by the simulation.

There are two sources of redundancy here. The first type of redundancy arises from nodes in tree that have only one child. In Algorithm W we do not attempt to track coalescence events but simply record all parent-child relationships in the history of the population. As such, my of these edges will record the simple passing of genealogical information from parent to child and only some small subset will correspond to coalesences within the marginal trees. The second source of redundancy in the output of Algorithm W is due to the fact that lineages die out: there will be a large number of individuals in the simulation that leave no ancestors in the present day population. Node 26 in Figure 2a, for example, leaves no ancestors in the current population and so the entire path tracing back to the root is redundant.

One of the reasons that it is more efficient to generate mutations on the genealogies after we have completed the forwards in time simulation is because we avoid the cost of generating mutations on these dead-end branches. It is only with the benefit of hindsight that we can know which lineages end up being ancestral to the sample, and we can avoid a substantial cost of generating and maintaining mutational information on these evolutionary dead-ends. Assuming mutations are rare, another reason that it is more efficient to place mutations on the trees afterwards is that we have far fewer edges in the trees: because we have removed all the intermediate 'unary' nodes, we have fewer edges to generate mutations on.

There are many advantages to having minimal genealogies such as show in Figure 2. Computing this minimal representation of the edges output by a forward-time simulation is an instance of a more general problem that we refer to as 'tree sequence simplification'. We discuss this problem and an efficient solution in the next subsection.

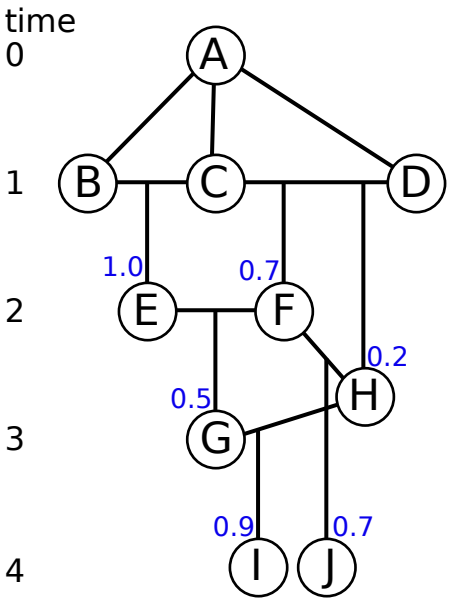
Tree sequence simplification

Suppose we have a tree sequence consisting of a set of nodes and edges as described earlier, and we have some subset of the nodes in this tree sequence that we are interested in (our 'samples'). We wish to reduce the input tree sequence into the minimum representation of the topologies that include the specified samples. The output tree sequence must have the following properties:

1. we must have the same marginal trees with respect to the samples as the input;
2. within the marginal trees, all non-sample vertices must has at least two children (i.e., unary tree vertices are removed);
3. any nodes and edges not reachable from the sampled nodes are removed;
4. there are no adjacent redundant edges, i.e, pairs of edges (ℓ, x, p, c) and (x, r, p, c) which can be represented with a single edge (ℓ, r, p, c).

In the current context of running forwards in time simulations, the tables of nodes and edges that we record all of history for everyone alive at any time through the simulation. This is much more than we need to reconstruct the genealogies and sequences of the current day population. We can use the process of simplification here to reduce this down to the minimal set of nodes and edges required to represent the information that we are interested in. We can also use simplification if we have some very large tree sequence representing a large dataset and we wish to extract the information relevant to a subset of the samples.

Roughly, simplification works by tracing ancestry from the samples backwards through the recorded history, adding node and edge records to the output only when coalescent events are reached. This works exactly as in `msprime`, allowing substantial re-use of algorithms; the main difference being that parental choice, mutations, and recombination locations are determined by the input tree sequence rather than randomly generated. An example is shown in Figure 3.

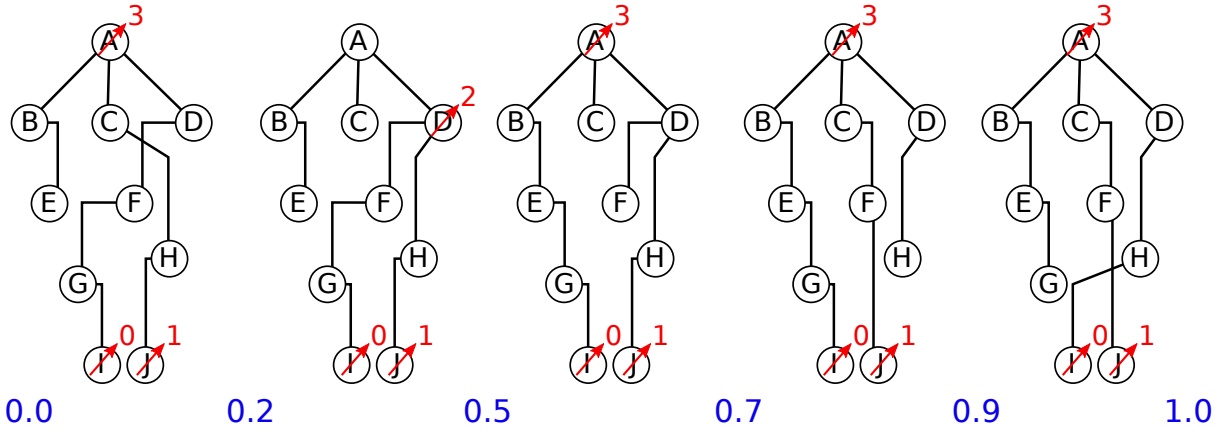


Nodes:

label	time
A	0
B	1
C	1
D	1
E	2
F	2
G	3
H	3
I	4
J	4

Edgesets:

left	right	parent	child
0.0	1.0	A	B
0.0	1.0	A	C
0.0	1.0	A	D
0.0	1.0	B	E
0.0	0.7	D	F
0.7	1.0	C	F
0.0	0.5	F	G
0.5	1.0	E	G
0.0	0.2	C	H
0.2	1.0	D	H
0.0	0.9	G	I
0.9	1.0	H	I
0.0	0.7	H	J
0.7	1.0	G	J



Simplified for I,J:

Nodes:

	label	time ago
I	0	0
J	1	0
D	2	3
A	3	4

Edgesets:

left	right	parent	children
0.0	0.2	3	0,1
0.2	0.5	2	0,1
0.5	1.0	3	0,1

Figure 3: A simple example of the method. **Top:** the diagram on the left relates ten haploid individuals to each other. It is recorded, in forwards time, in 10 node records (one for each individual) and 14 edge records (one for each distinctly inherited segment). Blue numbers denote crossing over locations in each meiosis. The individuals B, C, and D inherit clonally from A. **Center:** the five distinct trees relating all individuals to each other found across the chromosome (blue numbers denote locations on the chromosome). Labels after simplification are shown in red. **Bottom:** tables recording the tree sequence after simplification with nodes I and J as samples. The mapping from labels in the forwards time simulation to nodes in the tree sequence is shown in red, which allows additional records to be added as the simulation progresses.

The approach that we take is based on Hudson's algorithm for simulating the coalescent with recombination [Hudson, 1983, Kelleher et al., 2016]. The main state of the algorithm is a set of ancestral segments; each segment (ℓ, r, u) represents a tract of ancestral material in which the node u is associated with the genomic interval $[\ell, r)$. In the same manner as Hudson's algorithm, we represent the set of extant lineages as a set of individuals, where each ancestral individual is composed of a linked list of these segments. The node u in each ancestral sequence is the node ID associated with this segment in the output tree sequence. We maintain a map A such that A_j is segment chain for node j in the input tree sequence.

I'm not sure this is the right level of detail to tackle this description at. What's the goal of this algorithm description? Are we trying to establish some properties of the algorithm or just give the reader a high-level flavour of how it works??

In this scheme, at any point in the simulation genealogical history is recorded in a tree sequence. This has two additional advantages. First, simplification can be run periodically through the simulation, taking the set of samples to be the entire currently alive population. This is important as it keeps memory usage from growing linearly (and quickly) with time. Second, the simulation can be *begun* with a tree sequence produced by some other method – for instance, by a coalescent simulation with `msprime`. This allows for incorporation of deep-time history beyond the reach of individual-based simulations. Since geographic structure from times longer ago than the mixing time of migration across the range has limited effect on modern genealogies [**?**] (other than possibly changing effective population size **?**), this may not negatively affect realism.

Overview of the API

The `msprime` Python API provides a powerful platform for working with tree topology and mutation data. We refer to the part of `msprime` that is dedicated to tree sequence input and output as the 'Tables API', as the API is organised around simple tables of data. There are four key tables: nodes, edges, sites and mutations. Briefly, nodes and edges define the topology of a tree sequence (as defined above) and the sites and mutations define mutational processes on this topology. Figure 1 gives an informal depiction of this encoding in terms of these tables.

The tables API is primarily designed to facilitate efficient interchange of data between programs or between different modules of the same program. Following the current best-practises [citations: apache arrow, etc] data is stored in a columnar format. There are many advantages to this approach, but the principle advantage for our purposes is that it allows for very efficient interchange of large amounts of numerical data. In principle, this enables zero-copy semantics, where a data consumer can read the information directly from the memory of a producer without incurring the overhead of a copy [citation?] Our implementation uses the numpy C API [citation] to efficiently copy data from Python into the low-level C library used to manipulate tree sequences.

The tables API provides basic input and output operations via the numpy array interface, which provides a great deal of flexibility as well as efficiently. This makes transferring data from various sources such as HDF5 [citation], Dask, Zarr etc, straightforward. (For small scale data and debugging purposes, a simple text format is also supported.) Along with these operations we also provide a function to sort a set of tables to ensure that the records are in the form required to input into an `msprime` tree sequence object. The `simplify_tables` function implements tree sequence simplification, as described in the previous subsection.

This interchange API is very efficient. [Describe a quick example where we generate a many-gigabyte tree sequence using fwdpp, and the time required to copy the node and edge data into the tables]. By using a simple numerical encoding of tree topologies and contiguous arrays of data to store this encoding, we can achieve data transfer rates that would be impossible under any text-based approach while retaining excellent portability.

Results

Estimates of run-time complexity Suppose that we wish to run a forwards-time simulation of N individuals for T generations, in which there are S selected loci and L neutral loci using a similar method to Algorithm W.

We will estimate run-time complexity and memory usage for both a "naive" strategy that carries along neutral loci and an "ancestry-tracking" strategy like that we consider here. To do this, we assume that each individual must carry along its entire genotype. More advanced schemes are used in some simulators, but these increase efficiency by utilizing redundancy introduced by shared ancestry, which is effectively an intermediate scheme. We omit the cost of computing a fitness function.

Both schemes must choose mates and recombination breakpoints, and pass on selected genotypes. The difference between the two comes from the tradeoff between (a) passing on neutral genotypes, and (b) recording and simplifying the tree sequence, and adding neutral genotypes afterwards. (We assume here that selected genotypes are stored in the same way for both.) Passing on neutral genotypes naively records L items per individual each generation, discarding the previous generation, giving an overall complexity of $O((L+S)NT)$. Tracking the S selected loci and recording a tree sequence using Algorithm W requires $O(SNT)$ time and space, since we record at most two edges for each individual in each generation. However, after simplification the tree sequence contains $O(??)$ edges since []. The cost of generating L neutral mutations is then $O(L+??)$. Assuming that N, T and L are large, this is very much smaller than the straightforward $O((L+S)NT)$ time required to simulate all mutations directly.

Not sure where ρ comes in here now. Thinking about this, shouldn't we be able to come up with some expression for the number of edges? Assuming the very simple single breakpoint per generation of Alg W, what is the expected number of breakpoints? This is a function of N and T, right? It's not clear to me how many breakpoints this ends up giving you in the output tree sequence and how many edges this corresponds to. It's probably worthwhile thinking about this a bit.

Comparison of simulation with/without msprime, using simuPOP or maybe just a simple haploid simulation with 1000 QTL and stabilizing selection on a trait (say).

Maybe an estimate of how long *just* the ARG recording and simplification takes, so that then we can say how fast the simulator would have to be to do 10^6 whole chromosomes for 10^7 generations in a day.

Conclusion

This works great and very fast.

Having results in a tree sequence is really good downstream too: The tree sequence encoding is compact but it is also efficient to process. Many algorithms to compute statistics of interest for population genetics are naturally expressed in terms of tree topologies. For example, the pairwise nucleotide diversity π, is defined as the average number of differences between sequences in the sample. Computing π directly from observed sequence data requires $O(n^2 m)$ time, since we must compare all pairs of samples at every site. However, given the topology of the trees at every site and the locations of mutations much better algorithms are possible. Using the fact that we can count the number of samples below a given node efficiently using previously described tree sequence algorithms [Kelleher et al., 2016], the time required to compute π becomes roughly $O(n \log n + m)$. The `msprime` API provides a method to compute π among arbitrary subsets of the samples in a tree sequence, and calculating π over all 500K samples in the example above required about 1.2 seconds. *I haven't checked the analysis of computing π here and not thought about it too deeply. I guess we should also compare this with something else in order to show that this time is pretty good. We could get a subset of the sites and push the data into pylibseq maybe, or scikit-allel??*

This is a general-purpose strategy that can be applied to other methods.

All sorts of good reasons to want to have whole-genome simulations.

Acknowledgements

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Data structures:

Moved from above.

First we describe the data structures we use for recording genealogical history, as implemented in `msprime`. These derive from those described by Kelleher et al. [2016], but have been generalised and modified to remove redundancy. The tables below give the example tree sequence of Figure 4.

To clarify terminology, below a *tree* refers to a genealogical tree describing how a collection of individuals are related to each other. A *tree sequence* contains information sufficient to reconstruct the genealogical tree relating all samples to each other at any point along the genome. In the context of a tree sequence, *nodes* refer to distinct ancestors, and correspond to the vertices in the trees of a tree sequence. Since each node represents a certain ancestor, it has a unique "time", thought of as her birth time, which determines the height of any branching points she is associated with. A given node will be associated with branching points of all trees across a region if that node is the most recent common ancestor to the subtending tips across that region. This information is stored in the columns of a **Node Table**:

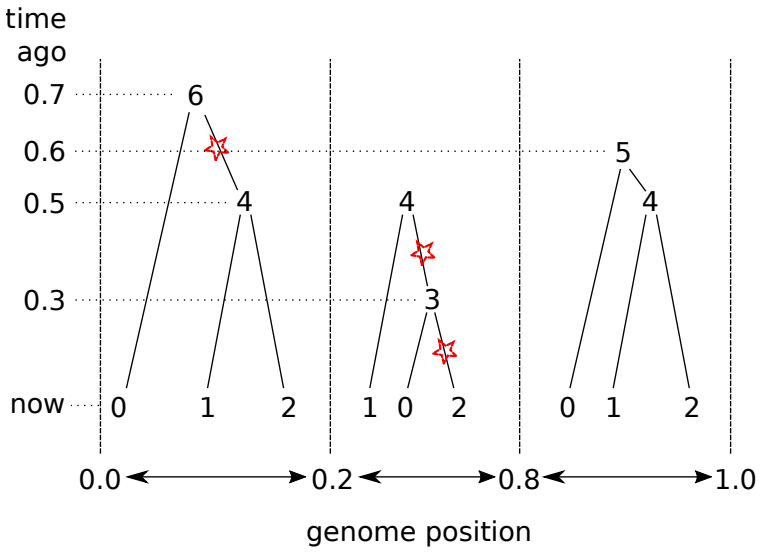

Figure 4: A pictorial representation of a tree sequence relating three samples to each other over a chromosome of length 1.0. Mutations shown in the example tables of the text are marked with red stars.

id	is_sample	population	time
0	1	0	0
1	1	0	0
2	1	0	0
3	0	0	0.3
4	0	0	0.5
5	0	0	0.6
6	0	0	0.7

where "flags" records other information (e.g., a binary mask of '1' indicates the node is a sample). Importantly, the **node ID** of a node is given implicitly by the (zero-based) index of its corresponding row in the Node Table.

Tree sequences are constructed by specifying over which segments of genome which nodes inherit from which other nodes. This information is stored by recording the endpoints of each distinctly inherited ancestral segment, the parental node, and a list of children nodes who have inherited that segment. As each such record describes a collection of edges across a swatch of trees in the tree sequence, we call these *edgesets* and store them in the columns of an **Edgeset Table:**

left	right	parent	children
0.2	0.8	3	0,2
0.0	0.2	4	1,2
0.2	0.8	4	1,3
0.8	1.0	4	1,2
0.8	1.0	5	0,4
0.0	0.2	6	0,4

To record information about genetic variants we need to also record each mutation and which nodes have inherited that mutation. The tree structure takes care of inheritance – all we need to do is to record the highest node in the tree at the mutated site that inherited that mutation. As more than one mtuation may occur at a given site, we separate this information into two tables, first, the **Site Table** records for each variant site

id	position	ancestral_state
0	0.1	0
1	0.5	0

Here "position" is a (floating point) position along the chromosome, and "ancestral state" is the genotype of the root of the tree at that site. As for nodes, **site IDs** are given implicitly by the (zero-based) index of the rows. Then, we record in a **Mutation Table**

site	node	derived_state
0	4	1
1	3	1
1	2	0

in which "site" is the ID of the site at wihch this mutation occurred, "node" is the ID of the highest node that has inherited this mutation, and "derived state" is the genotype at this site of any individuals inheriting this mutation, unless another mutation occurs.

Definition of valid tables Here are the formal requirements for a set of nodes and edgesets to make sense, and to allow "msprime"'s algorithms to work properly.

To disallow time travel and multiple inheritance:

1. Offspring must be born after their parents (and hence, no loops).
2. The set of intervals on which each individual is a child must be disjoint.

For algorithmic reasons, we also require:

3. The leftmost endpoint of each chromosome is 0.0.
4. Node times must be strictly greater than zero.
5. The list of offspring in an edgeset must be sorted.
6. Edgesets must be sorted in nondecreasing time order.
7. The set of intervals on which each individual is a parent must be disjoint.
8. Each edgeset must contain at least two children.

Note that since each node time is equal to the amount of time since the *birth* of the corresponding parent, time is measured in clock time, not in meioses.

A forwards-time simulation does **not** naturally emit genealogical information satisfying requirements 5–8. However, `msprime` implements two algorithms that will take a set of tables satisfying only 1–4 and produce tables satisfying all requirements. Trivially, `sort_tables` enforces requirements 5 and 6 and does not renumber nodes; then, `simplify` enforces requirements 7 and 8 (and does much more; see below).

A More general method for recording the pedigree

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Concretely, this is done as follows. Suppose that the forwards simulation algorithm labels (haploid) individuals by integers, which we call "input labels", to distinguish them from the "node IDs" given to these same individuals in the (output) tree sequence. The algorithm maintains at all times a set of tables (`nodes`, `edgesets`, `sites`, `mutations`) that record a relaxed tree sequence, and an associative array L that maps input labels to output node IDs, so that if x is an input label, then $L[x]$ is the corresponding output node ID. We also always maintain n to be the number of rows currently in the node table, (so that with

zero-indexed IDs, the next to be added will have node ID n), T_0 to be the time of last simplification, and n_0 the number of rows in the node table at that time.

Initially, we begin with n and n_0 equal to the number of rows in the initial node table, and $L[j] = i_j$ for each $0 \leq j < N$ if the initial input generation is labeled $i_0, \ldots, i_{N-1}$.

At a reproduction event where haploid parents x and y produce offspring u at time t in population p,

1. add a (flags $= 0$, population $= p$, time $= t$) row to the node table,
2. set $L[u] = n$,
3. and increment $n \mathrel{+}= 1$.

Then, for each interval $[\ell, r)$ that u inherits from parent z (where z is either x or y),

4. add a (left $= \ell$, right $= r$, parent $= z$, children $= (u,)$) row to the edgeset table.

If furthermore there have been mutations at genomic locations $s_1, \ldots, s_k$ on this interval, with derived states $q_1, \ldots, q_k$, then for each $1 \leq j \leq k$,

5. if s_j is not in the site table, add a row (position $= s_j$, ancestral_state $= 0$),
6. find the site index i whose position is s_j,
7. and add a row (site $= i$, node=u, derived_state $= q_j$) to the mutation table.

To **simplify** the tree sequence at time T,

1. add $T - T_0$ to each time in the first n_0 rows of the node table, and replace each remaining time t with $T - t$.

Then, pass the set of currently alive input IDs, $i_0, \ldots, i_{N-1}$ to the simplificaiton algorithm, which produces a tree sequence that has node ID j corresponding to input ID i_j for $0 \leq j < N$, and

2. empty L,
3. let $L[j] = i_j$ for $0 \leq j < N$,
4. set n to be the number of nodes in the new tree sequence and set $n_0 = n$, and finally
5. set $T_0 = T$.

Simplification keeps the tables to a managable size. Since the map L is updated to maintain the association between individuals in the simulation and nodes in the tree sequence, simplification can be run regularly, as the simulation progresses.