

Estimating Population Dynamics using Coalescent Simulations

Piyush Agarwal

Department of Mathematics, Simon Fraser University. Email: paa54@sfu.ca

January 5, 2023

Abstract

Population Dynamics describes how and why population sizes and structures have changed over time. Besides answering historical questions, they have become valuable tools in modern public health. From the past few decades, population dynamics have been inferred from relevant gene sequences using the coalescent framework. Till the turn of the century, demographic models of constant or exponential population sizes were assumed and parameters were then inferred using the coalescent. The methodology changed with the introduction of the skyline plot (Pybus, Rambaut, and Harvey 2000). Skyline plots are non-parametric estimates of population dynamics and don't require any assumed demographic model. They were further improved in the form of generalized skyline (Strimmer and Pybus 2001) and Bayesian Skyline (Drummond *et al.* 2005). Bayesian Skyline is a state of the art in inferring population dynamics but yet is limited computationally, as it cannot incorporate thousands of sequences. In this paper, we propose to incorporate thousands of sequences by using times of coalescence for large number of randomly selected pairs of sequences to identify time intervals of the underlying coalescent tree and then infer population dynamics from those intervals. We find that on simulated coalescent trees, population dynamics inferred from our methods is comparable to estimates obtained using the whole tree.

Keywords: Population Dynamics, Coalescent Theory, Skyline Estimates

1 Introduction

Population dynamics has been used as a convenient framework to answer diverse questions in biological problems. Few such questions are in epidemiology, (i) Which subtype of the Hepatitis C Virus is going to be fatal in the next decade or so (Pybus *et al.* 2001), (ii) What are the differences in the HIV epidemic growth in sub-Saharan Africa and the developed world (Walker *et al.* 2005) and; in conservation biology, (iii) Were humans responsible for the steep decline in population of the historic bison millennia ago? (Shapiro *et al.* 2004).

Information on population dynamics have been extracted from member gene sequences using methods based on coalescent theory. A point to note here is that coalescent theory talks about the effective population size instead of our well understood census population size. The effective population size (N_e) is an abstract property and is defined as the ratio of consensus size (N) to the variance in the number of off-springs for each individual in a large population. This does not aloof us from determining interesting properties about our population, as the census size being a mere scaled version has the same variation in time as the effective size. We can also compare effective sizes of different subtypes in a population and identify which subtypes are growing faster than others; growth of which subtypes have waned etc. In fact this was what Pybus *et al.* 2001 used to answer the first question, that subtype 1a of the Hepatitis C Virus has the greatest threat to public health in the coming years. The study was done in 2001, and now in 2022, subtype 1a is the most prevalent Hepatitis C virus in the developed world. Going forward, we regard effective population size as population size.

As we increase our sequencing capabilities and our gene pool increases, there is a need to improve methods of analysis to ensure maximum data utilization. Modern Methods to infer population dynamics from gene sequences start off with construction of the phylogeny (Classical Skyline from Pybus, Rambaut, and Harvey 2000, Generalized skyline from Strimmer and Pybus 2001). Bayesian Skyline from Drummond *et al.* 2005 don't require phylogenetic tree to start off but samples tree at every iteration. Phylogenetic tree construction for large number of sequences is computationally expensive and so we propose an alternative methodology to population estimation which does not require tree construction for the entire set of sequences. Given the set of sequences and a nucleotide substitution model, we sample random pairs of sequences and then estimate time for the most recent common ancestor of the pair. Doing this for a large number of pairs, we get a distribution of the time of most recent common ancestors and use it to identify coalescent event times of the underlying tree. I call this methodology as the random-pairs sampling strategy. With coalescent times available, we estimate population dynamics using a maximum likelihood approach identical to the classical skyline.

Validating this approach is a goal for the project and so instead of working with sequences, we start with coalescent trees simulated under given population dynamics. We use our random-pairs sampling strategy to reconstruct the population dynamics of the sequences manifested as tips of the trees. We apply this approach to coalescent trees generated under constant, exponential and a step-wise constant population for varying number of random-pairs, and sizes of coalescent trees. Coalescent trees are generated using MSPrime (Baumdicker *et al.* 2021), with the simulation model elaborated in the methods section. I was advised with the strategy by my supervisors and performed all the further analysis and plotting. MSPrime package was used for generating and plotting trees and for calculating time for the most common ancestor for each sampled pair.

2 Methods

2.1 Background for Simulation

The Coalescent is modeled as follows: Given a large, freely-mixing haploid population (size N) of genes with no recombination and mutation, a sample (size n) can be drawn from it at $t = 0$. Then moving backwards in time, at different times $\{u_i\}_{i=1}^{n-1}$, two genes are chosen randomly from the sample and coalesced to give the pair a common parent whereas other genes have unique parents. This continues till the most recent common ancestor of the sample. Let $u_n = 0$, then on constructing the genealogy of the sample, the tree has n lineages from $t = u_n = 0$ to $t = u_{n-1}$, and at $t = u_{n-1}$, two lineages coalesce to give a single lineage resulting in $n - 1$ lineages. The tree has $n - 1$ lineages from $t = u_{n-1}$ to $t = u_{n-2}$ and then the next coalescent event happens at $t = u_{n-2}$. This goes on till there is only one lineage in the tree at $t = u_1$. We also call this genealogy as the coalescent tree of the sample and use them interchangeably. We define $T[i]$, $2 \leq i \leq n$ as the time interval when the tree has i lineages, so $T[i] = u_{i-1} - u_i$.

Two important properties of the Coalescent are:

- The coalescence times $T[i]$ are independent and exponentially distributed with rate $\lambda = \frac{1}{N} \binom{i}{2}$
- At any coalescent event, any pair of lineages can coalesce to a single lineage. This makes all possible genealogies equally likely.
- Thus, the probability of a genealogy g is:

$$\mathbb{P}(g|T[i]) = \prod_{i=2}^n \frac{\binom{i}{2}}{N} \exp\left(-\frac{1}{N} \binom{i}{2} T[i]\right)$$

Kingman 1982 showed that a large class of population model approximates to the coalescent in the limit. I'll portray this for the Wright Fisher population model.

Under the Wright Fisher Population model, the population in every generation is constrained to have a constant size (say N_{wf}), and in every generation, all individuals die and give birth to new individuals. Suppose G_0, G_1 are two consecutive generations with G_1 being the ancestor of G_0 . Then by population size constraint we have $|G_0| = |G_1| = N_{wf}$. The model says that every member in G_0 has an independent ancestor and each member in G_1 is equally likely to be an ancestor. We now try to relate the Wright-Fisher model with the coalescent. First, pick a sample S of size n_{wf} from G_0 . Denote the probability of each member in S having unique ancestors in G_1 by P_1 , and exactly two members in S having the same ancestor by P_2 . Then we have:

$$\begin{aligned} P_1 &= \frac{N_{wf}}{N_{wf}} \frac{(N_{wf} - 1)}{N_{wf}} \frac{(N_{wf} - 2)}{N_{wf}} \dots \frac{(N_{wf} - (n_{wf} - 1))}{N_{wf}} \\ &= \prod_{i=1}^{n_{wf}-1} \left(1 - \frac{i}{N_{wf}}\right) \approx 1 - \frac{1}{N_{wf}} \binom{n_{wf}}{2} \\ P_2 &= \left(\binom{n_{wf}}{2} \frac{N_{wf}}{N_{wf}} \frac{1}{N_{wf}}\right) \frac{(N_{wf} - 1)}{N_{wf}} \dots \frac{(N_{wf} - (n_{wf} - 2))}{N_{wf}} \\ &= \left(\frac{1}{N_{wf}} \binom{n_{wf}}{2}\right) \prod_{i=1}^{n_{wf}-2} \left(1 - \frac{i}{N_{wf}}\right) \approx \frac{1}{N_{wf}} \binom{n_{wf}}{2} \end{aligned}$$

From table 1, it is evident that if $\frac{n_{wf}}{N_{wf}}$ is very small, we have $P_1 + P_2 \approx 1$ which means that at any point of time there will be no coalescence or exactly two lineages will coalesce to a common ancestor. Note that as $\frac{n_{wf}}{N_{wf}}$ becomes larger then the coalescent structure does not hold and it is possible to

Table 1. Approximation of the Wright Fisher to the Coalescent $P_1 + P_2$, (rounded off to 6 decimal places)

Gene genealogies, variation and evolution				
$n_{wf} \downarrow N_{wf} \rightarrow$	5000	50000	100000	200000
10	0.99997	1.0	1.0	1.0
20	0.999386	0.999994	0.999998	1.0
50	0.975572	0.99972	0.999929	0.999999
100	0.741931	0.995524	0.998845	0.999988
200	0.091082	0.939553	0.982835	0.999807
500	0.0	0.287985	0.645982	0.992871
1000	0.0	0.00048	0.040259	0.910099

have more than two lineages sharing a common ancestor at the same point.

Now, Probability that the first time any two members in S coalesce to a single ancestor is generation G_k is given by:

$$\mathbb{P}\{G_k \text{ is the first coalescent generation}\} = (P_1)^{k-1} P_2 = \left(1 - \frac{1}{N_{wf}} \binom{n_{wf}}{2}\right)^{k-1} \frac{1}{N_{wf}} \binom{n_{wf}}{2}$$

This tells us that the time for coalescence T is geometrically distributed and as N_{wf} increases, we can approximate it to the exponential distribution with rate $\frac{1}{N_{wf}} \binom{n_{wf}}{2}$.

2.2 Simulation of Coalescent Trees

Constant Population Size

We first simulate a coalescent tree with specified number of lineages (or tips) (n) and a constant population N . The coalescent tree is under the simplest of assumptions with no mutation, no recombination and no population structure model. Define $T[i]$ as the time interval when the coalescent tree has i lineages. The coalescent tree is simulated as follows:

1. Start with $i = n$ lineages and $t = 0$.
2. Generate an exponential random variable $T[i] \sim \exp(\lambda)$ with $\lambda = \frac{i(i-1)}{2N}$
3. Pick two lineages uniformly randomly and coalesce to get a single lineage. Assign $i = i - 1$ and $t = t + T[i]$
4. Repeat steps 2 and 3 until $i = 1$

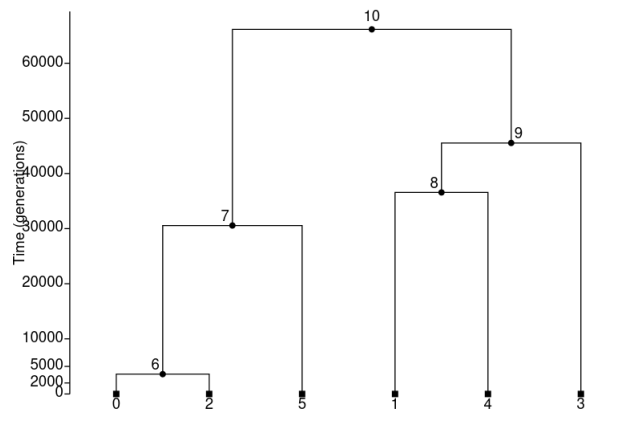


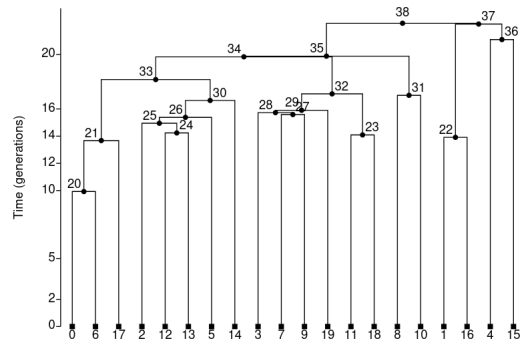
Figure 1. Simulated Coalescent Tree with $N = 100,000$ and $n = 6$

Variable Population Size (This is from Hein, Schierup, and Wiuf 2004) With Population varying with time, the time for coalescence is still exponentially distributed but with a time dependent rate. The rate depends on the previous times for coalescence and so the coalescent times $T[i]$ are no longer independent. In general if $N(t)$ is the time-dependent population size, and $t = u_k$ is the time when a coalescent event happened to give k lineages we have

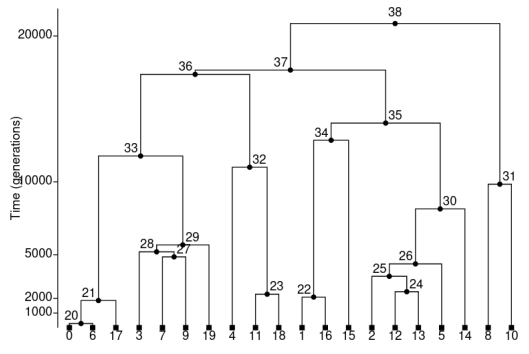
$$T[k] = (u_{k-1} - u_k) \sim \exp\left(\left(\frac{k}{2}\right) \int_{u_{k-1}}^{u_{k-1}+t} \frac{d\tau}{N(\tau)}\right)$$

Denote $\Lambda(t) = \int_0^t \frac{d\tau}{N(\tau)}$ then to simulate the Coalescent Tree, we can use the following algorithm:

1. Start with $i = n$ lineages and $t = 0$
2. Generate a uniform random variable u and solve $\Lambda(t + T[i]) - \Lambda(t) = -\frac{1}{\binom{i}{2}} \ln(u)$ for $T[i]$
3. Pick two lineages uniformly randomly and coalesce to get a single lineage. Assign $i = i - 1$ and $t = t + T[i]$
4. Repeat steps 2 and 3 until $i = 1$



(a) Samples belonging to an exponentially rising population, growth rate being 0.5



(b) Samples belonging to a population with a massive growth at $t = 10000$ generations (measured from final coalescent) from 10^4 to 10^5

Figure 2. Coalescent trees generated for variable size Population. Exponential and Step-wise

2.3 Random Sampling and Coalescent Interval Reconstruction

We use 'sim_ancestry' function under the MSPRime package in Python to generate coalescent trees. After generating the coalescent tree, the next step is to draw random pairs from the collection of tips to identify the coalescent event times. The idea is rather simple. At the moment the number of pairs we draw is: $n_pairs = \frac{n^2}{10}$ and store their time for coalescence $(t_1, t_2, \dots, t_{n_pairs})$. Note that

most of the times in this list are repeats, because a lot of pairs coalesce at the last set of coalescent events. This observation helps us to identify the last few coalescent events with high confidence. We consider that the first bar in the histogram (with each bar being just a single value) marks the last coalescent time, second bar indicates the second last coalescent event and so on. This gives us $T[i]$ required for defining the probability of the genealogy. Important to note is that as i increases the probability of missing a coalescent event increases and so we will not likely get all the coalescent intervals. After obtaining these coalescent intervals, we can then obtain an estimate of the population dynamics using different inference methods.

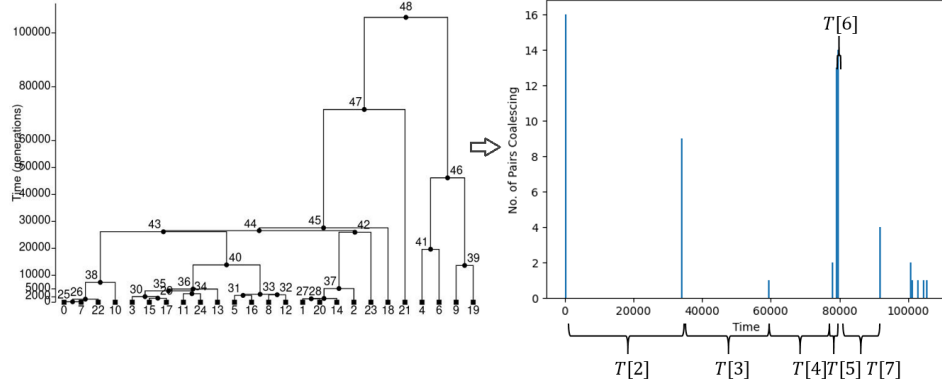


Figure 3. Left: Simulated Coalescent Tree with $N = 100,000$ and $n = 25$. Right: Histogram of the number of pairs coalescing with time ($n_pairs = 65$). Remark: Time in the right plot is calibrated such that the last coalescent event happens at $t = 0$

2.4 Constant Population Size MLE

If we assume a demographic model with a constant population size θ , we can get a maximum likelihood estimate of θ by maximizing the likelihood of θ given the coalescent tree g . Given g has times $T[i]$ when there are i lineages then we can write

$$\mathcal{L}(\theta|g) = \prod_{i=2}^n \frac{i(i-1)}{2\theta} \exp\left(-\frac{i(i-1)T[i]}{2\theta}\right)$$

Maximizing with likelihood with respect to θ gives the most likelihood estimate $\hat{\theta}$

$$\hat{\theta} = \frac{1}{n-1} \sum_{i=2}^n \left(\frac{i(i-1)}{2} T[i] \right)$$

2.5 Classical Skyline

The classical skyline is a piece-wise constant plot of population size as a function of time. It assumes that the population size only changes at the coalescent events and remains constant in between. To obtain the population sizes in between the events, a maximum likelihood approach is employed. Suppose that the coalescent tree g has population sizes $\Theta = \{\theta_i\}_{i=2}^n$ and times $T[i]$ when there are i lineages then the likelihood function is given by:

$$\mathcal{L}(\Theta|g) = \prod_{i=2}^n \frac{i(i-1)}{2\theta_i} \exp\left(-\frac{i(i-1)T[i]}{2\theta_i}\right)$$

Maximizing with likelihood with respect to Θ gives the most likelihood estimate $\hat{\Theta}$

$$\hat{\Theta} = \{\hat{\theta}_i\}_{i=2}^n = \left\{ T[i] \frac{i(i-1)}{2} \right\}_{i=2}^n$$

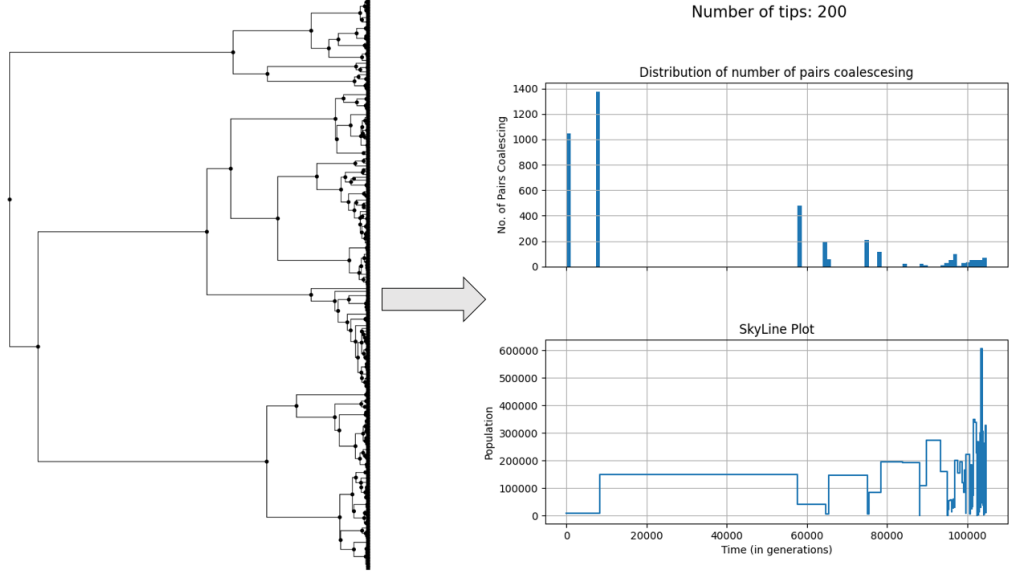


Figure 4. Left: Simulated Coalescent Tree with $N = 100,000$ and $n = 200$, Right: Histogram of the number of pairs coalescing with time and Estimated Classical Skyline Plot with $n_pairs = 4000$

3 Results

3.1 Accuracy of the Random-Pairs Sampling Strategy

First, we observe how good is the random-pairs sampling strategy in identifying coalescent events. We measure its accuracy in terms of two scores: (i) Event Score (ii) Time Score.

Event Score measures the fraction of consecutive coalescent events (starting from the final coalescent event in reverse order) the random-pairs sampling strategy correctly identifies out of all possible coalescent events ($n - 1$). Time Score measures the percentage of time in the tree spent among those correctly identified coalescent events. We observe that the method is robust in identifying the last few coalescent events, and since a large portion of the time is spent in those last events, we have a high Time Score inspite of a low Events Score.

We present accuracy scores as a function of sample size n and number of random-pairs sampled (n_pairs) in Fig 5. For both the plots, we simulated 200 trees under constant population size of $N = 100,000$ and calculated the mean, max and min statistics of the Event and Time scores for the 200 trees. In the first plot, the sample size (n) is varied, with number of random pairs being sampled satisfying $n_pairs = n^2/10$. In the second, the random-pairs sampling size is varied from $n^2/10 \leq n_pairs \leq 8n^2/10$ in steps of $n^2/10$.

In the top right plot, we see that the mean event score roughly stays the same as n increases. More significant is the top left plot which shows that the few coalescent events that are identified correctly take the majority of the time in the tree. An interesting observation is the zero time score for the first point. On further probe, I found that the zero time score was in 2 trees out of the 200 due

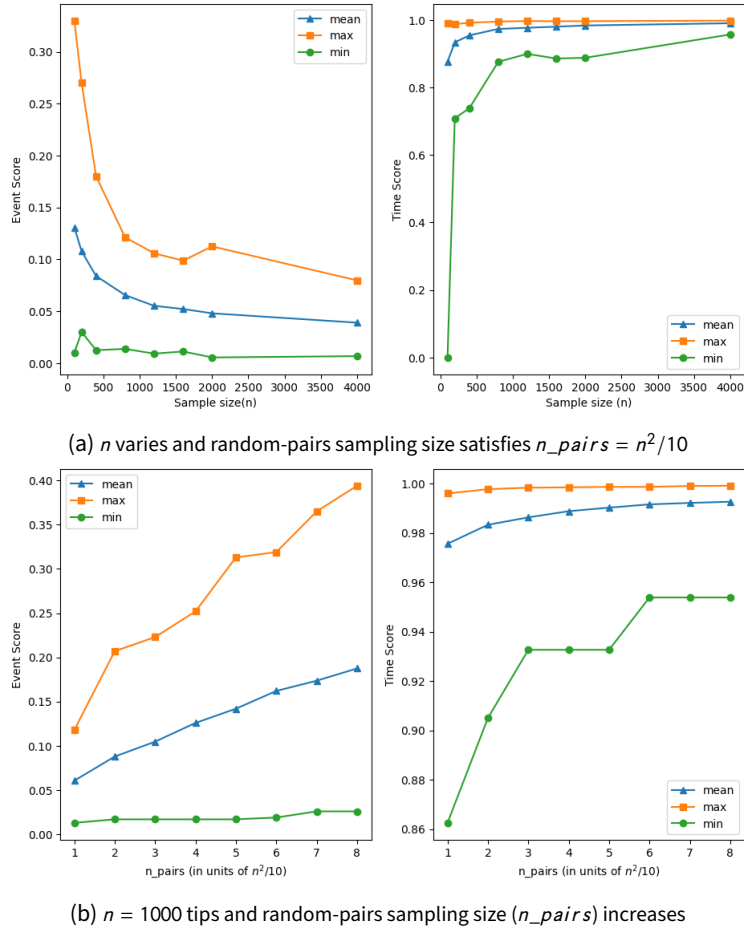
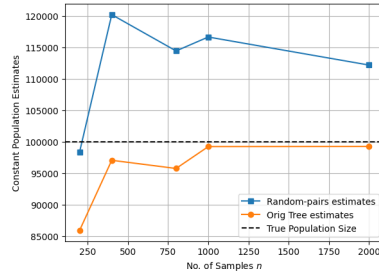


Figure 5. Acc. results for 200 sim. trees for varying sample size(n) and random-pairs sampling size(n_{pairs})

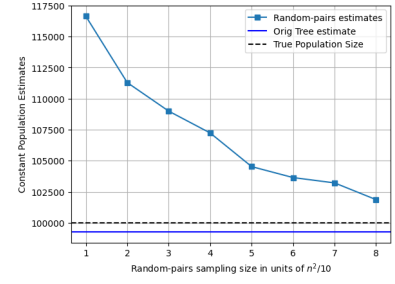
to failure in identifying the second coalescent event. The number of pairs coalescing at that event is just 2 for one of them. This presents a possible pitfall if collection of sequences are such that a lot of members are closely related and there are a few other members such that the groups coalesce at one of the last coalescent events. One possible way to mitigate is to sample more random-pairs but is not certain that it will capture the coalescent event considering that the frequency of pairs coalescing at that point is too low. The bottom plots present the fairly simpler idea of getting better results as more information is extracted. From the min curves in the event and time score bottom plots, its evident how slight improvement in event score improves time score significantly.

3.2 Population Dynamics Estimates Using Parametric Estimation (Constant Population)

We use maximum likelihood estimation as elaborated in methods to get constant population estimates. Constant population estimates for varying n and n_{pairs} are presented in Fig 6. The estimates from the true tree are closer to the random pairs strategy which is expected. This clearly shows that the random-pairs strategy is indeed an approximation to the coalescent tree and as more number of pairs are sampled, the approximation becomes better (Right sub-figure).



(a) n varies and random-pairs sampling size satisfies $n_pairs = n^2/10$



(b) $n = 1000$ tips and random-pairs sampling size (n_pairs) increases

Figure 6. Constant Population Estimates for varying sample size(n) and random-pairs sampling size(n_pairs)

3.3 Population Dynamics Estimates Using Classical Skyline

In Figures 6 and 7, classical skyline estimates of the population dynamics are presented for varying sample sizes (n) and random-pairs sampling size (n_pairs) respectively. Trees were generated under constant, exponential and step-wise constant population dynamics.

In both figures, we have a good fit between the skyline estimate constructed with our strategy and the true skyline estimate. This means that our strategy approximates the tree well in the sense of skyline estimates. The fits are perfect in the start (close to the last coalescent) which are a reflection of the last coalescent events being perfectly captured by our strategy. Fit in the end becomes increasingly better as more random-pairs are sampled (Fig 6). As evident from the plots, it is not

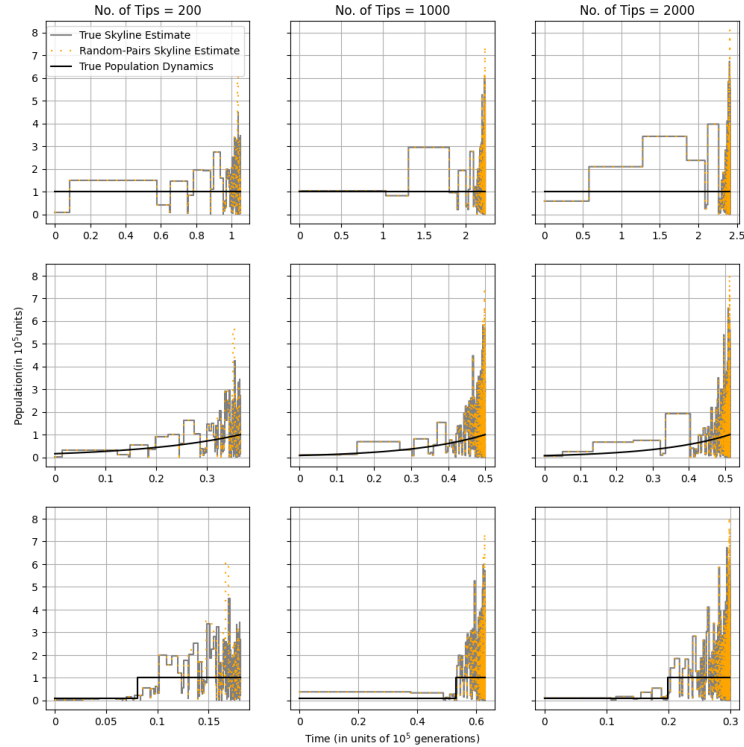


Figure 7. Comparison of True Tree Skyline estimates, Random-Pairs Sampling estimate and the true Population Dynamics for constant ($N = 10^5$), exponential ($N = 10^5, r = 10^{-5}$) and step-wise population ($N_0 = 10^5, N_1 = 10^4, T = T_{max} - 10^4$) for different n with $n_pairs = n^2/10$, T_{max} is the entire time duration

easy to infer the true population dynamics from the classical skyline estimates. Though the skyline

estimate does seem to resemble the population dynamics, they are not conclusive. If we restrict our attention to the skyline curves in the step-wise plot and exponential plots (last column) in Fig 5, it is not easy to differentiate between the two. And this was one reason why improved methods were developed especially the Bayesian Skyline Drummond *et al.* 2005.

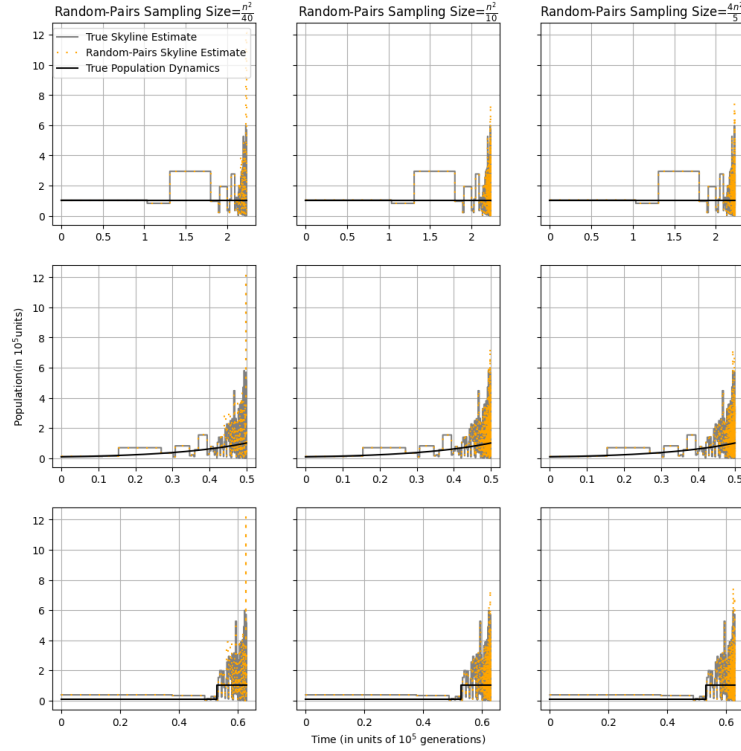


Figure 8. Number of Tips: $n = 1000$. Comparison of True Tree Skyline estimates, Random-Pair Sampling estimate and the true Population Dynamics for constant, exponential and step-wise population (same parameters as previous one) for different random-pair sampling sizes n_pairs

4 Discussion and Conclusion

We get good results from the random-pairs sampling strategy for coalescent trees. The skyline estimates and constant population estimates are comparable to the estimates from the complete tree. The coalescent tree being an extremely large space will always have pathological examples where the random-pairs strategy will not work. It becomes interesting to see how frequent these pathological examples are when trees are reconstructed from gene sequences. So the next step is to obtain pair coalescent times from actual sequences. Another challenge in this regard rises due to noise in the coalescent time for each random pair. This makes it difficult to identify the coalescent event times of the underlying tree. In this study, fixing the coalescent tree led to fixed singular values for each coalescent event but moving to sequences, we'll get distributions for each coalescent event instead of fixed single time values.

We observed large variations in the classical skyline at the end of the time period. This made it difficult to assess the fit between the two classical skylines. So the next critical step is to base the random-pairs strategy in the Bayesian framework and obtain the Bayesian skylines. Bayesian skylines are smoother estimates of population dynamics with uncertainty intervals. This will make it easier to assess the performance of the random-pairs sampling strategy with the complete

coalescent tree.

A major motivation to adopt the random sampling strategy was to make inference computationally efficient. Though it seems that the strategy is more efficient than generating and using the complete tree, and provides freedom to the user by allowing the amount of information to be extracted in the form of n_pairs but a thorough investigation on the computational aspects of the strategy is required.

5 Acknowledgement

I want to take the opportunity to thank course instructor Dr. Alexander Rutherford who believed we could make good projects and devoted a lot of time in talking and consulting us through. I am grateful to my supervisors Dr. Caroline Colijn and Dr. Cedric Chauve for providing me with the idea and guiding me all the way to completion. I also want to thank my group members for solving my doubts and housemates for their constant support.

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