Inference of Population History using Coalescent HMMs: Review and Outlook

Jeffrey P. Spence\textsuperscript{a}, Matthias Steinrücken\textsuperscript{b}, Jonathan Terhorst\textsuperscript{c}, and Yun S. Song\textsuperscript{d,e,*}

\textsuperscript{a}Computational Biology Graduate Group, University of California, Berkeley
\textsuperscript{b}Department of Ecology and Evolution, University of Chicago
\textsuperscript{c}Department of Statistics, University of Michigan
\textsuperscript{d}Computer Science Division and Department of Statistics, University of California, Berkeley
\textsuperscript{e}Chan Zuckerberg Biohub, San Francisco
*To whom correspondence should be addressed: yss@berkeley.edu

Abstract

Studying how diverse human populations are related is of historical and anthropological interest, in addition to providing a realistic null model for testing for signatures of natural selection or disease associations. Furthermore, understanding the demographic histories of other species is playing an increasingly important role in conservation genetics. A number of statistical methods have been developed to infer population demographic histories using whole-genome sequence data, with recent advances focusing on allowing for more flexible modeling choices, scaling to larger data sets, and increasing statistical power. Here we review coalescent hidden Markov models, a powerful class of population genetic inference methods that can effectively utilize linkage disequilibrium information. We highlight recent advances, give advice for practitioners, point out potential pitfalls, and present possible future research directions.

1 Introduction

Using genetic data to understand the history of a population has been a long-standing goal of population genetics \cite{1}, and the emergence of massive data sets with individuals from many populations (e.g., \cite{2–4}), often including ancient samples \cite{5}, have enabled the inference of increasingly realistic models of the genetic history of human populations, e.g., \cite{6–8}. The progress in other species is no less impressive, with demographic models inferred for dogs \cite{9}, horses, \cite{10}, pigs \cite{11}, and many others.

These demographic models are frequently of interest in their own right for historical or anthropological reasons, and failing to account for demographic history when performing tests of neutrality \cite{12}, disease associations, \cite{13}, or recombination rate inference \cite{14,15} can lead to spurious results. Demographic models also play an important role in conservation genetics, informing breeding strategies for maintaining genetic diversity in endangered populations, e.g., \cite{16}.

Yet, inferring complicated demographic models — often including multiple populations with continuous migration, admixture events, and changes in effective population size — is challenging both statistically and computationally, and numerous methods have been developed to address this problem. Even under neutral evolution, computing the likelihood of observing a set of genotypes given a demographic model is computationally and analytically intractable. Hence, demographic inference methods must make simplifying approximations and can be broadly divided into three classes: those based on allele frequencies; those based on identity-by-descent (IBD) or identity-by-state (IBS); and coalescent hidden Markov models (coalescent-HMMs).

Allele frequency-based methods summarize a collection of DNA sequence data as the multipopulation sample frequency spectrum (SFS) and use these summary statistics to infer either parametric \cite{17,21} or non-parametric \cite{22} models. For computational purposes, these methods assume that all loci are independently
evolving, an assumption obviously violated by physically-linked loci (although this has recently been relaxed
to allow pairwise dependencies [24]). This necessarily ignores the rich information contained in such linkage.
Yet, these methods tend to be very fast, with recent methods capable of scaling to data sets with hundreds of
individuals from tens of populations [21], making them ideal for quickly exploring a wide variety of potential
models (e.g., testing models with different number of admixture events). Yet, there are a number of concerns
about statistical identifiability ([24] but see [25]), power [26, 27], and stability [28].

IBD- and IBS-based methods use patterns of pairwise haplotype sharing to infer demographic models,
making the distribution of observed IBD or IBS tract lengths to the distribution expected under the
inferred demographic model. While IBD-based methods, such as [29–31], can be powerful — especially for
learning about the recent past — they rely on having access to unobserved IBD tracts. Many methods have
been developed for inferring IBD tracts [32, 33], but those methods rely either explicitly or implicitly on
the unknown demographic history of the samples, resulting in a chicken/egg problem. The effect of these
assumptions on IBD-based methods has not been thoroughly explored, although see [34]. To sidestep this
issue, [35] works directly with IBS tracts, a promising direction for further methodological development.

The final class of methods, coalescent-HMMs, is the focus of this review. Below, we provide a historical
overview of coalescent-HMMs and present a unifying framework for them. We then explore recent advances
in the field; discuss caveats, pitfalls, and best practices for applying coalescent-HMMs to data; and conclude
with open problems and promising future research directions.

2 A brief history of coalescent-HMMs

All coalescent-HMMs can trace back to the seminal work of [36]. The coalescent — a stochastic model of the
genealogy of a sample of homologous chromosomes — was first developed for a single non-recombining locus
[37] and then extended to incorporate recombination [38], but had always been thought of as a process going
backward in time. In [36] the multi-locus coalescent was viewed not as a process through time, but rather
as a process along the genome (the so-called sequential coalescent). Unfortunately, the sequential coalescent
was analytically complicated and non-Markovian (the genealogy at a locus depended on the genealogies at
all previous loci). Simpler Markovian models were later proposed (the sequentially Markovian coalescent;
SMC) [39–41] that were highly accurate approximations of the original model [42].

Under the SMC, sequence data could be viewed as coming from a hidden Markov model (HMM) [43] by
treating the genealogy of the sampled individuals at a given locus as an unobserved, latent variable. Because
the demographic model impacts the distribution of genealogies (e.g., without migration, samples from different
populations cannot have a common ancestor more recent than the divergence of those populations) and
the observed sequence data are directly dependent on the underlying genealogy, coalescent-HMM methods
have the potential to be extremely powerful. An additional benefit of coalescent-HMMs is that the HMM
framework enables integrating over all possible genealogies to make inferences about the demographic model
— even if there is substantial uncertainty about the genealogy of a given sample, the set of genealogies likely
to have given rise to that sample may be highly informative about its demographic history.

In principle, the HMM framework enables efficient inference of demographic parameters, but there are
a number of complications. First, except for very special cases (e.g., Kalman Filters [44] and iHMMs
[45]), HMM algorithms require that the state space of the latent variable be finite; this is problematic in the
coalesscent-HMM case since the genealogy at a given locus has an uncountably infinite, continuous component
(the lengths of the branches of the tree). All coalescent-HMMs work around this issue by discretizing time.
Having a finite state space is not enough for efficient inference, however, as the number of tree topologies grows
super-exponentially in the sample size, making the full coalescent-HMM impractical for all but the smallest
sample sizes. The menagerie of coalescent-HMM methods then arises by making different approximations
to this idealized coalescent-HMM: instead of keeping track of the whole genealogy of the sample as a latent
variable, these methods only track some subset of the genealogy or some of its features.

Briefly, CoalHMM [46, 47], originally developed for studying the divergence of great apes, assumes that
there is one sampled genome per species and tracks only the topology of the genealogy and the branch of the
species tree in which the lineages coalesce and cannot scale to more than a few species. PSMC [35] can be
applied only to a pair of genomes but exactly tracks their genealogy up to the discretization of time and some
simplifying approximations to the SMC. The ideas underlying PSMC were extended to handle up to tens
Figure 1: The sequentially Markovian coalescent views the genealogy relating a sample of individuals as a sequence of trees along the genome. The number of possible trees relating a sample grows super exponentially with sample size, making such a model computationally intractable for inference. The commonly used coalescent-HMMs make various simplifications to this full process. PSMC, SMC++, and ASMC only track the genealogy of a “distinguished” pair of haplotypes. PSMC ignores the rest of the sample, while SMC++ and ASMC use the other samples to inform the genealogy of the distinguished pair. ASMC was designed to work on genotype array data and so skips over sites not included on the array (middle genealogy). MSMC tracks only the most recent coalescence event in the whole sample, while diCal tracks the first coalescence event involving a particular haplotype.
of genomes in MSMC [49], which tracks only the first coalescence time and which individuals were involved in the first coalescence event. The first version of diCal [50], inspired by the copying model of [51] and the subsequent work on conditional sampling distributions (CSDs) [52, 53], considers a particular haplotype and tracks when and with which other haplotype that haplotype first coalesces, with some approximations for computational efficiency. PSMC makes the fewest simplifying assumptions, but as it can only be applied to two haplotypes it is less powerful than MSMC or diCal, especially in the recent past.

Furthermore, the different methods allow for the inference of different types of demographic models. PSMC, MSMC, and diCal v1 can all infer piece-wise constant population size histories for a single panmictic population. CoalHMM and MSMC are both capable of making inferences about multiple populations: CoalHMM fits a parametric model, directly inferring ancestral population sizes and divergence times between the populations, and MSMC performs non-parametric inference, reporting “cross-coalescence rate” curves (CCRs). While such CCRs have been interpreted in terms of divergence times [4, 49], a thorough exploration of what types of models can give rise to a particular CCR has not been performed: if the goal of a study is to fit a particular demographic model (e.g., a two population isolation migration model), the CCR curves output by MSMC can be a useful diagnostic, but are difficult to interpret and cannot replace parametric model fitting. All of the coalescent-HMMs discussed here are summarized visually in Figure 1.

3 Recent advances

In response to many of the aforementioned issues, there has been much progress in coalescent-HMM methodology. In particular, diCal version 2 allows for the parametric inference of more complex demographic models involving several populations, and SMC++ and ASMC push the boundaries of scalability for coalescent-HMMs.

Building on the first version of diCal [50] and advances to the CSD framework [54, 55], diCal v2 [56] was developed to perform parametric inference of essentially arbitrarily complex demographic models, including estimating divergence times, continuous and pulse migration, and population sizes with possible exponential growth. The method can scale to tens of haplotypes and has been tested on models with three populations, but can, in principal, handle an arbitrary number of populations (but at an increased computational cost). Like diCal v1, version 2 also considers a particular haplotype, and keeps track of when and with which other haplotype it first coalesces. Since first coalescence events tend to happen in the recent past, this makes diCal well-powered to investigate recent history, such as the peopling of the Americas [7, 57]. It is also possible to use coalescent-HMMs in a hypothesis testing framework: diCal v2 was used in [57, Supplementary Information, section 18.4] to test a null model of a clean split between two populations against a model of gene flow following that split, providing a principled and powerful technique for performing model selection and also for falsifying testable hypotheses. Furthermore, the CSD framework used by diCal v2 allows it to perform local ancestry or admixture calling, which was recently used to infer tracts of Neanderthal introgression in modern humans [58].

SMC++ [59] combines the power of SFS-based methods with the simplicity of PSMC and its lack of making assumptions beyond the SMC. SMC++ tracks the coalescence time of a single “distinguished” pair of lineages like PSMC, but then computes the likelihood of observing the sequence data of both the distinguished lineages and the rest of the sample. Like PSMC, SMC++ does not require phased data. The simplicity of the hidden state allows SMC++ to scale to sample sizes in the hundreds, which is about an order of magnitude larger than any other coalescent-HMM presented above. This in turn gives SMC++ substantial power in both the recent and ancient past. It also achieves a substantial speedup by taking advantage of the fact that genotype data contains long stretches of non-segregating loci which may be effectively “skipped over” — an idea similar in spirit to [60]. Furthermore, instead of inferring unrealistic piece-wise constant population sizes, SMC++ fits population sizes as smooth splines, reflecting a more realistic scenario of non-instantaneous population size changes. SMC++ is also capable of inferring divergence times for a pair of populations but currently makes the assumption that there has been no migration between the populations since their divergence, which may not be appropriate for some populations.

Recently, ASMC [61] has been developed to extend SMC++ to genotype array data by accounting for ascertainment bias in the frequency of alleles measured by genotyping arrays. ASMC also takes advantage of certain symmetries in computing likelihoods in the underlying HMM to obtain extremely fast runtimes
Figure 2: Performance of various coalescent-HMMs on simulated data. The scenarios considered here are: a population experiencing a sharp bottleneck; a single panmictic population of constant size; samples from a large population that is exchanging migrants with a smaller population; and a population that has recently experienced exponential growth. Each scenario has 10 replicate data sets, with each data set containing 30 haploids with eight 125 Mb chromosomes per haploid. PSMC was run with the options `-N 25 -p 4+20*3+4` on a single pair of haploids. MSMC was run with the default hyperparameter settings with the ‘fixedRecombination’ flag, using only 4 of the 30 haploids. The same 4 haploids were used for diCal v2, and inference was performed by taking the composite likelihood over all pairs of those 4 haplotypes, and running 30 EM iterations. SMC++ was run with the ‘--timepoints 33’ and ‘--thinning 500’ options.

— an idea first explored in [62]. In fact, its speed allowed ASMC to be run on all pairs of haplotypes from 113,756 phased British individuals [2] although still at considerable computational cost.

We present the results of a small simulation study in Figure 2 showing the performance of various coalescent-HMMs for a number of common demographic scenarios. The four scenarios considered were:

- A sharp bottleneck.
- Constant size ($N_e = 10^4$).
- An isolation-with-migration model involving two populations.
- Exponential growth beginning 500 generations ago.

For each scenario, we used msprime [63] to simulate 10 replicate data sets each consisting of 30 haploids with eight 125 Mb chromosomes per haploid. The code used to simulate data and infer population sizes is fully reproducible and available at https://github.com/terhorst/coal_hmm_review.

4 Caveats, pitfalls, and best practices

Despite their power and flexibility, coalescent-HMMs are not without their pitfalls. All coalescent-HMMs contain tuning parameters that are crucial for good performance. A critical factor is the way that time is
discretized. Finer discretization leads to a more accurate approximation, but the runtime of all methods is impacted by the number of discretization points so care is needed to balance computational and accuracy considerations. Additionally, all of the methods discussed above, save SMC++, group adjacent loci and assume that they have the same genealogy. This assumption helps to substantially decrease the runtime, but is certainly violated in practice. Depending on the method and application, it may be acceptable to perform the grouping at a kb scale, but care should be taken to check that such grouping does not influence the results. Furthermore, the likelihoods optimized by coalescent-HMMs—and demographic inference methods more broadly—tend to be highly non-convex: they have many local optima and so initializing the methods at different initial values will result in different inferred models. As such it is important to take the best of several runs with different initializations as the final inferred model.

Users should also be careful about the model used to fit data. As an example, SMC++ infers population splits in the absence of gene flow. If there has been pervasive migration between the populations of interest, then the model inferred by SMC++ is unlikely to be reflective of reality. Also, note that even seemingly non-parametric methods, like PSMC, make implicit assumptions such as the data coming from a single panmictic population that has been evolving neutrally. Recent studies [64, 65] used simulated data to investigate these model violations and showed that pervasive selective sweeps or structured populations bias the results of coalescent-HMMs. Another study [66] showed that when applied to simulated data, coalescent-HMMs infer models that have an expected SFS similar to that of the data, but when applied to real data the SFS of the inferred models does not match that of the data. This suggests that real data violate the idealized models that are commonly used for simulation and inference.

We also urge caution in over-interpreting the results of any demographic inference method. For instance, all methods infer “effective population sizes”, which are defined as the inverse of the coalescence rate for a pair of haplotypes. Under many models effective population size is correlated with census population size, but does not need to be; e.g., a structured population will have a larger effective size than a panmictic population of the same census size.

To avoid the aforementioned pitfalls, we recommend using multiple methods utilizing different aspects of the data, such as frequency-based methods and coalescent-HMMs. While the exact models inferred by different methods will differ, one can have some confidence in aspects of the model that are robustly inferred across methods. We also recommend using the results of either a pilot run of the coalescent-HMM or the results of another method (or even PCA [67] [68], or STRUCTURE-like programs [69] [72]) to inform model selection — e.g., if the data appear to come from unadmixed populations based on this initial fit, it may be appropriate to assume a clean split model instead of modeling gene flow. After fitting a model, it is crucial to measure goodness-of-fit, for example by comparing the SFS and MSMC’s CCR curves for data simulated from the inferred models to those computed directly from the real data.

It is also important to understand sources of bias and noise present in data. Because most coalescent-HMMs make use of both segregating and non-segregating sites it is crucial to use “masks” that indicate which regions of the genome have been reliably genotyped. Additionally, when working with ancient DNA, which tends to show an excess of transitions due to postmortem cytosine deamination [73], we have found that restricting analysis to only transversions and adjusting the mutation rate correspondingly improves inference.

Finally, as with any statistical analysis, it is important to study uncertainty in the inferred model, e.g., by bootstrapping, either parametric via simulation or non-parametric by resampling the data as in [48]. While parametric bootstrapping is more straightforward, it is only capable of estimating uncertainty in the estimation procedure, whereas non-parametric bootstrapping captures uncertainty in both modeling and estimation, but cannot reveal bias in the estimates. Note that in demographic inference, bootstrapping does not produce statistically valid confidence intervals due to using the data to perform model selection prior to estimating statistical uncertainty, but providing some quantification of uncertainty is still important.

5 Outlook

While there has been much recent work on improving the flexibility, and computational and statistical efficiency of coalescent-HMMs, there are still a number of open problems and interesting directions for future research.
As alluded to above, when the sample size is greater than 2, every coalescent-HMM treats only a part of the whole genealogy relating the sample as a latent variable. Such choices are made primarily for analytic convenience to ensure computational tractability, based on intuition. Tree length has recently been explored as such a choice \cite{74}. Finding more optimal ways of modeling genealogical information using a small number of discrete parameters remains a challenging open problem.

While coalescent-HMMs work extremely well on simulated data, they, like most inference methods in population genetics, seem to be less stable on real data \cite{66}. This is likely due to rampant model misspecifications: coalescent-HMMs make many unrealistic assumptions, such as assuming constant recombination \cite{75, 76} and mutation \cite{77–79} rates across the genome. In addition, all methods must simplify the “true” demographic model: reality is always more complicated than any model with a handful of parameters. The impact of these misspecifications has not been thoroughly explored, and there is a need for more robust methods.

A major challenge, especially in studying non-model organisms, is that with the exception of PSMC and SMC++\cite{5}, coalescent-HMMs are currently unable to handle unphased data. Overcoming this challenge is an important task for future methods.

Lastly, despite their excellent behavior in practice, our understanding of coalescent-HMMs is based entirely on intuition and numerical experiments. In contrast to frequency-based methods, which have a rich literature on their theoretical properties \cite{24–28}, coalescent-HMMs are poorly understood from a theoretical perspective. While there has been some work on how accurately demographic history can be inferred directly from genealogies \cite{80, 81}, in the more realistic coalescent-HMM setting even the basic question of whether demographic models are statistically identifiable is unanswered.

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