Inference of population splits and mixtures from genome-wide allele frequency data

Joseph K. Pickrell[1,3,†], Jonathan K. Pritchard[1,2,†]

[1] Department of Human Genetics and

[2] Howard Hughes Medical Institute, University of Chicago

[3] Current address: Department of Genetics, Harvard Medical School

† To whom correspondence should be addressed: joseph_pickrell@hms.harvard.edu, pritch@uchicago.edu

March 1, 2012

Abstract

Many aspects of the historical relationships between populations in a species are reflected in genetic data. Inferring these relationships from genetic data, however, remains a challenging task. In this paper, we present a statistical model for inferring the patterns of population splits and mixtures in multiple populations. In this model, the sampled populations in a species are related to their common ancestor through a graph of ancestral populations. Using genome-wide allele frequency data and a Gaussian approximation to genetic drift, we infer the structure of this graph. We applied this method to a set of 55 human populations and a set of 82 dog breeds and wild canids. In both species, we show that a simple bifurcating tree does not fully describe the data; in contrast, we infer many migration events. While some of the migration events that we find have been detected previously, many have not. For example, in the human data we infer that Cambodians trace approximately 16% of their ancestry to a population ancestral to other extant East Asian populations. In the dog data, we infer that both the boxer and basenji trace a considerable fraction of their ancestry (9% and 25%, respectively) to wolves subsequent to domestication, and that East Asian toy breeds (the Shih Tzu and the Pekingese) result from admixture between modern toy breeds and "ancient" Asian breeds. Software implementing the model described here, called *TreeMix*, is available at `http://treemix.googlecode.com`.

Introduction

The extant populations in a species result from an often-complex demographic history, involving population splits, gene flow, and changes in population size. It has long been recognized that genetic data can be used to learn about this history [1–3]. In humans, early approaches to inferring history from genetics were limited to using a relatively small number of blood group or other protein polymorphisms [1, 4–6]. These types of studies were then superseded by analyses of DNA markers, which have progressed from single marker studies [3] to studies involving hundreds of thousands of markers [7]. It is now feasible to collect genome-wide genetic data in any species; to a large extent it is no longer the data collection, but rather the statistical models used for analysis, that limit the historical insight possible.

There are many statistical approaches to demographic inference from genetic data. One approach is to develop an explicit population genetic model for the history of a set of populations, framed in terms of the effective population sizes of the populations, the times of population splits, the times of demographic events (such as population bottlenecks), and other relevant parameters. The values of these parameters can then be learned from the data using a variety of techniques, often involving simulation [8–16]. These approaches have the advantage of allowing flexible modeling of a wide variety of demographic scenarios, but the disadvantage that they can only be applied to one or a few populations at a time.

Another type of approach to learning about population history uses methods that summarize the major components of genetic variation in a sample by clustering or principal components analysis [17–20]. Although these methods do not model history explicitly, the inferred components can often be interpreted *post hoc* as representing historical populations, and individuals or populations that are mixtures of different components as evidence of admixture between these populations (e.g., [17, 21–23]). However, these methods are not directly informative about history; indeed, the relationship between the major components of genetic variation and true underlying demography is not always intuitive [24–26].

A different class of approaches focuses on the relationships between populations, by representing a set of populations as a bifurcating tree [1, 27–32]. In these models, the details of the demographic histories of the population are absorbed into the branch lengths of the tree [1, 33]. This approach has the advantage of being applicable to large numbers of populations; however, a major caveat when modeling the history of populations as a tree is that gene flow violates the assumptions of the model [2, 34, 35]. It is often difficult to know, *a priori*, how well the history of the populations in a species fits a simple bifurcating tree. Explicit tests for the violation of a tree model have been developed [35–39]. These tests have been used, most notably, to infer the existence of gene flow between modern and archaic humans [39–41], as well as between diverged modern human populations [37, 42, 43].

In this paper, we present a unified statistical framework for building population trees and testing for the presence of gene flow between diverged populations. In this framework, the relationship between populations is represented as a graph, allowing us to model both population splits and gene flow. Graph-based models are of growing interest in phylogenetics [44, 45], but have been rarely used in population genetics (but see Dyer et al. [46] and Reich et al. [37]).

Results

The starting point for our model was first proposed by Cavalli-Sforza and Edwards [1], and we draw additionally on related models by Nicholson et al. [33] and Coop et al. [47]. Our goal is to provide a statistical framework for inference of networks of populations that is motivated by an explicit population genetic model, but sufficiently abstract to be computationally feasible for genome-wide data from many populations (say, 10-100). Our primary aim is to represent the topology of relationships between populations, rather than the precise times of demographic events.

Our approach to this problem is to first build a maximum likelihood tree of populations. We then identify populations that are poor fits to the tree model, and model migration events involving these populations. Below, we first describe this approach in an idealized setting, and then describe the modifications necessary for implementation in practice.

Model

In the most simple case, consider a single SNP, and let the allele frequency of one of the alleles at this SNP in an ancestral population be x_A (we use a lowercase x to denote that this is a parameter rather than a random variable; in all that follows we consider distributions conditional on x_A). Now consider a descendant population B. We model X_B, the allele frequency of the SNP in population B, as:

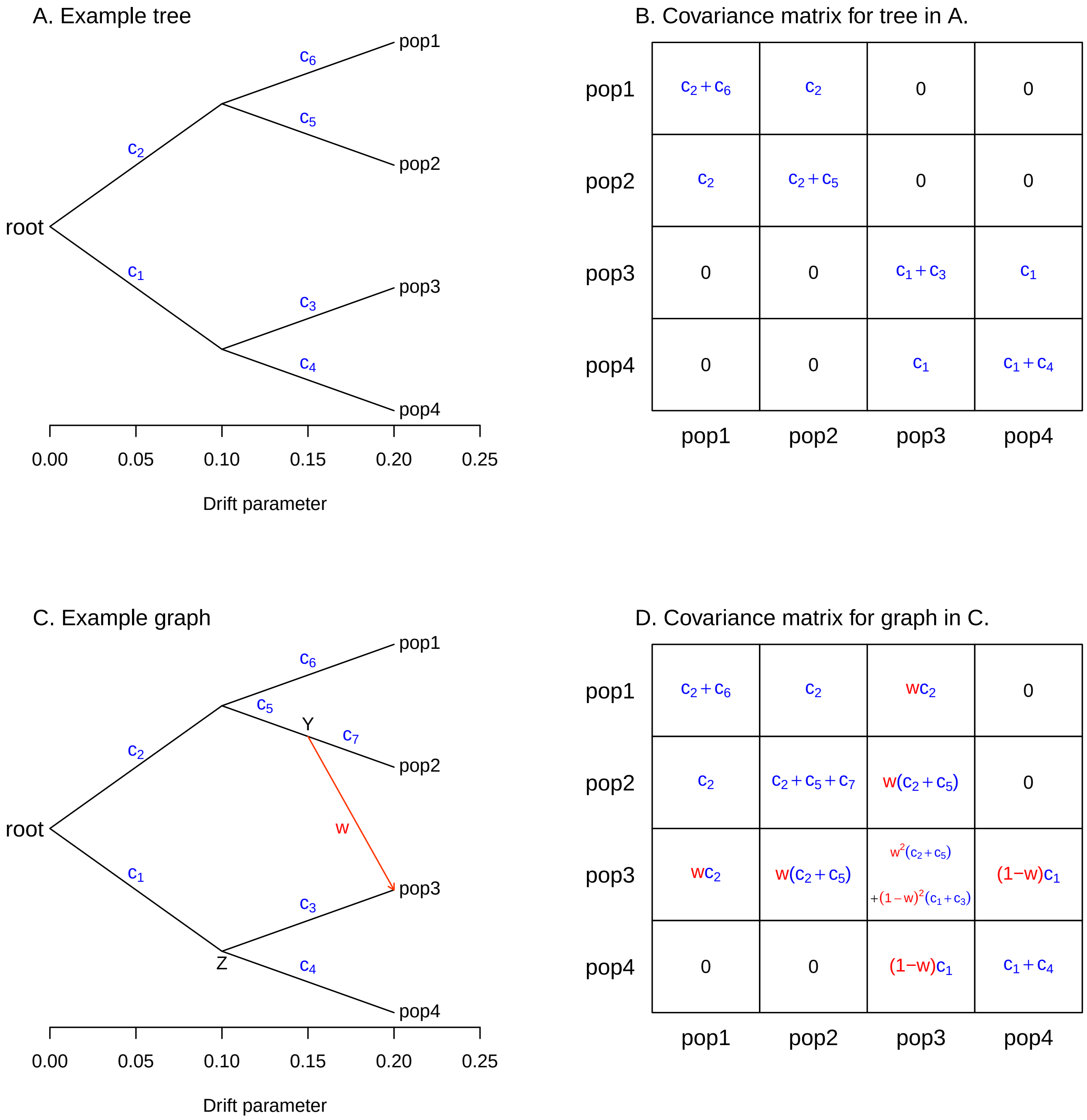
$$X_B = x_A + \epsilon_B \tag{1}$$

with

$$\epsilon_B \sim N(0, c_B x_A[1 - x_A]) \tag{2}$$

where c_B is a factor that corresponds to the amount of genetic drift that has occurred between the ancestral population and B. This Gaussian model was first introduced by Cavalli-Sforza and Edwards [1], and the motivation for this model is outlined in Nicholson et al. [33]. Briefly, if the amount of genetic drift between the two populations is small (at most on a timescale of the same order as the effective population size), then the diffusion approximation to a Wright-Fisher model of genetic drift leads to Equation 2 with $c_B \approx \frac{t}{2N_e}$, where t is the number of generations separating the two populations, and N_e is the effective population size [33]. We do not model the boundaries of the allele frequencies at zero and one, nor do we consider new mutations. This means that this model will be most accurate for alleles that were at intermediate frequency in the ancestral population.

Now consider a descendant population of B; let us call this population C, and the allele fre-


A. Example tree

B. Covariance matrix for tree in A.

	pop1	pop2	pop3	pop4
pop1	c_2+c_6	c_2	0	0
pop2	c_2	c_2+c_5	0	0
pop3	0	0	c_1+c_3	c_1
pop4	0	0	c_1	c_1+c_4

C. Example graph

D. Covariance matrix for graph in C.

	pop1	pop2	pop3	pop4
pop1	c_2+c_6	c_2	wc_2	0
pop2	c_2	$c_2+c_5+c_7$	$w(c_2+c_5)$	0
pop3	wc_2	$w(c_2+c_5)$	$w^2(c_2+c_5)$ $+(1-w)^2(c_1+c_3)$	$(1-w)c_1$
pop4	0	0	$(1-w)c_1$	c_1+c_4

Figure 1**: Simple examples. A.** An example tree. **B.** The covariance matrix implied by the tree structure in A. Note that the covariance here is with respect to the allele frequency at the root, and that each entry has been divided by $x_A[1-x_A]$ to simplify the presentation. **C.** An example graph. The migration edge is colored red. Parental populations for population 3 are labeled Y and Z; see the main text for details. **D.** The covariance matrix implied by the graph in C; again, each entry has been divided by $x_A[1-x_A]$. The migration terms are in red, and the non-migration terms are in blue.

quency in the population X_C. Using the same model:

$$\begin{aligned} X_C &= X_B + \epsilon_C \tag{3} \\ &= x_A + \epsilon_B + \epsilon_C \tag{4} \end{aligned}$$

where

$$\epsilon_C \sim N(0, c_C X_B[1 - X_B]). \tag{5}$$

We can write down the expectation and variance of X_C as:

$$\begin{aligned} E[X_C] &= E[x_A + \epsilon_B + \epsilon_C] \tag{6} \\ &= x_A \tag{7} \end{aligned}$$

and:

$$\begin{aligned} Var(X_C) &= Var(x_A + \epsilon_B + \epsilon_C) \tag{8} \\ &= Var(\epsilon_B) + Var(\epsilon_C) + 2Cov(\epsilon_B, \epsilon_C). \tag{9} \end{aligned}$$

We then assume the amount of genetic drift between all the populations is small. This implies that X_B is well-approximated by x_A, which in turn implies that the amount of genetic drift between A and B is approximately independent of the amount of genetic drift between B and C [35]. With these simplifications:

$$\begin{aligned} Var(X_C) &\approx Var(\epsilon_B) + Var(\epsilon_C) \tag{10} \\ &\approx (c_B + c_C)x_A[1 - x_A]. \tag{11} \end{aligned}$$

We thus have a model for X_C, conditional on x_A:

$$X_C \sim N(x_A, (c_B + c_C)x_A[1 - x_A]). \tag{12}$$

Multiple populations. Now consider a set of four populations, all related to an ancestral population by a tree, as depicted in Figure 1A. Let the allele frequencies in the four populations be denoted X_1, X_2, X_3, and X_4, respectively, and the vector of all four frequencies be $\vec{X}$. We want to write down a joint distribution for $\vec{X}$ given the tree. We start by writing down the covariance between any two populations with respect to the ancestral allele frequency (i.e. $Cov(X_1, X_2) = E[(X_1 - x_A)(X_2 - x_A)]$). This is simply the variance of the common ancestor of the two populations:

$$\begin{aligned} Cov(X_1, X_2) &= c_2 x_A[1 - x_A] \tag{13} \\ Cov(X_3, X_4) &= c_1 x_A[1 - x_A] \tag{14} \\ Cov(X_1, X_3) &= 0 \tag{15} \end{aligned}$$

and so on (Figure 1B).

Let us denote as $\mathbf{V}$ the variance-covariance matrix of allele frequencies between populations implied by the tree. Now, if we knew the value of x_A, we could model $\vec{X}$ as:

$$\vec{X} \sim MVN(\vec{x}_A, \mathbf{V}) \tag{16}$$

where $\vec{x}_A = [x_A, x_A, x_A, x_A]$ and MVN denotes the multivariate normal distribution. This multivariate normal model was proposed by Felsenstein [28]. Additionally, a multivariate normal model was used by Coop et al. [47] and Weir and Hill [48], although these authors did not explicitly model the variance-covariance matrix in terms of a tree.

In this tree model, the position of the root is not identifiable; this follows from the fact that the evolution of allele frequencies along the tree is reversible under the Gaussian model when drift is assumed to be small.

Modeling migration. To extend this framework to include migration, we allow populations to have ancestry from multiple parental populations. The contribution of each parental population is weighted; if we assume admixture occurs in a single generation, these weights can be interpreted as the fraction of alleles in the descendant population that originated in each parental population. Consider population 3 in Figure 1C (recall that the allele frequency in this population is X_3). We have labeled the two parental populations Y and Z; let the allele frequencies in these populations be X_Y and X_Z, respectively. We model X_3 as:

$$X_3 = wX_Y + (1 - w)(X_Z + \epsilon_3) \tag{17}$$

where $\epsilon_3 \sim N(0, c_3 x_A[1 - x_A])$. Note that there is some question as to how to weight ϵ_3, the genetic drift specific to population 3. In reality, it comes from three sources: drift since Y but before the population mixture, drift since Z but before the population mixture, and drift since the mixture. These three components should have weights w, $1 - w$, and 1, respectively. However, the three components are not all separately identifiable. For ease of computation, we estimate only a single drift parameter in this situation, and weight it by $1 - w$ (Supplementary Information).

The variance of X_3 can be written in this mixture case as:

$$\begin{aligned} Var(X_3) &= Var(wX_Y + (1 - w)(X_Z + \epsilon_3)) & (18) \\ &= w^2 Var(X_Y) + (1 - w)^2[Var(X_Z) + Var(\epsilon_3)] + 2w(1 - w)Cov(X_Y, X_Z) & (19) \end{aligned}$$

We can now consider multiple populations related by a graph instead of a tree (Figure 1C). If we restrict the space of possible graphs to those without cycles (i.e., no population can contribute genetic material to its own ancestor), the variance-covariance matrix $\mathbf{V}$ can be filled in as before, but now including terms for migration (Figure 1D). This model can be written in terms of a directed acyclic graph, where the c parameters correspond to edge lengths (Supplementary Material). Also not that for subsets of up to four populations, this model is closely related to the "$f-$ statistics" used as tests for treeness by Reich et al. [37] (Supplementary Material).

In this graph model, the position of the root is now partially identifiable. However, in all that follows we assume that the position of the root is fixed using prior information about known outgroups.

Normalization. As described above, $\mathbf{V}$ depends on the ancestral allele frequency x_A. This means that the true variance-covariance matrix will differ by a scaling factor between SNPs with different values of x_A. In much work on this type of model, investigators have normalized allele frequencies to account for this. One potential normalization is the arcsine square-root transformation [1]. However, a drawback to this normalization is that it is non-linear; the expected value of the allele frequency in the descendant populations is no longer x_A, but pushed towards the boundaries, which could induce spurious correlations between the most drifted populations [49]. Another plausible transformation would be to scale all allele frequencies by $\hat{\mu}(1-\hat{\mu})$, where $\hat{\mu}$ is the mean allele frequency across populations [19, 33]. Both of these transformations increase the influence of polymorphisms that were rare in the ancestral population. However, these are precisely the loci where the approximation of our model to a true population genetics model is most likely to break down. For these reasons, we choose to work directly with untransformed allele frequencies.

Accounting for unknown ancestral allele frequencies. In practice, the multivariate normal model in Equation 16 is impractical because we do not know the ancestral values of allele frequencies, but instead only the values in sampled descendant populations. This means that $\mathbf{V}$ cannot be calculated directly from data. However, consider instead the covariance matrix calculated with respect to the sample mean; i.e. $Cov(X_i, X_j) = E[(X_i - \hat{\mu})(X_j - \hat{\mu})]$, where $\hat{\mu} = \frac{\sum_{i=1}^{m} X_i}{m}$, m is the number of populations, and X_i and X_j are the sample allele frequencies in populations i and j. We call this matrix $\mathbf{W}$. Let us define the vector of mean-centered allele frequencies $\vec{X'} = \vec{X} - \hat{\mu}$. We can now write down a model similar to that in Equation 16, replacing $\mathbf{V}$ with $\mathbf{W}$:

$$\vec{X'} \sim MVN(\vec{0}, \mathbf{W}) \tag{20}$$

where $\vec{0}$ is an $m-$vector of zeros. $\mathbf{W}$ is related to $\mathbf{V}$ as follows:

$$\begin{aligned}
\mathbf{W}_{ij} &= E[(X_i - \hat{\mu})(X_j - \hat{\mu})] && (21)\\
&= E[(X_i - x_A - \hat{\mu} + x_A)(X_j - x_A - \hat{\mu} + x_A)] && (22)\\
&= E[(X_i - x_A)(X_j - x_A) - (X_i - x_A)(\hat{\mu} - x_A) - (X_j - x_A)(\hat{\mu} - x_A) + (\hat{\mu} - x_A)^2] && (23)\\
&= \mathbf{V}_{ij} - \frac{1}{m}\sum_{k=1}^{m}\mathbf{V}_{ik} - \frac{1}{m}\sum_{k=1}^{m}\mathbf{V}_{jk} + \frac{1}{m^2}\sum_{k=1}^{m}\sum_{k'=1}^{m}\mathbf{V}_{kk'}. && (24)
\end{aligned}$$

Finite samples and multiple (potentially correlated) SNPs. Now assume that we have genotyped n SNPs in each of m populations. Let the sample allele frequency at SNP k in population i be $\hat{X}_{ik}$. We can estimate the sample covariance matrix $\hat{\mathbf{W}}$:

$$\hat{\mathbf{W}}_{ij} = \frac{\sum_{k=1}^{n}[(\hat{X}_{ik} - \hat{\mu}_k)(\hat{X}_{jk} - \hat{\mu}_k)]}{n-1} \tag{25}$$

where $\hat{\mu}_k = \frac{1}{m}\sum_{i=1}^{m}\hat{X}_{ik}$. Since in practice we have finite samples from each population (indeed, this method is informative even with single samples from each population), this expression provides a biased estimate of the true covariance matrix; hence we adjust the entries of $\mathbf{W}$ to remove this bias (Supplementary Material). Additionally, with multiple SNPs, we are working with SNPs with many different values of x_A. In this case, the $x_A[1-x_A]$ terms described above can be thought of as $\overline{x_A[1-x_A]}$; i.e., the mean across SNPs of $x_A[1-x_A]$.

We now want to write down a likelihood for $\hat{\mathbf{W}}$ given $\mathbf{W}$. One possibility would be to use the Wishart distribution, since the sample covariance matrix of n independent and identically distributed multivariate normal random variables has this form. However, computation of the Wishart density involves computationally-intensive matrix inversion, so we took an alternative approach. Consider the observed covariance between populations i and j, $\hat{\mathbf{W}}_{ij}$. If we had a large number of independent genomic regions and estimated $\hat{\mathbf{W}}_{ij}$ in each independent region, the sampling distribution would be approximately normal (by appeal to the central limit theorem). We thus model $\hat{\mathbf{W}}_{ij}$ as:

$$\hat{\mathbf{W}}_{ij} \sim N(\mathbf{W}_{ij}, \sigma_{ij}^2) \tag{26}$$

where σ_{ij} is the standard error in the estimation of $\hat{\mathbf{W}}_{ij}$. Because the allele frequencies at nearby SNPs are correlated (i.e., there is linkage disequilibrium), a naive estimate of σ_{ij} that treated each SNP as independent would be too small. We instead take a resampling approach to estimate σ_{ij}. We split the genome into p blocks, such that there are K SNPs per block (with K chosen so that the block sizes are larger than blocks of linkage disequilibrium) [36]. (If K does not divide evenly into n, we discard the remaining SNPs.) We then calculate $\hat{\mathbf{W}}$ separately in each block. Let $\hat{\mathbf{W}}_{ijk}$ be the covariance between two populations i and j in block k. Now,

$$\hat{\mathbf{W}}_{ij} = \frac{\sum_{k=1}^{p}\hat{\mathbf{W}}_{ijk}}{p} \tag{27}$$

and

$$\hat{\sigma}_{ij} = \sqrt{\frac{\sum_{k=1}^{p}(\hat{\mathbf{W}}_{ijk} - \hat{\mathbf{W}}_{ij})^2}{p(p-1)}}. \tag{28}$$

If we take each pair of populations in turn, we can write down a composite likelihood for $\hat{\mathbf{W}}$:

$$L(\hat{\mathbf{W}}|\mathbf{W}) = \Pi_{i=1}^{m}\Pi_{j=i}^{m}N(\hat{\mathbf{W}}_{ij}|\mathbf{W}_{ij}, \hat{\sigma}_{ij}^2) \tag{29}$$

where $N(\hat{\mathbf{W}}_{ij}|\mathbf{W}_{ij}, \sigma_{ij})$ is a Gaussian density with mean $\mathbf{W}_{ij}$ and variance σ_{ij}^2 evaluated at $\hat{\mathbf{W}}_{ij}$.

Finally, we wanted to define measures for how well the model fits the data. First, we define the matrix of residuals in this model, $\mathbf{R}$. These quantities are useful for visualization and fitting:

$$\mathbf{R} = \hat{\mathbf{W}} - \mathbf{W}. \tag{30}$$

Positive residuals indicate pairs of populations where the model underestimates the observed covariance, and thus populations where the fit might be improved by adding additional edges. These residuals can be used to define a measure of the fraction of the variance in $\hat{\mathbf{W}}$ that is explained by $\mathbf{W}$. Let us call this fraction f:

$$f = 1 - \frac{\sum_{i=1}^{m}\sum_{j=i+1}^{m}(\mathbf{R}_{ij} - \overline{\mathbf{R}})^2}{\sum_{i=1}^{m}\sum_{j=i+1}^{m}(\hat{\mathbf{W}}_{ij} - \overline{\hat{\mathbf{W}}})^2} \tag{31}$$

where $\overline{\mathbf{R}} = \frac{\sum_{i=1}^{m}\sum_{j=i+1}^{m}\mathbf{R}_{ij}}{m(m-1)/2}$ and $\overline{\hat{\mathbf{W}}} = \frac{\sum_{i=1}^{m}\sum_{j=i+1}^{m}\hat{\mathbf{W}}_{ij}}{m(m-1)/2}$. This fraction approximates the fraction of the variance in relatedness between populations that is accounted for by the model.

Estimation. We implemented an algorithm, called *TreeMix*, that uses the composite likelihood in Equation 29 to search for the maximum likelihood graph. Searching the space of all graphs is infeasible unless m is very small, so to simplify the search we make the assumption that the history of the sampled populations is approximately tree-like. We thus start by building the maximum likelihood tree, taking an algorithmic approach similar to Felsenstein [30]. After building the tree, we calculate the residual covariance matrix, $\mathbf{R}$, and add migration edges in a directed matter. First, we find the M pairs of populations with the maximum residuals. We then attempt adding a migration edge between populations in the vicinity of each of the M population pairs. For each attempted graph (or tree) topology, we optimize the branch lengths and migration edge weights (Methods). After finding the single migration edge that most increases the likelihood, we attempt a series of local changes to the graph structure (Methods). We then iterate over this procedure to add additional migration edges. In principle, migration edges could be added until they are no longer statistically significant (see the following paragraph). In our experience in practice, however, we prefer to stop adding migration events well before this point so that the resulting graph remains interpretable.

Significance testing. After building the maximum likelihood graph, we would like to quantify our uncertainty in the resulting graph structure. In particular, we would like to quantify our confidence in individual migration events. However, because the likelihood in Equation 29 is a composite likelihood, it cannot be used directly for formal tests for significance. Instead, we take a resampling approach to test the support for individual migration edges.

Consider a given migration edge, with corresponding weight w. We wish to calculate a p-value for this weight (under the null hypothesis that $w = 0$, and for a fixed graph structure). To do this, we use the Wald statistic $\frac{\hat{w}}{se(\hat{w})}$, where $se(\hat{w})$ is the standard error in the estimate of the weight, which is distributed $N(0, 1)$ under the null. To obtain the standard error, recall that we have split the genome into p independent blocks. We use the jackknife estimates of both $\hat{w}$ and the standard error in $\hat{w}$ (where we jackknife over blocks). Let i index blocks, and $w_{\cdot i}$ be the estimated weight computed using all blocks *except* i. Then:

$$\hat{w} = \frac{\sum_{i=1}^{p} \hat{w}_{\cdot i}}{p} \tag{32}$$

$$se(\hat{w}) = \sqrt{\left(\frac{p-1}{p}\right) \sum_{i=1}^{p} (\hat{w}_{\cdot i} - \hat{w})^2} \tag{33}$$

This allows us to calculate a p-value for the migration edge. There are a number of complications to the interpretation of this p-value. First, there is the issue of multiple testing–there are at least $2m-2$ edges in the graph (recall that m is the number of populations), and thus around $4m^2$ possible migration events. More importantly, the p-value is generated under a heavily parameterized model: we are comparing a fixed graph structure with a migration event to that same graph without the migration event. A "significant" p-value simply indicates that the hypothesized migration event significantly improves the fit to the data; this does not account for the possibility of errors in the graph structure, or indicate that the particular migration event tested is the correct one (rather than a migration event between a different pair of populations). For this reason, we treat the precise p-value generated by this procedure with caution, and use additional, less-parameterized methods like three- and four-population tests [37] to test the robustness of the inference.

Simulations

We tested the performance of the *TreeMix* method in simulations. We generated coalescent simulations from several histories; the basic structure was a set of 20 populations produced by a serial bottleneck model like that used by DeGiorgio et al. [50] to model human history (Figure 2A). The parameters of the simulations were chosen to be reasonable for non-African human populations; we used an effective population size of 10,000, and a history where all 20 populations share a common ancestor 2000 generations in the past. Each individual simulation involved 400 regions of approximately 500kb each, and thus recapitulated many aspects of real data, including hundreds of thousands of loci and the presence of linkage disequilibrium.

Tree simulations. First, we tested the performance of the algorithm on truly tree-like data. We generated 100 independent simulations of 20 chromosomes from each population using the above demographic model without migration, and inferred population trees. The inferred trees perfectly matched the simulated model in all cases (Figure 2B), and the fitted tree model accounted for an average of 99.8% of the variance in relatedness between populations. To test the effect of SNP ascertainment, we then inferred trees using only SNPs that were polymorphic in one of the populations (either population 1 or population 20); this ascertainment scheme did not decrease accuracy of the inferred topology, though it did alter the inferred branch lengths (Supplementary Figure 2).

We used these simulations without migration to test the calibration of our p-values for migration events. For each simulation, after building the maximum likelihood tree, we introduced a migration event between two random populations and tested it for significance. As expected if the p-values are properly calibrated, their distribution is approximately uniform (Supplementary Figure 3).

Finally, we performed tree simulations in a situation where fixed differences and new mutations (rather than shared polymorphisms inherited from a common ancestor) were common between the populations; in this context the population genetic interpretation of the model breaks down. We performed simulations where all the true branch lengths were 50 times longer than in the original model, corresponding to a history where the 20 populations share a common ancestor approximately 100,000 generations in the past. Again, we see no errors in the topology of the inferred trees (Supplementary Figure 4). In this situation, the covariances between closely-related populations tend to be slightly underestimated; in more extreme situations this could lead to spurious inferences of migration (Supplementary Figure 4). However, overall, these simulations suggest that the model will still be useful even in situations where the population genetic interpretation is not strictly correct.

Simulations with migration. We then introduced migration events into our simulations. We generated simulations under the same model described above; however, we now simulated an admixture event approximately 100 generations before the present where one population receives a fraction of its ancestry (either 10% or 30%) from one of the other populations. We tried ten different pairwise combinations of populations, and generated 100 simulations for each pair. For each simulation, we ran *TreeMix* and allowed it to infer a migration event. We then judged the error rate of the algorithm as the fraction of times the inferred topology of the graph was not exactly correct (this is a conservative estimate of the error rate, in that inferred graph topologies that are very close to the truth are counted as errors). In general, *TreeMix* was able to correctly infer the graph structure in these simulations (Figure 2C). However, accuracy dropped considerably when migration was between closely related populations without outgroups present in the data (these are populations 1 and 20 in the model; Figure 2C). The major types of errors produced in the simulations were incorrectly inferred directions of migration arrows and inference of admixture in populations related to the truly admixed population (Supplementary Material, Supplementary Figure 5).

We next asked whether the mixture “weights” inferred in the model can be interpreted as admixture proportions. To do this, we simulated admixture events of varying proportion between the first and tenth population in the serial bottleneck model described above, set the graph to the true topology, and estimated the mixture weight. The weights are indeed correlated with the true ancestry fraction, but underestimate relatively high admixture proportions in these simulations (Figure 2D). The precise bias in the estimation of this parameter will depend, in real data, on largely unknowable parameters (Supplementary Material).

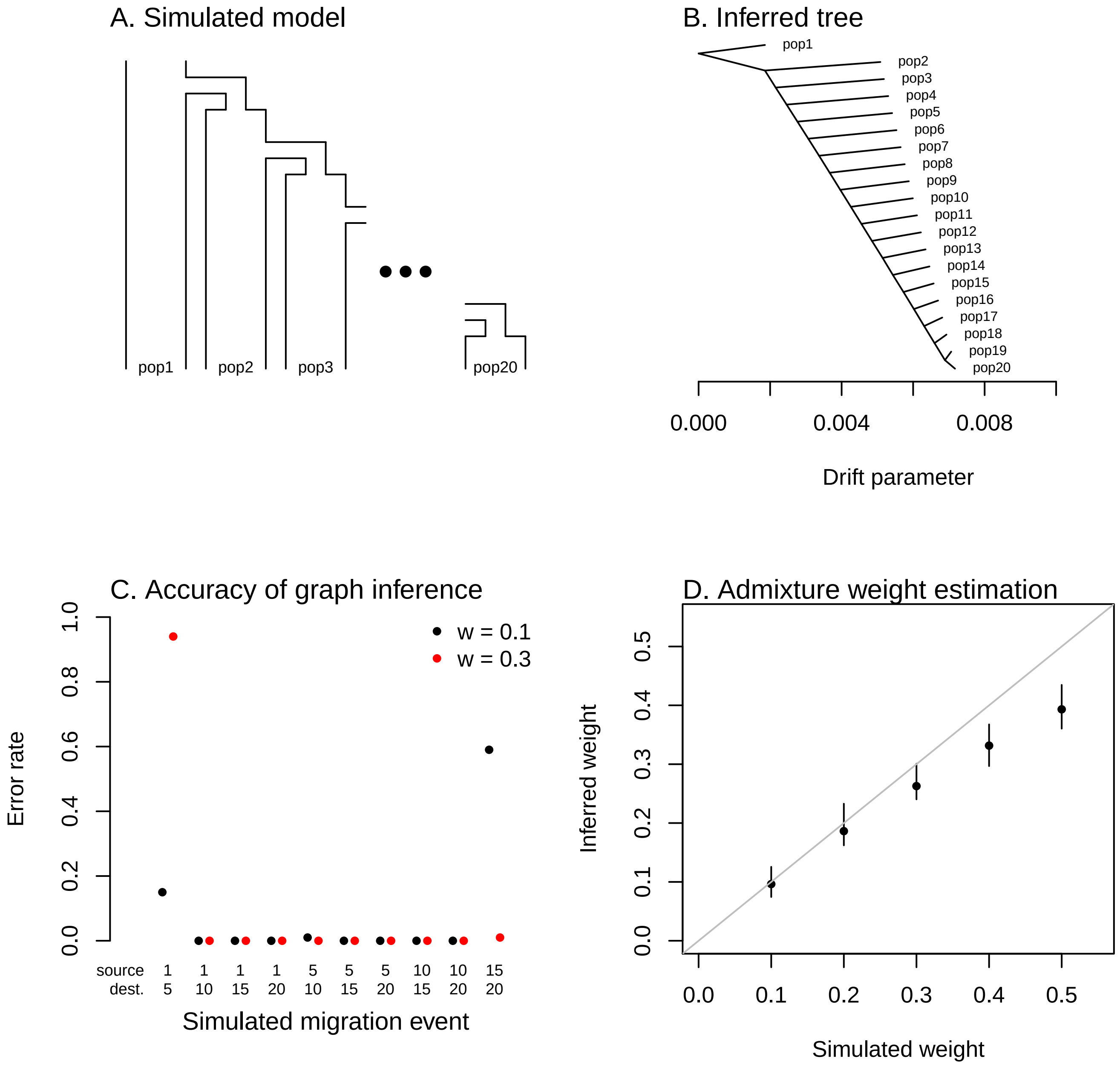


Figure 2: **Performance on simulated data. A.** The basic outline of the demographic model used. **B. Trees inferred by *TreeMix*.** We simulated 100 independent data sets, under the demographic model in **A.**, and inferred the tree. All simulations gave the same topology; plotted are the mean branch lengths. **C. Performance in the presence of migration.** We added migration events to the tree in **A.** and inferred the structure of the graph. Each point represents the error rate over 100 independent simulations, defined as the fraction of simulations where the inferred graph topology does not perfectly match the simulated topology. On the x-axis we show the populations involved in the simulated migration event; e.g., if the source population is 1 and the destination population is 10, this is a migration event from population 1 to population 10, as labeled in **A. D. Admixture weight estimation.** We simulated admixture events with different weights from population 1 to population 10, and inferred the weight. Each point is the mean across 100 simulations, and the bar represents the range.

Application to humans

To test the performance of the *TreeMix* model with real data, we applied it to humans, whose genetic history has been studied extensively [7, 21, 51, 52]. We applied the model to a dataset consisting of about 125,000 SNPs ascertained by low-coverage genome sequencing in a single Yoruban individual and then genotyped in 55 modern and archaic human populations [53]. In all that follows, we excluded the two Oceanian populations because they gave inconsistent results across datasets. We believe this difficulty results from the fact that these populations contain ancestry from multiple sources, making the graph estimation somewhat unstable when they are included (Supplementary Material). We first built the tree of all 53 remaining populations (Figure 3A). This tree largely recapitulates the known relationships among population groups [7], and explains 98.8% of the variance in relatedness between populations (though this is high, it is less than the 99.8% observed in the simulations of a true tree model). We examined the residuals of the model's fit to identify aspects of ancestry not captured by the tree (Figure 3B). A number of known admixed populations stand out: in particular, these include the Mozabite and Middle Eastern populations.

We then sequentially added migration events to the tree. In Figure 4, we show the inferred graph with ten migration edges; p-values for all reported migration edges are less than 1×10^{-30} (we show the graph with the maximum likelihood over several independent runs of *TreeMix* with random orders of input populations). This graph model explains 99.8% of the variance in relatedness between populations. As expected from examination of Figure 3B, the migration events recapitulate many known events in human history. We infer that the Mozabite are the result of admixture between an African and a southern European population (with about 30% of their ancestry from Africa), and that Middle Eastern populations also have African ancestry (Palestinians and Bedouins: $w = 13\%$ from Africa; Druze: $w = 6\%$). This is consistent with previously reported admixture proportions from these populations [42, 54]. Additionally, we identify the known European ancestry in the Maya ($w = 12\%$) [21], and infer that the Uyghur and Hazara populations are the result of admixture between west Eurasian and East Asian populations ($w = 46\%$ and 47% from west Eurasia, respectively) [20, 21, 55].

Several additional migration events in the human data have not been previously examined in detail, but are consistent with previous clustering analysis of these populations [7, 20, 21]. These include migration from Africa to the Makrani and Brahui in Central Asia ($w = 5\%$) and from a population related to East Asians and Native Americans (which we interpret as likely Siberian) to Russia ($w = 11\%$).

Two inferred edges were unexpected. First, perhaps the most surprising inference is that Cambodians trace about 16% of their ancestry to a population equally related to both Europeans and other East Asians (while the remaining 84% of their ancestry is related to other southeast Asians). This is partially consistent with clustering analyses, which indicate shared ancestry between Cambodians and central Asian populations [7]. To confirm that the Cambodians are admixed, we turned to less parameterized models. The predicted admixture event implies that allele frequencies in Cambodia are more similar to those in African populations than would be expected based on their East Asian ancestry. To test this, we used three-population tests [37]. We tested the trees [African, [Cambodian,Dai]] for evidence of admixture in the Cambodians (Methods). When using any African population, there is strong evidence of admixture (when using Yoruba, $Z = -7.0$ [$p = 1 \times 10^{-12}$]; when using Mandenka, $Z = -7.3$ [$p = 1 \times 10^{-12}$]; when using San, $Z = -4.8$ [$p = 8 \times 10^{-7}$]). We conclude that the Cambodian population is the result of an admixture event involving a southeast Asian population related to the Dai and a Eurasian population only distantly related to those present in these data.

Finally, we infer an admixture edge from the Orcadians (a northern European population isolate) to all of the Native American populations ($w = 8\%$). Though recent European ancestry is clear in the Mayans and (to a lesser extent) the Colombians in these data [7, 21], the other Native American populations do not show evidence of recent admixture in clustering analyses. To confirm the presence of gene flow between Europe and the Americas, we turned to four-population tests (three-population tests have dramatically lower power to detect admixture in drifted populations [37], so we do not use them in the Americas). These tests, of the form [[A,B][C,D]] (where A, B, C, and D are populations), are expected to have a standard normal distribution if A and B form a clade relative to C and D. Negative values can be obtained if A and D (or B and C) are more closely related than would be expected under a tree model, while positive values can be obtained if A and C (or B and D) are more closely related than would be expected under a tree model. In this case, we tested trees of the form [[Yoruba,Orcadian],[Han,Native American]]. When using any Native American population, these trees fail, with levels of significance that range from $Z = 6.6$ ($p = 2 \times 10^{-11}$) when using Colombians as the Native American population, to $Z = 10.0$ ($p < 1 \times 10^{-12}$) when using Mayans as the Native American population. We conclude that there has been gene flow between populations related to extant northern Europeans and all of the Native American populations in these data, though with these methods we cannot determine whether this event was recent or ancient, or whether there were multiple events.

To test the robustness of our results to SNP ascertainment, we additionally ran *TreeMix* on the same set of populations using a set of SNPs ascertained in a single French individual. The inferred graph was nearly identical (Supplementary Figure 7). Additionally, as noted above, different random input orders for the populations gave very similar results (Supplementary Figure 6). We conclude from this that the model is able to consistently and accurately infer the major mixture events in the history of a species. This approach is computationally efficient: building the tree took around five minutes on a standard desktop computer (with a processor speed of 3.1 GHz), and adding ten migration events to the tree took about four and a half hours (the major computational cost is in the iterative estimation of migration weights).

Application to dogs

While human populations have been extensively studied, we next applied the model to dogs, a species where considerably less is known about population history. In particular, we applied the model to a dataset consisting of about 60,000 SNPs genotyped in 82 dog breeds or wild canids

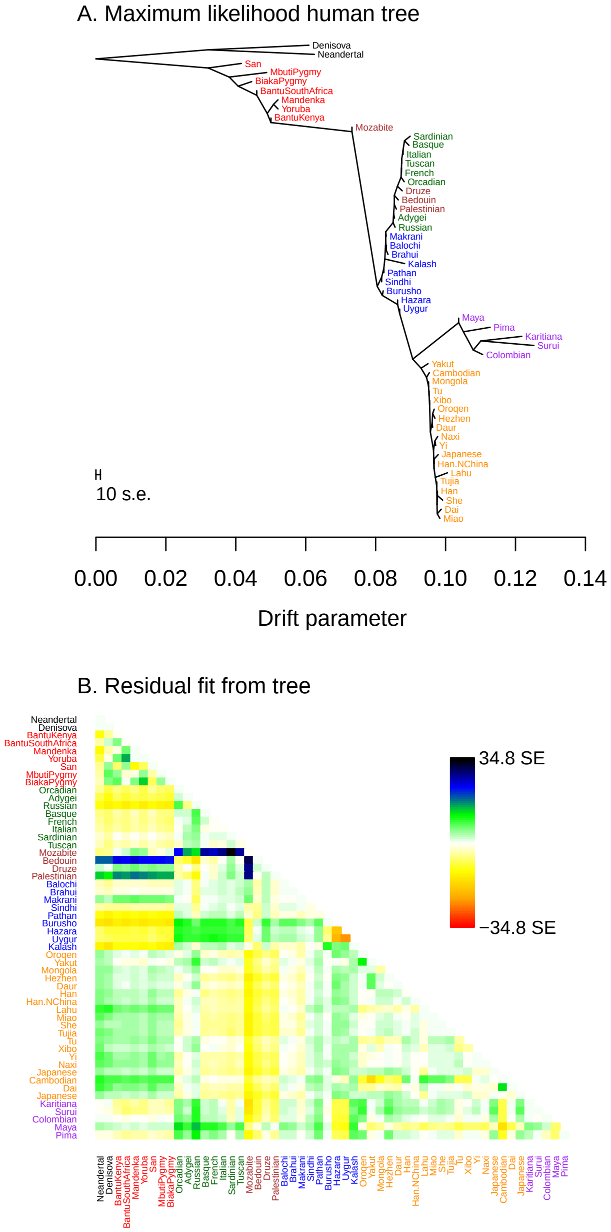


Figure 3: **Inferred human tree. A. Maximum likelihood tree.** Plotted is the maximum-likelihood tree. Populations are colored according to geographic location (black: archaic humans, red: Africa, brown: Middle East, green: Europe, blue: Central Asia, purple: America, orange: East Asia). The scale bar shows ten times the average standard error of the entries in the covariance matrix ($\hat{\mathbf{W}}$). For analysis including Oceania, see Supplementary Figures 8 and 9. **B. Residual fit.** Plotted is the residual fit from the maximum likelihood tree in **A.** We divided the residual distance between each pair of populations i and j by the average standard error across all pairs. We then plot in each cell $[i, j]$ this scaled residual. Colors are described in the palette on the right. Residuals above zero represent populations that are more closely related to each other in the data than in the best-fit tree, and thus are candidates for admixture events.

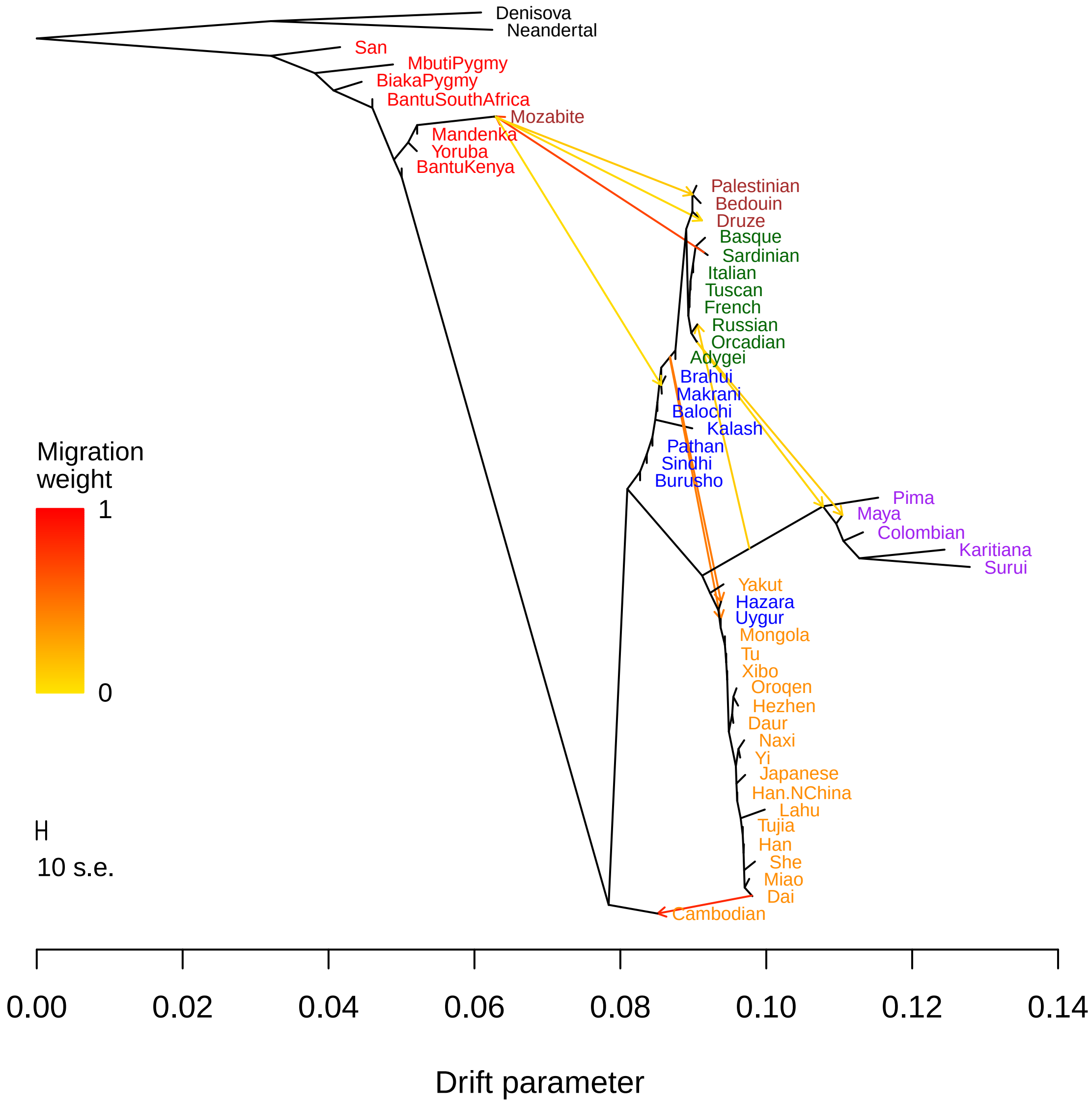


Figure 4**: Inferred human tree with mixture events.** Plotted is the structure of the graph inferred by *TreeMix* for human populations, allowing ten migration events. Migration arrows are colored according to their weight. Horizontal branch lengths are proportional to the amount of genetic drift that has occurred on the branch. The scale bar shows ten times the average standard error of the entries in the covariance matrix ($\hat{\mathbf{W}}$).

[56]. As for humans, we first inferred the maximum likelihood tree (Figure 5A). The differences in history between dogs and humans are striking: there are long terminal branches leading to each dog breed in the inferred tree (Figure 5A, recall that the terminal branch lengths account for sample size). This is consistent with the known strong bottlenecks in the establishment of dog breeds [23]. However, examining the residuals from the model revealed a number of populations that do not fit a strict tree model (Figure 5B); indeed, the tree model explained 94.7% of the variance in relatedness between breeds, somewhat less than between human populations.

We sequentially added migration events to the tree in Figure 5A. In Figure 6, we show the inferred graph with ten migration events, which explains 96.8% of the variance in relatedness between breeds (which suggests that additional events exist in the data). In the following paragraphs, we describe some of these events.

We infer that the bull mastiff is the result of an admixture event between bulldogs and mastiffs. This is a known event [57]; we estimate the admixture proportions as 33% bulldog and 67% mastiff. We further examined this event using four-population tests for treeness. As expected given the known history, the tree [[boxer,bulldog],[mastiff,bull mastiff]] fails the four-population test ($Z = 3.5$, $p = 0.002$), while replacing the bull mastiff with other related breeds (that we do not predict to be involved in the admixture event) results in trees that pass this test (for example, the tree [[boxer,bulldog],[mastiff,Boston terrier]] passes the four-population test with $Z = -0.3$).

The most visually apparent residuals in Figure 5B are accounted for in the graph by an admixture event from the grey wolf into the basenji, an ancient African breed of dog ($w = 25\%$). Such a high mixture fraction is consistent with previous clustering analyses of these data [23]. We again sought to confirm this signal in a less-parameterized model. We tested the four-population tree [[wolf,ancient breed],[basenji, Afghan hound]] with various “ancient” dog breeds. We could not find a tree that passed the four-population test (with Akita as the ancient breed, $Z = 11.7, p < 1\times10^{-30}$; with Alaskan Malamute, $Z = 13.0, p < 1\times10^{-30}$), confirming the presence of gene flow in these trees. Replacing the basenji with the saluki in these analyses resulted in trees that pass the four-population test (for example, the tree [[wolf, Akita],[Afghan hound, saluki]] passes with $Z = -0.03, p = 0.51$). Though we cannot have complete confidence in the precise migration events, these results are consistent with admixture between gray wolves and the basenji.

Another breed that stands out in this analysis is the boxer (note that many of the SNPs used in this study were ascertained by virtue of being heterozygous in a single boxer individual, so we may have increased power to identify migration events involving this breed). We infer a significant genetic contribution from wolves to the boxer ($w = 9\%$), and migration between the boxer and the Chinese shar-pei, a distantly-related ancient breed ($w = 9\%$). To further examine these events, we again turned to four-population tests. To test the wolf mixture, we tested the tree [[wolf, ancient breed],[boxer, bulldog]]. We did not find a tree that passed the four-population test (with Akita as the ancient breed, $Z = 3.1, p = 0.001$; with Afghan Hound, $Z = 3.4, p = 0.0003$). Replacing the Boxer with the Mastiff in these analyses led to trees that passed the four-population test (for example, with Akita as the ancient breed, $Z = 0.3, p = 0.38$). To test the gene flow from the Boxer to the Chinese shar-pei, we tested the tree [[Chinese shar-pei, Akita],[boxer, bulldog]]; this tree fails the four-population test ($Z = 3.0, p = 0.001$), while the tree [[Chow Chow, Akita],[boxer,bulldog]] passes this test ($Z = -0.48, p = 0.3$).

Previous analyses of these data have noted that the "toy breeds" of dog cluster together [23]. We find that the Chinese toy breeds (the Pekingese and the Shi Tzu) result from admixture between a population related to ancient East Asian dog breeds and a modern population related to the Brussels griffon and the pug ($w = 73\%$ from the modern population). To confirm the presence of gene flow, we tested four-population trees of the form [[Asian toy breed, Akita/Chow Chow],[Pug,mastiff]]. These trees fail, with varying levels of significance, ranging from [[Chow Chow, Shi Tzu],[Pug, mastiff]] ($Z = -2.7, p = 0.003$) to [[Akita, Pekingese],[Pug, mastiff]] ($Z = -4.7, p = 1 \times 10^{-6}$).

Overall, we conclude that there has been considerable gene flow between dog breeds over the course of domestication; there are many additional migration events that merit further examination (Figure 6, Supplementary Material).

Discussion

In this paper, we have developed a unified model for inferring patterns of population splits and mixtures from genome-wide allele frequency data. We have shown that this model is accurate in simulations, largely recapitulates the known relationships between well-studied human populations, and is able to identify new relationships between populations in both humans and dogs.

The *TreeMix* model can be thought of as a complement to methods for the identification of population structure [18–20]. These latter methods are powerful tools for clustering together individuals into relatively homogenous populations (and to identify individuals that are genetic outliers in their population)[18–20]. However, once population structure in a species has been identified, these methods are not well-suited for describing *how* it arose, and are only indirectly informative about the historical relationships between different populations. The model developed in this paper is designed to more directly address these historical questions.

Modeling assumptions. There are a number of assumptions, both implicit and explicit, in the interpretation of the *TreeMix* model. First, we have motivated the model in terms of inferring the historical splits and mixtures of populations. However, a given covariance structure of allele frequencies between populations can be a consequence of either a non-equilibrium demography (population splits and mixtures) or an equilibrium demography (populations at long-term stasis with a fixed migration structure) [2]. For the species analyzed in this paper, population equilibrium over the entire species range is not a tenable hypothesis; however, some subsets of populations may be at equilibrium, and there may be species where this alternative historical interpretation of the model is plausible.

We also have modeled migration between populations as occurring at single, instantaneous time points. This is, of course, a dramatic simplification of the migration process. This model will work best when gene flow between populations is restricted to a relatively short time period. The relevance of this assumption will depend on the species and the populations considered. In

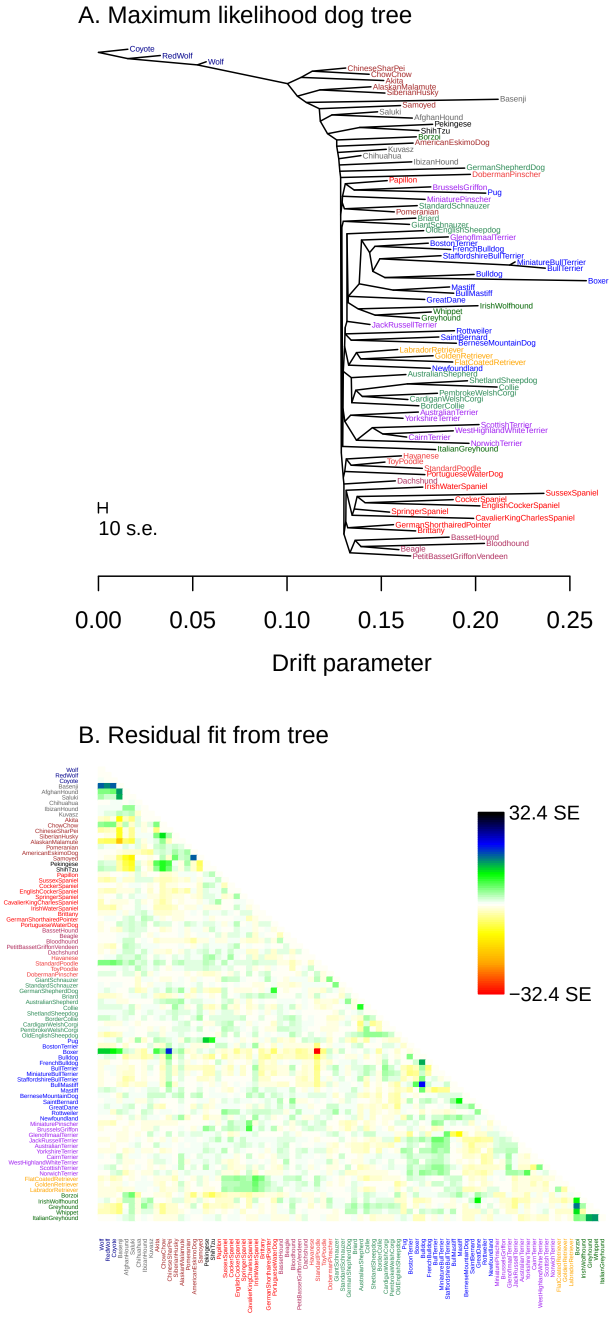


Figure 5**: Inferred dog tree. A. Maximum likelihood tree.** Populations are colored according to breed type. Dark blue: wild canids, grey: ancient breeds, brown: spitz breeds, black: toy dogs, red: spaniels, maroon: scent hounds, dark red: working dogs, light green: herding dogs, light blue: mastiff-like dogs, purple: small terriers, orange: retrievers, dark green: sight hounds. The scale bar shows ten times the average standard error of the entries in the covariance matrix ($\hat{\mathbf{W}}$). **B. Residual fit.** Plotted is the residual fit from the maximum likelihood tree in **A.** We divided the residual distance between each pair of populations i and j by the average standard error across all pairs. We then plot in each cell $[i, j]$ this scaled residual. Colors are described in the palette on the right.

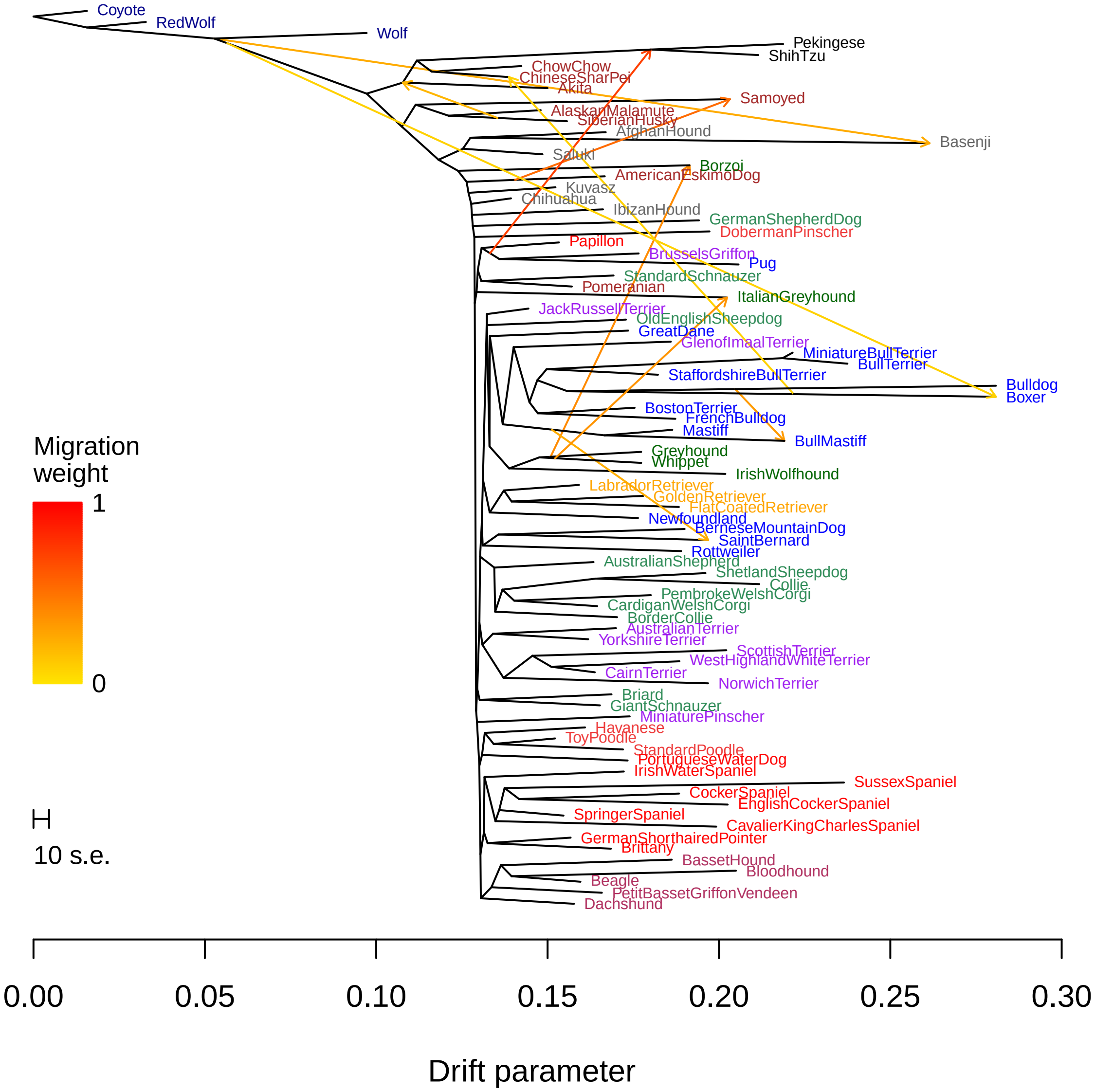


Figure 6**: Inferred dog graph.** Plotted is the structure of the graph inferred by *TreeMix* for dog populations, allowing ten migration events. Migration arrows are colored according to their weight. The scale bar shows ten times the average standard error of the entries in the covariance matrix ($\hat{\mathbf{W}}$). See the main text for discussion.

humans, the relevance of continuous versus discrete mixture events is an open question–some aspects of genetic variation appear compatible with continuous migration [58], while other aspects do not [37]. Indeed, both sorts of models are likely relevant at different time scales [59].

We also rely on the implicit assumption that the history of the species being analyzed is largely tree-like. We have made this assumption to simplify the search for the maximum likelihood graph; improvements to the search algorithm could allow this assumption to be relaxed. Currently, if the number of admixed populations is large relative to the number of unadmixed populations, this assumption breaks down. For example, in the human data, note that we see no evidence of the documented gene flow from Neandertals to all non-African populations [39] (Figure 3B). The reason for this is that the large number of populations with admixture can be accommodated in the tree by allowing the branch from Neandertals to Africans to be slightly underestimated (additionally, by using SNPs ascertained in Africa, we have selected against sites that are informative about Neandertal ancestry). If only a single non-African population is included in the analysis, the relationship between Neandertals and the non-African population is clearer (Supplementary Figure 10).

Conclusions. A number of extensions to the sort of model described here are of potential interest. First, the historical relationships between populations could be useful as null demographic models for the detection of natural selection [47]. Second, in a given individual, the best-fit graph relating the individual to other populations may change along a chromosome; this sort of information could be of use in local ancestry inference. Finally, we have not used the information about demographic history present in linkage disequilibrium; approaches that explicitly use this information may provide additional power to detect migration events and estimate their timing, at an additional computational cost [20, 52, 60].

Methods

Graph estimation. As described in the Results, we developed an algorithm called *TreeMix* that uses the composite likelihood in Equation 29 to search for the maximum likelihood graph. Estimation involves two major steps. First, for a given graph topology, we need to find the maximum likelihood branch lengths and migration weights. Second, we need to search the space of possible graphs. First consider a given graph topology. We iterate between optimizing the branch lengths and weights. If the edge weights are known, the observed entries of the covariance matrix can be written down as an overdetermined system of linear equations (as in Equations 13-15). We solve this system by non-negative least squares [61]. Though the least squares solution is the maximum composite likelihood solution in the case where all entries of the covariance matrix have equal variance, it is not strictly the maximum likelihood solution in cases with unequal variances. The algorithm could be extended to unequal variances using a weighted least squares approach, but we have not implemented this. We then do a golden section search for the optimal weight (between zero and one) on each migration edge [62]. At each step in the golden section search, we update the branch lengths. We optimize the weight of each migration edge in turn, and iterate over migration edges until convergence.

To search the space of possible graphs, we take a hill-climbing approach. We start by finding a local optimum tree, taking an algorithmic approach similar to Felsenstein [30]. We randomly select three populations, optimize the branch lengths for all three possible trees, and choose the best (in terms of the composite likelihood) tree. Then, we add the remaining populations one by one in a random order. To add a population, we try attaching it to all branches of the current tree, optimizing the branch lengths for each one as described above, and find the most likely spot. We then perform a round of local rearrangements (i.e., nearest-neighbor interchanges [49]) around each internal node, keeping the resulting tree only if it increases the likelihood.

After adding all populations, we calculate the residual covariance matrix, R. We then add migration edges in a directed matter. First, we find the M pairs of populations with the maximum residuals (these are the pairs of populations with the worst fit under the model). In the results reported, $M = 4$. We define a "neighborhood" around each population of a pair as the tips within a distance of E edges of the focal population. In applications above, we use $E = 3$. This defines a set of pairs of populations that either have a poor fit, or are located in the graph near populations with a poor fit. We take each of these pairs in turn. For each pair, we identify the set of nodes in the path from each member of the pair to the root of the graph. This gives us two sets of nodes. We take all pairwise combinations of nodes in each set, and look at residuals between the populations that are the descendants of each node. If all of the residuals are positive, we add a migration edge between the two nodes and estimate its maximum likelihood weight. We then keep only the single edge that most increases the likelihood of the graph. After adding a migration edge, we attempt nearest-neighbor interchanges at the source and destination of the migration event, attempt changing the source and destination of all migration events, and attempt changing the direction of all migration arrows. Once we have reached the local maximum by this method, we attempt nearest-neighbor interchanges at all internal nodes. We iterate over this procedure for a predetermined number of migration edges. We then test the migration edges for significance as described.

The *TreeMix* source code is available at `http://treemix.googlecode.com`.

Three- and four-population tests of treeness. We implemented three- and four-population tests as described in Reich et al. [37]. For the relationship between the $f-$statistics and the covariance model underlying *TreeMix*, see the Supplementary Material. For the three-population test, we estimated f_3 as in Reich et al. [37], and tested whether is it less than zero. We report the Z-score for this test. To obtain a standard error on the estimate of f_3, we used a block jackknife similar to Reich et al. [37]. However, Reich et al. [37] split the genome into blocks based on distance (with variable numbers of SNPs per block); we split the genome into blocks of K SNPs (and thus the blocks will be of variable size).

For the four-population test for treeness, we calculate the f_4 statistic as in Reich et al. [37], and test whether it is different than zero. Again, we report a Z-score for this test. Standard errors for the f_4 statistic were obtained as for the f_3 statistic.

Human data. The human data we used were downloaded from `http://www.cephb.fr/en/hgdp/` on August 16th, 2011 (the data set labeled Harvard HGDP-CEPH genotypes). They consist of several panels of SNPs ascertained from low-coverage genome sequencing of single individual from different populations and then genotyped in the Human Genome Diversity Panel [53]. Additionally, at each site, a single sequencing read from the Denisova and Neandertal genome sequencing projects was sampled and the allele reported. These data have the property that they allow for complete control of the ascertainment strategy, and allow us to test the robustness of inference to different ascertainment schemes. For the main analyses, we used the panel of autosomal SNPs ascertained in a single Yoruban individual; there are 124,115 such sites. For some analyses, we also used the panel of autosomal SNPs ascertained in a single French individual; there are 111,970 such sites. For all analyses with *TreeMix*, we used a window size ($-K$) of 500; this corresponds to a window size of approximately 10Mb. For all *TreeMix* analyses, we set the Neandertal and Denisova samples as the outgroups.

Since we have only a single allele from the Neandertal and Denisova populations, we cannot calculate heterozygosity in these populations for unbiased estimation of the covariance matrix (see Supplementary Information). To account for this, we simply chose a relatively low level of heterozygosity and assigned it to both populations. In the Yoruba ascertained SNPs, we used a heterozygosity of 0.13, and for the French ascertained SNPs, we used a heterozygosity of 0.2. In practice, this only affected the lengths of the terminal branches to Neandertal and Denisova; running *TreeMix* with a heterozygosity of zero in both populations resulted in the same graph topologies (not shown).

Dog data. Allele counts for the dog breeds and wild canids reported in Boyko et al. [56] were downloaded from `http://genome-mirror.bscb.cornell.edu/` on July 30, 2011. These data consist of counts of reference and alternate alleles at 61,468 sites in 85 dog breeds and wild canids. We removed the Jackal and Scottish Deerhound for having relatively high amounts of missing data, and the village dogs because it is unclear if they represent a coherent population. We also removed all SNPs on the X chromosome. This left us with 60,615 SNPs in 82 populations. We ran *TreeMix* with a window size ($-K$) of 500. This corresponds to a window size of approximately 20 Mb. For all *TreeMix* analyses, we set the coyote as the outgroup.

The ascertainment scheme used for SNP discovery in dogs was complicated. In particular, some SNPs were ascertained by virtue of being different between the boxer and poodle assemblies. This should lead to an overestimation of the distance between the boxer an the poodle in our analysis. Indeed, in Figure 5B, a considerable negative residual between the boxer and poodle is visible.

Simulations. All simulations were performed using *ms* [63]. The exact commands used are listed in the Supplementary Material. When running *TreeMix* on simulations without ascertainment, we used a window size of 5000 SNPs; for simulations with ascertainment we used windows of 1000

SNPs. Consensus trees were generated using SumTrees v.3.1.0. [64]

Acknowledgements. We thank David Reich, Nick Patterson, Graham Coop, Peter Ralph, Daniel Falush, and Daniel Lawson for helpful comments and suggestions.

References

[1] Cavalli-Sforza LL, Edwards AW (1967) Phylogenetic analysis. Models and estimation procedures. Am J Hum Genet 19: 233-57.

[2] Felsenstein J (1982) How can we infer geography and history from gene frequencies? J Theor Biol 96: 9-20.

[3] Cann RL, Stoneking M, Wilson AC (1987) Mitochondrial DNA and human evolution. Nature 325: 31-6.

[4] Nei M, Roychoudhury AK (1974) Genic variation within and between the three major races of man, Caucasoids, Negroids, and Mongoloids. Am J Hum Genet 26: 421-43.

[5] Nei M, Roychoudhury AK (1993) Evolutionary relationships of human populations on a global scale. Mol Biol Evol 10: 927-43.

[6] Cavalli-Sforza LL, Piazza A, Menozzi P, Mountain J (1988) Reconstruction of human evolution: bringing together genetic, archaeological, and linguistic data. Proc Natl Acad Sci U S A 85: 6002-6.

[7] Li JZ, Absher DM, Tang H, Southwick AM, Casto AM, et al. (2008) Worldwide human relationships inferred from genome-wide patterns of variation. Science 319: 1100–1104.

[8] Pritchard JK, Seielstad MT, Perez-Lezaun A, Feldman MW (1999) Population growth of human Y chromosomes: a study of Y chromosome microsatellites. Mol Biol Evol 16: 1791-8.

[9] Beaumont MA, Zhang W, Balding DJ (2002) Approximate Bayesian computation in population genetics. Genetics 162: 2025-35.

[10] Schaffner SF, Foo C, Gabriel S, Reich D, Daly MJ, et al. (2005) Calibrating a coalescent simulation of human genome sequence variation. Genome Res 15: 1576–1583.

[11] Gronau I, Hubisz MJ, Gulko B, Danko CG, Siepel A (2011) Bayesian inference of ancient human demography from individual genome sequences. Nat Genet .

[12] Gutenkunst RN, Hernandez RD, Williamson SH, Bustamante CD (2009) Inferring the joint demographic history of multiple populations from multidimensional SNP frequency data. PLoS Genet 5: e1000695.

[13] Hey J, Nielsen R (2004) Multilocus methods for estimating population sizes, migration rates and divergence time, with applications to the divergence of Drosophila pseudoobscura and D. persimilis. Genetics 167: 747-60.

[14] Beerli P, Felsenstein J (1999) Maximum-likelihood estimation of migration rates and effective population numbers in two populations using a coalescent approach. Genetics 152: 763-73.

[15] Becquet C, Przeworski M (2007) A new approach to estimate parameters of speciation models with application to apes. Genome Res 17: 1505-19.

[16] Kubatko LS (2009) Identifying hybridization events in the presence of coalescence via model selection. Syst Biol 58: 478-88.

[17] Menozzi P, Piazza A, Cavalli-Sforza L (1978) Synthetic maps of human gene frequencies in Europeans. Science 201: 786-92.

[18] Pritchard JK, Stephens M, Donnelly P (2000) Inference of population structure using multilocus genotype data. Genetics 155: 945-59.

[19] Patterson N, Price AL, Reich D (2006) Population structure and eigenanalysis. PLoS Genet 2: e190.

[20] Lawson DJ, Hellenthal G, Myers S, Falush D (2012) Inference of Population Structure using Dense Haplotype Data. PLoS Genet 8: e1002453.

[21] Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, et al. (2002) Genetic structure of human populations. Science 298: 2381–2385.

[22] Liti G, Carter DM, Moses AM, Warringer J, Parts L, et al. (2009) Population genomics of domestic and wild yeasts. Nature 458: 337-41.

[23] vonHoldt BM, Pollinger JP, Lohmueller KE, Han E, Parker HG, et al. (2010) Genome-wide SNP and haplotype analyses reveal a rich history underlying dog domestication. Nature 464: 898-902.

[24] François O, Currat M, Ray N, Han E, Excoffier L, et al. (2010) Principal component analysis under population genetic models of range expansion and admixture. Mol Biol Evol 27: 1257-68.

[25] McVean G (2009) A genealogical interpretation of principal components analysis. PLoS Genet 5: e1000686.

[26] Novembre J, Stephens M (2008) Interpreting principal component analyses of spatial population genetic variation. Nat Genet 40: 646-9.

[27] Saitou N, Nei M (1987) The neighbor-joining method: a new method for reconstructing phylogenetic trees. Mol Biol Evol 4: 406-25.

[28] Felsenstein J (1973) Maximum-likelihood estimation of evolutionary trees from continuous characters. Am J Hum Genet 25: 471-92.

[29] RoyChoudhury A, Felsenstein J, Thompson EA (2008) A two-stage pruning algorithm for likelihood computation for a population tree. Genetics 180: 1095-105.

[30] Felsenstein J (1981) Evolutionary trees from gene frequencies and quantitative characters: finding maximum likelihood estimates. Evolution 35: 1229–1242.

[31] Sirén J, Marttinen P, Corander J (2011) Reconstructing population histories from single nucleotide polymorphism data. Mol Biol Evol 28: 673-83.

[32] Nielsen R, Mountain JL, Huelsenbeck JP, Slatkin M (1998) Maximum-likelihood estimation of population divergence times and population phylogeny in models without mutation. Evolution 52: 669–677.

[33] Nicholson G, Smith AV, Jónsson F, Gústafsson Ó, Stefánsson K, et al. (2002) Assessing Population Differentiation and Isolation from Single-Nucleotide Polymorphism Data. Journal of the Royal Statistical Society Series B (Statistical Methodology) 64: pp. 695-715.

[34] Cavalli-Sforza LL (1973) Analytic review: some current problems of human population genetics. Am J Hum Genet 25: 82-104.

[35] Cavalli-Sforza LL, Piazza A (1975) Analysis of evolution: evolutionary rates, independence and treeness. Theor Popul Biol 8: 127-65.

[36] Keinan A, Mullikin JC, Patterson N, Reich D (2007) Measurement of the human allele frequency spectrum demonstrates greater genetic drift in East Asians than in Europeans. Nat Genet 39: 1251-5.

[37] Reich D, Thangaraj K, Patterson N, Price AL, Singh L (2009) Reconstructing Indian population history. Nature 461: 489-94.

[38] Durand EY, Patterson N, Reich D, Slatkin M (2011) Testing for Ancient Admixture between Closely Related Populations. Mol Biol Evol 28: 2239-52.

[39] Green RE, Krause J, Briggs AW, Maricic T, Stenzel U, et al. (2010) A draft sequence of the Neandertal genome. Science 328: 710-22.

[40] Reich D, Green RE, Kircher M, Krause J, Patterson N, et al. (2010) Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature 468: 1053-60.

[41] Reich D, Patterson N, Kircher M, Delfin F, Nandineni MR, et al. (2011) Denisova admixture and the first modern human dispersals into Southeast Asia and Oceania. Am J Hum Genet 89: 516-28.

[42] Moorjani P, Patterson N, Hirschhorn JN, Keinan A, Hao L, et al. (2011) The history of African gene flow into Southern Europeans, Levantines, and Jews. PLoS Genet 7: e1001373.

[43] Rasmussen M, Guo X, Wang Y, Lohmueller KE, Rasmussen S, et al. (2011) An Aboriginal Australian genome reveals separate human dispersals into Asia. Science 334: 94-8.

[44] Huson D, Rupp R, Scornavacca C (2010) Phylogenetic Networks. Concepts, Algorithms and Applications. Cambridge University Press.

[45] Huson DH, Bryant D (2006) Application of phylogenetic networks in evolutionary studies. Mol Biol Evol 23: 254-67.

[46] Dyer RJ, Nason JD (2004) Population Graphs: the graph theoretic shape of genetic structure. Mol Ecol 13: 1713-27.

[47] Coop G, Witonsky D, Di Rienzo A, Pritchard JK (2010) Using environmental correlations to identify loci underlying local adaptation. Genetics 185: 1411-23.

[48] Weir BS, Hill WG (2002) Estimating F-statistics. Annu Rev Genet 36: 721-50.

[49] Felsenstein J (2003) Inferring Phylogenies. Sinauer Associates, 2nd edition.

[50] DeGiorgio M, Jakobsson M, Rosenberg NA (2009) Out of Africa: modern human origins special feature: explaining worldwide patterns of human genetic variation using a coalescent-based serial founder model of migration outward from Africa. Proc Natl Acad Sci U S A 106: 16057-62.

[51] Jakobsson M, Scholz SW, Scheet P, Gibbs JR, VanLiere JM, et al. (2008) Genotype, haplotype and copy-number variation in worldwide human populations. Nature 451: 998-1003.

[52] Hellenthal G, Auton A, Falush D (2008) Inferring human colonization history using a copying model. PLoS Genet 4: e1000078.

[53] Lu Y, Patterson N, Zhan Y, Mallick S, Reich D (2011). Technical design document for a SNP array that is optimized for population genetics. URL `ftp://ftp.cephb.fr/hgdp_supp10/8_12_2011_Technical_Array_Design_Document.pdf`.

[54] Price AL, Tandon A, Patterson N, Barnes KC, Rafaels N, et al. (2009) Sensitive detection of chromosomal segments of distinct ancestry in admixed populations. PLoS Genet 5: e1000519.

[55] Xu S, Huang W, Qian J, Jin L (2008) Analysis of genomic admixture in Uyghur and its implication in mapping strategy. Am J Hum Genet 82: 883-94.

[56] Boyko AR, Quignon P, Li L, Schoenebeck JJ, Degenhardt JD, et al. (2010) A simple genetic architecture underlies morphological variation in dogs. PLoS Biol 8: e1000451.

[57] American Kennel Club (2006) The complete dog book. Ballantine Books.

[58] Novembre J, Johnson T, Bryc K, Kutalik Z, Boyko AR, et al. (2008) Genes mirror geography within Europe. Nature 456: 98-101.

[59] Novembre J, Ramachandran S (2011) Perspectives on human population structure at the cusp of the sequencing era. Annu Rev Genomics Hum Genet 12: 245-74.

[60] Myers S, Hellenthal G, Lawson D, Busby G, Leslie S, et al. (2011). LD patterns in dense variation data reveal information about the history of human populations worldwide. URL http://www.ichg2011.org/cgi-bin/ichg11s?&sort=ptimes&sbutton=Detail&absno=21708&sid=806980.

[61] Lawson CL, Hanson RJ (1995) Solving least squares problems. Philadelphia, PA: Society for Industrial Mathematics, 3rd edition.

[62] Press WH, Teukolsky SA, Vetterling WT, Flannery BP (1992) Numerical recipes in C (2nd ed.): the art of scientific computing. New York, NY, USA: Cambridge University Press.

[63] Hudson RR (2002) Generating samples under a Wright-Fisher neutral model of genetic variation. Bioinformatics 18: 337-8.

[64] Sukumaran J, Holder MT (2010) DendroPy: a Python library for phylogenetic computing. Bioinformatics 26: 1569-71.

Supplementary Material for: Inference of population splits and mixtures from genome-wide allele frequency data

Joseph K. Pickrell[1,3,†], Jonathan K. Pritchard[1,2,†]

[1] Department of Human Genetics and

[2] Howard Hughes Medical Institute, University of Chicago

[3] Current address: Department of Genetics, Harvard Medical School

† To whom correspondence should be addressed: joseph_pickrell@hms.harvard.edu, pritch@uchicago.edu

March 1, 2012

Correcting covariances for finite sample size. In the main text, we define the variance-covariance matrix $\hat{\mathbf{W}}$ of allele frequencies between populations without accounting for sampling variance. Here, we show the calculations corrected for sample size. Consider n biallelic loci typed in m populations of diploid individuals, and let the sample size in population i at locus k be N_{ik} (with missing data, the number of individuals can vary across loci). Let the counts of the two alleles in population i at locus k be n_{ik} and $2N_{ik} - n_{ik}$ (with one allele being arbitrarily defined as the reference in all that follows), the true allele frequency in the population be X_{ik}, and the observed allele frequency be $\hat{X}_{ik} = \frac{n_{ik}}{2N_{ik}}$. We assume the n_{ik} are binomially distributed with parameters $2N_{ik}$ and X_{ik}, and are independent for all i and k. Recall that the allele frequency in the ancestral population is x_A, and that the covariance between populations i and j with respect to the ancestral frequency x_A is $\mathbf{V}_{ij}$. We begin by defining $\mathbf{V}_{ij}$ using the observed allele frequencies at a single SNP k:

$$\begin{aligned}\mathbf{V}_{ij} &= E[(\hat{X}_{ik} - x_A)(\hat{X}_{jk} - x_A)] && (1)\\ &= E\big[[(\hat{X}_{ik} - X_{ik}) + (X_{ik} - x_A)][(\hat{X}_{jk} - X_{jk}) + (X_{jk} - x_A)]\big] && (2)\\ &= E[(X_{ik} - x_A)(X_{jk} - x_A)] + E[(\hat{X}_{ik} - X_{ik})(\hat{X}_{jk} - X_{jk})]. && (3)\end{aligned}$$

The bias in the estimate of $\mathbf{V}_{ij}$ is thus $E[(\hat{X}_{ik} - X_{ik})^2]$ if $i = j$ (i.e., it is the sampling variance in X_{ik}) and zero otherwise. This follows from the fact that the x_{ik} are assumed to be independent across i.

Now consider all n SNPs, and let the mean bias across all SNPs be B_i. At a given SNP k, the sampling variance in population j is $\hat{X}_{ik}$ is $\frac{X_{ik}(1-X_{ik})}{2N_{ik}}$ (from the binomial sampling of x_{ik}), so the mean bias across SNPs is proportional to $\overline{X_{ik}(1 - X_{ik})}$ (i.e., the mean across all SNPs of $X_{ik}(1 - X_{ik})$). A natural estimator of B_i is then:

$$B_i = \frac{h_i}{4N_i} \tag{4}$$

where h_i is an unbiased estimate of the heterozygosity in population i averaged over all SNPs [Nei, 1978]:

$$h_i = \frac{1}{n}\sum_{k=1}^{n}\frac{n_{ik}(2N_i - n_{ik})}{N_i(2N_i - 1)}. \tag{5}$$

As derived in the main text, the covariance of populations i and j with respect to the sample mean, $\mathbf{W}_{ij}$, is:

$$\mathbf{W}_{ij} = \mathbf{V}_{ij} - \frac{1}{m}\sum_{k=1}^{m}\mathbf{V}_{ik} - \frac{1}{m}\sum_{k=1}^{m}\mathbf{V}_{jk} + \frac{1}{m^2}\sum_{k=1}^{m}\sum_{k'=1}^{m}\mathbf{V}_{kk'}. \tag{6}$$

The bias in the estimate of $\hat{\mathbf{W}}_{ij}$ (let us call this B'_{ij}) is then:

$$B'_{ij} = I_{[i=j]}B_i - \frac{B_i}{m} - \frac{B_j}{m} + \frac{\sum_{k=1}^{m} B_k}{m^2} \tag{7}$$

where $I_{[i=j]}$ is an indicator that evaluates to 1 if $i = j$ and zero otherwise. We can then estimate the unbiased covariance $\hat{\mathbf{W}}_{ij}$ as:

$$\hat{\mathbf{W}}_{ij} = \frac{\sum_{k=1}^{n} (\hat{X}_{ik} - \mu_k)(\hat{X}_{jk} - \mu_k)}{n-1} - B'_{ij} \tag{8}$$

where $\mu_k = \frac{\sum_{i=1}^{m} \hat{X}_{ik}}{m}$. If there is missing data in either population i or population j, we simply ignore the SNP for that pairwise comparison of populations. Since the mean allele frequency across populations is important here, large amounts of missing data (or correlated missingness between populations) could result in skewed covariances. We thus exclude populations with large amounts of missing data.

Nonidentifiability of the drift parameters in an admixed population. In the main text, we write down a model for the allele frequencies in an admixed population, and claim that the amount of genetic drift occurring before and after the mixture event are nonidentifiable. Consider the graph in Supplementary Figure 1. We can write down the expected variances and covariances involving the admixed population (the allele frequency in this population is denoted X_2):

$$\mathbf{V}_{12} = (1-w)c_4 x_A[1-x_A] \tag{9}$$

$$\mathbf{V}_{23} = w c_5 x_A[1-x_A] \tag{10}$$

$$\mathbf{V}_{22} = [c_1 + w^2(c_2 + c_5) + (1-w)^2(c_3 + c4)]x_A[1-x_A] \tag{11}$$

and we are interested in estimating w, c_1, c_2, and c_3. It is clear from the above that c_1, c_2, and c_3 do not appear except as a linear combination. Adding additional populations does not add additional information about these parameters, unless they are assumed to result from the same mixture event.

We choose to set c_2 and c_1 to zero, and estimate only c_3, which can now be thought of as a composite branch length that sums all the three components of genetic drift. A subtle point is that all of this drift is weighted by $(1-w)$. When estimating w, then, the true relative contributions of c_1, c_2, and c_3 could lead to a bias in the estimation of w. For example, if c_1 and/or c_2 are large, this could bias the estimation of $(1-w)$ upwards. We believe this is likely the cause of the downward bias in w in the simulations in Figure 2D in the main text.

Graph representation of the *TreeMix* model. In the main text, we describe a specification of $\mathbf{V}$ (the variance/covariance matrix of allele frequencies, defined with respect to an ancestral population) in terms of a system of linear equations. A useful alternate notation describes $\mathbf{V}$ in terms of a graph. Let G be a rooted, directed, acyclic graph with a set of nodes N and a set of directed edges E. Each edge e has an associated length, c_e, and a weight, w_e (between zero and one). A special class of edges, called migration edges, are forced to have length zero. The sum of weights of edges entering a given node is one. There is one node which is the root (a node with only outgoing edges), and each population corresponds to a tip (a node with only incoming edges).

Define $\{P_i\}$ to be the set of all possible paths in G from the root to the tip corresponding to population i (if the graph is a tree, there is only one such path). Each individual path p has a weight, $w(p) = \Pi_{e \in p} w_e$. Now define the overlap between two paths as:

$$O(p_i, p_j) = \sum_{e \in p_i} w(p_i) w(p_j) I[e \in p_j] c_e \tag{12}$$

where $I[e \in p_j]$ is a function that evaluates to one if edge e is in p_j, and zero otherwise. We can now write down the expected covariance between populations i and j as:

$$\mathbf{V}_{ij} = \sum_{p_i \in \{P_i\}} \sum_{p_j \in \{P_j\}} O(p_i, p_j). \tag{13}$$

In the special case where G is a tree, there is only one path per population and all of the edges have weight one, and so $\mathbf{V}_{ij}$ reduces to a sum of the lengths of branches shared by the two populations.

Relationship of this model to $f-$ statistics. Tests for "treeness" in three and four-population trees [Keinan et al., 2007; Reich et al., 2009] have used a framework in which the distances between populations are quantified in terms of "$f-$statistics" comparing the allele frequencies between the populations. Below, we briefly describe these tests in the notation of our model. Consider the expected f_3 statistic calculated between populations 1, 2, and 3, with corresponding allele frequencies X_1, X_2, and X_3.

$$f_3(X_1; X_2, X_3) = E[(X_1 - X_2)(X_1 - X_3)] \tag{14}$$

$$= E\big[[(X_1 - x_A) - (X_2 - x_A)][(X_1 - x_A) - (X_3 - x_A)]\big] \tag{15}$$

$$= \mathbf{V}_{11} - \mathbf{V}_{12} - \mathbf{V}_{13} + \mathbf{V}_{23}. \tag{16}$$

Consider the situation where populations 1 and 3 form a clade relative to 2 (i.e., population 2 is an outgroup). If population X_1 is not admixed, this reduces to:

$$f_3(X_1; X_2, X_3) = \mathbf{V}_{11} - \mathbf{V}_{13}. \tag{17}$$

This is necessarily greater than zero (since $\mathbf{V}_{13} <= \mathbf{V}_{11}$). If X_1 is admixed, then $\mathbf{V}_{12}$ can be important and the f_3 statistic can be negative. A test for a negative f_3 statistic is thus a test for admixture in population X_1 [Reich et al., 2009]. However, this signal can be weakened by large amounts of drift in X_1 (i.e., a large $\mathbf{V}_{11}$), or mixture between X_2 and X_3 [Reich et al., 2009].

Similarly, consider the expected f_4 statistic computed on the tree [[1,2],[3,4]], where 1, 2, 3, and

4 are populations, and X_1, X_2, X_3 and X_4 are the corresponding allele frequencies:

$$\begin{aligned} f_4(X_1, X_2; X_3, X_4) &= E[(X_1 - X_2)(X_3 - X_4)] && (18)\\ &= E\big[[(X_1 - x_A) - (X_2 - x_A)][(X_3 - x_A) - (X_4 - x_A)]\big] && (19)\\ &= \mathbf{V}_{13} - \mathbf{V}_{23} - \mathbf{V}_{14} + \mathbf{V}_{24} && (20)\\ & && (21) \end{aligned}$$

If the tree is correct (i.e., if populations 1 and 2 are a clade relative to populations 3 and 4), all of these quantities are zero. A test for a non-zero f_4 statistic is thus a test for treeness [Reich et al., 2009].

Simulation commands. For all simulations, we used *ms* [Hudson, 2002]. To generate the tree-like data depicted in Figure 2A in the main text, the command is:

```
ms 400 400 -t 200 -r 200 500000 -I 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20
20 20 20 20 20 -en 0.00270 20 0.025 -ej 0.00275 20 19 -en 0.00545 19 0.025 -ej 0.00550
19 18 -en 0.00820 18 0.025 -ej 0.00825 18 17 -en 0.01095 17 0.025 -ej 0.011 17 16 -en
0.01370 16 0.025 -ej 0.01375 16 15 -en 0.01645 15 0.025 -ej 0.01650 15 14 -en 0.01920
14 0.025 -ej 0.01925 14 13 -en 0.02195 13 0.025 -ej 0.02200 13 12 -en 0.02470 12 0.025
-ej 0.02475 12 11 -en 0.02745 11 0.025 -ej 0.02750 11 10 -en 0.03020 10 0.025 -ej 0.03025
10 9 -en 0.03295 9 0.025 -ej 0.03300 9 8 -en 0.03570 8 0.025 -ej 0.03575 8 7 -en 0.03845
7 0.025 -ej 0.03850 7 6 -en 0.04120 6 0.025 -ej 0.04125 6 5 -en 0.04395 5 0.025 -ej
0.04400 5 4 -en 0.04670 4 0.025 -ej 0.04675 4 3 -en 0.04945 3 0.025 -ej 0.04950 3 2
-en 0.05220 2 0.025 -ej 0.05225 2 1
```

To create trees with considerably longer branch lengths, we multiplied all branch lengths by 50:

```
ms 400 400 -t 200 -r 200 500000 -I 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20
20 20 20 20 20 -en 0.135 20 0.025 -ej 0.1375 20 19 -en 0.2725 19 0.025 -ej 0.275 19
18 -en 0.41 18 0.025 -ej 0.4125 18 17 -en 0.5475 17 0.025 -ej 0.55 17 16 -en 0.685
16 0.025 -ej 0.6875 16 15 -en 0.8225 15 0.025 -ej 0.825 15 14 -en 0.96 14 0.025 -ej
0.9625 14 13 -en 1.0975 13 0.025 -ej 1.1 13 12 -en 1.235 12 0.025 -ej 1.2375 12 11
-en 1.3725 11 0.025 -ej 1.375 11 10 -en 1.51 10 0.025 -ej 1.5125 10 9 -en 1.6475 9
0.025 -ej 1.65 9 8 -en 1.785 8 0.025 -ej 1.7875 8 7 -en 1.9225 7 0.025 -ej 1.925 7
6 -en 2.06 6 0.025 -ej 2.0625 6 5 -en 2.1975 5 0.025 -ej 2.2 5 4 -en 2.335 4 0.025
-ej 2.3375 4 3 -en 2.4725 3 0.025 -ej 2.475 3 2 -en 2.61 2 0.025 -ej 2.6125 2 1
```

For simulations with migration, we added a migration event approximately 100 generations before the present. For example, migration from population 1 to population 10:

```
ms 400 400 -t 200 -r 200 500000 -I 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20
```

```
20 20 20 20 20 -em 0.002675 10 1 4000 -en 0.00270 20 0.025 -em 0.00270 10 1 0 -ej 0.00275
20 19 -en 0.00545 19 0.025 -ej 0.00550 19 18 -en 0.00820 18 0.025 -ej 0.00825 18 17
-en 0.01095 17 0.025 -ej 0.011 17 16 -en 0.01370 16 0.025 -ej 0.01375 16 15 -en 0.01645
15 0.025 -ej 0.01650 15 14 -en 0.01920 14 0.025 -ej 0.01925 14 13 -en 0.02195 13 0.025
-ej 0.02200 13 12 -en 0.02470 12 0.025 -ej 0.02475 12 11 -en 0.02745 11 0.025 -ej 0.02750
11 10 -en 0.03020 10 0.025 -ej 0.03025 10 9 -en 0.03295 9 0.025 -ej 0.03300 9 8 -en
0.03570 8 0.025 -ej 0.03575 8 7 -en 0.03845 7 0.025 -ej 0.03850 7 6 -en 0.04120 6 0.025
-ej 0.04125 6 5 -en 0.04395 5 0.025 -ej 0.04400 5 4 -en 0.04670 4 0.025 -ej 0.04675
4 3 -en 0.04945 3 0.025 -ej 0.04950 3 2 -en 0.05220 2 0.025 -ej 0.05225 2 1
```

Discussion of simulation errors. In Figure 2C in the main text, we showed that *TreeMix* was extremely accurate in most simulation situations. However, there are a few situations in which it performed poorly. Most notably, this was for simulated admixture between population 1 and 5. The errors in these simulations tended to be of the same type (Supplementary Figure 5). Additionally, in the simulations of migration from population 15 to population 20 with a weight of 10%, there was also a considerable error rate. However, these errors were not consistent across simulations, and are likely due to the algorithm simply not detecting the admixture event at all.

Analysis of human data including Oceanian populations. As described in the main text, in the human HGDP data we used two sets of allele frequencies with different ascertainment schemes– one at SNPs ascertained by sequencing a single Yoruban individual, and one at SNPs ascertained by sequencing a single French individual. We initially ran *TreeMix* on both data sets using all populations to estimate the maximum likelihood trees. The trees estimated using the two ascertainment schemes are nearly identical (Supplementary Figure 8). We then used *TreeMix* to identify migration events. The algorithm arrived at quite different conclusions about the Oceanian populations in the two different data sets (recall that these are the exact same individuals, just genotyped at different SNPs) (Supplementary Figure 10). In the Yoruba-ascertained data, the East Asian populations are inferred to be admixed, with the Melanesians as a source population. However, in the French-ascertained data, the Oceanians are inferred to be admixed. When the Oceanian populations are excluded from analysis, the algorithm comes up with nearly the same graph in both datasets (Figure 4 in the main text and Supplementary Figure 7).

It is not immediately clear why there is a discrepancy between these two datasets when looking at Oceanian populations. However, Oceania has a particularly complicated genetic makeup, involving at least four distinct components of ancestry: Denisovan gene flow, Neandertal gene flow, native Oceanian, and gene flow from Austronesian speakers [Reich et al., 2010, 2011; Wollstein et al., 2010]. These different components of ancestry may be picked up to differing extents by SNPs from the different ascertainment panels, leading to conflicting results.

List of migration events inferred in the human data. Here we list the ten migration edges inferred in the human data and present in Figure 4 in the main text:

1. Sardinian → Mozabite, $w = 70\%$
2. Mozabite → (Palestinian,Bedouin), $w = 13\%$
3. Mozabite → Druze, $w = 6\%$
4. Mozabite → (Brahui, Makrani), $w = 5\%$
5. Dai → Cambodian, $w = 84\%$
6. (All Europe, Middle Eastern excluding Mozabite) → Hazara, $w = 47\%$
7. (All Europe, Middle Eastern excluding Mozabite) → Uygur, $w = 46\%$
8. All Native Americans → Russian, $w = 11\%$
9. Orcadian → Maya, $w = 11\%$
10. Orcadian → All Native Americans, $w = 8\%$

List of migration events inferred in the dog data. Here we list the ten migration edges inferred in the dog data and present in Figure 6 in the main text:

1. Greyhound → Borzoi, $w = 40\%$
2. American Eskimo Dog → Samoyed, $w = 53\%$
3. Wolf → Basenji, $w = 25\%$
4. (Brussels Griffon, Pug) → (Pekingese, Shih Tzu), $w = 73\%$
5. Bulldog → Bull mastiff, $w = 33\%$
6. Boxer → Chinese shar-pei, $w = 9\%$
7. Siberian Husky → ((Pekingese, Shih Tzu),(Chow Chow, Chinese shar-pei),Akita), $w = 20\%$
8. Wolf → Boxer, $w = 9\%$
9. (Mastiff, Bull Mastiff) → Saint Bernard, $w = 24\%$
10. Whippet → Italian Greyhound, $w = 35\%$

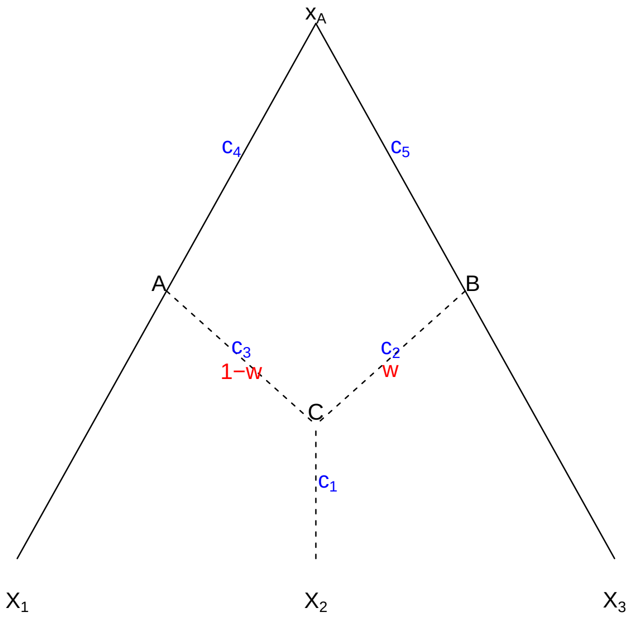


Figure 1: **A graph with a mixture event.** Capital letters represent nodes, branch length parameters are in blue, and weight parameters are in red.

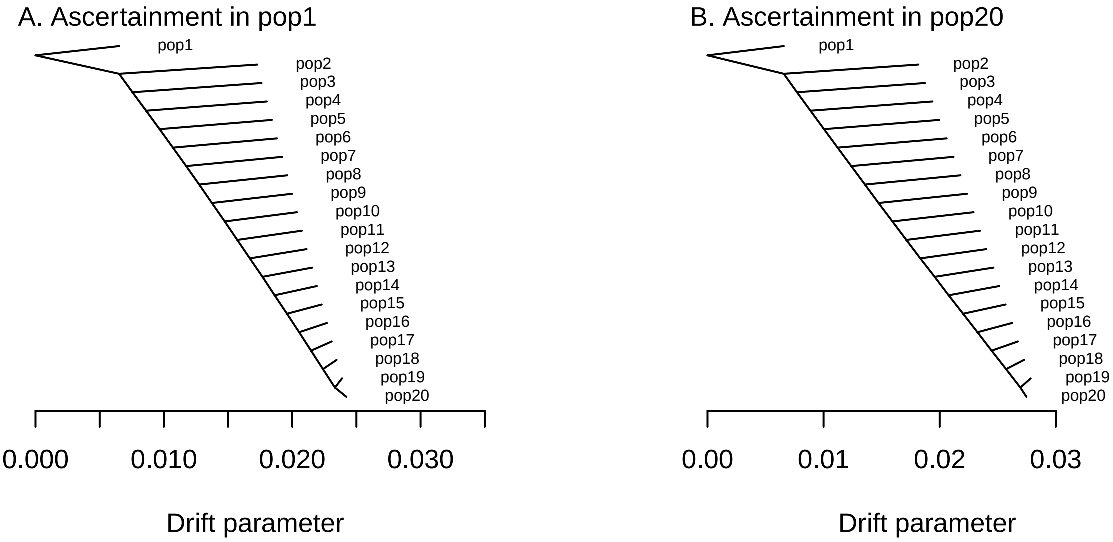


Figure 2**: Inferred trees on ascertained data.** We generated tree-like data using the topology in Figure 1A in the main text. We then used only the SNPs that were polymorphic in either population 1 (**A.**) or population 20 (**B.**) to infer the trees. The correct topology was obtained in all 100 simulations; the branch lengths in each figure are the mean across all simulations.

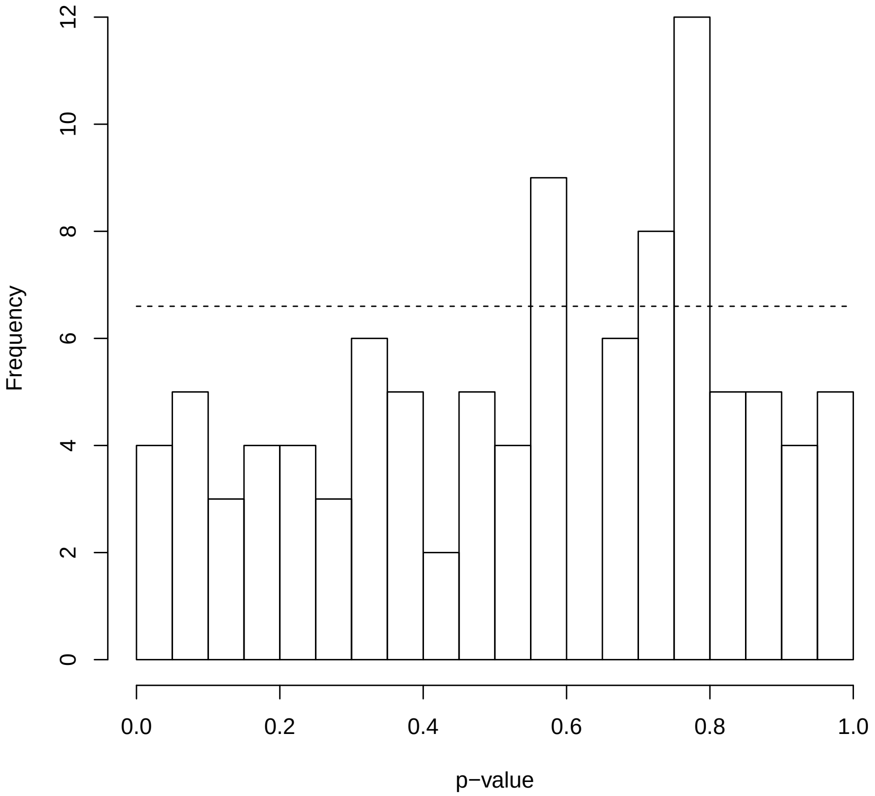


Figure 3**: Histogram of p-values for migration in simulated data.** We generated 100 tree-like datasets using the topology in Figure 1A in the main text. We then randomly chose two populations (without replacement), added a migration edge between the two populations, and tested for significance using the procedure described in the main text. Plotted is the histogram of p-values for the significance test. If the p-values are properly calibrated, this distribution should be uniform (dotted line). Though the distribution is not completely uniform, there is no skew towards low p-values.

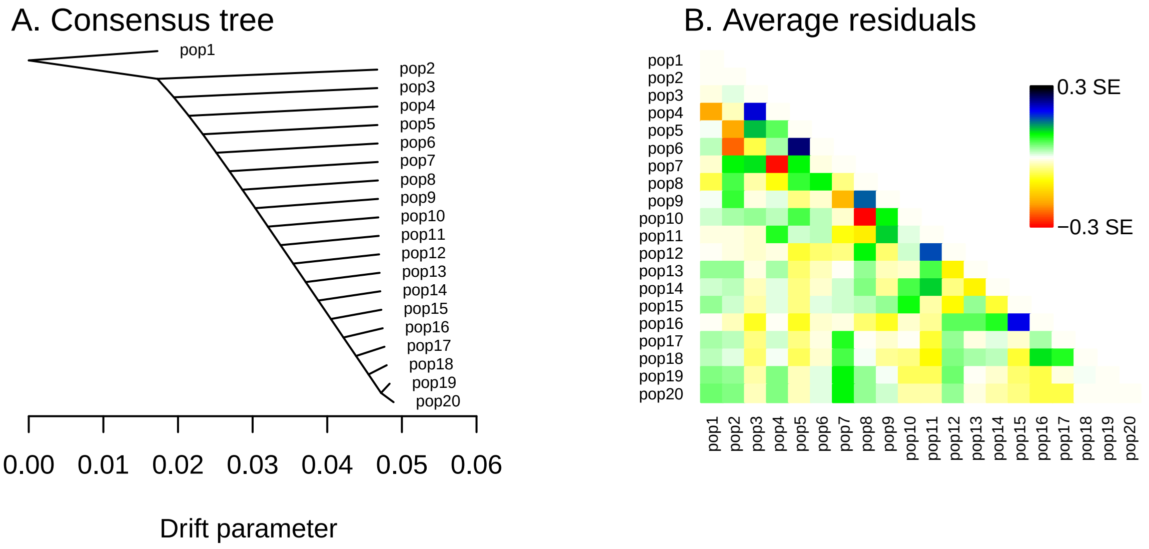


Figure 4: **Consensus tree in simulations with long branches.** We generated 100 tree-like datasets using the topology in Figure 1A in the main text, multiplying all branch lengths by 50. We then inferred the maximum likelihood tree. **A.** Plotted are the mean branch lengths from the simulations. All simulations resulted in the same inferred topology. **B.** In each simulation, we scaled the residuals by the average standard error, then averaged these scaled residuals across simulations. Plotted are the mean scaled residuals across the 100 simulations. The most extreme residuals are not large (around 0.3 standard errors), but tend to be present between closely related populations.

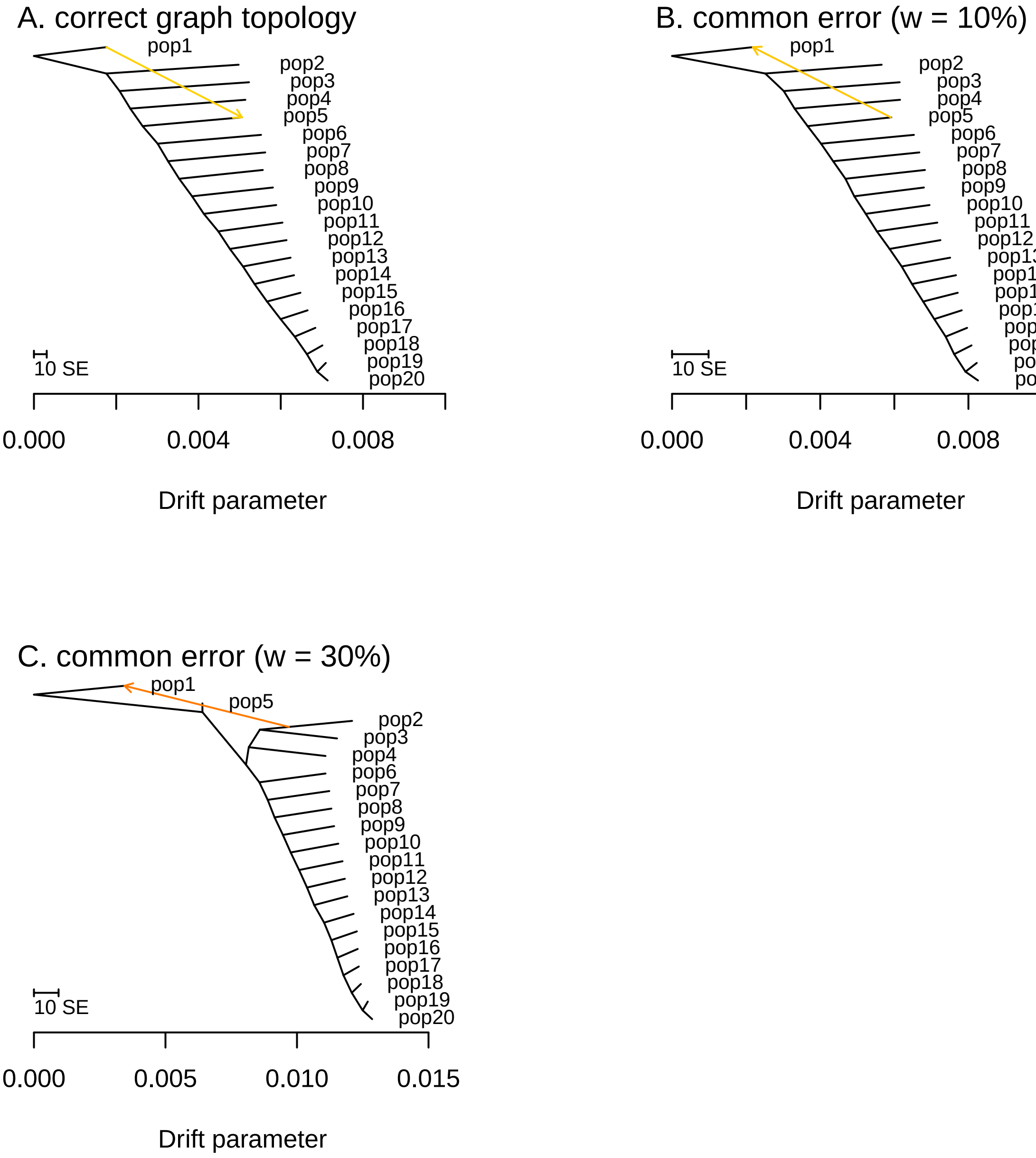


Figure 5: **Representative errors in simulations.** We examined the simulations in which *Treemix* did not reach the correct answer. **A.** The correct topology for the simulations presented in the other panels. **B.** A representative example of an incorrect topology inferred from the simulations of a migration event with weight 10% from population 1 to population 5 (this topology accounted for all observed errors). **C.** A representative example of an incorrect topology inferred from the simulations of a migration event with weight 30% from population 1 to population 5 (this topology accounted for 95% of all errors).

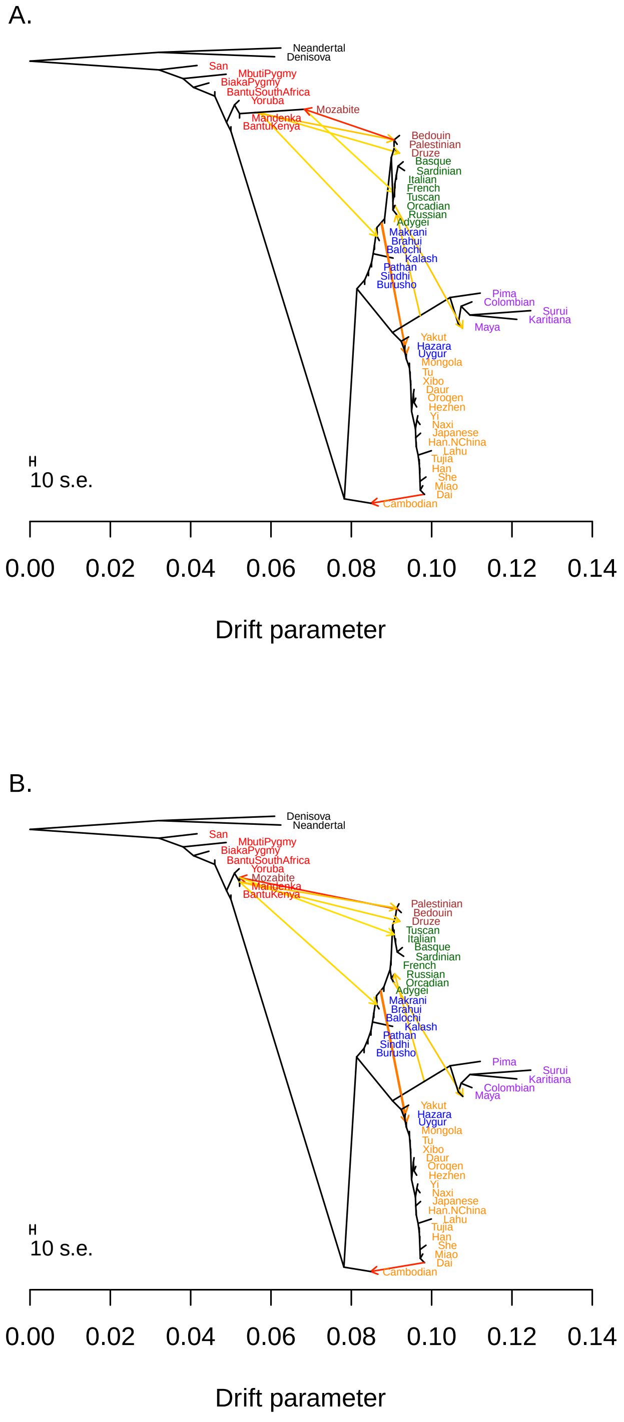


Figure 6**: Replicate graphs inferred in the human data.** These graphs were generated in an identical manner as Figure 4 in the main text, but using different random input orders for populations during tree-building. All random input orders gave very similar results.

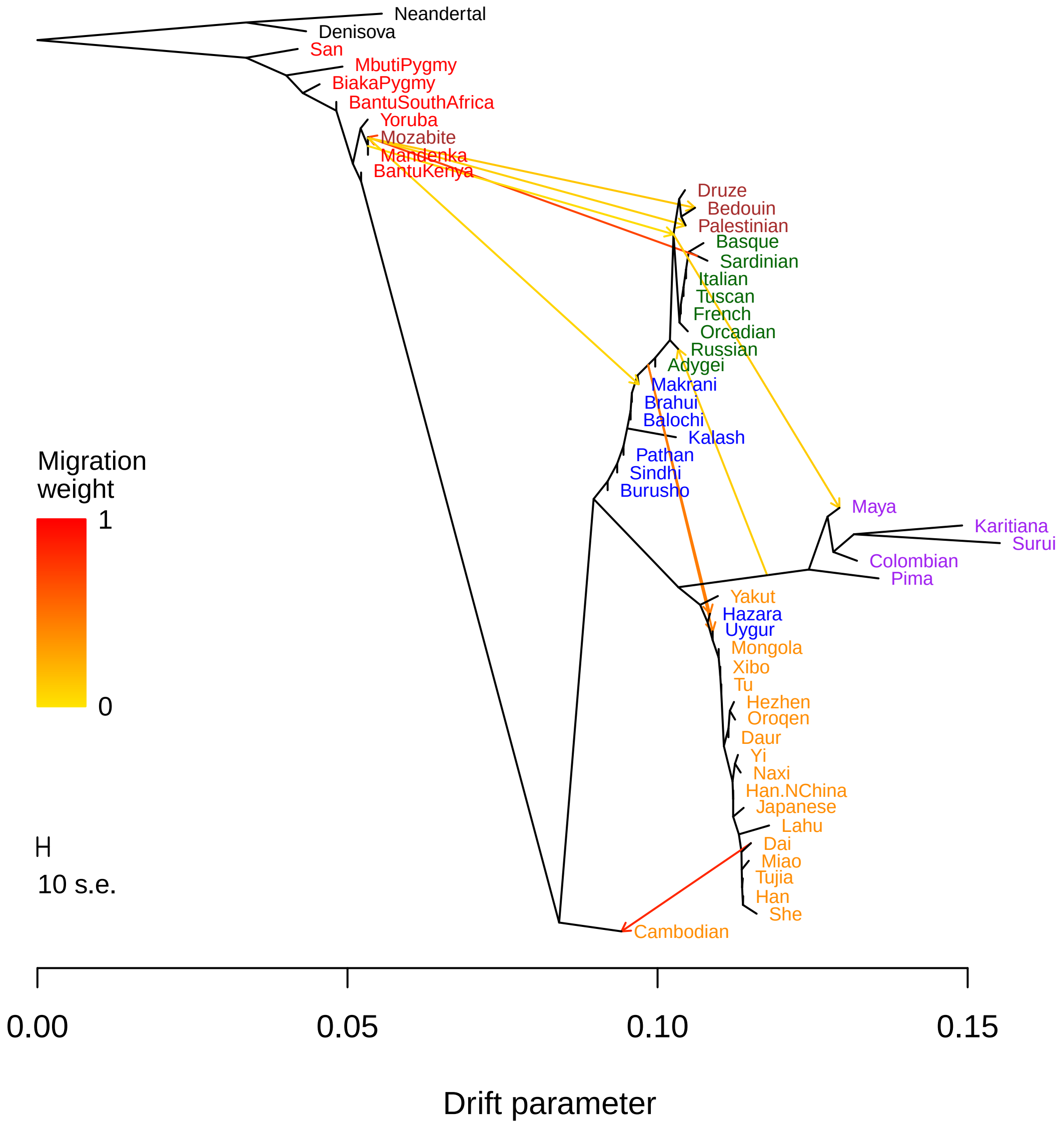


Figure 7: **Graph inferred from SNPs ascertained in a single French individual.** The graph was generated in an identical manner as Figure 4 in the main text, but using a panel of SNPs ascertained in a single French, rather than a single Yoruban, individual. The inferred graph is extremely similar to that in Figure 4. Note that the migration event from the Orcadians to all Native Americans (present in Figure 4 in the main text) is absent in this graph with 10 migration events. In fact, this would be the 11th migration event in these data (not shown).

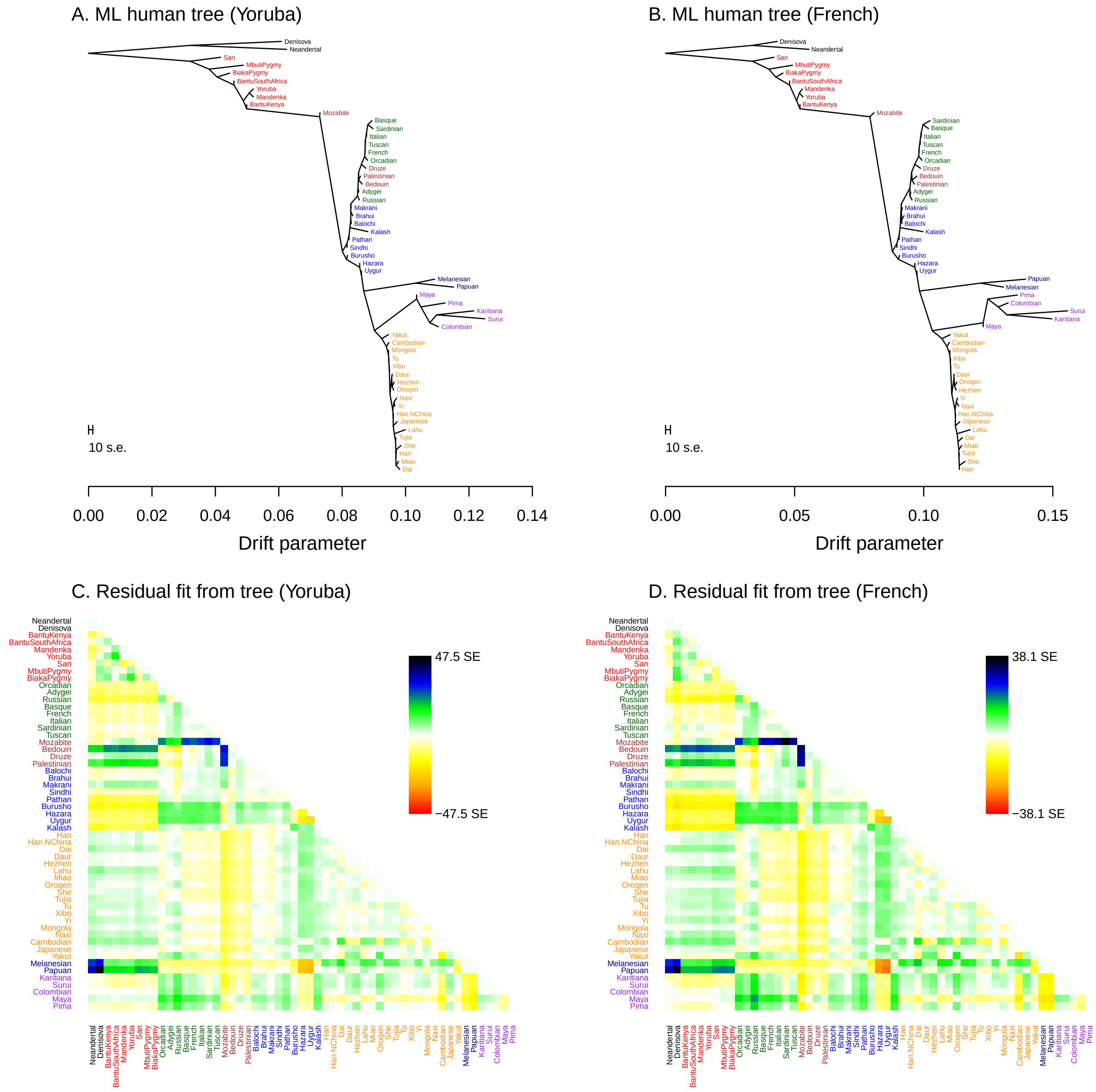


Figure 8**: Trees inferred using the human data including the Oceanians.** We show the maximum likelihood trees and residuals for the human data including the Oceanian populations, plotted in the same manner as in Figure 3 in the main text. Trees were inferred using the panel of SNPs ascertained in a single Yoruban individual (**A.** and **C.**) and the panel of SNPs ascertained in a single French individual (**B.** and **D.**). See Supplementary Material for discussion.

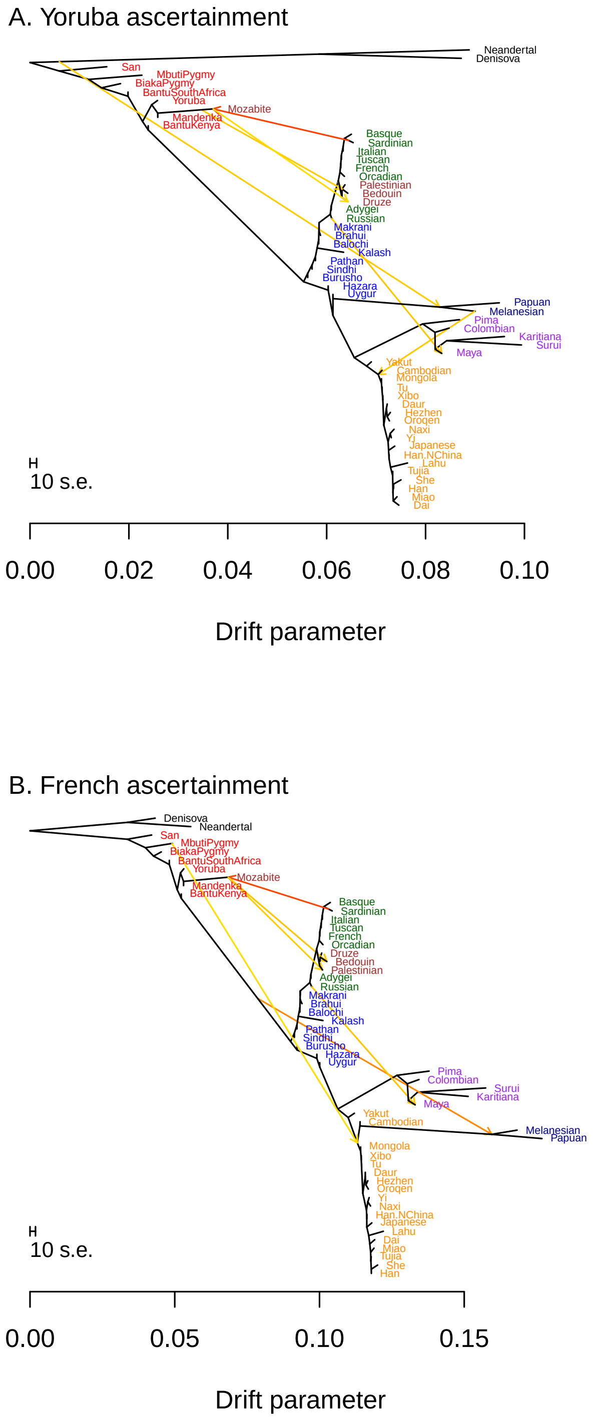


Figure 9: **Graphs inferred using the human data including the Oceanians.** We show the maximum likelihood graphs for the human data including the Oceanian populations, plotted in the same manner as in Figure 4 in the main text. Six migration edges were inferred in each graph. Graphs were inferred using the panel of SNPs ascertained in a single Yoruban individual (**A.**) and the panel of SNPs ascertained in a single French individual (**B.**). See Supplementary Material for discussion.

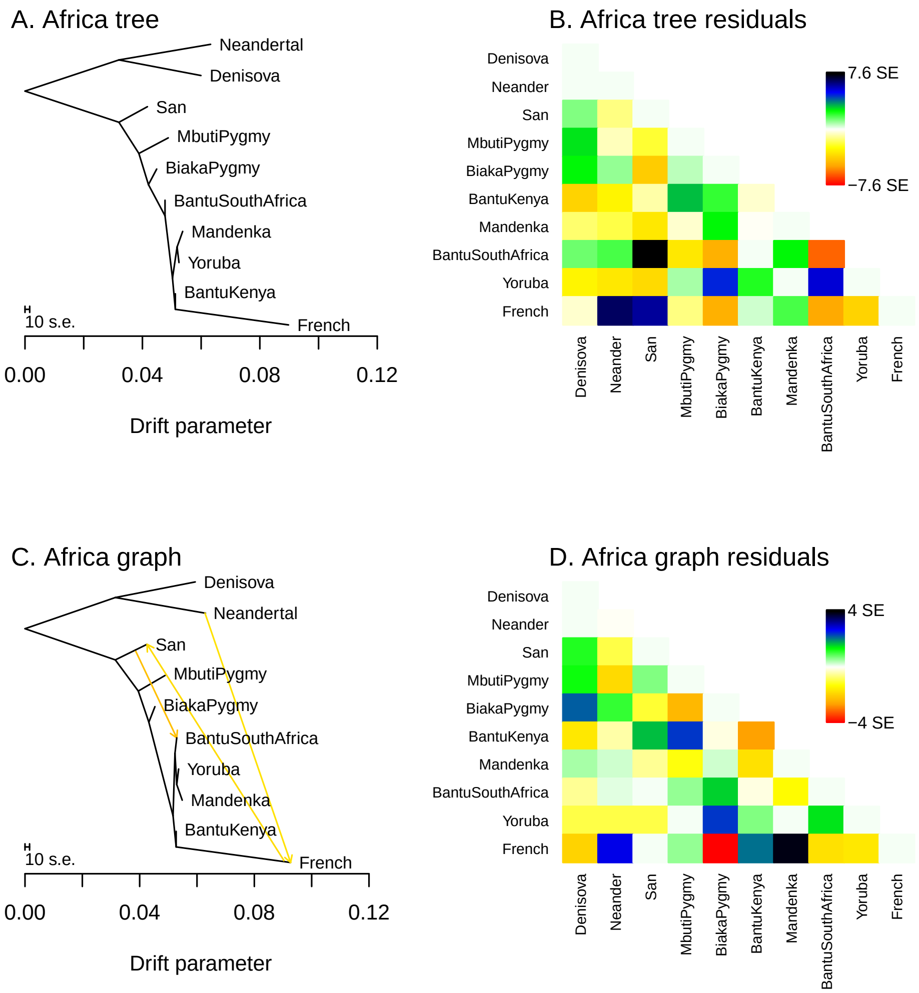


Figure 10: ***TreeMix* run on human data using only a single non-African population.** We inferred the maximum likelihood tree (**A.**) using only the African populations and one non-African population (French), using SNPs identified in a single Yoruban individual. In examining the residuals (**B.**), a relationship between the French and the Neandertal is clear. We then inferred three migration events (**C.**), where we do see that the French contain some Neandertal ancestry ($w = 1.2\%$). Residual fit for this graph is shown in **D.**

References

Cavalli-Sforza, L. L. and Piazza, A., 1975. Analysis of evolution: evolutionary rates, independence and treeness. *Theor Popul Biol*, **8**(2):127–65.

Hudson, R. R., 2002. Generating samples under a Wright-Fisher neutral model of genetic variation. *Bioinformatics*, **18**(2):337–8.

Keinan, A., Mullikin, J. C., Patterson, N., and Reich, D., 2007. Measurement of the human allele frequency spectrum demonstrates greater genetic drift in East Asians than in Europeans. *Nat Genet*, **39**(10):1251–5.

Nei, M., 1978. Estimation of average heterozygosity and genetic distance from a small number of individuals. *Genetics*, **89**(3):583–90.

Reich, D., Green, R. E., Kircher, M., Krause, J., Patterson, N., Durand, E. Y., Viola, B., Briggs, A. W., Stenzel, U., Johnson, P. L. F., *et al.*, 2010. Genetic history of an archaic hominin group from Denisova Cave in Siberia. *Nature*, **468**(7327):1053–60.

Reich, D., Patterson, N., Kircher, M., Delfin, F., Nandineni, M. R., Pugach, I., Ko, A. M.-S., Ko, Y.-C., Jinam, T. A., Phipps, M. E., *et al.*, 2011. Denisova admixture and the first modern human dispersals into Southeast Asia and Oceania. *Am J Hum Genet*, **89**(4):516–28.

Reich, D., Thangaraj, K., Patterson, N., Price, A. L., and Singh, L., 2009. Reconstructing Indian population history. *Nature*, **461**(7263):489–94.

Wollstein, A., Lao, O., Becker, C., Brauer, S., Trent, R. J., Nürnberg, P., Stoneking, M., and Kayser, M., 2010. Demographic history of Oceania inferred from genome-wide data. *Curr Biol*, **20**(22):1983–92.