Joint inference of identity by descent along multiple chromosomes from population samples

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Abstract

There has been much interest in detecting genomic identity by descent (IBD) segments from modern dense genetic marker data, and in using them to identify human disease susceptibility loci. Here we present a novel Bayesian framework using Markov chain Monte Carlo (MCMC) realizations to jointly infer IBD states among multiple individuals not known to be related, together with the allelic typing error rate and the IBD process parameters. The data are phased single nucleotide polymorphisms (SNP) haplotypes. We model changes in latent IBD state along homologous chromosomes by a continuous time Markov model having the Ewens sampling formula as its stationary distribution. We show by simulation that this model for the IBD process fits quite well with the coalescent predictions. Using simulation data sets of 40 haplotypes over regions of 1 and 10 million base pairs (Mbp), we show that the jointly estimated IBD states are very close to the true values, although the presence of linkage disequilibrium decreases the accuracy. We also present comparisons with the *ibd_haplo* program which estimates IBD among sets of four haplotypes. Our new IBD detection method focuses on the scale between genome-wide methods using simple IBD models and complex coalescent-based methods which are limited to short genome segments. At the scale of a few Mbp, our approach offers potentially more power for fine scale IBD association mapping.
1 Introduction

Identity by descent (IBD) is a fundamental concept in genetics to describe the ancestral relationships among current copies of homologous DNA. It was first introduced by Cotterman (1940) and Malécot (1948) to generalize the coefficients of inbreeding and relatedness of Wright (1921, 1922). Copies of DNA at a locus are IBD if they descend from the same ancestral DNA. Thus IBD is by definition relative to some ancestral reference population. The IBD state for a sample of homologous DNA copies can be specified as a partition into disjoint sets; copies within a set share a common ancestor relative to the ancestral reference population. To avoid confusion with alternate sets of chromosomes, alleles, or haplotypes, we will refer to the members of the sample of haploid DNA copies under consideration as gametes.

The concept of IBD has many uses in genetics, including detecting unknown familial relationships (Stevens et al. 2011), family or population based genetic mapping (Albrechtsen et al. 2009; Han and Abney 2011), genotype imputation and haplotype inference (Kong et al. 2008), measuring population structure (Weir and Cockerham 1984), and detecting natural selection (Albrechtsen et al. 2010). There has therefore been much recent interest in inferring IBD from genetic marker data, but the focus of these approaches has been pairs of gametes or pairs of diploid individuals. Leutenegger et al. (2003) developed a method to estimate inbreeding coefficients from individual genotypic data, and Browning (2008) used the same model for pairs of population haplotypes. Purcell et al. (2007) and Albrechtsen et al. (2009) summarize the latent IBD state at a locus as the number (0, 1, or 2) of gametes that are IBD at the locus between two diploid individuals. Browning and Browning (2010, 2011) further reduced the state space at a locus to none (0) or any (1) shared IBD between two individuals. The primary goal of this paper is to extend the models and methods to inference of IBD among an arbitrary number of gametes. This allows inference of joint patterns of IBD among individuals and across a segment of genome for use in subsequent genetic analyses (Browning and Thompson 2012; Glazner and Thompson 2012).

The complete historical relationship among current gametes can be described by the
genealogical tree of coalescent theory (Kingman 1982), in which ancestry is traced backward in time from the present to the most recent common ancestor of the gametes. However, for practical purposes, a reference population must be specified. In a pedigree-based study, the gametes of the pedigree founders serve naturally as the reference population. In other cases, there may be a well-defined founder population. However, in population samples without external pedigree information, there is often no clear way to specify the ancestral reference population. In this paper, we define IBD by specifying a reference population at $t_0$ generations in the past. If mutations occurring subsequent to the $t_0$ time point are ignored, this specification is the same as the concept of equivalence class used by Kingman (1982) in the formulation of the standard coalescent.

The choice of $t_0$ will depend on the purpose of inferring IBD. Here we consider the range of time depth $t_0$ of tens to a hundred generations. This is “recent” IBD (Browning 2008; Browning and Browning 2010), intermediate between pedigree-based IBD among close relatives and the ancient IBD that is a source of linkage disequilibrium (LD) in population haplotypes. The time depth $t_0$ is often specified indirectly by the probability $\eta$ of IBD between a pair of gametes. For a constant diploid population with effective size $N_e$, the ancestral coalescence rate between two gametes is $1/(2N_e)$ and thus $\eta = 1 - \exp \left[ -t_0/(2N_e) \right]$. The pairwise probability $\eta$ of IBD is approximately equal to the scaled time depth $\tau_0 = t_0/(2N_e)$, for small time depth $t_0$ ($< 10^2$ generations) and large effective size $N_e$ ($> 10^4$ for most recent human populations).

Since the IBD state at a site is the partition determined by a given time depth in the genealogical tree, the process of changing IBD states along a chromosome is determined by the process of changing genealogy due to historical recombination. In coalescent theory, it has been shown that the sequence of coalescent trees along a chromosome can be well approximated by a Markov process (McVean and Cardin 2005; Marjoram and Wall 2006). Stam (1980) first introduced a Markov model for the IBD process between two gametes, where the lengths of both IBD and non-IBD segments are exponentially distributed, and a parameter $\lambda$ measures the overall rate of change in IBD state. The two parameters $\eta$ and $\lambda$ jointly determine the level of IBD at a site and the chromosomal extent of a segment of
shared ancestry (IBD).

Thompson (2008) developed a continuous time Markov model for four gametes with a state space consisting of fifteen IBD states (the partitions of four gametes). Thompson (2009) extended the model to any number $n$ of gametes, but used it to infer IBD states across a chromosome only for $n = 2$ and $n = 4$. In this model transitions in IBD state were restricted to single gametes joining or leaving larger sets. Brown et al. (2012) relaxed the restriction by allowing any move of one gamete between the subsets of an IBD partition and implemented this model for sets of four gametes. Moltke et al. (2011) presented a model for multiple gametes, but with much more restricted state transitions.

Model-based approaches to inference of latent IBD states from population single nucleotide polymorphism (SNP) data generally use a hidden Markov model (HMM) approach. This includes the original two-gamete model of Leutenegger et al. (2003) the generalizations of Purcell et al. (2007) and Albrechtsen et al. (2009) to pairs of diploid individuals, and the more general 15-state model implemented by Brown et al. (2012). These approaches use exact HMM computational algorithms such as the forward-backward algorithm (Baum et al. 1970; Baum 1972; Rabiner 1989).

In this paper, we extend the previous work of Brown et al. (2012) to jointly estimate IBD along a chromosome among any number $n$ of gametes using the same IBD process model. However, exact HMM computations cannot be applied for larger numbers of gametes because the state space increases extremely fast with $n$ (Bell 1940). In the Methods section, we develop a Bayesian inference framework and a reversible jump Markov chain Monte Carlo (MCMC) method to estimate the latent IBD states along a chromosome, the IBD process parameters, and the allelic typing error rate. Reversible jump MCMC is needed since the number of IBD transition points can vary over MCMC realizations. We will call the new method JointIBD.

Earlier methods computed IBD probabilities (Brown et al. 2012) or sampled IBD realizations (Moltke et al. 2011) only at locations of SNP markers. By sampling IBD transition points, we achieve a more flexible MCMC process which realizes the IBD state at all points on the chromosome. This means that a long stretch of bases without SNPs may contain
multiple IBD state transitions, allowing IBD state to change substantially between one SNP
and the next. Moltke et al. (2011) achieve a similar effect by allowing multi-step transitions
between marker locations.

JointIBD combines five extensions to previous approaches. (1) It can handle an arbitrary
number of gametes (we present results based on 40 gametes), as can the method of Moltke
et al. (2011), whereas other methods can handle only a small number. (2) It models the
full set of IBD partitions at a locus, and relaxes some restrictions on IBD state transitions.
(3) As do some earlier approaches, it explicitly models typing error, and as a byproduct
may be less sensitive to non-modeled recent mutations. (4) It allows transitions of IBD at
any point on the sequence, not only at SNP locations. (5) It provides Bayesian estimates
of parameters which can be related directly to the underlying processes of coalescence at a
locus, and recombination across the genome.

In the Simulations section, we show results using simulated data from Brown et al. (2012).
We compare JointIBD results for subsets of four gametes with results from exact compu-
tation using the ibd_haplo program as implemented in the MORGAN v3.2 (2013) release
(http://www.stat.washington.edu/thompson/Genepi/MORGAN/Morgan.shtml). We con-
clude with a Discussion section.

2 Methods

2.1 The HMM Model

The data, \( y = \{y_{ij}\} \) consist of SNP haplotypes, with \( y_{ij} \) being the observed allele at SNP
site \( i (=1, \ldots, m) \) of gamete \( j (=1, \ldots, n) \). Within the population, we assume that there
are only two alleles (denoted as allele 1 and allele 2) at each SNP site. Let \( \ell \) be the length
of the chromosome in base pairs (bp), and let \( \pi_i \) be the population frequency of allele 1 at
SNP site \( i \). These allele frequencies are assumed to be known. In practice, they would be
estimated from a large population sample. We build a hidden Markov model for SNP data
\( y \), where the latent variables are the IBD states across a genome segment.
At genome location $x$, the IBD state, $Z(x)$, among gametes is represented as a partition of the $n$ gametes into IBD subsets, $v$, where each set is a collection of gametes that are IBD at a location. Thus an IBD state at a site is a partition of the set of integers $1, 2, \ldots, n$. For example $n = 6$, $Z(x) = \{\{1, 2, 6\}, \{3, 5\}, \{4\}\}$ means that at a given location $x$ gametes 1, 2 and 6 are IBD, gametes 3 and 5 are IBD, and gamete 4 is not IBD with any of the others. The ordering of subsets and of the elements within each is irrelevant. Conventionally, here we order the elements in each subset in increasing order, and order the subsets according to the smallest member of each. The Ewens sampling formula (ESF, Ewens (1972)) provides a single-parameter probability model for the $n$-gamete IBD partition at a site:

$$p_n(z|\theta) = \frac{\Gamma(\theta)^{|z|}}{\Gamma(n + \theta)} \prod_{v \in z} \Gamma(|v|),$$

where $\theta > 0$, $|v|$ denotes the number of elements in set $v$, and $\Gamma(v)$ denotes the Gamma function. From equation (1), $p_2(\{\{1, 2\}\} | \theta ) = 1/(1 + \theta)$. Thus, the parameter $\theta$ is inversely related to the probability that two elements fall in the same subset, or, in our application, that two gametes are IBD at this site. The pairwise IBD probability $\eta$ is simply $1/(1 + \theta)$.

We model the latent process of IBD transitions along chromosomes by a continuous-time reversible Markov process whose stationary distribution is given by the ESF (1). We assume that the distance to the next potential transition event along the chromosome is exponentially distributed with mean $1/\lambda$ bp. Given current state $z$ and a potential transition event, the resulting IBD state $w$ is sampled from the transition probability $p(w|z)$ specified by the modified Chinese restaurant process (MCRP, Brown et al. (2012)). Thompson (2009) and Brown et al. (2012) model SNP-to-SNP transitions in IBD state, and so build in additional flexibility by incorporating the possibility of IBD transitions independent of the current state, where the new IBD state is sampled from the stationary ESF distribution (1). Since in our model IBD transitions occur in a continuum, multiple state transitions can occur between adjacent SNPs. There is therefore no need to include this additional model component.

We briefly describe the MRCP transition process as follows. First, insert a new gamete. The gamete is inserted into any set of size $k$ with probability $k/(n + \theta)$, or as a new singleton with probability $\theta/(n + \theta)$. Next, randomly delete one of the $n + 1$ gametes. The newly
inserted gamete, if not deleted, takes the identity of the deleted one. Thus the MCRP allows any one gamete to move from one IBD subset to another. It has been shown that the IBD process along the chromosome is reversible with respect to ESF (Appendix A of Brown et al. (2012)). Using the MCRP model, we formulate the transition probability for two consecutive IBD states $z$ and $w$ along a chromosome. These transitions can result in the same IBD state ($z = w$) or a different state ($z \neq w$).

The probability of a transition for which $z = w$ is given by:

$$
p(z \mid z, \theta) = \frac{\theta}{n + \theta} \cdot \frac{a_1 + 1}{(n + 1)} + \sum_{v \in z} \frac{|v|}{n + \theta} \cdot \frac{|v| + 1}{n + 1},
$$

where $a_1$ denotes the number of singletons in $z$. Here the first term on the right hand side refers to the case in which the new gamete is inserted as a singleton and one of the singletons is then deleted, and the second term refers to the case in which the new gamete is inserted into an existing set (denoted $v$) and one of the gametes in that set is then deleted. Since some potential transitions do not produce state changes, the number of transitions predicted by a given value of $\lambda$ will generally be greater than the number of actual (i.e. state-changing) transitions. Throughout this paper, whenever we measure the number of transitions or the distance between transitions, we refer to actual transitions only. This is consistent with usage in earlier methods (Leutenegger et al. 2003; Thompson 2009; Moltke et al. 2011).

In cases where the transition changes IBD state ($z \neq w$), suppose that the new gamete is inserted into a set of size $l_1$ and the deleted gamete is from a set of size $l_2$. The transition probability $p(w \mid z, \theta)$ is given by

$$
p(w \mid z, \theta) = \begin{cases} 
\frac{\theta}{n + \theta} \cdot \frac{1 + I(l_2 = 2)}{(n + 1)} & l_1 = 0 \\
\frac{l_1}{n + \theta} \cdot \frac{1 + I(l_1 = l_2 = 1)}{(n + 1)} & l_1 > 0
\end{cases},
$$

where $I(S) = 1$ if the statement $S$ is true and 0 otherwise. This extra term arises when one doubleton splits into two singletons ($l_1 = 0, l_2 = 2$) or two singletons merge into one doubleton ($l_1 = 1, l_2 = 1$). The same state will result whichever of the two gametes is deleted (for the former case) or inserted (for the latter case). For any two states $z$ and $w$, we define the IBD distance $|z - w|$ to be the minimum number of IBD transitions necessary to transfer one into the other according to the MCRP.
We model the emission probability of SNP data given the latent IBD states. We do not model linkage disequilibrium in the ancestral reference haplotypes, so the SNP data at each site $i$ are conditionally independent given the latent IBD states. We assume that the ancestral allelic states for each IBD subset are independent among subsets and across sites, and are randomly sampled from a locus-specific ancestral allele frequency $\pi_i$. Since we consider common SNP variation and short scaled time depth $\tau_0$, we use separately estimated current allele frequencies as proxies for $\pi_i$.

Our typing error model assumes that each observed allele has a probability of $\varepsilon$ of being toggled to the alternative allele. Consider an IBD set of size $l$ at site $i$. The probability of the corresponding data vector consisting of, for example, $k$ alleles of type 1 and $(l - k)$ alleles of type 2, is proportional to

$$\pi_i (1 - \varepsilon)^k \varepsilon^{(l-k)} + (1 - \pi_i)(1 - \varepsilon)^{(l-k)} \varepsilon^k.$$ 

We assume that the scaled time depth $\tau_0$ defining the reference population is small enough that mutations on the lineages from ancestral reference alleles to the current sample can be ignored. Mutations which do occur will be interpreted as typing errors, potentially resulting in an overestimate of $\varepsilon$.

For our Bayesian prior distributions on parameters, we assign priors of high variance that suggest low levels of IBD among the $n = 40$ gametes. For the error probability $\varepsilon$, we assign a uniform distribution on the range $[0, 1]$. For the IBD level parameter $\theta$ we use a gamma distribution with shape $\alpha_\theta = 2$ and scale $\beta_\theta = 2n$. This distribution has mean 160 and standard deviation $\sim 113$, corresponding to values of $\eta$ of order of magnitude $0.006$, but permitting much higher values where the data provide evidence of IBD. For $\lambda$ we use a gamma distribution with shape $\alpha_\lambda = 2$ and scale $\beta_\lambda = 10^{-4}$, giving a mean distance 5000 bp to the next potential transition point, but again allowing for much longer or shorter segments.

For marker data with high levels of linkage disequilibrium (LD), our method tends to overestimate IBD levels due to haplotype similarities in the reference founder population (Purcell et al. 2007; Brown et al. 2012). This, in effect, increases the scaled time depth $\tau_0$ of the ancestral reference population, and hence also the IBD level $\eta$. We therefore also...
used a more informative prior distribution for $\theta$ by including a constraint, truncating the gamma prior distribution, so that $\theta \geq \theta_c = n = 40$. That is, the pairwise IBD probability $\eta$ is bounded above by $1/(1+\theta_c)$. In addition, we restrict the total number of transitions to be no greater than $K_c = 2 \times 10^{-5} \ell$.

### 2.2 Parameter Estimation

We update $Z(x)$ by reversible jump MCMC and the model parameters $\theta$, $\lambda$, and $\varepsilon$ by Gibbs sampling. As the reversible jump MCMC procedure is the novel part of this process, we describe it here: updates for other parameters are described in Supplemental Materials S4.

We define three proposal distributions for use in MCMC updates. These are briefly described here; their formal definitions are in Supplemental Materials S3.

1. The proposal distribution $q(z|z_A)$ or “one-side distribution” samples the IBD state of the new $z$, starting from the left-side $z_A$, using the MCRP. This could, for example, be used to draw a new successor ($z$) to the most rightward interval on the chromosome ($z_A$).

2. The proposal distribution $q(z|z_A, z_B)$ or “two-side distribution” samples a new $z$ which is an intermediate between the left side $z_A$ and the right side $z_B$, which must be no more than 2 steps apart; the new $z$ must be no more than 1 step from each of $z_A$ and $z_B$.

3. The proposal distribution $q(z|z_A, z_B, z_C)$ or “propagation distribution” considers a situation in which $z_A$ and $z_B$ are consecutive IBD states along the chromosome and are thus no more than 1 step apart, and where $z_C$ is a state exactly 1 step from $z_A$. If $z_B$ and $z_C$ are no more than 1 step apart, the propagation stops, that is, $z$ is set to $z_B$. Otherwise, we choose a new $z$ which is no more than 1 step from both $z_B$ and $z_C$, and is two steps from $z_A$.

This proposal distribution is used when changes of an IBD state (modification, insertion, or deletion) have to be propagated through a subsequent interval in order to avoid a violation of the MCRP model. Proceeding rightward, new values for each of the IBD segments are drawn from the propagation distribution where $z_B$ is the original state of the segment being redrawn, $z_A$ is the state of its original leftward neighbor, and $z_C$ is the state of its current leftward neighbor. This redrawing process stops as soon as a segment which is legal without modification is reached, or at the end of the chromosome.
Updates of K, x, and z use six move types briefly described here (details and proposal ratios are given in Supplemental Materials S4, as well as handling for special cases such as the end of the chromosome).

1. Update a transition location. A transition location is chosen at random and set to a new location chosen uniformly between its flanking transitions.

2. Update an IBD segment. A segment is chosen at random. A new state for this segment is chosen from the two-side distribution, with its two neighbor IBD states being the two sides.

3. Update an IBD state with adjustments to downstream material. A segment is chosen at random. A new state for this segment is chosen from the two-side distribution, with the leftward neighbor and the current IBD state as $z_A$ and $z_B$. Downstream IBD segments are drawn from the propagation distribution.

4. Insert a transition with adjustments to downstream material. A random IBD segment is chosen and a new transition location is chosen uniformly within it. The new IBD state associated with that transition is sampled from the one-side distribution based on its leftward neighbor. The downstream IBD segments are drawn from the propagation distribution.

5. Delete a transition with adjustments to downstream material. A random IBD segment is deleted. The downstream IBD segments are drawn from the propagation distribution.

6. Update segments of IBD by swapping their gamete labels. A pair of gametes is chosen at random and partitioned into segments which are IBD and segments which are not. Independently for each run of non-IBD material, we choose randomly whether or not to swap the labels for that pair of gametes.

3 Results

3.1 Generation and analysis of simulated data

We test model performance using part of the population simulation of Brown et al. (2012). In those data, a constant population of 3500 males and 3500 females was simulated over $t_0 = 200$ generations. In each generation, repeated 3500 times, a random male and a random
female were chosen to generate a son and a daughter. This mating system yields a mean of 2 diploid offspring and a variance of 4, resulting in an effective population size of $N_e = 7000 \times 4/6 \approx 4667$ (Crow and Kimura 1970). The gamete segregating from a parent is obtained by generating recombinants between the two homologous chromosomes of the parent with rate $10^{-8}$ per bp. Each founder gamete is given a unique founder label; descendant gametes are specified as a list of segments descending from the founder genomes with the same label. Among a set of sampled gametes, homologous chromosome segments with the same founder label are IBD.

The haplotypes of descendant individuals can be created by assigning founder haplotypes to the labels. Briefly, Brown et al. (2012) generated founder haplotypes as follows. First a BEAGLE haplotype cluster model (Browning and Browning 2007) was fit to a set of 1917 real haplotypes with high LD levels. These haplotypes also provided the assumed values of the SNP allele frequencies $\pi_i$. The program beaglesim (Glazner and Thompson 2012) was then used to simulate new haplotypes from the BEAGLE model. In beaglesim, a parameter $\gamma$ controls generation of data sets at varying LD levels. In generating a haplotype from the BEAGLE model, $\gamma$ is the probability of random switching among haplotype clusters at each SNP marker and thus LD is broken on average every $1/\gamma$ markers. In this paper we use only the high-LD ($\gamma = 0.05$) and no-LD ($\gamma = 1$) data sets of Brown et al. (2012). We then impose additional typing error on the data sets of Brown et al. (2012). After constructing the current generation-200 haplotypes from the founder haplotypes and the descendant founder genome segments, we simulate allelic typing errors using the same error model assumed by our analysis. We apply error independently for each marker and each gamete with probability $\varepsilon = 0.005$.

Simulated data were analyzed with JointIBD as follows: For each data set, two independent replicates were run. For each, 4 equally spaced temperatures were used, chosen adaptively during burn-in. (The length of burn-in varied among the data sets.) After burn-in, samples were taken every 20 iterations for a total of 20,000 iterations or 1000 samples. The two replicates were pooled to give 2000 samples. Potential Scale Reduction Factors (PSRFs, Gelman and Rubin (1992)) were computed between the two replicates to assess
MCMC mixing; a PSRF below about 1.05 indicates satisfactory mixing. Run conditions and PSRF values are shown in Table 1.

<table>
<thead>
<tr>
<th>Data set</th>
<th>Total steps</th>
<th>( \text{logl} )</th>
<th>( \theta )</th>
<th>( \varepsilon )</th>
<th>( \rho )</th>
<th>Transitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-NoLD</td>
<td>42,550</td>
<td>1.0007</td>
<td>1.0013</td>
<td>0.9995</td>
<td>1.0012</td>
<td>0.9998</td>
</tr>
<tr>
<td>S-LD</td>
<td>42,040</td>
<td>1.0171</td>
<td>1.0019</td>
<td>0.9996</td>
<td>0.9998</td>
<td>0.9997</td>
</tr>
<tr>
<td>L-NoLD</td>
<td>43,770</td>
<td>0.9997</td>
<td>0.9997</td>
<td>1.0037</td>
<td>1.0006</td>
<td>1.0013</td>
</tr>
<tr>
<td>L-LD</td>
<td>39,790</td>
<td>1.0480</td>
<td>0.9999</td>
<td>1.0090</td>
<td>0.9999</td>
<td>0.9998</td>
</tr>
</tbody>
</table>

Table 1: JointIBD run conditions

3.2 Fit between simulated IBD and theoretical models

Here we test the adequacy of the ESF and the MCRP to model IBD data drawn from a more detailed population model. Using the simulated population of Brown et al. (2012), we first construct samples of sets of 40 gametes (20 individuals) from the final generation and examine the true IBD transitions in these data. We partition the gametes of 3500 final-generation females into 175 sets of 40 gametes. (Only females are chosen to minimize the chance of sampling full sibs.) Recall we define the IBD distance between states as the minimum number of MCRP transitions necessary to transform one into the other. Among 534,438 state transitions, 95% have distance 1, 4.7% have distance 2, and only 0.3% have distance 3 or more. These results indicate that it is reasonable to model only IBD transitions of distance 1; those involving the move of a single gamete. Our model can explain a transition of distance 2 or more as multiple closely spaced transitions. Figure 1A shows the distribution of the bp distances between transitions. It has somewhat heavier tails and larger variance than an exponential distribution with the same mean.

We examine the empirical stationary distribution of the IBD process along chromosomes by sampling IBD states every 0.05 Mbp. As shown in Figures 1B and C, the simulated distribution of IBD states is very close to the distribution based on coalescent theory (Hein
et al. 2005) with scaled time depth $\tau_0 = t_0/(2N_e) \approx 0.0214$. The slight discrepancies may be due to the use of only one realization of the underlying population pedigree or to differences between the coalescent model and the simulation model used for IBD descent.

Figure 1B and D compare the simulation distribution with the ESF (Eq. 1). The value of $\theta$ is set to 41 so that the mean number of IBD sets is the same as for the empirical distribution. This is slightly smaller than the value calculated from the relation $\theta = (1 - \eta)/\eta \approx (1 - \tau_0)/\tau_0 \approx 46$. The distribution of the number of IBD sets based on the ESF is more dispersed than the simulated one (Figure 1B). Consistently, Figure 1D shows that the more frequent IBD states are a little under-represented by the ESF while the less frequent IBD states are a little over-represented. Overall, the ESF distribution fits the empirical distribution reasonably well.

### 3.3 MCMC inference of IBD

To assess the performance of JointIBD we use the 40 haplotypes of the first 20 female individuals from the 200th generation of the simulated population of Brown et al. (2012). We reset the location of the first marker as the origin. Bayesian estimation via MCMC simulations is computationally intensive, and thus for each of the two data sets we analyze only the initial 1Mbp (“short”) and 10Mbp (“long”) from each haplotype, corresponding to distances used in fine scale gene mapping. We analyze four data sets: short and long haplotypes with no LD ($\gamma = 1$, data sets S-NoLD and L-NoLD), and short and long haplotypes with strong LD ($\gamma = 0.05$, data sets S-LD and L-LD). There are 85 markers in the 1Mbp data sets and 860 markers in the 10Mbp data sets. In the Figures results for no-LD data are shown on the left throughout.

We first examine estimates from no-LD data for the parameters $\varepsilon$, $\theta$, $\lambda$, and the average density of IBD transitions (the number of transitions divided by the length of the chromosome). As shown in the left panels of Figure 2, the prior distributions (dashed lines) are essentially non-informative. As expected, longer sequences give a tighter posterior distribution. By chance, S-NoLD had a realized error rate of only 0.0035, while L-NoLD had a realized error of 0.0053; as a result, the estimate of $\varepsilon$ was low for the S data. The ESF pa-
Parameter $\theta$ is estimated to be around 40 from both data sets (Figure 2C), which is consistent with $t_0 = 200$ generations (see section 3.1).

Since the "true" transition rate $\lambda$ is unknown, we estimate it based on coalescent theory, and then compare the result with its posterior distribution (Fig. 2E). The average number of lineages (or IBD sets) at $\tau_0 \approx 0.0214$ for $n = 40$ gametes is estimated to be around 28 (Hein et al. (2005); see also Figure 5A). The average total coalescent branch length $L(\tau_0)$ backward to $\tau_0$ can be obtained as $L(\tau_0) = \sum_{i=28}^{40} 1/i = 0.387$. Thus, from $N_e = 4667$ and $\rho = 10^{-8}$ per generation per bp we can roughly estimate $\lambda = 2N_e\rho L(\tau_0) \approx 36$ per Mbp. This estimate falls in the range of the posterior distribution from $S$-NoLD, although it is slightly larger than the estimate from $L$-NoLD.

The number of IBD state changes realized from $S$-NoLD (Figure 2G) is not significantly smaller than the true empirical value of 18; the MCMC-based probability that this number of actual transitions is more than 18 is 0.083. The number of actual IBD transitions estimated from $L$-NoLD is around the true value of 169. Note that the transition rate $\lambda$ suggests a higher number of transitions than are actually realized, because some potential transitions do not result in a changed IBD state.

Ancestral LD is due to shared population history beyond $t_0$ generations in the past, and is not accounted for in our model. Ancestral LD results in decreased $\theta$ and increased $\lambda$ and thus an increased number of IBD transitions (right panels of Figure 2). Figures 2D and H show that, particularly for the large data set ($L$-LD), the estimated $\theta$ and the average density of IBD transitions become very sharply distributed just above the truncation thresholds (see section 2.1). As a consequence the posterior distribution of $\lambda$ is essentially identical to its prior (Figure 2E). Ancestral LD has effectively shifted the reference population backward and increased the scaled time depth $\tau_0$. Our results confirm previous studies (Purcell et al. 2007; Brown et al. 2012) showing that high LD regions are miscalled as shared IBD segments. The mismatch between our model and the LD data also leads to an overestimate of the allelic typing error rate (Figure 2B), since the miscalled IBD segments show strong haplotypic similarity but not identity.

Figure 3 evaluates our estimation framework for the detection of IBD segments, begin-
ning with the transition locations. The cumulative distributions of IBD transition location estimated from \textit{S-NoLD} and \textit{L-NoLD} are very close to the true distributions (Figure 3A and C). Gray lines in Figure 3 panels B and D show the difference between the cumulative distributions and the truth based on Figures 3A and C. Dark lines show the contrast with the method’s performance in the presence of ancestral LD. Runs with LD deviate much further from the truth, especially for \textit{S-LD}.

To assess accuracy of state reconstruction, at each SNP marker location we evaluate the inferred marginal IBD state by the probability that the distance between a random estimated IBD state and the true IBD state is no greater than 2. As shown in Figure 4, IBD states are not well estimated in the presence of LD in the founder genomes. This is explained by the increased number of inferred IBD transitions (see Figure 2G and H) so that on average fewer markers provide information about each IBD state. Estimation of IBD state is also affected by the local density of SNP markers, as indicated by the poorer estimation of IBD around the 8Mbp location in Figure 4C. There are only 31 SNP markers between 7.5 and 8.5 Mbp, far less than the global average of 86 markers per Mbp. As shown in the left panels of Supplemental Figure S2, this region also shows high false positive probability and large posterior uncertainties in the number of IBD subsets and pairwise IBD probability. Finally, longer data sets do better than shorter ones in their area of overlap (Figure 4A and B), presumably because of better parameter inference.

In addition, at each SNP marker location we evaluate the inferred IBD state by the number of IBD subsets and the pairwise IBD probability. We define the false positive probability at a location as the probability of a false claim of IBD between a random pair. Results from the short data sets are shown in Figure 5, and from the long data sets in Supplemental Figure S2. For the results estimated from \textit{S-NoLD} (left panels of Figure 5), the true values of the number of IBD sets and the pairwise IBD probability fall within their marker-specific posterior central 95\% intervals (Figure 5A and C), and the IBD states in the middle region are well estimated as shown by the small posterior intervals (Figure 5A, C and E) and low false positive probability (Figure 5E). In fact, a randomly sampled IBD state in the middle region (0.35 to 0.7 Mbp) has a probability of around 0.91 being exactly the same as the true
In the presence of LD in the founder genomes (S-LD), the number of IBD sets at a SNP marker in the middle region is underestimated (Figure 5B), consistent with our earlier interpretation of the increased scaled time depth. This results in a larger pairwise IBD probability and a higher false positive probability than in the absence of LD. However, even in the presence of LD the rate of false claims of IBD remains below 1%.

3.4 Comparison with ibd_haplo

Browning and Browning (2010, 2011) compared the performance of fastIBD to that of PLINK (Purcell et al. 2007) and GERMLINE (Gusev et al. 2009), and Brown et al. (2012) compared ibd_haplo to fastIBD. Here we compare JointIBD to ibd_haplo, using data based on those in Brown et al. (2012). However, our results for ibd_haplo performance are not directly comparable to the previous results. First, the program has been substantially updated; we used the version of the MORGAN v3.2 (2013) release. More significantly, Thompson (2009) and Brown et al. (2012) incorporate the additional possibility of IBD transitions independent of the current state. The ibd_haplo program models SNP-to-SNP changes in IBD state, and this additional flexibility may be important in area where SNPs are sparse. However, for closer analogy with the JointIBD model, we do not here allow ibd_haplo these additional transitions. Finally, the data of Brown et al. (2012) did not include typing error, but an error rate of 0.01 was used in the analysis, to accommodate aberrant IBD changes or (in real data) mutations and other anomalies. In this paper, we added typing error at rate 0.005, but used only this same lower value in the ibd_haplo analyses.

For each of the two large data sets L-NoLD and L-LD, we ran ibd_haplo for all 190 possible pairs out of 20 individuals, and obtained the most probable pairwise IBD state at each marker location. In each run, we set $\varepsilon = 0.005$, the simulation value, and $\eta = 0.025$ so that $\theta = 39$ close to the “true” value in terms of the number of IBD sets (Fig. 1B). Following Brown et al. (2012), we used 0.05 per Mbp for the IBD change rate parameter since the analysis of that paper has shown that keeping this parameter small provides more robustness in the presence of LD. To compare with the results of Brown et al. (2012), we
first extracted the posterior distribution of pairwise IBD states from that of joint IBD states among \( n = 20 \) individuals, and then found the most probable pairwise state for each pair of individuals and at each marker location.

The results are shown in Figure 6. As shown in the left panels of Figure 6 for the results estimated from data without LD, both methods perform very well and \( \text{ibd\_haplo} \) performs slightly better than \( \text{JointIBD} \). The number of pairs showing any IBD as estimated by \( \text{ibd\_haplo} \) is almost identical to the true value, whereas \( \text{JointIBD} \) underestimates this around the location of 7 Mbp (Figure 6A). \( \text{ibd\_haplo} \) shows fewer false IBD calls (Figure 6C) and fewer false no-IBD calls (Figure 6E). On the other hand, in the presence of LD (right panels of Figure 6), \( \text{JointIBD} \) performs better than \( \text{ibd\_haplo} \). The latter shows large overestimation of the probability of any IBD (Figure 6B), which results in a large number of false IBD calls (Figure 6D) at corresponding locations. Neither method does well at detecting all the pairwise IBD (Figure 6F).

The differences in performance between \( \text{ibd\_haplo} \) and \( \text{JointIBD} \) are partly due to the different specifications of the prior distributions. In the absence of LD in founder genomes, the data are informative for the number of IBD transitions, and thus the results are not sensitive to the \( \text{ibd\_haplo} \) assumption of a relatively low IBD change rate. The \( \text{ibd\_haplo} \) program also fixed the parameter values of \( \varepsilon \) and \( \theta \), whereas \( \text{JointIBD} \) uses non-informative prior distributions for these parameters. This may explain the slightly better performance of \( \text{ibd\_haplo} \).

In contrast, LD in founder genomes tends to be interpreted as IBD segments as such LD is not modeled in these methods. Thus the number of IBD transitions is overestimated. While \( \text{ibd\_haplo} \) puts a soft constraint on the number of IBD transitions by assigning a small value to the IBD change-rate, \( \text{JointIBD} \) puts a hard upper bound on the number of IBD transitions. Thus the false positive rate (calls of IBD given no IBD) is more effectively controlled by \( \text{JointIBD} \) (Figure 6D).
4 Discussion

We have presented JointIBD, a Bayesian inference framework for the joint detection of IBD segments among multiple gametes. We discuss three main assumptions in our model. First, we assume that IBD processes along chromosomes are independent of allelic states. Thus, the SNP loci are assumed to be selectively neutral and the effects of mutation negligible. For the inference of IBD we use common SNP variation, not rare variants, and we aim to infer IBD relative to a reference population at scaled time depth $\tau_0$ in the past. Processes such as natural selection and demographic history are relevant only from $\tau_0$ to the present. Our interest is in relatively recent IBD, where $\tau_0$ is of order 0.02. Therefore, in contrast to detection of ancient IBD (large $\tau_0$), our method is largely immune to natural selection, unless the selection is very strong.

The second main assumption is the modeling of IBD processes along chromosomes by the modified Chinese restaurant process (MRCP) with the ESF as the stationary distribution. In the ESF the gametes are exchangeable, and thus we implicitly assume there is no geographical or social population structure among the small sample of individuals who provide the gametes. To validate the ESF, we make comparisons with coalescent theory, which assumes that the recent genealogical process of the population can be described by a Wright-Fisher model with constant effective population size. We have verified that the ESF is a good approximation of the probability distribution of IBD states at $\tau_0$ predicted by coalescent theory, although the number of IBD subsets has slightly higher variance under ESF (Figure 1B). The MRCP has an approximate biological basis. IBD transitions involving only one gamete correspond qualitatively to historical recombination events occurring on terminal branches of coalescent trees along chromosomes in the sequential Markov coalescent (McVean and Cardin 2005; Marjoram and Wall 2006). For small scaled time depth $\tau_0$, the large majority of recombination events occur in the terminal branches.

Lastly, we assume that the ancestral allelic states for IBD sets are independent both within loci and across loci. As we do not model LD in founder genomes, we have evaluated its impact on detection of IBD segments. Our results have shown that LD is confounded with
the underlying IBD states, indicating the desirability of accommodating LD. Albrechtsen et al. (2009) modeled the non-independence of marker data given hidden IBD states by pairwise haplotype probabilities. Browning (2008) and Browning and Browning (2010) built a joint hidden Markov model for haplotype frequencies and pairwise IBD states. Their model for haplotype frequencies incorporating LD models localized haplotype clusters as a variable-length Markov chain (Browning 2006). However, in order to estimate joint IBD states among multiple gametes, we have necessarily simplified the data model. Joint inference in the presence of LD remains an important direction for future work.

We have compared JointIBD to ibd_haplo, using data from Brown et al. (2012). In the absence of LD in founder genomes, both methods perform well, and comparably. In the presence of LD in founder genomes, JointIBD controls the false positive calls of IBD more effectively, but otherwise does not outperform ibd_haplo in terms of inferring pairwise IBD. It is not surprising that the pairwise summaries of IBD are similar under the two methods, as both use almost the same model for the IBD process. However, although the output of JointIBD can be reduced to a pairwise summary, there is no straightforward way to obtain a joint inference from ibd_haplo. The IBD states for all the 190 pairs of individuals obtained separately from pairwise methods are not always consistent, and even at a single locus probabilities of IBD states obtained from different pairs cannot be easily combined. Combining pairwise inferences to form estimates IBD states among multiple individuals across loci is a challenging open problem. It is joint information, such as is provided directly by JointIBD, that helps to increase power in IBD-based mapping (Moltke et al. 2011).

The only comparable published method for detecting joint IBD states among multiple individuals is that of Moltke et al. (2011). Both methods use MCMC and are thus computationally intensive, and neither accommodates LD. However, their model specifications are very different. Moltke et al. (2011) use integer IBD indicators for a gamete at a locus, where 0 represents non-IBD with any other gamete (singletons) and gametes with the same positive indicator are IBD. The authors modeled IBD processes across a chromosome by a reversible birth and death process of zero indicators. Direct transitions between positive indicators are not allowed, so they must be implemented by inserting intermediate zero indicators. Thus,
there are many more IBD transitions in their model than are required by the underlying historical recombination events.

In contrast to the single ESF parameter, $\theta$, the stationary distribution of IBD indicators in Moltke et al. (2011) is determined by two parameters: the maximum positive indicator and the probability of being a zero indicator. Whereas the parameter $\eta = 1/(1 + \theta)$ has a natural interpretation as the pointwise probability of IBD between a pair of gametes, it is not clear how the Moltke et al. (2011) parameters relate to the reference population or to the descent from an ancestral origin allele to each IBD group. The maximum positive indicator limits the number of non-singleton IBD groups. It was fixed to be 1, 2, or 3 in various analyses of Moltke et al. (2011), but it is unclear how it should be set in practice.

*JointIBD* can only analyze haplotype data at this time. For genotype data, unknown phase could potentially be integrated out using the methods described by Albrechtsen et al. (2009) and Moltke et al. (2011). Missing data can be easily accommodated in our method, for example, by assuming that data are missing independently of allelic type. Alternatively, a program such as BEAGLE (Browning and Browning 2007) can be used to infer the most probable phase and to impute missing allelic states, while incorporating additional information contained in reference panels of data if these are available.

Software availability. *JointIBD* is freely available as Mathematica code from the web site http://www.stat.washington.edu/thompson/pangaea.shtml.

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References


Figure 1: Comparison of simulated IBD with theoretical predictions. (A) Distribution of the distances between successive IBD states along chromosomes. Dots show distances from the simulation, with y-axis frequencies binned using a bin size of 0.002 Mbp; the dashed gray line shows an exponential distribution with the same mean (0.049 Mbp). (B) Distribution of the number of IBD subsets. Magenta dots denote the simulated data, circles the distribution based on coalescent theory with scaled time depth $\tau_0 = 0.0214$, and rectangles the distribution calculated from the ESF with $\theta = 41$. (C) Comparison of simulated frequency for each distinct IBD state with coalescent predictions. Here we represent an IBD state by vector $\mathbf{a}$ with element $a_l$ being the number of IBD subsets of size $l=1 \ldots n$. Dashed line denotes $y = x$. The linear correlation coefficient is 0.999. (D) Comparison of simulated frequency with ESF predictions. The linear correlation coefficient is 0.942.
Figure 2: Posterior parameter distributions. Thin lines represent short data sets and thick lines long data sets; left panels are no-LD results and right panels are LD results. Panels show allelic typing error rate $\varepsilon$ (A and B), ESF parameter $\theta$ (C and D), IBD transition rate $10^6\lambda$ (E and F), and average density of actual (state-changing) IBD transitions (G and H). Cyan lines denote the marginal prior distributions, and the magenta dots in A and B denote the true typing error rate (0.005).
Figure 3: Estimation of IBD transition locations along chromosomes. Lefthand panels A and C show inferred cumulative transition frequency (black), true cumulative transition frequency (magenta), and the prior expectation (dashed cyan line) for S-NoLD and L-NoLD, respectively. Righthand panels B and D contrast results from data sets without LD (gray lines) and with LD (black lines) for short and long data sets, respectively. Residual frequency is defined as the inferred frequency minus the true frequency, so that a residual frequency of 0.0 represents perfect recovery. Short vertical lines on the top of each panel indicate the true transition locations.
Figure 4: Detailed recovery of IBD states. Each panel shows the probability that the distance between a random estimated IBD state and the true IBD state is no greater than 2 at each SNP marker location. Throughout, heavy lines represent long datasets and narrow lines represent short ones. Panel A contrasts \textit{S-NoLD} and the first 1Mbp of \textit{L-NoLD}; panel B contrasts \textit{S-LD} and the first 1Mbp of \textit{L-LD}. Panels C and D show results for the full length of \textit{L-NoLD} and \textit{L-LD}, respectively.
Figure 5: Overall IBD state recovery performance. This Figure shows estimates of IBD states at each SNP location based on S-NoLD (left panels) and S-LD (right panels). They are evaluated in terms of the number of IBD sets (A and B), the pairwise IBD probability (C and D) and the false positive probability (E and F). Error bars denote the 95% central posterior intervals with black lines connecting the medians. In panels A-D, magenta lines denote the true values.
Figure 6: JointIBD versus ibd_haplo. Comparisons of JointIBD estimates (black lines) to the pairwise estimates (cyan lines) obtained by ibd_haplo from the data sets L-NoLD (left panels) and L-LD (right panels). Magenta lines denote the true values. Panels A and B show the number of pairs inferred to have any IBD. Panels C and D show the counts of false IBD calls (false positives), and Panels E and F show the counts of false no-IBD calls (false negatives). “No IBD” refers to the IBD state consisting of 4 singletons; all other IBD states for two individuals are grouped as “any IBD”.

Figure 6
Supplemental Material

S1: The full posterior distribution

Following the notation in the main paper’s Methods section, the model parameters consist of $\theta$, $\varepsilon$, $\lambda$, and $Z(x)$. We represent the transitions of IBD states $Z(x)$ along chromosomes by transition location $x_k$ and the resulting state $z_k = Z(x_k)$ for $k = 1, ..., K$, where an IBD transition occurs between nucleotide sites at $x_k - 1$ and $x_k$ for $k \geq 2$. For convenience we set $x_1 = 1$ and $x_{K+1} = \ell + 1$, where $\ell$ is the length of the chromosome in base pairs (bp). Let $\mathbf{x} = \{x_k\}_{k=1..K+1}$ and $\mathbf{z} = \{z_k\}_{k=1..K}$ denote the vectors of transition points and IBD partitions. Let $\mathbf{s} = \{s_i\}_{i=1..m}$ and $\mathbf{\pi} = \{\pi_i\}_{i=1..m}$ denote the vectors of SNP sites and their minor allele frequencies. These allele frequencies $\mathbf{\pi}$ and SNP locations $\mathbf{s}$ are assumed to be known. Finally, let $\mathbf{y}_i = \{y_{ij}\}_{j=1..n}$ denote the vector of observed alleles at SNP site $i$ over gametes $j$, and $\mathbf{y} = \{y_{ij}\}_{i=1..m,j=1..n}$ the complete data over all gametes and sites. Note that subscript $i$ indexes the SNP sites, $j$ the gametes, and $k$ the IBD transition locations.

The full posterior distribution is given by

$$p(\theta, \varepsilon, \lambda, K, \mathbf{x}, \mathbf{z} | \mathbf{y}, \mathbf{\pi}, \mathbf{s}) \propto p(\mathbf{y} | \mathbf{\pi}, \mathbf{s}, K, \mathbf{x}, \mathbf{z}, \varepsilon) \ p(K, \mathbf{x}, \mathbf{z} | \theta, \varepsilon) \ p(\theta) \ p(\lambda) \ p(\varepsilon),$$

where each term is explained as follows. First, the SNPs are assumed to be independent given the latent IBD state, so that the likelihood term is a product over SNP sites:

$$p(\mathbf{y} | \mathbf{\pi}, \mathbf{s}, K, \mathbf{x}, \mathbf{z}, \varepsilon) = \prod_{i=1}^{m} p(\mathbf{y}_i | Z(s_i), \pi_i, \theta, \varepsilon).$$

Additionally, since we assume independence of the allelic type of non-IBD DNA, each term in the product over SNPs is again a product over the IBD subsets of gametes. Second, the IBD process along the chromosome is modeled as a continuous time Markov process, with the prior distribution given by

$$p(K, \mathbf{x}, \mathbf{z} | \theta, \lambda) = p(\mathbf{z} | K, \theta) \ p(K, \mathbf{x} | \lambda).$$
The probability of the vector \( z \) of IBD partitions is given by

\[
p(z | K, \theta) = p(z_1 | \theta) \prod_{i=1}^{K-1} p(z_{i+1} | z_i, \theta),
\]

where the distribution for the initial IBD state \( z_1 \) is given by the ESF (main paper Equation 1), and the transition probability \( p(z_{i+1} | z_i, \theta) \) can be calculated from the modified Chinese restaurant processes (MCRP) (main paper Equations 2 and 3).

Since \( \lambda \ll 1 \) and thus \( K \ll \ell \), the geometrically distributed discrete inter-transition base-pair counts are approximated by exponential distributions for the inter-transition distances. That is, if \( K \) is not constrained,

\[
p(K, x | \lambda) \propto (1 - \lambda)^{x_{K+1}-x_K-1} \prod_{i=1}^{K-1} ((1 - \lambda)^{x_{i+1}-x_i-1}\lambda) \approx \lambda^{K-1}e^{-\lambda\ell}.
\]

If \( K \) is bounded by \( K_c < \infty \), the distribution of \( K \) will involve a normalization constant that depends on \( \lambda \). That is

\[
p(K, x | \lambda) \propto C(\lambda)\lambda^{K-1}e^{-\lambda\ell},
\]

where \( C(\lambda) = \Gamma(K_c, \lambda\ell)/\Gamma(K_c) \), and the numerator is the incomplete Gamma function:

\[
\Gamma(a, b) = \int_b^\infty t^{a-1}e^{-t}dt.
\]

(Note \( C(\lambda) = 1 \) if \( K_c = \infty \).) Thus \( x \) is uniform on the space \( 1 = x_1 < x_2 < ... < x_{K+1} = \ell+1 \) and \( \int dx = \ell^{K-1}/(K-1)! \). Then

\[
p(K | \lambda) = \int p(K, x | \lambda) dx = \begin{cases} C(\lambda)(\lambda\ell)^{K-1}e^{-\lambda\ell}/(K-1)! & \text{if } K \leq K_c \\ 0 & \text{if } K > K_c \end{cases}.
\]

That is, the prior distribution for \((K-1)\) is a truncated Poisson distribution with mean \( \lambda\ell \).

The prior distributions for \( \theta \) and \( \lambda \) are Gamma distributions, where that for \( \theta \) is bounded below by \( \theta_c \). Thus if \( G[u | \alpha, \beta] = (\Gamma(\alpha)\beta^\alpha)^{-1}u^{\alpha-1}e^{-u/\beta} \) denotes the gamma probability density on \( u > 0 \) with shape parameter \( \alpha \) and scale parameter \( \beta \), the prior distribution of \( \theta \) is

\[
p(\theta) \propto \begin{cases} G[\theta | \alpha_\theta, \beta_\theta] & \text{if } \theta \geq \theta_c \\ 0 & \text{if } \theta < \theta_c \end{cases},
\]

34
and the prior distribution of $\lambda$ is

$$p(\lambda) = \Gamma[\lambda | \alpha \lambda, \beta \lambda]$$

The prior distribution of $\varepsilon$ is the uniform distribution in $[0, 1]$:

$$p(\varepsilon) =\begin{cases} 1 & \text{if } 0 \leq \varepsilon \leq 1 \\ 0 & \text{otherwise}. \end{cases}$$

In general $\lambda$ must be sampled via a Metropolis algorithm, but if $K_c = \infty$ the full conditional distribution for $\lambda$ is the gamma distribution $G(\lambda | (K + \alpha - 1), (\beta^{-1} + \ell)^{-1})$. In this case $\lambda$ can be integrated out to obtain the posterior distribution on the other parameters:

$$p(\theta, \varepsilon, K, x, z | y, \pi, s) \propto p(y | \pi, s, K, x, z, \varepsilon) p(z | K, \theta) p(K, x) p(\theta) p(\varepsilon). \quad (S1)$$

where

$$p(K, x) = \int p(K, x | \lambda) p(\lambda) d\lambda \propto \Gamma(K + \alpha - 1) (\beta^{-1} + \ell)^{-(K + \alpha - 1)}.$$ 

**S2: Possible transitions between two IBD states $z_A$ and $z_B$**

In this section we list all the transformations between two IBD states that differ by at most two steps ($|z_A - z_B| \leq 2$). In describing these transformations, we use lower case letters $a$, $b$, $c$ and $d$ to denote gametes, and upper case $X$, $Y$, $P$ and $Q$ to denote IBD subsets. The notation $\{a, X\}$ will denote the subset $\{a\} \cup X$. Note that any specified gamete such as $a$ is not in any specified subset such as $X$. We denote the size of subset $X$ by $|X|$, and group the transformations by the pair of sizes $(|z_A|, |z_B|)$ for the numbers of subsets in the two IBD states that are involved in the transformation. Note that the IBD subsets shared between $z_A$ and $z_B$ are irrelevant.

Case $|z_A - z_B| = 0$: If $z_A = z_B$ no transformation is needed.

Case $|z_A - z_B| = 1$: Recall that one step of our process can move one gamete $a$ from a source subset $S$ to a target set $T$. This move results from proposing the new gamete in set $T$, and then deleting $a$ from $S$, and the transformation is denoted $(a : S \rightarrow T)$. In Table S1, we give both the transformation from $z_A$ to $z_B$ and the transformation from $z_B$ to $z_A$. 

35
Case $|z_A - z_B| = 2$: In Table S2, we denote the intermediate state by $z_I$, and give the transformations from $z_A$ to $z_I$ and from $z_B$ to $z_I$.

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<th>Subsets in $z_B$</th>
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Table S1: List of transformations for $|z_A - z_B| = 1$. 
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Table S2: List of transformations for |z_A − z_B| = 2.
S3: The proposal distributions of an IBD state

We define three IBD proposal distributions used in the Metropolis type sampling from the full posterior distribution (section S4).

1. One-side distribution. Let $q(z|z_A)$ be the proposal distribution where the IBD state $z$ is proposed from $z_A$ according to the MCRP.

2. Two-side distribution. Let $q(z|z_A, z_B)$ be a proposal distribution for $z$ as an intermediate state between $z_A$ and $z_B$. Thus $|z_A - z_B| \leq 2$, and the proposed $z$ must satisfy $|z - z_A| \leq 1$ and $|z - z_B| \leq 1$. We define $q(z|z_A, z_B)$ for three cases:

   - $|z_A - z_B| = 0$ ($z_A = z_B$). We sample $z$ from $q(z|z_A)$.
   - $|z_A - z_B| = 1$. We sample $z = z_A$ with probability $1/4$, $z = z_B$ with probability $1/4$, and otherwise generate the proposal by the following three steps:
     - Insert a new gamete into a subset of $z_A$ of size $j$ with probability $j/(n + \theta)$, or insert it as a new singleton with probability $\theta/(n + \theta)$.
     - Delete the gamete that is deleted in a randomly chosen transformation from $z_A$ to $z_B$ (see Table S1).
     - Label the new gamete as the deleted one.
   - $|z_A - z_B| = 2$. We list all the possible intermediate states, and randomly choose one of them (Table S2).

3. Propagation distribution. Suppose that $z_A$ and $z_B$ are two consecutive IBD states along the chromosome ($|z_A - z_B| \leq 1$) and also that $|z_A - z_C| = 1$. Let $q(z|z_A, z_B, z_C)$ be the proposal distribution of an IBD state $z$ satisfying $|z - z_B| \leq 1$ and $|z - z_C| \leq 1$. Thus there are four cases as shown in Figure S1.

   - I: $|z_A - z_B| = 0$ and $|z_B - z_C| = 1$. Set $z = z_B$.
   - II: $|z_A - z_B| = 1$ and $|z_B - z_C| = 0$. Set $z = z_B$.
   - III: $|z_A - z_B| = 1$ and $|z_B - z_C| = 1$. Set $z = z_B$.
Figure S1: The possible scenarios for state $z$ under $q(z|z_A, z_B, z_C)$. The distance between each pair of states is shown on the joining lines.

- IV: $|z_A - z_B| = 1$ and $|z_B - z_C| = 2$. Sample $z$ uniformly from all the possible IBD states satisfying the distance constraints (Table S2). If there is no such IBD state, reject the proposal.

Note that $q(z_B|z_C, z, z_B)$ is the reverse proposal distribution to $q(z|z_A, z_B, z_C)$.

Cases I and II are paired in this reversal, while cases III and IV remain unchanged.

### S4 Sampling the posterior distribution via MCMC

We estimate the model parameters $\theta$, $\lambda$, $\varepsilon$, $K$, $\mathbf{x}$, and $\mathbf{z}$ by MCMC, using several versions of the Metropolis algorithm. Our general notation for the target distribution of state variables $\omega$, is $p(\omega)$, and the proposal distribution for a new state given current state $\omega_t$ is $q(\cdot|\omega_t)$. The acceptance probability of proposed state $\omega^*$ is

$$
\min \left( 1, \frac{p(\omega^*)}{p(\omega_t)} \cdot \frac{q(\omega^*|\omega_t)}{q(\omega_t|\omega^*)} \right) .
$$

(S2)

If the proposal is accepted $\omega_{t+1} = \omega^*$, and otherwise $\omega_{t+1} = \omega_t$. We refer to the ratio $p(\omega^*)/p(\omega_t)$ in equation S2 as the target ratio, and the ratio $q(\omega^*|\omega_t)/q(\omega_t|\omega^*)$ as the proposal ratio. In the case of reversible jump MCMC, the acceptance probability also includes a Jacobian factor (Green 1995).
The full conditional distributions of $\theta$, $\varepsilon$ and $\lambda$ are given by

$$
p(\theta | \cdot) \propto p(z | K, \theta) \ p(\theta)
$$

$$
p(\varepsilon | \cdot) \propto p(y | \pi, s, K, x, z, \varepsilon) \ p(\varepsilon)
$$

$$
p(\lambda | \cdot) \propto p(K, x | \lambda) \ p(\lambda) \quad \text{in general}
$$

and $p(\lambda | \cdot) = \Gamma(\lambda|K + \alpha, \lambda - 1, 1/ (\beta^{-1} + \ell))$ if $K_c = \infty$ (equation S1).

To sample $\theta$, $\varepsilon$ and $\lambda$ from their full conditional distributions, we use random walk Metropolis algorithms (Gelman et al. 1996) for each parameter separately (except in the case where $\lambda$ can be sampled directly). In this case the proposal ratio in equation S2 is equal to 1, and only the target ratio is required. In each case the proposal distribution is a normal distribution centered at the current value with the variance adjusted to give an acceptance ratio around 0.44 (Gelman et al. 2004).

Since the insertion or deletion of IBD change points involves a change in the dimension of the parameter space, we update $K$, $x$, and $z$ by reversible jump MCMC (Green 1995). We use six move types in the sampler: (1) update a transition location, (2) update an IBD state, (3) update an IBD state with downstream modification, (4) insert an IBD transition, (5) delete an IBD transition, and (6) update segments of IBD states by swapping their gamete labels. We denote by $\varphi_i$ ($i = 1..6$) the sampling probability for move type $i$. In move types (4-5), the parameter dimensions change by a transition location and an IBD state at the location, and the Jacobian factor is 1.

In the following, we describe the proposals and give the proposal ratios for all the move types (1-6), the target ratios for move types (4-5), and the full conditional distributions for move types (1-3) and (6) from which the target ratio can be obtained.

1. Single update of a transition location. First randomly choose $2 \leq k \leq K$, and then sample a proposal value $x_k^*$ from a discrete uniform distribution in the range from $x_{k-1} + 1$ to $x_{k+1} - 1$. The full conditional posterior distribution is

$$
p(x_k | \cdot) \propto \prod_{\{i | x_{k-1} < s_i < x_{k+1}\}} p(y_i | Z(s_i), \pi_i, \theta, \varepsilon).
$$

The proposal ratio is 1 as the proposal distribution is symmetric.
2. **Single update of an IBD state.** First randomly choose 1 \( \leq k \leq K \). If there are no IBD transitions \((K = 1)\), a proposal state is sampled from \(q(z^*_1|z_1)\). If the focal IBD state is at an end of the chromosome \((k = 1 \text{ or } K)\), a proposal state is sampled from \(q(z^*_1|z_2)\) for \(k = 1\) and from \(q(z^*_K|z_{K-1})\) for \(K\). Otherwise, a proposal state \(z^*_k\) is sampled from \(q(z^*_k|z_{k-1}, z_{k+1})\). The full conditional posterior distribution is

\[
p(z_k) \propto \prod_{\{i|x_k \leq s_i < x_{k+1}\}} p(y_i|Z(s_i), \pi_i, \theta, \varepsilon) \, p(z_{k+1}|z_k, \theta) \, p(z_k|z_{k-1}, \theta),
\]

where \(p(z_{K+1}|z_K, \theta) = p(z_1|z_0, \theta) = 1\) for the cases \(k = 1\) or \(K\).

The proposal ratio is

\[
q(z^*_1|z_1)/q(z_1|z^*_1) \quad \text{if } K = 1, \text{ and otherwise } q(z^*_1|z_2)/q(z_1|z_2) \text{ if } k = 1,
\]

\[
q(z^*_K|z_{K-1})/q(z_K|z_{K-1}) \quad \text{if } k = K, \text{ and otherwise } q(z^*_k|z_{k-1}, z_{k+1})/q(z_k|z_{k-1}, z_{k+1}).
\]

3. **Single update of an IBD state with downstream modification.** First randomly choose \(k, 1 \leq k \leq K\). If \(K = 1\) or \(k = K\), update using move type (2). If \(k = 1\), sample \(z^*_1\) from \(q(z^*_1|z_1)\). Otherwise for \(k > 1\), set \(z^*_l = z_l\) for \(l = 1 \ldots k - 1\), and sample \(z^*_k\) sampled from \(q(z^*_k|z_{k-1}, z_k)\). If \(z^*_k = z_k\) we set \(l' = k + 1\). Otherwise we iteratively sample \(z^*_l\) from \(q(z^*_l|z_{l-1}, z_l, z^*_{l-1})\) from \(l = k + 1\) until there exists \(l' \geq k + 1\) such that \(z^*_l = z_l\) or \(l' = K + 1\). If \(l' < K\), we set \(z^*_l = z_l\) for \(l = l' + 1 \ldots K\). The full conditional distribution is

\[
p(\{Z(x)\}_{x_k \leq x < x_{l'}}|\cdot) \propto \prod_{\{i|x_k \leq s_i < x_{l'}\}} p(y_i|Z(s_i), \pi_i, \theta, \varepsilon) \prod_{l=k}^{l'-1} p(z_{l+1}|z_l, \theta),
\]

where \(p(z_{K+1}|z_K, \theta)\) is set to be 1 for \(l' = K + 1\). The proposal ratio is given by

\[
\frac{q(z^*_k|z_k) \prod_{l=k}^{l'-1} q(z^*_l|z_{l-1}, z_l, z^*_l)}{q(z_k|z_k^*) \prod_{l=k}^{l'-1} q(z_l, z^*_l, z^*_l, z_{l-1})}
\]

if \(k = 1\), and otherwise \((1 < k < K)\) by

\[
\frac{q(z^*_k|z_k, z_{k-1}) \prod_{l=k}^{l'-1} q(z^*_l|z_{l-1}, z_l, z^*_l)}{q(z_k|z_k^*, z_{k-1}) \prod_{l=k}^{l'-1} q(z_l, z^*_l, z^*_l, z_{l-1})}
\]
4. **Insert one IBD transition.** First randomly choose \(k, 1 \leq k \leq K\). Then insert an IBD transition location into \(x\) to give \(x^*\) with \(x_{k+1}^*\), sampled from the discrete uniform distribution in the range from \(x_k + 1\) to \(x_{k+1} - 1\). Set \(z^*_l = z_l\) for \(l = 1 \ldots k\), and insert \(z_{k+1}^*\) sampled from \(q(z_{k+1}^*|z_k)\). If \(k = K\) we set \(l' = K + 2\), and if \(z_{k+1}^* = z_k\) we set \(l' = k + 2\). Otherwise we iteratively sample \(z_l^*\) from \(q(z_l^*|z_{l-2}, z_{l-1}, z_{l-1}^*)\) from \(l = k + 2\) until there exists \(l' \geq k + 2\) such that \(z_l^* = z_{l'}\) or \(l' = K + 2\). If \(l' < K + 1\), we set \(z_l^* = z_{l-1}\) for \(l = l' + 1 \ldots K + 1\). The target ratio is

\[
\frac{p(K + 1, x^*, z^*|\cdot)}{p(K, x, z|\cdot)} = \frac{\prod_{\{i|z_i^* < s_i < x_i^*\}} p(y_i|Z^*(s_i), \pi_i, \theta, \varepsilon) \prod_{l=k}^{l'-1} p(z_{l+1}^*|z_l^*, \theta) p(K + 1, x^*)}{\prod_{\{i|x_k < s_i < x_{l'}\}} p(y_i|Z(s_i), \pi_i, \theta, \varepsilon) \prod_{l=k}^{l'-2} p(z_{l+1}^*|z_l^*, \theta) p(K, x)},
\]

where the term \(p(K + 1, x^*)/p(K, x)\) is replaced by \(p(K + 1, x^*|\lambda)/p(K, x|\lambda)\) if \(\lambda\) is sampled (equation S1), \(p(z_{K+1}|z_K, \theta)\) and \(p(z_{K+2}|z_{K+1}, \theta)\) are set to be 1 for \(l' = K + 2\). The proposal ratio is given by

\[
\frac{\varphi_4 K^{-1}(x_{k+1} - x_k - 1)^{-1} q(z_{k+1}^*|z_k) \prod_{l=k+2}^{l'-1} q(z_l^*|z_{l-2}, z_{l-1}, z_{l-1}^*)}{\varphi_5 K^{-1} \prod_{l=k+1}^{l'-2} q(z_l|z_l^*, z_{l+1}^*, z_{l-1})}.
\]

5. **Delete one IBD transition.** First randomly choose \(k, 2 \leq k \leq K\). (If \(K = 1\), we do not change anything.) Set \(x^*\) by deleting \(x_k\) from \(x\), and set \(z_l^* = z_l\) for \(l = 1 \ldots k - 1\). If \(k = K\) we set \(l' = K\), and if \(z_{k-1}^* = z_k\) we set \(l' = k\). Otherwise, we iteratively sample \(z_l^*\) from \(q(z_l^*|z_l, z_{l+1}, z_{l-1}^*)\) from \(l = k\) until there exists \(l' \geq k\) so that \(z_l^* = z_{l'}\) or \(l' = K\). If \(l' < K - 1\), we set \(z_l^* = z_{l+1}\) for \(l = l' + 1 \ldots K - 1\). The target ratio is

\[
\frac{p(K - 1, x^*, z^*|\cdot)}{p(K, x, z|\cdot)} = \frac{\prod_{\{i|z_i^* < s_i < x_i^*\}} p(y_i|Z^*(s_i), \pi_i, \theta, \varepsilon) \prod_{l=k+1}^{l'-1} p(z_{l+1}^*|z_l^*, \theta) p(K - 1, x^*)}{\prod_{\{i|x_k < s_i < x_{l'+1}\}} p(y_i|Z(s_i), \pi_i, \theta, \varepsilon) \prod_{l=k+1}^{l'-2} p(z_{l+1}^*|z_l^*, \theta) p(K, x)},
\]

where the term \(p(K - 1, x^*)/p(K, x)\) is replaced by \(p(K - 1, x^*|\lambda)/p(K, x|\lambda)\) if \(\lambda\) is sampled (equation S1), \(p(z_{K+1}|z_K, \theta)\) and \(p(z_{K+2}|z_{K+1}, \theta)\) are set to be 1 for \(l' = K\). The proposal ratio is given by

\[
\frac{\varphi_5 (K - 1)^{-1} \prod_{l=k}^{l'-1} q(z_l^*|z_l, z_{l+1}, z_{l-1}^*)}{\varphi_4 (K - 1)^{-1} (x_k^* - x_{k-1}^* - 1)^{-1} q(z_k|z_{k-1}^*) \prod_{l=k+1}^{l'-2} q(z_l|z_{l+2}^*, z_{l-1}^*, z_{l-1})}.
\]

6. **Update segments of IBD states.** We first randomly choose one pair of gametes and partition them into IBD and non-IBD segments. Independently for each non-IBD
segment, we propose IBD states by swapping the labels for the pair of gametes. Let \( k \) and \( l \) \((l > k)\) be the two ends of the segment so that \( z_k \) and \( z_l \) are IBD for the pair of gametes. We set \( k = 0 \) for the first segment, and \( l = K + 1 \) for the last segment. The full conditional distribution is

\[
p(\{z(x)\}_{x_{k+1} \leq s < x_l}) \propto \prod_{\{i|x_{k+1} \leq s_i < x_l\}} p(y_i|Z(s_i), \pi_i, \theta, \varepsilon),
\]

which does not depend on the IBD transition probabilities. The proposal ratio is 1 for this symmetric proposal distribution.

In each iteration of a single MCMC, we update \( \theta, \lambda, \varepsilon \) one by one, update \( Z(x) \) \( 10^{-5} \ell \) times with move types (1-5), and update IBD states \( n/2 \) times with move type (6). To improve the mixing of the MCMC, with probability 0.5 we reverse the direction of the chromosome in every iteration. When \( \lambda \) is not sampled (equation S1) move types (1-5) are sampled with probabilities \( \varphi = ((1 - 2c)/3, (1 - 2c)/3, (1 - 2c)/3, c, c) \), respectively. Here \( c \) is a tunable constant, and it is set to be 0.2. When \( \lambda \) must also be sampled due to the bounding of \( K \) by \( K_c \), we set \( c \) to be a small value of 0.05, as the number of IBD transitions is distributed sharply around \( K_c \) due to the LD in the founder genomes.

We run two independent groups of MCMC chains. In each group there are four MCMC chains, and parallel algorithms are used where the full conditional distribution is raised to the power \( \sigma, 0 < \sigma \leq 1 \) (Metropolis-coupled MCMC, (Geyer 1991)). The power \( \sigma \) is set to 1 for the coldest chain, and decreases with equal interval \( \Delta \sigma \), which is adjusted so that the accept probability for swapping a pair of chains is 0.5. Only the coldest chain in each group is saved.
S5 IBD estimates from large data sets

Figure S2: Overall recovery of IBD states from long data sets. Estimated IBD states along gametes obtained from the data sets L-NoLD (left panels) and L-LD (right panels). They are evaluated in terms of the number of IBD sets (A and B), the pairwise IBD probability (C and D) and the false positive probability (E and F). Error bars denote the 95% posterior intervals with black lines connecting the medians. In panels A-D, magenta lines denote the true values. Compare with Figure 5 in the main text.
Supplemental Literature Cited


