The coalescent and its descendants

Peter Donnelly and Stephen Leslie

Abstract

The coalescent revolutionised theoretical population genetics, simplifying, or making possible for the first time, many analyses, proofs, and derivations, and offering crucial insights about the way in which the structure of data in samples from populations depends on the demographic history of the population. However statistical inference under the coalescent model is extremely challenging, effectively because no explicit expressions are available for key sampling probabilities. This led initially to approximation of these probabilities by ingenious application of modern computationally-intensive statistical methods. A key breakthrough occurred when Li and Stephens introduced a different model, similar in spirit to the coalescent, for which efficient calculations are feasible. In turn, the Li and Stephens model has changed statistical inference for the wealth of data now available which documents molecular genetic variation within populations. We briefly review the coalescent and associated measure-valued diffusions, describe the Li and Stephens model, and introduce and apply a generalisation of it for inference of population structure in the presence of linkage disequilibrium.

AMS subject classification (MSC2010) 60J70, 62M05, 92D10

a Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, and Department of Statistics, 1 South Parks Road, Oxford OX1 3TG; donnelly@stats.ox.ac.uk

b Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG; leslie@stats.ox.ac.uk
1 Introduction

John Kingman made a number of incisive and elegant contributions to modelling in the field of genetics, several of which are described elsewhere in this volume. But it is probably the coalescent, or ‘Kingman coalescent’ as it is often known, which has had the greatest impact. Several authors independently developed related ideas around the same time [20], [53], [30] but it was Kingman’s description and formulation, together with his proofs of the key robustness results [34], [33], [32] which had the greatest impact in the mathematical genetics community.

More than 25 years later the coalescent remains central to much of population genetics, with book-level treatments of the subject now available [54], [28], [55]. As others have noted, population genetics as a field was theory rich and data poor for much of its history. Over the last five years this has changed beyond recognition. The development and wide application of high-throughput experimental techniques for assaying molecular genetic variation means that scientists are now awash with data. Enticing as this seems, it turns out that the coalescent model cannot be fully utilised for analysis of these data—it is simply not computationally feasible to do so. Instead, a closely related model, due to Li and Stephens, has proved to be computationally tractable and reliable as a basis for inference for modern genetics data. Alternative approaches are based on approximate inference under the coalescent.

Our purpose here is to give a sense of these developments, before describing and applying an extension of the Li and Stephens model to populations with geographical structure. We do not attempt an extensive review.

The initial historical presentation is necessarily somewhat technical in nature, and provides some explanation of the theoretical developments leading up to the Li and Stephens model. Readers interested in just the Li and Stephens model and its application may begin at Section 4 as the presentation of this material does not heavily depend on the previous sections.

Before doing so, one of us (PD) will indulge in a brief personal reminiscence. John Kingman was my doctoral supervisor. More accurately, he acted as my supervisor for a year, before leaving Oxford to Chair the then UK Science and Engineering Research Council (I have always hoped the decision to change career direction was unrelated to his supervisory experiences). During the year in question, Kingman wrote his three seminal coalescent papers. A photocopy of one of the manuscripts,
There is a certain irony to the fact that although the coalescent was the unifying theme of much of my academic work for the following 20 years, it formed no part of my work under Kingman’s supervision. John’s strategy with new research students, or at least with this one, was to direct them to the journals in the library, note that some of the papers therein contained unsolved problems, and suggest that he would be happy to offer advice or suggestions if one were stuck in solving one of these. This was daunting, and the attempts were largely unsuccessful. It was only as Kingman was leaving Oxford that he passed on copies of the coalescent manuscripts, and, embarrassingly, it was some years before I saw the connection between the coalescent and aspects of my doctoral work on interacting particle systems, then under Dominic Welsh’s supervision.

2 The coalescent and the Fleming–Viot process

To set the scene, we briefly outline the context in which the coalescent arises, and then describe the coalescent itself along with the corresponding process forward in time, the so-called Fleming–Viot measure-valued diffusion. We aim here only to give a brief flavour of the two processes rather than a detailed exposition.

The most basic, and oldest, models in population genetics are finite Markov chains which describe the way in which the genetic composition of the population changes over time. In most cases, these models are not tractable, and interest moves to their limiting behaviour as the population size grows large, under suitable re-scalings of time. When examined forward in time, this leads to a family of measure-valued diffusions, called Fleming–Viot processes. In a complementary, and for many purposes more powerful, approach one can instead look backwards in time, and focus on the genealogical tree relating sampled chromosomes. In the large population limit, these (random) trees converge to a particular process called the coalescent.

We start with the simplest setting in which individuals are haploid; that is they carry a single copy of their genetic material which is inherited from a single parent. Many organisms, including humans, are diploid, with each cell carrying two copies of the individual’s DNA—these copies being inherited one from each of the individual’s two parents. It turns out that the haploid models described below also apply to dip-
loid organisms provided one is interested in modelling the evolution of
small contiguous segments of DNA—for many purposes we can ignore
the fact that in diploid organisms these small segments of DNA occur
in pairs in individuals, and instead model the population of individual
chromosomes, or more precisely of small segments of them taken from
the same genomic region, in each individual. In what follows, we will
respect this particular perspective and refer to the haploid ‘individuals’
in the population we are modelling as ‘chromosomes’.

One simple discrete model for population demography is the Wright–
Fisher model. Consider a population of fixed size \( N \) chromosomes which
evolves in discrete generations. The random mechanism for forming the
next generation is as follows: each chromosome in the next generation
chooses a chromosome in the current generation (uniformly at random)
and copies it, with the choices made by different chromosomes being
independent. An equivalent description is that each chromosome in the
current generation gives rise to a random number of copies in the next
generation, with the joint distribution of these offspring numbers being
symmetric multinomial.

In addition to modelling the demography of a population, a population
 genetics model needs to say something about the genetic types carried by
the chromosomes in the population, and the way in which these change
(probabilistically) when being copied from parental to offspring chro-
mosomes. Formally, this involves specifying a set, \( E \), of possible types
(usually, if unimaginatively, called the type space), and a matrix of trans-
ition probabilities \( \Gamma \) whose \( i, j \)th entry, \( \gamma_{ij} \), specifies for each \( i, j \in E \),
the probability that an offspring chromosome will be of type \( j \) when the
parental chromosome is of type \( i \). The generality has real advantages:
different choices of type space \( E \) can be used for modelling different kinds
of genetic information. In most genetic contexts, offspring are extremely
likely to have the same type as their parent, with changes to this type,
referred to as mutations, being extremely rare.

Under an assumption of genetic neutrality, all variants in a popula-
tion are equally fit and are thus equally likely to be transmitted. This
assumption allows a crucial simplification: the random process describing
demography is independent of the genetic types carried by the individu-
als in the population. In this case, one can first generate the demography
of the population using, say, the Wright–Fisher model, and then inde-
pendently superimpose the genetic type for each chromosome, and the
details of the (stochastic) mutation process which may change types.
The separation of demography from genetic types lies at the heart of
The coalescent and its descendants

The simplification offered by the coalescent: the coalescent models the parts of the demography relevant to the population at the current time; information about genetic types can be added independently. The extent to which the neutrality assumption applies is rather controversial in general, and for humans in particular, but it seems likely that it provides a reasonable description for many parts of the genome.

The Wright–Fisher model may also be extended to allow for more realistic demographic effects, including variation in population size, and geographical spatial structure in the population (so that offspring chromosomes are more likely to be located near to their parents). We will not describe these here. Somewhat surprisingly, it transpires that the simple model described above, (constant population size, random mating, and neutrality—the so-called ‘standard neutral’ model), or rather its large population limit, captures many of the important features of the evolution of human and other populations. There is an aphorism in statistics that “all models are false, but some are useful”. The standard neutral model has proved to be extremely useful.

In a Wright–Fisher, or any other, model, we could describe the genetic composition of the population at any point in time by giving a list of the genetic types currently present, and the proportion of the population currently of each type. Such a description corresponds to giving a probability measure on the set $E$ of possible types. It is sometimes helpful to think of this measure as the distribution of the type of an individual picked at random from the population. Note that summarising the population composition in this way at a particular time point involves an assumption of exchangeability across individuals: it is only the types present, and the numbers of individuals of each type, in a particular population which matter, with information about precisely which individuals carry particular types not being relevant. In this framework, when we add details of the mutation process to the Wright–Fisher model, by specifying $E$ and $\Gamma$, we obtain a discrete time (probability-) measure-valued Markov process. As $N$ becomes large a suitable rescaling of the process converges to a diffusion limit: time is measured in units of $N$ generations, and mutation probabilities, the off-diagonal entries of the matrix $\Gamma$ above, are scaled as $N^{-1}$. For general genetic systems, the limit is naturally formulated as a measure-valued process, called the Fleming–Viot diffusion. The classical so-called Wright–Fisher diffusion is a one-dimensional diffusion on $[0, 1]$ which arises when there are only two possible genetic types and one tracks the population frequency of one of the types. This is a special case of the Fleming–Viot diffusion,
in which we can identify the value of the classical diffusion, \( p \in [0, 1] \), with a probability measure on a set with just two elements. The beauty of the more general, measure-valued, formulation is that it allows much more complicated genetic types, which could track DNA sequences, or more exotically even keep track of the time since particular mutations arose in the population.

The Fleming–Viot process can thus be thought of as an approximation to a large population evolving according to the Wright–Fisher model. As noted, for the Wright–Fisher model, time is measured in units of \( N \) generations in this approximation (and the approximation applies when mutation probabilities are of order \( N^{-1} \)). In fact the Fleming–Viot process arises as the limit of a wide range of demographic models (and we refer to such models as being within the domain of attraction of the Fleming–Viot process), although the appropriate time scaling can differ between models. (See, for example, [14].) For background, including explicit formulations of the claims made above, see [10], [11] [13], [14], [15].

Donnelly and Kurtz [10], [11] give a discrete construction of the Fleming–Viot process. As a consequence, the process can actually be thought of as describing the evolution of a hypothetically infinite population, and it explicitly includes the demography of that population. Exchangeability figured prominently in Kingman’s work in genetics. It provides a linking thread here: the Donnelly–Kurtz construction embeds population models for each finite population size \( N \) in an infinite exchangeable sequence. The value taken by the Fleming–Viot diffusion at a particular time point is just the de Finetti representing measure for the infinite exchangeable sequence. Given the value of the measure, the types of individuals in the population are independent and identically distributed according to that measure.

The coalescent arises by looking backwards in time. Consider again the discrete Wright–Fisher model. If we consider two different chromosomes in the current generation, they will share an ancestor in the previous generation with probability \( 1/N \). If not, they retain distinct ancestries, and will share an ancestor in the generation before that with probability \( 1/N \). The number of generations until they share an ancestor is thus geometrically distributed with success probability \( 1/N \) and mean \( N \). In the limit for large \( N \), with time measured in units of \( N \) generations, this geometric random variable converges to an exponential random variable with mean 1.

More generally, if we consider \( k \) chromosomes, then for fixed \( k \) and
large $N$, they will descend from $k$ distinct ancestors in the previous
generation with probability
\[
1 - \binom{k}{2} \frac{1}{N} + O(N^{-2}).
\]
Exactly two will share a common ancestor in the previous generation
with probability $\binom{k}{2} \frac{1}{N} + O(N^{-2})$, and more than a single pair will share
a common ancestor with probability $O(N^{-2})$. In the limit as $N \rightarrow \infty$,
with time measured in units of $N$ generations, the time until any of the
$k$ share an ancestor will be exponentially distributed with mean $1/\binom{k}{2}$,
after which time a randomly chosen pair of chromosomes will share an
ancestor.

Thus, in the large population limit, with time measured in units of
$N$ generations, the genealogical history of a sample of size $n$ may be
described by a random binary tree. The tree initially has $n$ branches, for
a period of time $T_n$, after which a pair of branches (chosen uniformly at
random, independently of all other events) will join, or coalesce. More
generally, the times $T_k$, $k = n, n-1, \ldots, 2$ for which the tree has $k$
branches are independent exponential random variables with
\[
E(T_k) = \binom{k}{2}^{-1},
\]
after which a pair of branches (chosen uniformly at random independently
of all other events) will join, or coalesce. The resulting random
tree is called the $n$-coalescent, or often just the coalescent. Note that
we have described the coalescent as a random tree. Kingman’s original
papers elegantly formulated the $n$-coalescent as a stochastic process on
the set of equivalence relations on $\{1, 2, \ldots, n\}$. The two formulations
are equivalent. We view the tree description as more intuitive.

In a natural sense the tree describes the important part of the gene-
alogical history of the sample, in terms of their genetic composition.
It captures their shared ancestry, due to the demographic process. As
noted above, a key observation is that in neutral models the distribution
of this ancestry is independent of the genetic types which happen to be
carried by the individuals in the population. Probabilistically, one can
thus sample the coalescent tree and then superimpose genetic types. For
example, at stationarity, first choose a type for the most recent common
ancestor of the population (the type at the root of the coalescent tree)
according to the stationary distribution of the mutation process, and
then track types forward through the tree from the common ancestor, where they will possibly be changed by mutation.

The preceding recipe gives a simple means of simulating the genetic types of a sample of size $n$ from the population. Note that this is an early example of what has more recently come to be termed ‘exact simulation’: a finite amount of simulation producing a sample with the exact distribution given by the stationary distribution of a Markov process. In addition, it is much more computationally efficient than simulating the entire population forward in time for a long period and then taking a sample from it. Finally, it reveals the complex structure of the distribution of genetics models at stationarity—the types of each of the sampled chromosomes are (positively) correlated, exactly because of their shared ancestral history.

We motivated the coalescent from the Wright–Fisher model, but the same limiting genealogical tree arises for any of the large class of demographic models in the domain of attraction of the Fleming–Viot diffusion. See Kingman [34] for an elegant formulation and proof of this kind of robustness result. Moreover, the ways in which the tree shape changes under different demographic scenarios (e.g. changes in population size or geographical population structure) is well understood [55], [28].

The discrete construction of the Fleming–Viot process described above actually embeds the coalescent and the forward diffusion in the same framework, so that one can think of the coalescent as describing the genealogy of a sample from the diffusion.

There is even a natural limit, as $n \to \infty$, of the $n$-coalescents, introduced and studied by Kingman [32]. This can be thought of as the limit of the genealogy of the whole population, or as the genealogy of the infinite population described by the Fleming–Viot process (though this perspective was not available when Kingman introduced the process). The analysis underlying the relevant limiting results for this population-genealogical process is much more technical than that outlined above for the fixed-sample-size case [5], [9], [10]. It is easiest to describe this tree from the root, representing the common ancestor of the population, forward to the tips, each of which represents an individual alive at the reference time. The tree has $k$ branches for a random period of time $T_k$, after which a branch, chosen uniformly at random, independently for each $k$, splits to form two branches. The times $T_k$, $k = 2, 3, \ldots$, are independent exponential random variables, and independent of the
topology of the tree, with

$$E(T_k) = \binom{k}{2}^{-1}.$$

Write

$$T = \sum_{k=1}^{\infty} T_k$$

for the total depth of the tree, or equivalently for the time back until the population first has a common ancestor. Note that $T$ is a.s. finite.

In fact $E(T) = 2$.

To date, we have focussed on models for a small segment of DNA. For larger segments, in diploid populations, one has to allow for the process of recombination. Consider a particular human chromosome inherited from a parent. The parent will have two (slightly different) copies of this chromosome. Think of the process which produces the chromosome to be passed on to the offspring as starting on one of the two chromosomes in the parent and copying from it along the chromosome. Occasionally, and for our purposes randomly, the copying process will ‘cross over’ to the other chromosome in the parent, and then copy from that, perhaps later jumping back and copying from the original chromosome, and so on. The chromosome passed on to the offspring will thus be made up as a mosaic of the two chromosomes in the parent. The crossings over are referred to as recombination events. In practice, these recombination events are relatively rare along the chromosome: for example in humans, there will typically be only a few recombination events per chromosome.

The formulation described above can be extended to allow for recombination. In the coalescent framework, the consequence is that in going backwards in time, different parts of a chromosome may be inherited from different chromosomes in the previous generation. One way of conceptualising this is to imagine each position in the DNA as having its own coalescent tree, tracing the ancestry of the DNA in that position. This coalescent tree, marginally, will have the same distribution as the coalescent. As one moves along the DNA sequence, these trees for different positions are highly positively correlated. In fact, two neighbouring positions will have the same tree if there is no recombination event between those positions, on a lineage leading to the current sample, since their joint most recent common ancestor. If there is such a recombination, the trees for the two positions will be identical back to that point, but (in general) different before it. The correlation struc-
ture between the trees for different positions is complex. For example, when regarded as a process on trees as one moves along the sequence, it is not Markov. Nonetheless it is straightforward to simulate from the relevant joint distribution of trees, and hence of sampled sequences. The trees for each position can be embedded in a more general probabilistic object (this time a graph rather than a tree) called the ancestral recombination graph [21], [22].

3 Inference under the coalescent

The coalescent has revolutionised the way we think about and analyse population genetics models, and changed the way we simulate from these models. There are several important reasons for this. One is the separation, for neutral models, of demography from the effects of mutation. This means that many of the properties of samples taken from genetics models follow from properties of the coalescent tree. A second reason is that the coalescent has a simple, indeed beautiful, structure, which is amenable to calculation. Most questions of interest in population genetics can be rephrased in terms of the coalescent, and the coalescent is a fundamentally simpler process than the traditional forwards-in-time models.

The body of work outlined above has an applied probability flavour; some of it more applied (for example solving genetics questions of interest), and some more pure (for example the links with measure-valued diffusions). Historically, much of it occurred in the 10–15 years after Kingman’s coalescent papers, but even today ‘coalescent methods’ as they have become known in population genetics, are central to the analysis of genetics models.

If an applied probability perspective prevailed over the first 10–15 years of the coalescent’s existence, the last 10–15 years have seen a parallel interest in statistical questions. Since the early 1990s there has been a steady growth in data documenting molecular genetic variation in samples taken from real populations. Over recent years this has become a deluge, especially for humans. Instead of trying to study probabilistic properties of the coalescent, the statistical perspective assumes that some data come from a coalescent model, and asks how to do statistical inference for parameters in the model, or comparisons between models (for example arising from different demographic histories for the population).
There have been two broad approaches. One has been to attempt to use all the information in the data, by basing inference (in either a frequentist or Bayesian framework) on the likelihood under the model: the probability, regarded as a function of parameters of interest, of observing the configuration actually observed in the sample. This is the thread we will follow below. Full-likelihood inference under the coalescent turns out to be a difficult problem. A second approach has been to summarise the information in the data via a small set of summary statistics, and then to base inference on these statistics. One particular, Bayesian, version of this approach has come to be called approximate Bayesian computation (ABC): one approximates the full posterior distribution of parameters of interest conditional on the data by their conditional distribution given just the summary statistics.

Full-likelihood inference under the coalescent is not straightforward, for a simple reason. Although the coalescent enjoys many nice properties, and lends itself to many calculations, no explicit expressions are available for the required likelihoods. There is one exception to this, namely settings in which the mutation probabilities, $\gamma_{ij}$, that a chromosome is of type $j$ when its parent is of type $i$, depend only on $j$. This so-called parent-independent mutation is unrealistic for most modern data, notwithstanding the fact that any two-allele model (that is, when the type space $E$ consists of only two elements) can be written in this form. For parent-independent mutation models, the likelihood is multinomial.

In the absence of explicit expressions for the likelihood, indirect approaches, typically relying on sophisticated computational methods, were developed. Griffiths and Tavaré were the pioneers. They devised an ingenious computational approach whereby the likelihood was expressed as a functional of a Markov chain arising from systems of recursive equations for probabilities of interest. Felsenstein later showed the Griffiths–Tavaré (GT) approach to be a particular implementation of importance sampling. In contrast to the GT approach, Felsenstein and colleagues developed Markov chain Monte Carlo (MCMC) methods for evaluating coalescent likelihoods. These were not without challenges: the space which MCMC methods explored was effectively that of coalescent trees, and thus extremely high-dimensional, and assessment of mixing and convergence could be fraught. As subsequent authors pointed out, failure of the Markov chains to mix properly resulted in poor approximations to the likelihood.

Donnelly and Stephens adopted an importance sampling approach. They reasoned that if the GT approach was implicitly doing
importance sampling, under a particular proposal distribution which arose automatically, then it might be possible to improve performance by explicitly choosing the proposal distribution. In particular, they noted that the optimal proposal distribution was closely related to a particular conditional probability under the coalescent, namely the probability that an additional, \( n + 1 \)st sampled chromosome will have type \( j \) conditional on the observed types in a sample of \( n \) chromosomes from the population. This conditional probability under the coalescent does not seem to be available explicitly (except under the unrealistic parent-independent mutation assumption)—indeed an explicit expression for this probability leads naturally to one for the required likelihoods, and conversely.

Donnelly and Stephens exploited the structure of the discrete representation of the Fleming–Viot diffusion to approximate the key conditional probabilities. In effect, in the Donnelly–Kurtz process they fixed the types on the first \( n \) levels and ran the level \( n+1 \) process. This led naturally to an approximation to the conditional distribution of the \( n + 1 \)st sampled chromosome given the types of the first \( n \) chromosomes, which in turn leads naturally to importance sampling proposal distributions. As had been hoped, importance sampling under this family of proposal distributions was considerably more efficient than under the GT scheme \cite{gt}.

There has been considerably more activity in the area of inference under the coalescent over the last 10 years. We will not pursue this here, as our narrative will take a different path. Interested readers are referred to \cite{hudson} and \cite{fearnhead2004}.

4 The Li and Stephens model

As we have noted, statistical inference under the coalescent is hard. From our perspective, a key breakthrough came earlier this decade from Li and Stephens \cite{li2003}. Their idea was very simple, and it turns out to have had massive impact. Li and Stephens argued that instead of trying to do inference under the coalescent one should appreciate that the coalescent is itself only an approximation to reality, and that one might instead do inference under a model which shares many of the nice properties of the coalescent but also enjoys the additional property that full likelihood inference is straightforward.

Li and Stephens changed the model. Inference then became a tractable problem. What matters is how good these inferences are for real data
sets. Although not obvious in advance, it turns out that for a very wide
range of questions, inference under the Li and Stephens model works
well in practice.

A forerunner to the Li and Stephens approach arose in connection
with the problem of estimating haplotype phase from genotype data.
Stephens, Smith, and Donnelly [52] introduced an algorithm, PHASE,
in which the conditional distribution underpinning the Donnelly-Stephens
importance-sampling proposal distribution was used directly in a pseudo
Gibbs sampler. PHASE has been widely used, and even today provides one
of the most accurate methods for computational recovery of haplotype
phase. (Several recent approaches aim to speed up computations to allow
phasing of genome-wide data sets, typically at a slight cost in accuracy
e.g. Beagle [5], [4]; FastPhase [46]; and IMPUTE 2 [29]. See [39] for a
review of some of these methods.)

We now describe the Li and Stephens model. For most modern data
sets it is natural to do so in the context of ‘SNPs’. A SNP, or single
nucleotide polymorphism, is a position in the DNA sequence which is
known to vary across chromosomes. At the overwhelming majority of
SNPs there will be exactly two variants present in a population, and we
assume this here. For ease, we will often code the variants as 0 and 1.
To simplify the description of the model we assume haplotype data are
available. This is equivalent to knowing the types at each SNP separ-
ately along each of the two chromosomes in a diploid individual. (Most
experimental methods provide only the unordered pair of types on the
two chromosomes at each SNP, without giving the additional informa-
tion as to which variant is on which chromosome. As noted above, there
are good statistical methods for estimating the separate haplotypes from
these genotype data.)

It is convenient, and for many purposes most helpful, to describe the
Li and Stephens model via the conditional probabilities it induces, and
in particular by specifying the probability distribution for the $n+1$st
sampled chromosome given the types of the first $n$ chromosomes. This
in turn can be described by a recipe for simulating from this conditional
distribution. (We return below to a probabilistic aside on this perspec-
tive.)

In effect, the Li and Stephens model simulates the $n+1$st chromosome
as an imperfect mosaic of the first $n$ chromosomes. To simulate the $n+1$st
chromosome, first pick one of the existing $n$ chromosomes at random.
At the first SNP copy the type from the chosen chromosome, but with
random ‘error’ in a way we will describe below. With high probability
(specified below) the second SNP will be probabilistically copied from the same chromosome. Alternatively, the chromosome for copying at the second SNP will be re-chosen, uniformly and independently. Having simulated the type on the \( n + 1 \)st chromosome at the \( k \)th SNP, the \( k + 1 \)st SNP will be copied from the same chromosome as the \( k \)th SNP with high probability, and otherwise copied from a chromosome chosen independently, and uniformly at random, from the first \( n \). It remains to specify the probabilistic copying mechanism: with high probability at a particular SNP, the value of the \( n + 1 \)st chromosome will be the same as that on the chromosome being copied, otherwise it will have the opposite type.

The connection with the coalescent comes from the following. Consider the position of the first SNP on the \( n + 1 \)st chromosome. Ignoring coalescences amongst the first \( n \) sampled chromosomes at this position, the ancestry of the \( n + 1 \)st sampled chromosome coalesces with exactly one of the lineages leading to the \( n \) sampled chromosomes. Ignoring mutation, the type of the \( n + 1 \)st chromosome at this position will be the same as the type on the chromosome with which its ancestry coalesces. To incorporate mutation one allows mis-copying of the ancestral type. This mis-copying is an oversimplification of the effect of mutation on the coalescent tree at this position. Now, moving along the \( n + 1 \)st chromosome, there will be a segment, up to the first recombination event in the relevant history, which shares the same ancestry (and so is copied from the same one of the sampled chromosomes). The effect of recombination is to follow different ancestral chromosomes and this is mimicked in the Li and Stephens approach by choosing a different chromosome from which to copy. The probabilities of this change will depend on the recombination rates between the SNPs, and in a coalescent also on \( n \), because coalescence of the lineage of the \( n + 1 \)st chromosome to one of the other lineages happens faster for larger \( n \).

We now describe the model more formally. Suppose that \( n \) chromosomes (each of which can be thought of as a haplotype) have been sampled from the population, where the \( j \)th haplotype has the SNP information at \( l \) SNPs, \( c^j = \{ c^j_1, c^j_2, \ldots, c^j_l \} \). Let us call this set of chromosomes \( C \). Now suppose an additional chromosome \( i \) has been sampled and has SNP information \( h^i = \{ h^i_1, h^i_2, \ldots, h^i_l \} \). We seek to determine the probability of sampling this chromosome, based on its SNP haplotype and the SNP haplotypes of the previously sampled chromosomes \( C \). The model takes as input fine-scale estimates of recombination rates in the region: \( r = \{ r_0, r_1, \ldots, r_l \} \) where \( r_{j+1} - r_j \) is the average rate
of crossover per unit physical distance per meiosis between sites $j$ and $j + 1$ times the physical distance between them. We set $r_0 = 0$. We obtain this map from elsewhere (for example [31]) rather than estimating it for ourselves. Note that the SNPs (and the map) are ordered by the position of the SNP (or map point) on the chromosome (for convenience we refer to the first SNP position as the leftmost position and the $l$th SNP position as the rightmost). We define the per-locus recombination probability $\rho_s = 1 - \exp(-4N_e(r_{s+1} - r_s)/n)$ and then define transition probabilities for a Markov chain on $\{1, 2, \ldots, n\}$ from state $j$ (indicating that it is the $j$th haplotype of those that have been previously sampled that is ‘parental’) at position $s$ to state $k$ at position $s + 1$:

$$q(j_s, k_{s+1}) = \begin{cases} 
1 - \rho_s + \rho_s/n, & j = k, \\
\rho_s/n, & j \neq k,
\end{cases} \quad (4.1)$$

where $N_e$ is the so-called effective population size, a familiar quantity in population genetics models. Equation (4.1) is related to the fact that recombination events occur along the sequence as a Poisson process. Here we use the Poisson rate $4N_e(r_{s+1} - r_s)/n$. Given the rate, the probability that there is no recombination between sites $s$ and $s + 1$ is $\exp(-4N_e(r_{s+1} - r_s)/n) = 1 - \rho_s$. The probability of at least one recombination between sites $s$ and $s + 1$ is thus $\rho_s$. In this case the model has the assumption that it is equally likely that the recombination occurs with any of the $n$ sampled haplotypes. In particular, as $\rho_s$ incorporates the probability that multiple recombinations occur between sites $s$ and $s + 1$, the first case in Equation (4.1) includes a $\rho_s$ term to allow for the possibility that the same haplotype is parental at each site $s$ and $s + 1$ even when one or more recombinations have occurred.

We define the copying probabilities in terms of the ‘population mutation rate’ for the given sample size ($\theta$, defined below), another familiar quantity from population genetics. The mismatch (or not) between the SNP allele of the $j$th ‘parent’ chromosome at SNP $s$, $c_{js}$, and the SNP allele of the $i$th additional ‘daughter’ chromosome, $h_{is}$, is defined as

$$e(h_{is}, c_{js}) = \begin{cases} n/n + \frac{1}{2} \frac{\theta}{n+\theta}, & h_{is} = c_{js}, \\
\frac{1}{2} \frac{\theta}{n+\theta}, & h_{is} \neq c_{js}.
\end{cases} \quad (4.2)$$

Notice that as $\theta \to \infty$ the alleles 0 and 1 at any given site become

1 In fact, Li and Stephens developed their model precisely for estimating the genetic map, but for our purposes we wish to utilize the model for inference in other settings and thus we utilize a known genetic map.
Peter Donnelly and Stephen Leslie

Equally likely. Equation (4.2) is motivated by a similar coalescent argument to that used for the transition probabilities above. In this case the probability of no mutations occurring at the site \( s \) is \( n/(n + \theta) \) and thus the probability of at least one mutation occurring at \( s \) is \( \theta/(n + \theta) \). It is possible to allow for the population mutation rate to vary sitewise if it is necessary to account for known variable mutation rates.

The particular form of the transition and copying probabilities in the model follow from the informal coalescent arguments given four paragraphs above ([36]). We noted that the recombination probabilities typically come from available estimates. It turns out that the accuracy of these estimates can be important in applications of the model. In contrast, such applications are generally not especially sensitive to the exact value of \( \theta \) used. Thus, for the mutation probabilities, we follow Li and Stephens and set

\[
\theta = \left( \sum_{z=1}^{n-1} \frac{1}{z} \right)^{-1}. \tag{4.3}
\]

We can view the Li and Stephens process as defining a path through the previously sampled sequences \( C \). This is illustrated in Figure 4.1.

A key feature of the conditional probabilities just described for the Li and Stephens model is that they take the form of a hidden Markov model (HMM) ([12]). The path through the sampled chromosomes is a Markov chain on the set \( \{1, 2, \ldots, n\} \) which indexes these chromosomes; the value of the chain at a particular SNP specifies which chromosome is being copied at that SNP to produce the new chromosome. In the language of HMMs, the transition probabilities specify the probability of either continuing to copy the same chromosome or choosing another chromosome to copy, and the emission probabilities specify the probability of observing a given value at the SNP on the new chromosome given its type on the chromosome being copied. The latter have the simple form that with high probability the new chromosome will just copy the type from the chromosome being copied, with the remaining probability being for a switch to the opposite type from that on the chromosome being copied. Viewed this way, the transition probabilities relate to the recombination process and the emission probabilities to the mutation process. The reason that the HMM structure is crucial is that very efficient algorithms are available for calculations in this context. For example, under the Li and Stephens model, given values for all the SNPs on the \( n + 1 \)st chromosome, and good computational resources, one can
calculate the conditional probability of each possible path through the first $n$ chromosomes, or of the maximum likelihood path (see [12] for details).

Not only is the Li and Stephens model tractable, in a way that the coalescent is not, but it turns out that its use for inference in real populations has been very successful. Examples include inference of haplotype phase [46], [51], [37], [38]; inference of fine-scale recombination rates [36]; imputation of unobserved genotype data [40], [47]; and imputation of classical HLA types from SNP data [35]. It seems that the model captures enough of the features of real data to provide a good framework for inference. Because inference under the coalescent is impossible, it is not known whether this would have properties which are better or worse
than those under Li and Stephens, though we would not expect major differences.

We have specified the Li and Stephens model via its conditional probabilities, and these are what is crucial in most applications. But there is a probabilistic curiosity which is worth mentioning. One could calculate the probability, under the model, for a particular configuration of \(n\) chromosomes via these conditional probabilities: for a particular ordering, this would simply be the product of the marginal probability for the first chromosome, the Li and Stephens conditional probability for the second chromosome given the first, the Li and Stephens conditional probability for the third given the first and second, and so on. In fact, Li and Stephens themselves referred to their model as the product of approximate conditionals, or PAC, likelihood. The probabilistic curiosity is that in this formulation the likelihood, or equivalently sampling probabilities, in general depend on the order in which the chromosomes are considered. One could solve the problem by averaging over all possible orders, or approximately solve it by averaging over many orders, the approach adopted by Li and Stephens. But for most applications, including the one we describe below, it is the conditional distributions which matter, either in their own right (e.g. [55]) or for use in what resembles a Gibbs sampler. This latter approach gives rise to another curiosity: one can write down, and implement, an algorithm using the Li and Stephens conditionals as if it were a Gibbs sampler, even though the conditionals do not obviously correspond to a proper joint distribution. These algorithms (of which PHASE was perhaps the first) often perform extremely well in practice, notwithstanding the gap in their probabilistic pedigree, an observation which might warrant further theoretical investigation.

5 Application: modelling population structure

In this section we describe an extension of the Li and Stephens model appropriate for geographically structured populations, and then show how inference under the model performs well on real data.

Real populations often consist of genetically distinct subpopulations, and there has been considerable interest in the development of statistical methods which detect such subpopulations, and assign sampled individuals to them, on the basis of population genetics data [3], [44], [45], [16], [6], [7]. Understanding population structure is of interest
in conservation biology, human anthropology, human disease genetics, and forensic science. It is important to detect hidden population structure for disease mapping or studies of gene flow, where failure to detect such structure may result in misleading inferences. Population structure is common amongst organisms, and is usually caused by subpopulations forming due to geographical subdivision. It results in genetic differentiation—frequencies of variants, (called alleles in genetics) that differ between subpopulations. This may be due to natural selection in different environments, genetic drift (stochastic fluctuations in population composition) in distinct subpopulations, or chance differences in the genetic make up of the founders of subpopulations [27].

Model-based approaches to detecting and understanding population structure have been very successful [45], [16], [6], [7]. Broadly, one specifies a statistical model describing data from different subpopulations and then performs inference under the model. These models are examples of the statistical class of mixture models, in which observations are modelled as coming from a (typically unknown) number of distinct classes. In our context the classes consist of the subpopulations, and what is required is a model for the composition of each, and the way in which these are related. Model-based approaches to understanding population structure have several natural advantages. Results are readily interpretable, and, at least for Bayesian inference procedures, they provide a coherent assessment of the uncertainty associated with the assignment of individuals to subpopulations, and the assessment of the number of populations in the sample.

Where the data consist of SNPs taken from distinct regions of the genome it is natural to model these as being independent of each other, within subpopulations, and it remains only to model the frequency of the alleles at each SNP in each subpopulation, and the joint distribution of these across subpopulations. This approach was taken by Pritchard, Stephens and Donnelly [45] and implemented in the program STRUCTURE which has been successfully used in a variety of applications.

In some contexts the population in question arose from the mixing, or admixing as it is known in genetics, of distinct populations at some time in the relatively recent past. African-American populations are an example of admixture, in this case between Caucasian and African populations. Such admixture is well known to lead to correlations between SNPs over moderately large scales (say 5–10 million bases) across chromosomes, known as admixture linkage disequilibrium. Falush, Stephens and Pritchard [10] adapted the model underlying STRUCTURE to incor-
SNPs which are close to each other on the chromosome exhibit correlations, known in genetics as *linkage disequilibrium*, due to their shared ancestral history. Both the coalescent with recombination and the Li and Stephens model explicitly capture these correlations for a single randomly-mating population. To employ a model-based approach to population structure for nearby SNPs with linkage disequilibrium, one needs to model these correlations within and between subpopulations. We introduce such a model below as a natural extension of the Li and Stephens model.

For simplicity throughout, we describe our model assuming the haplotypes of the sampled individuals are known, so we assume that the phase of the data is known, either directly or by being inferred using a phasing method such as [52] or [46]. Given the accuracy of statistical phasing methods, this is a reasonable assumption in most cases, but as we note below, the assumption can be dropped, at some computational cost.

Suppose we have DNA sequence data (SNPs) for $N$ haploid individuals (or $N$ phased haplotypes) sampled from $K$ populations at $L$ loci. Call these data $H = \{h_1, \ldots, h_N\}$, where the index $i$ represents individual $i$. Define the population assignment of individual $i$ to be the discrete random variable $Z_i$ which can take values in $\{1, \ldots, K\}$. In contrast to the previous methods, however, we make no assumption that the SNPs are independent (or merely loosely dependent as is the case for [16]) i.e. we explicitly deal with linkage disequilibrium. In order to model linkage disequilibrium, by applying the model of Li and Stephens [36], we require a genetic map of the region covering the $L$ loci. We assume we have such a map, obtained from other sources (e.g. the program LDhat [41], [42], [1] or from applying the Li and Stephens method for estimating recombination rates [36]). In specifying the model we assume we know the value of $K$.

We wish to allocate sequences to populations based on the data $H$. As is natural in mixture models, we do so in a Bayesian framework, via Gibbs sampling (or to be more precise, as we note below, via pseudo-Gibbs sampling) over the unobserved allocation variables, the $Z_i$. To do so we need to specify the conditional distribution of $Z_i$ given the data $H$ and the values of the allocation variables $Z$ for individuals other than individual $i$. 
We specify the prior distribution on the $Z_i$ to be uniform, i.e.

$$
\mathbf{P}(Z_i = 1) = \mathbf{P}(Z_i = 2) = \cdots = \mathbf{P}(Z_i = K) = \frac{1}{K}
$$

for every $i = 1, \ldots, N$. It is a simple matter to include an informative prior if required. Furthermore, we assume that in the absence of any data $h_i$, $Z_i$ is independent of all of the $Z_j$ and $h_j$ for $i \neq j$.

We first informally describe the model in the special case in which the ancestry of any chromosome only ever involves chromosomes in its own population. In effect this means that there has been no migration between subpopulations over the time back to the common ancestors of sampled chromosomes. In this special case, we can think of calculating the conditional distribution as follows. (We describe the calculation of the conditional distribution of $Z_1$ given $H$ and the other $Z_i$.) Suppose we know the current population assignments in our sampler of all of the haplotypes. We wish to update the assignment of haplotype 1 based on the assignments of all of the other haplotypes. First, we remove haplotype 1 from the population it is currently assigned to. Then, we calculate the Li and Stephens conditional probability that $h_1$ would be the next sampled haplotype from each of the $K$ populations. We normalize these probabilities by dividing by their sum and draw the new population assignment of haplotype 1 from the multinomial distribution with these normalized probabilities as the population weights.

We now introduce the general version of our new model, which extends the simple Li and Stephens models above to incorporate migration or recent admixture, and use this as the basis for our method for classifying individuals into populations. Importantly, the model reduces to the Li and Stephens model in certain limiting cases. The method uses SNP haplotype data and explicitly models correlations between SNP loci using the model and estimates of recombination rates between the loci. We test our method on a sample of individuals from three continents and show that it performs well when classifying individuals to these continental populations.

We extend the Li and Stephens\cite{Li05} model to incorporate admixture or inter-population migration by adding another parameter to the model, represented by $\alpha$, which models the extent of shared ancestry between populations. This parameter attempts to capture the contribution to an individual’s ancestry which is derived from a population other than its own. It does not have a natural interpretation in terms of the dynamics of the populations forward in time. In this sense it has more in common
with parameters in statistical models than in probability models. This extended model is perhaps best understood by considering the ‘copying path’ representation of the Li and Stephens model (see Figure 4.1). For simplicity we present the extended model for the case of two populations (i.e. $K = 2$) with a fixed value of $\alpha$. We discuss further generalizations after the initial presentation of the model.

As in the special case above, the model allows calculation of the probability that a particular haplotype is sampled from a given population. Normalising these probabilities then gives the probabilities for resampling the allocation variables.

The extension of Li and Stephens relates to recombination, or in the sense of Figure 4.1, to the step when there is a potential change to the chromosome being copied. When such a potential change occurs in the simple model a new chromosome is chosen to be copied uniformly at random (including the chromosome currently being copied). In the extension described above, this remains the case, but with the new chromosome allowed to be chosen only from the population being considered. Our generalisation allows the possibility that the copying process could switch to a chromosome in a different population, and the parameter $\alpha$ controls the relative probability of this.

We now give the details of the model we use. Suppose that $n_1$ and $n_2$ (where $n_1 + n_2 = n$) chromosomes have been sampled from populations 1 and 2 respectively, where the $j$th haplotype in the total population has the SNP information at $l$ SNPs, $c^j = \{c^j_1, c^j_2, \ldots, c^j_l\}$. Let us call this set of chromosomes $C = C_1 \cup C_2$, where $C_1$ are the chromosomes sampled from Population 1, and $C_2$ from Population 2. Now suppose an additional chromosome $i$ has been sampled and has SNP information $h^i = \{h^i_1, h^i_2, \ldots, h^i_l\}$. Without loss of generality we seek to determine the probability of sampling this chromosome from Population 1, based on its SNP haplotype and the SNP haplotypes of the previously sampled chromosomes $C$. We define the per locus recombination probability $p_s = 1 - \exp(-4N_e(r_{s+1} - r_s)/(n_1 + \alpha_1 n_2))$ and then define the transition probabilities from state $j$ (indicating that it is the $j$th haplotype of those that have been previously sampled that is ‘parental’) at position
The coalescent and its descendants

$s$ to state $k$ at position $s + 1$:

\[
q(j_s, k_{s+1}) = \begin{cases} 
1 - \rho_s + \frac{\rho_s}{n_1 + \alpha_1 n_2}, & j = k, \ j \in C_1, \\
\rho_s \frac{\rho_s}{n_1 + \alpha_1 n_2}, & j \neq k, \ j \in C_1, \ k \in C_1, \\
\frac{\rho_s}{n_1 + \alpha_1 n_2}, & j \neq k, \ j \in C_1, \ k \in C_2, \\
1 - \rho_s + \alpha_1 \frac{\rho_s}{n_1 + \alpha_1 n_2}, & j = k, \ j \in C_2, \\
\frac{\rho_s}{n_1 + \alpha_1 n_2}, & j \neq k, \ j \in C_2, \ k \in C_1, \\
\alpha_1 \frac{\rho_s}{n_1 + \alpha_1 n_2}, & j \neq k, \ j \in C_2, \ k \in C_2, 
\end{cases} 
\tag{5.1}
\]

where $N_e$ is the effective population size. Notice that when $\alpha_1 = 0$ the transition probabilities so defined reduce to the Li and Stephens transition probabilities for a single sample from Population 1. Also note that when $\alpha_1 = 1$ we have effectively combined the two samples into a single sample from one population and again we obtain the Li and Stephens transition probabilities for this case.

We define the emission probabilities in terms of the ‘population mutation rate’ for our given sample size, where in this case our ‘sample size’ is $n_1 + \alpha_1 n_2$,

\[
\theta = \left( \sum_{z=1}^{n_1-1} \frac{1}{z} + \sum_{z=n_1}^{n_1+n_2-1} \frac{\alpha_1}{z} \right)^{-1}. \tag{5.2}
\]

Again, we obtain the desired Li and Stephens population mutation rates for the $\alpha_1 = 0$ and $\alpha_1 = 1$ cases. We then define the mismatch (or not) between the SNP allele of the $j$th ‘parent’ chromosome at SNP $s$, $c_j^s$, and the SNP allele of the $i$th additional ‘daughter’ chromosome, $h_i^s$:

\[
e(h_i^s, c_j^s) = \begin{cases} 
\frac{n_1 + \alpha_1 n_2 + \theta}{2 n_1 + \alpha_1 n_2 + \theta}, & h_i^s = c_j^s, \\
\frac{1}{2 n_1 + \alpha_1 n_2 + \theta}, & h_i^s \neq c_j^s.
\end{cases} \tag{5.3}
\]

As before, notice that these emission probabilities reduce to the analogous Li and Stephens emission probabilities for the cases $\alpha_1 = 0$ and $\alpha_1 = 1$.

As was the case for a single population, we can view this process as defining a path through the previously sampled sequences $C$. This is illustrated in Figure 5.1.

Using this model we proceed as before. To calculate the conditional probability of observing the additional haplotype we sum over all possible paths through the potential parental chromosomes $C$. We use the forward algorithm which gives a computationally efficient means of performing the required summation \cite{12}. For each of the $n$ previously sam-
Figure 5.1 A pictorial representation of the calculation for a single path using the new model. Here we have sampled sequences $c^1, \ldots, c^6$ from two populations, represented by the first three rows and the second three rows in the figure, respectively. We seek to calculate the probability of sampling $h^i$ (seventh row) from the first population by summing the probabilities obtained over all possible paths. We illustrate this with a single path. The arrows indicate the ‘path’ taken through the sampled sequences, indicating which of the $c^i$ has the ‘parental’ type at a given SNP locus. Recombination with another parental sequence is indicated by changing the sequence being copied (for example, between the second and third loci). The dark box on the path at the fifth locus indicates that a mutation occurred in the copying of that locus. A dashed arrow indicates that the copying at the next position is taking place with a sequence not in the population we are interested in (in this case the first population) and thus the recombination term in the model is scaled by the $\alpha$ parameter for these terms.

pled chromosomes, we initialise the forward algorithm:

\[
f^1_j = \begin{cases} 
\frac{1}{n_1 + \alpha_1 n_2} \times e(h^i_1, c^j_1), & j \in C_1, \\
\frac{\alpha_1}{n_1 + \alpha_1 n_2} \times e(h^i_1, c^j_1), & j \in C_2. 
\end{cases}
\]  
(5.4)
The forward algorithm moves along the sequence such that at each SNP $s$, where $1 < s \leq l$,

$$f^s_j = e(h^s_i, c^s_j) \sum_{k=1}^{n} f^k_{s-1} \times q(k_{s-1}, j_s). \quad (5.5)$$

The probability of observing the SNP configuration of the additional chromosome is given by

$$\hat{\pi}(h^1|C, \theta, \rho) = \sum_{j=1}^{n} f^1_j. \quad (5.6)$$

A simple extension for $K > 2$ treats the current population of interest as one population and all other populations are combined to form the second population, thus reducing this case to the $K = 2$ case. This is what we consider here. To further generalize the model one may define a matrix of $\alpha$ parameters for each ordered pair of populations. Inference for the number of populations represented in the sample ($K$) may be performed using the method of [45] or by other methods. We focus here only on the problem of classifying individuals where the number of subpopulations is known.

As noted above, it is a slight abuse of terminology to refer to the process just described as Gibbs sampling. In this case, we cannot be certain that our approximations do in fact correspond to a proper joint probability. Nonetheless, there are successful precedents for this use of ‘pseudo-Gibbs’ sampling, notably the program PHASE [52], [50] which has proved successful for inferring haplotypes from genotypes. Furthermore, our method is successful in practice. Given these caveats, we continue our abuse of terminology throughout.

It is also possible to set the proportion of the sample coming from each population as a parameter and update this value at each step. This would allow us to deal easily with populations of different sizes in a straightforward manner, although we have not implemented this extension. Extending the model to incorporate genotypes rather than haplotypes is also straightforward in principle, for example by analogy with [40].

Our model applies when SNPs are sampled from the same small chromosomal region. In practice, it is more likely that data of this type will be available for a number of different, separated, chromosomal regions. In this context we apply the model separately to each region and combine probabilities across regions multiplicatively. We implement this by
setting $\rho_s = 1$ in Equation (5.1) for the transition from the last SNP in one region to the first SNP in the next region (the order of the regions is immaterial).

We tested the method on phased data available from the Phase II HapMap [31]. In particular the data consisted of SNP haplotypes from samples from four populations: Yoruba ancestry from Ibadan in Nigeria (YRI); European ancestry from Utah (CEU); Han Chinese ancestry from Beijing (CHB); and Japanese ancestry from Tokyo (JPT). We use the SNP haplotype data available from the HapMap and the recombination map estimated in that study from the combined populations. The YRI and CEU HapMap samples are taken from 30 parent offspring trios in each case. Of these we used the data from the parents only, giving 60 individuals (120 haplotypes) in each population. The Chinese and Japanese samples derive from 45 unrelated individuals (90 haplotypes) in each case. Following common practice, we combine the Chinese and Japanese samples into a single ‘analysis panel’, which we denote by CHB+JPT. Thus our sample consists of a total of 420 haplotypes deriving from three groups.

From these data we selected 50 independent regions each of 50 kilobases in length (i.e. regions not in linkage disequilibrium with each other). Within these regions we selected only those SNPs that are variable in all three populations and have a minor allele frequency of at least 0.05. A summary of the data is given in Table 5.1.

We then applied our new method to these data. In all cases we set the effective population size for our model, $N_e$, to 15,000 and set $\alpha = \alpha_1 = \alpha_2$ (this may be thought of as the simple situation when there is an equal amount of gene flow in each direction).

As a first test of using the new model we decided to test the sensitivity to the number of regions used and the number of SNPs selected across those regions, where we specify the correct number of populations in the sample ($K = 3$) and set $\alpha = 0.1$. In our experiments we ignore the information as to which haplotypes come from which populations—this is what we aim to infer, and we can then compare inferences with the truth. We denote by $r$ the number of independent regions chosen, where $r \in \{5, 10, 20, 30, 40, 50\}$, and by $s$ the number of SNPs selected in the selected regions, where $s \in \{10, 20, 50, 80, 100\}$. For every pair of values $r$ and $s$ we independently at random selected $r$ regions and then selected $s$ SNPs from the selected region to be included in the analysis. We did this 20 times for each pair of values $r$ and $s$ and tested the method on each of the resulting samples from our data.
Table 5.1 Summary of the data: The data consist of HapMap samples for 420 haplotypes (120 CEU, 180 CHB+JPT, 120 YRI) sampled from 50 independent regions of ∼50kb each, taken across all autosomes. SNPs with a minor allele frequency of less than 0.05 in any of the population groups have been excluded.

For each region the number of SNPs segregating in all populations is shown, as well as the region size, which is the distance between the first and last SNP in the region.

| Chromosome Number | Region ID | Number of SNPs | Region Size (bp) | Chromosome Number | Region ID | Number of SNPs | Region Size (bp) | Chromosome Number | Region ID | Number of SNPs | Region Size (bp) |
|-------------------|-----------|----------------|------------------|-------------------|-----------|----------------|------------------|-------------------|-----------|----------------|------------------|
| 1                 | 0         | 6              | 38600            | 1                 | 22        | 68             | 47223            | 1                 | 44        | 6              | 44916            |
| 2                 | 1         | 42             | 48726            | 2                 | 23        | 56             | 49044            | 2                 | 45        | 24             | 47963            |
| 3                 | 2         | 20             | 46100            | 3                 | 24        | 42             | 48586            | 3                 | 46        | 16             | 46999            |
| 4                 | 3         | 49             | 49031            | 4                 | 25        | 38             | 47651            | 4                 | 47        | 32             | 46961            |
| 5                 | 4         | 82             | 43511            | 5                 | 26        | 56             | 44973            | 5                 | 48        | 31             | 49698            |
| 6                 | 5         | 53             | 49377            | 6                 | 27        | 139            | 49617            | 6                 | 49        | 25             | 48619            |
| 7                 | 6         | 37             | 48387            | 7                 | 28        | 34             | 47905            |                 |           |                |                  |
| 8                 | 7         | 86             | 49212            | 8                 | 29        | 35             | 47465            |                 |           |                |                  |
| 9                 | 8         | 55             | 49700            | 9                 | 30        | 34             | 49603            |                 |           |                |                  |
| 10                | 9         | 59             | 49620            | 10                | 31        | 23             | 49827            |                 |           |                |                  |
| 11                | 10        | 29             | 46888            | 11                | 32        | 25             | 49406            |                 |           |                |                  |
| 12                | 11        | 76             | 49762            | 12                | 33        | 63             | 45207            |                 |           |                |                  |
| 13                | 12        | 30             | 48056            | 13                | 34        | 53             | 49803            |                 |           |                |                  |
| 14                | 13        | 23             | 49648            | 14                | 35        | 26             | 45723            |                 |           |                |                  |
| 15                | 14        | 33             | 47289            | 15                | 36        | 26             | 44137            |                 |           |                |                  |
| 16                | 15        | 85             | 47207            | 16                | 37        | 30             | 44109            |                 |           |                |                  |
| 17                | 16        | 38             | 47062            | 17                | 38        | 42             | 48621            |                 |           |                |                  |
| 18                | 17        | 61             | 48001            | 18                | 39        | 38             | 49694            |                 |           |                |                  |
| 19                | 18        | 33             | 48359            | 19                | 40        | 38             | 47725            |                 |           |                |                  |
| 20                | 19        | 44             | 48119            | 20                | 41        | 80             | 44893            |                 |           |                |                  |
| 21                | 20        | 45             | 49195            | 21                | 42        | 77             | 47874            |                 |           |                |                  |
| 22                | 21        | 1              | 0                | 22                | 43        | 8              | 23443            |                 |           |                |                  |

In each run we used a burn-in of 200 iterations and then kept the following 1,000 iterations. We ran several analyses to confirm that these values are sufficient for convergence. Haplotypes were assigned to the cluster in which they spent the majority of iterations (after the burn-in). To check whether label-switching was occurring we kept the pairwise
assignments matrix for each run. As with [15] and [16], label-switching was not observed and thus the clusters are well-defined. In order to assess performance, clusters were labelled by the population from which the majority of their assigned samples were derived. As we shall see, given the accuracy of the method, this does not result in any ambiguity. Performance was measured as the proportion of haplotypes assigned to the correct population, where we measured these proportions for each sample population individually, and also for the combined sample. We show the average performance over the 20 runs for each pair of values $r$ and $s$ in Figure 5.2.

Examination of Figure 5.2 reveals some insights about the performance of the method. As would be expected, across all populations, for each fixed value of the number of regions selected ($r$), average performance increases with the number of SNPs used. Thus, the more SNP information we have, the more accurate are our population allocations. In general, increasing the number of independent regions used has less effect on the accuracy of the population assignments, although accuracy does increase with increasing the number of regions used. We conclude that applying our method to data sets comprising at least 80 SNPs derived from at least 10 independent regions will give high accuracy (≥ 95%) with good precision (the standard deviation over all runs observed in this case was less than 2%).

We then tested the effect of varying the $\alpha$ parameter, for $\alpha$ in the range (0, 0.3). In this case we used a single set of SNPs for testing. We used a set of 50 SNPs derived from each of 10 regions which had given average accuracy over previous tests (approximately 90% of individuals classified correctly in the initial tests). We selected this set as it represents a typical possible application of the method and also gives reasonable scope to examine the effect of $\alpha$ both in decreasing and increasing accuracy. For each value of $\alpha$ we ran the method 10 times with randomly chosen initial assignments, using a burn-in of 200 iterations and retaining 1,000 iterations after the burn-in. We observe that for a given value of $\alpha$ up to 0.2 the sampler converges to virtually the same result over all ten runs for all population groups. For $\alpha$ in this range, performance varies across populations but remains consistently above 90% of total chromosomes assigned correctly. The best overall performance is observed when $\alpha = 0.01$. For values of $\alpha$ greater than 0.2 the method no longer converges and the average accuracy of assignments is reduced. The number of individuals classified correctly for various values of $\alpha$ in the range 0 to 0.2 differs by only a small amount, so it is
Figure 5.2 Proportion of haplotypes assigned to the correct population. In this application of our method the number of populations is set to the correct number \((K = 3)\), only SNPs with minor allele frequency (MAF) > 0.05 are included in the analysis, and \(\alpha = 0.1\). Each entry at position \((r, s)\) in the four charts relates to a random selection of \(r\) regions out of the 50 regions in the data, with \(s\) SNPs then randomly selected for each region. Values shown are averaged over 20 runs of the method in each case, with a burn-in of 200 iterations and 1000 samples kept after the burn-in. Sequences are allocated to the cluster to which they are assigned for the majority of the iterations after the burn-in. The top left chart shows the proportion of CEU haplotypes assigned correctly to the CEU cluster. The second, third and fourth charts show the equivalent proportions for the YRI, CHB+JPT and Total Population respectively.

difficult to draw too many conclusions from the limited experiments we have performed. Close examination of the posterior probabilities for all
individuals in the analyses may provide fruitful insights, although this is left to future work.

In conclusion, the method performed well and, provided sufficient SNPs from sufficient independent regions are available for the haplotypes that are to be classified, gives better than 95% accuracy for classifying sequences into these continental populations. The method converges rapidly: in most cases investigated, a burn-in of 200 iterations with a further 1,000 iterations retained for analysis was seen to be sufficient, but we would advocate the use of more iterations than this. It is feasible to apply the method to data sets of the scale considered here.

Note that there are natural, more sophisticated, approaches to handling the uncertainty associated with assignment of individuals to populations. Long-run proportions of time spent in different assignments naturally lead to posterior probabilities for assignment. These could be carried through into subsequent analyses, or thresholded at some (high) value, so that population assignments are made only when these posterior probabilities are close to unity.

**Acknowledgement** PD acknowledges support from the Royal Society.

**References**

[1] Auton, A., and McVean, G. 2007. Recombination rate estimation in the presence of hotspots. *Genome Research*, 17(8), 1219.

[2] Beaumont, M. A., Zhang, W., and Balding, D. J. 2002. Approximate Bayesian computation in population genetics. *Genetics*, 162(4), 2025–2035.

[3] Bowcock, A. M., Ruiz-Linares, A., Tomfohrde, J., Minch, E., Kidd, J. R., and Cavalli-Sforza, L. L. 1994. High resolution of human evolutionary trees with polymorphic microsatellites. *Nature*, 368(6470), 455–457.

[4] Browning, B. L., and Browning, S. R. 2009. A unified approach to genotype imputation and haplotype-phase inference for large data sets of trios and unrelated individuals. *American J. Human Genetics*, 84(2), 210–223.

[5] Browning, S. R., and Browning, B. L. 2007. Rapid and accurate haplotype phasing and missing-data inference for whole-genome association studies by use of localized haplotype clustering. *American J. Human Genetics*, 81(5), 1084–1097.

[6] Corander, J., Waldmann, P., Marttinen, P., and Sillanpaa, M. J. 2004. BAPS 2: enhanced possibilities for the analysis of genetic population structure. *Bioinformatics*, 20(15), 2363–2369.
The coalescent and its descendants

[7] Dawson, K. J., and Belkhir, K. 2001. A Bayesian approach to the identification of panmictic populations and the assignment of individuals. Genetical Research, 78(1), 59–77.

[8] Donnelly, P. 1991. Weak convergence to a Markov chain with an entrance boundary: ancestral processes in population genetics. Ann. Probab., 1102–1117.

[9] Donnelly, P., and Joyce, P. 1992. Weak convergence of population genealogical processes to the coalescent with ages. Ann. Probab., 322–341.

[10] Donnelly, P., and Kurtz, T. G. 1996. A countable representation of the Fleming-Viot measure-valued diffusion. Ann. Probab., 24(2), 698–742.

[11] Donnelly, P., and Kurtz, T. G. 1999. Particle representations for measure-valued population models. Ann. Probab., 27(1), 166–205.

[12] Durbin, R., Eddy, S. R., Krogh, A., and Mitchison, G. 1998. Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids. Cambridge: Cambridge Univ. Press.

[13] Ethier, S. N., and Kurtz, T. G. 1986. Markov Processes: Characterization and Convergence. Wiley Ser. Probab. Math. Stat. New York: John Wiley & Sons.

[14] Ethier, S. N., and Kurtz, T. G. 1993. Fleming-Viot processes in population genetics. SIAM J. Control Optim., 31(2), 345–386.

[15] Ewens, W. J. 2004. Mathematical Population Genetics, vol. I: Theoretical Introduction. 2nd edn. Interdiscip. Appl. Math., no. 27. New York: Springer-Verlag.

[16] Falush, D., Stephens, M., and Pritchard, J. K. 2003a. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. Genetics, 164, 1567–1587.

[17] Falush, D., Wirth, T., Linz, B., Pritchard, J. K., Stephens, M., Kidd, M., Blaser, M. J., Graham, D. Y., Vacher, S., Perez-Perez, G. I., Yamaoka, Y., Mégraud, F., Otto, K., Reichard, U., Katzowitsch, E., Wang, X., Achtman, M., and Suerbaum, S. 2003b. Traces of human migrations in Helicobacter pylori populations. Science, 299(5612), 1582.

[18] Fearnhead, P., and Donnelly, P. 2002. Approximate likelihood methods for estimating local recombination rates. J. R. Stat. Soc. Ser. B Stat. Methodol., 64, 657–680.

[19] Felsenstein, J., Kuhner, M. K., Yamato, J., and Beerli, P. 1999. Likelihoods on coalescents: a Monte Carlo sampling approach to inferring parameters from population samples of molecular data. Pages 163–185 of: Seillier-Moiseiwitsch, F. (ed). Statistics in Molecular Biology and Genetics. IMS Lecture Notes Monogr. Ser., vol. 33. Hayward, CA: Inst. Math. Statist. Selected Proceedings of the Joint AMS-IMS-SIAM Summer Conference, 1997.

[20] Griffiths, R. C. 1980. Lines of descent in the diffusion approximation of neutral Wright–Fisher models. Theor. Population Biology, 17(1), 37–50.

[21] Griffiths, R. C., and Marjoram, P. 1996. Ancestral inference from samples of DNA sequences with recombination. J. Comput. Biol., 3, 479–502.
Griffiths, R. C., and Marjoram, P. 1997. An ancestral recombination graph. Pages 257–270 of: Donnelly, P., and Tavaré, S. (eds), Progress in Population Genetics and Human Evolution. IMA Vol. Math. Appl., vol. 87. Berlin: Springer-Verlag.

Griffiths, R. C., and Tavaré, S. 1994a. Ancestral inference in population genetics. Statist. Sci., 307–319.

Griffiths, R. C., and Tavaré, S. 1994b. Sampling theory for neutral alleles in a varying environment. Phil. Trans. R. Soc. Lond. Ser. B Biol. Sci., 344(1310), 403–410.

Griffiths, R. C., and Tavaré, S. 1999c. Simulating probability distributions in the coalescent. Theor. Population Biology, 46(2), 131–159.

Griffiths, R. C., and Tavaré, S. 1999. The ages of mutations in gene trees. Ann. Appl. Probab., 9(3), 567–590.

Hartl, D. L., and Clark, A. G. 1997. Principles of Population Genetics. 3rd edn. Sunderland, MA: Sinauer Associates.

Hein, J., Schierup, M. H., and Wiuf, C. 2005. Gene Genealogies, Variation and Evolution: a Primer in Coalescent Theory. Oxford: Oxford Univ. Press.

Howie, B. N., Donnelly, P., and Marchini, J. 2009. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genetics, 5(6).

Hudson, R. R. 1983. Properties of a neutral allele model with intragenic recombination. Theor. Population Biology, 23(2), 183–201.

International HapMap Consortium. 2007. A second generation human haplotype map of over 3.1 million SNPs. Nature, 449, 851–861.

Kingman, J. F. C. 1982a. The coalescent. Stochastic Process. Appl., 13(3), 235–245.

Kingman, J. F. C. 1982b. Exchangeability and the evolution of large populations. Pages 97–112 of: Koch, G., and Spizzichino, F. (eds), Exchangeability in Probability and Statistics. Amsterdam: Elsevier. Proceedings of the International Conference on Exchangeability in Probability and Statistics, Rome, 6th-9th April, 1981, in honour of Professor Bruno de Finetti.

Kingman, J. F. C. 1982c. On the genealogy of large populations. Pages 27–43 of: Gani, J., and Hannan, E. J. (eds), Essays in Statistical Science: Papers in Honour of P. A. P. Moran. J. Appl. Probab., Special Volume 19A. Sheffield: Applied Probability Trust.

Leslie, S., Donnelly, P., and McVean, G. 2008. A statistical method for predicting classical HLA alleles from SNP data. American J. Human Genetics, 82(1), 48–56.

Li, N., and Stephens, M. 2003. Modelling linkage disequilibrium and identifying recombination hotspots using single-nucleotide polymorphism data. Genetics, 165, 2213–2233.

Li, Y., Ding, J., and Abecasis, G. R. 2006. Mach11.0: Rapid Haplotype Reconstruction and Missing Genotype Inference. Paper presented at the Annual Meeting of the American Society of Human Genetics, 9–13
The coalescent and its descendants

October 2006, New Orleans, LA. Abstract 2290, http://www.ashg.org/genetics/ashg06s/index.shtml

[38] Li, Y., Willer, C. J., Ding, J., Scheet, P., and Abecasis, G. R. 2007. In Silico Genotyping for Genome-Wide Association Studies. Paper presented at the Annual Meeting of the American Society of Human Genetics, 23–27 October 2007, San Diego, CA. Abstract 2071, http://www.ashg.org/genetics/ashg07s/index.shtml

[39] Marchini, J., Cutler, D., Patterson, N., Stephens, M., Eskin, E., Halperin, E., Lin, S., Qin, Z. S., Munro, H. M., Abecasis, G. R., and Donnelly, P., for the International HapMap Consortium. 2006. A comparison of phasing algorithms for trios and unrelated individuals. American J. Human Genetics, 78(3), 437–450.

[40] Marchini, J., Howie, B., Myers, S., McVean, G., and Donnelly, P. 2007. A new multipoint method for genome-wide association studies by imputation of genotypes. Nature Genetics, 39, 906–913.

[41] McVean, G. A. T., Awadalla, P., and Fearnhead, P. 2002. A coalescent-based method for detecting and estimating recombination from gene sequences. Genetics, 160(3), 1231–1241.

[42] McVean, G. A. T., Myers, S. R., Hunt, S., Deloukas, P., Bentley, D. R., and Donnelly, P. 2004. The fine-scale structure of recombination rate variation in the human genome. Science, 304(5670), 581–584.

[43] Patterson, N., Price, A. L., and Reich, D. 2006. Population structure and eigenanalysis. PLoS Genetics, 2(12), e190.

[44] Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., and Reich, D. 2006. Principal components analysis corrects for stratification in genome-wide association studies. Nature Genetics, 38(8), 904–909.

[45] Pritchard, J. K., Stephens, M., and Donnelly, P. 2000. Inference of population structure using multilocus genotype data. Genetics, 155, 945–959.

[46] Scheet, P., and Stephens, M. 2006. A fast and flexible statistical model for large-scale population genotype data: applications to inferring missing genotypes and haplotypic phase. American J. Human Genetics, 78(4), 629–644.

[47] Servin, B., and Stephens, M. 2007. Imputation-based analysis of association studies: candidate regions and quantitative traits. PLoS Genetics, 3(7), e114.

[48] Stephens, M. 2007. Inference under the coalescent. Chap. 26, pages 878–908 of: Balding, D., Bishop, M., and Cannings, C. (eds), Handbook of Statistical Genetics, 3rd edn., vol. 2. Chichester: Wiley-Interscience.

[49] Stephens, M., and Donnelly, P. 2000. Inference in molecular population genetics. J. R. Stat. Soc. Ser. B Stat. Methodol., 62, 605–655.

[50] Stephens, M., and Donnelly, P. 2003. A comparison of Bayesian methods for haplotype reconstruction from population genotype data. American J. Human Genetics, 73, 1162–1169.

[51] Stephens, M., and Scheet, P. 2005. Accounting for decay of linkage disequilibrium in haplotype inference and missing-data imputation. American J. Human Genetics, 76(3), 449–462.
[52] Stephens, M., Smith, N. J., and Donnelly, P. 2001. A new statistical method for haplotype reconstruction from population data. *American J. Human Genetics*, 68, 978–989.

[53] Tajima, F. 1983. Evolutionary relationship of DNA sequences in finite populations. *Genetics*, 105(2), 437–460.

[54] Tavaré, S. 2004. Ancestral inference in population genetics. Pages 1–188 of: Picard, J. (ed), *École d’Été de Probabilités de Saint-Flour XXXI—2001*. Lecture Notes in Math., vol. 1837. New York: Springer-Verlag.

[55] Wakeley, J. 2009. *Coalescent Theory: an Introduction*. Greenwood Village, CO: Roberts & Co.