Estimating individual admixture from finite reference databases

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Abstract

The concept of individual admixture (IA) assumes that the genome of individuals is composed of alleles inherited from \( K \) ancestral populations. Each copy of each allele has the same chance \( q_k \) to originate from population \( k \), and together with the allele frequencies in all populations \( p \) comprises the admixture model, which is the basis for software like STRUCTURE and ADMIXTURE. Here, we assume that \( p \) is given through a finite reference database, and \( q \) is estimated via maximum likelihood. Above all, we are interested in efficient estimation of \( q \), and the variance of the estimator which originates from finiteness of the reference database, i.e. a variance in \( p \). We provide a central limit theorem for the maximum-likelihood estimator, give simulation results, and discuss applications in forensic genetics.

Keywords: Structure; admixture model; Central Limit Theorem; Biogeographical Ancestry

1 Introduction

The software STRUCTURE (Pritchard et al., 2000), its successor ADMIXTURE (Alexander et al., 2009) and various others (reviewed in Wollstein and Lao, 2015) are today used to infer the ancestry of individuals or a group of individuals using genetic markers. This topic, sometimes referred to as biogeographical ancestry, is relevant in various fields today, including population history (see e.g. Rosenberg et al. (2002)) and forensic genetics (see e.g. Kidd et al. (2021) for a recent contribution). Most algorithms rely on a probabilistic model with \( K \) ancestral populations, where each population comes with its own allele frequencies at \( M \) genetic markers (SNPs), collected in some array \( p = \langle p_{kim} \rangle_{k=1,...,K,i=1,...,4,m=1,...,M} \), where \( p_{kim} \) is the frequency of allele \( i \) in population \( k \) at locus \( m \). In this model, it is assumed that every individual with diploid genotype \( x \) (storing the number of copies for each of the \( M \) loci) is a mixture of the ancestral populations, i.e. each allele originates in one of

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the $K$ ancestral populations, modeled by the individual admixture $q$. Given population data $x$, the software then simultaneously estimates $p$ and $q$ using a Bayes approach.

Our main goal is to study the variance of the point estimate of $q$, and put an emphasis on applications in forensic genetics. To be more precise, point estimates $\hat{q}$ for individual admixture have a variance which depends on (i) the data $x$; (ii) the $M$ loci used for the analysis and (iii) the allele frequencies $p$. Recently, the so-called inter-individual variance was studied (Divers et al., 2011; Morrison et al., 2021), i.e. the variance depending on $x$, if data from a homogeneous group of individuals is available. For (ii) and (iii), we note that in some applications, a reference database is used which has clearly distinct, homogeneous groups, and markers which separate these groups as good as possible (denoted Ancestry Informative Markers or AIMs). On average, this leads to interpretable results in the estimation of $q$. However, the clearly distinct groups might be small, such that a variance in $\hat{q}$ can be introduced by a limited sample size of the reference database. As examples, consider two marker sets used in forensic genetics, with an available reference database available on the homepage of the software SNIPPER (Phillips et al., 2007); see also Section 4.2 for more details. The first marker set consists of 56 SNPs, which nearly fits with the set found in Kidd et al. (2014). Interestingly, this set is implemented in the commercially available VEROFORENSEQ DNA SIGNATURE KIT. The second marker set stems from the recently developed VISAGE BASIC TOOL, which uses 115 SNPs (15 of them tri-allelic) (Xavier et al., 2020), collected from the EUROFORGEN Global AIMs Panel (Eduardoff et al., 2016), complemented by other informative SNPs, which are e.g. informative for Middle-East populations (Pereira et al., 2019) or South-East Asia (Phillips et al., 2013). On http://mathgene.usc.es/snipper/, a reference database for these SNPs can be used or downloaded. Here, the reference database consists of 654 and 520 individuals for the two marker sets, respectively, the majority coming from the 1000 genomes dataset (1000 Genomes Project Consortium et al., 2015), which in total covers more than 3000 individuals. In our numerical results, we will see which variance was introduced by restricting the reference data.

In our analysis, we go one step back from the model used in STRUCTURE and ADMIXTURE, since we will assume that allele frequencies $p$ are given from an external source (i.e. the reference database), and we maximize the likelihood only with respect to $q$. Actually, this approach has been treated long before the invention of STRUCTURE. In Elston (1971), the same model is discussed, including the possibility to obtain estimates of $q$ using maximum likelihood (ML), based on Krieger et al. (1965). While these very early papers rely on phenotype frequencies, the interest in the same model increased at the time when genetic data was available. A very good overview is contained in Chakraborty (1986). While various studies assume population data from $K = 2$ ancestral and one hybrid (admixed) population, Hanis et al. (1986) treats the interesting case that there is only a single admixed individual, and the individual admixture is to be estimated. This is exactly the situation of the present manuscript, but we use a mixture of $K$ (rather than two) populations. In Theorem 1, we will describe a new method for obtaining the ML estimate, which is based on an iterative scheme. Our main result on the approximate normality of the We are not only interested in the efficient computation of the ML estimator of $q$, but also in its variance if allele frequencies $p$ are estimated from a finite reference populations, i.e. carry some degree of uncertainty. For computational efficiency, we show in Theorem 1 of Section 2 that the ML-estimator can be computed as the only stable fixed point of some
function, which is connected to the log-likelihood. The central limit theorem for the ML estimator, including an analysis of its variance, is given in Theorem 2. Formally, our derivation is an application of the theory of \( M \)-estimation; see e.g. van der Geer (2009). However, we keep all our proofs self-contained and only use standard results from calculus. While Theorems 1 and 2 are treating the case of multi-allelic loci (i.e. three and four-fold degenerate loci are allowed), we specialize our results in Section 3 to bi-allelic. This then simplifies the implementation of our results, which we use for examples from a forensic database in Section 4. We start by introducing some notation which is required in the sequel.

**Remark 1.1 (Notation).** We denote by \( x \in \mathbb{R}^n \) (for some \( n = 2, 3, \ldots \)) a column vector, and by \( x^\top \) the corresponding row vector, i.e. \( \top \) denotes a transposition. The standard scalar of \( p, q \in \mathbb{R}^n \) is \( \langle q, p \rangle = p^\top \cdot q \). We use \( E_n \) for the identity matrix with \( n \) rows and columns and \( \text{diag}(x) \) the diagonal matrix with \( x_1, \ldots, x_n \) on the diagonal.

We frequently need \( S := S_K \), the \( K - 1 \)-dimensional simplex, i.e.

\[
S := \{ q = (q_1, \ldots, q_K) \in \mathbb{R}_{\geq 0} : q_1 + \cdots + q_K = 1 \}.
\]

The inner of \( S \), denoted by \( S^\circ \), is \( S^\circ := \{ q = (q_1, \ldots, q_K) \in S : q_1, \ldots, q_K > 0 \} \). For some smooth \( f : \mathbb{R}^n \rightarrow \mathbb{R} \), let \( \nabla f(x) \in \mathbb{R}^n \) be the gradient of \( f \), evaluated at \( x \), with entries \( \frac{\partial f(x)}{\partial x_i}, i = 1, \ldots, n \), and by \( \nabla^2 f(x) \in \mathbb{R}^{n \times n} \) the (symmetric) Hessian of \( f \), with entries \( \frac{\partial^2 f(x)}{\partial x_i \partial x_j}, i, j = 1, \ldots, n \). On a locally compact metric space \( E \), we denote by \( M_n(E) \) the set of measures (defined on the Borel-sigma-field of \( E \)) with total mass \( n \), and on the set \( M_1(E) \) of probability measures, we denote weak convergence by \( \Rightarrow \).

## 2 Model and main results

In Pritchard et al. (2000), Tang et al. (2005), and elsewhere, the following model was used: Assuming a diploid species, there are \( K \geq 2 \) populations (classes) and \( M \) loci (features) with possible (genotypes \{AA, AC, AG, AT, CC, CG, CT, GG, GT, TT\} (where we do not distinguish phase, i.e. \( AC \) and \( CA \) are indistinguishable) and for locus \( m \), each \( i = 1, \ldots, 4 \) (where \( 1 \equiv A, 2 \equiv C, 3 \equiv G, 4 \equiv T \)) in class \( k \) has frequency \( p_{kim} \) and \( p_{kim} + \cdots + p_{k4m} = 1 \), for \( k = 1, \ldots, K, m = 1, \ldots, M \). Now, the genotype of an individual is characterized by \( x = (x_1, \ldots, x_M) \) with \( x_m = (x_{im})_{i=1,\ldots,4} \in \{0,1,2\}^4 \) with \( x_{1m} + \cdots + x_{4m} = 2 \). In addition, the genome of the individual is a mixture of the \( K \) (non-admixed) classes according to some probability vector \( q \in S \). This means that each copy of each locus has a chance \( q_k \) to originate from population \( k \) for \( k = 1, \ldots, K \). We will call \( q \) the individual admixture (IA) of \( x \). This leads to the following definition of the statistical model we treat here:

**Definition 2.1 (Admixture model).** Let \( p = (p_{-m})_{m=1,\ldots,M} = (p_{k-m})_{k=1,\ldots,K,m=1,\ldots,M} \in \mathbb{S}_4^{K \times M} \) (i.e. for all \( k \in K, m \in M \), we have \( p_{k-m} \in \mathbb{S}_4 \)) and \( q \in S \) be given. Then, the probability of obtaining the (test) data \( X = (X_1, \ldots, X_M) \in \{0,1,2\}^{4 \times M} \) is given by \( X_m \sim \text{Multi}(2, (\langle q, p_{im} \rangle)_{i=1,\ldots,4}) \) (the multinomial distribution with 2 trials and probabilities \( \langle q, p_{im} \rangle \) of all
Thus, the log-likelihood (scaled by $2M$) is given by

$$
\ell(p, q|x) := \frac{1}{2M} \log \mathbb{P}_{p,q}(X_1 = x_1, \ldots, X_M = x_M)
$$

$$
:= \frac{1}{2M} \sum_{m=1}^{M} \log(\text{Multi}(2, (\langle q, p_{im} \rangle)_{i=1}^{4}))(x_m)
$$

$$
= \frac{1}{2M} \sum_{m=1}^{M} \left( \log \left( \frac{2}{x_m} \right) + \sum_{i=1}^{4} x_{im} \log(\langle q, p_{im} \rangle) \right)
$$

$$
= C_x + \int z \log((q, \alpha)) \mu_{p,x}(d\alpha, dz),
$$

where $C_x$ is a constant only depending on $x$ (but not on $p, q$), and

$$
\mu_{p,x} = \frac{1}{2M} \sum_{m=1}^{M} \sum_{i=1}^{4} \delta(\langle p_{im}, x_{im} \rangle) \in \mathcal{M}_2([0, 1]^K \times \{0, 1, 2\})
$$

is an empirical measure.

**Assumption 1.** If $x_{im} > 0$, there exists some $k$ with $p_{kim} > 0$ or, equivalently,

$$
\mu_{p,x}\{ (\alpha, z) : z > 0, \alpha = 0 \} = 0.
$$

In other words, if we observe allele $i$ at locus $m$ in our test data, there is at least one population $k$ where the same allele has also been observed.

**Remark 2.2.** If Assumption 1 holds, and if $q \in \mathbb{S}^\circ$, we have that $z \log((q, \alpha)) > -\infty$ for $\mu_{p,x}$-almost all $(z, \alpha)$. In particular, $\ell(p, q|x) > -\infty$ for all $q \in \mathbb{S}^\circ$, and extrema of $q \mapsto \ell(p, q|x)$ can be found by differentiation.

### 2.1 Estimating $q$ via Maximum Likelihood

In this section, our goal is to compute the Maximum-Likelihood-estimator (or ML-estimator) for $q$, i.e. we need to find the maximizer $\hat{q}$ of $q \mapsto \ell(p, q|x)$ (for given $p, x$). We start by computing the first two derivatives, i.e. the gradient and Hessian of $q \mapsto \ell(p, q|x)$. We immediately obtain from (1)

$$
\nabla \ell(p, q|x) = \int z \frac{\alpha}{\langle q, \alpha \rangle} \mu_{p,x}(d\alpha, dz),
$$

$$
\nabla^2 \ell(p, q|x) = -\int z \frac{\alpha \cdot \alpha^\top}{\langle q, \alpha \rangle^2} \mu_{p,x}(d\alpha, dz).
$$

Computing the ML-estimator of $q$ is actually an exercise of applying the theory of Lagrange multipliers, used for maximization under equality constraints. In addition, note that the right-hand-side of (3) implies that $q \mapsto \ell(p, q|x)$ is concave, which helps to give sufficient conditions for a maximum. For uniqueness of the maximum, we need another assumption:
Assumption 2. Let \( s \in \mathbb{R}^K \) with \( \langle s, 1 \rangle = 0 \). Then, there is \( i \) and \( m \) such that \( \langle s, p_{i,m} \rangle \neq 0 \). In other words,

\[
\mu_{p,x} \{ (\alpha, z) : \langle s, \alpha \rangle \neq 0 \} > 0 \text{ for all } s \in \mathbb{R}^K \text{ with } \langle s, 1 \rangle = 0,
\]

Remark 2.3. In order to explain Assumption 2 better, assume that it does not hold. Then, there exists \( s \in \mathbb{R}^K \) with \( \langle s, 1 \rangle = 0 \) and \( \langle s, \alpha \rangle = 0 \) for \( \mu_{p,x} \)-almost-all \( \alpha \). In this case, for \( q \in \mathbb{S}^o \) and \( h \) small, we find \( \langle q, \alpha \rangle = \langle q, hs, \alpha \rangle \) for \( \mu_{p,x} \)-almost-all \( \alpha \), implying \( \ell(p, q|x) = \ell(p, q + hs|x) \). So, if Assumption 2 does not hold, we cannot hope for uniqueness of the ML-estimator.

Lemma 2.4 (ML-estimator). Let Assumption 1 hold. Let \( x = (x_{i,m})_{i=1,4,m=1,\ldots,M} \in \{0, 1, 2\}^{4 \times M} \) and \( p \in \mathbb{S}_4^{K \times M} \). The function \( \ell : \mathbb{S} \rightarrow \mathbb{R}, q \mapsto \ell(p, q|x) \) is concave. If Assumption 2 holds, it is even strictly concave. In this case, \( \ell(p, |x|) \) has a unique local maximum, which is also global, and equals \( \hat{q} \), the ML-estimator for \( q \). Moreover, under Assumption 2, \( q^* \in \mathbb{S}^o \) maximizes \( \ell(p, .|x) \) if and only if \( \nabla \ell(p, q^*|x) = 0 \).

Proof. From (3), we see that \( \nabla^2 \ell(p, q|x) \) is non-positive definite for all \( q \), which already implies concavity of \( \ell \). For strict concavity, let \( q \in \mathbb{S}^o \) and \( s \in \mathbb{R}^K \) be such that \( q + hs \in \mathbb{S}^o \) for small \( h \), which implies that \( \langle s, 1 \rangle = 0 \). Then, if Assumption 2 holds,

\[
\ell(p, q + hs|x) = \ell(p, q|x) + h \nabla \ell(p, q|x) \cdot s + \frac{1}{2} h^2 \nabla^2 \ell(p, q|x) + o(h^2)
\]

\[
= \ell(p, q|x) + h \nabla \ell(p, q) \cdot s - \frac{1}{2} h^2 \int z \frac{(s, \alpha)^2}{(q, \alpha)^2} \mu_{p,x}(d\alpha, dz) + o(h^2)
\]

\[
< \ell(p, q|x) + h \nabla \ell(p, q) \cdot s + o(h^2),
\]

implying strict concavity of \( \ell(p, .|x) \). For such a function, defined on a compact set, it is well-known that a unique (local and global) maximum exists.

Now, let \( q^* \in \mathbb{S}^o \) maximize \( q \mapsto \ell(p, q|x) \). We use the theory of Lagrange multipliers and impose the restriction \( \langle q, 1 \rangle = 1 \). Then, \( q^* \) solves, for some \( \lambda \in \mathbb{R} \), using (2),

\[
\nabla \ell(p, q^*|x) = \int z \frac{\alpha}{\langle q^*, \alpha \rangle} \mu_{p,x}(d\alpha, dz) = \lambda, \quad \langle q^*, 1 \rangle = 1.
\]

From this, we can eliminate \( \lambda \), since

\[
\lambda = \langle q^*, \lambda \rangle = \int z \frac{\langle q^*, \alpha \rangle}{\langle q^*, \alpha \rangle} \mu_{p,x}(d\alpha, dz) = \frac{1}{2M} \sum_{m=1}^{M} \sum_{i=1}^{4} x_{i,m} = 1
\]

i.e. \( q^* \) solves \( \nabla \ell(p, q^*|x) = 1 \). Next, if \( q^* \in \mathbb{S}^o \) satisfies \( \nabla \ell(p, q^*|x) = 1 \) and if Assumption 2 holds, then, for \( s \in \mathbb{R}^K \) with \( \langle s, 1 \rangle = 0 \) and \( h \) small,

\[
\ell(p, q^* + hs|x) = \ell(p, q^*|x) + h\langle 1, s \rangle + \frac{1}{2} h^2 \int z \frac{(s, \alpha)^2}{\langle q^*, \alpha \rangle^2} \mu_{p,x}(d\alpha, dz) + o(h^2) < \ell(p, q^*|x),
\]

i.e. \( q^* \) is a local maximum of \( \ell(p, .|x) \). This finishes the proof. \( \square \)
Computing the ML-estimator \( \hat{q} \), i.e. solving \( \nabla \ell(p,q|x) = 1 \) for \( q \) is possible by Newton-Raphson iteration. However, care must be taken in order to ensure that \( \langle \hat{q}, 1 \rangle = 1 \) and \( q_k \geq 0 \) for all \( k = 1, \ldots, K \). We have found a different iterative way of finding \( \hat{q} \) which guarantees that \( \hat{q} \in S \). It is based on finding a stable fixed point of some \( S \)-valued function \( q \mapsto L(p,q|x) \).

**Theorem 1** (The ML-estimator as a stable fixed point). Let \( p \in S^{K \times M}_4 \), \( x = (x_{im})_{i=1,\ldots,4,m=1,\ldots,M} \in \{0,1,2\}^{4 \times M} \), and let Assumptions \( \square \) and \( \square \) hold (i.e., \( \ell \) is strictly concave). Let \( \ell(p,q|x) \) be as above and define

\[
L(p,q|x) : \begin{cases} 
S & \rightarrow S \\
q & \mapsto \text{diag}(q) \cdot \nabla \ell(p,q|x) = \text{diag}(q) \cdot \int z \frac{\alpha}{\langle q, \alpha \rangle} \mu_{p,z}(d\alpha, dz).
\end{cases}
\]

Then, for \( q^* \in S^\circ \), the following are equivalent:

1. \( q^* \) is the unique and global maximum of \( \ell(p,q|x) \);
2. \( q^* \) is a local maximum of \( \ell(p,q|x) \);
3. \( q^* \) is a locally stable fixed point of \( L(p,q|x) \).
4. \( q^* \) is the unique locally stable fixed point of \( L(p,q|x) \).

**Remark 2.5** (Computing \( \hat{q} \) using \( L \)). Given that Assumption \( \square \) holds, the above result together with Lemma \( \square \) implies that \( q^* \in S^\circ \) is ML-estimator if and only if \( L(p,q^*|x) = q^* \). Hence, if the iteration \( q_{n+1} := L(p,q_n|x) \), converges, we are sure to have found the ML-estimator. In our numerical applications in Section \( \square \), we will compute ML-estimators in this way.

One word of caution is necessary if \( q \in \partial S = S \setminus S^\circ \), the edge of \( S \). In this case, Lemma \( \square \) and Theorem \( \square \) are inconclusive, but our numerical results suggest ML-estimators are still stable fixed points of \( L \). Moreover, note that \( \partial S \) is the union of lower-dimensional simplices, and often we can apply Lemma \( \square \) and Theorem \( \square \) on these lower-dimensional manifolds.

**Remark 2.6** (A fact from Linear Algebra needed in the proof). In the proof, we need the following fact from linear algebra for \( A,B \in \mathbb{R}^{n \times n} \): The eigenvalues of \( A \cdot B \) and \( B \cdot A \) coincide.

Indeed: First, 0 is eigenvector of \( A \cdot B \) iff \( \det(A \cdot B) = \det(A) \det(B) = 0 \). This is the case iff \( \det(B \cdot A) = 0 \), i.e. iff 0 is eigenvalue of \( B \cdot A \). Now, let \( v \) be an eigenvector of \( A \cdot B \) for the eigenvector \( \lambda \neq 0 \). Then,

\[
\lambda B \cdot v = B \cdot \lambda v = B \cdot A \cdot (B \cdot v),
\]

i.e. \( B \cdot v \) is eigenvector of \( B \cdot A \) for the same eigenvalue \( \lambda \).

**Proof of Theorem \( \square \)** Clearly, 1. \( \Rightarrow \) 2. and 4. \( \Rightarrow \) 3. are immediate. By strict concavity of \( \ell \), we also find 2. \( \Rightarrow \) 1. Assuming that 2. \( \iff \) 3. is established, assume that 4. does not hold, but 3. Then, there is a second locally stable fixed point \( \theta^* \) of \( L(p,q|x) \). This would (by 3. \( \iff \) 2. \( \iff \) 1.) be another global maximum of \( \ell \), which is a contradiction. Hence, 3. \( \Rightarrow \) 4. follows, and we are left with showing
2. \[\iff\] 3. For this, we will use the fact shown in Lemma 2.4 that \(q^*\) maximizes \(\ell(p, |x)\) if and only if the gradient of \(\ell(p, q|x)\) is zero. Recall the gradient of \(\ell(p, |x)\) and the Hessian of \(\ell(p, |x)\) from (2) and (3). We start by noting that

\[
\nabla L(p, q|x) = \text{diag}(\nabla \ell(p, q|x)) + \text{diag}(q) \cdot \nabla^2 \ell(p, q|x).
\]

Since \(\ell\) is strictly concave, for all \(q \in \mathbb{S}\), all eigenvalues of \(\nabla^2 \ell(p, q|x)\) are negative.

2. \(\Rightarrow\) 3. From the definition of \(L\) and Lemma 2.4, we already see that if \(q^* \in \mathbb{S}^\circ\) is a global/local maximum of \(\ell(p, |x)\), then \(\nabla \ell(p, q^*|x) = 1\), hence \(L(p, q^*|x) = \text{diag}(q^*) \cdot 1 = q^*\), i.e. \(q^*\) is a fixed point of \(L(p, |x)\). It remains to show local stability. According to the Stable-Manifold-Theorem for discrete dynamical systems (see e.g. Theorem 4.7 of Galor (2007)), we must show that all eigenvalues of \(\nabla L(p, q^*|x)\) have absolute value less than 1. We have from (4)

\[
\nabla L(p, q^*) = E_K - B, \quad B = -\text{diag}(q^*) \cdot \nabla^2 \ell(p, q^*) = \int z \frac{\text{diag}(q^*) \cdot \alpha \cdot \alpha^\top}{\langle q^*, \alpha \rangle^2} \mu_p(x) (d\alpha, dz).
\]

We note that all entries of \(B\) are non-negative and

\[
1^\top \cdot B = \int z \frac{(q^*)^\top \cdot \alpha \cdot \alpha^\top}{\langle q^*, \alpha \rangle^2} \mu_p(x) (d\alpha, dz) = \int z \frac{\alpha^\top}{\langle q^*, \alpha \rangle} \mu_p(x) (d\alpha, dz) = \nabla \ell(p, q^*)^\top = 1^\top,
\]

i.e. \(B\) is the transpose of a stochastic matrix. Moreover,

\[
B \cdot q^* = \int z \frac{\text{diag}(q^*) \cdot \alpha \cdot \alpha^\top \cdot q^*}{\langle q^*, \alpha \rangle^2} \mu_p(x) (d\alpha, dz) = \text{diag}(q^*) \cdot \nabla \ell(p, q^*) = \text{diag}(q^*) \cdot 1 = q^*,
\]

i.e. \(q^*\) is a right-eigenvector for the eigenvalue 1. We also see that the Markov chain with transition matrix \(B^\top\) is irreducible and aperiodic, hence there are (up to constant factors) unique left- and right-eigenvectors of \(B\) to the eigenvalue 1. Also, note that according to Remark 2.6, 1, the eigenvalues of \(B\) and of

\[
\text{diag}(\sqrt{q^*}) \cdot \left( \int z \frac{\alpha \cdot \alpha^\top}{\langle q^*, \alpha \rangle^2} \mu_p(x) (d\alpha, dz) \right) \cdot \text{diag}(\sqrt{q^*})
\]

coincide, the latter being symmetric and positive definite (since \(q^* \in \mathbb{S}^\circ\) and strict concavity of \(\ell(p, |x)\)). All eigenvalues of such a matrix are real and in \((0, \infty)\). Since \(B^\top\) is stochastic, this implies – according to Perron-Frobenius-theory – that all eigenvalues of \(B\) are in \((0, 1]\). Hence, all eigenvectors of \(\nabla L(p, q^*|x) = E_K - B\) are in \([0, 1]\), and 2. \(\Rightarrow\) 3. follows.

3. \(\Rightarrow\) 2.: If \(q^* \in \mathbb{S}^\circ\) is a fixed point of \(L\), we find that, for any \(k = 1, \ldots, K\),

\[
q_k^* = L(q^*)_k = \left( \text{diag}(q^*) \cdot \int z \frac{\alpha}{\langle q^*, \alpha \rangle} \mu_p(x) (d\alpha, dz) \right)_k = q_k^* \int z \frac{\alpha_k}{\langle q^*, \alpha \rangle} \mu_p(x) (d\alpha, dz).
\]

Since \(q_k^* > 0\), this implies \(\int z \frac{\alpha_k}{\langle q^*, \alpha \rangle} \mu_p(x) (d\alpha, dz) = 1\), i.e. \(\nabla \ell(p, q^*|x) = 1\). This shows 2. \(\square\)

2.2 A central limit theorem for the ML-estimator

For the variance of the ML-estimator, we apply an approach involving a central limit theorem already discussed in [Tang et al. (2005)], and which is based on the theory of asymptotic normality of ML-estimators. While this paper is dealing with the task of simultaneously estimating \(p\) and \(q\), they
conclude that this theory is hardly applicable since it requires inversion of a large matrix. However, when only estimating \( q \), this inversion only involves a \( K \times K \)-matrix (see \( \Lambda \) in Theorem 2) which is easily done since \( K \leq 7 \) in almost all applications.

We are treating the situation where the number of markers \( M \) is fixed, but the frequencies \( p \) come with some uncertainty since they are only estimated from a reference database of finite size \( N \). We are going to study the dependence of the ML-estimator \( \hat{q} \) on the distribution of the frequencies \( P \). Our main example is \( N_k P_{k-m} = (2N_k P_{kim})_{i=1,\ldots,4} \sim \text{Mult}(N_k, (p_{kim})_{i=1,\ldots,4}) \) for a fixed family \((p_{kim})_{k=1,\ldots,K},i=1,\ldots,4,m=1,\ldots,M\) and \((N_k)_{k=1,\ldots,K}\) with \( N_k \approx r_k N \) for some \( r \in \mathbb{S}^\circ \), and \((N_k P_{k-m})_{k=1,\ldots,K},m=1,\ldots,M\) are independent. Here, \( N_k \) is the number of haploid individuals (i.e. chromosomes) in a sample of population \( k \) comprising the reference database with \( N = N_1 + \cdots + N_K \) individuals. Note that \( N \cdot \text{COV}[P_{kim}, P_{kjm}] = p_{kim}(\delta_{ij} - p_{kjm})/r_k \) in this case. We now formulate the (abstract/mathematical) result. Application involving simulations and forensic genetic databases can be found in Section 4.

**Theorem 2** (Central Limit Theorem for large reference databases). Let \( r \in \mathbb{S}^\circ, p \in S^{4 \times M}_4, x = (x_{im})_{i=1,\ldots,4,m=1,\ldots,M} \in \{0, 1, 2\}^{4 \times M} \), and let Assumptions 7 and 8 hold. For the log-likelihood \( \ell(\cdot, \cdot | x) \) for fixed \( x \) from (1), let \( P = P^N \) be random and such that \( P^N \overset{N \to \infty}{\to} p \) in probability, and

\[
\sqrt{N}(P_{k-m} - p_{k-m}) \overset{N \to \infty}{\to} Z_{km} \sim N(0, \Sigma(r_k, p_{k-m})) \text{ with } (\Sigma(r, p))_{ij} = r^{-1} \cdot p_i(\delta_{ij} - p_j),
\]

and \((Z_{km})_{k=1,\ldots,K},m=1,\ldots,M\) are independent. Moreover, let \( \hat{Q}^N \) be the ML-estimator based on \( P^N \), i.e. \( \hat{Q}^N \) maximizes \( q \mapsto \ell(P^N, q | x) \), and \( \hat{q} \in \mathbb{S}^\circ \) the ML-estimator for infinite \( N \), i.e. \( \hat{q} \) is the unique maximizer of \( q \mapsto \ell(p, q | x) \). Then, if (2) holds,

\[
\sqrt{N}(\hat{Q}^N - \hat{q}) \overset{N \to \infty}{\to} Z \sim N(0, \Lambda \cdot \Gamma \cdot \Lambda)
\]

with

\[
\Lambda^{-1} := \int \frac{\alpha \cdot \alpha^\top}{\langle \hat{q}, \alpha \rangle^2} \mu_{p,x}(d\alpha, dz) \text{ symmetric},
\]

\[
\Gamma := \frac{1}{4M^2} \sum_{m=1}^M \sum_{i,j=1}^4 x_{im}x_{jm} \Delta(p_{im}) \cdot \text{diag}(r^{-1}) \cdot \text{diag}(p_{im}(\delta_{ij} - p_{jm})) \cdot \Delta(p_{jm})^\top,
\]

\[
\Delta(p) := \left( \frac{E_K}{\langle \hat{q}, p \rangle} - \frac{p \cdot \hat{q}^\top}{\langle \hat{q}, p \rangle^2} \right).
\]

**Remark 2.7** (\( Z \) is degenerate). We note that \( 1^\top \cdot (\hat{Q}^N - \hat{q}) = 0 \) since both, \( \hat{Q}^N \) and \( \hat{q} \) sum to 1. With \( Z \) as in (5), we now show that \( 1^\top \cdot Z = 0 \) as well, i.e. \( Z \) from (5) has a degenerate normal distribution. Indeed: \( 1^\top Z \) has covariance \( 1^\top \Lambda \cdot \Gamma \cdot \Lambda^\top \cdot 1 \). Since \( \hat{q} \) is the ML-estimator, we find that \( \Lambda^{-1} \cdot \hat{q} = 1 \) (see Lemma 2.4) which implies \( \Lambda \cdot 1 = \hat{q} \). Since for \( m = 1, \ldots, M \),

\[
\hat{q}^\top \cdot \Delta(p) = \frac{\hat{q}^\top}{\langle \hat{q}, p \rangle} - \frac{\hat{q}^\top \cdot p \cdot \hat{q}^\top}{\langle \hat{q}, p \rangle^2} = 0,
\]

we find that \( 1^\top \Lambda \cdot \Gamma \cdot \Lambda^\top \cdot 1 = 0 \). This implies that \( 1^\top \cdot Z = 0 \).
Proof of Theorem 2. First, we write (recall from (1))
\[ \ell(P_N, q|x) = C_x + \int z \log(\langle q, \alpha \rangle) \mu_{P_N,x}(d\alpha, dz). \]
with \( C_x \) not depending on \( P_N \) and \( q \). From \( P_N \overset{N \to \infty}{\to} p \) in probability, we see that \( \mu_{P_N,x} \overset{N \to \infty}{\to} \mu_{p,x} \) and therefore
\[ \nabla \ell(P_N, \hat{q}|x) = \int z \frac{\alpha}{\langle \hat{q}, \alpha \rangle} \mu_{P_N,x}(d\alpha, dz) \overset{N \to \infty}{\to} \nabla \ell(p, \hat{q}|x) = 1, \]
\[ \nabla^2 \ell(P_N, \hat{q}|x) = -\int z \frac{\alpha \cdot \alpha^T}{\langle \hat{q}, \alpha \rangle^2} \mu_{P_N,x}(d\alpha, dz) \overset{N \to \infty}{\to} -\Lambda^{-1}. \] (7)

We need to make the first convergence more precise and write, using a Taylor approximation,
\[ \sqrt{N} (\nabla \ell(P_N, \hat{q}|x) - 1) = \sqrt{N} \left( \left( \frac{1}{2M} \sum_{m=1}^{M} \sum_{i=1}^{4} x_{im} \frac{P_{im}^N}{\langle \hat{q}, P_{im}^N \rangle} \right) - 1 \right) \]
\[ = \frac{1}{2M} \sum_{m=1}^{M} \sum_{i=1}^{4} x_{im} \left( \frac{E_K}{\langle \hat{q}, P_{im} \rangle} - \frac{P_{im}^N \cdot q^T}{\langle \hat{q}, P_{im}^N \rangle^2} \right) \cdot \sqrt{N} (P_{im}^N - p_{im}) + o_P(1), \] (8)
where \( o_P(1) \) is a sequence converging to zero in probability. We obtain that for \( N \to \infty \), the right-hand-side converges weakly to a normal distribution with covariance matrix \( \Gamma \). Now, using that \( \hat{Q}^N \) is the ML-estimator based on \( P_N \), again using a Taylor approximation,
\[ 1 = \nabla \ell(P_N, \hat{Q}^N|x) = \nabla \ell(P_N, \hat{q}|x) + \nabla^2 \ell(P_N, \hat{q}|x) \cdot (\hat{Q}^N - \hat{q}) + o_P(1/\sqrt{N}). \]

Using the convergence of \( \nabla^2 \ell(\hat{q}, P_N|x) \) from (7), and the convergence from (8), we find, solving the last equation for \( (\hat{Q}^N - \hat{q}) \) and multiplying with \( \sqrt{N} \),
\[ \sqrt{N} (\hat{Q}^N - \hat{q}) \overset{N \to \infty}{\to} \Lambda \cdot Y. \]

Now, the result follows since \( \Lambda \) is symmetric and hence \( \Lambda \cdot Y \sim N(0, \Lambda \cdot \Gamma \cdot \Lambda) \).

3 The bi-allelic case

We now treat the case of bi-allelic loci, i.e. \( p_{kim} \neq 0 \) and \( x_{im} \neq 0 \) for at most two different \( i \in \{1, 2, 3, 4\} \). In this case, we denote by \( i_m \) the reference allele, and by \( j_m \) the non-reference allele at locus \( m \). Our results are invariant for changes in reference and non-reference allele.

For this bi-allelic case, we set \( b_{km} \coloneqq p_{kim} \) (hence \( 1 - b_{km} = p_{jim} \)), \( y_m \coloneqq x_{im} \) (hence \( 2 - y_m = x_{jm} \)). The log-likelihood from (1) then reads (for \( \ell(b, q|y) \coloneqq \ell(p, q|x) \))
\[ 2\ell(b, q|y) = \frac{1}{M} \log \mathbb{P}_{b,q}(Y_1 = y_1, ..., Y_M = y_m) \]
\[ = \frac{1}{M} \sum_{m=1}^{M} \log \left( \frac{2}{y_m} \right) + y_m \log(q, b_m) + (2 - y_m) \log(q, 1 - b_m) \]
\[ = C_y + \int (z \log(\langle q, \alpha \rangle) + (2 - z) \log(\langle q, 1 - \alpha \rangle)) \mu_{b,y}(d\alpha, dz) \] (9)
with
\[ \mu_{b,y} = \frac{1}{M} \sum_{m=1}^{M} \delta(b_{m,x_m}) \in \mathcal{M}_1([0, 1]^K \times \{0, 1, 2\}) \]
for some \( C_y \) only depending on \( y \) and not on \( b, q \). In order to reformulate our assumptions in terms of \( \mu_{b,y} \), note that Assumption 1 translates to
\[ \mu_{b,y} \{(\alpha, z) : z > 0, \alpha = 0 \text{ or } z < 2, \alpha = 1\} = 0, \]
and Assumption 2 is the same as above, i.e.
\[ \mu_{b,y} \{(\alpha, z) : \langle s, \alpha \rangle \neq 0\} > 0 \text{ for all } s \in \mathbb{R}^K \text{ with } \langle s, 1 \rangle = 0. \] (10)

For the first two derivatives of \( \ell \), we have
\[
2\nabla \ell(b, q|y) = \int \left( z \frac{\alpha}{\langle q, \alpha \rangle} + (2 - z) \frac{1 - \alpha}{\langle q, 1 - \alpha \rangle} \right) \mu_{b,y}(d\alpha, dz),
\]
\[
2\nabla^2 \ell(b, q|y) = -\int \left( z \frac{\alpha \cdot \alpha^\top}{\langle q, \alpha \rangle^2} + (2 - z) \frac{(1 - \alpha) \cdot (1 - \alpha)^\top}{\langle q, 1 - \alpha \rangle^2} \right) \mu_{b,y}(d\alpha, dz).
\]

From Lemma 2.4, we know that any maximizer \( q \in \mathbb{S}^o \) of \( q \mapsto \ell(b, q|y) \) satisfies
\[ \nabla \ell(b, q|y) = \frac{1}{2} \int \left( z \frac{\alpha}{\langle q, \alpha \rangle} + (2 - z) \frac{1 - \alpha}{\langle q, 1 - \alpha \rangle} \right) \mu_{b,y}(d\alpha, dz) = 1. \]

We now reformulate our two main results for the bi-allelic case. Theorem 1 can be translated directly to the bi-allelic case.

**Corollary 3.1** (The ML-estimator as a stable fixed point in the bi-allelic case). Let \( b \in [0, 1]^{K \times M} \), \( y = (y_1, \ldots, y_M) \in \{0, 1, 2\}^M \) and let (10) hold. (I.e., \( \ell \) is strictly concave). Let \( \ell(b, .|y) \) be as above and define
\[
L(b, q|y) = \frac{1}{2} \text{diag}(q) \cdot \int \left( z \frac{\alpha}{\langle q, \alpha \rangle} + (2 - z) \frac{1 - \alpha}{\langle q, 1 - \alpha \rangle} \right) \mu_{b,y}(d\alpha, dz).
\]

Then, for \( q^* \in \mathbb{S}^o \), the following are equivalent:
1. \( q^* \) is the unique and global maximum of \( \ell(b, .|y) \);
2. \( q^* \) is a local maximum of \( \ell(b, .|y) \);
3. \( q^* \) is a locally stable fixed point of \( L(b, .|y) \).
4. \( q^* \) is the unique locally stable fixed point of \( L(b, .|y) \).

For Theorem 2 the bi-allelic case in fact allows for some more simplifications:
Corollary 3.2 (Central Limit Theorem in the bi-allelic case). Let \( r \in \mathcal{S}^o \) and \( y \in \{0, 1, 2\}^M \). For the log-likelihood \( \ell(., | y) \) for fixed \( y \) from (9), let \( B = B^N \) be random and such that \( B^N \xrightarrow{N \to \infty} b \), and

\[
\sqrt{N}(B^N_{km} - b_{km}) \xrightarrow{N \to \infty} Z_{km} \sim N(0, \Sigma(r, b_{km})) \text{ with } (\Sigma(r, b))_{ij} = r^{-1} \cdot b(1-b),
\]

and \((Z_{km})_{k=1,\ldots,K, m=1,\ldots,M}\) are independent. Moreover, let \( \hat{Q}^N \) be the ML-estimator based on \( B^N \), i.e. \( \hat{Q}^N \) maximizes \( q \mapsto \ell(B^N, q|y) \), and \( \hat{q} \in \mathcal{S}^o \) the ML-estimator for infinite \( N \), i.e. \( \hat{q} \) maximizes \( q \mapsto \ell(b, q|y) \). Then, if (10) holds,

\[
\sqrt{N}(\hat{Q}^N - \hat{q}) \xrightarrow{N \to \infty} Z \sim N(0, \Lambda \cdot \Gamma \cdot \Lambda)
\]

with

\[
\Lambda^{-1} := \frac{1}{2} \int (z \frac{\alpha \cdot \alpha^\top}{\langle \hat{q}, \alpha \rangle^2} + (2 - z) \frac{(1 - \alpha) \cdot (1 - \alpha)^\top}{\langle \hat{q}, 1 - \alpha \rangle^2}) \mu_{b,y}(d\alpha, dz), \\
\Gamma := \frac{1}{4M} \int \left( (z\Delta(\alpha) - (2 - z)\Delta(1 - \alpha)) \cdot \Pi(r, \alpha) \cdot (z\Delta(\alpha) - (2 - z)\Delta(1 - \alpha))^\top \right) \mu_{b,y}(d\alpha, dz), \\
\Delta(b) := \left( \frac{E_K}{\langle \hat{q}, b \rangle} - \frac{b \cdot \hat{q}^\top}{\langle \hat{q}, b \rangle^2} \right), \quad \Pi(r, b) := \text{diag}(r^{-1}) \cdot \text{diag}(b(1-b)).
\]

Proof. The only task is to simplify \( \Gamma \) by evaluating the sums over \( i \) and \( j \), which leads from (6) to

\[
\Gamma = \frac{1}{4M^2} \sum_{m=1}^{M} y_m^2 \Delta(b_m) \cdot \Pi(r, b_m) \cdot \Delta(b_m)^\top + (2 - y_m)^2 \Delta(1 - b_m) \cdot \Pi(r, b_m) \cdot \Delta(1 - b_m)^\top \\
- y_m(2 - y_m) \Delta(b_m) \cdot \Pi(r, b_m) \cdot \Delta(1 - b_m)^\top - y_m(2 - y_m) \Delta(1 - b_m) \cdot \Pi(r, b_m) \cdot \Delta(b_m)^\top \\
= \frac{1}{4M^2} \sum_{m=1}^{M} (y_m \Delta(b_m) - (2 - y_m) \Delta(1 - b_m)) \cdot \Pi(r, b_m) \cdot (y_m \Delta(b_m) - (2 - y_m) \Delta(1 - b_m))^\top \\
= \frac{1}{4M} \int \left( (z\Delta(\alpha) - (2 - z)\Delta(1 - \alpha)) \cdot \Pi(r, \alpha) \cdot (z\Delta(\alpha) - (2 - z)\Delta(1 - \alpha))^\top \right) \mu_{b,y}(d\alpha, dz).
\]

\[
\square
\]

4 Applications

We applied our results to both, simulated data and real data from a database used in forensic genetics.

4.1 Simulations

In a situation involving only bi-allelic loci, we take \( K = 3 \) and \( \beta(5, 5) \)-distributed, independent allele frequencies \( b \), and \( q = (0.4, 0.3, 0.3) \). We realize data \( y \) for \( M = 500 \) and \( M = 1000 \) diploid loci. Then, we estimate \( q \) using \( \hat{q} \) as stable fixed point from \( L(b, q|y) \) as in Corollary 3.1. In addition, we generate a finite reference database by choosing \( N/3 \) (haploid) datasets from each class \( k \), compute
Figure 1: For a single test dataset \( y \), we compute \( \hat{q} \) from the true allele frequencies in all classes \( A, B, C \). In addition, we use 1000 bootstrap samples from the allele frequencies in order to estimate \( Q^N \) from a finite reference dataset. (A): \( M = 500, N = 30 \); (B) \( M = 1000, N = 30 \); (C) \( M = 500, N = 60 \); real \( q \) is \((0.4, 0.3, 0.3)\).

the corresponding allele frequencies for all \( m = 1, \ldots, M \), and again compute the ML-estimator \( \hat{Q}^N \). In total, we do this for \( N = 30 \) or \( N = 60 \) such bootstrap samples. The distribution of \( \hat{Q}^N \) around \( \hat{q} \) is described by Corollary 3.2, so we also plot the eigenvectors of \( \Lambda \cdot \Gamma \cdot \Lambda \) and choose the length according to the 5\% and 95\% quantiles of the corresponding normal distribution in the direction of the eigenvector. Note that the covariance matrix is symmetric and 1 is eigenvector for the eigenvalue 0; see Remark 2.7.

In Figure 1, we give two representations of these simulation results. Since \( K = 3 \), we can display the two-dimensional simplex in a ternary plot in the plane. Within the resulting triangle, we display the true \( q \) as well as all bootstrap estimators and the eigenvectors as described above. When taking into account the variance in allele frequencies due to the finiteness of the reference database, we see that Theorem 2 (or Corollary 3.2) matches well with the bootstrap samples. Fewer details are shown in classical structure barplots, where each ancestral population is given through one color; see also Figure 1. Here, the uncertainty in the estimators of \( q \) in the bootstrap (bs) samples and the CLT from Theorem 2 are displayed by mixing colors of the respective classes.

4.2 Examples from a database used in forensic genetics

SNIPPER is by now a standard classification tool in forensic genetics (Phillips et al., 2007). While this tool aims at classifying a genetic trace into one continental group, the same training data can be used for applications of the admixture model we treat here. The webpage [http://mathgene.usc.es/snipper/forensic_mps_aims.html](http://mathgene.usc.es/snipper/forensic_mps_aims.html) comes with several training data. We used a set of \( M = 56 \) bi-allelic features (markers, SNPs or Ancestry Informative Markers, AIMs) and a reference database with several samples from the 1000 genomes dataset (1000 Genomes Project Consortium et al., 2015) (abbreviated 1k) and the HGDP-CEPH line (Cann et al., 2002) (abbreviated HGDP). To be more specific, we use the FORESEQ 56 GRID available from the above webpage.
Figure 2: For three samples of the Simons Genome Diversity Project (Mallick et al., 2016), we present the results for our analysis. (A) A Hawaiian sample; (B) A Saharwi sample; (C) An Abkhasian sample.

(accessed September 23, 2021). Here, the sheet Snipper Reference Grid comes with 654 samples from seven continental groups: 108 Africans (AFR) from Yoruba (YRI, 1k); 79 (native) Americans (AMR) comprised of 20 Brazils (Surui, HGDP), 7 Colombians from Colombia (HGDP), 18 Peruvians (PEL, 1k) and 34 Maya from Mexico (HGDP); 103 East-Asian (EAS) Han Chinese from Beijing (1k); 99 Europeans (EUR), i.e. Utah residents with Western and Northern European ancestry (CEU, 1k); 134 from the Middle East (MEA) from Israel (42 Carmel, 46 Central, 46 Negev, HGDP); 28 Oceanians (OCE) from Papua New Guinea and 103 South-Asian (SAS) Gujarati Indians in Houston (1k).

For the test data, we use the SGDP Test Samples from the same file. These samples come from the Simons Genome Diversity Project Mallick et al., 2016, and we present the analysis for some individuals in Figure 2. We use the same representation of the results as in the barplots of Figure 1. Namely, the upper barplot gives the point estimate for \( q \), based on Corollary 3.1. Then, we produce both, bootstrap samples (bs) of the reference database, leading to an estimate in the uncertainty of \( \hat{q} \) (middle barplot), and the CLT from Corollary 3.1 (lower barplot). Here, we have to use the estimated allele frequencies from the full reference database in order to obtain \( \hat{q} \).

Figure 2(A) shows the result for a Hawaiian sample, where we see a distinction between the South-Asian and Oceanian ancestry with a rather small uncertainty on the admixture proportions. (B) is based on a Saharawi sample, coming from a population around southern Marocco and Western Sahara. The algorithm here finds admixture between African ancestry and ancestry from Europe and the Middle East, where admixture proportions between Europe and Middle East have a high degree of uncertainty. These findings match previous results on genetic analyses of similar samples (Henn et al., 2012). Last, (C) is an Abkhasian sample from a population from the eastern coast of the black sea. Here, again, the proportion of European and Middle East ancestry is rather uncertain, and in addition, ancestry from South-Asia also seems to be uncertain, concluding that the sample is some mix between these three continental groups, with quantitatively rather uncertain proportions.

Figure 2 shows some limitations of the interpretations of the results from the admixture model. Here, (A) is a sample from a population living in Borneo (Dusun). As Yew et al. (2018) find, this population is closely related to some Taiwan natives Filipinos, but the individuals admixture does not show South-Asian ancestry, but almost uniquely Oceanian. In (B), a sample from the Aleut people, which are divided between Alaska and Russia is shown. The admixture model find some rather uncertain ancestry proportions from EAS, EUR, OCE and SAS, leaving the researcher with some
5 Discussion

While barplots generated by STRUCTURE or ADMIXTURE are today found in many publications, they only serve as a point estimate for the individual admixture. The goal of our presentation is to implement one source of randomness (finiteness of the reference population) in the model, and the consequences for the distribution of the point estimate. Other such sources, which we do not study here, are the choice of markers and groups in- or excluded from the reference data. In our graphical results representing the central limit theorem, we try to illustrate the uncertainty of the width of ancestries in the barplot by a color gradient. As a result, we e.g. see that European and Middle-East ancestry is in some cases hard to distinguish, see e.g. Figure 2(C)), a fact which is known from the literature (Truelsen et al., 2021).

Technically, our analysis of the approximative normality of the Maximum-Likelihood estimator (Theorem 2) is dealing with a simplified population model, where geographic origins of individuals from the reference database are known. The reason for this simplification is that we are treating the supervised case where a reference database with known ancestry is available, which is in contrast to the unsupervised case implemented in STRUCTURE or ADMIXTURE, where allele frequencies in all groups $p$ are estimated simultaneously with $q$ for all datasets. We are restricting ourselves to the simpler supervised case for two reasons: First, analytical results only seem to be available if $p$ is known, and second, in forensic applications, the test and training/reference data are two independently collected datasets.

It is important to note that other sources of uncertainty in estimates of individual admixture, $q$, are not treated here. First, the marker set has to be tailored to the distinction between all groups in the reference dataset, which led in the past to inclusion of new markers able to draw different distinctions; see e.g. (Pereira et al., 2019; Phillips et al., 2013). Another restriction, which can be seen in Figure 3, appears if several populations are estimated to have contributed to an individual, or the sample comes from a region far apart from the samples in the reference database. Here, we stress that the method presented here always comes up with a $\hat{q}$, even if the individual comes from a population outside of the reference database. However, the interpretation of the results in the last two examples of Figure 3...
is rather inconclusive, since training data in several parts of the world are missing. One way out is to implement an option saying that the reference database is inconclusive about the test sample; see Tvedebrink et al. (2018). Another would be to study the distribution of $\hat{q}$ under misspecification of the model, where the test data is generated under a model involving more populations than used for obtaining the IA. Studying all these sources of randomness for IA inference will eventually lead to more robust results.

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