Genetics and population analysis

**Struct-f4: a Rcpp package for ancestry profile and population structure inference from $f_4$-statistics**

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**Abstract**

Summary: Visualization and inference of population structure is increasingly important for fundamental and applied research. Here, we present Struct-f4, providing automated solutions to characterize and summarize the genetic ancestry profile of individuals, assess their genetic affinities, identify admixture sources and quantify admixture levels. Availability and implementation: Struct-f4 is written in Rcpp and relies on $f_4$-statistics and Markov Chain Monte Carlo (MCMC) optimization. It is freely available under GNU General Public License in Bitbucket (https://bitbucket.org/plibradosanz/structf4/).

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Next-generation sequencing has opened for the routine characterization of genome variation at the population scale, including in non-model organisms, which provides invaluable insights into evolution (Nielsen et al., 2017). Enhanced characterization of population structure has also found a range of applications in medicine, forensics, conservation biology and more. Many statistical methods are available to visualize (e.g. Principle Component Analysis; Patterson et al., 2006) and model population structure, e.g. as combinations of $K$ ancestry clusters (e.g. ADMIXTURE; Alexander et al., 2009). However, these methods can be biased by the amount of genetic drift exclusive to single populations (Lawson et al., 2018). Other methods based on shared drift aimed to overcome such limitations and increasingly gained popularity in the last decade (Patterson et al., 2012). For example, qpGraph and qpAdm leverage patterns of allele sharing between population quartets (the so-called $f_4$-statistics) to model evolutionary histories, including admixture coefficients. This methodology is, however, highly supervised through the specification of homogeneous groups, potentially acting as admixture sources, and requires to assess alternative models individually. This becomes practically challenging as the number of populations and/or admixture events increase, rapidly exceeding the current capacity of automated solutions (Lepala et al., 2017).

To remediate this situation, we developed Struct-f4, a package leveraging the power of $f_4$-statistics and automating statistical inference within an MCMC framework. Struct-f4 first estimates the shared drift across pairs of individuals, allowing visualization of population structure through Multi-Dimensional Scaling (MDS). It also models individual genetic profiles as mixtures from $K$ ancestral populations, not assumed to follow Hardy–Weinberg equilibrium, and accommodates both supervised and unsupervised analyses.

2 Materials and methods

Struct-f4 was originally proposed by Fages et al. (2019) to visualize the genetic structure within ancient and modern horse populations. The methodology involved maximum likelihood optimization to place individuals within the 3D-Euclidean space that best fits the observed combination of $f_4$-statistics. Here, we redesigned the underlying statistical model to retrieve direct estimates of the shift in allele frequency that occurred between pairs of individuals, as follows:

$$f_4(H_1, H_2; H_3, H_4) = (p_{H_1} - p_{H_2})(p_{H_3} - p_{H_4}) = d_{H_1H_2}d_{H_3H_4},$$

where $d_{H_1H_2}$ the difference in allele frequency between individuals $H_1$ and $H_2$. Assuming $f_4$-statistics follow normal distributions, the likelihood of the $d_i$ parameters can be calculated, allowing for their optimization within an adaptive Metropolis-Hastings MCMC framework (Supplementary Information). This approach can be generalized to model individual profiles as mixtures of $K$ ancestral populations, where $K$ is user-defined

$$f_4(H_1, H_2; H_3, H_4) = \left( \sum_{i=1}^K Q_{iH_1} \sum_{j=1}^K Q_{iH_2} d_i \right) \left( \sum_{i=1}^K Q_{iH_3} \sum_{j=1}^K Q_{iH_4} d_j \right),$$

and $d_i$ now represents the allele frequency shift that occurred between the ancestral components $i$ and $j$, while $Q_{iH}$ the proportion

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of the \( i \) ancestry inherited by individual \( H_1 \) (i.e. its mixture coefficient).

Struct-f4 is implemented in Rcpp for computational efficiency and requires a matrix of \( f_2 \)-statistics as input. We also provide the Calc-f4 C program, which was parallelized and optimized for fast computation of \( f_2 \)-statistics. This reduces the running time to calculate 82,215 \( f_2 \)-statistics on a single 2700 MHz core to 48’49”, versus 101’11” for qpDstat. Struct-f4 outputs posterior mean values and credible intervals for each estimated parameter, together with the full MCMC sample and the corresponding probability used to assess convergence. It also provides (i) an MDS plot of genetic affinities between individuals (Supplementary Fig. S1), (ii) an unsupervised clustering based on the allele frequency shifts that occurred across pairs of individuals and/or \( K \) ancestral populations (Supplementary Fig. S2) and (iii) a barplot representation of ancestry profiles (Fig. 1).

3 Results

We evaluated Struct-f4 using the same simulation framework as that implemented by (Harney et al., 2021) for assessing qpAdm performance. Individuals simulated as belonging to populations either closely related or increasingly connected by gene-flow appeared next to each other in the MDS space. Each individual was found to cluster according to the phylogenetically closest cladal group in the simulated model and showed genetic profiles consistent with the intensity of admixture (Fig. 1). Slight underestimates of the admixture proportions were returned for unsupervised analyses, if sampling only three haploid individuals per population. Supervised inference, nevertheless, completely fixed this bias (Fig. 1). Therefore, Struct-f4 can be used even when sampling efforts are limited, advantageously expanding the analytical toolkit in statistical genomics by providing a robust, flexible and user-friendly platform to automatically characterize population genetic structure. We successfully applied Struct-f4 to characterize the population structure underlying 284 ancient and modern horse genomes from over 11 million permutations of \( f_2 \)-statistics (Librado et al., 2021).

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