

## RESEARCH

# Methods to compute the composite log-likelihood (CLL) of allelic frequencies for the detection of signatures of selection in diploid genomes

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## Abstract

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## Background

Selection, both natural and artificial, is one of the major forces that can shape the genome of living organisms and change allele frequencies. A mutation that is beneficial for the adaptation of an organism to its environment, or that is of agricultural or industrial interest, tends to increase in frequency in the population, together with neighbouring genomic regions which tend to be hitch-hiked in the process ([1]). Through the last decade, the on-going genomic revolution has been making available hundreds of thousands of genetic markers for several animal, microbial and plant species. By looking at the allele frequency at marker loci along the genome of populations experiencing different selective pressures, it is possible to identify genomic regions -and ultimately genes- involved in processes such as domestication, adaptation, evolution and artificial selection. There are a number of methods based on allele frequencies that have been developed to detect such signatures of selection. A popular method is Wright's  $F_{ST}$  ([2, 3]) that has been applied to studies in humans ([4]), plants ([5]) and animals ([6]). Alternatively, the likelihood of the difference between allele frequencies in different populations can be estimated and used to detect the presence of signatures of selection ([7, 8]). However, there are several ways in which such likelihoods can be computed, and these might differ in computation requirements and statistical properties, such as the sensitivity to detect signals of selection or the behaviour along the margins of the dimensional space. (add examples?) It may therefore be of interest to investigate the statistical properties of different estimators for the likelihood of the difference between allele frequency, and assess how well they are capable of detected actual signals of selection.

In this study we evaluated 4 different ways to estimate the likelihood of the difference in allele frequency between populations. The logarithm of the likelihoods thus calculated were then computed and combined across sliding windows along the genome (CLL, composite log-likelihood) in order to detect signatures of selection. The proposed CLL approaches were compared among them and with approaches

based on  $F_{ST}$  and on simple squared distances between genotypes. All methods were first analysed numerically along the entire dimensional space (frequencies in analysed populations ranging from 0 to 1) and then tested with real data where strong signals of selection are known to be present. The methods hereby presented have been developed having in mind biallelic genetic markers (namely SNPs), but can in principle be adapted to any kind of markers (discuss this in “Results and discussion”?).

## Methods

Let's assume we have a test population  $T$  (the population on which we want to detect signatures of selection) and a null or reference population  $N$  (the contrasting population(s)). On these populations  $F_{ST}$ , the squared difference of the allelic frequencies, and four different likelihood measures of allele frequency differences have been computed and evaluated in terms of their ability to detect signatures of selection. First, we present numerical details of the different calculations, then examples with real data on which the different estimators were tested.

### Numerical illustration

#### $F_{ST}$

The  $F_{ST}$  (Wright's  $F$  statistics for *Subpopulation* vs *Total*), a.k.a. *fixation index*, is a measure of the genetic differentiation between (sub)populations (e.g. the test and reference populations in our case). For any given locus,  $F_{ST}$  was calculated as described by Nei ([3]); partitioning the total expected heterozygosity ( $H_T$ , or gene diversity) into the *interpopulation* diversity ( $D_{ST}$ ) and the *intrapopulation* diversity ( $\bar{H}_S$ , average of the expected heterozygosity - $H_S$ - in the subpopulations weighted by their size), the  $F_{ST}$  is defined as the proportion of gene diversity due to differentiation among subpopulations:

$$F_{st} = \frac{D_{st}}{H_T} = \frac{H_T - \bar{H}_S}{H_T} = 1 - \frac{\bar{H}_S}{H_T} \quad (1)$$

where  $\bar{H}_S = \sum_{i=1}^k w_i H_{S_i}$  is the weighted average of the expected heterozygosities within  $k$  subpopulations each accounting for a proportion  $w_i$  of the total population size ( $H_{S_i} = 1 - \sum_{j=1}^m p_j^2$  is the expected heterozygosity within subpopulation  $i$  -with  $m$  alleles at the given locus);  $H_T = 1 - \sum_{i=1}^m \bar{p}_i^2$  is the expected heterozygosity in the overall population, with  $\bar{p}_i = \sum_{k=1}^k w_k p_k$ , the average allele frequency at the given locus across  $k$  subpopulations each accounting for a proportion  $w_i$  of the total sample size.

$F_{ST}$  measures the differentiation between the null and reference populations, and was used in this study as primary benchmark against which other methods were evaluated.

#### Squared difference ( $D^2$ )

A very simple and naive approach for the estimation of the genetic distance between populations is the squared difference of their allele frequencies. For any given locus, the allele frequencies of the minor allele in the test and null populations ( $q_1$  and

$q_2$ ) were calculated, and their squared difference used to measure the degree of differentiation between the two populations:

$$D^2 = (q_1 - q_2)^2 \quad (2)$$

While  $F_{ST}$  was chosen as benchmark due to its long-standing theoretical development and its wide-spread use in the detection of population substructure,  $D^2$  has been used as additional naive benchmark against which more sophisticated methods can be compared.

*Binomial log-likelihood (BLL)*

Three cases: A vs B, B vs A and A vs A+B

$$LL_{ij} = \binom{n}{k} (1-q)^k q^{n-k} \quad (3)$$

*Multiplicative log-likelihood (MLL)*

*Hypergeometric log-likelihood (HGLL)*

*Distribution of the differences (DIFF)*

Two cases: parametrical test, resampling method

“Ballons d'essai”

Data from a population of xxx Holstein-Frisian (zzz males and xxx females) and yyy Piedmontese (males and females?) cattle were available. The first breed has been long selected for dairy production, the latter for meat production. All animals were genotyped with the Bovine 54k SNP-chip. Genotypes were edited for individual and marker call-rate (> 95% ?) and for MAF (> 0.05 ?). Remaining missing genotypes were imputed using (check this!). Xxx SNPs were eventually available for analysis. We selected the zzz SNPs on chromosome 3 (BTA-3) as working example to test the different estimators of the CLL of the allele frequency difference between populations and the reference methods ( $F_{ST}$  and Euclidean distances) for the detection of signatures of selection. BTA-3 is known to host, within the gene *SLC35A3* (position: 43400328-43445390 bps, approximately halfay along the chromosome), the point mutation responsible for CVM (Complex Vertebral Malformation) in Holstein-Frisian cattle ([9]). CVM is a recessive inherited disorder that frequently causes abortion or perinatal death in Holstein-Frisian calves. Other cattle breeds -including Piedmontese- are not affected by the condition. A strong signal is therefore expected to be found at this site, making this an ideally suited comparison to test different methods for the detection of signatures of selection.

¿ Also DGAT1, Myostatin, Caseins ?

*Working example*

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### Testing significance

When analysing tens or hundreds of thousands of markers the problem of multiple comparisons is incurred. This is a known statistical problem in general ([10]), and specifically in the field of genetic studies ([11, 12]). As the number of independent tests increases, the probability of obtaining at least one false positive, under  $H_0$ , approaches one. This probability is a function of the number of tests  $n$  and of the chosen significance threshold  $\alpha$ :  $P(\text{false\_positive}) = 1 - (1 - \alpha)^n$ . When, for instance, 50000 SNP markers are tested along the genome in search of signatures of selection, for  $\alpha = 0.01$ , 500 false positive associations are expected on average, just by mere chance.

### Sliding windows

$$CLL_{ij} = \frac{1}{w} \sum_{j=1}^{j+w-1} LL_{ij} \quad (4)$$

### Software

- Bonferroni correction: very strict; implicit prior assumption that the probability that *all* tests are null ( $H_0$  is true) is not small. If we believe that all tests could be null, then aiming to make the number of false positives zero is justifiable ([13])
- FDR
- Permutation test

## Results and discussion

For biallelic loci,  $D^2$  is intrinsically symmetric:  $(p_1 - p_2)^2 = ((1 - p_1) - (1 - p_2))^2$

### Competing interests

The authors declare that they have no competing interests.

### Author's contributions

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### Acknowledgements

Data (Marras ...)? ...

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Figures

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Tables

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