

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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Keywords: composite log-likelihood; signatures of selection; diploid genomes

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 6 different ways to estimate the likelihood of the difference in allele frequency between populations: 1) 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 (Euclidean?) 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 results of the study are hereby presented and discussed.

Methods

Six different methods to

Numerical illustration

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Working example

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.

Working example

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Sub-sub-sub heading for section

$$\begin{aligned}
 E[Z_1(vT_x)] &= E\left[\mu T_x \int_0^{v \wedge 1} Z_0(uT_x) \exp(\lambda_1 T_x(v-u)) du\right]. \\
 E[Z_1(vT_x)] &= \frac{\mu}{r} \log x \int_0^{v \wedge 1} x^{1-u} x^{(\lambda_1/r)(v-u)} du \\
 &= \frac{\mu}{r} x^{1-\lambda_1/\lambda_0 v} \log x \int_0^{v \wedge 1} x^{-u(1+\lambda_1/r)} du \\
 &= \frac{\mu}{\lambda_1 - \lambda_0} x^{1+\lambda_1/rv} \left(1 - \exp\left[-(v \wedge 1) \left(1 + \frac{\lambda_1}{r}\right) \log x\right]\right). \quad (1)
 \end{aligned}$$

Results and discussion

Text ...

Competing interests
The authors declare that they have no competing interests.

Author's contributions
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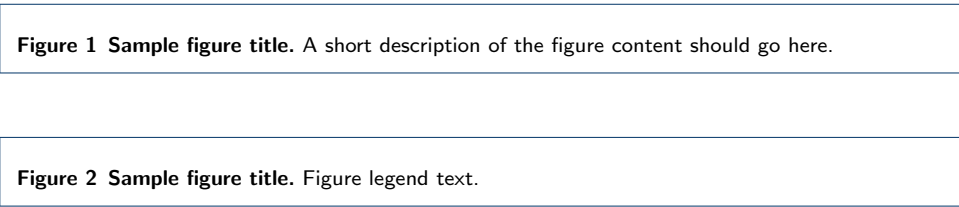
Acknowledgements
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References

1. Braverman, J.M., Hudson, R.R., Kaplan, N.L., Langley, C.H., Stephan, W.: The hitchhiking effect on the site frequency spectrum of dna polymorphisms. *Genetics* **140**(2), 783–796 (1995)
2. Wright, S.: The genetical structure of populations. *Annals of eugenics* **15**(1), 323–354 (1949)
3. Nei, M.: Analysis of gene diversity in subdivided populations. *Proceedings of the National Academy of Sciences* **70**(12), 3321–3323 (1973)
4. Akey, J.M., Zhang, G., Zhang, K., Jin, L., Shriver, M.D.: Interrogating a high-density snp map for signatures of natural selection. *Genome research* **12**(12), 1805–1814 (2002)
5. Zhao, K., Wright, M., Kimball, J., Eizenga, G., McClung, A., Kovach, M., Tyagi, W., Ali, M.L., Tung, C.-W., Reynolds, A., *et al.*: Genomic diversity and introgression in o. sativa reveal the impact of domestication and breeding on the rice genome. *PLoS One* **5**(5), 10780 (2010)
6. Kijas, J.W., Lenstra, J.A., Hayes, B., Boitard, S., Neto, L.R.P., San Cristobal, M., Servin, B., McCulloch, R., Whan, V., Gietzen, K., *et al.*: Genome-wide analysis of the world's sheep breeds reveals high levels of historic mixture and strong recent selection. *PLoS biology* **10**(2), 1001258 (2012)
7. Nielsen, R., Williamson, S., Kim, Y., Hubisz, M.J., Clark, A.G., Bustamante, C.: Genomic scans for selective sweeps using snp data. *Genome research* **15**(11), 1566–1575 (2005)
8. Stella, A., Ajmone-Marsan, P., Lazzari, B., Boettcher, P.: Identification of selection signatures in cattle breeds selected for dairy production. *Genetics* **185**(4), 1451–1461 (2010)
9. Thomsen, B., Horn, P., Panitz, F., Bendixen, E., Petersen, A.H., Holm, L.-E., Nielsen, V.H., Agerholm, J.S., Arnbjerg, J., Bendixen, C.: A missense mutation in the bovine slc35a3 gene, encoding a udp-n-acetylglucosamine transporter, causes complex vertebral malformation. *Genome research* **16**(1), 97–105 (2006)

Figures



Tables

Table 1 Sample table title. This is where the description of the table should go.

	B1	B2	B3
A1	0.1	0.2	0.3
A2
A3

Additional Files
Additional file 1 — Sample additional file title
Additional file descriptions text (including details of how to view the file, if it is in a non-standard format or the file extension). This might refer to a multi-page table or a figure.

Additional file 2 — Sample additional file title
Additional file descriptions text.