Accounting for Linkage Disequilibrium in genome scans for selection without individual genotypes: the local score approach

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Outline

1. Motivations
2. The FLK & hapFLK approaches
3. The local score approach
4. Simulation results
5. Examples
6. Conclusions

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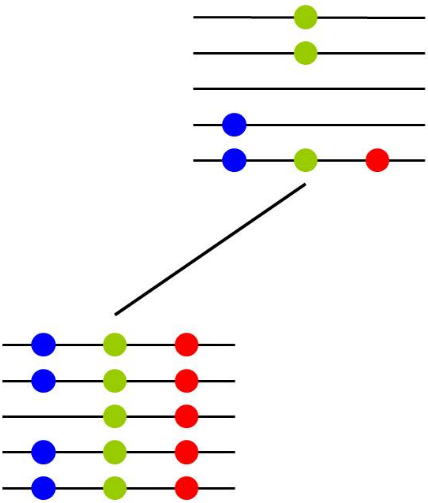
Genome scans for selection

- Most genomic regions are neutral, but some of them are (or have been) under selection (natural or artificial).
- Detecting the regions under selection is important for theory (evolution) and applications (medicine, agronomy).
- Genome wide scans for selection now possible from dense genotyping (SNP chips) or sequencing (NGS) data.
- Focus on positive (adaptative) selection.

Population differentiation approach

Look for markers with contrasted allele frequencies between populations.



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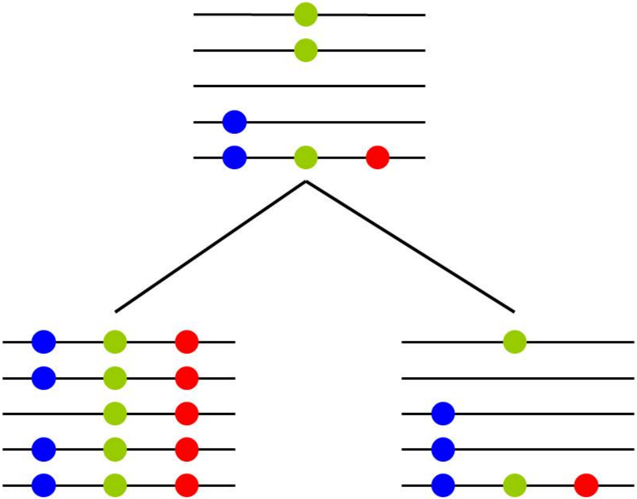
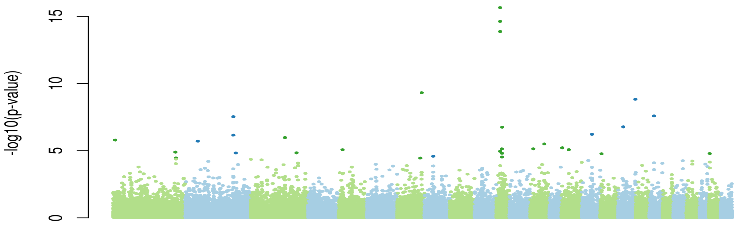


Linkage Disequilibrium (LD) helps!



- **Single-marker statistics** have a **large variance**, high values can be reached just by chance due to drift.
- Due to LD, markers in the **neighborhood of a selected locus** also show **elevated differentiation** between populations.

→ Account for LD in selection scans by:

1. using haplotype tests
2. looking for clusters of markers with high differentiation

Windowing approaches

- **Cut the genome into fixed windows** and computes a summary of the single-marker statistics within each window.
- **Summarize each window** using:
  - the average of single-marker statistics (Weir *et al*, 2005).
  - the number of markers exceeding a given threshold (Myles *et al*, 2008).
  - the number of markers differentially fixed between populations (Johansson *et al*, 2010).
- **Individual genotypes not required** (pooled sequencing).
- Limitations:
  - How to choose **window size**? the **single-marker threshold**?
  - How to decide that a **window** is **under selection?**

→ **Overcome these issues** using the statistical **local score** theory.

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F_{ST} based tests

$p = (p_1, \dots, p_i, \dots, p_n)$: allele frequencies at one SNP in several populations.

$\overline{p}$ and s_p^2: observed mean and variance of p.

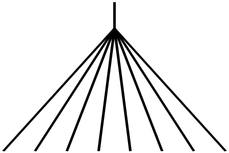
$$F_{ST} = \frac{s_p^2}{\overline{p}(1-\overline{p})}$$

- H_0 : "neutral evolution" (genetic drift) vs H_1 : "positive selection in one (or more) population ".
- H_0 rejected if F_{ST} too large.

Lewontin et Krakauer (LK) test (1973)

$$LK = \frac{n-1}{\bar{F}_{ST}} F_{ST}$$

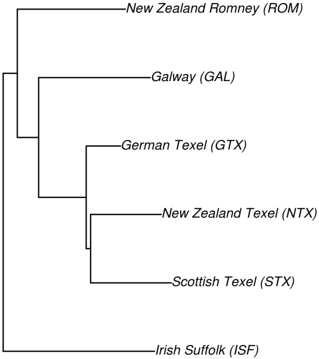
- LK **distribution under** H_0 **is** χ^2 with $n-1$ degrees of freedom.
- But, only true if populations have a **star like phylogeny with equal population sizes**.



FLK test (Bonhomme *et al*, 2010)

Extension of LK accounting for

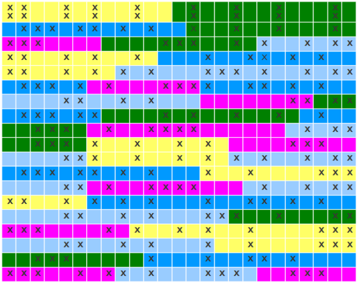
- differences in effective size between populations.
- differences in correlations between population pairs.



(first estimated from genome wide data)

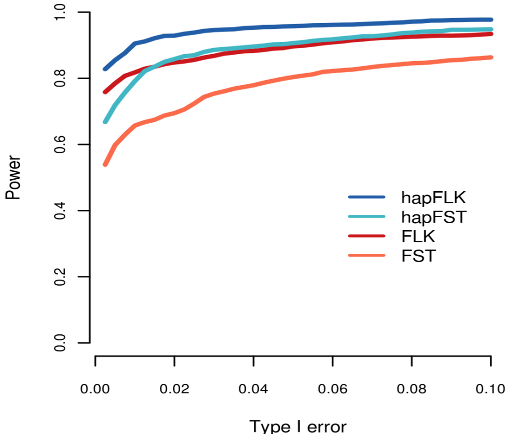
hapFLK test (Fariello *et al*, 2013)

- **Define local haplotypes** around each SNP position using the model of Scheet and Stephens (2006).



- **Compute haplotype frequencies** in each population.
- Apply FLK, considering haplotypes as alleles.

Detection power



4 populations with hierarchical structure, 1 under selection.

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Definition

- For each marker m, define the **score**:

$$X_m = -log10(p_m) - \xi$$

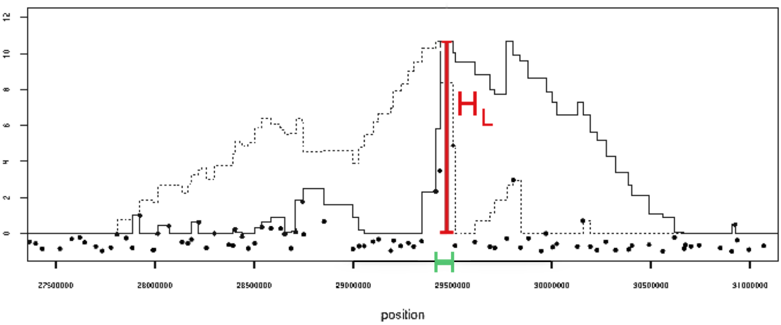
  p_m p-value of a test for selection, ϵ fixed threshold.

- Low p-value $=$ H_0 (neutral evolution) unlikely $=$ high score.
- **Cumulate scores** using the so-called **Lindley process**:

$$h_0 = 0, \quad h_m = max(0, h_{m-1} + X_m)$$

- Look for **local maxima of the Lindley process**, which are asociated to **genomic regions** that are **enriched in high scores / low p-values**.
- Here p_m is the p-value of FLK.

Example



- The Lindley process (black line) has several **excursions above 0** (local maxima).
- The **global maximum** (H_L) is called the **local score**.
- Each excurion is associated to an interval enriched in high scores (in green).

choosing ξ

- **p-value threshold** in log10 scale.
- Ex: $\xi = 2$ cumulates p-values below 10^{-2}.
- For **high** ξ, only **most significant markers** contribute:
  $\rightarrow$ similar to single point approach.
  $\rightarrow$ **strong selection**.
- For **low** ξ, more markers contribute:
  $\rightarrow$ **longer** intervals.
  $\rightarrow$ **recent selection**.

Statistical evidence for selection

- How likely is a given excursion under neutrality?
- Depends on:
  - the number of markers in the sequence (M).
  - the correlation between scores (ρ).
- We provided **two approaches** allowing to **compute significance thresholds for excursions** :
  1. **analytical formula:** valid if single-marker p-values are unifrom under neutrality.
  2. **re-sampling approach:** valid for all datasets, but requires some computing time.

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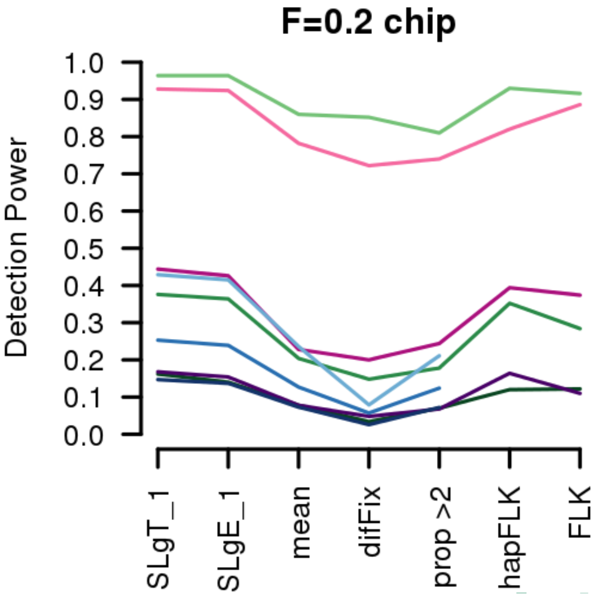
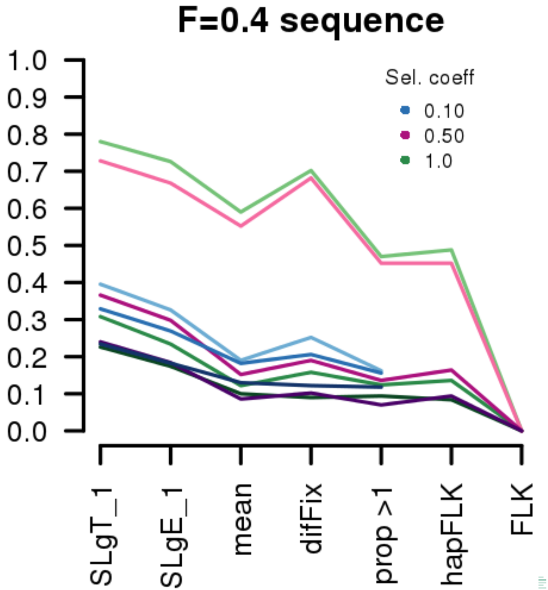
Simulation procedure

- **Two populations** with same effective size, one neutral and **one under selection**.
- Genomic region of **10Mb** with **one selected site**.
- Several statistics compared, in different scenarios.
- **Detection threshold** of each statistic such that selection is detected in 5% of the **neutral samples** (type I error 5%).
- For the local score, also computed using our re-sampling approach
  → observed type I error 6%.
- Tunning parameters (window size, ξ ...) chosen to optimize detection power.

Results


F=0.2 chip
Detection Power
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
SLgT_1
SLgE_1
mean
difFix
prop >2
hapFLK
FLK

Results


F=0.4 sequence
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Sel. coeff
0.10
0.50
1.0
SLgT_1
SLgE_1
mean
difFix
prop >1
hapFLK
FLK

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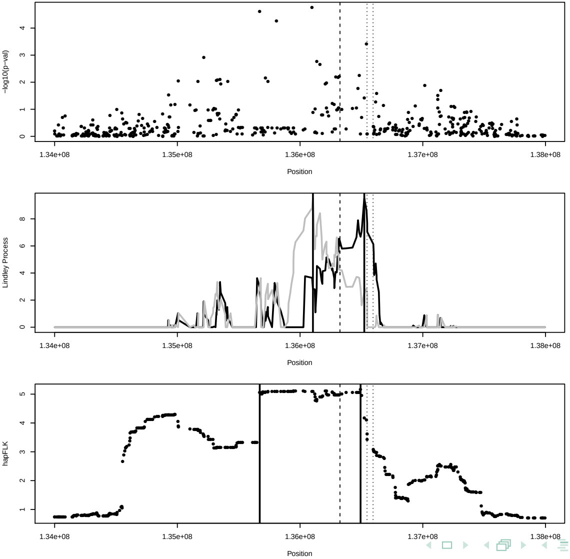
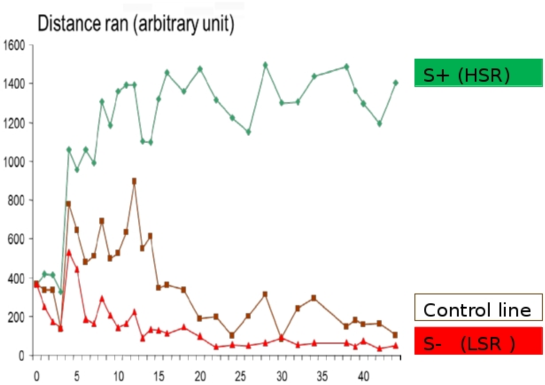
Lactase region in Humans

Test of selection based on HapMap genotypes (Europea and Asia).

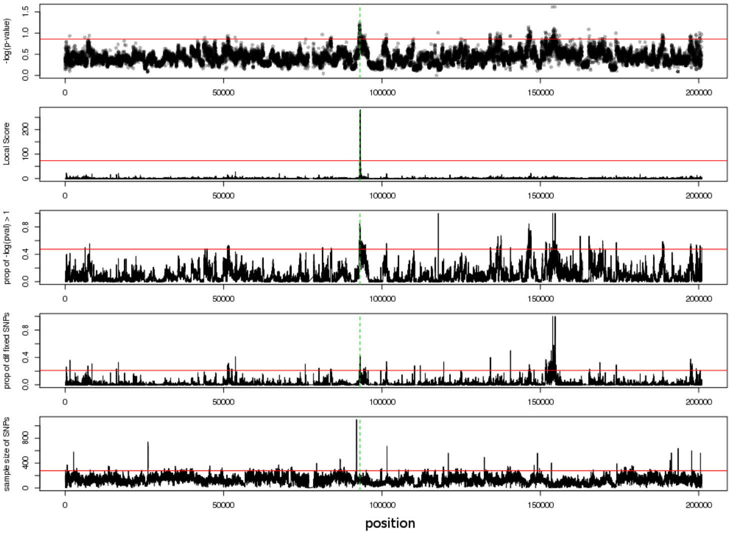


Divergent selection experiment on behaviour in Quail



- **Pooled DNA** from each line sequenced at generation 50
- **Strong drift** ($F = 0.4$).

Selection scan on chromosome 1



Significant regions genome-wide

Chr.	Position	L (kb)	Genes
1	92,963,481-93,182,440	219	NSUN3, **ARL13B**
2	1,584,033-1,688,400	104	VIPR1
3	61,586,217-61,604,464	19	ECHDC1, RNF146
3	75,088,250-75,170,494	82	MMS22L
4	11,412,372-11,452,609	40	GLOD5
4	90,953,044-91,008,245	56	**CTNNA2**
6	35,234,870-35,336,720	102	FOXI2, **PTPRE**
6	6,311,718-6,644,395	333	UBE2D1, CISD1, **IPMK**
10	17,825,157-17,825,227	0.07	
25	1,296,647-1,296,706	0.059	

Genes **in bold** have been associated to **autistic disorders** or **behavorial traits** in Humans.

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Detecting selection using the local score

- Accounts for **LD whithout individual genotypes**.
- One single tunning parameter, ξ, with intuitive interpretation. $\xi = 1$ recommended for detection power.
- **Statistical significance** of candidate regions easy to compute.
- **Increased detection power** compared to single-marker, window-based or haplotype-based tests.
- Convincing results on 2 real datasets with different features.
- Can be applied to **any single-marker test providing p-values**, for selection scans or **any** other **context**.
- Ref: Fariello *et al*, Molecular Ecology 2017.

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Advertising

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- Influence of population structure on past population size estimation (Mazet *et al*, Heredity 2017).