# Inference of selection from genetic time series using various parametric approximations to the Wright-Fisher model

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labex CeMeb
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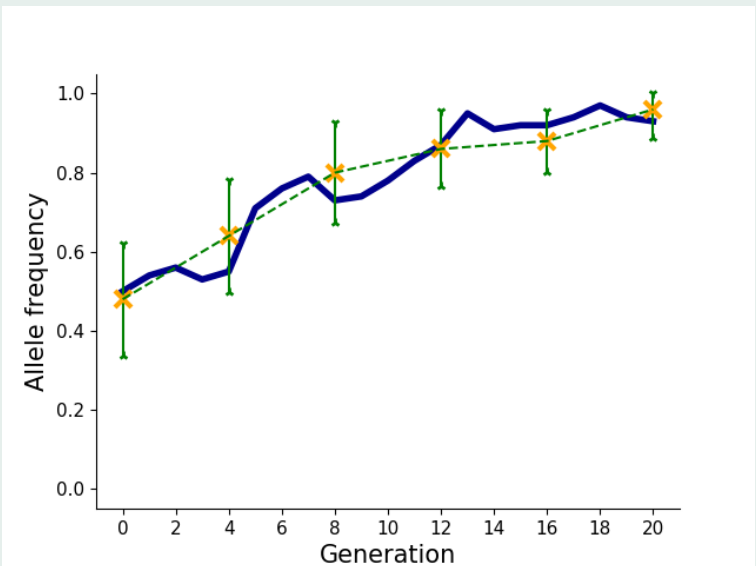
# Introduction

## Context

- Increasing availibility of genomic time series data: experimental evolution, gene banks, ancient DNA ...
- **Objective:** detect selection and estimate its intensity

## Selection and time series




## Data

- One time series per SNP
- Sample size
- Reference allele count

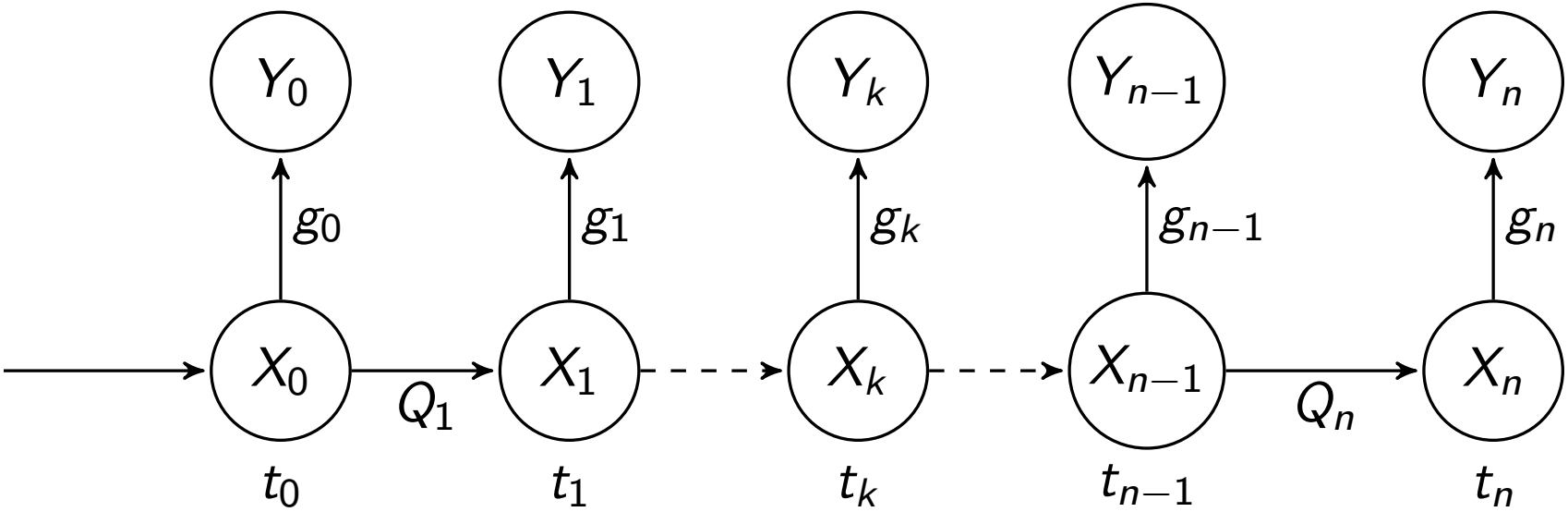
## Need to model

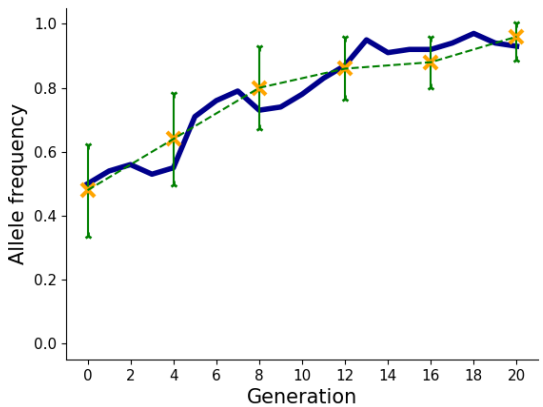
- Allele frequency evolution
- Sampling variability

# Outline

# Outline

# Hidden Markov Model (Bollback *et al*, 2008)

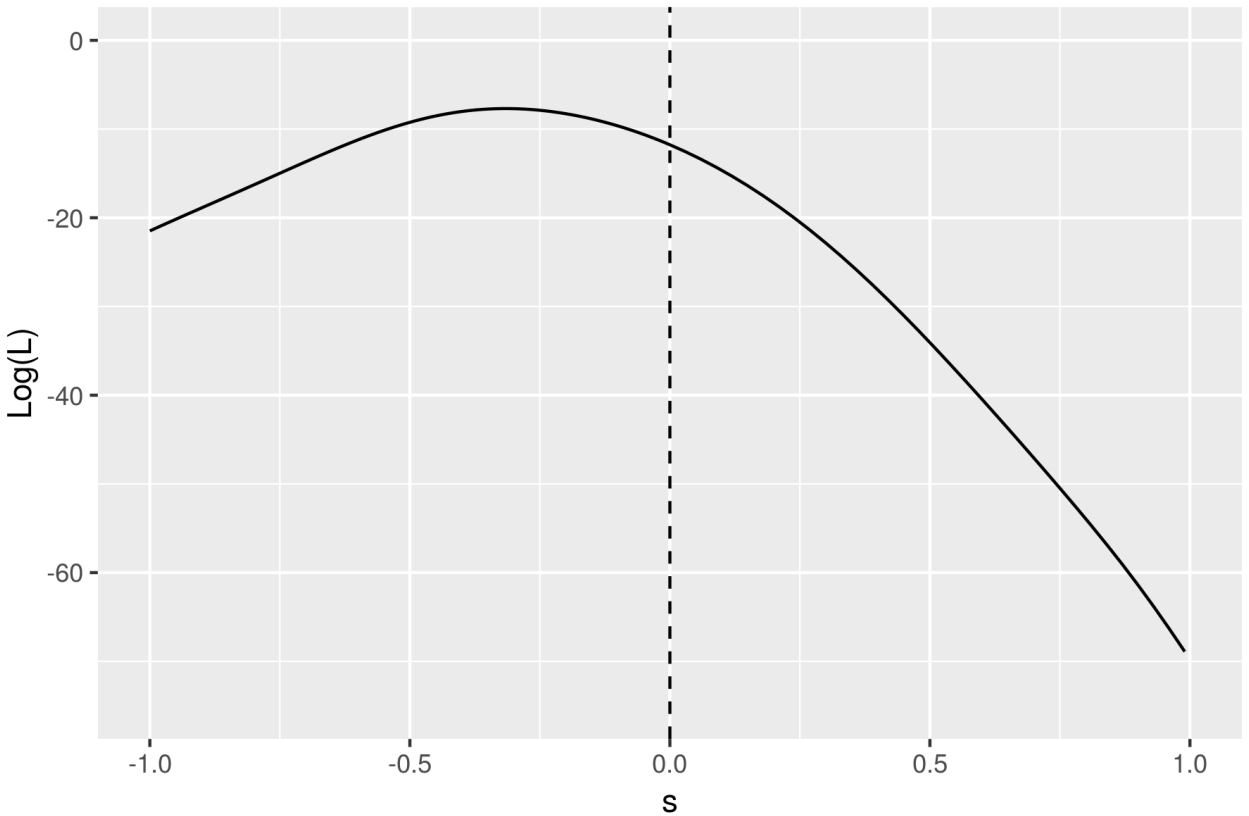



- Hidden states $\{X_k\}_{k\geq 0}$: Population allele frequencies, Markov chain, **transition** $Q = Q^{s,h,N}$
- Observations $\{Y_k\}_{k\geq 0}$: Sample allele counts, independent given $\{X_k\}_{k\geq 0}$, **emission g**

# Selection Inference

- Likelihood $L(y_0, \ldots, y_n; Q, g)$ efficiently computed using the Forward algorithm.
- $L(y_0, \ldots, y_n; Q, g) = L(y_0, \ldots, y_n; s, N, h)$
  $\rightarrow$ evaluate on a grid for different values of $s, N, h$.



# Selection inference

- Estimate $s$ by maximum likelihood
- Test selection using the Likelihood Ratio Statistic

$$2(\log L(y_0, \ldots, y_n; \hat{s}, N, h) - \log L(y_0, \ldots, y_n; 0, N, h))$$

  chi-quare distributed under $s = 0$ (neutrality)
- **Computation of Q?**

# Reference model: Wright-Fisher

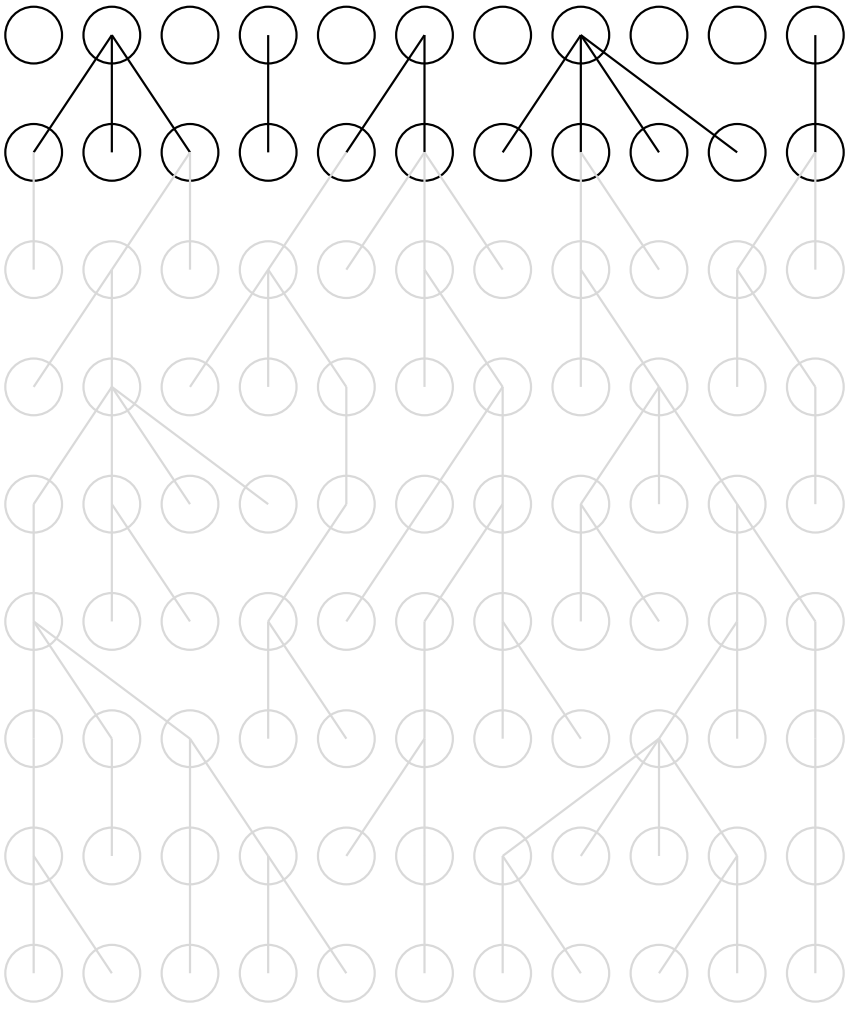
## Hypotheses

- Panmixia, non overlapping generations
- Constant population size ($N$)
- $X_t$: allele frequency at generation $t$
- $X_{t+1}|X_t \sim \frac{1}{N}\mathcal{B}(N, X_t)$

## Adding Selection

- | $A_1A_1$ | $A_1A_0$ | $A_0A_0$ |
  |---|---|---|
  | $1+s$ | $1+sh$ | $1$ |
- $f_s$: fitness function
- $X_{t+1}|X_t \sim \frac{1}{N}\mathcal{B}(N, f_s(X_t))$, $P$
- $X_{t+u}|X_t$, $Q = P^u$

# Reference model: Wright-Fisher



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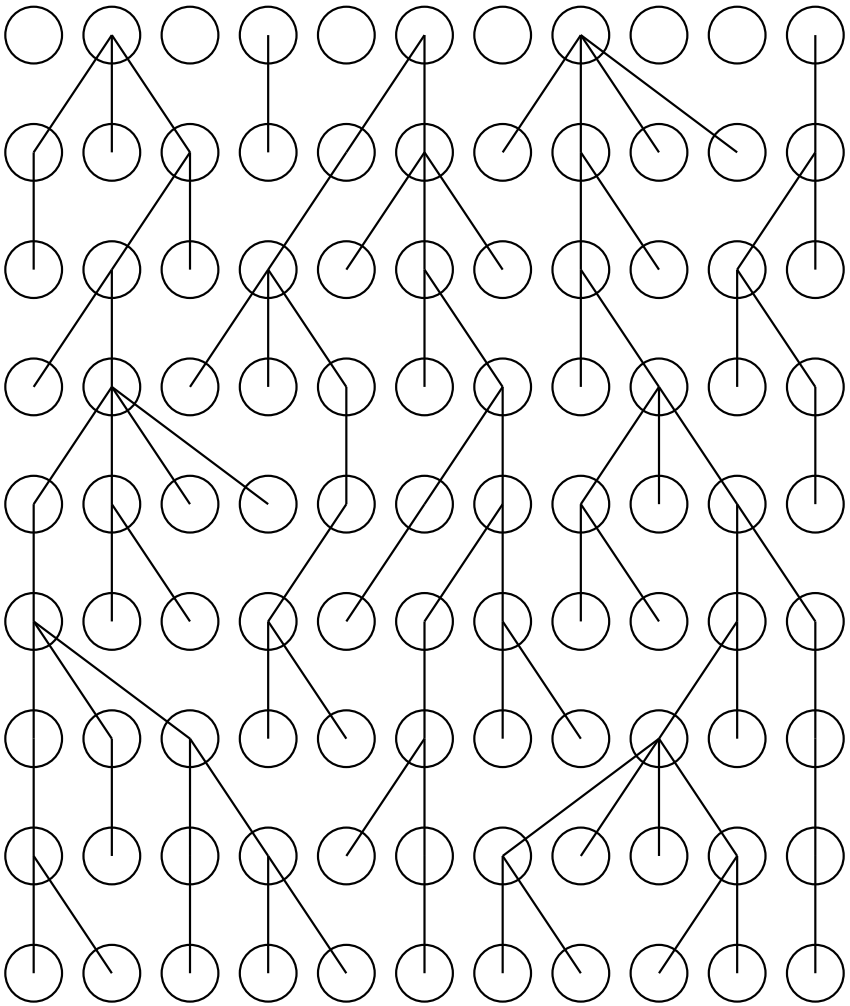

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# Wright-Fisher's Limitations

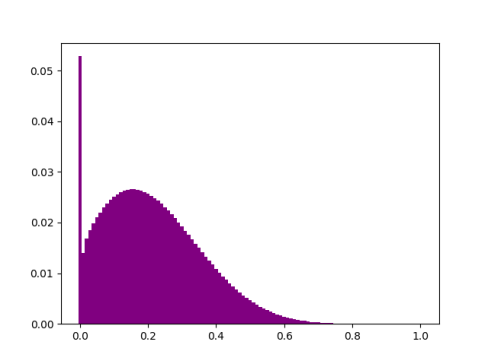
- Wright-Fisher model:
  - Matrix $Q$ has dimension $N \times N$
  - Computing time: $Q = P^u$ + forward algorithm
  - Memory load
- Alternative: find a good approximation
  - Control $Q$ dimension
  - Fits Wright-Fisher transitions
  - Mimics the statistical properties obtained with Wright-Fisher transitions (parameter estimation and detection power)

# The method of moments (Lacerda and Seoighe, 2014)

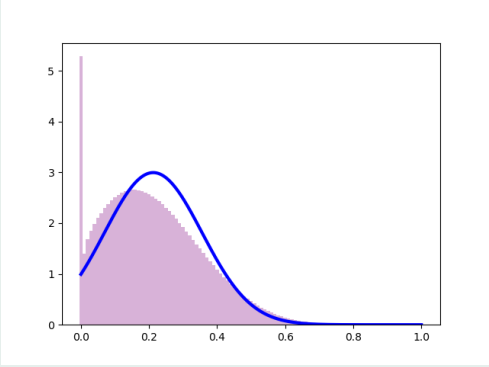
- Choose a parametric distribution
- Set parameters such that its moments fit those of the Wright-Fisher (WF).
- **Gaussian model (Ga):** Popular approximation for short time and intermediate allele frequency (Cavalli-Sforza *et al*, 1964; Lacerda and Seoighe, 2014; Terhorst *et al.*, 2015).
- **Nicholson Gaussian model (NG):** Allocate the mass outside $(0, 1)$ to point masses in 0 and 1 (Nicholson *et al*, 2002).
- **Beta model (Be):** Wide variety of shapes, distributed in $[0, 1]$ (Balding and Nichols, 1995; Hui and Burt, 2015).
- **Beta with spikes model (BwS):** Adds fixation probabilities to Beta model (Tataru *et al*, 2016).

# Moment fitting examples

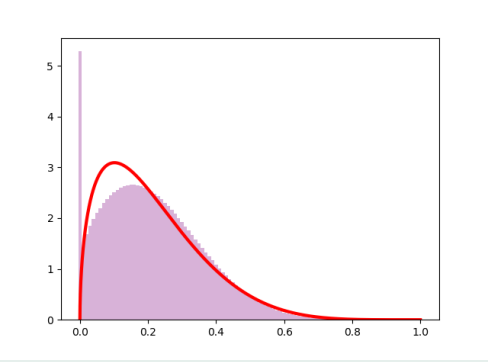
## Wright-Fisher distribution



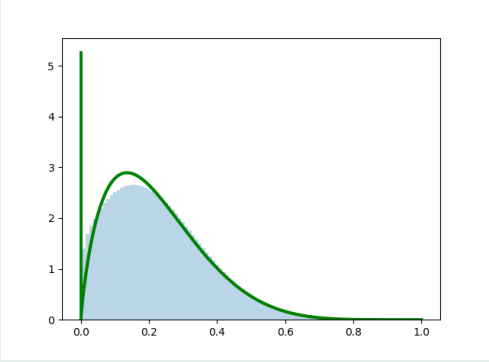

## Gaussian distribution




## Beta distribution




## Beta with spikes distribution

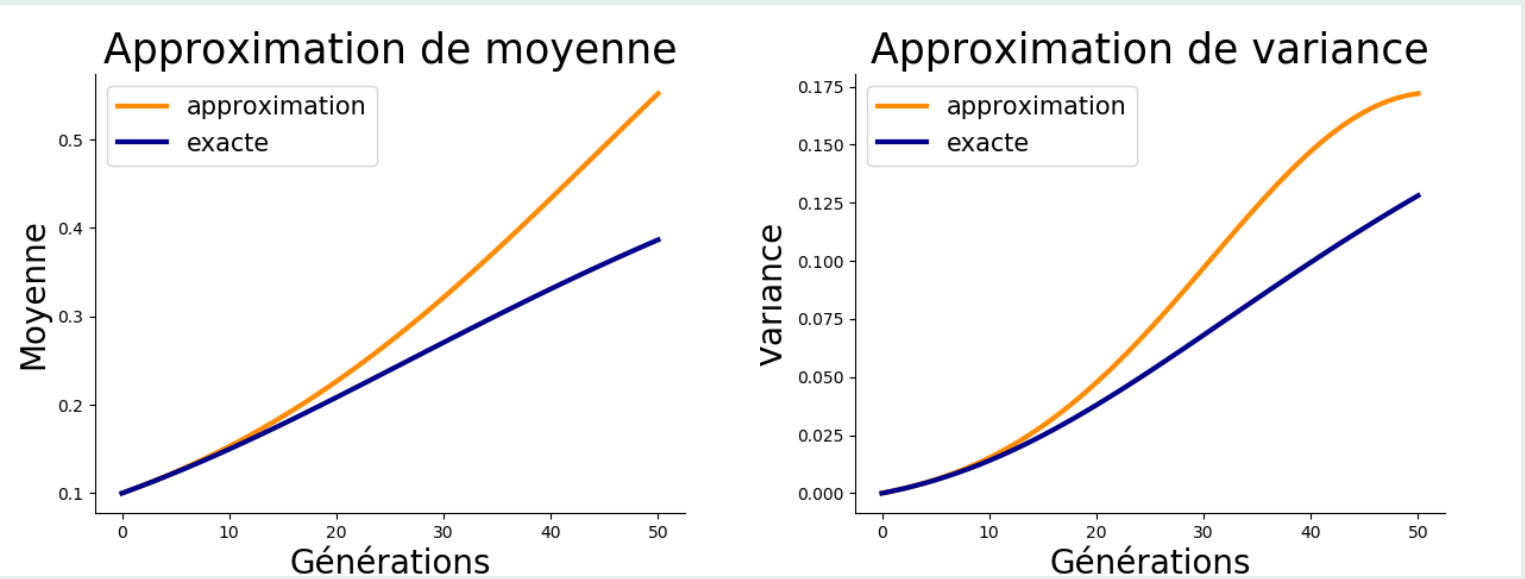


# Moment approximation: Delta-method

## Taylor approximation (Lacerda and Seoighe, 2014)

$$\begin{array}{rcl@{\qquad}rcl} \mu_{n+1} & \approx & f(\mu_n) & \mu_n & \approx & E(X_n) \\ \sigma^2_{n+1} & \approx & f'(\mu_n)^2\sigma^2_n & \sigma^2_n & \approx & Var(X_n) \end{array}$$

## Accuracy ($x_0 = 0.1, N = 100, s = 0.1$)




- BwS: fixation proba. also approximated (Tataru *et al*, 2016).

# Outline

# Simulations 1: fit to the WF model

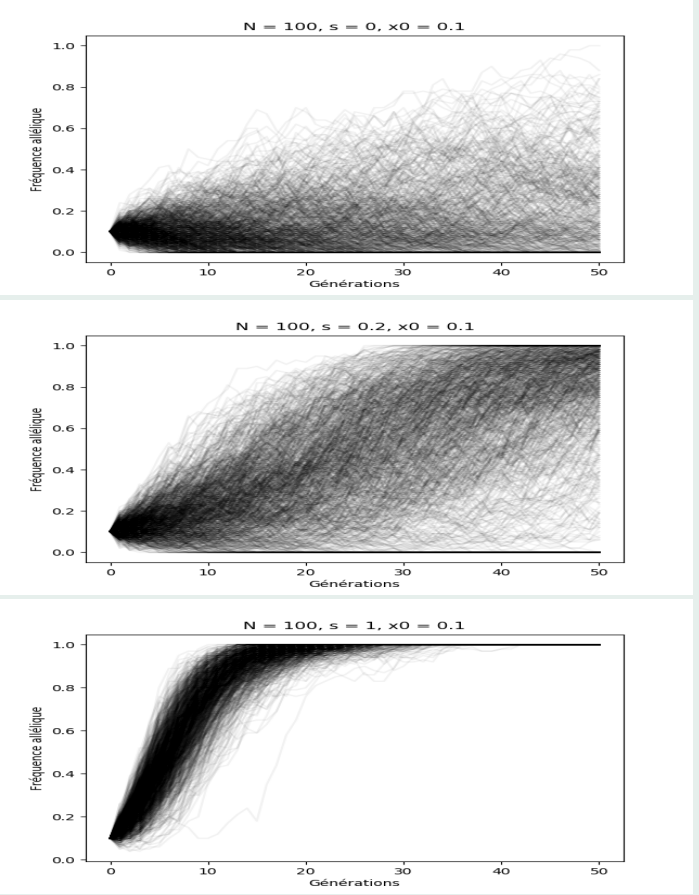
## Simulated process

- Wright-Fisher with selection

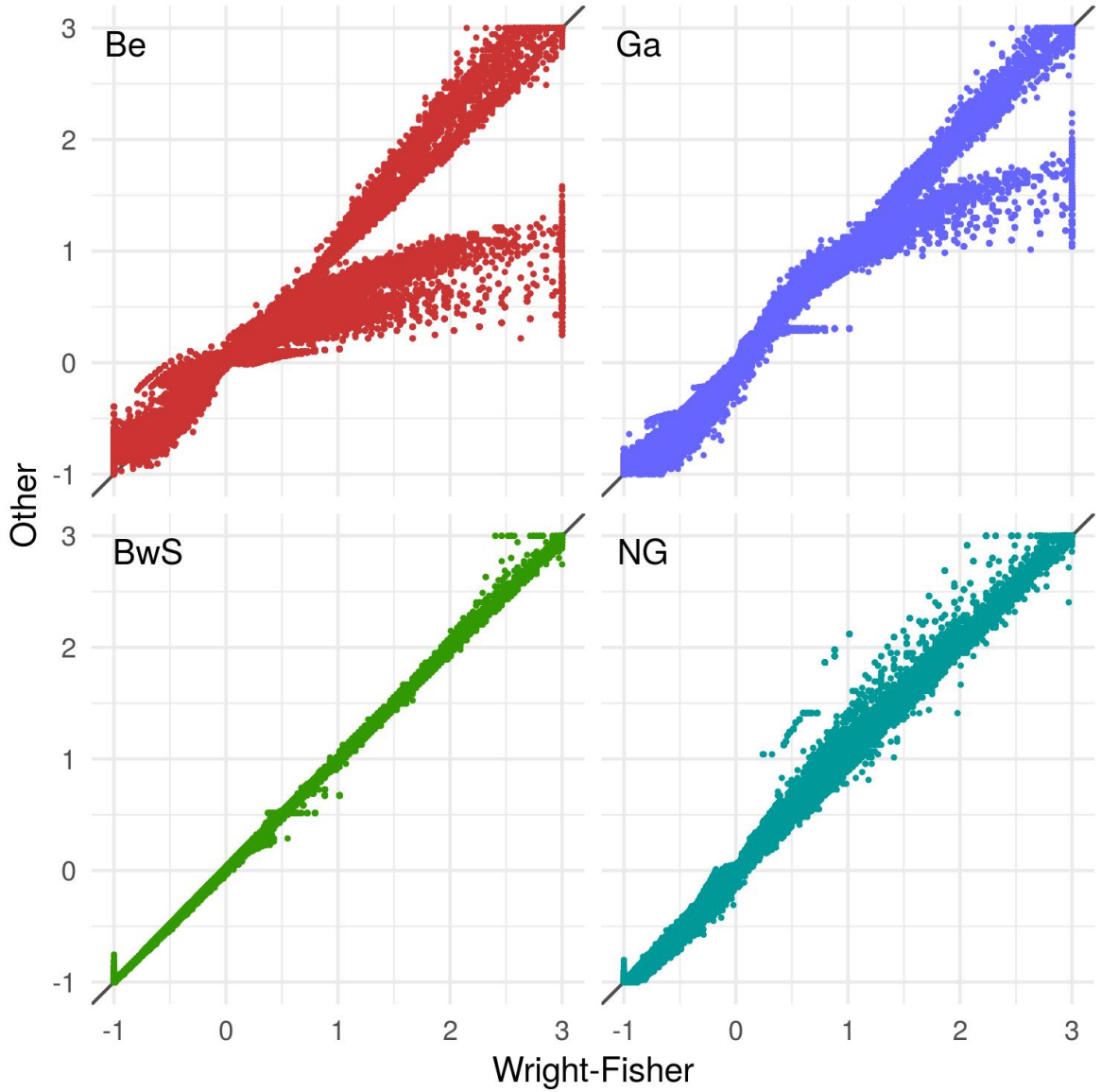
## Parameters

- $N = 100$
- $x_0 = 0.1$ or $0.5$
- $s = 0$ to $1$
- 10 sampling dates
- 30 alleles per sample
- Total evolution time: $T = 9$ to 180 generations

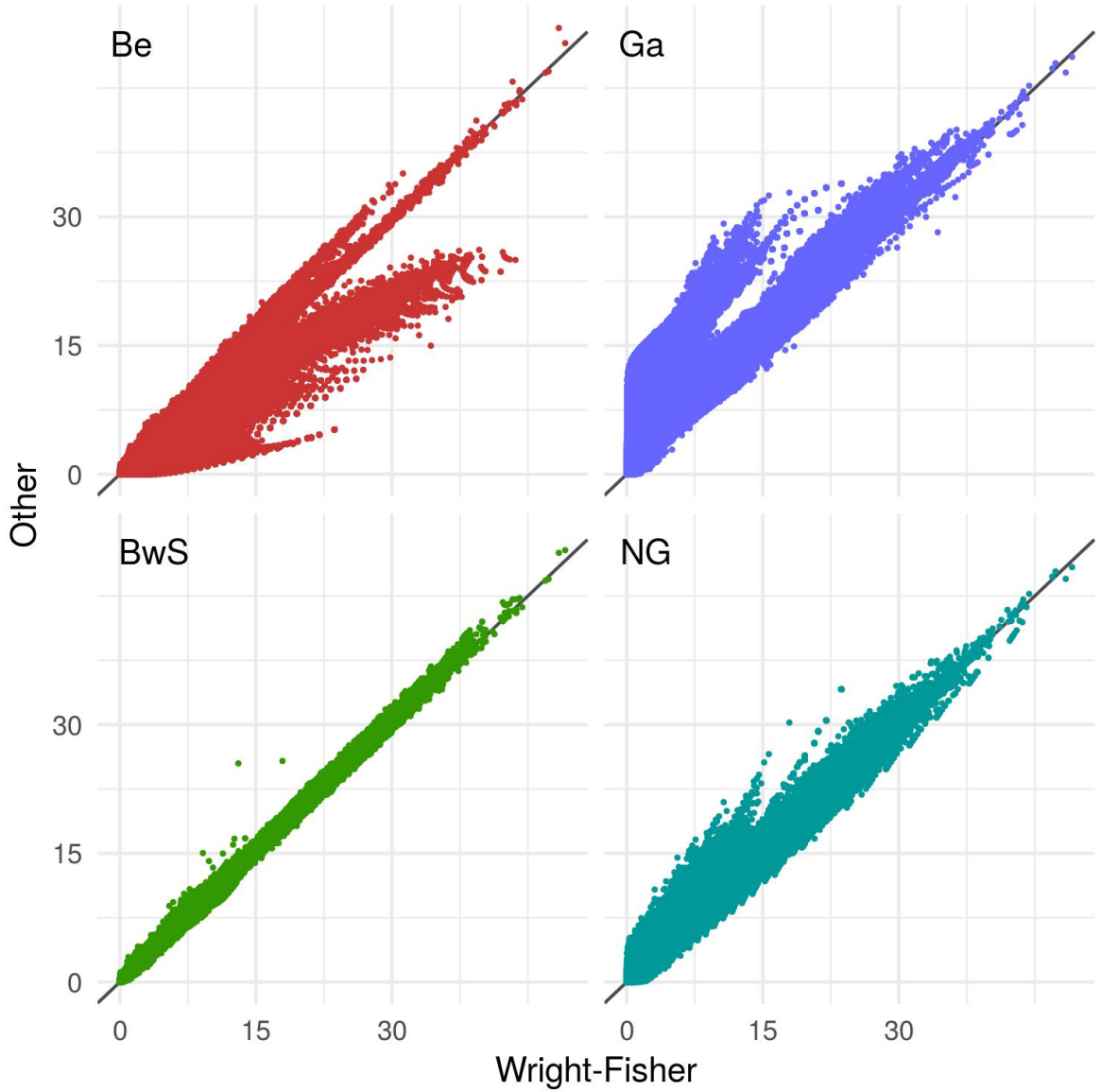
## Simulation examples



# Maximum Likelihood Estimation



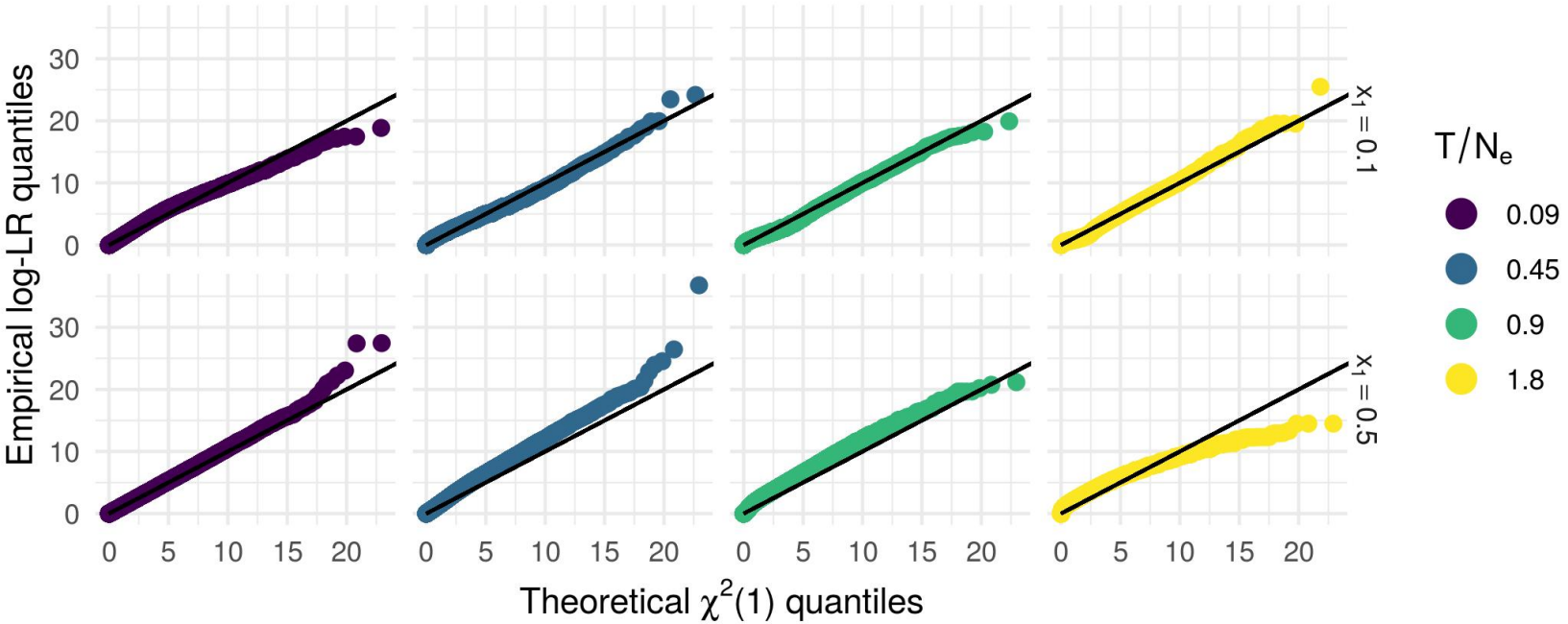
# Likelihood Ratio Statistic



# Simulations 2: statistical properties

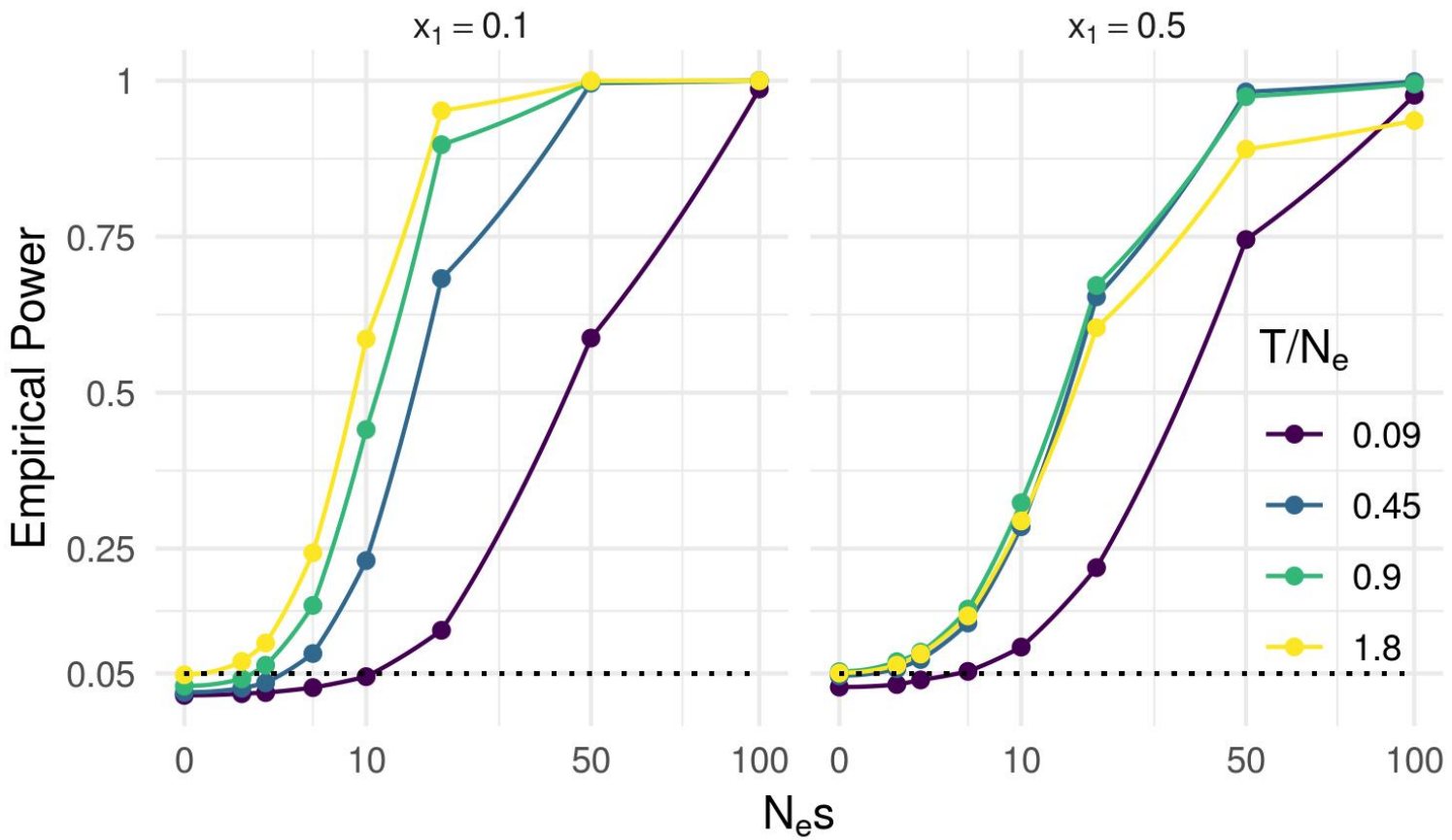
- Data analysis only with BwS transitions.
- $N = 100$, 1000 or 10000.
- $x_0$ and sampling design as before.
- $T/N$ as before: from 0.09 to 1.8.
- $Ns$ as before: from 0 to 100.

# Likelihood Ratio Test calibration



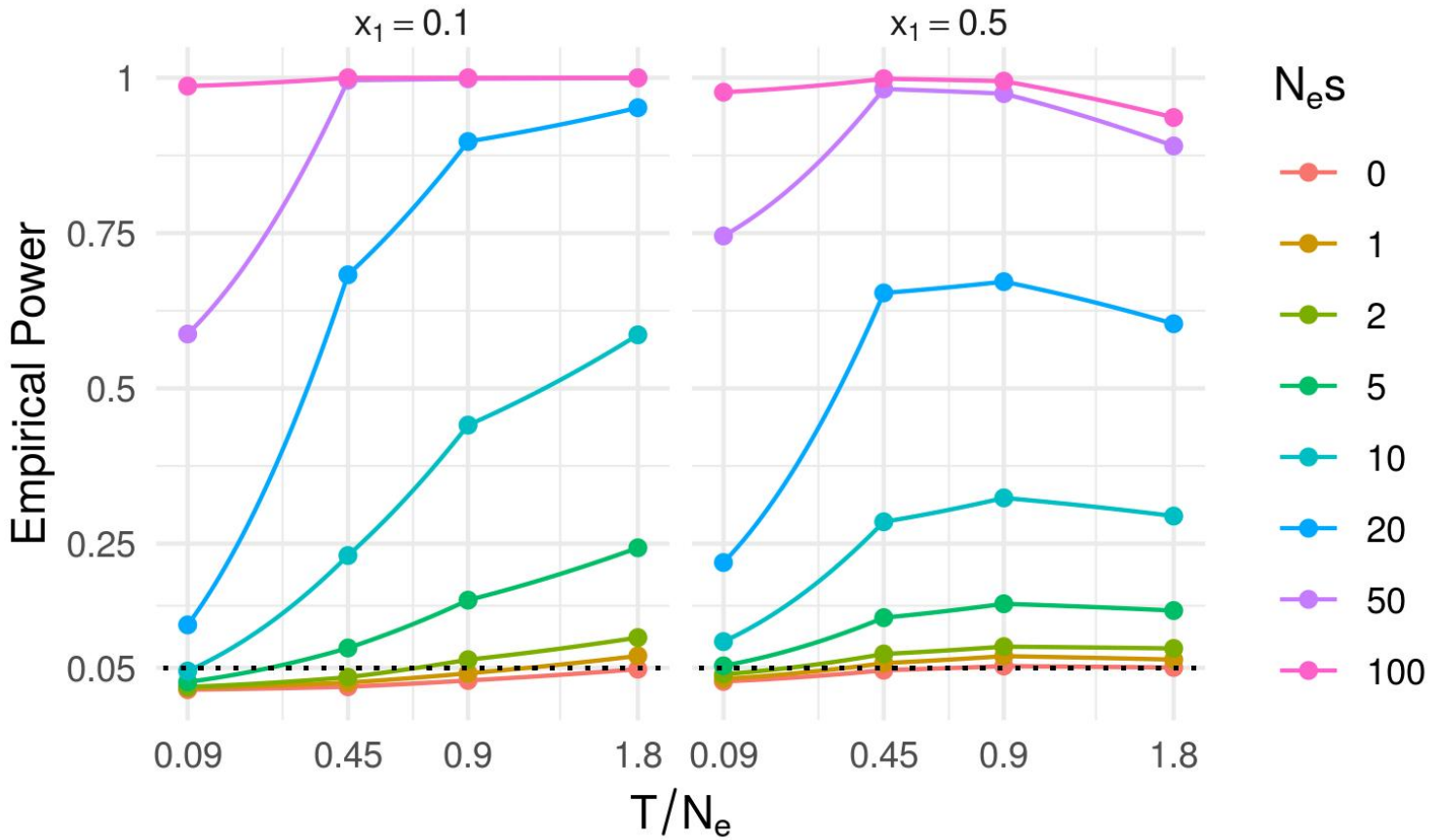

- Neutral simulations
- Good fit to the chi-quare distribution, except for $(T = 1.8, x_0 = 0.5)$.

# Detection Power

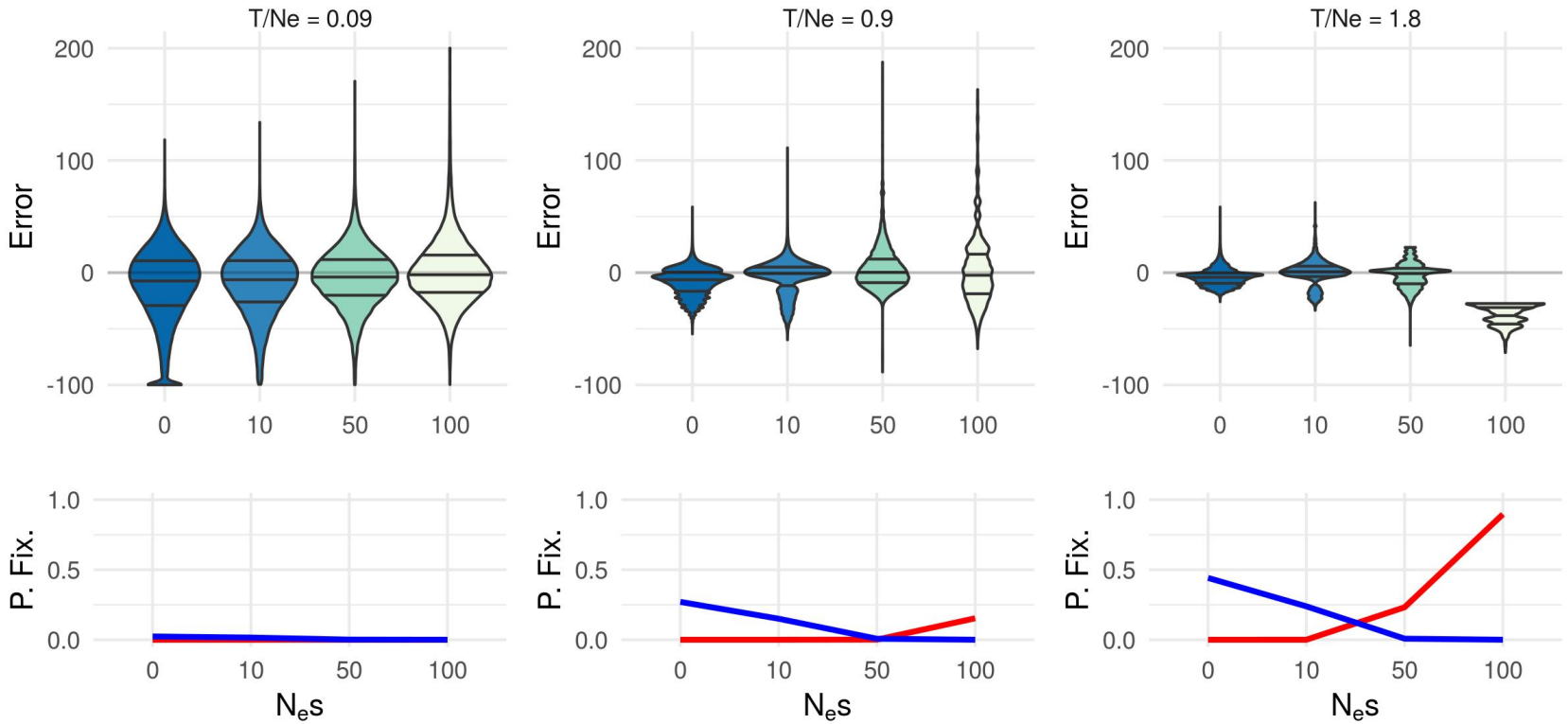



- Increases with $Ns$, $T/N$ (up to a certain point).

# Detection Power



# Estimation of $s$




- Unbiased except for $(Ns, T/N)$ large (fixation probabilities).
- Lower variance for large $T/N$.

# Outline

# Motivation

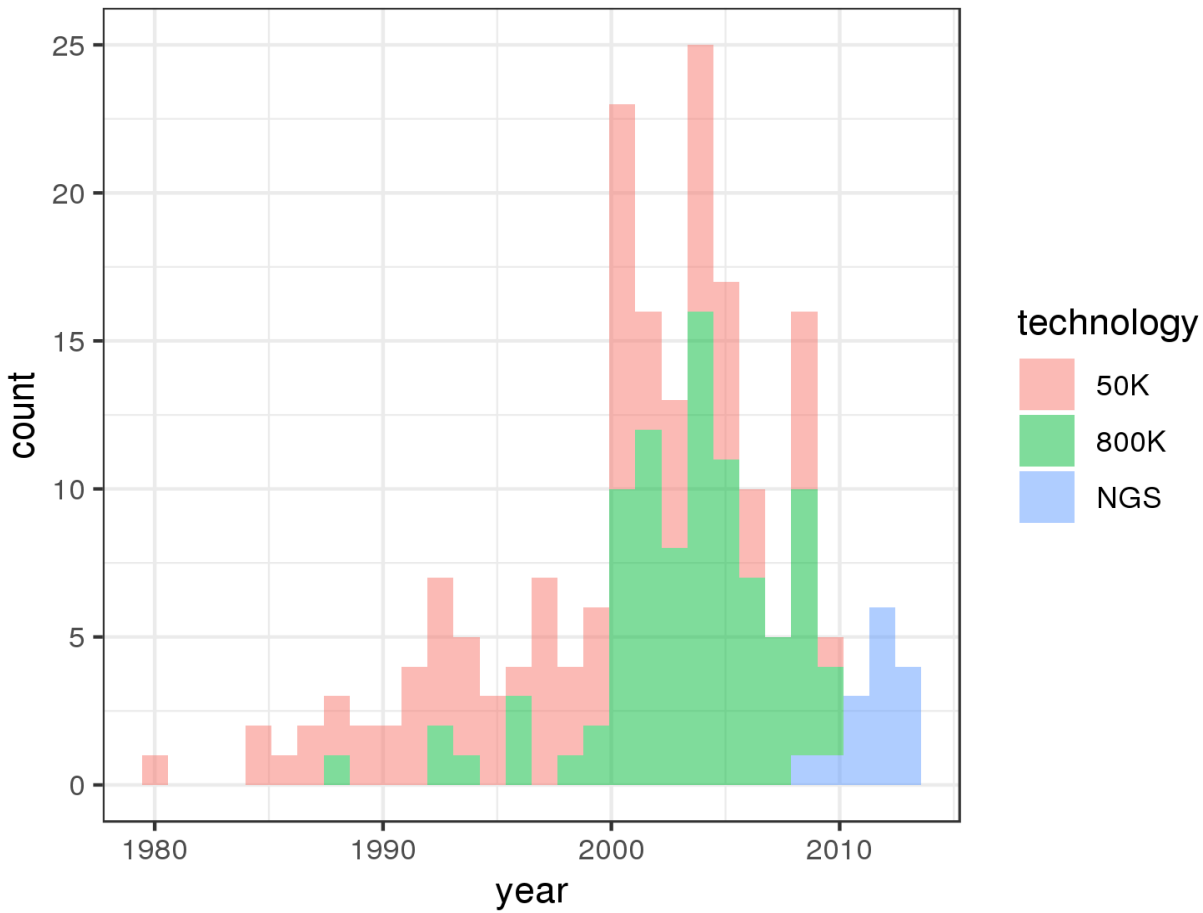
- Past positive selection can be detected from present time molecular data.
- Annotation of selection events more difficult: onset and intensity of selection? adaptive trait?
- Usefulness of time series (biobanks) to (i) detect recent selection or (ii) annotate signatures of historical selection?

# Case study: Asturiana de los Valles

- Spanish autochtonous beef cattle breed.
- North of Spain (Asturias).
- Semi-extensive breeding conditions.
- Evolution of genetic diversity along 35 years (1980 – 2015).

# Data

- Genotype data (50K or 800K) for 137 animals.
- 15 animals sequenced at $\approx$ 8X coverage.
- After quality filters, 14,328,987 SNPs detected from NGS data, 35,656 in common with the chips.



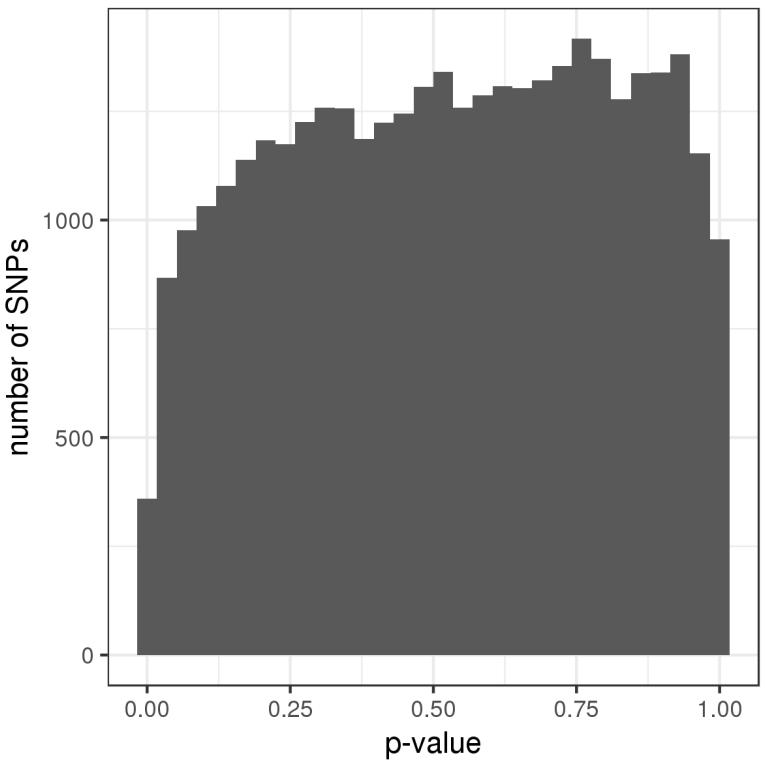
# Final time series dataset

- Generation time of 4 years.
- Inbred or related animals removed.

| Generation | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| First year | 1980 | 1984 | 1988 | 1992 | 1996 | 2000 | 2004 | 2008 | 2012 |
| Initial sample size | 1 | 5 | 11 | 15 | 21 | 40 | 38 | 12 | 10 |
| Final sample size | 0 | 4 | 8 | 13 | 17 | 28 | 29 | 9 | 9 |

# Selection signatures: time series approach

- Population size estimated with R package NB (Hui and Burt, 2015): $N = 400$ diploids.
- No evidence of selection at the single SNP level.
- 5 regions enriched in low p-values using a local score approach (Fariello *et al*, 2017).



# Candidate regions

- Candidate genes related to carcass and meat traits (RBPMS2, OAZ2) or milk traits (ARFIP1).

| Chr | Start (bp) | End (bp) | Length (bp) | Nb SNP | Genes |
|---|---|---|---|---|---|
| 10 | 45387461 | 45564676 | 177215 | 7 | RBPMS2, OAZ2 ZNF609, RF00413 |
| 13 | 41414256 | 41529941 | 115685 | 3 | - |
| 17 | 4675045 | 4750693 | 75648 | 4 | FHDC1, ARFIP1 |
| 17 | 31268164 | 31632465 | 364301 | 8 | - |
| 22 | 39414833 | 39491373 | 76540 | 3 | PTPRG |

# Selection signatures: present time data approach

- Signatures of historical selection detected from NGS data only (15 animals from generations 8 and 9).
- nSL statistic (Ferrer-Admetlla *et al*, 2014): looks for long haplotypes at high frequency.
- No proper p-value associated to a given nSL score: outlier approach.
- Focus on SNPs in common with the chip data: 5 regions with 'outlier' p-values.

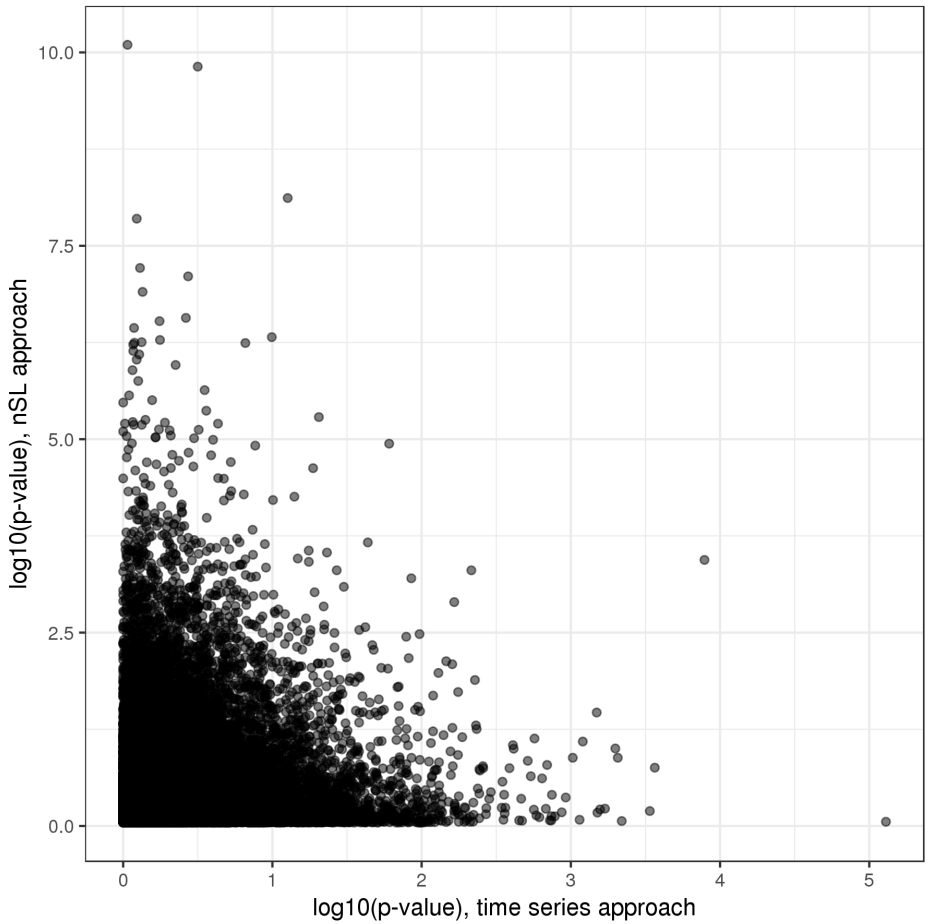
# Selection signatures: present time data approach

| Chr | Start (bp) | End (bp) | Nb SNP | log10(pval) | Genes |
|---|---|---|---|---|---|
| 2 | 7169804 | 7270116 | 2 | 9.82 | COL5A2, COL3A1 |
| 2 | 8476975 | 8476975 | 1 | 8.12 | - |
| 6 | 55360713 | 55360713 | 1 | 7.85 | - |
| 10 | 98290813 | 98290813 | 1 | 10.10 | FLRT2 |
| 25 | 13647777 | 13647777 | 1 | 7.10 | PARN, BFAR, PLA2G10 |

- One region close to the MSTN gene (Chr2, $\approx$ 6,2Mb), whose allele nt821(del11) associated to double muscling has been selected in Asturiana (Dunner *et al*, 2003).
- FLRT2: embryonic development, associated to calf birth weight in Holstein (Cole *et al*, 2014).

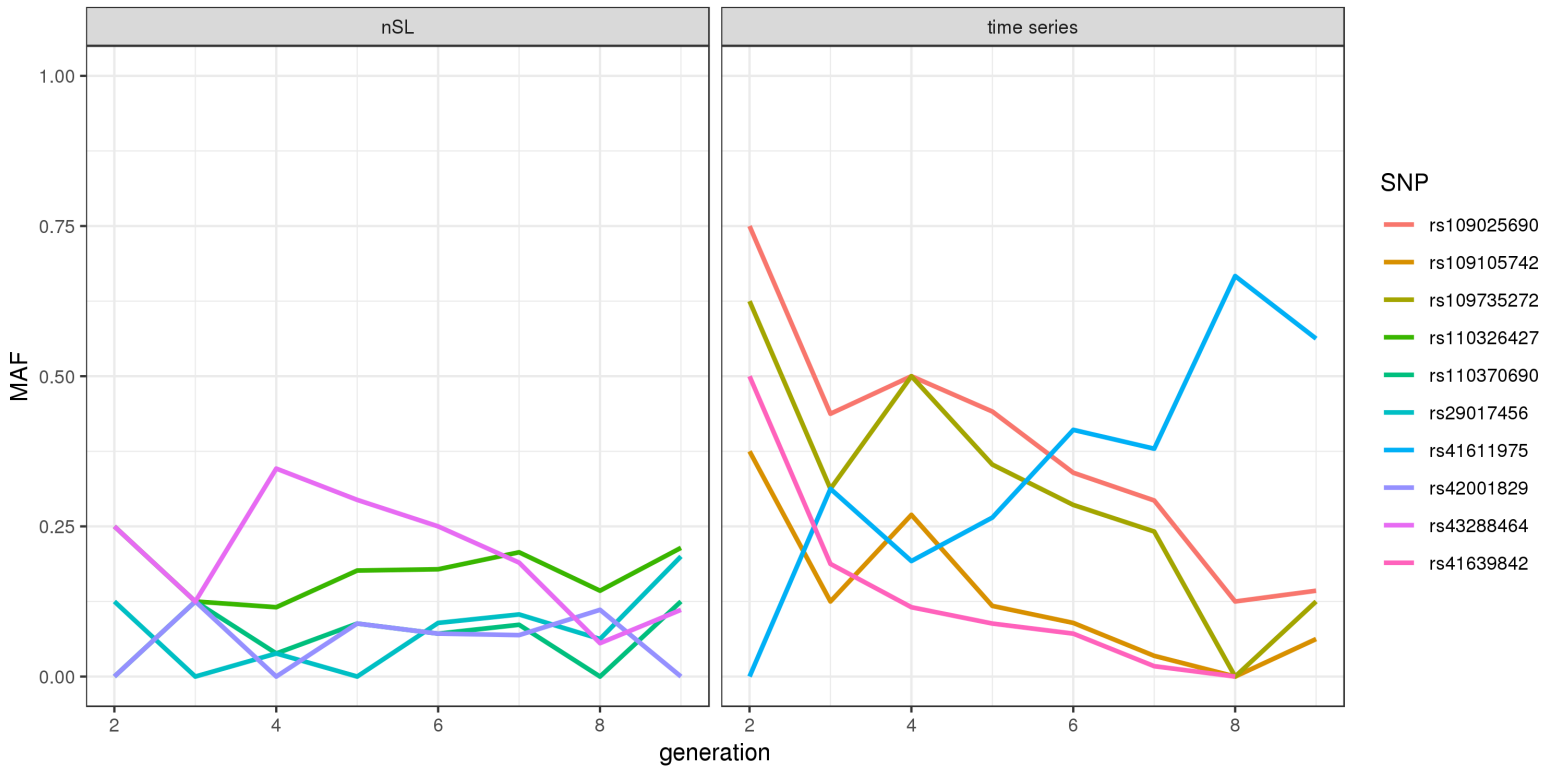
# Comparison between approaches

- Almost no correlation between the p-values obtained from the time series and the nSL approach.



# Comparison between approaches

- The top 5 SNPs of the time series approach show a clear shift in allele frequency since 1980.
- The top 5 nSL SNPs show a stable allele frequency since 1980, suggesting selection at these loci is older.



# Outline

# Data (Le Bihan-Duval *et al*, 2018)

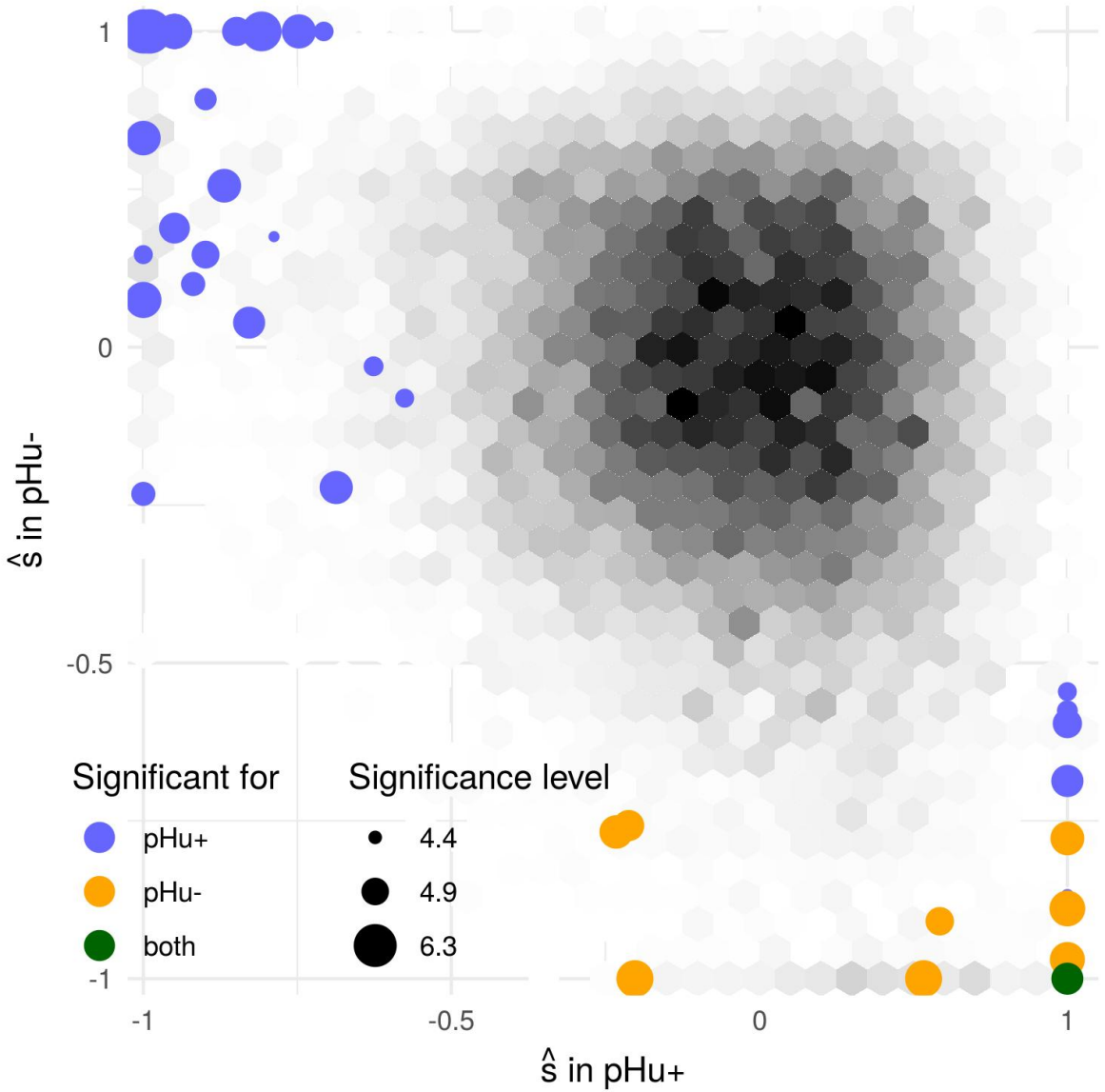
- Two chicken lines, 5 generations of divergent selection for low or high muscular ultimate pH (pHu).
- Genotypes at 40,199 SNPs.
- Haploid sample sizes:

| Dates (in generations) | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| pHu+ | 102 | 28 | 42 | 56 | 54 | 60 |
| pHu- | 102 | 34 | 46 | 44 | 54 | 56 |

# Results

- Estimated population sizes: $N = 157$ haploids in pHu+ and $N = 123$ with pHu-.
- 39 significant SNPs detected, at a FDR of 5%.
- 12 regions: 8 in pHu+, 1 in pHu-, 3 in both.
- Comparison with tests based on the differentiation between lines : FLK (Bonhomme *et al*, 2009) and hapFLK (Fariello *et al*, 2013):
  - 6 regions in common, 6 new.
  - New regions: allele frequency change only in one line.

# Results


1
0
-0.5
-1
-1
-0.5
0
1
ŝ in pHu-
ŝ in pHu+
Significant for
pHu+
pHu-
both
Significance level
4.4
4.9
6.3

# Outline

# Conclusions

- Beta with Spikes: perfect fit to the WF (for the problem considered here), very good alternative for large $N$ (computation time).
- Inclusion of fixation probabilities.
- $Ns = 10$ generally sufficient to detect selection from time series, but depends on $T/N$, $x_0$ and sampling design.
- Estimation of $s$ difficult for $(T/N, Ns) \geq (1, 100)$.
- Time series complimentary to present time data and allow a better annotation of selection events.
- Publication in G3 (early online), code in github.

# Perspectives

- Joint estimation of $N$ and $s$ (genome-wide data).
- Optimize the code.
- Account for variations of $N$ and $s$.
- Extend to halotype data.

# Acknowledgements


- IMAGE project, European Union's Horizon 2020 Research and Innovation Programme, grant agreement no. 677353.
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