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

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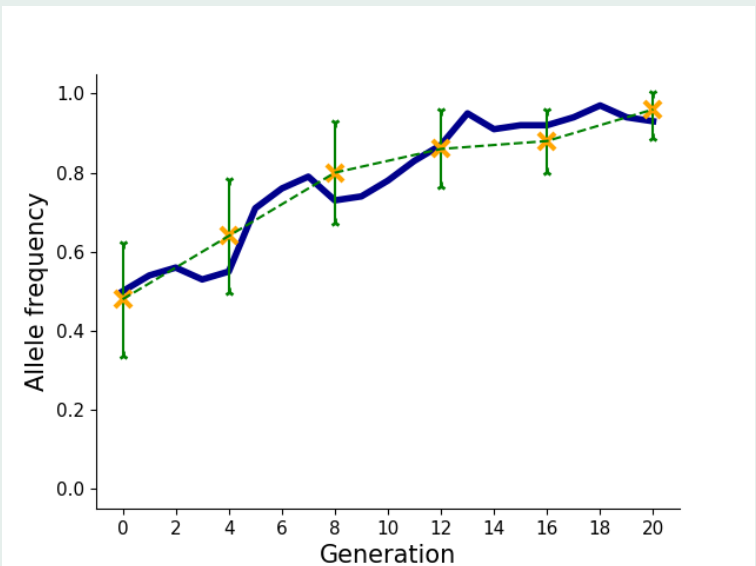
Introduction

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

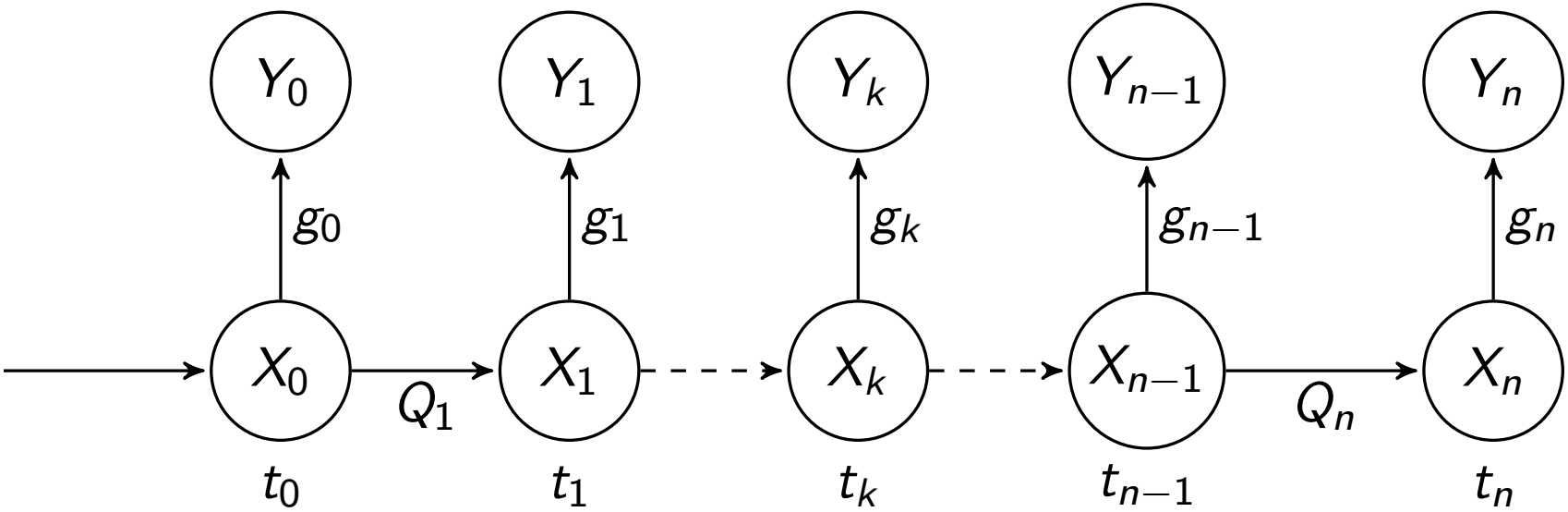
Need to model

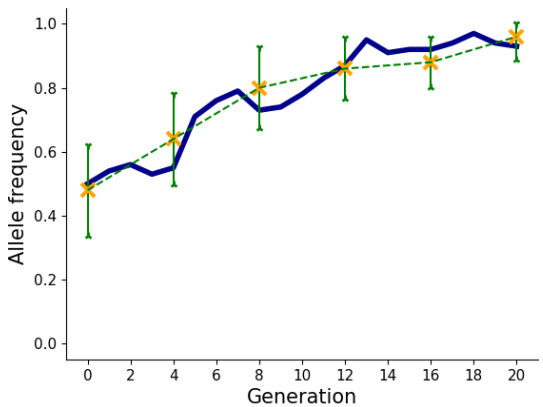
- Allele frequency evolution
- Sampling variability

Outline

Outline

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

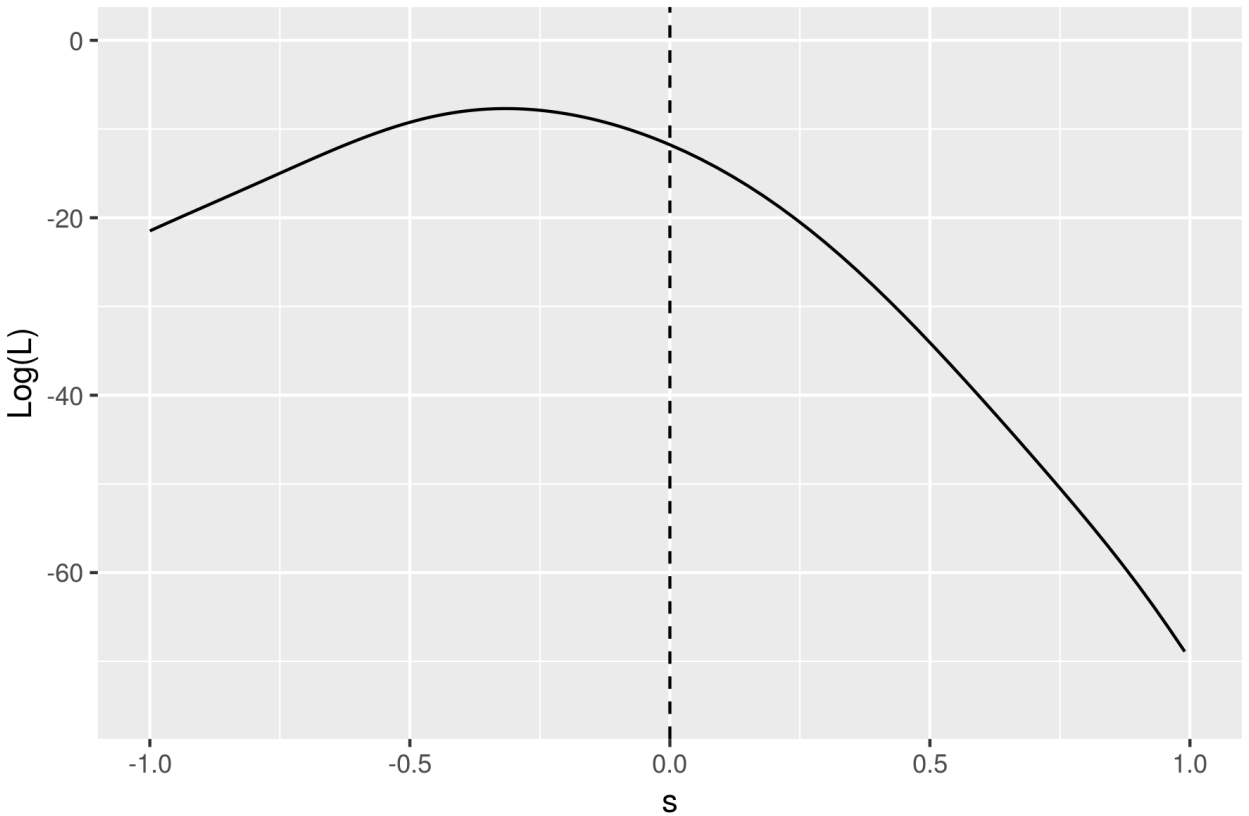




- Hidden states $\{X_k\}_{k\geq 0}$: Population allele frequencies, Markov chain, **transition** $Q = Q^{s,h,N}$
- Observations $\{Y_k\}_{k\geq 0}$: Sample allele counts, independent given $\{X_k\}_{k\geq 0}$, **emission g**

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

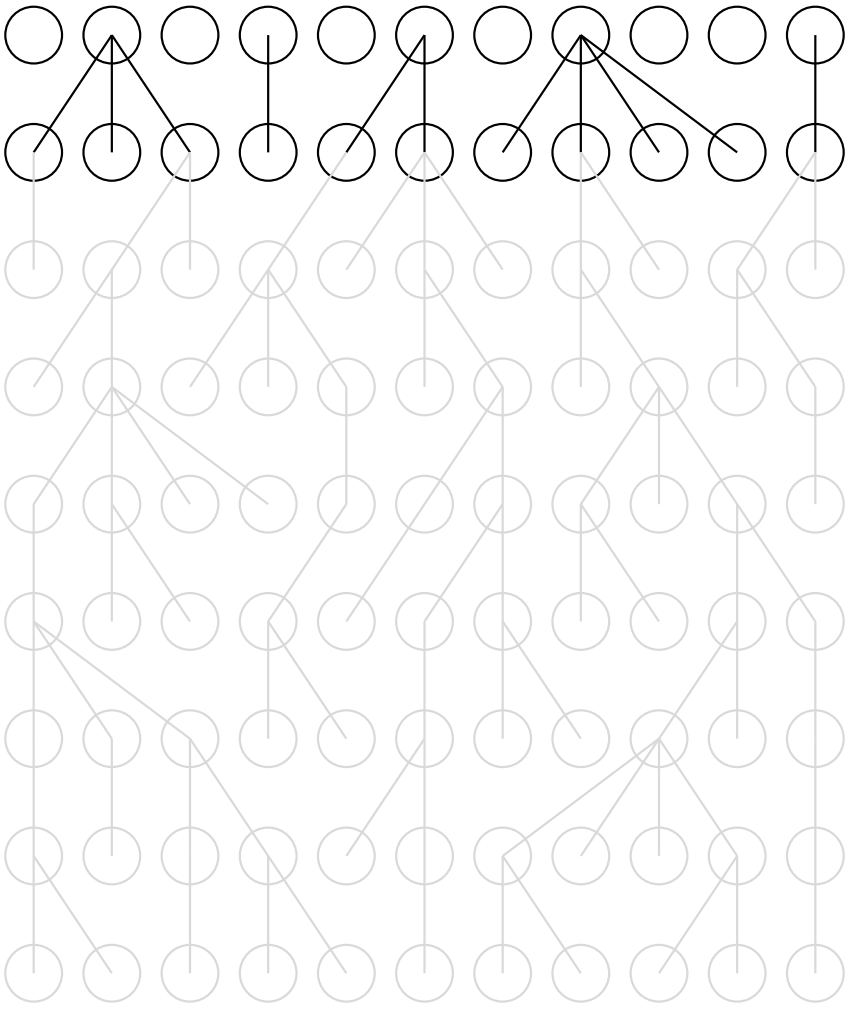
Hypotheses

- 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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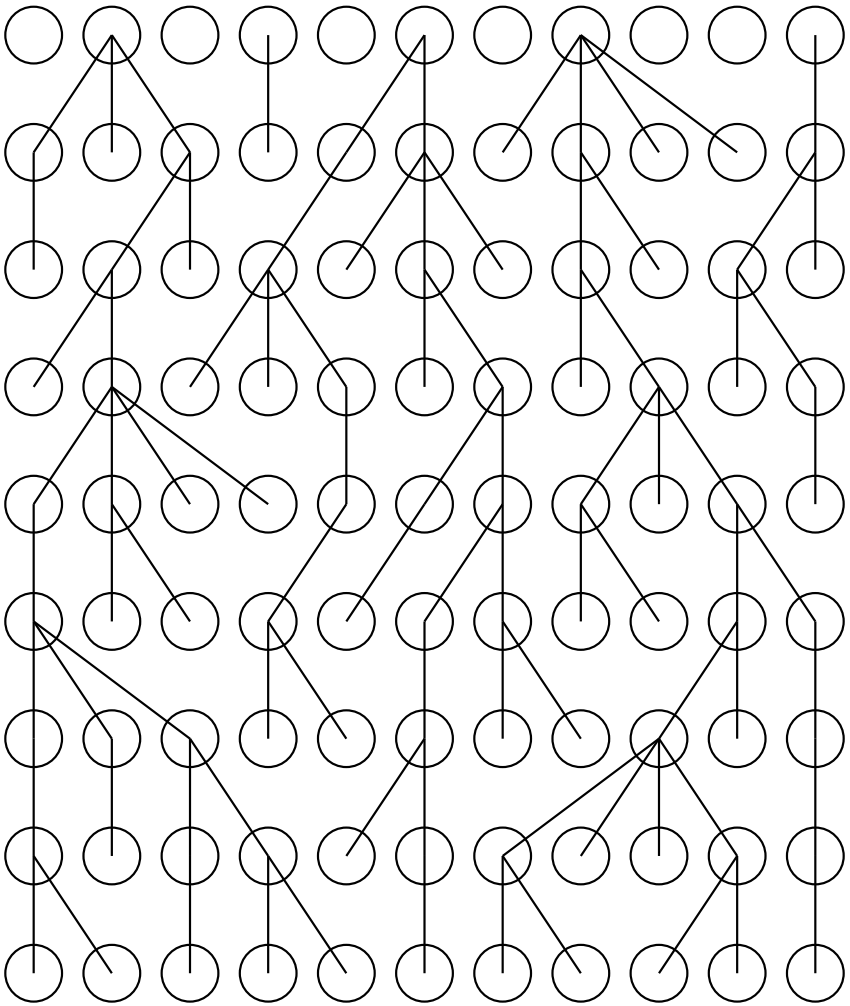

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Wright-Fisher's Limitations

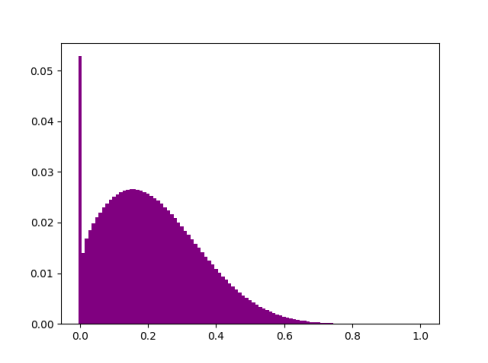
- Wright-Fisher model:
  - Matrix Q has dimension $N \times N$
  - Computing time: $Q = P^u$ + forward algorithm
  - Memory load
- Alternative: find a good approximation
  - Control Q dimension
  - Fits Wright-Fisher transitions
  - Mimics the statistical properties obtained with Wright-Fisher transitions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

The method of moments (Lacerda and Seoighe, 2014)

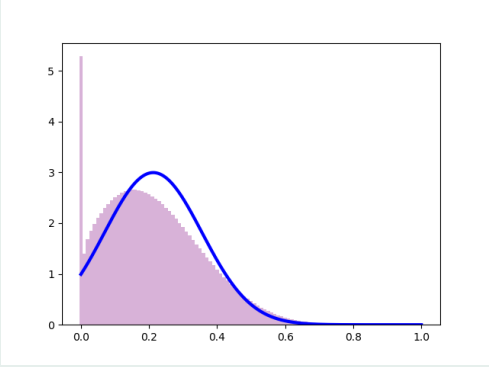
- Choose a parametric distribution
- Set parameters such that its moments fit those of the Wright-Fisher (WF).
- **Gaussian model (Ga):** Popular approximation for short time and intermediate allele frequency (Cavalli-Sforza *et al*, 1964; Lacerda and Seoighe, 2014; Terhorst *et al.*, 2015).
- **Nicholson 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

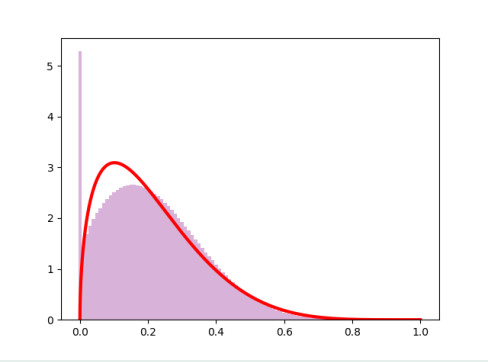
Wright-Fisher distribution



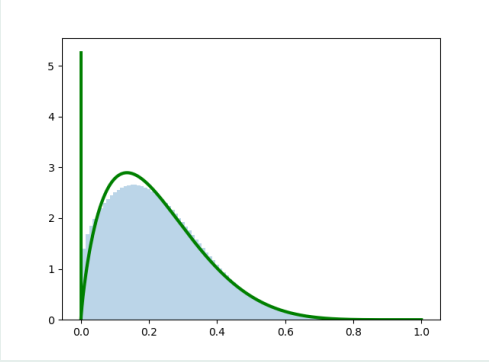
Gaussian distribution



Beta distribution



Beta with spikes distribution

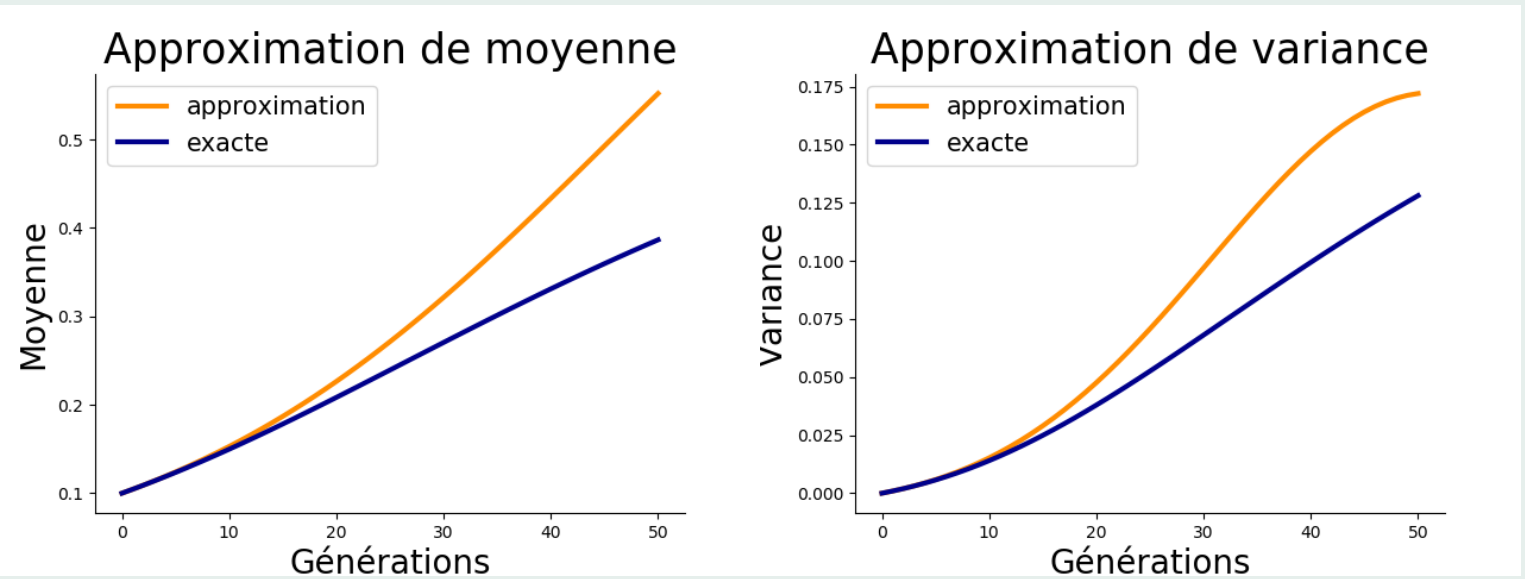


Moment approximation: Delta-method

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

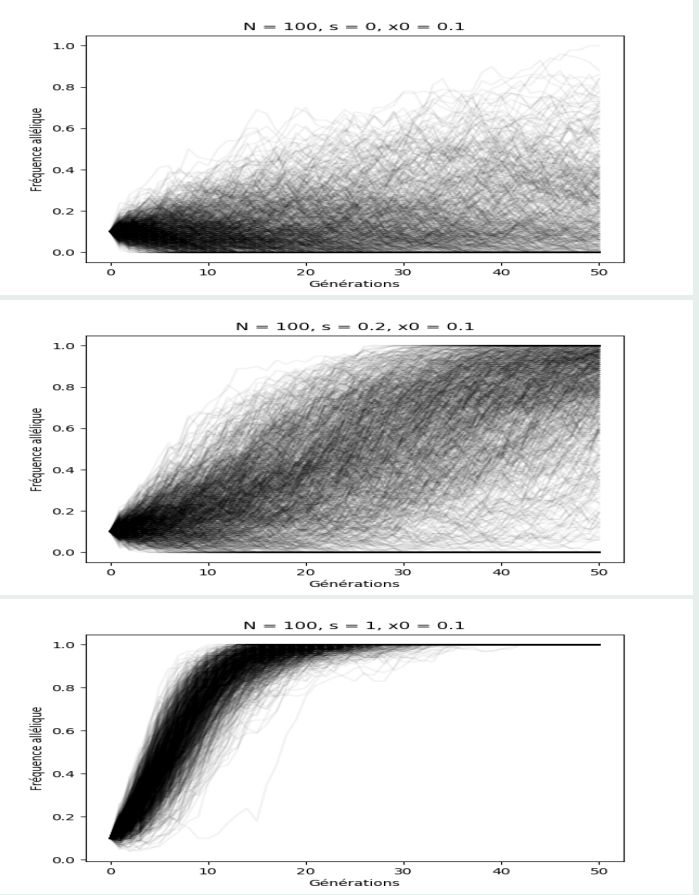
Simulated process

- Wright-Fisher with selection

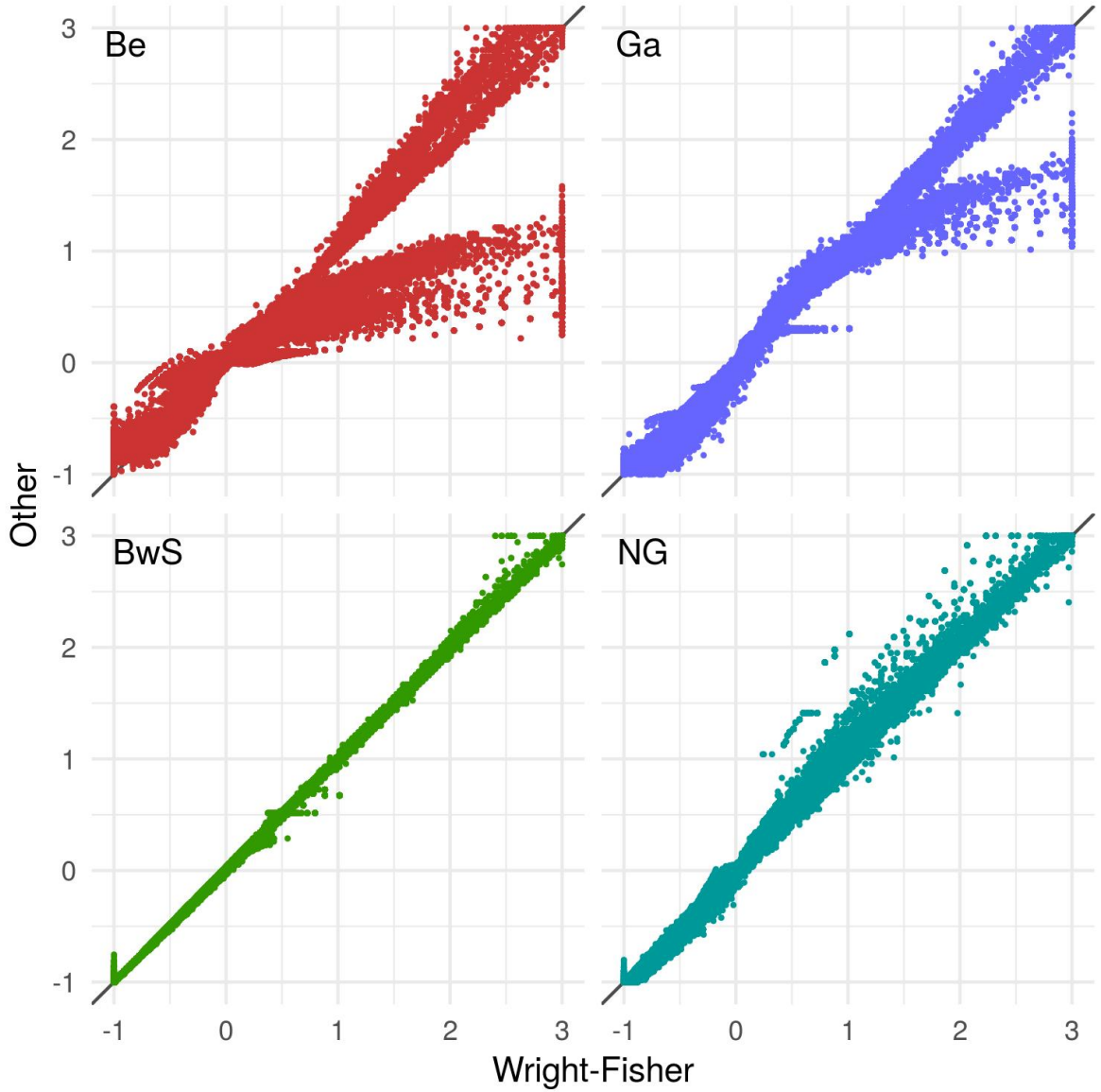
Parameters

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

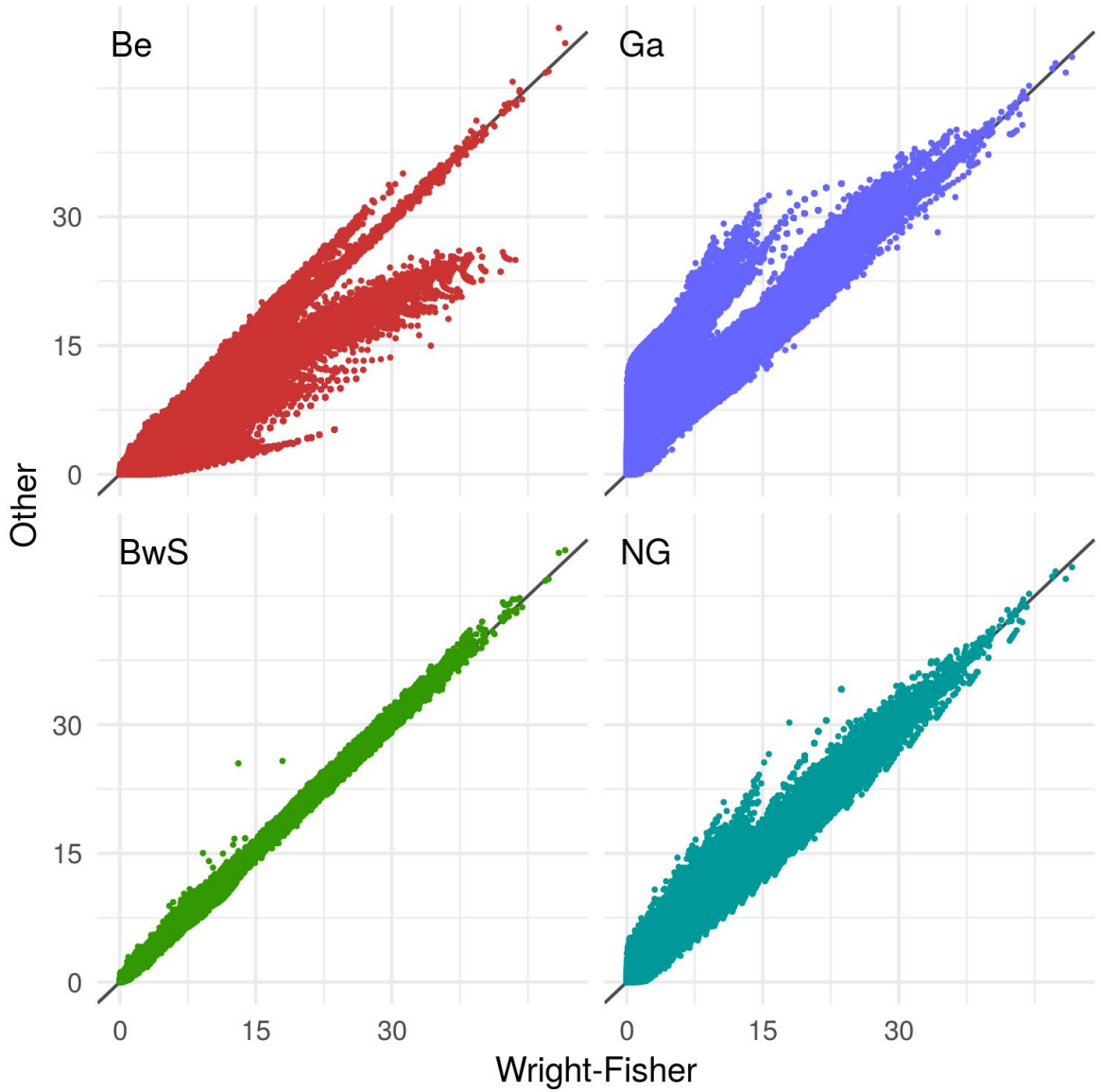
Simulation examples



Maximum Likelihood Estimation



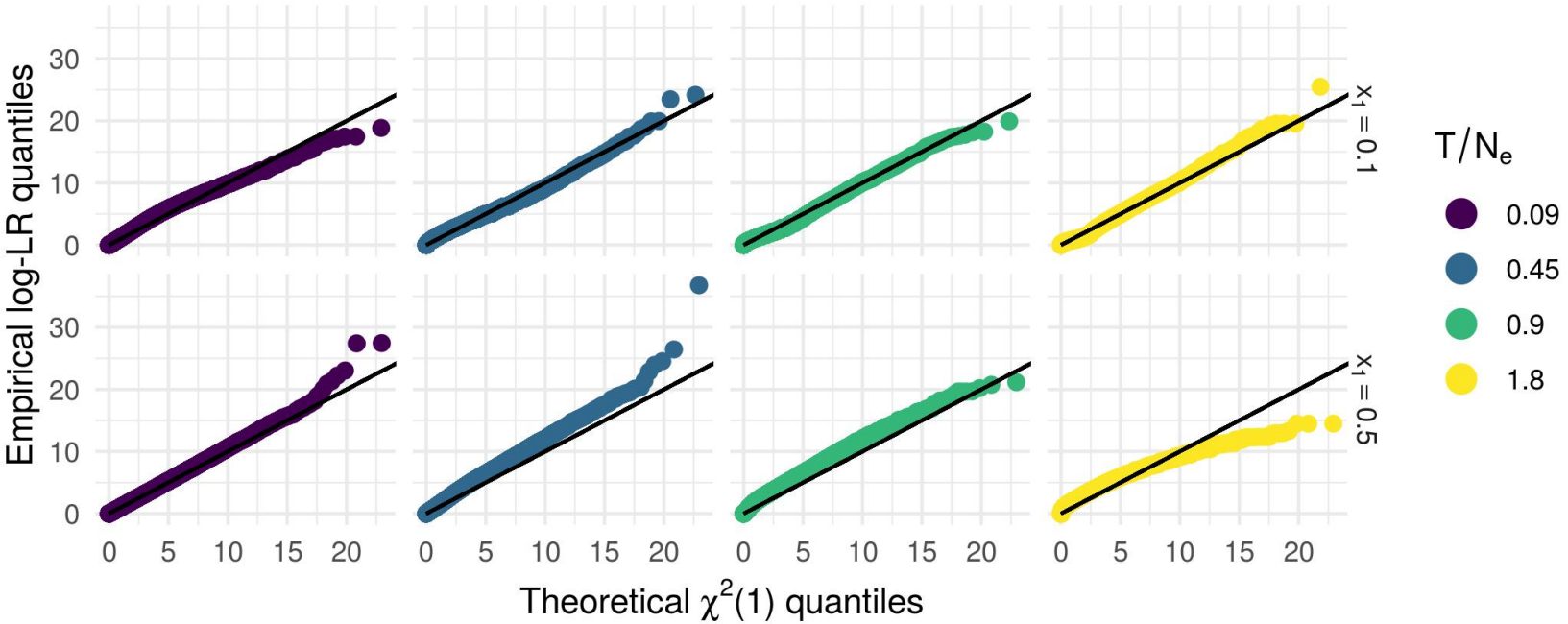
Likelihood Ratio Statistic



Simulations 2: statistical properties

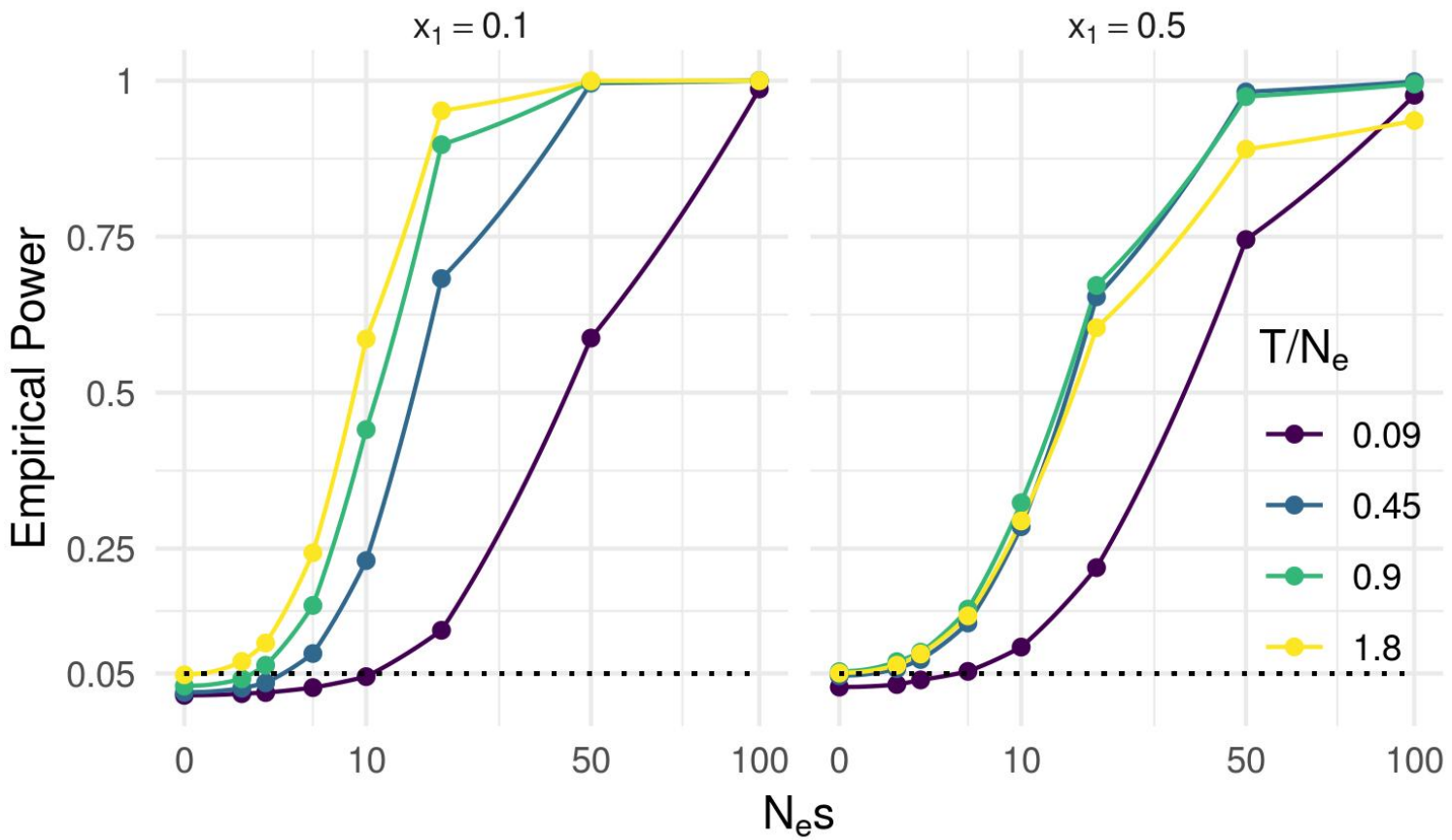
- Data analysis only with BwS transitions.
- $N = 100$, 1000 or 10000.
- x_0 and sampling design as before.
- T/N as before: from 0.09 to 1.8.
- Ns as before: from 0 to 100.

Likelihood Ratio Test calibration



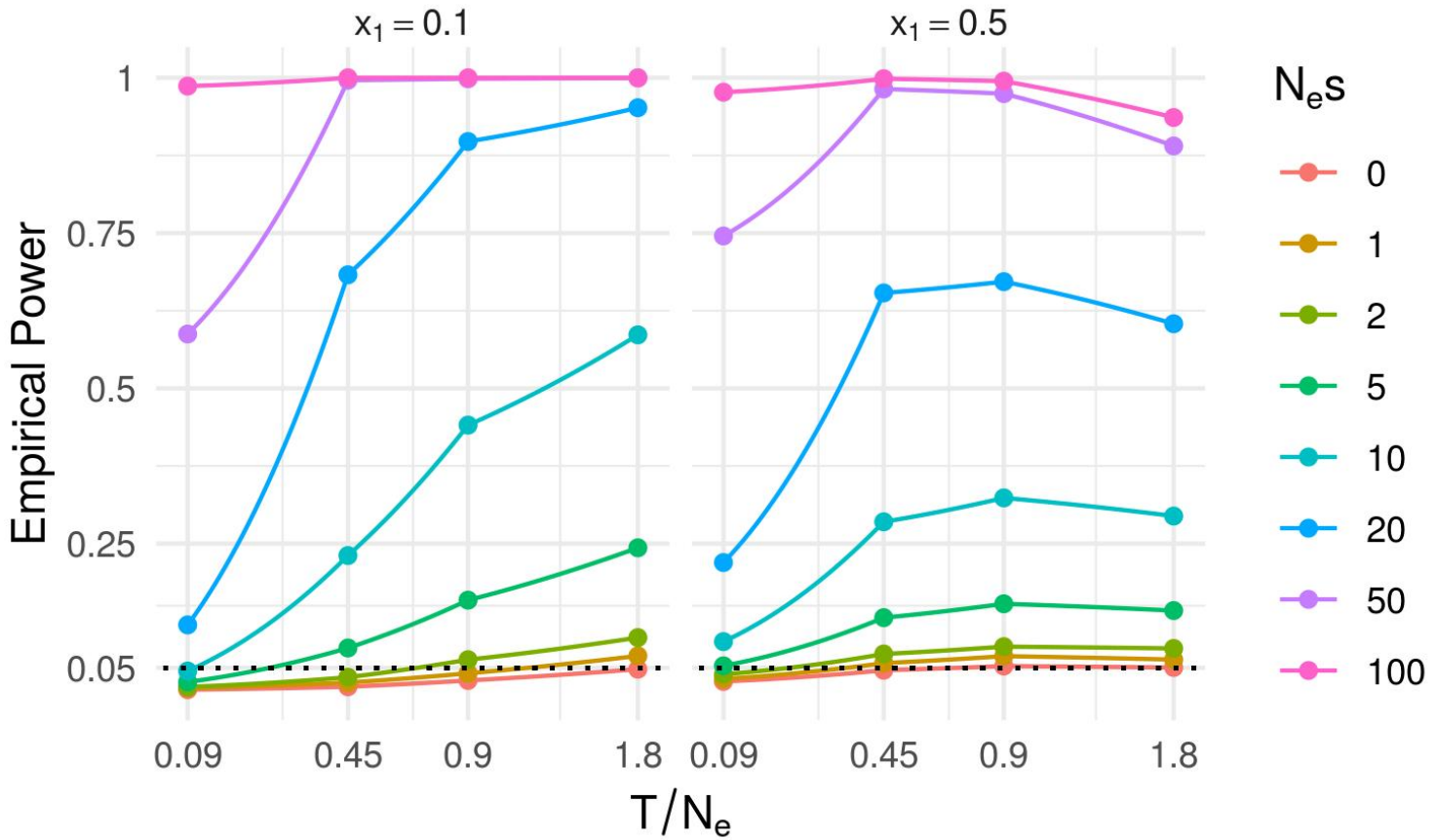
- Neutral simulations
- Good fit to the chi-quare distribution, except for $(T = 1.8, x_0 = 0.5)$.

Detection Power

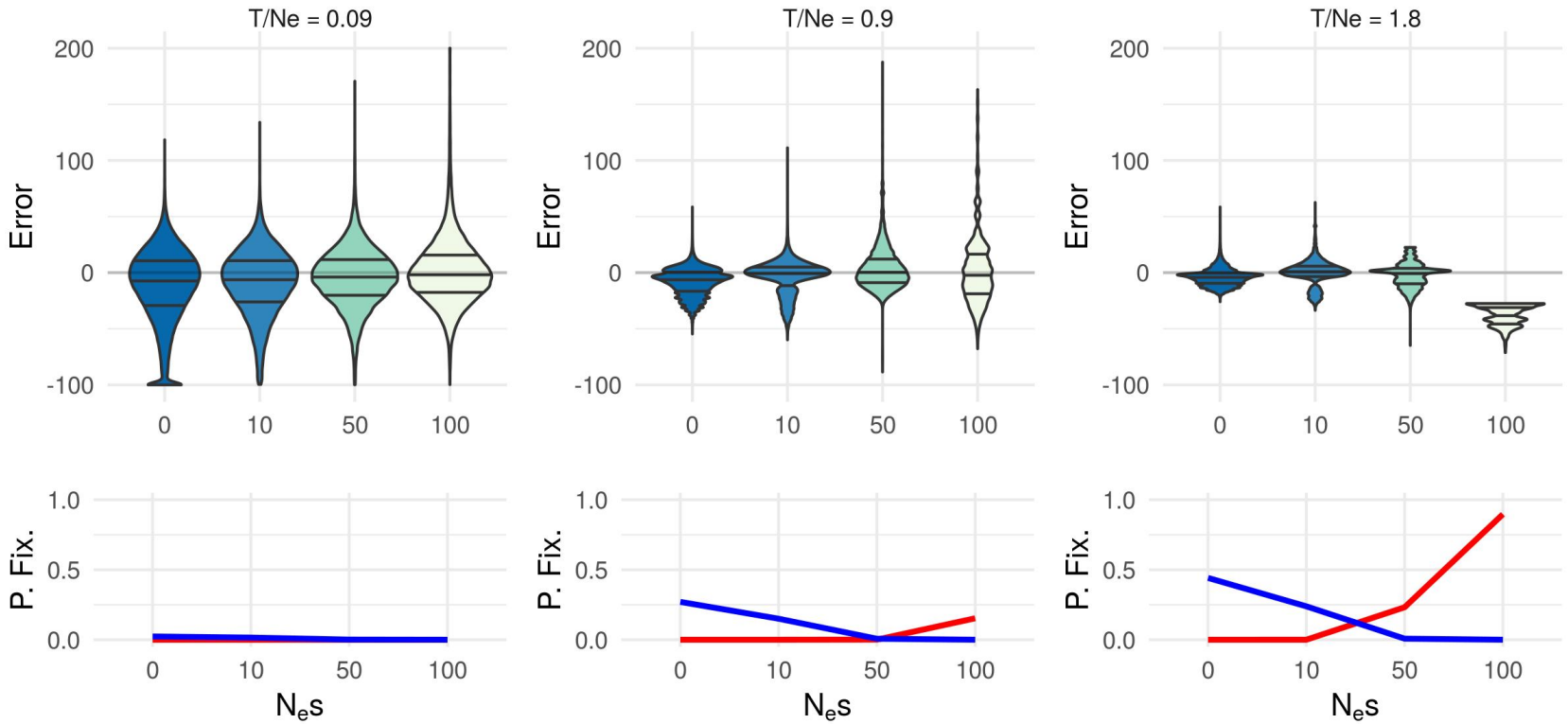


- Increases with Ns, T/N (up to a certain point).

Detection Power



Estimation of s



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

Outline

Motivation

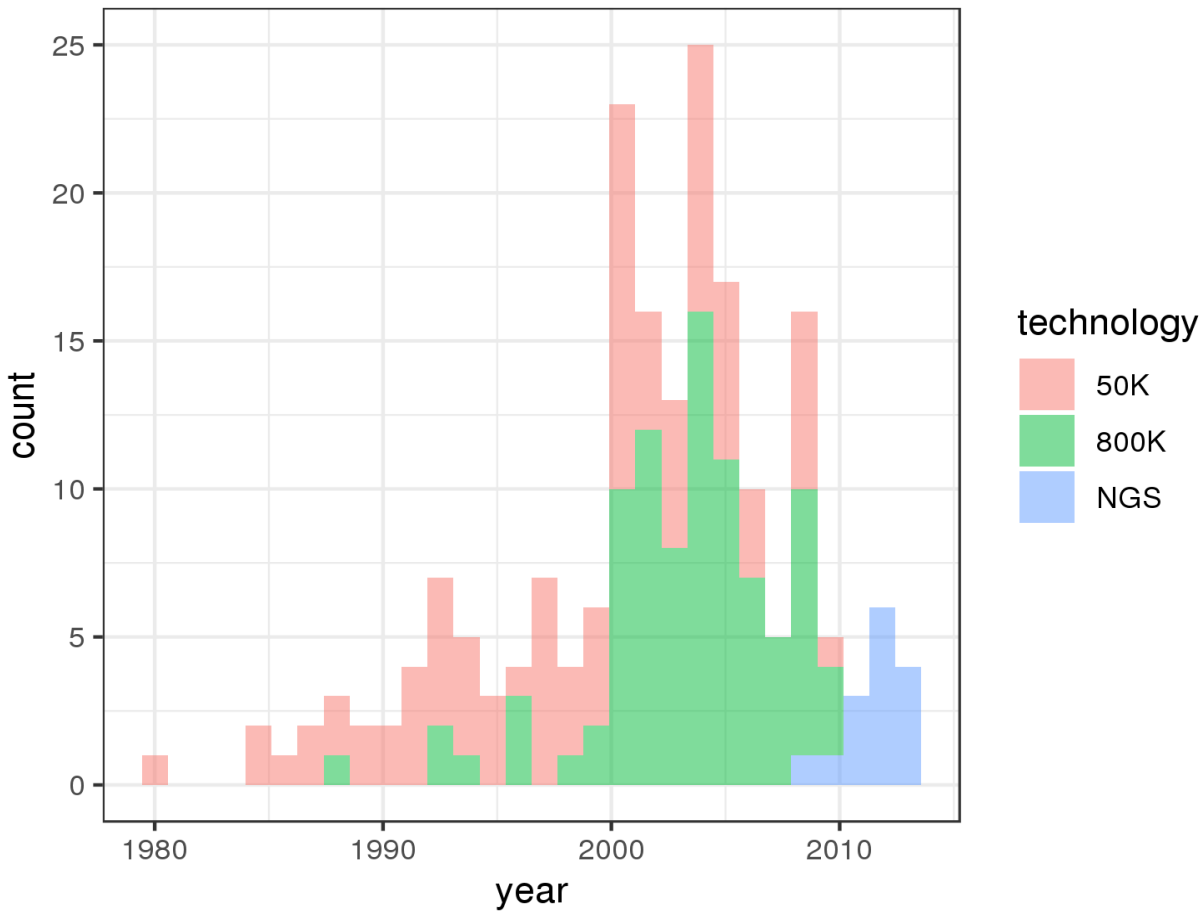
- Past positive selection can be detected from present time molecular data.
- Annotation of selection events more difficult: onset and intensity of selection? adaptive trait?
- Usefulness of time series (biobanks) to (i) detect recent selection or (ii) annotate signatures of historical selection?

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.



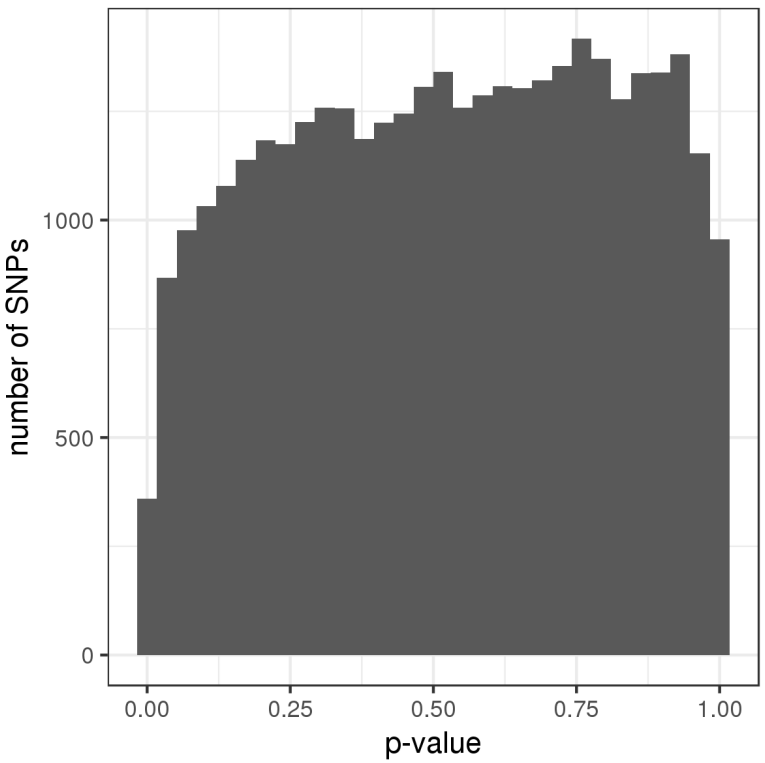
Final time series dataset

- 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.

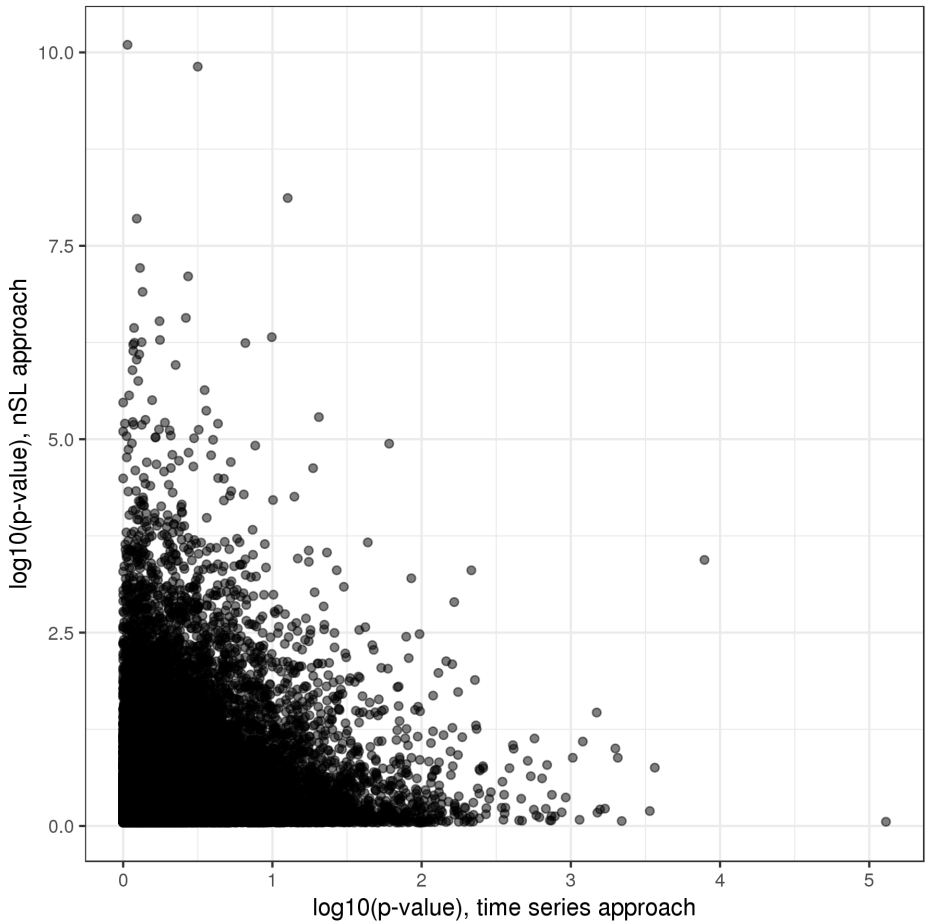
Selection signatures: present time data approach

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).

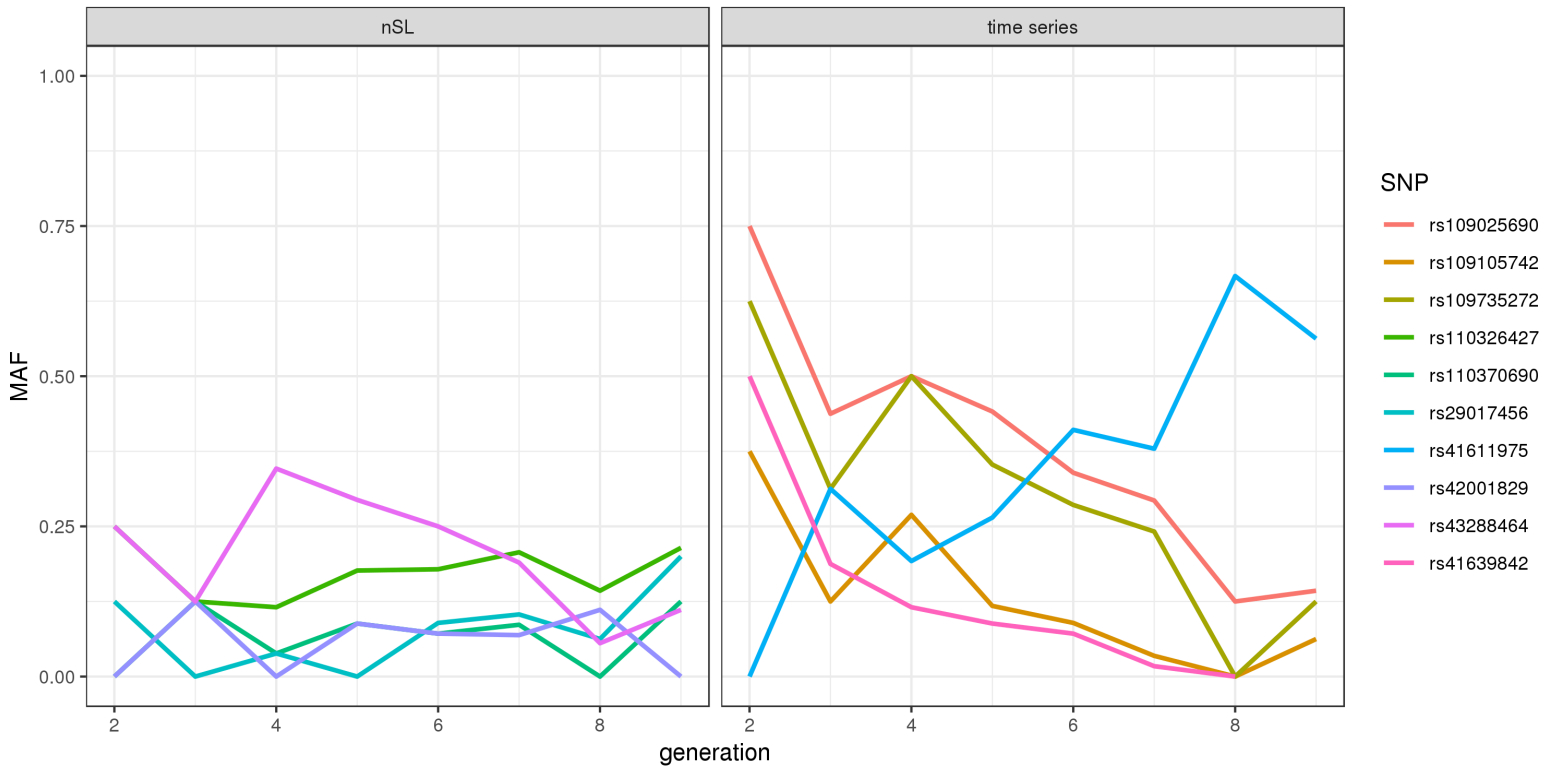
Comparison between approaches

- 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)

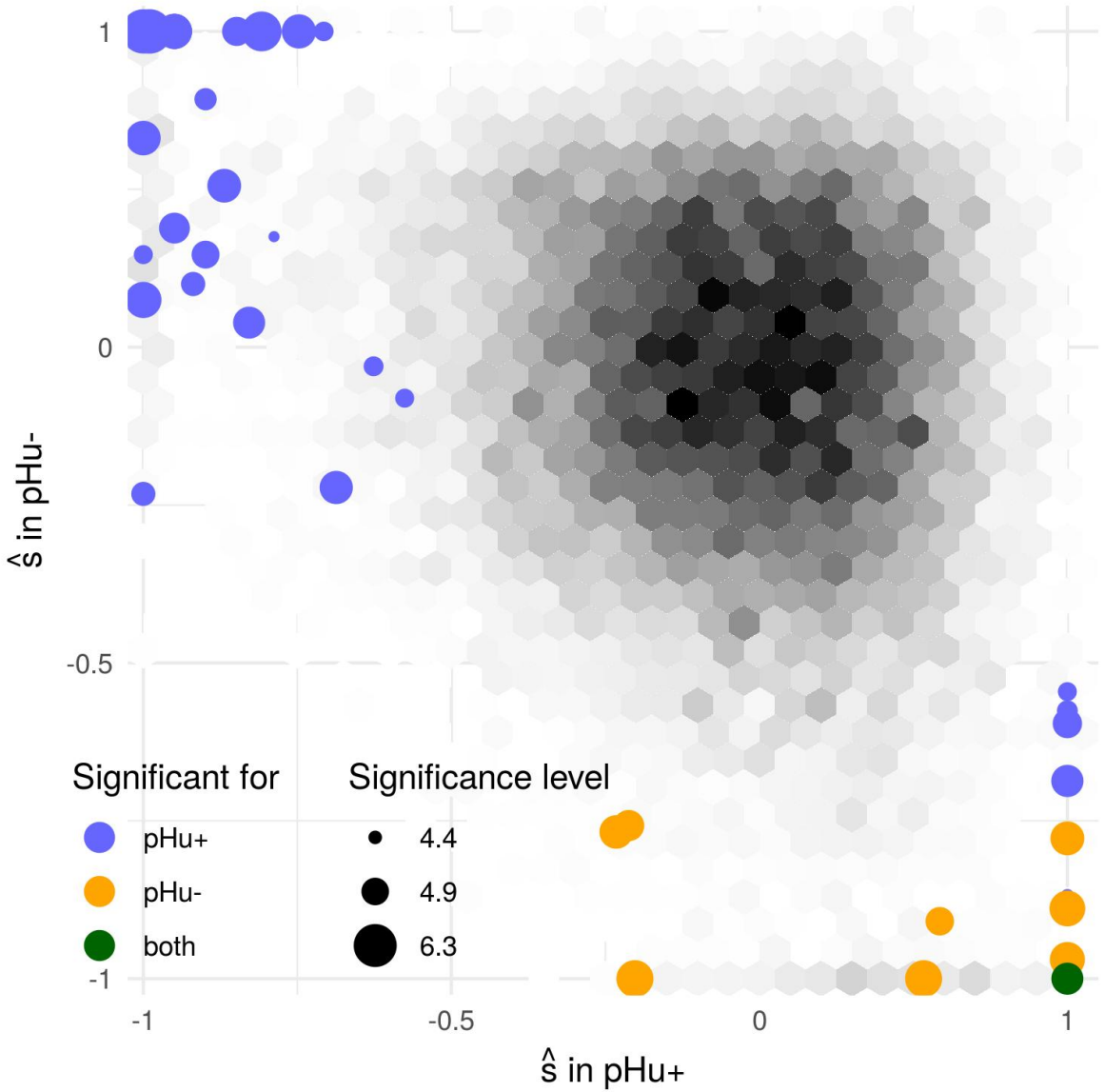
- Two chicken lines, 5 generations of divergent selection for low or high muscular ultimate pH (pHu).
- Genotypes at 40,199 SNPs.
- Haploid sample sizes:

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.

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