Detecting Selection in Experimental Evolution Experiment

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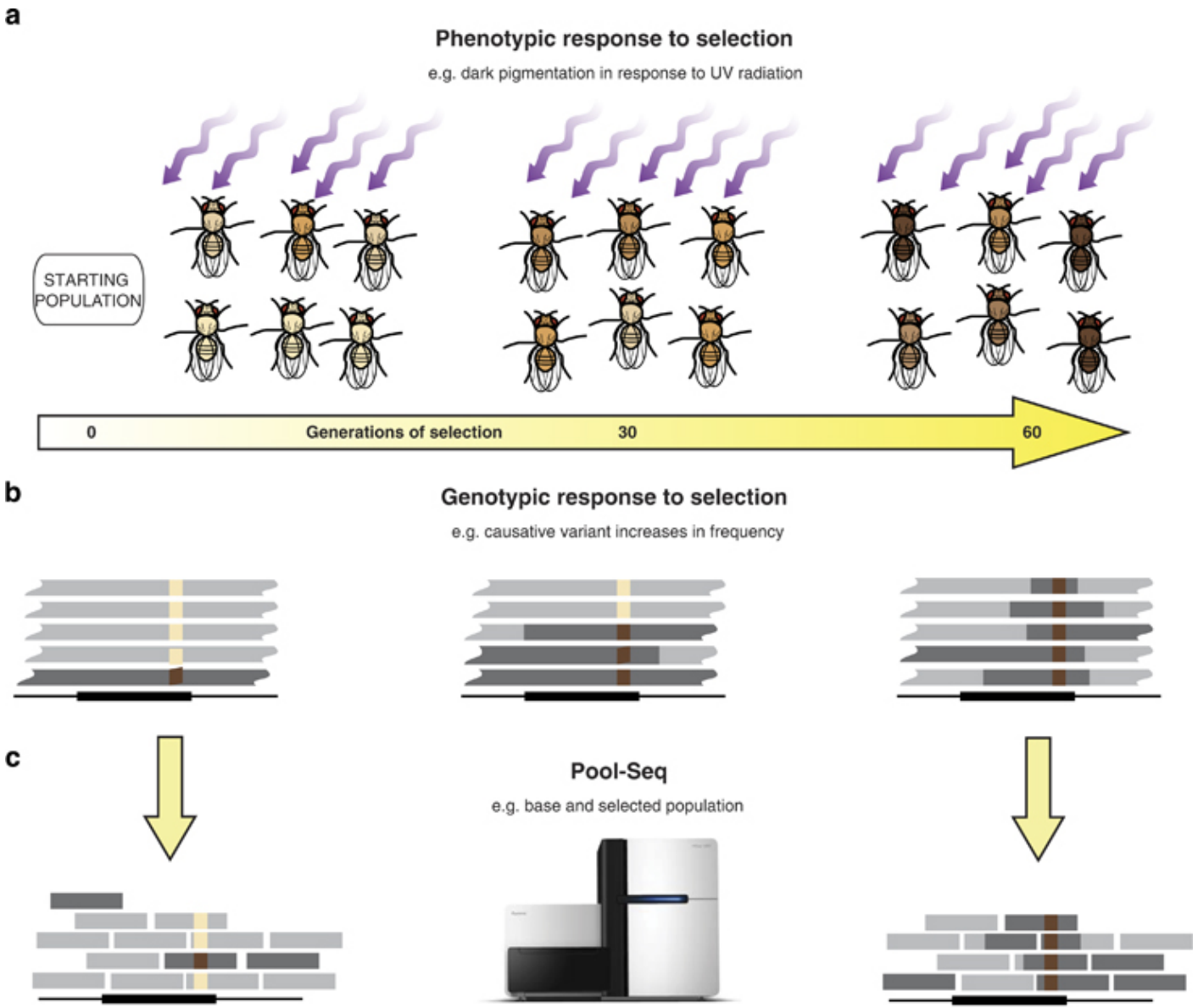
Introduction

- We are interested in identifying genetic adaptations in different organisms in find genes (or alleles) that are beneficial w.r.t. a selective pressure.
- Examples of interesting selective pressures: harsh environmental conditions, antibiotics, chemotherapy, etc.

History

- Traditionally, detecting/locating selection is done by analysing Allele Frequency Spectrum(AFS) or Haplotypes of a region (say 50Kbp).
- **Now**
  1. We can sequence the population at different generations
  2. We can't wait until fixation.

Experimental Evolution



Goals

- Given the genome time series data (allele frequencies) we are interested in
  - I Detecting selection
  - II Locating selection
    - (i) Identify gene under selection
    - (ii) Identify the mutation
  - III Estimating model parameters

Simulations

(i) For each simulation, population of $F = 200$ founder lines is created in `msms` program with parameters
- window size $L = 50$Kbp.
- mutation rate $\theta = 200$.

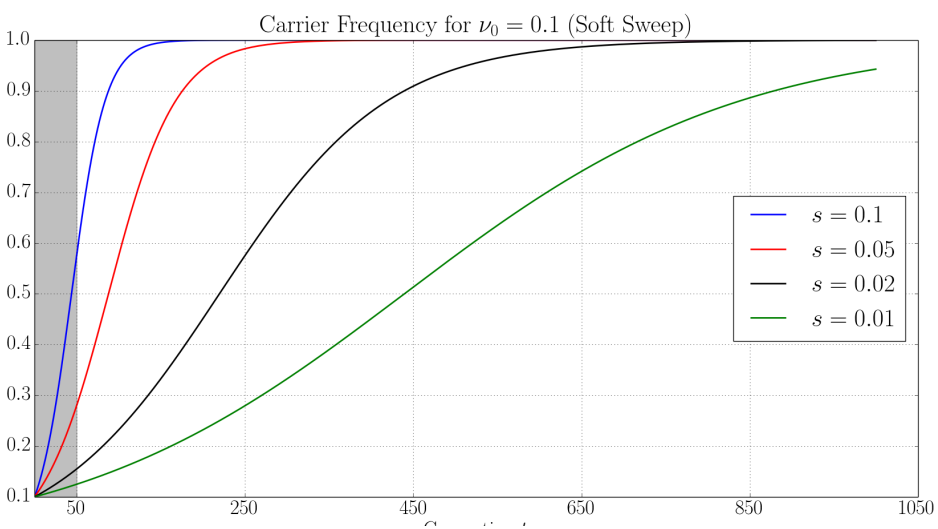
(ii) Using $F = 200$ founder lines a population diploid is created.

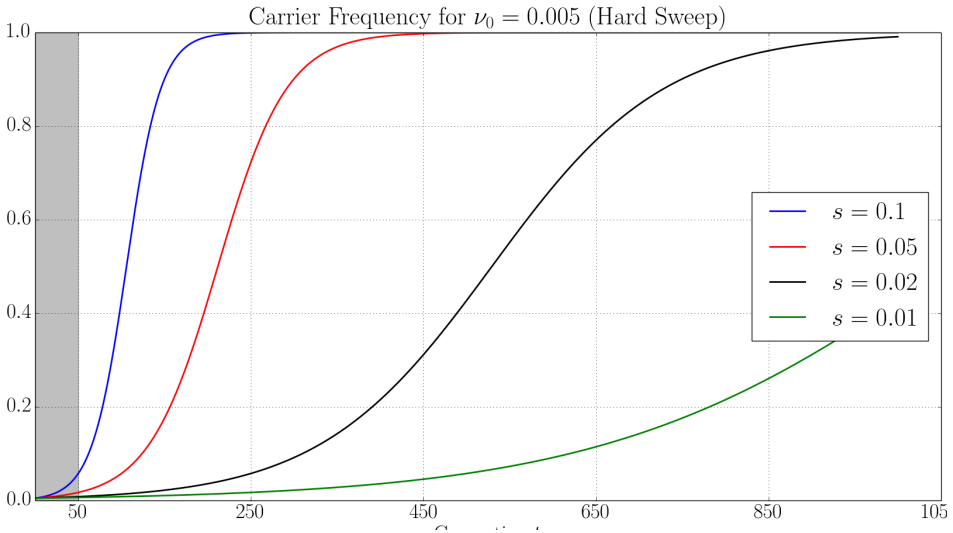
(iii) Using forward simulator population is evolved and AF is sampled every 10 generation for 50 generations.

(iv) This procedure is repeated 100 times for each $s = \{0.1, 0.05, 0.02, 0.01, 0\}$.

Single Locus Logistic Model: Carrier Frequency

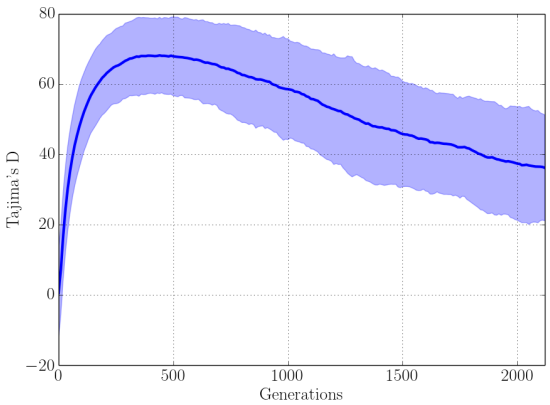
Dynamics of sweep extremely depend on s as well as initial carrier frequency.Sampling times are very important prediction performance!

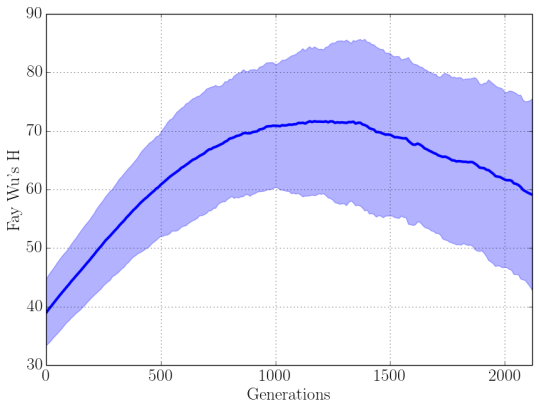


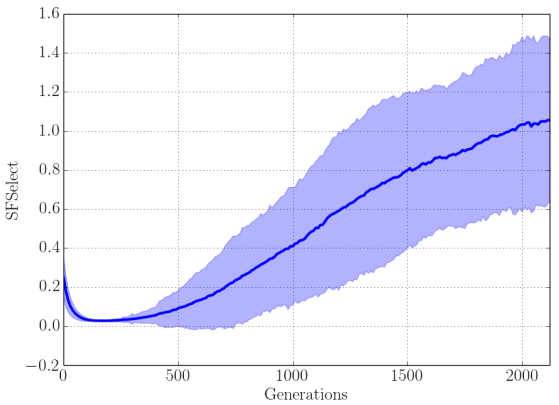


Bottleneck

- side-effect of not tracking new mutations and restricting population to founder-lines.







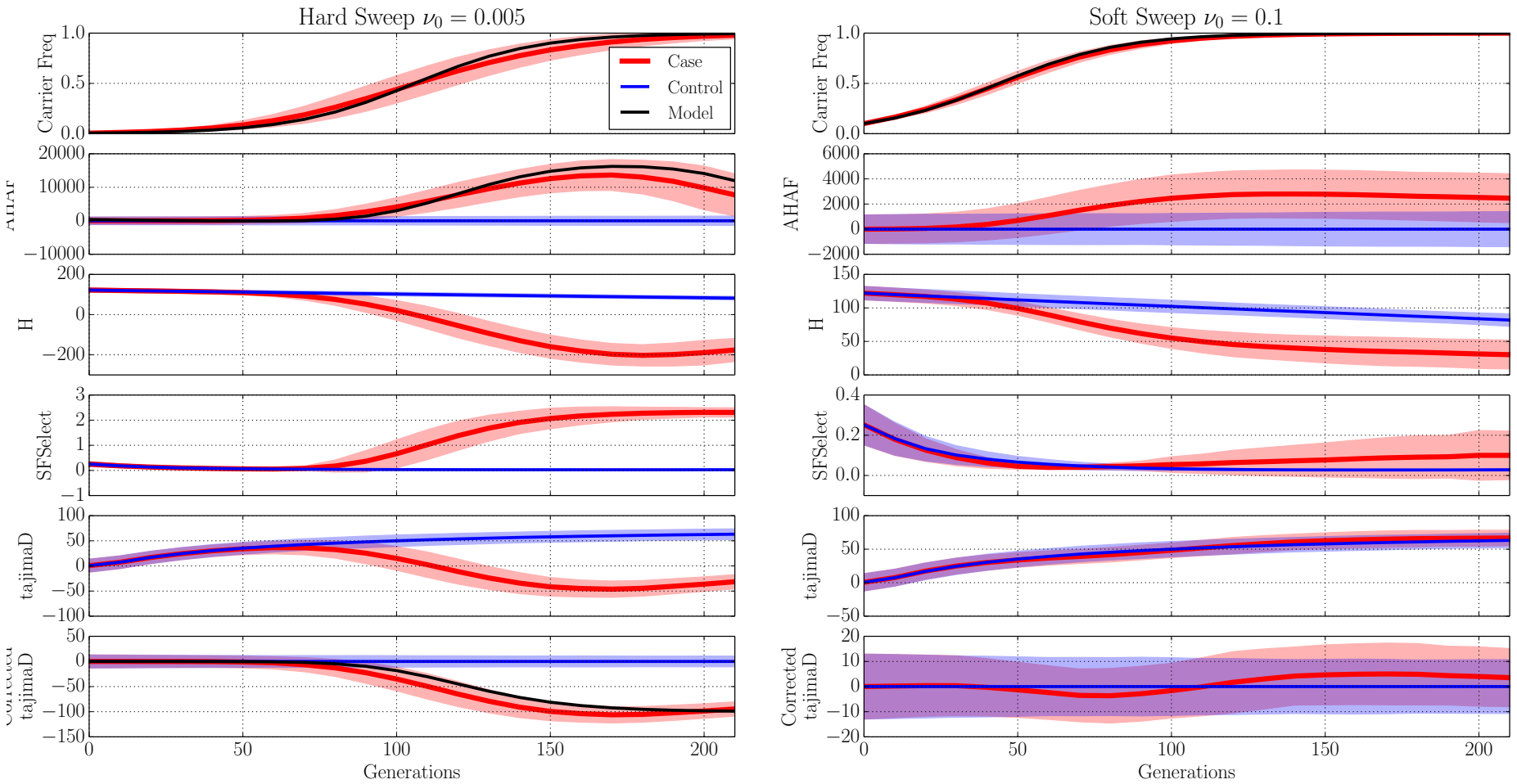


Figure: Mean and 95% CI of 1000 simulations for strong selection.

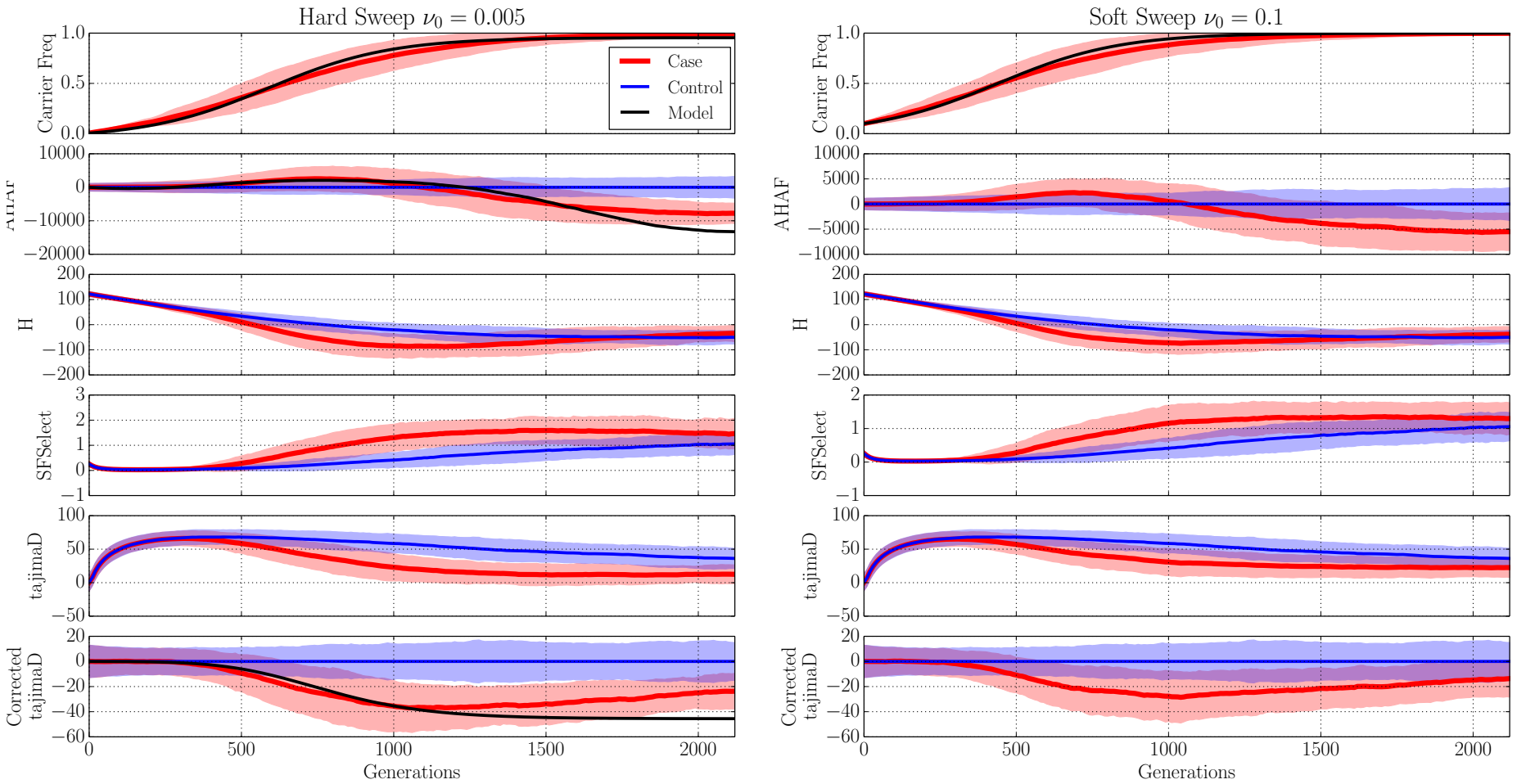
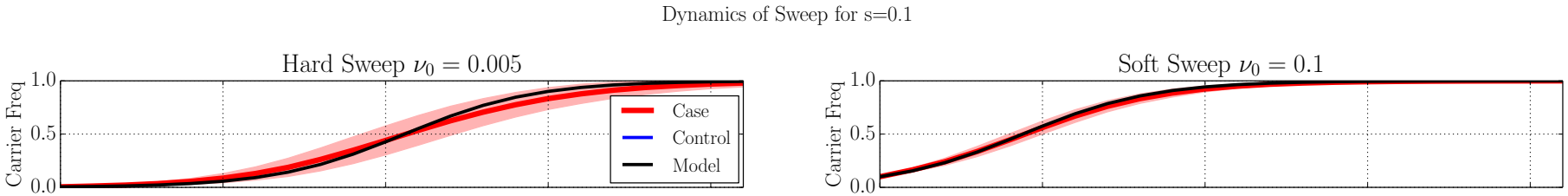


Figure: Mean and 95% CI of 1000 simulations for weak selection.

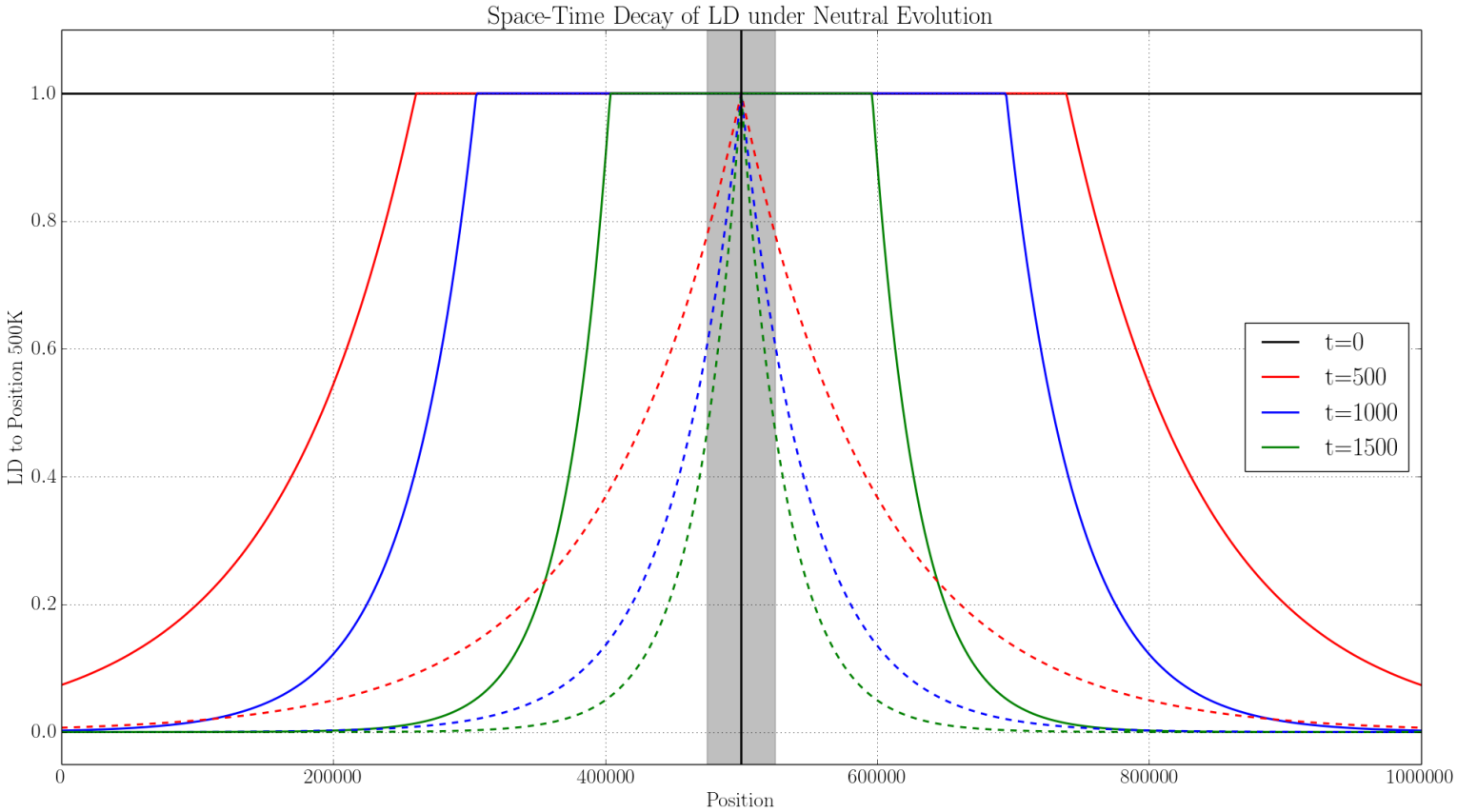
Single-Locus Least-Squares Method I

1. Model is consistent with observations



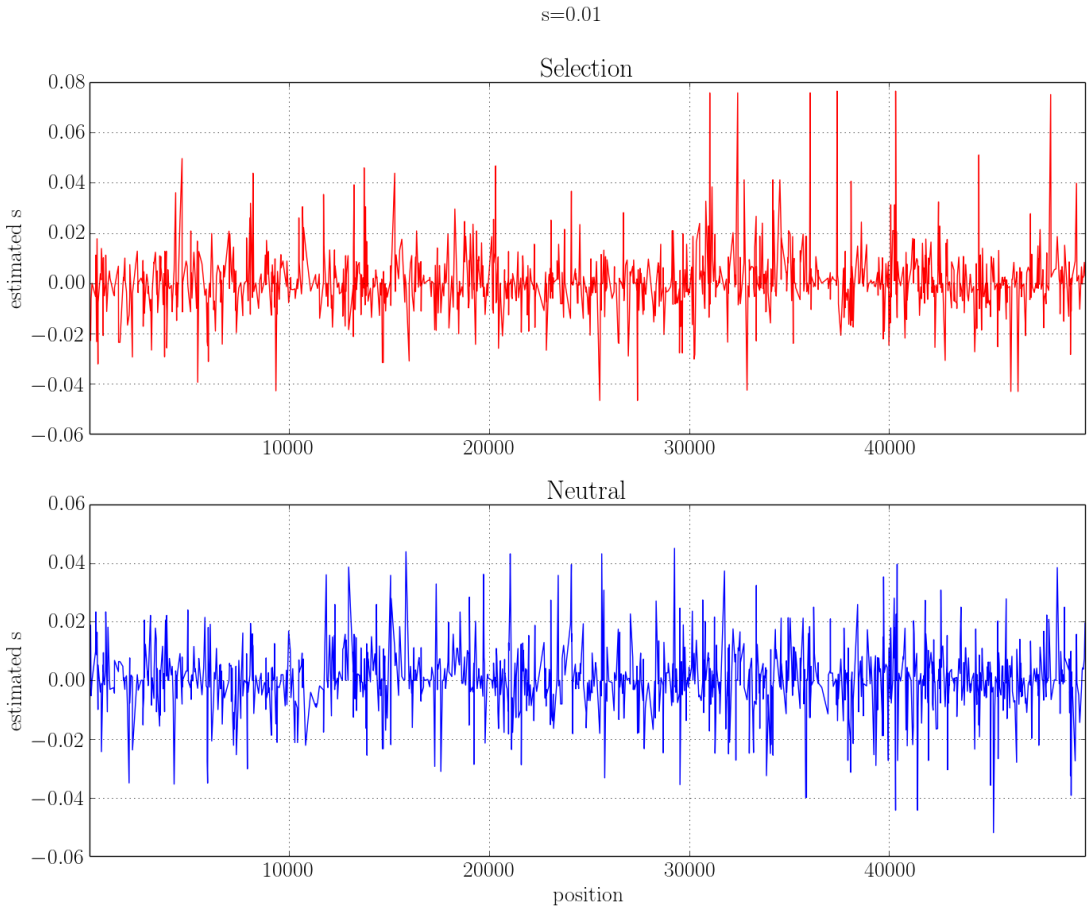
Single-Locus Least-Squares Method II

2. strong linkage in a window



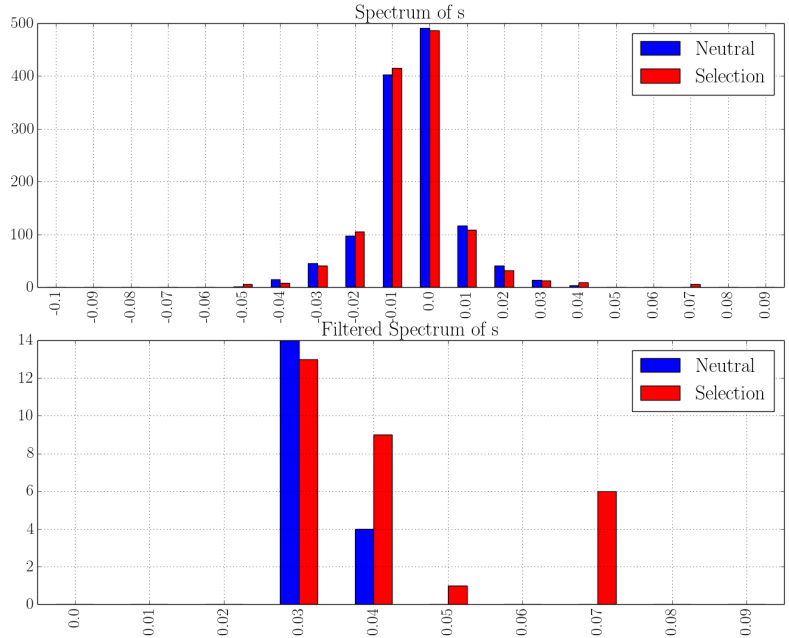
Single-Locus Least-Squares Method III

3. Estimating s at each site



Single-Locus Least-Squares Method IV

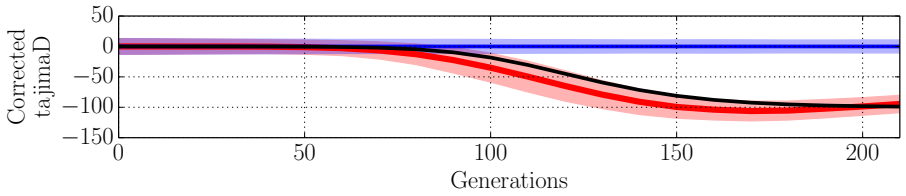
4. spectrum of $\hat{s}$ for a window

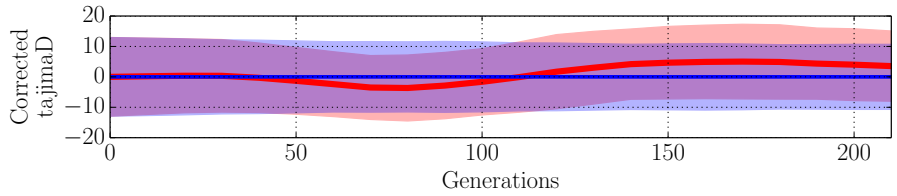


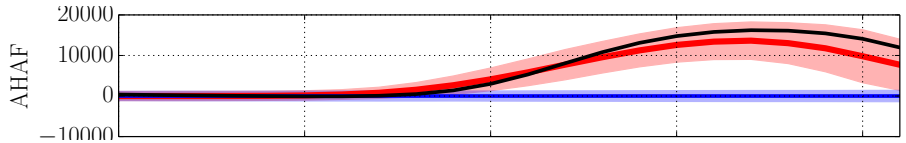
5. We considered avg of top $\hat{s}$ as a predictor of selection for a window.

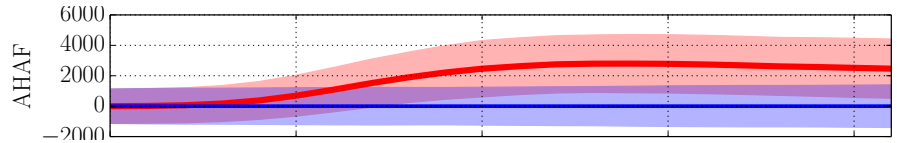
Tajima's D and Fay Wu's H

1. After correcting observations for bottleneck effect the model look like observations, but it has a higher variance.





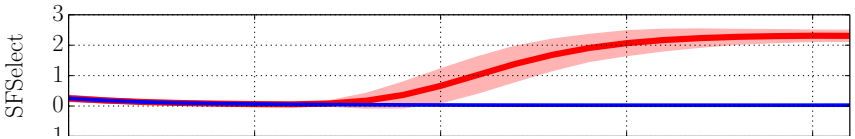


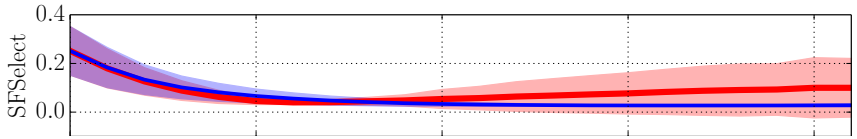


2. The parametric models assumes hard-sweep, so the model become ivalid in soft sweep.

SFSelect and Gaussian Process

1. SFSelect process is a monotone process, so we summed all the values in the time series to get a predictor for selection.





2. GP is the state-of-the art model, proposed by Terhorst et al, which fits a Gaussian process on the time series data.

Experiments

- for each setting we performs 200 simulations, (100 neutral and 100 selection), and predictive performance of all the methods in detecting selection.
- We computed ROC curve and defined power of a method as area under ROC curve when False-Positive rate is less than 0.1.

Summary

- Behaviour of different population statistics in time is studied.
- A method based on single locus AF is proposed and shown to have superior performance than multi-locus and traditional methods.
- Analysis of real data and locating genes in the genome is our next step.

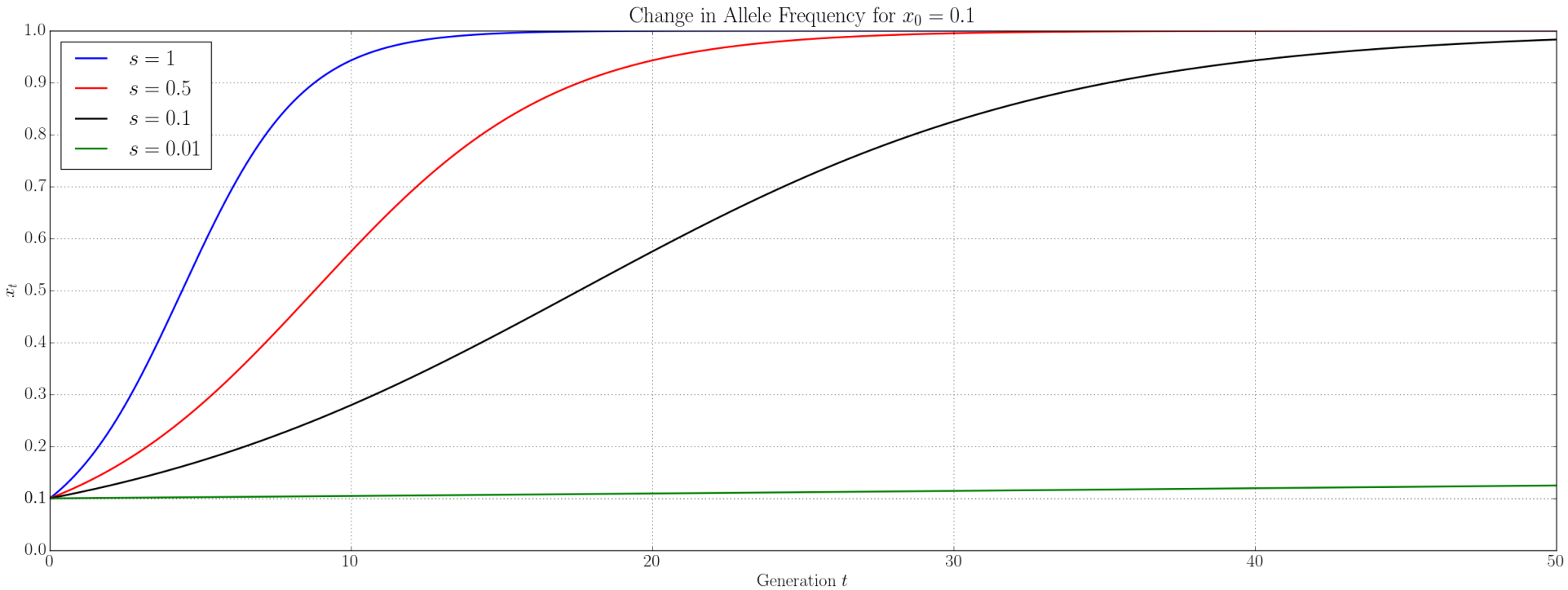
Thanks!

Single Locus Model: Carrier Frequency

- By differentiating update equations ($x_{t+1} = x_t + \frac{sx_t(1-x_t)}{2+2sx_t}$ w.r.t. t and solving differential equation, we have

$$\nu_t = \sigma\left(st/2 + \eta(\nu_0)\right)$$

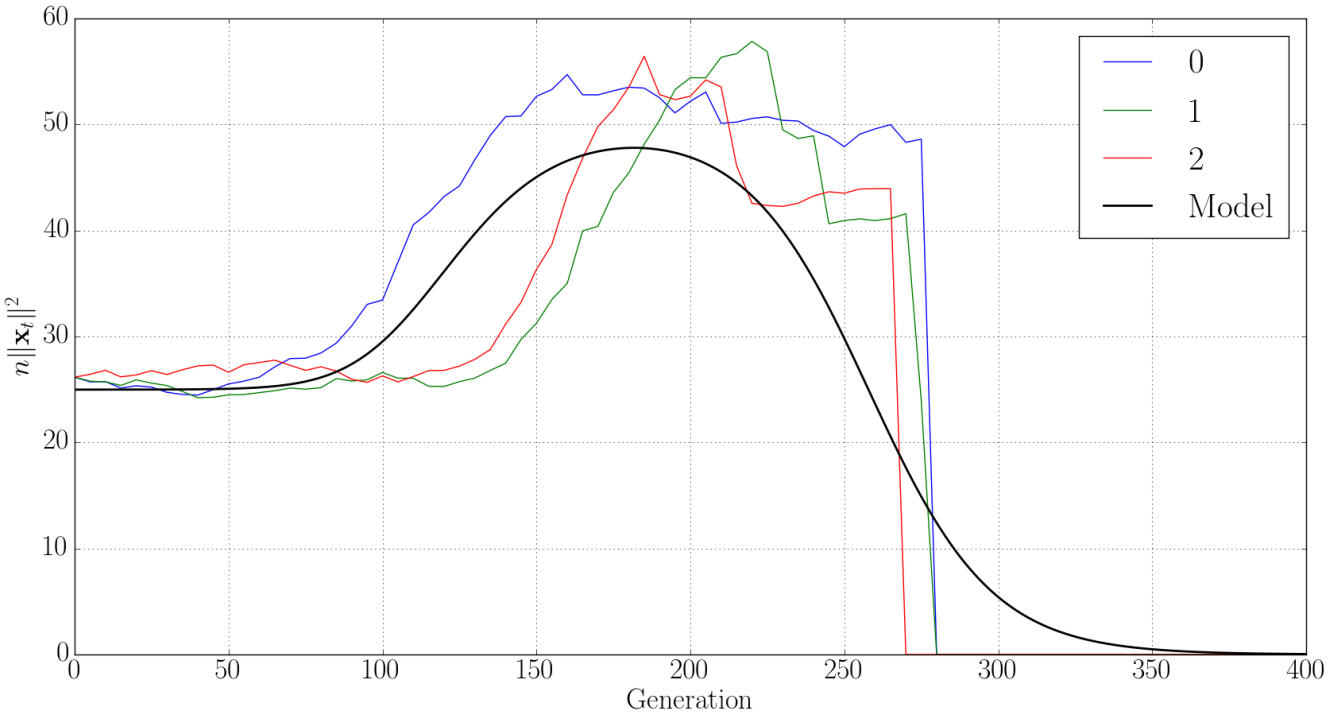
where $\sigma(.)$ is logistic function and $\eta = \sigma^{-1}$ is the logit function and ν_t is the frequency of the carrier at time t.



Multi Locus Model: Average Haplotype Allele Frequency

$$\mathbb{E}[\text{1-HAF}(t)] = \|\mathbf{x}_t\|^2 \approx \theta\nu_t \left(\frac{\nu_t+1}{2} - \frac{1}{(1-\nu_t)n+1}\right) + \theta(1-\nu_t)\left(\frac{n+1}{2n} - \frac{1}{(1-\nu_t)n+1}\right)$$

where $\mathbf{x}_t$ is vector of AF at time t and $\nu_t = \sigma\left(st/2 + \eta(\nu_0)\right)$.



Critics to GP

- Its too complex, likely to overfit with small number of iid replicates.
- Although the likelihood model is based on different parameters, in practice, it can learn only one parameter at a time.
- not tractable, its time complexity is quartic!
- worse, each iteration requires `maxGeneration` recursion which makes it very hard to analyse late epochs of sweeps.
- In addition to PoolSeq data, it requires initial population haplotypes.
- Despite its elegant theory, it has not compared with classical methods.
- In practice, single locus scan is performed and multi-locus (with 3-7 seg. sites.) model is fitted at regions of interests.