Identifying Selection in Experimental Evolution

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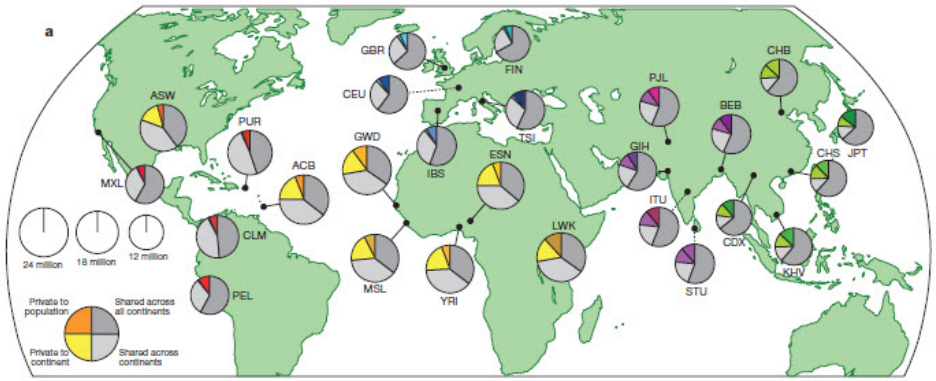
Introduction

- Next generation sequencing has made whole-genome & whole-population sequencing possible.



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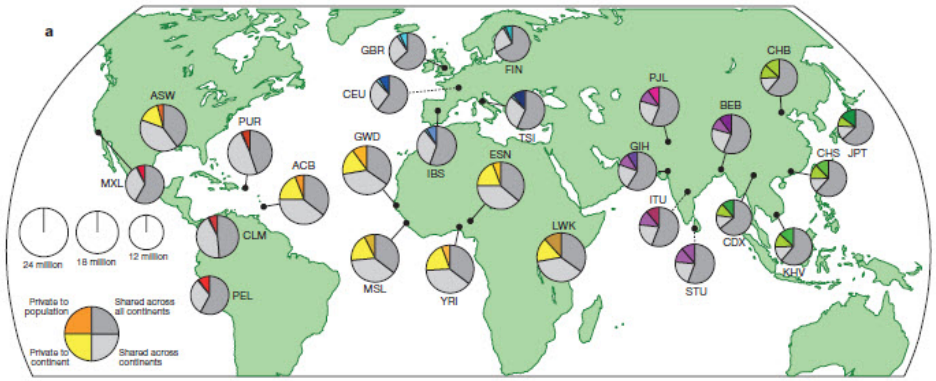

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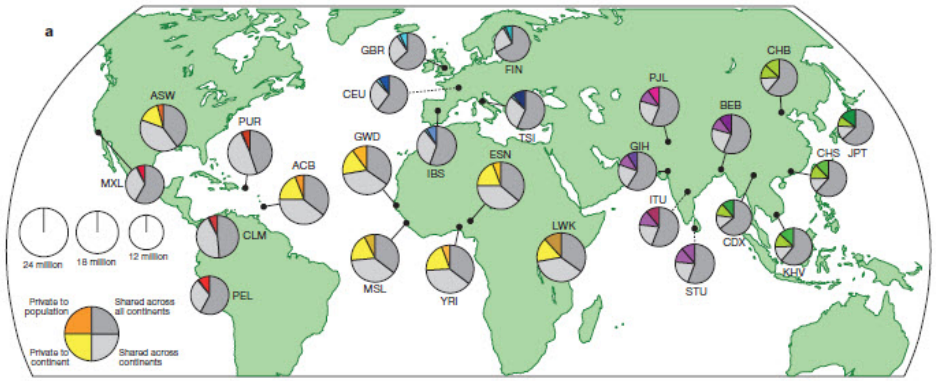

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- For organisms with "short-generation-time", (e.g., yeast, *E. coli*, *D. melanogaster* etc.) it is also possible to collect time-series data of population.
- Given rise of these modern datasets (population longitudinal data), new techniques required to answer classical population genetics questions on real data.

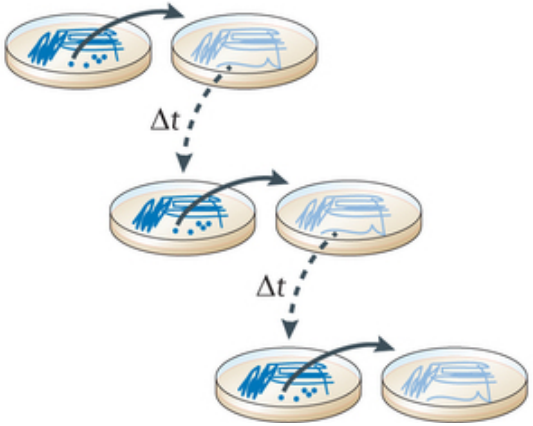
Goals

Design a method which

- Detect regions under selection.
- Localizing adaptive allele within the candidate region.
- Estimating selection parameters.

Experimental Evolution (EE)

- EE is a long tradition in biology, which studies the phenotype in time by reducing environmental effects .



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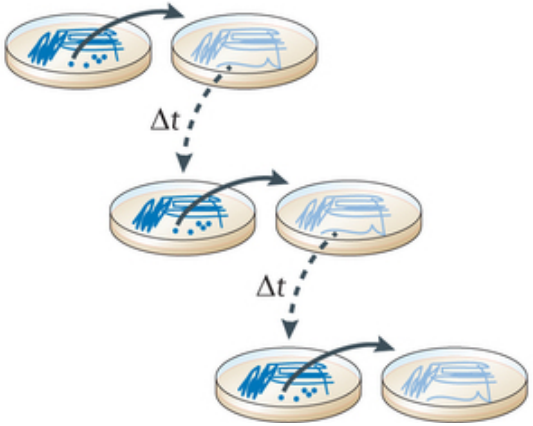

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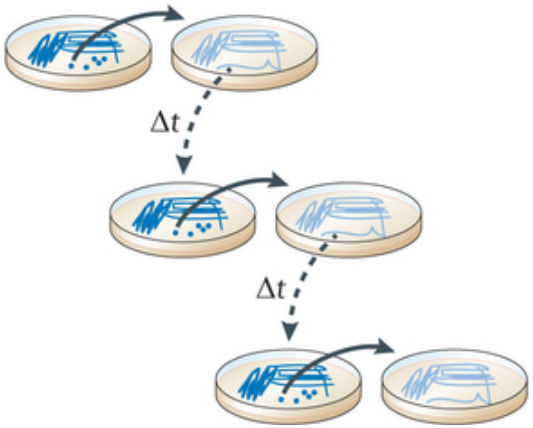

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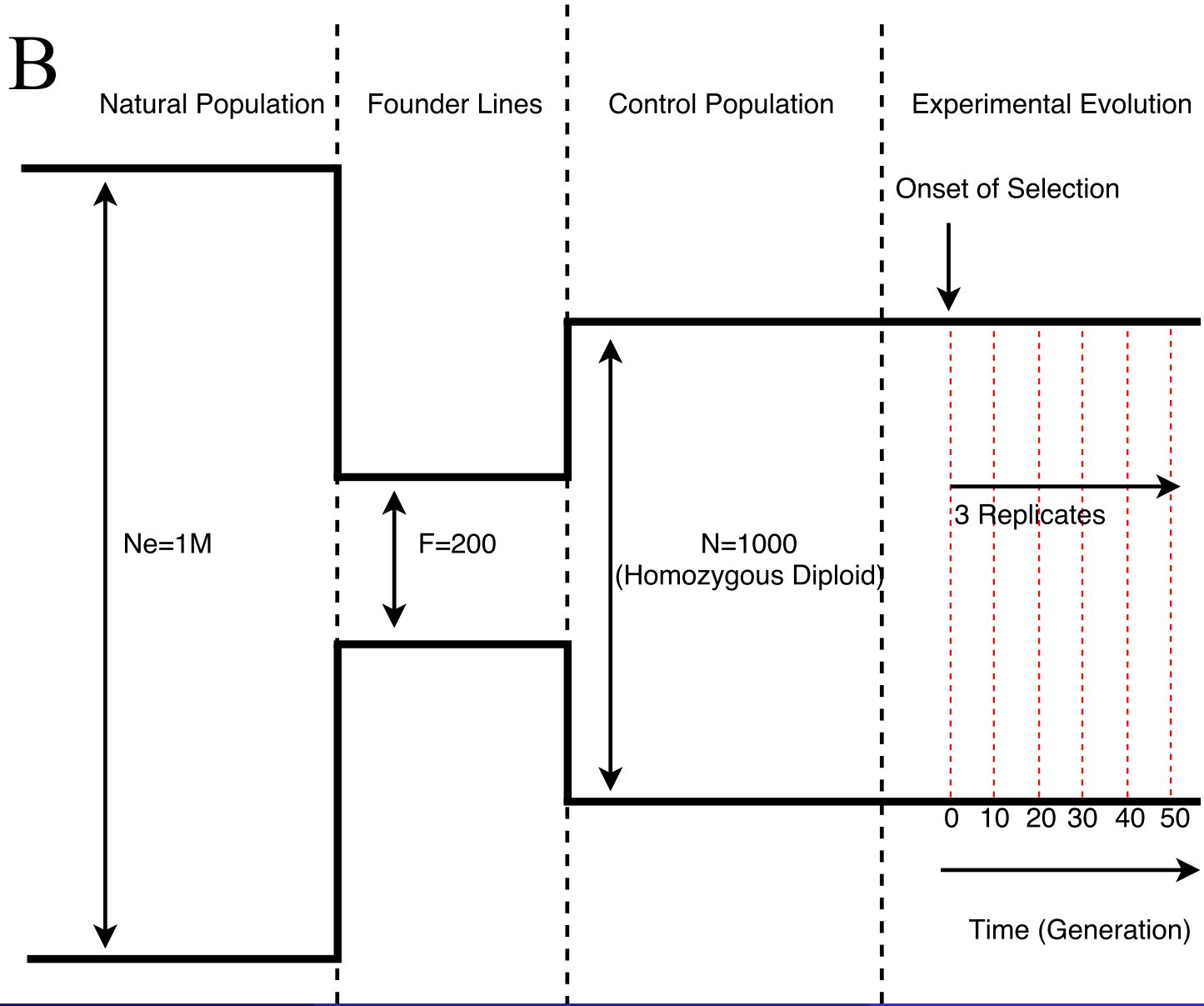
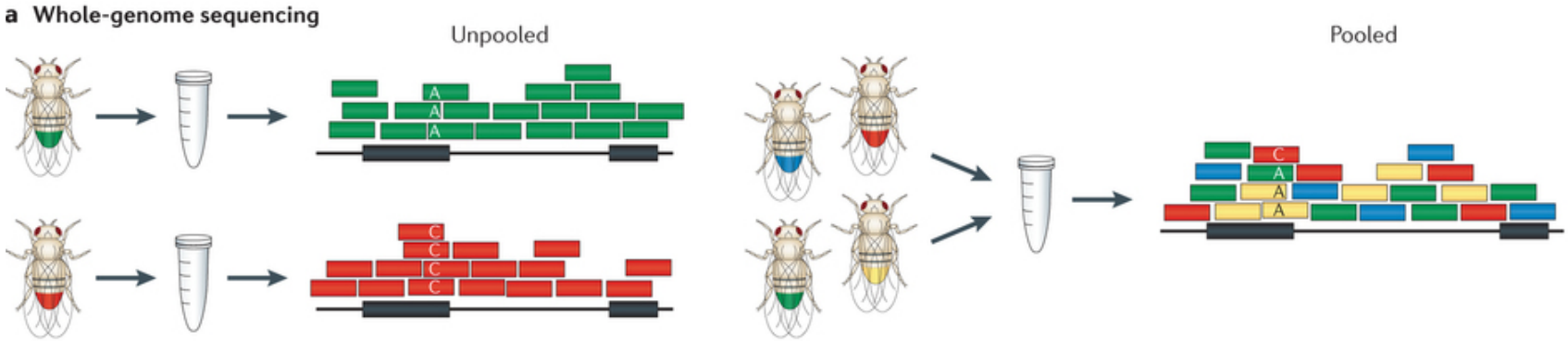
- In a controlled environment, EE evolves a homogeneous population.
- Let phenotype of interest be the response to a selection pressure, e.g., response to
  - antibiotic
  - low oxygen conditions
  - hot and cold temperatures
  - etc.

An experiment design for *D. melanogaster*



Whole-Genome Whole-Population Sequencing

- Pooled-Sequencing



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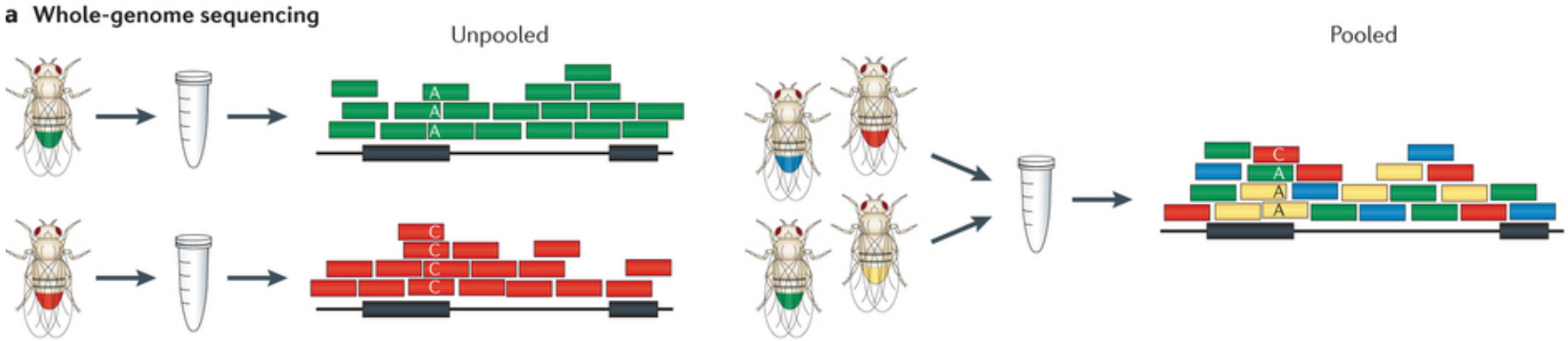

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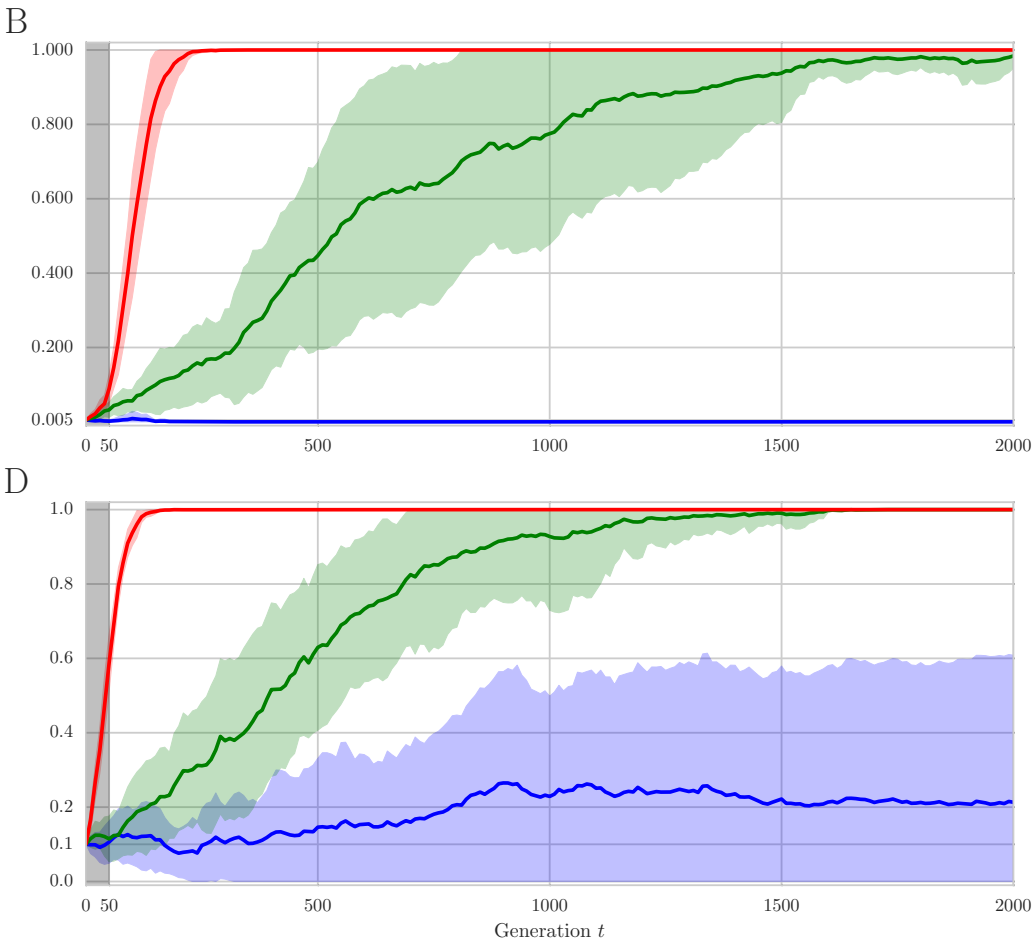
- Implication: only population allele frequency can be computed.

Dynamic of population allele frequency

under different initial conditions and *selection strengths* frequency change differently



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- Suppose we have sequenced a whole (diploid, size=N) population every generation (eg, for 6 generations) and exact allele frequency are given.

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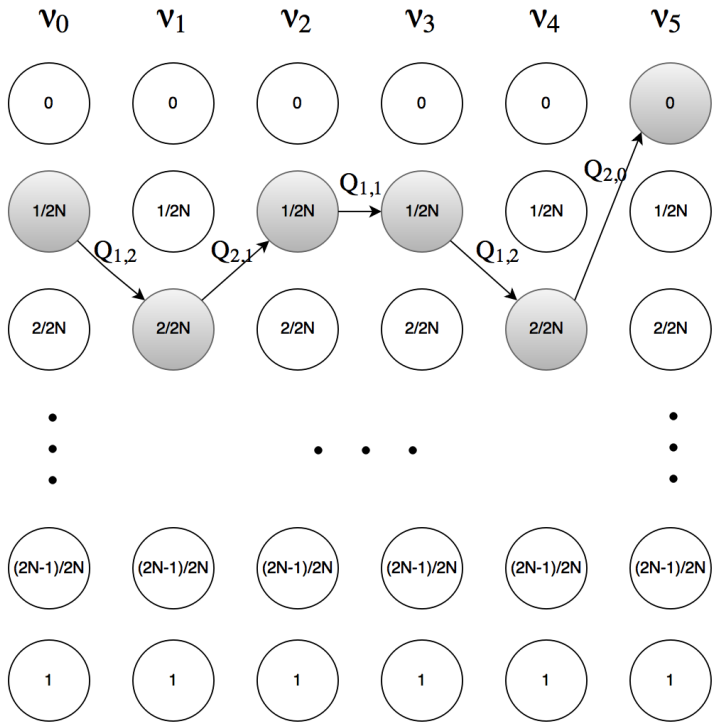
- A discrete-time discrete-state model, Markov chain, can generate such a data.



$$P(\nu_0, \dots, \nu_5) = Q_{1,2}\ Q_{2,1}\ Q_{1,1} Q_{1,2}\ Q_{2,0}$$

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- perform maximum likelihood to find $\hat{s}$, $\hat{h}$.
- compute likelihood ratio, M statistic for each SNP:

$$M = \frac{\text{likelihood of data as if being under selection with } \hat{s},\hat{h}}{l\text{ikelihood of data as if being neutral}}$$
$$= \frac{\mathcal{L}(\hat{s},\hat{h}|\{\nu_0,\ldots,\nu_5\})}{\mathcal{L}(0,0|\{\nu_0,\ldots,\nu_5\})}$$

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- Similarly,

$$H = \frac{\text{likelihood of read-count data as if being under selection}}{\text{likelihood of read-count data as if being neutral}}$$

Composite Likelihood for a Region (I)

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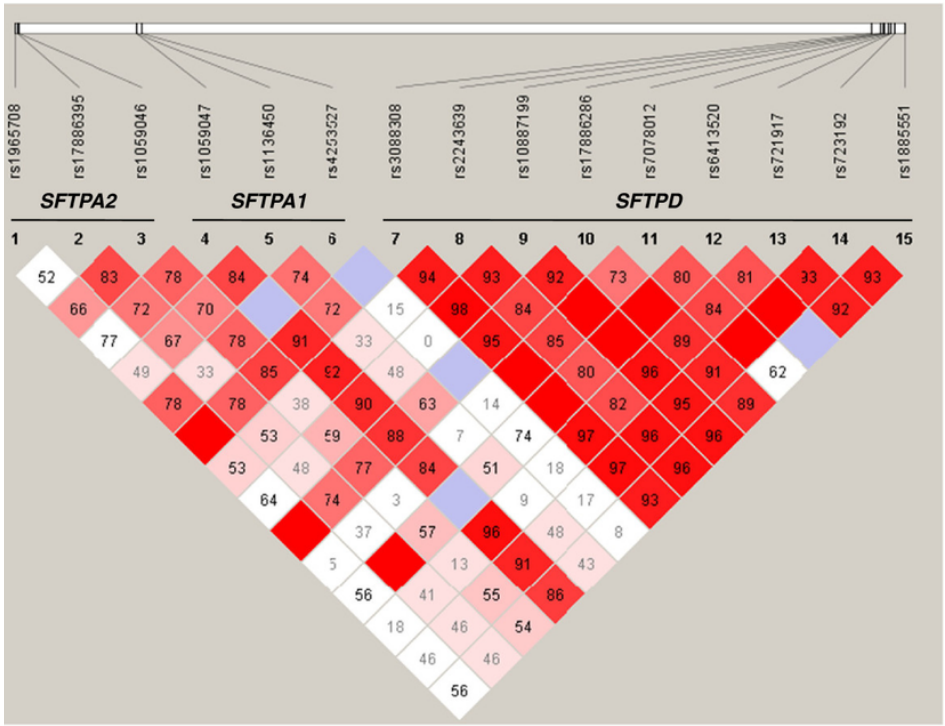
- For a small region with L variants we can simply take the max score in the region, which is prone to false positives.
- We know that variants are correlated



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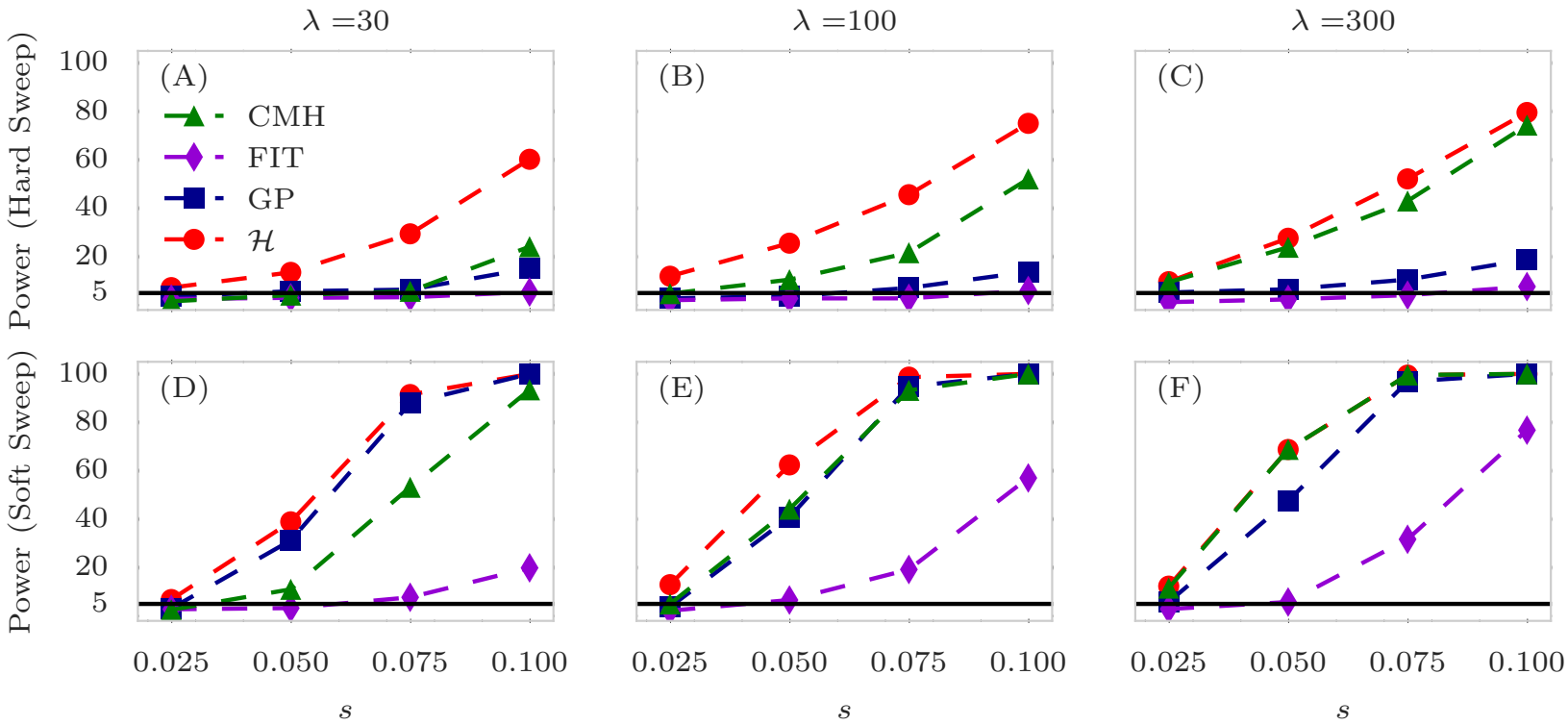
- Computing joint likelihoods of SNPs is infeasible (haplotypes are required) and intractable (requires estimating covariance).
- A heuristic is to compute composite (aka, pseudo) likelihood of the region L to reduce false-positives

$$\mathcal{H} = \frac{1}{|L|} \sum_{\ell \in L} H_\ell$$

Performance in Detecting Regions under Selection

Each point represent power (TPR when FPR$\leq$0.05) of detection in 1000 simulations (500 neutral, 500 selection) of a 50Kbp window, for different coverages.



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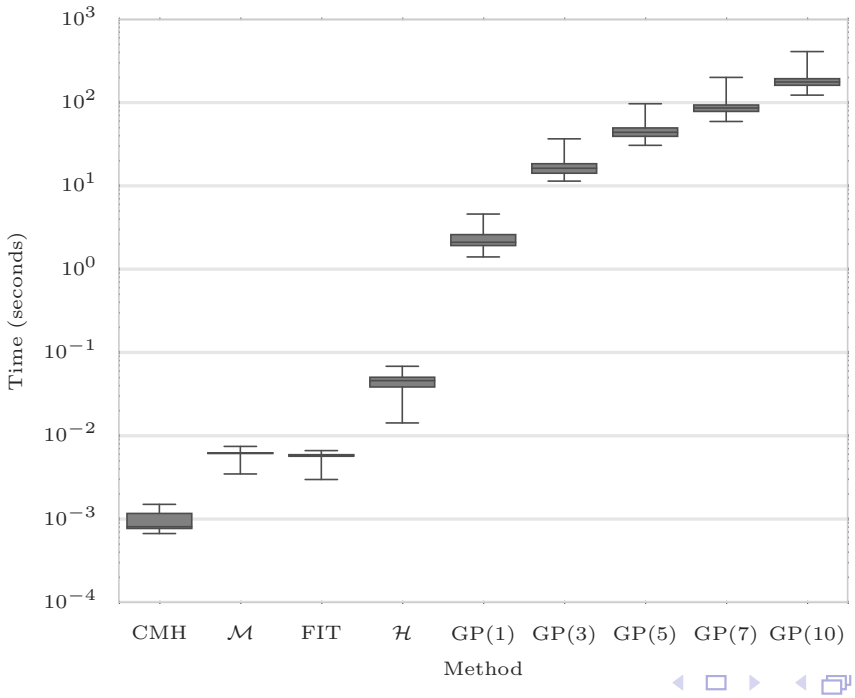
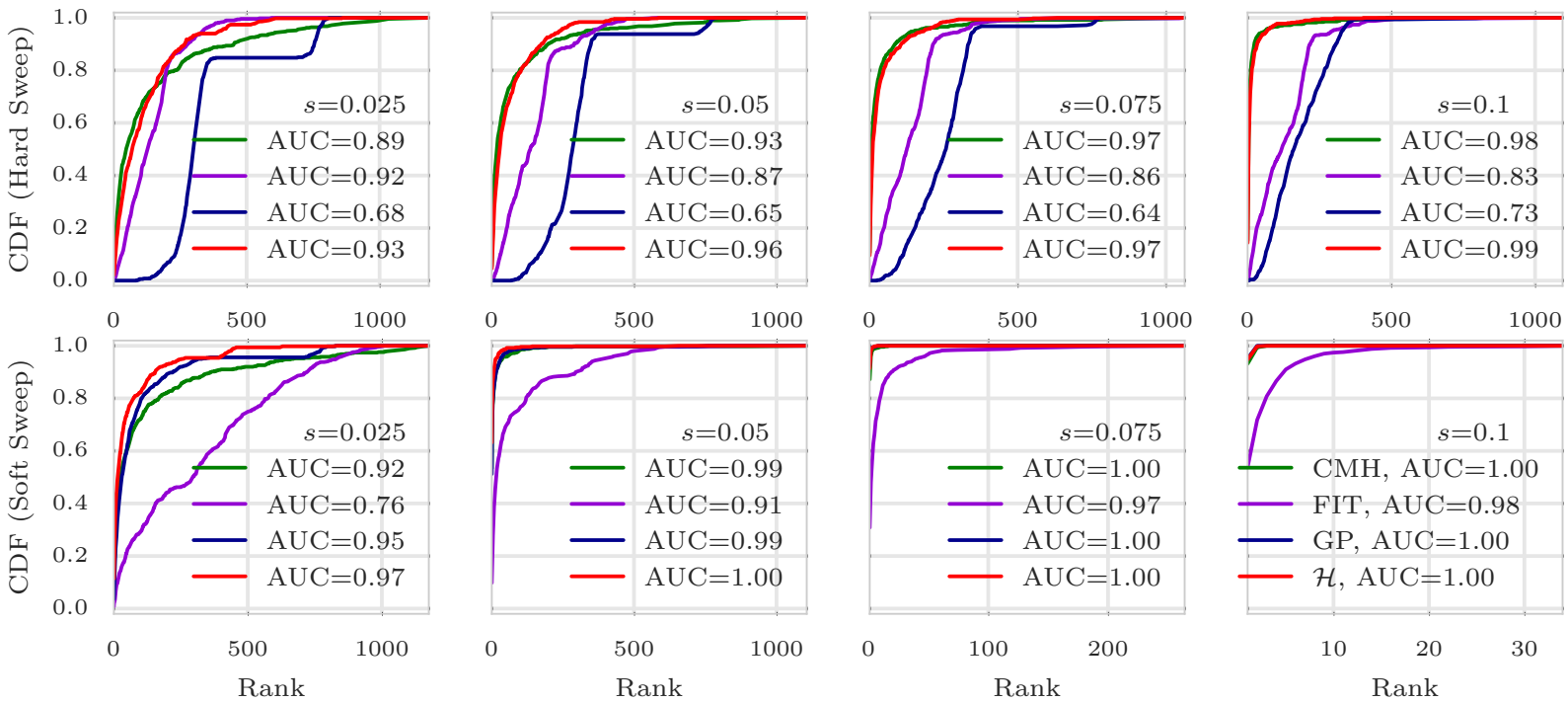
(iii) Run time is better or comparable with others.



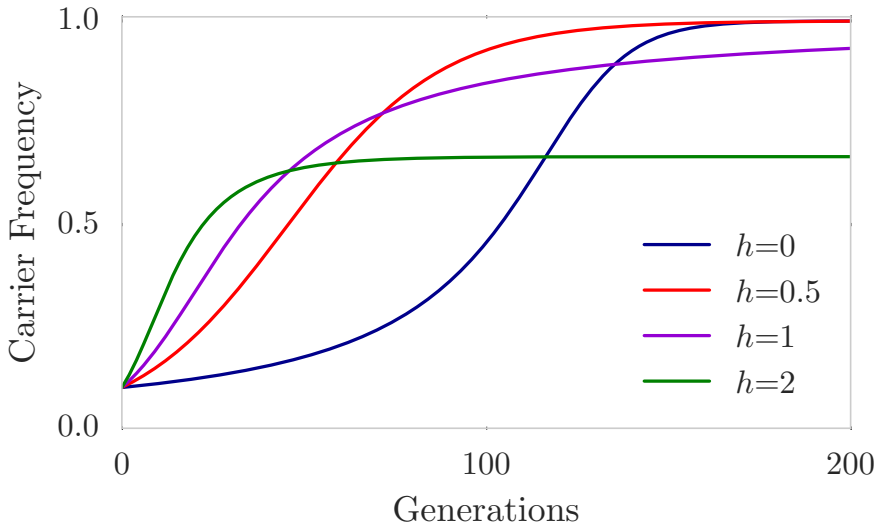
Localizing favored allele

Each curve depicts cumulative distribution of the rank of favored allele among (≈ 1150) variants, in 500 simulations.



Estimating parameters (I)

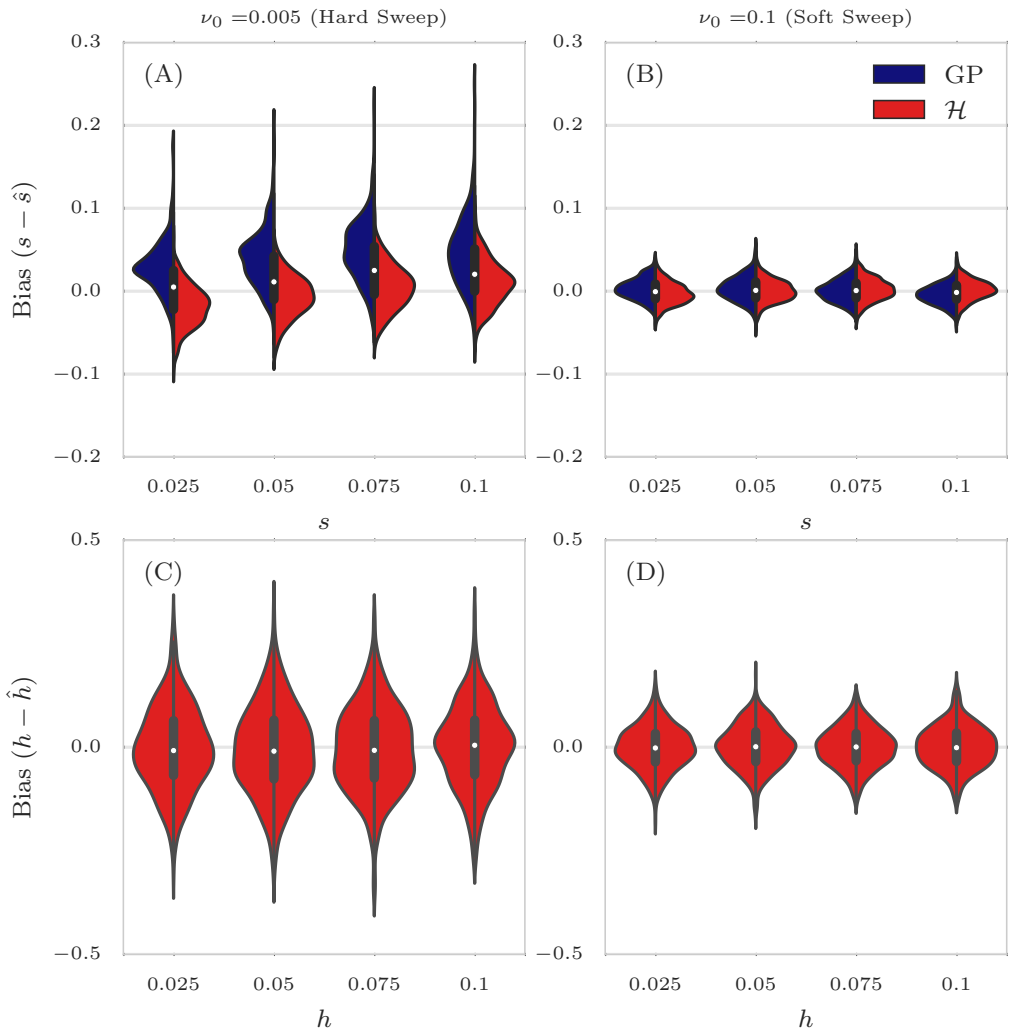
Our model estimates strength of selection s and overdominance h parameter for each variant.



- $h = 0$: recessive adaptive allele
- $h = 0.5$: directional selection
- $h = 1$: dominant adaptive allele
- $h > 1$:overdominance

Estimating parameters (II)

Distribution of bias of parameters in 500 simulations.



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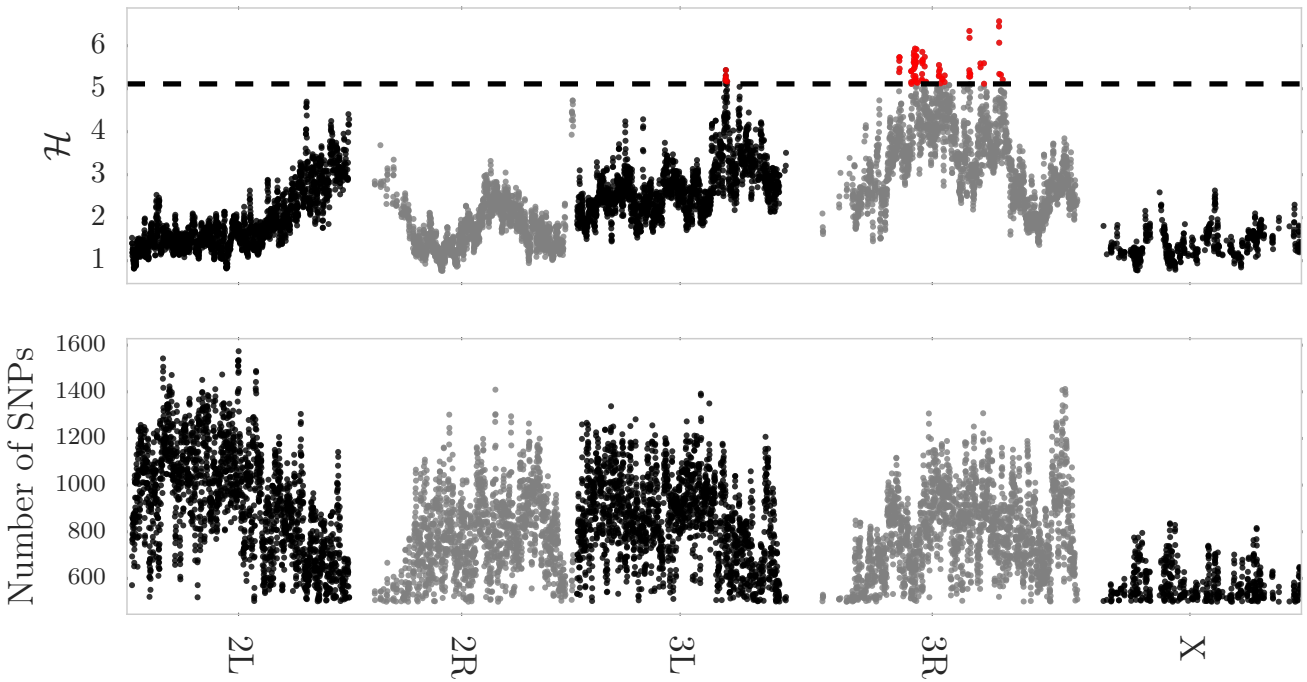
- Genome scan for sliding window size=50Kbp, steps=10Kbp



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- By computing composite likelihood $\mathcal{H}$ statistic is more robust to false positives.
- When initial frequency of the favored allele is low, stronger selection helps detecting selection but makes locating favored allele a harder task.
- Next step is to apply to new dataset with a well defined phenotype, e.g. response to hypoxia.

Thanks!