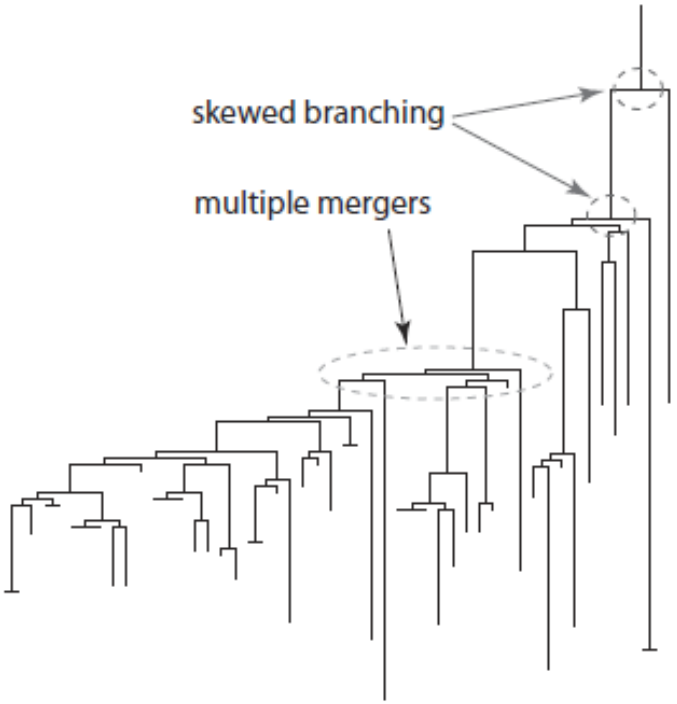
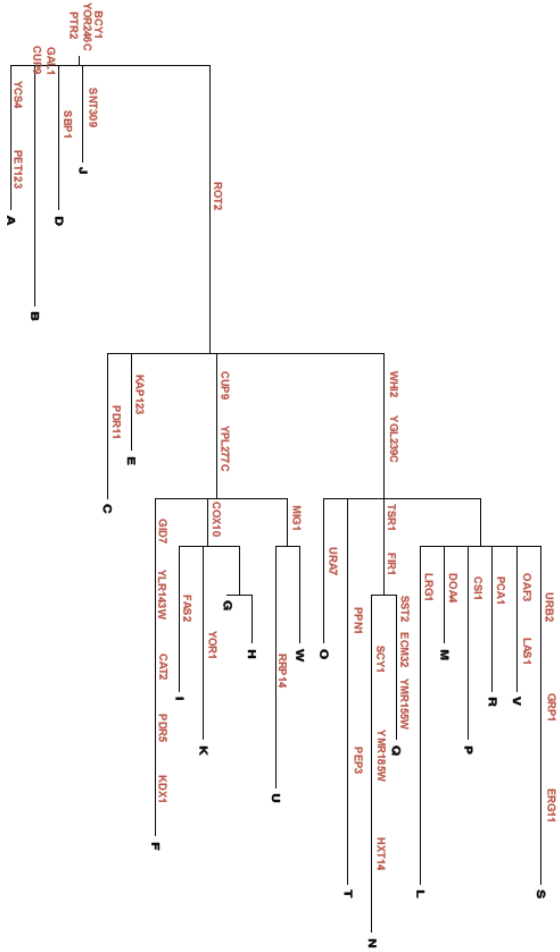
Genetic Diversity When Selection is Pervasive

Michael Desai, Harvard University

Genetic Diversity in the Interference Selection Limit



[Influenza, Neher 2013]

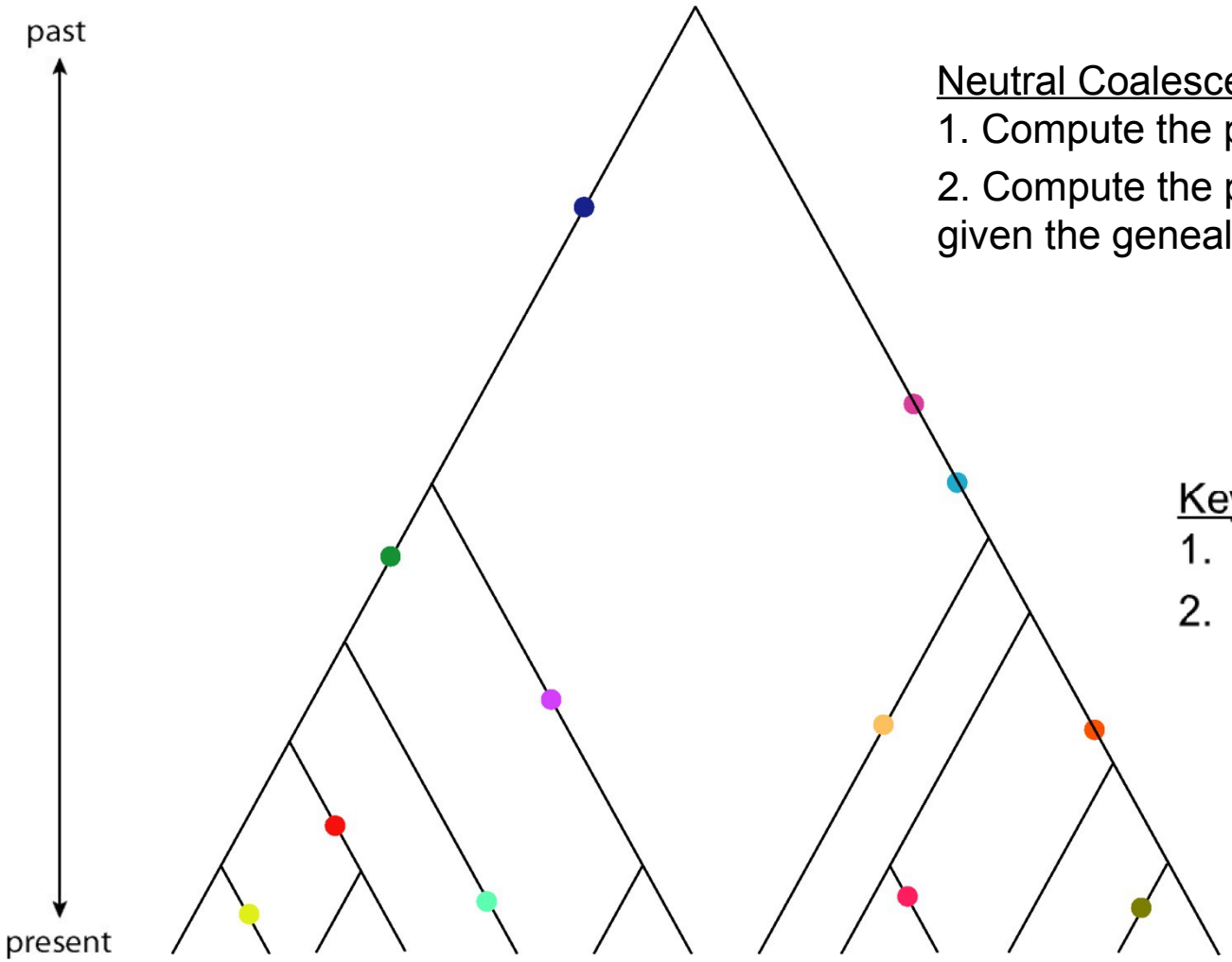


[Experimental Yeast Populations]

Ben Good

How does pervasive natural selection alter patterns of genetic diversity?

Standard methods describe neutral evolution

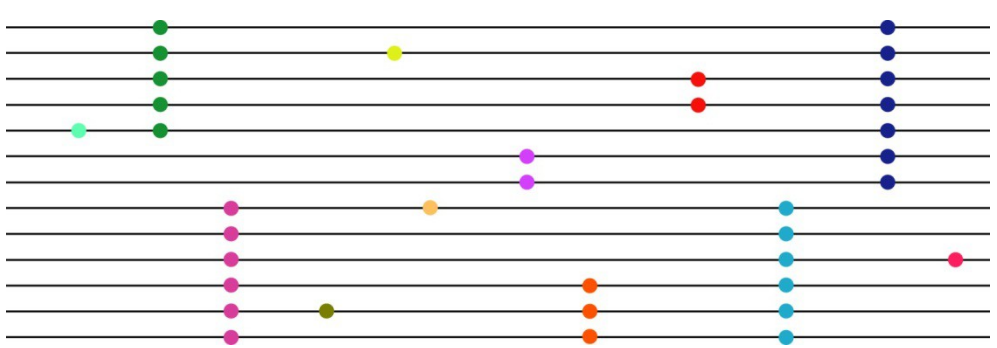


Neutral Coalescent Theory:

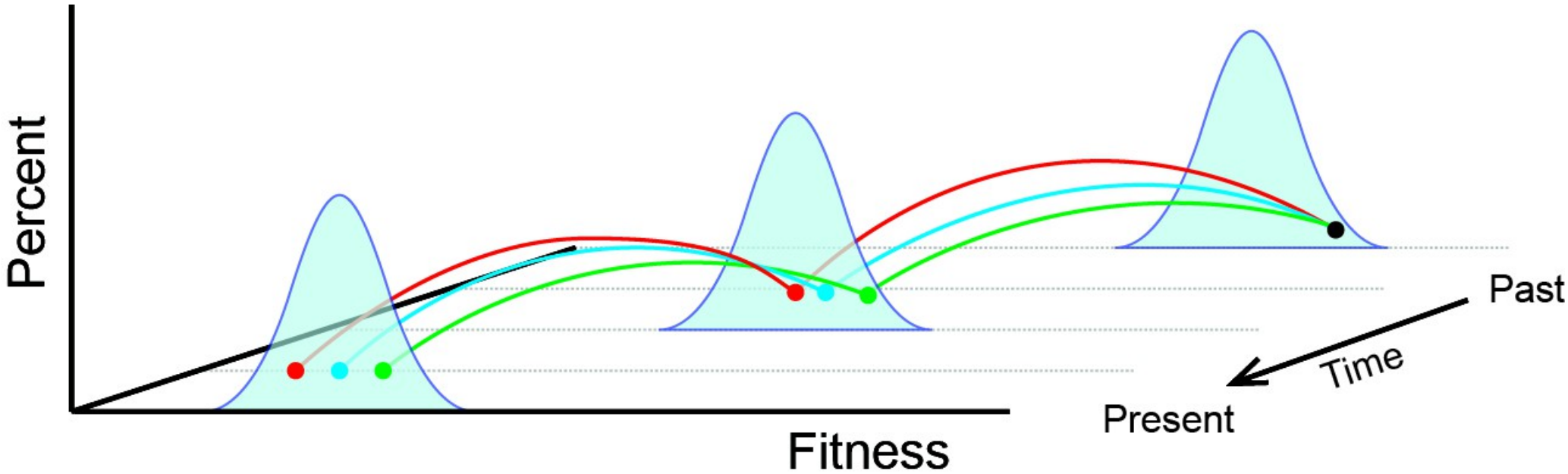
1. Compute the probability of a genealogy
2. Compute the probability of observed diversity given the genealogy

Key Predictions:

1. Diversity $\pi \propto N$
2. Frequency spectrum $f(i) \propto \frac{1}{i}$

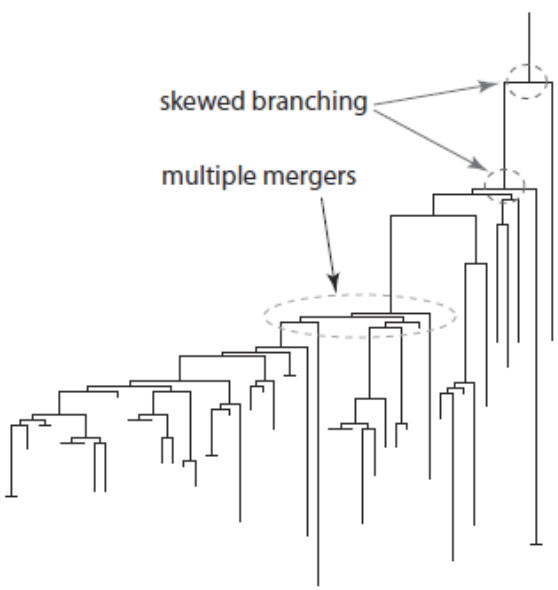


Selection and the Shape of Genealogies



Trace individual lineages through the fitness distribution:

- -Present individuals are descended from the fittest ancestors.
- -Looks like a reduction in population size in the past
- -Multiple mergers become more common
- -Lineages are no longer exchangeable



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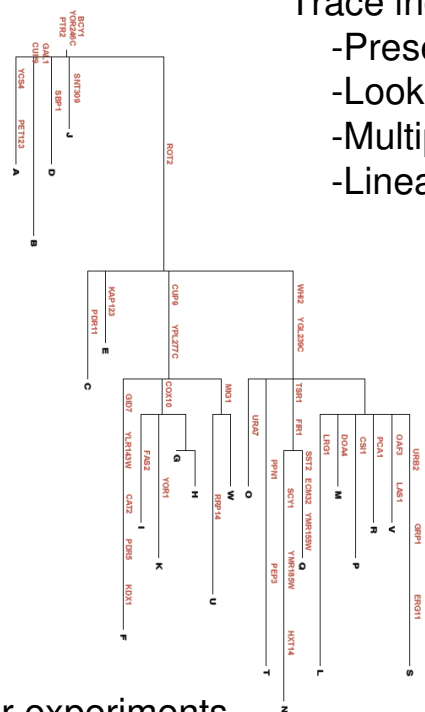


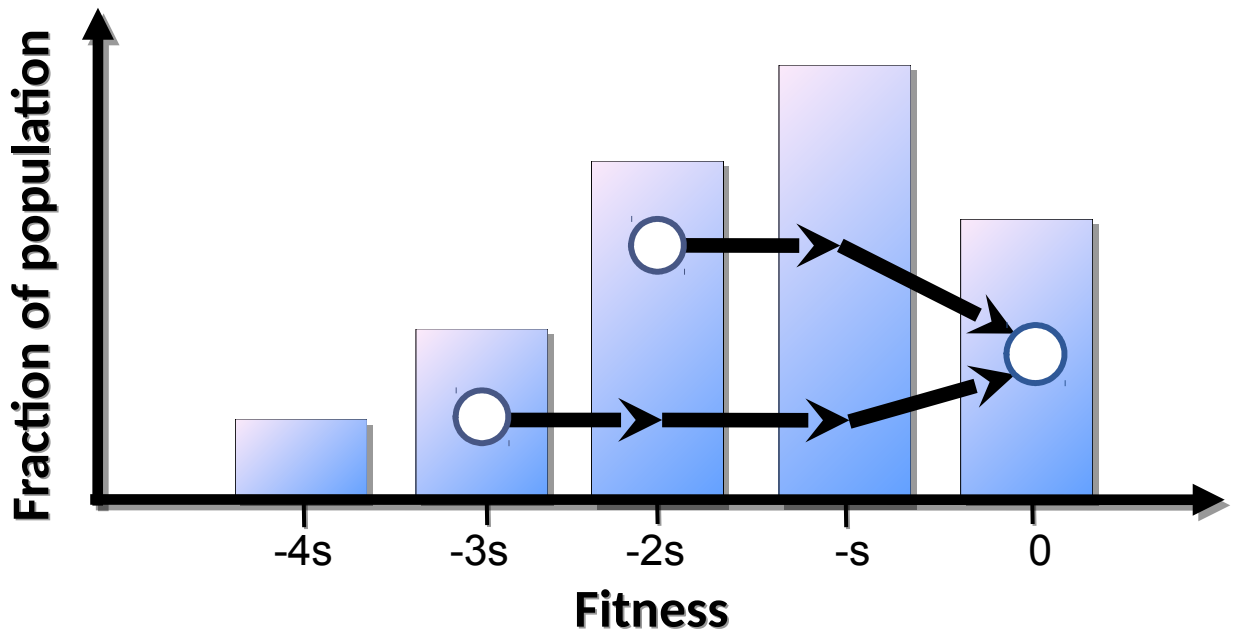
Our experiments

[Good, Walczak, Neher, Desai *PLoS Genetics* 2014]
[Nicolaisen and Desai, *MBE* 2012]
[Walczak, Nicolaisen, Plotkin, Desai, *Genetics* 2012]

How does purifying selection shape diversity?

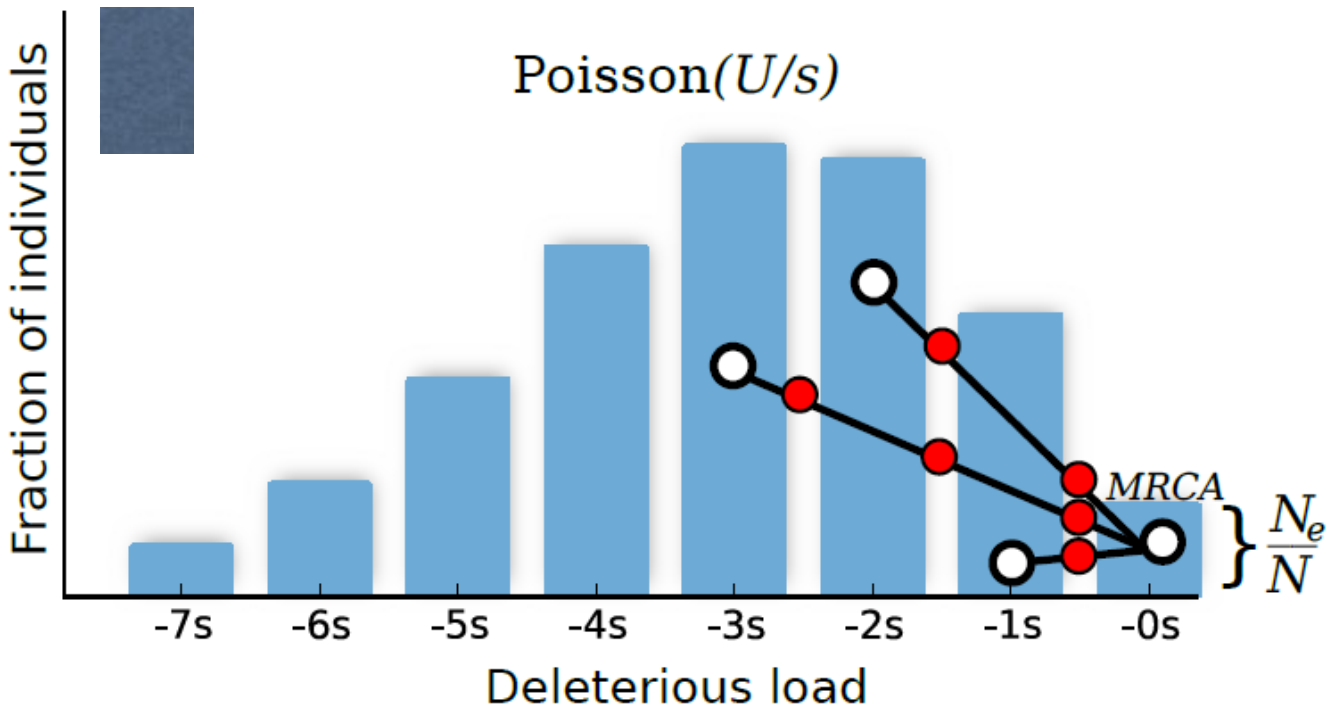
<u>A simple model:</u>
Population size: N
Mutation rate: U
Fitness effects: $\rho(s)$
Recombination rate: R

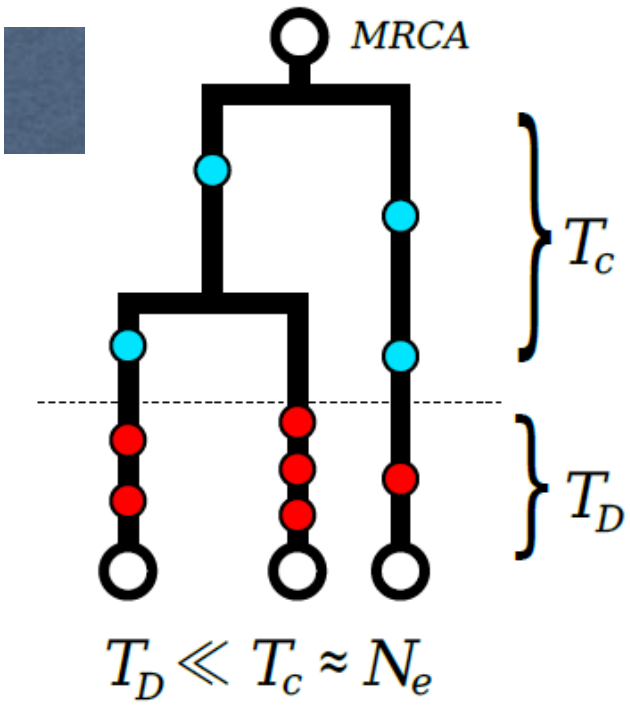
<u>An even simpler model:</u>
Population size: N
Neutral mutation rate: U_n
Deleterious mutation rate: U_d
Fitness effect: s



<u>Structured Coalescent:</u>
Steady state distribution of fitness within the population.
"Migrate" between fitness classes by mutations.
Exchangeability *within* each fitness class.

Strong purifying selection: “Background Selection”

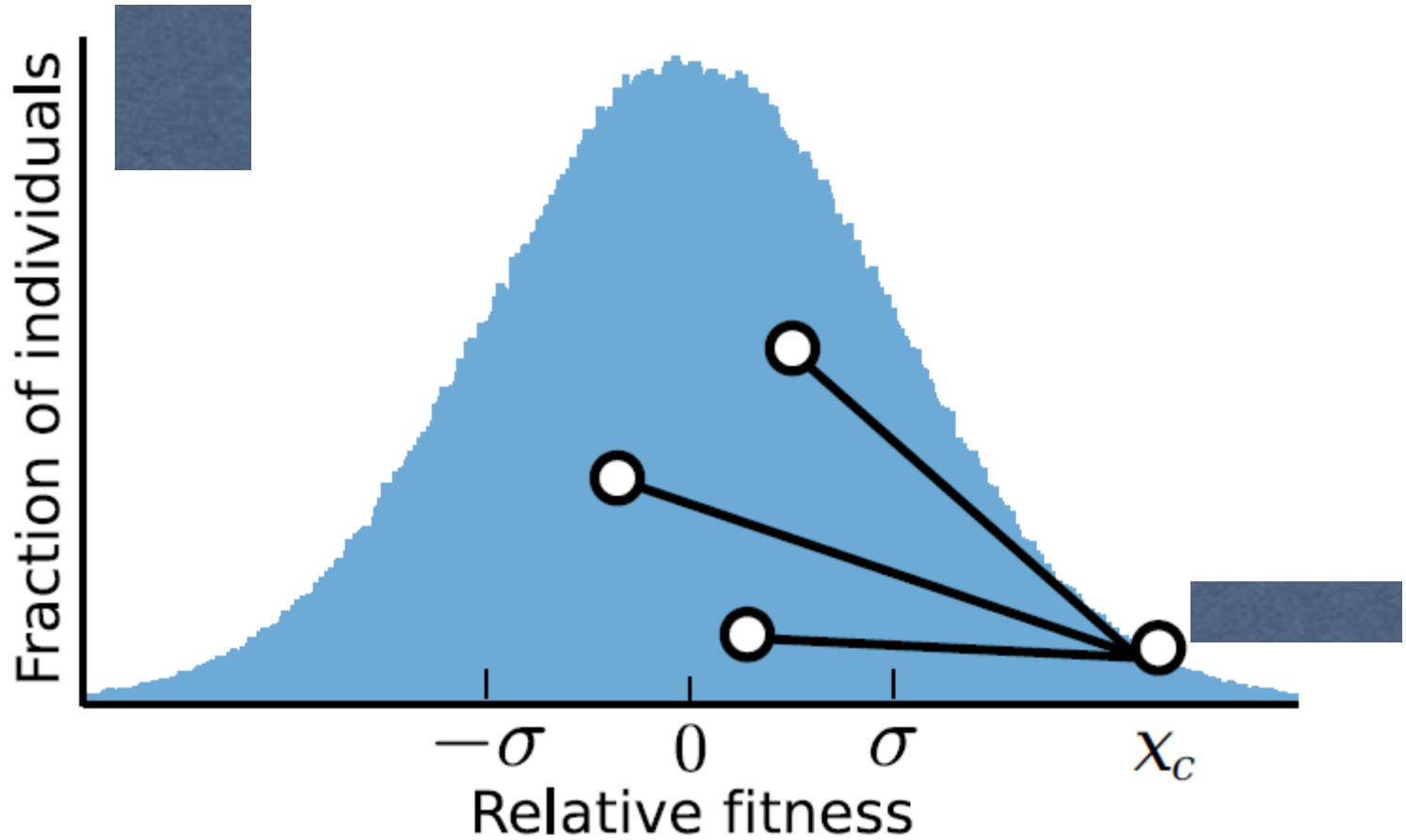




Strong purifying selection reduces effective population size.
Exact in the limit *Ns* ⎵ ∞ while holding *NU/Ns* constant.

Corrections for large but finite *Ns* from the S*tructured Coalescent*

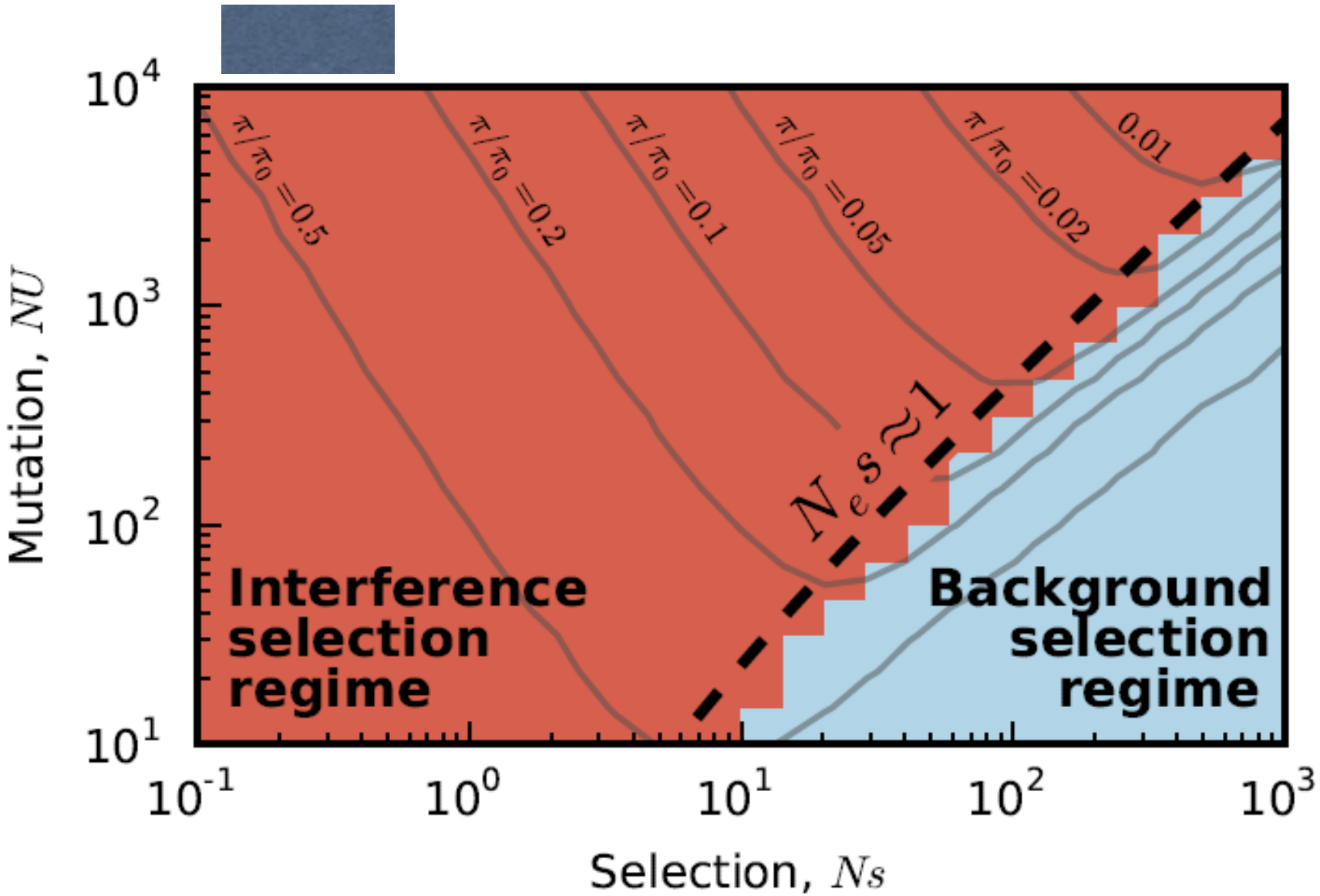
What about weak or pervasive selection?



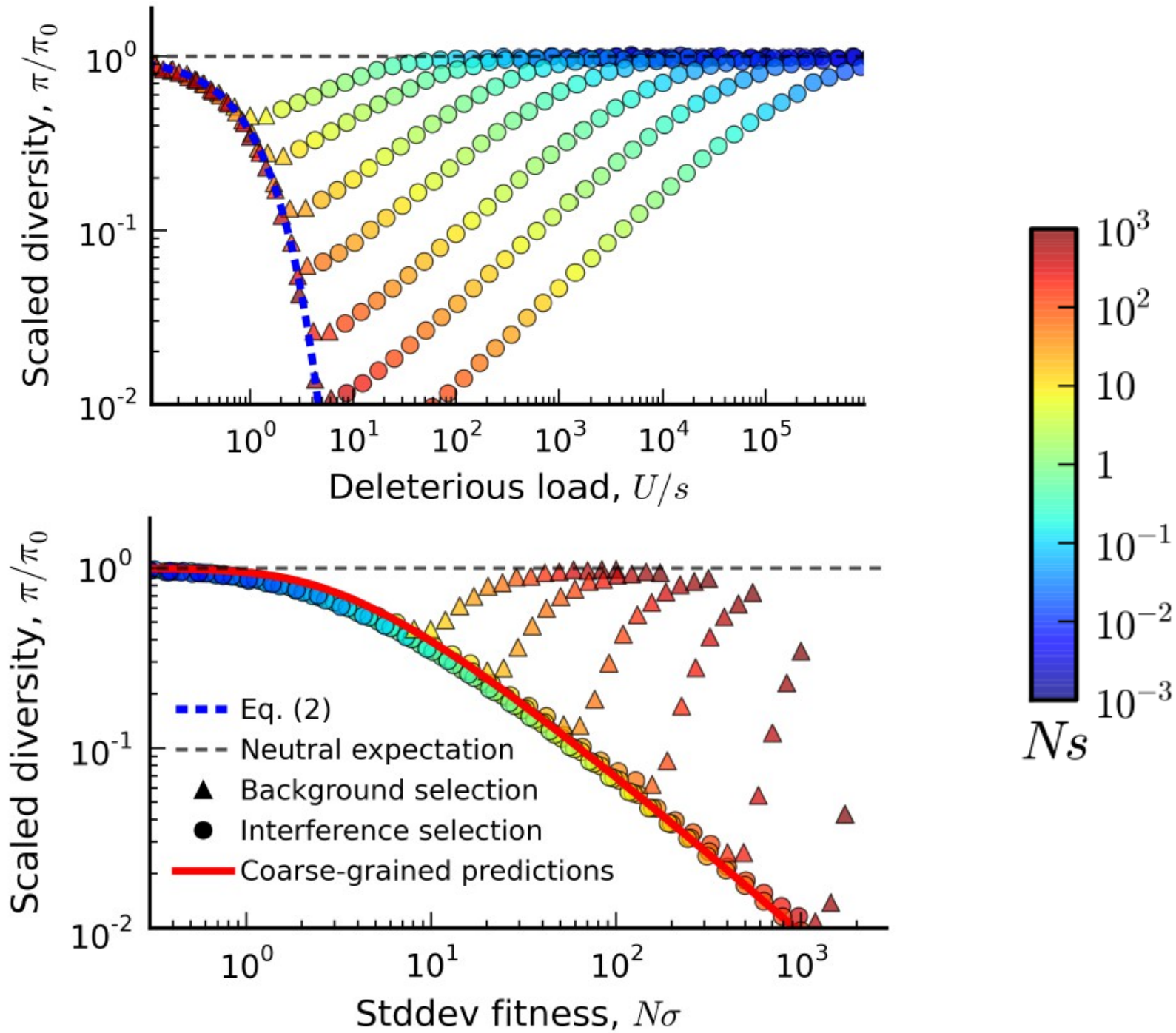
When $Nse^{-U/s} \sim 1$ or less, the distribution fluctuates too much underneath, so the structured coalescent does not make sense.

[Good, Walczak, Neher, Desai *PLoS Genetics* 2014]
[Good and Desai *TPB* 2013]

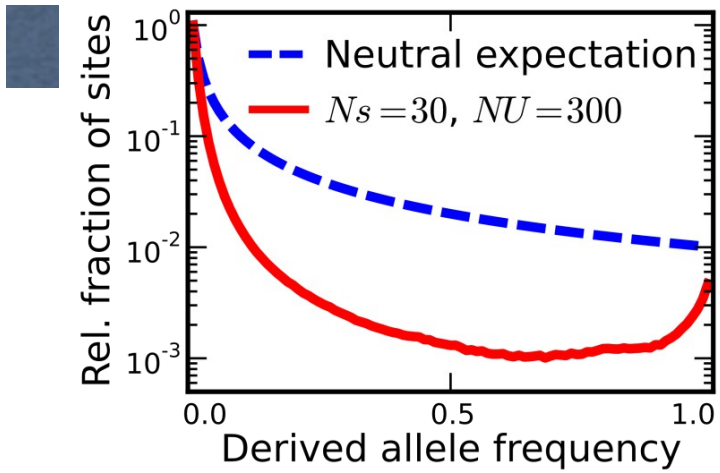
BGS/Structured Coalescent Break Down for Weak Selection

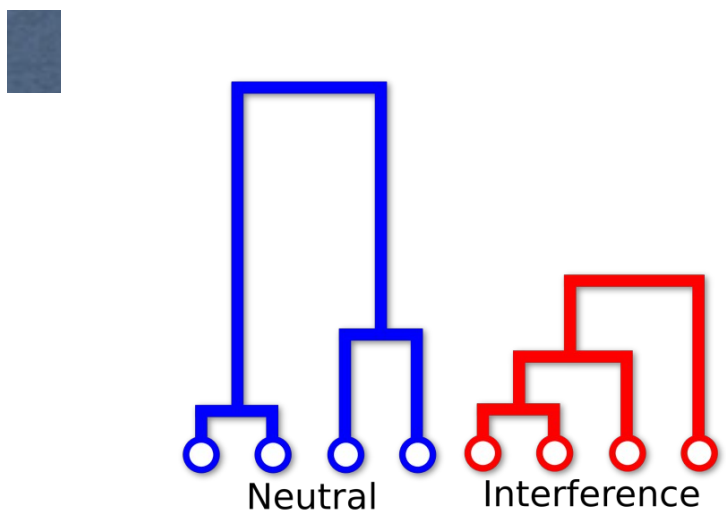


Collapse with U/s (BGS) or with Nσ (IS)



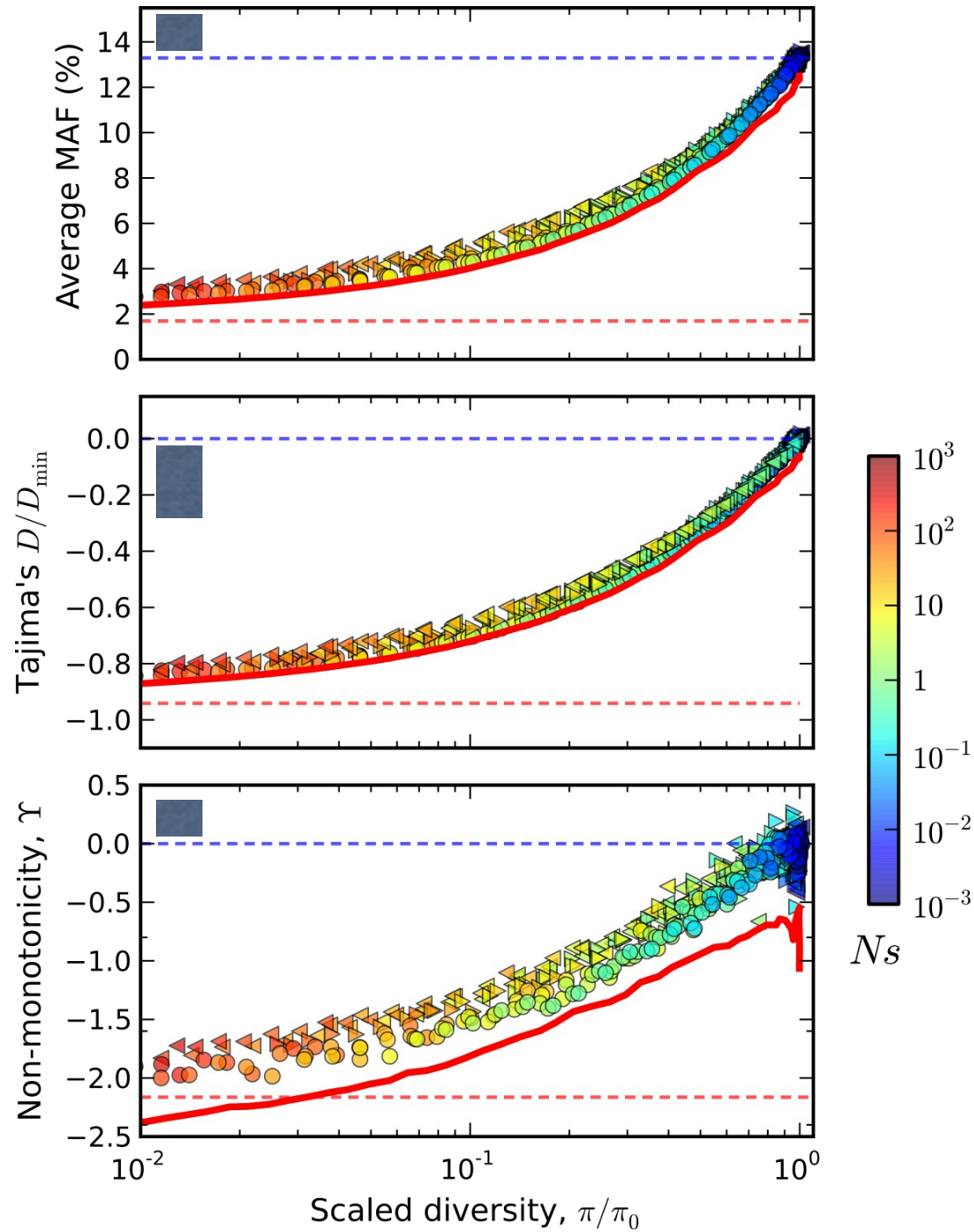
Interference Selection collapse holds generally



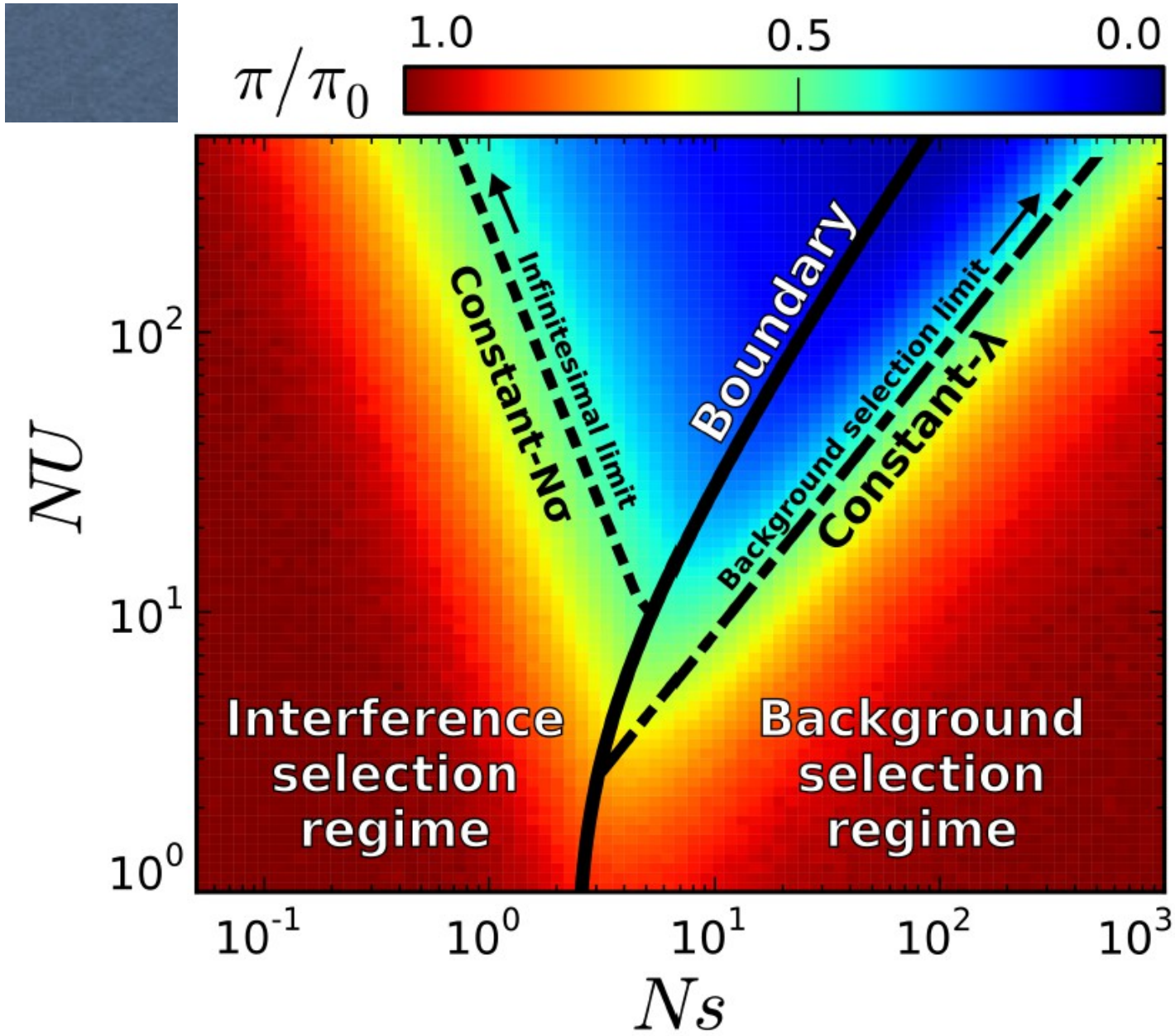


Legend:

- ● Asexual
- ► $NR = 10$
- ◄ $NR = 100$
- Neutral expectation
- Coarse-grained predictions
- Large $N\sigma$ limit

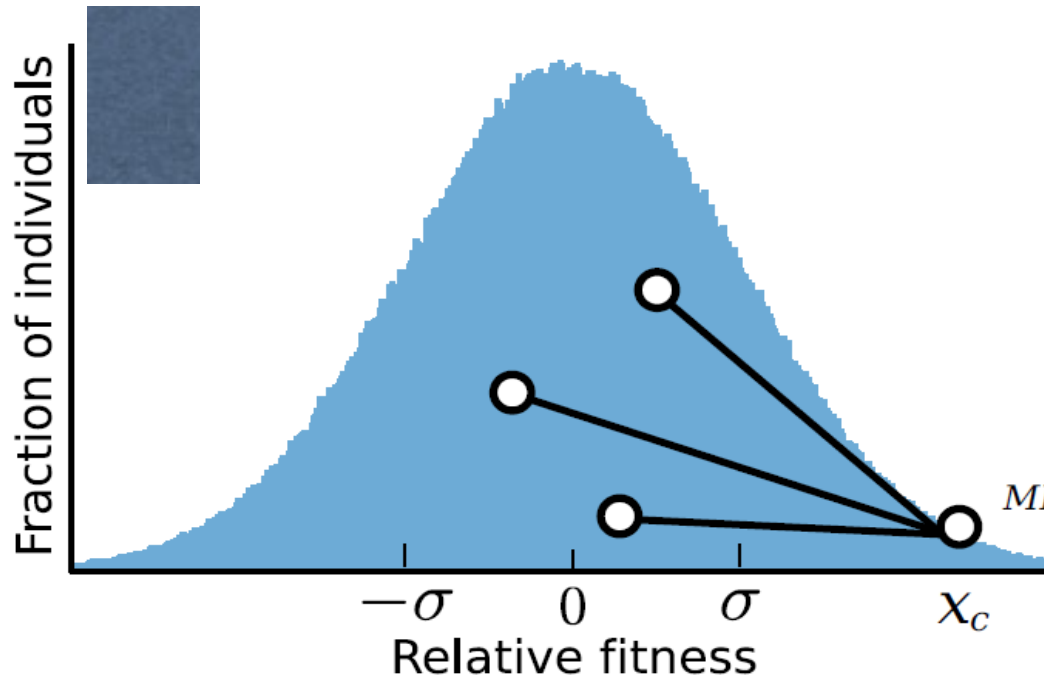


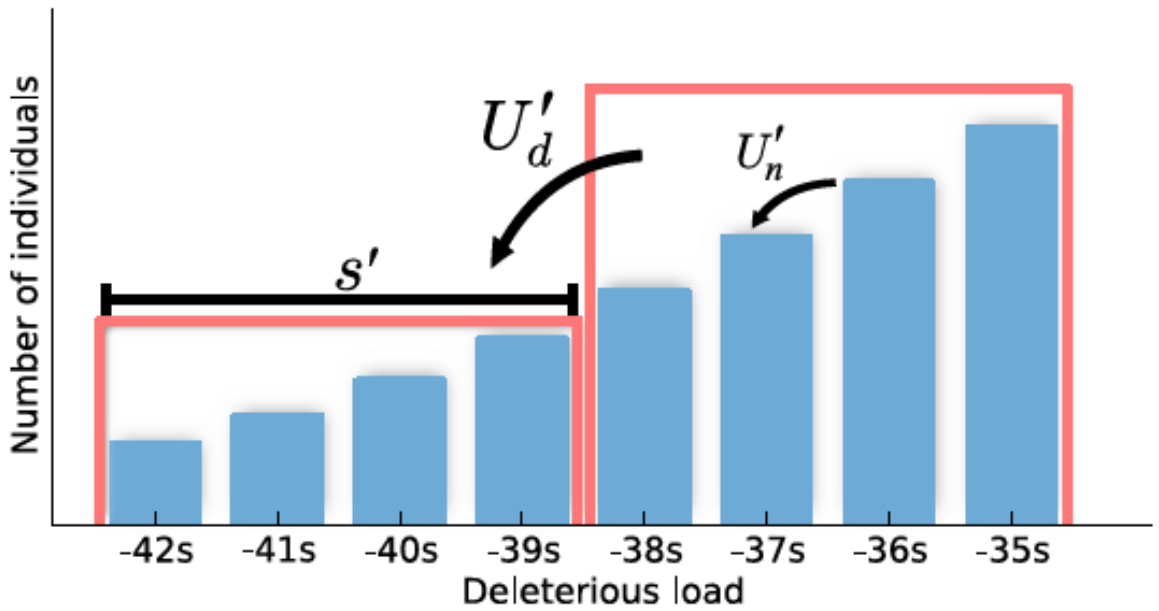
Two limits: background selection and interference selection



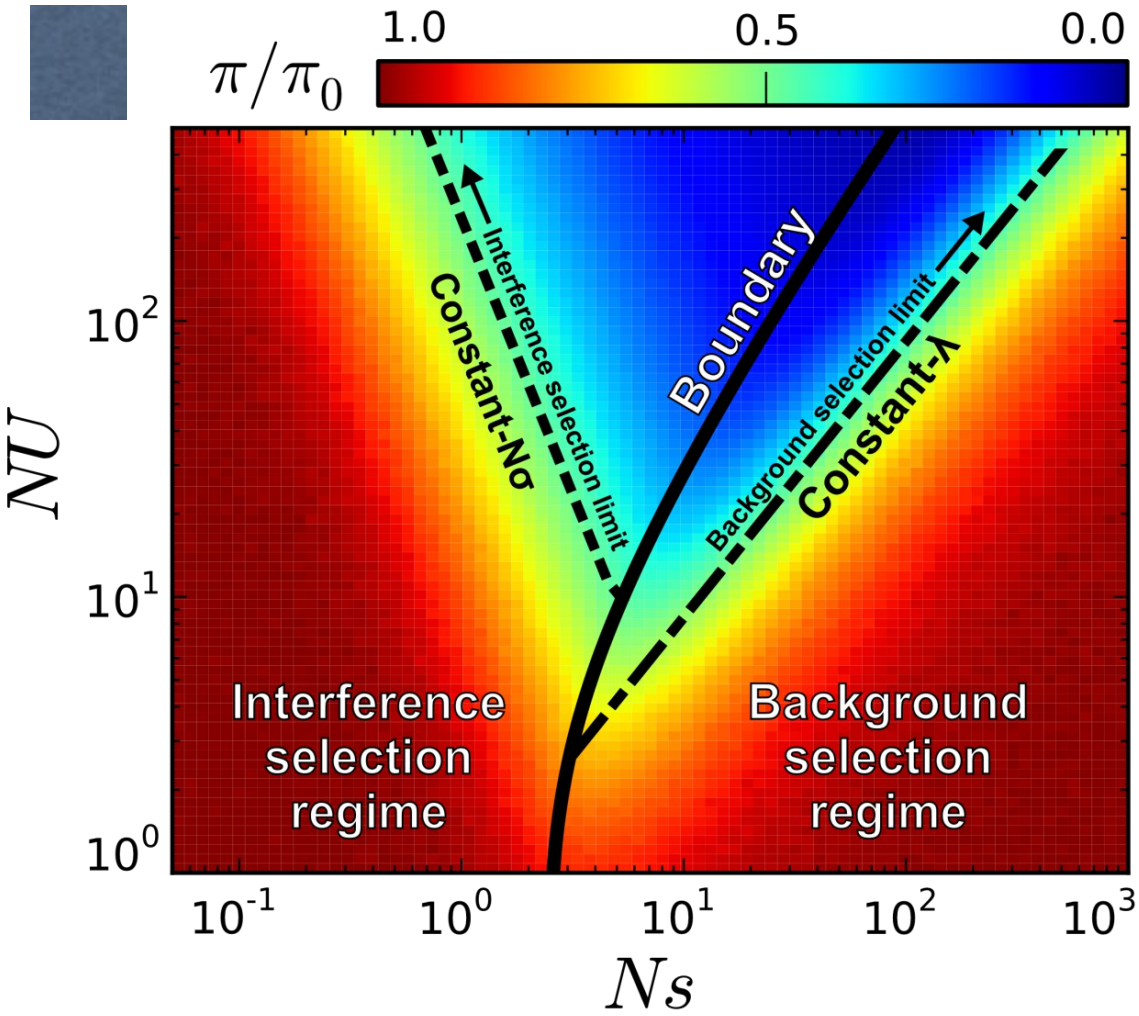
Background selection: *Ns* → ∞ while holding *NU/Ns* constant
Inteference selection: *Ns* → 0 while holding *Nσ* constant

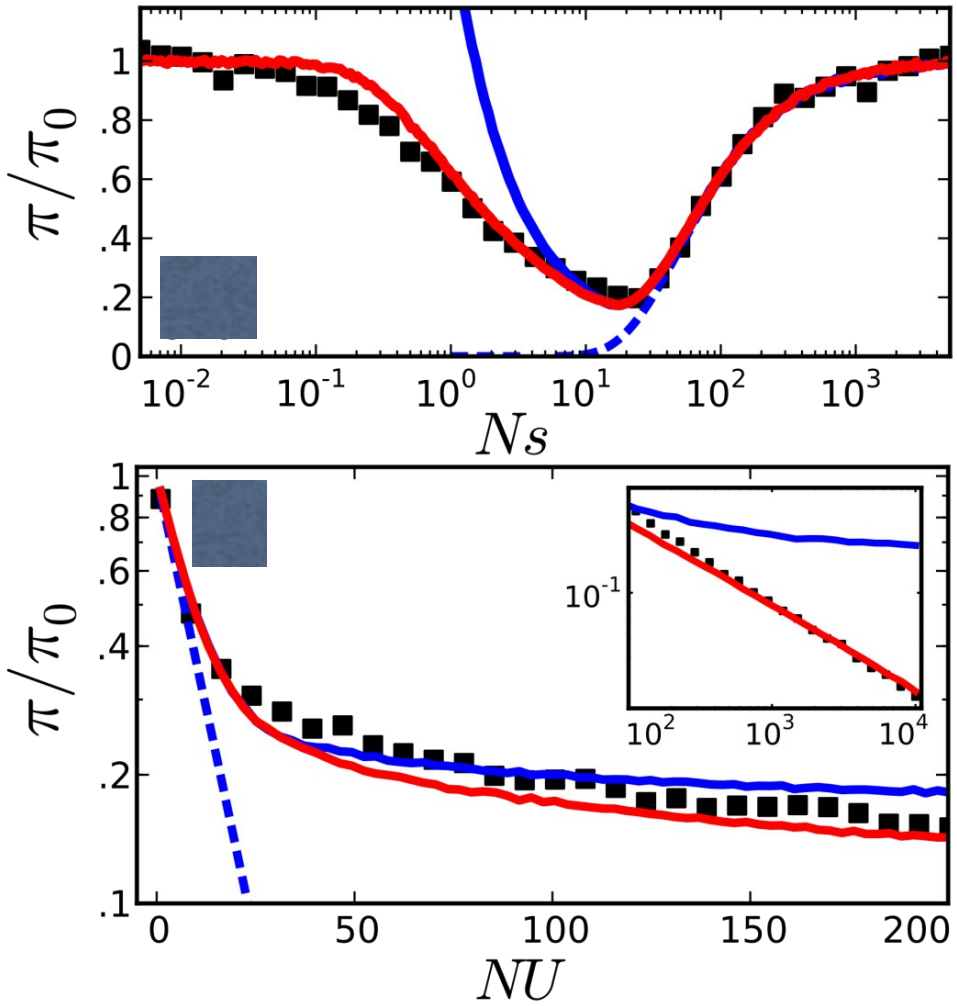
Intuition: “coarse-graining” the fitness distribution





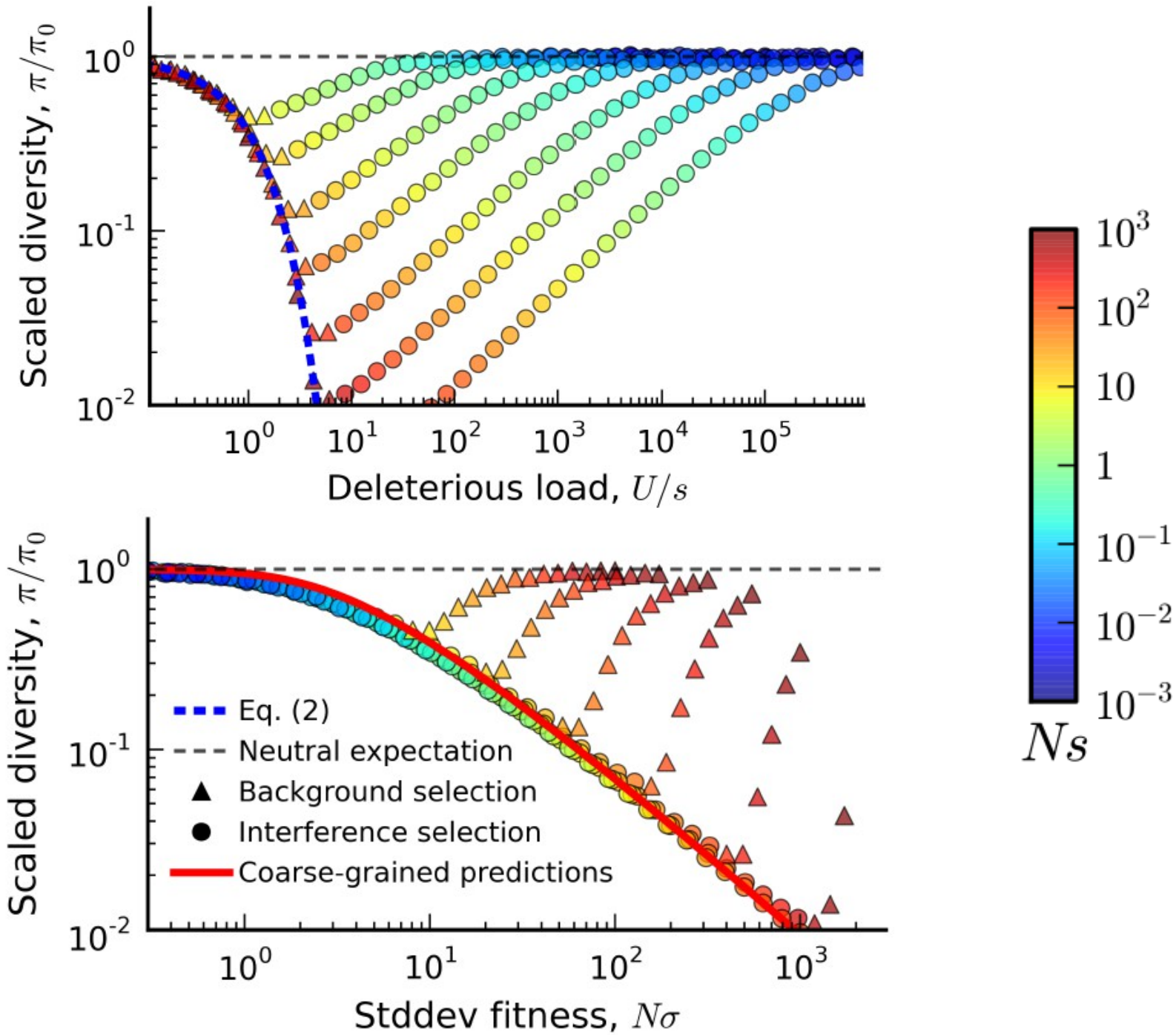
This allows us to predict diversity



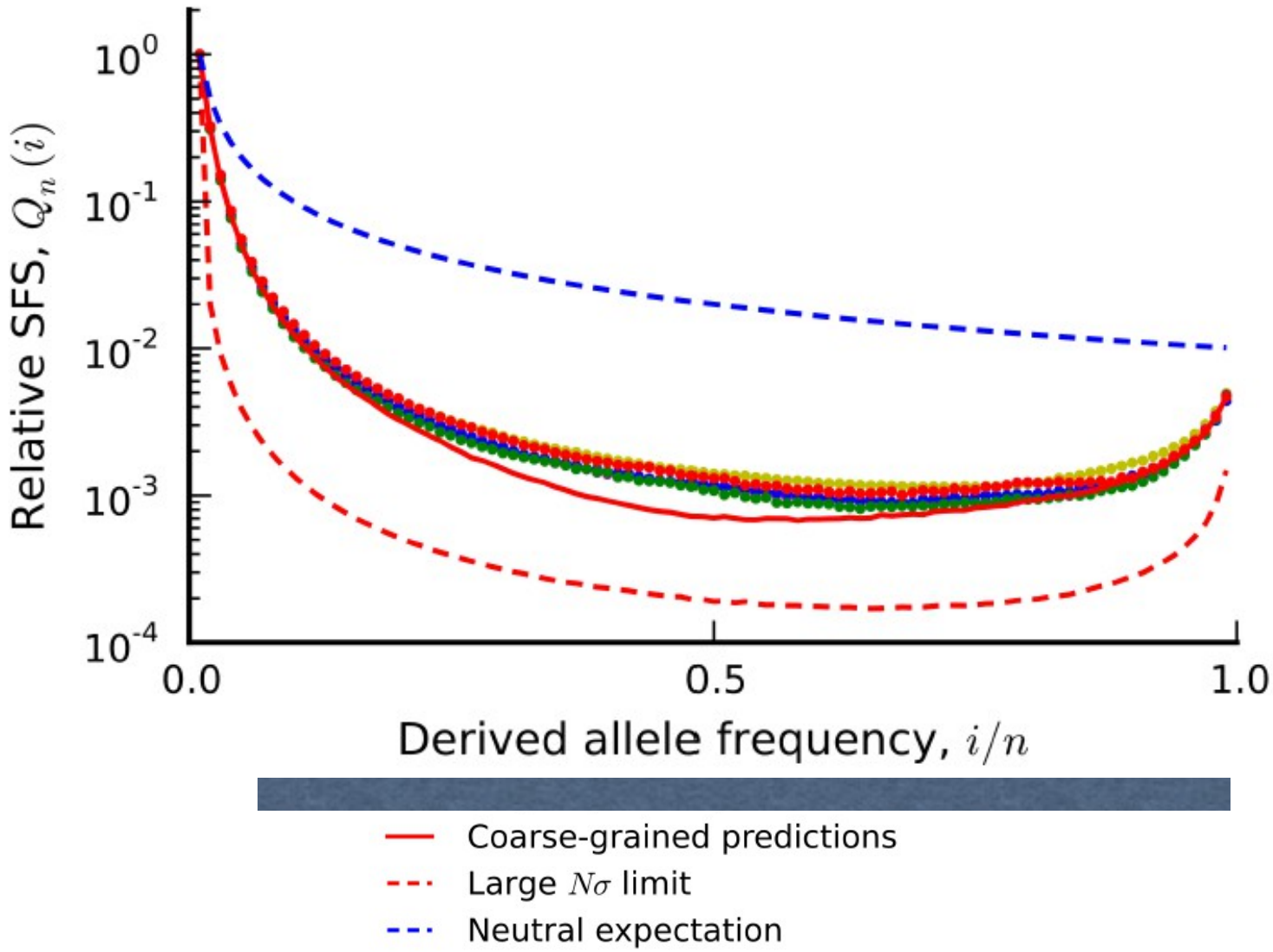


There is a fundamental problem of identifiability:
Many different parameter values lead to *identical* patterns of diversity.

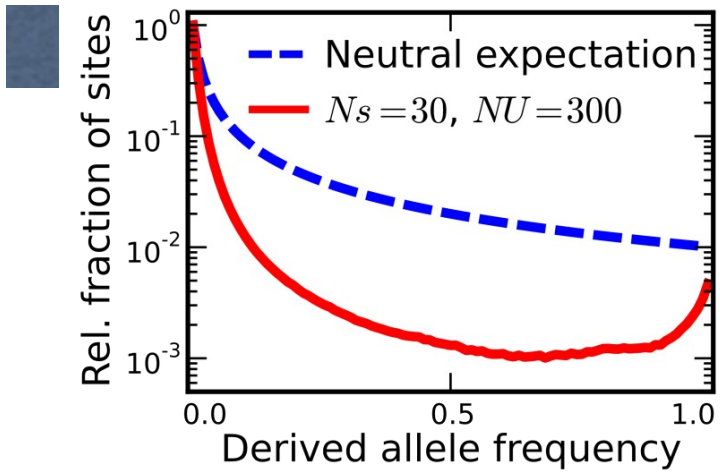
Coarse-Grained Predictions

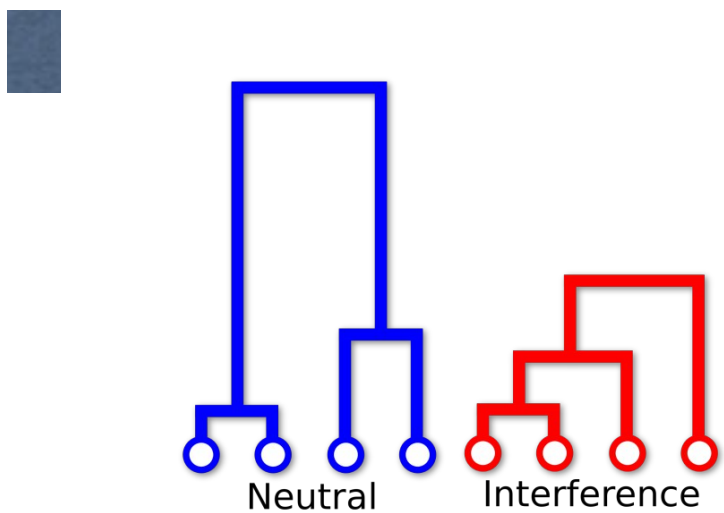


Coarse-Grained Predictions



Coarse-Grained Predictions





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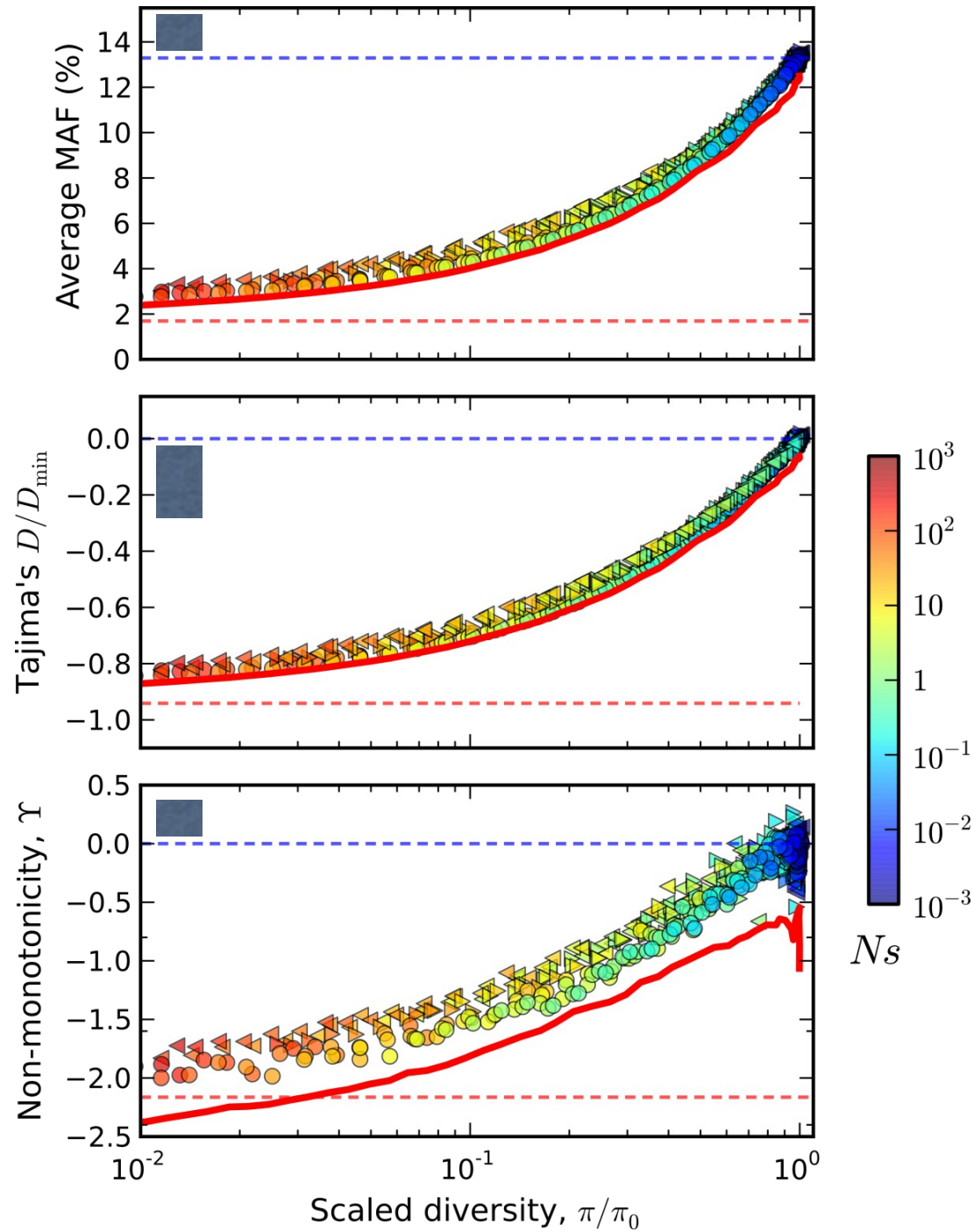
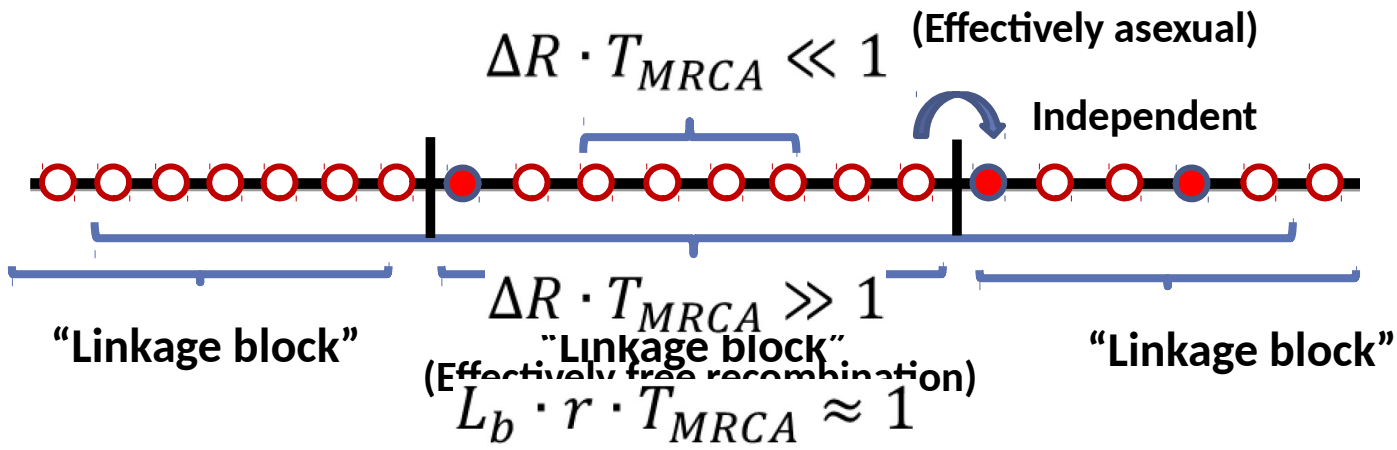
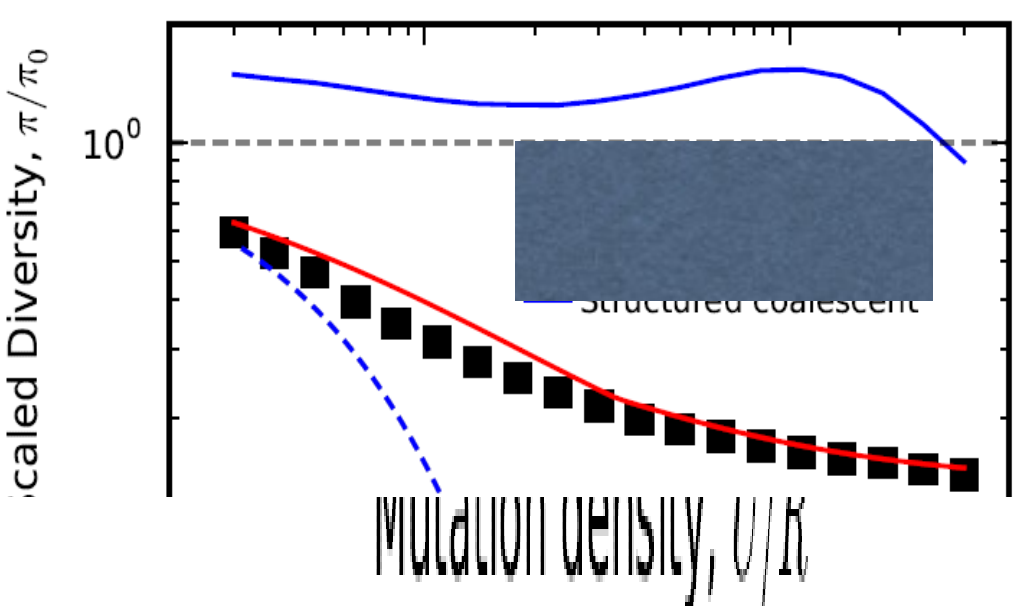
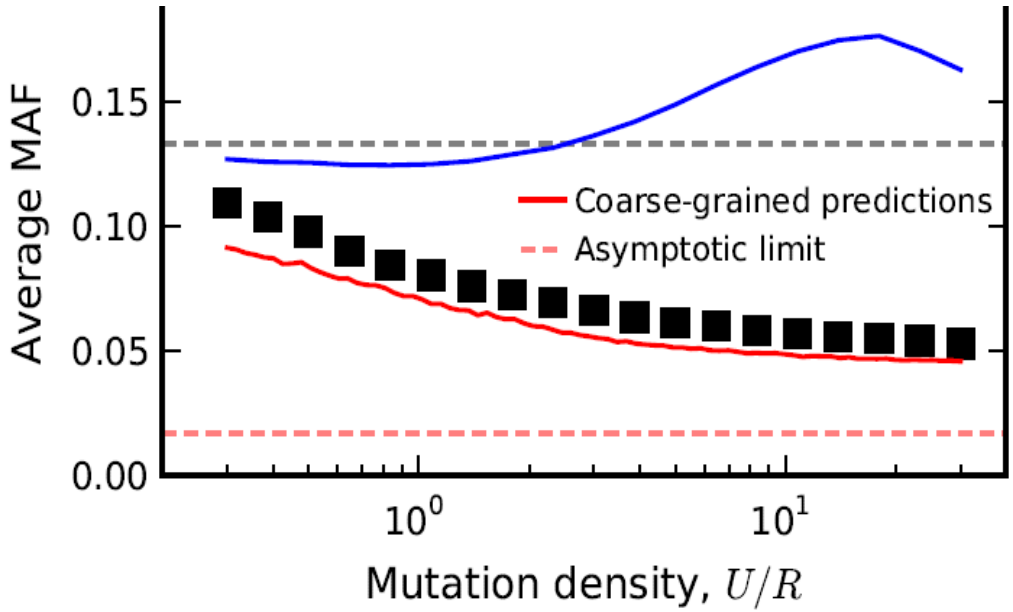


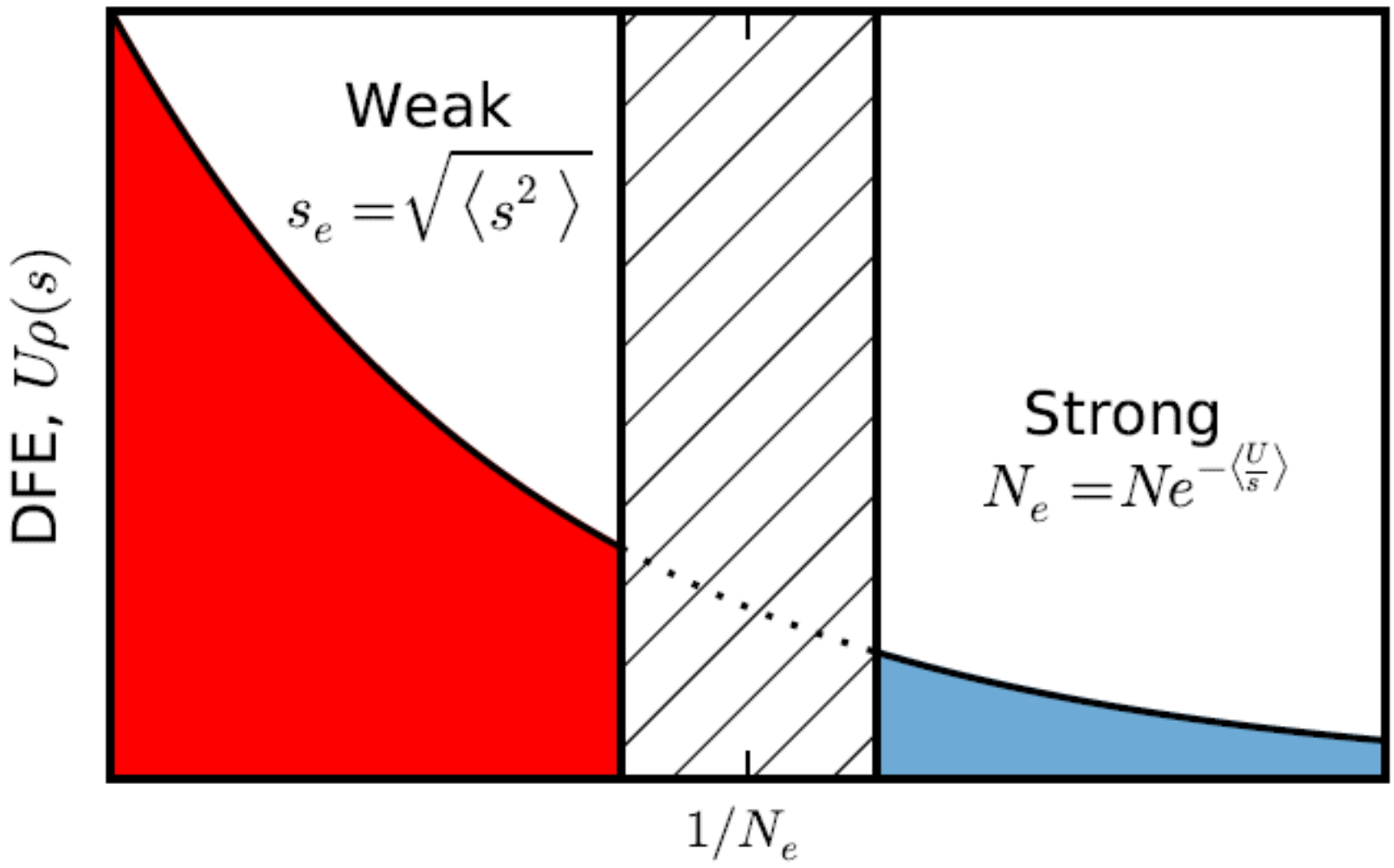
A Linkage-Block Approximation for Recombining Genomes



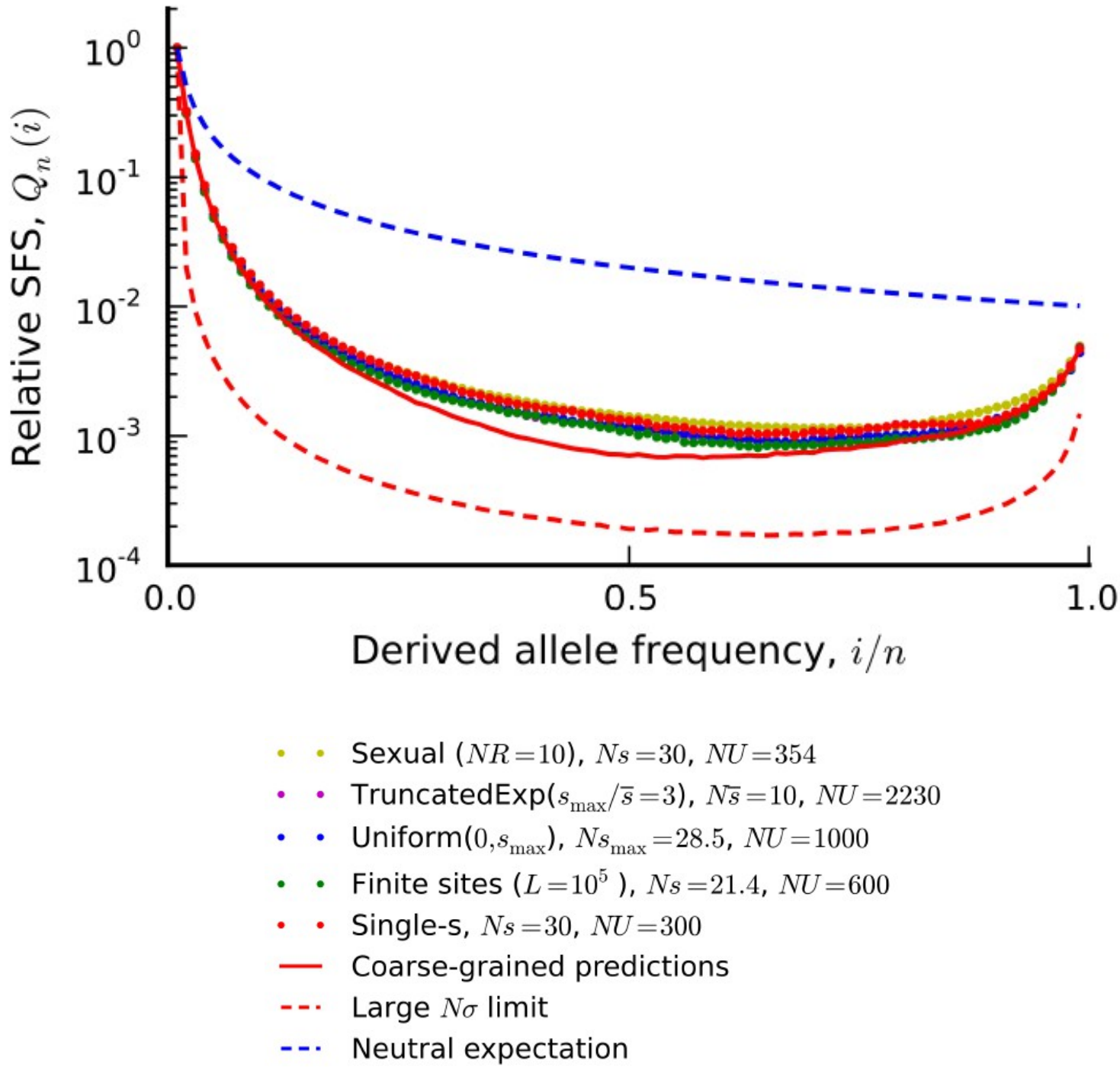




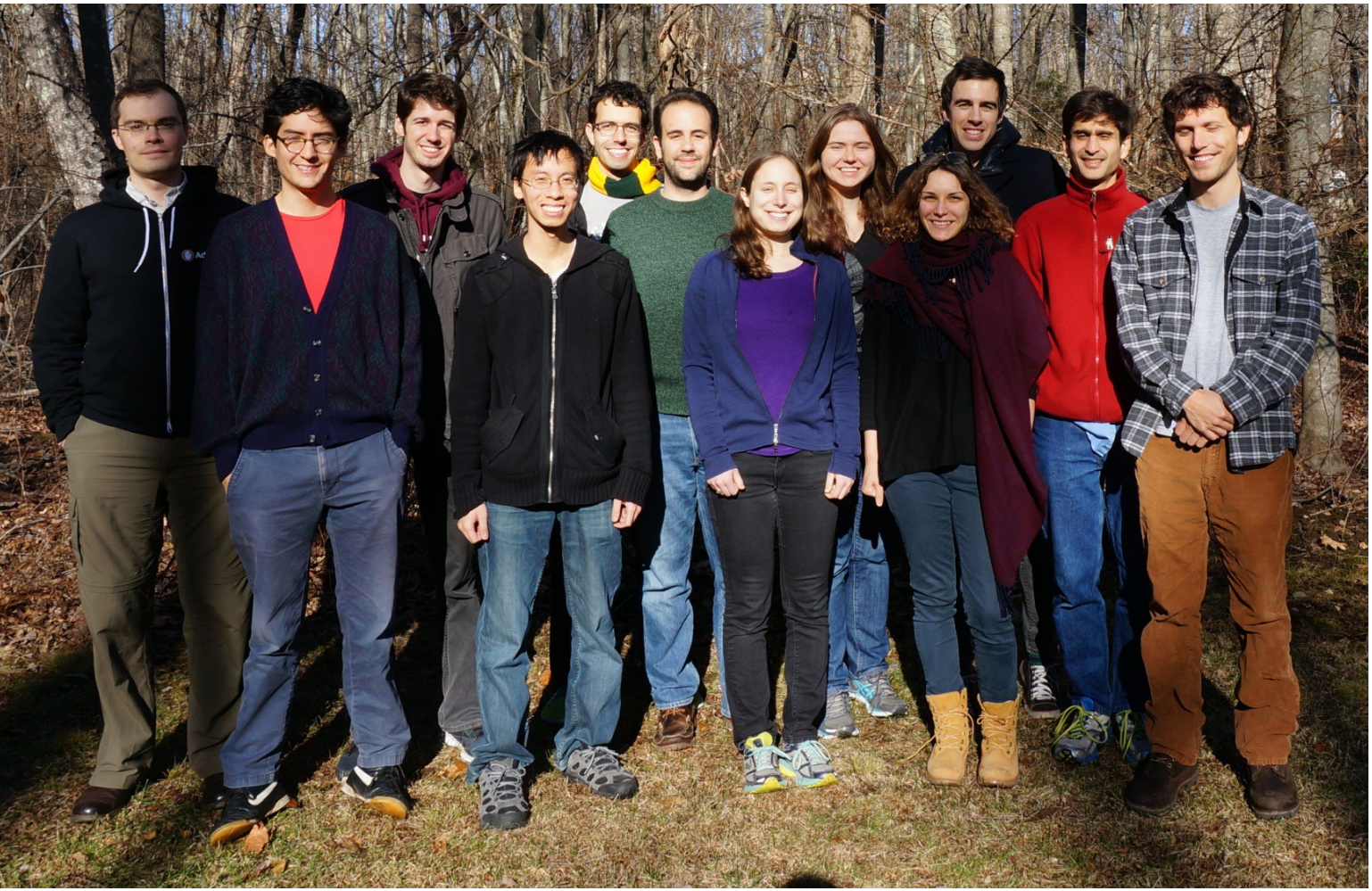
Distributions of Fitness Effects



Interference Selection Still Applies



Acknowledgements



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