From fitness landscapes to seascapes:

Non-equilibrium dynamics of selection and adaptation

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Acknowledgments

- Michael Lässig

  From fitness landscapes to seascapes [submitted manuscript (2008)].

  Molecular evolution under fluctuating selection [PRL (2008)].

  Adaptive evolution in Drosophila species [PNAS (2007)].

  Evolutionary population genetics of promoters [PNAS (2005)].

- Justin Kinney, Curt Callan & Michael Lässig

  Evolutionary analysis of binding sites in yeast species [PNAS (2008)].

What is the genomic signature of adaptive evolution?

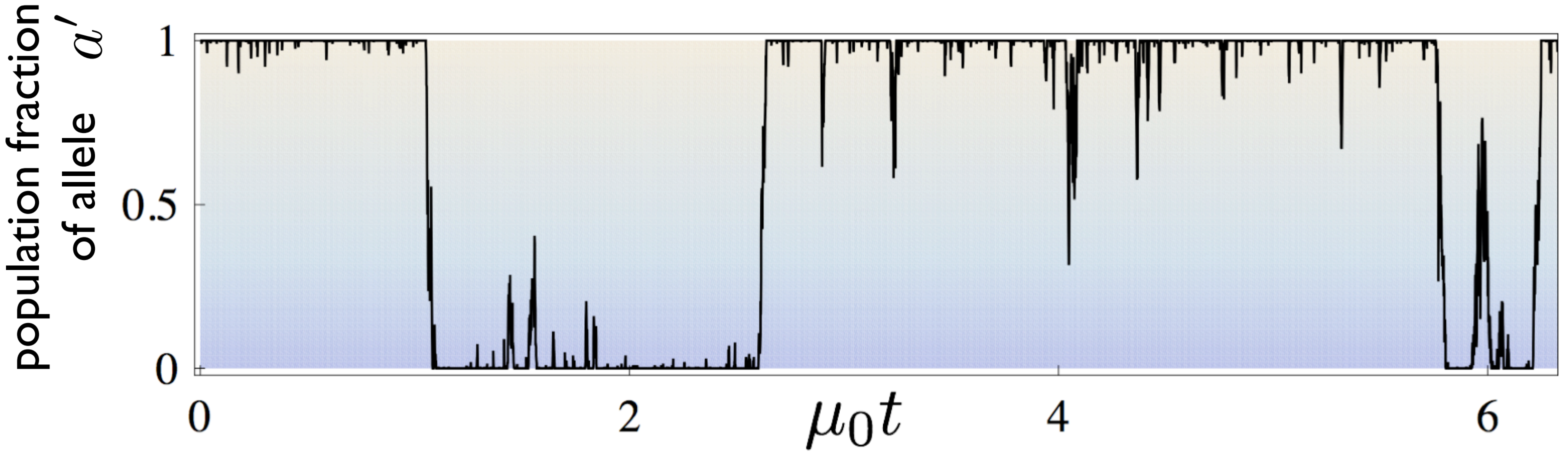
- Positive selection alone is not enough to prove adaptive evolution.
- Adaptation should be viewed as *a non-equilibrium phenomenon* quantified by a positive fitness flux Φ.
- Two case studies to illustrate the difference between positive selection and adaptation:
    1. Yeast binding sites with positive selection but no apparent adaption.
    2. Fruit fly genomes show evidence of adaptive evolution.

Example of a static fitness landscape: the one locus two alleles model

- Wright-Fisher process with drift, mutation, and selection.

$\mu_0 N \ll 1$ $\sigma = 2N(F(a') - F(a))$

lighter shading indicates the fitter state



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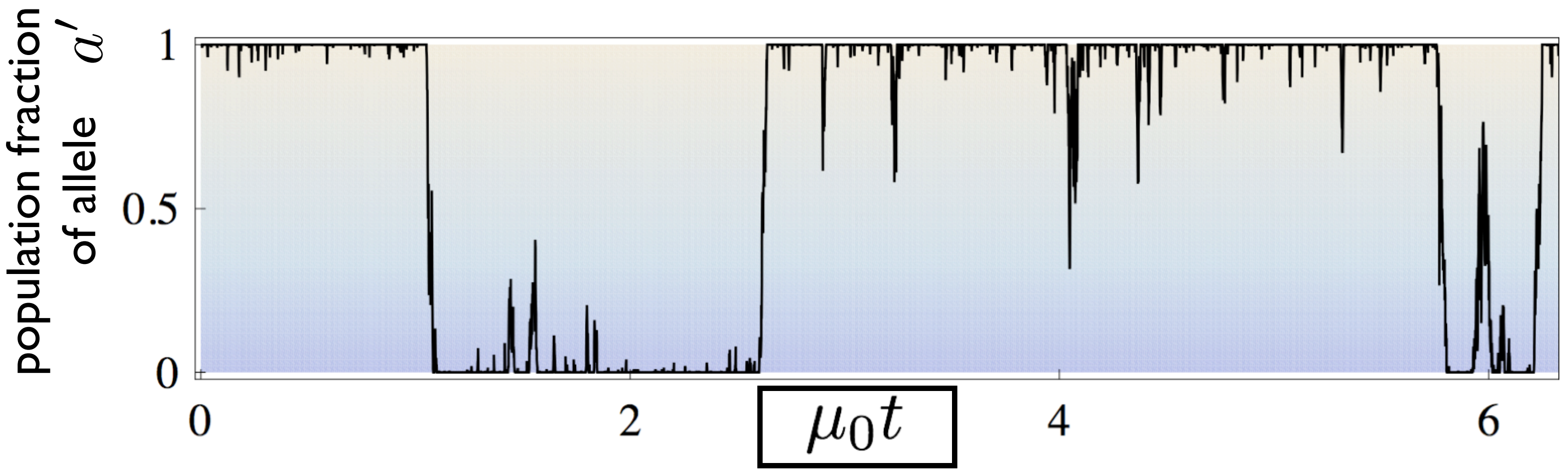

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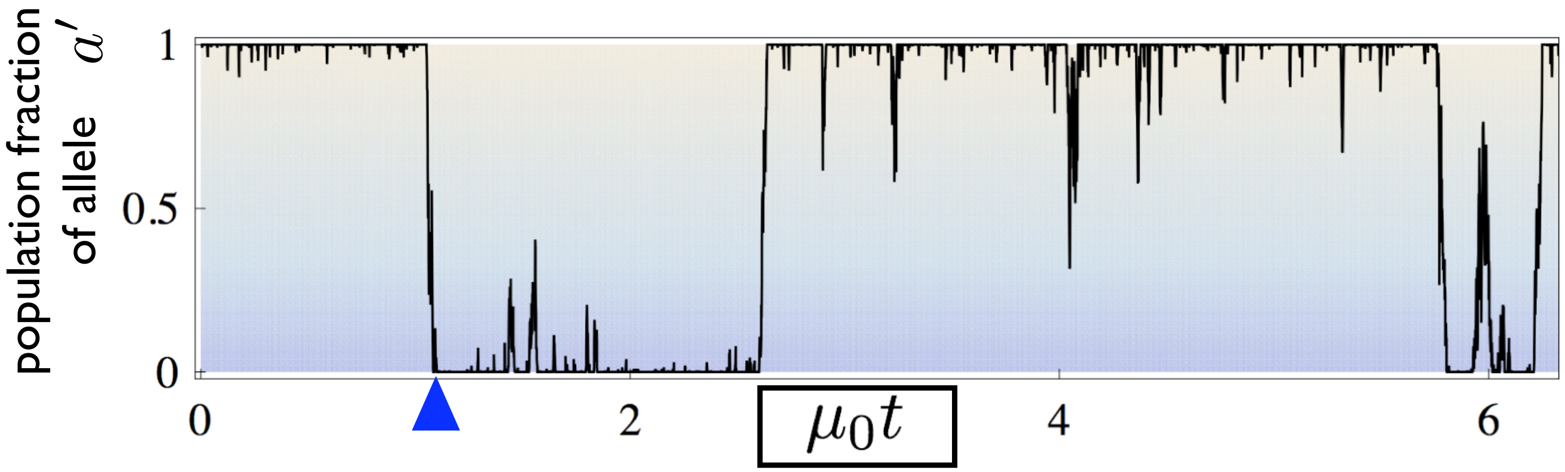

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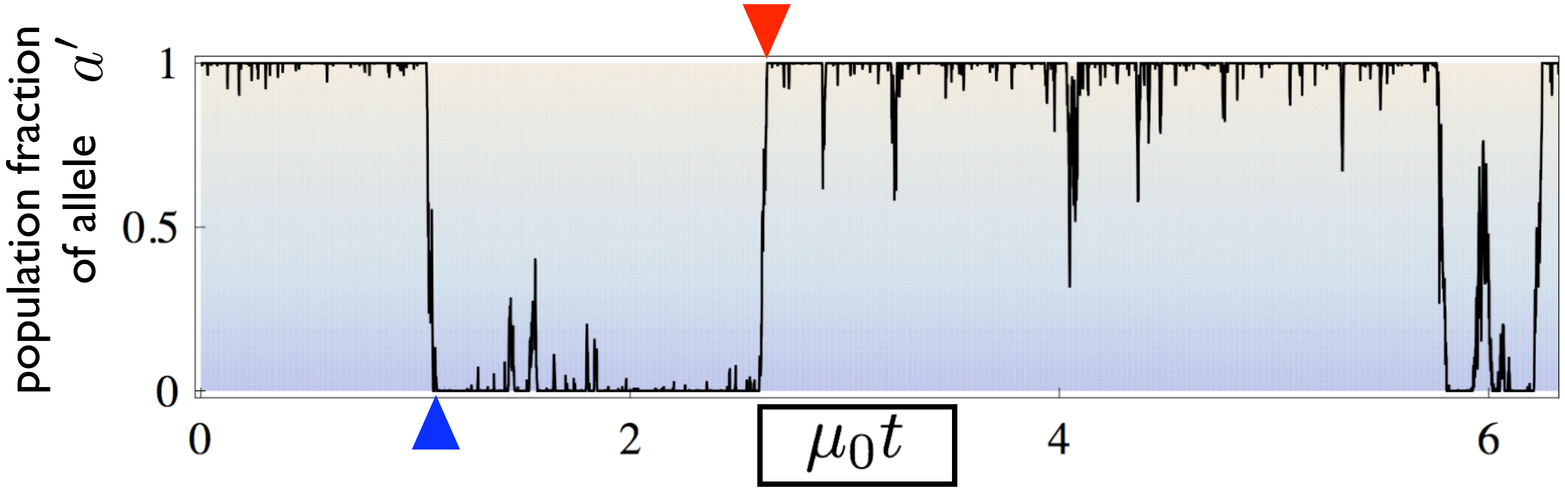

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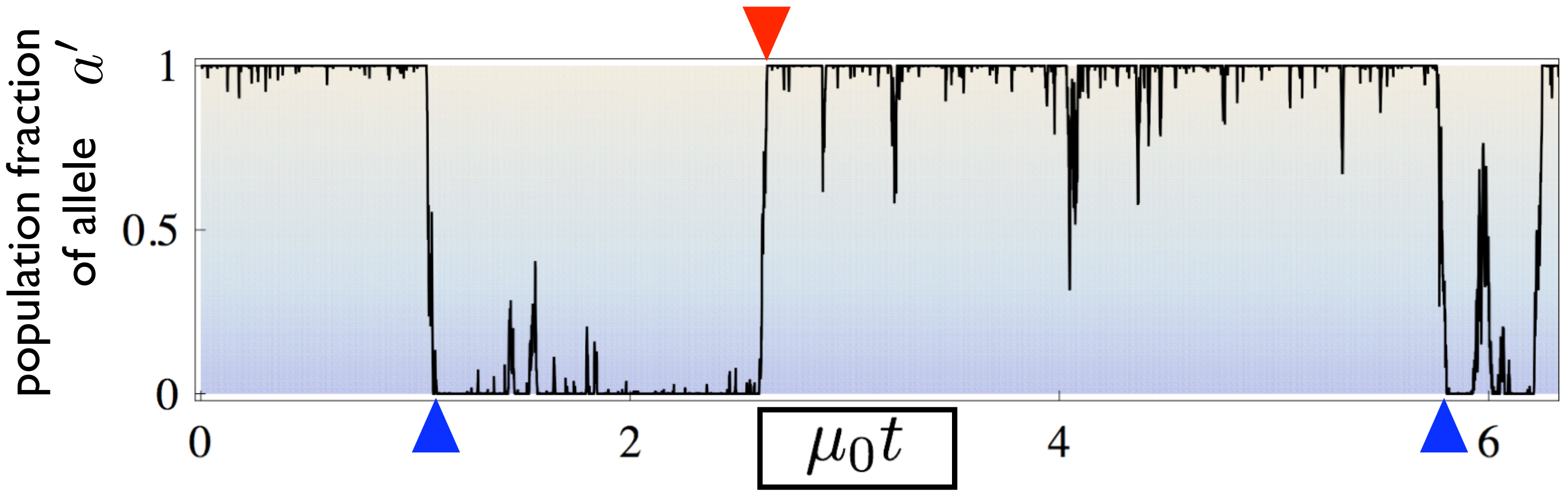

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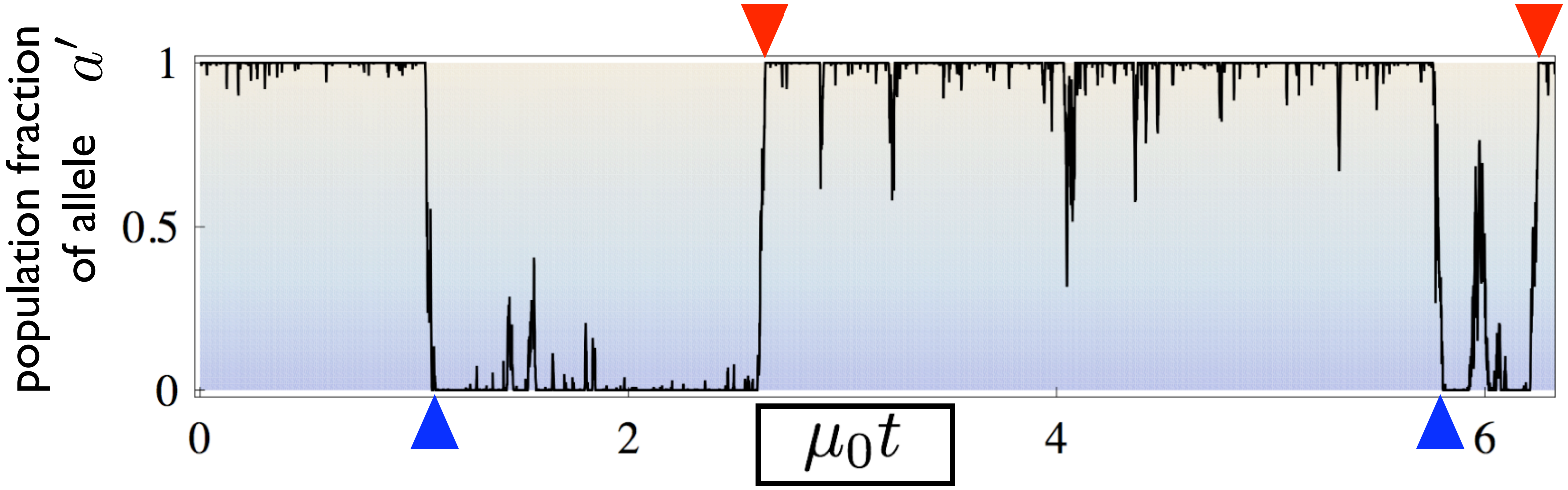
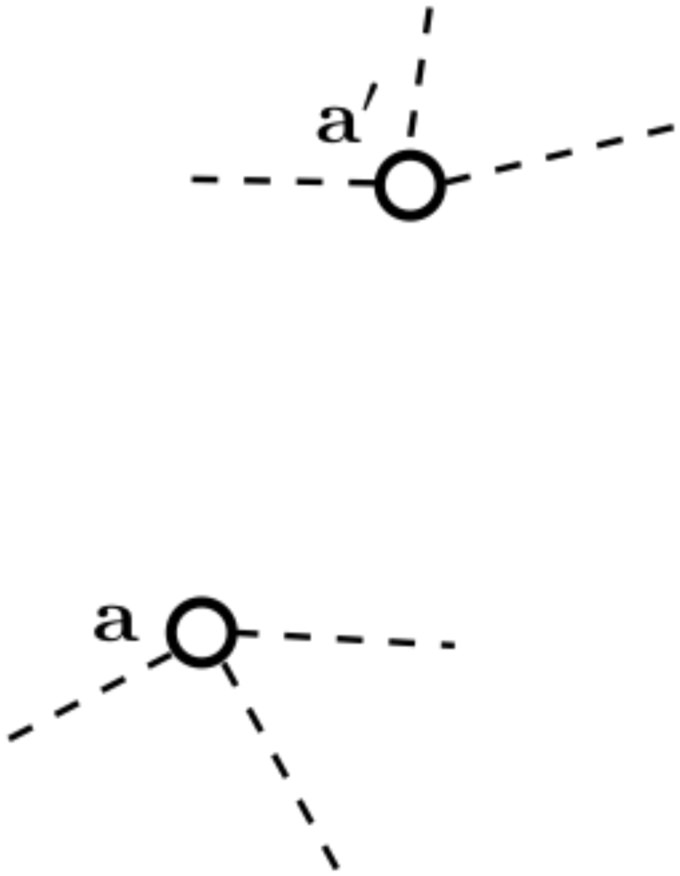


Detailed balance defines equilibrium:

$$
\begin{aligned}
\mathbf{j}_{\mathbf{a}\to\mathbf{a}'} &\equiv j_{\mathbf{a}\to\mathbf{a}'} - j_{\mathbf{a}'\to\mathbf{a}} \\
&= Q(\mathbf{a})u_{\mathbf{a}\to\mathbf{a}'} - Q(\mathbf{a}')u_{\mathbf{a}'\to\mathbf{a}} \\
&= 0
\end{aligned}
$$



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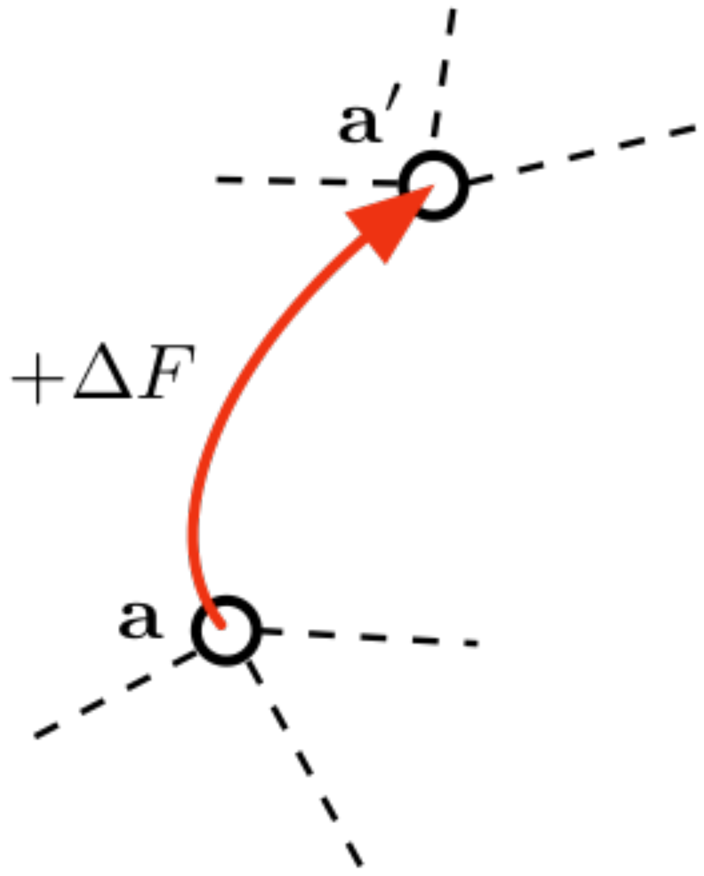

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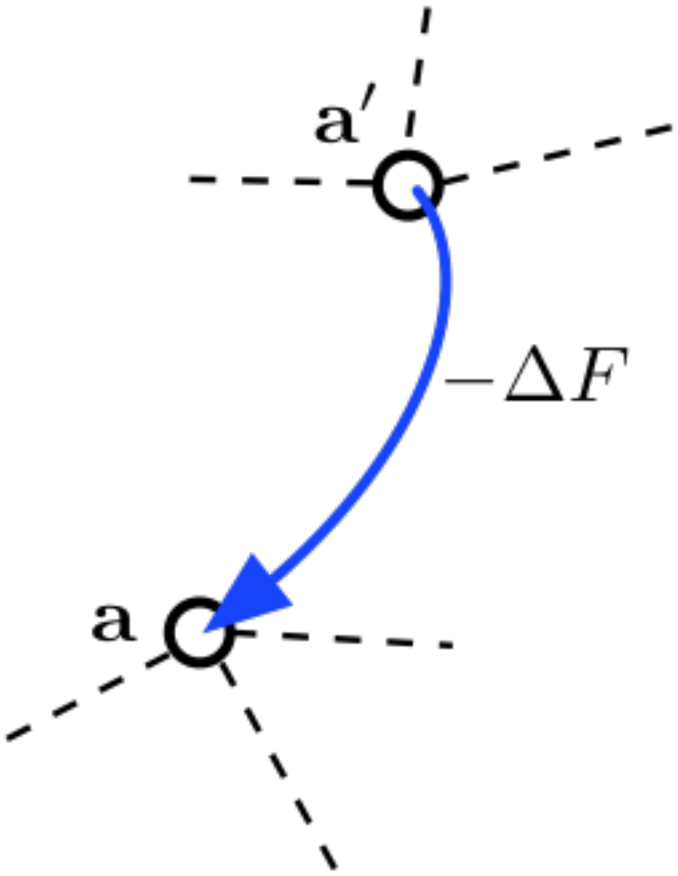

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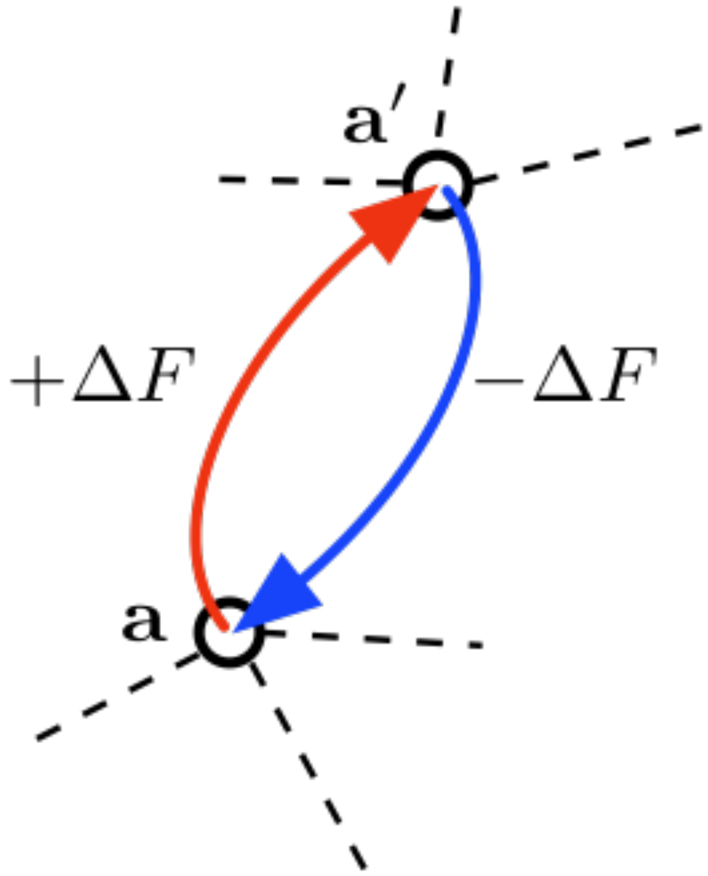

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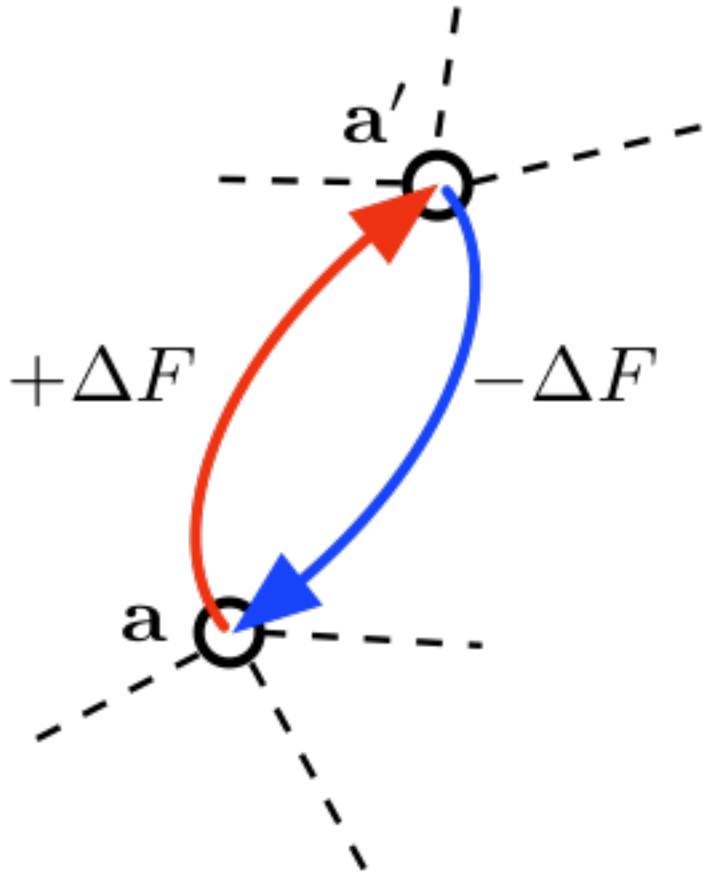
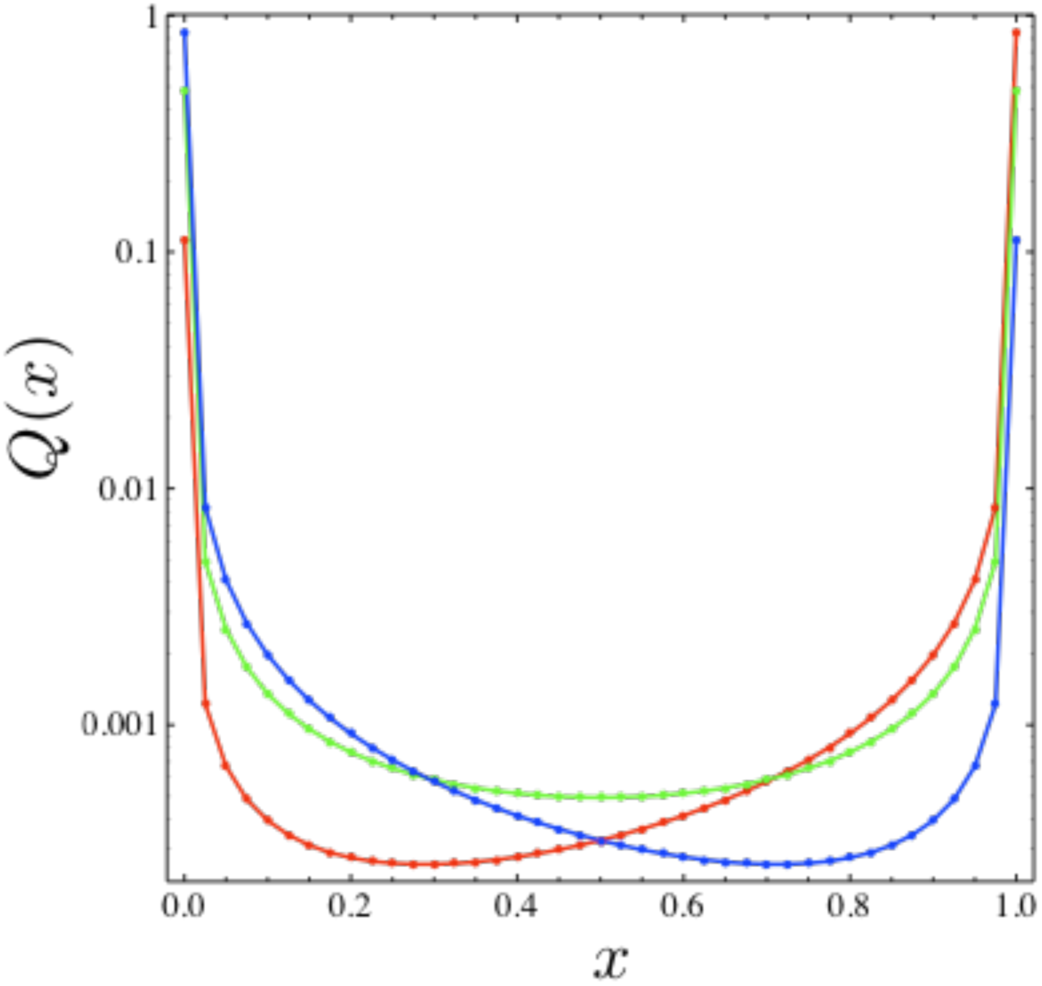


- Fitness flux is zero at equilibrium:

$$\Phi \equiv \Delta F \mathbf{j}_{\mathbf{a}\to\mathbf{a}'} = 0$$

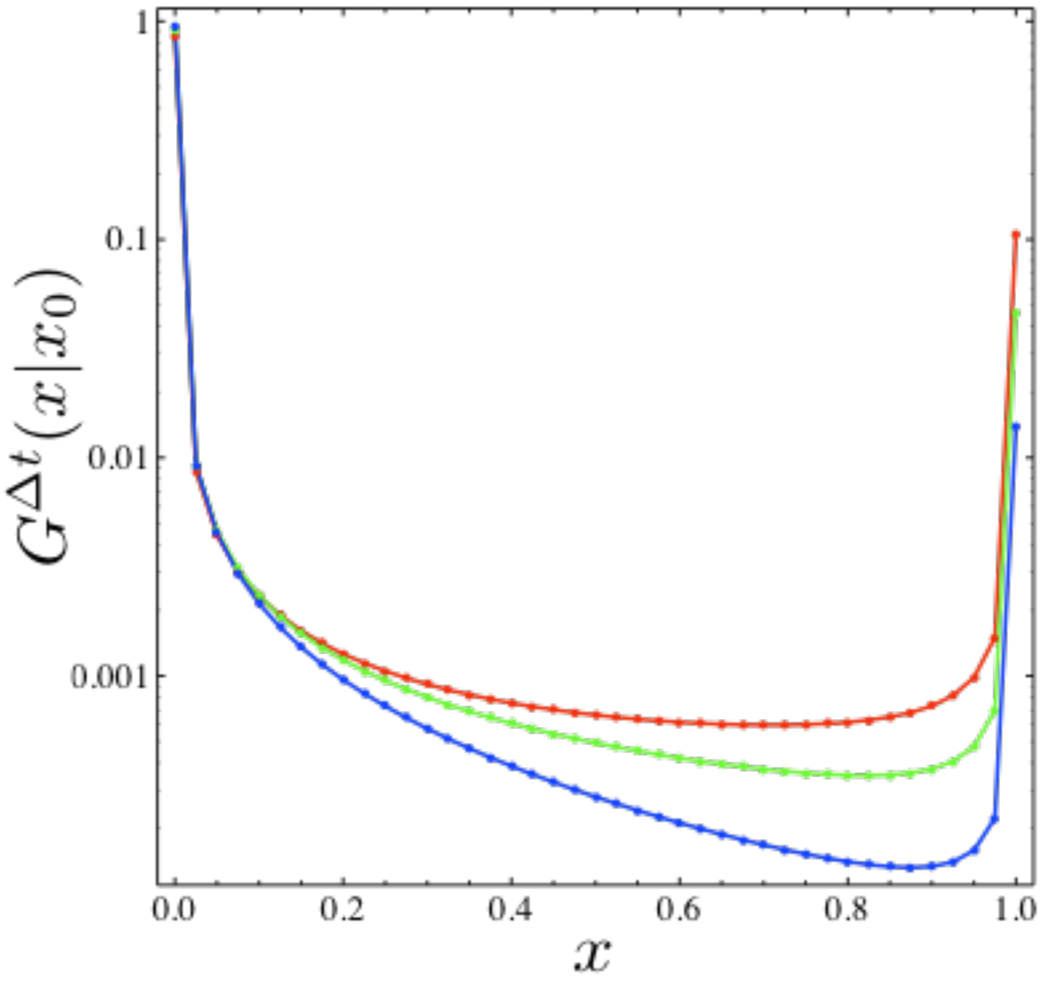
One locus two alleles model: looking at the averages

Equilibrium distributions



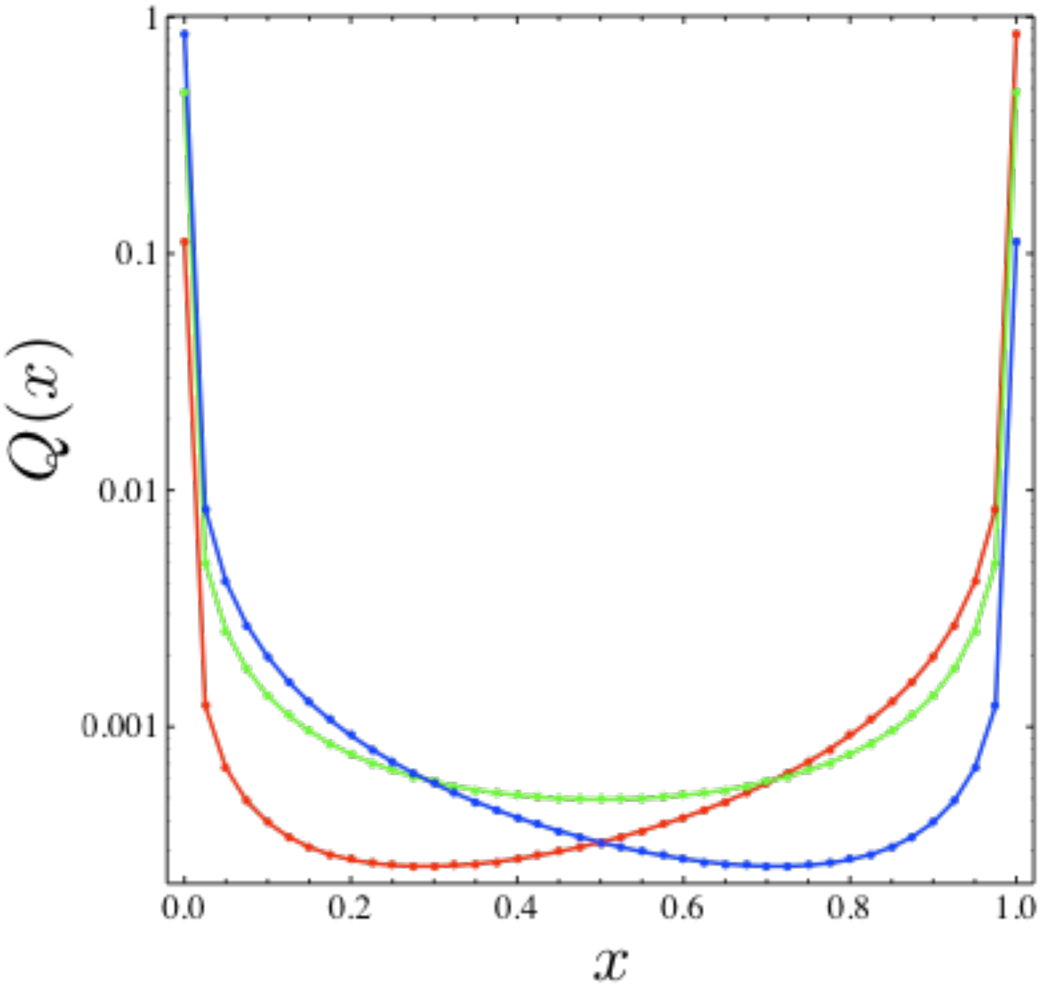
One locus two alleles model: looking at the averages

Time evolution from x(0)=0



One locus two alleles model: looking at the averages

after infinite time



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- Evolution reaches an equilibrium state where the number of substitutions with positive selection coefficients equals that of negative ones.
- Positively selected substitutions merely compensate for the previous deleterious substitutions.
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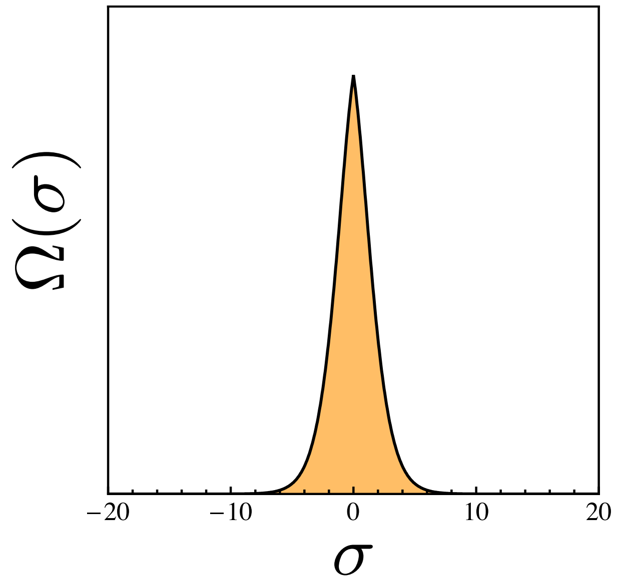
Selection coefficient distribution of genomic substitutions is symmetric



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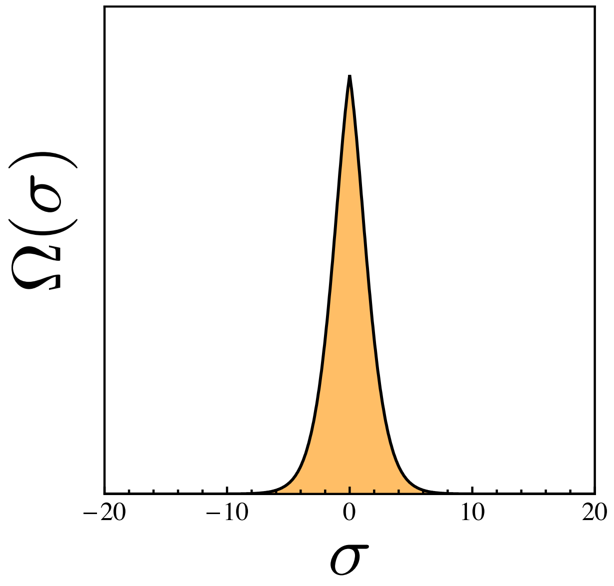

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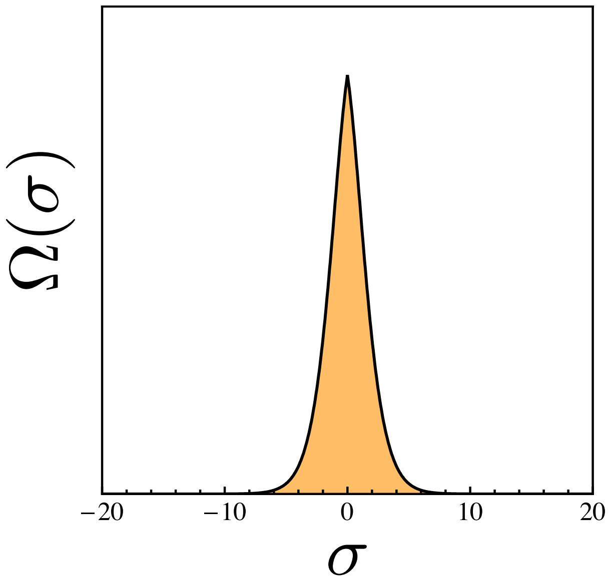

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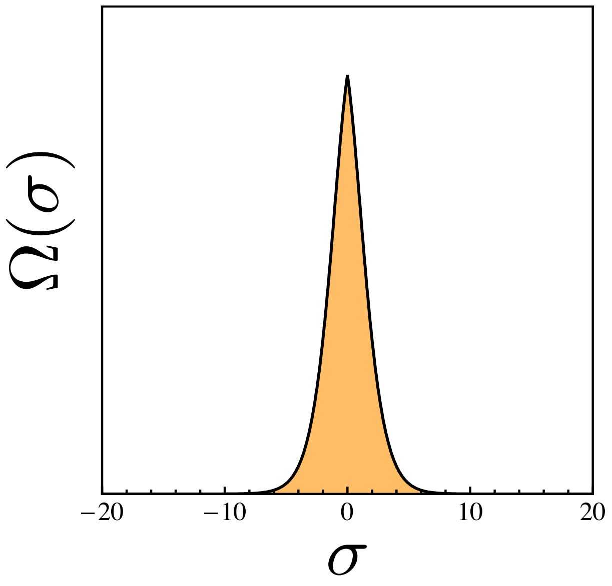


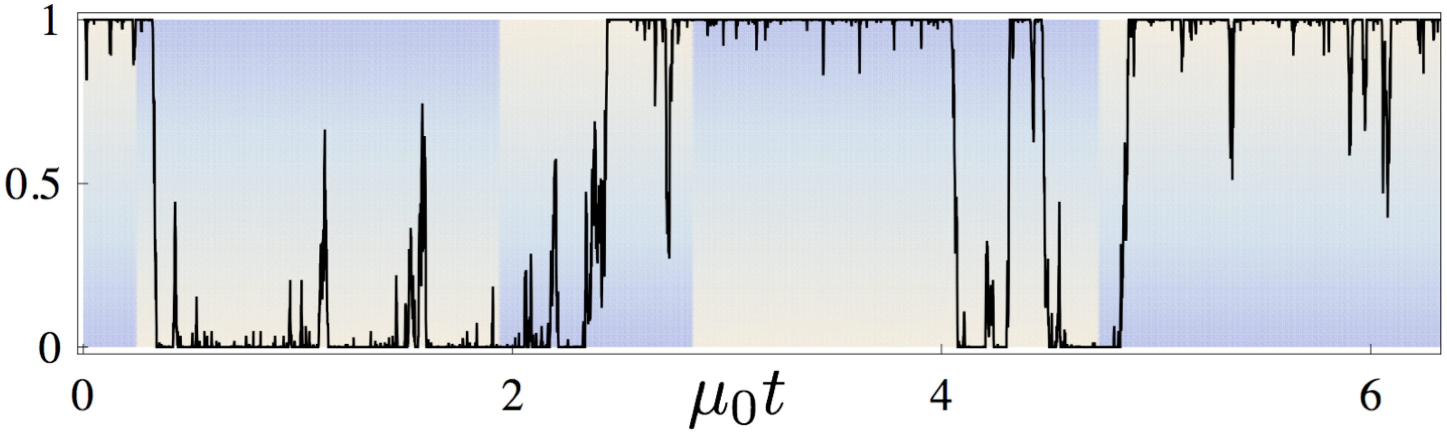
Fitness flux is zero

$$\Phi = 0$$

- No sustained adaptive evolution is possible.

A minimal model for adaptive evolution: *a macro-evolutionary fitness seascape*

- Wright-Fisher process with drift, mutation, and time-dependent selection which switches at a rate γ between $+\sigma, -\sigma$



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- System reaches a non-equilibrium steady state with more genomic substitutions with positive than with negative selection coefficients.
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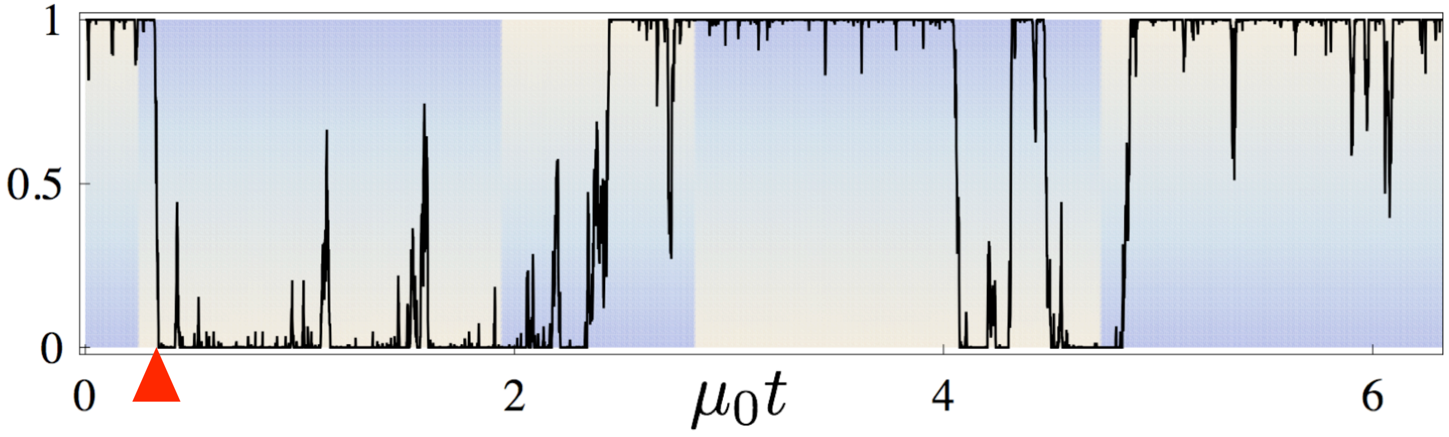

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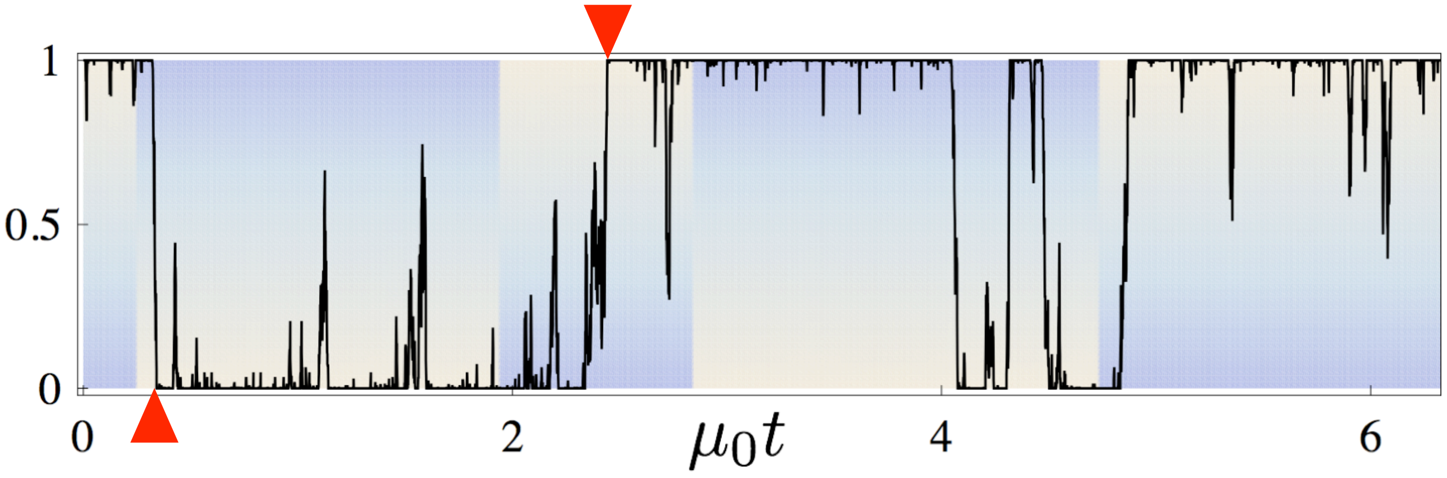

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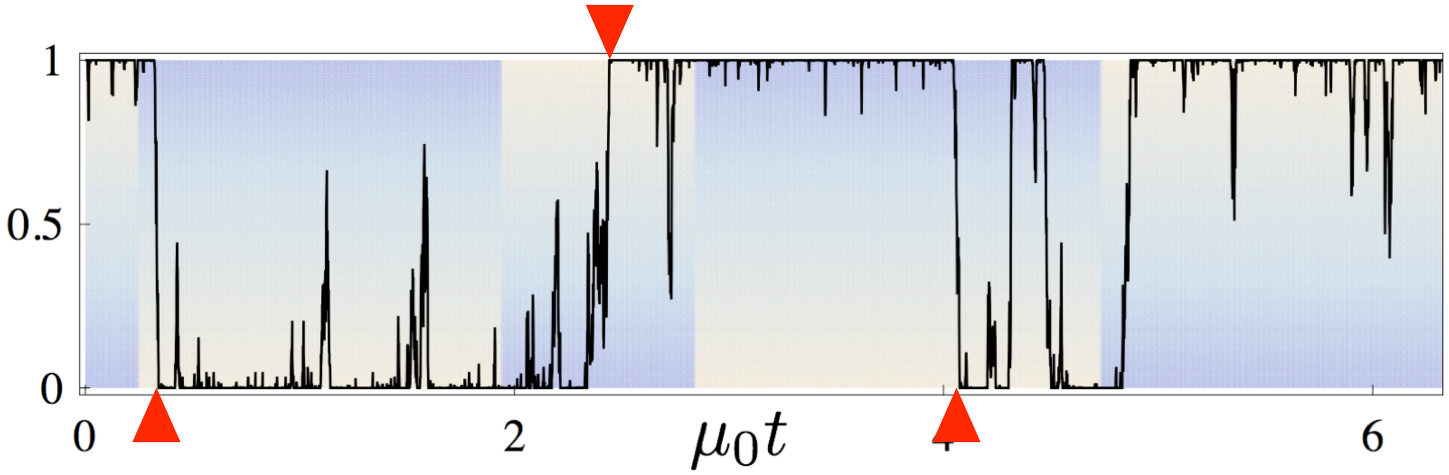

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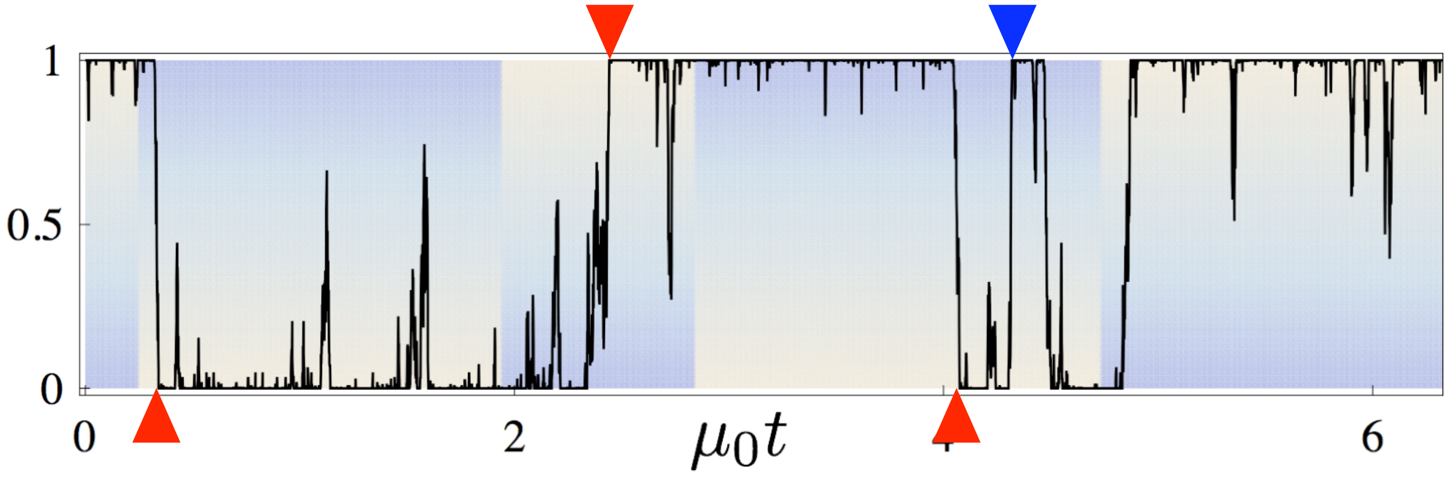

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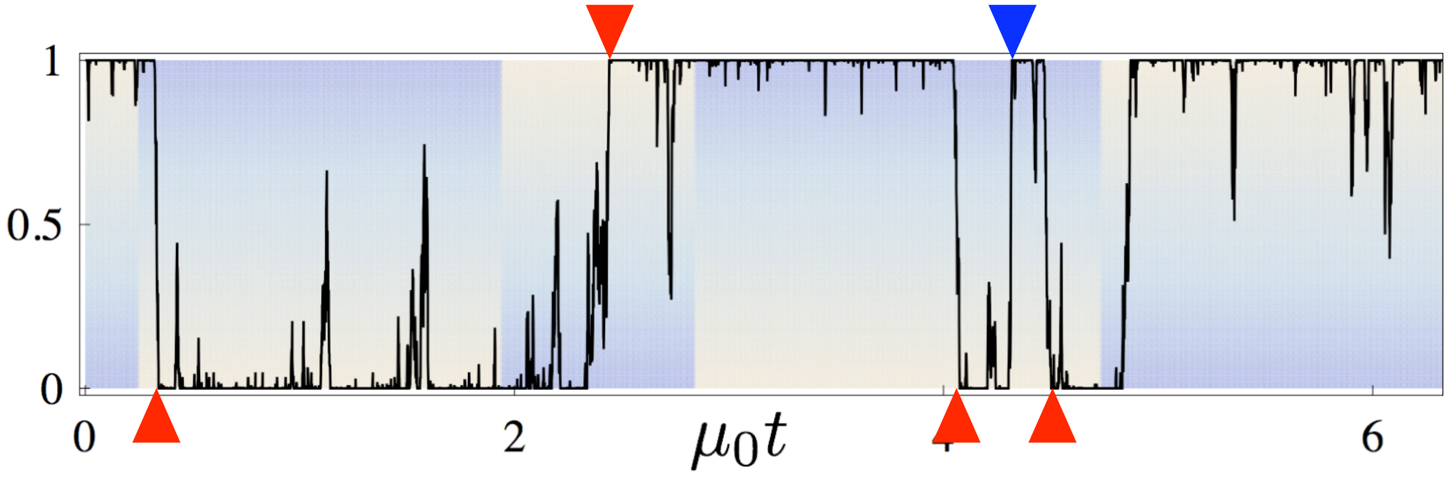

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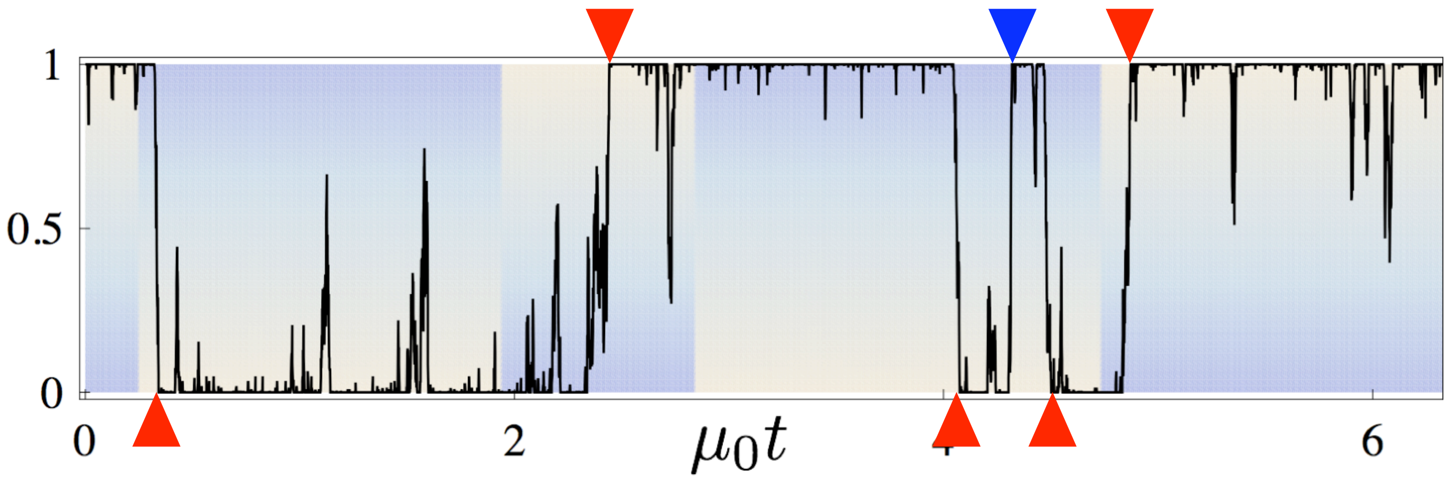

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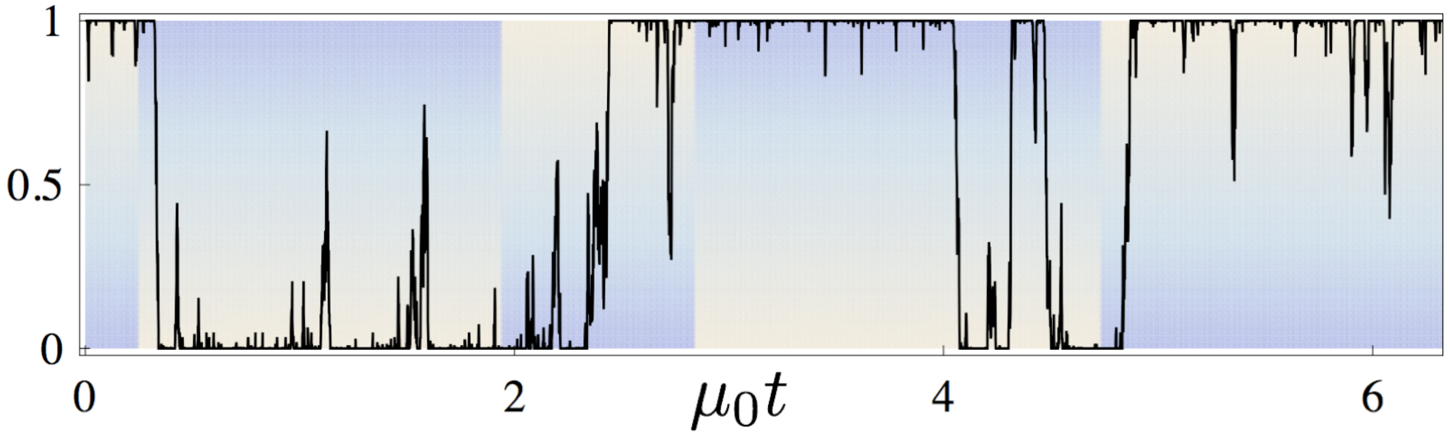
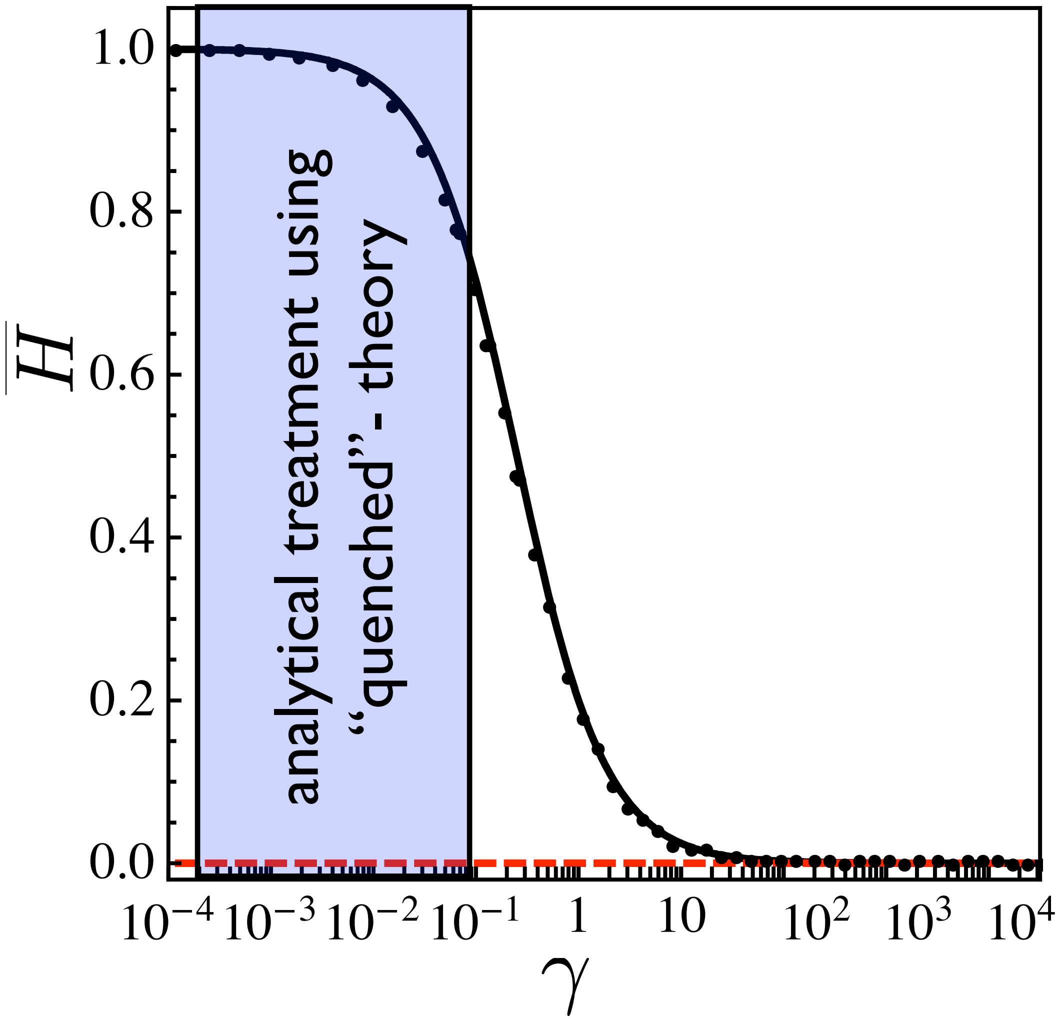
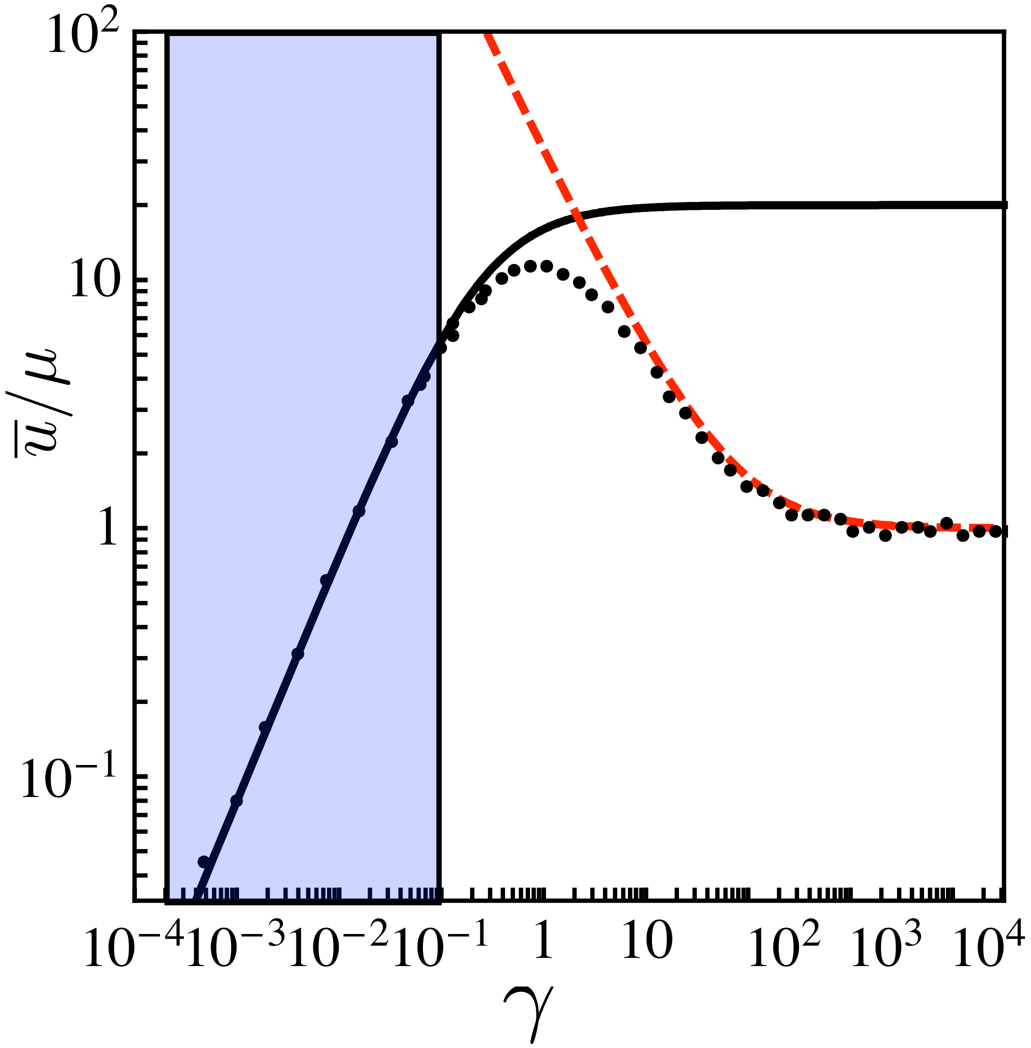
Macro-evolutionary fitness seascape



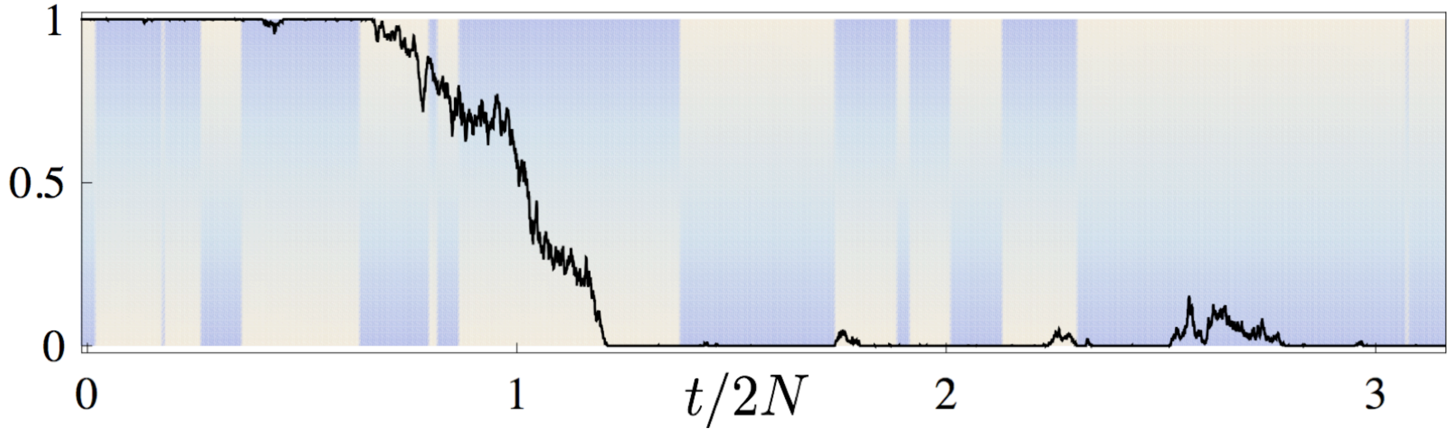
degree of adaptation

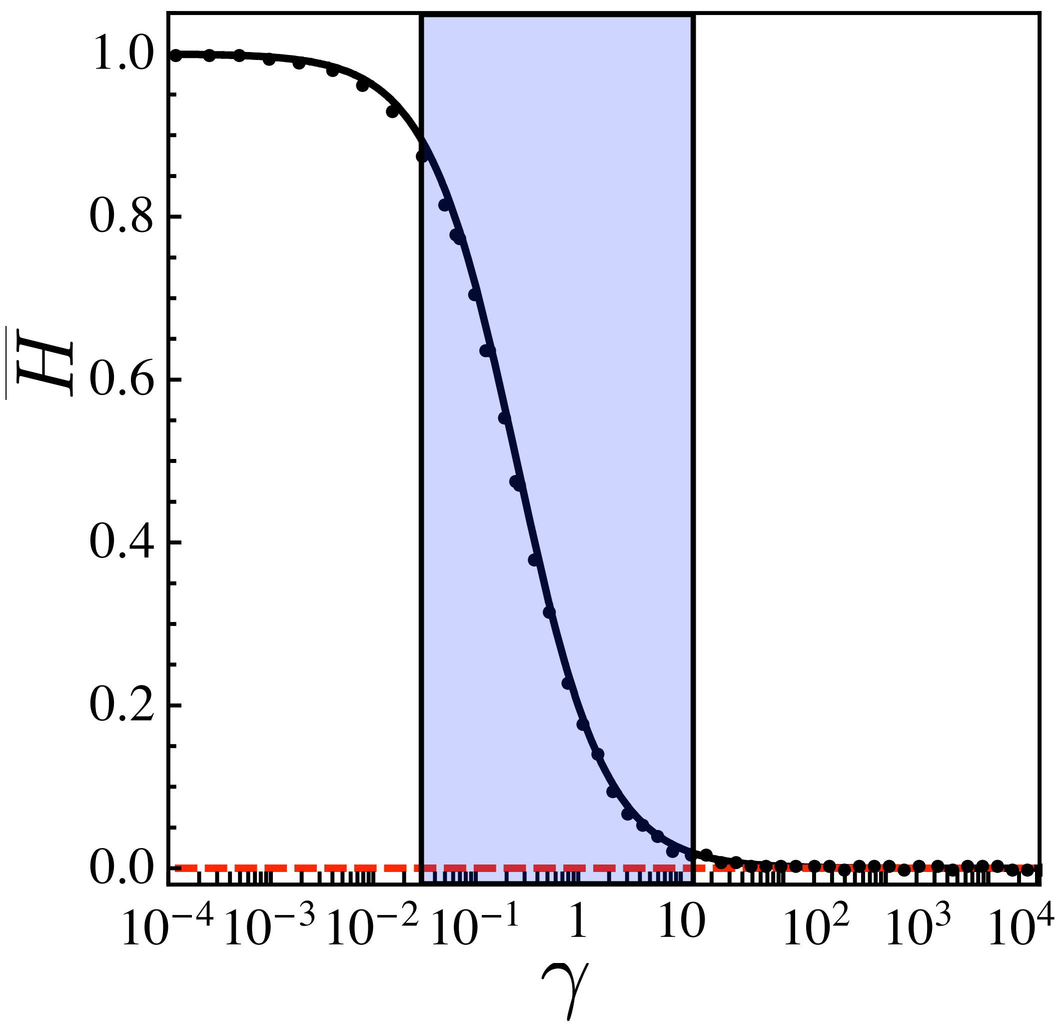


substitution rate/neutral rate



Cross-over from macro- to micro-evolutionary fitness seascape

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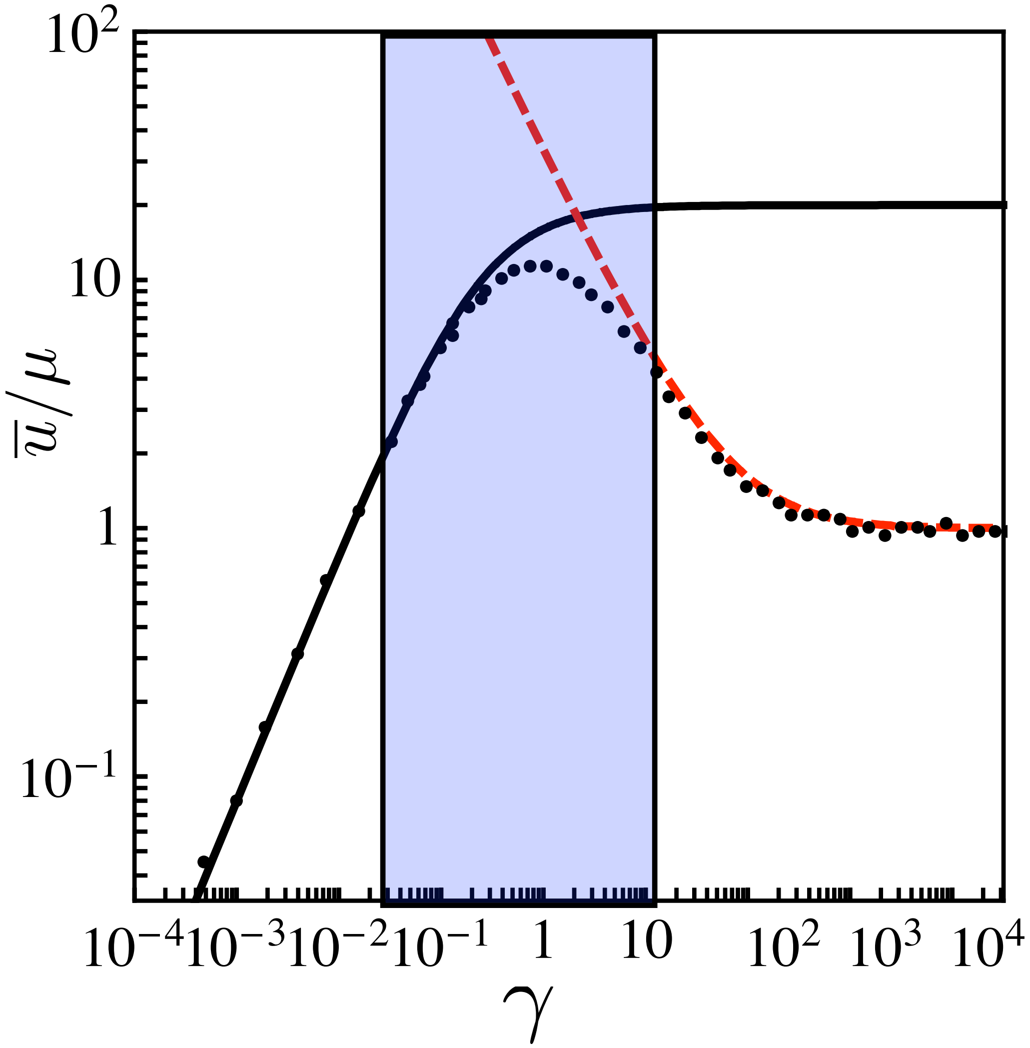
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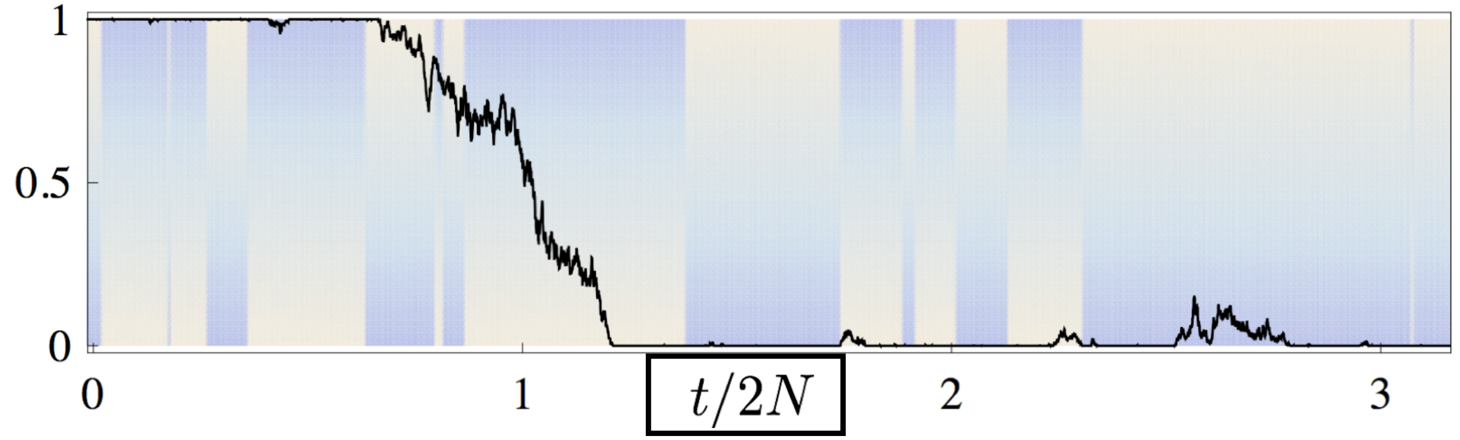

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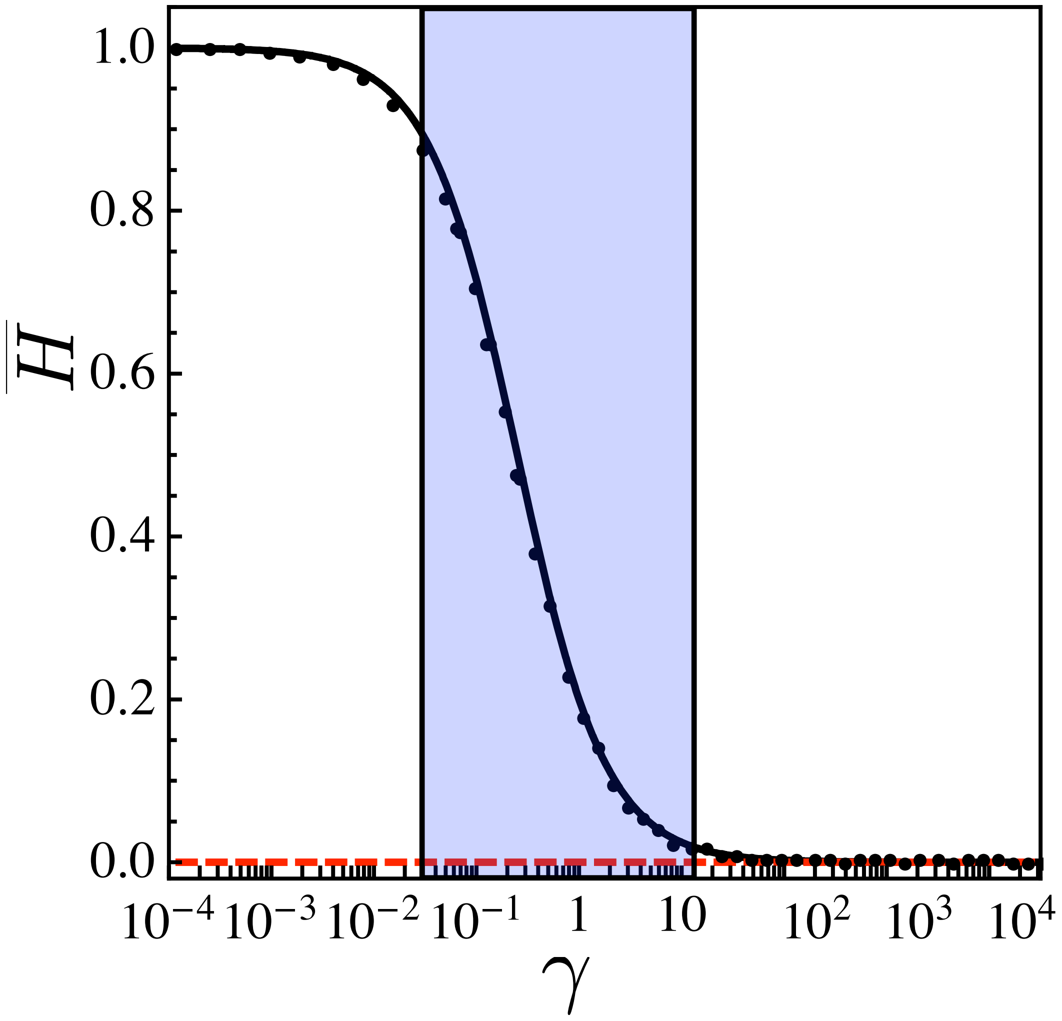

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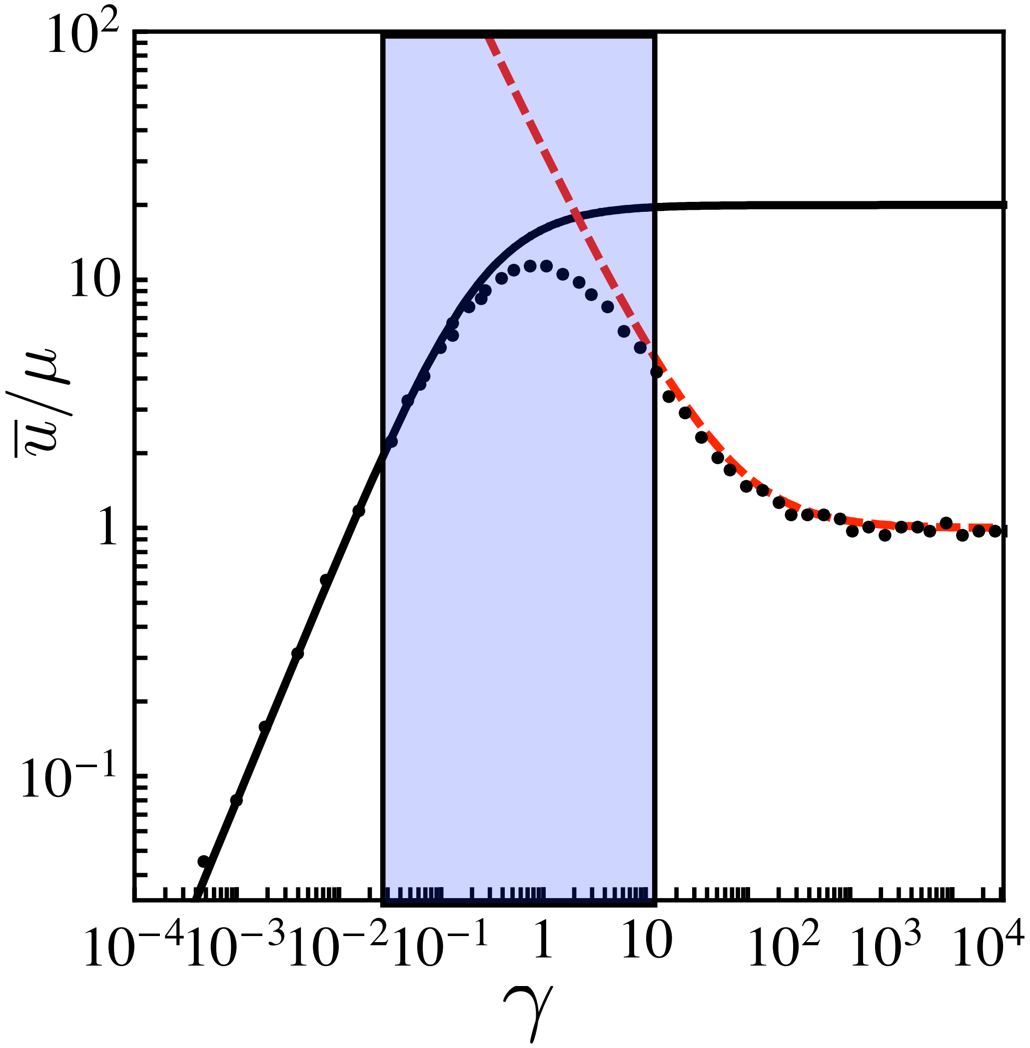
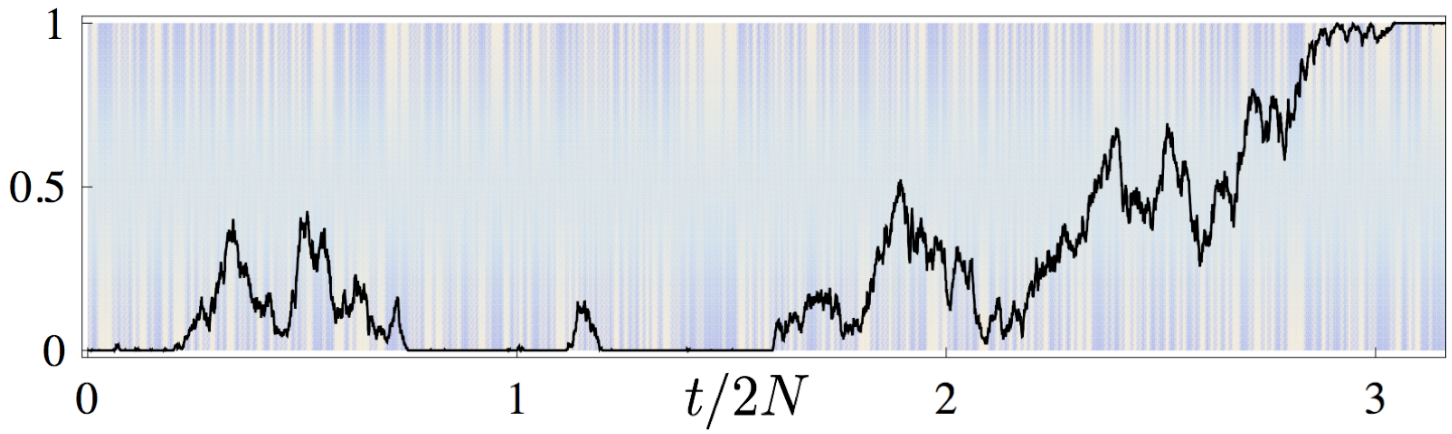


Micro-evolutionary fitness seascape



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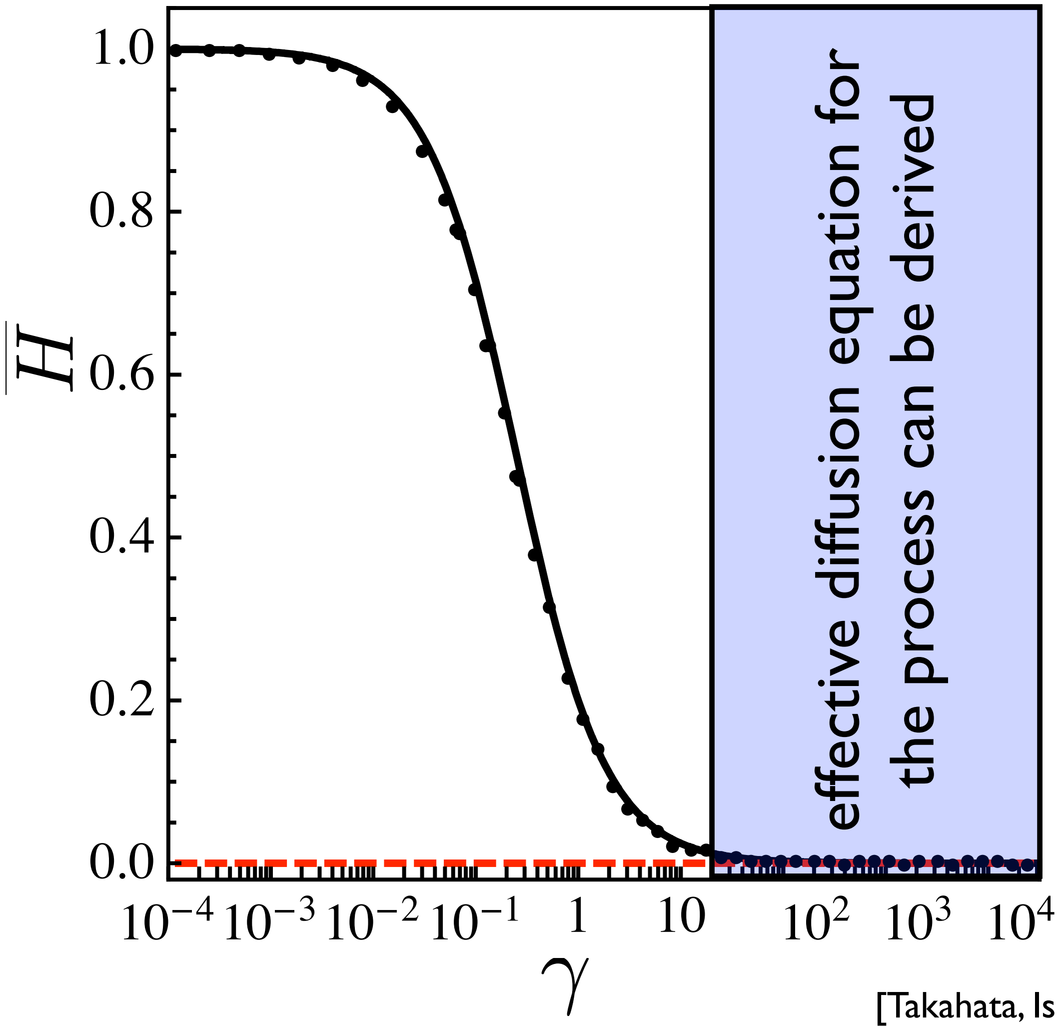

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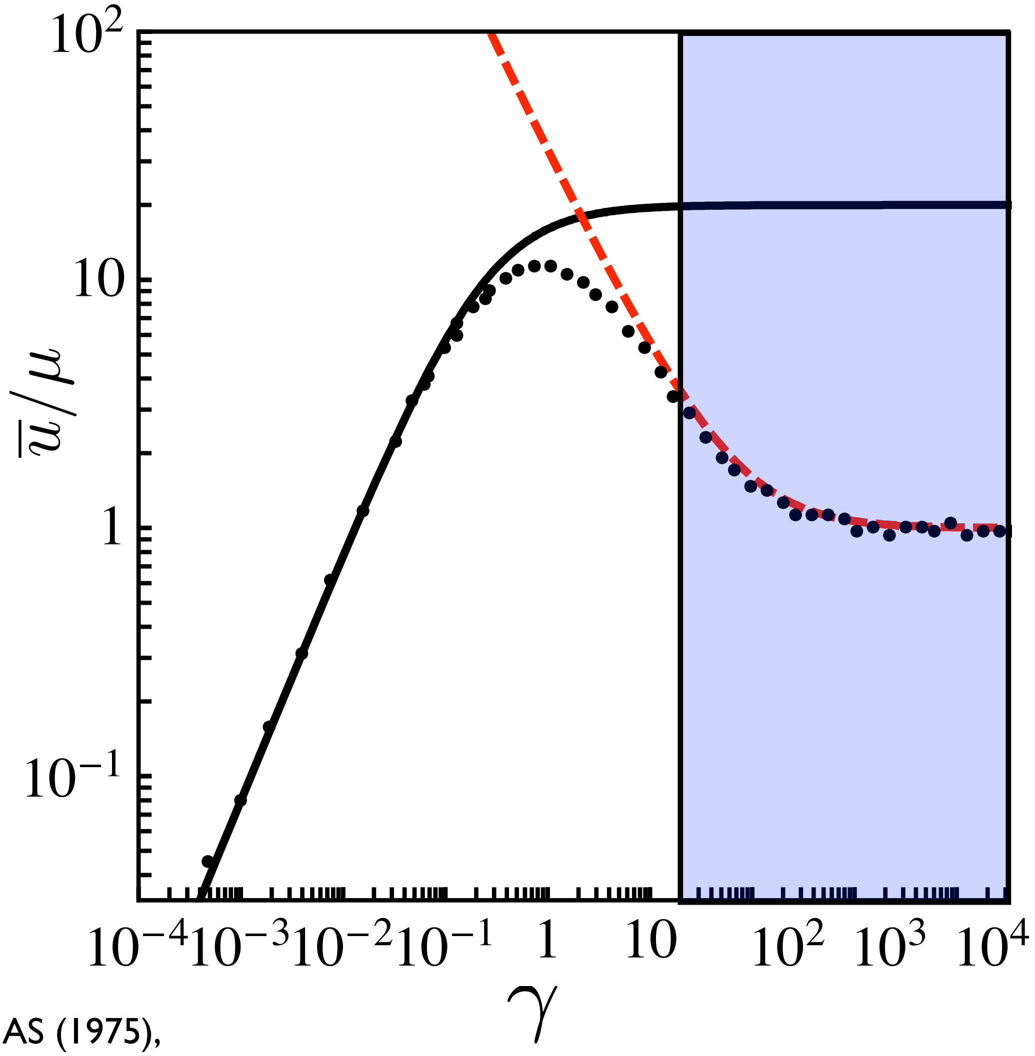

[Takahata, Ishii, Matsuda PNAS (1975),
Takahata, Kimura PNAS (1979)]

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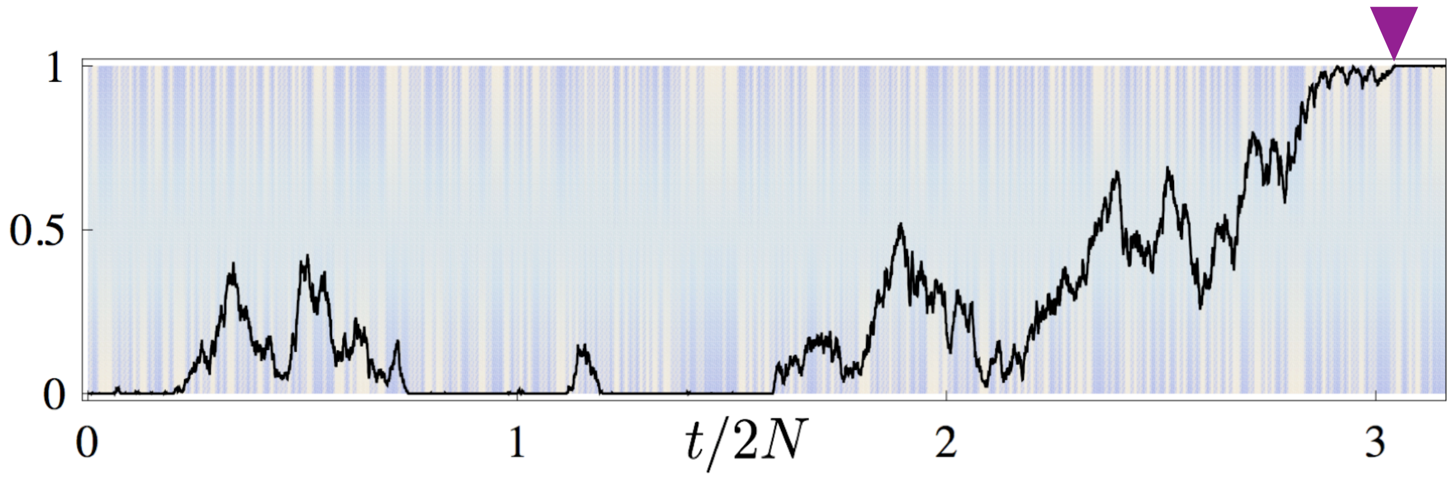

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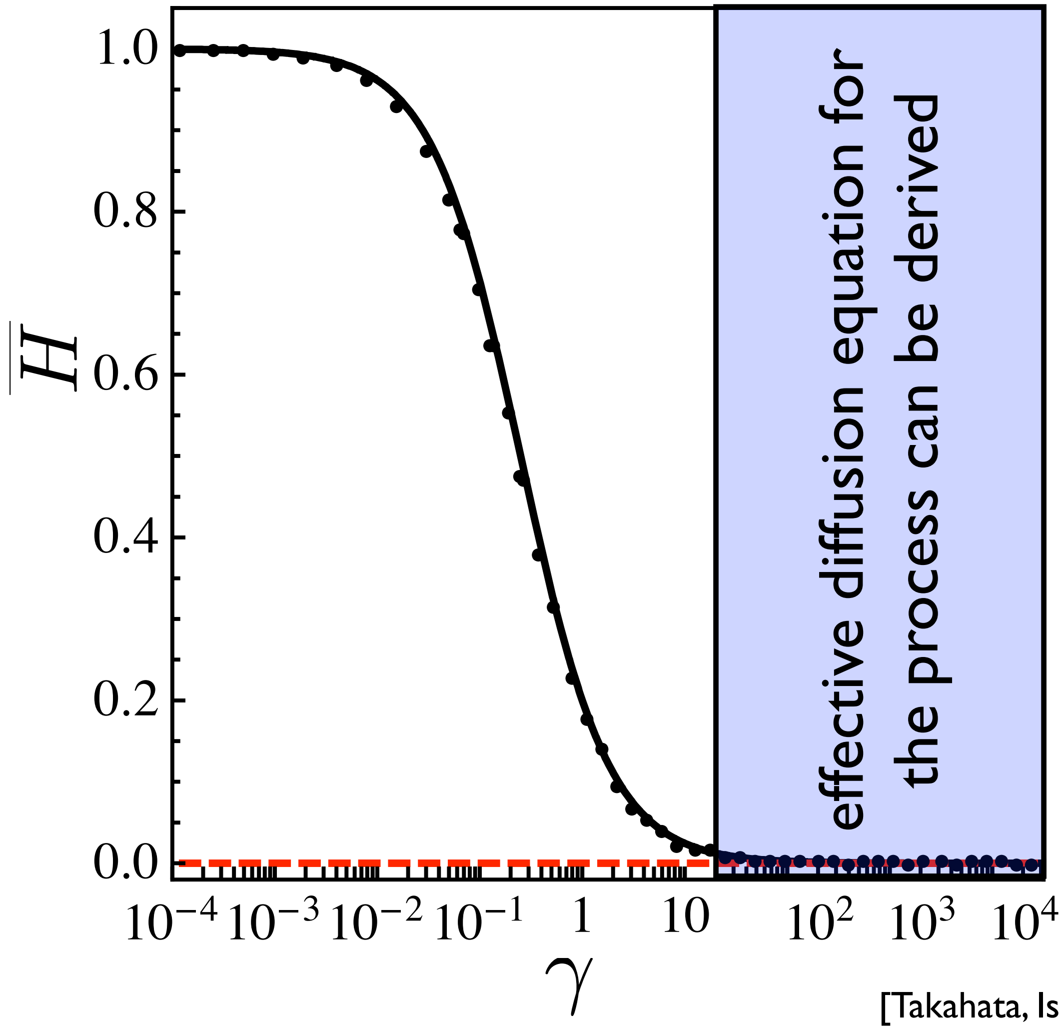

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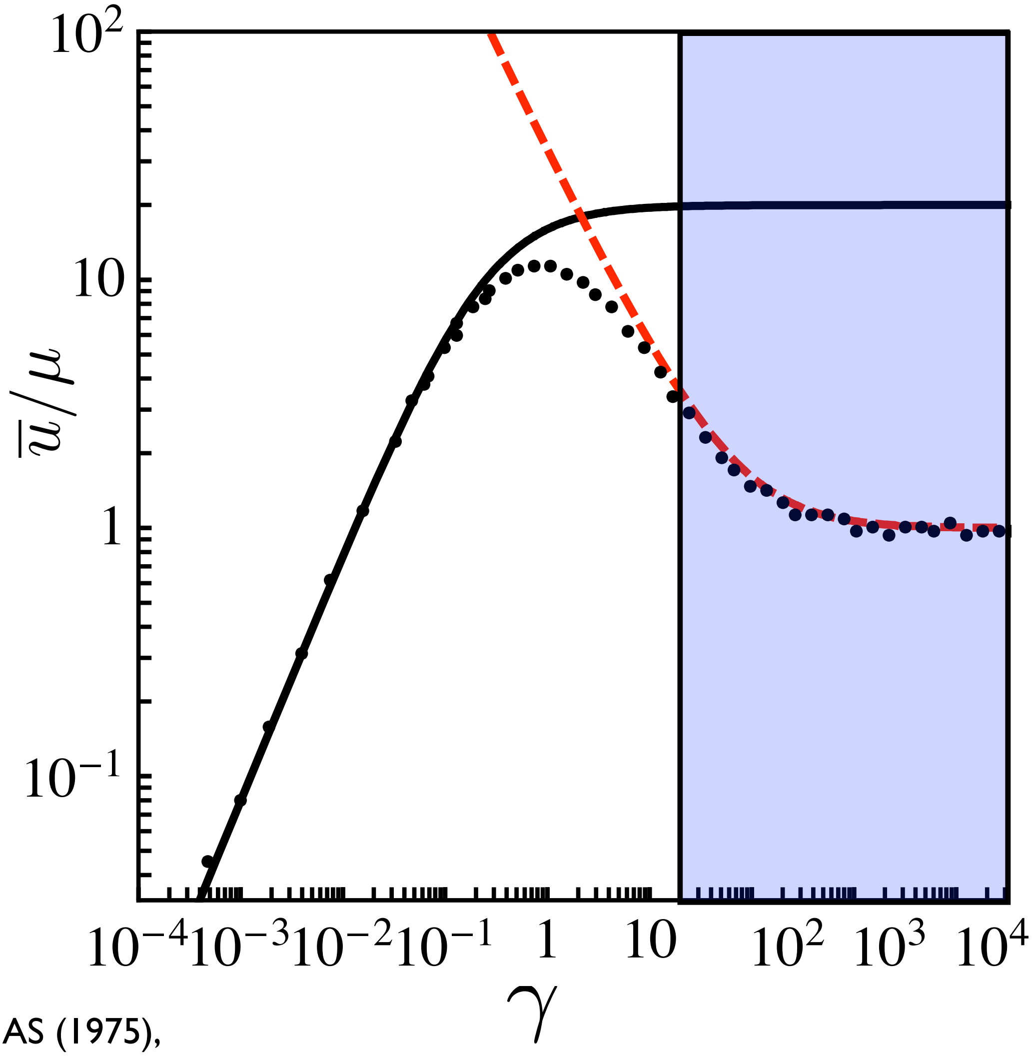

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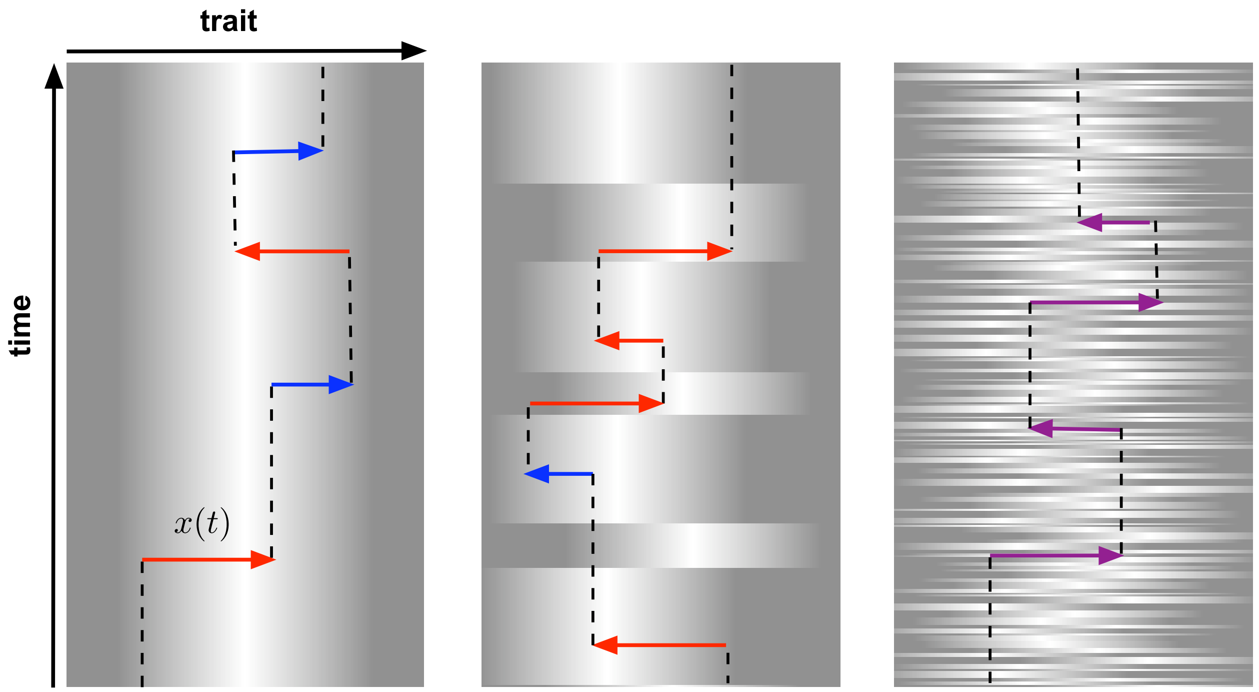
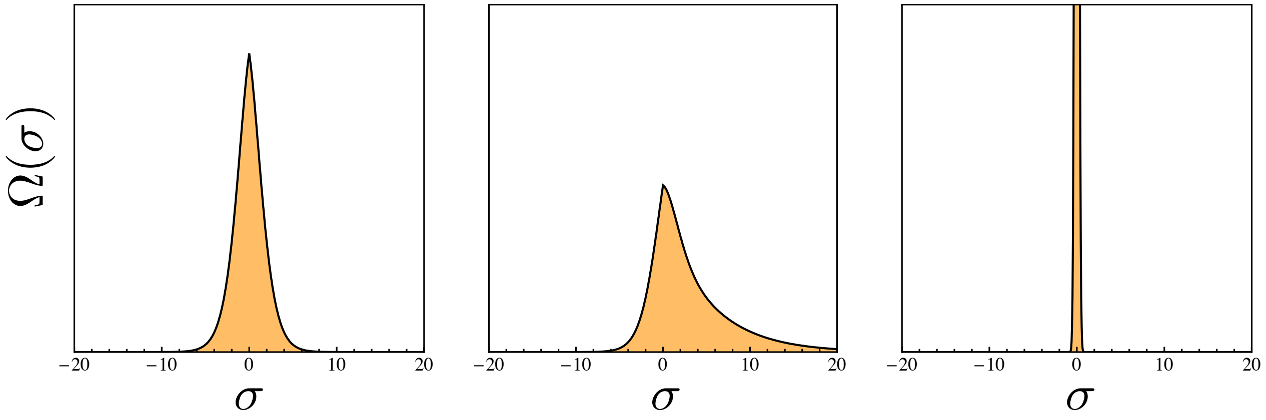
Implications of part I



(a) **static landscape** $(\kappa = 0)$ (b) **macro-evolutionary seascape** $(\kappa \ll \kappa^*)$ (c) **micro-evolutionary seascape** $(\kappa \gg \kappa^*)$

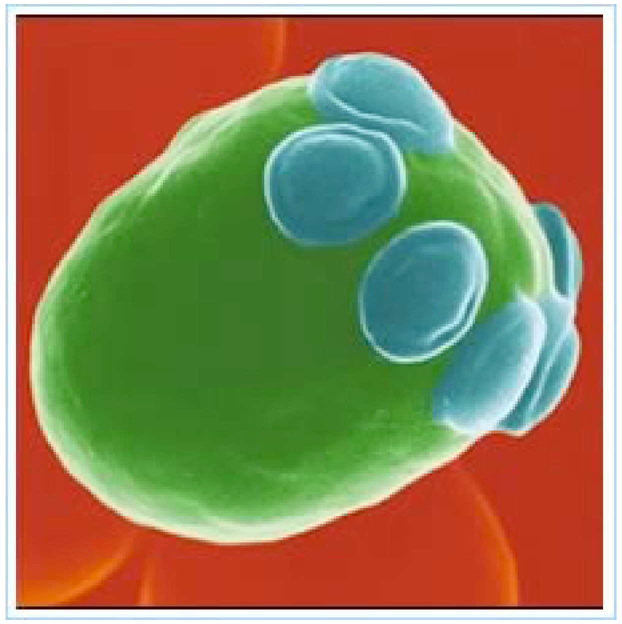


compensatory substitutions $(\Phi = 0)$

adaptative substitutions $(\Phi > 0)$

quasi-neutral substitutions $(\Phi \to 0)$

Case study I: evolution of yeast transcription factor binding sites



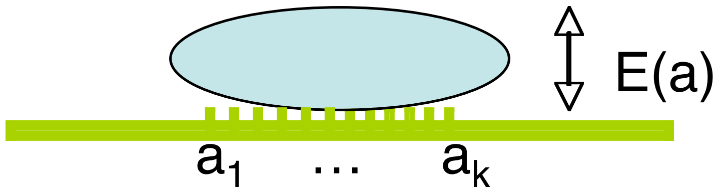
http://www.microbeworld.org/htm/aboutmicro/gallery/gallery_06_sacc.htm; originally published: Microbiol. Rev. 54: 381-431, 1990.

Biophysics of sites determines biological function

- Binding energy E(**a**) depends additively on the site sequence

  a = (a_1,…,a_k) (ABF1 sites: k=14):

  [Berg and v. Hippel (1986), Fields et al. J.Mol.Biol. (1997)]

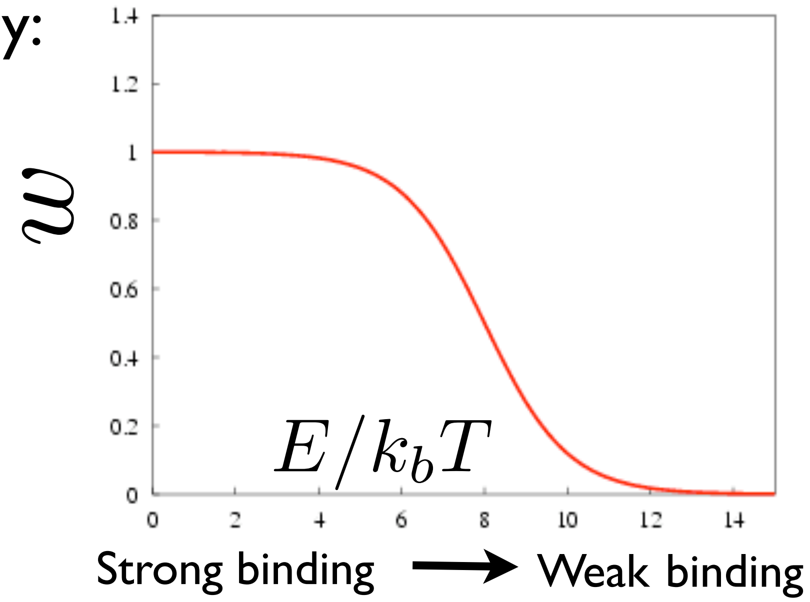


$$E(\mathbf{a}) = \sum_{i=1}^{k} \epsilon_i(a_i)$$

- Binding probability depends nonlinearly on binding energy:

  [Gerland, et al. PNAS (2002)]

$$w(E) = \frac{1}{1+\exp\left[(E-\rho)/k_b T\right]}$$

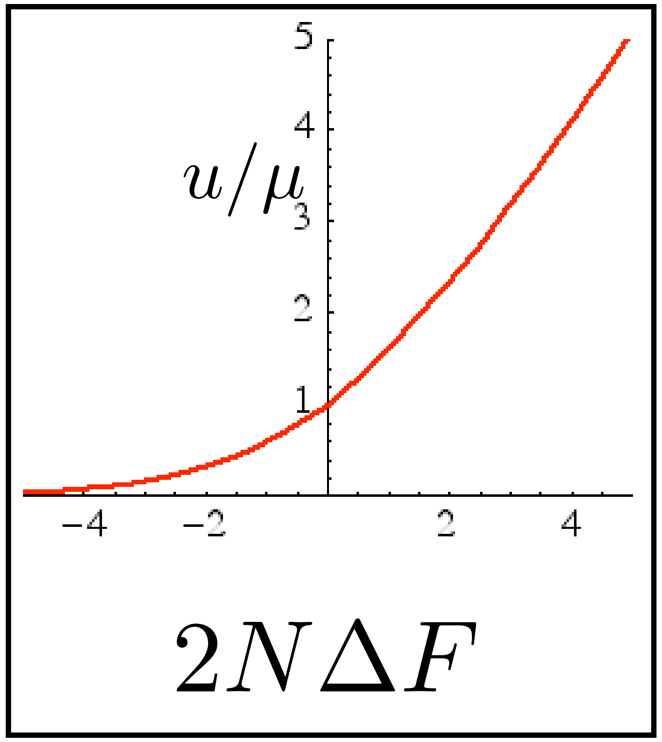


- Binding energy is a quantitative molecular phenotype

Population dynamics of binding sites

- Wright-Fisher process with drift, mutation, and selection.
- Study the process at the level of substitution dynamics.
- Kimura-Ohta rates:

$$u_{\mathbf{a}\to\mathbf{b}} = \mu_{\mathbf{a}\to\mathbf{b}} N \frac{1-\exp[-2(F(\mathbf{b})-F(\mathbf{a}))]}{1-\exp[-2N(F(\mathbf{b})-F(\mathbf{a}))]}$$



- Stationary distributions under neutral evolution:

$$P_0(\mathbf{a}) \qquad \text{such that} \qquad \frac{P_0(\mathbf{a})}{P_0(\mathbf{b})} = \frac{\mu_{\mathrm{b}\to\mathrm{a}}}{\mu_{\mathrm{a}\to\mathrm{b}}}$$

- under selection (as given by the Kimura-Ohta rates):

$$Q(\mathbf{a}) = P_0(\mathbf{a}) \exp[2NF(\mathbf{a}) + \text{const.}]$$

[J.Berg, S.Willmann, M.Lässig, BMC Evol. Biol. (2004)]

Measuring genomic fitness landscapes

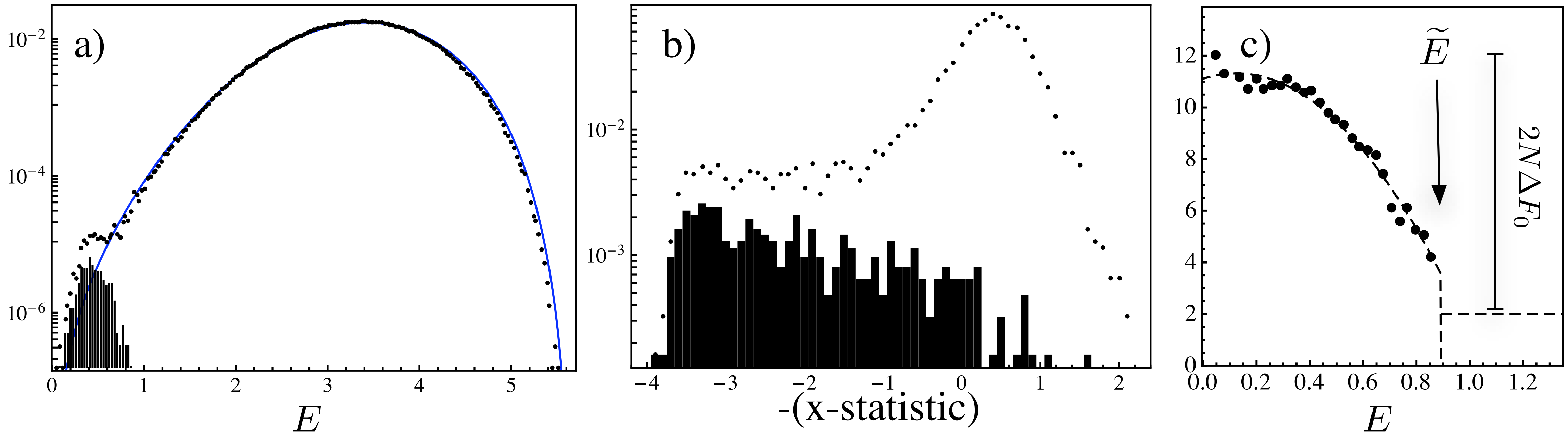
- Project ensembles onto phenotype:

$$\Rightarrow P_0(E), Q(E)$$

- Hidden Markov Model for total counts:

$$W(E) = (1 - \lambda)P_0(E) + \lambda Q(E)$$

ABF1 in yeast



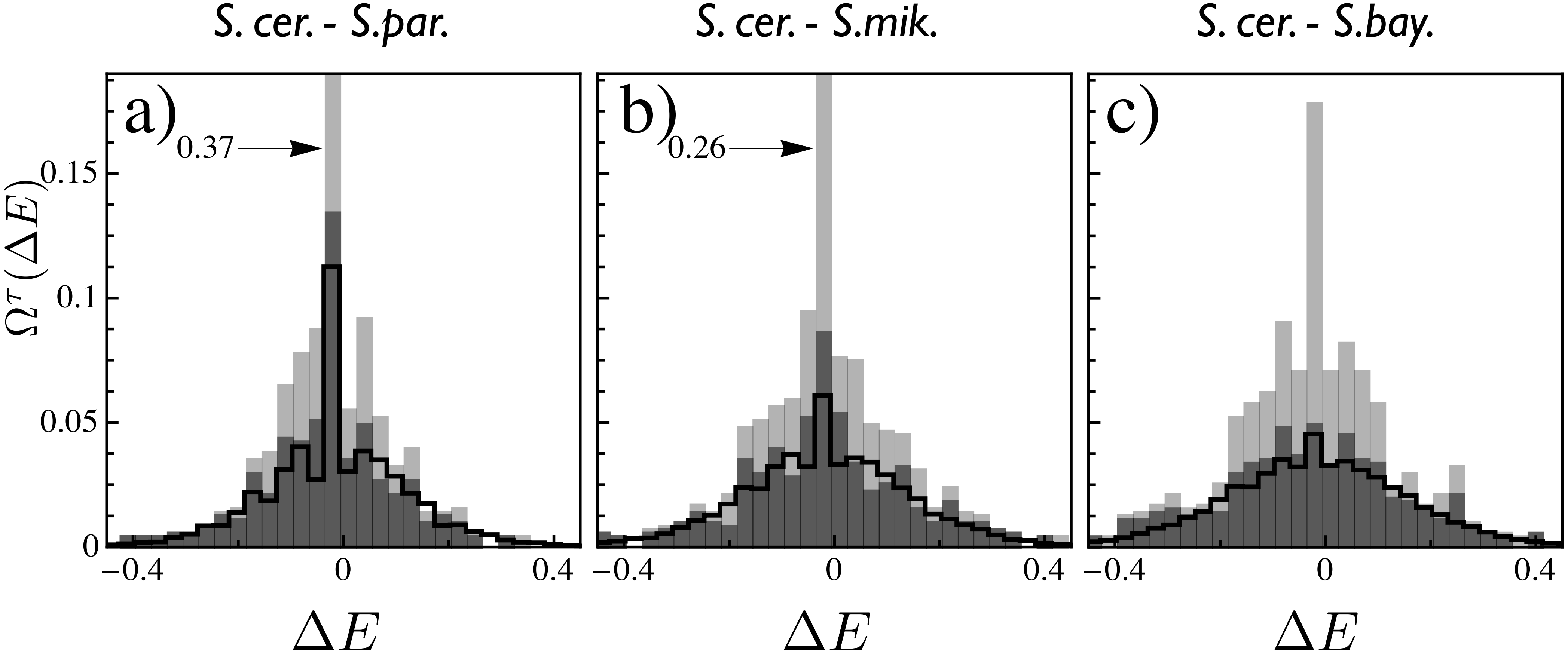
genomic energy distributions

experimental log intensities
[data from Lee et al. Science (2003)]

fitness landscape

[VM, Kinney, Callan, Lässig, PNAS (2008)]

Predicting cross-species evolution: binding energy divergence between orthologous site pairs

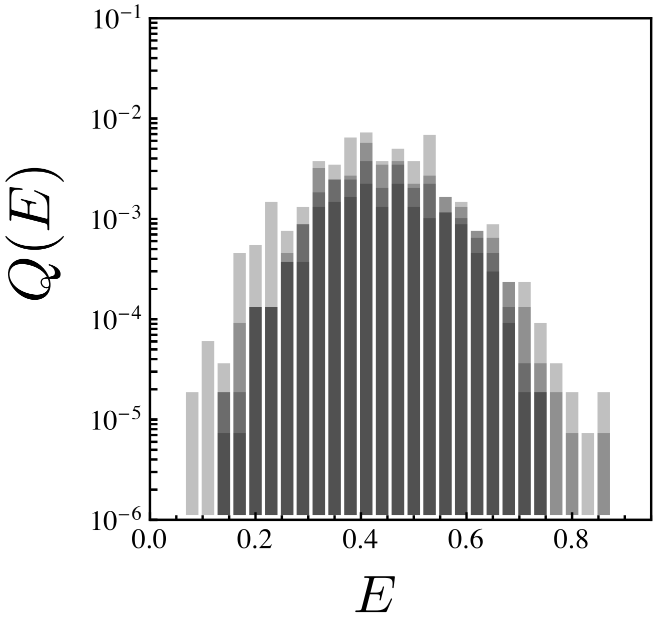


Dark part of the bars: binding sites without overlap with other binding sites.

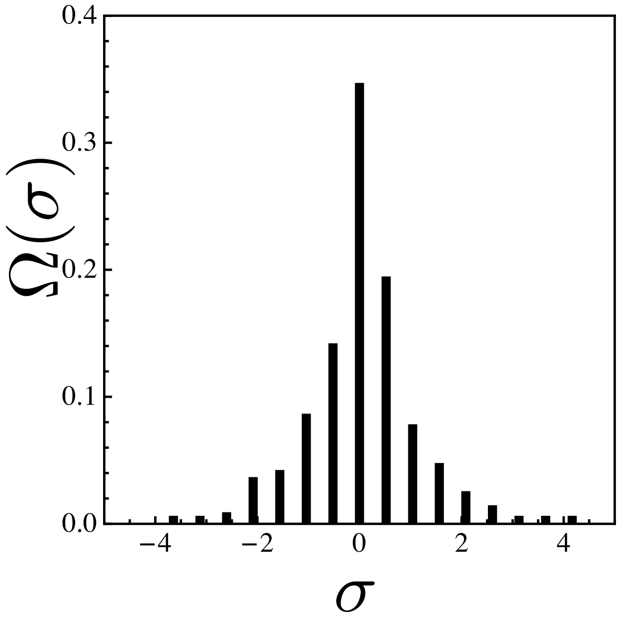
Simulation under the inferred fitness landscape shown as a solid line.

ABF1 sites consistent with equilibrium

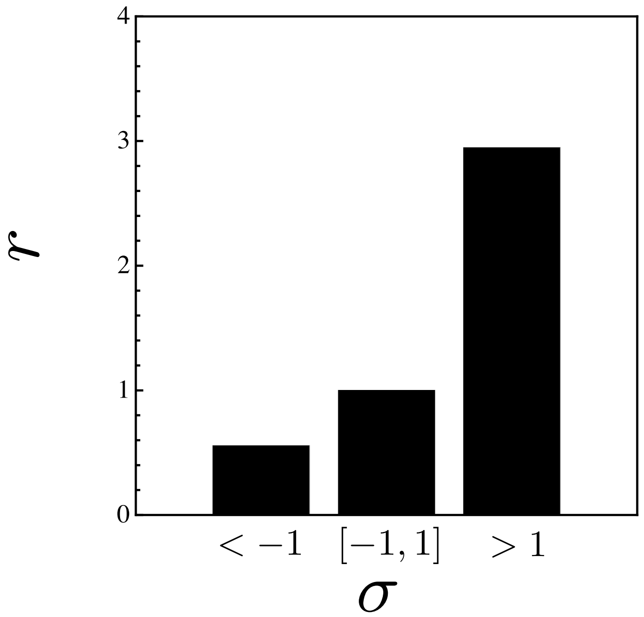
phenotype distributions agree closely in four yeast species



distribution of fitness differences (black) between *(S.cer-S.par) is* closely symmetric



McDonald-Kreitman ratio

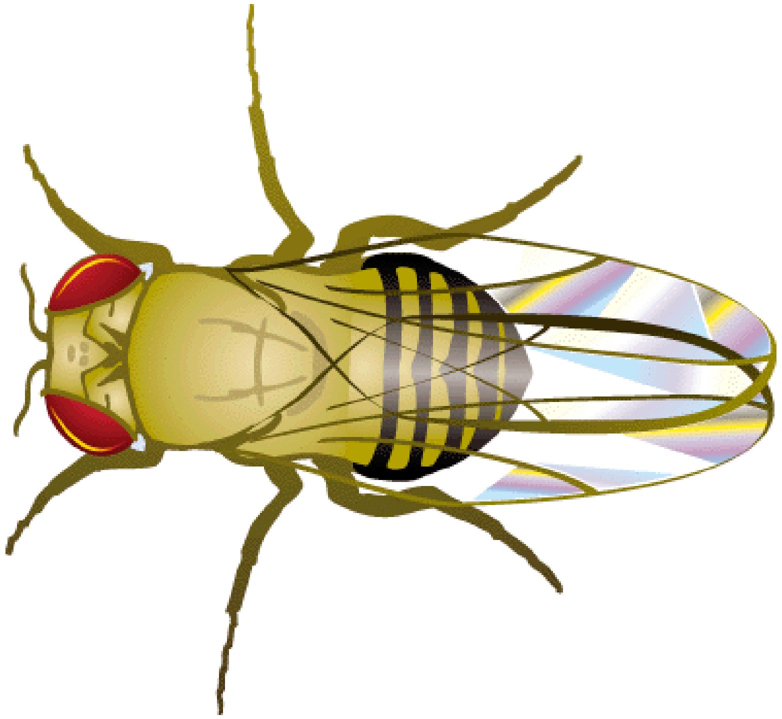


- Evolution a series of compensatory substitutions with no systematic change in the molecular phenotype.
- Fitness flux: $\Phi \sim 0$.
- Plenty of evidence for positively selected substitutions - yet no evidence for adaptation.

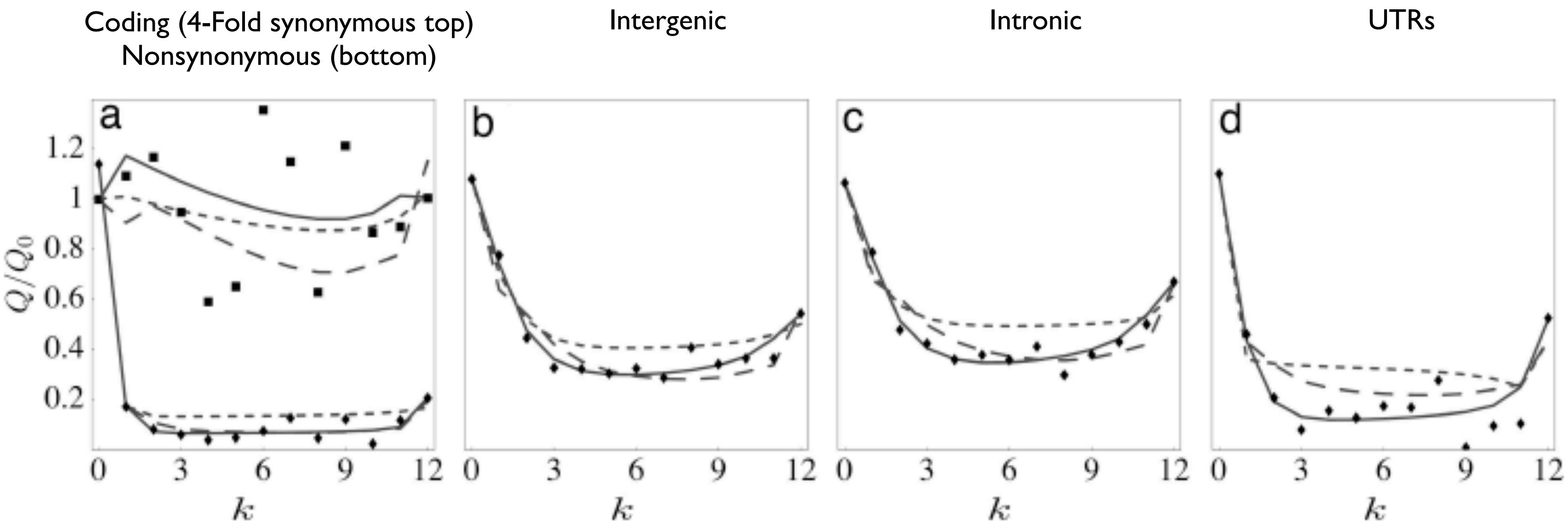
[see also Moses et al. BMC Evol. Biol. (2003)]

Case study II: fruit fly evolution

- Data consist of out-group directed polymorphism spectrums of different genomic classes in *Drosophila* species [Glinka et al. 2003, Andolfatto 2005 & Ometto et al. 2005].
- Do model based inference of the evolutionary parameters using the minimal macro-evolutionary fitness seascape model.
- Is there evidence for adaptation: $\Phi > 0$?



http://www.exploratorium.edu/exhibits/mutant_flies/normal.gif


Coding (4-Fold synonymous top)
Nonsynonymous (bottom)

Intergenic

Intronic

UTRs

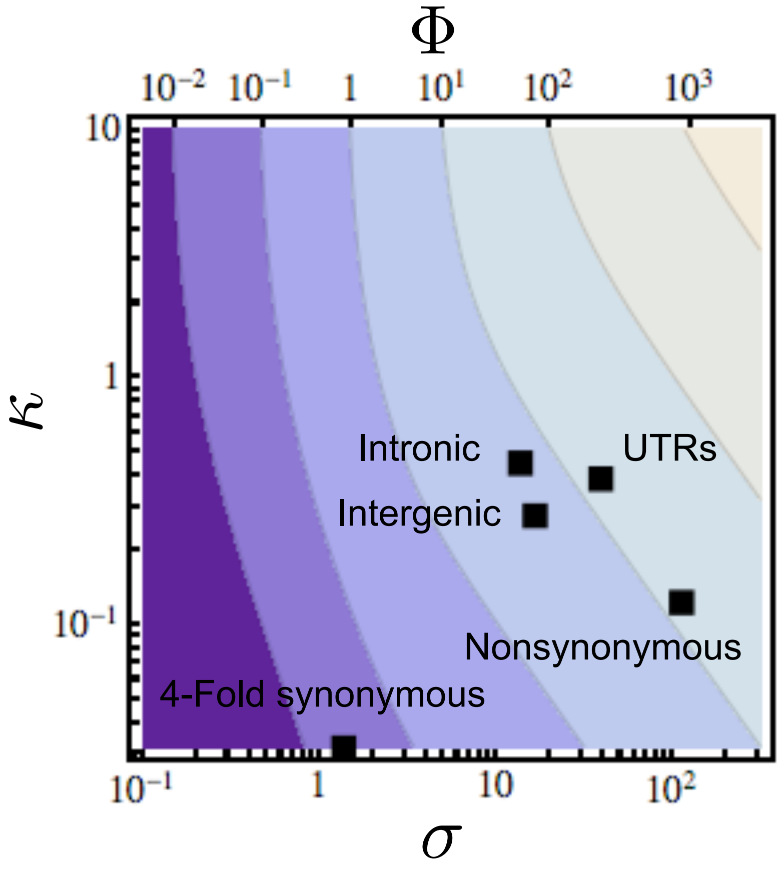
- Competing models:

  1. macro-evolutionary seascape (solid line)
  2. demographical model with a population bottleneck and equilibrium selection (long dashed line)
  3. equilibrium selection (short dashed line)

- Assume stationary ancestral state and sum over it.

- Do Bayesian Inference of evolutionary parameters using both polymorphism and substitution data (correct scores for linkage effects).

Macro-evolutionary seascape gives a consistent description of fly genomes evolution



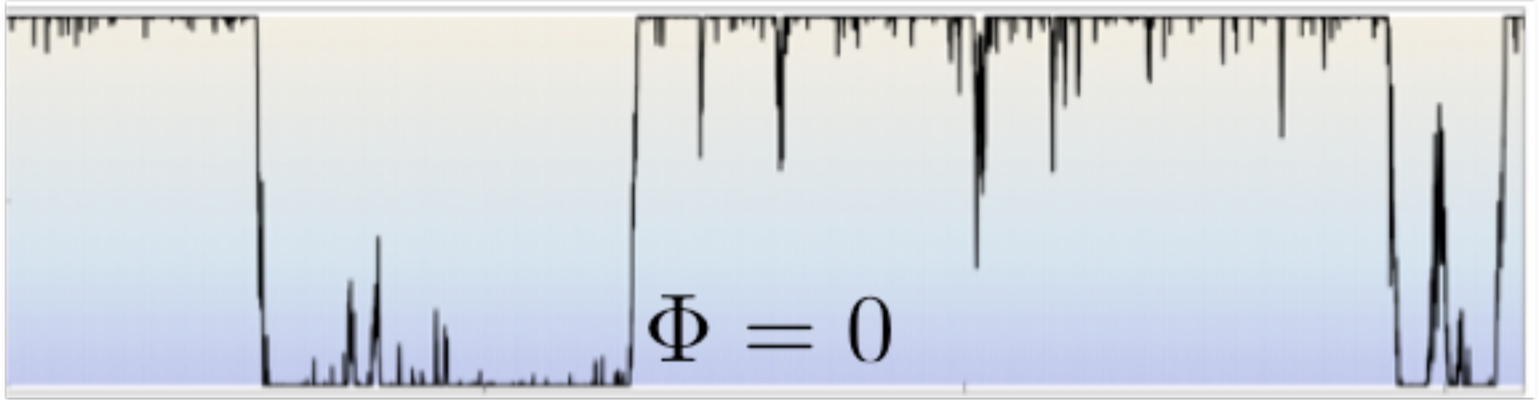
- All genomic categories (except 4-Fold synonymous) have **positive fitness flux** $\Phi > 0$ i.e. $\sigma \gg \kappa > 0$ and are **highly adapted**.

- What are possible reasons for the observed time-dependent selection?

1. Epistasis (substitutions in other loci change the preferred allele somewhere else).
2. External changes, e.g. environment.
3. …

Conclusions

- Positive selection alone is not enough to prove adaptive evolution.
- Adaptive substitutions take place at *a macro-evolutionary seascape* and give rise to *a positive fitness flux*.
- Changes in selection trigger adaptive substitutions and thus fix the arrow of time in molecular evolution.



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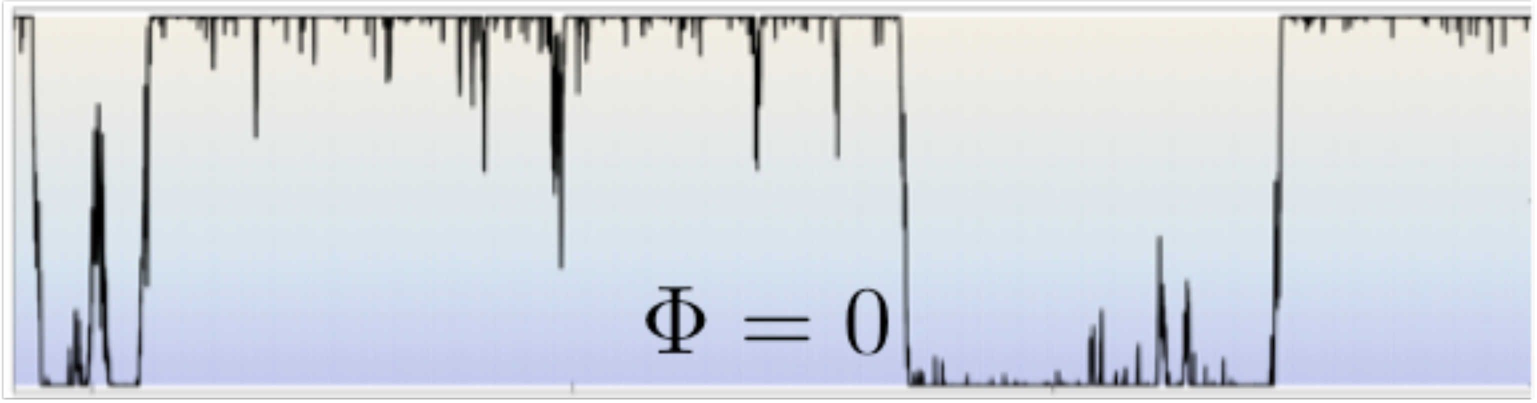

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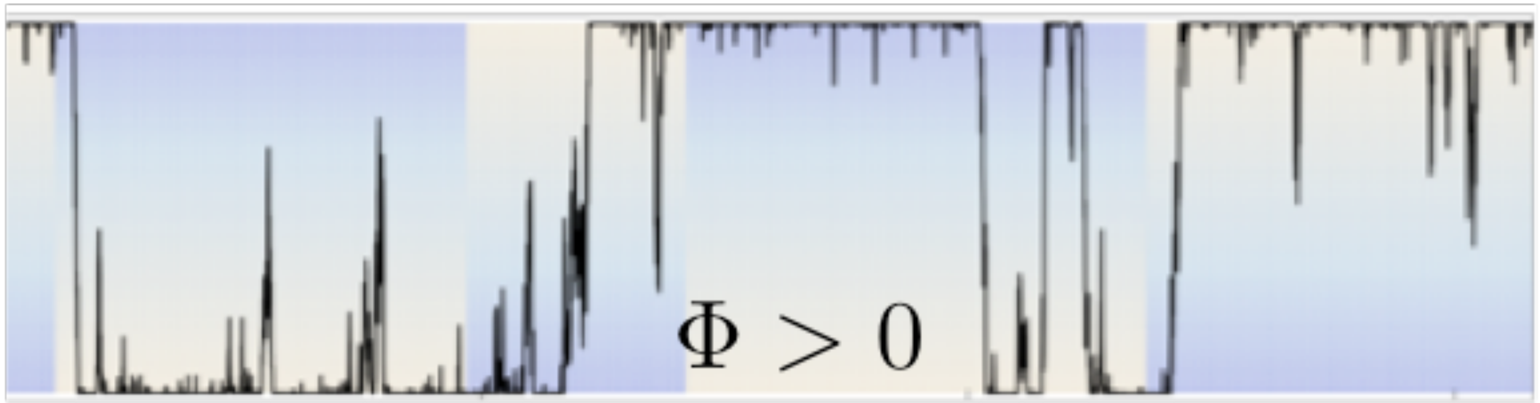

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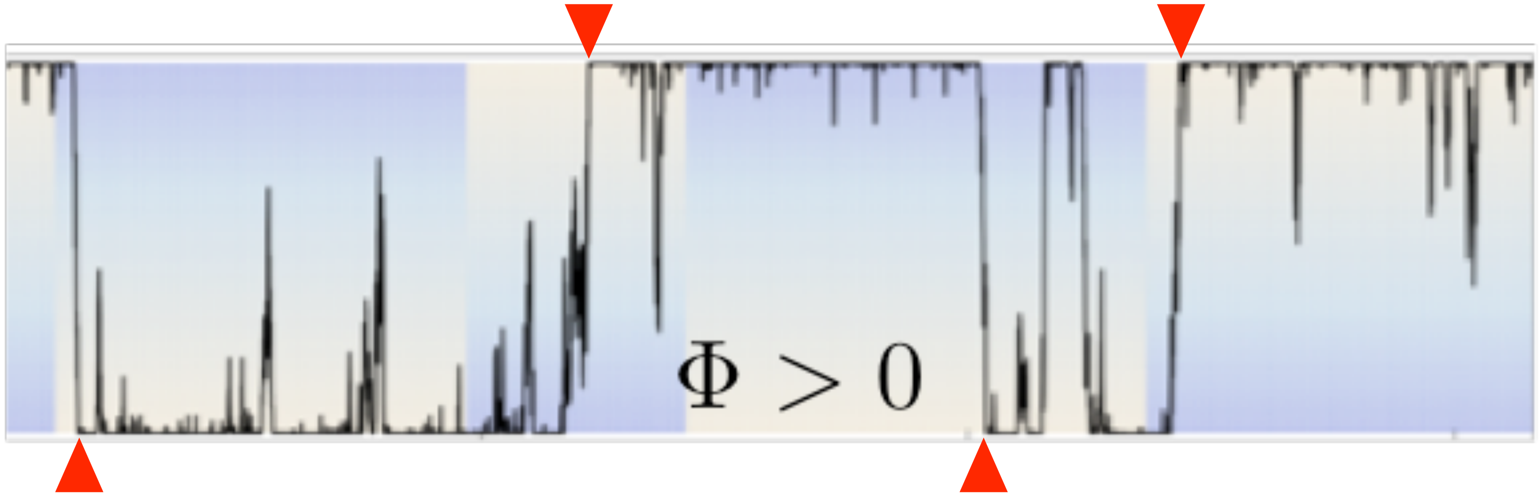

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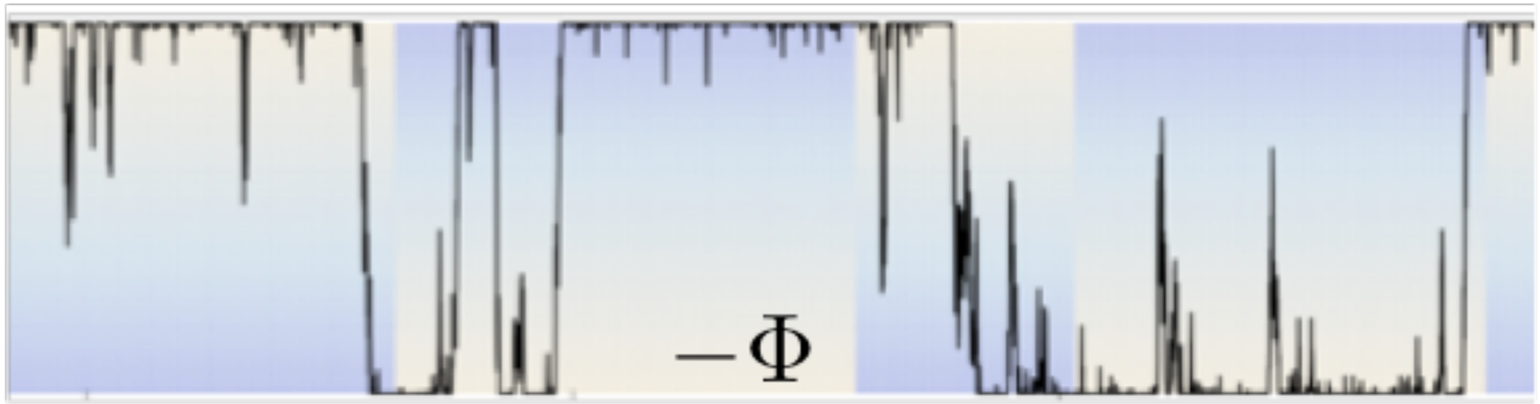

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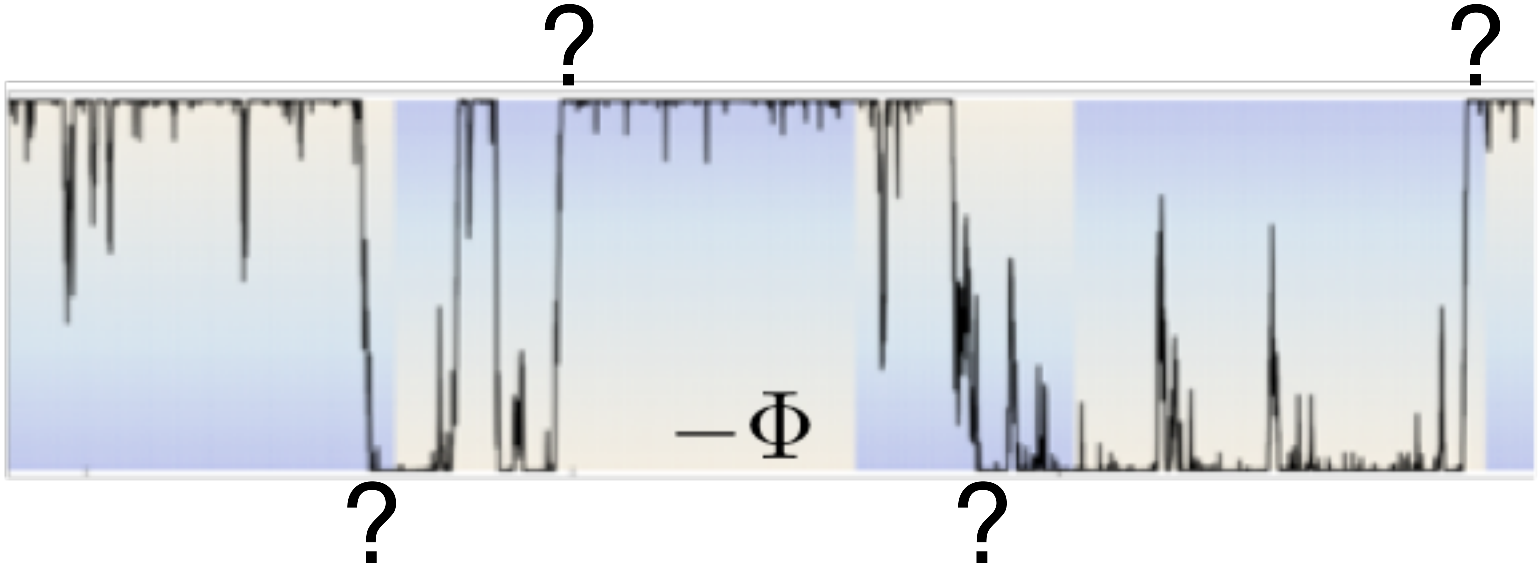

Data Acknowledgments

- **Yeast:** Kellis et al. 2003, Lee et al. 2003 & Saccharomyces Genome Resequencing Project
- **Fruit fly:** Glinka et al. 2003, Andolfatto 2005 & Ometto et al. 2005