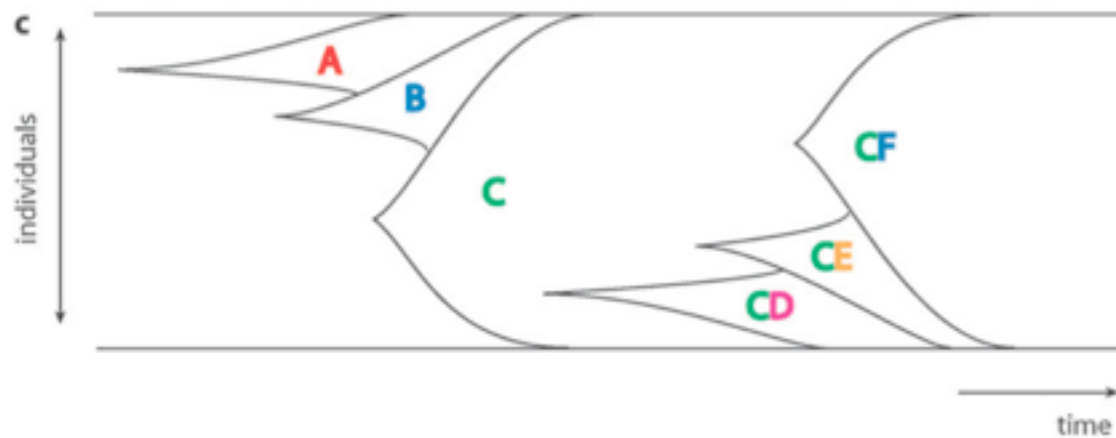


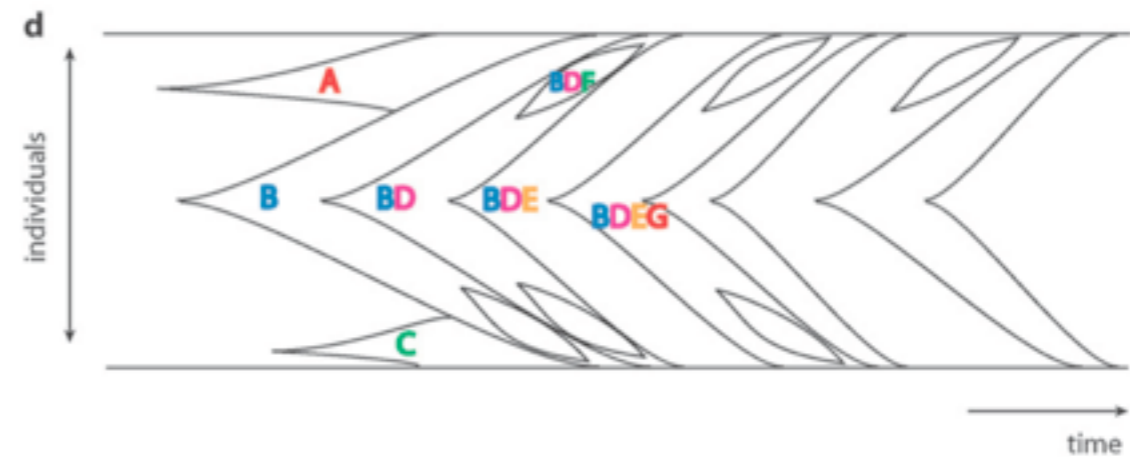
Emergent Neutrality in Adaptive Genome Evolution

Stephan Schiffels

Adaptation in Asexuals



Few beneficial mutations of *different* strength
➔ clonal interference
(Gerrish and Lenski, 1998)

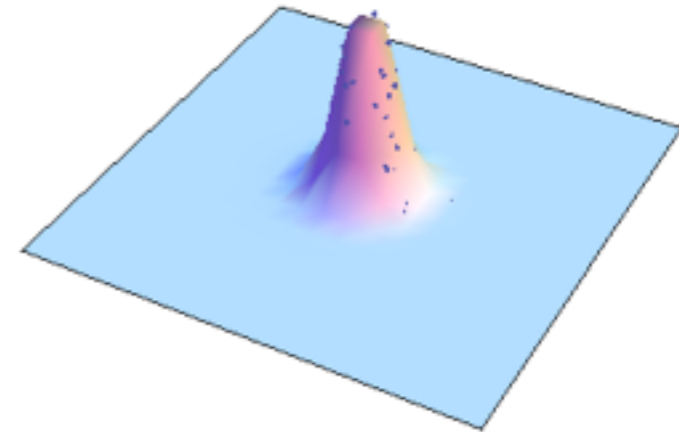


Many beneficial mutations of *similar* strength
➔ multiple mutations
(Desai and Fisher, 2007)

- How can we reconcile clonal interference and multiple mutations?
- What about neutral and deleterious mutations?

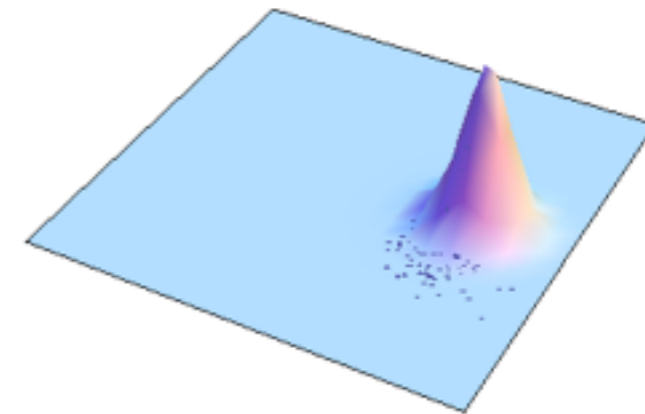
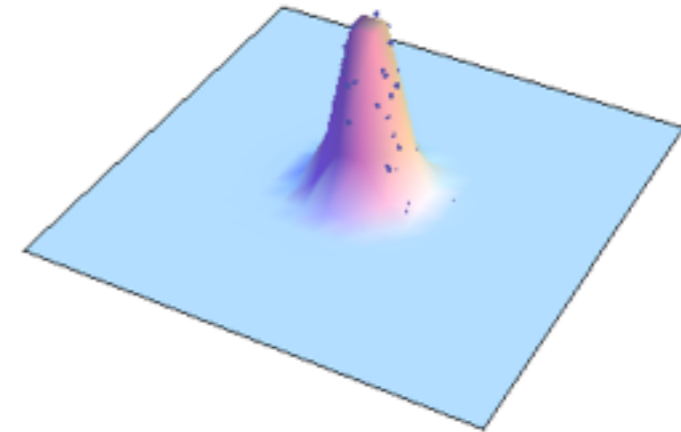
Equilibrium vs. Adaptive Evolution

- Equilibrium (mutation - selection - drift): rate of beneficial substitutions *equals* rate of deleterious substitutions.



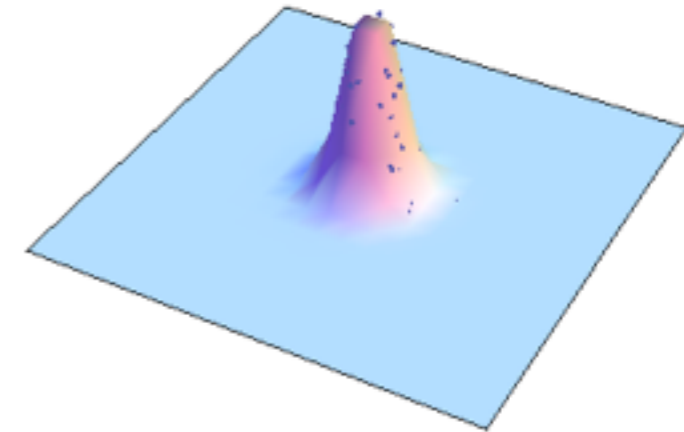
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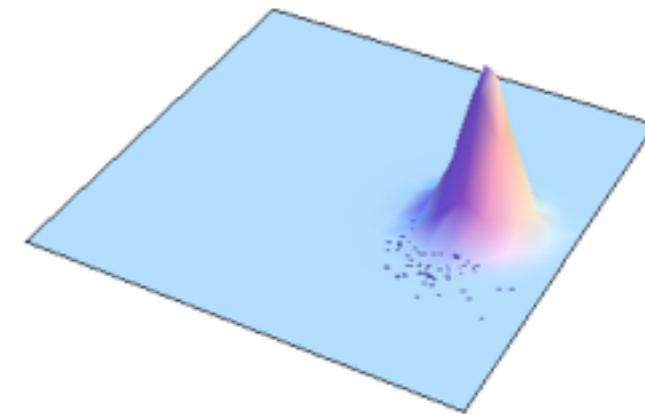


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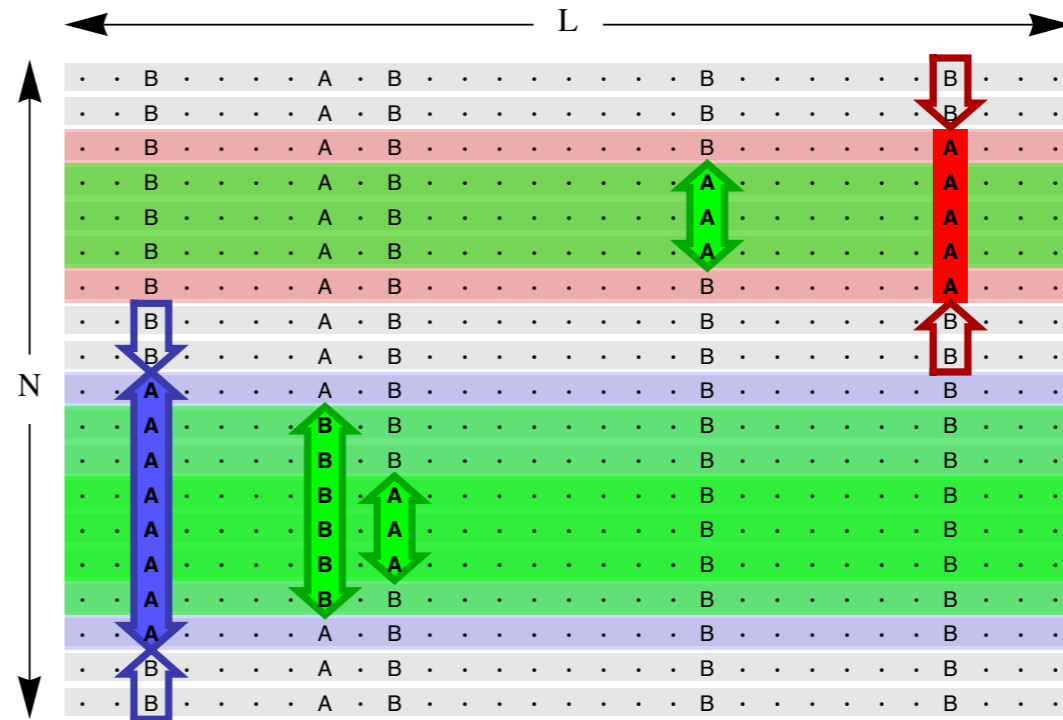
- Adaptive evolution: *surplus* of beneficial substitutions over deleterious ones.



- How far is the population from the peak?
- How does this affect the genomic state?

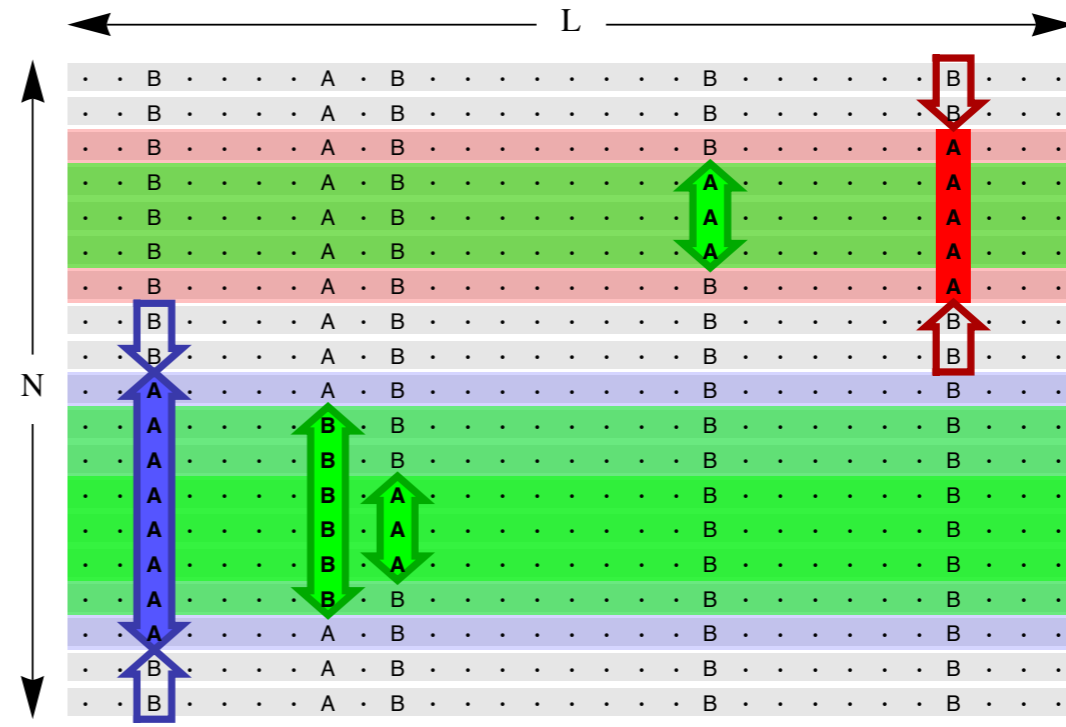
Adaptive Evolution in Linked Genomes

- N aligned genomic samples
- L sites
- Beneficial, neutral and deleterious polymorphisms



Adaptive Evolution in Linked Genomes

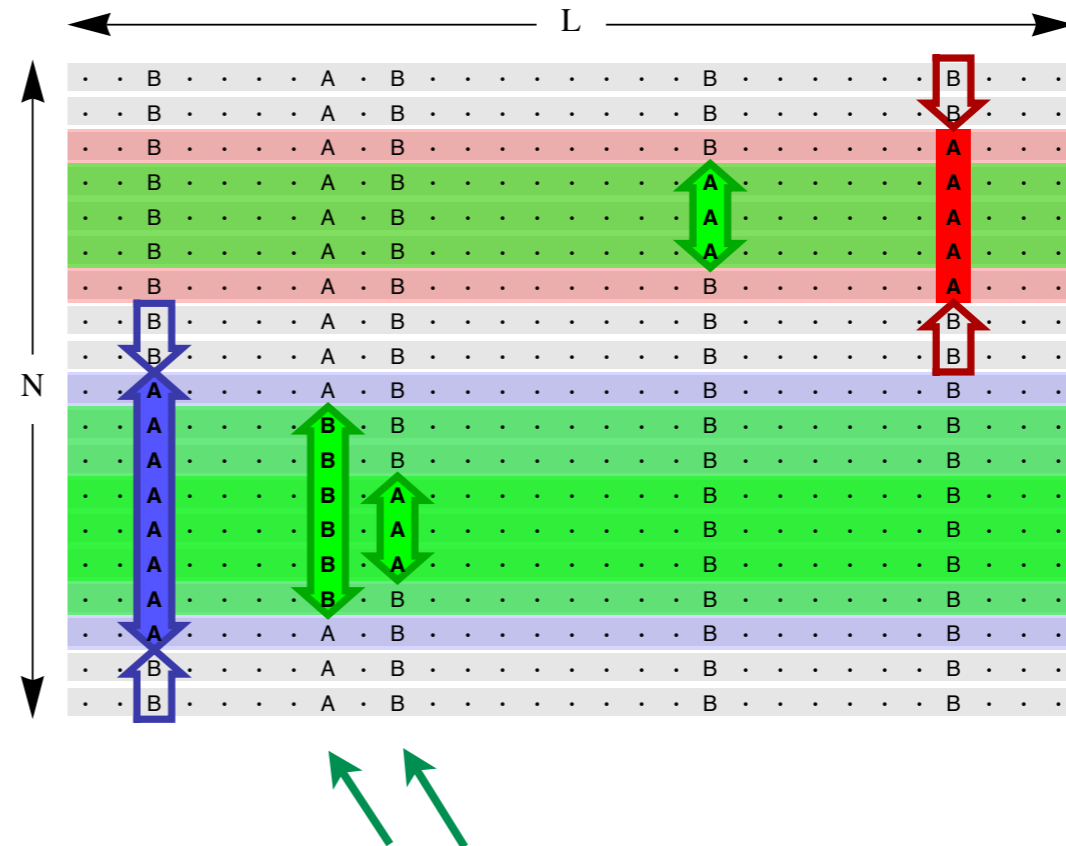
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- Clonal interference

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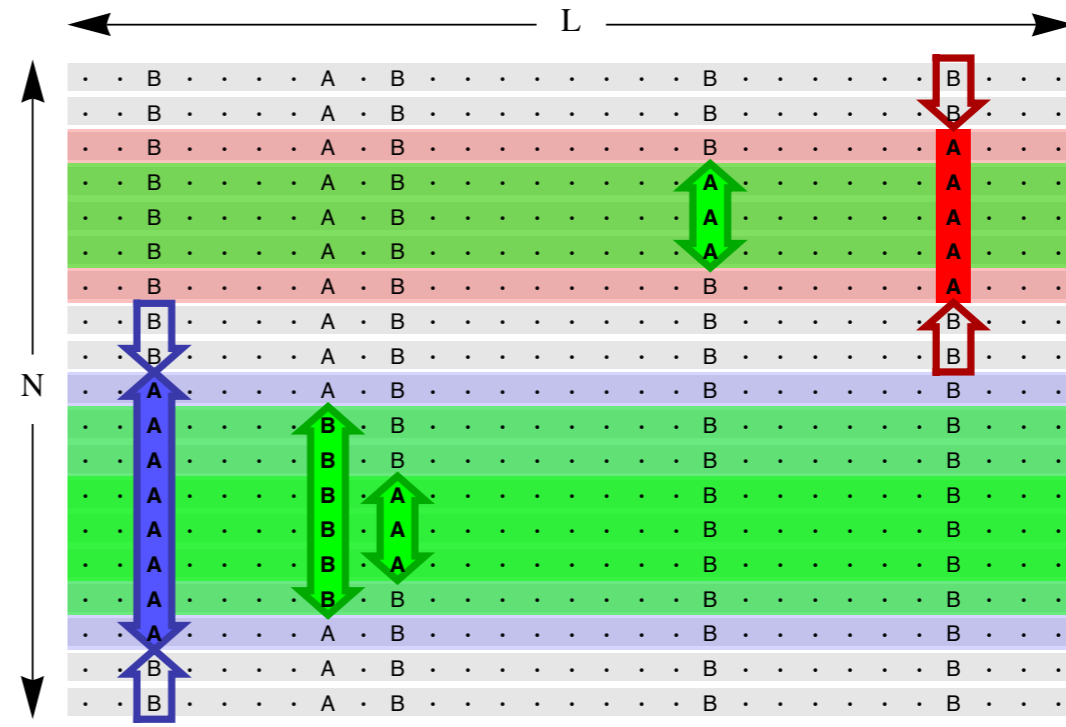
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- Multiple mutations

Adaptive Evolution in Linked Genomes

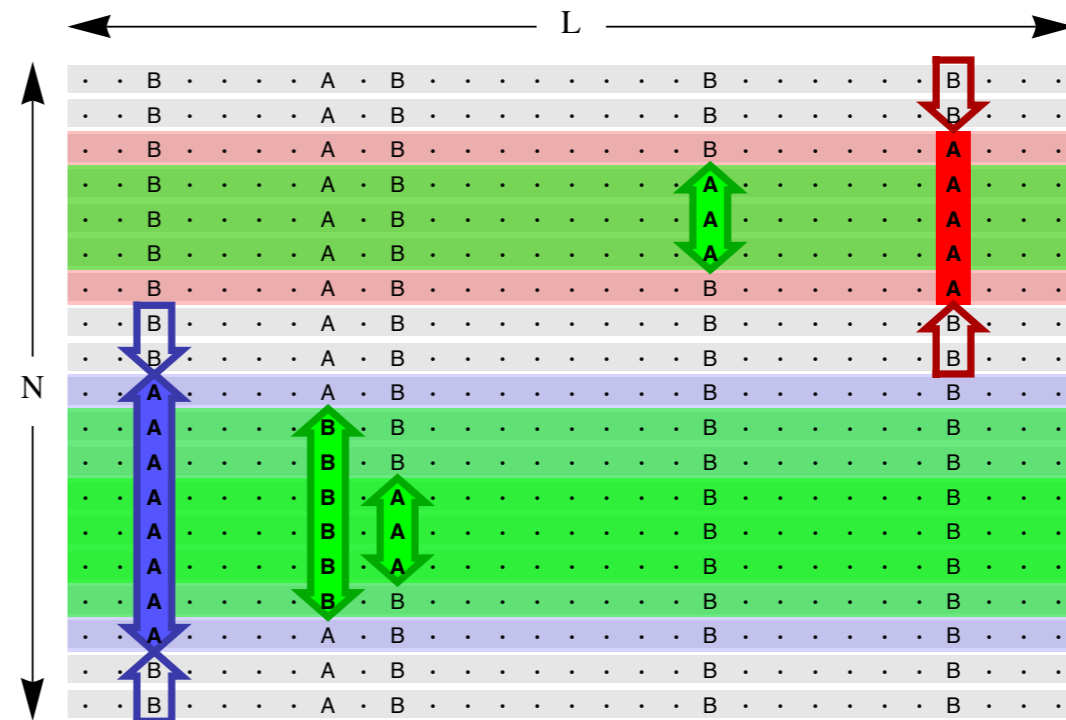
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- Genetic hitchhiking (Gillespie 2001, Barton 2000)

Adaptive Evolution in Linked Genomes

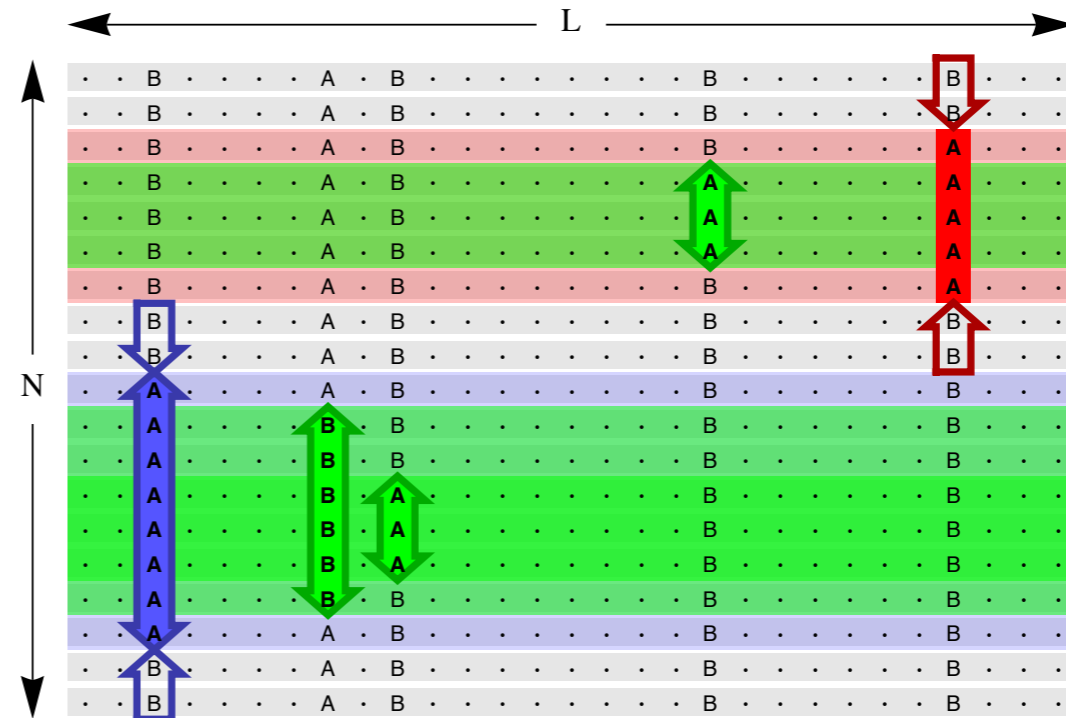
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A Minimal Genomic Model

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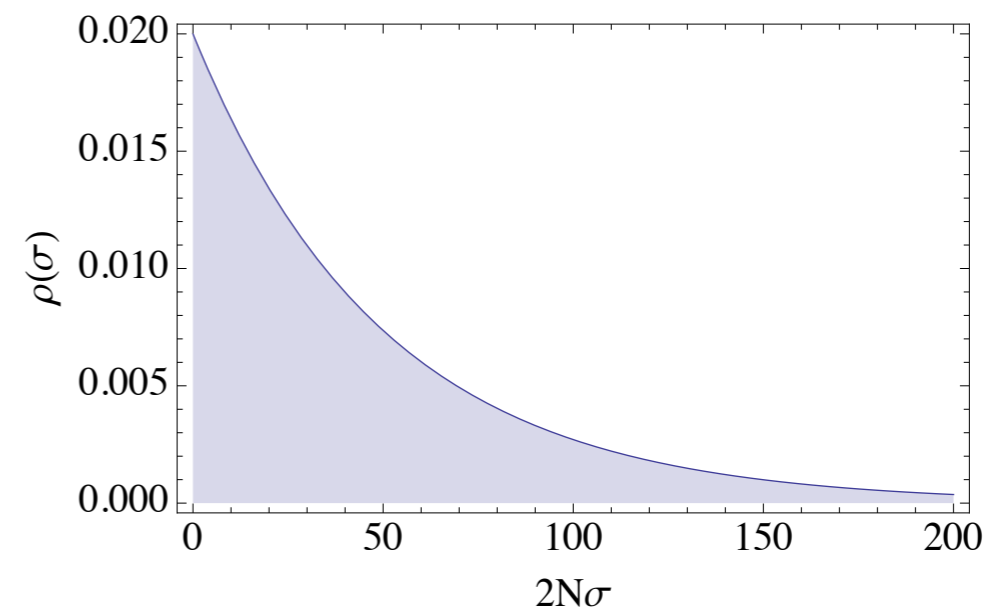
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A Minimal Genomic Model

- N individuals, L sites, 2 alleles
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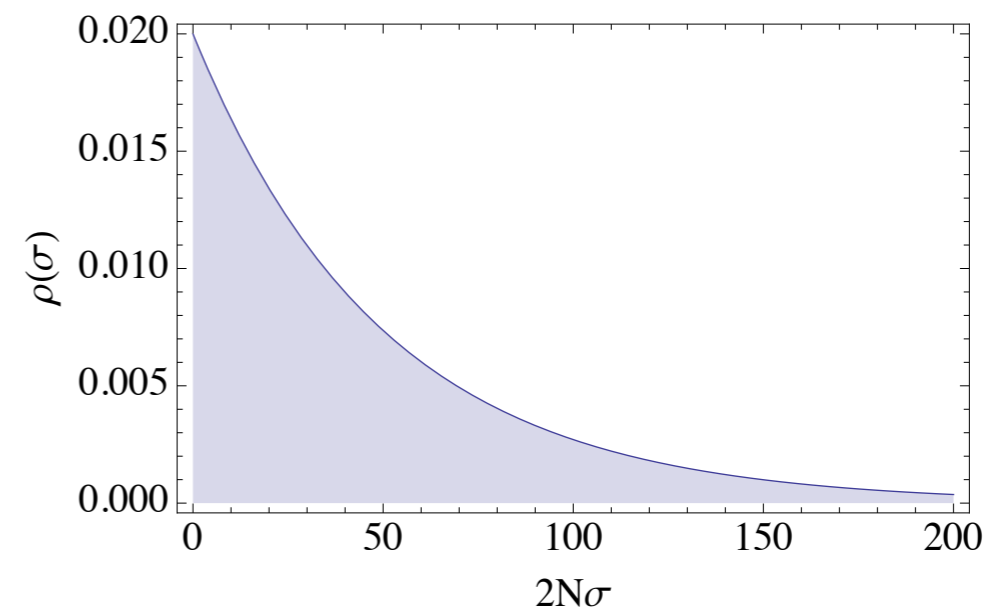
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- N individuals, L sites, 2 alleles
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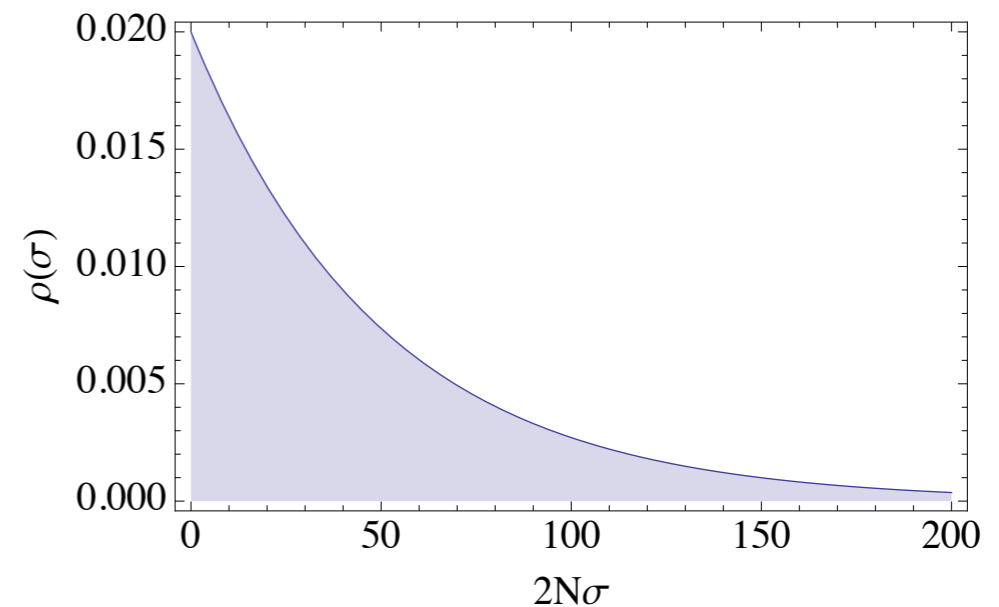
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A Minimal Genomic Model

- N individuals, L sites, 2 alleles
- Mutation rate μ
- Sites contribute fitness, drawn from a distribution $\rho(\sigma)$
- Additive fitness landscape, no epistasis
- Occasional allele preference flips with rate Υ , independent at each site
(Mustonen and Lässig, 2007)



Genome State and Degree of Adaptation

- Probability of being fixed at the fitter allele:

$$p_+(\sigma)$$

- Probability of being fixed at the less fit allele:

$$p_-(\sigma) = 1 - p_+(\sigma)$$

- Genome state determines rate of beneficial mutations:

$$U_b(\sigma) = \mu L \rho(\sigma) p_-(\sigma)$$

- Degree of adaptation measures distance to (moving) fitness peak:

$$\alpha(\sigma) = p_+(\sigma) - p_-(\sigma)$$

A Selfconsistent Link between Genomic State and Mutations

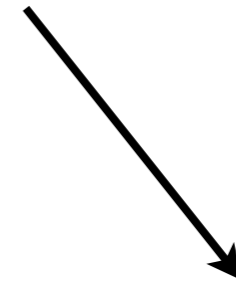
Probability of fixed alleles:

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A Selfconsistent Link between Genomic State and Mutations

Probability of fixed alleles:

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Mutation rates:

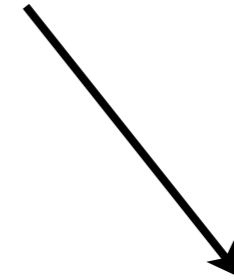
$$U_b(\sigma) = \mu L \rho(\sigma) p_-(\sigma)$$

$$U_d(\sigma) = \mu L \rho(\sigma) p_+(\sigma)$$

A Selfconsistent Link between Genomic State and Mutations

Probability of fixed alleles:

$$p_+(\sigma) = 1 - p_-(\sigma)$$



Substitution rates:

$$V_b(\sigma) = U_b(\sigma)G(\sigma)$$

$$V_d(\sigma) = U_d(\sigma)G(-\sigma)$$



Mutation rates:

$$U_b(\sigma) = \mu L \rho(\sigma) p_-(\sigma)$$

$$U_d(\sigma) = \mu L \rho(\sigma) p_+(\sigma)$$

A Selfconsistent Link between Genomic State and Mutations

Probability of fixed alleles:

$$\frac{d}{dt}p_+(\sigma) = \frac{1}{L\rho(\sigma)} [V_b(\sigma) - V(-\sigma)] + \gamma[p_-(\sigma) - p_+(\sigma)]$$

Substitution rates:

$$V_b(\sigma) = U_b(\sigma)G(\sigma)$$
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A Selfconsistent Link between Genomic State and Mutations

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⚡ Linkage

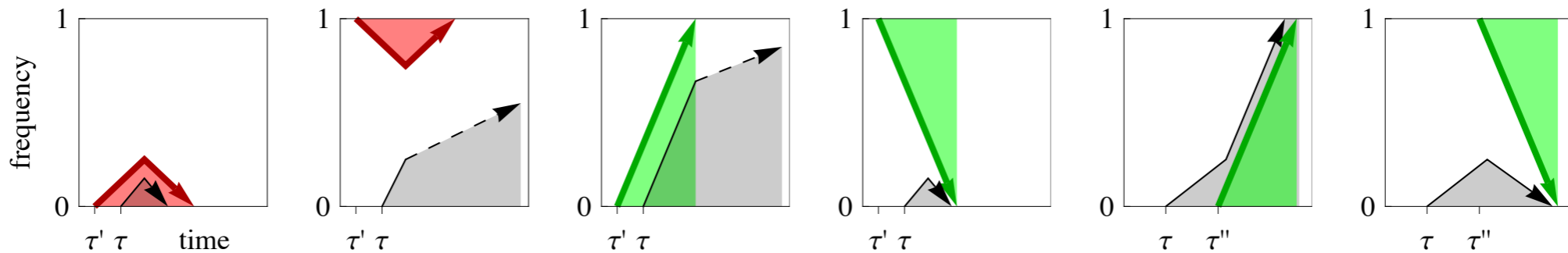
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$$V_b(\sigma) = U_b(\sigma)G(\sigma)$$
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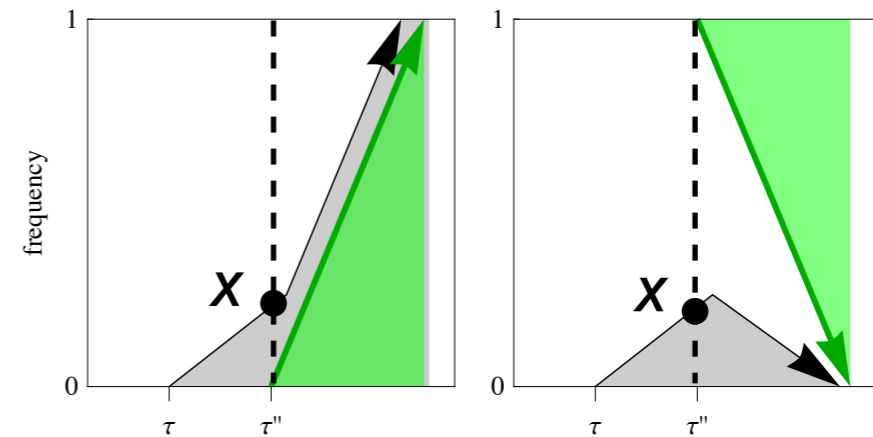
Interfering Mutations Affect Fixation Probability



- Goal: compute the fixation probability of a mutation in the context of many interfering mutations
- Strategy: distinguish *target* mutation (black) from *interfering* mutation (green or red)
- Each interfering mutation is itself a target mutation to all other interfering mutations
- This effectively sums up all interactions via pairwise interferences

Integrating Hitchhiking and Interference

- Assume strictly hierarchical interactions
- Integrate over all substitutions $|\sigma'| > |\sigma|$
- Integrate over all times $\tau' > \tau$
- Integrate over all frequencies $0 < x < 1$



$$G(\sigma) = \int_{\sigma}^{\infty} d\sigma' \int_{\tau}^{\infty} d\tau' \int_0^1 dx xG(\sigma, x, \tau' - \tau)w(\sigma', \tau' - \tau)$$

Result: Fixation Probability

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- Most mutations are *neutral* regarding their substitution rate!

Result: Fixation Probability

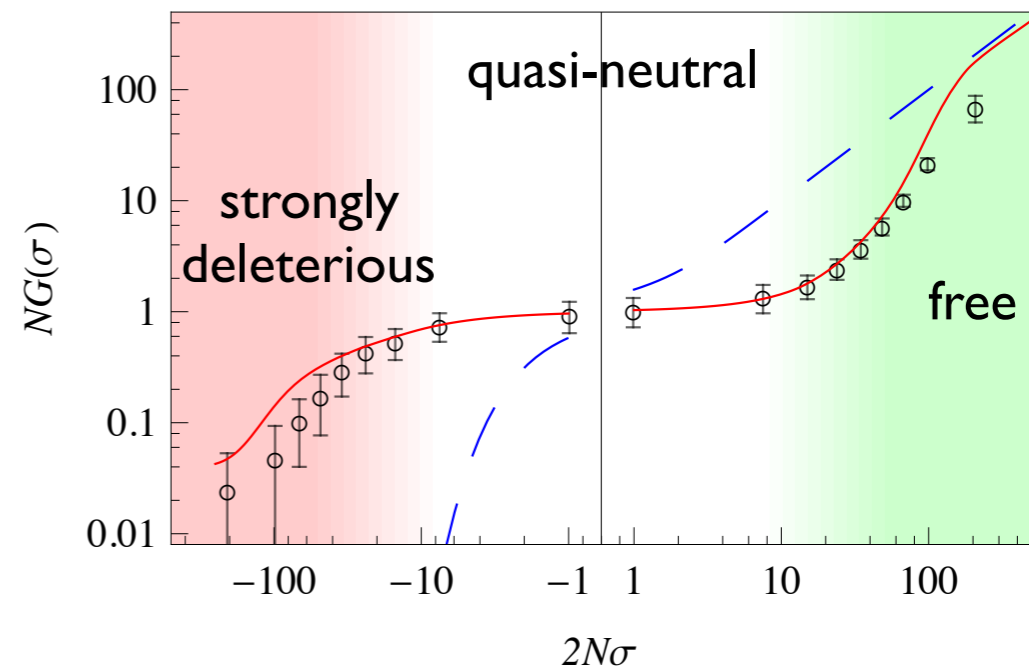
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Result: Fixation Probability

- Most mutations are *neutral* regarding their substitution rate!
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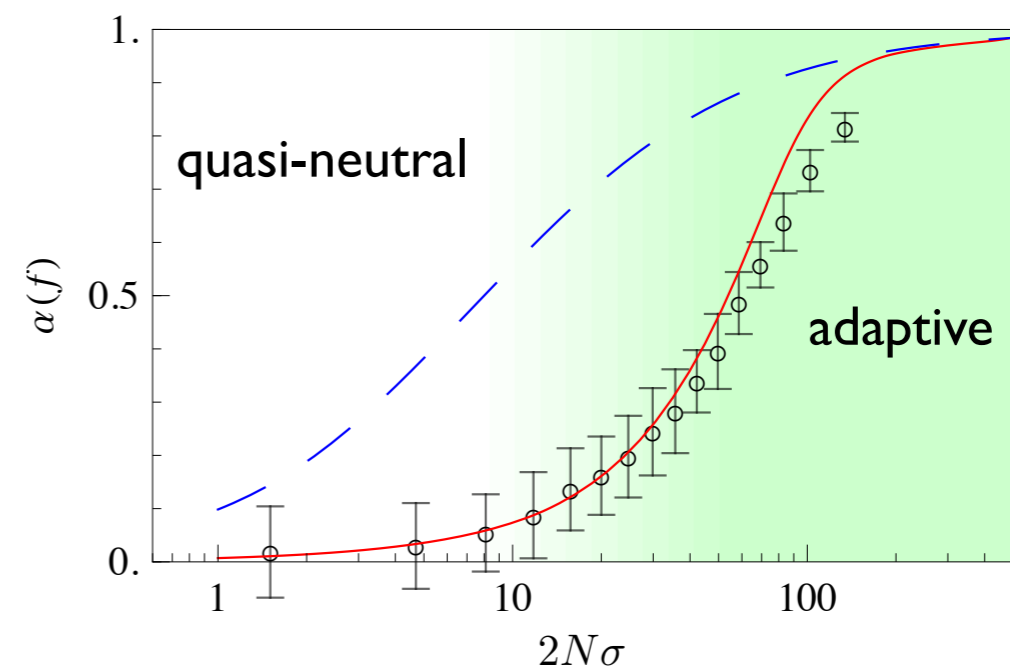
Result: Fixation Probability

- Most mutations are *neutral* regarding their substitution rate!
- Strongly deleterious mutations have highly increased substitution rates
- Strongly beneficial mutations have free substitution rates
- Linkage effects are *not* reproduced by reduced effective population size

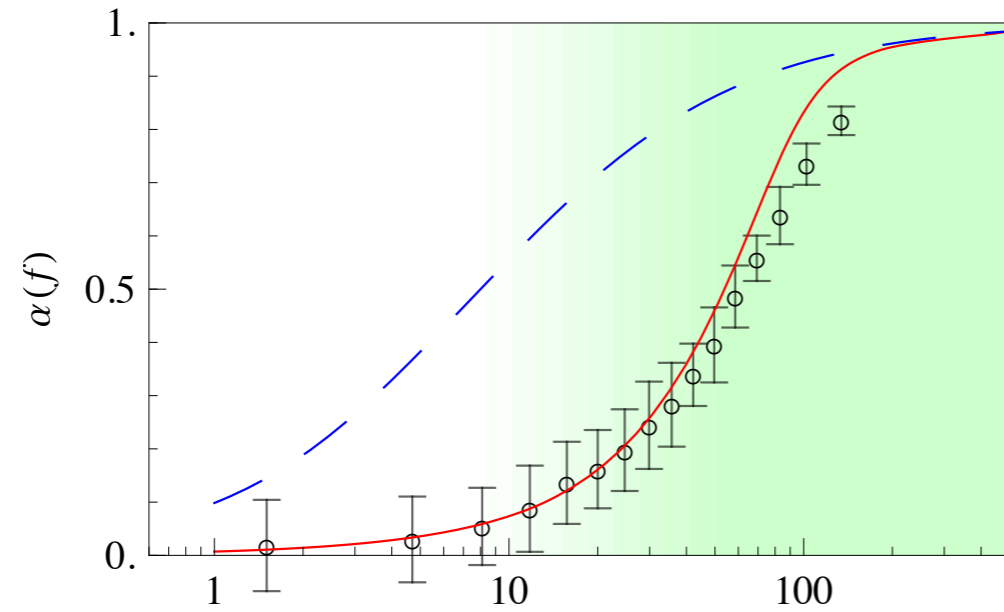


Result: Degree of Adaptation

- Most sites are *randomly* fixed at beneficial and deleterious alleles!
- Sites with strong selection coefficient are well adapted
- Genome is suffering genetic load

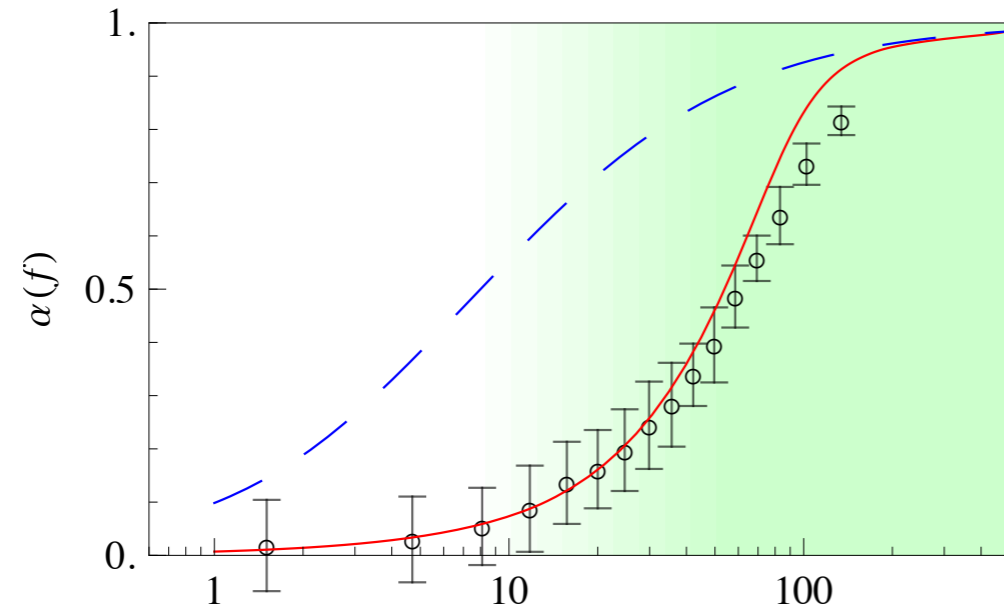


Threshold of Emergent Neutrality



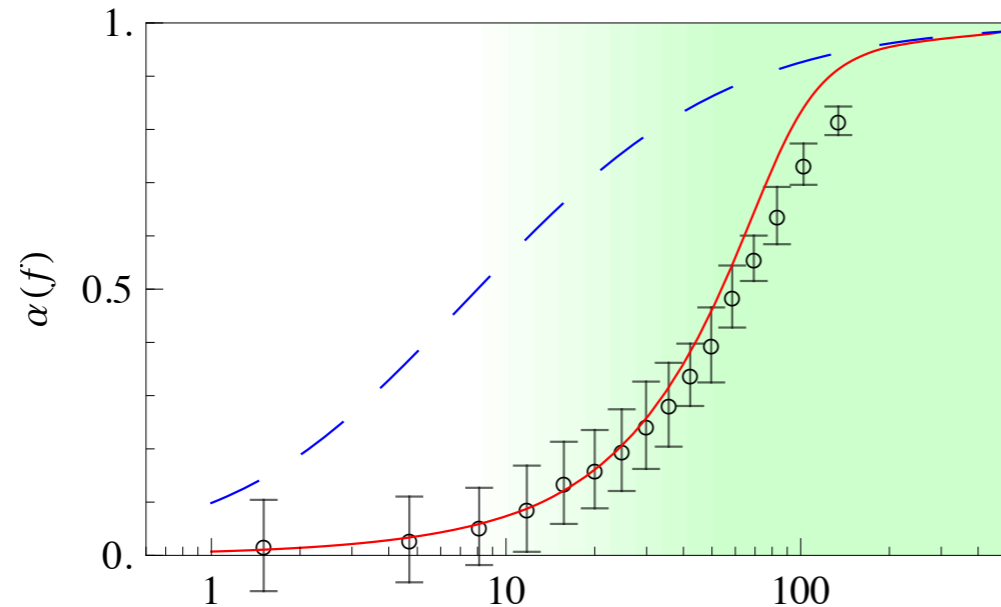
$$\tilde{\sigma} = \frac{1}{2N}$$

Threshold of Emergent Neutrality



$$\tilde{\sigma} = \frac{1}{2N} + \int_0^{\infty} V_{\text{drive}}(\sigma) d\sigma$$

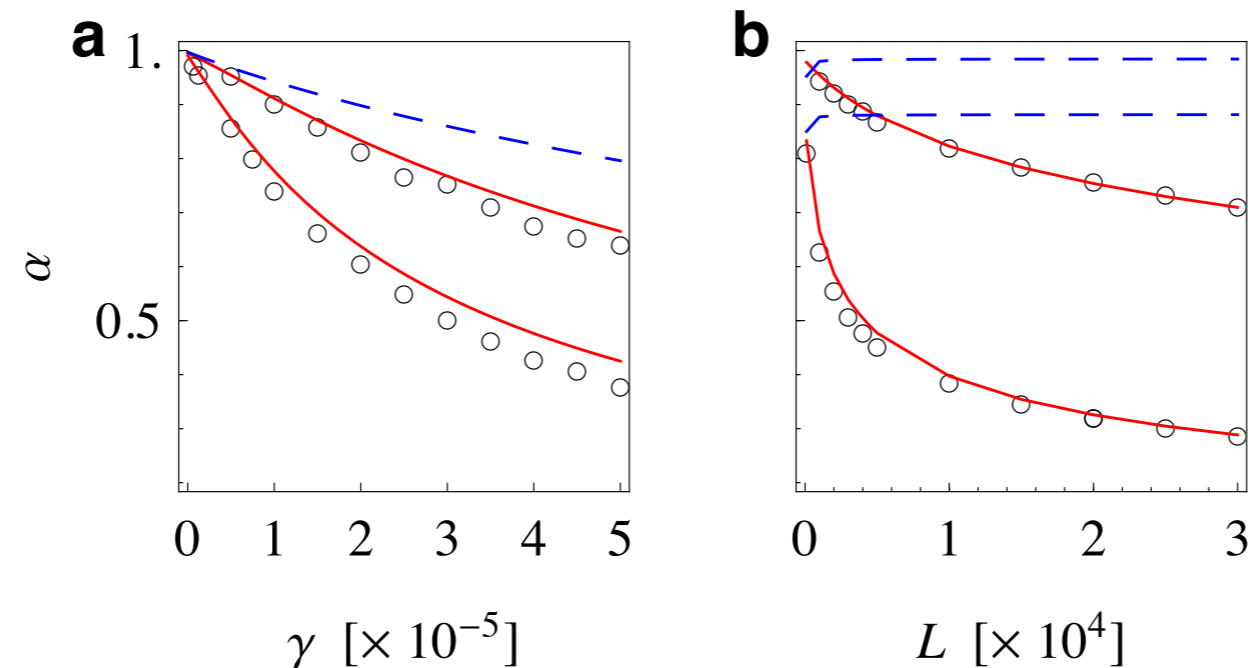
Threshold of Emergent Neutrality



$$\tilde{\sigma} = \frac{1}{2N} + \int_0^{\infty} V_{\text{drive}}(\sigma) d\sigma$$

- The neutrality threshold is directly related to the total rate of driver substitutions
- It marks the onset of clonal interference: $\tilde{\sigma} \gg \frac{1}{2N}$

How Far Is the Population from the Peak?



- Linkage reduces the degree of adaptation (i.e. fitness)
- A simple formula connects speed and degree of adaptation:

$$\Phi = L\gamma\bar{\sigma}\alpha$$

- Increases in the speed of adaptation result in low fitness

Conclusions

- Emergent neutrality of mutations
- Emergent neutrality of genomic sites
- Model advance: sum many interacting mutations by selfconsistent pairwise interactions

Outlook

- Integrate recombination into the model
- Predict polymorphism frequency distributions
⇒ population genetic tests for selection
- Application to approach-to-equilibrium scenarios
(e.g. long-term evolution experiments)

Thank you!

- *Adaptation in Linked Genomes* (submitted).
Stephan Schiffels, Gergely Szöllösi, Ville Mustonen, Michael Lässig



Bonn-Cologne Graduate School
of Physics and Astronomy

