

# How Large Asexual Populations Adapt

or

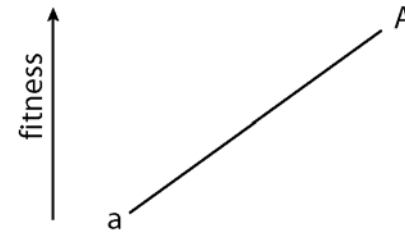
## How Linkage Affects Positive Selection

Michael Desai, Lewis-Sigler Institute  
Princeton University

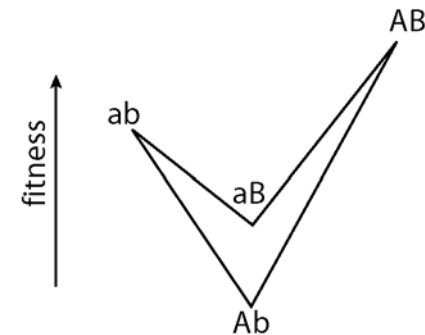
# How Does Evolution Work?

Many big and small numbers  
How should they be put together?  
How do things scale?

“Uphill” evolution easy



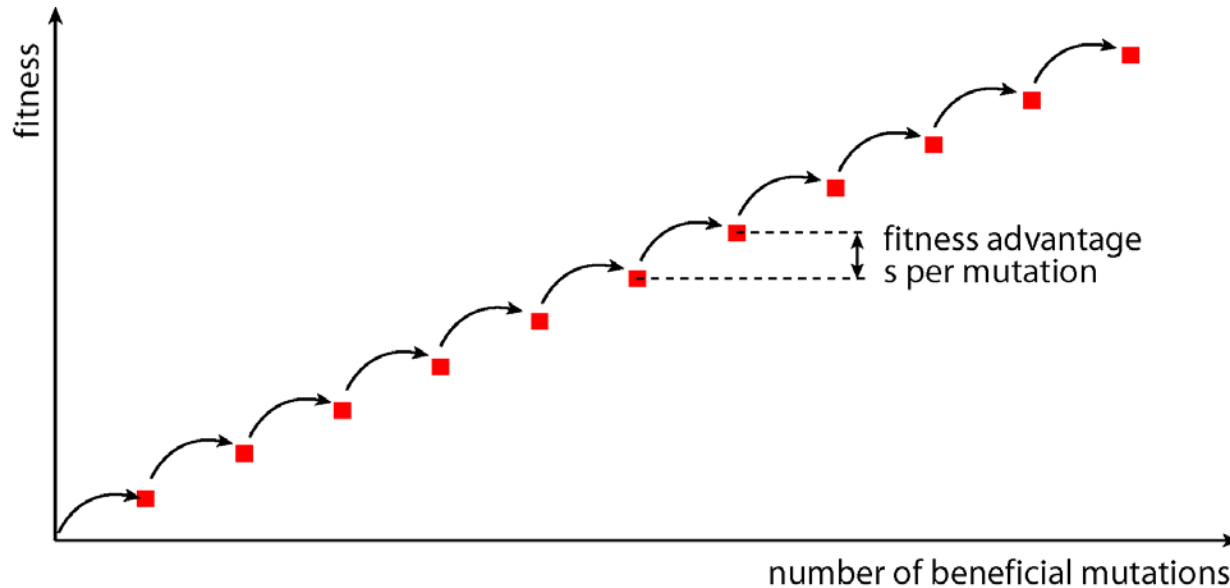
Other things harder:



Constraints on Evolution:  
What's routine?  
What's impossible?

Sex? Mutators?

# How does a population climb a hill?

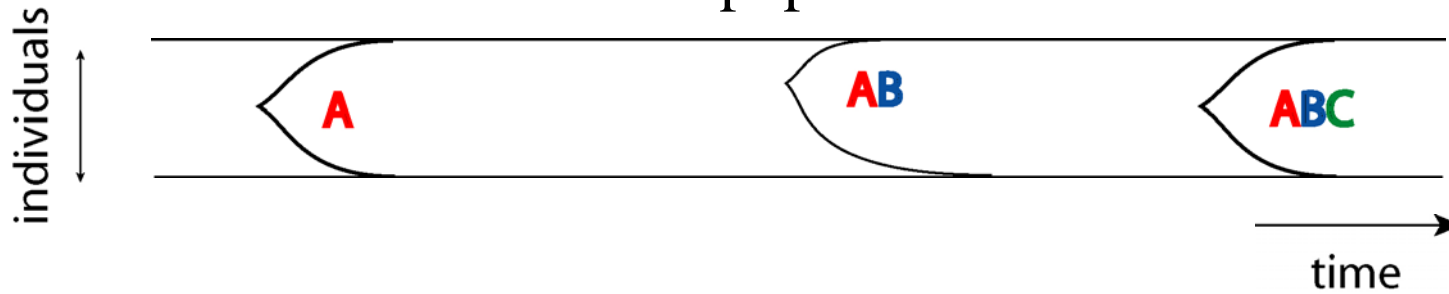


How quickly can we run uphill?

Dependence on population parameters?

# Beneficial mutations must occur *and* spread

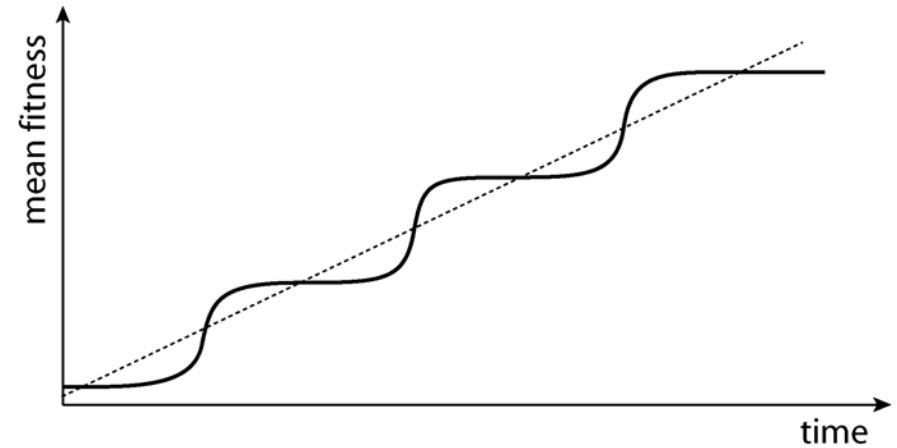
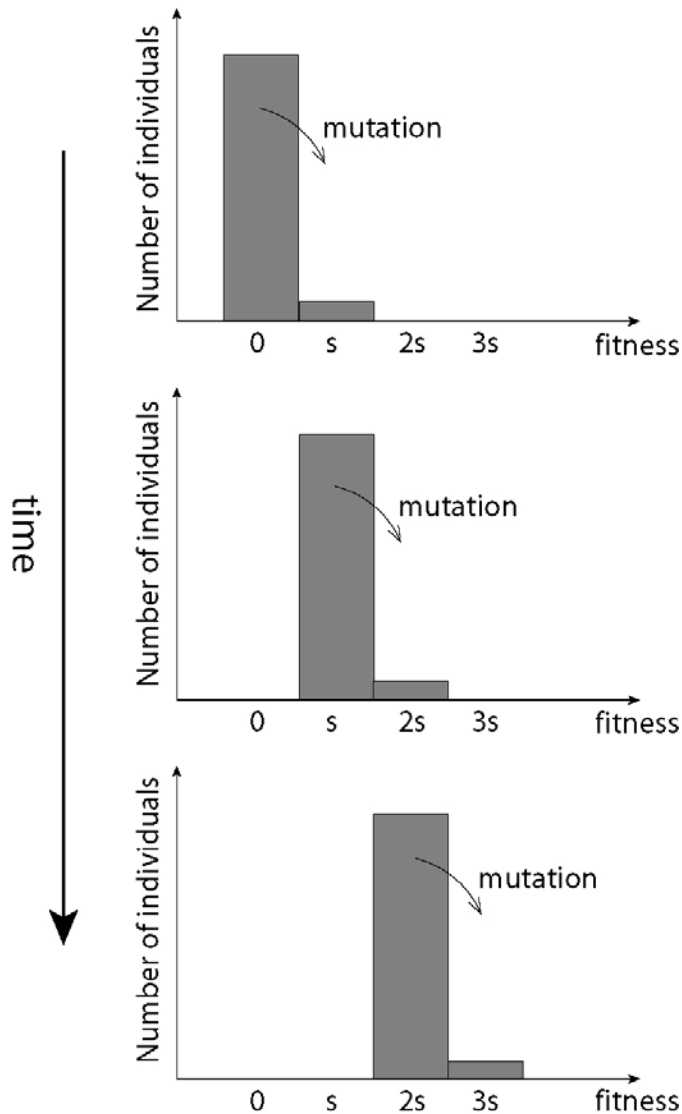
Small population:



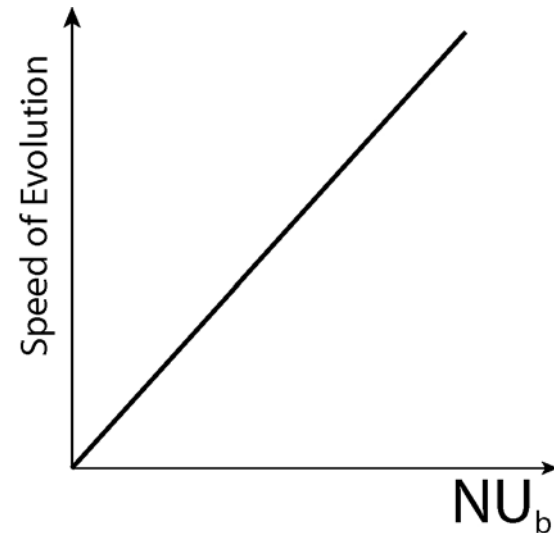
Large population:



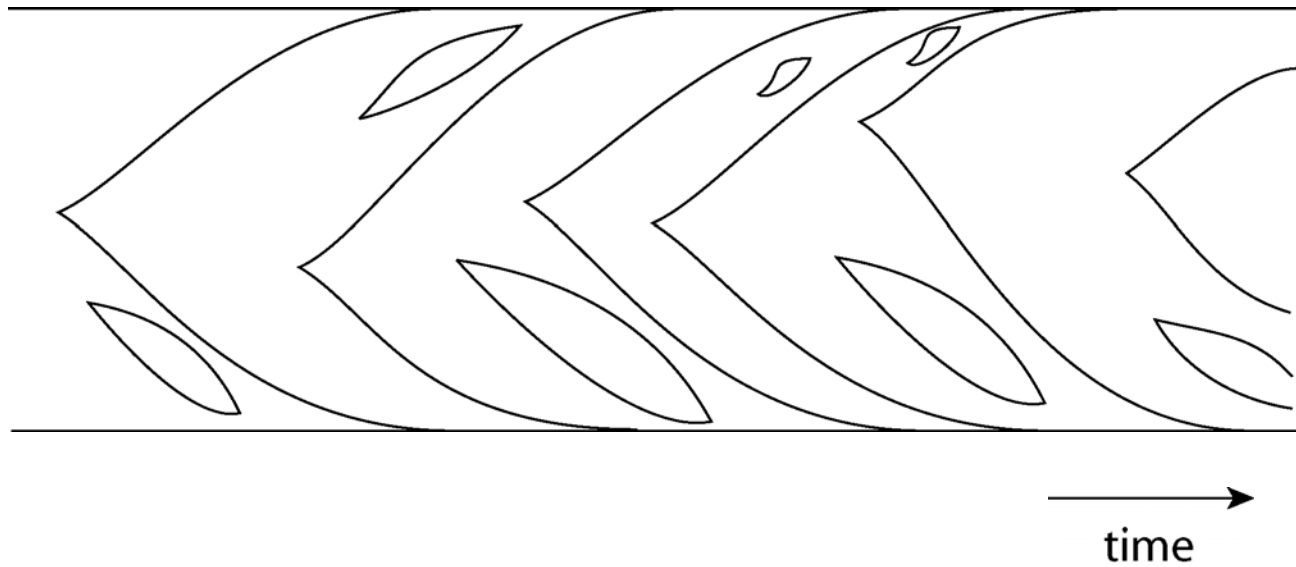
# When Mutations are Rare: One-Locus Theory



Mutation Limited:  $v = NU_b s^2$

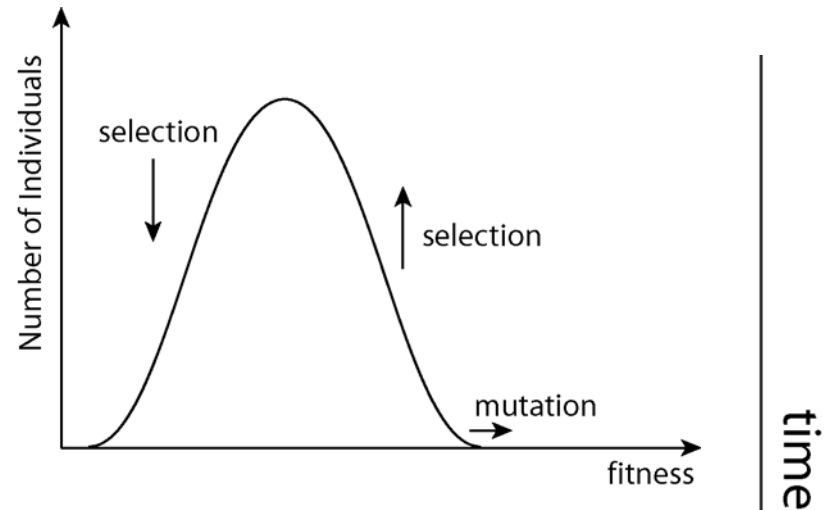
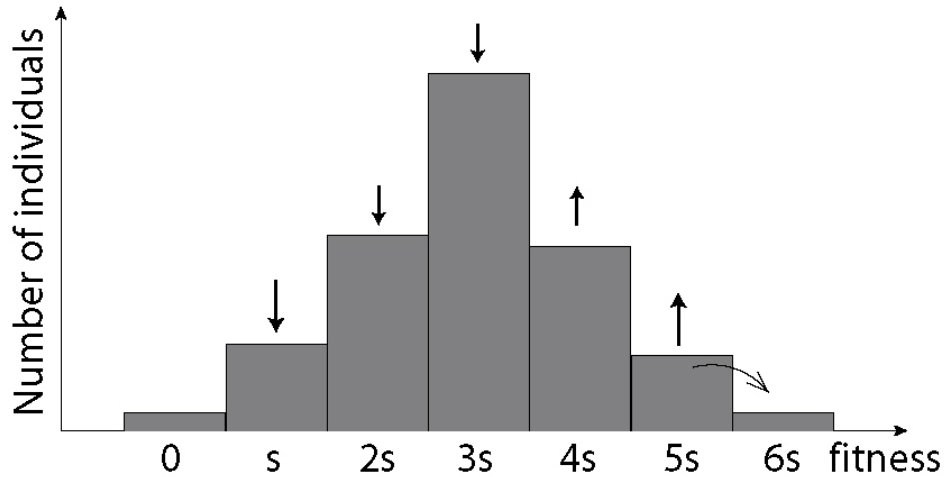


# When Multiple Mutations Compete

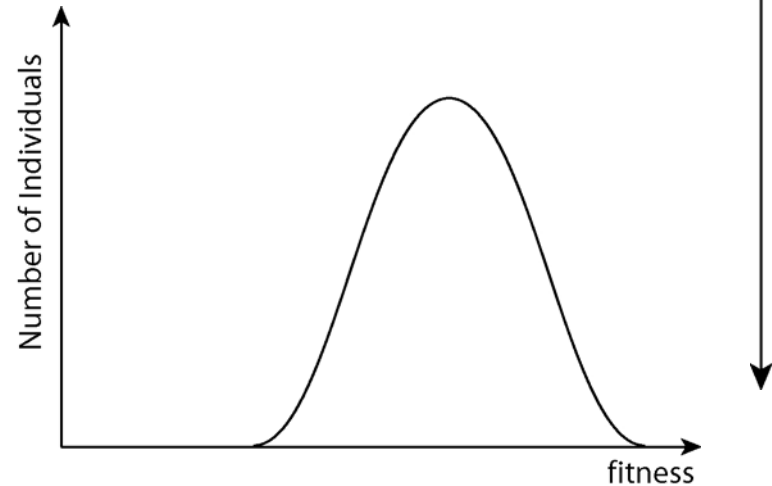
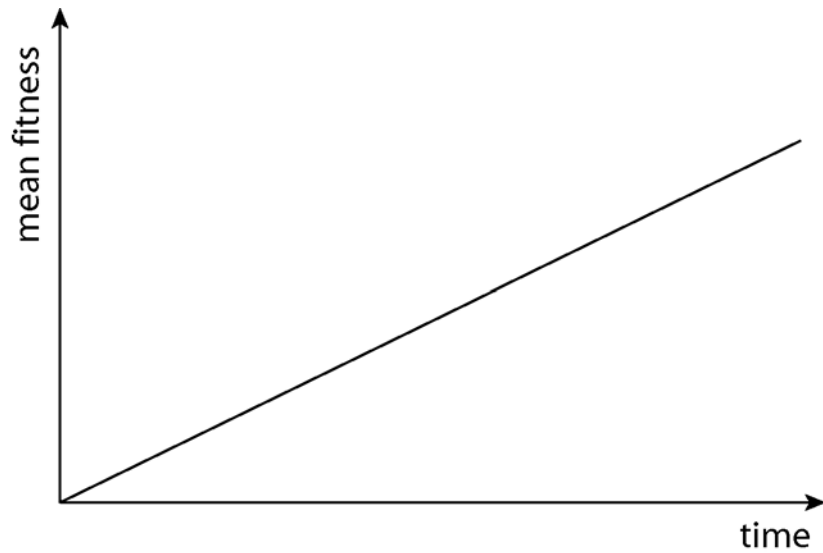


Theory with Daniel Fisher

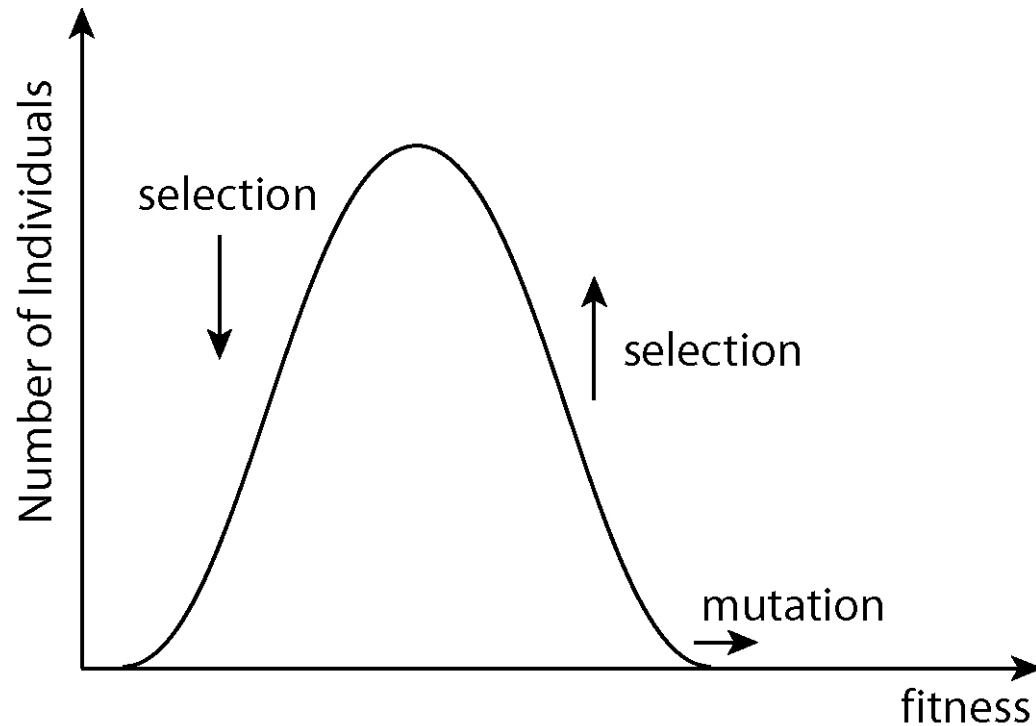
# Beneficial Mutation-Selection Balance



Mean fitness increases smoothly:



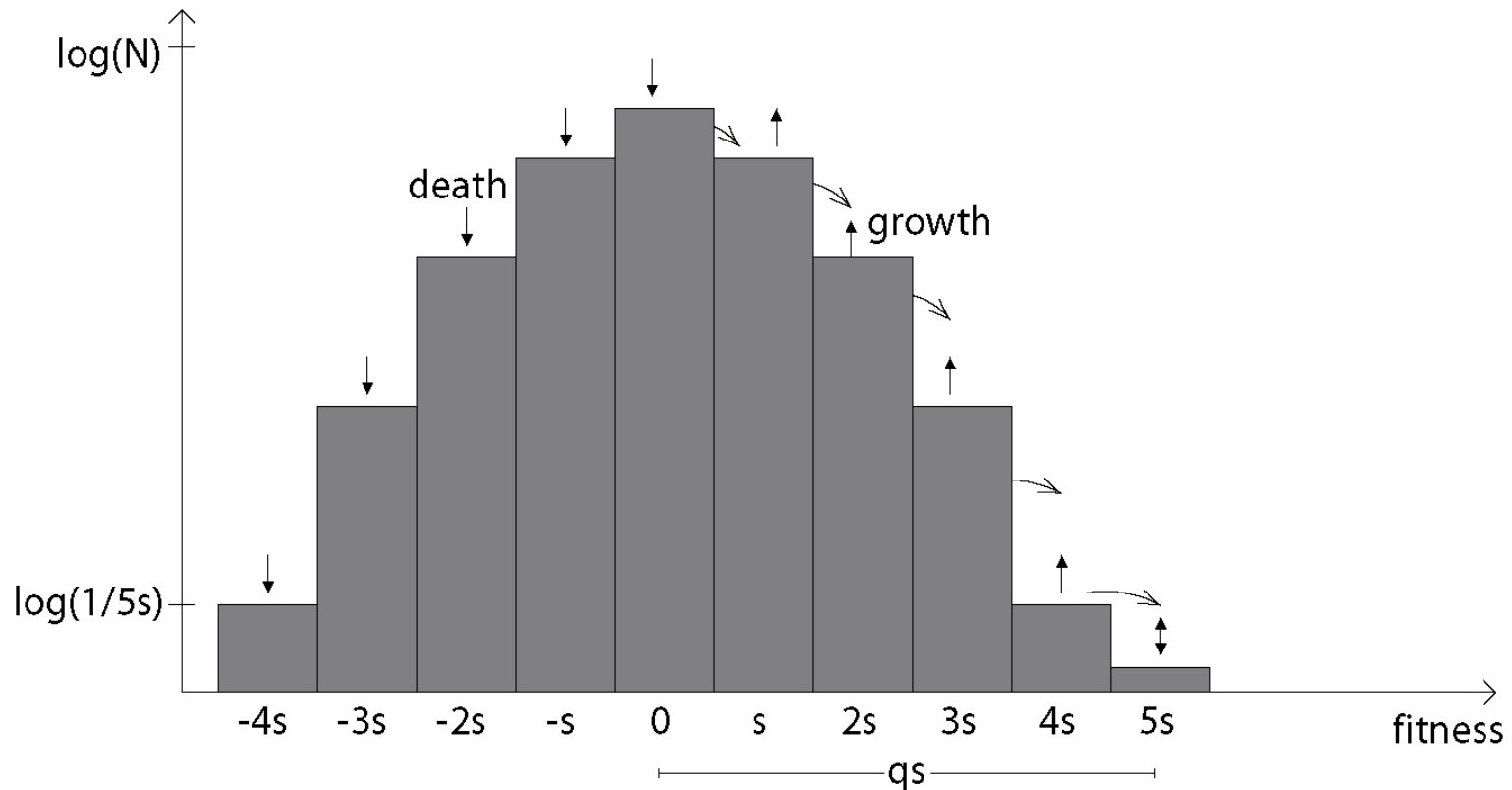
# Deterministic and Moment-Based Approaches



$$\frac{\partial f(x)}{\partial t} = U \int f(x') \rho(x' - x) dx' - U f(x) + (x - \langle x \rangle) f(x) + \text{noise}$$

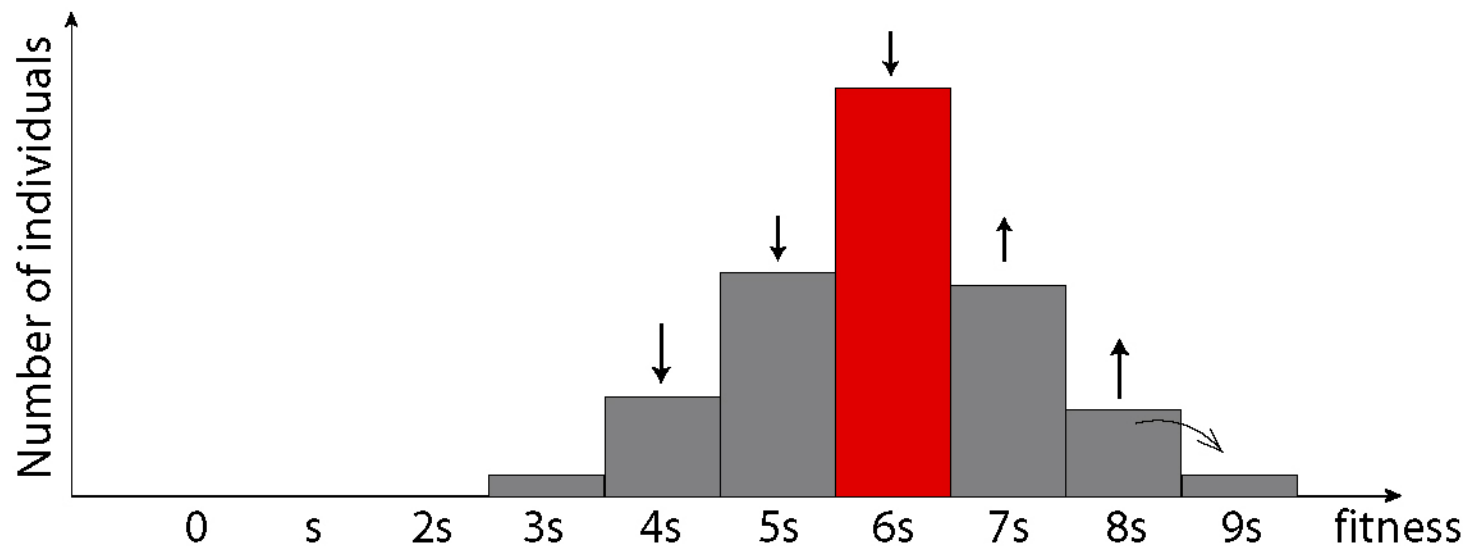


# Beneficial Mutation-Selection Balance



Discreteness at front crucial  
Width sets the speed. What sets the width?

# Heuristic Analysis



Mutation:

Selection:

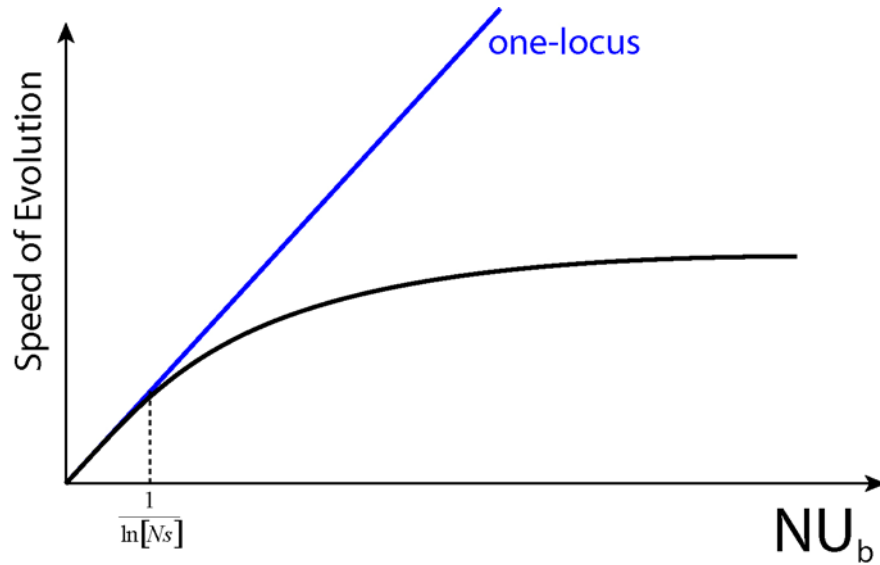
$$U_b \int_0^\tau e^{qst} dt \approx 1$$

$$v \approx \frac{s}{\tau}$$

$$q\tau \approx \frac{\ln[Nqs]}{qs/2}$$

$$\tau \approx \frac{1}{qs} \ln \left[ \frac{s}{U_b} \right]$$

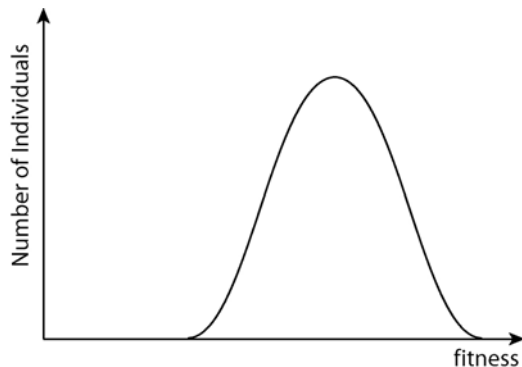
# Key Predictions



$$v = \frac{2s^2 \ln[Ns] - s^2 \ln[s/U_b]}{\ln^2[s/U_b]}$$

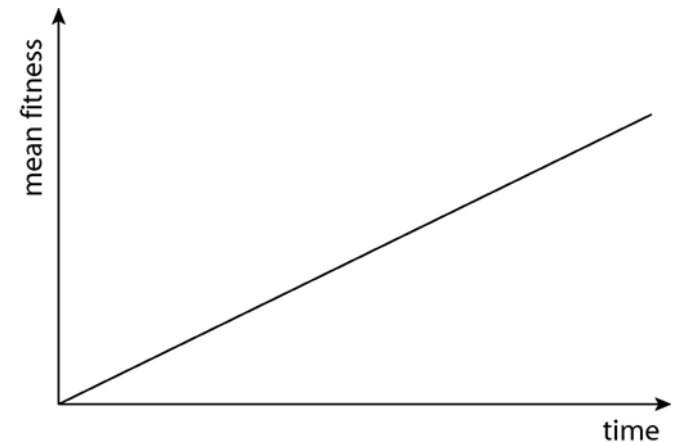
Speed logarithmic in  $N$ ,  $U_b$

Gaussian fitness distribution:  
Width logarithmic in  $N$ ,  $U_b$



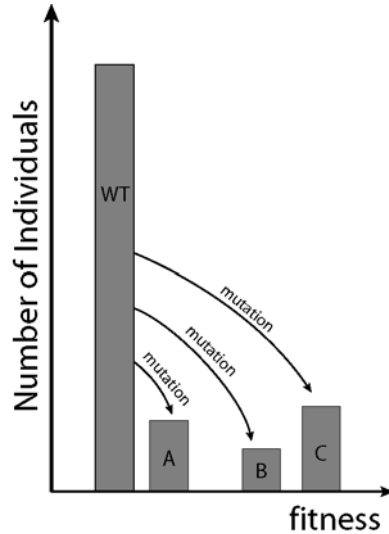
$$q = \frac{2 \ln[Nqs]}{\ln[qs/U_b]}$$

Steady increase in fitness:

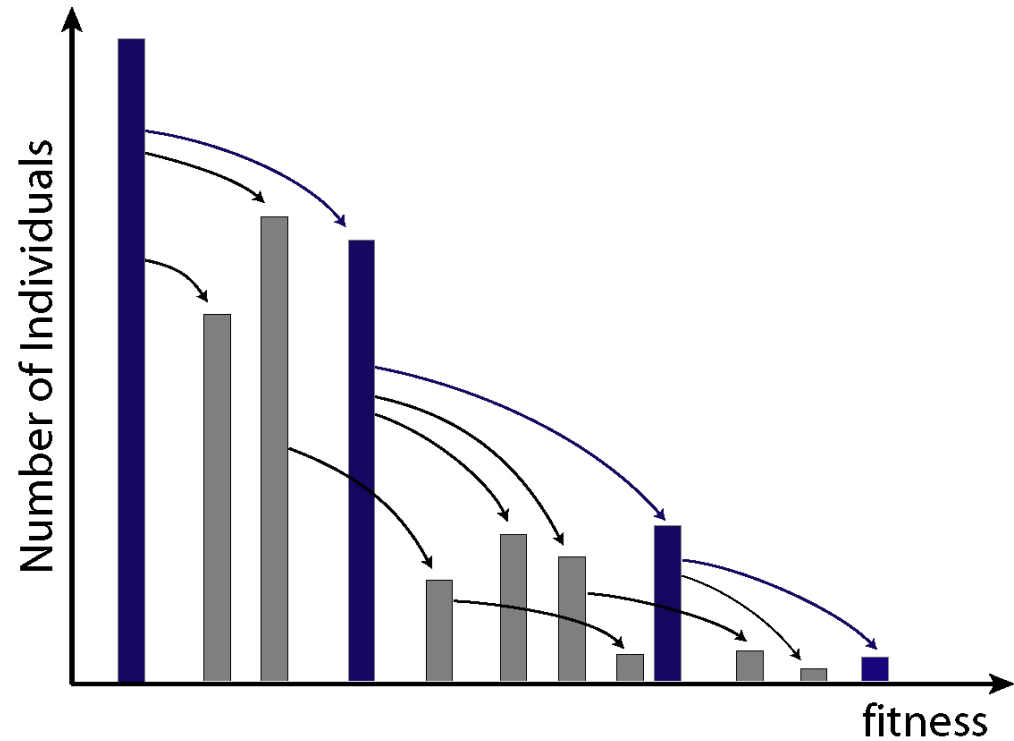
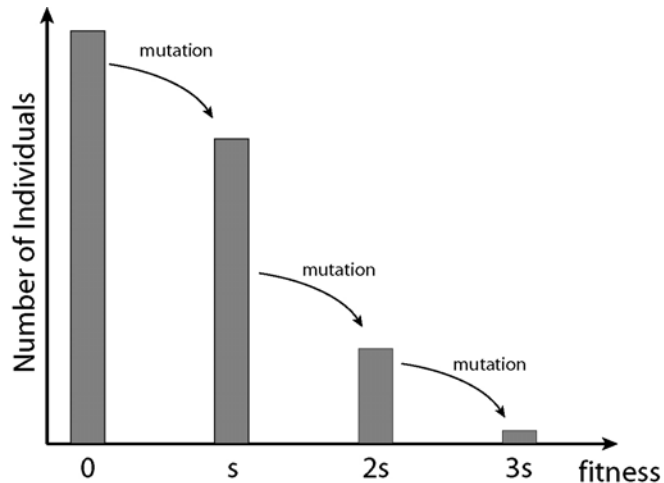


# Beneficial mutations of various sizes

Clonal Interference Analysis:

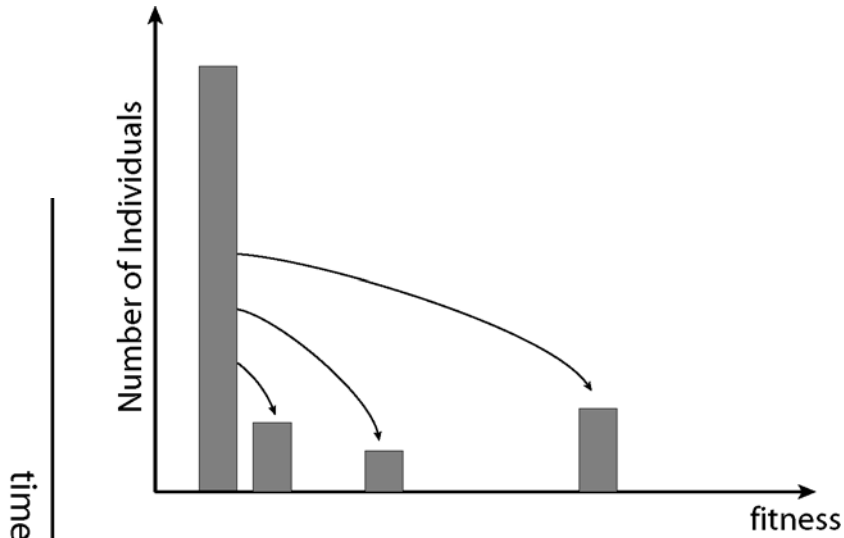


Multiple Mutation Analysis:

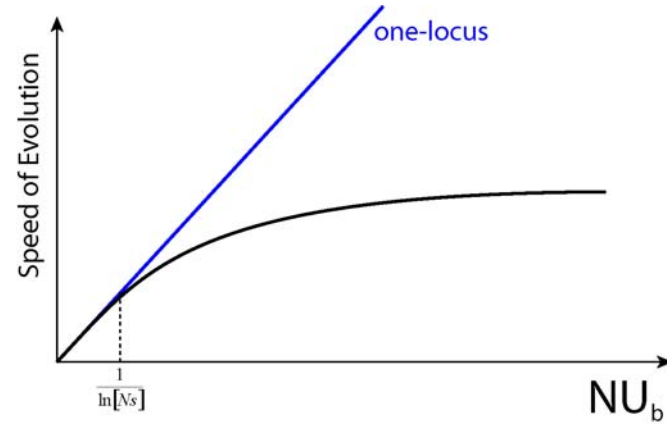


A Combined Theory

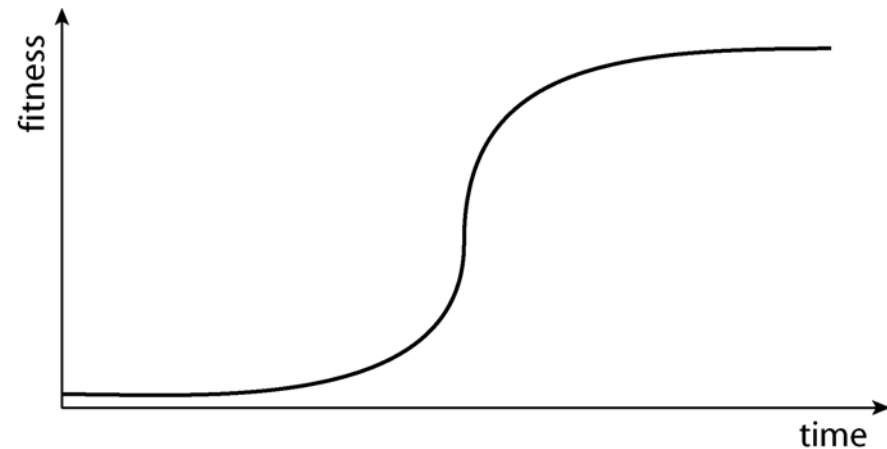
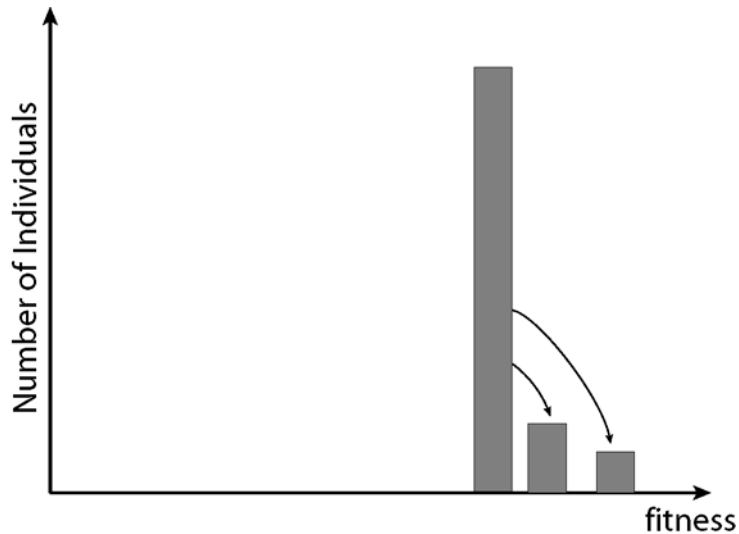
# Clonal Interference Theory



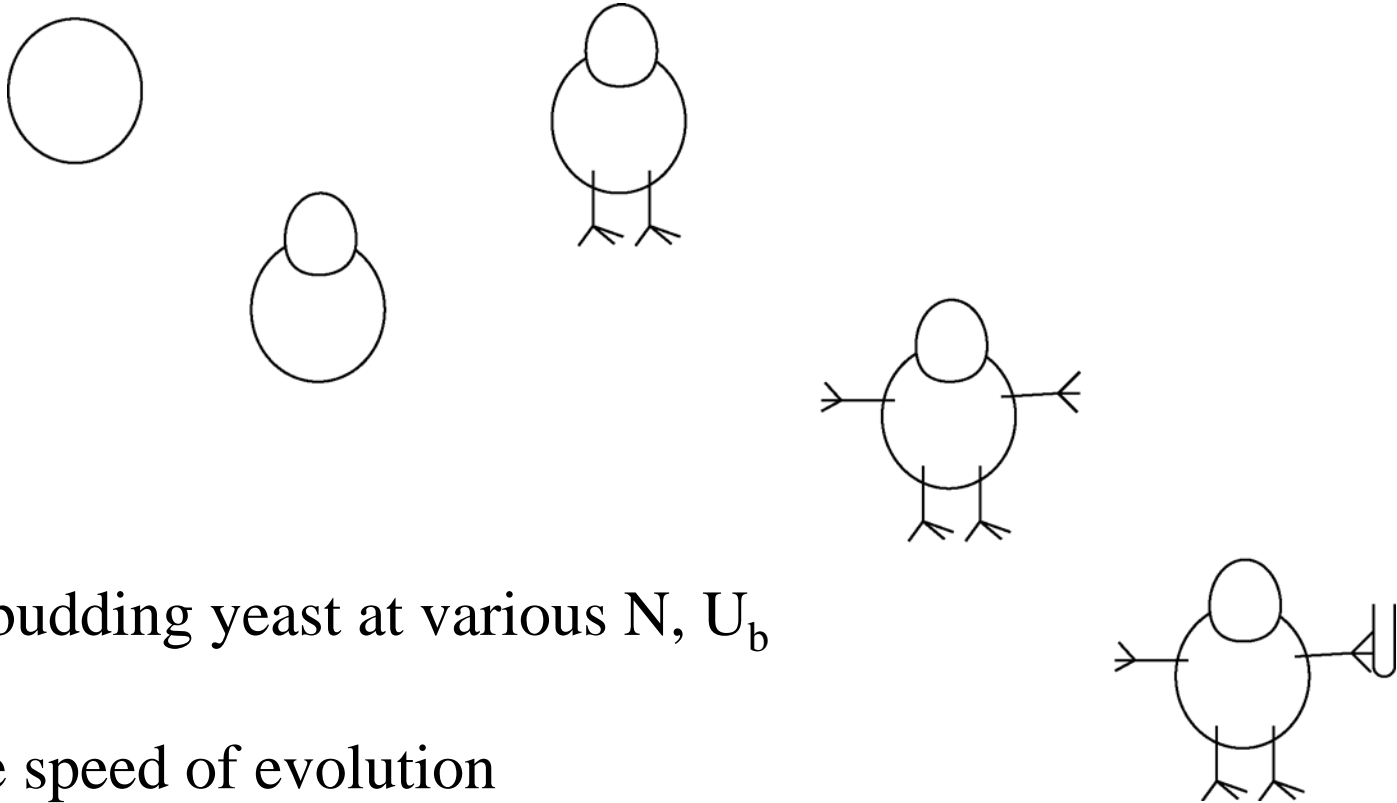
Speed of evolution also limited



Rare large mutations dominate:



# Experimental Tests



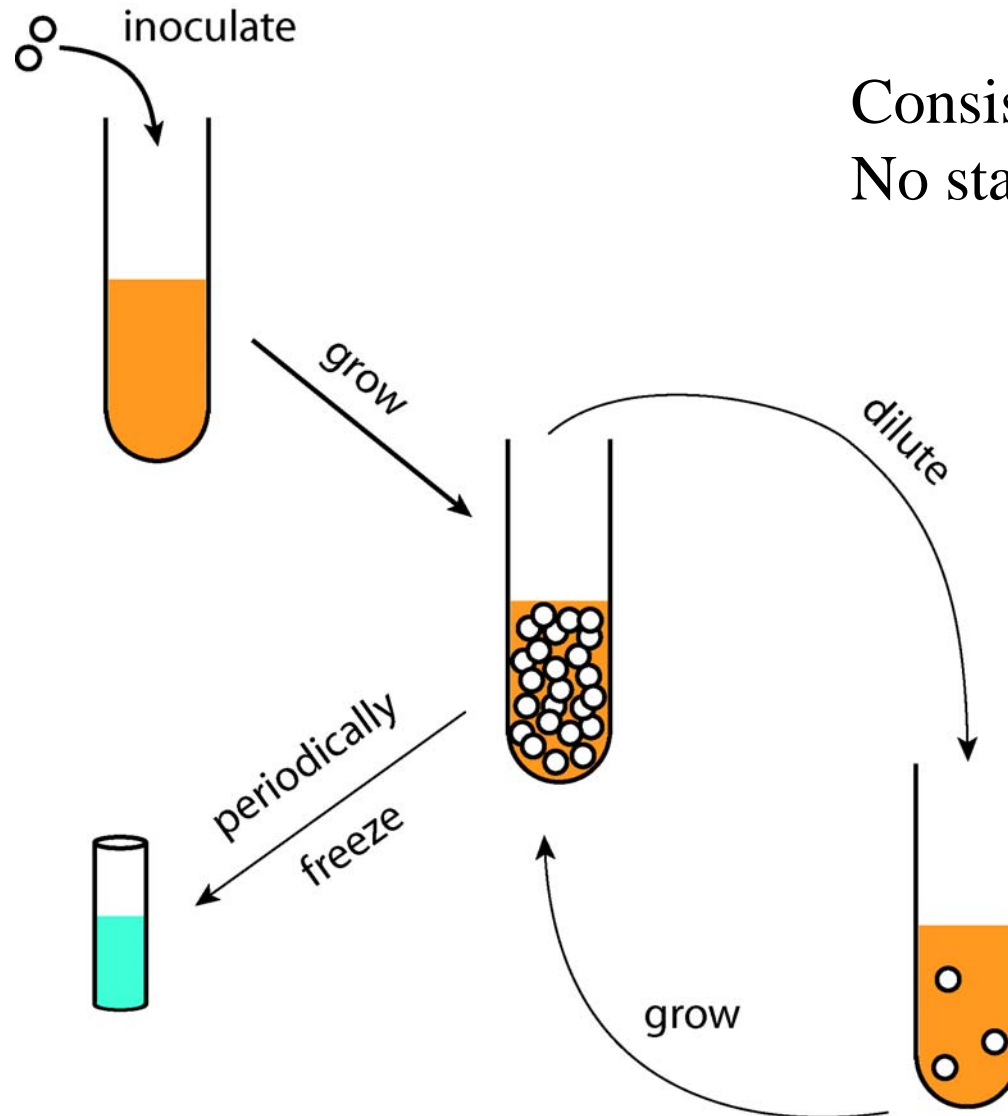
Evolve budding yeast at various  $N$ ,  $U_b$

Measure speed of evolution

Measure fitness distributions

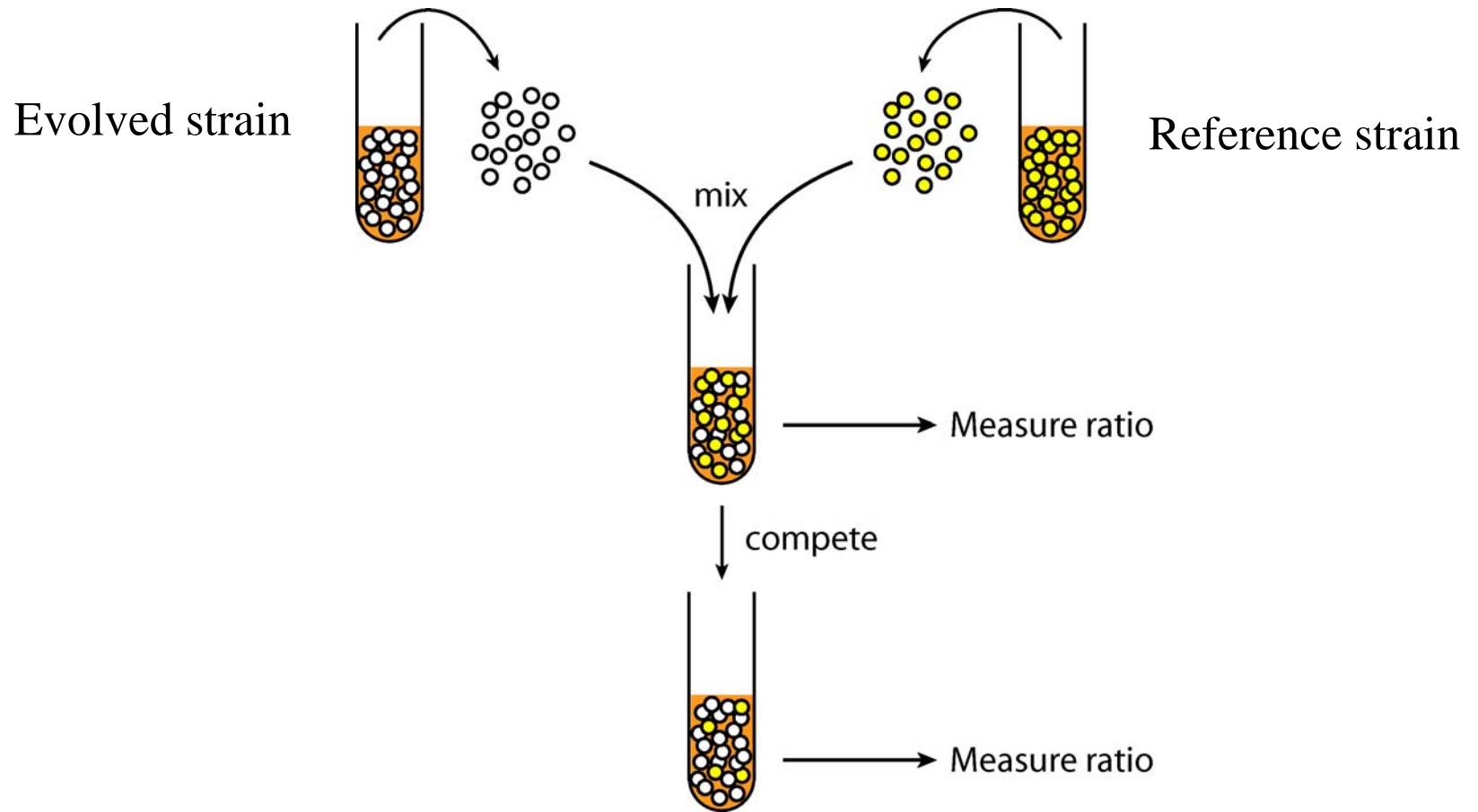
With Andrew Murray

# Maintaining Evolving Populations



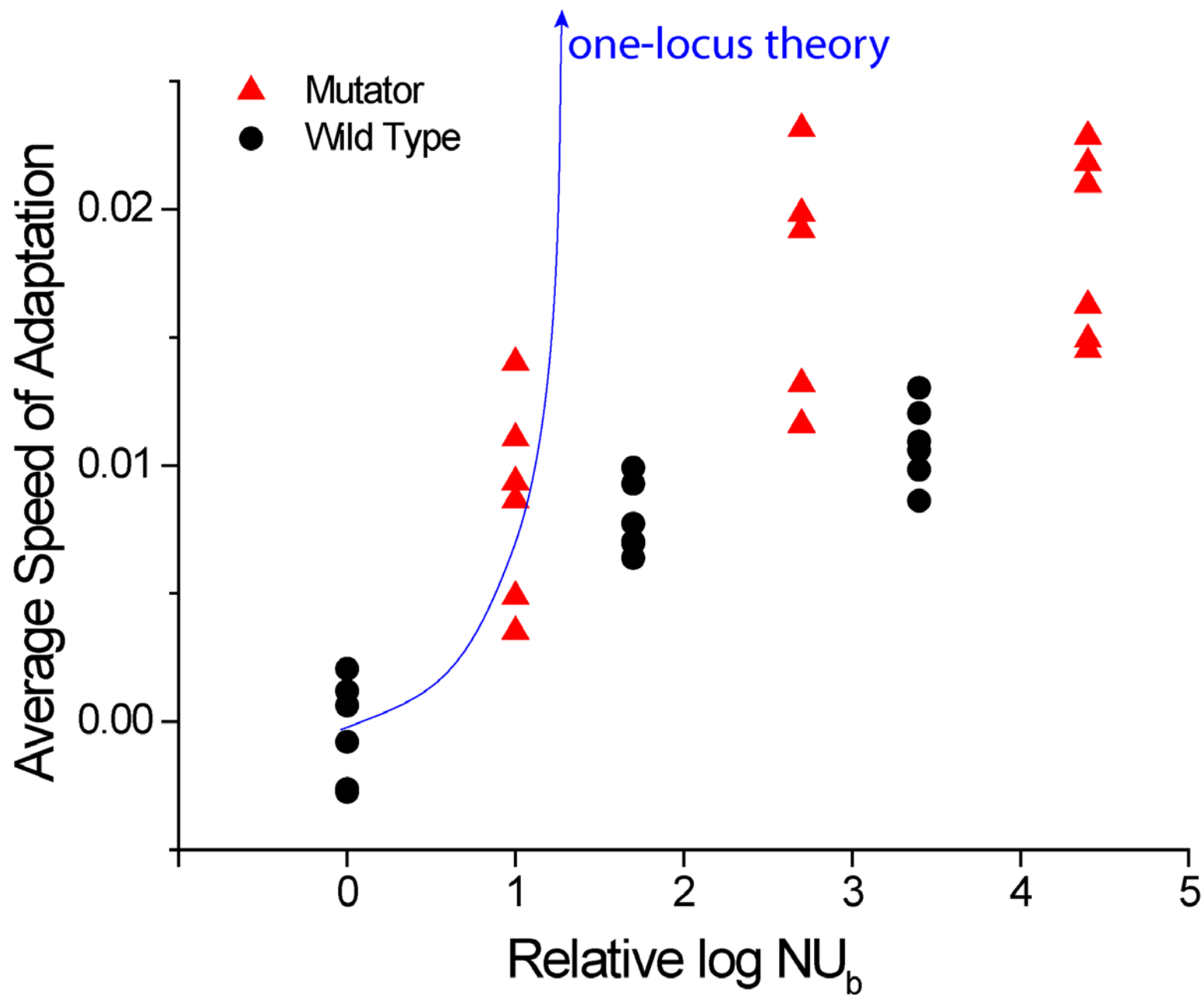
Consistent conditions crucial:  
No stationary phase!

# Measuring Fitness

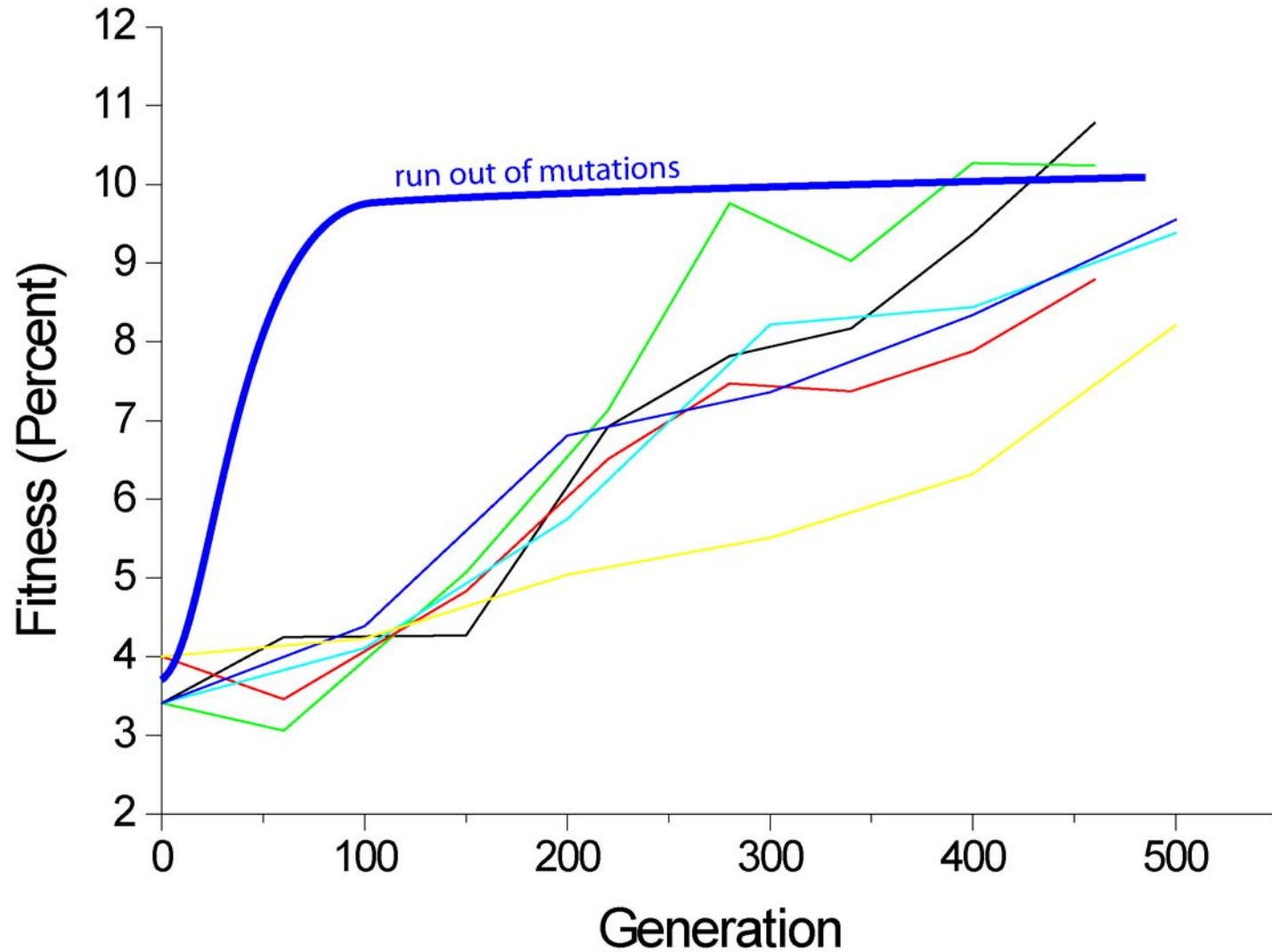




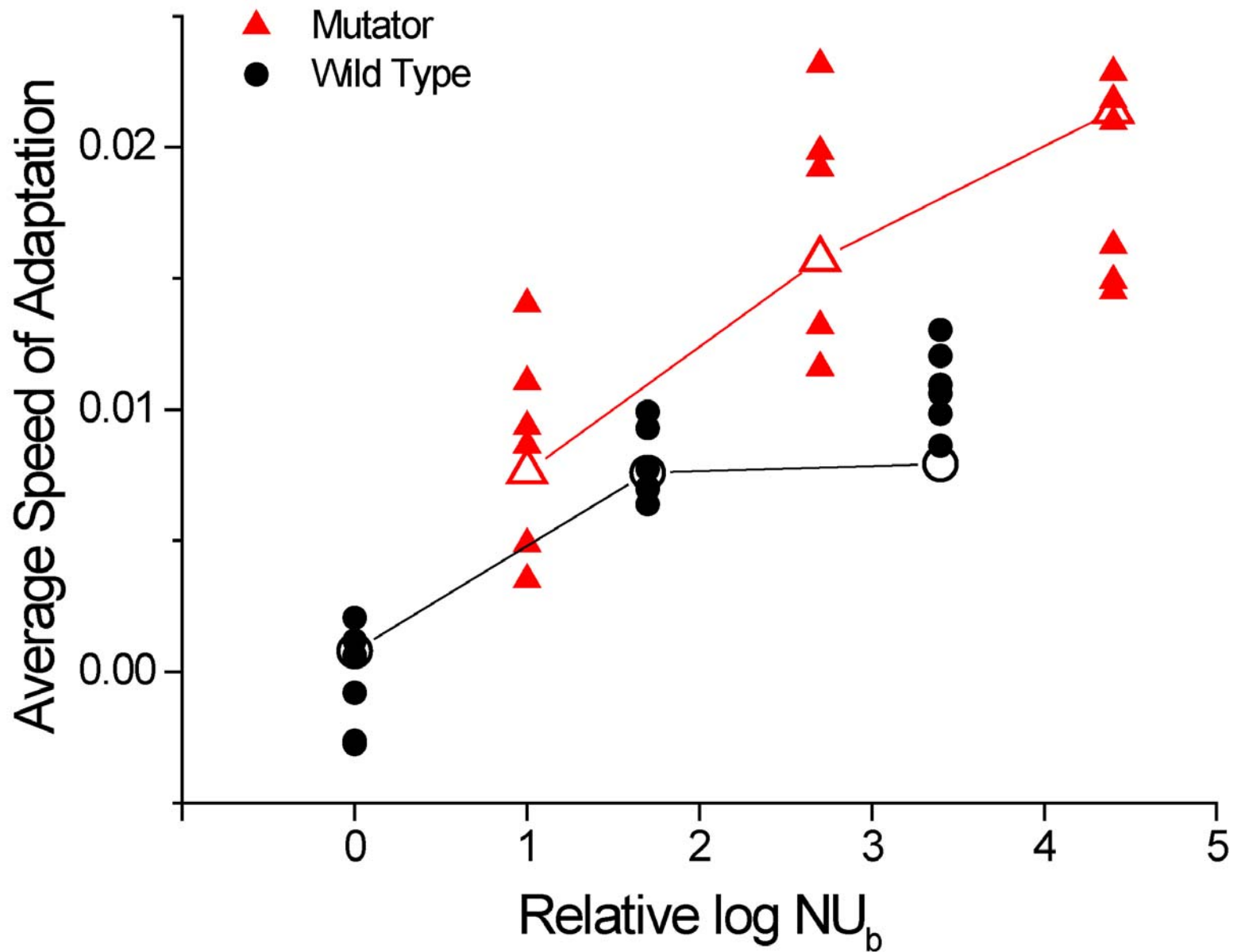
# Speed of Adaptation



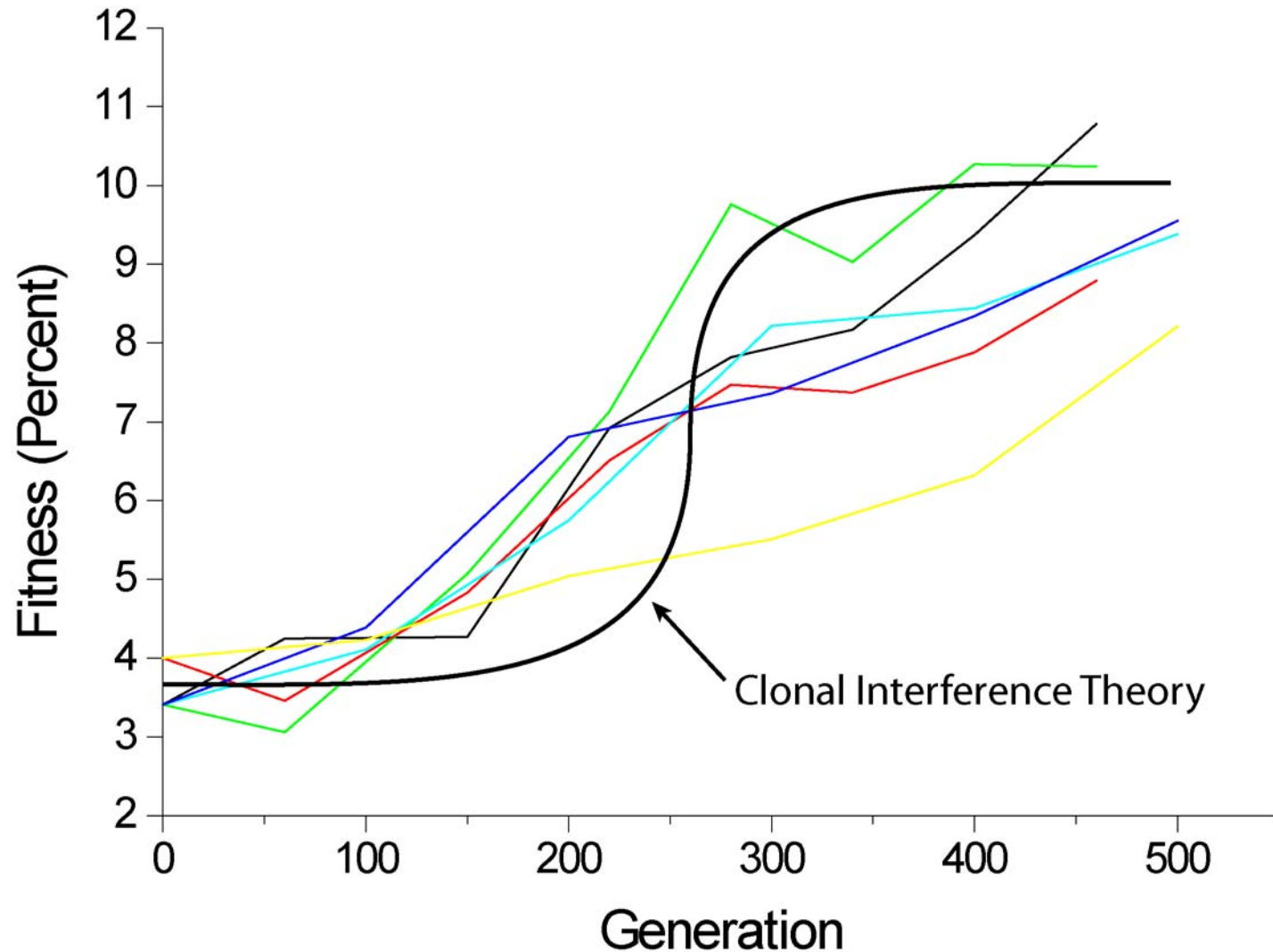
# Historical Fitness Changes



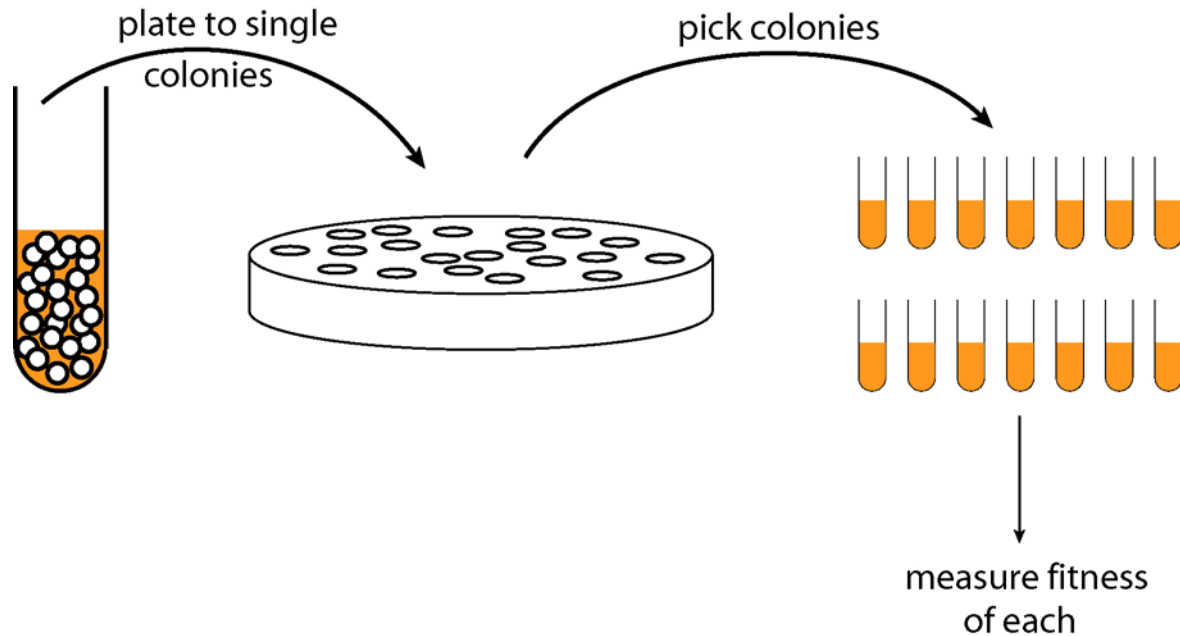
# Speed of Adaptation



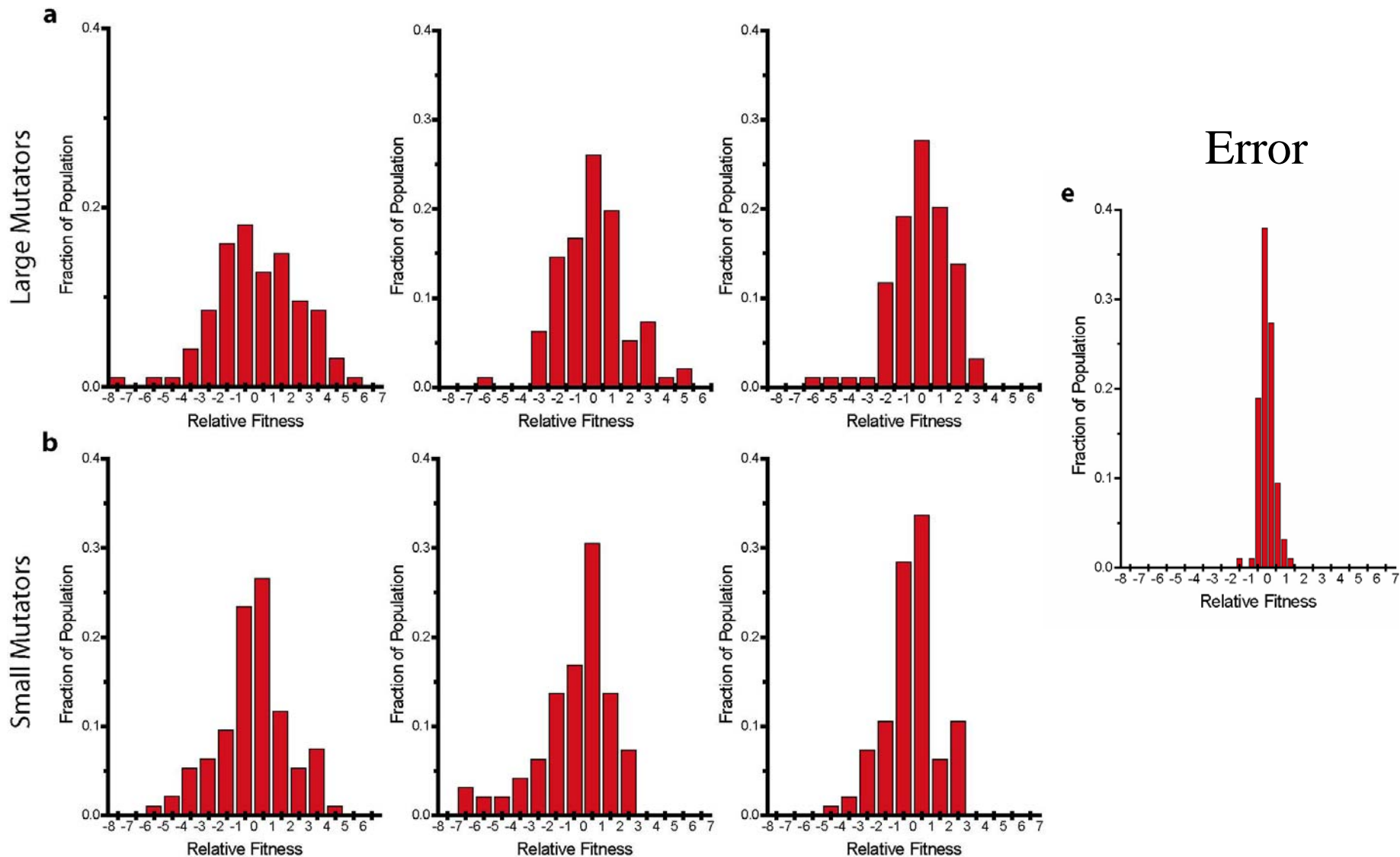
# Historical Fitness Changes



# Measuring Fitness Distributions

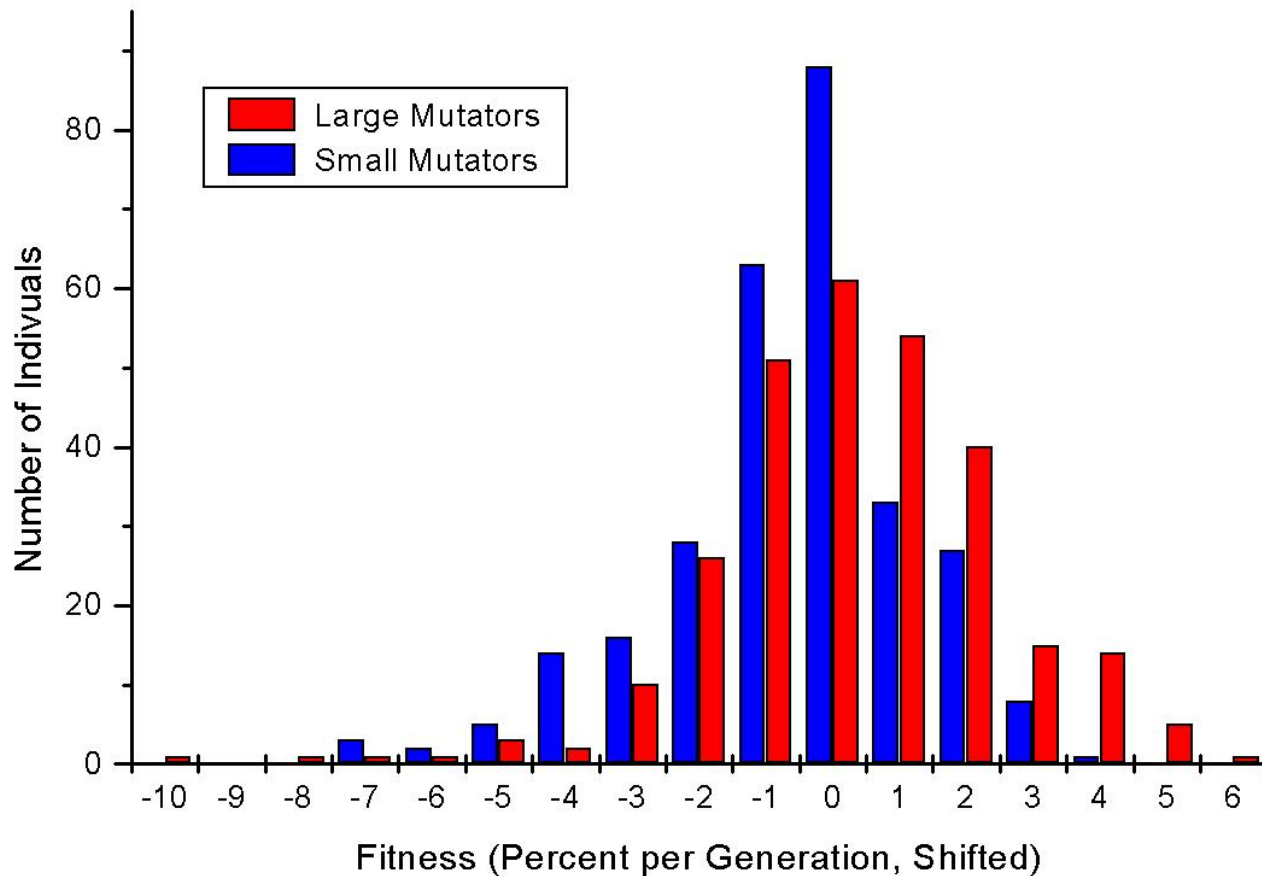


# Mutator Fitness Distributions

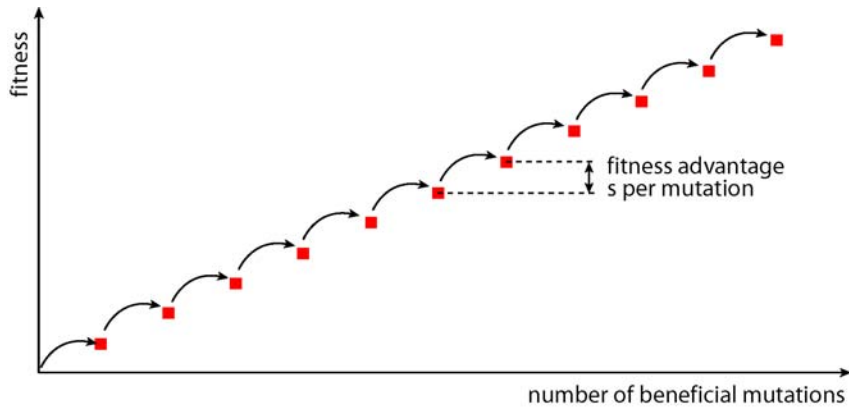


# Comparing Distribution Widths

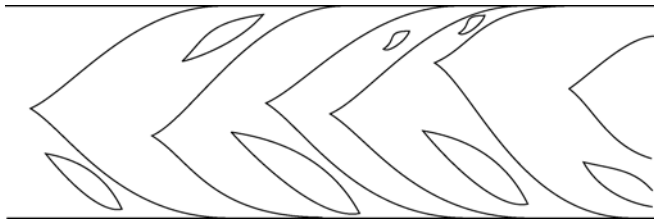
Mutator Fitness Distributions (Merged)



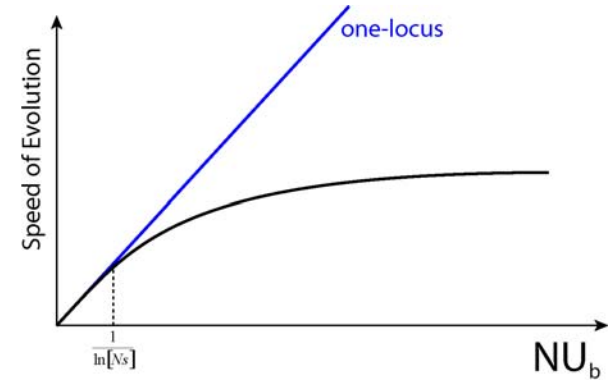
# Conclusions



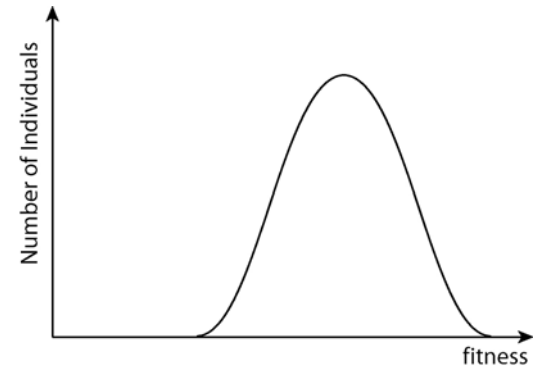
Climbing a hill is harder than it looks



Typical populations feel these effects



Large populations not much faster than small



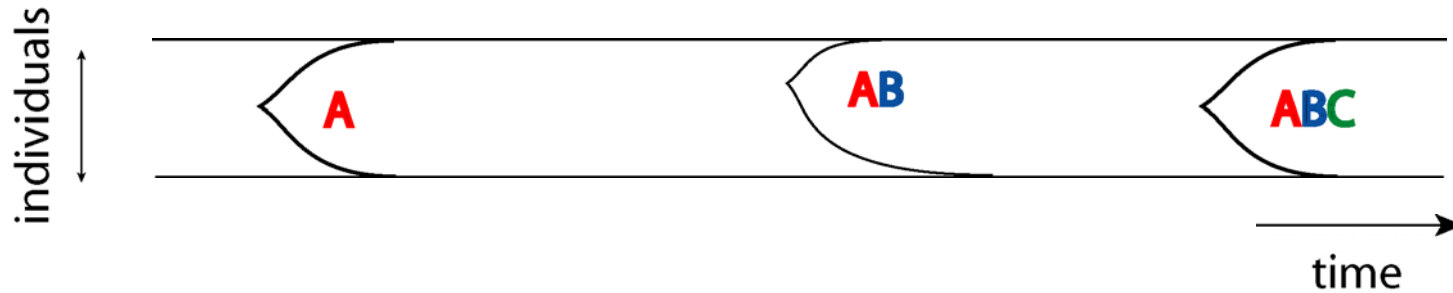
Multiple small mutations matter



# Diversity and Polymorphism Data

## What can Sequence Data Tell Us?

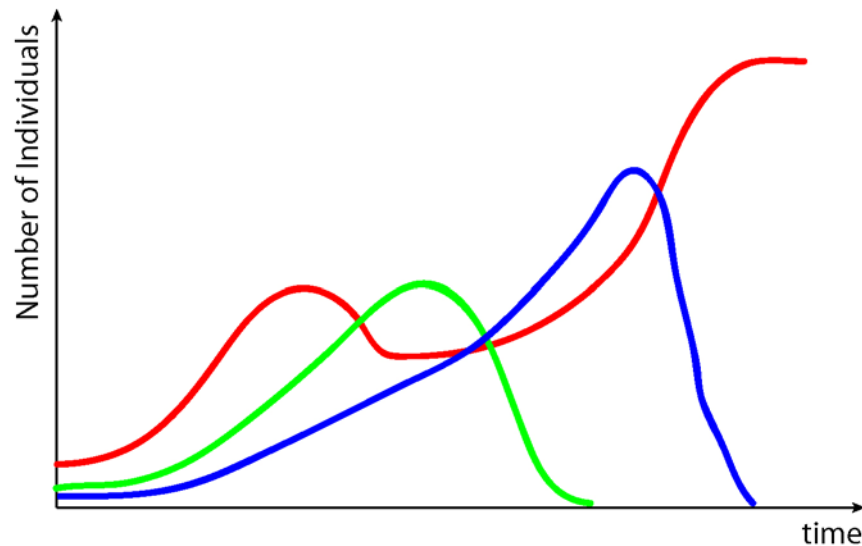
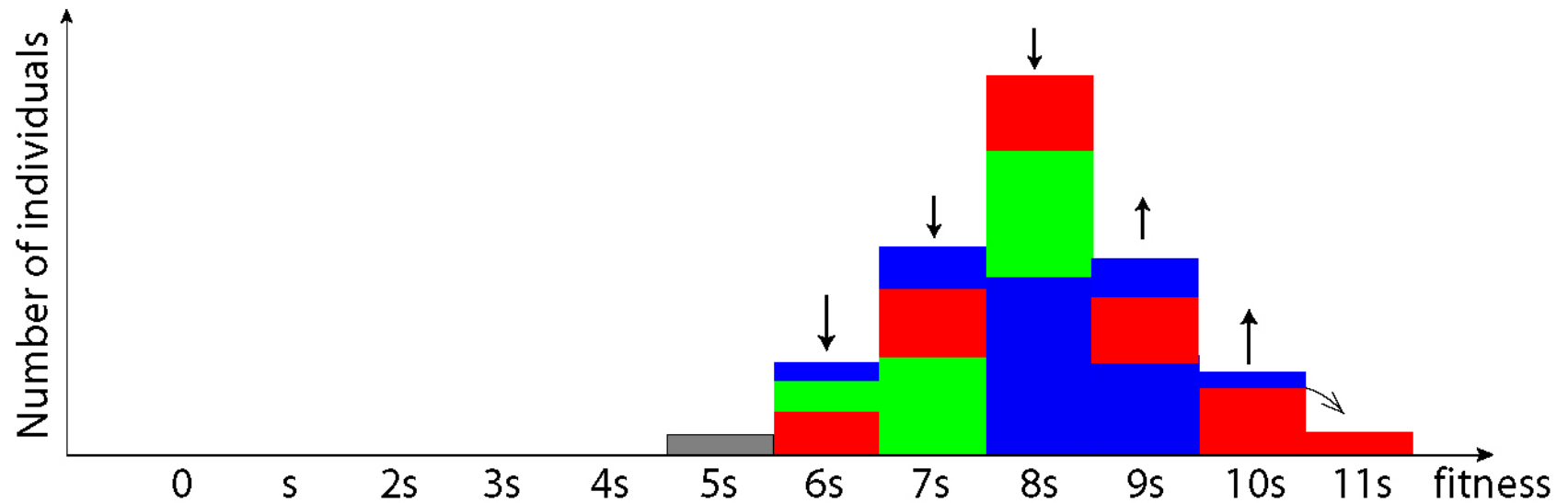
Small population:



Large population:

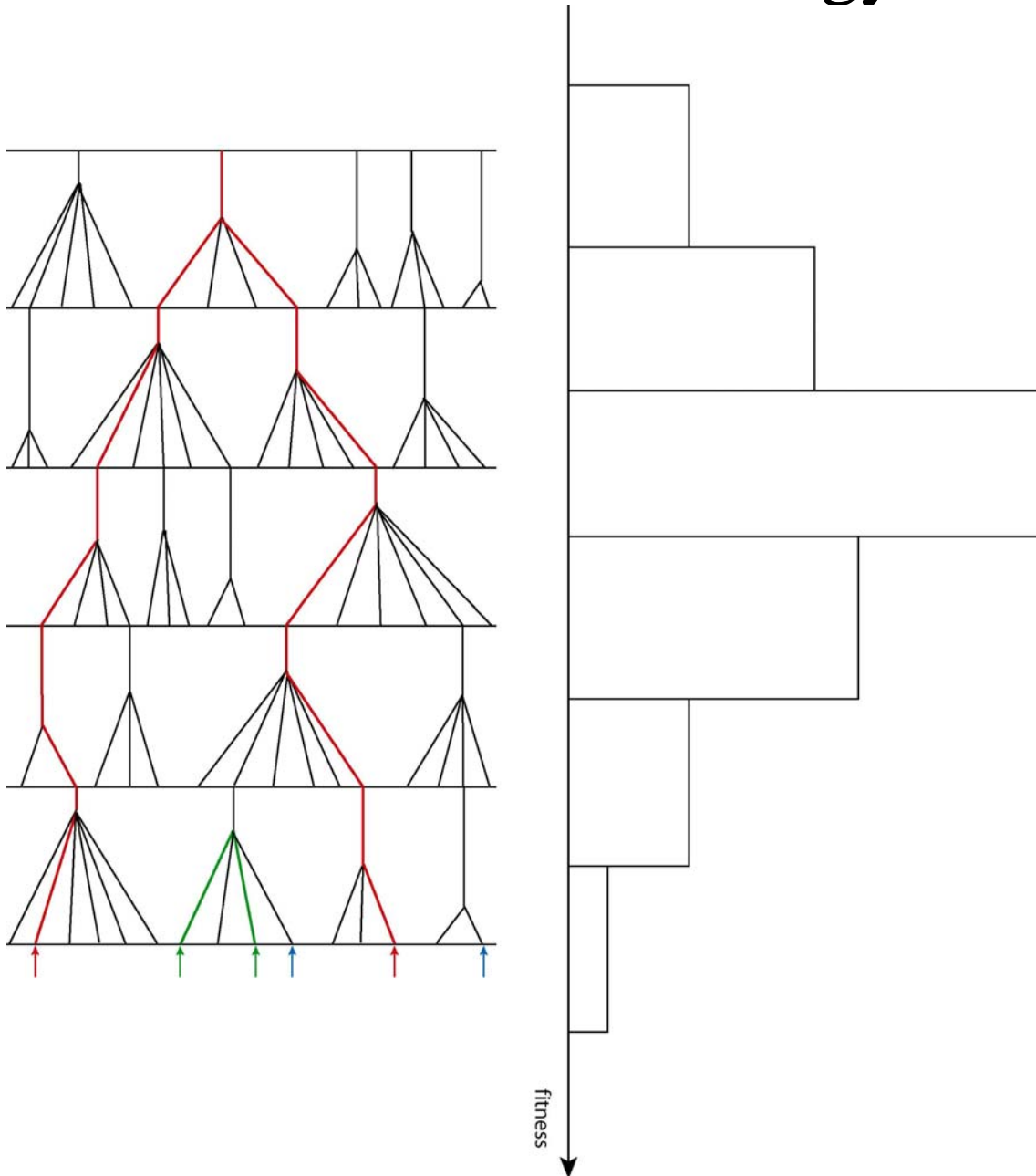


# Diversity in a Single Fitness Class

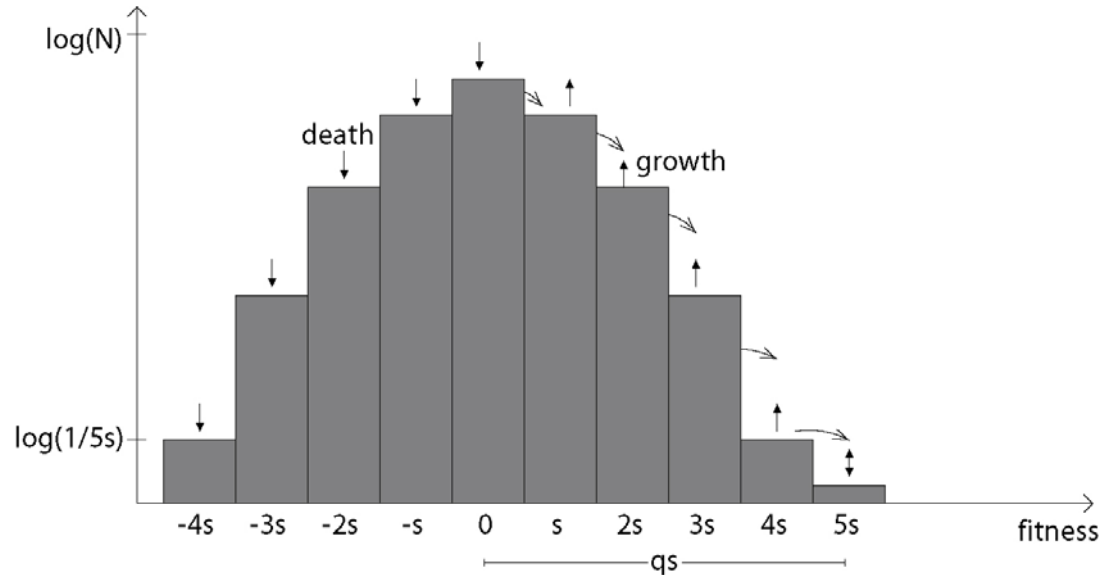


# A Coalescent Analogy

$$p \approx \frac{1}{q^2}$$



# Typical Sequence Divergence



Typical Sequence Difference:

Compare Neutral Result:

$$\langle \pi \rangle \approx \frac{8 \ln^2[Ns]}{\ln^2[s/U_b]} + \frac{2U_n}{s} \ln[s/U_b] \sqrt{\frac{\ln[Nu_n]}{\ln[Ns]}}$$

$$\langle \pi \rangle = 2NU_n$$

Selected

Neutral

# Acknowledgements

## My advisors:

Daniel Fisher

Andrew Murray

## Maintaining cultures:

Dawn Thompson

Sheri Simmons

## FACS fitness assays:

Larry Shumway

George Kenty

Doug Melton

## Conversations:

John Wakeley

Dan Weinreich

Rich Lenski

Herbie Levine

Igor Rouzine

Allen Orr

Sally Otto

Marc Feldman