

# The Evolution of Stress-Induced Mutagenesis

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Stanford University

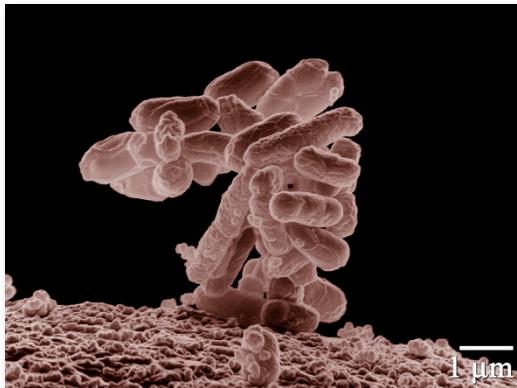
Hebrew University of Jerusalem  
13 December 2016

# Variability in mutation rates

## Between species

Average number of measurable mutations  
per genome per generation

Bacteria: 0.0004  
Wielgoss et al. G3 2011



Flies: 0.455  
Keightley et al. Gen Res 2009



Humans: 41  
Lynch, PNAS 2010



# Evolution in a constant environment

- Direction of selection doesn't change
- Balance between **mutation** and



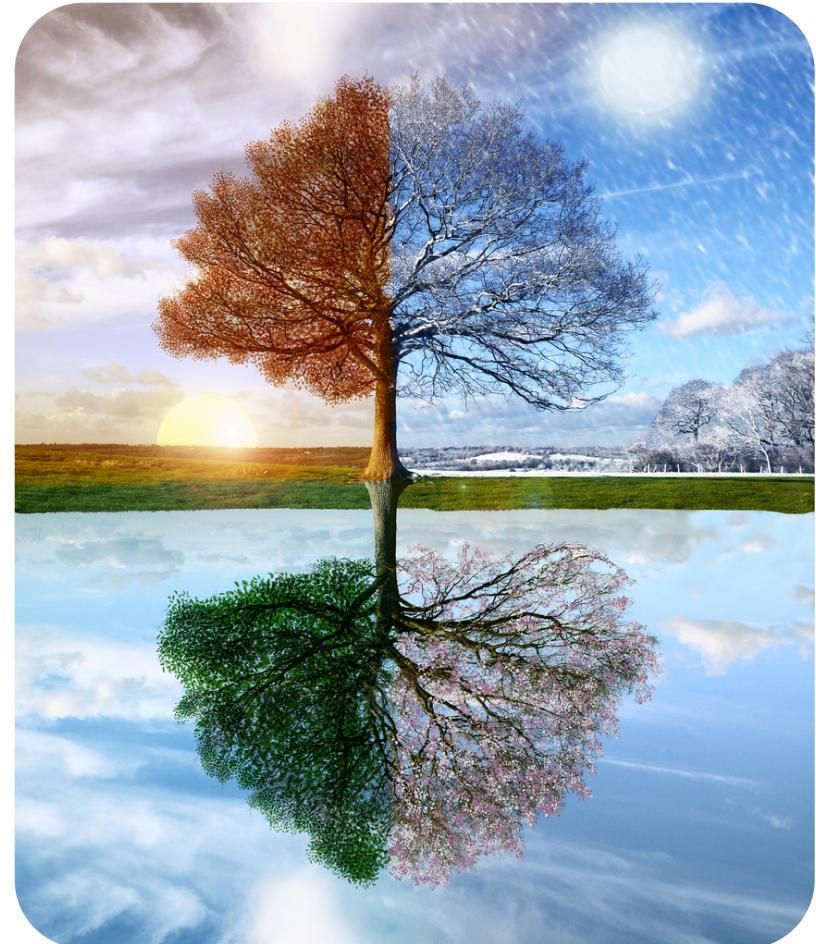
# Mutation-selection balance

- $\bar{\omega} = e^{-U}$
- High mutation rates reduce *adaptedness* of populations
- Selection will reduce the mutation rate to it's lowest attainable level - the **reduction principle**

Liberman & Feldman 1986
- What sets this level?
  - Physical or physiological constraints Kimura 1967
  - *Cost of DNA replication fidelity* Dawson 1999
  - *Drift barrier hypothesis* Lynch 2010

# Evolution in a changing environment

- In changing environments **rapid adaptation** can be favored by natural selection
- The mutation rate must **balance** between *adaptability* and *adaptedness*



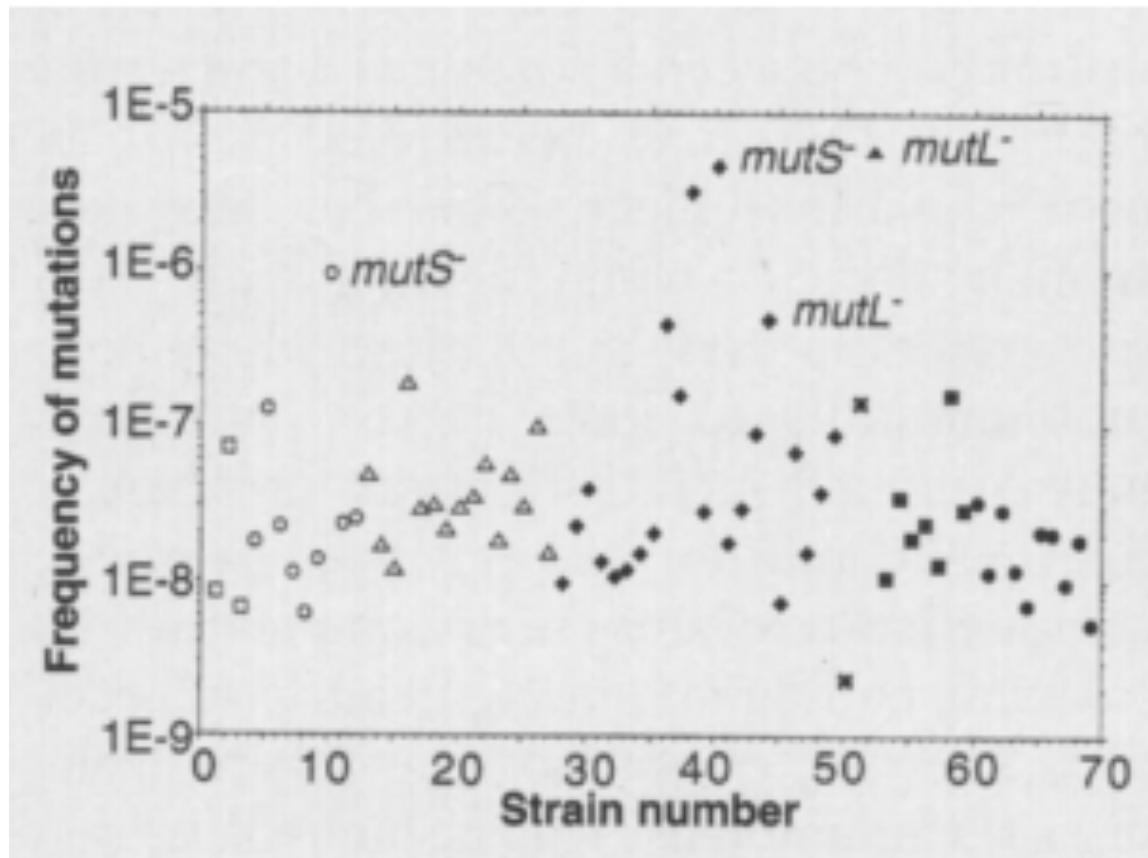
Leigh 1973

# Variability in mutation rates

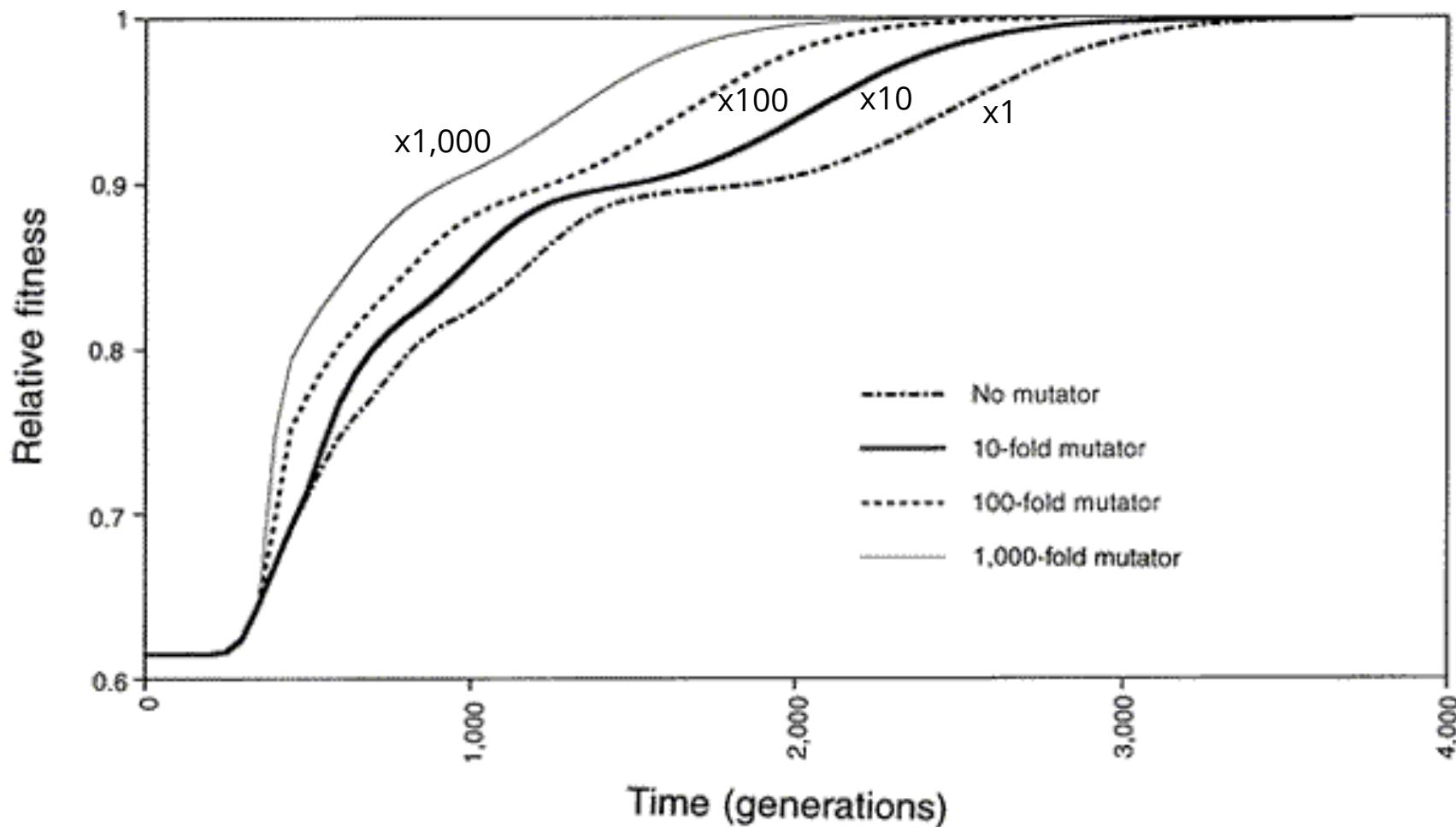
## Within species

Mutation rate in 69 natural populations of *E. coli*

Matic et al. 1997



# Adaptation with mutator alleles

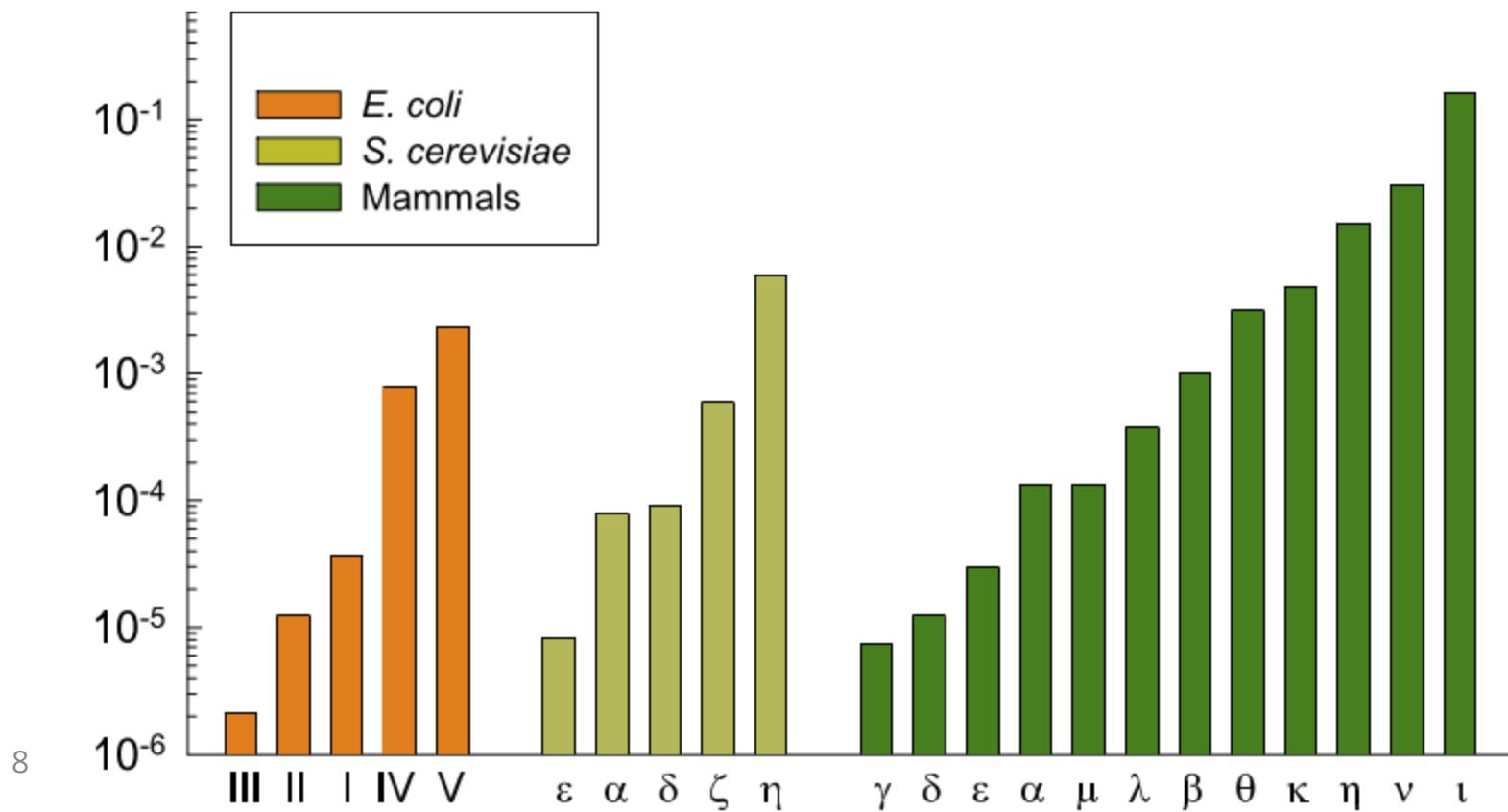


# Variability in mutation rates

## Within individuals

DNA polymerase error rate

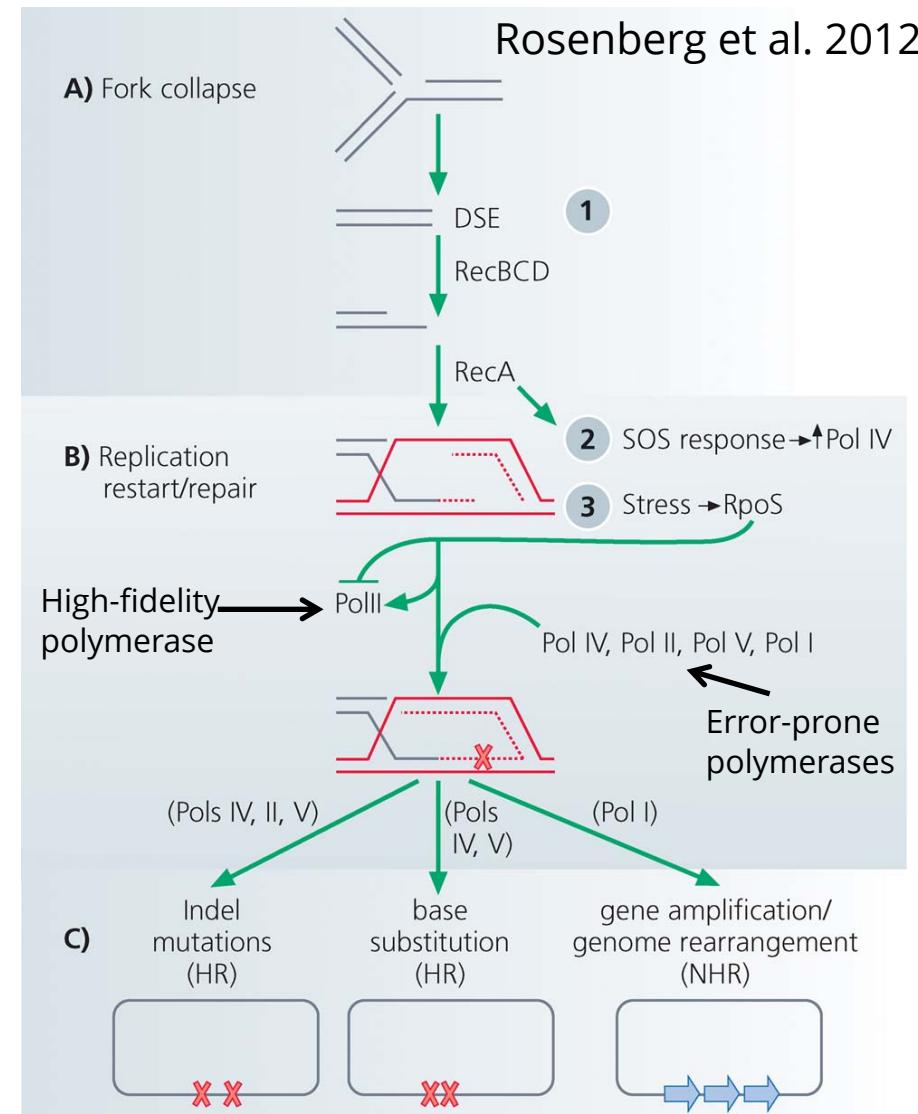
Lynch 2011

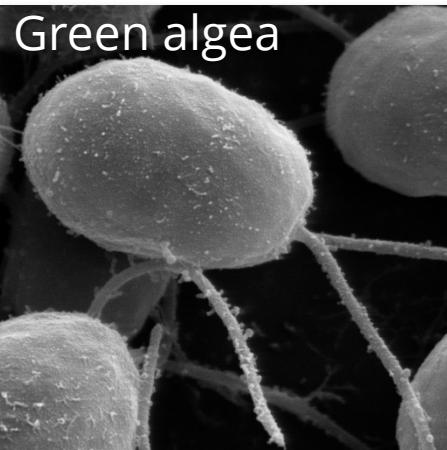


# Stress-induced mutagenesis

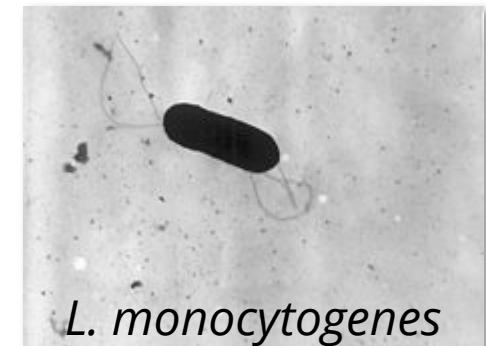
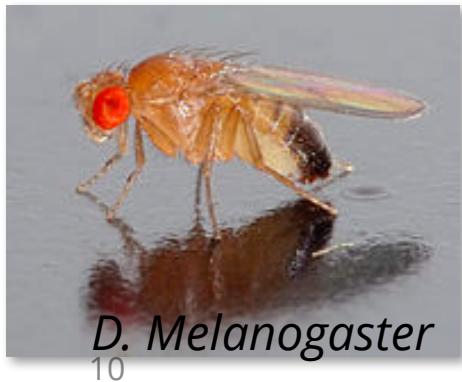
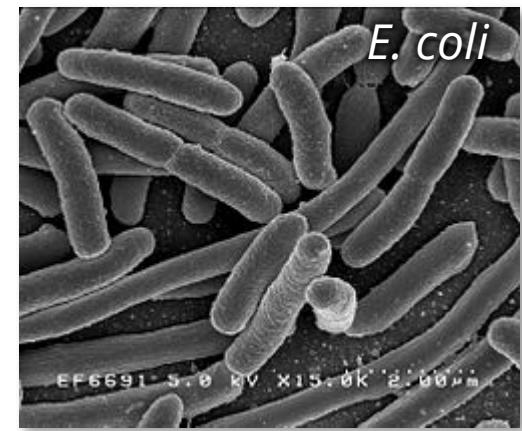
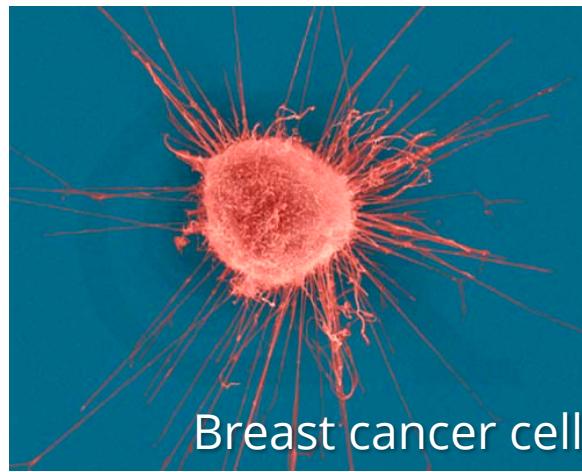
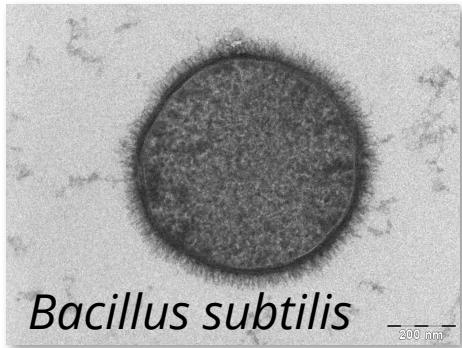
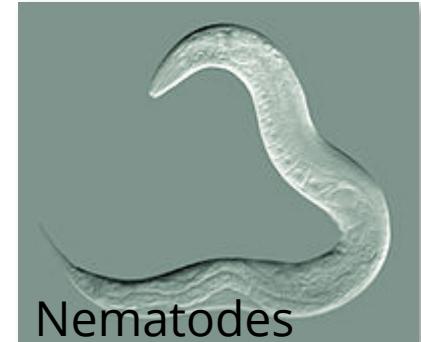
In *E. coli*:

- Error prone polymerase induced by stress responses:
  - SOS response
  - DNA damage
  - Starvation
- Mismatch repair system
- Other mechanisms:
  - Galhardo et al. 2007
  - Al Mamun, Science 2012





# Evidence



# Evolution of stress-induced mutagenesis

## Null hypothesis

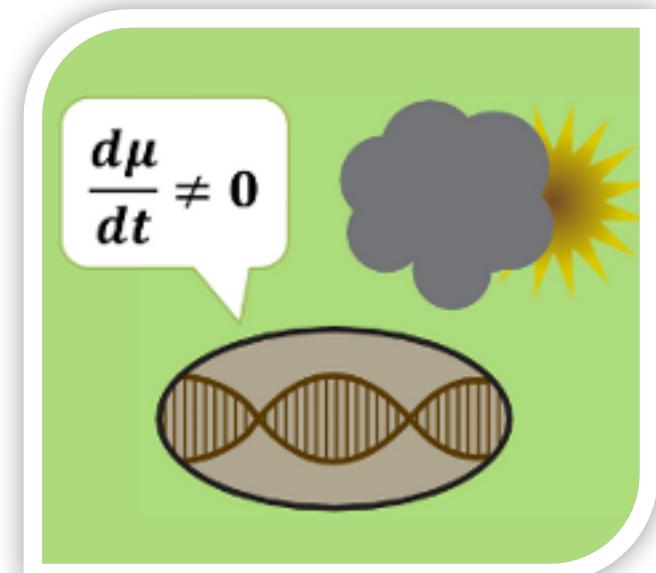
- Mutagenesis is the by-product of stress

## Alternative non-adaptive hypotheses

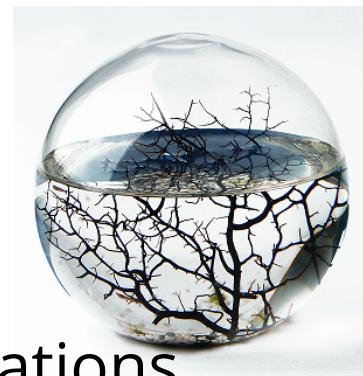
- Cost of replication fidelity

## Adaptive hypothesis

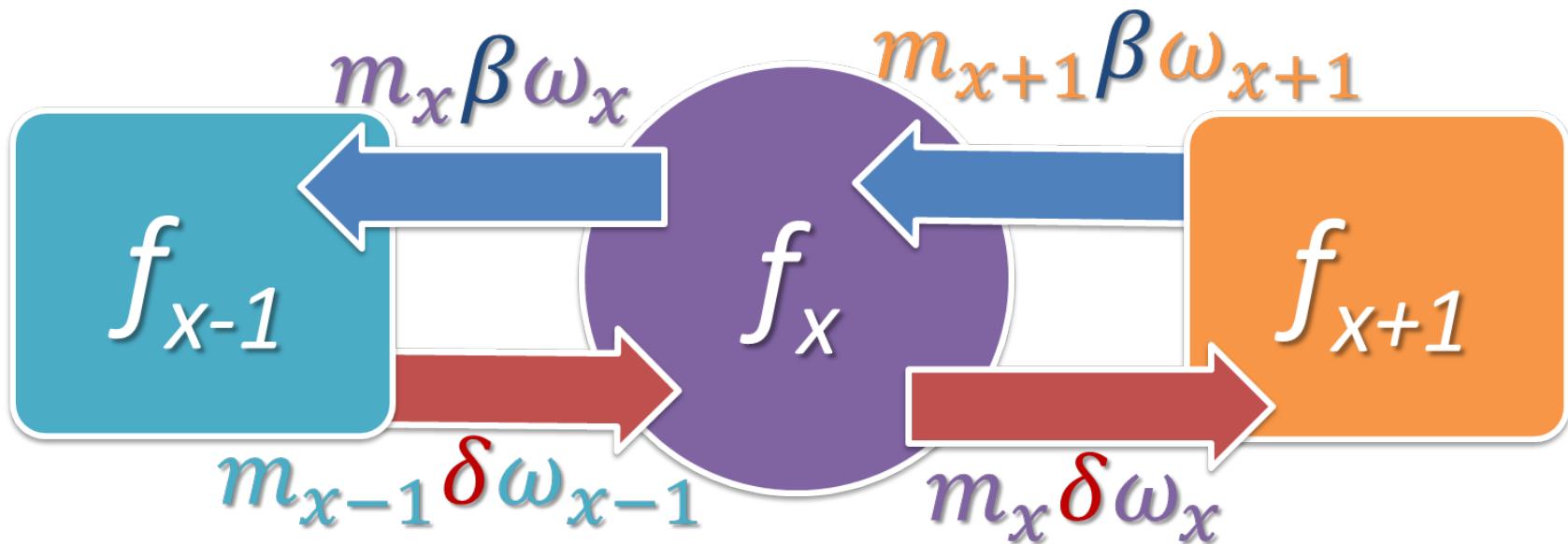
- 2<sup>nd</sup> order selection



# Constant environment



Selection against generation of deleterious mutations



$x$  - number of harmful alleles

$f_x$  - frequency

$\omega_x$  - fitness

$m_x$  - mutation probability

$\delta$  - deleterious mutation     $\beta$  - beneficial mutation

# Constant environment

General solution



$$\text{sign} \frac{\partial \bar{\omega}}{\partial m_x} = \text{sign} (\bar{\omega} - \omega_x)$$

**Increasing the mutation rate of individuals with below average fitness increases the population mean fitness**

**Selection doesn't always reduce the mutation rate!**

# Changing environments

## The Red Queen hypothesis

van Valen, 1973

*It takes all the running you can do,  
to keep in the same place.*

- Lewis Carroll, Through the Looking Glass

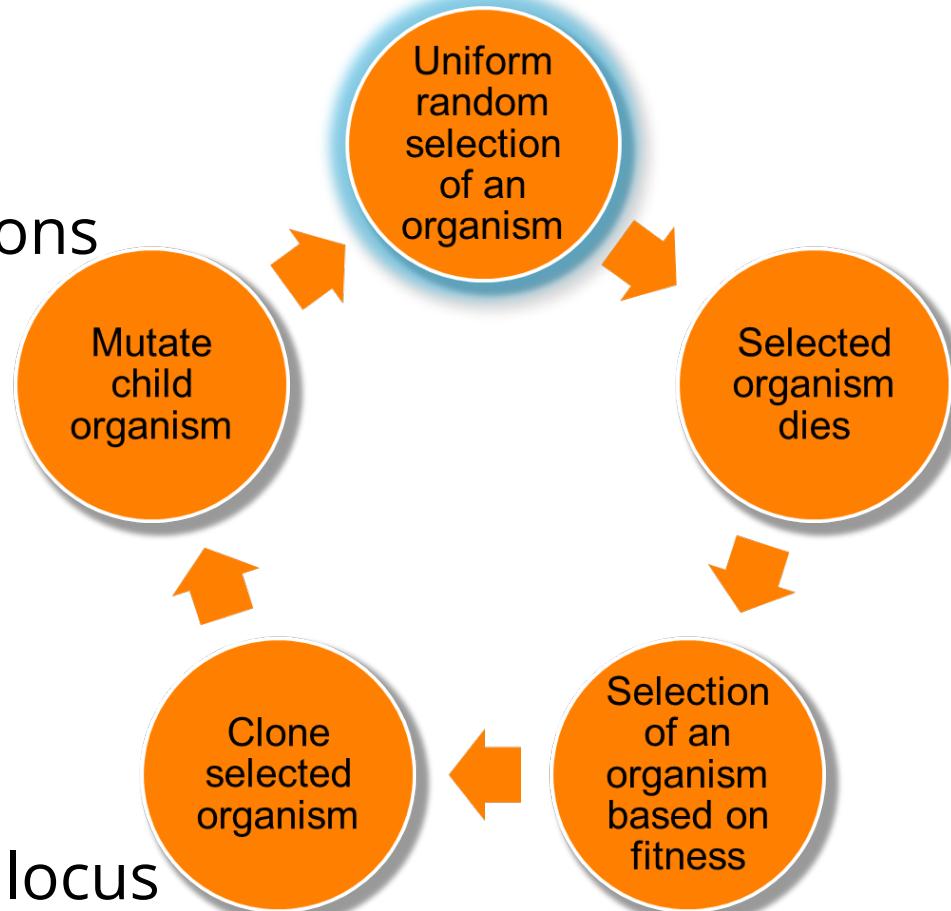
**What happens when the  
environment changes frequently?**



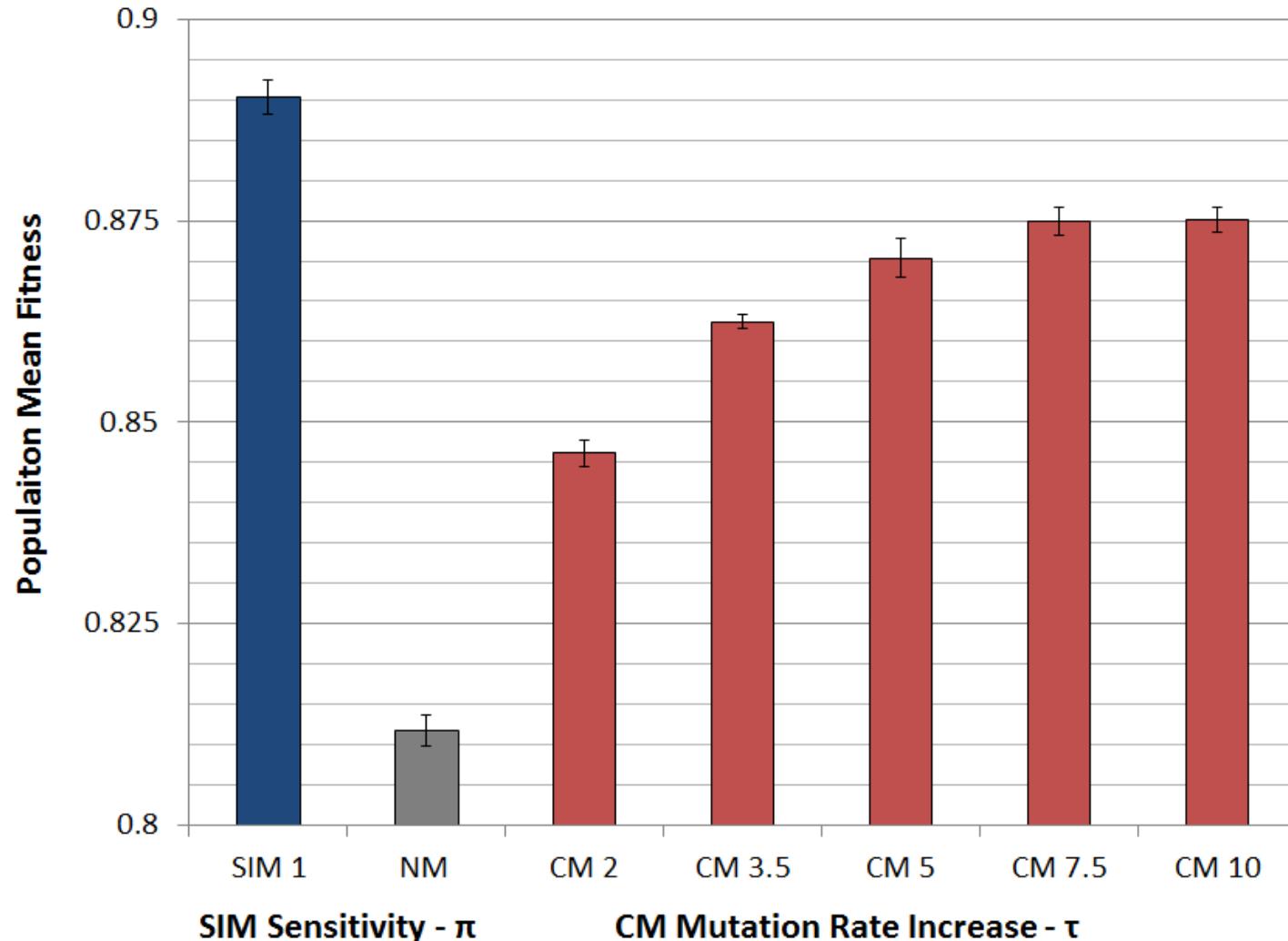
# Changing environments

## Simulations

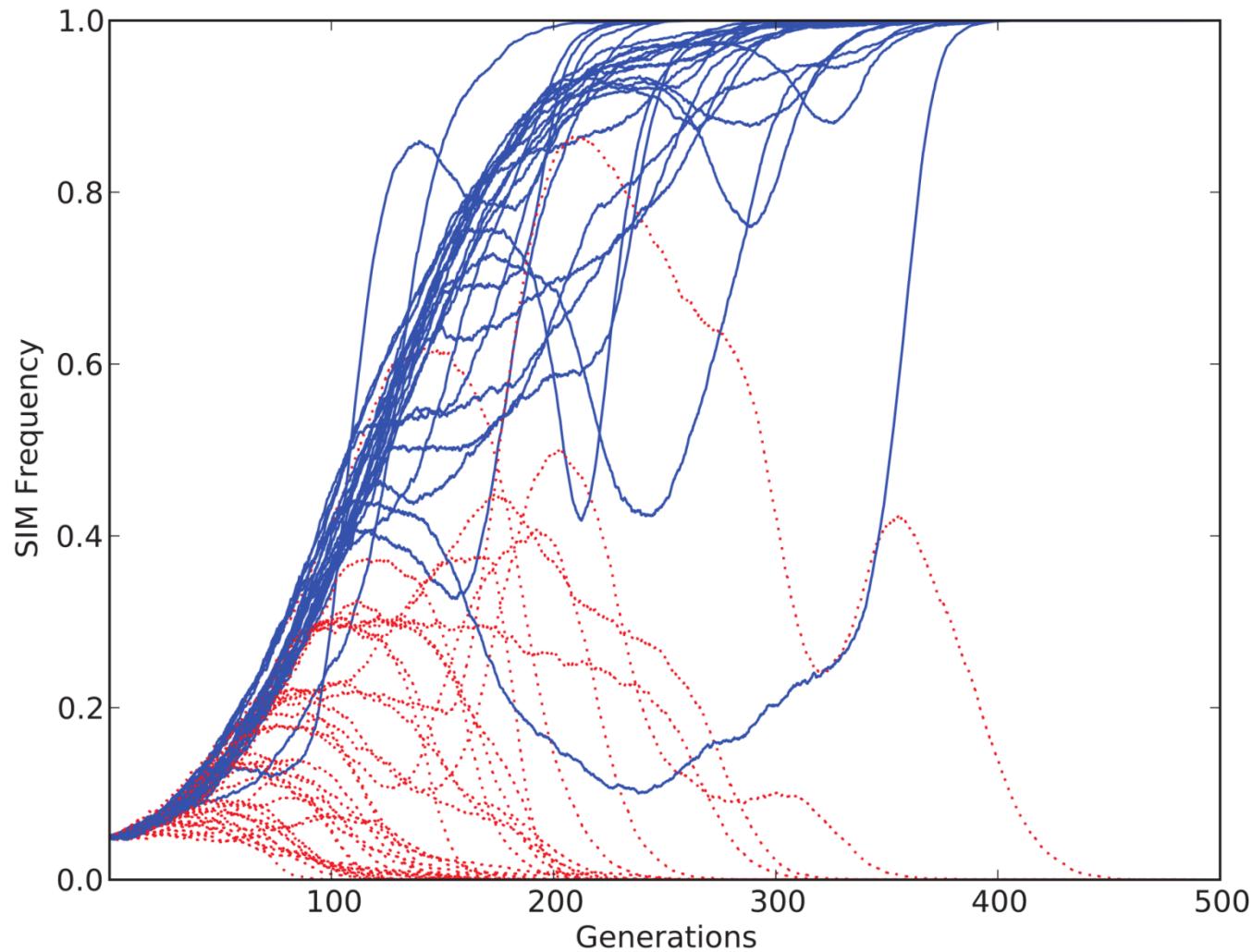
- Moran process
- Individual-based simulations
- **100,000 individuals**
- 1,000 loci
- Asexual, Haploid
- Overlapping generations
- No recombination
- No segregation
- No mutations at mutator locus
- Environmental changes



# Populations with SIM are fitter

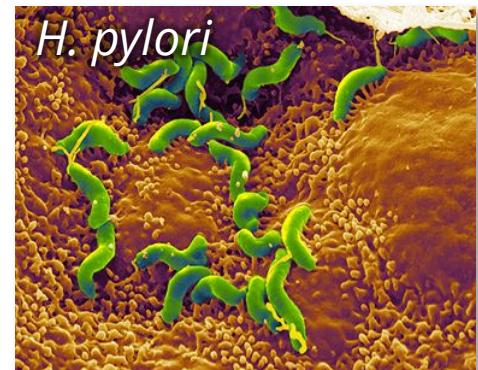


# SIM wins competitions



# Conclusions

- **Stress-induced mutators evolve:**
  - In constant & changing environments
- **2<sup>nd</sup> order selection** can lead to the evolution of stress-induced mutagenesis in asexual populations
  - Selection for evolvability



# In the presence of recombination

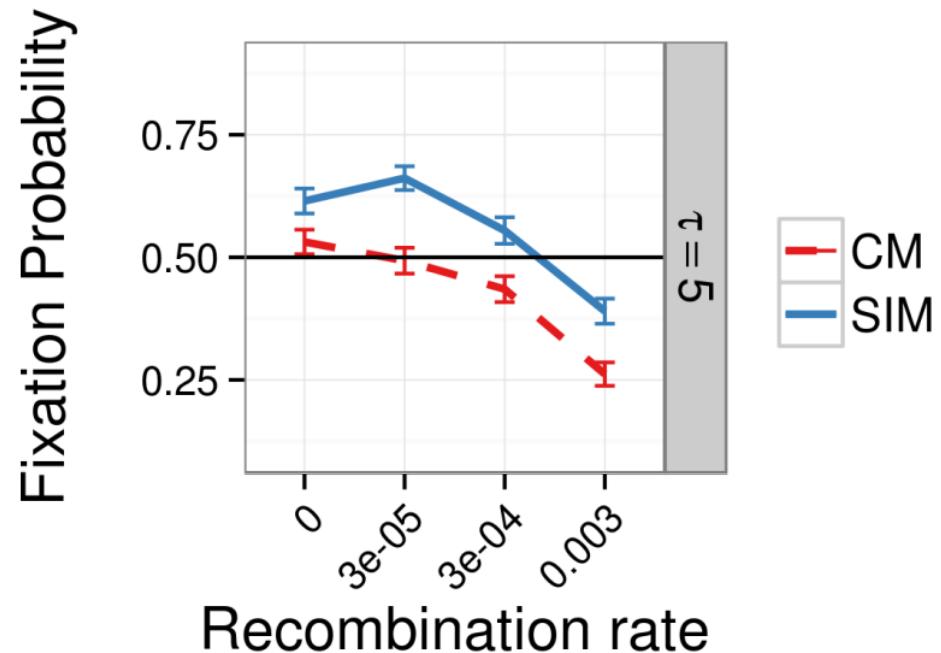
- Recombination can:
  - Separate mutator from beneficial mutations
  - Increase non-mutator adaptation rate
  - Save constitutive mutators from deleterious mutations

# In the presence of recombination

Results suggest:

- $SIM > CM$
- $SIM \geq NM$
- As long as recombination is as not much stronger than mutations

Sexual populations??



# Consequences of Stress-Induced Mutagenesis

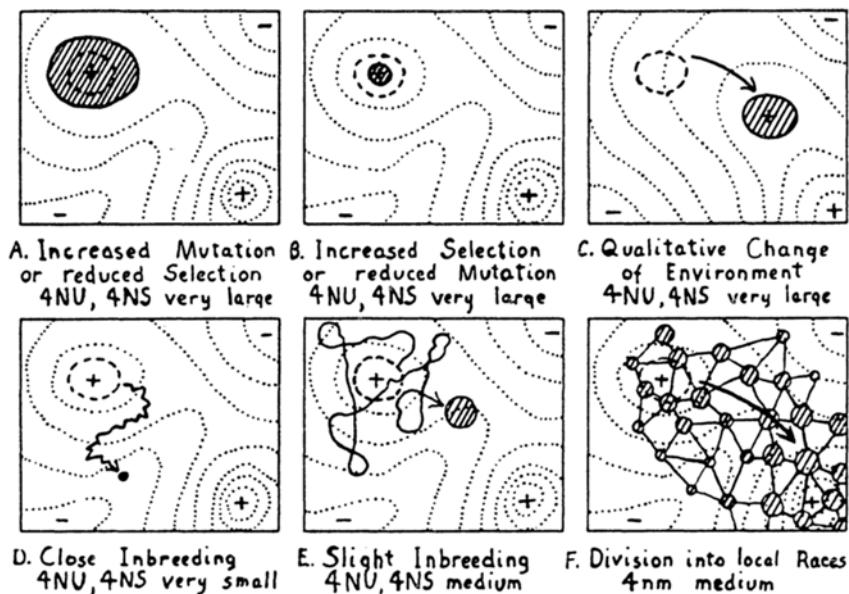
How does stress-induced mutagenesis affect adaptation?



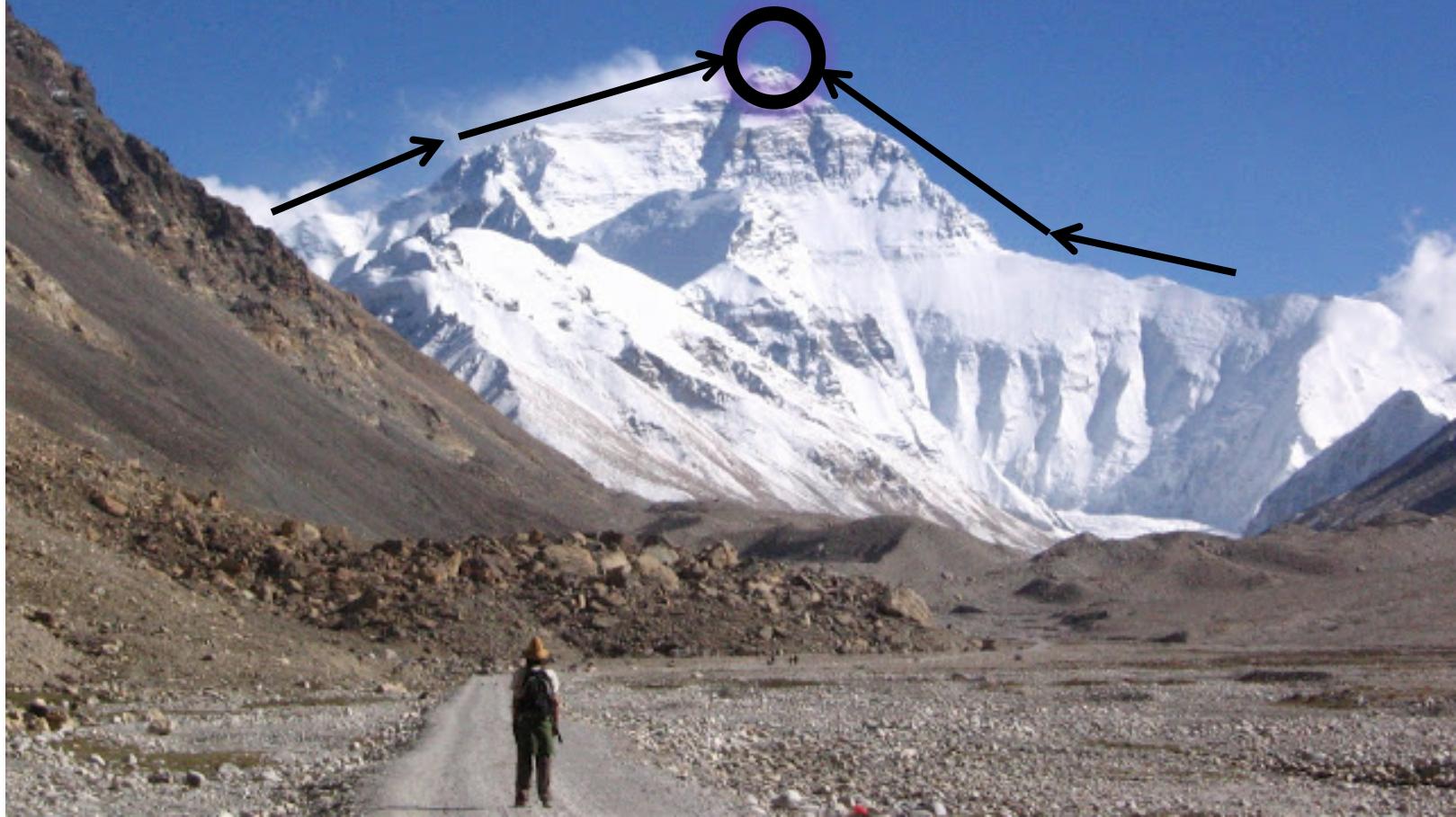
# Adaptive peak shifts

Sewall Wright, 1931:

*If a new adaptation requires several, separately deleterious mutations, how can it evolve?*



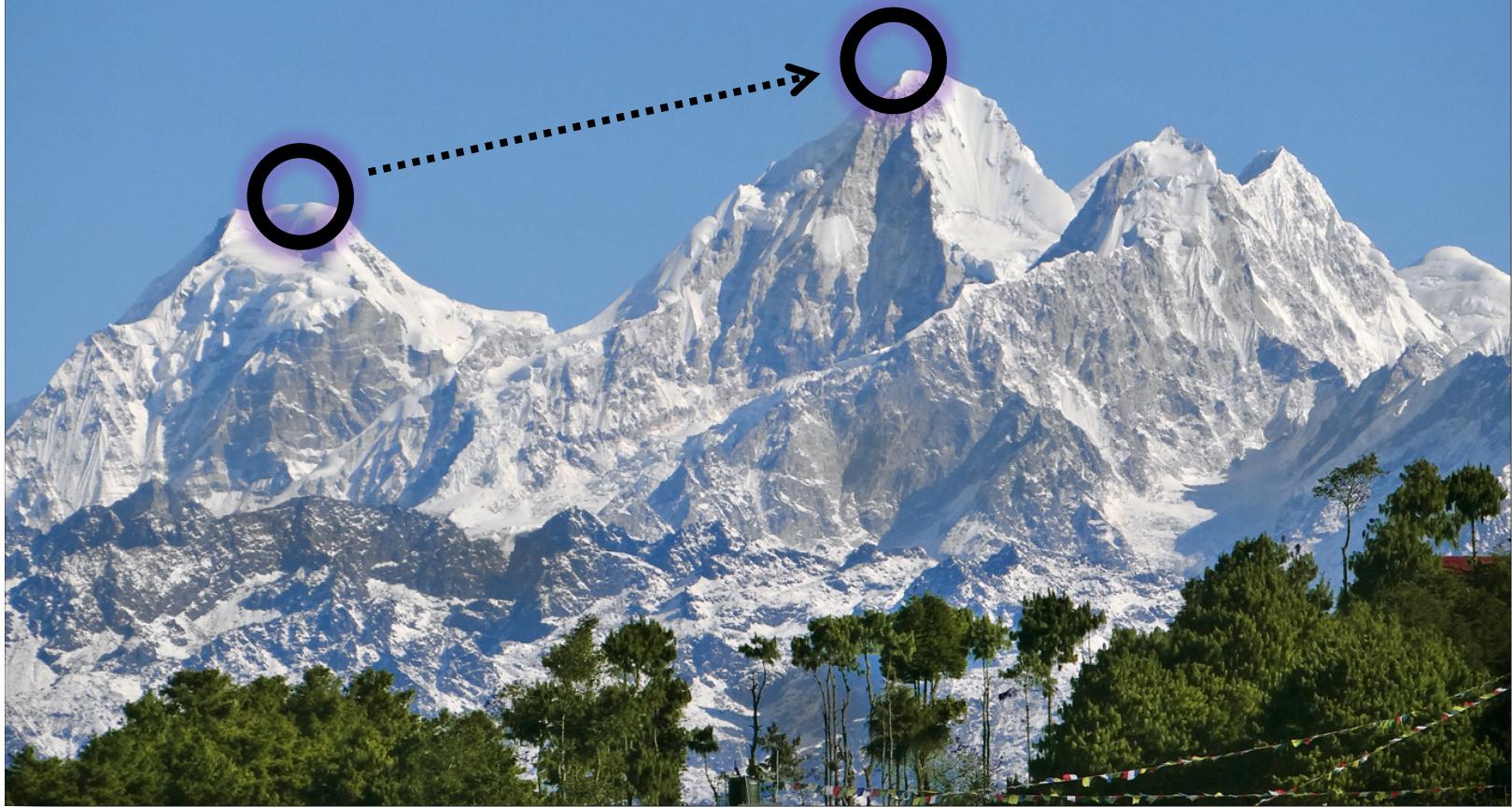
# Simple landscape



# Rugged landscape

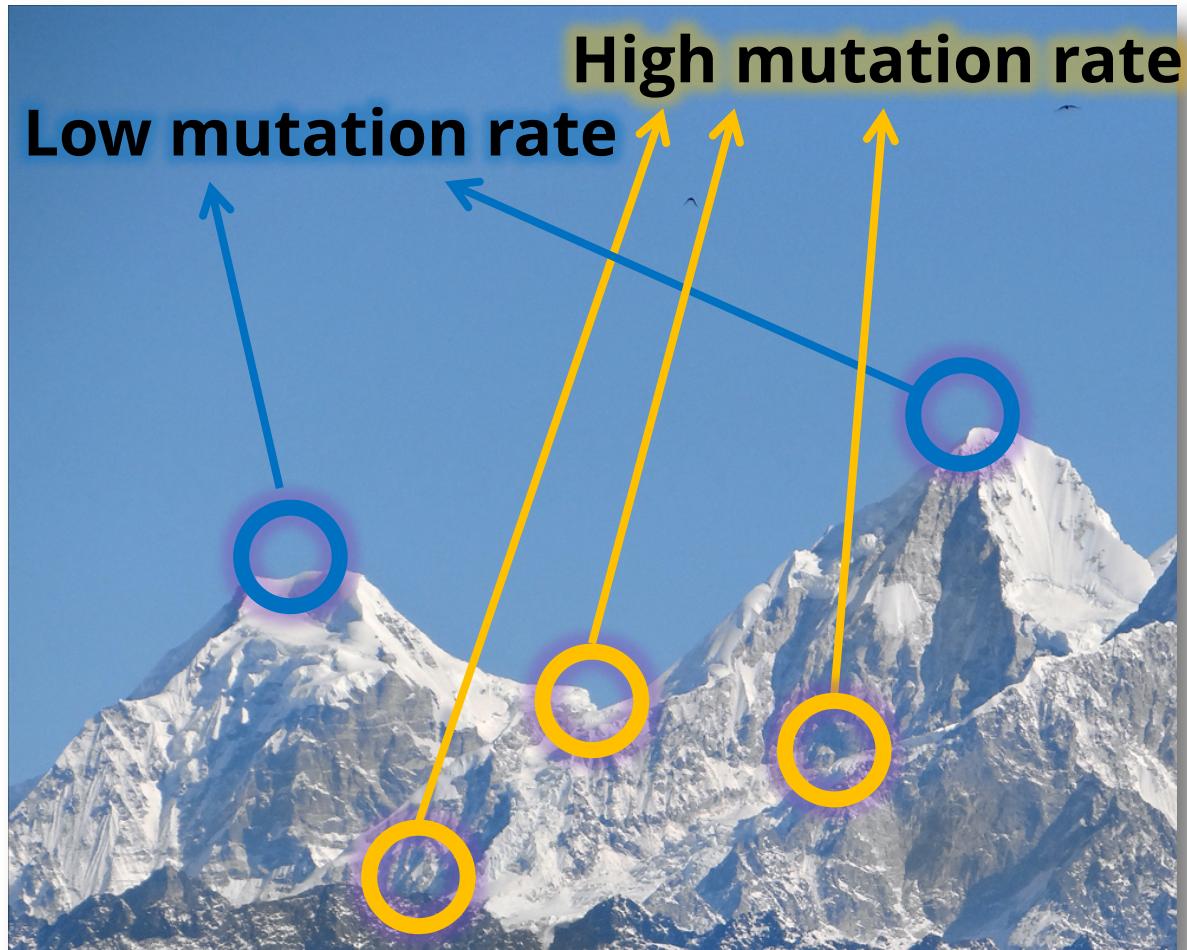


# Adaptive peak shift

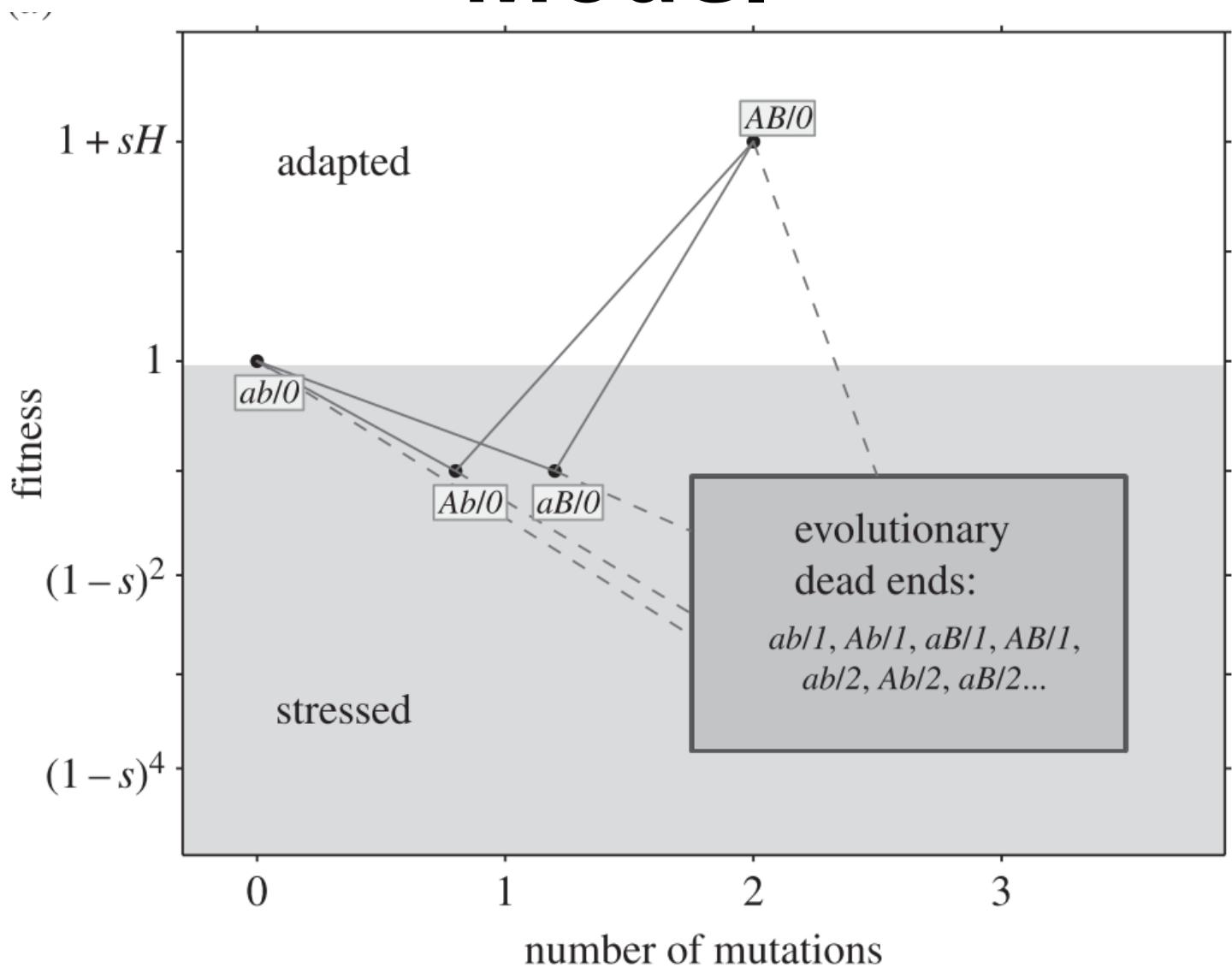


# SIM & rugged landscapes

Increasing the mutation rate in individuals below both peaks

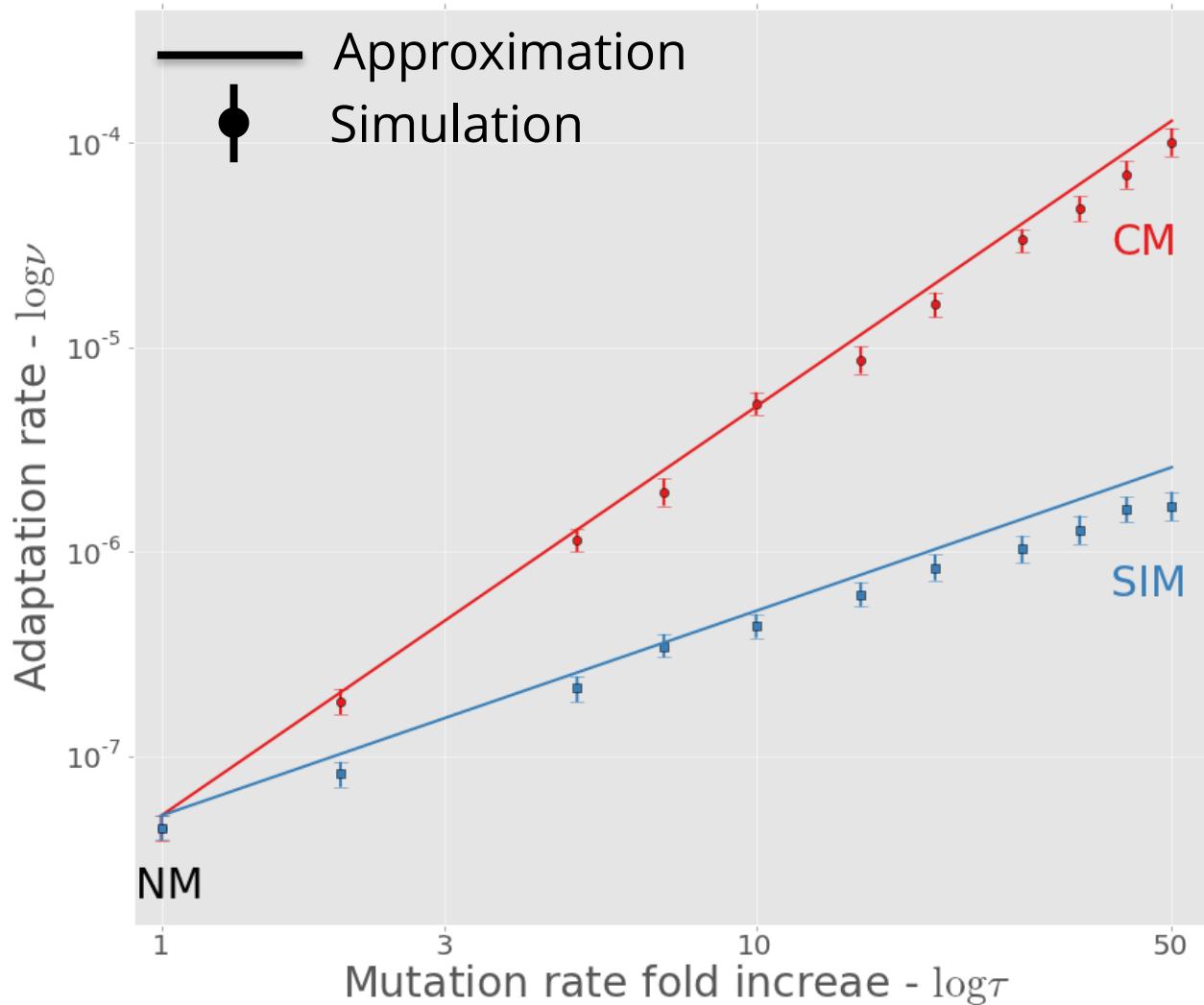


# Model

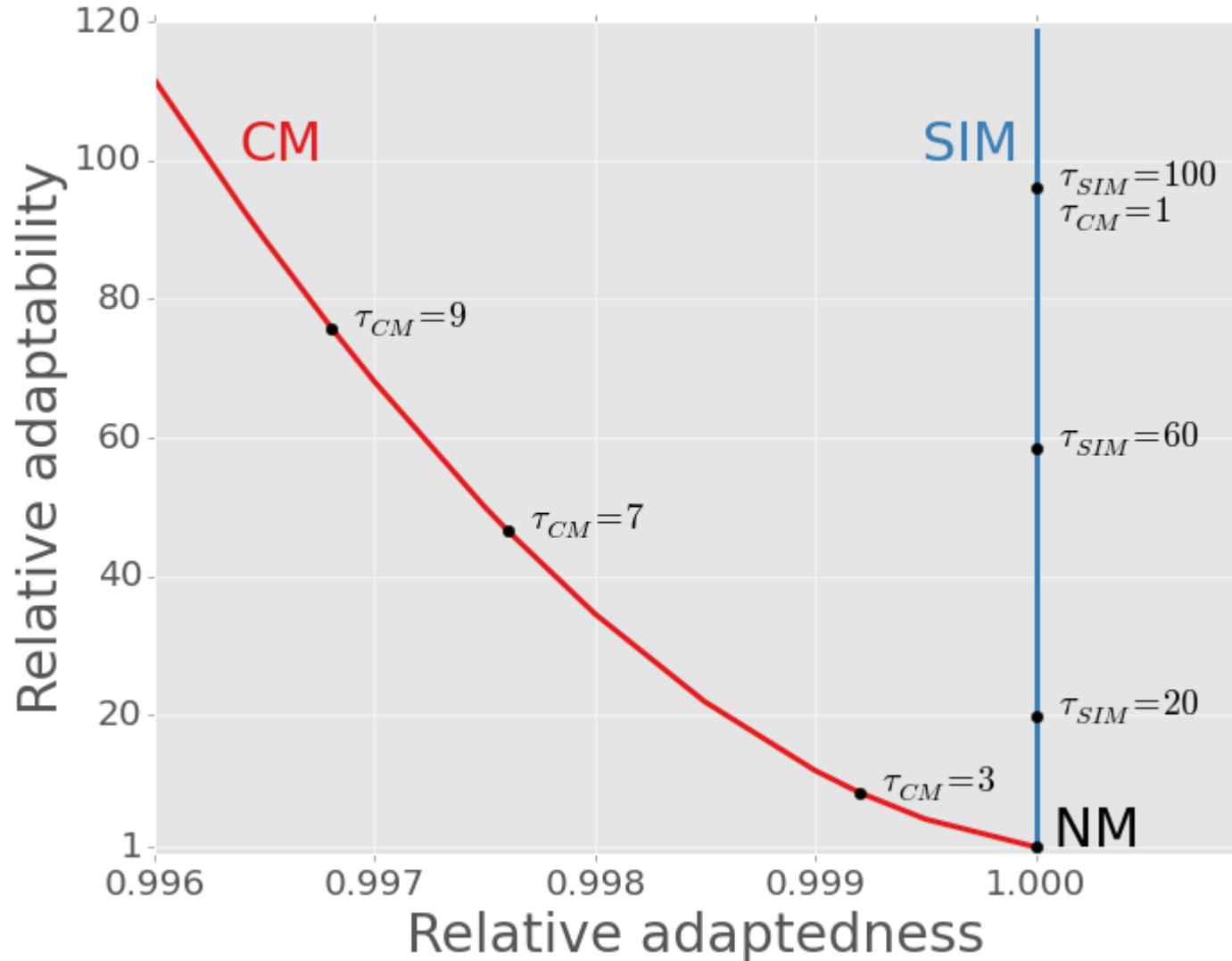


# Adaptation rate

$$\nu_{CM} \approx \tau^2 \cdot \nu_{NM}$$
$$\nu_{SIM} \approx \tau \cdot \nu_{NM}$$



# SIM Breaks the *adaptability-adaptedness* trade-off



# Conclusions

## Effects of stress-induced mutagenesis:

- SIM increases the adaptation rate without reducing the population mean fitness
- Breaks the trade-off between *adaptability* and *adaptedness*

Ram & Hadany, PRSB 2014

# Predicting Microbial Growth in a Mixed Culture

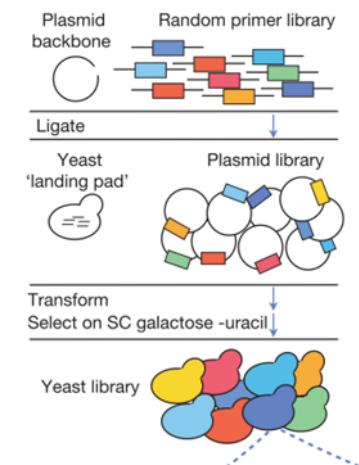
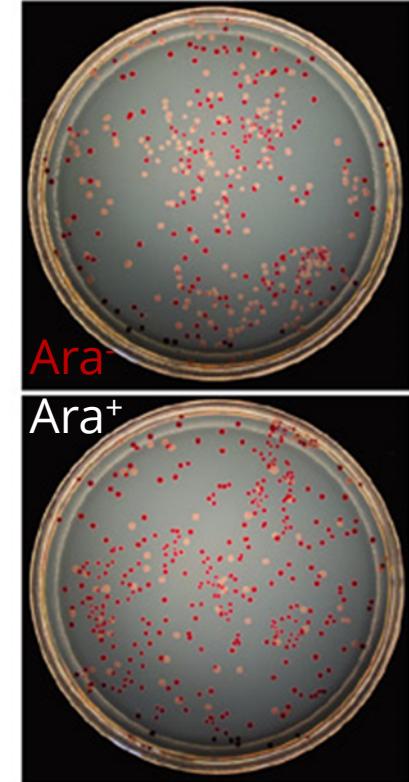
# Competition experiments

Strains must have a genotypic or phenotypic marker.

**Problem:** Laborious and costly, more so for non-model organisms.

**Our Solution:** Computational framework that predicts growth in mixed culture:

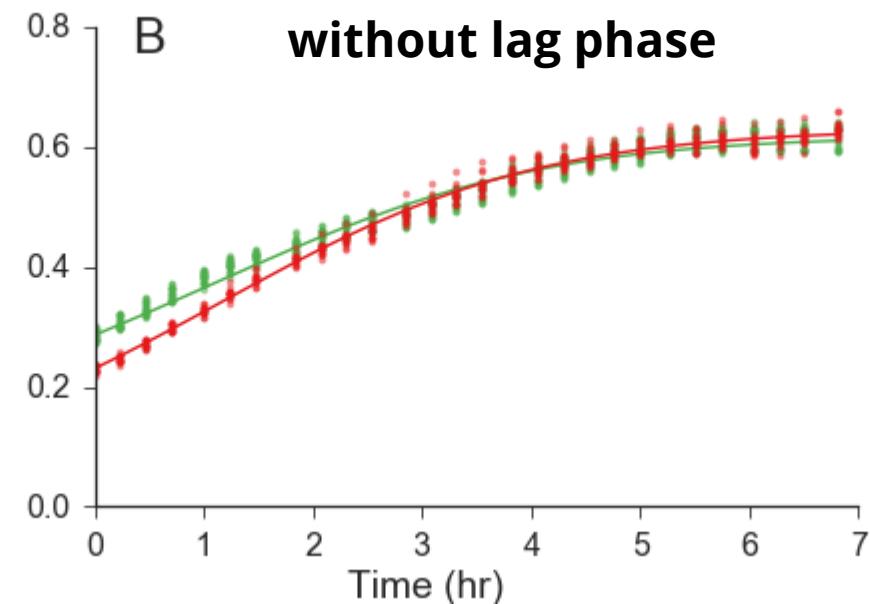
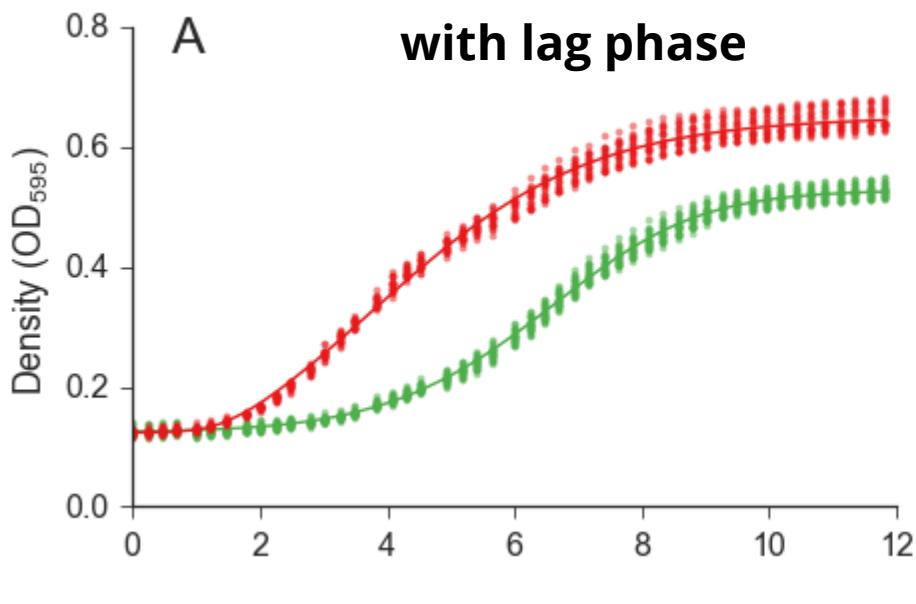
1. Fit growth models to growth curves
2. Predict competition results
3. Infer fitness



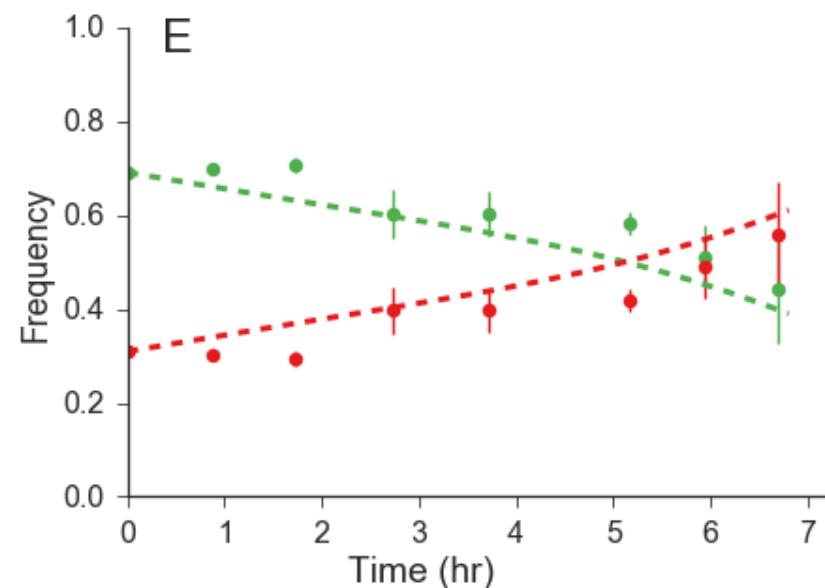
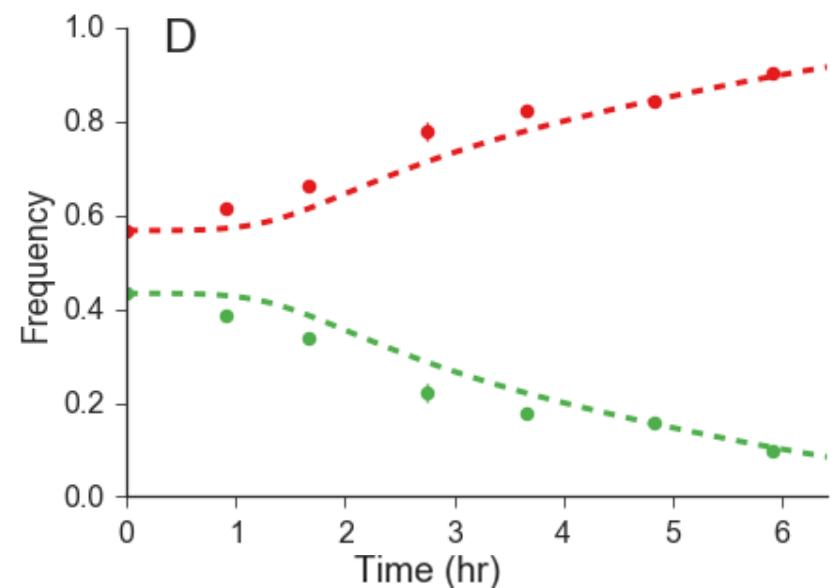
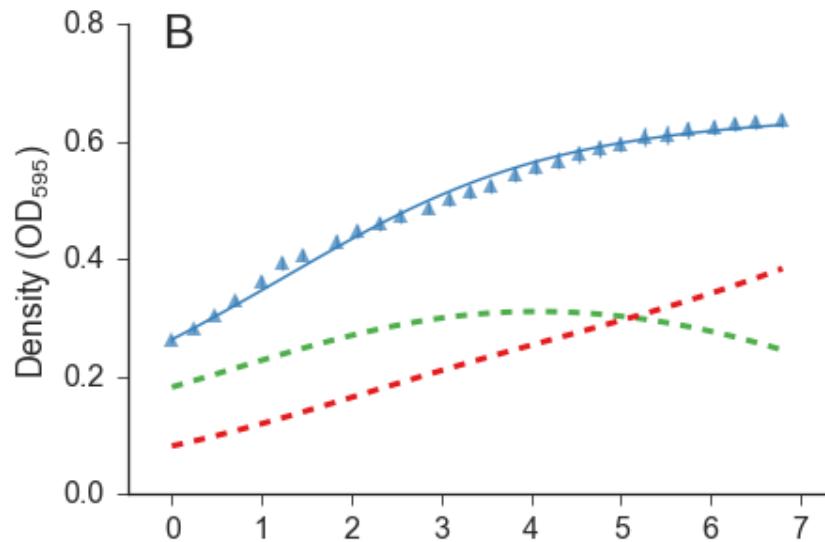
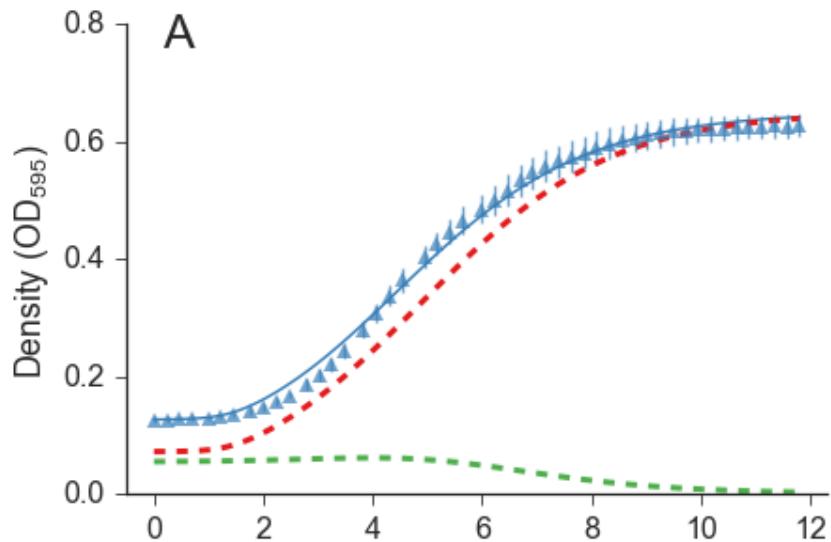
# Growth curve data

Data from two experiments with *E. coli* strains: (DH5 $\alpha$  vs. TG1) fitted a growth model

Baranyi & Roberts, 1994



# Mixed culture prediction



# Summary

1. Fit growth models to growth curves
2. Predict competition results
3. Infer fitness

## Preprint:

Ram et al. (2015) *Predicting microbial relative growth in a mixed culture from growth curve data*. bioRxiv, doi:[10.1101/022640](https://doi.org/10.1101/022640)

**Software website:** [curveball.yoavram.com](http://curveball.yoavram.com)

# Future directions

- **Complex growth curves:**
  - Bi-phasic growth:
  - Deep stationary phase
  - Cell death
- **Null model for detection of frequency-dependent interactions:**
  - Cooperation
  - Interference
- **Compete hypothetical strains**
- **Predict adaptive evolution**
- **Interpret fitness differences**

# Summary

## Stress-induced mutagenesis

- Can **evolve** due to 2nd order selection
- In **constant & changing** environments
- In **asexual** populations

Ram & Hadany, Evolution 2012

- In the presence of rare **recombination**

Ram & Hadany, in preparation

- Increases the rate of **complex adaptation rate**
- Without reducing the **population mean fitness**
- Breaks the **trade-off** between *adaptability* and *adaptedness*

Ram & Hadany, PRSB 2014

## Predicting microbial growth in a mixed culture

Ram et al., bioRxiv preprint

# Acknowledgments

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Lab Evolution