

# **STRESS, MUTATION, EVOLUTION, AND MATHEMATICAL MODELS**

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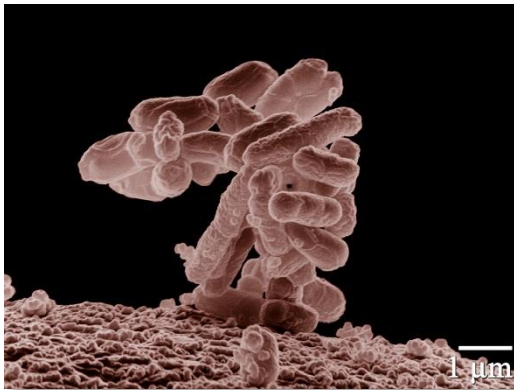
# VARIABILITY IN MUTATION RATES

## Between species

Rates are in average number of measurable mutations per genome per generation

Bacteria: 0.0004

Wielgoss et al. G3 2011



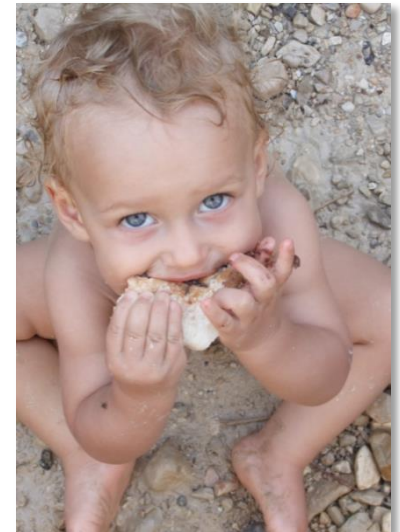
Flies: 0.455

Keightley et al. Gen Res 2009



Humans: 41

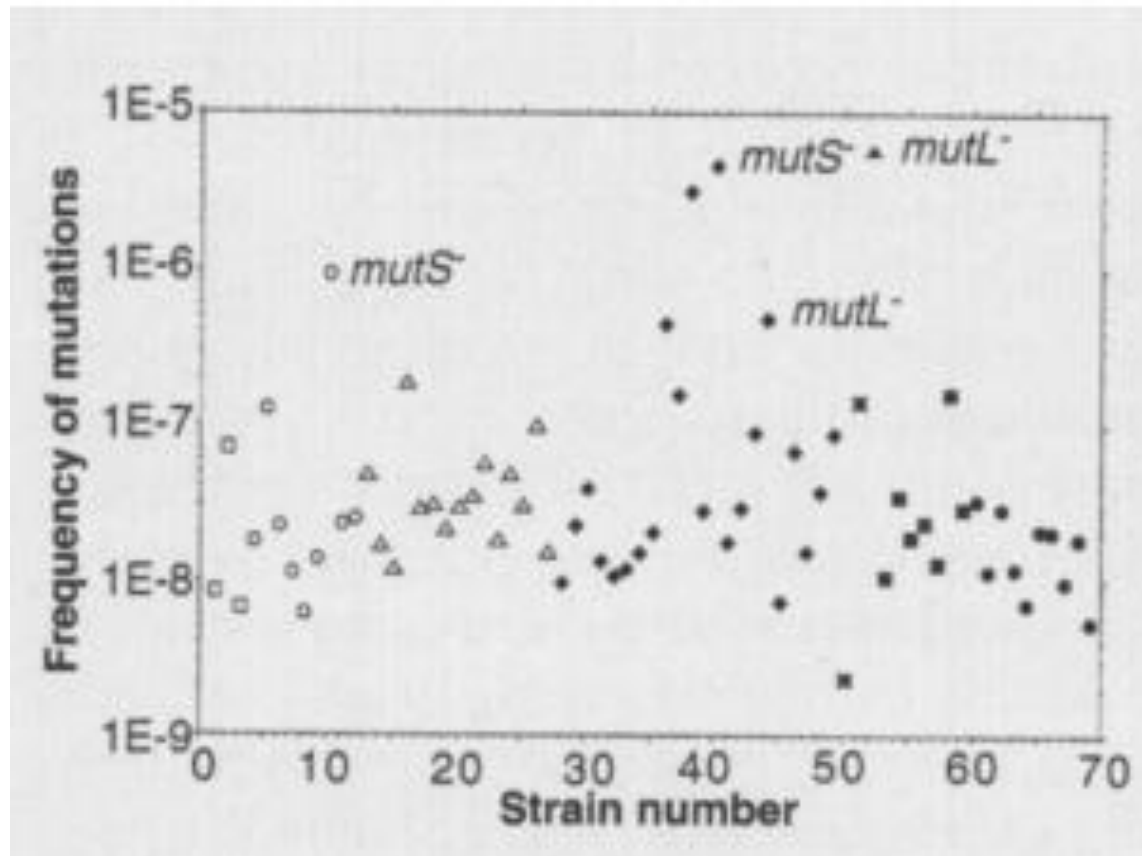
Lynch, PNAS 2010



# VARIABILITY IN MUTATION RATES

## Within species

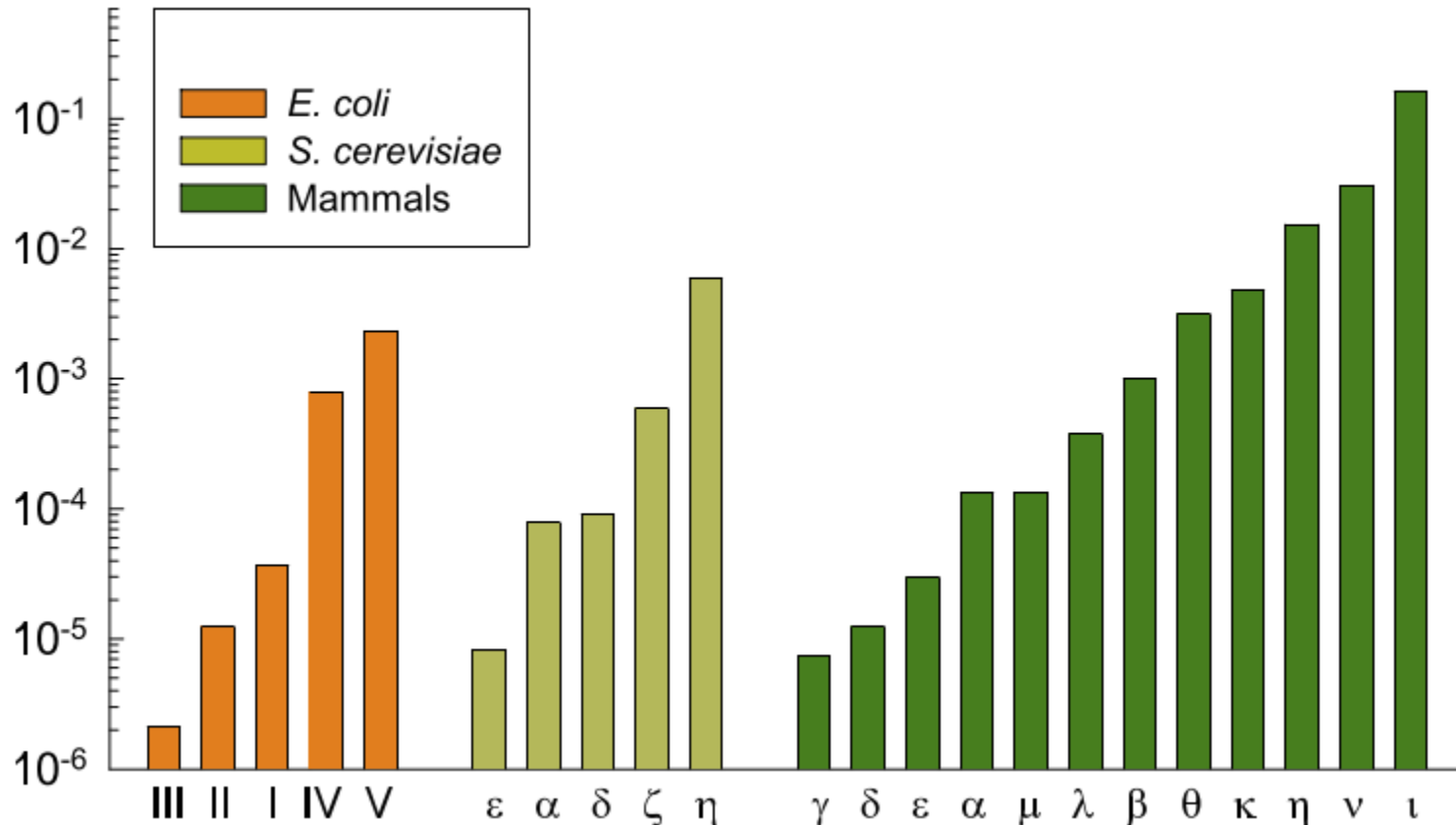
Mutation rate in 69 natural populations of *E. coli* – Matic et al. 1997



# VARIABILITY IN MUTATION RATES

## Within individuals

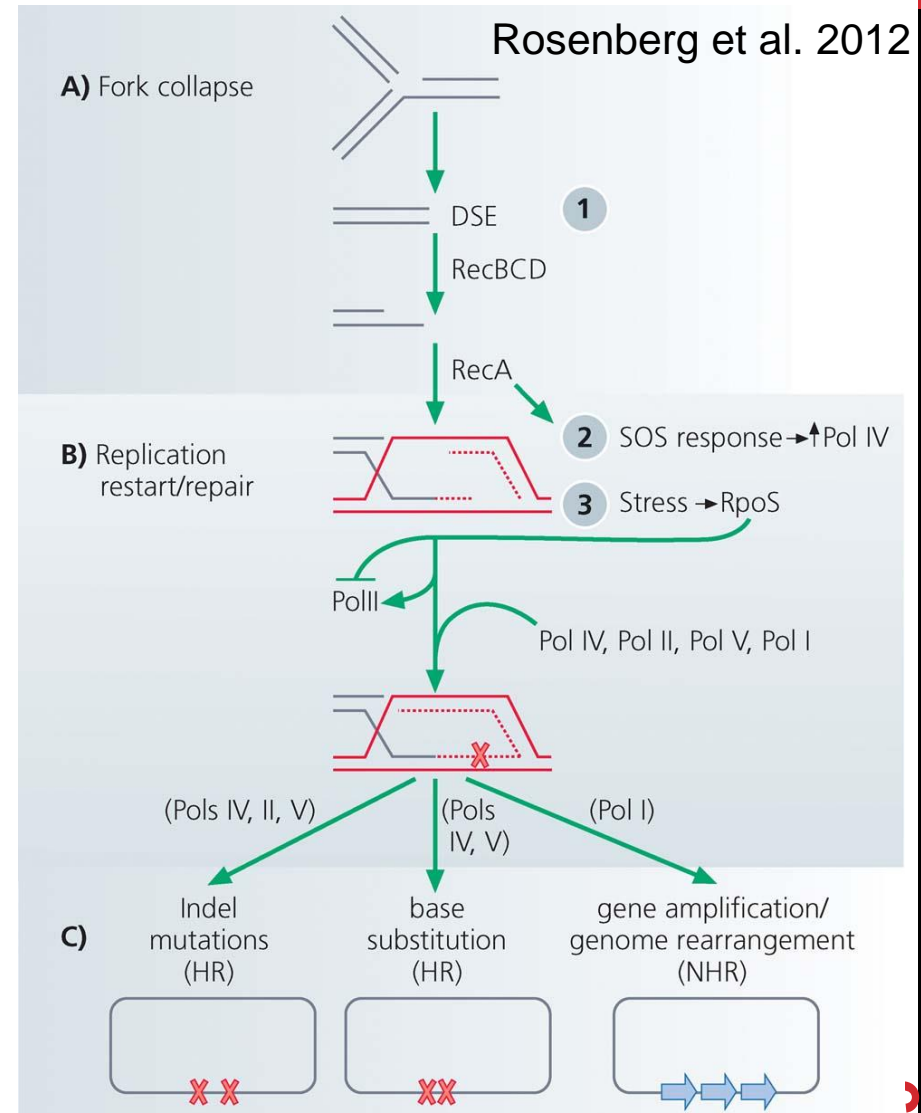
DNA polymerase error rate – Lynch 2011



# STRESS-INDUCED MUTATION

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

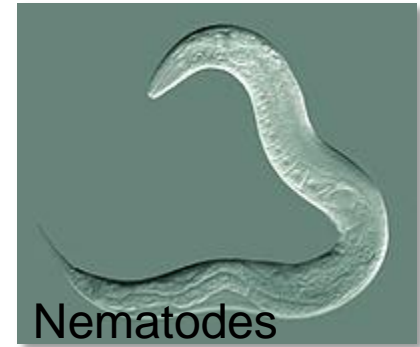


Green alga

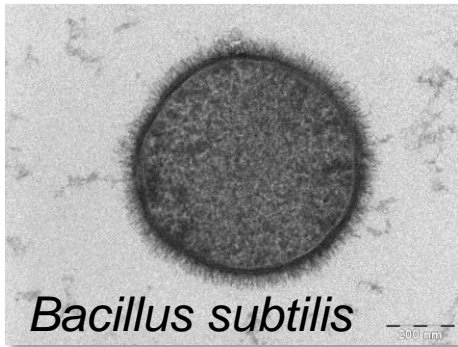


# EVIDENCE

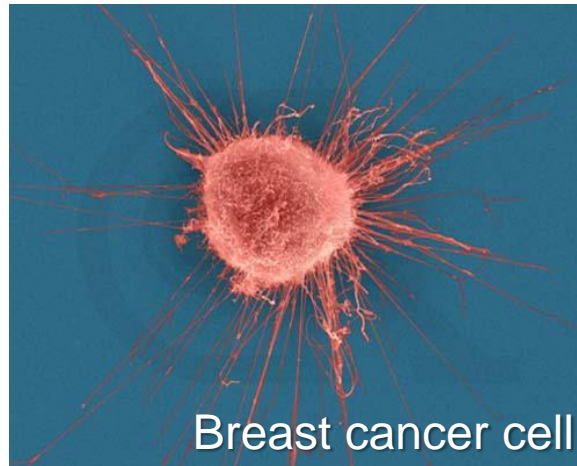
Nematodes



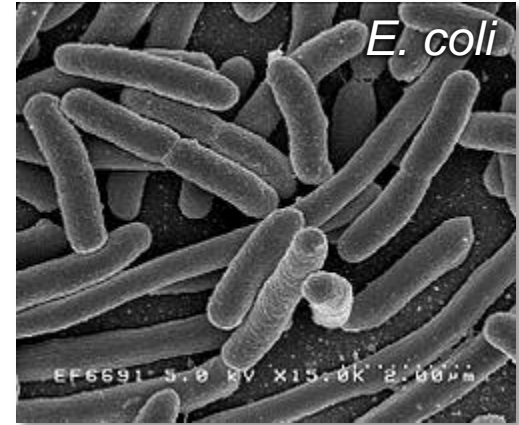
*Bacillus subtilis*



Breast cancer cell



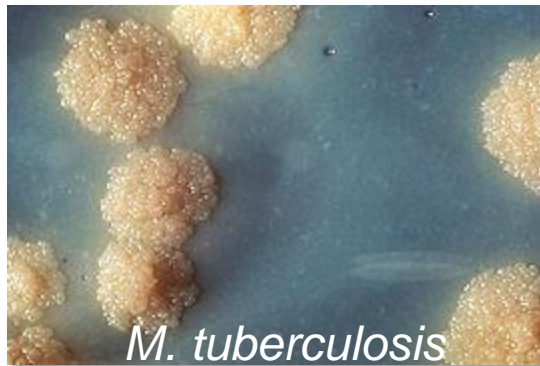
*E. coli*



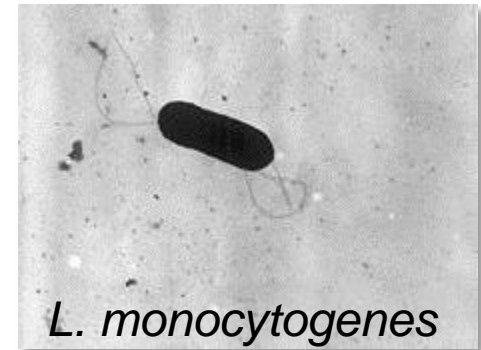
*D. Melanogaster*



*M. tuberculosis*



*L. monocytogenes*



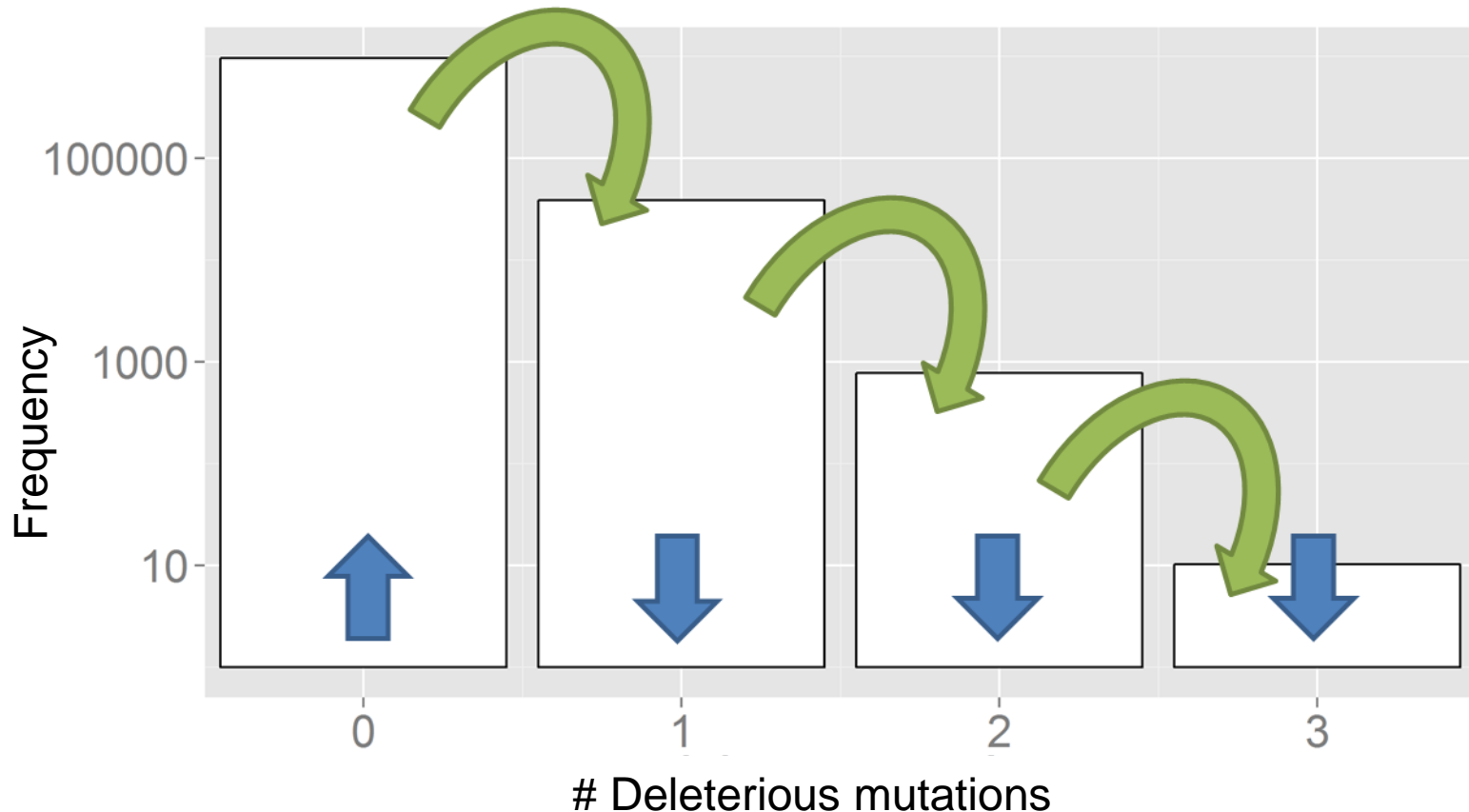


# EVOLUTION IN A STATIC ENVIRONMENT



# EVOLUTION IN A STATIC ENVIRONMENT

- Directional selection without change
- A balance between **mutation** and **natural selection**





# SINGLE LOCUS MODEL

- One bi-allelic locus: wild-type  $A$  and mutant  $a$
- $\omega(A) > \omega(a)$  ( $\omega$  – fitness)
- $u$  – probability of mutation from  $A$  to  $a$
- The model describes the **change in the frequency of  $A$** :

$$f'(A) = f(A) \frac{\omega(A)}{\bar{\omega}} (1 - u)$$

In a static environment we can look for an **equilibrium**:

$$f'(A) = f(A)$$

- With some algebraic operations we get:

$$\bar{\omega}^* = \omega(A)(1 - u)$$

# SINGLE LOCUS MSB

- The population mean fitness at the **mutation-selection balance** (MSB) :

$$\bar{\omega}^* = \omega(A) \cdot (1 - u)$$

- In words:

**The population mean fitness is equal to the product of the **fitness** of the wild-type and the probability that the wild-type does not **mutate**.**

- Therefore, the higher the mutation rate the lower the mean fitness:

$$\bar{\omega}^* \sim 1 - u$$

# MULTIPLE LOCUS MSB

$f_x$  - frequency of individuals with  $x$  deleterious mutations

$\omega_x$  - fitness of individuals with  $x$  deleterious mutations

$U$  - mutation rate: number of deleterious mutations per individual. Usually this is Poisson distributed with parameter  $U$  and pmf:  $\phi_x = e^{-U} \frac{U^x}{x!}$

The change in  $f_x$  per generation:

$$f'_x = \sum_{k=0}^x \frac{\omega_k}{\bar{\omega}} f_k \phi_{x-k}$$

# MULTIPLE LOCUS MSB

$$f'_x = \sum_{k=0}^x \frac{\omega_k}{\bar{\omega}} f_k \phi_{x-k}$$

Or in matrix form:

$$\bar{\omega} f' = M f$$

Where  $M_{x,k} = \begin{cases} \omega_k \phi_{x-k}, & x \geq k \\ 0, & x < k \end{cases}$  is a triangular matrix:

$$\bar{\omega} M = \begin{pmatrix} \phi_0 \omega_0 & 0 & 0 & \dots \\ \phi_1 \omega_0 & \phi_0 \omega_1 & 0 & \vdots \\ \phi_2 \omega_0 & \phi_1 \omega_1 & \phi_0 \omega_2 & \vdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

# MULTIPLE LOCUS MSB

The MSB can be found by setting  $f' = f$ :

$$\bar{\omega}^* f^* = M f^*$$

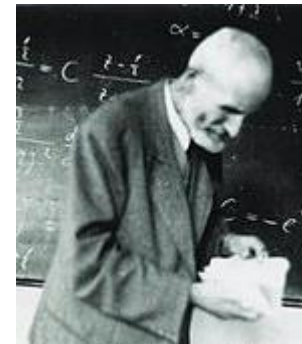
$M$  is triangular so by the **Perron-Frobenius** theorem,

$\bar{\omega}^*$  is the dominant eigenvalue of  $M$  and  $f^*$  is the only non-negative right eigenvector of  $\bar{\omega}^*$ .

The dominant eigenvalue is  $M_{0,0} = \omega_0 \phi_0 = e^{-U}$ .

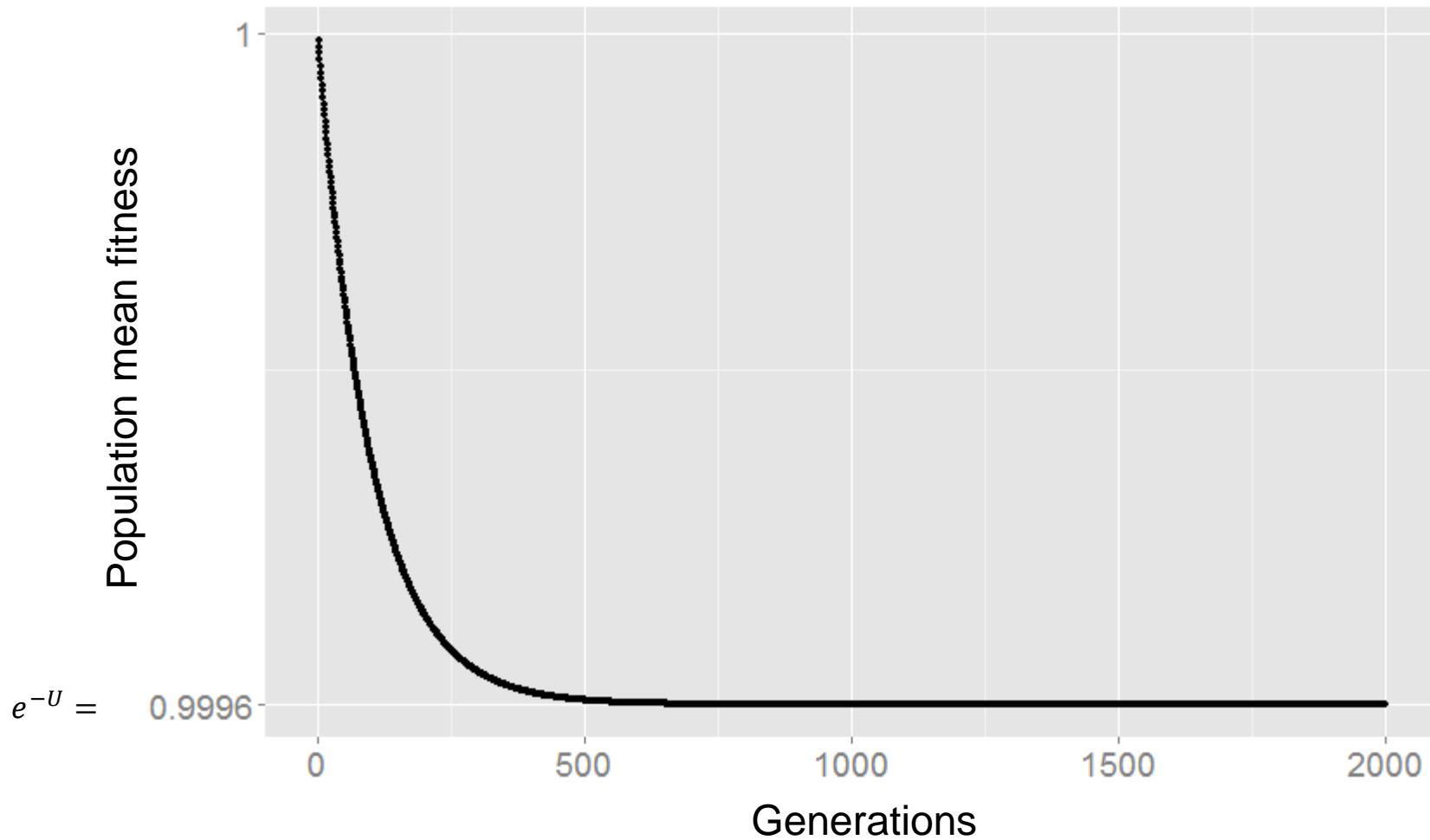


Ferdinand G. Frobenius  
1849-1917, Germany



Oskar Perron  
1880-1975, Germany

# SIMULATION RESULTS



# MUTATION RATE IN STATIC ENVIRONMENTS

$$\bar{\omega} = e^{-U}$$

- High mutation rates reduce *adaptedness* of populations
- Selection will **reduce** the mutation rate to it's lowest attainable level
- What sets this level?
- Kimura 1967 - physical or physiological
- Dawson 1999 – “cost of fidelity”
- Lynch 2010 – “Drift barrier hypothesis”





# MY RESEARCH: EVOLUTION OF STRESS- INDUCED MUTATION

## Null hypothesis

Mutagenesis is the by-product of stress

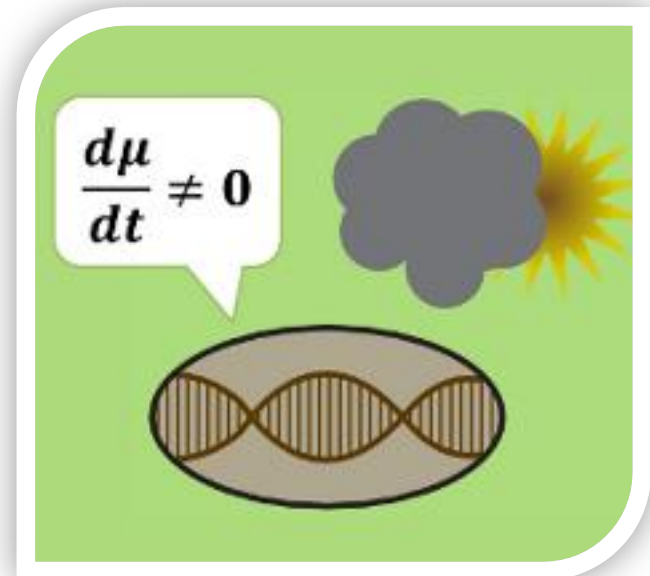
## Alternative non-adaptive hypotheses

Cost of fidelity

Drift barrier hypothesis

## Adaptive hypothesis

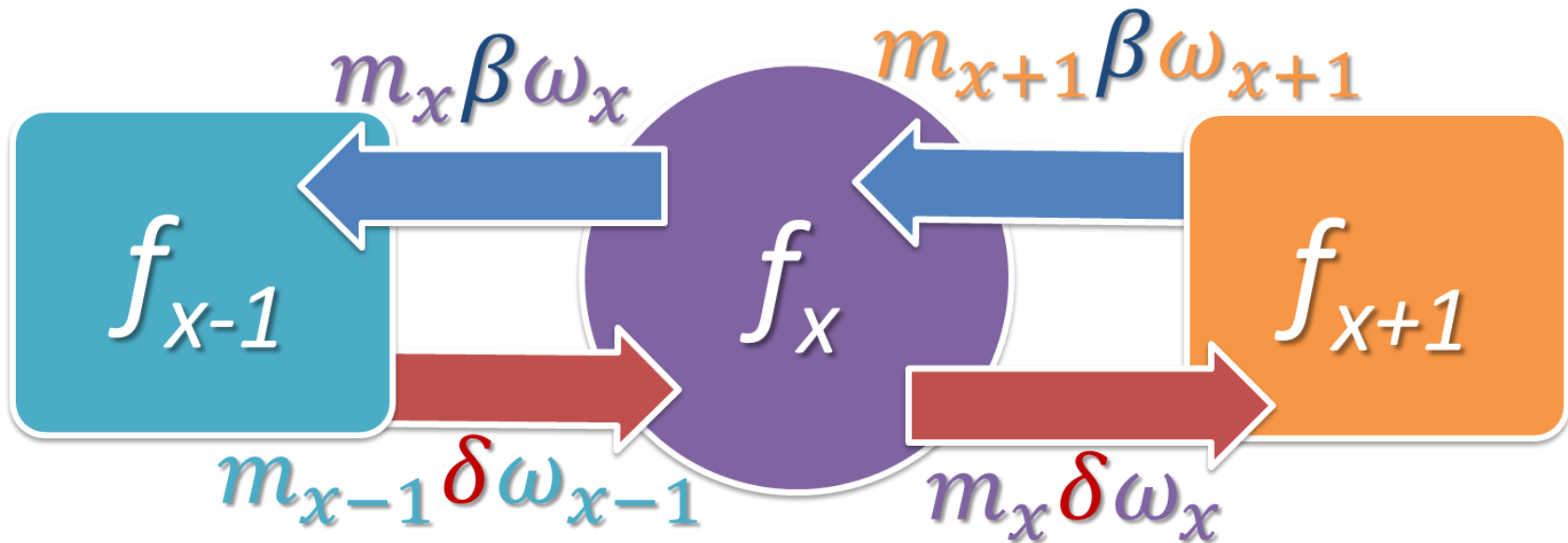
Second order selection



# STRESS-INDUCED MUTATION IS STATIC ENVIRONMENTS



Selection against generation of deleterious mutations



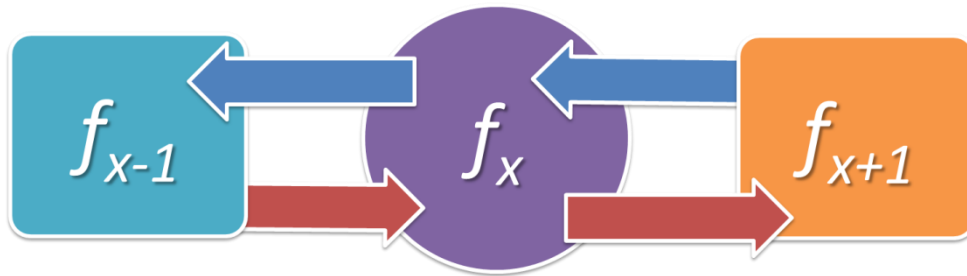
$x$  - number of harmful alleles

$f_x$  - frequency

$\omega_x$  - fitness

$m_x$  - mutation probability

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



$x$  # of harmful alleles  
 $f_x$  frequency  
 $\omega_x$  fitness  
 $m_x$  mutation probability  
 $\delta$  deleterious mutation  
 $\beta$  beneficial mutation  
 $\bar{\omega}$  population mean fitness

$$f'_x = (1 - m_x(\delta + \beta)) \frac{\omega_x}{\bar{\omega}} f_x + m_{x-1} \delta \frac{\omega_{x-1}}{\bar{\omega}} f_{x-1} + m_{x+1} \beta \frac{\omega_{x+1}}{\bar{\omega}} f_{x+1}$$

$$M = \begin{pmatrix} (1 - m_0 \delta) \omega_0 & m_1 \beta \omega_1 & 0 & \dots \\ m_0 \delta \omega_0 & (1 - m_1(\beta + \delta)) \omega_1 & m_2 \beta \omega_2 & \vdots \\ 0 & m_1 \delta \omega_1 & (1 - m_2(\beta + \delta)) \omega_2 & \vdots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

$$\bar{\omega} f = M f$$

$x$  # of harmful alleles  
 $f_x$  frequency  
 $\omega_x$  fitness  
 $m_x$  mutation probability  
 $\delta$  deleterious mutation  
 $\beta$  beneficial mutation  
 $\bar{\omega}$  population mean fitness

$$\bar{\omega}f = Mf \Rightarrow \frac{\partial \bar{\omega}}{\partial m_x} = v \frac{\partial M}{\partial m_x} f$$

$\bar{\omega}$  is eigenvalue of  $M$

$v, f$  are **left** and **right** eigenvectors of  $\bar{\omega}$

# STATIC ENVIRONMENT

## General solution

$$\frac{\partial \bar{\omega}}{\partial m_x} = \frac{f_x v_x}{m_x} (\bar{\omega} - \omega_x)$$

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

# STATIC ENVIRONMENT

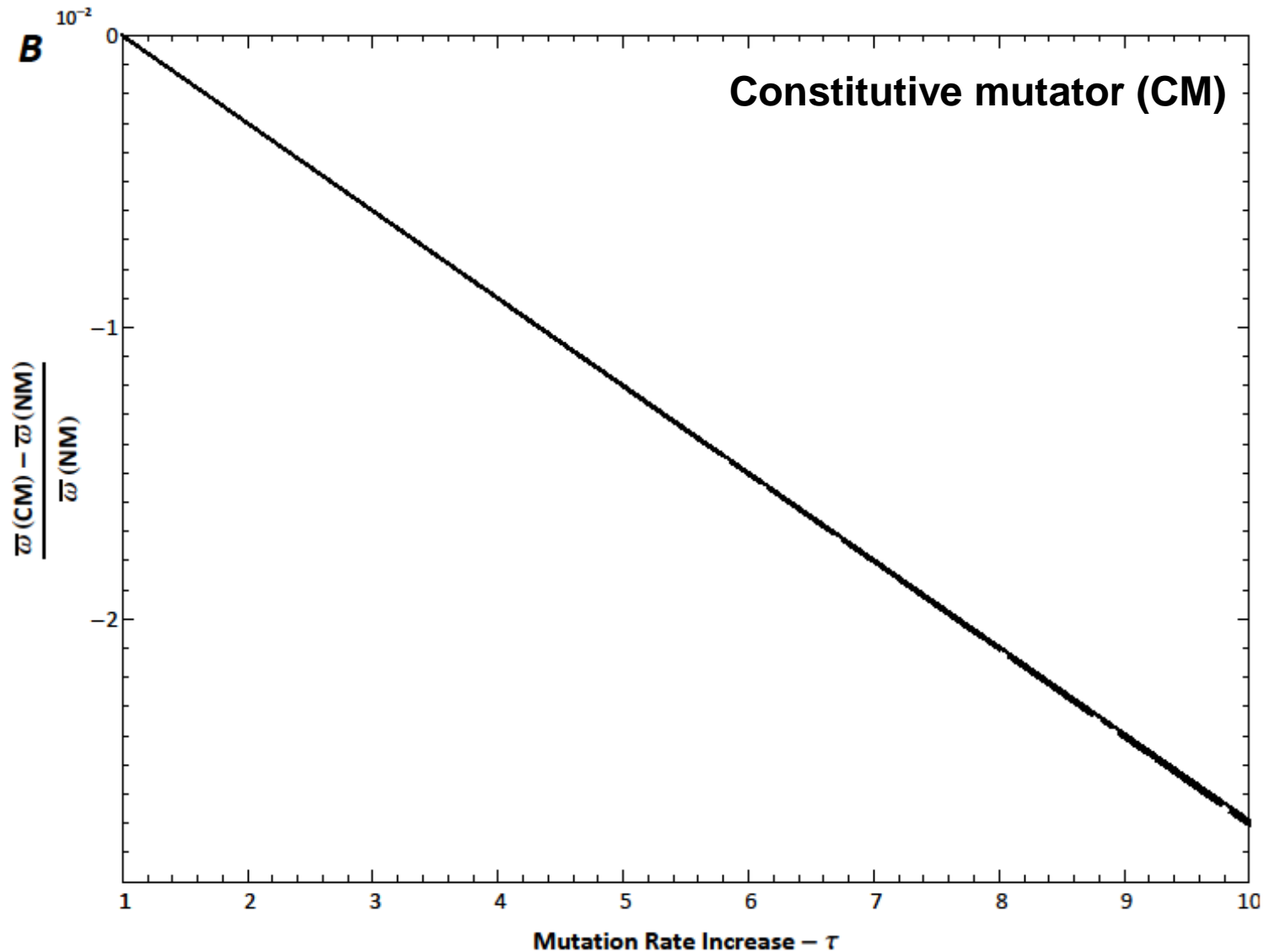
## General solution

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

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

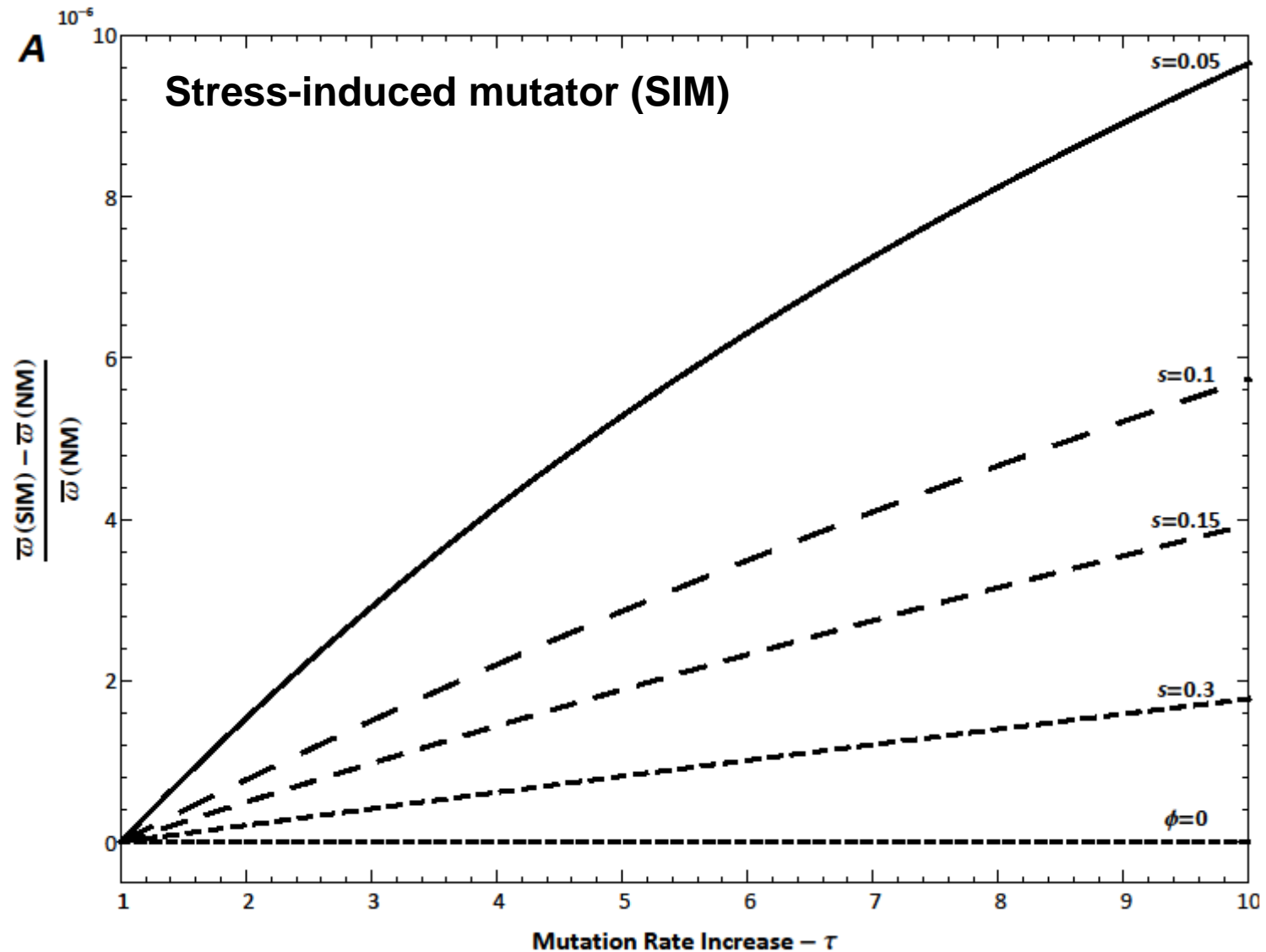
Selection doesn't reduce the mutation rate!

# STATIC ENVIRONMENTS





# STATIC ENVIRONMENTS



# EVOLUTION IN A DYNAMIC ENVIRONMENT

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



# RAPIDLY CHANGING ENVIRONMENTS

## The Red Queen hypothesis

- van Valen, 1973

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

- Lewis Carrol, Through the Looking Glass

What happens when the environment changes frequently?



# CHANGING ENVIRONMENTS

## Simulation model

Moran process

Individual-based simulations

100,000 individuals

1,000 loci

Asexual, Haploid

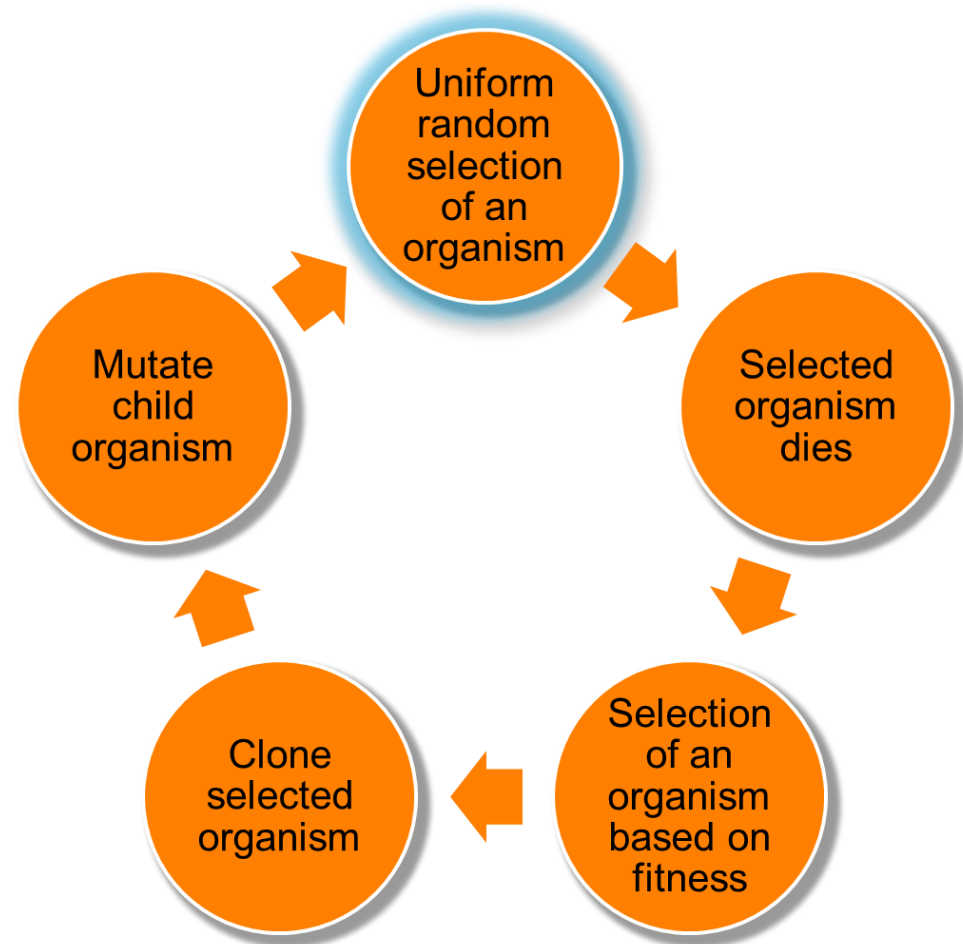
Overlapping generations

No recombination

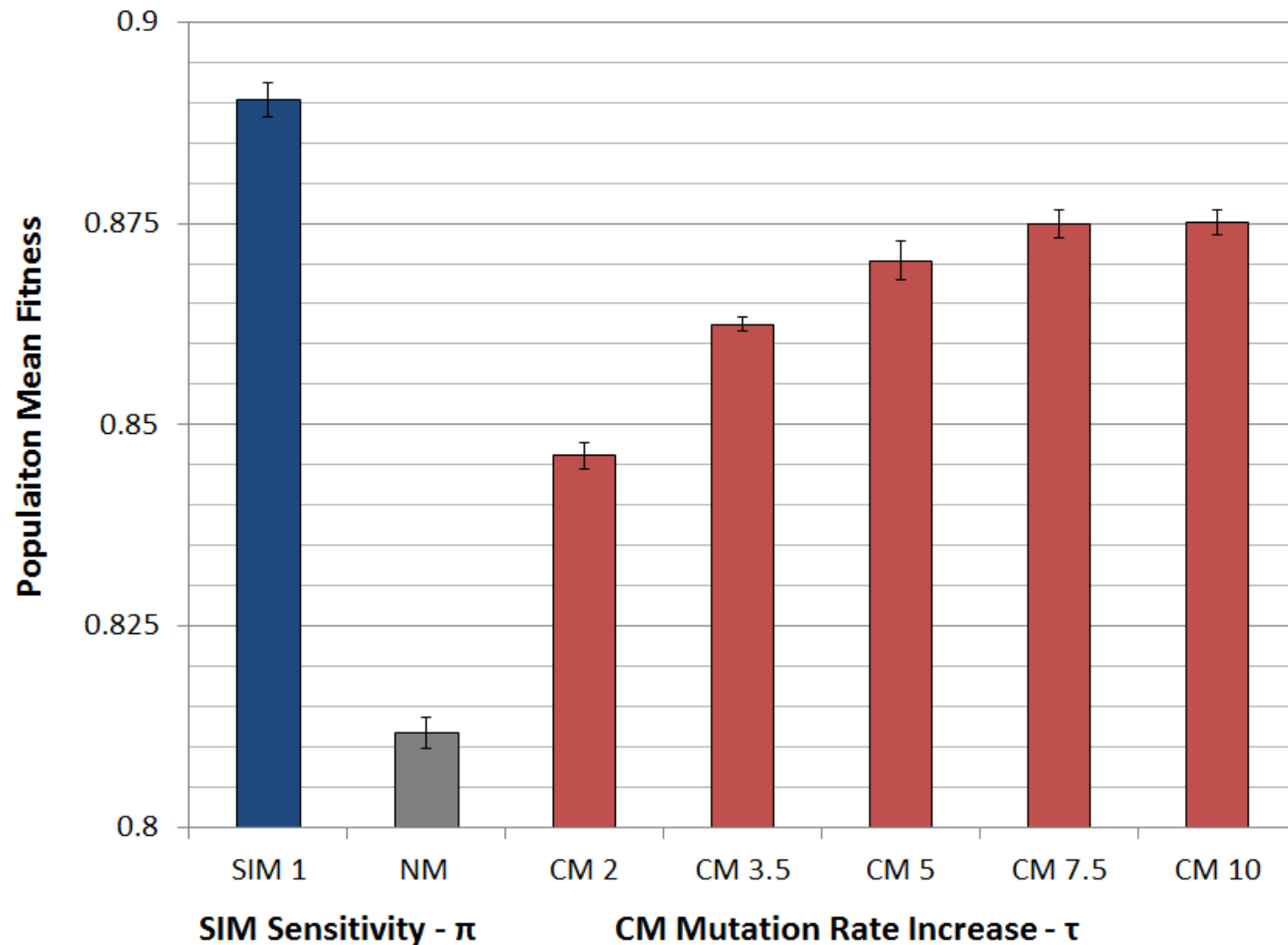
No segregation

No mutations at mutator locus

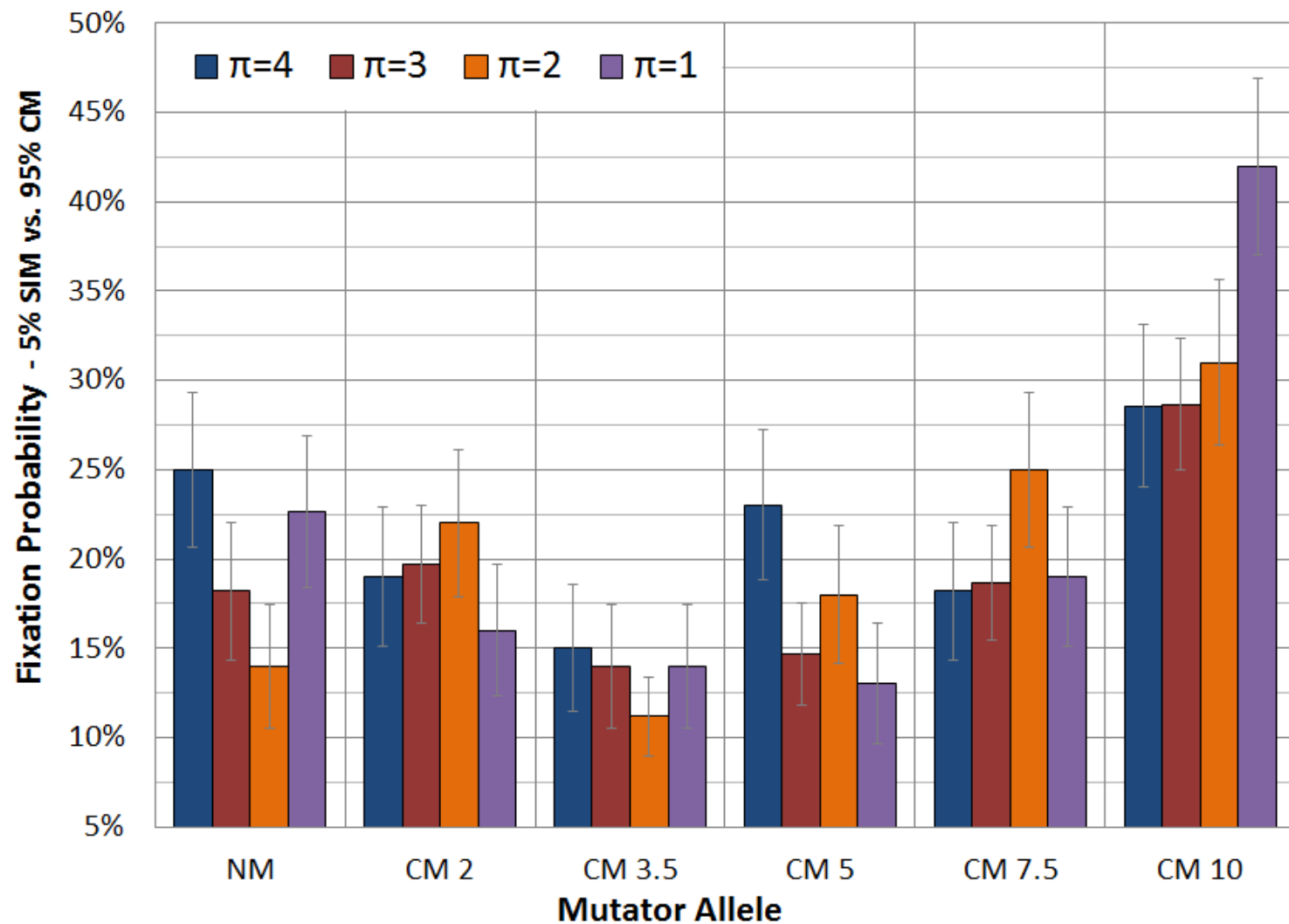
Environmental changes



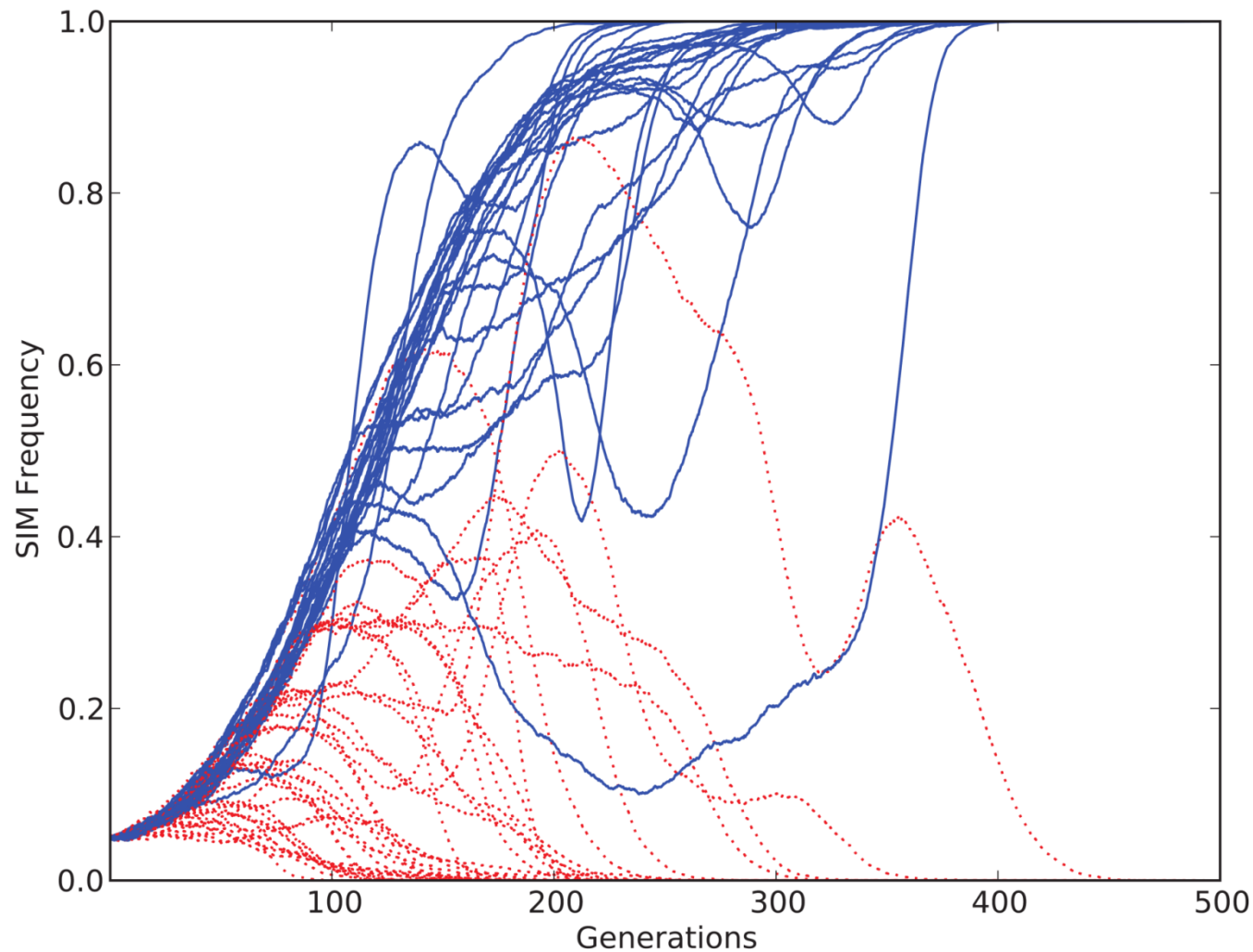
# POPULATIONS WITH SIM ARE FITTER



# SIM WINS COMPETITIONS



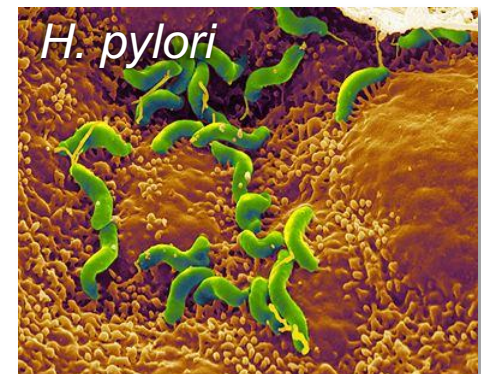
# SIM WINS COMPETITIONS





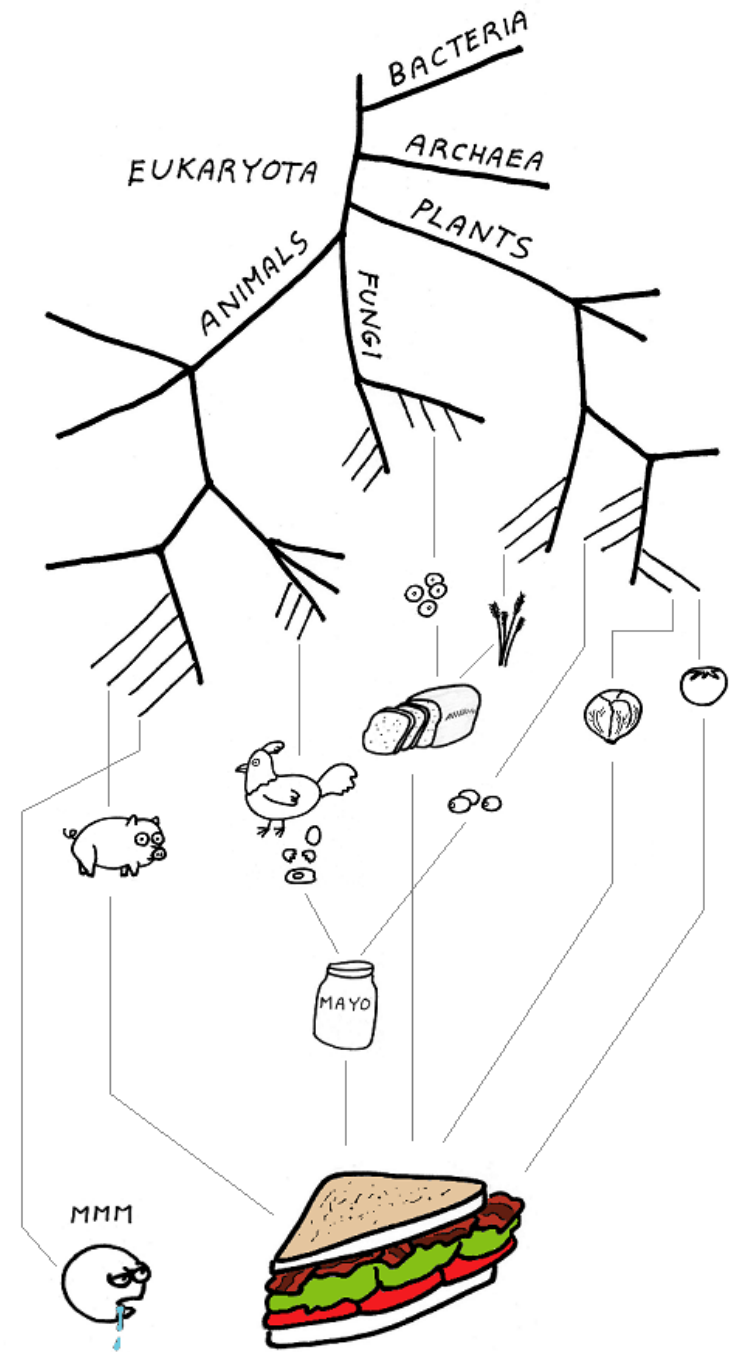
# SUMMARY: EVOLUTION OF STRESS-INDUCED MUTATION

- Stress-induced mutators evolve:
  - In finite & infinite populations
  - In constant & changing environments
- **Second-order selection** can lead to the evolution of stress-induced mutagenesis in asexual populations
- Selection for evolvability



# CONSEQUENCES OF STRESS-INDUCED MUTATION RATE

How does SIM affect evolution?



# ADAPTIVE PEAK SHIFTS

This problem was introduced by Sewall Wright in 1931:

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



# EXAMPLES

## Criteria

- Adaptation requires a change in two or more traits
- Change in only one trait causes reduced fitness

## Wings and bones

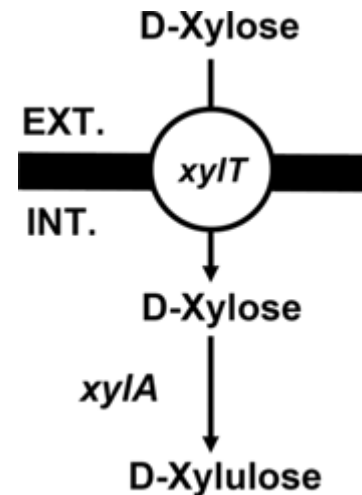
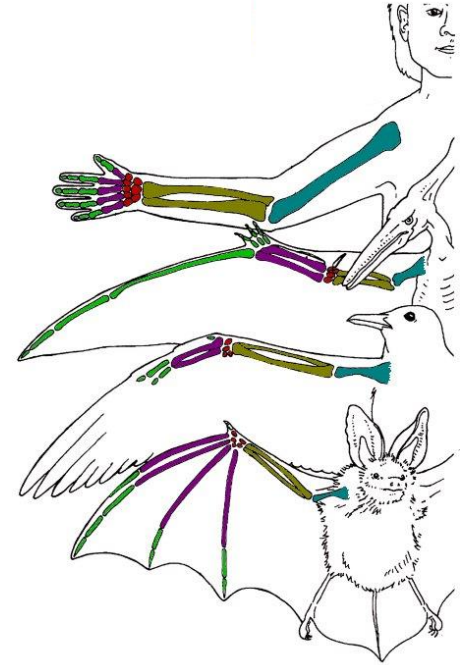
- Flying with heavy bones is costly
- Walking and climbing with light bones is dangerous

## New metabolic pathway

- Two new proteins required – pump and enzyme
- each is wasteful without the other

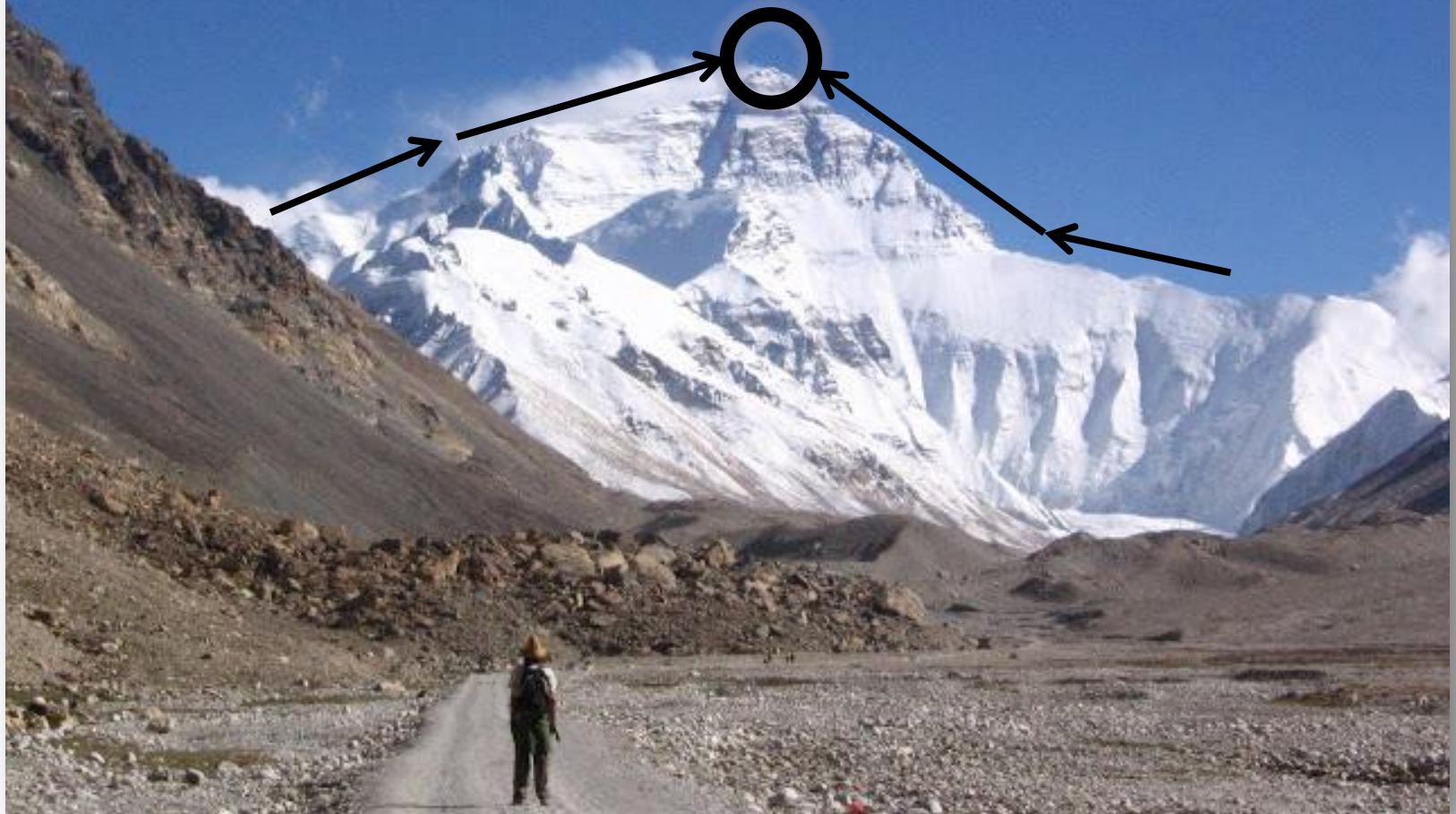
## Adaptation to high UV (Haldane 1932, p. 175)

- Dark skin – increased pigmentation
- Vitamin D storage in the liver



Xiao et al. 2011

# SIMPLE LANDSCAPE





# RUGGED LANDSCAPE

No wings  
Heavy bones



No wings  
Light bones

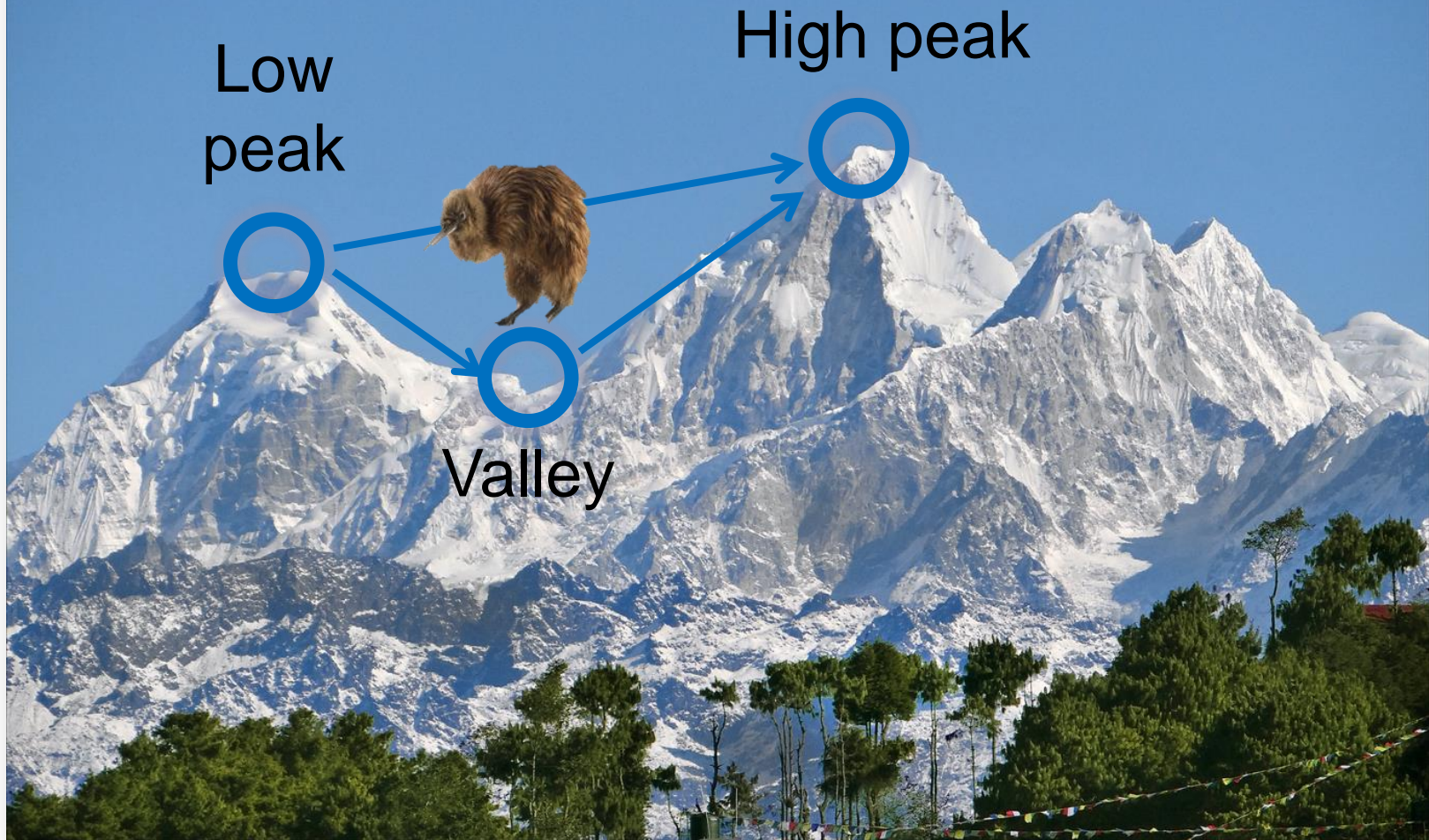


Wings  
Light bones





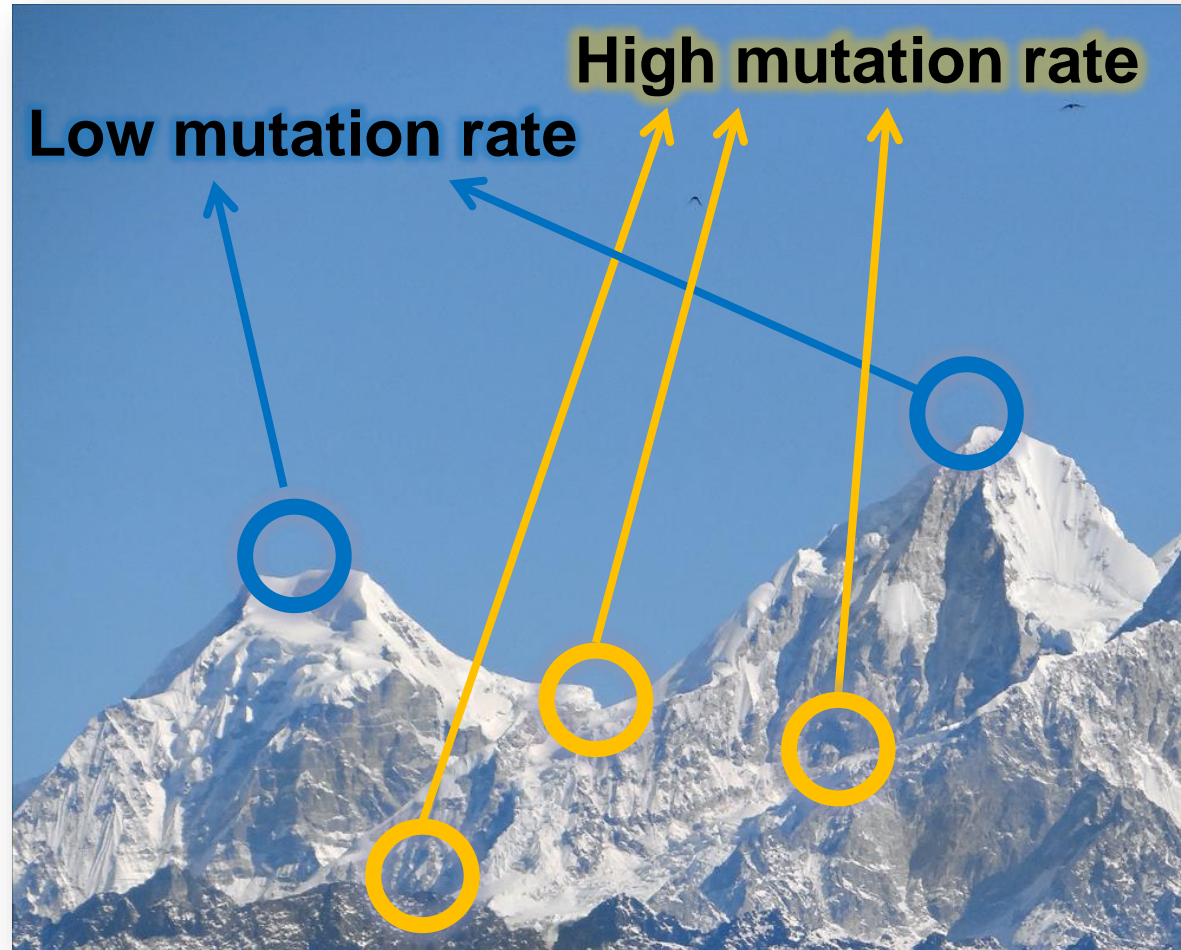
# ADAPTIVE PEAK SHIFT



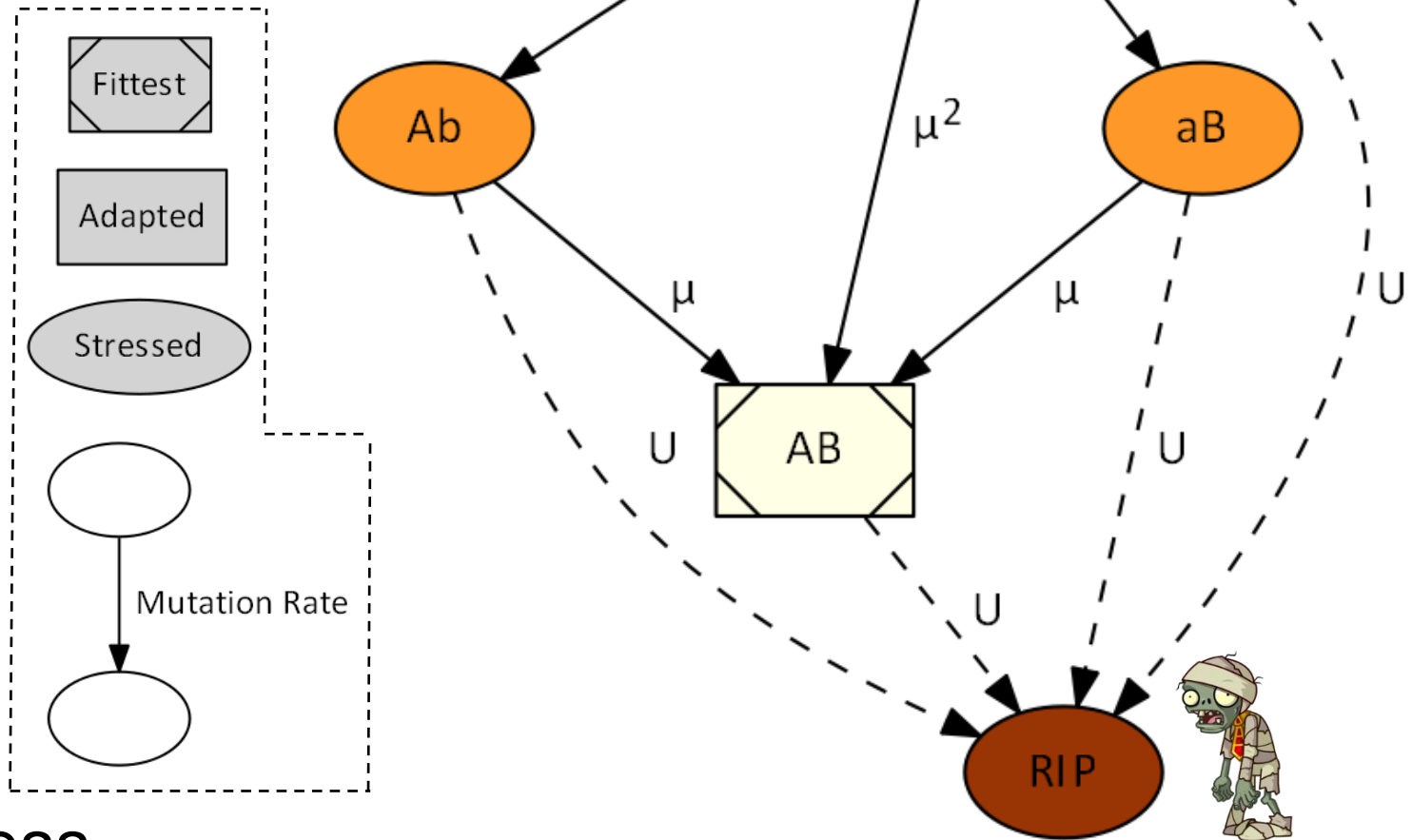


# SIM & RUGGED LANDSCAPE

Increasing the  
mutation rate in  
individuals below  
**both** peaks



# DETERMINISTIC MODEL



fitness



Probability that a random offspring is a double mutant:

$$q = \mu^2 e^{-\frac{U}{s}-U} + 2 \frac{\mu^2}{s} e^{-\frac{U}{s}-U} \approx 2 \frac{\mu^2}{s} \left(1 - \frac{U}{s}\right)$$

With stress-induced mutation:

$$q_{SIM} = \mu^2 e^{-\frac{U}{s}-U} + 2 \frac{\tau \mu^2}{s} e^{-\frac{U}{s}-\tau U} \approx q \cdot \tau (1 - \tau U)$$

The probability that a single double mutant avoids extinction:

$$\rho \approx 2sH$$

Probability there are double mutants in the next generation:

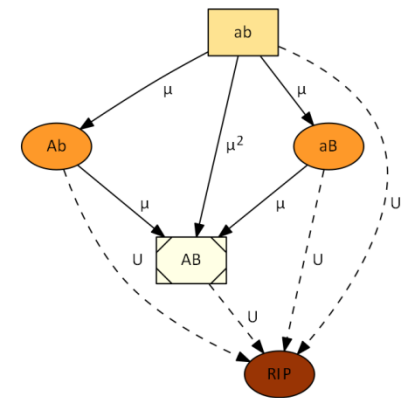
$$(1 - q)^N \approx Nq$$

Waiting time for a double mutant that will go to fixation:

$$E[T] = \frac{1}{Nq\rho}$$

Adaptation rate:

$$\nu = E[T]^{-1} = Nq\rho$$



$\nu$  – adaptation rate;  $N$  – population size;  $\tau$  – mutation rate increase;  $H$  – double mutant advantage;  $\mu$  – beneficial mutation rate

# DETERMINISTIC RESULTS

The rate of adaptation without **normal mutation**:

$$v_{NM} \approx 4NH\mu^2$$

The rate of adaptation without **high mutation**:

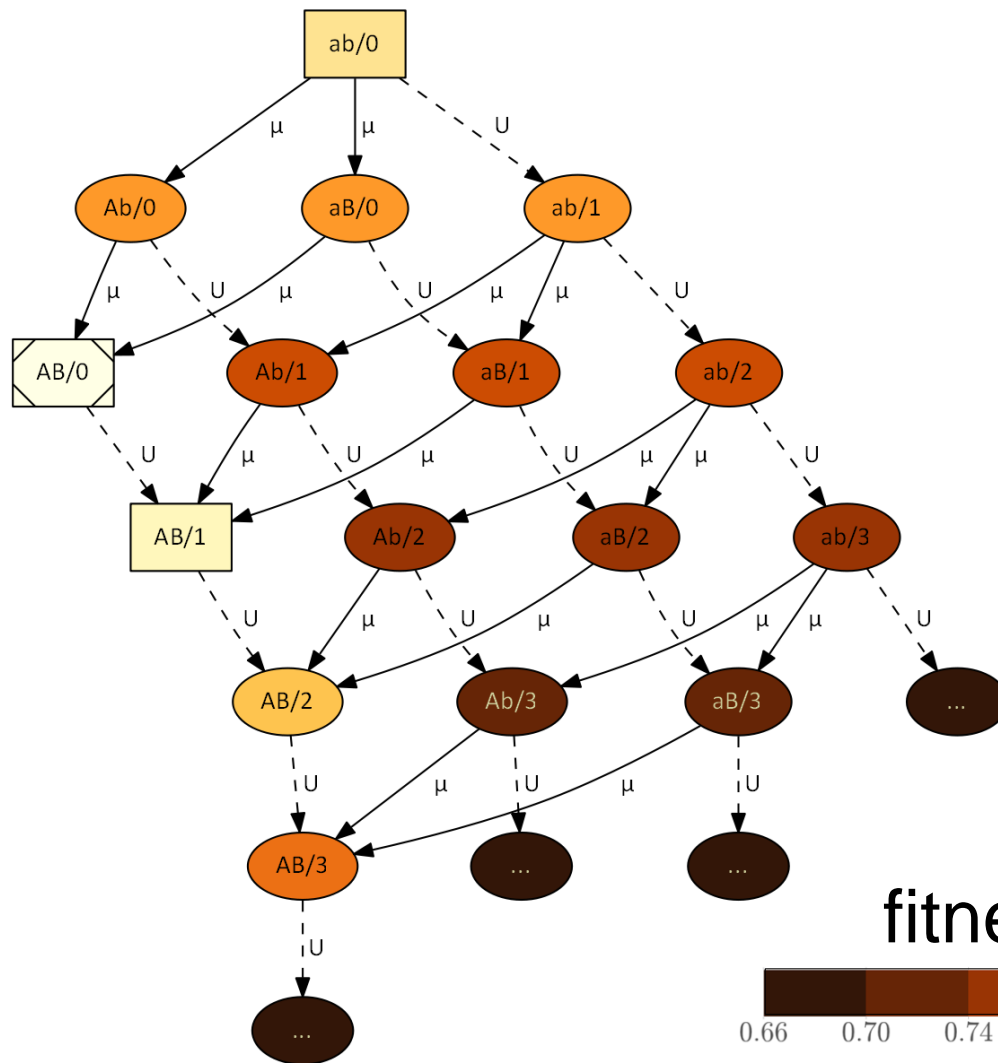
$$v_{CM} \approx \tau^2 \cdot v_{NM}$$

The rate of adaptation without **stress-induced mutation**:

$$v_{SIM} \approx \tau \cdot v_{NM}$$

$v$  – adaptation rate;  $N$  – population size;  $\tau$  – mutation rate increase;  $H$  – double mutant advantage;  $\mu$  – beneficial mutation rate

# STOCHASTIC MODEL



No MSB assumption

No



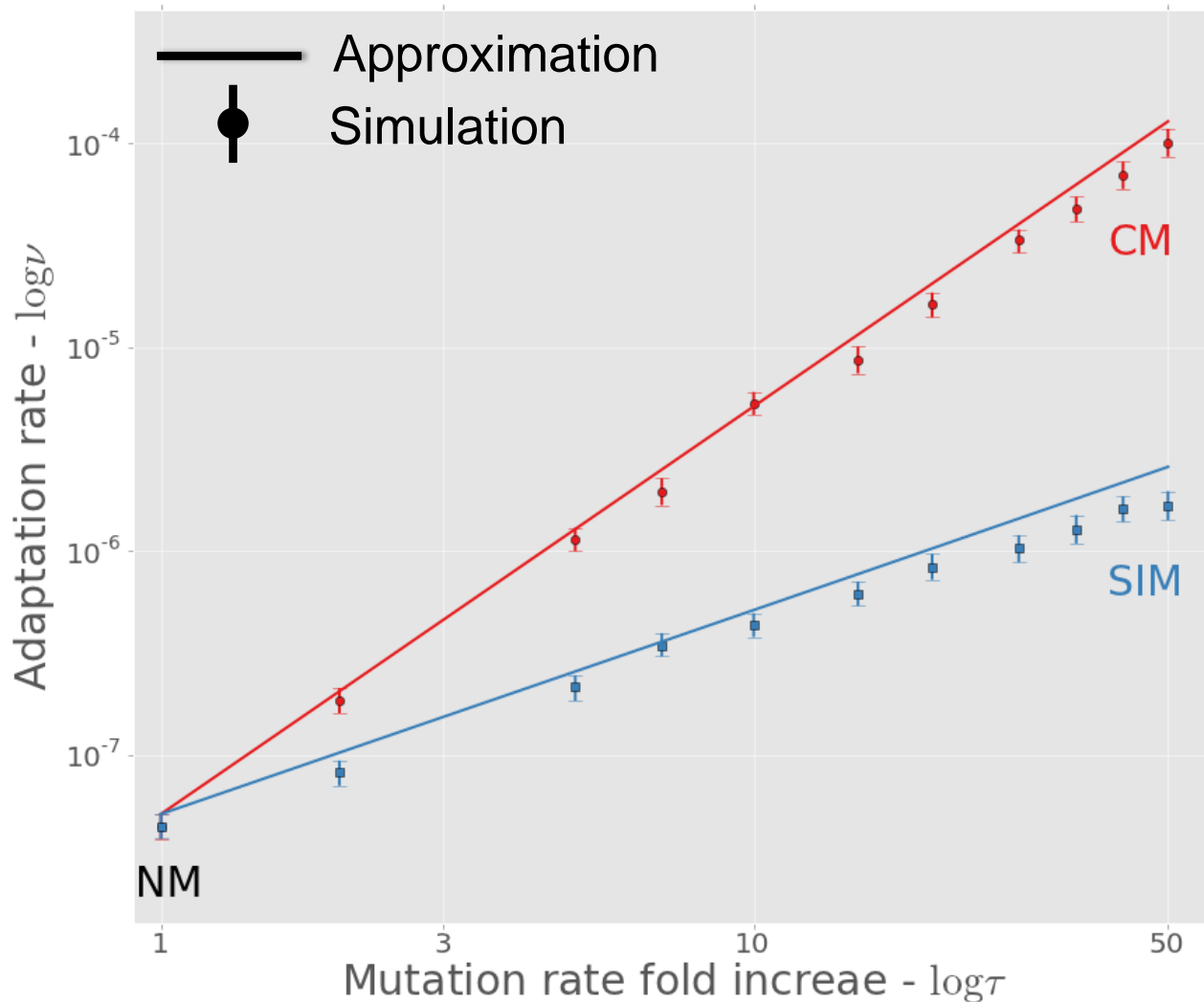
fitness



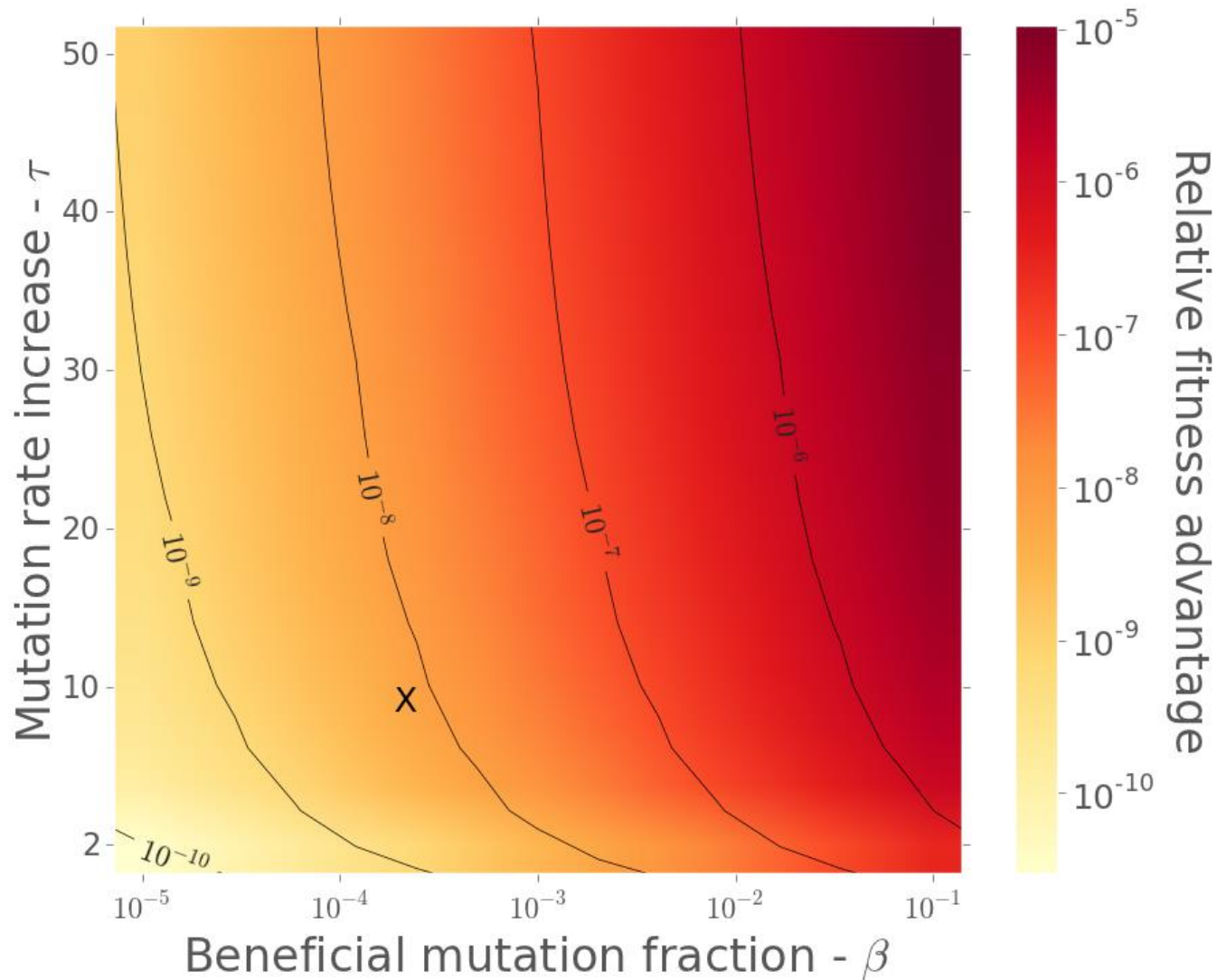
$$\nu_{CM} \approx \tau^2 \cdot \nu_{NM}$$

$$\nu_{SIM} \approx \tau \cdot \nu_{NM}$$

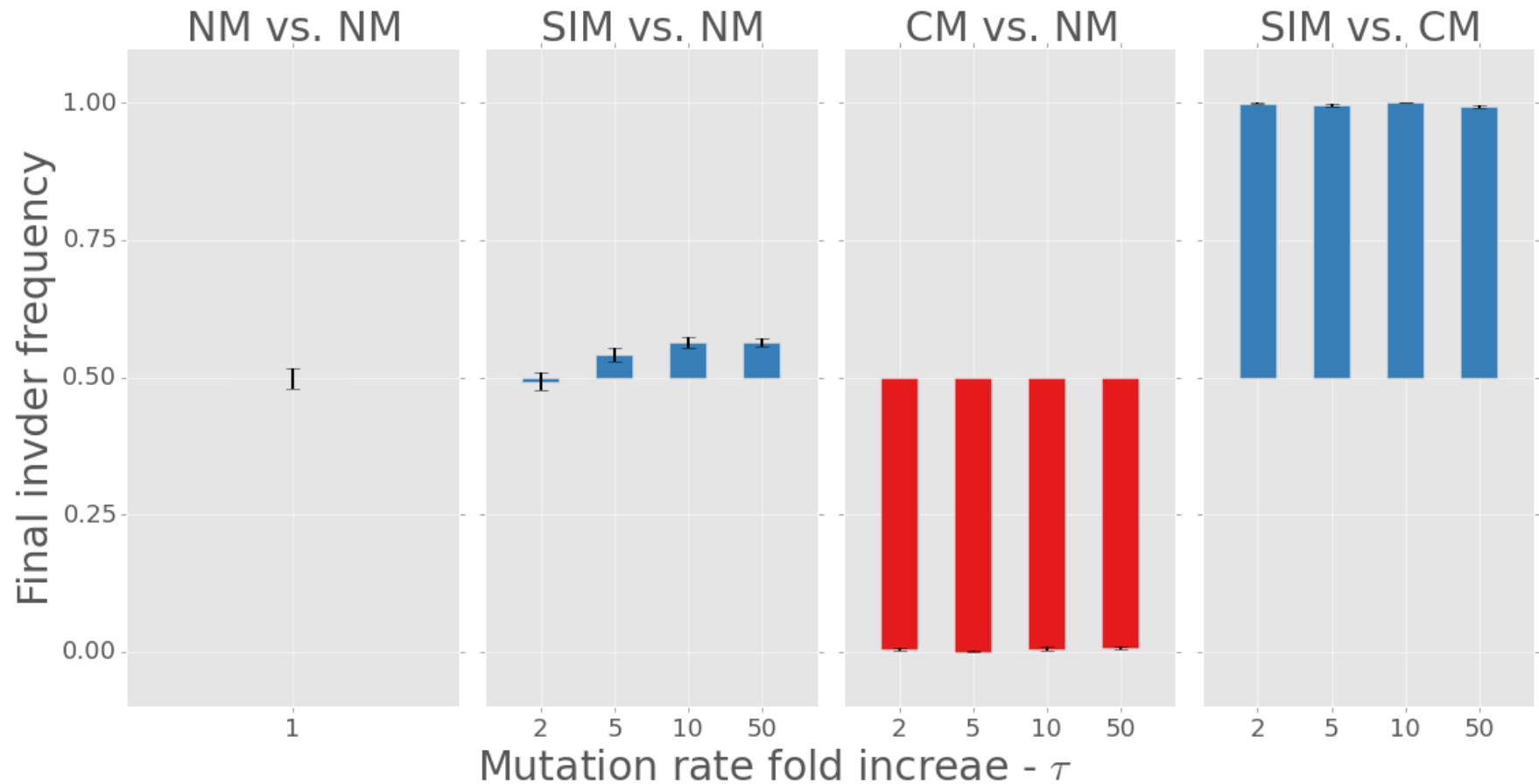
# ADAPTATION RATE



# MEAN FITNESS IN MSB

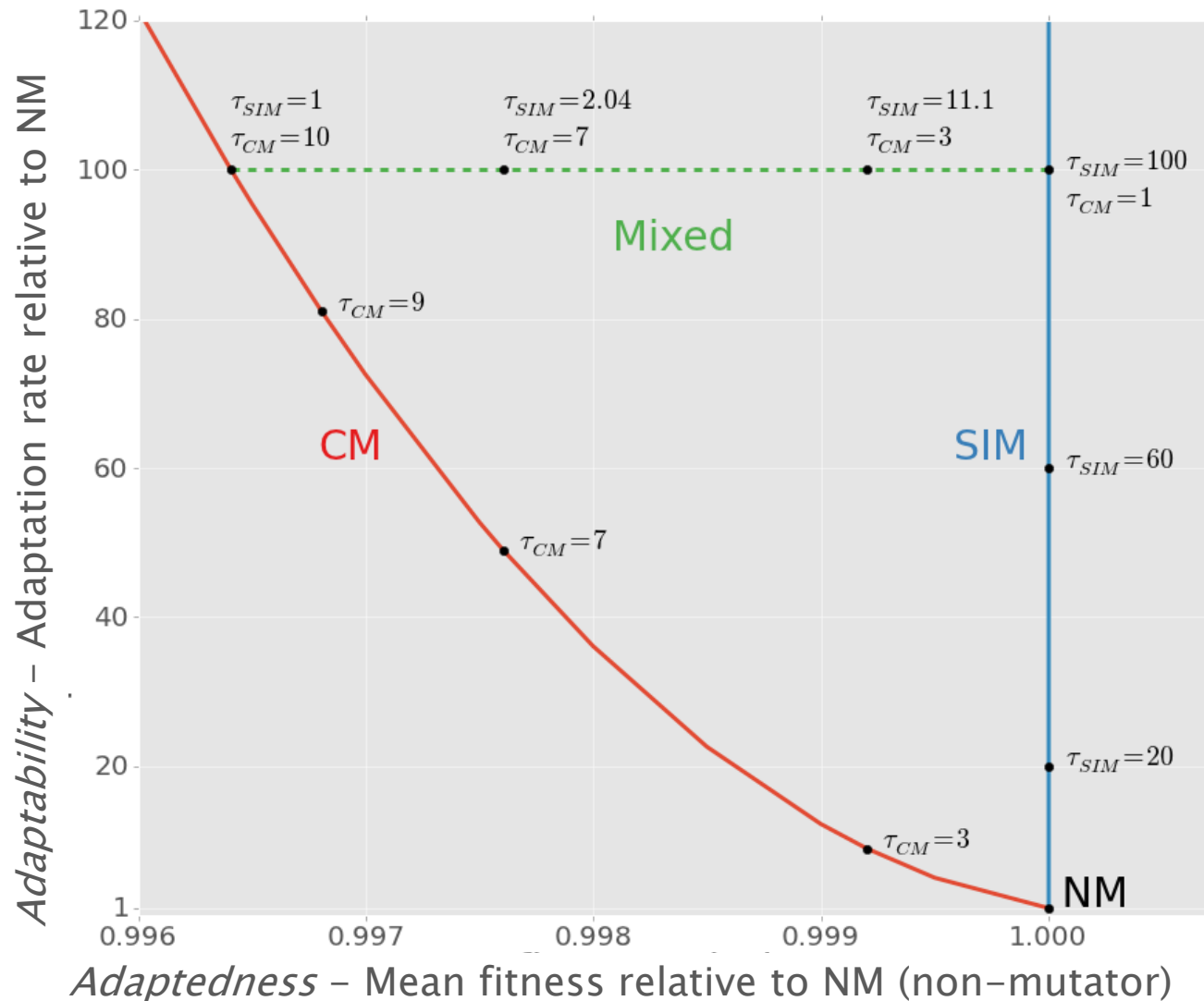


# COMPETITIONS





# SIM BREAKS THE *ADAPTABILITY-ADAPTEDNESS* TRADE-OFF



# CONCLUSION

- **Evolution of Stress-induced mutagenesis:**
  - SIM can evolve due to second order selection
  - In constant and changing environments
- **Effects of stress-induced mutagenesis:**
  - SIM increases the adaptation rate without reducing the population mean fitness
  - Breaks the trade-off between *adaptability* and *adaptedness*