

WHAT CAN POPULATION GENETICS TELL US ABOUT THE EVOLUTION OF THE MUTATION RATE?

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EVOLUTIONARY THEORY & POPULATION GENETICS / FALL 2013

LIFE SCIENCES FACULTY

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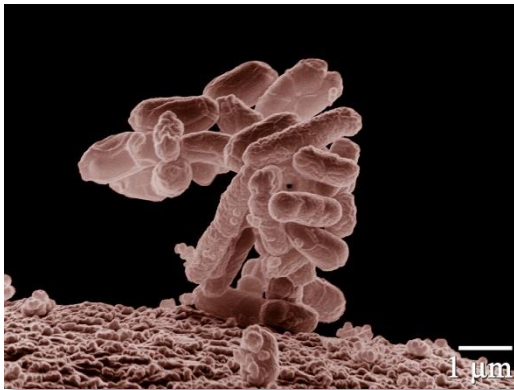
15 JANUARY 2014

VARIABILITY IN MUTATION RATES

Between species

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

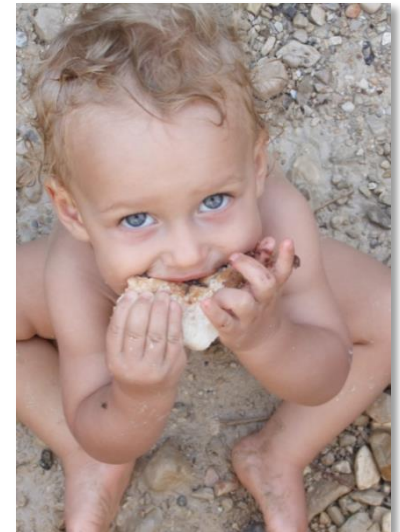
Bacteria: 0.0004
Wielgoss et al. G3 2011



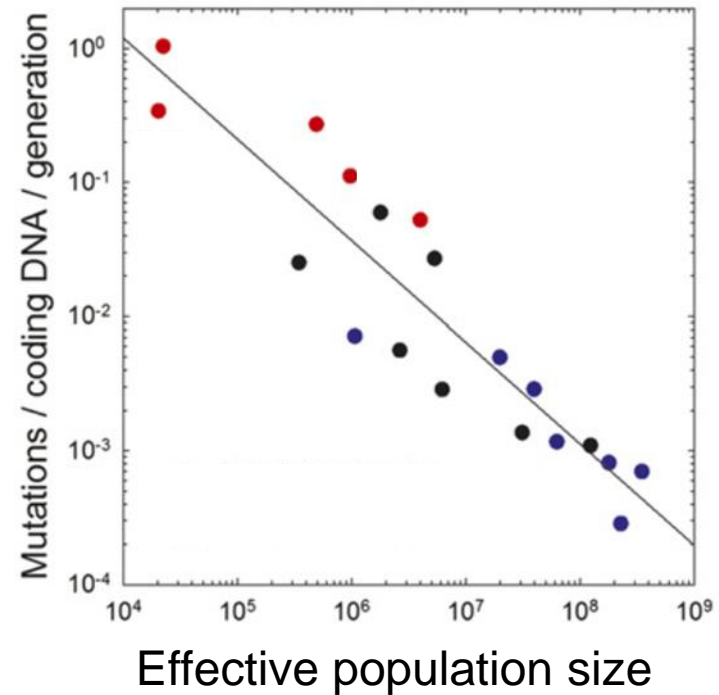
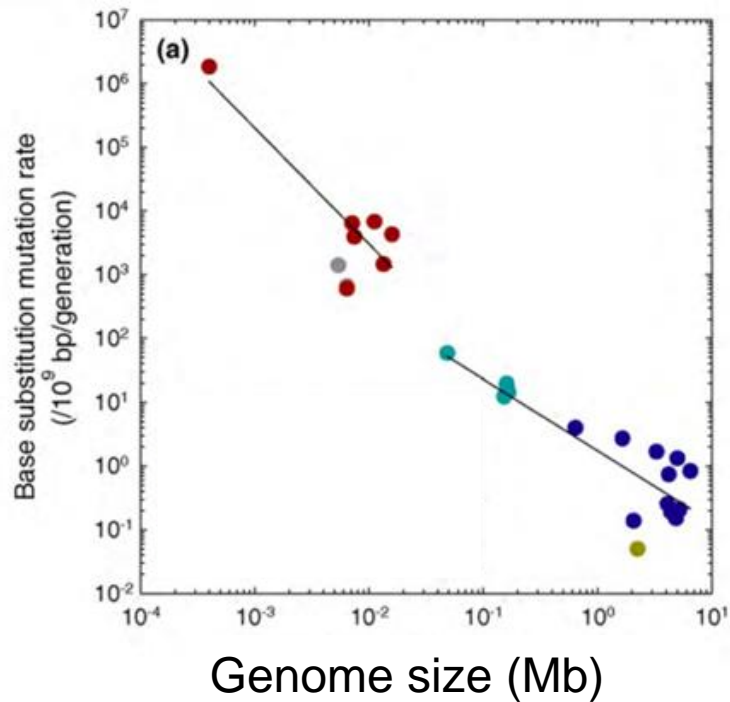
Flies: 0.455
Keightley et al. Gen Res 2009



Humans: 41
Lynch, PNAS 2010



NON-ADAPTIVE HYPOTHESES



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
- $\omega(A) > \omega(a)$ (ω – fitness)
- The model describes the **change in the frequency of A** :

$$f'(A) = f(A) \frac{\omega(A)}{\bar{\omega}} \text{Pr}(\text{no mutations})$$

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

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

- With some algebraic operations we get:

$$\bar{\omega}^* = \omega(A) \cdot \text{Pr}(\text{no mutations})$$

SINGLE LOCUS MSB

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

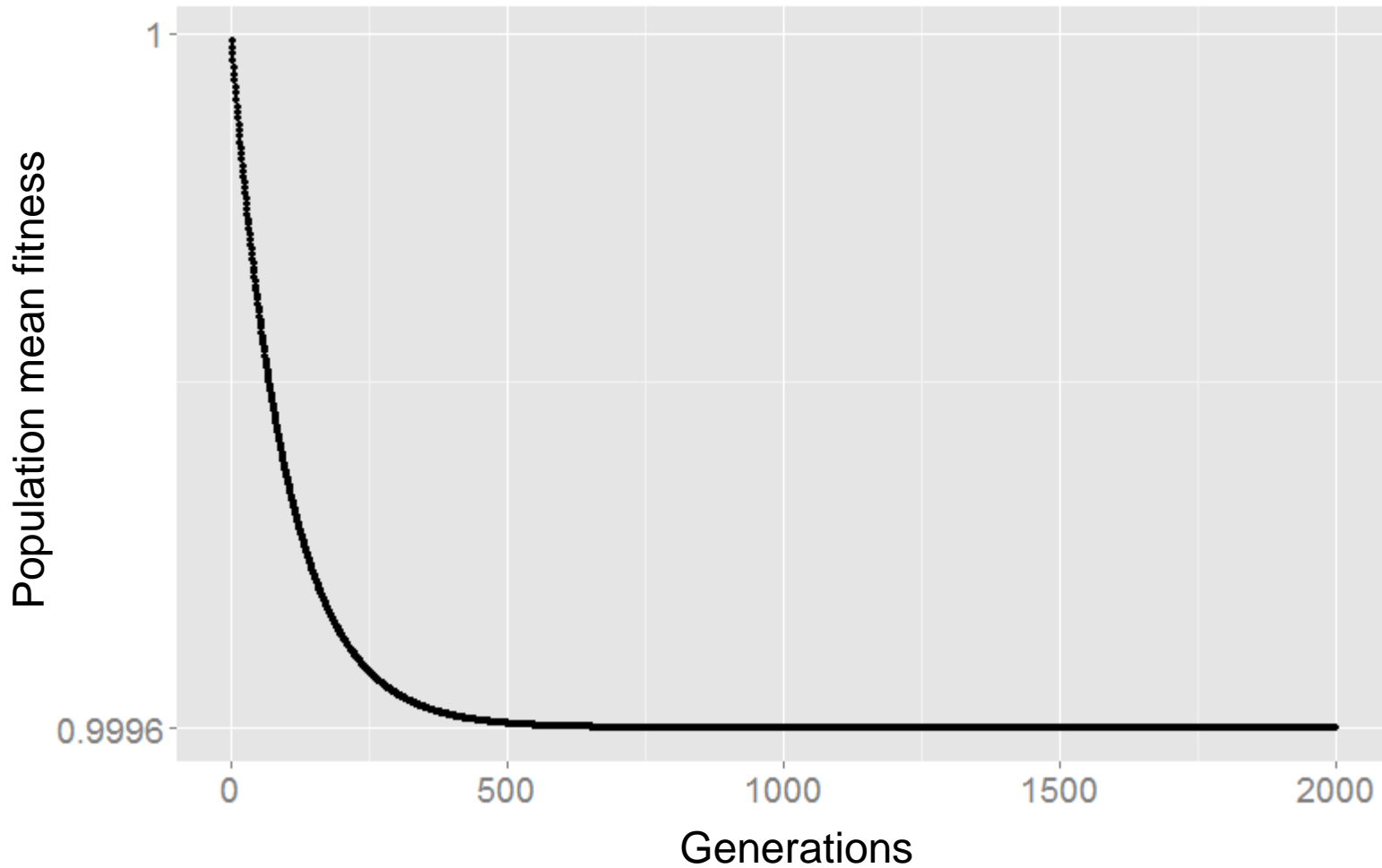
$$\bar{\omega}^* = \omega(A) \cdot \Pr(\text{no mutations})$$

- 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

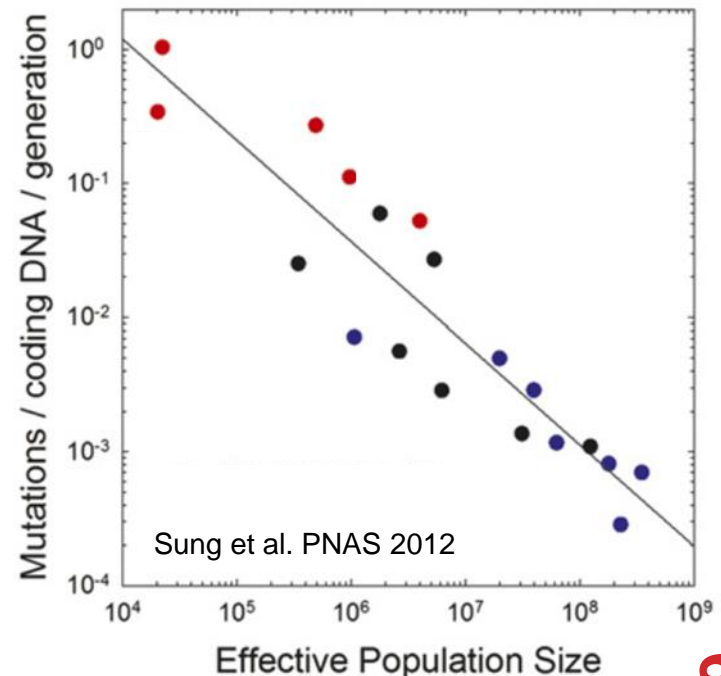
SIMULATION RESULTS



MUTATION RATE IN STATIC ENVIRONMENTS

$$\bar{\omega}^* \sim \Pr(\text{no mutations}) = e^{-U} \approx 1 - U$$

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



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*



MUTATORS IN OSCILLATING ENVIRONMENTS

- Model: Leigh, Am Nat 1970
 - Fitness locus with alleles A and a like before
 - The environmental changes every n generations
 - When it changes, $\text{fitness}(A) < \text{fitness}(a)$ and vice versa
 - **The optimal mutation rate is now $1/n$**
 - For $n=1,000$ the mutation rate is 10^{-3}
 - Much higher than 10^{-7} , the rate of mutation per gene
- (Drake, PNAS 1991)

MUTATORS IN OSCILLATING ENVIRONMENTS

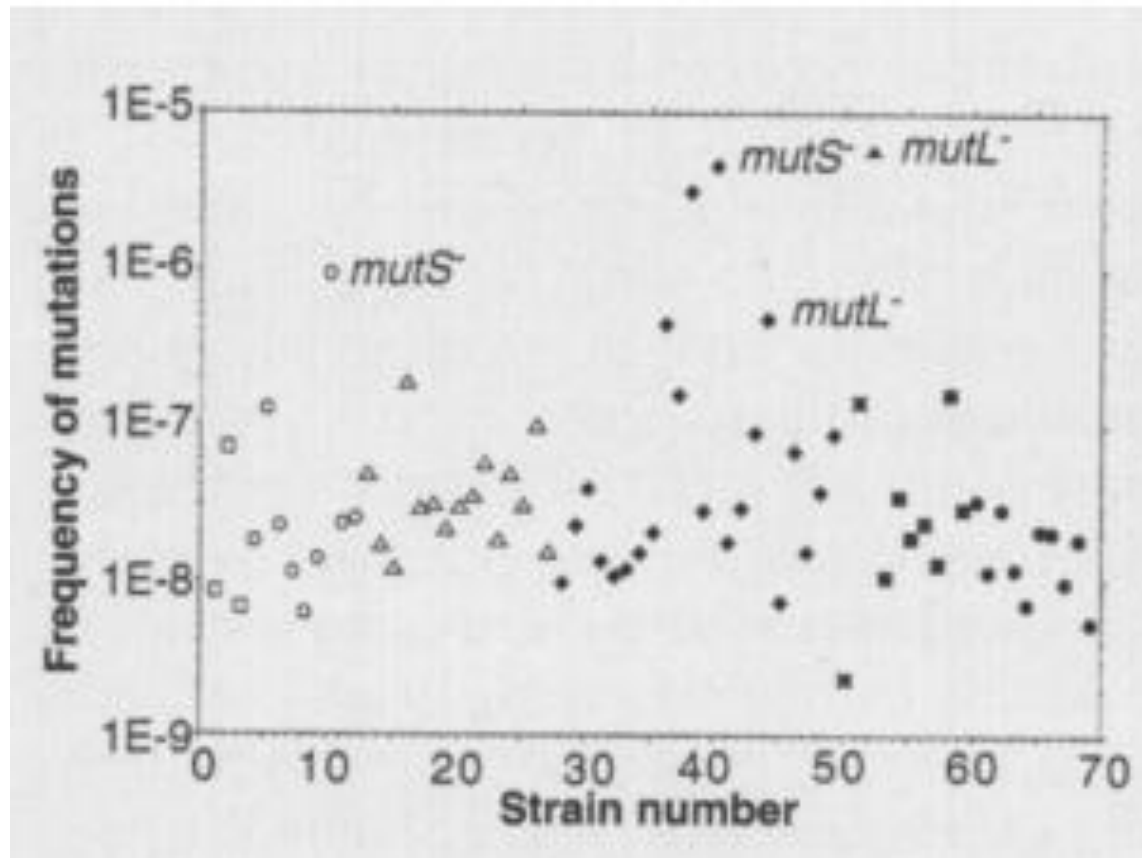
The optimal mutation rate is now $1/n$

- MSB model $\rightarrow n$ is large \rightarrow slowly changing environments
- Selection for the standing variation generated by mutators
- Local mutators? Same n for all loci? Averaging on all loci?

VARIABILITY IN MUTATION RATES

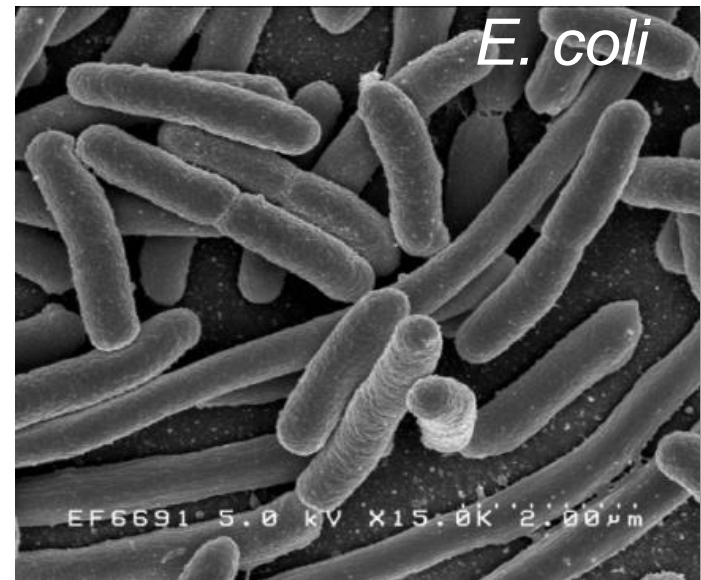
Within species

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

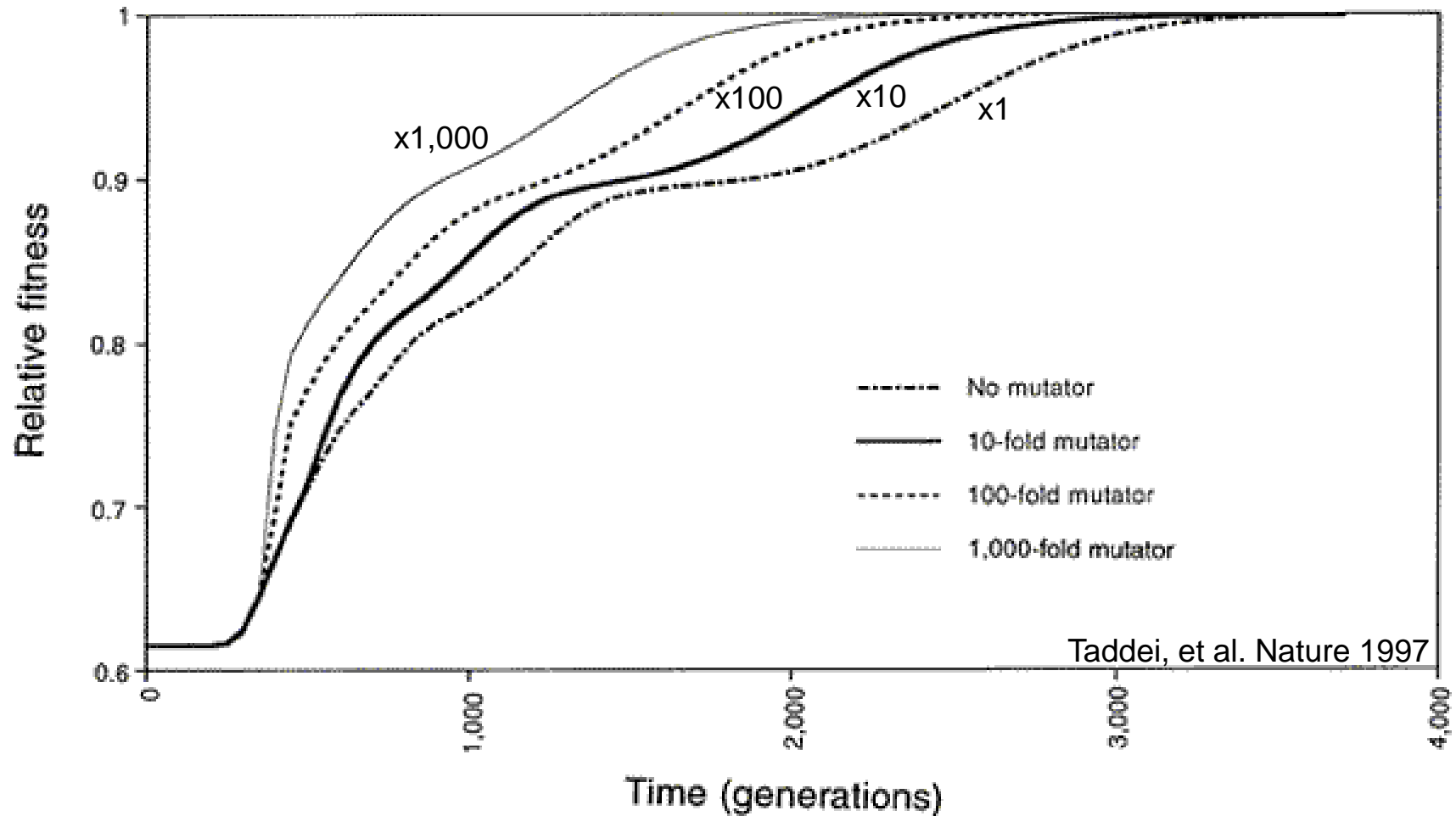


MUTATORS IN ADAPTIVE EVOLUTION

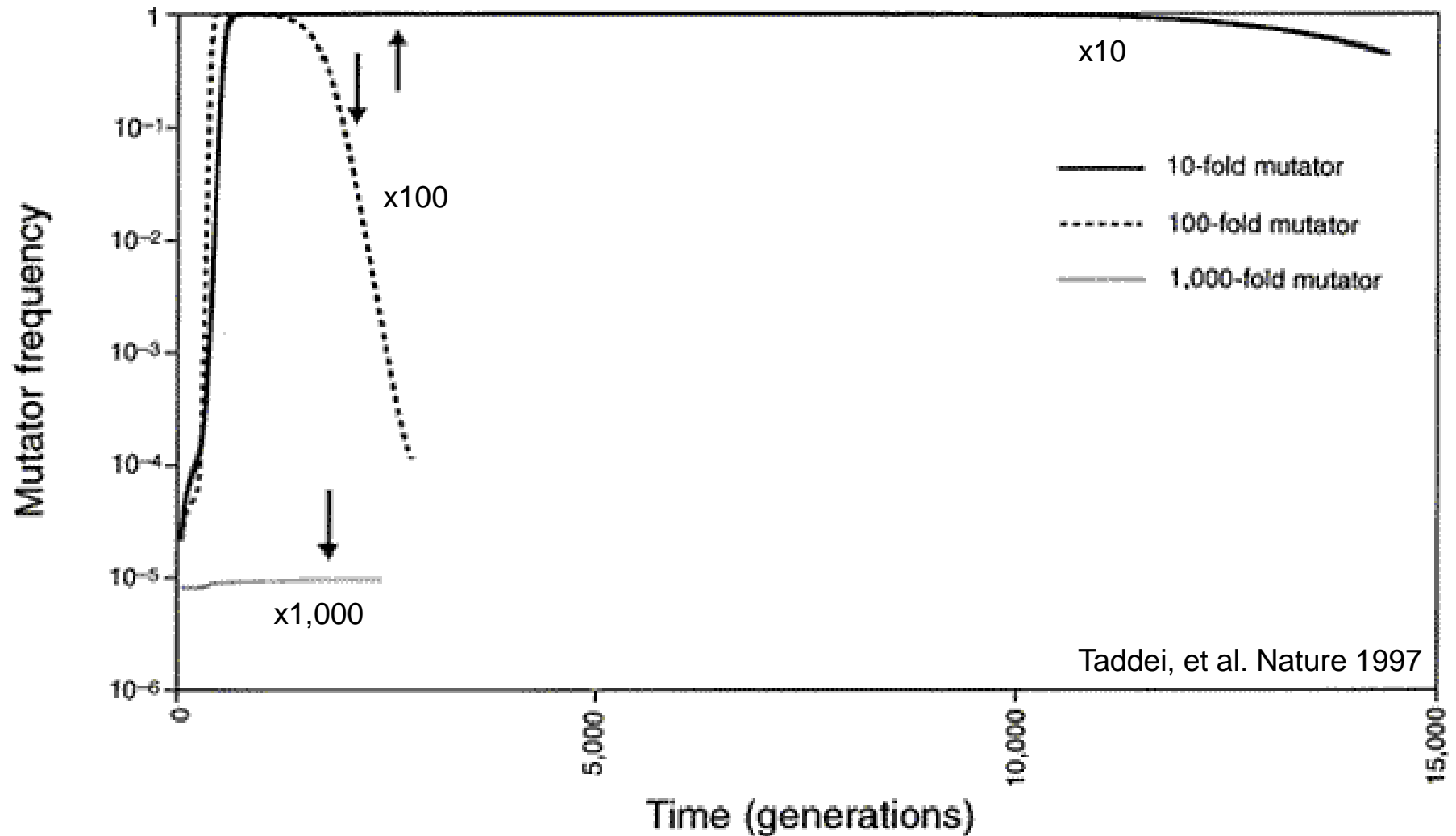
- Model: Taddei et al., Nature 1997
- Multiple-locus simulations
- Single environmental change
- No standing variation
- Mutation at the mutator locus



ADAPTATION WITH MUTATOR ALLELES



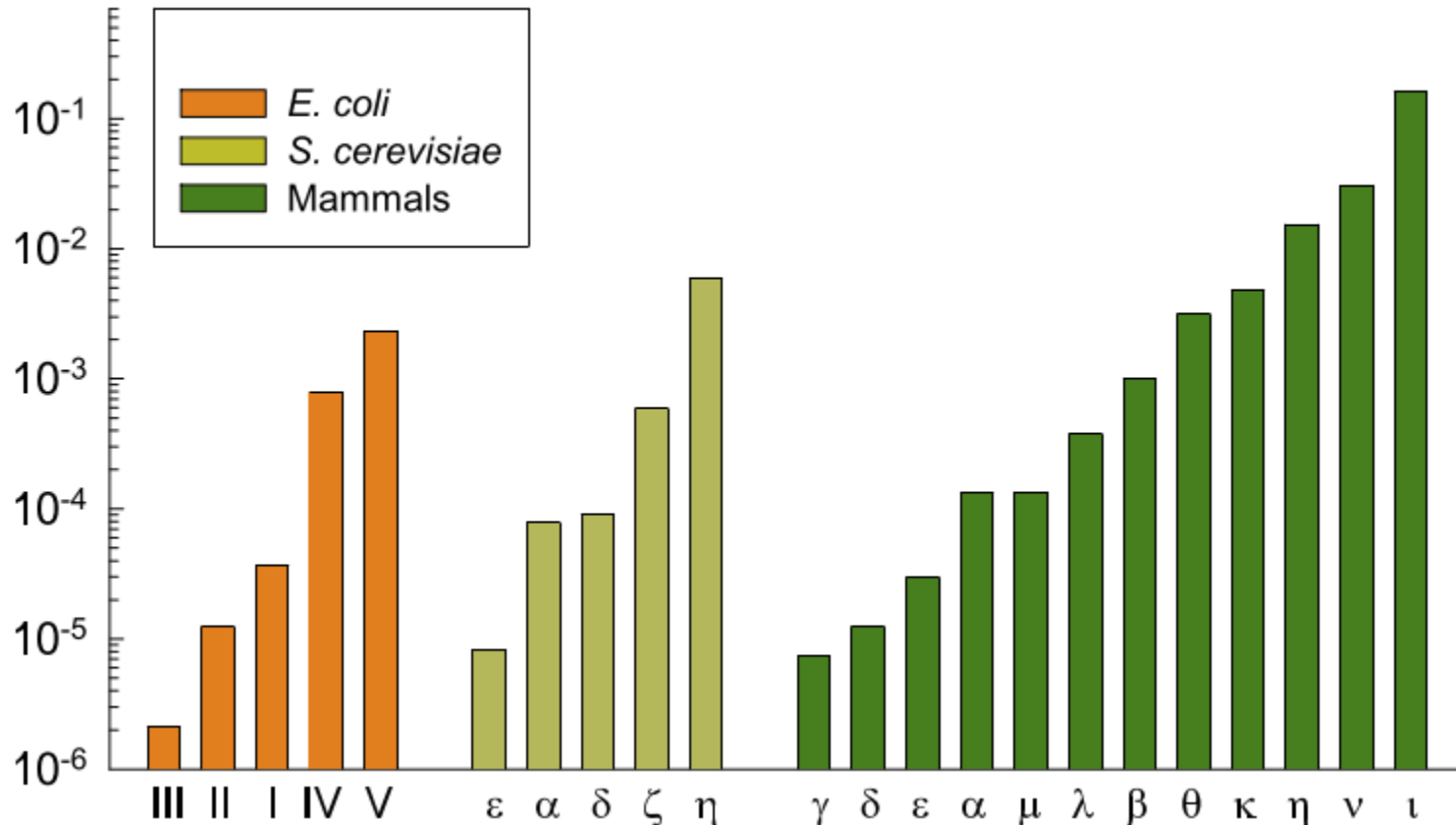
RISE AND FALL OF THE MUTATOR ALLELE



VARIABILITY IN MUTATION RATES

Within individuals

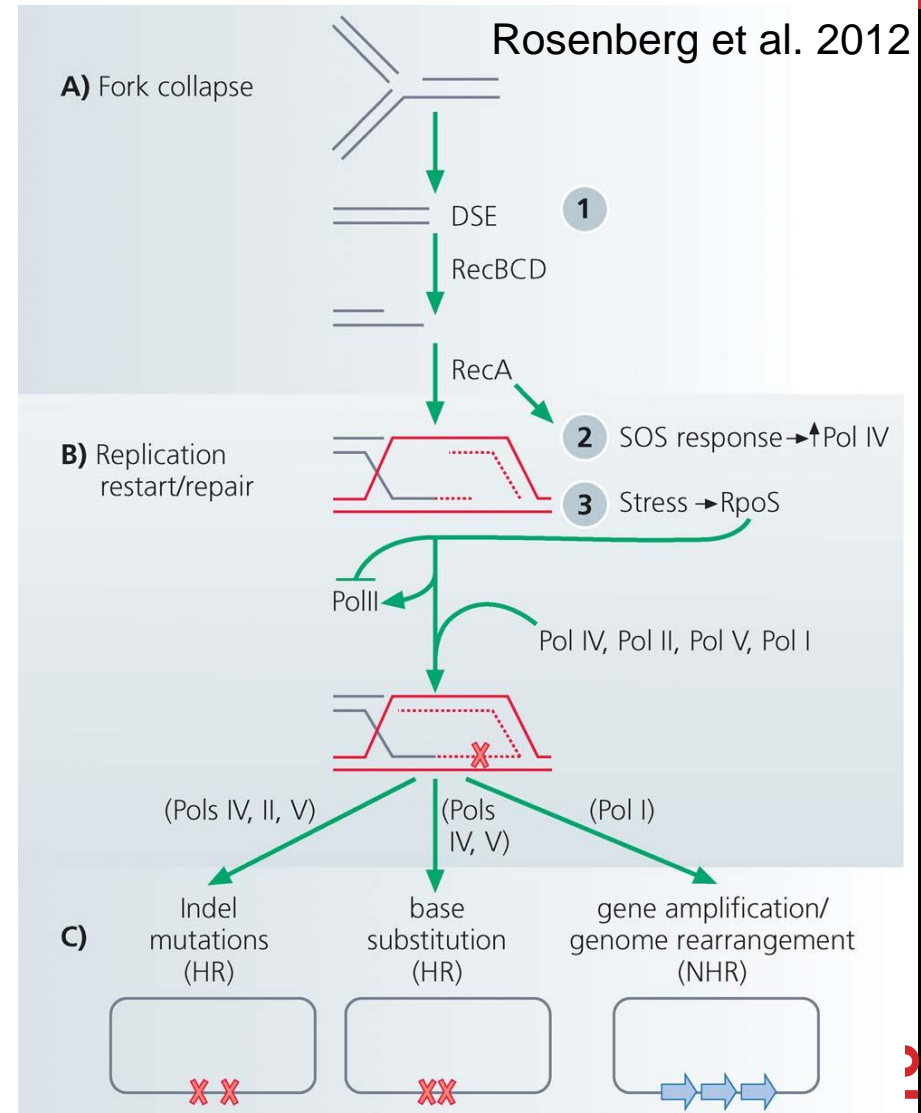
DNA polymerase error rate – Lynch 2011



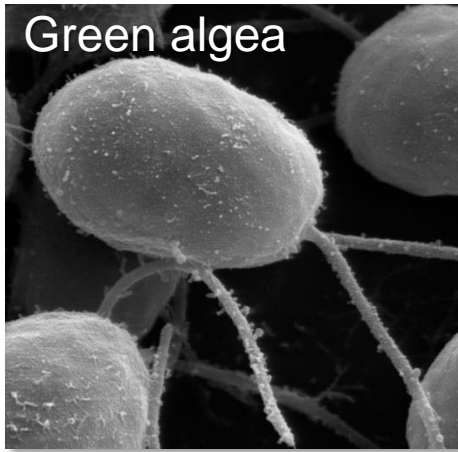
STRESS-INDUCED MUTATION

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

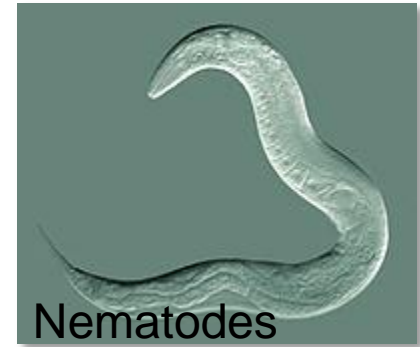


Green alga

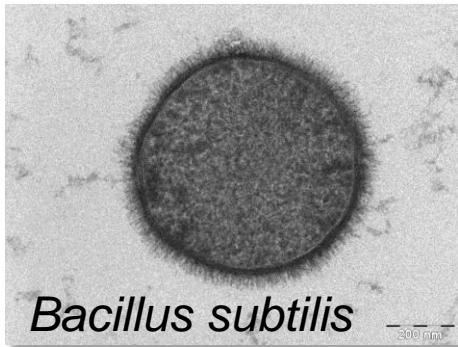


EVIDENCE

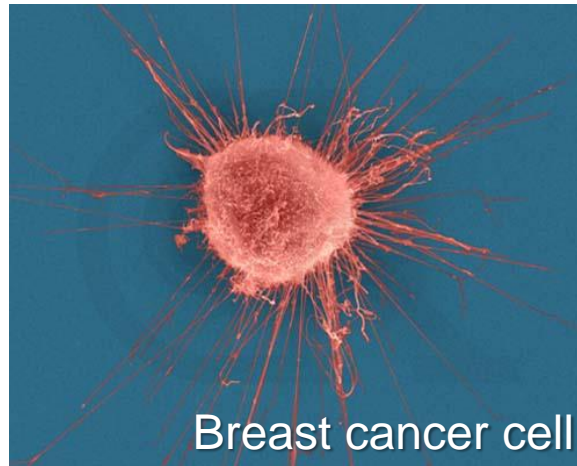
Nematodes



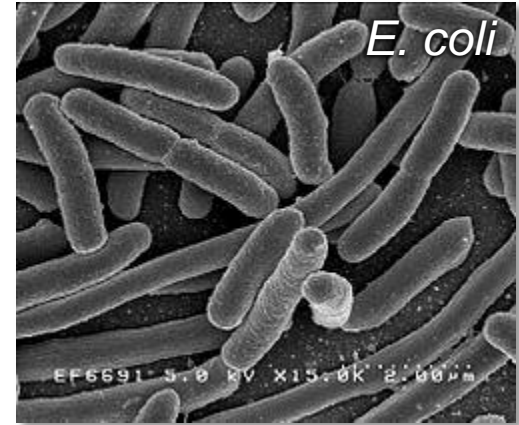
Bacillus subtilis



Breast cancer cell



E. coli



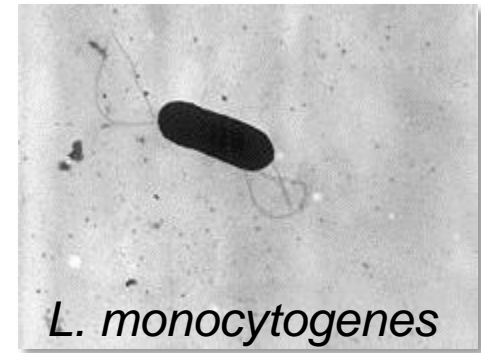
D. Melanogaster



M. tuberculosis



L. monocytogenes



EVOLUTION OF STRESS-INDUCED MUTATION

Null hypothesis

Mutagenesis is the by-product of stress

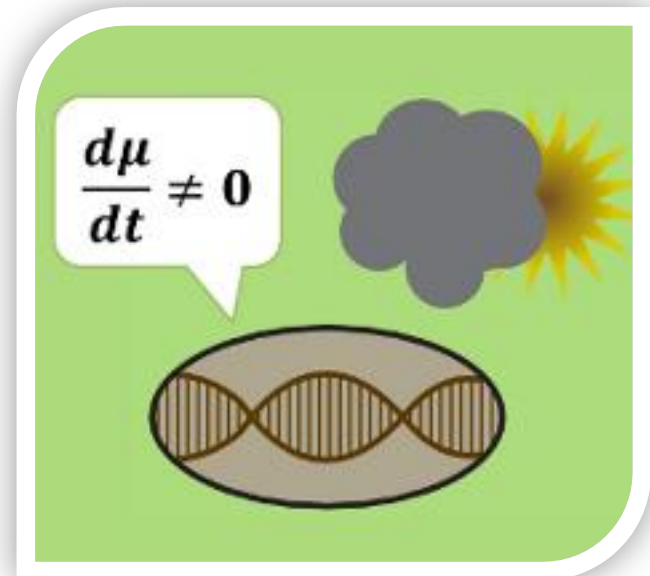
Alternative non-adaptive hypotheses

Cost of fidelity

Drift barrier hypothesis

Adaptive hypothesis

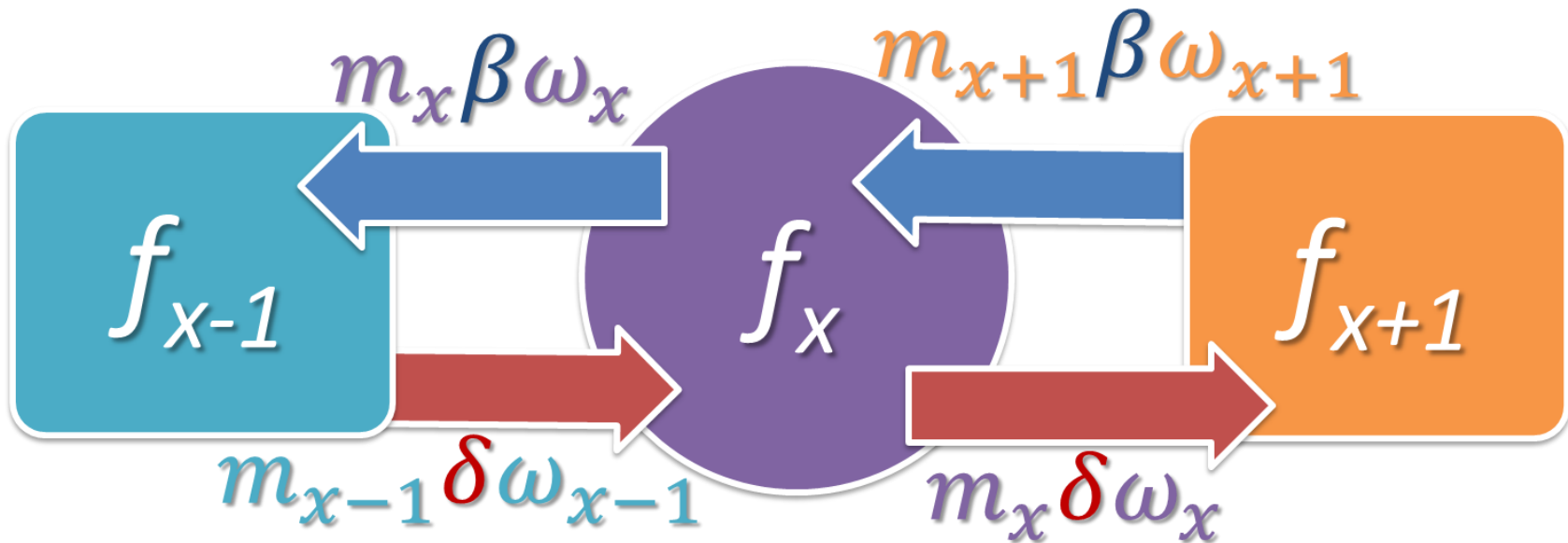
Second order selection



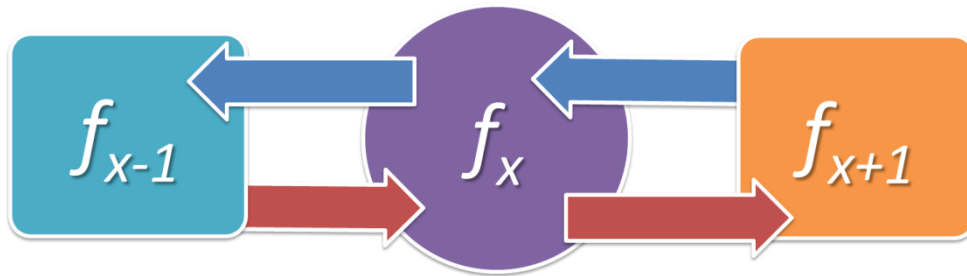
STATIC ENVIRONMENT



Selection against generation of deleterious mutations



- x - number of harmful alleles
- f_x - frequency
- ω_x - fitness
- m_x - mutation probability
- δ - deleterious mutation β - beneficial mutation



x # of harmful alleles
 f_x frequency
 ω_x fitness
 m_x mutation probability
 δ deleterious mutation
 β beneficial mutation
 $\bar{\omega}$ population mean fitness

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

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

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

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

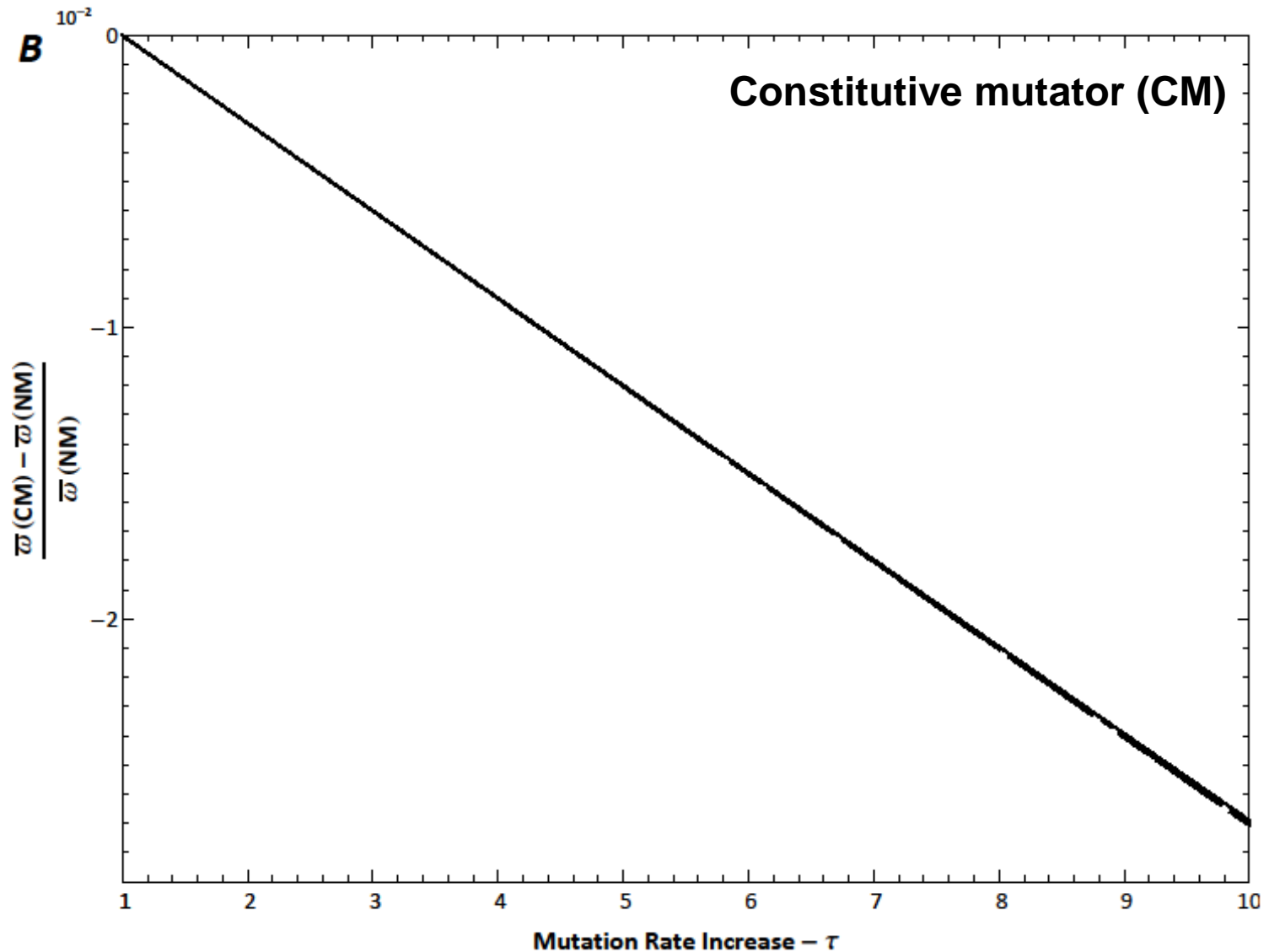
General solution

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

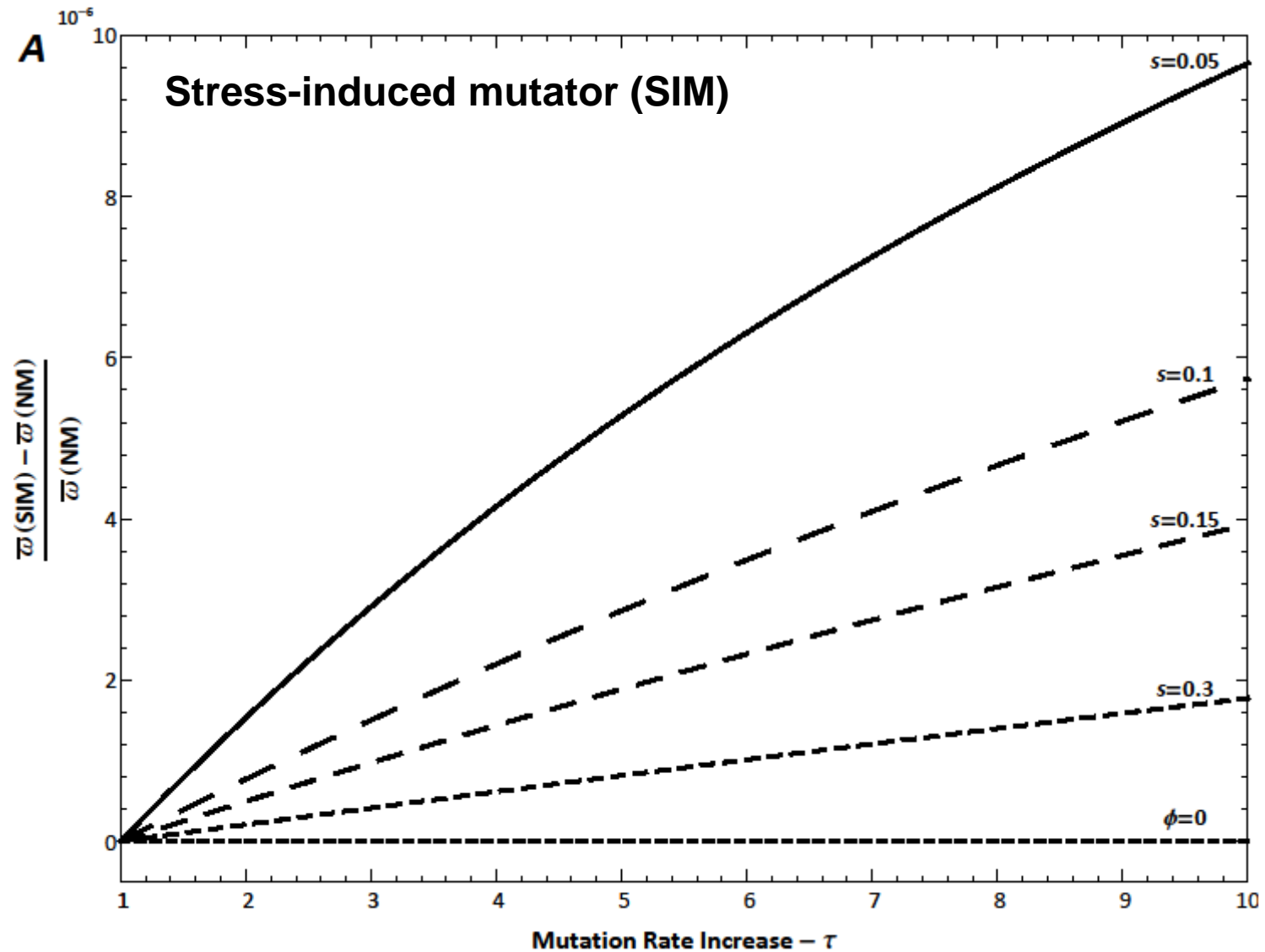
“Increasing the mutation rate of individuals with below average fitness increases the population mean fitness”

Selection doesn't reduce the mutation rate!

STATIC ENVIRONMENTS



STATIC ENVIRONMENTS



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

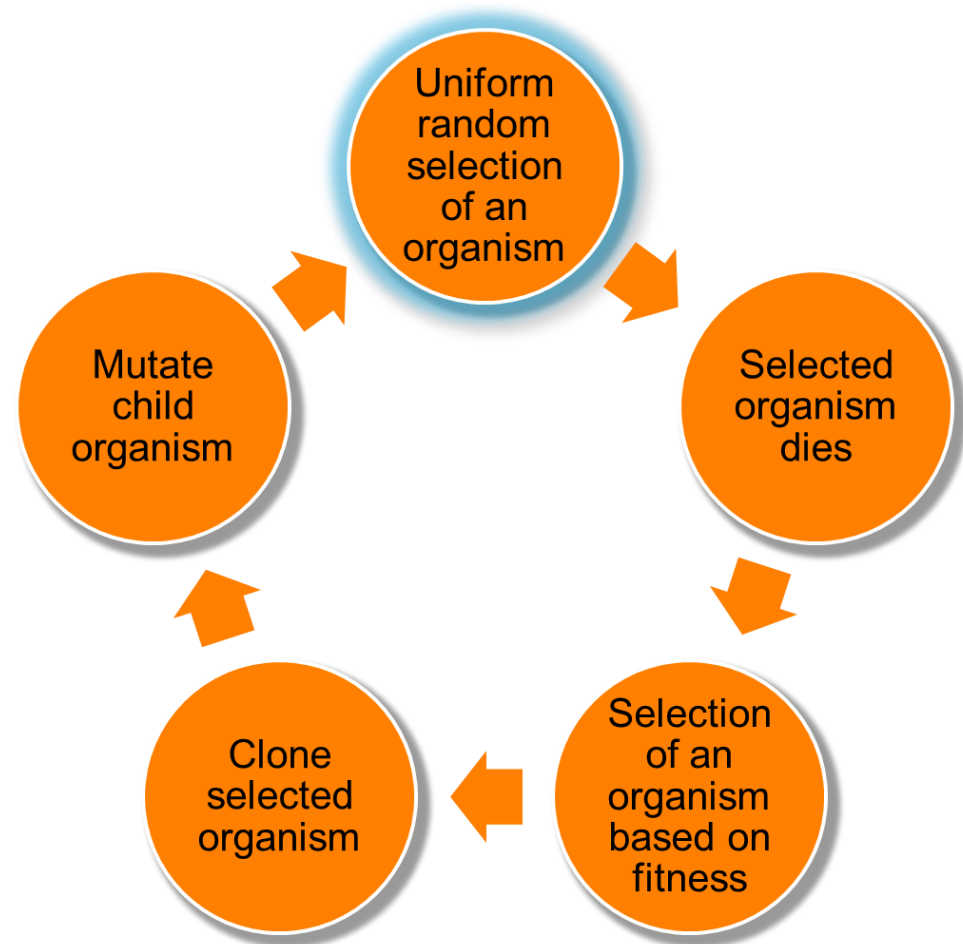
Overlapping generations

No recombination

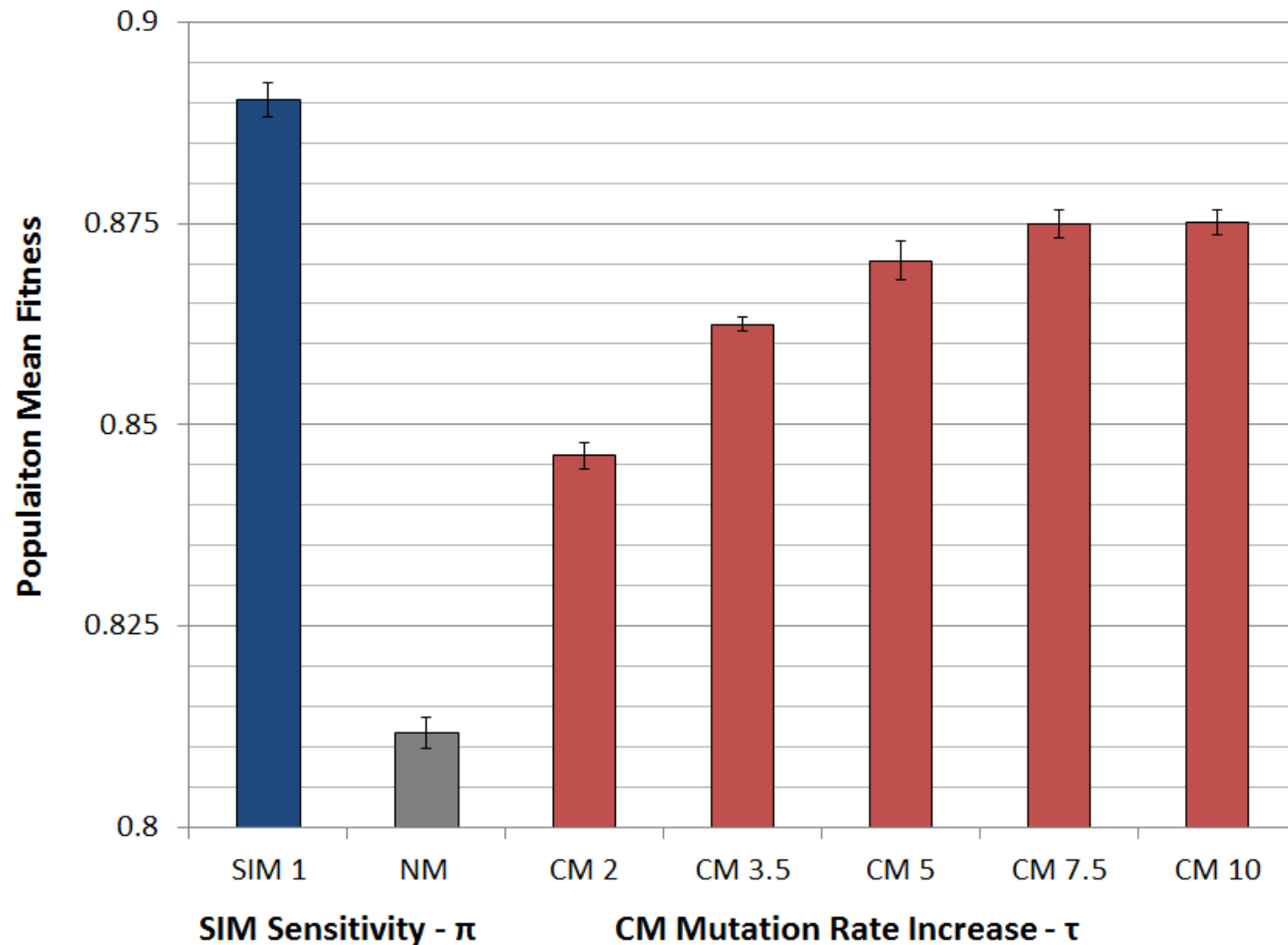
No segregation

No mutations at mutator locus

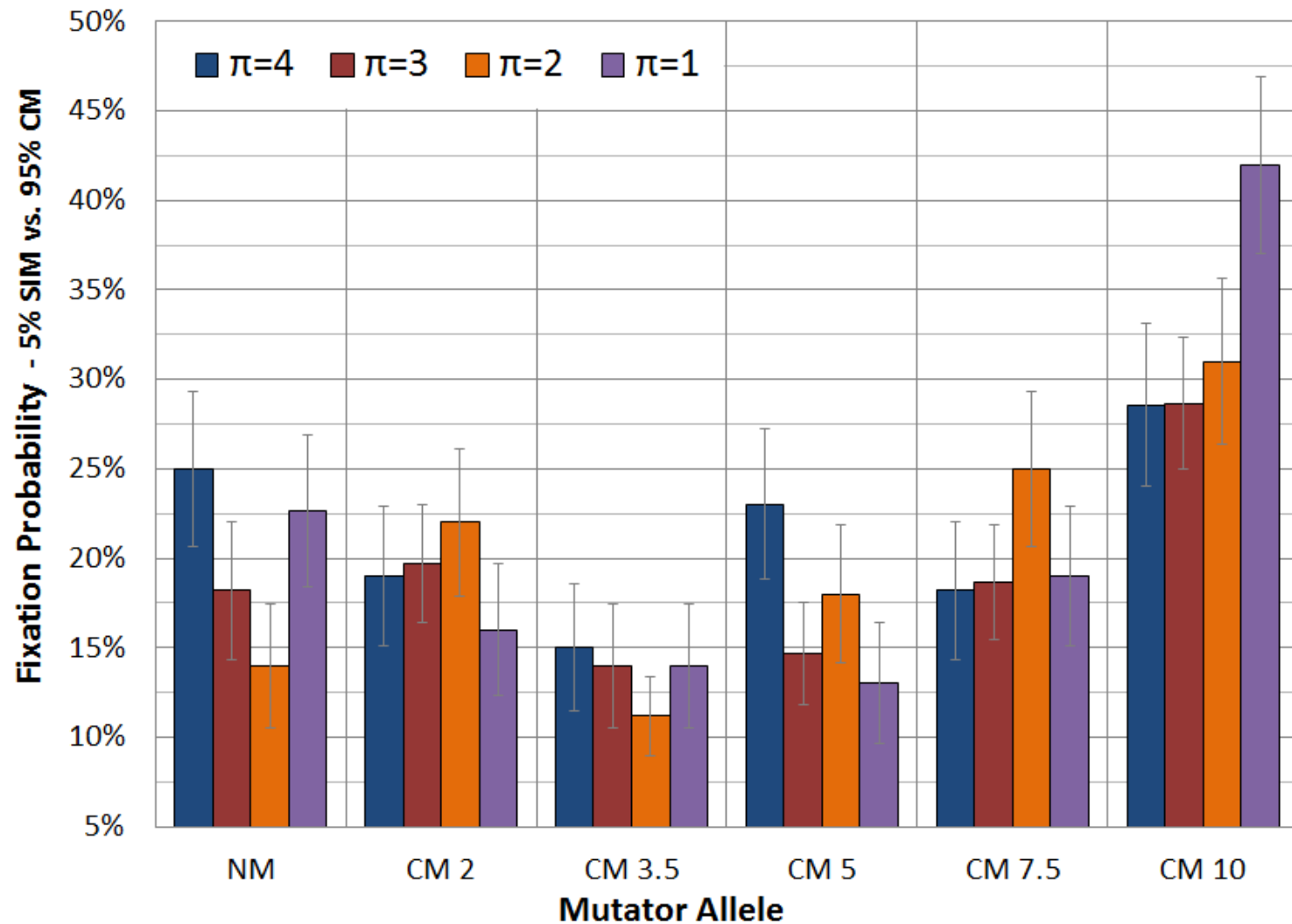
Environmental changes



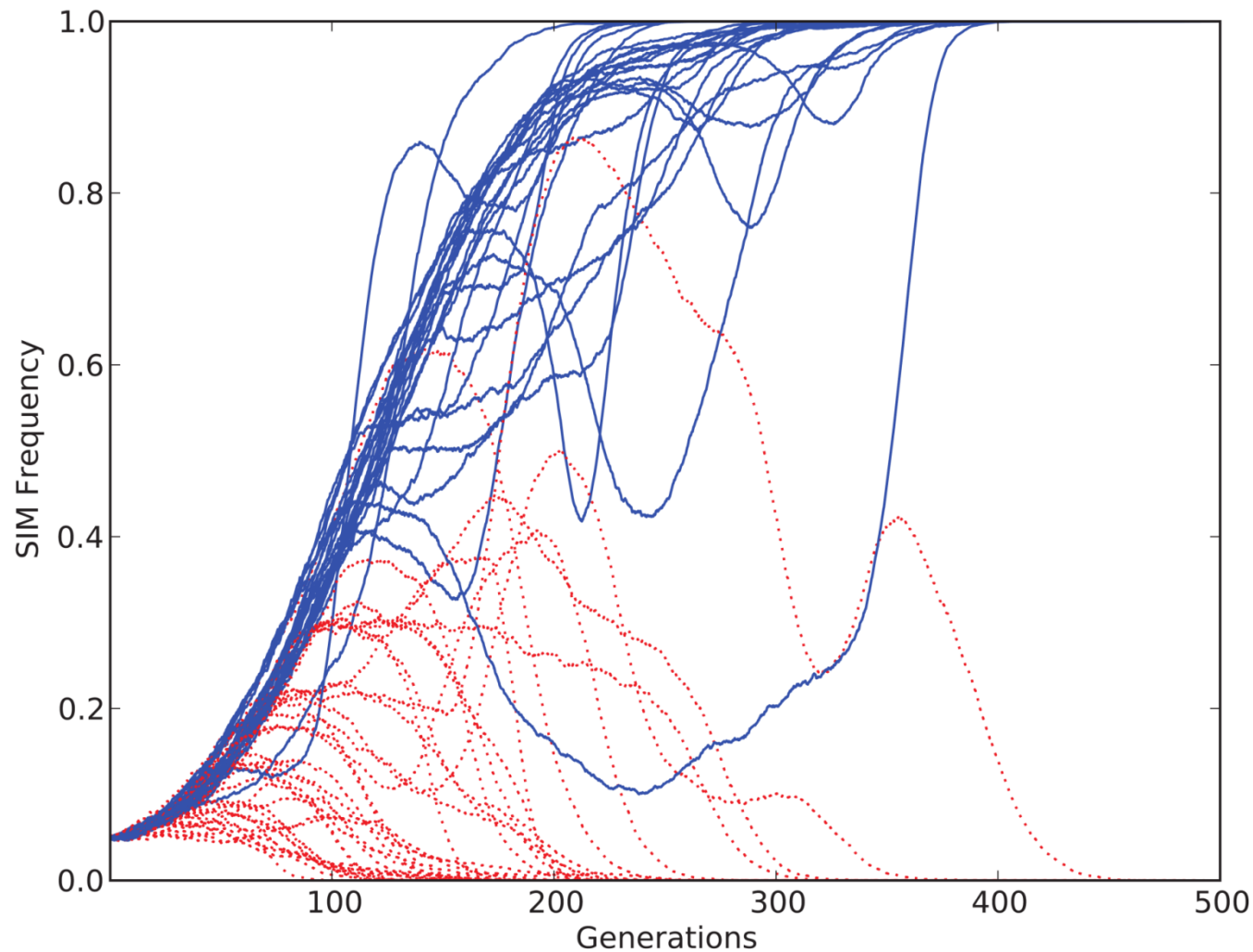
POPULATIONS WITH SIM ARE FITTER



SIM WINS COMPETITIONS

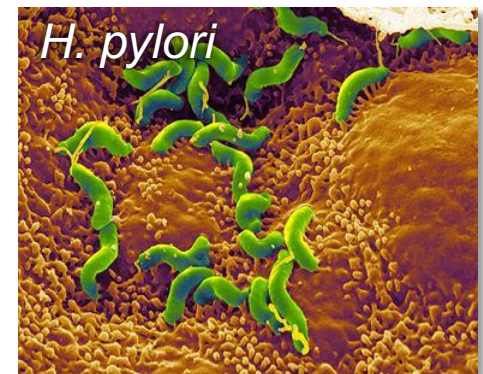


SIM WINS COMPETITIONS



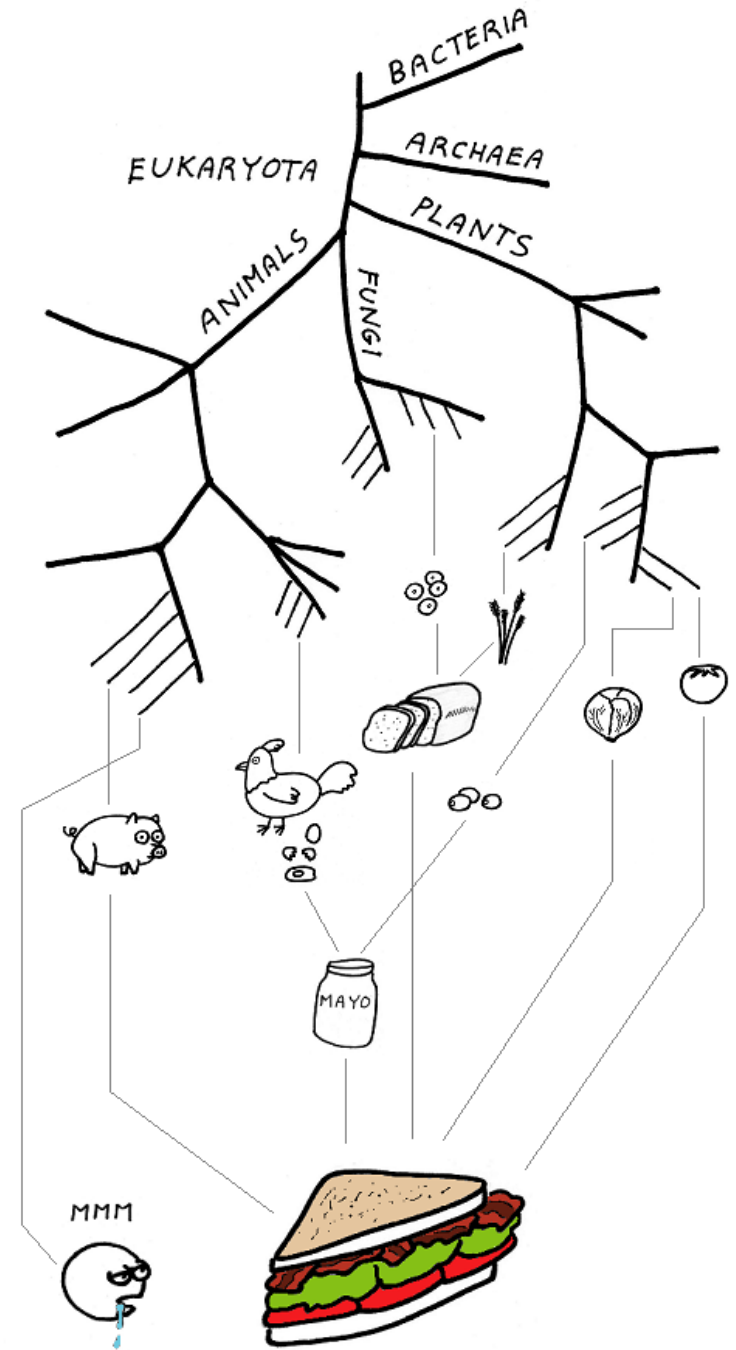
SUMMARY: EVOLUTION OF STRESS-INDUCED MUTATION

- 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

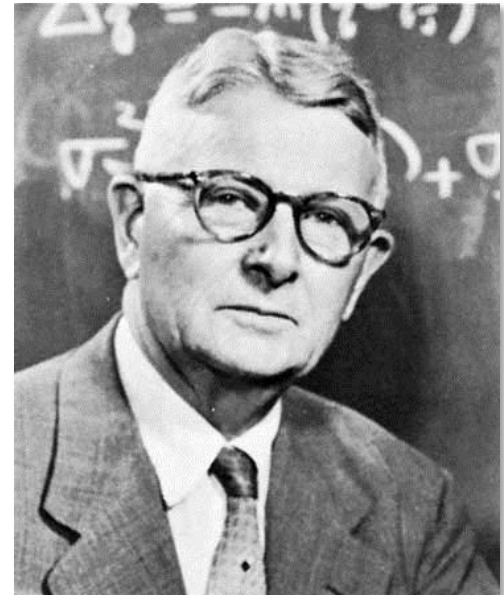
How does SIM affect evolution?



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

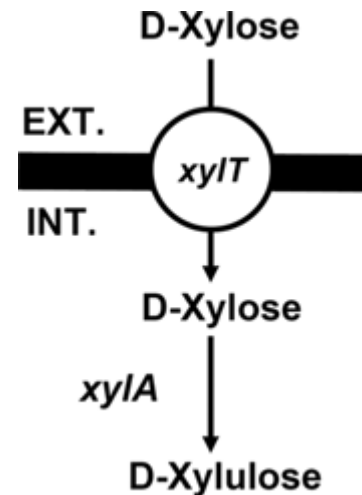
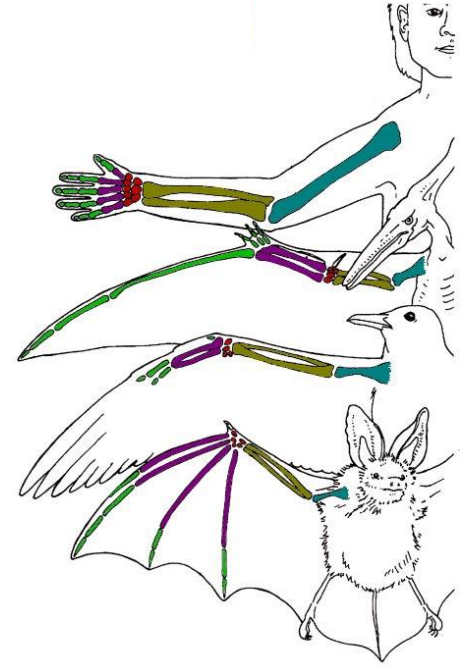
- Flying with heavy bones is costly
- Walking and climbing with light bones is dangerous

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

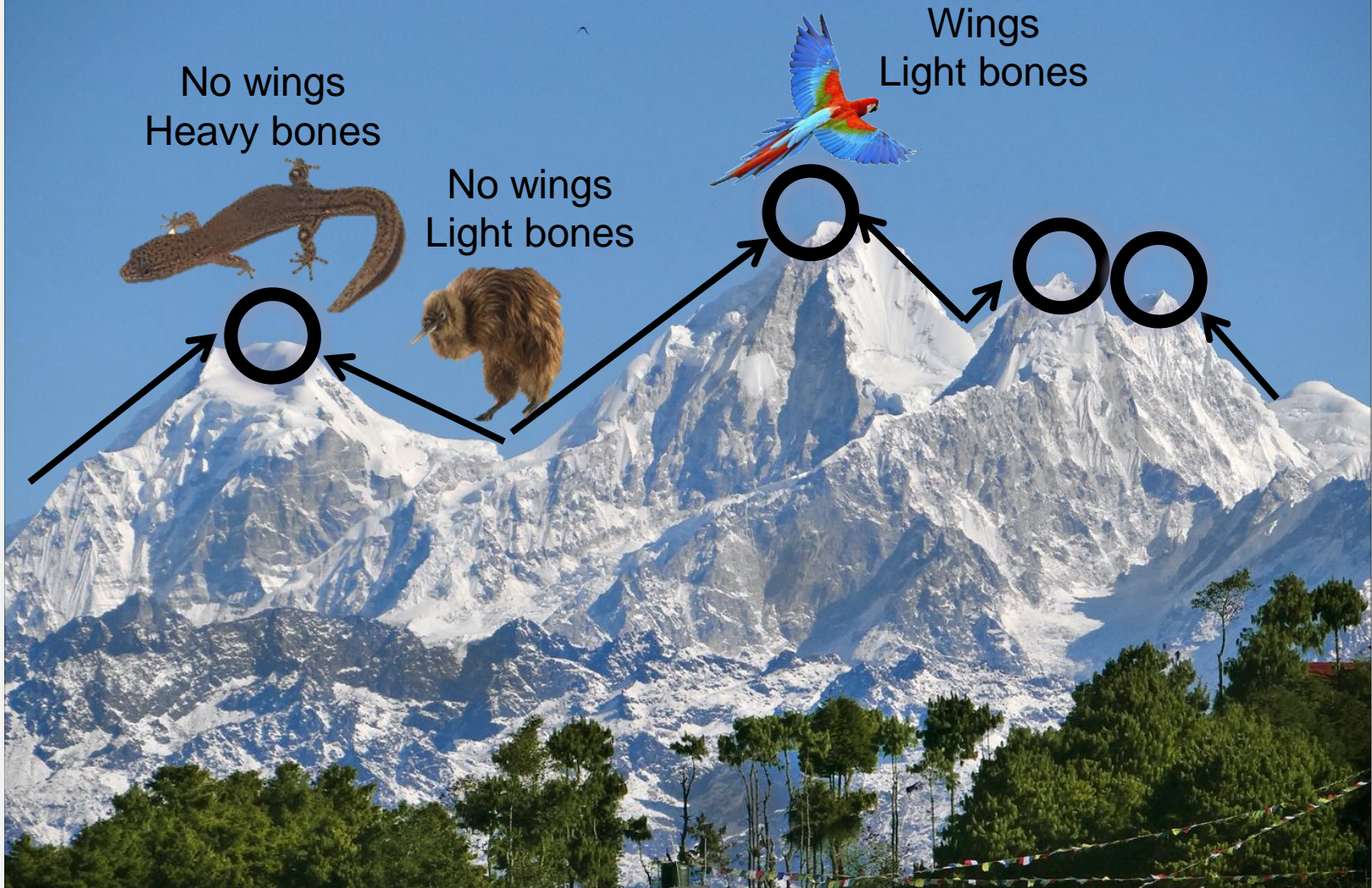
No wings
Heavy bones



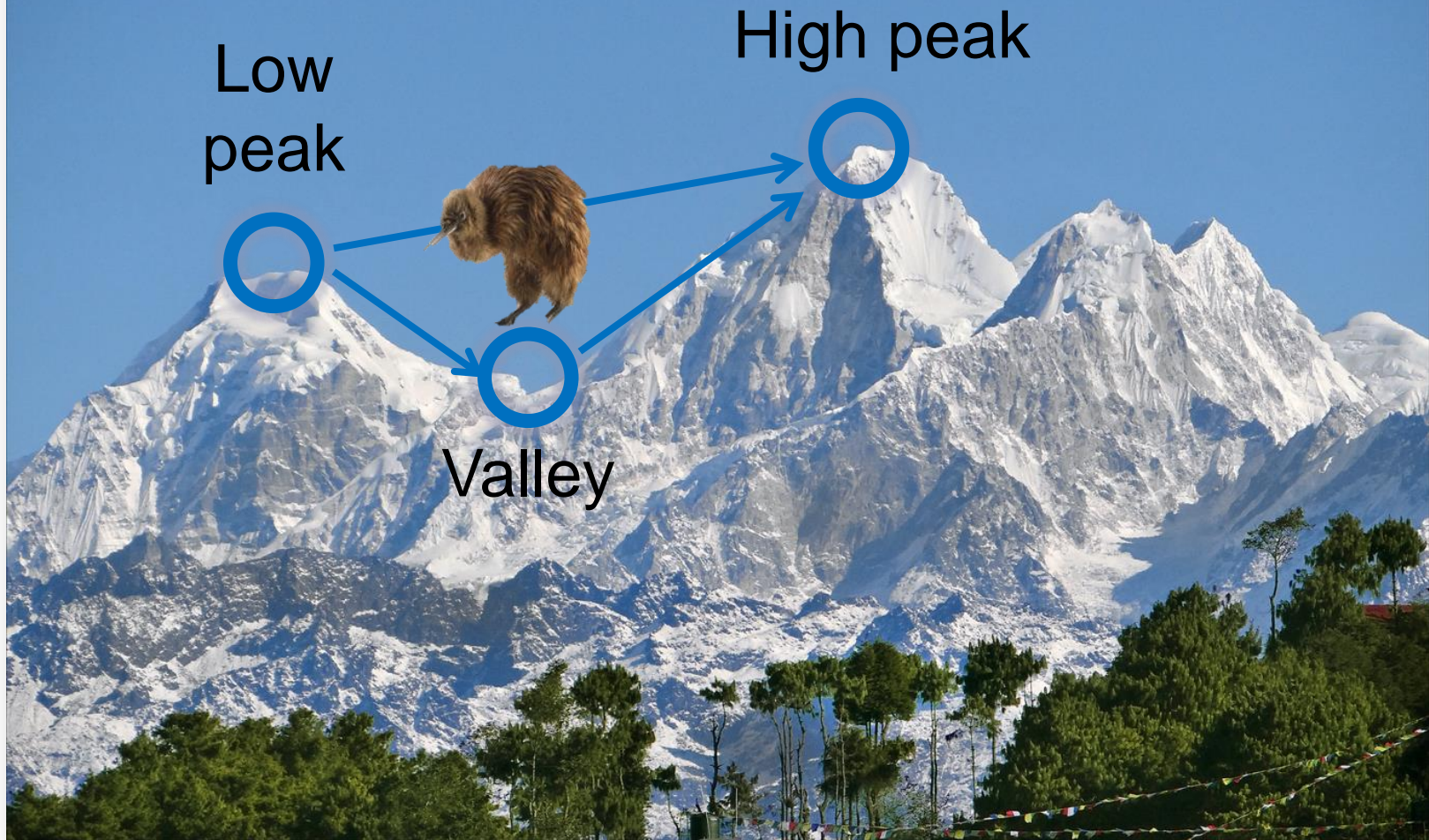
No wings
Light bones



Wings
Light bones

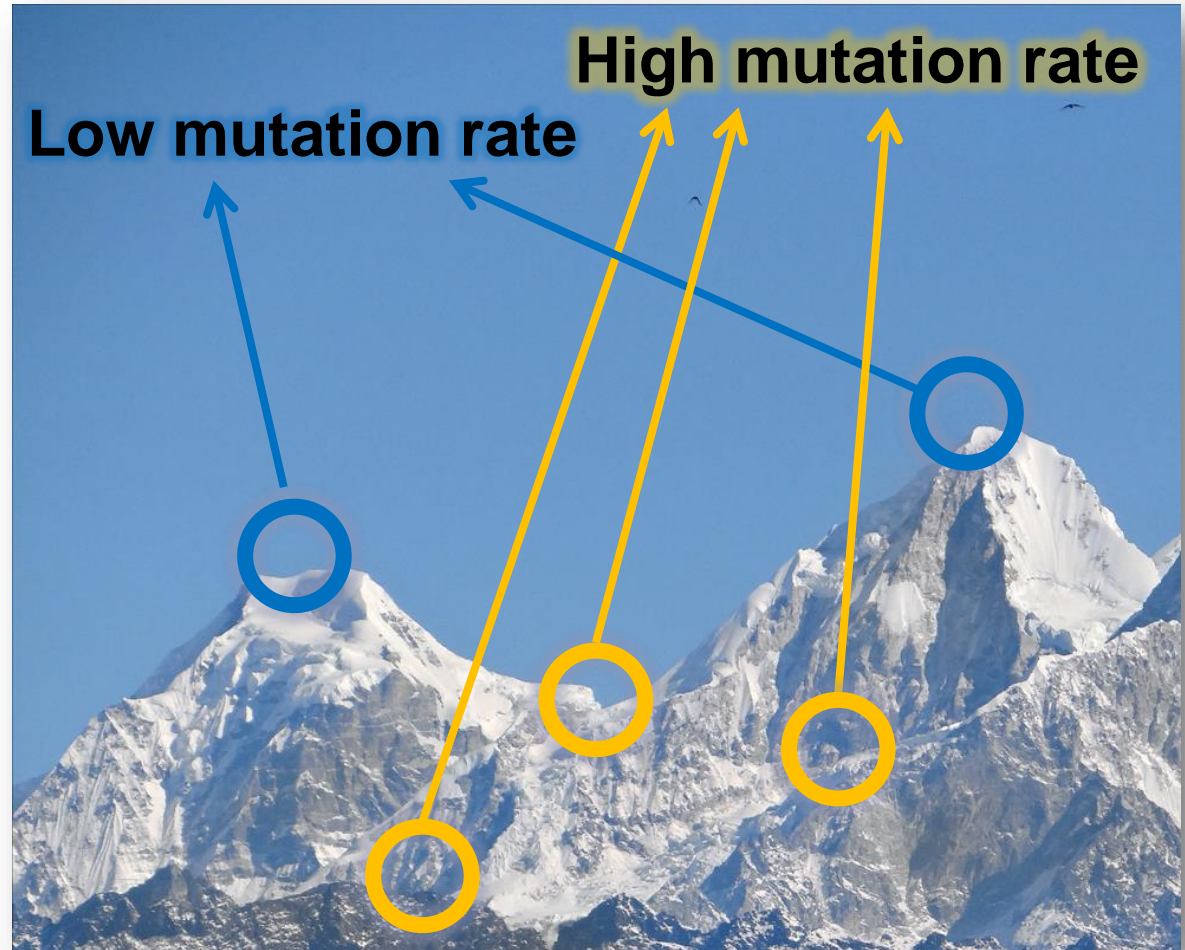


ADAPTIVE PEAK SHIFT

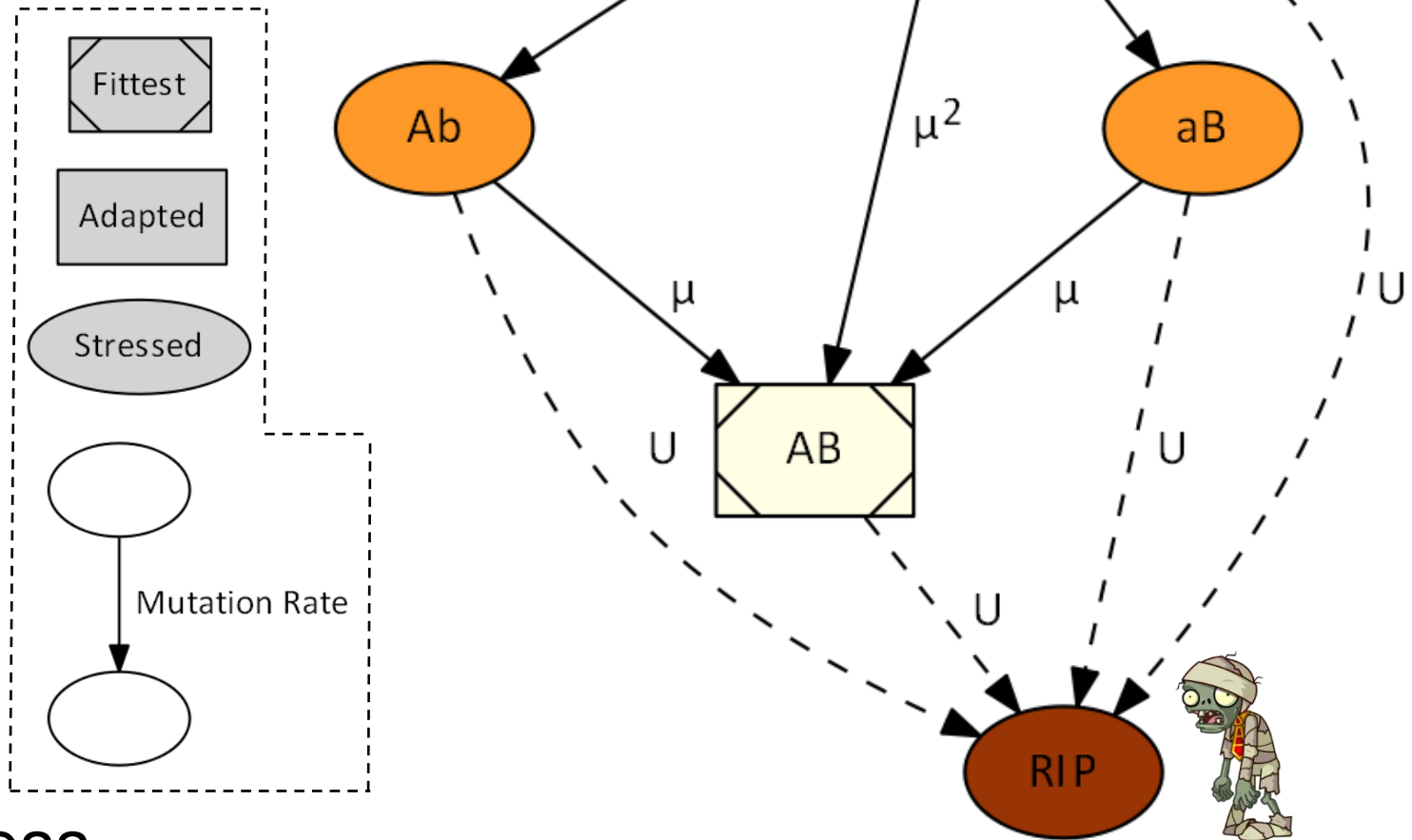


SIM & RUGGED LANDSCAPE

Increasing the
mutation rate in
individuals below
both peaks



DETERMINISTIC MODEL



fitness



DETERMINISTIC RESULTS

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

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

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

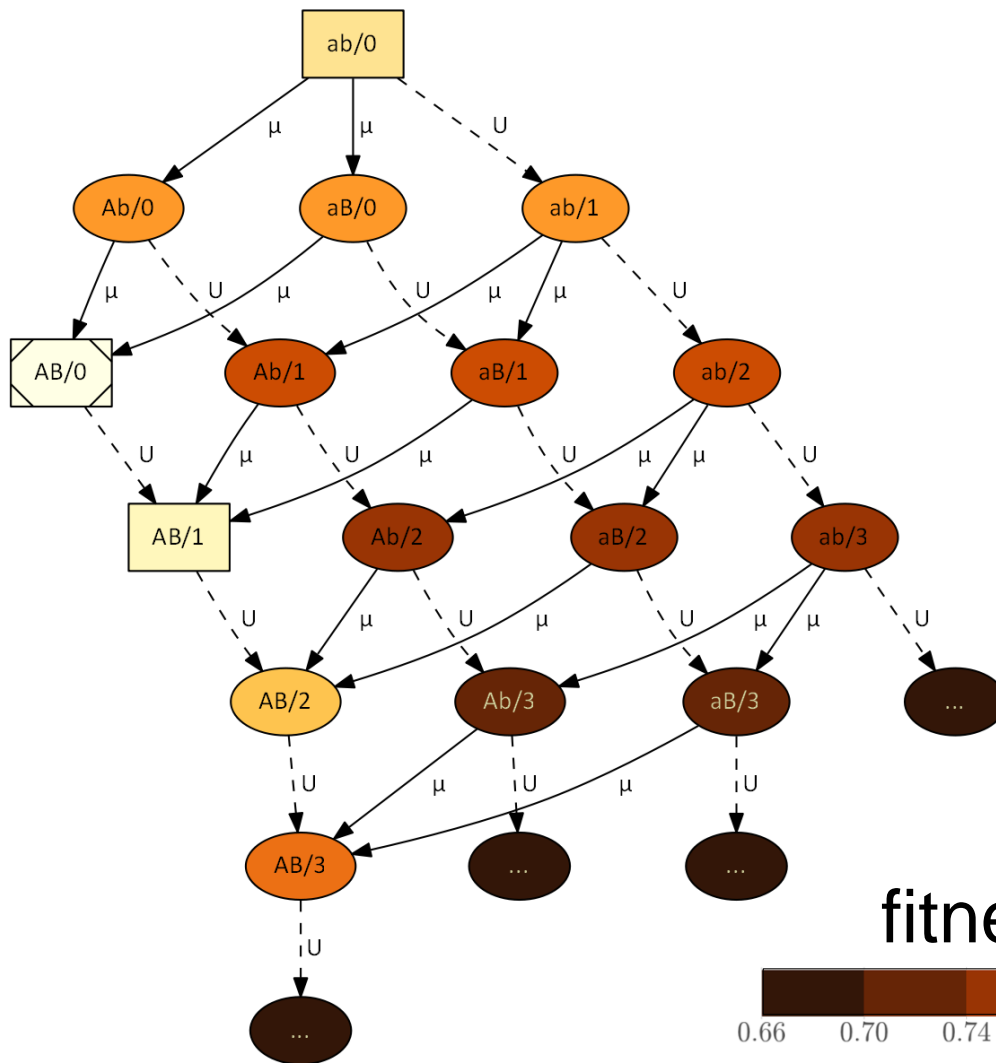
$$v_{CM} \approx \tau^2 \cdot v_{NM}$$

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

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

v – adaptation rate; N – population size; τ – mutation rate increase; H – double mutant advantage; μ – beneficial mutation rate

STOCHASTIC MODEL



No MSB assumption

No



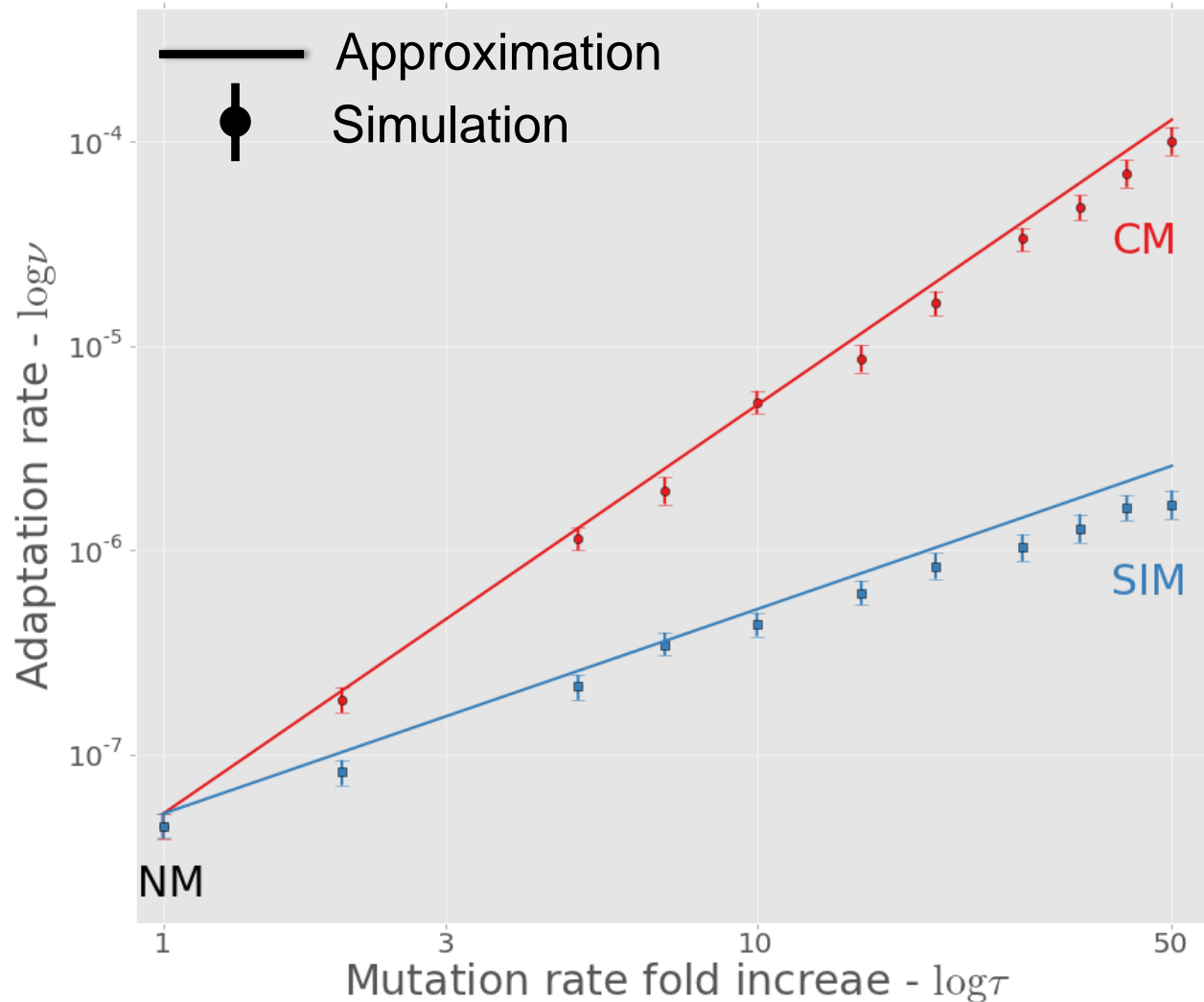
fitness



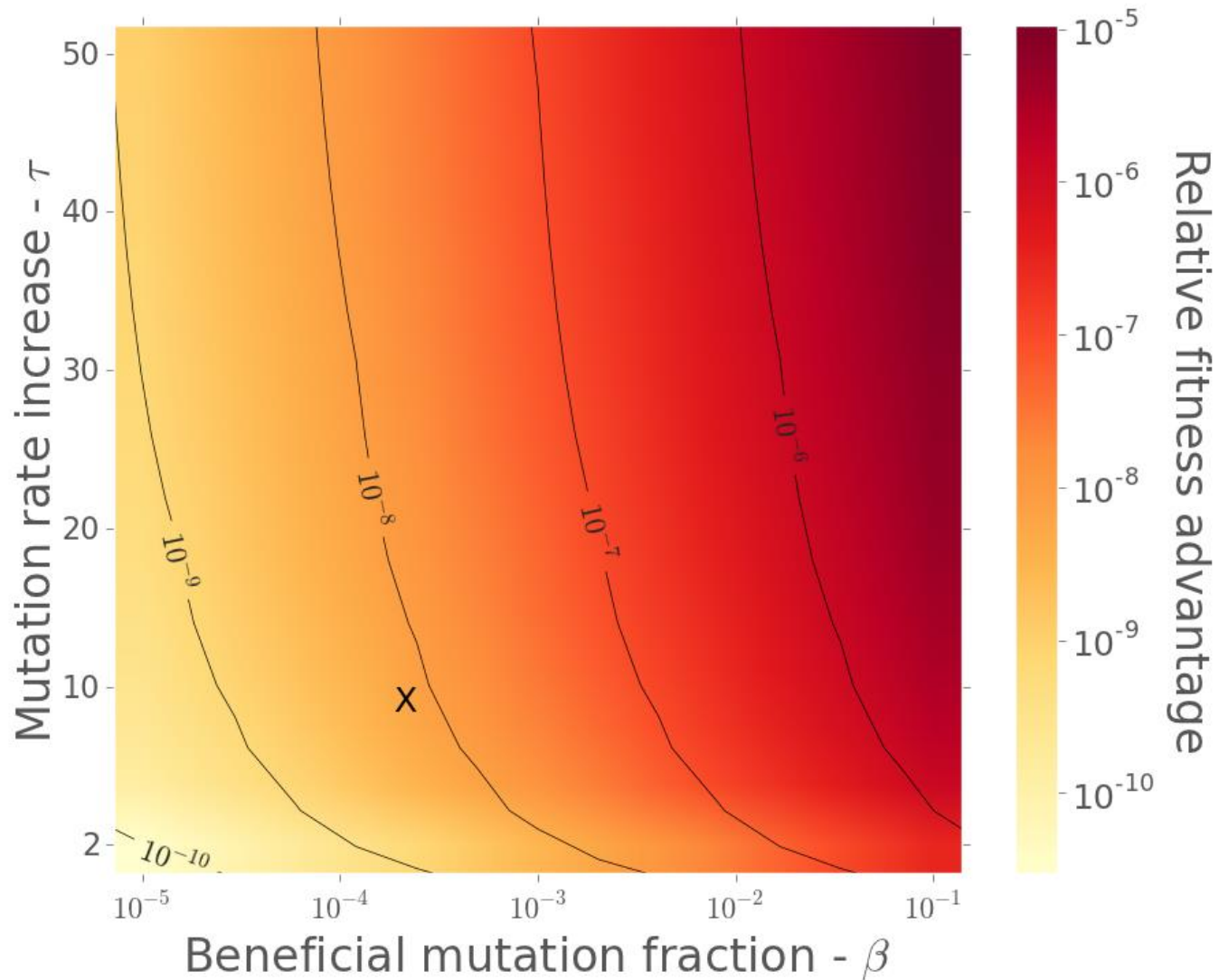
$$\nu_{CM} \approx \tau^2 \cdot \nu_{NM}$$

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

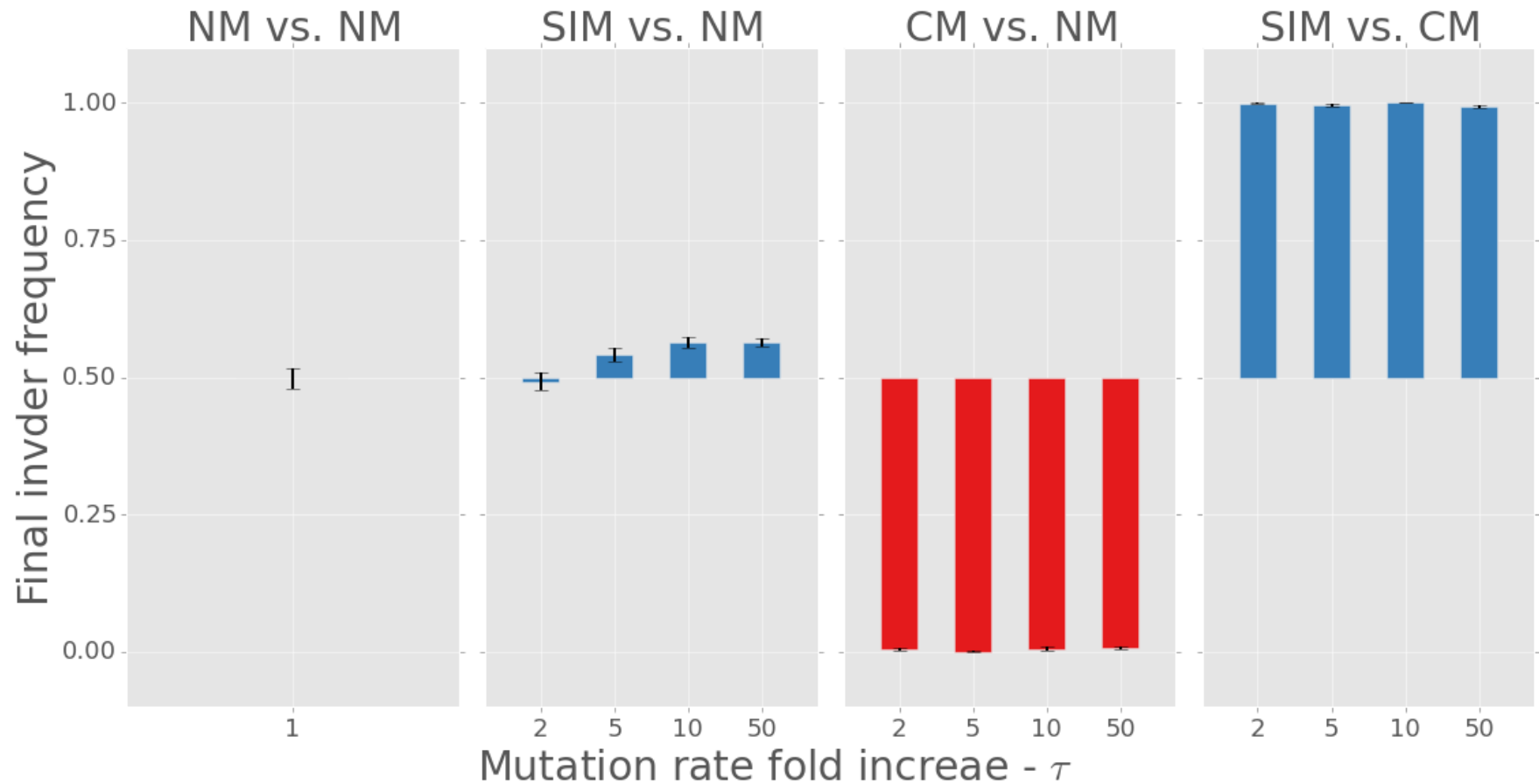
ADAPTATION RATE



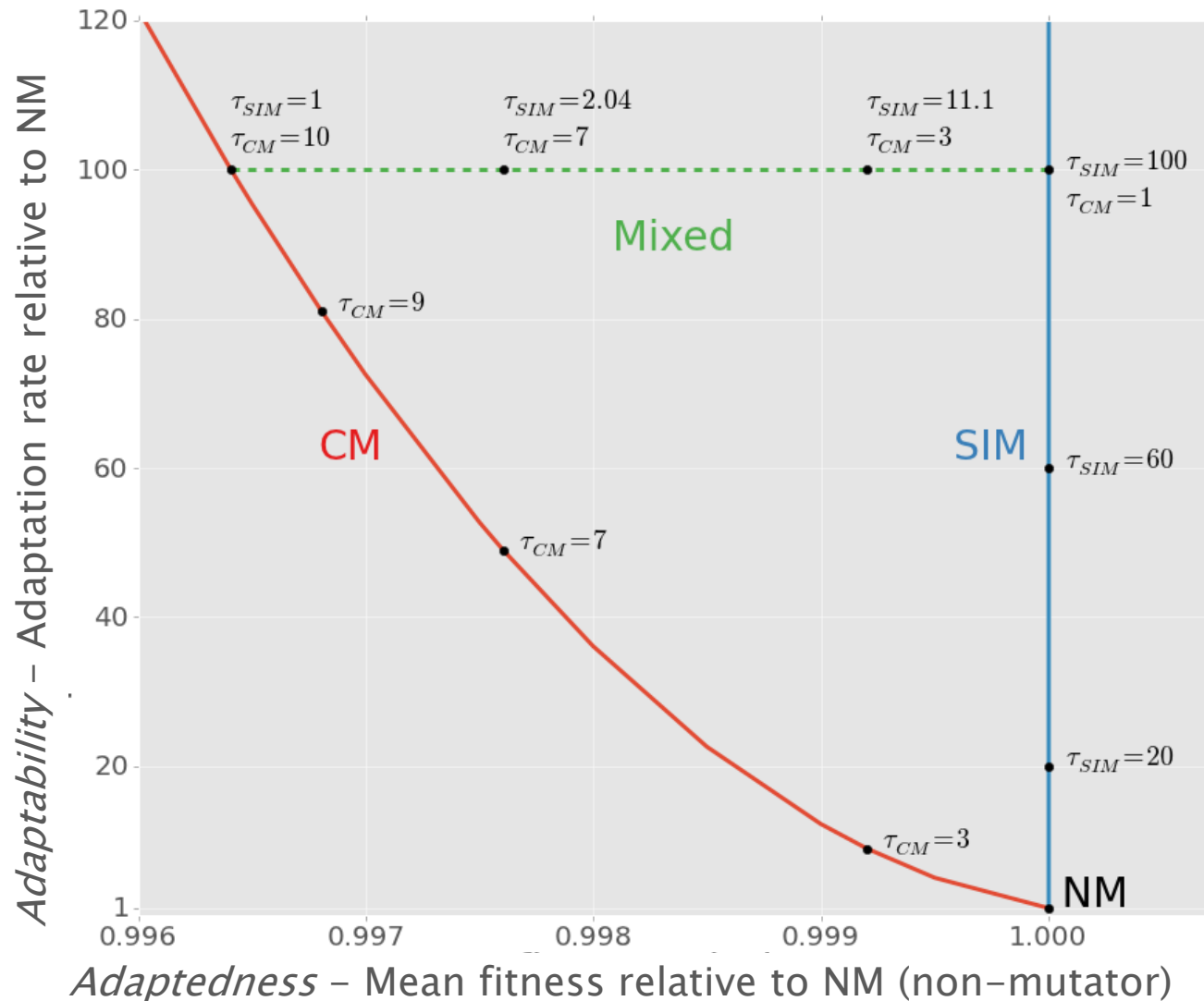
MEAN FITNESS IN MSB



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*

Presentation:

PowerPoint: <http://git.io/BipxcA>

PDF: <http://git.io/nno1Pw>