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

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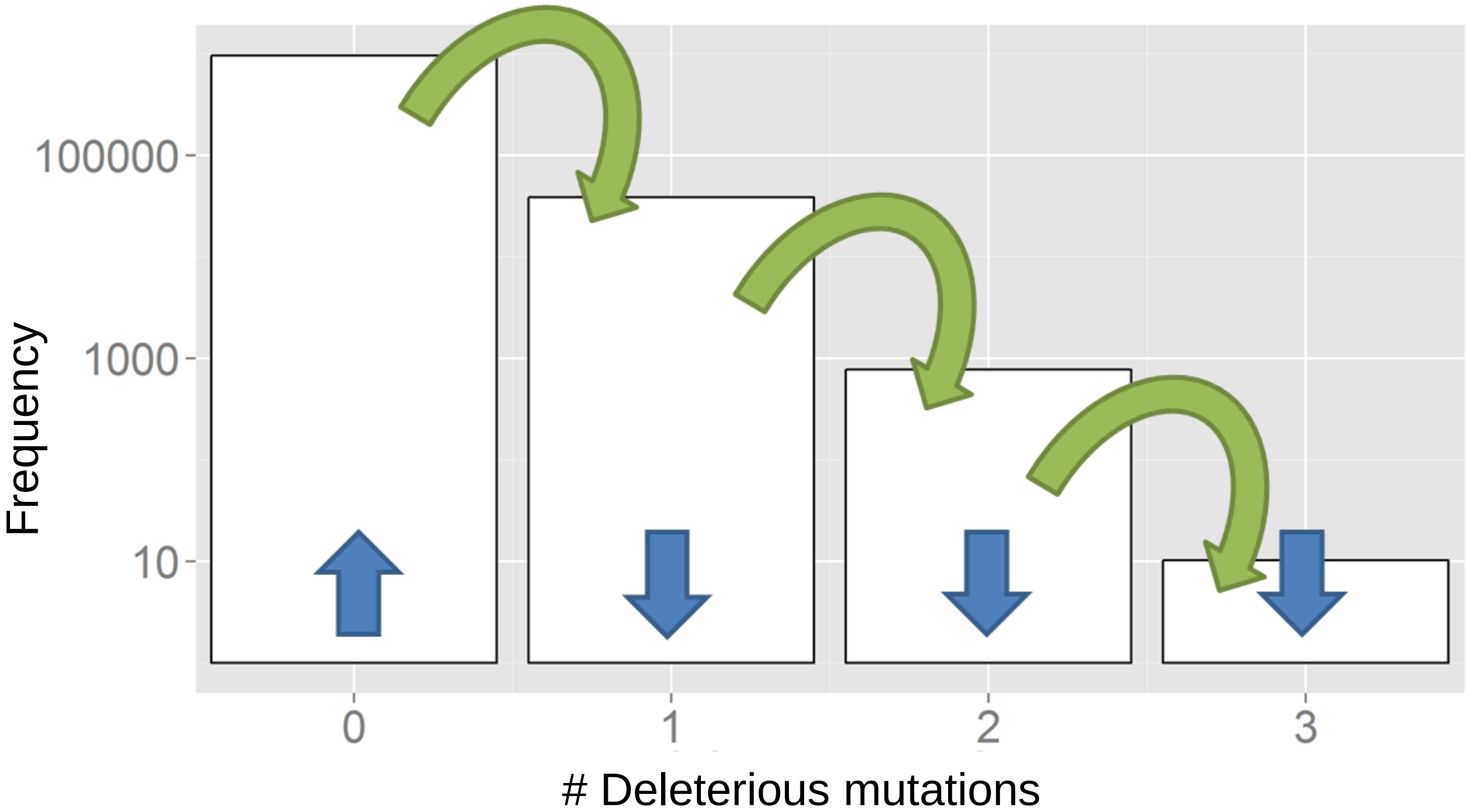
OVERVIEW

- Evolution of the mutation rate
- Static and dynamic environments
- Stress-induced mutation
- Evolution of Stress-induced mutation
- Consequences of Stress-induced mutation

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*
- fitness(*A*) > fitness(*a*)
- The model describes the **change in the frequency of *A***:

$$freq(A)_{next} = \frac{freq(A)_{now} \cdot fitness(A) \cdot Pr(no\ mutation)}{current\ mean\ fitness}$$

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

$$freq(A)_{next} = freq(A)_{now}$$

- With some algebraic operations we get:

$$stable\ mean\ fitness = fitness(A) \cdot \mathrm{Pr}(no\ mutation)$$

SINGLE LOCUS MSB

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

$$stable\ mean\ fitness = fitness(A) \cdot \Pr(no\ mutation)$$

- In words:

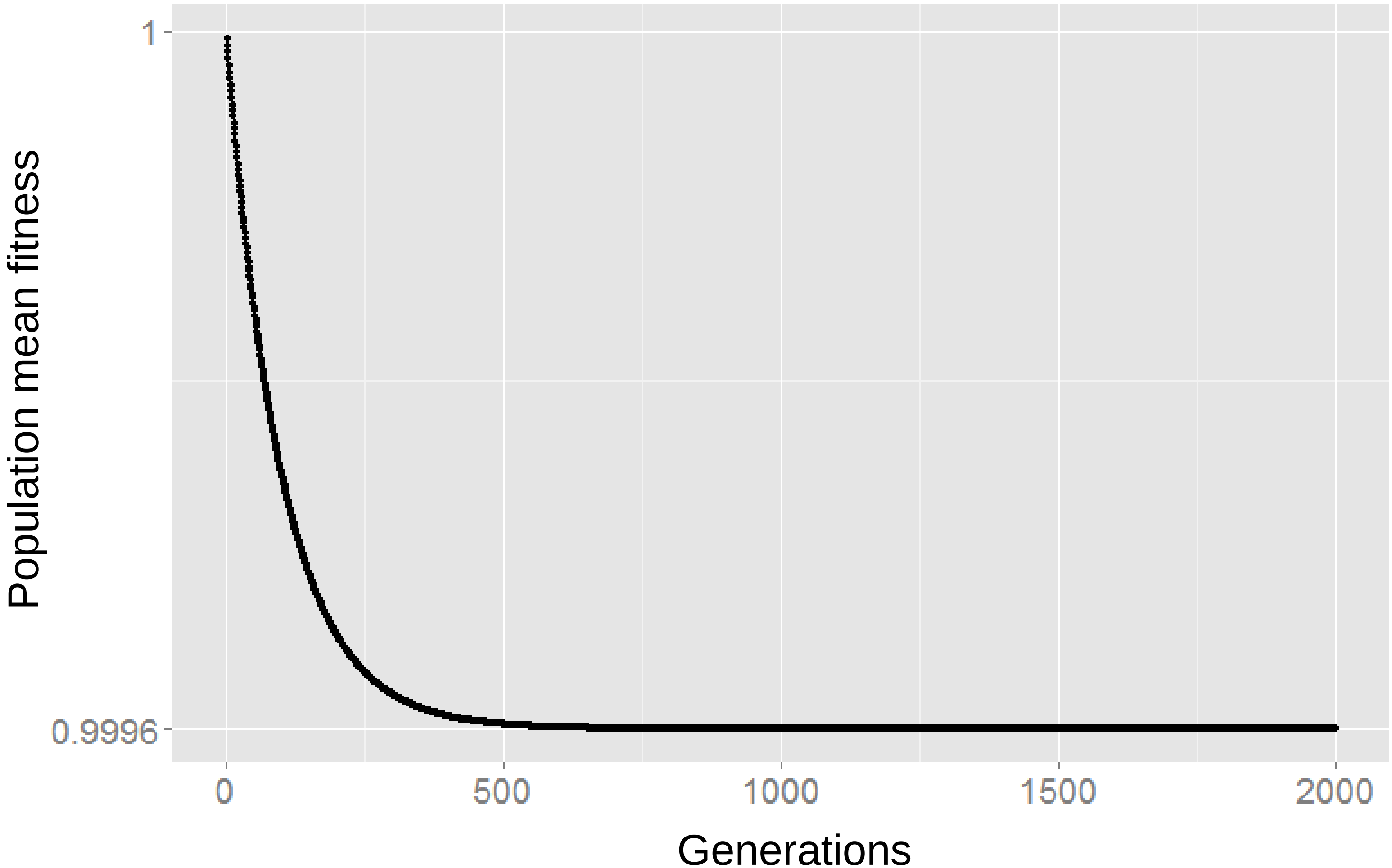
The population mean fitness is equal to

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

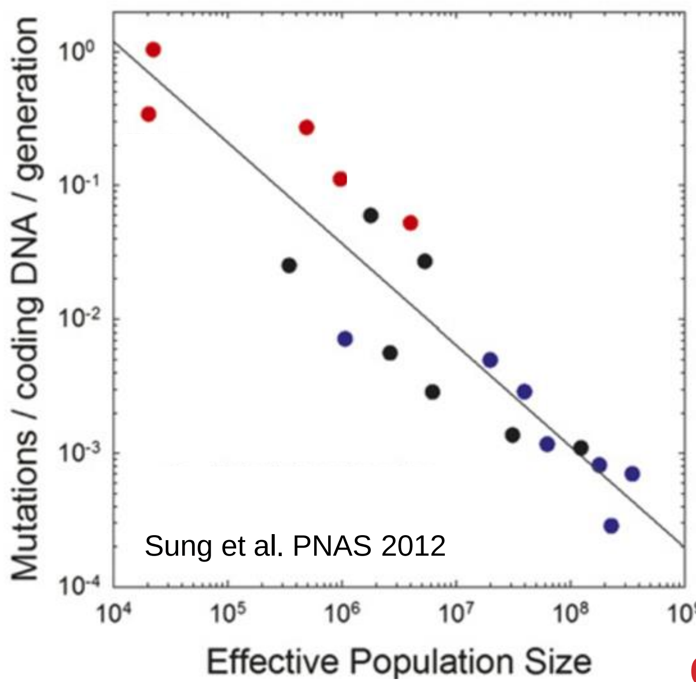
SIMULATION RESULTS



MUTATION RATE IN STATIC ENVIRONMENTS

$$stable\ mean\ fitness \propto \Pr(no\ mutation)$$

- 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"



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, fitness(*A*) < 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)

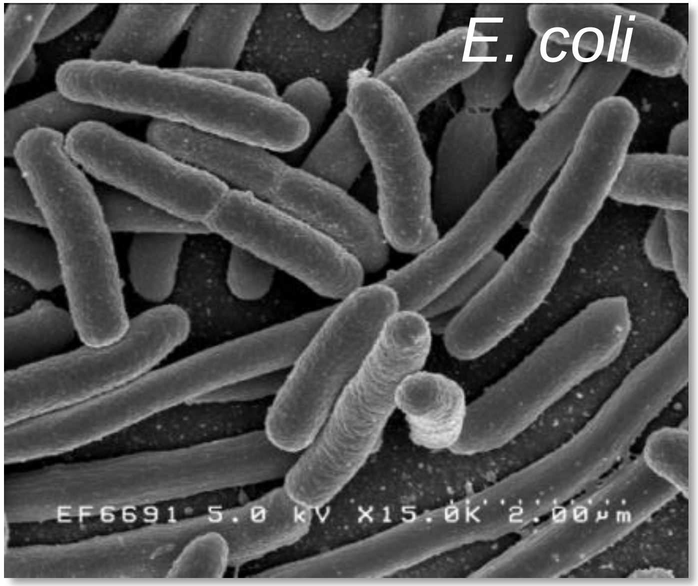
MUTATORS IN OSCILLATING ENVIRONMENTS

The optimal mutation rate is now 1/*n*

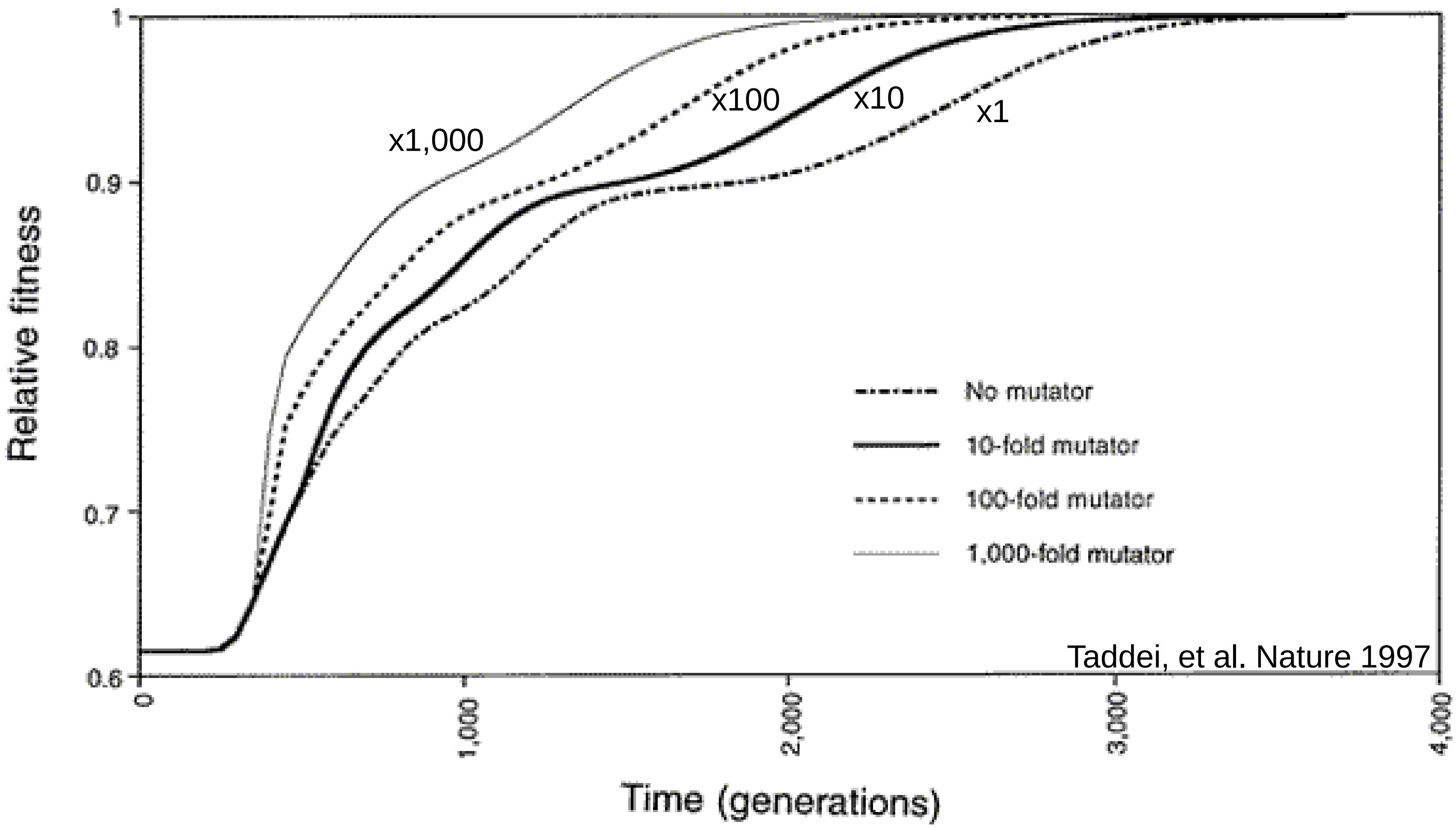
- MSB model -> *n* is large -> slowly changing environments
- Selection for the standing variation generated by mutators
- Local mutators? Same *n* for all loci? Averaging on all loci?

MUTATORS IN ADAPTIVE EVOLUTION

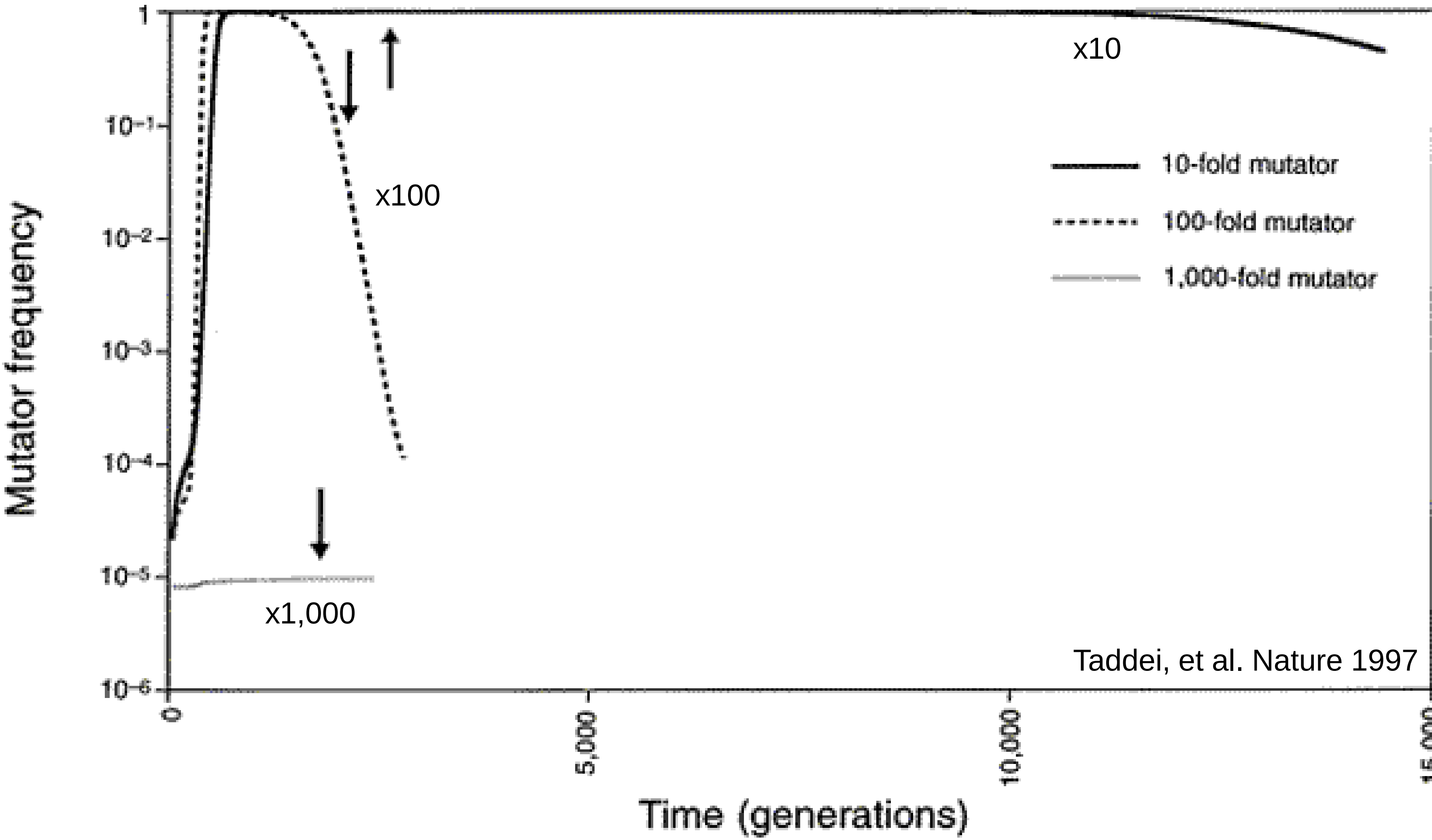
- Model: Taddei et al., Nature 1997
- Multiple-locus simulations
- Single environmental change
- No standing variation
- Mutation at the mutator locus



ADAPTATION WITH MUTATOR ALLELES



RISE AND FALL OF THE MUTATOR ALLELE

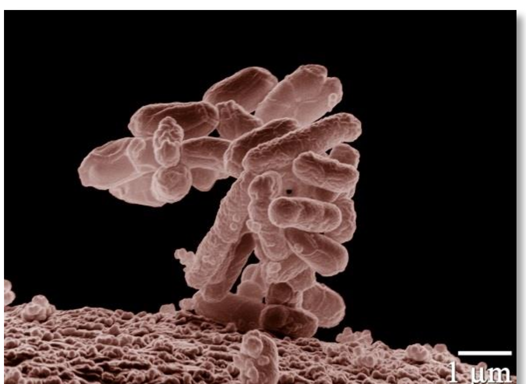


VARIABILITY IN MUTATION RATES

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

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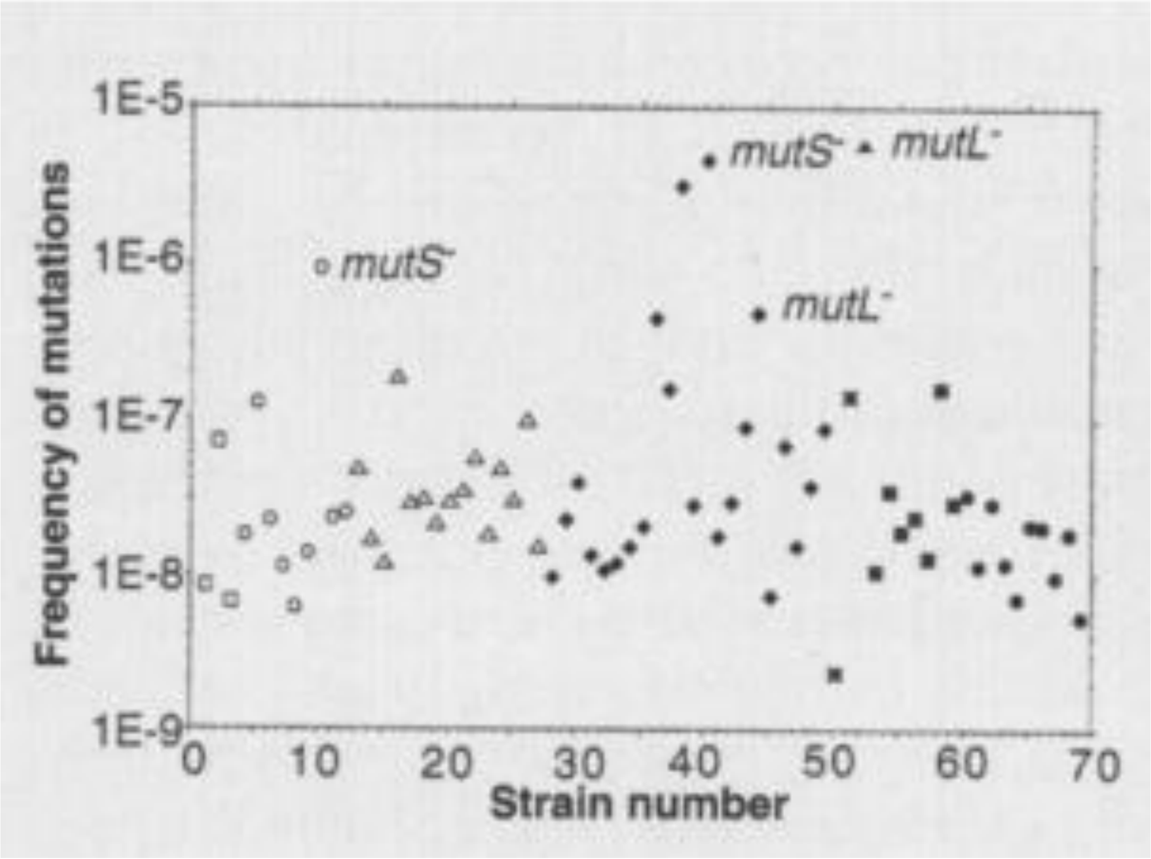
VARIABILITY IN MUTATION RATES

Within species

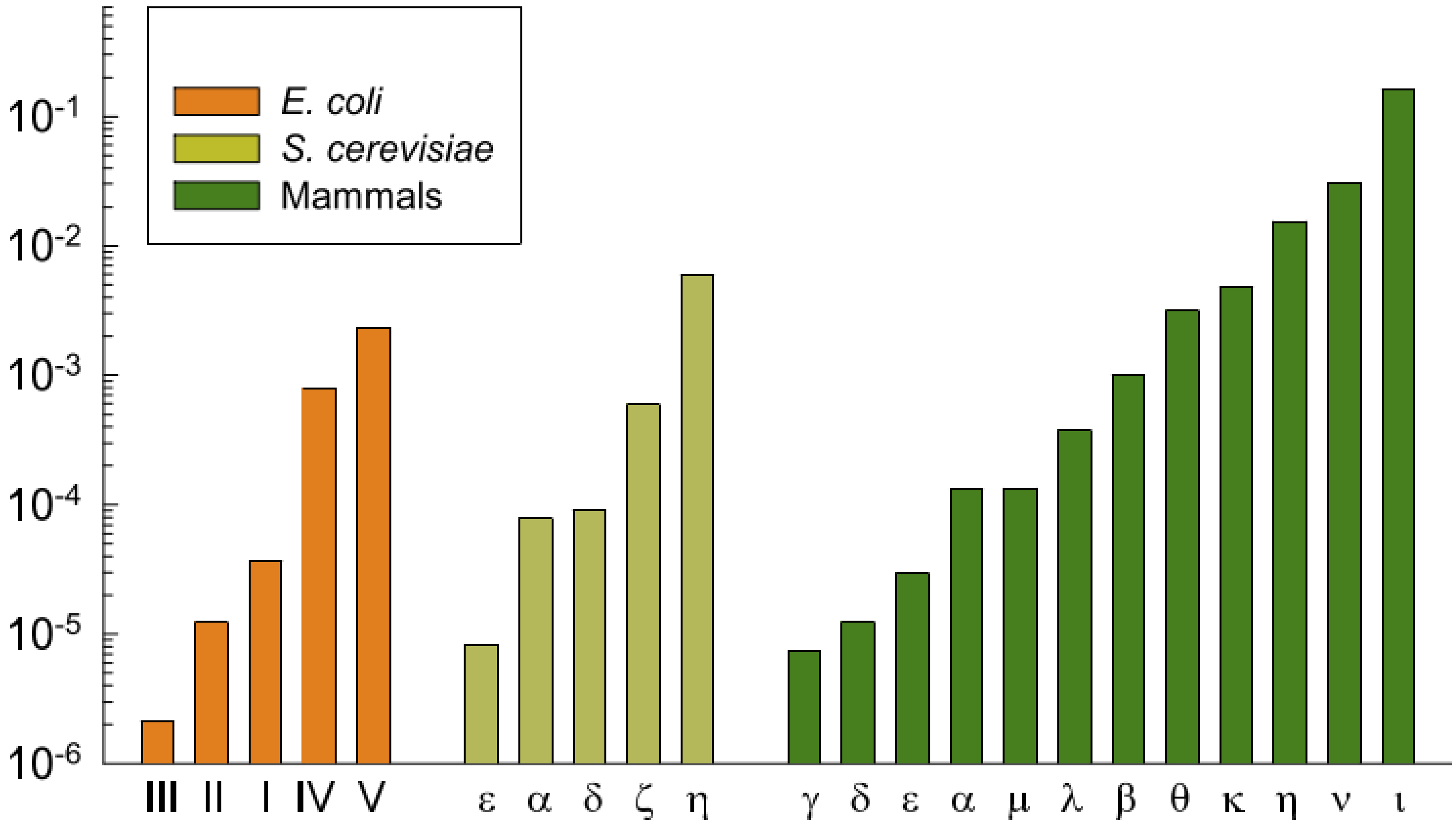
Mutation rate in 69 natural populations of *E. coli* – Matic et al. 1997



VARIABILITY IN MUTATION RATES

Within individuals

DNA polymerase error rate – Lynch 2011

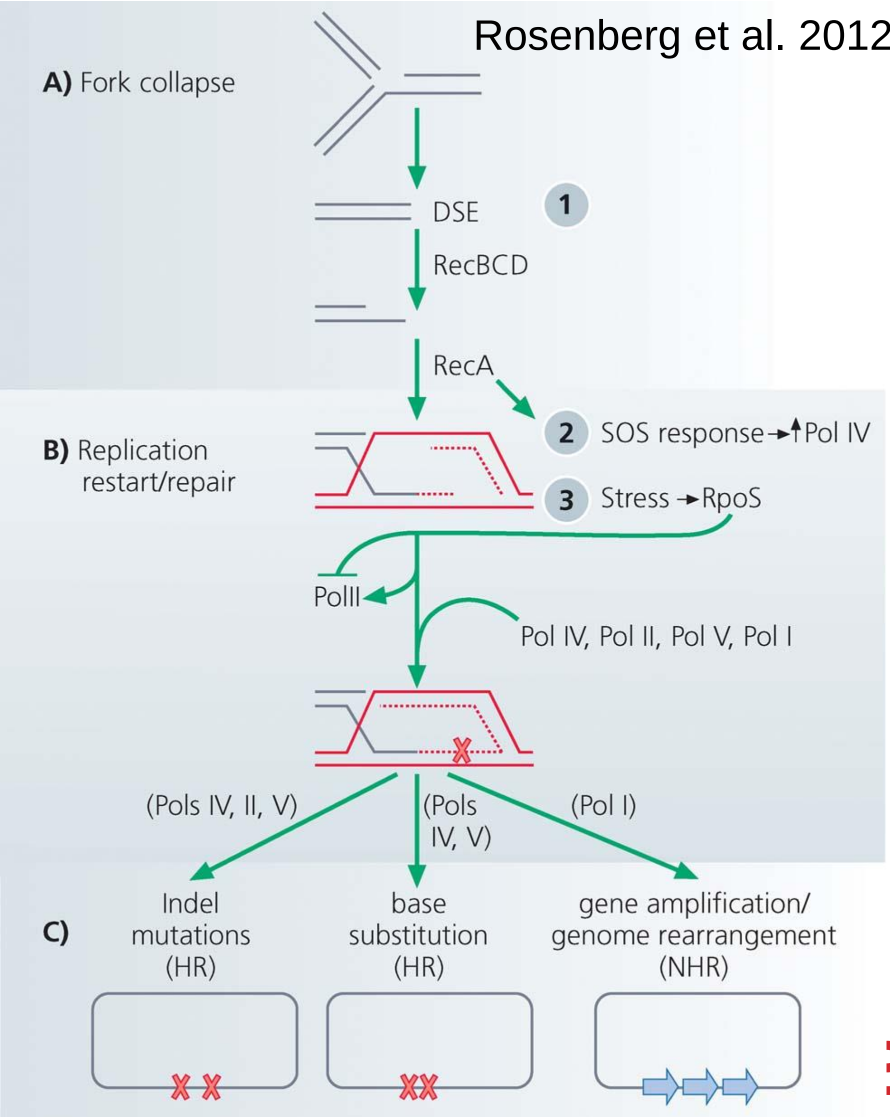


STRESS-INDUCED MUTATION

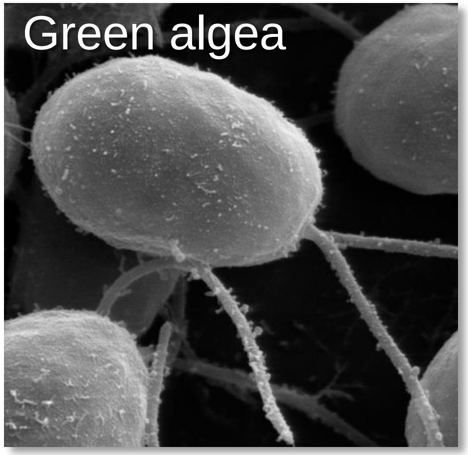
In *E. coli:*

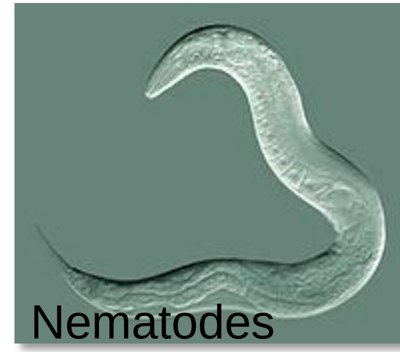
- Error prone polymerase induced by stress responses:
  - SOS response
  - DNA damage
  - Starvation
- Mismatch repair system
- Other mechanisms:
  - Galhardo et al. 2007
  - Al Mamun, Science 2012

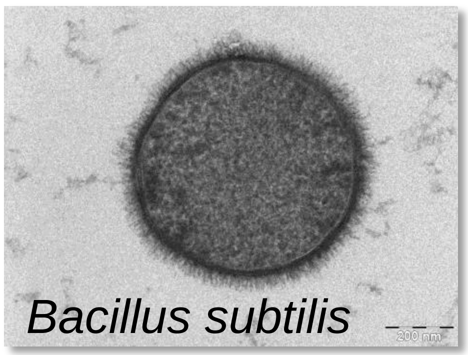
Rosenberg et al. 2012



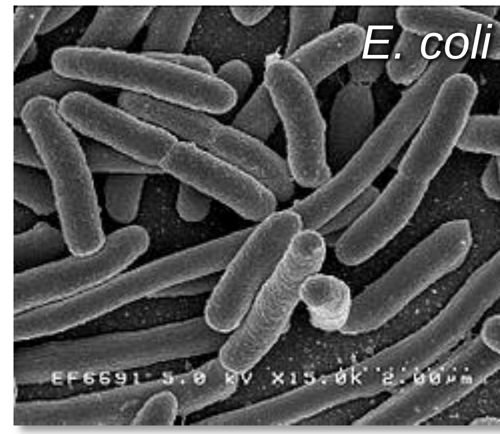
EVIDENCE


Green algea

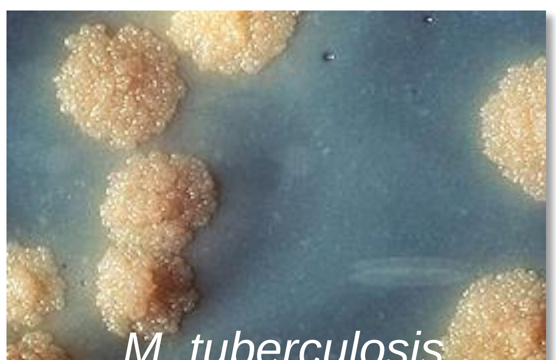

Nematodes

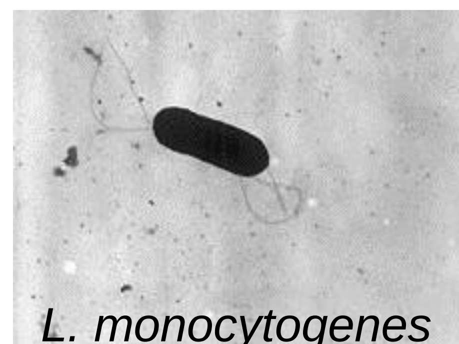

Bacillus subtilis


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

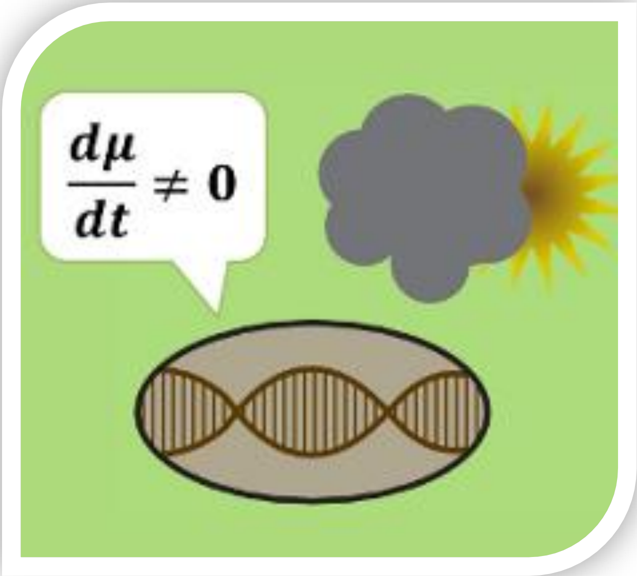
Alternative non-adaptive hypotheses

Cost of fidelity

Drift barrier hypothesis

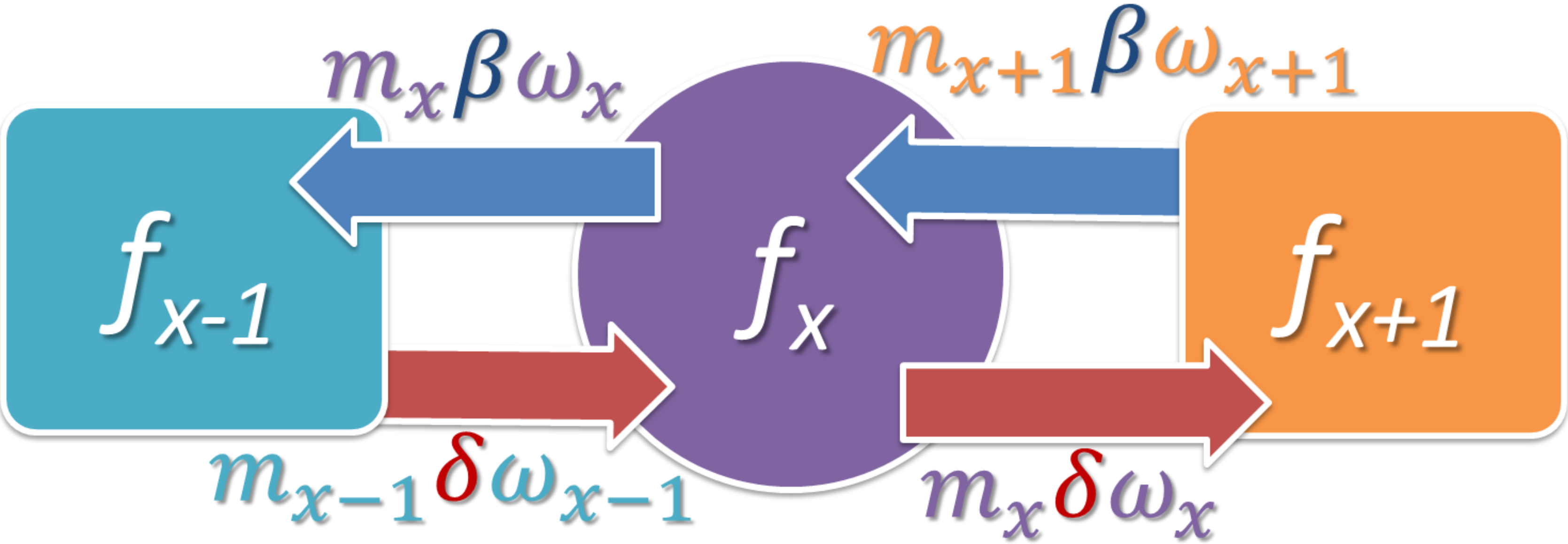
Adaptive hypothesis

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

STATIC ENVIRONMENT

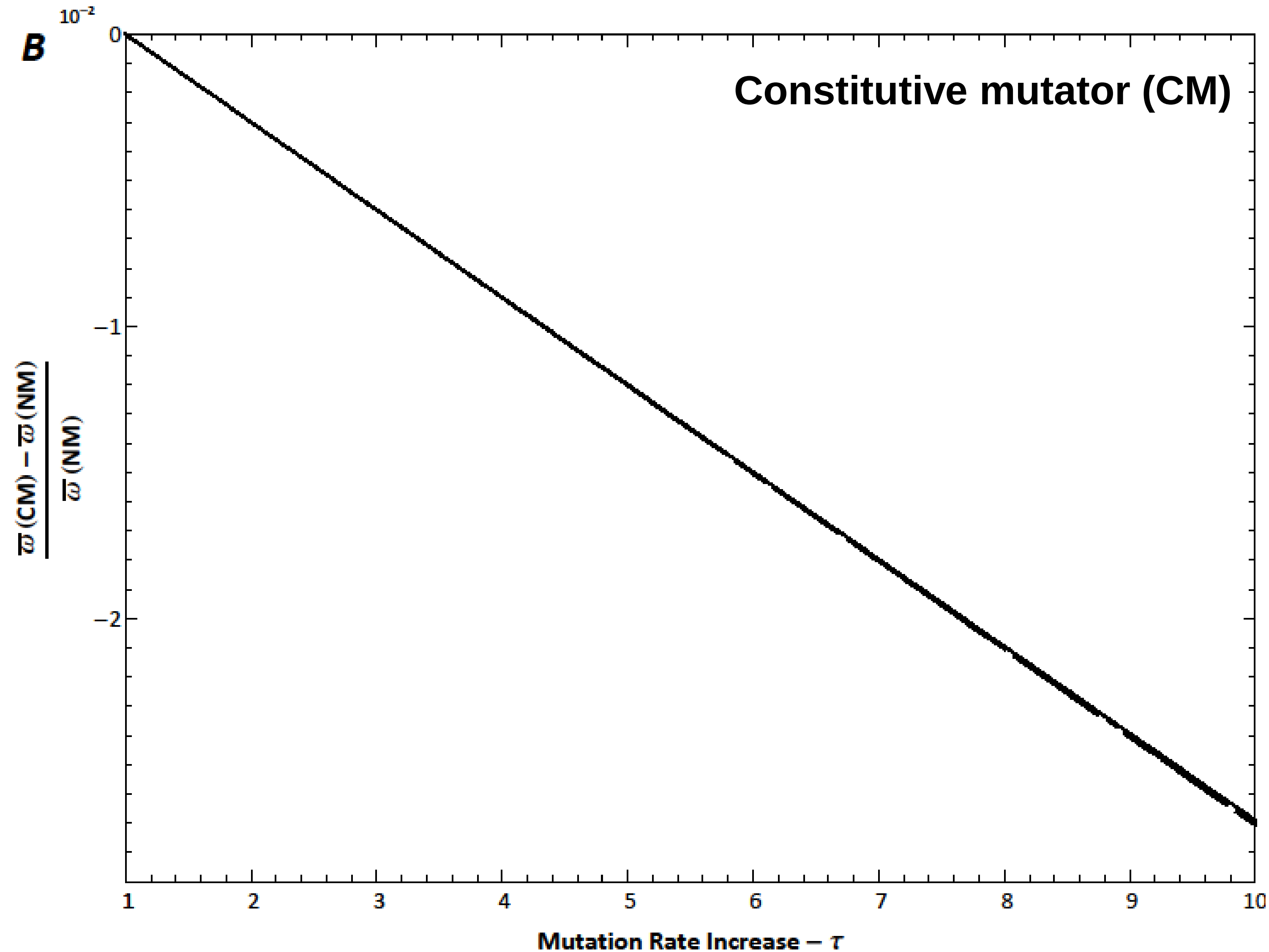
General solution

$$sign \frac{\partial \overline{\omega}}{\partial m_x} = sign\,(\overline{\omega} - \omega_x)$$

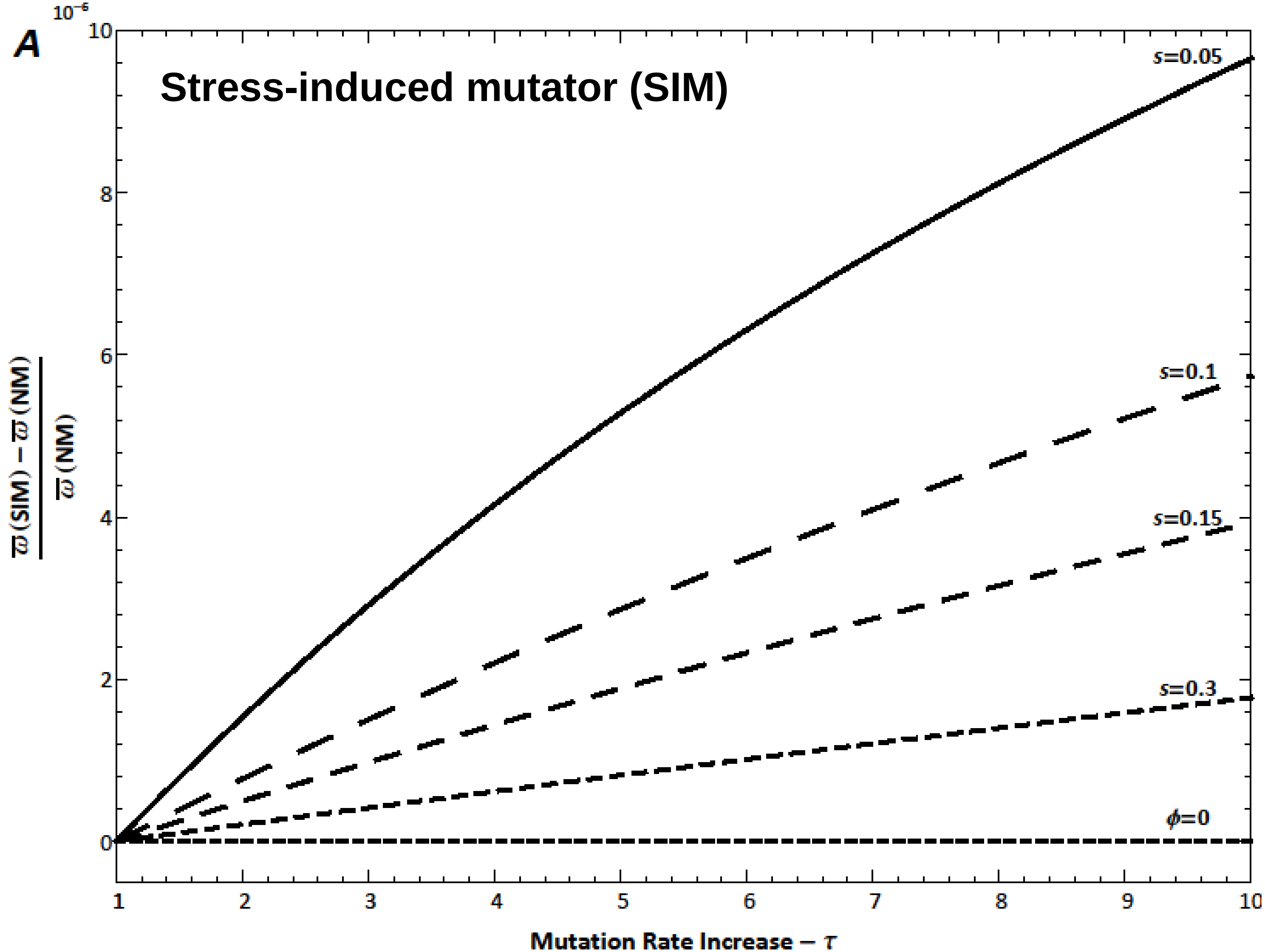
"Increasing the mutation rate of individuals with below average fitness increases the population mean fitness"

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

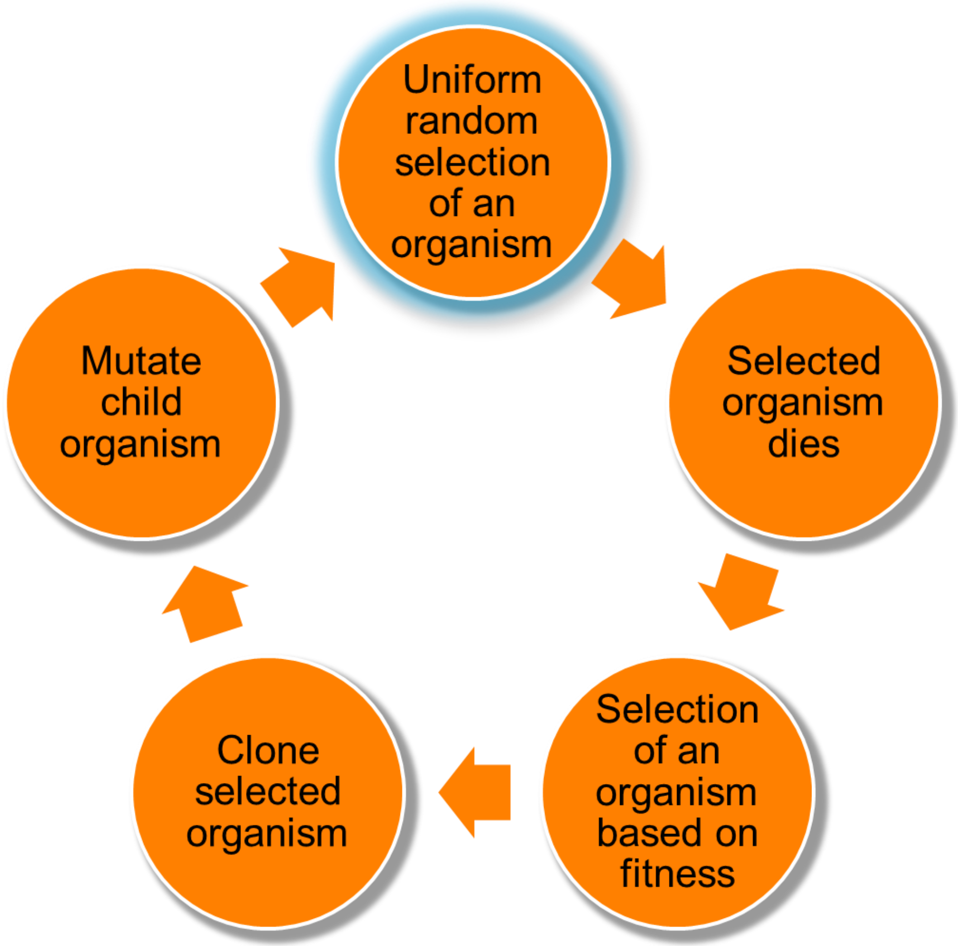
Overlapping generations

No recombination

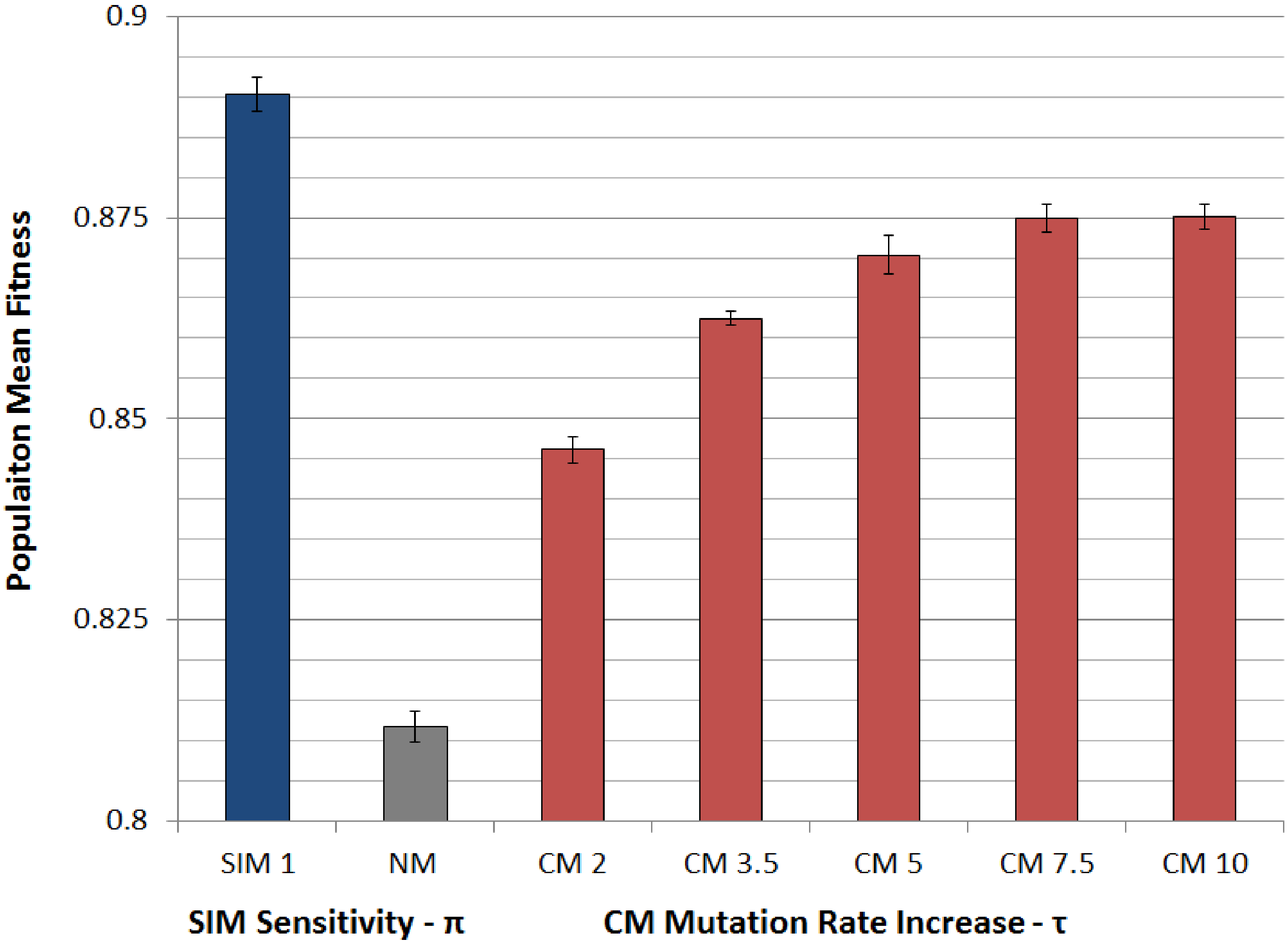
No segregation

No mutations at mutator locus

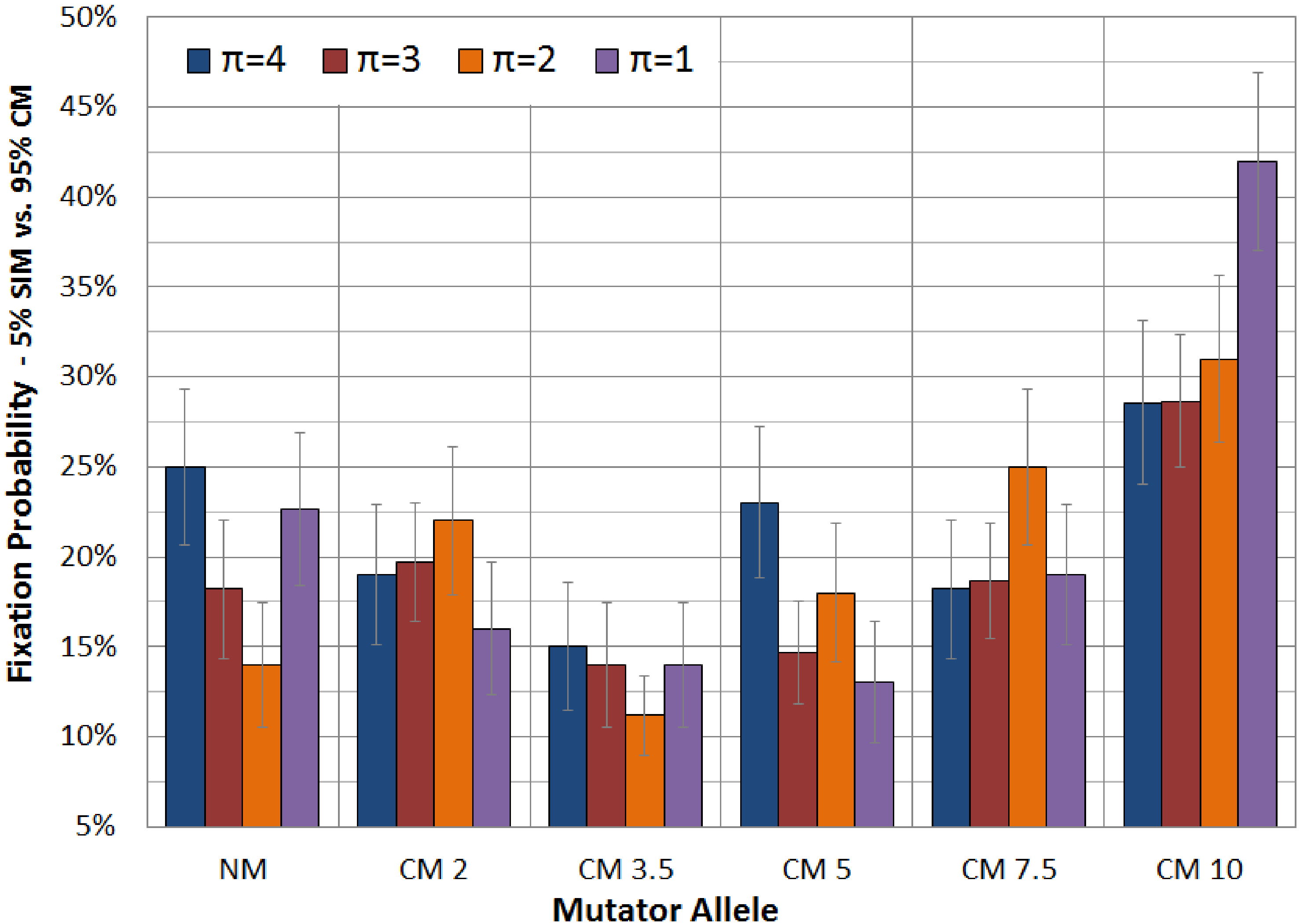
Environmental changes



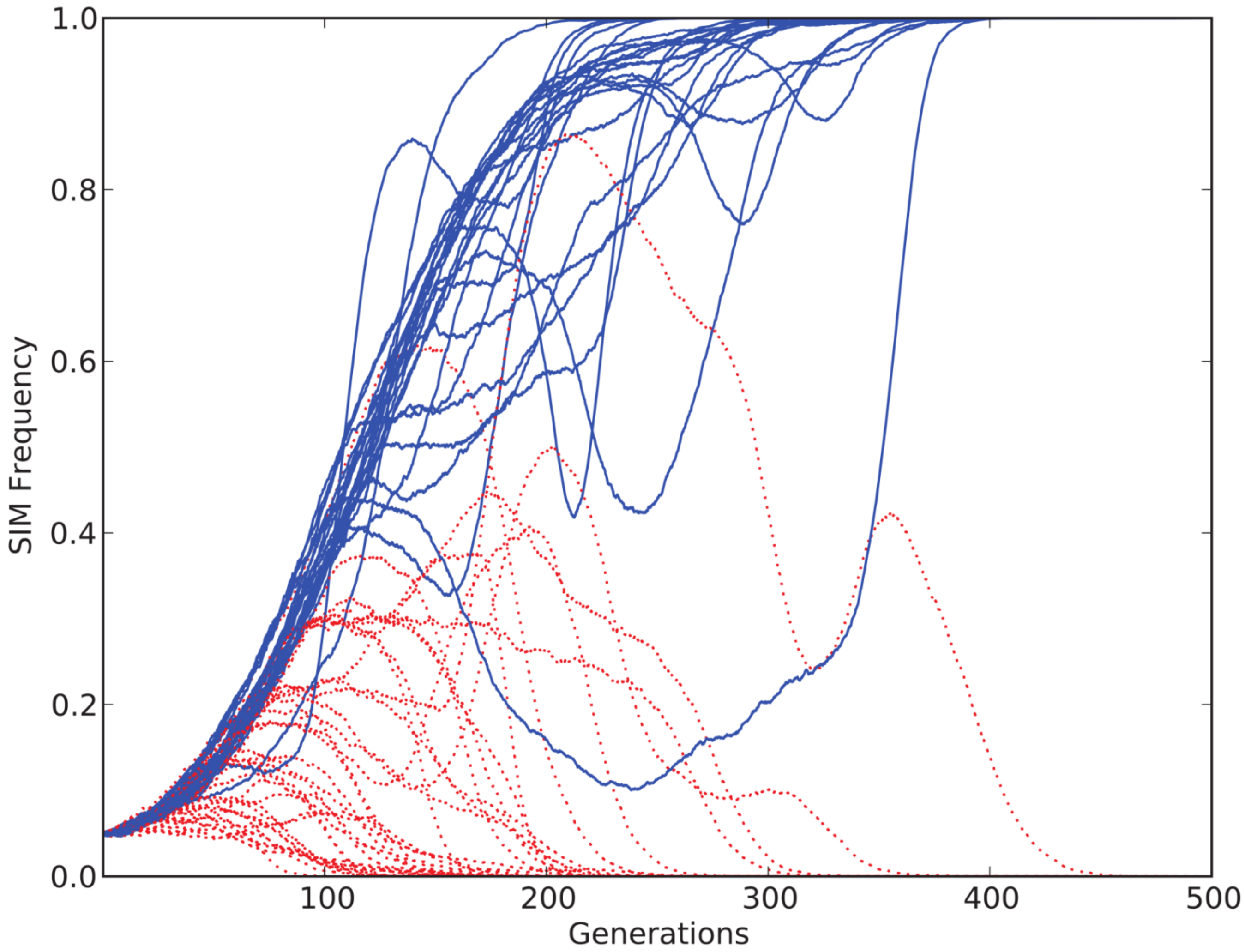
POPULATIONS WITH SIM ARE FITTER



SIM WINS COMPETITIONS



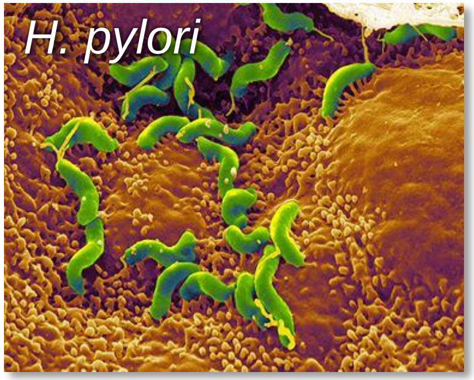
SIM WINS COMPETITIONS



SUMMARY: EVOLUTION OF STRESS-INDUCED MUTATION

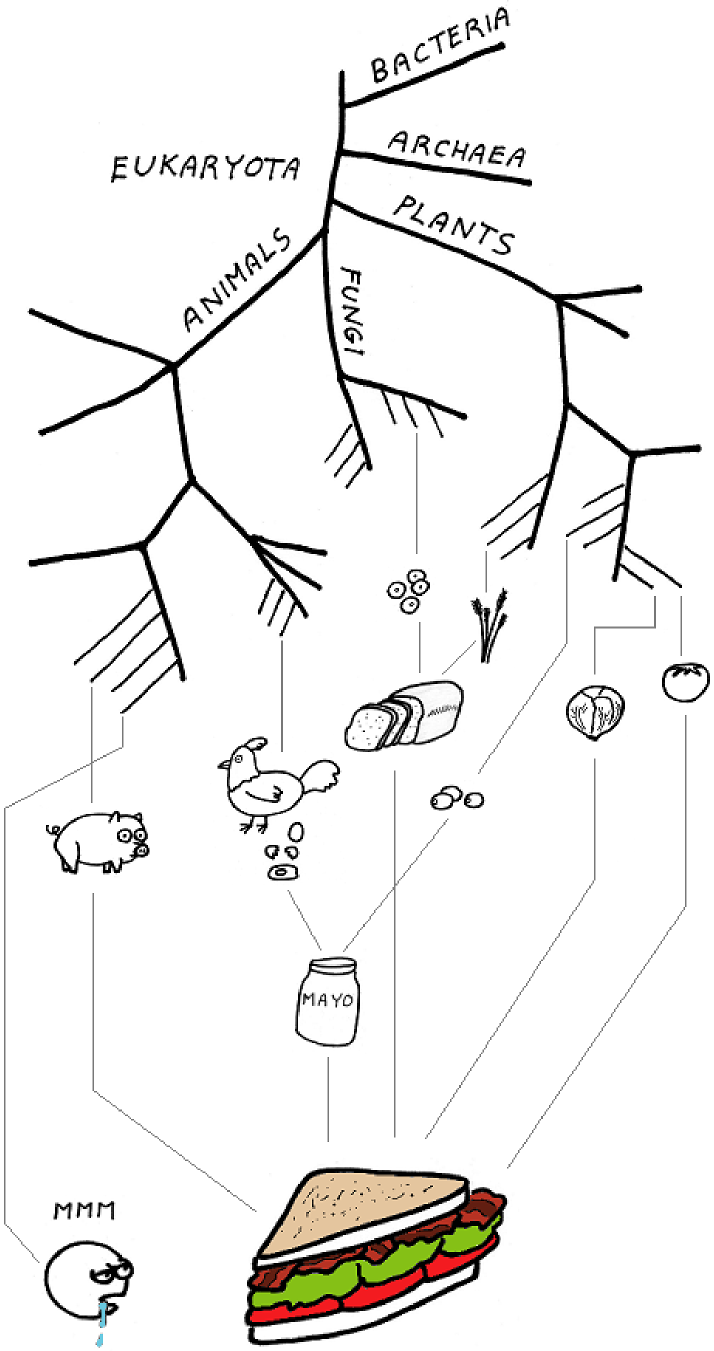
- Stress-induced mutators evolve:
  - In finite & infinite populations
  - In constant & changing environments

- **Second-order selection** can lead to the evolution of stress-induced mutagenesis in asexual populations
- Selection for evolvability



CONSEQUENCES OF STRESS-INDUCED MUTATION RATE

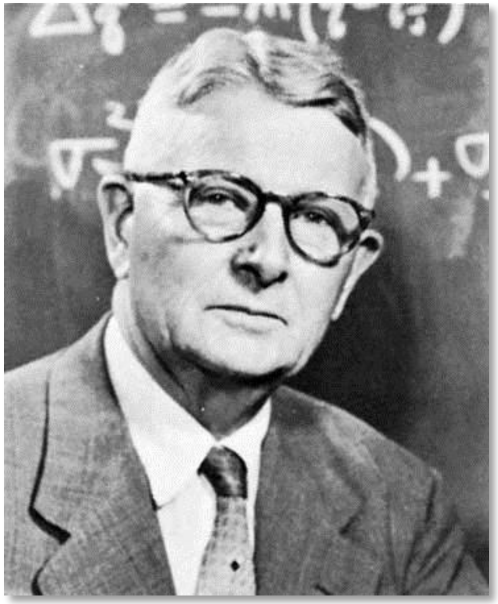
How does SIM affect evolution?



ADAPTIVE PEAK SHIFTS

This problem was introduces 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

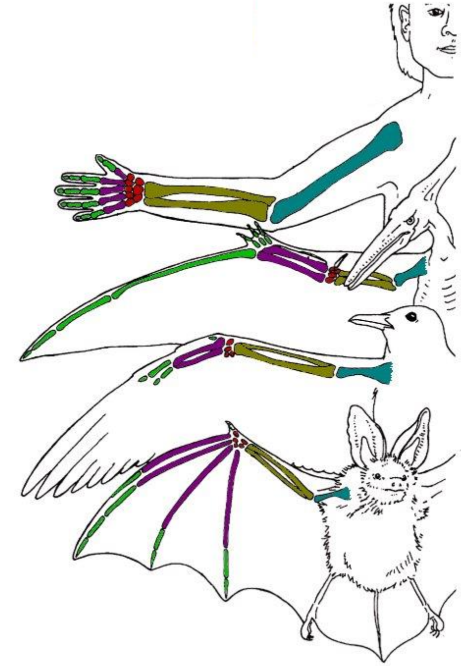
- Flying with heavy bones is costly
- Walking and climbing with light bones is dangerous

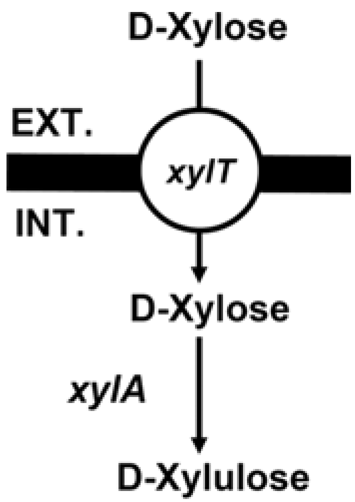
New metabolic pathway

- 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

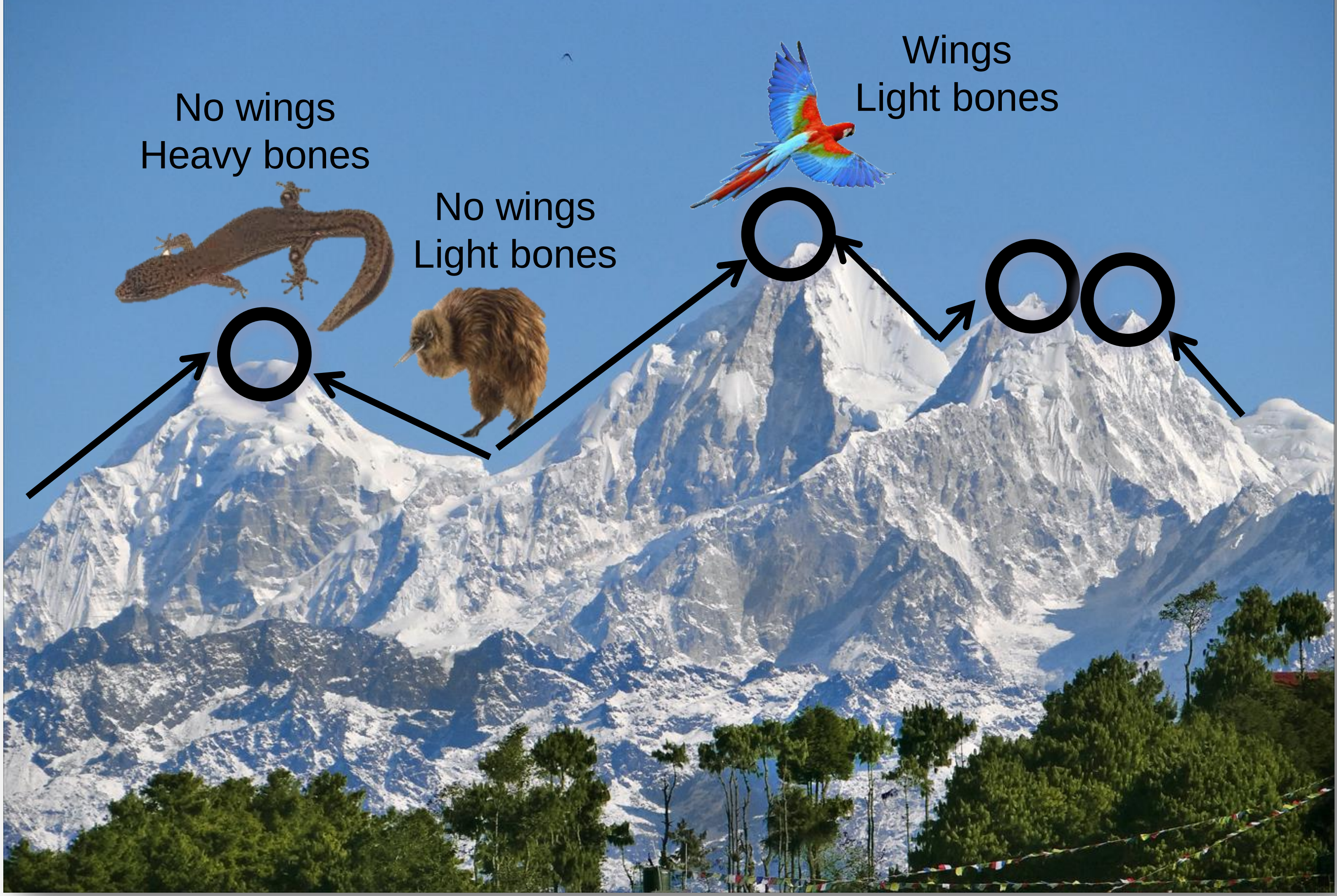




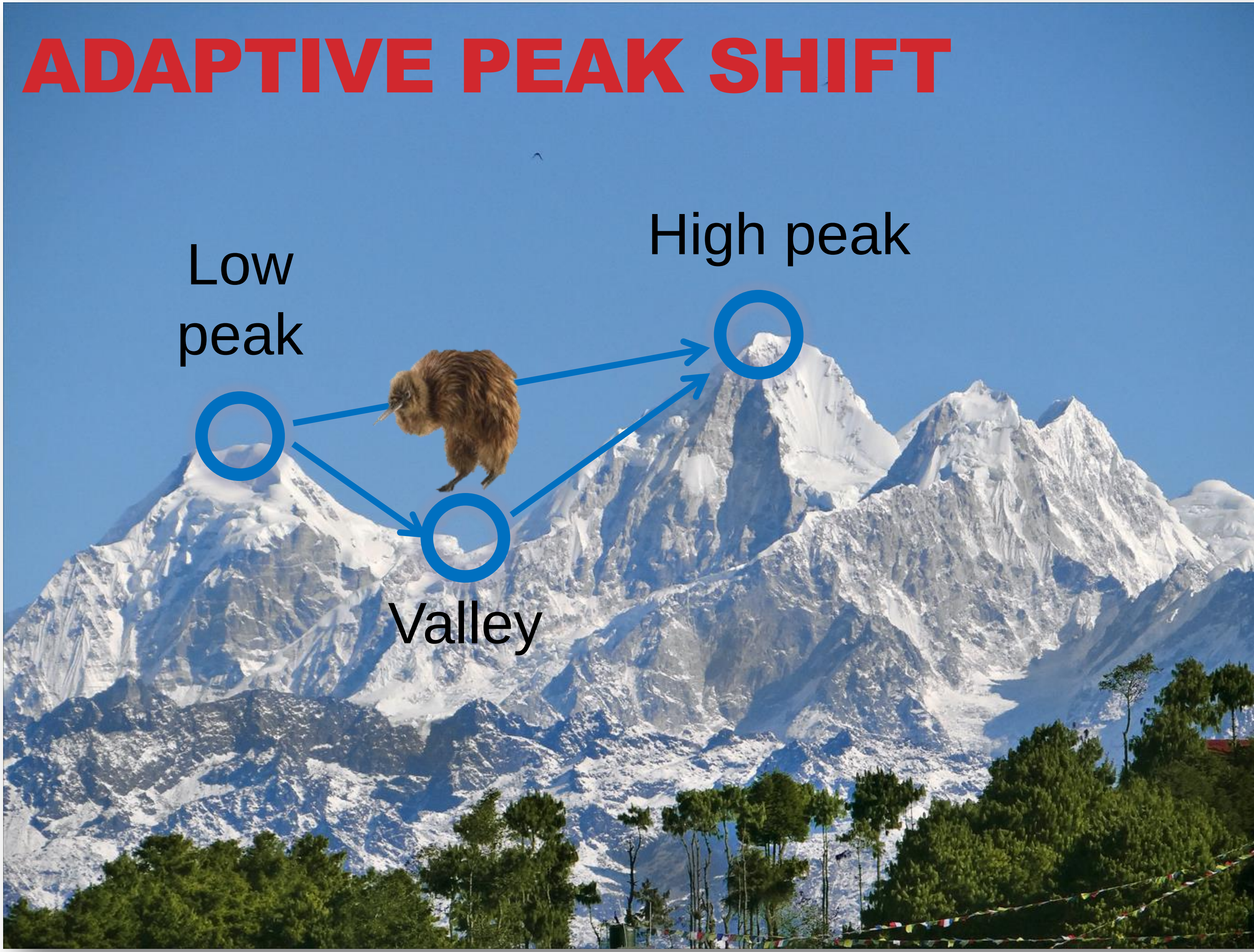
Xiao et al. 2011

SIMPLE LANDSCAPE

RUGGED LANDSCAPE

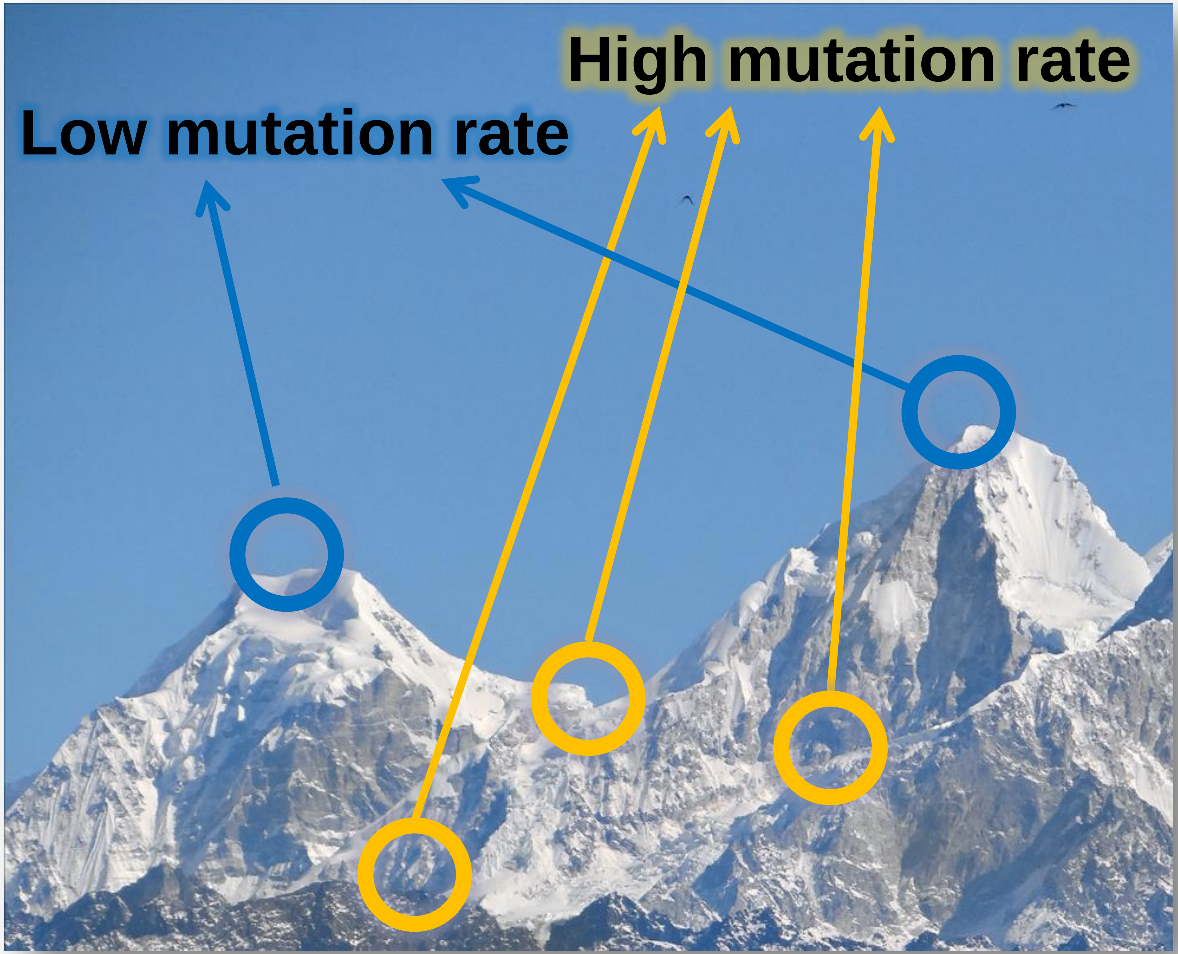


ADAPTIVE PEAK SHIFT

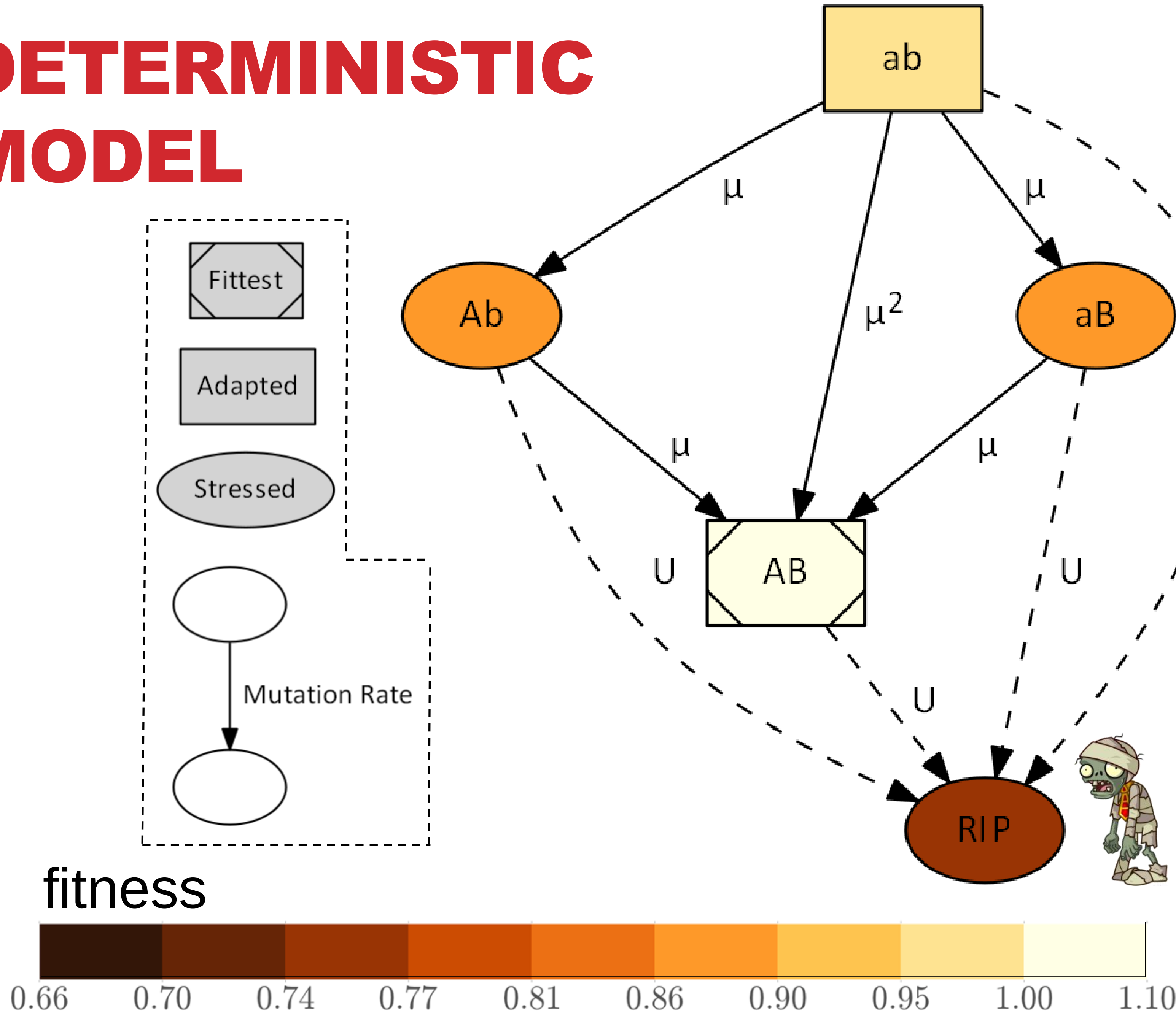


SIM & RUGGED LANDSCAPE

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



DETERMINISTIC MODEL



DETERMINISTIC RESULTS

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

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

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

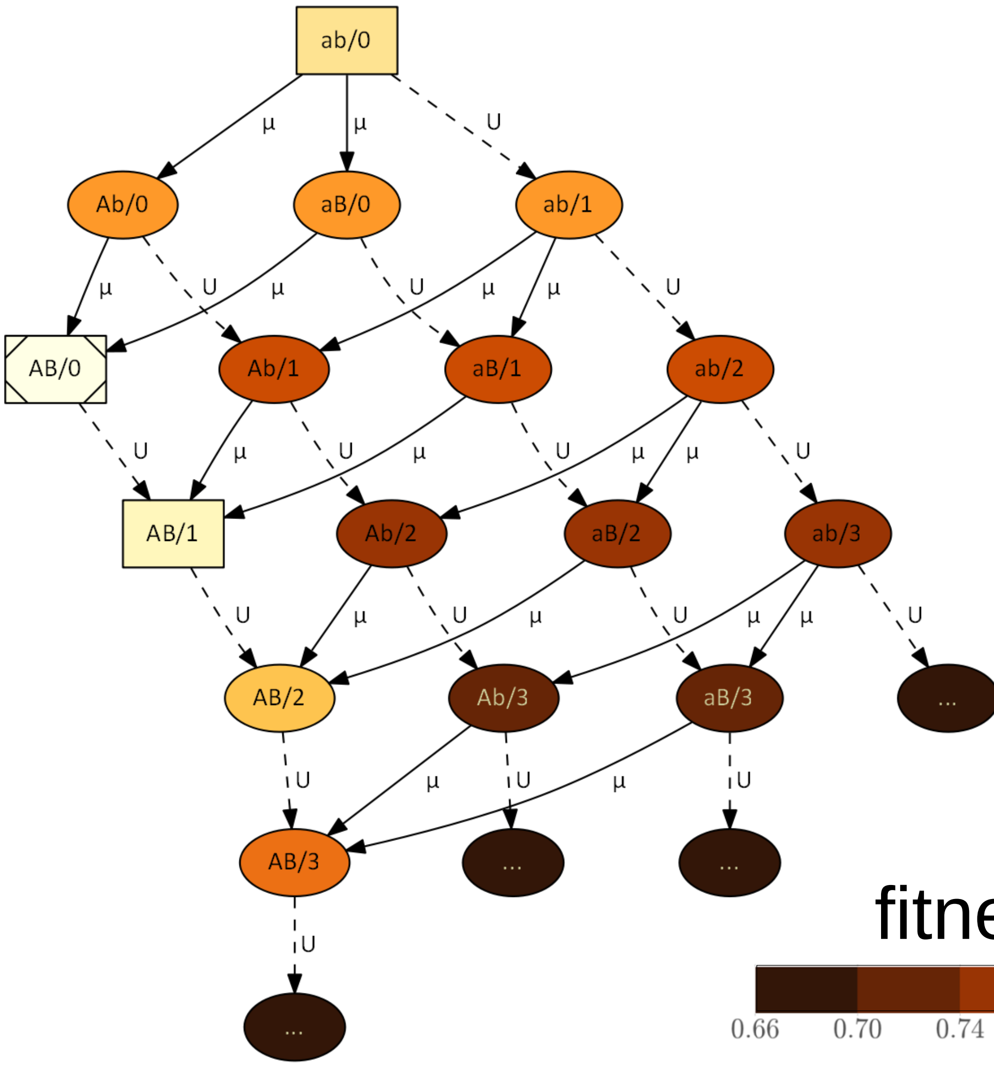
$$\nu_{CM} \approx \tau^2 \cdot \nu_{NM}$$

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

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

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

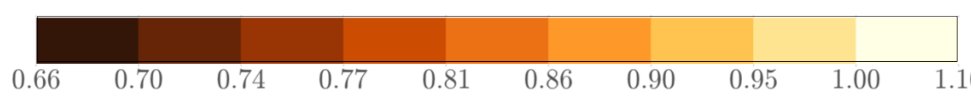
STOCHASTIC MODEL



No MSB assumption

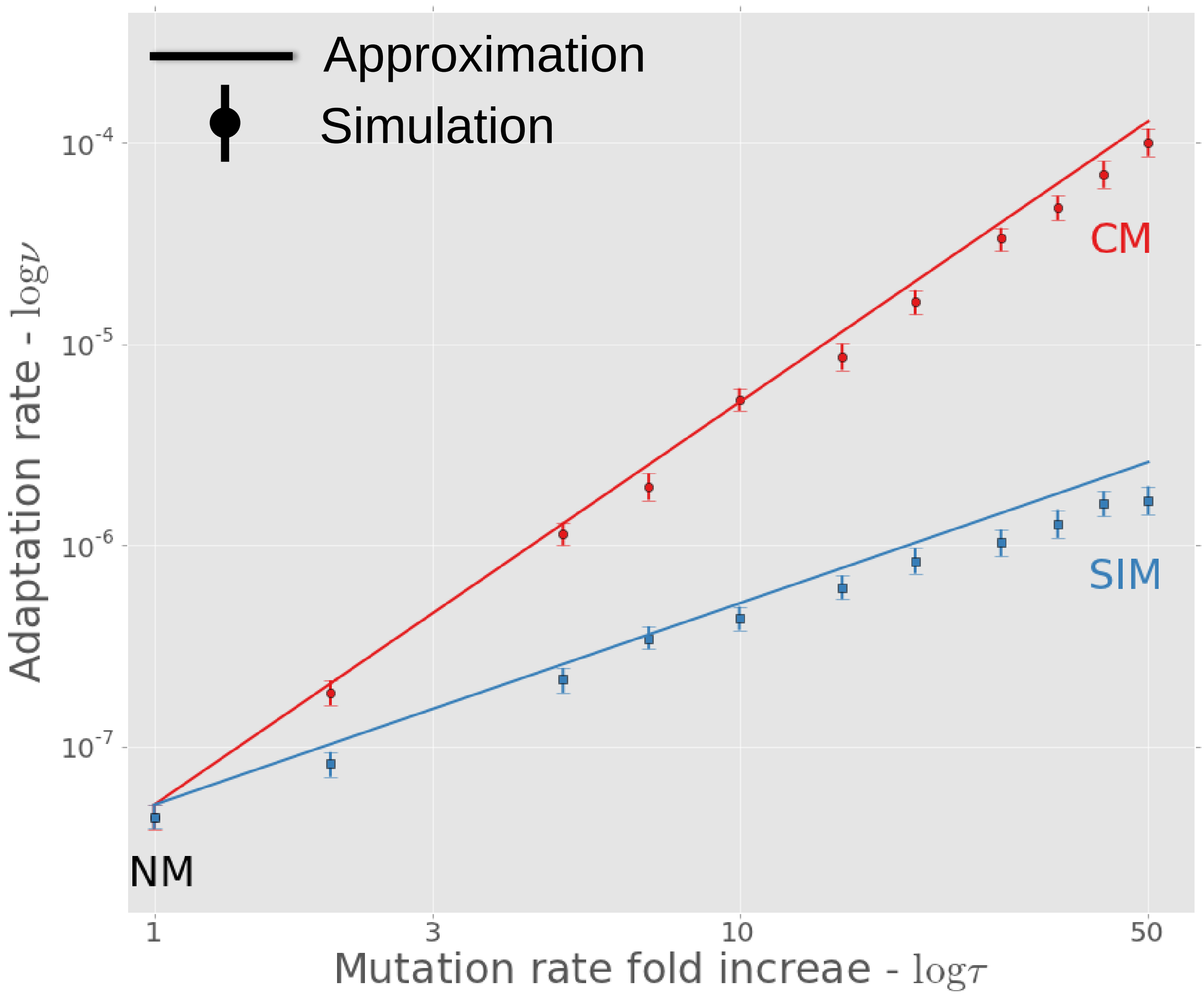
No 

fitness

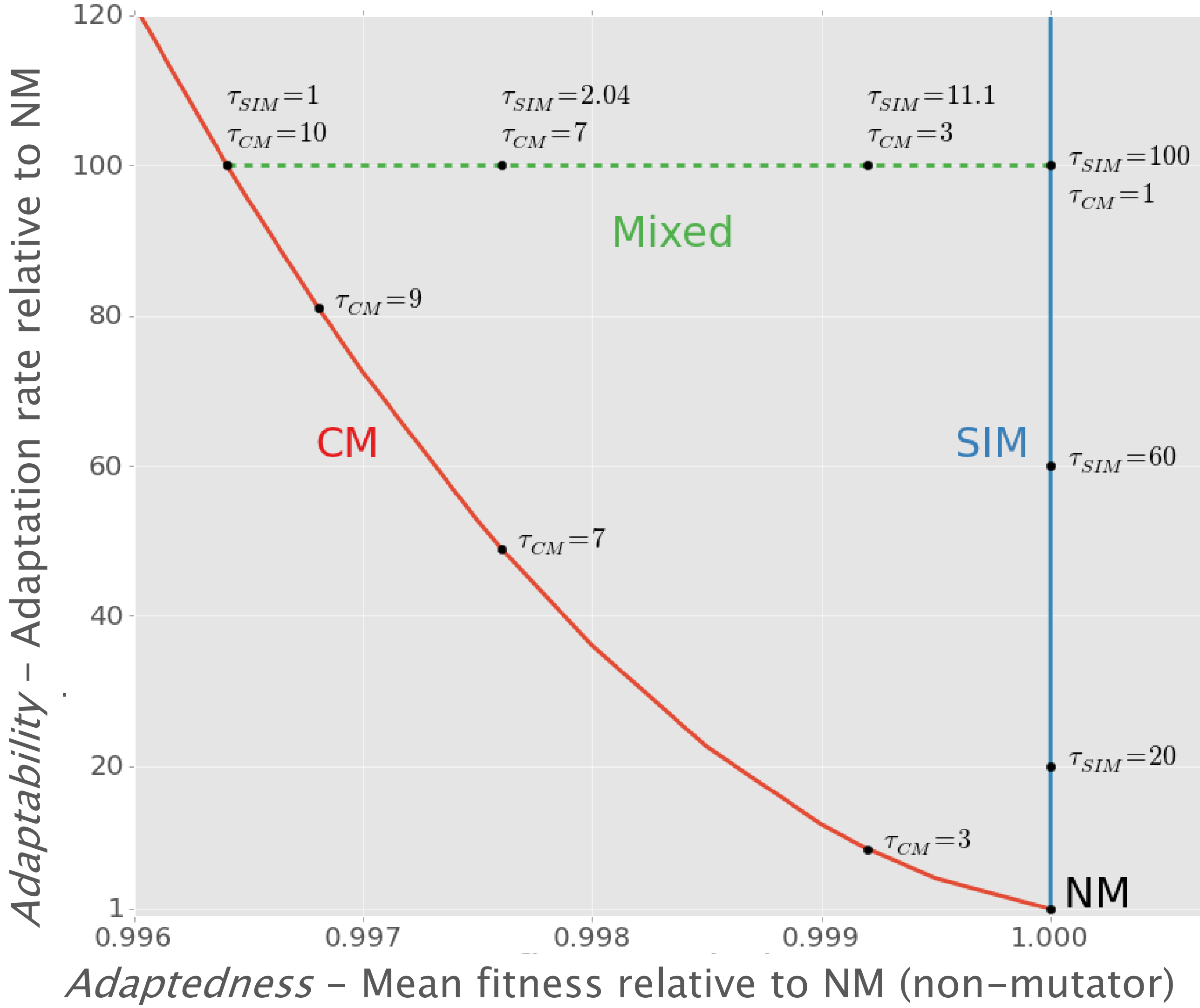


$$\nu_{CM} \approx \tau^2 \cdot \nu_{NM}$$
$$\nu_{SIM} \approx \tau \cdot \nu_{NM}$$

ADAPTATION RATE



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*

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