Stress-Induced Mutagenesis: Evolutionary perspective

Yoav Ram
Hadany Lab
Tel-Aviv University
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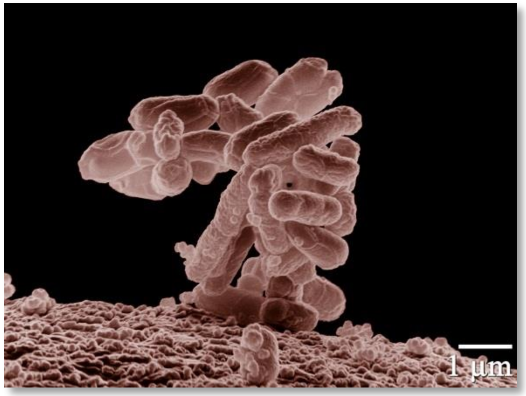
Variability in mutation rates

Between species

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

Bacteria: 0.0004
Wielgoss et al. G3 2011

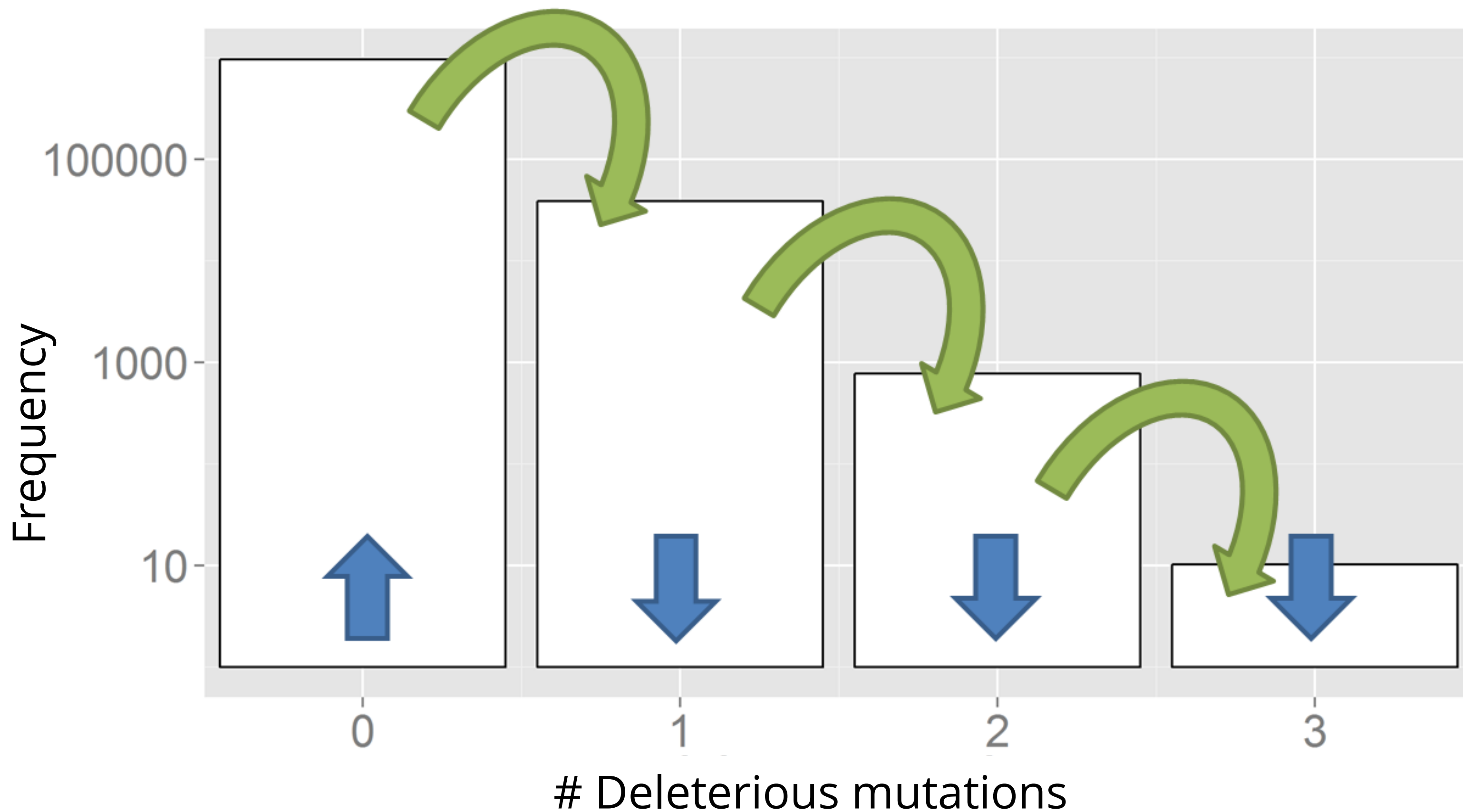


Flies: 0.455
Keightley et al. Gen Res 2009

Humans: 41
Lynch, PNAS 2010

Evolution in constant environments

- Directional selection without change
- A balance between mutation and



Mutation rate in constant environments

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

Changing environments

In changing environments rapid adaptation can be favored by natural selection (*adaptability*)

The **mutation rate** must balance between ***adaptability*** and ***adaptedness***

Leigh 1973

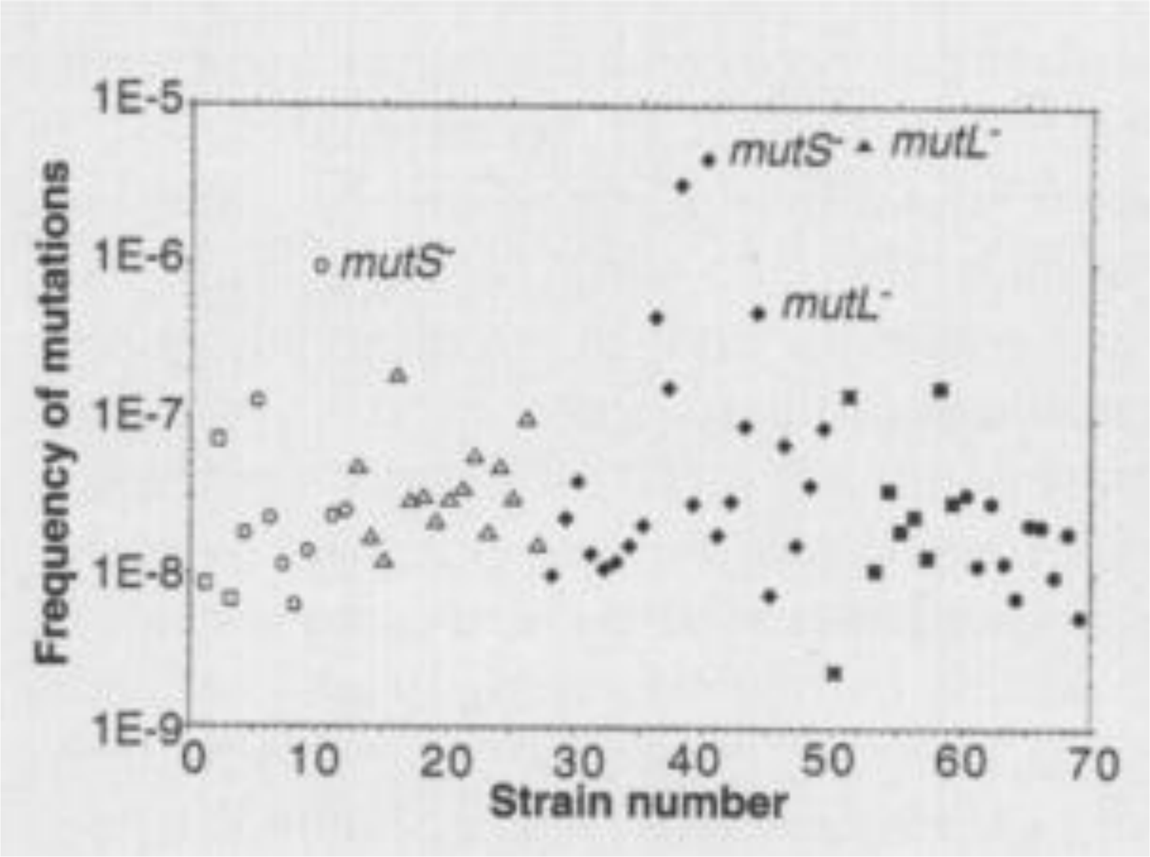
Shujun Wong 2009

Variability in mutation rates

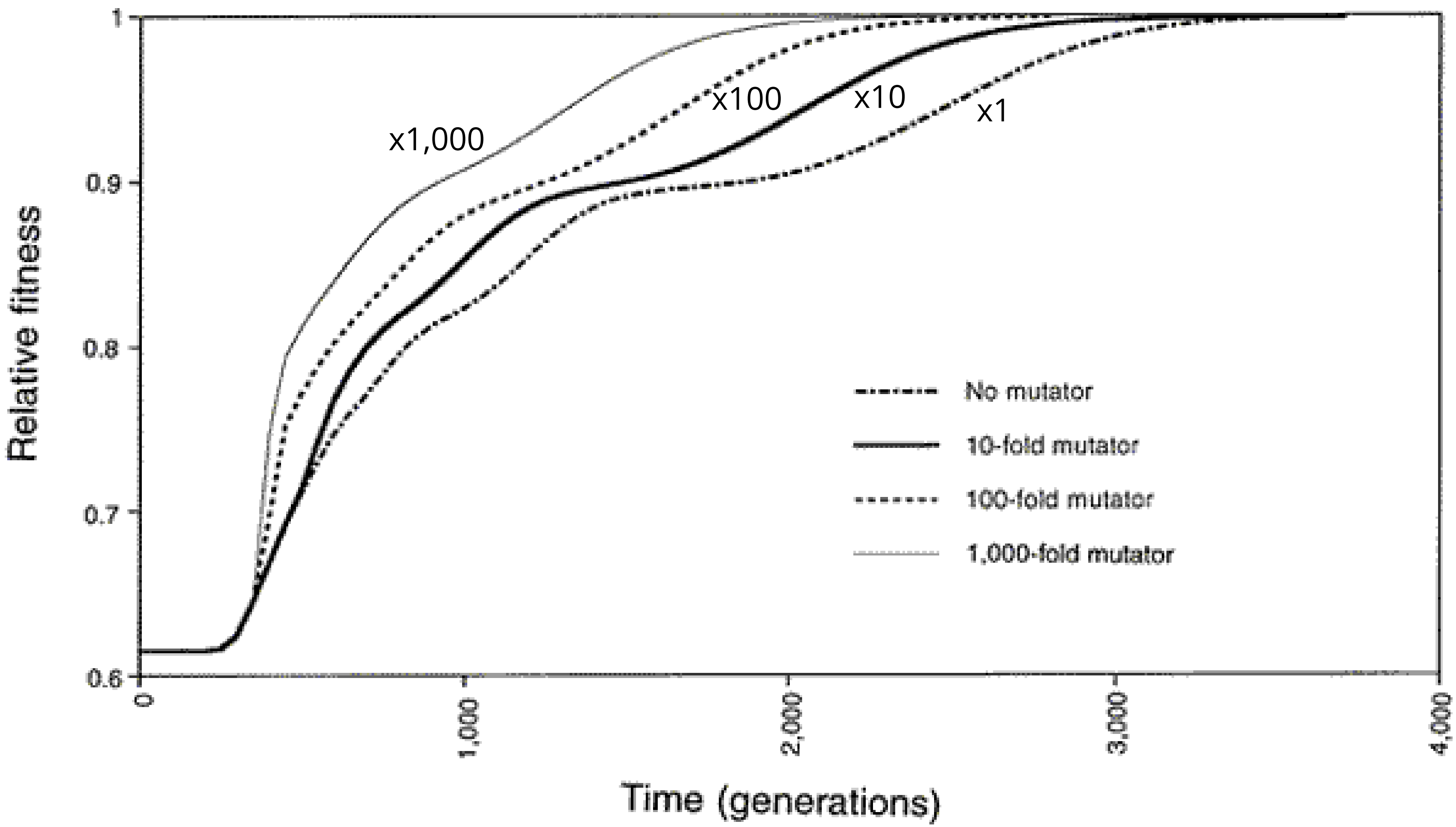
Within species

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

Matic et al. 1997



Adaptation with mutator alleles



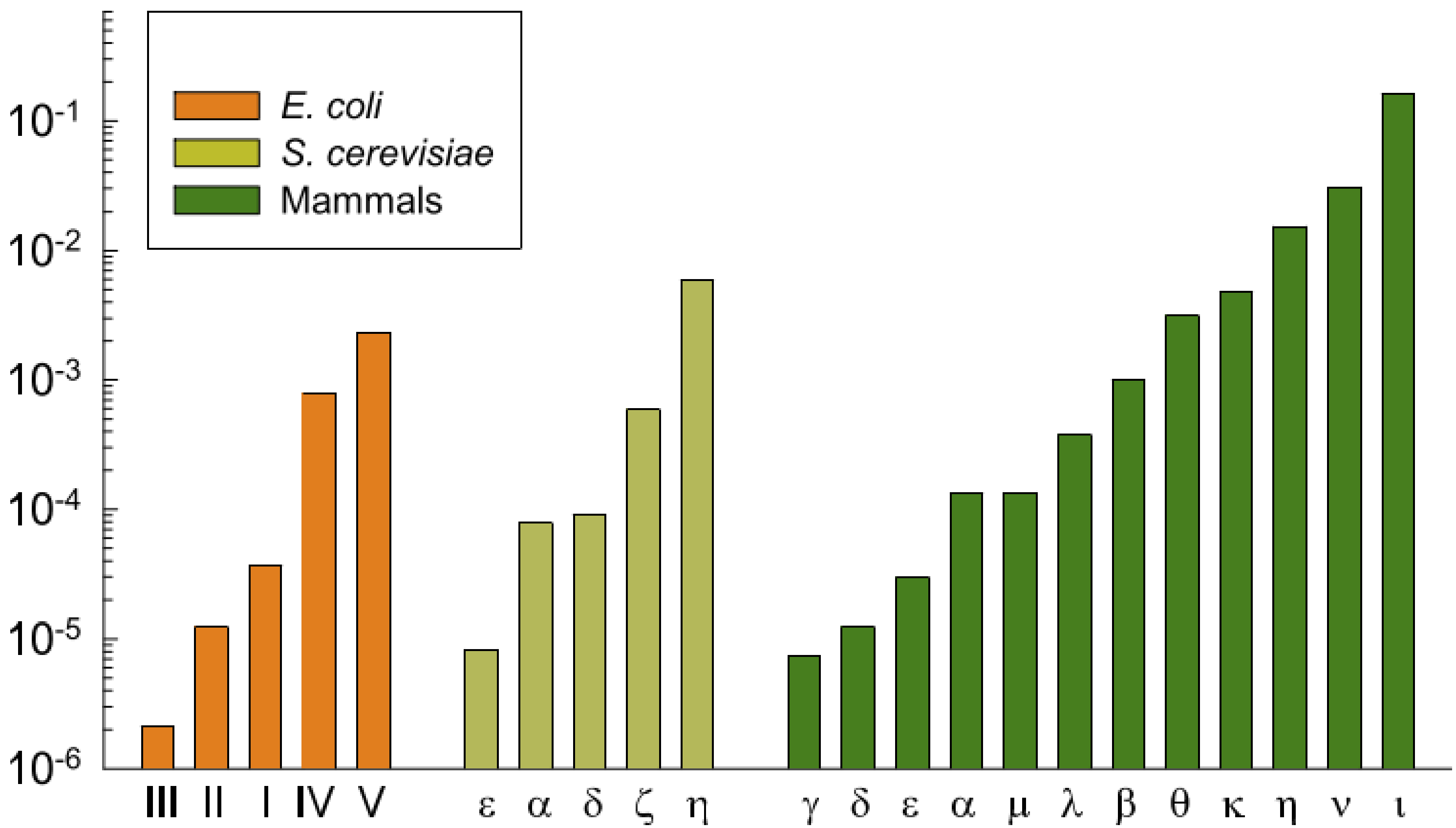
Taddei et al. Nature 1997

Variability in mutation rates

Within individuals

DNA polymerase error rate

Lynch 2011

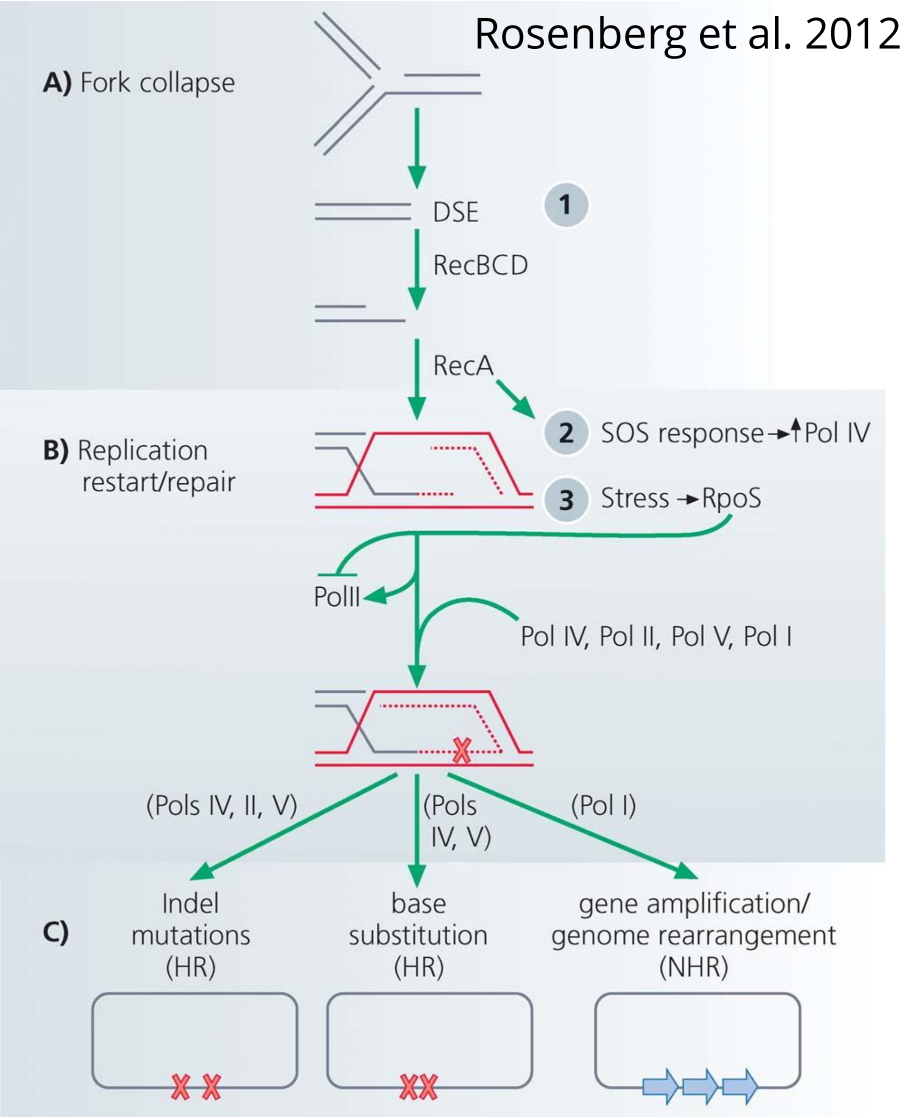


Stress-induced mutation

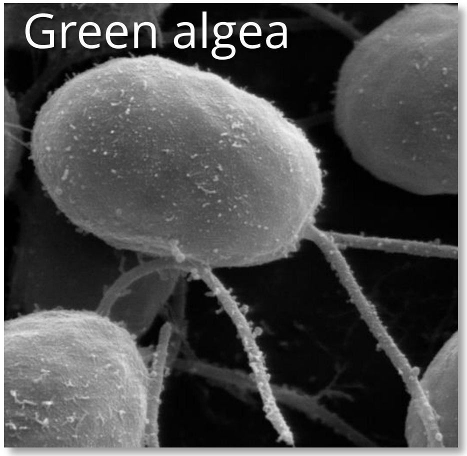
In *E. coli:*

- 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

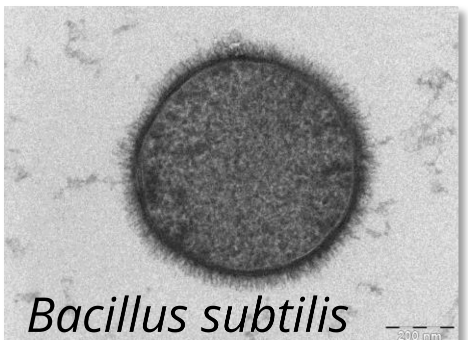
Rosenberg et al. 2012

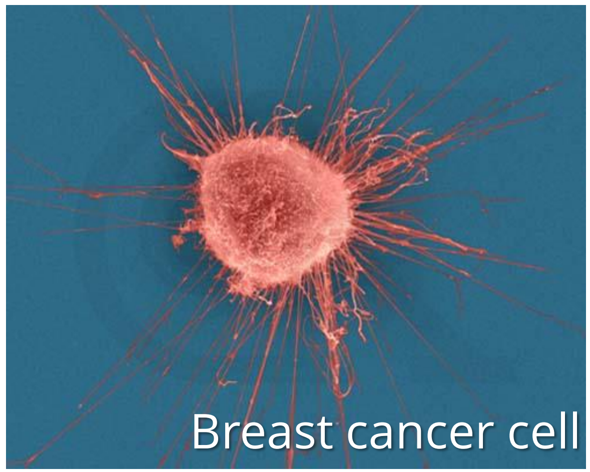


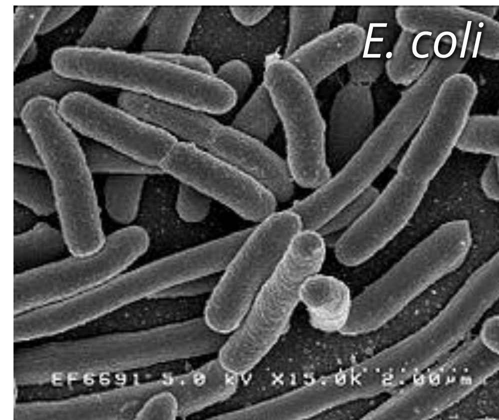
Evidence


Green algea

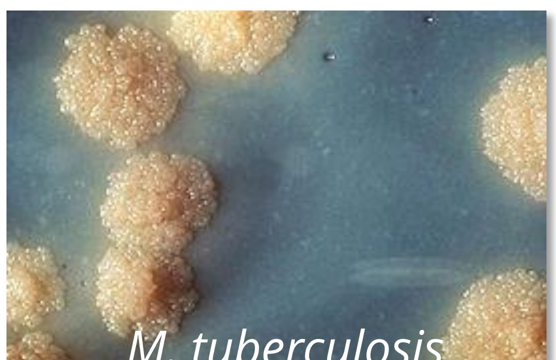

Nematodes

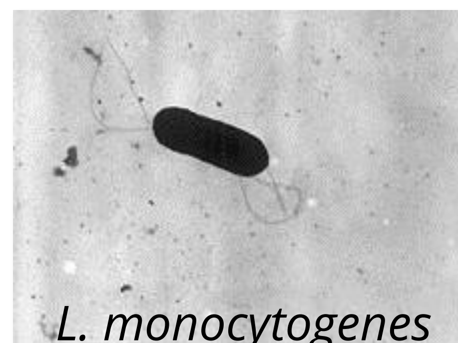

Bacillus subtilis


Breast cancer cell


E. coli


D. Melanogaster


M. tuberculosis

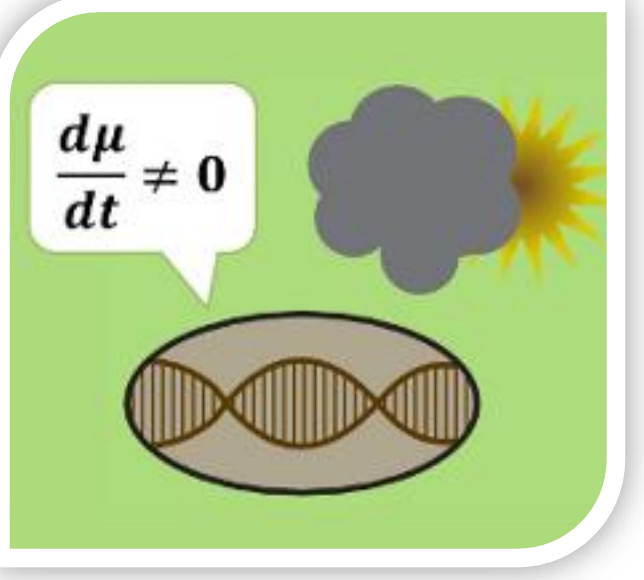

L. monocytogenes

Evolution of stress-induced mutation

Null hypothesis
- Mutagenesis is the by-product of stress

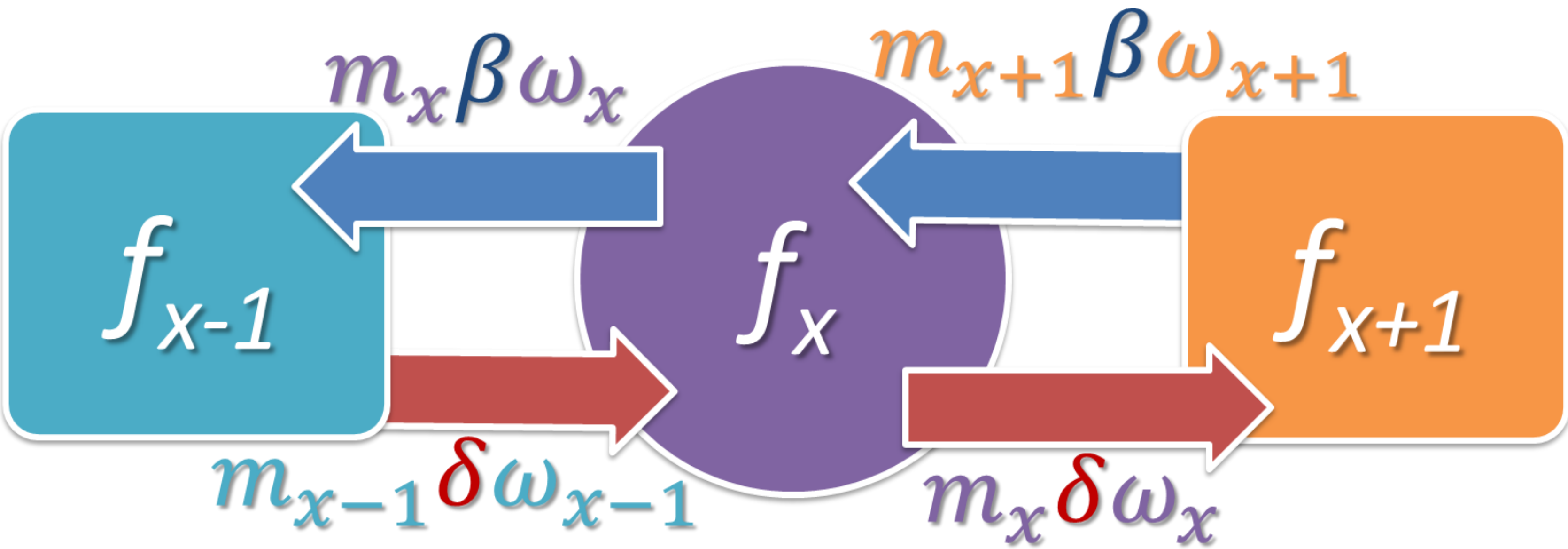
Alternative non-adaptive hypotheses
- Cost of replication fidelity
- Drift barrier hypothesis

Adaptive hypothesis
- 2^{nd} order selection



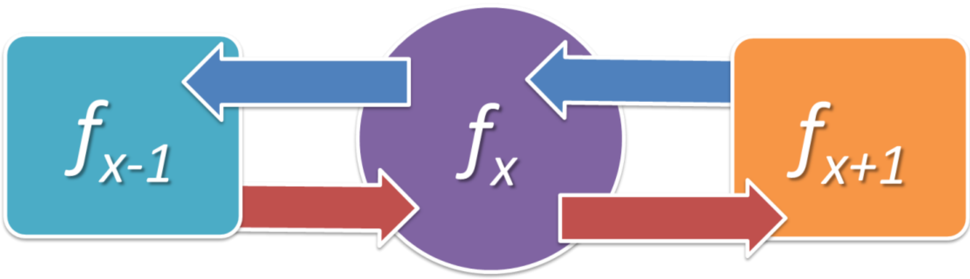
Constant environment

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

Ram & Hadany, Evolution 2012



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

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

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

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

Ram & Hadany, Evolution 2012

Constant environment

General solution

$$\frac{\partial \overline{\omega}}{\partial m_x} = \frac{f_x v_x}{m_x} \left(\overline{\omega} - \omega_x\right)$$

Ram & Hadany, Evolution 2012

Constant environment

General solution

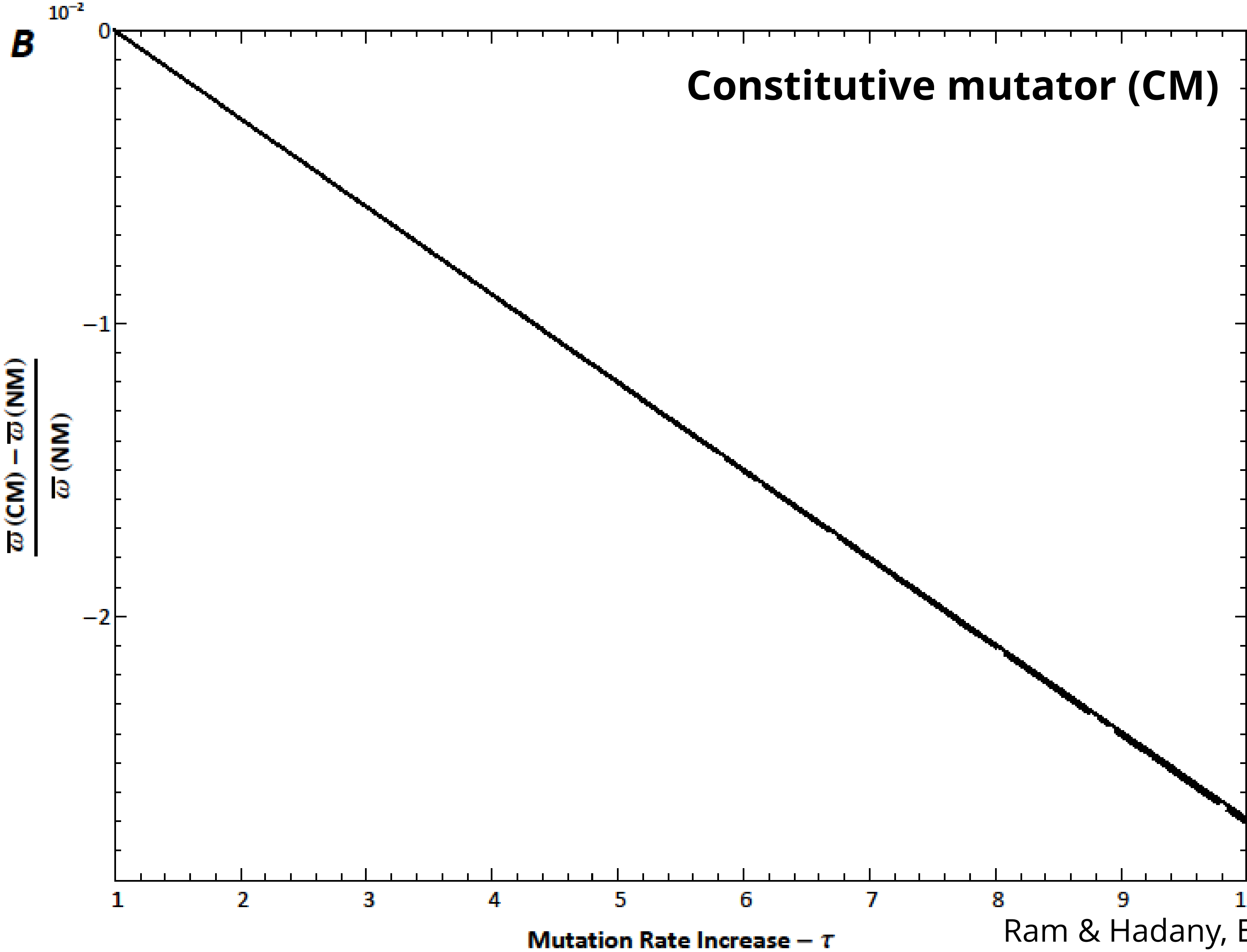
$$sign \frac{\partial \bar{\omega}}{\partial m_x} = sign\,(\bar{\omega} - \omega_x)$$

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

Selection doesn’t always reduce the mutation rate!

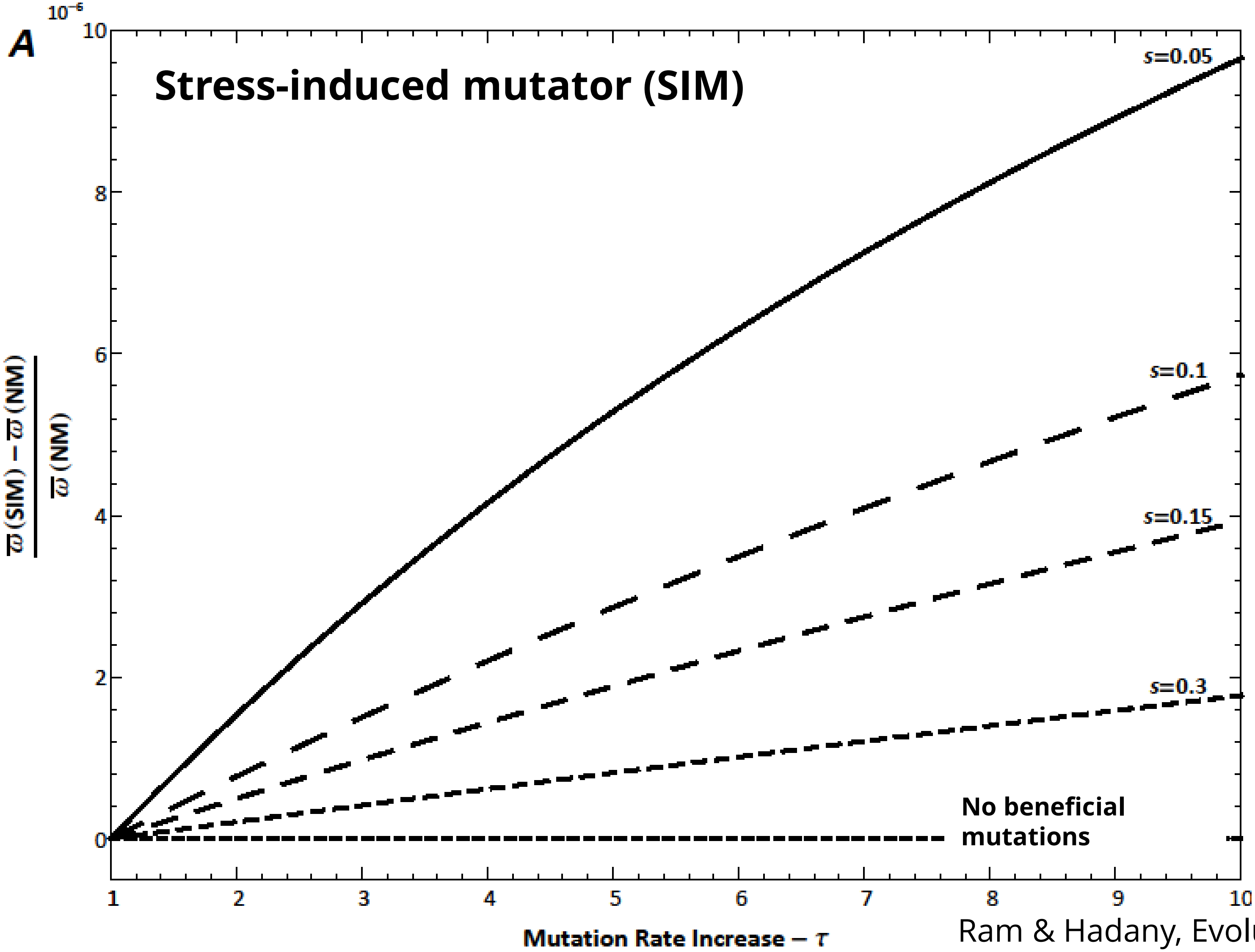
Ram & Hadany, Evolution 2012

Constant environment



Ram & Hadany, Evolution 2012

Constant environment



Ram & Hadany, Evolution 2012

Changing environments

The Red Queen hypothesis:

van Valen, 1973

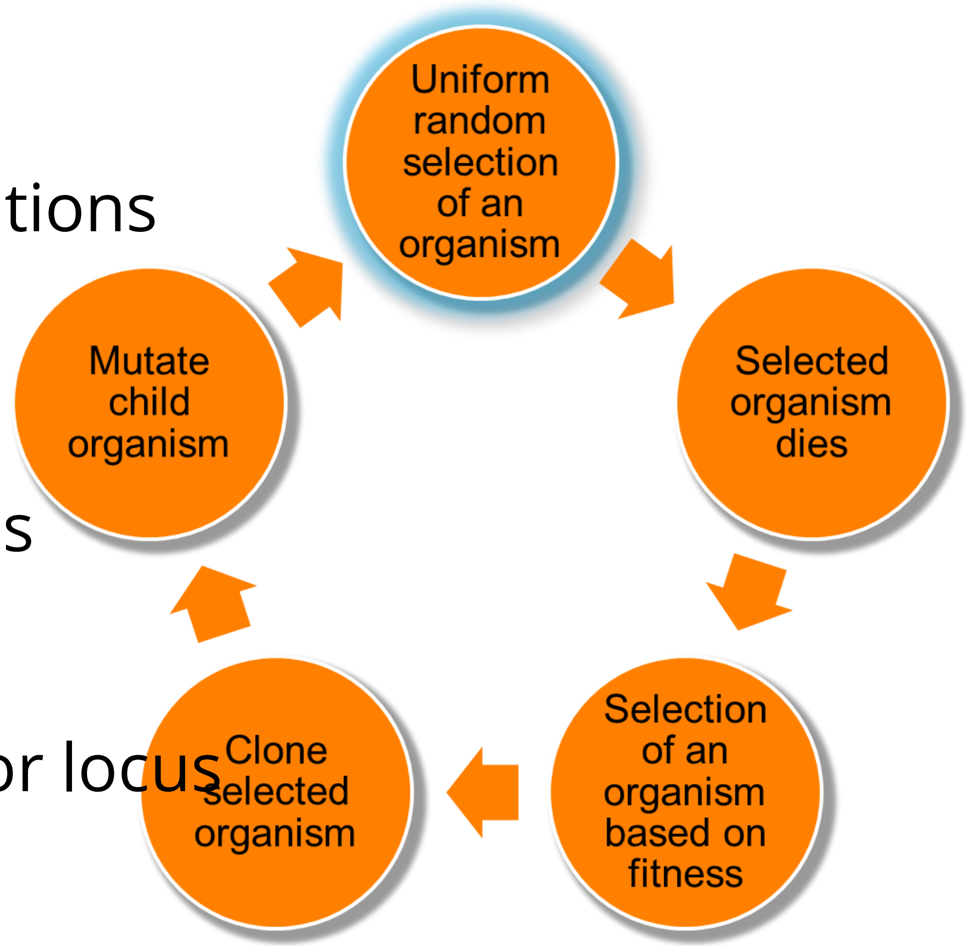
It takes all the running you can do, to keep in the same place.

- Lewis Carrol, Through the Looking Glass

Changing environments

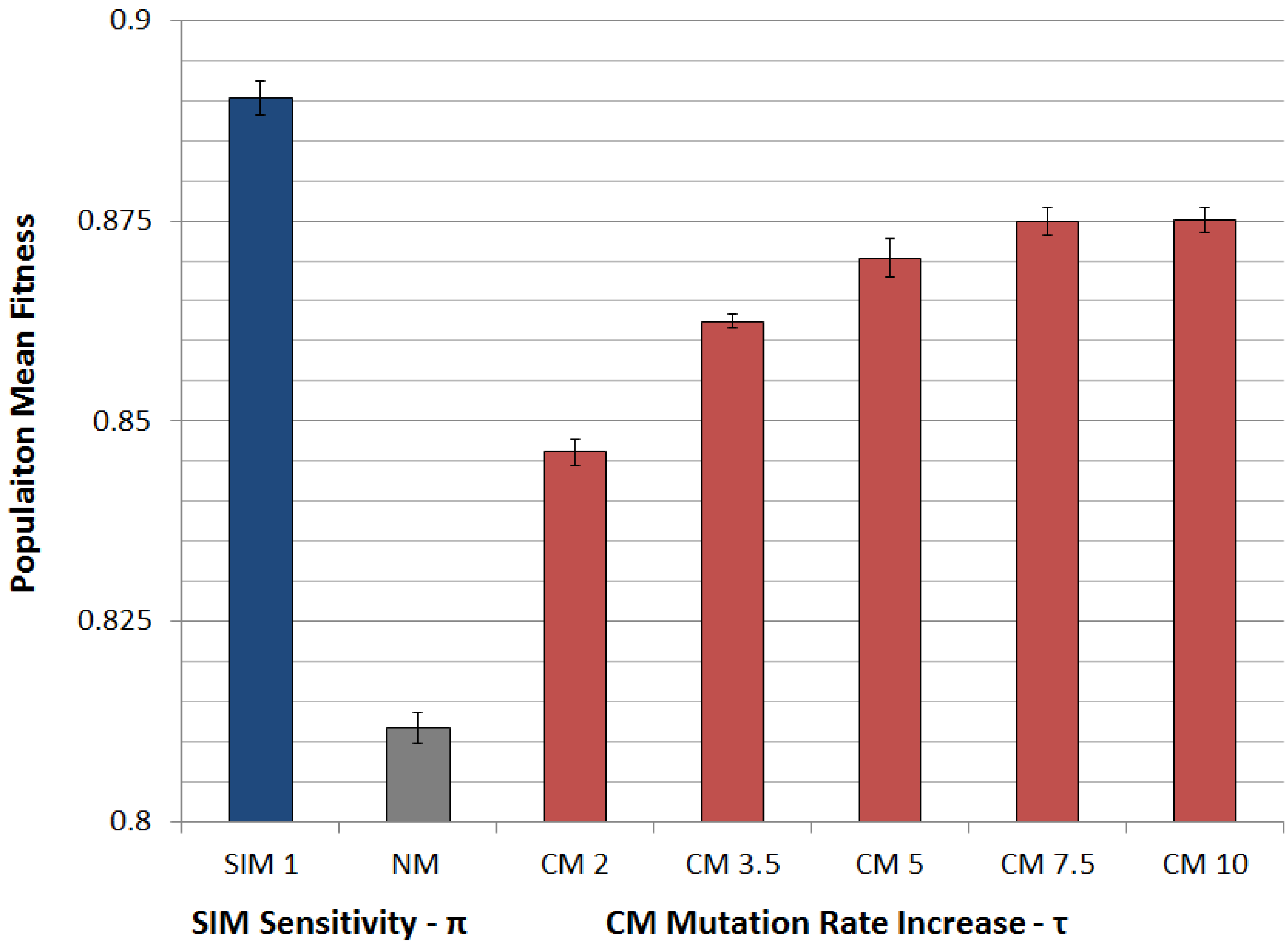
Simulations

- 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



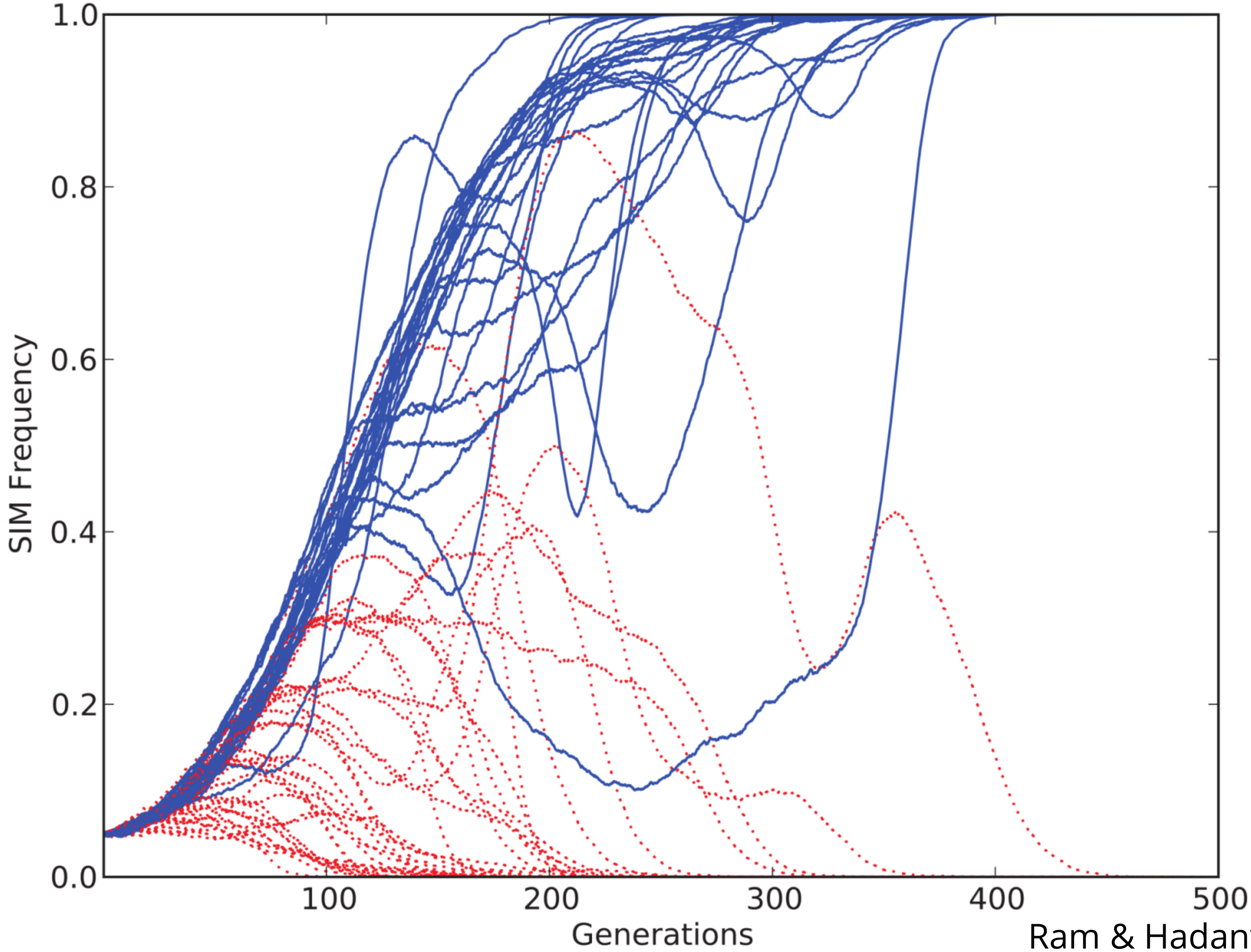
Ram & Hadany, Evolution 2012

Populations with SIM are fitter



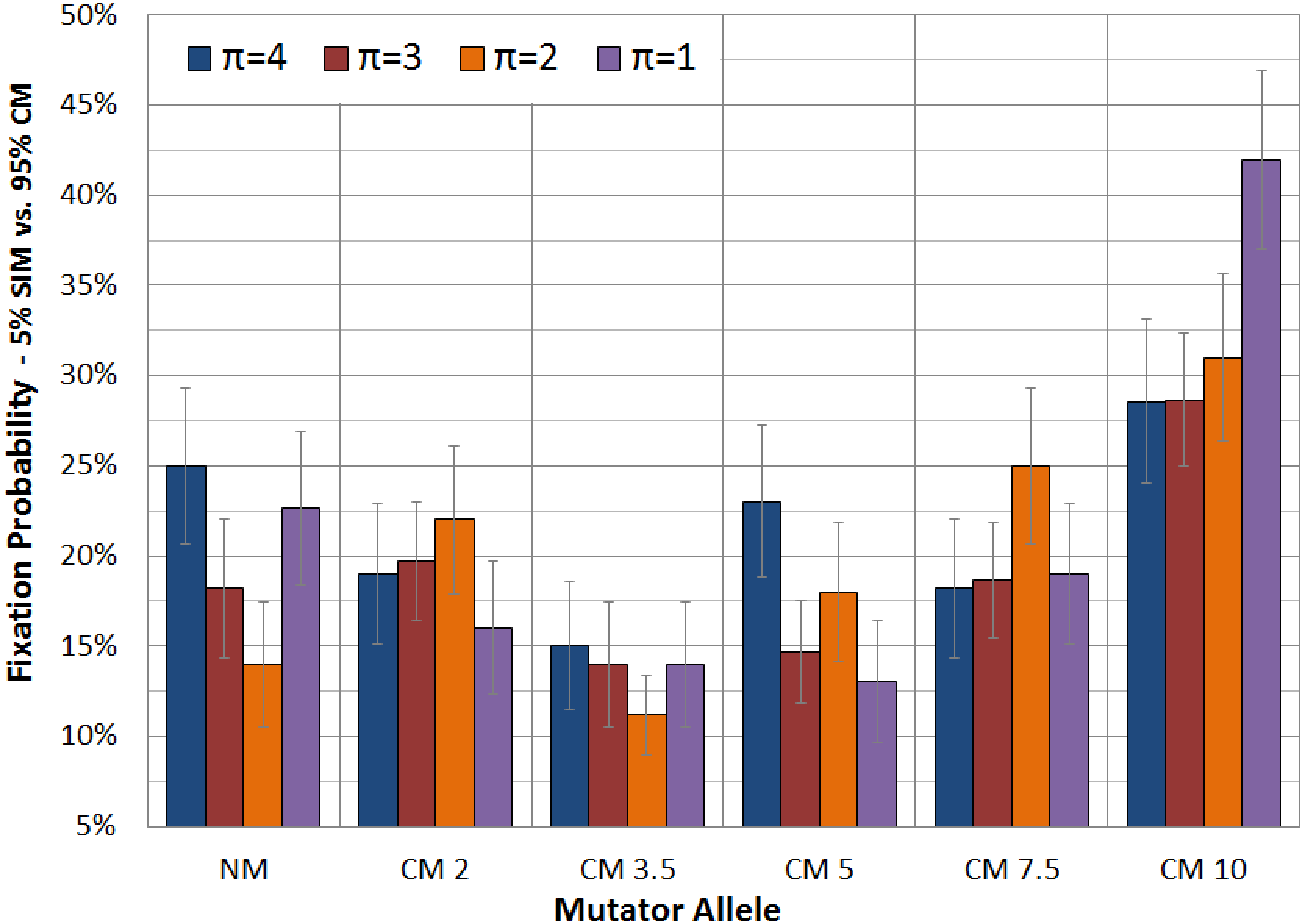
Ram & Hadany, Evolution 2012

SIM wins competitions



Ram & Hadany, Evolution 2012

SIM wins competitions

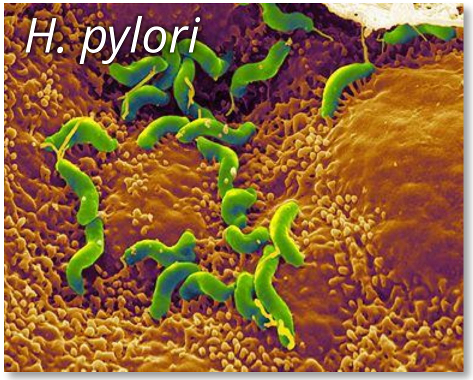


Ram & Hadany, Evolution 2012

Summary:
Evolution of stress-induced mutation

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

- **2nd order selection can lead to the evolution of stress-induced mutagenesis in asexual populations**
- Selection for evolvability

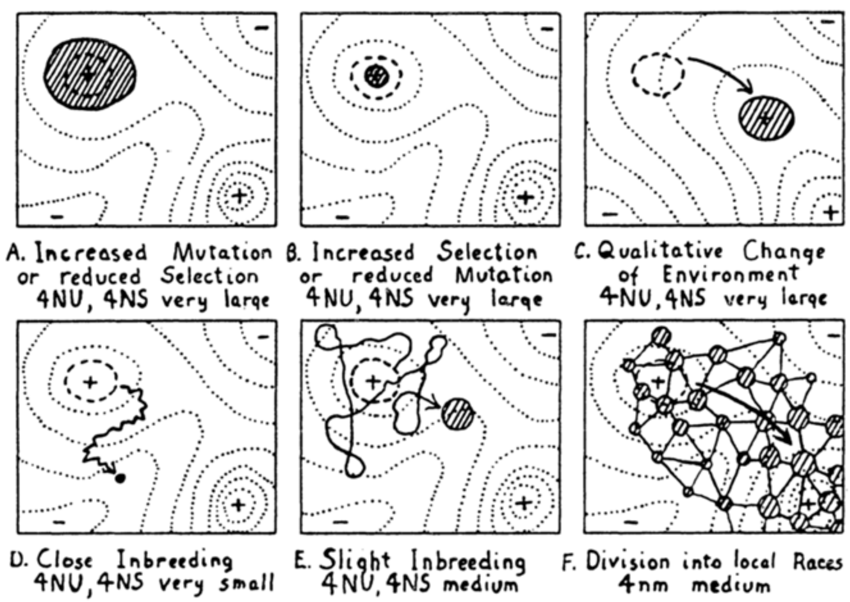


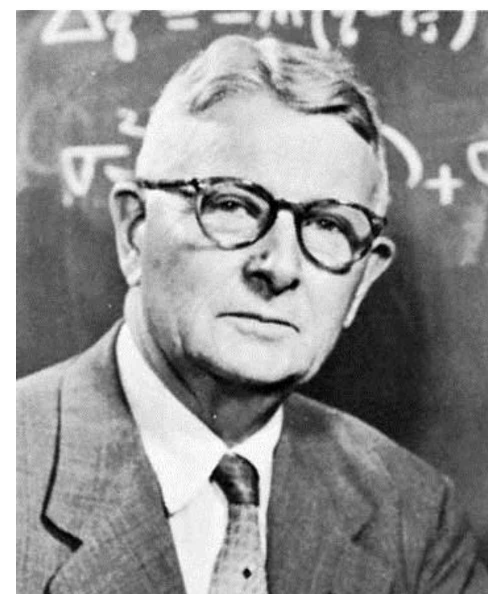

Consequences of Stress-Induced Mutagenesis
Can SIM make adaptation **faster?**
Malene Thyssen

Adaptive peak shifts

Sewall Wright, 1931:

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

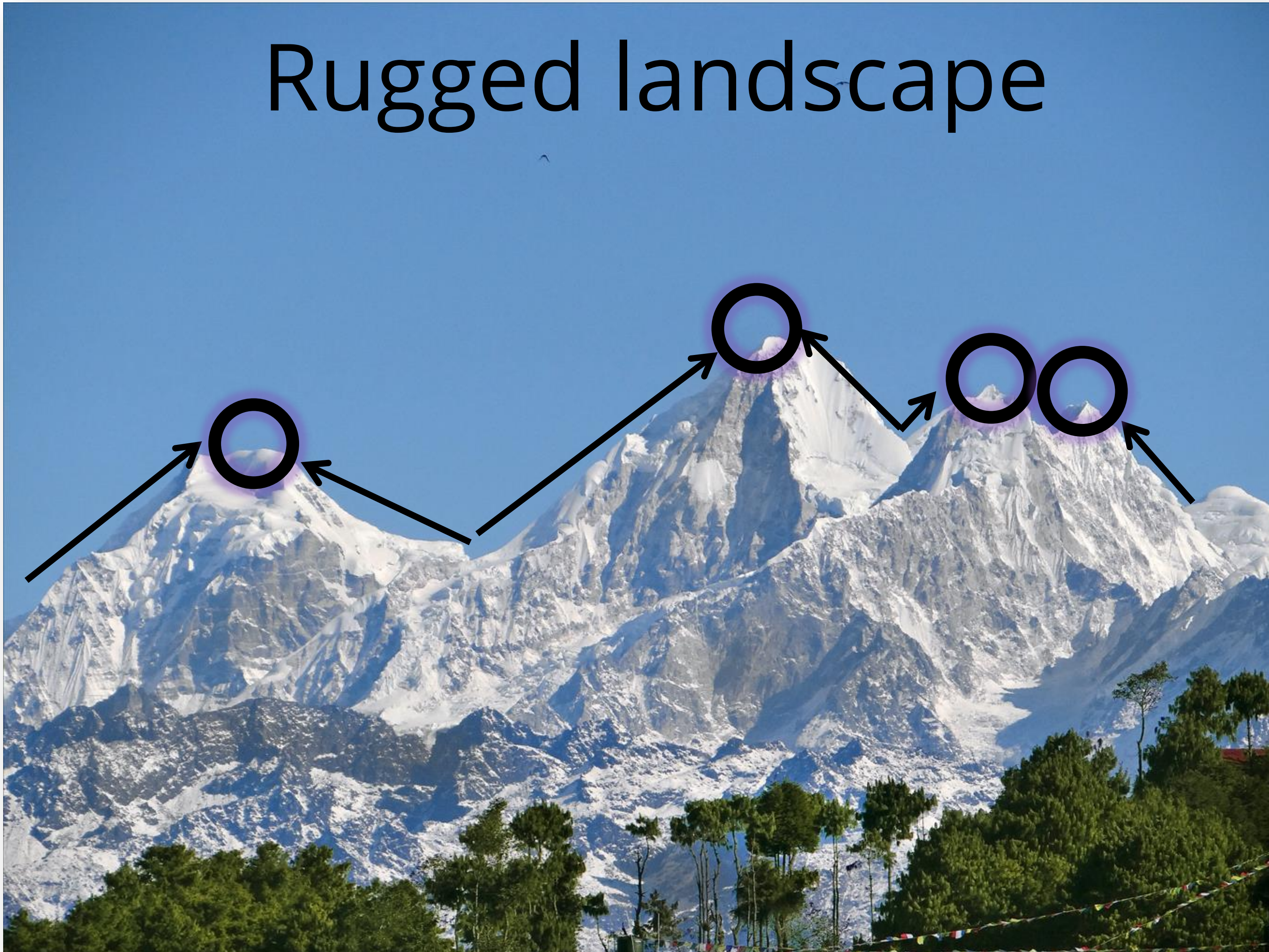


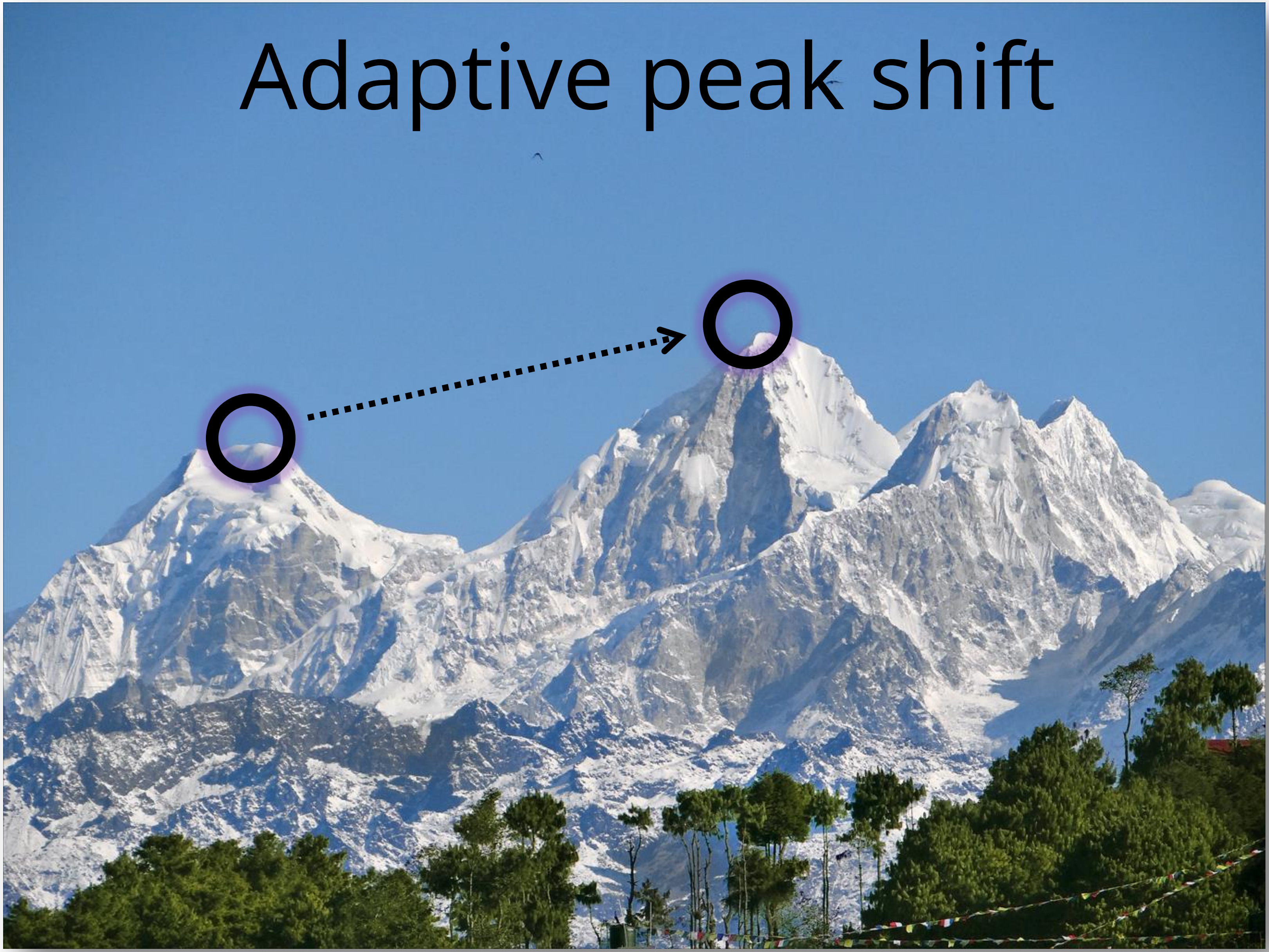


Wright, Am. Nat. 1988


Simple landscape

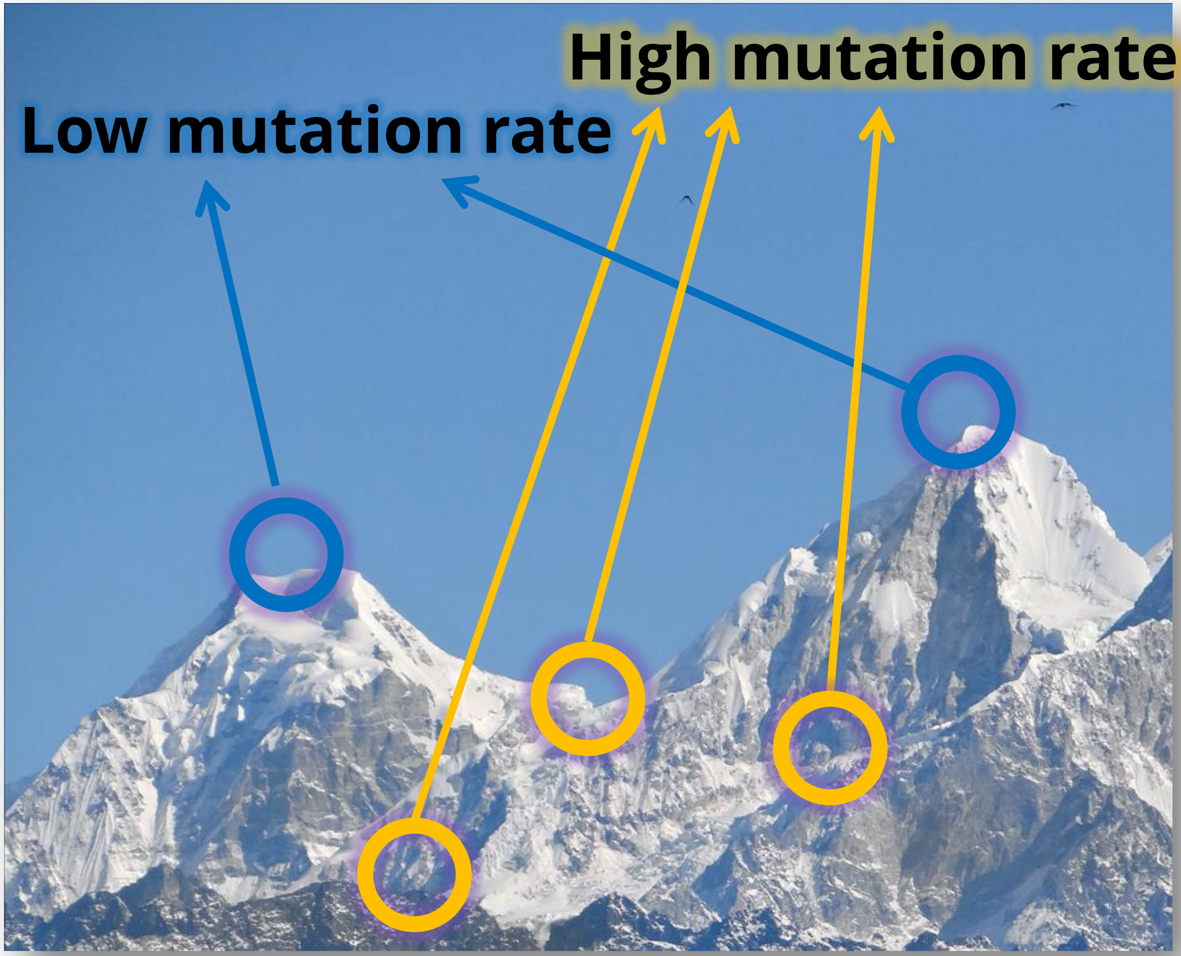
Rugged landscape




Adaptive peak shift

SIM & rugged landscapes

Increasing the mutation rate in individuals below both peaks



Deterministic model

The adaptation process is composed of

- Waiting for the double mutant to appear
- Fixation / extinction of the double mutant

Deterministic results

The rate of adaptation with normal mutation (NM):

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

The rate of adaptation with high mutation (CM):

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

The rate of adaptation with stress-induced mutation (SIM):

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

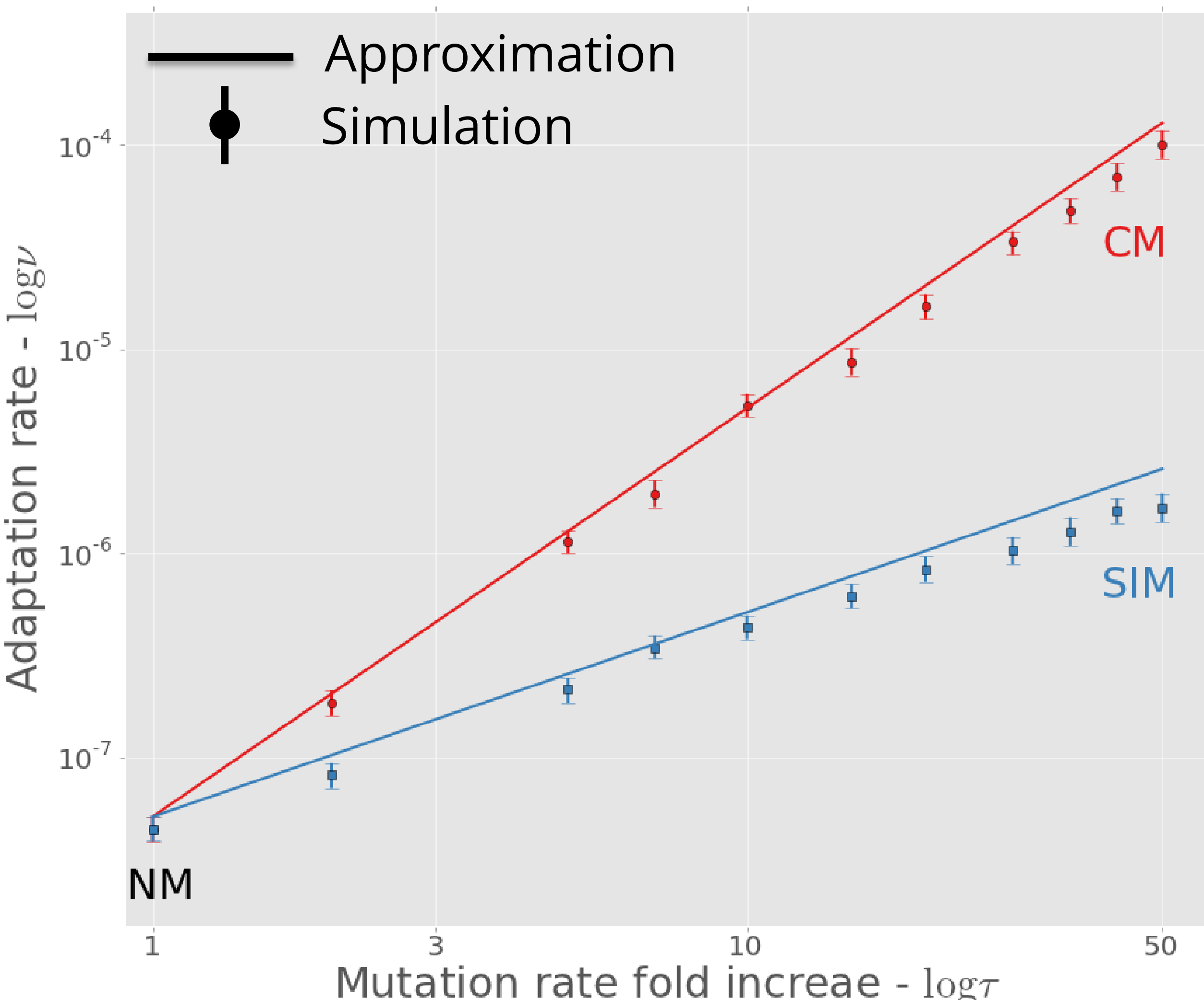
ν – adaptation rate; N – population size; τ – mutation rate increase; H – double mutant advantage; μ – beneficial mutation rate

Ram & Hadany, PRSB 2014

https://github.com/yoavram/ruggedsim

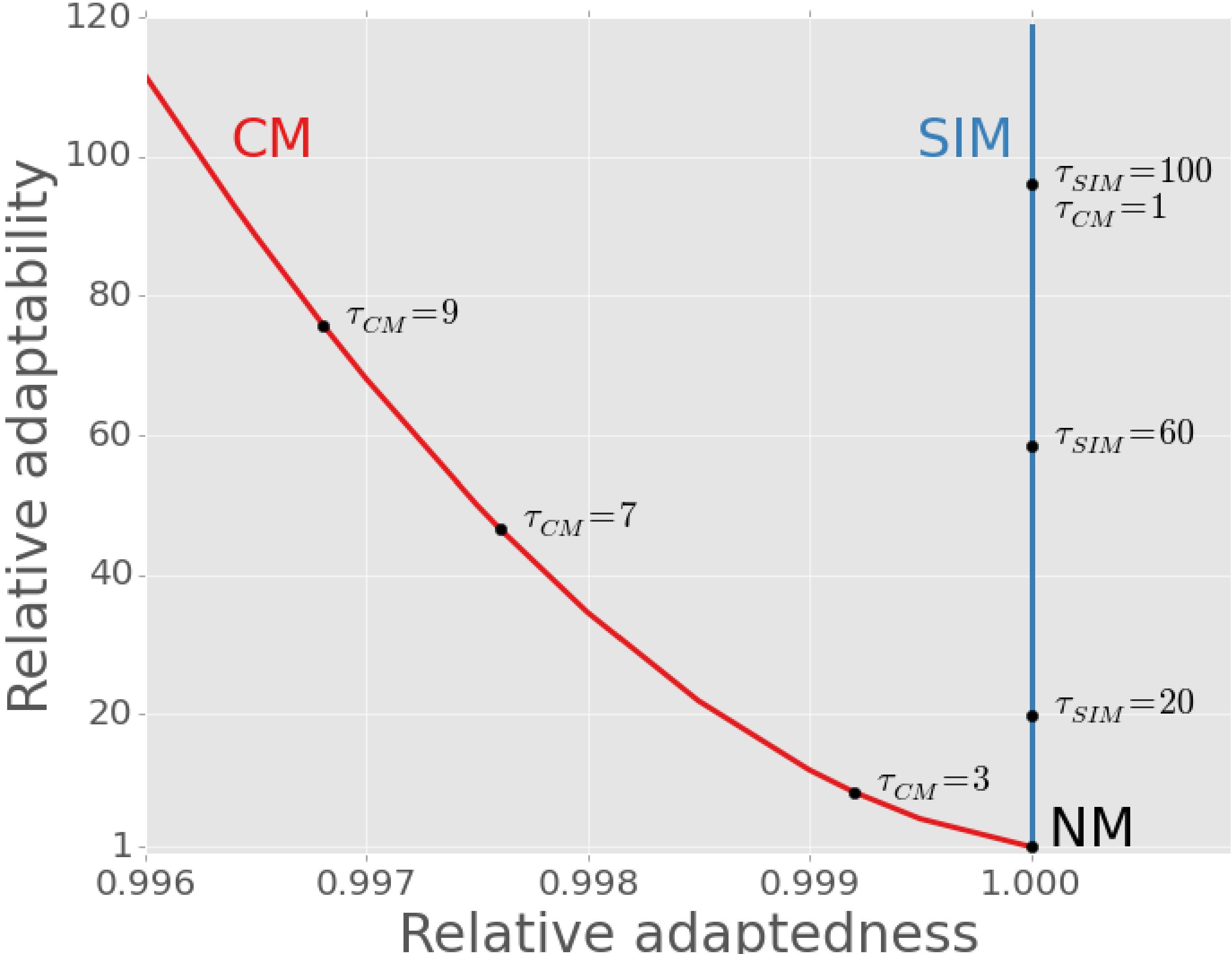
Adaptation rate

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



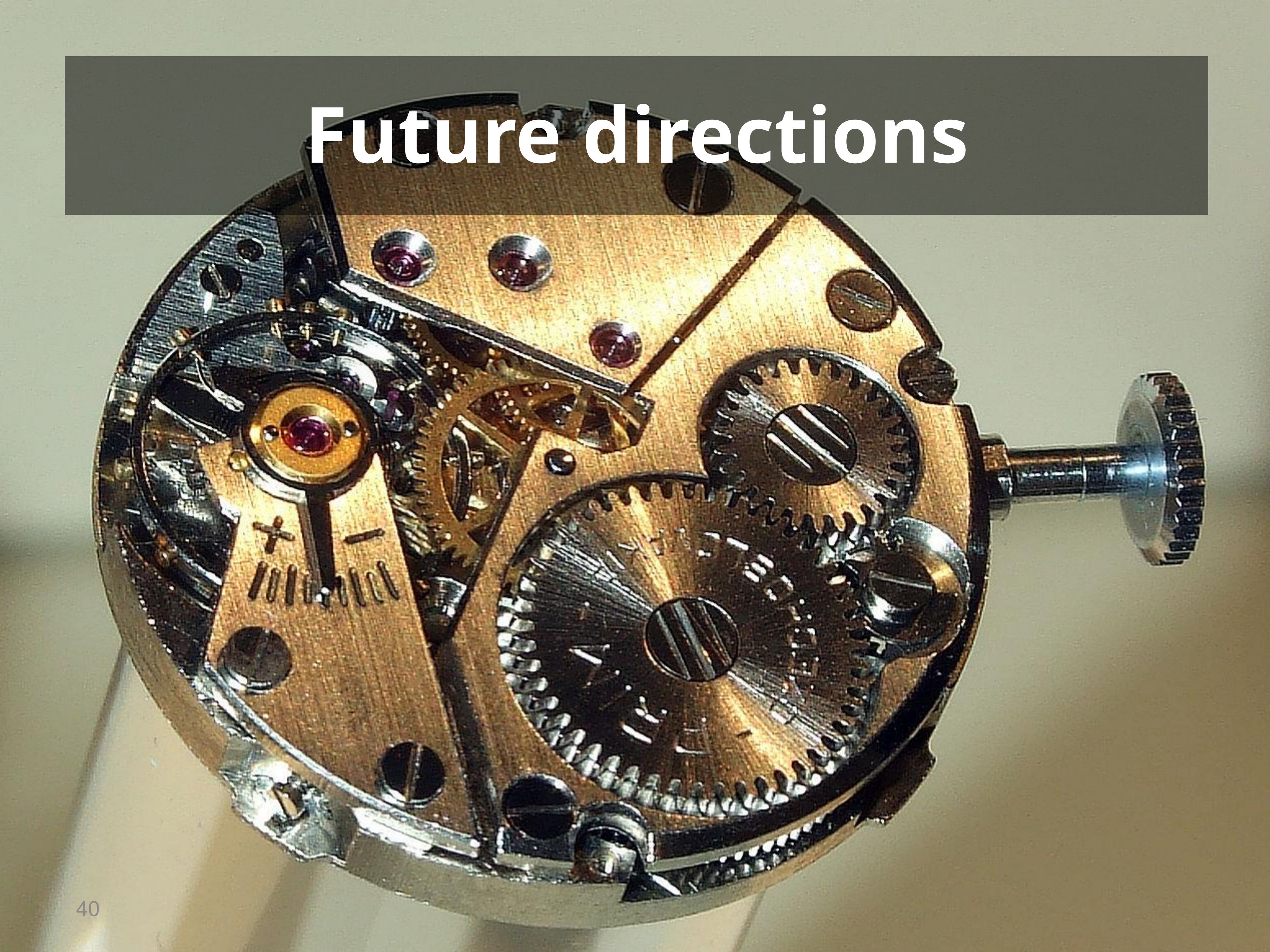
Ram & Hadany, PRSB 2014

SIM Breaks the *adaptability-adaptedness* trade-off



Ram & Hadany, PRSB 2014

Future directions



In the presence of rare recombination

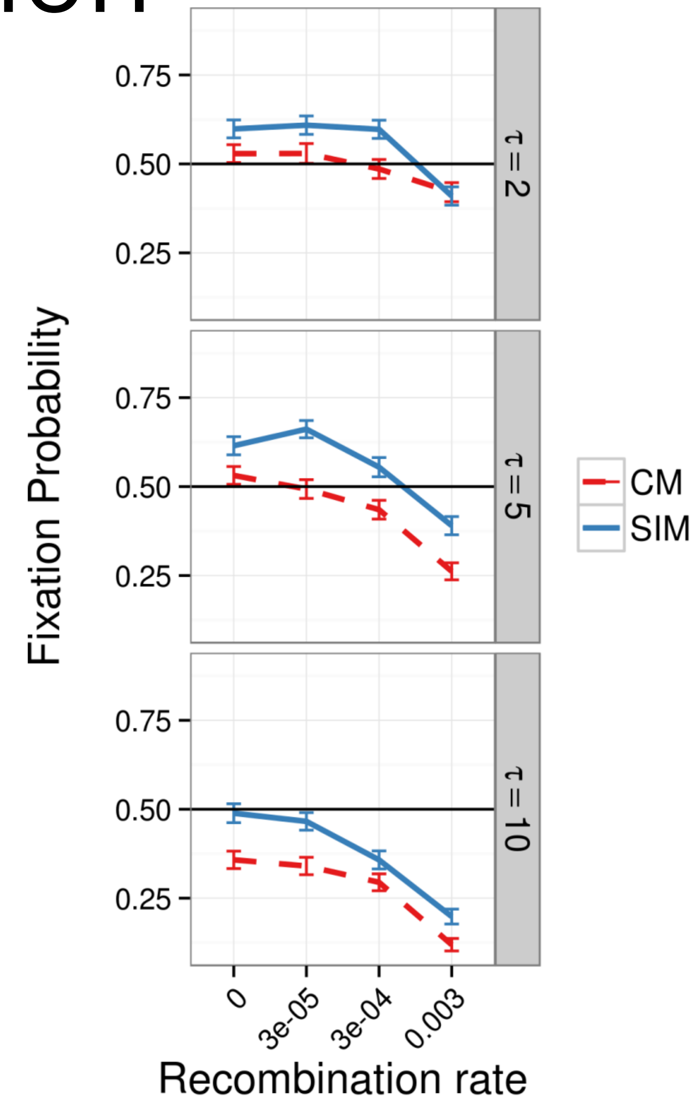
- **Recombination** can:
  - Separate mutator from beneficial mutations
  - Increase non-mutator adaptation rate
  - Save constitutive mutators from deleterious mutations

In the presence of rare recombination

Results suggest:

- **SIM** > **CM**
- **SIM** >= **NM**
- As long as **recombination is as not much stronger than mutation**

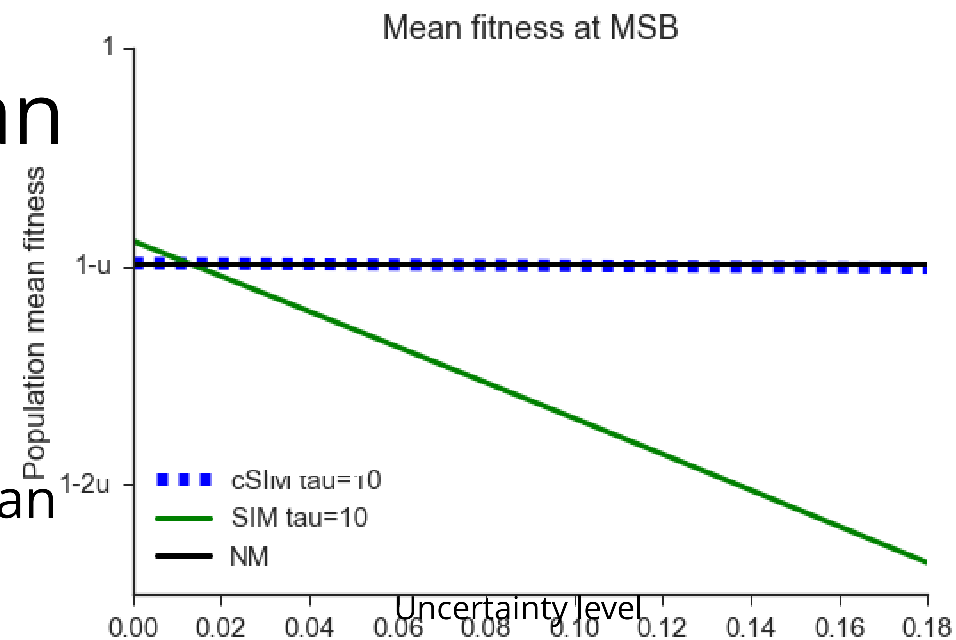
Sexual populations??



Ram & Hadany, in preparation

Stress-induced mutagenesis under uncertainty

- **Uncertainty**
  - should you mutate?
- **SIM** decreases mean fitness
- **Communication**
  - Increase in mutation rate depends on population mean fitness
  - Robustness to uncertainty



Gur-Dellus, Ram & Hadany, in preparation

Conclusions

Evolution of stress-induced mutagenesis:

- SIM can evolve due to 2nd order selection
- In constant and changing environments

Ram & Hadany, Evolution 2012

- In the presence of rare recombination

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

yoav@yoavram.com
@yoavram
github.com/yoavram
www.yoavram.com