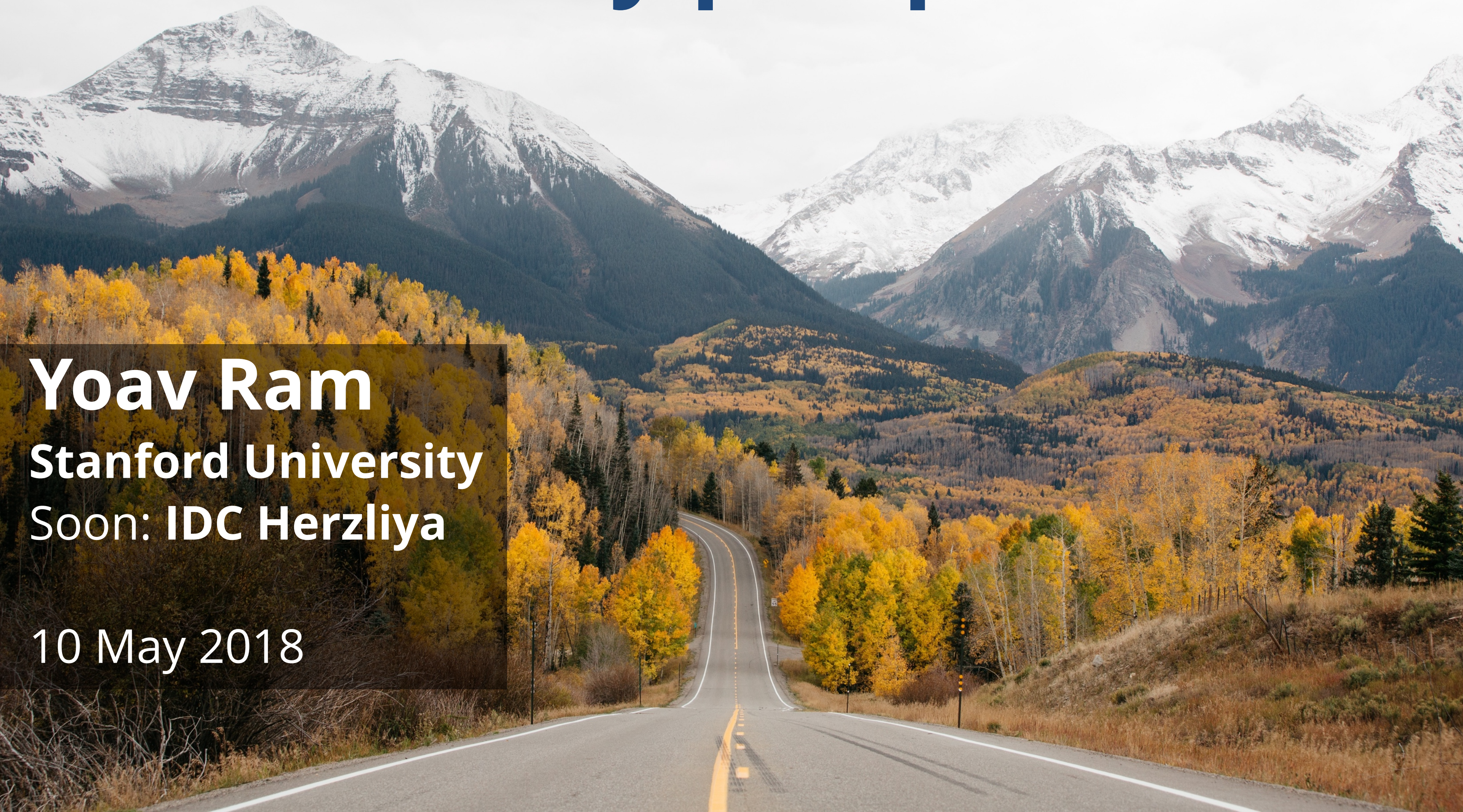
Stress-induced mutagenesis: Evolutionary perspective



Yoav Ram
Stanford University
Soon: **IDC Herzliya**

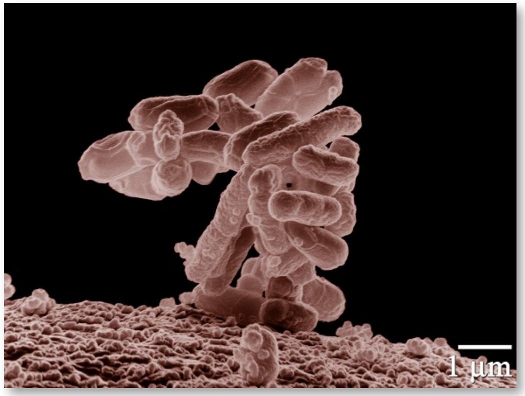
10 May 2018

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

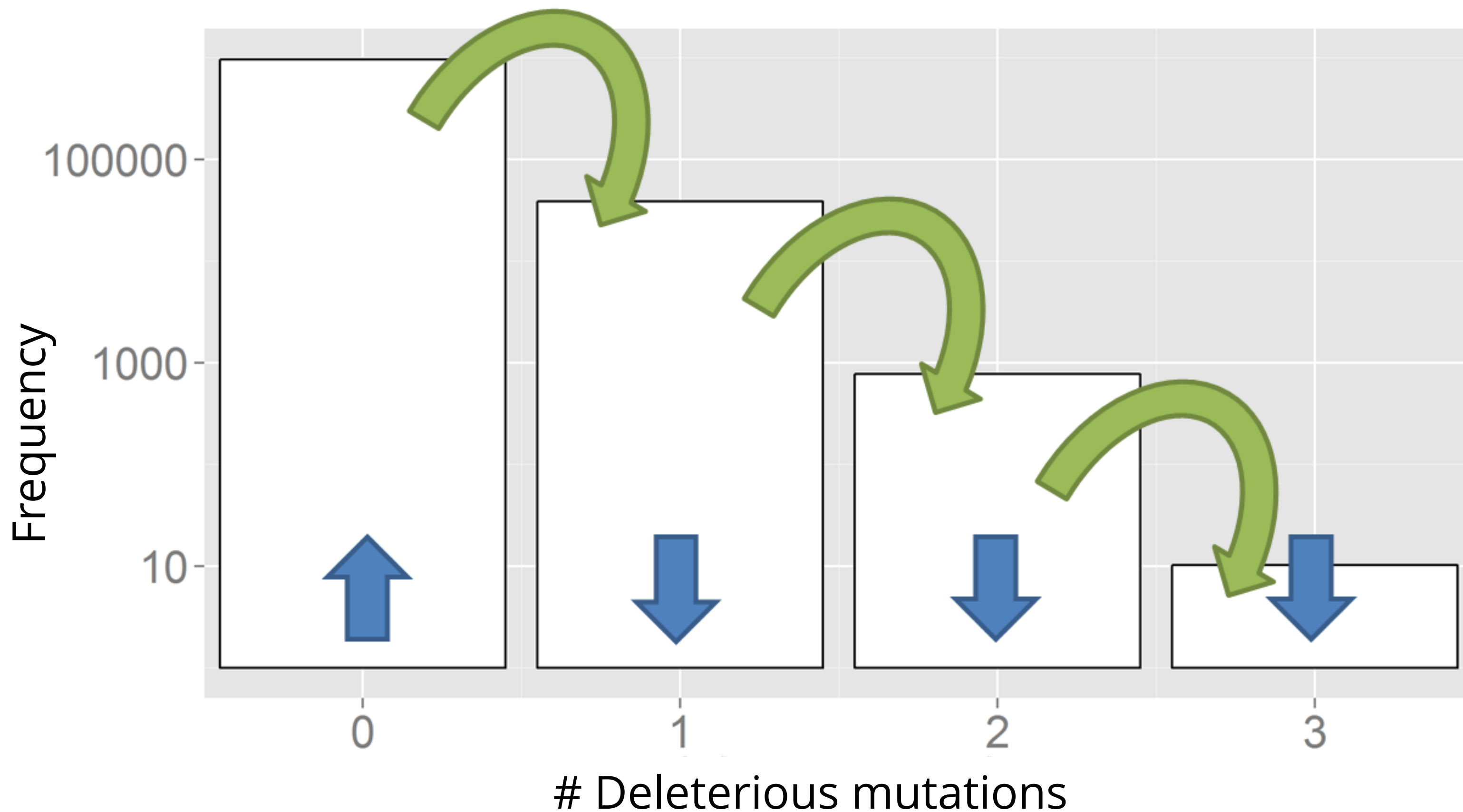


Flies: 0.455
Keightley et al. Gen Res 2009

Humans: 41
Lynch, PNAS 2010

Evolution in constant environments

- Directional selection without change
- A balance between mutation and



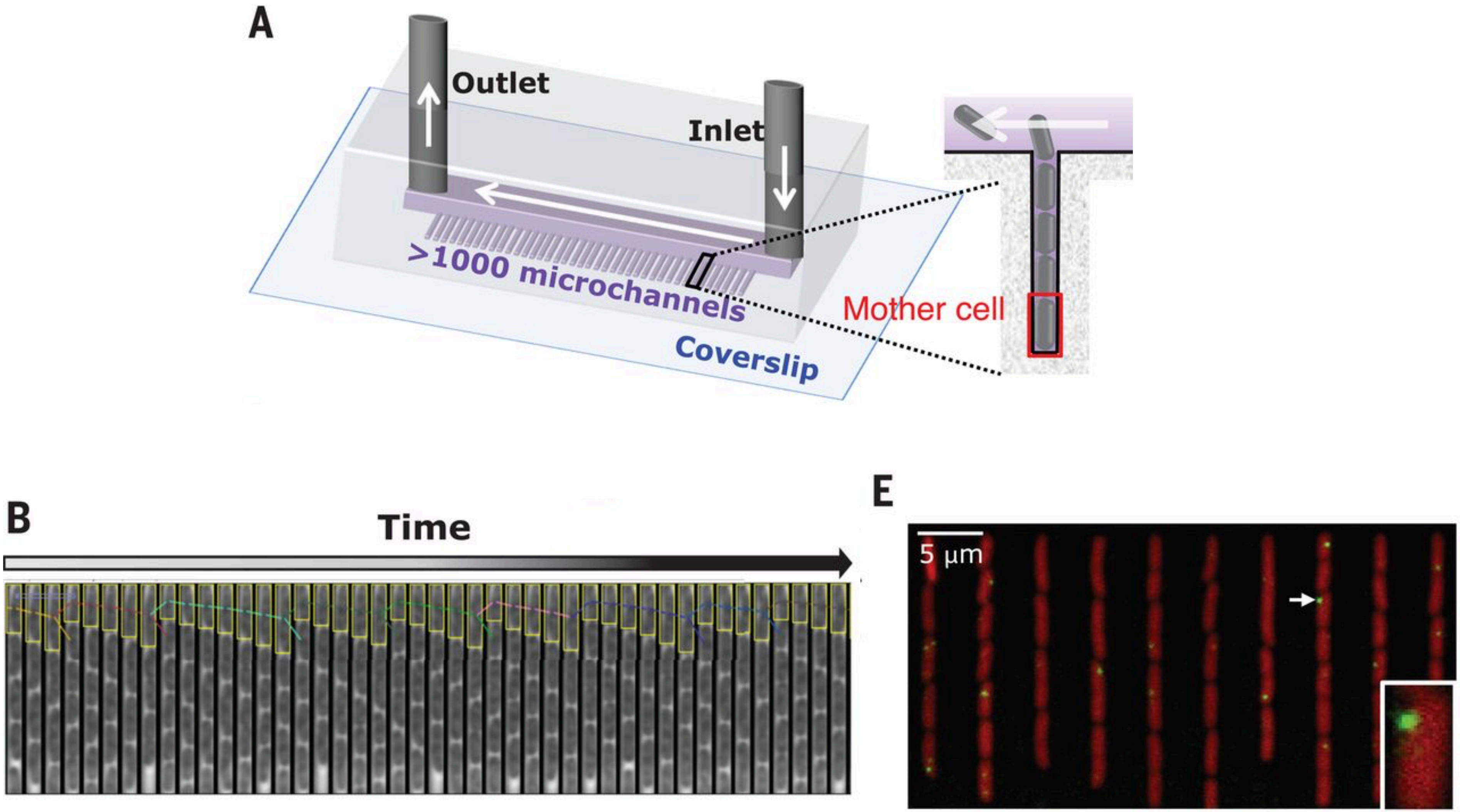
Mutation rate in constant environments

- $\bar{\omega} = e^{-U}$
- 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; Altenberg, Liberman, & Feldman 2017

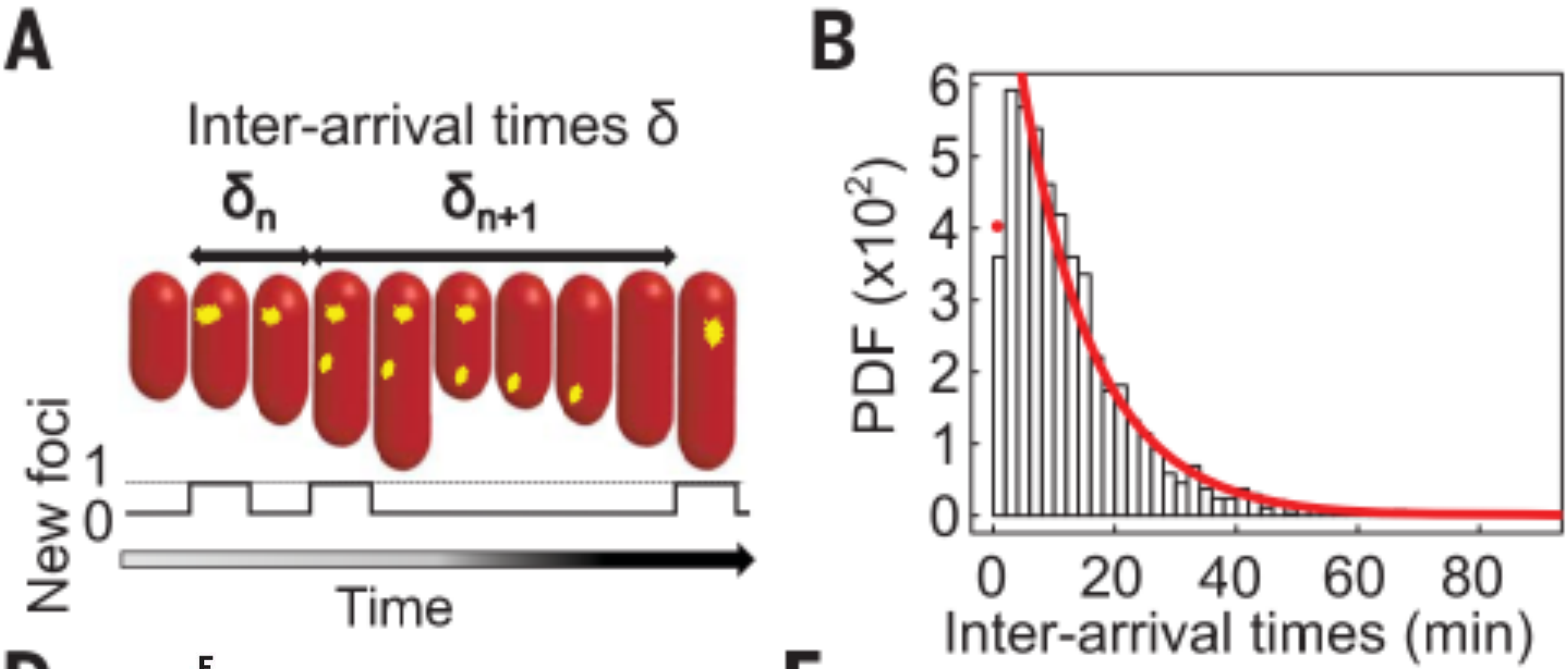
- What sets this level?
  - Physical or physiological constraints — Kimura 1967
  - *Cost of DNA replication fidelity* — Dawson 1999
  - *Drift barrier hypothesis* — Lynch 2010

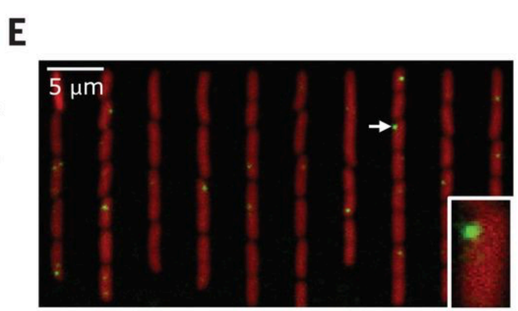
Real-time mutations



Robert et al., Science 2018

Real-time mutations





Robert et al., Science 2018

Changing environments

Changing environments

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

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

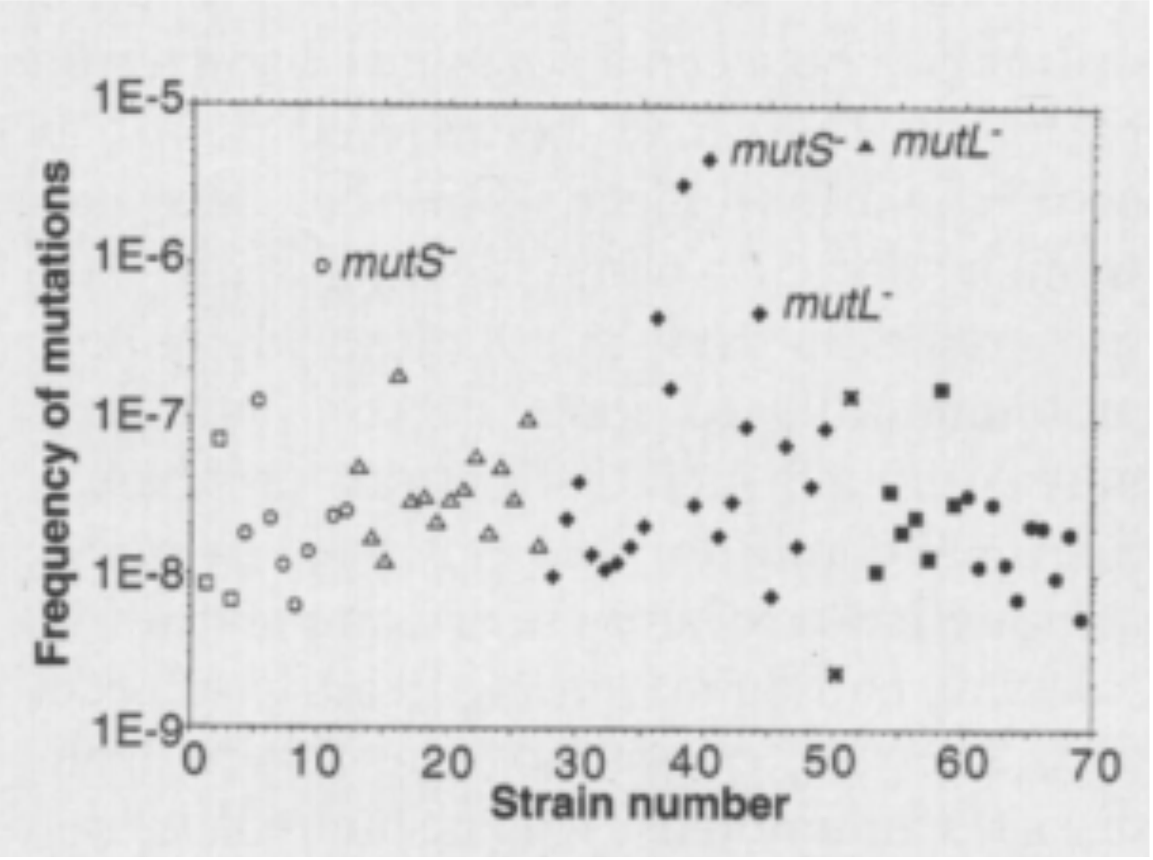
Leigh 1973

Variability in mutation rates

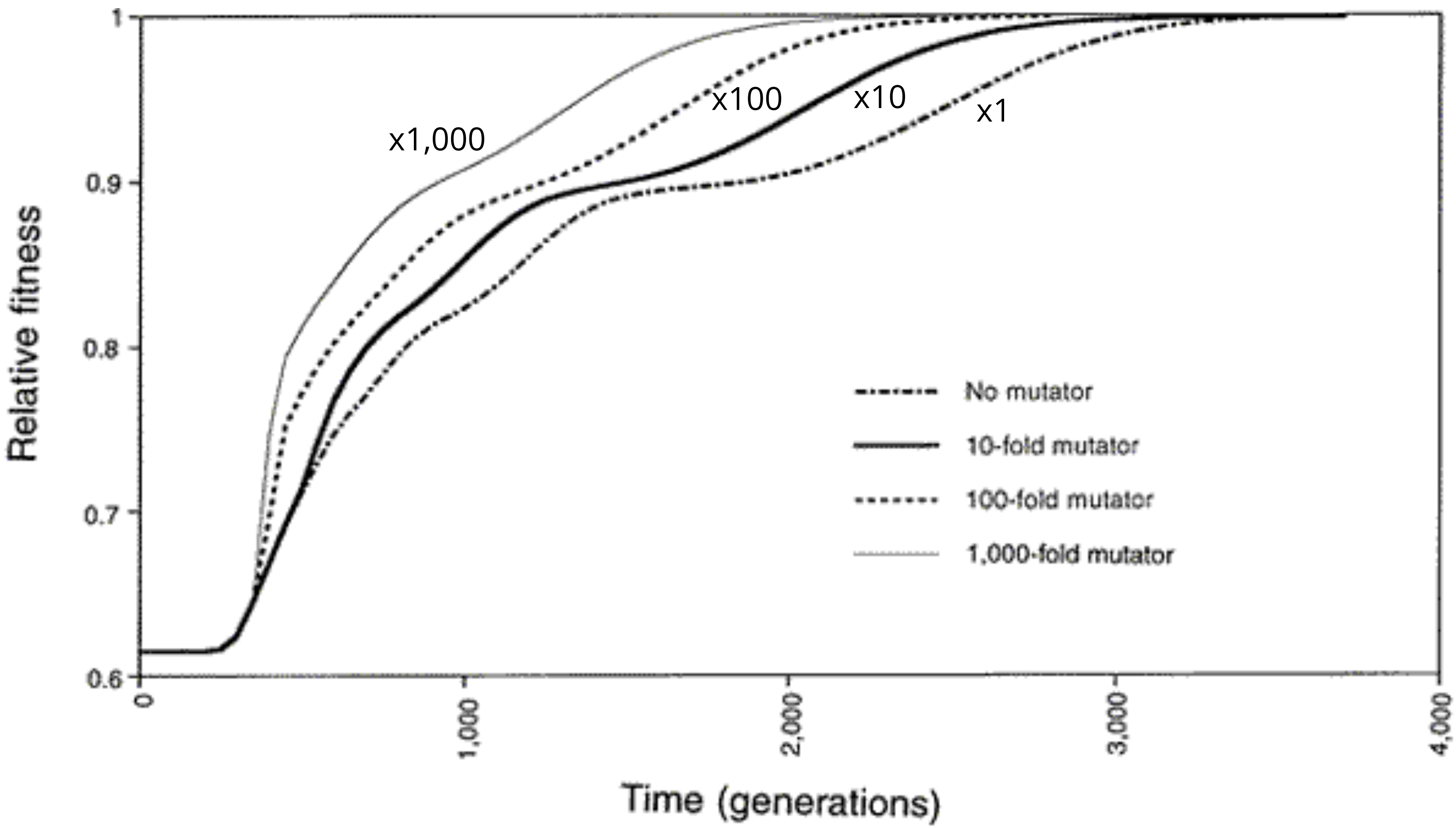
Within species

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

Matic et al. 1997

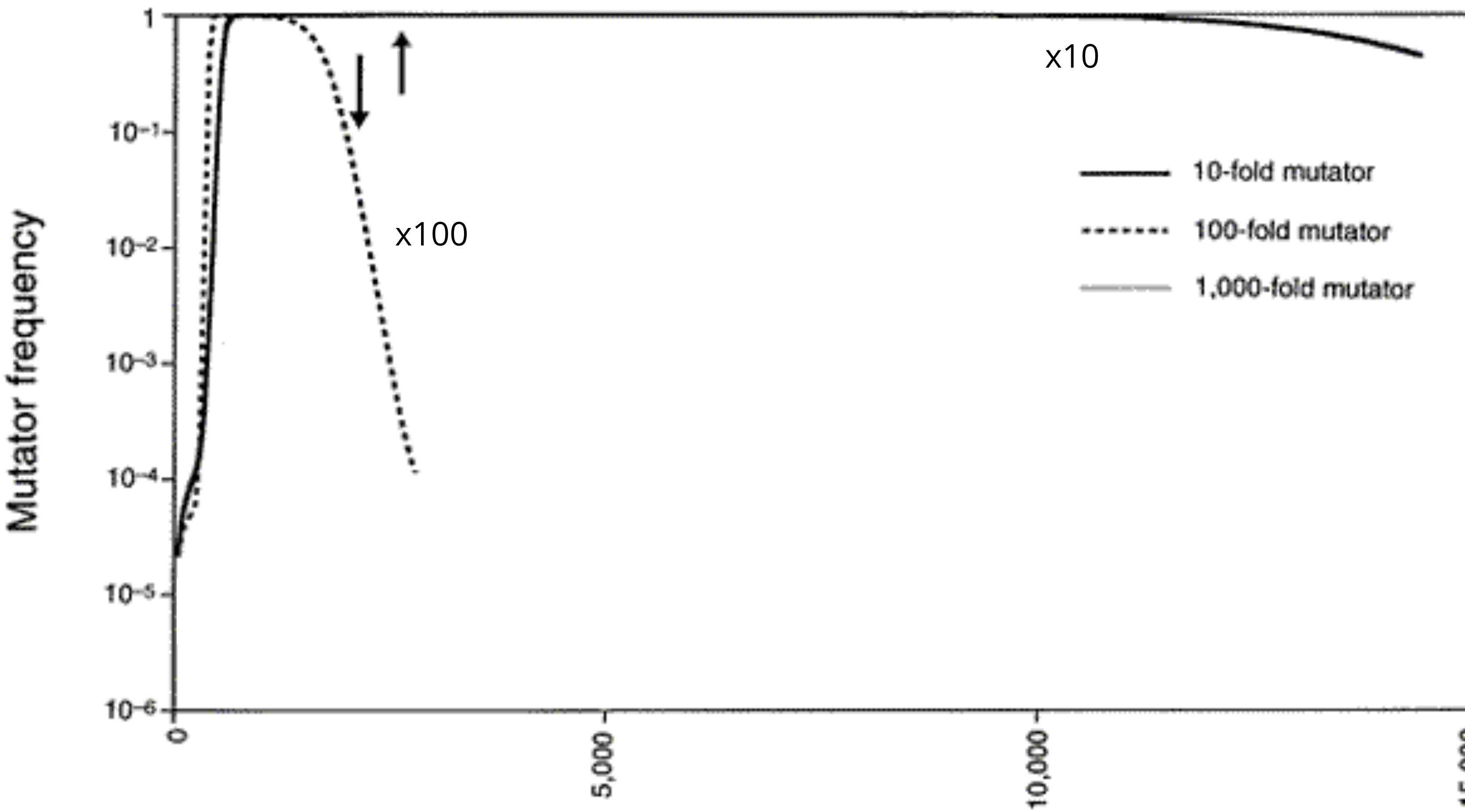


Adaptation with mutator alleles



Taddei et al. Nature 1997

Rise and fall of the mutator allele

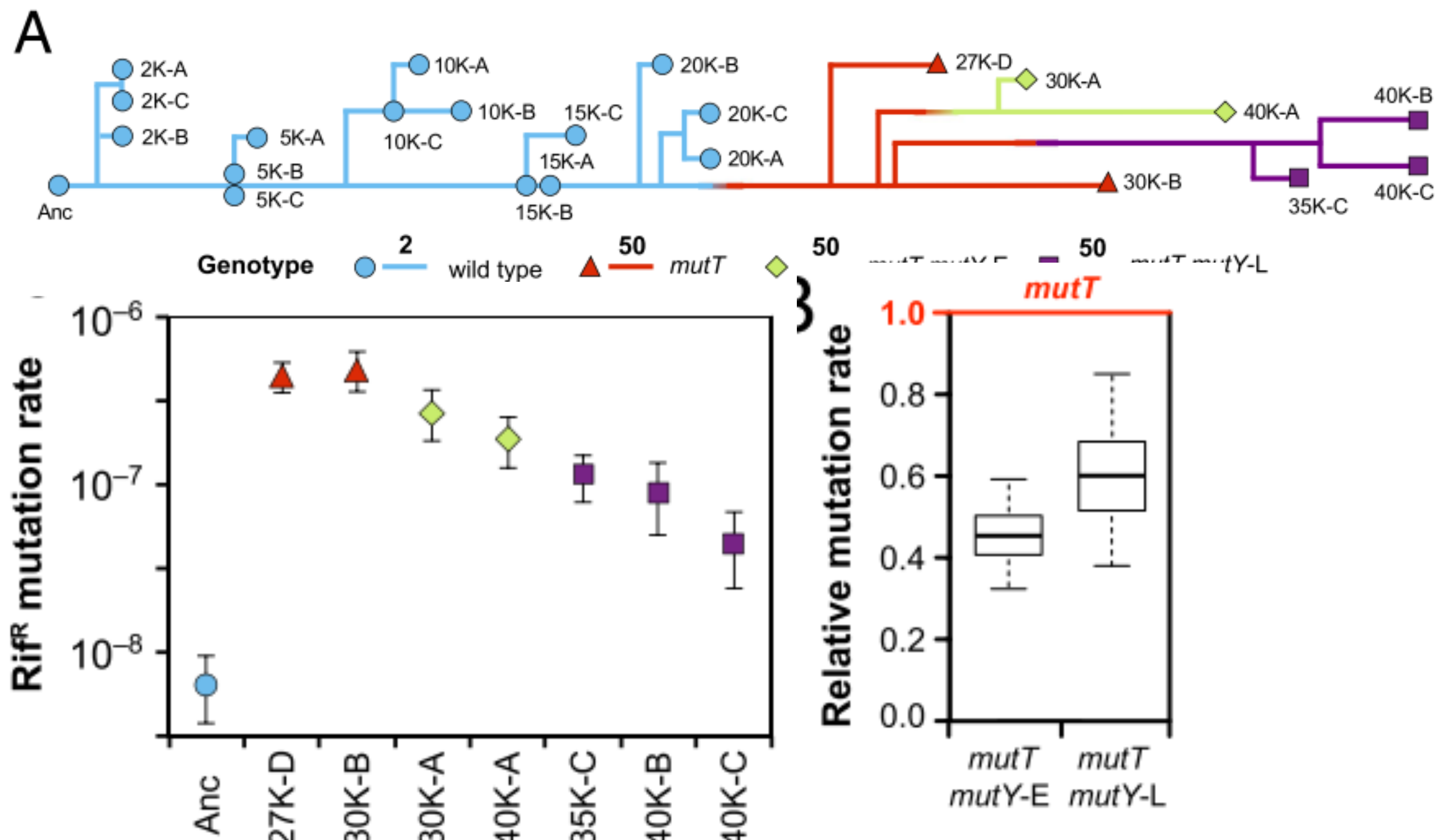


Taddei et al. Nature 1997

Rise and fall: LTEE

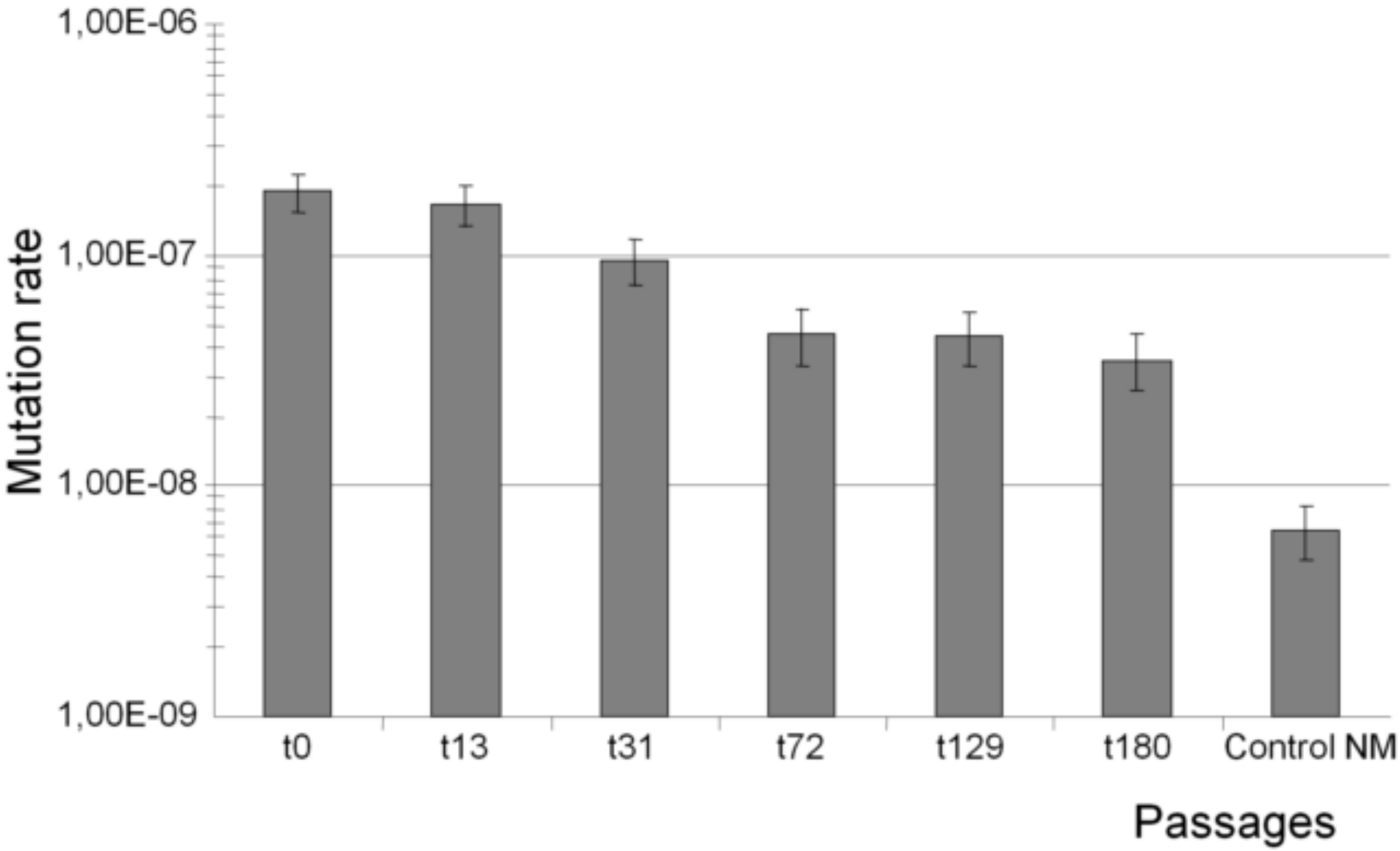
- LTEE: Long term evolutionary experiment
- Richard Lenski
- *E. coli*
- Daily transfer
- Started Feb 1988
- >10,000 transfer
- > 66,000 generations

Rise and fall: LTEE



E. coli, LTEE: Wielgoss et al., PNAS 2012

Fall of the mutator allele



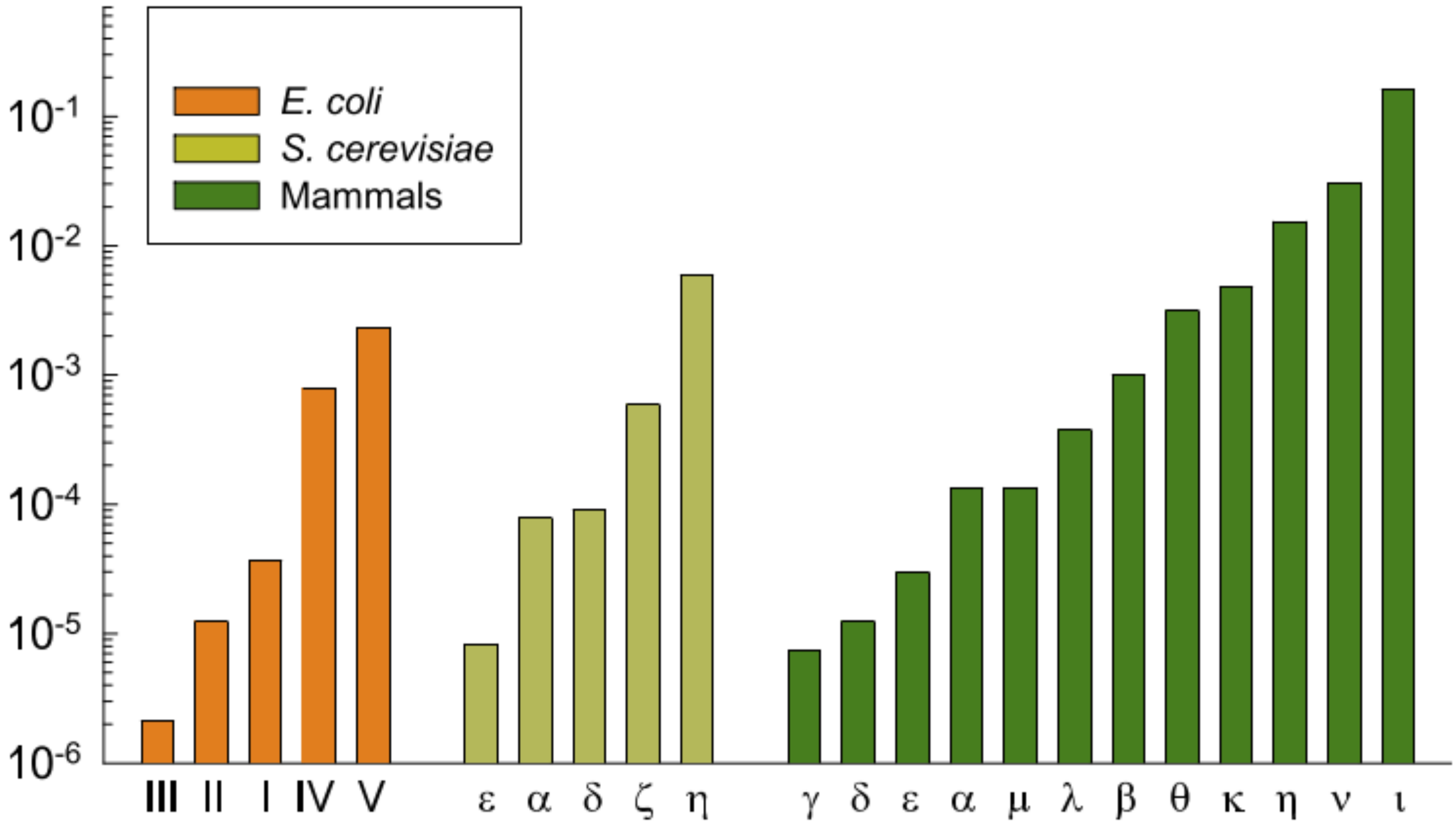
E. coli, MutS: Turrientes et al. PLOS One 2013

Variability in mutation rates

Within individuals

DNA polymerase error rate

Lynch 2011

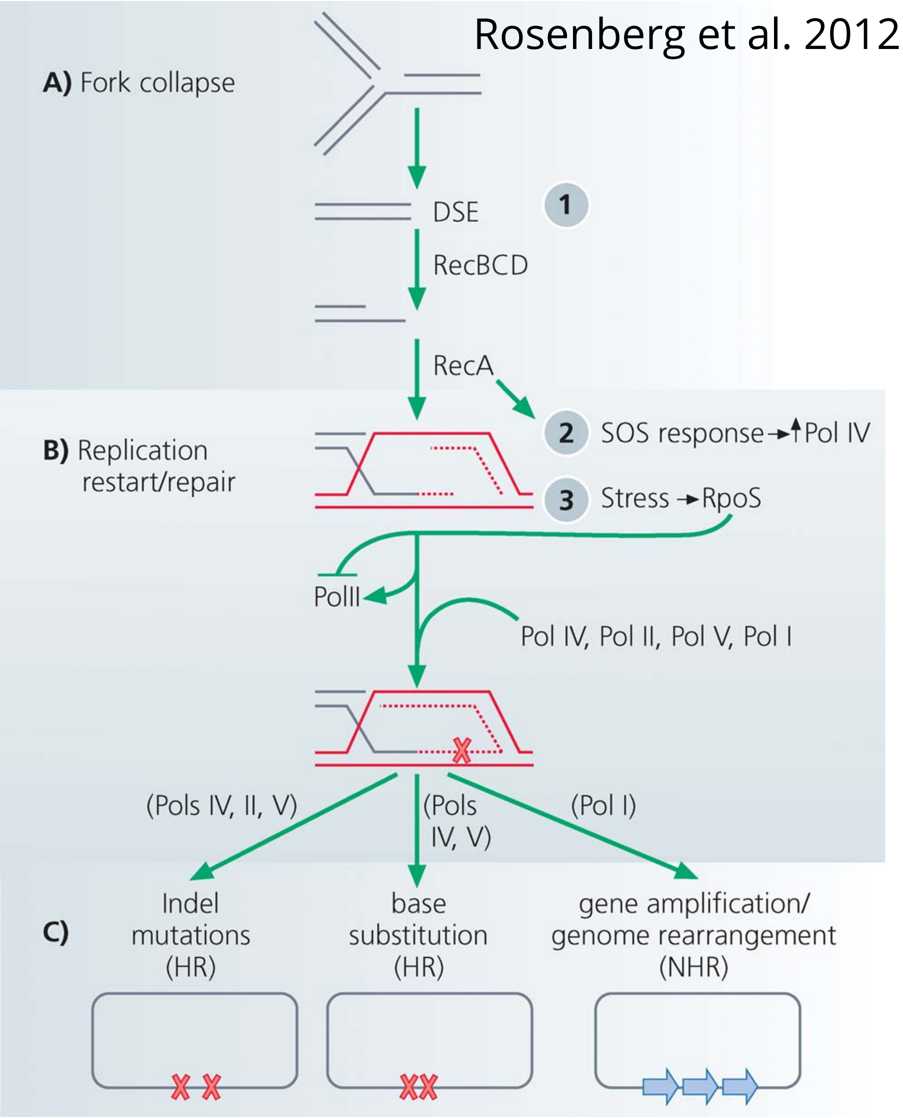


Stress-induced mutation

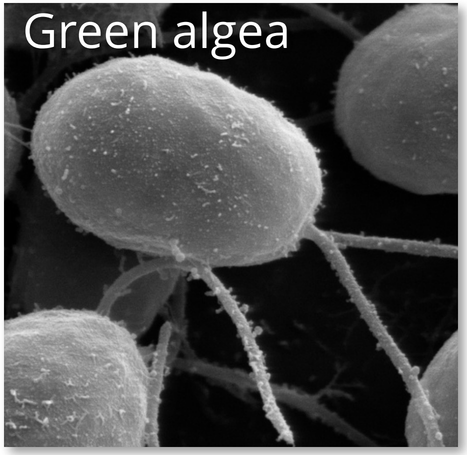
In *E. coli:*

- 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

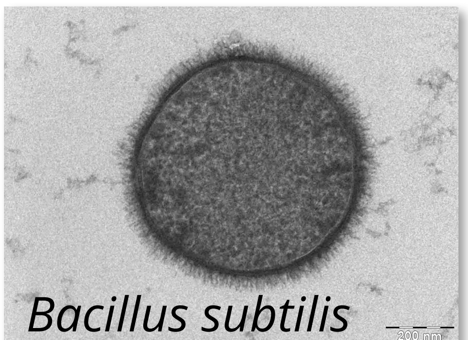
Rosenberg et al. 2012

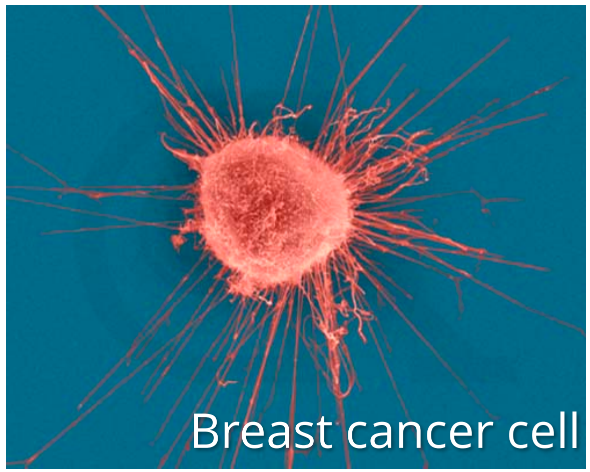


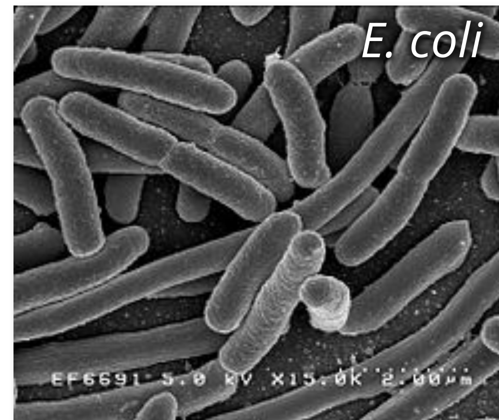
Evidence


Green algea

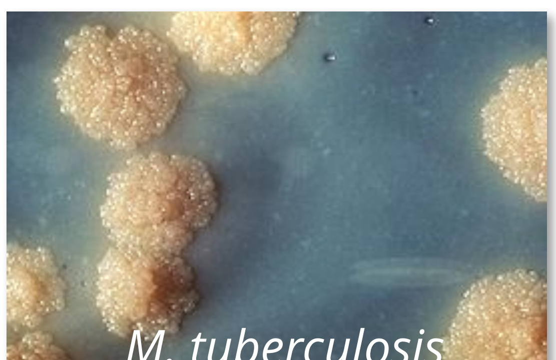

Nematodes

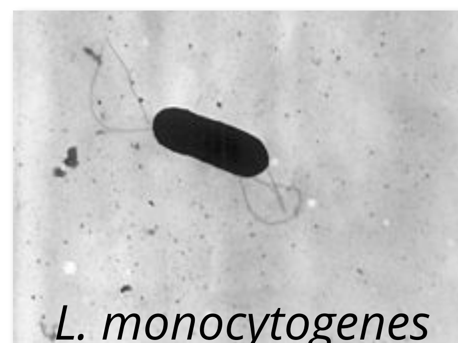

Bacillus subtilis


Breast cancer cell


E. coli


D. Melanogaster


M. tuberculosis


L. monocytogenes

Evolution of stress-induced mutation

Null hypothesis

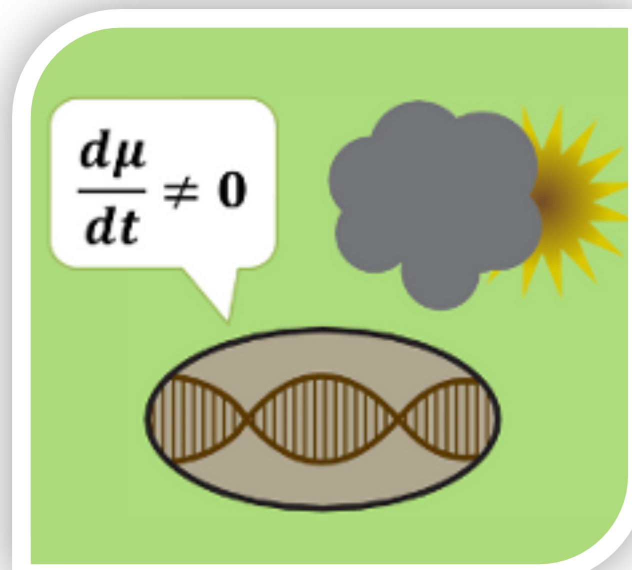
- Mutagenesis is the by-product of stress

Alternative non-adaptive hypotheses

- Cost of replication fidelity
- Drift barrier hypothesis

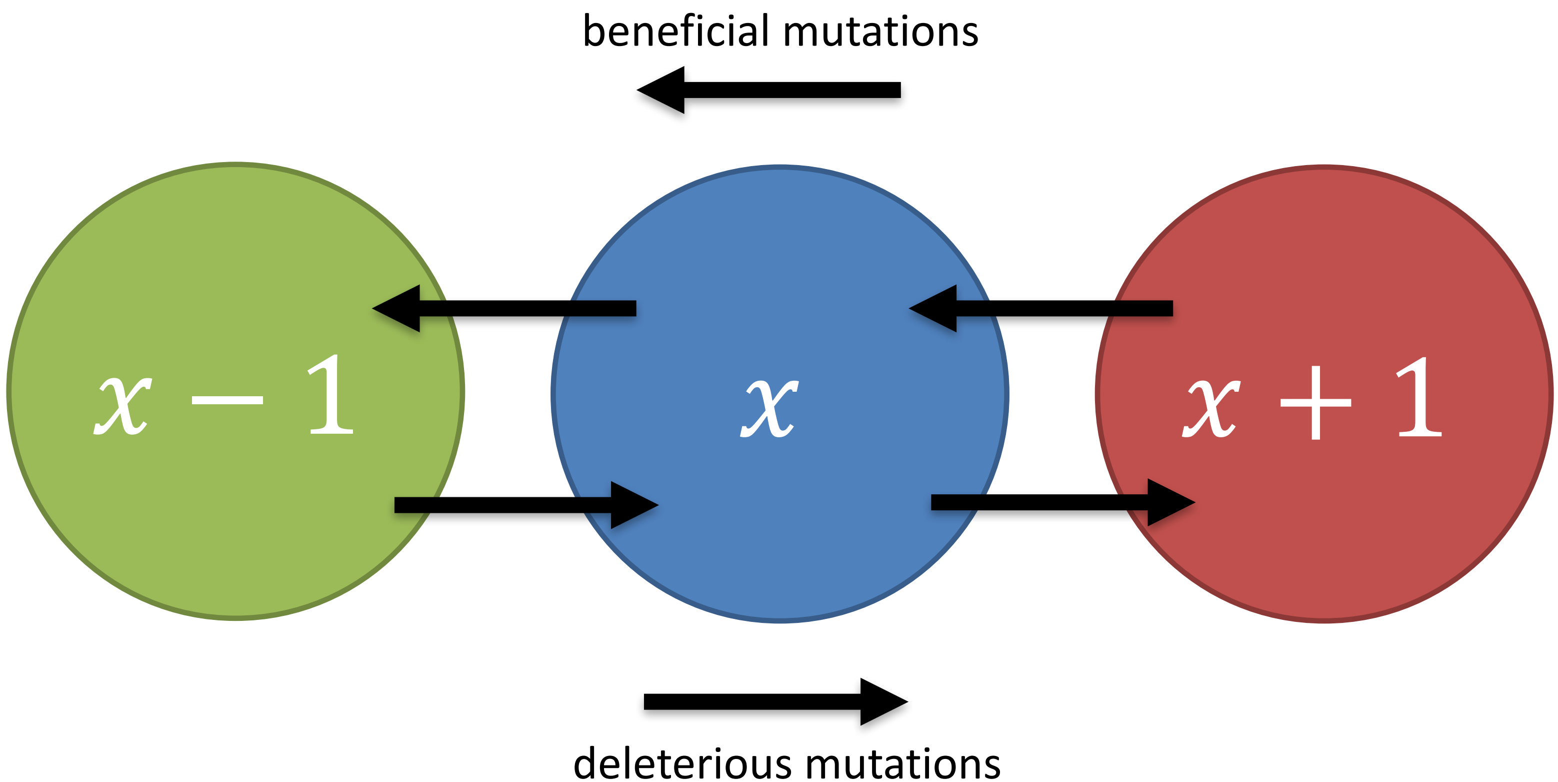
Adaptive hypothesis

- 2nd order selection

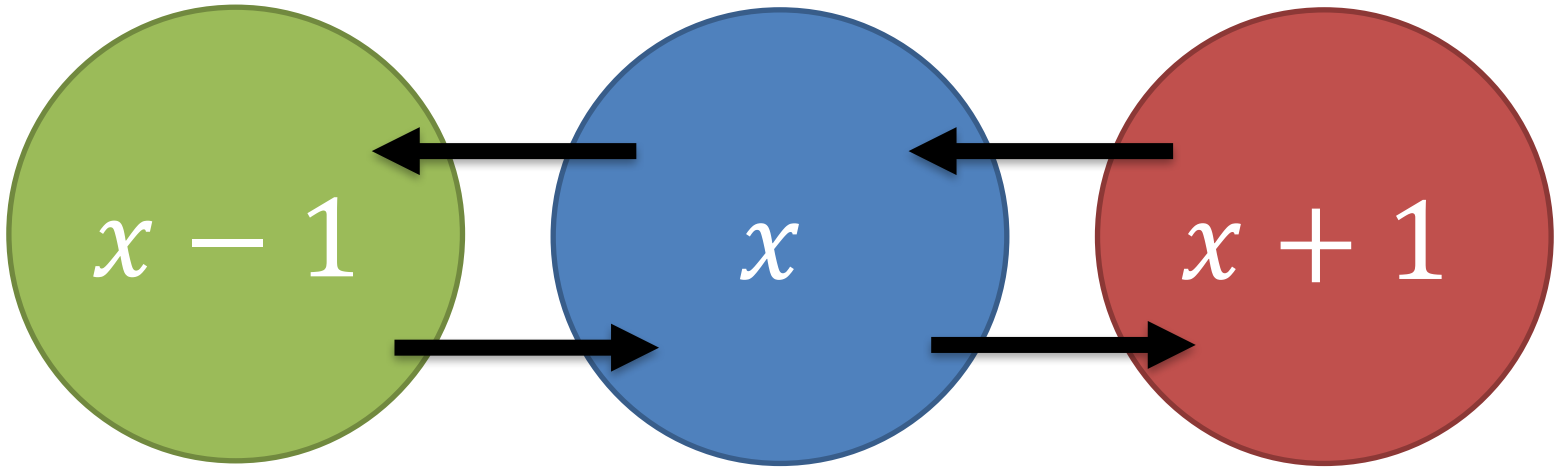


Constant environment

x – number of mutant genes



Ram & Hadany, Evolution 2012



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

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

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

Ram & Hadany, Evolution 2012

Constant environment

General solution

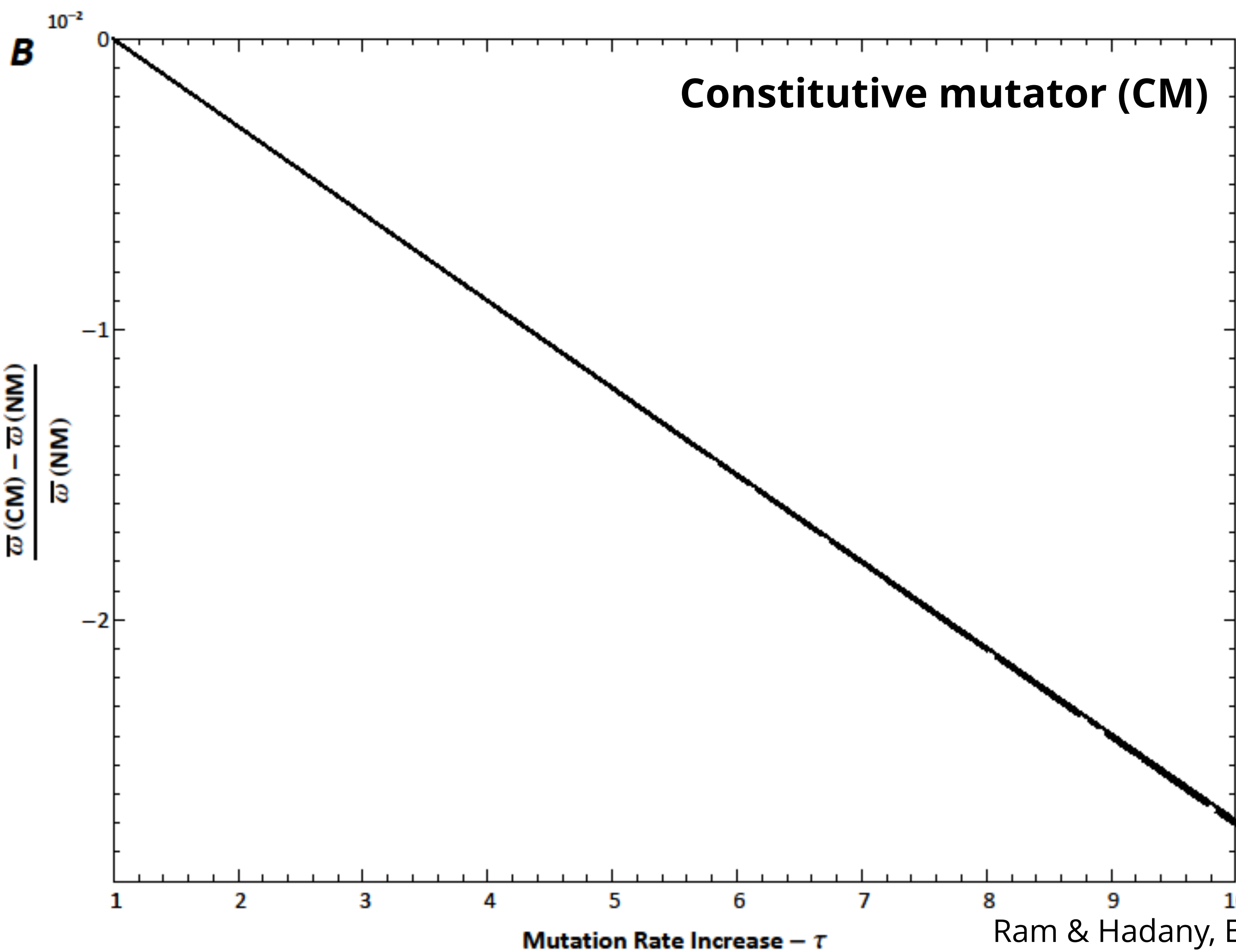
$$sign\frac{\partial \overline{\omega}}{\partial m_x} = sign\,(\overline{\omega} - \omega_x)$$

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

Selection doesn’t always reduce the mutation rate!

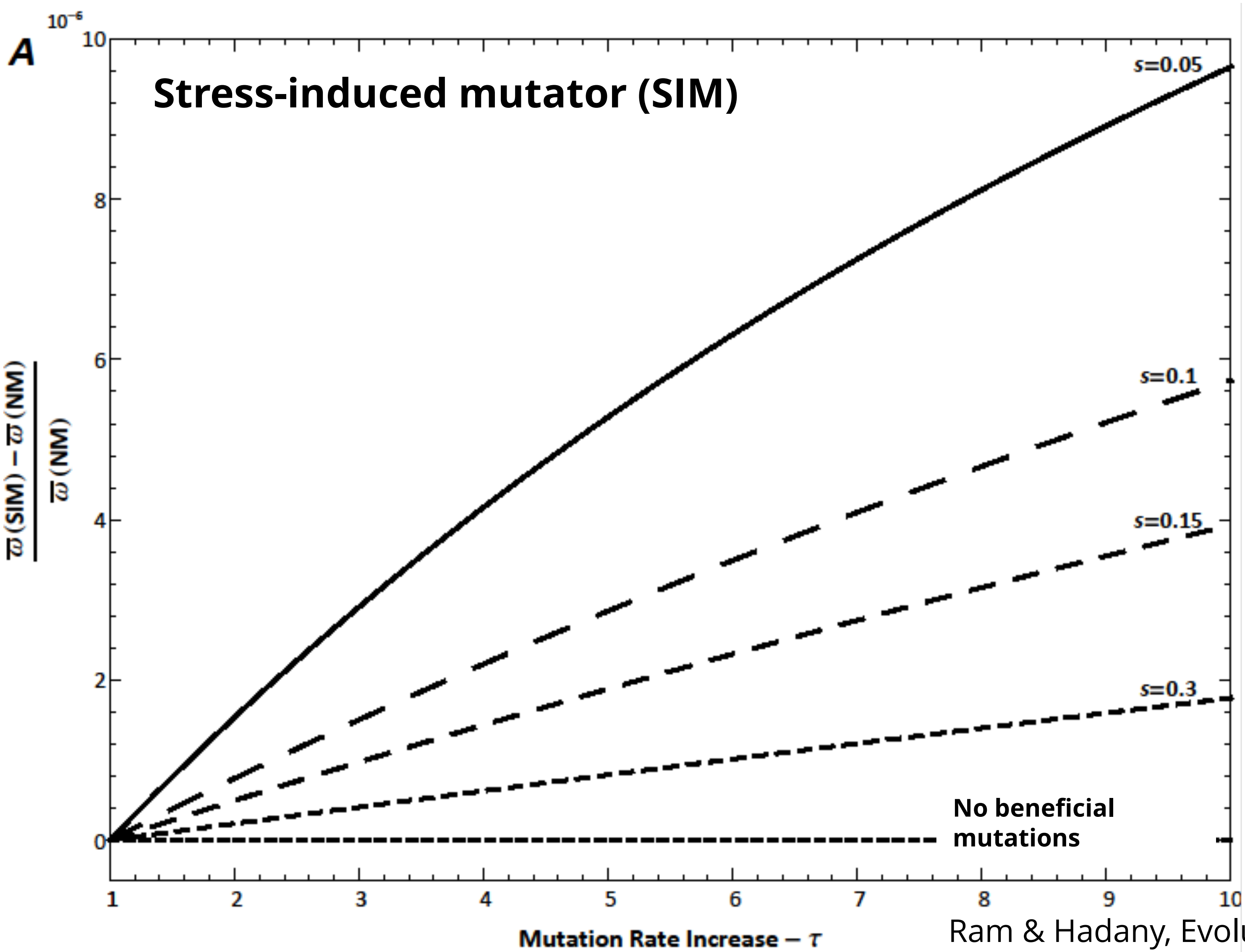
Ram & Hadany, Evolution 2012

Constant environment



Ram & Hadany, Evolution 2012

Constant environment



Ram & Hadany, Evolution 2012

Modified Mean Fitness Principle

Mutation, migration, individual learning…

Increasing generation of variation in below-average individuals increases the population mean fitness

Modifier allele favored by selection

Ram, Altenberg, Liberman, Feldman, TPB 2018

Changing environments

The Red Queen hypothesis:

van Valen, 1973

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

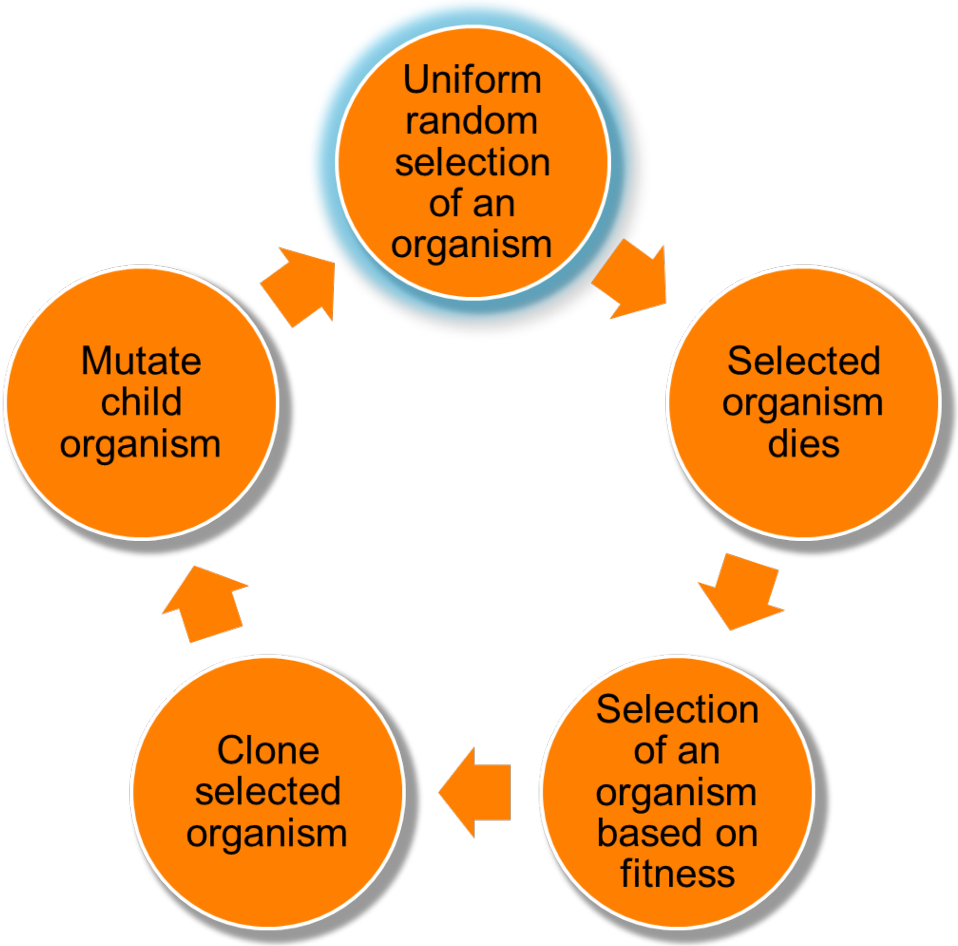
- Lewis Carrol, Through the Looking Glass

Changing environments

Evolutionary simulations

- 100,000 asexual individuals
- 1,000 genes
- Random environmental changes
- Competitions between mutator alleles

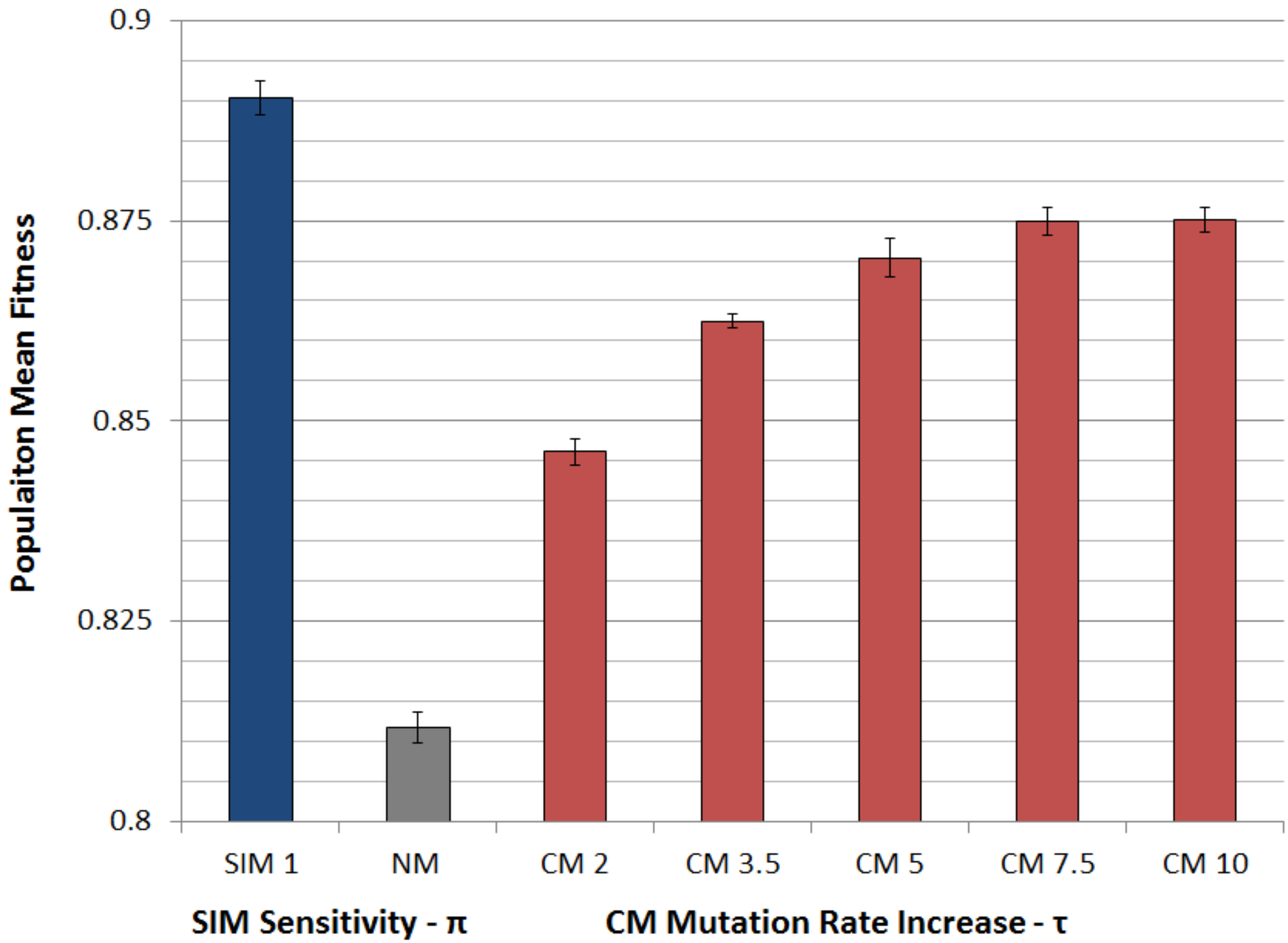
100,000s simulations, run on dedicated cluster with 400-500 cores



https://github.com/yoavram/proevolutionsimulation

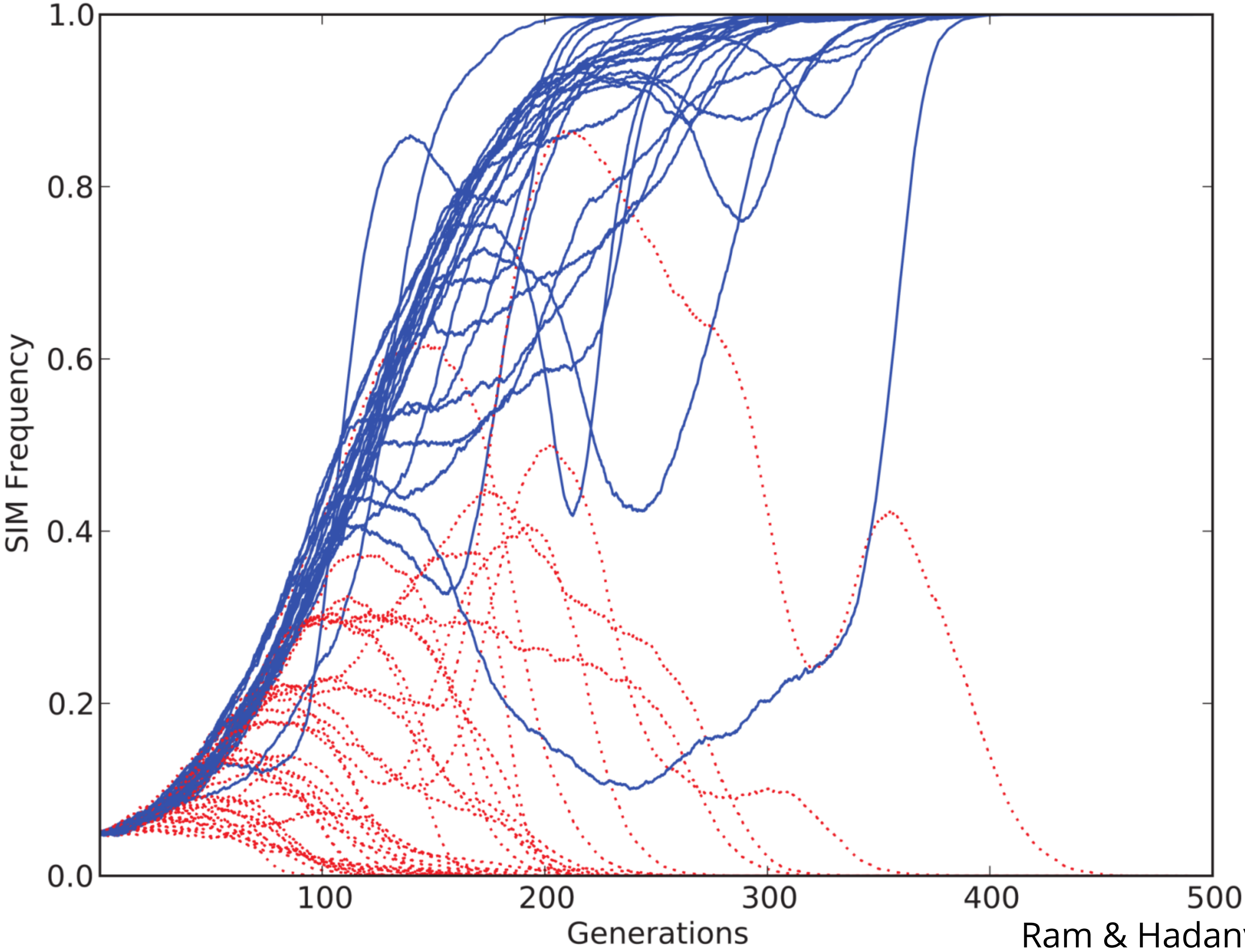
Ram & Hadany, Evolution 2012

Populations with SIM are fitter



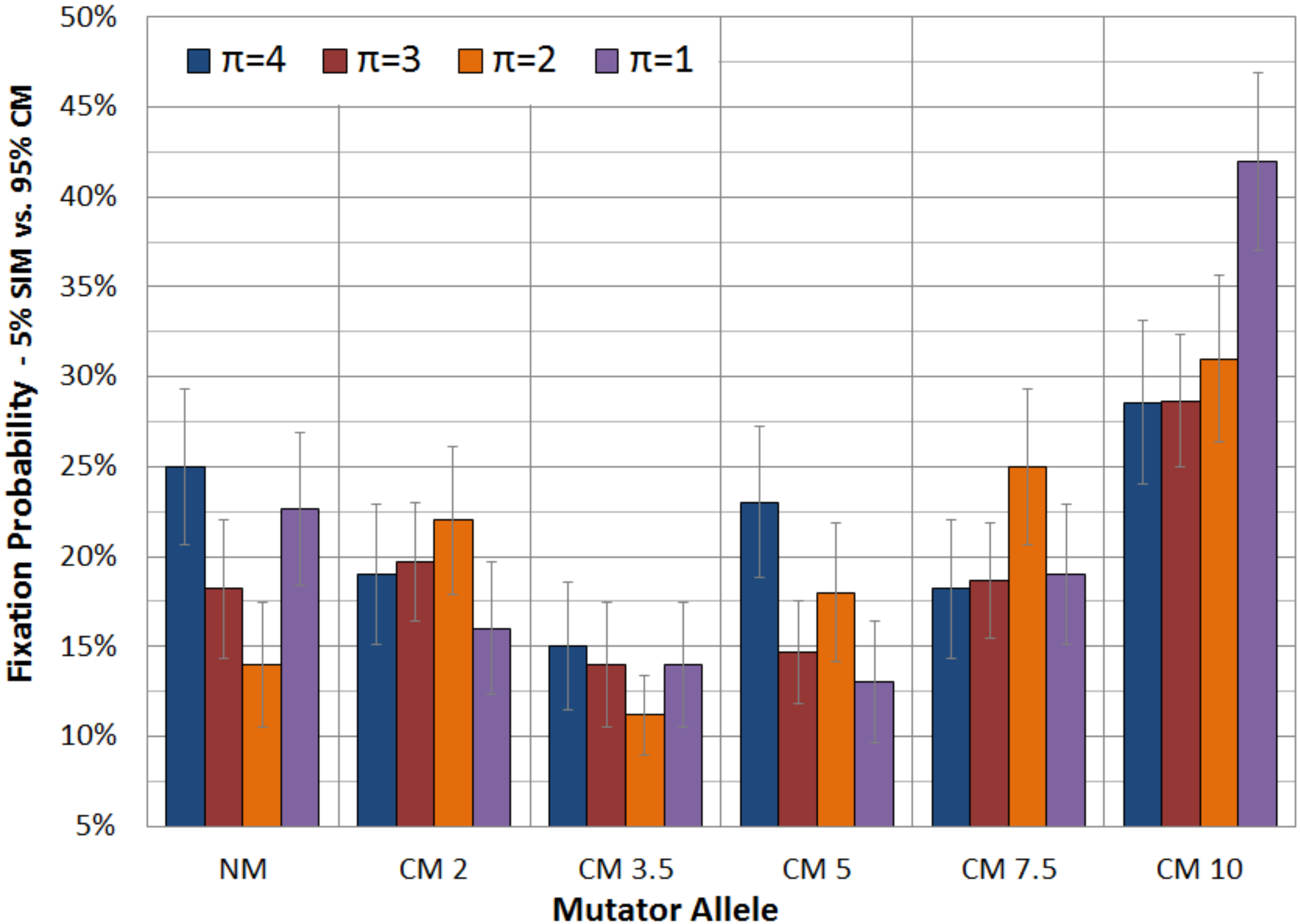
Ram & Hadany, Evolution 2012

SIM wins competitions



Ram & Hadany, Evolution 2012

SIM wins competitions

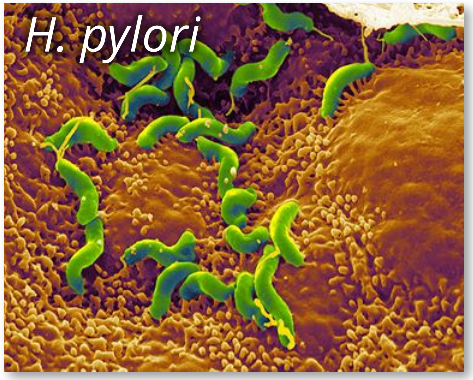


Ram & Hadany, Evolution 2012

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 <u>evolvability</u>



Consequences of Stress-Induced Mutagenesis

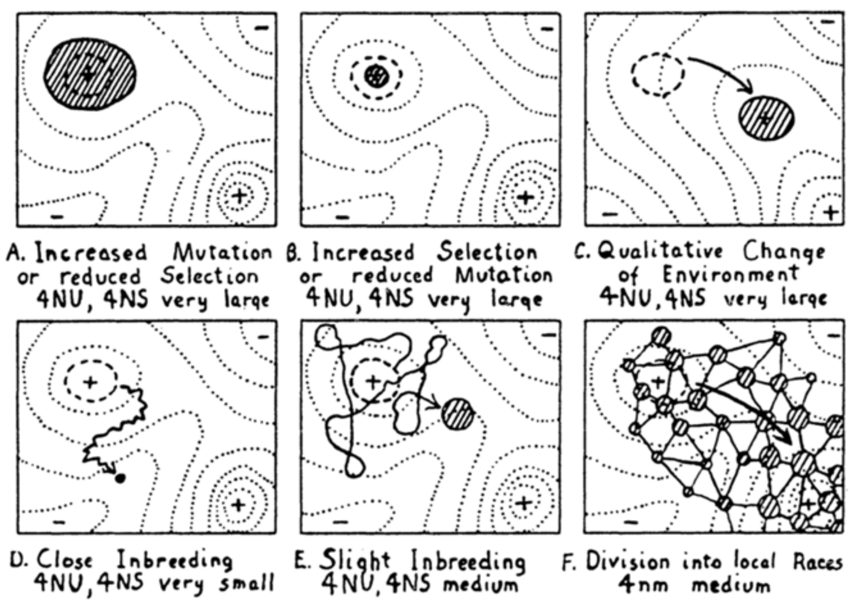
Can SIM make adaptation **faster?**

Malene Thyssen

Adaptive peak shifts

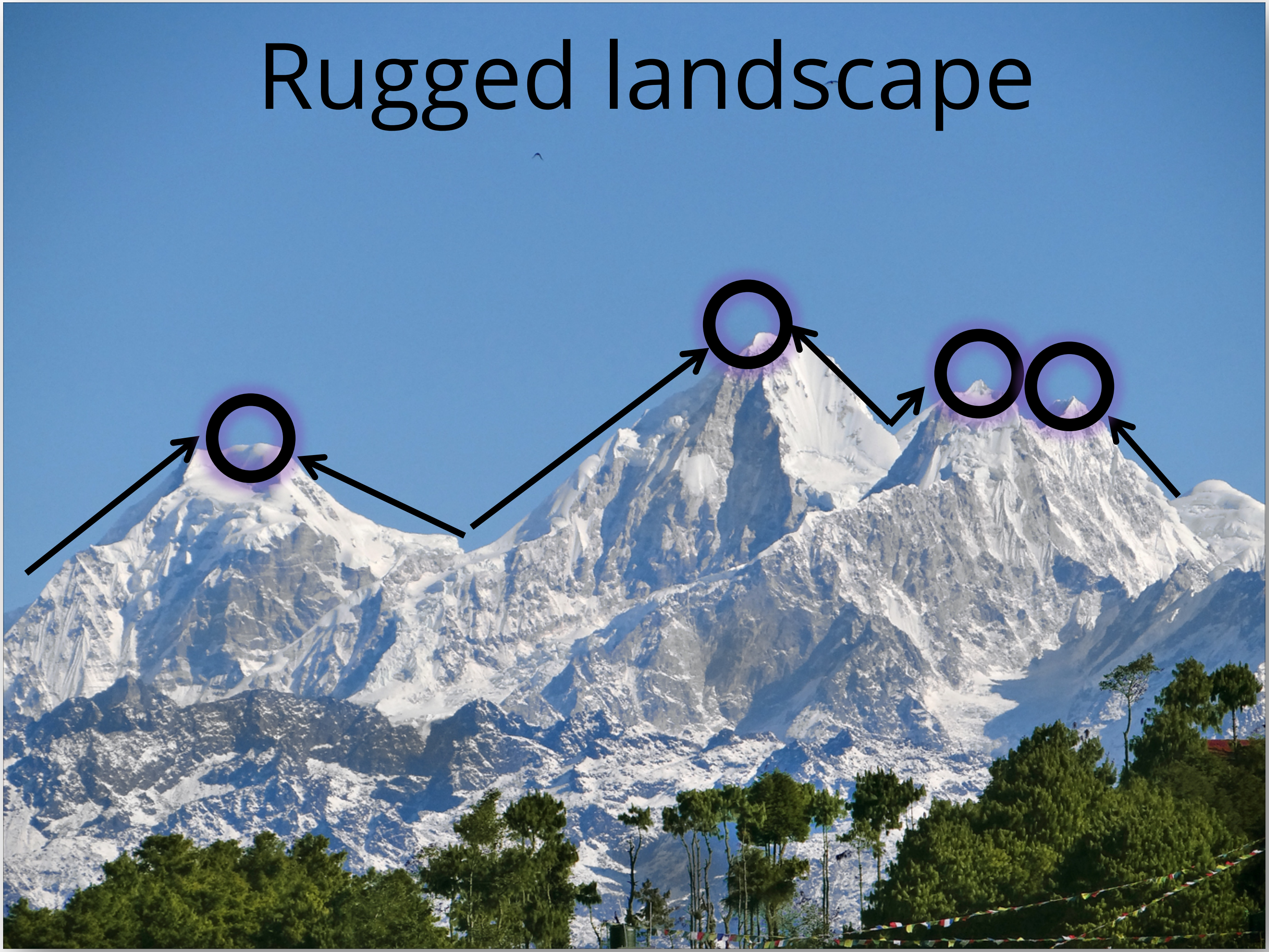
Sewall Wright, 1931:

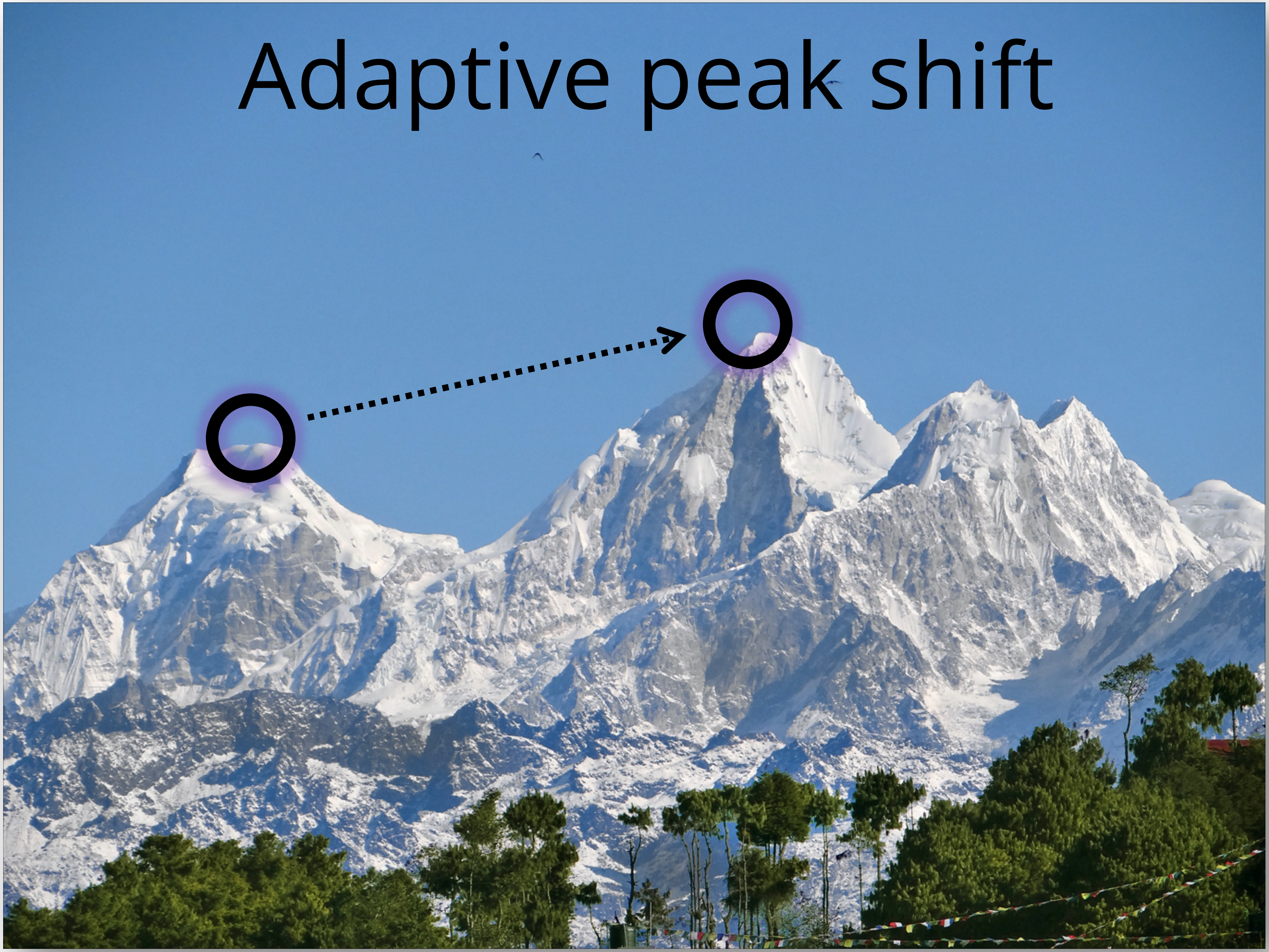
If a new adaptation requires several, separately deleterious mutations, how can it evolve?



Wright, Am. Nat. 1988

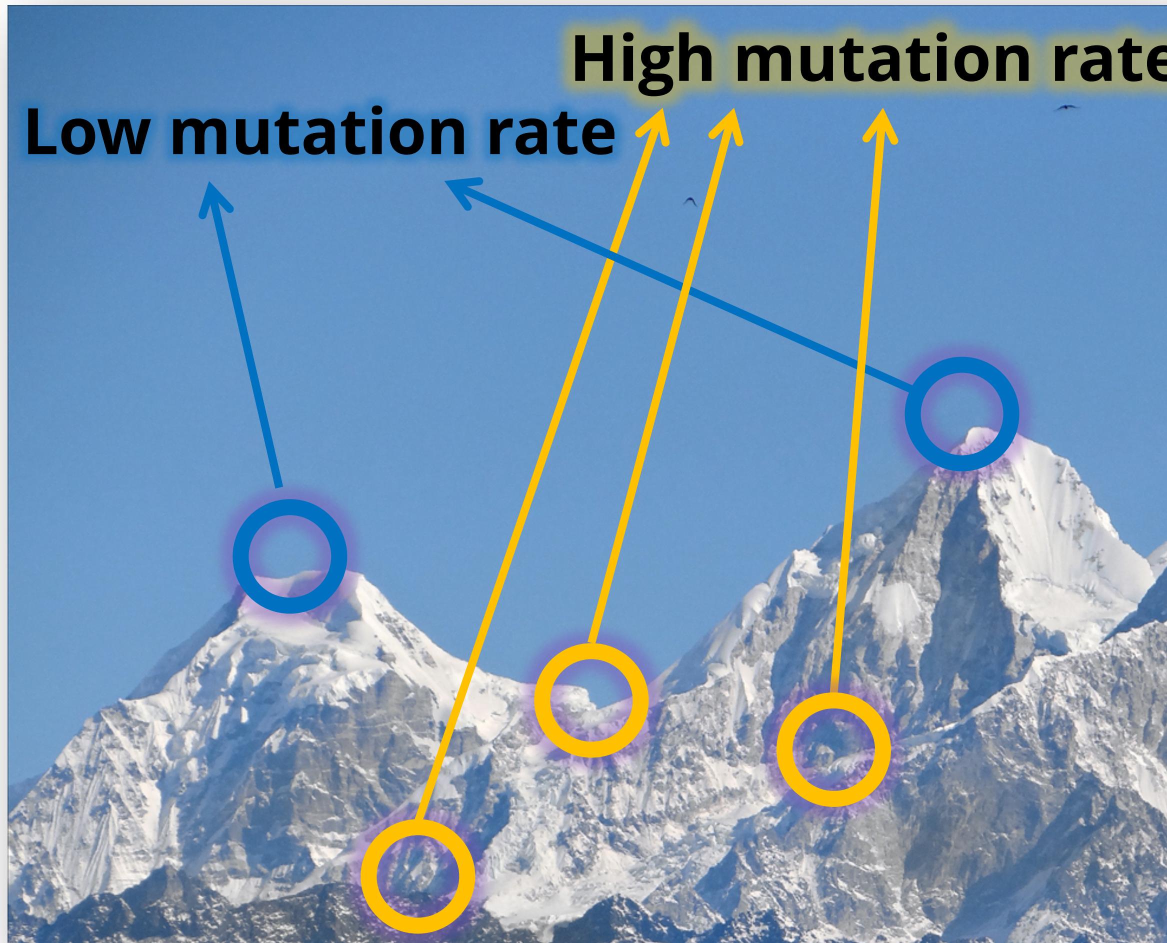

Simple landscape


Rugged landscape

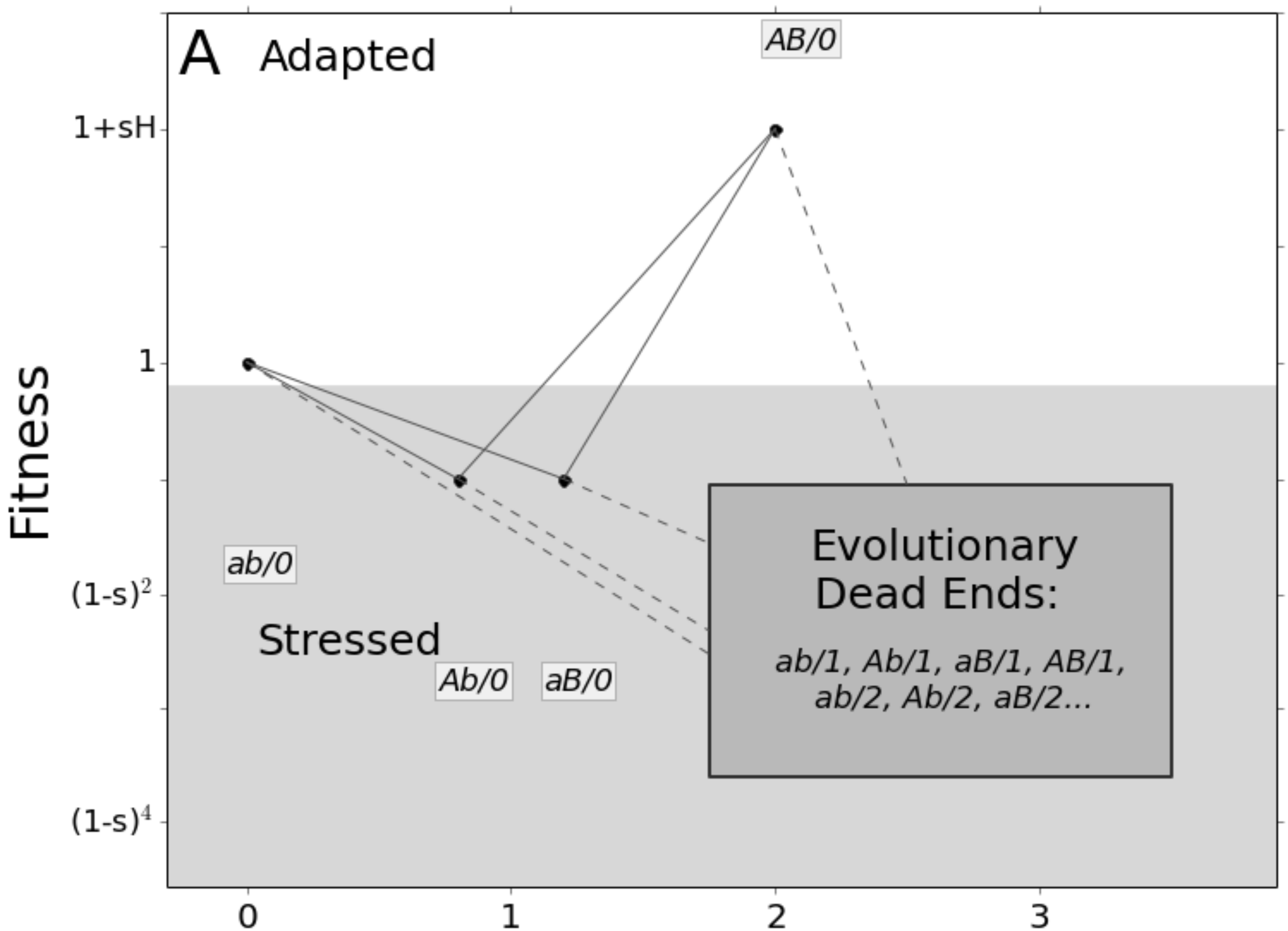

Adaptive peak shift

SIM & rugged landscapes

Increasing the mutation rate in individuals below both peaks



Deterministic model



Ram & Hadany, PRSB 2014

Estimating adaptation time

Adaptation has two stages:

1. **Waiting for the double mutant**
2. **Fixation of the double mutant**

Estimating adaptation rate

Adaptation has two stages:

1. **Waiting for the double mutant**
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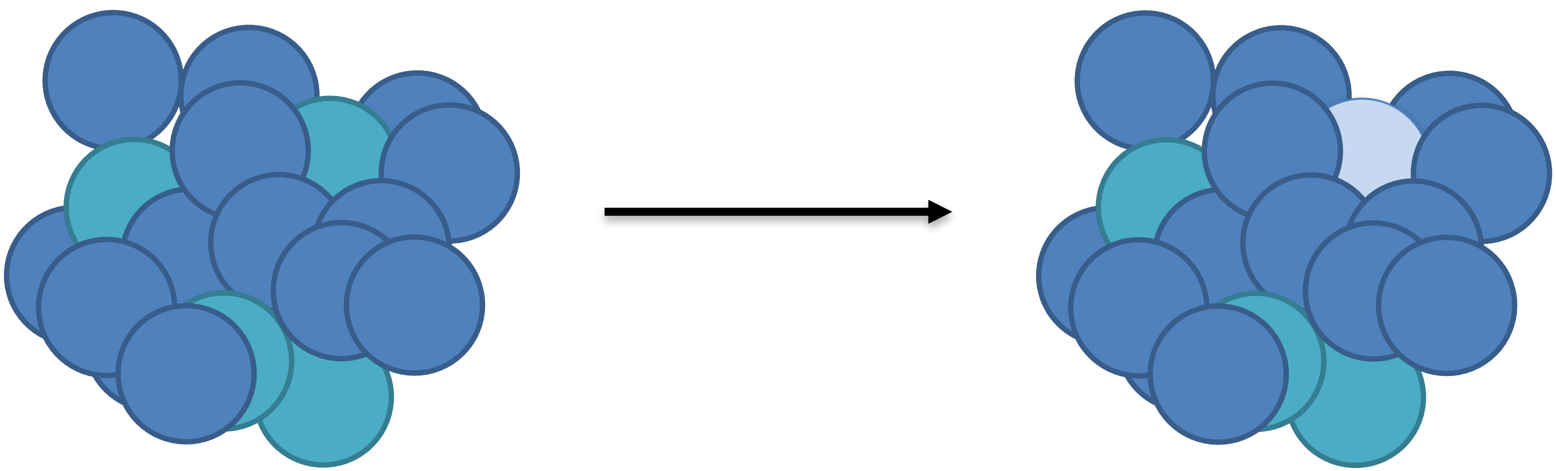

Estimating adaptation rate

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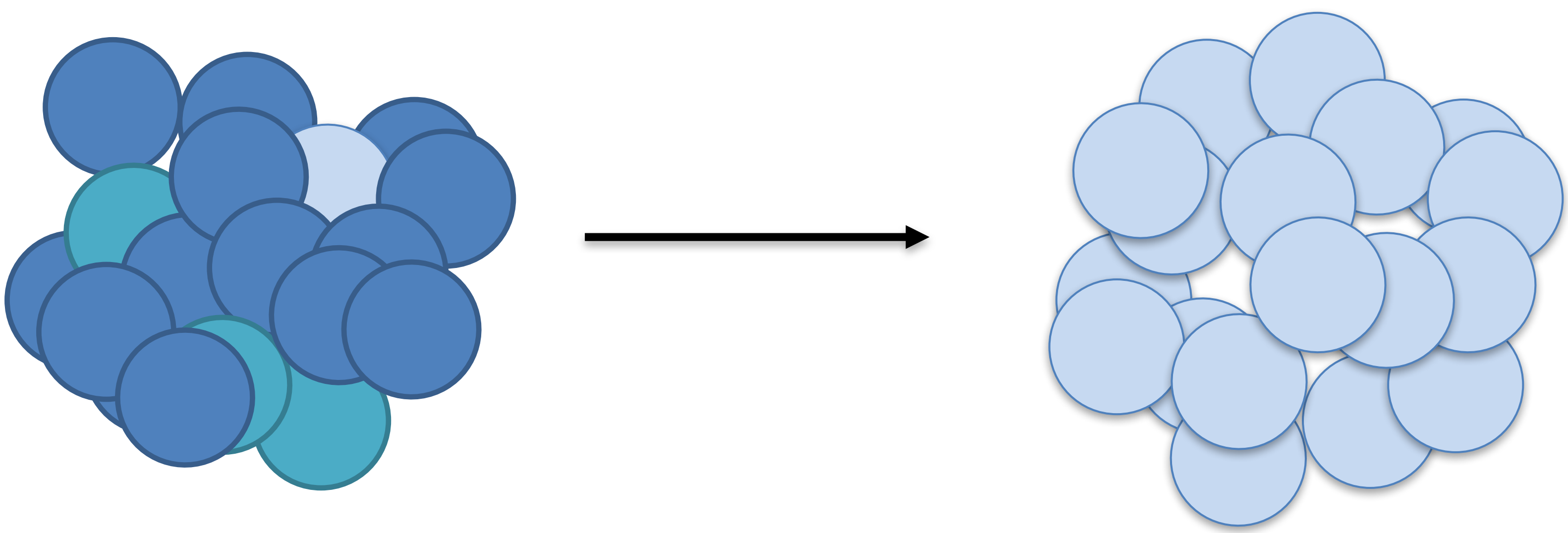


Deterministic model

The probability q that a random offspring is a double mutant, given there are no double mutants in the current generation:

$$q = \mu^2 \mathrm{e}^{-\mathrm{U}} \cdot e^{-\frac{U}{s}} + \mu e^{-U} \cdot 2\frac{\mu}{s} e^{-\frac{U}{s}}$$

$$q_{SIM} = \mu^2 \mathrm{e}^{-\mathrm{U}} \cdot e^{-\frac{U}{s}} + \boldsymbol{\tau} \mu e^{-\boldsymbol{\tau} U} \cdot 2\frac{\mu}{s} e^{-\frac{U}{s}}$$

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

Ram & Hadany, PRSB 2014

Deterministic model

The fixation probability of the double mutant:

Eshel 1981

$$\rho = 2\frac{sH}{1+sH} \approx 2sH$$

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

Ram & Hadany, PRSB 2014

Deterministic model

The probability that one or more double mutants appear in the next generation:

$$\mathbf{1 - (1 - \boldsymbol{q})^{\boldsymbol{N}} \approx \boldsymbol{Nq}}$$

This waiting time follows a geometric distribution with rate

$$\boldsymbol{\nu = Nq\rho}$$

which is the adaptation rate.

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

Ram & Hadany, PRSB 2014

Deterministic results

The rate of adaptation with normal mutation (NM):

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

The rate of adaptation with high mutation (CM):

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

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

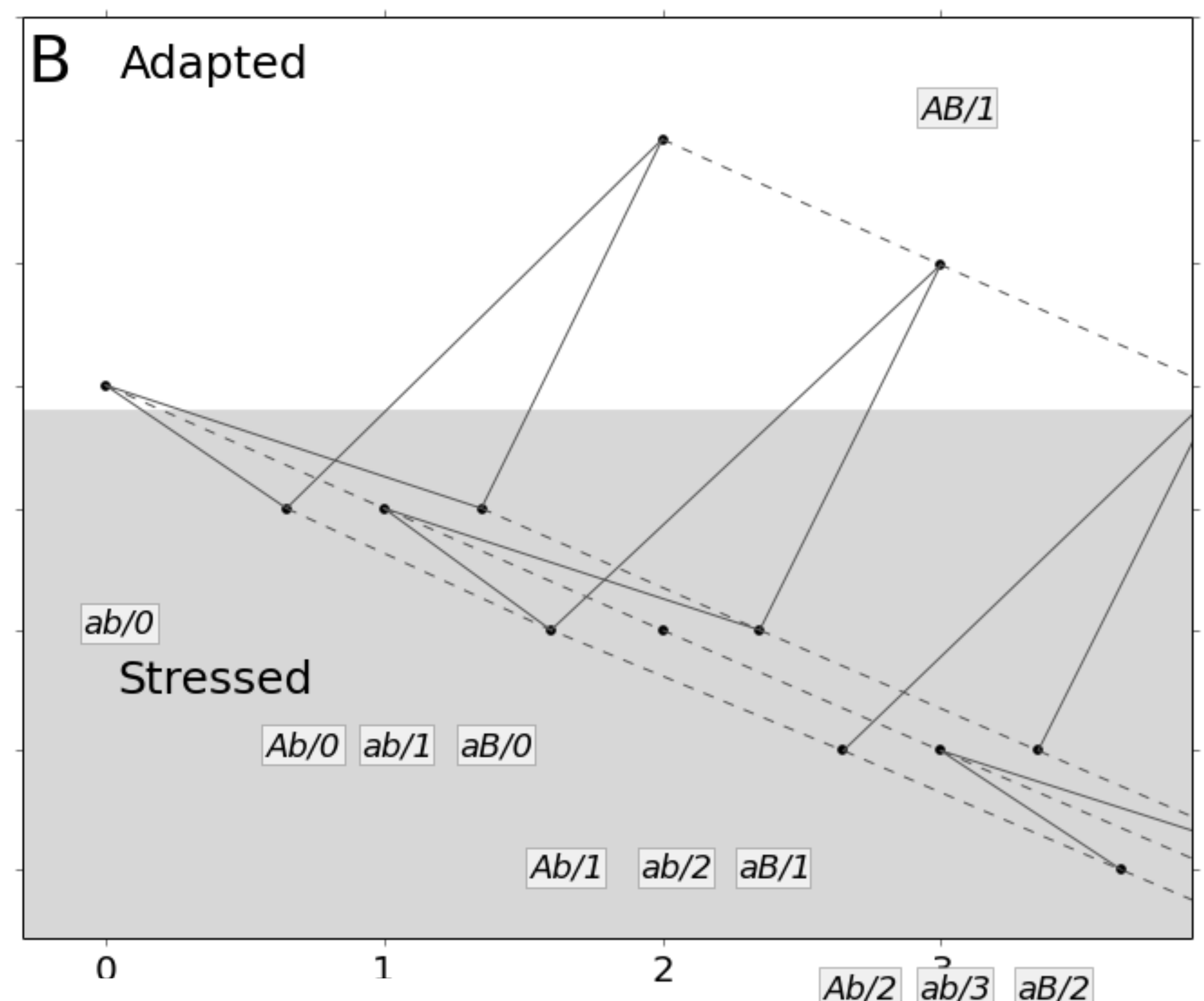
$$\nu_{SIM} \approx \boldsymbol{\tau} \cdot \nu_{NM}$$

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

Stochastic model



No MSB assumption

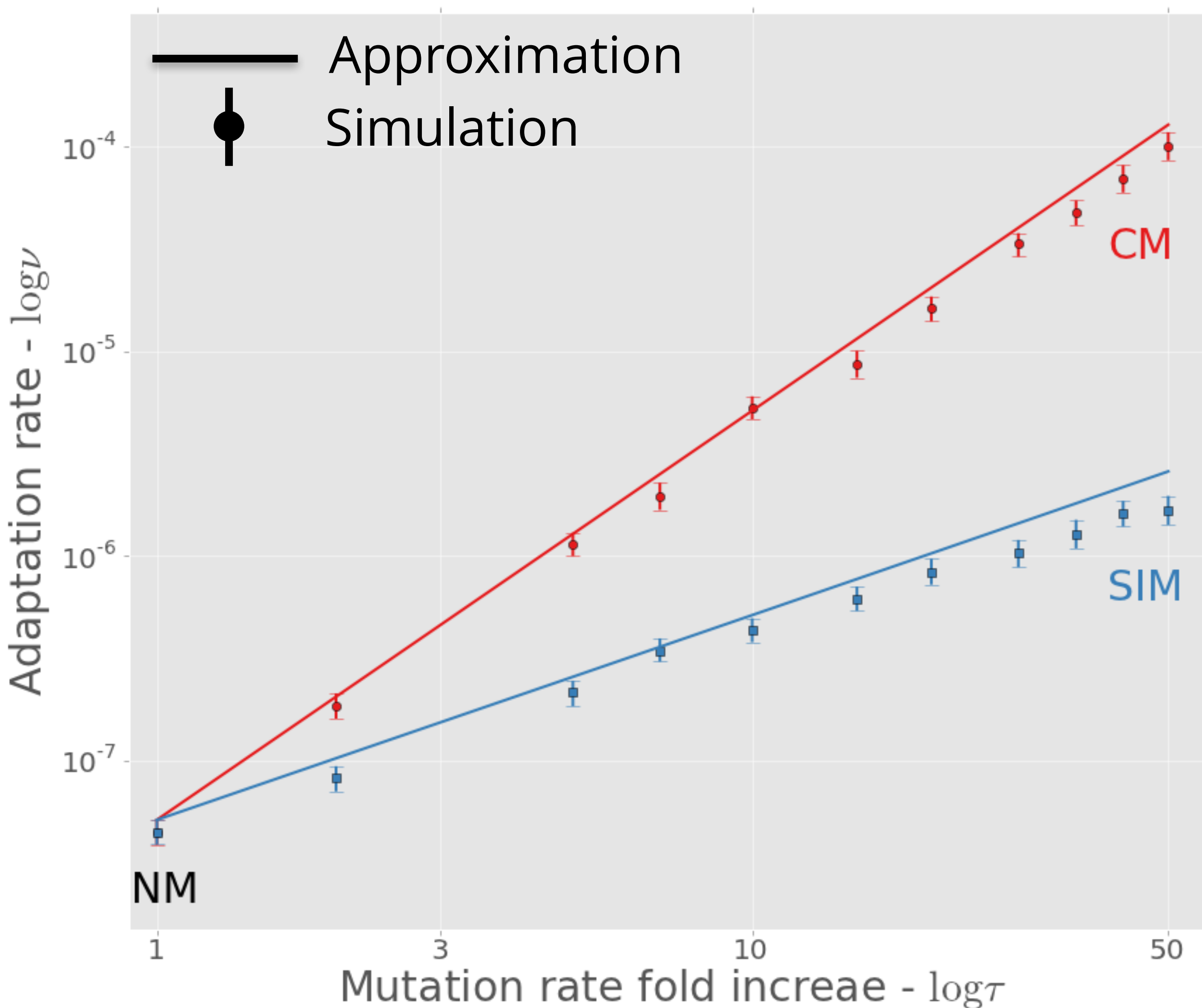
No Dead Ends

Genetic drift

Ram & Hadany, PRSB 2014

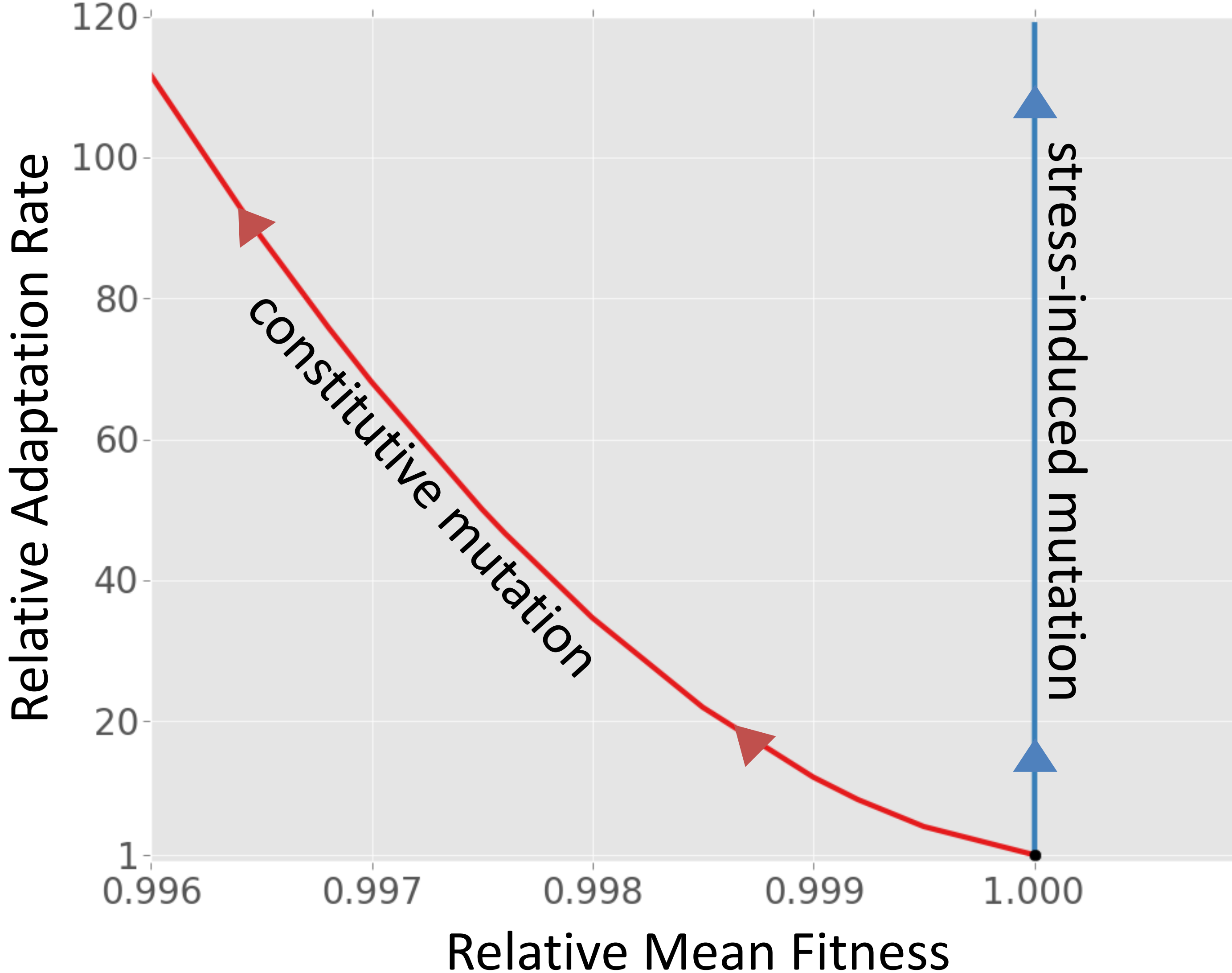
https://github.com/yoavram/ruggedsim

Adaptation rate



Ram & Hadany, PRSB 2014

Stress-induced mutation increases adaptation rate without jeopardizing mean fitness



Ram & Hadany, Proceedings B, 2014

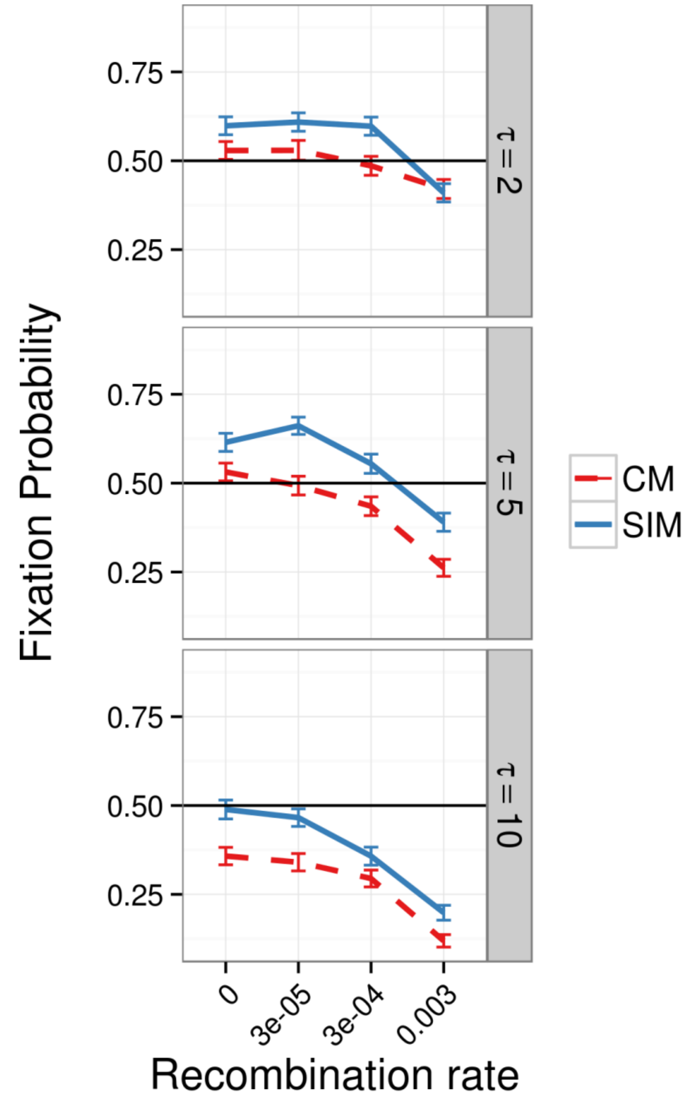
In the presence of rare recombination

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

In the presence of HGT

Results suggest:

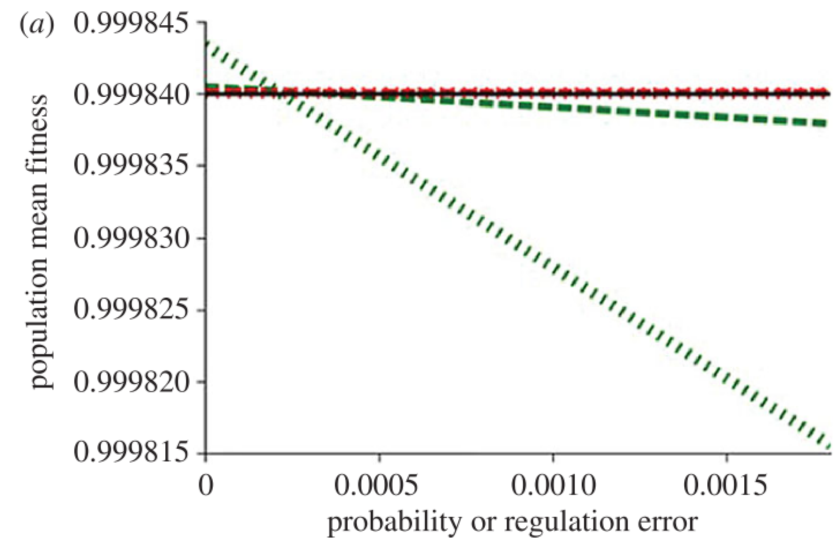
- **SIM** > **CM**
- **SIM** >= **NM**
- When **HGT is not much more frequent than mutation**



Ram & Hadany, under review

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, Roy Soc Open Sci 2017

Evolution of stress-induced mutation

- **In constant environments**

Ram & Hadany, Evolution 2012

Ram, Altenberg, Liberman, Feldman, TPB 2018

- **In complex & changing environments**

Ram & Hadany, Evolution 2012

Ram & Hadany, Proceedings B 2014

- **In the presence of rare recombination**

Ram & Hadany, under review

- **In the face of regulation errors**

Dellus-Gur, Ram & Hadany, Royal Society Open Science 2017

Ongoing: experimental validation

Cooper lab, University of Houston

Computational Evolution Lab

IDC Herzliya

- Generation & transmission of variation
- Microbial evolution & ecology
- Cultural evolution

Now recruiting:

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