The Evolution of Stress-Induced Mutagenesis

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Variability in mutation rates

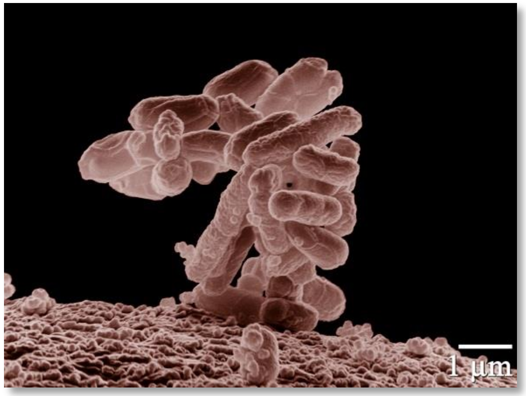
Between species

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 a constant environment

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

Mutation-selection balance

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

Evolution in a changing environment

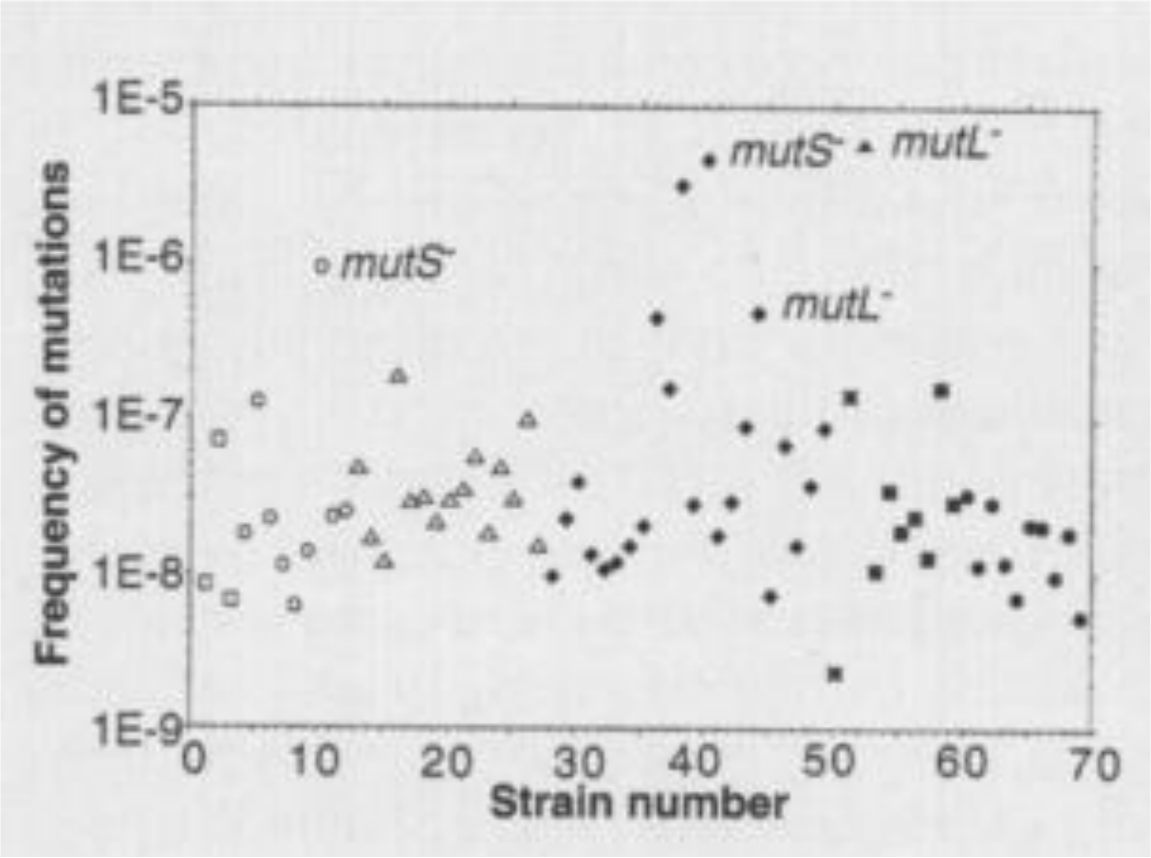
- In changing environments **rapid adaptation** can be favored by natural selection (*adaptability*)
- The mutation rate must **balance** between *adaptability* and *adaptedness*

Leigh 1973

Variability in mutation rates

Within species

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

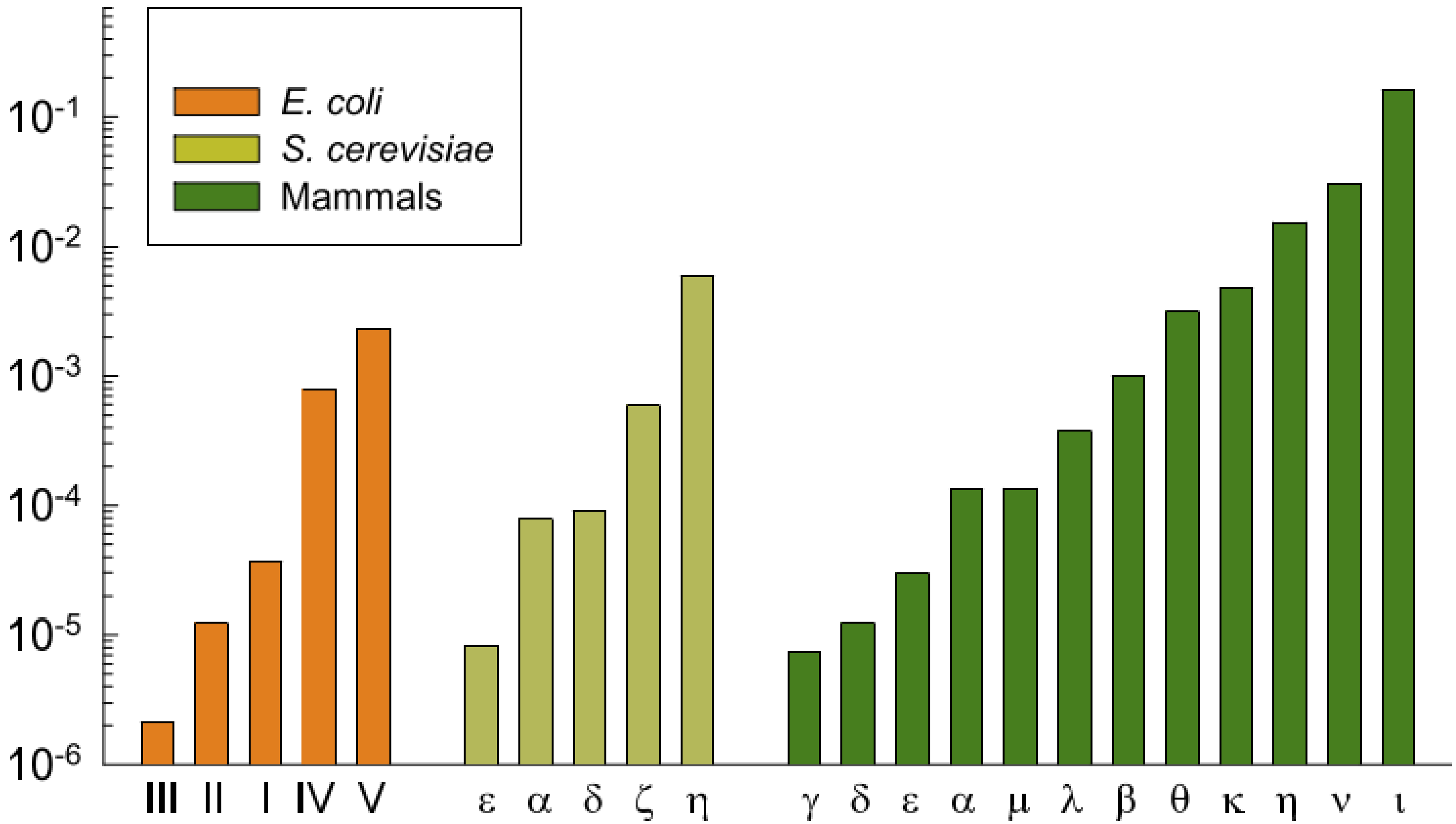


Variability in mutation rates

Within individuals

DNA polymerase error rate

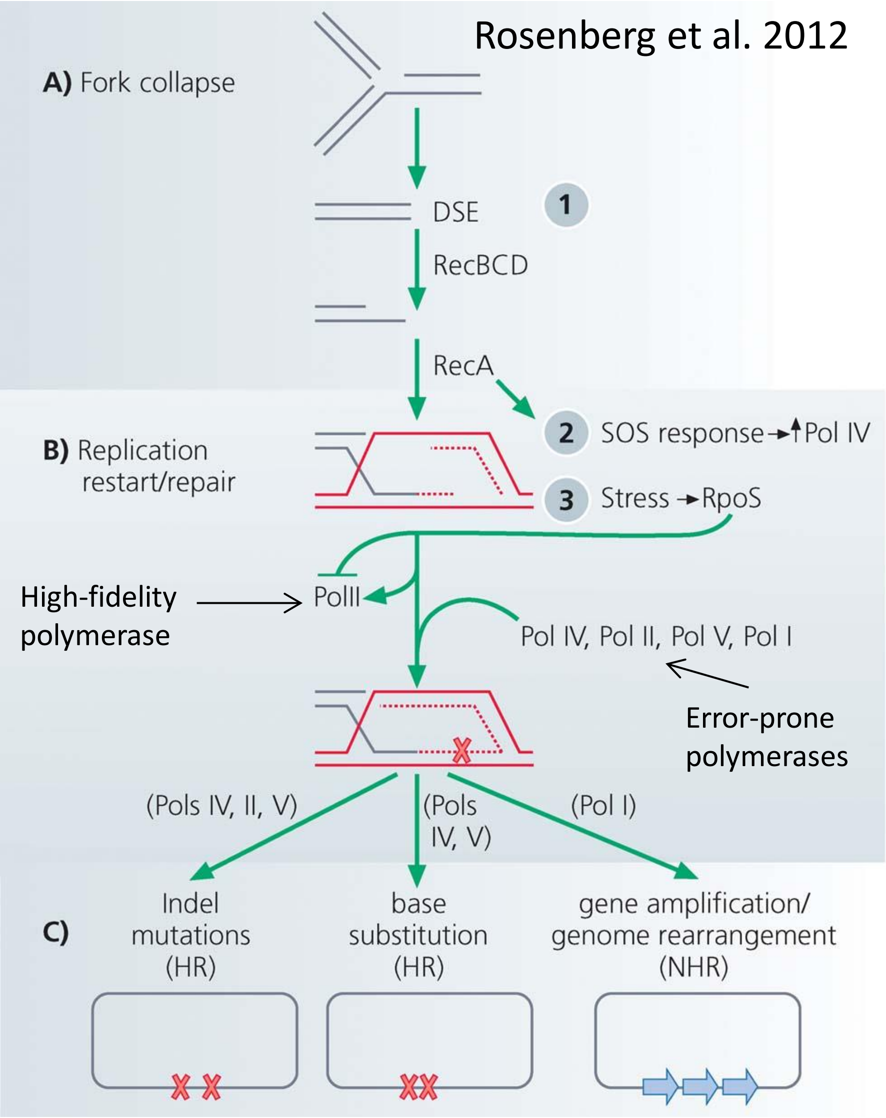
Lynch 2011



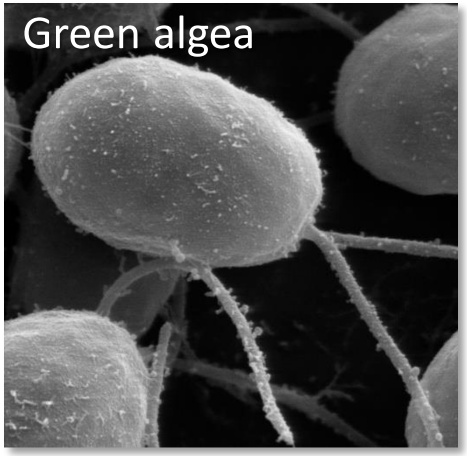
Stress-induced mutagenesis

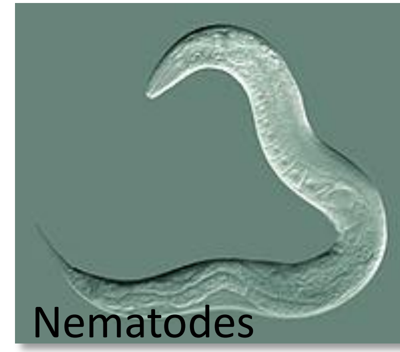
In *E. coli:*

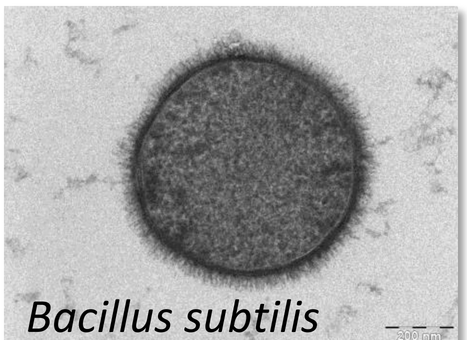
- Error prone polymerase induced by stress responses:
  - SOS response
  - DNA damage
  - Starvation
- Mismatch repair system
- Other mechanisms:
  - Galhardo et al. 2007
  - Al Mamun, Science 2012



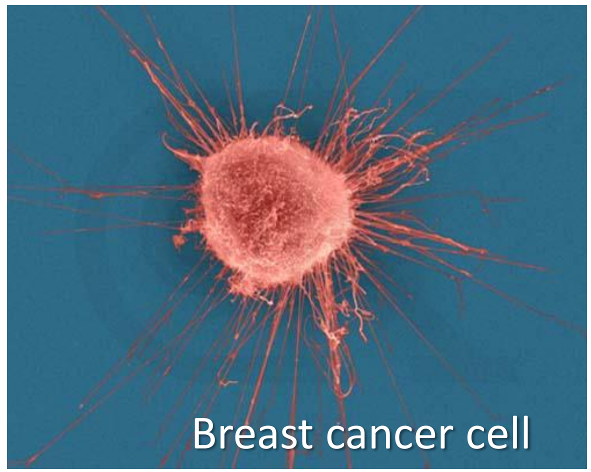
Evidence

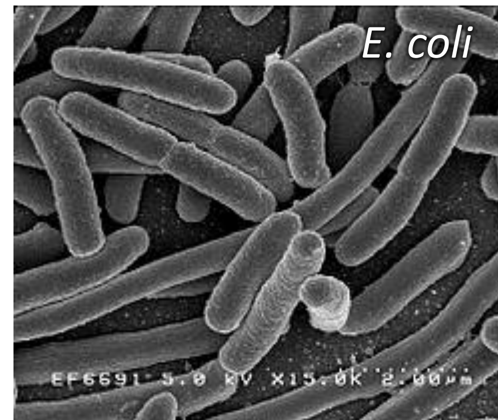

Green algea


Nematodes



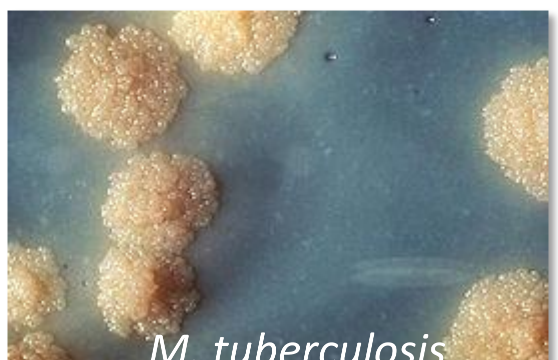
Bacillus subtilis

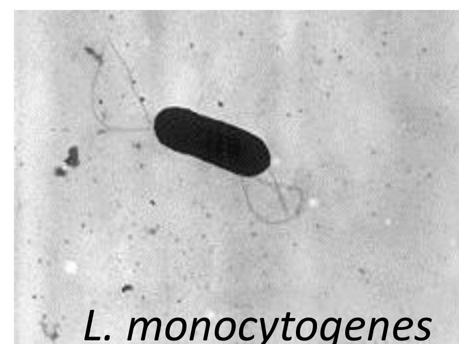

Breast cancer cell



E. coli


D. Melanogaster


M. tuberculosis


L. monocytogenes

Evolution of stress-induced mutagenesis

Null hypothesis

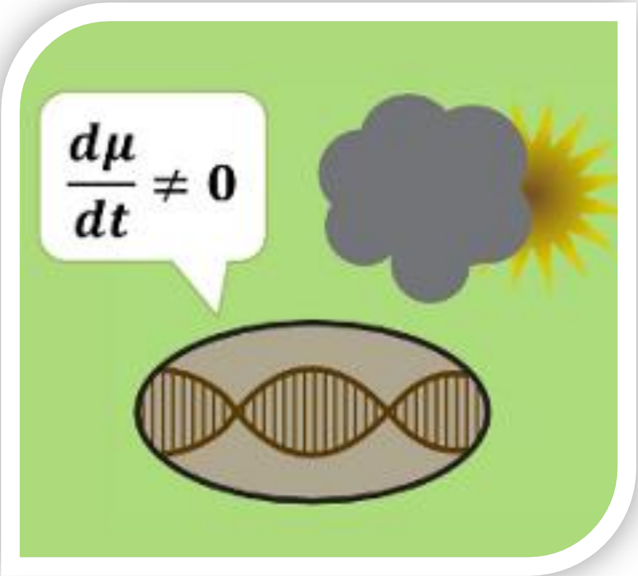
- Mutagenesis is the by-product of stress

Alternative non-adaptive hypotheses

- Cost of replication fidelity

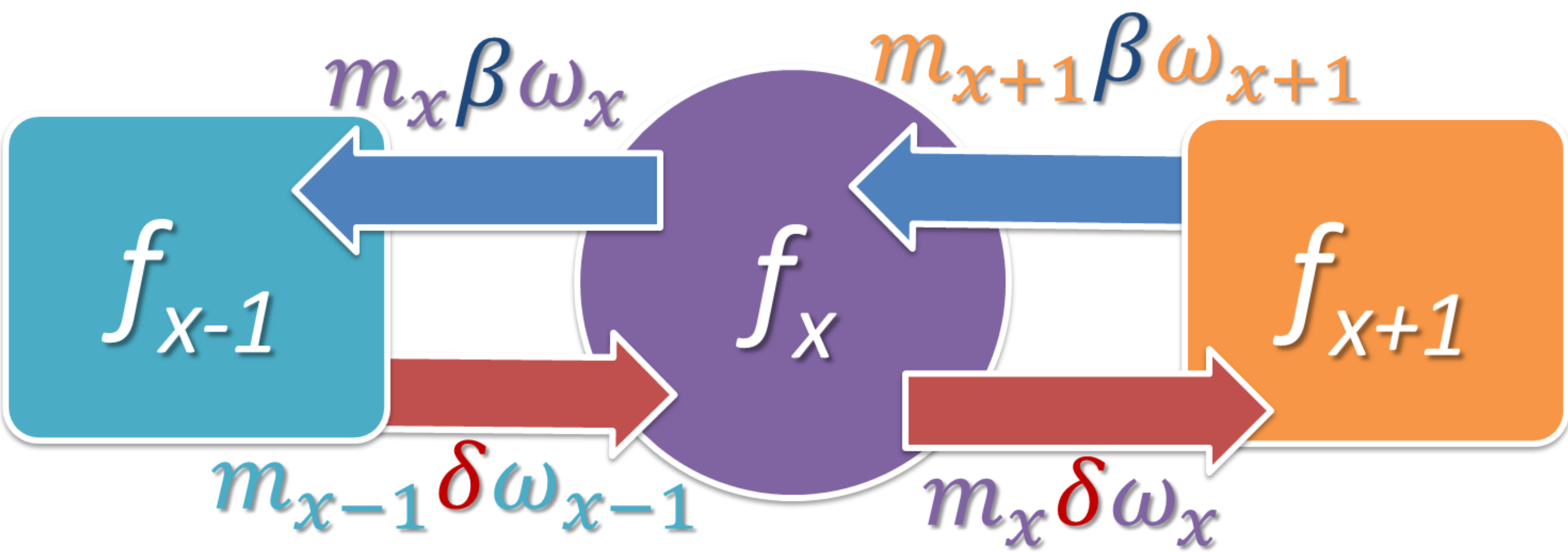
Adaptive hypothesis

- 2nd 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

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

Rapidly changing environments

The Red Queen hypothesis (van Valen, 1973):

It takes all the running you can do,

to keep in the same place.

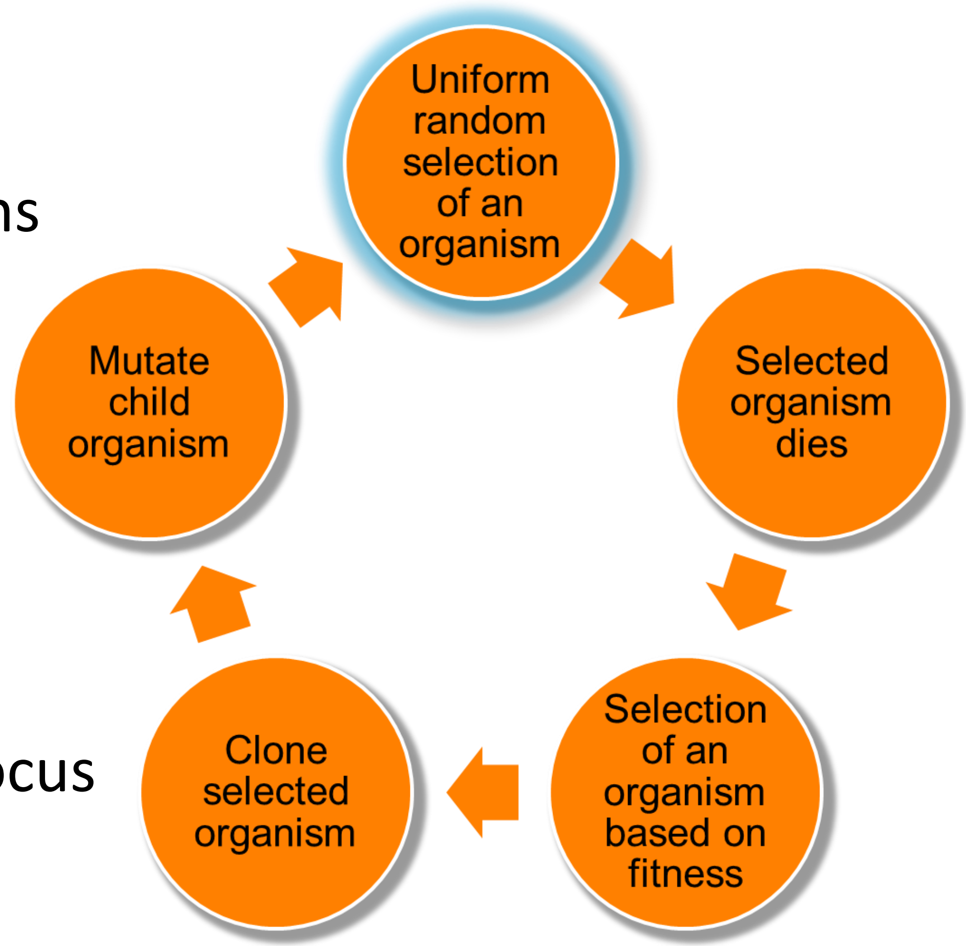
- Lewis Carrol, Through the Looking Glass

What happens when the environment changes frequently?

Changing environments

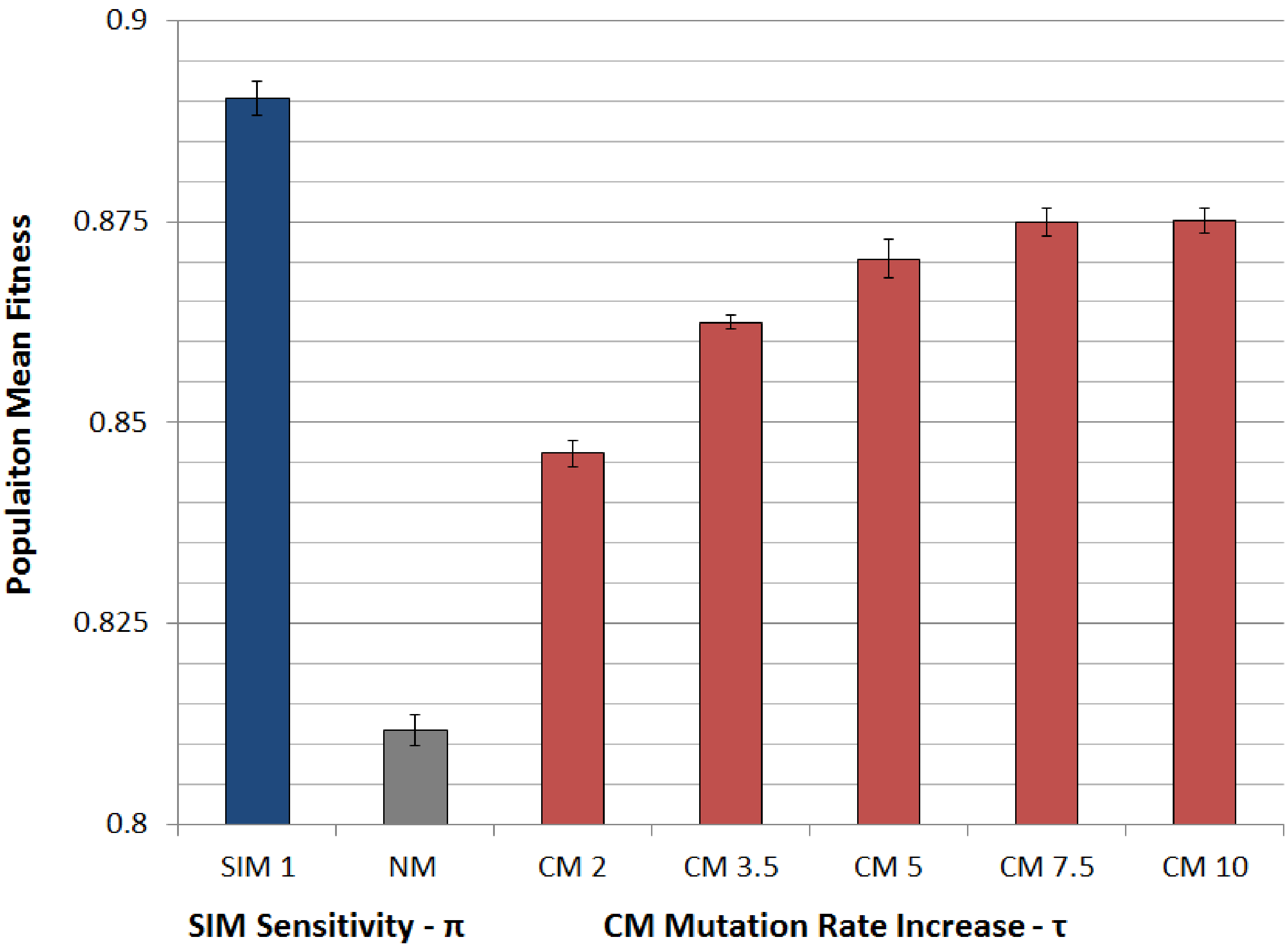
Simulations

- 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



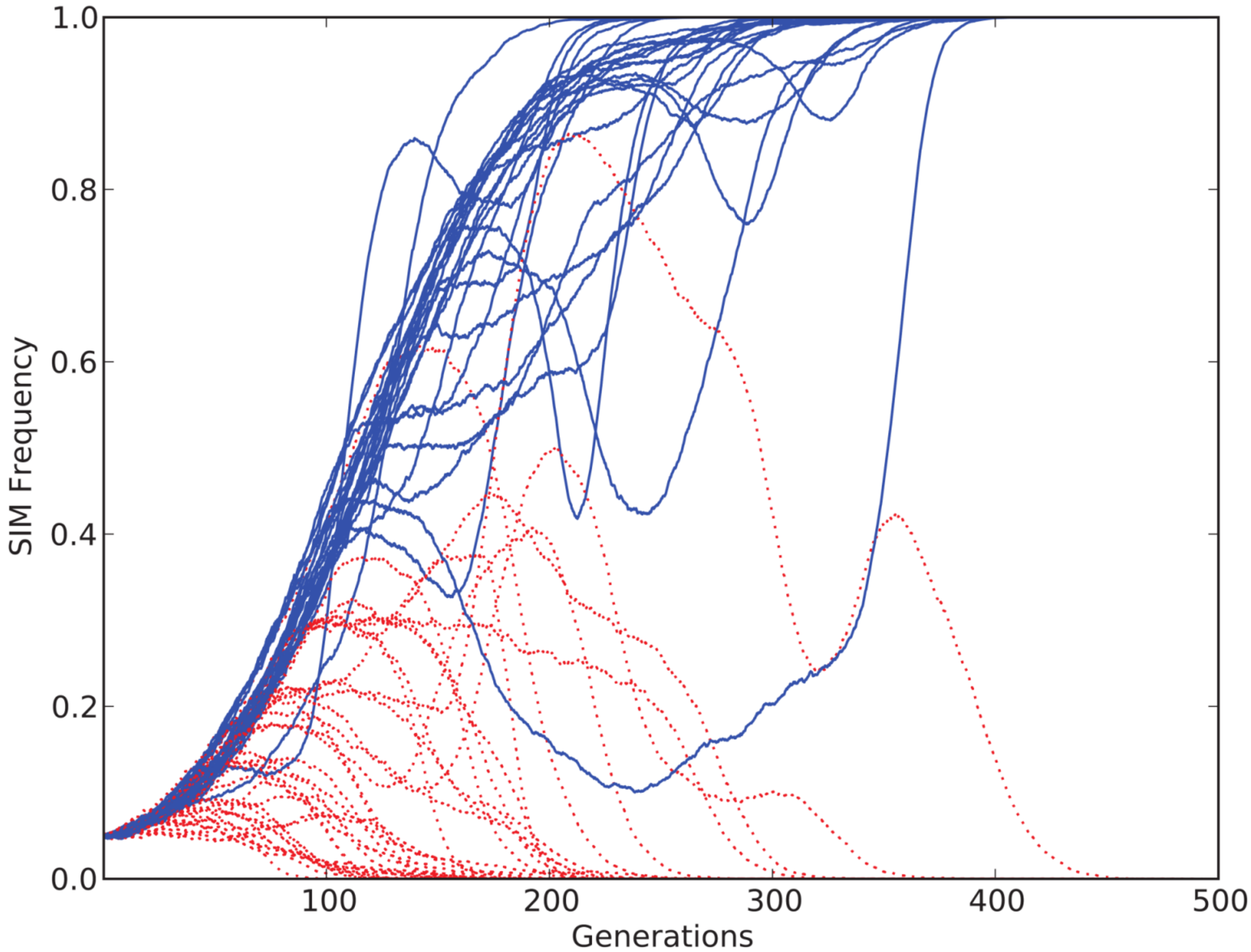
Ram & Hadany, Evolution 2012

Populations with SIM are fitter



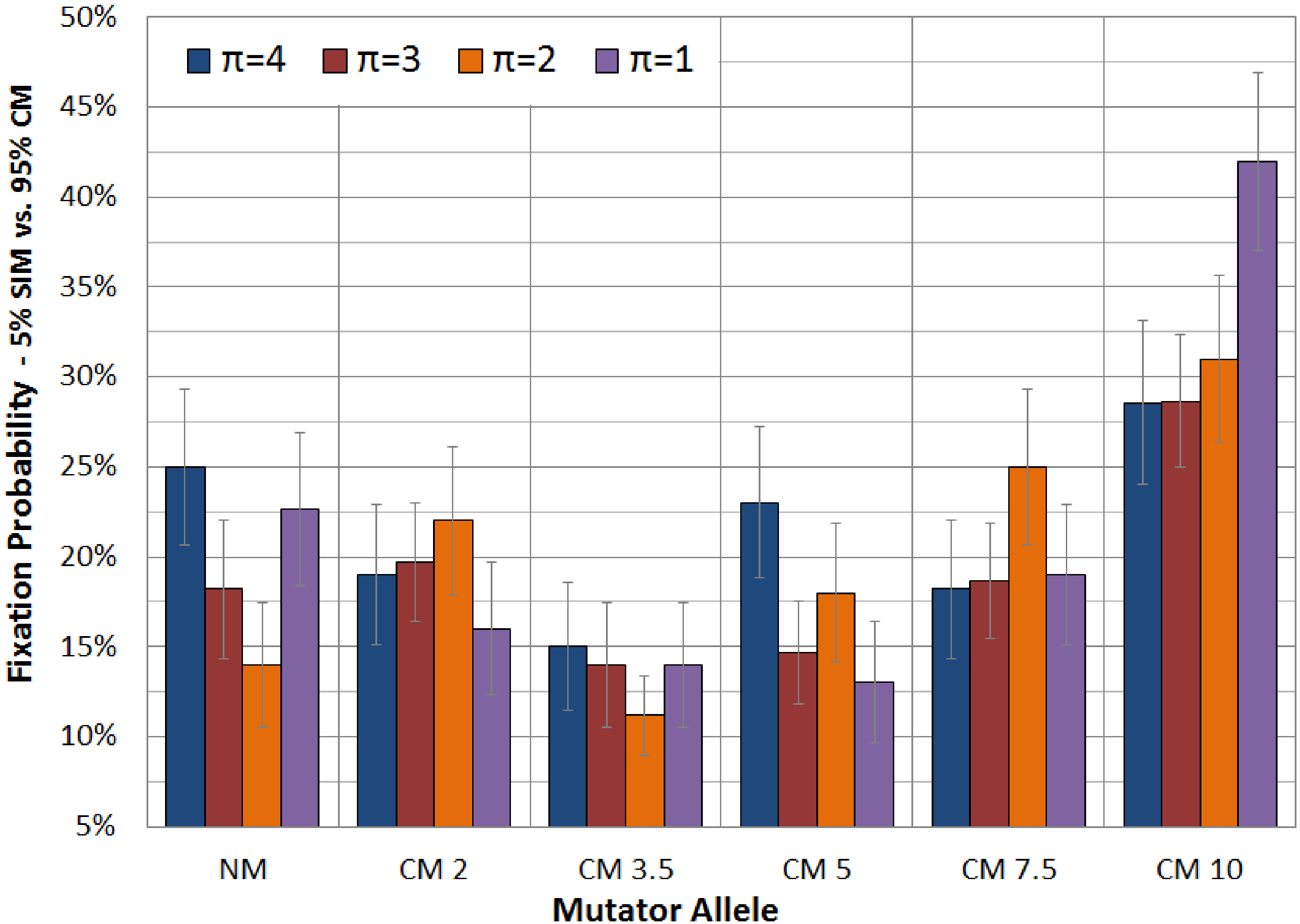
Ram & Hadany, Evolution 2012

SIM wins competitions



Ram & Hadany, Evolution 2012

SIM wins competitions

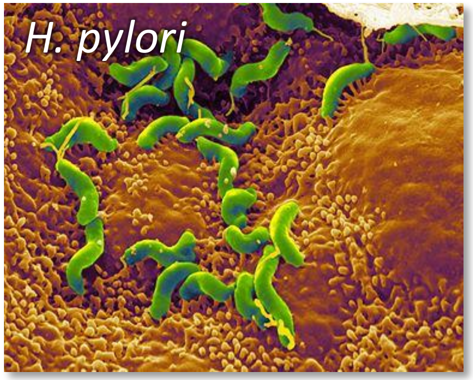


Ram & Hadany, Evolution 2012

Conclusions

- **Stress-induced mutators evolve:**
  - In constant & changing environments

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



In the presence of rare recombination

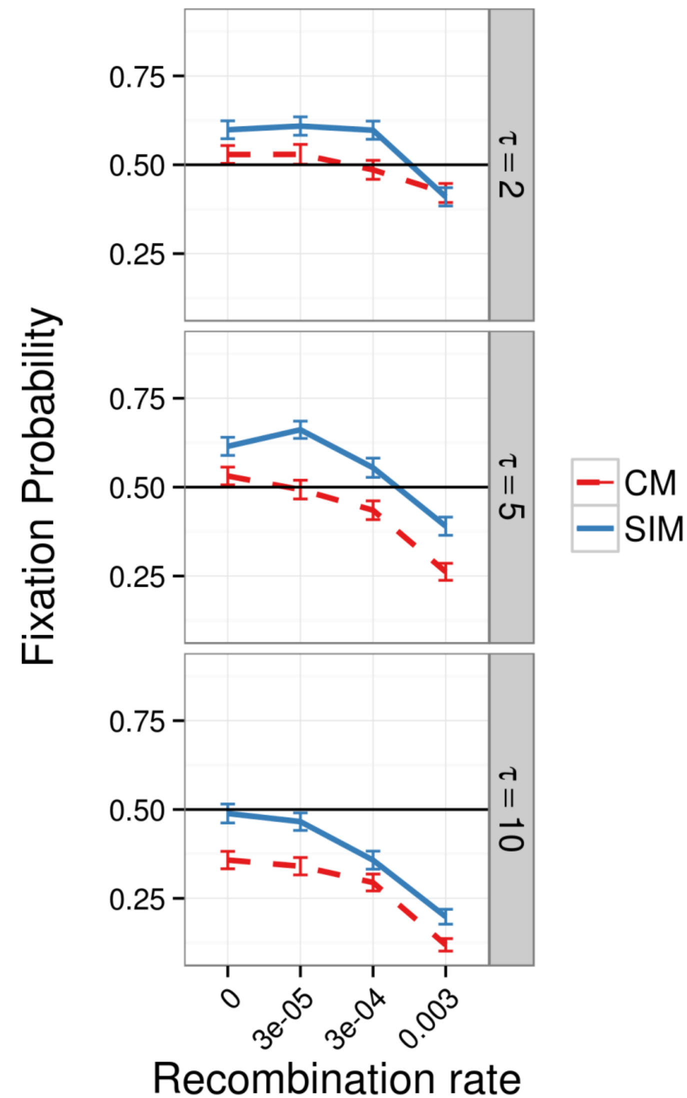
- Recombination can:
  - Separate mutator from beneficial mutations
  - Increase non-mutator adaptation rate
  - Save constitutive mutators from deleterious mutations

In the presence of rare recombination

Results suggest:

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

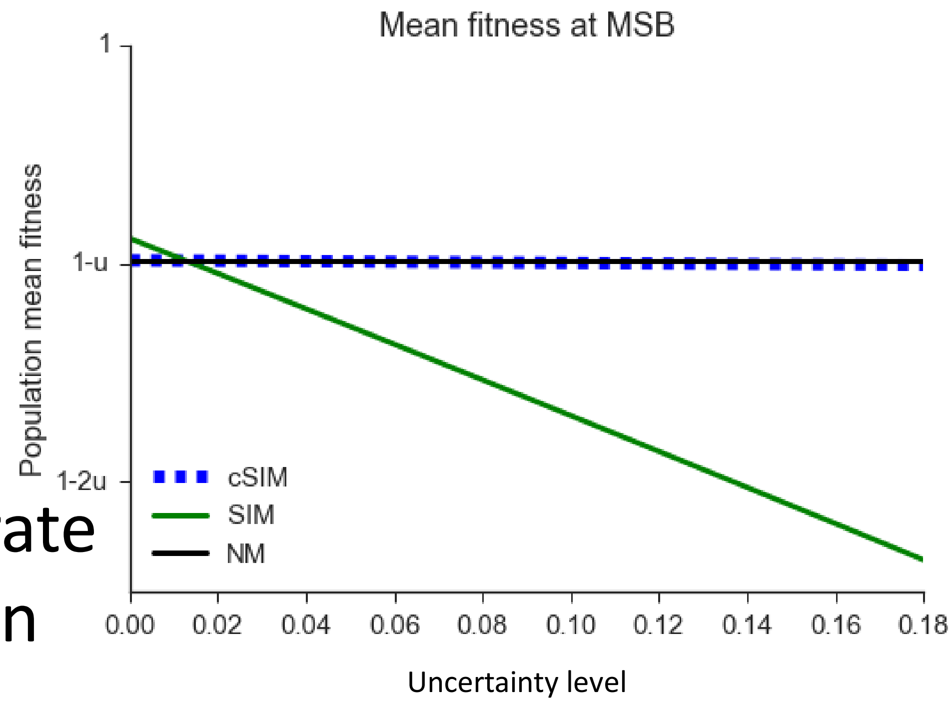
Sexual populations??



Ram & Hadany, in preparation

Stress-induced mutagenesis under uncertainty

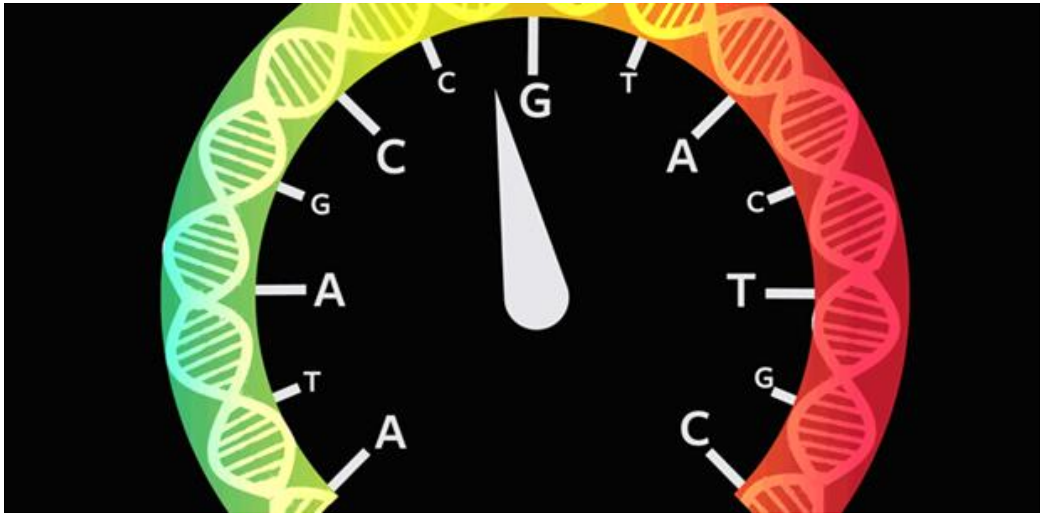
- Uncertainty
  - should you mutate?
- SIM decreases mean fitness
- Communication
  - Increase in mutation rate depends on population mean fitness
  - Robustness to uncertainty



Gur-Dellus, Ram, and Hadany, in preparation

Consequences of Stress-Induced Mutagenesis

How does stress-induced mutagenesis affect adaptation?

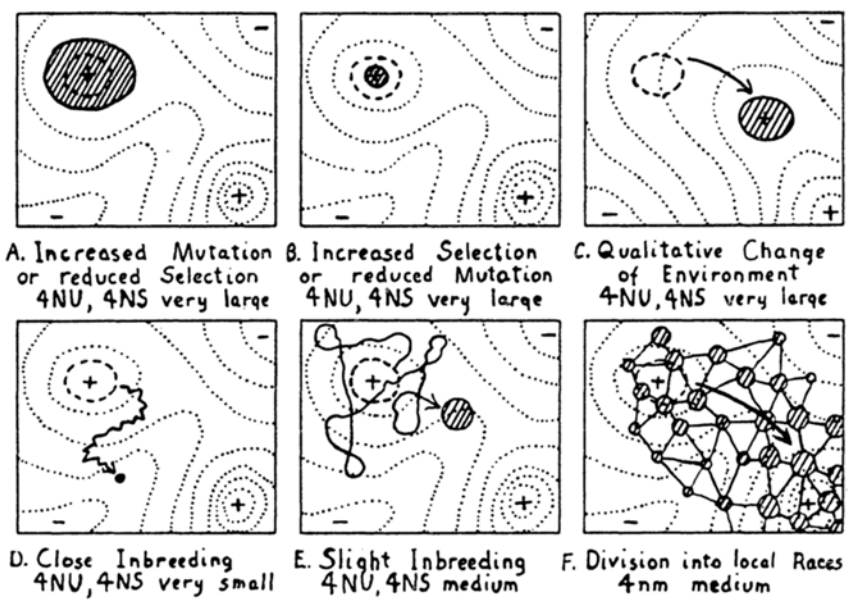


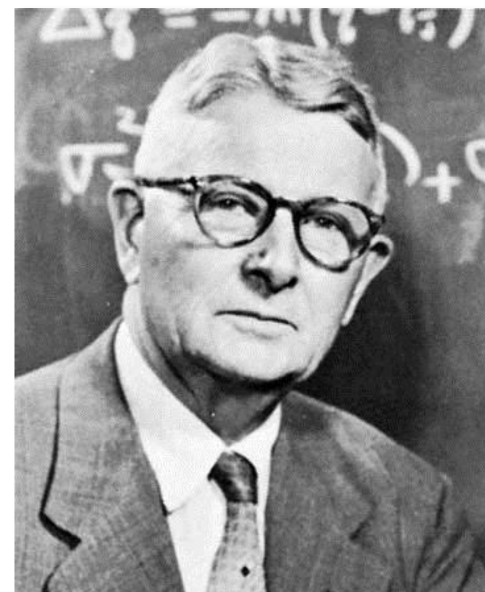
http://nautil.us/issue/34/adaptation/does-stress-speed-up-evolution

Adaptive peak shifts

Sewall Wright, 1931:

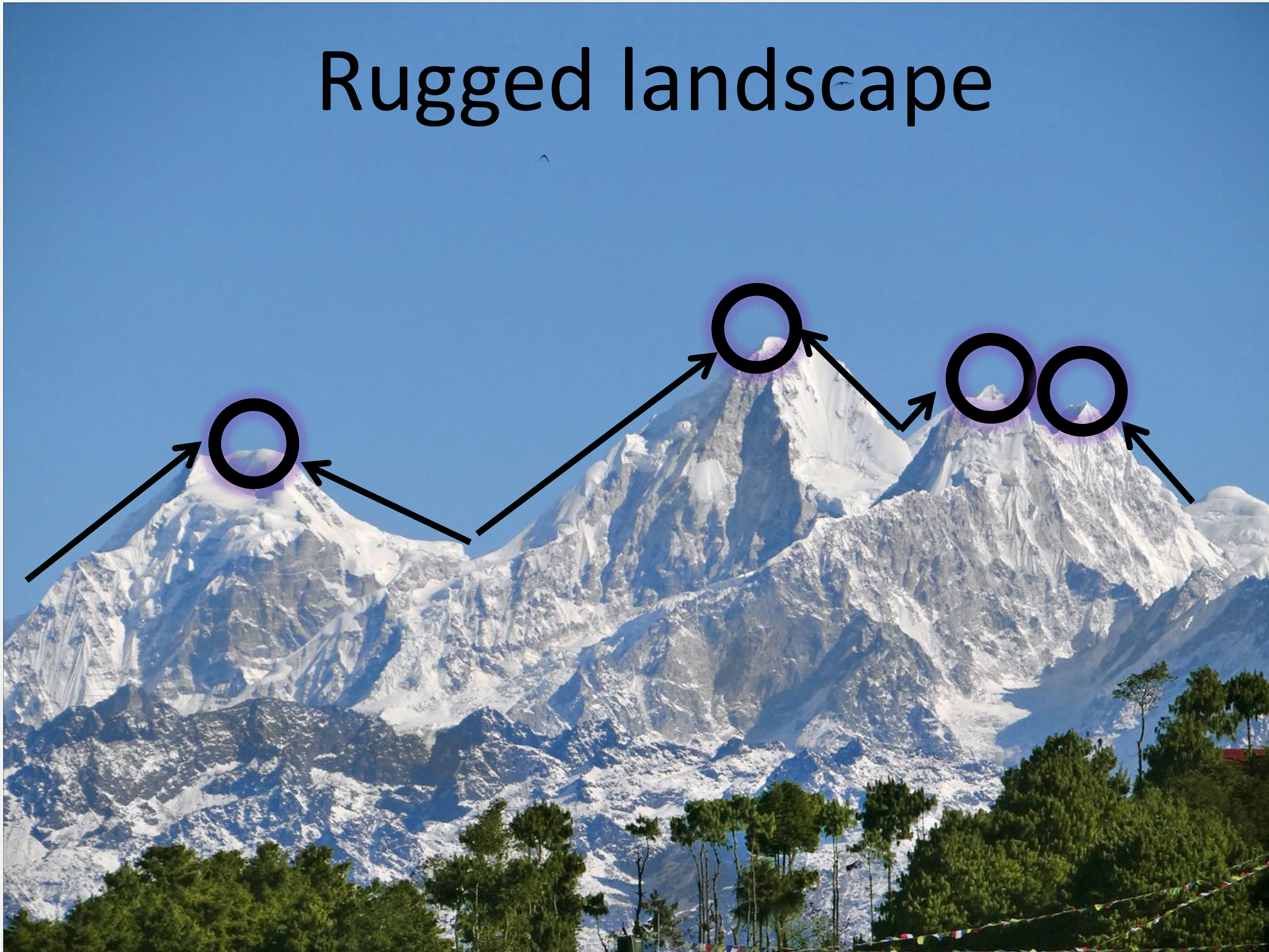
If a new adaptation requires several, separately deleterious mutations, how can it evolve?



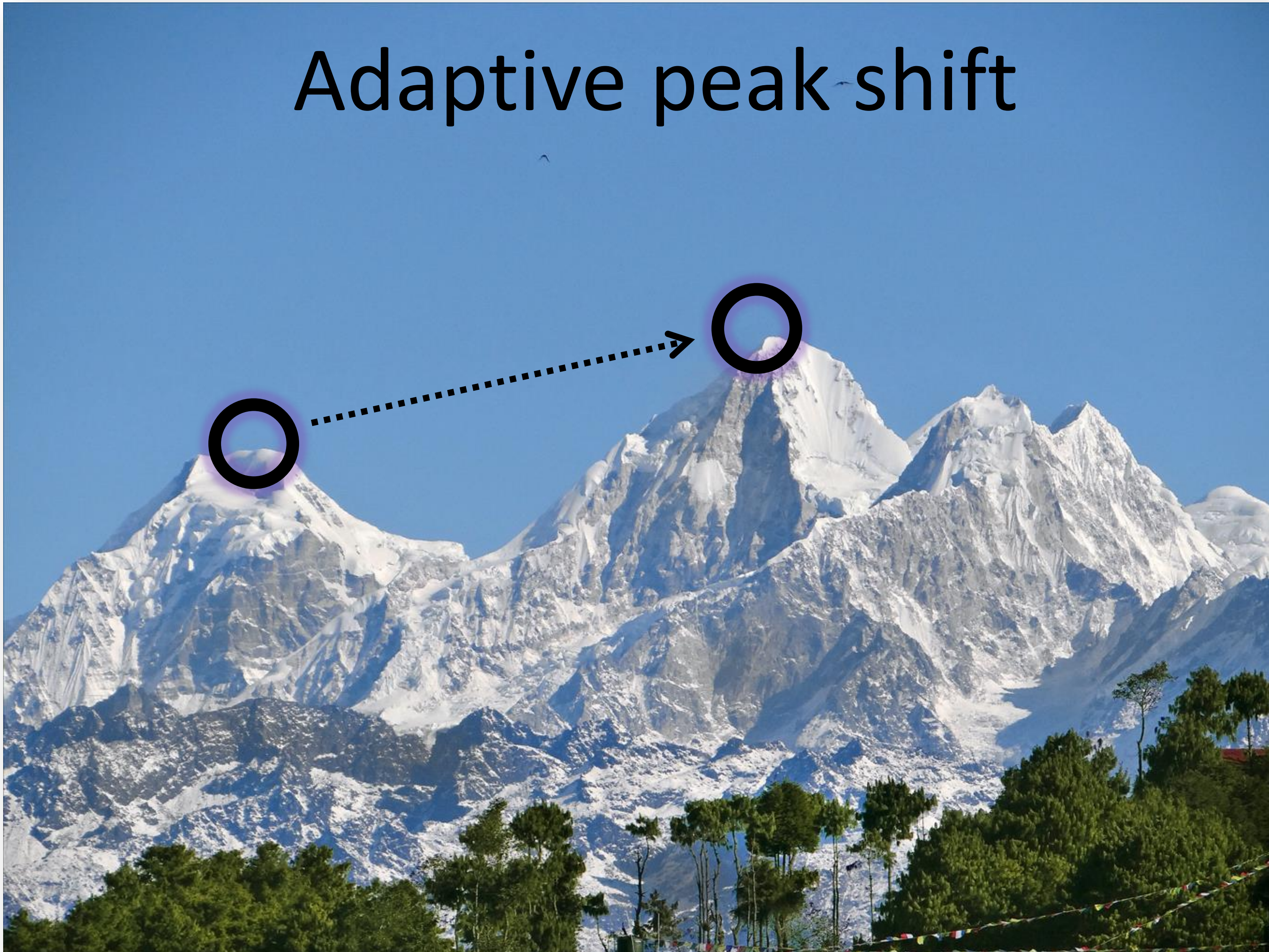


Wright, Am. Nat. 1988

Simple landscape

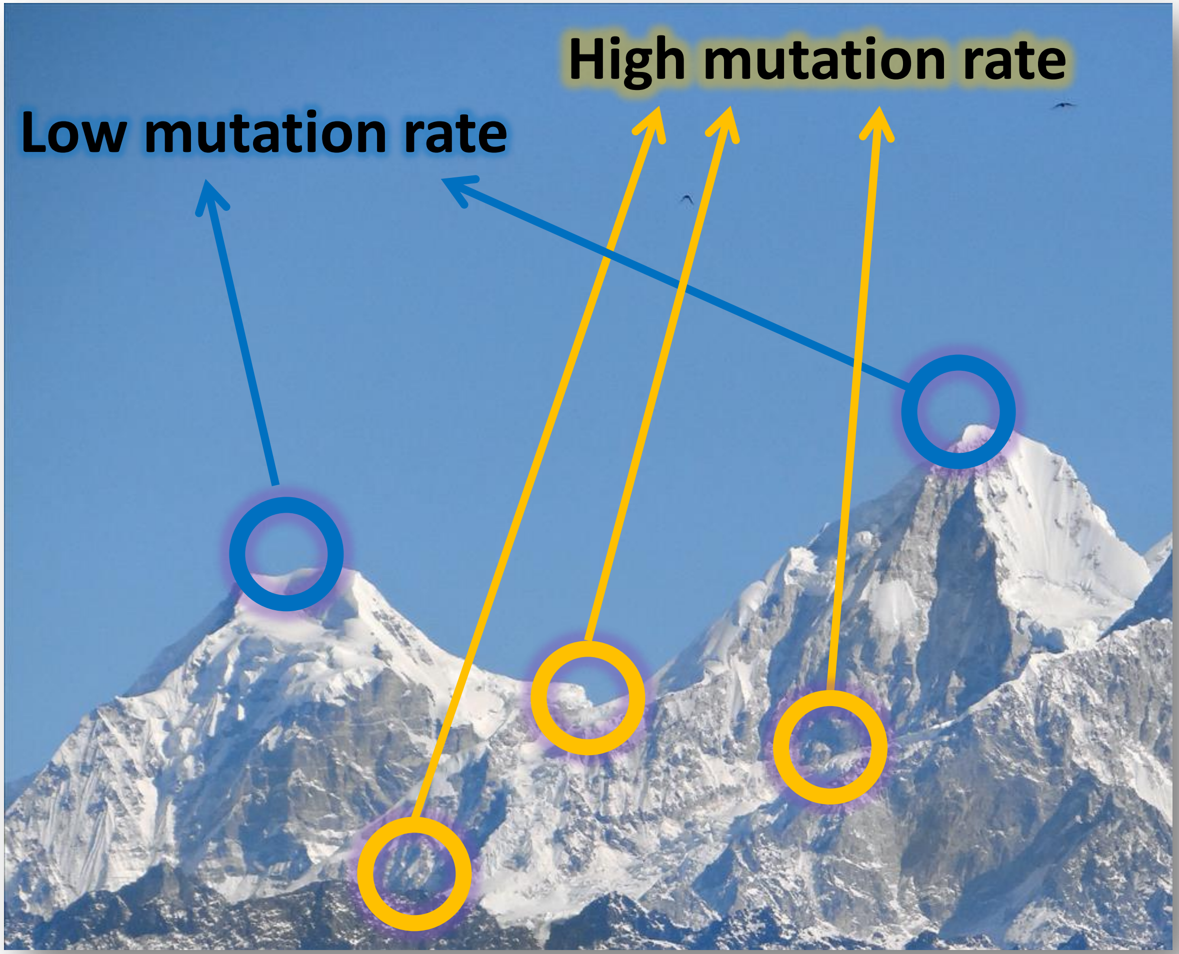

Rugged landscape

Adaptive peak shift



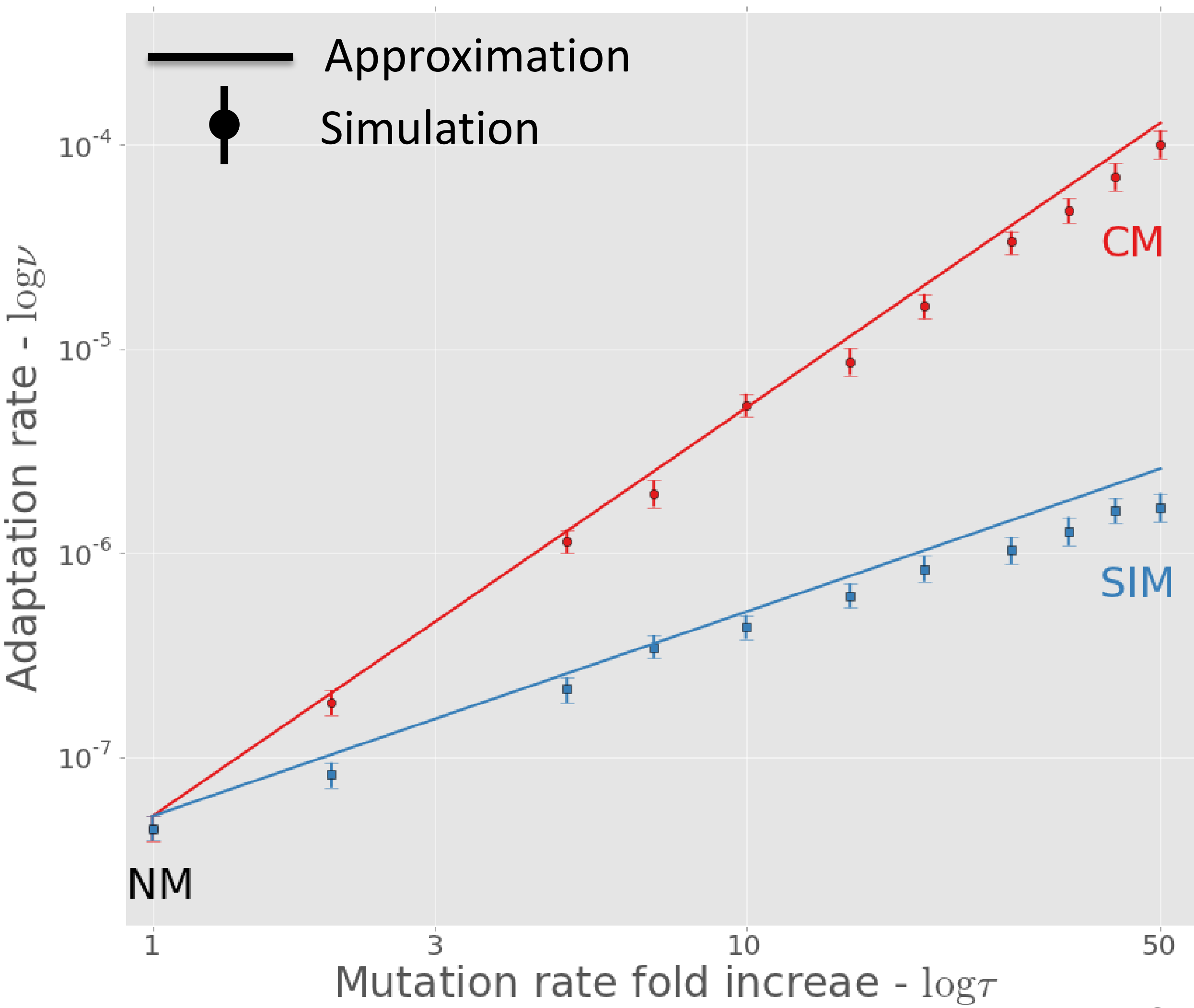
SIM & rugged landscapes

Increasing the mutation rate in individuals below both peaks



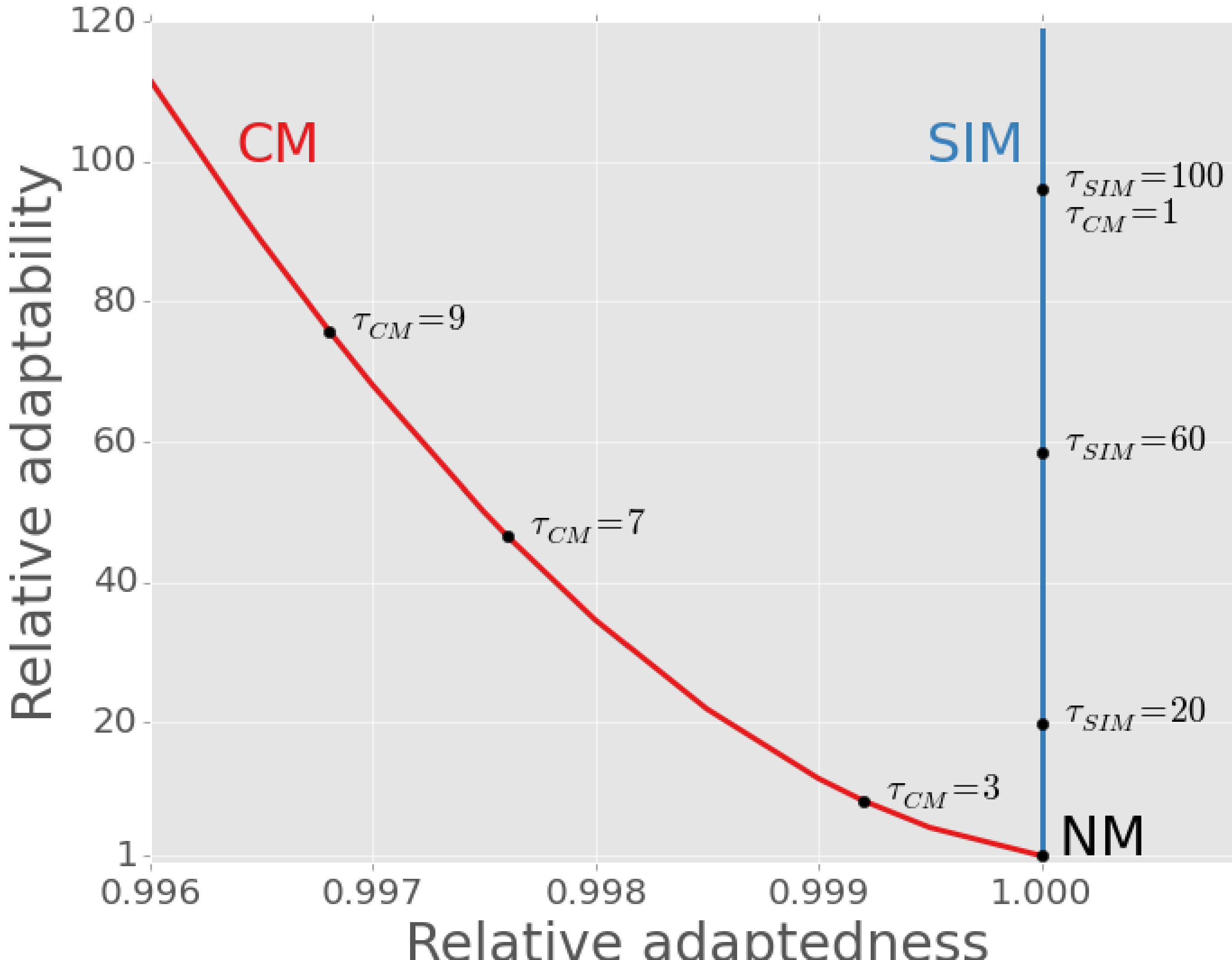
Adaptation rate

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



Ram & Hadany, PRSB 2014

SIM Breaks the *adaptability-adaptedness* trade-off



Ram & Hadany, PRSB 2014

Conclusions

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

Predicting microbial growth in a mixed culture

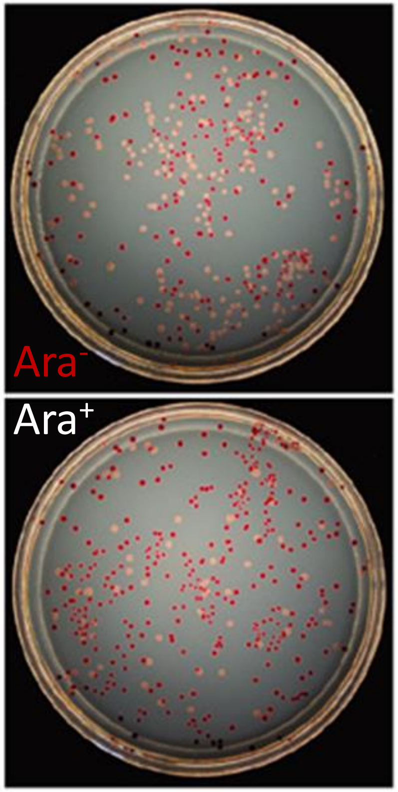
Competition experiments

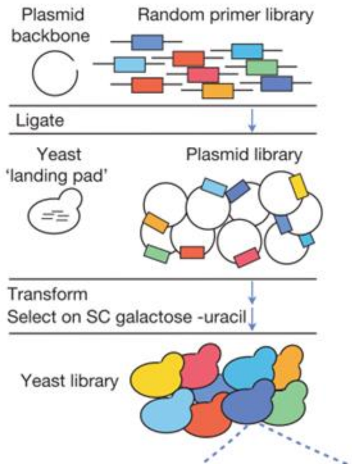
Strains must have a genotypic or phenotypic marker.

Problem: Laborious and costly, more so for non-model organisms.

Our Solution: Computational framework that predicts growth in mixed culture:

1. Fit growth models to growth curves
2. Predict competition results
3. Infer fitness

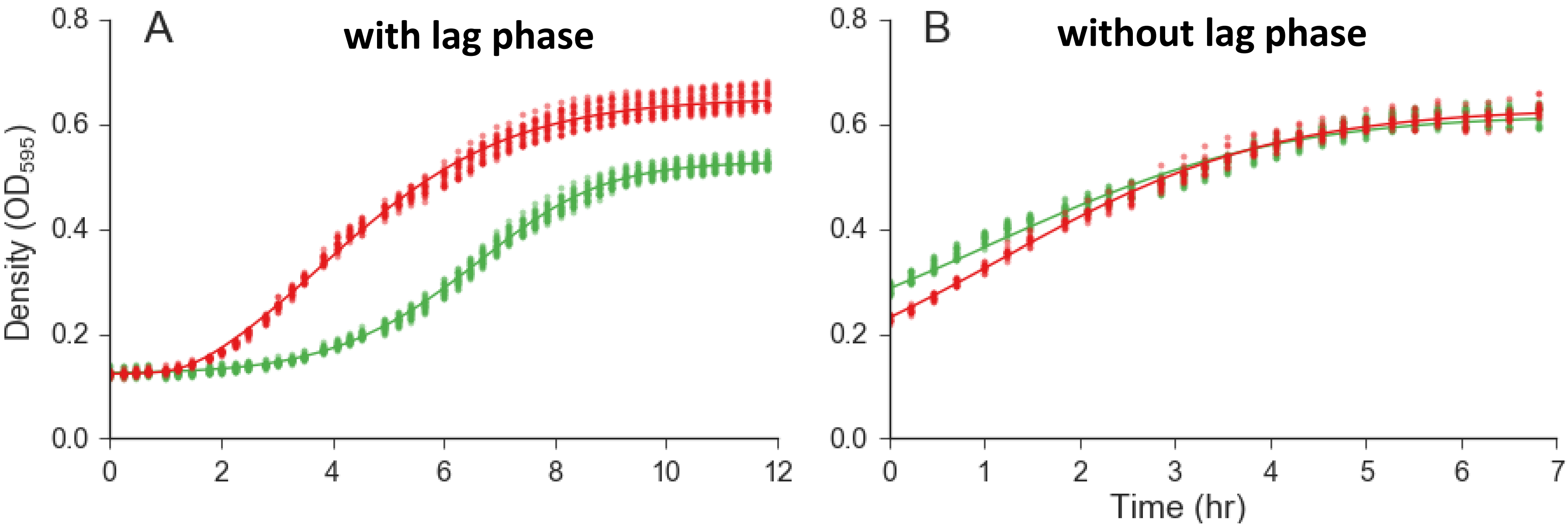




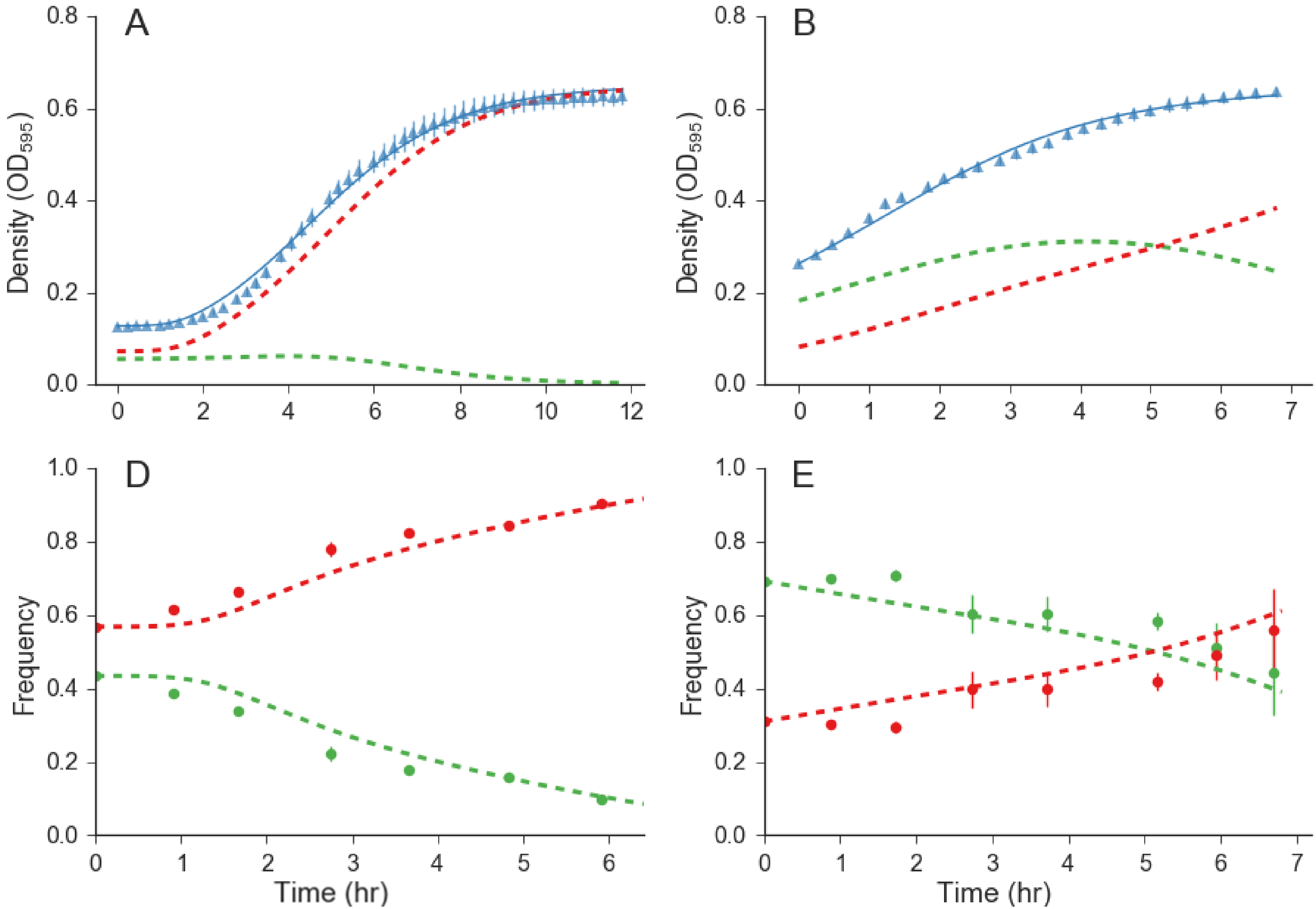
Growth curve data

Data from two experiments with *E. coli* strains: (DH5α vs. TG1) fitted a growth model

Baranyi & Roberts, 1994



Mixed culture prediction



Summary

1. Fit growth models to growth curves
2. Predict competition results
3. Infer fitness

Preprint:

Ram et al. (2015) *Predicting competition results from growth curves*. bioRxiv, doi:10.1101/022640

Software website: curveball.yoavram.com

Future directions

- Complex growth curves:
  - Bi-phasic growth:
  - Deep stationary phase
  - Cell death
- Null model for detection of frequency-dependent interactions:
  - Cooperation
  - Interference
- Compete hypothetical strains
- Predict adaptive evolution
- Interpret fitness differences

Summary

Stress-induced mutagenesis

- Can **evolve** due to 2nd order selection
- In **constant & changing** environments
- In **asexual** populations

Ram & Hadany, Evolution 2012

- In the presence of rare **recombination**

Ram & Hadany, in preparation

- Increases the rate of **complex adaptation rate**
- Without reducing the **population mean fitness**
- Breaks the **trade-off** between *adaptability* and *adaptedness*

Ram & Hadany, PRSB 2014

Predicting microbial growth in a mixed culture

Ram et al., bioRxiv preprint

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