THE ROLE OF STRESS-INDUCED MUTATION IN THE EMERGENCE OF COMPLEX ADAPTATIONS

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http://sideer2013.yoavram.com

Mutation

"Mutations … supply the raw materials for evolution"

Dobzhansky, *Genetics and Origin of Species* 1937

"Mutation is the ultimate source of variation on which natural selection acts"

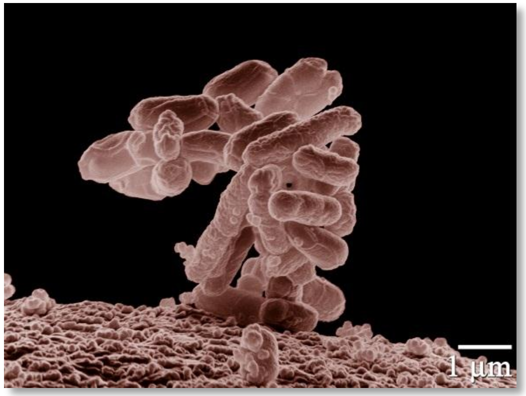
Lynch, 2007

Variation in mutation rates

Between species

"Noticeable" mutations per genome per generation

Bacteria *(E. coli)*:
0.003 (Drake 1991)



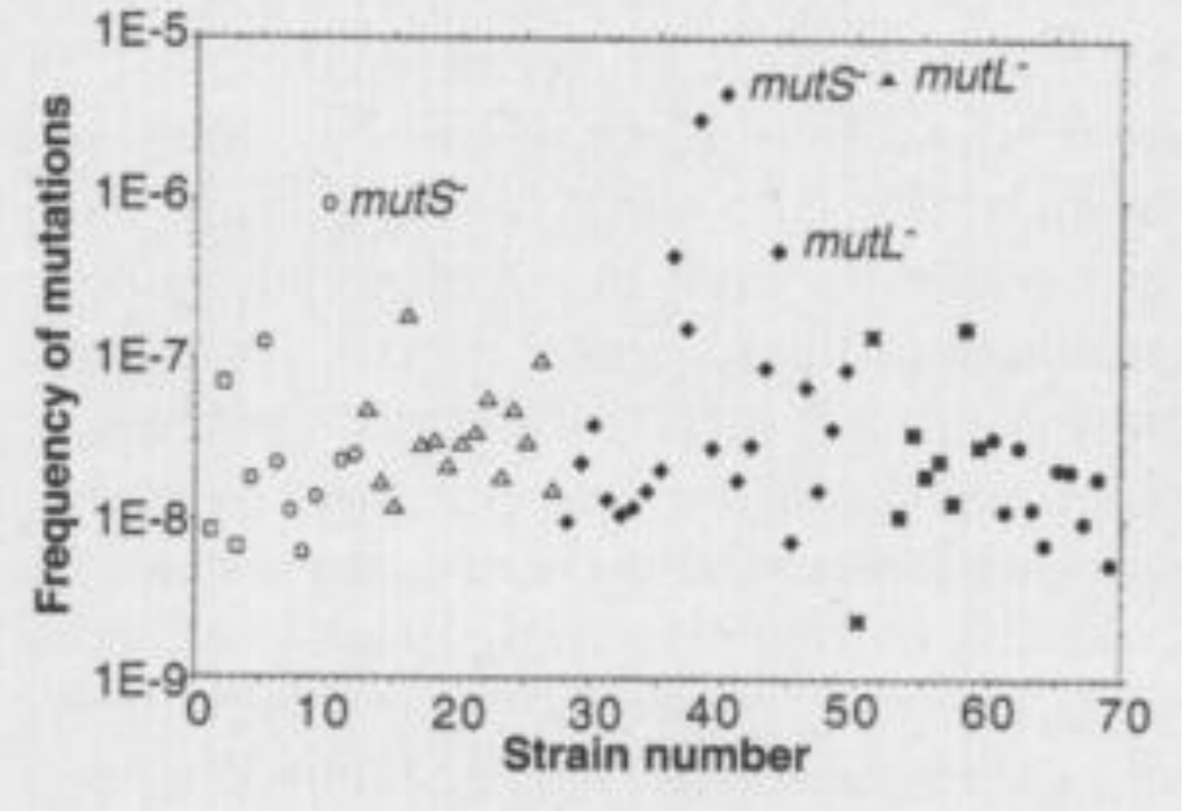
Flies *(D. melanogaster)*:
0.455 (Keightley et al. 2009)

Mammals *(H. sapiens)*:
41 (Lynch PNAS 2010)

Variation in mutation rates

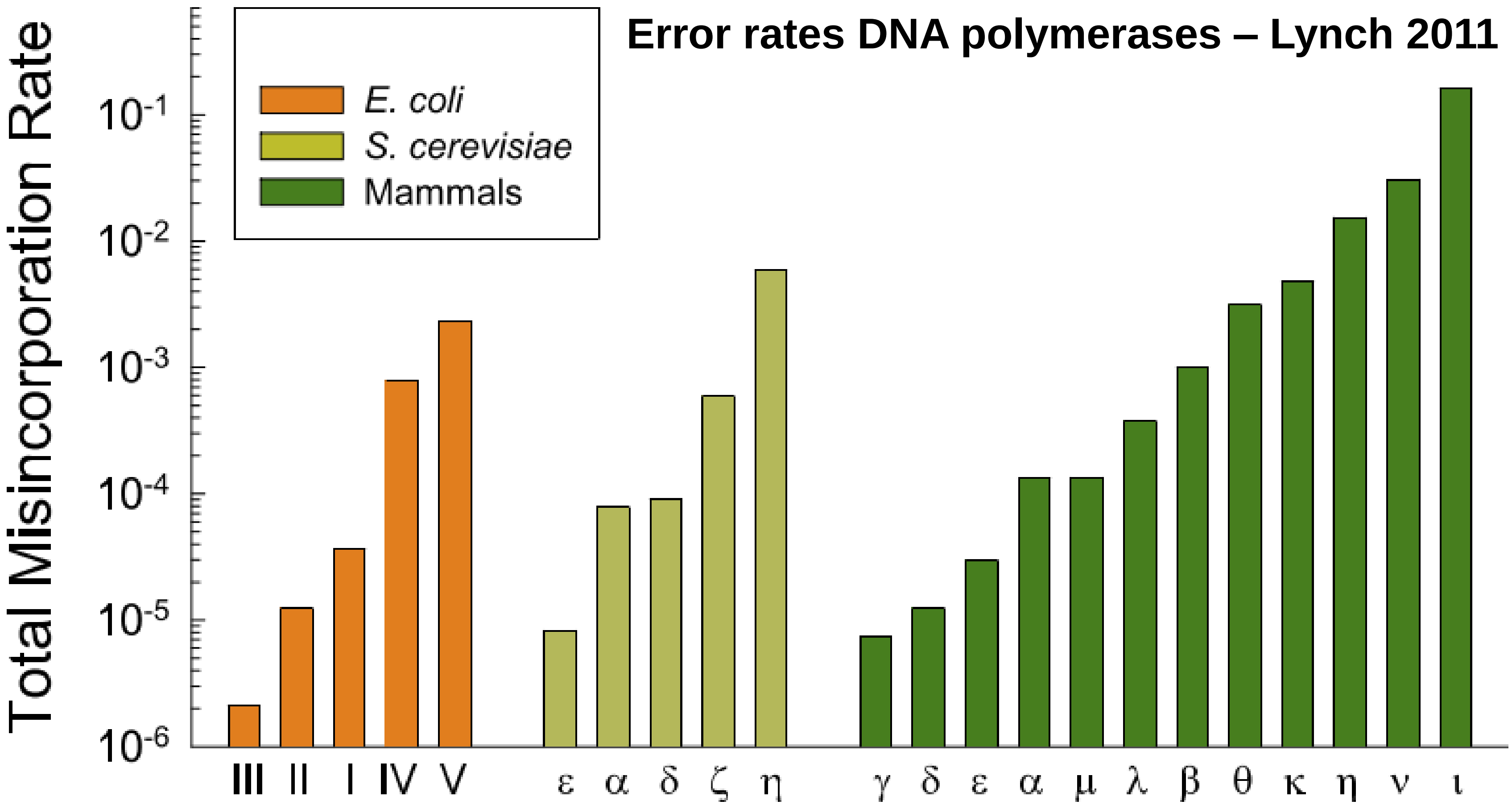
Between populations

Mutation rate of 69 natural isolates of *E. coli* - Matic et al. 1997



Variation in mutation rates

Within individuals



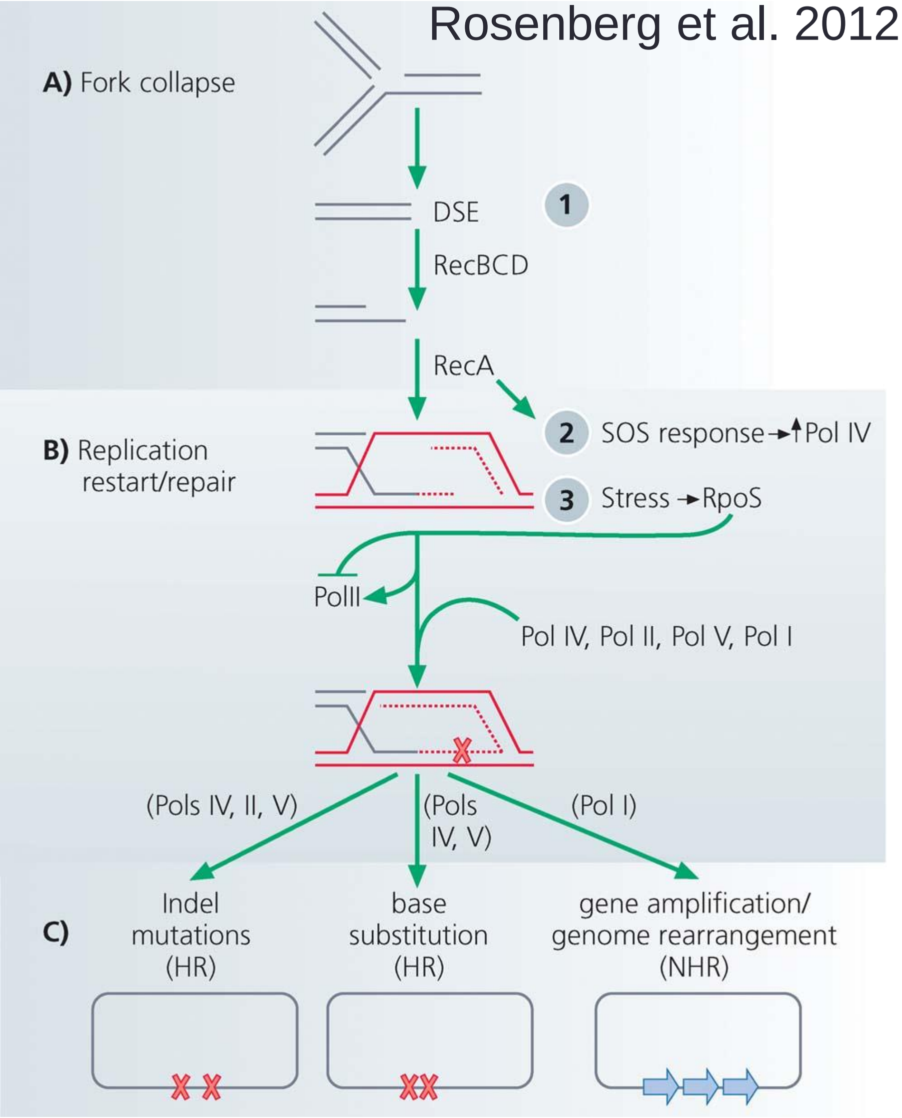
Stress-induced mutation

E. coli:

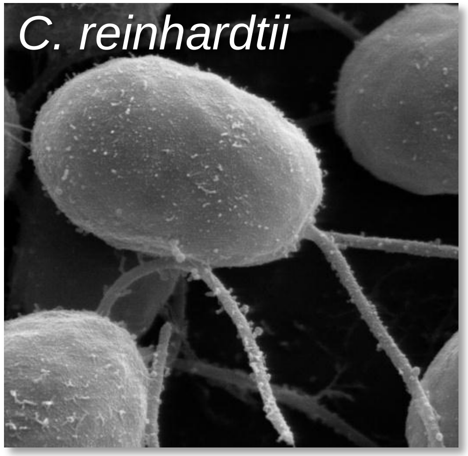
Error prone DNA polymerases are induced by stress responses:

- SOS response
- Carbon starvation
- DNA damage

Rosenberg et al. 2012

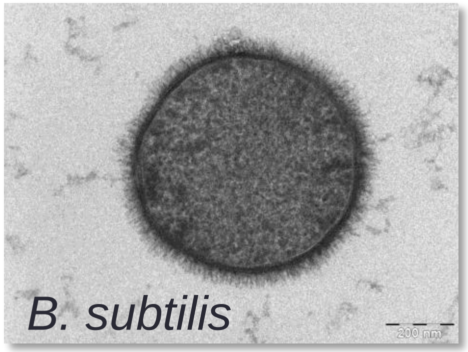


Evidence



Bacteria

- *Escherichia coli* — Bjedov et al. 2003
- *Bacillus subtilis* — Sung & Yasbin 2002
- *Pseudomonas putida* — Kivisaar 2010
- *Pseudomonas aeruginosa* — Weigand & Sundin 2012
- *Listeria monocytogenes* — van der Veen et al. 2010
- *Staphylococcus aureus* — Cirz et al. 2007
- *Mycobacterium tuberculosis* — Boshoff et al. 2003



Eukaryote

- *Chlamydomonas reinhardtii* — Goho & Bell 2000
- *Saccharomyces cerevisiae* — Hall 1992; Heidenreich 2007
- *Caenorhabditis elegans & briggsae* — Matsuba et al. 2012
- *Drosophila melanogaster* — Sharp & Agrawal 2012
- *Human cancer cells* — *Hara et al. 2005; Bristow & Hill 2008*

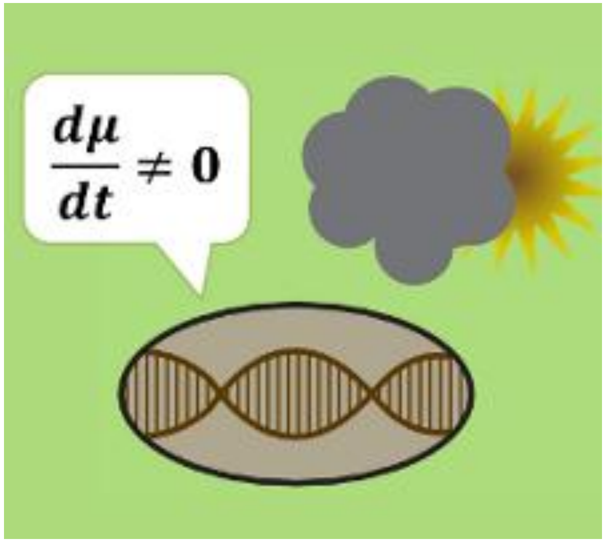
Reviewed by Foster 2007; Galhardo et al. 2007; Poole 2012

Evolution of stress-induced mutation

- Null Hypothesis: mutation is a by-product of stress
- Alternative, non-adaptive hypotheses:
  - Cost of DNA replication fidelity (Dawson 1998)
  - Drift barrier hypothesis (Lynch 2010, 2011)

- Adaptive hypothesis:
  - **"…the evolutionary consequence of SIM is that bacteria are able to adapt rapidly to stressful environments…"**

MacLean et al. 2013

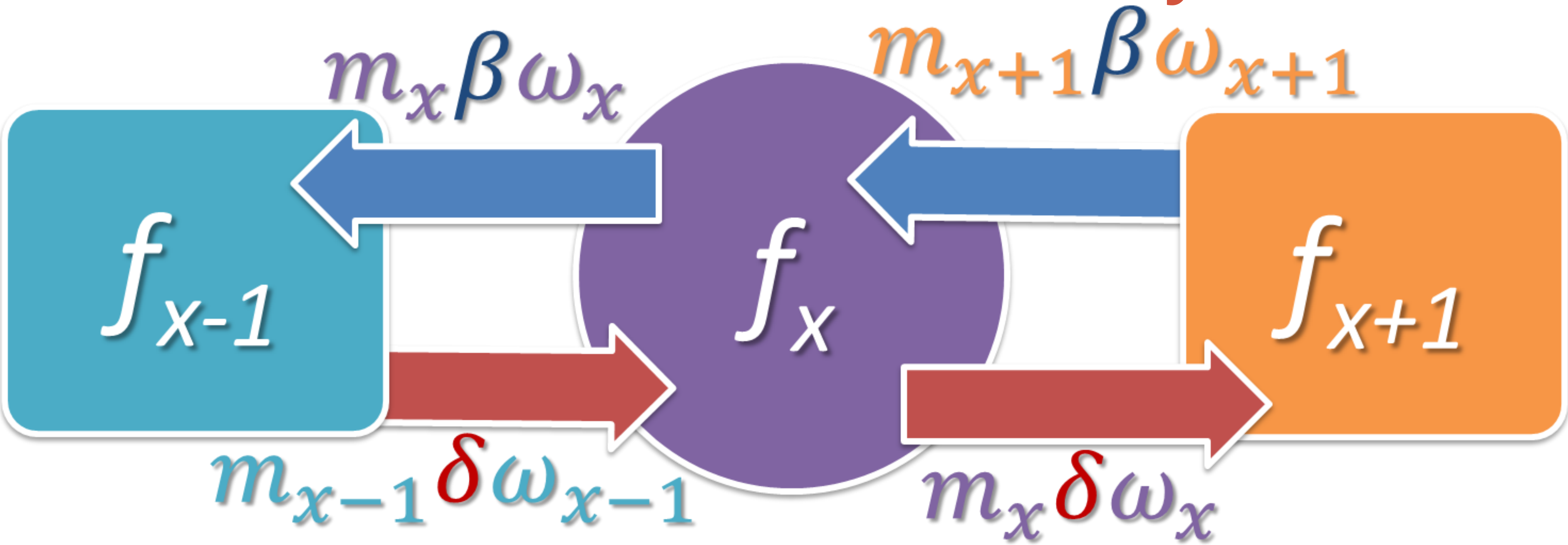


Research overview

- Evolution of stress-induced mutation
  - Deterministic model for a constant environment
  - Stochastic model for a changing environment

- Consequences of stress-induced mutation
  - Emergence of complex adaptations

Constant environment, steady state



x - number of deleterious mutations

f_x - frequency

ω_x - fitness

m_x - mutation probability

δ - deleterious mutation β - beneficial mutation

Model predictions: The unfit should hypermutate

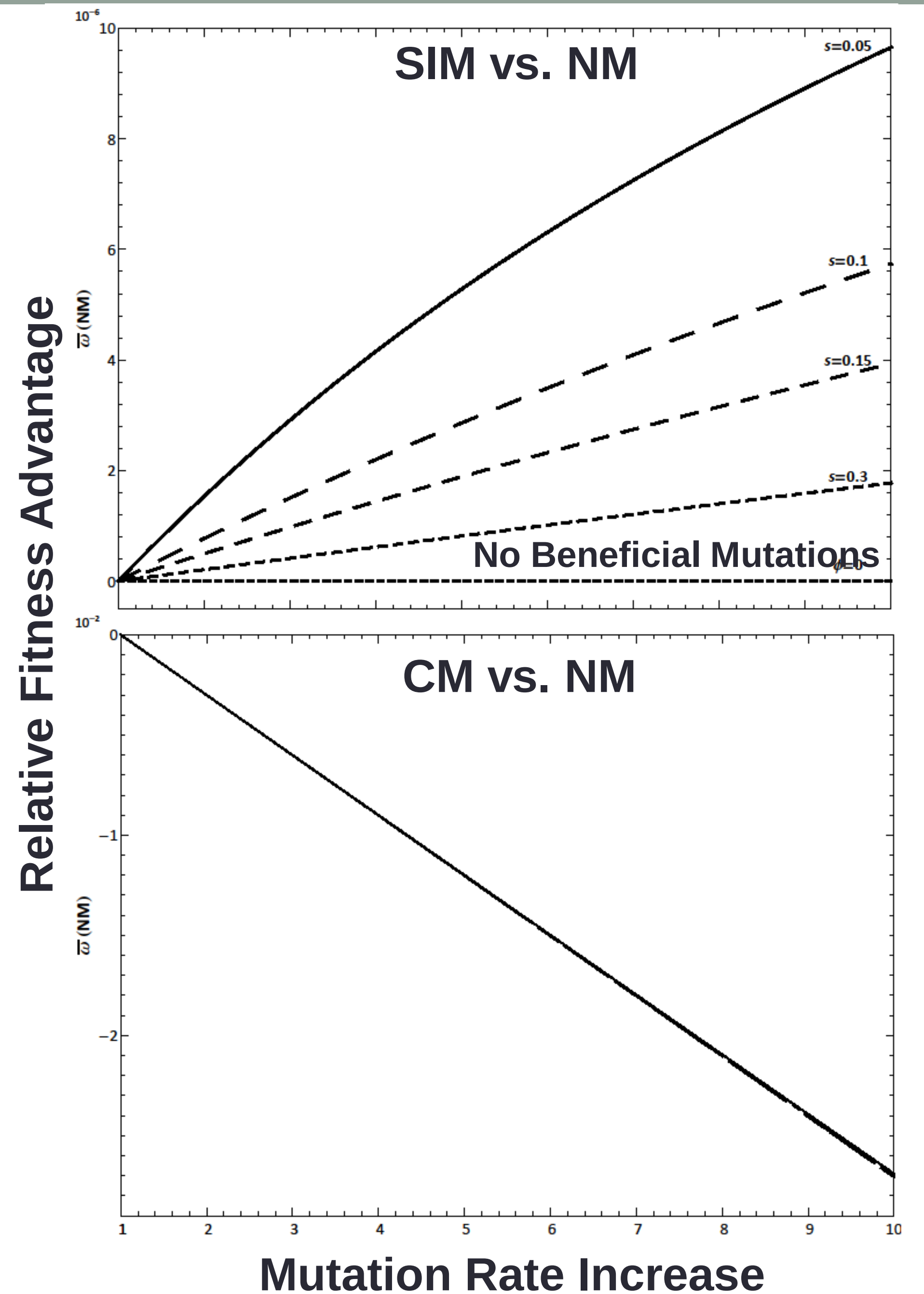
$$sign \frac{\partial \bar{\omega}}{\partial m_x} = sign\left(\bar{\omega} - \omega_x\right)$$

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

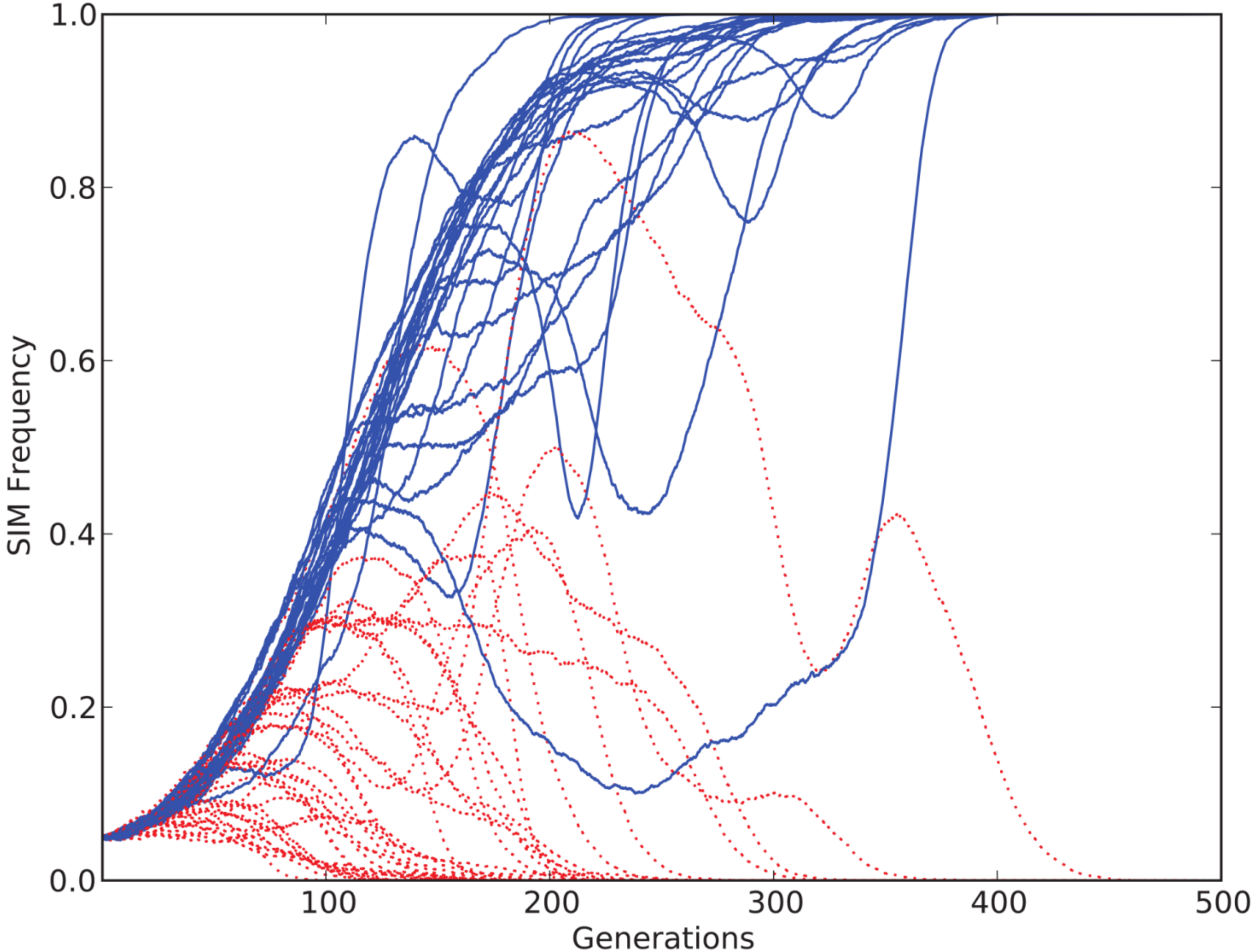
Ram & Hadany, Evolution 2012

Advantage to SIM

- **NM - Non-mutators**
  - constant low rate of mutation
- **CM - Constitutive mutators**
  - Constant high rate of mutation
- **SIM - Stress-induced mutators**
  - Low mutation rate when well-adapted
  - High mutation rate when stressed



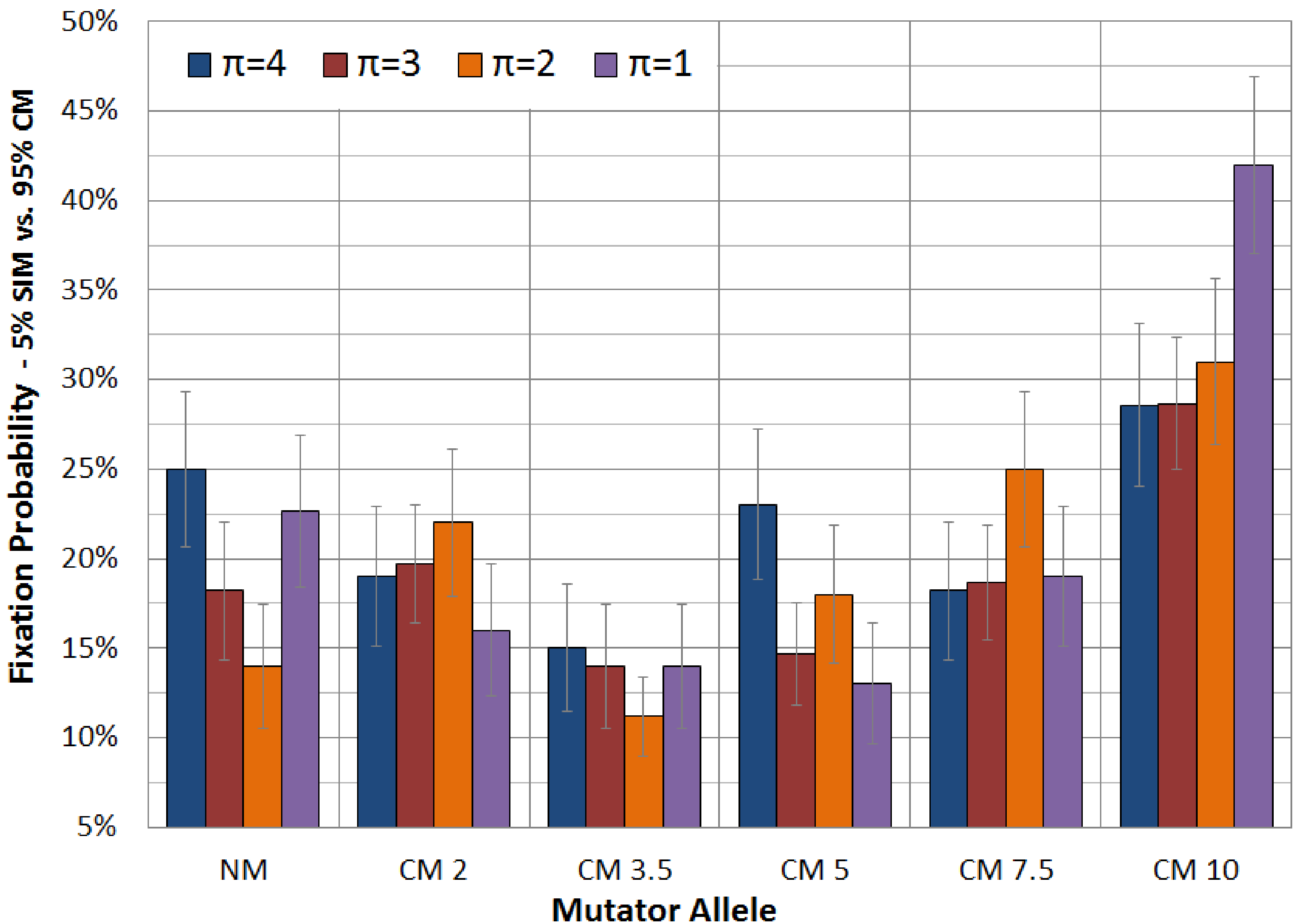
Changing environment, competitions



SIM Wins

SIM Loses

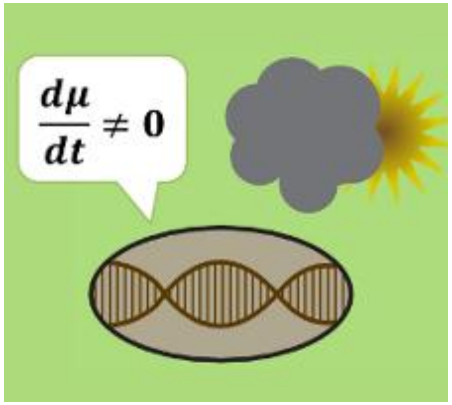
SIM wins all competitions



Evolution of stress-Induced mutation

Part I Summary

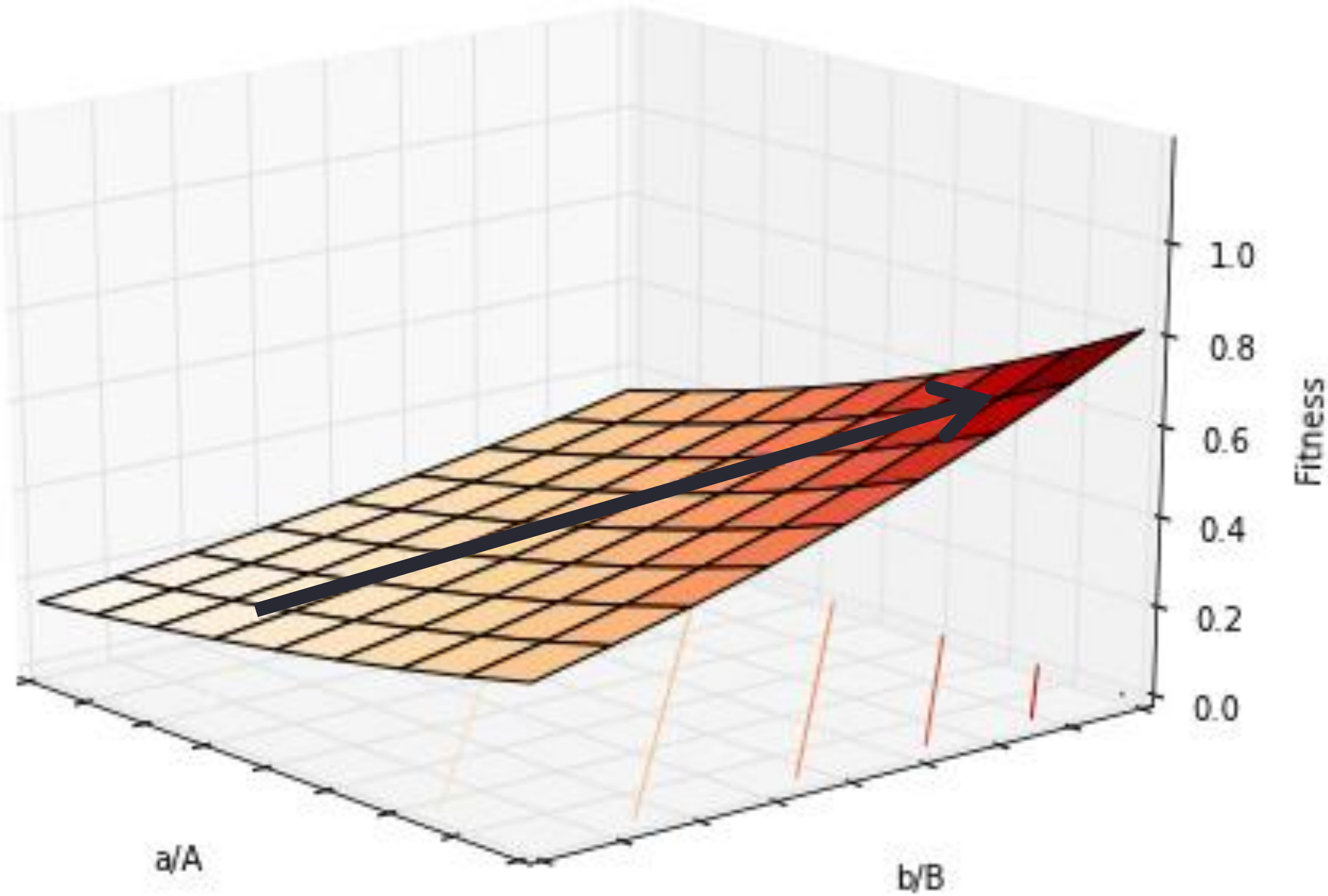
- Stress-induced mutation rate **favored by selection** over constant mutation rate
- Both in changing and constant environments
- Due to its effect on **evolvability**



Ram & Hadany, Evolution 2012

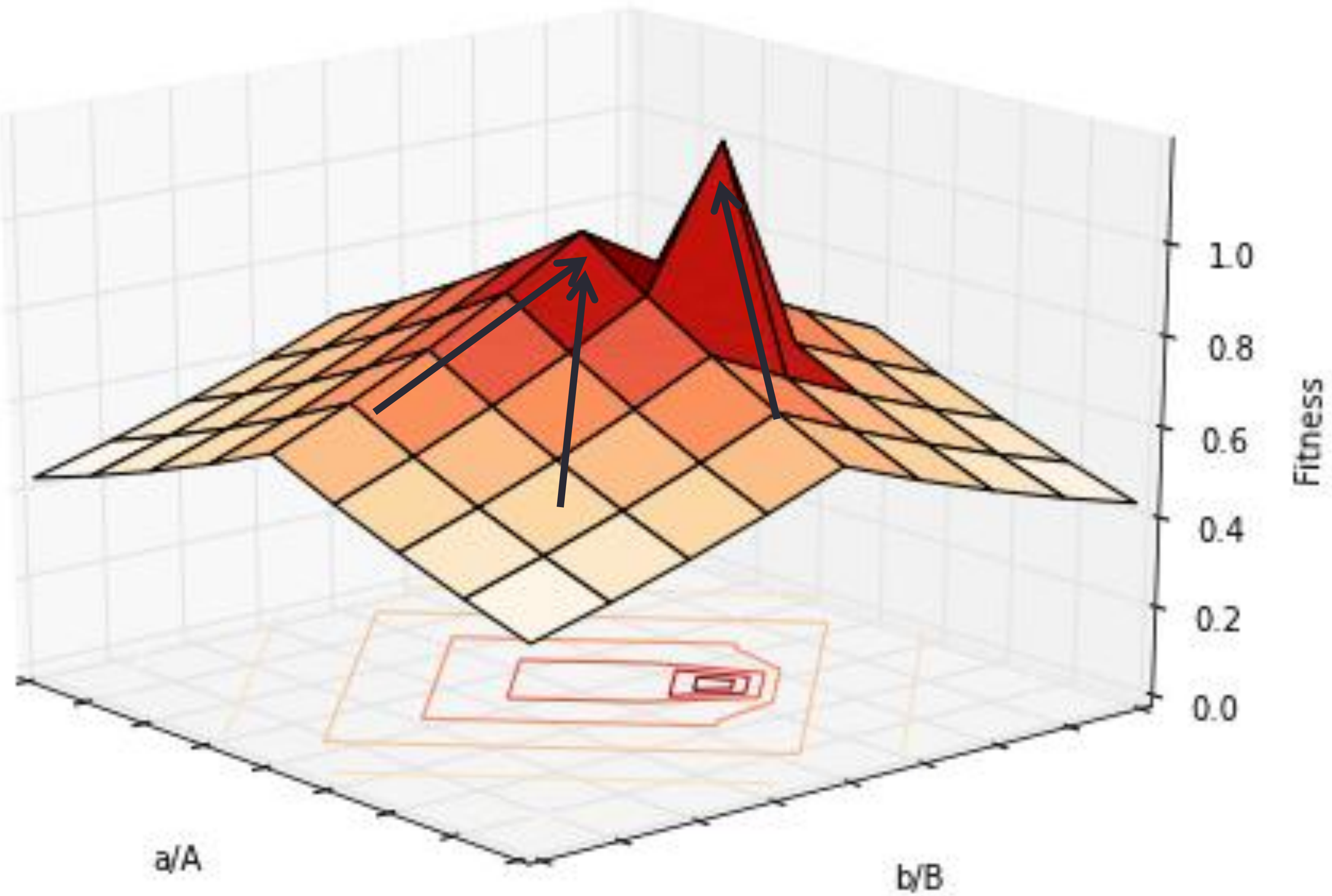
Smooth fitness landscape

Fitness:
ab $(1-s)^2$
Ab 1-s
aB 1-s
AB 1

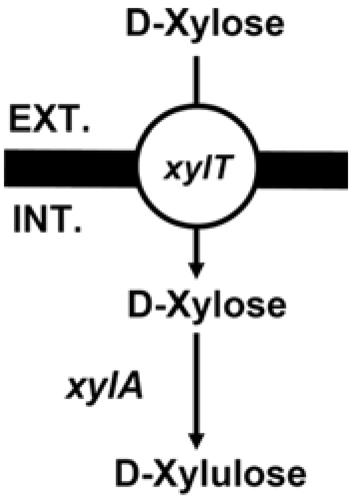


Rugged fitness landscape

Fitness:
ab 1
Ab 1-s
aB 1-s
AB 1+s



Rugged landscape examples



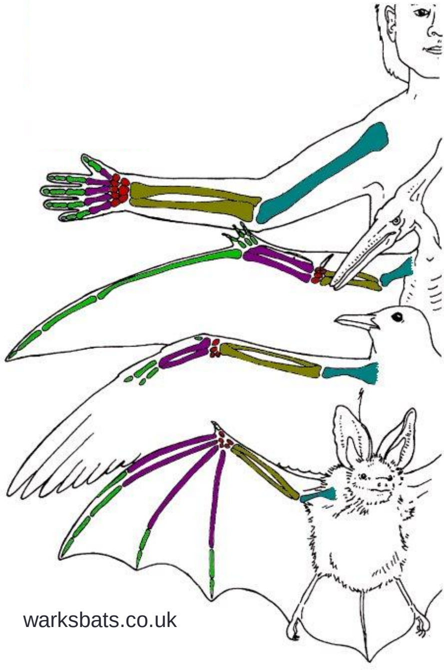
Xiao et al. 2011

Criteria

- Two traits must change for adaptation
- Changing a single trait leads to decreased fitness

Wings and bones

- Flying with heavy bones is wasteful
- Walking and climbing with light bones is risky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New carbon source

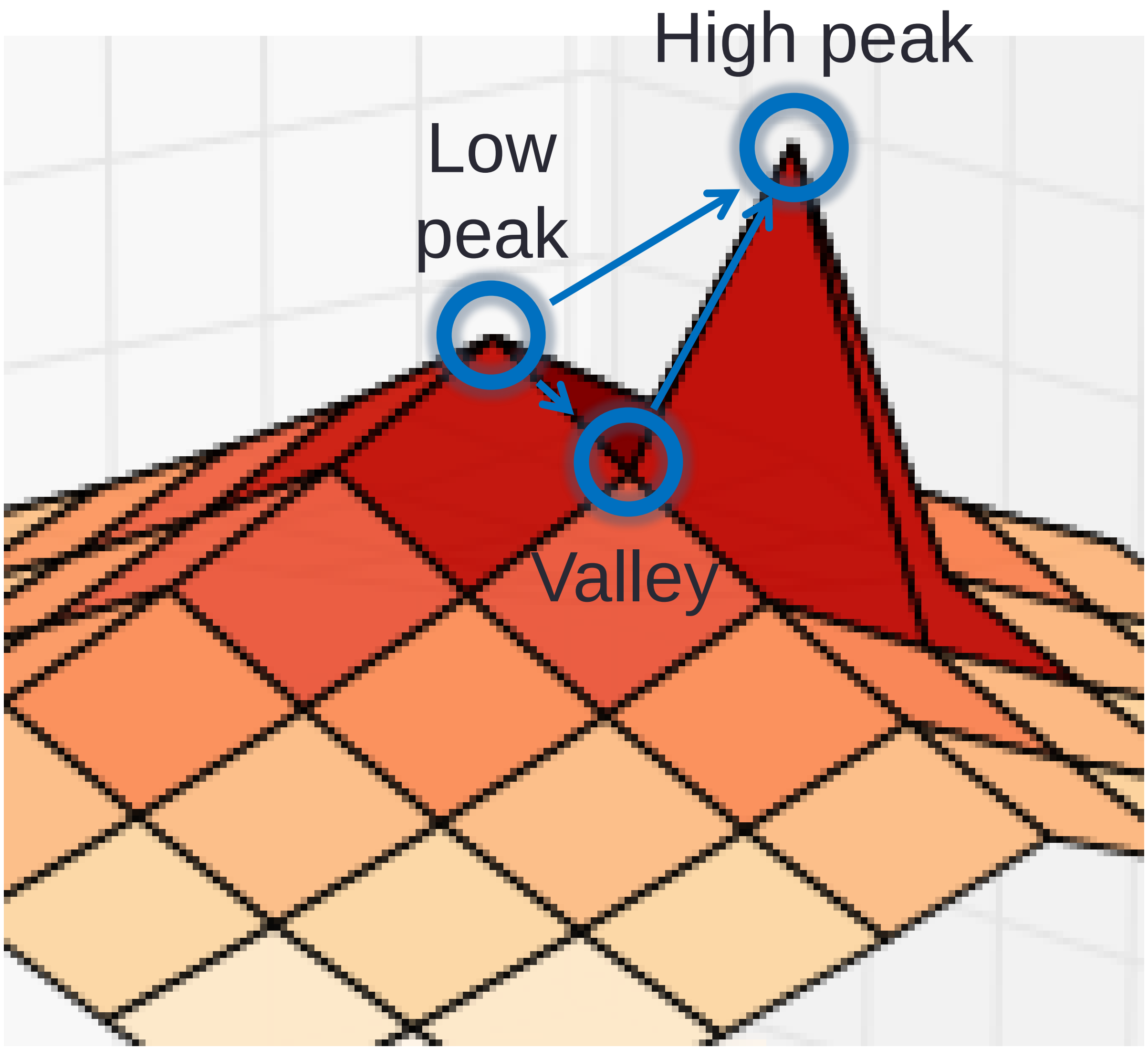
- Two new proteins required, but each is costly on its own:
  - Pump to transport new sugar into cell
  - Enzyme to metabolize sugar

Signaling and language

- Broadcasting exposes you to predation
- Building receivers is costly and noisy

Shifting to a higher fitness peak

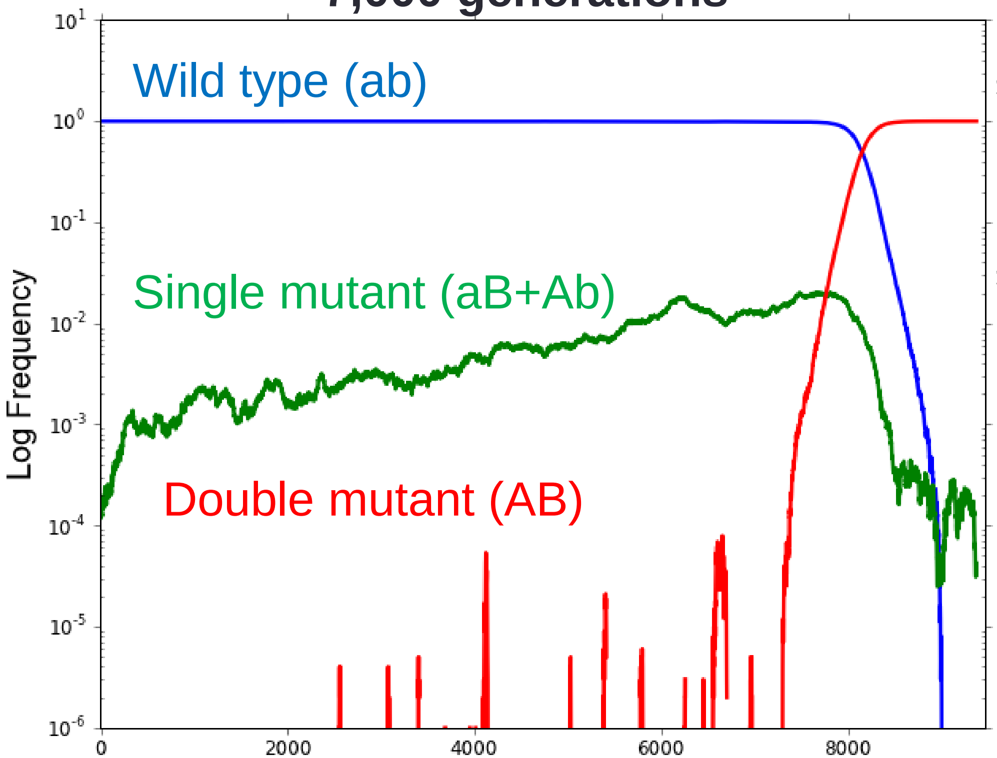
Fitness:
ab 1
Ab 1-s
aB 1-s
AB 1+s

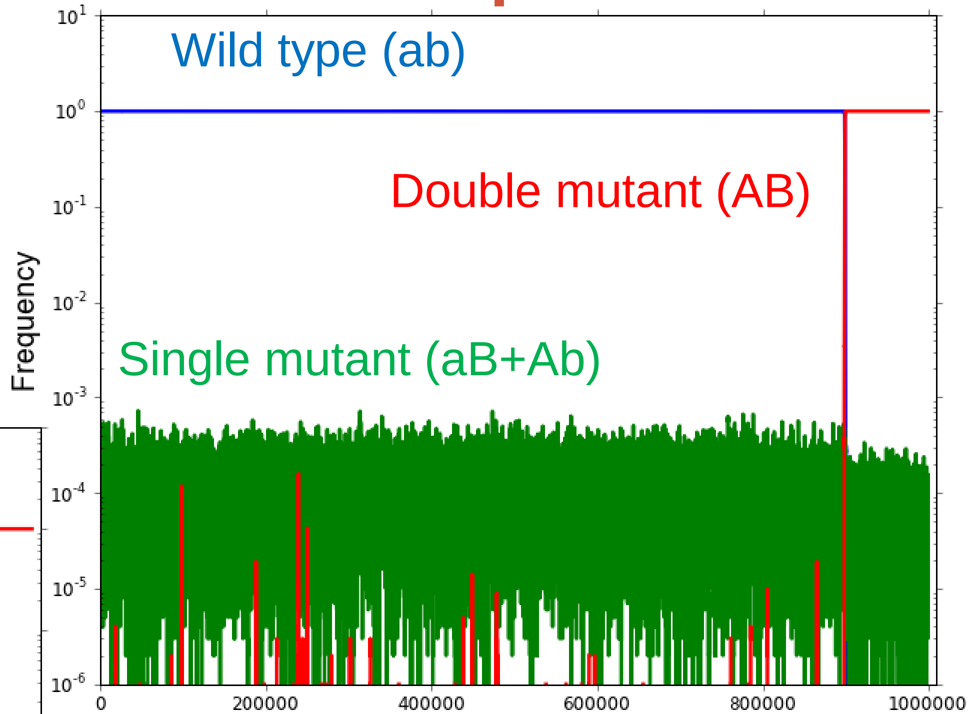


Adaptation on fitness landscapes

Smooth Landscape

7,000 generations



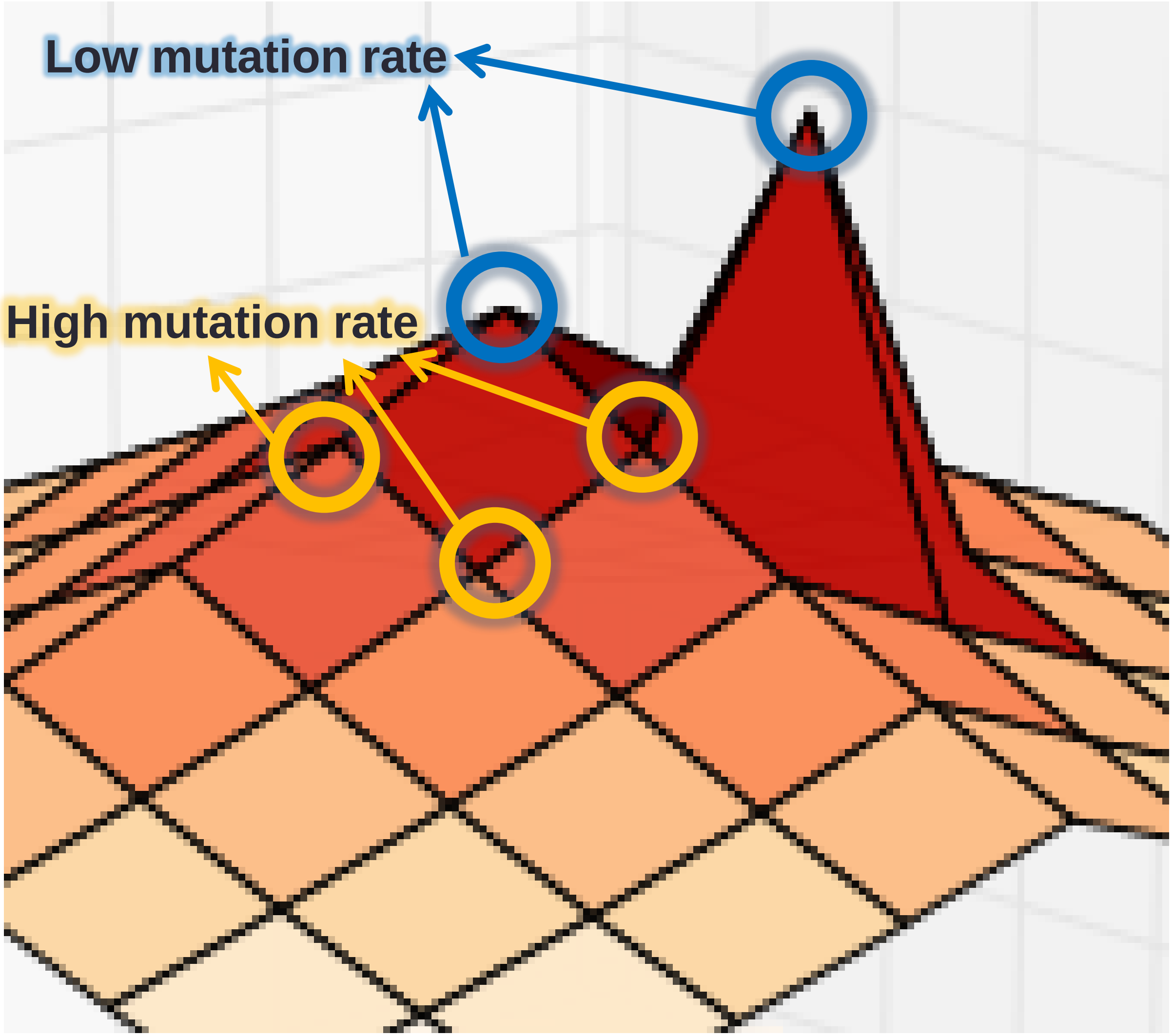


90,000 generations

Rugged Landscape

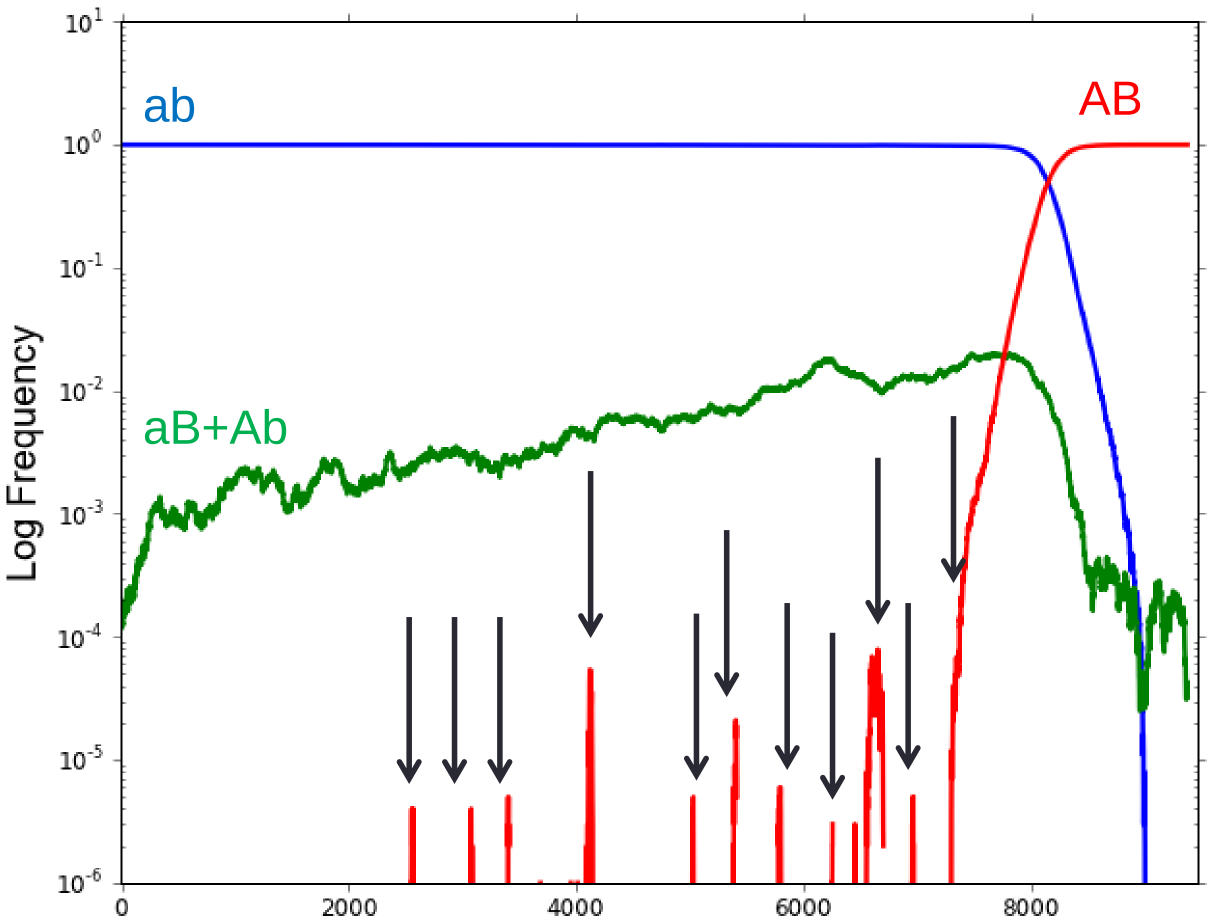
Stress-induced mutation on rugged landscapes

Mutation rate increased in individuals *below the peaks*



Appearance of a double mutant

- The probability of the appearance of a double mutant



Non-mutator:

$$e^{-U}\frac{\mu^2}{s}(2+s-U)$$

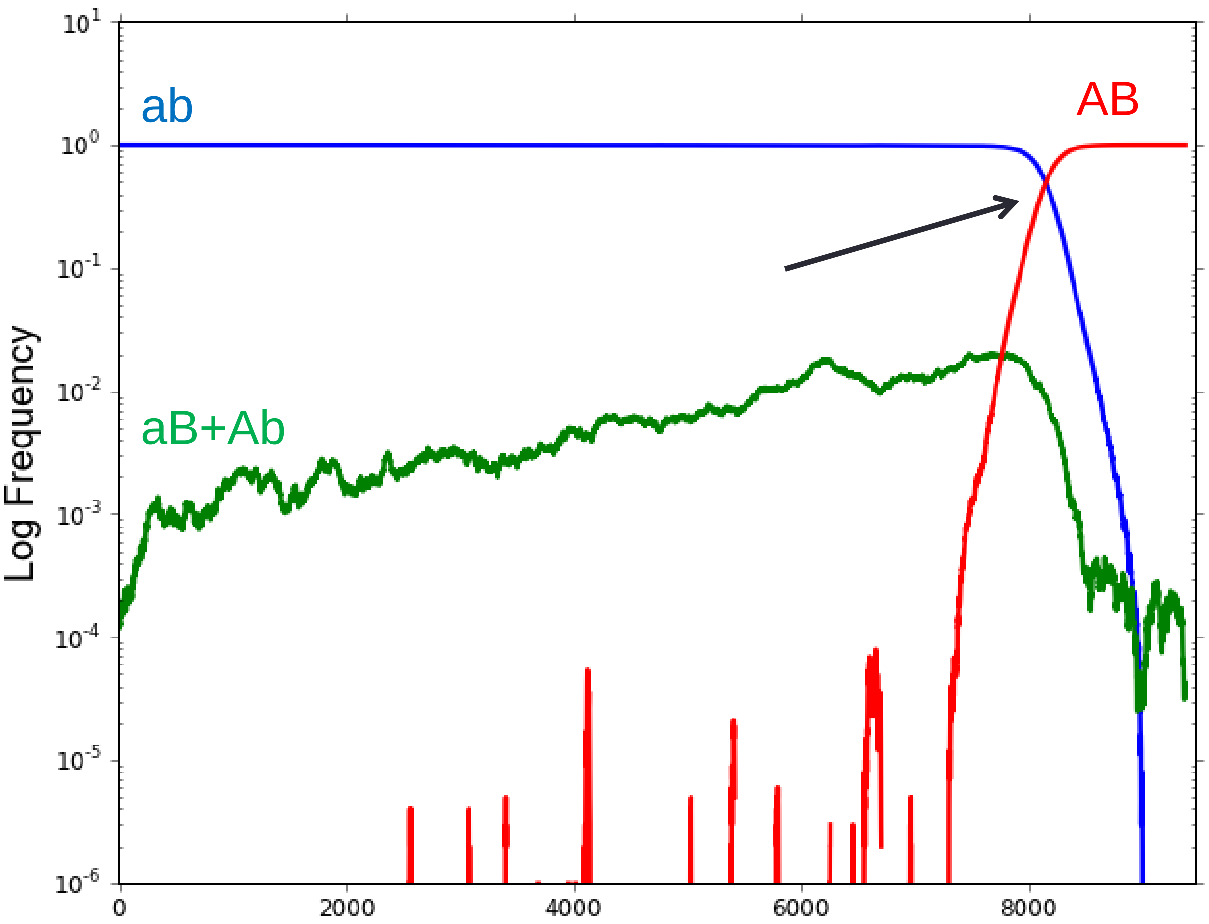
Stress-induced mutator:

$$e^{-U}\frac{\mu^2}{s}(2\tau e^{-U(\tau-1)}+s-U)$$

SIM > NM

Fixation of a double mutant

- The probability of the fixation of a double mutant



Non-mutator:

$$\approx 2s$$

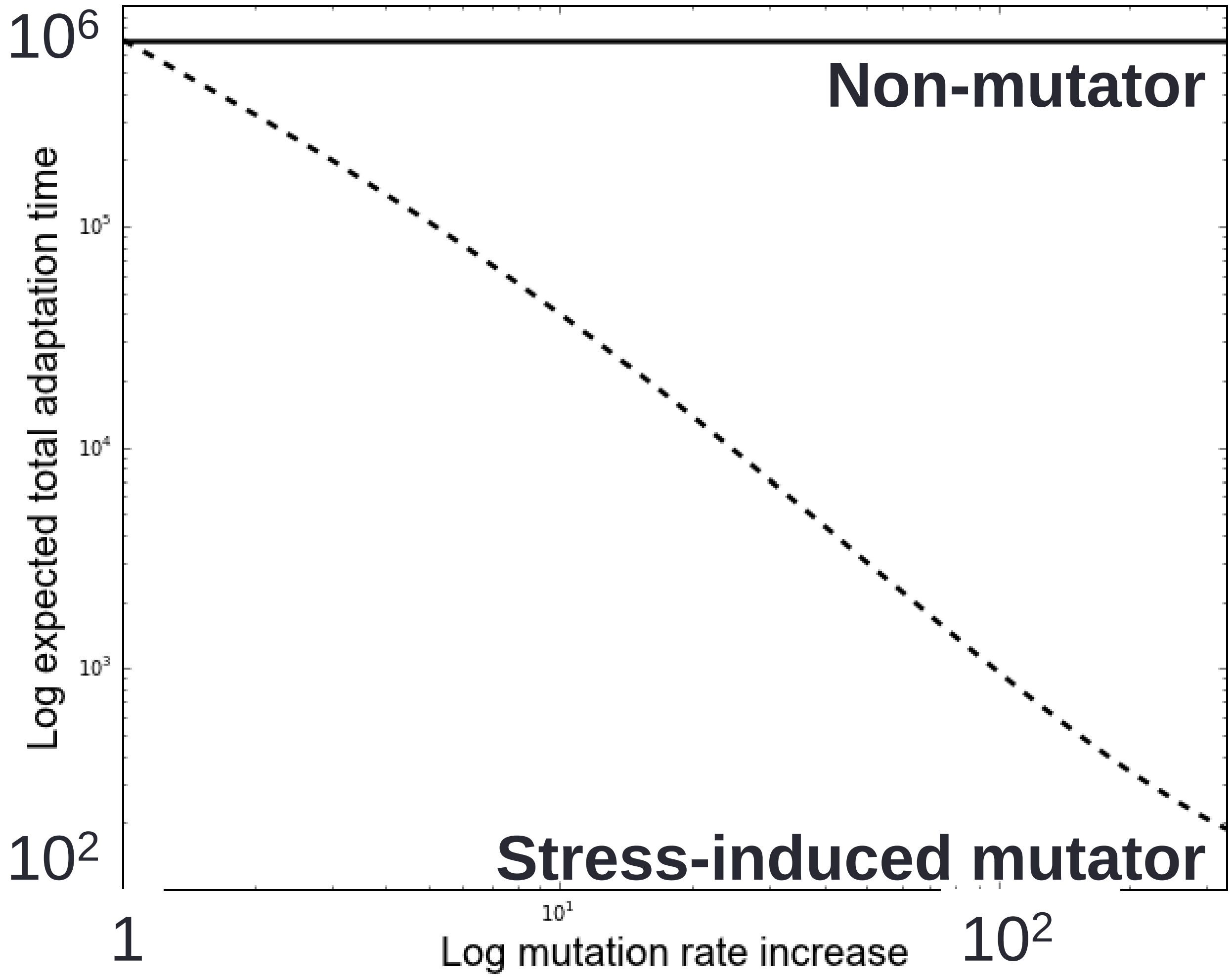
Stress-induced mutator:

$$\approx 2 - 2\frac{1 - \frac{U^2}{s}(\tau - 1)(1 - s)}{1 + s}$$

SIM > NM

Stress-induced mutation reduces adaptation time

Total adaptation time = Waiting time / fixation probability



Evolutionary advantages of stress-induced mutation

Part I – Evolution **of** stress-induced mutations:

- Stress-induced mutation rate **favored by selection** over constant mutation rate
- Both in changing and constant environments
- Due to its effect on **evolvability**

Part II – Evolution **with** stress-induced mutation

- Stress-induced mutation **accelerates adaptation** on rugged fitness landscapes
- The higher rate of hypermutation, the faster the adaptation

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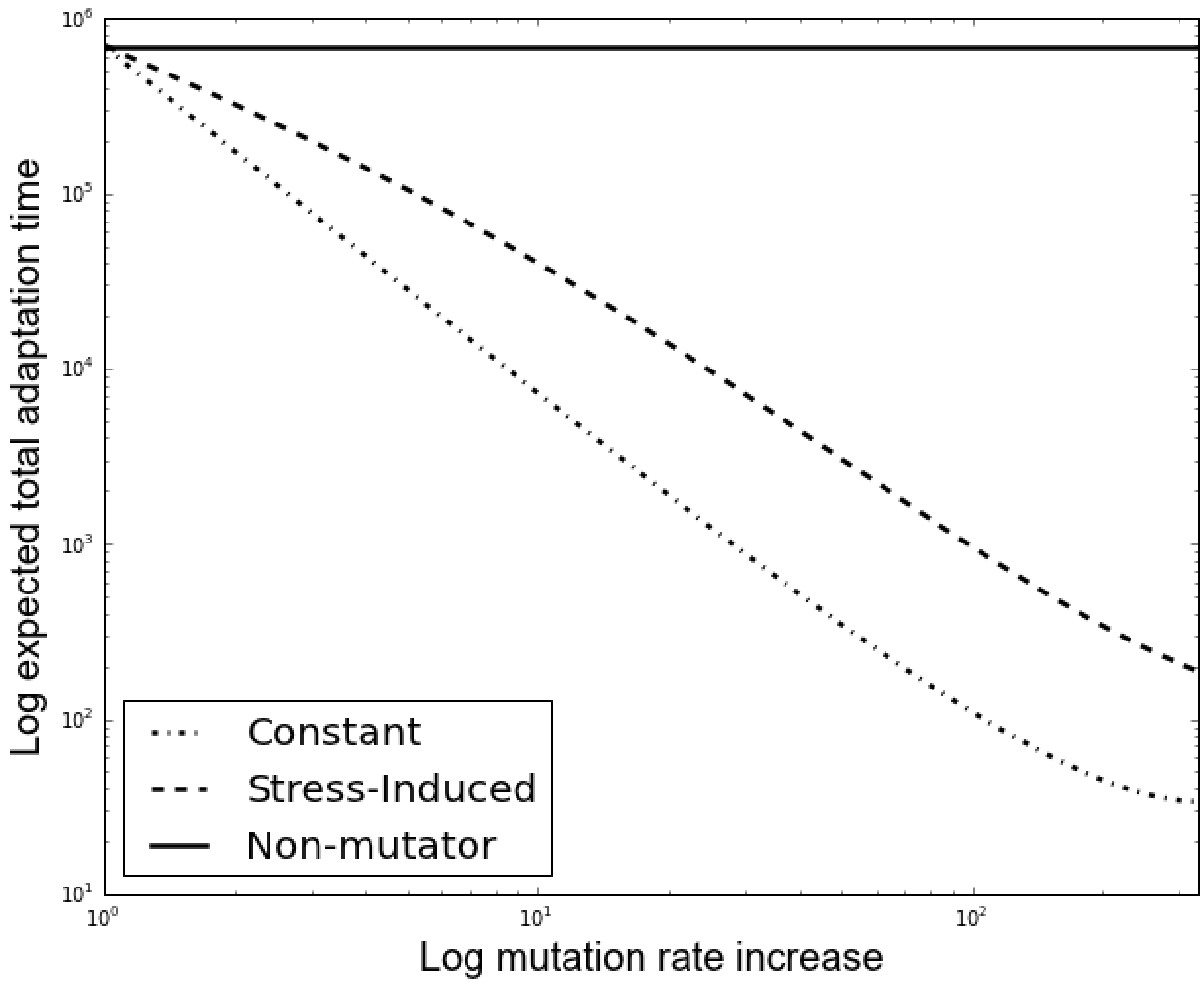
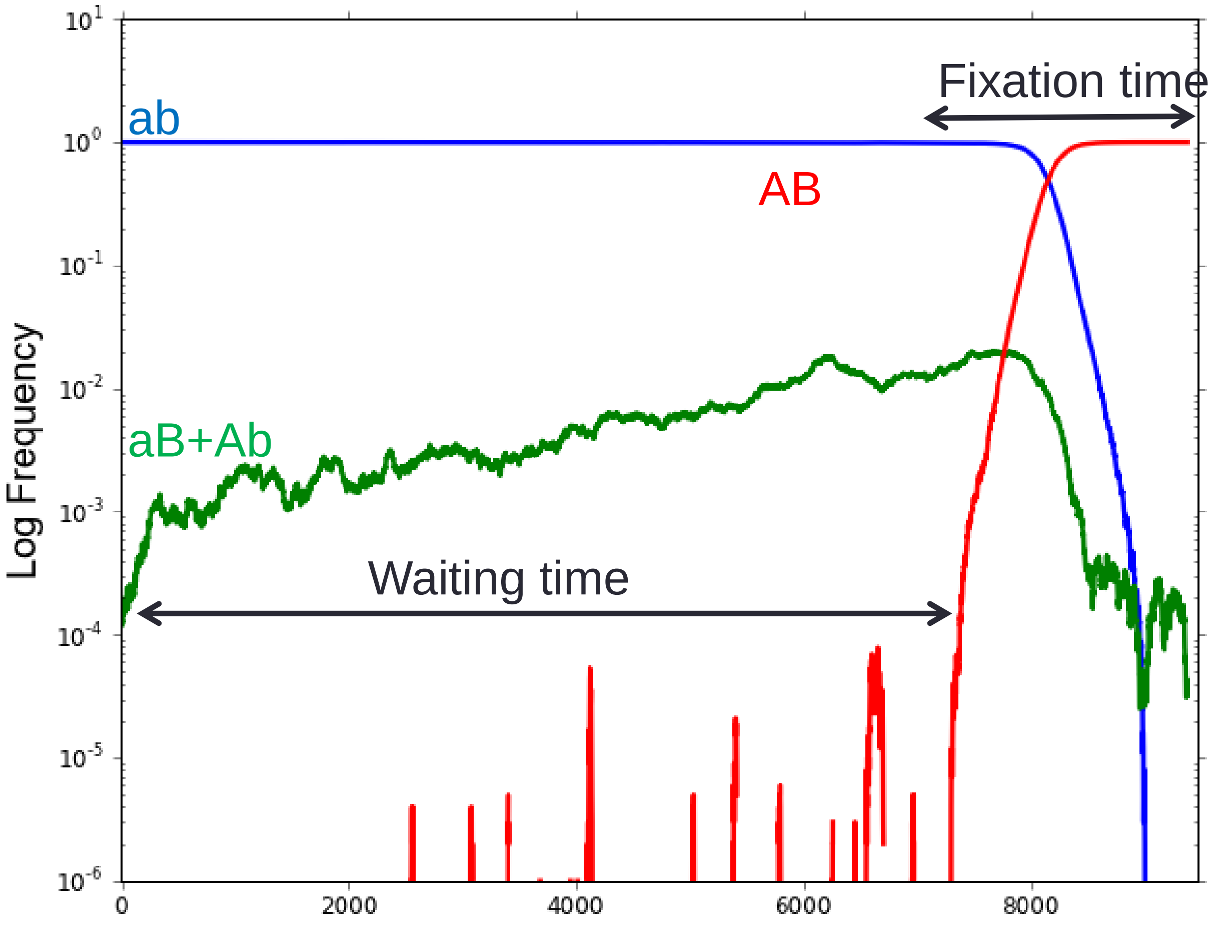
Additional slides

Total adaptation time



Competition before fixation

- The time before a double mutant starts fixation is long



SIM outcompetes CM

- During this time stress-induced mutators outcompete constitutive mutators
- Stress-induced mutators co-exist with non-mutators